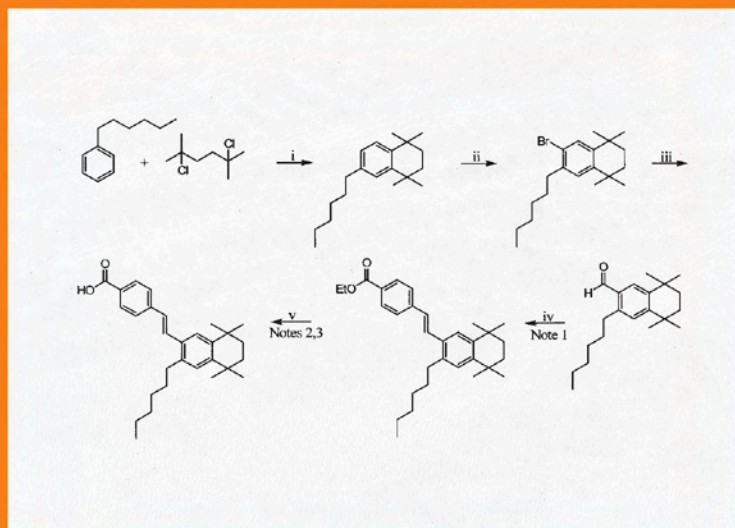


Advances in Synthetic Organic Chemistry and Methods Reported in US Patents

Thomas F. DeRosa



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To my loving wife,

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Introduction

The first US Patent was issued to inventor John Ruggles on July 13, 1836 for improved Traction Wheels for locomotive-engines. The Traction Wheels addressed the need for locomotives to efficiently climb ‘inclined plains and hills with heavy loads drawn up to the same with more facility and economy than heretofore.’ US Patent 130 was the first chemical invention patent issued on February 16, 1837 to English chemist Webster Flockton. Flockton had developed a method of preserving wood by treating lumber with ‘the essential oil of vegetable tar saturated with the oxide of iron.’

This initially small stream of issued patents has become a deluge. In February, 2005, 12,915 US patents were granted; on March 1, 2005, US Patent 6,862,742 issued. Assignees are not limited to individuals and small and large corporations, but also include academic institutions and national and international government agencies.

The purpose of this book is to provide academic and industrial chemists with significant advances in current chemical research in 46 subject areas as reported in the US Patent literature. This objective is best achieved using four inter-connected components. First, chemical reactions necessary to achieve the inventor’s stated goal are depicted for each patent. All structural transformations, reagents, chemical intermediates, as well as experimental conditions have been supplied. Second, chemical agents have been classified by both their Functional Group Type and Product Utility. For example, water soluble fullerenes derivatives are classified as ‘Acids and Derivatives’ under Functional Group Type and as ‘Pharmaceuticals, Virucides’ under the Product Utility designation. Third, explicit laboratory procedures for synthesizing targeted compounds, intermediates, and derivatives have been provided to assist in the preparation, isolation, characterization, and assaying of chemical agents of interests. Where available, relevant prior art US Patent references are incorporated throughout the text which are assessable from the US Patent and Trademark Office database (www.uspto.gov). Finally, individual Reagent, Product, and Name Reaction indices are incorporated to more efficiently access required information.

*Thomas F. DeRosa,
May, 2005*

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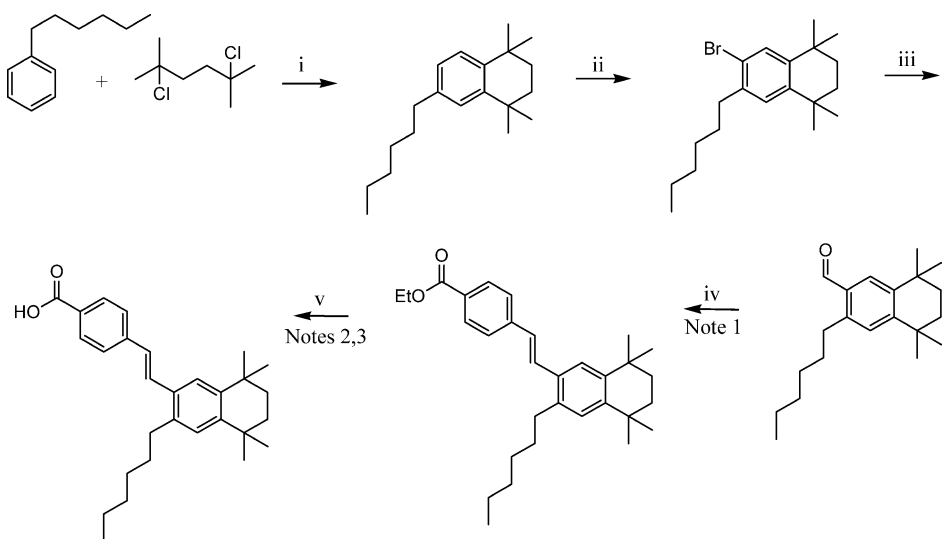
Acids and Derivatives

Patent: Aromatic Carboxylic Acid Derivatives
M. Klaus *et al*, US Patent 6,610,877 (August 26, 2003)

Assignee: Hoffman-La Roche Inc.

Utility: Treatment of Photodamaged Skin

Reaction



i- Aluminium trichloride, carbon disulfide

ii- Carbon tetrachloride, iron, bromine

iii- t-Butyl lithium,

N,N-dimethylformamide, THF

iv- Diethyl(4-carboethoxybenzyl)

phosphonate, sodium hydride,

dimethylsulphoxide, THF

v- Ethyl alcohol, potassium hydroxide

Experimental

1. 1,1,4,4-Tetramethyl-6-hexyl-1,2,3,4-tetrahydro-naphthalene

6-Hexylbenzene (83 ml) and AlCl_3 (1.8 g) were mixed while cooling and 2,5-dichloro-2,5-dimethyl-hexane (40 g) dissolved in 300 ml CS_2 added dropwise. Thereafter, the mixture was stirred 2 hours, poured into 6 M HCl in ice, extracted with EtOAc, and the crude product isolated as a colorless oil, bp = 141–152 °C at 0.8 mm Hg.

2. 7-Bromo-1,1,4,4-tetramethyl-6-hexyl-1,2,3,4-tetrahydro-naphthalene

The product from Step 1 (10 g) was dissolved in 100 ml CCl_4 followed by the addition of a spatula full of iron and bromine (6.4 g) and the mixture stirred at 0 °C for 3 hours. The mixture was poured into ice water, extracted with diethyl ether, and purified by column chromatography on silica gel with hexane/EtOAc, 9:1, the product isolated as a pale yellow oil.

3. 2-Formyl-3-hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene

The product from Step 2 (10 g) was dissolved in 100 ml THF and treated with 40 ml 1.4 M t-BuLi in pentane and 60 ml DMF and stirred 1 hour at –78 °C. The mixture was poured into ice water acidified with 2 M HCl, extracted with diethyl ether, purified by column chromatography on silica gel using hexane/EtOAc, 19:1, and the product isolated as a yellow oil.

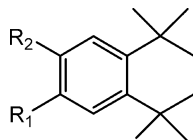
4. Ethyl-p-[(E)-2-(3-hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthyl)vinyl]benzoate

Diethyl(4-carboethoxybenzyl)phosphonate (20 g) was dissolved in 50 ml DMSO and treated with pentane-washed NaH (3.2 g) in 50 ml DMSO at ambient temperature for 2 hours and the product from Step 3 (9 g) dissolved in 50 ml THF added dropwise. The mixture was heated to 40 °C for 3 hours and the product isolated as in Step 3.

5. p-[(E)-2-(3-Hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthyl)vinyl]benzoic acid

The product from Step 4 (8 g) was dissolved in 50 ml ethyl alcohol and treated with 10 g KOH dissolved in 10 ml apiece ethyl alcohol and water. Thereafter 50 ml THF was added and the mixture heated to 40 °C 4 hours, poured into ice water containing 6 M HCl, extracted with EtOAc, and the crude product re-crystallized using hexane/EtOAc, mp = 134–136 °C.

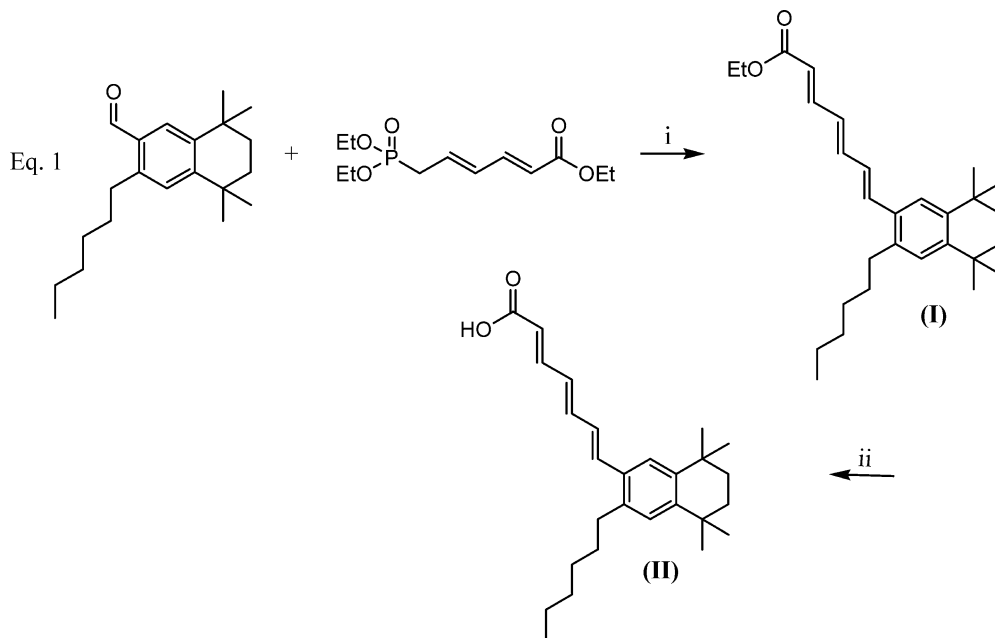
Derivatives



R_1	R_2	Melting Point (°C)
Pentyl	(2E, 4E, 6E)-3-Methyl-hepta-trienoic acid	170–174
Octyl	E-[(5H-Benzocyclohepten-2-yl)vinyl]benzoic acid	183–183
Allyloxy	E-Vinylbenzoic acid	191–192

Notes

1. This is an example of the Horner-Wadsworth-Emmons reaction and is discussed (1)
2. (2E, 4E, 6E)-7-(3-Hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthanen-2-yl)-3-methyl-hepta-2,4,6-trienoic acid (II) was also prepared by reacting 2-formyl-3-hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene with ethyl (E,E)-6-(diethoxyphosphinyl)-3-methyl-2,4-hexdienolate followed by basic hydrolysis illustrated in Eq. 1 as described below by the author.



i- Dimethyl sulfoxide

ii- Potassium hydroxide, ethyl alcohol, THF

Procedure-1, Step 1

Ethyl (2E, 4E, 6E)-7-(3-hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthanen-2-yl)-3-methyl-hepta-2,4,6-trienoate (I)

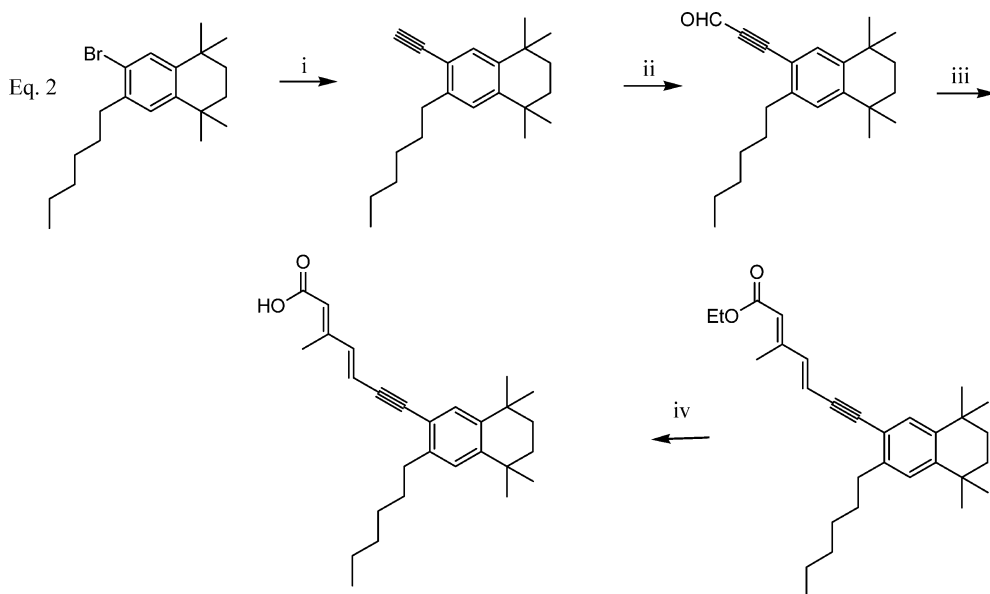
Pentane-washed NaH (4.1 g) was suspended in 70 ml DMSO and a solution of ethyl (E,E)-6-(diethoxyphosphinyl)-3-methyl-2,4-hexdienolate (24.5 g) dissolved in 70 ml DMSO added. The reaction was stirred for 30 minutes at ambient temperature and 2-formyl-3-hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene (11.3 g) dissolved in 70 ml DMSO and 35 ml THF added. The mixture was stirred 2 hours and the product precipitated in ice water acidified with 6M HCl. The mixture was extracted with EtOAc and purified by flash chromatography on silica gel with hexane/methyl t-butyl ether, 98:2, and the product isolated as a pale yellow oil.

Step 2

(2E, 4E, 6E)-7-(3-Hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthanen-2-yl)-3-methyl-hepta-2,4,6-trienoic acid (II)

The product from Procedure-1 step 1 (8.5 g) was dissolved in 160 ml EtOH and 30 ml THF, treated with 12.8 g KOH dissolved in 60 ml water and the mixture stirred for 3 hours at 45 °C. The mixture was poured into ice water acidified with 1 M HCl, extracted with EtOAc, and re-crystallized with hexane/EtOAc forming yellow crystals, mp = 173–174 °C.

3. Alkyne-containing aromatic carboxylic acid derivatives were also prepared by the author illustrated in Eq. 2:



- i- Piperidine, tetrakis(triphenylphosphine)palladium, copper(I) iodide, triphenylphosphine, ethynyl-trimethylsilane, tetrabutylammonium fluoride
 ii- THF, n-butyl lithium, DMF
 iii- Sodium hydride, dimethylsulfoxide, ethyl 4-ethoxyphosphinyl-3-methyl-crotonate
 iv- Potassium hydroxide, ethyl alcohol, THF

4. The preparation of other 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthanen-2-yl-benzoic acid derivatives is provided (3).

References

1. J. Boutagy, Chem. Rev. 79, 87 (1974)
2. M. Klaus *et al*, US Patent 5,700,836 (December 23, 1997)
3. H.-H.Wuest *et al*, US Patent 4,801,733 (January 31,1989)

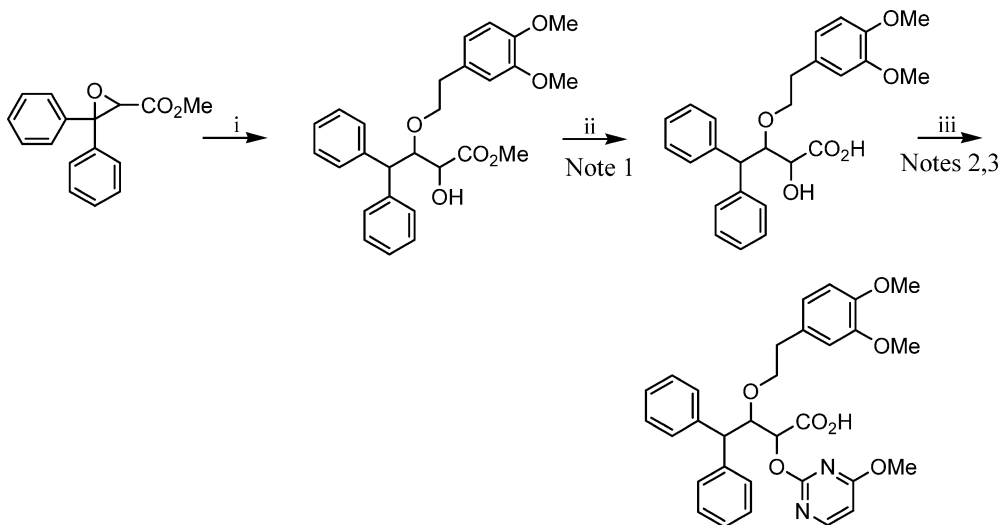
Patent: Azinyloxy, and Phenoxy-Diaryl-Carboxylic Acid Derivatives, Their Preparation and Use as Mixed ETA/ETB Endothelin Receptor Antagonists

W. Amberg *et al*, US Patent 6,670,367 (December 30, 2003)

Assignee: Abbott GmbH & Co., KG

Utility: Treatment of Vasoconstrictive Disorders

Reaction



i- 2-(3,4-Dimethoxyphenyl)ethanol, CH_2Cl_2 , boron trifluoride etherate

ii- Dioxane, sodium hydroxide

iii- N,N-dimethylformamide, sodium hydride, 4-methoxy-6-methyl-2-methylsulfonylpyrimidine

Experimental

1. Methyl 2-hydroxy-3-(2-(3,4-dimethoxyphenyl)ethoxy)-3,3-diphenylpropionate

Methyl 3,3-diphenyl-2,3-epoxypropionate (27.5 mmol) and 2-(3,4-dimethoxy-phenyl) ethanol (30.2 mmol) were dissolved in 20 ml CH_2Cl_2 at ambient temperature and 5 drops boron trifluoride etherate added. The mixture was stirred for 2 hours, concentrated, and the residue isolated in 89% yield and used without further purification.

2. 2-Hydroxy-3-(2-(3,4-dimethoxyphenyl)ethoxy)-3,3-diphenyl-propionic acid

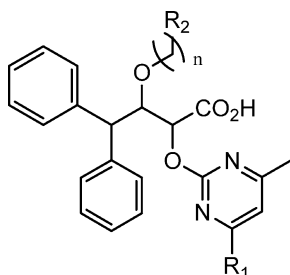
The product from Step 1 (27.5 mmol) was dissolved in 110 ml dioxane, 55 ml 1 M NaOH added, and the mixture stirred at 80°C for 2 hours. Water was added to the mixture and the aqueous phase extracted twice with diethyl ether. The aqueous phase was acidified with 1 M HCl, extracted with ether, and the combined organics, dried, and concentrated.

The residue was recrystallized from diethyl ether/n-hexane and the product isolated in 87% yield, mp = 133–135 °C.

3. **2-(4-Methoxy-6-methyl-2-pyrimidinyl-2-ethoxy)-3-(2-(3,4-dimethoxyphenyl)-ethoxy)-3,3-diphenylpropionic acid**

The product from Step 2 (2.3 mmol) was dissolved in 10 ml N,N-dimethylformamide, NaH (340 mg, 50% suspension) added, stirred 15 minutes, and 4-methoxy-6-methyl-2-methylsulfonylpyrimidine (526 mg) added. The reaction stirred 3 hours at ambient temperature, water was then added, and the mixture extracted with diethyl ether. The aqueous phase was acidified with 1 M HCl, extracted with diethyl ether, dried, and concentrated. The residue was purified by liquid chromatography, and the product isolated in 52% yield. ¹H-NMR and MS data supplied.

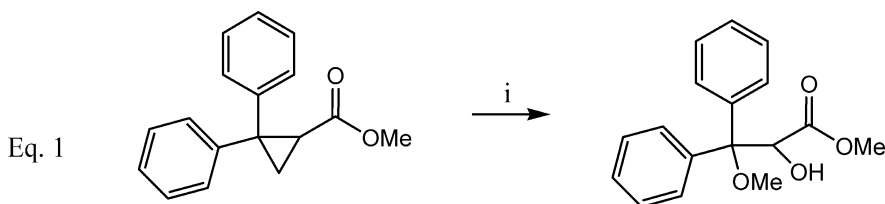
Derivatives



R ₁	R ₂	n	Melting Point (°C)
Methyl	4-Chlorophenyl	2	150–152
Methoxy	4-Ethoxy-3-methoxy-phenyl	2	166–169 (dec)
Methoxy	3,4-Methylenedioxyphenyl	2	146–148 (dec)
Methyl	Methyl	3	153–155 (dec)

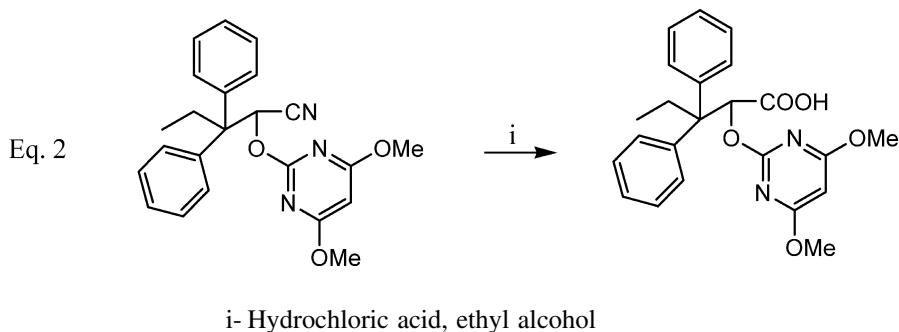
Notes

- Other 6-methyl-2-methylsulfonylpyrimidine derivatives were prepared by the author in the current invention starting from 6-dimethyl-1-methylthiopyrimidine and are described.
- Other derivatives of the Step 1 reagent have been prepared (1) as illustrated in Eq. 1 were also prepared by the author.

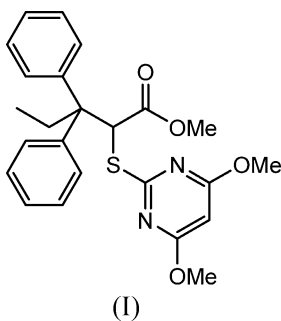


i- Borontrifluoride etherate, methyl alcohol

3. 2-(4,6-Dimethoxy-2-pyrimidinyl)-3,3-diphenylvaleronitrile has previously been prepared and converted to 2-(4,6-dimethoxy-2-pyrimidinyl)-3,3-diphenylvaleric acid by hydrolysis (2) as illustrated in Eq. 2:



4. In an earlier investigation by the author (3), the thio analogue of the current invention, methyl 3,3-di(4-methoxyphenyl)-2-(4,6-dimethylpyrimidine-2-sulfanyl)-pentanoate, (I), was prepared.



References

1. H. Riechers *et al*, US Patent 5,969,134 (October 19, 1999) and US Patent 5,932,730 (August 3, 1999)
2. D. Klinge *et al*, US Patent 6,686,369 (February 3, 2004)
3. W. Amberg *et al*, US Patent 6,235,903 (May 22, 2001)

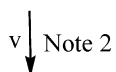
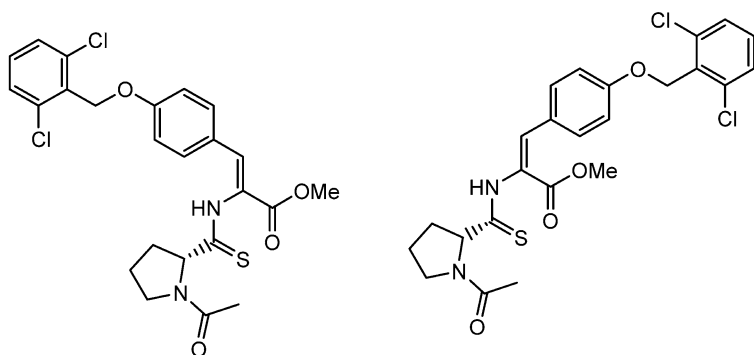
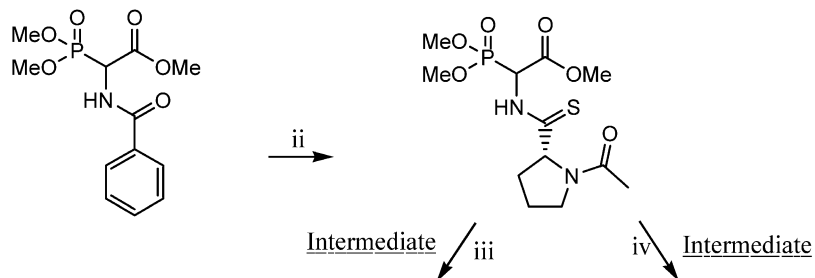
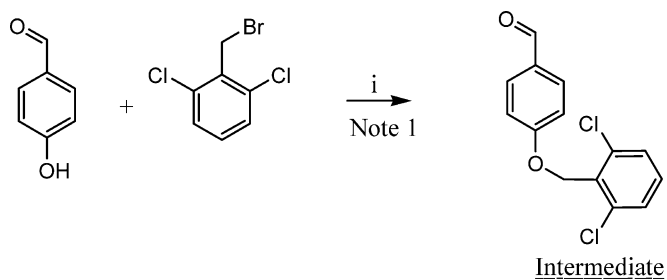
Patent: Cinnamic Acid Derivatives

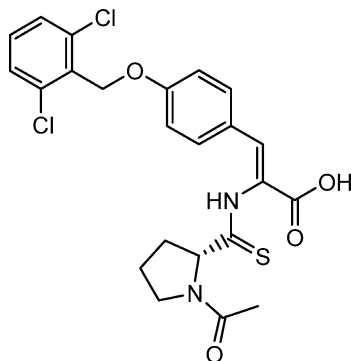
S.C. Archibald *et al*, US Patent 6,329,362 (December 11, 2001)

Assignee: Celltech Therapeutics Limited

Utility: Treatment of Immune or Inflammatory Disorders

Reaction





- i- Potassium carbonate, N,N-dimethylformamide
- ii- 10% Palladium on carbon, methyl alcohol,
N-acetyl-thiopropine, 1-hydroxybenzotriazole,
N-methylmorpholine,
 CH_2Cl_2 , 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
- iii- THF, sodium hydride
- iv- Lithium diisopropylamide, THF
- v- THF, lithium hydroxide monohydrate

Experimental

1. 4-(2,6-Dichlorobenzoyl)benzaldehyde

A suspension of 4-hydroxybenzaldehyde (157.5 mmol), 2,6-dichlorobenzylbromide (150 mmol) and K_2CO_3 in 150 ml DMF was stirred overnight at ambient temperature. The mixture was filtered, evaporated, and the residue dissolved in 500 ml diether ether. It was washed with 100 ml apiece water and brine, dried, and evaporated under reduced pressure. The solid was re-crystallized in diisopropylether to give the product in 85% yield, mp = 70–71 °C. $^1\text{H-NMR}$ and elemental analysis data supplied.

2. N-Acetyl-D-thiopropine- α -phosphonoglycine trimethyl ester

A mixture of N-(benzyloxycarbonyl)- α -phosphonoglycine trimethyl ester (15 mmol) and 10% palladium on carbon (500 mg) in 50 ml methyl alcohol was stirred under a hydrogen atmosphere (balloon) at ambient temperature for 4 hours. The mixture was filtered and the solvent evaporated. N-acetyl thiopropine (15 mmol), 1-hydroxybenzotriazole (15 mmol), N-methylmorpholine (16.5 mmol) dissolved in 75 ml CH_2Cl_2 , and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (16.5 mmol) were added to the residue and the mixture stirred overnight at ambient temperature. Thereafter it was diluted with CH_2Cl_2 , washed with 50 ml apiece 1 M HCl, NaHCO_3 and water. It was purified by column chromatography on silica gel using CH_2Cl_2 /methyl alcohol, 93:7, and the product isolated in 53% yield. $^1\text{H-NMR}$ data supplied.

3. N-Acetyl-D-thioprolino-O-(2,6-dichlorobenzyl)-(Z)-didehydrotirosine methyl ester

The product from Step 2 (2.06 mmol) was dissolved in 10 ml THF and added dropwise to a stirred suspension of NaH (2.27 mmol) in 5 ml THF at ambient temperature. After 15 minutes, the product from Step 1 (2.1 mmol) dissolved in 5 ml THF was added, the mixture stirred for several hours and was then quenched with 1 ml water. The organic phase was evaporated and the residue purified by column chromatography on silica with CH₂Cl₂/methyl alcohol, 95:5, yielding a Z/E geometric isomer ratio of 76:24, respectively. The desired Z-isomer was isolated by re-crystallization, mp = 189–190 °C. ¹H-NMR and mass spectrum data supplied.

4. N-Acetyl-D-thioprolino-O-(2,6-dichlorobenzyl)-(E)-didehydrotirosine methyl ester

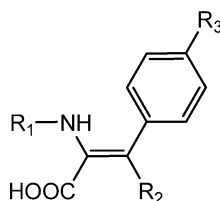
The product from Step 2 (1.45 mmol) was dissolved in 10 ml THF and added to a solution of 2 M LDA (1.45 mmol) in 5 THF at –78 °C. The mixture warm to 0 °C and the product from Step 1 (1.45 mmol) dissolved in 3 ml THF added followed by 2 ml DMF. The solution was stirred overnight at ambient temperature and then the solution evaporated. The residue yielded Z/E geometric isomer ratio of 56:44, respectively. The mixture was purified by column chromatography on silica gel using CH₂Cl₂/methyl alcohol, 97:3, providing 105 mg of the desired E-isomer. ¹H-NMR data supplied.

5. N-Acetyl-D-thioprolino-O-(2,6-dichlorobenzyl)-(Z)-didehydrotirosine (Note 2)

The product from Step 3 (0.75 mmol) was dissolved in 7.5 ml THF and 7.5 ml water to which was added lithium hydroxide monohydrate (0.83 mmol) and the mixture stirred overnight at ambient temperature. The organic solvent was removed, the aqueous phase acidified with 1 M HCl, and the product extracted twice with 50 ml CH₂Cl₂. The organic phase was dried and evaporated under reduced pressure. The Z-isomer was isolated by lyophilisation from a mixture of methyl alcohol and water in 95% yield. ¹H-NMR data supplied.

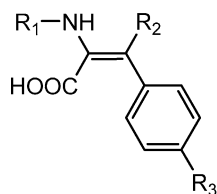
Derivatives

(Note 3)



R ₁	R ₂	R ₃	MS (M+1)
N-Acetyl-(L)-thioprolino	Hydrogen	o-Benzoyl	449
N-Acetyl-(L)-thioprolino	Phenyl	Acetamide	378
(2-Chloro-3-pyridinyl)carbonyl	Hydrogen	o-2,6-Dichlorobenzyl	477
Trimethylacetal	Phenyl	2,6-Dichlorobenzylamino	435

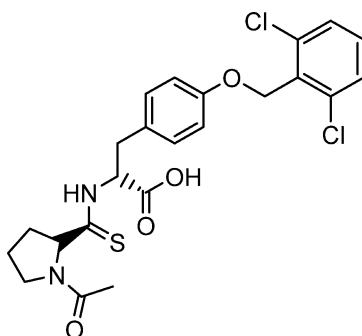
(Note 4)



R ₁	R ₂	R ₃	MS (M+1)
Trimethylacetal	Phenyl	2,6-Dichlorobenzylamino	435
N-Acetyl-(L)-thiopropine	Phenyl	2,6-Dichlorobenzylamino	508
N-Acetyl-(L)-thiopropine	Hydrogen	o-Benzoyl	427
N-Acetyl-(L)-thiopropine	Hydrogen	o-2,6-Dichlorobenzyl	495

Notes

1. The preparation of other polyaromatic intermediates of the current invention is described (1).
2. A method for preparing N-acetyl-L-thiopropine-(2,6-dichlorobenzyl)-L-tyrosine (I) is provided (2).



(I)

3. N-Acetyl-D-thiopropine-O-(2,6-dichlorobenzyl)-(E)-didehydrotyrosine was also prepared by the author in the current invention and is described.
4. ¹H-NMR data for all derivatives supplied by author.

References

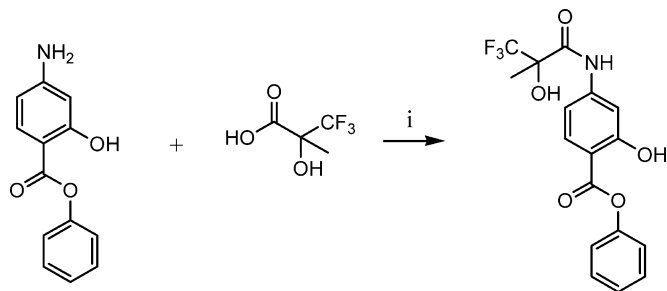
1. N. Chandrakumar *et al*, US Patent 5,773,646 (June 30, 1998); G.A. Cain *et al*, US Patent 5,523,302 (June 4, 1996)
2. J.C. Head *et al*, US Patent 6,039,696 (July 25, 2000)

Patent: Compounds Derived from Benzoic Acid Esters, Composition Containing Said Compounds and Use Thereof
J.-B. Galey *et al*, US Patent 6,602,869 (August 5, 2003)

Assignee: L'Oreal S.A.

Utility: Treatment of Alopecia

Reaction



i- N,N-Dimethylacetamide, thionyl chloride

Experimental

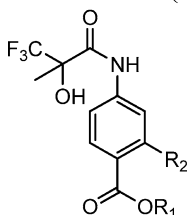
1. Phenyl 2-hydroxy-4-(3,3,3-trifluoromethyl-2-hydroxy-2-methylpropionylamino) benzoic acid

3,3,3-Trifluoromethyl-2-hydroxy-2-methylpropanoic acid (2.1 g) was dissolved in 20 ml DMAc and cooled to -20°C . Thereafter, 1 ml SOCl_2 was added dropwise and the mixture stirred for 1 hour followed by the addition of phenyl 4-aminosalicylate. The reaction came to ambient temperature, and was stirred an additional 12 hours then poured into 100 ml ice water. The mixture was extracted 3 times with 50 ml CH_2Cl_2 , washed with water, dried and concentrated.

The oil was dissolved in 20 ml toluene/heptane, 1:1, and the product isolated by chromatography on silica gel with CH_2Cl_2 in 50% yield. Elemental analysis data supplied.

Derivatives

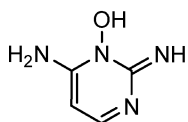
(Note 1)



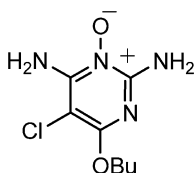
R_1	R_2
3-(N-Morphino)-1-propyl	Hydroxyl
Methyl	Ethyl
4-n-Octylphenyl	Hydroxyl
3,5-Di-trifluoromethylbenzyl	Hydroxyl
4-(O-Methyloxime)phenyl	Hydroxyl
Methyl	Methoxy

Notes

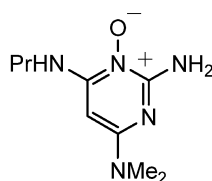
1. Although structural conformation of compounds of this invention were confirmed by 500 MHz $^1\text{H-NMR}$ in $d_6\text{-DMSO}$, spectra were not supplied by author. Derivatives, however, were used in skin lotion formulations and results provided.
2. Phenyl 2-hydroxy-4-(3,3,3-trifluoromethyl-2-hydroxy-2-methylpropionylamino)benzoic acid is the latest chemical agent designed to treat alopecia supplanting 6-amino-1,2 dihydro-1-hydroxy-2-aminopyrimidine (Minoxidil) (I) (1) and pyrimidine oxide derivatives (II) (2), (III) (3), and (IV) (4).



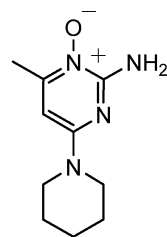
(I)



(II)



(III)



(IV)

References

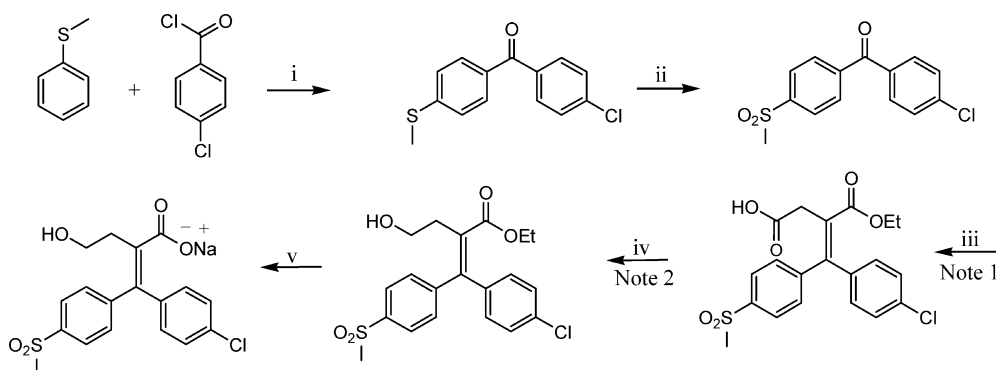
1. W.C. Anthony *et al*, US Patent 3,461,461 (August 12, 1969)
2. E. Terranova *et al*, US Patent 5,466,694 (November 14, 1995)
3. M. Hocquaux *et al*, US Patent 5,772,990 (June 30, 1998)
4. D. Dufetel *et al*, US Patent 5,760,043 (June 2, 1998)

Patent: 1,2-Diarylmethylene Derivatives, Their Methods of Preparation, and Their Uses in Therapeutics
E. Nicolai *et al*, US Patent 5,972,950 (October 26, 1999)

Assignee: Laboratories UPSA

Utility: Anti-Inflammatory and Analgesic Agents

Reaction



- i- CH_2Cl_2 , aluminum chloride
 ii- CH_2Cl_2 , 3-chloroperbenzoic acid
 iii- Ethyl succinate, potassium t-butoxide, t-butyl alcohol
 iv- THF, borane/dimethyl sulfide
 v- Sodium hydroxide, ethyl alcohol

Experimental

1. 4-Chloro-4'-methylthiobenzophenone

Thioanisole (0.852 mol) and 4-chlorobenzoyl chloride (0.894 mol) were dissolved in 600 ml CH_2Cl_2 , AlCl_3 (0.98 mol) added, and the mixture stirred while maintaining the temperature between 0°C and -5°C for 2 hours. Thereafter it stood overnight and was then refluxed for 6 hours. The mixture was poured into ice water containing dilute HCl, the aqueous phase extracted with CH_2Cl_2 and combined with the organic phase, dried, and the product is isolated, mp = 134°C .

2. 4-Chloro-4'-methanesulphonylbenzophenone

The product from Step 1 (0.152 mol) was dissolved in 700 ml CH_2Cl_2 and 70% 3-chloroperbenzoic acid (0.335 mol) added while the temperature was maintained at 5°C . The mixture was then stirred at ambient temperature and crystals filtered off. The filtrate was washed with sodium carbonate, dried, concentrated, and the product isolated, mp = 176°C .

3. **(Z)-3-Ethoxycarbonyl-4-(4-chlorophenyl)-4-(4-methanesulfonyl-1-phenyl)but-3-enoic acid.**

The product from Step 2 (1.16 mol), ethyl succinate (1.85 mol), potassium t-butoxide (1.74 mol) and 2.5 L t-butyl alcohol were mixed and a temperature rise to 45 °C observed. Thereafter, the mixture was stirred for 7 hours at ambient temperature and then poured into ice water acidified with HCl to pH 3. The product was extracted with diethyl ether and dried. Overnight the Z isomer precipitated from solution, was filtered from the mixture, re-crystallized in isopropanol, and had a mp = 184–186 °C. The corresponding (E) isomer was obtained upon evaporation of the solvent.

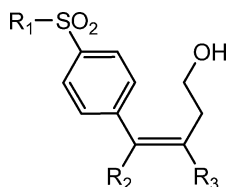
4. **Ethyl (Z)-3-(4-chlorophenyl)3-(4-methanesulphonylphenyl)-2-(hydroxyethyl) prop-2-enolate**

The product from Step 3 (0.0775 mol) was dissolved in 90 ml THF and borane/dimethyl sulfide added dropwise. The mixture was stirred at ambient temperature for 8 hours and 23.5 ml ethyl alcohol added. The mixture was evaporated to dryness, the residue re-dissolved in EtOAc, washed, dried, and the product isolated after re-crystallization in isopropanol, mp = 128 °C.

5. **Sodium (Z)-3-(4-chlorophenyl)3-(4-methanesulphonylphenyl)-2-(hydroxyethyl) prop-2-enolate**

The product from Step 4 (0.0122 mol) was dissolved in 10 ml ethyl alcohol and 11 ml 1 M NaOH added. The mixture was refluxed for 2 hours then evaporated to dryness. The crystals were washed with EtOAc and diethyl ether and isolated, mp = 257–259 °C.

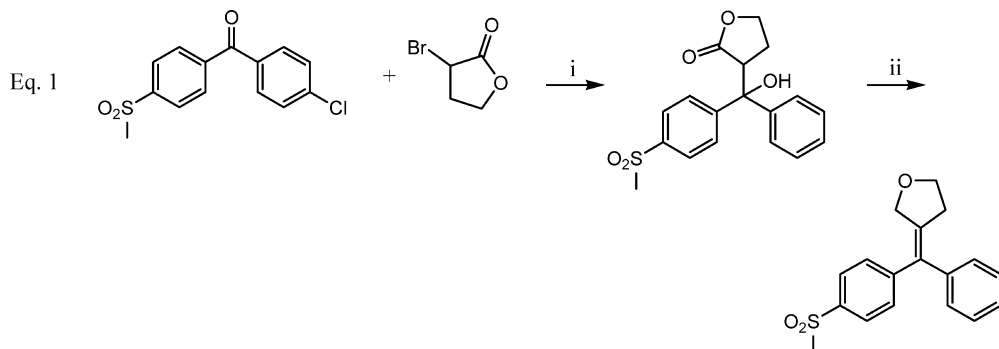
Derivatives



R ₁	R ₂	R ₃	MP(°C)
Ethyl	4-Fluorophenyl	Carboxylic acid	155–156
Methyl	3,5-Dichlorophenyl	Carboxylic Acid	207–209
Ethyl	4-Fluorophenyl	Ethoxycarbonyl	130
Ethyl	4-Fluorophenyl	Carboxylic acid	207–209
Amine	3-Methylphenyl	Carboxylic acid	161

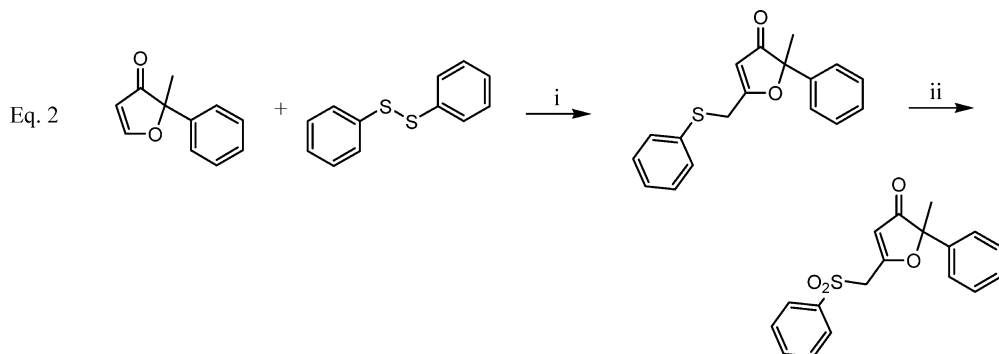
Notes

1. (E)- and (Z)-isomers were separated and purified by re-crystallization in isopropanol. In a typical separation procedure 82% of the (E)-isomer remained dissolved while the (Z)-isomer precipitated from solution and was isolated by filtration.
2. Diarylmethylenefuran derivatives of the current invention have also been prepared (1) using a modified Reformatsky reaction illustrated in Eq. 1:



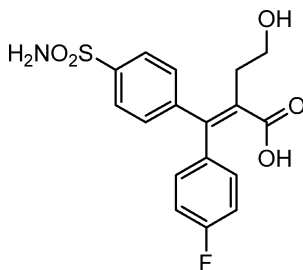
i- N,N-Diethylamine, bromoethane, magnesium, diethyl ether
 ii- Trifluoroacetic acid/trifluoroacetic anhydride

3. 4- or 5-Sulfonylmethyl-3(2H)-furanone derivatives have also been prepared (2) as illustrated in Eq. 2:



i- Sodium hydride, THF
 ii- m-Chloroperbenzoic acid

4. 2,3,4,5-Tetrahydrofuran-2-one derivatives were previously prepared by the author by cyclization of (E)-3-(4-fluorophenyl)-3-(4-sulfamoyl-phenyl)-2-(2-hydroxyethyl)propen-2-enoic acid, (I), and are discussed (3).



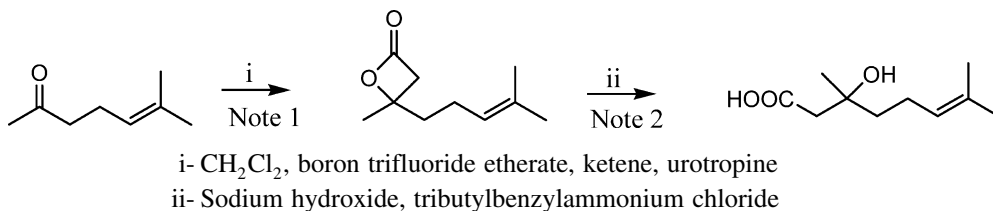
(I)

References

1. E. Nicolai *et al*, US Patent 5,807,873 (September 15, 1998)
2. S.W. Felman *et al*, US Patent 5,389,673 (February 14, 1995)
3. E. Nicolai *et al*, US Patent 5,840,753 (November 24, 1998)

Patent: Geranic Acid Derivatives
P. Frankhauser *et al*, US Patent 6,384,242 (May 7, 2002)
Assignee: Firmenich SA and Lonza AG
Utility: Fragrance and Perfume Component

Reaction



Experimental

1. 4-Methyl-4-(4-methylpent-3-en-1-yl)-oxetane-2-one

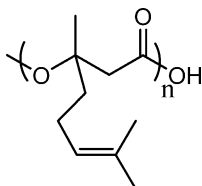
A vessel was charged with 6-methyl-5-hepten-2-one (1.0 mol) and 516 g CH_2Cl_2 , cooled to -19°C , and boron trifluoride etherate (0.5 mol) and ketene gas metered in over the course of 4 hours. Throughout this period the temperature was maintained between -12°C and -14°C . Thereafter urotropine (2.5 mmol) was added and the solution stirred for 30 minutes at 0°C . The solvent was evaporated at 15 mbarr at 20°C and the product isolated in 80.9% yield by vacuum distillation. $^1\text{H-NMR}$ and mass spectrum data supplied.

2. (+/-)-3-Hydroxy-3,7-dimethyl-oct-6-enoic acid [3-hydroxycitronellic acid]

The product from Step 1 (0.259 mol) was dissolved in 180 ml 2M NaOH containing tributylbenzylammonium chloride (0.49 g) whereupon the temperature rose to 51°C and stirred for 2.5 hours. The mixture was cooled to 20°C and stirred overnight. The product was extracted twice with 100 ml diethyl ether, acidified with 390 ml 1 M HCl, dried, and the product isolated in 83.4% yield as a yellow oil.

Notes

1. The oligomeric ester, (I), of the product of Step 1 was also by the author and is described:



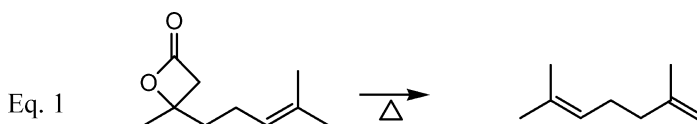
(I)

Procedure

To the product from Step 1 (0.118 mol) at 10 °C was added 98% H₂SO₄ (0.2 g) dropwise so that the temperature remained below 28 °C. After the exotherm had subsided, the mixture was stirred 7 hours at 25 °C resulting in a slightly viscous solution. Titration with Bu₄NOH in methyl alcohol determined the oligomer had a molecular weight of 450 AMU.

Thermal decomposition of the oligomeric ester produced α - and β -cyclogeranic acids in 47% and 30% yields, respectively. Other preparative methods for these acids is described (1).

2. When the product of Step 1 was heated to between 180 °C and 250 °C, decarboxylation occurred forming 2,6-dimethyl-hepta-1,5-diene as illustrated in Eq. 1:



Decomposition conversions at considerably lower temperatures have been observed when the reaction was performed in protonated DMF (2).

3. The preparation of α , ω -dicarboxylic acid diesters is described (3).

References

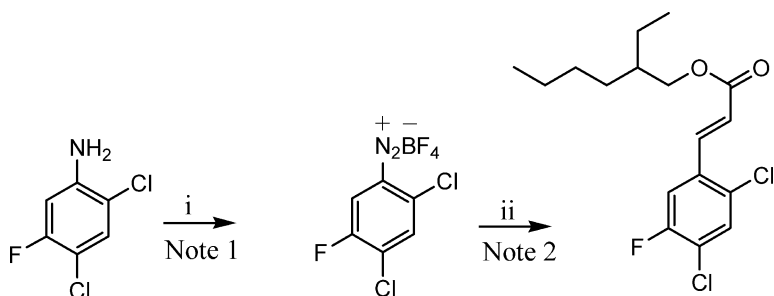
1. K-H. Schulte-Eite, US Patent 3,887,625 (June 3, 1975)
2. M. Fujisawa *et al*, Bull. Soc. Chem. Jpn., 55, 3555 (1982)
3. R. Fischer, US Patent 5,453,535 (September 26, 1995)

Patent: Halogenated Cinnamic Acids and Esters Thereof, Processes for the Preparation Thereof and Halogenated Aryldiazonium Salts
M. Beller *et al*, US Patent 5,516,932 (May 14, 1996)

Assignee: Hoechst Aktiengesellschaft

Utility: Sun Screen Additive

Reaction



i- THF, tetrafluoroboric acid, sodium nitrite

ii- 2-Ethylhexyl acrylate, dimethylsulfoxide, 5% palladium on carbon

Experimental

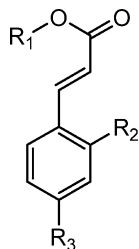
1. 2,4-Dichloro-5-fluorophenyldiazonium tetrafluoroborate

To 2,4-dichloro-5-fluoroaniline (100 g) was added 150 ml THF and 333 ml 50% tetrafluoroboric acid with cooling. Thereafter, sodium nitrite (57.5 g) dissolved in 117 ml water was added at such a rate the temperature remained between 7 and 13 °C. The temperature was lowered to 0 °C, the solution filtered, and the residue washed with THF and ice-cold water yielding 80% product. ¹H- and ¹⁹F-NMR data supplied.

2. 2-Ethylhexyl-2,4-dichloro-5-fluorocinnamate

The product from Step 1 (31.5 mmol) and 2-ethylhexyl acrylate were suspended in 40 ml DMSO and 5% palladium on carbon (0.32 mmol) added at 0 °C. The mixture was heated to 60 °C 1 hour, stirred 12 hours, cooled, and filtered to remove the catalyst. The mixture was diluted with 100 ml CH₂Cl₂ and washed 3 times with 60 ml water. The crude material was purified by chromatography with EtOAc/petroleum ether, 1:8, and the product isolated in 84% yield, bp = 363 °C (extrapolated from GC). ¹H- and ¹⁹F-NMR and mass spectrum data supplied.

Derivatives



R ₁	R ₂	R ₃	Yield (%)
Ethyl	Chloro	Chloro	93
n-Butyl	Chloro	Chloro	86
2-Ethylhexyl	Fluoro	Fluoro	87

Notes

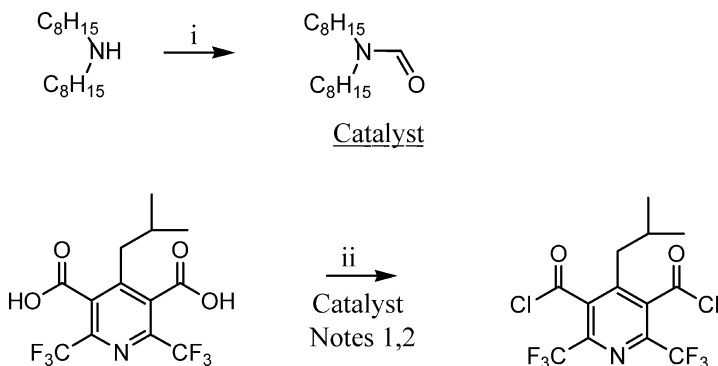
1. When 4-methoxyaniline was substituted for 2,4-dichloro-5-fluoro-aniline, the corresponding diazonium tetrafluoroborate was not formed.
2. Replacing the catalyst in Step 2 with 5% palladium on alumina left cinnamate yields unchanged.
3. The preparation of other polyhalobenzoic acid cinnimates is described (1).
4. The preparation of 2,4,5-trihaloaniline analogues of the current invention is described (2).
5. In a subsequent investigation by the author, cis- and trans-4-(2,2,3,3-tetrafluoropropoxy)-cinnamionitrile derivatives were prepared (3).

References

1. S. Kuami *et al*, US Patent 5,093,515 (May 3, 1992)
2. D.S. Davenport *et al*, US Patent 4,346,248 (August 24, 1984)
3. M. Beller *et al*, US Patent 5,663,410 (September 2, 1997)

Patent: Halogenation Catalyst
D.D. Graves *et al*, US Patent 6,206,819 (March 27, 2001)
Assignee: Rohm and Haas Company
Utility: Acetyl Chlorination Catalyst

Reaction



i- Formamide, hydrochloric acid, cumene
 ii- Pridine, n-Butyl ether, thionyl chloride

Experimental

1. Di-n-octylformamide

Di-n-octylamine (0.021 mol), 37% HCl (0.062 mol), and cumene (40 g) were refluxed for 1 hour to remove water and then cooled to 120 °C. Thereafter, formamide (0.056 mol) was added and the reaction monitored by gas chromatography until completed. The mixture was cooled to ambient temperature, washed 3 times with 40 ml of water, the organic layer concentrated by vacuum distillation, and the product isolated as a yellow oil in 95% yield.

2. 2,6-Trifluoromethyl-4-sec-butyl-3,5-di-carboxychloridepyridine

The product from Step 1 (0.0074 mol), n-butyl ether (50 g), 2,6-trifluoromethyl-4-sec-butyl-3,5-di-carboxylic acid pyridine (0.146 mol) were heated to 95 °C and thionyl chloride (0.438 mol) added to the reaction pot over 3 hours. Both excess thionyl chloride and the reaction solvent were removed by vacuum distillation at 100 °C at 5 mm Hg. The product was isolated by vacuum distillation at 130 °C at 1–2 mm Hg in 86.2% yield.

Notes

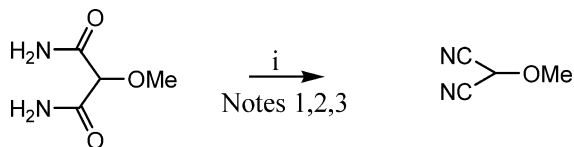
1. The author also prepared the product from Step 1 in 91% crude yield using di(hydrogenated tallow) formamide as the catalyst. This catalyst was prepared by reacting di(hydrogenated tallow) amine (MW $\sim$ 480 g/mol; 0.104 mol), concentrated sulfuric acid (0.116 mol), and formamide (1.12 mol) as described in the Step 1 procedure. Tallow is a mixture consisting predominately of $C_{16}H_{33}$, $C_{18}H_{37}$ and lesser amounts of $C_{14}H_{29}$, $C_{15}H_{31}$ and $C_{17}H_{35}$ hydrocarbon chains.
2. Previously N-methylstearylamine was used as an acid halide catalyst using either thionyl chloride or phosgene (1).
3. An alternative method for preparing the product of Step 1 is by the catalytic oxidation of tertiary amines using $CuCl_2$ and either NaI or NH_4I in an atmosphere of 500 psig oxygen and is described (2).
4. Hydrogenation of isocyanates using 10% palladium-on-carbon catalyst has also been used to prepare N-alkyl formamides (3).

References

1. H.U. Blank *et al.*, US Patent 4,880,576 (November 14, 1989)
2. H.E. Bellis, US Patent 4,281,193 (July 28, 1981)
3. H.G. Howell, US Patent 4,125,724 (November 14, 1978)

Patent: Method for Producing Alkoxy Malonic Acid Dinitriles
J. Bartek *et al*, US Patent 6,673,957 (January 6, 2004)
Assignee: Lonsa AG
Utility: Anesthetic Intermediate

Reaction



i- Acetonitrile, aluminum chloride, phosphorous oxychloride

Experimental

1. Methoxymalonitrile

Phosphorous oxychloride (87.0 mmol) and AlCl_3 (2.3 mmol) were added to a solution of methoxymalonamide (75.5 mmol) dissolved in 50 ml CH_3CN and refluxed 4 hours. Thereafter, the solvent was distilled off, water added, the product extracted 3 times with 50 ml diethyl ether, dried, and the solvent removed. The product was purified by Kugelrohr distillation at 100°C at 20 mbar and the product isolated in 61% yield as a colorless oil. ^1H - and ^{13}C -NMR data supplied.

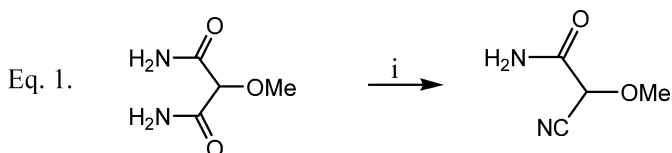
Notes

1. Trifluoroacetic anhydride can be used as an alternative dehydrating agent for phosphorous oxychloride as described below by the author:

Procedure

Methoxymalonamide (75.5 mmol) was dissolved in 100 ml dioxane containing pyridine (278 mmol). The solution was cooled to $2-5^\circ\text{C}$, trifluoroacetic anhydride (230 mmol) added, and the mixture reacted at ambient temperature for 24 hours. Thereafter, 200 ml apiece water and CH_2Cl_2 were added at 10°C , the mixture extracted with 200 ml CH_2Cl_2 , and the product isolated by distillation at $27-30^\circ\text{C}$ at 1.6 mbar in 33% yield.

2. The half cyanide, 2-cyano-2-methoxyacetamide, was also prepared as described below by the author and illustrated Eq. 1:



i- Acetonitrile, aluminum chloride, phosphorous oxychloride

Procedure

Phosphorous oxychloride (44 mmol) and AlCl_3 (1.14 mmol) were added to 100 ml acetonitrile containing methoxymaloamide (38 mmol), refluxed 3 hours, and cooled. Thereafter 100 ml aqueous NaHCO_3 was added, the mixture extracted 5 times with 100 ml EtOAc, and the product isolated by chromatography on silica gel using hexane/EtOAc, 3:1, in 81% yield as an oil which solidified upon cooling. ^1H - and ^{13}C -NMR data supplied.

3. The preparation of other malononitrile derivatives is provided (1).
4. The procedure for converting 2-cyano-2-methoxyacetamide into 2-cyanoacetamide is described (2).
5. Methoxymalonitrile is used in the preparation of sevoflurane, 1,3-di(trifluoromethyl)-propyl-2-fluoromethylether. Methoxymalonitrile is initially reacted with either boron trifluoride or hydrogen fluoride then condensed with 1, 3-di(trifluoromethyl)propyl-2-chloromethylether (3,4) and is described.

References

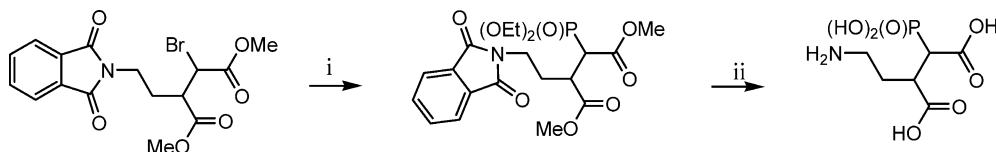
1. P. Chen *et al*, US Patent 6,020,515 (February 1, 2000)
2. N.S. Ibrahim *et al*, Heterocycles, 22(8), 1677 (1984)
3. R.C. Terrell, US Patent 5,969,193 (October 19, 1999)
4. L.V. Kudzma *et al*, US Patent 5,886,239 (March 23, 1999)

Patent: Phosphonosuccinic Acid Derivatives, Processes for Their Preparation and Medicaments Containing These Compounds
C. Tsaklakidis *et al*, US Patent 5,538,957 (July 23, 1996)

Assignee: Boehringer Mannheim GmbH

Utility: Treatment of Calcium Metabolic Disorders

Reaction



i- Toluene, sodium hydride, phosphonoacetic acid triethyl ester

ii- Hydrochloric acid

Experimental

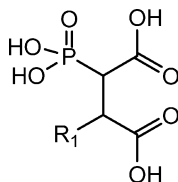
1. 2-Diethylphosphono-3-methoxycarbonyl-5-phthaloylimidovaleric acid ethyl ester

Sodium hydride (10 mmol) dispersed in 10 ml toluene was added to phosphonoacetic acid triethyl ester (10 mmol) followed by 2-bromo-3-methoxycarbonyl-5-phthaloylimidobutyric acid methyl ester (10 mmol) dissolved in 70 ml toluene and the mixture stirred for 24 hours at ambient temperature. Thereafter, the solution was neutralized with 1 ml ethereal HCl, concentrated, purified by chromatography on silica gel with acetone/toluene, 1:1, and the product isolated as a colorless oil in 60% yield.

2. 3-(3-Aminoethyl)-2-phosphonosuccinic acid

The product from Step 1 (3.2 mmol) was refluxed 8 hours in 40 ml 6 M HCl, reduced in volume to 10 ml, filtered, and concentrated. The residue was stirred with 3 ml water, filtered, concentrated, re-dissolved in 2 ml water, and passed over an Amberlite IR 120, H⁺ ion exchanger. The column was eluted with water and the product isolated in 40% yield as a white powder, mp = 127–130 °C (dec).

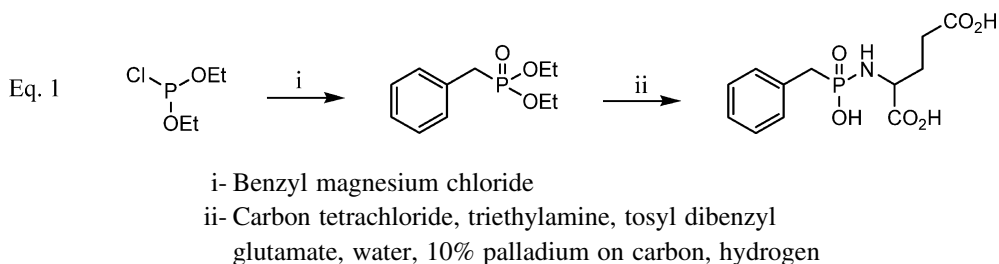
Derivatives



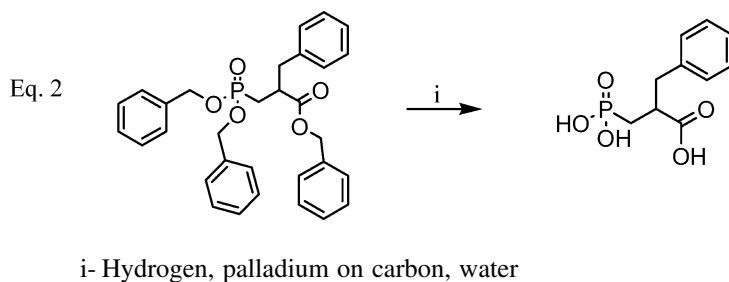
R_1	Yield (%)	Melting Point (°C)
Pyrrolidin-1-ylmethyl	74	122–124
Imidazol-1-ylmethyl	47	135–137
4-(Imidazol-1-yl)-butyl	52	161–164 (dec)

Notes

1. In a subsequent investigation by the author (1) 2-phosphono-3-(3,4-dimethoxyphenyl) methyl-succinic acid and other aromatic derivatives were prepared.
2. Phosphoramidates of the current invention were prepared (2) as illustrated in Eq. 1:



3. The Step 2 analogue, 2-benzyl-3-phosphonopropanoic acid, has been prepared by the hydrogenation of dibenzyl 3-(dibenzylphosphono)-2-benzylpropanoate (3) as illustrated in Eq. 2:



References

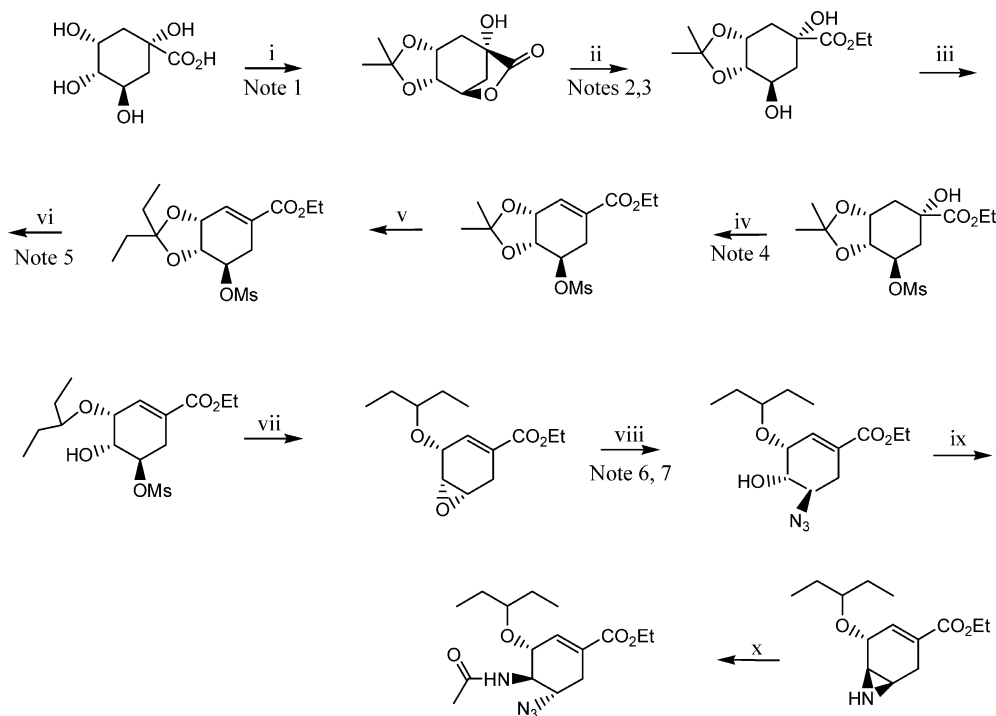
1. C. Tsaklakidis *et al*, US Patent 5,683,994 (November 4, 1997)
2. P.F. Jackson *et al*, US Patent 5,863,536 (January 26, 1999)
3. P.F. Jackson *et al*, US Patent 6,288,046 (September 11, 2001)

Patent: Preparation of Cyclohexane Carboxylate Derivatives
K.M. Kent *et al*, US Patent 6,518,438 (February 11, 2003)

Assignee: Gilead Sciences, Inc.

Utility: Industrial Preparation of Neuraminidase Inhibitors

Reaction



- i- 2,2-Dimethoxypropane, p-toluenesulfonic acid, water
- ii- Ethyl alcohol, sodium ethoxide
- iii- CH_2Cl_2 , methanesulfonyl chloride, triethylamine
- iv- CH_2Cl_2 , pyridine, sulfur chloride
- v- 3-Pentanone, perchloric acid, water
- vi- CH_2Cl_2 , borane-methyl sulfide, trimethylsilyl trifluoromethanesulfonate
- vii- Potassium hydrogen carbonate, water
- viii- Sodium azide, ammonium chloride, water
- ix- Acetonitrile, triphenylphosphine, THF
- x- Sodium azide, ammonium chloride, triphenylphosphine oxide, water, acetic anhydride

Experimental

1. 1-Hydroxy-3,4-(2,2-dimethyl-1,3-dioxolane)-1,5-butyrolactone-cyclohexane

A solution of 1,3,4,5-tetrahydroxycyclohexanoic acid (104 mol) (quinic acid, $[\alpha]_D = 43.7^\circ$) and p-toluenesulfonic acid monohydrate (1.05 mol) dissolved in acetone (80 kg) were refluxed for 2 hours, quenched with 21% sodium ethoxide (1.05 mol) in ethyl alcohol, and the solvent removed. The residue was partitioned between EtOAc/water, 108 kg/30 kg, the organic layers isolated, washed with 5% NaHCO_3 (14 kg), and a yellow solid isolated and used directly.

2. 1, 5-Dihydroxy-3,4-(2,2-dimethyl-1,3-dioxolane)-1-ethoxycarbonyl cyclohexane

The crude lactone from Step 1 (70 kg) was treated with 20% sodium ethoxide (1.05 mol) in ethyl alcohol. After 2 hours at ambient temperature, HOAc (1.05 mol) was added, the solvent removed, and the product mixture isolated in 70% yield and used directly.

3. 1-Hydroxy-3,4-(2,2-dimethyl-1,3-dioxolane)-5-mestyl-1-ethoxycarbonyl-cyclohexane

The crude mixture from Step 3 (72 mol) was dissolved in CH_2Cl_2 (77 kg), cooled to 5°C , and treated with methanesulfonyl chloride (77 kg) followed by the slow addition of TEA (100 mol). Additional methanesulfonyl chloride (7.3 mol) was added and after 1 hour 3% HCl (11 kg) added. The layers were separated and the organic solvent removed. The mixture was dissolved in EtOAc at -10 to -20°C whereupon the mestyl lactone crystallized and isolated in 84.3% yield.

4. 3,4-(2,2-Dimethyl-1,3-dioxolane)-5-mestyl-1-ethoxycarbonyl-1-cyclohexene

The product from Step 3 (30.4 mol) was dissolved in pyridine (183 mol) and CH_2Cl_2 (63 kg), cooled to -20 to -30°C , and treated portionwise with sulfonyl chloride (46 mol). After the exotherm subsided, the slurry was quenched with ethyl alcohol (2.4 kg), warmed to 0°C , and washed with 16% sulfuric acid (35 kg) and 5% aqueous NaHCO_3 (1 kg). The allylic mesylate impurity was removed by treating the product mixture with pyrrolidine (31.9 mol) and tetrakis(triphenylphosphine) palladium(0) at ambient temperature for 5 hours then washing the mixture with 16% sulfuric acid (48 kg). The reaction solvent was removed, the mixture further purified by refluxing in EtOAc (5.3 kg) to which hexane (5.3 kg) was added, and the purified product isolated by crystallization in 43.4% yield, mp = 102 – 103°C .

5. 3,4-(2,2-(1-Propyl)-1,3-dioxolane)-5-mestyl-1-ethoxycarbonyl-1-cyclohexene

The product from Step 4 (27.8 mol) was dissolved in 3-pentanone (279 mol) containing 70% perchloric acid (0.39 mol), stirred for 18 hours, the volatiles removed, and fresh 3-pentanone (348 mol) added. The reaction mixture was filtered, toluene (18 kg) added, and the solution washed successively with 6% aqueous NaHCO_3 (19 kg), water (18 kg), and brine (24 kg). The mixture was distilled and toluene (24 kg) gradually added until no additional toluene distilled over and the ketal isolated in 100% yield.

6. 3-(3-Pentyoxy)-4-hydroxy-5-methyl-1-ethoxycarbonyl-1-cyclohexene

The product from Step 5 (25 mol) was dissolved in CH_2Cl_2 (90 kg), cooled to -30 to -20°C , and borane-methyl sulfide (27.5 mol) and trimethylsilyl trifluoromethanesulfonate (32.5 mol) added. After 1 hour, 10% aqueous NaHCO_3 (40 kg) was added, the mixture warmed to ambient temperature, stirred for 12 hours, and the isomers isolated in 90% yield.

7. 3-(3-Pentyoxy)-4,5-epoxy-1-ethoxycarbonyl-1-cyclohexene

The isomeric ethers from Step 6 (22.3 mol) were dissolved in ethyl alcohol (26 kg), and heated to 55 – 65°C with KHCO_3 (35 mol) in water (22 kg) for 2 hours. The mixture was extracted twice with hexanes (31 kg, then 22 kg). The hexanes were removed and the product isolated as a flocculent white crystal in 60% yield, $\text{mp} = 54.6^\circ\text{C}$.

8. 3-(3-Pentyoxy)-4-hydroxy-5-azido-1-ethoxycarbonyl-1-cyclohexene and 3-(3-Pentyoxy)-4-azido-5-hydroxy-1-ethoxycarbonyl-1-cyclohexene

The epoxide from Step 7 (2.0 mol), sodium azide (2.4 mol) and NH_4Cl (2.4 mol) were dissolved in water (2.4 mol) and 1.0 L ethyl alcohol then heated to 70 – 75°C for 8 hours. Thereafter, 0.42 L 8% NaHCO_3 was added and ethyl alcohol distilled off. The aqueous layer was extracted with 1 L EtOAc and the extract washed with 0.5 L water, dried, and concentrated to yield a mixture of isomeric hydroxyl azides in quantitative yield as a brown oil.

9. 3-(3-Pentyoxy)-4,5-aziridinyl-1-ethoxycarbonyl-1-cyclohexene

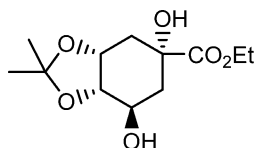
The hydroxyl azide mixture from Step 8 (2.0 mol) was dissolved in 1 L acetonitrile, triphenylphosphine (1.83 mol) dissolved in 100 ml THF and 0.92 L acetonitrile added dropwise over 2 hours. The mixture refluxed for 6 hours, concentrated in vacuo to leave a yellow paste, triturated with diethyl ether (0.35 L), and filtered to remove triphenylphosphine oxide. The dark brown oil was dissolved in 500 ml 20% aqueous methyl alcohol, extracted 3 times with 1 L hexanes and the product isolated in 96.8% yield.

10. 3-(3-Pentyoxy)-4-acetamido-5-azido-1-ethoxycarbonyl-1-cyclohexene

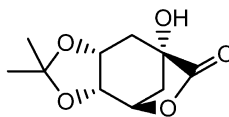
The product from Step 9 (1.93 mol), triphenylphosphine oxide (108 g), sodium azide (2.33 mol) and ammonium chloride (2.33 mol) were dissolved in 1.3 L DMF heated to 80 – 85°C 5 hours, and NaHCO_3 (0.39 mol) and dissolved in 0.66 l water added. The amino azide was isolated from the mixture by extraction with hexanes (1 L), concentrated to 0.45 L, and 1.05 L CH_2Cl_2 added. The organic phase was washed with 8% aqueous NaHCO_3 (3.88 mol), reacted with acetic anhydride (1.94 mol), and concentrated to yield the product in 55% yield, $\text{mp} = 126$ – 132°C .

Notes

1. The product mixture consists of an undisclosed ratio of lactone/(–)-quinoic acid.
2. The product ratio of hydroxy ester, (I), and hydroxyl lactone, (II), was 6.5:1.0, respectively.

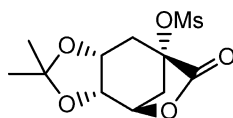


(I)



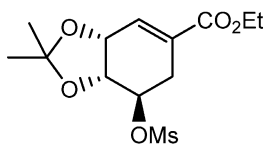
(II)

3. The lactone mesylate, (III), was also formed during Step 1 and was removed by crystallization.

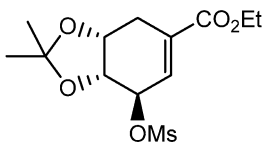


(III)

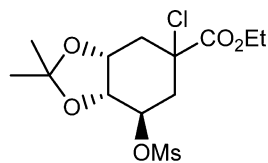
4. The product mixture consisted of three components in a 4:1:1 ratio, respectively, (IV), (V), and, (VI). Allyl, (V), was removed by selective solubility in ethyl acetate containing pyrrolidone; a 4:1 ratio of (IV) and (VI) was used directly in the trans-ketalization reaction.



(IV)

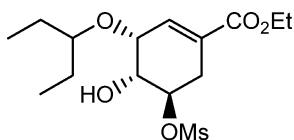


(V)

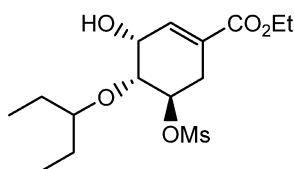


(VI)

5. Two isomeric pentyl ethers, (VII), and, (VIII), were also formed although only (VII) was epoxidized.

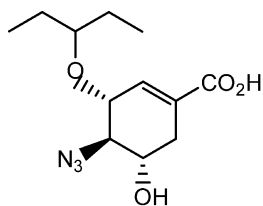


(VII)

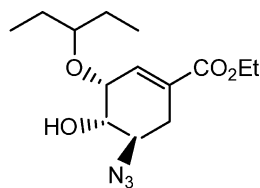


(VIII)

6. Two isomeric hydroxyl azides, (VIII), and, (IX), were produced when epoxide intermediates were reacted with sodium azide. Both isomers were subsequently converted to the desired aziridine.

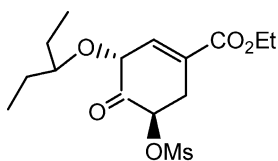


(VIII)



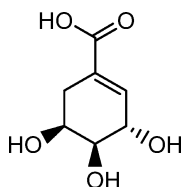
(IX)

7. In a previous investigation (1) the author proposed the synthesis of keto intermediate, (X), as an alternative to Step 8 of the current invention.



(X)

8. Methods for preparing skikimic acid (XI) from (–)-quinic acid are described (2).



(XI)

9. Other methods for preparing ester and diamine analogues of the current invention are disclosed (3).

References

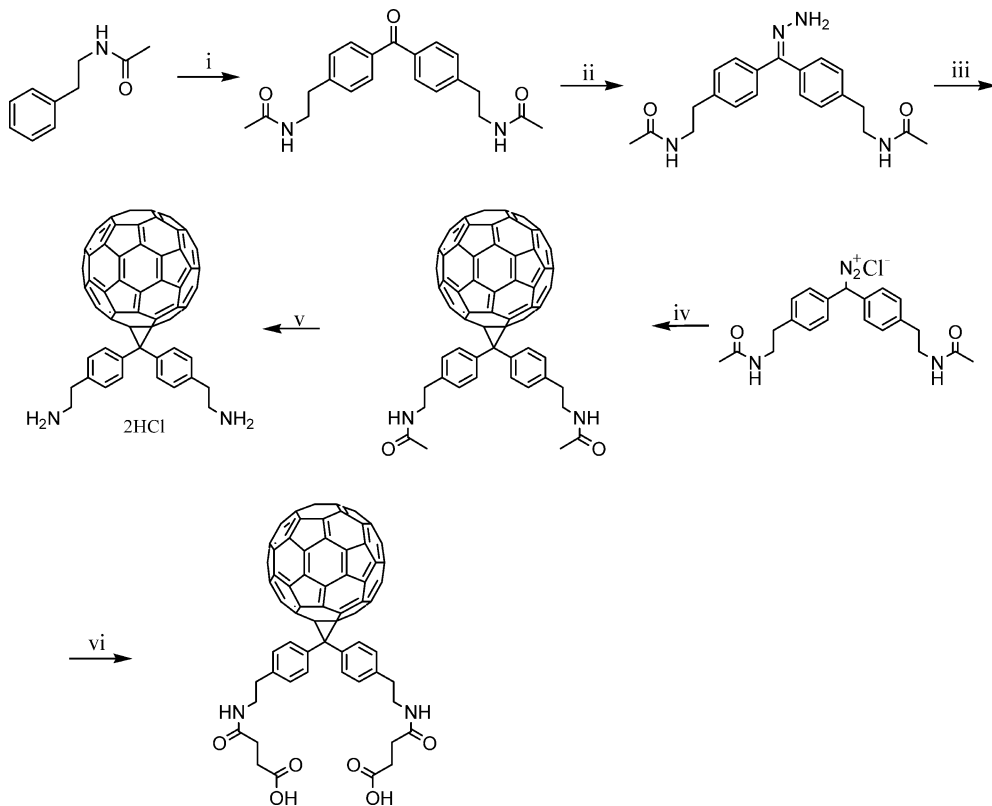
1. K.M. Kent *et al*, US Patent 6,204,398 (March 20, 2001)
2. H-J. Mair, US Patent 6,130,354 (October 10, 2000)
3. C.U. Kim *et al*, US Patent 6,111,132 (August 29, 2000)

Patent: Water Soluble Fullerenes with Antiviral Activity
S.M. Friedman *et al*, US Patent 6,204,391 (March 20, 2001)

Assignee: The Regents of the State of California

Utility: Antiviral and Virucide to Inhibit Human Retroviral Replication

Reaction



i- Carbon tetrachloride, aluminum chloride, hydrochloric acid, sodium hydroxide

ii- Ethyl alcohol, hydrazine, acetic acid

iii- THF, nickel peroxide, sodium hydroxide, ethyl alcohol

iv- C₆₀ Buckminsterfullerene, toluene, THF, 1,2-dichlorobenzene

v- Acetic acid, hydrochloric acid

vi- Succinic anhydride, pyridine

Experimental

1. 4,4'-Bis(N-acetyl-2-aminoethyl)benzophenone

N-Acetyl-2-phenylethylamine (24.2 mmol) was dissolved in 80 ml CCl_4 , cooled in an ice bath, AlCl_3 (100 mmol) added, and the mixture stirred 12 hours at ambient temperature. The mixture was poured into 2 M HCl, made basic with concentrated KOH solution, and extracted with 400 ml CH_2Cl_2 . The organic layer was evaporated, the mixture purified by column chromatography on silica gel using CH_2Cl_2 /methyl alcohol, 95:5, and the product isolated in 82% yield. ^1H NMR, IR, and elemental analysis data supplied.

2. 4,4'-Bis(N-acetyl-2-aminoethyl)benzophenone hydrazone

The product from Step 1 (1.22 mmol) was dissolved in 70 ml dry ethyl alcohol, 3.5 ml hydrazine and 7 ml acetic acid added, and the reaction refluxed 2 hours. The mixture was concentrated, the mixture purified by chromatography using neutral alumina and CH_2Cl_2 /methyl alcohol, 98:2, and the product isolated in 66% yield. ^1H NMR and elemental analysis data supplied.

3. 4,4'-Bis(N-acetyl-2-aminoethyl)diphenyldiazomethane

The product from Step 2 (0.086 mmol) was dissolved in 20 ml THF and one drop of a saturated solution of NaOH dissolved in ethyl alcohol and nickel peroxide (51 mg) added. The mixture was stirred over 4 Å molecular sieves for 2 hours, the solution was filtered over a celite pad, and used directly for the next step. ^1H NMR, IR, and UV data supplied.

4. 4,4'-Bis(N-acetyl-2-aminoethyl)diphenyl C_{61} buckminsterfullerene

To a solution of C_{60} buckminsterfullerene (0.139 mmol) dissolved in 400 ml toluene was added a solution of the product from Step 3 (0.137 mmol) dissolved in 70 ml THF and the mixture stirred overnight. The solvent was removed and the residue purified by chromatography on silica gel using toluene/methyl alcohol, 93:7. Thereafter, the purified product was heated 16 hours in refluxing o-dichlorobenzene. The solvent was removed in vacuo and the product isolated in 38% yield. ^1H NMR, IR, and elemental analysis data supplied.

5. 4,4'-Bis(2-aminoethyl)diphenyl C_{61} buckminsterfullerene $\cdot 2\text{HCl}$

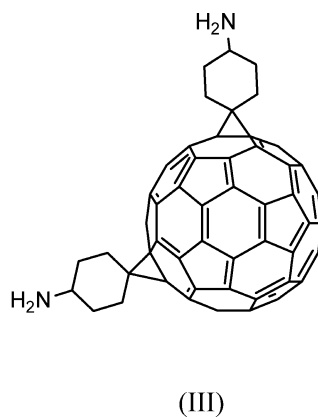
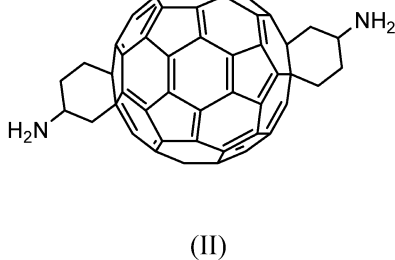
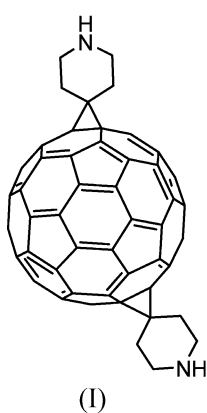
The product from Step 4 (25.7 mg) was mixed with 7.5 ml acetic acid and 2 ml concentrated HCl and then refluxed overnight. The solvent was evaporated in vacuo and the product isolated in 98% yield. ^1H -NMR, IR, and elemental analysis data supplied.

6. 4,4'-Bis(succinic acid-mono-2-aminoethylamide)diphenyl C_{61} buckminsterfullerene

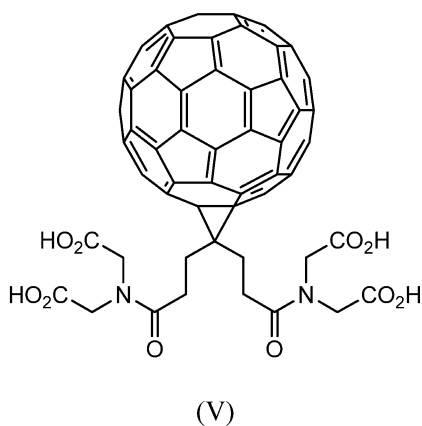
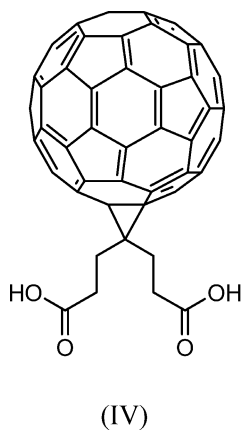
The product from Step 5 (0.024 mmol) was added to succinic anhydride (1.02 mmol) dissolved in 10 ml dry pyridine and the mixture stirred overnight. Thereafter, the reaction mixture was poured into 100 ml 2 M HCl and centrifuged. The precipitate was washed twice with water and dissolved in 25 ml 0.1 M aqueous NaOH. The solution was re-centrifuged and the product isolated in 93% yield by acidifying the supernatant with concentrate with HCl acid. ^1H -NMR, IR, and elemental analysis data supplied.

Notes

1. In an earlier investigation by the author (1) a series of water soluble monosuccinamide C_{60} buckminsterfullerenes derivatives using the C_{60} diamines, (I), (II), (III), illustrated below:



2. Polyhydroxylated fullerenes have also been prepared (2).
3. In a subsequent investigation by the author (3), acid functionalized C_{60} intermediates, (IV), (V), were used to prepare water soluble derivatives.



References

1. S.H. Friedman *et al*, US Patent 5,811,460 (September 22, 1998)
2. L.Y. Chiang *et al*, US Patent 5,177,248 (January 5, 1993)
3. S.H. Friedman *et al*, US Patent 6,613,771 (September 2, 2003)

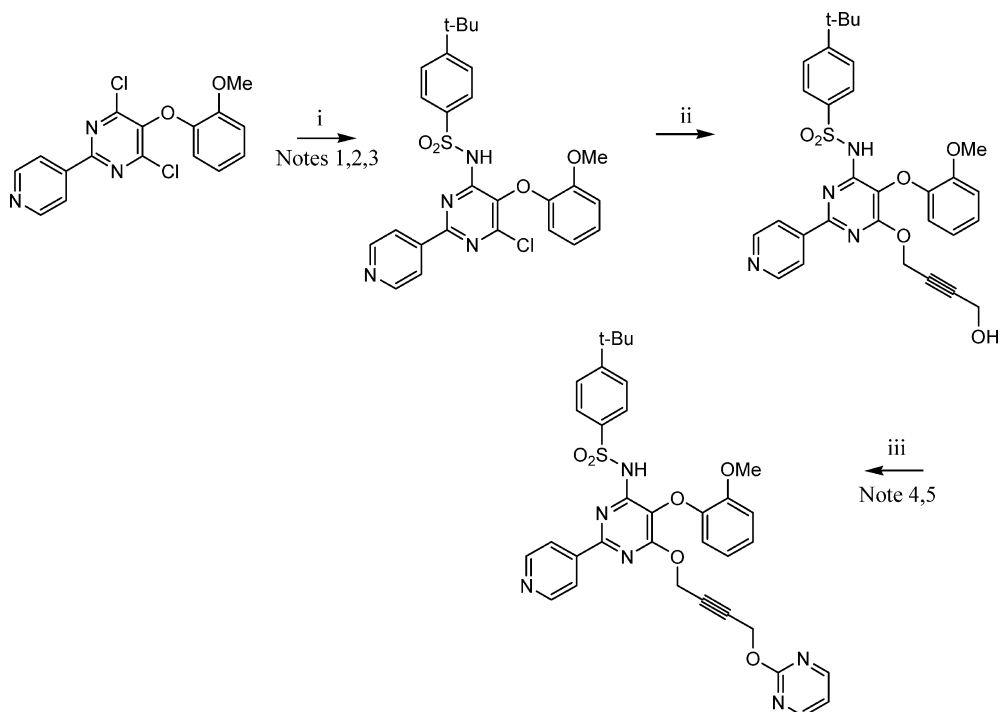
Alcohols

Patent: Butyne Diol Derivatives
M. Bolli *et al*, US Patent 6,720,322 (April 13, 2004)

Assignee: Actelion Pharmaceuticals Ltd.

Utility: Endothelin Receptor Antagonists in Treating Hypertension

Reaction



- i- 1,1-Dimethylformamide, 4-t-butyl-benzene sulfonamide potassium salt
- ii- Sodium hydride, 2-butyne-1,4-diol, 1,1-dimethylformamide, 1,3-dimethyl-3,4,5,6-tetramethyl-2(1H)-pyrimidinone
- iii- Sodium hydride, THF, 2-chloropyrimidine

Experimental

1. 4-t-Butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]benzene sulfonamide

To a solution of 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (6 g) dissolved in 100 ml THF was added 4-t-butyl benzene sulfonamide potassium salt at ambient temperature and the mixture stirred overnight. The reaction mixture was then poured into 150 ml of water and diethyl ether and the pH adjusted to 5 by the addition of HOAc. Thereupon a precipitate formed and the product isolated by filtration as a beige crystal. MS data supplied.

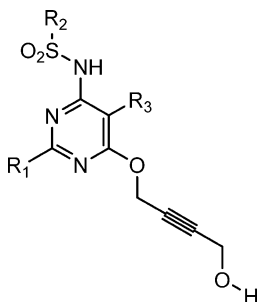
2. 4-t-Butyl-N-[6-(4-hydroxy-2-butynyloxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]benzene sulfonamide

At ambient temperature, 2-butyne-1,4-diol (6.9 g) was added to a slurry of NaH in 25 ml DMF containing 5 ml DMPU and thereafter the product from Step 1 (2.1 g) added and the mixture stirred at 90°C 48 hours. The solvent was removed and the resulting oil treated with 150 ml 10% HOAc. The product was extracted with CH₂Cl₂, dried, purified by chromatography on silica gel using toluene/EtOAc, 4:1 to 1:4, and the product isolated as a beige foam. MS data supplied.

3. 4-t-Butyl-N-[6-(4-(2-pyrimidinylloxy)-2-butynyloxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]benzene sulfonamide

To a suspension of NaH (76 mg) in 15 ml THF was added the product from Step 2, the mixture stirred 2 hours, 2-chloro-pyrimidine (71 mg) added, and the mixture stirred 42 hours. The solvent was removed and the residue partitioned between 50 ml 10% HOAc and 50 ml EtOAc. The residue was purified by chromatography on silica gel eluting with a gradient of 5–10% methyl alcohol and CH₂Cl₂. MS data supplied.

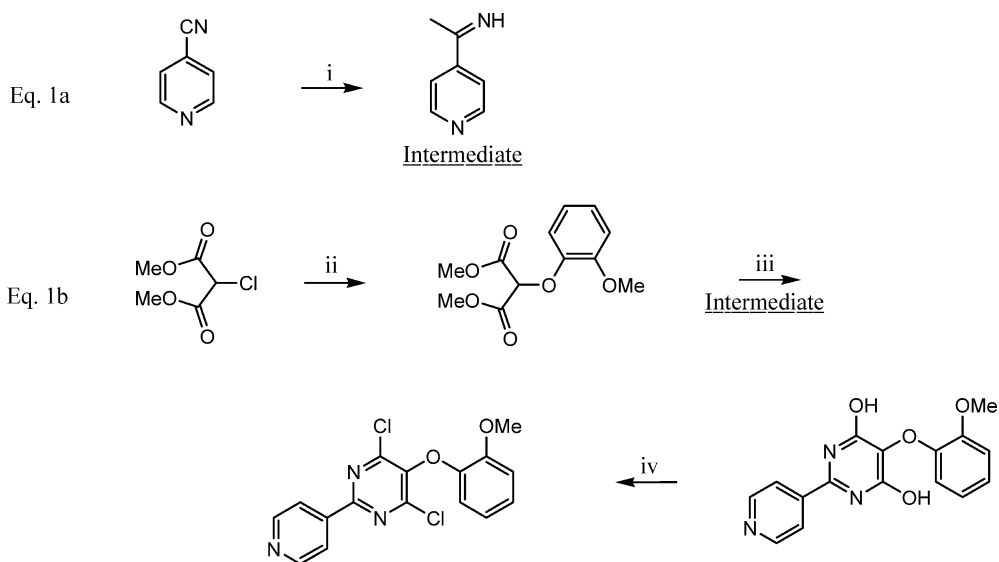
Derivatives



R₁	R₂	R₃	MS (M+1)
2-Pyrimidinyl	4-t-Butylphenyl	2-Methoxy-phenoxy	576
2-N-Morpholino	5-i-Propyl-2-pyridine	2-Methoxy-phenoxy	570
2-Pyridinyl	5-i-Propyl-2-pyridine	2-Methoxy-phenoxy	485
2-Pyridinyl	5-i-Propyl-2-pyridine	4-Methyl-1-phenyl	541

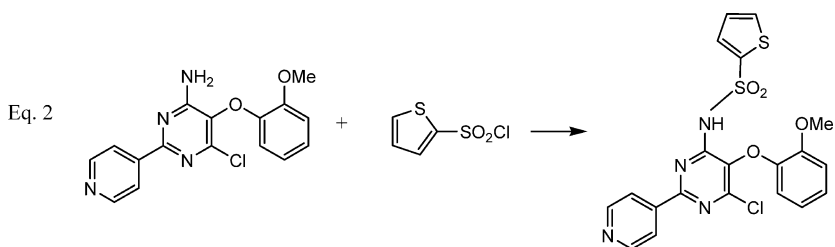
Notes

1. The reagent of Step 1, 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine, was prepared as illustrated in Eq. 1a and 1b and is described (1).

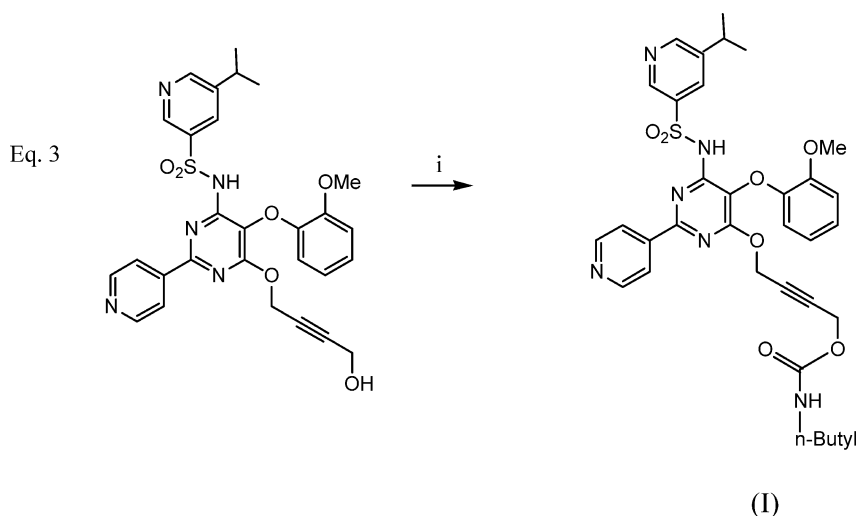


- i- Sodium methoxide, methyl alcohol, ammonium chloride, diethyl ether
- ii- 2-Methoxyphenol, potassium carbonate, acetone
- iii- Sodium methoxide, methyl alcohol
- iv- Di-isopropylethylamine, tetraethylammonium chloride, phosphorous pentachloride

2. 4-(2-Naphthyl)- and 2-thiophene sulfonamide analogues have also been prepared by reacting the corresponding arylsulfonyl chloride with a amino pyrimidine derivative (2) as illustrated in Eq. 2 using 2-thiophene sulfonyl chloride.



3. A general method for preparing sulfonamide potassium salts is provided (3).
4. A Step 3 derivative of the current invention, 5-isopropyl-N-[6-(4-hydroxy-2-butyntyloxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-2-pyridine sulfonamide, was converted into the butyl carbamate derivative, (I), by reacting with butyl isocyanate as illustrated in Eq. 3 and described by the author.

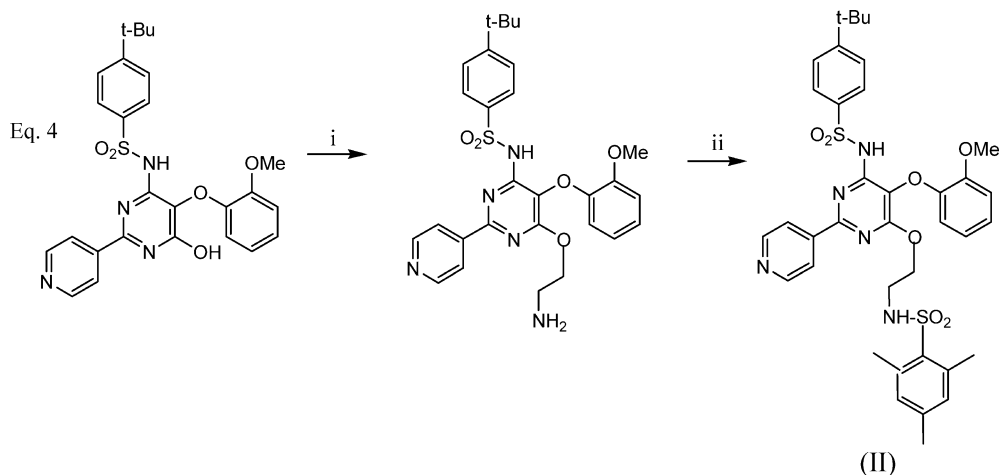


i- Chloroform, 4-dimethylaminopyridine, butylisocyanate

Procedure

To a solution of 5-isopropyl-N-[6-(4-hydroxy-2-butyntyloxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-2-pyridine sulfonamide (50 mg) and 4-dimethylaminopyridine (10 mg) dissolved in 5 ml chloroform was added 25 μ l n-butyl-isocyanate and the solution stirred for 42 hours at 65 °C. After 6, 18, and 28 hours additional 25 μ l portions of n-butyl isocyanate were added. Thereafter, the solution was diluted with 50 ml EtOAc, dried, purified by chromatography on silica using hexane/EtOAc, 1:1, then CH_2Cl_2 containing 4% methyl alcohol, and the product isolated. MS data supplied.

5. In an earlier investigation the author prepared p-t-butyl-N-[6-(ethoxy-2-methanesulfonamido)-5-(o-methoxyphenoxy)-2-(2-pyrimidyl)-pyrimidinyl]benzene-sulfonamide, (II), as illustrate in Eq. 4 and is discussed (1).



i- Sodium hydride, 2-hydroxyethylamine, THF
 ii- Diisopropylethylamine, CH₂Cl₂, dimethylformamide,
 mesylchloride

References

1. M. Bolli *et al*, US Patent 6,596,719 (June 22, 2003)
2. K. Yamada *et al*, US Patent 5,739,333 (April 14, 1998)
3. H. Berg *et al*, Bioorg. Med. Chem. Lett., 7, 2223 (1997)

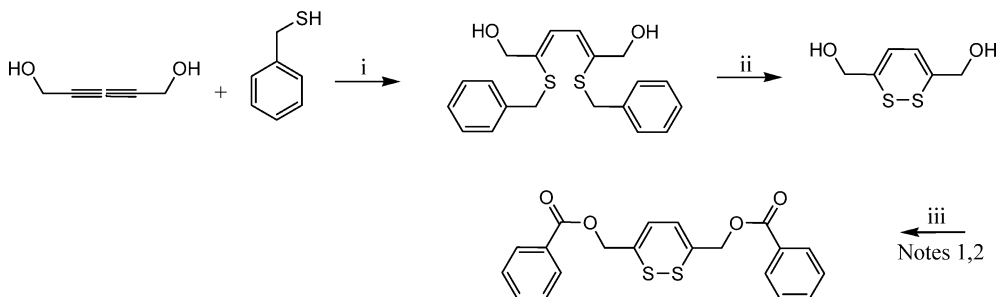
Patent: 1,2-Dithin Antiinfective Agents

T.V. Truong *et al*, US Patent 5,668,168 (September 16, 1997)

Assignee: Shaman Pharmaceuticals, Inc.

Utility: Antifungal Agents Caused by *Candida albicans*, *Cryptococcus neoformans*, or *Aspergillus fumigatus*.

Reactions



i- N,N-dimethylformamide, potassium hydroxide, water

ii- Lithium, ammonia, THF, potassium iodide, iodine

iii- Pyridine, benzoyl chloride

Experimental

1. 2,-Bis(thiobenzyl)-2,4-hexadiene-1,6-diol

A reactor was charged with 40 ml DMF, 1 ml water, and KOH (0.3 g). To this was added benzylthiol (22 mmol), the reaction stirred 10 minutes, and 1,6-dihydroxy-2,4-hexadiyne (10 mmol) added. The resulting exotherm was cooled in a water bath, the reaction stirred 3 hours, and poured into 150 ml water. The mixture was extracted with EtOAc, once with 200 ml and once with 100 ml, washed with water and brine, dried, and concentrated. The residue was re-crystallized in hexanes/chloroform/EtOAc and the product isolated in 65% yield, mp = 121.5–123 °C.

2. 3,6-Bis(hydroxymethyl)-1,2-dithiin

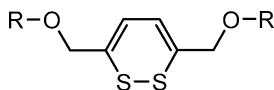
A reactor was charged with 10 ml liquid ammonia at –78 °C to which was added lithium (4 eq) and the product from Step 1 (53 mg) in 4 ml THF. The mixture was stirred and a blue color appeared; an additional amount of lithium was added to maintain the color of the mixture. The mixture was stirred 1 hour at –78 °C, several drops of methyl alcohol added until the blue color disappears, and the mixture warmed to ambient temperature and concentrated. The residue was treated with 6 ml water and 10 ml diethyl ether, cooled to 0 °C, then treated with iodine (3.00 mmol) dissolved in 15 ml 20% aqueous KI. The

mixture was warmed to ambient temperature and the aqueous layer extracted twice with 20 ml diethyl ether, washed, and dried. The product was purified by chromatography on silica gel using EtOAc/hexanes, 1:1, and the product isolated as a red solid in 47% yield, mp = 64–66°C. $^1\text{H-NMR}$ data supplied.

3. 3,6-Bis(benzoyloxymethyl)-1,2-dithiin

To the product from Step 2 (20 mg) dissolved in 1.0 ml pyridine was added 0.13 ml benzoyl chloride and the reaction stirred in the dark overnight. The mixture was subsequently diluted with 10 ml diethyl ether then partitioned between 20 ml 3.0 M H_3PO_4 and 5.0 ml diethyl ether. The ether layer was subsequently washed with 20 ml saturated NaHCO_3 , dried, and concentrated. The oily residue was purified by chromatography on silica gel using diethyl ether/hexanes, 1:3, and the product isolated as a red oil. $^1\text{H-NMR}$ data supplied.

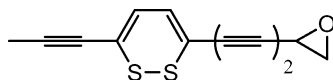
Derivatives



R	Yield (%)
Methoxymethyl	90
Acetyl	98.2

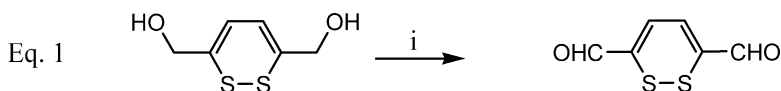
Notes

1. The product of Step 2 was also converted into the corresponding di-ether by reacting it with 2 equivalents of an alkyl halide with N,N-diisopropylamine dissolved in CH_2Cl_2 and is described by the author.
2. Epoxide derivatives of 1,2-dithiin have been prepared, (I), (1).



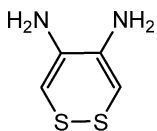
(I)

3. 3,6-Di-formyl-1,2-dithiin was also prepared by the author as illustrated in Eq. 1:



i- CH_2Cl_2 , 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one

4. The preparation of 4,5-diamine 1,2 dithiane, (II), from butadiene diepoxide is described and reviewed (2).



(II)

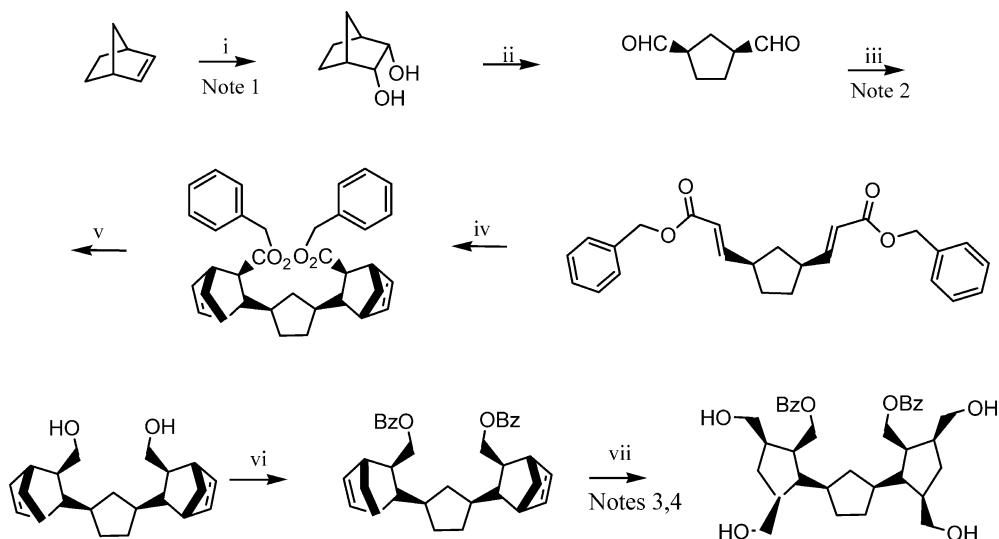
5. Silyl, amides, and azo-derivatives of the current invention have been prepared and are described (3).

References

1. G.H.N. Towers *et al*, US Patent 5,202,348 (April 13, 1993)
2. M.T. DuPriest *et al*, US Patent 4,659,733 (April 21, 1987)
3. D.E. Bierer *et al*, US Patent 5,583,235 (December 10, 1996)

Patent: Oligiocycloalkanoid Compounds and Methods of Use
B.L. Miller *et al*, US Patent 6,562,782 (May 13, 2003)
Assignee: University of Rochester
Utility: Drug Delivering Agent

Reaction



- i- Potassium ferricyanide, potassium carbonate, methylsulfonamide, quinuclidine, potassium osmate, t-butyl alcohol, water
- ii- Sodium periodate, THF, water
- iii- Potassium t-butoxide, 1-(2-phenylethyl)-2-diisopropylphosphoacetate, THF
- iv- Cyclopentadiene, CH_2Cl_2 , trimethylaluminum, aluminum trichloride, nitromethane
- v- Lithium aluminum hydride, THF
- vi- Benzoyl chloride, triethylamine, CH_2Cl_2
- vii- Ozone, methyl alcohol, CH_2Cl_2 , sodium borohydride

Experimental

1. endo-1,2-Hydroxynorborane

Norbornylene was dissolved in a 1:1 solution of t-butyl alcohol and an oxidant mixture consisting of $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , $\text{CH}_3\text{SO}_2\text{NH}_2$, quinuclidine and $\text{K}_2\text{OsO}_4 \cdot \text{H}_2\text{O}$ added. The product was isolated and used directly thereafter (Note 1).

2. **cis-1,3-Cyclopentylidialdehyde**

The product from the Step 1 was dissolved in a 3:1 mixture of THF and water and NaIO_4 added at 0°C . The mixture reacted 12 hours while gradually warming to ambient temperature. The product was purified by flash filtration and isolated in 57% yield.

3. **cis-1,3-(Bis(3-benzylacrylate))cyclopentane**

1-(2-Phenylethyl)-2-di-isopropylphosphoacetate (191.4 mmol) was dissolved in THF to prepare a 0.5 M solution at 0°C . To this was added potassium t-butoxide (178.78 mmol), the mixture stirred 20 minutes at 0°C , and 2 additional hours at ambient temperature. The product from Step 2 (85.1 mmol) was dissolved in THF to prepare a 2 M solution, cooled to -78°C for 30 minutes, the aforementioned anionic solution added via cannula, the mixture warmed to 40°C , and then stirred overnight. The reaction was quenched with 400 ml water, the aqueous layer extracted with diethyl ether, washed with brine, dried, purified by flash chromatography on silica gel using hexane/ether, 80:20 to 60:40, and the product isolated in 61% yield, E,E,E,Z > 20:1.

4. **cis-1,3-[1-(exo(2-Oxybenzylcarbonyl)-5-norbornene)]cyclopentane**

The product from Step 3 was dissolved in CH_2Cl_2 to prepare a 0.3 M solution, cooled to 0°C for 15 minutes, $(\text{CH}_3)_3\text{Al}$ (2.39 mmol in hexanes) added, the mixture reacted for 10 minutes, and 0.5 M AlCl_3 (23.85 mmol) dissolved in nitromethane added. To this mixture was added 4.0 M cyclopentadiene (477 mmol) dissolved in CH_2Cl_2 over 30 minutes and the materials stirred 12 hours at 40°C . The reaction was quenched with 20 ml pyridine, the slurry passed through 300 ml silica, and washed 5 times with 100 ml diethyl ether. Azeotropic removal of nitromethane was accomplished using pyridine and four additions of 50 ml heptane. The product was isolated using flash chromatography on silica gel with 95:5 hexanes/diethyl ether in 70% yield, endo,endo:endo:exo = 18:1.

5. **cis-1,3-[1-(exo-(2-Hydroxymethyl)-5-norbornene)]cyclopentane**

Lithium aluminum hydride (96.24 mmol) was slurried into 130 ml THF at ambient temperature and the product from Step 4 (16.04 mmol) dissolved in 30 ml THF added over 15 minutes. Thereafter, the mixture stirred 3 hours, was quenched sequentially with 3.6 ml water, 3.6 ml 15% NaOH, 15 ml water, and the contents stirred for 2 hours. The mixture was filtered through celite and the filtrate concentrated to a yellow oil. The product was isolated by flash chromatography on silica using hexanes/EtOAc, 66:34 in 53% yield.

6. **cis-1,3-[1-(exo-(2-Benzoxymethyl)-5-norbornene)]cyclopentane**

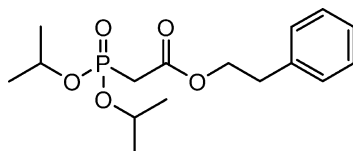
The product from Step 5 (9.85 mmol) was slurried to form a 0.2 M solution in CH_2Cl_2 whereupon benzoyl chloride (35.7 mmol) and Et_3N (39.36 mmol) were added and the reaction stirred 4 hours. The reaction was quenched with 25 ml water and then poured into 100 ml diethyl ether. The organic layer was washed twice with 100 ml apiece water, buffered aqueous solution of $\text{H}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ /concentrated HCl having a $\text{pH} = 2$, Na_2CO_3 , and 100 ml brine. The product was isolated by the method of Step 4 in 91% yield.

7. *cis*-1,3-[1-(2-Benzoxmethyl-3,5-hydroxymethyl-cyclopentyl)]-cyclopentane

The product from Step 6 (8.42 mmol) was dissolved in 1:1 CH_2Cl_2 /methyl alcohol to form a 0.1 M solution, cooled to -78°C , and ozone bubbled into the solution causing it to turn deep blue. An additional five minutes of ozone was applied, followed by oxygen to removed excess ozone. Once the blue color dissipated the reaction was warmed to 0°C , NaBH_4 (118 mmol) added in one gram portions over 1 hour, and the reaction stirred 4 hours at ambient temperature. The reaction was quenched with 10% HCl until the $\text{pH} = 1$. The aqueous layer was extracted and washed 4 times with 100 ml apiece with EtOAc, once with water, twice Na_2CO_3 , and finally brine. The solvents were removed and white solid purified by flash chromatography on silica gel using CH_2Cl_2 /methyl alcohol/HOAc, 90:9:1, and product isolated in 60% yield.

Notes

1. The oxidative cleavage of norbornylene was achieved using the two-step procedure consisting of the Sharpless dihydroxylation and NaIO_4 oxidation of the resulting diols and is discussed (1).
2. The preparation of 1-(2-phenylethyl)-2-di-isopropyl-phosphoacetate (I) used in Step 3 was provided by the author and described below:

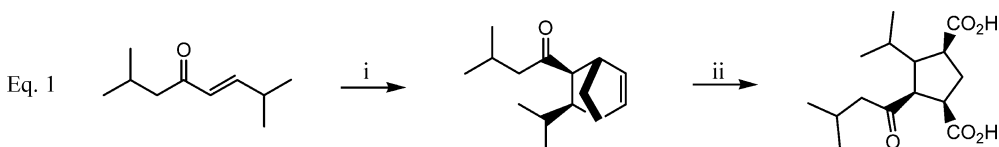


(I)

Procedure

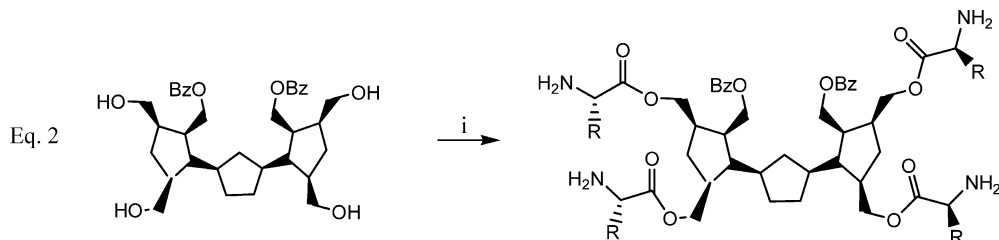
Tri-isopropyl phosphate (37.75 mmol) was heated to $120\text{--}130^\circ\text{C}$, bromoacetate phenylethyl ester (37.75 mmol) added and after 90 minutes 2-bromopropane distilled off at $60\text{--}65^\circ\text{C}$. After distillation ceased the reaction mixture was stirred at 120°C 2 hours and the product was isolated by flash chromatography on silica gel using hexanes/EtOAc, 75:25, in 92% yield.

3. Experimental details were also provided by the author for preparing non-oligocycloalkanoid derivatives of Step VII as illustrated in Eq. 1:



- i- Aluminum chloride, trimethylaluminum, cyclopentadiene
 ii- Ozone, triphenylphosphine, CH_2Cl_2 , sodium chlorite,
 sodium hydrogenphosphate

4. Other methods for preparing oligocyclopentyls are described (2).
 5. Water soluble derivatives of the current invention were also prepared by the author as illustrated in Eq. 2:



- i- 1,3-Dicyclohexylcarbodiimide, 4-dimethylaminopyridine,
 CH_2Cl_2 , N-Boc amino acid trifluoroacetic acid

Amino Acid	Yield (%)
Glycine	30
Phenylalanine	22
Tryptophan	20

6. Other mono- and bis-cyclopentyl derivatives of the current invention are described (3).

References

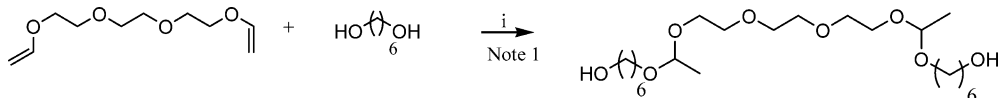
1. R. Becker *et al*, Tetrahedron, 51, 1345 (1995)
2. G.E. Goheen, J. Am. Chem. Soc., 63, 744 (1941)
3. D.S. Yamashita, US Patent 6,057,362 (May 2, 2000)

Patent: Polymers with Controlled Physical State and Bioerodibility
J. Heller *et al*, US Patent 5,968,543 (October 19, 1999)

Assignee: Advanced Polymer Systems, Inc.

Utility: Polymer Precursor Diols for Drug Release Delivery Agents

Reaction

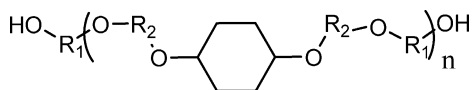


Experimental

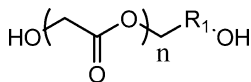
1. Trimethyleneglycol-di-(6-acetal-1-hydroxyl)hexane

Triethyleneglycol divinylether (100 mmol) and 1,6-hexanediol (200 mmol) were dissolved in 100 ml THF and a catalytic amount (approximately 10 mg) of p-toluenesulfonic acid. The mixture refluxed 30 minutes, was concentrated, and the product isolated as a colorless oil.

Derivatives



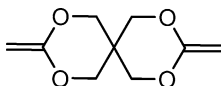
R_1	R_2	n
$(CH_2)_6$	$CH(CH_3)$	1
$(CH_2)_6$	$CH(CH_3)$	3



R_1	n
$(CH_2CH_2O)_3$	2
$CH_2C_6H_{10}CH_2$	1
$(CH_2)_5$	2
CH_2	1

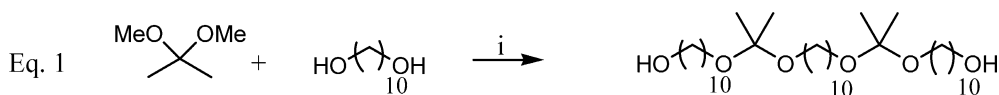
Notes

1. The oligomeric diols of the current invention were subsequently used to prepare polyester derivatives by reacting with 3,9-di(ethylidene)-2,4,8,10-tetraoxaspiro[5.5]undecane (I). Its preparation is described (1).

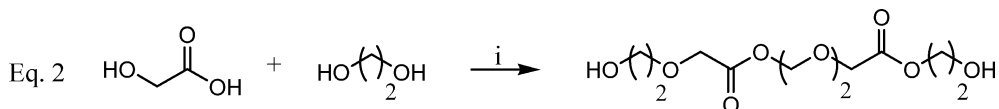


(I)

2. Two other methods for preparing oligomeric diols by reacting either an acetal or α -hydroxyl acid and a diol were also provided by the author as illustrated in Eq. 1 and Eq. 2, respectively:



i- THF, p-toluenesulfonic acid

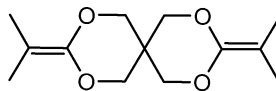


i- THF, p-toluenesulfonic acid

3. Analogues of the current invention have also been prepared using derivatives of 3,9-di(ethylidene)-2,4,8,10-tetraoxaspiro[5.5]undecane, (II), (III), and are described (2,3), respectively.



(II)



(III)

References

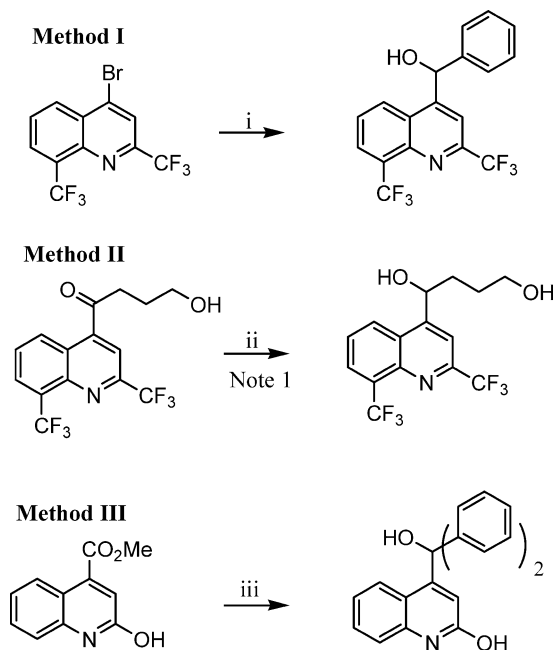
1. R.F. Helwig, US Patent 4,532,335 (July 30,1985)
2. J. Heller *et al*, US Patent 4,304,767 (May 15, 1980)
3. J. Heller *et al*, J. Polymer Sci., Polymer Letters Ed. 18, 293 (1980)

Patent: 4-Quinolinemethanol Derivatives as Purine Receptor Antagonists
R.J. Gillespie *et al*, US Patent 6,583,156 (June 24, 2003)

Assignee: Vernalis Research Limited

Utility: Treatment of Neurodegenerative Disorders or Movement Disorders

Reaction



i- Diethyl ether, n-butyllithium, benzaldehyde
 ii- Ethyl alcohol, sodium borohydride
 iii- THF, phenyl lithium

Experimental

Method I

1. 2,8-Bis(trifluoromethyl)- α -phenyl-4-quinolinemethanol

A solution of 2,8-bis(trifluoromethyl)-4-bromoquinoline (1.45 mmol) dissolved in 10 ml diethyl ether at -78°C was added to 0.64 ml 2.5 M n-butyl lithium followed by 0.15 ml benzaldehyde and the mixture stirred 1 hour. The mixture was quenched with 10 ml water, slowly warmed to ambient temperature, and extracted 3 times with 20 ml diethyl ether. The combined extracts were dried, concentrated, purified by chromatography on silica gel using heptane/EtOAc, 3:1, and the product isolated in 36% yield as a pale-yellow solid, mp = $151\text{--}152^{\circ}\text{C}$. $^1\text{H-NMR}$, IR, and elemental data supplied.

Method II

2. 1-(2,8-Bis(trifluoromethyl)-4-quinolinyl)-4-hydroxybutanol

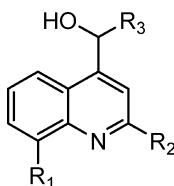
A solution of 1-(2,8-bis(trifluoromethyl)-4-quinolinyl)-4-hydroxyl-butanone (2.13 mmol) dissolved in 4 ml ethyl alcohol at 0 °C was treated with a solution of NaBH₄ (2.13 mmol) in 0.2 ml water, stirred 30 minutes, poured into 15 ml water, extracted twice with 10 ml EtOAc, dried, and concentrated. The material was purified by chromatography on silica gel with EtOAc/heptane, 2:1, and the product isolated in 82% yield as a colorless oil. ¹H-NMR, IR, and elemental data supplied.

Method III

3. α,α -Diphenyl-2-hydroxy-4-quinolinemethanol

A solution of methyl 2-hydroxy-4-quinolinecarboxylate (2 mmol) dissolved in 20 ml THF at 0 °C was treated with a solution of 2.3 ml 1.8 M phenyl lithium (4.2 mmol), stirred at ambient temperature 2 hours, then poured into 100 ml water. The precipitate was filtered, dried, and the product isolated in 97% yield as a cream colored solid, mp >350 °C. ¹H-NMR, IR, MS, and elemental data supplied.

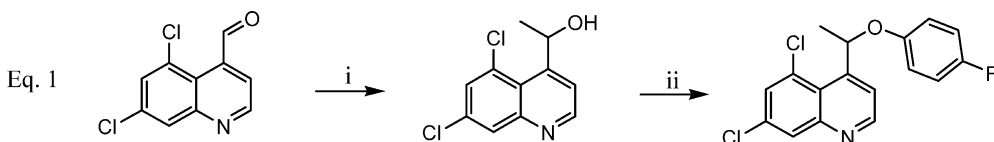
Derivatives



R ₁	R ₂	R ₃	Yield (%)	Melting Point (°C)
Trifluoromethyl	Trifluoromethyl	Tetrahydropyranyl	33	oil
Hydrogen	Methyl	3-Thienyl	54	200
Dibenzylamino	Hydrogen	Phenyl	28	158.8–174.7
iso-Butylcarboxylate	Methyl	Cyclohexylmethyl	27	—

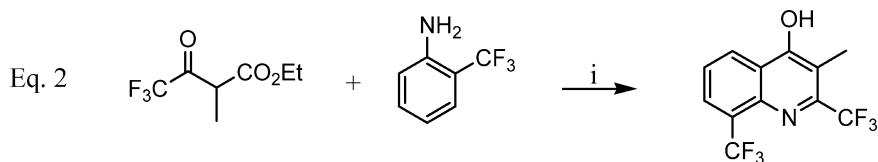
Notes

- The preparation of other fluoro 4-quinoline intermediates is provided (1) and illustrated in Eq. 1:



- i- Toluene, methylmagnesium bromide, THF
- ii- Diethyl azodicarboxylate, triphenylphosphine, chloroform, 4-fluorophenol

2. The reagent of Step 2 was prepared by reacting 2,8-bis(trifluoro-methyl)-bromoquinoline with 4-hydroxymethylbutyl ketone and is described by the author. The preparations of other 4-quinolinol intermediates was also provided by the author and others (2) as illustrated in Eq. 2:



- i- Polyphosphoric acid

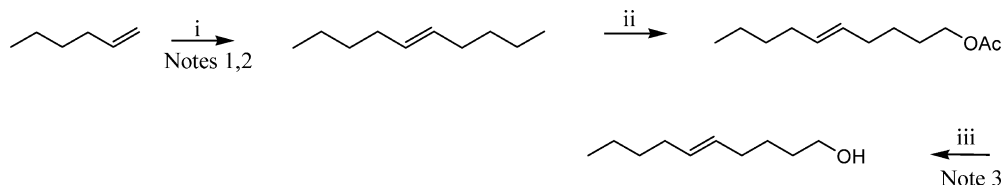
3. Piperidyl- and adamantly-4-quinolinemethanol derivatives of the current invention have been prepared and are discussed (3).

References

1. J. Daeuble *et al*, US Patent 6,117,884 (September 12, 2000)
2. W.R. Arnold *et al*, US Patent 5,240,940 (August 31, 1993); B.A. Dreikorn *et al*, US Patent 5,114,939 (May 19, 1992)
3. T. Novotny *et al*, J. Pharm. Sci., 63, 1264 (1994)

Patent: Synthesis of 5-Decenyl Acetate and Other Pheromone Components
R.L. Pederson *et al*, US Patent 6,215,019 (April 10, 2001)
Assignee: Tillie Chemical, Inc.
Utility: Insect Pheromone Based Insecticides

Reaction



i- Bis(tricyclohexylphosphine)dichlororuthenium(II)benzylidene
ii- 5-Hexenyl acetate
iii- Sodium hydroxide, methyl alcohol

Experimental

1. 5-Decene

To a dry flask was added 1-hexene (2.67 mol) and bis(tricyclohexyl-phosphine) dichloro ruthenium(II)benzylidene (2.7 mmol) and the reaction stirred for 18 hours at ambient temperature. Thereafter the mixture was filtered through 200 g Silica Gel 60–200 mesh in a 1.5" $\times$ 22" chromatography column to remove the catalyst and 115 g product isolated.

2. 5-Decenyl acetate

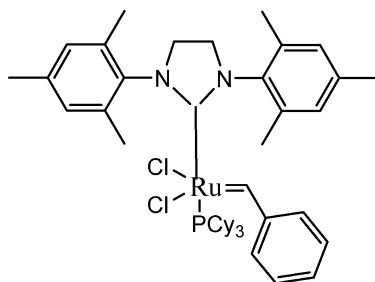
To the product from Step 1 (0.81 mol) was added 5-hexenyl acetate (0.158 mol) and bis(tricyclohexylphosphine)dichloro ruthenium(II) (1.66 mmol) and the reaction stirred for 16 hours under an 8 mm Hg vacuum. Thereafter the vacuum was removed and the mixture stirred an additional 12 hours. The product was isolated as in Step 1 in 99.4% purity consisting of a trans/cis isomeric ratio of 81:19, respectively.

3. 5-Decenol

The product from Step 2 (67 mmol), 35 ml methyl alcohol, and 34 ml 2 M NaOH were mixed together and stirred 3 hours at ambient temperature. Thereafter 10 ml hexane was added and the solution washed with 10 ml apiece of 1 M HCl, NaHCO₃, and brine. The organic phase was dried, concentrated, and 9.4 g of product isolated without any change in the isomeric ratio.

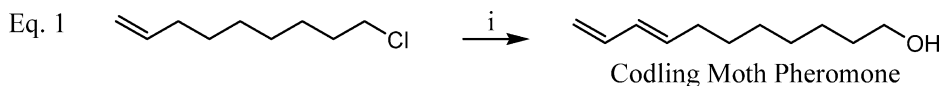
Notes

1. The preparation of bis(tricyclohexylphosphine)dichloro ruthenium, Grubbs' catalyst, is described (1).
2. 5-Decenyl acetate was also prepared using a modified Grubbs catalyst (I) containing the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand. Other synthetic applications of this catalyst are described (2).

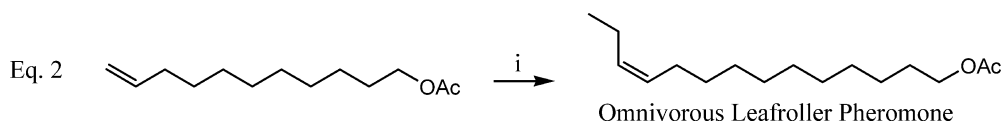


(I)

3. Other insect pheromones have been prepared by the co-author (3) using similar cross metathesis routes as illustrated in Eqs 1 and 2. Descriptions of other insect pheromones are provided (4).



i- trans,trans-2,4-Hexadiene, bis(tricyclohexylphosphine)
dichloro ruthenium(II)



i- 1-Pentene,
bis(tricyclohexylphosphine)dichloro-ruthenium(II)

4. E,E-8,10-Dodecadienol and 11-tetradecyl acetate were also prepared by the author.

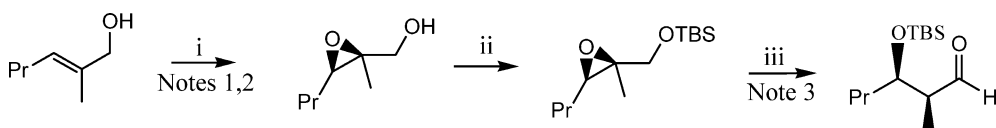
References

1. R.H. Grubbs *et al*, US Patent 5,831,108 (November 3, 1998)
2. R. Scholl *et al*, Organic Lett., 1, 953–956 (1999)
3. R.L. Pederson *et al*, US Patent 5,916,983 (June 29, 1999)
4. R.C. Pearce *et al*, US Patent 5,775,026 (July 7, 1998); A. Yamamoto *et al*, US Patent 4,923,119 (May 8, 1990)

Aldols

Patent: Stereospecific Synthesis of Aldols
M.E. Jung *et al*, US 5,426,206 (June 20, 1995)
Assignee: The Regents of the University of California
Utility: Stereospecific Routes to Polypropinates and Chiral
2-Substituted-1,3 Diols

Reaction



- i- (-)-Diisopropyl tartrate (DIPT) (Note 4), 4 Å molecular sieves, titanium(IV)isopropoxide, t-butyl hydroperoxide, CH_2Cl_2
ii- Di-isopropylethylamine, 4-dimethylaminopyridine, t-butyldimethylsilyl chloride, CH_2Cl_2
iii- 4 Å Molecular sieves, di-isopropylethylamine, t-butyldimethylsilyl trifluoromethanesulfonate, CH_2Cl_2

Experimental

1. (2R,3R)-2-Methyl-3-propyloxiranemethanol

(-)-DIPT (1.35mmol), 500 mg powdered 4 Å molecular sieves, and 10 ml CH_2Cl_2 were cooled to -10°C , treated with $\text{Ti}(\text{O}-i\text{Pr})_4$ (0.97 mmol) and 4.25 M TBHP (13.39 mmol), cooled to -32°C , and (E)-2-methyl-2-hexen-1-ol (7.80 mmol) dissolved in CH_2Cl_2

added. After 2 hours the reaction was quenched with water and 1 ml 30% NaOH and stirred 2 hours. The mixture was purified by chromatography using silica gel with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 4:1, and the product isolated in 97.3% yield, 95.5% ee. $^1\text{H-NMR}$ data supplied.

2. (2R,3R)-2-[(t-Butyldimethylsiloxy)methyl]-2-methyl-3-propyloxirane

The product from Step 1 (0.4 mmol) dissolved in 3 ml CH_2Cl_2 was treated with DIPEA (0.59 mmol), DMAP (1 crystal), and TBSCl (0.51 mmol) and refluxed 12 hours. It was poured into 20 ml 0.2 M pH 7 phosphate buffer, extracted with petroleum ether, and isolated as a clear oil in 89.6% yield. $^1\text{H-NMR}$ and IR data supplied.

3. (2S, 3R)-3-(t-Butyldimethylsiloxy)-2-methylhexanal

The product from Step 2 (0.46 mmol) was dissolved in 4 ml CH_2Cl_2 , treated with 100 mg of 4 Å powdered molecular sieves, DIPEA (0.74 mmol), and cooled to -42°C . TBSOTf (0.68 mmol) was added dropwise, the mixture stirred 80 minutes, was then poured in 20 ml diethyl ether, and shaken with 5 mls pH 5.5 buffer. The product was purified by chromatography using $\text{EtOAc}/\text{hexane}/\text{TEA}$, 2:97:1, and isolated in 78% yield.

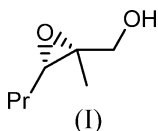
Notes

1. The reagent in Step 1, (E)-2-methyl-2-hexen-1-ol, was prepared using a modified Morita-Baylis-Hillman procedure with ethyl acrylate and 1,4-diazabicyclo[2.2.2]octane. Other examples of the Bayliss-Hilman reaction are provided (1). The stereoisomer, (Z)-2-methyl-2-hexen-1-ol was used to prepare other aldol stereoisomers. The preparation of the (Z)-isomer is provided below by the author:

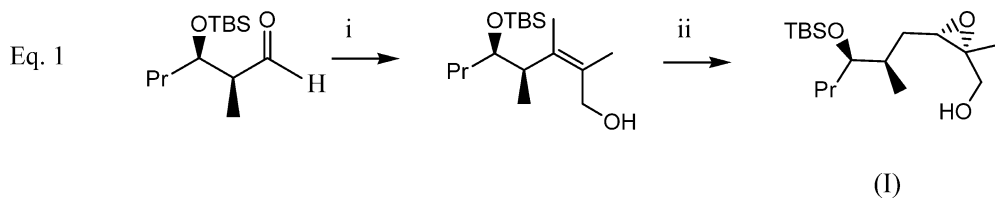
Procedure

To bis(2,2,2-trifluoroethyl) ethyl 2-phosphopropionate (3.75 mmol), 18-crown-6 (10.18 mmol) in 30 ml of THF at -42°C was added solid KHMDS (3.68 mmol). The solution was cooled to -78°C , butyraldehyde (2.5 mmol) added dropwise, and the mixture stirred 8 hours at -78°C and 12 hours at -20°C . The mixture was re-cooled to -78°C , 1.0 M LiBEt_3H (10.0 mmol) in THF added, the reaction warmed to 25°C over 4 hours, and stirred an additional 10 hours. The reaction was quenched with EtOAc and poured over distilled water. The mixture was purified chromatography on silica gel with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 97:3, and the product isolated as an oil in 90% yield.

2. (2S, 3S)-2-Methyl-3-propyloxiranemethanol, (I), was also prepared by reacting (E)-2-methyl-2-hexen-1-ol with L-(+)-DIPT and is described by the author.

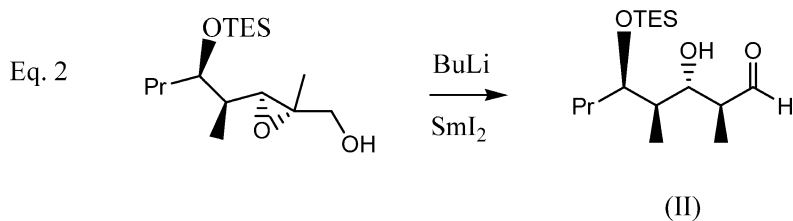


3. The product from Step 3 was subsequently used to prepare (2R, 3S, 4S, 5R)-5-(*t*-butyldimethylsiloxy)-2,3-epoxy-2,4-di-dimethyl-1-octanol, (I), as described by the author and illustrated in Eq. 1:



i- Bis(2,2,2-trifluoroethyl) ethyl 2-phosphonopropionate,
lithium triethylborohydride
ii- *m*-Chloroperbenzoic acid

4. Other asymmetric epoxidation using D-(–)-diisopropyl tartarate are described (2).
5. Triethylsiloxy epoxyalcohol was also converted into the corresponding chiral octanal, (II), using a rare earth catalyst as illustrated in Eq. 2 and described by the author.



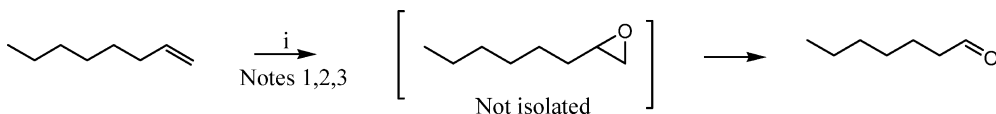
References

1. M. Shi, *J. Org. Chem.*, 66, 406 (2001); E. Ciganek, *Org. React.*, 51, 201 (1997); R. Hansen *et al*, *J. Org. Chem.*, 51, 1822 (1986)
2. D. Basavaiah *et al*, *J. Chem. Soc. Chem. Commun.*, 955 (1992)

Aldehydes

Patent: Process for Selective Catalytic Oxidation of Olefins to Aldehydes, Ketones with Cleavage of C=C Bonds
R.W. Fischer *et al*, US Patent 6,303,828 (October 16, 2001)
Assignee: Aventis Research & Technologies and GmbH & Co. KG
Utility: Olefin Oxidizing Reagent

Reaction



i- Methyl t-butyl ether, hydrogen peroxide, dirhenium heptoxide, hydrochloric acid.

Experimental

1. Oxidizing solution preparation

The appropriate amount of 85% H_2O_2 (5:1 v/v H_2O_2 /solvent) was added to the solvent to reach the required concentration. The mixture was then cooled to 0–5 °C and MgSO_4 added to remove moisture. The mixture was filtered and peroxide activity determined by iodometry.

2. Heptaldehyde

1-Octene was mixed with the dirhenium heptoxide catalyst (0.1 mol % to 2 mol % based of olefin), cooled, and the oxidizing solution (in the reagent ratio range of 1:2 to 1:14 olefin/peroxide) added. After the reaction was complete, the reaction was filtered, cooled, unreacted peroxide removed by addition of sodium sulfite, and desiccant added to remove water. The product was isolated by vacuum distillation.

Derivatives

Alkene	Catalyst	Oxidizing Solution	Products (%)
1-Octene	None	H ₂ O ₂ /t – BuOH	> 5% products
2-Ethyl-1-butene	Methyltrioxorhenium	H ₂ O ₂ /t – BuOH	76% 3-Pentanone 24% 2-Ethyl-1,2-butanediol
1-Octene	Methyltrioxorhenium	H ₂ O ₂ /t – BuOH	42% 1,2-epoxioctane 47% 1,2-octanediol
1-Hexene	Methyltrioxorhenium	H ₂ O ₂ /MTBE	68% 1-Pentanal 32% 1,2-Hexanediol

Notes

1. In addition to dirhenium heptoxide, methylrhodium trioxide and cyclopentadienyl- and cyclopropylrhodium trioxide were also effective as oxidation catalysts and are described by the author.
2. Although epoxide intermediates were not isolated or characterized by the author in the current investigation, others have isolated epoxide intermediates in quantitative yields using methylrhodium trioxide and hydrogen peroxide (1).
3. The direct conversion of alkenes to carboxylic acids using dirhenium heptoxide in a solution of acetic anhydride and dioxane is illustrated below for the oxidative cleavage of 1-octene to form n-heptanoic acid (2):

Procedure

1-Octene (0.05 mol) was dissolved in a mixture of 10 ml apiece of acetic anhydride and dioxane, Rh₂O₇ (0.25 g) added, and the temperature raised to 90°C. Thereafter, 85% H₂O₂ (10 g, H₂O₂/dioxane, 5:1) was added dropwise with stirring and the mixture heated for 16 hours. The mixture was cooled to 0°C and 30 ml saturated Na₂SO₃ added. The mixture was acidified with 10% HCl, extracted with diethyl ether, and the product isolated in 53% yield.

4. The catalyst of the current invention has also been prepared on a γ -alumina support (3).

References

1. S. Warwel, US Patent 5,321,158 (July 14, 1994)
2. W.A. Herrmann *et al*, US Patent 5,155,247 (October 13, 1992)
3. J. Schwartz *et al*, US Patent 5,126,490 (June 30, 1992)

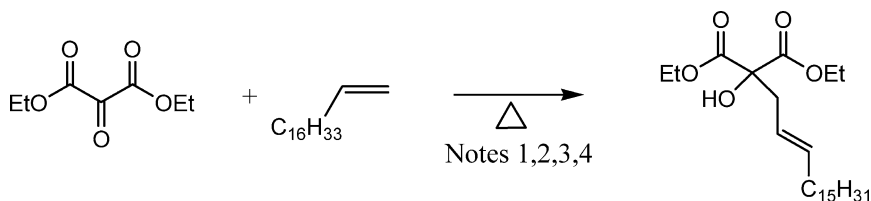
Alkenes

Patent: Carbonyl-Containing Compounds S.J. Brois, US Patent 6,730,747 (May 4, 2004)

Assignee: Infineum USA L.P.

Utility: Automotive Chemical Additive Intermediate

Reaction



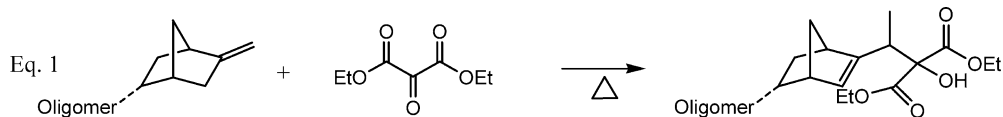
Experimental

1. Diethyl 2-hydroxy-2-(2-octadecene-1-yl)malonate

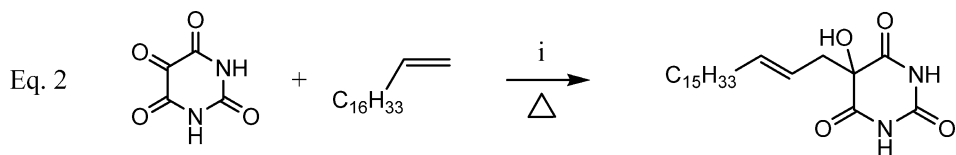
A mixture of diethyl ketomalonate (6.12 g) and 1-octadecene (8.84 g) were stirred and heated to 160–170 °C 3 hours. The temperature was then increased to 200 °C for 30 hours. Upon cooling a solid was obtained which was re-crystallized in diethyl ether and the product isolated. MS and IR data supplied.

Notes

1. The preparation of this product is through the ene synthesis. Retroene reactions occur simultaneously by the reverse pathway and are discussed (1).
2. An oligomer containing pendent ethylidene norbornene was also reacted with diethyl ketomalonate as illustrated in Eq. 1 and discussed by the author.

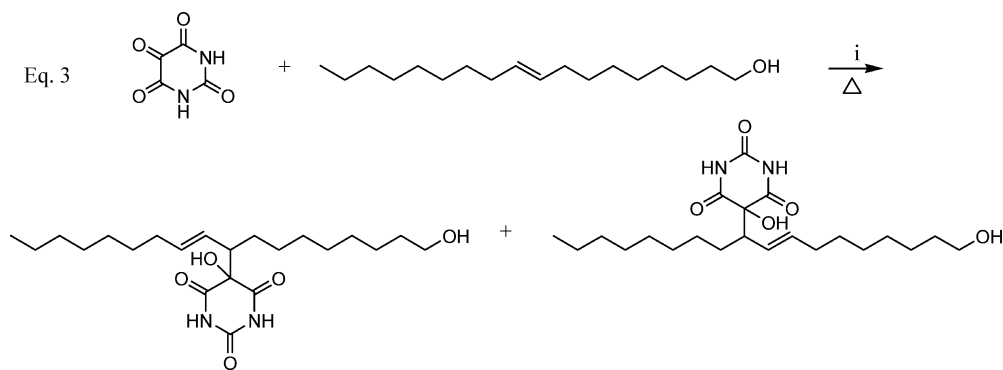


3. The ene reaction has also been used alloxan hydrate and terminally unsaturated 1-octadecene (2) as illustrated in Eq. 2:



i- 1,4-Dioxane

4. When the ene synthesis was performed using alloxan hydrate with internally unsaturated 1-hydroxyl-9-octadecene (3) two products were isolated as illustrated in Eq. 3:



i- 1,4-Dioxane

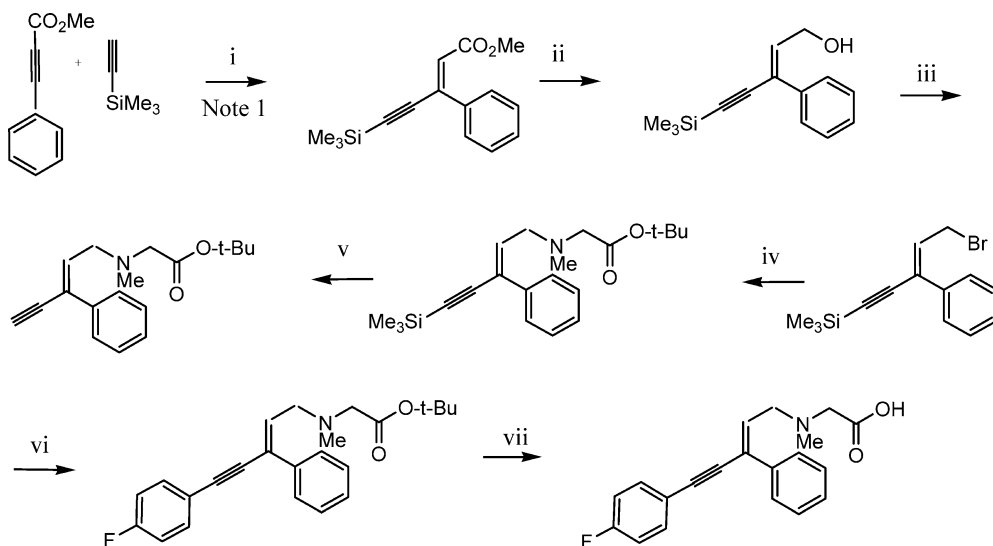
References

1. J. Achmatowitz *et al*, J. Org. Chem., 45, 1228, 1980; P. Papadopoulos *et al*, Tetrahedron Lett., 22, 2773 (1981)
2. S.J. Brois, US Patent 5,550,241 (August 27, 1996)
3. S.J. Brois, US Patent 5,057,564 (October 15, 1991)

Alkynes

Patent: Diaryl-enynes
I. Egle *et al*, US 6,426,364 (July 30, 2002)
Assignee: NPS Allelix Corp
Utility: Glycine Uptake Inhibitors

Reaction



- i- Tris(2,6-methoxyphenyl)phosphine, palladium(II)acetate, toluene
ii- Diisobutylaluminum hydride, toluene
iii- N-Bromosuccinimide, triphenylphosphine, CH_2CH_2

- iv- Potassium iodide, t-butyl sarcosine hydrogen chloride, acetonitrile
- v- Potassium carbonate, acetonitrile
- vi- 4-Fluoriodobenzene, tetrakis(triphenylphosphine)-palladium, copper(I)iodide, acetonitrile
- vii- Formic acid

Experimental

1. 1-Methoxycarbonyl-2-phenyl-4-trimethylsilyl-1-buten-4-yne

To palladium acetate (0.125 mmol) in 5 ml toluene was added tris(2,6-dimethoxyphenyl) phosphine (0.125 mmol), methyl phenylpropiolate (6.24 mmol) and trimethylsilylacetylene (6.24 mmol) and the mixture stirred 16 hours. The product was purified by column chromatography using EtOAc/hexanes, 10:90, and isolated in 86% yield as a yellow oil. ¹H-NMR data supplied.

2. 1-Hydroxy-3-phenyl-5-trimethylsilyl-2-penten-4-yne

The product from Step 1 (5.03 mmol) was dissolved in toluene, cooled to -78°C , 1.0 M DIBAL (12.6 mmol) in toluene added, and the mixture stirred 15 minutes before quenching with Na_2SO_4 solution. The product was isolated as a yellow oil in 71% yield. ¹H-NMR data supplied.

3. 1-Bromo-3-phenyl-5-trimethylsilyl-2-penten-4-yne

The product from Step 2 (3.56 mmol) was dissolved in 20 ml CH_2Cl_2 , cooled to -78°C , and triphenylphosphine (5.34 mmol) and N-bromosuccinimide (5.34 mmol) added. The mixture was stirred 30 minutes, quenched with NaHCO_3 solution, and the crude product used directly in Step 4.

4. N-(3-Phenyl-5-trimethylsilyl)-2-penten-4-yne-1-yl)-sarcosine, butyl ester

The product from Step 3 (5.34 mmol) was dissolved in 15 ml acetonitrile and t-butyl sarcosine hydrogen chloride (3.90 mmol), KI (17.8 mmol), K_2CO_3 (35.5 mmol) added, and the mixture stirred 16 hours. The mixture was filtered through celite, washed with EtOAc, and purified by chromatography using EtOAc/hexanes, 25:75. The product was isolated as a pale yellow oil in 58% yield for 2 steps. ¹H-NMR data supplied.

5. N-(3-Phenyl-2-penten-4-yne)-sarcosine, butyl ester

The product from Step 4 (2.06 mmol) dissolved in 10 ml methyl alcohol was added to K_2CO_3 (10.3 mmol), the mixture stirred 20 minutes, extracted with EtOAc, and isolated in 99% yield as an off-white solid. ¹H-NMR data supplied.

6. N-(5-(4-Fluorophenyl)-3-phenyl-2-penten-4-yne-1-yl)-sarcosine, t-butyl ester

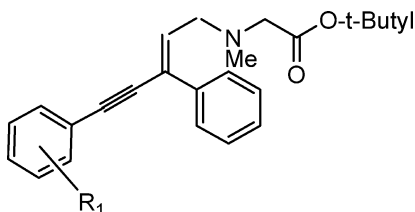
The product from Step 5 (0.175 mmol) in 2 ml TEA was added to 4-fluoriodobenzene (10.228 mmol), tetrakis(triphenylphosphine)-palladium (0.0175 mmol) and

copper(I)iodide (0.0525 mmol) and the mixture stirred 16 hours. Thereafter, it was diluted with CH_2Cl_2 , filtered, and the product isolated by chromatography as in Step 4 as yellow oil in 77% yield.

7. N-(5-(4-Fluorophenyl)-3-phenyl-2-penten-4-yne-1-yl)-sarcosine

A solution of the product from Step 6 (0.155 mmol) dissolved in 96% formic acid was heated to 40°C 16 hours and concentrated. The residue was dissolved in CH_2Cl_2 and passed through a 2 gram solid phase extracting tube, and isolated by solvent to provide the amino acid as a colorless foam in 90% yield (Note 2).

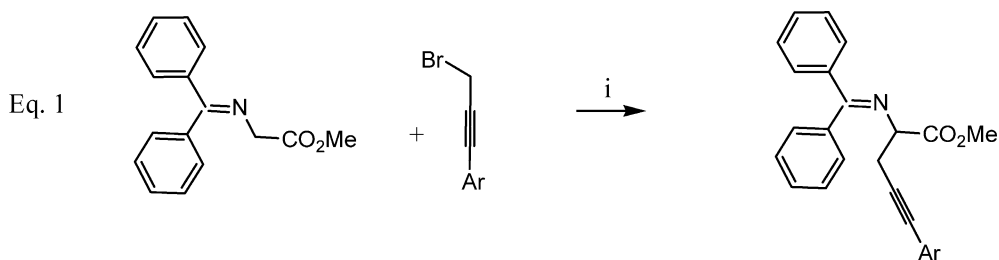
Derivatives



R_1	Yield (%)
4-Fluoro	77
4-t-Butyl	86
4-Phenyl	85
3,5-Trifluoromethyl	46
4-Thiomethyl	70

Notes

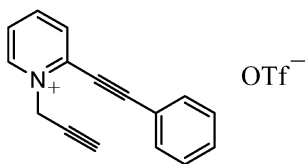
1. Suzuki imine and an alkyne coupling reactions (1) have been used for preparing diaryl aminoacid Step 1 analogues of the current invention as illustrated in Eq. 1:



i- Tetrakis(triphenylphosphine)palladium, copper(I)iodide, propargyl alcohol, triethylamine

2. Step 7 t-butylester derivatives have been prepared and are described (2).

3. In a subsequent investigation, pyridinium analogues, (I), of the current investigation were prepared.



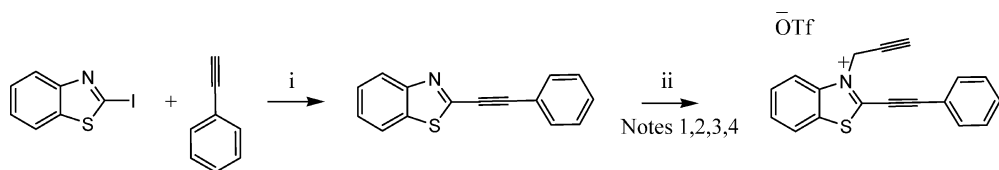
(I)

References

1. S.C. Bell *et al*, US Patent 6,103,743 (August 15, 2000)
2. I. Egle *et al*, US Patent 6,579,987 (June 17, 2003)
3. S.E. Kerwin *et al*, US Patent 6,686,345 (February 3, 2004)

Patent: DNA-Cleaving Anti-Tumor Agents
S.M. Kerwin *et al*, US Patent 6,297,284 (October 2, 2001)
Assignee: Research Development Foundation
Utility: Anti-Neoplastic Agent

Reaction



i- Dichlorodi(triphenylphosphine)palladium, Cu(I)iodide,
triethylamine
 ii- Propargyl triflate

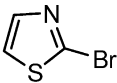
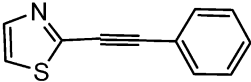
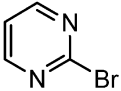
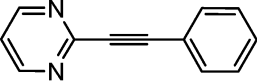
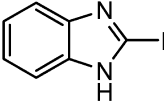
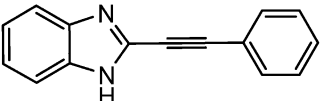
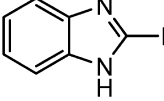
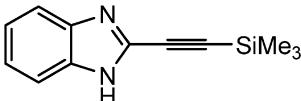
Experimental

1. 1-(2-Benzothiazol)-2-phenylethyne and 1-[2-(N-propargyl-benzothiazolium)]-2-phenylethyne

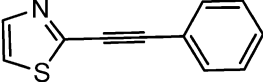
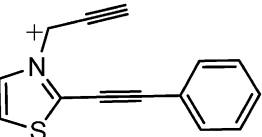
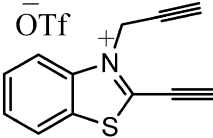
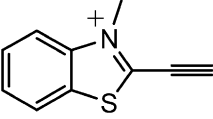
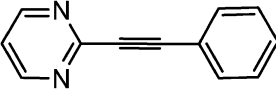
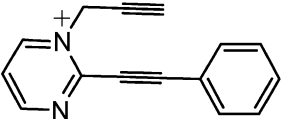
The general synthetic scheme employing the reaction of 2-halo-substituted heterocyclics with the appropriate acetylenes in the presence of palladium catalyst affords the 2-alkyne-substituted heterocyclics, 1-(2-benzothiazol)-2-phenylethyne was used followed by N-alkylation with methyl or propargyl triflate produces 1-[2-(N-propargyl-benzothiazolium)]-2-phenylethyne.

Derivatives

2-Alkynyl Heterocyclics

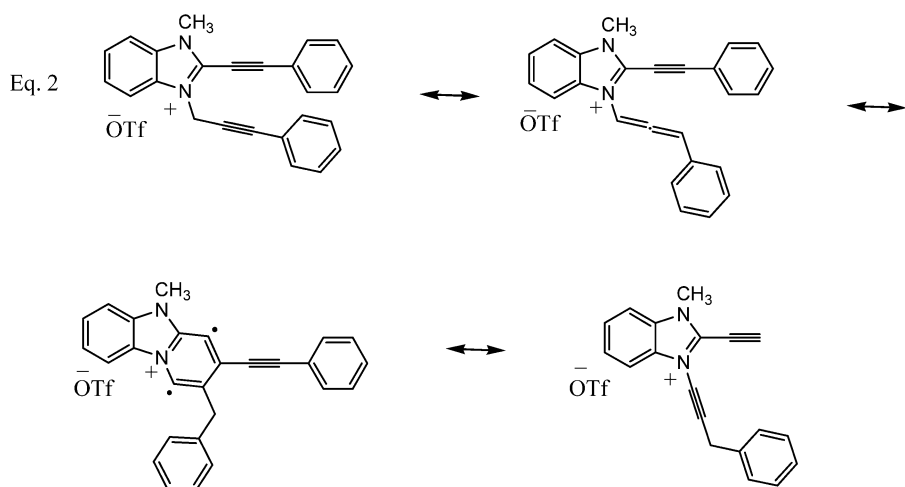
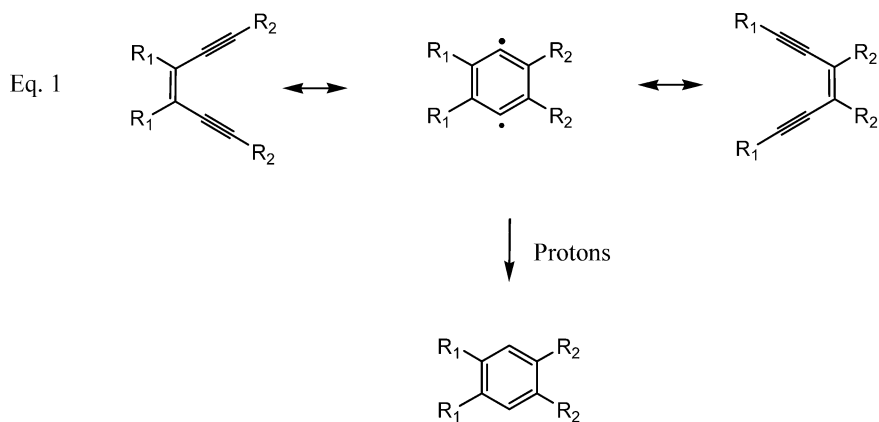
<u>Halo Heterocyclic</u>	<u>Acetylene</u>	<u>Product</u>	<u>Yield (%)</u>
	Phenyl		42
	Phenyl		42
	4-Methylphenyl		30
	Trimethylsilyl		65

2-Alkynyl Heterocyclic Triflate Salts

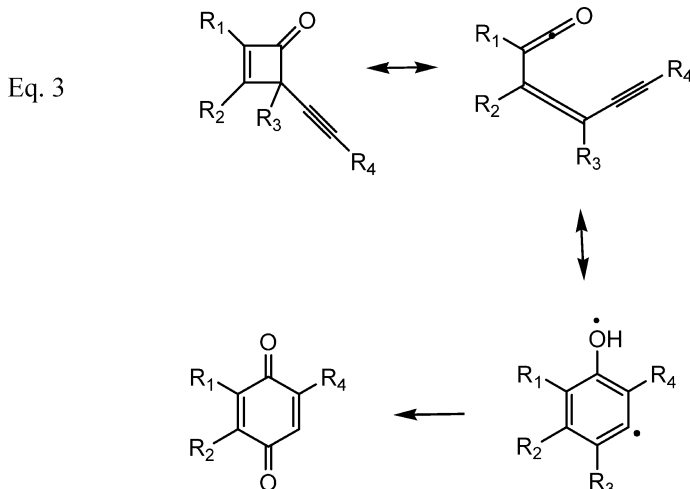
<u>2-Alkynyl Heterocyclic</u>	<u>R-OT_f</u>	<u>Triflate</u>	<u>Yield (%)</u>
	Propargyl		84
	Methyl		74
	Propargyl		78

Notes

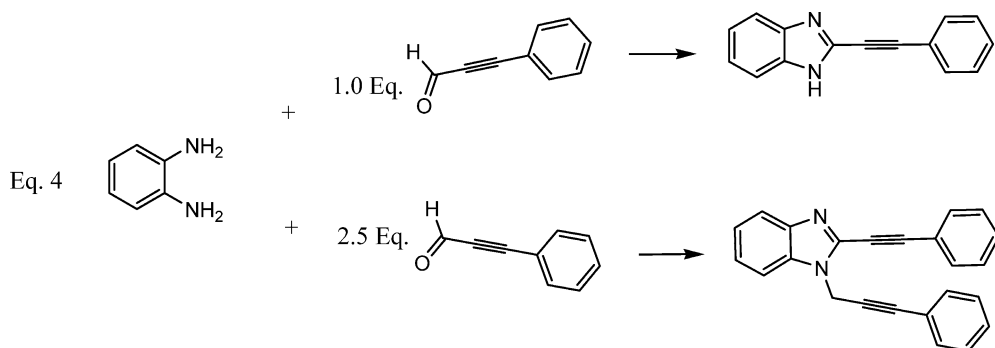
1. Aza-enediynes are a new class of anti-neoplastic agents that produce a cytotoxic effect through an aza-Bergman cyclization (1) of an enediyne core to a 1,4-didehydrobenzene reaction intermediate. Both Bergman and benzothiazolium salt diradical cyclizations are illustrated in Eq. 1 and Eq. 2, respectively.



2. Cyclobutenones and enyne ketenes undergo a similar cyclization through intermediate diradicals as illustrated in Eq. 3 and discussed by the author. The preparation of cyclobutenones is described (2).



3. Additional aza-enediynes, aza-enyne allenes, and aza-di-allenes derivatives of the current invention were prepared by the author in subsequent investigations (3).
4. Salt-free aza-enediynes were prepared by reacting 1,2-diaminobenzene with varying stoichiometric amounts of 3-phenyl-propargyl aldehyde as illustrated in Eq. 4 and are described by the author.



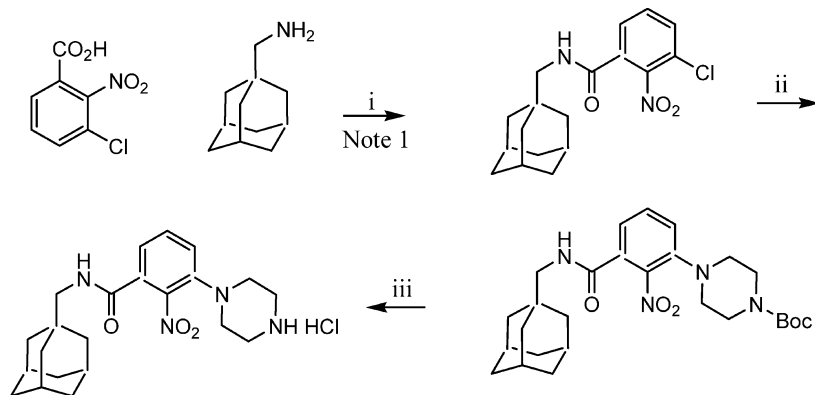
References

1. R.G. Bergman, *Acc. Chem. Res.*, 6, 25 (1973)
2. D. Dube *et al*, US Patent 5,817,700 (October 6, 1998)
3. S.M. Kerwin *et al*, US Patent 6,686,345 (February 3, 2004) and US Patent 6,610,877 (August 26, 2003)

Amides

Patent: Adamantane Derivatives
L. Alcaraz *et al*, US Patent 6,492,355 (December 10, 2002)
Assignee: AstraZeneca AB
Utility: Treatment of Cardiovascular Disorders

Reaction



- i- Oxalyl chloride, CH₂Cl₂, N,N-dimethylformamide
- ii- Piperazine-1-carboxylic acid, t-butyl ester, dimethylsulfoxide
- iii- Hydrochloric acid, dioxane, THF

Experimental

1. 3-Chloro-2-nitro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

To 3-chloro-2-nitrobenzoic acid (2.68 g) suspended in 10 ml CH₂Cl₂ was added 3 ml oxalyl chloride and 1 drop DMF. The mixture was stirred 1 hour at 0 °C, concentrated, the

residue was dissolved in 10 ml CH_2Cl_2 , and 1-adamantanemethylamine (2.19 g) dissolved in 11 ml diisopropylethylamine and 10 ml CH_2Cl_2 added. Thereafter, the reaction stirred at ambient temperature 2 hours. The mixture was then poured into water, washed with 2 M HCl, NaHCO_3 , and re-crystallized from i-propanol, and the product isolated. $^1\text{H-NMR}$ data supplied.

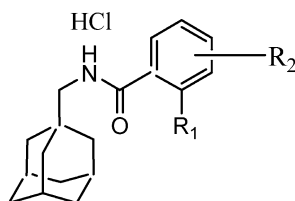
2. **3-(4-{1,1-Dimethylethyl}oxocarbonyl)-piperazin-1-yl-2-nitro-N-(tricycle[3.3.1.1^{3,7}]dec-1-ylmethyl-benzamide**

The product from Step 1 (2.80 g) and piperazine-1-carboxylic acid, t-butyl ester were added to 10 ml DMSO, heated to 120°C 2 hours, cooled, diluted with water, and extracted with EtOAc. The material was purified using chromatography on silica gel with iso-hexane/EtOAc, 2:1, and the product isolated. $^1\text{H-NMR}$ data supplied.

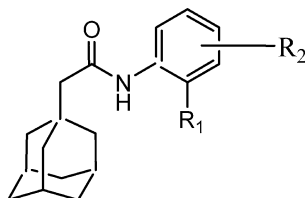
3. **2-Nitro-piperazin-1-yl-N-(tricycle[3.3.1.1^{3,7}]dec-1-ylmethyl-benzamide hydrogen chloride**

The product from Step 2 (0.58 g) was added to 6.4 ml 4 M HCl in dioxane containing 20 ml THF at ambient temperature, stirred 18 hours, and concentrated. Thereafter, it was washed with water, neutralized with NaHCO_3 solution, and extracted with CH_2Cl_2 . The product was purified as in Step 2 and isolated.

Derivatives



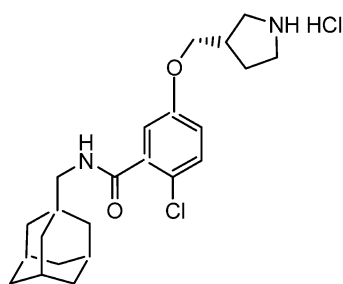
R_1	R_2HCl	$\text{MS}(\text{M}+1)$
Chloro	5-[(Hexahydro-1H-1,4-diazepin-1-yl)methyl]	418
Chloro	(+/-)-5-(3-Aminopyrrolidyl)	489
Chloro	5-(4-Piperidinyloxy)	419
Chloro	5-[(Amino-1-piperidinyl)methyl]	418
Amino	3-Piperazin-1-yl	369



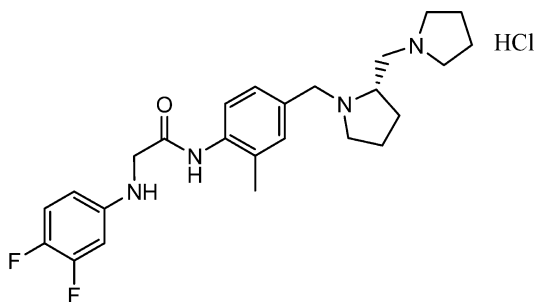
R_1	$R_2 \cdot 2HCl$	MS(M+1)
Chloro	5-[(Hexahydro-1H-1,4-diazepin-1-yl)]ethyl	418
Chloro	5-[2-[2(Hydroxymethyl)-1-(piperidinyl)] ethyl]	446
Chloro	5-(Piperidin-4-ylsulfanyl)	421
Methyl	4-(3-Aminopyrrolidin-1-yl)	368

Notes

1. Adamantanyl iso- and nicotinate derivatives were prepared by others (1) using the synthetic route of the current invention.
2. In subsequent investigations, adamantane derivatives, (I), and other analogues, (II), were prepared by the author (2) and others (3), respectively.



(I)



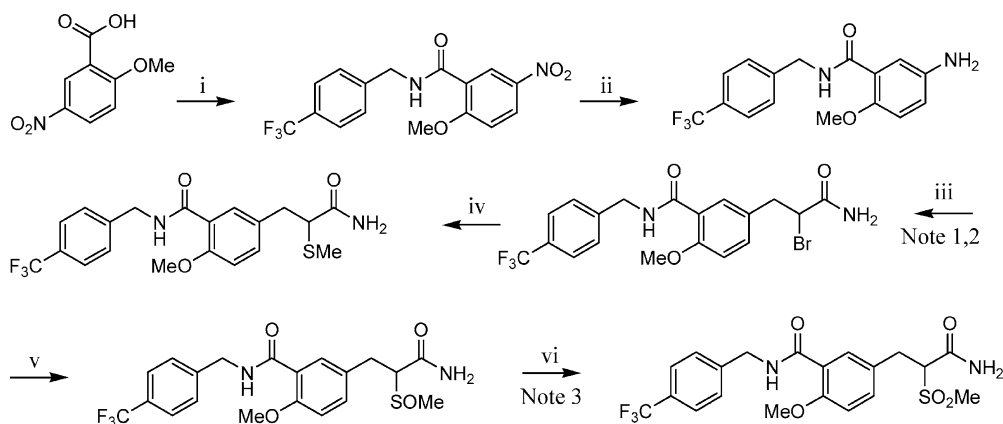
(II)

References

1. C.P. Krimmel, US Patent 3,464,998 (September 2, 1969)
2. L. Alcaraz *et al*, US Patent 6,720,452 (April 13, 2004)
3. M. Furber *et al*, US Patent 6,555,541 (April 29, 2003)

Patent: o-Anisamide Derivatives
H. Satoh, US Patent 6,706,763 (March 16, 2004)
Assignee: Kyorin Pharmaceutical Company
Utility: Treatment of Metabolic Diseases

Reaction



- i- Oxalyl chloride, 4-trifluoromethylbenzylamine, CH_2Cl_2
 ii- 10% Palladium on carbon, EtOAc, hydrogen
 iii- Hydrobromic acid, sodium nitrite, water, copper(II)oxide, acrylamide
 iv- Sodium thiomethoxide, ethyl alcohol
 v- m-Chloroperbenzoic acid, CH_2Cl_2
 vi- m-Chloroperbenzoic acid, CH_2Cl_2

Experimental

1. 2-Methoxy-5-nitro-N-(4-trifluoromethylbenzyl)benzamide

A suspension of 17.2 g 2-methoxy-5-nitrobenzoic acid in 35 ml CH_2Cl_2 was added to 35 ml oxalyl chloride with 1 drop DMAc and stirred for 1 hour at ambient temperature. The solvent was removed, 150 ml DMF, 15 ml TEA, and 16.9 g 4-trifluoromethylbenzylamine added, the mixture stirred for 2 hours at ambient temperature, poured into water, and product extracted with EtOAc. The residue was recrystallized from hexane/EtOAc and the product isolated, mp = 108–109°C. Elemental analysis data supplied.

2. 5-Amino-2-methoxy-N-(4-(trifluoromethylbenzyl)benzamide

The product from Step 1 (26.6 g) was dissolved in 270 ml EtOAc and hydrogenated using 2.6 g 10% palladium on carbon in a hydrogen atmosphere at ambient temperature for

8 hours. The mixture was filtered through celite, purified by column chromatography on silica gel using EtOAc, and 24.5 g of product isolated, mp = 115–117 °C. Elemental analysis data supplied.

3. **5-(2-Brom-2-carbamoyl-ethyl)-2-methoxy-N-(4-trifluoro-methylbenzyl)benzamide**

The product from Step 2 (2.26 g) was dissolved in 27 ml acetone and 11 ml methyl alcohol, 5.6 ml 47% HBr, 540 mg NaNO₂, and 2 ml water added and stirred for 10 minutes. Thereafter, 3.0 g acrylamide was added, the mixture heated to 30 °C, 135 mg copper(II)oxide added, and the mixture stirred for 2 hours. The solvent was removed, 25% NH₄OH added, the product extracted with EtOAc, and re-crystallized from hexane/EtOAc, 1:1, and the product isolated, mp = 192–193 °C. Elemental analysis data supplied.

4. **5-[2-Carbamoyl-2-(methylthio)ethyl]-2-methoxy-N-(4-trifluoro-methylbenzyl)benzamide**

The product from Step 3 (1.00 g), 60 ml ethyl alcohol, and NaSCH₃ were mixed, refluxed for 3 hours, and allowed to stand overnight. The solvent was removed, water added to the residue, and the product extracted with EtOAc. The product was purified using column chromatography on silica gel with hexane/EtOAc, 1:1, and 865 mg product isolated, mp = 152.5–153.5 °C. Elemental analysis supplied.

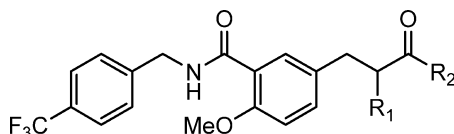
5. **5-[2-Carbamoyl-2-(methylsulfinyl)ethyl]-2-methoxy-N-(4-trifluoro-methylbenzyl)benzamide**

The product from Step 4 (639 mg) was dissolved in 70 ml CH₂Cl₂, 368 mg m-CPBA added, and the mixture stirred 3 hours with ice cooling. The mixture was washed with NaHCO₃, brine, dried, and concentrated. The product was purified by chromatography using CH₂Cl₂/methyl alcohol, 50:1 to 20:1, and the product isolated, mp = 170–171 °C. Elemental analysis data supplied.

6. **5-[2-Carbamoyl-2-(methylsulfonyl)ethyl]-2-methoxy-N-(4-trifluoro-methylbenzyl)benzamide**

The product from Step 5 (274 mg) was added to 100 ml CH₂Cl₂, 155 mg m-CPBA added, the mixture reacted and purified as in Step 5, and the product isolated, mp = 219–220 °C. Elemental analysis data supplied.

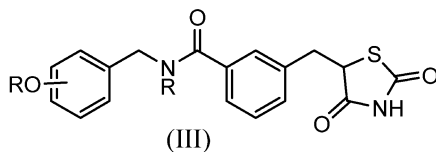
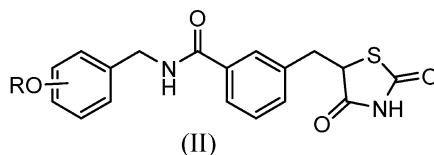
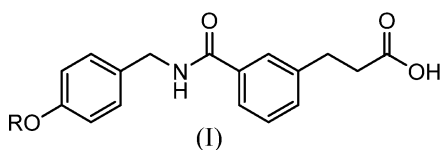
Derivatives



R_1	R_2	Melting Point ($^{\circ}\text{C}$)
Hydrogen	Hydroxyl	192–193
Mercaptan	Amide	159–161
Methylsulfonyl	Hydroxyl	144–145

Notes

1. The conversion of the product of Step 2 into 2-bromo-3-[4-methoxy-3-[N-(4-trifluoromethylbenzyl)]carbamoyl phenyl]amide is an example of the Meerwin-Schuster acylation reaction (1).
2. By reacting the product of Step 2 with methyl acrylate, the corresponding ester, methyl 2-bromo-3-[4-methoxy-3-[N-(4-trifluoromethylbenzyl)]-carbamoylphenyl]propanic acid, was prepared by the author.
3. Other examples are illustrated below, (I), (II), and, (III), (2), (3), (4), respectively.



References

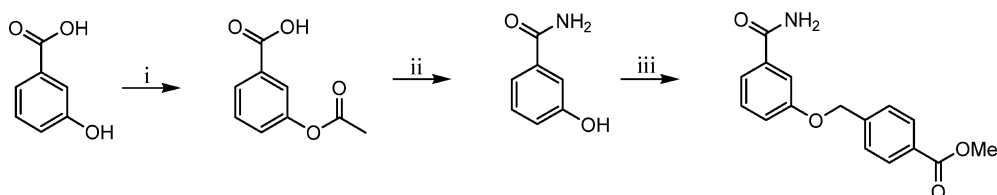
1. H. Krauch *et al*, Organic Name Reactions, J. Wiley & Sons, New York, NY 1964, pp. 310–311; C.S. Rondestvandt, Jr., Org. Reactions, 189, 1960
2. M. Nomura *et al*, US Patent 6,506,797 (January 14, 2003)
3. T. Maeda *et al*, US Patent 6,147, 101 (November 14, 2000)
4. T. Maeda *et al*, US Patent 5,948,803 (September 7, 1999)

Patent: Benzamide Analogues Useful as PARP (ADP-Ribosyltransferase, ADPRT) DNA Repair Enzyme Inhibitors
R.J. Griffin *et al*, US Patent 5,756,510 (May 26, 1998)

Assignee: Newcastle University Ventures

Utility: DNA Repair Enzyme Inhibitors

Reaction



- i- Sodium hydroxide, acetic anhydride, hydrochloric acid
ii- Thionyl chloride, ammonium hydroxide
iii- Methyl 4-chloromethylbenzoate, potassium carbonate, acetonitrile

Experimental

1. 3-Acetoxybenzoic acid

3-Hydroxybenzoic acid (7.29 mmol) was added to a cooled solution of NaOH (15.2 mmol in 2 ml of water) and cold acetic anhydride (7.9 mmol) added with crushed ice (2 g). The mixture was stirred for 1 hour, acidified with 3 ml 6 M HCl, whereupon a white precipitate formed. The mixture was extracted with CH_2Cl_2 , dried, concentrated, recrystallised from boiling water, and the product isolated in 86%. $^1\text{H-NMR}$ data supplied.

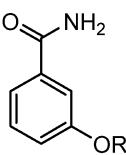
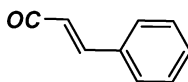
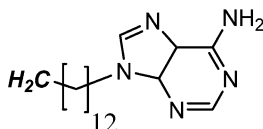
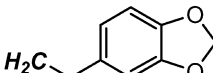
2. 3-Hydroxybenzamide

The product from Step 1 (0.5 g) was dissolved in thionyl chloride (1.74 ml) and refluxed 3.5 hours. Excess thionyl chloride was removed by distillation to yield a yellow oil. The oil was added dropwise to a cooled solution of 35% NH_4OH and stirred for 30 minutes. Thereafter, the mixture was boiled to 50% reduced volume and the product crystallized. The product was re-crystallised from boiling water and isolated in 60% yield. $^1\text{H-NMR}$ data supplied.

3. 3-(4-Carboxymethoxybenzyloxy)benzamide

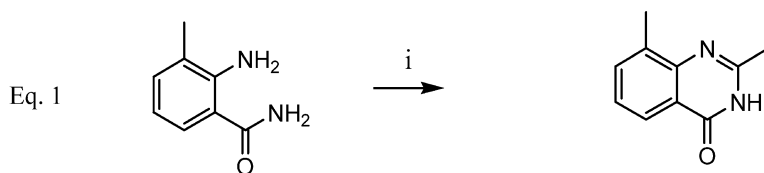
The product from Step 2 (10 mmol) was added to K_2CO_3 (10 mmol) and methyl 4-chloromethylbenzoate (10 mmol) dissolved in 50 ml anhydrous acetonitrile and the mixture refluxed 5 hours. Thereafter, it was concentrated, the residue dissolved in water, extracted with CH_2Cl_2 , dried, concentrated, the solids re-crystallised from boiling ethyl acetate and petrol, and the product isolated in 65% yield. $^1\text{H-NMR}$, IR, and elemental analysis data supplied.

Derivatives

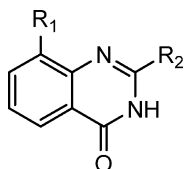
	
<u>R</u>	<u>MP</u> (°C)
$\text{CH}_2\text{-CH=CH}_2$	116–117
	131–138
	199–199.5
	141

Notes

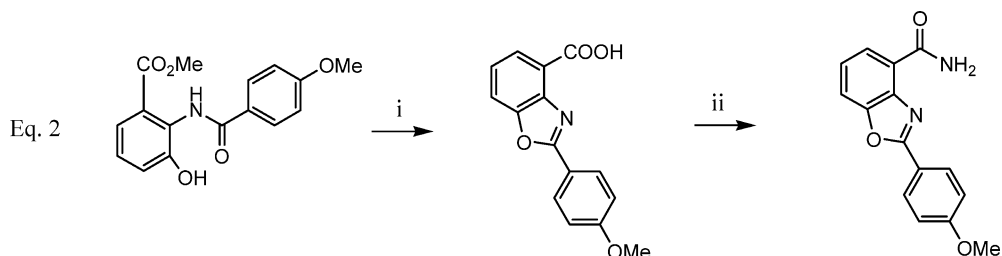
1. Quiniazolyn-4-[3H] and benzoxazole derivatives were also prepared by the author as illustrated in Eq.1 and Eq. 2, respectively:



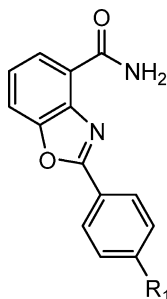
i- Acetyl chloride, pyridine, THF



R ₁	R ₂	MP (°C)
Methoxy	Methyl	202–204 (sublimes)
Methoxy	Phenyl	252–256
Hydroxy	Phenyl	280–284
Methyl	Methyl	217–220



i- m-Xylene, triethylamine, pyridinium-4-toluene sulfonate
 ii- Ammonia, EtOAc, petrol



R ₁	Yield (%)
Phenyl	70
Methyl	85
Butyl	73

- The preparation of alkyl, alkoxy, and radiolabelled benzamides of the current invention is provided (1).
- The preparation of quinoxalin-3-yn and benzodioxanyl precursors (2,3), respectively, are described.

References

- R.A. Nosal, *et al*, US Patent 5,223,539 (June 29, 1993); W.W. Lee *et al*, US Patent 5, 032,617 (July 16, 1991); S.D. Wyrick *et al*, US Patent 4,499,303 (February 12, 1985)
- R.A. LeMahieu *et al*, US Patent 4,281,127 (July 28, 1981)
- M. Thominet *et al*, US Patent 4,323,503 (April 6, 1982)

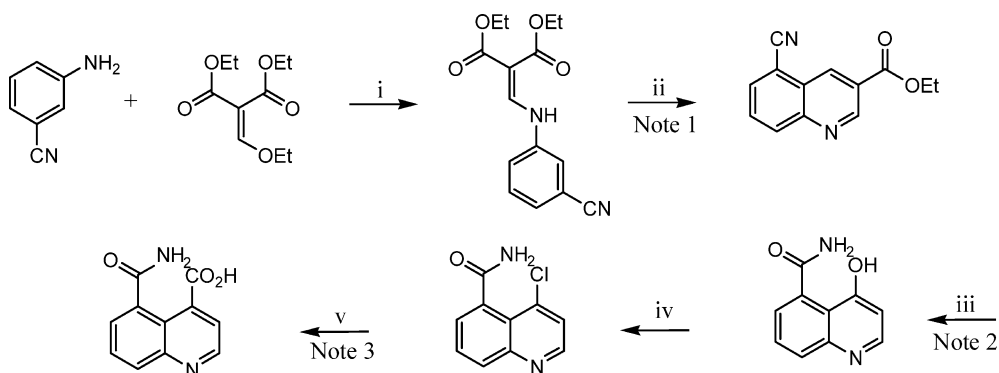
Patent: Carboxamide Compositions, Methods, and Compositions for Inhibiting PARP Activity

J.-H. Li *et al*, US Patent 6,395,749 (May 28, 2002)

Assignee: Guilford Pharmaceuticals Inc.

Utility: Treatment of Neurodegenerative Disorders

Reaction



i- Heat

ii- Diphenylether

iii- Polyphosphoric acid

iv- Phosphorous oxychloride

v- THF, n-butyllithium, carbon dioxide

Experimental

1. Ethyl- α -carboxyethoxy- β -(m-cyanoanilino)acrylate

A mixture of m-cyanoaniline (8.46 mmol) and diethylethoxymalonate (9.13 mmol) were stirred at 100–110 °C 1 hour. The solution was cooled, pale yellow crystals collected, and the product isolated in 100% yield, mp = 109–111 °C.

2. 5-Cyano-3-ethoxycarbonylquinoline

The product from Step 1 was added in portions to boiling diphenyl ether. After a few minutes crystals formed and the mixture was heated an additional 30 minutes. The solution was cooled, the crystals isolated and washed with n-hexane, and the product isolated as regioisomers in 89.5% yield, mp = 305–307 °C (dec).

3. 4-Hydroxyquinoline-5-carboxamide

The product mixture from Step 2 (2.33 mmol) was added to heated polyphosphoric acid over a period of 8 minutes then heated to 255–265 °C for 20 minutes. The mixture was cooled then poured into ice- water and filtered to remove the

desired regioisomer, 7-aminocarbonyl-4-hydroxyquinoline. The second isomer, 4-hydroxyquinoline-5-carboxamide, was isolated in 31.5% yield by adjusting the solution pH to 5–6 using NaHCO_3 and filtering the precipitate and had a mp $>250^\circ\text{C}$.

4. 4-Chloroquinoline-5-carboxamide

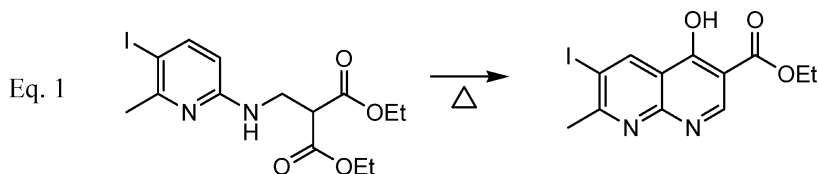
The product from Step 3 (5.88 mmol) was suspended in phosphorous oxychloride and the mixture heated to 130°C 2 hours. Thereafter, the reaction mixture was cooled, poured into ice water, basified with 10% NaOH to a pH ~ 9 , and a purple precipitate isolated. The material was dissolved in methyl alcohol and de-colored with activated carbon. The product was isolated after vacuum removal of the solvent in 25% yield, mp = $205\text{--}207^\circ\text{C}$.

5. 5-Carbamoylquinoline-4-carboxylic acid

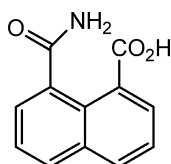
The product from Step 4 (1.94 mmol) was dissolved in 10 ml THF, cooled to -78°C , and *n*-butyllithium (3.88 mmol) in hexane added. Thereafter, CO_2 was bubbled through the mixture for 15 minutes followed by the addition of 20 ml saturated solution of NH_4Cl . The mixture was warmed to ambient temperature, concentrated, and dissolved in a saturated solution of Na_2CO_3 . The aqueous mixture was washed with ether, acidified with 1 M HCl , and 124 mg of product isolated.

Notes

1. Ethyl-4-hydroxy-6-iodo-7-methyl[1,8]naphthyridine-3-carboxylate has been prepared by thermal rearrangement of diethyl-{[(5-iodo-6-methyl-2-pyridinyl)amino]-methylene}malonate in diphenyl ether as illustrated in Eq. 1 and is described (1).

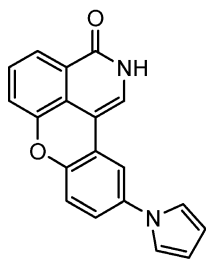


2. The regioisomer, 7-cyano-3-ethoxycarbonyl-quinoline, was also formed. It was subsequently acid hydrolyzed to 7-aminocarbonyl-4-hydroxyquinoline and isolated in 59.1% yield as a white solid.
3. The naphthyl analogue, 8-carbamoyl-naphthalene-1-carboxylic acid, (I), is commercially available.

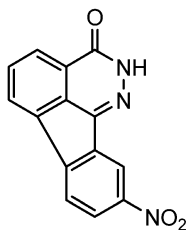


(I)

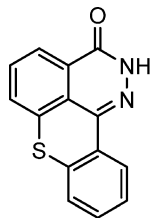
4. In subsequent investigations by the author, (II), (2) and others, (3) (III), (IV), (V), analogues of the current invention were prepared.



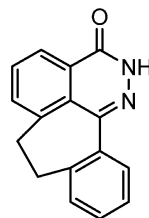
(II)



(III)



(IV)



(V)

References

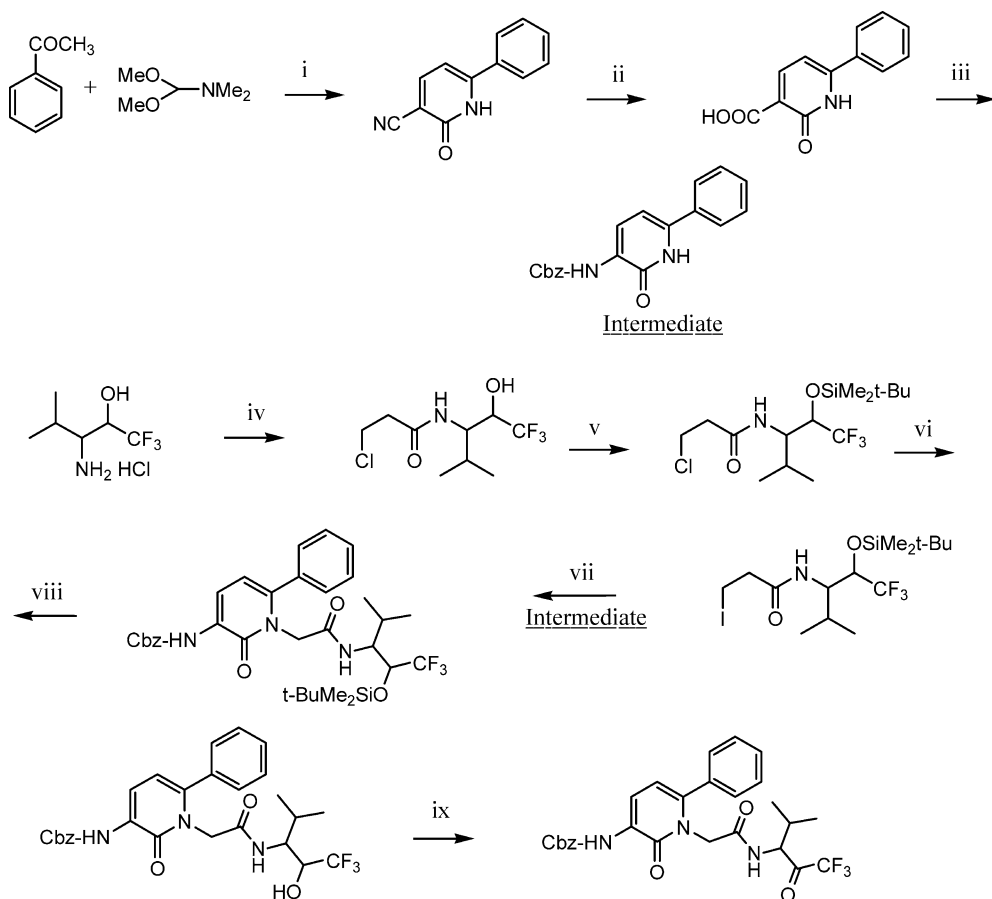
1. V.A. Vaillancourt, US Patent 6,413,958 (July 2, 2002)
2. J.-H. Li *et al*, US Patent 6,514,983 (February 4, 2003)
3. P.F. Jackson *et al*, US Patent 6,635,642 (October 21, 2003)

Patent: Heterocyclic Amides
P.R. Bernstein *et al*, US Patent 5,521,179 (May 28, 1996)

Assignee: Zeneca Limited

Utility: Human Neutrophil Elastase Inhibitor in the Treatment of Respiratory Disorders

Reaction



- i- Acetonitrile, cyanoacetamide, sodium methoxide
- ii- Acetic acid, hydrobromic acid, sodium hydroxide
- iii- Diphenylphosphoryl azide, dioxane, triethylamine, benzyl alcohol
- iv- THF, 4-methylmorpholine, chloroacetyl chloride
- v- CH_2Cl_2 , 2,6-lutidine, t-butyldimethylsilyl trillate
- vi- Sodium iodide, acetone

- vii- Sodium hydride, N,N-dimethylformamide, hydrochloric acid
- viii- THF, tetrabutylammonium fluoride
- ix- 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrogen chloride, toluene, dichloroacetic acid, dimethylsulfoxide

Experimental

1. 6-Phenylpyrid-2-one-3-carbonitrile

Acetophenone (30.6 g) and N,N-dimethylformamide dimethylacetal (100 g, 94% by weight) in acetonitrile were refluxed overnight, cooled, and concentrated. The solid was dissolved in 400 ml DMF, cyanoacetamide (19.4 g) and sodium methoxide added, and the mixture heated 5 hours at 100 °C. It was cooled, diluted with water, acidified with HCl to a pH = 5, and the product isolated. ¹H-NMR data supplied.

2. 6-Phenylpyrid-2-one-3-carboxylic acid

The product from Step 1 (8.54 g) was suspended in 100 ml HOAc and 50 ml HBr, refluxed overnight, cooled, diluted with 50 ml water, brought to pH 5 using 10% NaOH, and the product isolated. MS and ¹H-NMR supplied.

3. 3-Benzoyloxycarbonylamino-6-phenylpyrid-2-one

The product from Step 2 (10 g) was suspended in 260 ml dioxane containing 7.8 ml triethylamine, 11.1 ml diphenylphosphoryl azide added, and the mixture heated 4 hours at 120 °C. Benzyl alcohol (9.58 g) was added, the mixture refluxed overnight, cooled, diluted with 600 ml water, and a solid isolated. The solid was purified by chromatography using chloroform/methanol, 20:1, recrystallized using chloroform, and the product isolated. ¹H-NMR data supplied.

4. 2-Chloro-N-(3,3,3-trifluoro-2-hydroxy-1-isopropyl-propyl)-acetamide

3-Amino-1,1,1-trifluoro-4-methyl-2-pentanol hydrogen chloride (20 g) was dissolved in 480 ml THF, 4-methylmorpholine (21.8 g) added followed by 7.7 ml chloroacetyl chloride 40 ml in THF, and the mixture stirred overnight. The reaction mixture was filtered, the product extracted with EtOAc, purified by chromatography with CH₂Cl₂/methyl alcohol, 95:5, and the product isolated. MS data supplied.

5. N-(2-t-Butyldimethylsiloxy-3,3,3-trifluoro-1-isopropyl-propyl)-2-chloroacetamide

The product from Step 4 (23.79 g) was dissolved in 96 ml CH₂Cl₂ and 22.5 ml 2,6-lutidine and 33 ml t-butyldimethylsilyl trillate added. The exothermic reaction was cooled and the mixture stirred overnight. It was washed with 10% HCl, NaHCO₃ solution, extracted with EtOAc, purified by chromatography on silica gel using hexane/EtOAc, gradient 100:0, 93:7, 85:15, and 80:20, and the product isolated.

6. N-(2-t-Butyldimethylsiloxy-3,3,3-trifluoro-1-isopropyl-propyl)-2-iodoacetamide

The product from Step 5 (15.56 g) was added to a solution of NaI (19.3 g) dissolved in 130 ml acetone, stirred overnight, whereupon a yellow precipitate formed. The mixture was filtered, washed with water, $\text{Na}_2\text{S}_2\text{O}_3$ solution, purified by chromatography as in Step 4 with a gradient of 80:20, and 50:50, and the product isolated. MS data supplied.

7. 2-(3-Benzoyloxycarbonylamino-2-oxy-6 phenyl-1,2-dihydro-1-pyridyl)-N-(2-t-butyldimethylsiloxy-3,3,3-trifluoro-1-isopropyl-propyl)acetamide

The product from Step 3 (1.7 g) was added to a suspension of NaH in 50 ml DMF, stirred 15 minutes, the product from Step 6 (2.65 g) added, and the mixture stirred overnight. The mixture was diluted with 125 ml 10% HCl, extracted with EtOAc, purified by flash chromatography with EtOAc/ CH_2Cl_2 , a gradient elution of 1–4% EtOAc, and the product isolated. $^1\text{H-NMR}$ data supplied.

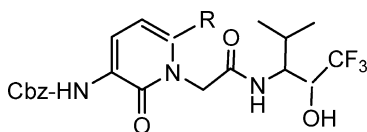
8. 2-(3-Benzoyloxycarbonylamino-2-oxy-6 phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-propyl)acetamide

The product from Step 7 (0.96 g) was dissolved in 8 ml THF, 1.62 ml 1 M NBu_4F in THF added, and stirred 4.5 hours. The mixture was extracted with 75 ml EtOAc and concentrated. The mixture was purified by flash chromatography using EtOAc/chloroform with a gradient of 5:95 to 10:90 and the product isolated as a white solid. $^1\text{H-NMR}$ data supplied.

9. 2-(3-Benzoyloxycarbonylamino-2-oxy-6 phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide

The product from Step 8 (0.78 g) was dissolved in 4 ml apiece of toluene and DMSO. Thereafter, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrogen chloride (2.81 g) and 0.48 ml dichloroacetic acid were added and the mixture stirred overnight. It was extracted with EtOAc, washed with 10% HCl, NaHCO_3 , brine, and concentrated. The mixture was purified by chromatography using $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 95:5, and the product isolated. $^1\text{H-NMR}$, MS, and elemental analysis data supplied.

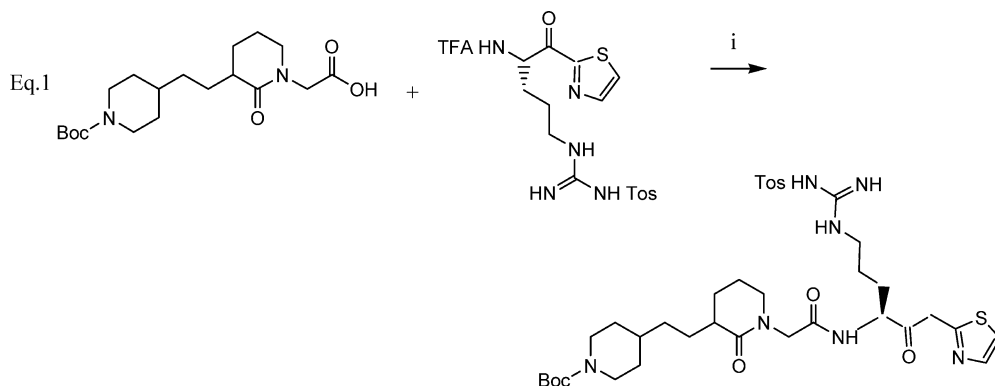
Derivatives



R	MS
3-Pyridyl	531
3,5-Dimethoxyphenyl	590
3-Chlorophenyl	564
trans-Styryl	556

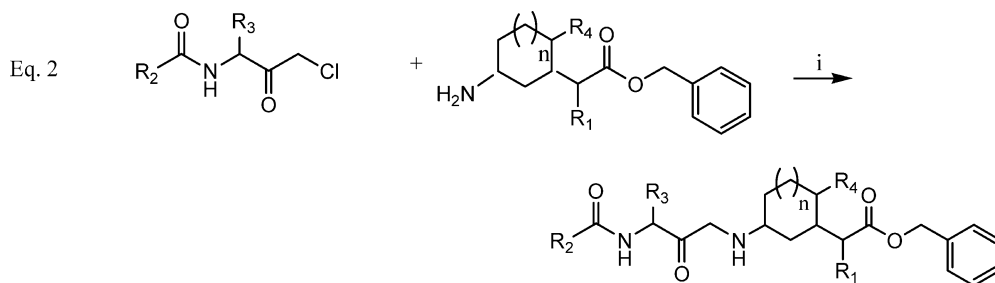
Notes

1. Other Step 1 lactams of the current invention have been prepared (1) as illustrated in Eq. 1:

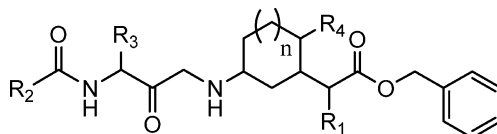


i- DMF, diethylamine,
benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium
hexafluorophosphate

2. The preparation of analogous lactams of varying ring sizes (2,3) have also been prepared as illustrated in Eq. 2:



i- Sodium hydroxide, methyl alcohol



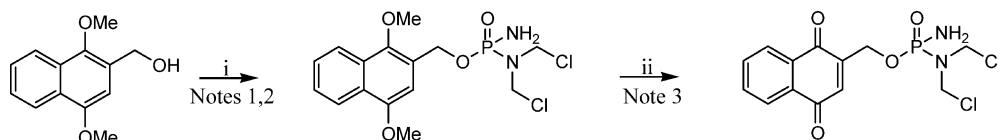
n	R ₁	R ₂	R ₃	R ₄
4	Hydrogen	Phenyl	Benzyl	Hydrogen
1	Hydrogen	Phenyl	1-Ethyl-2-(1-furyl)	Ethyl
3	Hydrogen	Phenyl	1-Butyl-4-(4-pyridyl)	Benzyl
2	Methyl	3-Pyridyl	1-Butyl-4-phenyl	Hydrogen

References

1. B.-Y. Zhu *et al*, US Patent 6,194,435 (February 27, 2001)
2. P.D. Edwards *et al*, US Patent 5,164,371 (November 17, 1992)
3. E.M. Gorden *et al*, US Patent 4,474,778 (October 2, 1984)

Patent: Phosphoramidate Compounds
R.F. Borch *et al*, US Patent 6,656,926 (December 2, 2003)
Assignee: Purdue Research Foundation
Utility: Anti-Neoplastic Agent for Animals

Reaction



i- THF, lithium bis(trimethylsilyl)amide, bis(2-chloroethyl)
phosphoramidic dichloride, ammonia
ii- Acetonitrile, ceric ammonium nitrate

Experimental

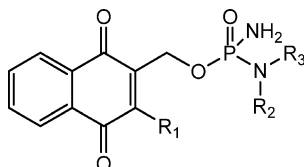
1. 2-(1,4-Dimethoxynaphthyl)methyl-N,N-bis(2-chloroethyl) phosphorodiamidate

Lithium bis(trimethylsilyl)amide (2.50 mmol, 1.0 M in THF) was added dropwise to a solution of 1,4-dimethoxy-2-(hydroxymethyl)naphthalene (2.29 mmol) dissolved in 10 ml THF at -78°C . This was then added dropwise to a solution of bis(2-chloroethyl)phosphoramidic dichloride (2.75 mmol) dissolved in 20 ml THF, the reaction mixture stirred at -78°C 90 minutes, warmed to -20°C , and ammonia passed through the mixture 10 minutes. Thereafter, the mixture stirred an additional 10 minutes, 30 ml 2% HCl added, and then extracted 4 times with EtOAc. The combined organic layers were washed twice with saturated brine, dried, filtered, and evaporated. The mixture was purified by chromatography using methyl alcohol/EtOAc, 2:98, and the product isolated in 50% yield as a yellow oil, $R_f = 0.59$. ^1H - and ^{31}P -NMR data supplied.

2. 2-(1,4-Naphthoquinonyl)methyl N,N-bis(2-chloroethyl) phosphorodiamidate

Ceric ammonium nitrate (2.85 mmol) dissolved in 10 ml water was added in portions over 15 minutes to the product of Step 1 (1.14 mmol) dissolved in 30 ml acetonitrile. The solution was stirred at ambient temperature 1 hour, extracted 3 times with chloroform, dried, filtered, and evaporated. The mixture was purified by chromatography using methyl alcohol/chloroform, 6:94, and the product isolated in 81% yield as a yellow solid, $R_f = 0.45$, mp = $105\text{--}107^{\circ}\text{C}$. ^1H - and ^{31}P -NMR, IR, and elemental analysis data supplied.

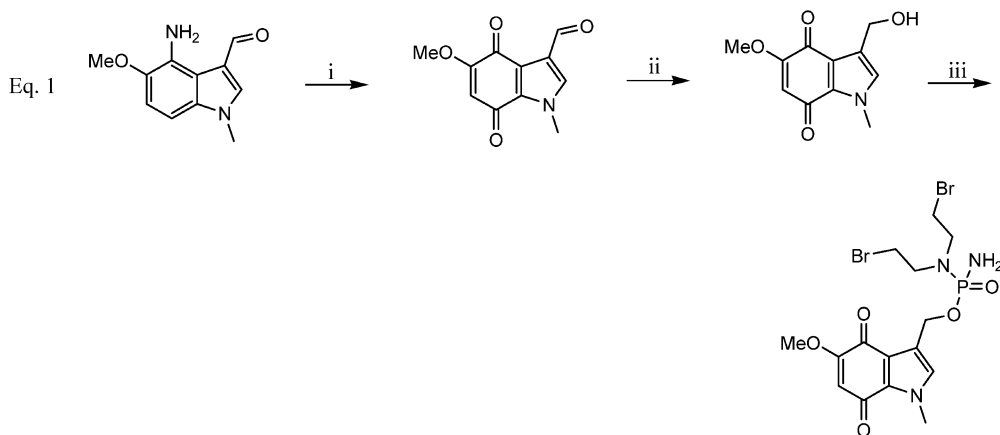
Derivatives



R ₁	R ₂	R ₃	MP (°C)	Yield (%)
Hydrogen	Hydrogen	2-Chloroethyl	109–110	74
Methyl	Methyl	2-Bromoethyl	—	57
Hydrogen	Methyl	2-Chloroethyl	Oil	87
Thiomethyl	2-Chloromethyl	2-Chloromethyl	Oil	57

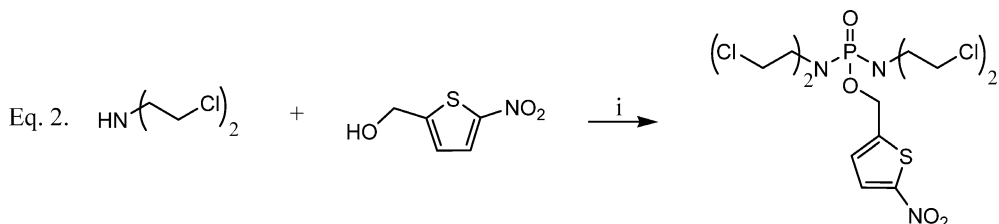
Notes

1. Beginning with 1,4-dihydroxy-2-naphthoic acid the preparation of the Step 1 reagent is described by the author.
2. Bromoethyl derivatives were prepared using bis(2-bromoethyl)-phosphoramidic dichloride and its preparation is provided by the author.
3. Indolequinolyl derivative 3-(5-methoxy-1-methyl-4,7-indolequinonyl) methyl N,N-bis(2-bromoethyl)phosphorodiamidate was also prepared by the author as illustrated in Eq. 1:



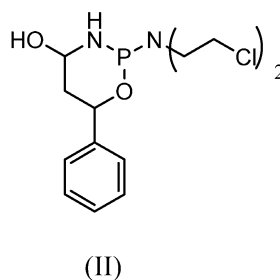
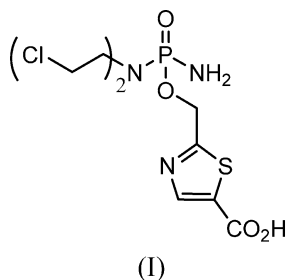
- i- Potassium nitrosodisulfonate, water
 ii- Sodium borohydride, methyl alcohol,
 iii- THF, bis(2-bromoethyl)phosphoramidic dichloride

4. 5-Nitro-2-thiophenylmethyl-N,N,N',N'-tetrakis(2-chloroethyl)-phosphoramidate was prepared by the author in an earlier investigation (1) and illustrated in Eq. 2:



i- CH_2Cl_2 , phosphorous trichloride, t-butylperoxide

5. The preparation of other analogues of the current invention including 2-{2-[N,N-bis(2-chloroethyl)diamido-phosphoryloxy] ethyl}-thiazolidine-4-carboxylic acid, (I), (2), and 4-hydroxy-6-phenylcyclophosphamide, (II), (3) is described.



References

1. R.F. Borch *et al*, US Patent 5,472,956 (December 5, 1995)
2. H.-J. Hohorst *et al*, US Patent 4,997,822 (March 5, 1991)
3. R.F. Borch *et al*, US Patent 5,190,929 (March 2, 1993)

Amines

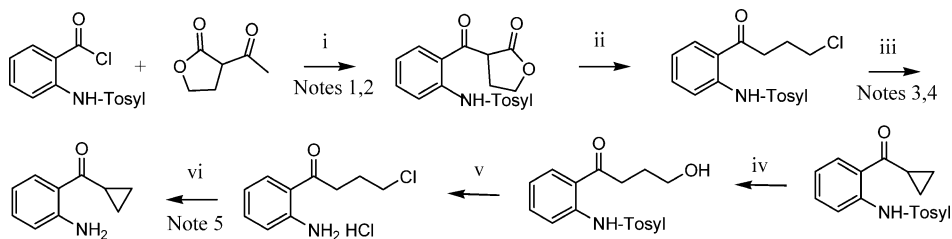
Patent: Aminophenyl Ketones Derivatives and a Method for the Preparation Thereof

D.A. Cortes *et al*, US Patent 6,127,576 (October 3, 2000)

Assignee: American Cyanamide Company

Utility: Herbicide Intermediate

Reaction



- i- Magnesium ethoxide, toluene
- ii- Hydrochloric acid, toluene
- iii- Sodium hydroxide, toluene
- iv- Sulfuric acid
- v- Hydrochloric acid, water
- vi- CH_2Cl_2 , tetrabutylammonium chloride, sodium hydroxide, 1,2-dichloroethane

Experimental

1. 2'-(Tetrahydro-2-oxo-3-furoyl)-p-toluenesulfonanilide

A mixture of 40 ml toluene and magnesium ethoxide (178 mmol) at 5°C was charged with 2-acetylbutyrolactone (36 mmol) and the mixture stirred for 1.5 hours at 20°C and

then treated with N-p-tolylsulfonyl-anthranoyl chloride (32 mmol) in 20 ml toluene. The mixture was stirred an additional 2 hours at 45 °C, 120 ml water added, and the slurry stirred 4 hours at 65 °C. The pH was adjusted to 1, the organic layer separated, and the product was isolated by filtration in 83% yield, mp = 138–141 °C.

2. 4-Chloro-1-(2-N-tosylaminophenyl)-1-butanone

The product from Step 1 (1.0 mmol) was added to a 2 phase mixture of 25 ml toluene and 20 ml 37% HCl and refluxed 12 hours. The mixture was cooled, filtered, and the product isolated in 90% product, mp = 108–113 °C.

3. 2-(Cyclopropylcarbonyl)-p-toluenesulfonanilide

To the product from Step 2 (4.6 mmol) in 10 ml toluene was added NaOH (17.3 g 6.6%) solution, the mixture refluxed 1 hour, and the pH adjusted to 1 with concentrated sulfuric acid. The organic phase was separated and the product isolated in 100% yield, mp = 92–100 °C.

4. 1-(o-Aminophenyl)-4-hydroxyl-butanone

The product from Step 3 (4.7 mmol) was treated with 96% sulfuric acid, heated to 90 °C 15 minutes, cooled, the pH adjusted to 9 using NH_4OH , and the mixture extracted with CH_2Cl_2 to obtain 80% product, mp = 58–61 °C.

5. 1-(o-Aminophenyl)-4-chloro-1-butanone hydrochloride

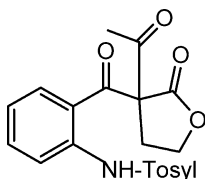
The product from Step 4 (5.1 mmol) was dissolved in 26 ml water, 90 ml 37% HCl, refluxed 6.5 hours, cooled, and filtered to and 73% product isolated, mp = 142–145 °C.

6. o-Aminophenyl cyclopropyl ketone

The product from Step 5 (1.3 mmol) was dissolved in 3 ml apiece CH_2Cl_2 and $\text{CH}_2\text{ClCH}_2\text{Cl}$, treated with 1.2 g 10% aqueous NaOH and 0.5 g 75% aqueous NBu_4Cl , and heated to 50 °C for 5 hours. The mixture was cooled and the product isolated in 70% yield.

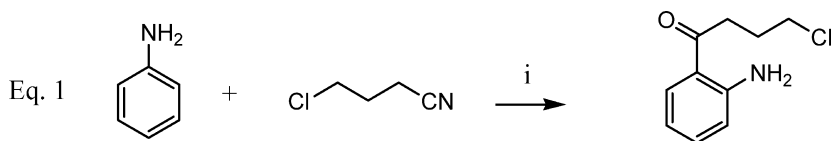
Notes

1. A second Step 1 product (I) was also formed in Step 1 and was removed by either by hydrolysis or re-crystallization.



(I)

2. In an earlier investigation by the author (1) 4-halo-2-tributylphenone derivatives were prepared following a similar pathway to those described in Steps 4 and 5.
3. Another method for preparing 1-(o-aminophenyl)-4-butanone entails a Friedle-Crafts reaction of 4-chlorobutyronitrile with BCl_3 and aniline then post-reacting with AlCl_3 as illustrated in Eq. 1 and described below (1,2,3).

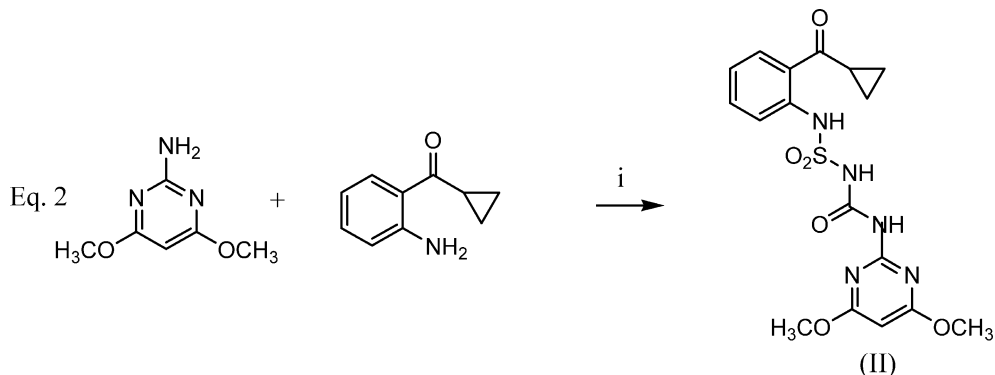


i- 1,2-Dichloroethane, borontrichloride, aluminum trichloride

Procedure

A mixture of BCl_3 (0.5 mol) in $\text{CH}_2\text{ClCH}_2\text{Cl}$ was treated with 4-chlorobutyronitrile (0.64 mol) at -8 to 0°C 1 hour, stirred for 1 hour at 5°C , and treated with aniline (0.485 mol) over 1 hour at $2-9^\circ\text{C}$. Thereafter, AlCl_3 (0.515 mol) was added in a single portion at ambient temperature. The reaction was refluxed 17 hours, cooled, a 2-fold volume of water added, the mixture stirred at 35°C for 30 minutes, the phases separated, and product isolated.

4. The preparation of other cyclopropylketone derivatives by ring closure of the 4-chlorobutyryl group is provided (4).
5. o-Aminophenylcyclopropylketones are intermediates in the preparation of sulfamoyl-pyriminyl urea derivatives (II). The derivatives are prepared by reacting with chloro-sulfonyl isocyanate and 2-amino-4,6-dimethoxypyrimidine (5) as depicted in Eq. 2.



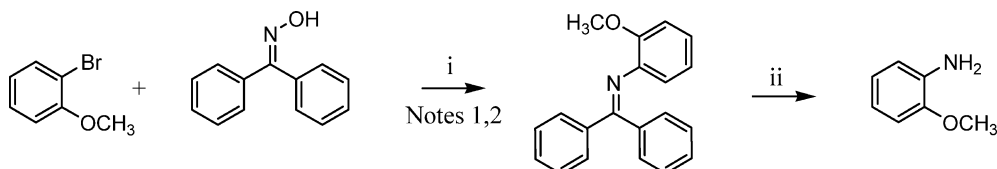
i- Chlorosulfonylisocyanate

References

1. D.A. Cortes, US Patent 5,414,136 (May 9, 1995)
2. A.A. Cevasco, US Patent 5,405,998 (April 11, 1995)
3. I. Sugawara *et al*, US Patent 4,160,785 (July 10, 1979)
4. A. Douglas *et al*, US Patent 5,426,230 (June 20, 1995)
5. M.E. Condon *et al*, US Patent 5,492,884 (February 20, 1996)

Patent: Arylamine Synthesis
J.P. Wolfe *et al*, US Patent 6,323,366 (November 27, 2001)
Assignee: Massachusetts Institute of Technology
Utility: Arylamine Synthetic Method

Reaction



i- Tris(dibenzylideneacetone)dipalladium,
bis[(2-diphenylphosphino)phenyl]ether, toluene, sodium
t-butoxide, sodium chloride, water
 ii- Hydrochloric acid, water

Experimental

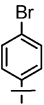
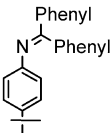
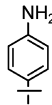
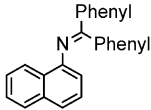
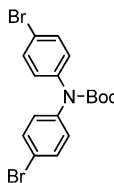
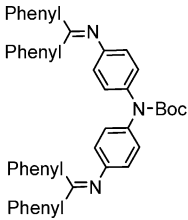
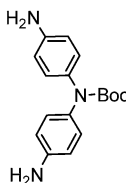
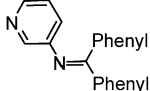
1. N-(Diphenylmethylene)-2-methoxyaniline

A test tube was charged with tris(dibenzylideneacetone)dipalladium (0.005 mmol), bis[(phenylphosphino)phenyl] ether (0.015 mmol), benzophenone imine (1.05 mmol), 2-bromoanisole (1.0 mmol) and 2 ml toluene. The mixture stirred 5 minutes, t-BuONa (1.4 mmol) was added, and the mixture stirred an additional 23 minutes. Thereafter, it was heated to 80°C, stirred 2 hours 10 minutes, cooled and 1 ml diethylether added followed by 2 ml saturated aqueous NaCl. The product was purified by flash chromatography on silica gel EtOAc/hexanes, 1:10, and isolated in 75% yield.

2. 2-Methoxyaniline

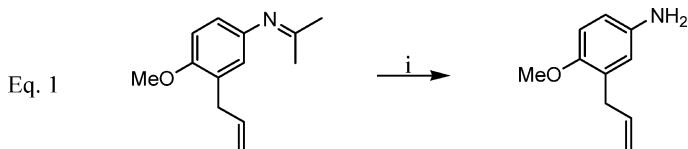
To a 0.3 M THF solution of product from Step 1 was added 2.0 M HCl and the mixture stirred 5 minutes to 20 minutes. Thereafter, it was partitioned between 0.5 M HCl and hexane/EtOAc, 2:1, and the aqueous layer made alkaline. The product was extracted with CH₂Cl₂, dried, and isolated (Note 2).

Derivatives

Aryl Precursor	Step 1 Diphenylimine	Yield (%)	Step 2 Aromatic Amine	Yield (%)
		90		95
		85		96
		91		95
		----		71

Notes

1. The two component catalyst consists of a 1:3 molar ratio of tris(dibenzylideneacetone)dipalladium and bis(2-diphenylphosphino)phenyl)ether, respectively.
2. The preparation of the co-catalyst, bis[(2-diphenylphosphino)-phenyl]ether, is described (1).
3. Another method for preparing arylamine compounds of the current invention entails reacting an in situ generated aminostannane with an aromatic halide in toluene and is described (2).
4. An alternative transamination procedure described by the author using hydroxylamine as an hydrolysis component is illustrated in Eq. 1:



i- Sodium acetate, methyl alcohol, hydroxylamine hydrogen chloride

Procedure

To a solution of the imine in 0.1 M CH₃OH at ambient temperature was added NaOAc (2.5 eq) and hydroxylamine hydrochloride (1.8 eq). The solution was partitioned between 0.1 M NaOH and CH₂Cl₂ and the organic layer dried and concentrated. The purified amine was isolated using chromatography on silica gel.

References

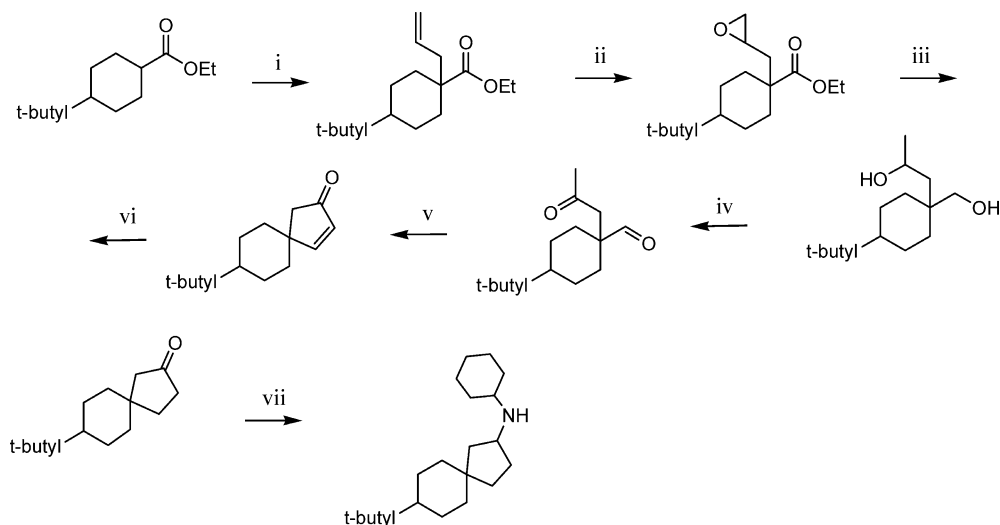
1. B.M Trost *et al*, US Patent 5,739,396 (April 14, 1998)
2. S.L. *et al*, US Patent 5,576,460 (November 19, 1996)

Patent: Fungicidal Spirocyclic Amines
W.F.A. Pfrengle, US Patent 5,849,802 (December 15, 1998)

Assignee: American Cyanamid Company

Utility: Phytopathogenic Fungicide

Reaction



- i- Lithium diisopropylamide, THF, allylbromide
- ii- m-Chloroperbenzoic acid, CH_2Cl_2
- iii- Lithium aluminum hydride, THF
- iv- Dimethylsulfoxide, oxalylchloride, triethylamine
- v- Lithium diisopropylamide, THF, p-toluenesulfonic acid
- vi- Raney nickel, hydrogen
- vii- Cyclohexylamine, zinc chloride, sodium cyanoborohydride

Experimental

1. Ethyl 1-allyl-4-*t*-butylcyclohexylcarboxylate

Lithium diisopropylamine (0.2 mol) dissolved in 300 ml THF at -20°C was added to ethyl 4-*t*-butylcyclohexylcarboxylate (0.2 mol), stirred 1 hour, and the temperature lowered to -70°C . Thereafter, allylbromide (0.2 mol) was added and the mixture allowed to come to ambient temperature overnight. The mixture was quenched with NH_4Cl solution, the organic layer concentrated, and the product distilled at $75\text{--}82^\circ\text{C}$ at 0.03 mbar and 46 g of product isolated as a colorless oil.

2. Ethyl 1-(2,3-epoxyprop-1-yl)-4-t-butylcyclohexylcarboxylate

To a solution of m-CPBA (0.08 mol) in CH_2Cl_2 was added the product from Step 1 (0.067 mol) in 200 ml CH_2Cl_2 and the reaction stirred overnight. Thereafter the mixture was filtered and 17 g product isolated as a colorless oil.

3. 1-Hydroxymethyl-1-(2-hydroxyprop-1-yl)-4-t-butylcyclohexane

Lithium aluminum hydride (0.132 mol) in 100 ml THF was added to the product from Step 2 (0.063 mol) dissolved in THF and the mixture stirred overnight. Excess lithium aluminum hydride was hydrolyzed using aqueous Na_2CO_3 solution and the hydrolysis product filtered from solution. The product was isolated and re-crystallized in light petroleum, mp = 93°C.

4. 1-(Propan-2-one-1-yl)-4-t-butylcyclohexane carboxaldehyde

Oxalylchloride (0.165 mol) dissolved in 50 ml CH_2Cl_2 was added to 21 ml DMSO in 50 ml CH_2Cl_2 , the reaction cooled to -70°C , the product from Step 3 (0.075 mol) added, and the mixture stirred 30 minutes. To this was added 100 ml TEA and the reaction warmed to ambient temperature. Thereafter the reaction mixture was washed with brine, dried, 15 g impure product isolated with a mp = 68–72°C and used without further purification Step 5.

5. 8-t-Butyl-spiro[4.5]dec-3-en-2-one

The product from Step 4 (0.0625 mol) dissolved in 200 ml THF was cooled to -70°C , 35 ml 2 M LDA added, the mixture stirred 1 hour at -70°C , warmed to -20°C , and quenched with 100 ml NH_4Cl solution. The crude product was dissolved in 200 ml toluene containing 0.3 g p-toluenesulfonic acid and refluxed 30 minutes. The purified product was isolated by flash chromatography on silica gel with light petroleum ether/EtOAc, 10:1.

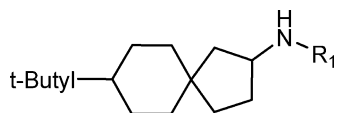
6. t-Butyl-spiro[4.5]decane-2-one

The product from Step 5 (7.5 g) was dissolved in 100 ml ethyl alcohol and hydrogenated with a mixture of Raney nickel and palladium on carbon at 50°C and 60 psi until hydrogen uptake ceased. The catalyst was filtered, the mixture concentrated, purified by flash chromatography on silica gel using toluene/acetone, 10:1, and the product isolated, mp = 78–82°C.

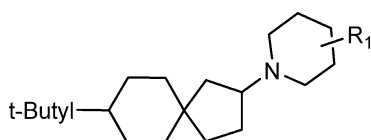
7. t-Butyl-spiro[4.5]decane-2-cyclohexylamine

The product from Step 6 (4 mmol), cyclohexylamine (4.2 mmol) and zinc chloride (3 mmol) were dissolved in 20 ml ethyl alcohol. Sodium cyanohydride (5 mmol) was added and the mixture stirred overnight. The solvent was removed, the residue dissolved in 20 ml EtOAc, washed with 20 ml 1 M NaOH, 20 ml water, and dried over MgSO_4 . The product was purified by chromatography on silica gel with toluene/EtOAc/TEA and the product isolated, mp = 67–69°C.

Derivatives



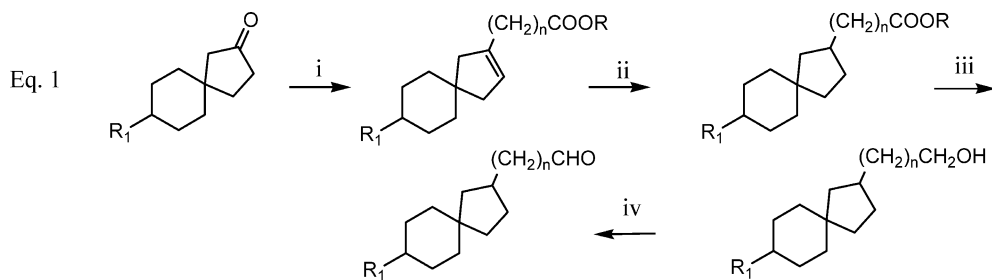
R₁	Melting Point (°C)
Cyclohexyl	67–69
4-Chlorobenzyl	53–57



R₁	Melting Point (°C)
3-Methyl	128
3,5-Dimethyl	50

Notes

1. Descriptions and preparations of other spiroheterocyclics is provided (1).
2. The author also provided a generic method for extending the amino substituent in the 2 position in the product of Step 6 using the Knoevenagel-Doebner reaction as illustrated in Eq. 1:

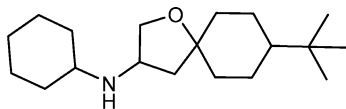


i- $\text{XMg}(\text{CH}_2)_n\text{C}(\text{OR})_3$

ii- Hydrogenation

iii- Reduction

iv- Oxidation



(I)

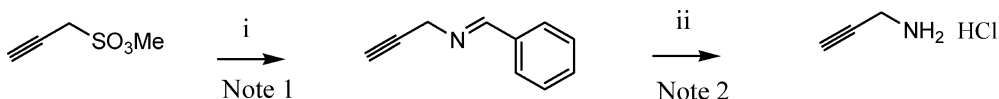
3. In an earlier investigation by the author (2), spirocyclic heterocyclic derivatives, (I), were prepared.

Reference

1. M. Zipplies *et al*, US Patent 5,268,351 (December 7, 1993) and US Patent 5,175,295 (December 29, 1992)
2. W.F.A. Pfrengle *et al*, US Patent 5,591,741 (January 7, 1997) and US Patent 5,641,883 (June 24, 1997)

Patent: Method for Producing Propargylamine Compounds
S. Seko *et al*, US 5,756,769 (May 26, 1998)
Assignee: Sumitomo Chemical Company
Utility: Aminopropargyl Chemical Intermediates

Reaction



i- Benzaldehyde, ammonium hydroxide, toluene
 ii- Hydrochloric acid, toluene, i-propyl alcohol

Experimental

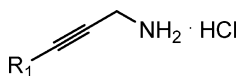
1. N-Benzylidene-2-propylimine

Propargyl methanesulfonate (0.35 mol) and benzaldehyde (0.44 mol) were dissolved in 148 g toluene and 28% NH_4OH (2.96 mol) added at 24°C over 7.5 hours. Thereafter, the mixture was stirred 15 hours, the organic phase concentrated, and the product isolated in 80% yield, bp = 80–83°C at 2.5 mm Hg (Note 3).

2. Propargylamine hydrochloride

The product from Step 1 (0.17 mol) was dissolved in 24.8 g toluene, 36% HCl (0.20 mol) added dropwise at 60°C over 1 hour, and the mixture stirred 90 minutes. The organic phase was washed with water, recombined with the aqueous phase containing 64 g i-propyl alcohol, heated to 60°C, and product crystals isolated in 60% yield.

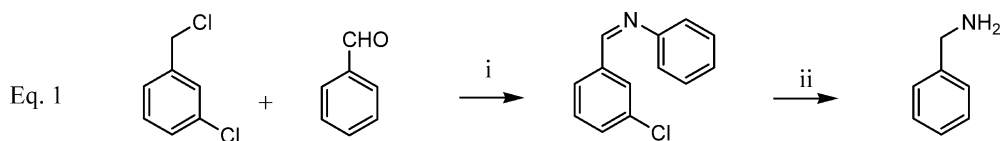
Derivatives



R_1	Yield (%)
Hydrogen	85
Methyl	94
2-Thienyl	77
Phenyl	78

Notes

1. Only marginal yields of propargyl amine hydrogen chloride were obtained when propargyl chloride, -bromide or -benzenesulfate were coupled with benzaldehyde followed by hydrolysis.
2. An analogous amine preparation reaction entails converting 3-chloro-benzylchloride into the corresponding imine by reacting with benzaldehyde followed by hydrolysis as illustrated in Eq. 1 and is described (1).

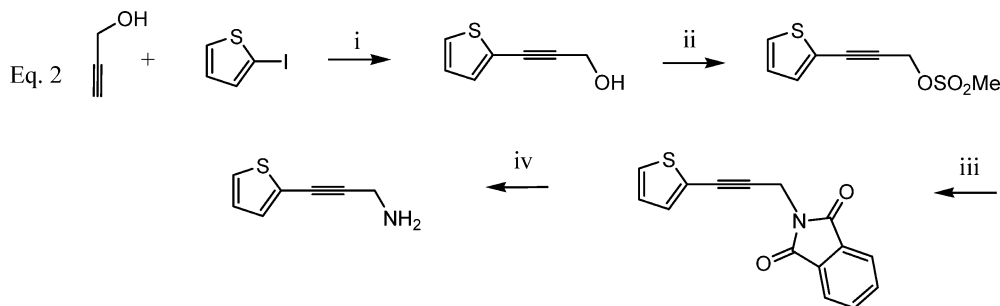


- i- Ammonium hydroxide, tetrabutylammonium hydroxide,
 ii- Hydrochloric acid, chlorobenzene

Procedure

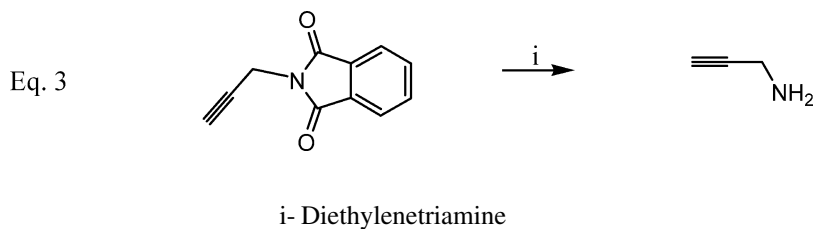
To a 1 liter 4-neck flask containing 728 g 7% NH_4OH at $70^\circ C$ was added 3-chlorobenzyl chloride (0.5 mol), benzaldehyde (0.5 mole) and 0.1 g tetrabutylammonium hydroxide and the mixture stirred 4 hours. It was cooled to ambient temperature whereupon an oil phase appeared. The oil phase was isolated and heated to $80^\circ C$ for 30 minutes. In a separate flask, 548 g 5% HCl and 300 g chlorobenzene were charged and added to the oil followed by 69 g chlorobenzene. The chlorobenzene phase was isolated and washed with 48% aqueous sodium chloride solution, whereupon a second oil phase appeared. The oil phase was washed, dried, distilled at 20 Torr, and the product isolated in 73% yield.

3. Heterocyclic-2-propyne-1-amine derivatives have been prepared from propargylamine using the Gabriel synthesis (2,3) as illustrated in Eq. 2:



- i- Di-(triphenylphosphine)palladium dichloride,
 copper(I)iodide, triethylamine
 ii- Methanesulfonylchloride, triethylamine
 iii- Potassium phthalimide, N,N-dimethylformamide
 iv- Hydrazine hydrate

4. Transamination of the propargyl phthalimide derivatives has been used to prepared propargyl amines as illustrated in Eq. 3 and described (4).



References

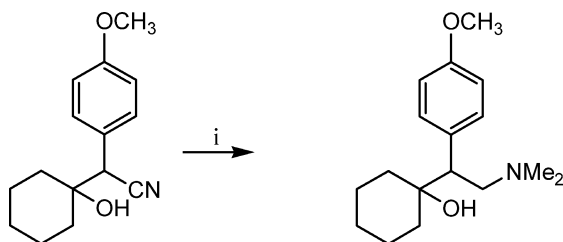
1. T. Sugiyama *et al*, US Patent 5, 210,303 (May 11, 1993)
2. J. S. Gibsen, *Angew. Chem. Int. Ed.* 7, 919 (1968)
3. T. M. Bargar *et al*, US Patent 4,743,617 (May 10, 1988)
4. A.R.J. Castaigne, US Patent 3,914,312 (October 21, 1975)

Patent: One Pot Process for the Preparation of
1-[2-Methylamino-(4-Methoxyphenyl)-Ethyl]Cyclohexanol
S.P. Chavan *et al*, US Patent 6,350,912 (February 26, 2002)

Assignee: Council of Scientific and Industrial Research

Utility: Anti-Depressant Intermediate

Reaction



i- Methyl alcohol, Raney nickel, hydrogen, formaldehyde

Experimental

1. 1-[2-Methylamino-(4-methoxyphenyl)-ethyl]cyclohexanol

1-[Cyano-(4-methoxyphenyl)methyl]cyclohexanol (5.0 parts, 0.02 mol) was dissolved in methyl alcohol (100 parts) and added to a 35% formalin solution (25 parts) and Raney nickel (5 ml, settled material). The mixture was hydrogenated at 200 psi 6 hours at 60°C, filtered, Raney nickel washed 4 times with 25 ml methyl alcohol, and the solvent removed. The oil was dissolved in EtOAc, partitioned between 10% HCl and EtOAc, the pH raised to 10 using 25% aqueous NaOH, and then extracted with EtOAc. The product was dried and isolated in 28% yield, mp = 74–76°C. ¹H-NMR data supplied.

Notes

1. The reagent precursor, p-methoxyphenylacetonitrile, has been prepared and is described (1).
2. In a subsequent investigation by the author, a one-step preparation of the Step 1 reagent was prepared by the condensation of cyclohexylketone with 4-methoxyphenylacetonitrile, potassium hydroxide, and tetrabutylammonium iodide (2).
3. Other N-methylations of 1-[cyano-(4-methoxyphenyl)-methyl]cyclohexanol using formaldehyde, formic acid, and excess water by a modified Eschweiler-Clarke reaction are described (3).

References

1. G.E. Morris Husbands *et al*, US Patent 4,535,186 (October 26, 1983)
2. S.P. Chavan *et al*, US Patent 6,504,044 (January 7, 2003)
3. T.J. Tilford *et al*, J. Am. Chem. Soc., 76, 2431 (1954)

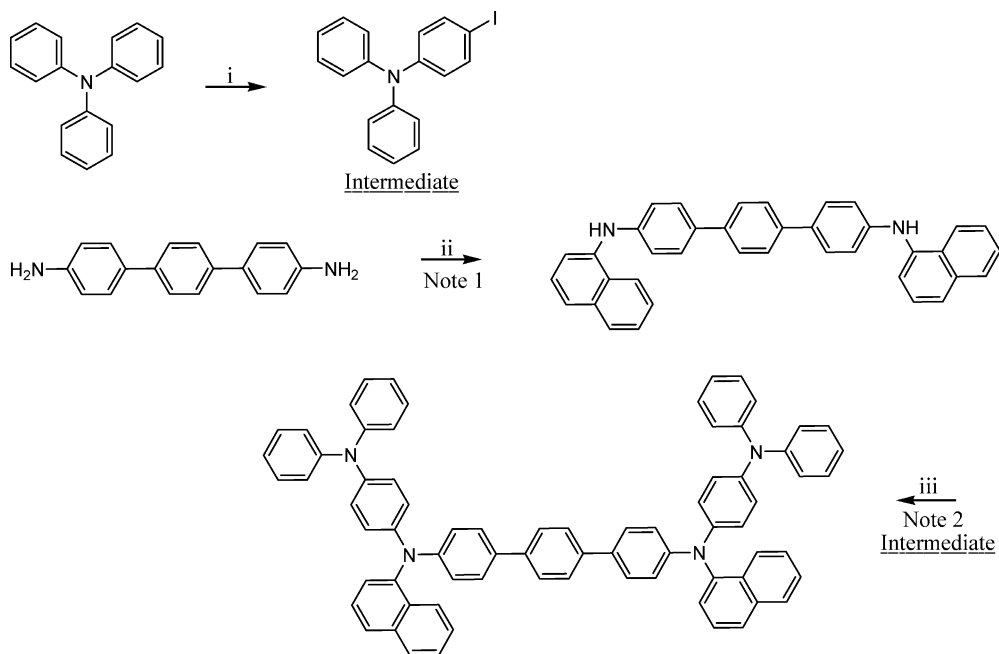
Patent: Organic Electroluminescence Device and Phenylenediamine Derivative

H. Kawamura *et al*, US Patent 6,541,129 (April 1, 2003)

Assignee: Idemitsu Kosan Co., Ltd

Utility: Electroluminescence Device for Voltage Reduction

Reaction



i- Mercury(II)oxide, iodine, ethyl alcohol

ii- 1-Iodonaphthalene, potassium carbonate, copper, nitrobenzene

iii- Potassium carbonate, copper, nitrobenzene

Experimental

1. 4-Iodotriphenylamine

Triphenylamine (125 g) was dissolved in 5 L ethyl alcohol, HgO (150 g) added at 60°C, followed by I₂ (100 g), and the reaction refluxed 2 hours. Thereafter, the mixture was hot filtered, the residue washed with acetone, and upon cooling, crystals deposited. The crystals were purified by chromatography using silica gel with toluene and 52 g product isolated.

2. N,N'-4,4''-Bis(1-Naphthylamino)-p-terphenylene

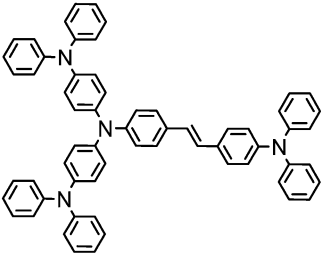
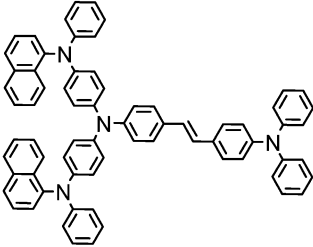
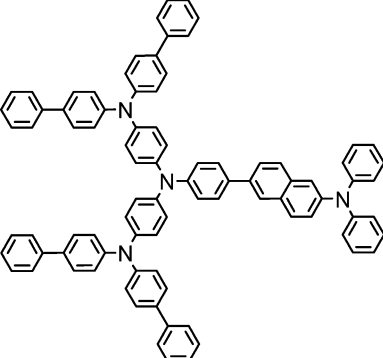
4,4''-Diamino-p-terphenylene (10 g), 1-iodonaphthalene (20 g), K₂CO₃, (20 g), Cu powder (1 g) and 100 ml nitrobenzene were heated to 200°C 48 hours. The mixture was filtered,

concentrated, and the residue purified by chromatography as in Step 1 and 8.4 g product isolated.

3. 4,4''-Bis(1-Naphthylamino-(4-triphenylamine)]-p-terphenylene

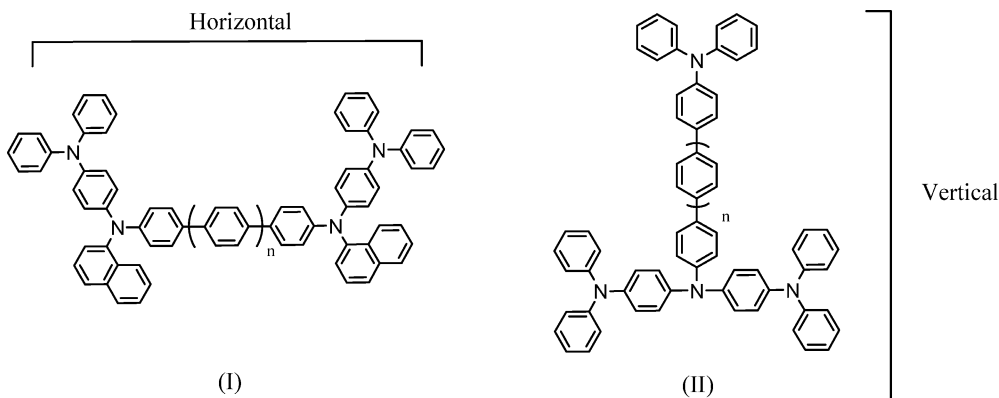
The product from Step 1 (5 g) was mixed with the product from Step 2, K_2CO_3 (20 g), Cu powder (1 g), 100 ml of nitrobenzene added, and the mixture heated to 200°C 60 hours. The product mixture was purified using toluene and hexane, 1:2, sublimed at 0.01 mm Hg, and 0.8 g product isolated. MS and elemental analysis data supplied.

Derivatives

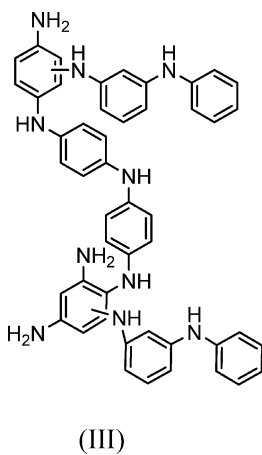
<u>Derivative</u>	<u>MS (M+1)</u>
	822
	1099
	936

Notes

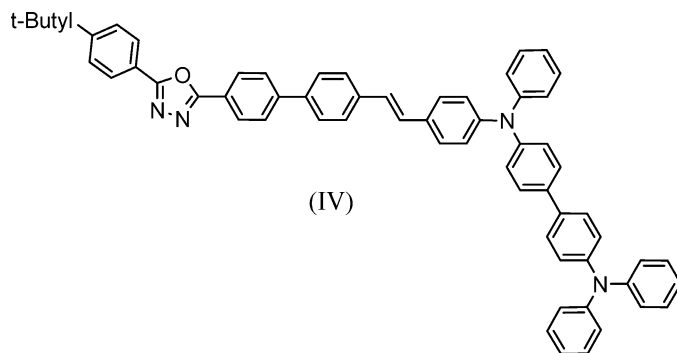
1. This is an example of the Ullman coupling reaction. Other polyaromatic coupling reactions are provided (1).
2. Polyaromatics of the current invention were characterized as horizontal, (I), and vertical, (II), by the author as illustrated below.



3. Electroluminescence devices derived from aniline trimers, (III), and phenylenediamine derivatives have also been prepared and are described (2), (3).



4. The preparation of heteroaromatic olefinic electroluminescing derivatives is described (3) and illustrated, (IV).

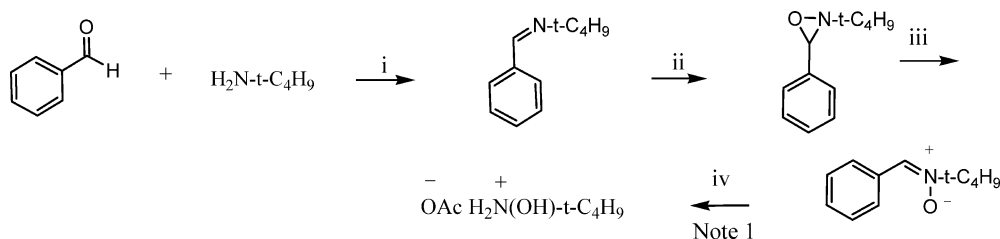


References

1. H. Brockman *et al*, US Patent 2,707,704 (May 3, 1955)
2. T. Sakai *et al*, US Patent 6,437,373 (April 20, 2002)
3. T. Inoue *et al*, US Patent 6,344,283 (February 5, 2002)
4. H. Higashi *et al*, US Patent 6,406,804 (June 18, 2002)

- Patent:** Process for Preparing N-Substituted Hydroxylamines and Salts Thereof
M. Dockner *et al*, US Patent 6,559,340 (May 6, 2002)
- Assignee:** Bayer Aktiengesellschaft
- Utility:** Improved Method for Preparing N-Substituted Hydroxylamines and Derivatives

Reaction



- i- Toluene
 ii- m-Chloroperbenzoic acid, toluene, ethyl alcohol
 iii- Heat 130°C 13 hours
 iv- Sulfuric acid, toluene, acetic acid

Experimental

1. N-Benzylidene-t-butylamine

Benzaldehyde (0.62 mol), t-butylamine (1.1 eq), and toluene (350 g) were refluxed using a Dean-Stark trap at 130°C for 7 hours. Gas chromatography indicated a 99.7% conversion. ¹H-NMR data supplied.

2. 2-t-Butyl-3-phenyloxaziridine

To the product from Step 1 in toluene was added Na₂CO₃ (0.62 mol) dissolved in 400 ml water, m-chloroperbenzoic acid (0.65 mol) dissolved in toluene (300 g) and ethyl alcohol (150 g), and the mixture cooled to 10°C. The temperature was slowly increased to 20°C over 30 minutes. Gas chromatography indicated the reaction was completed within 30 minutes. ¹H-NMR data supplied.

3. N-t-Butylphenylnitronium

The product from Step 2 was heated to 130°C for 13 hours, cooled to 20°C, filtered, concentrated, and 93.9 g product isolated. MS and ¹H-NMR data supplied.

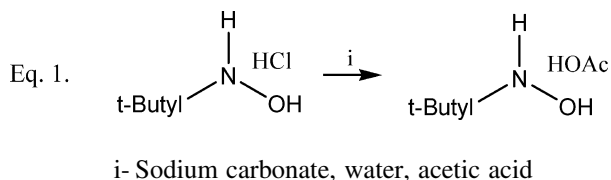
4. N-t-Butylhydroxylammonium acetate

The product from Step 3 (0.25 mol) was dissolved in 134 g toluene, 97% sulfuric acid (0.27 mol) diluted with 134 ml water added, stirred 2 hours at 50°C, and then cooled to

20°C. The organic phase was discarded and HOAc (1 eq) and 45% aqueous NaOH added until the pH was 5.5. The product was extracted with EtOAc, dried, concentrated, and a pale yellow solid isolated in 70% yield with a purity of 99.7%, mp = 67.7°C, bp = 72°C at 20 mbar, neutral pH = 5.5.

Notes

1. An alternative method for preparing N-t-butylhydroxylammonium acetate was also provided by the author as illustrated in Eq. 1:



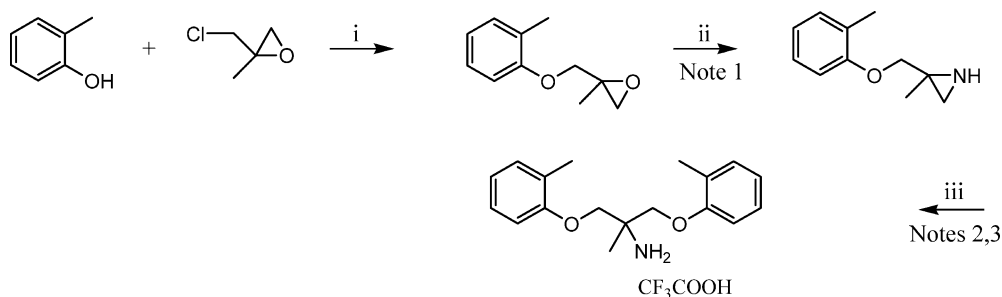
2. Other N-substituted hydroxylamine salts have been prepared through acid hydrolysis of oxaziridines and are discussed (1).

Reference

1. J. Blixt, US Patent 6,512,143 (January 28, 2003)
2. A.J.J. Paine, J. Am. Chem. Soc., 109, 1496 (1987)

Patent: Sodium Channel Modulators
S.-K. Choi *et al*, US Patent 6,646,012 (November 11, 2003)
Assignee: Theravance, Inc.
Utility: Treatment of Neuropathic Pain

Reaction



- i- Sodium hydroxide, water
- ii- Sodium azide, 2-ethoxyethanol, acetonitrile, triphenylphosphine
- iii- 2-Chlorophenol, borontrifluoride etherate, toluene

Experimental

1. 2-(2-Methylphenoxy)methylether-2-methyloxirane

To o-cresol (0.14 mol) dissolved in 200 ml water containing NaOH (0.125 mol) was added 2-chloromethyl-2-methyloxirane (0.188 mol) and the mixture stirred for 1 hour in an ice bath. Thereafter the mixture stirred 24 hours at ambient temperature and the mixture extracted with 300 ml diethyl ether/hexane, 2:5. The extract was washed twice with 150 ml 1 M NaOH, dried, concentrated, purified by chromatography with hexane/EtOAc with a gradient of 8:1 to 5:1, and the product isolated as an oil. ¹H-MNR data supplied.

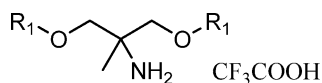
2. 2-(2-Methylphenoxy)methylether-2-methylaziridine

The product from Step 1 (0.063 mol) was dissolved in 130 ml cold 2-ethoxyethanol to which was added 30 ml water containing sodium azide (0.127 mol) and (NH₄)₂SO₄ (0.076 mol). The mixture stirred in an ice bath 2 hours and then 36 hours at ambient temperature. The product was extracted twice with 300 ml diethyl ether, washed with brine, dried, and evaporated to dryness giving a colorless oil. The oil was dissolved in 100 ml acetonitrile to which was slowly added triphenylphosphine (0.053 mol) dissolved in 100 ml acetonitrile. Thereafter the mixture stirred 3 hours at ambient temperature, heated to 90°C 6 hours, cooled, and concentrated in vacuo yielding a white semi-solid. The product was purified by chromatography on silica gel using EtOAc/hexane, 1:1, to 5% methyl alcohol in EtOAc/hexane, 1:1, and isolated as an oil. ¹H-MNR data supplied.

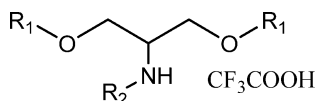
3. Bis-1,3-(2-methylphenoxy)-2-methyl-2-aminopropane

The product from Step 2 (0.2 mmol), 2-chlorophenol (0.2 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.2 mmol) were dissolved in 0.5 ml toluene and heated to 90°C for 24 hours. After cooling to ambient temperature it was treated with 1 ml 5% trifluoroacetic acid dissolved in 50% aqueous acetonitrile. The product was purified by preparative reverse HPLC and isolated as a TFA salt. Mass spectra data supplied.

Derivatives



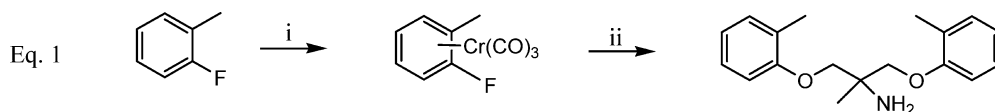
R_1	MS(M+1)
2-Isopropylphenyl	314
2,6-Dichlorophenyl	340
6-Hydroxyquinoline	322
2-Cyanophenyl	296
4-Chloro-2,6-dimethylphenyl	334



R_1	R_2	MS(M+1)
2-Methylphenyl	N-2-Ethyl-N-methyl-pyrrolidine	383
2-Chloro-6-methylphenyl	N-2-Ethyl-N-methyl-pyrrolidine	451
2,6-Dimethylphenyl	N-Ethylmorpholine	413
2-Methylphenyl	4-Aminomethylpiperidine	368

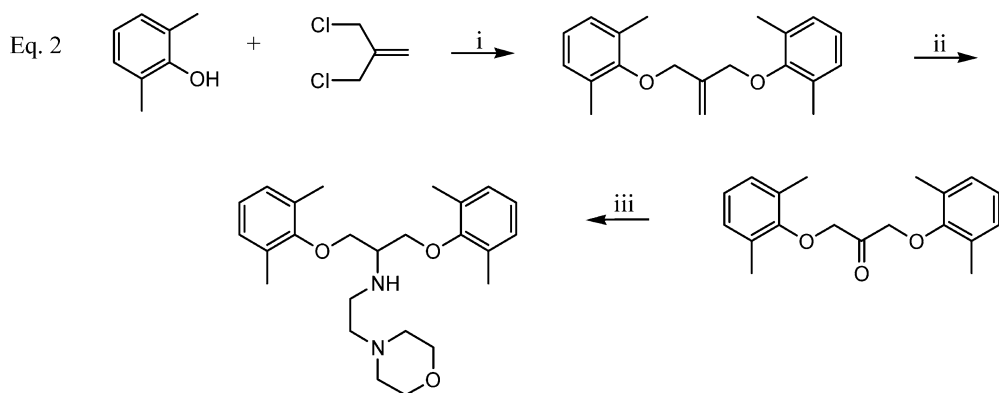
Notes

- ^1H -NMR data of azido alcohols were supplied by the author.
- An alternative method for preparing the product of the current invention was also provided by the author and illustrated in Eq. 1:



- i- THF, chromium hexacarbonyl
 ii- Sodium hydride, THF, 2-amino-2-methyl-1,3-propanediol

3. A second method for preparing N-alkylated derivatives of the current invention was also provided by the author as illustrated in Eq. 2:



- i- Acetone, potassium carbonate
 ii- Dioxane, water, sodium periodate, osmium tetroxide, potassium t-butoxide
 iii- N-(2-Aminoethyl)-morpholine, toluene, sodium cyanoborohydride

4. Structural and stereoisomeric derivatives of the current invention have been prepared and are described (1,2). The preparation of diamine analogues is provided (3).

References

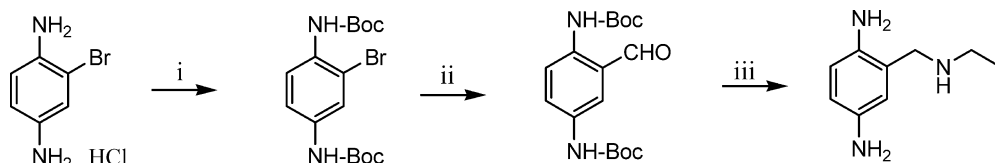
1. A.L. Zeitlin, US Patent 5,985,933 (November 16, 1999); H. Koppe *et al*, US Patent 3,954,872 (May 4, 1976)
2. J. Berger *et al*, US Patent 5,688,830 (November 18, 1997)
3. J.-M. Ferland *et al*, US Patent 4,140,779 (February 20, 1979)

Patent: Substituted 2-Aminoalkyl 1,4-Diaminobenzene Compounds and Oxidation Dye Precursor Containing the Same
L. Chassot *et al*, US 6,436,152 (August 20, 2002)

Assignee: L'Oreal

Utility: Hair Coloring Agent Component

Reaction



i- Di-t-butyl dicarbonate, sodium hydroxide,
trifluoromethyltoluene

ii- Methyl lithium, t-butyl lithium, N,N-dimethylformamide

iii- Ethylamine, CH_2Cl_2 , acetic acid,
sodium triacetoxy-borohydride

1. 2,5-Bis-t-butyloxycarbonylamino bromobenzene

Bromo-p-phenylenediamine hydrochloride (0.07 mol) and di-t-butyl-dicarbonate (0.15 mol) were dissolved in 250 ml apiece of 2 M NaOH and trifluoromethyltoluene, heated to 45°C, and stirred 3 days. Thereafter, additional di-t-butyl dicarbonate (0.14 mol) was added, the layers separated, and the aqueous phase extracted with CH_2Cl_2 . The combined extracts were evaporated to dryness and the residue mixed with 200 ml hexane. The precipitate was filtered, washed, and the product isolated in 82% yield, mp = 130°C.

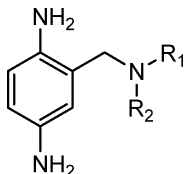
2. 2,5-Bis-t-butyloxycarbonylamino benzaldehyde

The product from Step1 (0.01 mol) was dissolved in 100 ml THF, 17 ml 1.6 M methyl lithium (0.03 mol) added, cooled to -20°C, and 7 ml 1 M t-butyl lithium (0.01 mol) gradually added. Dimethyl formamide (0.02 mol) was added and the mixture stirred 1 hour. After slowly warming to ambient temperature the mixture was hydrolyzed with water, poured into diethyl ether, and concentrated. The material was purified by chromatography on silica gel with petroleum ether/EtOAc, 9:1, and the product isolated.

3. (N-Ethyl)aminomethyl-1,4-diaminobenzene

The product from Step 2 (0.0001 mol) and ethylamine (0.00015 mol) were dissolved in CH_2Cl_2 , 0.1 ml 1 M HOAc in CH_2Cl_2 and $\text{NaBH}(\text{OAc})_3$ (0.0003 mol) added, and the mixture stirred 5 hours at ambient temperature. Thereafter, the mixture was poured into 10 ml EtOAc, neutralized with NaHCO_3 , dried, concentrated, and purified as in Step 2.

Derivatives



R₁	R₂	Yield (%)
Hydrogen	Ethyl	91
Methyl	Methoxide	86
Hydrogen	2-Succinimic amic acid	100
Hydrogen	Pyrrolidin-2-carboxylic Acid	72
Hydrogen	2-(4-Chloro-1-phenol)	67

Notes

1. 2-(N-Alkylaminomethylations) have also been used on 4-aminohydroxybenzene (1) and are discussed.
2. N-(Tetrahydrofuranmethylation) derivatives of p-phenylenediamine have been prepared and are described (2).

References

1. T. Clausen *et al*, US Patent 4,797,130 (January 10, 1989)
2. A. Bugaut *et al*, US Patent 4,149,848 (April 17, 1979)

Aminoacids

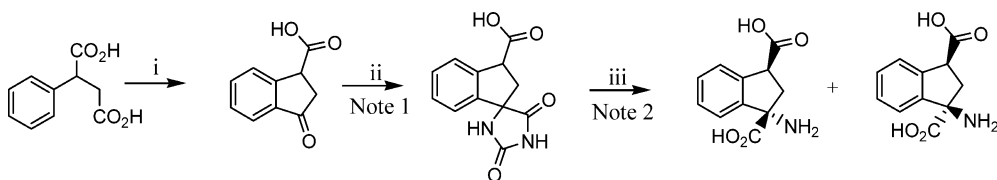
Patent: Aminoindanes

K. Curry, US Patent 6,699,909 (March 2, 2004)

Assignee: Prescient NeuroPharma Inc.

Utility: Treatment of Chronic Neurodegenerative Diseases

Reaction



i- Thionyl chloride, aluminum chloride, nitrobenzene

ii- Potassium cyanide, ammonium carbonate, water

iii- Sodium hydroxide, hydrochloric acid, propylene oxide

Experimental

1. 3-Carboxy-1-indanone

Phenylsuccinic acid (4.0 g) and 4 ml thionyl chloride were refluxed 30 minutes, 8 ml nitrobenzene and aluminum chloride (4 g) added, and stirred 2 hours at 85°C. The mixture was poured into 125 ml water, nitrobenzene removed by steam distillation, and the product isolated after re-crystallization in water in 80% yield. ¹H-NMR data supplied.

2. cis/trans-3-Carboxy-1-indane-5,5'-hydantoin

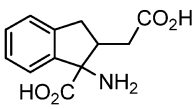
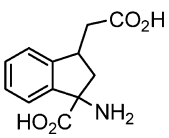
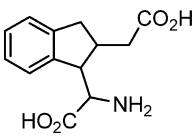
The product from Step 1 (1.0 mmol) was dissolved in 20 ml water in a sealed tube containing KCN (1.0 mmol) and (NH₄)₂CO₃ (2.0 mmol) then heated to 90–100°C 16 hours.

The dark solution was cooled, acidified with 6 M HCl, concentrated, extracted with ethyl alcohol, filtered, and used in Step 3 without further purification.

3. *cis/trans*-1-Aminoindane-1,3-dicarboxylic acid

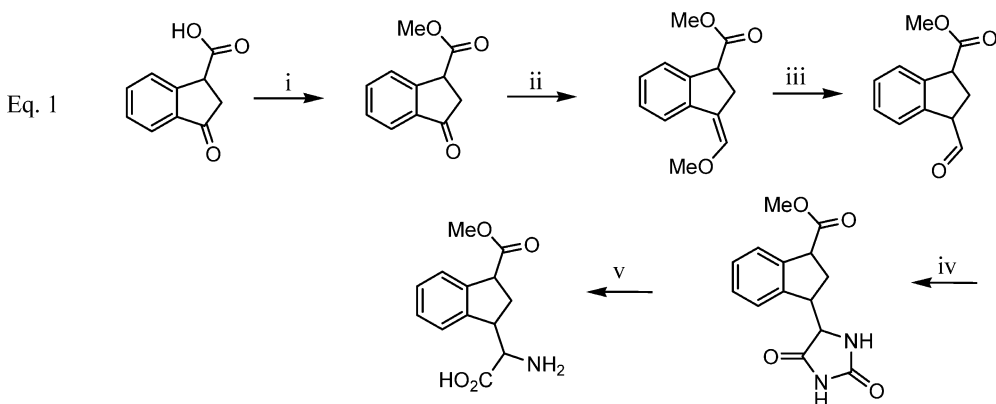
The product from Step 2 was refluxed in 45 ml 2 M NaOH 16 hours, cooled, acidified with 6 M HCl, and extracted with ethyl alcohol. The mixture was purified by chromatography on Spectrum 1X4 anion exchange resin with dilute HOAc. The stereoisomers were isolated and re-crystallized in ethyl alcohol/water. ¹H-NMR data for each isomer supplied.

Derivatives

<u>Derivative</u>	<u>Yield (%)</u>
	90
	77
	14

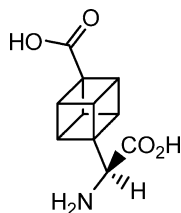
Notes

- Other examples of the Bucherer reaction used in preparing aminoacid hydantoins are provided (1).
- Aminoindolanes of the current invention having extended carbon chain lengths at the 2 position were also prepared by the author as illustrated in Eq. 1:



- i- Methyl alcohol, dicyclohexylcarbodiimide
- ii- Sodium azide, tetramethylsilane, triphenylethermethyl chloromethyl ether
- iii- 1-Trimethylsilylimidazole, pyridine
- iv- Potassium cyanide, ammonium carbonate, water
- v- Sodium hydroxide, benzylchloroformate, palladium on carbon, hydrogen

3. In subsequent investigations (2,3) cubane derivatives, (I), of the current invention were prepared and are described.



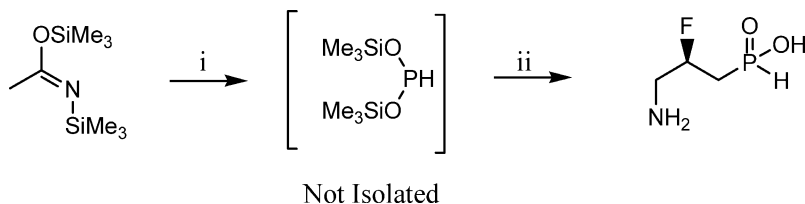
(I)

References

1. G. Zoller *et al*, US Patent 5,939,556 (August 17, 1999); J.H. Lee *et al*, US Patent 6,384,061 (May 7, 2002); H.U. Stilz *et al*, US Patent 6,514,952 (February 4, 2003)
2. H. Pajouhesh *et al*, US Patent 6,784,202 (August 31, 2004)
3. R. Pellicciari *et al*, Bioorg. Med. Chem.Lett. 8, 1569 (1998)

Patent: Aminopropylphosphinic Acids
T. Elebring *et al*, US Patent 6,576,626 (June 10, 2003)
Assignee: AstraZeneca AB
Utility: Treatment of Upper Gastrointestinal Tract Disorders

Reaction



i- Ammonium hypophosphite, CH_2Cl_2

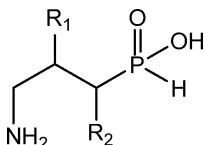
ii- t-Butyl(2S)-2-fluoro-3-iodopropylcarbamate, CH_2Cl_2 ,
ammonium hydroxide, hydrogen chloride, methyl alcohol

Experimental

1. (2S)-(3-Amino-2-fluoropropyl)phosphinic acid

To ammonium hypophosphite (0.70 mol) was added N,O-bis-(trimethylsilyl)acetamide (0.71 mol) at such a rate that the temperature remained between 35–40°C. The mixture was stirred 45 minutes, 150 ml CH_2Cl_2 added, and stirred an additional 45 minutes. At ambient temperature, t-butyl(2S)-2-fluoro-3-iodopropylcarbamate (0.14 mol) dissolved in 300 ml CH_2Cl_2 was added, the mixture stirred, then cooled to 0°C. The reaction was quenched with 150 ml methyl alcohol and 60 ml water, concentrated, and the residue pH adjusted to 8 using 50 ml NH_4OH . The residue was dissolved in 400 ml CH_2Cl_2 and 250 ml methyl alcohol, the solids filtered, and the filtrate concentrated. The residue was triturated with 400 ml CH_2Cl_2 /methyl alcohol/ NH_4OH , 80:20:1, filtered, concentrated, and dissolved in 400 ml methyl alcohol. Thereafter, 600 ml EtOAc saturated with HCl gas was added, the mixture stirred 3 hours, filtered, and concentrated. The mixture was passed through a Dowex.RTM. 50WX8-200 mesh H^+ form column using methyl alcohol/water, 1:1, and product eluted with NH_4OH /methyl alcohol, 1:3. The mixture was further purified by chromatography using CH_2Cl_2 /methyl alcohol/ NH_4OH , 6:3:1, and the product isolated in 17% yield as a white solid. ^1H -NMR data supplied.

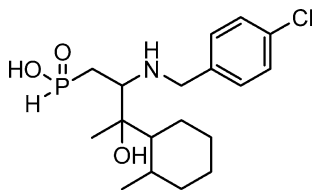
Derivatives



R ₁	R ₂	Yield (%)
Hydrogen	Hydroxyl	59
Hydrogen	Oxypropyl	73
Fluorine	Hydrogen	34
Hydroxyl	Fluorine	56

Notes

1. Aminopropylphosphinic acids have also been prepared by reacting alkylphosphonite derivatives with propylene oxide followed by amination (1).
2. The preparation of 3-methyl-3-hydroxy-3-(2-methylcyclohexyl)-2-(4-chlorobenzylamine)-propyl phosphinic acid, (I), is described (2).



(I)

3. 2-Oximinoalkylphosphonic acid esters have also been prepared (3).

References

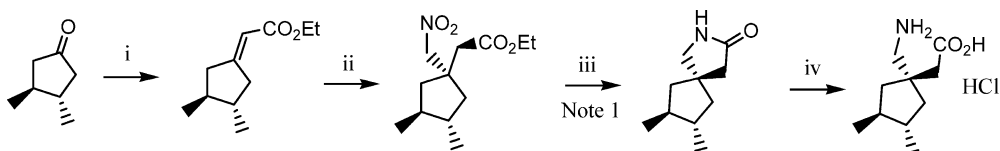
1. R.G. Hall *et al*, US Patent 5,567,840 (October 22, 1996) and US Patent 5,461,040 (October 24, 1995)
2. C. Marescavy *et al*, US Patent 5,407,922 (April 18, 1995)
3. D.S. Soriano *et al*, US 4,507,251 (March 26, 1985)

Patent: Cyclic Aminoacids and Derivatives Thereof Useful as Pharmaceutical Agents
J.S. Bryans *et al*, US Patent 6,635,673 (October 21, 2003)

Assignee: Warner-Lambert Company

Utility: Treatment of Neuropathological Diseases

Reaction



i- Triethylphosphonoacetate, sodium hydride, THF
 ii- Nitromethane, tetrabutylammonium fluoride, THF
 iii- Raney nickel, methyl alcohol, hydrogen
 iv- Hydrochloric acid, dioxane

Experimental

1. trans-3,4-Dimethyl-cyclopentylidene-acetic acid, ethyl ester

NaH, 60% dispersion in oil (18.25 mmol) was suspended in 50 ml THF and triethylphosphonoacetate (19.30 mmol) added. It was stirred 15 minutes at 0°C and trans-3,4 dimethyl-cyclopentyl ketone (17.54 mmol) in 10 ml THF added. The mixture was warmed to ambient temperature, stirred 2 hours, then partitioned between 200 ml diethylether and 150 ml water. The organic phase was dried, concentrated, the residue purified by flash chromatography using silica gel with EtOAc/heptane, 1:9, and the product isolated in 94% yield. MS and ¹H-NMR data supplied.

2. trans-(3,4-Dimethyl-1-nitromethyl-cyclopentyl)-acetic acid, ethyl ester

The product from Step 1 (16.2 mmol) was dissolved in 10 ml THF, added to nitromethane (35.2 mmol) and 22 ml 1 M Bu₄NF in THF, and stirred at 70°C 6 hours. The mixture was cooled to ambient temperature and extracted with 50 ml EtOAc. The extract was treated with 30 ml HCl, 50 ml brine, and the product isolated as in Step 1 in 29% yield. IR, MS, and ¹H-NMR data supplied.

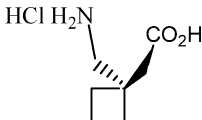
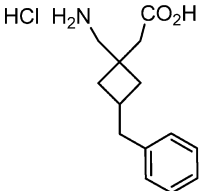
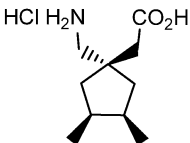
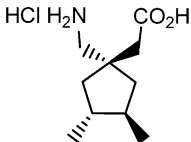
3. (+/-)-trans-7,8-Dimethyl-spiro[4.4]-1-aza-nonan-2-one

The product from Step 2 (4.7 mmol) was dissolved in 50 ml methyl alcohol and hydrogenated using Raney nickel under 40 psi hydrogen at 30°C for 5 hours. The product was isolated by filtration through celite in 95% yield. IR, MS, and ¹H-NMR data supplied.

4. (+/-)-trans-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid hydrochloride

The product from Step 3 (4.40 mmol) was dissolved in 5 ml dioxane, 15 ml 6 M HCl added, and the mixture refluxed 4 hours. Thereafter, it was diluted with 20 ml water, washed 3 times with 30 ml CH_2Cl_2 , and concentrated. The residue was triturated with EtOAc and the product isolated in 69% yield. MS, and ^1H -NMR data supplied.

Derivatives

<u>Aminoacid</u>	<u>Name</u>	<u>MS</u>
	(1-Aminomethyl-cyclobutyl)-acetic acid · HCl	144
	(cis/trans)-(1-Aminomethyl-benzyl)-acetic acid · HCl	234
	(1 α , 3 β , 4 β)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid · HCl	186
	(3R,4R)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid · HCl	186

Notes

1. The preparation of spiro-lactone intermediates of the current invention is described (1)
2. Alternative methods for preparing cyclopentane- β -amino acids are discussed (2).
3. Cyclohexyl- β -amino acids have been prepared by the hydrogenation of 1-cyanocyclohexanecarboxylic acid and are described (3).

References

1. J. Doyle *et al*, J. Org. Chem., 60, 3035 (1995)
2. J. Mittendorf *et al*, US Patent 5,631,291 (May 20, 1997)
3. R.A. Jennings *et al*, US Patent 5,362,883 (November 8, 1994)

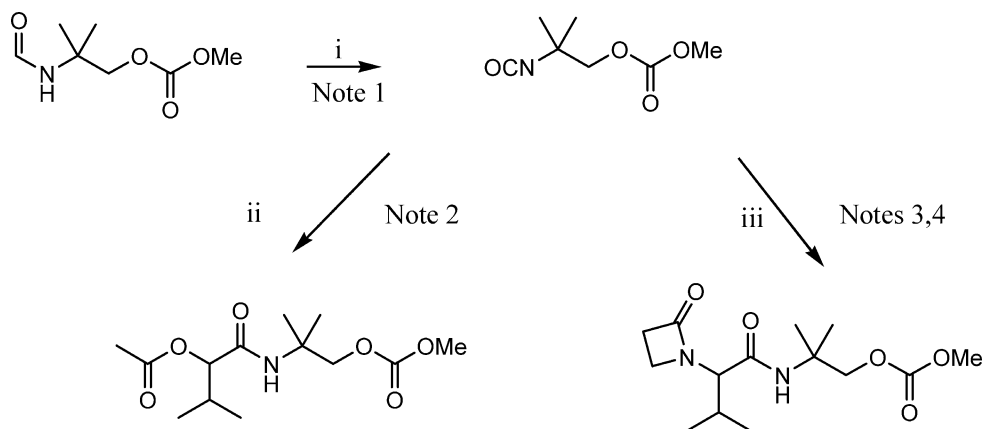
Patent: Isocyanoalkyl, Carbonic Acid Derivatives, Their Conversion into Secondary Amidoalkyl Carbonic Acid Derivatives by Isocyanide Multicomponent Reactions, as well as these Secondary Amidoalkyl Carbonic Acid Derivatives

I. Ugi *et al*, US Patent 6,147,240 (November 14, 2000)

Assignee: Ugichem GmbH

Utility: Amino Acid Precursors

Reaction



i- CH_2Cl_2 , triphosgene, triethylamine

ii- Isobutyraldehyde, acetic acid, THF

iii- Isobutyraldehyde, β -alanine, trifluoroethyl alcohol

Experimental

1. (2-Isocyano-2-methyl)-propyl-1-carbonic acid methyl ester

(2-Formamido-2-methyl)-propyl-1-carbonic acid methyl (0.1 mol) and triethylamine (0.3 mol) were dissolved in CH_2Cl_2 , cooled to -20°C , and triphosgene (0.033 mol) introduced in portions. Thereafter the reaction was stirred 2 hours at 0°C then quenched by pouring into 10% NaHCO_3 ice water solution. The mixture was extracted 3 times with CH_2Cl_2 , the product purified by chromatography using alumina, and isolated in 80% yield.

2. 2-(2-Aceto-3-methyl-butylamido)-2-methyl-propyl-1-carbonic acid, methyl ester

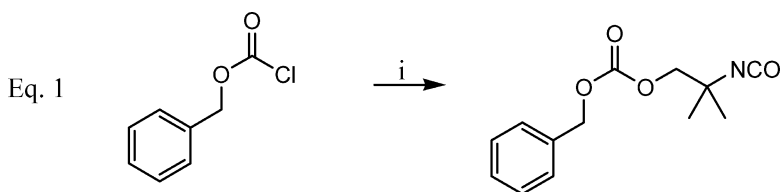
The product from Step 1 (10 mmol) was dissolved in 100 ml THF to which was added 10 mmol apiece of HOAc and isobutyraldehyde. The mixture was kept at 25°C and monitored until the reaction was completed. Thereafter the solvent was removed, the residue dissolved in CH_2Cl_2 , and the product isolated using the procedure described in Step 1.

3. 2-(2-N-azidiny-2-one)-3-methyl-propyl-1-carbonic acid, methyl ester

Ten millimoles apiece of isobutyraldehyde, β -alanine and trifluoroethyl alcohol along with molecular sieves were reacted for 24 hours at 25°C. Thereafter, the product from Step 1 (10 mmol) was added, and the mixture stirred and monitored until the reaction was complete. Thereafter, it was filtered through celite and the product isolated according to the procedure in Step 1.

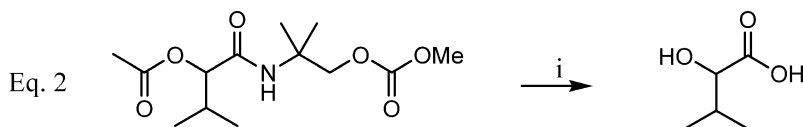
Notes

1. An alternative method for preparing isocyano carboxylic esters using methyl isocyanate, acetone, and chloroformic acid benzyl ester was also described by the author and illustrated in Eq. 1:



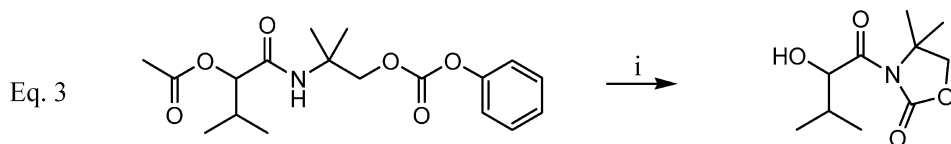
i- Acetone, methyl isocyanide

2. When treated with sodium hydroxide dissolved in THF the product of Step 1 was converted into 2-propyl- α -hydroxy-acetic acid as is illustrated in Eq. 2:



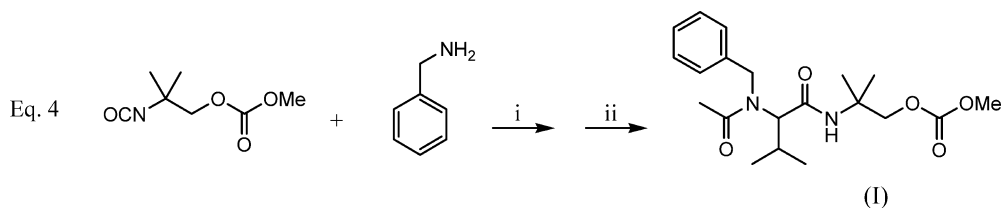
i- THF, sodium hydroxide

In addition, when the Step 2 phenyl ester was hydrolyzed with potassium t-butoxide, the corresponding oxazolidinone was obtained as illustrated in Eq. 3:



i- THF, potassium t-butoxide

3. By reacting the product of Step 1 with benzyl amine and then introducing co-reagents, the product, 2-(N-benzyl-N-acyl-3-methyl-butylamido)-2-methyl-propyl-1-carbonic acid, methyl ester, (I), was also prepared by the author as illustrated in Eq. 4:



i- Acetic acid, methyl alcohol
ii- Isobutyraldehyde

4. Other Ugi peptide preparations using an amino acid, aldehyde, and isocyanate (1) or isocyanide (2) are described.
5. Additional isocyanoalkylcarbonic acid derivatives of the current investigation were prepared by the author in a subsequent investigation and are discussed (3).

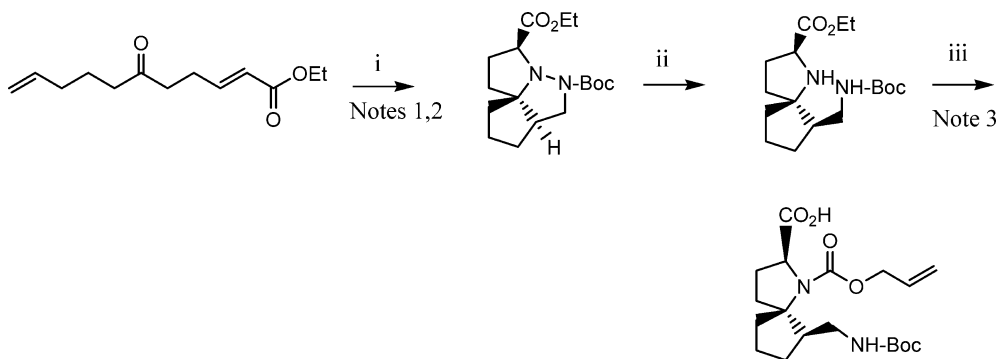
References

1. I. Ugi, *Angew. Chem.*, 89, 267 (1999); T. Yamada, *Chem. Lett.*, 723 (1987); S. Marcaccini, *Synthesis*, 765 (1994)
2. I. Ugi, *et al*, *Tetrahedron*, 52, 35, 11657 (1996).
3. I. Ugi *et al*, US Patent 6,509,463 (January 21, 2003)

Patent: Spirodiamino Acid Scaffold for Combinatorial Synthesis
R.E. Dolle *et al*, US Patent 6,175,020 (January 16, 2001)
Assignee: Pharmacopeia, Inc.
Utility: Template for Synthetic Receptor and Enzyme Intermediates

Reaction

Phase I: Azaspirononane Synthesis



- i- t-Butylcarbazate, diethyl ether
 ii- Trifluoroacetic acid, CH_2Cl_2 , platinum(IV)oxide, hydrogen,
 N-t-butylcarboxy anhydride
 iii- Disopropylethylamine, allylchloroformate

Experimental

Azaspirononane Intermediate

1. 1-N-Boc-3-Ethoxycarbonyl-1,2-diazatricyclodecane

A solution of ethyl 2,10-di-ene-6-keto-undecanoic acid (3.30 mmol) and t-butylcarbazate in 10 ml diethyl ether was stirred at ambient temperature overnight and the resulting white precipitate isolated by filtration in 97% yield, mp = 103–105°C. $^1\text{H-NMR}$, IR, and elemental analysis data supplied.

2. 2-Ethoxycarbonyl-8-N-Boc-aminomethylene-1-azaspirononane

The product from Step 1 (34.21 mmol) was dissolved in 25% TFA in CH_2Cl_2 , stirred for 1 hour, concentrated, and the residual dissolved in 100 ml 1 M HCl in methyl alcohol. To this was added PtO_2 (4.41 mmol) and the mixture hydrogenated at 80 psi overnight.

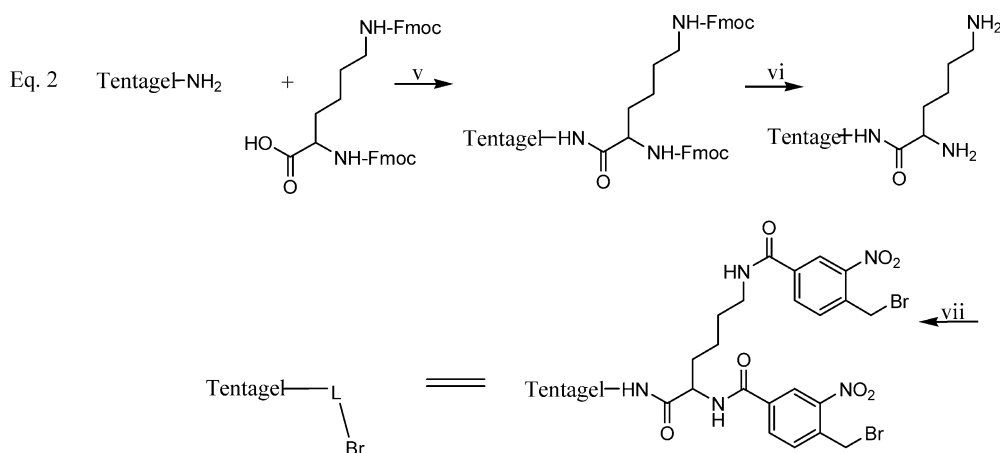
The resulting oil was dissolved in 250 ml CH_2Cl_2 containing 9.5 ml TEA and Boc anhydride (51.32 mmol) and stirred overnight at ambient temperature. The mixture was concentrated, purified by column chromatography with hexanes/EtOAc, 1:1, to remove

excess Boc reagent followed by CH_2Cl_2 /methyl alcohol/ NH_4OH , 10:1:0.1, and the product isolated in 87% yield. MS data supplied.

3. 1-Allylcarbamoyl-2-hydroxycarbonyl-8-N-Boc-aminomethylene-1-azaspiroonane

The product from Step 2 (39.18 mmol) was dissolved in 200 ml CH_2Cl_2 , treated with 20.6 ml DIEA and allylchloroformate (78.22 mmol), and stirred overnight. The solvent was removed, the residual treated with 0.5 M citric acid, and extracted 3 times with 50 ml CH_2Cl_2 . The product was purified by chromatography with hexanes/EtOAc, 4:1, and isolated in 77% yield. MS data supplied.

Phase II : Preparation of Tentegel Polymer Anchor



v- Bis-Fmoc-lysine, hydroxybenzotriazole,
diisopropylcarbodiimide

vi- Piperidine, N,N-dimethyl formamide, DMF,

vii- 4-bromomethyl-3-nitro benzoic acid,
hydroxybenzotriazole, diisopropylcarbodiimide

5. Tentegel-graft-(bis-2,6-Fmoc-lysine)amide

Tentegel (1.2 g, 0.32 mmol/g, 0.384 mmol) was suspended in a solution of bis-Fmoc lysine (1.12 mmol) and hydroxybenzotriazole (1.12 mmol) and diisopropylcarbodiimide (2.2 mmol) added. The suspension was shaken overnight, drained, washed with DMF, methyl alcohol and CH_2Cl_2 and the product isolated.

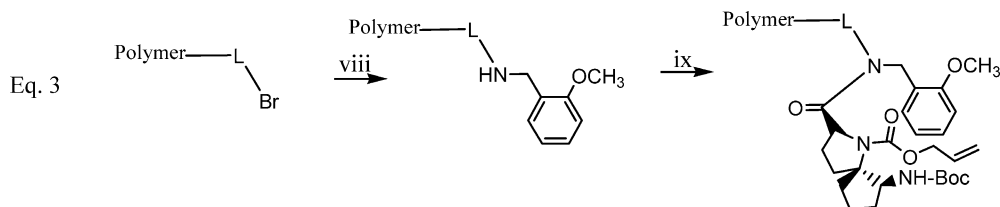
6. Tentegel-graft-lysine amide

The resin from Step 5 (1.2 g) was dissolved in piperidine/DMF, 1:1, shaken for 90 minutes, drained, and washed as in Step 5 and the product isolated.

7. Tentagel-graft-(2,6-di-benzylbromo-3-nitro-benzamide)lysine

The product from Step 6 was suspended in 4 ml DMF, treated with 4-bromomethyl-3-nitro benzoic acid (2.2 mmol), hydroxybenzotriazole (2.3 mmol) and 1 ml diisopropylcarbodiimide dissolved in 6 ml DMF. The suspension was shaken overnight, drained, washed as in Step 5, and the product isolated.

Phase III: Azaspiroonane Attachment to Scaffold



viii- 2-Methoxybenzylamine, THF

xi- 1-Allylcarbamoyl-2-hydroxycarbonyl-8-N-Boc-aminomethylene-1-azaspiroonane, 1-hydroxybenzotriazole, diisopropylcarbodiimide, N,N-dimethyl-formamide

8. Tentagel-graft-N-(2-methoxybenzyl)amine

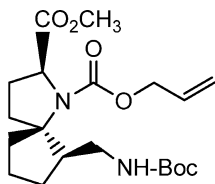
A suspension of the resin from Step 7 (1 g) in 10 ml THF was mixed with 2-methoxybenzylamine (3 mmol) and shaken overnight. It was drained and washed as in Step 5 filtered, dried, and the product isolated.

9. Tentagel-graft-N-[(2-methoxybenzyl)-N-(1-allylcarbamoyl-8-N-Boc-aminomethylene-1-azaspiroonane)]-2-amide

The product from Step 8 was suspended in 5 ml DMF and treated with the product from Step 3 (2.2 mmol), hydroxybenzotriazole (2.3 mmol) and 1 ml diisopropylcarbodiimide dissolved in 6 ml DMF. The suspension was shaken overnight, drained, washed as in Step 7, and the product isolated.

Notes

1. The product of Step 1 using vinyl 2,10-di-ene-6-keto-undecanoic acid was previously prepared by the author and is described (1).
2. Diazatricyclodecane was prepared by the author by the reaction of hydrazone and ethyl 2,10-undecadienoic and is described.
3. 1-Allylcarbamoyl-2-methoxycarbonyl-8-N-Boc-aminomethylene-1-azaspiroonane, (I), was also provided by the author and is described below:



(I)

The product from Step 3 (30.40 mmol) was dissolved in 50 ml 1 M NaOH in methyl alcohol, stirred 5 hours, and concentrated. The residue was treated with 100 ml aqueous NaHCO_3 , washed with CH_2Cl_2 , the pH acidified with citric acid, and the mixture extracted with 50 ml EtOAc. The product was purified using column chromatography with hexanes/EtOAc, re-crystallized in the eluting solvent, and isolated in 80% yield. ^1H -NMR and MS data supplied.

4. In subsequent investigations by the author, combinatorial hydroxy-amino acid amide (2), amide alcohol (3), and ester amide (4) libraries were prepared.

Reference

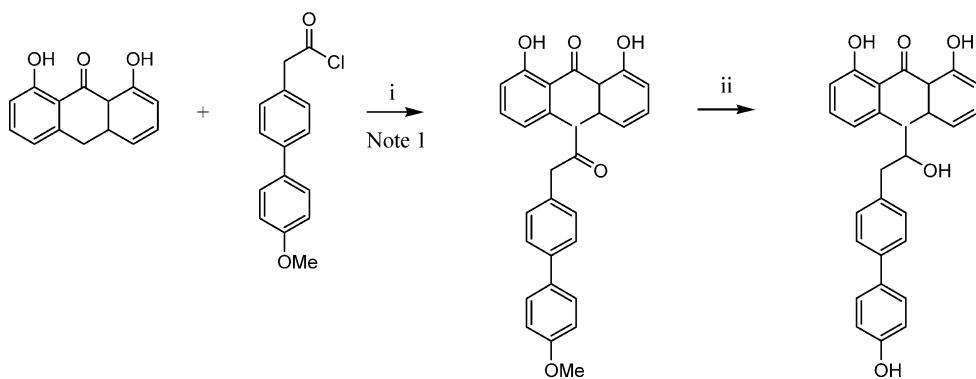
1. K.S. Armstrong, J. Chem. Soc., Chem. Comm., 1327 (1987)
2. R.E. Dolle, III, *etal*, US Patent 6,218,551 (April 17, 2001)
3. R.E. Dolle, III, *etal*, US Patent 6,265,228 (July 24, 2001)
4. R.E. Dolle, III, *etal*, US Patent 6,255,120 (July 3, 2001)

Anthracenones

Patent: 10-Substituted 1,8-Dihydroxy-9(10H) Anthracenone Pharmaceuticals
K. Muller *et al*, US Patent 5,952,390 (September 14, 1999)
Assignee: Teva Pharmaceutical Industries Ltd.
Utility: Anti-Inflammatory Agents

Reaction

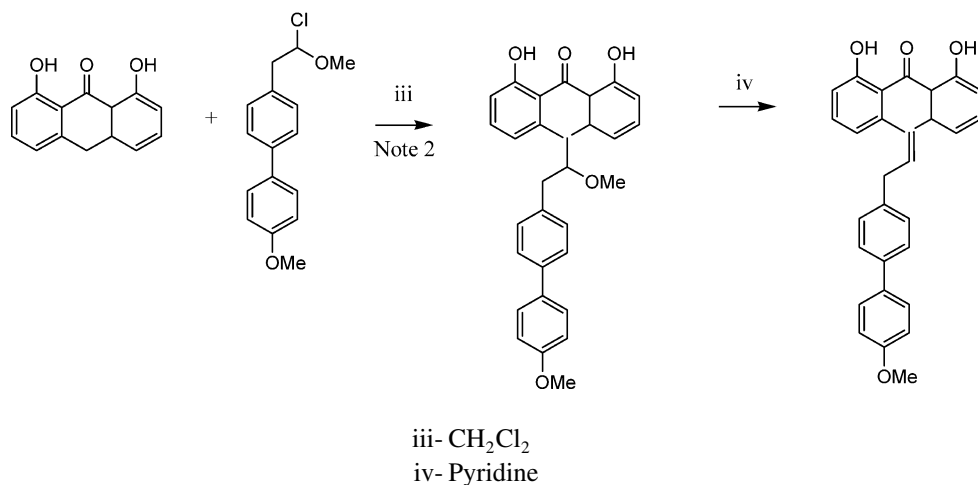
Modification 1



i- Pyridine, toluene, pyridine

ii- 10% palladium on carbon, THF, hydrogen

Modification 2



Experimental

(I) Modification-1

1. **1,8-Dihydroxy-10-[1-oxo-2-(4-(4'-methoxyphenyl)phenyl)ethyl)]-9(10H)-anthracenone**

To a solution of anthralin (5 mmol) dissolved in 80 ml toluene and 0.55 ml pyridine was added to 2-(4-(4'-methoxyphenyl)phenyl)acetyl chloride and the mixture heated to 80°C 3 hours, cooled, filtered, and concentrated. The product was purified by using CH_2Cl_2 . The purified fraction was concentrated and a small amount of hexane added to induce precipitation.

2. **1,8-Dihydroxy-10-[1-hydroxy-2-(4-(4'-methoxyphenyl)phenyl)-ethyl)]-9(10H)-anthracenone**

The product from Step 1 (1.11 mmol) was dissolved in 50 ml THF and hydrogenated over 10% palladium on carbon (150 mg) at ambient temperature and atmospheric pressure. The catalyst was removed by filtration, concentrated, and the product purified using CH_2Cl_2 /diethylether, 3:2. The purified fraction was concentrated and isolated as in Step 1.

(II) Modification-2

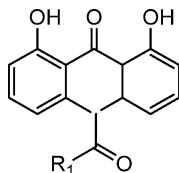
3. **1,8-Dihydroxy-10-[1-methoxy-2-(4-(4'-methoxyphenyl)phenyl)-ethyl)]-9(10H)-anthracenone**

To a solution of anthralin (4.4 mmol) dissolved in 50 ml CH_2Cl_2 was added drop-wise at 0°C a solution of 2-(4-(4'-methoxyphenyl)-phenyl)-1-chloro-1-methoxyethane (5.5 mmol) and the solution stirred 30 minutes. The mixture was thoroughly shaken with 2 M HCl and the organic phase washed with brine, dried, purified by chromatography using CH_2Cl_2 , and the product isolated as in Step 1.

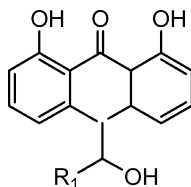
4. **1,8-Dihydroxy-10-[2-(4-(4'-methoxyphenyl)phenyl)ethylene)]-9(10H)-anthracenone**

A solution of the product from Step 3 (1.15 mmol) dissolved in 10 ml pyridine was refluxed 30 minutes and monitored using thin layer chromatography. The mixture was cooled, poured into 200 ml water acidified with 6 M HCl, and extracted 3 times using 20 ml CH₂Cl₂. The product was isolated as in Step 1.

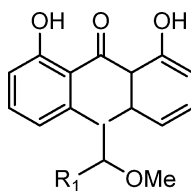
Derivatives



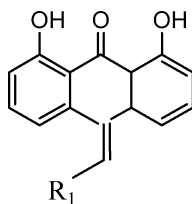
R ₁	Melting Point (°C)
3-Methoxy-cinnamoyl	225
4-Nitro-acetyl	209–211
3-(3,4,5-Trimethoxyphenyl)propinoyl	118–120



R ₁	Melting Point (°C)
3,4-Dihydrophenyl	180
3,4,5-Trihydrophenyl	200



R ₁	Melting Point (°C)
1-(Chloromethoxymethyl)-4-methylbenzene	137–138
1-(Chloromethoxypropyl)-4-methylbenzene	83–85



R₁	Melting Point (°C)
4-Methylphenyl	146-147
4-Methoxyphenyl	134-136
3-Phenylpropyl	84-86

Notes

1. The preparation of acid chlorides of Step 1 is described (1).
2. 2-Alkyl-1-chloro-1-methoxyethane derivatives used in Step 3 were prepared from the corresponding acetals (2).
3. The preparation of other 10-substituted anthralin derivatives including thiol and polyhydroxyalkyl-yl-N-carbamoylsuccinimides derivatives is provided (3).

References

1. C.R. Clark *et al*, J. Pharm. Sci., 76, 18-20 (1987)
2. J. Klein *et al*, J. Am. Chem. Soc., 79, 3452 (1957)
3. J.M. Bruce, US Patent 4,997,961 (March 5, 1991); B.S. Shroot *et al*, US Patent 4,826,991 (May 2, 1989); K.K. Mustakallio *et al*, US Patent 4,299,846 (November 10, 1981)

Aza and Diaza Bi- and Tricyclics

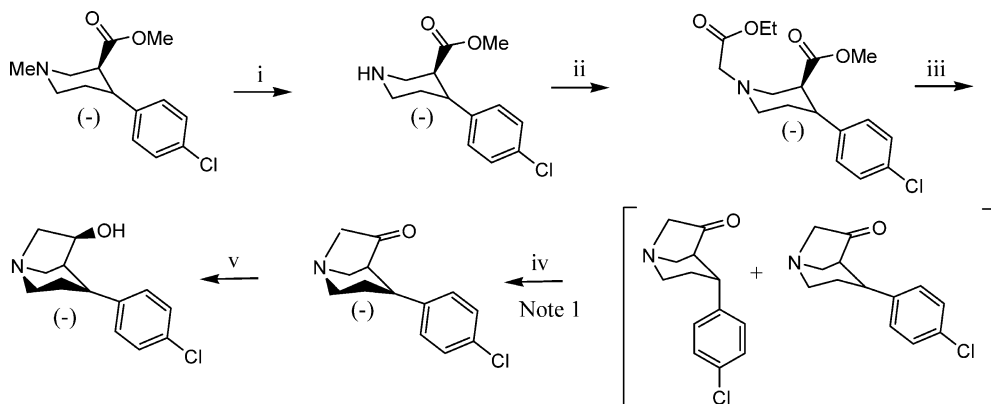
Patent: Bi- and Tri-Cyclic Aza Compounds and Their Uses
A.P. Kozikowski *et al*, US Patent 6,150,376 (November 21, 2000)

Assignee: Georgetown University

Utility: Neurotransmitter Re-Uptake Inhibitors

Reaction

Piperidine Derived Aza Tricyclics



i- Chloroethyl chloroformate, CH_2Cl_2 , hydrochloric acid,
methyl alcohol

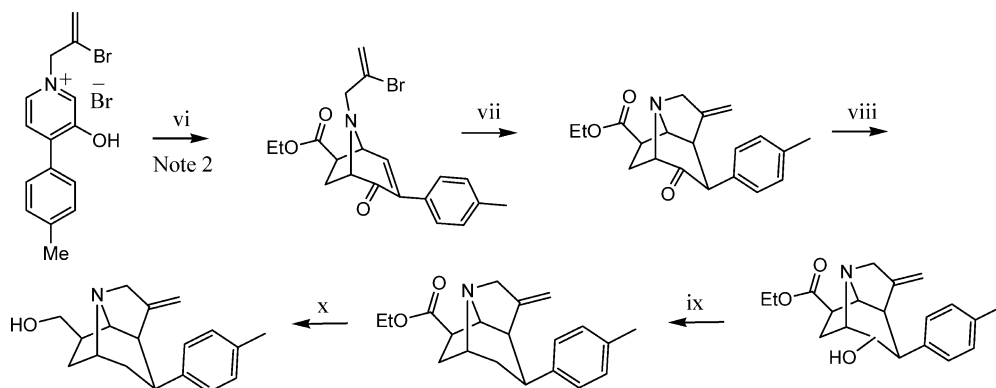
ii- Ethyl-2-bromoacetate, ethyl alcohol

iii- Ethyl alcohol, toluene, potassium hydride

iv- (1R)-(-)-10-Camphorsulfonic acid, EtOAc

v- Diisobutylaluminum hydride, hexanes, CH_2Cl_2

Pyridinium Bromide Derived Aza Tricyclics



vi- Hydroquinone, triethylamine, EtOAc

vii- 2,2'-Azobis(2-methylpropionitrile), tributyltin hydride,
benzene

viii- Sodium borohydride, ethyl alcohol

ix- Potassium hexamethyldisilazane, THF, phenylthioformate,
EtOAc

x- Lithium aluminum hydride, diethyl ether

Experimental

(I) Piperidine Derived Materials

1. (3S, 4S) Methyl-4-(4-chlorophenyl)-piperidine-3-carboxylate

(3S, 4S) Methyl-4-(4-chlorophenyl)-1-methylpiperidine-3-carboxylate (33 mmol) and 5.4 ml chloroethyl chloroformate were dissolved in 30 ml CH_2Cl_2 , refluxed 3 hours, cooled, and 40 ml 1M HCl added. The mixture was filtered through silica gel and purified using column chromatography on silica with EtOAc/ETA, 9:1, and the product isolated in 78% yield as a clear oil. $^1\text{H-NMR}$ data supplied.

2. (3S, 4S) Methyl 4-(4-chlorophenyl)-1-ethoxycarbonylmethyl)-piperidine-3-carboxylate

The product from Step 1 (25 mmol), ethyl 2-bromoacetate (37 mmol) dissolved in 100 ml ethyl alcohol and K_2CO_3 (49 mmol) were suspended 15 hours at 50°C , diluted with water, and extracted 3 times with 100 ml CH_2Cl_2 . The mixture was purified by chromatography on silica gel using hexanes/EtOAc, gradient 1:0 to 1:1, and the product isolated in 100% yield. $^1\text{H-NMR}$ data supplied.

3. (4SR, 5SR) 4-(4-Chlorophenyl)-1-aza-bicyclo[3.2.1]octane-6-one

KH (41 mmol) and 2.4 ml ethyl alcohol were refluxed 1 hour, the product from Step 3 dissolved in 50 ml toluene added, and the mixture refluxed until 20 ml solvent collected in a Dean-Stark trap. Thereafter, the mixture was refluxed 4 additional hours. The suspension was cooled, extracted 10% HCl, heated 16 hours, made basic with 10% NaOH, and extracted with CH_2Cl_2 . The mixture was purified by chromatography with EtOAc/ETA, 9:1, and the product isolated in 17% yield. $^1\text{H-NMR}$ data supplied.

4. (4R, 5R) 4-(4-Chlorophenyl)-1-aza-bicyclo[3.2.1]octane-6-one

The mixture from Step 3 (4.3 mmol) dissolved in 50 ml EtOAc was added to (1R)-(-)-10-camphorsulfonic acid (3.72 mmol) and stirred at ambient temperature for 16 hours then filtered. The white solids were washed with 10 ml EtOAc, 50 ml saturated NaHCO_3 , 75 ml EtOAc, and the product isolated, $[\alpha]_D = +162^\circ$.

5. (4R, 5R, 6R) 4-(4-Chlorophenyl)-1-aza-bicyclo[3.2.1]octane-6-ol

To the product from Step 4 (0.59 mmol) dissolved in 20 ml CH_2Cl_2 was added 1.2 ml 1M DIBAL in hexanes at -78°C and the mixture slowly warmed to ambient temperature over 3 hours. The reaction was quenched with saturated NaHCO_3 , stirred 1 hour, dried, and filtered through celite. The solids obtained were washed with methyl alcohol and the product isolated in 97% yield, $[\alpha]_D = -41^\circ$. $^1\text{H-NMR}$ data supplied.

(II) Pyridinium Bromide Derived Materials**6. (SR, 5SR, 6RS)-6-(2'-Bromoallyl)-7-ethoxycarbonyl-3-(p-tolyl)-8-azabicyclo[3.2.1]oct-2-en-3-one**

A mixture of N-(2'-bromoallyl)-3-hydroxy-4-(p-tolyl) pyridinium bromide hydroquinone (100 mg) dissolved in ethyl acrylate were heated 1.5 hours, (27 mmol), 7.5 ml TEA and cooled, and diluted with 200 ml diethyl ether. The suspension was filtered and the product isolated by chromatography using hexanes/EtOAc, 4:1, in 52% yield. $^1\text{H-NMR}$ data supplied.

7. (1RS, 2SR, 4RS, 6RS, 7SR)-6-Ethoxycarbonyl-10 methylene-2-(p-tolyl)-8-azotricyclo[5.2.0.0^{4,8}]decan-3-one

The product from Step 6 (9.7 mmol), 2, 2'-azobis(2-ethylpropionitrile) (7.7 mmol), and Bu_3SnH 19.1 mmol) were added to 50 ml benzene, the mixture refluxed 6 hours, cooled and concentrated. The material was purified by chromatography with hexanes/EtOAc, gradient, 4:1 to 1:1, and the product isolated as a clear oil in 49% yield. $^1\text{H-NMR}$ data supplied.

8. (1RS, 2SR, 4RS, 6RS, 7SR)-6-Ethoxycarbonyl-10-methylene-2-(p-tolyl)-8-azotricyclo[5.2.0.0^{4,8}]decan-3-ol

NaBH_4 (4.6 mmol) was added portionwise to the product from Step 7 in 25 ml ethyl alcohol. The mixture reacted 1 hour, was quenched with 100 ml 10% NH_4Cl , and

extracted 3 times with CH_2Cl_2 . The material was purified by chromatography using EtOAc/TEA, 9:1, and isomers obtained in 86%. $^1\text{H-NMR}$ data for each isomer supplied.

9. (1RS, 2SR, 4RS, 6RS, 7SR)-6-Ethoxycarbonyl-10-methylene-2-(p-tolyl)-8-azotricyclo[5.2.0.0^{4,8}]decane

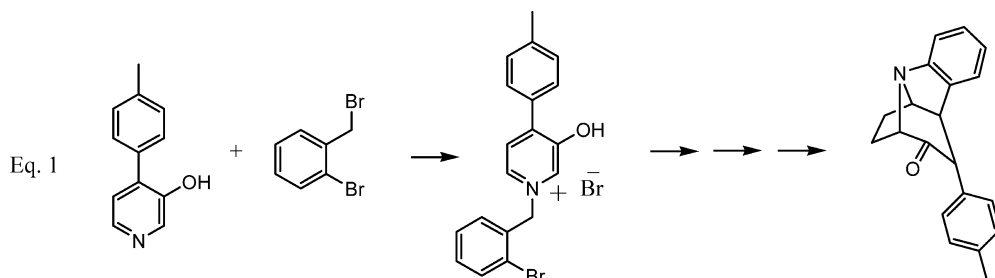
The isomeric product mixture from Step 8 (4 mmol) was dissolved in 50 ml THF and 4.0 ml 1M solution LiHMDS added dropwise at -78°C . After 15 minutes at this temperature 1.1 ml phenyl thioformate was added and the mixture warmed to ambient temperature over 90 minutes. The solution was washed with 100 ml saturated Na_2CO_3 and extracted with EtOAc. The reaction material was purified using chromatography with hexanes/EtOAc, gradient, 2:1 to 0:1, and the product isolated as colorless oil in 30% yield. $^1\text{H-NMR}$ data supplied.

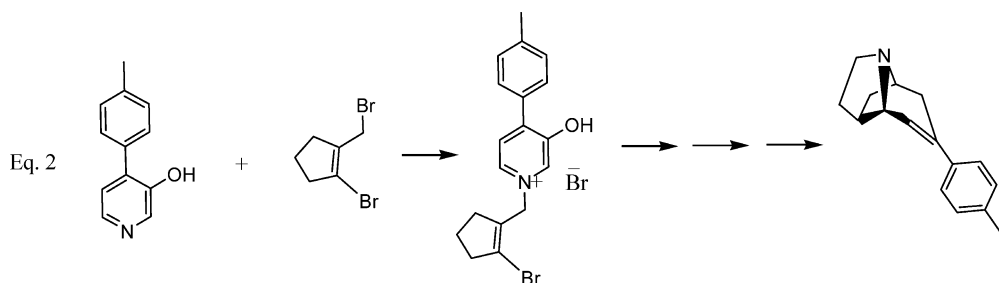
10. (1RS, 2SR, 4RS, 6RS, 7SR)-6-Hydroxymethyl-10-methylene-2-(p-tolyl)-8-azotricyclo[5.2.0.0^{4,8}]decane

To the product from Step 9 (1.3 mmol) dissolved in 10 ml diethyl ether was added LiAlH_4 (22.6 mmol) portionwise, the mixture stirred 30 minutes, was quenched with 50 ml saturated NaHCO_3 solution, and extracted with diethyl ether. The material was purified by chromatography using EtOAc/i-propyl alcohol/TEA, gradient 9:0:1 to 4:4:1, and the product isolated in 45% yield. $^1\text{H-NMR}$ data supplied.

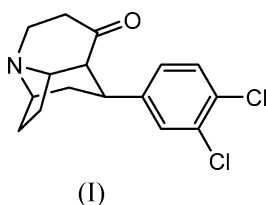
Notes

1. Dibenzyl-L-tartaric acid was used to separate the isomers in Step 4.
2. By first N-alkylating 3-hydroxyl-4 (p-tolyl)pyridine with either 2-bromo-benzylbromide or halomethyl unsaturated cyclics, other aza tricyclics of the current invention became accessible as shown in Eq. 1 and Eq. 2, respectively, and are described by the author.





3. The preparation of the azotricyclic derivative (1S,2S,4S,7R)-2-(3,4-dichlorophenyl)-8-azatricyclo[5.4.0.0^{sup}.4,8]undecan-11-one, (I), is described (1,2,3).



4. In subsequent investigations by the author, synthetic methods of the current invention were used to prepare tropane (4) and cocaine analogues (5).

References

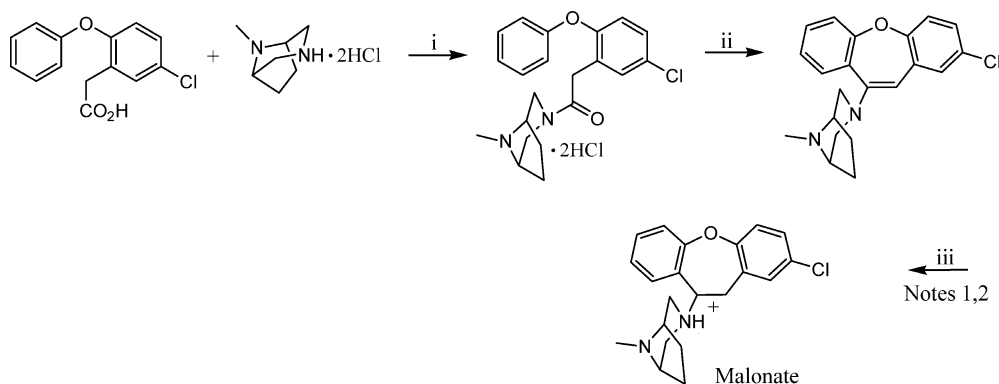
1. Smith *et al*, Tetrahedron Lett., 39, 197 (1998)
2. A.P. Kozikowski *et al*, J. Med. Chem., 41, 1962 (1998)
3. J. Scheel-Kruger *et al*, US Patent 5,998,405 (December 7, 1999)
4. A.P. Kozikowski *et al*, US Patent 6,350,758 (February 26, 2002)
5. A.P. Kozikowski *et al*, US Patent 6,806,281 (October 19, 2004)

Patent: Certain Tricyclic Substituted Diazabicyclo[3.2.1]octane Derivatives
A. Hutchison *et al*, US Patent 6,156,751 (December 5, 2000)

Assignee: Neurogen Corporation

Utility: Treatment of Schizophrenia

Reaction



- i- Thionyl chloride, CH_2Cl_2 , diisopropylethylamine, hydrogen chloride, ethyl acetate
- ii- Phosphorous oxychloride, ammonium hydroxide
- iii- Sodium cyanoborohydride, ethyl alcohol, acetic acid, hydrochloric acid, malonic acid

Experimental

1. 5-Chloro-2-phenoxyphenyl-(8-methyl-3,8-diazabicyclo[3.2.1]octane) acetamide $\cdot 2\text{HCl}$

A mixture of 5-chloro-2-phenoxyphenylacetic acid (1.5 g) and 15 ml thionyl chloride were stirred at ambient temperature 16 hours. The excess thionyl chloride was removed, the acid chloride dissolved in 10 ml CH_2Cl_2 and added dropwise to a mixture of 8-methyl-3,8-diazabicyclo[3.2.1]octane dihydrochloride and 5 ml diisopropyl-ethylamine dissolved in 15 ml CH_2Cl_2 at 0°C . After 1 hour the mixture was washed with NaHCO_3 solution, dried, and the crude amide isolated as a glassy solid. The corresponding dihydrochloride salt was prepared from HCl in EtOAc.

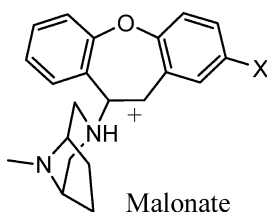
2. 3-(2-Chloro-10,11-dibenzo[b,f]oxepin-10-yl)-8-methyl-3,8-diazabicyclo[3.2.1]octane

The product from Step 1 and 25 ml phosphorous oxychloride were refluxed 30 hours. Thereafter the excess phosphorous oxychloride was removed in vacuo, the residue treated with NH_4OH in diethyl ether, dried, and the product isolated as a glassy solid.

3. **3-(2-Chloro-10,11-dihydro-dibenzo[b,f]oxepin-10-yl)-8-methyl-3,8-diazabicyclo [3.2.1] octane monomalonate**

The product from Step 2 (1.5 g), sodium cyanoborohydride (1.1 g), 45 ml ethyl alcohol and 1.7 ml HOAc were mixed then heated to 80°C 1 hour. Thereafter the solvent was removed and 3 M HCl dissolved in diethyl ether added. The aqueous layer was basified and extracted with diethyl ether and dried. The solvent was removed, the residue re-dissolved in ethyl alcohol, malonic acid (0.5 g) added, and the mixture warmed until a clear solution was obtained. After cooling to -20°C overnight, the product was isolated as white crystals, mp = 169–170°C.

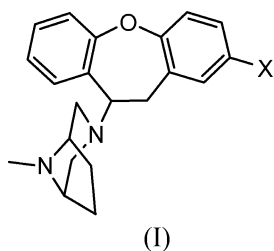
Derivatives



X	MP(°C)
Chloro	161–170
Methyl	179–184

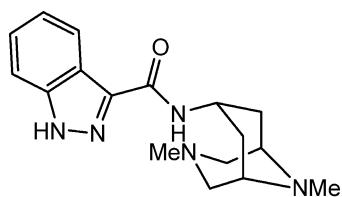
Notes

1. In a previous investigation by the author (1) other free base hydrogenated Step 3 derivatives were prepared (I) as indicated below.



X=F, Br, OCH₃, SCH₃

2. endo-3,9-Dimethyl-3,9-diazabicyclo[3.3.1]non-7-yl-1-cyclopropylmethylindazole-3-carboxamide, (II), and other derivatives of the current invention have also been prepared and are discussed (2).



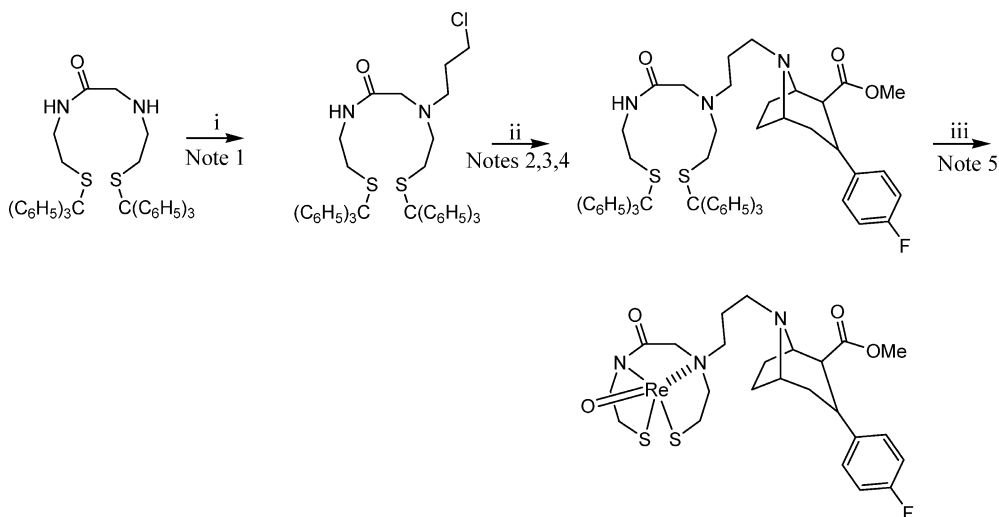
(II)

References

1. A. Hutchison *et al*, US Patent 5,952,501 (September 14, 1999)
2. H. Satoh *et al*, US Patent 5,344,831 (September 6, 1994)

- Patent:** Dopamine Transporter Imaging Agent
P.C. Meltzer *et al*, US Patent 6,171,576 (January 9, 2001)
- Assignee:** Organix Inc. and President & Fellows of Harvard College; and
Massachusetts Institute of Technology
- Utility:** Early Diagnosis Agent for Neurodegenerative Disorders

Reaction



- i- CH_2Cl_2 , 3-chloropropyltriethylammonium salt
- ii- nor-3- β -(4-Fluorophenyl)tropane-2- β -carboxylic acid
methyl ester, acetonitrile, potassium iodide, potassium
carbonate
- iii- Ethyl alcohol, tin(II)chloride, sodium perrhenate,
hydrochloric acid, acetonitrile

Experimental

1. N-{2-((3'-Chloropropyl)(2((triphenylmethyl)thio)ethyl)amino)-acetyl}-S-(triphenylmethyl)-2-aminoethanethiol

N-{2-((2-((Triphenylmethyl)thio)ethyl)amino)acetyl}-S-(triphenylmethyl)-2-aminoethanethiol (16 mmol) was dissolved in 10 ml CH_2Cl_2 , 3-chloropropyltriethylammonium salt (8 mmol) added, the mixture stirred at ambient room temperature 2 hours, and an additional 90 ml CH_2Cl_2 added. The solution was filtered, purified by chromatography using silica gel with EtOAc/hexanes, 1:1, and the product isolated in 72%, mp = 55–56°C. $^1\text{H-NMR}$, IR, elemental analysis data supplied.

2. **N-2-(3'-N'-Propyl-(1''R-3''-β-(4-fluorophenyl)tropane-2''-β-carboxylic acid methyl ester))((2-((triphenylmethyl)thio)-ethyl)amino)-acetyl}-S-(triphenylmethyl)-2-aminoethanethiol**

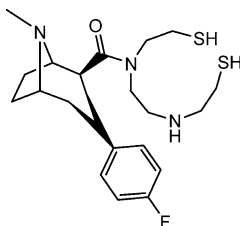
To a solution of nor-3-β-(4-fluorophenyl)tropane-2-β-carboxylic acid methyl ester (0.2 mmol) dissolved in 10 ml acetonitrile was added in succession the product from Step 1 (0.2 mmol), KI (0.2 mmol), and K₂CO₃ (2.0 mmol), and the slurry refluxed overnight. The solution was cooled, 2 g silica gel added, and concentrated. The residue was purified by chromatography on a silica gel column with NH₄OH/EtOAc/hexanes, 0.5%1:1, and the product isolated in 72% yield. The product was then converted into the dihydrogen chloride salt which had a mp = 166–168°C. ¹H-NMR, IR, elemental analysis data supplied.

3. **(R,S)-N-{2-((3'-N'-Propyl-(1''R-3''-β-(4-fluorophenyl)tropane-2''-β-carboxylic acid methyl ester))2-mercaptoethyl)amino)acetyl}-2-aminoethanethiolato}rhenium(V) oxide**

The product from Step 2 (0.1 mmol) was dissolved in a mixture of 1.5 ml boiling ethyl alcohol, SnCl₂ (21 mg in 200 μL 0.05 M HCl) and sodium perrhenate (30 mg in 200 μL 0.05 M HCl). Thereafter, 10 ml acetonitrile was added and the mixture refluxed overnight. The mixture was then filtered through celite and the cake washed twice with 20 ml boiling acetonitrile. Silica gel (1 g) was added to the filtrate, the mixture concentrated, purified by chromatography on silica with EtOAc, and the product isolated in 30% yield.

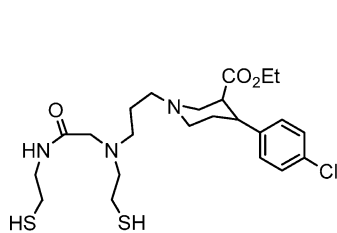
Notes

1. The preparation of the Step 1 reagent is described (1).
2. Tropane isomers of the current invention, (I), have been prepared and are discussed (2).

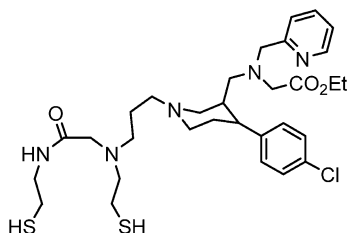


(I)

3. In subsequent investigations by the author, piperidine, (II), (3) and pyridine, (III), (4) Step 3 derivatives were prepared.

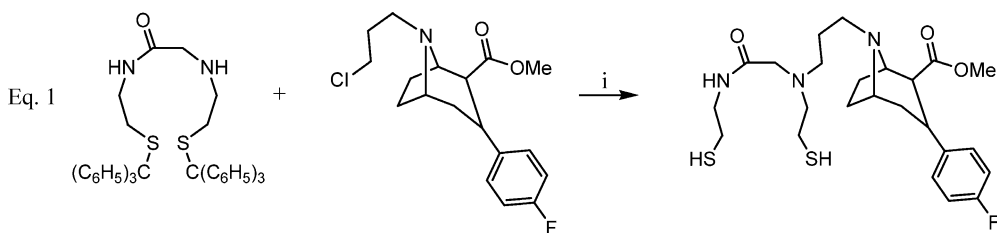


(II)



(III)

4. An alternative route for preparing the rhenium(V) ligand was also provided by the author and illustrated in Eq. 1:



i- Acetonitrile, potassium iodide, potassium carbonate

5. The corresponding radiopharmaceutical technetium ^{99}Tc analogue was also prepared by using sodium ^{99}Tc -pertechnetate instead of sodium perrhenate in Step 3.

References

1. M.S. Katzenellenbogen *et al.*, *Inorg. Chem.*, 33, 319 (1994)
2. J.Kung *et al*, US Patent 5,980,860 (November 9, 1999)
3. J.W. Babich *et al*, US Patent 6,515,131 (February 4, 2003)
4. J.W. Babich *et al*, US Patent 6,677,454 (January 13, 2004)

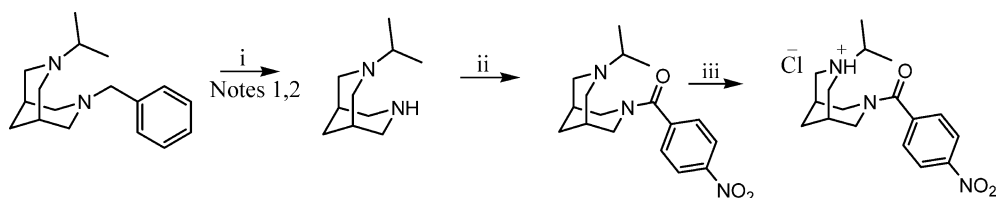
Patent: N-Alkyl and N-Acyl Derivatives of 3,7-Diazabicyclo-[3.3.1] Nonanes and Selected Salts Thereof as Multiclass Antirhythmic Agents

K.D. Berlin *et al*, US Patent 5,786,481 (July 28, 1998)

Assignee: Board of Regents, Oklahoma State University

Utility: Antiarrhythmic Agents

Reaction



i- Methyl alcohol, 10% palladium on carbon, ammonium formate

ii- 4-Nitrobenzoyl chloride, CH_2Cl_2 , sodium hydroxide

iii- Hydrogen chloride, diethyl ether

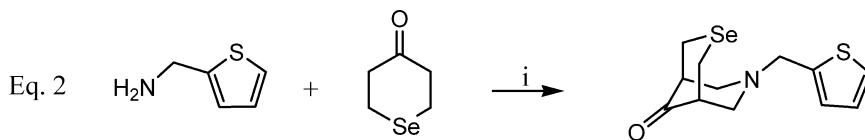
Experimental

1. 7-Isopropyl-3,7-diazabicyclo[3.3.1]nonane

A dried flask was flushed with nitrogen for 15 minutes and thereafter 10% palladium on carbon (30 mg catalyst/mmol amine) added in one portion. Dry and de-oxygenated CH_3OH was poured over the catalyst, 3-benzyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane added, followed by anhydrous $\text{NH}_4\text{CO}_2\text{H}$ (83.1 mmol), and the mixture boiled over nitrogen for 30 minutes. Thereafter the mixture was cooled, filtered through a celite pad, and concentrated. The mixture was dissolved in water, made basic to pH 12 using 10% NaOH, extracted four times with 60 ml CCl_4 , dried over Na_2SO_4 , filtered, and concentrated to give the neat product.

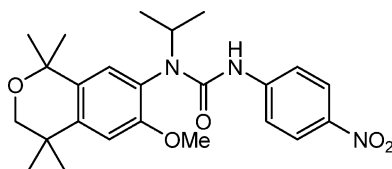
2. 3-(4-Nitrobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane

The product from Step 1 (22.70 mmol) was dissolved in 25 ml CH_2Cl_2 containing 10% NaOH (56.80 mmol) and then added dropwise to 4-nitrobenzoyl chloride (24.9 mmol) in 15 ml CH_2Cl_2 over 15 minutes. The heterogeneous mixture was stirred an additional 3 hours and 100 ml water added forming two layers. The aqueous layer was extracted three times with 50 ml CH_2Cl_2 and the aliquots combined and dried. Upon standing, a solid precipitate formed and was isolated in 94% yield as a yellow solid, mp = 119–120°C. IR and ^1H - and ^{13}C -NMR data supplied.



i- Glacial acetic acid, formaldehyde, methyl alcohol

3. In a subsequent investigation by the author (3), heteroarotinoid derivatives, (III), containing urea or thiourea linker were prepared.



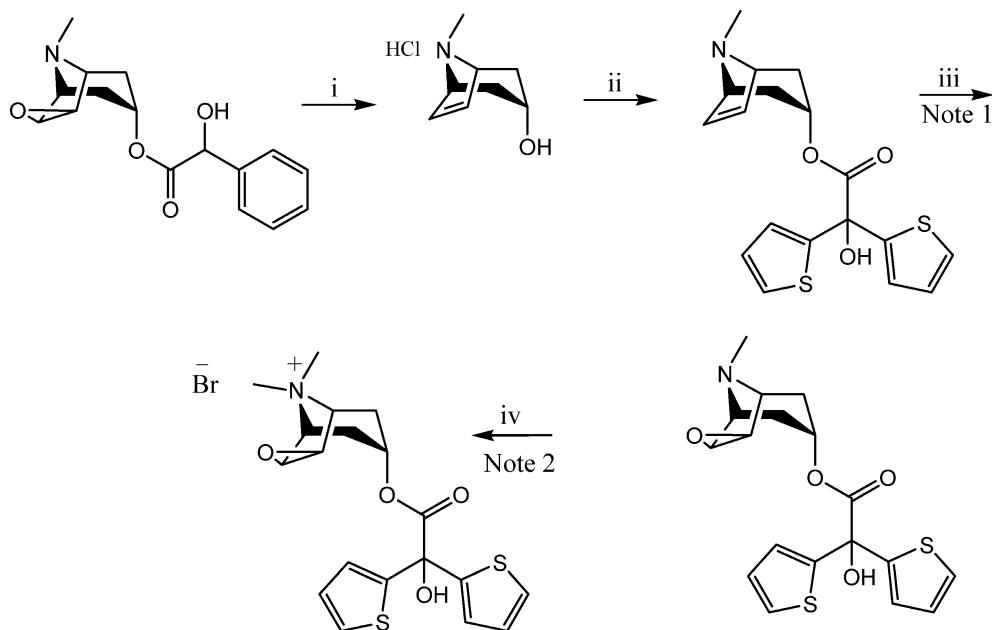
(III)

References

1. K.D. Berlin *et al*, US Patent 5,084,572 (January 28, 1992)
2. K.D. Berlin *et al*, US Patent 5,043,445 (August 27, 1991)
3. K.D. Berlin *et al*, US Patent 6,586,460 (July 1, 2003)

Patent: Process for the Manufacture of Tropenol
 R. Sobotta *et al* US Patent 6,610,849 (August 26, 2003)
Assignee: Boehringer Ingelheim Pharma KG
Utility: Industrial Preparation of Tropenol

Reaction



- i- Zinc, hydroiodic acid, copper(II)bromide, hydrobromic acid, sodium hydroxide, water
- ii- Methyl di-(2-thienyl)glycolate, ammonia, toluene
- iii- N,N-Dimethylformamide, hydrogen peroxide-urea, water, vanadium(V)oxide,
- iv- Methyl bromide, N,N-dimethylformamide

Experimental

1. Tropenol Hydrochloride

A reactor was charged with 3 L water, 390 g of zinc powder ($<63\ \mu\text{m}$), 66 ml of 57% aqueous HI solution, stirred at ambient temperature 5 minutes, and 67.2 g of Cu(II)bromide dissolved in 260 ml water slowly added. Thereafter, a solution of 910.2 g scopolamine-2-hydroxyl-2-phenylacetate dissolved in 2.6 L water was slowly added, the pH adjusted to 4.5–5 with 227 ml 62% aqueous HBr, the mixture heated to 75–80°C 2 hours, cooled to

65°C, and saponified with 480 ml 45% aqueous NaOH. The mixture was further cooled to 40°C and zinc salts filtered off then washed with 200 ml of water. The filtrate was extracted with CH_2Cl_2 , concentrated, dissolved in 1.5 L isopropyl alcohol, and filtered to remove tropic acid metal salts. The filtrate was cooled to 10°C, 120 g HCl dissolved in 780 ml isopropyl alcohol added to obtain a final pH of 2.5–4.0, and the HCl salt suspension filtered. The residue was washed with 600 ml acetone and the product isolated in 77.4 % yield.

2. Tropenol, di-(2-thienyl)glycolate ester

Ammonia (1.8 kg) was piped into 10.9 kg of the product from Step 1 dissolved in 95 L toluene at 25°C, the suspension stirred 1 hour, and NH_4Cl filtered off. The temperature was increased to 50°C and 60 L toluene distilled off in vacuo. Thereafter the mixture was cooled 25°C, 15.8 kg methyl di-(2-thienyl)glycolate added, and the mixture heated to 50°C. In a separate vessel, 40 L toluene were mixed with 2.7 kg NaH then added to the mixture of tropenol and di-(2-thienyl)methyl glycolate at 30°C. This was heated to 75°C under reduced pressure 7 hours with stirring, methyl alcohol being distilled off. The mixture was then cooled, added to a mixture of 958 L water and 13.2 kg 36% HCl. The aqueous phase was separated, washed with 56 L CH_2Cl_2 , and the pH adjusted to with 9.6 kg Na_2CO_3 dissolved in 45 L water. The CH_2Cl_2 phase was separated, concentrated, and the residue dissolved in 166 L toluene at 95°C. When the solution was cooled to 0°C, crystallization occurred and the product isolated in 83% yield, mp = 160°C.

3. Scopine di-(2-thienyl)glycolate

A reactor was charged with 260 L of DMF, heated to 50°C, the product from Step 2 (16.2 kg) added, the temperature lowered to 40°C, and 10.2 kg hydrogen peroxide-urea complex dissolved in 13 L water and vanadium(V)oxide (0.7 kg) added. The contents were heated to 50°C 3 hours, cooled to 20°C, and the pH adjusted to 4.0 with 36% HCl. Sodium bisulfite (2.4 kg) dissolved in 24 L water was added, 210 L solvent distilled off in vacuo, and the mixture combined with Clarcel (3.2 kg). The pH was adjusted to 2.0 with 36% HCl (0.8 kg dissolved in 440 L water), filtered, then extracted with 58 L CH_2Cl_2 . An additional 130 L CH_2Cl_2 was added to the aqueous phase and the pH adjusted to 10.0 with Na_2CO_3 (11.0 kg dissolved in 51 L water). The CH_2Cl_2 phase was separated off, the aqueous phase extracted twice with 136 L CH_2Cl_2 , and 175 L CH_2Cl_2 distilled off from the combined CH_2Cl_2 phases. The reaction contents were cooled to 20°C, acetyl chloride (0.5 kg) added, and the mixture stirred 40 minutes at 20°C. The reaction mixture was transferred into a second apparatus, the pH adjusted to 2.0 using HCl (4.7 kg 36% HCl dissolved in 460 L water) at 20°C, and the CH_2Cl_2 phase was separated off and discarded. The aqueous phase was washed with 39 L CH_2Cl_2 , the pH adjusted to 10.0 with Na_2CO_3 (7.8 kg Na_2CO_3 dissolved in 38 L water), 114 kg DMF added, and remaining CH_2Cl_2 distilled off. The residue was isolated and used directly in the next step without purification.

4. Tiotropium Bromide

Methyl bromide (5.1 kg) was piped into the product from Step 3 at 20°C and the mixture stirred for 3 days at 30°C. Thereafter, 70 L DMF was distilled off in vacuo at 50°, the solution transferred to a smaller reactor, and then rinsed with 10 L DMF. An additional 100 L DMF was distilled off and the remaining solution stirred 2 hours at 15°C. The product was isolated by filtration in 88% yield, mp = 200–230°C. The yield increased to 96% yield after recrystallizing 10.3 kg crude material in 66 L methyl alcohol, mp = 228°C.

Notes

1. The preparation of the Step 1 reagent is described (1).
2. The crystalline structure of tiotropium bromide monohydrate is provided (2).
3. Subsequent industrial processes for preparing tropenol using dimethylformamide, dimethylacetal, meteloidin (3), 2,2-diphenylpropionic acid, and scopolin ester-metho-bromide (4) are described.

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2. R. Banholzer *et al*, US Patent 6,777,423 (August 17, 2004)
3. R. Banholzer *et al*, US Patent 6,747,153 (June 8, 2004)
4. J. Brandenburg *et al*, US Patent 6,747,154 (June 8, 2004)

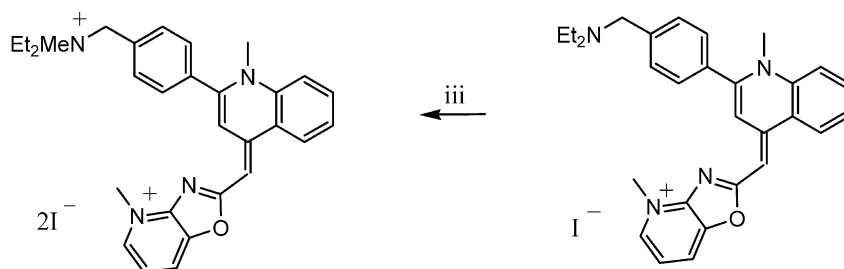
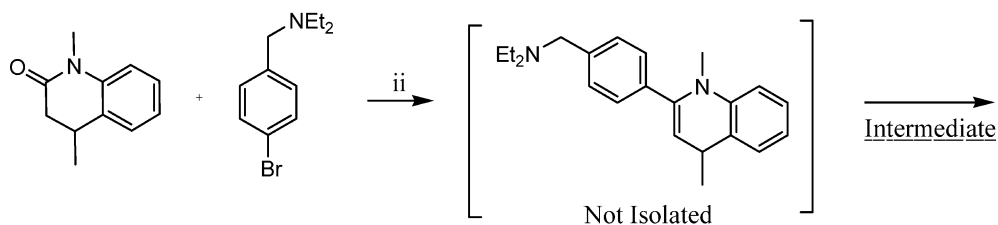
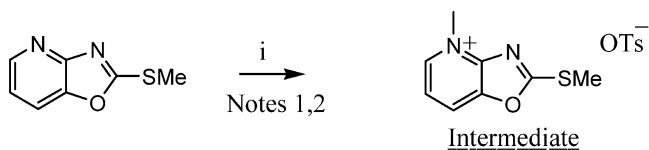
Aza Benzazolium Salts

Patent: Aza-Benzazolium Containing Cyanine Dyes R.P. Haugland *et al*,
US Patent 6,664,047 (December 16, 2003)

Assignee: Molecular Probes, Inc.

Utility: Fluorescing Molecular Probes

Reaction



- i- Methyl tosylate
- ii- THF, n-butyl lithium, acetic acid, sodium hydroxide, sodium iodide
- iii- Methyl iodide

Experimental

1. 4-Methyl-2-thiomethyl-4-aza-benzoxazolium tosylate

Equimolar amounts of 2-methylthioxazolpyridine and methyl tosylate were heated together at 100–110°C 1 hour (1) and the product isolated and used directly without purification in step 2.

2. 4-Methyl-2-((1-methyl-2-N,N-diethylmethyleamine-4-(methylene-2-(4-aza-benzoxazolium tosylate))-dihydroquinoline iodide (cyanine dye intermediate)

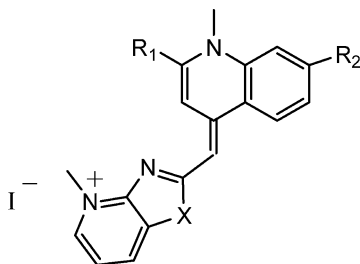
To 10 ml THF was added 4-bromobenzyl diethylamine, the mixture cooled to -78°C , 0.8 ml 2.5 M n-BuLi added, followed by 0.173 g 1,4-dimethyl-2-quinolone dissolved in 10 ml THF. After one hour, 1 ml HOAc and the product from Step 1 (0.67 g) were added followed by 1 ml TEA. At ambient temperature the volatiles were evaporated and 7 ml methyl alcohol, 2.25 g NaI, and NaOH (0.8 g in 50 ml) added.

The product was isolated and re-crystallized from a mixture of DMF and EtOAc.

3. 4-Methyl-2-((1-methyl-2-N,N-diethylmethyleammonium-4-(methylene-2-(4-aza-benzoxazolium tosylate))-dihydroquinoline di-iodide (Cyanine dye probe)

The product from Step 2 (0.1 g) was dissolved in 5 ml DMF containing 0.5 ml MeI and heated to 60°C in a sealed tube. After cooling, 5 ml EtOAc was added and the product isolated by filtration.

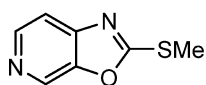
Derivatives



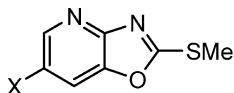
R_1	R_2	X	Sensitivity Limit Using 530 nm Excitation (ng/ml)
Phenyl	Methoxy	O	0.5
4-(N,N-Diethyl)-aminomethyl-phenyl	Hydrogen	O	0.2
2-Thiopyridine	Hydrogen	S	1.0

Notes

1. Other aza-benzoxazole intermediates in the current invention were prepared by the author using 4-methyl-2-methylthioxazolo[4,5-b] pyridine, (I), and 6-halo-4-methylthioxazolo pyridines, (II).



(I)



(II)

X = F, Cl, Br, CF₃

2. The preparation of other asymmetrical cyanine dyes is provided (2).
3. In a previous investigation, the author prepared asymmetric cyanine dyes containing activated substituents such as anhydrides, acyl chlorides, and succinimidyl esters and are described (3).
4. Permeability studies with selected asymmetric cyanine dyes is provided (4).

References

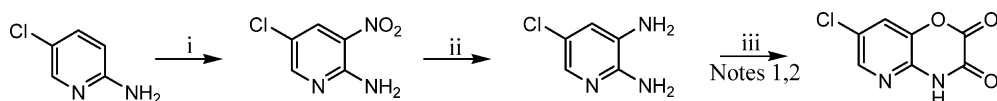
1. R.Y. Chu-Moyer *et al*, J. Org. Chem., 60, 5721 (1995)
2. S.T. Yue *et al*, US Patent 5,582,977 (December 10, 1996) and US Patent 5,410,030 (April 25, 1995)
3. R.P. Haugland *et al*, US Patent 5,863,753 (January 26, 1999)
4. S.T. Yue *et al*, US Patent 5,658,751 (August 19, 1997)

Aza-Dihydroquinoxaline

Patent: 8-Aza, 6-Aza and 6,8-Diazo-1,4-dihydroquinoxaline-2,3-diones and the Use Thereof as Antagonists for the Glycine/NMDA Receptor
S.X. Cai *et al*, US Patent 5,863,916 (January 26, 1999)

Assignee: State of Oregon, Acting by and Through the Oregon State Board of Higher Education and The Regents of the University of California

Utility: Treatment of Pathophysiologic Conditions Associated with Neural Degeneration



- i- Sulfuric acid, nitric acid
ii- Hydrochloric acid, tin(II)chloride
iii- Oxalic acid, hydrochloric acid

Experimental

1. 2-Amino-5-chloro-3-nitropyridine

To 100 ml 97% H_2SO_4 cooled in an ice bath was added portionwise 2-amino-5-chloropyridine (0.2 mol) and the resulting mixture heated to 55°C . Thereafter 13.5 ml 70% HNO_3 was added dropwise over 2 hours and the solution heated one hour at $55\text{--}60^\circ\text{C}$. The mixture was poured into ice water and neutralized with 200 ml 40% NaOH. A yellow precipitate that formed was isolated, washed with water, dried, and the product obtained in 56% yield. $^1\text{H-NMR}$ data supplied.

2. 2,3-Diamino-5-chloropyridine and 2,3-diamino-5,6-dichloropyridine

To 100 ml 37% HCl was added portionwise SnCl_2 (0.2 mole) and the mixture slowly added to the product from Step 1 (0.050 mol). The mixture refluxed for 30 minutes,

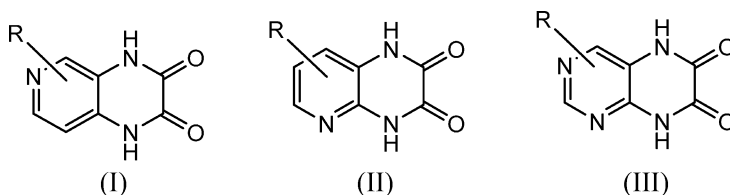
cooled, then basified using 40% NaOH to pH 12. Thereafter, it was re-heated to 90–100°C 2 hours and cooled to ambient temperature. The mixture was filtered and the solid boiled with 100 ml water while the mother liquid was boiled with 200 ml water. Two bands were observed using TLC (20 × 20 cm) developed using chloroform/methyl alcohol, 4:1, under UV light. The bands were separated and isolated using chloroform/methyl alcohol, 3:1, and the 2,3-diamino-5-chloropyridine isolated. ¹H-NMR data supplied.

3. 6-Chloro-8-aza-1,4-dihydroquinoxaline-2,3-dione

The product from Step 2 (0.28 mmol) was added to 2 ml 2 M HCl containing oxalic acid (0.33 mmol), refluxed 2 hours, and cooled to ambient temperature. The product was isolated as a brown solid in 23% yield, mp >250°C. ¹H-NMR data supplied.

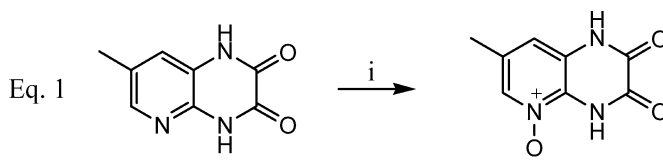
Derivatives

1. Diamines used in Step 3 for preparing of 6-, 8-aza and 6,8-diaza, (I), (II), (III), respectively, are listed below:



Diamine Precursor	Amine	Product MP (°C)
3,4-Diaminopyridine	6-Aza	>250
3,4-Diamino-2,6-dichloro	6-Aza	>250
2,3-Diamino-5,6-dichloropyridine	8-Aza	>250
2,3-Diamino-5-bromo-6-methylpyridine	8-Aza	186–188
4,5-Diaminopyrimidine	6,8-Diaza	>250

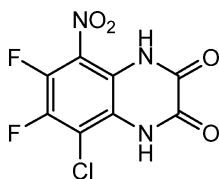
2. (N-oxy)-Aza derivatives were prepared by the author and others (1) in the current invention by reacting the product of Step 3 with 3-chloro-perbenzoic acid as illustrated in Eq. 1 and summarized below:



i- Trifluoroacetic acid, 3-chloroperbenzoic acid

Amine Substrate	Amine N-Oxide mp (°C)
6-Methyl-8-aza-1,4-dihydroquinoxaline-2,3-dione	228–230 (dec)
5-Trifluoromethyl-8-aza-1,4-dihydroquinoxaline-2,3-dione	329–330
6,8-Diaza-1,4-dihydroquinoxaline-2,3-dione	>370
5-Aza-5-methyl-1,4-dihydroquinoxaline-2,3-dione	>370

- Monoketo analogues of 8-aza-1,4-dihydroquinoxaline-2,3-dione and tautomers have been prepared (2).
- Methods for preparing 7-imidazolyl-8-aza-1,4-dihydroquinoxaline-2,3-dione and derivatives are described (3).
- In a subsequent investigation by the author (4) 5-chloro-6,7-difluoro-5-nitro-1,2-dihydro-2,3-quinoxalinedione, (IV), was prepared.



(IV)

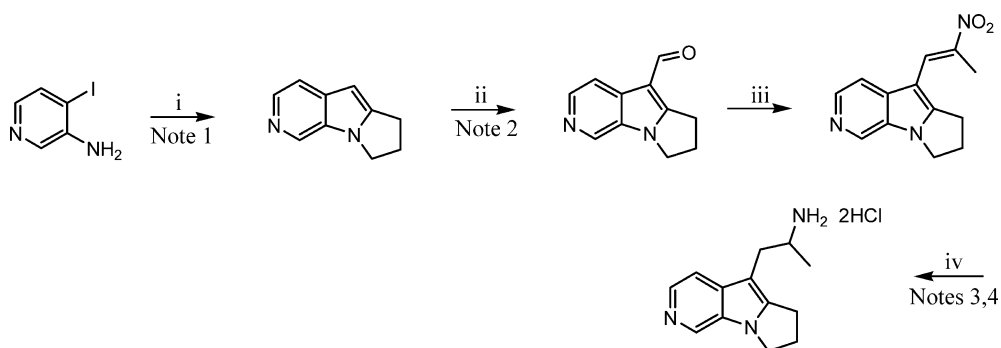
References

- J.F.W. Keana *et al*, US Patent 5,801,183 (September 1, 1998)
- U.-M. Billhardt-Troughton *et al*, US Patent 5,424,311 (June 11, 1995)
- S. Sakamoto *et al*, US Patent 5,283,244 (February 1, 1994)
- S.X. Cai *et al*, US Patent 6,147,075 (November 14, 2000)

Aza-Indolyls

Patent: Aza-Indolyl Derivatives for Treating Obesity
J.M. Bentley *et al*, US Patent 6,583,134 (June 24, 2003)
Assignee: Hoffman-LaRoche Inc and Vernnalis Research Limited
Utility: Treatment of Gastrointestinal Disorders

Reaction



- i- Acetonitrile, trifluoroacetic anhydride, potassium carbonate, bis(triphenylphosphine)palladium(II)chloride, copper(I)iodide, 5-chloro-1-pentyne, sodium iodide, sodium hydride
- ii- N,N-dimethylformamide, phosphorus oxychloride
- iii- Nitroethane, ammonium acetate
- iv- Lithium aluminum hydride, sodium-potassium tartrate, THF, hydrochloric acid

Experimental

1. 2,3-Dihydro-1H-3a,6-diaza-cyclopenta[a]indene

To 3-amino-4-iodopyridine (10.00 mmol) dissolved in 25 ml acetonitrile was added 1.67 ml trifluoroacetic anhydride at 0°C and K_2CO_3 (30 mmol) and the mixture stirred 10 minutes at ambient temperature. To this was added bis(triphenylphosphine)-palladium(II)chloride (0.25 mmol), copper(I)iodide (0.50 mmol), and 5-chloro-1-pentyne (12.00 mmol) and the mixture refluxed 3 hours. Thereafter, the mixture was cooled, partitioned between water and EtOAc, and the organic phase extracted with water at pH 1.00. The aqueous phase was mixed with CH_2Cl_2 and the pH raised to 10 by the addition of 2 M NaOH. The organic phases were combined, dried, concentrated, and the residue dissolved in 20 ml acetonitrile. To this brownish solution was added NaI (20 mmol) and NaH (ca 55%, 20 mmol), the mixture stirred 2 hours, poured onto ice, partitioned between 100 ml apiece of water and EtOAc, and the phases separated. The organic phase was extracted 5 times with 50 ml water at pH 1.00, mixed with 100 ml CH_2Cl_2 , and the pH raised to 10 using 2 M NaOH. The phases were separated, the organic phase dried, concentrated and the product isolated in 51% yield, mp = 95–96°C after re-crystallization in *t*-butyl-methylether. Elemental analysis data supplied.

2. 2,3-Dihydro-1H-3a,6-diaza-cyclopenta[a]indene-8-carbaldehyde

To 0.3 ml DMF was added 0.33 ml phosphorus oxychloride at 0°C and the mixture stirred 10 minutes at ambient temperature. A solution of the product from Step 1 (0.63 mmol) dissolved in 0.1 ml DMF was added and the mixture stirred 3 hours. Thereafter, the reaction was quenched with ice (5 g), the pH raised to 9 by addition of 28% NaOH, the mixture refluxed 10 minutes, cooled, and extracted 3 times with 5 ml EtOAc. The extracts were dried, concentrated, and the product isolated in 97% yield, mp = 150–151°C after re-crystallization from EtOAc. Elemental analysis data supplied.

3. 8-(2-Nitro-propenyl)-2,3-dihydro-1H-3a,6-diaza-cyclopenta[a]indene

To a solution of the product from Step 2 (1.6 mmol) in 3 ml nitroethane was added NH_4OAc (3.9 mmol) and the mixture heated to 100°C 4 hours. The mixture was cooled, purified by chromatography on silica gel first using EtOAc and then EtOAc/methyl alcohol, 9:1, and the product isolated in 77% yield, mp = 141–142°C after re-crystallization from EtOAc. Elemental analysis data supplied.

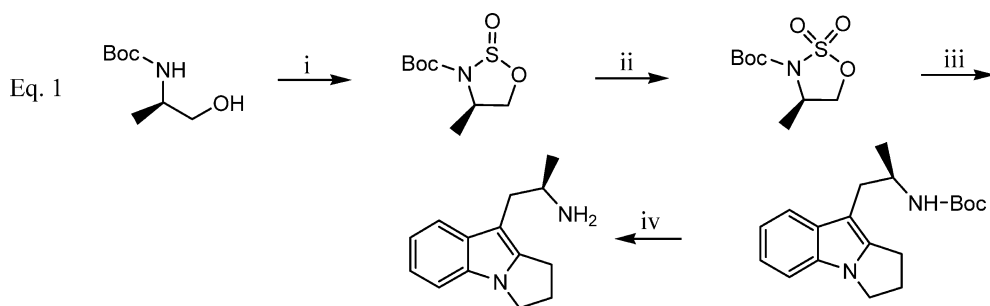
4. (R,S)-2-(2,3-Dihydro-1H-3a,6-diaza-cyclopenta[a]inden-8-yl)-1-methylethylamine · 2HCl

To a solution of the product from Step 3 (3 mmol) in 2 ml THF was added lithium aluminum hydride (2 mmol, 2 ml 1M in THF) at 0°C and the mixture refluxed 4 hours. After cooling, 5 ml of a 10% solution of sodium-potassium tartrate was added, the mixture briefly heated to reflux, cooled, and filtered through a pad of dicalite. The clear filtrate was extracted with CH_2Cl_2 , the organic phase dried, concentrated, and the residue purified by chromatography on silica gel using CH_2Cl_2 /methyl alcohol/ NH_4OH (conc.), 9:1:0.1.

The free base was isolated as a yellowish oil in 51% yield. To a solution of this oil (0.37 mmol) in 3 ml THF was added hydrochloric acid (1.1 mmol, 5.5 M in diethyl ether), the resulting solid which formed was collected by filtration, and the product isolated in 93% yield, mp >280 °C. ¹H-NMR and analytical data supplied.

Notes

1. Palladium catalysed cyclization methods for preparing indoles using o-aminophenylacetylenes are discussed (1).
2. This is an example of the Vilsmeier reaction. It can also be performed with other N,N-dimethylamide derivatives using POCl₃, POBr₃, COCl₂, or SOCl₂. Experimental conditions and illustrations are provided (2).
3. Stereospecific analogues of the current invention were also described by the author in the current invention and illustrated in Eq. 1:



i- Thionyl chloride, triethyl amine

ii- Sodium periodate, ruthenium dioxide dihydrate

iii- Step 1 product

iv- Trifluoroacetic acid

4. The compound of the current invention was previously prepared (3).
5. The preparation of indole derivatives containing the chiral cyclic amine appendage, 2(R)-pyrrolidinyl-, is described (4).

References

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2. J.R Carson, US Patent 4,119,639 (October 10, 1978); A.H. Philipp *et al*, US Patent 3,950,343 (April 13, 1976); S.S. Rooney *et al*, US Patent 3,993,653 (November 23, 1976)
3. L. Xu *et al*, Tetrahedron Lett., 39(29), 5159–5162 (1998)
4. M.J. Wythes *et al*, US Patent 5,639,779 (June 17, 1997)

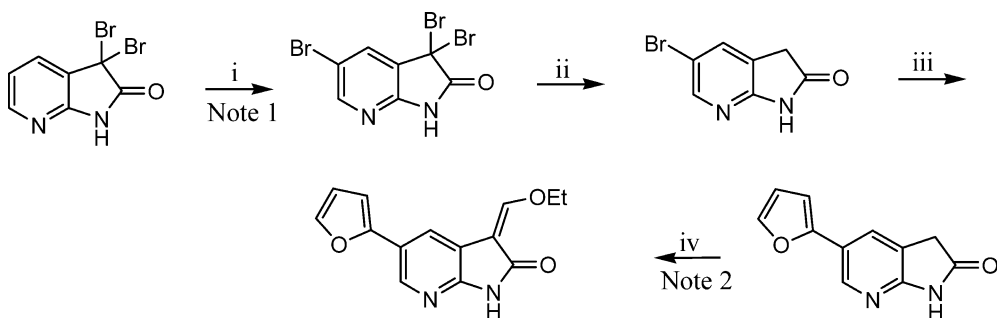
Aza-Oxindoles

Patent: Substitued Aza-Oxindole Derivatives
P.A. Harris *et al*, US Patent 6,624,171 (September 23, 2003)

Assignee: SmithKline Beecham Corporation

Utility: Agent for Reducing Epithelial Cytotoxicity Induced During Chemotherapy

Reaction



- i- *t*-Butyl alcohol, water, bromine
- ii- THF, zinc, ammonium chloride
- iii- 2-Tributyltinfuran, tetraethylammonium chloride hydrate, acetonitrile, bis(triphenylphosphine)-dichloropalladium(II), potassium fluoride
- iv- Diethoxymethyl acetate, acetic acid

Experimental

1. 3,3,5-Tribromo-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one

At ambient temperature 3,3-dibromo-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (13.4 mmol) was dissolved in 100 ml apiece t-butyl alcohol and water followed by the dropwise addition of bromine (34.3 mmol) over 20 minutes. Thereafter 15 ml NaHCO_3 was added over 30 minutes to raise the pH to 6.5. A yellow solid formed and was removed. The filtrate was reduced to 100 ml, extracted twice with 50 ml chloroform, dried, concentrated, and the product isolated in 98% yield. $^1\text{H-NMR}$ data supplied.

2. 5-Bromo-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one

The product from Step 1 (13.4 mmol) was dissolved in 100 ml apiece THF and a saturated solution of NH_4Cl , placed in a water bath, and activated zinc dust (230 mmol) added. The mixture stirred 20 minutes and was then filtered through a pad of diatomaceous earth. The organic layer was separated and the aqueous layer extracted with 20 ml THF. The organic phase was washed with brine, dried, and concentrated. The residue was triturated with 20 ml water and the product isolated in 71% yield as a tan solid. $^1\text{H NMR}$ data supplied.

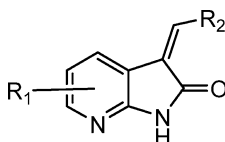
3. 5-(2-Furyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one

The product from Step 2 (3.52 mmol), 2-tributyltinfuran (3.52 mmol), and $\text{NEt}_4\text{Cl}\cdot\text{H}_2\text{O}$ (10.6 mmol) were dissolved in 10 ml acetonitrile, bistrisphenylphosphine dichloropalladium (II) (0.35 mmol) added, and the reaction mixture heated to 85°C 16 hours. Thereafter, it was cooled to ambient temperature, 60 ml 10% aqueous KF added, the mixture stirred 20 minutes, and 60 ml EtOAc added. The solution was passed through celite, the layers separated, volatiles removed, and the residue triturated with diethyl ether. The product was isolated as a light yellow solid in 36% yield. $^1\text{H NMR}$ data supplied.

4. 3-[Ethoxymethylidene]-5-(2-furyl)-1H-pyrrolo[2,3-b]pyridin-2-one

The product from Step 3 (0.19 mmol) and diethoxymethyl acetate (0.97 mmol) were dissolved in 1 ml HOAc and heated to 110°C 1 hour. The reaction was cooled and the product precipitated by the addition of diethyl ether. The mixture was filtered and the product isolated. $^1\text{H-NMR}$ data supplied.

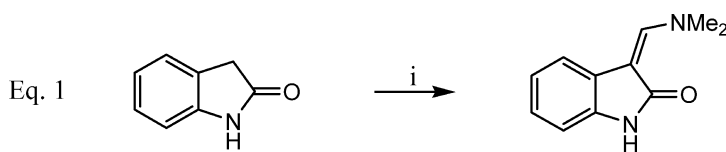
Derivatives



R_1	R_2	MS(M+H)
3-(1H-Imadazole-6-ylamino)	Hydrogen	278
Hydrogen	3-(6-Quinolinylamino)	289
5-(3-Thienyl)	1H-Indazol-1-yl-amino	360
4-Aminosulfonylanilino	Ethoxycarbonyl	389

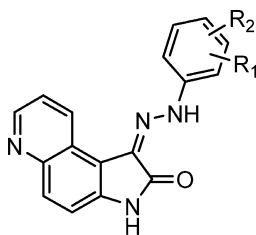
Notes

1. The preparation of the reagent of Step 1 from pyrrolo[2,3-b]pyridine using peridinium perbromide is described by the author.
2. N,N-dimethylformamide-di-t-butyl acetal has also been used to prepare by the author (1) to prepare other Step 4 derivatives illustrated in Eq. 1:



i- N,N-dimethylformamide-di-t-butyl acetal

3. The single step preparation of 1-acetyl-(1-ethoxy-1-phenylmethylidene)-2-indolinone using triethylorthoobenzoate is described (2).
4. Quinoloyl derivatives, (I), of the current invention were prepared by the author in a subsequent invention (3).



(I)

References

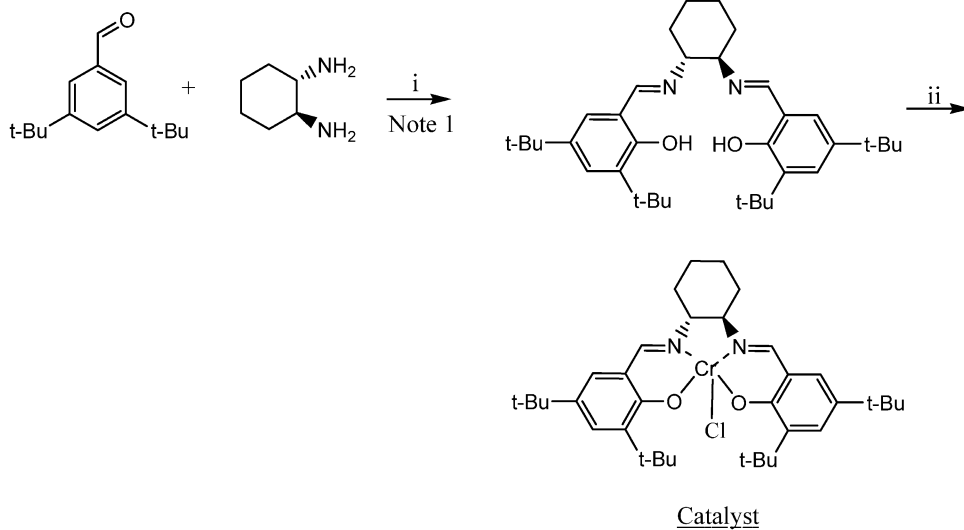
1. K.C. Glennon *et al*, US Patent 6,350,747 (February 26, 2002)
2. W. Grell *et al*, US Patent 6,043,254 (March 28, 2000)
3. P.A. Harris *et al*, US Patent 6,815,439 (November 9, 2004)

Azides

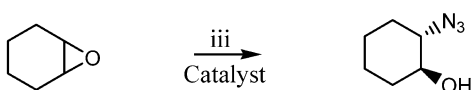
Patent: Stereoselective Ring Opening Reactions
E.N. Jacobsen *et al*, US Patent 6,262,278 (July 17, 2001)
Assignee: President and Fellows of Harvard College
Utility: Stereochemical Intermediates

Reaction

Catalyst Preparation



Reaction



- i- Ethyl alcohol
- ii- Chromium(II)chloride, THF
- iii- Diethyl ether, trimethylsilylazide,
(1S)-(+)-10-camphorsulfonic acid

Experimental

1. (R,R)-1,2-Bis(3,5-di-t-butylsalicylide-amino)cyclohexane (Catalyst preparation)

To a 0.2 M solution of (R,R)-1,2-diaminocyclohexane (1 eq) dissolved in ethyl alcohol was added 3,5-di-t-butylsalicylaldehyde (2 eq), the mixture refluxed 1 hour, and water added dropwise to the cooled yellow solution. The yellow precipitate was collected by filtration, washed with a small amount of 95% ethyl alcohol, and the product isolated in 90% to 97%. ¹H- and ¹³C-NMR data supplied.

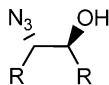
2. (R,R)-[1,2-Bis(3,5-di-t-butylsalicylide-amino)cyclohexane] chromium(III)chloride

The product from Step 1 (2.29 mmol) was dissolved in THF, CrCl₂ (2.52 mmol) added and the solution stirred under nitrogen 3 hours and 3 hours in air. The solution was diluted with 250 ml MTBE, washed 3 times apiece with 50 ml saturated NH₄Cl and brine, and the product isolated in >98% yield. ¹H- and ¹³C-NMR data supplied.

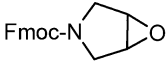
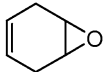
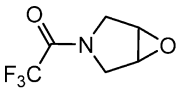
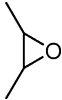
3. (R,R)-Azido-1-cyclopentanol (Catalyzed ring opening)

A flask was charged with the catalyst from Step 2 (42 mg) and 1 ml diethyl ether. 1,2-Meso cyclopentane epoxide (0.060 mmol) was added and the mixture stirred 15 minutes at which time trimethylsilylazide (3.15 mmol) was added and the mixture stirred an addition 28 hours. Thereafter, the solution was concentrated and the residue filtered through a 10 ml plug of silica gel with 5% to 20% EtOAc/hexanes mixture. Desilylation was performed by dissolving the purified intermediate into 5 ml methyl alcohol to which was added (1S)-(+)-10-camphorsulfonic acid (0.15 mmol), the mixture stirred 30 minutes, purified by flash chromatography, and the product isolated in 80% yield, 94% ee.

Derivatives

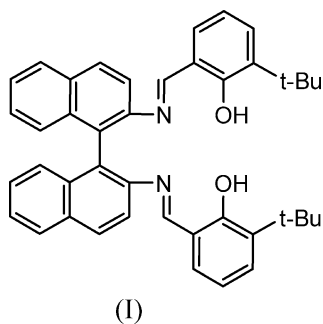


<u>Epoxide</u>	<u>Reaction Time (hr)</u>	<u>Isolated Yield (%)</u>	<u>ee (%)</u>
	28	80	94
	18	80	98

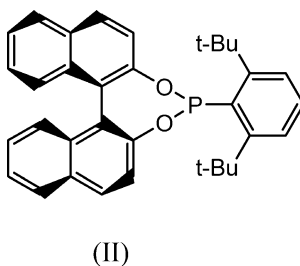
	36	80	95
	44	72	81
	16	90	95
	30	65	82

Notes

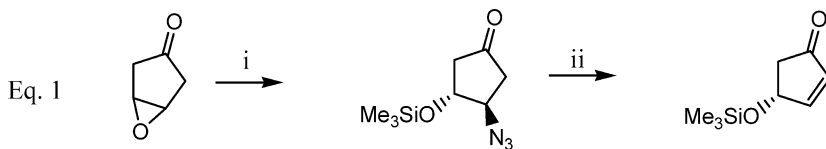
- Both (R,R)- and (S,S)-1,2-bis(3,5-di-*t*-butylsalicylide-amino)cyclohexane intermediates were prepared using the appropriate diaminocyclohexane stereoisomers and are described. The catalytic intermediate, 2,2'-bis(3-*t*-butylsalicylideamino)-1,1'-binaphthyl, (I), was also prepared by the author.



- The phosphorous analogue of 2,2'-bis(3-*t*-butylsalicylideamino)-1,1'-binaphthyl prepared, (II), and used in asymmetric hydroformylation reactions (1). Manganese analogues of (II) have been prepared and behave as asymmetrically epoxidizing agents in the presence of idosobenzene (2).

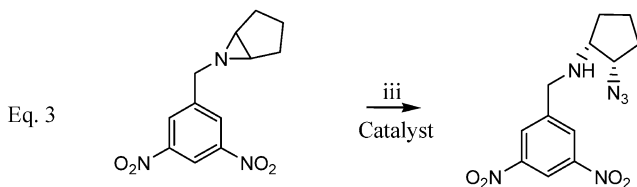
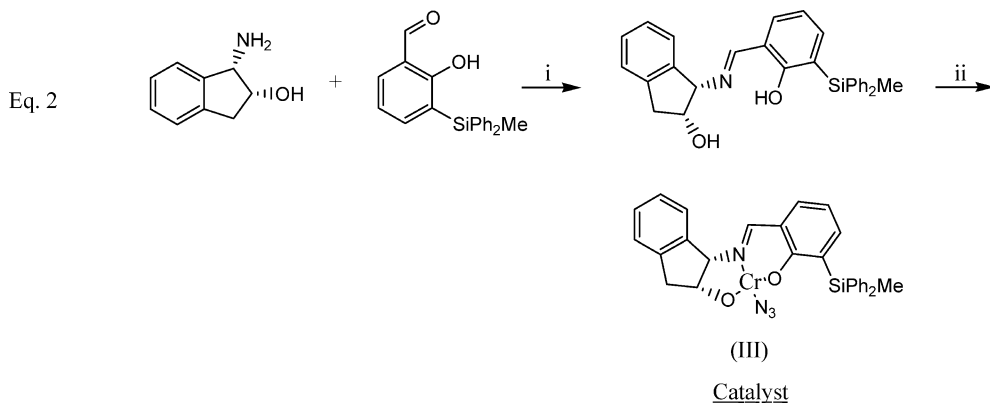


3. Using (R,R)-[1,2-bis(3,5-di-*t*-butylsalicylide-amino)cyclohexane]-chromium(III)azide, (R)-4-trimethylsiloxy-2-cyclopentanone was prepared in two steps from 3,4-epoxycyclopentanone as illustrated in Eq.1 and described by the author.



i- (R,R)-[1,2-Bis(3,5-di-*t*-butylsalicylide-amino)cyclohexane]-chromium(III)azide, diethyl ether, trimethylsilylazide
 ii- CH_2Cl_2 , basic alumina

5. Using the asymmetric catalyst, (III), prepared by reacting (S,S)-1-amino-2-hydroxyindane and 2-hydroxyl-3-(diphenylmethyl)-benzaldehyde, illustrated in Eq. 2, a stereospecific aziridine cis-opening was described by the author in the current invention and depicted in Eq. 3:



i- Ethyl alcohol
 ii- THF, 2,6-lutidine, chromium(III)chloride · THF, azidotrimethylsilane
 iii- Acetone

6. Aymmetric ring-opening reactions of other meso epoxides using catalysts derived from trimethylsilyl azide with titanium isopropoxide are described (3).

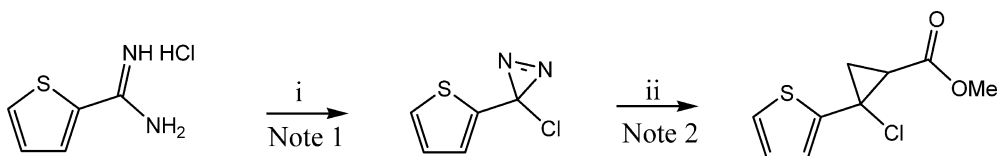
References

1. J.E. Babin *et al*, US Patent 5,360,938 (November 1, 1994)
2. T. Katsuki *et al*, US Patent 5,352,814 (October 4, 1994)
3. M. Emziane *et al.*, J. Organometallic Chem., 346, C7-C10 (1988)

Aziridines/Diazirines

Patent: Diazirine Derivatives of Aromatic Heterocyclic Compounds
M.S. Baird *et al*, US Patent 5,120,861 (June 9, 1992)
Assignee: Shell Research Limited
Utility: Halodiazirine and Cyclopropane Derivatives

Reaction



i- Lithium chloride, dimethylsulfoxide, petroleum ether,
sodium hypochlorite, sodium chloride
ii- Methylacrylate, tetrachloroethylene

Experimental

1. 3-Chloro-3-(thien-2-yl)-3H-1,2-diazirine

To 50 ml DMSO was added 3-aminidothiophene hydrochloride (18.5 mmol), 5 g lithium chloride, the solution stirred, and 50 ml petroleum added. Thereafter, 200 ml 1.2 M aqueous NaOCl containing dissolved NaCl was quickly added so that the reaction temperature increased to 50°C and the solution rapidly stirred 45 minutes while maintaining the temperature at 45°C. The phases were separated, the aqueous phase extracted 3 times with 40 ml petroleum, dried, and solvent removed to provide a clear orange oil in 70% yield. The product was purified by column chromatography on silica gel with light petroleum ether to provide a pale green oil in 61% yield. ¹H-NMR and IR data supplied.

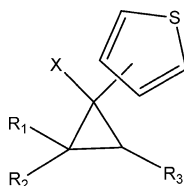
2. Methyl 2-chloro-2-(thien-2-yl)cyclopropanecarboxylate

The diazirine from Step 1 (9.5 mmol) was dissolved in methylacrylate (90 mmol) and 10 ml tetrachloroethylene then refluxed 20 minutes. The crude products consisted of an isomeric cyclopropane mixture with a syn/anti ratio of 3.8:1. The mixture was purified by chromatography on silica with light petroleum/EtOAc, 5:1, and the product mixture isolated 68% yield with no change in the isomer ratio. ¹H-NMR and data supplied.

Derivatives



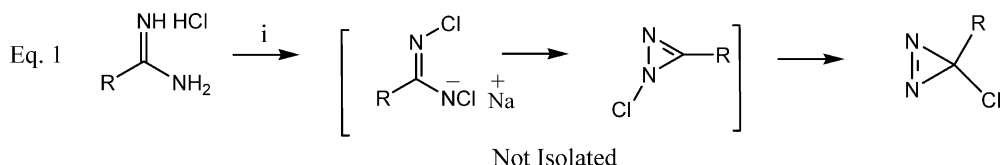
R	Yield (%)
2-Pyridinyl	32
Thiene-3-yl	61
Thiene-2-yl	65



Thiophene	X	R ₁	R ₂	R ₃	Yield (%)	Anti/Syn
2-yl	Chloro	Methyl	Methyl	Methyl	35	1.35:1
2-yl	Chloro	Chloro	Chloro	Cyano	84	5.3:1
3-yl	Chloro	Methyl	Methyl	Methylcarboxylate	65	5.3:1
2,5-Dibromo-3-yl	Bromo	Methyl	Methyl	Methyl	84	1:1

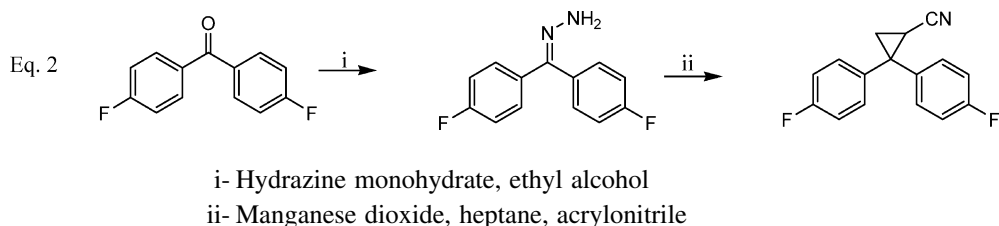
Notes

1. This is an example of the Graham diazine synthesis (1) as illustrated in Eq. 1:

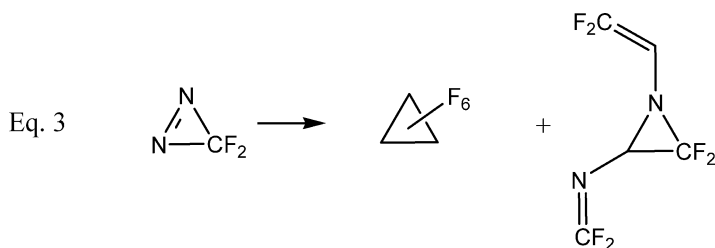


i- Sodium hypochlorite, dimethyl sulfoxide

2. Diazirines are thermally unstable and generate a carbene radical intermediate. This property has been used with hydrazones as a route for forming cyclopropanes (2) as illustrated in Eq. 2:



3. In the absence of a carbene acceptor during thermal decomposition of diazirines, cyclopropanes can still be formed (3) as illustrated in Eq. 3:



References

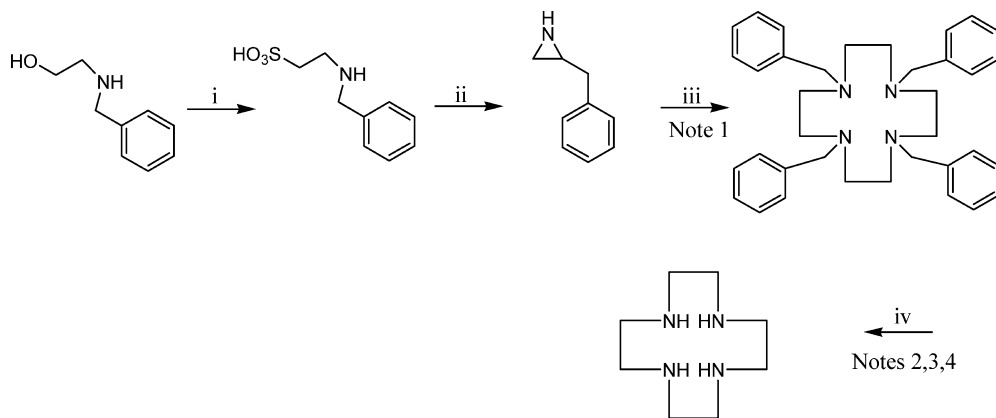
1. W.H. Graham, J. Am. Chem. Soc., 87, 4396 (1965)
2. N. Bru-Magniez *et al*, US Patent 5,219,839 (June 15, 1993)
3. R.A. Mitsch, US Patent 4,446,068 (May 1, 1984)

Patent: Preparation of N-Arylmethyl Aziridine Derivatives
1,4,7,10-Tetraazacyclododecane Derivatives Obtained Therefrom
and N-Arylethyl-ethanolamine Sulfonate Esters as Intermediates
J. Vasilevskis *et al*, US Patent 6,288,224 (September 11, 2001)

Assignee: Nycomed Saluter, Inc. and University of Iowa Research Foundation

Utility: Biological Imaging Agent

Reaction



- i- Sulfuric acid, water
 ii- Toluene, sodium hydroxide, water
 iii- Paratoluenesulfonic acid monohydrate, ethyl alcohol
 iv- 10% Palladium on carbon, ethyl alcohol, hydrogen

Experimental

1. N-Benzylethanolamine sulfonate ester

N-Benzylethanolamine (0.2 mol) was dissolved in 15 ml water, cooled, and slowly added to 96.5% H_2SO_4 (0.2 mol) dissolved in 11 ml water. Thereafter the mixture was heated to 80°C under a water aspirator vacuum to remove water and a solid formed. The solid was slurried in 100 ml ethyl alcohol and the product isolated by filtration in 74% yield. $^1\text{H-NMR}$ data supplied.

2. N-Benzylaziridine

The product from Step 1 (0.13 mol) was dissolved in 50 ml water by heating the mixture to 50°C , cooled, and a solution of 28 g NaOH dissolved in 40 ml water quickly added. The mixture was added to 100 ml toluene containing KOH pellets, heated 3 hours, and the distillate collected. The distillate was poured into a separation funnel, the organic layer isolated, and the mixture dried by the addition of NaOH pellets. The mixture was

concentrated and the product purified by vacuum distillation at 56–58°C at 2 mm Hg through a 7.5 inch Vigreux column. The product was isolated in 81% yield. ^1H - and ^{13}C -NMR data supplied.

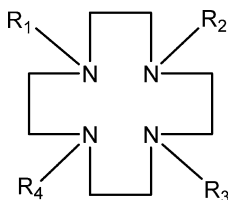
3. $\text{N,N',N'',N'''}\text{-Tetrabenzylcyclen}$

The product from Step 2 (15.4 mmol) was added to a solution of paratoluenesulfonic acid monohydrate (0.25 g in 37.5 ml ethyl alcohol), refluxed 6 hours, then cooled. The resulting white solid was re-crystallized from methyl alcohol/ CH_2Cl_2 , 2:1, and the product isolated in 100% yield. ^1H - and ^{13}C -NMR data supplied.

4. Cyclen

The product from Step 3 (0.9 mmol) was dissolved in 50 ml ethyl alcohol and 0.5 g 10% palladium on carbon added. The mixture was hydrogenated at 3 hours at 80°C at 100 psig and the product isolated in 100% yield. ^1H - and ^{13}C -NMR data supplied.

Derivatives



R_1	R_2	R_3	R_4	MS(M+)
Benzyl	Benzyl	Benzyl	Benzyl	837
Benzyl	Hydrogen	Benzyl	Hydrogen	352
2-Acetic acid, sodium	2-Acetic acid, sodium	2-Acetic acid, sodium	2-Acetic acid, sodium	628

Notes

- Other aziridine cyclization methods are described (1).
- ^1H - and ^{13}C -NMR data for all products supplied by the author.
- N-Benzyl aziridine was also oligomerized by the author and others (2) by acid catalysis as summarized below:

Acid	Aziridine Dimer (%)	Aziridine Tetramer (%)	Aziridine Pentamer (%)	Oligomers (%)
Paratoluenesulfonic	0.3	23.6	6.0	70.2
Sulfuric	0	17.0	4.7	78.3
Hydrochloric	3.6	13.8	3.8	78.8
Acetic	0.2	5.2	1.5	0

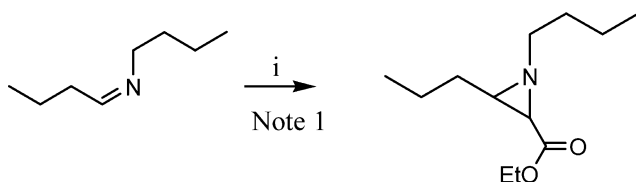
4. In the current invention, the author converted 1,4,7,10-tetra-carboxylhydroxy-1,4,7,10-tetraazacyclododecane into the gadolinium salt by reacting with gadolinium(III)oxide.

References

1. L. Lanclois *et al*, Tetrahedron Lett., 25, 2085 (1969); B.T. Thill, US Patent 3,855,217 (December 17, 1974); V. Hansen *et al*, J. Hetero. Chem., 5, 2, 305 (1968)
2. G.E. Ham *et al*, US Patent 4,093,615 (June 6, 1978); S.P. Cournier *et al*, US Patent 3,828,023 (August 6, 1971)

Patent: Process for Producing Aziridine Compounds
Y. Ishii *et al*, US Patent 6,323,346 (November 27, 2001)
Assignee: Daicel Chemical Industries, Ltd.
Utility: Amino Acid and β -Lactam Antibiotic Intermediates

Reaction



i- Ethyl diazoacetate,
di- μ -chlorotetrakis-(cyclooctene)diirridium(I), THF

Experimental

1. 1,3-Di-n-Butyl-3-ethoxycarbonylaziridine

A mixture of N-butylidenebutylimine (0.5 mol), ethyl diazoacetate (0.5), di- μ -chlorotetrakis(cyclooctene)diirridium(I) (0.015 mol), and 0.5 ml THF were stirred at ambient temperature three hours and the product isolated in 29% yield.

Derivatives

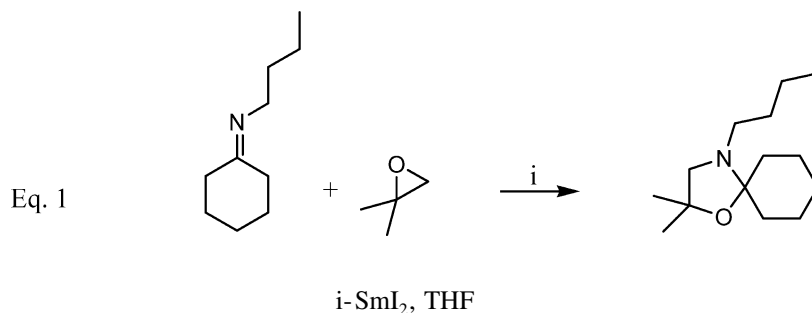


R_1	R_2	Reaction Temperature ($^{\circ}C$)	Aziridine (%)
n-Butyl	Butylidene	25	29
n-Butyl	2-Methoxypropylidene	-5	61
n-Butyl	Benzylidene	-5	36
t-Butyl	2-Methoxypropylidene	-5	75

Notes

- The author also performed this catalytic reaction using insitu generated imines. Thus when n-butylamine was reacted with butyraldehyde at $-5^{\circ}C$ in THF containing ethyl diazoacetate, 1,3-di-n-butyl-3-ethoxycarbonylaziridine was isolated in 74% yield.

2. In earlier investigations, the author developed catalytic methods for preparing ketones and polyketones using acetylacetonato-vanadium(III) (1). Oxidative process for ethers using acetylacetonatocobalt(II) are also described by the author (2).
3. Analogues of the reagent of Step 1 were used by the author to prepare 1,3-oxazolidine derivatives by reacting oxirane derivatives with imines as illustrated in Eq.1 and are described (3).



References

1. Y. Ishii, US Patent 6,232,258 (May 15, 2001)
2. Y. Ishii, US Patent 6,037,477 (March 14, 2000)
3. Y. Ishii *et al*, US Patent 6,271,387 (August 7, 2001)

Benzodiazepines

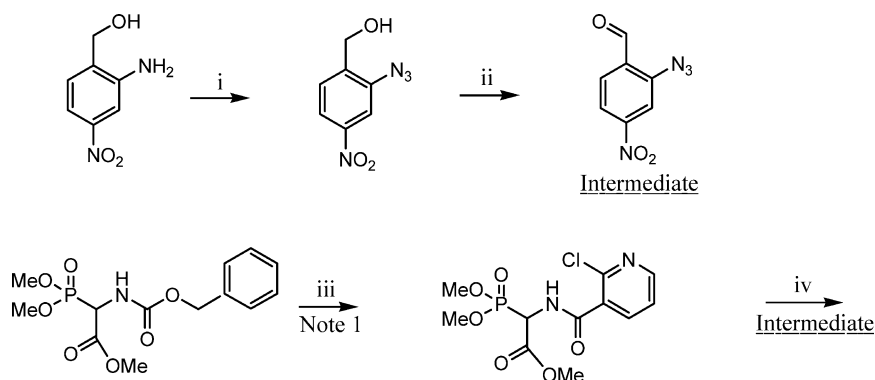
Patent: Benzodiazepines

J.A. Brown *et al*, US Patent 6,274,577 (August 14, 2001)

Assignee: Celltech Therapeutics Limited

Utility: Cell Adhesion Modulator in Regulating Immune and Inflammatory Responses

Reaction



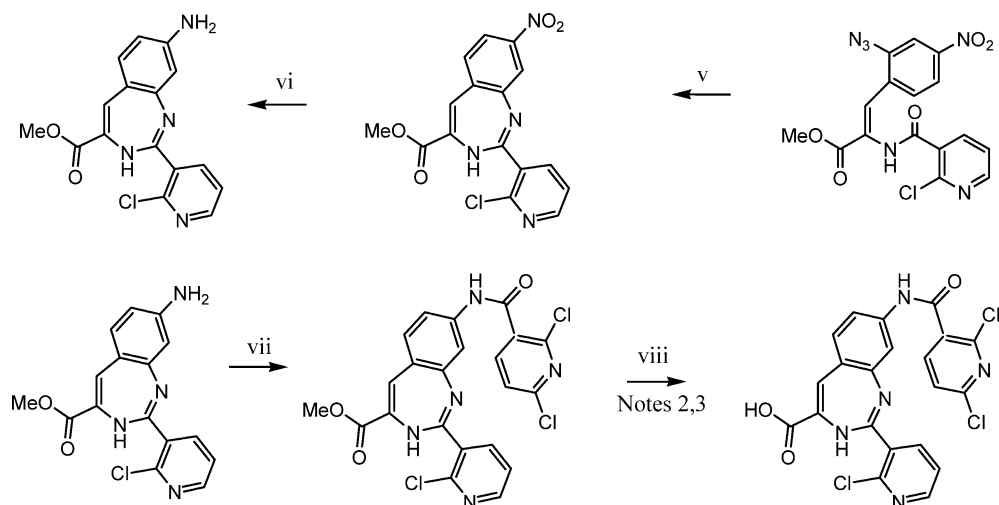
(con't)

i- Hydrochloric acid, sodium nitrite, sodium acetate, sodium azide

ii- Manganese dioxide, CH_2Cl_2

iii- 10% Palladium on carbon, methyl alcohol, hydrogen, N-(2-chloronicotinoyl)- α -phosphonoglycine trimethyl ester, N-methyl-morpholine, 2-chloronicotinyl chloride, CH_2Cl_2

iv- CH_2Cl_2 , 1,8-diazobicyclo[5.4.0]undec-7-ene



v- Toluene, triphenylphosphine

vi- Methyl alcohol, tin(II)chloride dihydrate

vii- Triethylamine, 2,6-dichloronicotinyl chloride, CH_2Cl_2

viii- Lithium hydroxide, THF, water

Experimental

1. 2-Azido-4-nitrobenzyl alcohol

To a suspension of 2-amino-4-nitrobenzyl alcohol (0.5 g) dissolved in 15 ml of 1:1 concentrated HCl/water at -50°C was added sodium nitrite (0.24 g) in 2.5 ml water at such a rate the temperature did not rise above 0°C , and then added to a solution of sodium acetate (0.2 g in 10 ml water). The resulting solid was isolated in 78% yield as a brown powder. $^1\text{H-NMR}$ data supplied.

2. 2-Azido-4-nitrobenzaldehyde

The product from Step 1 (0.6 g) dissolved in 100 ml CH_2Cl_2 was added to MnO_2 [5μ activated, 6 g] portionwise. The mixture was stirred 90 minutes then passed through celite and isolated in 91% yield as a pale yellow solid. $^1\text{H-NMR}$ data supplied.

3. N-(2-Chloronicotinyl)- α -phosphonoglycine trimethyl ester

A mixture of N-(benzyloxycarbonyl)- α -phosphonoglycine trimethyl ester (014.7 mmol) and 10% Pd/C (2 g) in 60 ml methyl alcohol was stirred under a hydrogenated atmosphere balloon for 4 hours, filtered through celite, and solvent removed under vacuum. 2-Chloronicotinyl chloride (14.7 mmol), N-methyl-morpholine (15 mmol) dissolved in 75 ml CH_2Cl_2 were added and the mixture stirred overnight at ambient temperature. The mixture was diluted with 30 ml CH_2Cl_2 , washed with 50 ml apiece with dilute HCl and saturated NaHCO_3 , and the product isolated as a colorless gum in 91% yield. $^1\text{H-NMR}$ data supplied.

4. Methyl (Z)-3-(2-azido-4-nitrophenyl)-2-[[[(2-chloro-3-pyridinyl)-carbonyl]amino]-2-propenate

The product from Step 3 (0.44 g) was dissolved in 10 ml CH_2Cl_2 at 0°C and added to the product from Step 2 (0.23 g) followed by 0.18 ml DBU and stirred 1 hour. The mixture was partitioned between 100 ml diethyl ether and 50 ml water, the organic portion isolated, washed four times with 50 ml apiece with water and brine, and the product isolated in 87% yield as a pale yellow solid. $^1\text{H-NMR}$ data supplied.

5. Methyl-2-(2-chloro-3-pyridinyl)-8-nitro-3H-1,3-benzodiazepine-4-carboxylate

To the product from Step 4 (3.92 g) dissolved in 250 ml toluene was added triphenylphosphine (2.6 g) and the mixture stirred overnight at ambient temperature. The resulting suspension was refluxed 24 hours, cooled, and concentrated to approximately 50 ml. The precipitate was filtered through celite and the product isolated in 80% yield as a red solid. $^1\text{H-NMR}$ data supplied.

6. Methyl-8-amino-2-(2-chloro-3-pyridinyl)-3H-1,3-benzodiazepine-4-carboxylate

The product from Step 5 (0.25 g) dissolved in 50 ml methyl alcohol at ambient temperature was added to $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.79 g) and the mixture stirred overnight. The residue was dissolved in 10 ml CH_2Cl_2 and partitioned between 150 ml EtOAc and 100 ml 15% NaHCO_3 , dried, and the product isolated in 52% yield as a dark red solid. $^1\text{H-NMR}$ data supplied.

7. Methyl 2-(2-chloro-3-pyridinyl)-8-[(3,5-dichloroisonicotinoyl)amino]-3H-1,3-benzodiazepine-4-carboxylate

The product from Step 6 (0.12 g) was dissolved in 5 ml CH_2Cl_2 at 0°C and 0.07 ml TEA and 2,6-dichloroisonicotinyl chloride (80 mg) dissolved in 1 ml CH_2Cl_2 added. The reaction was concentrated in vacuum at 40°C , this operation being repeated twice, then partitioned between 100 ml EtOAc and 50 ml water. The organics were then washed with 50 ml apiece with water and brine. The product was isolated by chromatography using EtOAc in 73% yield. $^1\text{H-NMR}$ data supplied.

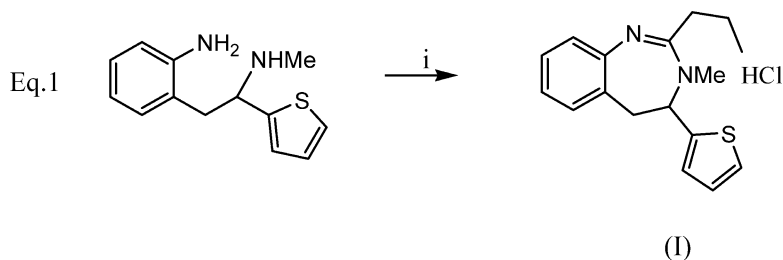
8. 2-(2-Chloro-3-pyridinyl)-8-[(3,5-dichloroisonicotinoyl)amino]-3H-1,3-benzodiazepine-4-carboxylic acid

To the product from Step 7 (120 mg) dissolved in 4 ml THF and 2 ml water was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (15 mg) and the mixture stirred for 3 hours then partitioned between 15 ml apiece EtOAc and saturated NaHCO_3 . The organics were separated and washed with 15 ml apiece water and brine and the product isolated in 30% yield as a pale brown powder. $^1\text{H-NMR}$ data supplied.

Notes

1. The preparation of 3-(1-aza-2-amino-1-cycloheptyl) benzoic acid analogues of Step 3 is described (1).

2. Only the product of Step 8, 2-(2-chloro-3-pyridinyl)-8-[(3,5-dichloroisonicotinoyl) amino]-3H-1,3-benzodiazepine-4-carboxylic acid, was prepared by the author.
3. 4,5-Dihydro-3-methyl-2-(1-methylethyl)-4-(2-thienyl)-3H-1,3-benzodiazepine hydrochloride, (I), has been prepared (2) by the reaction of 2-amino-N-methyl- α -(2-thienyl)benzeneethaneamine with trimethyl orthoisobutyrate as illustrated in Eq. 1:



i- Acetic acid, trimethyl orthoisobutyrate

4. The preparation of 4,1-benzothiazepine-3-acetic acid derivatives (3) is described.

References

1. N. Chandrakumar *et al*, US Patent 5,773,646 (June 30, 1998)
2. L.A. Martin *et al*, US Patent 5,510,346 (April 23, 1996)
3. H. Yukimasa *et al*, US Patent 5,698,691 (December 16, 1997)

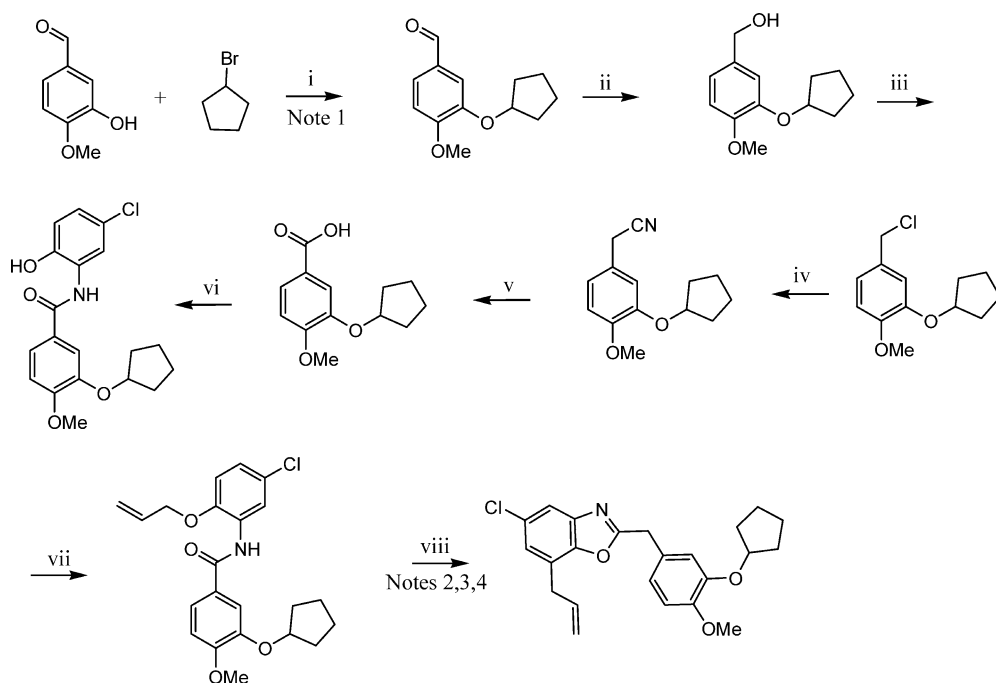
Benzoxazoles

Patent: Benzoxazoles
M. Chasin *et al*, US Patent 6,372,770 (April 16, 2002)

Assignee: Euro-Celtique, S.A.

Utility: Phosphodiesterases (PDEs) Inhibitor for Treating Asthma

Reaction



- i- Potassium carbonate, N,N-dimethylformamide
- ii- Ethyl alcohol, sodium borohydride
- iii- CH_2Cl_2 , hydrochloric acid
- iv- CH_2Cl_2 , potassium cyanide, benzyltriethylammonium chloride, water
- v- Ethyl alcohol, sodium hydroxide
- vi- 1,1'-Carbonyl diimidazole, CH_2Cl_2 , 2-hydroxy-5-chloroaniline
- vii- Ethyl alcohol, sodium hydroxide, methyl alcohol, allyl chloride
- viii- Diphenyl ether

Experimental

1. 3-Cyclopentyloxy-4-methoxybenzaldehyde

3-Hydroxy-4-methoxybenzaldehyde (0.26 mole), K_2CO_3 (0.29 mol) and cyclopentyl bromide (0.31 mol) were dissolved in 250 ml DMF and heated 4 hours at 100°C . After 4 hours additional cyclopentyl bromide (0.08 mol) was added and the mixture cooled and filtered. The filtrate was concentrated, the residue partitioned between diethyl ether and aqueous NaHCO_3 . The organic phase was washed with aqueous Na_2CO_3 , the product purified by flash chromatography using 2:1, hexanes/diethyl ether, and the product isolated in 89% yield. Elemental analysis provided.

2. 3-Cyclopentyloxy-4-methoxybenzyl alcohol

The product from Step 1 (0.17 mol) was dissolved in 40 ml ethyl alcohol, NaBH_4 (0.043 mol) added, and the mixture stirred 2 hours at ambient temperature. The mixture was diluted with water, the product extracted with EtOAc, isolated in 98% yield, and used without further purification.

3. 3-Cyclopentyloxy-4-methoxybenzyl chloride

The product from Step 2 (0.50 mol) was dissolved in 1 L CH_2Cl_2 containing concentrated HCl (1.2 mol) and stirred 3 hours. The layers were separated, the organic phase washed with water, and the product obtained in 100% yield.

4. 3-Cyclopentyloxy-4-methoxyphenylacetonitrile

The product from Step 3 (0.49 mol), KCN (1.09 mol), 120 ml CH_2Cl_2 , benzyltriethylammonium chloride (0.015 mol) and were dissolved in 120 ml water, stirred at ambient temperature 48 hours, and the 2 phases separated. The product was obtained in 95% yield and used without further purification.

5. 3-Cyclopentyloxy-4-methoxyphenylacetic acid

The product from Step 4 (0.43 mol) was dissolved in 1.3 L water containing NaOH (1.3 mol) and the mixture heated to reflux 48 hours. The mixture was distilled to remove

500 ml ethyl alcohol, the residue stirred with 11 g Norit A for 2 minutes, filtered through celite, and acidified with HCl. The product was obtained by extraction with diethyl ether, purified by dissolution in 400 ml toluene containing 10.5 g Norit A, filtered, and the product isolated in 67% yield, mp = 79–80°C.

6. N-(3-Cyclopentyloxy-4-methoxyphenylacetyl)-2-hydroxyl-5-hloroaniline

A slurry of 1,1'-carbonyl diimidazole (0.044 mol) dissolved in 40 ml CH_2Cl_2 was added to the product from Step 5 (0.040 mol) dissolved in 20 ml CH_2Cl_2 , heated 2 hours, and 2-hydroxyl-5-chloroaniline (0.042 mol) dissolved in 75 ml CH_2Cl_2 added. The mixture was stirred overnight, the phases separated, and the organic phase washed with 100 ml portions water dilute aqueous HCl and water. The solvent was removed and product obtained in 71% yield, mp = 151–152°C.

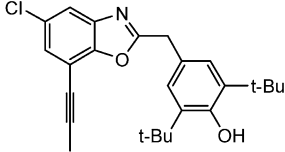
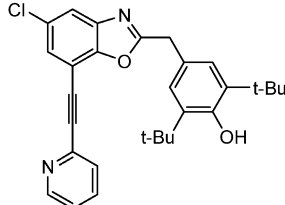
7. N-(3-Cyclopentyloxy-4-methoxyphenylacetyl)-2-alloxy-5-chloroaniline

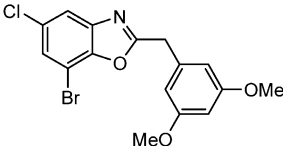
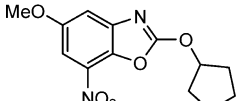
To the product from Step 6 (0.21 mol) dissolved in 600 ml ethyl alcohol containing 213 ml 1 M NaOH was added allyl bromide (0.31 mol) and the mixture refluxed 8 hours. The mixture was cooled, extracted twice with EtOAc, re-crystallized in methyl alcohol, and the product isolated in 65% yield, mp = 75–76°C.

8. 7-Allyl-5-chloro-2-(3-cyclopentyloxy-4-methoxybenzyl)-benzoxazole

The product from Step 7 (0.092 mol) was dissolved in 200 ml diphenyl ether, heated to 180°C 8 hours, cooled, diluted with 500 ml petroleum ether, and purified by flash chromatography on silica gel with petroleum ether followed by CH_2Cl_2 . The purified product was re-crystallized from hexane and the product isolated in 52% yield, mp = 43–44°C.

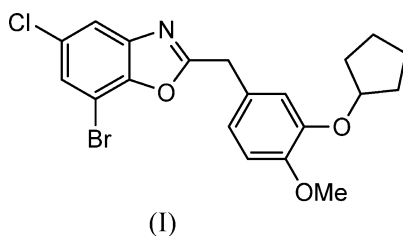
Derivatives

Benzoxazole	MP (°C)
	152–155
	138–139

Benzoxazole	MP (°C)
	123–124
	95–98

Notes

1. The preparation of di- and tri-substituted cyclopentyloxy derivatives for use as Step 1 reagents in the current investigation is described (1).
2. The preparation of benzothiazole analogues are described (2).
3. Methods for preparing 7-(p-C₄H₉-C₁₀H₂₁ alkoxyaromatic)-benzoxazole derivatives of Step 8 is described (3).
4. 7-Bromo-5-chloro-2-(3-cyclopentyloxy-4-methoxybenzyl)-benzoxazole, (I), and other derivatives have been prepared and are reviewed (4).



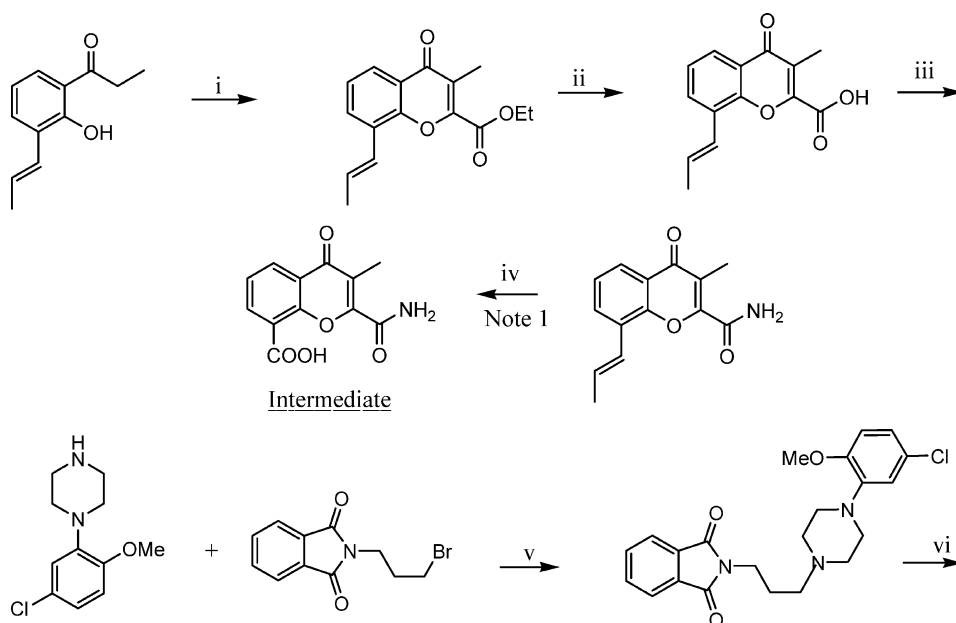
References

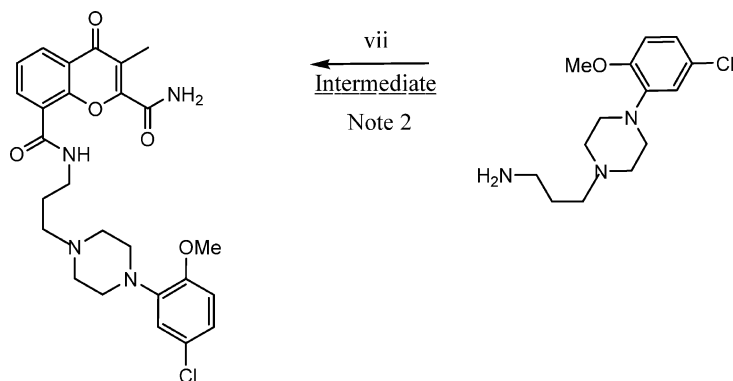
1. G.J. Warrelow *et al*, US Patent 5,622,977 (April 22, 1997)
2. A. Marfat *et al*, US Patent 5,322,847 (June 21, 1994)
3. T. Shiota *et al*, US 5,496,853 (March 5, 1996)
4. J.D. Cavalla *et al*, US Patent 5,665,737 (September 9, 1997)

Benzopyrans

Patent: Benzopyran Derivatives
A. Leondardi *et al*, US Patent 6,403,594 (June 11, 2002)
Assignee: Recordati S.A. Chemical and Pharmaceutical Company
Utility: α_1 -Adrenergic Receptor Inhibitors

Reaction





- i- Sodium ethoxide, diethyl oxalate, toluene
- ii- Methyl alcohol, sodium hydroxide
- iii- Thionyl chloride, CH_2Cl_2 , ammonia,
N,N-dimethylformamide
- iv- Sodium dichromate, sulfuric acid
- v- Potassium carbonate, acetonitrile
- vi- Hydrazine hydrate, ethyl alcohol, hydrochloric acid
- vii- Diethyl cyanophosphate, triethylamine

Experimental

1. 2-Ethoxycarbonyl-3-methyl-4-oxo-8-(1-propenyl)-4H-1-benzopyran 1/4 H_2O

To a solution of sodium ethoxide prepared using 4.6 g sodium and 100 ml ethyl alcohol was added 2-hydroxy-3-(1-propenyl)-propionphenone (10 g), 71.2 g diethyl oxalate dissolved in 160 ml toluene, and the reaction stirred at 50°C 3.5 hours. Thereafter 16 ml 98% H_2SO_4 was added dropwise, the reaction stirred an addition 30 minutes at 50°C , cooled, and the organic phase washed 3 times with 200 ml water. The crude product was isolated in 62% yield, mp = $131\text{--}135^\circ\text{C}$.

2. 2-Hydroxycarbonyl-3-methyl-4-oxo-8-(1-propenyl)-4H-1-benzopyran

The product from Step 1 (9.03 g) was dissolved 110 ml methyl alcohol and 90 ml 1 M NaOH, stirred at ambient temperature 3 hours, 100 ml water added, and the alcohol removed by vacuum distillation. The aqueous phase was kept at 50°C 24 hours, acidified with 1 M HCl, and the product isolated by filtration in 96% yield, mp = $224\text{--}228^\circ\text{C}$.

3. 2-Carbamoyl-3-methyl-4-oxo-8-(1-propenyl)-4H-1-benzopyran

To the product from Step 2 (2.0 g) dissolved in 30 ml CH_2Cl_2 and 1 ml DMF was added 0.66 ml thionyl chloride, the solution stirred for 2 hours at ambient temperature, and then sat overnight. Thereafter an additional 0.15 ml thionyl chloride was added and the solution stirred for 2 additional hours. The solvent was removed, the product extracted with CH_2Cl_2 , and evaporated to dryness. The residue was dissolved in THF, 5 ml 32% NH_4OH added,

the mixture stirred 30 minutes, then poured into 200 ml water. After sitting overnight, a precipitated was isolated in 57% yield, mp = 243–245°C.

4. 2-Carbamoyl-8-hydroxycarboxy-3-methyl-4-oxo-4H-1-benzopyran

To a solution of the product from Step 3 (0.6 g) dissolved in 30 ml acetone and 10 ml DMF was added 1.5 ml of aqueous 70% $\text{Na}_2\text{Cr}_2\text{O}_7$ and 1.8 ml 70% H_2SO_4 and the solution stirred 4 hours at 50°C. Thereafter, an additional 3 ml of 70% $\text{Na}_2\text{Cr}_2\text{O}_7$ and 3.6 ml 70% H_2SO_4 were added and the mixture heated 6 hours at 50°C and 6 hours at 70°C. The mixture was cooled, poured into 100 ml water containing sodium hydrosulfite, stirred for 30 minutes, and the product isolated by filtration in 83% yield, mp >250°C.

5. 1-(5-Chloro-2-methoxyphenyl)-4-[3-(N-phthalimido)-propyl]piperazine

A mixture of 1-(5-chloro-2-methoxyphenyl)piperazine (28.64 g), K_2CO_3 (44.6 g) and N-(3-bromopropyl)phthalimide (33.65 g) were dissolved in 250 ml acetonitrile and refluxed 8 hours. The mixture was cooled, poured into 800 ml water, filtered, recrystallized in methyl alcohol, and the product isolated in 91% yield, mp = 131–133°C.

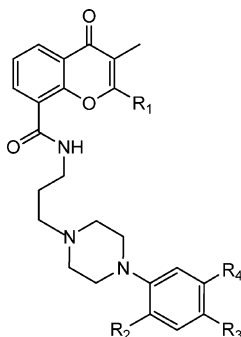
6. 1-(3-Aminopropyl)-4-(5-chloro-2-methoxyphenyl)piperazine trihydrochloride 2.15 H_2O

The product from Step 5 (20.7 g) and 8.6 ml 85% hydrazine hydrate were dissolved in 300 ml ethyl alcohol, refluxed 3 hours, cooled, diluted with 400 ml water, acidified with 37% HCl, and stirred 30 minutes. The product was isolated as a precipitated in 96% yield, mp = 200–202°C.

7. 2-Carbamoyl-8-{3-[4-(5-chloro-2-methoxyphenyl)-1-piperazinyl]-propylcarbamoyl}-3-methyl-4-oxo-4H-1-benzopyran

To a solution of the products from Step 4 (0.60 g) and Step 6 (0.45 g) dissolved in 30 ml of DMF was added 0.35 ml 93% diethyl cyanophosphonate and 0.45 ml TEA, the mixture stirred 4 hours between 0°C and 25°C, and then poured into 200 ml water. The product was isolated by filtration after resting overnight in 69% yield, mp = 184–192°C.

Derivatives



R₁	R₂	R₃	R₄	Melting Point (°C)	Yield (%) (Last Step)
1,1-Dimethylethoxycarbonyl	Hydrogen	Hydrogen	Methoxy	200–203	60
Ethoxycarbonyl	Methoxy	Hydrogen	Chlorine	176–179	73
Methylcarbamoyl	Methoxy	Propylcarbamoyl	Chlorine	212–215	70
Dimethylcarbamoyl	Methoxy	Hydrogen	Chlorine	151–153	51

Notes

1. The preparation of bicyclicheterocyclic- and N-phenylaminoalkyl benzopyran derivatives is described, (1), (2), respectively.
2. The preparation of pyrimidinedione derivatives of the current invention have been prepared and are described (3).

References

1. A. Leonardi *et al*, US Patent 5,474,994 (December 12, 1995) and US Patent 5,605,896 (February 25, 1997)
2. A. Leonardi *et al*, US Patent 6,071,920 (June 6, 2000)
3. T. Katakami *et al*, US Patent 5,332,739 (June 26, 1994)

Benzothiophenes

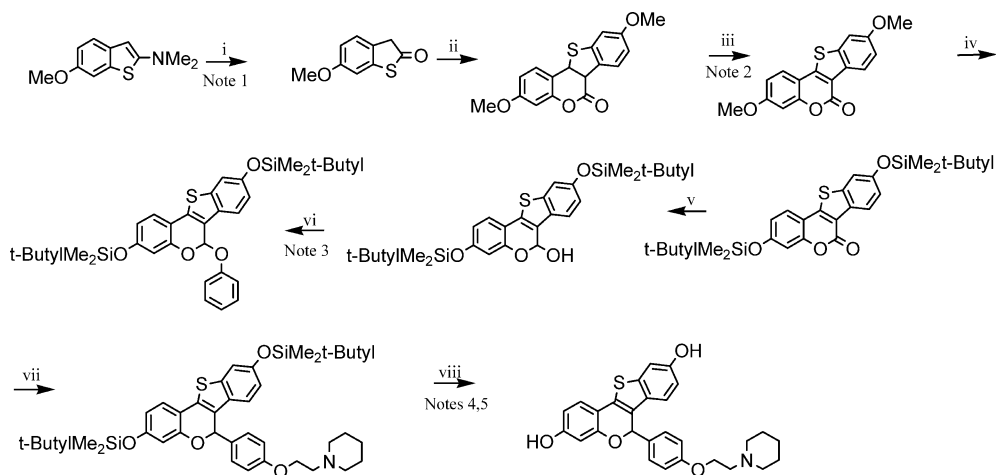
Patent: Pentacyclic Compounds, Intermediates, Processes, Compositions, and Methods

T.A. Grese, US Patent 6,004,971 (December 21, 1999)

Assignee: Eli Lilly and Company

Utility: Treatment of Post-Menopausal Syndrome

Reaction



- v- Toluene, diisobutylaluminum hydride
- vi- Phenol, CH_2Cl_2 , magnesium sulfate
- vii- Toluene, 4-[2-(1-piperidinyl)ethoxy]phenylmagnesium bromide
- viii- THF, tetra-n-butylammonium fluoride

Experimental

1. 6-Methoxybenzo-[b]-thiophene-2-one

To 2-dimethylamino-6-methoxybenzo-[b]-thiophene (96.5 mmol) dissolved in 200 ml tetrahydrofuran was added 200 ml 1 M HCl and the mixture refluxed 3 hours. Once cooled, the layers were separated, the aqueous layer extracted with 300 ml CH_2Cl_2 , washed with 250 ml water, dried, and concentrated. The residue was recrystallized using ethyl alcohol and the product isolated in 80% yield, mp = 80–82°C. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

2. 11a-Dihydro-3,9-dimethoxy-6-H-[1]benzothieno[3,2-c][1] benzopyran-6-one

To a solution of the product from Step 1 (111 mmol) dissolved in 100 ml ethyl alcohol and 50 ml CH_2Cl_2 was added 4-methoxy-salicylaldehyde (115 mmol) and triethylamine (5.6 mmol) and the mixture stirred at ambient temperature overnight. The mixture was diluted with 1 L cold hexane, filtered, recrystallized, and the product isolated in 82% yield. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

3. 3,9-Dimethoxy-6-H-[1]benzothieno[3,2-c][1]benzopyran-6-one

The product from Step 2 (14.3 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (15 mmol) were dissolved in 100 ml dichloroethane, heated briefly to 80°C, and filtered hot. The precipitate was rinsed with CH_2Cl_2 , combined, and concentrated. The residue was dissolved in hot CH_2Cl_2 , filtered, and re-concentrated. The product was isolated in 88% yield after being recrystallized from toluene. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

4. 3,9-Bis[(t-butyl)dimethylsilyl]oxy]-6-H-[1]benzothieno-[3,2-c][1]benzopyran-6-one

The product from Step 3 (38.4 mmol) was dissolved in 220 ml CH_2Cl_2 and ethanethiol (192 mmol) followed by the portionwise addition of AlCl_3 (288 mmol). The mixture stirred at ambient temperature 5 hours, cooled to 0°C, and was then quenched with 250 ml apiece THF and NaHCO_3 . The mixture was further diluted with 1 L THF, the layers separated, and the aqueous layer washed with THF. The combined organic layers were dried, concentrated, and 102% of crude diphenol intermediate isolated. Thereafter, the crude product was slurried in 200 ml CH_2Cl_2 and triethylamine (200 mmol), t-butyl)dimethylsilylchloride (134.4 mmol) added, and the mixture stirred 5 hours at ambient temperature. After dilution with 600 ml hexane, the mixture was washed with brine and the aqueous layer extracted with 300 ml hexane.

The organic phase was dried, concentrated, recrystallized from hexane, and the product isolated 91% yield, mp = 142–144°C. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

5. **3,9-Bis[(t-butyldimethylsilyl)oxy]-6-H-[1]benzothieno-[3,2-c][1]benzopyran-6-ol**

The product from Step 4 (3.9 mmol) was dissolved in 200 ml toluene, cooled to -92°C , diisobutylaluminum hydride (11.3 mmol) added, and the mixture stirred at -77°C 3 hours. It was then quenched with 5 ml methyl alcohol and 50 ml 10% hydrochloric acid. Thereafter it was diluted with 200 ml CH_2Cl_2 , washed with 100 ml saturated potassium sodium tartrate, the aqueous layer extracted with CH_2Cl_2 , and the organic phase washed with brine. The mixture was dried, concentrated, purified by chromatography on silica gel with EtOAc/hexane with a gradient of 1–15% EtOAc, and the product isolated in 18% yield, mp = 162–164°C. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

6. **3,9-Bis[(t-butyldimethylsilyl)oxy]-6-phenoxy-6-H-1]benzothieno[3,2-c][1]benzopyran**

The product from Step 5 (8.78 mmol) and phenol (43.9 mmol) were dissolved in 100 ml CH_2Cl_2 , anhydrous magnesium sulfate (4.5 g) added, and the slurry stirred at ambient temperature 4 hours. The mixture was filtered, concentrated, and the residue dissolved in chlorobenzene then re-concentrated. The residue was dissolved in 300 ml CH_2Cl_2 , washed with Na_2CO_3 , water, dried, concentrated, and the product isolated in 99% yield. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

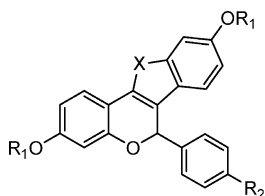
7. **3,9-Bis[(t-butyldimethylsilyl)oxy]-6-[4-[2-(1-piperidinyl) ethoxy]phenyl]-6-H-[1]benzothieno[3,2-c][1]benzopyran**

The product from Step 6 (6.7 mmol) was dissolved in 100 ml toluene at 0°C , 4-[2-(1-piperidinyl)ethoxy]phenylmagnesium bromide (13.5 mmol) added, and the mixture stirred 90 minutes at ambient temperature. It was quench with 300 ml water, extracted with EtOAc, dried, concentrated, and purified by chromatography on silica gel with hexane/EtOAc/ NH_4OH /, 3:1:0.1%, and the product isolated in 82% yield. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

8. **3,9-Dihydroxy-6-[4-[2-(1-piperidinyl)ethoxy]phenyl]-6-H-[1] benzothieno[3,2-c][1]benzopyran**

The product from Step 7 (5.5 mmol) was dissolved in 150 ml THF, 1.0 M NBu_4F dissolved in THF (27.4 mmol) added, and the mixture stirred at ambient temperature 2 hours. It was diluted with 300 ml EtOAc, washed with 300 ml NH_4Cl , extracted with 150 ml EtOAc, washed, dried, and concentrated. The mixture was purified by chromatography on silica gel using [hexane/EtOAc(1:1)]/methyl alcohol/ NH_4OH , 1:1:0.1%, crystallized from methyl alcohol, and the product isolated in 90% yield, mp = 242 – 245°C. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

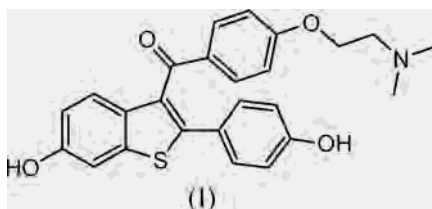
Derivatives



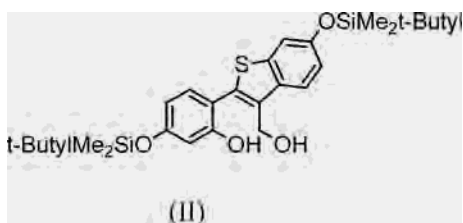
R₁	R₂	X	Melting Point (°C)
Hydrogen	2-(1-Piperidinyloxy)phenyl	S	237–240 (dec)
Methyl	4-hydroxyphenyl-	O	310
Hydrogen	2-(2-Oxo-1-pyrrolidinyl)	S	150–160 (dec)
Methyl	2-(1-Piperidinyloxy)phenyl]	S	176

Notes

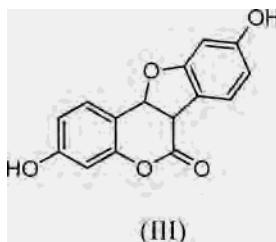
- Step 1 analogues 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-dimethylamino-ethoxy) benzoyl]benzo[β]thiophene, (I), and 2(5H)-furanone derivatives have been prepared and are described (1), (2), respectively.



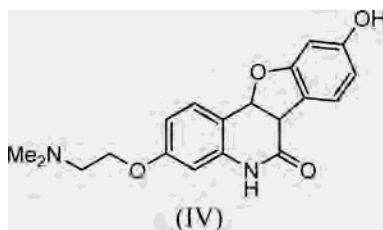
- The formation of coumarin derivatives using phenols or phenolic analogues is an example of the von Peckman-Duisberg coumarin synthesis reaction and is reviewed (3).
- The Step 5 diol, (II), was also isolated in 16% yield.



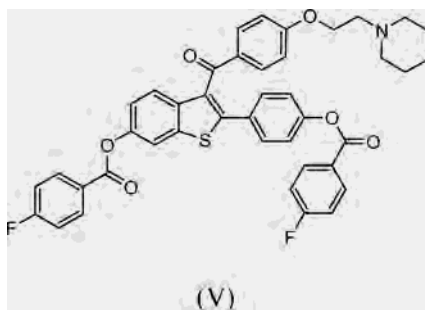
- H-benzofuro[3,2-c][1] benzopyran derivatives were also prepared by the author in the current invention using coumestrol, (III), directly or by reacting tetralone or indanone with the appropriate phenol.



5. The Step 8 derivative of quinol-6-one analogues such as 3-(2-dimethylethoxy)-5H-benzofurano[3,2-c]-quinolin-6-one, (IV), was also prepared by the author and others (4).



6. Another Step 8 derivative, benzo[b][2-(piperidin-1-yl)ethoxy-phenyl]methanone, (V), and derivatives have been prepared and are described (5)



References

1. A.G. Godfrey, US Patent 5,420,349 (May 30, 1995)
2. J.P. Sabatucci, US Patent 5,466,830 (November 14, 1995)
3. S. Sethna *et al*, Organic Reactions, 7 (1953)
4. T. Kamijo *et al*, US Patent 5,073,553 (December 17, 1991)
5. L. Black *et al*, US Patent 5,457,117 (October 10, 1995)

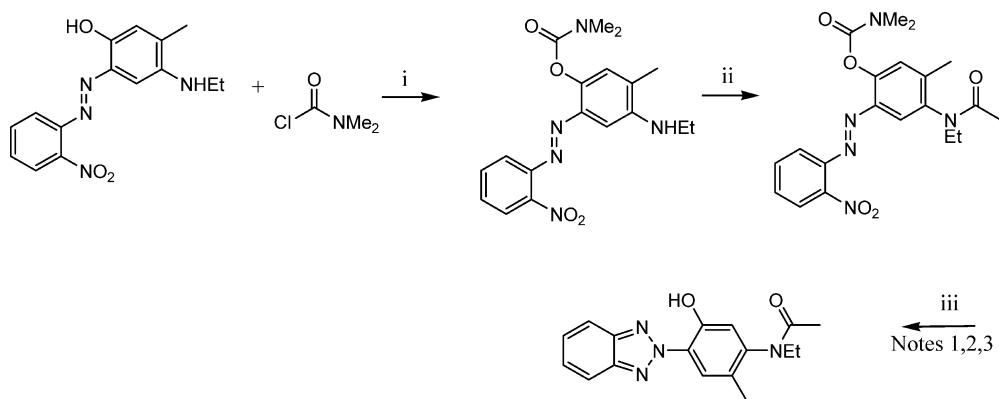
Benzotriazole

Patent: Method of Synthesizing t-Amido-Substituted 2-(2-Hydroxyphenyl)benzotriazole Compounds in a One-Step Process L.C. Vishwakarma *et al*, US Patent 5,739,348 (April 14, 1998)

Assignee: Eastman Kodak Company

Utility: UV Light Absorbing Coating Additive

Reaction



i- Acetone, triethylamine, N,N-dimethylaminopyridine

ii- Dimethylformamide, N,N-dimethylaminopyridine, acetyl chloride

iii- 4% and 1% Palladium on carbon, t-butylamine, hypophosphorus acid, hydrogen, methyl alcohol

Experimental

1. 2-(2-Nitrophenylazo)-4-(N-ethylamine)-5-methylphenyl N,N-dimethyl carbamate

2-(2-Nitrophenylazo)-4-N-ethylamino-5-methylphenol (1.232 mol) was dissolved in 2.5 L acetone, dimethylcarbamy chloride (2.83 mol), TEA (2.83 mol), N,N-dimethylaminopyridine (0.156 mol) added, and the mixture stirred 2 hours. Thereafter, an additional 265 ml dimethylcarbamy chloride and 25 g of N,N-dimethylaminopyridine were added, the mixture refluxed 16 hours, then poured into an ice brine solution. The mixture rested 40 hours and the product isolated by filtration. ¹H-NMR, MS, and HPLC data supplied.

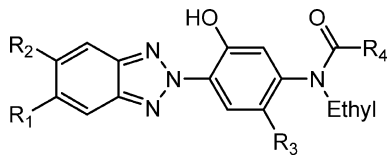
2. 2-(2-Nitrophenylazo)-4-(N-acetyl-N-ethylamino)-5-methylphenyl-N,N-dimethyl carbamate

The product from Step 1 (0.1 mol) was dissolved in 1 L DMF, N,N-dimethylaminopyridine (0.2 mol) and 12.2 ml acetyl chloride added, and the mixture stirred at 0°C. Thereafter, TEA (0.2 mol) was added dropwise and the mixture refluxed 3 days. The product was isolated by precipitation in an ice brine solution and purified by flash chromatography using silica gel. MS, ¹H-NMR, UV-Vis data supplied.

3. 2-(Benzotriazol-2-yl)-4-methyl-5-(N-acetyl-N-ethylamino)phenol

The product from Step 2 (0.052 mol), 0.25 g of 1% Pd/C and 4% Pd/C, 26.2 g t-butylamine, 35.5 g hypophosphorus acid and 1.1 L methyl alcohol were charged into stainless steel autoclave. The mixture was hydrogenated at ambient temperature at 75 psi 1 hour and 50°C 12 hours. The catalyst was removed through a filtration pad and the product isolated.

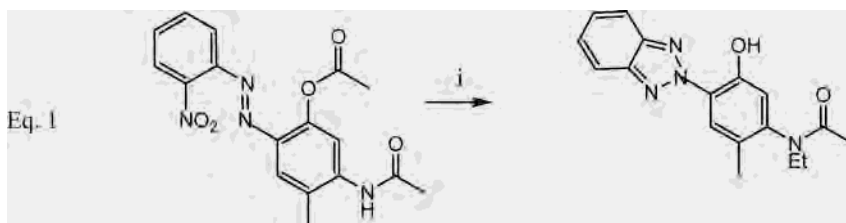
Derivatives



R ₁	R ₂	R ₃	R ₄	UV-Vis λ _{max} (nm) [MeOH]
Chloride	Chloride	Hydrogen	n-Pentyl	344
Hydrogen	Hydrogen	Methyl	n-Butyl	337
Hydrogen	Hydrogen	Methyl	n-Hexyl	336
Chloride	Hydrogen	Methyl	2-(RS)-Heptyl	343

Notes

1. A modified method for reductive ring closure and selective O-deacylation was also provided by the author as illustrated in Eq. 1 and described below:

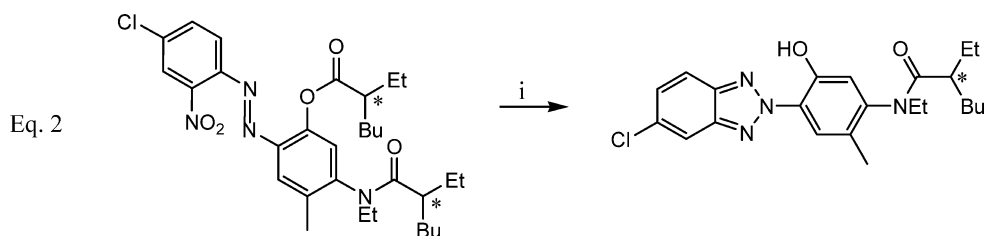


i- 1% and 4% Palladium on carbon, t-butylamine, hypophosphorus acid, hydrogen, methyl alcohol, hydrochloric acid

Procedure

Hydrogenation was performed as described in Step 3. After filtration the solvents were removed by rotary evaporator, the residue diluted with brine and acidified with HCl until Congo Red indicator turned blue. The aqueous layer was decanted off, the mixture diluted with brine, and extracted with 500 ml EtOAc. The viscous fluid was purified by vacuum distillation or by chromatography on silica gel using CH_2Cl_2 . The solvent was removed, triturated with CH_2Cl_2 /pentane, 1.0:50, and air dried to obtain 64% product. $^1\text{H-NMR}$ data supplied.

2. The reductive ring closure and selective O-deacylation procedure was also used for preparing optically active benzotriazole derivatives illustrated in Eq. 2:



i- 1% and 4% Palladium on carbon, t-butylamine, hypophosphorus acid, hydrogen, methyl alcohol

3. Odeacylation does not occur with non-ester protecting groups such as a carbamato group.
4. Other reduction methods for forming triazole derivatives using saccharide aldehydes and catalytic amounts of fluorenol are described (1).
5. Other UV-active triazole derivatives similar to those of the current invention are described (2).

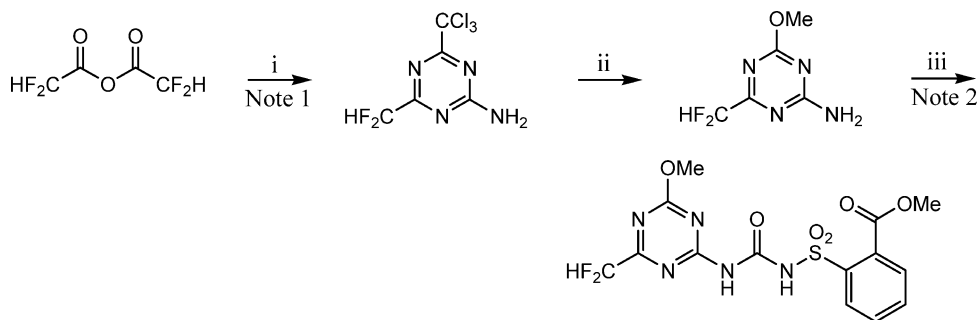
References

1. S. Moshchitsky *et al*, US Patent 5,262,541 (November 16, 1993)
2. L.C. Vishwakarma, US Patent 5,500,332 (May 19, 1996)

Carbamates/Ureas

Patent: Herbicidal Sulfonylureas, Their Preparation and Use
H. Mayer *et al*, US Patent 6,413,911 (July 2, 2002)
Assignee: BASF Aktiengesellschaft
Utility: Herbicidal Intermediate

Reaction



- i- Diethyl ether, N-(trichloroacetamido)guanidine,
- ii- Sodium methoxide, methyl alcohol
- iii- CH_2Cl_2 , 2-methoxycarbonylbenzenesulfonyl isocyanate

Experimental

1. 2-Amino-4-difluoromethyl-6-trichloromethyl-1,3,5-triazine

Difluoroacetic anhydride (0.4 mol) dissolved in 200 ml diethyl ether, treated with N-(trichloroacetamido)guanidine (0.2 mol) at 0°C , and then stirred at ambient temperature 3 hours. The volatile fractions were removed at 40°C , the residue partitioned between 400 ml water and 200 ml CH_2Cl_2 , and the organic phase neutralized with 2%

NaOH solution. The mixture was concentrated, the crude product isolated in 75% yield, and used without further purification. $^1\text{H-NMR}$ data supplied.

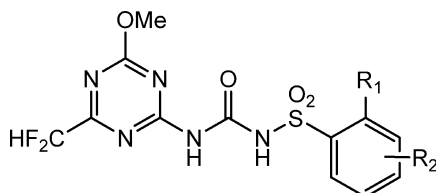
2. 2-Amino-6-difluoromethyl-6-methoxy-1,3,5-triazine

The product from Step 1 (85 mmol) was dissolved in 100 ml methyl alcohol, treated at 0°C with 1.6 g 30% sodium methoxide (9 mmol) in methyl alcohol, and the mixture stirred at ambient temperature 16 hours. Thereafter, an additional 1.6 g of 30% sodium methoxide (9 mmol) in methyl alcohol was added and the mixture stirred an additional 3 hours. The solution pH was lowered to 7 using 3 M HCl, the mixture concentrated, stirred in 400 ml water, and the product isolated in 71% yield. $^1\text{H-NMR}$ data supplied.

3. Methyl [2-[[[(4-chlorodifluoromethyl-6-methoxy-1,3,5-triazin-2-yl)-aminocarbonyl] aminosulfonyl]benzoate

The product from Step 2 (20 mmol) was dissolved in 20 ml of CH_2Cl_2 at 25°C , 2-methoxycarbonylbenzenesulfonyl isocyanate (20 mmol) dissolved in 5 ml CH_2Cl_2 added, the mixture stirred 16 hours, then concentrated. The residue was stirred with 100 ml hexane/diethyl ether, 1:1, the product separated by filtration, recrystallized using methanol/water, and isolated in 35% yield, $\text{mp} = 174\text{--}175^\circ\text{C}$.

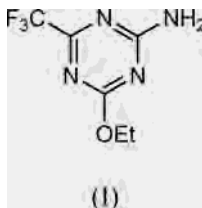
Derivatives



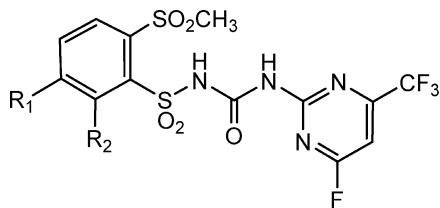
R_1	R_2	Melting Point ($^\circ\text{C}$)
Trifluoromethyl	Hydrogen	172–175
Nitro	Hydrogen	181
Dimethylaminosulfonyl	Hydrogen	152–154
Thiomethyl	6-Thiomethyl	>200
Methoxycarboxylate	5-Methoxide	155–160

Notes

1. The preparation of 2-amino-4-ethoxy-6-trifluoromethyl-1,3,5-triazine, (I), using cyanoguanidine or derivatives is described (1).



2. Pyrimidine derivatives of the current invention have previously been prepared, (II), (2).

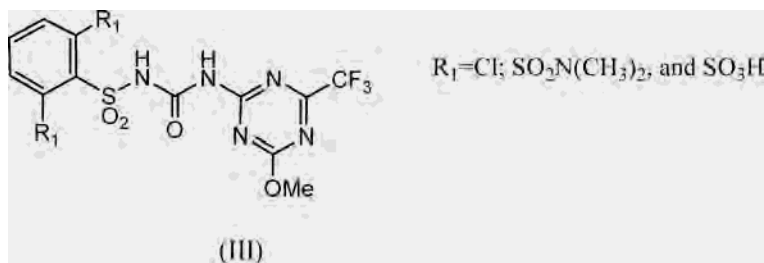


$R_1 = \text{Cl, CH}_3, \text{ and OCH}_3$ and $R_2 = \text{H}$

$R_2 = \text{Cl, CH}_3, \text{ and OCH}_3$ and $R_1 = \text{H}$

(II)

3. The preparation of 2-chloro, 2-dimethylaminosulfonyl, and methylsulfonyl analogues, (III), of the current invention are described (3,4,5), respectively.



$R_1 = \text{Cl; SO}_2\text{N}(\text{CH}_3)_2, \text{ and SO}_3\text{H}$

References

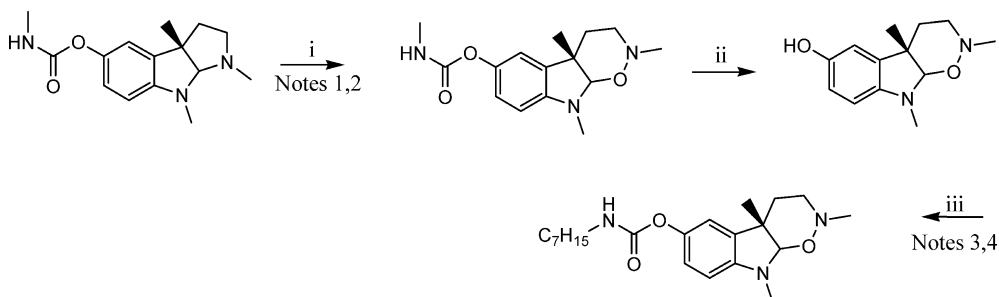
1. B. Schafer *et al*, US Patent 5,739,328 (April 14, 1998)
2. G. Hamprecht *et al*, US Patent 5,591,694 (January 7, 1997)
3. G. Levitt, US Patent 4,120,691 (October 17, 1978); L. Nusslein *et al*, US Patent 4,169,718 (October 2, 1979)
4. G. Levitt, US Patent 4,310,346 (January 12, 1982)
5. H. Mayer *et al*, US Patent 5,434,124 (July 18, 1985)

Patent: Process for the Preparation of Aminocarbonyl Derivatives of Geneseroline Having Selective Brain Anticholinesterase Activity
P. Chiesi *et al*, US Patent 6,297,237 (October 2, 2001)

Assignee: Chiesi Farmaceutici S.p.A.

Utility: Anticholinesterase Inhibitor in Treating Neurological Disorders

Reaction



i- Methyl alcohol, potassium bicarbonate, hydrogen peroxide, sodium chloride

ii- Sulfuric acid, ammonium hydroxide

iii- Potassium carbonate, EtOAc, heptylisocyanate, tetrabutylammonium bromide

Experimental

1. Geneserine

Eserine (0.1455 mol) was dissolved in 80 ml methyl alcohol and cooled in an ice bath. KHCO_3 (0.1455 mol) was added with vigorous stirring followed by the dropwise addition of 21.2 ml 35% H_2O_2 over 10 minutes and the mixture stirred 3 hours. Thereafter 150 ml of 25% NaCl solution was added and the solution stirred an addition of 2 hours in an ice bath. The solution was concentrated and the residue extracted 3 times with 150 ml chloroform. The organic phases were evaporated at reduced pressure giving the crude geneserine as a foaming oily residue.

2. Geneseroline

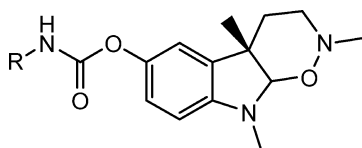
The product from Step 1 was dissolved in 100 ml of 62% H_2SO_4 and the solution heated to 85°C 2 hours, cooled to ambient temperature, and poured onto 100 g of ice. Thereafter, 120 ml aqueous 30% NH_4OH was added to the solution and the reaction temperature kept below 20°C with a water bath. When the pH was 4 the solution was extracted with

250 ml EtOAc, solution washed, dried, and the product isolated in 78% yield as a solid, mp = 142.5–146°C.

3. *n*-Heptylaminocarbonylgeneseroline

Geneseroline (0.31 mol) was dissolved in 1.1 L EtOAc at 37°C, K₂CO₃ (11 g) added, and the mixture stirred 10 minutes. Heptylisocyanate (48 g) was quickly added and the mixture stirred 3 hours. Thereafter, NBU₄Br (1 g) was added followed by a second addition of heptylisocyanate (4.3 g). The reaction mixture was cooled, filtered through a celite pad, and concentrated. The residue was extracted twice with 400 ml toluene, dissolved in 600 ml of warm hexane, cooled, and the product isolated by filtration in 84.5% yield.

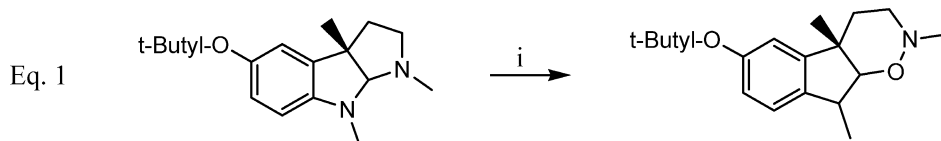
Derivatives



R	Salt	Yield	MP (°C)
2-Ethylphenyl	None	83.1	—
2-Ethylphenyl	HCl	70.2	179–181
3-Methylphenyl	HCl	—	178.5–179.5
2-Methylphenyl	HCl	—	172–174 (dec)

Notes

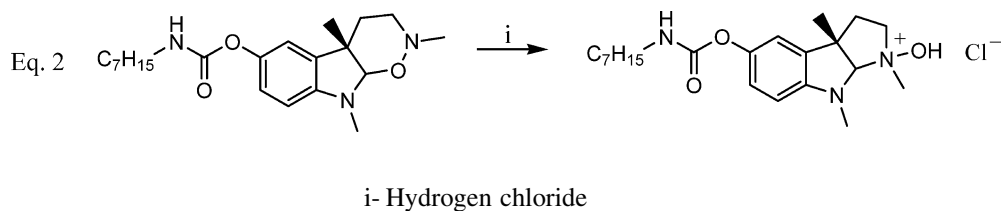
1. This is an example of the Polonovsky N-oxide rearrangement (1) which was previously used to prepare 3-hydroxy-1,4-benzodiazepine-2-ones (2).
2. The Polonousky N-oxide rearrangement was also used by the author to convert eseretole to geneseretole as illustrated in Eq. 1:



i- Hydrogen peroxide, potassium bicarbonate, methyl alcohol

3. In an earlier investigation by the author, N-alkyl imidazolureas were used as carbamation agents (3).

4. In the salt-free form, geneserine derivatives have a 1,2-oxazine orientation but tautomerize when converted into the salt form as illustrated in Eq. 2:



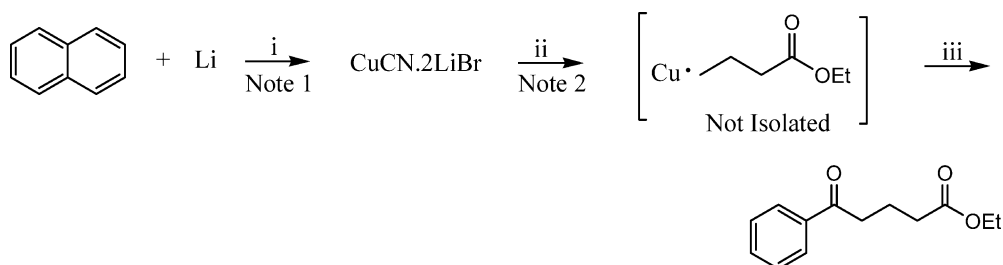
References

1. G. Lewin, *Tetrahedron*, 46, 7775 (1990); C.C. Bell, *J. Org. Chem.*, 27, 1601 (1962)
2. L. Schlager, US Patent 4,388,313 (June 14, 1983)
3. P. Chiesi *et al*, US Patent 5,538,968 (July 23, 1996)

Catalysis

Patent: Highly Reactive Form of Copper and Reagents Thereof
R.D. Rieke, US Patent 5,490,952 (February 13, 1996)
Assignee: University of Nebraska
Utility: Organo Copper Reagents

Reaction



i- THF, lithium bromide, copper(I)cyanide
ii- Ethyl 4-bromobutyrate, benzoyl chloride

Experimental

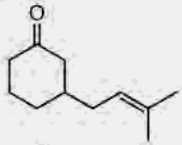
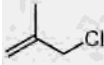
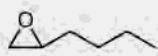
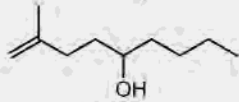
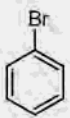
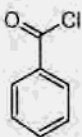
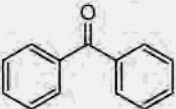
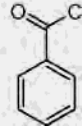
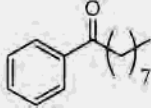
1. Copper(I)cyanide di(lithium bromide)

Lithium (8.46 mmol) and naphthalene (10.1 mmol) were mixed with 15 ml THF, stirred 2 hours, and then cooled to -100°C . In a separate reaction vessel, CuCN (8.0 mmol) and LiBr (17.27 mmol) in 5 ml THF were stirred until the Cu(I) salt dissolved. The solution was cooled to -40°C and transferred into lithium naphthalide using a cannula and the mixture stirred 5 minutes. The catalytic agent was ready for immediate use.

2. Ethyl 4-ketophenylbutyrate

The product from Step 1 was warmed to -35°C , charged with ethyl 4-bromobutyrate (1.95 mol), stirred 10 minutes, and benzoyl chloride (3 equiv.) added via syringe at -35°C . The solution was stirred 30 minutes, quenched with NH_4Cl , and the product isolated by flash chromatography techniques.

Derivatives

Halide	Electrophile	Product	Yield (%)
			81
			67
			87
			82

Notes

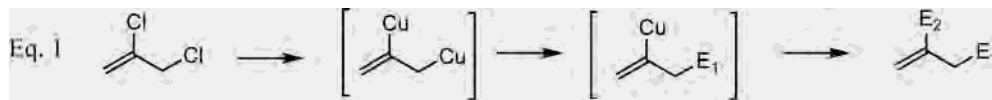
1. A second method for preparing the Step 1 zerovalent copper reagent was also provided by the author and described below:

Procedure

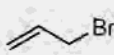
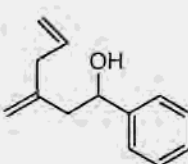
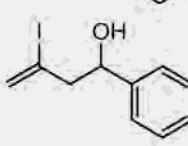
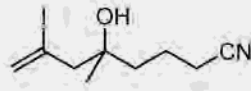
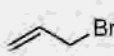
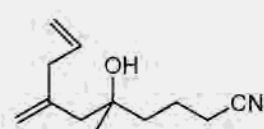
Lithium metal (8.40 mmol) and naphthalene (9.20 mmol) were mixed in 10 ml THF at ambient temperature 2 hours and then cooled to -108°C . Lithium 2-thienylcyanocuprate (32 ml 0.25 M) was added via cannula at -50°C and the solution stirred at -108°C 30 minutes. The resulting zerovalent copper species was ready for immediate use.

2. Other methods for preparing zerovalent copper of the current invention are provided (1,2,3).

3. Bisorganocopper reagents were also prepared by the author using 2,3-dichloropentene and subsequently reacted with two electrophiles as illustrated in Eq. 1:



Derivatives

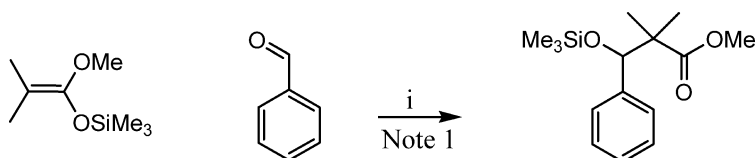
<u>E₁</u>	<u>E₂</u>	<u>Product</u>	<u>Yield (%)</u>
PhCHO			71
PhCHO	I ₂		69
	I ₂		32
			54

References

1. E.J. Corey *et al*, Tetrahedron Lett., 26, 6015, (1985); *ibid.*, 26, 6019 (1985); A. Alexakis *et al*, *ibid.*, 27, 1047 (1986)
2. W.J. Bartlet *et al*, US Patent 4,687,877 (August 18, 1987)
3. M.S.Cohen *et al*, US Patent 4,152,303 (May 1, 1979)

Patent: Lewis Acid Catalyst Composition
J. Nishikido *et al*, US Patent 6,436,866 (August 20, 2002)
Assignee: Asahi Kasei Kabushiki Kaisha
Utility: Lanthanide Lewis Acid Catalysts

Reaction



i- Ytterbium tris(tris(perfluorooctanesulfonyl)methide), toluene,
perfluorooctane, toluene

Experimental

1. Methyl 3-trimethylsiloxy-2,2-dimethyl-3-phenylpropionate

Benzaldehyde (81 mg) and methyl trimethoxysilyl dimethylketene acetal (165 mg) were added to a mixture of 3 ml perfluorooctane and 4 ml toluene. To this mixture was added 1 mol % (based on benzaldehyde) ytterbium tris(tris(perfluorooctanesulfonyl)methide) and the reaction stirred 15 minutes at 40°C. Mixing and heating were stopped and the mixture separated into upper toluene layer and lower perfluorooctane layer. Each layer was analyzed by gas chromatography; 99% of the product was detected in the lower layer. Atomic emission spectrometry indicated that at least 99% of the catalyst was also present in the lower layer.

Catalyst Preparation

1. Preparation of ytterbium tris(tris(perfluorobutanesulfonyl)-methide)

Tris(perfluorobutanesulfonyl)methide (3.0 g) was added to a solution of 15 ml acetonitrile, 15 ml water, and ytterbium carbonate (0.39 g). The mixture was stirred 7 hours at ambient temperature and was then heated to 50°C one hour. The mixture was filtered and the product isolated by vacuum drying at 50°C at 1–10 mm Hg followed by drying at 90°C at 0.01 mm Hg for 24 hours. Elemental analysis supplied.

2. Preparation of scandium tris(tris(perfluorooctanesulfonyl)methide)

Tris(perfluorooctanesulfonyl)methide (5.0 g) was added to a solution containing 10 ml acetonitrile, 10 ml water, and scandium acetate (0.25 g). The mixture stirred 5 hours at ambient temperature and then heated to 50°C one hour. The product was isolated as in the aforesaid method. Elemental analysis supplied.

Catalyst Summary

1. Preferred combinations of Lewis acid catalyst and perfluoro co-solvent are listed below:

Cation (III)	Counterion	Perfluoro Solvent
Ytterbium	Perfluorobutanesulfonylmethide, (C ₄ F ₉ SO ₂) ₃ C	Perfluorooctane, C ₈ F ₁₈
Lanthanum	Perfluorooctylsulfonylimide, (C ₈ F ₁₅ SO ₂) ₂ N	Perfluorocyclohexane, C ₆ F ₁₂
Scandium	Perfluorobutylsulfonylmethide, (C ₄ F ₉ SO ₂) ₃ C	Perfluorotoluene C ₆ F ₅ CF ₃

Catalyzed Reactions

1. Catalytic effectiveness was assessed using the reaction of anisole and acetic anhydride forming 4-methoxyacetophenone in chlorobenzene and are summarized below:

Catalyst	Yield (%)
None	0.1
AlCl ₃	4.0
((C ₄ F ₉ SO ₂) ₃ C) ₃ Yb	80
((C ₄ F ₉ SO ₂) ₃ C) ₃ La	83
((C ₈ F ₁₇ SO ₂) ₃ C) ₃ Sc	78

3. The effectiveness of the Lewis acid catalysts in electrophilic substitution, esterification, Diels-Adler cyclization, and lactonization reactions, respectively, is summarized below:

Reaction Type	Reagent 1	Reagent 2	Catalyst	Product	Yield (%)
Electrophilic	Anisole	Acetic anhydride	((C ₄ F ₉ SO ₂) ₂ N) ₃ Yt	4-Methoxy-acetophenone	97
Esterification	Cyclohexanol	Acetic anhydride	(C ₄ F ₉ SO ₂) ₃ Yb	Cyclohexyl-acetate	98
Diels-Adler	2,3-Dimethyl-butadiene	Methyl vinyl ketone	((C ₄ F ₉ SO ₂) ₂ N) ₃ La	4-Acetyl-1,2-dimethyl-cyclohexene	86
Lactonization	2-Adamantanone	Hydrogen Peroxide	((C ₈ F ₁₇ SO ₂) ₂ N) ₃ Sc	Baeyer-Villiger lactone	61

Notes

1. These Lewis acids require a two solvent medium for optimum utility. The perfluoro aliphatic component constitutes the first which dissolves the catalyst (1). The second component is preferably consists of a halocarbon such as dichloro- and dibromomethane; mono- and dichlorobenzene; chlorotoluene; and bromobenzene. Toluene has also been found to be effective. Interfacial agents have also been used and are discussed (2).

2. Gallium perfluoroalkanesulfonates Lewis acid catalysts have also been prepared and used in isomerization of branched-chain alkanes (3,4).
3. Lanthanum derivatives containing either bis(2-ethylhexyl)phosphate or 4-nonylphenoxide ligands have been found effective in polymerizing trans-butadiene (5).

References

1. I. Prakash, US Patent 6,642,406 (November 4, 2003)
2. I.T. Horvath *et al*, US Patent 5,463,082 (October 31, 1995)
3. G.A. Olah, US Patent 5,110,778 (May 5, 1992)
4. G.A. Olah, US Patent 4,721,559 (January 26, 1988)
5. T.J. Lynch, US Patent 6,184,168 (February 6, 2001)

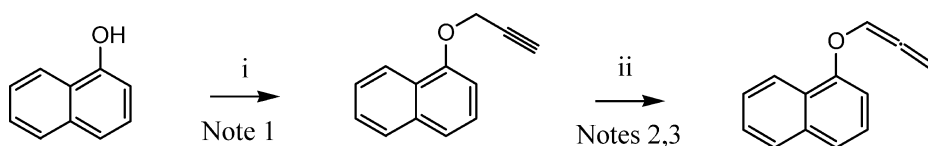
Cumulenes

Patent: Aromatic Allene Compounds of the Formula
 $(\text{CH}_2 = \text{CH-O})_n\text{-R-(A)}_m$ in Which R is an Aromatic Group and
Preparation Thereof
M. Yamada *et al*, US Patent 5,340,931 (August 23, 1994)

Assignee: Nippon Paint Co., Ltd.

Utility: Chemical Intermediate and Paint Component

Reaction



i- Propargyl bromide, tetrabutylammonium hydroxide,
sodium hydroxide, water

ii- Potassium t-butoxide, t-butyl alcohol, water

Experimental

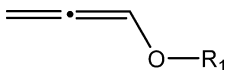
1. 1-Propargyloxynaphthalene

A reaction flask was charged with 21.3 parts 1-naphthanol, 53.0 parts deionized water, 6.7 parts NaOH, and 0.10 parts NBu_4OH . The mixture was stirred, 18.9 parts propargyl bromide added, and heated 6 hours at 80°C . The mixture was separated by column chromatography using silica gel and the product isolated in 63.6% yield.

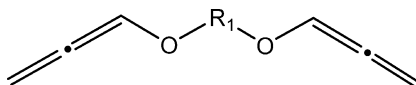
2. 1-Alleneoxynaphthylene

A flask was charged with 1.532 parts potassium t-butoxide, 6.8 parts t-butyl alcohol, 10.0 parts of the product from Step 1, and 23.3 parts t-butyl alcohol. The mixture was heated 1 hour at 50 °C, quenched with water, purified as in Step 1 and the product isolated in 43% yield.

Derivatives



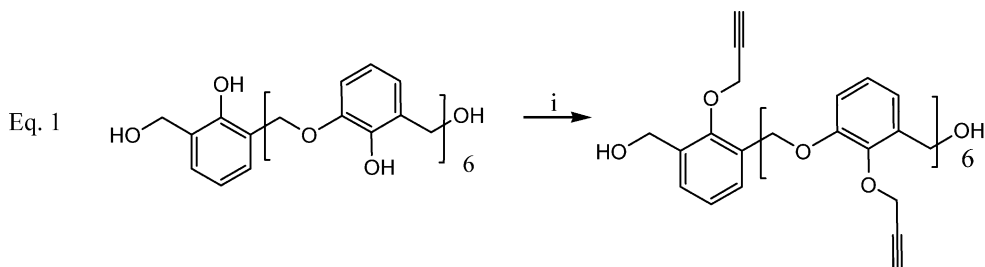
R ₁	MP(°C)	Yield (%)
1-(10-Methylantracene)	78.2–82.5	53
4-(Azobenzene)	oil	22.3
3-(Anthracene-2-carboxylic acid)	178.2–182.5	32
1-(2-Methyl-benzene-4-sulfonic acid)	oil	43.2
2-(Naphthalene-6-sulfonic acid)	80.5–83.5	45

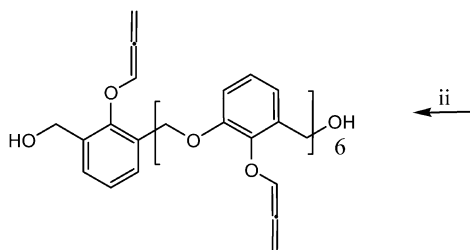


R ₁	MP(°C)	Yield (%)
1,4-(Naphthalene-2-carboxylic acid)	77.3–82.3	52.3
4-(4'-(3-Chlorobiphenyl))	140.5–143	54
2,7-Naphthalene	80.5–86	45.3

Notes

- Oligomeric allene derivatives were also prepared using phenolic-formaldehyde oligomers illustrated in Eq. 1:





i- Propargyl bromide, tetrabutylammonium hydroxide,
sodium hydroxide, water

ii- Potassium t-butoxide, t-butyl alcohol, water

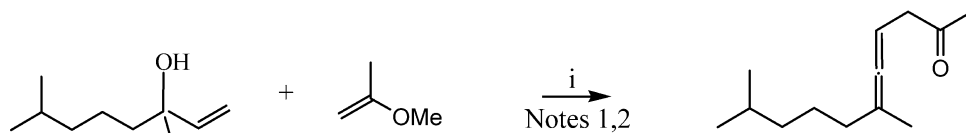
2. Other methods for preparing allene derivatives of the current invention are discussed (1).
3. In a previous investigation by the author, carbonates of acetylenic alcohols were prepared (2).

References

1. J. Takahashi *et al*, US Patent 4,946,865 (August 7, 1990)
2. M. Yamada *et al*, US Patent 5,258,542 (November 2, 1993) and US Patent 5,194,653 (May 16, 1993)

Patent: Preparation of Unsaturated Ketones
J.H. Teles *et al*, US Patent 6,184,420 (February 6, 2001)
Assignee: BASF Aktiengesellschaft
Utility: Chemical Intermediate

Reaction



i- Methyl alcohol, potassium hydrogensulfate, zinc support catalyst

Experimental

1. Zn/SiO₂ Support Catalyst

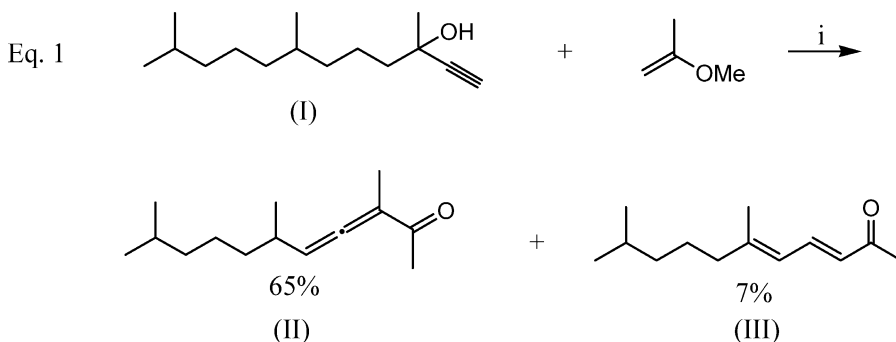
The catalyst was prepared by impregnating amorphous SiO₂ beads having a 3–6 mm diameter with a BET surface area of 358 m²/g, a water absorptivity of 0.9 ml/g, and a hardness of 43 N/molding, with ammonium zinc acetate solution. Thus, 225 g of SiO₂ carrier was impregnated with 151.7 g Zn(OAc)₂ · 2H₂O, dissolved in 220 g 9% NH₄OH at ambient temperature, dried 16 hours at 120°C and 4 hours at 250°C. The catalyst acetate/Zn ratio was 0.9 mol/mol.

2. 6,10-Dimethylundeca-4,5-dien-2-one

Approximately 90 ml of the catalyst from Step 1, 600 g hydro-hydrolinalool (1.30 mol), 306 g of an azeotropic mixture of 2-methoxypropene (3.9 mol) and methanol, and 1 g dried and powdered KHSO₄ were introduced into a pressure-resistant vessel. The mixture was heated to 140°C 20 minutes at a pressure of 5 bar, then heated an additional 2.5 hours at 120°C. The product yield was 249 g in 85% purity.

Notes

1. The author also converted 3,7,11-trimethyldodec-1-yn-3-ol into 6,10,14-pentadeca-4,5-diene-2-one, (I), using excess KHSO₄ as illustrated in Eq. 1 and described below.

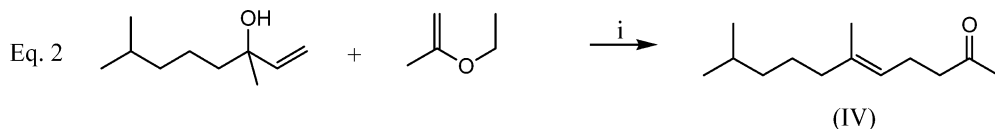


i- Methyl alcohol, potassium hydrogensulfate, zinc support catalyst

Procedure-1

A reactor was charged with 3,7,11-trimethyldodec-7-yn-3-ol (45 g), (I), (0.848 mol), 2-methoxypropene (2.78 mol), and KHSO_4 (0.58 g in 1.74 g water). The reactor was sealed and heated 1 hour at 120°C whereupon an additional KHSO_4 (0.58 g in 1.74 g water) added. The mixture was re-heated 1 hour at 120°C , products separated by distillation, and 6,10,14-pentadeca-4,5-diene-2-one, (II), and 6,10, 14-trimethylpentadeca-3,5-diene-2-one, (III), isolated in 65% and 7% yields, respectively.

- When KHSO_4 was replaced by 75% phosphoric acid, the corresponding non-conjugated unsaturated ketone was obtained as illustrated in Eq. 2 described below.



i- Methyl alcohol, potassium hydrogensulfate, zinc support catalyst, phosphoric acid

Procedure-2

A reactor was charged with 25.9 g hydrolinalool, 45.5 g of isopropenyl ethyl ether, and 93 mg 75% H_3PO_4 . The mixture was heated 12 hours at 175°C and the product, 6,10-dimethylundec-5-ene-2-one, (IV), isolated in 83% yield by atmospheric distillation.

- In previous investigations alkynes and alkyne derivatives containing enol ethers, alkoxy and acetal and ketal olefins were prepared by the author and are described (1).

4. Catalytic addition of nucleophiles to alkyne and allene derivatives using the Lewis acid and triphenylphosphine gold(I)trifluoroacetate are described (2).

References

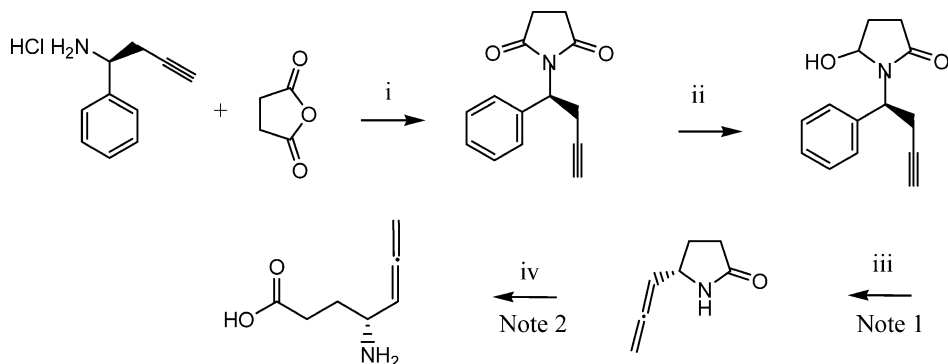
1. J.H. Teles *et al*, US Patent 6,211,416 (April 3, 2001) and US Patent 6,120,744 (September 19, 2001)
2. M. Schultz *et al*, US Patent 6,037,482 (May 14, 2000)

Patent: (S)-4-Amino-Hepta-5,6-Dienoic Acid and Intermediates Thereof
H.M. Kolb, US Patent 5,756,762 (May 26, 1998)

Assignee: Merrell Pharmaceuticals

Utility: Irreversible GABA-T Inhibitor

Reaction



- i- Triethylamine, toluene
- ii- Lithium triethylborohydride, THF
- iii- Trifluoroacetic acid, CH_2Cl_2
- iv- Hydrochloric acid, water

Experimental

1. (R)-N-(1-Phenyl-but-3-yn-1-yl)succinimide

(R)-1-Amino-1-phenyl-but-3-yn-1-ol hydrochloride (22.1 mmol), succinic anhydride (44.2 mmol) and 3.1 ml triethylamine dissolved in 200 ml toluene were refluxed 1 hour then cooled to ambient temperature. A second addition of 3.1 ml triethylamine was added and the mixture refluxed 18 hours. The aqueous layer was extracted with EtOAc, concentrated, purified by flash chromatography using EtOAc/heptane, 35:65, and the product isolated after re-crystallization in 2-propanol/heptane.

2. (1R, 5'R and 1R, 5'S)-N-(1-Phenyl-but-3-yn-1-yl)-5'-hydroxybutyrolactam

The product from Step 1 (0.44 mmol) was dissolved in 2 ml THF, cooled to -78°C , 1 M lithium triethylborohydride (0.66 mmol in THF) added at such a rate the temperature did not exceed -66°C , and the mixture stirred 1 hour after the addition was completed. The reaction was quenched using NaHCO_3 solution, extracted with EtOAc and purified as in Step 1 to give a 7:3 mixture of diastereomers at the 5' position.

3. (S)-5-Propadienylbutyrolactam

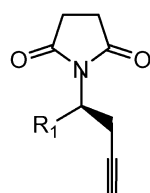
Trifluoroacetic acid (15.6 mmol) was added dropwise to the stereo-isomers from Step 2 (7.29 mmol) dissolved in CH_2Cl_2 , stirred for 2 hours, and then treated with water. The

organic layer was dried with MgSO_4 , purified by flash chromatography with methyl alcohol/ CH_2Cl_2 , 2:98, and the product isolated.

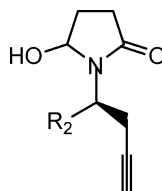
4. (S)-4-Amino-hepta-5,6-dienoic acid

The product from Step 3 (0.89 mmol) and 4 ml 1 M HCl were heated to 90°C 18 hours, cooled, and neutralized with 1 M NaOH solution. The product mixture was purified by ion exchange chromatography using Dowex 1X2, 100 mesh, hydroxide form using 0.25 M acetic acid, to give 0.1 g of product, mp = 135°C .

Derivatives



Succinimide

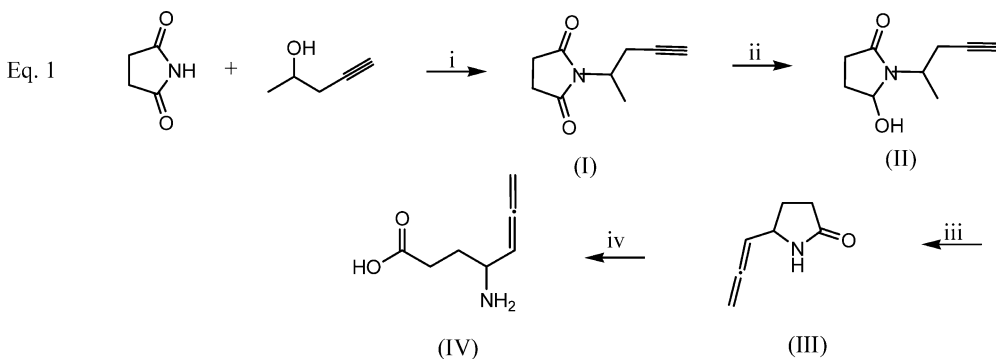


Butyrolactam

R_1	$[\alpha]_D^{25}$	R_2	$[\alpha]_D^{25}$
R-1-(4-Butylphenyl)	$[\alpha]_D^{25} = 20.0$ (c = 1.000)	R-1-(4-Butylphenyl)	$[\alpha]_D^{25} = 23.2$ (c = 2.000)

Notes

1. The preparation of other γ -allenic amino acids by the aza-Cope rearrangement is described (1).
2. The racemic product mixture of Step 4 was also prepared using succinimide (2) as illustrated in Eq.1 and described below by the author:



- i- Triphenylphosphine, diethylazodicarboxylate, THF
- ii- Sodium borohydride, methyl alcohol
- iii- Formic acid, trifluoroacetic acid
- iv- Hydrochloric acid, water

Procedure

The intermediates N-(1-methyl-but-3-yne)succinimide, (I), (2) and N-(1-methyl-but-3-yne)-5-hydroxysuccinimide, (II), (3,4) were previously prepared.

5-(1,2-Propadien-yl-2-pyrrolidone, (III),

N-(1-Methyl-but-3-yne)-5-hydroxysuccinimide, (II), (1.0 g) was dissolved in 10 ml 20% hydrofluoric acid and 80% CH_2Cl_2 at ambient temperature and left standing 5 days. The product was isolated by chromatography on silica gel using EtOAc.

4-Amino-5,6-diene-heptanoic acid, (IV)

The intermediate from Step 3 (3.0 g) was dissolved in 30% HCl and heated to 80°C 2 days. The product pH was adjusted to 3 using 1 M NaOH, extracted with diethyl ether and passed through ion exchange column Ag 50W X 8 using 20% pyridine-water. The product was re-crystallized from acetone and had a mp = 171°C. ^1H - and ^{13}C -NMR data supplied.

References

1. A.L. Castelhana *et al*, J. Amer. Chem. Soc., 106, 1877 (1984)
2. A. Krantz *et al*, US Patent 4,668,703 (May 26, 1987)
3. M. Mitsunobu *et al*, J. Am. Chem. Soc., 94, 679 (1972)
4. A.R. Chamberlin *et al*, Tetrahedron Lett., 23, 2619 (1982)

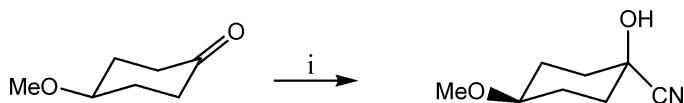
Cyanohydrins

Patent: Method for the Stereoselective Production of Substituted Cyclohexylanhydrins
F. Effenberger *et al*, US Patent 6,465,222 (October 15, 2002)

Assignee: BayerAktiengesellschaft

Utility: Pesticide and Herbicide Intermediate

Reaction



i- (S)-Oxynitrilase, hydrocyanic acid, diisopropyl ether,
hydrogen cyanide, diisopropyl ether

Experimental

1. trans-4-Methoxycyclohexylcyanohydrin

(R)-Oxynitrilases was adsorbed on either cellulose or nitrocellulose which had previously been swollen in a 20 mM citrate buffer solution having a pH = 3.3. To this was added 4-methoxycyclohexanone (1 mmol) and HCN (3.9 mmol) dissolved in 5 ml diisopropyl ether at ambient temperature. The reaction stirred 4.5 hours and the product isolated having a trans/cis ratio of 92:8, respectively, isolated.

Reaction Scoping

1. The effect of the enzyme source upon the formation of 4-methoxycyclohexylcyanoanhydrin is summarized below:

Enzyme Source	Units/mmol	Rx. Time (hr)	Conversion (%)	Trans/Cis Ratio
<i>Prunus amygdalus</i>	100	4.5	92	92:8
<i>Manihot esculenta</i>	100	1	100	70:30
<i>Hevea brasiliensis</i>	1000	2	100	65:35

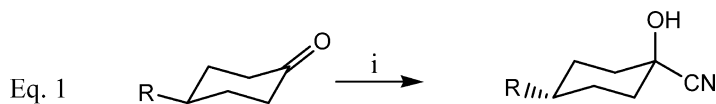
2. Solvent effects upon the formation and stereoselectivity of 4-methoxycyclohexylanhydrin using the (R)-oxynitrilase enzyme derived from *P. amygdalus* was also determined by the author and summarized below:

Solvent	Rx. Time (hr)	Conversion (%)	Trans/Cis Ratio
Diisopropyl ether	4.5	92	92:8
t-Butylmethyl ether	23	82	87:13
EtOAc	24	17	74:26

3. The effect upon formation of 4-methoxycyclohexylanhydrin using either (R)- and (S)-oxynitrilases contrasted with an uncatalyzed cyclohydrin reaction are summarized below:

Enzyme	Source	Conversion (%)	Cis/Trans Ratio
None	None	6	54:46
(S)-Oxynitrilase	Cassava	99	35:65
(R)-Oxynitrilase	Bitter Almonds	92	92:8

4. Substituent effect upon 4-substituted cyclohexylanhydrin formation, illustrated below in Eq. 1, using canna-derived (S)-oxynitrilase in 100 units/mmol on a nitrocellulose matrix in diisopropyl ether is summarized below:



i- (S)-Oxynitrilase, hydrocyanic acid, diisopropylether

R	Rx. Time (hr)	Conversion (%)	Cis/Trans Ratio
Ethyl	3	93	26:74
Ethoxy	1	99	39:61
n-Propyl	5	96	4:96
i-Propyl	5	93	3:97
Propoxy	2	91	13:87
Phenyl	3	95	1:99

Notes

1. Extraction methods for isolating (R)-oxynitrilase from bitter almonds (1) and (S)-oxynitrilase from cassava (2) are described.
2. The synthesis of optically active cyanohydrins using almond meal is discussed (3).
3. In an earlier investigation by the author, (S)-cyanohydrins were prepared using (S)-oxynitrilase obtained freeze-dried manioc leaves from Columbia (4).

References

1. W. Becker *et al*, Biochem. Z., 337, 156 (1963); *ibid*, 340, 301 (1966)
2. F. J. P. DeCampas Carvalho, "Dissertation", University of California, Davis (March 25, 1981)
3. P. Zandbergen *et al*, Synthetic Commun., 21, 1387 (1991)
4. F. Effenberger *et al*, US Patent 5,885,809 (March 23, 1999)

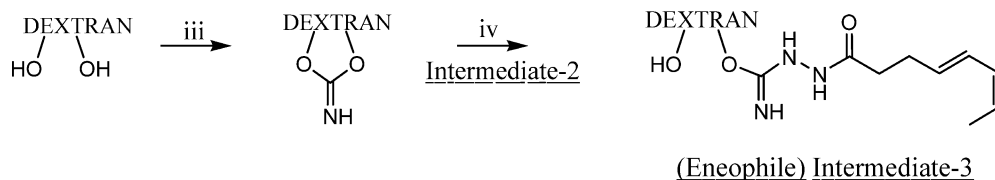
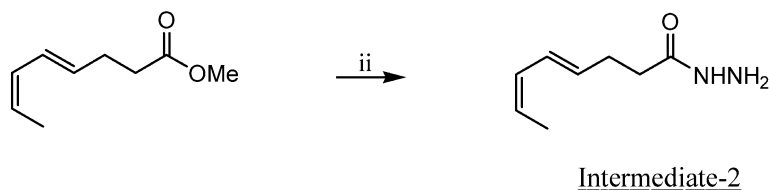
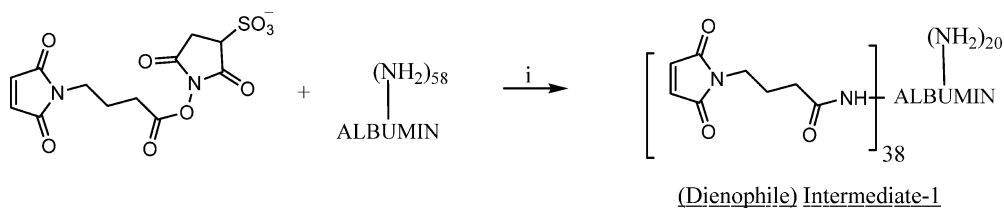
Cyclodextrane/Dextrane

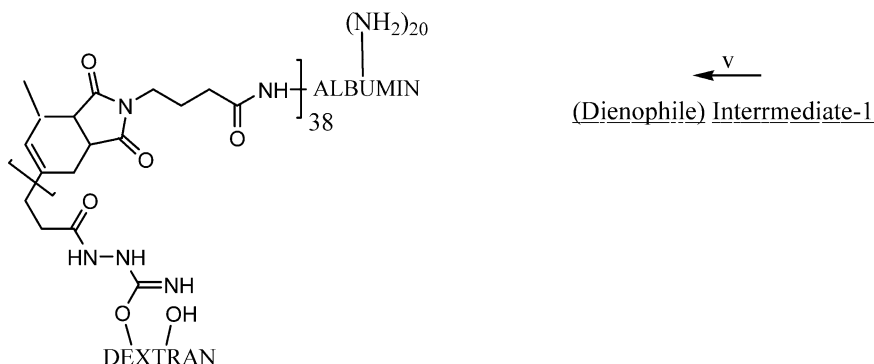
Patent: Conjugation of Biomolecules Using Diels-Adler Cycloaddition
V. Pozegay, US Patent 6,673,905 (January 6, 2004)

Assignee: United States of America as Represented by the Department of Health and Human Services

Utility: Analytical and Diagnostic Reagents Useful as Immunogens

Reaction





- i- Water, phosphate buffer solution
- ii- Hydrazine, methyl alcohol
- iii- Water, sodium hydroxide, cyanogen bromide, acetonitrile, phosphate buffer
- iv- Dimethylsulfoxide
- v- Water

Experimental

1. Albumin-g-N-(4-(N-succinimidyl)-butylamide (Dieneophile Intermediate-1)

Treatment of human serum albumin with 1.6 molar excess (based on 58 available amino groups) of 3-sulfosuccinimidyl-4-maleimidobutyrate in pH 7.5 phosphate solution provided the product as indicated by MALDI-TOF mass spectroscopy.

2. Octa-4,6-dienoic acid hydrazine (Intermediate-2)

To a solution of methyl octa-4,6-dienate (6 g) dissolved in 10 ml methyl alcohol was added 3 ml hydrazine and the mixture stirred 24 hours at ambient temperature. The mixture was filtered and the product isolated as a colorless crystal.

3. Dextran-graft-2-Imido-1,3-dioxolane

To a solution of dextran (MW ~ 3000 Da, $2.25 \mu\text{mol}$) dissolved in 2.2 ml water at 5°C was added 0.1 M NaOH until pH 10.5 was obtained. To this mixture was added 5 M cyanogen bromide ($50 \mu\text{l}$) dissolved in acetonitrile and the pH kept between 10.5 and 10.8. After 6 minutes the pH range was adjusted to 8.5 by the addition of pH 8 phosphate buffer and the product isolated.

4. Dextran-graft-Octa-4,6-dienoic acid hydrazine-N-imidoether (Eneophile Intermediate-3)

To the product from Step 3 was added the product from Step 2 ($25 \mu\text{mol}$) in 0.5 ml DMSO. The mixture was stirred for 3 hours, the pH stabilized at 8.18 over 5 minutes, and the product isolated.

5. Albumin-co-dextran

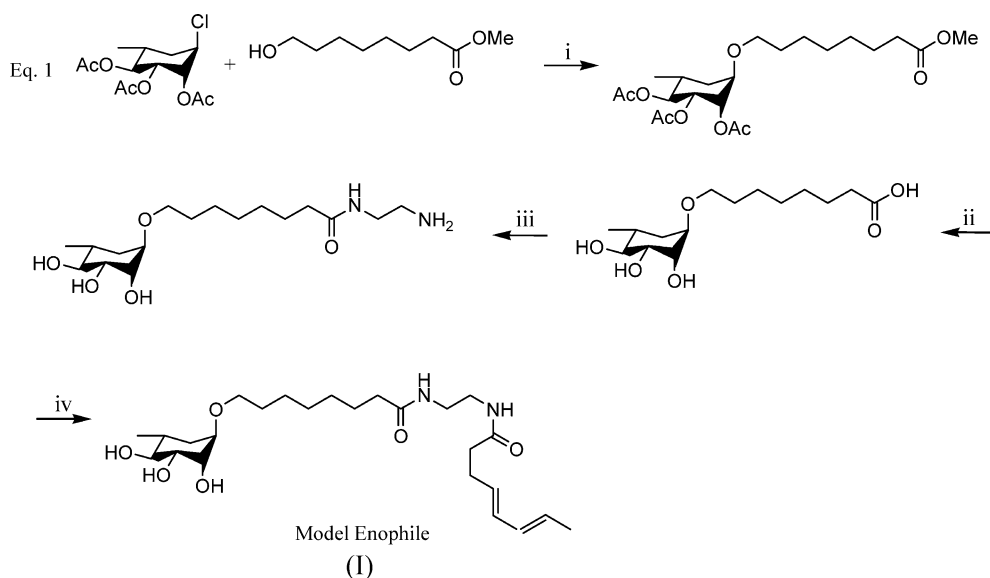
The products from Steps 1 and 4 were combined, their total volume being 1 ml, and reacted 22 hours at room temperature. The product was diafiltered through a YM-10 membrane using 6 changes of 5 ml water and the residue freeze-dried. MALDI mass spectrometry indicated the product had an average molecular weight of 90 kDa.

Derivatives

Diene Component	Dienophile Component
Polysaccharide of <i>Salmonella typhi</i>	<i>Pseudomonas aeruginosa</i>
Dextran	Human serum albumin
Hapten	Human serum albumin

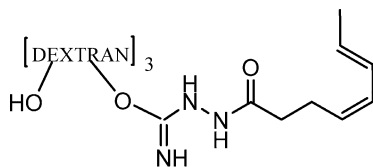
Notes

- For characterization purposes, a model enophile, (I), (1) was prepared by the author as illustrated below in Eq. 1:



- i- CH_2CH_2 , silver triflate, 2,6-di-*t*-butyl-4-methyl pyridine
- ii- Methyl alcohol, sodium methoxide
- iii- Ethylenediamine, ethyl alcohol
- iv- 4,6-Octadienoic acid

- Other model enophiles eneophiles, (II), were previously prepared by the author (2) and used in Diels-Alder reactions with human serum albumin.



(II)

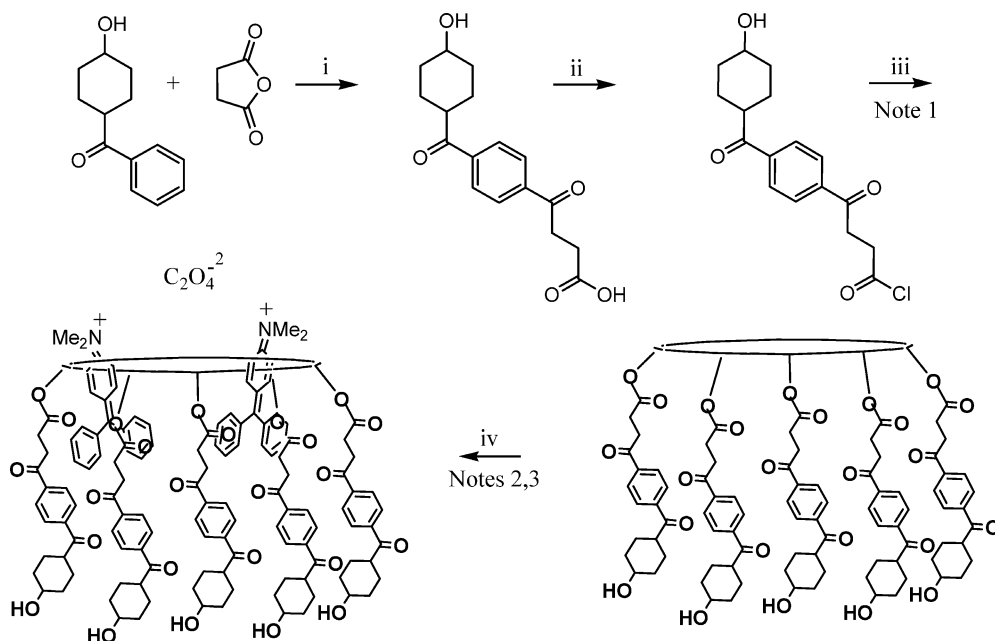
3. The preparation and use of other substrates is described (3).

References

1. S. Sabesan *et al*, J. Am. Chem. Soc., 108, 2068 (1986)
2. V. Pozsgay, J. Org. Chem., 63, 5983 (1998)
3. A. Lubineau *et al*, J. Chem. Soc. Perkin, 1, 3011 (1990)

Patent: Nohr-McDonald Elimination Reaction
J.G. McDonald *et al*, US Patent 6,211,383 (April 3, 2001)
Assignee: Kimberly-Clark Worldwide, Inc.
Utility: Colorant Stabilizer from UV Light

Reaction



Cyclodextrin Inclusion Complex

- i- THF, aluminum trichloride
- ii- Diethyl ether, sulfonyl chloride
- iii- β -Cyclodextrin, N,N-dimethylformamide
- iv- Malachite Green oxalate, N,N-dimethylformamide

Experimental

1. 4-(4-(Hydroxycyclohexylcarbonyl)phenyl)succinic acid

A reactor was charged with 1-hydroxycyclohexyl phenyl ketone (0.05 mol), 100 ml THF, succinic anhydride (0.05 mol) and $AlCl_3$ (6.7 g). The mixture was stirred at $0^\circ C$ 60 minutes, warmed to ambient temperature, and stirred 2 hours. Thereafter, the contents were

poured into 500 ml ice- water and 100 ml diethyl ether. The ether layer was isolated, dried and evaporated under reduced pressure and the product isolated in 87% yield.

2. 4-(4-(Hydroxycyclohexylcarbonyl)phenyl)succinyl chloride (Note 1)

The product from Step 1 (0.04 mol), 50 ml diethyl ether and thionyl chloride (0.05 mol) were mixed and stirred at 30°C 30 minutes. The solvent was removed at 0.01 Torr and the product isolated in 94% yield.

3. β -Cyclodextrin-graft-4-(4-(hydroxycyclohexylcarbonyl)phenyl) succinate

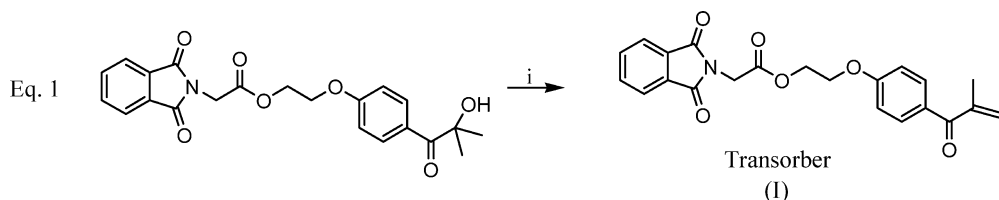
A reactor was charged with 100 ml DMF, the product from Step 2 (98 mmol), β -cyclodextrin (9.8 mmol) added, the mixture heated to 50°C, 0.5 ml TEA added, and the reaction continued one hour. Once at ambient temperature, the reaction volume was reduced by 90% by distillation and the remaining contents poured into iced brine solution. A precipitate formed and was isolated, dried, and powdered. It was purified using a 7.5 cm column containing 15 g silica gel using DMF.

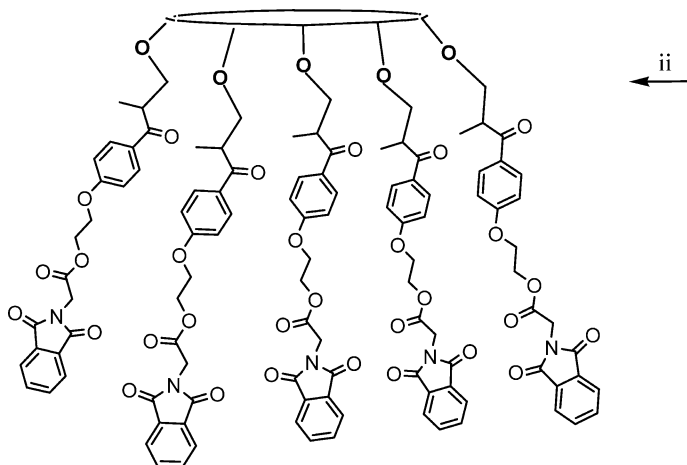
4. β -Cyclodextrin-graft-4-(4-(hydroxycyclohexylcarbonyl)phenyl) succinate-Malachite Green oxalate inclusion complex

The product from Step 3 (3.6 mmol) was dissolved in 150 ml DMF, Malachite Green oxalate (3.6 mmol) added, and the reaction stirred at ambient temperature 1 hour. The product was obtained as a blue-green powder the purified as described in Step 3.

Notes

1. A transorber is a chemical agent which absorbs radiation at a specific wavelength to protect a colorant from fading.
2. The Nohr-McDonald elimination reaction is a high temperature tertiary alcohol dehydration performed using a high boiling point aromatic solvent with zinc chloride and is described by the author. A second transorber, (I), was prepared by the author using the Nohr-McDonald elimination reaction and subsequently used to prepare the β -cyclodextrin graft polymer as illustrated in Eq. 1:





(I)

i- Zinc chloride, p-xylene

ii- N,N-dimethylformamide, p-toluenesulfonic acid,
 β -cyclodextrin

3. Transorber (I) of the current invention was also epoxidized and grafted onto thiol- β -cyclodextrin. Thereafter, the Victoria Pure Blue inclusion complex was prepared.
4. In a previous investigation by the author, imines (1), porphorins (2), and triiodiphenyl tetrahydrofuran (3) derivatives were prepared as colorant stabilizers from UV light and are described.

References

1. R.S. Nohr *et al*, US Patent 6,099,628 (April 8, 2000)
2. R.S. Nohr *et al*, US Patent 6,168,654 (January 2, 2001)
3. R.S. Nohr *et al*, US Patent 6,168,655 (January 2, 2001)

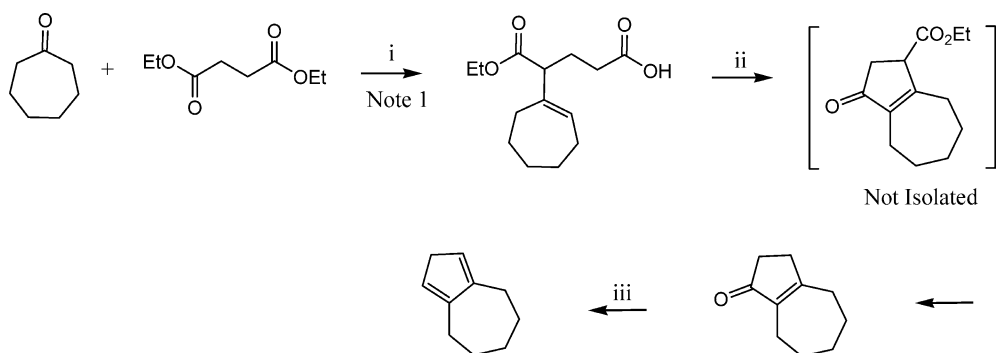
Cyclopentadiene

Patent: Cyclopentadienyl Derivatives and Process for Their Preparation
P. Biagini *et al*, US Patent 5,900,517 (May 14, 1999)

Assignee: Enichem S.p.A.

Utility: Co-components in Zirconium or Titanium Catalysts in α -Olefin Polymerisation Reactions

Reaction



- i- N,N-Dimethylformamide, potassium t-butoxide
ii- Phosphoric acid, phosphorous pentoxide, acetic acid,
hydrochloric acid
iii- Lithium aluminum hydride, diethyl ether

Experimental

1. Ethyl α -(α' -Cycloheptenyl)- β -hydroxycarbonylpropionate

A solution of cycloheptanone (0.5 mol), diethyl succinate (0.63 mol) dissolved in 500 ml DMF and potassium t-butoxide (0.67 mol) were mixed together while maintaining the temperature between 20 and 30°C. After 2 hours the mixture was poured into 2 L of water, HCl added to obtain a pH = 2–3, and the product extracted with diether ether and isolated in 99% yield.

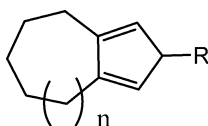
2. 3,4,5,6,7,8-Hexahydro-2H-azulen-1-one

The product from Step 1 was added to a mixture of 400 g 85% H_3PO_4 and 650 g P_2O_5 then heated to 90–95°C 4 hours. The mixture was hydrolyzed with water, extracted with diethyl ether, and a 65% yield of crude product isolated. The material was purified by dissolving in 100 ml HOAc, 100 ml water and 10 ml concentrated HCl and refluxing overnight. After neutralization, drying, and solvent removal the product was isolated in 64% yield.

3. 2,4,5,6,7,8-Hexahydroazulene

The product from Step 2 (16 g) was dissolved in 200 ml diethyl ether, LiAlH_4 (3 g) mixed in 300 ml diethyl ether added, and the reaction stirred between 5 and 10°C. The mixture was hydrolyzed, extracted with ether, purified by chromatography on silica gel using petroleum ether and the product isolated in 98% yield.

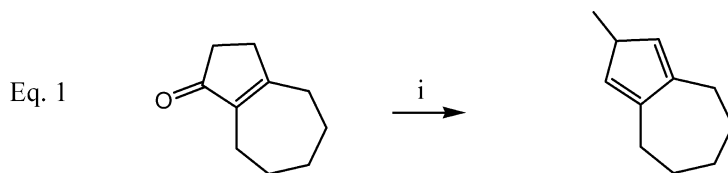
Derivatives



R	n	Yield (%)
Hydrogen	5	48
Hydrogen	6	20
Hydrogen	10	99
Methyl	10	~40

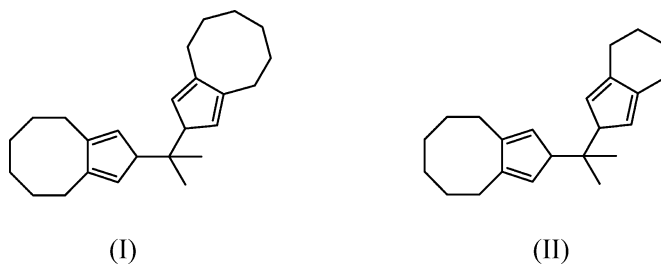
Notes

1. This is an example of the Stobbe condensation reaction and is discussed (1).
2. Alkylated 2,4,5,6,7,8-hexahydroazulene derivatives were also prepared by reacting the product of Step 2 with methyl lithium in diethyl ether overnight as illustrated in Eq. 1. Thereafter, the product was purified as described in Step 3 and isolated.

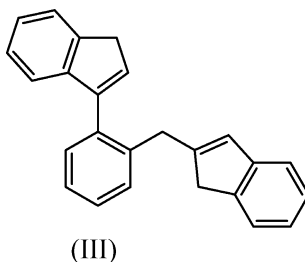


i- Methyl lithium, diethyl ether, p-toluenesulfonic acid,
methyl lithium

3. In a subsequent investigation by the author (2), symmetrical, (I), and asymmetrical, (II), bridged analogues of the current invention were prepared.



4. Other bridged analogues, (III), have been prepared and are described (3).



5. In a subsequent investigation, the products of the current invention were used with zirconium as catalyst co-components in the preparation of elastomeric copolymers of ethylene (4).

References

1. W.S. Johnson *et al*, Org. React., Vol 6, 2, (1951)
2. V. Banzi *et al*, US Patent 6,139,484 (October 31, 2000)
3. R. Santi *et al*, US Patent 6,417,418 (July 9, 2002)
4. V. Banzi *et al*, US Patent 5,917,072 (July 9, 2002)

Cyclopropanes

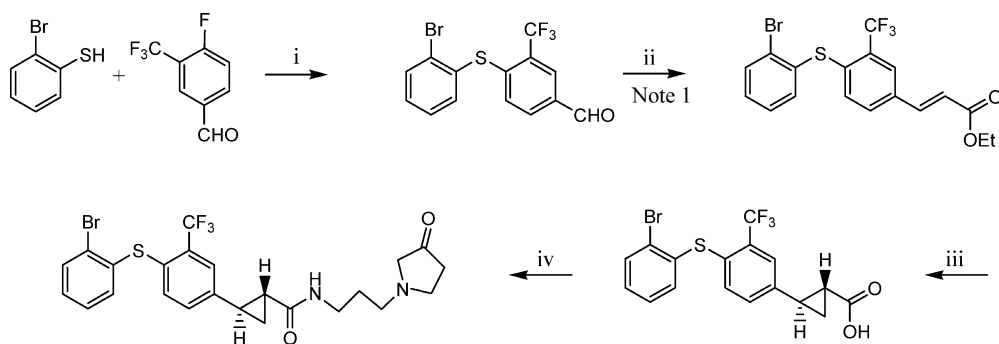
Patent: Aryl Phenylcyclopropyl Sulfide Derivatives and Their Use as Cell Adhesion Inhibiting Anti-Inflammatory and Immune Suppressive Agents

J.T. Link *et al*, US Patent 6,521,619 (February 18, 2003)

Assignee: Icos Corporation and Abbott Laboratories

Utility: Anti-Inflammatory and Immune Suppressive Agents

Reaction



i- Potassium carbonate, N-methyl pyrrolidine

ii- (Ethoxycarbonylmethyl)triphenylphosphonium chloride,
sodium hydride, THF

iii- Trimethylsulfoxonium iodine, dimethylsulfoxide,

iv- 1-(3-Aminopropyl)-2-pyrrolidinone,
1-[3-dimethylamino)propyl]-3-ethylcarbodiimide
hydrochloride, 1-hydroxylbenzotriazole hydrate,
N,N-dimethylformamide

Experimental

1. 4-[(2-Bromophenyl)thio]-3-trifluoromethylbenzaldehyde

To 100 ml N-methyl pyrrolidine containing K_2CO_3 (32.5 mmol) was added 2-bromothiophenol (32.5 mmol) and 4-fluoro-3-trifluoro-methylbenzaldehyde (26 mmol) and the mixture heated to $85^\circ C$ 12 hours. The mixture was cooled, partitioned between water and diethyl ether, the organic layer washed twice with brine, dried and the product isolated by chromatography using silica gel with hexane/EtOAc, 4:1, in 93% yield.

2. (2-Bromophenyl)[2-trifluoromethyl-4-(E-ethoxycarbonyl)ethenyl]-phenyl)sulfide

Sodium hydride (45 mmol) was added to (ethoxycarbonylmethyl)-triphenylphosphonium chloride (45 mmol) dissolved in 112 ml THF, stirred 1 hour, and the product from Step 1 (24.9 mmol) dissolved in 60 ml THF added dropwise. After 1 hour the reaction was quenched with saturated 50 ml aqueous NH_4Cl , the crude products dissolved in diethyl ether, washed, dried, purified by flash chromatography on silica gel using hexane/EtOAc, 6.5:1, and the product isolated in 85% yield.

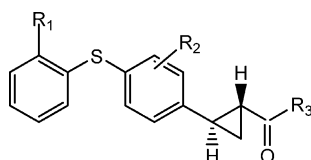
3. (+/-)-(2-Bromophenyl)[2-trifluoromethyl-4-trans-(2-carboxycyclo-prop-1-yl)phenyl)sulfide

NaH (18.5 mmol) was added to a solution of trimethylsulfoxonium iodine dissolved in 74 ml DMSO, stirred 1 hour, followed by the dropwise addition of the product from Step 2 (17.6 mmol) dissolved in 17.6 ml DMSO. The reaction turned red and was stirred 12 hours at ambient temperature. The mixture was worked up as in Step 2 using a 10:1 to 4:1 elution gradient, and the product isolated in 98% yield.

4. (+/-)-2-Bromophenyl[2-trifluoromethyl-4-(trans-(2-((3-(1-pyrrolidin-2-onyl)-prop-1-ylamino)carbonyl)cycloprop-1-yl)phenyl)sulfide

To 18 ml DMSO was added 1-(3-aminopropyl)-2-pyrrolidinone (6.7 mmol), the product from Step 3 (4.79 mmol), 1-[3-dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (5.99 mmol) and 1-hydroxybenzotriazole hydrate (7.2 mmol), and the reaction stirred overnight at ambient temperature. The crude products were diluted with EtOAc, rinsed with saturated NH_4Cl solution, and washed twice with water. The organic layer was dried, concentrated, purified by chromatography on silica gel using CH_2Cl_2 /methyl alcohol, 9:1, and the product isolated in 95% yield.

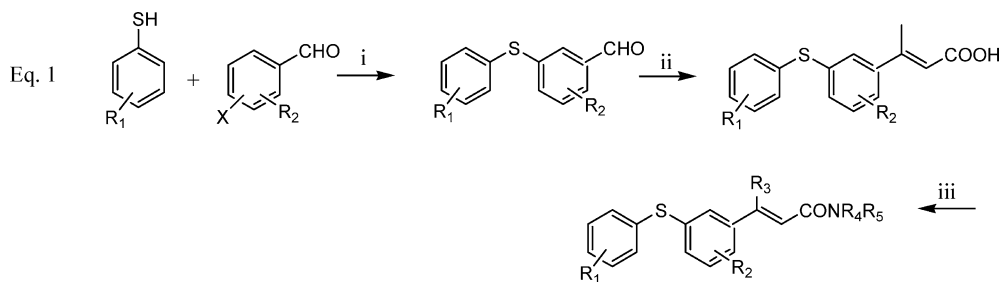
Derivatives



R_1	R_2	R_3	MS (M+1)
i-Propyl	2,3-Dichloro	N-Piperidine-3-carboxy	468
Methoxy	2-Trifluoromethyl	3-(1-pyrrolidin-2-onyl-prop-1-yl)amine	495
Morpholine	2-Trifluoromethyl	3-(1-pyrrolidin-2-onyl-prop-1-yl)amine	548
Bromine	2,3-Dichloro	Hydroxy	543

Notes

1. In an earlier investigation by the author, cinnamide-substituted diaryl sulfides (1) were prepared as illustrated in Eq.1:

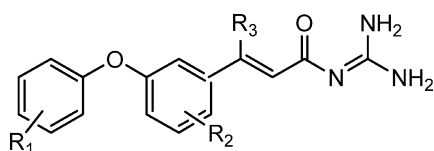


i- N,N-dimethylformamide, potassium carbonate

ii- Malonic acid, CH_2Cl_2 , piperidine

iii- Oxalyl chloride, Hunig's base, primary or secondary amine

2. Cinnamic acid guanidine phenoxide, (I), derivatives of the current invention have been prepared (2).



(I)

References

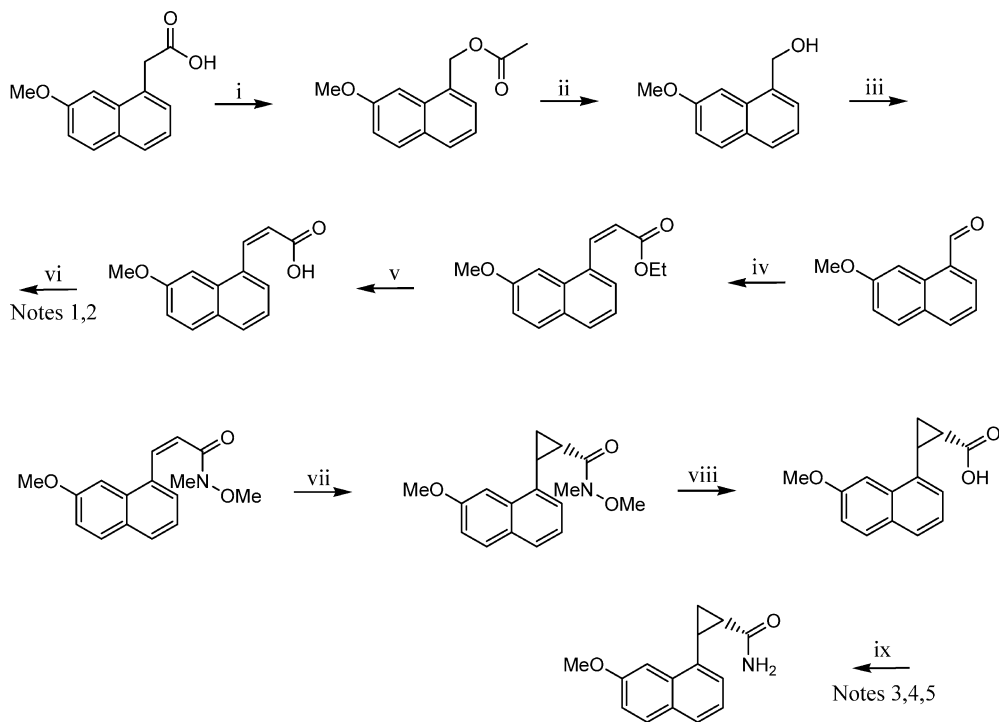
1. J. Link *et al*, US Patent 6,110,922 (August 29, 2000) and E. Poetsch *et al*, US Patent 5,817,862 (October 6, 1998)
2. J.-R. Schwark *et al*, US Patent 5,883,133 (March 16, 1999)

Patent: Cyclic Compounds Having a Cycloalkylene Chain
M. Langlosis *et al*, US Patent 6,583,319 (June 24, 2003)

Assignee: Les Laboratoires Servier

Utility: Preventing and Treatment of Sleep Disorders

Reaction



- i- Benzene, acetic acid, lead tetraacetate
- ii- Potassium hydroxide, methyl alcohol
- iii- CH_2Cl_2 , manganese oxide
- iv- THF, sodium hydride, triethylphosphonoacetate
- v- Ethyl alcohol, sodium hydroxide
- vi- Oxalyl chloride, N,O-dimethylhydroxylamine, CH_2Cl_2 , sodium carbonate
- vii- Dimethylsulfoxide, trimethylsulfonium iodide, sodium hydride
- viii- Potassium t-butoxide
- ix- Ethyl chloroformate, triethylamine, sodium azide, toluene, hydrochloric acid

Experimental

1. (7-Methoxy-1-naphthyl)methyl acetate

7-Methoxy-naphtha-1-yl-acetic acid (0.225 mol) was dissolved in a mixture of 700 ml benzene and 300 ml HOAc and $\text{Pb}(\text{OAc})_4$ (0.225 mol) added. The mixture heated to 60–70°C, refluxed 30 minutes, cooled, concentrated, extracted with 200 ml CH_2Cl_2 . 500 ml Diethyl ether was added causing a creamy white precipitate which was filtered through Celite. The ethereal solution was dried and concentrated from which the product recrystallized when chilled and was isolated.

2. (7-Methoxy-1-naphthyl)methanol

The product from Step 1 (0.15 mol) was dissolved in 300 ml methyl alcohol containing KOH (0.60 mol) and the mixture stirred 3 hours at ambient temperature. The mixture was hydrolyzed over ice containing concentrated HCl, the precipitate isolated, dried, re-crystallized in a mixture of CH_2Cl_2 and cyclohexane, and the product isolated as white crystals.

3. 7-Methoxy-1-naphthaldehyde

The product from Step 2 (0.10 mol) was dissolved in 300 ml CH_2Cl_2 and manganese oxide (65 g) added in three stages ($t = 0$, 25 g; $t = 90$ minutes, 25 g; and $t = 24$ hours, 15 g). The mixture was filtered over silica gel to yield an oil which solidified upon cooling.

4. Ethyl 3-(7-methoxy-1-naphthyl)-2-propenate

The product from Step 3 (10.7 mmol) was dissolved in 20 ml THF and NaH (60% in oil, 1.2 eq) and 2.5 ml triethyl phosphonoacetate (1.2 eq) added. The mixture stirred 3 hours, refluxed overnight, and the product isolated as a dark oil.

5. 3-(7-Methoxy-1-naphthyl)-2-propenoic acid

The product from Step 4 (32.8 mmol) was dissolved in 150 ml ethyl alcohol containing 40 ml 2 M NaOH and stirred at ambient temperature 3 hours and refluxed overnight. The product was isolated as a white solid.

6. N-Methoxy-N-methyl-3-(7-methoxy-1-naphthyl)-2-propenamide

The product from Step 5 (28.5 mmol) was initially converted into the acid chloride by reacting with 5 ml oxalyl chloride then added to a suspension of N,O-dimethylhydroxylamine chloride (5.6 g) in a mixture of CH_2Cl_2 and water containing Na_2CO_3 (3 g). The protected acid was isolated as a pale yellow solid.

7. trans-N-Methoxy-N-methyl-2-(7-methoxy-1-naphthyl)-1-cyclopropanecarboxamide

The product from Step 6 (21.4 mmol) was dissolved in 30 ml DMSO and added to a suspension of ylid produced starting from $(\text{CH}_3)_3\text{SOI}$ (10.6 g) dissolved in 50 ml hot DMSO and NaH (1.25 g). It was stirred 15 hours at ambient temperature and 4 hours at 50°C and the product isolated as a brown oil.

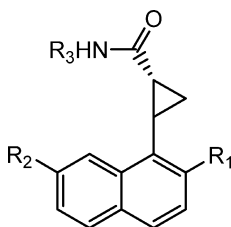
8. **trans-2-(7-Methoxy-1-naphthyl)-1-cyclopropanecarboxylic acid**

The product from Step 7 (21 mmol) was dissolved in 50 ml diethyl ether containing 15.4 g potassium t-butoxide and stirred 2 days at ambient temperature. A brownish solid was isolated and used without purification.

9. **trans-2-(7-Methoxy-1-naphthyl)-1-cyclopropanamine**

The product from Step 8 and ethyl chloroformate (1.5 eq) in Et₃N and acetone were reacted to yield the mixed anhydride which was treated with sodium azide (1.3 eq) and heated to 80°C in toluene. The resulting isocyanate was stirred 36 hours in an aqueous solution of 20% HCl and the amine isolated.

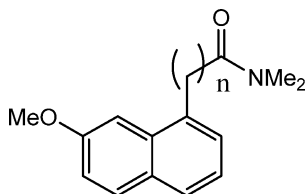
Derivatives



R ₁	R ₂	R ₃	Melting Point (°C)
Hydrogen	Methoxy	n-Butyl	119
Methoxy	Hydrogen	Methyl	155
Methoxy	Methoxy	Methyl	128
Methoxy	Methoxy	n-Propyl	135

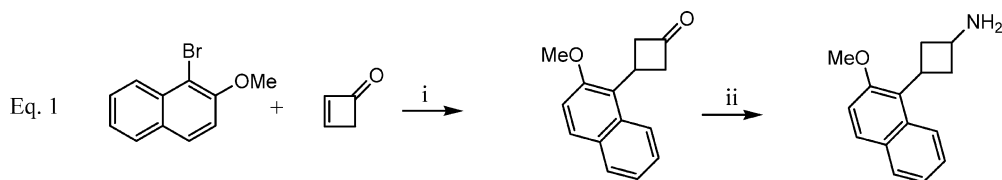
Notes

1. A method for preparing (7-methoxy-1-naphthyl)-N,N-dimethylacetamide and chain extension analogues, (I), is described (1).
2. Methods for preparing 1,2,3,4-tetrahydronaphthyl acetamide derivatives are described (2).



(I)

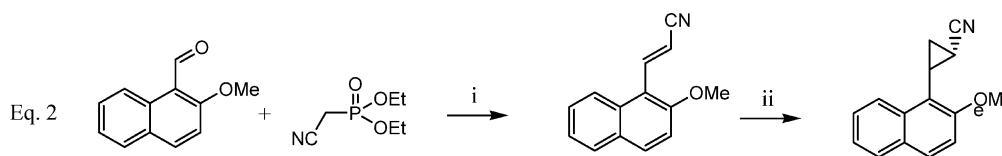
3. The preparation of cyclobutane, cyclopentyl, and cyclohexyl, Step 9 derivatives of the current invention were also provided by the author as illustrated in Eq. 1:



i- Magnesium, THF; hydrochloric acid

ii- Hydroxylamine, THF, Raney nickel, hydrogen

4. Step 9 an example of the Curtis rearrangement (3).
 5. A method for preparing carbonitrile Step 8 analogues of the current invention was also provided by the author as illustrated in Eq. 2:



i- THF, sodium hydride

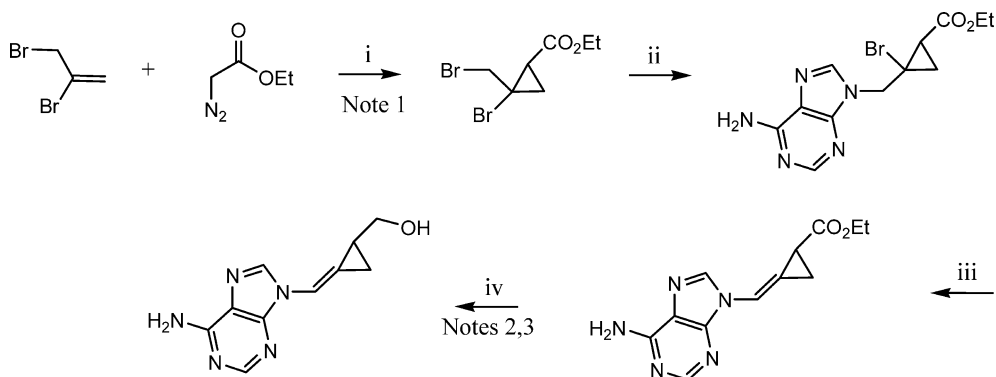
ii- Trimethylsulfoxonium iodide, sodium hydride,
dimethylsulfoxide

References

1. D. Lesieur *et al*, US Patent 5,731,352 (March 24, 1998)
2. D. Lesieur *et al*, US Patent 5,780,512 (July 14, 1998)
3. J.M. Sanders, Chem. Rev., 43, 205 (1948)

- Patent:** 2-Hydroxymethylcyclopropylidene-methylpurines and -Pyrimidines as Antiviral Agents
J. Zemlicka *et al*, US Patent 6,352,991 (March 5, 2002)
- Assignee:** Wayne State University, The Regents of the University of Michigan
- Utility:** Antiviral Agent for Treatment of HCMV, HSV-1, HSV-2, HHV-6, HIV, EBV and HBV

Reaction



- i- CH_2Cl_2 , dirhodium tetraacetate, potassium permanganate, sodium thiosulfate
- ii- Adenine, sodium hydride, N,N-dimethylformamide
- iii- Potassium t-butoxide, N,N-dimethylformamide
- iv- Diisobutylaluminum hydride, THF

Experimental

1. cis- and trans-Ethyl-2-bromo-2-bromomethylcyclopropane-1-carboxylate

Ethyl diazoacetate (0.20 mol) was added at ambient temperature to a solution of $\text{Rh}_2(\text{OAc})_4$ (0.05 mol) along with 2,3-dibromopropane (0.34 mol) dissolved in 3 ml CH_2Cl_2 at a rate of 1.1 ml/hr using a syringe pump. The mixture was distilled under vacuum and volatiles trapped in a cold finger. To the oily residue was added 100 ml water followed by the portionwise addition of 30 g KMnO_4 , excess reagent removed using sodium thiosulfate. The mixture was filtered and the solids washed 4 times with 86 ml diethyl ether using a sonicator. The ether solution was washed twice with 100 ml saturated NaHCO_3 , 250 ml water, brine, and dried. The cis/trans mixture was isolated in

91% yield and used directly in Step 2. ^1H - and ^{13}C -NMR, IR and EIMS data supplied for both dibromoesters esters.

2. **cis- and trans- N^9 -(1-Bromo-2-carboethoxycyclopropyl methyl)adenine**

The mixture from Step 1 (3.0 mmol) was added to a suspension of sodium adenine [prepared from adenine (3.0 mmol) and NaH (3.0 mmol) in 25 ml DMF] and the mixture heated to 80°C 12 hours. The solvent was removed, the residue adsorbed on 3 g silica gel of a 70 g silica gel column, and the mixture eluted using CH_2Cl_2 /methyl alcohol, gradient 96:4 to 94:6. The cis isomer was isolated in 29.9% yield, mp = $200\text{--}203^\circ\text{C}$; trans isomer, 17.6% yield, mp = $186\text{--}189^\circ\text{C}$. ^1H - and ^{13}C -NMR, IR, UV-Vis and EIMS data supplied for both isomers.

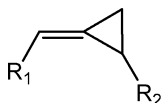
3. **syn- and anti- N^9 -(2-Carboethoxycyclopropylidenemethyl)adenine**

The isomeric mixture from Step 2 (1.023 mmol) was dissolved in 35 ml DMF at 0°C to which potassium t-butoxide (4.5 mmol) was added and the mixture stirred for 2 hours. Thereafter the solution was added dropwise into 20 ml saturated aqueous NH_4Cl and stirred 15 minutes. The solvents were removed, the residue purified by chromatography on silica gel using CH_2Cl_2 /methyl alcohol, 9:1, and isomers isolated in 70% yield as a white powder, mp = $166\text{--}175^\circ\text{C}$. ^1H - and ^{13}C -NMR, IR, UV-Vis and EIMS data supplied for both isomers.

4. **syn- and anti- N^9 -2-Hydroxymethylcyclo propylidenemethyl)adenine**

The isomers from Step 3 (3.4 mmol) were dissolved in 50 ml THF at 0°C and 27.2 ml 1 M diisobutylaluminum in THF added. Thereafter, the mixture stirred 4 hours. Saturated aqueous NH_4Cl was then added and a gel-like solid formed and was filtered. The residue was purified by chromatography on silica gel using CH_2Cl_2 /methyl alcohol, gradient 9:1 to 85:15, and isomers isolated in 75% yield. A solution of the product mixture (2.56 mmol) was dissolved in 30 ml DMF containing 0.51 ml N,N-dimethylformamide dimethyl acetal and stirred at ambient temperature 14 hours. The solvent was removed and a viscous yellow syrup isolated. The mixture was purified by flash chromatography on silica gel using CH_2Cl_2 /methyl alcohol, gradient 92:8 to 85:15, and the syn and anti isomers separated in 37.8% and 37.2%, respectively. ^1H - and ^{13}C -NMR data supplied.

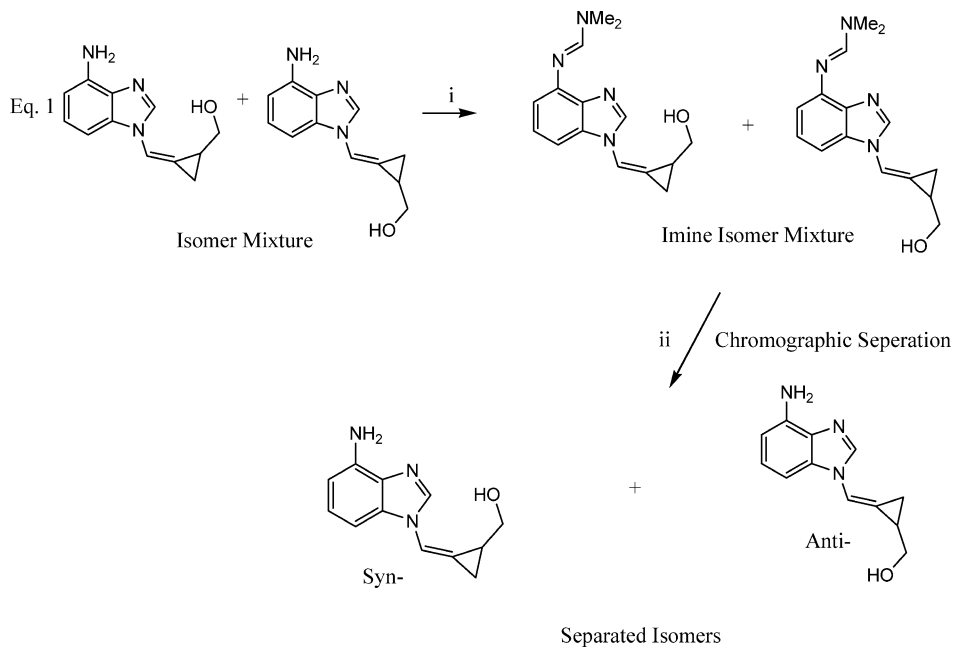
Derivatives



R_1	R_2	MP(°C)
2-Amino-6-chloropurin- N^9 -yl	Hydroxymethyl	Syn, 214–216; Anti, 201–204
Cytosin	Hydroxymethyl	Syn, 189–193; Anti, 177–181
Guanin- N^9 -yl	Hydroxymethyl	Syn, >300 Anti, >300
Adenin- N^9 -yl	Methyl phenylphosphono-L-alaninate	Syn, 135–141

Notes

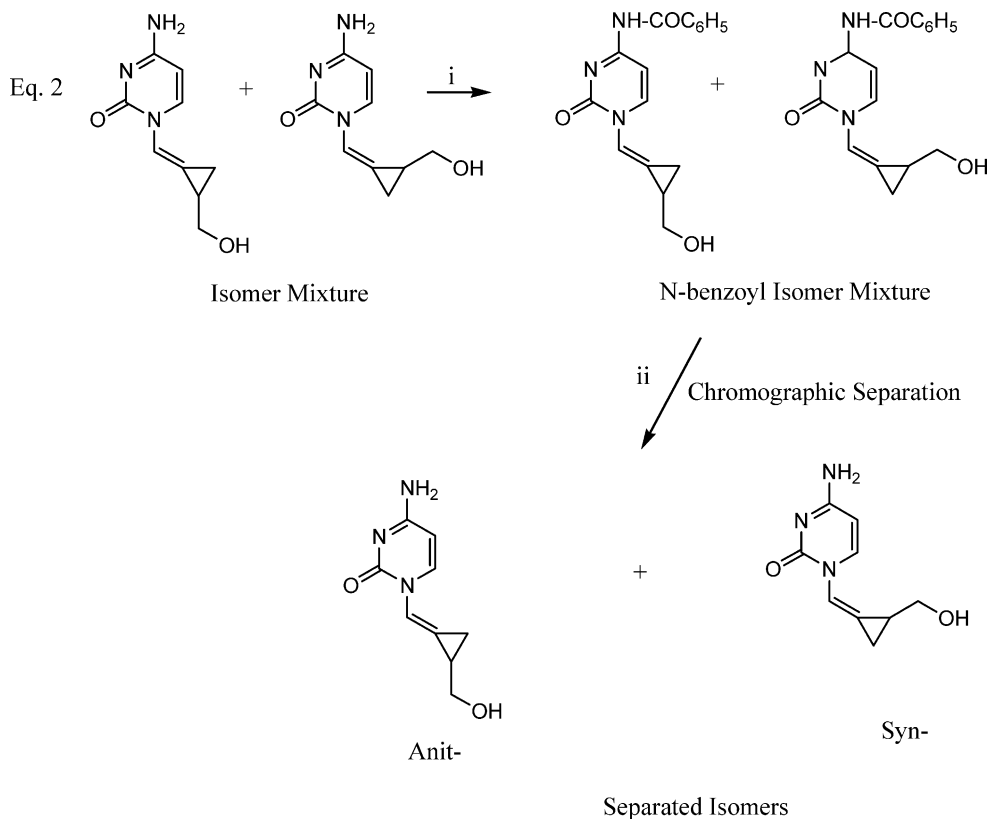
- Although both *cis*- and *trans*-ethyl-2-bromo-2-bromomethylcyclo propane-1-carboxylates were generated in the first reaction, only a single isomer is depicted. The *syn*- and *anti*-isomers of Step 4, N^9 -(2-hydroxymethylpropylidenemethyl)adenine, were separated in the last step.
- Adenine isomers were separated by converting *syn*- and *anti*- N^9 -(2-hydroxymethylpropylidenemethyl)-adenine to the corresponding imines using *N,N*-dimethylformamide dimethyl acetal (1) as illustrated in Eq.1:



i- *N,N*-dimethylformamide, *N,N*-dimethylformamide dimethyl acetal

ii- Ammonia, methyl alcohol

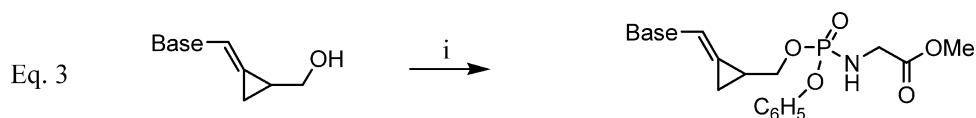
3. In an earlier investigation, cytosin- N^1 -yl syn/anti-isomers were isolated and separated by converting to the N^4 -benzoylcytosin- N^1 -yl intermediate as illustrated in Eq. 2 and discussed (2):



i - Benzoic anhydride, ethyl alcohol

ii - Ammonia, methyl alcohol

4. Phosphoamido derivatives of Step 4 were also prepared (3) by using phenylmethoxalaninyl phosphorochloridate with Step 4 syn- or anti-hydroxymethylcyclopropane derivatives as illustrated in Eq. 3:



i - Phenylmethoxalaninyl phosphorochloridate,
N-methylimidazole, THF and pyridine

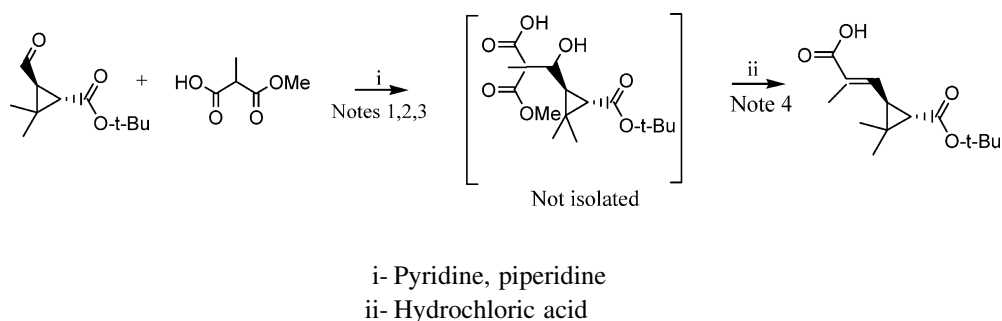
5. The preparation of pyrimidine and purine 1,2-butadiene-4-ol derivatives of the current invention is described (4).

References

1. J. Zemlicka *et al.*, Collect. Czech. Chem. Commun., 32, 3159 (1967)
2. M.R. Harnden *et al.*, J. Med. Chem., 33, 187 (1990)
3. C. McGuigan *et al.*, Antiviral Res., 17, 311 (1992)
4. S. Broder *et al.*, US Patent 4,935,427 (June 19, 1990)

Patent: Process of Producing Cyclopropanecarboxylate Compounds
T. Furukawa *et al*, US Patent 6,414,181 (July 2, 2002)
Assignee: Sumitomo Chemical Company, Limited
Utility: Pyrethroid Precursor

Reaction



Experimental

1. t-Butyl (+/-)-trans-2,2-dimethyl-3-2-carboxy-(E)-1-propenylcyclopropane carboxylate

t-Butyl (+/-)-trans-2,2-dimethyl-3-formyl-cyclopropanecarboxylate (0.202g) was dissolved in 5 ml pyridine, 0.2 ml piperidine and methyl malonic acid (0.242 g) added, and the mixture stirred at 60°C 1 hour.

2. t-Butyl (+/-)-trans-2,2-dimethyl-3-hydro-3-((2-methyl)-methyl malonic acid) cyclopropanecarboxylate

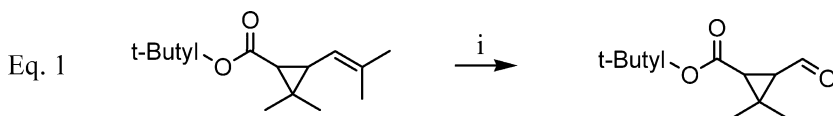
At ambient temperature, 100 ml dimethyl ether was added to the product from Step 1 and the solution washed with 3 M HCl and brine. The organic layer was isolated, dried, removed under reduced pressure, the product purified using chromatography on silica with n-hexane/EtOAc, 3:1, and isolated in 96% yield. ¹H-NMR data supplied.

Optimization Studies

Amine	Vol (ml)	Solvent	Reaction Temp. (°C)	Reaction Time (hr)	Yield (%)
Piperidine	0.96	Pyridine	75	1	79.7
Diisopropylamine	1.3	Pyridine	80	4	0
Trimethylamine	1.5	Toluene	80	5	11.1
Dibutylamine	1.0	Pyridine	65	5	25.1

Notes

1. The synthetic route of this instant invention has distinct advantages over the Horner-Emmon reaction utilizing phosphonates (1) or the Matsui process using selenium dioxide (2) both of which discussed.
2. The preparation of the reagent of Step 1 and other ester derivatives is described (3) and illustrated in Eq. 1:



i- Ozone

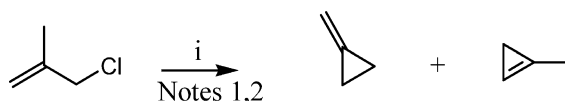
3. Decarboxylation of malonic esters occurs in the presence of specific secondary amines, preferably, piperidine, morpholine, pyrrolidine, diethylamine or N-methylethanolamine (3).
4. Cyclopropylacetylene has been prepared by converting the product of Step 2 into (E,Z)-1-bromocyclopropylethene followed by dehydrobromination using DMSO and potassium t-butoxide and is described (4).

References

1. S. Sugivama *et al*, Agric. Biol. Chem., 36, 565 (1972)
2. T. Matsui *et al*, Agric. Biol. Chem., 27, 373 (1963)
3. P. R. Ortiz de Montellano *et al.*, J. Org. Chem., 43, 4323 (1978)
4. J.M. Fortunak *et al*, US Patent 6,049,019 (April 11, 2000)

Patent: Process for the Preparation of Methylenecyclopropane
P. Binger, US Patent 5,723,714 (March 3, 1998)
Assignee: Studiengesellschaft Kohle mbH.
Utility: Industrial Preparation of Methylene-cyclopropane

Reaction



i- Potassium bis(trimethylsilyl)amide, o-xylene

Experimental

1. Methylene-cyclopropane

Potassium bis(trimethylsilyl)amide (0.31 mol) was dissolved in 100 ml o-xylene and β -methallylchloride (0.25 mol) added dropwise at 145°C over 60 minutes. The released gas was trapped at -78°C in a cold trap of which 97% consisted of methylene-cyclopropane and 3% of 1-methylcyclopropane.

Optimization Studies

Bis(trimethylsilyl)-amide Cation	Reaction Solvent	Product Yield (%)	Methylene Cyclopropane Composition (%)	1-Methyl-cyclopropane Composition (%)
Sodium	Toluene	86	77	23
Sodium	Di-n-Butyl ether	79	86	14
Lithium	Toluene	80	88	12
Potassium	o-Xylene	68	97	3

Notes

- The reaction of β -methallylchloride with sodium and potassium amide was originally designed for the preparation of 1-methylcyclopropene when using a low boiling solvent (1). Using higher boiling point solvents, however, both 1-methylcyclopropene and methylenecyclo-propane are produced. Conversions of 98% of methylenecyclopropane were observed using DMSO as the reaction solvent (2).
- Methylcyclopropene has also been prepared by reacting 3-chloro- or bromo-2-methylpropene with sodium amide or lithium di-isopropylamide in mineral oil and the product trapped in an α -dextrin matrix (3). In addition, it has been prepared in mineral oil using catalytic amounts of hexamethyldisilazane (4) as described below:

Procedure

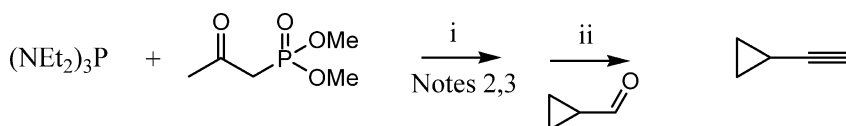
Sodium amide (2.79 mol) and 110 ml light mineral oil were heated to 45°C whereupon hexamethyldisilazane (0.03 mol) was added. Over 50 minutes, 3-chloro-2-methylpropene (2.23 mol) was slowly added and the evolving gas scrubbed with water then condensed in a dry ice cooled trap. The total product weight consisted of 39.5 g of which 39.3 g comprised 1-methyl-cyclopropene.

References

1. F. Fischer *et al*, J. Org. Chem., 30, 2089 (1965)
2. R. Koster *et al*, Synthesis, 6, 322 (1971)
3. J. Daly *et al*, US Patent 6,313,068 (November 6, 2001)
4. R.M. Jacobson, US Patent 6,452,060 (September 17, 2002)

- Patent:** Synthesis of Cyclopropaneacetylene by a One Pot Process
K.M.J. Brands, US Patent 6,552,239 (April 22, 2003)
- Assignee:** Merck & Co., Inc.
- Utility:** Precursor for the Preparation of HIV Reverse Transcriptase (Note 1)

Reaction



- i- Bromine, acetonitrile, sodium azide,
1,8-diazabicyclo[5.4.0]undec-7-ene
- ii- Methyl alcohol, potassium carbonate

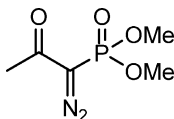
Experimental

1. Cyclopropaneacetylene

A solution of bromine (31.5 mmol) dissolved in 20 ml acetonitrile was cooled to -15°C and hexaethylphosphorous triamide (34.1 mmol) added at such a rate the temperature was kept below 10°C . When the addition was completed sodium azide (34.2 mmol) was added and the resulting suspension allowed to warm to ambient temperature over 2 hours. The mixture was re-cooled to -15°C and dimethyl-2-oxopropyl phosphate (28.6 mmol) and DBU (0.65 mmol) added. The solids were filtered off after 45 minutes, washed with acetonitrile, cyclopropanecarboxaldehyde (24.5 mmol) dissolved in 200 ml methyl alcohol containing K_2CO_3 (57.8 mmol) added, and the mixture stirred at ambient temperature 16 hours. The mixture was cooled to 0°C , diluted with 250 ml ice-cold water, and the product extracted 3 times with 30 ml n-octane. The extracts were combined, dried, and the product isolated in 73% yield.

Notes

- The reverse HIV transcriptase inhibitor is (–)-6-chloro-4-cyclopropyl-enthyne-1,4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.
- Two reaction intermediates were generated neither of which were isolated. The first, azidotris(diethylamino)phosphonium bromide, $(\text{Et}_2\text{N})_3\text{P}^+\text{N}_3\text{Br}^-$, was formed by the reaction of hexaethyl phosphorous triamide, bromine and sodium azide. It has also been prepared starting with phosphorous trichloride (1). The second reaction intermediate, dimethyl β -keto- α -diazo phosphate (I), is the base catalysis product of azidotris(diethylamino)-phosphonium bromide and dimethyl-2-oxopropyl phosphate.



(I)

3. In a separate experiment, the author reports that when azidotris (diethylamino)phosphonium bromide was isolated and purified before adding to dimethyl-2-oxopropyl phosphate, the yield of cyclopropaneacetylene was increased to 95%.
4. Other methods for preparing cyclopropaneacetylene include dehydrochlorination of either 1-chloro-1-cyclopropylethylene or 1,1-dichloro-2-cyclopropylethylene (2); dehydrobromination of 1-bromo-2-cyclopropylethylene (3); dehydration of 1-hydroxyl-2-cyclopropyl-ethylene (4); and decarboxylation of cyclopropaneacetylene derivatives (5).

References

1. M. McGuinness *et al*, Tetrahedron Lett., 4987 (1990)
2. Z. Wang *et al*, US Patent 6,359,164 (March 19, 2002)
3. J.M. Fortunak *et al*, US Patent 6,297,410 (October 2, 2001) and US Patent 6,049,019 (April 11, 2000)
4. Z. Wang *et al*, US Patent 6,288,297 (September 11, 2001)
5. K.M.J. Brands, US Patent 6,313,364 (November 6, 2001)

Dentrimers

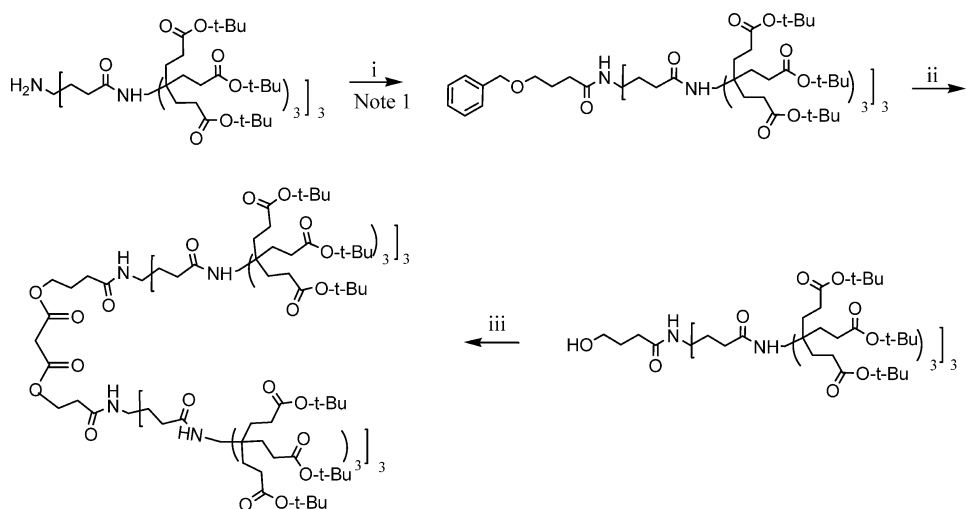
Patent: Dentrimeric Fullerene Derivatives, Process for Their Preparation, and Use as Neurprotectants

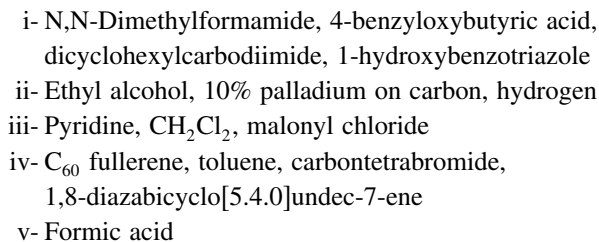
A. Hirsch, US Patent 6,506,928 (January 14, 2003)

Assignee: Siemens Axiva GmbH & Co.

Utility: Neuroprotectants

Reaction





1. **9-Cascade:[(N-(4-Benzyloxybutyl)aminomethane)[3]:(2-aza-oxopentylidyne):t-butyl propanate**

Aminocarboxylic ester, 9-cascade aminomethane [3]:(2-aza-oxopentylidene):t-butyl propionate (4.58 g), 4-benzyloxybutyric acid (0.61 g), dicyclohexylcarbodiimide (0.66 g) and 1-hydroxybenzo-triazole (0.43 g) were dissolved in 50 ml DMF and stood 24 hours at ambient temperature. The solvent was removed in vacuo, the residue taken up in EtOAc, washed with 10% cold HCl, water, 10% NaHCO₃, and concentrated brine. Thereafter the material was dried, purified by chromatography on silica using hexane/EtOAc, 1:1, and the product isolated in 60% yield.

2. 9-Cascade:[N-4-Hydroxybutyl)aminomethane)][3]:(2-aza-oxopentylidyne):t-butyl propanate

The product from Step 1 (2.97 g) was dissolved in 100 ml ethyl alcohol, 10% palladium on carbon (0.1 g) added, and the mixture hydrogenated at ambient temperature and atmospheric pressure. Thereafter the mixture was filtered and the product isolated in 95% yield.

3. 18-Cascade:Methane[2]:2-aza-7-oxa-3,8-dioxooctylidene): (2-aza 3-oxopentylidyne): t-butyl propanate

The product from Step 2 (1.6 g) was dissolved in pyridine (0.08 g), added to 50 ml CH_2Cl_2 , cooled to 0°C , and malonyl chloride (0.07 g) slowly added. The mixture stirred 2 hours at 0°C and 12 hours at ambient temperature. Thereafter the product was purified as in Step 1 and isolated in 26% yield.

4. 18-Cascade:Methano- C_{60} -fullerene[2]:2-aza-7-oxa-3,8-dioxooctylidene): (2-aza 3-oxopentylidyne):t-butyl propanoate

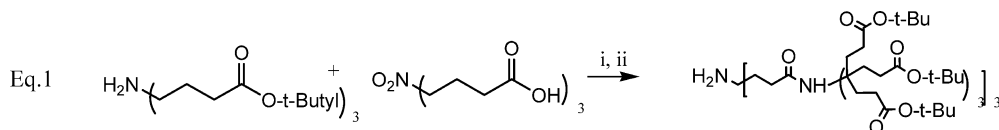
The product from Step 3 (0.425 g), C_{60} -fullerene (98 mg), CBr_4 (45 mg), and DBU (23 mg) were dissolved in 100 ml toluene and stirred 22 hours at ambient temperature. The mixture was purified by chromatography on silica gel first using toluene to remove unreacted C_{60} -fullerene, and using toluene/EtOAc, 1:1, and the product isolated by HPLC in 21% yield.

5. 18-Cascade:Methano- C_{60} -fullerene[2]:2-aza-7-oxa-3,8-dioxooctylidene): (2-aza 3-oxopentylidyne):propanic acid

The product from Step 4 (0.10 g) was dissolved in 15 ml formic acid and stirred 20 hours. Thereafter the solvent was removed and the product isolated in 95% yield as a red-brown powder.

Notes

- The reagent of Step 1 was prepared by reacting nitrotricarboxylic acid with 6-cascade:methane[2]:(2-aza-7-oxo-3,8-dioxooctylidyne):t-butyl propanate followed by reduction using Raney nickel illustrated below in Eq. 1:



i- Dicyclohexylcarbodiimide, 1-hydroxybenzotriazole

ii- Raney nickel, hydrogen

- Other methods of preparing cyclopropane-modified C_{60} fullerenes using diethyl bromomalonate are described (1).

3. 18-Cascade:methano-C₆₀-fullerene[2]:2-aza-7-oxa-3,8-dioxooctylidene): (2-aza 3-oxopentylidyne):propanic acid is water soluble. Other examples of water soluble fullerenes are described (2,3).

References

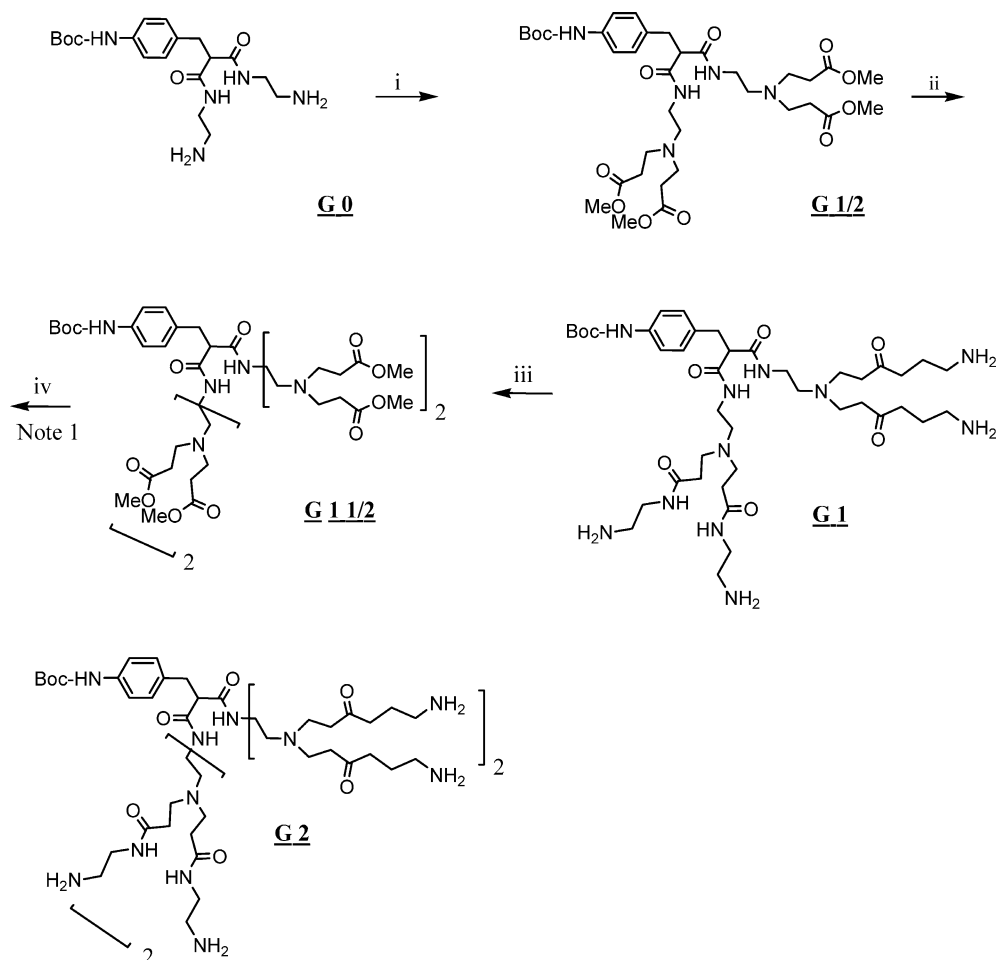
1. C. Bingel, US Patent 5,739,379 (April 14, 1998)
2. S.H. Friedman *et al*, US Patent 6,204,391 (March 20, 2001) and US Patent 5,811,460 (September 22, 1998)
3. B.F. Erlanger *et al*, US Patent 6,593,137 (July 15, 2003)

Patent: Starburst Conjugates
D.A. Tomalia *et al*, US Patent 6,177,414 (January 23, 2001)

Assignee: The Dow Chemical Company

Utility: Agricultural and Pharmaceutical Intermediate

Reaction



i- Methyl alcohol, methyl acrylate
ii- Methyl alcohol, ethylenediamine
iii- Methyl alcohol, methyl acrylate
iv- Methyl alcohol, ethylenediamine

Experimental

1. 3-Cascade:[N-t-butoxycarbonylphenol][1]:4,8-diazara-5,7-dioxoundecane]-1,11-diazatetramethylproponate (G1/2)

N-t-Butoxycarbonyl-1,4,8,11-tetraazara-5,7-dioxoundecane (13 mmol) was dissolved in 100 ml methyl alcohol, methyl acrylate (68 mmol) added, and the reaction stirred at ambient temperature 72 hours. Thereafter the solution was concentrated to 30% solids and methyl acrylate (32 mmol) again added. The mixture was stirred 24 hours at ambient temperature until no partially alkylated moieties were detected using HPLC (Spherisorb ODS1, acetonitrile/0.04 M NH_4OAc , 40:60). The solvent was removed at 30°C by rotary evaporation pumping down to 1 mm Hg for 24 hours and the product isolated in 7.81 g of a viscous oil.

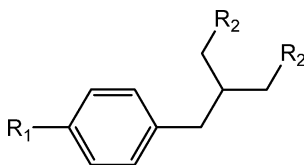
3-Cascade:[N-t-butoxycarbonylphenol][1]: 4,8-diazara-5,7-dioxoundecane]-1,11-diazatetra-(6-amino-3-keto)hexane (G 1)

The product from Step 1(10.45 mmol) was dissolved in 75 ml methyl alcohol and added dropwise over 2 hours to a stirred solution of ethylenediamine (7.41 mol) dissolved in 50 ml methyl alcohol. The reaction stirred at ambient temperature and excess ethylenediamine and solvent removed. The residue was dissolved in 90 ml methyl alcohol and purified from residual ethylenediamine by reverse osmosis (Filmtec TC-30 membrane and AmiconTC1R channel separator, methyl alcohol as solvent). After 48 hours no ethylenediamine could be detected by gas chromatography (Column, Tenax 60/80) and the product isolated in 6.72 g as a glassy solid.

Subsequent generations were prepared following the aforelisted Steps.

Derivatives

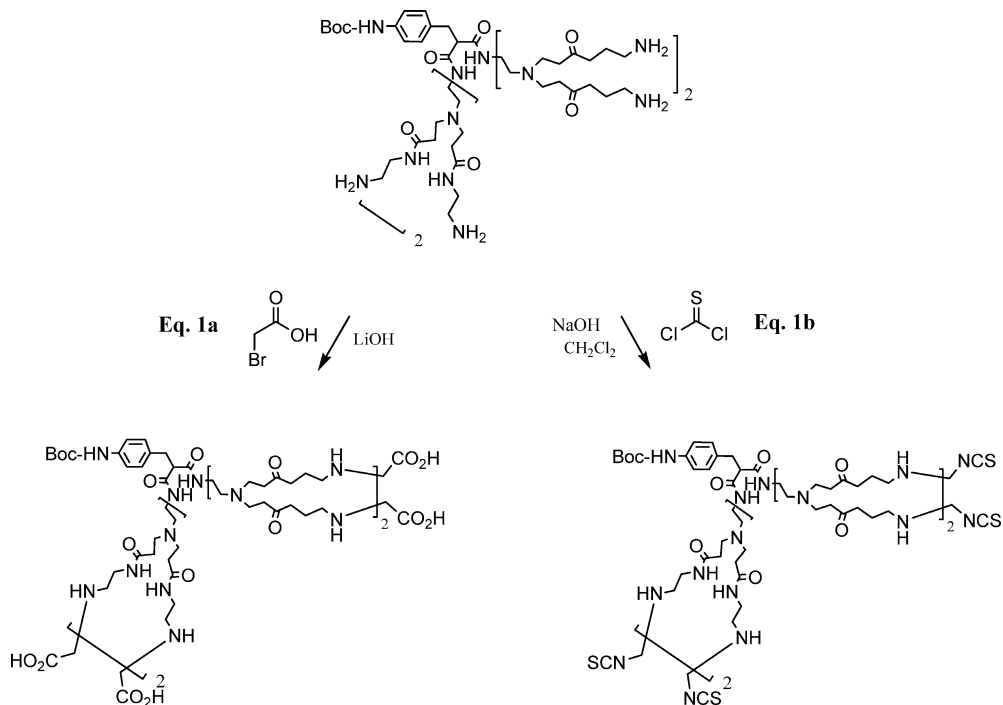
- Multi-generation dendrimers were also prepared by the author using other initiators indicated below. The preparation of these initiators is provided by the author.



R_1	R_2	Highest Dendrimer Generation (G_N)
NH_2	CH_2NH_2	2
NO_2	NH_2	3
NO_2	CH_2NH_2	3
NO_2	$\text{CH}_2\text{N}(\text{CH}_2\text{NH}_2)\text{CH}_2\text{CH}_2\text{NH}_2$	6.5

Notes

1. The G2 amine termini were converted into carboxylic acid and isothiocyanate derivatives by reacting with bromoacetic acid and thiophosgene, respectively, as illustrated below in Eq. 1a and Eq. 1b, respectively:



2. Half-generation starburst polyamidoamines were hydrolyzed by the author by reacting with NaOH in methyl alcohol. This generated spheroidal molecules with negative charges dispersed on the periphery. Counterions consisted of Na^+ , K^+ , Cs^+ or Rb^+ . Other examples are described (1,2,3).
3. 4-Nitrobenzene starburst polymers were also prepared by reacting amine-termini intermediates with 4-fluoro-nitrobenzene. Thereafter the nitro component was reduced using 5% palladium on carbon and is described by the author.

References

1. A. Rembaum *et al.*, US Patent 4,036,808 (July 19, 1977)
2. K.F. Kraft *et al.*, US Patent 5,039,512 (August 13, 1991)
3. G.R. Killat *et al.*, US Patent 4,871,779 (October 13, 1989)

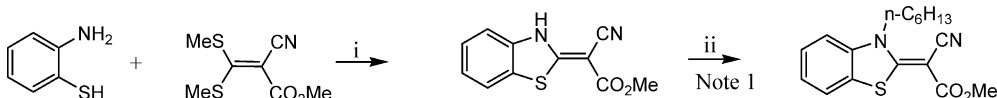
Enamines

Patent: Use of Enamines as Light Protection Agents
T. Habeck *et al*, US Patent 6,603,014 (August 5, 2003)

Assignee: BASF Aktiengesellschaft

Utility: UV-A Absorbers in Cosmetic Preparations

Reaction



i- Ethyl alcohol

ii- N,N-Dimethylformamide, 1-bromohexane, potassium carbonate

Experimental

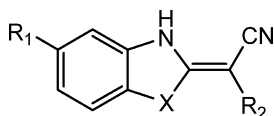
1. Methyl 2,3-dihydrobenzothiazole-1-cyanoacrylate

Methyl 2,2-bismethylmercapto-1-cyanoacrylate (0.1 mol) and 2-mercaptoaniline (0.1 mol) were stirred overnight in 100 ml ethyl alcohol at ambient temperature. The precipitate that formed was filtered, dried, and the product isolated in 87% yield as a white powder.

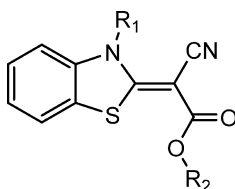
2. Methyl N-hexyl-2,3-dihydrobenzothiazole-1-cyanoacrylate

The product from Step 1 (250 mmol) was dissolved in 50 ml DMF, mixed with K₂CO₃ (250 mmol) and 1-bromohexane (250 mmol) then refluxed 1 hour. Thereafter 50 ml water was added and the precipitate isolated by filtration in 63% yield.

Derivatives



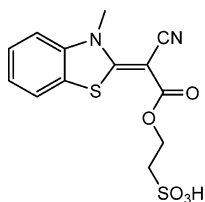
R_1	X	R_2	$\lambda_{\max}$	E^1_1
Hydrogen	S	Methoxycarbonyl	336	1723
Hydrogen	NH	Methoxycarbonyl	316	1986
Methoxide	NH	Cyano	328	1784
Hydrogen	O	Cyano	308	1844
Hydrogen	S	Cyano	334	1776



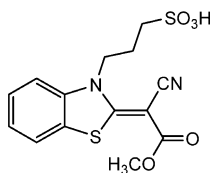
R_1	R_2	$\lambda_{\max}$	E^1_1
Methyl	2-Ethylhexyl	340	1150
n-Hexyl	Methyl	340	1200
n-Butyl	n-Butyl	340	1250
n-Hexyl	2-Ethylhexyl	340	830

Notes

1. In a subsequent investigation by the author Step 2 analogues (I), UV-A enamine sulfonic acid derivatives, (I), and (II), were prepared and are described (1).

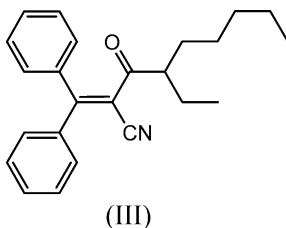


(I)

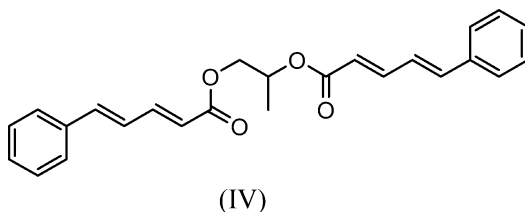


(II)

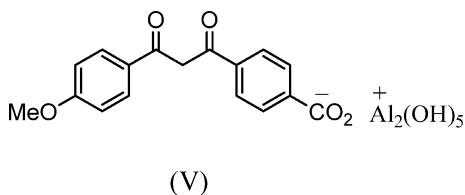
2. Alkyl- β,β -diphenyl acrylates and α -cyano- β,β -diphenyl acrylates, (III), have also been effective as UV-A absorbers and their preparation is provided (2).



3. The preparation of other unsaturated UV-A absorbers such as 1,2-propylene glycol di(2-methyl-5-phenyl-2,4-pentadienoate), (IV), is described (3).



4. Aluminum hydroxide carboxylic acid salts of dibenzoyl methane derivatives, (IV), are also effective as UV-A absorbers (4).



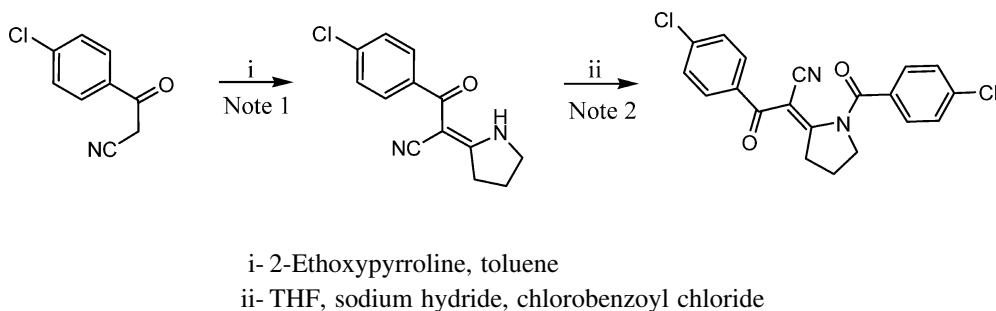
References

1. T. Habeck *et al*, US Patent 6,413,503 (July 2, 2002)
2. A. Deflandre *et al*, US Patent 5,587,150 (December 24, 1996)
3. C.J. Phalangas *et al*, US Patent 4,950,467 (August 21, 1990)
4. H. Hotta *et al*, US Patent 4,837,010 (June 6, 1989)

Enaminones

Patent: Phenyl-Substituted Cyclic Enaminones
R. Fischer *et al*, US Patent 6,455,472 (September 24, 2002)
Assignee: Bayer Aktiengesellschaft
Utility: Pesticide

Reaction



Experimental

1. 3-(4-Chlorophenyl)-3-oxo-2-pyrrolidin-2-ylidene-propionitrile

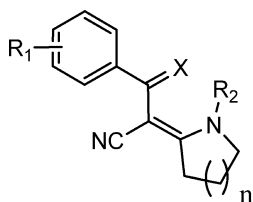
2-Ethoxypyrrolidine (1.2 g), 4-chlorobenzoylacetone (1 g) and 20 ml toluene were heated to 100°C 1 hour and ethyl alcohol azeotropically distilled off. The mixture was cooled, crystals precipitated upon the addition of hexane, and the product isolated in 74% yield, mp = 156–158°C.

2. 2-[1-(4-Chlorobenzoyl)pyrrolidin-2-ylidene]-3-(4-chlorophenyl)-3-oxo-propionitrile

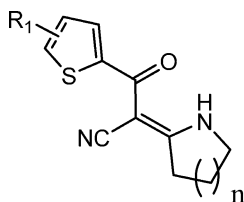
At 0°C, the product from Step 1 (1 g) was dissolved in 10 ml THF, NaH (0.3 g, 60% pure) added, and the mixture warmed to 20°C 2 hours. Thereafter, chlorobenzoyl chloride

(0.8 g) dissolved in 10 ml THF was added and the mixture stirred 24 hours. The reaction was quenched by pouring into ice water, extracted with EtOAc, dried and concentrated. The residue was purified by chromatography on silica gel with n-hexane/acetone, 7:3, and the product isolated in 14% yield, mp = 218°C.

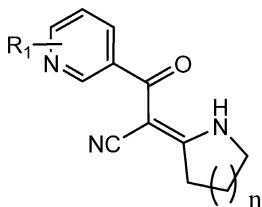
Derivatives



R₁	R₂	X	n	Melting Point (°C)
4-Chloro	Hydrogen	S	2	137
3,5-Trifluoromethyl	Hydrogen	O	3	129
2,5-Trifluoromethyl	Methyl	O	1	158



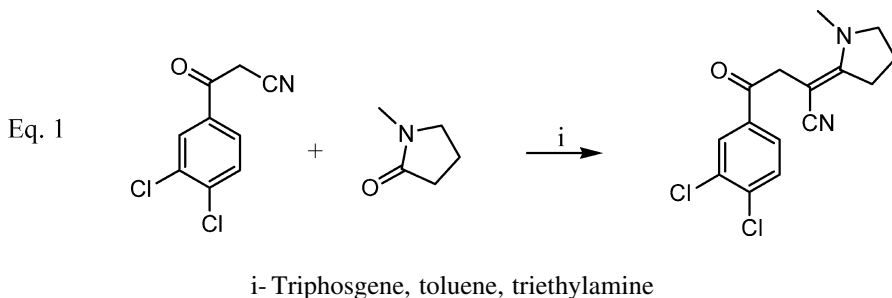
R₁	n	Melting Point (°C)
3-Bromo	3	162
3-(4-Chlorophenyl)-2-trifluoromethyl	1	176
2-(3,5-Trifluoromethyl)phenyl	2	> 223



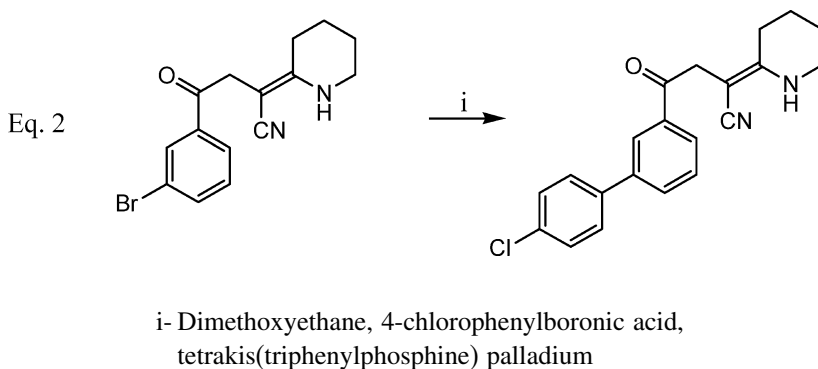
R₁	n	Melting Point (°C)
2-Chloro	1	156–158
2,6-Dichloro	2	121
2-Thioacetic acid	2	155

Notes

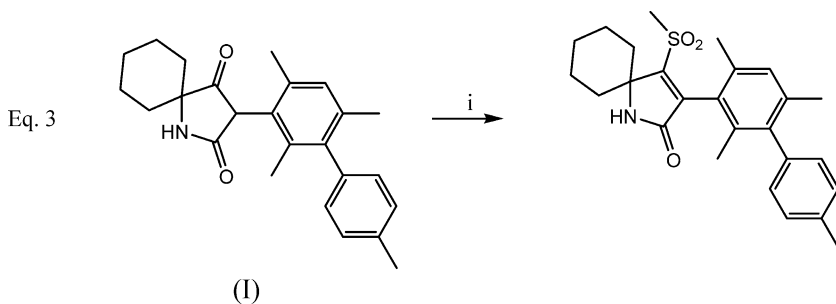
1. The reagent of Step 1 and derivatives were prepared by reacting pyrrolidine with triethoxyoxonium tetrafluoroborate (Meerwin's salt) and is described (1).
2. Cyclic enaminones of the current invention were also prepared by reacting benzoyl-acetonitrile with methylpyrrolidone with triphosgene as described by the author and illustrated in Eq. 1:



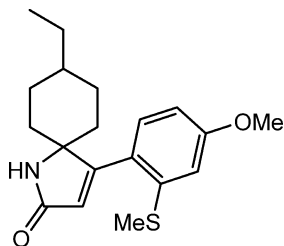
3. Biphenyl derivatives were also prepared by the author as illustrated in Eq. 2:



4. In previous investigations by the author (2) and others (3), sulfonyl enaminone derivative of 2-[(2,4,6-trimethyl-3-(4-methyl-phenyl))-phenyl]-5,5-pentamethylene-pyrrolidine-2,4-dione (I) was prepared by reacting with methanesulphonyl chloride as illustrated in Eq. 3:



5. Spiroenaminone derivatives, (II), were previously prepared by the author and are discussed (4).



(II)

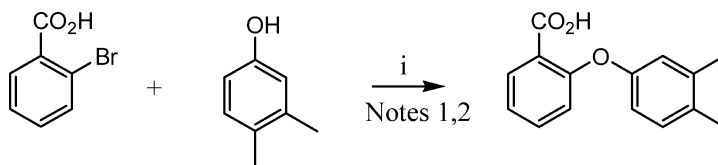
References

1. J. Pendrak *et al*, J. Org. Chem., 60, 2912 (1995)
2. R. Fischer *et al*, US Patent 6,469,196 (October 22, 2002)
3. F. Lieb *et al*, US Patent 6,458,965 (October 1, 2002) and US Patent 6,451,843
4. R. Fischer *et al*, US Patent 6,358,887 (May 19, 2002)

Ethers

Patent: Diaryl Ether Condensation Reactions
J.-F. Marcoux *et al*, US Patent 6,395,939 (May 28, 2002)
Assignee: Massachusetts Institute of Technology
Utility: Aromatic Ether Coupling Reagent

Reaction



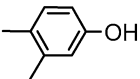
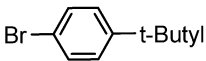
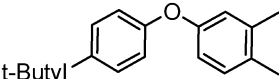
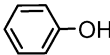
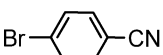
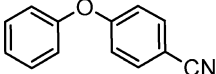
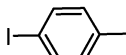
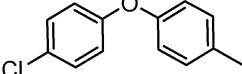
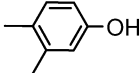
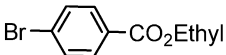
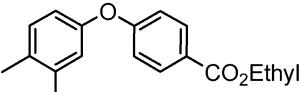
i- Cesium carbonate, di(copper triflate) · benzene, toluene,
ethyl acetate

Experimental

1. 2-(3',4'-Dimethylphenoxy)benzoic acid

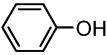
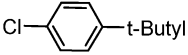
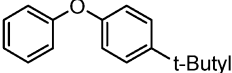
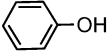
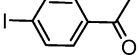
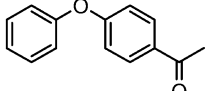
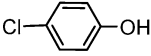
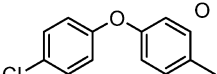
A test tube was charged with 2-bromobenzoic acid (2.5 mmol), 3,4-dimethylphenol (3.5 or 5.0 mmol), Cs₂CO₃, (CuOTf)₂ · benzene (0.0625 mmol, 5.0 mol % Cu), EtOAc (0.125 mmol), and 2.0 ml toluene. The tube was sealed with a septum and heated to 110°C until 2-bromobenzoic acid was consumed as determined by GC. The mixture was cooled, diluted with diethyl ether, washed with 5% aqueous NaOH, water, and brine. The organic layer was concentrated, the product purified by flash chromatography using diethyl ether/pentane, 1:4, and the product isolated as a white solid in 77% yield, mp = 98°C. ¹H- and ¹³NMR and IR data supplied.

Derivatives

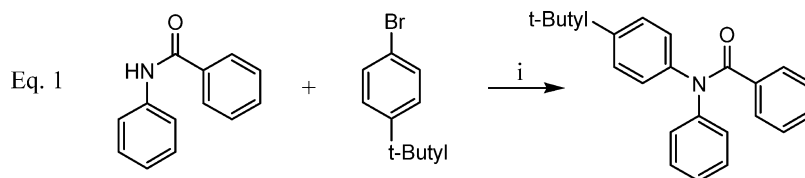
<u>Phenol</u>	<u>Halide</u>	<u>Product</u>	<u>Yield (%)</u>
			90
			86
			79
			63

Notes

1. This instant invention represents an improvement in the Ullman coupling reaction. This investigation represents the first general method for coupling electron deficient phenols and unactivated aryl halides (1,2,3,4). The basis of the improvement lay in the high solubility of $(\text{CuOTf})_2 \cdot \text{benzene}$ and cesium phenolate or copper phenolate in the reaction solvent, toluene.
2. In cases where the catalysts had limited solubility in the reaction solvent, stoichiometric amounts of 1-naphthoic acid and molecular sieves were added to promote higher yields as summarized below.

<u>Phenol</u>	<u>Halide</u>	<u>Product</u>	<u>Yield (%)</u> 1-Naphthoic acid absent	<u>Yield (%)</u> 1-Naphthoic acid present
			0	81
			0	93
			34	79

3. N-Arylation of amides was also performed by the author using $(\text{CuOTf})_2 \cdot \text{benzene}$ and Cs_2CO_3 with co-catalysts, 1,10-phenanthroline and dibenzylidene acetone, as illustrated in Eq. 1 below:



i- Cesium carbonate, di(copper triflate) · benzene, toluene,
1,10-phenanthroline, dibenzylidene acetone

References

1. J. Lindley, *Tetrahedron*, 40, 1433 (1984)
2. D.A. Evans *et al*, *J. Am. Chem. Soc.*, 111, 1063 (1984)
3. D.L. Boger *et al*, *J. Org. Chem.*, 55, 6000 (1990)
4. A. Afzeli *et al*, *Synthetic Commun.*, 13(4), 335 (1983)

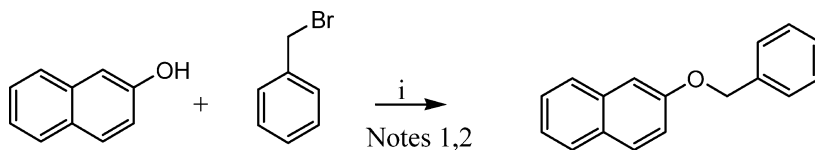
Patent: Preparation and Use of Ionic Liquids in Microwave-Assisted Chemical Transformations

J. Westman, US Patent 6,596,130 (July 22, 2003)

Assignee: Personal Chemistry I Uppsala AB

Utility: High Yielding Alkylations Using Ionic Solvents

Reaction



i- 1-Ethyl-3-methylimidazolium tetrafluoroborate, potassium hydroxide, microwave radiation

Experimental

1. 2-Naphthol benzyl ether

2-Naphthol (0.35 mmol) was dissolved in 2 ml 1-ethyl-3-methylimidazolium tetrafluoroborate containing benzyl bromide (1.5 eq) and KOH (2 eq). The mixture was reacted in a microwave apparatus at 200°C 2 minutes, the product extracted with diethyl ether, and isolated in quantitative yield.

Derivatives

<u>Reactant</u>	<u>Alkylating Agent</u>	<u>Ionic Liquid</u>	<u>Product</u>	<u>Yield (%)</u>
		1-Butyl-3-methylimidazolium BF ₄		>90
		1-Methyl-3-methylimidazolium BF ₄		100
		1-Methyl-3-methylimidazolium BF ₄		>90
		1-Methyl-3-methylimidazolium BF ₄		100

Notes

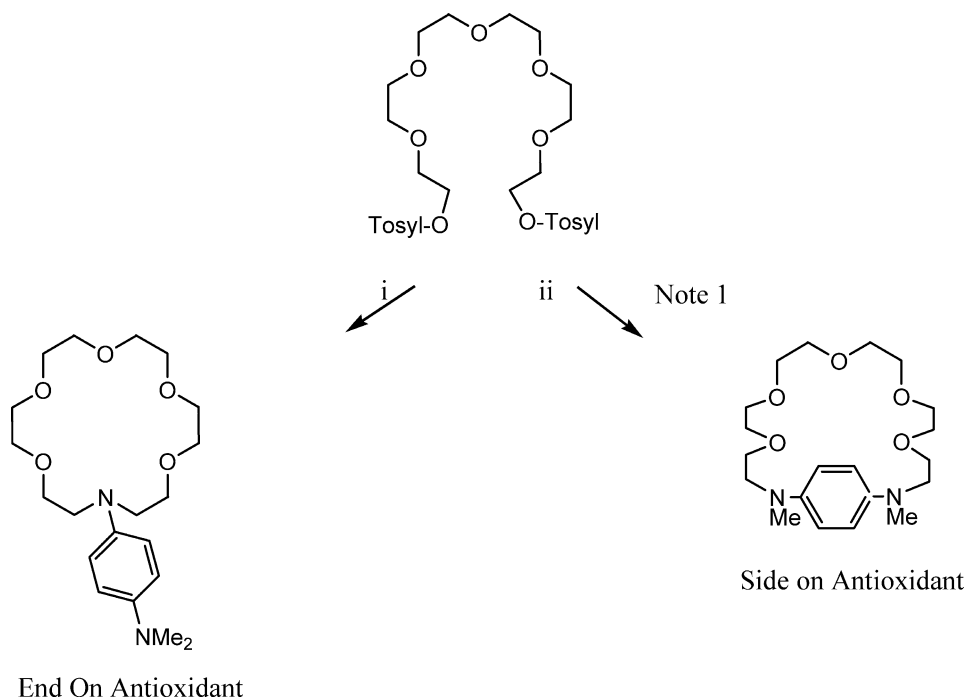
1. Microwave radiation used in these alkylations had a frequency range of between 500 MHz and 100 GHz, available in most commercial microwave units. A typical microwave apparatus is described (1).
2. In the absence of microwave radiation high product yields have been observed when reactions were conducted at ambient temperature for up to 3 hours in ionic liquids (2).
3. The use of 1,3-dialkylimidazolium tetrafluoroborates and other ionic solvents in catalytic reactions is discussed.

References

1. H.M. Kingston, US Patent 5,883,349 (March 16, 1999)
2. M.J. Earle *et al*, Chem. Commun., 2245 (1998)
3. C.M. Gordon *et al*, J. Mater. Chem., 8, 2627, (1998); K.R. Sedden, Kinetics Catalysis, 37, 693 (1996); and J. Howarth *et al*, Tetrahedron Lett., 38, 3097 (1997)

Patent: Wurster's Crown Ligands
J.W. Silbert, US Patent 6,441,164 (August 27, 2002)
Assignee: East Carolina University
Utility: Liquid Crystal Displays

Reaction



i- N,N-Dimethyl-1,4-phenylenediamine, acetonitrile, sodium carbonate, hexaethyleneglycol di-p-toluenesulfonate

ii- N,N'-Dimethyl-1,4-phenylenediamine dihydrogen bromide, acetonitrile, sodium carbonate, hexaethyleneglycol di-p-toluenesulfonate

Experimental

1. "End on" Wurster's Crown

At ambient temperature N,N-dimethyl-1,4-phenylenediamine (6.47 mmol) was dissolved in 250 ml acetonitrile followed by the addition of Na_2CO_3 (3.7 g) and hexaethyleneglycol di-p-toluenesulfonate (6.46 mmol) and the mixture refluxed 72 hours. The mixture

was cooled, purified by chromatography on neutral or basic alumina using methyl alcohol/chloroform in a 0.5–1.0% gradient, and the compound isolated in 22% yield. ^1H - and ^{13}C -NMR data supplied.

2. “Side on” Wurster’s Crown

At ambient temperature $\text{N,N}'$ -dimethyl-1,4-phenylenediamine dihydrogen bromide (3.4 mmol) was dissolved in 150 ml acetonitrile, Na_2CO_3 (3.9 g) and hexaethyleneglycol di-*p*-toluenesulfonate (3.4 mmol) added, and reacted as in Step 1. The crude product was partitioned between CH_2Cl_2 and water and the product isolated in 25% yield. ^1H - and ^{13}C -NMR data supplied.

Notes

1. Analogues of the Step 2 product have been previously prepared (1).
2. The incorporation of 1,4-phenylenediamine as part of the crown ether produces redox-active macroscopic ligands. Macroscopic redox active ligands containing ferrocene-, tetrathiafulvalene- and quinone derivatives have been prepared and are discussed (2).
3. Other macroscopic redox active crown ether ligands containing bis-adamantyl- and *t*-butylacetyl are described (4).

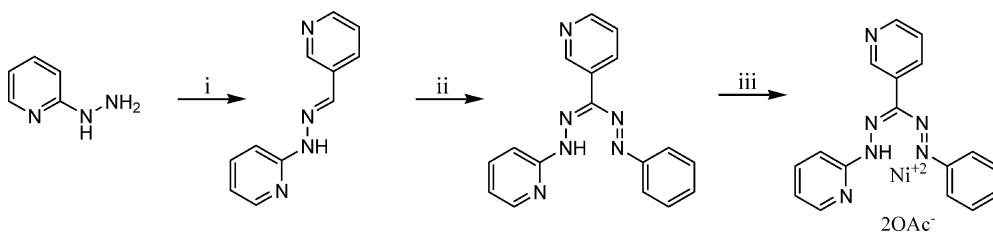
References

1. L. Michaelis *et al.*, J. Chem. Soc., 1939, 61 (1981)
2. J.W. Sibert, US Patent 6,441,164 (August 27, 2002)
3. Z. Chen and L. Echegoyen in ‘Crown Compounds Toward Future Applications’, p. 27 (S. Cooper, Ed., 1992).
4. J. Manero *et al.*, US Patent 5,445,762 (August 29, 1995)

Formazan

Patent: Formazan Metal Complexes
K. Yano *et al*, US Patent 6,645,595 (November 11, 2003)
Assignee: Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo
Utility: Organic Dyes

Reaction



- i- 3-Pyridylaldehyde, methyl alcohol
ii- Dioxane, methyl alcohol, aniline, hydrochloric acid, sodium nitrite
iii- Methyl alcohol, nickel acetate tetrahydrate

Experimental

1. N-2-Pyridyl-N'-3-pyridylimine hydrazone

2-Pyridylhydrazine (5 g) and 3-pyridylaldehyde (5 g) were dissolved in 100 ml methanol, heated to 60°C 2 hours, cooled to 10°C, mixed with 50 ml of water, and stirred 30 minutes. Thereafter, the crystals were collected by filtration, washed with water then methanol, dried by heating to 65°C, and 7.4 g product isolated.

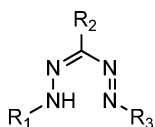
2. Formazan

A reaction vessel was charged with 100 ml 1,4-dioxane/methanol, 3:2, aniline (0.93 g), the product from Step 2 (2.0 g), 2.5 ml concentrated HCl and 5 ml of water and cooled to 0° to −3°C. While at this temperature, 5 ml of an aqueous solution of sodium nitrite (0.72 mg) was added over 20 minutes followed by 10 ml solution of NaOH (1.38 g) and the mixture stirred 2 hours. Thereafter, the product was purified as in Step 1 and 1.6 g product isolated.

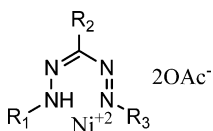
3. Formazan-nickel acetate

A reaction vessel was charged with 40 ml methyl alcohol and the product from Step 2 (2.0 g), heated to 50°C, and 40 ml methyl alcohol containing nickel acetate tetrahydrate (1.0 g) added over 30 minutes. Thereafter, 80 ml of water was added, the mixture cooled to 10°C, filtered, and 0.9 g purple solid isolated.

Derivatives



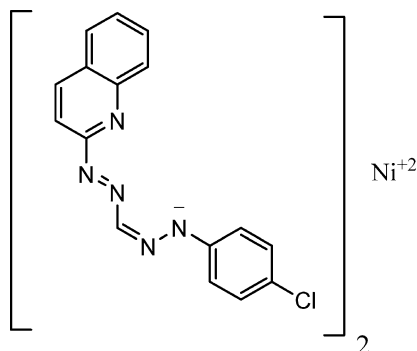
R₁	R₂	R₃
5-Nitro-2-pyridyl	2-Pyridyl	4-Cyanophenyl
5-Trifluoromethyl-2-pyridyl	3-Pyridyl	2,5-Dimethoxyphenyl
2-Pyridyl	2-Furan	2,4-Dimethoxyphenyl
3-Chloro-5-trifluoromethyl-2-pyridyl	3-Pyridyl	4-Ethoxyphenyl
5-Nitro-2-pyridyl	2-Butyl	2,5-Dimethoxyphenyl



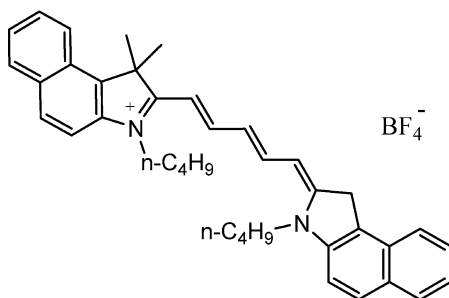
R₁	R₂	R₃	Absorption Max (nm)	Extinction Coefficient (ε)	MP (°C)
2-Pyridyl	2-Pyridyl	Phenyl	599	25,300	290–295
2-Pyridyl	2-Pyridyl	2,5-Dimethoxyphenyl	597	27,500	—
5-Trifluoromethyl-2-pyridyl	3-Pyridyl	4-Cyanophenyl	629	43,500	220–230
5-Nitro-2-pyridyl	2-Pyridyl	2,5-Dimethoxyphenyl	611	90,400	230–231
3-Nitro-2-pyridyl	2-Furan	3-Methyl	670	—	212–215

Notes

1. The preparation of other formazans and metallized derivatives is provided (1,2).
2. The preparation of optical recording elements having recording layers containing mixtures of metallized formazan, (I), and cyanine dyes, (II), is provided (3).



(I)



(II)

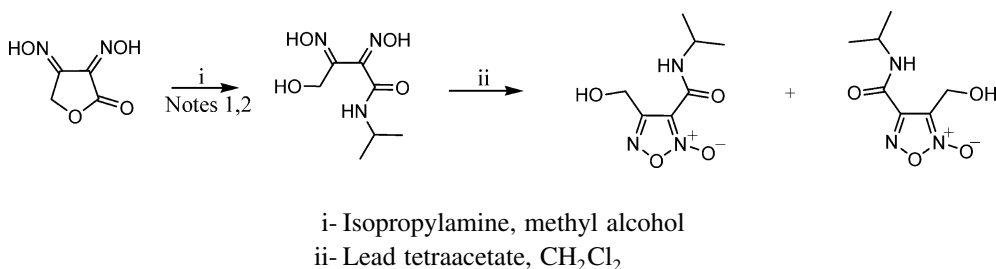
References

1. D.D. Chapman *et al*, US Patent 5,922,429 (July 13, 1999) and US Patent 5,773,193 (January 30, 1998)
2. T. Suzukai *et al*, US Patent 5,604,004 (February 18, 1997)
3. M.P. Cunningham *et al*, US Patent 5,547,728 (August 20, 1996)

Furazancarboxylic Acid Derivatives

Patent: Hydroxymethylfurazancarboxylic acid derivatives
K. Schonafinger *et al*, US Patent 5,486,531 (January 23, 1996)
Assignee: Cassella Aktiengesellschaft
Utility: Muscle Relaxants

Reaction



Experimental

1. 4-Hydroxy-N-isopropyl-2,3-dioximinobutyramide

A reactor was charged with 3,4-dioximino-2-oxotetrahydrofuran (9.4 g) suspended in 50 ml methyl alcohol, isopropylamine (4.2 g) added, and the mixture stirred 3 hours. The mixture was cooled in an ice bath and 8.5 g product isolated by filtration, mp = 133–134°C.

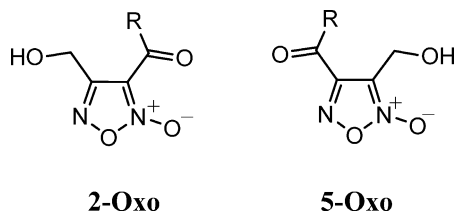
2. 4-Hydroxymethyl-N-isopropyl-2-oxyfurazan-3-carboxamide and

4-Hydroxymethyl-N-isopropyl-5-oxyfurazan-3-carboxamide

The product from Step 1 (10 g) was dissolved in 120 ml CH₂Cl₂ containing lead tetraacetate (22 g) and stirred 5 hours. The water-soluble constituents were extracted

3 times with 100 ml water, the organic phase isolated, dried with Na_2SO_4 , and concentrated in vacuo. The mixture was purified by chromatography using silica gel and CH_2Cl_2 /methyl alcohol, 99:1. The products consisted of 3.6 g 4-hydroxymethyl-N-isopropyl-2-oxyfuran-3-carboxamide and 1.8 g 4-hydroxymethyl-N-isopropyl-5-oxyfuran-3-carboxamide and were isolated as oils. $^1\text{H-NMR}$ data supplied.

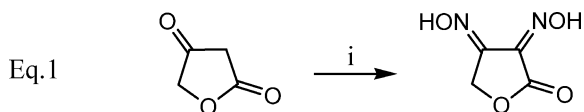
Derivatives



R	MP _{2-Oxo} (°C)	MP _{5-Oxo} (°C)
N-Methyl	104–106	86–88
N-Benzyl	94–96	Not prepared
N-(3-Imidazol-1-yl)-propyl	Not prepared	145–147
N-(3-Pyridinemethyl)	Not prepared	154–155
N-Cyclohexyl	97–98	Not prepared

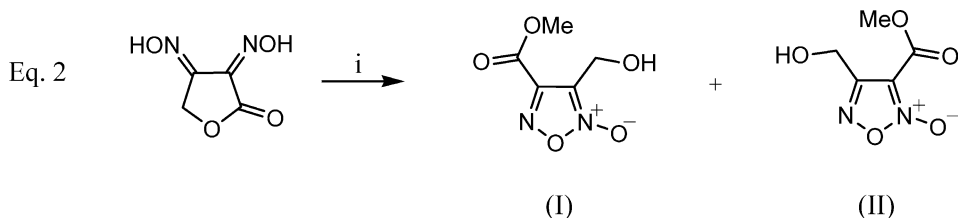
Notes

- The preparation of the Step 1 reagent is described by the author and illustrated in Eq. 1:



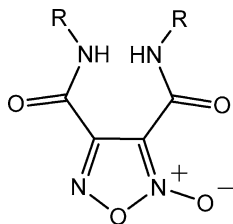
i- Sodium nitrite, water, hydrochloric acid

- The author also prepared methyl 1-hydroxymethyl-2-oxyfuran-3-carboxylate, (I), and methyl 4-hydroxymethyl-5-oxyfuran-3-carboxylate, (II), by treating the reagent of Step 1 with lead tetraacetate as illustrated in Eq. 2:



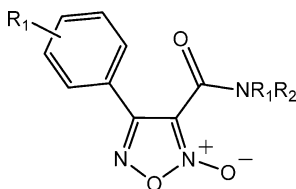
i- Methyl alcohol, lead tetraacetate, CH_2Cl_2

3. The conversion of the product mixture of Step 2 into 1,2,5-oxidiazole-2-oxide-3,4-diamide derivatives, (III), where R a aliphatic or cycloaliphatic, is described (1).



(III)

4. 1,2,5-Oxidiazole-2-oxide derivatives containing either 3-amide and 4-methyl or 3-methyl and 4-amide substituents were prepared by the author in an earlier investigation and are described (2).
5. The preparation of 4-phenyl-1,2,5-oxadiazolecarboxamide-2-oxides, (IV), is provided.



(IV)

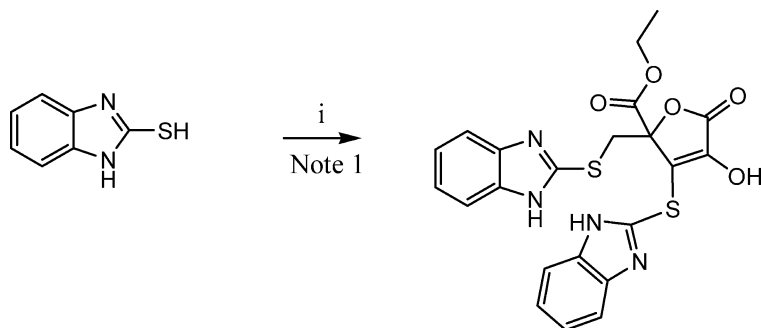
References

1. K. Schonafinger *et al*, US Patent 4,356,178 (October 26, 1982)
2. K. Schonafinger *et al*, US Patent 4,416,893 (November 22, 1983)
3. K. Schonafinger *et al*, US Patent 5,424,326 (January 13, 1995)

Furanones

Patent: Furanone Derivatives
B. Wang *et al*, US Patent 6,667,330 (December 23, 2003)
Assignee: Galileo Pharmaceuticals, Inc.
Utility: Treatment of Neurodegenerative Disorders

Reaction



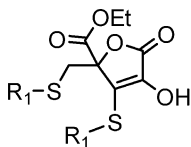
i- Ethyl bromopyruvate, acetone, ethyl alcohol,
4-dimethylaminopyridine

Experimental

1. 3-(1H-Benzimidazol-2-ylsulfanyl)-2-(1H-benzimidazol-2-yl-sulfanylmethyl)-4-hydroxy-5-oxo-2,5-dihydro-furan-2-carboxylic acid ethyl ester

A solution of 2-mercaptobenzimidazole (4.0 g) and 4 ml ethyl bromopyruvate dissolved in 40 ml ethyl alcohol and 50 ml acetone were mixed and stirred 16 hours at ambient temperature. Thereafter, 4.5 g pyruvate adduct was isolated, dissolved in CH₂Cl₂, treated with aqueous NaHCO₃ until pH 7 obtained, and dimethylaminopyridine (0.7 g) added. The mixture was stirred, purified by chromatography using silica gel and CH₂Cl₂/ethyl alcohol, 1:1, and 500 mg product isolated. ¹H- and ¹³C-NMR data supplied.

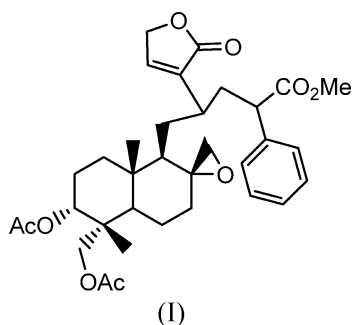
Derivatives



<u>R₁</u>	<u>Yield (%)</u>
4-Methylphenyl	65
	52
	98

Notes

1. The mechanism for product formation entails an aldol condensation between the two tautomeric pyruvate derivatives and is illustrated and discussed by the author.
2. 3-Phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanone derivatives of the current invention have also been prepared (1).
3. The preparation of 4,5-diaryl-3(2H) furanone derivatives is described (2).
4. The preparation of andrographolide derivatives, (I), is provided (3).



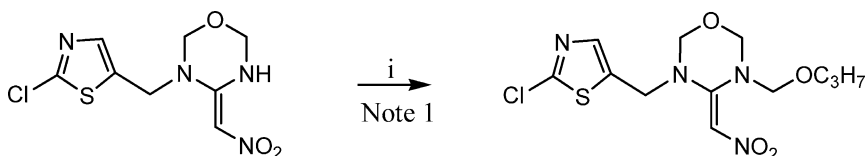
References

1. Z. Wand *et al*, US Patent 6,239,173 (May 29, 1991)
2. S.S. Shin *et al*, US Patent 6,492,416 (December 10, 2002)
3. S. Nanduri *et al*, US Patent 6,576,662 (June 10, 2003)

Guanidines

Patent: Cyclic Guanidine Derivatives and Their Use as Pesticides
K. Wagner *et al*, US Patent 6,683,028 (January 27, 2004)
Assignee: Bayer Aktiengesellschaft
Utility: Animal Pesticides

Reaction



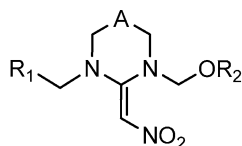
i- N,N-dimethylformamide, sodium hydride,
n-propoxymethyl chloride

Example

1. 3-(2-Chloro-thiazol-5-yl-methyl)-4-nitroiminino-5-n-propoxymethyl-perhydro-1,3,5-oxadiazine

3-(2-Chloro-thiazol-5-yl-methyl)-4-nitroiminino-perhydro-1,3,5-oxadiazine (5 mmol) was dissolved in 15 ml of DMF and NaH (6 mmol) added. The mixture was stirred at room temperature 15 minutes, propoxymethyl chloride (10 mmol) added, then the mixture stirred overnight. Thereafter, the mixture was concentrated, the residue extracted twice with CH_2Cl_2 , the product purified by chromatography on silica gel with acetonitrile/water, 70:30, and isolated in 29% yield, having a $\log P = 1.7$ ($\text{pH} = 2$) (Note 2).

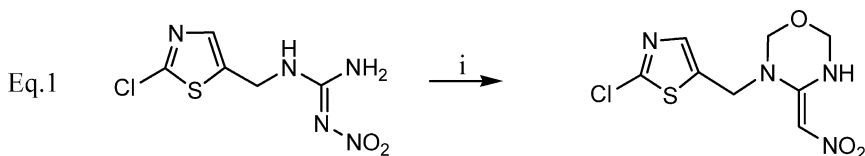
Derivatives



R_1	R_2	A	logP
	n-C ₃ H ₇	O	1.6
	n-C ₃ H ₇	NCH ₃	1.6
	COCH ₃	O	0.98
	n-CH ₂ CH=CH ₂	O	1.54

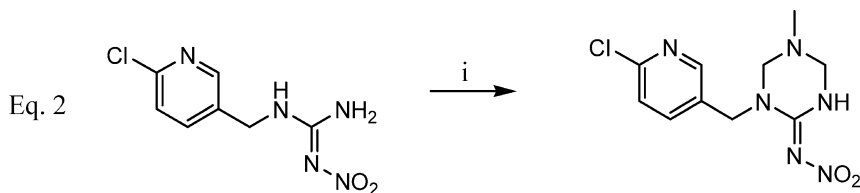
Notes

1. The preparation of the Step 1 reagent is described (1) and illustrated in Eq. 1:



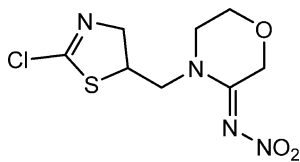
i- Paraformaldehyde, dioxane, triethylamine, toluene

2. The logP values were determined in accordance with EEC directive 79/831 Annex V. A8 by HPLC (gradient method, acetonitrile/0.1% aqueous phosphoric acid).
 3. Methods for preparing hexahydro-1,3,5-triazine analogues are provided (2) and illustrated in Eq. 2:



i- Bis(chloromethyl)methylamine, triethylamine

4. The preparation and alkylation of other heterocyclic nitroimino derivatives, (I), is provided (3).



(I)

References

1. P. Maienfisch *et al*, US Patent 5,852,012 (December 22, 1998)
2. F. Wu *et al*, US Patent 6,187,773 (February 13, 2001)
3. K. Shiokawa *et al*, US Patent 5,719, 146 (February 17, 1998) and US Patent 5,034,524 (July 23, 1991)

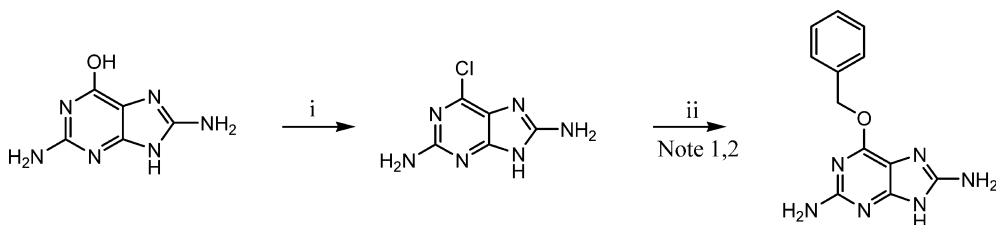
Guanines

Patent: Substituted O⁶-Benzyl-8-Aza-Guanines
R.C. Moschel *et al*, US Patent 6,436,945 (August 20, 2002)

Assignee: The United States of America as represented by Health and Human Services; Penn State Research Foundation; and Arch Development Corporation

Utility: Chemical Agents for Inactivating DNA Repair Protein
O⁶-Allylguanine-DNA Alkyltransferase

Reaction



i- Phosphorous oxychloride, 4-dimethylamineaniline

ii- Sodium, benzyl alcohol

Experimental

1. 2,8-Diamino-6-chloropurine

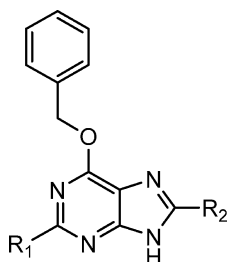
A suspension of 8-aminoguanine (18.1 mmol) dissolved in 90 ml phosphorus oxychloride and 3 ml 4-dimethylaniline was refluxed 30 minutes and excess phosphorus oxychloride removed. Ice (20 g) was slowly added to the solution, the pH adjusted to 6 with concentrated aqueous NaOH, and a yellow solid formed. The solid was filtered, washed, and

the product isolated in 63% yield, mp >275°C (dec). $^1\text{H-NMR}$ and elemental analysis data supplied.

2. 8-Amino-O⁶-benzylguanine

The product from Step 1 (4.9 mmol) was added to the solution of sodium (10 mmol) in 9.0 ml benzyl alcohol. The solution was heated to 130°C 5 hours then poured into 100 ml water. Undissolved solid was removed by filtration and the filtrate neutralized with HOAc. The solution was dissolved in 100 ml methyl alcohol and the product isolated in Fraction Numbers 100–130 using a Sephadex LH-20 column with methyl alcohol/water, (1:1), at a flow of 1 mL/minute, in 21% yield, mp = 269–271°C (dec). $^1\text{H-NMR}$, UV, MS, and elemental data supplied.

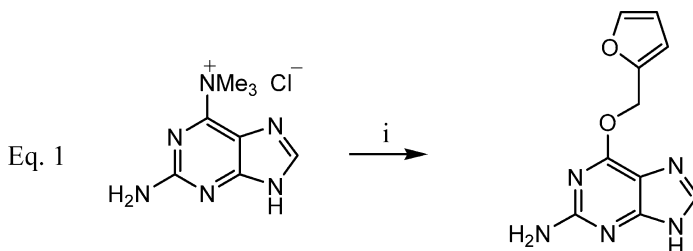
Derivatives



R ₁	R ₂	Yield (%)	MP(°C)
Hydroxyl	Hydrogen	52	145–147
Methylamine	Hydrogen	22	189–190
Dimethylamine	Hydrogen	46	220–221 (dec)
Amine	Methyl	44	214–216

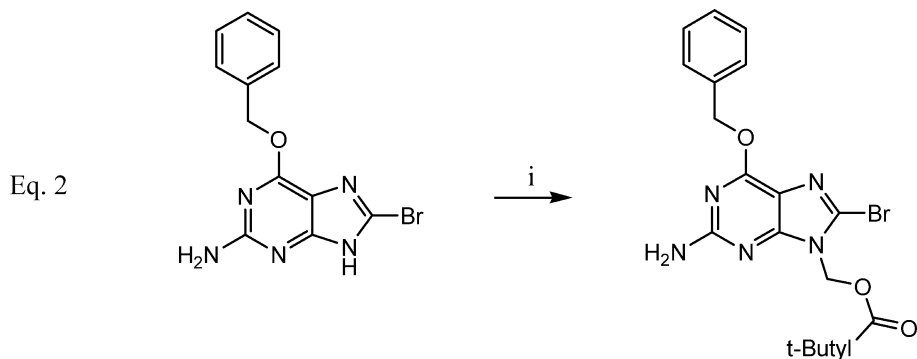
Notes

- Other methods have been used to prepare O⁶-heterocycle substituted guanines and are described (1,2) and illustrated in Eq. 1. Radiolabelled guanines have been prepared using this route (2).



i- Sodium, 2-furylmethyl alcohol, dimethyl sulfoxide

2. An analogue of the product from Step 2, O⁶-benzyl-8-bromo-9-pivaloyloxymethyl guanine, was prepared by the author in earlier investigations (3) as illustrated in Eq. 2:



i- Sodium ethoxide, ethyl alcohol, chloromethylpivalate

References

1. T.B. McMurray *et al*, US Patent 6,043,228 (March 28, 2002)
2. T.B. McMurray *et al*, US Patent 6,096,724 (August 1, 2000)
3. R.C. Moschel *et al*, US Patent 6,172,070 (January 9, 2001), US Patent 5,916,894 (June 29, 1999), and US Patent 5,958,932 (September 28, 1999)

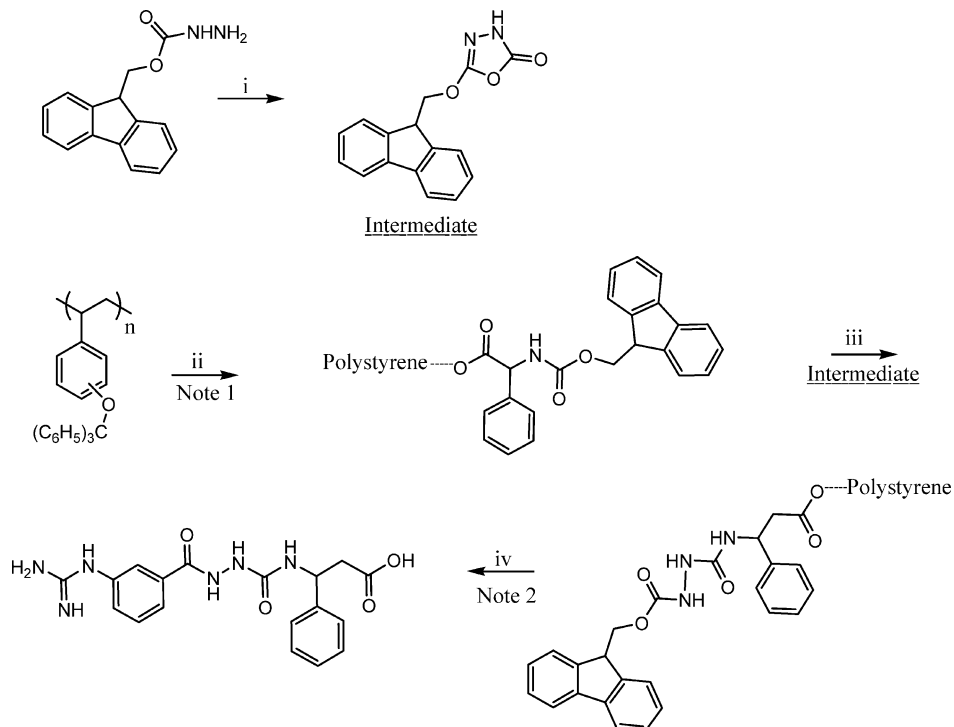
Hydrazine

Patent: Diacylhydrazine Derivatives
G. Holzemann *et al*, US Patent 6,649,613 (November 18, 2003)

Assignee: Merck Patent GmbH

Utility: Integrin Inhibitors

Reaction



- i- Phosgene, CH_2Cl_2 , sodium bicarbonate
- ii- 9H-Fluoren-9-ylmethoxy- β -phenylalanine-hydroxide,
N,N-dimethylformamide, diisopropylethylamine
- iii- CH_2Cl_2 , N-methylpyrrolidinone, 5-(9H-Fluoren-
9-yl-methoxy)-3H-[1,3,4]oxadiazol-2-one,
- iv- 3-(9H-Fluoren-9-ylmethoxycarbonylamino)benzoic acid,
O-benzotriazol-1-yl-N,N,N'-tetramethyl-uronium
hexafluorophosphate, collidine, N,N-dimethylformamide,
trifluoroacetic acid, triisopropylsilane, piperidine

Experimental

1. 5-(9H-Fluoren-9-ylmethoxy)-3H-[1,3,4]oxadiazol-2-one

In a dry flask containing 4.2 ml of 1.89 M phosgene in toluene was added a solution of 9H-fluoren-9-yl-methyl hydrazine carboxylate (3.91 mmol) dissolved in 40 ml of CH_2Cl_2 and 40 ml of saturated aqueous NaHCO_3 solution. The mixture was stirred 15 minutes and 58 mg of product isolated. IR data supplied.

2. Polystyrene-graft-9H-fluoren-9-ylmethoxy- β -phenylalanine-hydroxide

Polystyrene-graft-trityl chloride (2.0 g, theoretical load 1.8 mmol) was washed in 20 ml DMF. The resin was then mixed with a solution of 9H-fluoren-9-ylmethoxy- β -phenylalanine-hydroxide (2.7 mmol), diisopropylethylamine (2.25 mmol), dissolved in 20 ml of DMF, the mixture shaken at room temperature for 2 hours, and 1 ml methanol added. The mixture was washed 5 times with 20 ml CH_2Cl_2 , 3 times with 20 ml methyl alcohol, dried, and the product isolated.

3. Polystyrene-graft-9H-fluoren-9-ylmethoxy-azaglycine- β -phenylalanine-hydroxide

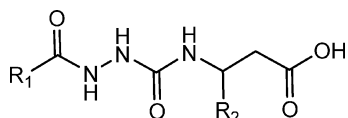
The product from Step 2 (0.48 mmol) was washed twice with 7 ml CH_2Cl_2 , once with 7 ml N-methylpyrrolidinone, and deprotected using 20% piperidine in 7 ml of DMF. The deprotected resin was washed 5 times with 7 ml N-methylpyrrolidinone and five times with 7 ml CH_2Cl_2 . Thereafter, it was mixed with a solution of the product from Step 1 (0.72 mmol) dissolved in 7 ml CH_2Cl_2 , shaken at ambient temperature 90 min, the product washed five times apiece with 7 ml with CH_2Cl_2 and N-methylpyrrolidinone, and dried.

4. 3-[4-(3-Guanidinobenzoyl)semicarbazido]-3-phenylpropionic acid, trifluoroacetate.

The product from Step 3 (0.24 mmol) was mixed with a solution of 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid (0.48 mmol), O-benzotriazol-1-yl-N,N,N'-tetramethyluronium hexafluorophosphate (0.48 mmol) and collidine (2.4 mmol) dissolved in 5 ml of DMF, and shaken at ambient temperature 90 min. The resin was washed and deprotected as described in Step 2. Thereafter, the resin was mixed with a solution of N,N'-bis-BOC-1-guanylpurazole (2.4 mmol) dissolved in 4 ml of chloroform and

stirred at 50°C 16 hours. The resin was then washed with CH₂Cl₂, methyl alcohol, and diethyl ether. To remove the BOC groups, the resin was shaken with a mixture of 5 ml 95% TFA and 5% triisopropylsilane at ambient temperature, first 90 minutes and then 30 minutes. Removal of the solvent and purification by preparative RP-HPLC gave 3-[4-(3-guanidinobenzoyl)semicarbazido]-3-phenylpropionic acid, trifluoroacetate. FAB-MS data supplied.

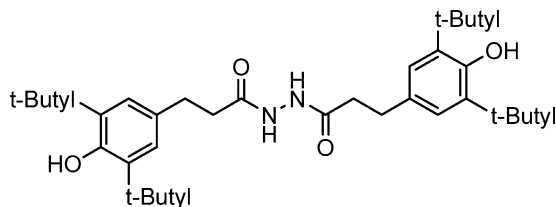
Derivatives



R ₁	R ₂	Salt	MS (m/e)
4-(N'-(5-Guanidinopentanoyl))	Phenyl	None	364.2
4-(3-Guanidinobenzoyl)	4-Trifluoromethoxyphenyl	None	468.5
4-(5-(4-Methylpyrid-2-ylamino)pentanoyl)	Phenyl	Acetate	414.5
4-(3-Guanidinobenzoyl)semicarbazido	4-Bromophenyl	Trifluoroacetate	464.3

Notes

1. The Merrifield resin, polystyrene-g-chloromethyl, or Wang resin can also be used as the polymeric substrate in the current invention.
2. In a previous study by the author (1), β -alanine derivatives analogous to those of the current invention were prepared without the aid of a polymeric substrate.
3. Salts and stereospecific derivatives of the current invention were prepared by the author in a previous investigation and are discussed (2).
4. A process for preparing mono- and diacyl-substituted hydrazine derivatives using carboxylic acids is described (3).
5. The preparation of the symmetrical diacyl hydrazine derivatives, (I), is described (4).



(I)

References

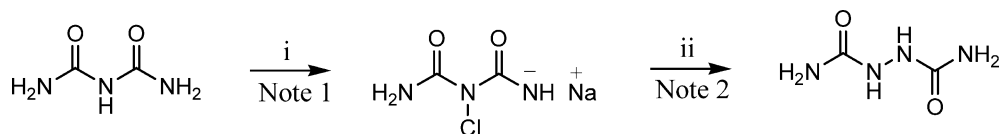
1. G. Holtzman *et al*, US Patent 6,576,637 (June 10, 2003)
2. G. Holtzman *et al*, US Patent 6,326,403 (December 4, 2001)
3. C. Dubuisson-Brengel *et al*, US Patent 6,096,890 (August 1, 2001)
4. F. Broussard *et al*, US Patent 6,444,848 (September 3, 2002)

Patent: Method for Synthesizing Hydrazodicarbonamide
C.-H. Lee *et al*, US Patent 6,635,785 (October 21, 2003)

Assignee: J&J Chemical Co., Ltd.

Utility: Blowing Agent for Plastics

Reaction



i- Sodium hypochlorite, water
ii- Ammonia, water

Experimental

1. Chlorobiuret Sodium Salt

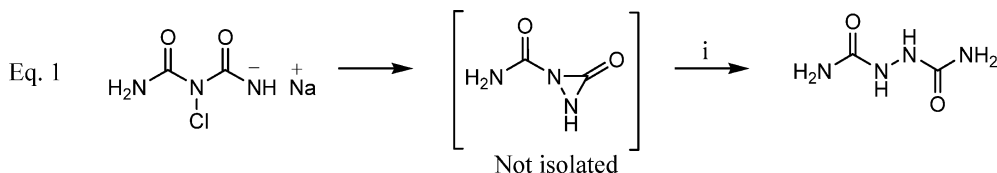
A 12.9% aqueous biuret slurry (0.287 moles) was placed in a 2-liter glass reactor, cooled to 5°C, 12% sodium hypochlorite solution (0.287 moles) added, and the reaction temperature kept at 5°C. Thereafter, the reaction product was analyzed by iodine titration method and liquid chromatography indicated the product yield was 98%.

2. Hydrazodicarbonamide

The entire product from Step 1 was added to a 2-liter glass reactor, the temperature raised to 100°C while adding liquid ammonia (8.8 moles), and the reaction temperature maintained at 100°C 30 minutes. After the reaction was completed, unreacted ammonia was removed, the reaction solution filtered, and the product isolated in 95% yield.

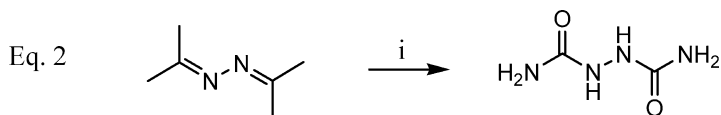
Notes

1. A modified method for preparing chlorobiuret sodium salt from biuret using chlorine gas and aqueous sodium hydroxide solution is described by the author.
2. The formation of hydrazodicarbonamide by the reaction of chlorobiuret sodium salt with ammonia is through the Favorskii reaction illustrated in Eq. 2:



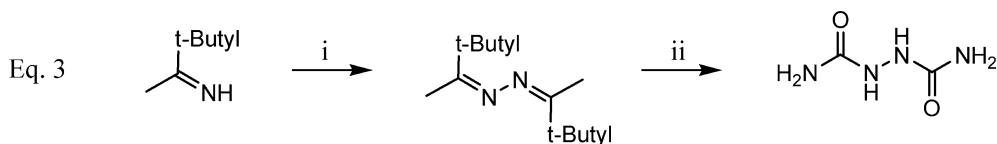
i- Ammonia

3. Two other methods exist for preparing hydrazodicarbonamide. In the first method urea and dimethylketazine are reacted in the presence of either ammonium sulfate or sodium sulfate decahydrate (1) as illustrated in Eq 2:



i- Urea, ammonium sulfate, water.

The second method first dimerizes t-butyl-methyl-2-ketimine (3) then reacts the product with urea as illustrated in Eq. 3:



i- Copper(I)chloride, oxygen, Zeolith 134, ammonium hydroxide

ii- Urea, N,N-dimethylformamide, water

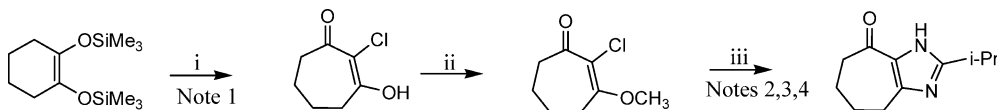
References

1. S. Ohno *et al*, US Patent 4,176,135 (November 27, 1979)
2. M. Jautelat *et al*, US Patent 6,472,560 (October 29, 2002)

Imidazole

Patent: Method for Preparing Cycloheptimidazoles
T. Tomiyama *et al*, US Patent 6,316,634 (November 13, 2001)
Assignee: Kotobuki Pharmaceutical Co., Ltd.
Utility: Treatment of Hypertension

Reaction



- i- Potassium t-butoxide, n-pentane, chloroform,
- ii- Trimethyl orthoformate, methyl alcohol
- iii- Butylamine hydrochloride, potassium carbonate, 1,4-dioxane

Experimental

1. 2-Chloro-3-hydroxycyclohept-1-one

To a mixture of 1,2-bis(trimethylsilyloxy)cyclohex-1-ene (67.6 g) and potassium tert-butoxide (52.1 g) dissolved in 600 ml of pentane, 25.1 ml chloroform was added over 30 minutes at ambient temperature. After an additional 30 minutes, 10 ml 10% HCl and 30 ml water were added and the mixture reacted one hour. The mixture was poured into 200 ml saturated NaHCO₃ solution, the aqueous layer washed twice with EtOAc, and the pH adjusted to 3 using 5% HCl. The product was extracted with chloroform, the solution washed, dried, and 22 g of product isolated. ¹H-NMR and MS data supplied.

2. 2-Chloro-3-methoxycyclohept-1-one

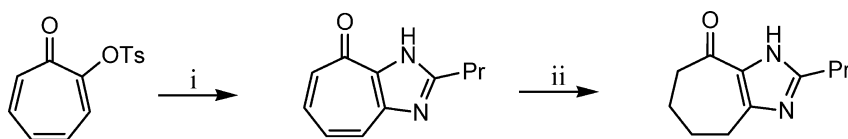
The product from Step 1 (5.0 g), 5.0 ml of trimethyl orthoformate and 30 ml methyl alcohol were stirred in the presence of IR 120H ion-exchange resin (0.5 g, pre-washed with methyl alcohol) at ambient temperature 3 hours. Thereafter, the mixture was filtered, extracted with EtOAc, washed with saturated NaHCO_3 solution and brine, dried, concentrated, and 2.8 g of product isolated. $^1\text{H-NMR}$ and MS data supplied.

3. 2-Propyl-4,5,6,7-tetrahydrocycloheptimidazole-8-one

A solution containing butylamidine hydrochloride (37.9 g) and K_2CO_3 (8.4 g) dissolved in 1,4-dioxane were to refluxed and the product from Step 2 (3.7 g) dissolved in 1,4-dioxane added. The mixture refluxed 2 hours, cooled to ambient temperature, extracted with EtOAc, washed with water, brine, dried, and concentrated. The crude product was dissolved in toluene and extracted with 10% aqueous NaOH . The solution was acidified to pH 5.0 with 10% HCl and extracted with EtOAc. The solution was concentrated, acidified using ethyl alcohol saturated with hydrochloric acid, and the solvent removed in vacuo. The residue was recrystallized from ethyl alcohol/diethyl ether and 3.1 g product isolated. $^1\text{H-NMR}$ and MS data supplied.

Notes

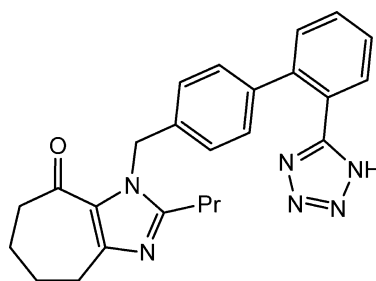
1. The preparation of the reagent of Step 1 described (1).
2. In an earlier investigation (2), the author prepared 2-propyl-4,5,6,7-tetrahydrocycloheptimidazole using tosyl tropone as illustrated in Eq. 1:



i- Sodium hydroxide, butylamidine, hydrochloride

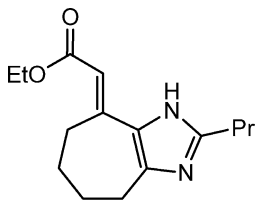
ii- Platinum(IV)oxide, hydrogen

3. The preparation of Step 3 N-substituted cycloheptimidazole derivatives, (I), is described by the author (2).



(I)

4. The conversion of the product of Step 3 into the ethoxycarbonyl analogue, (II), is described (3).



(II)

References

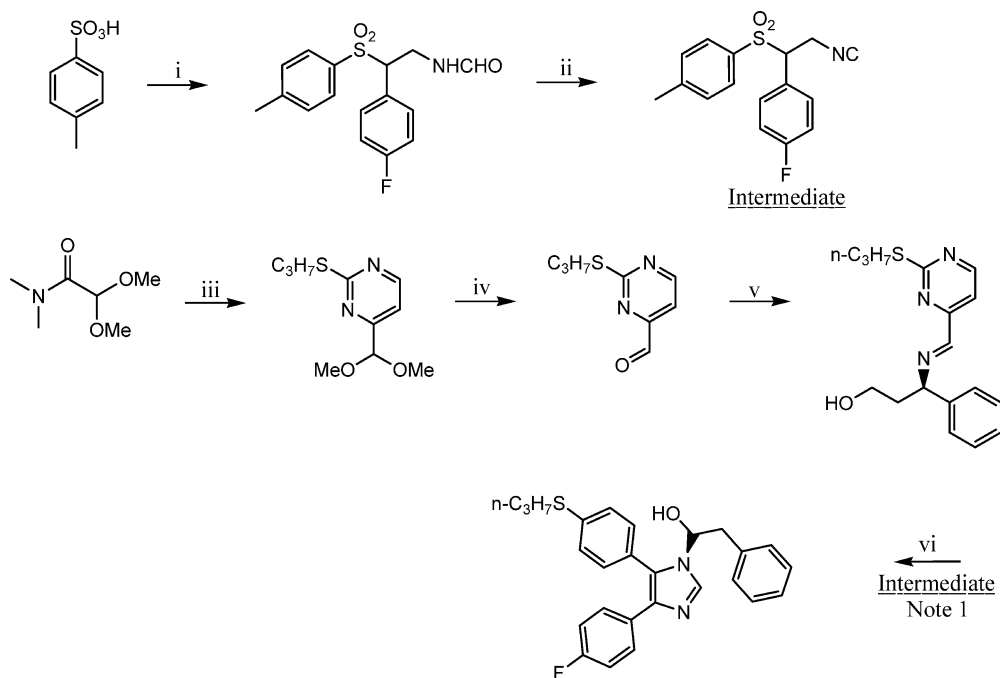
1. K. Rublmann, *Synthesis*, 236 (1971)
2. T. Tomiyama *et al*, US Patent 5,409,947 (April 25, 1995)
3. T. Tomiyama *et al*, US Patent 5,527,815 (June 18, 1996)

Patent: Substituted Imidazole Compounds
J.L. Adams *et al*, US Patent 6,569,871 (May 27, 2003)

Assignee: SmithKline Beecham Corporation

Utility: CSBP/p38 Kinase Inhibitor in the Treatment of Inflammation

Reaction



- i- p-Toluenesulfonic acid, p-fluorobenzaldehyde, formamide, camphor sulphonic acid
- ii- Ethyleneglycol dimethylether, phosphorous oxychloride, triethylamine
- iii- N,N-Dimethylformamide dimethyl acetal, pyruvaldehyde dimethyl acetal, thiourea, sodium methoxide, 1-bromopropane, EtOAc
- iv- THF, hydrochloric acid
- v- (S)-2-Amino-2-phenylethanol, CH_2Cl_2
- vi- N,N-Dimethylformamide, potassium carbonate

Experimental

1. 4-Fluorophenyl-tolylsulfonmethylformamide

p-Toluenesulfonic acid (140.6 mmol), p-fluorobenzaldehyde (206 mmol), formamide (503 mmol) and camphor sulphonic acid (17.3 mmol) were combined and stirred at 60°C 18 hours. The resulting solid was broken up and stirred with a mixture of 35 ml methyl alcohol and 82 ml hexane then filtered. The solid was suspended in 200 ml methyl alcohol/hexane, 1:3, stirred vigorously to break up remaining chunks, and the product isolated in 62% yield. ^1H NMR data supplied.

2. 4-Fluorophenyl-tolylsulfonmethylisocyanide

The product from Step 1 (6.25 mmol) was dissolved in 32 ml ethylene glycol dimethylether, cooled to -10°C , POCl_3 (16.3 mmol) added followed by the dropwise addition of triethylamine (32.6 mmol) dissolved in 3 ml ethylene glycol dimethylether, and the reaction temperature kept below -5°C . The mixture was gradually warmed to ambient temperature over 1 hour, quenched with water, and extracted with EtOAc. The organic phase was washed with saturated aqueous NaHCO_3 , dried, and concentrated. The residue was triturated with petroleum ether, filtered, and the product isolated in 90% yield. ^1H NMR data supplied.

3. 2-Propylthiopyrimidine-4-carboxaldehyde dimethyl acetal

A reactor was charged with N,N-dimethylformamide dimethyl acetal (700 mmol) and pyruvaldehyde dimethyl acetal (700 mmol), heated to 110°C 4 hours, cooled to 85°C , and thiourea (636.4 mmol) and sodium methoxide (700 mmol) dissolved in 160 ml methyl alcohol added. Thereafter, the mixture stirred 4 hours. The mixture was cooled to 65°C and 1-bromopropane (700 mmol) added over 15 minutes. After 1 hour, 100 ml EtOAc was added and the mixture heated to 95°C . The solvents were distilled off, 120 ml water added, the mixture stirred 10 minutes at 50°C , cooled, concentrated, and the product isolated as a yellow oil. ^1H NMR data supplied.

4. 2-Propylthiopyrimidine-4-carboxaldehyde

The product from Step 3 (105 mmol) was dissolved in 75 ml THF, 150 ml 3 M HCl added, and heated to 50°C 4 hours. THF was removed, the mixture cooled in an ice bath, and 300 ml EtOAc and NaHCO_3 added. The product was extracted with EtOAc and concentrated to give a brown oil. The residue was purified by flash chromatography on silica gel using 0–1% methyl alcohol/ CH_2Cl_2 , and the product isolated as a yellow oil. ^1H NMR data supplied.

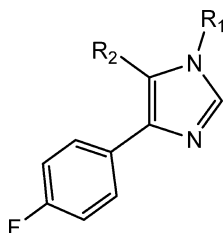
5. 2-Propylthiopyrimidine-4-carboxaldehyde[(S)-amino-2-phenylethanol]imine

To a solution of the product from Step 4 (11 mmol) dissolved in 30 ml CH_2Cl_2 was added (S)-2-amino-2-phenylethanol (14.3 mmol) and the solution stirred at room temperature 16 hours. The solution was concentrated and the product isolated. MS data supplied.

6. (S)-1-(1-Hydroxy-2-phenyleth-2-yl)-4-(4-fluorophenyl)-5-[2-propylthio)-pyrimidin-4-yl]imidazole

The product from Step 5 (11 mmol) was dissolved in 10 ml N,N-dimethylformamide, the product from Step 2 (7.7 mmol) and K_2CO_3 (8.8 mmol) added, and the mixture stirred at ambient temperature for 16 hours. The solvent was removed and the residue partitioned between EtOAc and water. The organic phase was separated, washed, dried, concentrated, purified by flash chromatography on silica gel using 0–4% methyl alcohol/ CH_2Cl_2 , and the product isolated as a yellow solid. MS data supplied.

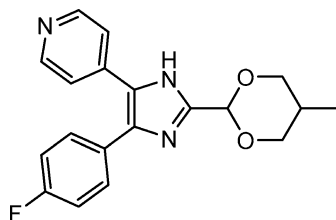
Derivatives



R_1	R_2	MS (m/e)
(S)-1-Hydroxyl-2-phenyleth-2-yl	2-Propylsulfonylpyrimidin-4-yl	391
(R,S)-1,3-Dihydroxyprop-2-yl	2-Methoxypyrimidin-4-yl	345
(R,S)-1-Dimethylamino-prop-2-yl	2-Methoxypyrimidin-4-yl	365
(R)-1-Hydroxy-3-phenylprop-2-yl	2-Methoxypyrimidin-4-yl	404
(S)-1-Hydroxyprop-2-yl	2-((N-Phenyl)amino)pyrimidin-4-yl	390

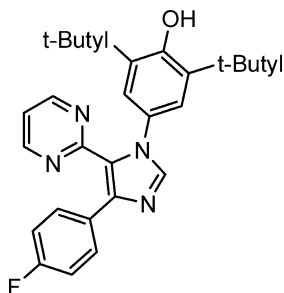
Notes

1. Imidazoles have also been prepared by thermal or catalyzed cyclization of N-formyl- β -imines using phosphorous pentachloride or phosphorous oxochloride and are reviewed (1).
2. In a subsequent investigation by the author, 2-[5-(4-fluoro-phenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-5-methyl-[1,3]dioxane, (I), was prepared (2).



(I)

3. Other Step 5 pyridyl imidazole derivatives, (II), have been prepared and are discussed (3).



(II)

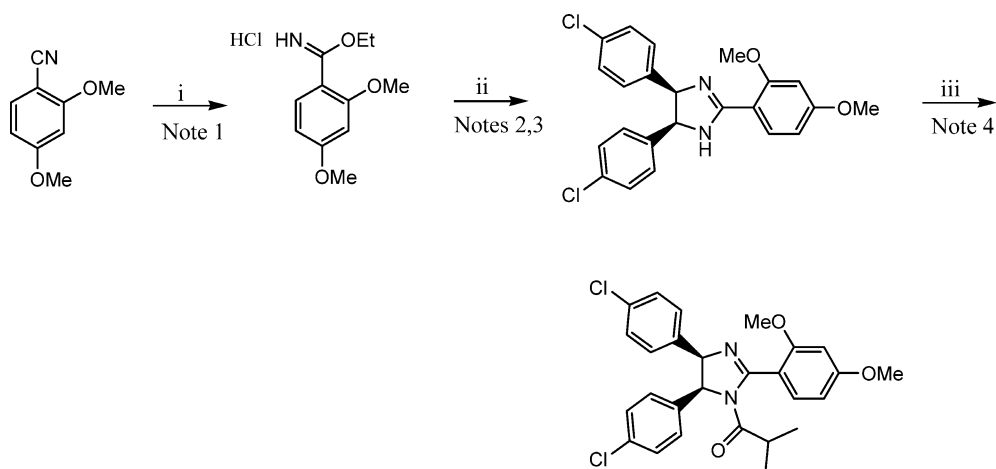
References

1. T. Strybny *et al*, J. Org. Chem., 28, 3381 (1963)
2. P.L. Bamborough *et al*, US Patent 6,602,877 (August 5, 2003)
3. P.W. Sheldrake *et al*, US Patent 5,663,334 (September 2, 1997)

Imidazolidine

Patent: Cis-Imidazolines
N. Kong *et al*, US Patent 6,734,302 (May 11, 2004)
Assignee: Hoffman-La Roche Inc.
Utility: Antiproliferation Agent

Reaction



- i- Hydrogen chloride, ethyl alcohol
- ii- meso-1,2-bis-(4-chlorophenyl)-ethane-1,2-diamine,
ethyl alcohol
- iii- Isobutyryl chloride, triethylamine

Experimental

1. Ethyl 2,4-dimethoxy-benzimidate hydrochloride

Hydrogen chloride gas was passed through a solution of 2,4-dimethoxy benzonitrile (32 mmol) dissolved in 200 ml ethyl alcohol at 0°C 7 hours and the mixture stirred overnight at ambient temperature. The solvent was removed, the residue triturated in diethyl ether, and the product isolated in 57% and used without purification.

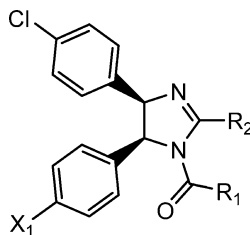
2. 4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-1H-imidazole

A solution of meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine (4.30 mmol) and the product from Step 1 (6.43 mmol) dissolved in 30 ml ethyl alcohol were refluxed 16 hours. The mixture was basified with 10 ml NaHCO₃ solution and extracted with EtOAc. The extract was washed with brine and dried over anhydrous sodium sulfate. The solids were filtered and the filtrate concentrated in vacuo. The product was purified by flash chromatography using the Biotage system, KP-Sil.TM. 32–63 μ m, 60 Å silica gel eluting with 2–6% methyl alcohol/CH₂Cl₂ and isolated in 60% yield.

3. 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one

Isobutyryl chloride (0.18 mmol) was added to a solution of triethylamine (0.18 mmol) containing the product from Step 2 (0.164 mmol) and the mixture stirred at ambient temperature 2 hours. It was then diluted with CH₂Cl₂, washed with water and brine, dried, and concentrated. The residue was purified by chromatography using silica gel with 0.5–1% methyl alcohol/CH₂Cl₂ and the product isolated. MS data supplied.

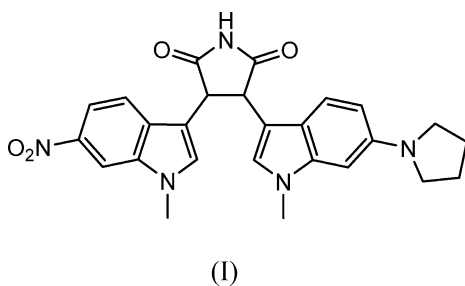
Derivatives



X ₁	R ₁	R ₂	Yield (%)	MS (m/e)
Chloro	4-Pyrrolidin-1-yl-piperidin-1-yl	2-i-Propylphenyl	72	605
Nitro	i-Propyl	4-Methoxyphenyl	40	478
Chloro	Piperazin-1-yl	2-Methoxyphenyl	—	539
Chloro	Methyl	2-Methoxyphenyl	—	510

Notes

1. This is an example of the Pinner imino ether synthesis (1). In the presence of an aqueous medium, the intermediate is hydrolyzed to the benzoic acid derivative.
2. Other cis-imidazoline derivatives of the current invention were prepared by the author in an earlier investigation (2).
3. The preparation of meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine is provided (3).
4. In an earlier investigation by the co-author (4) symmetrical indole succinimides, (I), were prepared.



References

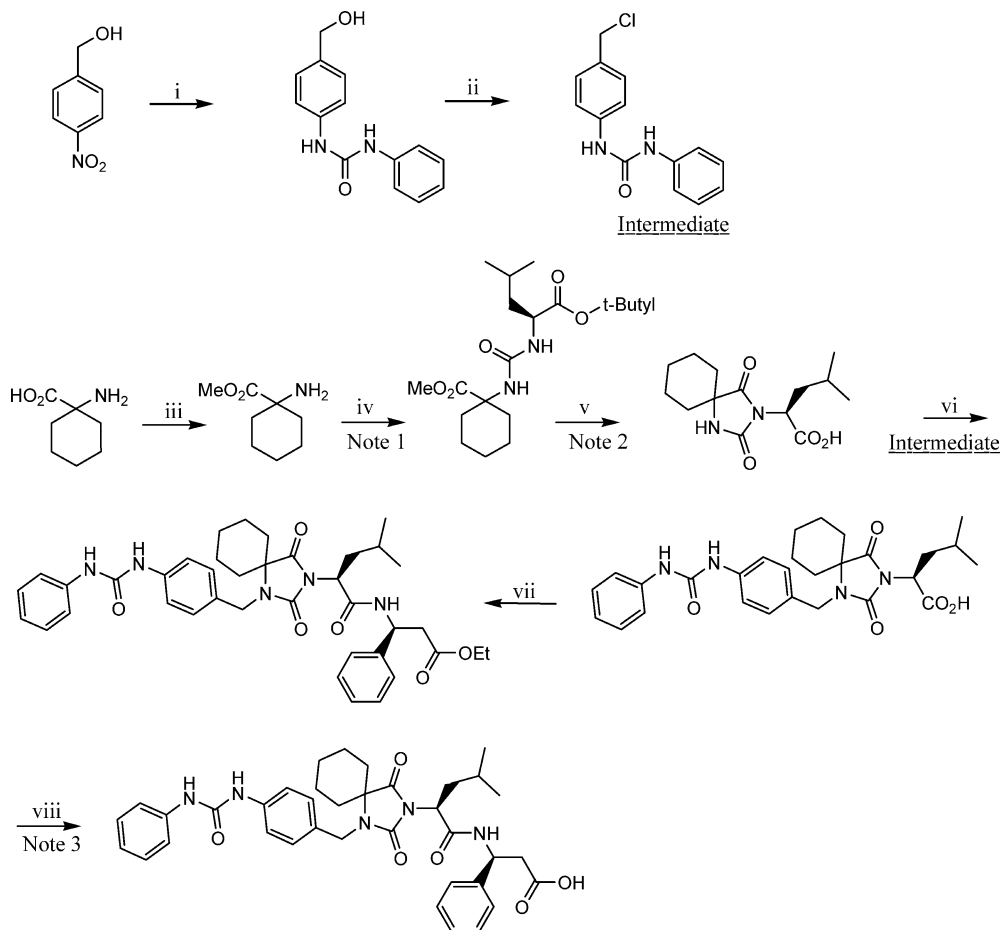
1. H. Schroeder *et al*, J. Am. Chem. Soc., 78, 2447 (1956)
2. N. Kong *et al*, US Patent 6,617,346 (September 9, 2003)
3. M. Jennerwein *et al*, Cancer Res. Clin. Oncol., 114, 347 (1988); F. Vogtle *et al*, Chem. Ber., 109, 1 (1976)
4. N. Fotouhi *et al*, US Patent 6,281,356 (August 28, 2001)

Patent: Spiroimidazolidine Derivatives, Their Preparation, Their use and Pharmaceutical Preparations Formed Therefrom
V. Wehner *et al*, 6,399,643 (June 4, 2002)

Assignee: Aventis Pharma Deutschland GmbH

Utility: Treatment of Rheumatoid Arthritis or Allergic Disorders

Reaction



i- 10% Palladium on carbon, methyl t-butyl ether,
phenyl isocyanate

ii- Thionyl chloride, CH_2Cl_2

iii- Thionyl chloride, methyl alcohol

iv- L-Leucine t-butyl ester isocyanate, N,N-dimethylformamide

v- Hydrochloric acid

- vi- *n*-Butyllithium, THF
- vii- O-((Cyano(ethoxycarbonyl)methylene)amino)-*N,N,N'*,
 N'-tetramethyluronium tetrafluoroborate,
 N,N-diisopropylethylamine, ethyl
 (*S*)-3-amino-3-phenylpropionate
- viii- Lithium hydroxide, methyl alcohol

Experimental

1. 4-(3-Phenylureido)benzyl alcohol

4-Nitrobenzyl alcohol (200 mmol) was hydrogenated over 1.0 g 10% palladium on carbon (50% water) in 500 ml methyl *t*-butyl ether. After absorption of hydrogen was completed the catalyst was removed by filtration and phenyl isocyanate (200 mmol) added to the filtrate at 15 °C over 30 minutes. The product was isolated by filtration in 89% yield.

2. 4-(3-Phenylureido)benzyl chloride

Thionyl chloride (354 mmol) was added dropwise at 30 °C to a suspension of the product from Step 1 (177 mmol) in 500 ml CH₂Cl₂ and the mixture stirred at 40 °C 1 hour. The mixture was treated with NaHCO₃ and after CO₂ evolution stopped, it was cooled to room temperature, and the precipitated product isolated in 96% yield.

3. Methyl 1-aminocyclohexane-1-carboxylate

To 1-aminocyclohexane-1-carboxylic acid (350 mmol) dissolved in 1.25 L of methyl alcohol in a glass reactor was added 51 ml thionyl chloride in portions at –5 °C. The mixture was stirred 5 hours then stood overnight. Thereafter, the mixture was concentrated, the residue mixed with water, the solution pH adjusted to 9 using Na₂CO₃, and extracted twice with CH₂Cl₂. The organic phase was dried, re-concentrated, and the product isolated in 66% yield.

4. Methyl 1-(3-((*S*)-1-*t*-butoxycarbonyl-3-methylbutyl)ureido)cyclohexanecarboxylate

The product from Step 3 (179 mmol) was added to a solution of L-leucine *t*-butyl ester isocyanate (179 mmol) dissolved in 300 ml DMF, stirred 2 hours at ambient temperature, then stood overnight. The solvent was removed, the residue treated with heptane, and the mixture stirred at ambient temperature 2 hours. The precipitate was filtered and the product isolated in 69% yield.

5. (*S*)-2-(4,4-Pentamethylene-2,5-dioxoimidazolidin-1-yl)-2-(2-methylpropyl)acetic acid

The product from Step 4 (30.8 mmol) was heated to 60 °C 8 hours in 200 ml 6 M HCl then stood at ambient temperature overnight. The product was extracted using diethyl

ether, concentrated in vacuo, the residue extracted with a little acetonitrile, washed with water, freeze-dried, and product isolated in 95% yield.

6. (S)-2-(4,4-Pentamethylene-3-(4-(3-phenylureido)benzyl)-2,5-dioximidazolidin-1-yl)-2-(2-methylpropyl)acetic acid

To the product from Step 5 (26.24 mmol) dissolved in 150 ml THF was added 21 ml n-butyllithium solution (2.5 M in hexane) at -76°C , the mixture stirred for 30 minutes, warmed 0°C , and the product from Step 2 (26.24 mmol) added in portions. After stirring at 0°C 30 minutes, the mixture pH was adjusted to 1 by the addition of 1 M HCl, diluted with water, and extracted with EtOAc. The two phases were separated, the organic phase dried, concentrated, purified by means of preparative HPLC, and the product isolated in 16% yield.

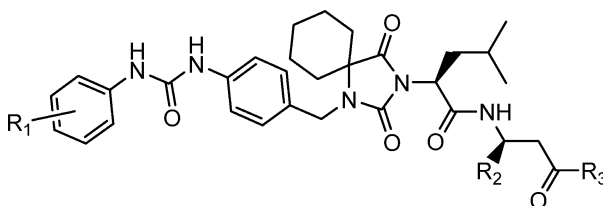
7. Ethyl (S)-3-((S)-2-(4,4-pentamethylene-3-(4-(3-phenylureido)benzyl)-2,5-dioximidazolidin-1-yl)-2-(2-methylpropyl)acetyl amino)-3-phenylpropionate

O-((Cyano(ethoxycarbonyl)methylene)amino)-N,N,N', N'-tetramethyluronium tetrafluoroborate (1.42 mmol) and N,N-diisopropylethylamine (1.35 mmol) were added successively with ice cooling to a solution of the product from Step 6 (1.42 mmol) and ethyl (S)-3-amino-3-phenylpropionate (1.42 mmol) dissolved in 20 ml DMF. After 1 hour at ambient temperature the solvent was removed and the residue dissolved in EtOAc. The solution was successively washed twice with aqueous solutions of KHSO_4 , NaHCO_3 , and brine. The organic phase was dried, concentrated, the product isolated by chromatography on silica gel using EtOAc/heptane, 1:1, and the product isolated in 85% yield.

8. (S)-3-((S)-2-(4,4-Pentamethylene-3-(4-(3-phenylureido)benzyl)-2,5-dioximidazolidin-1-yl)-2-(2-methylpropyl)acetyl amino)-3-phenylpropionic acid

To the product from Step 7 (1.2 mmol) was added 3.61 ml 1 M LiOH dissolved in 30 ml methyl alcohol and the mixture stirred at ambient temperature overnight. Thereafter, a second addition of 10 ml methyl alcohol and 1.2 ml of 1 M LiOH was added and the mixture stirred overnight a second night. To this was added 30 ml of water, methyl alcohol removed, and the pH adjusted to 1 with 1 M HCl. The mixture was extracted with EtOAc, washed, dried, and 639 mg of the product isolated.

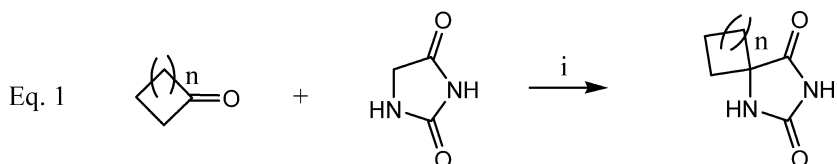
Derivatives



R ₁	R ₂	R ₃	MS (m/e)
Hydrogen	i-Propyl	Hydroxyl	634.4
2-Methyl	Phenyl	Hydroxyl	668.4
Hydrogen	Methyl	Amide	591.4

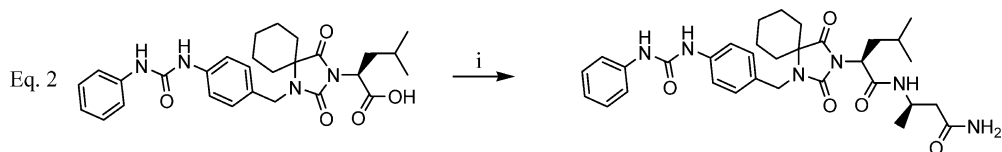
Notes

1. The preparation of L-leucine t-butyl ester isocyanate is described (1).
2. An alternative route suggested by the author for preparing hydantoin spiral intermediates is through the Bucherer reaction illustrated in Eq. 1:



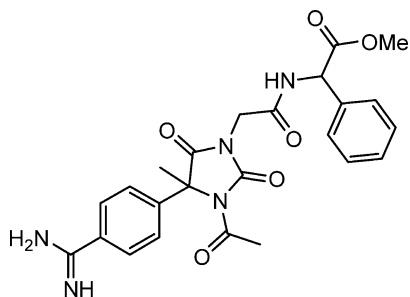
i- Ammonium carbonate, potassium cyanide

3. Ammonium, sodium, and tris(hydroxymethyl)ammonium salts of the product of Step 8 were prepared by the author by acid base neutralization reactions.
4. Amide and diamide derivatives were also prepared by the author as illustrated in Eq. 2:



i- (S)-3-Amino-3-phenylpropanamide

5. Analogues of the current invention have been prepared containing pyrrolidinone (2) and aminoacids, (I), (3) and are described.



(I)

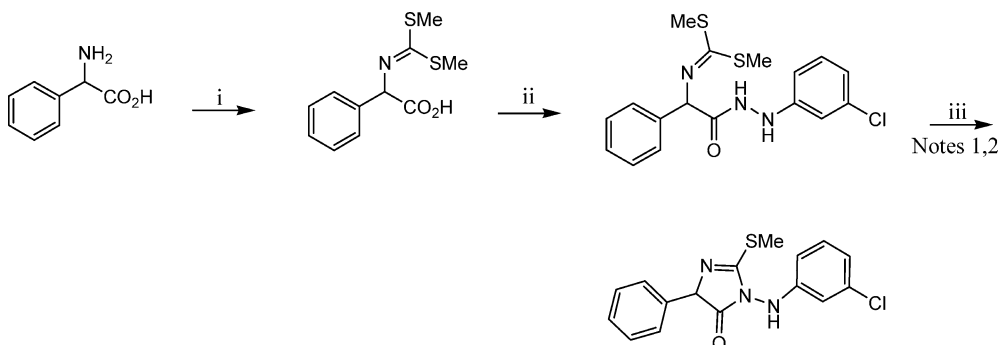
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1. J.S. Nowick *et al.*, J. Org. Chem., 61, 3929 (1996)
2. O. Klingler *et al.*, US Patent 5,658,935 (August 19, 1997)
3. W. Kong *et al.*, US Patent 5,686,421 (November 11, 1997); G. Zoller *et al.*, US Patent 5,397,796 (March 14, 1995) and US Patent 5,981,492 (November 9, 1999)

Imidazolone

Patent: Fungicidal 2-Imidazolin-5-ones and Imidazoline-5-thiones
G. Lacroix *et al*, US Patent 6,344,564 (February 5, 2002)
Assignee: Rhone-Poulenc, Inc.
Utility: Agricultural Fungicide

Reaction



- i- Potassium hydroxide, water, carbon disulfide, methyl iodide
- ii- Dicyclohexylcarbodiimide, CH_2Cl_2 ,
3-chlorophenyl-hydrazine
- iii- Xylene

Experimental

1. N-[Bis(methylthio)methylene]-2-phenylglycine

Phenylglycine (0.66 mol) was dissolved at 5°C in 22% aqueous KOH (1.3 mol) and CS_2 (55.3 g) added while the mixture stirred vigorously. A precipitate appeared and the

mixture turned orange in color. After stirring 3 hours at ambient temperature, methyl iodide (0.73 mol) was added. After stirring an additional 30 minutes 50% aqueous KOH (0.66 mol) was added. Finally, after 30 minutes of further stirring a second addition of methyl iodide (103 g) was added and the mixture stirred 1 hour. The mixture was diluted with 300 ml water, acidified to pH 4 with 1 M HCl, extracted with 500 ml EtOAc, dried, concentrated, and the product isolated in 31% yield, mp = 112°C.

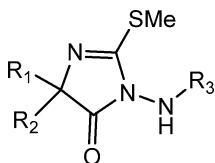
2. 2'-(3-Chlorophenyl) [N-bis(methylthio)methylene]-2-phenylglycyl]hydrazide

Dicyclohexylcarbodiimide (16.4 mmol) was added to a solution of the product from Step 1 (16.4 mmol) dissolved in 40 ml CH₂Cl₂ and the mixture stirred 30 minutes at ambient temperature. Thereafter, 3-chlorophenylhydrazine (16.4 mmol) was added and the mixture heated to 30°C 30 minutes. Insoluble material that formed was filtered off, the filtrate washed twice with 30 ml water, purified by chromatography on a silica gel, and the product isolated as a solid, mp = 146°C.

3. 1-(3-Chlorophenyl)amino-2-methylthio-4-phenyl-2-imidazolin-5-one

The product from Step 2 (5 mmol) was dissolved in 30 ml xylene and refluxed 4 hours. The mixture was concentrated and triturated with 10 ml of diethyl ether whereupon the product crystallized. The precipitate was filtered and the product isolated in 56% yield, mp = 196°C.

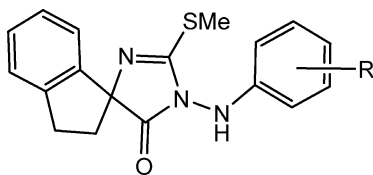
Derivatives



R ₁	R ₂	R ₃	MP (°C)
Hydrogen	Phenyl	2,4-Dichlorophenyl	144
Benzyl	Phenyl	Phenyl	166
Methyl	4-(4-Fluorophenoxy)phenyl	Phenyl	138
4-Chlorophenyl	Methyl	3-Methylpyridine	133

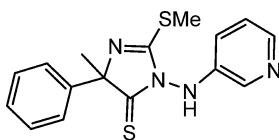
Notes

1. In an earlier investigation by the author (1) 4,4-spiro derivatives of the Step 3 product (I) were prepared.



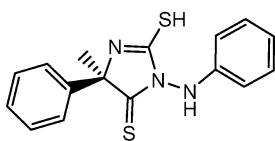
(I)

2. The 5-thione analogue of Step 3, 1-(3-pyridinylamine-2-thiomethyl-4-methyl-4-phenyl-2-imidazolin-5-thione, (II), and derivatives were previously prepared by the author and are described (1).

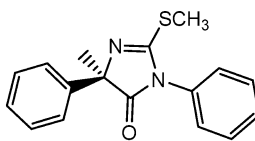


(II)

3. Optically active derivatives, (II), (III) have also been prepared (2).

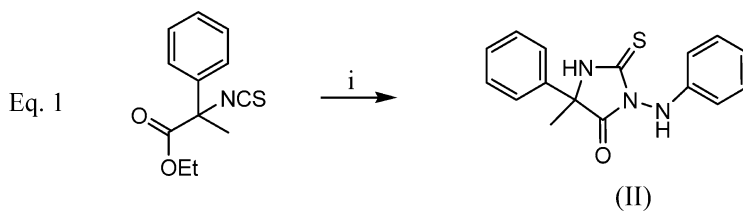


(II)



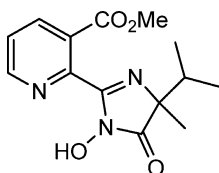
(III)

4. 2-Thiohydantoin analogues (IV) were also prepared in a previous investigation by the author (3) as illustrated in Eq. 1:



i- THF, phenylhydrazine

5. The preparation of 1-hydroxy-2-(2-nicotinic-3-methoxycarbonyl)-4-isopropyl-4-methyl-2-imidazolin-5-one, (IV), is described.



(IV)

References

1. G. Lacroix *et al*, US Patent 6,008,370 (December 28, 1999)
2. G. Lacroix *et al*, US Patent 5,650,519 (July 22, 1997)
3. G. Lacroix *et al*, US Patent 6,002,016 (December 14, 1999)
4. M.J. Guaciario, US Patent 5,213,607 (May 25, 1993)

Imidazotriazinones

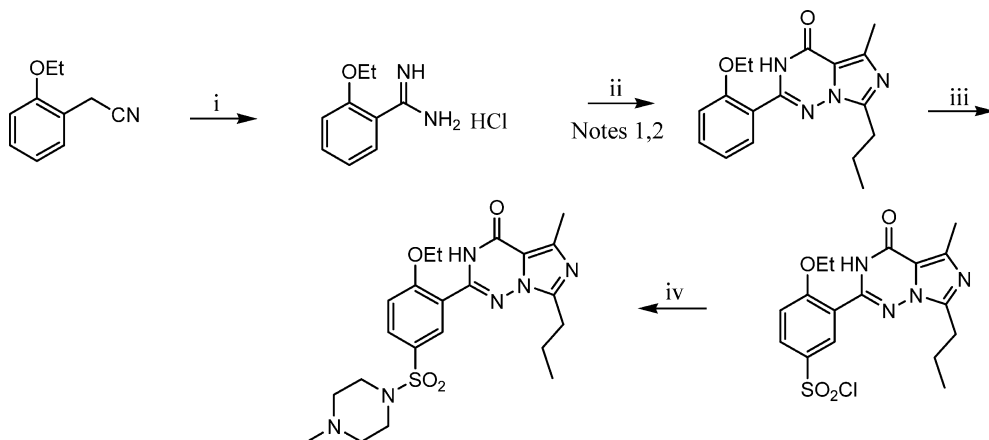
Patent: 2-Phenyl Substituted Imidazotriazinones as Phosphodiesterase Inhibitors

U. Niewohner *et al*, US Patent 6,362,178 (May 26,2002)

Assignee: Bayer Aktiengesellschaft

Utility: Treating of Cardiovascular Disorders

Reaction



i- Ammonium chloride, trimethylaluminum, toluene

ii- 2-Butyrylamino propionic acid, pyridine, THF,
4-dimethylaminopyridine, ethyl oxalyl chloride, phosphorus
oxychloride, ethyl alcohol, sodium bicarbonate,
hydrazine hydrate

iii- Chlorosulphonic acid

iv- CH_2Cl_2 , 4-dimethylaminopyridine, N-methylpiperazine

Experimental

1. 2-Ethoxybenzimidine hydrochloride

Ammonium chloride (400 mmol) was suspended in 375 ml toluene at 0°C, 200 ml 2 M solution of $(\text{CH}_3)_3\text{Al}$ in hexane added, followed by 2-ethoxybenzonitrile (200 mmol), and the mixture heated overnight at 80°C. Thereafter, the mixture was added to a suspension of 100 g silica gel and 950 ml chloroform, stirred at room temperature 30 minutes, filtered, and the residue washed with methyl alcohol. The mixture was concentrated, the residue stirred with a CH_2Cl_2 /methyl alcohol, 9:1, re-concentrated, and the product isolated. $^1\text{H-NMR}$ data supplied.

2. 2-(2-Ethoxy-phenyl)-5-methyl-7-propyl-3H-imidazol-[5,1-f][1,2,4]triazin-4-one

2-Butyrylaminopropionic acid (45 mmol) and pyridine (10.67 g) were dissolved in 45 ml THF, a spatula tip of 4-dimethylaminopyridine added, and the mixture refluxed. Thereafter ethyl oxalyl chloride (90 mmol) was added dropwise and the mixture refluxed 3 hours. It was poured into ice water, extracted with EtOAc, and concentrated. The residue was dissolved in 15 ml ethyl alcohol, NaHCO_3 (2.15 g) added, refluxed 2.5 hours, filtered, and the intermediate isolated.

In a separate vessel, hydrazine hydrate (45 mmol) at 0°C was added to the product from Step 1 (45 mmol) dissolved in 45 ml ethyl alcohol, and the suspension stirred at ambient temperature 10 minutes. The intermediate of this Step was added to this mixture and heated to 70°C 4 hours. The mixture was filtered, concentrated, the residue partitioned between CH_2Cl_2 and water, and re-concentrated. It was dissolved in 60 ml 1,2-dichloroethane, 7.5 ml phosphorus oxychloride added, and refluxed 2 hours. The contents were diluted with CH_2Cl_2 , neutralized with solid Na_2CO_3 and NaHCO_3 , dried, and concentrated. The product was purified by chromatography using CH_2Cl_2 /methyl alcohol, 95:5, crystallized in EtOAc, and isolated in 28% yield. $^1\text{H-NMR}$ data supplied.

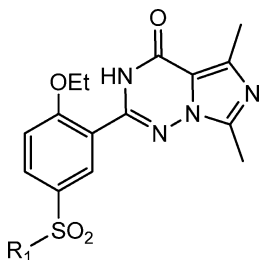
3. 4-Ethoxy-3-(5,7-dimethyl-4-oxo-3,4-dihydroimidazol-[5,1-f][1,2,4]triazin-2-yl)-benzenesulphonyl chloride

The product from Step 2 (6.4 mmol) and 3.1 ml chlorosulphonic acid were mixed, stirred overnight at ambient temperature, poured into ice water, precipitated crystals filtered, and the product isolated in 97% yield. $^1\text{H-NMR}$ data supplied.

4. 2-[2-Ethoxy-5-(4-methyl-piperazine-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazol[5,1-f][1,2,4]triazin-4-one

The product from Step 3 (3 mmol) was dissolved in 40 ml CH_2Cl_2 at 0°C containing a spatula tip of 4-dimethylaminopyridine to which N-methylpiperazine (9.00 mmol) was added and the mixture stirred overnight at ambient temperature. The mixture was diluted with CH_2Cl_2 , washed with water, dried, and concentrated. It was purified by crystallization using diethyl ether and the product isolated in 88% yield. $^1\text{H-NMR}$ data supplied.

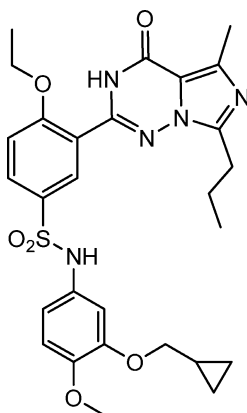
Derivatives



R_1	MS(M+H)
4-Hydroxyethylpiperazine	477
4-Methylpiperazine	447
3-Hydroxypyrrolidine	434
5-t-Butoxycarbonyl-aminomethylmorpholine	563

Notes

1. The preparation of the co-reagent of Step 2, 2-butyrylamino-propionic acid, beginning with d,l-alanine is described by the author.
2. Several reactions are occurring in this step that have been elucidated by others (1). First, an α -ketoester is the initial condensation product of an N-acyl-aminoacid and an alkyl oxalyl chloride via a Dakin-West reaction. Second, at reflux temperatures isomeric enol esters are formed that directly condense with hydrazine to form a triazinone intermediate followed by the second ring closure. Other purines have been prepared in an analogous reaction pathway (2).
3. Analogues of the Step 4 product, (I), were prepared by the author in a subsequent investigation and are described (3).



(I)

References

1. D. Hartley *et al*, US Patent 4,308,384 (December 29, 1981) and US Patent 4,278,673 (July 14, 1981)
2. S.F. Campbell, US Patent 6,100,270 (August 8, 2000); N.K. Terrett, US Patent 5,374,053 (March 31, 1998) and US Patent 5,482,941 (January 9, 1996); A.S. Bell *et al*, US Patent 5,719,283 (February 17, 1998)
3. U. Niewohner *et al*, US Patent 6,566,360 (May 20, 2003)

Imide Derivatives

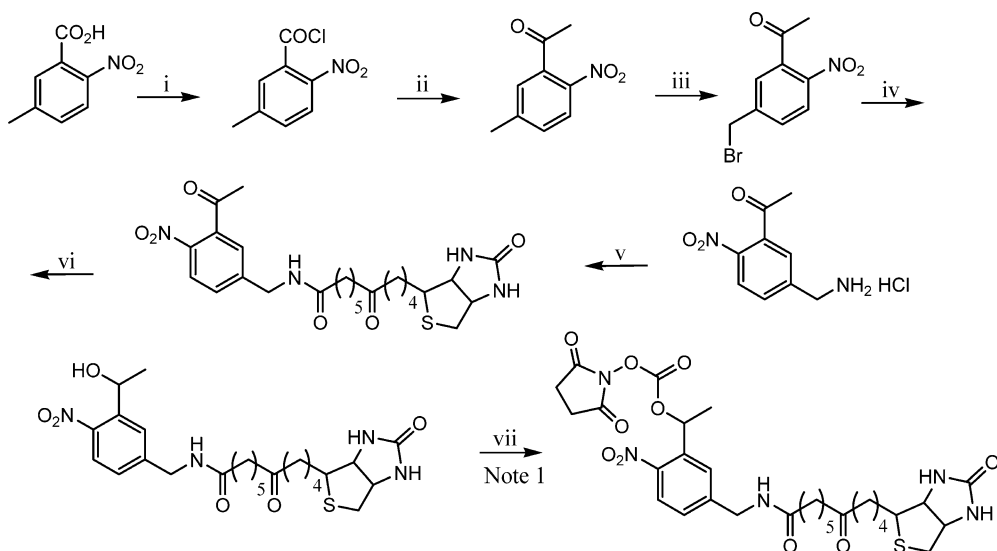
Patent: Photocleavable Agents and Conjugates for the Detection and Isolation of Biomolecules

K.J. Rothschild *et al*, US Patent 6,589,736 (July 8, 2003)

Assignee: The Trustees of Boston University

Utility: Biological Tagging Agent for Nucleic Acids

Reaction



i- Thionyl chloride

ii- Magnesium, ethyl alcohol, chlorobenzene,
carbon tetrachloride, diethyl malonate

- iii- N-Bromosuccinimide, benzoyl peroxide, carbon tetrachloride
- iv- Hexamethylenetetramine, chlorobenzene, hydrochloric acid
- v- N,N-Dimethylformamide, 6-biotinamido-caproic acid,
N-methylpyrrolidone, dicyclohexylcarbodiimide, triethylamine
- vi- Ethyl alcohol, sodium borohydride
- vii- N,N-Dimethylformamide, N,N'-disuccinimidyl carbonate,
triethylamine

Experimental

1. 5-Methyl-2-nitrobenzoyl chloride

5-Methyl-2-nitrobenzoic acid (27.6 mmol) was added in small portions to thionyl chloride (148 mmol) and the mixture stirred at ambient temperature 10 hours. Excess thionyl chloride was removed by vacuum to give the acid chloride.

2. 5-Methyl-2-nitroacetophenone

A mixture of magnesium turnings (442 mmol), 6 ml absolute ethyl alcohol, 8 ml chlorobenzene, and 0.1 ml CCl_4 were refluxed until most of the magnesium reacted. A solution of diethyl malonate (4.82 g) in 10 ml chlorobenzene was added followed by the product from Step 1 (5.49 g) dissolved in 10 ml chlorobenzene. The reaction stirred for 1 hour and 1.7 ml H_2SO_4 in 17 ml water added. The mixture stirred an additional 15 minutes and 20 ml chloroform added. The aqueous layer was extracted 3 times with 10 ml chloroform, the extracts combined, dried, and evaporated. The residue was dissolved in 8.25 ml HOAc in 5.4 ml water containing 1 ml H_2SO_4 and the mixture refluxed 6 hours. It was neutralized with aqueous Na_2CO_3 , extracted 3 times with 20 ml chloroform, dried and concentrated. The residue was re-crystallized from 70% ethyl alcohol and the product isolated in 81% yield.

3. 5-Bromomethyl-2-nitroacetophenone

The product from Step 2 (19.6 mmol), N-bromosuccinimide (20.6 mmol) and benzoyl peroxide (0.01 meq) were refluxed in 20 ml CCl_4 for 5 hours. The reaction mixture was filtered, concentrated, re-crystallized in CCl_4 , and the product isolated in 72% yield.

4. 5-Aminomethyl-2-nitroacetophenone hydrogen chloride

The product from Step 3 (7.75 mmol) was added to a solution of hexamethylenetetramine (8.13 mmol) dissolved in 15 ml chlorobenzene and stirred overnight. The resulting precipitate was collected and washed with 10 ml chlorobenzene and 20 ml diethyl ether. The precipitate (736 mmol) was suspended in 35 ml 95% ethyl alcohol containing 3.12 ml concentrated HCl, stirred overnight, and evaporated to dryness.

5. 5-(6-Biotinamido-caproamide)methyl-2-nitroacetophenone hydrogen chloride

The product from Step 4 was added to 10 ml N,N-dimethylformamide and 6-biotinamido-caproic acid (125 meq) dissolved in 35 ml N-methylpyrrolidone containing

dicyclohexylcarbodiimide (15 meq) and triethylamine (1.25 meq) added. The solution was stirred overnight and then precipitated in 700 ml of diethyl ether. The precipitate was dried, purified on silica gel using methyl alcohol/chloroform with a methyl alcohol gradient of 5–20%, and the product isolated in 58% yield.

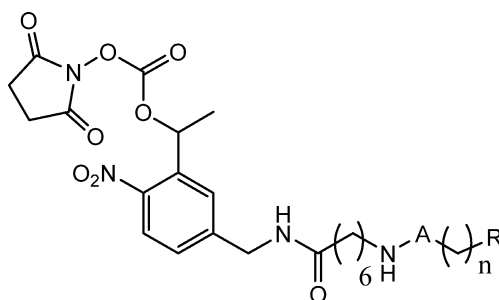
6. 5-(5-Biotinamidocaproamide)methyl-2-nitro- α -hydroxyl-ethylbenzene

The product from Step 5 (1.87 mmol) was dissolved in 15 ml 70% ethyl alcohol, cooled to 0°C, and sodium borohydride (4 meq) added. The solution was stirred at 0°C 30 minutes, 2 hours at ambient temperature, quenched with 1 ml acetone, and neutralized with 0.1 M HCl. The mixture was filtered, the filtrate washed with water, dried, and the product isolated in 71% yield.

7. 5-(5-Biotinamidocaproamidomethyl)-1-(2-nitro)-phenylethyl-N-hydroxysuccinimidyl carbonate

The product from Step 6 (2 mmol) was mixed with 10 ml N,N-dimethylformamide, N,N'-disuccinimidyl carbonate (1.5 meq) and triethylamine (3 meq), stirred 5 hours at ambient temperature, and concentrated. The residue was washed consecutively with 0.1 M NaHCO₃, water, dioxane, diethyl ether, dried, and the product isolated in 69% yield, mp = 113–114°C. ¹H-NMR, MS, and UV-Vis data supplied.

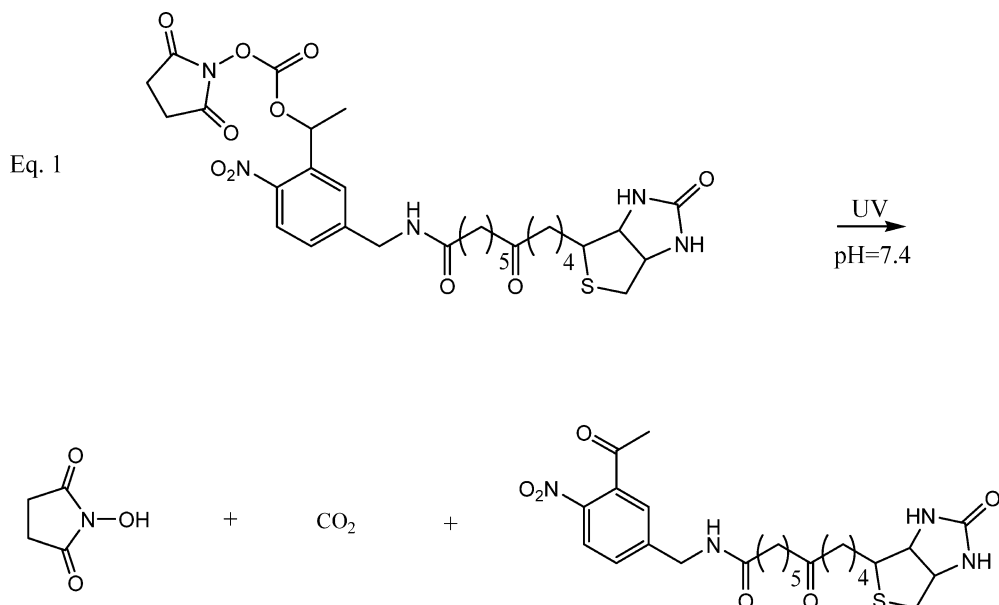
Derivatives



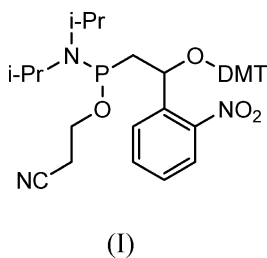
A	n	R
Carbonyl	6	Biotin
Sulfonyl	0	Dansyl
Carbonyl	1	Courmarin
Carbonyl	0	2,4-Dinitrophenyl
Carbonyl	0	1-Courmarin

Notes

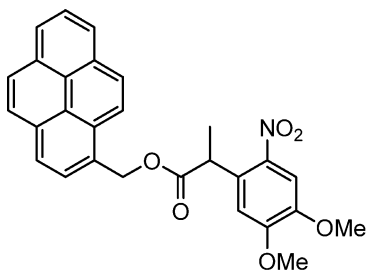
1. Photolysis was carried out in a quartz cuvette using a Black-Ray XX-15 UV-lamp, Model B-100, in a phosphate solution of pH 7.4. The photochemical decomposition of the product of Step 7 is illustrated in Eq. 1:



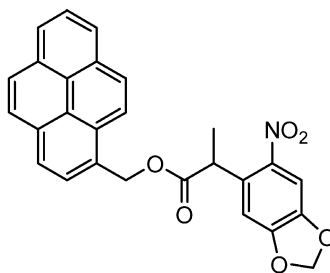
2. A biotin containing the cleavable aryl azido moiety, sulfosuccinimidyl-2-[6-biotinamido)-2-(p-azidobenzamido)-hexanoamido]ethyl-1,3'-dithiopropionate, has been prepared (1).
3. Nucleotides have also been photocleaved by incorporating [2-(2-nitrophenyl)-2-(O-dimethoxytrityloxy)-ethoxy]-N,N-diisopropylamino-2-cyanoethoxyphosphine, (I), and is discussed (2).



4. Photolabile 1-pyrenylmethyl derivatives, (II), and (III), have also been prepared and are described (3).



(II)



(III)

References

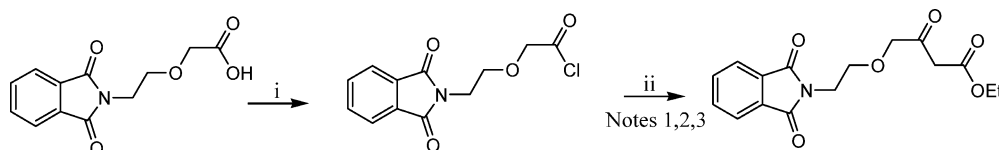
1. E.K. Fujimoto, US Patent 5,532,379 (July 2, 1996)
2. M.S. Urdea *et al*, US Patent 5,258,506 (November 2, 1993)
3. S.P.A. Fodor *et al*, US Patent 5,489,678 (February 6, 1996)

Patent: Process for the Preparation of Alkyl
4[2-(Phthalimido)ethoxy]-Acetoacetate
R.R. Joshi *et al*, US 6,562,983 (May 13, 2003)

Assignee: Council of Scientific and Industrial Research

Utility: Intermediate for Anti-Hypertensive and Anti-Ischaemic Drugs

Reaction



i- Thionyl chloride, toluene, N,N-dimethylformamide

ii- 2,2-Dimethyl-1,3-dioxane-4,6-dione, pyridine, CH_2Cl_2

Experimental

1. 2[(2-Phthalimido)ethoxy]acetyl chloride

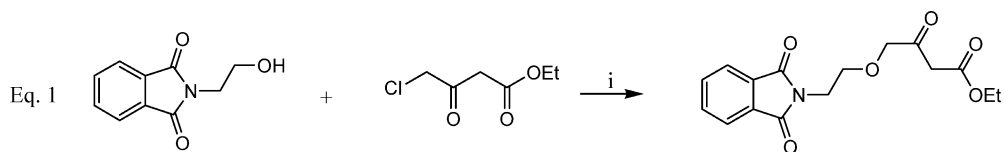
To the suspension of 2-[(2-phthalimido)ethoxy]acetic acid (0.4 mol) in 1.0 L toluene and 1 ml dimethylformamide was added thionyl chloride (1.46 mol) at ambient temperature and the mixture heated to 60°C 3 hours. The reaction mixture was concentrated under reduced pressure and the product isolated.

2. Ethyl [2-(phthalimido)ethoxy]-acetoacetate

2,2-Dimethyl-1,3-dioxane-4,6-dione (50 g) (Meldrum's acid) was dissolved in a solution of 100 ml pyridine and 400 ml CH_2Cl_2 , cooled to 5°C , and the product from Step 1 (10.00 g) added over 1 hour. The mixture was acidified using 400 ml 2 M HCl, the layers separated, and extracted with CH_2Cl_2 . The extracts were washed twice with 120 ml 2 M HCl, water, and concentrated. The residue was dissolved in 200 ml ethyl alcohol, refluxed 1 hour, and the reaction extent monitored by TLC on silica gel using EtOAc/petroleum ether, 40:60, where an $R_f = 0.7$, 0.1 for the product and starting material, respectively, was observed. The solution was concentrated, the residue extracted 3 times with toluene, washed twice with 100 ml water, 100 ml NaHCO_3 , dried, and concentrated. $^1\text{H-NMR}$ data supplied.

Notes

1. Preparation, reactions, and derivatives of Meldrum's acid are described (1).
2. An alternative method for preparing is by reacting N-(2-hydroxyl-ethyl)phthalimide with ethyl 4-chloroacetoacetate in the presence of sodium hydride as illustrated in Eq. 1 and described elsewhere (2).



i- THF, sodium hydride

3. The product of Step 2 was also used in the Hantzsch condensation to prepare phthaloyl amlodipine, a precursor for amlodipine besylate (3).

References

1. A.G. Releny *et al*, US Patent 4,613,671 (September 23, 1986); Y. Yamamoto *et al*, Chem. Pharm. Bull., 35, 1871 (1987); T. Oikawa *et al*, J. Org. Chem., 43 10, 2087 (1978)
2. S.F. Campbell *et al*, US Patent 4,572,909 (February 25, 1986)
3. M. Zia-Ebrahimi, US Patent 5,243,053 (September 7, 1993)

Iminocarboxylic Acid Methyl Amides

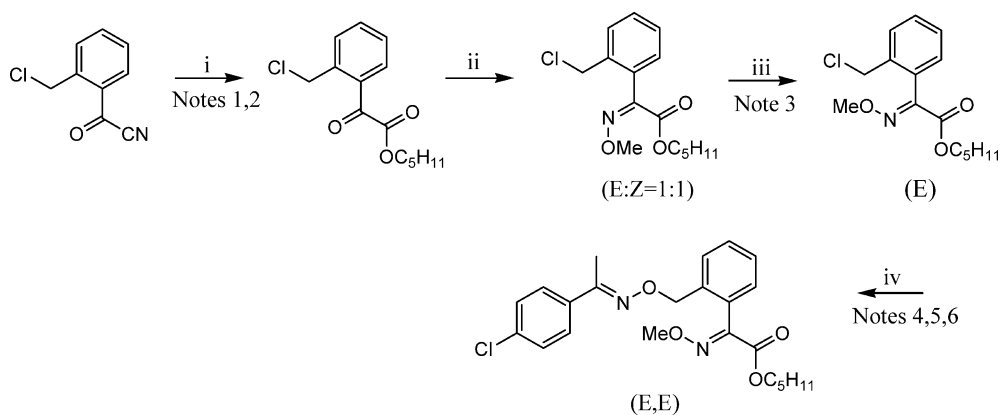
Patent: Preparation of α -Methoxyiminocarboxylic Acid Methylamides and Intermediates Therefore

H. Bayer *et al*, US Patent 5,856,560 (January 5, 1999)

Assignee: BASF Aktiengesellschaft

Utility: Fungicide Intermediate

Reaction



i- n-Pentyl alcohol, hydrogen chloride, toluene

ii- O-Methoxyamine hydrogen chloride, methyl alcohol

iii- Hydrogen chloride, diethyl ether

iv- Sodium hydride, N,N-dimethylformamide,
4-chloroacetophenone oxime

Experimental

1. **n-Pentyl 2-[(chloromethyl)phenyl]glyoxylate**

1-Pentanol (0.2 mol) was added to 1.8 ml water dissolved in toluene (80 g) and hydrogen chloride gas (0.4 mol) introduced. The temperature was lowered to 0°C, 2-(chloromethyl)-benzoyl cyanide (0.09 mol) added dropwise, and the mixture stirred 2 hours at ambient temperature. Thereafter, the mixture was heated to 60°C 8 hours then cooled. It was extracted once with 50 ml of 15% strength HCl, 3 times with 50 ml water, dried, concentrated, and isolated in 95% yield but containing 4.99% of the impurity, pentyl 2-(chloromethyl)benzoate. The product mixture was further purified by flash chromatography on silica gel 60 using cyclohexane/toluene, 2:1. ¹H-NMR data supplied.

2. **(E/Z)-n-Pentyl 2-methoxyimino-2-[(2'-chloromethyl)phenyl]acetate**

O-Methylhydroxylamine hydrochloride (0.4 mol) and 10 g 3 Å molecular sieves were added to a solution of the product from Step 1 (0.1 mol) dissolved in 50 ml methyl alcohol and the mixture stood at ambient temperature 16 hours. The solution was concentrated, the residue partitioned between methyl t-butyl ether and water, the organic phase washed, dried, concentrated and the product isolated in 100% yield as 1:1 E/Z isomer mixture. ¹H-NMR data supplied. (Note 3)

3. **(E)-n-Pentyl 2-methoxyimino-2-[(2'-chloromethyl)phenyl]acetate**

The product mixture from Step 2 (0.1 mol) was dissolved in 500 ml diethyl ether saturated with hydrogen chloride gas while cooling in ice and then stood 16 hours at ambient room temperature. Thereafter, it was concentrated, purified by chromatography on silica gel using methyl t-butyl ether/n-hexane, and the product isolated in 81% yield as a colorless oil. ¹H-NMR data supplied.

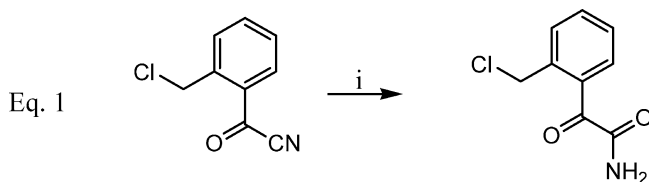
4. **(E,E)-n-Pentyl 2-methoxyimino-2-{2'-(1''-(4'''-chlorophenyl)-1''-methyl)iminooxymethylphenyl}acetate**

Sodium hydride (11 mmol) was added to 50 ml DMF, 4 portions of chloroacetophenone oxime (1.7 g) added, and the mixture stirred at ambient temperature 30 minutes. Thereafter, the product from Step 3 (10 mmol) dissolved in 10 ml DMF was added dropwise. The mixture stirred at ambient temperature 2 hours, poured into cold 2 M HCl, and the product extracted with methyl t-butyl ether. The combined organic phases were washed with water, dried, concentrated, purified by chromatography on silica gel using methyl t-butyl ether/n-hexane, and the product isolated in 80% as a colorless oil. ¹H-NMR data supplied.

Notes

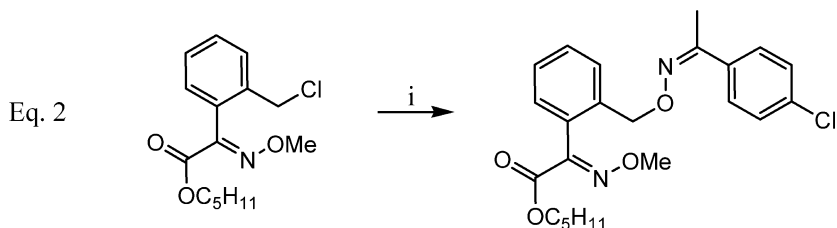
1. This is an example of the Pinner imido ether synthesis. The intermediate imido ester hydrogen chloride salt can be hydrolyzed to the ester or neutralized to the imino ester and is described (1).

2. In the absence of 1-pentanol, 2-(chloromethyl)phenylglyoxyamide was generated as the product of Step 1 as illustrated in Eq. 1:



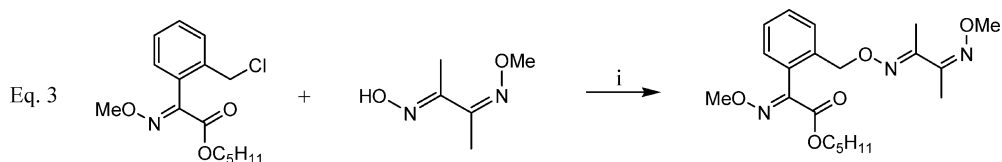
i- Hydrochloric acid, ethyl alcohol, hydrogen chloride

3. E,Z isomers of the product of Step 3 were separated by column chromatography on silica gel using methyl t-butyl ether/n-hexane. ¹H-NMR for each isomer supplied by the author.
4. A method for preparing (Z,E)-n-pentyl 2-methoxyimino-2'-(1''-(4'''-chlorophenyl)-1''-methyl)iminooxymethylphenyl}acetate was provided by the author and illustrated in Eq. 2:



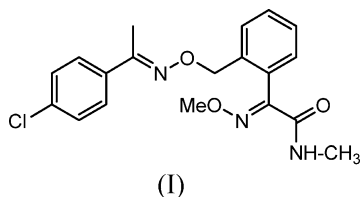
i- 4-Chloroacetophenone oxime, N,N-dimethylformamide, THF, Methyl alcohol, water

5. (E,E,E)-2-[[[2-(Methoxyimino)-1,2-(dimethyl)ethylidene]-amino]oxy]methyl]- α -methoxyiminophenylacetic acid monomethylamide was also prepared by reacting the product of Step 1 with (E,E)-2-hydroxyimino-3-methoxyiminobutane as illustrated in Eq. 3:

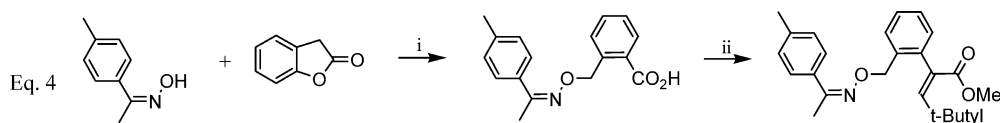


i- N,N-dimethylformamide

6. The only other additional E,E-derivative prepared by the author was (E,E)-2-methoxyimino-2-{2'-(1''-(4'''-chlorophenyl)-1''-methyl)imino-oxymethylphenyl}acetic acid monomethylamide, (I), mp = 117–119°C.



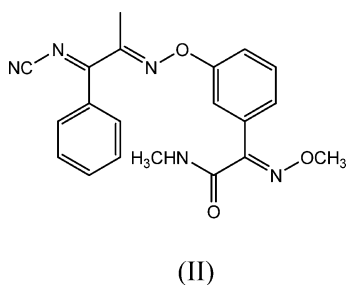
7. Other iminocarboxylic carboxylic acid derivatives have been prepared by reacting an hydroxyimino derivative with 2-coumaranone followed by the Pinner reaction of the Step 1 product (2,3) as illustrated in Eq. 4:



i- Sodium methoxide, methyl alcohol

ii- Thionyl chloride, sodium cyanide, t-butyl alcohol,
hydrogen chloride, toluene

7. In a subsequent investigation by the author, the materials of the current invention were converted into (E,E,E,-)cyanimino oxime ethers, (II), (4).



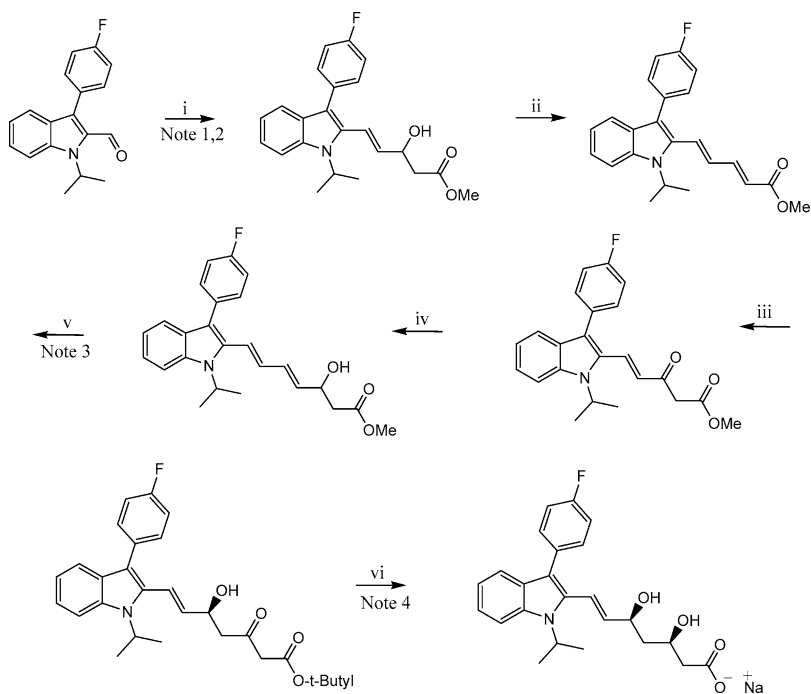
References

1. R. Roger, Chem. Rev., 61, 179 (1961)
2. R. Benoit *et al*, US Patent 5,393,920 (February 28, 1995)
3. R. Benoit *et al*, US Patent 5,530,156 (June 25, 1996)
4. H. Bayer *et al*, US Patent 6,063,813 (May 16, 2000)

A. Wolleb *et al*, US Patent 6,743,926 (June 1, 2004)

Ciba Specialty Chemicals

Chemical Precursor in the Treatment of Hyperlipoproteinaemia and Arteriosclerosis



- i- Sodium hydride, THF, methyl acetoacetate, acetic anhydride, butyllithium
- ii- Toluene, triethylamine, hydrochloric acid
- iii- THF, ammonium hydroxide
- iv- THF, sodium borohydride, t-butylacetate
- v- Diisopropylamine, THF, butyllithium
- vi- THF, sodium hydroxide

Experimental

1. 5-[3-(4-Fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-methylhex-2-enoic acid methyl ester

A slurry of sodium hydride (88.16 mmol) in 100 ml THF was cooled to 5°C and methyl acetoacetate (88.16 mmol) dissolved in 50 ml THF slowly added so that the temperature did not exceed 10°C. The mixture stirred 30 minutes, 1.6 M butyllithium (90.12 mmol) added dropwise, and the yellow solution stirred 20 minutes while cooling with ice. To this was added 3-(4-fluorophenyl)-1-isopropyl-1H-indole-2-carbaldehyde (53.32 mmol) dissolved in 100 ml THF and the mixture stirred 45 minutes. Thereafter a thick yellow suspension formed, acetic anhydride (533.2 mmol) was added, and the solution stirred 15 minutes then warmed to ambient temperature. The reaction mixture was poured into 250 ml 1 M HCl, extracted 3 times with EtOAc, washed twice with 50 ml brine, once with 100 ml of 5% NaHCO₃, and 3 additional times with brine. It was dried, concentrated, and the product isolated as an orange oil.

2. (E)-5-[3-(4-Fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-methylpenta-2,4-dienoic acid methyl ester

The product from Step 1 (2.0 g) was dissolved in 50 ml toluene, triethylamine (8.87 mmol) added, then refluxed 2 hours. Thereafter, the mixture was cooled, diluted with 50 ml toluene, washed once with 100 ml 1 M HCl, 3 times with 50 ml water, and concentrated. The residue was purified by flash chromatography using hexane/EtOAc, 10:1, and the product isolated in 30% yield as a mixture of keto and enol tautomers. An orange resin was obtained which, according to NMR, contained approximately 30% (E)-5-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-oxopent-4-enoic acid methyl ester.

3. (E)-5-[3-(4-Fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-oxopent-4-enoic acid methyl ester

The product from Step 2 (1.49 mmol) was dissolved in 20 ml THF, 4 ml 1 M NH₄OH added, and the mixture stirred 6 hours at ambient temperature. Thereafter, it is poured into 200 ml brine, extracted twice with 100 ml EtOAc, washed, dried and concentrated. The residue was purified by flash chromatography using hexane/ethyl acetate, 9:1, and the product isolated as an orange resin having a keto-enol equilibrium of 3:1, respectively.

4. (E)-5-[3-(4-Fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-hydroxypent-4-enoic acid methyl ester

The product from Step 3 (40.56 mmol) was dissolved in 300 ml of THF/methanol, 1:1, cooled to -65°C , and NaBH_4 (48.67 mmol) added over 75 minutes. The mixture was warmed to 0°C , stirred for 35 minutes, poured into 1.5 L water containing HOAc (0.39 mol), then extracted 3 times with 500 ml EtOAc. The organic phase was washed 3 times with 300 ml water, dried, filtered, and concentrated. The mixture was purified by flash chromatography using hexane/EtOAc, 3:1, and an orange resin isolated. The keto-enol tautomers were resolved by HPLC on a Chiracel AD column using n-hexane/ethyl alcohol, 9:1, at a flow rate of 1 ml/min, having retention times of 25.3 minutes and 28.0 minutes, respectively.

5. (E)-7-[3-(4-Fluorophenyl)-1-isopropyl-1H-indol-2-yl]-5-hydroxy-3-oxohept-6-enoic acid t-butyl ester

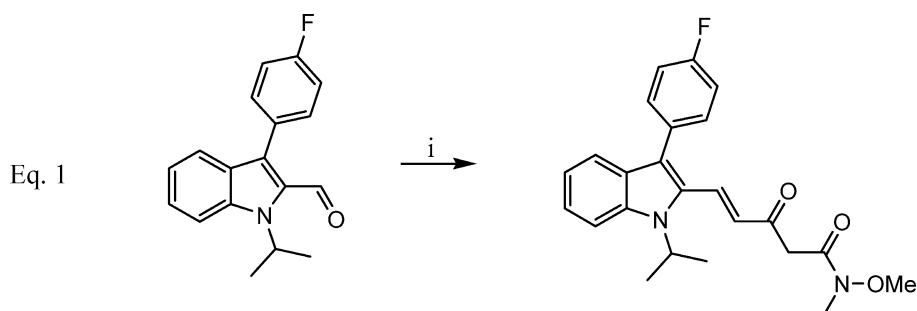
Diisopropylamine (112.72 mmol) was dissolved in 50 ml of THF, cooled to -50°C , and 1.6 M butyllithium (112.72 mmol) added over 30 minutes so that the temperature remained between -55° and -45°C . The reaction mixture was warmed to -5°C , cooled to -65°C , and t-butyl acetate (112.72 mmol) added dropwise over 30 minutes. Thereafter, the product from Step 4 (28.18 mmol) dissolved in 50 ml THF was added, stirred 1 hour at -60°C , warmed to -5°C over 45 minutes, and stirred 30 minutes at this temperature. The intermediate was hydrolyzed with 65 ml NH_4Cl solution and extracted twice with 250 ml EtOAc. The organic phase was washed with 10 ml 1 M HCl portions until the pH was acidic, then washed with brine until neutral, dried, concentrated, and an orange product isolated. The keto-enol tautomers were resolved by HPLC on a Chiracel OD column using n-hexane/ethyl alcohol, 98:2, at a flow rate of 1 ml/min, and had retention times of 21.7 minutes and 28.0 minutes, respectively.

6. Sodium erythro-(+/-)-(E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoate

The product from Step 6 (1.05 mmol) was dissolved in 5 ml ethyl alcohol, 1.00 ml 1 M sodium hydroxide solution added, and the mixture stirred 3 hours at ambient temperature. The clear solution was filtered, diluted with 6 ml water, then extracted twice with 7 ml t-butyl methyl ether. Approximately 2 ml water was distilled off and the remaining solution lyophilised yielding a slightly beige powder. NMR confirmed that the product of this Step was equivalent to the that of the commercial product, Fluvastatin (5).

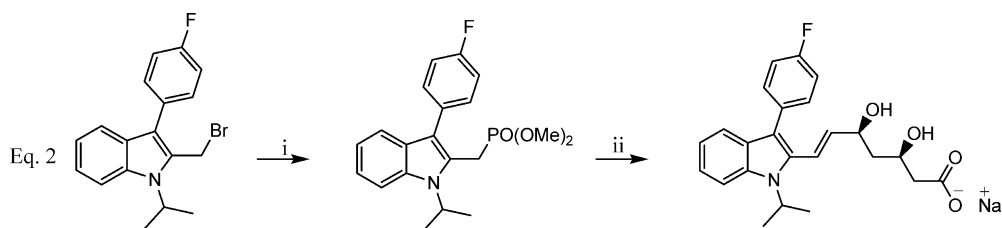
Notes

1. The Step 1 N-methoxy amide analogue of the current invention, E-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-N-methoxy-N-methylacryl-amide, was also prepared by reacting the reagent of Step 1 with diethyl (N-methoxy-N-methylcarbamoyl-methyl)phosphonate, as illustrated in Eq. 1 and described by the author.



i- Sodium hydride, diethyl (N-methoxy-N-methylcarbamoyl-methyl)phosphonate

2. The preparation of other Step 1 analogues including (a) 3-(4-fluorophenyl)-1-isopropyl-, (b) 2-carbaldehyde-, (c) 2-carboxylic acid-, and (d) 2-carboxylic acid-1H-indole methyl ester, are described by the author in the current invention.
3. A modified method for preparing erythro-(+/-)-(E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoic acid t-butyl ester using sodium borohydride diethyl methoxyborane in THF produces a syn/anti product of ratio >70:1 (1).
4. An alternative method for preparing sodium erythro-(+/-)-(E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoate using the Wittig reaction is illustrated in Eq. 2 and described (2).



- i- Trimethylphosphine
- ii- 3,5-(Diphenyl-t-butylsiloxy)-6-oxy-hexanoic acid methyl ester, tetrabutylammonium fluoride, sodium hydroxide

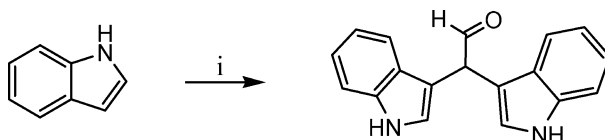
5. The preparation of Fluvastatin is provided and discussed (3).
6. The various crystalline forms of Fluvastatin, including hydrates, are described (4).

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2. K.-M. Chen *et al*, US Patent 4,870,199 (September 26, 1989)
3. F.G. Kathawala, US Patent 4,739,073 (April 18, 1998)
4. P.A. Van Der Schaaf *et al*, US Patent 6,696,479 (February 24, 2004)

Patent: Synthetic Compounds for Treatment of Inflammation
R.C. Jacobs *et al*, US Patent 6,589,975 (July 8, 2003)
Assignee: The Regents of the University of California and Harbor Branch
Oceanographic Institute
Utility: Treatment Anti-Immunogenic and Neurogenic Inflammation

Reaction



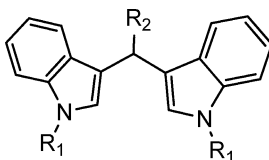
i- Acetaldehyde dimethyl acetal, water

Experimental

1. 2,2-Bis(3,3'indolyl) acetaldehyde

Two equivalents of indole were suspended in water, one equivalent of acetaldehyde dimethyl acetal added, and the mixture heated to 85°C 5 hours in the absence of light. The precipitate that formed was re-crystallized in methyl alcohol and the product isolated in 59% yield, mp = 172°C. ¹H-NMR data supplied.

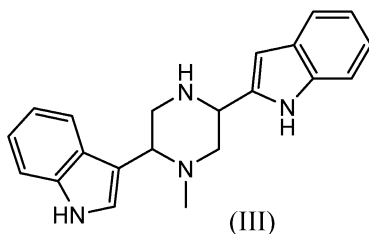
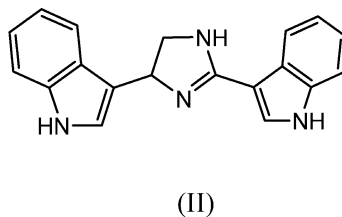
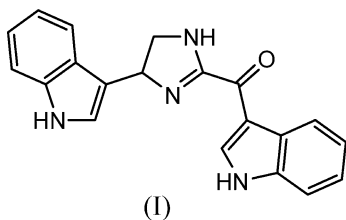
Derivatives



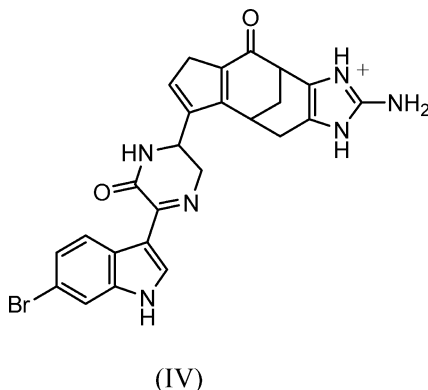
R ₁	R ₂	Melting Point (°C)
Hydrogen	Hydrogen	162
Hydrogen	Carboxylic Acid	172

Notes

1. The preparation of other 3-substituted indole derivatives of the current invention are depicted, (I), (II), and, (III), and described, (1, 2, 3), respectively.



2. The preparation of (3,3'-indolyl)methane derivatives are provided (4, 5).
3. Bis-heterocyclic analogues of the current invention such as Dragmacidin F, (IV), Topsentin D, and Topsentin E and their salts have been prepared and are reviewed (5).

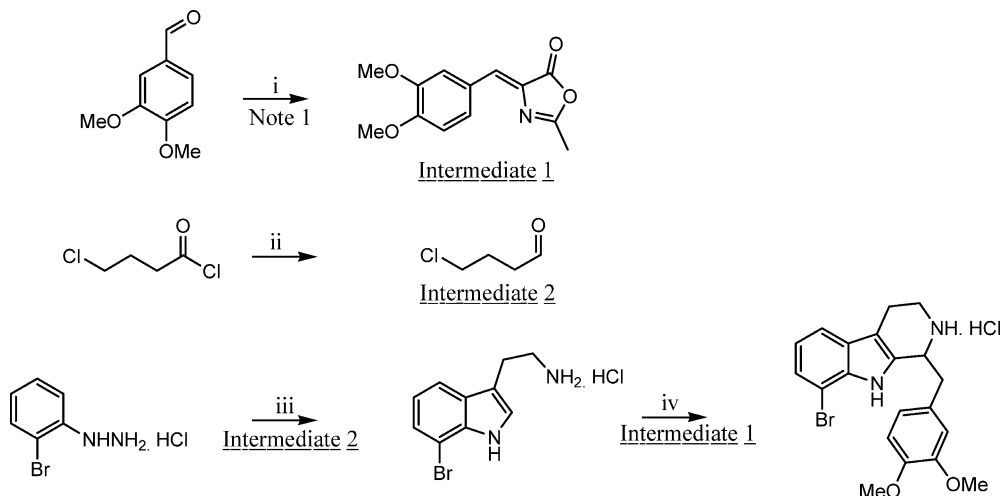


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1. S.P. Gunaskera *et al*, US Patent 4,866,084 (September 12, 1989)
2. H.H. Sun *et al*, US Patent 4,970,226 (November 13, 1990)
3. O.J. McConnell *et al*, US Patent 5,290,777 (March 1, 1994)
4. A.E. Wright *et al*, US Patent 6,444,697 (September 3, 2002)
5. A.E. Wright *et al*, US Patent 6,291,501 (September 18, 2001)

Patent: Tetrahydro- β -Carbolines
 J.E. Audia *et al*, US Patent 6,090,945 (July 18, 2000)
Assignee: Eli Lilly and Company
Utility: Treatment of Eating and Sexual Disorders

Reaction



- i- N-Acetylglycine, sodium acetate, acetic anhydride
- ii- THF, 2,6-lutidine, 5% palladium on carbon, hydrogen
- iii- Sodium carbonate, chloroform, hydrogen chloride, diethyl ether
- iv- Hydrochloric acid

Experimental

1. 8-Methyl-1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

A mixture of 3,4-dimethoxybenzaldehyde (0.15 mol), N-acetylglycine (0.15 mol) and NaOAc (0.15 mol) were dissolved in 135 ml acetic anhydride and heated to 100°C 12 hours. The mixture was cooled to ambient temperature, poured onto 300 ml ice, and 16.3 g product isolated by filtration.

2. 4-Chlorobutanal

4-Chlorobutyryl chloride (2.13 mol) was dissolved in 3 L THF, 252 ml 2,6-lutidine and 30 g 5% palladium on carbon added, and the mixture hydrogenated while shaking under 60 psi hydrogen 6 hours. Thereafter, the mixture was purged with nitrogen, filtered, and concentrated. The mixture was purified by distillation and 148.3 g product isolated.

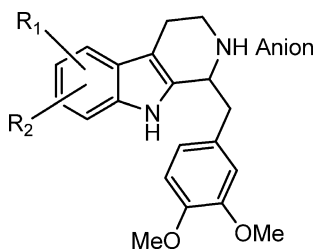
3. 7-Bromotryptamine hydrochloride

A stirred suspension of 2-bromophenylhydrazine hydrochloride (115 mmol) in 500 ml chloroform was added to 500 ml saturated Na_2CO_3 solution, the mixture stirred 30 minutes, then extracted twice with 200 ml chloroform. The organic phase was concentrated and the hydrazine free base isolated as a yellow oil. This oil was dissolved in 100 ml methyl alcohol, the product from Step 2 (115 mmol) slowly added, and the mixture placed in a sealable tube and heated to 95°C 18 hours. The solution was cooled to ambient temperature, concentrated, and the residue partitioned between chloroform/methyl alcohol, 3:1, and aqueous NaHCO_3 . The organic phase was concentrated and purified by flash chromatography on silica gel with a 0–25% methyl alcohol gradient in chloroform. The purified oil was then dissolved in 300 ml diethyl ether containing 1% methyl alcohol and treated with dry HCl gas. The hydrochloride salt was isolated by filtration, washed with 50 ml 2-propanol and 100 ml diethyl ether, dried and 3.6 g product isolated.

4. 8-Bromo-1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole hydrochloride

The product from Step 1 (4.7 mmol) and the product from Step 3 (3.6 mmol) were dissolved in 100 ml 1 M HCl and refluxed 24 hours. Thereafter, the mixture was cooled to ambient temperature and the crude product isolated by filtration. The brown solid was triturated 3 times with 50 ml isopropyl alcohol and washed 3 times with 50 ml diethyl ether. It was re-crystallized from ethyl alcohol and 860 mg of product isolated, $\text{mp} = 279\text{--}281^\circ\text{C}$ (dec). Elemental analysis data supplied.

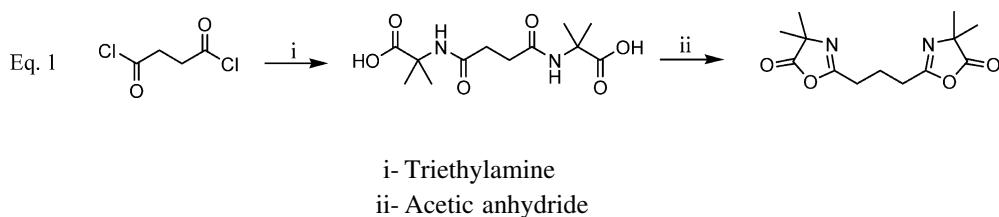
Derivatives



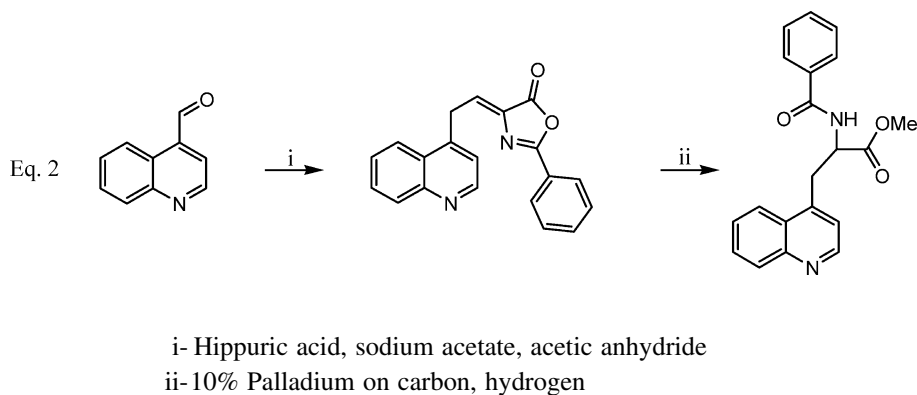
R_1	R_2	Anion	Melting Point ($^\circ\text{C}$)
6-Fluoro	8-Fluoro	Maleate	164–166 (dec)
6-Methyl	8-Bromo	Hydrogen chloride	251–253 (dec)
6-i-Propyl	Hydrogen	Hydrogen chloride	196–200
6-Methyl	7-Methyl	Maleate	197–200

Notes

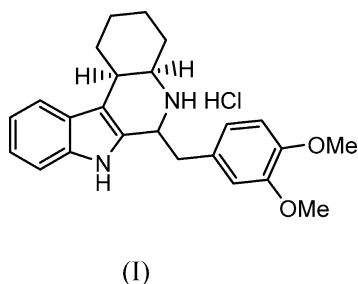
1. Mono- and trimethoxyphenyl azolactone intermediates of Step1 were also prepared by the author by condensing the corresponding mono- or trimethoxy benzaldehyde with N-acetyl glycine and are described.
2. Diazalactones have been prepared by reacting an acid dichloride with an aminoacid followed by dehydrocyclization (1) as illustrated in Eq.1:



3. Quinolyl azalactones have been prepared by the reaction of hippuric acid and 3-quinolinecarboxaldehyde in the preparation of 3-quinolyl-aminoacid ester derivatives (2) as illustrated in Eq. 2:



4. Other examples of tetrahydro- β -carboline, (I), prepared by the author are described (3).



5. The Fischer reaction has been used to prepare pyrrole intermediates of the current invention and is discussed (4).

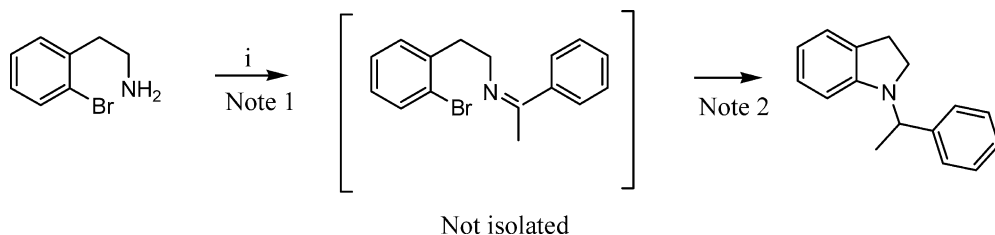
References

1. J.K. Rasmussen *et al*, US Patent 4,667,012 (May 19, 1987); C.S. Cleaver *et al*, J. Am. Chem. Soc., 77, 1544 (1955)
2. N.S. Bodor, US Patent 5,079,366 (January 7, 1992) and US Patent 4,888,427 (December 19, 1989)
3. J.E. Audia *et al*, US Patent 5,861,410 (January 19, 1999)
4. M.E. Flaugh, US Patent 4,614,807 (September 30, 1986)

Indoline

Patent: Amination Process
J.N. Johnston *et al*, US Patent 6,670,479 (December 30, 2003)
Assignee: Advanced Research and Technology Institute, Inc.
Utility: Method for Preparing Indoline Intermediates

Reaction



i- Benzene, acetophenone
ii- Tri-n-butyltinhydride, azobisisobutyronitrile, benzene

Experimental

1. o-Bromophenethyliminoacetophenone

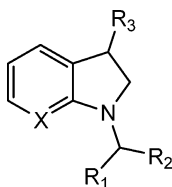
o-Bromophenethylamine (231 mmol), acetophenone (231 mmol), and 4 Å molecular sieves were stirred in 1 ml benzene at ambient temperature for 12 hours. Filtering the mixture through celite and removal of the solvent provided the ketimine as a >95:5 Z,E mixture, respectively. A benzene solution of tri-n-butyltinhydride (0.25 mmol) and azobisisobutyronitrile (93 mmol) dissolved in 0.7 ml benzene were added over 3 hours to a refluxing solution of the ketimine (231 mmol) dissolved in 23 ml benzene. The product

was purified by flash chromatography using 2% CH_2Cl_2 in hexanes and the product isolated in 87% as a colorless oil. $^1\text{H-NMR}$, MS, and IR data supplied.

2. N-(1-Methylbenzyl)indoline

A benzene solution of tri-n-butyltinhydride (0.25 mmol) and azobisisobutyronitrile (93 mmol) dissolved in 0.7 ml benzene were added over 3 hours to a refluxing solution of the product from Step 1 (231 mmol) dissolved in 23 ml benzene. The product was purified by flash chromatography using 2% CH_2Cl_2 in hexanes and the product isolated in 87% as a colorless oil. $^1\text{H-NMR}$, MS, and IR data supplied.

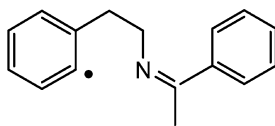
Derivatives



X	R ₁	R ₂	R ₂	MP(°C)
N	Phenyl	Phenyl	Hydrogen	101
CH	Methyl	4-Trifluoromethylphenyl	Hydrogen	79–82
CH	Methyl	Trifluoromethyl	Hydrogen	Oil
CH	Phenyl	Phenyl	Methoxide	Oil

Notes

1. In this reaction the sp^2 hybridized free radical intermediate, (I), is generated by homolytic trans-metalation in the presence of the free radical initiator. Optimum results were observed when the carbon atom was substituted by a suitable radical leaving (such as a halide).



Free Radical Intermediate
(I)

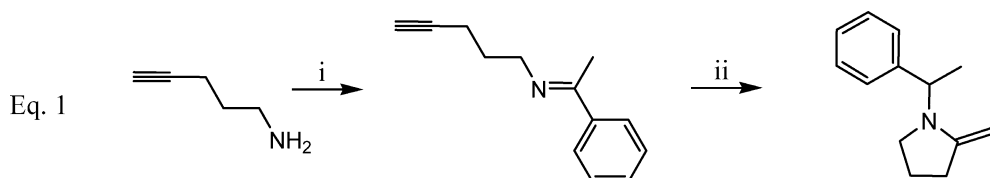
2. Step 2 product yields were optimized following the procedure provided by the author:

Procedure

A benzene solution of the ketimine (0.01 M) was warmed to 85°C in a round-bottomed flask equipped with a condenser. A 1 ml benzene solution of tri-n-butyltinhydride (1.1 eq) and azodiisobutylnitrile (0.4 eq) was loaded into a gas-tight syringe and attached to

a syringe pump. The syringe needle was attached through a septum at the top of the condenser so that the solution droplets would fall directly into the refluxing benzene. Following the addition, the reaction mixture was refluxed one hour and cooled to ambient temperature. An aliquot was removed, concentrated, and component ratios were measured by $^1\text{H-NMR}$ and/or GC-MS. The solution was treated with sodium borohydride (1.1 eq) and the slurry stirred for about 5 hours. The mixture was concentrated in vacuo, diluted with diethyl ether, and washed with water. The organic layer was separated, dried over MgSO_4 , and concentrated to furnish an oil. Flash chromatography of the crude mixture provided the analytically pure compounds.

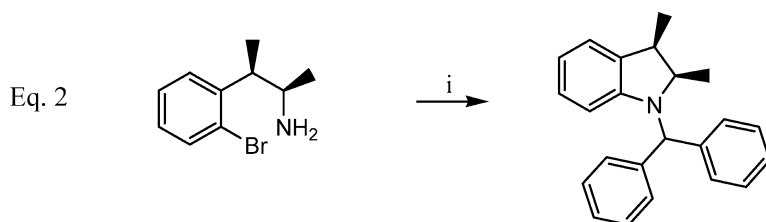
2. Other preparations of imines of the current invention are described (1).
3. Vinyl pyrrolidine derivatives were also prepared in the current invention as illustrated in Eq. 1:



i- Acetophenone, benzene, 4 Å molecular sieves

ii- Tri-*n*-butyltinhydride, azodiisobutyronitrile, benzene

4. The preparation of stereospecific indoline derivatives was also provided by the author as illustrated in Eq. 2:



i- Benzene, tri-*n*-butyltinhydride, diphenylketone,
azobisisobutyronitrile

5. Other examples of imine cyclizations are described (2).
6. Free radical reactions using tri-*n*-butyltinhydride for new carbon/carbon bond formations are discussed (3).

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2. Collective Vol. 5, pp. 520-2; M.J. O'Donnell *et al*, *J. Org. Chem.*, 47, 2663 (1982)
3. W.R. Bowman *et al*, *Tetrahedron Lett.*, 35, 6369 (1994)
4. D.J. Hart *et al*, *J. Am. Chem. Soc.*, 110, 1631 (1988)

Isocoumarins

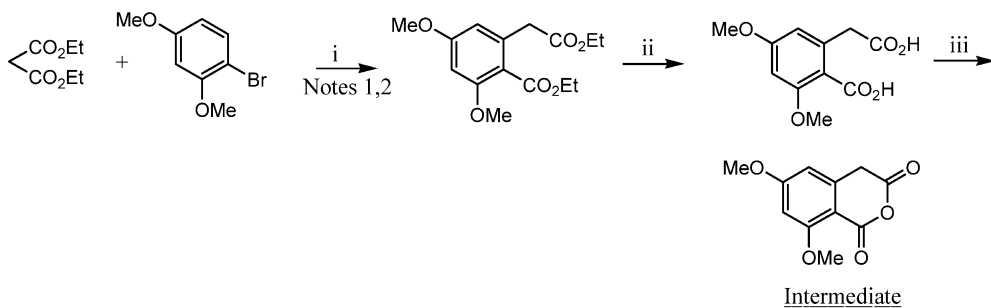
Patent: Process for Preparing Isocoumarins
W.E. Bauta *et al*, US Patent 6,664,401 (December 16, 2003)

Assignee: ILEX Products, Inc.

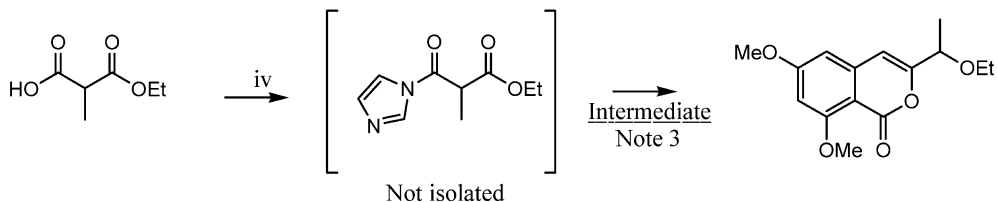
Utility: High Yielding Method for Preparing Isocoumarin Derivatives

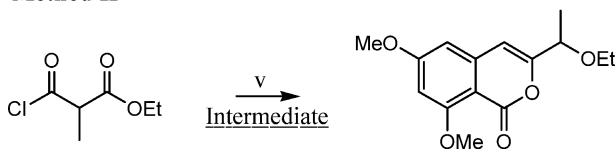
Reaction

Intermediate Preparation



Method I



Method II

- i- Sodium hydride, THF, 1,10-phenanthroline, diisopropylamine, lithium diisopropylamide
- ii- Ethyl alcohol, sodium hydroxide
- iii- Toluene, acetic anhydride
- iv- Carbonyl diimidazole, acetonitrile, triethylamine, acetonitrile
- v- Diazbicyclo[5.4.0]-undec-7-ene, acetonitrile

Experimental**1. 2-Carboxymethyl-4,6-dimethoxybenzoic acid diethyl ester**

Sodium hydride (0.8 g) was added to 50 ml THF and diethylmalonate added over 5 minutes. 1-Bromo-2,4-dimethoxybenzene (1.08 g) was then added in one portion and the reaction flask cooled to -20°C . A few crystals of 1,10-phenanthroline were added as an indicator and the flask further cooled to -60°C . A few drops of n-BuLi were added until the brown color of the indicator persisted. Thereafter n-BuLi (3.05 mmol) and 0.91 ml diisopropylamine was added to form lithium diisopropyl-amide. In order to observe a product conversion of 97%, a total of 2.5 ml LDA added dropwise via cannula in 24 minutes at -20°C to -24°C . The solution was acidified using 1.0 M HCl and the organic portion isolated, washed with brine and isolated in 93.2% purity as a yellow oil. $^1\text{H-NMR}$ data supplied.

2. 2-Carboxymethyl-4,6-dimethoxybenzoic acid

The product from Step 3 (2.56 g) was dissolved in 100 ml ethyl alcohol and 10 ml 10% NaOH added. The mixture was stirred at ambient temperature 105 minutes and an in-process control indicated that 87.5 conversion to the mono acid had formed. After the mixture was heated to reflux 4 hours only 28.6% of the diacid was observed. The hydrolysis was achieved in 94.8% yield when solid NaOH (3 g) was added and stirred 5 hours. The product was extracted with EtOAc, dried, washed and isolated in 88.3% purity. $^1\text{H-NMR}$ data supplied.

3. 6,8-Dimethoxyisochroman-1,3-dione

The product from Step 4 (3.97 g) was dissolved in 40 ml toluene, 1.72 ml acetic anhydride was added, and the mixture heated to 110°C 3 hours. Crystallization of 6,8-dimethoxyisochroman-1,3-dione occurred as the solution cooled and the product (3.05 g) isolated as a solid. $^1\text{H-NMR}$ data supplied.

Method I

Isocoumarin preparation (prior to current invention)

4. 2-(6,8-Dimethoxy-1-oxy-1H-isochromen-3-yl)-propionic acid ethyl ester

Ethyl-2-methyl malonate (0.2 g) and 10 ml acetonitrile were mixed and carbonyl diimidazole (0.291 g) dissolved in 3 ml acetonitrile added. After 10 minutes 0.25 ml TEA and product from Step 3 (0.20 g) dissolved in 4 ml acetonitrile were added, the mixture stirred at ambient temperature, and the product isolated in 28.8% yield. ¹H-NMR data supplied.

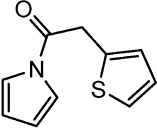
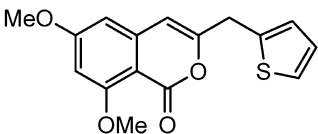
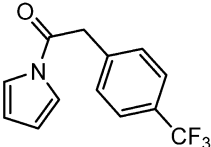
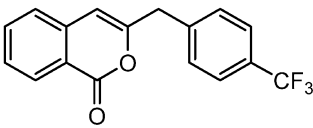
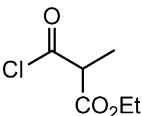
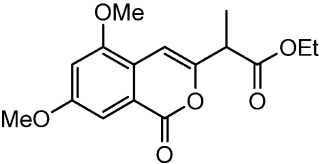
Method II

Isocoumarin preparation (current invention)

5. 2-(6,8-Dimethoxy-1-oxy-1H-isochromen-3-yl)-propionic acid ethyl ester

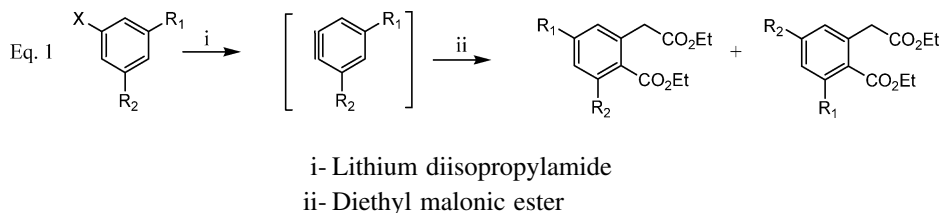
A reactor was charged with 5.0 ml acetonitrile, 0.3 ml 1,8-diazabicyclo[5.4.1]-undec-7-ene, and the product from Step 3 (0.22g) dissolved in 5.0 ml acetonitrile, and stirred 44 minutes at ambient temperature. Ethyl-2-methyl malonyl chloride (0.25 g) was added over 4 minutes and the mixture stirred an additional 10 minutes and a 96.5% product conversion obtained. ¹H-NMR data supplied.

Derivatives

Insitu Step 4 Coupling Agent	Isocoumarin	Yield (%)
		76
		91
		51

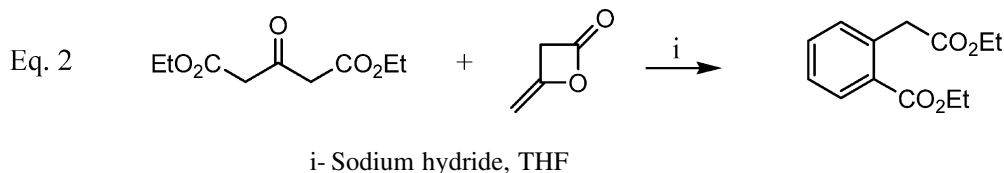
Notes

- Two homophthalic ester isomers are ordinarily generated when reacting diethylmalonate with an insitu benzyne intermediate as illustrated in Eq. 1:

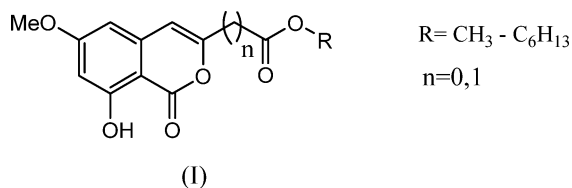


The author has developed a highly effective method for preparing a single isocoumarin isomer entailing (i) first reacting diethyl malonate with NaH and (ii) adding the halo-reagent slowly to the reactor while slowly adding LDA.

- Another route for preparing homophthalic esters is through the condensation of diethyl-diacetonedicarboxylate and diketene (1) illustrated Eq. 2:



- The Step 4 product yield was lowered because of a competitive self dimerization reaction of 6,8-dimethoxyisochroman-1,3-dione and is discussed by the author.
- Phosphorous pentachloride catalyzed cyclization of 2-bromoethyl-2-carboxyphenyl acetate as a route for preparing isocoumarin derivatives is described (2).
- Other methods for preparing Step 1 esters derivatives (I) of the current invention are discussed (3).



References

- T. Tuschida *et al*, US Patent 6,548,695 (April 15, 2003)
- J.C. Powers, US Patent 4,845,242 (July 4, 1989)
- S.-I. Hirano *et al*, US Patent 6,020,363 (February 1, 2000)

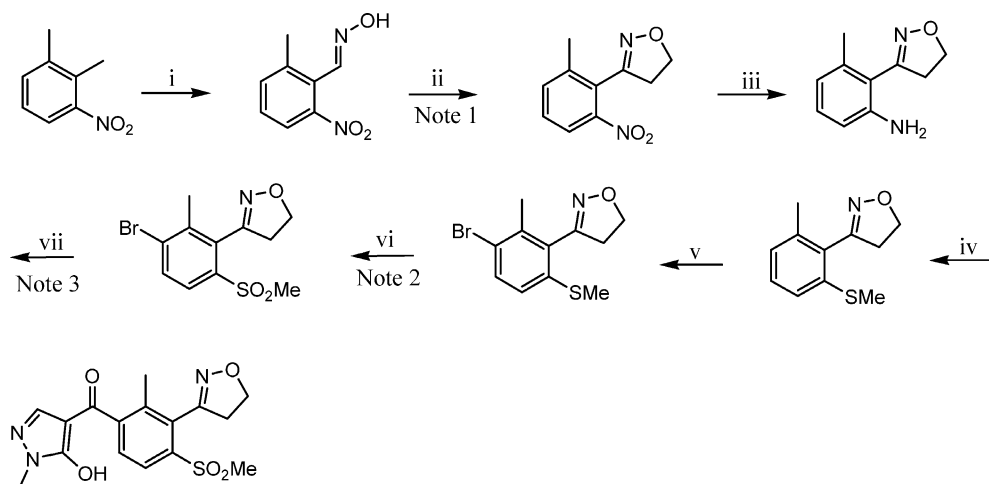
Isoxazolines

Patent: Method for Producing Isoxazoline-3-yl-acyl Benzene
J. Rheinheimer *et al*, US Patent 6,525,204 (February 25, 2003)

Assignee: BASF Aktiengesellschaft

Utility: Herbicide

Reaction



- i- Dimethylformamide, 3-nitro-o-xylene, potassium t-butoxide, n-butyl nitrite
- ii- N-chlorosuccinimide, acetonitrile, toluene, ethylene
- iii- EtOAc, 5% platinum on carbon, hydrogen.
- iv- Dimethyl disulfide, t-butyl nitrite, copper powder

- v- Sulfuric acid, bromine
- vi- Hydrogen peroxide, acetic acid, sodium tungstate hydrate
- vii- 1-Methyl-5-hydroxypyrazole, potassium carbonate, triethylamine, bis(triphenylphosphine)-palladium dichloride, 1,4-dioxane, carbon monoxide, trimethylamine

Experimental

1. 2-Methyl-6-nitrobenzaldoxime

A solution of n-butyl nitrite (2.6 mol) and 3-nitro-o-xylene (2.0 mol) dissolved in 750 ml of dimethylformamide were cooled to -60°C and potassium t-butoxide (4.56 mol) dissolved in 750 ml of dimethylformamide added over 3 hours. Thereafter, 300 ml water were added followed by 300 ml HOAc until a pH 5–6 reached. The mixture was then poured into 6 kg of ice water, the residue filtered, washed with water, and dried. The precipitate was placed in a suspension of about 3 L of toluene at $80\text{--}90^{\circ}\text{C}$ 2 hours, the mixture filtered, dried, and the product isolated in 77% yield, 98% purity, mp = $190\text{--}192^{\circ}\text{C}$.

2. 3-(2-Methyl-6-nitrophenyl)-4,5-dihydroisoxazole

At 60°C , N-chlorosuccinimide (28 mmol) dissolved in 30 ml acetonitrile was added to the product from Step 1 (28 mmol) dissolved in 50 ml acetonitrile and the mixture stirred 20 minutes, cooled, and concentrated. The residue was suspended in 50 ml of toluene for about 90 minutes, filtered, filled into a mini autoclave, and an ethylene pressure of 30 bar applied. Over a period of 5 hours, a solution of NaHCO_3 (4.7 g) dissolved in 50 ml water was metered in and the mixture stirred at 30 bar ethylene pressure 5 hours. Thereafter, the phases were separated, the toluene phase washed twice with NaHCO_3 , once with water, dried, concentrated, and the product isolated in 86% yield, mp = $100\text{--}105^{\circ}\text{C}$. $^1\text{H-NMR}$ data supplied.

3. 2-(4,5-Dihydroisoxazol-3-yl)-3-methylaniline

A mixture consisting of the product from Step 3 (0.57 mol) was dissolved in 1.2 L EtOAc, 5% platinum on carbon (11.7 g) added, and the mixture hydrogenated at $25\text{--}30^{\circ}\text{C}$ 48 hours at 20 bar hydrogen. Thereafter the mixture was filtered through silica gel and the solvent removed. The residue was dissolved in methyl t-butyl ether and water and extracted with 1 M HCl. The aqueous phase pH was adjusted to 10–11, then extracted with CH_2Cl_2 , dried, concentrated and the product isolated in 87% yield, 97% purity, mp = $86\text{--}88^{\circ}\text{C}$.

4. 3-(2-Methyl-6-methylthiophenyl)-4,5-dihydroisoxazole

The product from Step 3 (114 mmol) was dissolved in 100 ml dimethyl disulfide and added dropwise to t-butyl nitrite (170 mmol) containing copper powder (20 g) in 30 ml

dimethyl disulfide at 55°C. The mixture was diluted with CH_2Cl_2 and extracted with dilute HCl. The organic phase was washed with saturated NaHCO_3 solution, dried over sodium sulfate, filtered, concentrated, and excess dimethyl disulfide was removed under vacuum. The product was isolated in 99% yield, mp = 66–67°C.

5. 3-(3-Bromo-2-methyl-6-methylthiophenyl)-4,5-dihydroisoxazole

At 0°C the product from Step 4 (48 mmol) was slowly added to 120 ml concentrated H_2SO_4 , stirred 30 minutes, bromine (23 mmol) added dropwise, and the mixture stirred at 0°C 3 hours. The mixture was warmed to ambient temperature over 45 minutes, poured into ice water, extracted with CH_2Cl_2 , washed, dried, concentrated, and 11.4 g of product isolated.

6. 3-(3-Bromo-2-methyl-6-methylsulfonylphenyl)-4,5-dihydroisoxazole

At 45°C 30% hydrogen peroxide (100 mmol) was added dropwise to a solution of the product from Step 5 (40 mmol) dissolved in 100 ml HOAc containing sodium tungstate hydrate (400 mg) and stirred overnight at ambient temperature. The mixture was subsequently poured into ice water, extracted with CH_2Cl_2 , washed with sodium sulfite solution, dried over magnesium sulfate, concentrated, and the product isolated in 50% yield, mp = 137–139°C.

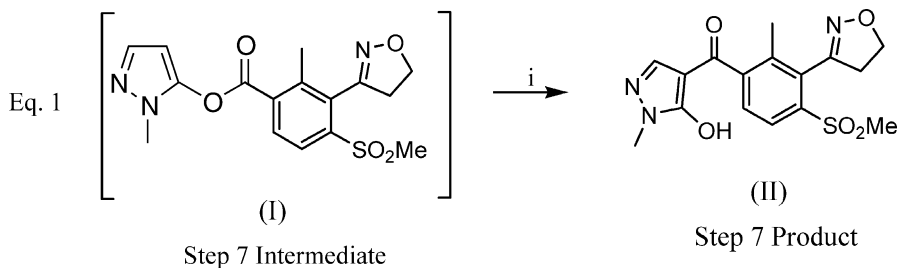
7. 1-Methyl-4-(3-(4,5-dihydroisoxazol-3-yl)-2-methyl-4-methylsulfonylbenzoyl)-5-hydroxypyrazole

The product from Step 6 (0.315 mol), 1-methyl-5-hydroxypyrazole (0.315 mol), potassium carbonate (0.63 mol), triethylamine (0.63 mol) and bis(triphenylphosphine)palladium dichloride (0.016 mol) were dissolved in 2.2 L of 1,4-dioxane and added to a 3.5 l autoclave. Carbon monoxide at a pressure of 10–20 kg/cm³ was introduced and the mixture heated to 130°C 24 hours. The mixture was concentrated, the residue dissolved in water and extracted with CH_2Cl_2 . The aqueous pH phase was lowered to 4 with 18% HCl, the precipitate filtered, washed 3 times with water, and dried. The filtrate was extracted with CH_2Cl_2 , dried, concentrated, and the product isolated in 85.6% yield, mp = 215–219°C. ¹H-NMR data supplied.

Notes

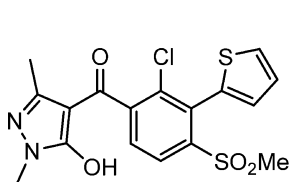
1. The author also prepared 3-(2-methyl-6-nitrophenyl)-4,5-dihydroisoxazole by dissolving 2-methyl-6-nitrobenzaldoxime in glacial acetic acid and saturating the mixture with chlorine gas. The mixture was purified as in Step 2 and the product isolated.
2. In an earlier investigation by the author (1), the product of Step 6 was isolated and converted into the carboxylic acid by reacting with magnesium then carboxylating with carbon dioxide.

3. At least one mole of potassium carbonate was used to ensure that the o-acylated pyrazole intermediate of Step 7, (I), was converted into the product of Step 7, (II), by the Fries rearrangement as illustrated in Eq. 1:

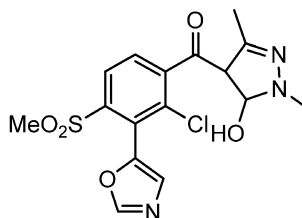


i- Potassium carbonate

4. The preparation of other 5-hydroxypyrazole benzoyl esters of the current invention are discussed (2).
5. The preparation of other Step 7 heterocyclics, (III), (IV), is described (3).



(III)



(IV)

Reference

1. J. Rheinheimer *et al*, US Patent 6,124,469 (September 26, 2000)
2. W. Von Deyn *et al*, US Patent 6,165,944 (December 26, 2000)
3. W. Von Deyn *et al*, US Patent 5,846,907 (December 8, 1998)

Ketones

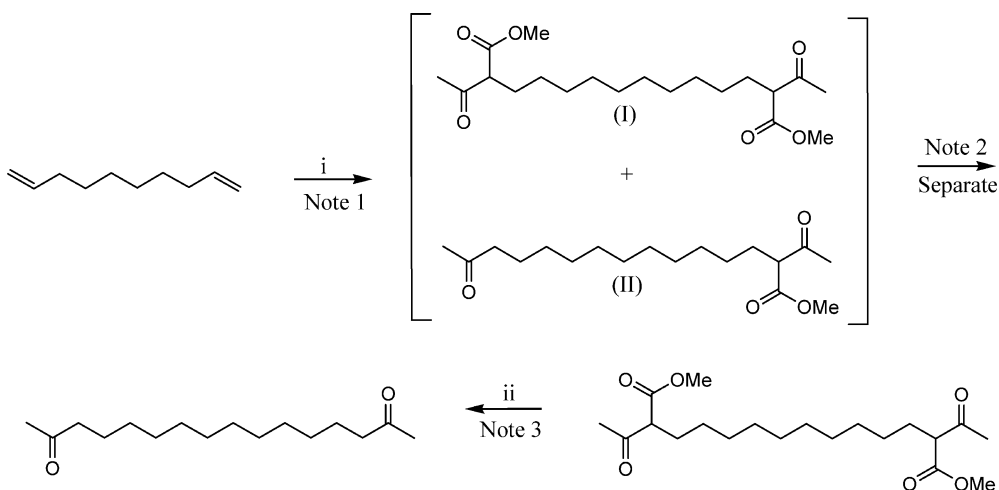
Patent: Acetoacetic Acid Derivatives, Process for Their Preparation and Their Use

K. Ebel, US Patent 6,515,154 (February 4, 2003)

Assignee: BASF Aktiengesellschaft

Utility: Perfume and Fragrance Intermediate

Reaction



i- Di-t-butyl peroxide, methyl acetoacetate

ii- Dimethylsulfoxide, sodium chloride, water

Experimental

1. Dimethyl 2,3-bisacetyl-1,14-tetradecanedioate and methyl 2-acetyl-14-oxopentadecanoate

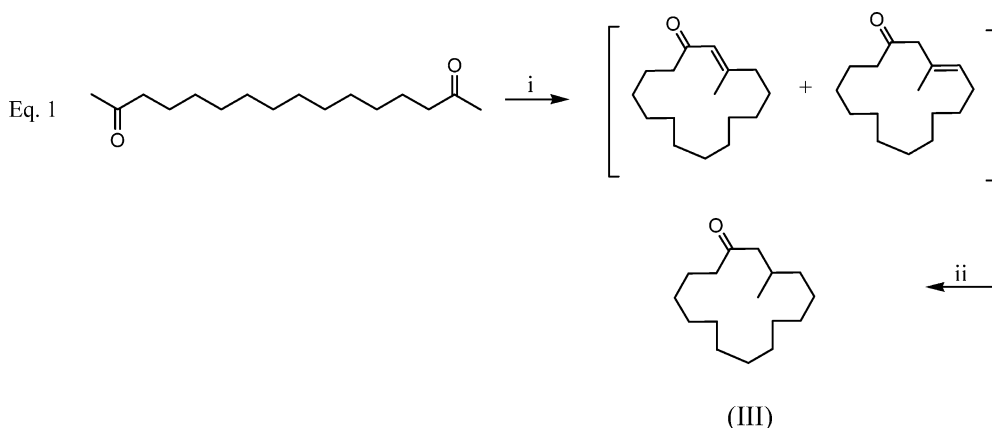
A mixture of methyl acetoacetate (1 mol), 1,9-decadiene (0.25 mol) and di-*t*-butyl peroxide (0.1 mol) were heated to 160°C and additional methyl acetoacetate (1.5 mol) added over 2 hours. Thereafter the mixture was stirred one hour at 160°C in order to decompose residue peroxide. Excess methyl acetoacetate was distilled off under reduced pressure and 82 g of residue consisting of 57% dimethyl 2,3-bisacetyl-1,14-tetradecanedioate (I) and 4% methyl 2-acetyl-14-oxopentadecanoate (II) obtained. The mixture was separated by column chromatography on silica using toluene/acetone, 4:1, and the products isolated.

2. 2,15-Hexadecanedione

The purified product from Step 1 (1 mmol) was dissolved in 20 ml DMSO, refluxed with NaCl (0.1 mmol) and water (2 mmol) 3 hours at 155–160°C, distilled under reduced pressure, and the product isolated in 82% yield.

Notes

1. General methods for preparing 2, 2'-bisacetoacetates are described (1).
2. When hydrolysis and decarboxylation in Step 2 were conducted with 2-acetyl-14-oxopentadecanoate present, the yield of 2,15-hexadecane-dione diminished to 36%.
3. Other methods for preparing 2,15-hexadecanedione are described (2).
4. The conversion of 2,15-hexadecanedione into the natural musk extract component, muscone(3-methylcyclopentadecanone), (III), is illustrated in Eq. 1 and discussed (2).



i- Titanium dioxide/sodium oxide

ii- Palladium-on carbon, hydrogen

5. The preparation of doubly unsaturated macrocyclic ketones is provided (3). The synthesis of functionalized macrocycles by ring closing metathesis methods are described (4).

References

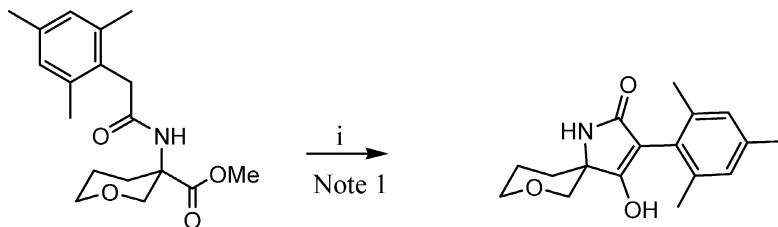
1. J.S. Witzeman *et al*, US Patent 5,247,122 (September 21, 1993)
2. M. Huellmann *et al*, US Patent 5,120,880 (June 9, 1992)
3. A. Lupo, Jr. *et al*, US Patent 6,200,254 (March 13, 2001)
4. A. Furstner *et al*, US Patent 5,936,100 (August 10, 1999)

Patent: Methods for Making Substituted Phenylketoenols
H. Hagemann *et al*, US Patent 6,630,594 (October 7, 2003)

Assignee: Bayer Aktiengesellschaft

Utility: Pesticide Intermediate

Reaction



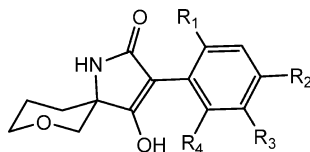
i- Potassium t-butoxide, THF, toluene

Experimental

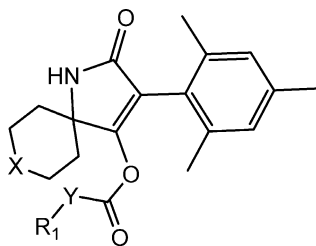
1. 3-(2,4,6-Trimethyl)phenyl-5,5-methyleneoxypropyl-pyrrolidine-2,4-dione

To a refluxing mixture of N-[(2,4,6-trimethyl)phenylacetyl]-3-amino-3-carboxymethyl-tetrahydropyran (17.3 g) dissolved in 160 ml toluene was added potassium t-butoxide (0.125 mol) dissolved in 54 ml THF and the mixture refluxed 90 minutes. After cooling, 160 ml water was added and the two phases separated. The organic phase was extracted with the addition of 80 ml water and the combined aqueous phases acidified with concentrated HCl causing a precipitation. The product was filtered and isolated in 77% yield, mp = 200 °C.

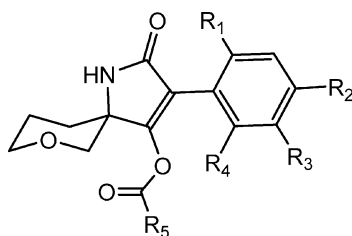
Derivatives



R ₁	R ₂	R ₃	R ₄	Melting Point (°C)
Bromine	Chloro	Methyl	Hydrogen	>220
Methyl	Methyl	Methyl	Methyl	219
Hydrogen	Bromine	Methyl	Methyl	145
Hydrogen	Chlorine	Chlorine	Hydrogen	>220
Methyl	Methyl	Hydrogen	Bromine	194



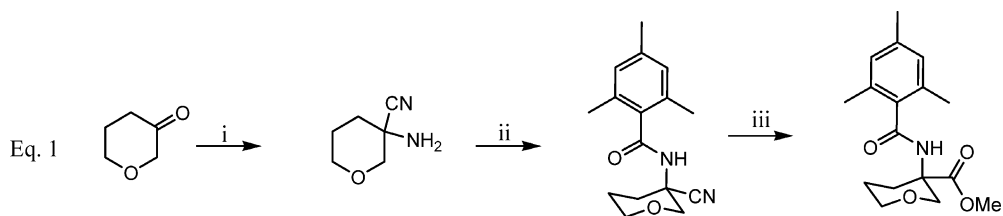
X	Y	R ₁	MP (°C)
O	S	i-Propyl	103–105
S	O	i-Propyl	119–121
O	O	sec-Butyl	111–113
O	O	i-Butyl	96–98



R ₁	R ₂	R ₃	R ₄	R ₅	Melting Point (°C)
Methyl	Methyl	Hydrogen	Methyl	Iso-propyl	163
Methyl	Bromine	Methyl	Hydrogen	2-Thienyl	>220
Chlorine	Hydrogen	Chlorine	Hydrogen	Iso-propyl	108
Methyl	Hydrogen	Methyl	Hydrogen	Sec-butyl	193

Notes

1. The preparation of the reaction of Step 1 is described (1) and illustrated in Eq 1:

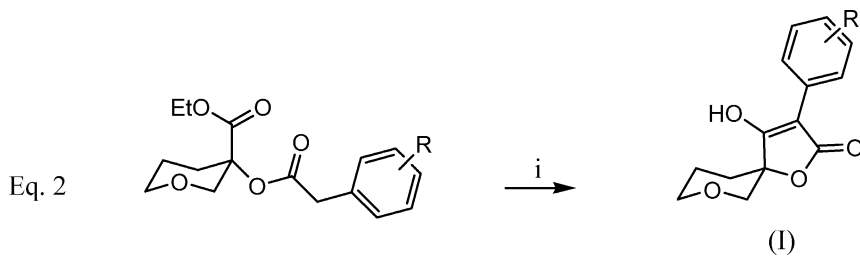


i- Ammonium hydroxide, sodium cyanide

ii- Mesityleneacetyl chloride, triethylamine

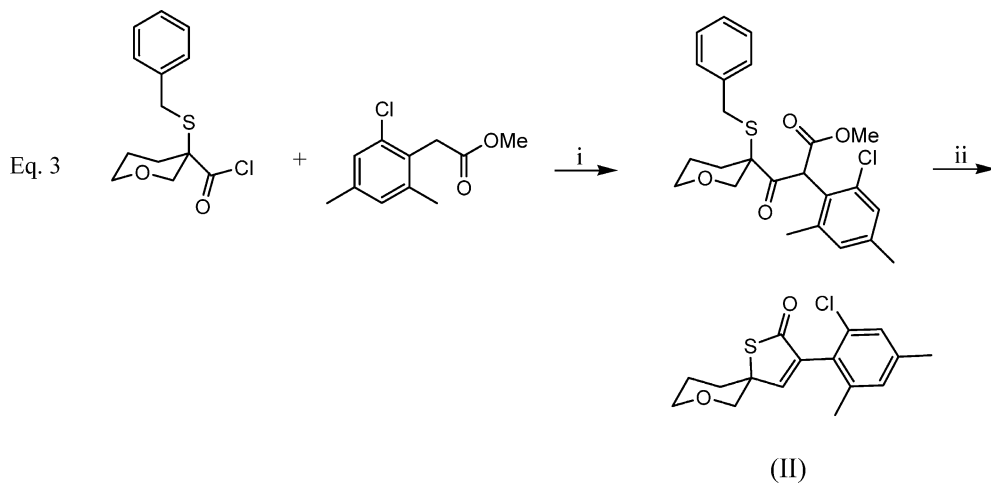
iii- Sulfuric acid, methyl alcohol

2. The preparation of dihydrofuran-2-one analogues, (I), of the current invention using phenylacetal-3-hydroxy-3-carboxyethyl-tetrahydropyran are described (2) and illustrated in Eq.2:



i- Potassium t-butoxide

3. Sulfur analogues, (II), of the current invention have also been prepared (3) as illustrated in Eq. 3:



i- Potassium t-butoxide
ii- Sulfuric acid

References

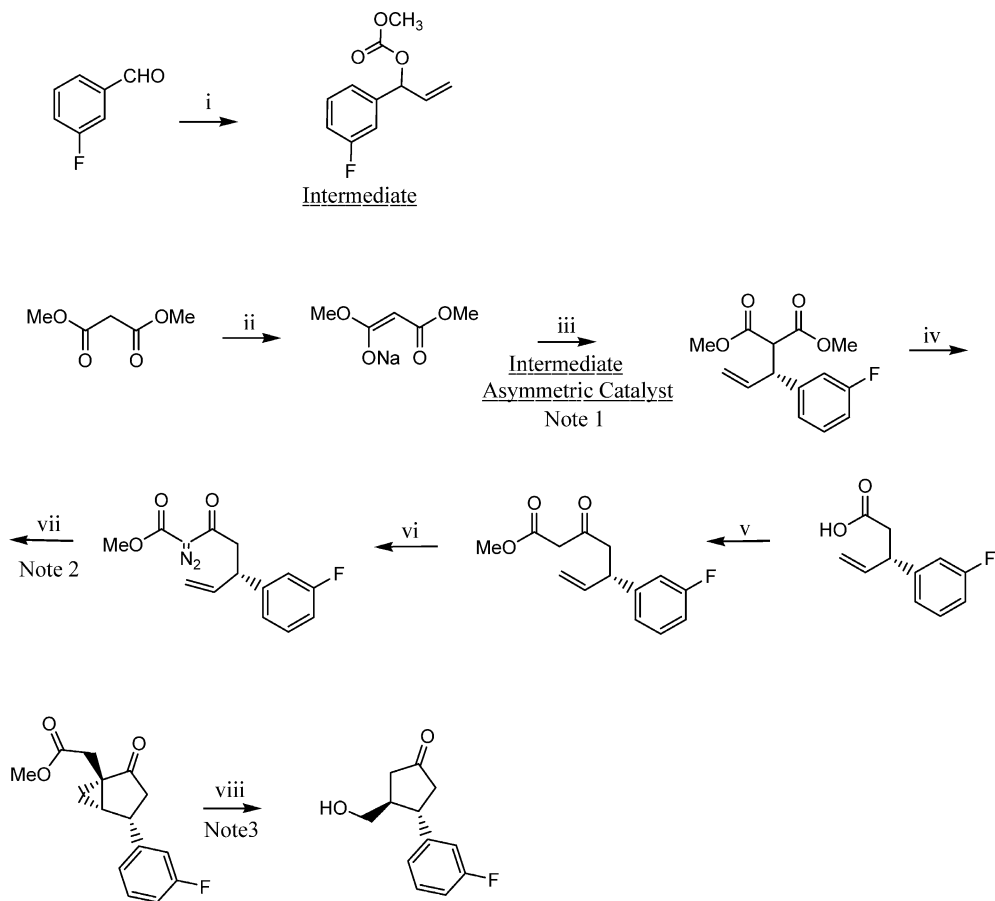
1. K. Leiber, Chem. Rev., 52, 237 (1953)
2. R. Fischer *et al*, US Patent 5,622,917 (April 22, 1997) and US Patent 5,830,825 (November 3, 1998)
3. M. Chambers *et al*, Chem. Soc. Commun., 1228 (1987)

Patent: Process for Preparing 3-Hydroxymethyl-4-(Aryl or Heterocyclic)-Cyclopentanones
N. Yasuda *et al*, US Patent 6,506,908 (January 14, 2003)

Assignee: Merck & Co., Inc.

Utility: Intermediate in Commerical Preparation of HIV Chemokine CCR-5 Receptor Antagonists

Reaction



- i- Vinylmagnesium bromide, toluene, methyl chloroformate
- ii- Toluene, sodium hydride
- iii- Molybdenum hexacarbonyl,
N,N'-bis-pyridine-trans-1,2-cyclohexylcarboxamide, toluene

- iv- Methyl-t-butylether, sodium hydroxide
- v- CH_2Cl_2 , monomethylmalonate potassium, magnesium chloride, 1,1'-carbonyldiimidazole
- vi- CH_2Cl_2 , 4-acetamidobenzenesulfonyl azide, triethylamine
- vii- Tetraacetonitrilecopper hexafluorophosphorous, CH_2Cl_2
- viii- Sodium acetate, acetic acid

Experimental

1. 3-(3-Fluorophenyl)-3-(methoxycarbonyl)oxypropene

Toluene (60 L) and 3-fluorobenzaldehyde (31.2 mole) were mixed, cooled to -5°C and 1.6 M vinylmagnesium bromide (32.8 mol) added over 90 minutes while maintaining the temperature below 0°C . The reaction was stirred one hour and methyl chloroformate (35.4 mol) added over 30 minutes while keeping the temperature below 0°C . After 1 hour 40 L 0.5 M HCl was added at such a rate the temperature exceeded 20°C , the organic layer separated, filtered through silica gel, concentrated, to obtain 56.7% of the product. $^1\text{H-NMR}$ data supplied.

2. Sodium dimethyl malonate

To dimethyl malonate (31.52 mol) dissolved in 50 L toluene was added NaH (29.94 mol) in 4 equal portions over 20 minutes. The mixture was heated to 70°C 45 minutes then cooled to 0°C . The slurry was filtered to give an 81% pure product.

3. trans-Methyl 3-(4-fluorophenyl)-3-(methoxycarbonyl)oxy-4-pentenate

A round bottom flask was charged with $\text{Mo}(\text{CO})_6$ (0.828 mol) and N,N'-bis-pyridine-trans-1,2-cyclohexylcarboxamide (1.242 mol) to which was added 4.36 L toluene, the mixture heated to 85°C 4 hours, and the asymmetric catalyst isolated.

In a separate flask the product of Step 2 (1.5 mol) was dissolved in 30.6 L toluene and heated to $55\text{--}60^\circ\text{C}$. Thereafter, the product of Step 1 (8.28 mol) dissolved in 3 L toluene added and the asymmetric catalyst were mixed and added to the product of Step 2. The 3 component mixture was heated 15 hours to 85°C , cooled to $20\text{--}25^\circ\text{C}$, filtered through silica gel, concentrated to give the product in 94.3% yield, ee = 96.1%, with a isomer ratio of 19:1 trans/cis, respectively. $^1\text{H-NMR}$ data supplied.

4. trans-3-(3-Fluorophenyl)-4-pentenoic acid

A 31.6 wt% solution of product from Step 3 (8.47 mol) in MTBE was added to 11 L water and 5 L of 5 M NaOH and the mixture refluxed 30 minutes. The mixture was cooled to $18\text{--}23^\circ\text{C}$ and 6.7 L volatiles distilled off at atmospheric pressure. The pH of the aqueous layer was lowered to 1.0 using 1.9 L concentrated HCl and the mixture refluxed an additional 12 hours. The mixture was cooled to 46°C , extracted with toluene, and product isolated 86.9% yield. $^1\text{H-NMR}$ data supplied.

5. trans-Methyl 3-keto-5-(3-fluorophenyl)-6-heptenate

The product from Step 4 (1.2 kg) was dissolved in 500 ml CH_2Cl_2 to which was added 5.5 L CH_2Cl_2 , MgCl_2 (618 g), the mixture cooled to $0-5^\circ\text{C}$, and 2.71 L Et_3N added over 5 minutes. The mixture was stirred 30 minutes at $0-5^\circ\text{C}$, warmed to 20°C , and stirred an additional 30 minutes. To this mixture was added 4 L CH_2Cl_2 , 1,1'-carbonyldiimidazole (1.10 kg) and monomethylmalonate potassium (1.52 kg) from which CO_2 vigorously evolved. After subsiding, the reaction was slowly heated to 41°C 90 minutes. The mixture was cooled to $0-5^\circ\text{C}$ and 10 L cooled 2 M HCl added to obtain a 2.9 solution pH. The two phases were separated, the aqueous phase being extracted with 3 L CH_2Cl_2 , and the product isolated in $>95\%$ yield. $^1\text{H-NMR}$ data supplied.

6. trans-Methyl 2-diazo-3-keto-5-(3-fluorophenyl)-6-heptenate

The product from Step 5 (1.3 kg in 8.8 kg solution of CH_2Cl_2) was added to 4-acetamidobenzenesulfonyl azide (1.25 kg) dissolved in 7 L CH_2Cl_2 and the solution heated to $18-21^\circ\text{C}$ with steam. Over a period of 40 minutes 2.17 L Et_3N was added, stirred 9 hours at $18-23^\circ\text{C}$ while monitoring the reaction by HPLC. When the reaction was completed, it was filtered, the cake was washed 3 times with 2 L CH_2Cl_2 , and the slurry washed once with 1 L CH_2Cl_2 . The washes and filtrate were combined and extracted with 7.4 L 2 M cool HCl. The organic extract was dried with Na_2SO_4 and the product isolated in $>95\%$ yield. $^1\text{H-NMR}$ data supplied.

7. trans-1-Methoxycarbonylmethyl-2-keto-4-(3-fluorophenyl)[3.1.0]-hexane

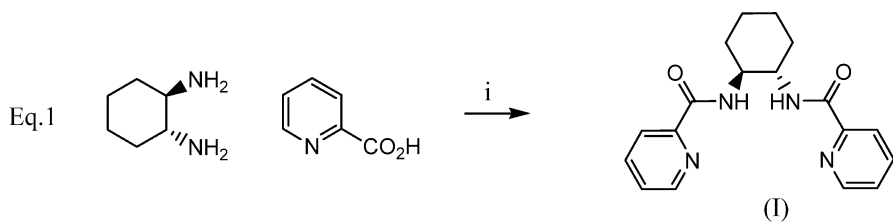
A flask was charged with 11 L CH_2Cl_2 and $(\text{CH}_3\text{CN})_4\text{CuPF}_6$ (0.149 mol), heated to 77°C , and the product from Step 6 (4.97 mol) dissolved in 1.4 L CH_2Cl_2 added over 8 hours. After the addition, the reaction was cooled with an ice bath and stirred an additional hour. The reaction mixture was rinsed with 30 L brine, dried, and the product isolated in 96.5%, 77.5% trans/trans (4.47:1 trans/cis). $^1\text{H-NMR}$ data supplied.

8. trans-3-Hydroxymethyl-4-(3-fluorophenyl)cyclopentanone

To the product from Step 7 (3.4 mol of the trans material) was added NaOAc (33.8 mol) and 14 L HOAc and the trans mixture heated to 105°C 15 hours followed by distillation of 12–13 L of HOAc. The mixture was cooled to 50°C and 15 L DMF added. To this was added 3 M NaOH until the pH >12 followed by heating to 70°C 30 minutes. The product was extracted with 30 L MTBE, organic layers combined, dried and isolated in 98% yield; $^1\text{H-NMR}$ data supplied.

Notes

1. The ligand component, (I), of the asymmetric catalyst was prepared as illustrated in Eq. 1:



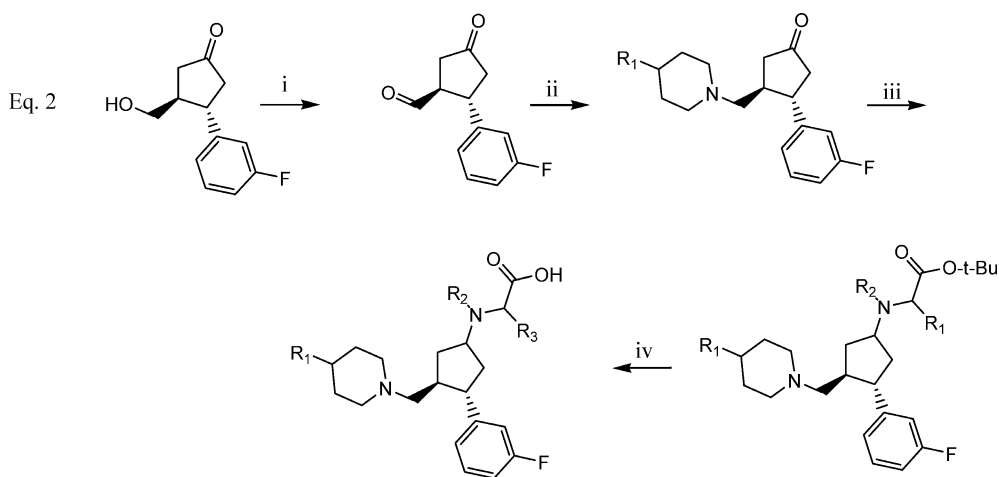
Asymmetric Catalyst Ligand Component

(I)

i- 1,1'-carbonyldiimidazole, THF

The asymmetric catalyst was prepared using the above ligand and molybdenum hexacarbonyl in a 1.5:1.0 molar ratio. Other preparations are described (1,2).

2. Other methods for preparing 3-formylcyclopentanone derivatives of Step 7 are described (3).
3. A similar intramolecular cyclopropanation of methyl 2-diazo-3-oxo-4-(2-cyclopentyl) butyrate was performed using copper (II) acetylacetonate as a method for preparing 2-ethoxycarbonyltricyclo-[3.3.1.0^{2,8}]octan-3-one and is discussed (4).
4. A method for converting the Step 8 product of the current invention into a piperidinyl-methylcyclopentyl aminoacid derivatives is illustrated in Eq. 2 and described by the author in the current invention.



i- Swern oxidation

ii- 1-Methylpyrrolidine

iii- Sodium triacetoxyborohydride, 1,2-dichloroethane,
t-butyl 2-R₁-2-(N-R₂)amine-acetate,

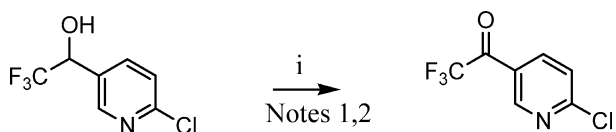
iv- Trifluoroacetic acid

References

1. T. Barnes *et al*, J. Chem. Eng. Data, 23, 349 (1978)
2. K. Kondo *et al*, US Patent 4,073,799 (February 14, 1978)
3. B. Trost *et al*, J. Am. Chem. Soc., 121,10416 (1999)
4. P. Callant *et al*, Tetrahedron, 37, 2079 (1981)

Patent: Process for Preparing Trifluoromethyl Ketones
U. Doller *et al*, US Patent 5,608,062 (March 4, 1997)
Assignee: Hoeschst Schering AgoEvo GmbH
Utility: Pesticide Precursor

Reaction



i- Tetrabutylammonium hydrogen sulfate, CH_2Cl_2 ,
sodium hypochlorite

Experimental

1. 2-Chloro-5-trifluoromethylacetylpyridine

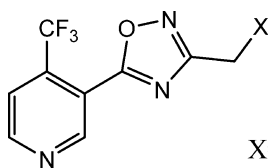
2-Chloro-5-(2,2,2-trifluoro-1-hydroxyethyl)pyridine (0.01 mol) and $\text{Bu}_4\text{N}^+\text{HSO}_4^-$ (0.0005 mol) were dissolved in 30 ml CH_2Cl_2 at ambient temperature. Thereafter, 10% NaOCl (0.012 mmol) was metered out over 5 minutes and the reaction stirred 2 hours. The reaction mixture was then added to 50 ml water and the aqueous layer extracted with CH_2Cl_2 . The organic layer was dried, the volatiles distilled off, and the product isolated by distillation in 54% yield.

Derivatives

Product	Yield (%)
2-(2,2,2-Trifluoroethoxy)5-trifluoroacetylpyridine	57
2-Chloro-5-trifluoroacetylpyridine	54
4-Trifluoroacetylbromobenzene	60.4
2-Trifluoroacetyldiphenyl ether	62.7
4-Trifluoroacetyltrifluoromethylbenzene	66.5

Notes

1. Chlorobenzene, toluene, and EtOAc were also effective as reaction solvents.
2. Other oxidizing agents that have been used to prepare trifluoroketone derivatives include Dess-Martin (1), permanganate (2), and chromic acid (3) and are described.
3. The preparation of other pesticides containing the trifluoromethyl-pyridyl component such as 2-halomethyl-5-(4-trifluoromethyl-3-pyridyl)-1,3,4-oxadiazole, (I), is described (4).



X=Cl, Br, I, OH, NH_2

(I)

References

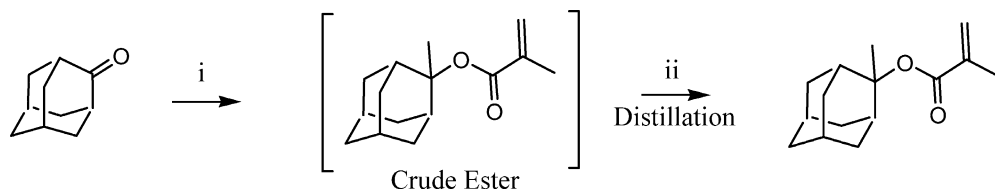
1. R. Ireland *et al*, J. Org. Chem., 58, 2899 (1993) and R. Ireland *et al*, *ibid.*, 54, 661 (1989); D. Dess *et al*, J. Am. Chem. Soc., 113, 7277
2. M.S. Tempesta, Tetrahedron Lett., 27, 2 (1986)
3. R. Jackson, J. Org. Chem., 33, 3, 1016 (1968)
4. S. Harmsen *et al*, US Patent 6,699,853 (March 2, 2004)

Patent: Process for the Preparation of High Purity Alkyladamanantyl Esters
H. Yamamoto *et al*, US Patent 6,696,595 (February 24, 2004)

Assignee: Tokuyama Component

Utility: Semiconductor Component

Reaction



- i- Methylmagnesium bromide, THF, methacrylic acid chloride, pyridine
ii- 3-Ethyl-3-hydroxymethyloxetane

Experimental

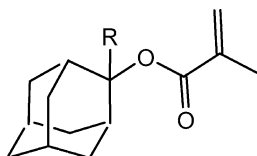
1. 2-Methyl-2-adamantyl methacrylate (Crude)

Adamantanone (30 g) was dissolved in THF and CH_3MgBr (200 ml 1 mol/liter) added thereto at ambient temperature. After 3 hours pyridine (5 g) and methacrylate acid chloride (26 g) were added and the reaction mixture stirred at 50°C 3 hours, concentrated, and hexane and 1 M NH_4OH added to the mixture. The organic phase was separated, washed with 5% NaOH solution, and adjusted to pH 8. The crude product was isolated in 90% by weight.

2. 2-Methyl-2-adamantyl methacrylate

The crude sample from Step 1 (100 parts) and 0.05 parts of the decomposition inhibitor, 3-ethyl-3-hydroxymethyloxetane, were distilled at 120°C at 3 mm Hg through an air cooled condenser containing a 5 cm vigoureux column and the product isolated in 95.3 % yield.

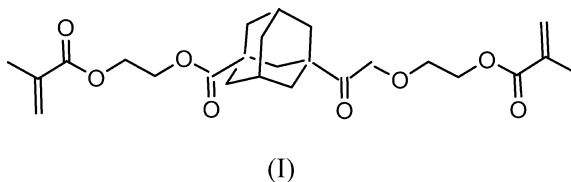
Distillation Summary



R	Decomposition Inhibitor	Amount (pbw)	Distillate (wt %)
Ethyl	Dioctylphenothiazine	5	93.4
Methyl	Diglycidyl bisphenyl F	0.1	96.3
Ethyl	1,4-bis{[(3-ethyl-oxetanyl)-methoxy]-3-methylbenzene	0.03	96.6
Methyl	None	0	85.3

Notes

1. The decomposition inhibitors are free radical polymerization inhibitors.
2. The product of Step 2 has also been prepared by the addition of methyllithium to 2-adamantanone, esterified using methacryloyl chloride (1), and purified by chromatography.
3. 1-Adamantylmethylvinylcarbonate has been prepared in high yields by reacting 1-adamantylmethyl alcohol with vinyl chloroformate (2) and purified by chromatography.
4. Bis(2-methacryloyloxyethyl)-1,3-adamantanedicarboxylate, (I), has also been prepared (3) and purified by chromatography.



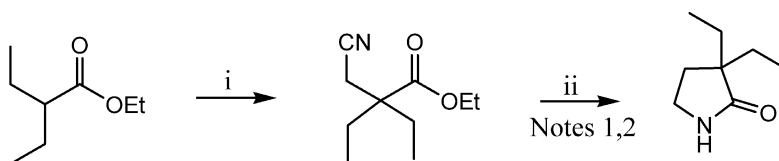
References

1. G.C. Barclay *et al*, US Patent 6,492,086 (December 2, 2002)
2. R.E. Bambury *et al*, US Patent 5,070,215 (December 3, 1991)
3. K. Inoue *et al*, US Patent 6,670,499 (December 30, 2002)

Lactams

Patent: Anticonvulsant and Anxiolytic Lactam and Thiolactam Derivatives
D.F. Covey *et al*, US Patent 6,066,666 (May 23, 2000)
Assignee: Washington University
Utility: Anticonvulsant

Reaction



i- THF, lithium diisopropylamide, bromoacetonitrile
ii- Cobalt(II)chloride hexahydrate, THF, water,
sodium borohydride, ammonium hydroxide

Experimental

1. Ethyl 2-cyanomethyl-2-ethylbutanoate

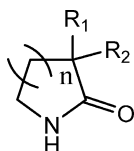
A solution of ethyl 2-ethylbutyrate (150 mmol) dissolved in 25 ml THF was added dropwise to a solution of lithium diisopropylamide (prepared by treating diisopropylamine (165 mmol) dissolved in 150 ml THF with butyllithium in hexanes (165 mmol) at -78°C 1 hour) in a nitrogen atmosphere and stirred 1 hour. Thereafter, bromoacetonitrile (180 mmol) dissolved in 50 ml THF was added over 30 minutes and the mixture stirred overnight at -78°C . The reaction was quenched with 250 ml 1 M HCl, the layers separated, and the aqueous phase extracted 3 times with 100 ml diethyl ether. The extracts

were combined, washed sequentially with 75 ml apiece NaHCO_3 , water, brine, and dried. The mixture was concentrated, vacuum distilled twice, and the product isolated in 45% yield, bp = 84–85 °C at 1.3 mm Hg.

2. 3,3-Diethyl-2-pyrrolidinone

A pink solution of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (22.5 mmol) and the product from Step 1 (45 mmol) dissolved in 158 ml THF containing 79 ml water was cooled to 0 °C and NaBH_4 (225 mmol) added over 30 minutes. The mixture stirred 24 hours at ambient temperature, 6 ml 28% NH_4OH added, the mixture refluxed 72 hours, centrifuged, and the supernatant biphasic liquid decanted. Thereafter, the sediment was washed with 15 ml of the original solvent mixture and concentrated. The aqueous residue was extracted 3 times with 75 ml chloroform, washed with 100 ml brine, dried, and concentrated. The material was purified by flash chromatography on silica gel using 1% methyl alcohol in chloroform/EtOAc, 1:1, and the product isolated in 70%, mp = 52–53 °C.

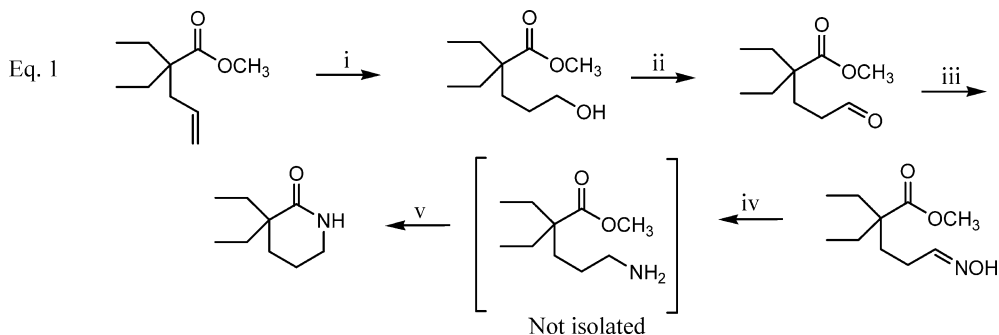
Derivatives



R_1	R_2	n	Melting Point (°C)
Methyl	Phenylmethyl	1	76–78
Ethyl	Phenylmethyl	2	101–102
Hydrogen	Diphenyl	1	120–122
Ethyl	1-Methylethyl	1	63–64

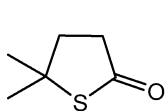
Notes

1. In an earlier investigation, 3,3-diethyl-2-piperidinone was also prepared by the author (1) as illustrated in Eq. 1:

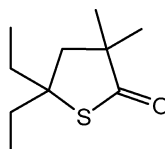


- i- Boron trifluoride, THF, hydrogen peroxide, water
- ii- Pyridinium chlorochromate, sodium acetate
- iii- Hydroxylamine, pyridine
- iv- Nickel(II)chloride hexahydrate, sodium borohydride, methyl alcohol

2. In another investigation α,α -di-alkyl-pyrrolidinone and α,γ -di-alkyl-piperidinone derivatives were prepared by the author (1) and are described (1).
3. α,α - and $\alpha,\alpha,\gamma,\gamma$ -Di- and tetra-alkyl-thiolactone derivatives, (I), (II), respectively, have been prepared by the author (2) and are described.



(I)



(II)

4. Other methods for preparing 3-alkyl- and 3,3-di-alkyl-2-pyrrolidone derivatives of the current investigation are described (3).

References

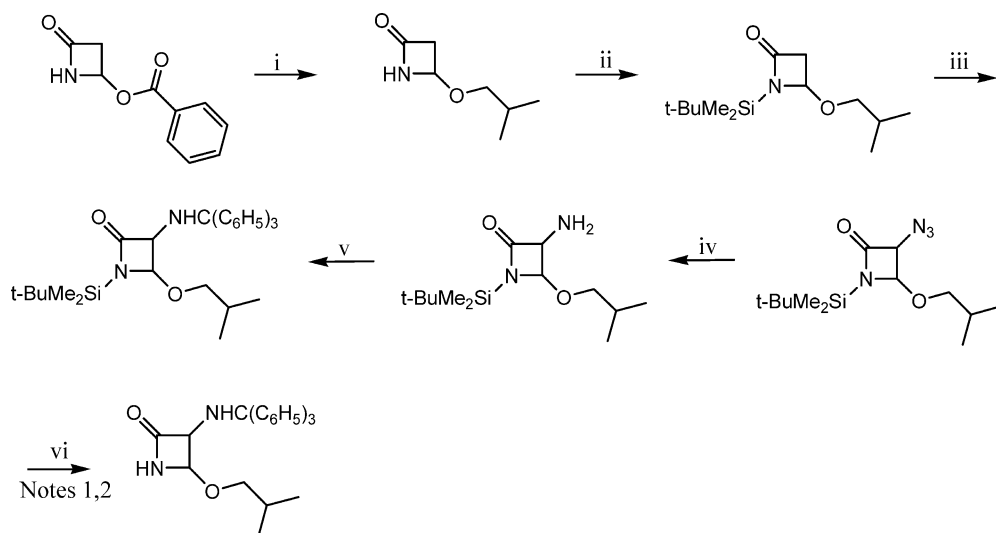
1. D.F. Covey *et al*, US Patent 5,776,959 (July 7, 1998)
2. D.F. Covey *et al*, US Patent 4,707,491 (November 17, 1987)
3. R. Menezes *et al*, Syn. Comm., 18, 1625 (1988); W.A.W. Cummings *et al*, J. Chem. Soc, C, 1060 (1964); J.A. Baker *et al*, *ibid.*, 2148 (1967); M. Rodriguez *et al*, US Patent, 4,420,568 (December 13, 1983)

Patent: β -Lactams as Antiproliferative Agents
J.D. Winkler *et al*, US Patent 6,451,785 (September 17, 2002)

Assignee: SmithKline Beecham Corporation

Utility: Cell Anti-Proliferation Agent in Mammals

Reaction



- i- Isobutyl alcohol, toluene, triethylamine, palladium acetate
- ii- t-Butyldimethylsilyl chloride, THF, triethylamine
- iii- N-Isopropylcyclohexylamine, n-butyllithium, THF, hexamethylphosphoramide, p-toluenesulfonyl azide, trimethylsilyl chloride
- iv- CH_2Cl_2 , triethylamine, hydrogen sulfide
- v- N,N-Dimethylformamide, diisopropylethylamine, trityl chloride
- vi- Tetrabutylammonium fluoride, acetic acid, THF

Experimental

1. 4-Isobutoxy-azetidin-2-one

A mixture of 4-benzoyloxy-azetidin-2-one (80 mmol) dissolved in 150 ml toluene was treated with isobutyl alcohol (0.16 mmol), NEt_3 (0.16 mol) and $\text{Pd}(\text{OAc})_2$ (16 mmol), stirred in an ice bath several hours, and at ambient temperature for hours. The mixture was filtered through Supercel, concentrated, and the residue purified by chromatography

on silica gel using EtOAc/hexane with an EtOAc gradient of 10–35%. The product was re-chromatographed on silica gel using EtOAc/hexane, with an EtOAc gradient of 10–25%.

2. 1-t-Butyldimethylsilyl-4-isobutoxy-azetidin-2-one

The product from Step 1 (33 mmol) was dissolved in 50 ml THF containing NEt_3 (66 mmol), cooled in an ice bath, and t-butyldimethylsilyl chloride (43 mmol) dissolved in 15 ml THF added dropwise. The cooled reaction mixture was stirred 5 hours then stored in a refrigerator 64 hours. The cooled mixture was poured into ice- cold water, extracted with EtOAc, and the extract washed with brine and dried. The residue was purified by chromatography using EtOAc/hexane, 1:9, and the product isolated in 79% yield.

3. (3RS,4RS)-3-Azido-1-t-butyldimethylsilyl-4-isobutoxy-azetidin-2-one

N-Isopropylcyclohexylamine (10 mmol) was dissolved in 18 ml THF, cooled to -15°C , and 48 ml 2 M n-butyllithium added dropwise. The mixture was stirred 40 minutes, the temperature lowered to -78°C , and the product from Step 2 (7 mmol) dissolved in 7 ml THF added. The reaction mixture was stirred an additional hour and p-toluenesulfonylazide (9 mmol) dissolved in 8 ml THF containing 2 ml HMPA added over 40 minutes. The mixture was stirred one hour at -50°C and 16 hours at -28°C . Thereafter, 5 ml trimethylsilyl chloride was added and the mixture stirred at ambient temperature for 45 minutes. The mixture was diluted with water, extracted with EtOAc, purified as in Step 2, and the product isolated in 30% yield.

4. (3RS,4RS)-3-Amino-1-t-butyldimethylsilyl-4-isobutoxy-azetidin-2-one

The product from Step 3 (0.67 mmol) was dissolved in 15 CH_2Cl_2 containing NEt_3 (0.7 mmol), cooled on an ice bath, and H_2S bubbled gently through the solution for 10 minutes. The mixture was stirred while cold 4 hours, concentrated, and the desired product isolated.

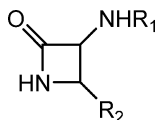
5. (3RS,4RS)-3-Amino-1-t-butyldimethylsilyl-4-isobutoxy-3-(triphenylmethylamino)azetidin-2-one

The product from Step 4 was dissolved in 8 ml DMF, cooled in an ice bath and treated with 0.1 ml diisopropylethylamine followed by trityl chloride (0.6 mmol). The mixture was stirred 18 hours, diluted with 40 ml water and extracted with EtOAc. The mixture was purified by chromatography on silica using EtOAc/hexane, 1:4, and the product isolated. MS data provided.

6. (3RS,4RS)-4-(Isobutoxy)-3-(triphenylmethylamino)azetidin-2-one

The product from Step 5 (0.3 mmol) was dissolved in 4 ml THF, cooled in an ice bath, treated with HOAc (0.4 mmol), and then with 1 M NBu_4F (0.6 mmol). The mixture was stirred 20 minutes and the product purified by chromatography on silica gel using EtOAc. MS data provided.

Derivatives



R_1	R_2	MS(M+1)
Triphenylmethyl	1-Octyloxy	457
(4-Iodophenyl)-diphenylmethyl	Isobutoxy	527
Triphenylmethyl	3-Acetyl-propoxy	445

Notes

1. Thio analogues were also prepared by the author in the current invention and by others (1). The preparation of (3R,4R)-4-isobutylthio)-3-(triphenylmethylamino)- and (3R,4R)-4-isobutylsulfonyl)-3-(triphenylmethylamino)azetidin-2-one, (I), (II), respectively, are illustrated below in Procedures 1 and 2. The preparation of other thio-and sulfonyl-azidin-2-one analogues is described (2).

Procedure-1

A solution of $Zn(OAc)_2$ (3 mmol) in 15 ml toluene and 2-methyl-propanethiol (8 mmol) was refluxed in a Dean-Stark trap for 45 minutes. Thereafter (3R,4R)-4-(methylsulfonyl)-3-(triphenylmethylamine)-azetidin-2-one (36 mmol) was added and the mixture heated to $90^\circ C$ 2 hours. The mixture was concentrated and the residue triturated with EtOAc and filtered. The filtrate was concentrated, the mixture purified by chromatography on silica gel using EtOAc/hexane, 1:4, and the product isolated. MS data supplied.

Procedure-2

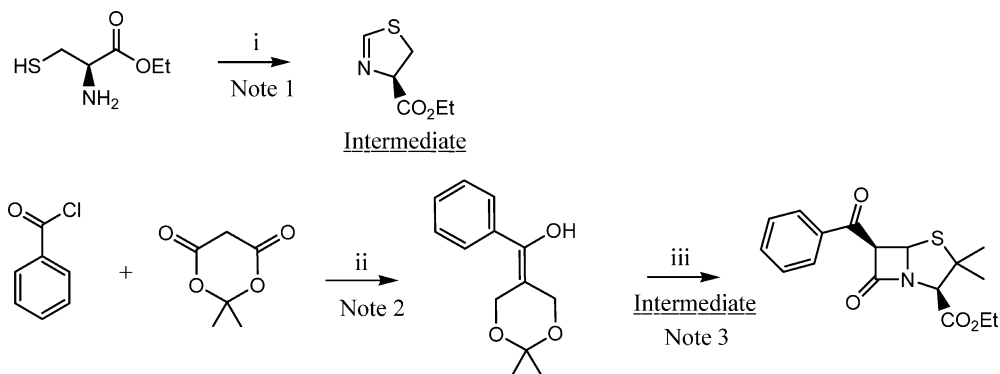
- The product from Procedure-1 (0.12 mmol) was dissolved in 2 ml CH_2Cl_2 , cooled in an ice bath, and then treated with 3-chloroperbenzoic acid (0.25 mmol). The mixture was stirred for three hours in a cold bath and then partitioned between 5 ml apiece 5% Na_2CO_3 and CH_2Cl_2 . Thereafter, the organic component was washed with 5% Na_2CO_3 and brine, dried, purified as in Procedure 1, and the product isolated in 47% yield. MS data supplied.
2. Mass spectrum data for most intermediates and all final products supplied by the author.
 3. (3R,4R)-4-(Isobutylthio)- and -(isobutylsulfonyl)-3-(triphenylmethyl-amino)azetidin-2-one derivatives were previously prepared (2).
 4. Amine derivatives of the current invention have also been prepared using the Gabriel synthesis and is discussed (3).

References

1. K.S. Smizener *et al*, J. Chem. Soc. Perkin Trans., I, 2268 (1979)
2. W.E. Bondinell *et al*, US Patent 6,221,860 (April 24, 2001)
3. R.J. Ponsford *et al*, US Patent 4,647,558 (May 3, 1987)

Patent: β -Lactam-like Chaperone Inhibitors
S.J. Huntgren *et al*, US Patent 6,495,539 (December 17, 2002)
Assignee: Washington University
Utility: Antibacterial Agents for Periplasmic Chaperones

Reaction



- i- Water, sodium carbonate, acetic anhydride, formic acid, paratoluenesulfonic acid
 ii- Chloroform, 4-dimethylaminopyridine
 iii- Hydrogen chloride, benzene

Experimental

1. trans-4-Ethoxycarboxythiazoline

L-Ethyl cysteinate and Na_2CO_3 were dissolved in a minimum amount of water and acetic anhydride (1.05 eq) and formic acid (1.2 eq) added. The pH of the solution was kept basic by the addition of solid Na_2CO_3 and the mixture stirred 60 minutes. The solids were removed and the mixture extracted 3 times with chloroform. The organic phase was neutralized with 6 M HCl, concentrated, the residue suspended in benzene containing a catalytic amount of paratoluenesulfonic acid and refluxed over night with a Dean-Stark trap. Thereafter the organic phase was evaporated, dissolved in chloroform, washed with NaHCO_3 , and the product isolated.

2. 2,2-Dimethyl-5-[(2-hydroxyl-2-phenyl)methylene-1,3-dioxane-4,6-dione]

A solution of benzoyl chloride (60 mmol) dissolved in 50 ml CCl_3H was added dropwise over 1 hour to a cold solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (50 mmol) dissolved in 150 ml CCl_3H containing 4-dimethylamino-pyridine (100 mmol). The cold mixture reacted one hour while stirring and then stood at ambient temperature for one hour. The mixture was washed three times with 30 ml 10% HCl, the organic

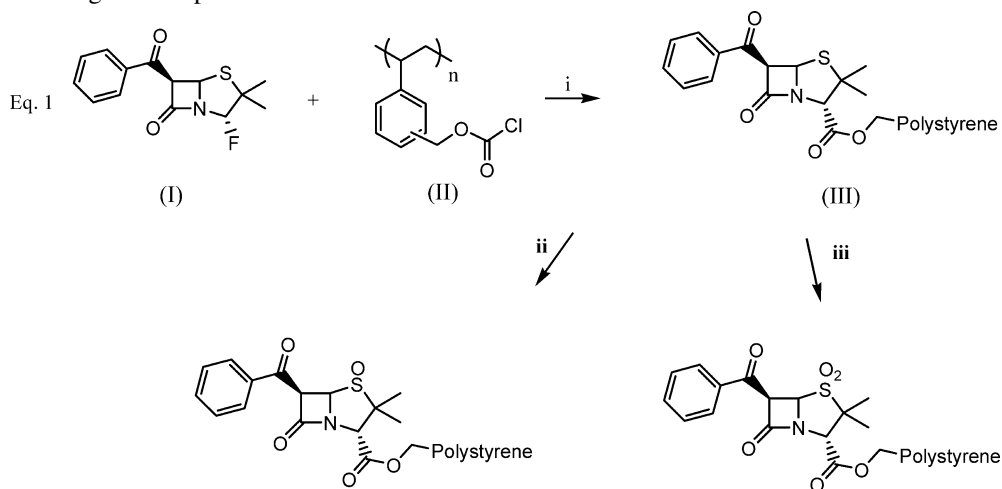
layer separated, washed, and the product isolated in 80% yield after re-crystallization in acetone.

3. **(1S,2R,5S,6R)-6-Benzoyl-7-oxo-4-thia-3,3-dimethyl-azabicyclo-[3.2.0]heptane-2-carboxylic acid, ethyl ester**

Gaseous HCl was passed into an ice- cold solution of 50 ml benzene containing the products from Step 1 (5 mmol) and Step 2 (5 mmol) until the solution was saturated. Thereafter, the mixture was refluxed for one hour then washed twice with 30 ml water. The organic layer was dried and the product purified using chromatography on silica gel with hexane/diethyl ether, 1:1, and the product isolated.

Notes

1. Other Meldrum acid condensation reactions are provided (1).
2. The preparation of other thiazoline derivatives is described (2).
3. Another aspect of this invention contemplated by the author is the preparation of 2-fluoro Step 3 analogues, (I), for use in a graft reaction with polystyrene-g-chloroformate, (II), forming polystyrene-graft- β -lactam, (III), as illustrated in Eq. 1 followed by oxidation using m-chloroperbenzoic acid.



i- Potassium fluoride, N,N-dimethylformamide

ii- m-Chloroperbenzoic acid

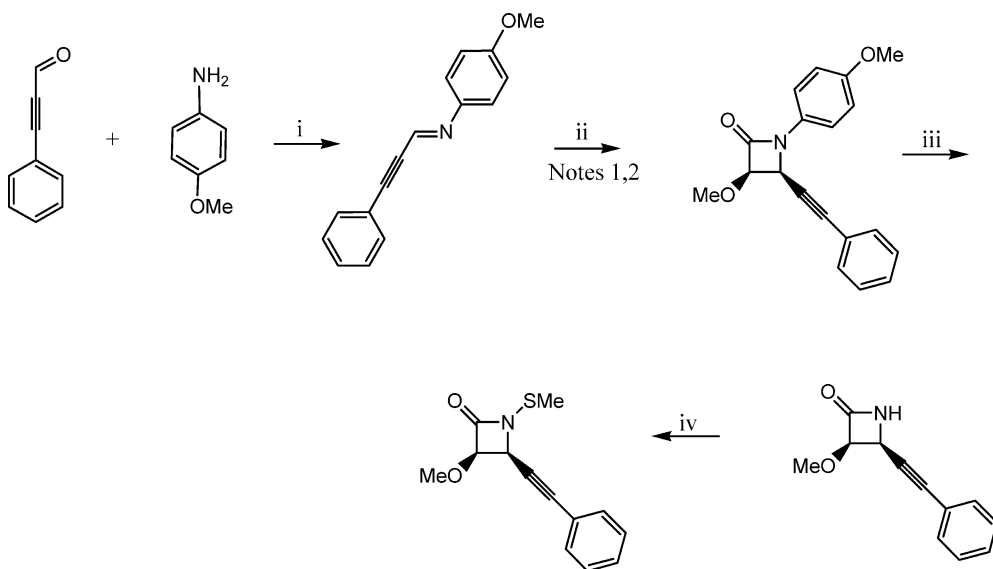
iii- m-Chloroperbenzoic acid (excess)

References

1. E.G. Brown *et al*, US Patent 5,861,532 (January 19, 1999)
2. F. Almquest *et al*, Tetrahedron Lett., 39, 2293 (1998)
3. Y. Yamamoto *et al*, Chem. Pharm. Bull., 35, 1871 (1987); T. Oikawa *et al*, J. Org. Chem., 43, 10, 2087 (1978)

Patent: N-Thiolated β -Lactam Antibiotics
 E. Turos *et al*, US Patent 6,476,015 (November 5, 2002)
Assignee: University of South Florida
Utility: Treatment of Bacteria Resistant to Multiple Antibiotics

Reaction



- i- Paratoluenesulfonic acid, benzene
 ii- Methoxy acetyl chloride, triethylamine, CH_2Cl_2
 iii- Ammonium cesium(IV)nitrate, acetonitrile, sodium bisulfite
 iv- Methyl methanethiolsulfonate, n-butyl lithium, THF

Experimental

1. N-(4-Methoxyphenyl)-phenylethynylimine (General procedure)

Phenylpropargyl aldehyde and 4-methoxyaniline were refluxed in a benzene solution in the presence of a catalytic amount of p-toluenesulfonic acid under Dean-Stark conditions. After cooling the mixture was filtered through silica gel to remove residual amine. The imine product was checked by $^1\text{H-NMR}$ and the product isolated.

2. N-(4-Methoxyphenyl)-4-phenylethynyl-3-methoxyazetidin-2-one

The product from Step 1 (8.0 mmol) was added to 75 ml CH_2Cl_2 containing NEt_3 (9.0 mmol) and thereafter methoxyacetyl chloride (10.0 mmol) dissolved in 20 ml CH_2Cl_2 added. The reaction was stirred 30 minutes and was then poured into 75 ml 5% aqueous

HCl. The product was extracted 3 times using 50 ml CH_2Cl_2 and extracts combined, dried, and filtered. The solvent was removed and a brown oil obtained which slowly crystallized, was purified by flash chromatography using CH_2Cl_2 /hexanes, 2:1, and the product isolated in 89% yield, mp = 116–117°C. ^1H - and ^{13}C -NMR and elemental analysis data supplied.

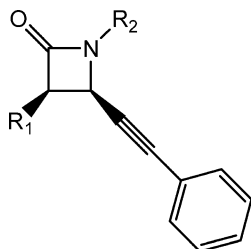
3. 4-Phenylethynyl-3-methoxy-azetidin-2-one (General dearylation procedure)

The product from Step 2 (7.2 mmol) was dissolved in 100 ml acetonitrile and ammonium cesium(IV)nitrate (21.6 mmol) dissolved in 100 ml water added over 5 minutes. The mixture was stirred 25 minutes, poured into 100 ml 5% NaHSO_3 , and the aqueous mixture extracted 3 times with 50 ml diethyl ether. The extracts were combined, washed with 100 ml 5% NaHCO_3 , dried, filtered, and concentrated. The product was purified as in Step 2 and isolated in 89% yield, mp = 121–122°C. ^1H -NMR data supplied.

4. N-(Thiomethoxy)-4-phenylethynyl-3-methoxy-azetidin-2-one (General N-methylthiolation procedure)

The product from Step 3 (6.4 mmol) dissolved in THF was cooled to -78°C and 5 ml 1.38 M butyl lithium in hexanes added. After 30 minutes methyl methanethiolsulfonate (6.6 mmol) was added and the mixture stirred 12 hours with gradual warming to ambient temperature. The mixture was poured into 50 ml 5% aqueous NH_4Cl , extracted 3 times with 50 ml CH_2Cl_2 , purified as in Step 2, and the product isolated 80% yield, mp = 74–76°C. ^1H - and ^{13}C -NMR, IR, and elemental analysis data supplied.

Derivatives

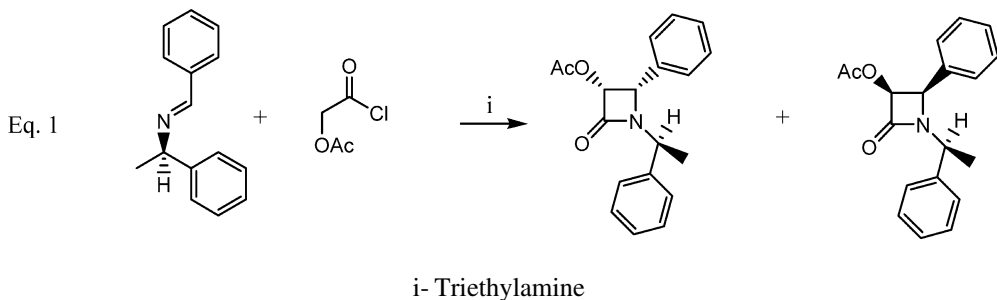


(Note 3)

R_1	R_2	Antibacterial/Antibiotic Activity
Methoxide	Thiomethyl	Active
Phthalimide	Methoxide	Inactive
Methoxide	Thiobenzyl	Mildly Active
Methoxide	Thiobenzyl	Inactive
Methoxide	Hydrogen	Inactive

Notes

1. Acid chlorides were prepared from the precursor acid by reacting with thionyl chloride in an inert solvent and are described by the author.
2. The formation of the azetidin-one ring is by a [2 + 2] imine-acid chloride cycloaddition via the insitu formation of methoxy ketene. Other β -lactams have been prepared using this route (1) as illustrated in Eq. 1. Spiro[3.5] β -lactams have also been prepared in this manner and are discussed (2).



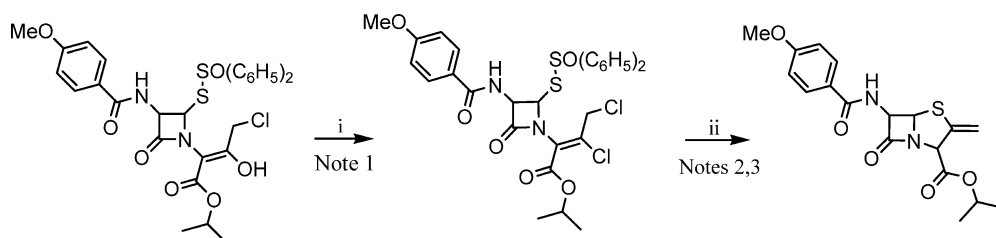
3. Only biological testing data were supplied by the author for prepared compounds in this invention.
4. Tandem Claisen [3 + 3] ketene reactions using acid chlorides for generating optically active intermediates are described (3).

References

1. D. de Vos *et al*, US Patent 6,225,462 (May 1, 2001)
2. G. Adams *et al*, US Patent 6,113,527 (September 5, 2000)
3. D.W.C. MacMillan, US Patent 6,552,226 (April 23, 2003) and 6,359,174 (March 19, 2002)

Patent: Process for Preparing β -Lactam Compounds
S. Torii *et al*, US Patent 6,197,185 (March 6, 2001)
Assignee: Otsuka Kagaku Kabushike Kaisha
Utility: Antibiotic Intermediate

Reaction



i- Phosphorous oxychloride, N,N-dimethylformamide

ii- Lead bromide, aluminum, N,N-dimethylformamide

Experimental

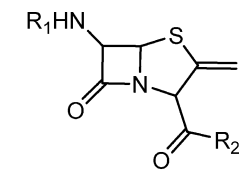
1. 1-(2-Isopropyl-3,4-dichloro-2-pentenyl)-3-(4-methoxyacetanilido)-4-(diphenylsulfonyl)sulfanyl-azidin-2-one

A 100 mg quantity of 1-(2-(isopropyl-3-hydroxy-4-chloro-2-pentenyl)-3-(4-methoxyacetanilido)-4-(diphenylsulfonyl)sulfanyl-azidin-2-one was dissolved in 1 ml DMF and added to 18 ml POCl_3 containing 1 ml DMF and stirred at ambient temperature 1 hour. The mixture was poured into water, extracted with EtOAc, washed with brine, dried, purified by chromatography using silica gel, and the product isolated in 92% yield. $^1\text{H-NMR}$ data supplied.

2. 3-Isopropoxycarbonyl-6-(4-methoxyacetanilido)-2-exo-methenepenam

One hundred milligrams apiece of the product from Step 1, lead bromide and aluminum powder were mixed with 2 ml DMF and reacted 1 hour at ambient temperature. Thereafter the mixture was poured into 1 M HCl, isolated and purified as in Step 1, and the product obtained in 99% yield.

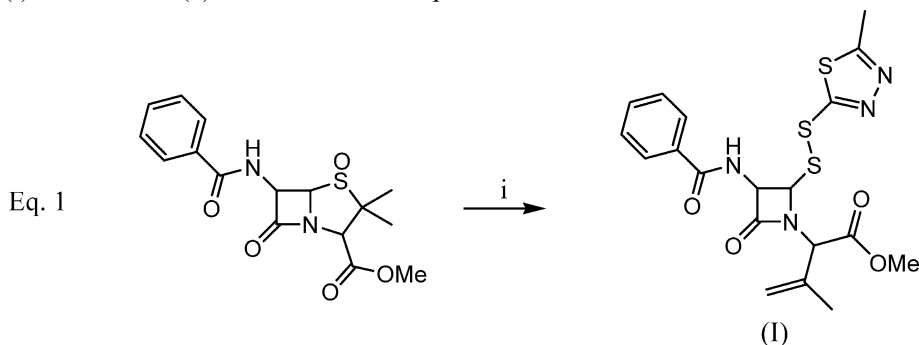
Derivatives



R_1	R_2	Yield (%) (Second Step)
PhCH_2CO	OCH_3	98
H	$\text{OCH}_2\text{C}_6\text{H}_4\text{OCH}_3\text{-p}$	90
PhCH_2CO	$\text{OCH}_2\text{C}_6\text{H}_4\text{OCH}_3\text{-p}$	86

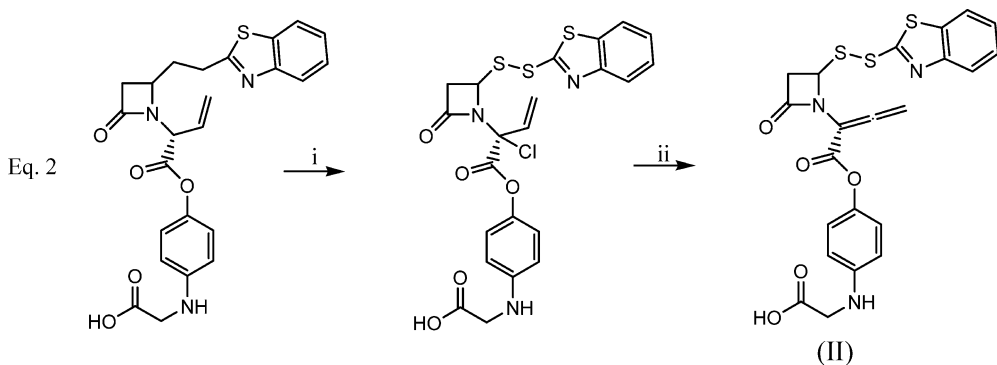
Notes

1. A general method for preparing other Step 1 reagents such as methyl 4-(5-methyl-1,3,4-thiadiazole-2-yl)dithio-3-(2-phenoxyacetamido)- α -isopropenyl-2-oxoazetidine-1-acetate, (I), is described (1) and illustrated in Eq. 1:



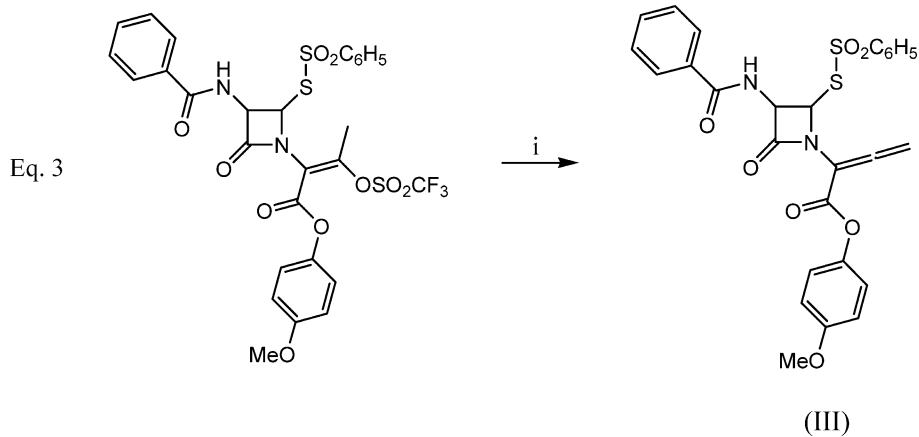
i- 5-Methyl-1,3,4-thiadiazole-2-thiol, t-butyl alcohol

2. The requirement for producing the 2-exo-methylenepanam derivatives of Step 1 is that the β -lactam is reduced with a metal having a standard oxidation–reduction potential of up to -0.3 v/sce in an amount of at least one mole per molecule of halide and with a metal compound having a higher standard oxidation–reduction potential than the metal.
3. Formation of the Step 2 product is through an allene intermediate. Other allene derivatives, (II), (III), of the current invention have been prepared by selectively altering leaving groups (2,3), respectively, as illustrated in Equations 2 and 3:



i- Phosphorous trichloride

ii- Sodium methoxide



i- Sodium methoxide

References

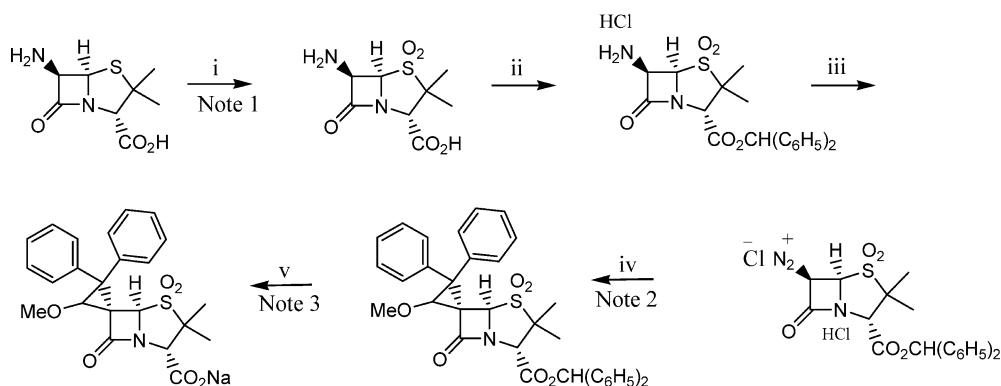
1. T. Kamiya *et al*, US Patent 4,071,527 (January 31, 1978)
2. R.G. Micetich *et al*, US Patent 4,496,484 (January 29, 1985)
3. S. Torij *et al*, US Patent 5,196,530 (March 23, 1993).

Patent: 6-(Spirocyclopropyl)-Penicillanic Acid-4,4-Dioxides
V.P. Sandanayaka *et al*, US Patent 6,489,316 (December 3, 2002)

Assignee: American Cyanamid Company

Utility: Antibiotic

Reaction



- i- Acetonitrile, water, potassium permanganate
- ii- Methyl alcohol, diphenyldiazomethane, CH_2Cl_2 , hydrochloric acid
- iii- Sodium nitrite, water, perchloric acid, CH_2Cl_2
- iv- Diphenylmethyl vinyl ether, rhodium acetate, CH_2Cl_2
- v- 10% Palladium-on-carbon, EtOAc, hydrogen, sodium bicarbonate

Experimental

1. (2S,5S,6S)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid 4,4-dioxide

To a 0°C solution of penicillanic acid (0.046 mol) in 32 ml water and 48 ml acetonitrile was slowly added KMnO_4 (0.061 mol) and 6 ml concentrated H_2SO_4 dissolved in 120 ml water. At the end of the addition 50% aqueous sodium bisulfite was added until a clear solution resulted and anhydrous ammonia passed into the solution until a pH of 3 was reached. Thereafter the sulfone intermediate precipitated and was collected in 78% yield. ^1H - and ^{13}C -NMR and IR data supplied.

2. (2S,5S,6S)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid, diphenylmethyl ester, hydrochloride salt, 4,4-dioxide

A suspension at 0°C of the product from Step 1 (0.28 mol) in 21 ml methyl alcohol was added to a solution of diphenyldiazo-methane (0.28 mol) dissolved in 50 ml CH_2Cl_2 and the reaction stirred for one hour. Dimethyl ether was then added to remove any unreacted

penicillanic reagent. The mixture was filtered and anhydrous HCl in diethyl ether added dropwise until a thick precipitate resulted. The solid was filtered and isolated in 78% yield. $^1\text{H-NMR}$, MS, and IR data supplied.

3. (2S,5S)-6-Diazo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid, diphenylmethyl ester, hydrochloride salt, 4,4-dioxide

The product from Step 2 (0.01 mol) was neutralized with 5% aqueous NaHCO_3 and extracted with 400 ml CH_2Cl_2 . The mixture was cooled to 0°C , NaNO_2 (0.0024 mol) dissolved in 400 ml water added, and 22.5 ml perchloric added portionwise. The mixture was stirred 2 hours at 0°C , the organic layer separated, washed three times with brine, water, dried and the product isolated in 90% yield. $^1\text{H-}$ and $^{13}\text{C-NMR}$, MS, and IR data supplied.

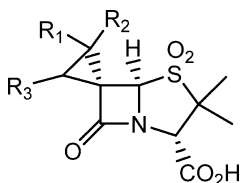
4. (2S,5R)-2-(Diphenylmethoxy)-3,3-dimethyl-7-spiro[cyclo-propane-1,6-[4]-thia-[1]azabicyclo[3.2.0]-heptane]-2-carboxylic acid, diphenylmethyl ester, 4,4-dioxide (General olefin insertion procedure)

At ambient temperature a solution of diphenylmethylvinyl ether (2 eq) dissolved in CH_2Cl_2 was added to a catalytic amount of rhodium acetate followed by the dropwise addition of 0.2 M CH_2Cl_2 solution of the product of Step 3. The mixture was stirred 2 hours, concentrated, and the purified by chromatography using silica gel.

5. (2S,5R)-2-(Diphenylmethoxy)-3,3-dimethyl-7-spiro[cyclo-propane-1,6-[4]thia[1]azabicyclo[3.2.0]-heptane]-2-carboxylic acid, 4,4-dioxide (General diphenylmethyl ester deprotection procedure)

A 0.2 M solution of the product from Step 4 dissolved in EtOAc was hydrogenated using 10% palladium on carbon at 45 lb/ft ^{2} hydrogen pressure 5 hours. Thereafter the mixture was filtered and treated with an equimolar amount of solid NaHCO_3 , then lyophilized to obtain the salt.

Derivatives



R_1	R_2	R_3	Yield (%) [3 Isomers]
t-Butoxide	Hydrogen	Hydrogen	55%
Allyl	Hydrogen	Hydrogen	54%
Phenyl	Phenyl	Methoxide	56%
Cyclohexyl	Hydrogen	Hydrogen	59%

Notes

1. Other methods using the Step 1 oxidant to prepare 6-amino-pencillanic acid-4,4-dioxide are provided (1).
2. The preparation of other spirocyclopropyl penicillanic derivatives is provided (2).
3. The Step 5 product isomers were separated by column chromatography on silica gel using a hexane gradient to 30% EtOAc/hexane.

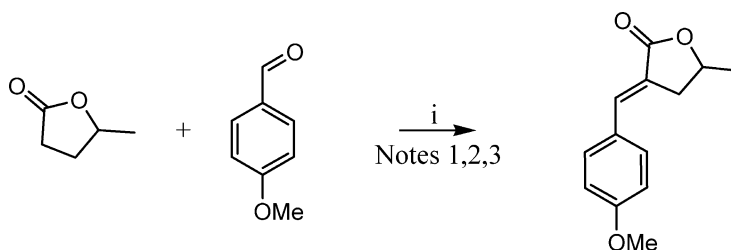
References

1. J.J. Bos *et al*, US Patent 4,695,628 (September 27, 1987)
2. J.C. Sheehan *et al*, J. Org. Chem., 43, 25, 4856 (1978); M.M. Campbell *et al*, Tetrahedron Lett., 16, 1441 (1971); and J.E. Arrowsmith *et al*, Tetrahedron, 39, 2469 (1983)

Lactones

Patent: Benzylidene- γ -Butyrolactones, Process for Their Preparation and Their Use as UV Absorbers
O. Koch *et al*, US Patent 6,258,963 (July 10, 2001)
Assignee: Haarmann & Reimer GmbH
Utility: Sunscreen in Cosmetics

Reaction



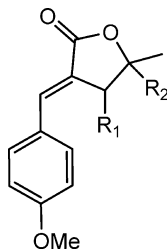
i- Sodium methoxide, methyl t-butyl ether

Experimental

1. 4-Methoxybenzylidene-4-methyl- γ -butyrolactone

To a suspension of sodium methoxide (0.5 mol) in 400 g methyl t-butyl ether was added 4-methyl- γ -butyrolactone (0.5 mol) and 4-methoxybenzaldehyde (0.5 mol) was added thereto over an hour. The mixture was refluxed one hour, cooled, and 200 g ice water added to the mixture while keeping the pH at about 5 using 10% sulfuric acid. The phases were separated and the product isolated in 48% yield by distillation.

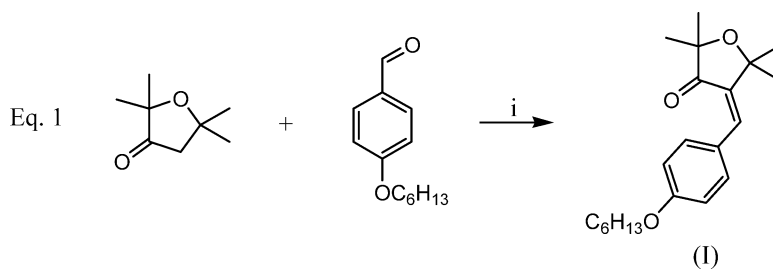
Derivatives



R_1	R_2	$E^{1/1}$	$\lambda_{\max}$
Hydrogen	Methyl	1,200	310
Ethyl	Butyl	940	312
Methyl	Hydrogen	1,050	314
Methyl	Butyl	810	312

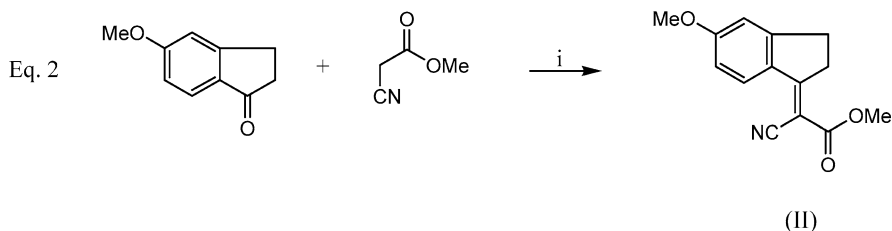
Notes

1. Structural isomers, (I), of the product of Step 1 have been prepared (1) as illustrated in Eq. 1:



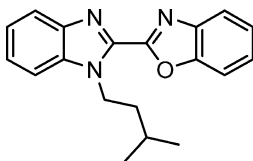
i- 1,2-Dimethoxyethane, sodium methoxide

2. Indanone derivatives, (II), were previously prepared by the author (2) and others (3) as illustrated in Eq. 2:



i- Propanoic acid, ammonium acetate

3. Benzimidazol-2-yl-benoxazole derivatives of the current invention have also been prepared, (III), (4).



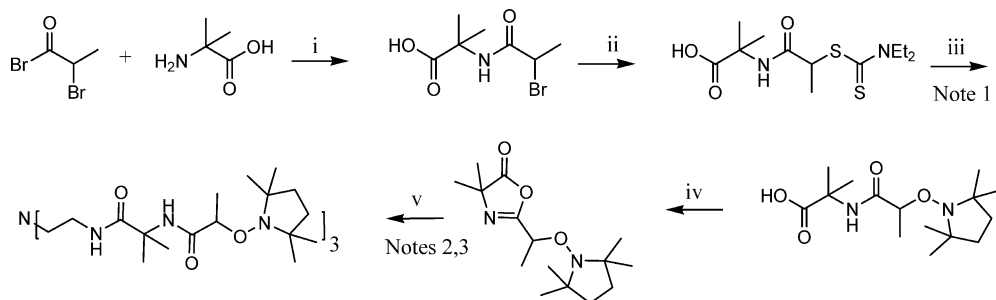
(III)

References

1. A. Lagrange *et al*, US Patent 5,217,709 (June 8, 1993)
2. O. Koch *et al*, US Patent 6,153,175 (November 28, 2000)
3. E. Dilk *et al*, US Patent 5,961,960 (October 5, 1999)
4. O. Koch *et al*, US Patent 5,965,066 (October 12, 1999)

Patent: Ring-Opened Azlactone Initiators for Nitroxide-Mediated Polymerization
D.D. Fansler *et al*, US Patent 6,680,362 (January 20, 2004)
Assignee: 3M Innovative Properties Companies
Utility: Azo-polymerization Initiators

Reaction



- i- Sodium hydroxide, water, chloroform
- ii- Acetone, sodium diethylthiocarbamate trihydrate
- iii- 2,2,6,6-tetramethylpiperidinyloxy, EtOAc, UV irradiation
- iv- TEA, acetone, ethyl chloroformate
- v- Tris(2-aminoethyl)amine, THF

Experimental

1. 2-(2-Bromopropionylamino)-2-methylpropionic acid

2-Aminoisobutyric acid (0.51 mol), NaOH (0.51 mol), 200 ml water and 50 ml chloroform were mixed then cooled to -12°C and 2-bromopropionyl bromide (0.46 mol) dissolved in 150 ml chloroform added. The mixture warmed to ambient temperature and the product isolated by filtration in 70% yield.

2. Diethylthiocarbonylsulfanylpropionylamino-2-methylpropionic acid

The product from Step 1 (0.021 mol) dissolved in 100 ml acetone was then added to sodium diethylthiocarbamate trihydrate (0.021 mol), stirred 17 hours, and the product isolated by filtration in 78% yield.

3. 2-Methyl-2-[2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-propionylamino]-propionic acid

The product from Step 2 (0.0132 mol), TEMPO (0.0132 mol) and 35 ml EtOAc were stirred 20 minutes and irradiated with a 350 nm UV lamp 65 hours. The mixture was concentrated and the product isolated by filtration in 42% yield.

4. **4,4-Dimethyl-2-[2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-ethyl]-4H-oxazol-5-one**

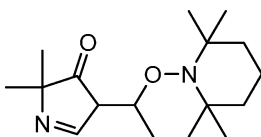
The product from Step 3 (0.0016 mol), TEA (0.0016 mol), and 5 ml acetone were added to ethyl chloroformate (0.0016 mol), stirred two hours, then concentrated. The product was extracted using hexane and isolated in 64% yield.

5. **N-{2-[Bis-(2-methyl-2-[2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-propionylamino]-propionylamino)-ethyl]-amino}-ethyl-2-methyl-2-[2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-propionylamino]-propionamide**

The product from Step 4 (0.00067 mol) and tris(2-aminoethyl)amine (0.00022 mol) in 2 ml THF was stirred 30 minutes and the product isolated in 51% yield.

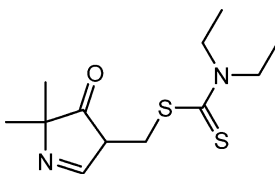
Notes

1. UV irradiation was performed using a Sylvania 350 Blacklight E15T8/350BL lamp.
2. Nitroxide mediated free radical polymerization is a 'living' or controlled polymerization process. It can be used to initiate or terminate polymerization reactions as needed (1). The use of Phosphino, aryloxy, silyl, boryl and seleno mediating agents are described (2).
3. Step 4 and Step 5 products were used by the author to prepare low molecular weight three-arm star styrene oligomers and are described in the current invention.
4. In a subsequent investigation, the author, (3), prepared the nitroxide-mediated polymerization agent, 4,4-dimethyl-2-[1-(2,2,6,6-tetramethylpiperidin-1-yloxy)-ethyl]-4H-oxazol-5-one, (I), as a method of preparing telechelic polymers.



(I)

5. The thio-nitroxide mediated polymerization agent, diethyl-dithiocarbamic acid 4,4-dimethyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl ester, (II), has also been prepared as an azlactone photoiniferters for controlled radical polymerizations (4).



(II)

References

1. F. Shirley, Chem. Rev., 3661 (2001)
2. G. Klaerner *et al*, US Patent 6,472,486 (October 29, 2002)
3. D.D. Fansler *et al*, US Patent 6,784,265 (August 31, 2004)
4. M.S. Wendland *et al*, US Patent 6,818,716 (November 16, 2004)

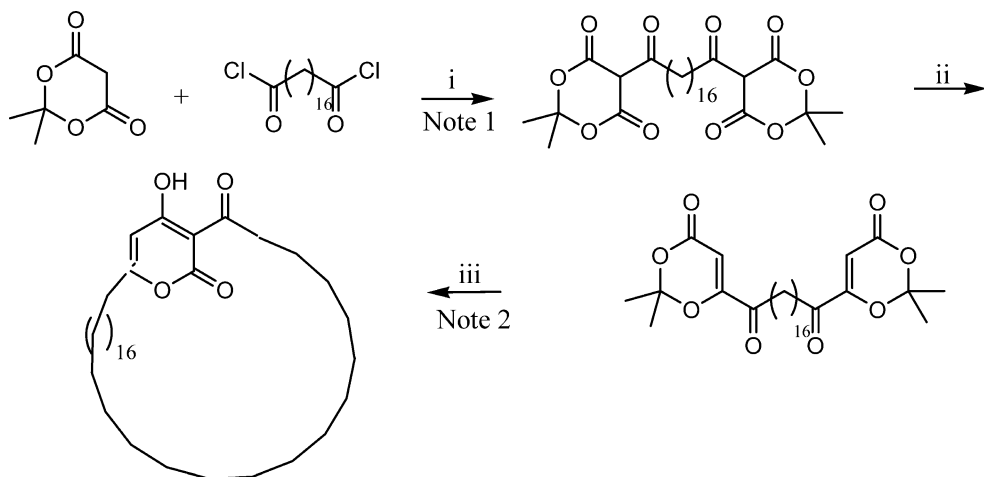
Macocyclic Rings

Patent: β -Diketone Compounds, β -Diketone Compounds Coordinated to Metal, Method of Organic Synthesis with These, and Catalyst
M. Yamaguchi *et al*, US Patent 6,303,796 (October 16, 2001)

Assignee: Chisso Corporation

Utility: Catalyst Co-component in Asymmetric Synthesis

Reaction



- i- CH_2Cl_2 , pyridine, octadecyl-1,18-dicarboxylic acid dichloride
- ii- Acetone, toluene
- iii- Chlorobenzene

Experimental

1. 1,18-Di-[3-(2,2-Dimethyl-1,3-dioxane-4,6-dione)-octadecyl)]-dione

2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (0.10 mol) and pyridine (0.25 mol) were dissolved in 200 ml CH_2Cl_2 and the mixture cooled with ice. Octadecyl-1,18-dicarboxylic acid dichloride (0.05 mol) dissolved in 50 ml CH_2Cl_2 added over 15 minutes, and the reaction mixture stirred 30 minutes while being kept cool with ice. The mixture was then treated with 100 ml apiece 10% HCl and CH_2Cl_2 and solvent removed under reduced pressure at ambient temperature. Thereafter, precipitated crystals were isolated by filtration, re-crystallized using CH_2Cl_2 /diethyl ether, 1:5, and the product isolated, MP = 96–98 °C. ^1H - and ^{13}C -NMR data supplied.

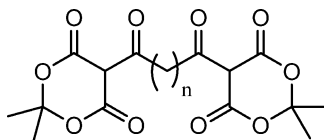
2. 1,18-Di-[4-(2,2-Dimethyl-3-(2H)pyran-4-one)-octadecyl)]-dione

The product from Step 1 (0.025 mol) and acetone (0.05 mol) were dissolved in 80 ml toluene and refluxed 1 hour. The crude product was isolated, purified by chromatography on silica using hexane/EtOAc, 3:1, and the product isolated, MP = 52–54 °C. ^1H - and ^{13}C -NMR data supplied.

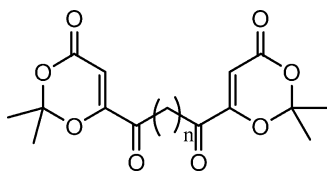
3. 2-Hydroxy-1,3-dien-1-(1-oxy-1,4-hepadecyl)-1-carboxy-[17.2.1]dodecane (General Procedure)

The product from Step 2 (1.0 mmol) was dissolved in 10 ml chlorobenzene and added dropwise to 250 ml refluxing anhydrous chlorobenzene over 20 hours. Thereafter, the mixture was refluxed an additional 30 minutes and the solvent removed to obtain an oily product. The product was distilled under reduced pressure and the product isolated as either an oil or crystal. ^1H - and ^{13}C -NMR data supplied.

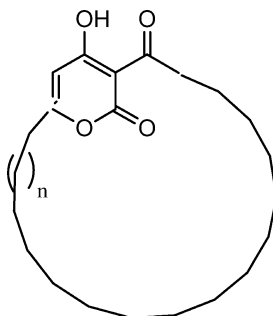
Derivatives



n	Yield (%)	Mp(°C)
6	76	94–98
8	74	88–89
10	75	90–91
12	70	89–91
16	87	96–98
18	83	100–102



n	Mp(°C)
6	54–55
8	42–46
10	25–26
12	28–29
16	54–55
18	62–62



n	Mp(°C)
8	oil
10	73–75
12	62–65
16	oil
18	oil

Notes

1. Method for preparing optically active 2,2-dimethyl-1,3-dioxin-4-ones are described (1).
2. Optically active macrocyclics were prepared in two methods. In Method-1, the product from Step 3 was converted to an imine using (R)-1-phenylethylamine and separated by chromatography [Procedure-1]. In Method-2 the optically active imines were hydrolyzed by base into the optically active β -diketone cyclophane enantiomers [Procedure-2] and then isolated by chromatography.

Procedure-1

Optically Active Imine Cyclophane

The racemic mixture of the product of Step 3 and (R)-1-phenyl-ethylamine (5.0 mmol) were dissolved in 30 ml benzene and the solution refluxed one hour. The resultant reaction mixture was subjected to silica gel column chromatography using hexane/EtOAc, 5:1, and the imines separated.

*Procedure-2*Optically Active β -Diketone Cyclophane (General procedure)

Potassium hydroxide (4.0 mmol) dissolved in 4 ml water was added to an optically active imine (1.0 mmol) dissolved in 5 ml THF and the mixture stirred at ambient temperature 20 hours. Thereafter, 2 ml 10% HCl was added, the solution made acidic, and the mixture extracted with diethyl ether. The organic layer was washed with brine, dried, concentrated, the residue either recrystallized from pentane or purified by chromatography using hexane/EtOAc, 10:1, and the product isolated.

2. A transition metal complex consisting of titanium tetrachloride and β -diketone cyclophane where $n = 10$ has been prepared and is described (2).
3. The preparation of other macrocycles analogous to those of the current invention are provided (3,4).

References

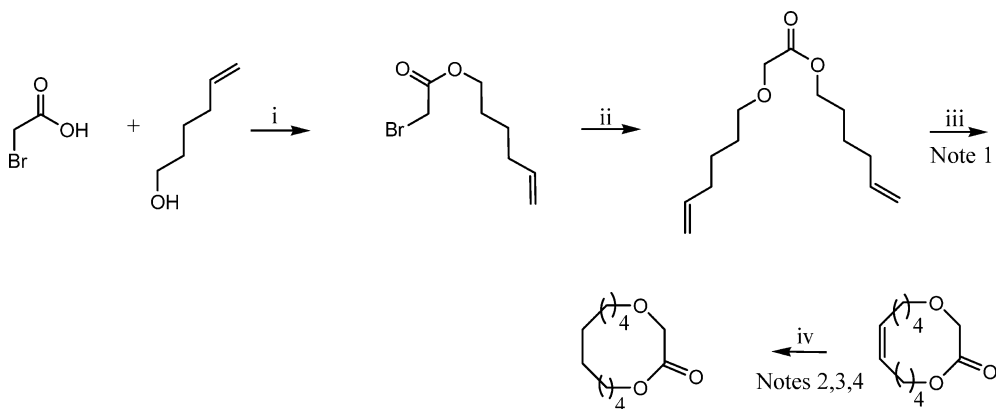
1. C. Kaneko *et al*, US Patent 5,256,800 (October 26, 1993)
2. N. Kanomata *et al*, Angew. Chem. Int. Ed. Engl., 36, 1207 (1997)
3. S. Sata *et al*, Tetrahedron, 47, 30, 5689 (1991)
4. A. Marciano *et al*, J. Am. Chem. Soc., 112, 20, 7320 (1990)

Patent: 1,4-Dioxacylcycloalkane-2-one and 1,4-Dioxacylcycloalkene-2-one
M. Eh *et al*, US Patent 6,573,391 (June 3, 2003)

Assignee: Haarmann & Reimer GmbH

Utility: Fragrances and Perfumes

Reaction



- i- Dimethylamino pyridine, CH_2Cl_2 ,
1,2-dicyclohexylcarbodiimide
- ii- THF, sodium hydride, 5-hexen-1-ol
- iii- Bis(tricyclohexylphosphine)dichloro
ruthenium(II)benzylidene, titanium tetraisopropoxide, CH_2Cl_2
- iv- Palladium on carbon, isopropyl alcohol, hydrogen

Experimental

1. Hex-5-enyl-2-bromoacetate

To 30 ml CH_2Cl_2 was added bromoacetic acid (3 mmol), dicyclohexylcarbodiimide (30 mmol), 4-dimethylaminopyridine (3 mmol) and 5-hexen-1-ol and the mixture stirred overnight at ambient temperature. The mixture was filtered and the filtrate concentrated. The concentrate was dissolved in pentane, washed, and used without further purification.

2. Hex-5-enyl-2-(5-hexenyloxy)-acetate

To 25 ml THF was added 5-hexen-1-ol (34 mmol) and NaH (28 mmol) suspended in 20 ml THF followed by the dropwise addition of the product from Step 1 (23 mmol) dissolved in 15 ml THF and the mixture refluxed overnight. Thereafter 2 M HCl was added and the product was extracted once with diethyl ether and twice with EtOAc. The crude product was purified by chromatography on silica gel using cyclohexane/EtOAc, 40:1, and isolated in 67% yield.

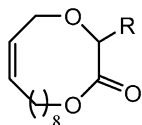
3. 1,4-Dioxa-(E/Z)-9-cyclotetradecen-2-one (General olefin metathesis procedure)

The product from Step 2 (0.7 mmol) was dissolved in 220 ml CH_2Cl_2 , $\text{Ti}(\text{O}-i\text{Pr})_4$ (0.21 mmol) added, and the mixture refluxed one hour. Thereafter, bis(tricyclohexylphosphine)dichlororuthenium(II)benzylidene (0.02 mmol) dissolved in 5 ml CH_2Cl_2 was added and the mixture refluxed 20 hours. The reaction was cooled, washed twice with 50 ml 1 M HCl, dried, and filtered over a short silica gel column. The solvent was removed by rotary evaporator and the product isolated as a colorless oil.

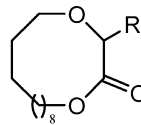
4. 1,4-Dioxacyclotetradecan-2-one (General hydrogenation procedure)

Hydrogenations were carried out by dissolving the product from Step 3 (1 mmol) in 10 ml isopropyl alcohol containing palladium on carbon (12 mg) at ambient temperature and atmospheric pressure. After 3 hours the mixture was filtered through Celite, purified by flash chromatography on silica using cyclohexane/diethyl ether, 30:1, and the product isolated.

Derivatives (Note 1)



R	Yield (%)
Methyl	95
Hydrogen	62
Allyl	52



R ₁	Yield (%)
Hydrogen	—
Methyl	74

Notes

1. Attempts to prepare macrocyclic compounds where both olefinic alcohols had chain lengths greater than 12 were unsuccessful because of competing oligomerization reactions (1).
2. ^1H - and ^{13}C -NMR provided for all products.
3. Other Metathesis catalysts useful in the presence of polar functional groups are reviewed (2).
4. The preparation of macrocyclic lactones by metathesis coupling reactions is described (3).

References

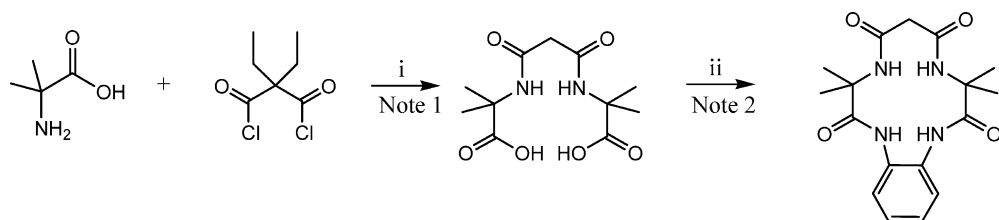
1. C.J. Roxbury, *Tetrahedron*, 51, 9767 (1995); G. Illuminati *et al*, *Acc. Chem. Res.*, 14, 95 (1981)
2. R.H. Grubbs *et al*, *Science* 243, 907, 915 (1989)
3. A.G. Van Loveren *et al*, US Patent 4,490,404 (December 25, 1984)

Patent: Synthesis of Macrocyclic Tetraamido-N Ligands
S.W. Gordon-Wylie *et al*, US Patent 6,011,152 (January 4, 2000)

Assignee: Carnegie Mellon University

Utility: Ligands for Oxidizing Complexes

Reaction



i- Pyridine

ii- 1,2-Diaminobenzene, pyridine, phosphorous trichloride

Experimental

1. 1,3-N,N'-(2,2-Dimethylacetic acid)malamide (Macrolinker)

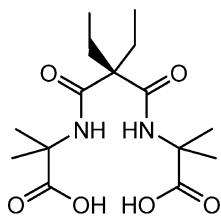
α -Amino isobutyric acid (0.2 mol) was dissolved in 250 ml pyridine, heated to 65 °C, and diethyl malonyl dichloride (0.135 mol) dissolved in 100 ml pyridine added dropwise over one hour. Thereafter the reaction mixture was heated 36 hours, quenched with 30 ml water, and stirred 24 hours. The solvent was removed and an oil isolated. The oil was treated with 25 ml 12 M HCl to obtain a final pH of 2–3. The mixture was placed in a refrigerator 15 hours, the resulting tar washed twice with 100 ml acetonitrile, and a solid white product isolated in 55% yield. ^1H -NMR and IR data supplied.

2. 1,2-Phenylene-3,6,10,13-tetraazatricyclodecane-4,9-dimethyl-3,6,8,11-tetra-one

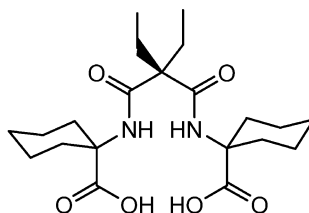
The product from Step1 (10 mmol) was dissolved in 50 ml pyridine and 1,2-benzene diamine (10 mol) added. The mixture was heated to 55 °C, PCl_3 (20 mmol) quickly added, and the mixture heated to 110–115 °C 48 hours. Thereafter, the contents were acidified with HCl to a final pH $\sim$ 2. The mixture was stirred with 300 ml CH_2Cl_2 3 hours, extracted twice with 150 ml CH_2Cl_2 , and dried. The combined organics were washed with twice 100 ml 0.1 M HCl and then dilute Na_2CO_3 . Solvents were removed and the crude product re-crystallized in 95% ethyl alcohol. ^1H - and ^{13}C -NMR and IR data supplied for products.

Notes

1. Tetramethyl diethyl, (I), and dicyclohexyl diethyl, (II), macrolinkers were also prepared in 60–65% and 70–75% yields, respectively, by the author.

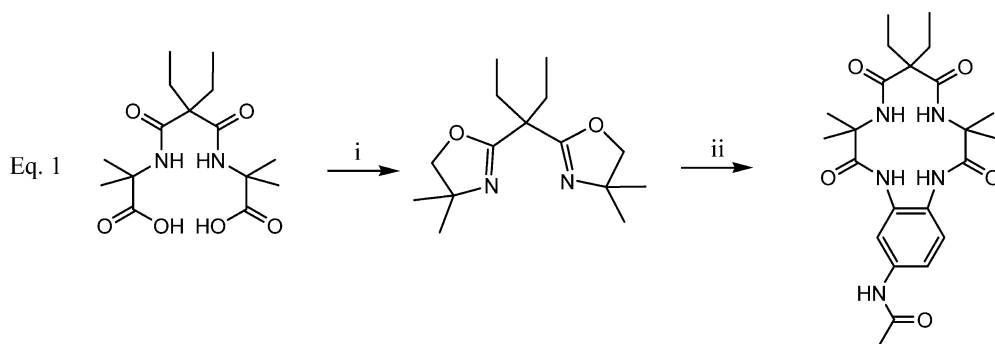


(I)



(II)

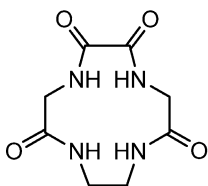
2. Another ring closure method entails converting the macrolinker intermediate into the corresponding di-oxazolone by refluxing with isobutyryl chloride and then reacting with 1,2-diamine-4-acetamide dihydrobromide as illustrated in Eq. 1 and discussed by the author.



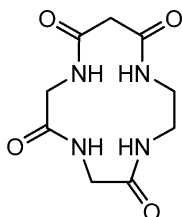
i- Isobutyryl chloride, pyridine

ii- 1,2-diamine-4-acetamide dihydrobromide

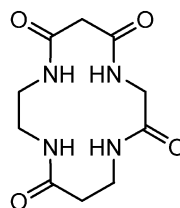
3. Non-aromatic macrocycles were also prepared by the author for ring sizes 12, (III), 13, (VI), and 14, (V), respectively.



(III)

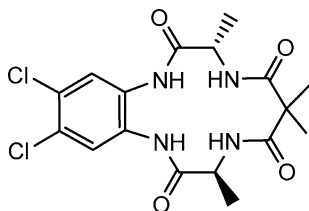


(VI)



(V)

4. In subsequent investigations (1, 2) macrocyclics were converted into macrocyclic metallic complexes. A particularly long-lived homogenous oxidation catalyst substrate, (VI), has been prepared and is described (3).



5. Tetra-N-isopropyl oxamide derivatives of the current invention have been prepared (4).

References

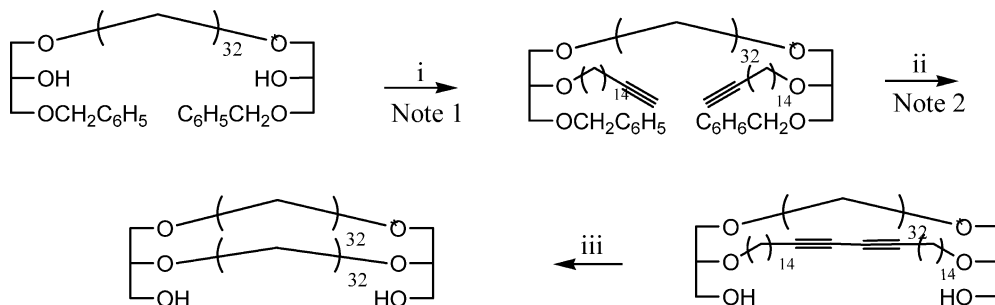
1. T.J. Collins *et al*, US Patent 6,054,580 (April 25, 2000)
2. D. Parker *et al*, US Patent 5,247,075 (September 21, 1993)
3. T.J. Collins *et al*, US Patent 5,847,120 (December 8, 1998)
4. G.P. Speranza *et al*, US Patent 5,298,618 (March 29, 1994)

Patent: The Preparation of Giant Ring Compounds
F.M. Menger, US Patent 5,391,726 (February 21, 1995)

Assignee: The Dow Chemical Company

Utility: Macrocyclic Lipids for Drug Delivery Agents

Reaction



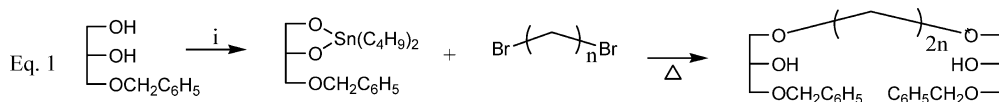
- i- THF, sodium hydride, 15-hexadecyn-1-yl-methanesulfonate
 ii- Xylene, tetramethylethylenediamine, copper(I)chloride, oxygen
 iii- 10% Palladium on carbon, THF, ethyl alcohol, hydrogen

Experimental

- 1,1'-(1,32-Dotriacontamethyleneoxy-2,2'-bis(hexadeca-15-yne)-3,3'-bis-benzylether**
 1,1'-Dotriacontamethylene-3-benzyl-glycol (1.1 mmol) was added to 10 ml THF and stirred with NaH (4.2 mmol) 2 hours. Thereafter, 15-hexadecyn-1-yl-methanesulfonate (2.6 mmol) was added and the mixture refluxed 48 hours. When cooled the solution was filtered through a short alumina column and concentrated. The product was purified by chromatography on silica using hexane/EtOAc, 10:1, and the product isolated in 64% yield.
- 1,1'-(1,32-Dotriacontamethylene-1,32-oxy)-2,2'-(1,32-dotriacontamethylene-14,17-di-yne-1,32-oxy)-3,3'-glycol**
 The product from Step 1 (0.63 mmol) was dissolved in 200 ml xylene to which was added 1.64 mmol apiece CuI and TMEDA. The mixture was reacted and purified as in Step 1 and the product isolated in 51% yield. ¹H- and ¹³C-NMR data supplied.
- 1,1'-(1,32-Dotriacontamethylene-1,32-oxy)-2,2'-(1,32-dotriacontamethylene-1,32-oxy)-3,3'-glycol**
 The product from Step 2 (0.22 g) was dissolved in 10 ml THF/ethyl alcohol, 4:1, and hydrogenated using 10% palladium on carbon at atmospheric pressure at 50°C. The product was re-crystallized from hexane/ethyl alcohol, 1:1, and isolated in 50% yield. FABMS data supplied.

Notes

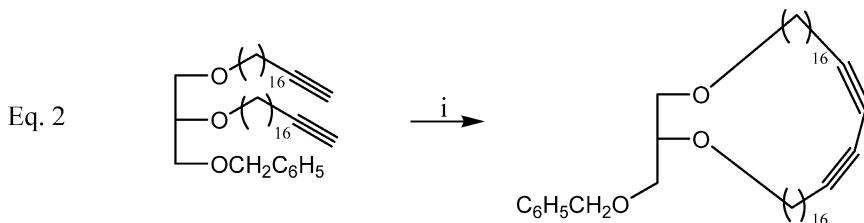
1. The reagent of Step 1 was provided by the author and illustrated in Eq. 1:



i- Dibutyltinoxide, toluene

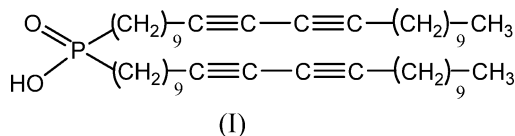
2. The cyclic coupling of alkynes of the current invention is a modified Glasser reaction and is described (1).

3. A method for preparing 1,4-oxy-3-benzoylmethyl-21,23-yne-cyclotetracontane by intra-alkyne coupling was also provided by the author as illustrated in Eq. 2:



ii- Xylene, copper(I)chloride, tetramethylethylenediamine, oxygen

4. Phospholipid analogues, (I), of the current invention have been prepared (3) and are discussed.



5. Other methods for preparing macrocyclic ethers are described (4,5).

References

1. F. Sondheimer, *Acc. Chem. Res.*, 15, 96 (1982)
2. H. Herbert *et al*, *J. Org. Chem.*, 57, 1777 (1992)
3. J. Klaveness *et al*, US Patent 5,536,490 (July 16, 1996)
4. J. DeRosa *et al*, *J.C.S. Chem. Comm.*, 12, 543 (1974)
5. H. Mori *et al*, US Patent 5,221,796 (June 22, 1993)

Morpholines

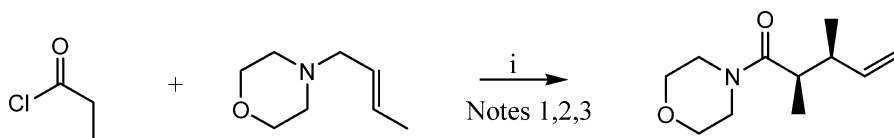
Patent: Lewis Acid-Catalyzed Claisen Rearrangements in the Preparation of Chiral Products

D.W.C. MacMillan *et al*, US Patent 6,359,174 (March 19, 2002)

Assignee: The Regents of the University of California

Utility: Method of Preparing Enantioselective Acylated Morpholine Derivatives

Reaction



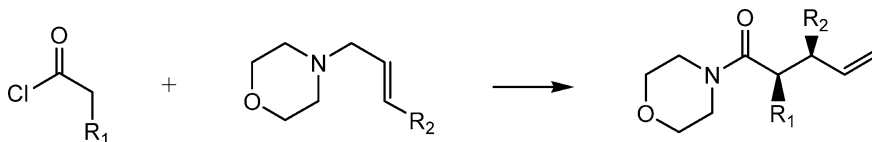
i- Titanium tetrachloride · 2THF, CH₂Cl₂,
di-isopropylethylamine

Experimental

1. (2S, 3S)-(2,3-Dimethyl-4-pentenoyl)morpholine

A reactor was charged with (E)-N-butenyl morpholine (0.81 mmol), titanium tetrachloride · 2THF (8 μmol), di-isopropylethylamine (1.22 mmol), propionyl chloride (0.98 mmol), and 8.1 ml CH₂Cl₂ and the mixture stirred until the allylic morpholine was consumed as determined by TLC. Thereafter, the mixture was diluted with an equal volume of diethyl ether, washed with aqueous 1 M NaOH, dried, and the product isolated by chromatography on silica gel using diethyl ether in 92% yield. ¹H- and ¹³C-NMR and HRMS (FAB) data supplied.

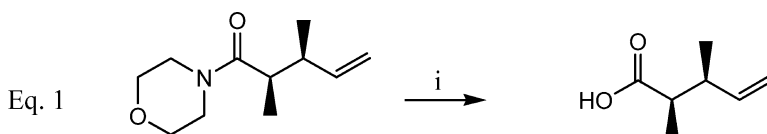
Derivatives



R ₁	R ₂	Yield (%)	Syn:Anti Ratio
Methyl	Phenyl	76	>99:1
Methyl	Chloro	95	99:1
Methyl	Methyl	92	>99:1
Thiophenyl	Methyl	81	92:8
Benzoxo	Chloro	84	90:10

Notes

1. The key reaction intermediate is an insitu alkyl ketene generated by the dehydrohalogenation of the acid chloride and is described (1).
2. In a subsequent investigation by the author tandem Claisen reactions were performed using di-allylic morpholines with acid chlorides (2).
3. To assay the product of Step 1, the reaction product was converted into (2*S*, 3*S*)-2, dimethyl-4-pentenoic acid and compared with the standardized acid sample (3). The conversion reaction is illustrated in Eq. 1:



i- Iodine, 1,2-dimethoxyethane, water, zinc, acetic acid, hydrochloric acid

4. Other Claisen rearrangements using organometallics are described (4).

References

1. M. Malherbe *et al*, J. Org. Chem., 48, 6, 860 (1983)
2. D.W.C. MacMillan, US Patent 6,552,226 (April 22, 2003)
3. H. Metz, Tetrahedron, 49, 6367 (1993)
4. M. Takai *et al*, Tetrahedron Lett., 22, 40, 3985 (1981)

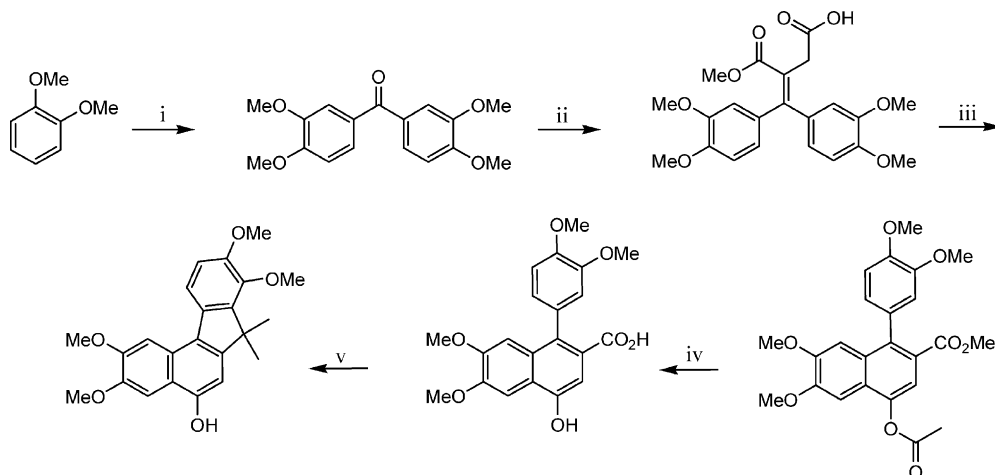
Naphthopyrans

Patent: Indeno-fused Photochromic Naphthopyrans
C.M. Nelson *et al*, US Patent 6,296,785 (October 2, 2001)

Assignee: PPG Industries Ohio, Inc.

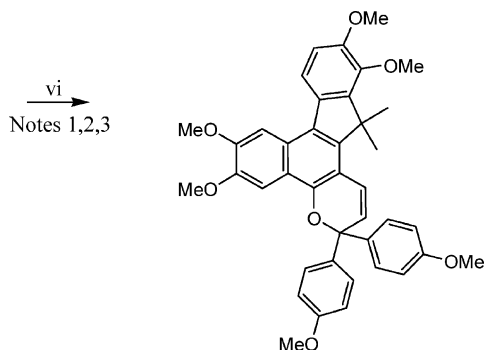
Utility: Photosensitive Ophthalmic Plastic Lenses

Reaction



(con't)

- i- 3,4-Dimethoxybenzoyl chloride, CH_2Cl_2 , aluminum chloride
- ii- Potassium t-butoxide, toluene, dimethyl succinate
- iii- Acetic anhydride, toluene
- iv- Hydrochloric acid, methyl alcohol
- v- Methyl magnesium chloride, dodecylbenzene sulfonic acid, THF



vi- 1,1-Di(4-methoxyphenyl)-2-propyn-1-ol, dodecyl-benzene
sulfonic acid

Experimental

1. 3,3',4,4'-Tetramethoxybenzophenone

To 1,2-dimethoxybenzene (74.5 g) was added 3,4-dimethoxy-benzoyl chloride (98.2 grams) dissolved in 500 ml CH_2Cl_2 , AlCl_3 (71.8 g) added, and the mixture stirred 3 hours at ambient temperature. Thereafter, the mixture was poured into 300 ml of a 1:1 mixture of ice and 1 M HCl and stirred vigorously 15 minutes. The mixture was extracted twice with 100 ml CH_2Cl_2 and washed with 50 ml of 10% NaOH followed by 50 ml water. The solvent was removed, a yellow solid isolated and re-crystallized in 95% ethyl alcohol, and 127 g product isolated, mp = 146–147 °C.

2. 4,4-Di(3,4-dimethoxyphenyl)-3-methoxycarbonyl-3-butenic acid

Potassium t-butoxide (55.4 g) and the product from Step 1 (100 g) dissolved in 600 ml of toluene were refluxed, dimethyl succinate (193 g) added over 1 hour, and the mixture refluxed 5 hours. Once cooled to ambient temperature a precipitate formed and was collected by filtration. The solid was washed with fresh toluene and 143 g crude product obtained. The material was dissolved in 200 ml water, acidified to pH 2 with 4 M HCl, extracted 5 times with 50 ml CH_2Cl_2 , and 102 g product isolated as a brown oil.

3. 1-(3,4-Dimethoxyphenyl)-2-methoxycarbonyl-4-acetoxy-6,7-dimethoxynaphthalene

A mixture consisting of the product from Step 2 (100 grams), 60 ml acetic anhydride, and 300 ml toluene were heated to 110 °C 6 hours, cooled to ambient temperature, and concentrated. The residue was dissolved in 300 ml CH_2Cl_2 , and 200 ml water containing NaHCO_3 added until CO_2 evolution ceased. The layers were separated, the aqueous layer extracted twice with 50 ml CH_2Cl_2 , combined with the organic phase, concentrated, re-crystallized in methyl alcohol, and 38.9 g product isolated, mp = 176–177 °C.

4. 1-(3,4-Dimethoxyphenyl)-2-methoxycarbonyl-4-hydroxy-6,7-dimethoxynaphthalene.

A mixture consisting of the product from Step 3 (5 grams), 5 ml 12 M HCl, and 30 ml methyl alcohol were refluxed 1 hour then cooled. A precipitate formed and was isolated

by vacuum filtration, washed with cold methyl alcohol, and 2.1 g product isolated, mp = 213–214°C.

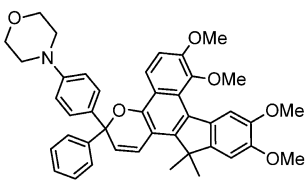
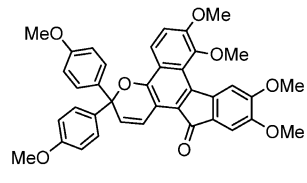
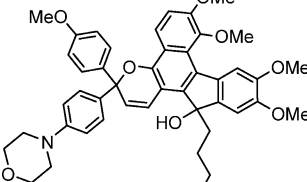
5. 7,7-Dimethyl-5-hydroxy-2,3,9,10-tetramethoxy-7H-benzo[c]fluorene

The product from Step 4 (0.9 grams) was dissolved in 20 ml THF, cooled in a dry ice/acetone bath, 9 ml 1 M methyl magnesium chloride added dropwise over 15 minutes, and the mixture stirred for 2 hours and at 0°C. Once warmed to ambient temperature, it was poured into a 50 ml ice water mixture, 20 ml diethyl ether added, and the layers separated. The aqueous layer was extracted twice with 20 ml diethyl ether, the organic portions combined, and concentrated. The residue was dissolved in 50 ml toluene containing 2 drops of dodecylbenzene sulfonic acid, refluxed 2 hours, cooled, and 0.73 g product isolated.

6. 3,3-Di(4-methoxyphenyl)-6,7,10,11-tetramethoxy-13,13-dimethyl-3H,13H-indeno[2,1-f]naphtho[1,2-b]pyran

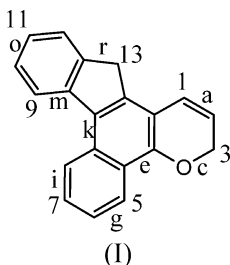
The product from Step 5 (450 mg), 1,1-di(4-methoxyphenyl)-2-propyn-1-ol (345 mg), 2 drops of dodecylbenzene sulfonic acid, and 15 ml toluene were mixed then stirred at ambient temperature for 4 hours. Thereafter 15 ml apiece toluene and water were added, the organic layer isolated, dried, concentrated, and 289 mg product obtained by chromatography on a silica gel using chloroform, mp = 213–214°C.

Derivatives

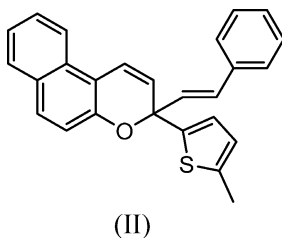
Naphthopyran Derivative	MP (°C)
	195–197
	249–250
	251–252

Notes

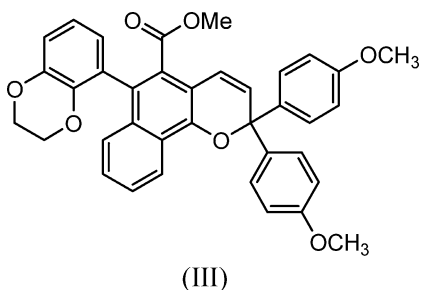
1. The position of ring atoms in naphthopyran, (I), is provided.



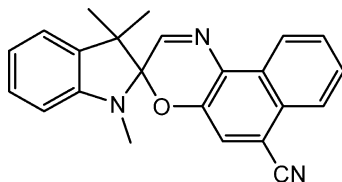
2. 3-(2,6-Difluorophenyl)-3(4-methoxyphenyl)-3H-naphtho[2,1-b]-pyran and other photochromatic derivatives have been prepared by others and are described (1).
3. Thienyl derivatives of the current invention including 3-(5-methyl-2-thienyl)-3-(2-phenylvinyl)-3H-naphtho[2,1-b]pyran, (II), have been prepared and are discussed (2).



4. In a subsequent investigation by the author (3) 2,2-diphenyl-5-methoxycarbonyl-6-phenyl-2H-[1,3]dioxolo[4', 5':8,9]naphtha-[1,2-b]pyran, (III), was prepared.



5. 6'-Cyano-1,3,3-trimethylspiro[indoline-[2,3']][3H]naphth-[2,1-b][1,4]-oxazin, (IV), has also been prepared and is described (4).



(III)

References

1. B. VanGemert *et al*, US Patent 5,066,818 (November 19, 1991)
2. B. VanGamert *et al*, US Patent 5,274,132 (December 28, 1993)
3. C.M. Nelson *et al*, US Patent 6,348,604 (February 19, 2002)
4. P. Lareginie *et al*, US Patent 5,936,016 (August 10, 1999)

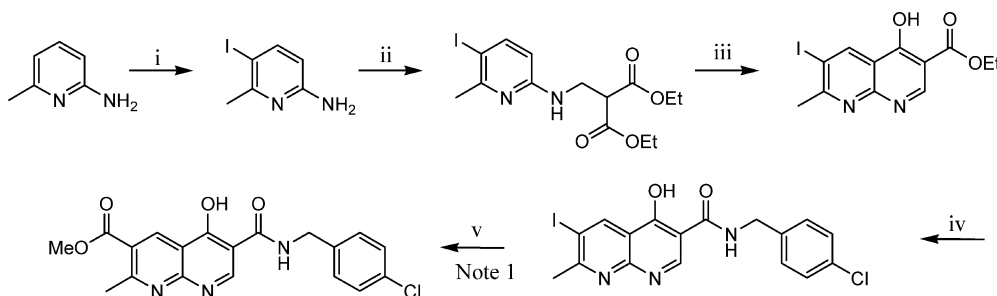
Naphthyridines

Patent: 4-Hydroxy-1,8-Naphthyridine-3-Carboxamides as Antiviral Agents
V.A. Vaillancourt, US Patent 6,413,958 (July 2, 2002)

Assignee: Pharmacia & Upjohn Company

Utility: Treatment of Herpes Simplex Viruses

Reaction



i- Iodine, periodic acid, acetic acid, sulfuric acid

ii- Diethyl ethoxymethylenemalonate

iii- Diphenyl ether

iv- 4-Chlorobenzylamine

v- N,N-Dimethylformamide, triethylamine, methyl alcohol,
di(triphenylphosphine)palladium dichloride, carbon monoxide

Experimental

1. 2-Amino-5-iodo-picoline

A mixture of 2-aminopicoline (5.4 g), periodic acid (2.28 g) and iodine (5.00 g) were heated in 30 ml HOAc, 6 ml water and 0.9 ml H₂SO₂ to 80 °C 3 hours. The reaction

was cooled, poured into 100 ml 10% NaHSO₃, extracted 3 times with 100 ml diethyl ether, and dried. The product was purified by chromatography using EtOAc and a yellow liquid isolated. It was further dried by vacuum drying and crystals isolated in 38% yield. ¹H-NMR data provided.

2. Diethyl-[[[(5-iodo-6-methyl-2-pyridinyl)amino]methylene]malonate

The product from Step 1 (4.48 g) and diethyl ethoxymethylenemalonate (4.25 ml) were heated to 95 °C 2 hours and the reaction cooled. The intermediate solid was treated with 20 ml hexanes, filtered, and the product isolated in 83% yield, mp = 138–139 °C. ¹H-NMR, IR, and MS data supplied.

3. Ethyl-4-hydroxy-6-iodo-7-methyl[1,8]naphthyridine-3-carboxylate

The product from Step 2 (1.09 g) was heated to 250 °C in diphenyl ether 2 hours, cooled, and 15 ml hexanes added to the solid. The crushed solid was dissolved in CH₂Cl₂/methyl alcohol and the product purified by chromatography on silica gel using 1 L CH₂Cl₂, 1 L 1% methyl alcohol/CH₂Cl₂, and 1 L 2% methyl alcohol/CH₂Cl₂. Thereafter, the product was isolated in 52% yield, mp = 275–277 °C (dec). ¹H-NMR, IR, and MS data supplied.

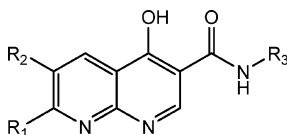
4. N-(4-Chlorobenzyl)-4-hydroxy-6-iodo-7-methyl[1,8]naphthyridine-3-carboxamide

The product from Step 3 (0.41 g) and 4-chlorobenzylamine were heated to 180 °C 1 hour, cooled, and the product extracted with 10 ml EtOAc and 20 ml hexanes. Following the Step 3 purification procedure, the product was isolated in 58% yield, mp = 276–277 °C. ¹H-NMR, IR, and MS data supplied.

5. Methyl 6-[[[(4-chlorobenzylamino)]-4-carbonyl]5-hydroxyl-2-methyl[1,8]naphthyridine-3-carboxylate

The product from Step 4 (0.26 g), 5 ml DMF, 0.16 ml NEt₃, 0.92 ml methyl alcohol and ditriphenylphosphine palladium dichloride were mixed, placed under a carbon monoxide/hydrogen balloon, and heated to 70 °C 24 hours. The reaction was then poured into 40 ml 1 M HCl, the solid isolated, and dissolved in CH₂Cl₂/methyl alcohol. Following the purification procedure of Step 3, the product was isolated in 59% yield, mp = 265–267 °C. ¹H-NMR, IR, and MS data supplied.

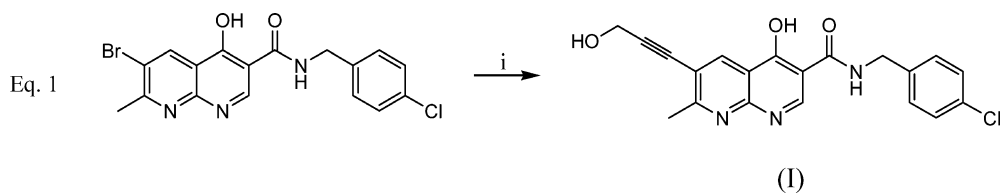
Derivatives



R ₁	R ₂	R ₃	MS (M+H)	Melting Point (°C)
Methyl	3-Propargyl alcohol	Benzyl	381.9	279–281
Hydrogen	Bromine	Benzyl	—	269–270
Methyl	Hydrogen	4-Chlorobenzyl	327	280–285 (dec)
Hydrogen	Iodine	4-Chlorobenzyl	253	276–277

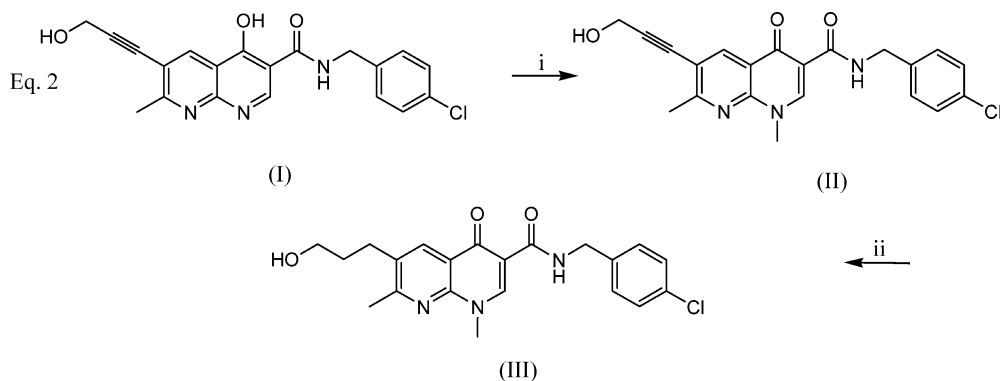
Notes

- By reacting propargyl alcohol with the bromine analogue of the product of Step IV, N-(chlorobenzyl)-4-hydroxy-6-(3-hydroxy-1-propynyl)-7-methyl-[1,8]naphthyridine-3-carboxamide, (I), was also prepared by the author as illustrated in Eq. 1:



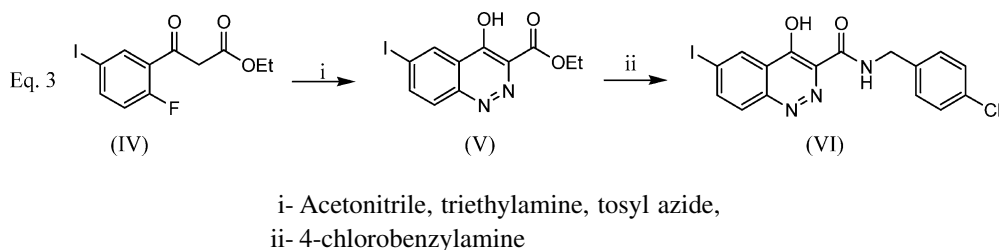
i- Propargyl alcohol, N,N-dimethylformamide, triethylamine, ditriphenylphosphine palladium dichloride

- In a subsequent investigation by the author, (I), (I), was converted into N-chlorobenzyl-6-(3-hydroxy-1-propynyl)-7-methyl[1,8]naphthyridine-3-carboxamide, (II), and then reduced to N-chlorobenzyl-6-(3-hydroxy-1-propyl)-7-methyl[1,8]naphthyridine-3-carboxamide, (III), as illustrated in Eq. 2:

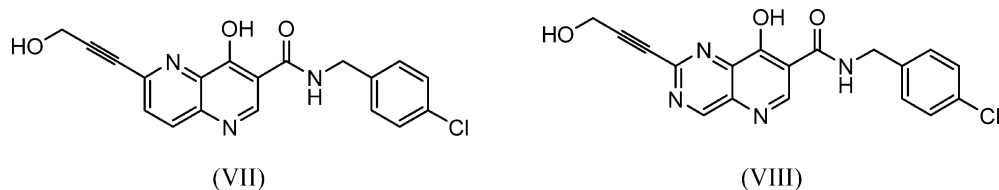


- i- Potassium carbonate, methyl iodide, N,N-dimethylformamide
 ii- CH₂Cl₂, methyl alcohol, 10% palladium on carbon, hydrogen

3. In another investigation by the author cinnoline derivatives of the current invention were prepared (2). The reaction analogue of Step 2, ethyl 3-(2-fluoro-5-iodophenyl)-3-oxopropanate, (IV), was initially converted into ethyl 4-hydroxy-6-iodo-3-cinnolinecarboxylate, (V), then amidated with 4-chlorobenzylamine forming N-(4-chlorobenzyl)-4-hydroxy-6-iodo-3-cinnolinecarboxamide, (VI), as illustrated in Eq. 3:



4. [1,5]Naphthyridine-, (VII), and [3,2-d]pyrimidine-, (VIII), derivatives of (I) have been prepared and are discussed (3).



5. The preparation of aliphatic amide derivatives of the current invention are described (4).

References

1. V.A. Vaillancourt *et al*, US Patent 6,451,811 (September 17, 2002)
2. V.A. Vaillancourt *et al*, US Patent 6,458,788 (October 1, 2002)
3. M.E. Schnute *et al*, US Patent 6,730,682 (May 4, 2004)
4. S.C. Beasley *et al*, US Patent 5,891,878 (April 6, 1999) and US Patent 5,753,666 (May 19, 1998)

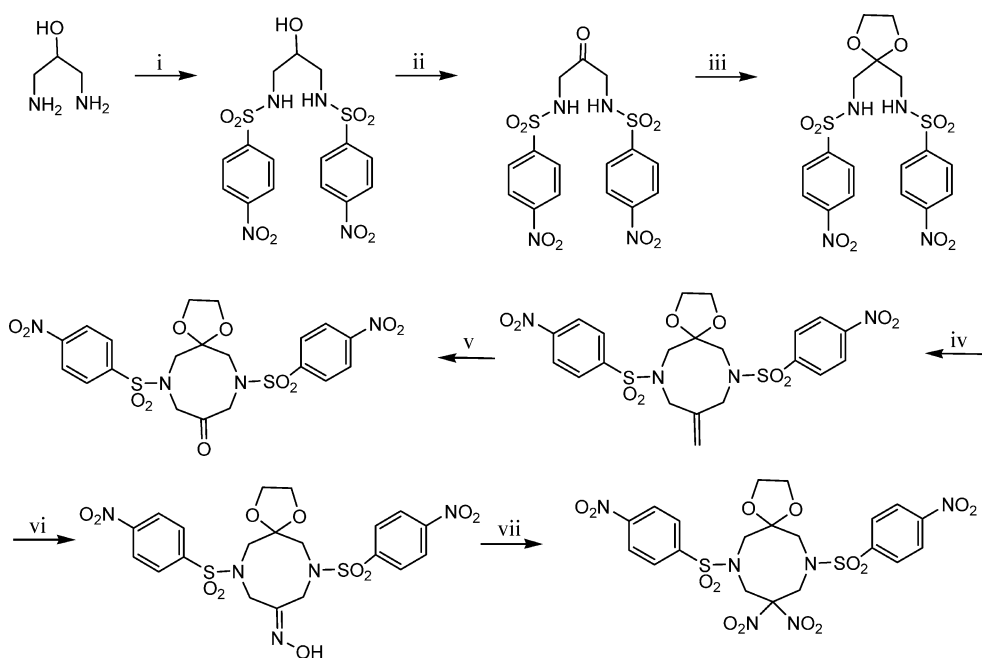
Nitro Derivatives

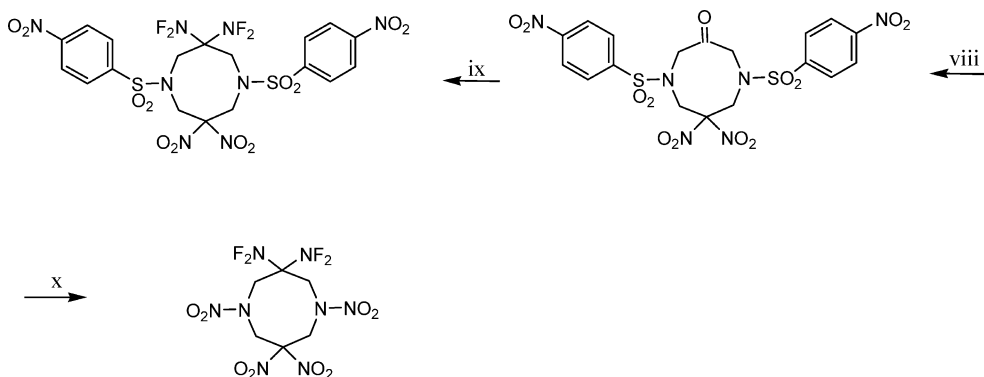
Patent: Geminal-Dinitro-1,5-Diazocine Derivatives
 R.D. Chapman *et al*, US Patent 6,562,985 (May 13, 2003)

Assignee: United States of America as Represented by the Secretary of The Navy

Utility: Energetic Chemical Agents

Reaction





- i- p-Nitrosulfonyl chloride, sodium carbonate, THF, water
- ii- Chromium trioxide, sulfuric acid, acetone
- iii- Ethylene glycol, toluene, p-toluenesulfonic acid
- iv- 3-Bromo-2-(bromomethyl)propene, potassium carbonate, acetone
- v- Ozone, CH_2Cl_2 , methylsulfide
- vi- Hydroxylamine hydrochloride, sodium acetate, ethyl alcohol
- vii- Nitric acid, ammonium nitrate, urea, CH_2Cl_2
- viii- Sulfuric acid, CH_2Cl_2
- ix- Trichlorofluoromethane, difluoroamine
- x- Triflic acid, nitric acid, antimony pentafluoride

Experimental

1. 1,3-Bis(4-nitrotoluenesulfonamide)-2-hydroxypropane

To a stirred solution of 1,3-diamine-2-hydroxypropane (58.8 mmol) and K_2CO_3 (155.8 mmol) dissolved in 100 ml of water at 0°C was added dropwise p-nosyl chloride (132.1 mmol) dissolved in 60 ml THF. Thereafter the solution was stirred at ambient temperature overnight and then concentrated. The product was purified by chromatography on silica using EtOAc/hexanes, 1:1, re-crystallized in acetone/hexanes, and isolated in 95% yield, mp = $210\text{--}212^\circ\text{C}$ (sub). ^1H - and ^{13}C -NMR data supplied.

2. 1,3-Bis(4-nitrotoluenesulfonamide)-propane-2-one

The product from Step 1 (22.35 mmol) was dissolved in 300 ml acetone and oxidized using a mixture of CrO_3 (58.2 mmol) in 15 ml water containing 6 ml 98% H_2SO_4 . After the addition was completed the mixture stirred overnight and was then poured into water. The resulting solid was filtered, washed, and isolated as a white solid in 91% yield, mp = 212°C (dec.). ^1H - and ^{13}C -NMR data supplied.

3. 1,3-Bis(4-nitrotoluenesulfonamide)-propane-2-ethylene ketal

The product from Step 2 (26.83 mmol), ethylene glycol (97.63 mmol) and p-toluenesulfonic acid monohydrate (~0.5 g) dissolved in 200 ml toluene were heated under reflux 3 days using a Dean-Stark trap to remove water. After cooling, the solid was washed, re-crystallized in DMF, and the product obtained in ~90% yield, mp = 237 °C. ¹H- and ¹³C-NMR data supplied.

4. Hexahydro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine-3-ethylene ketal-7-methylene

To a refluxing mixture of the product from Step 3 (92.01 mmol) and K₂CO₃ (5.21 mmol) in 50 ml acetone was added 3-bromo-2-(bromomethyl)propene dissolved in 20 ml acetone over one hour. The mixture was heated overnight, concentrated, and a yellow solid obtained. The product was re-crystallized using acetone/hexanes and isolated in 76% as a colorless solid, mp = 199–201 °C. ¹H- and ¹³C-NMR data supplied.

5. Hexahydro-1,5-bis (4-nitrobenzenesulfonyl)-1,5-diazocin-7-(2H)-one-3-ethylene ketal

To the product from Step 4 (1.77 mmol) dissolved in 100 ml CH₂Cl₂ was bubbled in ozone in oxygen at –100 °C until the solution turned blue; oxygen was then bubbled in to remove ozone. An excess of methyl sulfide was added, the mixture slowly warmed to ambient temperature, and stirred thereafter one hour. The residue was washed, filtered, and dried to afford a white solid in 95% yield, mp = 244 °C (dec). ¹H- and ¹³C-NMR data supplied.

6. Hexahydro-7-hydroxyimine-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine-3-ethylene ketal

The product from Step 5 (7.19 mmol), sodium acetate (33.52 mmol) and hydroxylamine hydrochloride (1.02 mmol) were dissolved in 200 ml ethyl alcohol, refluxed 24 hours, cooled, and then poured into ice water. The precipitate was collected, re-crystallized in acetone/hexanes, and the product isolated in 91% yield as a colorless solid, mp = 213 °C. ¹H- and ¹³C-NMR data supplied.

7. Hexahydro-7,7-dinitro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocin-3-ethylene ketal

A suspension of the product from Step 6 (3.06 mmol) in CH₂Cl₂ was refluxed and 15 ml 100% HNO₃, NH₄NO₃ (4.00 mol) and urea (3.83 mmol) in 50 ml CH₂Cl₂ added over one hour. Thereafter, the reaction was refluxed 90 minutes, cooled to 0 °C, 150 ml ice water added, and CH₂Cl₂ removed. The resulting precipitate was isolated, re-crystallized in acetone/hexanes, and the product obtained in 33% yield, mp = 258 °C (dec.). ¹H- and ¹³C-NMR data supplied.

8. Hexahydro-7,7-dinitro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocin-3-(2H)-one

The product from Step 7 (1.01 mmol) and 1 ml 98% H₂SO₄ in 20 ml CH₂Cl₂ stirred at ambient temperature 3 days followed by the addition of 50 ml ice water. The mixture was

filtered and the product isolated in 92% yield, mp = 230°C (dec.). ^1H - and ^{13}C -NMR data supplied.

9. 3,3-Bis(difluoroamino)octahydro-7,7-dinitro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine

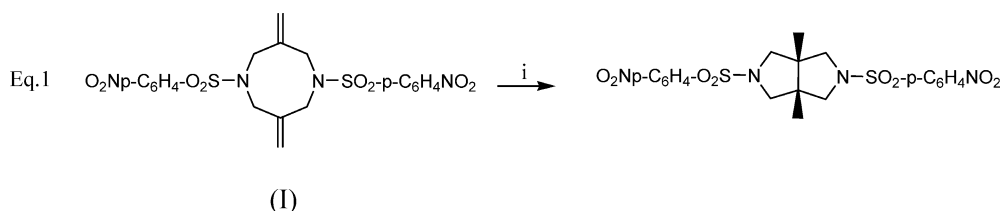
In a jacketed tube reactor, 2.0 ml 30% fuming H_2SO_4 and 10 ml trichlorofluoromethane were cooled -25°C , 2.0 g difluoroamine condensed into the mixture, warmed to 10°C to melt the acid layer, and the mixture re-cooled to -15°C . The product from Step 8 (0.36 mmol) was added, the reaction tube sealed at -15°C for 3 hours, then quenched in water. The solution was basified with NaHCO_3 to pH 12 and extracted 4 times with 100 ml CH_2Cl_2 . The solute was re-dissolved in CH_2Cl_2 , chloroform added, and the mixture concentrated. A precipitate formed and was re-dissolved in acetone, filtered through a medium porosity fritted filter, and the product isolated, mp = 208°C (explodes). ^1H - and ^{13}C -NMR data supplied.

10. 3,3-Bis(difluoroamino)octahydro-1,5,7,7-tetranitro-1,5-diazocine

To 10 ml triflic acid was added 1.0 ml 98–100% HNO_3 and the mixture stirred at ambient temperature for one hour. The mixture was cooled in an ice bath, the product from Step 9 (49.6 mg) added, and the resulting suspension warmed to 55°C in an oil bath. After re-cooling in an ice bath, an additional 1.0 ml of HNO_3 was added, the mixture re-heated to 55°C , and 10 ml triflic acid added to the reaction vessel. Thereafter the mixture stirred overnight and was stored in an over at 55°C 14 days. Approximately 25% of the mixture was removed, 10% by volume of SbF_5 added, and the mixture stored two days at ambient temperature. Triflic acid was removed in vacuo, the product purified by chromatography on silica using chloroform/ CH_2Cl_2 , and the product isolated. ^1H - and ^{19}F -NMR data supplied.

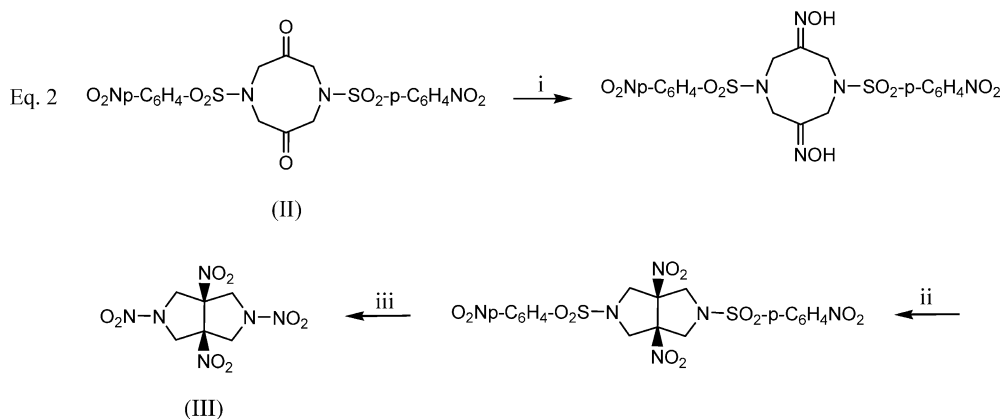
Notes

1. 3,7-Diazabicyclo derivatives have been prepared from reduction of a modified version of the product of Step 4, 3,7-bismethylene-1,5-diazacyclooctane (1), (I), as illustrated in Eq.1:



i- Lithium aluminum hydride, THF

2. 1,3,5,7-Tetranitro-3,7-diazabicyclo derivatives, (III), have been prepared from the di-keto version of the product of Step 8, 3,7-keto-1,5-diazacyclooctane, (I), (II), as illustrated in Eq. 2:

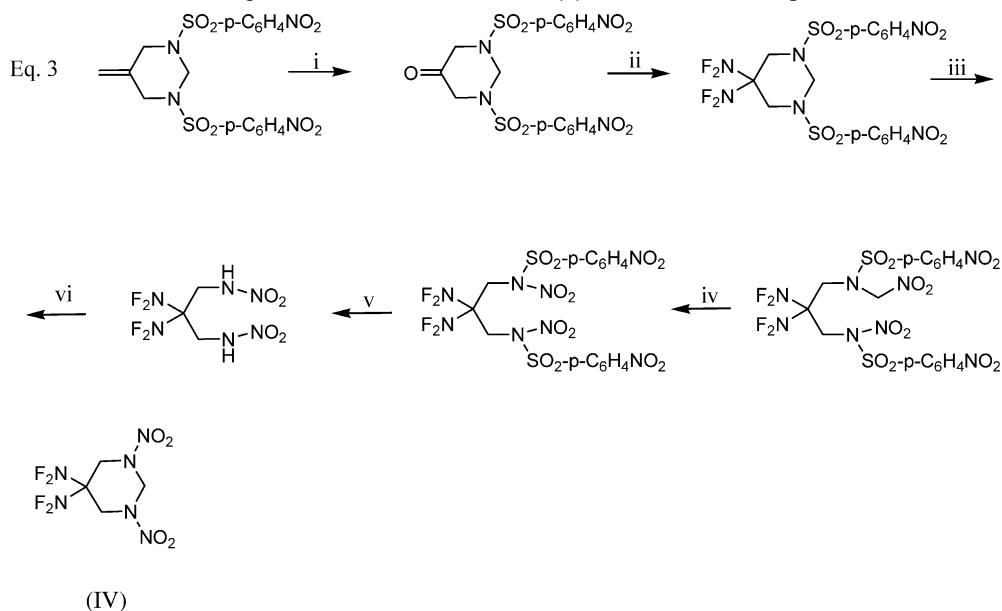


i- Hydroxylamine hydrochloride, sodium acetate,
methyl alcohol

ii- *m*-Chloroperbenzoic acid

iii- Trifluoroacetic anhydride, nitric acid, hydrochloric acid

3. 1,4-Diaza-3-keto-bicyclo derivatives of the current invention containing the peptide sequence Arg-Gly-Asp have been prepared (2).
4. Hexahydro-5-methylene-pyrimides, (IV), have also been prepared and converted into the 6-membered analogue of the current invention (3) as illustrated in Eq. 3.



- i- Ozone, acetone
- ii- Difluoroamine, sulfuric acid, trichlorofluoromethane
- iii- Nitric acid
- iv- 98% Nitric acid
- v- Water
- vi- Formaldehyde

References

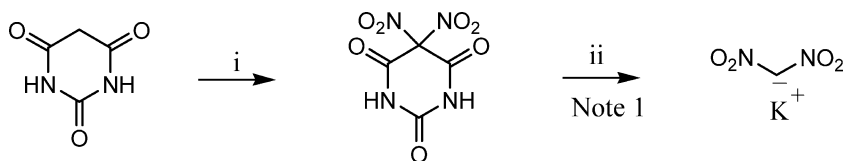
1. P.R. Dave *et al*, US Patent 5,831,099 (November 3, 1999)
2. J. Callahan *et al*, US Patent 5,539,104 (July 23, 1996)
3. R.D. Chapman *et al*, US Patent 6,395,899 (May 28, 2002) and 6,310,204 (October 30, 2001)

Patent: Methods of Preparing Salts of Dinitromethane
N. Latypov *et al*, US Patent 6,340,780 (January 22, 2002)

Assignee: Totalfursvarets Forkiningsinstitut

Utility: Energetic Chemical Agents and Intermediates

Reaction



i- Sulfuric acid, nitric acid
ii- Potassium hydroxide, water

Experimental

1. Gem-dinitro barbituric acid

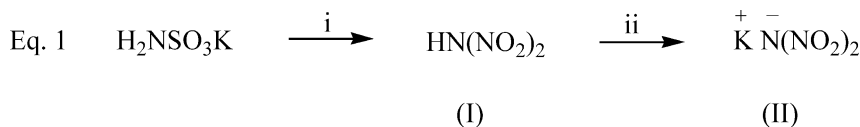
Barbituric acid (5 g) was dissolved in 40 ml 95% H_2SO_4 followed by the addition of concentrated HNO_3 (8.5 g) and the reaction temperature kept at 40°C . After 3 hours a copious amount of white precipitate formed and was filtered. The precipitate was washed with trifluoroacetic acid, dried under vacuum, and the product isolated in 80% yield.

2. Potassium dinitromethane

The product from Step 1 was dissolved in 30 ml ice water, the solution neutralized with 20% KOH, and the mixture heated to 80°C 2 hours. Upon cooling, a precipitate formed and was isolated. It was re-crystallized and the product isolated in 70% yield. UV absorption data supplied.

Notes

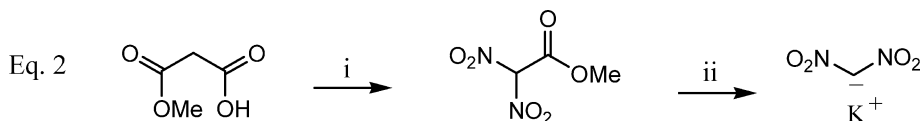
1. Ammonium dinitromethane was also prepared by the author in Step 2 using 25% ammonium hydroxide solution.
2. When the author nitrated 4,6-dihydroxy-2-methylpyrimidine with mixed acids and the intermediate hydrolyzed, equal amounts of potassium dinitromethane and 1,1-diamine-2,2-dinitroethene were formed.
3. Dinitramidic acid, (I), and potassium dinitroamate, (II), were also prepared by the author and others (1) as illustrated in Eq. 1:



i- Sulfuric acid, nitric acid

ii- Potassium hydroxide

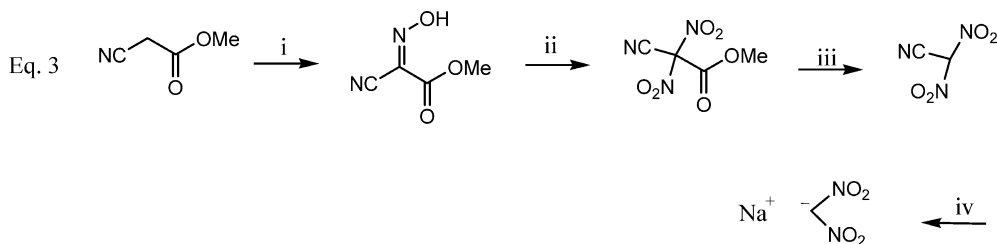
4. Alkali metal salts of dinitromethane have also been prepared (2) by nitrating methyl malonate to produce methyl dinitroacetate followed by saponification and decarboxylation as illustrated in Eq. 2:



i- Sulfuric acid, nitric acid

ii- Potassium hydroxide

5. Methyl cyanoacetate has also been converted into dinitromethane sodium as illustrated in Eq. 3 and is discussed (3).



i- Sodium nitrite, phosphoric acid

ii- Nitric acid, sulfuric acid

iii- Water

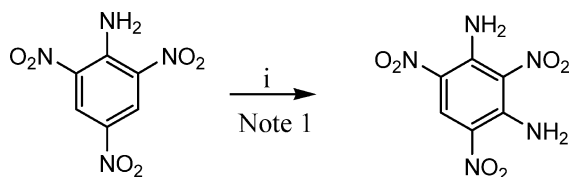
iv- Sodium hydroxide, water

References

1. A. Langlet *et al*, US Patent 5,976,483 (November 2, 1999)
2. V. Grakauskas, US Patent 4,233,249 (November 11, 1980)
3. V. Grakauskas, US Patent 4,233,250 (November 11, 1980)

- Patent:** Vicarious Nucleophilic Substitution Using 4-Amino-1,2,4-Triazole, Hydroxylamine or O-Alkylhydroxylamine to Prepare 1,3-Diamino-2,4,6-Trinitrobenzene or 1,3,5-Triamino-2,4,6-Trinitrobenzene
A.R. Mitchell *et al*, US Patent 5,633,406 (May 27, 1997)
- Assignee:** The Regents of the University of California
- Utility:** Energetic Chemical Agents and Intermediates

Reaction



i- Dimethylsulfoxide, methyl alcohol, sodium methoxide, hydroxylamine hydrochloride,

Experimental

1. 1,3-Diamino-2,4,6-trinitrobenzene

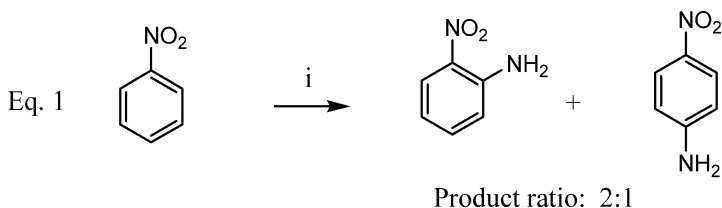
Hydroxylamine hydrochloride (10.2 mmol) and 2,4,6-trinitroaniline (2.09 mmol) were dissolved in 17 ml DMSO. Sodium methoxide (23.6 mmol) dissolved in 5.4 ml methyl alcohol was added and the resulting brown suspension stirred at ambient temperature 4 hours. Thereafter, the reaction mixture was poured into 200 ml saturated solution of NH_4Cl and the product isolated by filtration in 27% yield as a yellow solid.

Optimization Studies

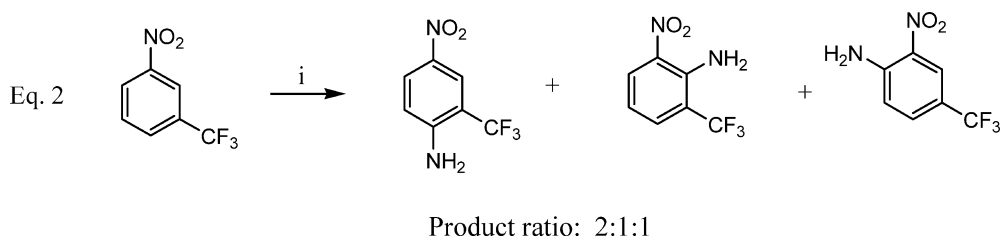
Hydroxyl Amine	Trinitro Aromatic Amine	Product	Yield (%)
Hydroxylamine · HCl	2,4,6-Trinitroaniline	1,3-Diamino-2,4,6-trinitrobenzene	27
O-Methyl Hydroxylamine · HCl	2,4,6-Trinitroaniline	1,3-Diamino-2,4,6-trinitrobenzene	89
O-Benzyl Hydroxylamine · HCl	2,4,6-Trinitroaniline	1,3-Diamino-2,4,6-trinitrobenzene	87
4-Amino-1,2,4-Triazole	2,4,6-Trinitro-1,3-diaminebenzene	2,4,6-Trinitro-1,3,5-triaminebenzene	91

Notes

1. Other examples of direct amination of symmetrical and non-symmetrical nitroaromatics using O-methylhydroxylamine hydrochloride are illustrated in Eq. 1 and Eq. 2, respectively, and discussed (1).



i- O-Methylhydroxylamine hydrochloride,
N,N-dimethylformamide, potassium t-butoxide



i- O-Methylhydroxylamine hydrochloride, cuprous iodide
N,N-dimethylformamide, potassium t-butoxide

2. Direct amination is not limited to nitroaromatics. In the presence of O-(2,4-dinitrophenyl)hydroxylamine hydrochloride, primary amines have directly replaced active hydrogen atoms of non-aromatic compounds (2).
3. The direct amination of other nitroaromatics using organo sulphenamides such as N,N-tetramethylenethiocarbamoylsulphenamide or N-phenyl-benzenesulphenamide has been demonstrated (3).

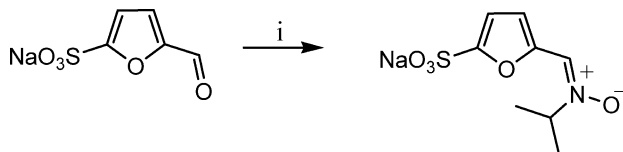
References

1. S. Seko, US Patent 5,466,871 (November 14, 1995)
2. P. Sheradsky *et al*, Tetrahedron, 28, 3833 (1977); S. Radhakrishna, J. Org. Chem., 44, 4836 (1979)
3. M. Makosza, US Patent 5,262,539 (November 16, 1993)

Nitrones

Patent: Furan Nitron Compounds
J.A. Kelleher *et al*, US Patent 6,376,540 (April 23, 2002)
Assignee: Centaur Pharmaceuticals, Inc.
Utility: Spin Radical Trapping Agent

Reaction



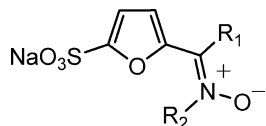
i- N-Isopropylhydroxylamine, methyl alcohol

Experimental

1. N-Isopropyl- α -(2-sulfofuran-5-yl) nitron, sodium

N-Isopropylhydroxylamine and 5-formylfuran-2-sulfonic acid, sodium salt hydrate (5.94 g), were refluxed in 200 ml methyl alcohol 24 hours. Thereafter, another portion of N-isopropylhydroxylamine was added and the mixture refluxed 24 hours, then solvent was removed and a yellow solid isolated. The solid was re-crystallized in EtOAc and the product isolated in 75% yield, mp = 230 °C (dec). ¹H- and ¹³C-NMR and IR data supplied.

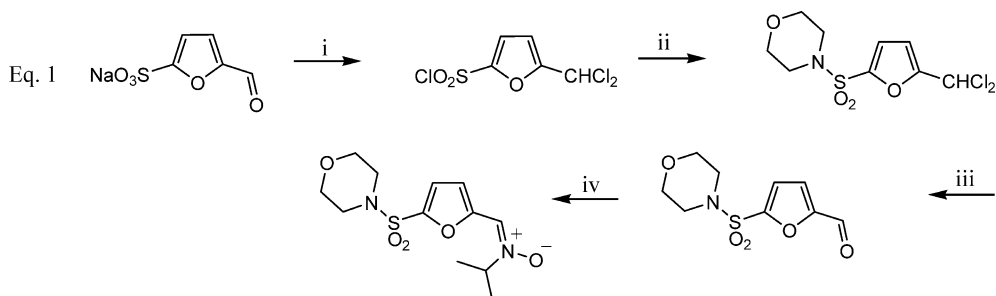
Derivatives



R ₁	R ₂	MP (°C)
Hydrogen	n-Propyl	230–233 (dec)
Hydrogen	Cyclohexyl	231.1 (dec)
Hydrogen	t-Butyl	216.9 (dec)
Morpholine	i-Propyl	163.7
Methyl	i-Propyl	79.0
Ethyl	i-Propyl	82.9

Notes

1. The preparation of the reagent of Step 1 and other alkylhydroxylamine analogues is provided by the author.
2. 2-[(Sulfamoyl-N-morpholino)furan-5-yl]nitron derivatives were also prepared by the author as illustrated in Eq. 1. Other derivatives are provided below.

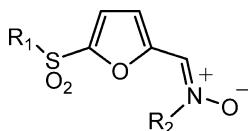


i- Phosphorous oxychloride, phosphorous pentachloride

ii- Diethyl ether, morpholine

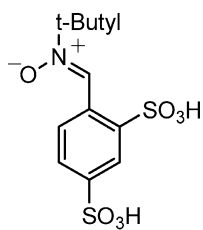
iii- Formic acid

iv- N-Isopropylhydroxylamine, chloroform



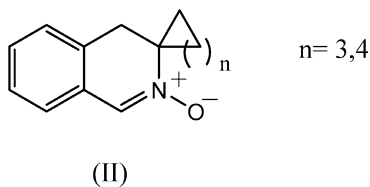
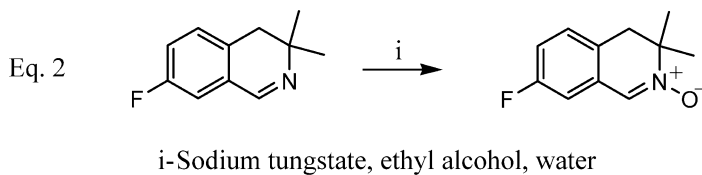
R₁	R₂	Yield (%)	Mp (°C)
Diethylamine	Isopropyl	40.4	82.9
N-4-Methyl-piperazine-1-yl	Isopropyl	35.6	111.5
N-(3-trifluoromethyl)-phenyl	t-Butyl	14.9	162
Methyl	t-Butyl	19.2	137.5

3. The preparation of 2,4-disulfonylphenyl-N-t-butylnitron, (I), is provided (1).

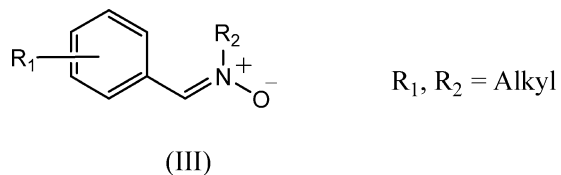


(I)

4. Cyclic nitrones have been prepared by the oxidation of 3,4-dihydroisoquinolines using sodium tungstate (2) as illustrated in Eq. 2. Spiro nitrones, (II), have also been prepared using this method.



5. In subsequent investigations by the author (3), α -aryl-N-alkylnitrones, (III), were prepared and are described.



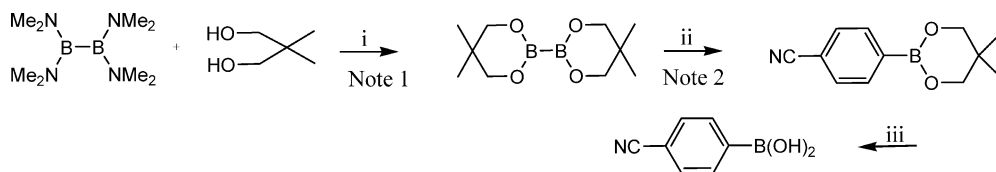
References

1. J.M. Carney, US Patent 5,780,510 (July 14, 1998)
2. A.A. Carr *et al*, US Patent 5,532,252 (July 2, 1996)
3. J.A. Kelleher *et al*, US Patent 6,433,008 (August 13, 2002) and US Patent 6,441,032 (August 27, 2002)

Organometallics

Patent: Aryl Borates
S.M. Marcuccio *et al*, US Patent 6,559,310 (May 6, 2003)
Assignee: Commonwealth Scientific and Industrial Research Organization
Utility: Arylboron Intermediates

Reaction



- i- Diethyl ether, hydrogen chloride
ii- 4-Iodobenzonitrile, dichloropalladiumdiphenylphosphinyl fluoride, potassium acetate, methyl alcohol
iii- Methyl alcohol, water

Experimental

1. Bis(neopentanediolato)diborane

Neopentanediol (0.093 mol), 100 ml diethyl ether and tetrakis(dimethylamino)diborane were mixed, cooled with an ice bath, and 76 ml 2.46 M anhydrous hydrogen chloride (0.187 mol) in ether added. The mixture came to ambient temperature and stirred overnight. The solution was filtered, the solvent evaporated and the product isolated in 23% yield. Residue precipitate was extracted twice with 200 ml benzene increasing the overall yield to 74%. The solid was re-crystallized in benzene/light petroleum and had a mp = 161–162 °C. ¹H-NMR data supplied.

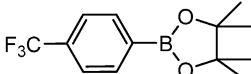
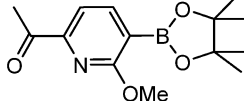
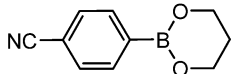
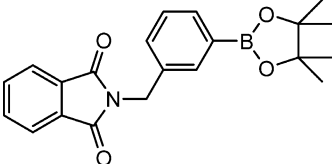
2. (4-Neopentanediolate)borane-benzonitrile

The product from Step 1 (1.66 mmol), 4-iodobenzonitrile (1.09 mmol) and $\text{PdCl}_2(\text{dppf})$ (3.27 mmol) dissolved in 6 ml methyl alcohol were stirred at ambient temperature 3 days. The mixture was poured into 20 ml water and the product extracted with 75 ml and 50 ml diethyl ether. The solvent was evaporated, the product purified by distillation at 80–100 °C at 0.001 mm Hg, and isolated in 72% yield. $^1\text{H-NMR}$ data supplied.

3. 3-Cyanophenylboric acid (Note 3)

The product from Step 2 was dissolved in methyl alcohol and the reaction monitored by HPLC (Waters 600E) using a Zorbax column (ODS) under the conditions of $L = 230 \text{ nm}$, 2 ml/min, 20% CH_3CN :80% water (initial) to 80% CH_3CN :20% water, and changed linearly from 9–17 minutes. A single peak was isolated within 5.8 minutes.

Derivatives

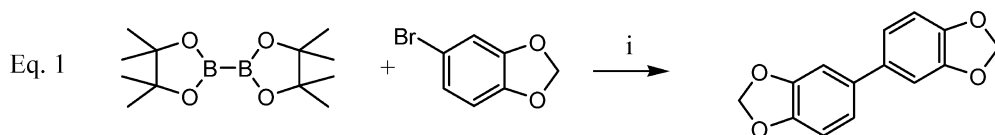
<u>Boronic Ester</u>	<u>MS (M+1)</u>
	217
	265
	188
	364

Notes

1. The author coupled the borane reagent in Step 1 with other diols including:

- meso-hydrobenzoin
- 1,3-propanediol
- 1-phenyl-1,2-ethanediol
- 1,2-diphenyl-1,2-ethanediol

2. 1,3,2-Dioxaneborane derivatives have been prepared by condensing 1,3-diols and phenylboric acid intermediates and are described (1).
3. Coupling of aromatic halides with the product of Step 1 was also described by the author and illustrated in Eq. 1. Other coupled products are provided below.



i- 10% Palladium on carbon, cesium carbonate, methyl alcohol

Procedure

A solution of the pinacol ester of diboronic acid (1 mmol), 1-bromo-3,4-methylenedioxy benzene (2 mmol), 10% Pd/C (80 mg) and Cs_2CO_3 (3.7 mmol) were dissolved in 10 ml methyl alcohol and heated to 55 °C 16 hours. GC analysis indicated that the product constituted of 83.5% 2-(bis1,3-benzodioxole and 16.5% 1-bromo-3,4-methylenedioxy)benzene.

<u>Coupled Products</u>	<u>MS (M+1)</u>
	313
	185
	157

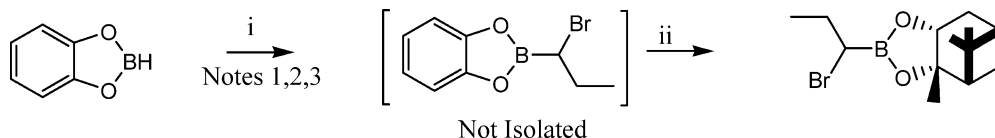
4. Coupling of boronic acid derivatives with aromatic halides (2) and perfluoroalkylsulfonates (3) are described.

References

1. V.S. Bezborodov *et al*, US Patent 4,853,150 (August 1, 1989)
2. S. Haber *et al*, US Patent 5,919,930 (July 6, 1999)
3. S. Haber *et al*, US Patent 5,686,608 (November 11, 1997)

Patent: Boric Ester Synthesis
S.M.A. Elgendy *et al*, US Patent 5,596,123 (January 21, 1997)
Assignee: Thrombosis Research Institute
Utility: Chiral Boron Intermediates

Reaction



i- 1-Bromo-1-propene

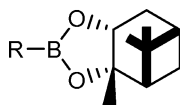
ii- (+) Pinandiol, THF

Experimental

1. (+) Pinanediol-1-bromo-propene boronate

Catechol borane (50 mmol) was added dropwise to 1-bromo-1-propene at **80 °C** and the mixture refluxed 24 hours. The crude product was treated with (+) pinandiol (50 mmol) dissolved in 20 ml THF and the reaction stirred 2 hours at ambient temperature. The solvent was removed, the product purified by chromatography on silica gel using hexane, and isolated in 76% yield as a colorless oil. ¹H- and ¹³C-NMR and MS data supplied.

Derivatives



R	Yield (%)
1,3-Dibromo-propyl	76
1-Bromo-2-phenyl-ethyl	59
1,3-Dichloro-propyl	79
1-Bromo-2-methyl-propyl	80

Notes

1. A general procedure for preparing and isolating other α -haloalkyl boronic esters was provided by the author and described below:

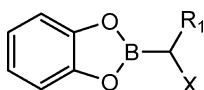
Procedure

Catecholborane (50 mmol) was added dropwise to a selected 1-haloalkene (50 mmol) and refluxed under argon while being monitored by the disappearance of olefinic protons using $^1\text{H-NMR}$. The α -haloalkylboronic ester was then purified by distillation between 90°C and 120°C at 0.05 mm Hg and the product isolated in 59–83% yields.

2. Catecholborane was selected as the original boronic ester substrate because of its resistance to hydrolysis. When dimethoxyborane was reacted with (E)-1,2-dichloroethene in Step 1 to prepare 2-chloroethyl-dimethoxyborane, boric acid was also generated (1).
3. α -Haloalkylboronic esters were also prepared by the author using Wilkenson's catalyst, $\text{RhCl}(\text{PPh}_3)_3$, as described below. The preparation of α -haloalkylboronic esters using Wilkenson's catalyst is described below:

Procedure

In the presence of Wilkenson's catalyst (0.05–0.5% mol eq) catecholborane (45 mmol) was added dropwise to 1-halo-1-alkene (3 mmol) in 5 ml benzene and refluxed while monitoring the reaction extent using $^1\text{H-NMR}$. Products were isolated using a Kugelrohr distillation apparatus and are summarized below.



R_1	X	Yield (%)
Methyl	Br	82
n-Butyl	Br	54
Phenyl	Br	87
Chloromethyl	Cl	71

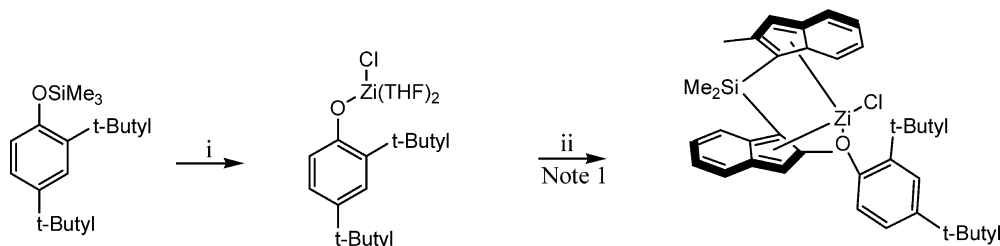
4. In a subsequent investigation by the author with others (2) (+)-pinanediol 4-bromo-(R)-aminobutane boronate hydrochloride and other α -bromo boronic esters have been used as intermediates in the preparation of peptide derivatives (2).

Reference

1. W.H. Schechter, US Patent 3,093,674 (June 11, 1963)
2. V.V. Kakkar *et al*, US Patent 5,648,338 (July 15, 1997), US Patent 5,858,979 (January 12, 1999), and US Patent 6,387,881 (May 14, 2002)

Patent: Method for Producing Monoaryloxy-ansa-Metallocenes
C. Binger *et al*, US Patent 6,620,953 (September 16, 2003)
Assignee: Bassell Polyolefine GmbH
Utility: Olefin Polymerization Catalyst

Reaction



i- THF, zirconium tetrachloride

ii- Dimethylbis(2-methyl-4,5-benzoindenyl)silane, toluene, THF,
n-butyllithium

Experimental

1. Zirconium monochloride mono(O-2,4-di-*t*-butyl)benzene · 2THF (1)

ZiCl₄ (30 mmol) and trimethyl (2,4-di-*t*-butyl-phenoxy)silane (30 mmol) were reacted in THF, re-crystallized, and the product isolated in 55% yield. ¹H-NMR data supplied.

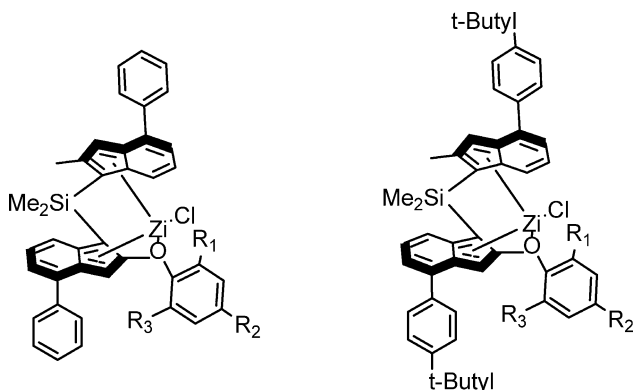
2. pseudo-*rac* Dimethylsilanediylbis(2-methyl-4,5-benzo-indenyl)zirconium monochloride mono(2,4-di-*t*-butylphenoxy)

and

meso-Dimethylsilanediylbis(2-methyl-4,5-benzo-indenyl)zirconium monochloride mono(2,4-di-*t*-butylphenoxy)

A solution of dimethylbis(2-methyl-4,5-benzoindenyl)silane (9.6 mmol) dissolved in 38 ml toluene was mixed with 7.2 ml 20% n-butyllithium in toluene and the mixture stirred at 60 °C 1 hour. The product from Step 1 (9.6 mmol) was added, the mixture stirred one hour at 30 °C, filtered through Celite, and the filter cake extracted with 125 ml hot toluene. The solution was concentrated, cooled to −30 °C, and a yellow crystalline precipitate isolated consisting of pseudo-*rac*/meso isomers, 4:1, respectively, in 44% yield. ¹H-NMR data supplied.

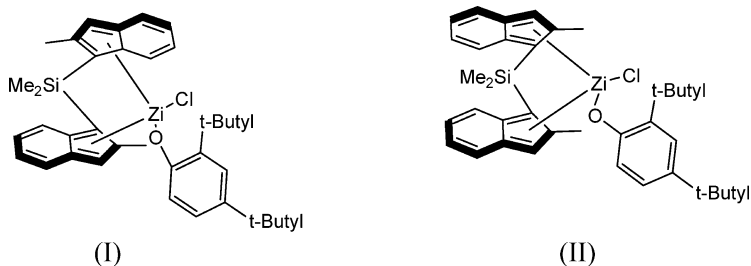
Derivatives



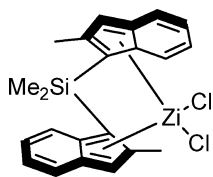
R_1	R_2	R_3
Methyl	Hydrogen	Methyl
Hydrogen	t-Butyl	t-Butyl

Notes

- Under the current reaction conditions, $^1\text{H-NMR}$ reaction monitoring indicated that a 4:1 isomeric product ratio of pseudo-rac and meso dimethylsilanediylbis(2-methyl-4,5-benzo-indenyl)zirconium monochloride mono(2,4-di-t-butylphenoxide), (I), and (II), respectively, were formed. The isomers were separated by extracting the racemic mixture with hot toluene.

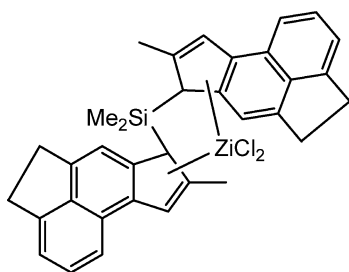


- Rac-dimethylsilanediylbis(2-methyl-4,5-benzo-indenyl)zirconium monodichloride, (II), was also prepared in Step 2 with ZrCl_4 .



(II)

3. The preparation of rac-dimethylsilanediylbis(2-methyl-4-(1- and 2-naphthyl)zirconium dichloride is described (2).
4. Rac-dimethylsilanediylbis(2-methyl- α -acenaphthindenyl) zirconium dichloride, (III), has also been prepared and used as a polymerization catalyst (3,4).



(III)

References

1. H. Yasuda *et al*, *Organometallics*, 1, 388 (1982)
2. F. Kuber *et al*, US Patent 5,840,644 (November 24, 1998)
3. J. Rohrmann *et al*, US Patent 5,830,821 (November 3, 1998)
4. F. Kuger *et al*, US Patent 5,786,432 (July 25, 1998) and US Patent 5,770,752 (June 23, 1998)

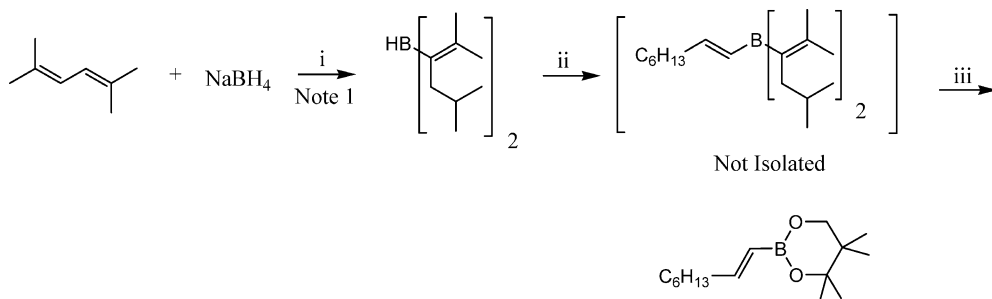
Patent: Process for Preparing Bisallylboranes and Non-Aromatic Boronic Acids

S. Scherer *et al*, UJS Patent 6,706,925 (March 16, 2004)

Assignee: Clariant GmbH

Utility: Suzuki Coupling Reagents

Reaction



i- Methylsulfate, diglyme
ii- 1-Octyne, formaldehyde, pinacol

Experimental

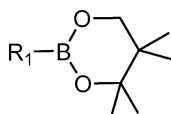
1. Di(1-isopropyl-3-methylbut-2-enyl)borane

NaBH_4 (20 mmol), 2,5-dimethylhexa-2,4-diene (50 mmol) and 20 ml diglyme were mixed, cooled in an ice bath, methylsulfate (20 mmol) added, and the reaction stirred 3 hours. The resulting product suspension was used directly without purification.

2. 4,4,5,5-Tetramethyl-2-[(E)-1-octenyl]-1,3,2-dioxaborolane

1-Octyne (20 mmol) was added over 20 minutes to a suspension of the product from Step 1 at -5°C . The mixture was warmed to 0°C 1 hour, slowly quenched with 3 ml water, stirred at ambient temperature 30 minutes, and 1.5 ml 37% formaldehyde quickly added. The reaction stirred 1 hour, pinacol (22 mmol) added, and the mixture stirred overnight at ambient temperature. The product was diluted with 40 ml water, extracted with 40 ml heptane, and isolated under reduced pressure (bulb type) in 67% yield, bp = $70-80^\circ\text{C}$ at 0.15 mm Hg. $^1\text{H-NMR}$, IR, and MS data supplied.

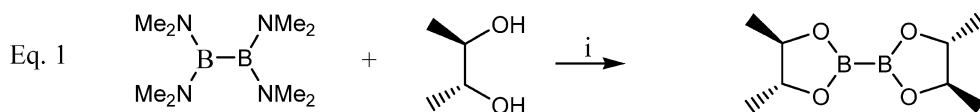
Derivatives



Unsaturated Reagent	R ₁	Yield (%)
Styrene	Phenylethyl	71
Acrolein diethyl acetal	3,3,-Diethoxypropyl	63
3-Phenyl-1-propyne	(Z)-1-Methyl-2-phenyl-1-ethenyl	70

Notes

1. Insitu borane is formed from NaBH₄ which selectively reacts with the diene to form bisallylborane. In the absence of a diene in Step 1, diborane is generated. Bisallyl boranes have previously been prepared by thermal disproportional reactions and are described (1).
2. Bisallylalkyl borane intermediates have previously been prepared and are discussed (2).
3. The preparation of 2,2'-bis-1,3,2-dioxaboralanes depicted in Eq. 1. is described (3).



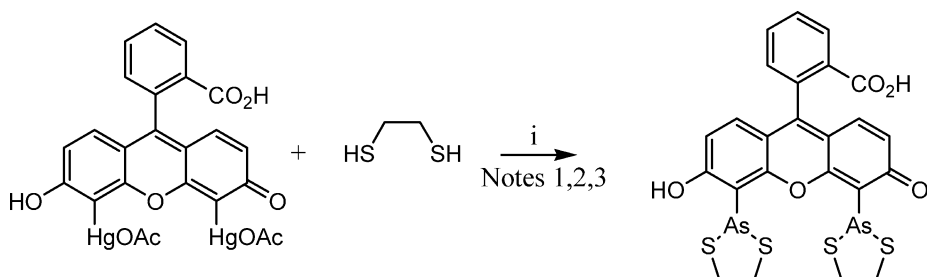
i- THF, sodium sulfate

References

1. Y.A. Bezmenov, Zelinski Institute of Organic Chemistry, Academy of Sciences, USSR, 12, 2111 (1965)
2. H.C. Brown, US Patent 4,978,794 (December 18, 1990)
3. S.M. Marcuccio *et al*, US Patent 6,515,160 (February 4, 2003) and US Patent 6,346,639 (February 12, 2002).

Patent: Synthetic Molecules That Specifically React with Target Sequences
R.Y. Tsien *et al*, US Patent 6,008,378 (December 28, 1999)
Assignee: The Regents of the University of California
Utility: DNA Labeling Agents

Reaction



i- Arsenic trichloride, N-methylpyrrolidinone,
palladium(II)acetate, diisopropylethylamine

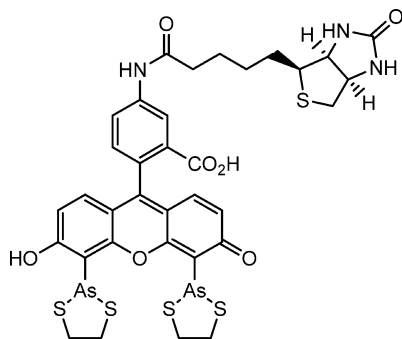
Experimental

1. 4',5'-Bis(2-arsa-1,3-dithiolan-2-yl)-fluorescein

Fluorescein mercuric acetate (85 μmol) was suspended in 1.5 ml N-methylpyrrolidinone and dissolved upon the addition of 144 μl AsCl_3 (1.7 mmol). A few grains of palladium diacetate and 120 μl of DIEA were then added. After 3 hours the mixture was added dropwise to a pH 7 solution of 20 ml 50% acetone containing 0.25M phosphate buffer. Thereafter, 285 μl 1,2-ethanediol (3.4 mmol) and 20 ml chloroform were added and the product extracted with chloroform. The material was washed with Na_2EDTA , dried over Na_2SO_4 , purified by chromatography on silica gel using 10% EtOAc/toluene and the product isolated in 37% yield. $^1\text{H-NMR}$ data supplied.

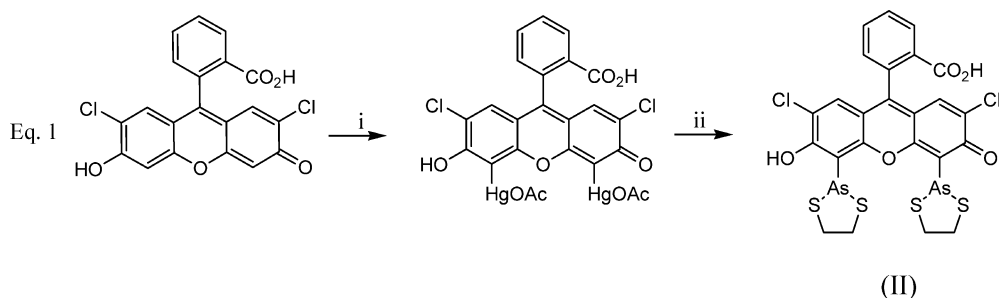
Notes

1. 4',5'-Bis(2-arsa-1,3-dithiolan-2-yl)-fluorescein is a non-fluorescing chemical agent. In the presence of at least 10 or more sequenced amino acids, four of which must consist of cysteine, it forms a fluorescent red shift complex.
2. The intermediate, 4',5'-bis-dichloroarsine fluorescein, was not isolated.
3. In a subsequent investigation by the author (1) the biotin conjugate (I), of Step 1 was prepared.



(I)

4. The Step 1 dichloro derivative, 2',7'-dichloro-4',5'-bis(2-arsa-,3-dithiolan-2-yl)fluorescein, (II), product was also prepared by the author as illustrated in Eq. 1:

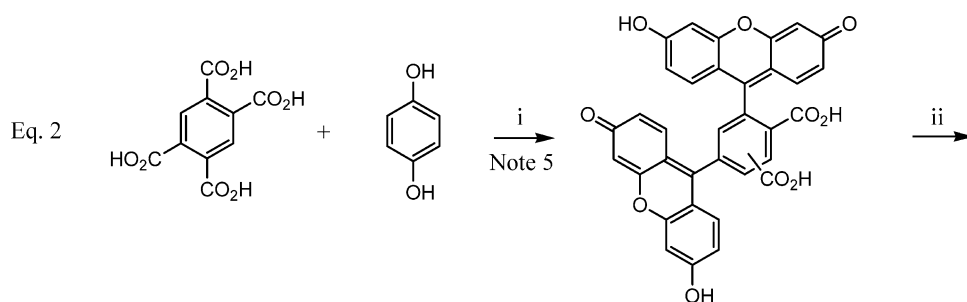


(II)

i- Mercuric acetate, acetic acid, water, ethyl alcohol

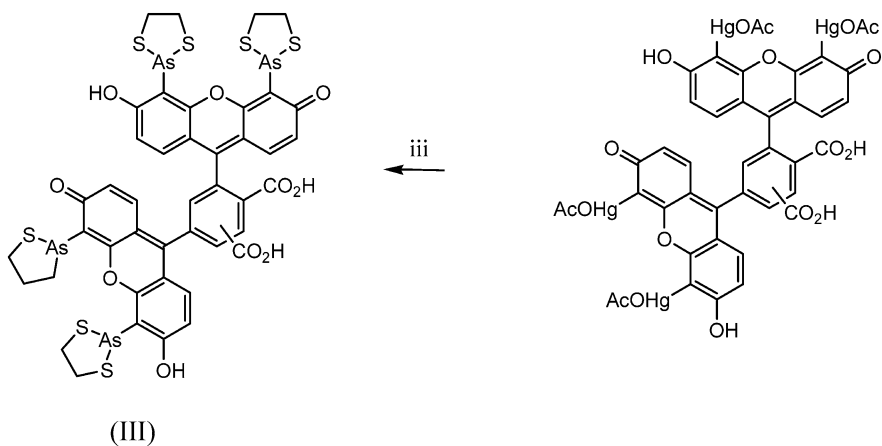
ii- Arsenic trichloride, N-methylpyrrolidinone,
palladium(II)acetate, 1,2-ethandiol, diisopropylethylamine

4. Tetraarsenical analogues, (III), (1), of the product of Step 1 were also prepared by the author as illustrated in Eq. 2:



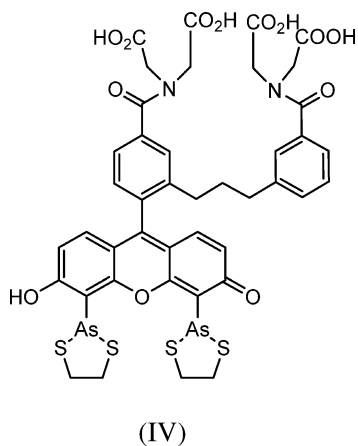
i- Pyromellitic acid, resorcinol

ii- Mercuric acetate, acetic acid, water



iii- Arsenic trichloride, N-methylpyrrolidinone,
palladium(II)acetate, diisopropylethylamine

5. The preparation of bifluorescein is described (2).
6. In a subsequent investigation by the author, metal chelator analogues, (IV), of the product of Step 1 were prepared and are described (3).



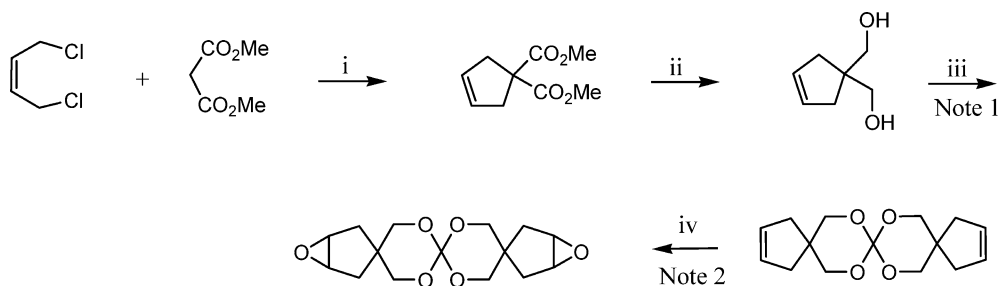
References

1. R.Y. Tsien *et al*, US Patent 6,451,569 (September 17, 2002)
2. S. Dutt, J. Chem. Soc., 1171 (1926); O. Silberrad, *ibid*, 89, 1787–1811(1952); R.Y. Tsien *et al*, US Patent 5,932,474 (August 3, 1999)
3. R.Y. Tsien *et al*, US Patent 6,686,458 (February 3, 2004)

Orthocarbonates, esters, and derivatives

Patent: Spiroorthocarbonates Containing Epoxy Groups
C.C. Chappelow *et al*, US Patent 6,653,486 (November 25, 2003)
Assignee: Curators of the University of Missouri
Utility: Photopolymerization Agents

Reaction



- i- Lithium hydride, N,N-dimethylformamide
- ii- Lithium aluminum hydride, THF
- iii- p-Toluenesulfonic acid, tetraethylorthocarbonate, toluene
- iv- CH₂Cl₂, m-chloroperbenzoic acid, sodium bicarbonate

Experimental

1. Dimethyl 3-cyclopentene-1,1-dicarboxylate

Dimethyl malonate (200 mmol) was dissolved in 300 ml DMF, cooled to 0 °C, and lithium hydride (500 mmol) added in one portion. To the cooled mixture was slowly added cis-1,4-dichloro-2-butene (228 mmol) and the mixture stirred 72 hours. Thereafter, the mixture was diluted with 500 ml 20% diethyl ether/hexanes then poured into 350 ml cold water. After washing with 300 apiece water and brine, the product was isolated in 50% yield, mp = 63.4 °C. ¹H-NMR and IR data supplied.

2. 1,1-Bis(hydroxymethyl)-3-cyclopentene

Lithium aluminum hydride (175 mmol) was added to 235 ml THF, cooled to 0 °C, the product from Step 1 dissolved in 58 ml THF added, and the reaction stirred 4 hours. The reaction was quenched with the sequential addition of 6 ml water, 6 ml 3 M aqueous NaOH, and 17.5 ml water. The resulting cake was washed with 250 ml refluxing THF. The product was isolated in 86.2% yield as white needles, mp = 81.2 °C. ¹H-NMR and IR data supplied.

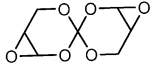
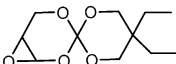
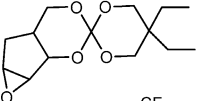
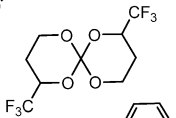
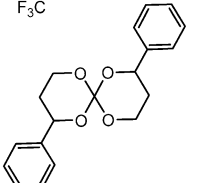
3. 7,9,17,18-Tetraoxatrispiro[4.2.2.4.2.2]nonadeca-2,13-diene

To the product from Step 2 (115.5 mmol) dissolved in 370 ml toluene was added p-toluenesulfonic acid (0.2 g) and tetraethylorthocarbonate (57.8 mmol) and the mixture refluxed until 12.5 ml ethyl alcohol was collected in a Dean-Stark apparatus. The mixture refluxed two hours and stirred at 102 °C overnight. The mixture was neutralized with 1 ml TEA, the product purified by flash chromatography on silica with CH₂Cl₂/hexanes, 2:1, and the product isolated as white crystals in 62% yield, mp = 174.5 °C. ¹H-NMR and IR data supplied.

4. 6,24-Dioxatrispiro[bicycle][3.1.0]hexane-3,5'-1,3-dioxane-2'2''-1,3-dioxane-5''3'''-bicyclo[3.1.0]hexane]

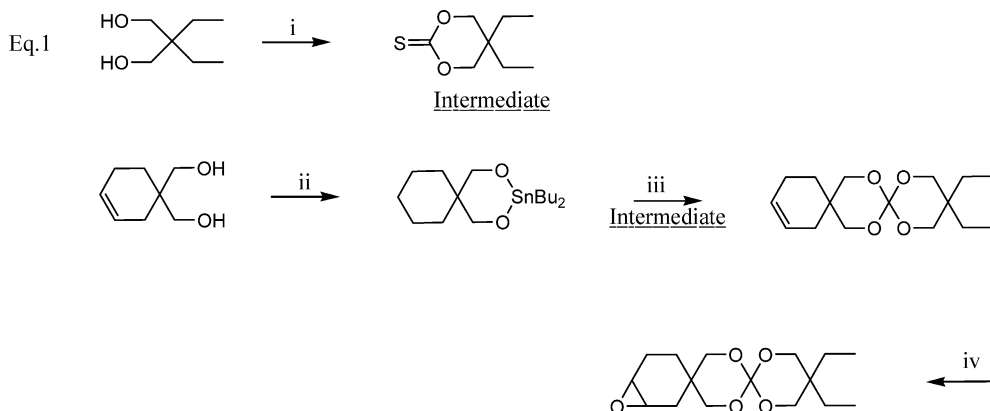
The product from Step 3 (16.27 mmol) was dissolved in 215 ml CH₂Cl₂, 113 ml 0.5 M aqueous NaHCO₃ added, the mixture stirred vigorously at ambient temperature, and MCPA (35.8 mmol) added over several portions. The reaction stirred overnight and was monitored using TLC on silica gel using CH₂Cl₂/diethyl ether, 1:1. The two phases were separated, washed twice with 150 ml 1 M NaOH, twice with 100 ml water, and the solvent removed to provide an off white solid. The product was purified by flash chromatography on silica gel using CH₂Cl₂/diethyl ether, 95:5, and isolated as white crystals in 75% yield, mp = 256.5 °C. ¹H-NMR and IR data supplied.

Derivatives

Derivatives	Melting Points (°C)
	184.7
	67.4
	93.2
	205.6
	122.4

Notes

1. An alternative method for preparing spiroorthocarbonates entails transesterifying 1,2-acetoxymethyl ethylene with tetraethylortho-carbonate derivatives (1). Similar preparations are discussed (2,3).
2. Photoinitiation conditions and methods using spiroorthocarbonates are described (4).
3. A method for preparing 5,5-diethyl-19-oxadispiro [1,3-dioxane-2,2'-1,3-dioxane -5',4''-bicyclo [4.1.0]heptane] was also provided by the author as illustrated in Eq.1:



- i- 4-Dimethylaminopyridine, toluene, thiophosphene
- ii- Dibutyltin oxide, toluene
- iii- Toluene
- iv- m-Chloroperbenzoic acid, sodium bicarbonate, CH_2Cl_2

References

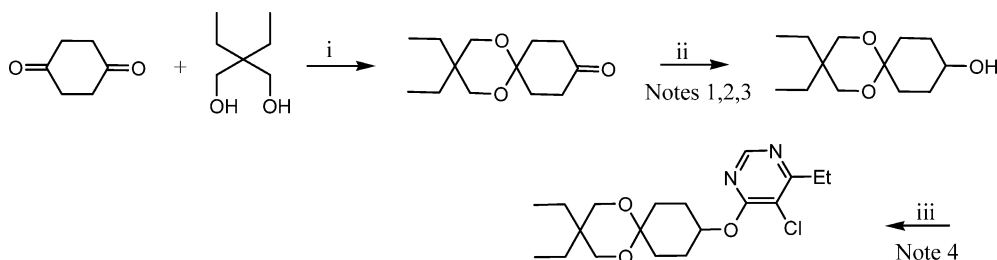
1. M.S. Cohen *et al*, US Patent 4,891,436 (January 2, 1990)
2. K. Mizutani *et al*, US Patent 4,849,529 (July 18, 1989)
3. P. Mues *et al*, US Patent 4,851,550 (July 25, 1989)
4. J.D. Oxman *et al*, US Patent 5,998,495 (December 7, 1999)

Patent: Substituted Spiroalkylamino and Alkoxy Heterocyclics, Processes for Their Preparation, and Their Use as Pesticides and Fungicides
W. Schaper *et al*, US Patent 5,859,009 (January 12, 1999)

Assignee: Hoechst Schering AgrEvo GmbH

Utility: Pesticides and Fungicides

Reaction



i- p-Toluenesulfonic acid, toluene

ii- Sodium borohydride, ethyl alcohol

iii- 4,5-Dichloro-6-ethylpyrimidine, sodium hydride, THF

Experimental

1. 3,3-Diethyl-1,5-dioxaspiro[5.5]undecan-9-one

Cyclohexane-1,4-dione (0.27 mmol), 2,2-diethylpropane-1,3-diol (0.27 mmol) and p-toluenesulfonic acid (0.36 g) were dissolved in 200 ml toluene and heated on a water bath. After the mixture had cooled to ambient temperature, water was removed, the organic phase was washed with aqueous NaHCO_3 , dried and the solvent removed. The residue was purified by flash chromatography using EtOAc/petroleum ether, 1:4, and the product isolated in 47% yield.

2. 3,3-Diethyl-1,5-dioxaspiro[5.5]undecan-9-ol

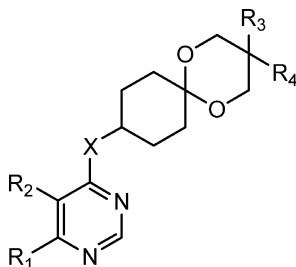
To the product from Step 1 (57.4 mmol) dissolved in 200 ml ethyl alcohol was added NaBH_4 (21.5 mmol) and the mixture stirred at ambient temperature 1 hour then stirred at 40°C 15 hours. Thereafter, 5 ml acetone was added and the mixture stirred 30 minutes. The solution was concentrated in vacuo, the product extracted with diethyl ether, washed with aqueous NH_4Cl , dried, and the product isolated in 90% yield.

3. 5-Chloro-4-(3,3-diethyl-1,5-dioxaspiro[5.5]undec-9-yloxy)-6-ethylpyrimidine

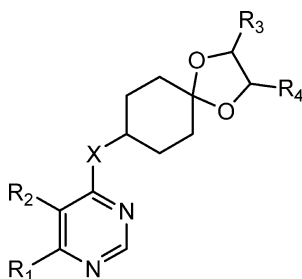
The product from Step 2 (8.8 mmol) was added to a suspension of NaH (13.2 mmol) in 20 ml THF and the mixture refluxed 2 hours. The reaction was cooled to 35°C , 4,5-dichloro-6-ethylpyrimidine (8.9 mmol) dissolved in 3 ml THF added, and the reaction

refluxed 2 hours. Thereafter, 3 ml isopropyl alcohol were added, the mixture stirred 30 minutes, and then poured into a 1:1 mixture of diethyl ether and aqueous NH_4Cl . The mixture was purified by chromatography with silica gel using petroleum ether/EtOAc, 3:2, and the product isolated in 60.3% yield.

Derivatives



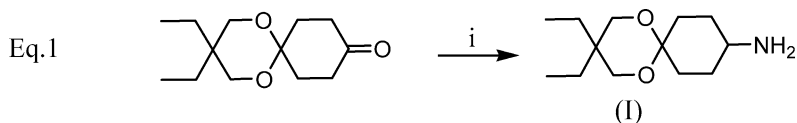
R_1	R_2	X	R_3	R_4	Mp ($^{\circ}\text{C}$)
Methoxymethyl	Methoxide	O	Ethyl	Ethyl	46–47
Methoxymethyl	Methoxide	NH	Methyl	Methyl	112–114
Ethyl	Chloro	NH	Methyl	Phenyl	Oil
Ethyl	Chloro	NH	Hydrogen	Methoxide	Oil



R_1	R_2	X	R_3	R_4	Mp ($^{\circ}\text{C}$)
Ethyl	Chloro	NH	Methyl	Methyl	62–63
Ethyl	Chloro	NH	Hydrogen	t-Butyl	94–95
Methoxymethyl	Methoxide	NH	Methyl	Methyl	107–108
Methoxymethyl	Methoxide	O	Hydrogen	n-Butyl	Oil

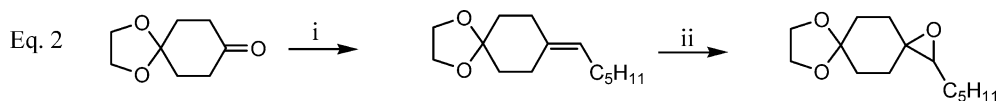
Notes

1. The author also converted the product from Step 1 into 3,3-diethyl-1,5-dioxaspiro[5.5]-undecan-9-amine (I) as illustrated in Eq. 1:



i- Raney nickel, ammonia, methyl alcohol

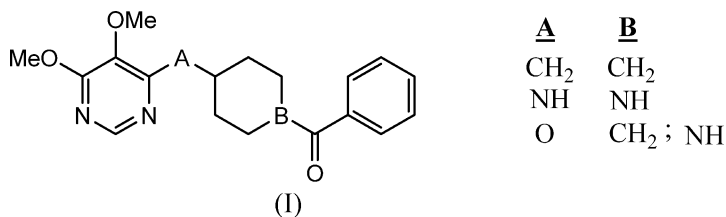
2. 1,4-Dioxaspiro[4.5]dec-8-ylamino and -8-yloxy pyrimidines were also prepared by the author using cyclohexane-1,4-dione ethylene monoketal.
3. Spiroepoxide derivatives of cyclohexane-1,4-dione ethylene monoketal have been prepared (1,2,3) as illustrated below in Eq. 2:



i- 1-Hexylidene triphenylphosphonium chloride

ii- m-Chloroperbenzoic acid

4. In a subsequent investigation by the author, other Step 3 products were prepared and are illustrated, (I), (3).



References

1. A. Maercker, *Organic Reactions*, 14, 270 (1965)
2. H.E. Simmons *et al*, *Organic Reactions*, 20, 1 (1973)
3. W. Schaper *et al*, US Patent 6,596,727 (July 22, 2003)

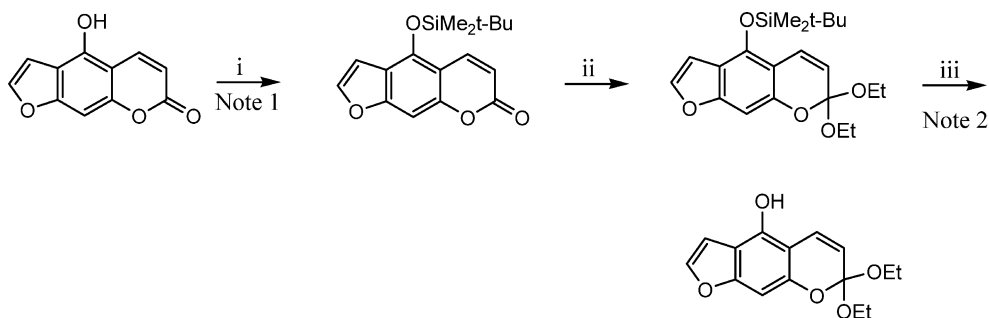
Patent: Synthesis of Spiro Orthoesters, Spiro Orthocarbonates, and Intermediates

R. Seemayer *et al*, US Patent 6,613,918 (September 2, 2003)

Assignee: Bioavailability Systems, LLC.

Utility: Polymer Precursor for Drug Delivery Devices

Reaction



i- N,N-Dimethylformamide, t-butyldimethylsilyl chloride, imidazole

ii- Triethyloxonium hexafluoroplatinate, CH_2Cl_2

iii- THF, tetrabutylammonium fluoride

Experimental

1. 4-Dimethyl-t-butylsiloxy-7H-furo[3,2-g][1]benzopyran-7-one (General method for preparing silyl-protected Bergaptol)

Bergaptol (50 mmol) was dissolved in 100 ml DMF containing imidazole (73.4 mmol) and t-butyldimethylsilyl chloride (72.8 mmol), stirred at ambient temperature 4 hours, then quenched with 500 ml EtOAc. The organic phase was washed 8 times with 100 ml brine, mixed with n-heptane, concentrated, and a yellow solid isolated. The solid was washed 3 times with 100 ml heptane and the product isolated in 82% yield. ^1H - and ^{13}C -NMR data supplied.

2. 4-Dimethyl-t-butylsiloxy-7H-furo[3,2-g][1]benzopyran-7-diethylorthoester (General method for preparing bergaptol orthoesters)

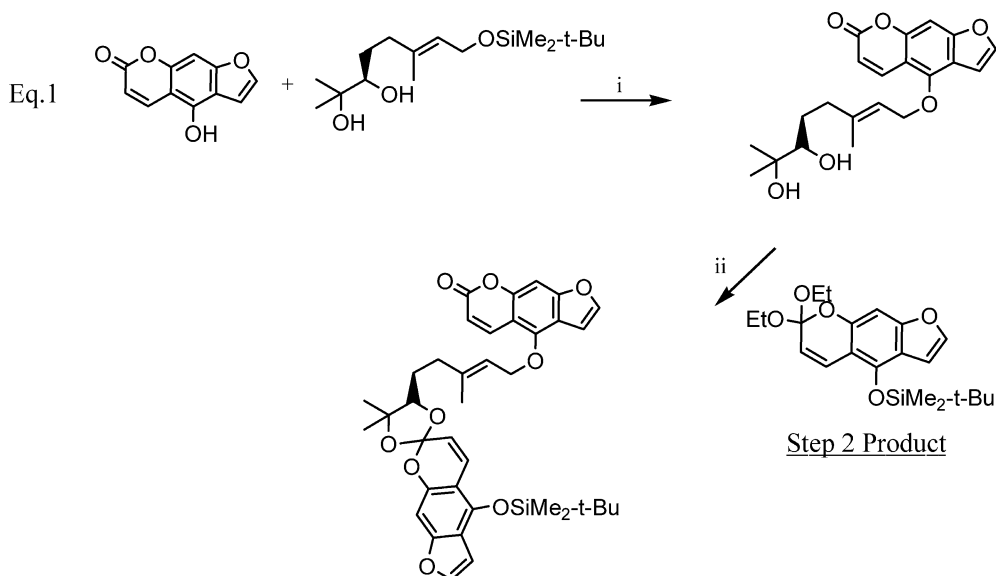
The product from Step 1 (10 mmol) was mixed with 20 ml 1 M $(\text{C}_2\text{H}_5)_3\text{OPF}_6$ dissolved in CH_2Cl_2 and stirred 16 hours at ambient temperature. Thereafter the mixture was cooled with ice water, added to sodium ethoxide (2 eq), and stirred for 30 minutes. It was then poured into 300 ml EtOAc/ NEt_3 , 95:5, and the organic phase concentrated to approximately 20 ml. The product was purified by chromatography with alumina using NEt_3 /EtOAc/heptane, 5:10:85, and isolated as an oil in 70% yield.

3. 4-Hydroxyl-7H-furo[3,2-g][1]benzopyran-7-diethylorthoester (General de-silylation procedure)

The product from Step 2 (1.27 mmol) was dissolved in 6 ml THF, chilled with ice water, and 1.4 ml 1 M Bu_4NF dissolved in THF added. After stirring 30 minutes at 0°C the mixture was poured into 20 ml EtOAc and then rinsed with 10 ml 1 M HCl and 20 ml brine. The solvent was removed and the residue purified by chromatography using hexane/EtOAc, 2:1, and the product isolated in 88% yield.

Notes

1. When bergaptol was orthoesterified in Step 2 using $(\text{C}_2\text{H}_5)_3\text{O})\text{BF}_4$ and t-butyldimethylsilyl chloride, product yields varied from 10% to 30%. The author suggests the low yields were the result of attack of the protecting group by trace fluoride or borontetrafluoro anions.
2. The product of Step 2 was converted into spiroorthoesters by the author as illustrated in Eq. 1:



3. The preparation of 7-methoxycoumarin orthoesters- and spiro orthospiroester derivatives is provided (1).
4. Methods for preparing orthoesters using lactones (2) or spiroorthocarbonates (3) with boron trifluoride are discussed.

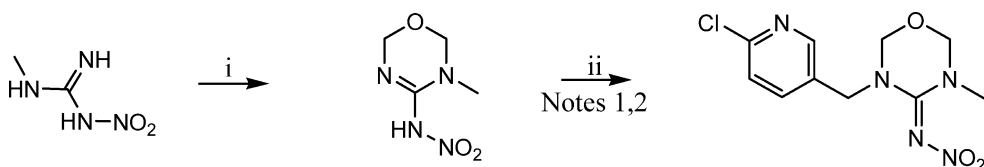
References

1. J.W. Harris, US Patent 6,248,776 (June 19, 2001), US Patent 6,162,479 (December 19, 2000), and US Patent 6,124,477 (December 30, 1997).
2. K. Alster, US Patent 4,990,631 (February 15, 1991)
3. M.S. Cohen *et al*, US Patent 4,891,436 (January 2, 1990)

Oxadiazines

Patent: Oxadiazine Derivatives
P. Malenfisch *et al*, US Patent 6,627,753 (September 30, 2003)
Assignee: Syngenta Investment Corporation
Utility: Pesticides

Reaction



- i- Paraformaldehyde, triethylamine, 1,4-dioxane, toluene
ii- 2-Chloro-5-chloromethylpyridine, potassium carbonate,
N,N,-dimethylformamide

Experimental

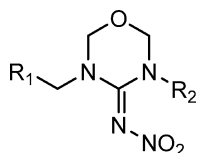
1. 3-Methyl-4-nitroamine-1,2,3,6-tetrahydro-1,3,5-oxadiazine

A reactor was charged with paraformaldehyde (30.5 g), N-methyl-N'-nitroguanidine (20 g), triethylamine (17 g) and 100 ml apiece toluene and dioxane, and the mixture refluxed 16 hours. Thereafter, the solvent was evaporated, the residue purified by column chromatography on silica using CH_2Cl_2 /methyl alcohol, 95:5, and the product isolated, mp = 137–139 °C.

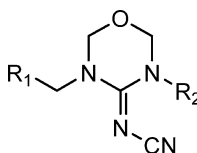
2. 5-(2-Chloropyrid-5-ylmethyl)-3-methyl-4-nitroiminoperhydro-1,3,5-oxadiazine

The product from Step 1 (1.44 g), 2-chloro-5-chloromethylpyridine (2.2 g), K_2CO_3 (3.7 g) and 20 ml DMF were heated to 50 °C 4 hours. The mixture was filtered, purified as in Step 1, and the product isolated, mp = 116–118 °C.

Derivatives



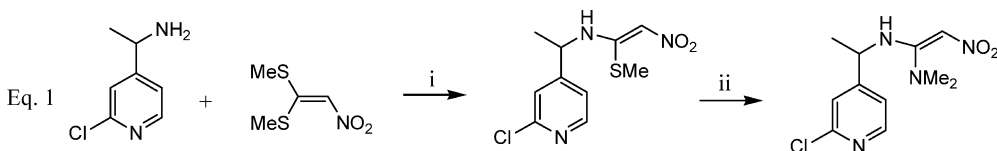
R_1	R_2	Melting Point (°C)
5-(2-Chloropyridine)-	Methyl	116–118
3-(Pyridine-N-oxide)-	Methyl	210 (dec)
5-(2-Chloropyridine)-	Propargyl	103–108



R_1	R_2	Melting Point (°C)
3-(5-Chloro-pyridine-N-oxide)-	Methyl	188–191
3-(5-Chloro-pyridine)-	n-Propyl	Resin
3-(6-Chloro-pyridine)-	Methyl	108–109
4-(2-Chloro-thiazole)-	Methyl	92–93

Notes

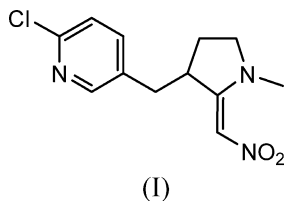
- Other methods have also been used to prepare nitroguanidine precursors as illustrated in Eq. 1 and discussed (1).



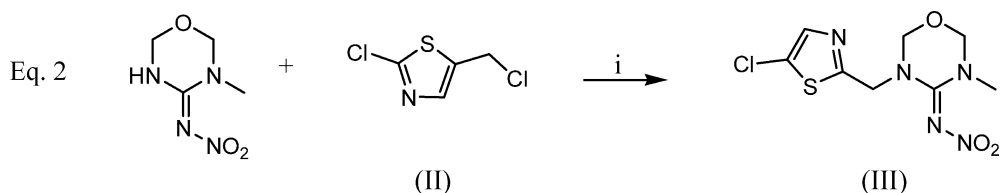
i- Ethyl alcohol

ii- Ethyl alcohol, water, diethylamine

2. In a subsequent investigation by the author, the Step 3 analogue, 3-(2-chloropyrid-5-yl-methyl)-2-nitromethylidene-pyrrolidine, (I), and derivatives were prepared and are described (2).

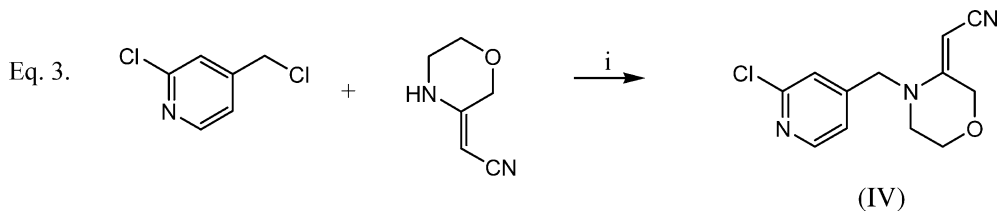


3. When the author reacted 2-chloro-5-chloromethyl-thiazole, (II), with 3-methyl-4-nitroamine-1,2,3,6-tetrahydro-5-(2-chloro-thiazole-4-yl)-methyl-1,3,5-oxadiazine, the Step 3 product, 3-methyl-4-nitroamine-1,2,3,6-tetrahydro-5-(2-chloro-thiazole-4-yl)-methyl-1,3,5-oxadiazine, (III), was isolated.



i- Dimethyl carbonate, tetrabutylammonium hydroxide
pentahydrate, potassium carbonate

4. Morpholine derivatives, (IV), have been prepared using 2-chloro-5-chloromethylpyridine as illustrated in Eq. 3 and are described (4).



i- Acetonitrile

References

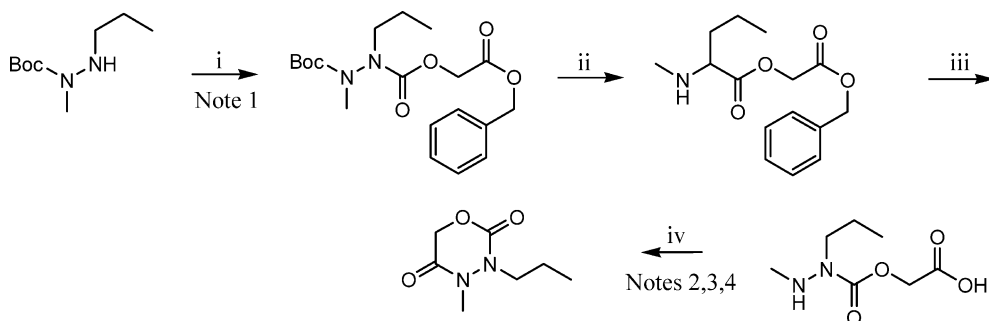
1. S. Kozo *et al*, US Patent 5,051,434 (September 24, 1991)
2. P. Malenfisch *et al*, US Patent 6,664,248 (December 16, 2003)
3. G. Seifert *et al*, US Patent 6,747,146 (June 8, 2004)
4. K. Shiokawa *et al*, US Patent 5,719,146 (February 17, 1998) and US Patent 5,034,524 (July 23, 1991)

Patent: 1,3,4-Oxadiazine Derivatives and Their Use as Pesticides
H. Dyker *et al*, US Patent 6,414,158 (July 2, 2002)

Assignee: Bayer Aktiengesellschaft

Utility: Pesticides

Reaction



- i- Cesium carbonate, N,N-dimethylformamide, carbon dioxide, benzyl bromoacetate
- ii- Trifluoroacetic acid, CH_2Cl_2
- iii- EtOAc, 10% palladium on carbon, hydrogen
- iv- Ethyldiisopropylamine, bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride, CH_2Cl_2

Experimental

1. Benzyl (2-t-butoxycarbonyl-2-methyl-1-propylhydrazyl)-carbonyloxy-acetate

For 1 hour CO_2 was introduced into a suspension of Ce_2CO_3 (22.8 g) and 1-t-butoxycarbonyl-2-methyl-1-propylhydrazine (6.55 g) dissolved in 140 ml DMF. Thereafter, benzyl bromoacetate (8.02 g) was added dropwise, CO_2 introduction continued for an additional 45 minutes, and the mixture stirred overnight. The mixture was poured into 300 ml semi-saturated NaCl solution, extracted 3 times with 150 ml EtOAc, dried, and concentrated. The mixture was purified by chromatography using silica gel with cyclohexane/EtOAc, 5:1, and the product isolated in 67% yield. $^1\text{H-NMR}$ data supplied.

2. Benzyl (2-methyl-1-propylhydrazyl)-carbonyloxy-acetate

At 0°C trifluoroacetic acid (16.9 g) was added to the product from Step 1 (6.65 g) dissolved in 50 ml CH_2Cl_2 , stirred 3 hours at 0°C , and then warmed to ambient temperature overnight. The mixture was concentrated, the residue dissolved in 300 ml EtOAc, washed with NaHCO_3 and brine solutions, and dried. The product was isolated in 100% yield after vacuum evaporation of solvent. $^1\text{H-NMR}$ data supplied.

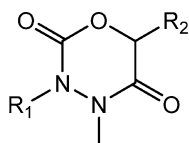
3. (2-Methyl-1-propylhydrazyl)-carbonyloxy-acetic acid

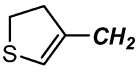
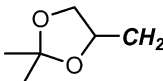
The product from Step 2 (4.36 g) was dissolved in 100 ml EtOAc, 10% palladium on carbon (100 mg) added, and the mixture hydrogenated at 1 bar at ambient temperature. Thereafter, the mixture was filtered through celite, concentrated, and the product isolated in 100% yield. ¹H-NMR data supplied.

4. 3-Propyl-4-methyl-1,3,4-oxadiazane-2,5-dione

At 0 °C, ethyldiisopropylamine (5.49 g) and bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride were added to the product from Step 3 (3.0 g) dissolved in 750 ml CH₂Cl₂. The mixture stirred 2 hours, warmed to ambient temperature, and stirred overnight. Thereafter, the solution was concentrated, dissolved in 300 ml EtOAc, washed, and dried. The product was purified by chromatography on silica gel using cyclohexane/EtOAc, 2:1, and isolated in 71% yield as a yellow-brown oil. ¹H-NMR data supplied.

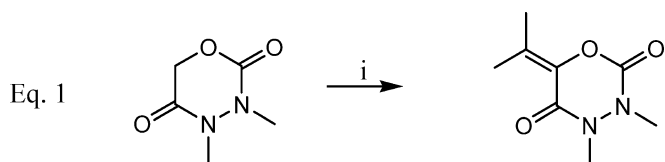
Derivatives



R ₁	R ₂	Melting Point (°C)
i-Butyl	Benzyl	70–71
	Hydrogen	86–88
	Hydrogen	70–72

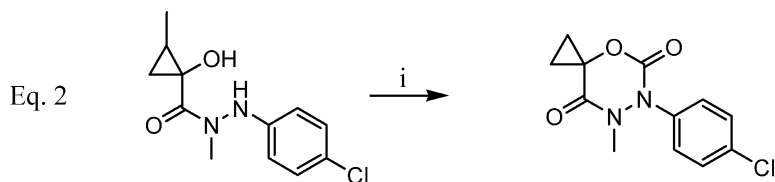
Notes

- Other base catalyzed methods for N-carboxylation of amines and hydrazines using CO₂ and CS₂ to generate the corresponding carbamate or thiocarbamate, respectively, are provided (1). Urea derivatives of Step 1 have also been prepared and are described (2).
- Step 4 derivatives of the invention were also functionalized in the 6-position by the author as illustrated in Eq. 1:



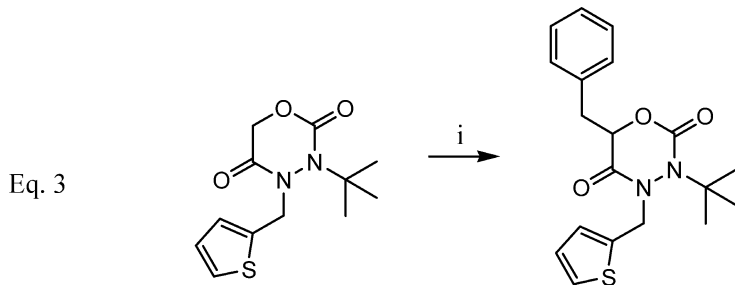
i- Acetone, sodium methoxide

3. 6-spiro derivatives were also prepared by the author as illustrated in Eq. 2:



i- Phosgene

4. In earlier investigations by the author highly substituted oxadiazines were prepared as illustrated in Eq. 3 and are discussed (3).



i- Benzyl bromide, ethyldiisopropylamine, CH_2Cl_2

References

1. O. Yamazaki *et al*, Tetrahedron Lett., 1191 (1974)
2. S. Ogura *et al*, Synthesis, 394 (1978)
3. H. Dyker *et al*, US Patent 6,342,599 (January 29, 2002) and US Patent 6,127,364 (October 3, 2000)

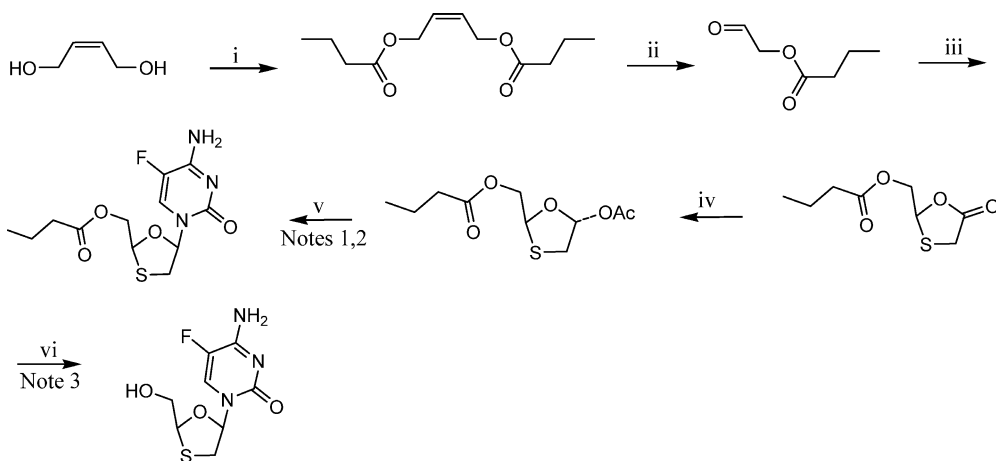
Oxathiolanes

Patent: Antiviral Activity and Resolution of 2-Hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-Oxathiolane
D.C. Liotta *et al*, US Patent 6,642,245 (November 4, 2003)

Assignee: Emory University

Utility: Antiviral Agent for Treatment of HIV

Reaction



i- Butyryl chloride,
4-dimethylaminopyridine, pyridine
ii- CH_2Cl_2 , oxygen, ozone, dimethylsulfide
iii- Thioglycolic acid, toluene

iv- THF, lithium tri(t-butoxide)
aluminum hydride, acetic anhydride
v- Trimethylsilyl-5-fluorocytosine,
tin(IV)chloride, CH_2Cl_2
vi- Sodium methoxide, methyl alcohol.

Experimental

1. 1,4-Dibutyl-2-butene-1,4-diol

A round bottom flask was charged with 2-butene-1,4-diol (1.135 mol), 1,4-dimethylaminopyridine (15 g) and 800 ml pyridine and cooled to 0°C. Thereafter, 260 ml butyryl chloride was added and the mixture stirred 1 hour. The reaction was quenched with a small amount of water, the organic layer washed once with a saturated solution of CuSO₄, twice with a saturated solution of NaHCO₃, and filtered through a celite plug. The concentrated solution was dissolved in diethyl ether and the product isolated under vacuum in almost quantitative yield.

2. 2-Butyryloxyacetaldehyde

The product from Step 1 (1.365 mol) was dissolved in 4 L CH₂Cl₂, cooled to -78°C, and purged with oxygen for 20 minutes. Thereafter, ozone was bubbled into the mixture at 8.5 psi, and upon completion, oxygen was re-bubbled into the solution. The mixture was treated with dimethylsulfide and then stirred at ambient temperature 2 days. The solvent was evaporated, the residue kept under vacuum several days, and the product isolated in 95% yield as a clear yellow liquid.

3. 2-Butyryloxy-methyl-5-oxo-1,3-oxathiolane

The product from Step 2 (1 eq) was dissolved in toluene to provide a 0.80 M to 0.85 M solution in a flask equipped with a Dean-Stark trap. Thioglycolic acid (1.1 eq) was added and the mixture refluxed 3 hours and then cooled. The organic phase was washed with equal volumes of saturated solution of NaHCO₃, water, dried, and filtered through celite. The solution was evaporated under vacuum and the product isolated in 90% yield.

4. 2-Butyryloxy-methyl-1,3-oxathiolane-5-acetate

The product from Step 3 (1.0 eq) was dissolved in THF to give a 0.23 M solution, cooled to 0°C, lithium tri(*t*-butoxide) aluminum hydride (1 eq) in THF added by canula, and the mixture stirred 3 hours. Thereafter, acetic anhydride (10 eq) was added and the mixture stirred 2 days. The reaction was quenched using a saturated solution of NaHCO₃ and the product isolated as an oily liquid in 70% purity.

5. 2-Butyryloxy-methyl-5-(5-fluorcytosine)-1,3-oxathiolane

To trimethylsilyl-5-fluorcytosine (0.124 mol) dissolved in 350 ml CH₂Cl₂ was added 135 ml 1 M SnCl₄ in CH₂Cl₂, the product of Step 4 (0.113 mol) dissolved in 400 ml CH₂Cl₂ and the reaction stirred at ambient temperature 2 hours. Thereafter the reaction was diluted with 500 ml CH₂Cl₂, quenched with 100 ml NH₄OH, and a white precipitate produced. The product was passed through a silica plug, eluted sequentially with 2 L apiece CH₂Cl₂ and EtOAc, and 4 L EtOAc/ethyl alcohol, 9:1, and the product isolated in 71% yield as a white solid.

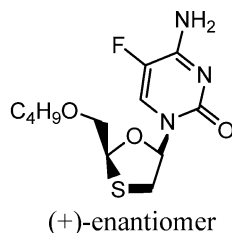
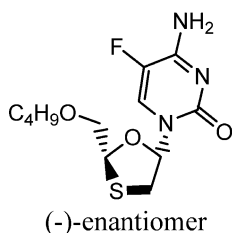
6. 2-Hydroxymethyl-5-(5-fluorcytosine)-1,3-oxathiolane

The product from Step 5 (0.026 mol) was dissolved in 250 ml methyl alcohol, sodium methoxide (0.052 mol) added, and the mixture stirred 1 hour at ambient temperature. The

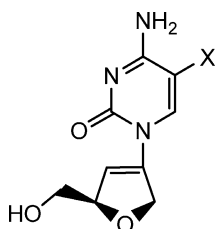
reaction was quenched by the addition of 10 ml NH_4OH and the solvent removed under vacuum. The product was purified by chromatography on silica gel using EtOAc/ethyl alcohol, 9:1, and isolated in 88% yield. $^1\text{H-NMR}$ data supplied.

Notes

1. Silylated 5-fluorocytosine was prepared by refluxing 5-fluorocytosine with at least 10 equivalents of hexamethyldisilazine containing a catalytic amount of $(\text{NH}_4)_2\text{SO}_4$ (0.05 to 0.10 eq) for two hours.
2. 5'-O-butyrate (+/-)-FTC were separated into enantiomers by lipase-catalyzed hydrolysis using pig liver esterase. A non-enzymatic method for this separation is also provided by the author using a Cyclobond I-Ac ($5\ \mu\text{m}$, $25\ \text{cm} \times 4.6\ \text{mm}$) column.



3. The preparation of other 1,3-oxathiolane nucleosides is provided (1).
4. In an earlier investigation by the author (2), cis- and trans-2-benzoyloxymethyl-5-(N-acetyl-5'-fluoro-cytosin-1'-yl)-1,3-oxathiolane were prepared then hydrolyzed into the corresponding alcohols.
5. 5-Fluoro-, amino- (2), -carboxamido-, -nitro-, -ethyl-, -ethynyl-, -amino-, and -cyano (3) 2',3'-unsaturated pyrimidine analogues (I) of the current invention have been prepared (I) and are described.



$\text{X} = \text{F}, \text{NH}_2, \text{CONH}_2, \text{NO}_2, \text{C}_2\text{H}_5, \text{C}_2\text{H}_3, \text{CN}$

(I)

References

1. G. Dionne, US Patent 5,618,820 (April 8, 1997); D.C. Liotta *et al*, US Patent 5,539,116 (July 23, 1996)
2. R.F. Schinazi *et al*, US Patent 6,391,859 (May 21, 2002)
3. R.F. Schinazi *et al*, US Patent 5,703,058 (December 30, 1997)

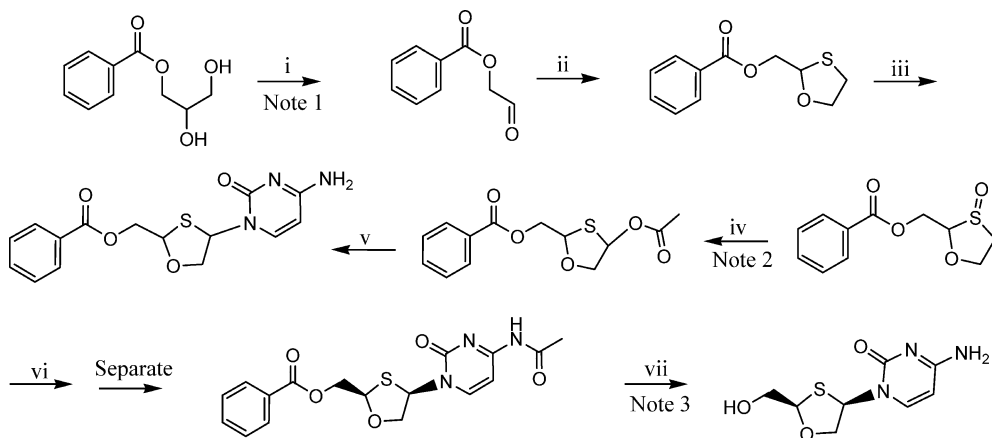
Patent: Substituted 1,3-Oxathiolanes with Antiviral Properties

T.S. Mansour *et al*, US Patent 6,369,066

Assignee: BioChem Pharma Inc.

Utility: HIV Replication Inhibitor

Reaction



i- Sodium periodate, water

ii- 2-Mercaptoethanol, para-toluenesulfonic acid, toluene

iii- Monoperoxyphthalic acid, magnesium salt,
tetrabutylammonium bromide, CH_2Cl_2 , water

iv- Tetrabutylammonium acetate, acetic anhydride

v- Cytosine, ammonium sulfate, hexamethyldisilazane,

vi- CH_2Cl_2 , tin(IV)chloride

vii- 4-Dimethylaminopyridine, acetic anhydride, pyridine

viii- Methanolic ammonia

Experimental

1. Benzoyloxyacetaldehyde

1-Benzoyl glycerol (50 g) dissolved in 500 ml CH_2Cl_2 and 25 ml water was added portion-wise to NaIO_4 under vigorous stirring conditions at ambient temperature. The solution was stirred 2 hours, MgSO_4 (100 g) added, and the mixture stirred an additional 30 minutes. The mixture was filtered, the solution concentrated, and the residue distilled at 92–94 °C at 0.25 mm Hg to obtain 50 g of product. $^1\text{H-NMR}$ data supplied.

2. 2-Benzoyloxymethyl-1,3-oxathiolane

The product from Step 1 (6.21 g), 3 ml 2-mercaptoethanol and para-toluenesulfonic acid (0.2 g) were dissolved in 150 ml toluene and the mixture heated under Dean-Stark conditions 3 hours. The mixture was cooled, washed with 50 ml NaHCO_3 solution and 2.5 ml water, dried, and concentrated. The mixture was purified using chromatography on silica gel with hexane/EtOAc, 9:1, and the product isolated in 90% yield. $^1\text{H-NMR}$ data supplied.

3. cis/trans 2-Benzoyloxymethyl-3-oxo-1,3-oxathiolane

To a solution of the product from Step 2 (20 g) containing NBu_4Br (0.4 g) in 200 ml apiece CH_2Cl_2 and water was added monoperoxy-yphthalic acid magnesium salt (28 g) portionwise with vigorous stirring. Thereafter, the mixture stirred 30 minutes at ambient temperature and the organic layer isolated. The filtrate was concentrated, purified by chromatography on silica gel using EtOAc, and a 1:2 cis/trans product ratio, respectively, isolated in 86% yield, mp = 70–72 °C. $^1\text{H-NMR}$ data supplied for each isomer.

4. cis/trans 2-Benzoyloxymethyl-4-acetoxy-1,3-oxathiolane

The product mixture from Step 3 (10.5 g) and NBu_4OAc (17g) dissolved in 250 ml acetic anhydride were heated to 110–120 °C 14 hours then cooled to ambient temperature. Excess acetic anhydride was removed under reduced vacuum. The residue was dissolved in 500 ml CH_2Cl_2 , washed twice with 200 ml apiece aqueous NaHCO_3 and brine, and dried. The solution was concentrated, the mixture purified by chromatography using silica gel and hexane/EtOAc, 8:1, and the product isolated in 60% yield as a cis/trans isomer mixture.

5. cis/trans 2-Benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane

Cytosine (206 mg), $(\text{NH}_4)_2\text{SO}_4$ (10 mg), and 10 ml hexmethyl-disilazane were heated to reflux until a clear solution resulted. Excess reagents were removed under high vacuum and the residue dissolved in 20 ml CH_2Cl_2 . To this was added the product from Step 4 (350 mg) dissolved in 20 ml CH_2Cl_2 followed by the addition of SnCl_4 in 20 ml CH_2Cl_2 at 0 °C. The mixture was stirred overnight at ambient temperature, refluxed 3 hours, cooled, and then diluted with 100 ml CH_2Cl_2 . Thereafter, the mixture was poured into a NaHCO_3 solution and the organic layer separated. The layer was washed twice with 75 ml water and then 100 ml brine. The organic layer was concentrated, the residue purified by chromatography using silica gel and EtOAc/methyl alcohol, and the product isolated in 35% yield in a 1:1 cis/trans ratio.

6. cis/trans 2-Benzoyloxymethyl-4-(N-4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane

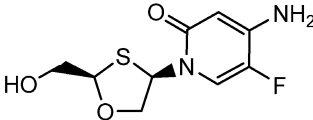
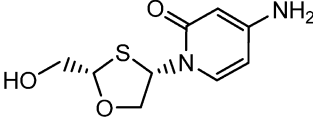
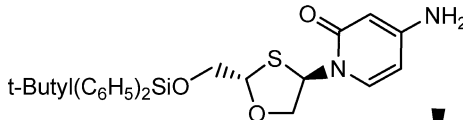
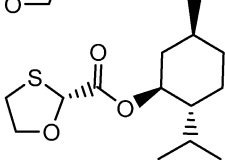
A solution of the product mixture from Step 5 (135 mg), 4-dimethyl aminopyridine (15 mg) and 44 ml acetic anhydride dissolved in 10 ml pyridine were stirred 16 hours at ambient temperature. The mixture was poured into 100 ml cold water, extracted three times with 50 ml CH_2Cl_2 , washed with water, dried, filtered, and concentrated in vacuum. Toluene was added to the residue, evaporated under high vacuum, and an oily residue

obtained. The residue was purified by chromatography on silica gel using EtOAc and 65 mg of the faster moving trans isomer and 60 mg of the cis isomer isolated. ^1H - and ^{13}C -NMR data supplied for both isomers.

7. cis 2-Hydroxymethyl-4-(cytosine-1'-yl)-1,3-oxathiolane

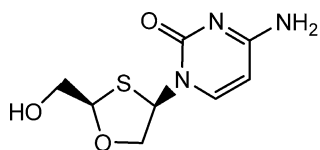
The cis isomer from Step 6 (54 mg) was dissolved in 50 ml methanolic ammonia and stirred overnight at ambient temperature. Thereafter, the solvent was removed and the product isolated in 90% yield, mp = 213–215 °C. ^1H - and ^{13}C -NMR data supplied.

Derivatives

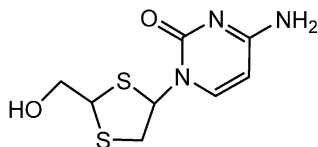
<u>Derivative</u>	<u>Yield (%)</u>	<u>MP.(°C)</u>
	81	183 (dec)
	81	220 (dec)
	78	-----
	87	Oil

Notes

1. A review of oxidative cleavage of glycols is provided (1).
2. This is an example of the Pummerer sulfoxide rearrangement and is discussed (2).
3. The preparation of (2R)-hydroxymethyl-4R-(cytosin-1'-yl)-1,3-oxathiolane, (I), and (cis/trans)-1,3-dithiolane, (II), derivatives of the current invention have also been prepared and are described (3, 4), respectively.



(I)



(II)

References

1. A. Augustine, *Oxidation*, Vol 1, pgs. 189–212, Marcel Dekker, NY (1969)
2. O. DeLucchi, *Org. React.*, 40, 157 (1991)
3. T.S. Mansour *et al*, US Patent 6,228,860 (May 8, 2001)
4. B. Belleau *et al*, US Patent 5,587,480 (December 24, 1996)

Oxazines

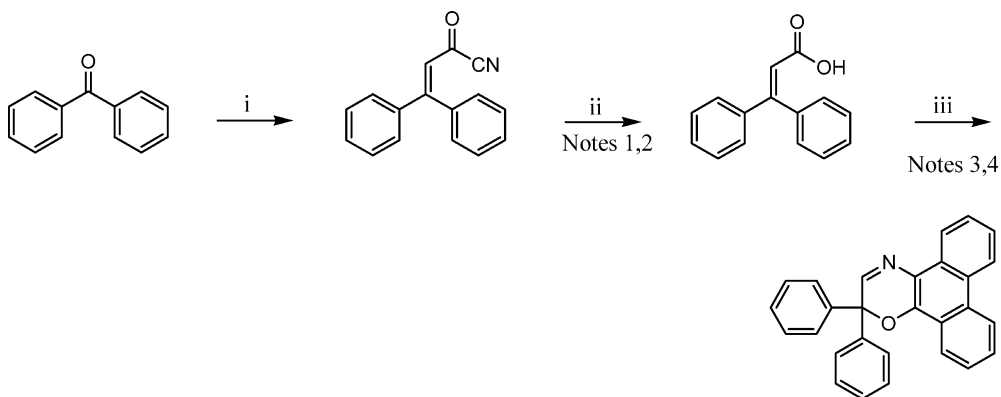
Patent: Photochromic Oxazine Compounds and Methods for Their Manufacture

W. Zhao *et al*, US Patent 6,720,420 (April 13, 2004)

Assignee: Johnson & Johnson Vision Care, Inc.

Utility: Sunlight-Induced Darkening Sunglasses

Reaction



i- Acetonitrile, potassium hydroxide

ii- Sodium hydroxide, ethylene glycol, water

iii- Diphenylphosphoryl azide, triethylamine,
phenanthrene-9,10-dione, triphenyl arsen oxide, toluene

Experimental

1. 3,3-Diphenylacrylonitrile

A flask was charged with KOH (0.05 mol) and 25 ml acetonitrile, heated to reflux, and benzophenone (0.5 mol) dissolved in 20 ml acetonitrile added. The mixture was refluxed 8 hours, poured onto 100 g crushed ice, and the product extracted 3 times with 15 ml CH_2Cl_2 . The extracts were combined, washed with water, dried, filtered and concentrated. The mixture was purified by flash chromatography using silica gel with diethyl ether/hexane, 1:5, and the product isolated in 77% yield. ^1H -NMR data supplied.

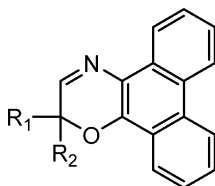
2. 3,3-Diphenylacrylic acid

The product from Step 1 (2.81 mmol), NaOH (280 mmol), 180 ml ethylene glycol, and 1 ml water were refluxed 3 days. Thereafter, the mixture was cooled, acidified to pH 1 using 5 M HCl, filtered, and washed with water. The paste was dissolved in EtOAc and washed with dilute HCl, dried, and the solvent evaporated. The residue was titrated with a small amount of hexane/EtOAc, 4:1, re-crystallized from hexane/EtOAc, and the product isolated in 84.8% yield. ^1H -NMR data supplied.

3. 2,2-Diphenyl-phenanthro (9,10)-2H-[1,4]-oxazine

The product from Step 2 (1.0 mmol), diphenylphosphoryl azide (1.2 mmol), triethylamine (5 mmol), phenanthrene-9,10-dione (0.7 mmol) and triphenyl arsen oxide (0.05 mmol) were dissolved in 12 ml toluene and heated 3 hours at 60°C . The product was purified by chromatography on silica gel using CH_2Cl_2 /hexane, 2:1, re-crystallized in CH_2Cl_2 /hexane, and the product isolated in 100% yield. ^1H - and ^{13}C -NMR data supplied.

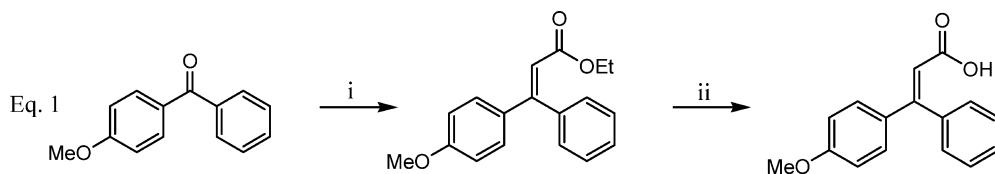
Derivatives



R_1	R_2	Oxazine Formation (%)
4-Methoxyphenyl	4-Methoxyphenyl	93.2
4-Methoxyphenyl	p-Morpholinophenyl	100
Cyclopropyl	p-Piperidinophenyl	80
Methyl	Phenyl	41.9

Notes

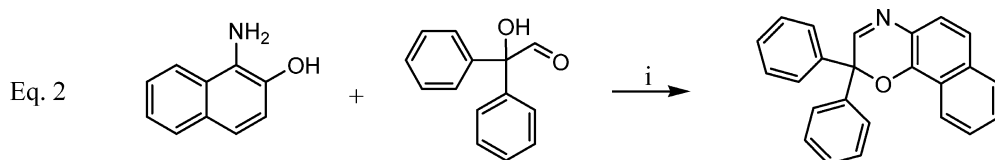
1. An alternative method for preparing the product of Step 3 using the Horner-Emmons reaction was described by the author and is illustrated in Eq. 1:



i- THF, sodium hydride, triethylphonoacetate, ethyl alcohol

ii- Potassium hydroxide, methyl alcohol

2. 2,2-Di-aryl-2H-naphtho[1,2-b]pyran derivatives containing strong, moderate, and weak electron-donating groups at the 8 and 9 positions have been prepared (1). They have also been polymerized (2).
3. A single-step process for preparing oxazine derivatives via the condensation of an α -hydroxyaldehyde and α -amino- β -hydroxy naphthalene (3) is illustrated in Eq. 2:



i- Toluene, paratoluenesulfonic acid

4. Step 3 spirooxazine derivatives of the invention have been prepared (4).

References

1. C.M. Nelson, US Patent 6,348,604 (February 19, 2002)
2. A. Miyashita, US Patent 5,252,742 (October 12, 1993); E. Fischer-Reimann *et al*, US Patent 5,488,119 (January 30, 1996)
3. M. Melzig *et al*, US Patent 5,801,243 (September 1, 1998)
4. H. Ono *et al*, US Patent 3,562,172 (February 9, 1971)

Oxazolidinones

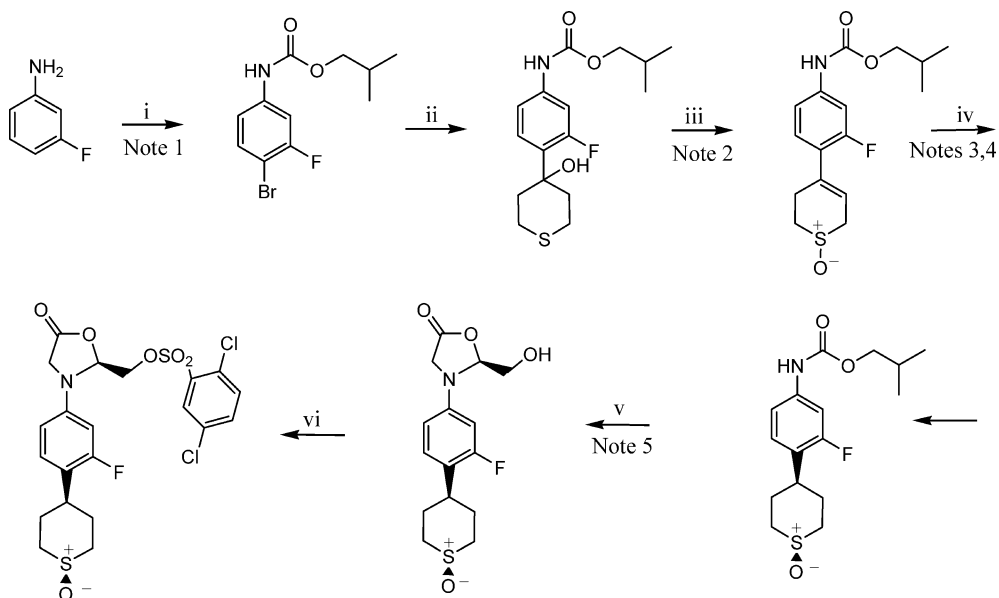
Patent: Process to Prepare Cyclic-Sulfur Fluorine Containing Oxazolidinones

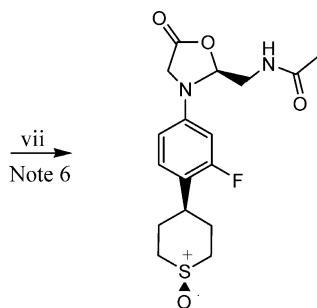
J.R. Gage, US Patent 6,239,283 (May 29, 2001)

Assignee: Pharmacia & Upjohn Company

Utility: Antibacterial Agents

Reaction





- i- CH_2Cl_2 , potassium carbonate, water, isobutyl chloroformate, dibromantin
- ii- Ethyl magnesium bromide, THF, trimethylchlorosilane, 1,10-phenanthroline monohydrate, N,N-tetramethylenediamine, tetrahydrothiopyran-4-one
- iii- CH_2Cl_2 , trifluoroacetic acid, sodium periodate
- iv- N,N-dimethylformamide, 5% palladium on carbon
- v- Lithium t-amylate, (S)-1,2-chloropropanediol
- vi- 2,5-dichlorobenzenesulfonyl chloride, triethylamine, CH_2Cl_2
- vii- Acetonitrile, methyl alcohol, water, CH_2Cl_2 , acetic anhydride

Experimental

1. 2-Methylpropyl-(4-bromo-3-fluoropropyl)carbamate

To 3-fluoroaniline (261.5 mmol) dissolved in 116 ml CH_2Cl_2 was added K_2CO_3 (197.3 mmol) dissolved in 116 ml water at ambient temperature. The mixture was heated to 32°C and isobutyl chloroformate ((282 mmol) added over 13 minutes with cooling and the mixture stirred 3 hours. The mixture was cooled and the pH adjusted to 1.9 using concentrated HCl. The phases were separated, the aqueous phase extracted with CH_2Cl_2 , washed, and added to the organic phase. Dibromantin (200.6 mmol) dissolved in 174 ml water was added to the combined organics and the mixture heated to 42°C for 12 hours. The mixture was cooled, filtered, and the organic phase dried. The solution was then cooled to -30°C whereupon the product precipitated from solution and was isolated by filtration, mp = $79\text{--}82^\circ\text{C}$. $^1\text{H-NMR}$ and MS data supplied.

2. 2-Methylpropyl[3-fluoro-4-(tetrahydro-4-hydroxy-2H-thiopyran-4-yl)phenyl]carbamate

To the product from Step 1, 1,10-phenanthroline monohydrate (2.97 mmol) dissolved in 1.5 L THF containing N,N-tetramethylenediamine (893 mmol) was added ethyl magnesium bromide (348.1 mmol) in THF along with trimethylchlorosilane (325.9 mmol) until a phenanthroline color change occurred. The mixture was cooled to -27°C until the halide

exchange was completed and tetrahydrothiopyran-4-one (382.1 mmol) added. Thereafter, the reaction was quenched using HOAc (1.915 mol) in 570 ml water. The phases were separated, washed once with NH_4Cl (43 g) dissolved in 30% aqueous NH_3 solution (43 g), twice with 570 ml water, and then back extracted with 568 ml methyl t-butyl ether and 220 ml branched octanes. The mixture was cooled to -3°C and the precipitated product isolated by filtration, mp = $148\text{--}151^\circ\text{C}$. $^1\text{H-NMR}$ and MS data supplied.

3. **2-Methylpropyl[4-(3,6-dihydro-1-oxide-2H-thiopyran-4-yl)-3fluorophenyl]carbamate**

The product from Step 2 (197.4 g, 90.1%) was dissolved in 194 ml CH_2Cl_2 and 28 ml trifluoroacetic acid added. The mixture was cooled to 15°C and K_2CO_3 (292 mmol) dissolved in 174 ml water added. The phases were separated and back extracted with CH_2Cl_2 to which was then added 500 ml methyl alcohol followed by the addition of NaIO_4 (233.3 mmol) dissolved in 490 ml water. The slurry was stirred 17 hours at 50°C , cooled to -1°C , and the product isolated by filtration, mp = $212\text{--}214^\circ\text{C}$.

4. **cis-2-Methylpropyl[3-fluoro-4-(tetrahydro-1-oxide-2H-thiopyran-4-yl)phenyl]carbamate**

A slurry of the product from Step 3 (165 mmol) and 5% palladium on carbon (0.055 eq) in 538 ml DMF was hydrogenated at 51 psig at ambient temperature 23 hours. Thereafter, hydrogen was vented and exchanged with nitrogen, the mixture heated to 63°C 2 hours, and the product isolated, mp = $178\text{--}180^\circ\text{C}$.

5. **[4(R)-cis]-3-[Fluoro-4-(tetrahydro-1-oxide-2H-thiopyran-4-yl)phenyl]-5-hydroxymethyl)-2-oxazolidinone**

The product from Step 4 was cooled to 14°C and treated with lithium t-amylate (504 mmol) followed by the addition of 16.7 ml (S)-1,2-chloropropanediol over 45 minutes. The temperature was maintained between 28 and 32°C 2 hours, quenched using 37.5 ml HOAc and 225 ml water, and the pH adjusted to 6 to 9 using NH_4OH . Solka flocc (53.74 g) was added and the mixture heated to 75°C . Thereafter, the solids were removed, washed with 805 ml THF, and the filtrate concentrated. The mixture was cooled to -10°C and the precipitated product isolated by filtration, mp = $194\text{--}197^\circ\text{C}$. $^1\text{H-NMR}$ and MS data supplied.

6. **[4(R)-cis]-[3-Fluoro-(tetrahydro-1-oxide-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl 2,5-dichlorobenzene sulfonate**

To the product from Step 5 (148.1 mmol) dissolved in 417 ml CH_2Cl_2 containing 40 ml triethylamine was added 2,5-dichlorobenzene-sulfonyl chloride, the mixture stirred 5 hours at 2°C , and 1 hour at 6°C . The mixture was quenched using K_2CO_3 (89.9 mmol) dissolved in 239 ml water, warmed to 30°C , and treated with 400 ml water and 600 ml CH_2Cl_2 . The phases were separated and the organic phase washed and concentrated. The concentrate was treated with 500 ml methyl alcohol, dried, and re-concentrated. The

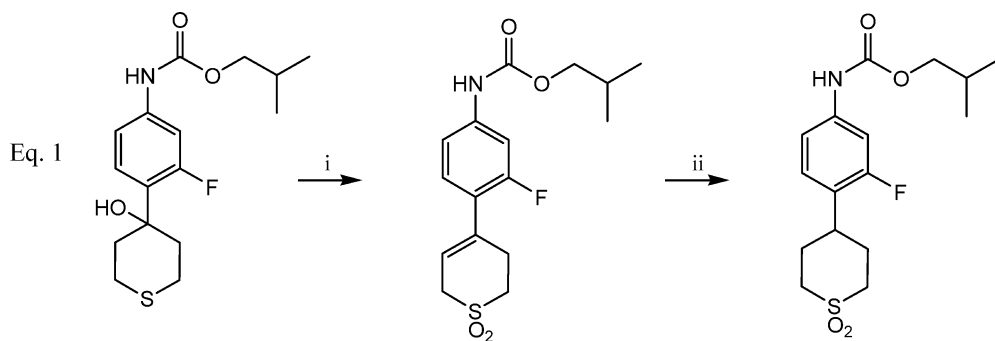
mixture was cooled to -10°C and the product isolated by filtration, mp = $91-93^{\circ}\text{C}$ (dec). $^1\text{H-NMR}$ and MS data supplied.

7. **[4(R)-cis]-N-[3-[3-Fluoro-(tetrahydro-1-oxide-2H-thiopyran-4yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide**

The product from Step 6 (126.19 mmol) was dissolved in 363 ml acetonitrile to which was added 122 ml methyl alcohol and 680 ml 29.6% NH_4OH . The mixture was heated to 34°C and 40°C for 19 hours, cooled, filtered, washed 3 times with 75 ml water, once with 440 ml CH_2Cl_2 , and 340 ml acetonitrile added. The phases were separated, the pH adjusted to 9.0 using NaOH (207.1 mmol), and then acetic anhydride (246.9 mmol) added. The resulting solids were removed by filtration and the mixture concentrated. The residue was dissolved in 500 ml EtOAc, concentrated, and re-dissolved in 500 ml EtOAc. The solution was concentrated under reduced pressure, cooled to -30°C , and the product isolated by filtration, mp = $201-203^{\circ}\text{C}$. $^1\text{H-NMR}$ and MS data supplied.

Notes

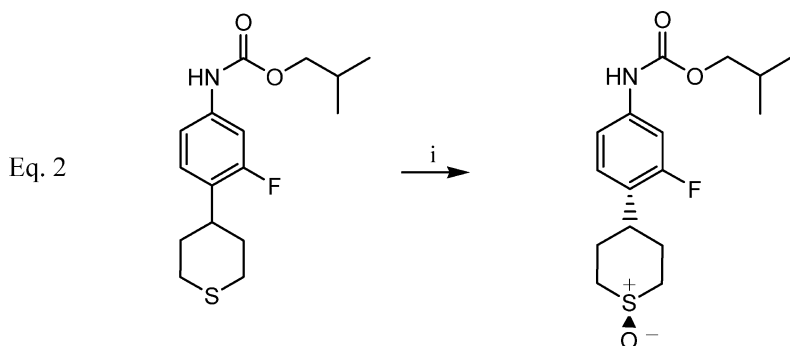
1. To mitigate the formation of benzyne intermediates that occur with o-halophenyl intermediates, m-fluoroaniline was used (1).
2. The author also converted the product of Step 2 into 2-methyl-propyl [4-(3,6-di-1,1-dioxide-2H-thiopyran-4-yl)-3-fluorophenyl]-carbamate by oxidation with Oxone as illustrated in Eq. 1:



i- CH_2Cl_2 , trifluoroacetic acid, Oxone

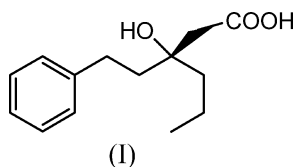
ii- N,N-dimethylformamide, 5% palladium on carbon

3. The trans isomer of the product of Step 3 was also prepared by the author as illustrated in Eq. 2:

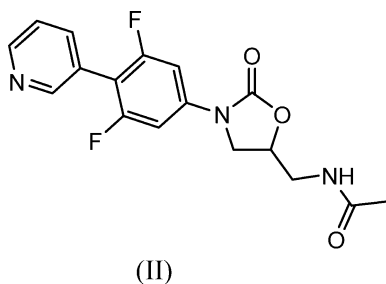


i- Diisopropyl L-tartrate, titanium(IV)isopropoxide,
t-butylhydroperoxide

4. Isomers were separated by HPLC using a 4.6 X.250 mm Zorbax RX C-8 column.
5. In a subsequent investigation by the author (2), methods for preparing (R)-3-hydroxy-3-(2-phenylethyl)-hexanoic acid, (I), derivatives are described.



6. The preparation of (+/-)-5-(acetamidomethyl)3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone, (II), and other phenyloxazolidinones of the current invention are described (3).



References

1. R.W. Hoffman, *Dehydrobenzene and Cycloalkynes*, Academic Press, NY (1967) pp. 31-33
2. J.R. Gage *et al*, US Patent 6,265,604 (July 24, 2001)
3. M.R. Barbachyn *et al*, US Patent 5,654,435 (April 5, 1997) and US Patent 5,523,403 (June 4, 1996)

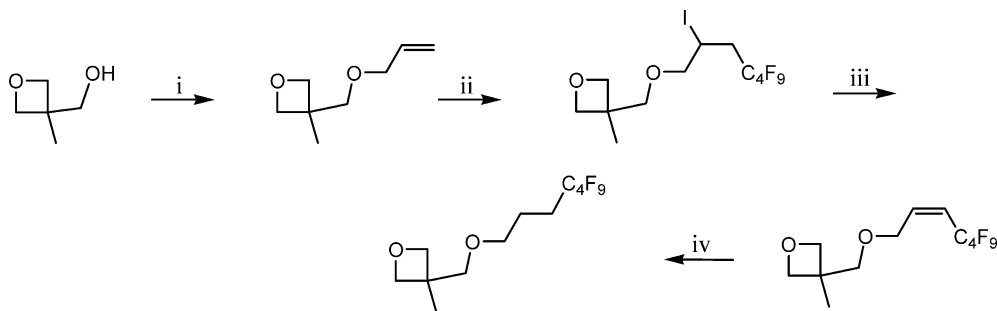
Oxetanes

Patent: Fluorinated Oxetane Derivatives and Production Process Thereof
T. Masutani *et al*, US Patent 6,673,948 (January 6, 2004)

Assignee: Daikin Industries, Ltd.

Utility: Perfluoroether Polymer Precursor

Reaction



- i- Sodium hydroxide, water, tetrabutylammonium chloride, allyl bromide, hexane
- ii- Nonafluorobutyl iodide, azobisisobutyronitrile
- iii- Methyl alcohol, potassium hydroxide
- iv- 5% Palladium on carbon, hydrogen

Experimental

1. 3-Alloxymethyl-3-methyloxetane

To 3-methyl-oxetane methanol (20.4 g) was added 50% aqueous NaOH (268 g), NBu_4Cl (2.8 g) and 300 ml hexane at ambient temperature. Thereafter, allyl bromide (19.4 g) was added dropwise and the solution refluxed 2 hours. The solution was cooled, the phases separated, and the aqueous phase extracted with EtOAc and added to the organic phase. The solvent was removed by distillation and the product isolated in 61% yield in 98% purity. ^1H -NMR data supplied.

2. 3-(4,4,5,5,6,6,7,7,7-Nonafluoro-2-iodoheptyloxy)-3-methyloxetane

The product from Step 1 (7.1 g), nonafluorobutyl iodide (51.9 g) and AIBN (0.245 g) were heated to 70°C 1 hour. Thereafter unreacted nonafluorobutyl iodide was removed by distillation and the product isolated in 85% yield in 94% purity. ^1H - and ^{19}F -NMR data supplied.

3. 3-(4,4,5,5,6,6,7,7,7-Nonafluoro-2-heptenyloxy)-3-methyloxetane

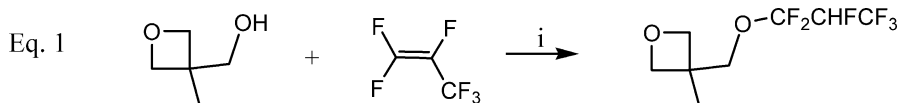
The product from Step 2 (19.5 g) and 25 ml methyl alcohol containing KOH (4.2 g) were reacted at ambient temperature overnight. Thereafter, the reaction was filtered, washed, dried, and the product isolated in 59% yield as cis/trans isomers, 78:22, respectively, in 93% purity. ^1H - and ^{19}F -NMR data supplied.

4. 3-(4,4,5,5,6,6,7,7,7-Nonafluoro-2-heptyloxy)-3-methyloxetane

The product from Step 3 (7.2 g) and 5% palladium on carbon were charged into a flask and hydrogenated at 60 ml/min for 4 hours at ambient temperature. The mixture was filtered through celite to remove the catalyst and the product isolated in 95% yield and 95% purity. ^1H - and ^{19}F -NMR data supplied.

Notes

1. A single step method for preparing other Step 4 perfluoroalkoxy-oxetane derivatives is illustrated in Eq. 1 and discussed (1).



i- Tetrabutylammonium chloride, hexane, sodium hydroxide, water

2. 3,3-Bis(perfluoroalkylthioether)oxetanes have been prepared and are described (2).
3. Other methods for preparing perfluoroalkyl- and perfluoroalkoxy oxetanes intermediates and derivatives of the current invention are described (3,4).

References

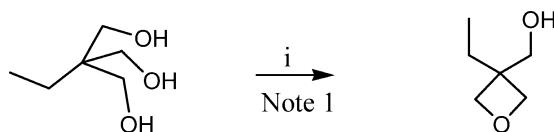
1. A. Yamamoto, US Patent 6,673,947 (January 6, 2004)
2. R.A. Falk *et al*, US Patent 5,097,048 (March 17, 1992)
3. V.A. Petrov *et al*, US Patent 5,481,028 (January 2, 1996)
4. A.A. Malik *et al*, US Patent 6,417,314 (July 9, 2002) and D.B. Pattison, US Patent 2,924,607 (February 9, 1960)

Patent: Process for the Production of 3-Alkyl-3-Hydroxymethyloxetanes
K.-U. Gaudi *et al*, US Patent 6,166,228 (December 26, 2000)

Assignee: Dainippon Ink and Chemicals, Inc.

Utility: Poly(hydroxymethyl)ether Precursor

Reaction



i- Diethyl carbonate, potassium carbonate

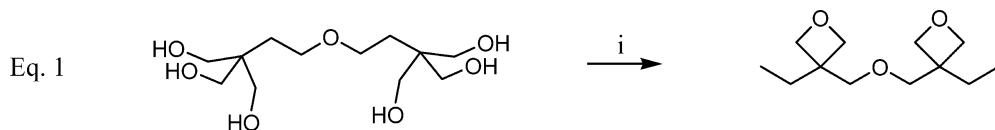
Experimental

1. 3-Ethyl-3-hydroxymethyloxetane

A 20 L steel reactor was charged with trimethylolpropane (55 mol), diethyl carbonate (55 mol) and K_2CO_3 (76 g) and stirred 6 hours at 103–105°C. Thereafter, the volatile components were distilled from the mixture at the same temperature. Toward the end of the reaction a pressure of 150–200 hPa was established at a temperature of 135–140°C. After an additional 4 hours, the pressure was further lowered to 33 hPa and product began to distill until a 87% yield was collected.

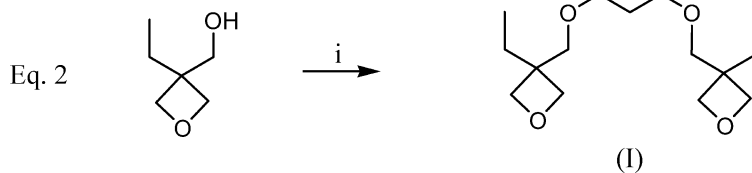
Notes

1. This is a 3 stage reaction. In the first stage, the reaction mixture is heated to reflux for 6 hours at a temperature range between 90 and 120°C. In the second stage, ethyl alcohol is distilled off at the same temperature. In the final stage, the mixture is heated to between 125 and 150°C to decarboxylate and de-oligomerize the intermediate and the product isolation by distillation.
2. A conversion of only 42% was observed in the preparation of 3-ethyl-3-hydroxymethyloxetane using identical reagents and analogous reaction stoichiometry when decarboxylation and de-oligomerization was conducted at 220°C (1).
3. 1,1-Di-(3-ethyloxetane)dimethylether was prepared using ditrimethylol-propane (2) as illustrated in Eq. 1:



i- Dimethyl carbonate, potassium carbonate

4. 1,3-(3-Ethyl-3-oxymethyl)oxetanyl-propane, (I), was prepared (1,3) by reacting the product of Step 1 with 1,3-dibromopropane as illustrated in Eq. 2:



i- 1,3-Dibromopropane, potassium hydroxide,
tetrabutylammonium bromide

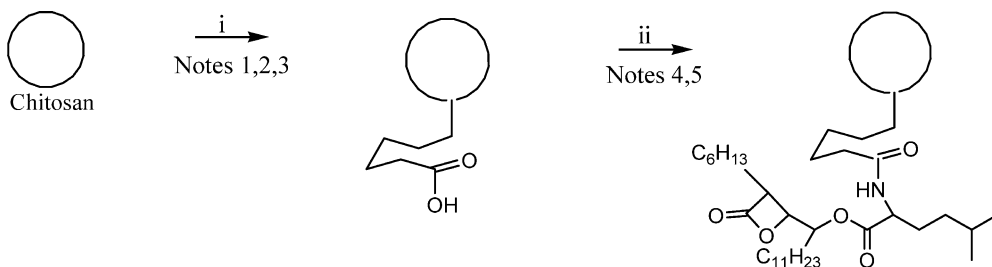
References

1. J.V. Crivello *et al*, US Patent 5,463,084 (October 31, 1995)
2. S. Takami *et al*, US Patent 5,721,020 (February 24, 1998)
3. R. Schaefer *et al*, US Patent 5,750,590 (May 12, 1998)

Oxetanones

Patent: Oxetanone Derivatives
J.J.G. Mullins, US Patent 6,342,519 (January 29, 2002)
Assignee: 2 Pro Chemical
Utility: Lipase Inhibitors for Lowering Serum Cholesterol

Reaction



- i- N,N-Dimethylformamide, sodium hydroxide, 6-bromohexanoic acid
- ii- THF, 1H-benzotriazolium-1-[bis-(dimethylamino)-methylene]-hexafluorophosphate(1-)-3-oxide, tetrahydrostatin L-leucine ester, diisopropylethylamine, N,N-dimethylformamide

Experimental

1. Chitosan-g-hexanoic acid

Chitosan (20 g) was dissolved in 350 ml DMF and the temperature raised to 50°C. A solution of NaOH (0.2 g) and 6-bromohexanoic acid (1 g) dissolved in 20 ml DMF

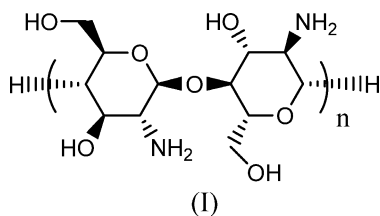
was slowly added and the reaction stirred 4 hours. The mixture was cooled, precipitated in 500 ml ethyl alcohol, and washed 3 times with cold ethyl alcohol. The crude product was re-dissolved in 1 M NaOH dissolved in ethyl alcohol and stirred hours. Thereafter, solution pH was neutralized with 1 M HCl, washed three times with water/ethanol alcohol, 4:1, and the product isolated.

2. **2S,3S,4S-[2-{(Chitosan-g-6-hexanoylamido)-4-methylvaleryloxy]-2-hexyl-hexadecanoic 1,3-lactone**

The product was Step 1 (9 g) was dissolved in 200 ml THF and 1H-benzotriazolium-1-[bis(dimethylamino)methylene]hexafluoro-phosphate(1-)-3-oxide) (10 mmol) dissolved in 10 ml DMF and added over 10 minutes. Tetrahydrostatin L-leucine ester (525 mg) dissolved in 100 ml THF was added, the reaction pH adjusted to 8.5 using diisopropylethylamine, and the mixture stirred overnight. Thereafter, the reaction volume was reduced by 50% and the product precipitated in 500 ml hexane. The crude product was washed 3 times with ethyl alcohol/water, 3:1, and dried under a lyophilizer.

Notes

1. The polymer substrate consisted of low viscosity chitosan, poly(D-glucosamine), (I), which had a Brookfield viscosity of a 120–200 cps in 1% acetic acid solution.



2. The author also prepared a second derivative by hydroxymethylating chitosan with paraformaldehyde and post-reacting with the lipase inhibitor tetrahydrosterastin. Other graft polymer derivatives of the current invention are described (1).
3. The preparation of 3,5-di-hydroxy-2-hexylhexadeca-7,10-dienoic 1,3-lactone and 3,5-di-hydroxy-2-hexylhexadecanoic 1,3-lactone is described (2).
4. In subsequent investigation by the author, 5-(3-chitosanoxypropyloxy)-2-hexyl-hexadecanoic 1,3-lactone was prepared and is described (4).
5. The objective of grafting absorbable lipases such as esterastin or tetrahydroesterastin onto a non-absorbable biocompatible substrate is to rendere the product non-absorbable. The non-absorbable lipase (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexa decanoic 1,3 acid lactone is described (1).

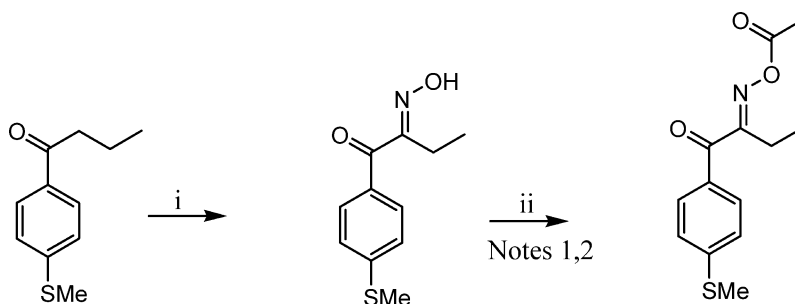
References

1. K.-D. Bremer *et al*, US Patent 5,643,874 (July 1, 1997); J.J.G. Mullins, US Patent 6,392,061 (May 21, 2002)
2. H. Umazaw *et al*, US Patent 4,202,824 (May 13, 1980) and US Patent 4,189,438 (February 19, 1980)
3. J.J.G. Mullins, US Patent 6,348,492 (February 19, 2002)

Oximes

Patent: O-Acyloxime Photoinitiators
A. Matsumoto *et al*, US Patent 6,596,445 (July 22, 2003)
Assignee: Ciba Specialty Chemicals
Utility: Photopolymerization Initiators

Reaction



i- Isoamyl nitrite, methyl alcohol, sodium methoxide, acetic acid
ii- THF, acetyl chloride, triethylamine

Experimental

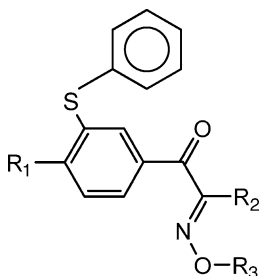
1. 1-(4-Methylsulfonyl-phenyl)-butan-1,2-dione-2-oxime

Sodium methoxide (0.206 mol) was suspended in 130 ml methyl alcohol and isoamyl nitrite (0.206 mol) and 1-(4-methylsulfonyl-phenyl)-butan-1-one dissolved 70 ml THF added. The solution was stirred at ambient temperature 2 days, concentrated, then neutralized with HOAc. The mixture was extracted with EtOAc, washed, dried, purified by chromatography on silica using EtOAc/hexane, 15:85, and the product isolated. ¹H-NMR data supplied.

2. 1-(4-Methylsulfanyl-phenyl)-butan-1,2-dione-2-oxime-O-acetate

The product from Step 1 (15.7 mmol) was dissolved in 20 ml THF and cooled in an ice bath. Thereafter, acetyl chloride (17.3 mmol) and triethylamine (23.6 mmol) were successively added, the reaction stirred 1 hour, and the mixture poured into water. The product was extracted with EtOAc, purified by chromatography on silica gel using EtOAc/hexane, 20:80, and the product isolated. ¹H-NMR data supplied.

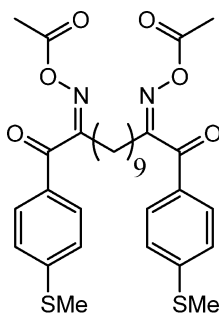
Derivatives



R ₁	R ₂	R ₃	MP(°C)
Hydrogen	Ethyl	Benzoate	78–80
Methoxide	Ethyl	Benzoate	89–93
Hydrogen	n-Hexyl	Acetate	oil
Hydrogen	n-Propyl	Benzoate	48
Hydrogen	Hydrogen	Acetate	70–71

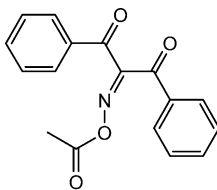
Notes

1. Photoinitiators of the current invention become activated in the region between 190 and 600 nanometers.
2. Dimer initiators, (I), were also prepared by the author and are described.



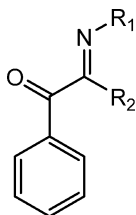
(I)

3. The preparation of 1,3-diketone-2-oxime photoinitiators, (II), activated between 400 and 600 nanometers is discussed (1).



(II)

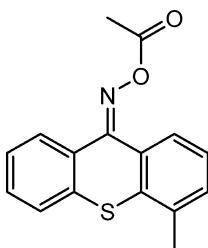
4. Other Step 3 N-alkoxy derivatives, (III), of the current invention have been prepared and are described (2).



(III)

R_1	R_2
Ethyl carbonate	Benzoyl
Benzoate	Ethyl carbonate
Benzoate	Phenylsulfonyl

5. O-Acyloxime thioxanthone photoinitiators, (IV), have been prepared and are discussed (3).



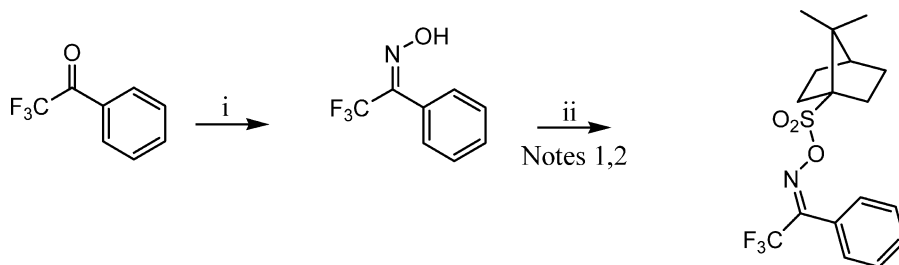
(IV)

References

1. H. Yamato *et al*, US Patent 6,673,850 (January 6, 2004)
2. H. Ai *et al*, US Patent 5,019,482 (May 28, 1991)
3. M. Itoh *et al*, US Patent 4,590,145 (May 20, 1986)

Patent: Oxime Derivatives and Their Use Thereof as Latent Acids
T. Asakura *et al*, US Patent 6,512,020 (January 28, 2003)
Assignee: Ciba Specialty Chemicals
Utility: Photoresist Latent Acid for Acid-Curable Resins

Reaction



i- Hydroxylamine hydrochloride, ethyl alcohol, sodium acetate, water

ii- THF, 10-camphorylsulfonyl chloride, triethylamine

Experimental

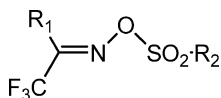
1. 2,2,2-Trifluoro-1-phenyl-ethanone-oxime

2,2,2-Trifluoro-1-phenyl-ethanone (25 g) was dissolved in ethyl alcohol at 80°C and hydroxylamine oxime (0.151 mol) and sodium acetate (0.245 mol) dissolved in 20 ml water added. The mixture refluxed overnight and was then concentrated. The residue was poured into water and a white precipitate isolated and directly in Step 2.

2. 2,2,2-Trifluoro-1-phenyl-ethanone-oxime-O-(10-camphoryl-sulfonate)

The product from Step 1 (10.6 mmol) was dissolved in 40 ml THF, cooled in an ice bath, and 10-camphoryl chloride (11.6 mmol) and triethylamine (15.9 mmol) added. The reaction was stirred at 0°C 3 hours, poured onto ice, and the product extracted with EtOAc. The organic phase was washed with water and brine, dried, and concentrated. The mixture was purified by flash chromatography on silica gel using EtOAc/hexane, 9:1, and the product isolated in 52% yield as Z/E isomers, 9:1, respectively. ¹H-NMR data supplied.

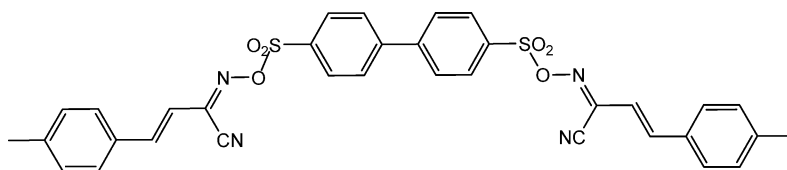
Derivatives



R₁	R₂	MP (°C)
4-Methoxyphenyl	4-Methoxyphenyl	112–115
2,4,6-Trimethylphenyl	2-Naphthyl	122–128
4-Methoxyphenyl	Benzyl	81–82
4-(4'-Benzyl)phenyl	n-Propyl	Oil

Notes

1. Resins blended with oximes of the current invention become cured when exposed to wavelengths between 190 and 700 nanometers. Sunlight or a Philips-TLO5 or -TLO9 fluorescent lamp have been used. Other related oxime photoinitiators are described (1).
2. Di-O-sulfonate oximes were also prepared by the author in the current invention using benzene 1,3-sulfonyl chloride.
3. The preparation I-line photoresists using sulfonate oximes are described (2).
4. The preparation of unsaturated oximes, (I), for use as photosensitive acid donors in positive and negative resists is described (3).



(I)

References

1. H. Yamato *et al*, US Patent 6,673,850 (January 6, 2004)
2. N. Munzel *et al*, US Patent 5,627,011 (May 6, 1997); G. Benner *et al*, US Patent 4,540,598 (September 10, 1985)
3. J.-L. Birbaum *et al*, US Patent 6,703,182 (March 9, 2004)

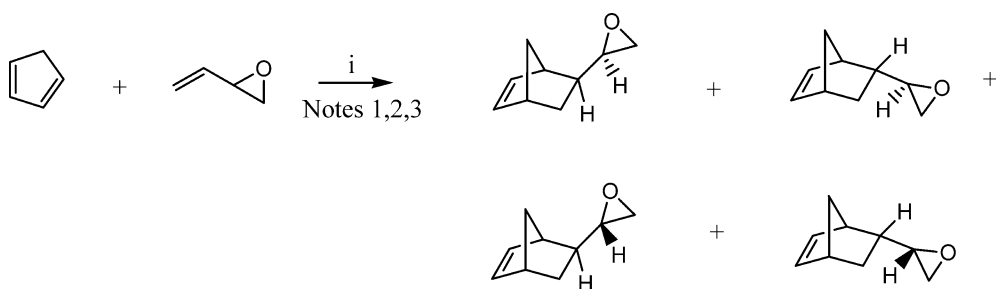
Oxirane

Patent: Diels-Adler Adducts of Epoxybutene and Epoxybutene Derivatives
M.E. Welker *et al*, US Patent 6,559,347 (May 6, 2003)

Assignee: Wake Forest University Health Sciences

Utility: Epoxybutene Derivatives

Reaction



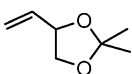
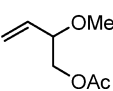
i- 170 °C, 66 hours

Experimental

1. 5-Norbornene-2-endo/exo-oxirane

A thick walled high pressure tube was charged with cyclopentadiene (12.42 mmol) and epoxybutene (117.40 mmol), degassed, and heated on an oil bath at 170 °C for 66 hours. The mixture was cooled, unreacted reagents distilled off, and products isolated using a spinning band distillation column in 92% yield, bp = 75 °C at 11 mm Hg.

Derivatives

Cyclopentadiene adducts			
<u>Dienophile</u>	<u>Rx Temp</u> (°C)	<u>Rx Time</u> (hr)	<u>Mixture Yield</u> (%)
	170	66	65
	170	66	65
	165	48	58
	195	48	40

Notes

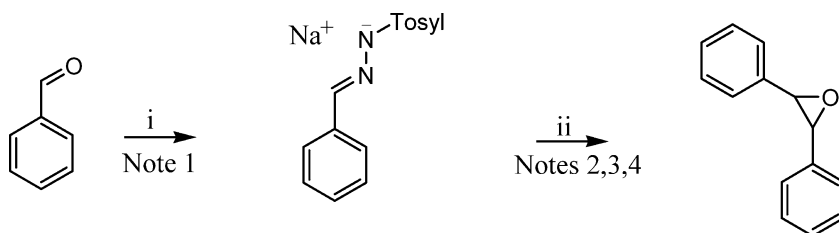
1. The author indicated that in a 1989 Kodak Research Technical Report, with the exception of the diphenylisobenzofuran, dienes used in the Diels-Adler reaction with epoxybutene failed to generate the indicated cycloadducts of the current invention (1).
2. The reaction product mixture consisted of an endo/exo ratio of 77:24.
3. The skewed reagent ratios are based on an earlier observation (2) that higher yields of Diels-Adler adducts were obtained when the diene/ene reagent ratio consistently kept low during the course of the reaction.
4. Low-yielding Diels-Adler reaction yields have been improved using ionic solvents salts as butyl-3-methyl-1-imidazolium tetrafluoroborate (3).

References

1. Godleski *et al*, 'Utilization of Butadiene Monoepoxide as a Dienophile, Kodak Research Technical Report, pp. 1-4, (August 10, 1989)
2. C. Bergstrom *et al*, US Patent 6,294,706 (September 25, 2001)
3. H. Olivier *et al*, US Patent 5,892,124 (April 6, 1999)

Patent: Process for the Preparation of an Oxirane, Aziridine or Cyclopropane
J.R. Studley *et al*, US Patent 6,559,323 (May 6, 2003)
Assignee: Avecia Limited
Utility: Epoxide Preparation Using Insitu Diazo Intermediates

Reaction



i- Tosyl hydrazone, sodium, methyl alcohol
ii- Tetrahydrothiophene, rhodium(II)acetate dimer,
benzyltriethylammonium chloride, benzaldehyde, acetonitrile

Experimental

1. Tosyl hydrazone benzylimine sodium

A 1 M sodium methoxide solution was prepared by adding Na (12.5 mmol) to 12.5 ml methyl alcohol with cooling, tosyl hydrazone (12.25 mmol) added, and the mixture stirred until all solids were dissolved. After stirring an additional 15 minutes the mixture was concentrated and the product ground to a fine powder. Elemental analysis, IR, and ¹H-NMR provided.

2. 2,3-Diphenyloxirane (General epoxidation procedure using achiral sulfides)

A stirred solution of tetrahydrothiophene (0.066 mol), rhodium(II)acetate dimer (0.003 mmol), benzyltriethylammonium chloride (0.066 mmol) and benzaldehyde (0.33 mol) dissolved in 1 ml acetonitrile was added to the product from Step 1 (0.495 mmol). The mixture was heated to 45 °C 3 hours, cooled, and 1 ml EtOAc/water, 1:1, added. The organic phase was dried, the epoxide purified by chromatography on silica with CH₂Cl₂/petroleum ether, 0–25%, and the product isolated.

Derivatives

Step 1 Aldehyde Reagent	Oxirane	Trans/Cis	Yield (%)
Benzaldehyde	2,3-Diphenyl	>98 : 2	95
4-Methoxy benzaldehyde	2-(4-Methoxyphenyl), 3-phenyl	>98 : 2	98
3-Formyl-pyridine	2-Phenyl-3-(3-pyridine)	100:0	71
n-Butanal	2-n-Butyl-3-phenyl	70:30	59

Step 1 Ketone Reagent	Oxirane	Trans/Cis	Yield (%)
Cyclohexanone	2-Cyclohexyl-3-phenyl	100:0	54
Phenylmethylketone	2,3-Diphenyl-2-methyl	100:0	15
4-Nitrophenyl-methylketone	2-(4-Nitrophenyl)-2-methylphenyl	100:0	69

Notes

1. The preparation of other Step 1 oxirane tosyl hydrazone salts is provided (1).
2. Epoxidations were also performed using lithium or ammonium benzaldehyde tosyl hydrazone salts as described by the author.

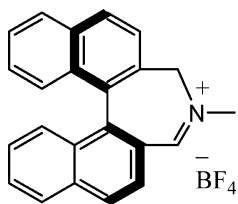
Procedure

Tosyl hydrazone lithium salt was prepared as the product of Step 1.

A solution of copper(II)acetylacetonate (5 mg), 4-chloro-benzaldehyde and tosyl hydrazone lithium salt (2.5 eq) were mixed and heated to 45 °C 3 hours, cooled, and 1 ml EtOAc/water, 1:1, added. The epoxide was isolated as a white solid in 54% yield with a trans/cis ratio of 2.8:1, respectively.

3. Epoxidations were also performed on ketones as described in Step 2 using pentamethylene sulfide (0.0666 mol) as the reaction solvent.
4. The epoxide mechanism consists of the following steps:
 - a. thermal degradation of the tosyl hydrazone to form a diazo intermediate and reaction with $(\text{Rh}(\text{OAc})_2)_2$;
 - b. reaction of the intermediate from Step 1 with the sulfide to form a cyclic intermediate;
 - c. methylene insertion into the Step 2 intermediate in (b) into the ketone or aldehyde carbonyl.
5. Oxirane, azirdine, and cyclopropane derivatives have also been prepared by the decomposition of phenyldiazomethane with $\text{Rh}_2(\text{OCOCH}_3)_4$ in the presence of dimethylsulphide and an aldehyde and are described (2).

6. Enantioselective epoxidation of the product of Step 1 using dinaphthazepinium salts, (I), have been prepared and are described (3).



(I)

References

1. W. Cleary, *Org. Synth.*, 64, 207 (1986)
2. V. Aggarwal *et al*, US Patent 5,703,246 (December 30, 1997)
3. V. Aggarwal *et al*, US Patent 6,063,920 (May 16, 2000)

Phenols

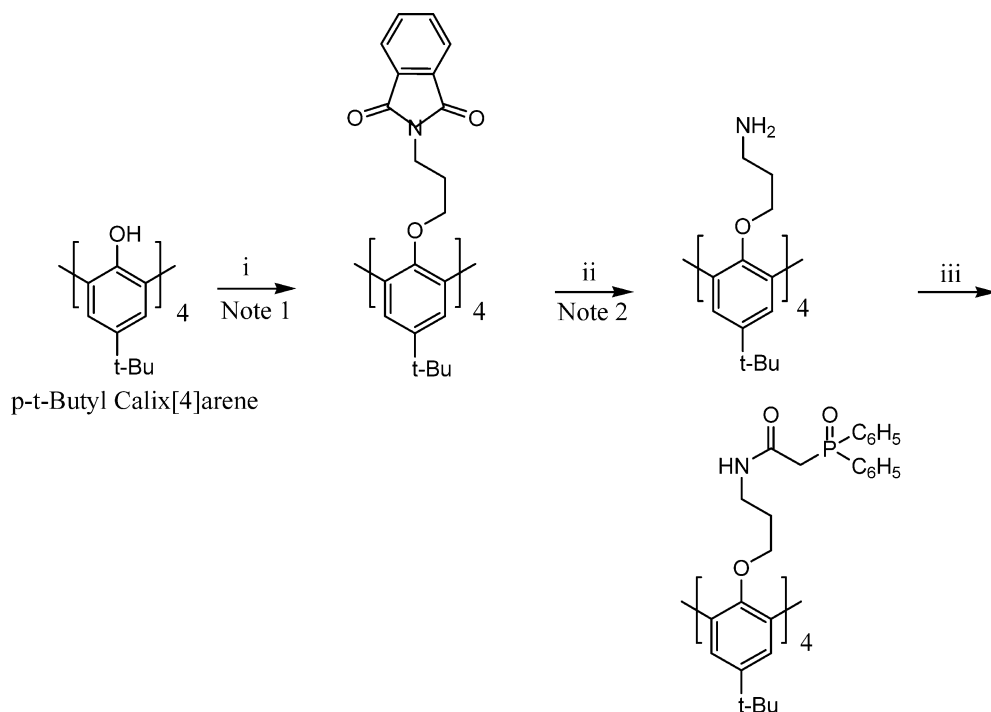
Patent: Calixarene Derivatives

J.-F. Dozol *et al.*, US Patent 6,657,081 (December 2, 2003)

Assignee: Commissariat à l'Energie Atomique

Utility: Chelating Agent for Actinide and Lanthanide Metal Cations

Reaction



- i- N,N-Dimethylformamide, sodium hydride,
N-(3-bromopropyl)phthalimide
- ii- Hydrazine, ethyl alcohol
- iii- Toluene, p-nitrophenyl(di-phenylphosphoryl)acetate

Experimental

1. Tetrakis(3-Phthalimidopropoxy)-p-t-butyl calix[4]arene

To a suspension of p-t-butyl calix[4]arene (15.44 mmol) in 200 ml DMF was added NaH (123.52 mmol) and 320 ml DMF, the mixture stirred 1 hour, and N-(3-bromopropyl)phthalimide (123.52 mmol) added. The mixture stirred 7 days at ambient temperature, 100 ml water added, and the resulting precipitate collected. The precipitate was dissolved in 200 ml chloroform, washed with 50 ml 15% HCl, dried, and the product isolated in 54% yield, mp = 213–215 °C. MS and ¹H-NMR data supplied.

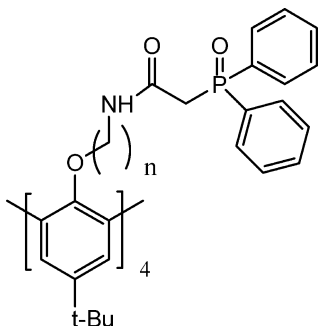
2. Tetrakis(3-Aminopropoxy)-p-t-butyl calix[4]arene

The product from Step 1 was suspended in 60 ml ethyl alcohol, hydrazine (273 mmol) added, the mixture refluxed 12 hours, then diluted with 100 ml water. The precipitate was extracted 4 times with 50 ml CH₂Cl₂ and the product isolated in 98% yield, mp = 197–201 °C. MS and ¹H-NMR data supplied.

3. Tetrakis(3-Diphenylphosphinoxide-acetamide-propoxy)-p-t-butyl calix[4]arene

The product from Step 2 (1.14 mmol) was dissolved in 40 ml toluene, p-nitrophenyl (di-phenylphosphoryl)acetate (5.72 mmol) added, and the mixture heated to 50 °C 18 hours. The solvent was removed, the residue dissolved in chloroform, washed with 5% Na₂CO₃, dried, and the solvent removed. The product was re-crystallized in chloroform/hexane and isolated as a white solid in 75% yield, mp = 244–246 °C. MS and ¹H-NMR data supplied.

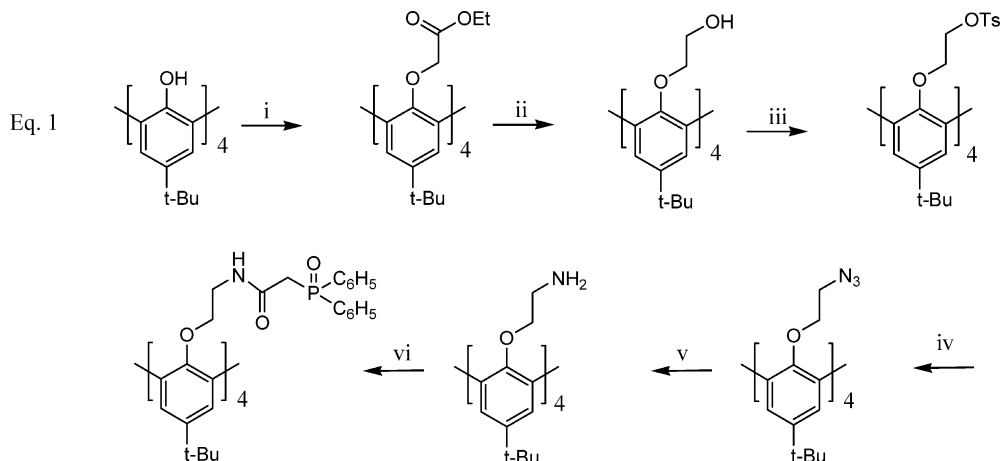
Derivatives



n	Yield (%) (last step)
2	43
3	75

Notes

1. The preparation of p-t-butyl calix[4]arene is described (1).
2. An alternative method for preparing tetrakis(3-aminoalkoxy)-p-t-butyl calix[4]arene was also provided by the author as illustrated in Eq.1:



i- Acetonitrile, potassium carbonate, ethyl bromoacetate

ii- Diethyl ether, lithium aluminum hydride

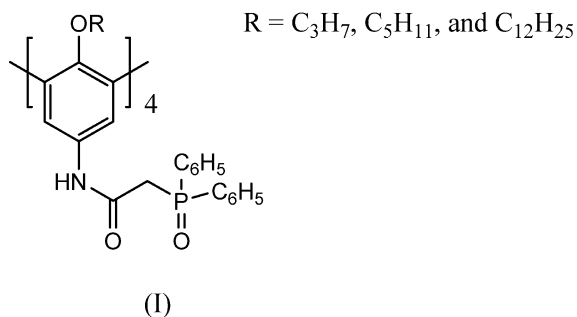
iii- p-Toluenesulfonyl chloride, CH_2Cl_2

iv- N,N-Dimethylformamide, sodium azide

v- Palladium on carbon, hydrogen

vi- Toluene, p-nitrophenyl(di-phenylphosphoryl)acetate

3. Beginning with 4-nitro calix[4]arene, alkoxy derivatives of tetrakis-4-diphenylphosphinoxide-propylamide)-calix[4]arene, (I), have been prepared and are described (2,3).



References

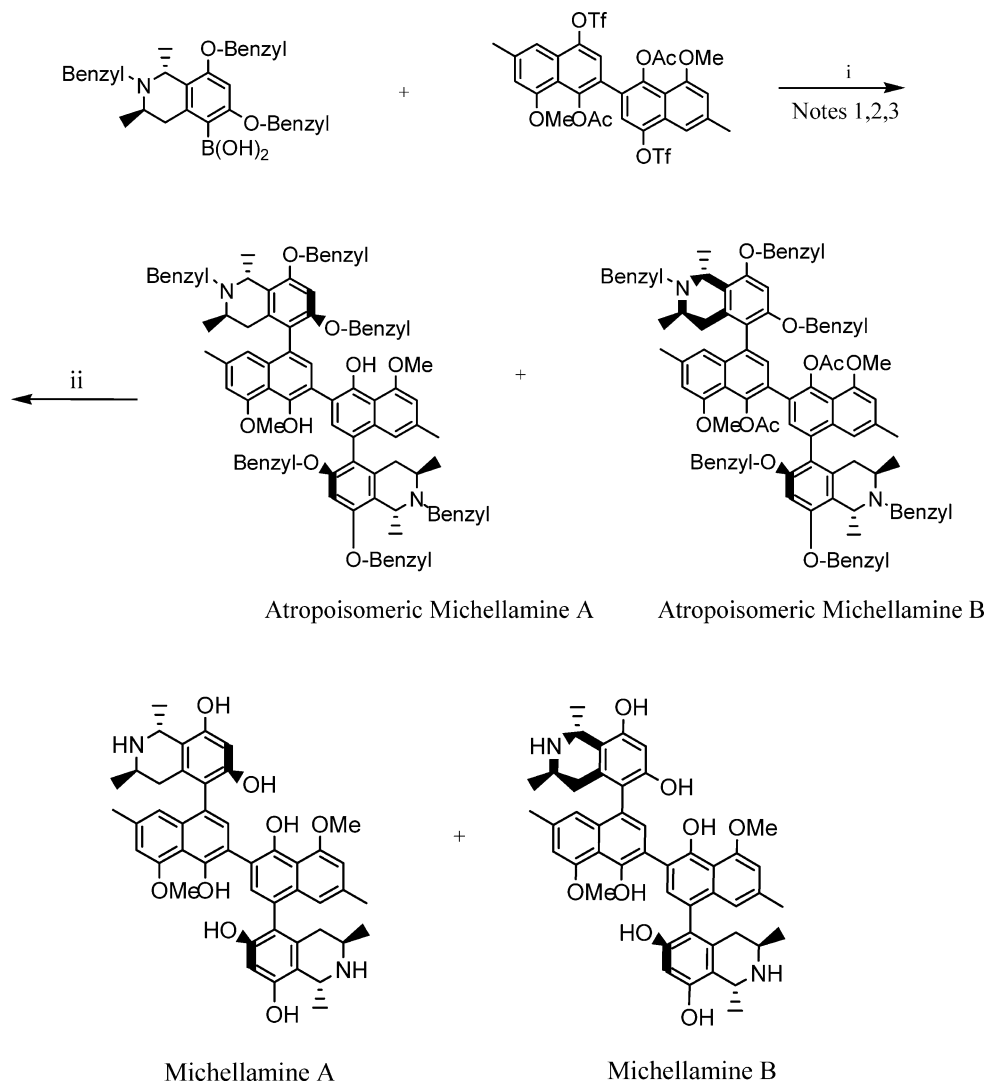
1. I. Alam *et al*, US Patent 5,482,520 (January 9, 1996)
2. L. Delmau *et al*, US Patent 6,312,653 (November 6, 2001) and 6,306,355 (October 23, 2001)
3. J.-F. Dozol *et al*, US Patent 5,866,087 (February 2, 1999)

Patent: Dimeric Arylisoquinoline Alkaloids and Synthesis Method Thereof
G. Bringman *et al*, US Patent 5,786,482 (July 28, 1998)

Assignee: The United States of America as Represented by the Department of Health; Trustees of Boston College

Utility: Antiviral Agent in the Treatment of HIV

Reaction



Experimental

1. Atropoisomeric Michellamines A and B

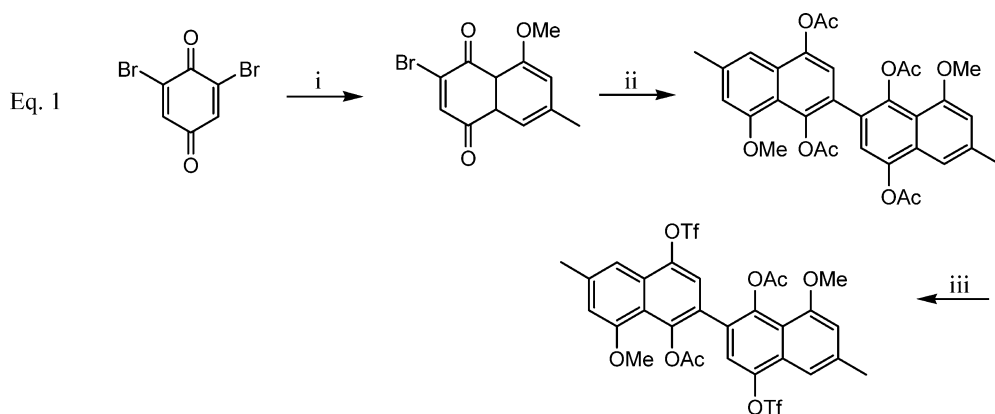
1,3-trans-Dimethyl-6,8-dibenzoyl-N-benzyl-tetrahydroisoquinoyl-5-boronic acid ($39.5\ \mu\text{mol}$) and 3,3'-bis(1-trifluoromethanesulfonyl-16-methyl-4-acetoxy-5-methoxy)-naphthalene ($14.2\ \mu\text{mol}$), a trace amount of tetra(triphenylphosphine)palladium, and barium hydroxide ($43.5\ \mu\text{mol}$) were dissolved in a mixture of 1.5 ml dimethyl ether and 0.5 ml water then heated to 80°C 6 hours. Thereafter, the solvent was removed under vacuo, the residue purified by preparative thin-layer chromatography using petroleum ether/diethyl ether, 2:1, and atropoisomeric michellamines A and B isolated in 31% and 71% yield, respectively.

2. Michellamines A and B

The products from Step 1 were dissolved in 2 ml methyl alcohol containing a trace amount of 10% palladium on carbon and hydrogenated 3 days at ambient pressure. After removal of the solvent, the residue was dissolved in 5 ml methanolic HCl, refluxed 10 hours, and the products isolated as a Michellamine A and B mixture in 85% yield, mp = $175\text{--}177^\circ\text{C}$. $^1\text{H-NMR}$ data supplied.

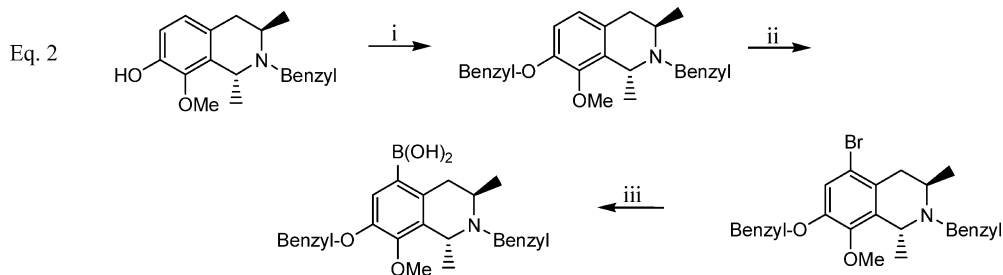
Notes

1. The preparation of the dinaphthanoid reagent of Step 1 is described by the author and illustrated in Eq.1:



- i- THF, 2-trimethylsiloxy-4-methyl-2,4-pentadiene, methyl iodide, silver oxide
- ii- N,N-Dimethylformamide, (activated) copper, tetra(triphenylphosphine)palladium, zinc, acetic anhydride, 4-dimethylaminopyridine
- iii- Triflic anhydride, 2,6-lutidine

2. The preparation of the co-reagent of Step 1, 1,3-trans-dimethyl-6,8-dibenzoyl-N-benzyl-tetrahydroisoquinoyl-5-boronic acid tetrahydroiso-quinoline, is illustrated in Eq. 2 and discussed (1).

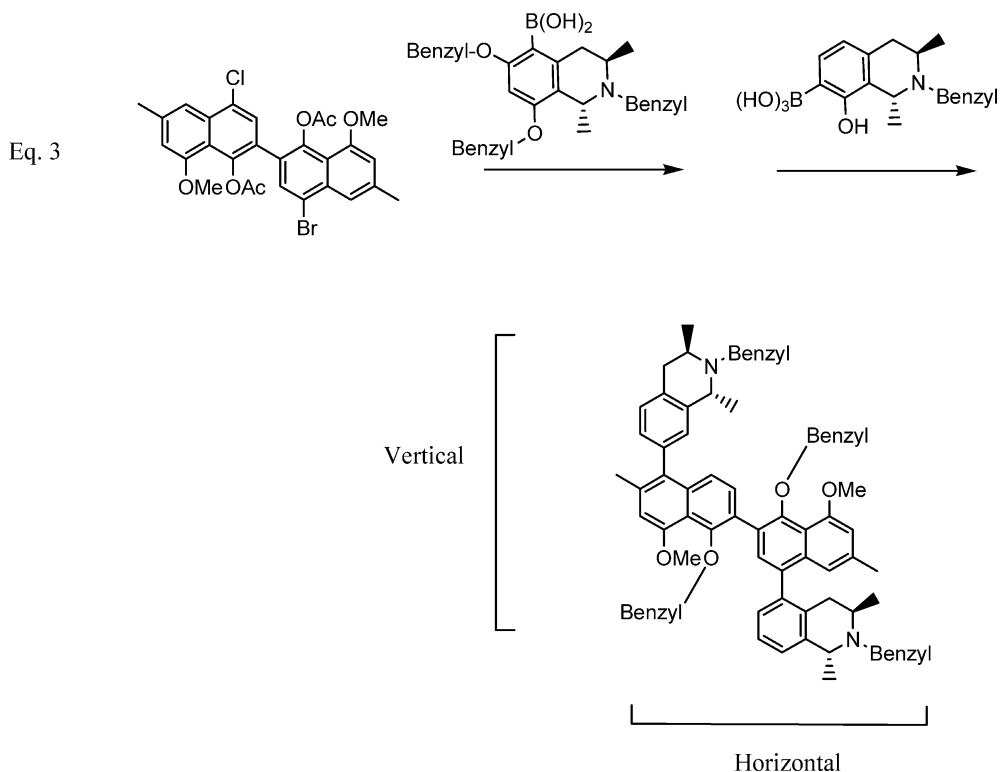


i- Benzyl bromide, potassium carbonate, acetone

ii- Bromine, CH_2Cl_2

iii- Trimethyl borate

3. By altering the coupling sites Step 1 co-reagents, the author prepared dimeric aryltetrahydroisoquinoline alkaloid derivatives containing different horizontal and vertical components as illustrated in Eq. 3:



4. Oxidative coupling of the Step 1 co-reagents with copper (II) acetate and ammonia have been used to prepare analogues of the current invention and are described (2).
5. Other chemical modifications of michellamines extracted from *Ancistrocladus novum* are described (3).

References

1. G. Bringman *et al*, US Patent 5,552,550 (September 3, 1996) and 5,578,729 (November 26, 1996); G. Francois *et al* 5,571,919 (November 5, 1996)
2. T.F. Rutledge, US Patent 4,096,190 (June 20, 1978)
3. M.R. Boyd *et al*, US Patent 5,654,432 (August 5, 1997)

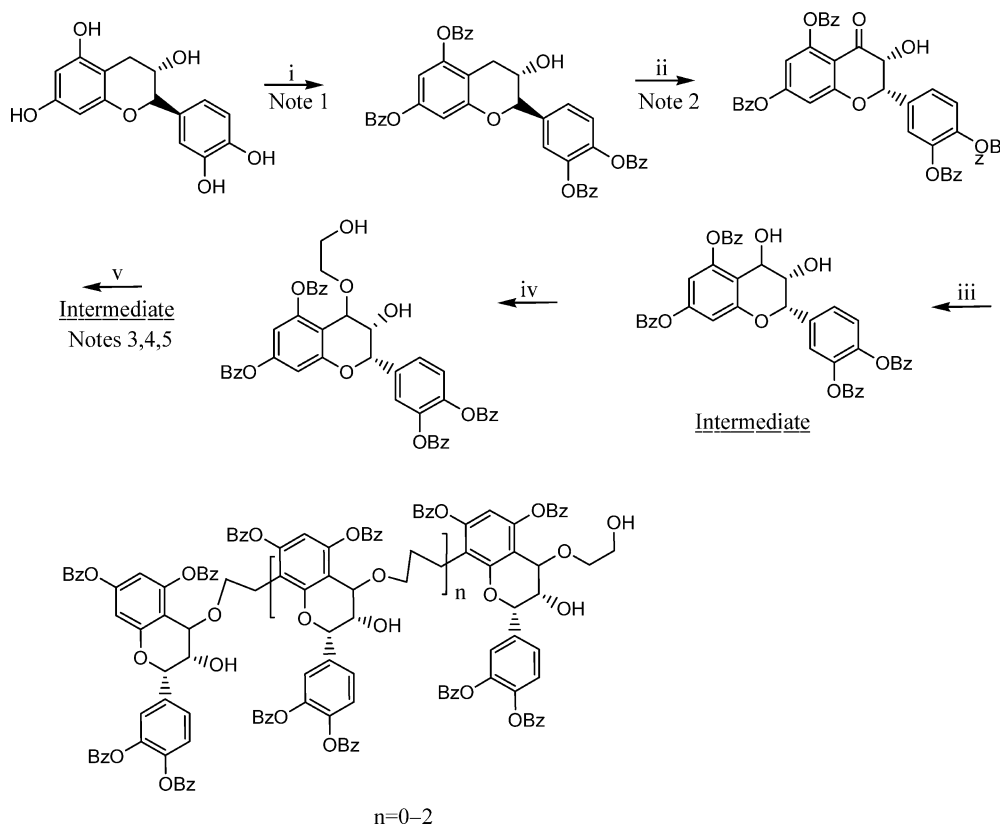
Patent: Process for Preparing Procyanidin (4 → 6 or 4 → 8) Oligomers and Their Derivatives

L.J. Romanczyk, Jr. *et al*, US Patent 6,207,842 (March 27, 2001)

Assignee: Mars Incorporated

Utility: Antineoplastic Agent

Reaction



i- Benzyl bromide, N,N-dimethylformamide, sodium hydride

ii- Periodinane, CH_2Cl_2 , sodium metabisulfite

iii- Lithium tri-*sec*-butylborohydride, THF, lithium bromide, hydrogen peroxide

iv- 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, ethylene glycol, CH_2Cl_2

v- Titanium tetrachloride, THF, CH_2Cl_2

Experimental

1. (2R,3S, trans)-5,7,3',4'-Tetra-O-benzylcatechin

(+)-Catechin (226.7 mmol) was dissolved in 720 ml DMF and NaH (975 mmol) in 180 ml DMF added. After stirring at ambient temperature 50 minutes, the flask was cooled to -10°C and benzyl bromide (1.02 mol) added dropwise over 80 minutes. The reaction mixture was warmed to ambient temperature overnight and the solution concentrated. The residue was dissolved in CH_2Cl_2 , washed with water, and extracted with chloroform. It was purified by chromatography using silica gel with acetone/chloroform/hexane, 1:12:7, the crude product re-crystallized in trichloroethene, and the product isolated 24% yield. $^1\text{H-NMR}$, IR, and MS data supplied.

2. (2R)-5,7,3',4'-Tetrakis(benzyloxy)flavan-3-one

The product from Step 1 (83.8 mmol) was dissolved in 420 ml CH_2Cl_2 and periodinane (92 mmol) added. The mixture stirred 30 minutes and a turbid solution formed upon the addition of 30 ml water-saturated CH_2Cl_2 . After an additional 20 minutes the mixture was diluted with 500 ml saturated solution of NaHCO_3 followed by 200 ml 10% solution of $\text{Na}_2\text{S}_2\text{O}_5$. The product was extracted with CH_2Cl_2 , purified by chromatography on silica gel using chloroform/EtOAc, 9:1, and the product isolated in 92% yield, mp = $144\text{--}144.5^{\circ}\text{C}$. $^1\text{H-NMR}$ data provided.

3. 5,7,3',4'-Tetra-O-benzylepicatchin

Lithium tri-sec-butylboronhydride (1 M, 100 ml) in THF was added to LiBr (402 mmol) in 100 ml THF, the mixture cooled to -78°C , and the product from Step 2 dissolved in 400 ml THF added over a period of 50 minutes. Thereafter, the mixture stirred at -78°C 135 minutes, then slowly warmed to ambient temperature, and 360 ml 2.5 M NaOH solution added. This was followed by the addition of 90 ml 30% H_2O_2 and 270 ml ethyl alcohol over 130 minutes. The mixture stirred overnight and 700 ml chloroform added to dissolve the crystallized product. The two layers were separated and the organic layer concentrated to provide the crude product. This product was dissolved in 600 ml boiling EtOAc/ethyl alcohol, 2:3, which crystallized upon cooling. It was purified by chromatography on silica gel using chloroform then chloroform/EtOAc, 12:1, and the product isolated in 81% yield, mp = $129.5\text{--}130^{\circ}\text{C}$. $^1\text{H-NMR}$ data supplied.

4. (2R,3S,4S)-5,7,3',4'-Tetra-O-benzyl-4-(2-hydroxyethoxy) epicatechin

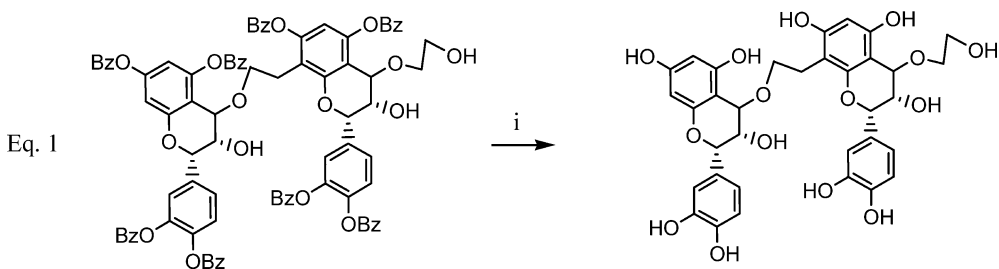
To the product from Step 3 (19.6 mmol) dissolved in 130 ml CH_2Cl_2 was added to ethylene glycol (115 mmol) followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (39.2 mmol) and the mixture stirred for 2 hours. Thereafter, 4-dimethylaminopyridine (39.2 mmol) was added and a green precipitate formed. After stirring 5 minutes silica gel (100 g) was added and the mixture concentrated under reduced pressure. The residue was purified by chromatography on silica gel using EtOAc/hexane, 1:1. It was then concentrated, re-purified by chromatography on silica gel using EtOAc/hexane, 2:3, and the product isolated in 52% yield, mp = $120\text{--}121^{\circ}\text{C}$. $^1\text{H-NMR}$ and elemental analysis data supplied.

5. O-Benzyl epicatechin ($4\beta \rightarrow 8$) Oligomers

The products from Step 4 (4.6 mmol) and Step 3 (18.4 mmol) were dissolved in 40 ml THF and 50 ml CH_2Cl_2 at 0°C and 4 ml 1 M TiCl_4 in CH_2Cl_2 added dropwise over 10 minutes. The mixture was stirred at 0°C for 5 minutes and an additional 90 minutes at ambient temperature. The reaction was terminated by the addition of 30 ml saturated NaHCO_3 solution followed by 100 ml water. The mixture was extracted twice with 20 ml CH_2Cl_2 , dried, and isolated in vacuo. The solid was re-dissolved in CH_2Cl_2 , filtered, and unreacted materials recovered. The oligomers were isolated by chromatography on silica gel using CH_2Cl_2 /hexane/EtOAc, 13:13:1, and crude dimer, trimer, and other oligomers isolated. The dimer and trimer were further purified by HPLC on a silica gel column using EtOAc/hexane. Dimer and trimer MS data supplied.

Notes

1. Other methods for preparing Step 1 (+)-catechin intermediates were subsequently developed by the author and are described (1).
2. The preparation of the Dess-Martin oxidant, periodinane, is described (2).
3. Procyanidin ($4 \rightarrow 8$) polymers containing up to 30 repeat units have been prepared under mild conditions using a low pH and excess (+)-catechin and are described (3).
4. Mono and tri-bromo intermediates of the current invention were prepared by the author in a subsequent investigation (4).
5. The epicatechin ($4\beta \rightarrow 8$) dimer of Step 5 was converted into the polyphenol as illustrated in Eq. 1 and is described.



i- Methyl alcohol, ethyl acetate, 10% palladium on carbon, hydrogen

6. ($4\beta \rightarrow 8$) Di-, tri-, and tetra-epicatechin gallates were prepared by condensing the respective O-benzyl di-, tri- and tetra-epicatechin ($4\beta \rightarrow 8$) reagent with tri-O-benzyl galloyl chloride with 20% $\text{Pd}(\text{OH})_2$ on carbon in methyl alcohol/water, 12:1, respectively, and is described (4).

References

1. L.J. Romanczyk, Jr. *et al*, US Patent 6,420,572 (July 16, 2002)
2. D. Dess *et al*, J. Am. Chem. Soc., 113, 7277 (1991); R. Ireland *et al* J. Org. Chem., 58, 2899 (1993)
3. J.A. Delcoun *et al*, J. Chem. Soc. Perkin Trans. I., 1711 (1983)
4. L.J. Romanczyk, Jr. *et al*, US Patent 6,528,664 (March 4, 2003)

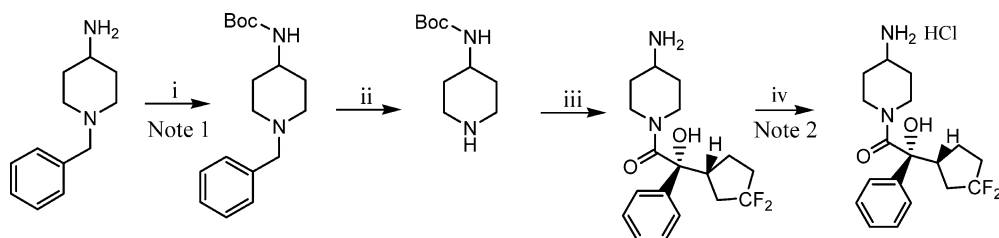
Piperidine

Patent: N-Acyl Cyclic Amine Derivatives
Y. Tsuchiya *et al*, US Patent 6,140,333 (October 31, 2000)

Assignee: Banyu Pharmaceutical Co., Ltd.

Utility: Treatment of Respiratory, Urinary and Digestive Diseases

Reaction



- i- Di-t-butyl dicarbonate, chloroform
- ii- Methyl alcohol, acetic acid, 10% palladium on carbon, hydrogen
- iii- (2R)-2-((1R)-3,3-Difluorocyclopentyl)-2-hydroxy-2-phenylacetic acid, chloroform, 1-hydroxybenzotriazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
- vi- Methyl alcohol, hydrochloric acid

Experimental

1. 1-Benzyl-4-t-butoxycarbonylaminopiperidine

To 4-amino-1-benzylpiperidine (25 g) dissolved in 150 ml chloroform was added di-t-butyl dicarbonate (31.4 g) with ice cooling followed by stirring 2 hours at ambient temperature. The reaction mixture was diluted with chloroform, washed with water, dried, and concentrated. After recrystallizing from hexane/diisopropyl ether, 35.65 g of product was isolated.

2. 4-t-Butoxycarbonylaminopiperidine

The product from Step 1 (59.0 g) was dissolved in 550 ml methyl alcohol containing 24 ml HOAc and 10% palladium-carbon (5 g) and hydrogenated. Thereafter, the mixture was filtered, concentrated, diluted with chloroform, washed with NaHCO_3 , brine, and dried. The solvent was distilled off and 53.7 g product isolated.

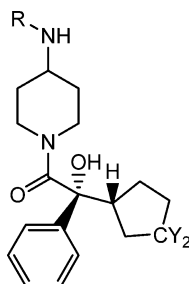
3. 4-t-Butoxycarbonylamino-1-{(2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylacetyl}piperidine

The product from Step 2 (220 mg) was mixed with (2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylacetic acid (256 mg) dissolved in 8 ml chloroform, 1-hydroxybenzotriazole (203 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (201 mg) added, and the mixture stirred 3 hours at ambient temperature. Thereafter, the mixture was diluted with EtOAc, washed with 1 M NaOH, brine, dried, and concentrated. The material was purified by chromatography on silica gel using hexane/EtOAc, 2:1, and 314 mg product isolated.

4. 4-Amino-1-{(2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylacetyl}piperidine hydrogen chloride

The product from Step 3 (84 mg) was dissolved in 2 ml 10% HCl dissolved in methyl alcohol and stirred 3 hours at ambient temperature. The mixture was concentrated, the residue recrystallized in EtOAc, and 60 mg of product isolated. $^1\text{H-NMR}$ and MS data supplied.

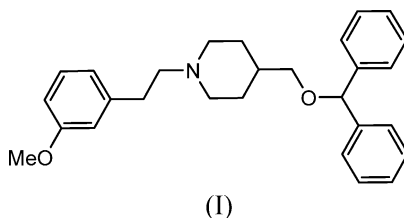
Derivatives



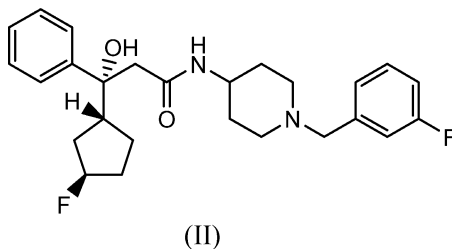
R	Y	HX	MS
Hydrogen	Hydrogen	HCl	303
Methyl	Fluoro	None	353
Methyl	Hydrogen	None	317
Ethyl	Fluoro	None	367
Ethyl	Hydrogen	None	331

Notes

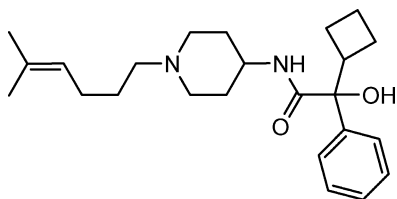
1. An alternative route to the Step 1 product was by hydrogenating the reaction product of N-t-butoxycarbonyl-4-piperidylethyl methane-sulfonate with sodium azide and is described by the author.
2. 4-(Diphenylmethoxymethyl)-1-(3-methoxyphenethyl)piperidine, (I), and pyrrolidine Step 4 derivatives have been prepared and are described (1).



3. (2R)-N-[1-(3-Fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide, (II), and other fluorine analogues of the current invention were prepared by the author (2) in an earlier investigation.



4. In an earlier investigation by the author, Step 5 cyclic derivatives, (III), were prepared and are discussed (3).



(III)

References

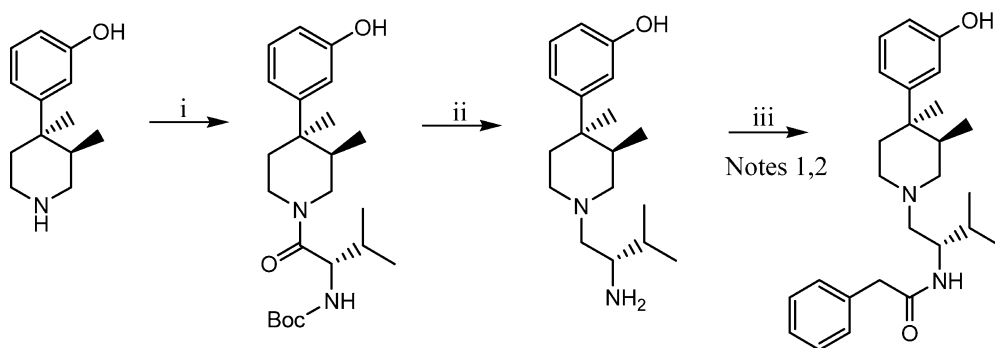
1. D. Alker *et al*, US Patent 5,344,835 (September 6, 1994)
2. Y. Tsuchiya *et al*, US Patent 6,040,449 (March 21, 2000) and US Patent 5,948,792 (September 7, 1999)
3. Y. Tsuchiya *et al*, US Patent 5,750,540 (May 12, 1998)

Patent: Opiate Compounds, Methods of Making and Methods of Use
F.I. Carroll *et al*, US Patent 6,593,348 (July 15, 2003)

Assignee: Research Triangle Institute

Utility: Opioid Receptor Antagonists

Reaction



- i- D-Valine-N-Boc,
benzotriazol-1-yloxy-tris(dimethylamino)phosphonium
hexafluorophosphate, triethylamine, THF, trifluoroacetic acid,
diethyl ether
- ii- Borane dimethylsulfide, THF
- iii- Benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium
hexafluorophosphate, N,N-dimethylformamide, phenylacetic
acid

Experimental

1. N-{(2'S)-[Propaneamido-N-Boc]propyl}-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine

(+)-(3R,4R)-Dimethyl-4-(3-hydroxyphenyl)piperidine (11.5 mmol), D-valine-N-Boc (11.5 mmol) and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (11.5 mmol) were dissolved in 150 ml THF and triethylamine (25.3 mmol) added. The mixture was stirred 1 hour, poured into 500 ml diethyl ether and 150 ml water, and the organic phase recovered. The organic layer was diluted with hexane until cloudy, dried, concentrated, dissolved in 100 ml chloroform, and re-concentrated. The crude material was dissolved in 45 ml CH_2Cl_2 , cooled to -20°C , 30 ml trifluoroacetic acid added in 3 portions, and the mixture stirred 30 minutes. The mixture was neutralized by pouring into 400 ml NaHCO_3 and 150 ml chloroform, the pH increased to 10, and extracted 5 times using $\text{CH}_2\text{Cl}_2/\text{THF}$, 3:1. The combined organic layers were dried, concentrated, and the product isolated as a yellow foamy solid.

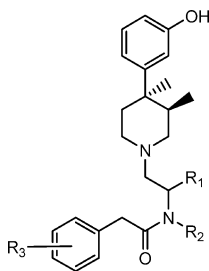
2. N-{(2'S)-[3-Aminopropaneamido]propyl}-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine

The product from Step 1 was dissolved in 150 ml THF, cooled to -20°C , 2 M borane dimethylsulfide (110 mmol) dissolved in THF added, and the mixture refluxed 3 hours. The mixture was re-cooled to -20°C , 72 ml methyl alcohol added and stirred one hour at ambient temperature. Thereafter, 16.4 ml 1 M HCl in diethyl ether was added, the solution concentrated, and the residue partitioned between $\text{CH}_2\text{Cl}_2/\text{THF}/\text{water}$, 3:1:1. The pH was adjusted to 10 with NaHCO_3 , the aqueous layer saturated with NaCl, and extracted with $\text{CH}_2\text{Cl}_2/\text{THF}$, 3:1. The combined organic layers were dried, concentrated, and purified by flash chromatography on silica gel using chloroform with a methyl alcohol gradient of 3–10%. The material was further purified by crystallization in EtOAc and the product isolated.

3. N-{(2'S)-[3-(4-Hydroxyphenyl)propanamido]propyl}-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine

A 20-mL scintillation vial containing a stirrer bar was charged with the product from Step 2 (0.05 mmol) dissolved in 2 ml THF, triethylamine (0.1 mmol), phenylacetic acid (0.05 mmol), and 50 μml 1M benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate dissolved in N,N-dimethylformamide. The vial was capped, stirred 1 hour at ambient temperature, 4 ml of diethyl ether and 2 ml water added, and the aqueous layer withdrawn. This procedure was repeated with 2 ml saturated NaHCO_3 and NaCl solutions. Thereafter, the solution was dried, transferred to a pre-weighed scintillation vial, rinsed with 2 ml chloroform, the material concentrated, and the product isolated.

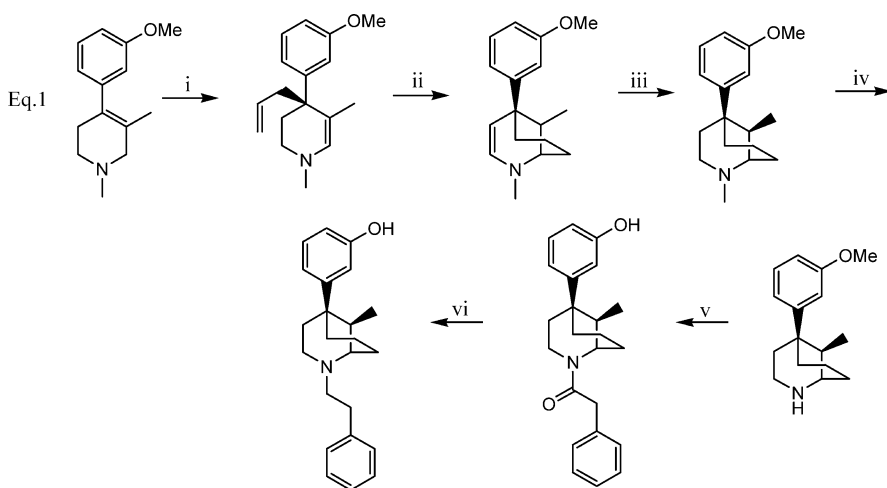
Derivatives



R_1	R_2	R_3	Yield (%)	MS ($\text{M} + 1$)
Hydrogen	2-Phenylethyl	3-Hydroxyl	86	487
4-Methylpentyl	Propyl	3-Hydroxyl	—	425
2-Cyclohexylethyl	Hydrogen	4-Hydroxy	63	331
Hydrogen	Methylbutyl	4-Hydroxy	74	439

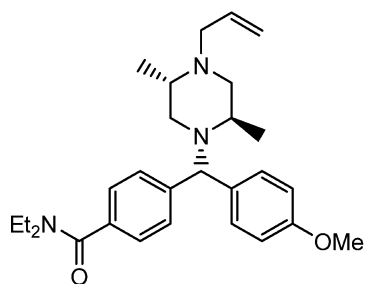
Notes

1. Methods for preparing 9 β -methyl-2-alkyl-7-oxo-5-arylmorphans were also described by the author and illustrated in Eq. 1:

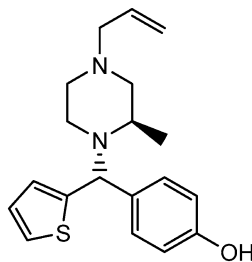


- i- n-Butyllithium, allyl bromide
 ii- Formic acid, phosphoric acid
 iii- Sodium triacetoxyborohydride, acetic acid
 iv- Phenyl chloroformate, potassium hydroxide
 v- Hydrobromic acid, acetic acid, phenyl acetic acid,
 tris(dimethylamino)-phosphonium hexafluorophosphate
 vi- Boron hydride dimethylsulfide

2. Diarylmethylpiperazines derivatives, (I), and, (II), have also been prepared as opioid receptor antagonists (1, 2), respectively, and are discussed.



(I)



(II)

3. In an earlier investigation by the author (3) and others (4), cocaine receptor binding ligands, 3 β -[4-iodophenyl]-tropan-2 β -carboxylic acid and derivatives, were prepared.

References

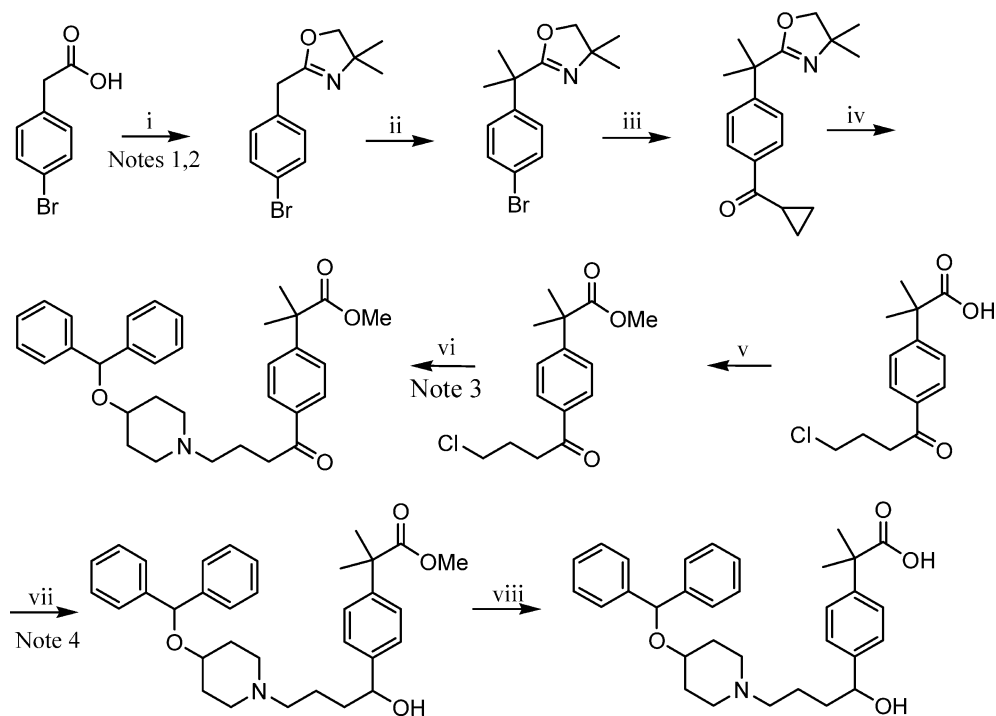
1. K.-J. Chang *et al*, US Patent 5,854,249 (December 29, 1998)
2. F.C. Tortella *et al*, US Patent 6,046,200 (April 4, 2000)
3. F.I. Carroll *et al*, US Patent 6,123,917 (September 26, 2000)
4. M.J. Kuhar *et al*, US Patent 5,935,953 (August 10, 1999) and US Patent 5,413,779 (May 9, 1995)

Patent: Process for Production of Piperidine Derivatives (Note 1)
T.E. D'Ambra *et al*, US Patent 6,458,958 (October 1, 2002)

Assignee: Albany Molecular Research, Inc.

Utility: Non-sedating Anti-histamine

Reaction



i- 2-Amino-2-methyl-1-propanol, xylenes

ii- THF, potassium hexamethyldisilazide, methyl iodide, acetic acid

iii- THF, n-butyllithium, N,N-dimethylcyclo-propylcarboxylic acid amide

iv- Hydrochloric acid, 1,4-dioxane

v- Methyl alcohol, hydrogen chloride

vi- Toluene (α,α-diphenyl)piperidine methanol, potassium carbonate

vii- Methyl alcohol, sodium borohydride

viii- Methyl alcohol, water, sodium hydroxide

Experimental

1. 4-Bromo- α -(4,4-dimethyloxazolin-2-yl)toluene

A mixture of 4-bromophenylacetic acid (0.800 mol), 2-amino-2-methyl-1-propanol (1.20 mol) and 900 ml xylenes were refluxed for 24 hours, cooled, filtered, and concentrated. Precipitated crystals were slurried in hexanes and the product isolated in 75% yield.

2. 4-Bromo- α,α -dimethyl- α -(4,4-dimethyloxazolin-2-yl)toluene

Potassium hexamethyldisilazide (0.0279 mol) was added to the product from Step 1 (0.0186 mol) dissolved in 50 ml THF, the mixture stirred 15 minutes at ambient temperature, and methyl iodide (0.0186 mol) added. After stirring 1 hour, a second equivalent of potassium hexamethyldisilazide and methyl iodide were added, stirred 1 hour, and an additional 0.2 ml methyl iodide then added. The mixture was quenched with 100 ml 10% HOAc in water and extracted with CH_2Cl_2 . The extract was washed with brine, dried, concentrated at ambient temperature at 0.1 mm Hg, and a residue obtained. The solid was slowly dissolved in 30 ml isopropyl alcohol containing 20 ml water until an oil formed. Thereafter, an additional 5 ml isopropyl alcohol was added with heating and the re-crystallized product isolated in 84% yield.

3. 4-(Cyclopropyl-oxo-methyl)- α,α -dimethyl- α -(4,4-dimethyloxazolin-2-yl)toluene

The product from Step 2 (0.0338 mol) was dissolved in 400 ml THF, cooled to -78°C , *n*-butyllithium (0.042 mol) added, and the mixture stirred at -78°C for 30 minutes. Thereafter, *N,N*-dimethylcyclopropyl-carboxylic acid amide (0.102 mol) dissolved in 30 ml THF was added and the mixture stirred 30 minutes. It was slowly warmed to -15°C , quenched with water, extracted with CH_2Cl_2 , and concentrated. The residue was cooled to 0°C , treated with acetonitrile, filtered, and the product isolated in 72% yield.

4. 4-(4-Chloro-1-oxobutyl)- α,α -dimethylphenylacetic acid

The product from Step 3 (0.15 mol) was dissolved in 150 ml apiece 12 M HCl and 1,4-dioxane and refluxed 18 hours. The mixture was extracted with EtOAc, purified by chromatography using silica gel with hexanes/ethyl acetate/acetic acid, 81:14:5, re-crystallized using CH_2Cl_2 , and the product isolated in 68% yield.

5. Methyl 4-(4-chloro-1-oxobutyl)- α,α -dimethylphenylacetate

The product from Step 4 (0.056 mol) was dissolved in 400 ml methyl alcohol saturated with hydrogen chloride and refluxed 1 hour. The mixture was concentrated, partitioned between EtOAc and water, the aqueous phase extracted with EtOAc, concentrated to an oil, purified by chromatography using silica gel with hexanes/ethyl acetate, 11:1, and the product isolated in 82% yield.

6. Methyl 4-[4-4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylphenylacetate

The product from Step 5 (12.6 g) was dissolved in 500 ml toluene, 4-(α,α -diphenyl)piperidinemethanol (8.8 g), K_2CO_3 (23 g) added, and the mixture refluxed

7 hours. The mixture was cooled, filtered, concentrated, and the residue dissolved in diethyl ether containing HCl. Thereafter, the mixture was re-concentrated, treated with EtOAc, filtered, and partitioned between EtOAc and 2 M Na₂CO₃. The organic extractions were combined, dried, filtered, concentrated in vacuo, and the product isolated.

7. Methyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylphenylacetate

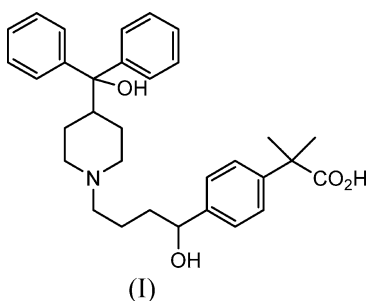
The product from Step 6 (13.5 g) was dissolved in 250 ml methyl alcohol, treated at 0°C with NaBH₄ (1.8 g), stirred 1 hour, concentrated, and the residue partitioned between EtOAc and a saturated NaHCO₃ solution. The aqueous portion was extracted with EtOAc, the organics combined, washed with brine, dried, concentrated, and the product isolated as a foam.

8. 4-[4-[4-Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylphenylacetic acid

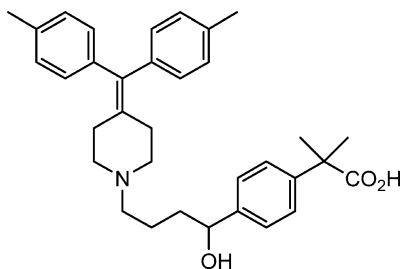
The product from Step 7 (9.5 g) was dissolved in 150 ml apiece methyl alcohol and water containing NaOH (10g), refluxed for 1 hour, and methyl alcohol removed in vacuo. The concentrate was diluted with water and chloroform, the pH adjusted to 5.5–6.0, and the phases separated. Thereafter, the aqueous phase was extracted with chloroform, the organics combined, dried, filtered, and concentrated. The mixture was purified by dissolving in CH₂Cl₂, purified by chromatography using Davisil Grade 633 silica gel using a gradient of chloroform/methyl alcohol, 10:1 to 3:1, and the product isolated.

Notes

1. Throughout this investigation the author refers to 'oxazole' derivatives as 'isoxazole'. ¹H-NMR and structures provided therein are consistent with oxazoles, since the nomenclature error has been corrected throughout.
2. The product of Step 1 was prepared by the Myers oxazole synthesis and is described (1).
3. The product of Step 4 has also been used in other investigations by the author (2) and others to prepare Step 7 hydroxyl analogues (I) and are described.



4. In a subsequent study by the author, 4-[4-[4-(diphenylmethylene)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethyl-3-hydroxybenzeneacetic acid, (II), was prepared and is discussed (4).



(II)

References

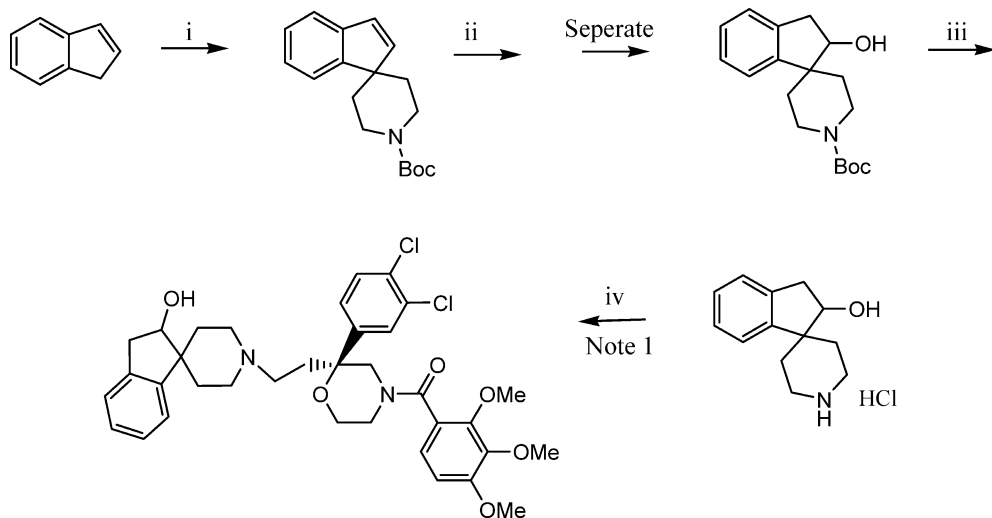
1. A. Myers *et al*, J. Org. Chem., 39, 2778 (1974) and 39, 2783 (1974)
2. T.E. D'Ambra, US Patent 5,581,011 (December 3, 1996) and US Patent 5,578,610 (November 26, 1996)
3. T.A. Ayers, US Patent 6,689,898 (February 10, 2004)
4. T.E. D'Ambra, US Patent 6,797,826 (September 28, 2004)

Patent: Spiropiperidine Derivatives
T. Nishi *et al*, US Patent 6,511,975 (January 28, 2003)

Assignee: Sankyo Company, Limited.

Utility: Tachykinin Receptor Antagonistics for Treating Respiratory Tract Contractions

Reaction



- i- Lithium bistrimethylsilylamide, THF,
N-t-butoxycarbonyl-bis(2-chloroethyl)amine
- ii- Borane THF, hydrogen peroxide, sodium hydroxide, THF
- iii- Ethyl alcohol, hydrogen chloride, dioxane
- iv- Dimethylacetamide, 2-[(2R)-(3,4-dichlorophenyl-4-(3,4,5-trimethoxybenzoyl)-morpholin-2-yl]ethanol,
methanesulfonate, sodium bicarbonate, sodium iodide

Experimental

1. N-t-Butoxycarbonyl-spiro(1H-indene-1,4'-piperidine)

Indene (0.10 mole) was dissolved in 60 ml THF, 200 ml 1.0 M lithium bistrimethylsilylamide (0.20 mole) in THF added over 1 hour, and stirred for 30 minutes. Thereafter, N-t-butoxy-carbonyl-bis(2-chloroethyl)amine (0.10 mole) dissolved in 50 ml THF was added, the mixture further stirred 2 hours, and then distilled under reduced pressure. The residue was purified by chromatography on silica gel using n-hexane/EtOAc, 97:3, and the product isolated in 89% yield. ¹H-NMR, IR, and MS data supplied.

2. N-t-Butoxycarbonyl-spiro[(2-hydroxy)indane-1,4'-piperidine]

and

N-t-butoxycarbonyl-spiro[(3-hydroxy)indane-1,4'-piperidine]

The product from Step 1 (35.0 mmol) was dissolved in 100 ml THF, borane-THF (52.5 mmol) added over 90 minutes, the mixture stirred 30 minutes under ice cooling, and then 4 hours at ambient temperature. Thereafter, 5 ml ethyl alcohol was added, the mixture stirred 5 minutes, followed by the addition of 13 ml 6 M borane THF. The mixture was stirred 20 minutes under ice cooling, 3 hours at ambient temperature, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel using n-hexane/EtOAc, 70:30 to 60:40. The two products, N-t-butoxycarbonyl-spiro[(2-hydroxy)indane-1,4'-piperidine] and N-t-butoxycarbonyl-spiro[(3-hydroxy)indane-1,4'-piperidine] were isolated in 55% and 40% yields, respectively. ¹H-NMR, IR, and MS data supplied.

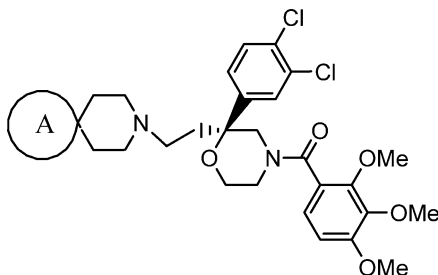
3. Spiro[(2-hydroxy)indane-1,4'-piperidine]hydrochloride

The (2-hydroxy)indane product from Step 2 (8.27 mmol), N-t-butoxycarbonyl-spiro[(2-hydroxy)indane-1,4'-piperidine] were dissolved in 10 ml ethyl alcohol, 10.0 ml 4 M HCl (40.0 mmol) dissolved in dioxane added, the mixture stirred 30 minutes under ice cooling, and then further stirred at ambient temperature 4 hours. The solvent was distilled off under reduced pressure, the residue recrystallized from methyl alcohol/diethyl ether, and the product isolated in 83% yield, mp = 250–251 °C. ¹H-NMR, IR, and MS data supplied.

4. 1-{2-[(2R)-(3,4-Dichlorophenyl-4-(3,4,5-trimethoxybenzoyl)-morpholin-2-yl)-ethyl]spiro}[(2S)-hydroxy)indane-1,4'-piperidine]

The product from Step 3 (0.602 mmol) was dissolved in 6.0 ml dimethylacetamide and 2-[(2R)-(3,4-dichlorophenyl-4-(3,4,5-trimethoxybenzoyl)morpholin-2-yl)ethanol, methane-sulfonate, NaHCO₃ (1.64 mmol) and NaI (0.821 mmol) added and the mixture heated to 80 °C 8 hours. Thereafter, water was added and the mixture extracted with EtOAc. The organic layer was washed with brine and the solvent distilled under reduced pressure. The residue was purified by chromatography on silica gel using hexane/EtOAc, 1:1, followed by CH₂Cl₂/methyl alcohol, 1:3 to 50:1 to 20:1, and the product isolated in 83% yield. ¹H-NMR, IR, and MS data supplied.

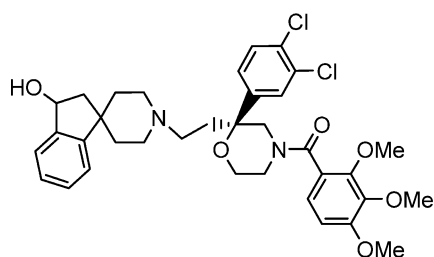
Derivatives



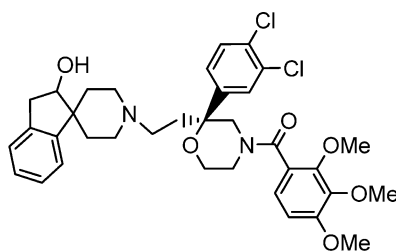
A	$[\alpha]_D^{25}$	MS (M+H)	Melting Point (°C)
3-Indanone	+4.3(c = 0.53)[chl]	653	—
3-Hydroxyindane	+8.3(c = 0.52)[chl]	654	—
2-Hydroxyindane	+23.6(c = 0.96)[chl]	—	121
2-Hydroxyindane · HCl	+30.5(c = 1.00)[MeOH]	655 (free base)	169

Notes

1. The preferred compounds of the current invention are 1-{2-[(2R)-(3,4-dichlorophenyl-4-(3,4,5-trimethoxybenzoyl)morpholin-2-yl)-ethyl]spiro[(2S)- and 3-hydroxy]indane-1,4'-piperidine], (I), and, (II), respectively.

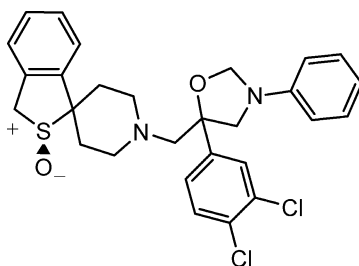


(I)



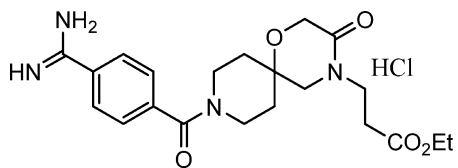
(II)

2. The preparation of the reagent of Step 4, 2-[(2R)-(3,4-dichlorophenyl-4-(3,4,5-trimethoxybenzoyl)morpholin-2-yl)ethanol, and derivatives are described (1).
3. In a previous study by the author spiro[benzo[c]thiophene-1-(3H), 4'-piperidine derivatives were prepared (III) and are described (2).



(III)

4. Spiropiperidine amidine analogues of the current invention, such as ethyl 4-(9-(4-(aminoiminomethyl)benzoyl)-3-oxo-1-oxa-4,9-diaza-spiro[5.5]undec-4-yl)butanoate hydrochloride, (IV), have also been prepared and are described (3).



(III)

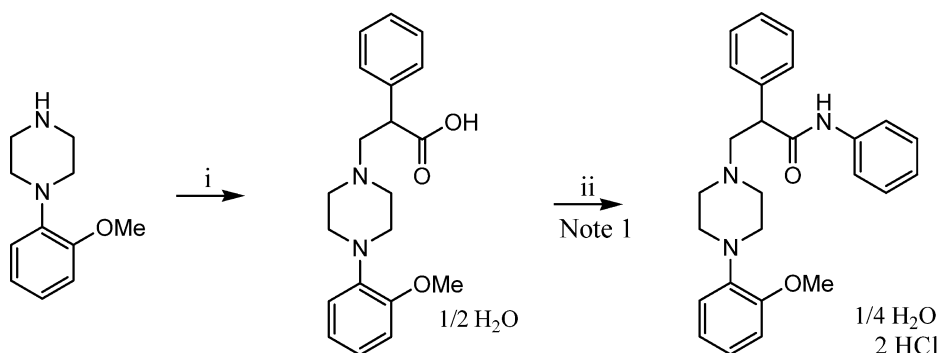
References

1. X. Emonds-Alt *et al*, US Patent 5,641,777 (June 24, 1997) and US Patent 5,411,971 (May 2, 1995)
2. T. Nishi *et al*, US Patent 6,159,967 (December 12, 2000)
3. M.J. Fisher *et al*, US Patent 6,693,109 (February 17, 2004)

Piperizines

Patent: Piperazine Derivatives
I.A. Cliffe, US Patent 5,541,326 (July 30, 1996)
Assignee: John Wyeth & Brother, Limited
Utility: Treatment of Anxiety

Reaction



i- Atropic acid, ethyl alcohol
ii- CH_2Cl_2 , 1,1'-carbonyldiimidazole, aniline

Experimental

1. α -{1-[(4-2-Methoxyphenyl)piperazinyl]methyl}benzeneacetic acid

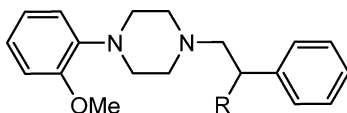
1-(2-Methoxyphenyl)piperazine (0.118 mol) and atropic acid (0.118 mol) were dissolved in 300 ml ethyl alcohol, refluxed 18 hours, cooled, and concentrated. The solid was

trituated 3 times with 100 ml acetone to give a first crop of product as white crystals. The filtrate was evaporated and an oil isolated which slowly crystallized over 1 month. The solid was trituated with 200 ml acetone and a second crop isolated, mp = 160–163 °C. Elemental analysis data supplied.

2. 3-{1-[4-(2-Methoxyphenyl)piperazinyl]}-2-phenyl-N-phenyl-propanamide

The product from Step 1 (3.2 mmol) was dissolved in 50 ml CH_2Cl_2 and treated with 1,1'-carbonyldiimidazole (3.6 mmol) and aniline (4.4 mmol), stirred 18 hours, concentrated, and purified by chromatography on silica gel using diisopropyl ether/diethyl ether. Thereafter, the product was dissolved in 10 ml hot propan-2-ol and the solution acidified with ethereal HCl. The material crystallized upon trituration with ether and 0.897 g product isolated as dihydrochloride quarter hydrate, mp = 250–255 °C (dec.). Elemental analysis data supplied.

Derivatives

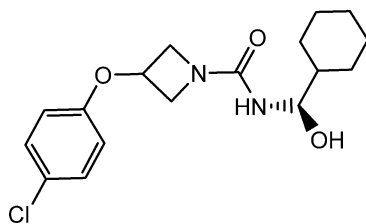


R	Melting Point (°C) (1/4 H ₂ O·2HCl)
Cyclopentyl amide	206–208
Phenylethyl carbamate	165–175
Methylethyl ester	208–212
Pyrrolidinyl amide	212–213

Notes

1. Amide derivatives of 1-(2-methoxyphenyl)piperazine acids were also prepared by the author in the current invention. Other amide derivatives have been prepared using N-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]-2,2-dimethylpropanoic acid and are described (1).
2. In a subsequent investigation by the author (2) the radiolabeled piperazine derivative, N-(2-(1-(4-(2-[³H-methoxy]phenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)cyclohexane carboxamide, was prepared.
3. N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))ethyl)-N-(2-thiazolyl)-cyclohexane carboxamide has also been prepared by the author (3).

4. Azetidinyl derivatives, (I), have been prepared by others and are described (4).



(I)

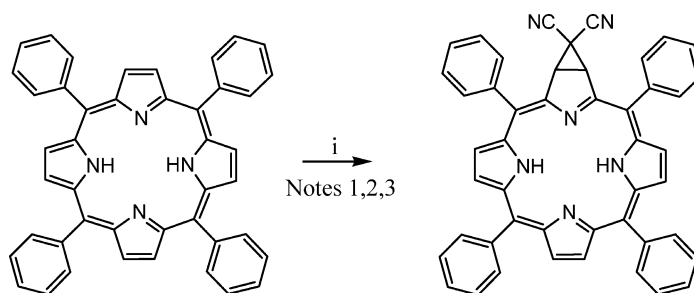
References

1. M.A. Abou-Gharbia *et al*, US Patent 4,988,814 (January 29, 1991)
2. I.A. Cliffe *et al*, US Patent 6,056,942 (May 2, 2000)
3. I.A. Cliffe *et al*, US Patent 6,127,357 (October 3, 2000)
4. D.R. Adams, US Patent 6,514,961 (February 4, 2003)

Porphyrins

Patent: 1,3-Dipolar Cycloadditions to Polypyrrolic Macrocycles
J.K. MacAlpine *et al*, US Patent 6,620,929 (September 16, 2003)
Assignee: University of British Columbia
Utility: Therapeutic Photosensitizing Agents in the Treatment of Tumors

Reaction



i- Tetracyanoethylene oxide, 1,2-dibromoethane

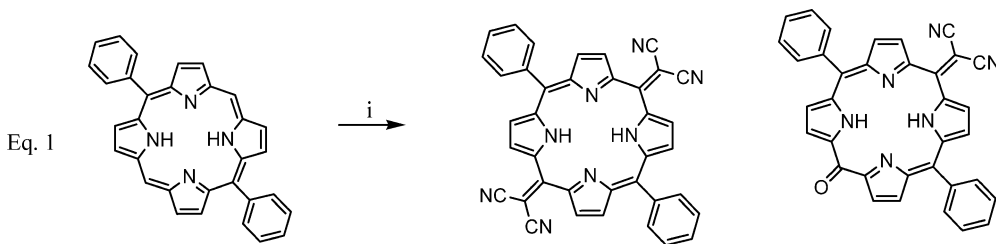
Experimental

1. 5,10,15,20-Tetraphenyl-2,3-(3'-dicyano)cyclopropano-2,3-chlorin

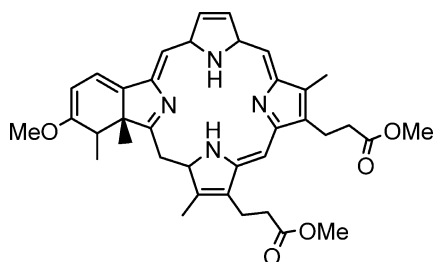
A solution of 5,10,15,20-tetraphenylporphyrin (0.08 mmol) and tetracyanoethylene oxide (0.34 mmol) dissolved in 2 ml 1,2-dibromoethane were refluxed 1 hour. The solvent was evaporated in vacuo and the product isolated by chromatography on silica using hexane/chloroform, 1:1. ¹H-NMR, UV-Vis, MS, and elemental analysis data supplied.

Notes

1. The preparation of 5,10,15,20-tetraphenylporphyrin is described (1,2).
2. A review of nucleophilic reactions involving tetracyanoethylene is provided (3).
3. When 5,15-diphenylporphyrin was refluxed 3 hours in toluene with tetracyanoethylene oxide, two compounds were formed by a β -addition as illustrated in Eq. 1. In a subsequent investigation by the author (4), however, it was discovered that if the mixture was refluxed 24 hours, only the tetracyano derivative would be obtained.



4. In a subsequent investigation it was observed that the reaction of tetracyanoethylene oxide with 5,10,15,20-tetraphenylporphyrin-zinc chelate produced the corresponding zinc chelated derivative of 5,10,15,20-tetraphenyl-2,3-(3'-dicyano)cyclopropano-2,3-chlorin and is described by the author (4).
5. Other reactions of tetrasubstituted azomethyne ylides prepared from tetracyanoethylene oxide are described, I, (5).



(I)

References

1. S. Narang *et al*, US Patent 4,908,442 (March 13, 1990)
2. X. Zhang *et al*, US Patent 5,274,090 (December 28, 1993)
3. W.L. Linn *et al*, J. Am. Chem. Soc., 87, 3651 (1965)
4. J.K. MacAlpine *et al*, US Patent 6,825,343 (November 30, 2004)
5. J.W. Lown *et al*, Can. J. Chem., 50, 534 (1972)

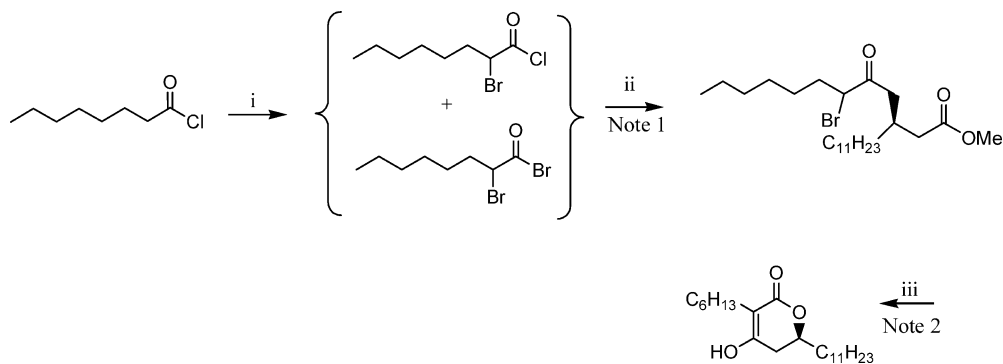
Pyrans

Patent: Synthesis of 3,6-Dialkyl-5,6-Dihydro-4-Hydroxy-Pyran-2-One
M.P. Fleming *et al*, US Patent 6,743,927 (June 1, 2004)

Assignee: Roche Colorado Corporation

Utility: Tetrahydrolipstatin Intermediate

Reaction



i- Bromine

ii- Methyl (3R)-3-hydroxytetradecanoate, pyridine, hexane

iii- Magnesium, iodine, 1,2-dibromoethane, THF

Experimental

1. 2-Bromooctanoyl chloride

and

2-bromooctanoyl bromide

Octanoyl chloride (1.67 mol) was heated to 55 °C, Br₂ (2.34 mol) added over 8 hours, and the reaction stirred overnight. Thereafter, the mixture was distilled at 111 °C at 8 mm Hg, and 100% yield of a mixture of 2-bromooctanoyl chloride and 2-bromooctanoyl bromide, 35:65, isolated.

2. Methyl (3R)-3-[(2-bromo-1-oxooctyl)oxy]tetradecanoate

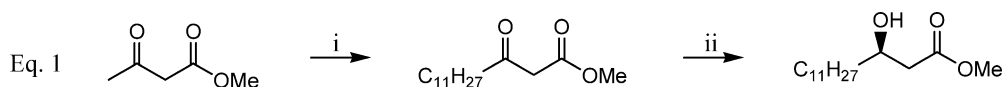
Methyl (3R)-3-hydroxytetradecanoate (193 mmol) was dissolved in 400 ml hexane, cooled to 0 °C, the product mixture from Step 1 (1.2 eq) added followed by the addition of pyridine (24 mmol) and 100 ml hexane. The mixture was stirred 2 hours, 200 ml apiece water and hexane added, the organic layer isolated, washed with 100 ml water, and concentrated. The product was isolated as a clear oil in 100% yield.

3. (6R)-3-Hexyl-4-hydroxy-6-undecyl-5,6-dihydropyran-2-one

Magnesium (0.572 g) and a small flake of I₂ (~45 mg) were warmed to 80 °C and the product from Step 2 (179 mmol) dissolved in 33.6 g 1,2-dibromoethane and 400 ml THF added. The mixture refluxed 1 hour, stirred overnight at 60 °C, filtered, and concentrated. Thereafter, it was re-dissolved in 1750 ml CH₂Cl₂ containing 700 ml ice water and 98 ml 10% HCl. The organic layer was isolated, washed with 200 ml brine, dried, filtered and concentrated. The product was slurried in 100 ml hexane, cooled to 0 °C, filtered, rinsed twice with 50 ml hexane, dried at 40 °C at 10 mm Hg, and the product isolated in 45–50% yield.

Notes

1. The preparation of methyl (3R)-3-hydroxytetradecanoate is described by the author and others (1) and illustrated in Eq. 1:

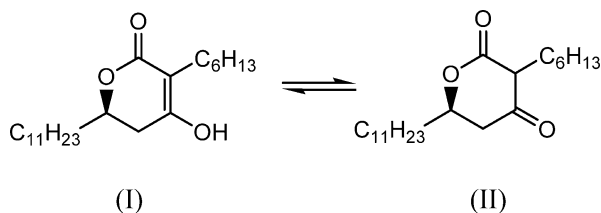


i- Calcium hydroxide, dodecanoyl chloride, HCl

ii- Hydrogen, hydrochloric acid, ruthenium diacetate
((R)-2,2-MeOBIPHEP)

2. The Step 3 product was also prepared by reacting the product of Step 2 with tri-methylsilyl chloride and isopropylmagnesium chloride followed by t-butyl- or t-amylmagnesium bromide with molecular sieves as methanol scavengers and is described by the author.

3. The product of Step 2 has also been prepared by the condensation of 2-bromooctanoic acid and (2)-3-hydroxyltetradecanate in 4-methyl-aminopyridine in the presence of 1,3-dicyclohexylcarbodiimide and is discussed (2).
4. A process for preparing a tautomeric mixture of the product of Step 3, (R)-3-hexyl-5,6-dihydro-4-hydroxy-6-undecyl-2H-pyran-2-one, (I), and (R)-5,6-dihydro-6-undecyl-2H-pyran-2,4(3H)-dione, (II), and (2), respectively, is described (3).



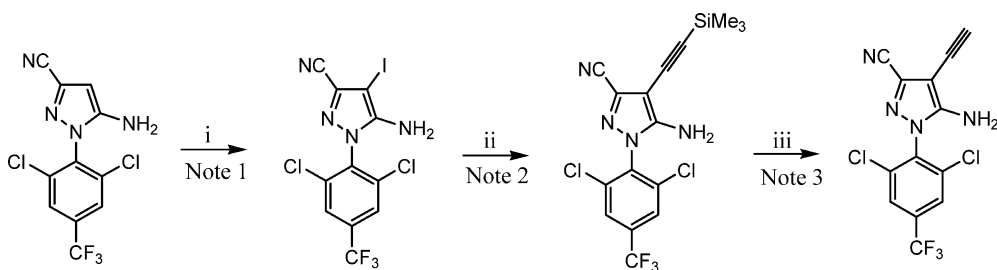
Reference

1. T. Sotoguchi *et al*, US Patent 5,945,559 (August 31, 1999)
2. K.M. Ramig *et al*, US Patent 5,420,305 (May 30, 1995)
3. K.M. Ramig *et al*, US Patent 5,274,143 (December 28, 1993)

Pyrazoles

Patent: Parasitocidal Compounds
B.J. Banks, US Patent 6,255,333 (July 3, 2001)
Assignee: Pfizer, Inc.
Utility: Treatment of Parasitic Infestations

Reaction



- i- N-iodosuccinimide, acetonitrile
ii- Triethylamine, dimethylformamide, trimethylsilylacetylene,
cuprous iodide, bis(triphenylphosphine)palladium(II)chloride
iii- Methyl alcohol, potassium carbonate

Experimental

1. 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-iodopyrazole

5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)pyrazole (5.0 g) was dissolved in 60 ml acetonitrile at ambient temperature and N-iodosuccinimide (3.52 g) added portionwise over 5 minutes. The mixture was stirred 1 hour, concentrated, and this crude

reaction product used in the next step. A sample of the crude mixture was, however, purified by partitioning between CH_2Cl_2 and water. Trituration with hexane provides the title compound as a white solid, mp = 213°C (dec).

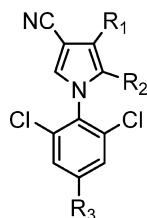
2. 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trimethylsilyl-ethynlpyrazole

To the crude product from Step 1 (6.96 g) dissolved in 30 ml triethylamine and 6 ml dimethylformamide at ambient temperature was added 3 ml trimethylsilylacetylene, CuI (150 mg) and bis(triphenyl-phosphine)palladium(II)chloride (300 mg). The mixture was heated 1 hour to 50–60°C, an additional 0.3 ml trimethylsilylacetylene added, and heating continued 30 minutes. The cooled mixture was diluted with 250 ml water, extracted with 250 ml diethyl ether, separated, dried, and concentrated. The material was purified by chromatography on silica gel using CH_2Cl_2 /hexane, 1:1, re-crystallized from diethyl ether/hexane, and the product isolated, mp = 181–182°C. $^1\text{H-NMR}$, MS, and elemental analysis data supplied.

3. 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-ethynlpyrazole

To the product from Step 2 (2.0 g) dissolved in 30 ml methyl alcohol was added K_2CO_3 (1 g) and after 10 minutes at ambient temperature the mixture was partitioned between 100 ml apiece diethyl ether and water. The organic layer was washed with brine, dried, concentrated, purified by chromatography on silica gel using CH_2Cl_2 , re-crystallized from diethyl ether, and the product isolated, mp = 215–216°C. $^1\text{H-NMR}$, MS, and elemental analysis data supplied.

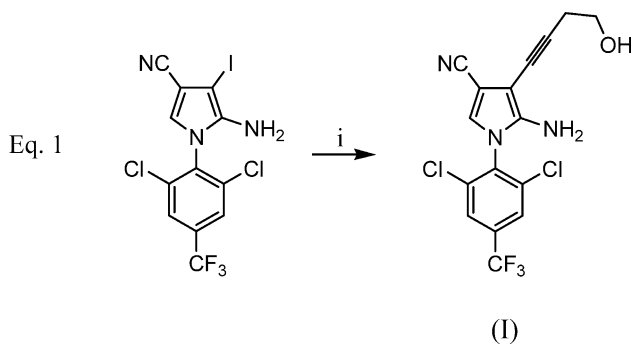
Derivatives



R_1	R_2	R_3	Melting Point (°C)
Ethynyl	Bromo	Trifluoromethyl	134–135
4-Hydroxy-but-1-yne	Amino	Trifluoromethyl	215–216
Hydrogen	Amino	Pentafluorothioethyl	250
Hydrogen	Amino	Trifluoromethyl	149–150

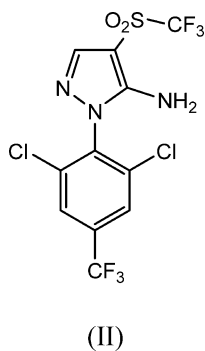
Notes

1. The preparation of the Step 1 reagent is described by the author and elsewhere (1).
2. 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(4-hydroxybut-1-ynyl) pyrazole, (I), was also prepared by the author as illustrated in Eq. 1:

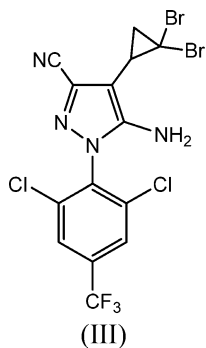


i- N,N-Dimethylformamide, cuprous iodide, 3-butyne-1-ol,
bis(triphenylphosphine)-palladium(II)chloride,
triethylamine

3. The preparation of 5-amino-4-trifluoromethylthio- and 4-trifluorosulfonyl)-1-(2,6-dichloro-4-trifluoromethylphenyl)pyrazole, (II), is described by the author and others (2).



4. In a subsequent investigation by the author (3) 3-cyano-4-(2,2-dibromocyclopropyl)-1-(2,6-dichloro-4-trifluoromethylphenyl) pyrazole, (III), and related derivatives were prepared.



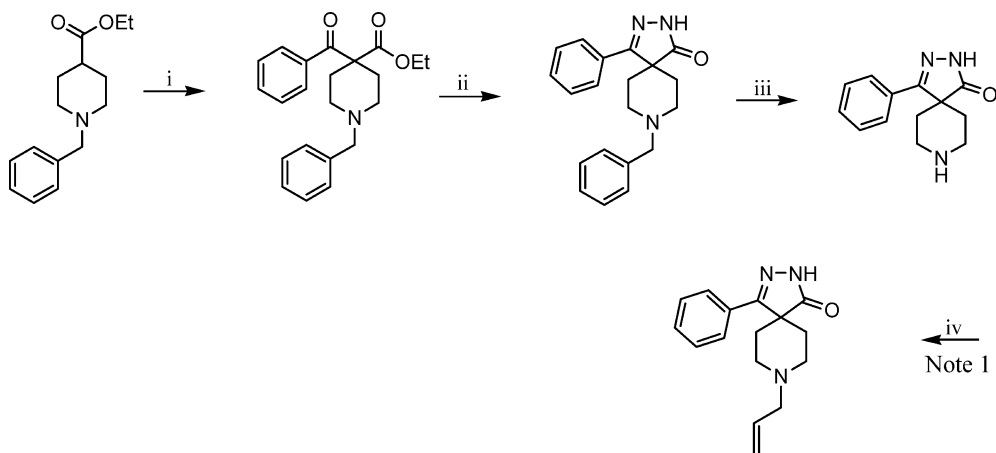
5. The preparation of 5-acetamido-3-bromo-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-nitropyrazole and derivatives is described (4).

References

1. L.R. Hattan *et al*, US Patent 5,608,077 (March 4, 1997)
2. U. Jensen-Korte *et al*, US Patent 4,945,165 (July 31, 1990)
3. B.J. Banks, US Patent 6,268,509 (July 31, 2001)
4. L.R. Hattan *et al*, US Patent 5,547,974 (August 20, 1996)

Patent: Spiropyrazole Compounds
R.R. Goehring *et al* US Patent 6,635,653 (October 21, 2003)
Assignee: Euro-Celtique S.A.
Utility: Opioid Receptor Ligand

Reaction



- i- Lithium di-isopropylamide, THF, benzoyl chloride
ii- Hydrazine hydrate, ethyl alcohol
iii- Palladium hydroxide, methyl alcohol, hydrogen
iv- Allyl bromide, triethylamine, methyl alcohol

Experimental

1. N-Benzyl-4-ethylformyl-4-benzoylpiperidine

4-Ethylformyl-N-benzylpiperidine (1 eq) was added to lithium diisopropylamide (1.1 eq) dissolved in THF at -40°C , the mixture warmed to ambient temperature, and stirred 1 hour. It was re-cooled to -20°C , benzoyl chloride (1.2 eq) dissolved in THF added dropwise, and stirred 1 hour at -20°C and 16 hours at ambient temperature. Thereafter, the mixture was poured into water, extracted with EtOAc, the organic phase washed with NH_4Cl , brine, dried, concentrated, and the product isolated. $^1\text{H-NMR}$ data supplied.

2. 8-Benzyl-4-phenyl-2,3,8-triazospiro[4.5]-dec-3-en-1-one

The product from Step 1 (1 eq) dissolved in ethyl alcohol was added to hydrazine hydrate (3 eq) and the mixture refluxed 12 hours. The mixture was cooled to ambient temperature and the crude product purified by re-crystallization in ethyl product. $^1\text{H-NMR}$ data supplied.

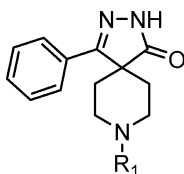
3. 4-Phenyl-2,3,8-triazospiro[4.5]-dec-3-en-1-one

The product from Step 2 (1 eq) and palladium hydroxide (0.2 eq) in methyl alcohol was hydrogenated at ambient temperature and 50 psi hydrogen 20 hours. The mixture was filtered, concentrated, re-crystallized in ethyl alcohol, and the product isolated. ¹H-NMR data supplied.

4. 8-Allyl-4-phenyl-2,3,8-triazospiro[4.5]-dec-3-en-1-one

To a solution of the product from Step 3 (1 eq) in methyl alcohol was added triethylamine (1 eq), followed by the addition of alkylbromide (or chloride) (1 eq). The mixture was heated to 80°C overnight, quenched with water, and the pH increased to 10 by addition of 1 M NaOH. The mixture was extracted with diethyl ether, dried, concentrated, and the product isolated by chromatography.

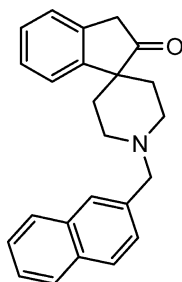
Derivatives



R₁	Alkylation Step Yield (%)
5-Methyl-hex-2-yl	100
1,2,3,4-Tetrahydro-2-naphthyl	95.3
4-(2-Propyl)-cyclohexyl	100
Cyclooctylmethyl	100

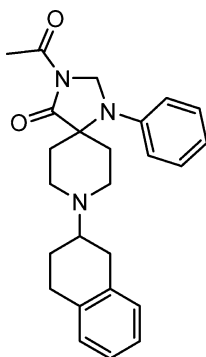
Notes

1. A reductive amination procedure for incorporating aldehydes or ketones into the product of Step 4 was also provided by the author.
2. N-Alkylation methods for preparing spiro(1H-indene-1,4-piperidines) and spiro(2,3-dihydrobenzofuran-3,4-piperidines) are described (1).
3. In a subsequent investigation by the author (2), spiro(piperidineindane) derivatives, (I), were prepared and are described.



(I)

4. Triazospiro 8-[1,2,3,4-tetrahydronaphthyl]-3-1-oxo-ethyl]-1-phenyl-1,3,8-triazospiro[4.5]decan-4-one, (II), has been prepared and is discussed (3).



(II)

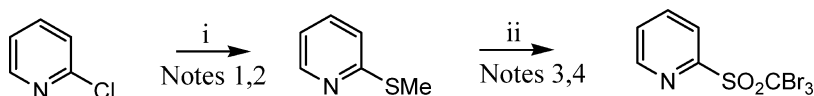
References

1. B. Evans *et al*, US Patent 5,091,387 (February 25, 1992)
2. R.R. Goehring *et al* US Patent 6,828,440 (December 7, 2004)
3. D. Kyle *et al*, US Patent 6,686,370 (February 3, 2004)

Pyridine

Patent: Process for Preparing Tribromomethylsulfonylpyridine
E. Fujisawa *et al*, US Patent 6,420,564 (July 16, 2002)
Assignee: Sumitomo Seika Chemicals Co., Ltd.
Utility: Improved Method for Preparing Tribromomethylsulfonylpyridine

Reaction



i- Sodium methanethiolate, sodium hydroxide, water
tetrabutylammonium bromide
ii- Sodium hypobromite, water

Experimental

1. 2-(Methylthio)pyridine

An aqueous solution consisting of sodium methanethiolate (0.24 mol), 95% NaOH (0.15 mol) and water (0.15 mol) was added to 2-chloropyridine (0.20 mol) and tetrabutylammonium bromide (2.3 g) over 2 hours at 80–90°C. Thereafter, the mixture stirred 5 hours at 90–100°C. The two layers were separated and the product isolated in 95% yield.

2. 2-(Tribromomethylsulfonyl)pyridine

A 27% solution of sodium hypobromite (1.2 mol) was prepared by adding bromine to 30% aqueous sodium hydroxide and then adding it to 95% sodium hydroxide (0.12 mol).

Thereafter, the mixture was cooled to 0°C, the product from Step 1 (23.8 g) added over 2 hours, and the mixture stirred for 5 hours at 5–10°C. The product precipitated out as crystals and was isolated in 99% yield, mp = 160–161°C.

Notes

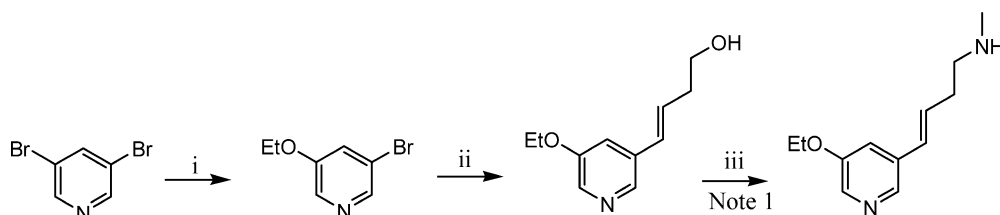
1. 2-Methylthiopyridine was prepared in this two phase system using tetrabutylammonium bromide as the phase transfer catalyst.
2. In a subsequent investigation by others (1), tetrabutylphosphonium bromide was used as the phase transfer catalyst.
3. Methods for preparing 3- and 4-(tribromomethylsulfonyl)pyridine were also described by the author.
4. 2-(Tribromomethylsulfonyl)-pyridine was previously been prepared by direct bromination of 2-(methylsulfonyl)pyridine using sodium hypobromite (2). This method, however, is hindered by (a) a reaction time that exceeds 24 hours and (b) a product re-crystallization step.
5. Methods for preparing heterocyclic thioalkyl intermediates of the current invention are provided (3).

References

1. E. Fujisawa *et al*, US Patent 6,509,470 (January 29, 2003)
2. R. Jensen *et al*, J. Org. Chem., 51, 3369 (1986)
3. M. Winter *et al*, US Patent 3,702,253 (November 7, 1972)

Patent: 3-Pyridinyl Compounds
W.S. Caldwell *et al*, 6,603,011 (August 5, 2003)
Assignee: Targacept, Inc.
Utility: Treatment of Parkinson's Disease

Reaction



- i- Sodium ethoxide, N,N-dimethylformamide
 ii- 3-Buten-1-ol, palladium(II)acetate, tri-o-tolylphosphine, triethylamine
 iii- CH_2Cl_2 , pyridine, tosyl chloride

Experimental

1. 3-Bromo-5-ethoxypyridine

3,5-Dibromopyridine (21.1 mmol) and sodium ethoxide (42.2 mmol) were dissolved in 10 ml N,N-dimethylformamide and heated to 65°C. 15 hours. The mixture was poured into 70 ml water, 155 ml diethyl ether added, and then filtered. The layers were separated, extracted with additional diethyl ether, and combined. The extracts were dried, concentrated, purified by vacuum distillation, and 17.9% product isolated, bp = 105°C at 5 mm Hg. ^1H - and ^{13}C -NMR data supplied.

2. (E)-4-[3-(5-Ethoxypyridin)yl]-3-buten-1-ol

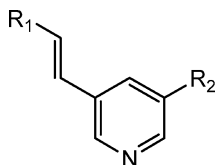
3-Buten-1-ol (2.0 mmol), the product from Step 1 (2.1 mmol), palladium(II) acetate (0.02 mmol), tri-o-tolylphosphine (0.08 mmol) and 0.5 ml triethylamine were mixed in 1 ml acetonitrile and refluxed for 21 hours. Thereafter, the mixture was diluted with 10 ml water and extracted with CH_2Cl_2 . The combined extracts were dried, concentrated, purified by chromatography on silica gel using a gradient of 100% methyl alcohol to methyl alcohol/ 8% EtOAc, and the product isolated in 66.3% yield. ^1H - and ^{13}C -NMR data supplied.

3. (E)-N-Methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine

The product from Step 2 (1.24 mmol) was dissolved in 1 ml CH_2Cl_2 containing 1 drop pyridine, tosyl chloride (1.36 mmol) added, and the mixture stirred 12 hours. Thereafter,

the mixture was concentrated, the residue dissolved in 3 ml methyl alcohol, 3 ml 40% aqueous methylamine added, and the solution stirred 5 hours. Thereafter, the mixture was re-concentrated, partitioned between 2 ml 1 M NaOH and 5 ml chloroform, separated, washed, filtered, and concentrated. It was purified by chromatography on silica gel using triethylamine/ethyl alcohol, 2.5:97.5, and the product isolated in 34.0% yield. ^1H - and ^{13}C -NMR data supplied.

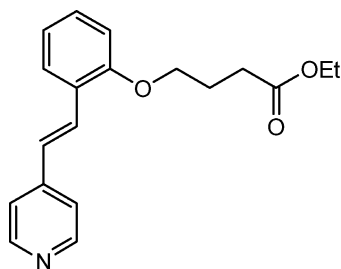
Derivatives



R_1	R_2	Yield (%)
4-Penten-2-ol-5-yl	Hydrogen	88.2
3-Butene-1-ol-4-yl	Methoxy	56.9
N-Methyl-3-buten-1-amide-4-yl	Methoxy	43.4

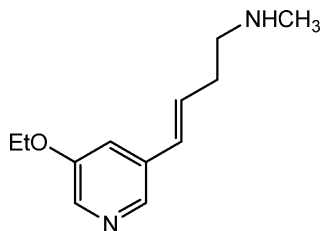
Notes

1. The 4-substituted analogue of the current invention, (E)-4-{4-[2-(4-pyridinyl)-ethenyl]-phenoxy}-butyric acid ethyl ester, (I), was also prepared by the author and is discussed.



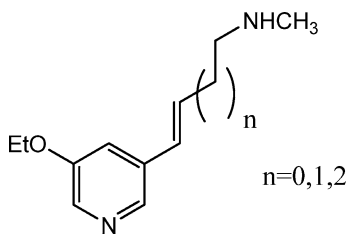
(I)

2. The preparation of amine analogues of the product of Step 3, (E)-N-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine, (II), and derivatives is described (2).



(II)

3. In an earlier investigation by the author (3) Step 3 amine derivatives, (III), were prepared and are described.



(III)

References

1. W.-G. Friebe *et al.*, US Patent 5,399,575 (March 21, 1995)
2. G.M. Dull *et al.*, US Patent 5,616,716 (April 1, 1997); P.A. Crooks *et al.*, US Patent 5,616,707 (April 1, 1997)
3. W.S. Caldwell *et al.*, US Patent 6,555,684 (April 29, 2003)

Pyridone and tetrahydropyridone

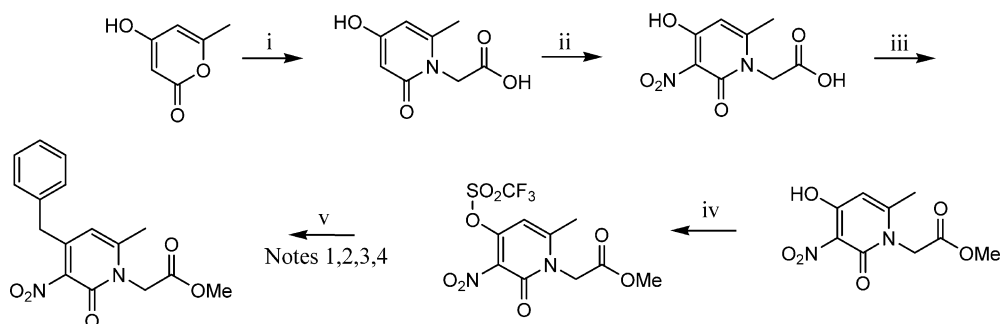
Patent: Pyridone Derivatives, Their Preparation and Their Use as Synthesis Intermediates

G. Lassalle *et al*, US Patent 6,252,082 (June 26, 2001)

Assignee: Sanofi-Synthelabo

Utility: Intermediate for Anticoagulants and Antithrombotics

Reaction



i- Glycine, sodium hydroxide

ii- Acetic acid, nitric acid

iii- Methyl alcohol, hydrogen chloride

iv- CH_2Cl_2 , triethylamine, trifluoromethanesulphonic anhydride

v- Zinc, THF, chlorotrimethylsilane, phenylmethyl bromide,
cuprous cyanide, lithium chloride

Experimental

1. 4-Hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-1-acetic acid

At ambient temperature, 4-hydroxy-6-methyl-2H-pyran-2-one (1.4 mmol) added portion-wise to glycine (1.4 mmol) dissolved in 1.4 L 1 M NaOH, refluxed 1 hour, and acidified with 500 ml 3 M HCl. The mixture was concentrated to half its volume, the precipitate filtered, washed, and the product isolated in 70% yield, mp = 240 °C.

2. 4-Hydroxy-6-methyl-3-nitro-2-oxo-1,2-dihydropyridine-1-acetic acid

The product from Step 1 (0.17 mol) was suspended in 255 ml HOAc and 24 ml 68% HNO₃ and heated to 80 °C. Thereafter, the mixture was concentrated, the residue dissolved in 200 ml water, re-concentrated, dissolved in toluene, re-crystallized from isopropyl alcohol, and the product isolated in 70% yield, mp = 205 °C.

3. Methyl 4-hydroxy-6-methyl-3-nitro-2-oxo-1,2-dihydropyridine-1-acetate

The product from Step 2 (0.11 mol) was treated with 250 ml methyl alcohol saturated with gaseous HCl, the mixture refluxed 4 hours, and the product isolated by filtration in 85% yield, mp = 187 °C.

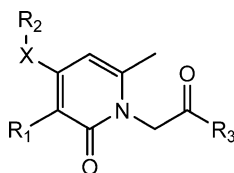
4. Methyl 6-methyl-3-nitro-2-oxo-4-[[[(trifluoromethyl)sulphonyl]oxy]-1,2-dihydropyridine-1-acetate

The product from Step 3 (0.11 mol) was suspended in 500 ml of CH₂Cl₂ containing 17.4 ml triethylamine, the mixture cooled to –70 °C, trifluoromethanesulphonic anhydride (0.12 mol) added, and the reaction stirred 1 hour at ambient temperature. Thereafter, it was washed with 200 ml water and 100 ml ice cold 1 M HCl solution. The organic phase was dried, concentrated, purified by chromatography on a silica gel using CH₂Cl₂/methyl alcohol, 98:2, and the product isolated in 98% yield, mp = 68–70 °C.

5. Methyl 6-methyl-3-nitro-2-oxo-4-(phenylmethyl)-1,2-dihydropyridine-1-acetate

A suspension of zinc (30.6 mmol) in 50 ml THF was treated with 200 µl chlorotrimethylsilane, stirred 30 minutes at ambient temperature, and then cooled to 0 °C. Phenylmethyl bromide (26.3 mmol) dissolved in 20 ml THF was added and stirred 2 hours. Thereafter, the mixture was treated with CuCN (25 mmol) and LiCl (50 mmol) at –10 °C, briefly stirred, and finally cooled to –70 °C. The product from Step 4 (19.5 mmol) dissolved in 50 ml THF was added, the mixture warmed to 0 °C, stirred 1 hour, then quenched by pouring into 100 ml 1 M HCl followed by 200 ml CH₂Cl₂. The precipitate was filtered, extracted with CH₂Cl₂, dried, and concentrated. The residue was purified by chromatography on a silica gel column with CH₂Cl₂/methyl alcohol, 98:2, recrystallized in ethyl alcohol, and the product isolated in 86% yield, mp = 146–147 °C.

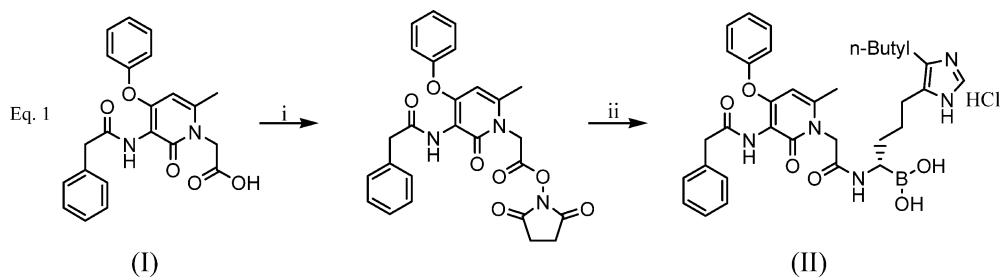
Derivatives



R₁	R₂	R₃	X	Melting Point (°C)
Nitro	3-Thiofuran	Methyl	CH ₂	157–158
N-(2-Methylpyridine)amine	Phenyl	Hydrogen	CH ₂	63 (dec)
Amino	Benzyl	Methyl	S	175
N-Benzylurea	Phenyl	Hydrogen	CH ₂	176

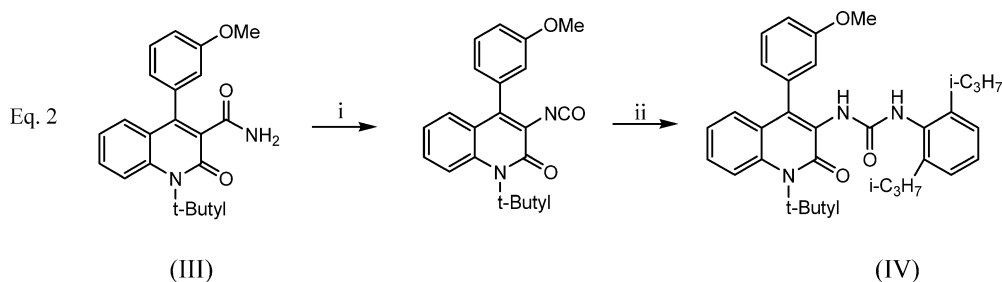
Notes

- Beginning with 6-methyl-2-oxo-4-phenoxy-3-[(benzyl-carbonyl)amino]-1,2-dihydropyridine-1-acetic acid, (I), a method for preparing (R)-N-borono[3-(1H-imidazol-4-yl)propyl]methyl]-3-[(benzyl-carbonyl)amino]-6-methyl-2-oxo-4-phenoxy-1,2-dihydropyridine-1-acetamide · HCl, (II), as illustrated in Eq. 1, is described by the author in the current invention.



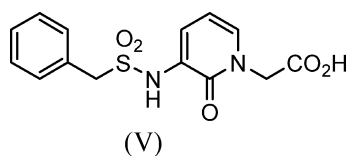
- N-Hydroxysuccinimide, 1,3-dicyclohexyl-carbodiimide, CH₂Cl₂
- [3α(S)-2(R),3α,4β,6β,7α.]α-[3α,5,5-Trimethyl-hexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]-1H-imidazole-4-butanamine, CH₂Cl₂, triethylamine, hydrogen chloride

2. 4-(3-Methoxyphenyl)-3-carboxylamino-N-t-butyl-2-oxo-1,2-dihydro-1,8-naphthyridine, (III), was converted into the corresponding 3-urea derivative, (IV), using the Hoffman rearrangement and is described (1,2). The procedure was also performed using 3-carboxylamino-2-oxo-pyridine (3).

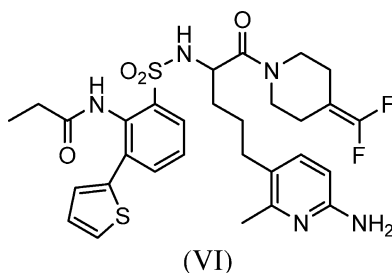


i- Sodium hydroxide solution, bromine,
tetrabutylammonium, hydrogen sulfate, toluene
ii- Acetic acid, 2,6-diisopropylaniline, toluene

3. [3-[(Benzylsulfonyl)amino]-2-oxo-1,2-dihydropyridyl]acetic acid and derivatives, (V), of the current invention have been prepared and are described (4).



4. Other heterocyclic analogues of the product of Step 3 have been prepared, (VI), and are described (5).

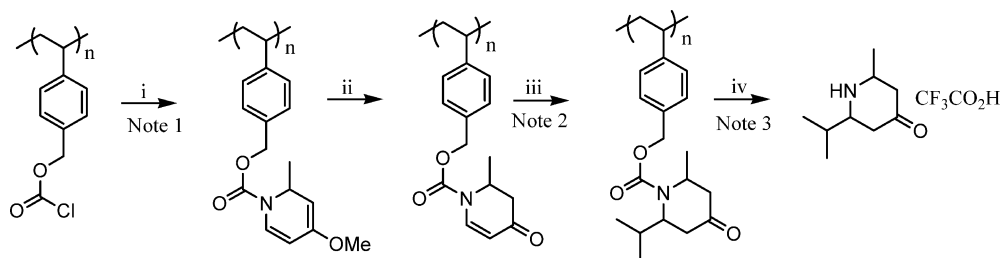


References

1. M. Muraoka *et al*, US Patent 6,300,500 (October 9, 2001)
2. M. Muraoka *et al*, US Patent 6,452,008 (September 17, 2001)
3. E.S. Hamanaka, US Patent 5,565,472 (October 15, 1996)
4. S.Y. Tamura *et al*, US Patent 5,658,930 (August 19, 1997) and US Patent 5,656,645 (August 12, 1997)
5. J.-M. Altenburger *et al*, US Patent 6,680,329 (January 20, 2004)

Patent: Solid Phase Synthesis of Heterocycles
 B. Munoz *et al*, US Patent 6,362,009 (March 26, 2002)
Assignee: Merck & Co., Inc.
Utility: Antibiotic Intermediates

Reaction



- i- 4-Methoxypyridine, methylmagnesium chloride, THF
 ii- Hydrochloric acid, THF
 iii- Isopropylmagnesium chloride, cuprous iodide, THF,
 borontrifluoride · diethyl ether
 iv- Trifluoroacetic acid, CH_2Cl_2

Experimental

1. Polystyrene-graft-2-methyl-2,3-dihydro-4-methoxypyridine

To a suspension of polystyrene-graft-chloroformate (0.5 g, 0.41 mmol based on loading of 0.81 mmol/g) dissolved in 6 ml THF was added 4-methoxypyridine (0.48 mmol) and methylmagnesium chloride (0.81 mmol) dissolved in 3 ml. Thereafter, additional THF was added, the mixture immediately filtered, and the modified graft polymer isolated. FTIR data supplied.

2. Polystyrene-graft-2-methyl-2,3-dihydropyridone

The product from Step 1 was washed successively with a mixture of 3 M HCl and THF, 1:1, 3 M HCl, methyl alcohol, N,N-dimethyl-formamide and diethyl ether, dried, and the modified graft polymer isolated. FTIR data supplied.

3. Polystyrene-graft-2-methyl-6-isopropyl-2,3,5,6-tetrahydropyridone

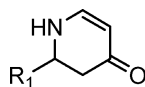
Isopropylmagnesium chloride (0.6 mmol) was added to CuI (0.6 mmol) in 3 ml THF at -25°C for 10 minutes, further cooled to -78°C , $\text{BF}_3 \cdot \text{diethyl ether}$ added, and the suspension reacted with the product from product from Step 2 (366 mg, 0.82 mmol/g,

0.3 mmol) 3 hours at ambient temperature. Thereafter the polymer was isolated by filtration, washed successively with THF and 1 M HCl, 1:1, 1 M HCl, methyl alcohol and CH_2Cl_2 , and the modified graft polymer isolated.

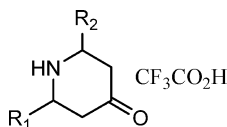
4. 2-Methyl-6-isopropyl-2,3,5,6-tetrahydropyridone trifluoroacetic acid salt

The product from Step 3 was suspended in 2 ml CH_2Cl_2 , 4 ml trifluoroacetic acid added, and mixture agitated 3 days. Thereafter, the mixture was filtered, washed with CH_2Cl_2 , methyl alcohol, the combined filtrates concentrated, dried under vacuum, and the product isolated as the trifluoroacetic salt in 32% yield, 90% purity. $^1\text{H-NMR}$, MS, and elemental analysis data supplied.

Derivatives



R_1	Yield (%)	Purity (%)
Isopropyl	48	93
Ethyl	31	94
t-Butyl	32	85
Phenyl	67	95
Benzyl	35	95



R_1	R_1	Yield (%)	Purity (%)
Methyl	Methyl	29	95
Methyl	4-Methylphenyl	21	—
Benzoyl	4-Methylphenyl	50	80
Benzoyl	2-Methylphenyl	58	76
2-Phenyl	4-Methylphenyl	23	—

Notes

1. Polystyrene-g-chloroformate was prepared by co-polymerizing 1% divinylbenzene with styrene, hydroxymethylating with formaldehyde, followed by treatment with phosgene.
2. 2-Methyl-2,3-dihydropyridone was isolated by hydrolyzing the Step 3 product with trifluoroacetic acid as described in Step 4.
3. Step 3 and Step 4 di- and tetrahydropyridone derivatives were also prepared by the author without using polystyrene modified reagents and are described.
4. The solid phase synthesis of oligomeric amides using polystyrene graft intermediates is described (1). Other examples of polymeric assisted syntheses of heterocycles are provided (2).
5. 2,3-Dihydropyridone and 2,3,5,6-tetrahydropyridine derivatives have previously been prepared and are described (3).

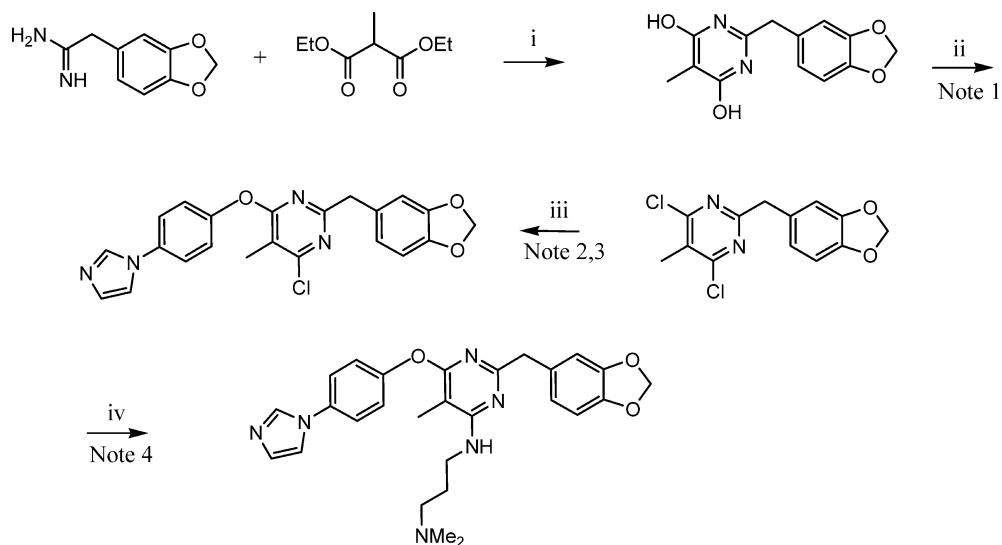
Reference

1. R.N. Zuckermann *et al*, US Patent 5,877,278 (March 2, 1999)
2. G.L. Bolton *et al*, US Patent 6,306,959 (October 23, 2001)
3. R.L. Hill *et al*, US Patent 6,028,033 (February 2, 2000) and M. Horst US Patent 4,001,259 (January 4, 1977)

Pyrimidines

Patent: N-Heterocyclic Derivatives as NOS Inhibitors
D.D. Davey *et al*, US Patent 6,525,051 (February 25, 2003)
Assignee: Schering Aktiengesellschaft
Utility: Nitric Oxide Synthase Inhibitors for Treatment of Inflammation

Reaction



- i- Methyl alcohol, sodium methoxide
- ii- Phosphorous oxychloride, N,N-dimethylaniline
- iii- Cesium carbonate, dimethyl sulfoxide,
1-(4-hydroxyphenyl)imidazole
- iv- Dimethyl sulfoxide, N,N-dimethylpropaneamine

Experimental

1. 2-[(1,3-Benzodioxol-5-yl)methyl]-4,6-dihydroxy-5-methylpyrimidine

To 250 ml ethyl alcohol was added 5-(amidino)methyl-1,3-benzodioxolane (0.23 mol), 50 ml diethyl methylmalonate, 125 ml 25% NaOH in methyl alcohol, and the mixture refluxed 5 hours. The solvent was removed, the residue dissolved in water, acidified with 6 M HCl, and the product isolated by precipitation.

2. 2-[(1,3-Benzodioxol-5-yl)methyl]-4,6-dichloro-5-methylpyrimidine

To the product from Step 1 (54 g) dissolved in 65 ml N,N-dimethylaniline was added 300 ml phosphorous oxychloride and the mixture heated 3 hours at 45°C. The mixture was cooled, the solvent removed, and the residue added to ice water. The solids were collected, dissolved in CH₂Cl₂, washed with K₂CO₃ solution, re-crystallized in hexane, and the product isolated.

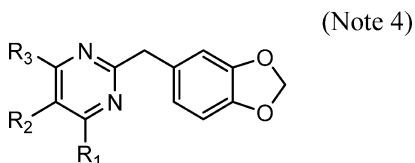
3. 2-[(1,3-Benzodioxol-5-yl)methyl]-6-chloro-4[4-(1H-imidazol-1-yl)phenoxy]-5-methylpyrimidine

To the product from Step 2 (5.3 mmol) dissolved in 5 ml DMSO was added 1-(4-hydroxyphenyl)imidazole (5.8 mmol) and Cs₂CO₃ (5.6 mmol) and the mixture heated to 90°C 18 hours. The reaction mixture was partitioned between water and EtOAc, concentrated, purified by chromatography on silica gel using EtOAc/hexanes, and the product isolated.

4. 2-[(1,3-Benzodioxol-5-yl)methyl]-6-[3-(dimethylamino)propyl-(methyl-amine-4[4-(1H-imidazol-1-yl)phenoxy]-5-methylpyrimidine

The product from Step 3 (2 g) was dissolved in 20 ml DMSO and 1.5 ml N,N-dimethylpropaneamine added. The mixture was heated to 40°C 24 hours, partitioned between aqueous KOH and CH₂Cl₂, and the product isolated.

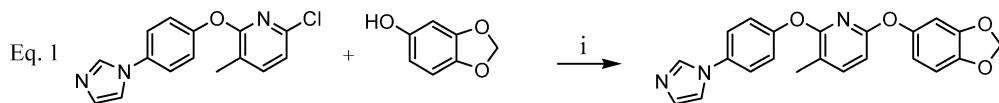
Derivatives



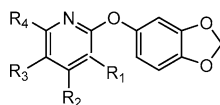
R ₁	R ₂	R ₃
Hydrogen	Methoxy	Chloro
Methoxycarbonyl	Chloro	Chloro
4-(1H-Imidazol-1-yl)phenoxy	Methyl	Hydrogen
Trifluoromethyl	4-(1H-Imidazol-1-yl)phenoxy	Trifluoromethyl

Notes

1. An alternative method for preparing the product of Step 5 was also prepared by the author as illustrated in Eq. 1.



i- Cesium carbonate, dimethyl sulfoxide



(Note 4)

R₁	R₂	R₃	R₄
Hydrogen	Hydrogen	Aminocarbonyl	Methoxycarbonyl
Fluoro	Fluoro	Bromo	Fluoro
Methoxy	Hydrogen	Methoxy	Fluoro
Hydrogen	Hydrogen	N-(Aminocarbonyl-methyl)ureido	Fluoro

2. Other Step 3 displacement derivatives are provided (1).
3. The preparation of other pyrimidyl imidazole derivatives is described (2).
4. ¹H-NMR data supplied by the author.
5. Pyrimidinyl-glutamic acid (3) and tricyclic pteridinones (4) derivatives of the current invention have been prepared and are discussed.

References

1. B.O. Buckman *et al*, US Patent 5,691,364 (November 25, 1997)
2. P.W. Sheldrake *et al*, US Patent 5,663,334 (September 7, 1997)
3. L.S. Gossett *et al*, US Patent 5,426,110 (June 20, 1995)
4. D.D. Davey, US Patent 6,025,489 (February 15, 2000)

Pyrrols

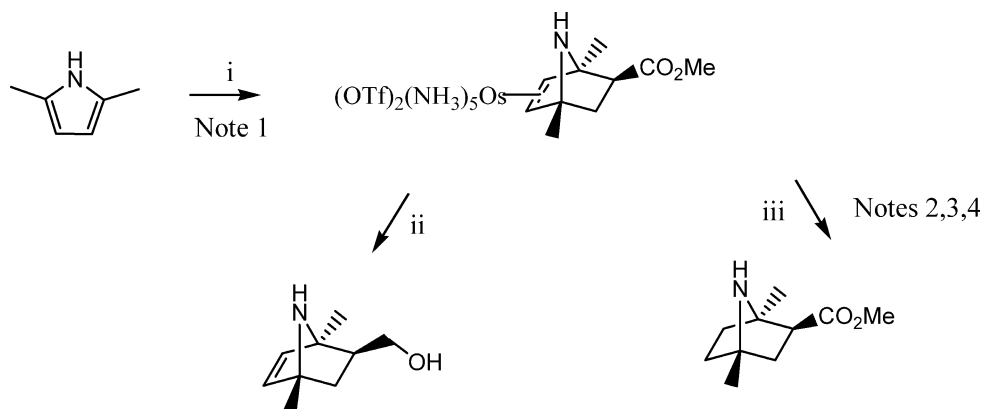
Patent: 7-Azabicyclo[2.2.1]Heptane and Heptene Derivatives as Cholinergic Receptor Ligands

T.Y. Shen *et al*, US Patent 6,255,490 (July 3, 2001)

Assignee: University of Virginia

Utility: Neurotransmitter Receptor Binding Agent

Reactions



i- Pentaammineosmium(II)triflate, N,N-dimethylacetamide, dimethyl ether, magnesium, methyl acrylate

ii- Ceric ammonium nitrate, triflic acid, acetonitrile

- iii- Acetonitrile, triflic acid,
2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 10% palladium
on carbon, hydrogen.

Experimental

1. 1,4-Dimethyl-2-methoxycarbonyl-7-azobicyclo[2.2.1]-heptene-pentaammoniumosmium triflate

A mixture of $[\text{Os}(\text{NH}_3)_5\text{OTf}](\text{OTf})_2$ (1.0 mmol), DMAC (1 g), 2,5-dimethylpyrrole (1 g) and magnesium (0.5 g) were stirred 1 hour and methyl acrylate (1.0–3.0 mmol) added directly to the mixture. The mixture was filtered and added to CH_2Cl_2 /diethyl ether, 1:1, and the product isolated in 95% yield.

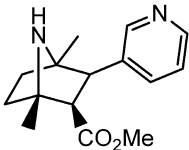
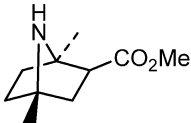
2. 1,4-Dimethyl-2-exo-(hydroxymethyl)-7-azabicyclo[2.2.1]hept-5-ene

The product from Step 1 (1.0 mmol) in CH_3CN (2 g) was treated with triflic acid (1.02 mmol) and $\text{Ce}(\text{NO}_3)_6(\text{NH}_4)_3$ (3.73 mmol) at -10°C and 1.0 ml to 2.0 ml water added to dissolve precipitated salts. The mixture was made basic with aqueous Na_2CO_3 , extracted with CH_2Cl_2 , and purified by column chromatography on silica gel using 15 wt% NH_3 in methyl alcohol/ CH_2Cl_2 , 1:10. The product was isolated as the picrate salt, mp = 186–188°C. $^1\text{H-NMR}$ data supplied.

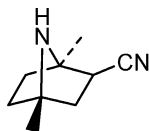
3. 1,4-Dimethyl-2-exo-carboxymethylcarbonyl-7-azabicyclo[2.2.1] heptane

The product from Step 1 (1.0 mmol) was dissolved in CH_3CN (4 g), protonated with triflic acid (3 eq to 5 eq), and treated with DDQ (1 eq). An additional 20 ml CH_3CN was added and the mixture hydrogenated with 10% palladium on carbon (0.5 g) under 1 atmosphere hydrogen. The solvent was evaporated, replaced with methyl alcohol (Note 3), and the product isolated using column chromatography on silica gel using $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$, 1:1.

Derivatives

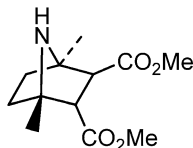
Step 1 Dienophile <u>Reagent</u>	Step 3 Hydrogenation <u>Product</u>	<u>Endo:Exo</u>
3-(3-pyridine)-methyl- acrylate		94:1
Methyl acrylate		1:1 (Note 5)

Acetonitrile



1:1

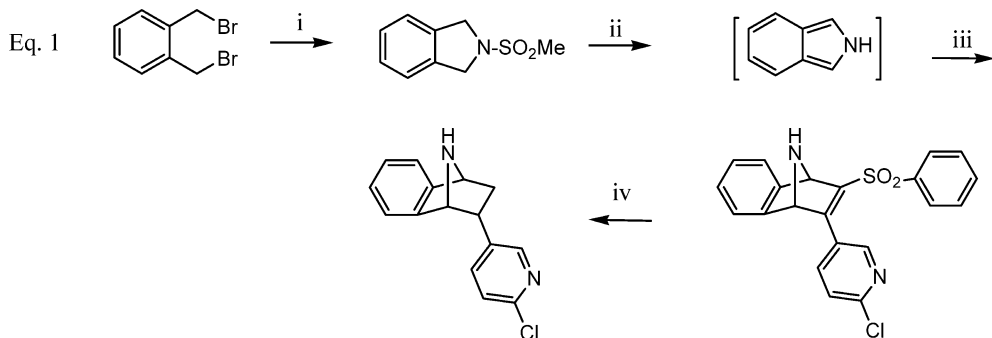
Dimethyl fumarate



1:1

Notes

1. The Step 1 product was isolated by filtering through a fritted glass funnel with the aid of 10 ml to 15 ml DMF and precipitated in 150 ml CH_2Cl_2 . The filtrate was washed with 20 ml CH_2Cl_2 , twice with diethyl ether, and isolated in 90% to 95% yield as a yellow orange solid with 8% binuclear impurity.
2. The solvent replacement was necessary because pyrrole complexes lacking a substituent on nitrogen undergo reductive amination to N-ethyl derivatives in CH_3CN .
3. The reaction of Step 3 was also used by the author and others (1) to prepare epibatidine derivatives (1), as illustrated in Eq. 1:



i- Methanesulfonamide

ii- Potassium t-butoxide

iii- 1-(6-Chloro-3-pyridyl)-phenylsulfonyl acetylene

iv- Sodium amalgam

4. The preparation of other epibatidine derivatives is described elsewhere (2, 3).
5. 1:1 Isomers were separated using preparative thin layer chromatography using $\text{HDMS}/\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 1:1:8.

References

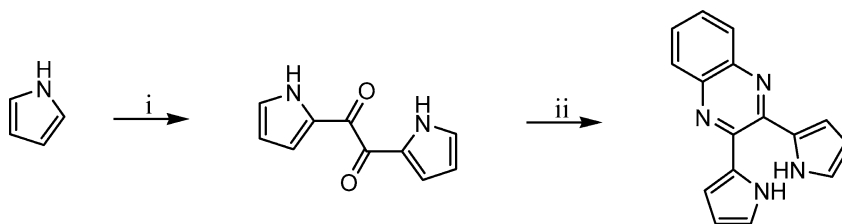
1. B. Zeeh *et al*, Synthesis, 45 (1972)
2. B. Williams *et al*, US Patent 5,459,270 (October 17, 1995)
3. R. Baker *et al*, US Patent 5,451,588 (September 19, 1995).

Patent: Colormetric Sensor Compositions and Methods
J. Sessler *et al.*, US Patent 6,482,949 (November 19, 2002)

Assignee: Board of Regents, University of Texas System

Utility: Analytic Reagents for Detection of Fluoride, Chloride, and Phosphate Anions

Reaction



i- Oxalyl chloride, CH_2Cl_2 , pyridine
ii- 1,2-Phenylenediamine, acetic acid

Experimental

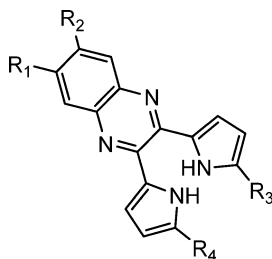
1. 1,2-Bis-(2-pyrrolyl)ethanedione

Oxalyl chloride (0.05 mol) and 25 ml CH_2Cl_2 were cool to -78°C and pyridine (0.12 mol) added causing the formation of a yellow precipitate. To this suspension was added pyrrole (0.1 mol) dissolved in 25 ml CH_2Cl_2 , the mixture stirred for 15 minutes at -60°C , and was then quenched with 100 ml 5 M HCl. The phases were separated, the aqueous portion extracted with 3 times with 30 ml CH_2Cl_2 , combined, washed with 100 ml water, filtered and concentrated. The material was purified by chromatography on silica gel using acetone/hexanes, 80:20, and the product isolated in 38% yield. ^1H - and ^{13}C -NMR data supplied.

2. 2,3-Bis-(2-pyrrolyl)quinoxaline

The product from Step 1 (3.03 mmol) was dissolved in 70 ml HOAc, 1,2-phenylenediamine (6.62 mmol) dissolved in 30 ml HOAc added, and the mixture refluxed 90 minutes. The mixture was concentrated, dissolved in 30 ml apiece CH_2Cl_2 and water, the phases separated, and the aqueous phase further extracted with CH_2Cl_2 . The organic phases were combined, washed with 50 ml apiece NaHCO_3 , water and brine, dried, and concentrated. The material was purified by chromatography on silica gel using CH_2Cl_2 and the product isolated in 94% as a yellow powder. ^1H - and ^{13}C -NMR, MS, and elemental analysis data supplied.

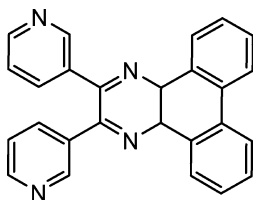
Derivatives



R ₁	R ₂	R ₃	R ₄	MP (°C)	Yield (%)
Hydrogen	Hydrogen	Hydrogen	Hydrogen	—	94
Methoxy	Methoxy	Hydrogen	Hydrogen	196–198	86
Hydrogen	Hydrogen	Bromo	Bromo	204–206	70
Nitro	Hydrogen	Hydrogen	Hydrogen	206–208	85 (Note 2)
Phenylcarbonyl	Phenylcarbonyl	Hydrogen	Hydrogen	—	44
Nitro	Nitro	Hydrogen	Hydrogen	215–217	80

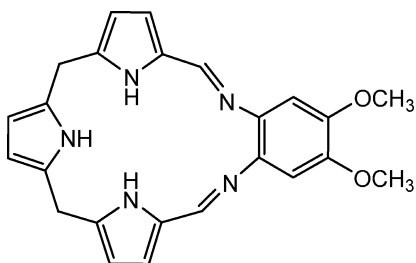
Notes

1. Calixpyrroles, calixpyridinopyrroles, and calixpyridines have been used as analytical tools for the detection of fluoride and phosphate anions (1). Other supramolecular agents used for recognizing, sensing, and transporting anions are discussed (2).
2. 2,3-Di-pyridin-2-yl-dibenzoquinoxaline, (I), (3) has been prepared and has photosensitive detection properties for fluoride and phosphate anions (1).



(I)

3. Texaphyrin, (II), (4), has a central core that is 20% larger than porphyrin. It has been prepared to encapsulate cations considerably larger than porphyrin containable counterpart.



(II)

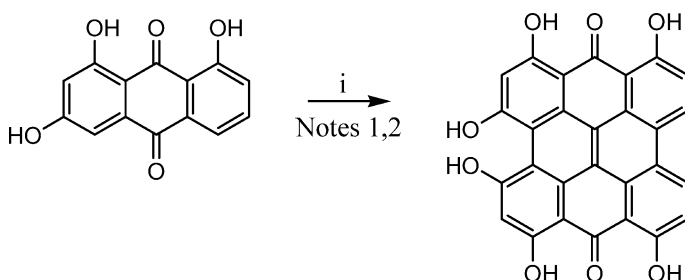
References

1. P.A. Gale *et al*, US Patent 6,262,257 (July 17, 2001)
2. B. Dietrich *et al*, J. Am. Chem. Soc., 103, 1282, 1981
3. X.-C.C. Li *et al*, US Patent 6,723,445 (April 20, 2004)
4. D. Magda *et al*, US Patent 6,657,058 (December 2, 2003)

Quinones

Patent: Compositions and Methods for Treating Viral Infections
D. Meruelo *et al*, US Patent 6,150,414 (November 21, 2000)
Assignee: New York University and Yeda Research and Development Co. Ltd.
Utility: Antiviral Agents for the Treatment of HIV-1 and HIV-2

Reaction



i- Potassium t-butoxide, hydroquinone, hydrochloric acid,
irradiation with visible light

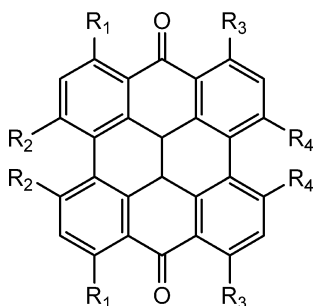
Experimental

1. Desmethylhypericin

1, 3, 8-Trihydroxyanthraquinone (300 mg) was dissolved in 10 ml water containing potassium t-butoxide (0.5 g) and hydroquinone (0.3 g), placed into a sealed glass ampule, and heated to 140°C 21 days. Thereafter, it was acidified with 1% HCl to pH 1, extracted with butanol/EtOAc, 1:1, washed with water until a neutral pH was obtained, and concentrated. The mixture was purified by chromatography on silica gel with EtOAc/methyl

alcohol, 100:5, dissolved in EtOAc, irradiated with visible light 1 hour, concentrated, and 44 mg product isolated. $^1\text{H-NMR}$ and λ_{max} data supplied.

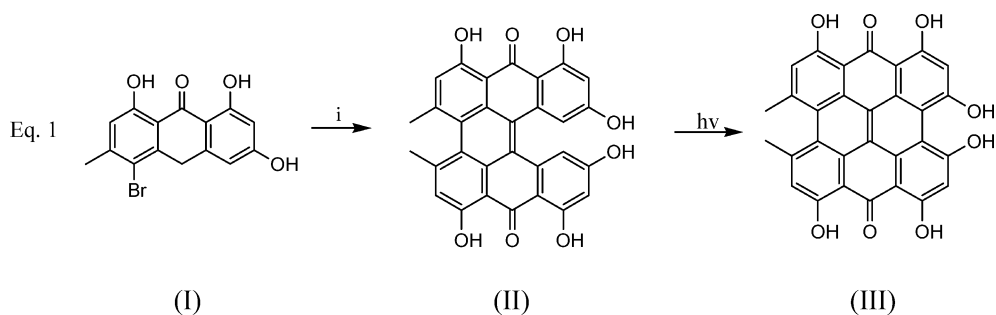
Derivatives



R₁	R₂	R₃	R₄	UVλ_{max}
Hydroxy	Methyl	Hydroxyl	Hydroxy	>800 (EtOH)
Acetate	Methyl	Acetate	Acetate	621 (EtOH)
Hydrogen	Hydrogen	Hydroxyl	Hydrogen	580 (MeOH)
Methyl	Hydroxyl	Hydroxyl	Acetate	(586 MeOH)

Notes

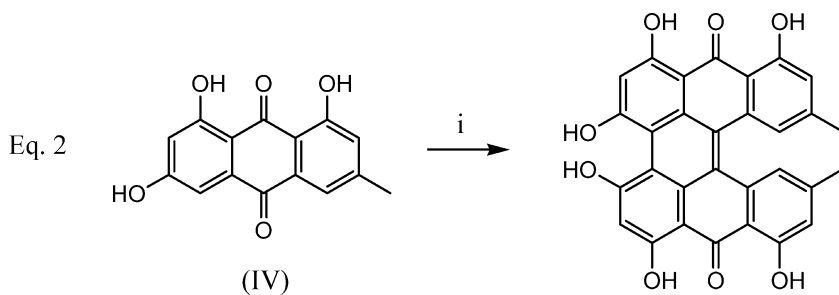
1. Preparation of the Step 1 reagent is described (1).
2. Oxidative dimerization of emodin, (I), has been used to prepared protohypercin, (II), and hypercin, (III), as illustrated in Eq. 1:



i- Pyridine, piperidine, ferrous sulfate heptahydrate, pyridine N-oxide

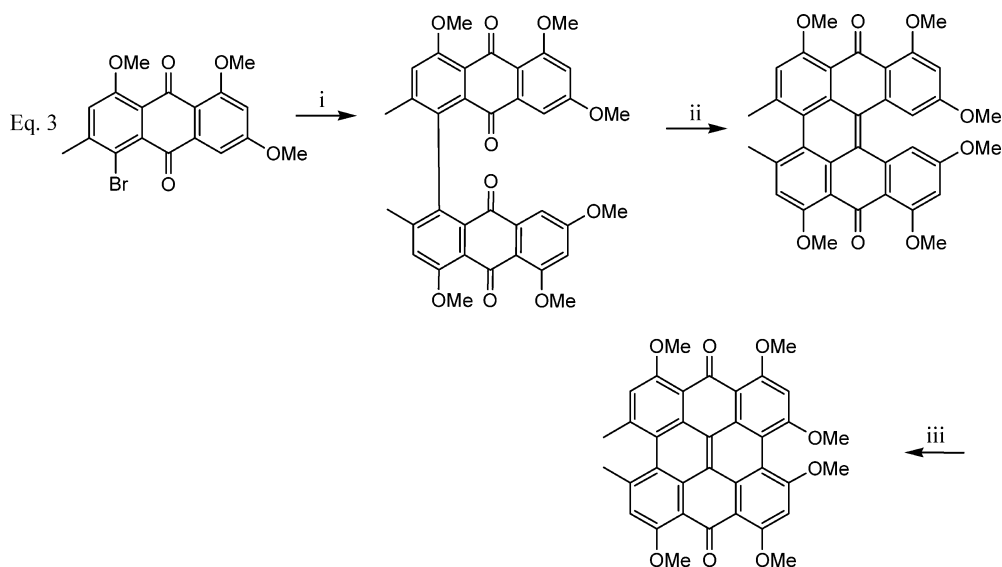
ii- Visible light

3. A modifier Step 1 procedure was used to dimerize 1,3,8-trihydroxy-3-methyl-anthraquinone, (IV), as illustrated in Eq. 2 and described by the author.



i- Potassium t-butoxide, hydroquinone, water, nitrogen,
visible light

4. Hypericin derivatives have also been prepared the Ullman biaryl coupling (3) reaction as illustrated in Eq. 1:

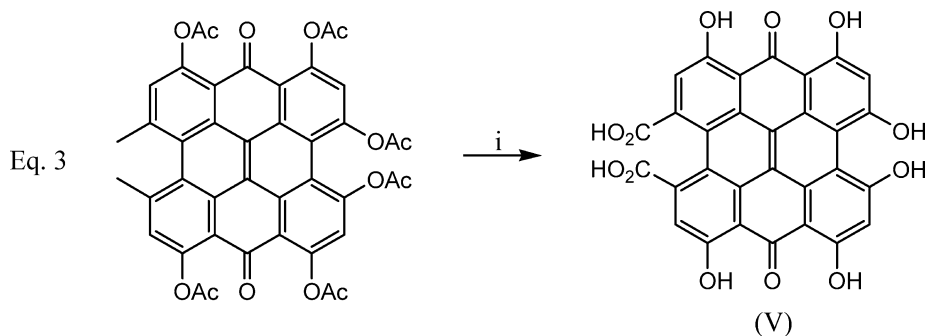


i- Activated copper bronze

ii- Pyridinium chloride

iii- Activated copper bronze, sulfuric acid, visible light

5. The preparation of hypercin dicarboxylic acid, (V), was also provided by the author and others (4) using 1,3,4,6,8,13-hexaacetate-10,11-dimethyl hypercin and illustrated in Eq. 3:



i- Acetic acid, chromium trioxide, water

References

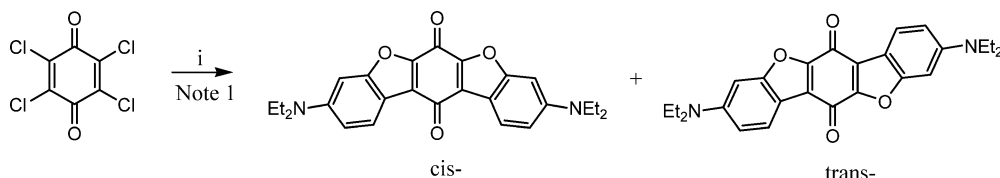
1. J.C. Lovie *et al.*, J. Chem. Soc., 485 (1961)
2. D.W. Cameron *et al.*, Aust. J. Chem., 29, 1523 (1976); Y. Mazur *et al.*, US Patent 5,120,412 (June 9, 1992)
3. H. Brockman *et al.*, US Patent 2,707,704 (May 3, 1955)
4. H. Brockman *et al.*, Tetrahedron Lett., 2, 37 (1975)

Patent: Quinone Compound, Liquid Crystal Composition, and Guest-Host-Type Liquid Crystal Cell Employing the Same
T. Katoh, US Patent 6,703,084 (March 9, 2004)

Assignee: Fuji Photo Film Co., Ltd.

Utility: Liquid Crystal Cells for Electrodes and Electrode Substrates

Reaction



i- Sodium methoxide, methyl alcohol,
3-N,N-diethylaminophenol

Experimental

1. **cis-2,3-(3-Diethylamino)benzo-5,6-[b]naphtho[2,3-d]furan-6-11-dione**

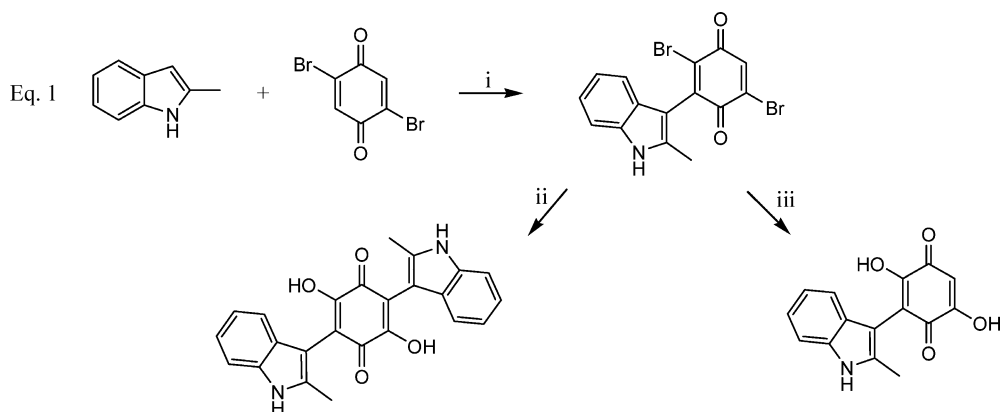
and

trans-2,3-(3-Diethylamino)benzo-5,6-[b]naphtho[2,3-d]furan-6-11-dione

2,3,5,6-Tetrachloro-p-quinone (1.2 g) and 3-N,N-diethylaminophenol (1.80 g) were dissolved in 50 ml methyl alcohol, 4.2 ml 28% aqueous solution sodium methoxide added, and the mixture refluxed 6 hours. Thereafter, the mixture was extracted with CH_2Cl_2 , dried, and concentrated. The product was purified by chromatography on silica gel using chloroform/hexane and cis- and trans-products, 0.42 g and 0.10 g, mp = 292 °C and 288 °C isolated, respectively. $^1\text{H-NMR}$ and absorption maxima and coefficients data supplied.

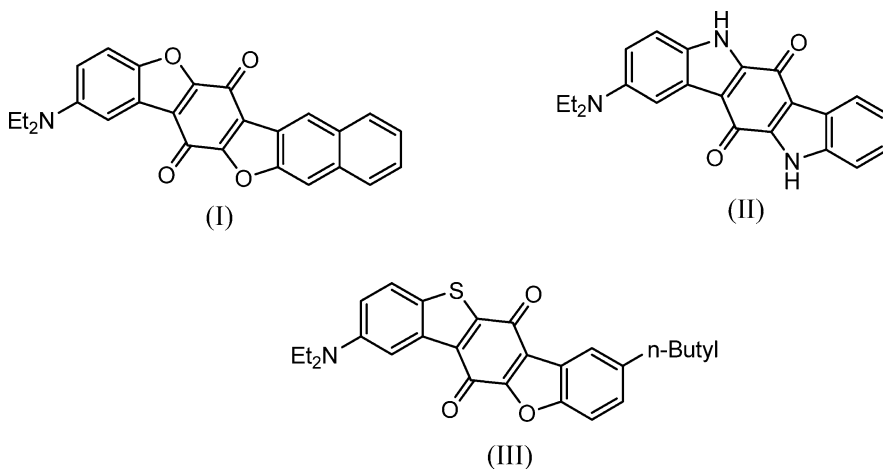
Notes

1. The UV absorption maxima for cis- and trans- Step 1 products dissolved in acetonitrile were 520 nm and 525 nm, respectively.
2. Liquid crystals have been prepared from 2-methylindoyl and derivatives and 2,5-dibromop-quinone (1) as illustrated in Eq. 1:

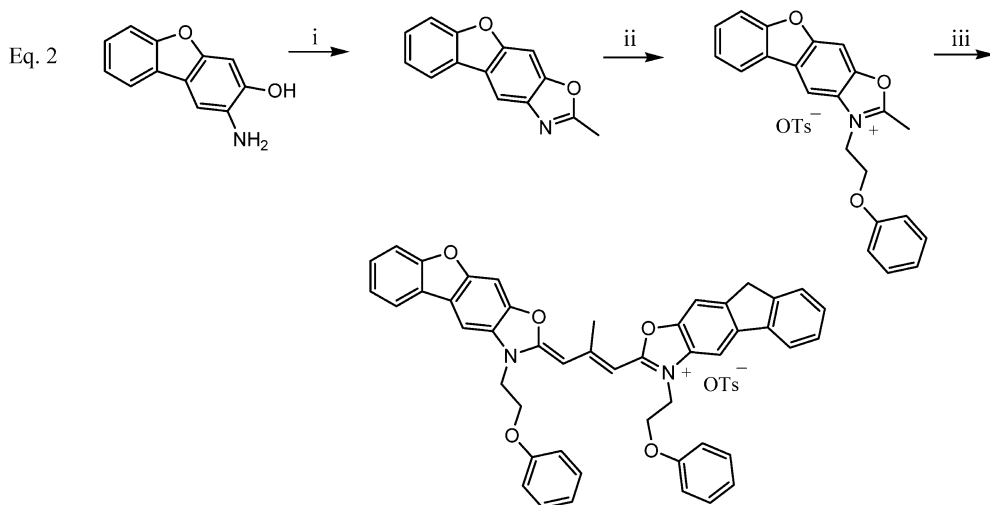


- i- Cesium carbonate, methyl alcohol
 ii- Cesium carbonate, 2-methylindole, sodium hydroxide, methyl alcohol
 iii- Sodium hydroxide, methyl alcohol

3. Other trans-heteroatom p-quinones liquid crystal compositions were prepared by the author as illustrated below, (I), (II), and, (III).



4. Other heterocyclics have been prepared (2) having similar optical properties to those of the current invention as illustrated in Eq. 2:



i- Trimethyl orthoformate, ethyl alcohol

ii- 2-Phenoxy-1-ethyltosylate

iii- Pyridine, triethyl orthoformate, 2-phenoxy-1-ethyltosylate

5. Naphthyl p-quinone liquid crystals derivatives have been prepared and are described (3).

References

1. P.C. Tang *et al*, US Patent 6,660,763 (December 9, 2003), US Patent 6,239,161 (May 29, 2001), and US Patent 5,780,496 (July 14, 1988)
2. K. Kobayshi *et al*, US Patent 6,667,405 (December 23, 2003)
3. K.Yoshida *et al*, Chem. Lett., 2049 (1990)

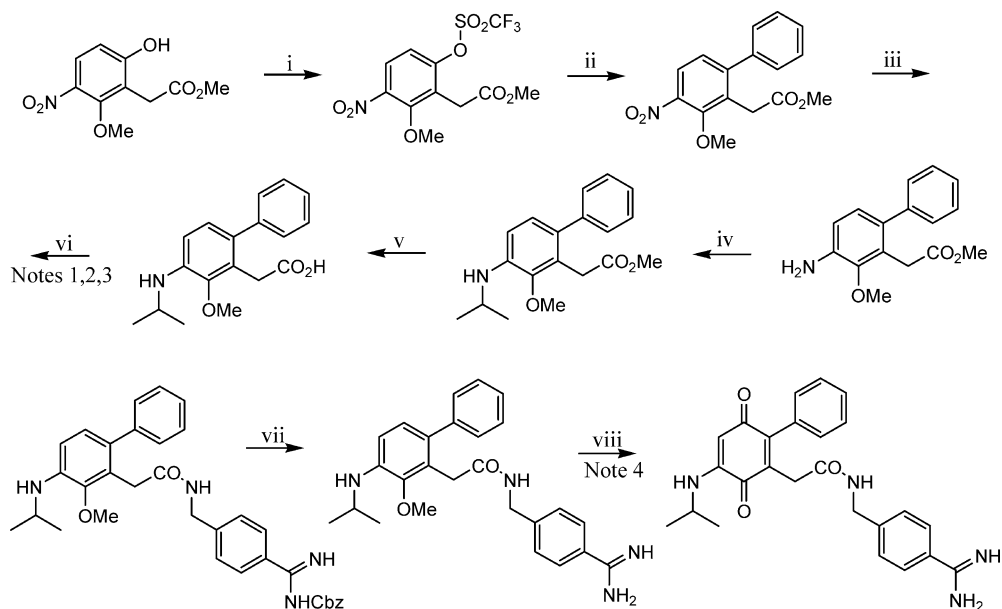
Patent: Polycyclic Aryl and Heteroaryl Substituted 1,4-Quinones Useful for Selective Inhibition of the Coagulation Cascade

M.S. Smith *et al*, US Patent 6,686,484 (February 3, 2004)

Assignee: Pharmacia Corporation

Utility: Treatment of Coronary Artery and Cerebrovascular Diseases

Reaction



i- Triethylamine, triflic anhydride, CH_2Cl_2

ii- Tri-*n*-butylphenylstannane, lithium chloride, tetrakis(triphenylphosphine)palladium, dioxane

iii- 5% Palladium on carbon, dioxane, methyl alcohol

iv- Sodium triacetoxymethylborohydride, acetone, acetic acid, THF, CH_2Cl_2

v- NaOH, methyl alcohol

vi- Polystyrene-graft-carbodiimide, hydroxybenzotriazole, Cbz-4-amidinobenzyl amine, N-methylmorpholine CH_2Cl_2 , N,N-dimethylformamide, polystyrene-graft-amine, polystyrene-graft-aldehyde

vii- Boron tribromide, CH_2Cl_2

viii- Potassium nitrosodisulfonate, water, dioxane

Experimental

1. Methyl 2[(2-methoxy-3-nitro-4-triflate)phenyl]acetate

Triethylamine (24.8 mmol) was added to methyl 2[(2-methoxy-3-nitro-4-hydroxyl)phenyl]acetate (20.7 mmol) followed by triflic anhydride (24.8 mmol) dissolved in CH_2Cl_2 at -10°C . After stirring at ambient temperature 3 hours, the solution was acidified with 2 M HCl, extracted with CH_2Cl_2 , washed with brine, dried, filtered, and concentrated. The material was purified by chromatography with EtOAc/hexane, 15:85, and the product isolated in 72% yield as an oil. $^1\text{H-NMR}$ and MS data provided.

2. Methyl 2[(2-methoxy-3-nitro-4-phenyl)phenyl]acetate

The product from Step 1 (14.8 mmol) was added to a solution of tri-*n*-butylphenylstannane (17.7 mmol), lithium chloride (44.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.29 mmol) in 74 ml dioxane and the mixture heated to 85°C 18 hours. The organic layer was washed with brine, dried, concentrated, purified as in Step 1, and the product isolated in 74% yield as a white solid. $^1\text{H-NMR}$ and MS data provided.

3. Methyl 2[(2-methoxy-3-amino-4-phenyl)phenyl]acetate

A catalytic amount of 5% palladium on carbon in dioxane was added to the product from Step 2 (11.0 mmol) dissolved in methyl alcohol/dioxane, 1:1, and hydrogenated at ambient temperature 4 hours. The mixture was filtered through celite, concentrated, and used in Step 4 without further purification.

4. Methyl 2[(2-methoxy-3-*N*-isopropylamino-4-phenyl)phenyl]acetate

Sodium triacetoxyborohydride (43.0 mmol) was added to a solution of the product from Step 3 (11.0 mmol) dissolved in 1 ml acetone containing 1 drop of HOAc in THF/ CH_2Cl_2 , 1:1, and stirred at ambient temperature 14 hours. Thereafter, an additional 1.0 ml acetone and excess HOAc were added, and the solution stirred 18 hours. The solution was diluted with diethyl ether and water, the organic layer purified as in Step 1, and the product isolated as an oil in 100% yield having a HPLC retention time of 2.57 minutes. $^1\text{H-NMR}$, and MS data provided.

5. 2[(2-Methoxy-3-*N*-isopropylamino-4-phenyl)phenyl]acetic acid

Aqueous 10% NaOH (19.0 mmol) was added to a solution of the product from Step 4 (4.81 mmol) dissolved in methyl alcohol, the mixture stirred at 60°C 3 hours, acidified with 2 M HCl, and extracted with diethyl ether. The solution was washed with brine, dried, filtered, concentrated, purified by chromatography using EtOAc/hexane, 4:6, and the product isolated in 31% yield. $^1\text{H-NMR}$ data supplied.

6. Cbz-4-Amidinobenzyl-2[(2-methoxy-3-*N*-isopropylamino-4-phenyl)phenyl]acetamide

To a slurry of the product from Step 5 (1.4 mmol) was added 1-hydroxybenzotriazole (1.4 mmol), Cbz-4-amidinobenzylamine (1.6 mmol), polystyrene-graft-carbodiimide (0.42 g; 1.4 mmol), *N*-methylmorpholine (5.6 mmol) and CH_2Cl_2 /*N,N*-dimethylformamide,

3:1, and the mixture agitated 18 hours. Thereafter, polystyrene-graft-amine (2.81 mmol/g; 2.8 mmol) and polystyrene-graft-aldehyde (1.0 g; 2.30 mmol) were added and the suspension agitated one hour. The mixture was then filtered, concentrated, purified as in Step 5, and the product isolated in 92% yield as a white solid having an HPLC retention time of 2.55 minutes. $^1\text{H-NMR}$ data provided.

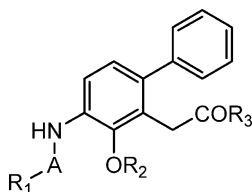
7. **4-Amidinobenzyl-2[(2-methoxy-3-N-isopropylamino-4-phenyl)phenyl]acetamide**

Boron tribromide (2.7 mmol) was added to a solution of the product from Step 6 (0.88 mmol) dissolved in CH_2Cl_2 at -10°C , stirred 90 minutes, quenched with water, and concentrated. The mixture was purified by reverse-phase chromatography and the product isolated in 60% yield as a white solid having an HPLC retention time of 1.42 minutes. $^1\text{H-NMR}$ and data provided.

8. **2-Phenyl-3-(4-amidinobenzyl-acetamide)-5-N-isopropylamine p-quinone**

A solution of potassium nitrosodisulfonate (Fremy's salt) (0.56 mmol) dissolved in 5 ml water was added to a solution of the product from Step 7 (0.18 mmol) dissolved in 5 ml dioxane, the mixture stirred at ambient temperature 2 hours, and concentrated. The material was purified by reverse phase chromatography and the product isolated in 54% yield having a HPLC retention time of 1.75 minutes.

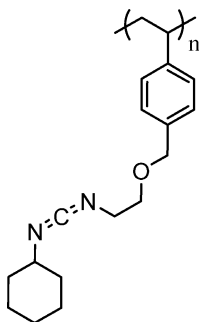
Derivatives



R_1	A	R_2	R_3	MS (M+H)
Phenyl	$-\text{CH}_2\text{CH}_2-$	Methyl	4-(Benzylcarbamate)amidinobenzylamide	627.30
Isopropyl	None	Methyl	Methoxide	376
Phenyl	$-\text{CH}_2\text{CH}_2-$	Hydrogen	4-Amidinobenzylamide	479.24

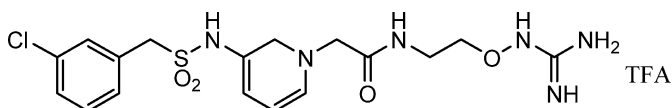
Notes

1. Polystyrene-graft-carbodiimide, (I), is used to facilitate amide formation; its preparation and use are described (1). Polystyrene-g-amine and -aldehyde were used to remove excess acid and amine reagents, respectively.



(I)

2. The sulfonylamide analogue of the current invention, 3-(3-chlorobenzylsulfonyl)amino-6-methyl-1-[(2-guanidinooxyethyl)-aminocarbonylmethyl]-2-pyridinone trifluoroacetate, (II), has been prepared and is described (2).



(II)

3. 1,2-Dihydro-1-pyridinyl and 1-pyrimidinyl Step 8 derivatives have been prepared and are described (3). The preparation of N-nitroamidine intermediates is also described (3).
4. The preparation and use of Fremy's reagent, potassium nitroso-disulfonate, $(KSO_3)_2N-O\cdot$, a stable free radical, is described (4).

References

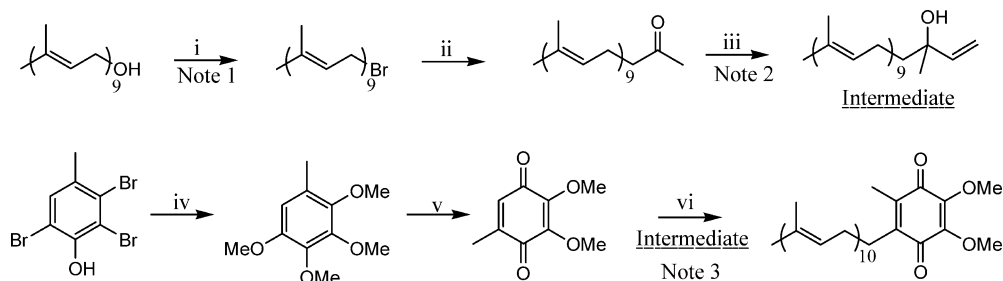
1. Y.S. Sanghui *et al*, US Patent 6,541,626 (April 1, 2003)
2. T. Lu *et al*, US Patent 6,037,356 (March 14, 2000)
3. S.Y. Tamura *et al*, US Patent 6,011,158 (January 4, 2000)
4. J.F.W. Blatchly, *Org. React.*, 19, 200 (1972)

Patent: Synthesis of Coenzyme Q10 (Ubiquinone)
 D.D. West, US Patent 6,686,485 (February 3, 2004)

Assignee: D.D. West

Utility: Improved Method for Preparing Ubiquinone

Reaction



- i- Diethylether, pyridine, phosphorous tribromide, hexane
- ii- Ethyl acetoacetate, sodium, ethyl alcohol
- iii- Magnesium, THF, iodine, methyl iodide, vinyl bromide, THF
- iv- Sodium, methyl alcohol, ethylene glycol, dimethyl ether, dimethyl carbonate, copper cyanide, 2,3,6-tribromo-4-methylphenol
- v- Pyridine-2,6 dicarboxylate, acetonitrile, water, ceric ammonium nitrate
- vi- Hexane, sodium bisulfite

Experimental

1. Solanesol bromide

Solanesol (10 g) was dissolved in 9.5 ml hexane and 13.5 ml diethyl ether containing 1.3 ml pyridine at 0 to 5 °C and 1.8 ml phosphorous tribromide dissolved in 13 ml hexane added over 30 minutes. The mixture was stirred 3 hours, added to ice water, and stirred an additional 10 minutes. The phases were separated, the aqueous layer extracted with diethyl ether, washed with 5% NaHCO₃, concentrated, and 11 g product isolated.

2. Solanesylacetone

Ethyl acetoacetate (25 g) was added to the product from Step 1 followed by sodium (0.4 g) in 18 ml ethyl alcohol over 20 minutes at 10 °C and the mixture kept at ambient temperature for 12 hours. Thereafter, the mixture was heated to 80 °C, 2.5 ml of 10%

NaOH added over 1 hour, and then stirred 4 hours. The reaction was quenched by pouring into ice water, extracted with diethyl ether, washed, concentrated, and 8 g product isolated.

3. Isodecaprenol

To magnesium (1.4 g) slurried in 18 ml THF was added a small crystal of iodine, 1 drop of methyl iodide and 0.1 ml of vinyl bromide. This was followed by an additional 4 ml vinyl bromide dissolved in 9 ml THF, and the mixture stirred for 1 hour at 50 °C. The mixture was cooled to 0 to –5 °C, the product from Step 2 (8 g) dissolved in 32 ml THF added, stirred 3 hours at ambient temperature, then re-cooled to 0–5 °C. NH_4Cl (4.2 g) dissolved in 10 ml water was added, the mixture stirred 10 minutes, extracted with diethyl ether, washed with water, dried, concentrated, and 9 g of product isolated.

4. 2,3,4,5-Tetramethoxytoluene

Sodium (23 g) was dissolved in 400 ml methyl alcohol, ethylene glycol, dimethyl ether and (9.3 g), 50 ml dimethyl carbonate added, and 300 ml methyl alcohol collected during distillation. Thereafter, copper cyanide (915 g) and 2,3,6-tribromo-4-methylphenol (34.4 g) dissolved in 100 ml ethylene glycol and dimethyl ether were added over 3 hours at 80 °C. The mixture was stirred 5 hours, 800 ml water added, cooled to 50 °C, and 100 ml methyl sulfate added. The mixture was stirred 2 hours at ambient temperature, concentrated, 250 ml NH_4OH added, and the product extracted with methyl chloride. The organic phase was washed with dilute HCl, water, dried, concentrated, and 20 g product isolated, bp = 100 °C at 0.1 mm Hg.

5. 2,3 Dimethoxy-5-methylhydroquinone

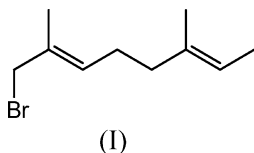
Pyridine-2,6 dicarboxylate 33.4 g was added to the product from Step 4 (17 g) dissolved in 400 ml of acetonitrile/water, 7:3, followed by $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ (110 g) dissolved in 400 ml acetonitrile/water, 1:1. The mixture was stirred 20 minutes at 0 °C and 10 minutes at ambient temperature, poured into 400 ml water and extracted with methyl chloride. The organic layer was dried, concentrated, and 14 g of red crystals isolated after chromatographic purification on silica gel using hexane/EtOAc, 20:1, mp = 59 °C.

6. Ubiquinone

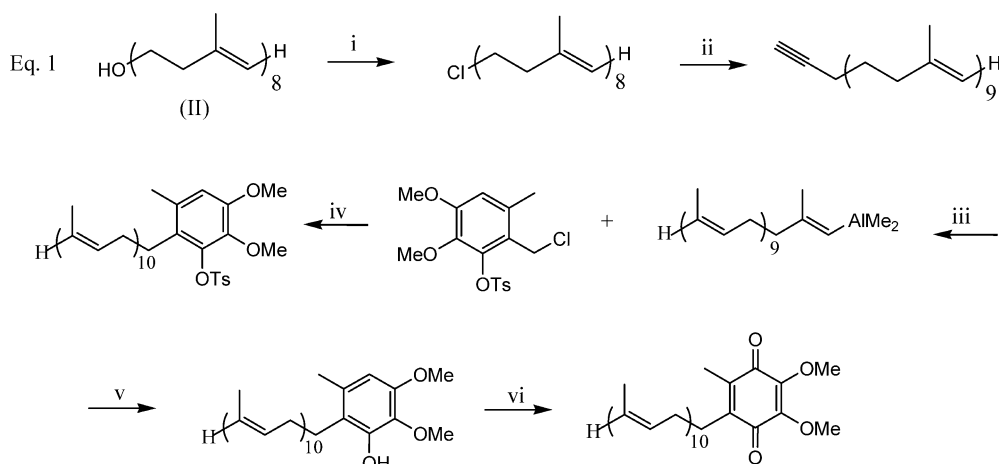
Equimolar amounts of the products from Step 3 and Step 5 were stirred at 43 °C 10 minutes in hexane and 2.5% NaHSO_3 solution added. Thereafter, the hexane layer was separated, dried, concentrated, the product purified by chromatography on silica gel using hexane/diethyl ether, 10:1, and ubiquinone isolated as a yellow solid.

Notes

1. Solanesol was isolated from waste tobacco by extracting with hexane, treating with KOH, and purifying by chromatography on alumina with hexane/diethyl ether, 9:1. It is also obtainable from potato leaves.
2. In a previous investigation, the author prepared ubiquinone starting from generyl bromide, (I), (1).

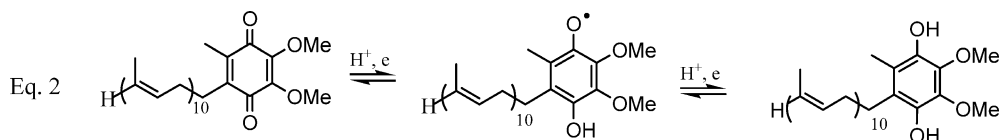


3. Using the synthetic route described by the author, only the E-isomer was obtained. Other methods for preparing all trans-form polyprenols are described (2).
4. Beginning with solanesol, (II), an alternative route for preparing ubiquinone is illustrated in Eq. 1 and described (3).



- i- Phosphorous trichloride, benzene
 ii- Ketene
 iii- Trimethyl aluminum, dicyclopentadienezirconium dichloride, 1,2-dichloroethane
 iv- Nickel, THF, chloromethyltosylate
 v- n-Butyllithium, diethyl ether
 vi- Cobalt salm, pyridine, toluene, sodium carbonate

4. The mechanism by which ubiquinone acts as an anti-oxidant is illustrated in Eq. 2 and described by the author.

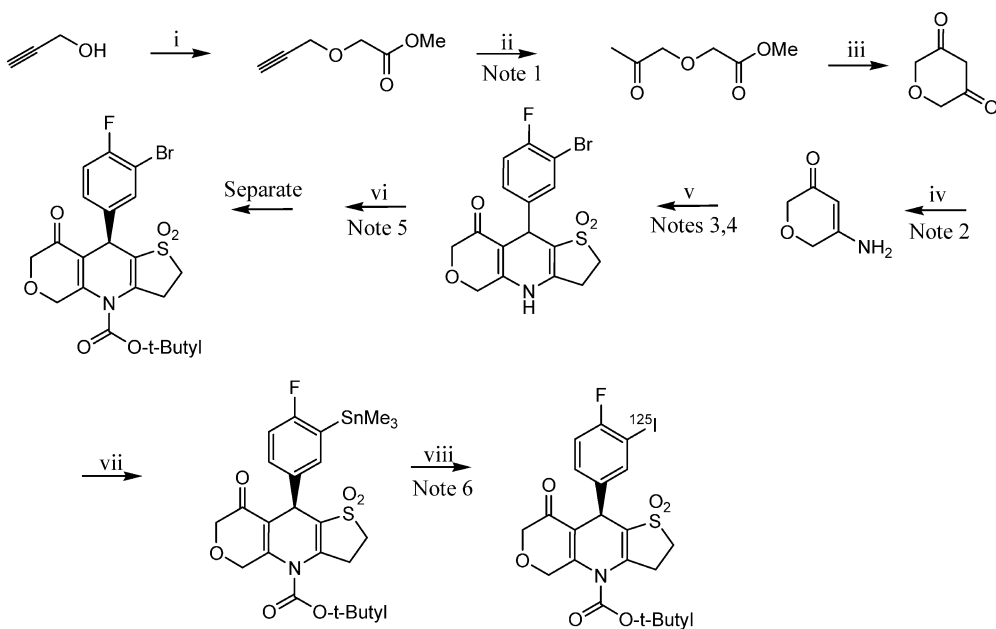


References

1. D.D. West, US Patent 6,506,915 (January 14, 2003)
2. G. Ananoma *et al*, US Patent 5,714,645 (February 3, 1998)
3. B.H. Lipshutz, US Patent 6,545,184 (April 8, 2003)

R.J. Altenbach *et al*, US Patent 6,632,418 (October 14, 2003)

Radiolabeled Reagent for Characterizing K_{ATP} Channels in Tissues



- i- THF, sodium hydride, methyl bromoacetate
- ii- Mercury(II)acetate, sulfuric acid, methyl alcohol, diethyl ether
- iii- Diethyl ether, potassium t-butoxide, t-butyl alcohol
- iv- Ethyl alcohol, sulfuric acid, methyl alcohol, ammonia,
- v- 3-Bromo-4-fluorobenzaldehyde, tetrahydrothiophene-3-oxo-1,1-dioxide, triethylamine, ethyl alcohol
- vi- Di-t-butyl dicarbonate, 4-dimethylaminopyridine, acetonitrile
- vii- 1,4-Dioxane, hexamethylditin, tetrakis(triphenyl-phosphine)palladium
- viii- Methyl alcohol, acetic acid, sodium ^{125}I iodide, N-chlorosuccinimide

Experimental

1. Methyl (2-propynyloxy)acetate

Sodium hydride (1.25 mol) was mixed in 800 ml THF at 0°C then added to propargyl alcohol (1.5 mol) dissolved in 175 ml THF. The mixture was stirred one hour, treated with methyl bromoacetate dissolved in 250 ml THF, stirred at 0°C 30 minutes, 2 hours at ambient temperature, and treated with 800 ml 2 M HCl. The organic layer was isolated and the aqueous layer extracted twice with 500 ml EtOAc. The combined organics were washed with 200 ml brine, dried, filtered, concentrated, distilled, and 83 g product isolated, bp = 75–85°C at 20 torr. $^1\text{H-NMR}$ data supplied.

2. Methyl (2-oxopropoxy)acetate

The product from Step 1 (0.44 mol) dissolved in 1.5 L methyl alcohol was treated with $\text{Hg}(\text{OAc})_2$ (44 mmol) and 3 ml concentrated H_2SO_4 then refluxed one hour. The mixture was cooled to ambient temperature, concentrated to a volume of 200 ml, treated with 500 ml 1 M HCl, and extracted twice with 300 ml CH_2Cl_2 . The combined CH_2Cl_2 extracts were dried, filtered, concentrated, distilled, and the product isolated, bp = 65–95°C at 1 torr. $^1\text{H-NMR}$ data supplied.

3. 2H-Pyran-3,5(4H,6H)-dione

The product from Step 2 (0.34 mol) was dissolved in 1.0 L diethyl ether and 1 M potassium t-butoxide dissolved in 340 ml t-butyl alcohol and 500 ml diethyl ether added over 2 hours. Thereafter, the mixture was treated with 200 ml 1 M HCl, the layers separated, and the aqueous layer extracted twice with 500 ml EtOAc. The combined organics were washed twice with 100 ml brine, dried, filtered, and concentrated while keeping the temperature below 30°C. The crude product crystallized on standing and was treated with 200 ml hexane/EtOAc. A total of 12.2 g purified product was isolated. $^1\text{H-NMR}$ data supplied.

4. 5-Amino-2H-pyran-3(6H)-one

The product from Step 4 (33 g) was dissolved in 800 ml ethyl alcohol containing 0.2 ml concentrated H_2SO_4 and refluxed 2 hours. It was cooled to 0°C , treated with 200 ml methyl alcohol saturated with ammonia, stirred 4 hours and concentrated. The residue was purified by flash chromatography using silica gel with a methyl alcohol gradient of methyl alcohol/ CH_2Cl_2 , 2%, 5%, 10%:1, and 5 g of product isolated. $^1\text{H-NMR}$ and MS data supplied.

5. 9-(3-Bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A mixture of the product from Step 4 (13 mmol), 3-bromo-4-fluorobenzaldehyde (16 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide (1.8 g, 13 mmol) and triethylamine (6.6 mmol) dissolved in 20 ml ethyl alcohol were stirred in a sealed tube at 80°C 60 hours, cooled and concentrated to dryness. The residue was treated with 50 ml ethyl alcohol, 1 M HCl in 5 ml diethyl ether, heated to reflux 5 minutes, and kept at ambient temperature 3 hours. The solid was collected by filtration, washed with ethyl alcohol, dried under vacuum 16 hours, and 3.2 g product isolated, mp $>260^\circ\text{C}$. $^1\text{H-NMR}$, MS, and analytical data supplied.

6. t-Butyl 9-(3-bromo-4-fluorophenyl)-8-oxo-2,3,5,7,8,9-hexahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide

The product from Step 5 (0.096 mmol), di-t-butyl dicarbonate (0.55 mmol) and 4-dimethylaminopyridine (0.016 mmol) were dissolved in 3 ml acetonitrile and stirred 2 hours at ambient temperature. The mixture was concentrated, the residue purified by chromatography on silica gel using hexanes/EtOAc, 2:1 then 1:1, and 0.035 g product isolated. MS data supplied.

7. t-Butyl 9-[4-fluoro-3-(trimethylstannyl)phenyl]-8-oxo-2,3,5,7,8,9-hexahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide

The product from Step 6 (0.068 mmol) was dissolved in 1 ml 1,4-dioxane, treated with hexamethylditin (0.5 mmol) and tetrakis(triphenylphosphine)-palladium (0.043 mmol), stirred at 100°C 1 hour, cooled, and concentrated. The residue was purified by chromatography on silica gel using hexanes/EtOAc, 3:2, and 0.031 g of product isolated. MS Data supplied.

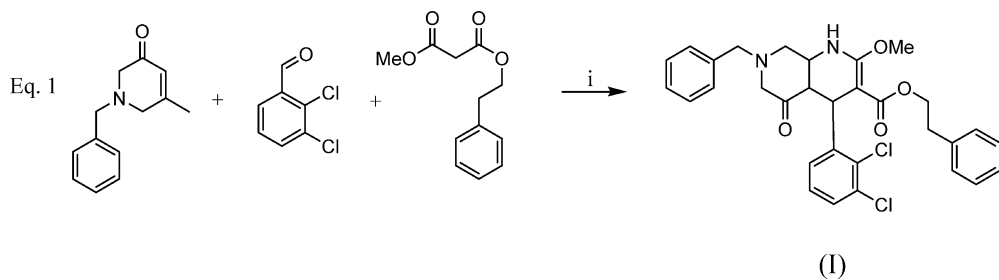
8. 9-(4-fluoro-3-[^{125}I]-iodophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A mixture of 29.4 μl methyl alcohol and 0.6 μl acetic acid were added to Na^{125}I (12.44 mCi, 6.22 nmol), followed by the product from Step 7 (41.8 nmol) dissolved in 29.4 μl methyl alcohol and 5 μl N-chlorosuccinimide dissolved in methyl alcohol. After incubating 10 minutes, sodium metabisulfate (52.6 nmol) dissolved in 24 μl water was added and the reaction mixture dried using a stream of nitrogen gas. The residue was treated with 50.4 μl trifluoroacetic acid, heated to 65°C 2 minutes, cooled, and solvents removed

using a stream of nitrogen. The product was purified by reversed-phase HPLC using a 4 mm $\times$ 250 mm C18 column with 5% to 90% acetonitrile in water over a 30 minute period. Both acetonitrile and water phases contained 0.1% TFA and had a withflow rate of 1 ml/minute at 35°C. Over a period of 18 minutes, and 0.4 ml sample was collected in 0.5 ml ethyl alcohol. The solution was diluted with 5.0 ml ethyl alcohol and 5 μ l to 15 μ l water added. Radiochemical purity by reversed-phase HPLC determined the product to have a purity >99.5%.

Notes

1. Methyl (2-oxopropoxy)acetate was obtained by oxomercuration of 1-trimethylsilyl propargyl ethers and is described by the author.
2. 2H-pyran-3,5(4H,6H)-dione was initially converted into the isolatable vinyl ether, 5-ethoxy-2H-pyran-3(6H)-one. The subsequent reaction of the Step 3 product with ammonia with the Step 4 intermediate produced the enaminone.
3. Step 8 pyrano-, piperidino-, and thiopyrano-derivatives of 2H-pyran-3,5(4H,6H)-dione have been prepared and are described (1).
4. The preparation of 4-(2,3-dichlorophenyl)-1,4,5,6,7,8-hexahydro-2-methyl-5-oxo-1,7-naphthyridine-3-carboxylic acid 2-methoxy-2-phenylethyl ester, (I), and other Step 5 condensation analogues of the current invention are described (2) and illustrated in Eq. 1:



i- Sodium acetate

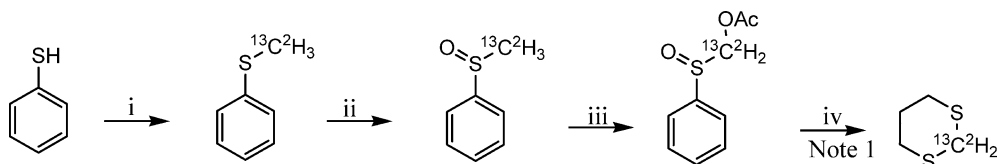
5. Diastereomers were isolated by reacting the Step 5 product mixture with (–)-8-phenylmenthol chloroformate. The diastereomers were separated by flash chromatography over silica gel using chloroform/hexanes/diethyl ether (3:2:1), and (1S,2R,5S)-5-methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl-9-(3-bromo-4-fluoro phenyl)-8-oxo-2,3,5,7,8,9-hexahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide isolated (3).
6. For analytical purposes, a 'cold' Step 8 version was prepared.

References

1. W.A. Carroll *et al*, US Patent 6,191,140 (February 20, 2001)
2. T.S. Sulkowski *et al*, US Patent 4,618,678 (October 21, 1986)
3. Y. Yamamoto, J. Amer. Chem. Soc., 114, 121 (1992)

- Patent:** Synthesis of ^2H - and ^{13}C -Substituted Dithanes
R.A. Martinez *et al*, US Patent 6,541,671 (April 1, 2003)
- Assignee:** The Regents of the University of California
- Utility:** Radiolabeled Reagent for Preparing Synthons for Mechanistic Studies of Proteins and Oligonucleotides

Reaction



- i- $^{13}\text{C}^2\text{H}_3$ -Methyl alcohol, sodium hydroxide, benzene
 ii- Hydrogen peroxide, ethyl alcohol
 iii- Acetic anhydride, sodium acetate
 iv- Toluene, 1,3-propanedithiol, Amberlyst RTM ion exchange resin

Experimental

1. $^{13}\text{C}^2\text{H}_3$ -Methyl phenyl sulfide

A flask was charged with $^{13}\text{C}^2\text{H}_3\text{OH}$ (0.987 mol), 540 ml 47 % HI, thiophenol (1.09 mole) and NaOH (2.47 mol) in 400 ml benzene and 300 ml water and heated to 85°C 2 hours. Thereafter, the mixture stirred overnight, 400 ml ethyl ether were added, the organic phase washed 3 times with 100 ml water, dried, concentrated, and the product isolated in 98.6% yield as a clear, slightly yellow oil. ^1H -NMR data supplied.

2. $^{13}\text{C}^2\text{H}_3$ -Methyl phenyl sulfoxide

Thirty percent aqueous hydrogen peroxide (0.17 mol) was added to 184 ml ethyl alcohol containing the product from Step 1 (0.14 mol) and the reaction stirred at ambient temperature 3 days. Thereafter, 300 ml EtOAc was added and the mixture transferred to a separatory funnel containing an equal volume of water. The organic layer was recovered and the aqueous layer extracted twice with 300 ml EtOAc. The combined organic phases were dried, filtered, concentrated, and the product isolated in 94% yield. ^1H -NMR data supplied.

3. $^{13}\text{C}^2\text{H}_2$ -Methanol (phenylthio)acetate

The product from Step 2 (0.07 mol) was dissolved in 50 ml acetic anhydride, solid sodium acetate (0.14 mol) added, and the mixture refluxed 24 hours. The reaction was

cooled, added to a mixture of 400 ml EtOAc and 200 ml NaHCO₃, stirred 2 hours, the organic layer isolated, and the aqueous layer was washed twice with 200 ml EtOAc. The combined organic phases were dried, filtered, concentrated, and the product isolated in 90% yield. ¹H-NMR data supplied.

4. 2-¹³C²H₂-1,3-Dithiane

The product from Step 3 (0.010 mol) was dissolved in 20 ml toluene, 1,3-propanedithiol (0.013 mol) added via a syringe, Amberlyst RTM ion exchange resin (2 g) added, and the mixture refluxed 3 days. The mixture was filtered, the ion exchange resin washed twice with 50 ml toluene, and the organic phase washed and dried. The mixture was purified by chromatography with silica gel using EtOAc/hexane, 1:9, and the product isolated in 99% yield with a purity >98%. ¹H-NMR data supplied.

Notes

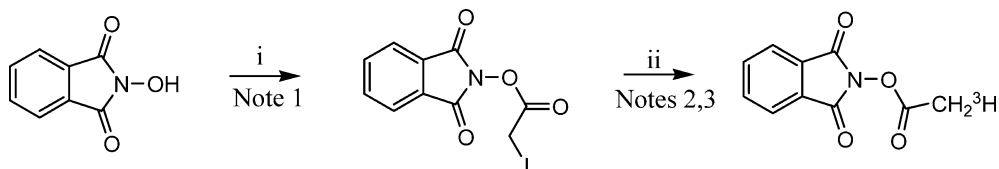
1. In a subsequent investigation by the author, ¹³C- and ²H₁¹³C-dithiane were prepared (1).
2. Other radiolabeled agents prepared by the author include ¹³C-methyl phenyl sulfide, ²H₁¹³C- and ²H₂¹³C-methyl iodide (1), ²H₁¹³C, ²H₂¹³C-, and ²H₃¹³C-methyl aryl sulfones and sulfoxides (2), ²H₁¹³C-methyl(phenylthio)-acetate (3), and oxalic acid derivatives (4).

References

1. R.A. Martinez *et al*, US Patent 6,713,044 (March 30, 2004)
2. R.A. Martinez *et al*, US Patent 6,764,673 (July 20, 2004)
3. R.A. Martinez *et al*, US Patent 6,730,805 (May 4, 2004)
4. R.A. Martinez *et al*, US Patent 6,753,446 (June 22, 2004)

Patent: Tritioacetylating Reagents and Processes for Preparation Thereof
M. Saljoughian *et al*, US Patent 6,160,128 (December 12, 2000)
Assignee: The Regents of the University of California
Utility: Radiolabeled Acetylating Reagent

Reaction



i- Iodoacetic acid, 1,3-dicyclohexylcarbodiimide, EtOAc
 ii- Tritium, hydrogen, 10% palladium on carbon, EtOAc,
 triethylamine

Experimental

1. N-Iodoacetoxyphthalimide

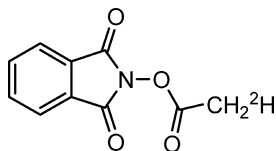
N-Hydroxyphthalimide (8.7 mmol), iodoacetic acid (8.7 mmol) and 1,3-dicyclohexylcarbodiimide (8.7 mmol) were dissolved in 250 ml EtOAc and stirred 5 hours at room temperature. The mixture was filtered, dried, the residue crystallized in ethanol, and the product isolated in 75% yield, mp = 120°C.

2. CH_2^3H -N-Tritioacetoxyphthalimide

The product from Step 1 (0.05 mmol) was dissolved in 1 ml EtOAc, 10% palladium on carbon (10 mg) and 4 μl triethylamine added and the mixture hydrogenated under one atmosphere 10% tritium gas 2 hours. Thereafter, 1 ml methyl alcohol was added, the catalyst removed, the residue dissolved in 1 ml d_8 -THF, and the product isolated. The total radioactivity was assessed by liquid scintillation counting as 10 μCi with a radioactivity yield of 7.2%.

Notes

1. The alternative method for preparing N-iodoacetoxyphthalimide is described (1).
2. The preparation of N-deuterioacetoxyphthalimide, (I), is described below by the author in the current invention and elsewhere (2).

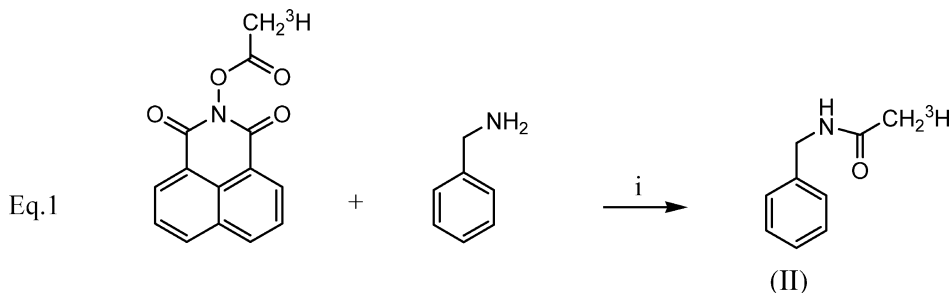


(I)

Procedure

A solution of the product from Step 1 (0.03 mmol) dissolved in 0.3 ml THF was added to a mixture of tributyltin deuteride (0.045 mmol) and triethyl borane (0.004 mmol) dissolved in 0.7 ml THF and the reaction stirred at ambient temperature 3 hours. Thereafter, the solvent was removed, the residue dissolved in 1 ml acetonitrile, extracted 5 times with 1 ml hexane, and the product isolated in 38% yield, mp = 190 °C; m/z = 206.

3. N-Tritioacetoxysuccinimide has also been prepared by the esterification of N-hydroxyphthalimide with $^3\text{H}_3$ -acetic acid and is described (3).
4. Other reagents prepared by the author in the current invention include, ^3H -acetylcholine iodide, ^3H -acetylated peptides, N-ditritio and N-tritritioacetoxypthalimides, and ^3H -amides as illustrated in Eq. 1 for N-tritritioacetylbenzyl amide, (II).



i- Dioxane

5. The preparation of tritium radiolabelled reagents using the reducing agent, LiEt_3BT , (Supertritide), is described (4).

References

1. P.K. Simmons *et al*, J. Org. Chem., 30, 448 (1965)
2. S. Manouchehr *et al*, J. Org. Chem., 61, 26, 9625 (1996)
3. A. Leber, J. Chem. Soc., Chem. Commun., 627 (1990)
4. H. Andres *et al*, US Patent 5,186,868 (February 16, 1993)

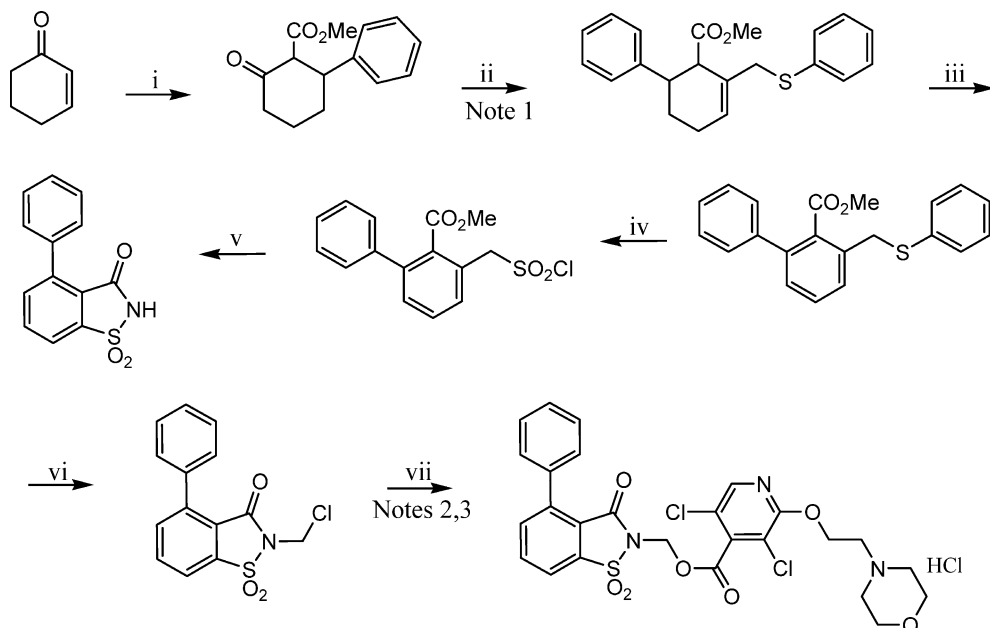
Saccharides

Patent: 2-Saccharinylmethyl Heterocyclic Carboxylates Useful as Proteolytic Enzyme Inhibitors and Compositions and Method of Use Thereof
R.P. Dunlap *et al*, US Patent 5,856,349 (January 4, 1999)

Assignee: Sanofi

Utility: Inhibition of Proteolytic Enzymes in the Treatment of Degenerative Diseases

Reaction



- i- THF, cuprous iodide, dimethyl sulfide, phenyl magnesium bromide, hexamethyl phosphoramidate, methyl cyanoformate
- ii- Benzyl mercaptan, Amberlyst RTM-15 resin, chloroform
- iii- 2,3-dichloro-5,6-dicyano-benzoquinone, toluene
- iv- CH_2Cl_2 , acetic acid, chlorine
- v- Ammonium hydroxide
- vi- CH_2Cl_2 , tetrabutylammonium bromide, toluene chloromethyl phenyl sulfide, sulfur chloride
- vii- Cesium carbonate, methyl alcohol, 3,5-dichloro-2-(2-(4-morpholinyl)ethoxy)pyridine-4-carboxylic acid hydrochloride

Experimental

1. Methyl 2-phenylcyclohexan-6-one carboxylate

To a suspension of cuprous iodide (0.03 mol) in 100 ml THF was added 25 ml dimethyl sulfide. The solution was cooled to -78°C , phenyl magnesium bromide (0.06 mol) dissolved in diethyl ether added, stirred one hour, and 2-cyclohexenone (0.03 mol) dissolved in 10 ml THF added. The mixture was warmed to 0°C over 2 hours then re-cooled to -78°C . It was treated with 15 ml hexamethyl-phosphoramidate, stirred 30 minutes, treated with methyl cyanoformate (0.09 mol), and warmed to ambient temperature overnight. The mixture was poured into 100 ml 2 M HCl, the organic phase separated, and the aqueous phase extracted with CH_2Cl_2 . The combined organic extracts were concentrated, the residue triturated with NH_4Cl , water, brine, dried, and 3.2 g product isolated as an oil.

2. Methyl 2-benzylthio-6-phenylcyclohex-1-ene carboxylate and

Methyl 2-benzylthio-6-phenylcyclohex-2-ene carboxylate

The product from Step 1 (0.013 mol), benzyl mercaptan (0.039 mol) and Amberlyst RTM-15 resin (1.0 g) in chloroform were refluxed 20 hours. The mixture was then treated with an additional 1.5 g resin and refluxed an additional 4 hours. The mixture was cooled, filtered, concentrated, triturated with hexane, and a solid collected by filtration to give a total product mixture of 19%.

3. Methyl 2-benzylthio-6-phenylbenzoate

The product mixture from Step 2 (0.0018 mol) was heated with 2,3-dichloro-5,6-dicyano-benzoquinone (2.0 g) dissolved in 25 ml toluene for 24 hours. The mixture was filtered through a pad of silica gel using CH_2Cl_2 /hexane, 2:1, dried, and a single product isolated in 67% yield.

4. Methyl 2-chlorosulfonyl-6-phenylbenzoate

The product from Step 4 (0.0016 mol) dissolved in 10 ml CH_2Cl_2 was diluted with 20 ml HOAc and 5 ml water, cooled to -10°C , and chlorine gas bubbled into the mixture.

Thereafter, the mixture stirred 10 minutes, concentrated, and the product isolated in 85% yield.

5. 4-Phenyl-saccharin

The product from Step 4 was dissolved in 10 ml THF and added to 25 ml concentrated NH_4OH while cooling in an ice/acetone bath. Once the reaction subsided, it was extracted with CH_2Cl_2 , the aqueous layer acidified to pH 1 using HCl, extracted with CH_2Cl_2 , washed with brine, dried, concentrated, and the product isolated in 97% yield.

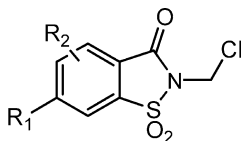
6. 2-Chloromethyl-4-phenylsaccharin

The product from Step 6 (0.0012 mol) was dissolved in 25 ml CH_2Cl_2 , containing NBu_4Br (0.025 mol) and chloromethyl phenyl sulfide (0.019 mol) dissolved in 15 ml toluene. The mixture was refluxed 16 hours, cooled, diluted with EtOAc, washed, and concentrated. The residue was treated with sulfonyl chloride (0.003 mol) dissolved in CH_2Cl_2 and the product isolated in 100% yield.

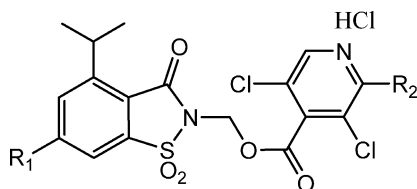
7. 4-Phenyl-2-saccharinylmethylene-3,5-dichloro-2-(2-(4-morpholinyl)ethoxy)pyridine-4-carboxylate hydrogen chloride (Note 3)

A solution of 3,5-dichloro-2-(2-(4-morpholinyl)-ethoxy)pyridine-4-carboxylic acid (0.01 mol) and cesium carbonate (0.015 mol) dissolved in 50 ml methyl alcohol was stirred 30 minutes. The solvent was then removed and the residue dissolved in 50 ml DMF. Thereafter, the product from Step 6 (0.01 mol) was added and the mixture heated to 80°C 3 hours. The solvent was removed in vacuo, the residue dissolved in CH_2Cl_2 , then filtered through charcoal. DMF was again removed, the residue dissolved in t-butyl-methylether, concentrated, and the residue treated with ethereal HCl. A gum was obtained which was triturated with acetonitrile and the product isolated in 9% yield, mp = $120\text{--}140^\circ\text{C}$.

Derivatives



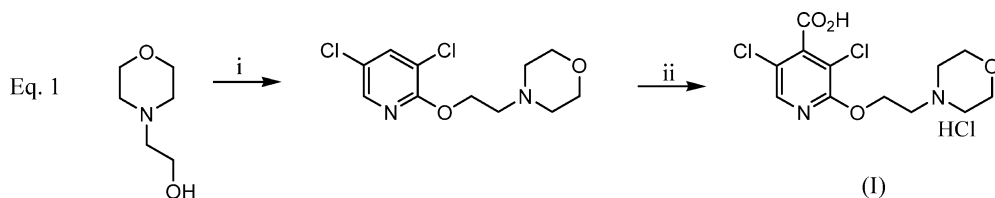
R_1	R_2	Yield (%)	Melting Point ($^\circ\text{C}$)
Hydroxyl	4-Iso-Propyl	84	127–129.5
Methoxide	4-Isopropyl	87	151
Methyl	4-Methyl	51	107–108
Hydrogen	4-Ethyl	66	—
Hydrogen	5-(1,1,3,3-Tetramethylbutyl)	41	—



R₁	R₂	Yield (%)	Melting Point (°C)
Methyl	2-(4-Morpholinyl)ethoxy	9	120–140
Methoxide	2-(Dimethylamine)ethoxy	2.1	155–160
Hydrogen	Hydrogen	15	93–95

Notes

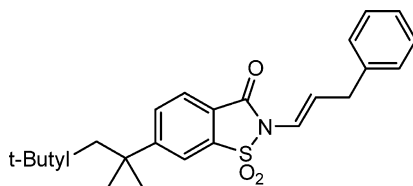
- Two additional Step 2 derivatives, methyl 2-benzylthio-6-phenylcyclohex-2-ene carboxylate and methyl 2-benzylthio-6-phenylcyclohex-1-ene carboxylate were also prepared by the author and aromatized using 2,3-dichloro-5,6-dicyano-benzoquinone and chlorine gas and are described.
- Preparation of the Step 7 co-reagent, 3,5-dichloro-2-(2-(4-morpholinyl)-ethoxy)pyridine-4-carboxylic acid hydrochloride, (I), was provided by the author and illustrated in Eq. 1:



i- THF, sodium hydride, 2,3,5-trichloropyridine

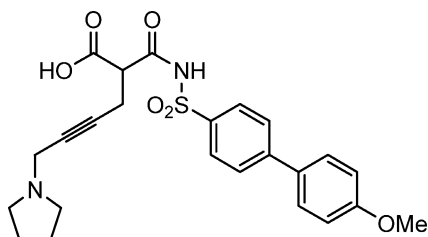
ii- THF, diisopropylamide, dry ice, hydrogen chloride

- The predominant 4-alkyl substituent in Step 7 saccharin was isopropyl.
- The preparation of other Step 4 2-saccharinylmethyl heterocyclic carboxylates is described (1).
- 1-(2-Saccharinyl)-propene derivatives, (II), have been prepared and are described (2).



(II)

6. The Step 7 thioamic acid analogue, 2-[[4'-methoxy(1,1'-biphenyl)-4-yl]-sulfonyl]-amino-6-pyrrolidinohex-4-ynoic acid, (III), has also been prepared (3) and is discussed.



(III)

References

1. R.P. Dunlap *et al*, US Patent 5,652,254 (July 29, 1997)
2. R.P. Dunlap *et al*, US Patent 5,874,432 (February 22, 1999)
3. M.G. Natchus *et al*, US Patent 6,197,770 (March 6, 2001)

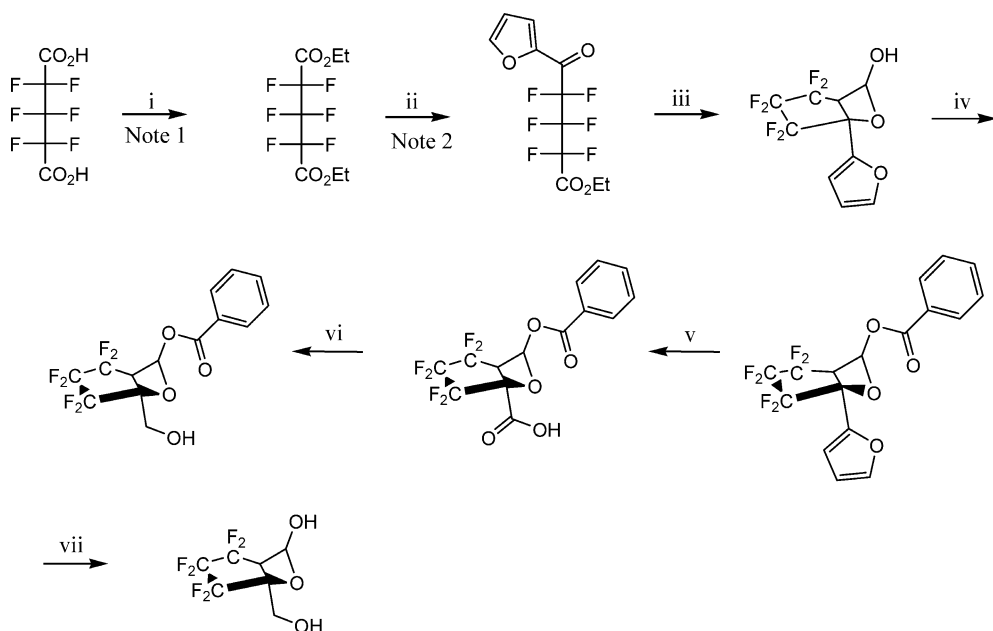
Sugars

Patent: Heavily Fluorinated Sugar Analogues
S.G. Dimagno, US Patent 6,392,032 (May 21, 2002)

Assignee: Board of Regents University of Nebraska-Lincoln

Utility: Anti-Neoplastic Agents

Reaction



- i- Ethyl alcohol, sulfuric acid
- ii- Butyllithium, THF, furan, hexane
- iii- Sodium borohydride, methyl alcohol
- iv- Benzoyl chloride, triethylamine, CH_2Cl_2
- v- Ruthenium(IV)oxide, acetonitrile, water, carbontetrachloride, sodium periodate
- vi- THF, boronhydride · THF, diisobutylaluminum hydride
- vii- Potassium carbonate, trifluoroethyl alcohol

Experimental

1. Diethyl 2,2,3,3,4,4-hexafluoropentanoate

2,2,3,3,4,4-Hexafluoropentanoate (0.47 mmol) was dissolved in 250 ml ethyl alcohol containing 5 ml concentrated H_2SO_4 and refluxed 7 days using a soxlet extractor and 65 pellets 1.4 Å molecular sieves. Ethyl alcohol was then removed and the residue neutralized to pH 7 using NaHCO_3 before adding water. The product was extracted 3 times with 100 ml diethyl ether, washed, and the product isolated in 81% yield. ^1H -NMR data supplied.

2. Ethyl-(2-furyl)-5-oxo-2,2,3,3,4,4-hexafluoropentanoate

In the absence of light, furan (12.4 mmol) was dissolved in 30 ml THF cooled to -78°C , 3 ml 2.5 M n-butyllithium added, and the mixture stirred 3 hours. The product from Step 1 (13.8 mmol) dissolved in 100 ml THF was added over 15 minutes and then stirred 30 minutes. The solvent was removed at ambient temperature, the mixture purified by chromatography on silica gel using hexanes/EtOAc, 9:1, and the product isolated in 39% yield. ^1H - and ^{19}F -NMR and elemental analysis data supplied.

3. 1-Hydroxyl-5-(2-furyl)-2,2,3,3,4,4-hexafluorooxetane

NaBH_4 (9.25 mmol) was added to a solution of the product from Step 2 (4.81 mmol) dissolved in 100 ml methyl alcohol at 0°C . After 3 hours, the solvent was removed and the residue acidified to pH 2 using 2 M HCl. The mixture was then neutralized with NaHCO_3 and the product extracted 3 times with 50 ml diethyl ether. The product was isolated as an oil, re-crystallized in hexane/chloroform, 3:1, and isolated in 96% yield as 1:1 trans/cis isomers, mp = $89\text{--}90^\circ\text{C}$. ^1H - and ^{19}F -NMR and elemental analysis data supplied.

4. 1-O-Benzoyloxy-5-(2-furyl)-2,2,3,3,4,4-hexafluorooxetane

Benzoyl chloride (10.0 mmol) and TEA (20 mmol) were added to a solution of the product from Step 3 (8.41 mmol) dissolved in 50 ml CH_2Cl_2 at ambient temperature. The solution was stirred 15 minutes, then quenched with excess TEA, and stirred an additional 15 minutes. The solvent was removed and the residue purified by chromatography on silica gel using hexane/EtOAc, 9:1, and the product isolated as 15:1 trans/cis isomers, respectively, in 97% yield. ^1H - and ^{19}F -NMR and elemental analysis data supplied.

5. 5-O-Benzoyloxy-2,2,3,3,4,4-hexafluorooxetanic acid

RuO_2 (5 mol) was added to the product from Step 4 (2.93 mmol) in a biphasic solution of 180 ml water, 60 ml acetonitrile and 120 ml CCl_4 containing NaIO_4 (116 mmol) and the mixture stirred vigorously 5 days. The volatile solvents were removed, the mixture extracted 3 times with 150 ml EtOAc, dried, and the product isolated in 96% yield. ^1H - and ^{19}F -NMR and elemental analysis data supplied.

6. 1-O-Benzoyloxy-5-(5'-hydroxymethyl)-2,2,3,3,4,4-hexafluorooxetane

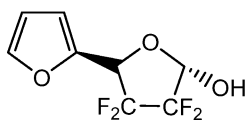
The product from Step 5 (6.42 mmol) was dissolved in 20 ml THF and treated with 39 ml 1 M $\text{BH}_3 \cdot \text{THF}$. The mixture was stirred 20 minutes at 0°C , 19 ml 1 M diisobutylaluminum hydride in THF added, and the mixture stirred an additional 30 minutes at ambient temperature. Thereafter, the reaction was quenched with 20 ml water at 0°C , neutralized to pH 2 with 20 ml 1 M HCl, and further neutralized to pH 7 with NaHCO_3 before extracting 3 times with 150 ml EtOAc. The mixture was purified by flash chromatography with silica gel using hexane/EtOAc, 10:1, and the product isolated in 82% yield. ^1H - and ^{19}F -NMR and elemental analysis data supplied.

7. 1-Hydroxyl-5-(5'-hydroxymethyl)-2,2,3,3,4,4-hexafluorooxetane

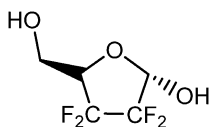
The product from Step 6 (1.44 mmol) and K_2CO_3 (0.47 mmol) dissolved in 20 ml trifluoroethyl alcohol were stirred at ambient temperature 12 hours. The solvent was removed and NaHCO_3 solution added to the residue. The mixture was extracted 3 times with 50 ml pentane, neutralized to pH 2 using 2 M HCl, re-extracted 3 times with 60 ml HOAc, and the product isolated in 99% yield. ^1H - and ^{19}F -NMR and elemental analysis data supplied.

Notes

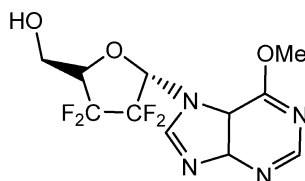
- Steps 2–5 were conducted in the absence of light.
- In a previous investigation by the author (I) fluoro analogues of the current invention were prepared using 2,2,3,3-tetrafluorodiethyl butanedioate in Step 1 and the corresponding 2,2,3,3-tetrafluorofuran, (I), -ribofuranose, (II), and nucleoside derivatives, (III), respectively, were prepared.



(I)



(II)



(III)

3. 2,3,7,8,12,13,17,18-Octafluoro-5,10,15,20-tetrakis(pentafluorophenyl) porphyrin has also been prepared by the author (1) by reacting pentafluorobenzaldehyde with 3,4-difluoropyrrole (2). Other preparations are described (3).
4. Electron-deficient porphyrins have been prepared using 2-(2,2,3,3,4,4,4-heptafluoro-1-hydroxybutyl)pyrrole. The pyrrole intermediate was prepared using heptafluorobutyraldehyde hydrate and is described (4).

References

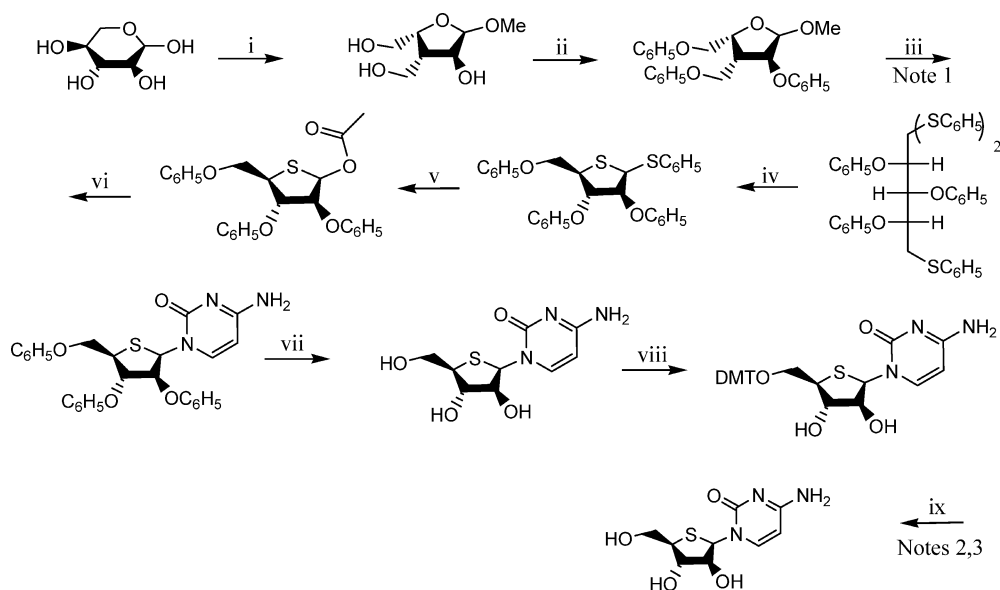
1. S.G. Dimagno, US Patent 6,013,790 (January 11, 2000)
2. S.G. Dimagno, US Patent 6,455,510 (September 26, 2000)
3. T. Wijesekera *et al*, US Patent 5,571,908 (November 6, 1996)
4. M.J. Therien *et al*, US Patent 5,599,924 (February 4, 1997)

Patent: Preparation of Thioarabinofuranosyl Compounds and Use Thereof
J.A. Secrist, III *et al*, US Patent 6,576,621 (June 10, 2003)

Assignee: Southern Research Institute

Utility: Anti-Neoplastic Agent Inhibitor of DNA Replication

Reaction



- i- Hydrochloric acid, Amberlite IRA-400 anion exchange resin
- ii- THF, sodium hydride, tetrabutylammonium iodide, benzyl bromide
- iii- CH_2Cl_2 , benzyl mercaptan, tin(IV)chloride
- iv- Toluene, acetonitrile, triphenylphosphine, iodine, imidazole
- v- Mercury(II)acetate, acetic acid
- vi- Cytosine, acetonitrile, hexamethyldisilazane, chlorotrimethylsilane, trimethylsilyltrifluoromethane sulfonate
- vii- Boron trifluoride, CH_2Cl_2
- viii- Pyridine, 4,4'-dimethoxytritylchloride
- ix- Trifluoroacetic, chloroform

Experimental

1. α - and β -Methyl L-xylofuranoside

L-Xylose (167 mmol) was stirred 5 hours in 675 ml 0.5% HCl in methyl alcohol at ambient temperature and neutralized with Amberlite IRA-400 OH anion exchange resin. The

combined filtrates were purified by chromatography on silica using chloroform/methyl alcohol, 2:8, and the products isolated in 95% yield as a 1:1 α,β mixture. MS data supplied.

2. Methyl-2,3,5-Tri-O-benzyl-L-xylofuranoside

The product from Step 1 (60.9 mmol) dissolved in 350 ml THF was treated with NaH (370 mmol) and then stirred 15 minutes at 0°C. Thereafter, benzyl bromide (214 mmol) and solid NBu_4I (0.96 mmol) were added and the mixture stirred 3 days at ambient temperature. It was quenched with 25 ml methyl alcohol, concentrated, purified by chromatography on silica gel with cyclohexane/EtOAc, 9:1, and the product isolated in 87% yield. $^1\text{H-NMR}$ and MS data supplied.

3. 2,3,5-Tri-O-benzyl-L-xylose dibenzyl dithioacetal

The product from Step 2 (97 mmol) was dissolved in 1 L CH_2Cl_2 and benzyl mercaptan (400 mmol) and tin(IV)chloride (18.9 mmol) added. The mixture stirred overnight at ambient temperature and was then neutralized with 750 ml 5% NaHCO_3 . The phases were separated, concentrated, purified by chromatography on silica gel using cyclohexane/EtOAc, 99:1, and the product isolated in 57% yield. $^1\text{H-NMR}$ and MS data supplied.

4. 2,3,5-Tri-O-benzyl-1-acetyl-4-thio-D-arabinofuranose

The product from Step 3 (20 mmol) was dissolved in 200 ml toluene and acetonitrile, 2:1, added to triphenylphosphine (60 mmol), iodine (50 mmol) and imidazole (80 mmol) and the mixture stirred at 90°C 24 hours. It was concentrated, purified by chromatography on by silica gel with cyclohexane/EtOAc, 4:1, and the product isolated in 83% yield. $^1\text{H-NMR}$, elemental analysis, and MS data supplied.

5. 2,3,5-Tri-O-benzyl-1-O-acetyl-4-thio-D-arabinofuranose

The product from Step 4 (10 mmol) was added to a suspension of mercuric acetate (22.9 mmol) in HOAc (96 g) and the mixture stirred at ambient temperature 2 hours. It was then diluted with 200 ml CH_2Cl_2 , washed with NaHCO_3 and KCl solutions, dried, and concentrated. The mixture was purified by chromatography using cyclohexane/EtOAc, 98:2, and a 1:1 mixture of α and β anomers isolated in 78% yield. $^1\text{H-NMR}$, elemental analysis, and MS data supplied.

6. 1-(2,3,5-Tri-O-benzyl-4-thio- α - and β -D-arabinofuranosyl)cytosine

The product from Step 5 (1 mmol) and cytosine (1 mmol) were dissolved in acetonitrile (25 mmol), hexamethyldisilazane (1 mmol) and chlorotrimethylsilane (4 mmol) added, and the mixture stirred at ambient temperature 30 minutes. The solution was cooled to -78°C , trimethylsilyltrifluoromethane sulfonate (1.2 mmol) added, and the solution stirred 2.5 hours. Thereafter, the mixture was warmed to ambient temperature, concentrated to 5 ml, diluted with 50 ml CH_2Cl_2 , washed with 20 ml water, dried, and concentrated. The residue was purified by chromatography over silica gel using chloroform/methyl alcohol, 98:2, and the product isolated in 77.5% yield. $^1\text{H-NMR}$, elemental analysis, and MS data supplied.

7. 1-(4-Thio- α - and β -D-arabinofuranosyl)cytosine

A solution of 1 ml M BF_3 in 7 ml CH_2Cl_2 was cooled to -78°C , the product from Step 6 (0.5 mmol) dissolved in 10 ml CH_2Cl_2 added, the mixture stirred overnight at -20°C , and concentrated. The residue was co-evaporated 4 times with 20 ml CH_2Cl_2 , neutralized with NaHCO_3 , purified using an H^+ cation exchange column with water to remove salts and then with NH_4OH , and the product isolated 85% yield. ^1H -NMR, elemental analysis, and MS data supplied.

8. 1-(5-O-Dimethoxytrityl-4-thio- β -D-arabinofuranosyl)cytosine

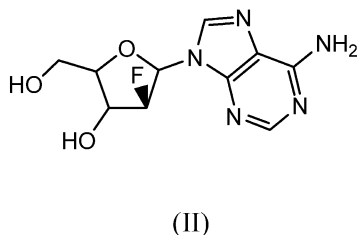
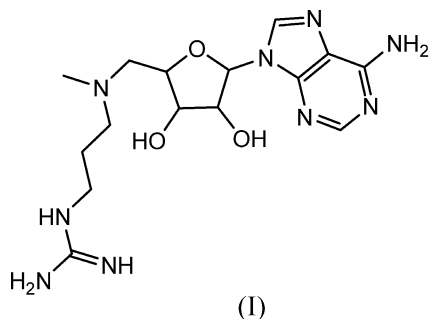
The product from Step 7 (0.38 mmol) was dissolved in 10 ml pyridine, added to 4,4-dimethoxytritylchloride (0.6 mmol), and the mixture stirred 2 hours at ambient temperature. Thereafter it was concentrated, dissolved in 20 ml EtOAc, washed with water, and re-concentrated. It was purified as in Step 6 and the product isolated in 90% yield. ^1H -NMR and MS data supplied.

9. 1-(4-Thio- β -D-arabinofuranosyl)cytosine

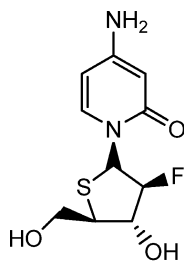
The product from Step 8 (0.16 mmol) was mixed with trifluoroacetic acid (22 mg) dissolved in 5 ml chloroform at ambient temperature for 10 minutes, neutralized with NaHCO_3 , purified as in Step 6, and the product isolated in 85% yield, mp = $218\text{--}220^\circ\text{C}$. ^1H -NMR, elemental analysis, and MS data supplied.

Notes

1. The products from Step 3 and Step 9 were previously prepared by the author and are discussed (1).
2. 5' Deoxy-5'-guanine adenosines derivatives, (I), were previously prepared by the author (2) and others (3). In an earlier investigation 2-fluoro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purin-6-amine, (II), and derivatives were also prepared by the author and are discussed (4).



3. The Step 9 analogue, 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)-cytosine, (III), has been prepared and is described (4).



(III)

4. 1-(4-Thio- β -D-arabinofuranosyl) cytosine derivatives have been prepared on a control-glass pore silica gel substrate (5).

References

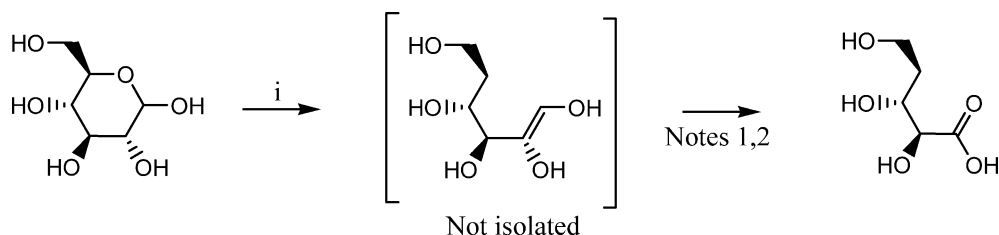
1. J.A. Secrist, III *et al*, Nucleosides Nucleotides, 14, 3, 675 (1995)
2. J.A. Secrist, III, US Patent 4,794,174 (December 27, 1988)
3. M. Manoharan *et al*, US Patent 6,593,466 (July 15, 2003) and US Patent 6,534,639 (March 18, 2003)
4. J.A. Secrist, III, US Patent 5,384,310 (January 24, 1995)
5. Y. Yoshimura *et al*, US Patent 6,147,058 (November 14, 2000)

Patent: Process for the Alkaline Oxidative Degradation of Reducing Sugars
G. Fleche *et al*, US Patent 5,817,780 (October 6, 1998)

Assignee: Roquette Freres

Utility: Industrial Processing of Reducing Sugars

Reaction



i- Sodium hydroxide, water, sodium anthraquinone 2-sulfonate,
hydrogen peroxide

Experimental

1. Arabinonic acid

Dextrose monohydrate (1.71 mol glucose) was dissolved in 7.0 liters water and introduced into a Biolafitte glass fermenter tank having a working capacity of 15 liters. The solution was aerated with an air flow rate of 20 liters/minute while stirring 650 rev/minute at 40°C.

Three additional solutions are also prepared. The first was a glucose solution containing 50% solids, prepared using 1443.4 g dextrose monohydrate and 1181 g water, thus containing 7.92 mol of glucose. The second was a 50% NaOH solution consisting of 840 g NaOH and 840 g water. The third was sodium anthraquinone 2-sulfonate (24 g) dissolved in 110 volumes of 30% H₂O₂.

Procedure

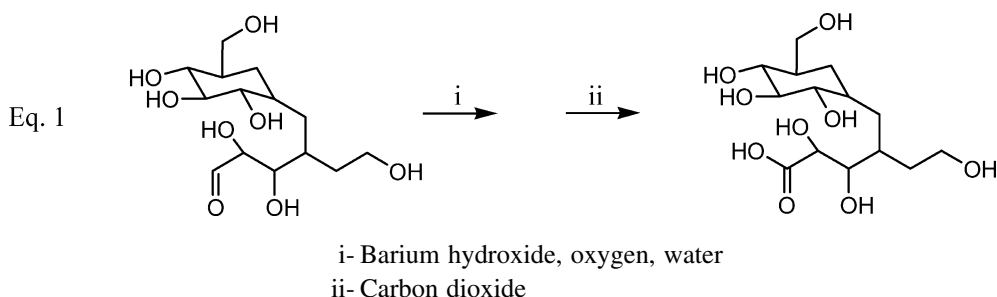
When dextrose monohydrate had been aerating for 30 minutes in the Biolafitte fermenter, sodium hydroxide and anthraquinone 2-sulfonate dissolved in hydrogen peroxide was added (Note 1). Stirring speed was then increased to 800 rev/min and the solution became clear, characteristic of the oxidized form of sodium anthraquinone 2-sulfonate. The 50% glucose solution was gradually added and the stirring speed adjusted so that the solution had a very light pink color. After 2 hours the reducing sugar content has fallen to 10 g/l and the temperature was gradually raised to 60°C. Thereafter the solution was cooled and arabinonic acid isolated in 84.7%.

Derivatives

Sugar	Oxidation Products	Yield (%)
Glucose syrup	Sodium arabinonate Sodium dextrose-arabinonate	100
Ketose	Sodium xylonate	75
Carboxymethyl-wheat starch	Carboxymethyl starch	—

Notes

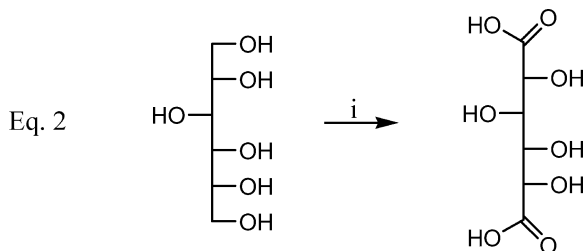
1. Sodium anthraquinone 2-sulfonate (SAM) is the reaction indicator. In the oxidized form it causes the solution to become deep red; it is colorless in the reduced state.
2. This oxidative method is a modified Spengler-Pfannenstiel (1) reaction (1). This reaction is illustrated in Eq. 1 and described for the preparation of 3-(α -D-glucosido)-D-arabonic acid below.



Procedure

A solution of maltose (53 mmol) dissolved in 200 ml water was added dropwise to a stirred suspension of $\text{Ba}(\text{OH})_2$ crystals (20 g) in 150 water under a flow of oxygen. In 22 hours the reaction consumed 1.25 L O_2 . Thereafter, the mixture was saturated with CO_2 and the product quantitatively isolated.

3. Sodium hypochlorite in the presence of the catalyst 2,2,6,6-tetra-methylpiperidin-1-oxyl (TEMPO) has been used to oxidize sugars to the corresponding di-acids without oxidative degradation. This is illustrated in Eq. 2 where sorbitol is oxidized to glucaric acid (2).



i- Demineralized water, 2,2,6,6-tetramethylpiperidin-1-oxyl, sodium hypochlorite

4. A novel clothing detergent was obtained when glucose syrup was oxidized in tandem by sodium anthraquinone 2-sulfonate/ H_2O_2 and then NaOCl/TEMPO and is described (2).
5. A single-pot method for oxidizing sodium arabinonate using molecular oxygen in the presence NaOH followed by subsequent lactonization is described (3).

References

1. E. Hardegger, *Helv. Chim. Acta*, 35, 618 (1952)
2. G. Fleche, US Patent 5,831,043 (November 3, 1998)
3. T. Vuorinen, US Patent 5,563,303 (October 8, 1996)

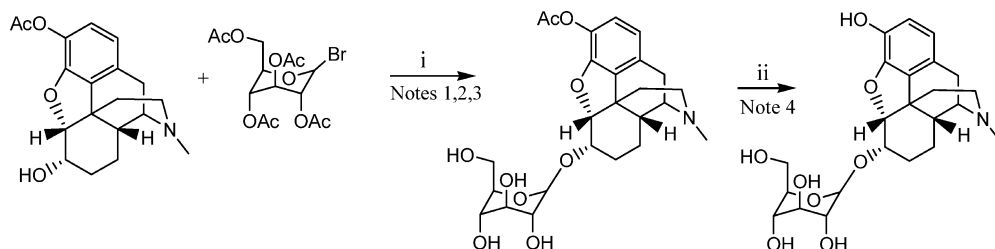
Patent: Sugar Derivatives of Hydromorphone, Dihydromorphone and Dihydroisomorphine Compositions Thereof and Uses for Treating or Preventing Pain

F. Gao *et al*, US Patent 6,740,641 (May 25, 2004)

Assignee: Euro-Celtique, S.A.

Utility: Analgesic

Reaction



i- Mercuric(II)cyanide, acetonitrile

ii- Methyl alcohol, sodium methoxide

Experimental

1. 3-Acetyl-6-O-glucosyldihydromorphone

A mixture of 3-acetyl-dihydromorphone (1 mmol), drierite (1 g) and $\text{Hg}(\text{OAc})_2$ (0.75 mmol) in 5 ml acetonitrile were stirred at room temperature 1 hour. Thereafter, 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (1.5 mmol) was added and the mixture stirred 4 days. The mixture was filtered, concentrated, washed with 1 M KOH, and diluted with CH_2Cl_2 . The product was isolated after chromatographic purification.

2. 6- β -O-Glucosyldihydromorphone

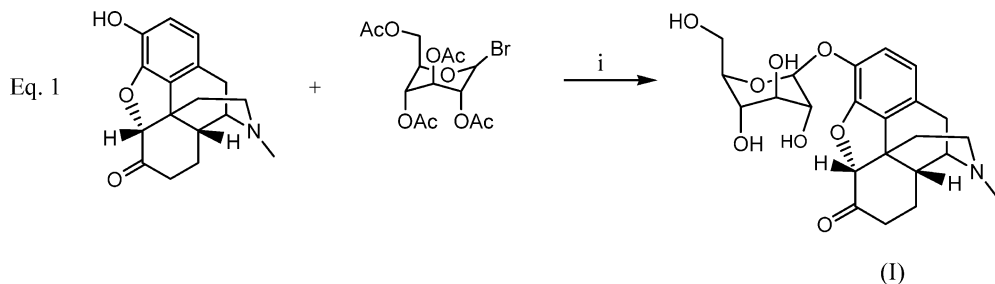
The product from Step 1 was dissolved in 5 ml methyl alcohol and the solution made alkaline by the addition of 1 M sodium methoxide. The solution stood 3 hours and was neutralized with Amberlite IR 120 exchange resin. The solvent was removed, the residue purified by column chromatography, and the product isolated.

Derivatives

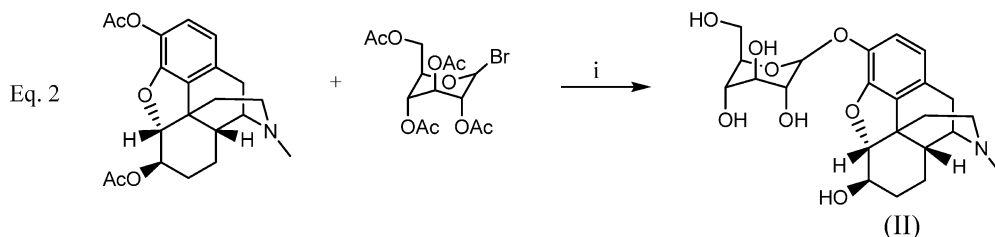
Opioid	Yield (%) (Second Step)
3-O- β -Glucosyldihydroisomorphine	45
3- β -O-Glucosyldihydromorphone	30

Notes

1. This is an example of the Koenings-Knorr glucosidation reaction where glucoside derivatives are prepared using halo- or acetoxy sugars in the presence of Lewis acids such as Ag^+ or Hg^{+2} . Glycosidations can also occur using $\text{NaOH-NBu}_4\text{OH}$ as the catalyst (1).
2. 3-O-Glucosylhydromorphine, (I), and 3-O- β -O-glucosyldihydro-isomorphine, (II), were also prepared by the author as illustrated in Eq. 1 and Eq. 2, respectively:

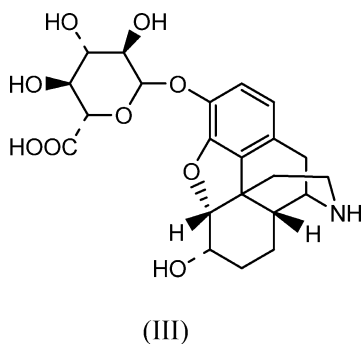


i- Lithium hydroxide, water



i- Lithium hydroxide, water

3. The preparation of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide and derivatives is described (2).
4. The preparation of glucosylhydromorphine derivatives containing N-alkyl, -acyl, or -oxides is provided (3).
5. Nordihydroisomorphine-3-glucuronide, (III), has been prepared and is described (4).



References

1. S. Gabrey, *Synthesis*, 1078 (1992); A. Knochel, *Tetrahedron Lett.*, 551 (1974); C.M. Ice, *J. Am. Chem. Soc.*, 74, 4606 (1952)
2. R.R. Tuttle *et al*, US Patent 4,774,230 (September 27, 1988)
3. F. Scheinmann, US Patent 6,046,313 (April 4, 2000)
4. K. Rice, *J. Org. Chem.*, 40, 1850 (1975)

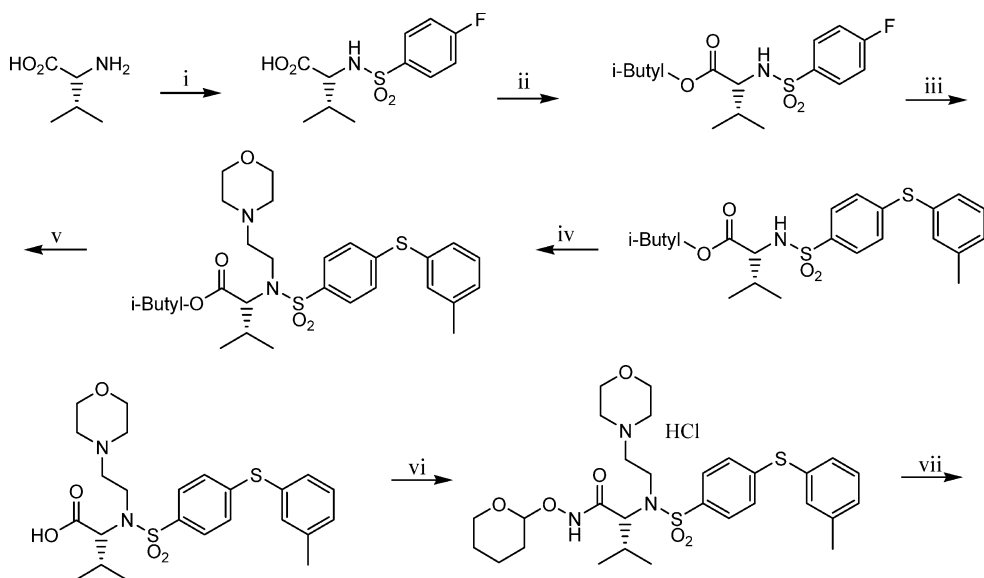
Sulfonamides

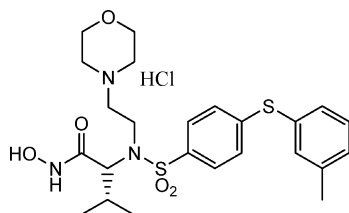
Patent: Thioaryl Sulfonamide Hydroxamic Acid Compounds
D.P. Getman *et al*, US Patent 6,087,359 (July 11, 2000)

Assignee: Pharmacia Corporation

Utility: Proteinase Inhibitors for Treatment of Matrix Metalloproteinase Disorders

Reaction





- i- Acetone, triethylamine, 4-fluorobenzenesulfonyl chloride
- ii- CH_2Cl_2 , dioxane, isobutylene, sulfuric acid
- iii- N,N-dimethylformamide, m-thiocresol, potassium carbonate
- iv- N,N-Dimethylformamide, 4-(2-chloroethyl)-morpholine hydrochloride, potassium carbonate
- v- Hydrochloric acid, water
- vi- 4-Methyl-morpholine, 2-hydroxybenzothiazole, N-(3-dimethyl-aminopropyl)-N'-ethylcarbodiimide hydrochloride, N,N-dimethylformamide, O-tetrahydro-2H-pyran-2-yl-hydroxylamine
- vii- Hydrogen chloride, ethyl alcohol

Experimental

1. N-[(4-Fluorophenyl)sulfonyl]-D-valine

To a solution of D-valine (54.6 mmol) dissolved in 62 ml water and 25 ml acetone was added triethylamine (117 mmol). The solution was cooled to 0°C and 4-fluorobenzenesulfonyl chloride (51.4 mmol) dissolved in 25 ml acetone added dropwise. After stirring at ambient temperature 20 hours, the solution was concentrated, the aqueous residue extracted twice with 50 ml toluene and then acidified with HCl to pH 1. The solution was extracted 3 times with 50 ml EtOAc, washed successively with 50 ml apiece of KHSO_4 , water, and brine, dried, concentrated, and triturated with hexane. The product was isolated in 89% yield. MS and elemental analysis data supplied.

2. N-[(4-Fluorophenyl)sulfonyl]-D-valine, 1,1-dimethylethyl ester

A solution of the product from Step 1 (29.1 mmol) in CH_2Cl_2 /dioxane was treated with isobutylene in the presence of H_2SO_4 at room temperature at a pressure of 18 psi. The reaction was quenched by adding 300 ml water containing NaHCO_3 (20 g). The mixture was extracted with EtOAc, washed, dried, and concentrated. The product was isolated in 73% yield after re-crystallization from diethyl ether/hexane. MS and elemental analysis data supplied.

3. N-[[4-[(3-Methylphenyl)thio]phenyl]sulfonyl]-D-valine, 1,1-dimethylethyl ester

To a solution of the product from Step 2 (9.06 mmol) in 35 ml N,N-dimethylformamide was added m-thiocresol (27.2 mmol), powdered K_2CO_3 (27.2 mmol) and the mixture

heated to 70°C 20 hours then cooled. The mixture was washed 4 times with 100 ml water, twice with 100 ml brine, dried, and concentrated. The mixture was purified by flash chromatography using EtOAc/hexane, 1:9, and the product isolated in quantitative yield. MS and elemental analysis data supplied.

4. N-[[4-[(3-Methylphenyl)thio]phenyl]sulfonyl]-N-[2-(4-morpholinyl)ethyl]-D-valine, 1,1-dimethylethyl ester

To a solution of the product from Step 3 (9.08 mmol) dissolved in 30 ml N,N-dimethylformamide was added 4-(2-chloroethyl)morpholine hydrochloride (27.2 mmol) and K₂CO₃ (27.2 mmol). Thereafter, the solution was heated to 63°C 24 hours. Additional K₂CO₃ (9.08 mmol) and 4-(2-chloroethyl)-morpholine hydrochloride (9.08 mmol) were added and the mixture re-heated for an additional 24 hours at 63°C. The mixture was partitioned between EtOAc and water, the organic phase washed 3 times with 30 ml brine, dried, and concentrated. The residue was purified by flash chromatography using EtOAc/hexane, 2:8, and 5.21 g product isolated. MS and elemental analysis data supplied.

5. N-[[4-[(3-Methylphenyl)thio]phenyl]sulfonyl]-N-[2-(4-morpholinyl)ethyl]-D-valine hydrogen chloride

A solution of the product from Step 4 (9.08 mmol) dissolved in 30 ml 12 M HCl and water was stirred for 30 minutes and refluxed 25 minutes. The mixture was concentrated in vacuo and 5.30 g product isolated. MS and elemental analysis data supplied.

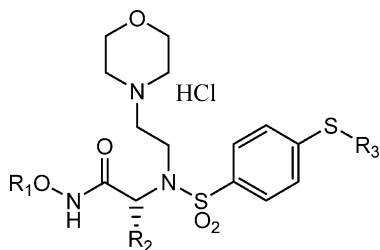
6. 3-Methyl-2R-[[[4-[(3-methylphenyl)thio]phenyl]-sulfonyl]-[2-(4-morpholinyl)-ethyl]amino]-N-[(tetrahydro-2H-pyran-2-yl)oxy]butanamide

The product from Step 5 (9.08 mmol), 4-methyl-morpholine (36.3 mmol), 2-hydroxybenzothiazole (10.9 mmol) and N-(3-dimethyl-aminopropyl)-N'-ethylcarbodiimide hydrochloride (12.7 mmol) were dissolved in 50 ml DMF and added to O-tetrahydro-2H-pyran-2-yl-hydroxylamine (13.6 mmol). The mixture stirred for 3 hours, was diluted with water, extracted 3 times with EtOAc, washed twice with 50 ml brine, dried, and concentrated. The mixture was purified by flash chromatography using acetone/hexane, 4:6, and the product isolated in 67% yield. MS and elemental analysis data supplied.

7. N-Hydroxy-3-methyl-2R-[[[4-[(3-methylphenyl)thio]phenyl]-sulfonyl]-[2-(4-morpholinyl)-ethyl]amino]butanamide, hydrogen chloride

A solution of the product from Step 6 dissolved in 50 ml methyl alcohol was cooled to 0°C and HCl bubbled into the solution for 15 minutes. The solution was concentrated, the residue dissolved in a minimum amount of ethyl alcohol, precipitated in diethyl ether, and the product isolated in 87% yield. MS and elemental analysis data supplied.

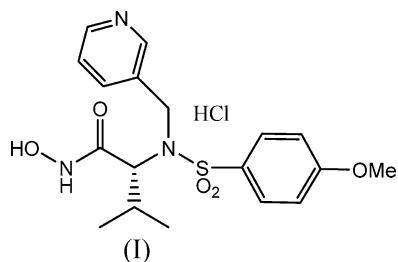
Derivatives



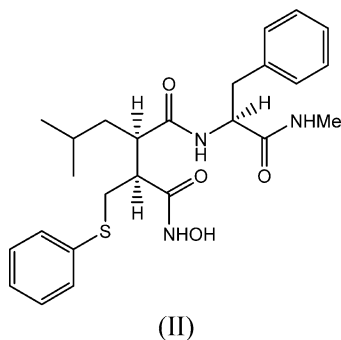
R₁	R₂	R₃	MS(MH⁺)
Hydrogen	Methyl	Phenyl	466
Methyl	Methyl	4-Methylphenyl	478
Hydrogen	Hydrogen	Cyclohexyl	458
Hydrogen	iso-Propyl	4-Methylphenyl	493

Notes

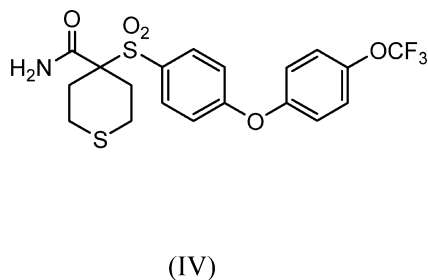
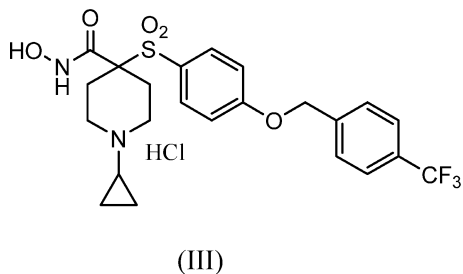
1. The Step 7 analogue, N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picoyl)amino]-3-methylbutanamide hydrochloride, (I), has been prepared and is described (1).



2. The L-phenylalanine derivative of Step 7, [4-(N-hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide, (II), has been prepared (2) and is discussed.



3. In subsequent investigations by others, Step 7 piperidine- and tetrahydro-2H-thiopyran-sulfonyl derivatives were prepared. These include 1-cyclopropyl-N-hydroxy-4-[[4-[4-(1-ethylethoxy)-phenoxy]-phenyl]-sulfonyl]-4-piperidinecarboxamide hydrogen chloride, (III), (3) and tetrahydro-4-[[4-trifluoromethoxy)-phenyl]sulfonyl]-2H-thiopyran-4-carboxamide, (IV), (4).



References

1. L.J. MacPherson *et al*, US Patent 5,646,167 (July 8, 1997)
2. C. Campion *et al*, US Patent 5,240,958 (August 31, 1993)
3. T.E. Barta *et al*, US Patent 6,750,233 (June 15, 2004)
4. T.E. Barta *et al*, US Patent 6,750,228 (June 15, 2004)

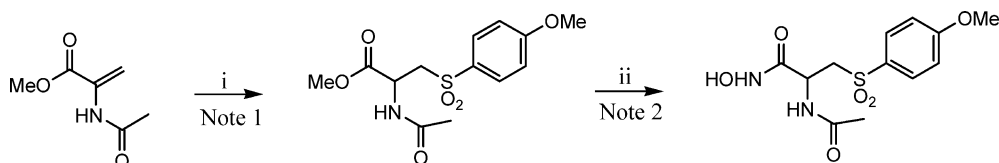
Sulfones

Patent: α -Amino- β -Sulfonyl Hydroxamic Acid Compounds
S.L. Hockerman *et al*, US Patent 6,583,299 (June 24, 2003)

Assignee: G.D. Searle & Co.

Utility: Proteinase Inhibitors MMP-2, MMP-9, or MMP-13 in the Treatment of Matrix Metalloproteinase Disorders

Reaction



i- Methyl alcohol, triethylamine, peroxymonosulfate (Oxone),
4-methoxythiophenol

ii- Water, hydroxylamine, methyl alcohol, THF

Experimental

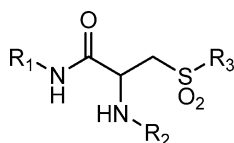
1. Methyl 3-[(4-methoxyphenyl)sulfonyl]-2-[(methylcarbonyl)amino]-propanoic acid

N-Acetyl dehydroalanine methyl ester, p-methoxythiophenol (9.9 g) and 10 ml triethylamine were dissolved in 100 ml methyl alcohol, stirred 1 hour, and concentrated. The residue was dissolved in 200 ml methyl alcohol and 150 ml water, treated with peroxymonosulfate (89 g), stirred 1 hour, filtered, and concentrated. The mixture was partitioned between EtOAc/water, washed with water, brine, concentrated, and 14 g product isolated.

2. Hydroxy-3-[(4-methoxyphenyl)sulfonyl]-2-[(methylcarbonyl)-amino]propanamide

The product from Step 1 (500 mg) and 1.2 ml 50% aqueous hydroxylamine were dissolved in 8 ml apiece methyl alcohol and THF, stirred 18 hours, and concentrated. Trituration with EtOAc yielded 380 mg product.

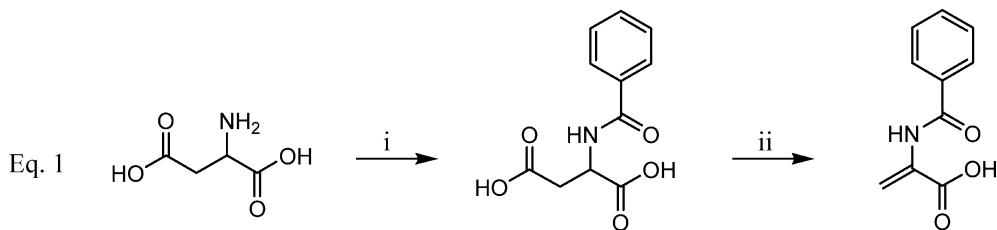
Derivatives



R ₁	R ₂	R ₃	Yield (%)
Hydrogen	Acetyl	4-Phenoxyphenyl	32
3,4,5,6-Tetrahydro-2H-pyran-2-yl	1,1-Dimethylethyl acetal	4-Phenoxyphenyl	58
3,4,5,6-Tetrahydro-2H-pyran-2-yl	Phenylethyl carbamate	4-Thiophenylphenyl	31
3,4,5,6-Tetrahydro-2H-pyran-2-yl	4-Methylphenyl-sulfonyl	4-Phenoxyphenyl	24

Notes

1. Other dehydroalanine Step 1 reagents were prepared by the author as illustrated in Eq. 1:

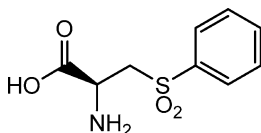


i- THF, sodium hydroxide, benzoyl chloride

ii- Methyl alcohol, sodium hypochlorite

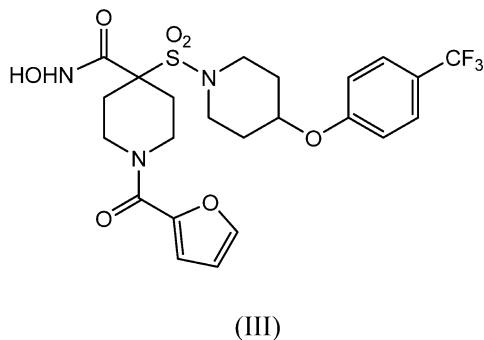
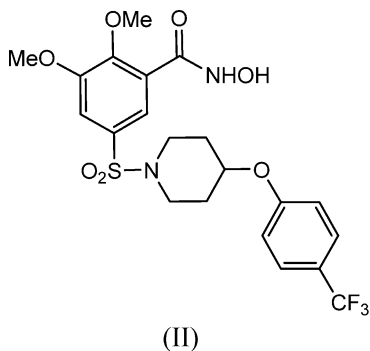
2. Hydrogen chloride salts of other α -amino- β -sulfonyl hydroxamic Step 2 products have been prepared and are described (1).

3. 3-Phenylsulfonyl-L-cysteine, (I), derivatives have been prepared and are discussed (2).



(I)

4. Extensive Step 2 derivatives of the current invention including N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidiny]sulfonyl]benzamide (3) and 1-(2-furanylcarbonyl)-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidiny]sulfonyl]-4-piperidinecarboxamide, (III), (4) are provided for review.

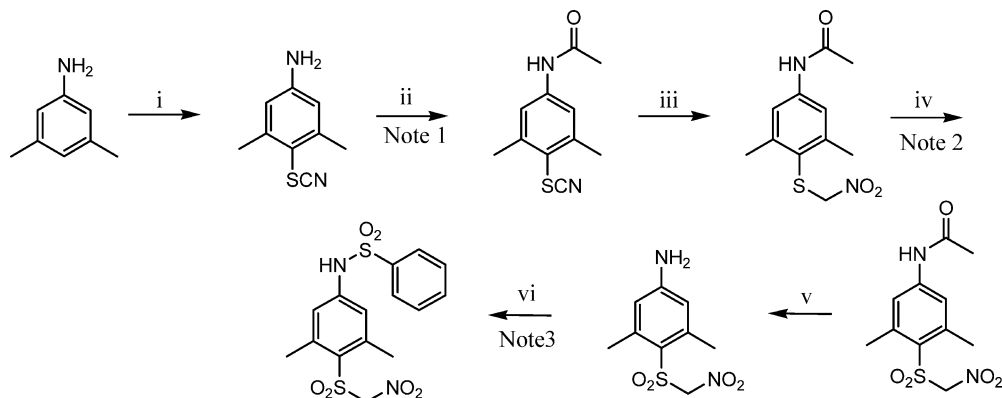


References

1. S. Genard *et al*, US Patent 5,871,755 (February 16, 1999)
2. R.S. Phillips *et al*, US Patent 5,516,936 (May 14, 1996)
3. L.J. Bedell *et al*, US Patent 6,794,511 (September 21, 2004)
4. G.A. DeCrescenzo *et al*, US Patent 6,800,646 (October 5, 2004)

- Patent:** Nitromethylthiobenzene Derivatives as Inhibitors of Aldose Reductase
F. Collonges *et al*, US Patent 6,509,499 (January 21, 2003)
- Assignee:** Merck Patent Gesellschaft
- Utility:** Treatment of Peripheral and Autonomous Complications from Diabetes

Reaction



- i- Ammonium thiocyanate, N,N-dimethylformamide, cupric sulfate
- ii- Triethylamine, CH_2Cl_2 , acetyl chloride,
- iii- Sodium methoxide, nitromethane, N,N-dimethylformamide
- iv- Potassium permanganate, acetic acid, sodium metabisulfite
- v- Sodium hydroxide, water,
- vi- Calcium carbonate, benzenesulfonyl chloride, THF

Experimental

1. 4-Amino-2,6-dimethylphenyl thiocyanate

Ammonium thiocyanate (3.30 mol) was added to 3,5-dimethylaniline (1 mol) dissolved in 1.75 L DMF and the mixture reacted 3 hours. Thereafter, CuSO_4 (1.65 mol) was added and the mixture stirred 3 days at ambient temperature. The mixture was poured into 8 L water and the pH brought to 7.5 by the addition of NaHCO_3 (6.55 mol), extracted with EtOAc, and the product isolated after re-crystallization from hexane in 72% yield. $^1\text{H-NMR}$ and IR data supplied.

2. 4-Acetamido-2,6-dimethylphenyl thiocyanate

The product from Step 1 (422 mmol) was dissolved in 500 ml CH_2Cl_2 containing triethylamine (463 mmol) and acetyl chloride (418 mmol) added dropwise. After 1 day,

the mixture was poured into 400 ml water and the product isolated by filtration in 67% yield, mp = 204–206°C. ¹H-NMR and IR data supplied.

3. N-[3,5-Dimethyl-4[(nitromethyl)thio]phenyl]acetamide

The product from Step 2 (58.6 mmol) dissolved in 140 ml DMF was added to a solution of sodium methoxide (174 mmol) containing nitromethane (128 mmol) in 140 ml DMF over 80 minutes. The mixture was stirred for 20 minutes then poured into 1 L water and the pH adjusted to 7 using dilute HCl. Thereafter, the mixture was extracted 4 times with 500 ml EtOAc and concentrated under reduced pressure. The mixture was purified by chromatography on silica gel using CH₂Cl₂/EtOAc, 2:1, and the product isolated in 56% yield, mp = 160–163°C. ¹H-NMR and IR data supplied.

4. N-[3,5-Dimethyl-4[(nitromethyl)sulphonyl]phenyl]acetamide

The product from Step 3 (39.3 mmol) was dissolved in 1 L HOAc and KMnO₄ (118 mmol) dissolved in 500 ml water quickly added. The reaction was maintained at 65°C for 30 minutes then cooled in an ice bath. Saturated Na₂S₂O₅ was added until decolorization occurred and the mixture poured into 2.5 L water and stirred one hour. The product was isolated by filtration in 54% yield, mp = 180–182°C.

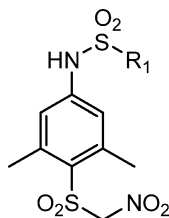
5. N-[3,5-Dimethyl-4[(nitromethyl)sulphonyl]phenyl]aniline

The product from Step 4 (45.8 mmol) was mixed with sodium hydroxide (265 mmol) in 150 ml water and heated to 80°C 1 hour. The mixture was poured into 850 ml water and the pH adjusted to 5 with HOAc causing a precipitate to form. The product was isolated by filtration in 95% yield, mp = 128–130°C.

6. N-[3,5-Dimethyl-4[(nitromethyl)sulphonyl]phenyl]benzene-sulphoamide

To the product from Step 5 (38.9 mmol) dissolved in 180 ml THF was added CaCO₃ (78.4 mmol) followed by benzenesulfonyl chloride (58.4 mmol) and the mixture refluxed 8 hours. Additional benzenesulfonyl chloride (19.6 mmol) was added and the mixture refluxed an additional 6 hours. This was followed by a second addition of benzenesulfonyl chloride (19.6 mmol) and 22 hours of additional refluxing. Thereafter, the mixture was poured into 600 ml water and the product extracted with CH₂Cl₂. Purification by chromatography on silica gel using CH₂Cl₂ followed by re-crystallization in hexane/CH₂Cl₂ provided the product in 41% yield.

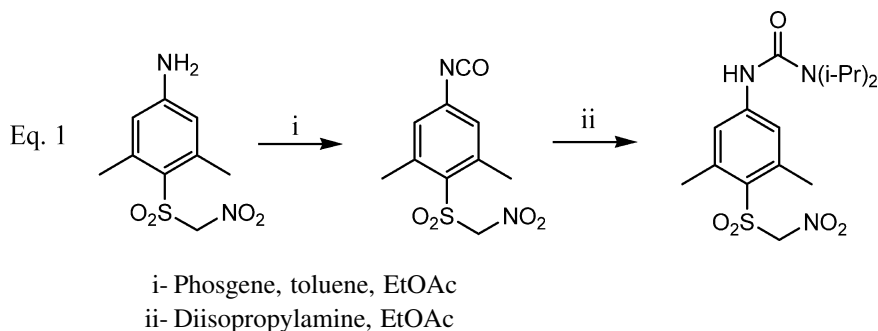
Derivatives



R_1	Yield (%)	Melting Point ($^{\circ}\text{C}$)
3-Chloromethylphenyl	42	130 (dec)
4-Methylsulphonylphenyl	26	—
2-Naphthyl	84	215
4-Bromophenyl	24	164
2,4-Difluorophenyl	22	154

Notes

1. Other Step 2 acetylating agents that can be used are described (1).
2. m-Chloroperbenzoic acid and peroxymonosulfate (Oxone) were previously used as oxidizing agents in Step 4 to prepare N-[3,5-dimethyl-4-[(nitromethyl)sulfonyl]phenyl]acetamide and are described (2,3), respectively.
3. Urea derivatives of the product of Step 4 have been prepared (4) as illustrated in Eq. 1:



References

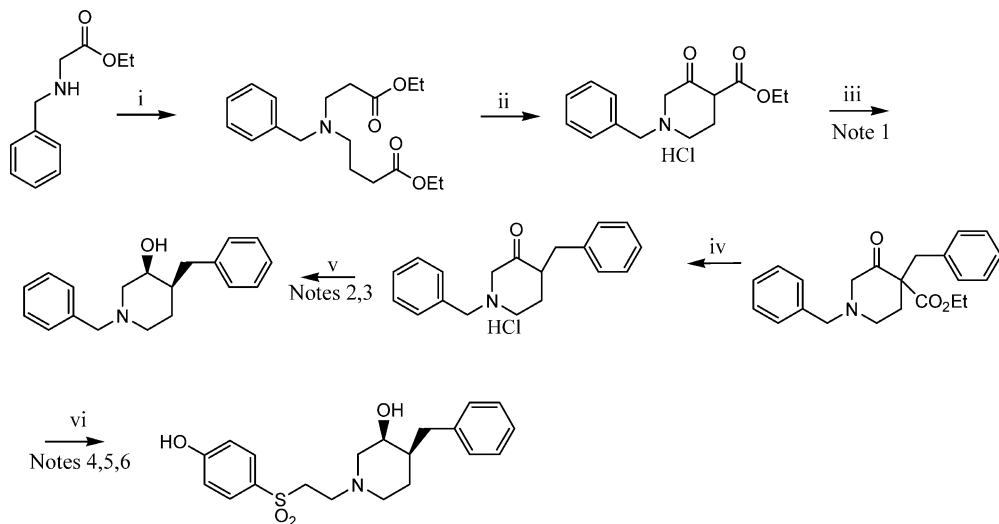
1. S.P. Brown *et al*, US Patent 5,153,227 (October 6, 1992)
2. D.R. Brittain *et al*, US Patent 5,270,342 (December 14, 1993)
3. D.R. Brittain *et al*, US Patent 5,430,060 (July 4, 1995)
4. D.R. Brittain *et al*, US Patent 5,110,808 (May 5, 1992)

Patent: Process for the Preparation of Ethanesulfonyl-piperidine Derivatives
Y. Cramer *et al*, US Patent 6,605,723 (August 12, 2003)

Assignee: Hoffman-La Roche Inc.

Utility: Treatment of Neurodegenerative Diseases

Reaction



- i- Ethyl-4-bromobutyrate, N,N-dimethylformamide, triethylamine
- ii- Toluene, sodium ethoxide, hydrochloric acid, methyl alcohol
- iii- Potassium t-butoxide, THF, benzyl bromide
- iv- Ethyl alcohol, hydrochloric acid
- v- Ruthenium dichloride((S)-(6,6'-dimethoxy-biphenyl-2,2'-di-yl)bis[bis(3,5-dimethyl-xylene)((R,R)-2-diphenylethylenediamine)]), isopropyl alcohol, hydrogen
- vi- CH₂Cl₂, 4-(2-chloroethylsulfonyl)phenol, triethylamine

Experimental

1. 4-(N-Benzyl-N-ethoxycarbonylpropylamino)-butyric acid ethyl ester

N-Benzylglycine ethyl ester (25.8 mmol) and ethyl 4-bromobutyrate (51.7 mmol) were dissolved in 40 ml dimethylformamide containing triethylamine (64.3 mmol), heated to 65°C 23 hours, and cooled. The mixture was concentrated, the residue treated with 100 ml apiece water and EtOAc, and the phases separated after extraction. The organic phase was washed twice with 100 ml water, dried, and concentrated. The residue was purified by chromatography over silica gel using hexane/EtOAc, 9:1, and the product isolated as a yellow oil in 88.8% yield. MS data supplied.

2. **rac-Ethyl N-benzyl-3-oxo-4-piperidine-carboxylate hydrogen chloride**

The product from Step 1 (9.1 mmol) was dissolved in 18 ml toluene containing sodium ethoxide (13.7 mmol), heated to 85°C 4 hours, cooled, and poured into 50 ml ice water. The phases were separated and the aqueous phase extracted with total of 100 ml EtOAc. The organic phases were washed with water, dried, and concentrated. When the crude product was treated with 3.7 ml 20% HCl in methyl alcohol white crystals formed and were isolated. They were re-crystallized by refluxing in 30 ml isopropyl alcohol, stirred 2 hours at ambient temperature, and the product isolated in 67.5% yield. MS data supplied.

3. **rac-1,4-Dibenzyl-3-oxo-piperidine-4-carboxylic acid ethyl ester**

Potassium t-butoxide (341.0 mmol) and 625 ml THF were stirred at ambient temperature 30 minutes, cooled to 0°C, and the product from Step 2 (168.0 mmol) added. The mixture was warmed to ambient temperature and stirred 60 minutes. Thereafter, it was re-cooled, benzyl bromide dissolved in 20 ml THF added, and the mixture stirred 4 hours at ambient temperature. The solution was re-cooled and 200 ml saturated NH₄Cl solution added. The aqueous phase was extracted twice with 100 ml ethyl acetate, the organic phases combined, washed, dried, concentrated, and the product isolated in 99.3% yield. MS Data supplied.

4. **rac-1,4-Dibenzyl-3-oxo-piperidine hydrogen chloride**

The product from Step 3 (336 mmol) was dissolved in 118.0 ml ethyl alcohol, 405 ml 37% HCl added while keeping the reaction temperature below 7°C, and refluxed 19 hours. Nucleation crystals of rac-1,4-dibenzyl-3-oxo-piperidine hydrogen chloride were added, the mixture cooled to ambient temperature, and stirred 2 hours. The resulting crop was washed with 60 ml water, dried, re-crystallized by refluxing in 400 ml EtOAc, and the product isolated in 78%, mp = 202–203°C. MS Data supplied.

5. **cis-1,4-Dibenzyl-3-hydroxy-piperidine**

A. **Ruthenium asymmetric catalyst**

The catalyst solution was prepared by adding ruthenium dichloride((S)-(6,6'-dimethoxybiphenyl-2,2'-di-yl)bis[bis(3,5-diisopropyl-phenyl)phosphine]][(R,R)-2-diphenylethylenediamine]) (0.050 mmol) to 20 ml iso-propyl alcohol and the mixture stirred 20 minutes at ambient temperature and stored.

B. **Hydrogenation process for cis-1,4-dibenzyl-3-hydroxy-piperidine**

The product from Step 4 (0.130 mol), 205 ml of isopropyl alcohol and potassium t-butyrate (0.156 mol) were mixed, transferred into a 380 ml stirred stainless steel autoclave, and 4.0 ml of the prepared ruthenium asymmetric catalyst solution added. The mixture was hydrogenated at ambient temperature at 4×10^6 Pa 3 hours. Thereafter, the mixture was filtered, concentrated, and the residue dissolved in a water/ethyl acetate mixture. It was treated with a 5% NH₄Cl solution and the organic phase dried. HPLC analysis of an aliquot indicated that the cis/trans product ratio was 99:1, respectively, with an enantiomeric excess of (S,S)-cis-1,4-dibenzyl-piperidin-3-ol of 91%.

6. (3S,4S)-4-Benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol

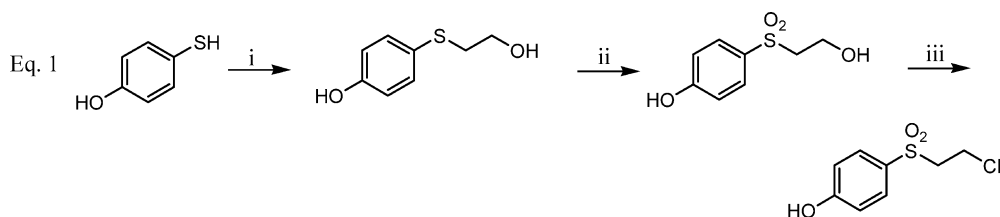
A solution of 4-(2-chloroethylsulfonyl)phenol (24.4 mmol) dissolved in 50 ml CH_2Cl_2 was treated at 37°C with triethylamine (26.4 mmol), stirred for 3.25 hour, and the product from Step 5 (22.0 mmol) dissolved in 40 ml CH_2Cl_2 added. The mixture was stirred at 37°C 3 hours, cooled to room temperature, and treated with 80 ml water and solid NaCl. The mixture was extracted 3 times with 70 ml CH_2Cl_2 , dried, concentrated to 70 ml, treated with 75 ml toluene, and concentrated to 100 ml. After 3 days at 0°C the suspension was concentrated to 50 ml, filtered, and crude product isolated as white crystals. They were purified by chromatography on silica gel using CH_2Cl_2 /t-butylmethyl ether, 19:1, and the product isolated in 87.1% yield, mp = $155.5\text{--}156.2^\circ\text{C}$. MS Data supplied.

Notes

1. An alternative method for preparing the product of Step 2, is described (1).
2. Additional stereospecific reductions were performed by the author using other ruthenium-(S)-diphosphines and to prepare the Step 5 products summarized below:

(S)-Diphosphine	cis/trans	% ee
MeOBIPHEP	7/3	66
(3,5-Xyl)-MeOBIPHEP	94/6	70
(3,5-Isopropyl)-MeOBIPHEP	98/2	97
(3,5-Ethyl)-MeOBIPHEP	99/1	95

3. The product of Step 5 were hydrogenated as both a free base and salt. The salt form is preferred, however, because of its limited solubility in base in the presence of the homogenous catalyst.
4. The preparation of other stereospecific hydrogenation catalysts such as ruthenium dichloride((S)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis[bis(3,5-dimethyl-xylene)((R,R)-2-diphenylethylene-diamine)]) is provided (2). Other suitable ligands such as 1,2-bis(2,5-dimethylphospholano)benzene are described (3).
5. (3R,4R)-4-Benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol was also prepared by the author and is described.
6. The preparation of the Step 6 reagent is described by the author and others (4) and illustrated in Eq. 1:



- i- Ethyl alcohol, 2-bromo-1-ethyl alcohol, sodium hydroxide
- ii- Ozone, methyl alcohol
- iii- Pyridine, thionyl chloride, CH_2Cl_2

References

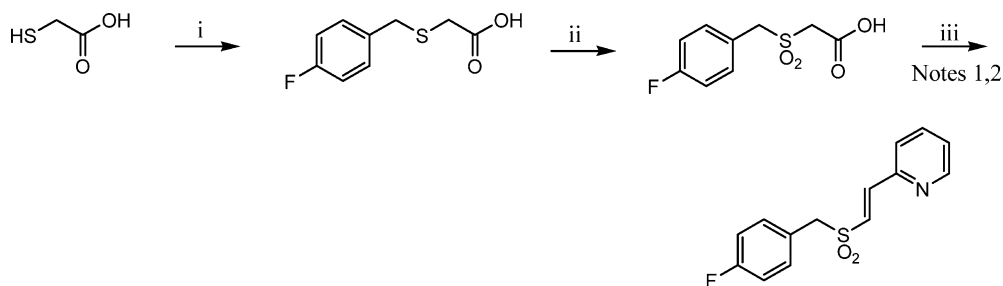
1. T. Talbach *et al*, J. Am. Chem. Soc., 71, 896 (1948)
2. J. Simmons, Angew. Chem. Int. Ed., 37, 1703 (1998)
3. M.J. Burk, US Patent 5,171,892 (December 15, 1992)
4. A. Alanine *et al*, US Patent 6,310,213 (October 30, 2001)

Patent: α, β -Unsaturated Sulfones for Treating Proliferative Disorders
E.P. Reddy *et al*, US Patent 6,599,932 (July 29, 2003)

Assignee: Temple University of the Commonwealth System of Higher Education

Utility: Anti-Neoplastic Agents

Reaction



- i- Methyl alcohol, sodium hydroxide, 4-fluorobenzyl chloride
- ii- Hydrogen peroxide, acetic acid
- iii- 2-Pyridinecarboxaldehyde, benzylamine, acetic acid

Experimental

1. 4-Fluorobenzylthioacetic acid

Thioglycolic acid (0.1 mol) was added to a solution of NaOH (0.2 mol) dissolved in 200 ml methyl alcohol followed by the addition of 4-fluorobenzyl chloride (0.1 mol) and the reaction refluxed 3 hours. The mixture was cooled to ambient temperature, poured onto crushed ice, neutralized with 200 ml HCl, and the product isolated.

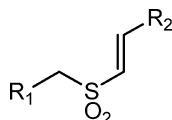
2. 4-Fluorobenzylsulfonylacetic acid

A mixture of the product from Step 1 (0.1 mol), hydrogen peroxide (0.12 mol) in 125 ml HOAc was refluxed 1 hour, cooled, re-crystallized in water, and the product isolated.

3. (E)-2-Pyridineethenyl-4-fluorobenzyl sulfone

The product from Step 2 (10 mmol) was mixed with 2-pyridine-carboxaldehyde (10 mmol) and 200 ml benzylamine in 12 ml HOAc, refluxed 3 hours, cooled, and treated with 50 ml diethyl ether. Any precipitation was removed by filtration. The filtrate was diluted with additional diethyl ether, washed successively with NaHCO₃, sodium bisulfite, HCl, and 35 ml water. The mixture was concentrated and the product isolated as solid.

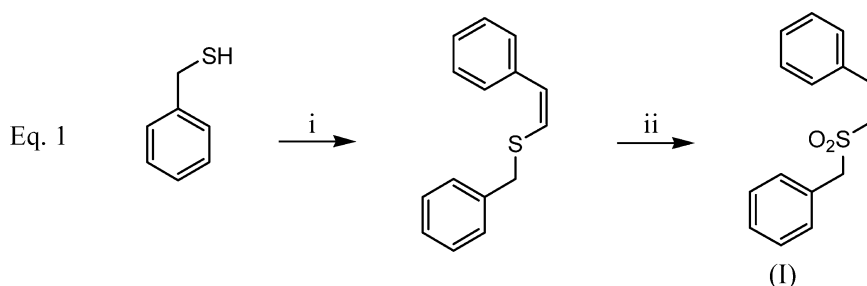
Derivatives



R₁	R₂	Yield (%)	Melting Point (°C)
4-Chlorophenyl	3-Pyridinyl	51	167–169
4-Fluorophenyl	3-Thiophenyl	53	159–161
4-Cyanophenyl	3-Thiophenyl	54	168–170
2,4-Dichlorophenyl	3-Furyl	53	104–106
4-Chlorophenyl	1-Naphthyl	63	142–145
1-Naphthylmethyl	2-Nitrophenyl	62	188–192

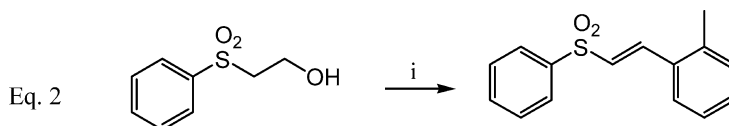
Notes

1. The condensation of 4-fluorobenzylsulfonylacetic acid with 2-pyridinecarboxaldehyde in the presence of benzylamine and acetic acid occurs by the Knoevenagel-Doebner reaction and is reviewed (1).
2. In a previous investigation by the author (2), (Z)-phenylethenyl-benzylsulfone, (I), and derivatives were prepared by the nucleophilic addition of sodium benzylthiolate to phenylacetylene derivatives followed by oxidation of the intermediate using hydrogen peroxide as illustrated in Eq. 1:



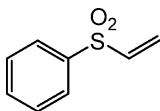
- i- Sodium methoxide, methyl alcohol, phenylacetylene
 ii- Acetic acid, hydrogen peroxide

3. A single step method for preparing (E)- α,β -unsaturated sulfones using 2-(phenylsulfonyl)ethanol is illustrated in Eq. 2 and described (3).



- i- Methane sulfonic acid, triethylamine, palladium acetate, tri(o-tolyl)phosphine

4. Phenylvinylsulfones (II) have been prepared by dehydrohalogenation of β -haloethylphenylsulfones and are discussed (4).



(II)

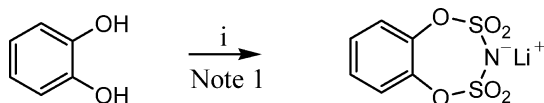
References

1. W.W. Johnson, *Org. React.*, 6, 1 (1951)
2. E.P. Reddy *et al.*, *Sulfur Lett.*, 13, 83 (1991) and E.P. Reddy *et al.*, US Patent, 6,576,675 (June 10, 2003)
3. J. Otera *et al.*, US Patent 6,201,131 (March 13, 2001)
4. S. Seko, US Patent 5,902,905 (March 11, 1999)

Sulfonylimides

Patent: Sulfonylimide Compounds
D.A. Fanta *et al*, US Patent 6,350,545 (February 26, 2002)
Assignee: 3M Innovative Properties Company
Utility: Electrolyte in Lithium Batteries

Reaction



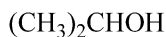
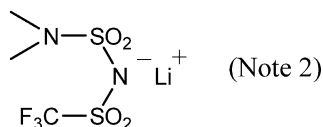
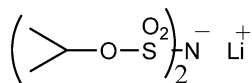
i- Acetonitrile, imidobis(sulfonyl chloride), triethylamine,
lithium hydroxide

Experimental

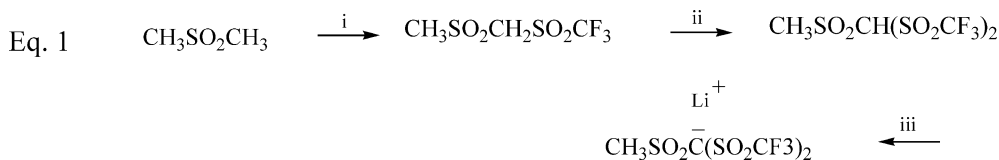
1. 1,2-Benzenesulphonylimide lithium

1,2-Dihydroxybenzene (17 g) was dissolved in anhydrous acetonitrile (75 g) and imido-bis(sulfonyl chloride) (42 g) dissolved in anhydrous acetonitrile (90 g) added. The solution was cooled to 0°C, anhydrous triethylamine (85 g) added dropwise, and the mixture stirred one hour at 0°C and an additional hour at ambient temperature. The reaction mixture was filtered, concentrated, and neutralized with 1 M aqueous LiOH (660.6 g) solution. Thereafter, the water was removed, the residue washed twice with 250 ml diethyl ether, concentrated, and the product purified by re-dissolving in THF and passing through a short column of basic alumina. ¹H-NMR and elemental analysis data supplied.

Derivatives

**Nucleophiles Reacting with
Iminobis(sulfonyl chloride)****Sulfonylimide lithium****Notes**

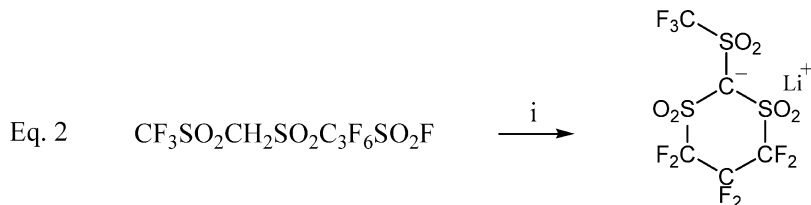
1. Imidobis(sulfonyl chloride) has previously been prepared and is described (1).
2. The preparation of bis(perfluoroalkylsulfonyl)imide and cyclic perfluoroalkylene disulfonylimide intermediates and salts is described (2).
3. Sulfonylimides have also been prepared by the direct condensation of an aromatic sulfonyl fluoride and a primary or secondary amine in the presence a tertiary amine and are described (2).
4. Methide electrolytic salts have also been prepared (3). This is illustrated in Eq. 1 and Eq. 2 for linear and cyclic salts, respectively.



i- Methylmagnesium chloride, trifluoromethylsulfonyl fluoride

ii- Potassium t-butoxide, trifluoromethylsulfonyl fluoride

iii- Lithium methoxide



i- Lithium di-isopropylamide

References

1. K. Walley, *Inorganic Synthesis*, Vol. VIII (1966) p. 105
2. F. Kita, US Patent 5,437,944 (August 1, 1995); W.M. Lamanna *et al*, US Patent 5,652,072 (July 29, 1997).
3. L.A. Dominey, US Patent 5,273,840 (December 28, 1993)

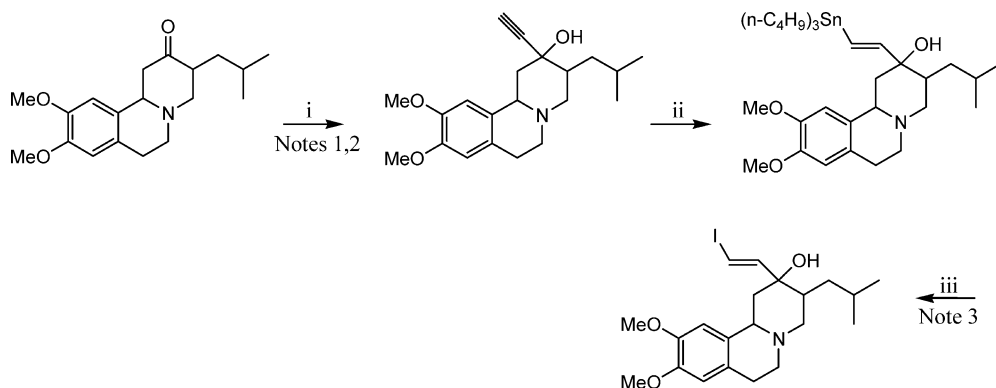
Tetrabenazine

Patent: Iodine Derivatives of Tetrabenazine
H.F. Kung, US Patent 5,278,308 (January 11, 1994)

Assignee: The Trustees of The University of Pennsylvania

Utility: Preparation of Monoamine Uptake Inhibitors and Radiolabeled Derivatives

Reaction



- i- Trimethylsilylacetylene, THF, n-butyl lithium, water,
ammonium chloride
- ii- Toluene, tri-n-butyltin hydride, azobisisobutyronitrile
- iii- Iodine, chloroform

Experimental

1. **2-Hydroxy-2-ethynyl-3-(2-methylpropyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolidizine**

To trimethylsilylacetylene (20.4 mmol) dissolved in 80 ml THF at -5°C was added *n*-butyl lithium (20.4 mmol) followed by the dropwise addition of 3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolidizin-2-one dissolved in 30 ml THF. The mixture was stirred at -5°C one hour, slowly warmed to 20°C , stirred 2 hours, and then quenched with NH_4Cl solution. THF was removed, the aqueous component extracted 3 times with 100 ml EtOAc, washed with water, brine, and concentrated. The residue was dissolved in 30 ml methyl alcohol containing 5 ml 5 M KOH, heated to 65°C 30 minutes, then cooled and quenched with NH_4Cl solution. The solution was concentrated, extracted 3 times with 50 ml EtOAc, washed, dried, and the product isolated in 53.7% yield as a slightly brown solid. Elemental analysis data supplied.

2. **2-(2-Tri-*n*-butyl)stannylethenyl)-2-hydroxy-3-(2-methylpropyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolidizine**

The product from Step 1 was dissolved in 50 ml toluene, tri-*n*-butyltin-hydride (9.7 mmol) added followed by azobisisobutyronitrile (30 mg). The mixture was heated to 95°C 5 hours, cooled, concentrated, purified by chromatography on silica gel using EtOAc/hexane, (1:1), and the product isolated in 60.8% yield as an oil. Elemental analysis data supplied.

3. **2-Hydroxy-2-iodovinyl-3-(2-methylpropyl)-9,10-dimethoxy-1,2,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolidizine**

The product from Step 2 (0.38 mmol) was dissolved in 15 ml chloroform at ambient temperature and 0.1 M iodine dissolved in chloroform added dropwise until a brown color persisted. Thereafter, the reaction was stirred 24 hours and then quenched with 2 ml 1 M KF dissolved in methyl alcohol and 2 ml 5% aqueous sodium bisulfite. The layers were separated, the aqueous layer extracted 3 times with 20 ml chloroform, washed, dried, concentrated, and the product isolated in 84.3% yield as a slightly yellow oil. Elemental analysis data supplied.

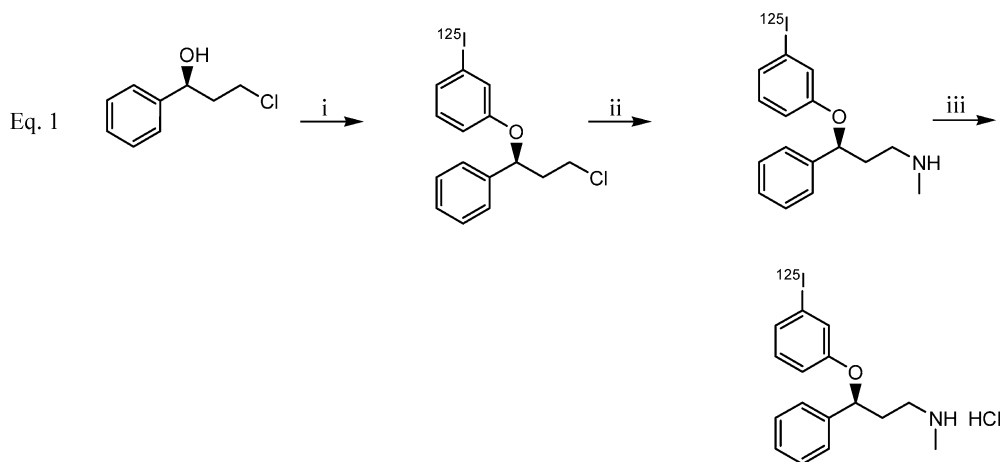
Notes

1. The preparation of benzo-[a]quinolidizines (1) and hexahydro-11bH-benzo[a] quinolidizines Step 1 reagents is described (2)
2. Optical isomers were separated by HPLC using a Chiracel OD Diacel chiral column using hexane/ethyl alcohol, 95:5 at 1 ml/min.
3. The ^{125}I radiolabeled counterpart of the product of Step 3 was also prepared by iodo-destannylation and is described below:

Procedure

The product from Step 2, hydrogen peroxide (1 mg/ml dissolved in ethyl alcohol), 200 μ l 0.1 N HCl, and 5 mCi Na¹²⁵I were combined in a sealed vial, reacted at ambient temperature 20 minutes, and the reaction terminated by addition of 0.1 ml sodium bisulfite (300 mg/ml). The mixture was neutralized with NaHCO₃, extracted 3 times with 1 ml EtOAc, and dried. The product was purified using HPLC on a reverse phase column (PRP-1, Hamilton) eluting with an isocratic solvent consisting of 90% acetonitrile-10% buffer (5 mmol 3,3'-dimethylglutaric acid, pH 7.0) at a flow rate of 1 ml/minute and the product isolated in 50% yield, purity > 98%). The radiolabeled compound was stable at room temperature for up to 15 hours.

4. In an earlier investigation by the author (3) prepared the radiolabeled agent [R]-(+)-1-chloro-3-phenyl-3-(3-¹²⁵I-iodophenoxy)propane hydrogen chloride was prepared as illustrated in Eq. 1:



- i- Triphenylphosphine, ethyl azodicarboxylate,
3-¹²⁵I-iodophenol, THF
ii- Methylamine, ethanol, water
iii- Hydrogen chloride, diethyl ether, CH₂Cl₂

References

1. R. Unger *et al*, US Patent 3,393,198 (July 16, 1968)
2. A. Brossi *et al*, US Patent 3,314,966 (April 18, 1967)
3. H.F. Kung, US Patent 5,320,825 (June 14, 1994)

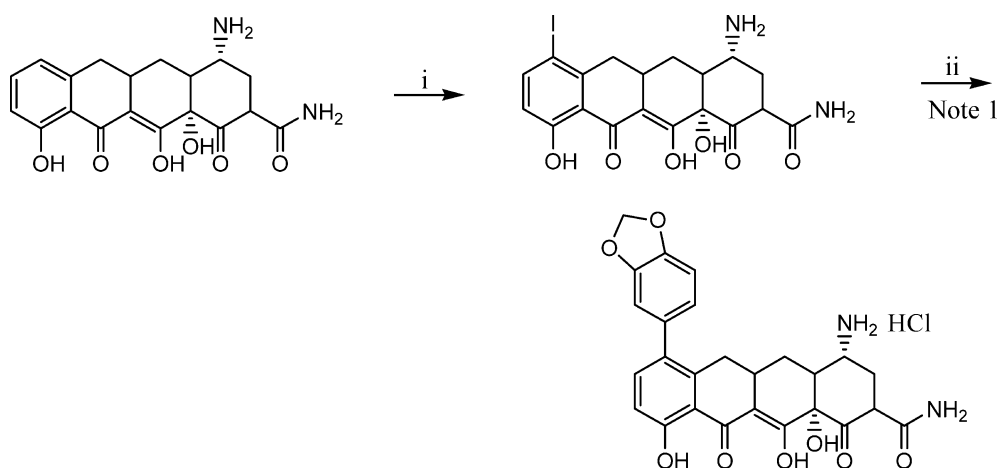
Tetracyclines

Patent: 7-Substituted Fused Ring Tetracycline Compounds
M.L. Nelson *et al*, US Patent 6,642,270 (November 4, 2003)

Assignee: Paratek Pharmaceuticals, Inc.

Utility: Antibiotic Compositions

Reaction



i- Trifluoroacetic acid, N-iodosuccinimide

ii- Palladium(II)acetate, methyl alcohol, sodium carbonate,
water, 3',4'-methylenedioxyphenyl boronic acid, hydrogen
chloride

Experimental

1. 7-Iodosancycline

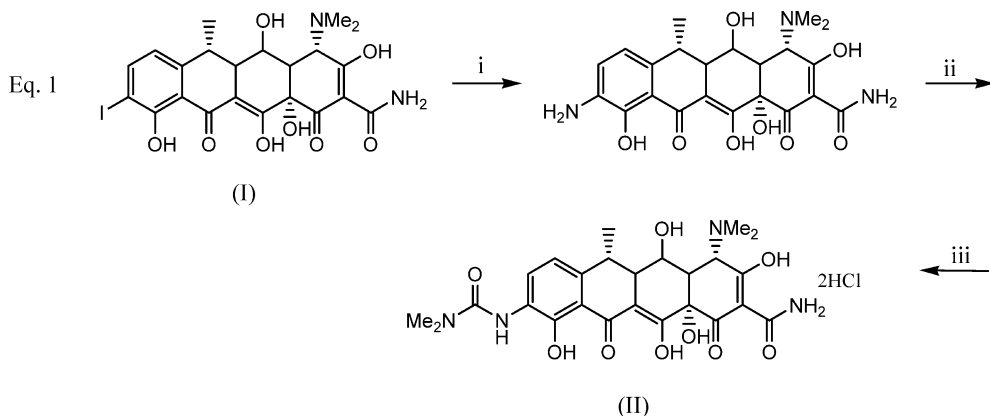
Sancycline (1 g) was dissolved in 25 ml trifluoroacetic acid, N-iodosuccinimide (1.2 eq) added, and the reaction stirred 40 minutes at 0°C and 5 hours at ambient temperature. The mixture was concentrated, dissolved in 3 ml methyl alcohol, and precipitated in diethyl ether. The product was purified by treating with activated charcoal, filtering through celite, and isolated in 75% yield. ¹H-NMR and MS data supplied.

2. 7-(3',4'-Methylenedioxyphenyl)sancycline hydrogen chloride

The product from Step 1 (0.3 mmol) was added to palladium(II)acetate (8.4 mg), 5 ml methyl alcohol, and Na₂CO₃ (3 eq) dissolved in 2 ml water. Thereafter 3',4'-methylenedioxyphenyl boronic acid (2 eq) dissolved in 5 ml methyl alcohol was added, the mixture reacted 2 hours, then concentrated in vacuo to produce the crude product. The mixture was purified by preparative HPLC using divinylbenzene as the solid phase with trifluoroacetic acid (0.1%)/acetonitrile with a gradient of 0–100% acetonitrile over 20 minutes. The fraction was removed, concentrated, the residue dissolved in methyl alcohol, and hydrogen chloride gas introduced. The salt was concentrated and the product isolated in 43% yield. ¹H-NMR and MS data supplied.

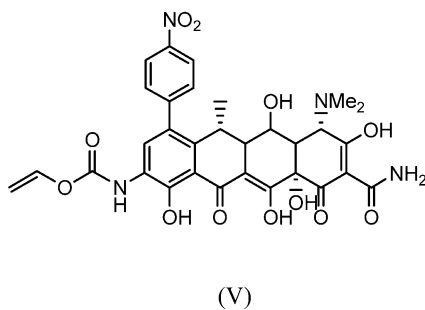
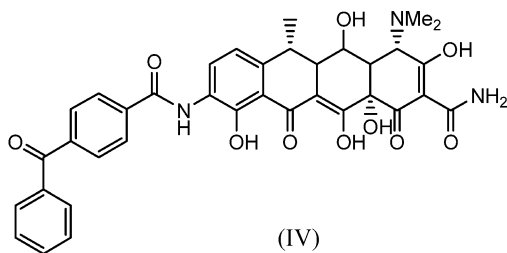
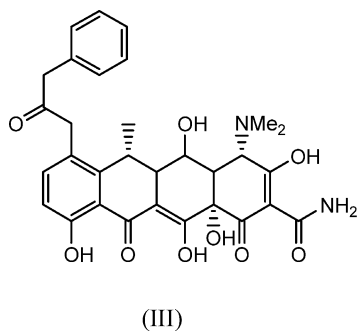
Notes

1. The coupling of 3',4'-methylenedioxyphenyl boronic acid to 7-iodosancycline in the presence of a palladium salt is an example of the Suzuki reaction and is described (1).
2. Beginning with 9-nitro-doxycycline sulfate, (I), 9-N,N-dimethylglycyl-amido-doxycycline dihydrochloride, (II), was prepared (2) as illustrated in Eq. 1:



- i- Platinum oxide, hydrochloric acid, methyl alcohol, hydrogen
- ii- 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, DMPU, acetonitrile, sodium carbonate, N,N-dimethyl-glycyl chloride hydrochloride

3. In subsequent investigations by the author 7-, 9-, and 7,9-substituted tetracycline derivatives, (III), (IV), (V), respectively, were prepared and are described (3).



References

1. A. Suzuki, *Pure Appl. Chem.*, 57, 1749 (1985) and A. Suzuki, *J. Am. Chem. Soc.*, 107, 972 (1985)
2. W-G. Su, US Patent 5,834,450 (November 10, 1998)
3. M.L. Nelson *et al*, US Patent 6,683,068 (January 27, 2004) and US Patent (November 16, 2004)

Tetrahydrobenzoquinoxaline Diones

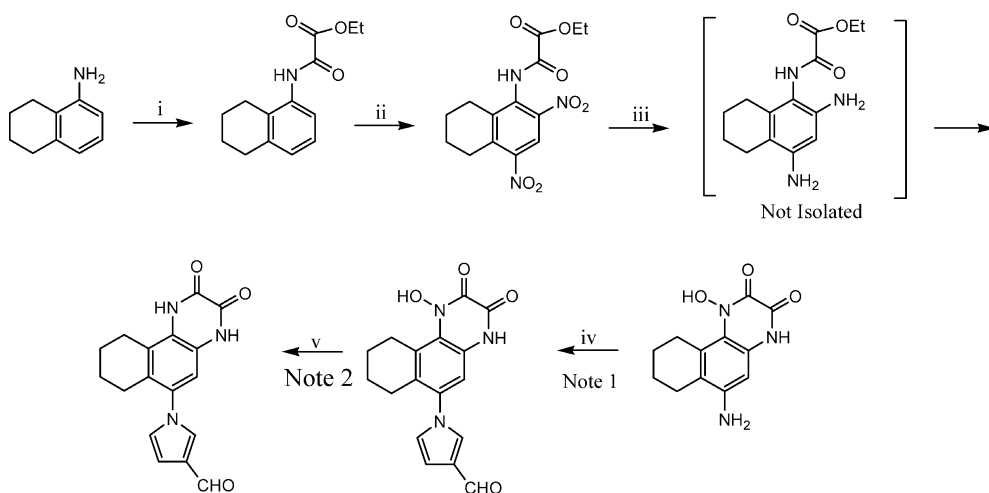
Patent: Pyrrolyl Tetrahydrobenzoquinoxaline Diones, Their Preparation and Use As Glutamate Receptor Antagonist

W. Lubisch *et al*, US Patent 5,849,744 (December 15, 1998)

Assignee: BASF Aktiengesellschaft

Utility: Treatment of Neurodegenerative Disorders

Reaction



i- Triethylamine, THF, ethyl oxalyl chloride

ii- Sulfuric acid, nitric acid

iii- THF, 10% palladium on carbon, hydrogen

iv- 2,5-dimethoxytetrahydrofuran-1-yl-carbaldehyde, acetic acid

v- Acetic acid, iron powder

Experimental

1. Ethyl 5,6,7,8-tetrahydro-1-naphthylloxamate

5,6,7,8-Tetrahydro-1-naphthylamine (0.68 mol) and triethylamine (1.36 mol) were dissolved in 1.5 L THF at 0 °C to 5 °C and ethyl oxalyl chloride (0.75 mol) added dropwise. The mixture stirred for 30 minutes, the precipitate filtered, and the filtrate concentrated. The residue was recrystallized in ethyl alcohol and the product isolated in 95% yield. ¹H-NMR data supplied.

2. Ethyl 2,4-dinitro-5,6,7,8-tetrahydro-1-naphthylloxamate

The product from Step 1 (0.64 mol) was dissolved in 1.5 L 18 M sulfuric acid, cooled to 10 °C, 83 ml 16 M nitric acid added dropwise, and the mixture stirred 30 minutes. Thereafter, the mixture was poured onto ice, the precipitate filtered, and the product isolated in 56% yield. ¹H-NMR data supplied.

3. 9-Amino-1-hydroxy-5,6,7,8-tetrahydrobenzo[f]quinoxaline-2,3-(1H,4H)-dione

The product from Step 2 (0.36 mol) was dissolved in 2 L THF and hydrogenated using 10% palladium on carbon (5 g). The mixture was filtered, the precipitate extracted by boiling with N,N-dimethyl-formamide, concentrated, the residue treated with ethanol, and the product isolated in 65% yield. ¹H-NMR data supplied.

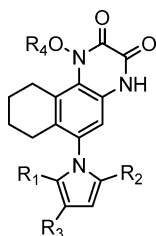
4. 9-(3-Formyl-1-pyrrolyl)-1-hydroxy-5,6,7,8-tetrahydrobenzo-[f]quinoxaline-2,3-(1H,4H)-dione

The product from Step 3 (9.7 mmol) and 2,5-dimethoxytetrahydrofuran-1-ylcarbaldehyde (9.7 mmol) were refluxed in 100 ml HOAc 30 minutes and concentrated. The residue was treated with ethyl alcohol and hot THF, filtered, and the product isolated in 74% yield, mp >250 °C. ¹H-NMR data supplied.

5. 9-(3-Formyl-1-pyrrolyl)-5,6,7,8-tetrahydrobenzo[f]quinoxaline-2,3(1H,4H)-dione

The product from Step 4 (1.5 mmol) was refluxed in 25 ml HOAc, iron powder (1.6 mmol) added in portions, and the mixture heated for 10 minutes. Thereafter, it was poured into water, the precipitate filtered, and the product isolated in 94% yield, mp >250 °C. ¹H-NMR data supplied.

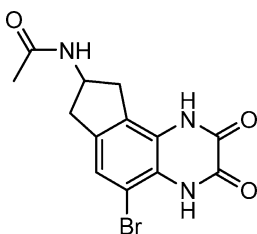
Derivatives



R ₁	R ₂	R ₃	R ₄	Melting Point (°C)
Hydrogen	Hydrogen	Aminomethyl	Hydrogen	>250
Hydrogen	Hydrogen	Trifluoroacetamide	Hydrogen	>230
Methyl	Methyl	Hydrogen	Benzyl	220 (dec)
Hydrogen	Hydrogen	Formyl	Ethoxycarbonylmethyl	>250
Hydrogen	Hydrogen	Trifluoroacetamidomethyl	Ethoxycarbonylmethyl	242–243
Hydrogen	Hydrogen	Methyl-N-(4-nitrophenyl)urea	Ethoxycarbonylmethyl	246

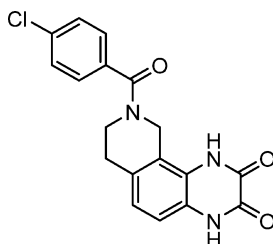
Notes

1. This is an example of the Paal-Knorr reaction and is discussed (1).
2. The cyclopentyl Step 5 analogue, N-(5-bromo-2,3-dioxo-2,3,4,7,8,9-hexahydro-1H-cyclopenta[f]quinoxalin-8-yl)acetamide, (I), has been prepared and is described (2).



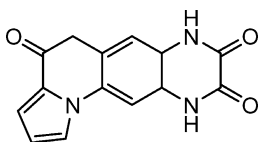
(I)

3. Another Step 5 analogue, 9-[(4-chlorophenyl)acetyl]-1,4,7,8,9,10-hexahydro-6-nitropyrido[3,4-f]quinoxaline-2,3-dione, (II), has also been prepared and is discussed (3).



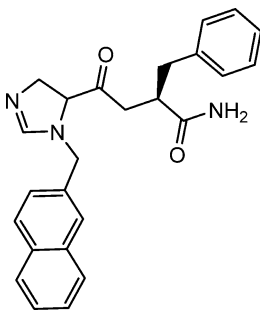
(II)

4. In a subsequent investigation by the author (4), 7,8(6H,9H)-dioxo-pyrazino[5,6-g]pyrrolo[1,2-c]quinoxalin-2(4H)-one, (III), and other 2,3(1H,4H)-quinoxalinediones derivatives were prepared and are described.



(III)

5. Imidazole, (IV), thiazole, pyrimidine, and pyridine amide derivatives were also prepared by the author in a subsequent investigation and are described (5).



(IV)

References

1. H.H. Wasserman, *Tetrahedron*, 32, 1863 (1976); A. Gossauer, *Synthesis*, 1336 (1996)
2. C.F. Bigge *et al*, US Patent 5,721,234 (February 24, 1998)
3. C.F. Bigge *et al*, US Patent 6,197,771 (March 6, 2001)
4. W. Lubisch *et al*, US Patent 5,852,017 (December 22, 1998)
5. W. Lubisch *et al*, US Patent 6,630,493 (October 7, 2003)

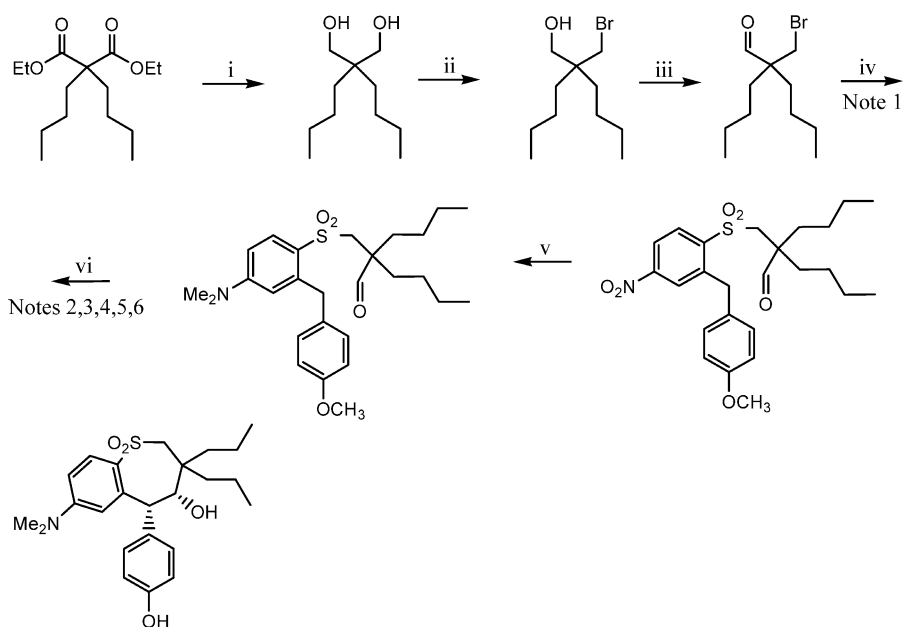
Tetrahydrobenzothiepines

Patent: Method for the Preparation of Tetrahydrobenzothiepines
K.A. Babiak *et al*, US Patent 6,586,434 (July 1, 2003)

Assignee: G.D. Searle, LLC

Utility: Ileal Bile Acid Transporter for Lowering Blood Serum Cholesterol

Reaction



- i- Lithium aluminum hydride, THF
- ii- Hydrobromic acid, acetic acid, ethyl alcohol, sulfuric acid
- iii- Triethylamine, sulfur trioxide · pyridine, dimethyl-sulfoxide
- iv- 1-Chloro-2-(4-methoxyphenyl)methyl-4-nitrobenzene, dimethylacetamide, sodium sulfide, benzonitrile, trimethyl orthoformate, p-toluenesulfonic acid, sodium acetate, peracetic acid
- v- Palladium on carbon, ethyl alcohol, formaldehyde, sulfuric acid, hydrogen
- vi- Potassium t-butoxide, THF

Experimental

1. 2,2-Dibutyl-1,3-propanediol

Lithium aluminum hydride (0.66 mol) in 662 ml THF was added dropwise to dibutyl-diethylmalonate (0.55 mol) dissolved in 700 ml THF while maintaining the temperature between -20 and 0°C and the mixture stirred overnight at ambient temperature. The reaction was re-cooled to -20°C and 40 ml water, 80 ml 10% NaOH, and 80 ml of water were successively added. The mixture was filtered, the filtrate dried, concentrated, and the product isolated in 95% yield.

2. 1-Bromo-2-butyl-2-(hydroxymethyl)hexane

To the product from Step 1 (20 g) was added 30% hydrobromic acid (57 g) in acetic acid. The mixture was heated to 80°C 4 hours and then concentrated. Thereafter, the mixture was re-heated to 80°C , 100 ml ethyl alcohol and 1.0 ml H_2SO_4 added, refluxed 2 hours, and then re-concentrated. The residue was dissolved in 100 ml apiece EtOAc and 2.5 M NaOH, agitated 15 minutes, and the aqueous layer removed. An additional 100 ml water was added and the above process repeated. The aqueous layer was separated, the solvent distilled off at 125°C , concentrated, and the product isolated in 96% yield.

3. 2-(Bromomethyl)-2-butylhexanal

To the product from Step 2 (26.0 g) containing with triethylamine (15.6 g) was added sulfur trioxide · pyridine (37.6 g) slurried in 50 ml of DMSO over 15 minutes at 22°C . Thereafter, 100 ml 2.5 M HCl was added, the mixture stirred 15 minutes, 100 ml EtOAc added, and the mixture again stirred 15 minutes. The aqueous layer was separated, concentrated, and the product isolated in 95% yield.

4. 1-(2,2-Dibutyl-S,S-dioxido-3-oxopropylthio)-2-((4-methoxyphenyl)methyl)-4-nitrobenzene

Dimethylacetamide (315.0 g) was heated to 30°C and 1-chloro-2-(4-methoxyphenyl)methyl-4-nitrobenzene (75 g) and Na_2S (39.2 g) dissolved in 90 ml water added over 25 minutes. The mixture was heated to 40°C 2 hours and the product from Step 3 (77.90 g)

added. Thereafter the mixture was heated to 65 °C 2 hours and 315 ml benzotrifluoride and 270 ml water added. The mixture was distilled at 63 °C at 195 mm Hg and 87 g apiece trimethyl orthoformate and p-toluenesulfonic acid dissolved in 164.1 ml methyl alcohol added to the residue. The mixture refluxed at 65 °C 2 hours and was again distilled as above, cooled to 15 °C, and 252 ml benzotrifluoride, NaOAc (22.2 g) in 30 ml water and 35% peracetic acid (256.7 g) added. After the initial exotherm, the mixture was heated to 30 °C for 3 hours. The organic layer was washed with 315 ml 6% Na₂SO₃, 40% H₂SO₄, heated to 75 °C two hours, 315 ml NaHCO₃ solution added, and the mixture distilled. The residue was recrystallized by dissolving in 600 ml isopropyl alcohol at 50 °C, cooling to 38 °C for one hour, further cooling to 15 °C for 30 minutes, and the product isolated in 79.4% yield.

5. 1-(2,2-Dibutyl-dioxido-3-oxopropylthio)-2-((4-methoxyphenyl)methyl)-4-dimethylaminobenzene

A mixture of the product from Step 4 (2.5 g), palladium on carbon (2.5 g), ethyl alcohol (60 g), formaldehyde (10 g, 36% aqueous solution), and H₂SO₄ (0.55 g) was hydrogenated at 60 psig at 22 °C. Thereafter, the mixture was filtered, and the product isolated in 89% yield.

6. (4R,5R)-3,3-Dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine

To potassium t-butoxide (45g) dissolved in THF was added the product from Step 5 dissolved in 45 ml THF over 2 hours and the reaction stirred at 20 °C 1 hour. The reaction was quenched with NH₄Cl and the phases separated. Crystallization occurred by treating the organic layer with 50 ml water and isopropyl alcohol (25 g). Thereafter, THF was removed by distillation and a slurry isolated. The slurry was filtered, washed with water/isopropyl alcohol, 2:1, solution, and 16.7 g of R,R and S,S isomers isolated.

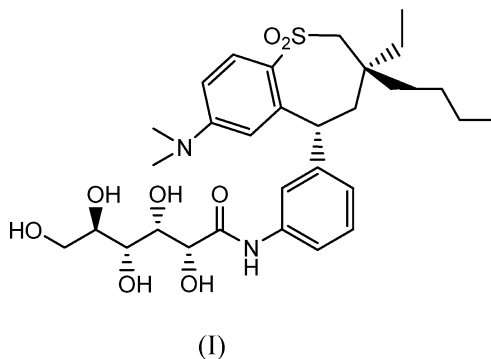
Notes

1. The preparation of 1-chloro-2-(4-methoxyphenyl)methyl-4-nitro-benzene is described by the author in the current invention.
2. Conditions used to separate (4R,5R) and (4S,5S) enantiomers were:

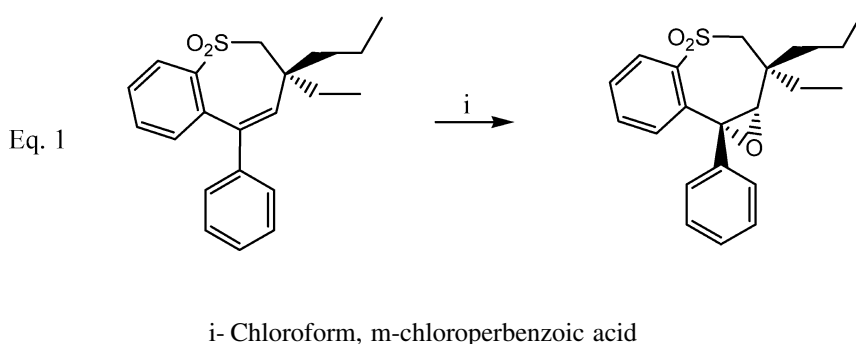
Column (CSP):	Di-methyl phenyl derivative of tartaric acid (Kromasil DMB)
Mobile Phase:	Toluene (100%)
Column Length:	6.5 cm
Column I.D.:	2.12 cm
Number of Columns:	8 columns
Zones:	2-3-2-1
Feed Concentration:	64 weight percent
Eluent Flowrate:	20.3 g/minute

Feed Flowrate: 0.5 g/minute
 Extract Flowrate: 4.9 g/minute
 Raffinate Flowrate: 15.9 g/minute
 Period: 8 minute
 Temperature: Ambient

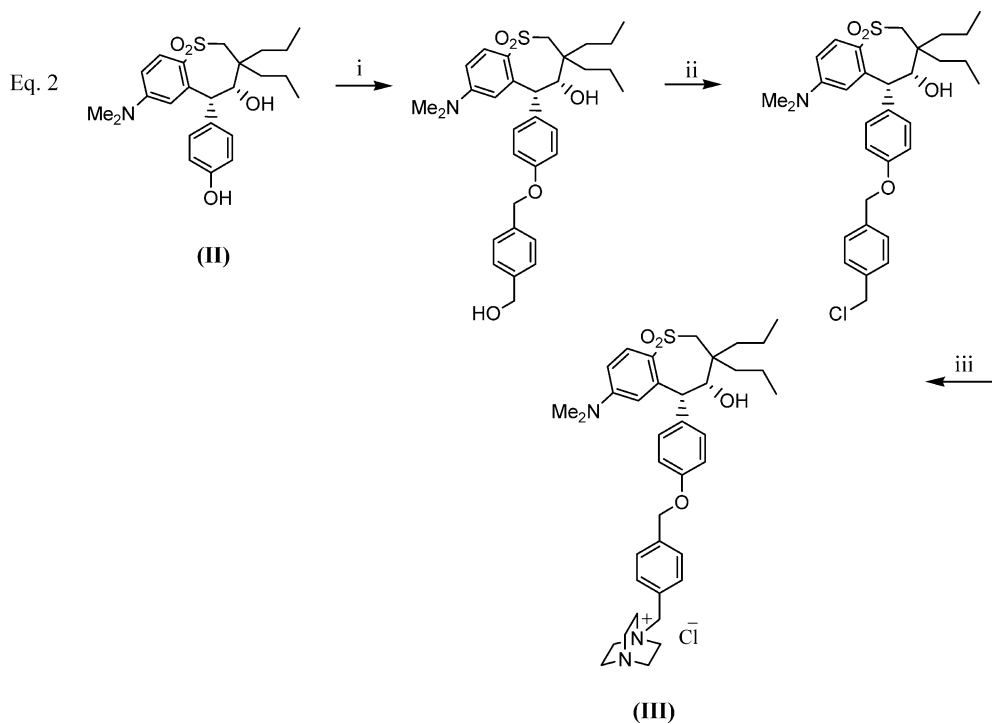
3. Step 6 analogues of the current invention are described (1).
4. The preparation of 3-amido-benzothiepine Step 6 derivatives is described, (I), (2).



5. The epoxide derivative of the current investigation was previously prepared (3) as illustrated in Eq. 1:



6. The product of Step 6, (II), was subsequently converted into (4R,5R)-1-((4-(4-(3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl)phenoxy)methyl)phenyl)-methyl-4-aza-1-azabicyclo[2.2.2]octane chloride, (III), as illustrated in Eq. 2 and is described 4.



- i- N,N-Dimethylacetamide, sodium hydroxide,
1-(chloromethyl)-4-(hydroxymethyl)benzene
ii- Thionyl chloride, toluene
iii- Methyl ethyl ketone, diazabicyclo[2.2.2]octane

References

1. L.F. Lee *et al*, US Patent 5,994,391 (November 30, 1999)
2. W. Frick *et al*, US Patent 6,221,897 (April 24, 2001)
3. T. Yasuma *et al*, US Patent 6,355,672 (March 12, 2002)
4. L.F. Lee *et al*, US Patent 6,387,924 (May 14, 2002)

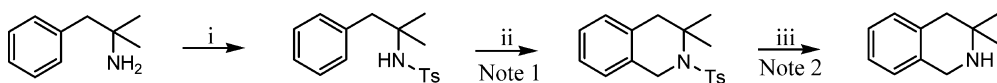
Tetrahydroisoquinolines

Patent: Pictet-Spengler Reaction for the Synthesis of Tetrahydroisoquinolines and Related Heterocyclic Compounds
T.J.-N. Watson, US Patent 5,808,071 (September 15, 1998)

Assignee: Hoechst Marion Roussell, Inc.

Utility: Free Radical Trapping Agents

Reaction



i- CH_2Cl_2 , triethylamine, 4-toluenesulfonyl chloride
ii- Dimethoxymethane, borontrifluoride etherate
iii- Naphthalene, dimethoxyethane, sodium

Experimental

1. N-Toluenesulfonyl-1,1-dimethyl-2-phenylethylamine

A solution of 1,1-dimethyl-2-phenylethylamine (0.019 mol) and 8.01 ml triethylamine dissolved in 20 ml CH_2Cl_2 were added to 4-toluenesulfonyl chloride (0.023 mol) and the mixture stirred at ambient temperature 12 hours. Thereafter, the reaction mixture was partitioned between 100 ml apiece CH_2Cl_2 and water, the organic layer separated, dried, concentrated, and the product isolated in 99% yield. ^1H - and ^{13}C -NMR, IR, MS, and elemental analysis data supplied.

2. N-Toluenesulfonyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline

The product from Step 1 (0.027 mol) was dissolved in 50 ml dimethoxymethane and added to boron trifluoride etherate (0.081 mol). The mixture stirred at ambient temperature

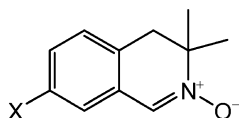
12 hours and was then partitioned between 100 ml apiece EtOAc and water. The organic layer was washed, dried, concentrated at 40°C at 50 torr, and the product isolated in 99% yield. ^1H - and ^{13}C -NMR, IR, MS and elemental analysis data supplied.

3. 3,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline

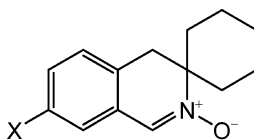
To a stirred solution of naphthalene (0.045 mol) dissolved in 50 ml dimethoxyethane was added sodium metal (0.039 mol) and the mixture stirred 4 hours until a dark green color persisted. The product from Step 2 (0.016 mol) dissolved in 20 ml dimethoxymethane was added, the reaction stirred 2 hours, and then quenched with saturated 70 ml brine. The mixture was partitioned between 250 ml apiece EtOAc and 10% HCl, the organic layer discarded, and 10% NaOH added to the aqueous layer until pH 7 obtained. The aqueous layer was extracted twice with 100 ml CH_2Cl_2 , dried, filtered, concentrated at 25°C at 150 torr, and the product isolated in 86% yield. ^1H - and ^{13}C -NMR, IR, MS and elemental analysis data supplied.

Notes

1. N-Hydroxymethylation occurs upon the catalytic decomposition of dimethoxymethane generating formaldehyde followed by Picket-Spengler cyclization forming the tetrahydroisoquinoline. A review of the Pictet-Spengler synthesis in the preparation of tetrahydroiso-quinolines is provided (1).
2. The preparation of 1,2,3,4-tetrahydroisoquinolines from N-sulfonylphenethylamines and aldehydes is described (2).
3. 7-Substituted-3,3-dimethyl-3,4-dihydroisoquinoline-N-oxide (I) and spiro[cyclohexane-1,3']-3,4-dihydroisoquinoline-N-oxide (II) derivatives have been prepared and are described (3).



(I)



(II)

X = F, Cl, OCH_3

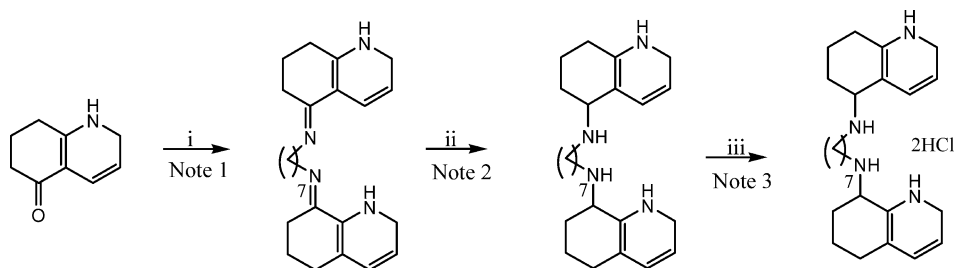
References

1. W.M. Whaley *et al*, *Org. React.*, 3, 151 (1951)
2. C. Ito, *et al*, *Chem. Pharm. Bull.*, 25, 7, 1732 (1977)
3. A.A. Carr, US Patent 5,292,746 (March 8, 1994)

Tetrahydroquinolines

Patent: Dimeric Compounds
P.R. Carlier *et al*, US Patent 6,472,408 (October 29, 2002)
Assignee: The Hong Kong University of Science and Technology
Utility: Treatment of Alzheimer's Disease

Reaction



- i- Benzene, 1,7-diaminoheptane, acetic acid
- ii- Methyl alcohol, sodium borohydride
- iii- Methyl alcohol, ethyl acetate, hydrochloric acid

Experimental

1. *rac*-/meso-*N,N'*-Di-5'-(5',6',7',8'-Tetrahydroquinolin-2-onyl)-1,7-heptanediimine

5,6,7,8-Tetrahydro-5-oxo-2(1H)-quinolinone (4.0 mmol), 1,7-diaminoheptane (2.0 mmol) and 5 drops of HOAc dissolved in 50 ml benzene were refluxed with azeotropic removal of water for 24 hours. The solution was cooled, concentrated, and the Schiff base used directly in Step 2.

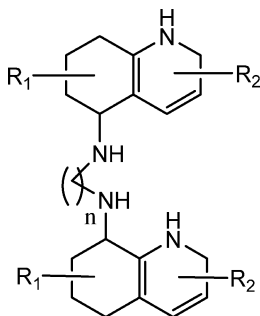
2. **rac-/meso-N',N'-Di-5'-(5',6',7',8'-Tetrahydroquinolin-2-onyl)-1,7-diaminoheptane**

The product from Step 1 was ground to a fine powder, suspended in 50 ml methyl alcohol, NaBH_4 (7.6 mmol) in methyl alcohol added dropwise, and the mixture stirred at ambient temperature 12 hours. The precipitate that formed was filtered and washed with methyl alcohol and water. The filtrate was concentrated, purified by passing through a silica plug using methyl alcohol/ NH_4OH , 50:1, from which additional material was obtained, and the product isolated in 50% yield, mp = 218–219°C. ^1H - and ^{13}C -NMR and MS data supplied.

3. **rac-/meso-N',N'-Di-5'-(5',6',7',8'-Tetrahydroquinolin-2-onyl)-1,7-diaminoheptane hydrogen chloride**

The product from Step 2 (200 mg) was dissolved in 10 ml methanolic HCl containing EtOAc and remained undisturbed for several days at ambient temperature. It was filtered, concentrated, and the product isolated in 67% yield, mp = 189–191°C (dec.). ^1H -NMR, HPLC, elemental analysis data supplied.

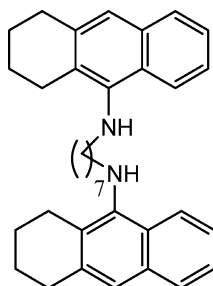
Derivatives



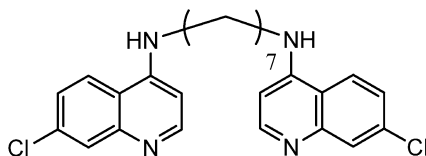
R_1	R_2	n	Salt	Melting Point ($^{\circ}\text{C}$)
7-Methyl	Hydrogen	7	Fumarate	161.5–163
Hydrogen	1-Methyl	10	Fumarate	156–157
5-Benzyl	2-Benzoxo	10	none	Oil

Notes

1. The preparation of the Step 1 reagent and derivatives is described (1)
2. 1,7-n-Heptylene-bis-9'-amino-1,2,3,4-tetrahydroacridine, (I), (2) and bis-(7-chloroquinolin-4-yl)heptane-1,7-diamine derivatives, (II), (3) have been prepared and are discussed.

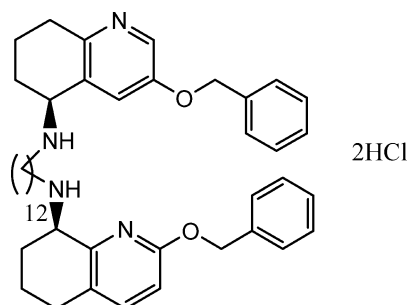


(I)



(II)

3. Beginning with 2-benzyloxy-5,6,7,8-tetrahydro-5-quinolinamine, (S,S)-(-)-N,N'-di-5'-(5',6',7',8'-tetrahydroquinolin-2-onyl)-1,12-diaminododecane hydrogen chloride, (III), was prepared by the author in the current invention and is described.



(III)

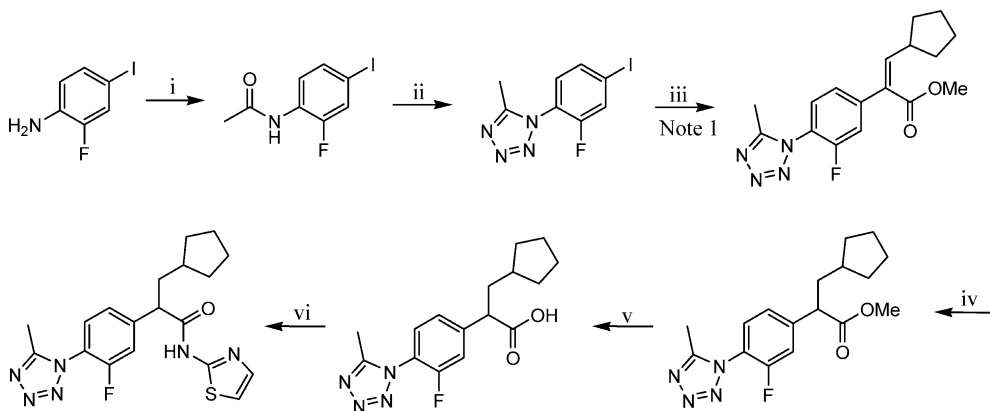
References

1. R.C. Effland *et al*, US Patent 5,110,815 (May 5, 1992)
2. Y.-P. Pang, US Patent 5,886,007 (March 23, 1999)
3. J.L. Vennerstrom, US Patent 5,510,356 (April 23, 1996)

Tetrazoles

Patent: Tetrazolyl-Phenyl Actamide Glucokinase Activators
A. Sidduri, US Patent 6,441,180 (August 27, 2002)
Assignee: Hoffmann-La Roche Inc.
Utility: Treatment for Type II Diabetes Disorder

Reaction



- i- THF, acetic anhydride
- ii- Acetonitrile, sodium azide, trifluoromethanesulfonic anhydride
- iii- Zinc dust, THF, 1,2-dibromoethane, trimethylsilyl chloride, bis(dibenzylideneacetone)palladium, triphenylphosphine, (E)-cyclopentyl-2-iodo-acrylic acid methyl ester
- iv- Nickel(II)chloride hexahydrate, methyl alcohol, sodium borohydride

- v- Ethyl alcohol, sodium hydroxide
- vi- Triphenylphosphine, CH_2Cl_2 , N-bromosuccinimide, 2-aminothiazole

Experimental

1. N-(2-Fluoro-4-iodophenyl)acetamide

A solution of 2-fluoro-4-iodoaniline (20 mmol) in 20 ml THF was cooled to 0 °C, treated with acetic anhydride (80 mmol), and stirred at 0 °C for 10 min and then for 2 hours at ambient temperature. The mixture was concentrated, the residue precipitated using 50 ml apiece diethyl ether and hexanes, and the product isolated in 92% yield, mp = 152–154 °C. Elemental analysis and MS data supplied.

2. 1-(2-Fluoro-4-iodophenyl)-5-methyl-1H-tetrazole

The product from Step 1 (18.24 mmol) was dissolved in 100 ml acetonitrile, cooled to 0 °C, and NaN_3 (54.7 mmol) and trifluoromethanesulfonic anhydride (48 mmol) added. The mixture was warmed to 25 °C, stirred overnight, concentrated, and treated with 100 ml apiece EtOAc and water. The organic extracts were washed with brine, dried, and concentrated. The product was purified by flash chromatography on silica gel using hexanes/EtOAc, and the product isolated in 62% yield, mp = 122–124 °C. Elemental analysis and MS data supplied.

3. (E)-3-Cyclopentyl-2-[3-fluoro-4-(5-methyl-tetrazol-1-yl)-phenyl]-acrylic acid methyl ester

In the first vessel, zinc dust (10 mmol) was activated by adding it to 1 ml THF and 1,2-dibromoethane (1 mmol), and heating to boiling and cooling; the process repeated 3 times. Trimethylsilyl chloride (1 mmol) was added followed by the addition of (E)-cyclopentyl-2-iodo-acrylic acid methyl ester (7.5 mmol) dissolved in 3 ml THF over 3 minutes. The mixture was stirred at 40–45 °C for 1 hour, overnight at ambient temperature, and then 5 ml THF added. In a second vessel, bis(dibenzylidene-acetone)palladium(0) (0.16 mmol) and triphenylphosphine (0.6 mmol) were added to 10 ml THF at ambient temperature and stirred for 10 minutes. The contents of the second vessel were then added to the product from Step 2 followed by the contents of the first vessel. Thereafter the mixture was heated to 40–45 °C for 4 hours then stirred at ambient temperature 48 hours. The reaction was quenched by pouring into 50 ml NH_4Cl , extracted with EtOAc, washed with brine, dried, and concentrated. The product was purified by flash chromatography on silica gel using hexanes/EtOAc, 4:1 to 1:1, and isolated in 62% yield, mp = 111–114 °C. Elemental analysis and MS data supplied.

4. (racemic) 3-Cyclopentyl-2-[3-fluoro-4-(5-methyl-tetrazol-1-yl)-phenyl]propionic acid methyl ester

To a solution of nickel (II) chloride hexahydrate (0.24 mmol) and the product from Step 3 dissolved in 10 ml methyl alcohol was added NaBH_4 (3.63 mmol) in two portions. The

mixture was stirred at 0°C for 15 minutes and 25°C for 15 hours, concentrated, and the residue treated with 30 ml 3 M HCl and 50 ml EtOAc. The organic phase was washed with brine, dried, and the product isolated as an oil in 99% yield. Elemental analysis and MS data supplied.

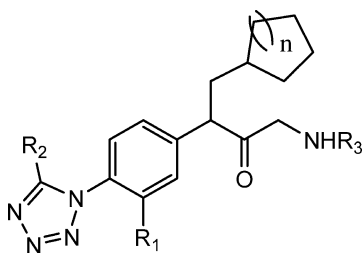
5. (racemic) 3-Cyclopentyl-2-[3-fluoro-4-(5-methyl-tetrazol-1-yl)-phenyl]-propionic acid

The product from Step 4 (1.2 mmol) was dissolved in 8 ml ethyl alcohol, treated with 2.5 ml 1 M NaOH, and heated to 45–50°C 5 hours. The mixture was concentrated, diluted with 40 ml water, and extracted with 50 ml diethyl ether. The aqueous layer was acidified with 1 M HCl, extracted with EtOAc, combined, purified as described in Step 3, and the product isolated in 94% yield. Elemental analysis and MS data supplied.

6. (racemic) 3-Cyclopentyl-2-[3-fluoro-4-(5-methyl-tetrazol-1-yl)-phenyl]-N-thiazol-2-yl-propionamide

A solution of triphenylphosphine (1.1 mmol) dissolved in 6 ml CH₂Cl₂ was cooled to 0°C, N-bromosuccinimide (1.1 mmol) added, stirred 30 minutes, and the product from Step 5 added (0.55 mmol). The solution was stirred 15 minutes, warmed to 25°C, and stirred an additional 90 minutes. The mixture was then treated with 2-aminothiazole (2.75 mmol), stirred 48 hours, and concentrated. The residue was treated with 50 ml EtOAc, 25 ml 1 M HCl, and the layers separated. The aqueous layer was extracted with EtOAc, organics combined, washed with 50 ml apiece 1 M HCl, NaHCO₃ solution and brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc, 2:1, and the product isolated in 36% yield. Elemental analysis and MS data supplied.

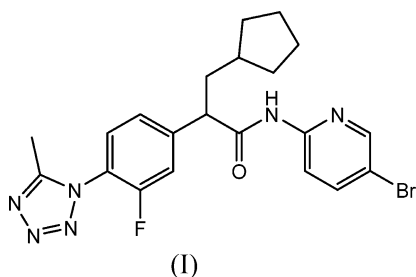
Derivatives



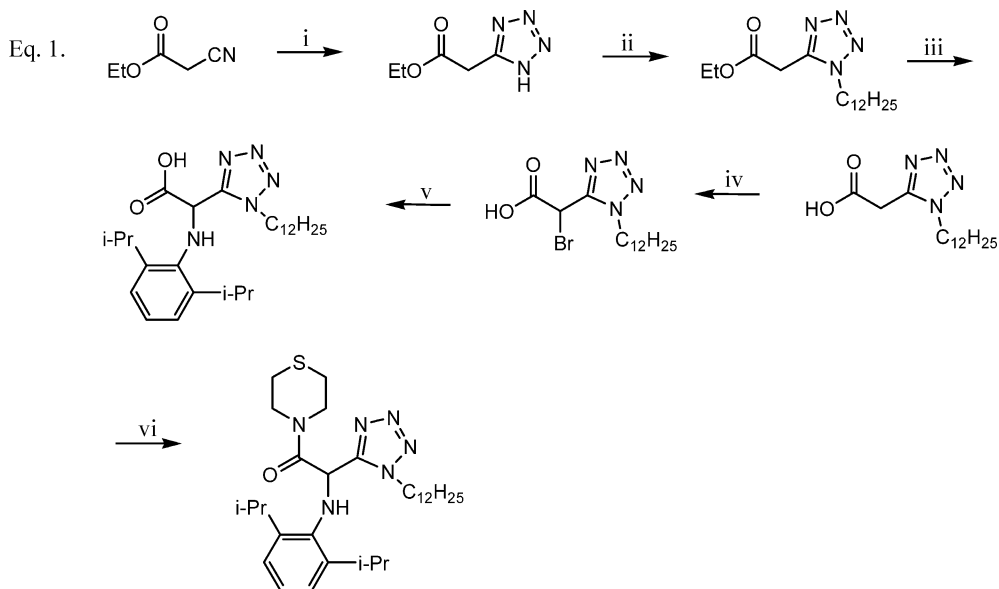
R ₁	R ₂	R ₃	n	MS
Fluoro	Methyl	5-Bromo-pyridin-2-yl	1	472
Chloro	Methyl	5-Methyl-tetrazol-1-yl	2	430
Chloro	Trifluoromethyl	5-Methyl-tetrazol-1-yl	2	484
Trifluoromethyl	Methyl	5-Bromo-pyridin-2-yl	1	522

Notes

1. The preparation of the Step 3 reagent, (Z)-cyclopentyl-2-iodo-acrylic acid methyl ester, is described by the author.
2. The Step 6 pyridine derivative of the current invention, N-(5-bromo-pyridin-2-yl)-3-cyclopentyl-2-[3-fluoro-4-(5-methyl-tetrazol-1-yl)-phenyl]-propionamide, (I), was prepared by the author in a previous investigation (1).



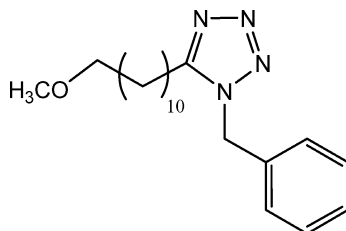
3. An alternative method for preparing Step 6 analogues of the current invention were also prepared as illustrated in Eq. 1 and described (2).



- i- Ethyl cyanoacetate, α -tributyltin azide, p-dioxane
 ii- Acetonitrile, triethylamine, 1-bromododecane
 iii- Ethyl alcohol, sodium hydroxide

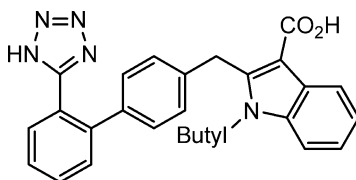
- iv- Carbon tetrachloride, bromine
- v- 2,6-Diisopropylaniline, dicyclohexylcarbodiimide
- vi- Thiomorpholine, THF

4. The fatty acid tetrazole, 5-(11-methoxyundecyl)-1-(phenylmethyl)-1H-tetrazole, (II), and derivatives have been prepared and is discussed (3).



(II)

5. In an earlier investigation (4) 1-butyl-2-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-indole-3-carboxylic acid, (III), and derivatives were prepared.



(II)

References

1. A. Sidduri, US Patent 6,369,232 (April 9, 2002)
2. P.M. O'Brien *et al*, US Patent 5,461,049 (October 24, 1995)
3. S.T. Nugent *et al*, US Patent 5,929,110 (July 27, 1999)
4. L.E. Fisher *et al*, US Patent 5,468,867 (November 21, 1995)

Thiazoles

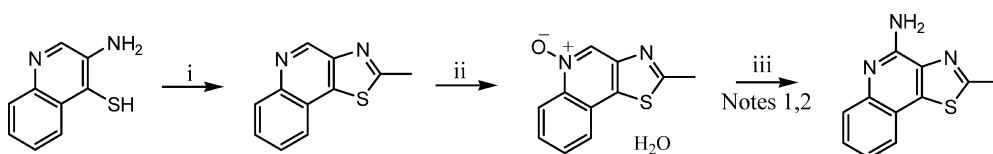
Patent: Oxazolo, Thiazolo and Selenazolo [4,5-c]-Quinolin-4-Amines and Analogues Thereof

J.F. Gerster *et al*, US Patent 6,440,992 (August 27, 2002)

Assignee: 3M Innovative Properties Company

Utility: Treatment of Viral and Neoplastic Diseases

Reaction



i- Acetic anhydride, acetic acid

ii- 3-Chloroperbenzoic acid, CH_2Cl_2

iii- CH_2Cl_2 , ammonium hydroxide, tosyl chloride

Experimental

1. 2-Methylthiazolo[4,5-c]quinoline

A suspension of 3-aminoquinoline-4-thiol (12 g) in 150 ml acetic anhydride and 300 ml acetic acid was refluxed overnight, filtered, and concentrated. The residue was diluted with ethyl alcohol, refluxed 30 minutes, concentrated, and diluted with water. The aqueous residue was made basic with NaOH, extracted with diethyl ether, extracts combined, dried, filtered, and concentrated. The product was isolated after recrystallization in hexane, mp = 95.5–97.5°C. Elemental analysis data supplied.

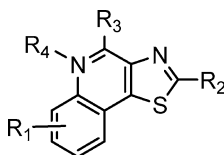
2. 2-Methylthiazolo[4,5-c]quinoline-5-N-oxide hydrate

The product from Step 1 (25 mmol), 3-chloroperbenzoic acid (9.5 g, 50–60%) and 150 ml CH_2Cl_2 were stirred together at ambient temperature 3 hours. Thereafter, 300 ml CH_2Cl_2 was added and the mixture extracted with Na_2CO_3 solution to remove acids. The organic layer was washed, diluted with EtOAc, dried, and concentrated. It was recrystallized from methyl alcohol and the product isolated, mp = 150–160°C. Elemental analysis data supplied.

3. 2-Methylthiazolo[4,5-c]quinoline-4-amine

The product from Step 2 (6.9 mmol) was added to 10 ml CH_2Cl_2 and 25 ml NH_4OH , tosyl chloride (10.4 mmol) dissolved in 10 ml CH_2Cl_2 added, and the reaction refluxed while being monitored by thin layer chromatography. Thereafter the mixture was concentrated, washed with water, dried, dissolved in HCl, and treated with charcoal. The product was precipitated using dilute NaOH, washed with water, dried, and isolated after recrystallization using methyl alcohol/ CH_2Cl_2 , mp = 184–187°C. Elemental analysis data supplied.

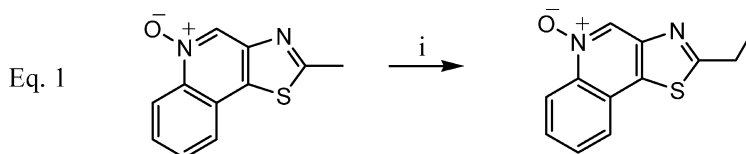
Derivatives



R_1	R_2	R_3	R_4	Melting Point (°C)
Hydrogen	Ethyl	Amine	none	175–178
7-Fluoro	n-Butyl	Amine	none	187–188
Hydrogen	n-Butyl	Hydrogen	Oxide	120–121
7-Fluoro	n-Propyl	Amine	none	184–187

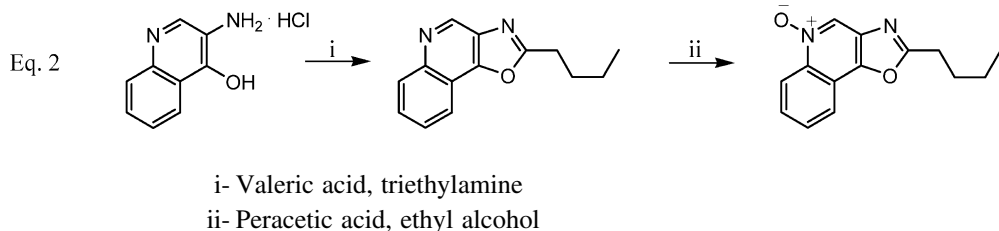
Notes

- Using the anhydrous product from Step 2, a method for extending the 2-position methyl chain length was provided by the author as illustrated in Eq. 1:

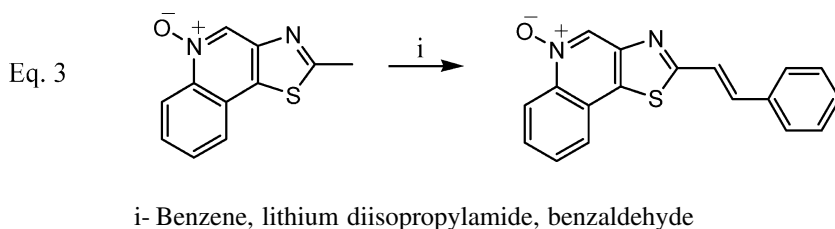


i- THF, lithium diisopropylamide, methyl iodide

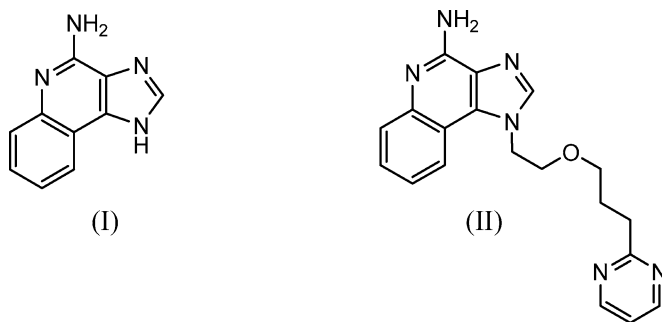
2. Step 1 oxazole and Step 2 N-oxide analogues were also prepared by the author as illustrated in Eq. 2:



3. In a subsequent investigation by the author (1) unsaturated Step 2 derivatives were prepared as illustrated in Eq. 3 for 2- β -styrylthiazolo-[4,5-c]quinoline-5-N-oxide.



4. Both 1H-imidazo[4,5-c]quinoline-4-amine, (I), (2), and 4-heterocyclic ether derivatives (II), (3), derivatives have also been prepared.

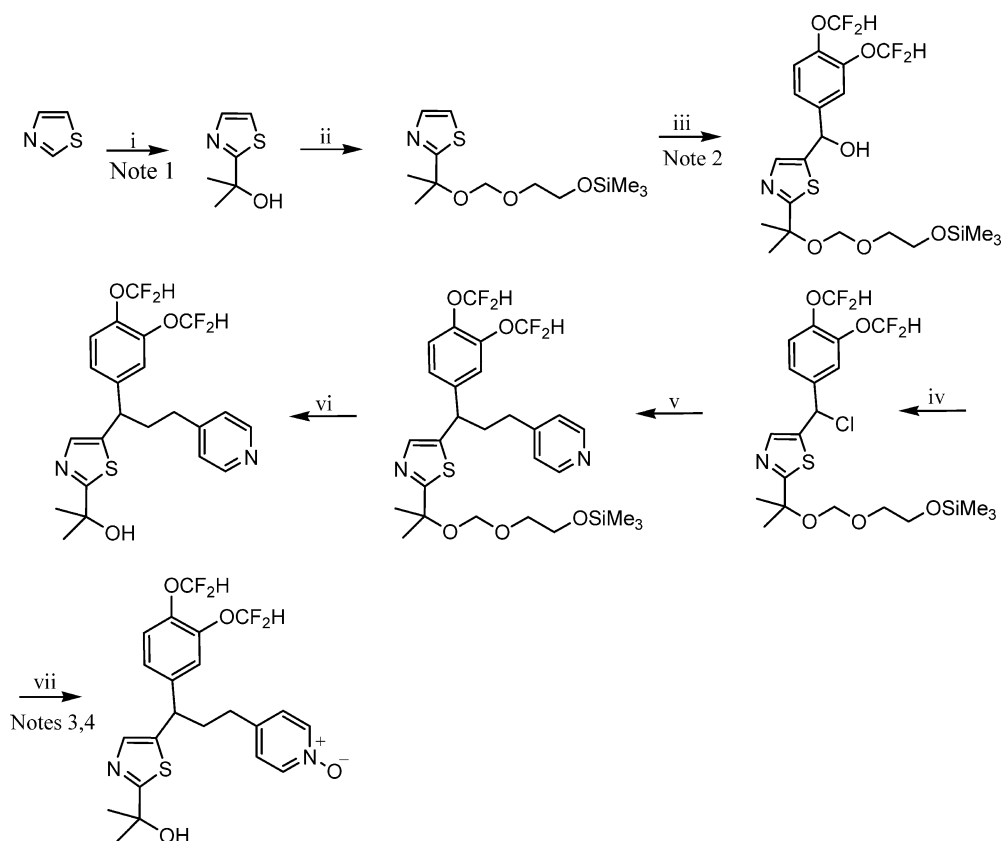


References

1. J.F. Gerster *et al*, US Patent 6,703,402 (May 9, 2004)
2. N. Nikolaides *et al*, US Patent 5,395,937 (March 7, 1995); J.-D. Andre *et al*, US Patent 4,988,815 (January 29, 1991)
3. L. Charles *et al*, US Patent 6,664,260 (December 16, 2003)

Patent: Tri-Aryl-Substituted-Ethane PDE4 Inhibitors
 B. Cote *et al*, US Patent 6,639,077 (October 28, 2003)
Assignee: Merck Frosst Canada & Co.
Utility: Anti-Asthmatic and Anti-Inflammatory Precursors

Reaction



- i- n-Butyl lithium, diethyl ether, acetone
- ii- Hunig's base, CH_2Cl_2 , 2-(trimethylsilyl)ethoxymethyl chloride
- iii- n-BuLi, diethyl ether, 3,4-bis(difluoromethoxy)-benzaldehyde
- iv- Hunig's base, toluene, thionyl chloride
- v- Ethyl 4-pyridylacetate, tetrabutylammonium fluoride, hexamethylphosphoramide, sodium bis(trimethylsilyl)-amide
- vi- CH_2Cl_2 , trifluoroacetic
- vii- Magnesium monoperoxyphthalate hexahydrate, CH_2Cl_2 , methyl alcohol

Experimental

1. 2-[(1-Hydroxy-1-methyl)ethyl]thiazole

n-Butyl lithium (64.2 mmol, 40.4 ml 1.65 M) was added to thiazole (58.8 mmol) dissolved in diether ether at -78°C , the mixture stirred 20 minutes, then acetone (76.4 mmol) added. After 25 minutes, the mixture was poured into NH_4OAc solution, extracted with EtOAc, washed with brine, dried, concentrated, and used directly in Step 2.

2. 2-{1-Methyl-1-[(2-trimethylsilylethoxy)methoxy]ethyl}thiazole

The product from Step 1 (59 mmol) and Hunig's base (48 mmol) were dissolved in 75 ml CH_2Cl_2 , 2-(trimethylsilyl)ethoxymethyl chloride (70.8 mmol) added, and the mixture stirred 3.5 hours at 50°C then 15 hours at ambient temperature. The mixture was poured into 200 ml NH_4OAc solution, extracted with EtOAc, purified by flash chromatography using silica gel with hexane/EtOAc, 9:1, and 9.6 g product isolated.

3. (+/-)-3,4-Bis(difluoromethoxy)phenyl-5-{2-(1-methyl-1-[(2-trimethylsilylethoxy)methoxy]ethyl}thiazolylcarbinol

The product from Step 2 (14 mmol) dissolved in 30 ml diethyl ether was added to a solution of 5.6 ml 2.5 M n-BuLi (14 mmol) in 50 ml diethyl ether at -78°C . After 70 minutes, 3,4-(bisfluoromethoxy)-benzaldehyde (11.7 mmol) dissolved in 20 ml diethyl ether was added, the mixture stirred at -78°C for 2.5 hours, then quenched with aqueous NH_4Cl . The mixture was warmed to ambient temperature, partitioned with EtOAc and water, and the aqueous phase extracted with EtOAc. Flash chromatography of the residue on silica gel using hexane/EtOAc, 4:1 to 7:3, provided 3.85 g product.

4. (+/-)-3,4-Bis(difluoromethoxy)phenyl-5-{2-(1-methyl-1-[(2-trimethylsilylethoxy)methoxy]ethyl}thiazolylchloride

Hunig's base (9.8 mmol) was dissolved in 8 ml toluene at 0°C , thionyl chloride (4.8 mmol) added, and the product from Step 3 (3.2 mmol) dissolved in 10 ml toluene added. The mixture was stirred at 0°C for 45 minutes, filtered through a pad of silica gel pre-wetted with diethyl ether while eluting with diethyl ether/hexane, 4:1, and concentrated to provide the crude chloride that was used immediately.

5. (+/-)-4-[2-[3,4-Bis(difluoromethoxy)phenyl]-2-[5-(2-(1-methyl-1-[(2-trimethylsilylethoxy)methoxy]ethyl)thiazolyl)ethyl] pyridine

Ethyl 4-pyridylacetate (12.8 mmol) dissolved in 20 ml NBu_4F and hexamethylphosphoramide (12.6 mmol) at ambient temperature was added to sodium bis(trimethylsilyl)amide (12.7 mmol, 12.7 ml 1 M solution in NBu_4F). The mixture stirred for 30 minutes, the product from Step 4 dissolved in 10 ml THF added, and the mixture stirred 15 hours at 25°C . It was quenched with NH_4Cl solution, the layers separated, and the aqueous phase extracted with EtOAc. The organic phase was washed with water, dried, and concentrated. Thereafter, the crude material was dissolved in a mixture of THF/methyl alcohol/water, 2:2:1, LiOH (1.5 g) added, and the mixture refluxed 90 minutes. The pH was lowered to

6 using 1 M HCl, extracted with EtOAc, purified by flash chromatography of the residue on silica gel using EtOAc/hexane, 4:1, and 745 mg product isolated.

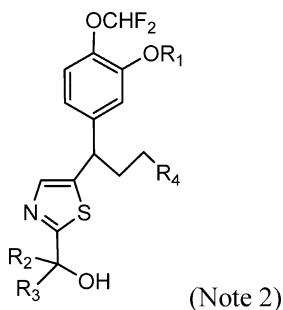
6. (+/-)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[5-(2-(1-hydroxy-1-methyl)ethyl)thiazolyl]ethyl}pyridine

The product from Step 4 (1.23 mmol) was dissolved in 20 ml CH₂Cl₂, trifluoroacetic acid (49.3 mmol) added, and the mixture stirred at 0°C 2.5 hours. Thereafter, it was poured into NH₄OAc solution, extracted with EtOAc, purified by flash chromatography using silica gel with EtOAc, and 394 mg product isolated.

7. (+/-)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[5-(2-(1-hydroxy-1-methyl)ethyl)thiazolyl]ethyl}pyridine N-oxide

The product from Step 6 (0.42 mmol) and magnesium monoperoxy-phthalate hexahydrate (0.42 mmol) were dissolved in 12 ml CH₂Cl₂ and 1 ml methyl alcohol and then stirred at ambient temperature for 22 hours. Thereafter, the mixture was filtered through celite, concentrated, purified by chromatography on silica gel using CH₂Cl₂/EtOH, 4:1, and 112 mg product isolated. ¹H-NMR data supplied.

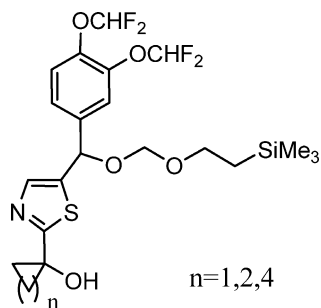
Derivatives



R ₁	R ₂	R ₃	R ₄
Cyclobutyl	Trifluoromethyl	Trifluoromethyl	2-Pyridinyl
Difluoromethyl	Phenyl	Trifluoromethyl	4-Pyridinyl
Difluoromethyl	1-(4-Ethyl)phenyl	Methyl	4-Pyridinyl
Cyclopropane	Methyl	Methyl	4-Pyridine N-oxide

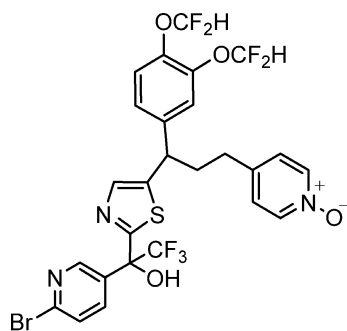
Notes

- ¹H-NMR and reaction product weight data for products supplied by the author.
- Three Step 7 cyclic thiazole products, (I), were prepared by the author and are described (Note 2).



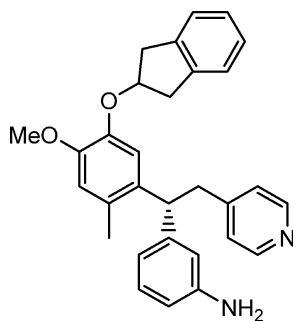
(I)

3. The di-pyridinyl derivative of the current invention, (+/-)-4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[5-(2-(1-hydroxy-1-(6-bromopyridin-3-yl)-2,2,2-trifluoroethyl)thiazolyl)ethyl]pyridine N-oxide, (II), has been prepared and is discussed (1).



(II)

4. The indane derivative (R)-4-[1-(3-(2-indanyloxy)-4-methoxyphenyl)-2-(4-pyridyl)ethyl]aniline, (III), and derivatives (2) have been prepared and is described.



(III)

5. The preparation of Step 7 tetra-substituted phenyl derivatives of the current invention is provided (3).

References

1. R. Freisen *et al*, US Patent 6,399,636 (June 4, 2002)
2. G.W. WarreLOW *et al*, US Patent 5,891,896 (April 6, 1999), US Patent 5,866,593 (February 2, 1999), and US Patent 5,859,034 (January 12, 1999)
3. R.R. Alexander *et al*, US Patent 5,780,478 (July 14, 1999)

Thiophenes

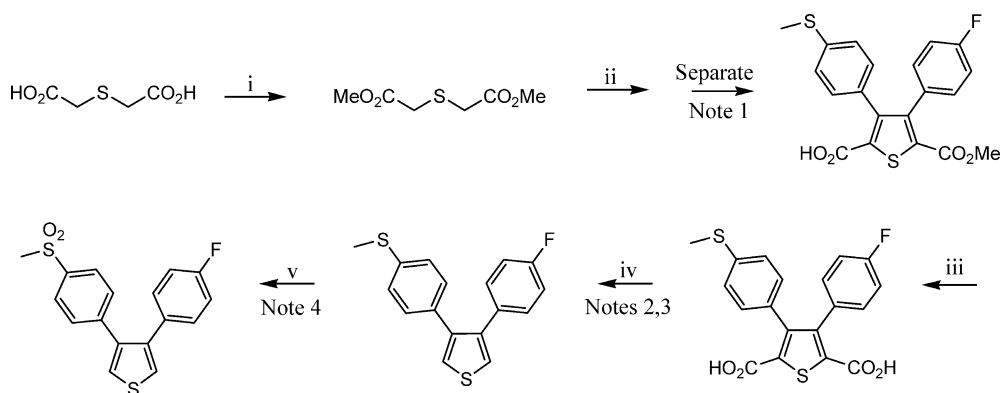
Patent: 3,4-Diaryl Thiophenes and Analogs Thereof Having Use as Anti-inflammatory Agents

J.J. Talley *et al*, US Patent 6,599,934 (July 29, 2003)

Assignee: G.D. Searle & Co.

Utility: Treatment of Arthritis

Reaction



i- Methyl alcohol, hydrogen chloride

ii- 4-Fluoro-4'-methylthiobenzil, THF, sodium methoxide, methyl alcohol

iii- THF, sodium hydroxide, methyl alcohol

iv- Quinoline, copper

v- CH_2Cl_2 , 3-chloroperbenzoic acid

Experimental

1. Dimethyl thiodiglycolate

Hydrogen chloride was bubbled in a solution of thiodiglycolic acid (2 mol) dissolved in 810 ml methyl alcohol for 30 minutes, the solution stirred 16 hours at 27 °C, and the mixture concentrated. The residue was dissolved in diethyl ether, washed with brine, NaHCO₃ solution, dried, distilled, and the product isolated in 64% yield. ¹H-NMR data supplied.

2. 2-Methoxycarbonyl-3-(4'-fluorophenyl)-4-(4'-methylthiophenyl)-thienyl-5-carboxylic acid monomethyl ester

and

2-Methoxycarbonyl-3-(4'-methylthiophenyl)-4-(4'-fluorophenyl)-thienyl-5-carboxylic acid monomethyl ester

4-Fluoro-4'-methylthiobenzil (122 mmol) and the product from Step 1 (244 mmol) were dissolved in 400 ml THF, 83.7 ml 25% NaOMe in methyl alcohol (366 mmol) added, and the mixture warmed to 65 °C for 2.5 hours. The mixture was cooled, poured into 1 L apiece 3 M NH₄OH and diethyl ether, shaken, and separated. The aqueous layer was acidified with HCl, extracted with 1 L EtOAc, dried, concentrated, recrystallized using EtOAc/iso-octane, and the product isolated in 82% yield. (Note 1)

3. 3-(4'-Methylthiophenyl)-4-(4'-fluorophenyl)-thienyl-2,5-dicarboxylic acid

The product from Step 2 (93.6 mmol) was dissolved in 450 ml THF, 468 ml 1 M NaOH in 75 ml methyl alcohol added to re-dissolve precipitates, and the mixture refluxed 90 minutes. The mixture was washed with 500 ml diethyl ether, acidified with HCl, extracted twice with 500 ml EtOAc, concentrated, and 36.84 g product isolated.

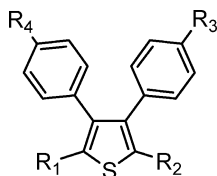
4. 3-(4'-Methylthiophenyl)-4-(4'-fluorophenyl)thiophene.

The product from Step 3 (94.9 mmol) was suspended in 400 ml quinoline, heated to 180–200 °C, copper powder (3.6 g) added, and the mixture stirred 3 hours. It was cooled to 130 °C, filtered, further cooled to ambient temperature, acidified with 3 M HCl, and extracted with diethyl ether. The diethyl ether was dried, concentrated, dissolved in a minimum amount of EtOAc, and passed over silica gel in hexane. Thereafter, the silica was washed with 50% ethyl acetate in hexane and the product isolated in 89% yield.

5. 3-(4-Methylsulfonylphenyl)-4-(4-fluorophenyl)thiophene

The product from Step 4 (70.9 mmol) was dissolved in 500 ml CH₂Cl₂, cooled to –78 °C, 3-chloroperbenzoic acid (142 mmol) added, stirred 90 minutes, and an additional 90 minutes at 0 °C. Thereafter, the mixture was washed with NaHSO₃, NaHCO₃, and brine. It was dried, concentrated, and the residue dissolved in 350 ml apiece CH₂Cl₂ and ethyl alcohol. CH₂Cl₂ was removed by boiling, the solution cooled to 10 °C, and 16 g of crystallized product isolated, mp = 190.5–191.5 °C.

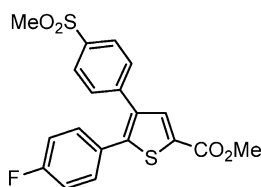
Derivatives



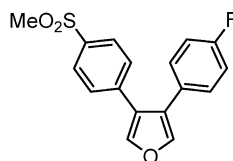
R ₁	R ₂	R ₃	R ₄	MS (M+1)
Bromo	Bromo	Fluoro	Methylsulfonyl	493
Bromo	Hydrogen	Methylsulfonyl	Methoxy	425
Hydrogen	Hydrogen	Methylsulfonyl	Methoxy	344
Hydrogen	Hydrogen	Hydrogen	Methylsulfonyl	314

Notes

1. The author separated the structural isomers of Step by recrystallization in EtOAc/isooctane.
2. Other decarboxylation routes using the Hindsburg reaction are described (1).
3. The isomeric Step 4 ester, 5-(4-fluorophenyl)-4-(4-(methylthio)-phenyl)thiophene-2-carboxylic acid methyl ester, (I), has been prepared (3). The Step 5 furan derivative, (II), 3-(4-fluorophenyl)-4-(4-(methyl-sulfonyl)phenyl)furan has also been prepared and is described (3).

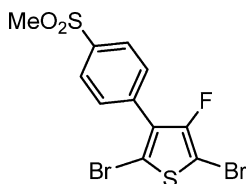


(I)



(II)

4. In an earlier investigation by the author (2) Step 5 derivatives containing 2,3,4-trihalothiophene, (III), were prepared.



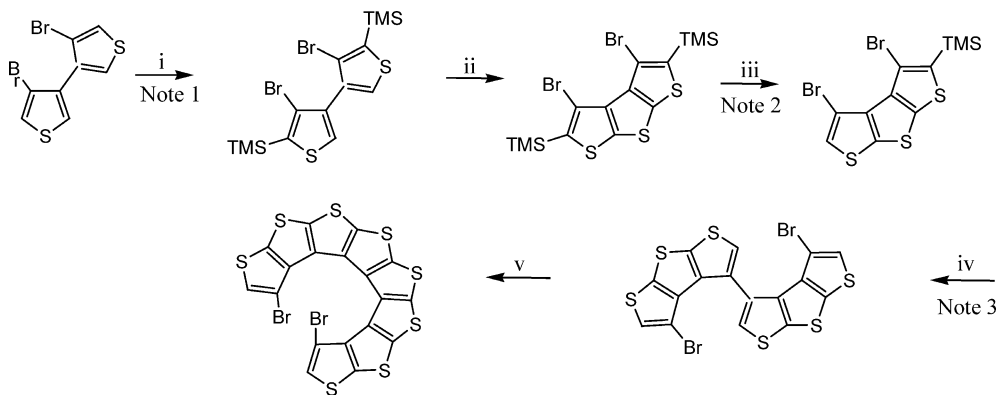
(III)

References

1. C. Overberger *et al*, J. Am. Chem. Soc., 72, 4958 (1950); D.J. Chadwick *et al*, Chem. Soc. Perkin I, 2079 (1972)
2. J.J. Talley *et al*, US Patent 6,274,590 (August 14, 2001)
3. Z. Wang *et al*, US Patent 6,239,173 (May 29, 2001)

Patent: Oligiothiophenes and Synthesis Thereof
A. Rajca, US Patent 6,515,144 (February 4, 2003)
Assignee: The Board of Regents of the University of Nebraska
Utility: Polythiophene Precursor

Reaction



- i- n-Butyllithium, di-isopropylamine, diethylether
- ii- n-Butyllithium, di-isopropylamine, diethylether, bis(phenylsulfonyl)sulfide
- iii- Trifluoroacetic acid, chloroform
- iv- Copper(II)iiodide, n-butyllithium, diethyl ether
- v- Bis(phenylsulfonyl)sulfide, lithium di-isopropylamine, diethylether

Experimental

1. 4,4'-Dibromo-5,5'-di(trimethylsilyl)-3,3'-dithienyl

n-Butyllithium (16.26 mmol, 1.94 M in hexane) was added dropwise to di-isopropyl amine (17.70 mmol) in 55 ml diethyl ether, the reaction stirred 1 hour at 0°C, and 4,4'-dibromo-3,3'-thienyl (7.39 mmol) added. The reaction stirred 3 hours at 0°C and a second addition of chlorotrimethylsilane (36.95 mmol) added at -78°C. After 3 hours, the mixture warmed to ambient temperature and continued to stir overnight. The product was extracted with 200 ml diethyl ether and washed 3 times with 150 ml water. The mixture was purified using flash chromatography on silica gel with hexane and the product isolated in 70% yield as a white solid, mp = 92–92.5°C. ¹H- and ¹³C-NMR and MS data provided.

2. 4,4'-Dibromo-5,5'-di(trimethylsilyl)-dithieno[2,2-b:3,2']dithiophene

1.94 M n-Butyllithium (5.08 mmol) was added dropwise to di-isopropyl amine (2.5 mmol) dissolved in 190 ml diethyl ether and the reaction stirred 1 hour at 0°C. Thereafter, the product from Step 1 (2.21 mmol) dissolved in 8 ml diethyl ether was added dropwise,

stirred 2 hours at 0°C, solid bis(phenylsulfonyl) sulfide (2.21 mmol) added, the reaction cooled to -78°C, and then stirred 3 hours. Thereafter, the reaction mixture warmed to ambient temperature and stirred overnight. The mixture was extracted 3 times with 100 ml water, dried, and concentrated. It was purified by chromatography as described in Step 1 and re-crystallized in chloroform/methyl alcohol. The product was isolated in 65% yield as a white solid, mp = 153.5–154°C. ¹H- and ¹³C-NMR and MS data provided.

3. 4,4'-Dibromo-5-trimethylsilanedithieno[2,3-b:3',2'-]thiophene

A stirred solution of the product from Step 2 (36.3 mmol) was dissolved in 100 ml chloroform and added dropwise to 2.0 ml trifluoroacetic acid. The mixture stirred 5 hours, the reaction mixture purified as in Step 1, and the product isolated in 58% yield, mp = 146–147°C. ¹H- and ¹³C-NMR and MS data provided.

4. Bis(dithieno[2,3-b:3,2'-d]thiophene)

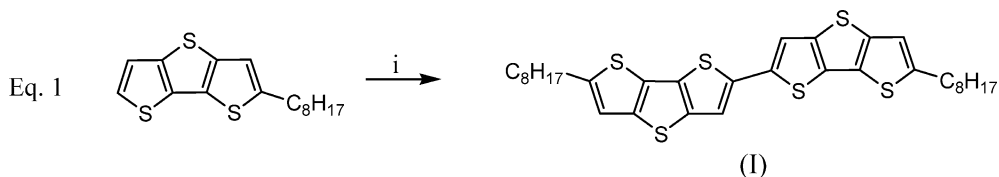
n-Butyllithium (2.10 M, 0.47 mmol) was added to the product from Step 3 dissolved in 12 ml diethyl ether. The solution was cooled to -78°C for 3 hours, CuI₂ (629 mg) added, and the reaction kept at -78°C for an additional 3 hours. The mixture warmed to ambient temperature and stirred 2 days. The mixture was purified following the description in Step 1 but using hexane/benzene, 14:1, and the product isolated in 35% yield, mp = 146–147°C. ¹H- and ¹³C-NMR and MS data provided.

5. Helicene

Lithium di-isopropylamide (2.3 eq) was added to the product from Step 4 dissolved in 12 ml diethyl ether at 0°C. After the mixture was stirred 2 hours, bis(phenylsulfonyl) sulfide (0.089 mmol) was added at -78°C and the mixture kept at this temperature 3 hours. Over a period of 12 hours the mixture slowly warmed to ambient temperature. Thereafter, it was purified as in Step 1 but using hexane/chloroform, 10:1, and the product isolated in 47% yield, mp = 311–325.5°C. ¹H- and ¹³C-NMR and MS data provided.

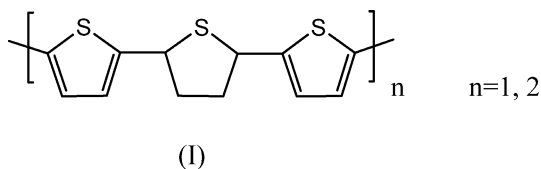
Notes

1. An alternative method for preparing the product of Step 1 is provided (1).
2. 4,4'-Dibromo-dithieno[2,3-b:3,2'-d]thiophene was also prepared by the author and had a mp = 181–182°C after de-silylation of 4,4'-dibromo-5-trimethylsilane-dithieno[2,3-b:3',2']thiophene. ¹H- and ¹³C-NMR and MS data also provided.
3. Step 3 dithieno[2,3-b:3',2'-1]thiophene derivatives, (I), have also been prepared by oxidative coupling using iron(III)acetylacacetate (2) as illustrated in Eq. 1 and described (2).



i- n-Butyl lithium, diethyl ether, iron(III)acetylacetonate, THF

4. Thiophene oligomer precursors containing tetrahydrothiophene components, (I), have also been prepared (3,4).



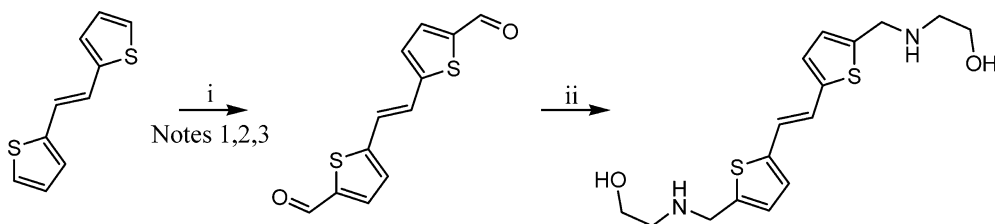
5. Methods for preparing crown ethers containing thiophene dimers, trimers, and higher analogues is described (5)

References

1. F. de Long *et al*, J. Org. Chem., 36, 1645 (1971)
2. A.B. Holmes *et al*, US Patent 6,403,809 (June 11, 2002)
3. K.H. Chmii *et al*, US Patent 6,184,540 (February 6, 2001)
4. K.H. Chmii *et al*, US Patent 5,919,951 (July 6, 1999)
5. T.M. Swager *et al*, US Patent 5,519,147 (May 21, 1996)

Patent: Polyaryl Antitumor Agents
C.T. Chang *et al*, US Patent 6,046,229 (April 4, 2000)
Assignee: Industrial Technology Research Institute
Utility: Anti-Neoplastic Agents for Inoperable or Metastatic Cancers

Reaction



i- Phosphorous oxychloride, N,N-dimethylformamide

ii- Methyl alcohol, ethanolamine, sodium borohydride

Experimental

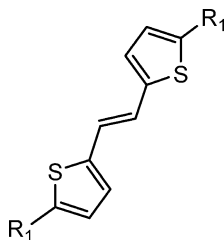
1. (E)-1,2-Bis[2-(5-formyl)-thienyl]ethene

A mixture of 5 ml N,N-dimethylformamide and phosphorous oxychloride (1.74 mmol) were stirred 30 minutes in an ice bath, (E)-1,2-bis(2-thienyl)ethene (1.58 mmol) added, and the mixture stirred at 50 °C for 48 hours. The mixture was cooled to ambient temperature, 10 ml 10% NaHCO₃ added, and extracted with CH₂Cl₂. The extract was washed with brine, dried, filtered and concentrated. The residue was purified by chromatography using silica gel with EtOAc/n-hexane, recrystallized in EtOAc, and the product isolated in 6% yield, mp = 209 °C. ¹H-NMR and MS data supplied.

2. (E)-1-(2-Thienyl)-2-[2-{5-[N-(2-hydroxyethyl)aminomethyl]}-thienyl]ethene

The product from Step 1 (5 mmol) was added to a mixture of 30 ml methyl alcohol and ethanolamine (10 mmol) containing several drops of HOAc. Thereafter, NaBH₄ was added, the mixture concentrated, and the residue treated with 50 ml apiece EtOAc and 0.1 N HCl. The mixture was filtered, washed with EtOAc, treated with 2 M NaOH until a pH > 12 observed, and re-extracted with EtOAc. The extract was washed with NaHCO₃, brine, dried, and concentrated. It was re-crystallized in n-hexane, and 1.22 g product isolated, mp = 91 °C. ¹H-NMR, MS, and IR data supplied.

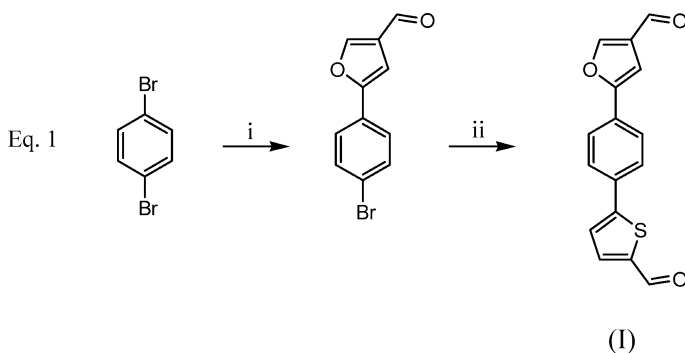
Derivatives



R_1	Melting Point ($^{\circ}\text{C}$)
Aminomethyl	160
Hydroxymethyl	133–4
N-[(2-Hydroxyethyl)aminoethyl]aminoethyl	51–52

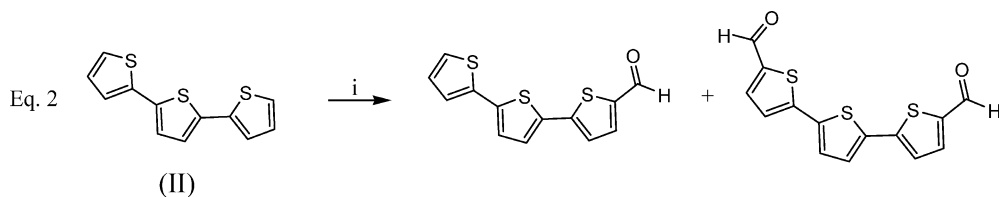
Notes

1. The preparation of the reagent of Step 1 is described (1).
2. Thiophenes were formylated by the insitu generation of the Vilsmeier-Haack reagent, $\text{MeN}^+ = \text{CHCl}_2^-$ (2).
3. The preparation of 1,2-bis[2-(5-formyl)- and 5-(hydroxymethyl)-thienyl]acetylene derivatives are also described by the author.
4. 1-(2-(5-Formyl-furyl)-4-(2-(5-formylthienyl)benzene, (I), was also prepared by the author as illustrated in Eq. 1:



- i- Tetrakis(triphenylphosphine)palladium (0), benzene,
sodium carbonate, methyl alcohol,
dihydroxy-(2-(5-formyl-furyl))borane
- ii- 2-(Diethoxymethyl)-5-(tributylstannyl)thiophene,
bis(triphenylphosphine)palladium(II) dichloride, THF

5. 2,2' and 2,2':5,2 Di- and terthiophenes, (II), were previously prepared and formylated by the author (3) as illustrated in Eq. 2:



i- N,N-dimethylformamide and phosphorous oxychloride

References

1. T. Montheard *et al*, Heterocycles, 104, 696 (1986)
2. J. Bergman, Tetrahedron Lett., 27, 1939 (1986); D. Konner, *ibid.*, 28, 955 (1987); H.G. Viehe, Angew. Chem. Int. Ed., 10, 575 (1971)
3. C.T. Chang *et al*, US Patent 5,602,170 (February 11, 1997)

Triazines

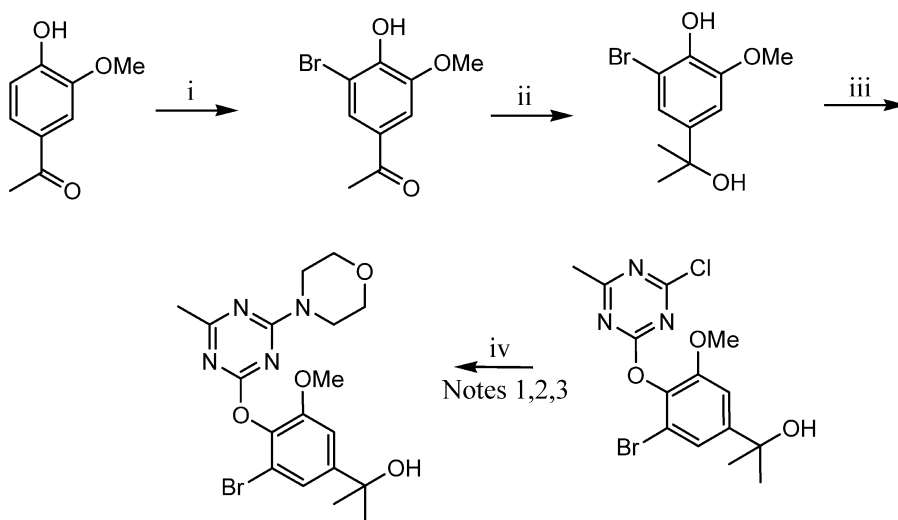
Patent: Aryloxy- and Arylthio-substituted Pyrimidines and Triazines and Derivatives Thereof

R.J. Chorvat *et al*, US Patent 6,326,368 (December 4, 2001)

Assignee: DuPont Pharmaceuticals Company

Utility: Treatment of Psychiatric Disorders and Neurological Diseases

Reaction



i- Bromine, chloroform

ii- Methyl magnesium bromide, diethyl ether, THF

iii- Sodium hydroxide, water, acetonitrile,
2,4-dichloro-6-methyl-1,3,5-triazine

iv- 1,4-Dioxane, morpholine

Experimental

1. 3-Bromo-4-hydroxy-5-methoxyacetophenone

Bromine (9.62 g) dissolved in 30 ml chloroform was added to acetovanillone (10.0 g) dissolved in 150 ml chloroform at 0 to -5°C , the mixture stirred 4 hours, and the residue isolated. The residue was washed with water, the organic layer dried, concentrated, triturated with diethyl ether, and the product isolated, mp = $148\text{--}152^{\circ}\text{C}$.

2. 3-Bromo-4-hydroxy-5-methoxy- α,α -dimethylbenzenemethanol

Methyl magnesium bromide (3 M in diethyl ether, 11.42 ml) was added to the product from Step 1 (3.0 g) dissolved in 60 ml THF at 0 to -5°C , stirred at ambient temperature 2 hours, then quenched with NH_4Cl solution. The organic layer was dried, concentrated, and the product isolated, mp = $107\text{--}112^{\circ}\text{C}$.

3. 3-Bromo-4-[[4-chloro-6-methyl-1,3,5-triazin-2-yl]oxy]-5-methoxy- α,α -dimethylbenzenemethanol

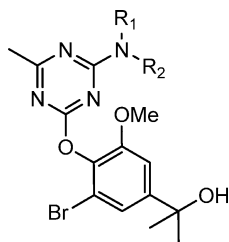
The product from Step 2 (1.16 g) was dissolved in 10% NaOH (1.78 g), 5 ml water added, concentrated, the salt dissolved in 50 ml acetonitrile, and the mixture cooled to 0 to -5°C . Thereafter, 2,4-dichloro-6-methyl-1,3,5-triazine (0.61 g) was added, the mixture stirred 1 hour, and then concentrated. The residue was extracted with CH_2Cl_2 , concentrated, and the product isolated.

4. 3-Bromo-4-[[6-methyl-4-(4-morpholinyl)-1,3,5-triazin-2-yl]oxy]-5-methoxy- α,α -dimethylbenzenemethanol

The product from Step 3 (3.0 g) was dissolved in 80 ml 1,4-dioxane, 1.39 ml morpholine added, the solution stirred 2 hours, concentrated, and then extracted with CH_2Cl_2 . The extract was dried, concentrated, and purified by chromatography on silica gel using EtOAc/hexane, 2:1, and the product isolated, mp = $199\text{--}201^{\circ}\text{C}$.

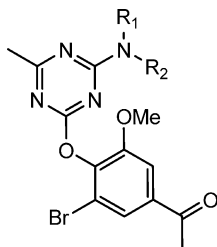
Derivatives

1. Step 4 derivatives are summarized below:



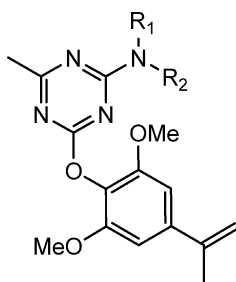
R₁	R₂	Melting Point (°C)
2-(1-Methoxy)ethyl	2-(1-Methoxy)ethyl	92–94
N-Propyl	3-n-Heptane	144–147
Cyclopentane	Cyclopentane	86–89

2. By omitting the Grignard reaction in Step 2 and proceeding directly to Step 4, acetophenone derivatives were prepared by the author and summarized below:



R₁	R₂	Melting Point (°C)
1-(2-methyl)ethyl	1-(2-Methoxy)ethyl	82–86
Ethyl	Ethyl	125–127
Hydrogen	Cyclopropane	111–115
Hydrogen	1-(2-Ethoxy)ethyl	159–162
Hydrogen	1-(2-thioethoxy)ethyl	158–172

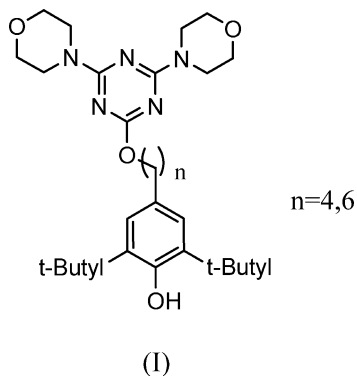
3. Step 4 dehydration products were also prepared by the author and summarized below:



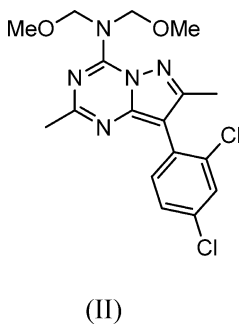
R₁	R₂	Melting Point (°C)
Ethyl	n-Butyl	Oil
Hydrogen	4-Methoxy-1-butyl	119–121
Hydrogen	Cyclohexane	103–105
1-(3-Pentene)	1-(3-Pentene)	51
Hydrogen	Tetrahydroisoquinoline	58

Notes

1. Other alkoxyated phenolic s-triazine derivatives, (I), have been prepared and are described (1).



2. Step 4 triazine pyrimidine derivatives have been prepared and are described (2).
3. Azolo triazines and pyrimidines analogues such as 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine, (II), have been prepared and are described (3).

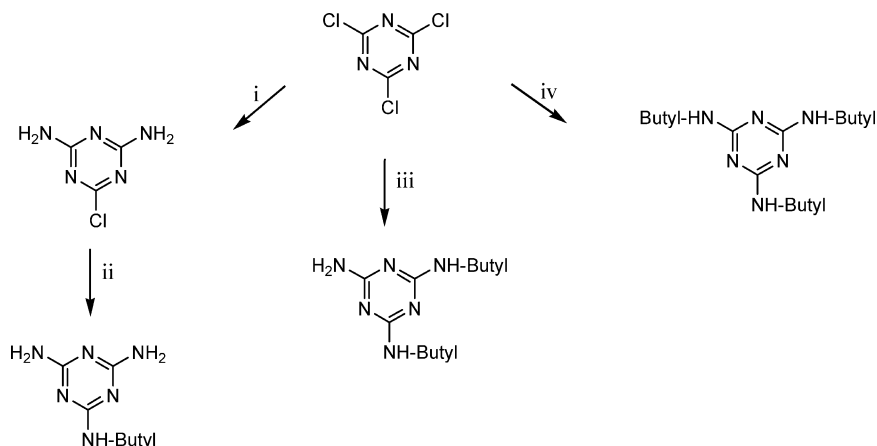


References

1. R. Pitteloud, US Patent 5,449,777 (September 12, 1995)
2. P. Rajagopalan *et al*, US Patent 6,258,809 (July 10, 2000)
3. L. He *et al*, US Patent 6,358,950 (March 19, 2002)

Patent: Method of Alkylating Triazine Derivatives
N. Tanaka *et al*, US Patent 6,130,332 (October 10, 2000)
Assignee: Nissan Chemical Industries, Ltd.
Utility: Resin and Fire-Retardant Materials

Reaction



- i- Ammonium hydroxide, acetonitrile
- ii- Butylamine, water
- iii- Acetonitrile, ammonium hydroxide, potassium bicarbonate, butylamine, water
- iv- Acetonitrile, ammonium hydroxide, potassium bicarbonate, butylamine, water

Experimental

1. 4,6-Diamino-2-chloro-1,3,5-triazine

Cyanuric chloride (1.0 mol) was dissolved in 800 ml acetonitrile, the solution cooled to 0°C, and 28% NH₄OH solution (5.0 mol) added over 2 hours while keeping the temperature less than 10°C. Thereafter, the mixture was stirred at ambient temperature one hour then warmed to 45°C for 4 hours. The mixture was filtered, washed with water, dried, and the product isolated in 79% yield.

2. 4,6-Diamino-2-n-butylamino-1,3,5-triazine

A mixture of the product from Step 1 (0.1 mol), 100 ml water, and butylamine (0.4 mol) were refluxed 6 hours, filtered, washed with water, toluene, and the product isolated in 96% yield, mp = 167 °C.

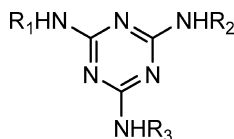
3. 2-Amino-4,6-bis(n-butylamino)-1,3,5-triazine

Cyanuric chloride (0.1 mol) was dissolved in 150 ml of acetonitrile at 0 °C and butylamine (0.1 mol) dissolved in 200 ml water added over 1 hour. Thereafter, a solution of KHCO_3 (0.1 mol) in 100 ml water was added dropwise, the mixture stirred 1 hour, and 28% NH_4OH solution (0.4 mol) added. The mixture was heated to 50 °C 5 hours, filtered, and washed with water. The crude product was suspended in 100 ml water containing dissolved butylamine (0.4 mol), refluxed 6 hours, and extracted with 200 ml toluene. Toluene was removed by distillation and the product isolated in 93% yield, mp = 73 °C.

4. 2,4,6-Tris(n-Butylamino)-1,3,5-triazine

To a solution of cyanuric chloride (0.1 mol) in 150 ml of acetonitrile at 0 °C was added butylamine (0.2 mol) dissolved in 20 ml water. Thereafter, KHCO_3 (0.2 mol) dissolved in 100 ml water was added dropwise and the mixture heated 8 hours at 45 °C. The crude product was isolated by filtration, suspended in a mixture of 100 ml water and butylamine (0.4 mol), and refluxed 6 hours. The material was purified as described in Step 3 and the product isolated 96% yield.

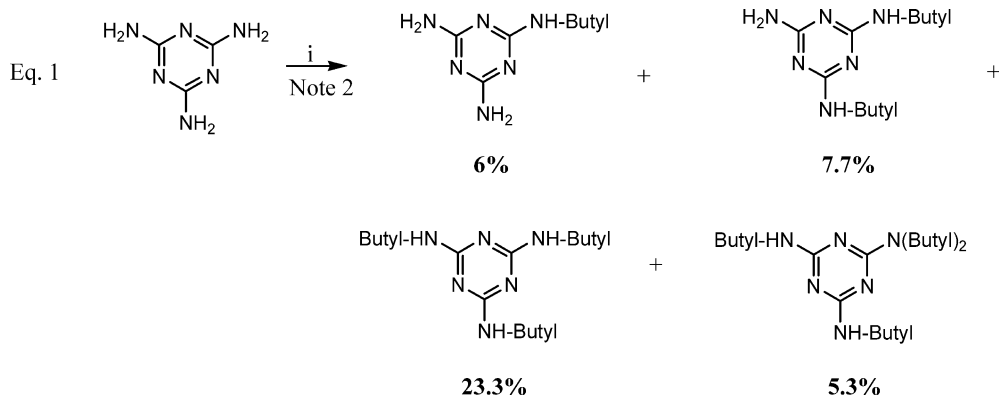
Derivatives



R_1	R_2	R_3	Melting Point (°C)	Yield (%)
Hydrogen	Hydrogen	Cyclohexyl	151	84
Hydrogen	Cyclohexyl	Cyclohexyl	153	56
Cyclohexyl	Cyclohexyl	Cyclohexyl	225	—

Notes

1. A procedure for alkylating melamine by reductive alkylation was described by the author and illustrated in Eq. 1. Other procedures are discussed (1).



i- Ruthenium trichloride hydrate, sodium diphenyl-phosphinobenzene-3-sulfonate, butyraldehyde, diethylene glycol dimethyl ether, synthesized gas (H_2/CO , 1:1)

2. The preparation of Step 2 secondary and tertiary amines by reacting an aldehyde with a primary or secondary amine, respectively, in the presence of a ruthenium hydrogenation catalyst is described (2).
3. In a previous investigation by the author, alkylated triazines of the current invention were prepared using melamine as the Step 1 reagent (3).
4. Alkylated triazines of the current have also been prepared by heating melamine or melamine derivative and an alcohol in the presence of a hydrogenation-dehydrogenation mixed catalyst such as 5% palladium on carbon (50% hydrated) with 25 mg of CuO/Cr₂O₃/NiO/BaO and is reviewed (4).

References

1. L.J. Ross *et al.*, US Patent 4,261,926 (August 14, 1981); A.F. Kirby *et al.*, US Patent 3,522,309 (July 28, 1970)
2. T. Imai, US Patent 4,207,260 (June 10, 1980)
3. N. Tanaka *et al.*, US Patent 5,792,867 (August 11, 1998)
4. N. Tanaka *et al.*, US Patent 6,307,046 (October 23, 2001)

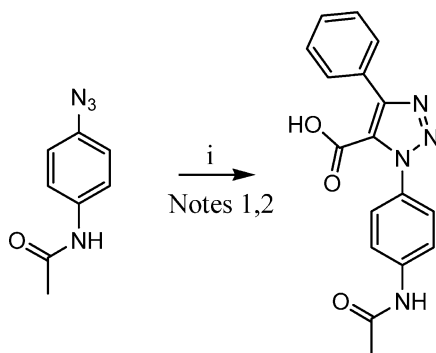
Triazoles

Patent: One Step Synthesis of 1,2,3-Triazole Carboxylic Acids
H.C. Kolb *et al*, US Patent 6,642,390 (November 4, 2003)

Assignee: Lexicon Pharmaceuticals, Inc.

Utility: Improved Method for Preparing 1,2,3-Triazole Carboxylic Acid Derivatives

Reaction



i- Potassium carbonate, ethyl benzoylacetate, ethyl alcohol, water

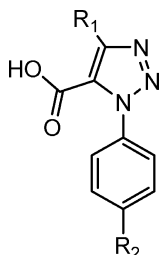
Experimental

1. 1-[4-(Acetylamino)phenyl]-4-phenyl-1,2,3-triazole-5-carboxylic acid

A suspension of 4-azidoacetanilide (25 mmol), K₂CO₃ (76 mmol) and ethyl benzoylacetate (27.6 mmol) dissolved in 45 ml 95% ethyl alcohol containing 15 ml water were heated to 80 °C 16 hours. The mixture was cooled, extracted with 100 ml EtOAc, and the

extract discarded. The aqueous phase was cooled to 0°C, neutralized with 150 ml 1 M HCl, filtered, the solid washed with 100 ml apiece cold water and methyl t-butyl ether, and the product isolated in 82% yield.

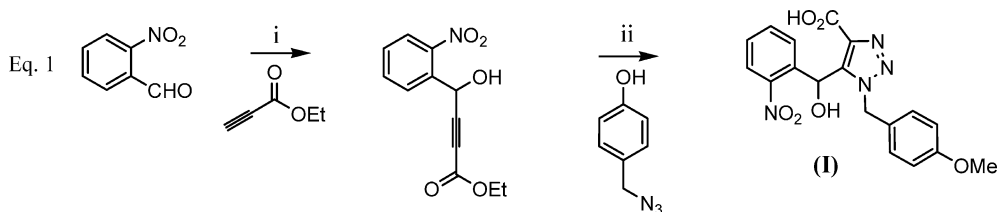
Derivatives



R ₁	R ₂	Yield (%)
Methyl	3,5-Difluorophenyl	87
n-Propyl	Phenyl	50
Methoxymethyl	4-Methoxyphenyl	48
2-Fluorophenyl	1-Methyl-2-fluorophenyl	94

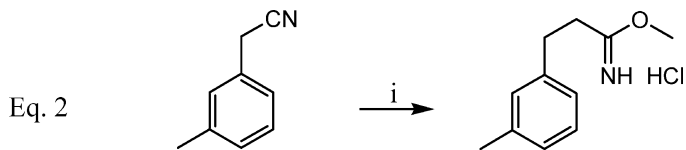
Notes

1. The preparation of small (~250 g) and large (~10 kg) scale quantities of aromatic azides or cyclic β -methoxy azides is described by the author.
2. Alternative procedure for preparing the Step 1 product are provided by the author and others (1).
3. Derivatives of the single step product are used in the preparation of 4-carboxy-1,2,3-triazole intermediates, (I), the latter which is used to prepare benzazepine and benzothiazepine derivatives (2). Prior to the current invention, the key intermediate was prepared in a two step process illustrated in Eq. 1:



i- n-Butyl lithium, THF
ii- Toluene

4. An earlier single step synthesis developed by the author (3) is the preparation of imidoesters using 1-methoxy-2-(3-methylphenyl)ethanimine as illustrated in Eq. 2.



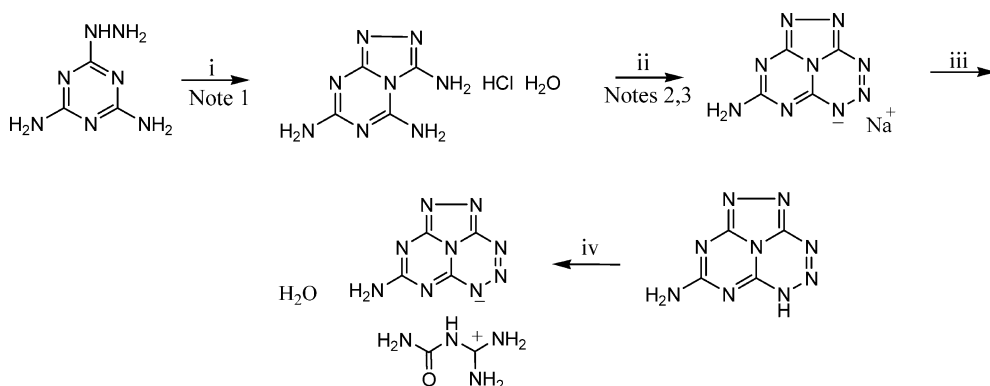
i- Dioxane, hydrochloric acid

References

1. Y. Oikawa *et al*, *Org. Synth.*, 7, 359 (1988); G. Capozzi, *J. Org. Chem.*, 58, 7932 (1993)
2. Y. Oikawa *et al*, US Patent 5,840,895 (November 24, 1998) and US Patent 6,093,714 (July 25, 2000)
3. H.C. Kolb *et al*, US Patent 6,806,380 (October 19, 2004)

- Patent:** Triazolyl-Tetrazinyl-Aminotriazine Compounds Useful in Pyrotechnic Compositions and Process Thereof
W.K. Koppes *et al*, US Patent 6,602,366 (August 5, 2003)
- Assignee:** The United States of America as Represented by the Secretary of the Navy
- Utility:** Smokeless and Low-Smoke Pyrotechnic Compositions

Reaction



- i- Cyanogen bromide, hydrochloric acid, potassium carbonate
ii- Sodium nitrite, hydrochloric acid
iii- Hydrochloric acid
iv- N-Guanyllurea hydrogen sulfate, hydrate, sodium hydroxide, water

Experimental

1. 1,2,4-Triazolo[4,3-a][1,3,5]triazine-3,5,7-triamine hydrogen chloride hydrate

2,4-Diamino-6-hydrazino-s-triazine (0.0570 mol) was mixed with 1 M HCl (126 g) at 25°C, stirred 10 minutes, then cyanogen bromide (0.0877 mol) added. Crystals began to precipitate after 1 hour and continued for an additional 24 hours. The crystals were filtered, washed with cold water, and the product isolated in 68.4% yield. IR and elemental analysis supplied.

2. Triazolyl-tetrazinyl-aminotriazine sodium

The product from Step 1 (0.0190 mol) was added to 75 ml HCl (0.08 mol), cooled to 0°C to form a slurry, and added in 7 portions over 15 minutes to sodium nitrite (0.24 mol) dissolved in 50 ml water. The mixture stirred 2 hours at 0°C, 20°C for 1 hour, 60°C for 30 minutes, and finally 60–65°C for 1 hour. The hot mixture was filtered, the filtrate

cooled to 5°C, concentrated, and the product isolated in 70% yield, mp >300°C (dec). ¹H-NMR and elemental analysis data supplied.

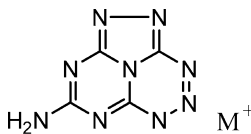
3. Triazolyl-tetrazinyl-aminotriazine

The product from Step 2 (0.0134 mol) was dissolved in 70 ml water, stirred at 25°C, and 15 ml 1 M HC added. The yellow precipitate was filtered and the parent acid isolated in 81% yield, mp = 215°C (dec). ¹H- and ¹³C-NMR and elemental analysis data supplied.

4. Triazolyl-tetrazinyl-aminotriazine guanylurea hydrate

Free base N-guanylurea was prepared by dissolving N-guanylurea sulfate hydrate (0.5 mmol) in 3 ml water and neutralizing with aqueous NaOH (1 mmol). This material was added to a stirred suspension of the product from Step 3 dissolved in 3 ml of water, stirred 2 hours at 25°C, further cooled to 5°C, filtered, and the product isolated in 96% yield, mp >300°C (dec). ¹H- and ¹³C-NMR and elemental analysis data supplied.

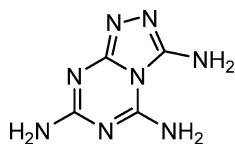
Derivatives



Cation (M+)	Melting Point (°C)	Yield (%)
Triaminoguanidinium	195	71
Aminoguanidinium	227	81
Methyltriphenylphosphonium	69–72	—
Diaminoguanidinium	196 (dec)	71
Magnesium	—	96

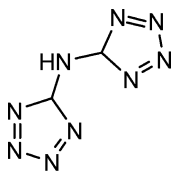
Notes

1. The preparation of the reagent of Step 1 is described (1).
2. A small amount of nitrotriazolo-diaminotriazine was also formed when preparing triazolyl-tetrazinyl-aminotriazine sodium. The impurity was removed by filtration when the reaction product mixture of Step 2 was dissolved in warm water. ¹H-NMR and elemental analysis data for this compound supplied by the author.
3. In a previous investigation, 1,2,4-triazolo[4,3-a][1,3,5]triazine-3,5,7-triamine, (I), and derivatives were prepared by the author (2).



(I)

4. The preparation of 5,5'-bis-1H-tetrazole and bis-(1(2)H-tetrazol-5-yl)-amine, (II), low smoke pyrotechnics are described (3).



(II)

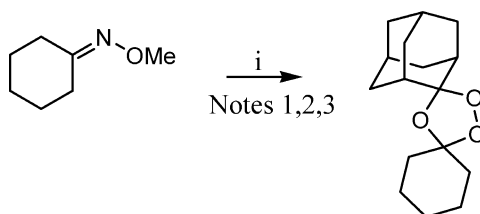
References

1. G.F. D'Aelio, US Patent 3,061,605 (October 30, 1962)
2. W.M. Koppes *et al*, US Patent 6,423,844 (July 23, 2002)
3. T.E. Highsmith *et al*, US Patent 5,682,014 (October 28, 1997)

Trioxolanes

Patent: Spiro and Dispiro 1,2,4-Trioxolane Antimalarials
J.L.Vennerstrom *et al*, US Patent 6,486,199 (November 26, 2002)
Assignee: Medicines for Malaria Venture MMV International Centre Cointrin
Utility: Prophylaxis and Treatment of Malaria

Reaction



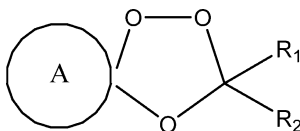
i- Pentane, 2-adamantanone, ozone

Experimental

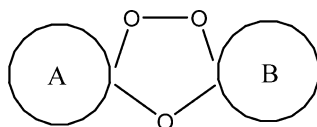
1. Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane

Ozone was produced with an OREC ozone generator (0.6L/min O₂, 60 V), cooled to -78°C, and then bubbled through a solution of O-methyl-cyclohexanone oxime (10 mmol) and 2-adamantanone (20 mmol) dissolved in 200 ml pentane for approximately 3–6 minutes. Thereafter, the solution was flushed with oxygen for 5 minutes before the mixture was concentrated, the residue purified by flash chromatography using silica gel in petroleum ether/diethyl ether, 98:2, and the product isolated. ¹H- and ¹³C-NMR data supplied.

Derivatives



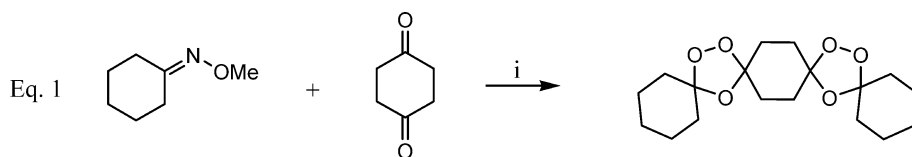
Spiro A	R ₁	R ₁	Melting Point (°C)	Yield (%)
Adamantyl	Phenyl	Cyano	137–138	51
Adamantyl	Hydroxyl	4-Fluoro-phenyl	143–145	30
4-Phenyl-cyclohexyl	4-Fluorophenyl	4-Fluoro-phenyl	87–89	27



Spiro A	Spiro B	Melting Point (°C)	Yield (%)
Adamantyl	4-Hydroxyl-4-(4-fluorophenyl)cyclohexyl	122–124	87
Cyclohexyl	2-Fluorocyclohexyl	oil	59
Adamantyl	4,4-Diphenylcyclohexyl	155–157	23

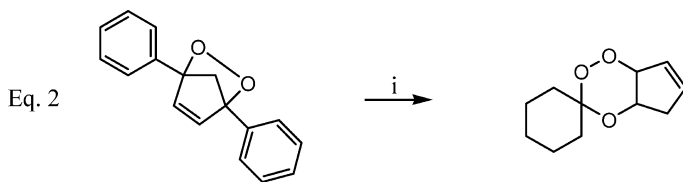
Notes

1. A general procedure for preparing the reagent of Step 1 and derivatives is provided by the author.
2. Low 1',2',4'-trioxolane product conversions were markedly improved by reversing the reagent order of addition.
3. Di-1,2,4-trioxolane derivatives were also prepared by the author as illustrated in Eq. 1:



i- CH₂Cl₂, pentane, ozone

4. An alternative method for preparing 1',2',4'-trioxolane derivatives using 1,4-diphenyl-1,4-epidioxycyclopent-2-ene is illustrated in Eq. 2 and described (1).



i- CH_2Cl_2 , trimethylsilyl trifluoromethanesulfonate

5. Other 1,2,4-trioxolanes have been prepared by ozonization of terpene hydrocarbons containing from 1 to 8 isoprene units (2).
6. The preparation of mono- and di-adamantyl 1,2-oxetane derivatives used as stable chemiluminescent agents is described (3).

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2. S. Herman, US Patent 5,364,879 (November 15, 1994)
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