



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 57

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 57

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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ACADEMIC PRESS, INC.

A Division of Harcourt Brace & Company

San Diego New York Boston

London Sydney Tokyo Toronto

Volume 57

This book is printed on acid-free paper. ∞

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Academic Press, Inc.

1250 Sixth Avenue, San Diego, California 92101-4311

United Kingdom Edition published by

Academic Press Limited

24–28 Oval Road, London NW1 7DX

International Standard Serial Number: 0065-2725

International Standard Book Number: 0-12-020757-5

PRINTED IN THE UNITED STATES OF AMERICA

93 94 95 96 97 98 QW 9 8 7 6 5 4 3 2 1

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Preface

Volume 57 of our series consists of five chapters. In the first, J. Barluenga and M. Tomas of the University of Oviedo, Spain, summarize the varied methods for the synthesis of heterocycles from azadienes with sections covering 1-azadienes, 2-azadienes, and 1,3-diazadienes, all classes of compounds whose importance has increased enormously in the past few years and to whose chemistry the Oviedo group has contributed most significantly.

1,2,4-Triazolo[1,5,*a*]pyrimidines are of particular importance in photography, with other significant applications in pharmaceuticals and agro-chemicals. Dr. G. Fischer of Leipzig, Germany, provides a comprehensive update of this subject, which was last reviewed in 1961.

H.-G. Henning and A. Gelbin (Humboldt University, Berlin, and Rutgers, The State University of New Jersey) cover tetramic acids, an important group of natural products showing significant biological activity, as well as some fascinating chemistry.

Piperazine-2,5-diones and related lactim ethers are covered by S. Rajappa and M. V. Natekar of the National Chemical Laboratory, Pune, India. Their chapter represents the first comprehensive review of these highly important intermediates for the preparation of a wide variety of natural products.

Finally, M. R. Grimmett from the University of Otago in New Zealand deals comprehensively with the halogenation of five-membered heterocycles in the first part of a survey that will ultimately cover the halogenation of all heterocycles.

A. R. KATRITZKY

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Synthesis of Heterocycles from Azadienes

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Universidad de Oviedo,
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I. Introduction

In recent years heterodienes, in particular azadienes, have become a useful tool for construction of heterocyclic compounds. In fact, their application toward natural product synthesis through pericyclic processes has been reviewed and their great potential in the field of the alkaloid

chemistry demonstrated [83MI1; 87AHC(42)245; 90JHC47, 90MI1]. Undoubtedly, the hetero Diels–Alder reaction employing heterodienes represents a very efficient, straightforward approach to nitrogen-containing six-membered heterocycles; in respect of this $[4 + 2]$ cycloaddition process, it must be noted that several reviews dealing primarily with azadienes have appeared (83T2869; 85JHC69; 87H777, 87MI1; 90MI2; 91MI1). In this chapter, the utility of aza- and 1,3-diazadienes in the synthesis of heterocycles of various ring sizes is described. Since the $[4 + 2]$ cycloaddition reactions of azadienes have been reviewed extensively in recent years, only selected examples regarding Diels–Alder cycloadditions, as well as the most recent work on this topic, will be discussed; therefore, special attention will be paid to processes not covered in previous reviews, e.g., polar heterocyclizations and electrocyclic ring closure reactions. Moreover, the cycloaddition reactions of heterocyclic azadienes have been summarized by Boger (86CRV781; 90BSB599) and hence they will not be included herein. In Section II the utility of 1-azadienes as precursors of five- to eight-membered heterocycles is surveyed; much emphasis will be put on N-substituted-4-amino-1-azabutadienes, which have been one of the major topics of research in our group for some years (76AG496; 88BSB545; 90PAC1957). Section III deals with the chemistry of 2-azadienes directed to the preparation of five- to seven-membered heterocycles; the study of electronically neutral 2-azadienes will be an important subject in this part, since very few reports had been reported up to the late 1980s. The chemistry of diazadienes will be focused in the utility of 1,3-diazadienes (Section IV). Other diaza derivatives have been less studied and their chemistry is mostly covered in the general references given above; in addition, leading papers dealing with the use of 1,2-diazadienes [91JCS(P1)3361] and 1,4-diazadienes (90H883; 91JOC2605) have been published.

II. Synthesis of Heterocycles Using 1-Azadienes

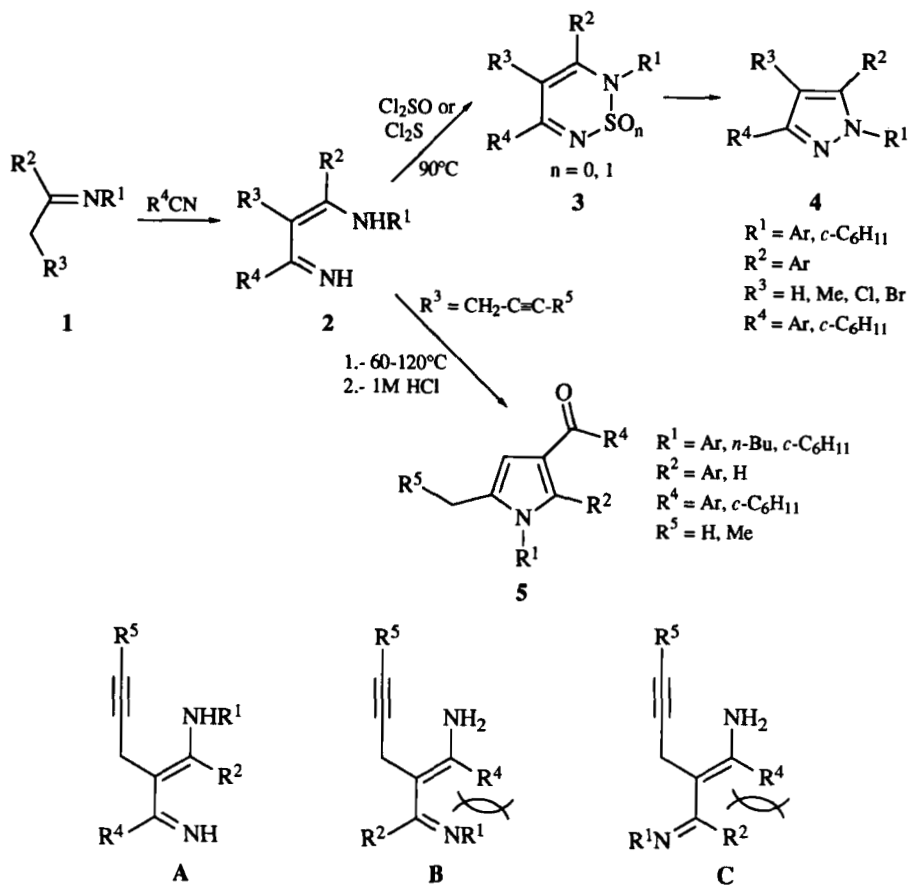
A. FIVE-MEMBERED RINGS

1. *From $[5 + 0]$ Fragments*

Reports on the synthesis of five-membered heterocycles by intramolecular nitrogen–nitrogen bond formation (N1–N5) came some years ago from our laboratory [79CC891; 81JCS(P1)1891; 83JCS(P1)2273]. Thus, 4-alkyl(aryl)amino-1-azabutadienes **2**, which are readily available in large scale from alkyl(aryl)imines **1** and aliphatic or aromatic nitriles (70S142;

73LA1075), were used as the appropriate substrates (Scheme 1). Treatment of a solution of azadienes **2** in pyridine with Cl_2S or Cl_2SO at 90°C for 8 h resulted in the formation of pyrazoles **4** in good yields. The reaction proceeds by means of the thiadiazine intermediate **3**, which undergoes at that temperature subsequent S or SO extrusion and nitrogen—nitrogen bond formation; a more detailed treatment of this process will be given in Section II,B,2.

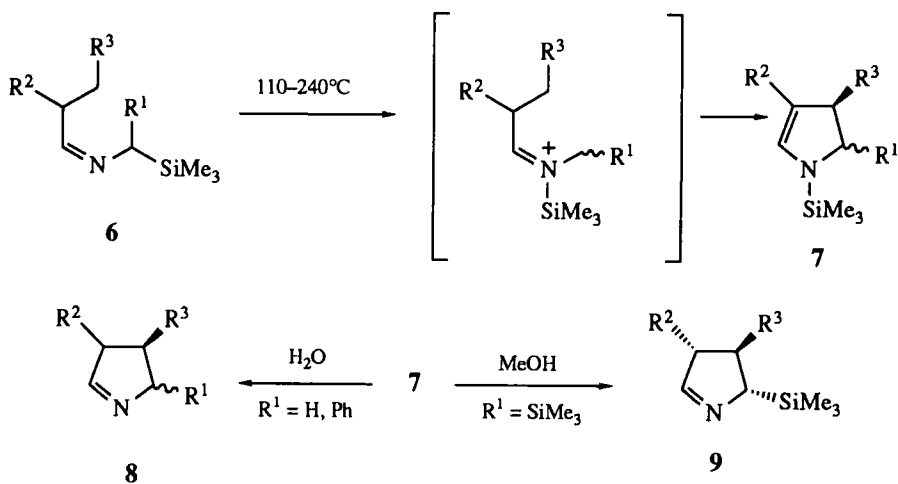
On the other hand, intramolecular carbon—nitrogen bond formation leading to N-substituted-3-acylpyrroles **5** smoothly occurs in 79–96% yield by heating a solution of azadiene **2** having a propargyl appendage at the enamine carbon atom ($\text{R}^3 = \text{CH}_2\text{—C}\equiv\text{C—R}^5$) in toluene or ethanol/



SCHEME 1

triethylamine (Scheme 1). The greater reactivity of the substituted nitrogen over the unsubstituted one was unexpected according to the general behavior found for systems **2**; conformational effects must play a decisive role in the reaction course and it can be assumed that conformation **A** should be preferred over **B** and **C** (90MI4). This process, which was observed previously by other authors (79JOC2323; 81JOC811; 84H1225), has also been shown by Taylor using alkynyl-substituted triazinones and coined as "intramolecular coplanar cycloamination" (ICC) (88JOC5093).

The group of Komatsu and Ohshiro reported in 1990 that azomethine ylides can be generated by thermal rearrangement of *N*-trimethylsilylmethyl imines (90CL575). Taking advantage of this reaction they prepared 1-pyrrolines **8** by starting with conjugated imines (1-azadienes) **6** ($R^1 = \text{H}$, Ph) (91TL5093) (Scheme 2). In this case heating **6** at 110–140°C resulted in the 1,2-shift of the silyl group and formation of the corresponding vinyl azomethine ylides, which can be trapped with *N*-phenylmaleimide; in the absence of a trapping agent these species undergo 1,5-electrocyclization leading predominantly to *trans* ($R^2 = \text{H}$) and *cis* ($R^2 = \text{Me}$) 2-pyrrolines **7** ($R^1 = \text{H}$, Me) (55–97% yield according to ^1H -NMR) and hydrolysis to 1-pyrrolines **8** (30–55% overall yield from azadienes **6**). Shortly prior to that report, Palomo *et al.* reported the diastereoselective construction of 1-pyrrolines **9** having three chiral carbon centers following the same strategy (91CC524). In this regard, they were able to cyclize 1-azadienes **6** ($R^1 = \text{SiMe}_3$) into *trans*-2-pyrrolines **7** ($R^1 = \text{SiMe}_3$) by heating at



SCHEME 2

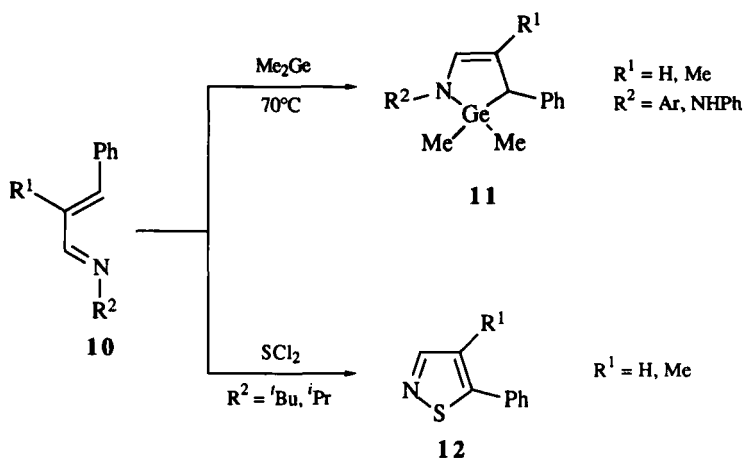
200–240°C (70–82% yield); methanolysis of the latter resulted in the formation of 3,4-disubstituted-5-trimethylsilyl-1-pyrrolines **9** as the sole stereoisomer (68–93% yield).

2. From [4 + 1] Fragments

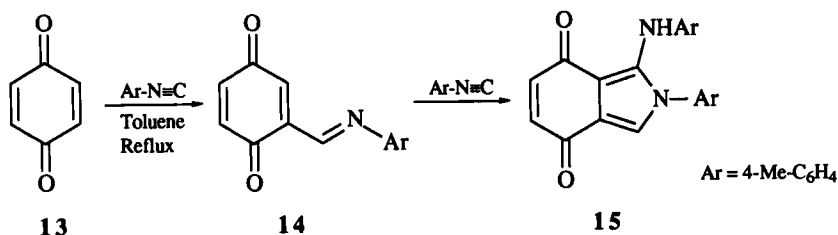
One process of this sort can be envisaged as a 1,4-cycloaddition of the 1-azadiene system to unsaturated species (chelotropic reaction). However, very few examples are known; thus, simple 1-azadienes **10** add to free singlet dimethyl germylene, generated from 7-germanorbornadiene, to form 1-aza-2-germacyclopent-4-enes **11** in 85–95% yield (89TL6669) (Scheme 3). Similarly, 1-azadienes **10** ($R = \textit{tert}$ -butyl, *iso*-propyl) were reported by Komatsu *et al.* to undergo [4 + 1] cycloaddition with sulfur dichloride to afford the corresponding isothiazoles **12** in good yields (83PS119).

Isocyanides, which are better candidates to react with dienes in a 1,4-fashion, were shown to cycloadd to 1-azadienes. Thus, the formation of isoindole derivative **15** as the major product (ca. 28% yield), upon treatment of benzoquinone **13** with two equivalents of *p*-tolyl isocyanide [81AG(E)982] was reported; the reaction involves the insertion of the isocyanide carbon atom into the C—H bond of **13** leading to the 1-azadiene derivative **14**, which in turn undergoes a [4 + 1] cycloaddition with a second isocyanide molecule (Scheme 4).

1-Zircona-2-azacyclopent-3-enes **18** have been synthesized by reaction of 1-azadienes **16** with the zirconocene equivalent (Cp_2Zr) **17** (91CC1743)



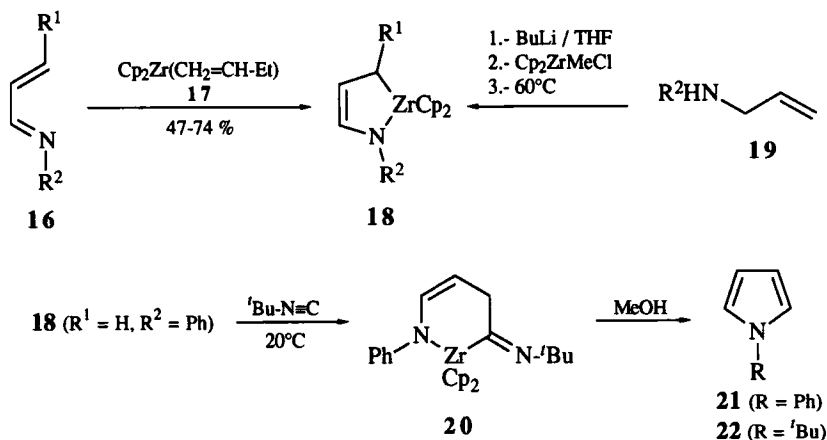
SCHEME 3



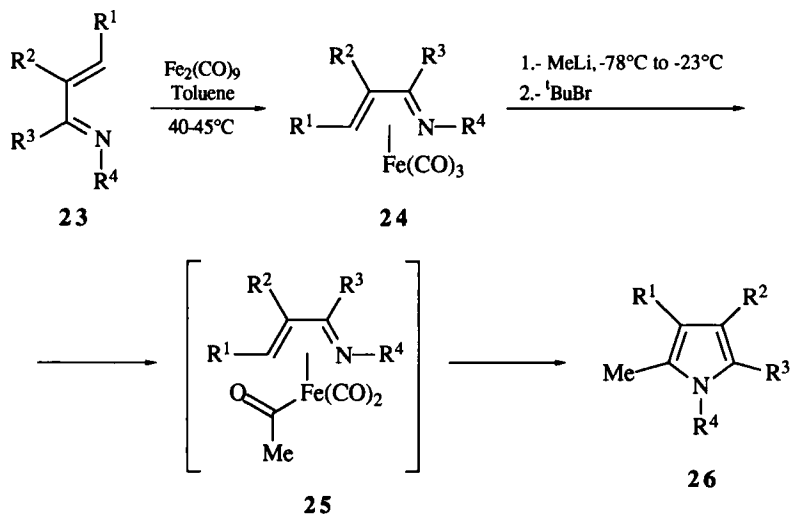
SCHEME 4

(Scheme 5). Whereas 5-substituted metallacycles **18** ($\text{R}^1 = \text{Me}, \text{Ph}$) are quite unreactive, derivative **18** ($\text{R}^1 = \text{H}; \text{R}^2 = \text{Ph}$), which is more efficiently prepared from the corresponding allyl amine **19** ($\text{R}^2 = \text{Ph}$), allows insertion of *tert*-butyl isocyanide to furnish metallacycle **20**; its methanolysis yielded a mixture of *N*-phenyl **21** and *N-tert*-butylpyrrole **22**.

The [4 + 1] annulation of 1-azadienes to pyrroles can also be achieved through their carbonyl iron complexes (Scheme 6). Novel complex (1,4-diphenyl-2-methyl-1-azabutadiene)tricarbonyliron (0) **24** was obtained in 40% yield from the corresponding azadiene **23** and $\text{Fe}_2(\text{CO})_9$; then nucleophilic attack by methyl lithium and quenching with *tert*-butyl bromide, as the proton source, gave 2,5-dimethyl-1,3-diphenylpyrrole **26** in 70% yield, probably through the anionic intermediate complex **25** [88TL1425; 90JCS(P1)761].



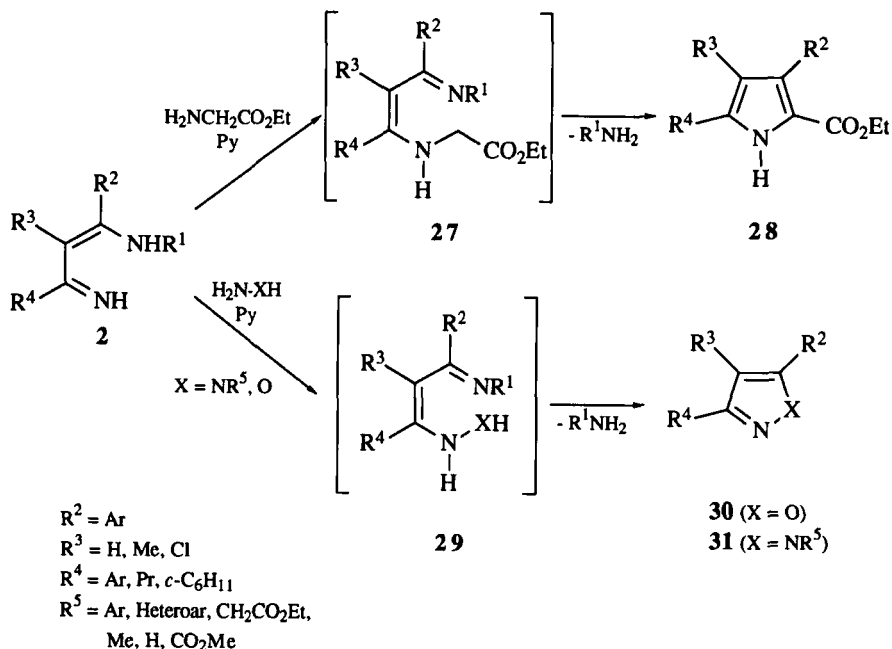
SCHEME 5



SCHEME 6

3. From [3 + 2] Fragments

Syntheses of five-membered heterocycles by assembling two fragments in a [3 + 2] fashion have been reported from our laboratories using azabutadienes **2** as the source of the three-carbon atoms unit (Scheme 7). First, compounds **2** reacted with glycine ethyl ester ($\text{H}_2\text{NCH}_2\text{CO}_2\text{Et}$) in pyridine at 80°C yielding substituted 2-ethoxycarbonylpyrroles **28** (81–90% yield); the process initiates by the imine–amine exchange reaction to form intermediates **27**, which undergo base-catalyzed cyclocondensation to **28** under the reaction conditions (82JOC1696). Extension of this methodology to the use of hydroxylamine and *N*-substituted hydrazines allowed regioselective preparation of substituted isoxazoles **30** (55–96% yield) [83JOC1379; 86JCR(S)464; 87JCR(S)215] and pyrazoles **31** (69–93% yield) [85JCR(S)124], respectively; evidence for the proposed reaction course was gained since the intermediate of type **29** could be isolated by reaction of **2** with *N*-methyl-*N*-phenylhydrazine. At this point it is worth noting that the most popular and simple route to pyrazoles and isoxazoles implies the reaction of hydrazines or hydroxylamine with 1,3-diketones, the major drawback being the formation of regioisomers in the case of starting from unsymmetrical diketones (82MI1). The use of diimino derivatives **2** permits circumvention of that problem, since they can be regarded as masked 1,3-diketones, in which both latent carbonyl groups show different chemical



SCHEME 7

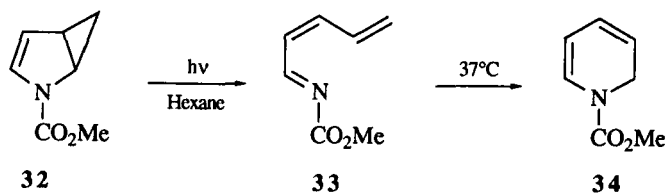
reactivity with respect to each other, the unsubstituted imine always being the most reactive imine function.

B. SIX-MEMBERED RINGS

1. From $[6 + 0]$ Fragments

This strategy should imply, in its simplest model, the electrocyclicization of 1-azatrienes. Kumagai *et al.* (91TL6895) have achieved this goal with the simple azatriene **33**; thus, photochemical ring opening of homopyrrole **32** leading to **33** is followed by disrotatory, thermal electrocyclic ring closure to furnish dihydropyridine **34** in 30–85% yield, depending on the irradiation conditions (Scheme 8).

The formation of substituted quinolines **35** (58–90% yield) by intramolecular cyclization of 4-arylamino-1-azabutadienes **2** has been carried out at 100°C using one equivalent of aluminium chloride; the reaction involves the diene moiety and one carbon—carbon double bond of the aromatic ring (87S82). The participation of the phenyl group attached to the α -

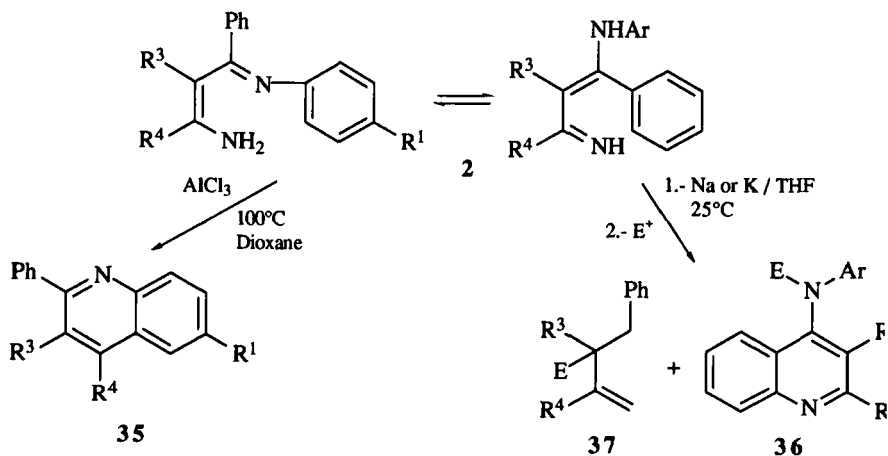


SCHEME 8

enamine carbon atom occurred in the reaction of **2** with sodium in THF, affording substituted 4-aminoquinolines **36** in 40–48% yield along with ketones **37** (89JOC2596) (Scheme 9).

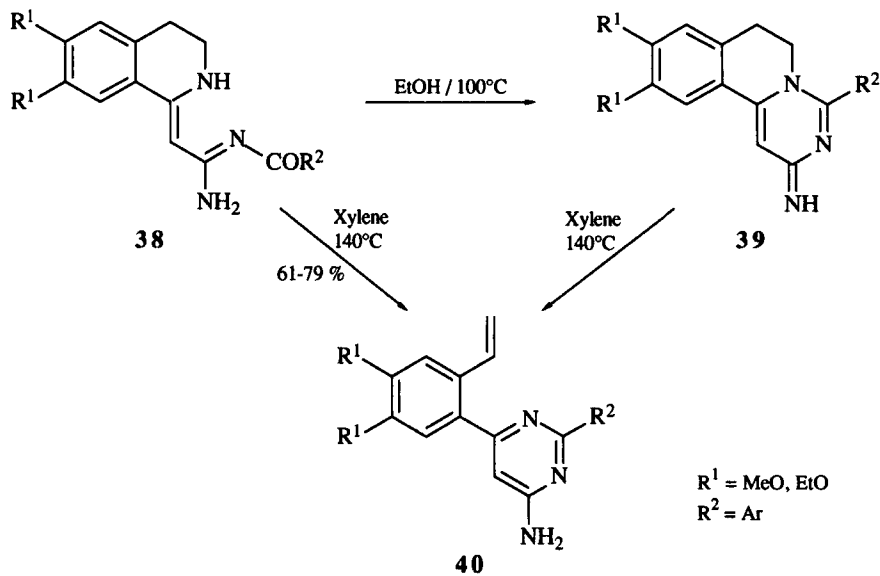
Similarly, Uneyama and Watanabe (91TL1459) have reported the synthesis of trifluoromethylated *N*-aryl-1-azabutadienes by palladium-catalyzed coupling of trifluoroacetimidoyl iodides with alkenes as well as the transformation of the azadiene derived from methyl acrylate into the corresponding 4-methoxycarbonyl-2-trifluoromethylquinoline in quantitative yield.

Korbonits *et al.* (91CB111) employed acyl-substituted 4-amino-1-azabutadienes for the construction of the pyrimidine ring (Scheme 10). Thus,



$R^1 = \text{H, Me}$
 $R^3 = \text{Me, Et, Bz}$
 $R^4 = \text{Ar, } c\text{-C}_6\text{H}_{11}$
 $\text{E} = \text{H, Me, Et}$

SCHEME 9

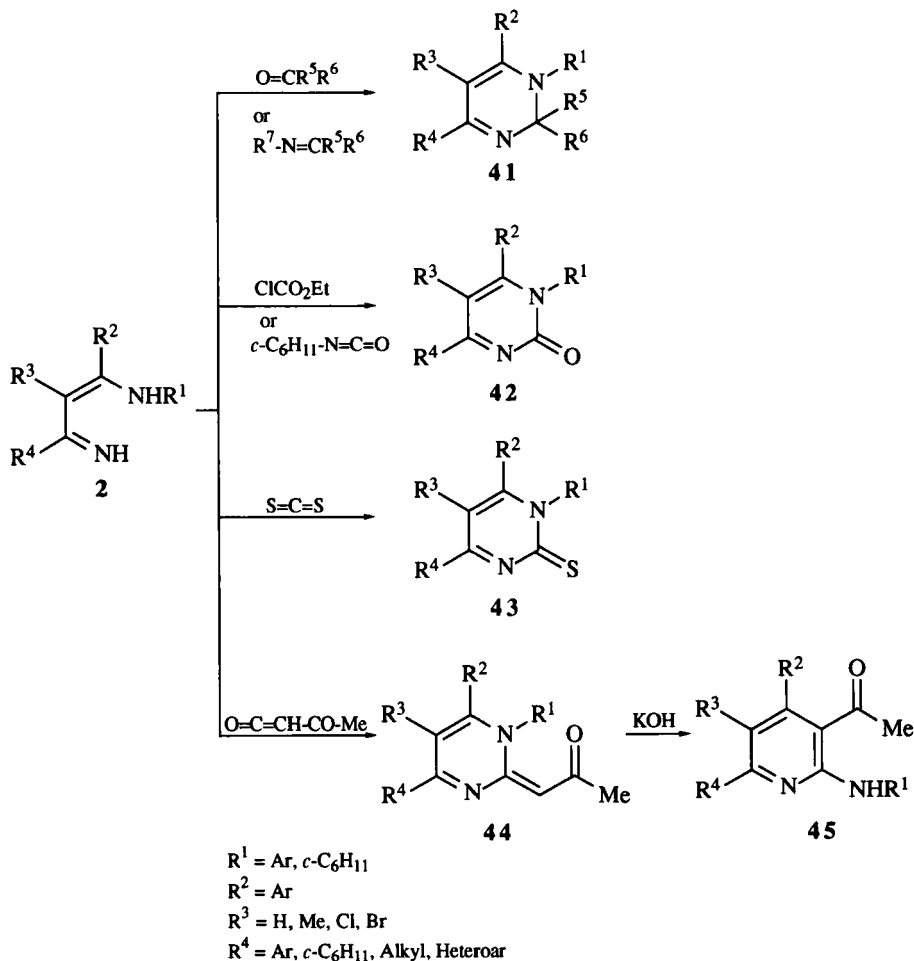


SCHEME 10

pyrimido[6,1-*a*]isoquinoline-2-imines **39** were isolated when an ethanolic solution of aminoazadiene **38** was evaporated at 100°C ; subsequent heating of **39** in xylene at 140°C resulted in a Hofmann-like elimination, giving rise to aminopyrimidines **40**. Compounds **38** were directly converted into **40** on heating at 140°C in 61–79% yield.

2. From [5 + 1] Fragments

The presence of two N—H functions at positions 1,5 (vinylogous amidines) makes azadienes **2** suitable starting materials for synthesis of different 1,3-diazines by double nucleophilic attack onto appropriated substrates. It was observed in all instances that the unsubstituted imine nitrogen is first involved in the cyclization reaction. Initial studies were directed at annulation of **2** using carbon reagents (Scheme 11). 1,2-Dihydropyrimidines **41** were prepared in excellent yields by condensation of azadienes **2** with aldehydes (79S346; 88CC410; 91MI5) or aldimines and ketimines (74S720) in the presence of a Lewis acid. The cyclocondensation of **2** with ethyl chlorocarbonate leading to **42** takes place at room temperature in pyridine and was found to be a suitable entry to the 2(1*H*)-pyrimidinone ring [79CC675; 83JCS(P1)2273]. Carbonyl and thiocarbonyl groups of a cumulene structure also reacted in the same way with **2**. Cyclohexyl



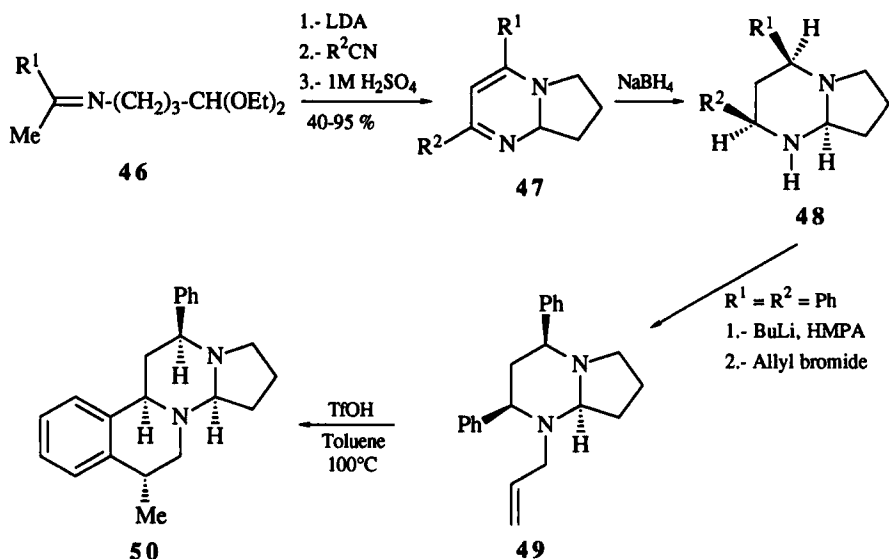
SCHEME 11

isocyanate gave pyrimidinones **42** (80JOC2592); however, this synthesis of **42** is very limited in scope (see Section II,B,3) and, therefore, it is not competitive from a synthetic point of view with the preceding procedure using ethyl chlorocarbonate. We (79CC675) and others [82JCS(P1)2149] observed that carbon disulfide itself does condense with C-3-substituted azadienes **2** ($\text{R}^3 = \text{Me}$) to form substituted pyrimidin-2(1*H*)-thiones **43** in 80–95% yield. Finally, deep-red colored dihydropyrimidines **44** were available in 75–85% yield upon stirring at 80°C equimolecular mixtures of azadienes **2** and diketene in toluene; these heterocycles underwent

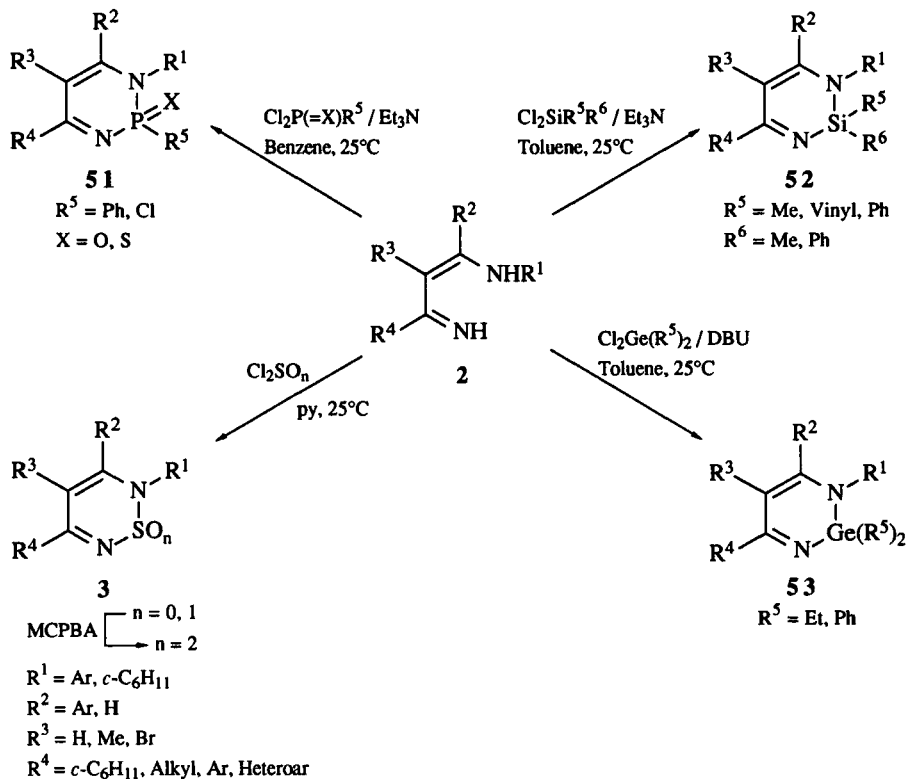
ring transformation—ring cleavage and recyclization—to pyridines **45** by hydrolysis with 6 *N* KOH–THF at 60°C [84JCR(S)154].

The intramolecular version of this heterocyclization was applied to a short synthesis of diazasteroids (Scheme 12). Thus, imines **46** were converted in one-pot into [1,2-*a*]pyrrolopyrimidines **47** when treated with LDA, nitrile, and acid (40–95% yield); the stereoselective reduction of **47** to octahydroderivatives **48** was effected in 70–92% yield with NaBH₄/MeOH at 60°C (89S230; 91MI5). Compound **48** (R¹ = R² = Ph) was successively allylated to **49** (94% yield) and cyclized in the presence of trifluoromethanesulfonic acid to afford a 86:14 mixture of diastereoisomers (C-5 epimers) in 86% yield, from which major component **50** was separated by column chromatography [90TL(31)2189].

We also found that six-membered heterocycles containing an additional heteroatom were readily available by reacting aminoazabutadienes **2** with derivatives of phosphorous, sulfur, silicon, and germanium (Scheme 13). 1,2-Dihydro-1,3,2-*P*^V-diazaphosphorines **51** were formed in 58–94% yield from **2** and the corresponding phosphorous (V) halide (83S370). In the same way, 1,2-dihydro-1,3,2-diazasilines **52** (92S106) and -diazagermines **53** (92MI1) were prepared by stirring a mixture of **2** and silicon and germanium dichloro derivatives, respectively; however, compounds **53** were not isolated in most cases, but prepared *in situ* and used in the next step (see Section II,C). Diazasilines **52** reacted with isocyanates, allowing us



SCHEME 12



SCHEME 13

to synthesize in excellent yields 2-imino-1,2-dihydropyrimidines, which are not available from azadienes **2** upon reaction with either isocyanates (see Scheme 11) or carbodiimides (87S489). On the other hand, it will be shown (Section II,C) that compounds **52** and **53** are suitable templates for making medium-size heterocycles. As mentioned in Section II,A,1, room temperature treatment of **2** with thionyl chloride and sulfur monochloride furnished in 73–87% yield 1,2,6-thiadiazines *S*-oxides **3** ($n = 1$) and 1,2,6-thiadiazines **3** ($n = 0$), respectively; *S*-dioxide derivatives **3** ($n = 2$) were available by MCPBA oxidation of **3** ($n = 0, 1$) [79CC891; 81JCS(P1)1891; 83JCS(P1)2273].

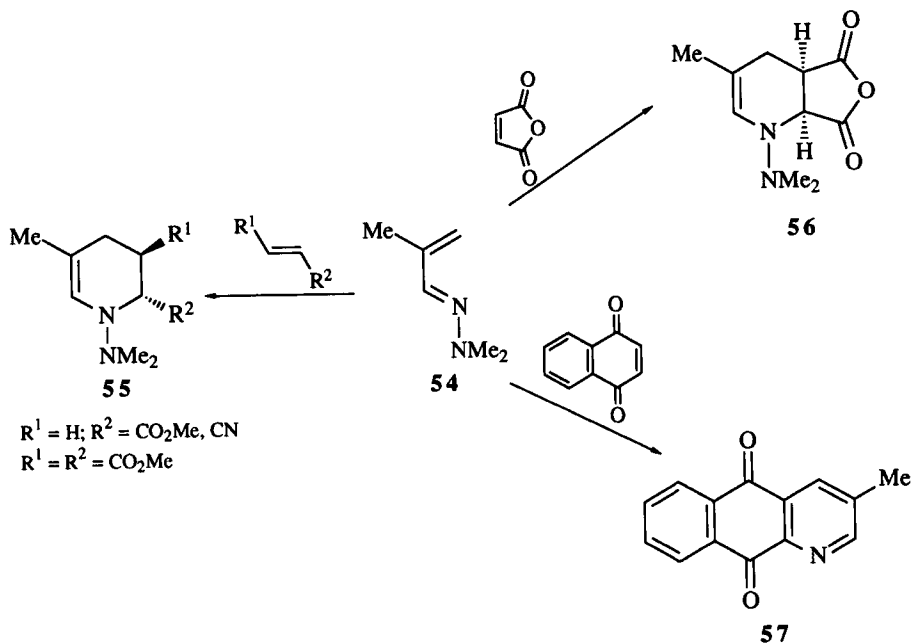
3. From [4 + 2] Fragments

Under this heading numerous syntheses of nitrogen-containing six-membered heterocycles can be found in the primary literature. The Diels–Alder route, which represents the most important entry into the

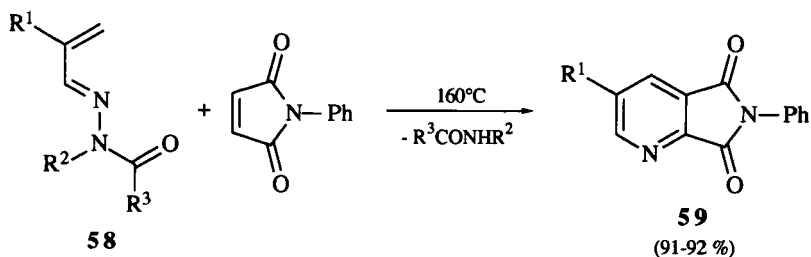
corresponding carbocycles, has received a great deal of attention and a number of groups have contributed, devising several nicely conceived strategies. Since some reviews have appeared in the last decade (see introduction), we will show selected or very recent examples covering the Diels–Alder reactions of 1-azadienes as a route to six-membered nitrogen heterocycles.

The pioneer work on this subject using simple 1-azadienes is due to Ghosez *et al.* (82TL3261; 85JHC69); they succeeded in reacting 1-azadienes as 4π -electron components in Diels–Alder cycloadditions. Thus, 1-dimethylamino-3-methyl-1-azabuta-1,3-diene (α,β -unsaturated hydrazone) **54** did undergo $[4 + 2]$ cycloaddition to typical electron-poor dienophiles, e.g., methyl acrylate, dimethyl fumarate, acrylonitrile, maleic anhydride, and naphthoquinone, producing pyridine derivatives **55–57** (Scheme 14).

Gilchrist and co-workers (91TL125) have reported on the inter- and intramolecular cycloaddition of α,β -unsaturated acylhydrazones **58** (Scheme 15). Heating at 160°C a mixture of *N*-phenylmaleimide and azadienes **58** in mesitylene furnished annulated pyridines **59** in yields higher than 90%. Significantly, the intermolecular cycloaddition to this deficient



SCHEME 14



$\text{R}^1 = \text{Me, Et}$

$\text{R}^2 = \text{H, Me}$

$\text{R}^3 = \text{Ph, (CH}_2)_2\text{-C}\equiv\text{CH, O-CH}_2\text{-C}\equiv\text{CH}$

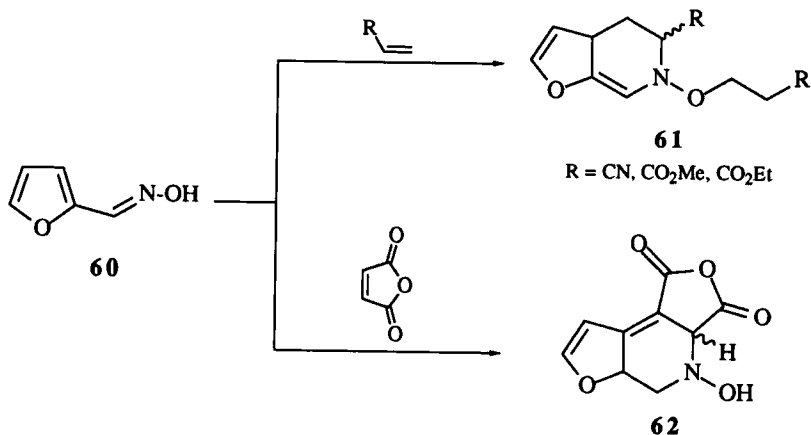
SCHEME 15

dienophile is more favorable than the intramolecular one to an unactivated triple bond, as the cycloaddition of azadienes **58** with an alkynyl appendage ($\text{R}^3 = \text{X-CH}_2\text{-C}\equiv\text{CH}$) follows the same pattern leading to **59**. This intramolecular reaction will be treated later.

Chakrabarty's group has synthesized an $[a]$ annellated γ -carboline in 30% yield by $[4 + 2]$ cycloaddition of *N*-methylmaleimide with the 1-azadiene that resulted from condensation of *N,N*-dimethylhydrazine and 1-ethoxycarbonylindole-3-carboxaldehyde (92TL117). Additional examples using this methodology have been published with minor variations (81CL411; 84CC114, 84S930; 87JOC2285; 88HCA486, 88HCA493, 88TL5913; 91TL1307).

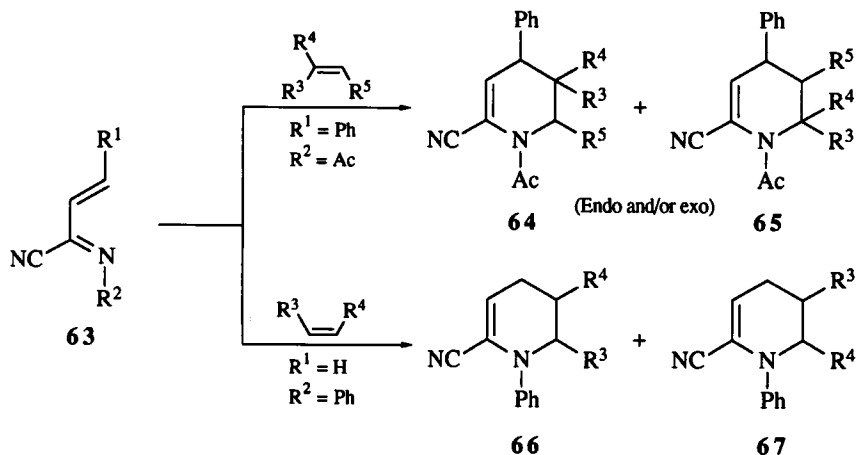
The oxime derived from 2-furfural has been used for the first time as an electron-rich 1-azadiene by Kusurkar and Bhosale (91TL3199) (Scheme 16). Thus, 2-furfuraldoxime **60** undergoes at 120°C $[4 + 2]$ cycloaddition to acrylonitrile, acrylic acid esters, and maleic anhydride to give stereoisomeric cycloadducts **61** and **62**. The isomeric fused pyridines obtained were not separated, but dehydrogenated to the corresponding furo[2,3-*c*]pyridine *N*-oxide derivatives.

On the contrary, the Fowler group has overcome the problem concerning the reluctance of 1-azadienes to participate in Diels–Alder reactions by incorporating electron-withdrawing substituents in the heterodiene structure, e.g., at nitrogen and/or carbon atoms (Scheme 17). *N*-Acyl- α -cyano-1-azadienes **63** ($\text{R}^2 = \text{Ac}$) reacted with dienophiles such as norbornene, ethyl vinyl ether, styrene, 1-hexene, methyl acrylate, and *cis*- and *trans*-1-phenylpropene, affording pyridines **64** and/or **65** in 5–92% yield (90JOC5646). The reactivity, regiochemistry, and stereochemistry observed are in agreement with a concerted mechanism with a transition state possessing a high degree of diradical character. Later, Fowler and



SCHEME 16

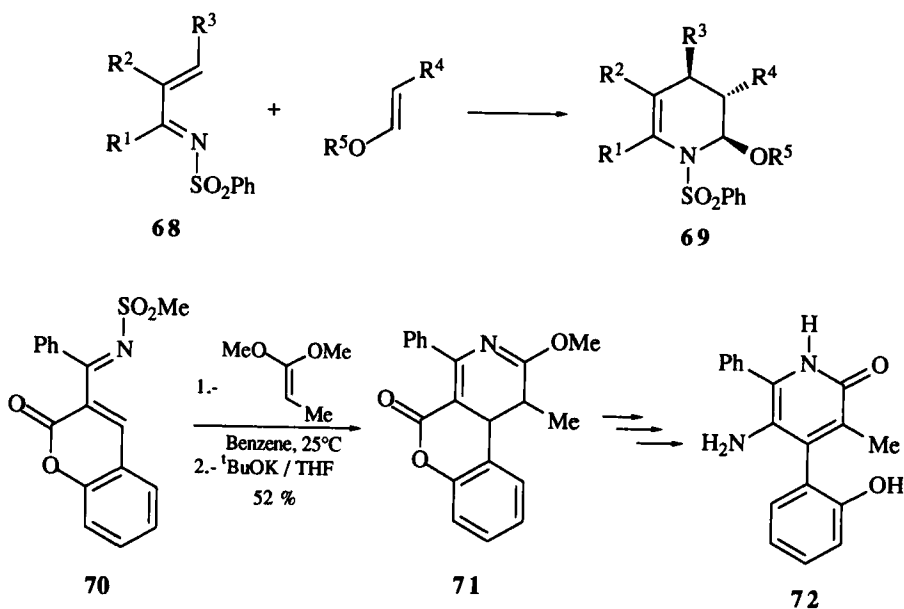
Grierson (91MI4) reported that the less activated *N*-phenyl-2-cyano-1-azadiene **63** ($R^2 = Ph$) is also capable of undergoing Diels–Alder cycloaddition reactions with both electron-rich and -poor dienophiles, giving tetrahydropyridines **66–67** in 25–75% yield (Scheme 17); the reaction with electron-rich olefines (ethyl vinyl ether, styrene, and dihydropyran) was shown to be regioselective, furnishing *ortho* adduct **66** ($R^3 = OEt$, Ph ; $R^4 = H$; and $R^3-R^4 = OCH_2CH_2CH_2$), whereas mixtures of *ortho* and *meta* regioisomers **66** and **67** ($R^3 = CO_2Me$, $COMe$), the former being predominant, were produced when methyl acrylate and methyl vinyl ketone were employed.



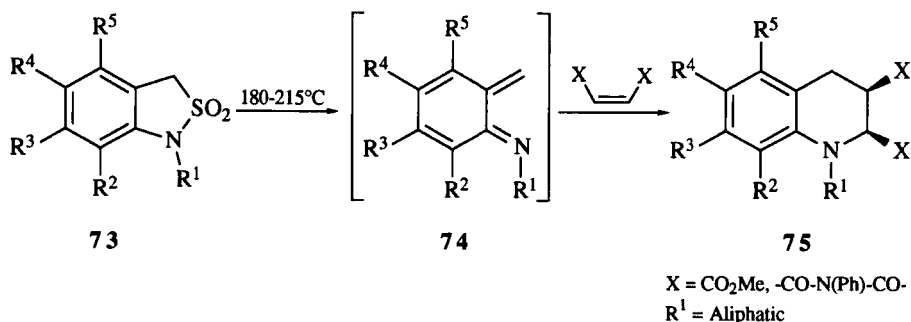
SCHEME 17

Relevant results have been reached by Boger, who used 1-sulfonyl-1-aza-1,3-butadienes as reactive 1-azadienes in inverse electron demand Diels–Alder cycloadditions; this work has been summarized (91MI1). They found that thermal- or pressure-promoted [4 + 2] cycloaddition reactions of *N*-(phenylsulfonyl)- and *N*-(methylsulfonyl)-1-azadienes **68** with electron-rich olefins (vinyl ethers, ketene acetals, methoxyallene, styrenes) provided single cycloadducts **69** derived from predominant cycloaddition through an *endo* transition state (Scheme 18). The presence of an extra electron-withdrawing substituent at C-2, C-3, or C-4 accelerates the process by lowering the LUMO diene energy (89JA1517; 90JOC2999, 90JOC5439; 91JA1713). Scheme 18 also illustrates the usefulness of this reaction with the synthesis of the C ring of the antibiotic streptonigrone **72** from azadiene **70**, which implies the formation of the key intermediate **71** (91JOC880).

Interestingly, 1-azadienes without activating groups have been shown to participate in [4 + 2] cycloaddition reactions. Thus, *o*-quinone methide imine **74**, generated *in situ* from benzoisothiazoline 2,2-dioxides **73** by sulfur dioxide extrusion, cycloadded to methyl maleate and *N*-phenylmaleimide, affording 1,2,3,4-tetrahydroquinoline-2,3-dicarboxylic acid derivatives **75** in 63–94% yield (91MI3) (Scheme 19). Earlier, Lancaster and



SCHEME 18

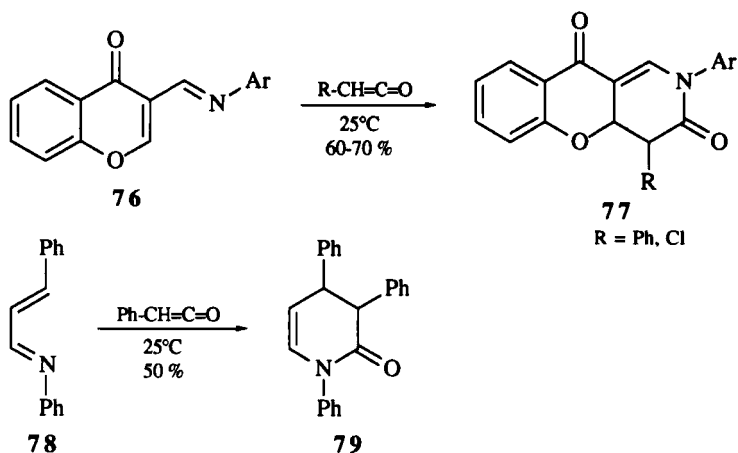


SCHEME 19

Smith obtained benzazetidines by photolysis of sultams **73**; they were able to trap the quinomethane imine intermediate **74** by forming the [4 + 2] cycloadduct with *trans*-chloroacrylic acid (80CC471).

Azadienes **76** and **78** have been shown by Sandhu *et al.* to give pyrimidinone derivatives **77** and **79** by reaction with phenyl- and chloroketene (Scheme 20) (91S1026). Additional examples in which 1-azadiene derivatives have been reported to give the [4 + 2] cycloadducts include reaction with enamines [82AG(E)213; 84JOC2691], mesoionic oxazolones [85JCS(P1)773; 87H777], and *Z*- β -silyloxyacrylonitrile (86TL2027).

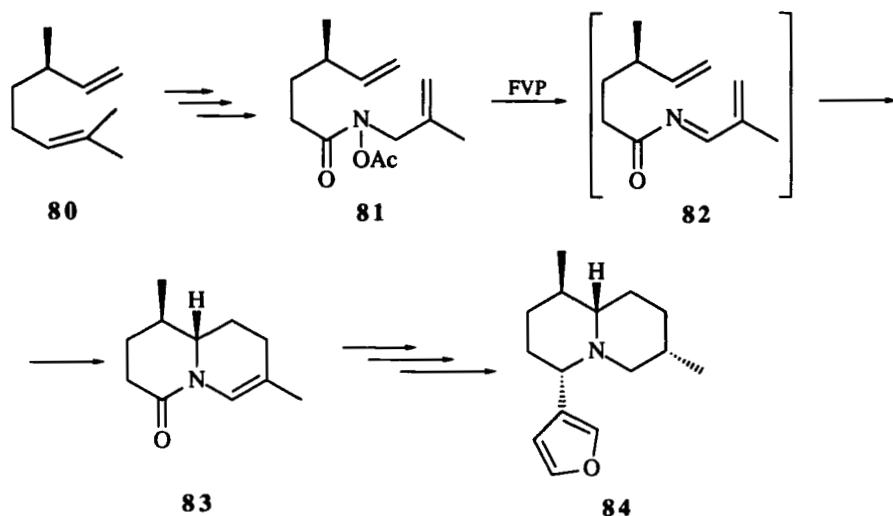
The intramolecular version of the [4 + 2] Diels–Alder cycloaddition was first reported by Fowler *et al.* using *N*-acylazadienes, generated in turn by thermal elimination of acetic acid from *o*-acetylhydroxylamine



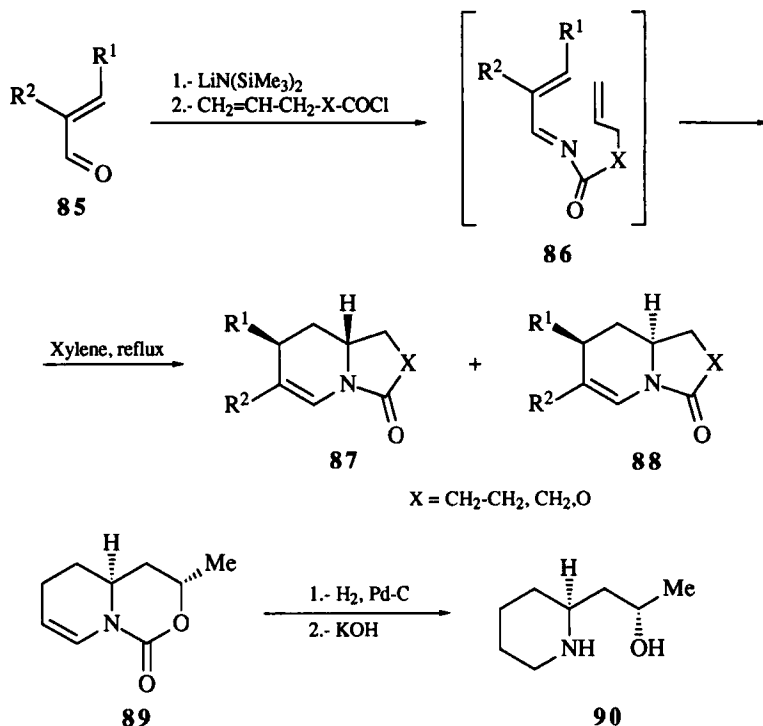
SCHEME 20

derivatives (81JA2090; 83JA7696; 89TL2481). Its usefulness in natural product synthesis was demonstrated in the preparation of alkaloid (-)-deoxynupharidine **84**, as outlined in Scheme 21 (85JOC2719). Chiral hydroxamic acid **81**, available in a few steps from (*R*)-dihydromircene **80**, was passed through a hot tube to generate azadiene **82**, which cycloaddaded to give diastereoisomer **83**, as the major reaction product; catalytic hydrogenation of the carbon—carbon double bond followed by introduction of the furan ring completed the synthesis.

Recently, Japanese workers [90TL(31)3753] described a simple approach to this type of *N*-acyl-1-azadiene system by means of trimethylsilylaldimines derived from α,β -unsaturated aldehydes (Scheme 22). Taking advantage of the chemistry of silylimines, aldehydes **85** were easily converted into 1-azadiene species **86**, which were heated to furnish *exo* **87** and/or *endo* **88** cycloadducts in 30–65% overall yield from **85**. They observed that the formation of quinolizinones (X = CH₂—CH₂) occurs exclusively via an *exo* transition state leading to **87**, whereas in the case of indolizinones (X = CH₂) and their oxa derivatives (X = O) the *endo* isomers **88** predominate. Following this strategy, the authors were able to achieve the total synthesis of piperidine alkaloid ($\pm$)-sedridine **90** in a few steps (Scheme 22); the process implies the diastereoselective intramolecular Diels–Alder reaction of the 1-azadiene derived from acrolein, lithium hexamethyldisilazane, and the homoallyl chlorocarbonate to give



SCHEME 21

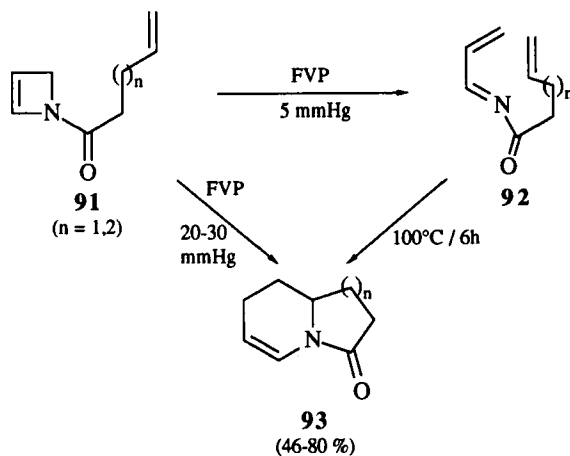


SCHEME 22

cycloadduct **89** in 30% yield, followed by reduction of the carbon—carbon double bond and cleavage of the urethane ring (91TL4371).

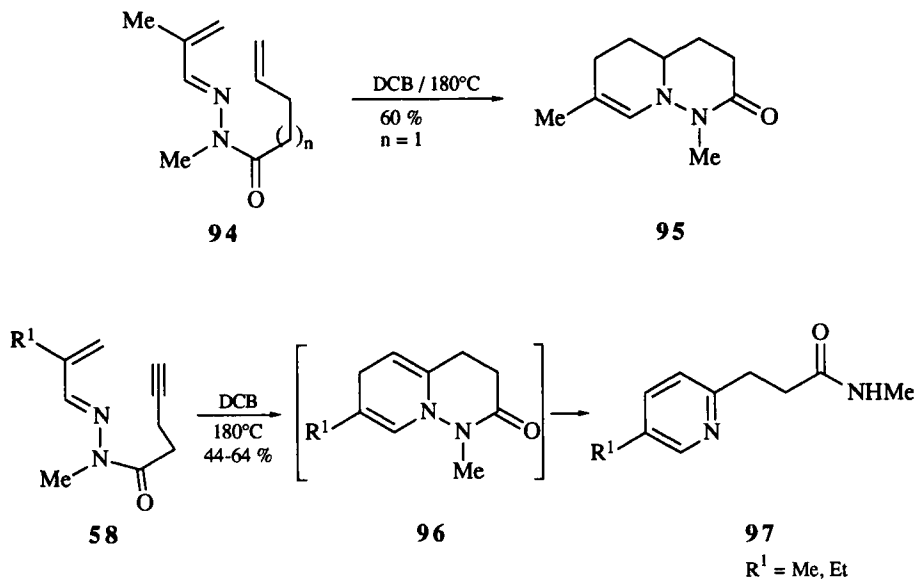
A completely different method for the preparation of 1-acyl-1-azabutadienes, namely thermal electrocyclic ring opening of 1-acyl-2-azetines, as well as for their intramolecular Diels–Alder reactions has been utilized by Jung and Choi (91JOC6729) (Scheme 23). Flash vacuum pyrolysis of **91** above 300°C at 5 mm Hg allowed isolation of azadiene derivatives **92**, which in turn were cyclized to **93** on heating in refluxing benzene; the direct isolation of **93** was effected by raising the pressure at the FVP stage to 20–30 mm Hg. Further elaboration of **93** ($n = 1$) to δ -coniceine was also reported.

The ability of related acylhydrazones **94** (Scheme 24), derived from α,β -unsaturated aldehydes, to participate in intramolecular Diels–Alder cycloaddition reactions has been proven to occur by Gilchrist and co-workers (91TL125). They reported that azadiene **94** ($n = 1$) cyclized to **95**, whereas compound **94** ($n = 0$) did not undergo intramolecular cycloadd-



SCHEME 23

dition on heating to 200°C . On the other hand, the unactivated alkyne function also cycloadded with the 1-azadiene system since pyridines **97** were formed in moderate yields when solution of **58** was heated in 1,2-dichlorobenzene; compounds **97** should arise from aromatization of intermediate Diels-Alder cycloadduct **96**.



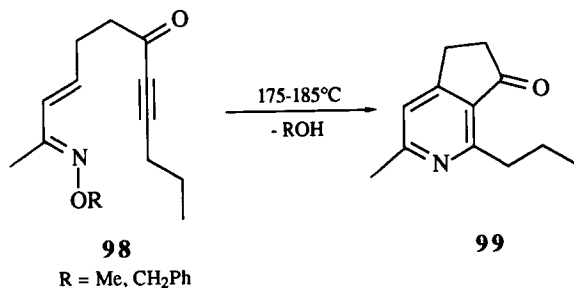
DCB = 1,2-dichlorobenzene

SCHEME 24

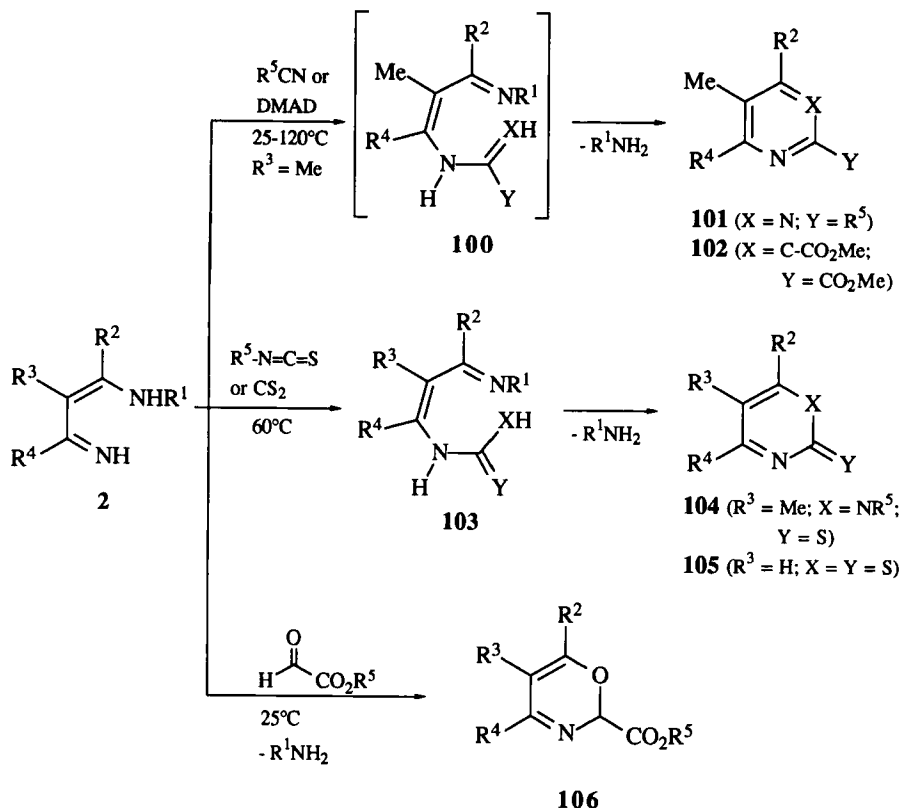
On the contrary, while working in the synthesis of the alkaloid rubrolone, Boger and Zhu (91TL7643) have found *O*-alkyl α,β -unsaturated oximes **98** to participate as effective 4π components of an intramolecular Diels–Alder reaction with an electron-deficient dienophile. Thus, **98** was prepared from butane-1,4-diol and heated in triisopropylbenzene to furnish 2-pyridine derivatives **99** by virtue of *in situ* elimination of alcohol (Scheme 25).

Among other leading workers in this field were Saegusa (81JA5250; 83TL2881; 86SC1073), Kametani (84TL4541; 85CC1159, 85H1097), and Dolle (88TL6349), who employed *o*-quinone methide imines, 2-trialkylsilyl-1-azabutadienes, and 1-dimethylamino-1-azabutadienes, respectively, as the reactive heterodienes in the intramolecular cycloaddition.

Despite the fact that 4-amino-1-azadienes **2** are not capable of undergoing Diels–Alder cycloaddition processes, they become suitable substrates for preparing six-membered nitrogen heterocycles by $[4 + 2]$ heterocyclizations (Scheme 26). Thus, pyrimidines **101** (70S363) and pyridines **102** (75S191) were obtained in high yields by treating **2** ($R^3 = \text{Me}$) with nitriles and dimethyl acetylenedicarboxylate, respectively; the cyclization is assumed to involve first addition of the imine N—H to the electrophilic reagent to form **100** and, second, intramolecular nucleophilic attack of the amidine nitrogen ($X = \text{N}$) or of the enamine β -carbon ($X = \text{C}-\text{CO}_2\text{Me}$) to the $\text{C}=\text{N}-\text{R}^1$ imine function followed by amine elimination. Heterocumulenes such as isothiocyanates (80JOC2592) and carbon disulfide [79TH1; 82JCS(P1)2149] furnished pyrimidine-2(1*H*)-thiones **104** and 1,3-thiazine-2-thiones **105** through isolated addition intermediates **103**. The carbon–oxygen double bond also proved to participate in this reaction, forming the 1,3-oxazine ring; in fact, stirring at room temperature a tetrahydrofuran solution of **2** and esters of glyoxylic acid followed by aqueous work-up resulted in a clean conversion into 2*H*-1,3-oxazines **106** in excellent yields (92UP1). It should be noted that **2** condensed with ordinary



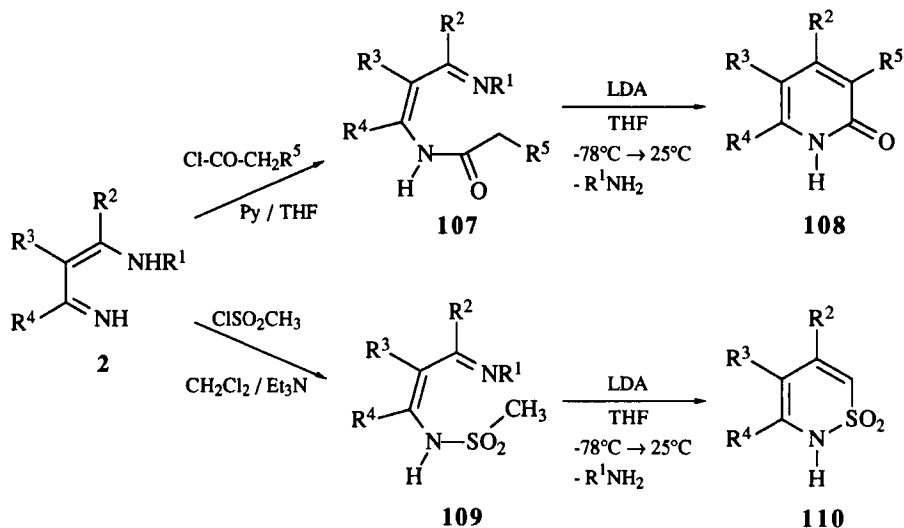
SCHEME 25

DMAD : $\text{MeO}_2\text{C-C}\equiv\text{C-CO}_2\text{Me}$

SCHEME 26

aldehydes and, occasionally, with heterocumulenes in a $[5 + 1]$ manner (Section II,B,2).

We have described (88TL4855) a simple synthesis of pyridin-2-ones by a two-step annulation of **2** with aliphatic acid chlorides (Scheme 27). The acylation of aminoazadienes **2** in pyridine furnished 4-amido-1-azabutadienes **107** in high yields (85JOC802); lithium diisopropylamide-catalyzed aldol-type cyclization of **107** afforded pyridin-2-ones **108** in 83–94% yield. Extension of this reaction to methanesulfonyl chloride permitted preparation of open-chain derivatives **109** in 88–90% yield, which in turn cyclized in the presence of lithium diisopropylamide to 2*H*-1,2-thiazines **110** in 82–92% yield (89TL4705). Earlier work by the Komatsu–Ohshiro group showed that the reaction of simple 1-azadienes



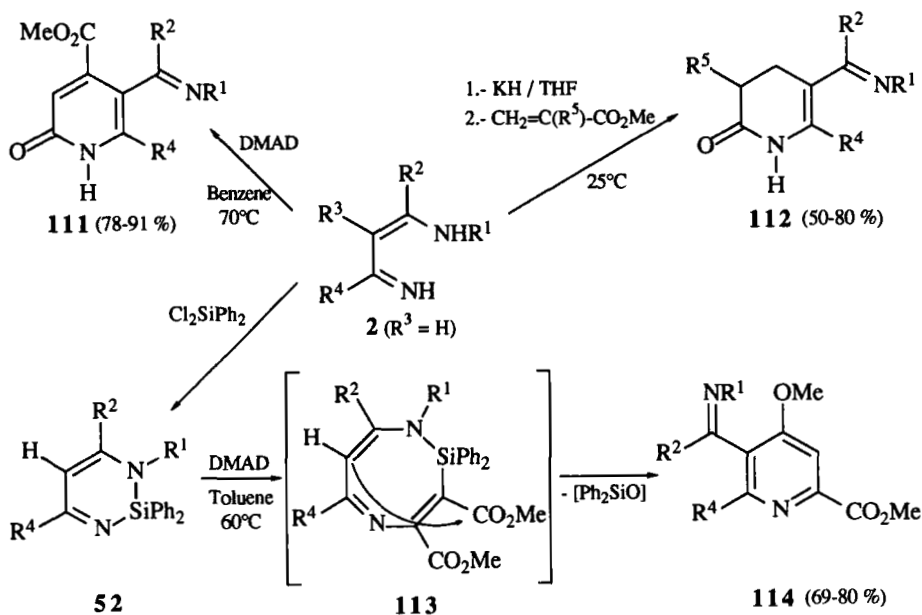
SCHEME 27

with enolates of substituted acetates gives rise to mixtures of 2-pyridones and isomeric dihydro-2-pyridones (81TL3769).

The [4 + 2] cycloaddition of benzo-1-azadienes with electrophilic carbon—carbon double bonds has been implemented by de Meijere and co-workers (90CC574); in this case, the authors used N-unsubstituted benzo-phenone imine and cyclopropylideneacetates, and the reaction represents a new isoquinoline ring synthesis.

3. From [3 + 3] Fragments

Azadienes **2** with no substitution at the C_β -enamine atom ($R^3 = H$) were found to form six-membered heterocycles in processes involving both C-3 and N-1 atoms (Scheme 28). In this context, the regioselective synthesis of pyridin-2(1H)-ones **111** and their 3,4-dihydro derivatives **112** was brought about by reacting **2** with esters of acetylenedicarboxylic acid (79S345) and acrylic or methacrylic acid (88S146), respectively. The course of this reaction can be modified by reacting dimethyl acetylenedicarboxylate with 1,3,2-diazasilines **52** in place of azadiene **2** itself (92S106). Treatment of **52** with DMAD at $60^\circ C$ gave rise to highly functionalized pyridines **114** in good yields. The reaction pathway seems to involve initial addition of the nitrogen—silicon bond to the activated carbon—carbon triple bond to form the diazasilocene **113**; further intramolecular nucleo-



DMAD : $\text{MeO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Me}$

SCHEME 28

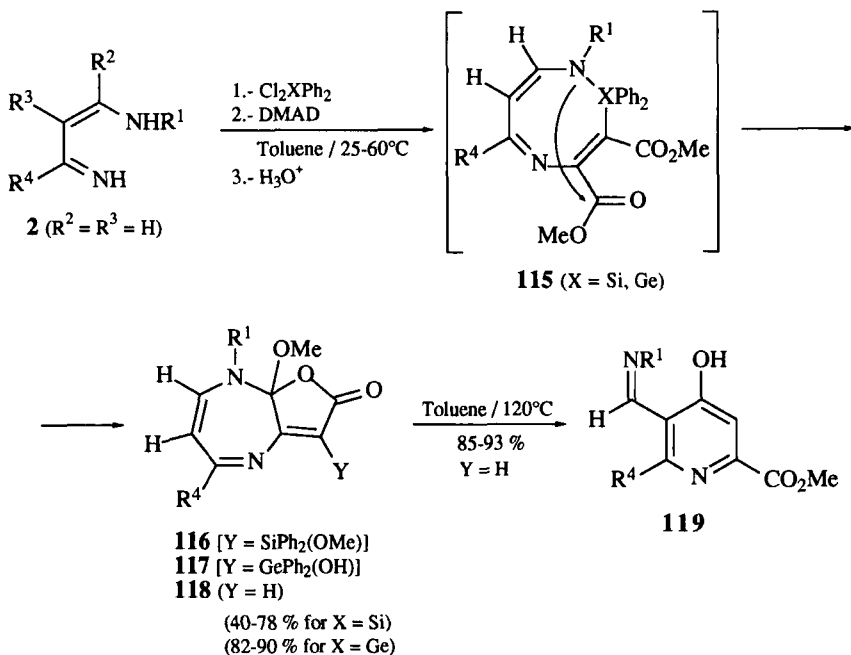
philic attack of the C_β -enamine carbon atom on the methoxycarbonyl group attached to the ring C-3 (1,6-attack) with loss of diphenyl oxide species accounts well for the formation of **114**.

C. MEDIUM-SIZE RINGS

These preliminary results on the different reactivity of diazasilines **52**, probably due to a template effect, compared to their aminoazadiene precursors **2** as pointed above, encouraged us to continue the study of the reactivity of both diazasilines **52** and diazagermines **53** with the aim of synthesizing novel medium ring heterocycles. We have found that, depending only on the substitution pattern of the starting azadiene **2**, the reaction of **52-53** with esters of acetylenedicarboxylic acid can be directed exclusively to the formation of seven- or eight-membered heterocycles. Since all the reactions were best run in a one-pot fashion from **2**, the diazasiline **52** and -germine **53** intermediates are omitted in Schemes 29–31.

The preparation of seven-membered heterocycles was accomplished by starting from azadienes **2** with no substituents at both C_α - and C_β -enamine carbon atoms ($R^2 = R^3 = H$) (Scheme 29). Sequential treatment of those azadienes **2** with dichlorodiphenylsilane or -germanium followed by reaction of the resulting solution with DMAD at 60 or 25°C (for silicon or germanium derivatives, respectively) gave new furo[2,3-*b*][1,4]diazepines **116** and **117**; either protodesilylation or protodegermylation to **118** (40–90% yield from **2**) was carried out by stirring at room temperature a dichloromethane solution of trifluoroacetic acid and **116** or **117**. Compounds **118** rearranged cleanly to pyridines **119** in refluxing toluene. The germanium—nitrogen bond seems to be more reactive than the silicon—nitrogen one since the process takes place in the former case at lower temperature and in higher yield. The formation of the seven-membered ring can be rationalized by taking in mind that the conformational effects seem to favor the intermediate **115** to undergo intramolecular carbon—nitrogen bond formation between N-1 and the carbonyl function linked to C-4 (1,5-attack) (91CC353; 92MI1, 92S106).

We also explored the reaction of diazasilines and -germines derived

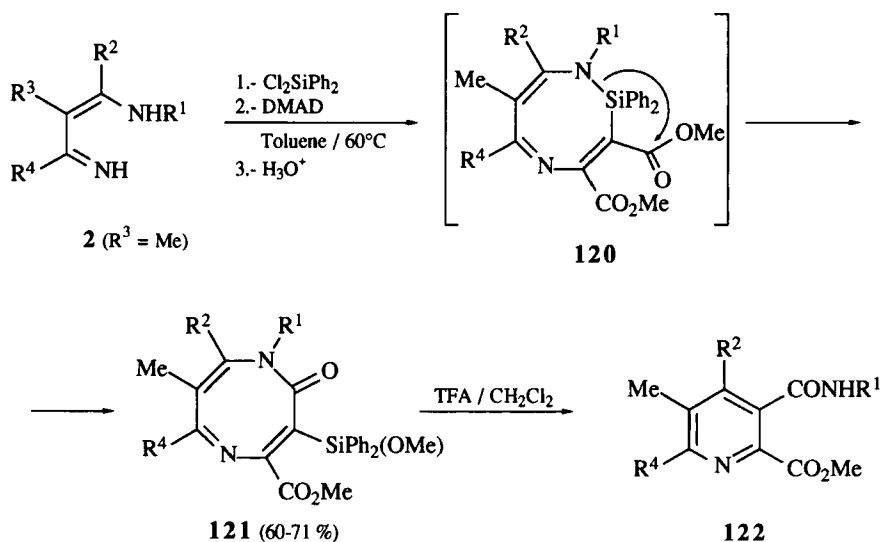


DMAD : $\text{MeO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Me}$

SCHEME 29

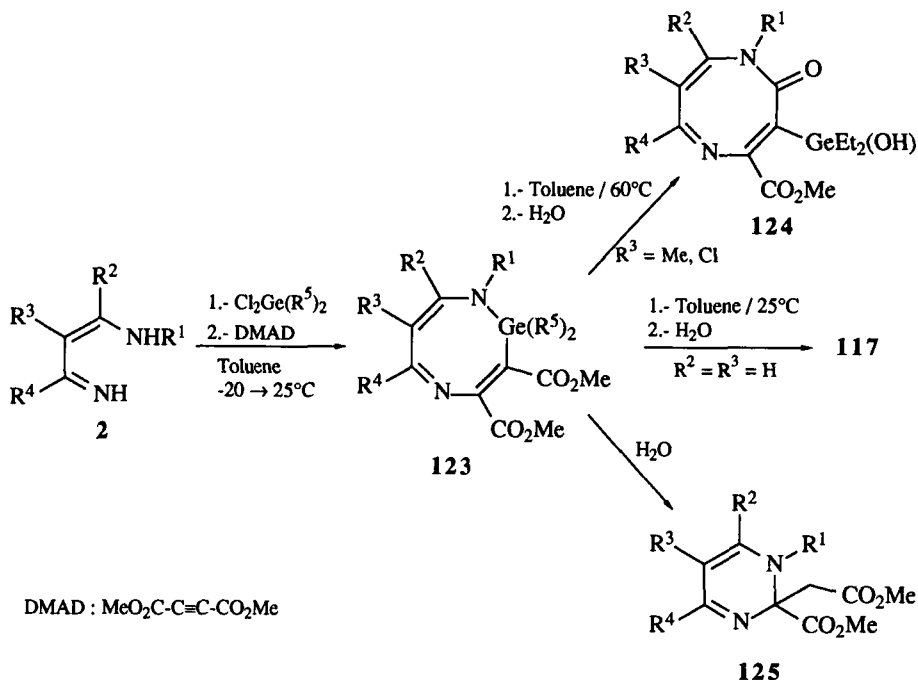
from azadienes **2** having R^2 and R^3 other than hydrogen toward dimethyl acetylenedicarboxylic acid (Scheme 30). When azadienes **2** ($R^2 = \text{Ph}$; $R^3 = \text{Me}$) and dichlorodiphenyl silane were stirred in toluene at room temperature and then heated at 60°C with dimethyl acetylenedicarboxylic acid, eight-membered heterocycles **121** were isolated in 60–71% yield. All attempts to desilylate compounds **121** preserving the ring structure failed; thus, the protodesilylation reaction induced by trifluoroacetic acid resulted in the simultaneous ring contraction to pyridines **122** in quantitative yield. The formation of **121** is now understood by nucleophilic attack of the enamine nitrogen atom—in this case attack by the C_β -enamine carbon is precluded because of methyl substitution—into the ester attached to C-3 in a rather conformationally rigid intermediate **120** [86AG(E) 181; 92S106].

Importantly, we succeeded in an extremely easy synthesis of novel eight-membered germanium-containing heterocycles from azadiene derivatives **2** with the intermediacy of reactive diazagermines **53** (92MI1) (Scheme 31). When a toluene solution of the diazagermine, generated from **2** and diphenyl or diethylgermanium dichloride, was stirred at room temperature with dimethyl acetylenedicarboxylate, 1,5,2-diazagermocines **123** ($R^3 = \text{Me}$, C1) were quantitatively isolated in pure form, after removal of the solvents; the structure of **123** was confirmed by an X-ray determination. As expected, compounds **123** rearranged on heating to germanium-



DMAD : $\text{MeO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Me}$

SCHEME 30



SCHEME 31

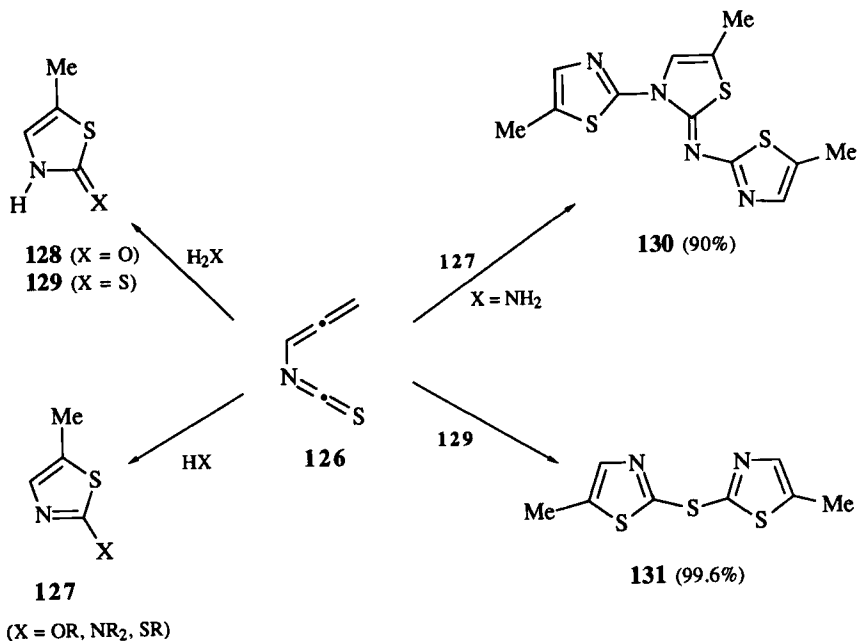
substituted 1,5-diazocine-2(1H)-ones **124**, and their aqueous hydrolysis gave quantitatively new 1,2-dihydropyrimidines **125** as well. In the case of starting with azadienes **2** having $R^2 = R^3 = H$, the formation of corresponding diazagermocines **123** takes place at $-20^\circ C$ and were not isolated, but either allowed to warm to room temperature to afford **117** or hydrolyzed to pyrimidines **125** ($R^2 = R^3 = H$).

III. Synthesis of Heterocycles Using 2-Azadienes

A. FIVE-MEMBERED RINGS

1. From $[5 + 0]$ Fragments

The highly reactive 2-azadiene with an allene and heterocumulene structure **126**, prepared by gas-phase thermolysis of propargyl thiocyanate, has been found by the Banert group to be an efficient precursor for thiazole derivatives by nucleophilic-induced heteroannulation through carbon and



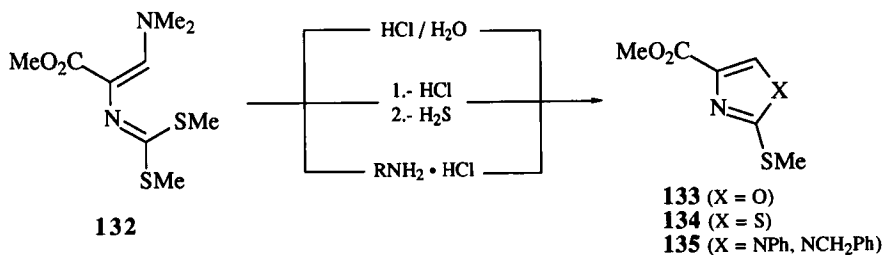
SCHEME 32

sulfur [92AG(E)90] (Scheme 32). Thus, reaction of **126** with alcohols, amines, and thiols gave thiazoles **127** in 40–82% yield, whereas treatment of **126** with water or hydrogen sulfide furnished thiazole derivatives **128** and **129** (86 and 53% yield, respectively). The use of **127** and **129** as nucleophiles resulted in the formation of **130** and **131**, respectively, in nearly quantitative yields.

2. From [4 + 1] Fragments

2-Azadiene **132**, containing electron-donor and -acceptor substituents, has been shown by Gomper and Heinemann [81AG(E)296] to be a suitable precursor of several five-membered rings by acid-catalyzed cyclization reactions (Scheme 33). Thus, oxazole **133** (86%), thiazole **134** (85%), and imidazoles **135** (22–38%) were obtained upon reaction of **132** with aqueous HCl, HCl/H₂S, and RNH₂·HCl, respectively.

Fleury and co-workers (87HCA187) reported that somewhat related 2-azadienes **136**, 4-(dialkylamino)-1,1-dicarbonitrile-2-aza-1,3-diene and their 1-methoxycarbonyl analogues, afforded imidazoles **137** when reacted with N-substituted or N,N-disubstituted hydrazines and hydrazides by double nucleophilic attack. Moreover, the addition of cyanide to **136**

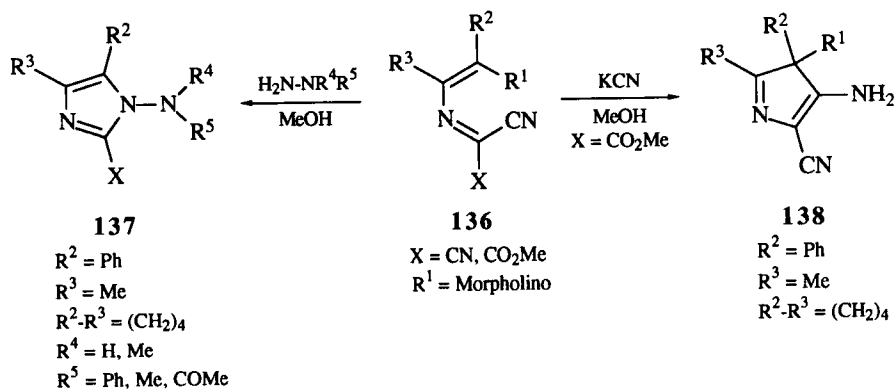


SCHEME 33

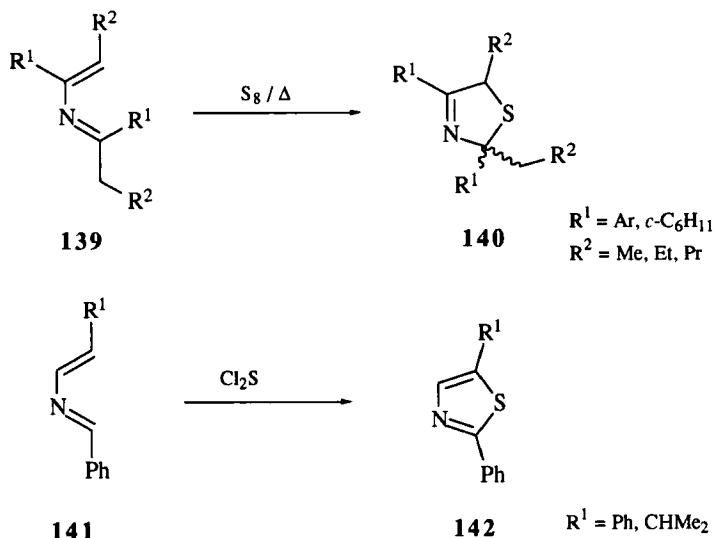
(X = CO₂Me) yielded, after decarboxylation, functionalized 3*H*-pyrroles **138** (Scheme 34).

During recent years we devoted some attention to simple, electronically neutral 2-azadienes **139** (90MI3). In contrast to the lack of methods for preparing these systems we have found that thermal- or Lewis acid-induced dimerization of imines provided those azadienes in large quantities (85CB3652). Using 2-azadienes **139**, we have prepared a number of Δ³-thiazolines **140** in yields higher than 81% by heating a mixture of azadiene and elemental sulfur without solvent (170°C) or in toluene (80°C) (92T9745). The diastereoisomeric ratio reached in this heterocyclization was in the range 1 : 1 to 1 : 3, thus improving previous results reported on this reaction (67AG953). Moreover, Komatsu *et al.* isolated thiazoles **142** on reaction of simple 2-azadienes **141** with sulfur dichloride (83PS119) (Scheme 35).

However, vinyl isocyanates have been nicely demonstrated by the Rigby group to be particularly useful intermediates in synthesis of pyrroli-



SCHEME 34

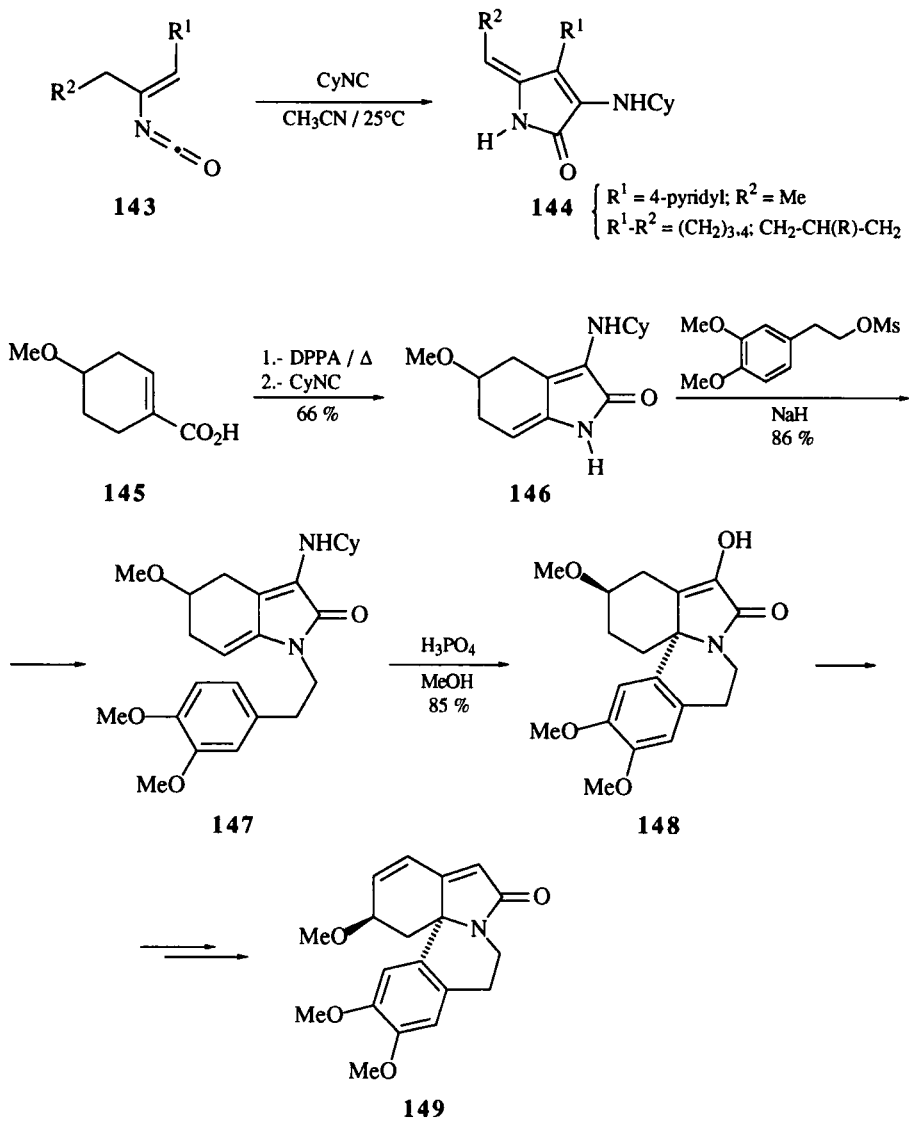


SCHEME 35

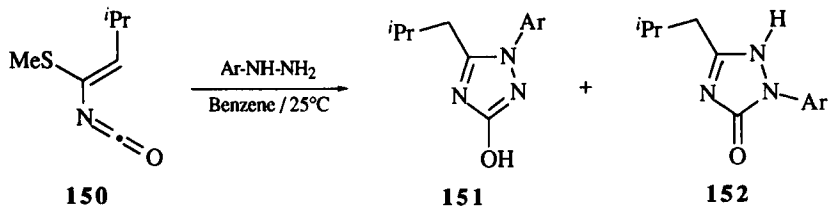
none derivatives (91JA8975) (Scheme 36). Vinyl isocyanates **143** were generated *in situ* from the corresponding α,β -unsaturated carboxylic acids and diphenyl phosphorazidate (DPPA) and then reacted at room temperature with cyclohexyl isocyanide to furnish pyrrolinones **144** in 68–84% yield. In order to illustrate the potential of this strategy, which gives access to structures of certain Amaryllidaceae alkaloids, the efficient, concise synthesis of erysotrine is outlined in Scheme 36. Pyrrolinone **146** was made in 66% yield by [4 + 1] heteroannulation of the isocyanate derived from carboxylic acid **145** and then alkylated with the appropriate mesylate to produce **147**; Friedel–Crafts cyclization of **147** gave compound **148**, precursor of erysotrine **149**, as the sole stereoisomer.

3. From [3 + 2] Fragments

Examples of synthesis of five-membered heterocycles following this strategy are limited in number. An approach to 1,3,4-triazoles involves bonding of C-1 and C-3 of vinyl isocyanate **150** to both nitrogen atoms of aromatic hydrazines (78JOC402) (Scheme 37). The reaction was run at room temperature and gave quantitatively regioisomer **151** or a mixture of **151** and **152** when *p*-nitrophenyl and phenylhydrazine, respectively, were employed.



SCHEME 36

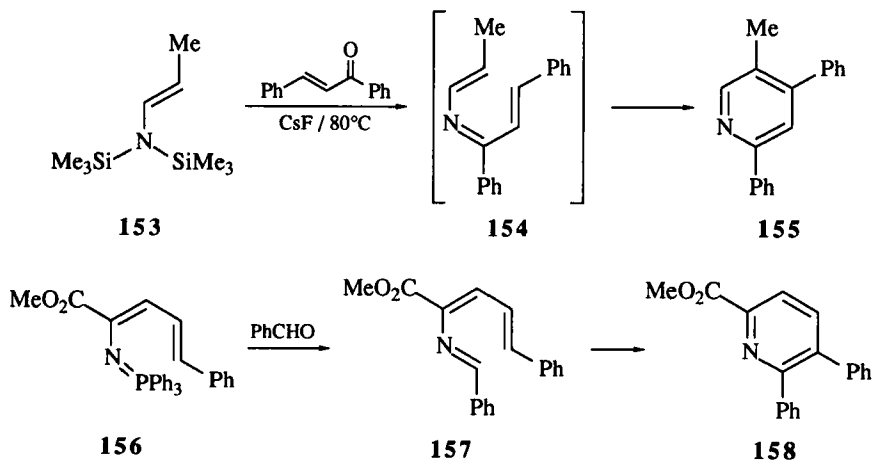


SCHEME 37

B. SIX-MEMBERED RINGS

1. From [6 + 0] Fragments

Electrocyclic ring closure reactions of vinyl or aryl 2-azadienes (aza-trienes) involving six electrons have been reported to occur at moderate temperatures and, in this respect, several pyridine syntheses have been described. While preparing 2-azadienes, Corriu *et al.* and our group have observed that electrocyclic ring closure takes place in some instances (Scheme 38). Corriu (82TL3257) obtained pyridine **155** in 67% yield by reaction of *N,N*-bis(trimethylsilyl)enamines **153** and chalcone, probably through intermediate **154**. In our case [90JCS(P1)2193], the aza-Wittig reaction of **156** and benzaldehyde at room temperature allowed isolation of 2-azatriene **157**, which on heating at 60°C gave **158**; direct conversion of phosphazene **156** into **158** was accomplished in 86% yield at 60°C .

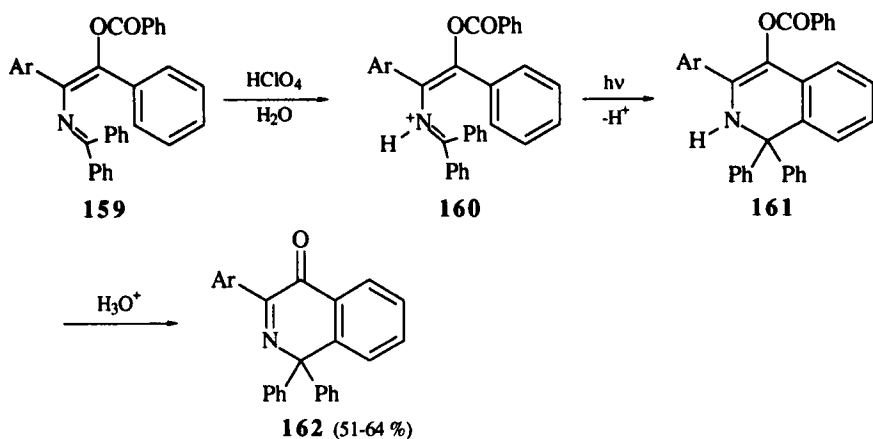


SCHEME 38

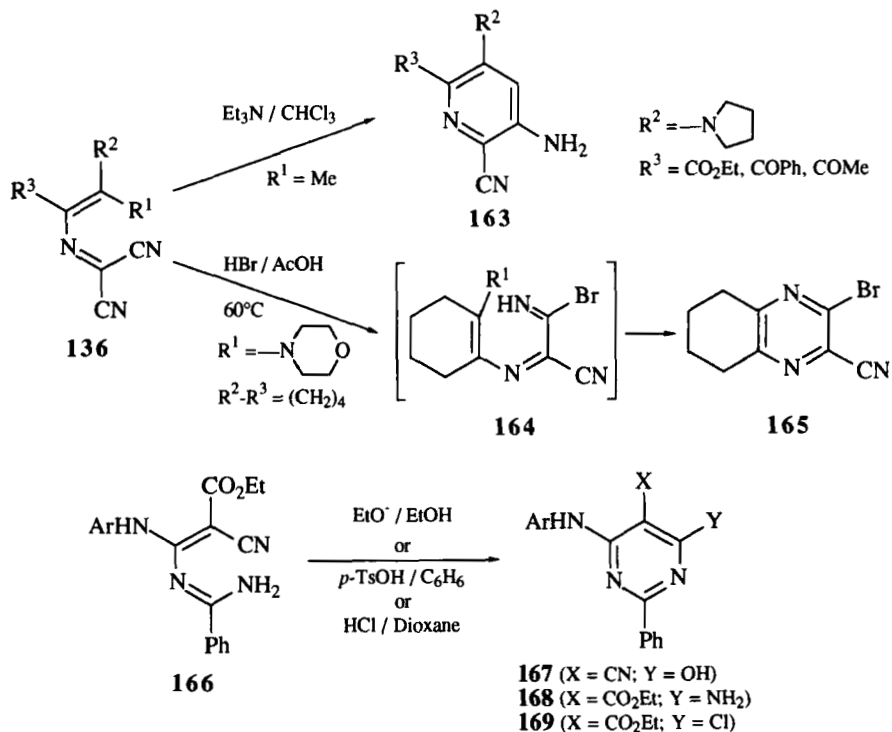
The photochemical electrocyclic cyclization of conjugated iminium salts **160**, formed by protonation of 2-azadienes **159**, led to isoquinolin-4-ones **162**, presumably through hydrolysis and oxidation of the dihydroisoquinoline intermediates **161** (85TL5213) (Scheme 39). A closely related reaction served as the key step for a short synthesis of the pentacyclic marine alkaloid ascididemin as reported by Moody, Rees, and Thomas [90TL(31)4375; 92T3589]; the central reaction involves a 6π -electron photocyclization of a *syn*-aza stilbene in sulfuric acid.

The thermal 6π -electrocyclic rearrangement of *o*-vinyl anils, generated by condensation of the corresponding 2-vinyl anilines with aldehydes lacking α -hydrogen atoms, has been accomplished by Qiang and Baine, who synthesized substituted quinolines in 38–86% yield by heating at 155–200°C (88JOC4218).

Heterocyclizations of 2-azadiene derivatives to pyridines and diazines involving carbon—carbon and carbon—nitrogen, respectively, bond formation have been described (Scheme 40). Fleury *et al.* studied the utility of 2-azadienes **136** as precursors of nitrogen-containing six-membered heterocycles; thus, **136** ($R^1 = \text{Me}$) underwent, in the presence of base, intramolecular 1,6 nucleophilic addition to the cyano group, giving rise to pyridines **163** in 85–90% yield (86HCA793). On the other hand, pyrazine **165** was isolated in 71% yield on exposure of the appropriate azadiene **136** to HBr; bromoimine **164** seems to act as intermediate in the process (90HCA1210). 2-Azadienes having cyano and amino substituents at positions 1,4 are expected to cyclize to the pyrimidine ring. This conversion has been performed by Devani and co-workers, who synthesized in



SCHEME 39



SCHEME 40

50–70% yield substituted pyrimidines **167**, **168**, and **169** by treatment of azadiene **166** with ethoxide ion, acid, and hydrogen chloride, respectively (84TL1291).

In recent years, increasing efforts have been focused in the study of unsaturated nitrogen-containing heterocumulenes as 2-azadiene equivalents; in this field the extensive work developed by the Molina group should be emphasized. Concerning the six-electron electrocyclization of

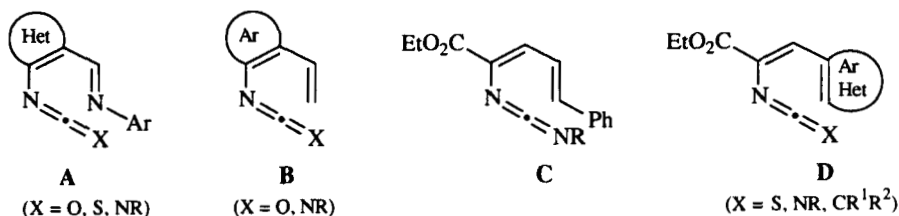
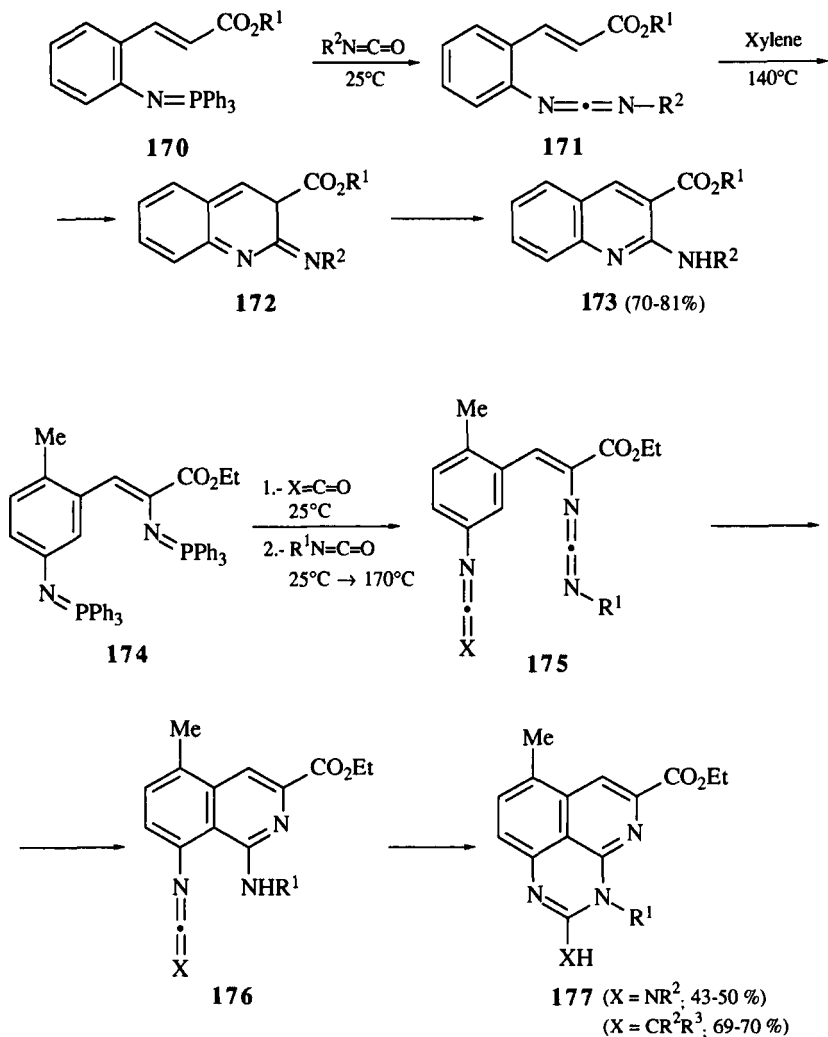


FIG. 1.

vinylazadienes of this type, they have reported on the cyclization of *N*-aryl(heteroaryl) systems **A** (88JOC4654) and **B** (90S474; 92JOC929) as well as of *N*-vinyl derivatives **C** (88TL379) and **D** (91T4175, 91T6737).

Representative examples by Saito and Motoki (92CC22) and Molina (91TL5379) leading to quinolines **173** and pyrido[2,3,4-*de*]quinazolines **177**, respectively, are shown in Scheme 41. Carbodiimides **171**, which



SCHEME 41

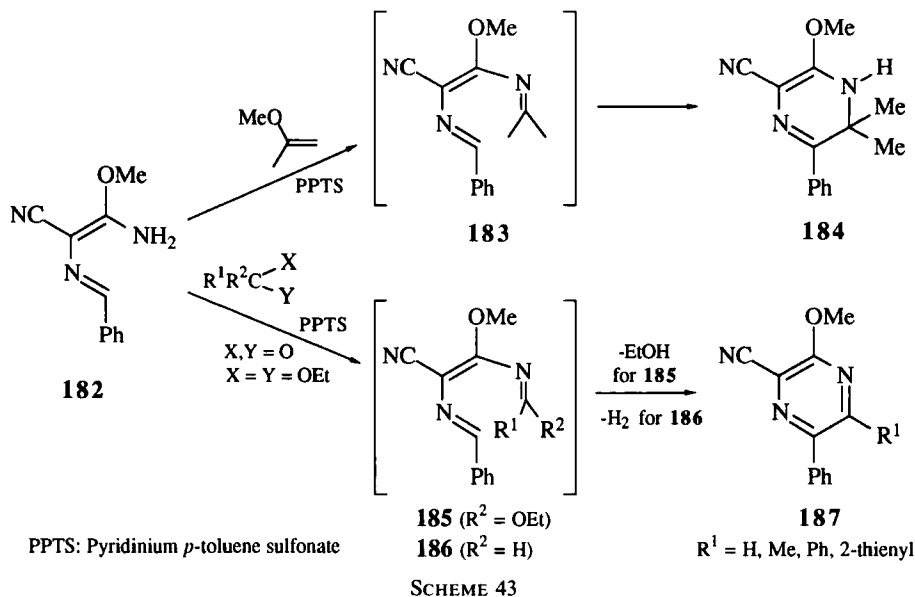
were prepared in more than 81% yield from iminophosphoranes **170** and aryl isocyanates, underwent electrocyclization at 140°C to produce 2-aminoquinolines **173** via prototropic aromatization of **172**. On the other hand, consecutive aza-Wittig reaction of bis(iminophosphorane) **174** with one molar equivalent of isocyanate or ketene and then with a second equivalent of isocyanate yielded bis-cumulenes **175**, which were converted into pyrido[2,3,4-*de*]quinazoline derivatives **177** upon heating at 170°C; the reaction course is explained in terms of pyrido annelation of **175** to **176** via electrocyclic ring closure of the styryl carbodiimide portion and intramolecular amination.

2. From [5 + 1] Fragments

The already-mentioned 2-azadienes **136** have become suitable starting materials for the synthesis of six-membered heterocycles as a five-atom fragment (Scheme 42). This protocol implies treatment of azadienes **136** with ammonia and primary amines to give regiospecifically moderate to nearly quantitative yields of substituted 2-aminopyrazines **178** (86HCA793) and 1-alkylpyrazinoneimines **179** (86HCA1025); compounds **179** made from diamines gave pyrazino[1,2-*a*]pyrimidine and imidazo[1,2-*a*]pyrazine derivatives **180** by heating above 90°C. This quite general strategy has been demonstrated for a number of acyclic and semicyclic heterodienes and, in some instances, the resulting pyrazines were transformed into pteridines by reaction with guanidine. Moreover, when 2-azadienes **136** were reacted with substituted amines or hydrazones having an electrophilic center at the β -position ($Z = \text{COMe}, \text{COPh}, \text{CO}_2\text{Et}, \text{CN}$), several heteropolycyclic structures **181** were obtained (87HCA187).

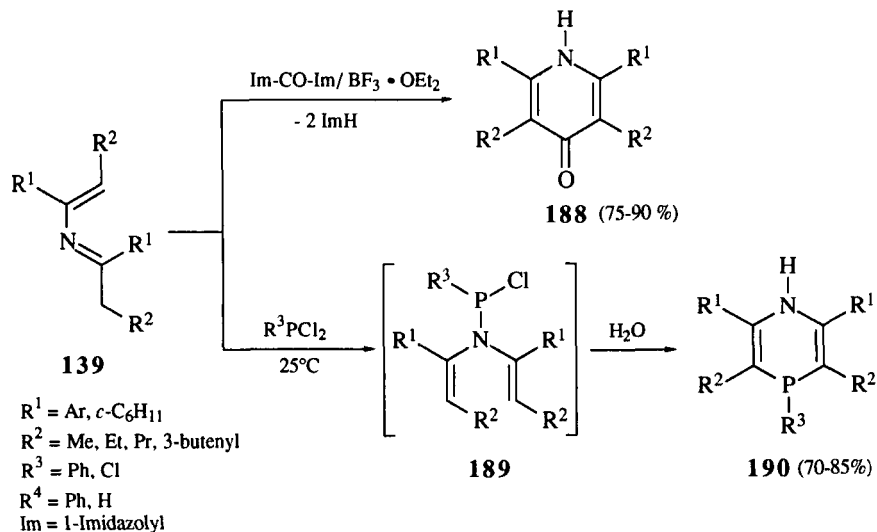
Freeman and Kim (92JOC550) have studied some heterocyclization reactions of substituted 4-amino-2-azadienes leading to pyrazines (Scheme 43). (1*E*,3*E*)-4-Amino-3-cyano-4-methoxy-1-phenyl-2-azabutadiene **182** was first reacted with 2-methoxypropene/pyridinium *p*-toluenesulfonate in refluxing toluene to give **184** in 82% yield. Diazatriene **183**, resulting from condensation of the amino group of the azadiene and the masked propanone, was proposed by the authors as the reaction intermediate; further six π -electron electrocyclization of **183** explains the formation of 4,5-dihydropyrazine structure **184**. Similarly, reaction of **182** with triethyl orthoesters and aromatic aldehydes afforded pyrazines **187** in 43–91% yield; diazatrienes **185** and **186** generated from orthoesters and aldehydes, respectively, underwent electrocyclic ring closure and aromatization by elimination of ethanol or dehydrogenation.

When working with substituted 2-azadienes **139**, we were aware of their behavior as divinyl amines; in fact, their reaction with trimethylsilyltriflate



1,4-azaphosphorine derivatives **190**, the divinylamine derivative **189** being assumed to be the intermediate species (88CC1596) (Scheme 44).

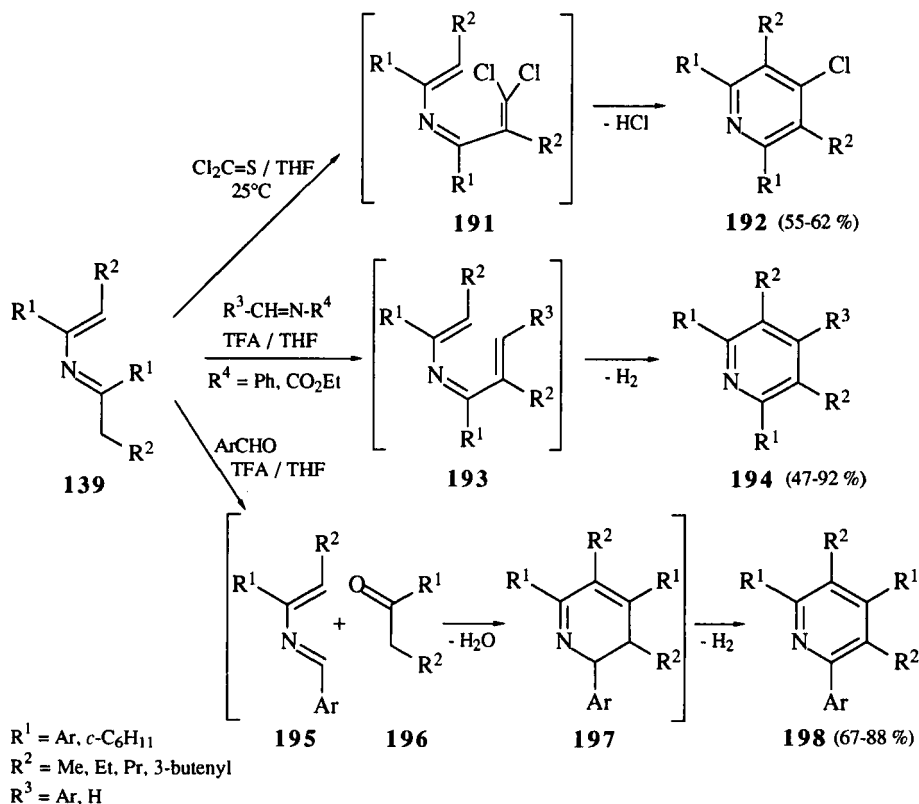
In contrast, the reaction between **139** and thiophosgene ($\text{Cl}_2\text{C}=\text{S}$) at room temperature did not afford, in light of the behavior depicted above for these azadienes, the expected pyridine-4(1*H*)-thiones, but 4-chloropyridines **192** were isolated in fair yields; mechanistically, condensation of the azadiene and the thiocarbonyl group giving intermediate **191** followed by electrocyclic ring closure and loss of HCl accounts for the formation of **192** (91JOC6751) (Scheme 45). Aldimines were found to behave in the same way as thiophosgene toward neutral 2-azadienes. Thus, *N*-phenyl imines were able to condense with **139** in the presence of trifluoroacetic acid in refluxing tetrahydrofuran to produce pentasubstituted pyridines **194**, after electrocyclization of azatriene intermediate **193** and spontaneous dehydrogenation; the use of the species $\text{CH}_2=\text{N}-\text{CO}_2\text{Et}$ gave rise to corresponding tetrasubstituted pyridines **194** ($\text{R}^3 = \text{H}$). At this point, the condensation reaction of **139** with aromatic aldehydes was studied and, surprisingly, we found that symmetrical pyridines **194** ($\text{R}^3 = \text{Ar}$) were not formed, but unsymmetrical regioisomers **198** were isolated in good yields. The formation of **198** is probably the result of a rapid ketimine–aldimine exchange to give new azadiene **195** and displaced ketone **196**, which undergo condensation to **197** and *in situ* oxidation (88JOC5960) (Scheme 45).



SCHEME 44

3. From [4 + 2] Fragments

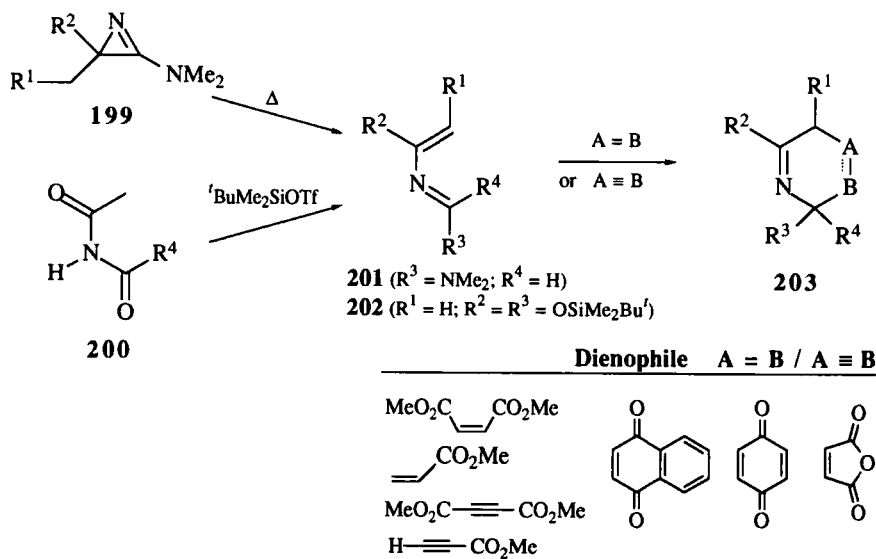
In this section the [4 + 2] Diels–Alder cycloadditions along with polar heterocyclizations will be considered, as in the case of 1-azabutadienes. In a study about *ab initio* molecular orbital calculations, González and Houk concluded that the transition structures for the Diels–Alder reactions of 2-azabutadienes with alkenes and alkynes are similar to the ones reported previously for the all-carbon Diels–Alder reactions (92JOC3031). It must be taken into account that until the last decade very few methods had been developed for preparing 2-azadienes and, therefore, their Diels–Alder cycloadditions were rather rare. Certainly, the most available and hence the best studied systems were 2-azabutadienes with electron-donating groups. These electron-rich heterodienes were first shown to react with electron-poor dienophiles in a Diels–Alder fashion by Ghosez and co-workers. Thus, azirines **199** (75JA4409) and imides **200** (82JA1428) served as precursors of 2-azadienes with electron-donating substituents **201** ($R^3 = \text{NMe}_2$) and **202** ($R^2 = R^3 = \text{OSiMe}_2\text{Bu}'$), respectively, which reacted with a variety of carbon-carbon double and triple bond dienophiles to give cycloadducts **203** (Scheme 46). Important pioneering work was also undertaken by Gomper and Heinemann, who synthesized the pyridine ring starting from 1,3-bis(dimethylamino)-2-azadienes [80AG(E)217] and 4-dimethylamino-3-methoxycarbonyl-2-azabutadienes [81AG(E)296].



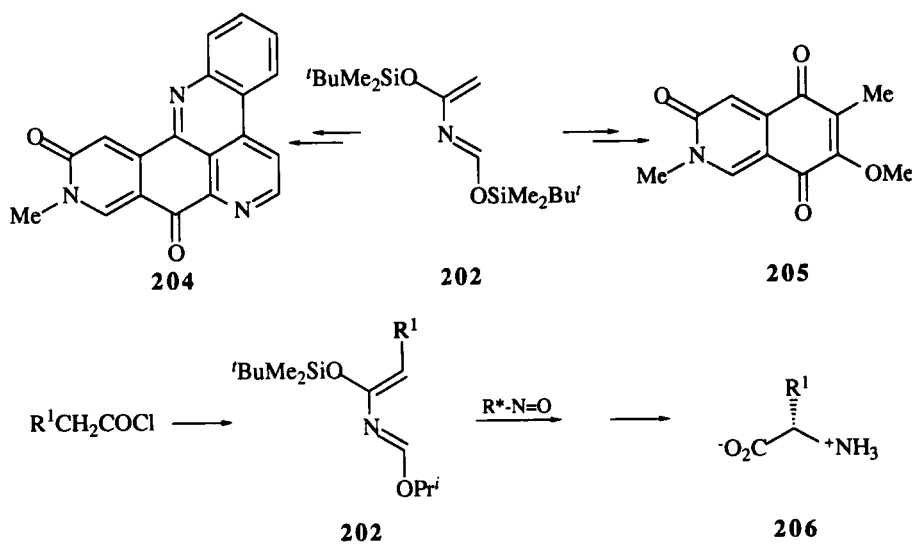
SCHEME 45

Further work has been carried out by Ghosez (88TL3799, 88TL4573, 88TL6115; 89TL5887, 89TL5891) and others (79CL187; 87CB657, 87HCA1255; 88TL4401). Moreover, the cycloaddition reaction of 2-azadiene **202** (Scheme 47) has been employed as the key step in the synthesis of alkaloid amphimedine **204** reported by Echavarren and Stille (88JA4051) and of marine antibiotic mimosamycin **205** carried out by McKillop and Brown (87SC657). Recently, Gouverneur and Ghosez (91TL5349) have described the asymmetric amination of carboxylic acids for synthesis of enantiomerically pure amino acids **206** via the Diels–Alder reaction of **202** with chiral nitroso dienophiles, as outlined at the bottom of Scheme 47.

The regiochemistry of the Diels–Alder reaction of 1-alkoxy-3-(*tert*-butyldimethylsilyl)oxy-2-azadienes and naphthoquinones, as a route to 2-azaanthraquinon-3-ones, has been investigated (91H915).



SCHEME 46

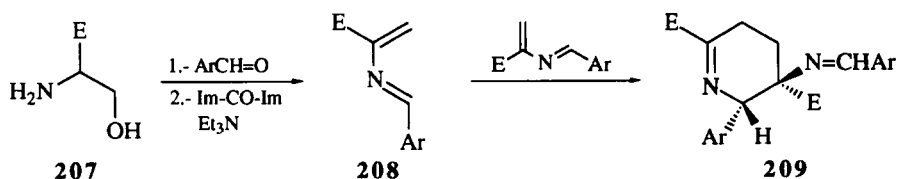


SCHEME 47

In sharp contrast to the development of the [4 + 2] cycloaddition reactions of electron-rich 2-azadienes, reports dealing with the chemistry of electron-poor 2-azadienes remained unknown until a few years ago. In fact, the first cycloaddition of an electron-withdrawing substituted 2-azadiene was observed in 1986 by Wulff and Böhnke [86AG(E)90] while they were preparing dehydroaminoacid derivatives (Scheme 48). They isolated *N*-(arylmethylene)dehydroalanine methyl esters **208** by dehydration of the Schiff base of the serine methyl ester **207** and found that it dimerized through a [4 + 2] cycloaddition to give tetrahydropyridine derivative **209** in 56% yield as a sole diastereoisomer.

A simple preparation of electron-poor 2-azadienes and the preliminary study of their ability to participate in [4 + 2] cycloadditions was done almost simultaneously by our group (87CC1195) (Scheme 49). The preparation of 2-azadienes **212** with two appended methoxycarbonyl groups was achieved, in a multigram scale and in nearly quantitative yield, by the insertion reaction of *N*-trimethylsilyl imines **210** into the carbon—carbon triple bond of dimethyl acetylenedicarboxylate to give **211** followed by protodesilylation with CsF/MeOH. Azadienes **212** underwent at room temperature inverse-electron demand [4 + 2] cycloaddition with cyclic enamines to give exclusively *exo*-cycloadducts **213** in 82–95% yield. Acid hydrolysis of them resulted in their aromatization to yield 2-pyridine ($n = 1$) and isoquinoline ($n = 2$) derivatives **214**.

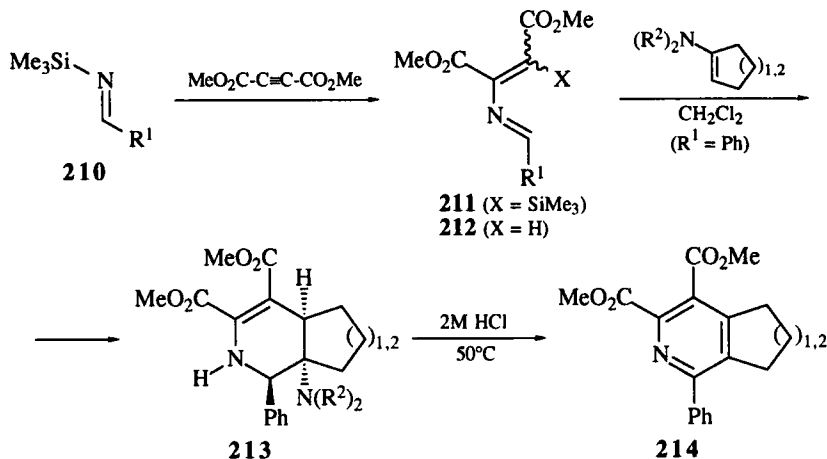
Imines derived from aniline and glyoxylic acid esters can be regarded as electron-poor 2-azadienes, in which an aromatic carbon—carbon double bond takes part of the diene system. In this context, Prato and Scorrano *et al.* were able to achieve the [4 + 2] cycloaddition of ethyl *N*-phenyl glyoxylate imines with dihydrofuran and indene leading to hexahydrofuro[3,2-*c*]- and tetrahydro-7*H*-indeno[2,1-*c*]quinolines, respectively, in moderate to good yields (88JHC1831). Similarly, tetrahydroquinoline derivatives were formed by [4 + 2] cycloaddition of 1,2-bis(trimethylsilyl-



E = CO₂Me

Im = 1-Imidazolyl

SCHEME 48

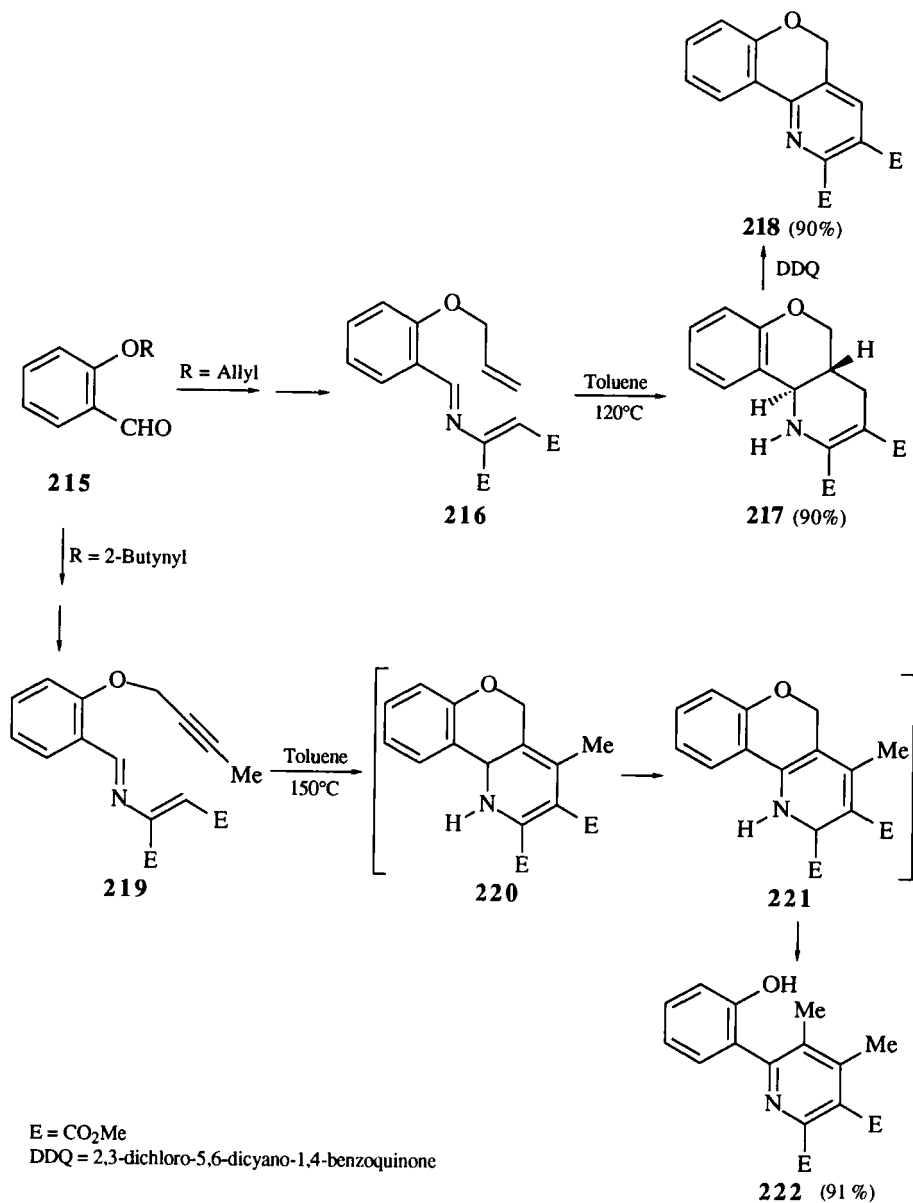


SCHEME 49

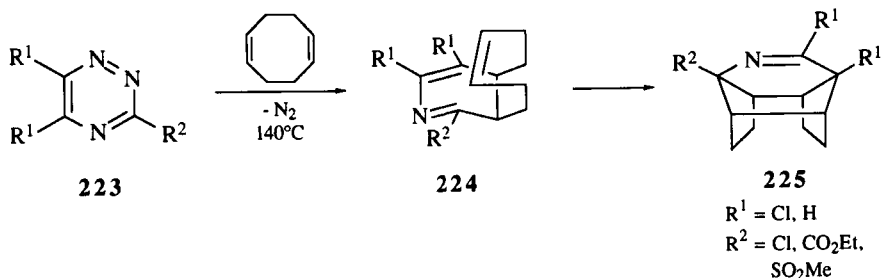
loxy)cyclobutene and imines derived from aromatic aldehydes and aniline (84H355).

We also discovered the ability of 2-azadienes of this sort to cycloadd to unactivated carbon—carbon double and triple bonds in an intramolecular fashion (89CC267) (Scheme 50); such a process appears to be one of the first examples of intramolecular $[4 + 2]$ cycloadditions of simple 2-azadienes. Azadiene **216** was made from *O*-allyl salicylaldehyde **215** ($\text{R} = \text{allyl}$) and heated at 120°C in toluene to furnish the *trans*-fused tricyclic adduct **217** in excellent yield; further dehydrogenation of **217** with DDQ afforded 5*H*-[1]-benzopyran[4,3-*b*]pyridine **218**. On the other hand, when *O*-(2-butyryl) salicylaldehyde **215** ($\text{R} = 2\text{-butynyl}$) was transformed into azadiene **219** and subjected to heating in a sealed tube at 150°C , pyridine **222** was isolated in very high yield. Its formation can be rationalized to occur via the expected Diels–Alder intermediate **220**; thus, $[1,5]\text{-H}$ shift in **220** would give rise to tautomer **221**, which would suffer electrocyclic ring-opening and aromatization to pyridine derivative **222**.

Sheldrake and co-workers devised an elegant approach to interesting cage compounds based on an intramolecular hetero Diels–Alder reaction (88CC1482) (Scheme 51). The $[4 + 2]$ cycloaddition of triazines **223** to 1,5-cyclooctadiene at 140°C resulted in the formation of 7-azatetracyclo[7.3.0.0^{2,6}.0^{5,10}]dodec-7-ene derivatives **225** in 44–66% yield. The initial formation of **224** followed by the intramolecular cycloaddition of the electron-poor 2-azadiene moiety to the second carbon—carbon double bond of the cyclooctadiene system accounts well for the process. The dienophile unit can be placed just over the diene system favoring



SCHEME 50



SCHEME 51

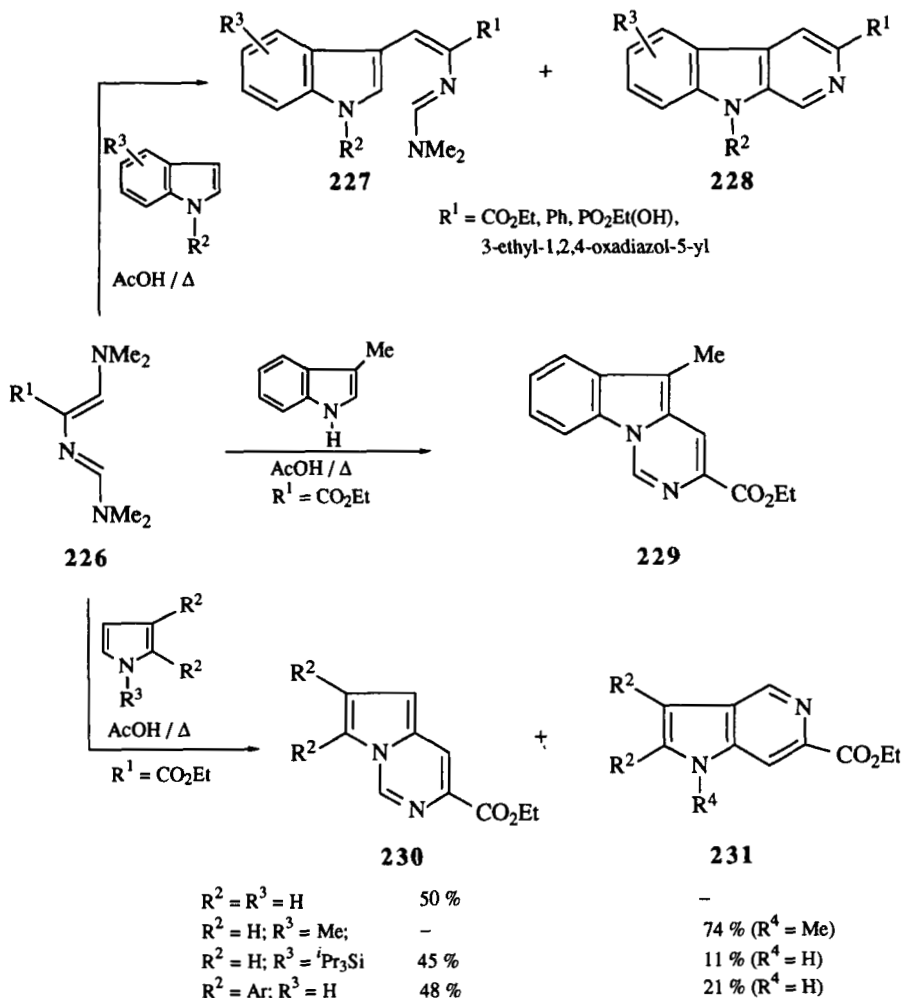
decisively the cycloaddition; in fact, using open-chain bis-dienophiles did result in the formation of alkenyl pyridines.

1,4-Bis(dimethylamino)-2-azabutadienes **226** have been reported by Biere *et al.* to undergo acid-catalyzed heterocyclization with indoles and pyrroles (Scheme 52). β -Carboline derivatives **228** were synthesized in 41–84% yield by refluxing a mixture of azadienes **226**, indole derivatives, and acetic acid; dehydrotryptophan derivatives **227** could be isolated under mild reaction conditions (86LA1749). Indolo[1,2-*c*]pyrimidine **229** was formed in 30% yield if 3-methylindole was used (87LA491). When this cyclization was extended to pyrroles, the authors found that, in some cases, mixtures of pyrrolo[1,2-*c*]pyrimidines **230** and pyrrolo[3,2-*c*]pyridines **231** were obtained, though in all cases the reaction initiates through the C-2 of the pyrrole. The **230**:**231** ratios reported are compiled at the bottom of Scheme 52 (87LA491).

Unexpectedly, Grieco discovered that immonium ions derived from aryl amines and aldehydes do not function as heterodienophiles toward cyclopentadiene, as was found in the case of simple immonium ions, but rather they acted as 2-azadienes leading to a novel synthesis of tetrahydroquinolines (88TL5855).

N-Vinyl heterocumulenes represent a new, highly reactive 2-azadiene species, which react, in general, with electron-rich alkenes and alkynes. Accordingly, we think it is of interest to complement the utility of electron-poor 2-azadienes in [4 + 2] cycloadditions by showing some examples involving *N*-vinyl isocyanates, -isothiocyanates, -carbodiimides, and -ketenimines.

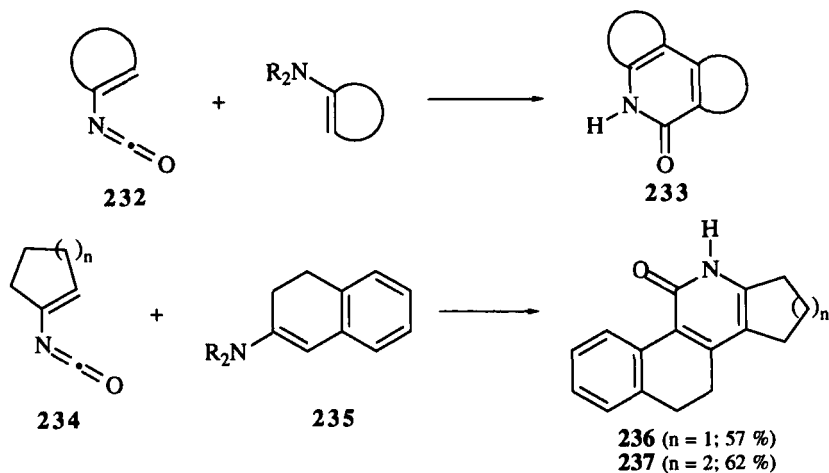
Vinyl isocyanates, readily available from the corresponding α,β -unsaturated acids by a Curtius procedure, have been by far the systems studied in more detail, mainly by the Rigby group, *e.g.*, in the construction of the pyridone ring (Scheme 53). Thus, heteropolycyclic compounds having 2-pyridone structure **233** were shown to be formed in moderate to



SCHEME 52

good yields by refluxing in toluene a mixture of alkenyl or cycloalkenyl isocyanates **232** and enamines derived from cyclic and acyclic ketones. Interestingly, assembling vinyl isocyanates **234** ($n = 1,2$) and enamine **235** permitted a rapid access to azasteroid **236** and azahomosteroid **237** derivatives (84JOC4569; 89JOC224).

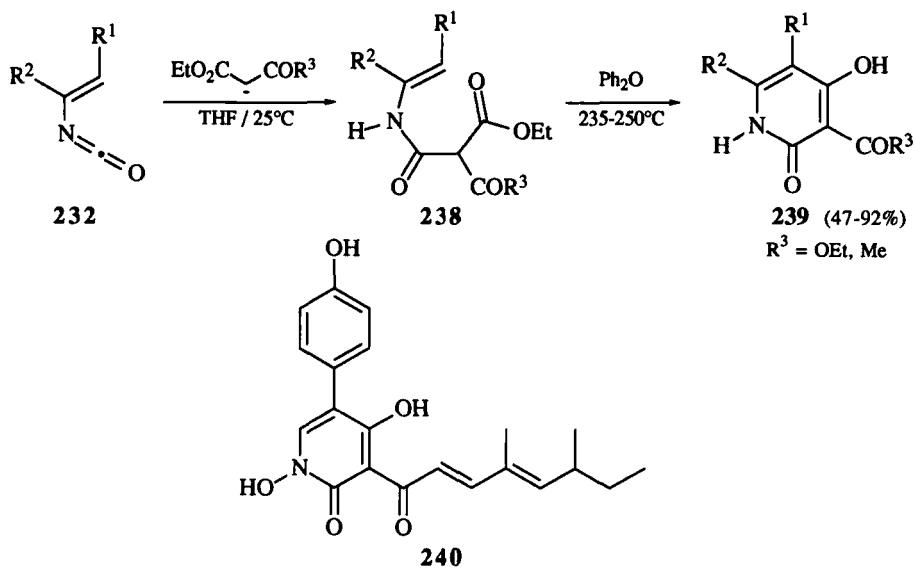
A direct entry into phenanthridinone and benzophenanthridinone skeletons was also disclosed by the formal $[4 + 2]$ cycloaddition of N -vinyl isocyanates **232** and benzyne (89JOC4019). On the basis of this cycloaddi-



SCHEME 53

tion, Rigby and Holsworth have reported a convergent synthesis of the benzo[*c*]phenanthridine alkaloid *N*-nornitidine (91TL5757).

In an extension of this reaction, the same group prepared functionalized 4-hydroxy-2(1*H*)-pyridones by reacting vinyl isocyanates with ester enolates (Scheme 54). The reaction of 2-azadienes **232** with enolates derived



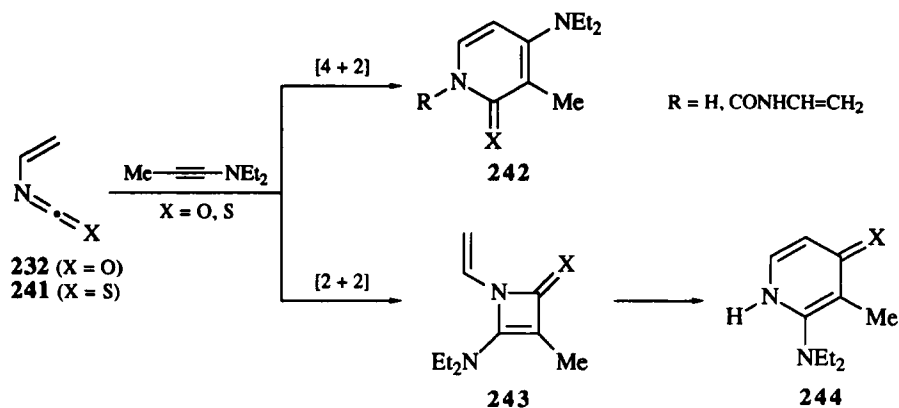
SCHEME 54

from diethyl malonate or ethyl acetylacetate at room temperature furnished the addition products **238**, which in turn were cyclized to pyridones **239** upon heating in phenyl ether (86JOC1374). Following this methodology, a short and convergent total synthesis of the fungal biochrome tenellin **240** was developed (89JOC5852).

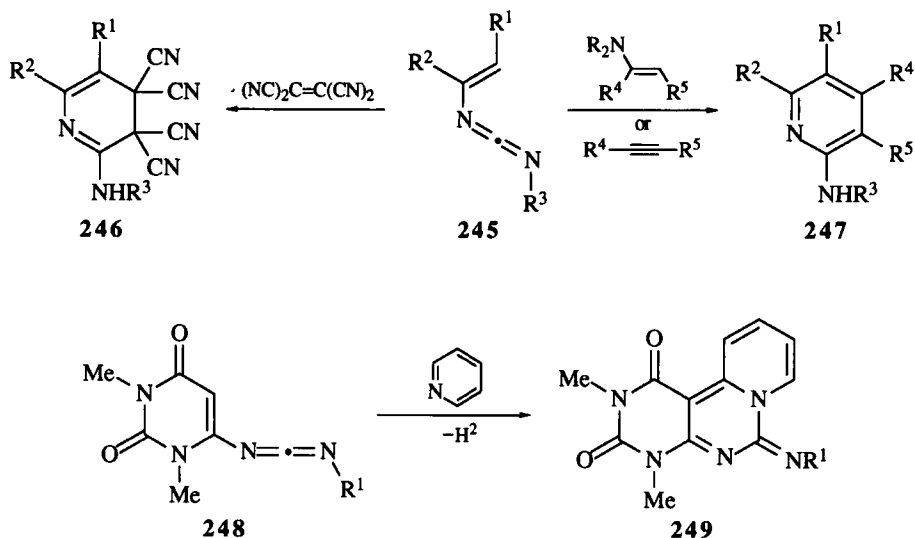
A systematic study of the reaction of *N*-vinyl isocyanate **232** and isothiocyanate **241** with ynamines was first performed by Dondoni and coworkers (82JOC3994) (Scheme 55). They found that mixtures of regioisomeric pyridones (X = O)/thiones (X = S) **242** and **244**, arising from competition between [4 + 2] and [2 + 2] cycloaddition reactions, were formed; structure **244** results from **243** by consecutive 4 π -electron ring-opening and 6 π -electron ring-closure. Pyridone **242** (X = O) was the major isomer in the case of isocyanates, whereas the [2 + 2] cycloaddition leading to **244** (X = S) was the preferred pathway for isothiocyanates. Giffard and Cousseau reported that vinyl isocyanates cycloadd to tetracyanoethylene in a [4 + 2] fashion leading to 3,4-dihydropyridine-2(1*H*)-thiones [85JCR(S)300].

Previous examples regarding cycloaddition reactions of vinyl isocyanates and -isothiocyanates with enamines and ynamines have been published [70AG(E)159, 70T2161, 78JOC402]. [4 + 2] Cyclization reactions of aryl isocyanates involving an aromatic carbon—carbon double bond with ynamines (68JOC4406), benzyne (65JOC3247), and ethoxyacetylene (57RTC999) have also been described.

Studies focused on the ability of *N*-vinyl carbodiimides to undergo cycloaddition reactions have been carried out in recent years (Scheme 56). Thus, 2-azadiene derivatives **245** reacted with tetracyanoethylene to yield dihydropyridines **246** (86CL135), whereas treatment of **245** with



SCHEME 55

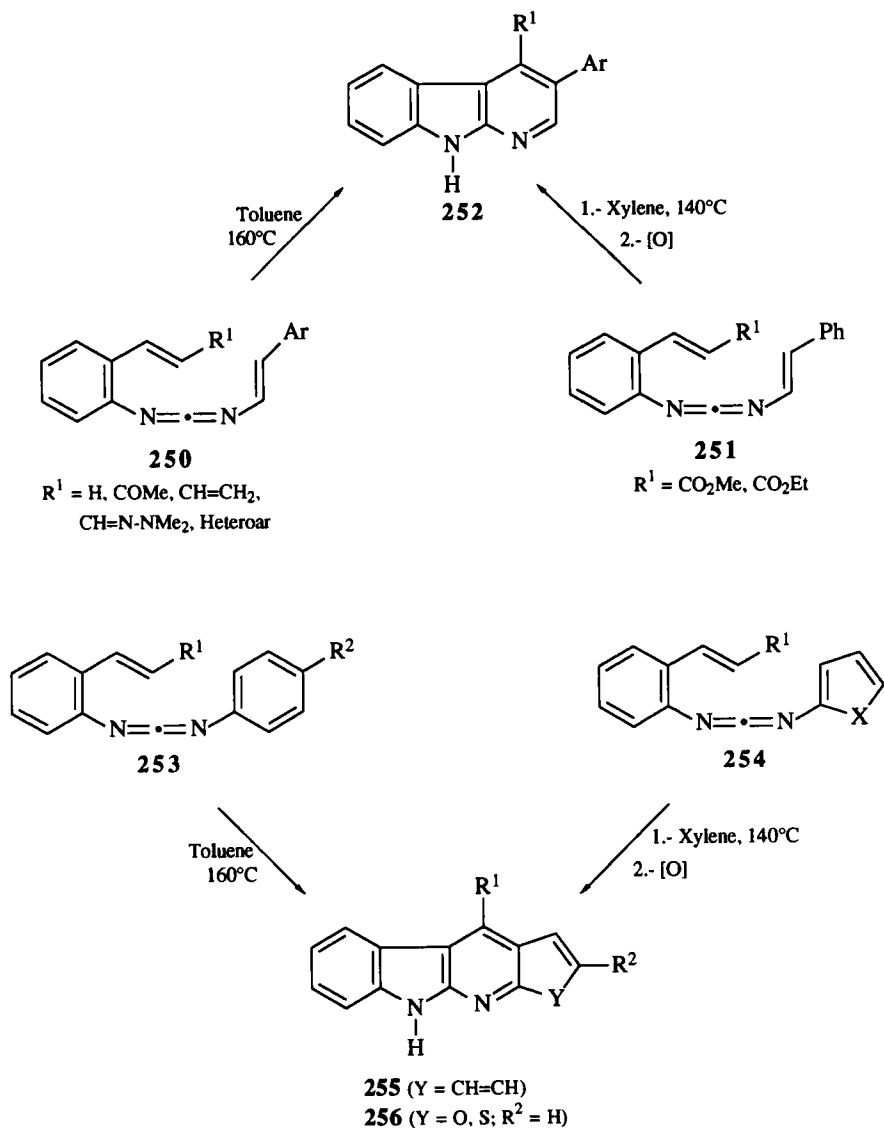


SCHEME 56

either enamines or electron-poor alkynes gave aminopyridines **247** (91BCJ1325). Wamhoff *et al.* have succeeded in the 1,2-annulation of pyridine itself to the vinyl carbodiimide unit of **248** to produce pyrido[1,2-*f*]pyrimido[4,5-*d*]pyrimidines **249** (91TL4473) (Scheme 56).

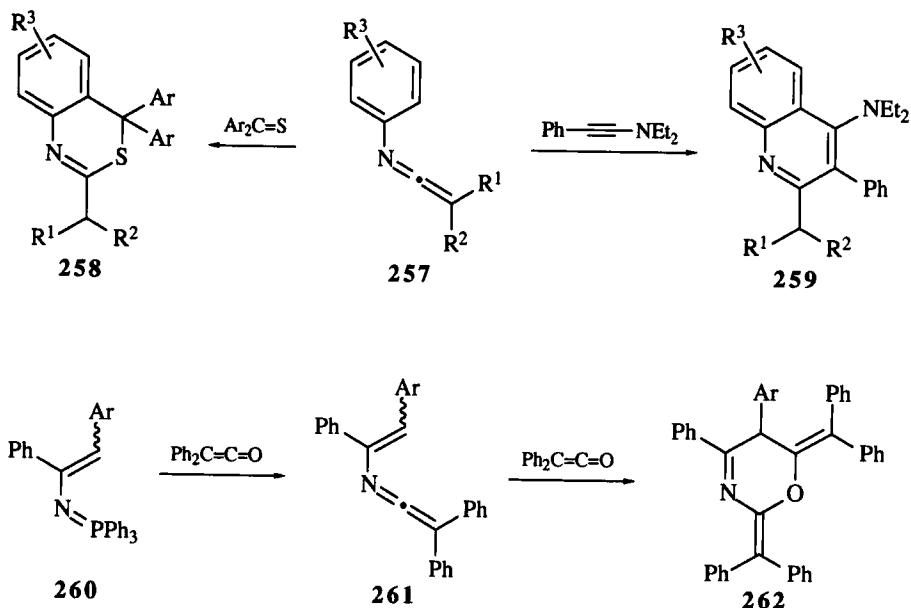
The intramolecular [4 + 2] cycloaddition of vinyl carbodiimides (Scheme 57) has been reported by the groups headed by Molina in Spain (90CC1277; 92JOC929) and by Saito and Motoki in Japan (92CC22). Molina *et al.* have been able to cyclize systems **250**, in which the dienophilic partner can be substituted with either electron-donating or -acceptor groups, to give α -carboline **252** in 31–55% yield; the participation of one aromatic carbon—carbon double bond in the cycloaddition process was also shown to occur since diaryl carbodiimides **253** furnished, under the same reaction conditions, quinindolines **255** in 28–54% yield. The Japanese group also obtained **252** in 33–45% yield by heating **251** followed by oxidation; these authors were able to increase the scope of this cycloaddition to furyl- and thienyl-substituted carbodiimides **254**, which gave **256** in 33–55% yield under the same reaction conditions.

Some examples dealing with the [4 + 2] cycloaddition of ketenimines have been recorded (Scheme 58). Thus, thioketones and ynamines reacted with *N*-aryl ketenimines **257** through the carbon—nitrogen and the conjugated aromatic carbon—carbon double bonds to yield benzothiazine derivatives **258** (80JOC3766; 82JOC3998) and substituted quinolines **259** (73JA5417), respectively. Simple ketenimines **261** were formed by reaction



SCHEME 57

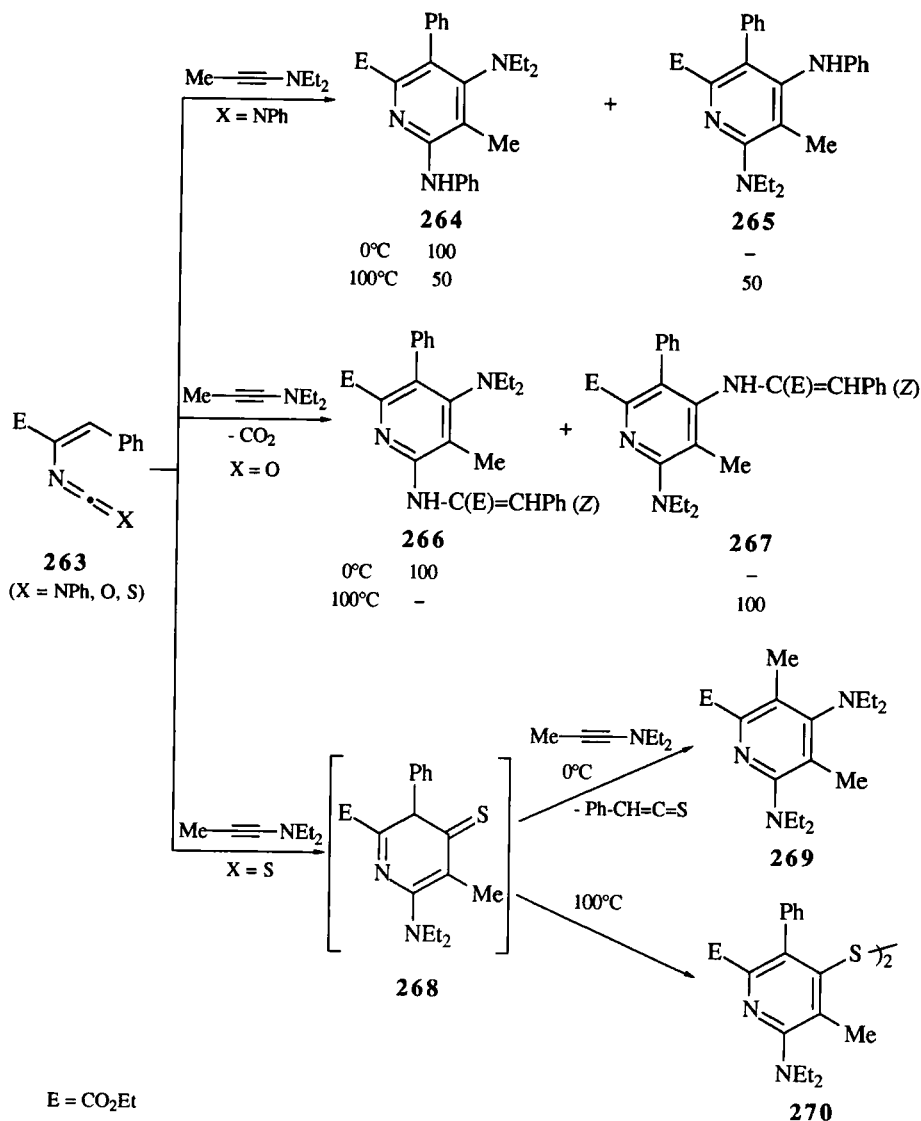
of iminophosphorane **260** and diphenylketene and cycloadded to a second molecule of diphenylketene to furnish 1,3-oxazine derivative **262** in 60% yield [89JCS(P1)2140]; in addition, the [4 + 2] cycloaddition reaction of **261** with aryl isocyanates and diaryl thioketones has just been reported (92LA15). Isolated examples of intramolecular [4 + 2] cycloaddition reac-



SCHEME 58

tions involving the 2-azadiene unit of a ketenimine have been published (91TL5379; 92JOC929).

Work directed at studying the behavior of ethoxycarbonylvinyl heterocumulenes **263** toward 1-diethylamine-1-propyne has been undertaken in our laboratory and the results are summarized in Scheme 59 (92UP2). It was found that both [2 + 2] and [4 + 2] cycloaddition reactions operate when starting with carbodiimides or isocyanates, whereas products assumed to arise from the [2 + 2] cycloadducts were obtained in the case of isothiocyanates. Thus, carbodiimide **263** (X = NPh) gave at 0°C the [4 + 2] cycloadduct **264** (95%) and none of the [2 + 2] derived cycloadduct **265**, whereas a 1 : 1 mixture of both isomers (93%) was formed at 100°C. Vinyl isocyanate reacted with ynamine in a 2 : 1 molar ratio to yield exclusively the [4 + 2] cycloadduct **266** (94%) at 0°C or the [2 + 2] one **267** (88%) at 100°C; the presence of the vinyl amine group in both pyridine rings can be understood if a second equivalent of isocyanate traps the hydroxyl substituent of the cycloadducts to form the corresponding carbamates that extrude CO₂. A different behavior was observed for the reaction of isothiocyanate **263** (X = S) since compounds **269** or **270**, depending on the reaction temperature, were isolated. Their formation presumably takes place by initial heterocumulene-ynamine [2 + 2] cycloaddition, leading to the nonisolated intermediate **268**; subsequent [4 + 2]



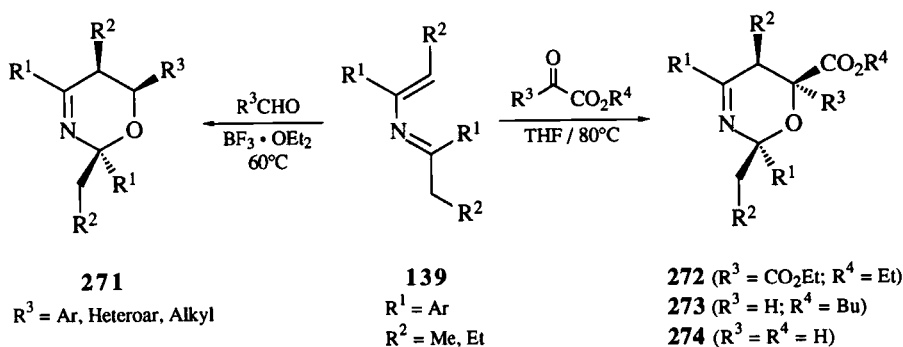
SCHEME 59

cycloaddition of this heterocyclic 2-azadiene with ynamine occurs at 0°C to give quantitatively **269**, whereas oxidative dimerization of **268** giving rise to **270** (83%) was the sole process observed at 100°C.

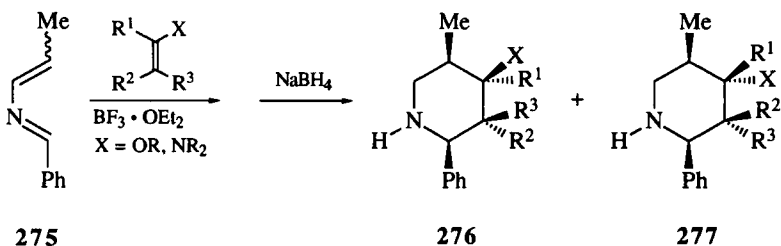
Despite the fact that relatively numerous examples of [4 + 2] cycloaddition reactions involving electron-rich and, to a lesser extent, electron-

poor 2-azadienes have been shown, reports dealing with electronically neutral 2-azadienes are scarcely found before the 1980s (84H355, 84JOC2691; 85JOC5678). On working in this particular field, we reported the first Diels–Alder reaction of simple neutral 2-azadienes **139** (Scheme 60). Treatment of aliphatic or aromatic aldehydes with substituted 2-azadienes **139** at 60°C in the presence of catalytic amounts of boron trifluoride etherate resulted in the stereoselective formation of 1,3-oxazine cycloadducts **271** in 70–95% yield, which arise from an *endo* transition state (85CB3652). Similarly, cycloadducts **272** and **273** were obtained in 70–90% yield on reaction of **139** with diethyl ketomalonate and butyl glyoxylate, respectively; moreover, hydrolysis and selective *exo* decarboxylation of **272** led to monoacid **274**, whose structure was confirmed by hydrolysis of **273** (89TL2685). On the other hand, adducts **271** have served as suitable precursors of 1,3-amino alcohols by reductive cleavage (89TL2001; 91S387).

2-Azadienes of this sort were studied simultaneously by Mariano *et al.*, who reacted mixtures of (1*E*,3*E*) and (1*E*, 3*Z*)-1-phenyl-2-aza-1,3-pentadiene **275** with several electron-rich alkenes, *e.g.*, enamines and enol ethers (85JOC5678) (Scheme 61). They found the (1*E*,3*E*)-stereoisomer to be reactive in this process affording stereoselectively *endo* **276** or *exo* **277** piperidine cycloadducts in 5–39% yield, after reductive work-up with sodium borohydride. The stereochemistry of the resulting adducts is in agreement with an *endo* transition state in the case of dienophiles lacking a *cis* alkyl substituent at the β -carbon (*n*-butyl vinyl ether, benzyl vinyl ether, and 1-morpholino cyclopentene), whereas an *exo* transition state was involved when dihydropyran or *cis*-propenyl benzyl ether were used. Finally, the authors reported that cyclohexene and dimethyl acetylenedicarboxylate failed to react with these unactivated 2-azadienes.

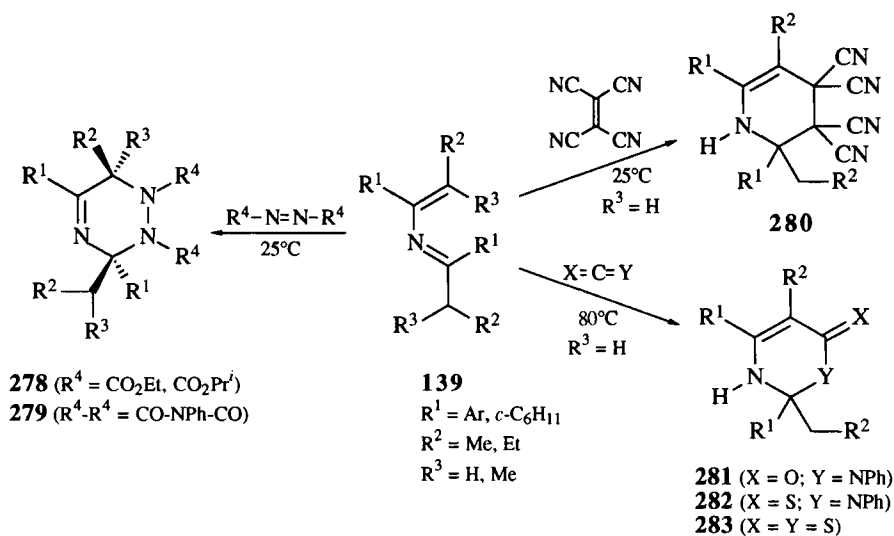


SCHEME 60



SCHEME 61

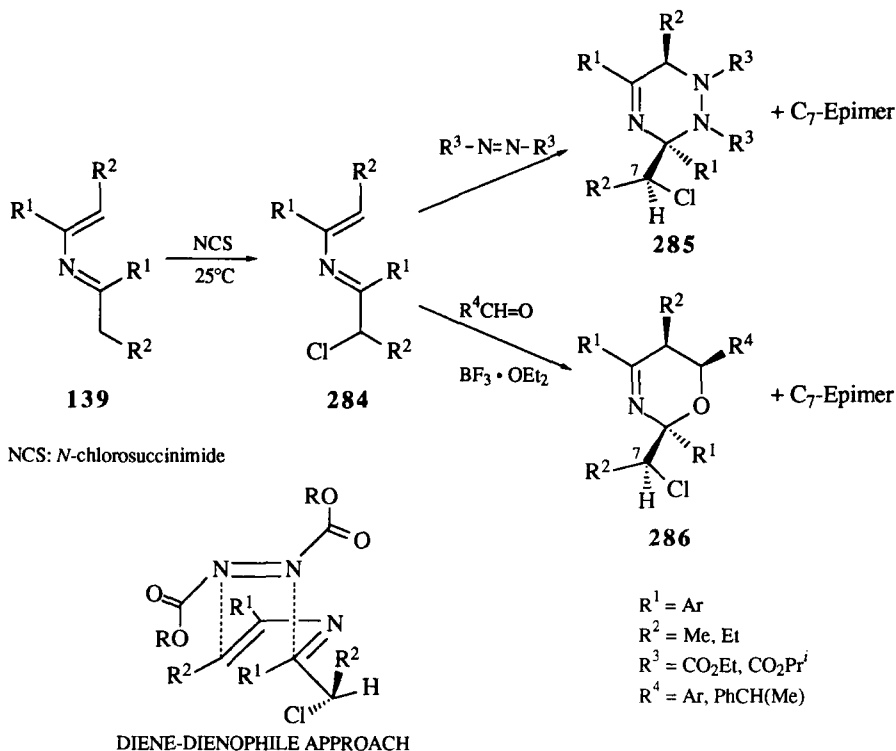
We were not able to obtain any cycloadduct from unactivated 2-azadienes **139** and esters of acetylenedicarboxylic acid. However, we found that **139** did cycloadd to typical electron-poor dienophiles such as esters of azodicarboxylic acid and tetracyanoethylene (Scheme 62). Thus, diethyl and diisopropyl azodicarboxylates underwent a concerted [4 + 2] cycloaddition with **139** to afford in a stereoselective manner triazines **278** in 85–90% yield (86CC1179). The minor reaction-rate variations observed with the solvent polarity excluded zwitterionic intermediates; on the other hand, $\Delta S^\ddagger$ was calculated to be 48.1 cal K⁻¹ mol⁻¹ in CCl₄, a value which is in the range of a concerted [4 + 2] cycloaddition. Azadienes **139** again reacted at room temperature with the cyclic azo derivative 4-phenyl-1,2,4-triazoline-3,5-dione, leading stereoselectively to bicyclic derivatives **279**



SCHEME 62

in good yields. Similarly, treatment of **139** with tetracyanoethylene at room temperature rendered substituted tetrahydropyridines **280** [86CC1179; 89JCR(S)66]. Finally, the capability of these azadienes to participate in [4 + 2] cycloadditions was extended by using heterocumulenes as dienophiles. Thus, derivatives of 1,3-oxazine **281** and 1,3-thiazine **282** were formed in 70–82% yield by heating at 80°C a mixture of **139** and phenyl isocyanate or phenyl isothiocyanate, respectively; moreover, 2-azadiene **139** and carbon disulfide, a very unusual dienophile, gave **283** in 50% yield on refluxing in benzene in the presence of a catalytic amount of boron trifluoride etherate [86CC1179; 88JCS(P1)1739].

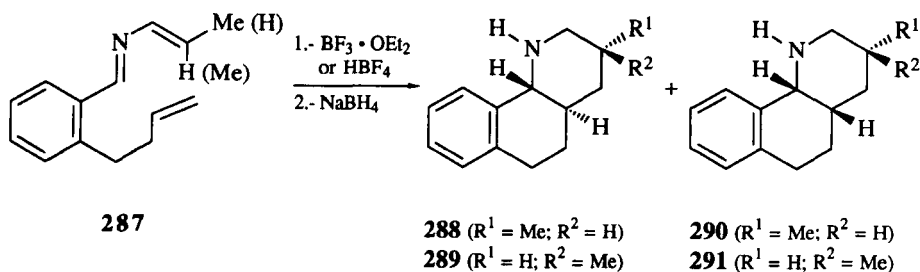
The diastereofacial selectivity of 2-azadienes with a stereogenic center attached to C-1 in Diels–Alder reactions has been investigated (Scheme 63). The synthesis of monochloro derivatives **284** was readily achieved in excellent yields by halogenation of **139** with *N*-chlorosuccinimide. The



SCHEME 63

Diels–Alder cycloaddition between **284** and diesters of azodicarboxylic acid took place at 25–40°C to give triazines **285** in good chemical yields (75–80%) and with very high face stereoselectivity (*de* 86–94%); the structure **285** was unambiguously ascertained by X-ray determination. The reaction of **284** with aldehydes at 25°C in the presence of boron trifluoride etherate afforded **286** (70–85% yield) as a mixture of C-7 epimers with lower selectivity (*de* 14–74%). Preliminary AM1 calculations on azadienes **284** indicate that the *syn*-coplanar conformation between the C=N double bond and the hydrogen attached to the carbon atom supporting the chlorine is the more stable by 1.6 kcal; in this situation the approach of the dialkyl azodicarboxylate to **284** occurs preferentially through the face opposite the chlorine in order to avoid the electronic repulsions between the carboxylate group and the chlorine atom, as outlined in Scheme 63 [90TL(31)397; 91JOC4459].

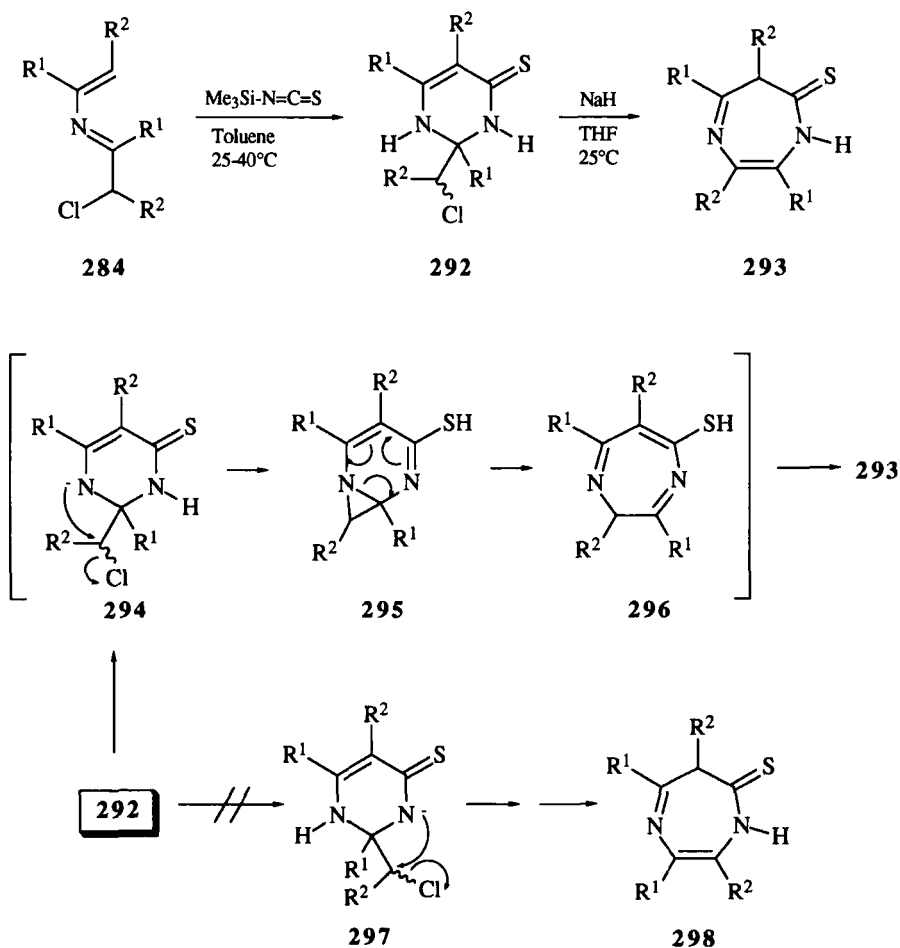
An isolated example regarding the intramolecular [4 + 2] cycloaddition of electronically neutral 2-azadienes has been provided by Mariano *et al.* (88TL4799) (Scheme 64). They synthesized the starting azadiene–dienophile system **287** as an 8 : 1 *E,E* : *E,Z* mixture and studied the intramolecular cycloaddition at temperatures in the range 5–45°C and in the presence of boron trifluoride etherate or tetrafluoroboric acid to obtain variable mixtures of **288–291** (43–70% yield), after reductive work-up. From the experimental results it was deduced that both stereoisomers of **287** undergo kinetically controlled, stereospecific cyclization and that the cyclization of *E,E*-**287** occurs preferentially via an *exo*-transition state because of the favorable arene–azadiene conjugation. Earlier, an acid-catalyzed intramolecular [4 + 2] cycloaddition involving the 2-azadiene–olefine couple was postulated for the cyclization of 4-(2-alkenylphenyl)-1,4-dihydropyridines (85JOC2427).



SCHEME 64

C. MISCELLANEOUS RINGS

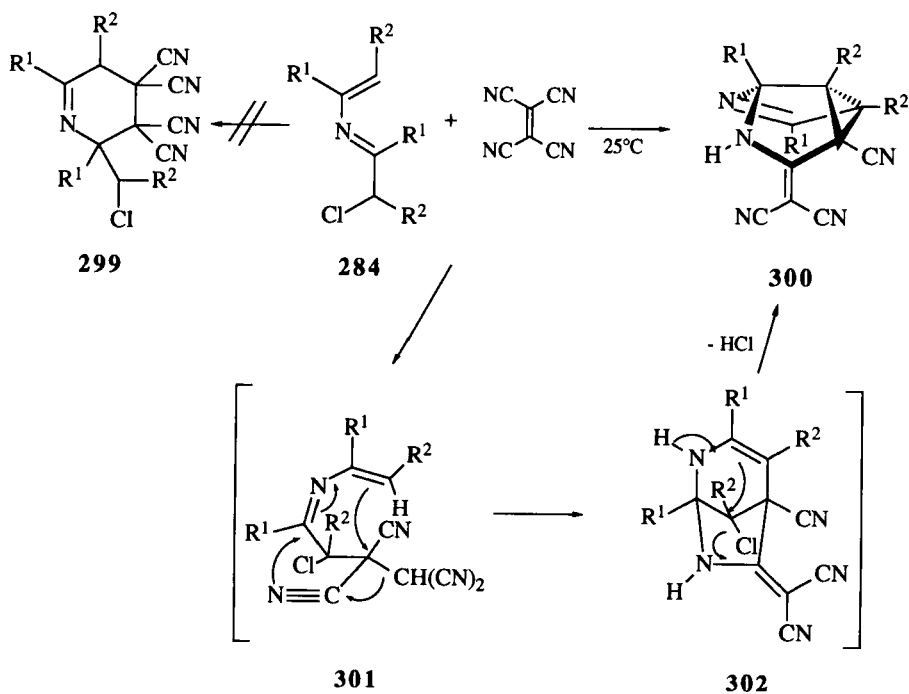
In this section two examples showing the utility of chloro-substituted 2-azadienes **284** for the synthesis of diazepines and diazasemibullvalenes are compiled. First, we realized that azadienes **284** could serve as precursors of nitrogen-containing seven-membered heterocycles by promoting the intramolecular chlorine displacement by the nitrogen atom in appropriate chloro-containing [4 + 2] cycloadducts (91CC1704) (Scheme 65). 1,2-Dihydropyrimidine-4(3*H*)-thiones **292** were obtained as mixtures of



SCHEME 65

stereoisomers (70–80% yield) by reaction of **284** and trimethylsilyl isothiocyanate at 25–40°C; compounds **292** were then reacted with an equivalent of sodium hydride at room temperature, affording 1*H*-1,4-diazepine-7(6*H*)-thiones **293** in 75–91% yield. The reaction was assumed to proceed by deprotonation of **292** at N-1 followed by chlorine displacement and tautomerization to give heteronorcaradiene intermediate **295**; electrocyclic rearrangement of **295** to **296** is then followed by hydrogen shifts to form **293**. Regioisomeric structure **298**, which would originate from **297** after initial deprotonation of **292** at N-3, was ruled out according to NMR studies.

Unexpectedly, the reaction of **284** toward tetracyanoethylene at room temperature resulted neither in the formation of the [4 + 2] adduct **299** nor in the formation of its azepine derivative, but the novel 4,6-diazasemi-bullvalene structure **300** was isolated as colorless crystals in 70–85% yield (90CC1057) (Scheme 66). Although mechanistic rationalization of this process is not a simple matter, a possible reaction course would involve the formation of Michael adduct **301**, which would undergo intramolecular



SCHEME 66

cyclization with 1,2-migration of the dicyanomethyl group to form **302** followed by elimination of HCl.

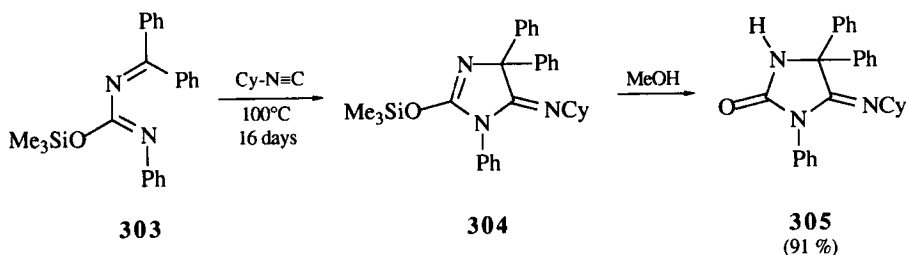
IV. Synthesis of Heterocycles Using 1,3-Diazadienes

A. FIVE-MEMBERED RINGS

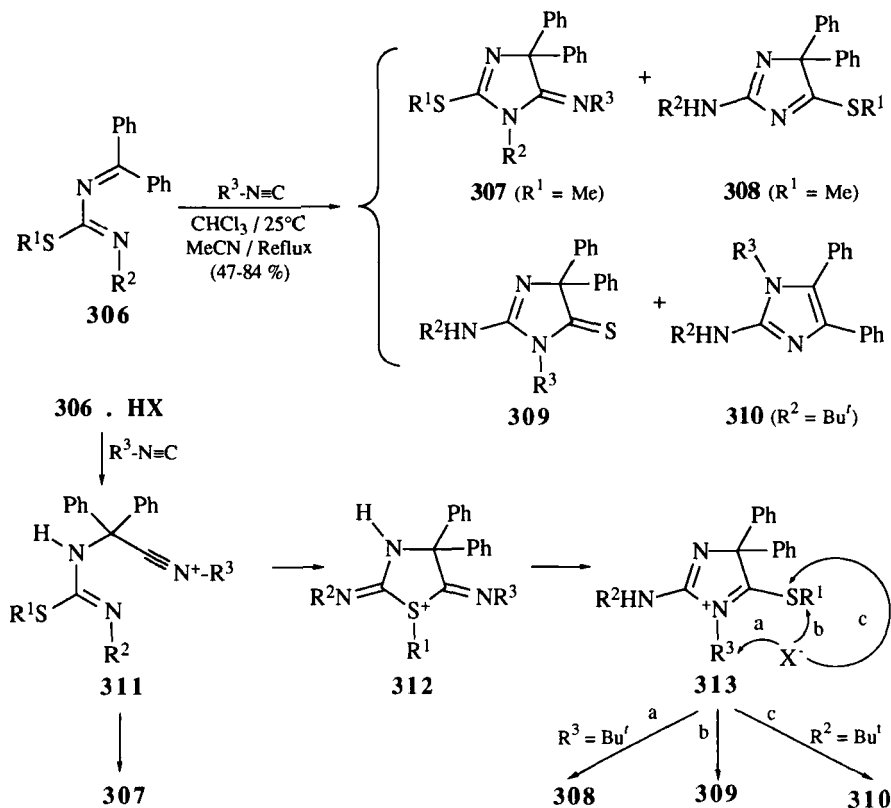
1,3-Diazadienes have been shown by various groups to be suitable precursors of imidazoline derivatives by means of [4 + 1] cycloaddition reactions. In 1976 Matsuda and co-workers were able to cycloadd heterodienes **303**, available from *N*-trimethylsilyl benzophenone imine and phenyl isocyanate, with cyclohexyl isocyanide to obtain **305** in 91% yield, after methanolysis of the initial adduct **304** [76JCS(P1)1523] (Scheme 67).

Foucaud's group reacted diazadienes **306**, as their hydrochloride salts, with different aliphatic and aromatic isocyanides (Scheme 68). They obtained in overall yields up to 84% of the expected iminoimidazolines **307** and/or rearranged imidazolines **308–310**, in which four and three atoms, respectively, of the heterodiene were incorporated into the heterocyclic structure (89JOC1185). The authors rationalized these results by means of the initial formation of the nitrilium salt **311**; its cyclization through attack of nitrogen would lead to **307**, whereas ring closure involving the sulfur atom to **312** followed by rearrangement would form imidazolium salts **313**. Hofmann-type elimination of **313** ($R^3 = Bu^t$) (via a) would furnish **308**, whereas **309** and **310** would arise from **313** by nucleophilic attack on the carbon (via b) or on the sulfur (via c) atoms, respectively, of the thioether function. Formation of imidazolines from very closely related heterodienes was previously reported by the same group (85JOC771).

Burger *et al.* have largely studied the synthetic utility of 1,3-diazadienes **314** as useful educts for the construction of five-membered heterocycles

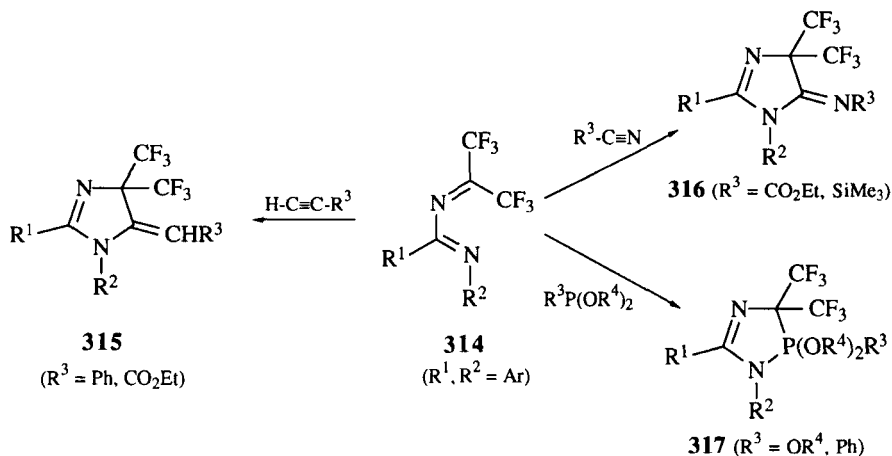


SCHEME 67



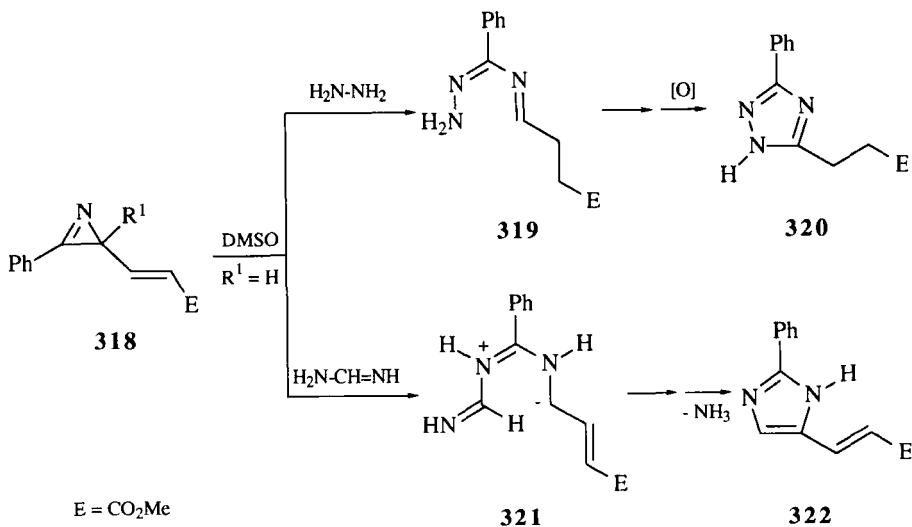
SCHEME 68

(Scheme 69). Thus, alkenylimidazolines **315** were formed by reaction of heterodienes **314** with phenyl acetylene and methyl propiolate (83CZ271). Moreover, ethyl cyanoformate reacted with **314** to give **316** ($R^3 = CO_2Et$), as the major product, contaminated with the [4 + 2] cycloadduct (84CZ209); in turn, treatment of **314** with trimethylsilyl cyanide resulted in the exclusive formation of **316** ($R^3 = SiMe_3$) in 84-91% yield (88S44). It is interesting to point out that, in these reactions, the dienophile skeleton is only partially incorporated into the ring system and that a 1,2-hydrogen, 1,2-ethoxycarbonyl, and 1,2-trimethylsilyl, respectively, migration was envisaged to occur. In addition, heterodienes **314** were also capable of introducing an additional heteroatom into the five-membered ring; thus, 1,4,2 λ^5 -diazaphospholines **317** were obtained in 83-90% yield upon room temperature reaction of **314** with phosphorous (III) reagents (78S526).



SCHEME 69

Methyl 1-azirine-3-acrylates **318** ($R^1 = \text{H}$) have recently been reported to yield five-membered heterocycles, e.g., triazoles **320** (35% yield) or imidazoles **322** (62% yield), by reaction with hydrazine and formamidine (91JOC7) (Scheme 70). The mechanism postulated by the authors to account for the formation of **320** and **322** implies initial addition of the



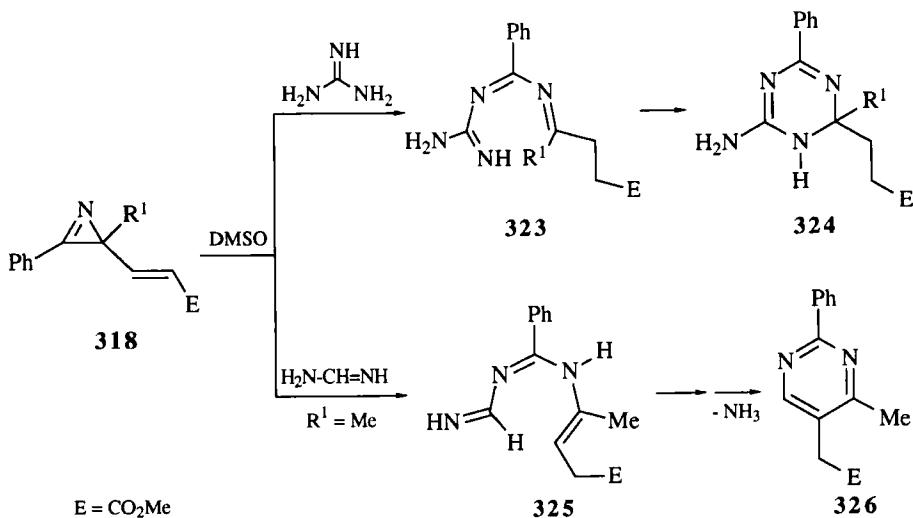
SCHEME 70

nucleophile to the azirine C=N bond followed by carbon—carbon bond cleavage of the resulting aziridine to give diazadiene derivatives **319** and **321**, respectively; then, intramolecular cyclization and aromatization (oxidation or loss of ammonia, respectively) would lead to the observed heterocycles.

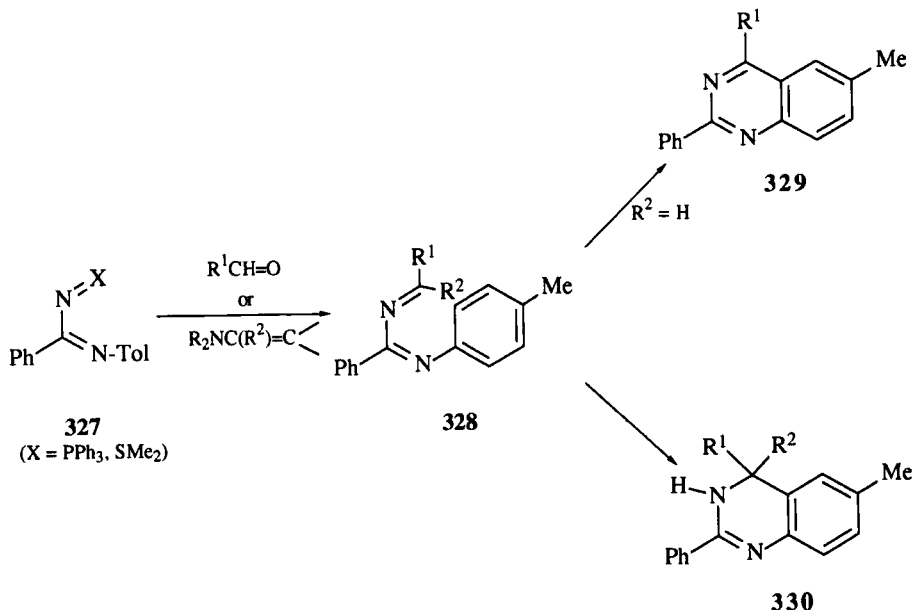
B. SIX-MEMBERED RINGS

Azirine derivatives **318** were shown in the same article to be precursors of triazines **324** (30–35% yield) and pyrimidines **326** (30% yield) upon treatment in DMSO with guanidine and formamidine, respectively (Scheme 71). A similar pathway to that outlined above is also invoked to explain these results; thus, intermediate **323** would yield **324** by electrocyclic ring closure, whereas **326** would be formed by heterocyclization of **325** and loss of ammonia (91JOC7).

The synthesis of various types of quinazoline derivatives **329–330** by thermal six-electron electrocyclic ring closure of 1-aryl-1,3-diazadienes **328** has been achieved by Rossi *et al.* (Scheme 72). Thus, *N*-imidoylimino triphenylphosphorane **327** (X = PPh₃) reacted with aliphatic and aromatic aldehydes in boiling xylene to give, through intermediate **328**, 3,4-dihydroquinazolines **330** and/or quinazolines **329** in 46–90% yield [90TL(31)903; 91T5819]. Similarly, *S,S*-dimethyl-*N*-(*N*-arylbenzimidoyl)



SCHEME 71

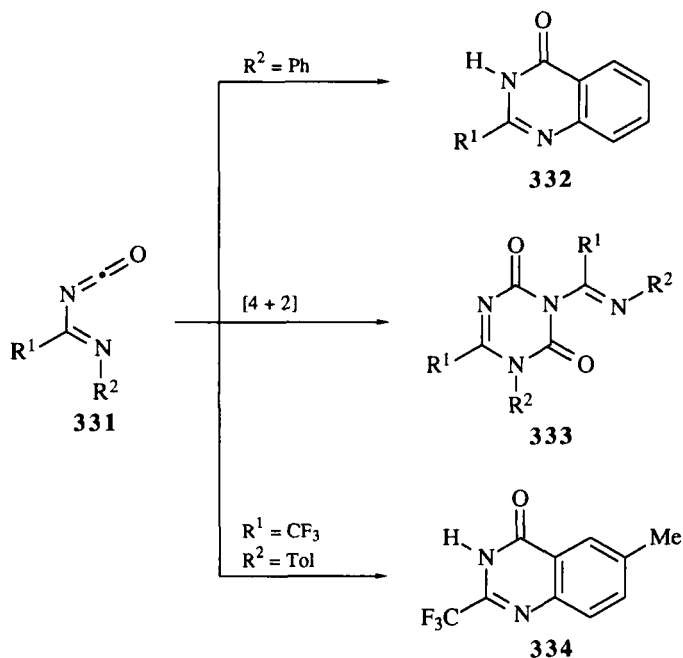


SCHEME 72

sulfimides **327** ($X = SMe_2$) furnished quinazolines **329** in 30–80% yield (89S214) or dihydroquinazolines **330** in 45–57% yield (90T3581) upon heating in refluxing tetraline with enamines derived from aldehydes and ketones, respectively.

Electrocyclic ring closure reactions of phenyl ketenimides **331** allow the construction of the quinazolone ring (Scheme 73). For instance, quinazolones **332** were synthesized some years ago in 4–85% yield by heating **331** ($R^2 = Ph$); in addition, dimerization through a $[4 + 2]$ cycloaddition leading to **333** (30–73% yield) was observed (78S760). Compound **331** ($R^1 = CF_3$) has been employed for the preparation of the trifluoromethylated quinazolone **334** (71% yield) [90TL(31)2717].

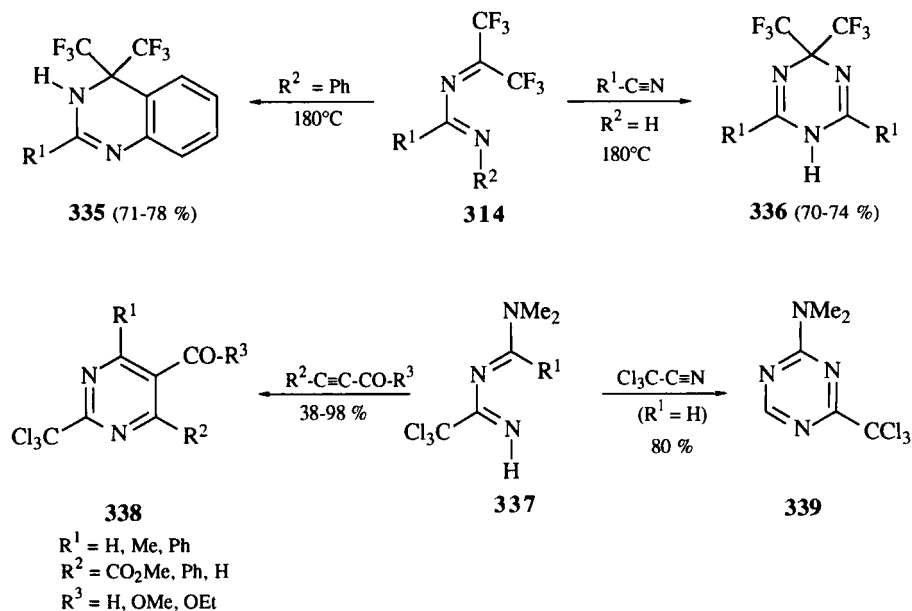
Diazadienes **314** ($R^2 = Ph$) afforded, in the same way, good yields of bis-trifluoromethyl dihydroquinazolines **335**, as reported by Burger and Penninger (Scheme 74). However, N-unsubstituted heterodienes **314** ($R^2 = H$) yielded upon heating with aromatic nitriles symmetrical triazine derivatives **336** through a $[4 + 2]$ cycloaddition (78S524). Muchowski and co-workers have employed the related 2-trichloromethyl-4-dimethyl-amino-1,3-diaza-1,3-butadienes **337** for synthesizing 2-trichloromethylpyrimidines **338** in 38–98% yield by cyclization with electron-deficient acetylenes; moreover, triazine **339** was obtained in 80% yield in the reaction of



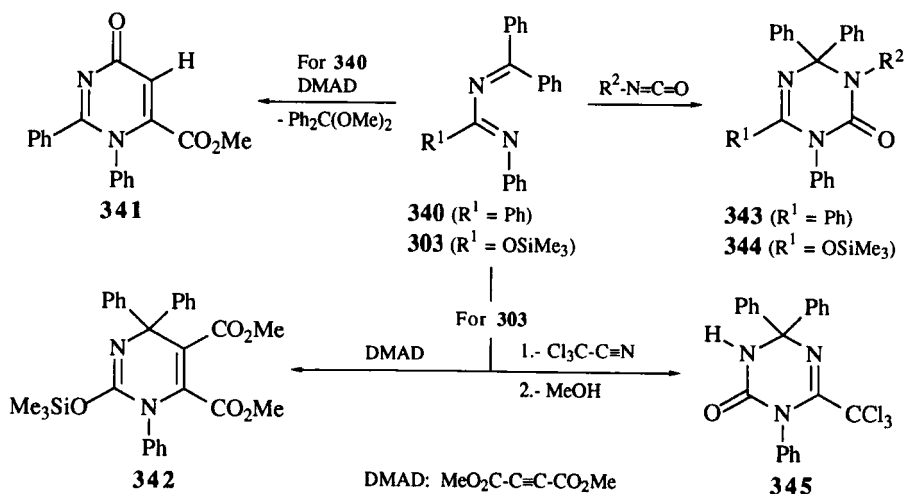
SCHEME 73

337 with trichloroacetonitrile (92TL3449) (Scheme 74). The cycloaddition reaction of 2-methylthio-4,4-diphenyl-1,3-diazabutadienes **306** with protonated isocyanides leading to 1,3,5-triazine derivatives has been recorded by Foucaud and co-workers (89JOC1185).

Matsuda's group focused attention into the reactivity of 4,4-diphenyl-1,3-diazadienes **340** and **303** toward dienophiles (Scheme 75) [72JCS(P1)1678; 76JCS(P1)1523, 767CS(P1)1528]. They found that **340** did not cycloadd to dimethyl acetylenedicarboxylate in a [4 + 2] manner, but pyrimidinone **341**, resulting from a [3 + 3] combination, was isolated in 49% yield. On the contrary, **303** did undergo [4 + 2] cycloaddition with activated acetylene to give **342** in 35% yield after prolonged heating (90–95°C, 22 days). Both diazadienes gave cycloadducts **343** (68–100% yield) and **344** (80–90% yield) when treated with aliphatic and aromatic isocyanates. Substituted triazinone **345** was formed in very low yield by heating for long time a benzene solution of diene **303** and trichloroacetonitrile; on the other hand, the use of dimethylcyanamide resulted in the formation of decomposition products (2-dimethylamino-1,4,4-triphenyl-1,3-diazabutadiene and trimethylsilyl isocyanate), instead of the corresponding [4 + 2] cycloadduct.



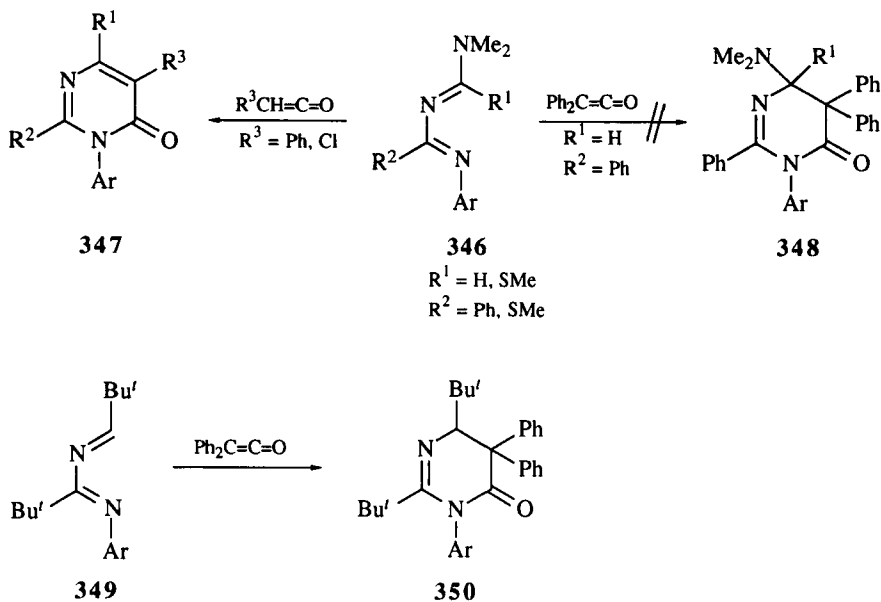
SCHEME 74



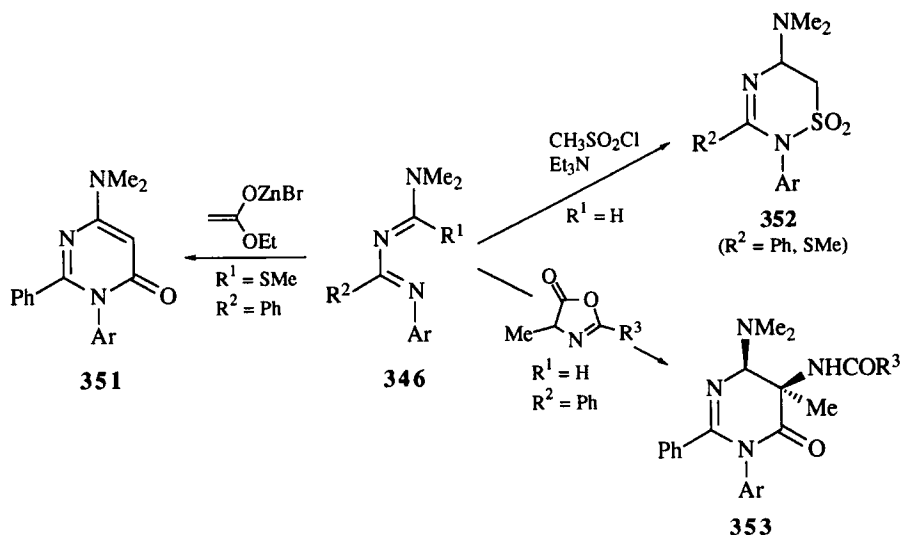
SCHEME 75

Certainly, most reports about the $[4 + 2]$ cycloaddition reactions of 1,3-diazadienes have come from several Indian groups (Scheme 76). Thus, Mahajan (86TL5875; 91T1473) and Sandhu (91S1026) reacted 4-dimethylamino-1,3-diazadienes **346** with monophenyl- and monochloro-ketene to obtain in yields higher than 80% 4(3*H*)-pyrimidinones **347**. The former group claimed that **346** also underwent $[4 + 2]$ cycloaddition toward diphenylketene leading to **348**. However, Würthwein (88TL921) concluded, on the basis of the NMR spectra, that the actual reaction products were β -lactames resulting from the $[2 + 2]$ cycloaddition; furthermore, they demonstrated that strained, 1,3-diazadienes, e.g., the *tert*-butyl derivative **349**, are capable of reacting with diphenylketene in a $[4 + 2]$ fashion to furnish **350** in 52% yield (Scheme 76).

Mazumdar and Mahajan [90TL(31)4215] have synthesized pyrimidinones **351** in 70–90% yield by reaction of **346** ($R^1 = \text{SMe}$) with the Reformatsky reagent derived from ethyl bromoacetate in refluxing toluene; therefore, this reagent behaves in this process as an unsubstituted ketene equivalent (Scheme 77). They also found heterodiene **346** to be reactive toward sulfene leading to 1,2,4-thiadiazine derivatives **352** (60–94% yield) (87TL2641). Sandhu and co-workers (91TL5151) carried out the cycloaddition between **346** and 4-methyl-2-oxazolin-5-ones, as masked methyl ami-



SCHEME 76



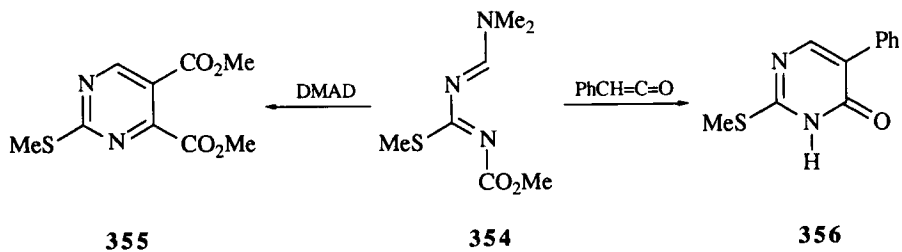
SCHEME 77

doketenes, giving rise in a stereoselective fashion to pyrimidin-6-ones **353** (82–90% yield) (Scheme 77).

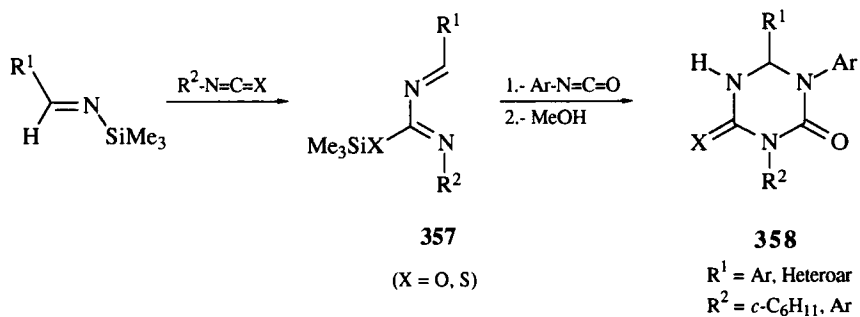
Sundaram and co-workers [90TL(31)7357] prepared 1-methoxycarbonyl-substituted diene **354** and reported its reaction with dimethyl acetylenedicarboxylate in refluxing benzene affording cycloadduct **355** in 72% yield (Scheme 78); there is no comment in the report on the aromatization step, which should imply loss of both dimethylamino and methoxycarbonyl groups. Similarly, the synthesis of pyrimidinone **356** (96% yield) was described to occur when **354** was stirred with phenylketene at room temperature.

Some attention has been paid in our group to 1,3-diazadienes while working with trimethylsilyl imines, since these reagents allowed us to readily prepare a variety of 2-trimethylsilyloxy- and 2-trimethylsilylthio-1,3-dienes **357** (89S228) (Scheme 79). We first tested their potential as heterodienes toward aromatic isocyanates and found that treatment of a dichloromethane solution of **357** and isocyanate at room temperature resulted in a clean conversion into triazinedione and 4-thioxotriazinone derivatives **358** in 84–96% yield.

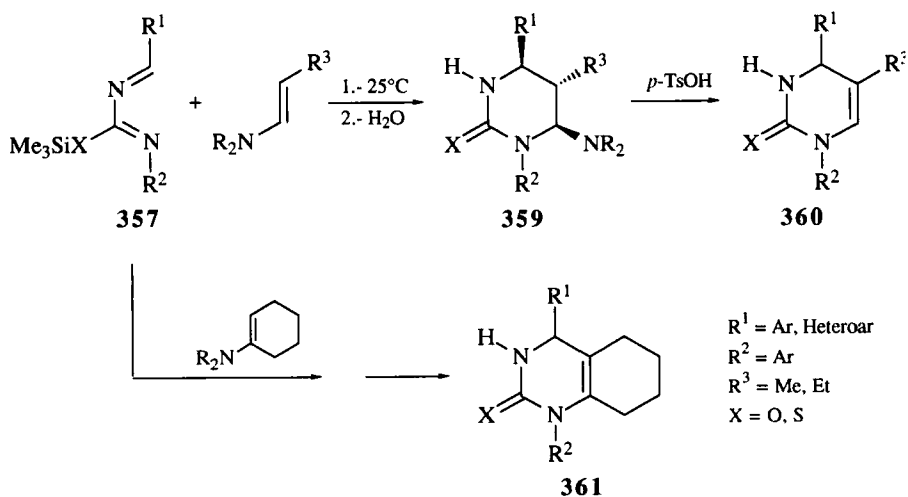
Since no cycloaddition reactions between 1,3-diazadienes and electron-rich dienophiles, e.g., enamines, were previously recorded in the literature, we studied the inverse-electron demand [4 + 2] cycloaddition of **357** with acyclic and cyclic enamines derived from pyrrolidine or morpholine (89TL4573; 90TH1) (Scheme 80). Thus, pyrimidinones and -thiones **359**

DMAD: $\text{MeO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Me}$

SCHEME 78



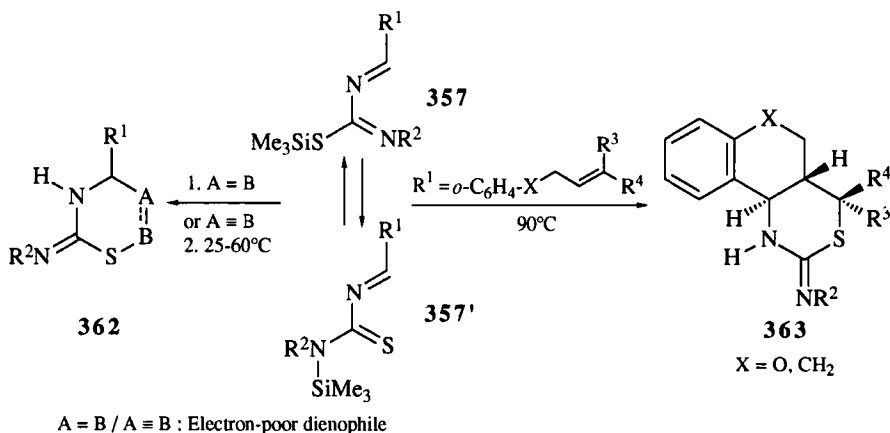
SCHEME 79



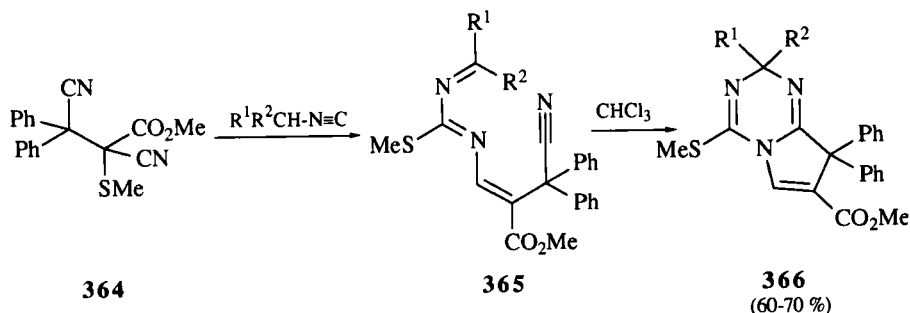
SCHEME 80

were formed in 80–93% yield on treatment of **357** with acyclic enamines in dichloromethane at room temperature; the cycloadducts were formed in a regio- and stereoselective manner, an *endo* transition state being involved in the reaction. Dehydration of **359** with *p*-toluenesulfonic acid afforded 3,4-dihydropyrimidinone and -thione derivatives **360** in more than 80% yield. This procedure permitted us to obtain quinazolinones **361** (X = O) and quinazolinethiones **361** (X = S), in 70–84% overall yields from **357**, by employing enamines derived from cyclohexanone. An isolated report concerning the cycloaddition of imidoyl isothiocyanates with enamines to give pyrimidinethione derivatives was published some years ago (66JOC722).

When the cycloaddition of heterodienes **357** with electron-poor dienophiles was attempted, we observed no reaction in the case of trimethylsilyloxy-containing heterodienes **357** (X = O). However, the reaction of trimethylsilylthio-substituted heterodienes **357** (X = S) with typical, electron-deficient carbon- and heteroatom-containing dienophiles at 25–60°C led regio- and stereoselectively to heterocycles **362** containing sulfur and nitrogen; the process showed complete chemoselectivity in favor of thiazadiene structure **357'** over diazadiene **357** (89TL6923; 91MI2) (Scheme 81). In summary, these heterodienes undergo cycloaddition reactions with electron-rich dienophiles through 1,3-diaza tautomer **357**, whereas the 1-thia-3-azadiene species **357'** appears to be the only reactive tautomer toward electron-poor dienophiles. Finally, 1-thia-3-azabutadiene also operates exclusively in the intramolecular Diels–Alder cycloaddition to unactivated carbon–carbon double bonds, affording in a stereospecific way heteropolycyclic compounds **363** (89CC1487; 91JOC5680).



SCHEME 81



SCHEME 82

An example dealing with the intramolecular [4 + 2] cycloaddition of 1,3-diazadienes with a nitrile was provided in 1985 by Foucaud *et al.* (85JOC771) (Scheme 82). They reacted ester **364** with isocyanides to give intermediates **365**, which underwent at room temperature intramolecular cycloaddition producing 1,3,5-triazabicyclo[4,3,0]nona-2,5,8-trienes **366** in 60–70% yield.

ACKNOWLEDGMENTS

The authors acknowledge the Dirección General de Investigación Científica y Técnica (Ministerio de Educación y Ciencia) for financial support through fellowships and research assistantships. We express our special gratitude to Dr. S. Fustero for his great contribution in developing the chemistry of 2-azadienes and to Dr. A. Ballesteros for his efficient help in the elaboration of this manuscript.

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1,2,4-Triazolo[1,5-*a*]pyrimidines

GUNTHER FISCHER

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I. Introduction

A. GENERAL SURVEY

The formation of 1,2,4-triazolo[1,5-*a*]pyrimidines (TP) (**1a**) was first reported by Bülow and Haas (09CB4638). Over the next 50 years, only a

few papers and patents on TPs were published, which were included in Mosby's comprehensive monograph on "Heterocyclic Systems with Bridgehead Nitrogen Atoms" [61HC(15)878].

The systematic studies reported since 1958 include those of the groups of Sirakawa (1958–1960), Makisumi (1958–1964), Allen and Williams (1959–1962), Levin (1963–1964), Kreutzberger (1966–1979), Reimlinger (1970–1971), and recently Reiter (since 1987).

Special aspects of synthesis and reactivity have been covered in reviews by Babichev and Kovtunenکو (77KGS147; 91UKZ172), Tisler (80PAC1611), Ivashchenko and Garicheva (82KGS579), Shaban *et al.* [91AHC(52)1], and in a valuable comparative study of certain azaindolizines by Maury [77HC(30)179].

B. SCOPE AND LIMITATION

This review is based—after smaller previous overviews (71MI1; 73MI2; 90ZC305)—on Mosby's work and reviews the literature mentioned in *Chemical Abstracts* up to Vol. 116 (June 1992). Patents are included if they reveal new synthetic aspects.

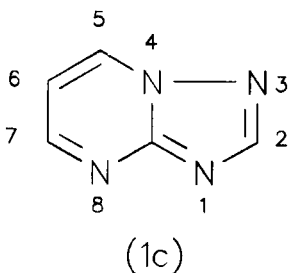
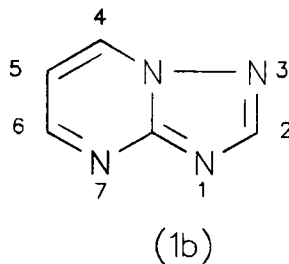
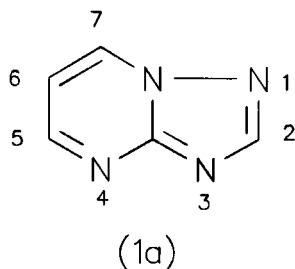
1,2,4-Triazolo[1,5-*a*]pyrimidines fused to various heterocycles represent particular ring systems and are, as a rule, not noted here. The isomeric 1,2,4-triazolo[4,3-*a*]pyrimidines (Section II,B,1) and reduced TPs (Sections II,A,6 and IV,E) are excluded unless they are precursors, potential synthetic intermediates, or reaction products of TPs.

C. NOMENCLATURE

1,2,4-Triazolo[1,5-*a*]pyrimidines are numbered as in **1a**. They sometimes are named 1,2,4-triazolo[2,3-*a*]pyrimidines, 1,3,4-triazaindolizines (both with same numbering), or 1,3,3a,7-tetrazaindenones (**1b**). Some authors use indolizine numbering **1c** for TPs.¹

For many hydroxy-, mercapto-, and amino-TPs, the exact position of tautomeric equilibria (Section III,E,1) is uncertain [77HC(30)179]. In such cases, the structure preferred by the authors or the most probable tautomeric form is used here.

¹ 66JHC269, 77HC(30)179, 78T2927, 79AP816, 79API003, 87JHC805, 87JHC1149, 87JHC1503, 87T2497, 90M173, 91JHC721.



II. Syntheses

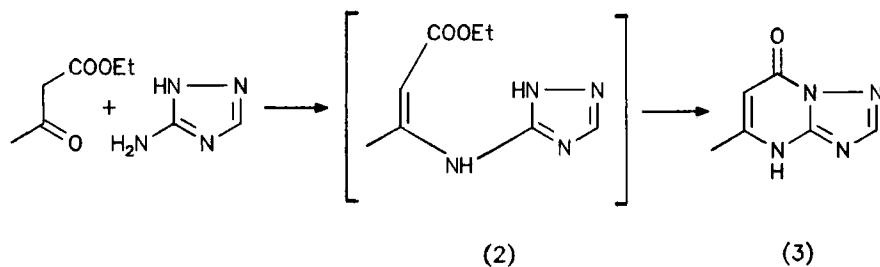
Most syntheses of TPs start either from a 1,2,4-triazole derivative or from a pyrimidine residue and need annulation of a second heterocyclic ring. Preferably 5-amino-1,2,4-triazoles (AT) and 2-hydrazinopyrimidines (HP), respectively, are used as starting synthons.

According to the reaction types these syntheses may be classified as cyclocondensations, cycloadditions, or oxidative cyclizations (80PAC1611). To some extent TPs are prepared by other transformations of the five- and/or six-membered ring.

A. 5-AMINO-1,2,4-TRIAZOLES AND 1,3-BIFUNCTIONAL SYNTHONS (SYNTHESIS A)

1. Principle and Conditions

An example of synthesis A is that of 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-on (MOT) (**3**) by Bülow and Haas (09CB4638) given in Scheme 1. This reaction is a pyrimidine synthesis: The C_3 -synthon condenses with a N—C—N moiety, which is a part of an AT. Apparently the reaction passes through the nonisolable intermediate **2** (Section II,A,2).



SCHEME 1

TABLE I
PRINCIPLE OF TP SYNTHESIS A FROM AT AND 1,3
BIFUNCTIONAL SYNTHONS

	A, B ^a	R', R'' ^a
	—CHO	H ^b
	—CH(OR) ₂	
	—CH=NR ₂	
	=CHOH	
	=CHOR	
	=CHSR	
	=CHNH ₂	
	=CHNHR	
	=CHNR ₂	
	=CHCl	
	≡CH	
	—COOR	OH ^c
	—COCl	
	—CSSR	SH ^c
	=C(SR) ₂	SR
	—CN	NH ₂
	=C(OR)NH ₂	
	=C(SR)NH ₂	
	—CONR ₂	NR ₂

^a R = alkyl, aryl.^b Analogously for alkyl, aryl, heterocyclyl, if these groups replace the H atom in A, B.^c tautomeric forms.

Table I illustrates this synthesis in schematic form. The first column lists all functions A and B of the 1,3-dicarbonyl compounds or their equivalents that are used to introduce certain substituents R' and R'' into positions 5 and 7; e.g., unsubstituted TP is formed by malondialdehyde, the 5,7-dione by diethyl malonate, and the 5,7-diamine by malonitrile.

Unsymmetrical C₃-synthons with different A and B moieties may form two isomeric TPs in which R' and R'' interchange their positions. The direction of attack depends on both synthon structure and reaction conditions.

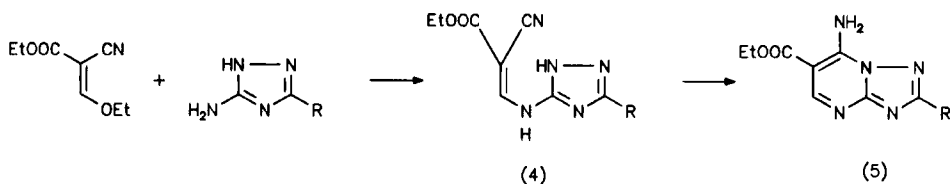
Generally, the cyclizations proceed without any condensing agent, either with an excess of the 1,3-bifunctional compound or in acetic acid, alcohols, and possibly nitrobenzene. Glacial acetic acid under reflux means "standard conditions" (89JHC1393).

Certain reactions must be catalyzed by aqueous alkali (90MI2; 91USP4988812) or by sodium ethoxide, e.g., the condensation of 3-mercapto-AT and ethyl acetoacetate (68UP1), which does not proceed in acetic acid (60JOC361), in contrast with the analogous reaction with acetylacetone (60JCS1829).

Generally, the isomeric 1,2,4-triazolo[4,3-*a*]pyrimidines (such as **18**, Section II,B,1) are not formed. Exceptions are found with 3-phenyl-AT (60JOC361) and condensations of propiolic acids and their esters (70CB3266; 71CB2702) [and, as minor side reactions, condensations of 3-ketovinyl compounds (83S44)].

2. Mechanism [cf. 77HC(30)179]

With regard to the formation of MOT (Scheme 1), Allen *et al.* (59JOC787) proposed a two-step mechanism involving first the interaction of the exocyclic amino group (assumed to be the most nucleophilic center of AT) with the enol of the ketonic carbonyl. The assumption of type 2 intermediates is substantiated by the isolation of analogous products (3-enaminoesters) in reactions of ATs with ethoxymethylene-malonate (62JCS2222), -nitroacetate (86KFZ178), and -cyanoacetate (60YZ952;



SCHEME 2

87JHC1149); for example, see **4** in Scheme 2. They are analogs of the enamide intermediates suggested by Katritzky *et al.* (87T5171) in certain types of Traube's pyrimidine synthesis.

In a second step cyclization of the intermediate occurs with a ring nitrogen atom at position 1 attacking the ester (**2**) or cyano group (**4**) and forming **3** and **5**, respectively.

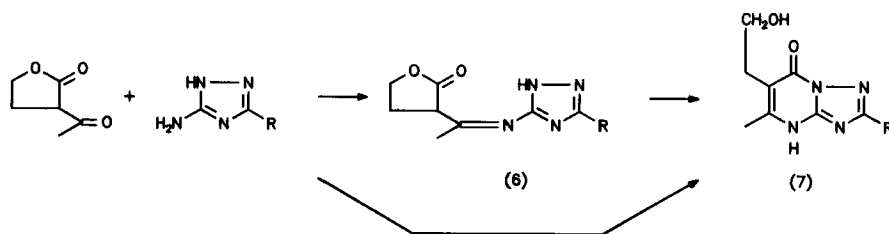
The analogous reaction of acetylbutyrolactone and ATs in acidic (68UPI), neutral, or basic media (65NEP6501015) leads directly to 6-(2-hydroxyethyl)-MOT (**7**, Scheme 3). Condensation in the presence of BF_3 allows the isolation of an intermediate azomethine **6**, which forms **7** on treatment with base (80JMC927).

3. Regioselectivity Studies

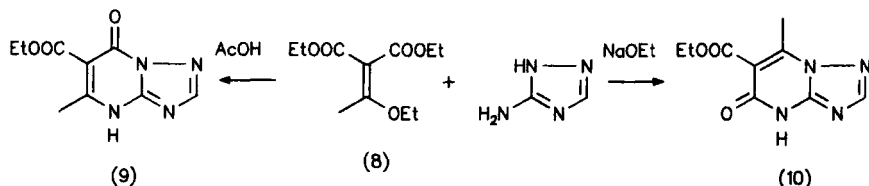
In reactions with unsymmetrical C_3 -synthons, the exocyclic amino group of an AT condenses, as a rule, preferentially with an aldehydic rather than a ketonic group and with the latter rather than an ester or nitrile function [77HC(30)179]. Nevertheless, in many cases the synthons (especially 3-ketovinylic compounds) form mixtures of two isomeric TPs with exchanged 5- and 7-substituents [e.g., 59YZ1482; 74KGS565; 79JCS(P1)3085] or, depending on the conditions, exclusively one or the other isomer.

Williams studied qualitatively the charge distribution in AT (61JCS3046) and found that the exocyclic nitrogen atom under acidic conditions and a ring nitrogen atom under basic conditions is the more nucleophilic site. The condensation of 1-ethoxyethylidene malonate (**8**) and AT indeed in acidic and basic media exclusively leads to products **9** and **10**, respectively (Scheme 4).

In a similar manner Mühlstadt *et al.* (70JPR254) explain the formation of 7- and 5-amino-6-cyano-TP (**24**, see below) from ethoxymethylene malonitrile and AT in acid and base, respectively.



SCHEME 3



SCHEME 4

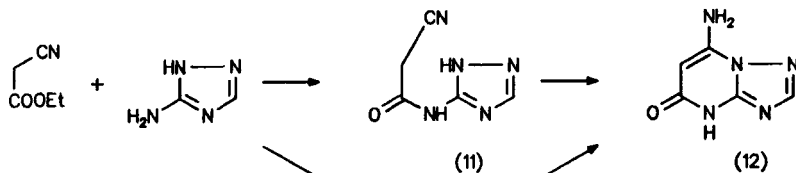
Following are further examples of reversed reactivity order. The formation of 5-oxo-TPs is achieved by means of condensations of AT (in the presence of sodium ethoxide) with ethyl 3,3-diethoxypropionate or 3-ethoxyacrylate (64ZOB499), propiolic acid (70CB3266), and cyanoacetate (61CPB801; 64CB1373, 64IZV1475), respectively. In the last case (formation of **12**), the fusion of reactants without catalyst allows the isolation of intermediate amide **11** (Scheme 5).

On the other hand, 3-ketoesters with unsubstituted AT nearly exclusively lead to "normal" 7-oxo-derivatives (71CB2702) as given in Scheme 1. An exception is the formation of 5-oxo-6-carbethoxy-7-methyl-TP from diethyl acetylmalonate (66UP1) in acetic acid, DMF, or DMSO (with poor yield only).

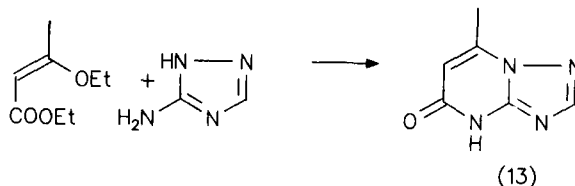
In most cases substituted ATs also react "normally," independent of the medium. Differences are observed with N-alkylated ATs (63CPB67, 63CPB851, 63CPB859, 63MI1, 68T2839); exclusively or preferentially 7-oxo- and 5-oxo-TPs are formed in acetic acid, and without solvent, respectively.

5-Oxo-7-methyl-TP (**13**), which is a positional isomer of MOT (**3**), was prepared from acetoacetate enolether (61JCS3046) or tetrolate (64ZOB499) and AT in the presence of sodium ethoxide (Scheme 6).

Kleschick and co-workers recently reported detailed studies on regioselectivity involving the condensation of 2-benzylthio-AT with different bi-functional synthons. They determined the ratios of products from ^1H -NMR spectra of the crude mixtures.



SCHEME 5



SCHEME 6

Using unsymmetrical 1,3-diketones in acetic acid, they obtained 82–97% of the corresponding 5-methyl-TP (89JHC1489). The exocyclic amino group of the AT reacts with the more reactive of the two carbonyl groups.

In contrast, the regioselectivity of the reaction with acetoacetaldehyde dimethylacetal under the same conditions is poor, resulting in 67% 5-methyl-TP (89JHC1393). In the presence of sodium ethoxide, the reaction leads to 5-methyl-TP exclusively. Here, in the present authors' opinion, the regioselection may be controlled by the reaction of the AT anion with the product of base-induced methanol elimination from the keto acetal.

In order to get the isomeric 7-methyl-TP, they added the AT derivative slowly to the mixture of acetal and acetic acid. If this forms a monocyclic enamine intermediate, direct cyclization (resulting in the desired TP) could be favored over reaction with a second AT (which would form a binuclear second intermediate without regioselection).

Reiter *et al.* studied the condensations of 3-methylthio-AT and 3-morpholino-AT, respectively, with ethoxymethylene-cyanoacetate (and -malonitrile) in acetic acid or DMF (or mixtures) and isolated only the corresponding 7-amino-TP (87JHC1149). Analogous reactions of aliphatic (90M173) and alicyclic 3-ketocarboxylic esters (87JHC1503; 890PP163; 91JHC721) always resulted in 7-oxo-TPs as the major products and 5-oxo-TPs as by-products.

4. Further Syntheses Achieving Substitution at Positions 5 and 7

These reactions are summarized in Tables II and III, collected according to the bifunctional synthons used and the substituents entering position 5 and/or 7 (marked R-5 and R-7), where R and R' mean alkyl (possibly substituted), partly aryl, heterocyclyl, and H.

Variations of the synthesis of MOT derivatives from AT include the reactions of 3-ketocarboxylic esters with 1-formylaminoguanidine, which is an intermediate in the preparation of AT (82JAP57/175193), or with AT *in situ* (83JAP58/124787).

TABLE II
SYNTHESIS A OF TP SUBSTITUTED AT POSITIONS 5 AND/OR 7 BY HYDROCARBON-
OR OXYGEN-CONTAINING GROUPS

Bifunctional synthon	R-5 ^a	R-7 ^a	Reference
1,3-Dialdehyde	H	H	81KGS1554
1,3-Diacetal	H	H	59JOC796
3-Chloroacrolein	H	H	86EUP188225 ^b
3-Aminoacroleininimium salt	H	H	85EUP142152
3-Ketoacetal	R	H	59JOC796
3-Ketovinylic ether	H	R	59JOC796
	R	H	59JOC796
	R	R'	70MI2
3-Ketoenamine	H	R	80USP4209621
			84USP4444774 ^c
1,3-Diketone	R	R'	60JCS1829
			90EUP353902
Acetonoxalic ester	COOEt	Me	59YZ1482
	Me	COOEt	59YZ1482
3-Ketoalkyne	R	R'	90MI1
3-Formylcarboxylic ester	H	OH	63ZOB2673
Enamine-3-carboxylic ester	H	OH	90JHC359
Acetylenedicarboxylic ester	COOMe	OH	71CB2702
3-Ketocarboxylic ester	R	OH	59JOC787
			59JOC793
Oxalacetic ester	COOEt	OH	59JOC793
Alkoxyalkylenemalonic ester	R	OH	80JCS(P1)1347
			91USP5061799 ^d
2,3-Dihalogencarboxylic ester	OH	R	67JCS(C)503
Unsat. β -lactone (diketene)	R	OH	59JOC787
Malonic ester ^e	OH	OH	61CPB801
Malonyl chloride	OH	OH	91USP5006656

^a OH: hydroxy or tautomeric oxo form.

^b Mucochloric acid (decarboxylation).

^c R-7 = pyridyl, thienyl.

^d Meldrum's acid derivative.

^e Diphenyl, bis-(2,4-dichlorophenyl), and bis-(2,4,6-trichlorophenyl) malonates are especially reactive esters (80JHC337; 89EUP322359).

5. Direct Introduction of Substituents onto Positions 1, 2, 3, 4, and 6

1,2,4-Triazolo[1,5-*a*]pyrimidines substituted at these sites may be synthesized from properly substituted precursors. Examples for positions 2 and 6 are listed in Table IV.

TABLE III
SYNTHESIS A OF TP SUBSTITUTED AT POSITIONS 5 AND/OR 7 BY SULFUR- OR
NITROGEN-CONTAINING GROUPS

Bifunctional synthon	R-5 ^a	R-7 ^a	Reference
Asymmetric dithiooxalic ester	OH	SH	61CPB801
2-Acylketene mercaptal	SR	R'	85CPB962
2-Carbalkoxyketene mercaptal	SR	OH	85CPB962
2-Cyanoketene mercaptal	SR	NH ₂	85CPB962
Alkoxyalkylene malonitrile	H	NH ₂	79GEP2918085 ^b
Alkylthioalkylene malonitrile	H	NH ₂	85CPB962
3-Ketonitrile	R	NH ₂	83GEP3130633
2,3-Unsat. 3-aminonitrile	R	NH ₂	63ZOB2678
Cyanoacetic ester	OH	NH ₂	64IZV1475
2,3-Unsat. 3-amino-3-alkoxycarboxylic ester	NH ₂	OH	81JHC1287
2,3-Unsat. 3-amino-3-alkylthiocarboxylic ester	NH ₂	OH	81JHC1287
2,3-Unsat. 3-chlorocarbonamide	R	NR' ₂	81JAP56/108772

^a OH, SH or tautomers oxo, thioxo, resp.

^b Cyclization in the presence of NaN₃ yields 6-(tetrazol-5-yl) derivative.

Condensations of cycloalkanone-2-carboxylic esters and similar synthons with ATs result in 5,6- and/or 6,7-cycloalkeno-TPs [e.g., 59YZ1487; 70MI1, 70MI2; 72MI2; 79JCS(P1)3085; 87JHC1503]. Recently Desenko *et al.* (91KGS694) reported an interesting variant using benzocycloalkenones (e.g., 1-tetralone) and DMF. (This mixture behaves as the corresponding 3-ketoaldehyde.)

Synthesis A also may lead to N-substituted TPs. 4-Alkyl-ATs and 5-alkylamino-1,2,4-triazoles are cyclized by 3-ketocarboxylic esters (and equivalents) forming 3- and 4-alkyl-oxo-TPs, respectively [67JCS(C)503; 70GEP1946315; 87T2497]. Similar reactions with 1,3-diketones afford the following 1,3,4-triazolo[1,5-*a*]pyrimidinium salts: 3-methyl (74KGS565), 4-phenyl (88UKZ880), and 1-phenyl and 3-amino derivatives (73UKZ-1036).

6. Syntheses via Dihydro Derivatives

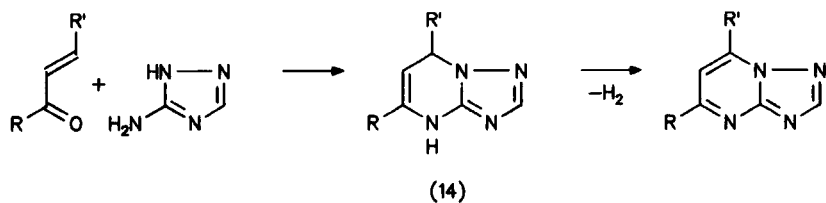
If a 2,3-unsaturated aroyl compound is used instead of the 1,3-dicarbonyl compound, then the primary product is a 4,7- or 6,7-dihydro-TP, e.g., **14** (Scheme 7).

TABLE IV
TP SUBSTITUTED ONTO POSITIONS 2 AND 6 FROM SYNTHESIS A

Position	Substituent ^a	Reference
2	Alkyl	63ZOB1309; 64IZV1475
	Alkylene-bis-	63ZOB1309; 82UKZ79
	Cl	88JAP63/267782
	OH	62JCS3854
	OR	83JHC735
	SH	75JHC1187; 83S44
	SR	61JCS3046; 82JMC420
	SO ₂ NHR'	87EUP244847; 91USP4988812
	NH ₂	61JCS3046; 66JCS(C)2031
	NR ₂	83JHC735; 87T2497
	NHSO ₂ R'	90MI2
	CH ₂ OH	59JOC793; 89EUP302633
	COOEt	64UP1
	Pyridyl	88IJC(B)825; 89IJC(B)242
6	Alkyl	63ZOB2673; 64IZV1475
	Cl, Br	61CPB808; 86USP4582833
	SO ₂ R''	85CPB962
	NO ₂	61CPB873; 86KFZ947
	NHCOCH ₃	61CPB873; 64CB1373
	N=N-aryl	61CPB878; 91CCC1560
	CH ₂ CH ₂ CH ₂ OH	83S44
	CH ₂ CH ₂ CH ₂ SH	81JHC1287
	CN	62JCS2222; 35CPB962
	COOH	91USP5061799
	COOR	62JCS2222; 85CPB962

^a R = alkyl; R' = aryl; R'' = alkyl or aryl.

Dehydrogenation proceeds by the means of *N*-bromosuccinimide (88KGS229; 90KGS938), Br₂, SeO₂, or aerial oxygen (90KGS1638), and aroylethylene in excess (90MI1), or spontaneously [88IJC(B)421]. A 2,3-diamino-dihydro-TP derivative (from 3,4,5-triamino-1,2,4-triazole) by elimination of NH₃ is transformed into the aromatic state (90KGS938).



SCHEME 7

B. 2-HYDRAZINOPYRIMIDINES AND C₁-SYNTHONS (SYNTHESIS B)

1. Principle

The second important reaction path similar to AT synthesis starts with aminoguanidine derivatives (in this case part of a HP) and proceeds via condensation with a synthon Z (see principle in Scheme 8). In a first step 1,2,4-triazolo-[4,3-*a*]pyrimidines (**15**) are formed; these are often isolable and nearly always transformable into the more stable TPs by Dimroth rearrangement.

The C₁-synthon is usually a carboxylic acid or a derivative of a carboxylic or carbonic acid and introduces substituent R¹. An example is the reaction of 4-oxo-6-methyl-HP (**16**) and formic acid in Scheme 9 (59JOC787).

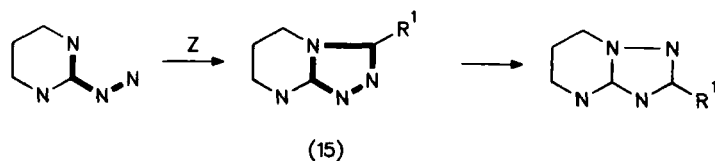
Under relatively mild conditions (formic acid at 50°C) [4,3-*a*] compound **18** is formed via (commonly not isolated) formyl derivative **17**. It rearranges to MOT (**3**) by formic acid at 100°C. When these harsher conditions exist from the beginning, both reaction steps proceed one after another and MOT is isolated directly.

The ease and direction of the cyclization are influenced by the substituents of the HP and by the nature of the C₁-synthon. With regard to the HP, oxo groups in positions 5 and 7 facilitate cyclization and phenyl renders it more difficult (77KGS147).

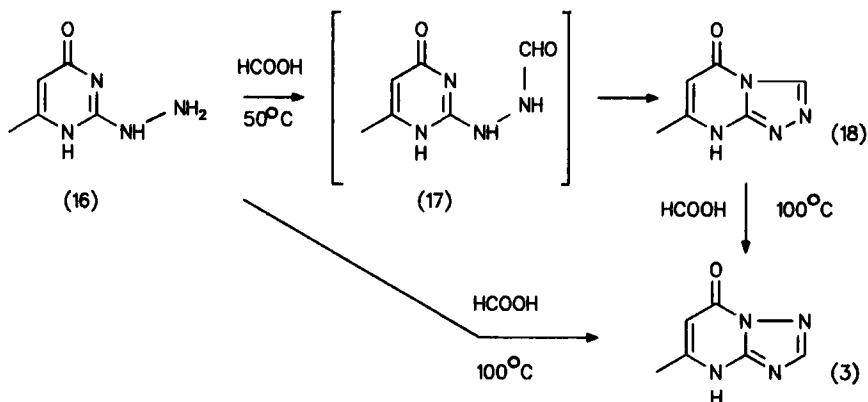
Under mild conditions the [4,3-*a*] intermediate is isolable in many cases, and always with aliphatic orthoesters; contrary reports (66JHC269) can be attributed to admixture of the corresponding carboxylic acid (77AJC2515). Orthobenzoic ester leads to the rearranged product (77AJC2515).

2. Regioselectivity

The acyl group of an intermediate acyl-HP (e.g., **17**) in principle may attack at either nitrogen atom of the pyrimidine ring. Therefore, in addition to ring isomerism another type of isomerism exists for synthesis B, caused by the position of substituents (positional isomerism).



SCHEME 8



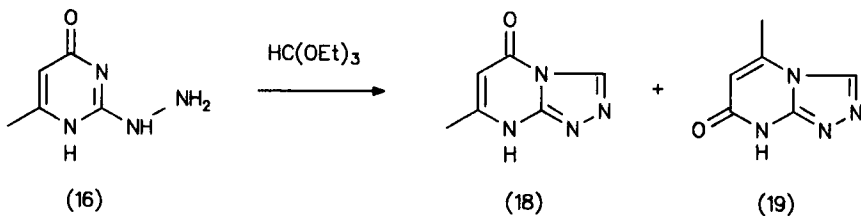
SCHEME 9

In reactions of 4-oxo-HPs (e.g., **16**) and carboxylic acids, N-3 is preferentially attacked, and triazolopyrimidin-7-ones (e.g., **18** or **3**) are formed. A few HPs with (58YZ1395) or without oxo groups (59YZ1482) can form mixtures even with carboxylic acids. On the other hand, orthoesters usually lead to mixtures (59JOC787; 60JOC361), e.g., **18** and **19** (Scheme 10), and only seldom react to give a single product (60YZ952).

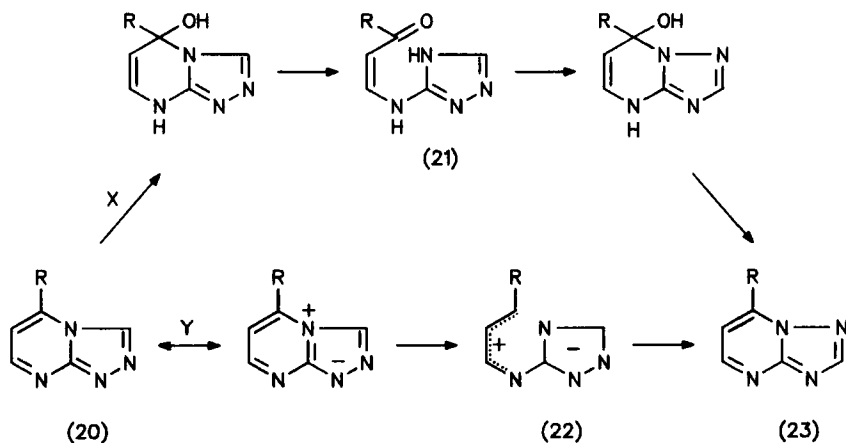
Exclusive attack on N-1 of HPs seems to occur with aromatic cyclizing agents, e.g., orthobenzoic ester (60JOC361), and in reactions of N-alkylated HPs (60JOC361, 60YZ1550).

3. Mechanisms of the Dimroth Rearrangement

The Dimroth rearrangement (69ZC241) including 1,2,4-triazolo[4,3-*a*]pyrimidines generally proceeds rather easily; therefore these compounds, when prepared, are often not isolable (or only by very carefully handling). The extremely fast rearrangement, compared, for example, with that of 1,2,4-triazolo[4,3-*a*]pyridines, is attributed to the increase in electron de-



SCHEME 10



SCHEME 11

iciency at C-7² owing to the second nitrogen atom of the pyrimidine ring (66JOC265).

This type of Dimroth rearrangement is strongly influenced by inductive and less by steric effects; Dimroth reactions, usually reversible, almost always proceed, in the case of TPs, from the kinetically favored [4,3-*a*] product to the thermodynamically more stable [1,5-*a*] isomer (70CB3266; 80PAC1611; 87JHC805, 87M601).

The rearrangement is promoted, by aqueous acids and bases (occasionally by boiling water), and also by heating >200°C. Accordingly, two mechanisms (Scheme 11) are proposed [66JCS(C)2031; 75JHC1187; 77HC(30)179].

In base- or acid-catalyzed reactions (path X), the initial is covalent hydration (Section IV,F,2) of **20**. The hydroxy group enters position 7, then the six-membered ring opens and forms the carbonyl intermediate **21**; the CO group then attacks the more nucleophilic N-2 of the triazole ring and cyclizes to the rearranged TP **23** (59JOC787). The thermal rearrangement (path Y) presumably involves a zwitterionic intermediate **22** (58YZ1395; 83S44).

Whereas there is no experimental proof for thermal mechanism Y, good arguments exist for an initial attack of OH⁻ on C-7 [77HC(30)179, 77KGS147]: Decreasing the electron density at C-7 or stabilizing the intermediate **21** facilitates rearrangement, e.g., by means of the COOEt group

² For convenience, the numbering of TP (Formula **1a**) is also used in the [4,3-*a*] series.

at C-6 [67JCS(C)498]. An oxo group in position 7 makes the reaction difficult and it is prevented by COOMe at this site (70CB3266). Alkyl groups in positions 1, 5, 6, and 7 may also slow down or prevent the rearrangement (68T2839; 77AJC2515).

This mechanism is strongly supported by results from Spickett and Wright [67JCS(C)498] and Bee and Rose [66JCS(C)2031]: In cyclizing HP by imino ethers, the [4,3-*a*] compound is not isolable unless R-7³ = oxo; otherwise it rapidly rearranges [67JCS(C)498].

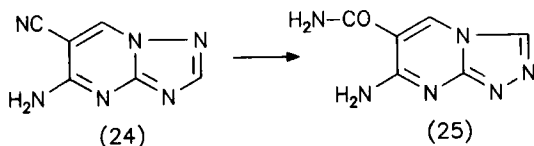
Finally, the rearrangement of 7-methoxy derivatives in aqueous alkaline solution supports the path via **21** [66JCS(C)2031]: As the authors suggest, hydration and ring opening lead to intermediate **21** (—CO—R = —COOCH₃), which then expels CH₃OH; indeed they isolated 7-oxo-TP.

Brown and Nagamatsu (77AJC2515) report kinetic studies on Dimroth rearrangements to TP in two pH ranges. Isomerization rates in alkali increase steeply in the range pH 10–12.5. In acid, they obtain maxima at pH values corresponding approximately to the pK_a of each substance (in the range pH 1.5–2.5). Kennewell *et al.* [86JCR(M)2000, 86JCR(S)232] describe a reaction similar to the Dimroth rearrangement.

For the retro-Dimroth rearrangement of a TP, apparently only one example has been found (70JPR254): 5-Amino-6-cyano-TP (**24**) under the influence of the unusual rearranging agent concentrated sulfuric acid leads to [4,3-*a*] derivative **25** (Scheme 12). The triazole ring is believed to be polyprotonated in this medium and to have its most nucleophilic site at N-4.

4. Further Syntheses Achieving Substitution at Position 2

These reactions are summarized in Table V and collected according to the C₁-synthons used and the substituents R¹ entering the newly formed triazole ring. Superscripts to references indicate formation of 1,2,4-triazolo[4,3-*a*] (*a*) and -[1,5-*a*]pyrimidines (*b*); a description of the re-



SCHEME 12

³ R-7 is the substituent in position 7.

TABLE V
SYNTHESIS B OF TP SUBSTITUTED AT POSITION 2

	(a)	(b)
Synthon Z ^e	R ¹ ^e	Reference
HCOOH	H	62BSF355 ^{a+b} ; 78T2927 ^{a/b, a+b, c, d}
(COOH) ₂	H ^f	68DIS(B)1303 ^b
HCOOH/HCONH ₂	H	62BSF355 ^b
DMF	H	86JHC833 ^{a/b, c}
HC(OEt) ₃	H	60JCS1829 ^{a, c} ; 86JHC833 ^{a, c}
CH ₃ COOH	CH ₃	59YZ899 ^{a, c}
CH ₃ COOPh	CH ₃	59JOC793 ^b
CH ₃ CSSEt	CH ₃	89H(28)239 ^{a, c, d}
RC(OEt) ₃	R	77AJC2515 ^{a, c} ; 80USP4209621 ^{a, c}
R' C(OEt)=NH·HCl	R'	67JCS(C)498 ^{a, c} or <i>b</i> , resp.
PhCHO/oxid.	Ph	77AJC2515 ^{a, c}
C(OR) ₄	OR	77AJC2515 ^b
CS ₂	SH	60YZ1542 ^{a, c} ; 75JHC1187 ^{a/b, a+b, c}
ClCN	NH ₂	66JCS(C)2031 ^{a, c, d}
BrCN	NH ₂	66CB2237 ^{a, c} ; 70PHA460 ^{a, c}

^a Triazolo [4,3-*a*] pyrimidine.

^b Triazolo [1,5-*a*] pyrimidine.

^{a+b} Mixture of *a* + *b*.

^{a/b} *a* or *b* under milder and harder reaction conditions, resp.

^c Rearrangement.

^d Mixture of two isomeric *a*.

^e R = alkyl; R' = alkyl, CH₂COOEt, CH₂CONMe₂.

^f Decarboxylation.

arrangement (c); and (additionally in cases of unsymmetrical HPs) the formation of mixtures of isomeric [4,3-*a*] derivatives with exchanged C-5 and C-7 substituents (*d*).

5. Use of Modified 2-Hydrazinopyrimidines

In the synthesis of TPs from HPs, intermediates (i.e., uncyclized HP derivatives like **17** in Scheme 9) are believed to exist and have been isolated in many cases [e.g., 67JCS(C)498; 70CB3266; 78T2927]. These products and other acylated HPs may serve as convenient starting materials for cyclization reactions (Table VI).

TABLE VI
HYDRAZINE DERIVATIVES USED IN TYPE B SYNTHESIS OF TP^g

Pyrimidin-2-yl ^e	R ¹ ^e	Reference
—NHNH—CHO	H	59YZ903 ^{a,c} ; 70CB3266 ^{a+b}
—NHNH—COCOOH	H ^f	58YZ1395 ^b
—NHNH—COCH ₃	CH ₃	59JOC793 ^b
—NHNH—C(=NH)—CH ₃	CH ₃	67JCS(C)498 ^b
—NHN=CHR''/oxid. ^h	R''	71GEP2004713 ^{a,c} ; 77CPB3137 ^{a,c}
—NHNH—COCH ₂ CH ₂ OH	CH ₂ CH ₂ OH	59JOC793 ^{a,b}
—NHNH—COCOOR	COOR	68DIS(B)1303 ^b
—NHNH—COOEt	OH	68DIS(B)1303 ^{a,b,c}
—NHNH—CSSNa	SH	78AJC397 ^{a,c}
(—NHNH—COCH ₂) ₂	Alkylene	58USP2853375 ^b

^g R¹ and superscript letters *a,b,c,e,f* as in Table V.

^h R'' = aryl, heterocyclyl (furyl).

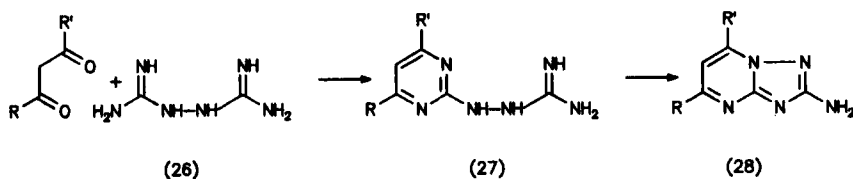
Acylated HPs were also prepared from 2-alkylthiopyrimidines and acylhydrazines and, further, cyclized *in situ* to triazolopyrimidines (58USP2852375).

Another one-pot synthesis was reported by Kreutzberger *et al.* (Scheme 13): 1,3-Dicarbonyl compounds (66CB2237; 70PHA460; 71AP856, 71T3247; 76AP148; 79AP1003, 79CZ267, 79JFC131; 80AP244) or acetoacetic ester (79AP816), respectively, are condensed with the diamidine **26** in alkaline medium at 100°C to give 2-amino-TPs (**28**). Sometimes, under mild conditions (20°C) intermediate **27** is isolated (79AP816, 79CZ267). The initial [4,3-*a*] compound is rearranged under the harsh conditions of the second cyclization step.

6. Direct Introduction of Substituents onto Positions 3, 4, 5, 6, and 7

The following typical examples have been reported:

onto position 5: phenyl (62BSF355; 71CB2702), CF₃ (80AP244), NH₂ (64CB1373);



SCHEME 13

onto position 6: COOEt and CN (60YZ952), alkylthio (86EUP190375); onto position 7: CF₃ (79JFC131), thien-2-yl (79CZ267); onto positions 3 and 4: alkyl [60YZ1550; 67JCS(C)498].

As 5,6-fused systems: cycloalkeno derivatives (59YZ1487) and benzo derivatives (86JHC833).

C. OTHER TRIAZOLE RING SYNTHESSES

Type B syntheses starting from HPs require a Dimroth rearrangement. By contrast, in the following reaction paths, the 1,3 orientation of two nitrogen atoms needed to form the triazole ring of the TP is preformed in the pyrimidine precursor.

1. From 2,3-Diaminopyrimidines and C₁-Synthons

Reactions starting from 2,3-diaminopyrimidin-4-ones and -quinazolin-4-ones [91AHC(52)1] and the reaction principle are summarized in Table VII. Intermediates could be isolated in the cyclizations involving orthoesters (85JHC1317).

Hu *et al.* (91MI1) report the Dimroth rearrangement of 2-hydrazino- to 2,3-diamino quinazolin-4-ones under catalysis of carboxylic acid derivatives; this reaction is followed by an *in situ* cyclization in which the same carboxylic acid derivatives serve as C₁-synthons. 1-Acylamino-2-alkylthiopyrimidines are hydrazinolyzed and cyclized to 3-amino-1,2,4-triazolo[1,5-*a*]pyrimidinium salts (89EGP270711).

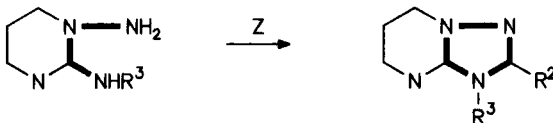
2-Amino-3-acylamino-4-ones can be cyclized by base (68ZC142; 72ZC20), and nonfunctionalized TP are prepared from 2,3-diaminopyrimidinium salts and C₁-synthons (75JHC107).

2. From Pyrimidin-2-ylcarbamidines or -carbamideoximes

In these routes, the N—C—N moiety of the triazole is first constructed as a substituent in the pyrimidine, and then this is cyclized (Table VIII). The mechanism is described as an electrocyclization of a nitrene formed thermally or by oxidation (90SC2617).

Special cases of this reaction are the syntheses of TP betaines (**53**, see below) from pyrimidin-2-ylcarbamoyl chlorides and trimethylsilyl azide [89JCS(P1)1727] and of TP-1-oxides (**31**, see below) from pyrimidin-2-yl sulfimides and nitrile oxides [76JCS(P1)2166].

TABLE VII
1,2,4-TRIAZOLO [1,5-*a*]PYRIMIDIN-7-ONES FROM 2,3-DIAMINOPYRIMIDIN-4-ONES

			
Synthon Z ^a	R ² ^a	R ³ ^b	Reference
7-oxo			
HCOOH	H	H	71CPB2530
DMF	H	H	87MI2
R'C(OEt) ₃	R'	H	85JHC1317
R'C(OEt) ₃	R'	NH ₂	85USP4546181
7-oxo-5,6-benzo			
HCOOH, RCOCl	H, R	Aryl	85PHA55
HCOOH, RCOCl	H, R	Pyridyl	88EGP253623
HC(OEt) ₃	H	H	79JCS(P2)1708
HC(OEt) ₃	H	<i>p</i> -Tolyl	86JCR(M)2001; 86JCR(S)232
HC(OEt) ₃	H	(CH ₂) _n NH ₂	82BRP2086903
HC(OEt) ₃	H	(CH ₂) ₃ OH, NHCOCH ₂ Cl	86JHC833
HC(OEt) ₃	H	NHCOCH ₃	87MI1
ClCOOEt	OH	NHCOCH ₃	87MI1
CS ₂	SH	— (R-1 = Ph) ^c	86MI1

^a R = alkyl; R' = H, alkyl.

^b If R³ = H, TP is 3H- or 4H-tautomer.

^c from 2-amino-3-anilinoquinazolin-4-one.

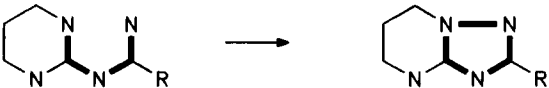
D. FURTHER PYRIMIDINE RING SYNTHESSES

Besides ATs (Section II,A), other 1,2,4-triazole derivatives may be used:

1. 2-Alkyl-5-(benzylideneamino)-1,2,4-triazoles are cyclized by dichloroacetic acid to 1-alkyl-5-aryl-6-chloro-7-oxo-TPs (88JHC173).

2. 4-Aryl-5-mercapto-1,2,4-triazoles condense with anthranilic acid forming 3-aryl-5,6-benzo-7-oxo-TPs [82IJC(B)377].

TABLE VIII
TP FROM PYRIMIDIN-2-YL-AMIDINES AND -AMIDOXIMES

			
Substituent at pyrimidine C-2	R	Condition	Reference
—NH—C(=NH)—Ph	Ph	Oxid. (Pb(Oac) ₄)	60YZ956; 90SC2617
5-Ph-tetrazol-1-yl- ^a	Ph	Decaline/180°C	88BCJ3791
Tetrazol-5-yl-amino- ^a	NH ₂	PPA/200°C	83M789
5-Oxo-1,2,4-oxadiazol-3-yl-amino- ^a	NH ₂	H ₂ O/100°C	83M789
(—NH—CN + NH ₂ OSO ₃ H) ^b	NH ₂	DMF/155°C	83M789
—NH—CH=NOH	H	PPA/95°C	73TL1677; 87M601
—NH—C(=NOH)—CH ₃	CH ₃	PPA, DMF-acetal, POCl ₃ , or pyridine	82JHC577
—NH—C(=NOH)—NH ₂	NH ₂	POCl ₃ /105°C	66JCS(C)2031

^a The amidine moiety is part of an azole.

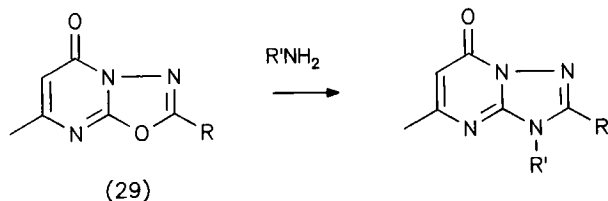
^b The amidine is cyclized *in situ*.

E. TRIAZOLOPYRIMIDINES FROM OTHER HETEROCYCLES

The TP system can be produced by transformation of the five-membered ring of other azolopyrimidines:

1. of 1,3,4-oxadiazoles in one or two steps (68ZC142; 72ZC20), e.g., **29** (Scheme 14; R = aryl, R' = alkyl or aryl);
2. of 1,3,4-oxadiazolium salts (73KGS1432; 75KGS1493),
3. of 1,3,4-thiadiazoles (74BCJ2813).

In a complicated reaction path via a convalent hydrate, TP derivatives can be synthesized from 1,2,4-triazolo[1,5-*c*]pyrimidinium salts [79JCS(P2)1708].



SCHEME 14

F. TRIAZOLOPYRIMIDINES FROM NONHETEROCYCLIC PRECURSORS

In special cases both five- and six-membered rings are cyclized in one-pot reactions, e.g., from

1. 2-hydrazinobenzoic acid and *N*-cyanoimides (80HCA1);
2. 2-methylaminobenzohydrazide and cyanamide (86AP188);
3. 1,3-thiazine-2,4-dithione and thiosemicarbazide, presumably via an intermediate 3-thioureidopyrimidine-2,4-dithione [80JCR(S)148].

III. Structure

A. X-RAY DIFFRACTION

X-ray structural analysis readily distinguishes among ring isomers [80JCS(P1)1347], positional isomers (89JHC1393, 89JHC1489), and conformers [83AX(C)1248]. Further, the structures of the silver salt of MOT (76MI2) and of several metal complexes of TPs (e.g., 87IC1902) have been obtained (Section IV,B).

B. MOLECULAR SPECTRA

The earliest studies deal with the UV and IR spectra of the compounds under review; later ^1H - and ^{13}C -NMR spectra became practical tools for characterizing substituted or isomeric triazolopyrimidine compounds. But many of the early rules proved to lack general validity. Now UV and ^{13}C -NMR seem to be the most useful diagnostic tools.

1. ^1H -NMR

Details were described by Maury [77HC(30)179] in a general report on the ^1H -NMR spectra of azaindolizines. The spectra provide much information about the structure of TPs and their aromaticity and the electron density distribution.

a. *Structure*. Assignments are based on the spectra of the unsubstituted TP or [4,3-*a*] system, respectively, and methyl derivatives (64CPB204; 66JHC269). The following chemical shifts δ (ppm) and coupling constants J (Hz) for the methine protons of the parent TP (**1a**) were reported:

$$\begin{array}{cccc}
 6 & 2 & 5 & 7 \\
 7,19 < 8,52 < 8,87 < 9,00 \\
 q & s & q & q \\
 J_{56} = 4,4 & J_{57} = 2 & J_{67} = 6,5
 \end{array}$$

Chemical shifts for methyl protons increase in the same order, but differences are smaller (64CPB204). Assignments to methyl groups use the following criteria:

1. Methyl at C-2 and C-5 does not couple with any ring proton.
2. Methyl at C-6 and C-7 couples with ring protons H-7 and H-6, resp.
3. Methyl at C-6 couples slightly with H-5.

By means of NMR spectra, the sites of protonation and N-alkylation were claimed to be determined (68JHC691; 74JOC1256); MOT (**3**) and its isomers **13**, **18**, and **19** as well as corresponding homologs could be distinguished (70CB3266; 78T2927). But according to recent papers (87JHC805, 87T2497), the differences among the signals of the four structures mentioned are not large enough to formulate any *general* rule.

b. *Electron Density*. Makisumi *et al.* (64CPB204) concluded from chemical shifts (see above) the following order of electron densities at the ring carbon atoms:

$$C-7 < C-5 < C-2 < C-6$$

The charge densities so determined show a good correspondence with results calculated by the simple Hückel HMO method.

Kleinpeter *et al.* (72JPR515) obtained linear relationships

1. between HMO electron densities at ring carbon atoms of different azaindolizines and their proton chemical shifts;
2. between substituent shielding constants (for substituents at C-2 and C-5 of TP) and their Hammett constants, which reflect the change in electron density at C-6.

2. ^{13}C -NMR

Such spectra were first used to distinguish N-3 and N-4 glycosides (74JOC3226). Similarly, positional and ring isomers could be identified [79JCS(P1)3085; 83S44]. The chemical shifts of the TP parent substance and four isomeric oxo derivatives are listed in Table IX. According to Reiter *et al.* (87T2497), the ^{13}C -NMR spectra give unequivocal proof of the four isomeric structures and confirm the conclusions drawn from UV measurements (Section III,B,4).

TABLE IX
¹³C-NMR CHEMICAL SHIFTS ^a OF TRIAZOLOPYRIMIDINES

Substance	1	2	3a	5	6	7
1a^b	—	155,8	154,7	155,5	110,9	137,3
2-SCH ₃ der. of 3^c	—	163,2	151,3	150,6	98,4	154,9
2-SCH ₃ der. of 13^c	—	162,8	150,7	160,6	104,3	146,9
1-SCH ₃ der. of 18^c	143,2	—	150,4	158,3	95,3	156,7
1-SCH ₃ der. of 19^c	142,7	—	150,2	160,3	107,9	145,0

^a δ (ppm) in DMSO-*d*₆.

^b (87JHC805).

^c (87T2497).

Pugmire *et al.* (87JHC805) studied the correlations of chemical shifts in a series of 22 parent systems (indolizine and azaindolizines including TP).

3. ¹⁵N-NMR

These spectra were reported for TPs substituted at C-2 and C-6 (83S44).

4. Ultraviolet Spectra

Allen *et al.* (59JOC779) and Maury [77HC(30)179] treated the UV spectra of TP in context with other nitrogen bridged bicyclic heterocycles. Generally the spectra are useful for the elucidation of tautomerism (Section III,E) or protonation and dissociation (Section IV,B). Many papers deal with the effects of substituents (e.g., 59JOC779; 61CPB808, 61JCS3046; 63ZOB2678), pH change (e.g., 63ZOB1309; 68T2839; 87JHC1149), and solvent polarity (71PHA539).

The most important use refers again to positional and ring isomerism (e.g., 60JOC361; 63ZOB2673; 70CB3266; 71CB2702; 77AJC2515). Especially 5- and 7-oxo-TP with their quasi *ortho*- and *para*-quinonoid structures, respectively, have characteristic absorptions [77HC(30)179]. With respect to the ring isomers, however, the results are partly contradictory.

Reiter *et al.* (87T2497) concluded that the various isomers are best characterized by their UV spectra taken in neutral (ethanolic, methanolic) solutions; here both the shape of the spectra and the position of maxima and minima differ significantly:

type **3**: 2 bands (230, 270 nm)
 type **13**: 2 bands (208, 290 nm)

type **18**: 3 bands (230, 260, 310 nm)

type **19**: 1 band (230 nm)

Reiter *et al.* (87JHC1503; 89OPP163; 90M173; 91JHC721) verified these rules and the confirming ^{13}C -NMR results (Section III,B,2) for many TP derivatives (type **3** and **13**) having substituents or a saturated homo- or heterocyclic ring attached to the pyrimidinone moiety, as well as their N-alkylation products. Exceptions are (a) the UV spectra of compounds with a lone pair (87JHC1503) or a double bond (89OPP163) that is conjugated to the oxo-TP chromophore and (b) the UV and ^{13}C -NMR spectra of 7-amino-TP-6-carboxylic (**5**) and 5-amino-TP-6-carboxylic esters, because of their extreme symmetry; after saponification, decarboxylation, and desamination the structures of the oxo derivatives could be differentiated (87JHC1149).

5. Infrared Spectra

Infrared spectra were used for investigations on tautomerism and isomerism. The frequencies of the carbonyl stretching bands seem to depend on mesomerism and inductive effects with respect to the positions of the carbonyl group and the substituents at the triazolopyrimidine system [77HC(30)179].

According to a rule established by Allen *et al.* (59JOC779; 61JCS3046), 5- and 7-oxo-TP can be distinguished by means of the CO band shifted to higher wave numbers in the latter case (by about 15 cm^{-1}). However, these and other authors were unable to identify ring isomers by IR. Isomeric N-3 and N-4 alkyl-TPs have been readily distinguished by IR (68T2839).

Reiter *et al.* (87T2497) could also differentiate between oxo-TPs and [4,3-*a*] isomers. (CO in TPs absorbs at $10\text{--}20\text{ cm}^{-1}$ higher wave numbers.) However, the influence of other substituents is more remarkable and consequently the IR spectra cannot be used *in general* for elucidation of the structure of the four isomeric types.

6. Mass Spectrometry (MS)

The MS fragmentation patterns have been investigated for the most important types of substitution of TPs. The parent compound and its methyl derivatives primarily lose either HCN (or CH_3CN , resp.) or N_2 [68DIS(B)1303; 77HC(30)179].

Antonowa *et al.* (75MI1) investigated the behavior of 7-oxo-TPs with various substituents in positions 2, 5, and 6. The main fragmentation

consists of a CO cleavage either followed by a double HCN elimination [or first (R-2)CN, then HCN] or by cleavage of a hydrogen atom, HCN, and HCN. This can take place either directly from the molecular ion or after complete or partial cleavage of R-2, R-5, and R-6.

According to the same authors (75ZC313) there are five common fragmentation patterns for 5-methyl-7-thioxo-TP, its thioethers, and its disulfide. Fragmentation is strongly influenced by the SH and SR groups.

Wierer *et al.* (74PHA692) and Bornschein *et al.* (78PHA51) recorded the mass spectra of 5-methyl-7-amino-TP, its derivatives substituted at NH₂, and related substances. If there is a substituted amino group, cleavage starts there and proceeds in a pattern typical for the substituent.

7. Electron Spectroscopy for Chemical Analysis (ESCA)

The ESCA spectrum of MOT provides evidence that the electron density at N-4 is lower than at N-1 and N-3 [88MI1, Ref. (28)].

C. OTHER ANALYTICAL METHODS

1,2,4-Triazolo[1,5-*a*]pyrimidines, especially MOT and its derivatives, were studied by means of potentiometric [88MI1, Refs. (19) and (56)] and polarographic methods (88MI1, Refs. (7) and (33)), then the results were related to the photographic activity of these compounds (Section V,C) and used for quantitative analysis (74ZC442).

Chromatography is used (*a*) preparatively (column chromatography, HPLC), for the separation of positional [79JCS(P1)3085; 89JHC1489] and ring isomers (83S44), and (*b*) for characterization (TLC), especially of oxo- and amino-TPs [67JCS(C)498; 71PHA539; 76PHA135].

D. AROMATICITY

It has been suggested that azaindolizines are "heteroaromatic." According to Tisler (80PAC1611), however, the polarity of C=N bonds increases with increasing number of nitrogen atoms and, therefore, the compounds studied can be understood as "aza analogs of a delocalized 10- π -electron system," a combination of a fused π -excessive and π -deficient part (five- and six-membered ring, resp.).

The ¹H-NMR methyl substituent effect is very different on the various ring protons of TP; from this Makisumi *et al.* (64CPB204) concluded the ring system possesses only a small aromaticity. The simple HMO method cannot be used for calculations of tautomerism of isomeric oxotriazolopyr-

imidines, according to Reiter *et al.* (88M341), due to the nonplanarity of the system.

Recent research by Kornilov *et al.* (91ZOR144) on the aromaticity of 6-nitro-TPs substituted at C-2 revealed that the experimentally detected values (by reversible covalent hydration) proved more sensitive to substituent effects than the modified aromaticity index $\Delta\bar{N}_s$ of Pozharskii did.

E. TAUTOMERISM

1. Prototropic Tautomerism: Experimental Results

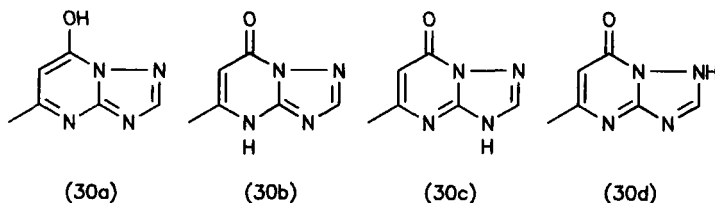
According to Katritzky *et al.* (91H(32)329), "annular tautomerism" is not possible in heterocyclic compounds like TP. With regard to OH-, SH-, and NH₂-derivatives (and their tautomers), TPs seem to behave in a manner similar to that of other heterocycles [generalizations described in Katritzky *et al.* (91H(32)329)].

For MOT (3), four tautomeric forms (30a–30d) are considered generally (Scheme 15): one "lactim" and three "lactam" forms.

In addition Levin *et al.* (70MI3) formulated a hydrogen-bridged analog of 30d and a "ketone" tautomer (7-oxo-6,7-dihydro-TP). Zwitterionic structures for 30a (60JA605), 30b (59JOC779), and the *N*-alkyl derivatives (68T2839) were also considered.

As a rule, hydroxyazaindolizines largely exist in the oxo form [76AHC(S1)539; 77HC(30)179; 80PAC1611]; however, contrary results have been reported (87JHC805). The IR spectra of most MOT derivatives and isomers show CO and NH but not OH vibrations; therefore the lactam structure is favored in the solid state and in neutral solution (63CPB67). Chambers (60JA605) first supposed the existence of an equilibrium mixture; later this conclusion was corrected (70MI3).

Similar UV spectra of MOT (or its isomers) and relevant *N*-alkylation products, especially the 4-alkyl derivatives (87T2497), strengthen evidence for the existence as the 4H tautomer 30b. Oxo tautomers and their *N*-alkyl derivatives, however, do not have necessarily the same UV spectra



SCHEME 15

and the latter cannot always be used as models. The application of NMR spectroscopy leads to less ambiguous results [77HC(30)179].

Sporadically, the 1H tautomer was also proposed for special derivatives (90JHC359).

The "lactim" tautomer **30a** may be fixed by means of a substituent in position 6 that is able to form H bonds. There are OH bands in the IR spectra of 6-chloro, -bromo, -piperidinomethyl (65UP1), -carbethoxy [80JCS(P1)1347], and -tolylazo derivatives (85H(23)2251) of **30a**.

Analogous to MOT the yellow 7-mercapto compound proves to be the thioxo tautomer (59JOC779). In 5,7-dialkyl-2-amino-TPs any imino structure is excluded by IR and NMR spectra (71AP856, 71T3247); aminoazaindolizines generally behave similarly (91H(32)329).

2. Quantum Chemical Calculations

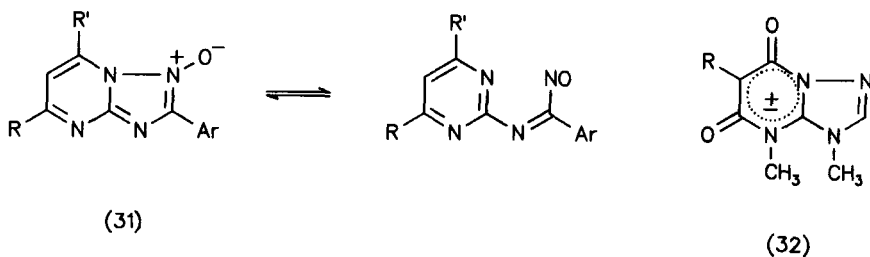
Knowledge about tautomerism derived from quantum chemical calculations is contradictory:

1. Glier *et al.* (72T5779, 72T5789) compared calculated (PPP) with experimental UV spectra; for MOT, its isomers, and most of the derivatives studied they found a correspondence for the tautomer of type **30b**. But the 6-chloro- and 6-bromo-TP lactim type **30a** fits the calculation better (IR results above).

2. Complete Neglect of Differential Overlap (CNDO) calculations by Náray-Szabó and Surján (80MI2), however, were interpreted to favor the lactim form **30a** of MOT which is in line with the experimental UV spectra.

3. Ring-Chain Tautomerism

In TP-1 oxides (**31**), a reversible ring-opening (Scheme 16) was detected by NMR spectroscopy [76JCS(P1)2166].



SCHEME 16

F. BETAINES AND MESOIONIC STRUCTURES

Starting from N-alkylated monocyclic precursors, 1,2,4-triazolo[1,5-*a*]-pyrimidin-2-olates (**53**, see below), the corresponding -2-thiolates [89JCS(P1)1727] and the mesoionic 3,4-dialkyl-TP derivatives **32** (80JHC337) were prepared.

IV. Reactivity

A. GENERAL SURVEY

According to Tisler (80PAC1611) azaindolizines show many aromatic substitution reactions, but also undergo other reactions explainable by appreciable bond localization. Among electrophilic reactions, protonation, N-quarternization, and N-alkylation generally occur at the five-membered ring. Most systems also undergo electrophilic C substitution at this ring, but TP as an exception is substituted at C-6.

With an increasing number of nitrogen atoms the azaindolizins become more susceptible to nucleophilic attack. Ring opening, Dimroth rearrangement, hydrogenation and reduction, and other addition reactions involve attack on the π -deficient six-membered ring.

Regarding TP, the six-membered ring in most reactions behaves like a pyrimidine; for the five-membered ring, reactions analogous to those of triazole are known.

B. PROTONATION AND DISSOCIATION

For TPs without oxo groups pK_a values have been reported (77AJC2515); they markedly differ from those of [4,3-*a*] isomers. N-3 was determined as the position of protonation (68JHC691) from NMR analogy with the product of methiodide reaction (Section IV,C,1).

The oxo-TPs are weak acids (70MI3; 73MI3). The pK_a value of MOT is 6.4 (between carboxylic acids and phenols); isomers are less acidic. The oxo-TPs are formulated as a mesomeric anion (60JA605; 74JOC3226), isolable salts with an N—metal bond (86KFZ178). MOT can be titrated in nonaqueous solution (DMF) with potassium methoxide (59JOC779).

5-Methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-on forms salts with primary and secondary aliphatic amines (61JOC3834). Rather soluble tetrabutylammonium salts may be convenient for synthesis (91JHC721). Products of synthesis A, formed from 2 mol of AT and 1 mol of acetoacetic ester,

regarded to be *N,N'*-bis-(triazolyl)-3-aminocrotonamides (59JOC787), proved to be salts consisting of MOT and AT (61JOC3834).⁴ They are detected in IR spectra (65UP1).

5-Methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-on is amphoteric and can be titrated with perchloric acid in glacial acetic acid (61JOC3834). Some derivatives form isolable hydrohalides (75PHA134). Glier *et al.* (72T5789) formulated a cationic structure at pH 1 from the UV spectrum contrary to that of Hill *et al.* (61JOC3834).

The photographic activity of MOT (Section V,C) is based on the formation of sparingly soluble silver salts (70MI3; 88MI1). A 3:2 Ag:MOT complex (80MI1) and adducts of TPs (with and without oxo groups) and inorganic silver salts (59YZ903; 70UP1) also were obtained. Furthermore, heavy metal salts and complexes are known, e.g., with Hg (75PHA134), Cu (64MI1), and Pt (85USP4546181). Since 1982 many complexes have been synthesized and characterized by means of molecular spectra, X-ray diffraction, and magnetic measurement (e.g., 87IC1902).

C. RING ALKYLATION

1. *N*-Alkylation and Quaternization

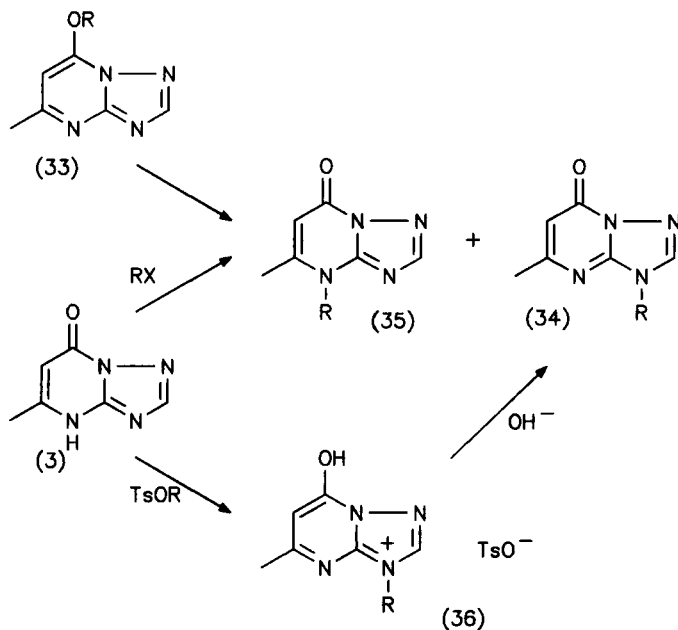
The study of *N*-alkylation provides models for protonation, tautomerism, and elucidation of structures, e.g., *N*-glycosides. Alkylation of MOT (**3**) with an alkyl halide (RX) and alkali does not lead to ether **33** but to a mixture of *N*-3- and *N*-4-alkyl derivative (**34** and **35**, resp.; Scheme 17).

Alkylating the silver salt (60JA605; 63CPB129) or thermally rearranging the otherwise prepared alkyl ether (**33**) gives the same mixture, whereas pure isomer **34** arises from quaternary salt **36** and alkali.

During the alkylation of oxo-TPs both *N*-3 and *N*-4 can be attacked; the product ratio partly depends on the alkyl residue (63MI1) or reaction conditions [75BSF(2)2561]. Mixtures usually are obtained (60YZ1550; 63CPB129); often the *N*-4 isomer predominates [67JCS(C)503; 80JCS(P1)1347] and sometimes it is the only product (87T2497).

Alkylation of *N*-1 of TP is an exception: 5,6-cycloalkeno-7-oxo-TPs react to form a mixture of 1-, 3-, and (predominantly) 4-benzyl-isomers (91JHC721). Acylation at *N*-1 is known (71AP856, 71T3247). O-alkylation of oxo-TP occurs as a side reaction (70CB3278).

⁴ cf., however, reactions of trifluoroacetoacetic ester (85JHC1317).



SCHEME 17

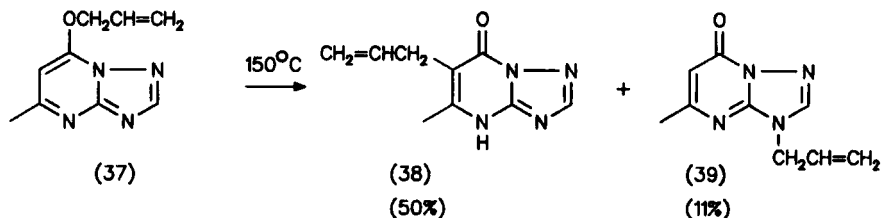
Quaternization of TP, e.g., by alkyl halide and tosylate or phenacyl halide, always attacks N-3 [79UP1; 85JCS(P1)2333] as demonstrated by degradation (68JHC691).

2. Alkyl Rearrangement

The thermal alkyl rearrangement of alkoxy-TPs (type **33**, Scheme 17) proceeds even on recrystallization or during melting. It follows an intermolecular mechanism (63CPB851) and again gives mixtures (63CPB67, 63MI1; 71JHC237).

7-Allyloxy-TPs unsubstituted in position 6 (like **37**) according to Maki-sumi (63CPB851) are subject to a competing *ortho*-Claisen rearrangement as the main reaction (Scheme 18). Besides **38** and **39** a few percentages of 4-allyl-, 3,6-diallyl-, and 4,6-diallyl-MOT are found. The *ortho*-Claisen rearrangement proceeds intramolecularly, involving a six-membered cyclic transition state. Independently, the migration of allyl groups to N-3 and N-4 occurs intermolecularly.

If position 6 is substituted (in **40**) then the 5-(buten-3-yl) derivative (**41**) is the main product (Scheme 19), in addition to a few percentages of



SCHEME 18

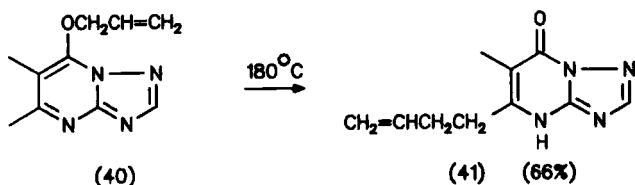
3- and 4-allyl compounds (63CPB859). The main rearrangement is an “out of ring” migration of the allyl group to an active methyl group proceeding through two consecutive cycles; each of these is accompanied by a reversal of the allyl group bonding site.

3. Glycoside Synthesis

N-alkylations and rearrangements are important for the synthesis of glycosides. N-3 and N-4 glycoside, e.g., of 5-oxo-TPs, are obtained under different conditions as the kinetically and thermodynamically controlled product, respectively [75BSF(2)2561]; therefore a thermal rearrangement from an N-3 to an N-4 glycoside is possible. Table X lists these glycosides; included are those derived from thioxo-TPs and mercaptomethyl-TPs.

D. ELECTROPHILIC REACTIONS AT CARBON RING ATOMS

These reactions exclusively proceed via attack at C-6, i.e., at the carbon atom with the highest electron density from NMR results (Section III,B,1).



SCHEME 19

TABLE X
 SYNTHESIS OF TP GLYCOSIDES

TP (Aglycone)	Method ^a	Position	Reference
Ribosides			
5-Oxo	SiD + TARC	3 ^b	75BSF(2)2561
	A + TR (melt)	4	
7-Oxo	SiD + TARC/TR	3 ^b + 4	76M11
	SiD + TR (I ₂ , 200°C)	4	
	SiD + TBRB	3 + 4	71JHC237
	SiD + TARB	3	85JHC1317
7-Thioxo	A + TR (melt)	3 + 4	78M11
MOT	SiD + TARB	3	74JOC1256
5-Cl-7-oxo	SiD + TARB	3 ^d	
7-NH ₂	SiD + TARB	4	
5-Oxo-7-NH ₂	SiD + TARB	3	
Glucosides			
MOT	AgC/HgC + TAGB	3	75PHA134
	Methyl ether + TAGB	3	
5-CH ₃ -7-thioxo	A + TAGB + HgCl ₂	3	
	A + TAGB + NaOH	S ^c	
	7-Cl-der. + TTG/STG	S	
2-Oxo-7-thioxo	7-Cl-der. + TTG	S	
2-CH ₂ SH-MOT	2-CH ₂ Cl-der. + TTG/STG	S	
5-CH ₂ SH-7-oxo	5-CH ₂ Cl-der. + TTG/STG	S	

^a A, aglycone; AgC, silver compound; HgC, mercury compound; SiD, silyl derivative; STG, sodium thioglucose; TAGB, triacetylglucosyl bromide; TARB, triacetylribosyl bromide; TARC, triacetylribosyl chloride; TBRB, tribenzoylribosyl bromide; TR, tetracetylribose; TTG, tetracetylthioglucose.

^b Rearrangement to 4-riboside (melt).

^c Rearrangement to 3-glucoside (HgBr₂).

^d Dehalogenation and reaction forming cyclonucleoside.

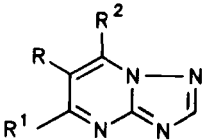
1. Electrophilic Substitutions

Nearly every substrate bears donor groups (OH, NH₂) in position 5 or 7 or both; these groups activate C-6 for possible substitution reactions (Table XI). Electrophilic brominations occur at the unprotonated species (68JOC1087).

2. Deuterium-Hydrogen Exchange

In acid medium, electrophilic substitution by D⁺ occurs again on the free base, not on the protonated species, since the exchange rate on the

TABLE XI
 ELECTROPHILIC SUBSTITUTION ON TP

			
R ^a	Reagents ^a	Substitution at C-5/C-7 ^{ab}	Reference
Cl, Br	Cl ₂ , Br ₂	H, CH ₃ ^c	61CPB808
Br	NBS	H	68DIS(B)1303
Cl, Br	Cl ₂ , Br ₂ , PCl ₅	MOT	59CPB903
Cl, Br	Cl ₂ , Br ₂	5 and/or 7 OH and/or NH ₂	59CPB907; 61CPB808
I	I ₂ /base	MOT	64UP1
I	I ₂ /base	5-CH ₃ -7-NH ₂	63ZOB2678
I	NIS	MOT	85JHC1317
OH	K ₂ S ₂ O ₈	MOT	59JOC787
OH	(NH ₄) ₂ S ₂ O ₈	5-CH ₃ -7-NH ₂	78PHA42
SCN	SCN ⁻ /Br ₂	MOT	64UP1
NO ₂	HNO ₃ /H ₂ SO ₄	5/7-OH/NH ₂ ^d	61CPB873
N=N—Ar	Ar—N ₂ ⁺	di-OH, 5-OH-7-NH ₂ ^e	61CPB878
NO	HNO ₂	5-OH-7-NH ₂	64CB1373
CHO	DMF/POCl ₃	7-OH, 5-R' or OH	89EGP264439
CH ₂ NR' ₂	CH ₂ O/HNR' ₂	7-OH	64UP1; 68FRP1555789

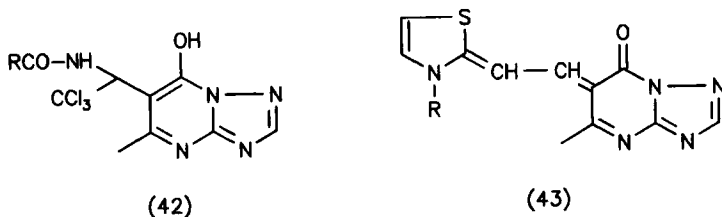
^a R' = alkyl.^b OH or tautomer oxo.^c Not both R¹ and R² = CH₃ (steric hindrance).^d At least R¹ or R² = OH.^e Both R¹ and R² = OH/NH₂.

N-3 methiodides is considerably lower (68JOC1087). Methyl groups in positions 5 and 7 prevent the H–D exchange [68DIS(B)1303]. With neutral D₂O the reaction is generally impossible, but mesoionic TP **32** (see above) slowly exchanges the proton at C-2 with D₂O (80JHC337).

Base-catalyzed exchange proceeds very quickly at C-7, more slowly at C-6, and very slowly at C-2 and C-5. The proton at C-2 of the methiodides exchanges about 1000 times faster than that in the free base (68JOC1087). The results are consistent with an ylide-type intermediate.

3. Addition Reactions

5-Methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-on reacts at the polarized C=N bond of *N*-acyl trichloroacetaldimines, again in position 6, to give



SCHEME 20

amides **42** (Scheme 20) (91JPR661). In related reactions with formylmethylene azoles or 1-aminoisoidolines, merocyanine and isoidoline dyes, respectively, e.g., **43**, were prepared (70FRP2009492; 89EUP322359).

E. NUCLEOPHILIC ADDITIONS

Hydrogenation and reduction proceed by attacking exclusively the pyrimidine ring. 1,2,4-Triazolo[1,5-*a*]pyrimidines free from oxo groups react with H_2/Pd , $\text{Na}/\text{Ethanol}$, or NaBH_4 to give 4,5,6,7-tetrahydro-TPs and with LiAlH_4 to form 4,7-dihydro derivatives [68DIS(B)1303; 90MI2]; 5-oxo-TP, however, gives with H_2/Pd the 6,7-dihydro compound (71CB3961). During O- or N-debenzylation by the same method the TP system is reported to resist hydrogenation (60JA605; 89OPP163).

The addition of organometallics leads to alkyl- or aryl-dihydro-TPs and can be followed by rearomatization. After the attack of phenyllithium on unsubstituted TP and aerial oxidation, the 5- and 7-phenyl-TPs are isolated (72JHC1157). Methylolithium, on the other hand, gives a mixture of 5-methyl-TP and its 4,5-dihydro derivative [68DIS(B)1303].

Rusinov and co-workers studied the reactivity of TP that were activated by a 6-nitro group for nucleophilic attack. Additions of resorcinols (89KGS811), *N,N*-dialkylanilines (91ZOR1100), pyrroles (88KGS1251), and indoles (86KGS1544) lead to 7-substituted 4,7-dihydro compounds, e.g., **44**. Addition to positions 4,5 is rare (88KGS1251). Adducts with water and ethanol are less stable (86KFZ947; 88KGS1251).

F. RING CLEAVAGE

Most cleavage reactions exclusively proceed by attack on the pyrimidine ring and initially involve fission of the bond between the bridgehead nitrogen and C-7.

1. By Hydrazines or Amines

Hydrazinolysis of TP proceeds under relatively mild conditions (80–120°C). From MOT and its derivatives, 3-methyl pyrazol-5-on (**45**, Scheme 21, formed from hydrazine and the inherent C₃-synthon) and an AT derivative were isolated (62ZC369). Other TPs (76KGS706; 91KGS665) including 3- and 4-alkyl (63CPB67; 68ZC142) and 3-amino derivatives (72ZC20) behave similarly; the reaction serves to elucidate the structures of the TPs. After cleavage of a 5-chloro-7-oxo-TP both rings remain linked in the structure of a 3-(1,2,4-triazolylamino)-pyrazol-5-on (74JOC1256).

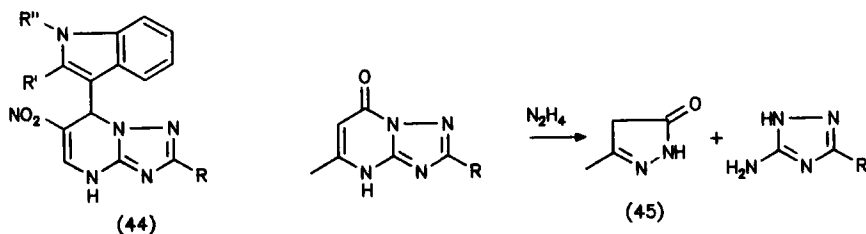
Cleavage by amines and ammonia seldom occurs (*a*) in a reaction under Chichibabin conditions [68DIS(B)1303] and (*b*) with substrates like 6-nitro-TP (91ZOR1100). Here the inherent C₃-synthon is scavenged as imine **50** (Scheme 24).

2. By Acids and Bases

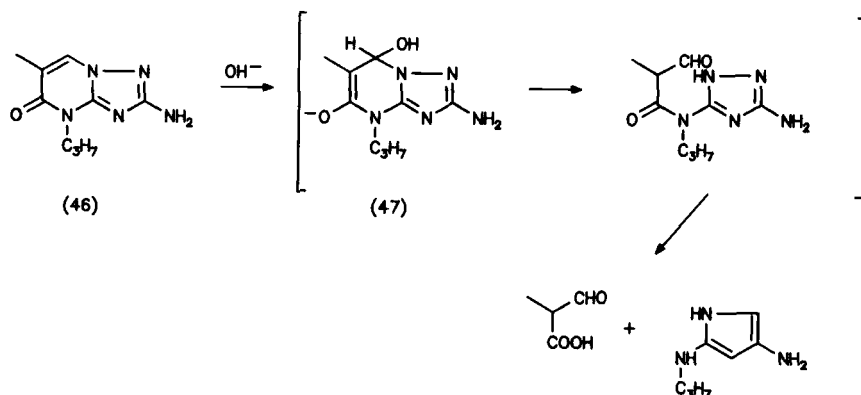
Dimroth rearrangement probably starts with a covalent hydration catalyzed by acids or bases (Section II,B,3). According to Dukes *et al.* [72JCS(P2)1695] there is evidence from pK_a values, kinetic measurements, and UV spectra that the alkaline hydrolysis of the amine **46** includes intermediate **47** (Scheme 22).

The alkali cleavage of MOT, first reported to be impossible (62ZC369), proceeds smoothly at least for 3- and 4-alkyl derivatives in ATs (68JHC691). An intermediate **48**, giving evidence for an attack at C-7, has been found (60YZ1550).

1,2,4-Triazolo[1,5-*a*]pyrimidines, especially 7-oxo and 7-amino derivatives, are more or less rapidly cleaved in the presence of alkali (71PHA539), HCl (64CB1373), or, preferably, HBr (58YZ1395), depending on the structure and the reaction conditions.



SCHEME 21



SCHEME 22

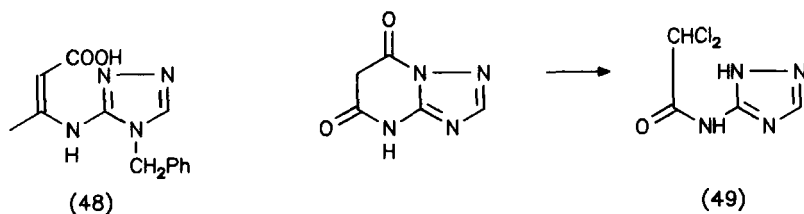
3. By Oxidants and Chlorine

Under oxidizing or chlorinating conditions, TPs sometimes undergo a cleavage reaction, e.g., from

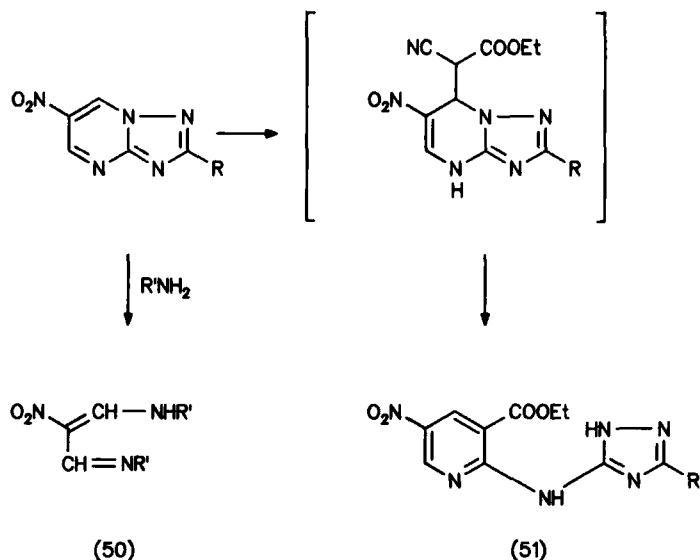
1. 7-amino-TP with hydrogen peroxide/acetic acid to AT and acetyl-AT (78PHA51);
2. 2-anilinosulfonyl-TP with alkaline oxidants (H_2O_2 , KMnO_4) to acyl-AT (87EUP244847);
3. 2-methylthio-MOT with chlorine to 3-methanesulfonyl-AT (62JCS3854);
4. 5,7-dioxo-TP with chlorine/acetic acid to the dichloro compound **49** (Scheme 23) (61CPB808).

4. By CH-Acidic Compounds

Nucleophilic attack of cyanoacetic ester or analogs on 6-nitro-TPs and the resultant cleavage leads to pyridyl-ATs, e.g., **51** (Scheme 24), which



SCHEME 23



SCHEME 24

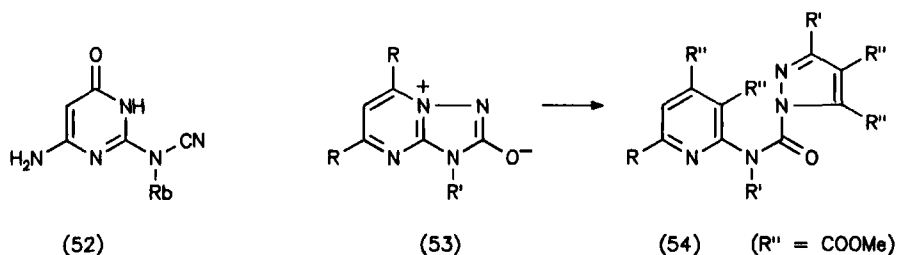
then cyclize to pyrido-TP by the action of sodium carbonate (90S713; 91KGS256).

5. Cleavage of the Triazole Ring

The stable triazole ring (72PHA539) can, in the case of severe reaction conditions or unusual structures, be cleaved:

1. Attempted perchlorination of the parent TP (PCl_5 , 220°C) leads to tetrachloropyrimidine (76JHC139).

2. A TP-3-glycoside in liquid ammonia is changed into cyanamide **52** (Rf = ribofuranosyl) (74JOC1256).



SCHEME 25

3. Ylides, obtained from quaternary 3-phenacyl salts, are cleaved to similar cyanamides [85JCS(P1)2333; 87JCS(P1)2531].

4. Betain **53** (Scheme 25) is cleaved to amide **54** by acetylene dicarboxylic ester [89JCS(P1)1727].

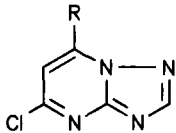
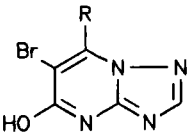
G. NUCLEOPHILIC SUBSTITUTION OF FUNCTIONAL GROUPS AT THE RING

1. Reactivity of Halogens in Positions 5, 6, and 7

The keynote reaction for introducing O-, S-, and N-containing functional groups in positions 5 and, especially, 7 is the chlorination of the corresponding oxo-TP by POCl_3 (61CPB801; 69EGP70311). The reactivity of chlorine in the six-membered ring is strongly dependent on position: $7 > 5 > 6$. 7-Chloro derivatives behave like acyl chlorides and are hydrolyzed by moist air (59JOC787).

According to Makisumi, halogens in positions 5 and 6 can be substituted only incompletely (Table XII): In position 5 they may be exchanged, but they are deactivated by amino and still more by oxo groups at C-7

TABLE XII
REACTIVITY OF 5- AND 7-HALOGEN-TP TOWARD
NUCLEOPHILIC REAGENTS

Species	R ^a	Halogen replaceable by ^a
	H NH ₂ OH	OH, NH ₂ (120°C), SH ^b OH, NH ₂ (160°C) ^b —
	NH ₂ OH	Piperidino, —S— ^c Piperidino, —SS— ^c

^a OH, SH or tautomers oxo, thioxo, resp.

^b Reagents: H⁺ or OH⁻, NH₃, thiourea, resp.

^c Reagents: piperidine, thiourea, resp.

(61CPB801; 75PHA134). In position 6 reactivity of halogens is as low as that in position 5 of pyrimidines; even when activated by two adjacent groups they react with only a few reagents (61CPB814).

The different reactivity of the halogens at C-7 and C-5 allows them to be reacted in two steps with two different nucleophilic agents: under mild conditions at C-7, and then under harsher conditions at C-5 (71PHA534; 81KFZ31; 91PHA184).

2. Reactivity of Halogens in Position 2

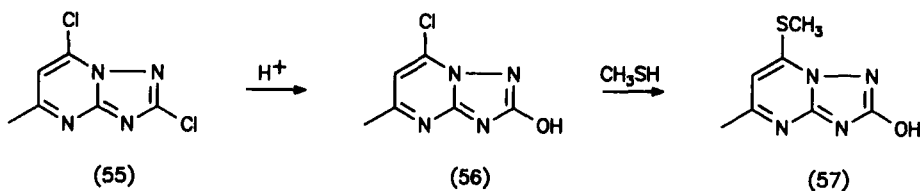
A similar graduation of reactivity, but in an unexpected manner, is exhibited by 2,7-dichloro-5-methyl-TP (**55**, Scheme 26): During hydrolysis first the chlorine at C-2 is substituted (70UP1); structure **56** of the product is confirmed by spectra and further reaction to methylthio derivative **57** (75ZC313). Only a few reactions are reported for 2-halo-TPs.

3. Further Substitutions of Halogens

These reactions are listed in Table XIII.

4. Substitution of O-, S-, and N-Containing Functions

Reactions including these leaving groups are listed in Table XIV. Generally, these reactions follow the same rules as the halogens. Thus, 5,7-dialkoxy-TPs may be hydrolyzed or transesterified in position 7 (63CPB845). Transamination (71PHA534) proceeds in analogy to transesterification. An alkanesulfonyl group at C-2 can be replaced by hydroxy or alkoxy groups, but does not react with ammonia or amines (62JCS3854). The 2-methylthio group cannot be exchanged via hydrazinolysis (62ZC369).



SCHEME 26

TABLE XIII
 NUCLEOPHILIC SUBSTITUTION OF CHLORINE (AND BROMINE)

Position	New substituent ^{ab}	Reagent ^b	Reference
2	OR	ROH/NaH ^c	90EUP353902 ^d
	SAr	ArSH/tt.-C ₄ H ₉ OK	89EUP337232
	NH ₂	NH ₃ /Cu ²⁺	88JAP63/222171 ^d
	NHR, NR ₂	Amines	66JCS(C)2031 ^d
5, 7	OR	RONa	63CPB845
	CN	KCN/crown ether	85USP4497814
5	SH	H ₂ S/(NH ₄) ₂ CO ₃	74JOC1256
	NHNH ₂	N ₂ H ₄	70CB3278
	N ₃	NaN ₃	70CB3278
	Benzotriazol-1-yl	Benzotriazol	70CB2828
7	SR''	R''SH/Et ₃ N	89EUP335319
	SCN	NH ₄ SCN	58CPB583
	NHR'', NR'' ₂	Amines	61JOC115
	NHSO ₂ Ar	ArSO ₂ NHNa	64ZOB502
	NHNH ₂ , NHNHR'	N ₂ H ₄ , NH ₂ NHR'	61JOC115
	N ₃	NaN ₃	59JOC787
	Pyridinio	Pyridine	64ZOB205
	Indazol-1-yl	Indazole/DBU	89EUP335319
	CH ₃	CH ₃ MgBr	89JHC1489
	I	HI	59CPB907

^a SH or tautomer thioxo.^b R = alkyl; R' = alkyl, aryl; R'' = alkyl, aryl, heterocyclyl.^c e.g., R = CH₂CF₃.^d Substitution of Cl or Br.

H. INTRODUCTION AND TRANSFORMATION OF INDIVIDUAL SUBSTITUENTS

This section includes reactions not mentioned formerly.

1. Carboxylic Acid Derivatives

Some relevant substituents are displayed in Table XV. Hydrolysis of esters or nitriles followed by thermal decarboxylation of 2-, 5-, 6-, and 7-carboxylic acids is often used for degradation reactions (61CPB883, 61JCS3046; 64UPI). 5-Amino-1,2,4-triazole-3-carboxylic acid is decarboxylated *in situ* by condensation to TP (83S44); TP-5-amideoxime is cyclized to the 5-(1,2,4-oxadiazol-3-yl) derivative (90EGP282009).

TABLE XIV
NUCLEOPHILIC SUBSTITUTION OF OXYGEN- AND SULFUR-CONTAINING GROUPS

Group ^{ab}	Position	New substituent ^{ab}	Reagent ^b	Reference
O ⁻	2	S ⁻	Lawesson's reagent	89JCS(P1)1727
OH	5, 7	Cl, Br	POCl ₃ ^c , POBr ₃	85USP4497814
		SH	P ₂ S ₅	70GEP1946315
OR ^l	5	Cl	COCl ₂	80HCA1
	5	OR', SR'	R'OM, R'SM	85EUP142152 ^d
		NR' ₂	R' ₂ NH	85EUP142152 ^d
	7	NHR'', NR'' ₂	Amines	71PHA534
SH	7	NHNH ₂	N ₂ H ₄	64ZOB502
		OH	Hg(OAc) ₂	75PHA134
		NHR'', NR'' ₂	Amines	71PHA534
		NHNH ₂	N ₂ H ₄	62BSF355
SR ^l	5	NHR', NR' ₂	Amines	85CPB962
	7	OH	H ⁺	59CPB903
		NH ₂	NH ₃	61CPB801
		NHR'', NR'' ₂	Amines	71PHA534
SO ₃ K	7	OH	H ⁺	64ZOB502
		NHNH ₂	N ₂ H ₄	64ZOB502

^a OH, SH or tautomers oxo, thioxo, resp.

^b R = alkyl; R' = alkyl, aryl; R'' = alkyl, aryl, heterocyclyl; R^l = other R in leaving group.

^c With POCl₃/C₆H₅NR₂: by-product 5- or 7-C₆H₄NR₂ (p), resp. (e.g., 91OPP413).

^d Convenient leaving group R^l = CH₂CF₃.

2. Sulfur-Containing Substituents

Relevant examples are listed in Table XVI.

3. Amines and Derivatives

6-Amino-1,2,4-triazolo[1,5a]pyrimidines generally behave like aromatic amines and can be diazotized and coupled (61CPB873), but 6-amino-5,7-dioxo-TP cannot be diazotized and is only acetylated with difficulty. 6,7-Diamino-5-oxo-1,2,4-triazolo[1,5-a]pyrimidine together with nitrous acid affords a fused triazolo-TP.

2-Amino-1,2,4-triazolo[1,5-a]pyrimidines may also be diazotized and coupled [66JCS(C)2031; 73GEP2304285], but are not reactive toward nitroso compounds, chloral, ethylene oxide (66 CB2237), and DMF dimethyl acetal (90ZC320).

TABLE XV
 CARBOXYLIC ACID DERIVATIVES

Group ^a	Position	Precursor ^a	Reagent ^a	Reference
COOMe	2	COOH	CH ₂ N ₂	70GEP1946315
COOR	5, 7	CN	ROH/H ⁺	85USP4497814
CO—O—COOEt	2	COOH	ClCOOEt/Et ₃ N	74UP1
COSR'	2	CO—O—COOEt	R'SH	74UP1
CONH ₂	2	COOEt	NH ₃	70GEP1946315
	6	COOEt	NH ₃	60YZ952
		CN	H ₂ SO ₄ , H ₂ O ₂ /OH ⁻	70JPR254
CONHPh	2	CO—O—COOEt	PhNH ₂	74UP1
CONR ₂	5	COOMe	R ₂ NH	71CB2702
CSNH ₂	7	CN	H ₂ S/Et ₃ N	85USP4497814
C(=NH)NH ₂	7	CN	NH ₃ /NH ₄ Cl	85USP4497814
CONHNH ₂	2	COOEt	N ₂ H ₄	70GEP1946315 ^b
		COCH ₂ CN	N ₂ H ₄	64UP1 ^b
CON ₃	2	CONHNH ₂	HNO ₂	70GEP1946315
CN	5	CH=NOH	Ac ₂ O	89EGP269149

^a R = alkyl; R' = alkyl, aryl.^b Pyrimidine ring is not hydrazinolyzed (Section IV,F,1).
 TABLE XVI
 SULFUR-CONTAINING SUBSTITUENTS

Group ^a	Position	Precursor ^{a,b}	Reagent ^a	Reference
SR	2	SNa	RX	79AJC2727
	7	SH	RX/OH ⁻	59JOC779
SCI	7	SH	SO ₂ Cl ₂	84GEP3340363
—SS—	2	SH	DMSO	70UP1
	7	SH	I ₂	64ZOB502
—SSR	2	SH	RSCl	70UP1
	7	SCI	RSH	84GEP3340363
SO ₂ Na	2	SH	H ₂ O ₂ /OH ⁻	68UP1
SO ₂ R	2	SR	H ₂ O ₂ , Cl ₂	62JCS3854
SO ₂ Ar	2	SAr	peracids	89EUP337232
SO ₂ Cl	2	SH, SR	Cl ₂	90MI2
SO ₂ NHAr	2	SO ₂ Cl	ArNH ₂	90MI2
			ArNHSiEt ₃	90EUP353902

^a R = alkyl; X = halogen.^b SH or tautomer thioxo.

5- and 7-amino derivatives have been reported to resist diazotization (61CPB873;63ZOB2678), apart from the desamination of a riboside (74JOC1256). Recently, Reiter *et al.* (87JHC1149) reported the degradation of 7-amino-TP (**5**, see above) by diazotization and hydrolysis to 7-oxo-TP.

Attack of halide ion from hydrogen halide acids on 2- and 6-diazonium salts gives the corresponding chloro [66JCS(C)2031; 83JHC735], bromo [66JHC(C)2031], and iodo compounds (68FRP1546271). The 4-amino-TPs as known from 4-amino-1,2,4-triazoles eliminate the amino group by diazotization (72ZC20; 75KGS1493).

Table XVII gives information about additional reactions and the substituents involved.

TABLE XVII
AMINES AND AMINE DERIVATIVES

Group ^a	Position	Precursor ^a	Reagent ^a	Reference
NH ₂	6	NO ₂	H ₂ /Pd	61CPB873
		N=N-Ar	H ₂ /Pd	61CPB878
		N ₃	H ₂ /Raney-Ni	59JOC787
NHCOR, N(COR) ₂	2	NH ₂	acylating agents	70GEP1946315
NHCOR	6	NO	Zn/RCOOH	64CB1373
HNSO ₂ Ar	2	NH ₂	ArSO ₂ Cl	90MI2
NHR, NR ₂	2	NH ₂	RX/NaH	70GEP1946315
NHR'	2	NR ¹ R'	H ₂ /Pd	70GEP1946315
		N(R')COOR	H ⁺	70GEP1946315
NEt ₂	7	NO ₂	H ₂ /Pd/CH ₃ CHO	86BEP903532
			NaBH ₄ /TsOH/CH ₃ CHO	86BEP903532
N(CH ₂ OH) ₂	2	NH ₂	HCHO	66CB2237
NHCOOR	2	NH ₂	ClCOOR	70GEP1946315
		NCO	ROH	70GEP1946315
		CON ₃	ROH	70GEP1946315
		NCS	ROH	70GEP1946315
NHCSOR	2	NCS	ROH	70GEP1946315
NCO	2	NH ₂	COCl ₂	70GEP1946315
NCS	2	NH ₂	CSCl ₂	70GEP1946315
NHCONHR	2	NH ₂	RNCO	70GEP1946315
NHNO ₂	2	NH ₂	HNO ₃ /H ₂ SO ₄	62BEP619423
	7	NH ₂	HNO ₃ /Ac ₂ O/ZnCl ₂	62BEP619423
N ₃	7	NHNH ₂	HNO ₂	81KFZ31
N=CHAr	2	NH ₂	ArCHO/ZnCl ₂ (or AcOH)	66CB2237
N=CHNMe ₂	6, 7	NH ₂ ^b	DMF-DMA ^c	90ZC320
NH—N=CHNMe ₂	7	NHNH ₂	DMF-DMA ^c	90ZC320
NHCH=NOH	6, 7	N=CHNMe ₂	NH ₂ OH	90ZC320
NHNHCH=NOH	7	NHN=CHNMe ₂	NH ₂ OH	90ZC320
N(CH ₃)CN	7	NHCH=NOH	DMF-DMA ^c	90ZC320
Pyrazol-1-yl	5	NHNH ₂	e.g., 1,3-diketones	91PHA184

^a R = alkyl; R' = H, alkyl; X = halogen; R¹ = other R in leaving group.

^b 6-Amino-7-oxo-TP: simultaneous methylation at N-4.

^c DMF-dimethyl acetal.

4. Elimination by Hydrogenation and Reduction

Catalytic dehalogenation (mostly by H_2/Pd) and desulfurization (by Raney-Ni) are important tools for structural analysis. This way chlorine can be removed from positions 2, 5, and 7 [64CPB204; 66JCS(C)2031]. Zinc was used for dechlorination at C-7 (59YZ903). The 5,7-dichloro-TPs (61CPB801) and 6,7-dichloro-TPs (59CPB903) in the presence of H_2/Pd first lose the more reactive chlorine from C-7; the remaining 6-chloro compound can be dechlorinated only by Raney-Ni.

2-Mercapto- and 2-methylthio-groups were also removed from MOT by Raney-Ni (60JOC361); the latter reaction proceeds more smoothly with the corresponding 4-carbethoxy derivative. H_2/Pd serves as the active reagent for the debenzylolation in position 4 (89OPP163).

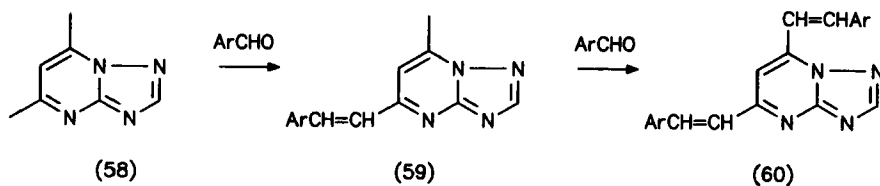
I. REACTIVITY OF SIDE CHAINS

1. Toward Electrophilic Reagents

Methyl groups at carbon atoms adjacent to a nitrogen atom in the six-membered ring have sufficient anionic character to react with aromatic aldehydes or with orthoesters [77HC(30)179]. The corresponding reaction starting from the TP **58** leads to styryl dyes **59** and **60** (Scheme 27). Here methyl at C-5 is more active than at C-7; methyl groups at C-2 do not react at all (61CPB883).

Reactivity is normally enhanced by quaternization [77HC(30)179]. In this case a methyl group at C-7 seems to be the most reactive toward both benzaldehydes (74KGS565) and orthoesters or malonic bisacetal (88UKZ880). Bis-quaternized methylene 2,2'-bis-TPs are attacked by benzaldehydes at the methylene carbon instead of the methyl group (82UKZ79).

Oxidation of methyl groups also shows selective reactivity: Only the methyl group at C-5 of 5,7-dimethyl-TP and of the corresponding 2-



SCHEME 27

hydroxymethyl derivative is oxidized to formyl by means of selenium dioxide (73ZC293; 74ZC357). With lead(IV)-acetate, hydroxymethyl in position 2 is oxidized to formyl (74ZC405); with chromic acid, the same reaction leads to a carboxyl group (70GEP1946315). Styryl compounds yield, with potassium permanganate, carboxylic acids (61CPB883).

Isoamylnitrite also attacks only the methyl group in position 5 forming oximinomethyl (89EGP269149). D-H exchange proceeds readily at the methyl groups in positions 5 and 7, but not in position 2, presumably via 3H-5- (or 7-) methylene tautomers [68DIS(B)1303].

2. *Toward Nucleophilic Reagents*

Reactions of 2- or 5-chloromethyl groups lead

1. to hydroxymethyl via the benzyl ether or the acetoxy compound (78PHA42);
2. to mercaptomethyl by means of sodium trithiocarbonate (70UP1);
3. to isothiuronium salts with thiourea (58USP2835581) and also to mercaptomethyl (86EUP190375);
4. to methyl by hydrogenation (Raney-Ni) (71PHA534).

Aminomethyl groups in position 6 (Section IV,D,1; Table XI) yield alkylthioalkyls with mercaptans (86EUP190375); 6-(2-chloroethyl)-7-chloro-TP (obtained from TP 7, see above) was cyclized to tricyclic compounds of type 62 (Section V,A) by means of the corresponding amines (80JMC927).

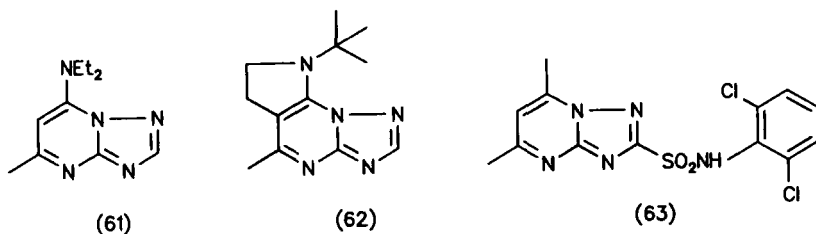
1,2,4-Triazolo[1,5-*a*]pyrimidines have been linked (via amide or ester bonds) with vinylic or acrylic monomers, which were polymerized to products bearing TP in side chains (84GEP3340571).

V. Applications

A. PHARMACEUTICAL USES

Many TPs [77HC(30)179] have been tested as potential growth inhibitors of microorganisms [58CPB583; 71GEP2004713; 78AJC397; 88IJC(B)825; 89IJC(B)242], since they are isomeric to purines and in some cases can be converted to nucleoside analogs (Section IV,C,3). Antimetabolic [88IJC(B)421] and anticancer activities (85USP4546181) have been described.

Pharmacological effects found are antipyretic, antiphlogistic, analgesic, antiallergic (70GEP1946315; 79GEP2918085), anxiolytic (80USP4209621; 84USP4444774), antirheumatic (88EGP253623), hypocholesteric



SCHEME 28

(70GEP1946315), hypotensive (86AP188, 86USP4582833), bronchodilatoric (70GEP1946315), and vasodilatoric effects (79GEP2918085; 82JMC420, 82MI1; 83JHC735).

An example for bronchodilators is the amine ICI 63197 (**46**) (73MI1; 76MI3). Important vasodilators are Trapymin or Rocornal (**61**, Scheme 28) (71PHA534, 71PHA539, 71PHA554) and Bumepidil (**62**) (80JMC927; 87MI2). A technical synthesis (90EGP280006) and the metabolism (78PHA51) of Trapymin have been reported.

B. AGROCHEMICAL USES

Applications claimed refer to pesticides, fungicides (83GEP3130633), nitrification inhibitors (85EUP142152), growth regulators (72MI1), and especially herbicides (85EUP142152; 89EUP337232; 90MI2). A typical herbicide is sulfonamide **63**; a different metabolic rate has been detected to be the reason for the selective herbicidal activity (90MI3).

C. PHOTOGRAPHIC USES

In 1935 Birr found the "stabilizing" activity of MOT (**3**) (52MI1). This discovery made it possible for the first time to stabilize the sensitometric properties of photographic materials during storage. Even today MOT is an inherent constituent of nearly every photographic product [70MI3; 74MI1; 83MI1; 92MI1]. Numerous derivatives have been synthesized: none is substantially more effective than MOT. 5-Methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-on and its analogs are able to form silver salts and can be absorbed and chemisorbed to silver halides.

Until 1970, the activity of MOT was interpreted in terms of Birr's conceptions based on nonadsorption (74MI1). In following years new ideas

were published (88MI1) by Cash (complexivity theory), Evva (interaction with silver), Tani (oxidation potential and a simultaneous sensitizing effect), and others. A comprehensive theory of stabilization does not exist.

D. OTHER USES

Other uses include azo and isoindoline dyes (73GEP2304285; 89EUP322359) and long-chained alkyl TP-carboxylates for metal extraction (86FRP2574432).

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Advances in Tetramic Acid Chemistry

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I. Introduction

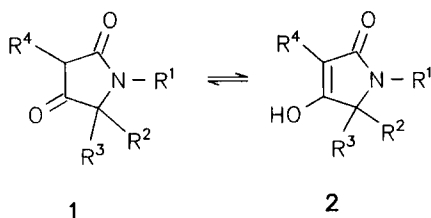
In 1901 Anschütz suggested the denotation "tetramic acid" for 1,5-dihydro-4-hydroxy-2-pyrrololone **2a**, a tautomer of 2,4-pyrrolidinedione **1a** (09LA55). By analogy to the term "tetronic acid," denoting the lactone of 4-hydroxy-3-oxo-butanoic acid (60QR292), "tetramic acid" is used to name the lactam of 4-amino-3-oxo-butanoic acid. (See Fig. 1.)

A. OCCURRENCE IN NATURE: BIOACTIVITY

Derivatives of tetramic acid are found in a number of natural substances. One example is tenuazonic acid **3** that was isolated from a culture filtrate of *Alternaria tenuis* (57BJ390; 59BJ332). Much work on the isolation of tenuazonic acid from plant is now being reported (89MI2; 90P3777; 91MI2), owing to its interesting pharmaceutical properties (63B1132, 63N(L)1338; 64BBR54; 65JMC483). For this reason, numerous partial and total syntheses have been described for tenuazonic acid, as well as for the more complex tetramic acid derivatives tirandamycin **4** and streptolydigin **5** (73JA4077; 78JA4225; 80BMI1; 83JOC1149, 83JOC2117; 86JA5549, 86JA5559; 88MI, 88P77, 88T3171; 91TL1749). (See Fig. 2.) Much synthetic work to be reported here was approached with the goal of providing new biologically effective compounds.

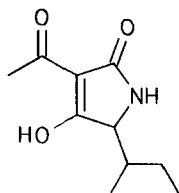
B. GENERAL PROPERTIES AND PROBLEMS

2,4-Pyrrolidinedione **1a** predominantly exists in solution in its enolized form, 1,5-dihydro-4-hydroxy-2-pyrrolone **2a**. The 1,5,5-trimethyl deriva-

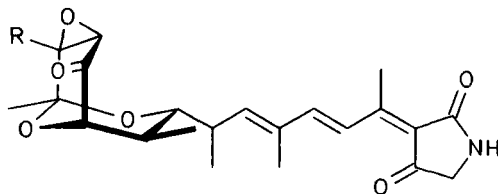
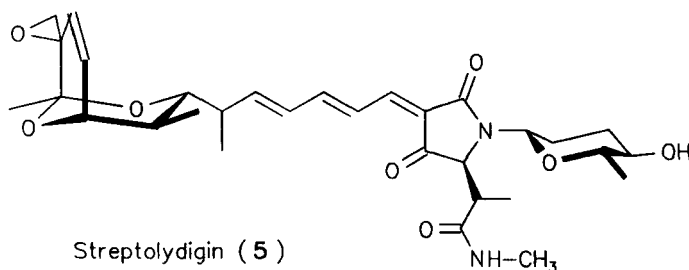


- a: $R^1 = R^2 = R^3 = R^4 = H$
 b: $R^1 = R^2 = R^3 = Me; R^4 = H$
 c: $R^1 = R^2 = R^3 = Me; R^4 = MeCO$

FIG. 1.



Tenuazonic Acid (3)

Tirandamycin (4); A: R=CH₃; B: R=CH₂OH

Streptolydigin (5)

FIG. 2.

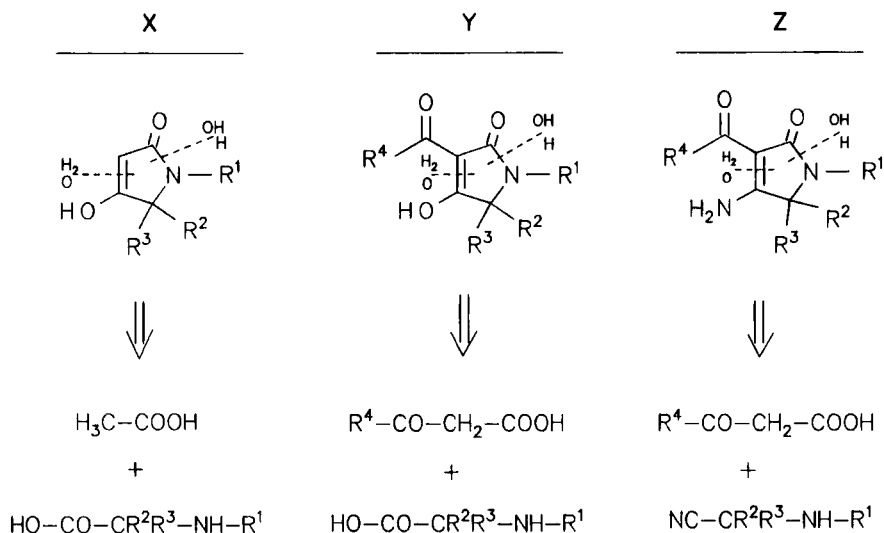
tive **1b/2b**, having a pK_a of around 4, dissolves in aqueous bases with formation of a salt. With these properties the tetramic acids parallel the series of 1,3-cyclopentanediones and 2,4-furanediones (tetronic acids) (60QR292).

Anions of tetramic acids show, as expected, only limited nucleophilic properties. Indeed, O-alkylation requires strongly alkylating agents. Acylation preferentially gives 4-acyloxy-1,5-dihydro-2-pyrrolones which, in the presence of Lewis acids, may undergo rearrangement to 3-acyl-1,5-dihydro-4-hydroxy-2-pyrrolones (Section III).

The CN = lactam bond of tetramic acids is remarkably stable. Treatment with strong acid or base changes ring substituents without opening the lactam ring. Therefore, a chemistry of tetramic acid exists that centers around derivatization and ring anellations without affecting the five-membered ring.

1. Retrosyntheses

The majority of syntheses for tetramic acids described in the literature follows a strategy that is derived from the following retrosynthetic consideration (Scheme 1). (The scissions of bonds are given as imaginary hydroly-



SCHEME 1. Retrosynthetic analysis of tetramic acid derivatives.

ses. By this approach one obtains directly the starting materials of the actual syntheses.)

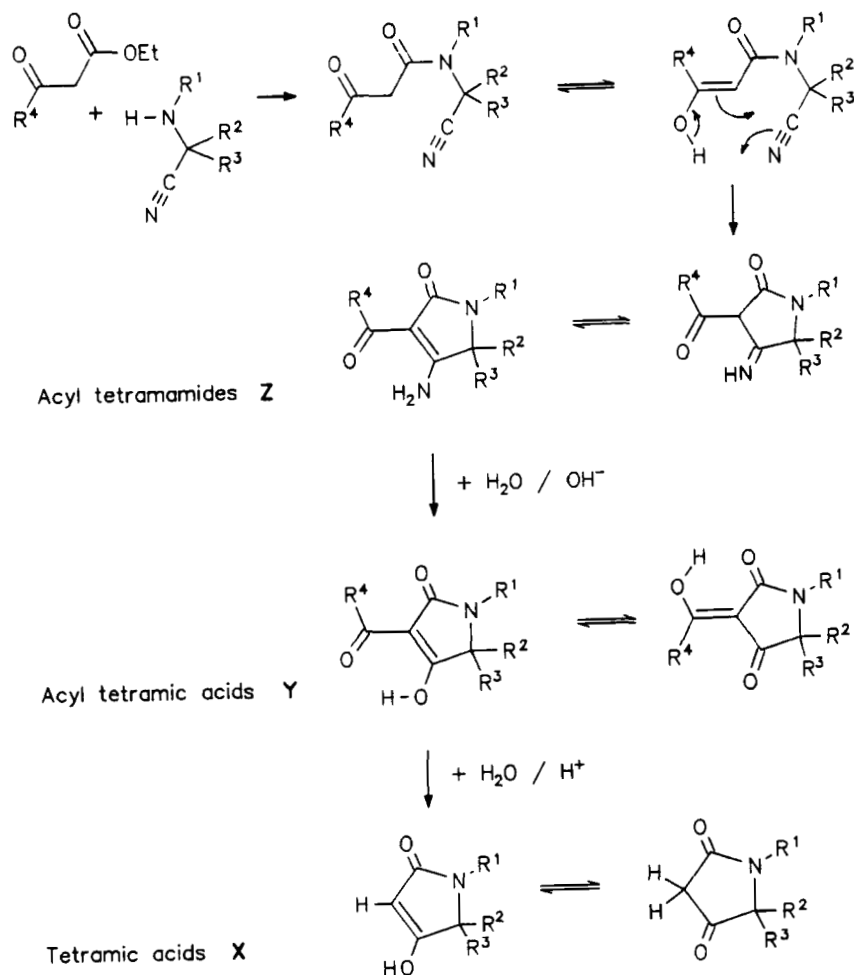
Thus, in the case of 3-unsubstituted tetramic acids (**X**), the synthesis would start from acetic acid and an α -amino carboxylic acid. (In practice the acid will be replaced by suitable carboxylic acid derivatives.) The problem in these syntheses is the low reactivity of the methyl group of acetic acid.

Use of a β -ketocarboxylic acid derivative may circumvent this problem; β -ketocarboxylic acid derivatives react with esters of α -amino carboxylic acids to give (**Y**); α -aminonitriles afford (**Z**) in a condensation step.

The considerations that (**Z**), as a vinylogous amide, may undergo hydrolysis to (**Y**) whereas (**Y**) and (**Z**), being derivatives of β -ketocarboxylic acids, can be subjected to acid cleavage suggest starting with (**Z**) itself as a general synthetic approach (Scheme 2).

Although specific syntheses of certain representatives of (**X**) and (**Y**) have been published, this general synthetic strategy is much followed in the literature. Compared to other methods it offers the advantage that a given configuration may be imposed on position 5 of the tetramic acid ring by way of the amino acid building block. This fact is expected to be beneficial to the activity of the substance as a potential drug.

The sequence of Sections in this chapter follows this synthetic strategy. Following some examples of the most important synthetic variants, an overview of the chemistry of the 3-acyl-4-amino-1,5-dihydro-2-pyrrolones



SCHEME 2. Strategy for the synthesis of tetramic acid derivatives (x-z).

(Z) is provided in Section II. Section III deals with the major reactions of 3-acyl-1,5-dihydro-4-hydroxy-2-pyrrolones (Y), compounds representing a wide variety of natural substances. Finally, Section IV presents an overview on the chemistry of the actual tetramic acids (X).

2. Synthetic Routes

The various published syntheses of tetramic acids and their derivatives may be divided into two basic methods, according to the retrosynthetic scheme (Scheme 1). The two methods differ only in the order of steps

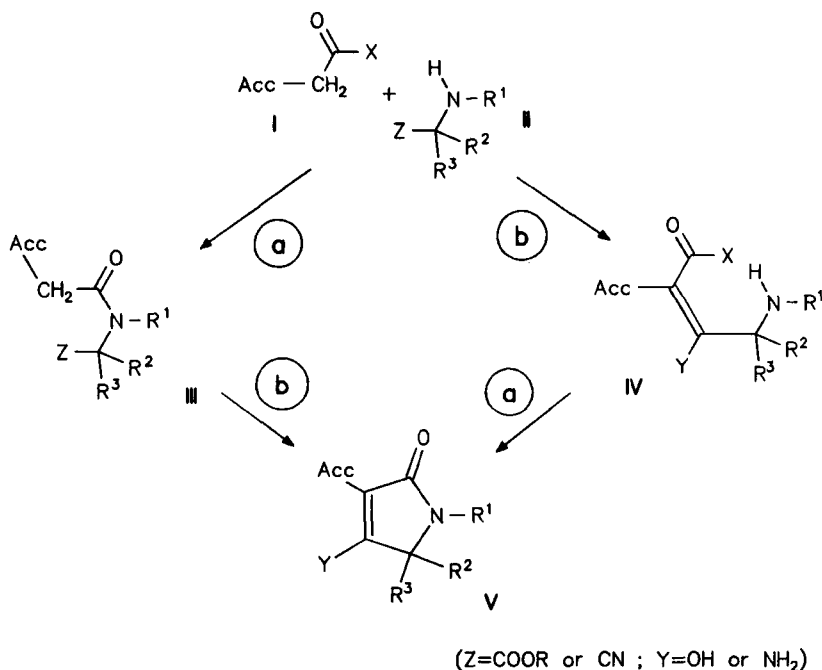
(a) and (b) (Scheme 3). Step (a) represents formation of a carboxamide, commonly by reacting an ester ($X = OR$) and a secondary amine. Step (b) is an ester condensation, normally in the presence of a base.

—Step (a) preceding step (b): Preparation of carboxamide (**III**) requires the use of an active methylene carboxylic acid derivative due to subsequent step (b). So far, three routes have been used:

1. 3-Oxocarboxylic acid esters (78JA4225; 85TH1) offer two distinct electrophilic sites to amine (**II**), the nucleophile. Selective nucleophilic attack at the ester function of (**I**) may be accomplished by selecting the reaction temperature.

2. Diketene (54JCS850; 65JMC478; 72JPJ1507, 72JPJ1515; 80CPB2494; 84CPB4197; 87TL1565) reacts unambiguously, but suffers one drawback: The acetyl group always acts as electron withdrawing group Acc in (**III**), which needs to be removed or displaced, as suitable, in the consecutive reaction steps.

3. 3-Acyl Meldrum's acids (83TH1; 87TH1), easily accessible from carboxylic acid chlorides and Meldrum's acid, may be viewed as protected 3-oxo-carboxylic acid esters (78JOC2087). The latter offer the advantage



SCHEME 3. Two different pathways for the construction of tetramic acid derivatives (**V**).

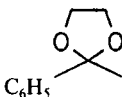
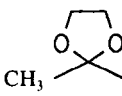
of reacting unequivocally with amines at the carbonyl carbon atoms of the ring. Here, group Acc can be selected from a broad range of choices.

With diketene, intermediates of type (III) were isolated and subsequently cyclized under basic conditions following step (b). In the case of 3-oxo-carboxylic acid esters or 3-acyl Meldrum's acids, cyclization step (b) immediately follows reaction step (a), if a slight excess of amine is employed (85TH1; 87TH1). Note that conversion of (III) to (V) involves the (III)-enol (Table I; cf. 75BSF2731). The relatively low yield in the case of malonic acid ester, as well as the failure of the reaction with the non-enolizable diphenyl phosphinylacetic ester and cyanoacetate, points to the participation of an enol structure of (III).

Additional variations such as use of acyl chlorides [72JCS(P1)2121; 85AJC1847] or of a modified derivative of Meldrum's acid (82JOC2823) as acid derivative (I) do not differ markedly from the above procedure.

—Step (b) preceding step (a): Syntheses of (V) involving intermediate products like (IV) appear in the literature less frequently. Often an activated amino acid derivative (II) ($Z = \text{COCl}$, COOAr) is used to acylate (I) at position 2 (84JOC3489; 85JHC1599). Again, ring closure of (IV) to (V) requires inclusion of a base (80JHC1195).

TABLE I
ENOL CONTENTS OF SOME ESTERS I YIELDS OF
2-PYRROLONES V, PREPARED FROM I^a

Acc	I-Enol (%) (solvent)	V-yield ^b (%)
(<i>p</i>)O ₂ N—C ₆ H ₄ —CO—	75 (CCl ₄)	62
C ₆ H ₅ —CO—	52 (CCl ₄)	34
CH ₃ —CO—	18 (C ₆ H ₆)	23
C ₂ H ₅ O—CO—	≈ 1 (—)	17
	—	0
	—	0
(C ₆ H ₅) ₂ P(O)—	≈ 0	0
N≡C—	≈ 0	0

^a (85TH1).

^b Average yields.

This method has also been modified. For example, Meldrum's acid was acylated with a *N*-protected amino acid at position 3. The intermediate was then cyclized via intramolecular nucleophilic attack of the amino group on one carbonyl group of the ring [87JCS(P1)1177; 90JCS(P1)611]. Further special methods will be mentioned below.

II. 3-Acyl-4-amino-1,5-dihydro-2-pyrrolones

A. 3-ALKANOYL-4-AMINO-1,5-DIHYDRO-2-PYRROLONES

1. *N*-Acylation

3-Acyl-4-amino-1,5-dihydro-2-pyrrolones (**6**) (type **Z** in Scheme 1) possess the features of cyclic enaminediones. The push-pull- π system decreases the nucleophilicity of the amino group. Therefore *N*-acylation with carboxylic acid chlorides requires relatively drastic conditions (dioxane, 100°C, K_2CO_3). In particular, the reaction of the highly reactive DMF-acetal **8** to formamidine **9** succeeds only while refluxing in benzene (87TH1). (See Fig. 3.)

The *N*-acyl compounds are very suitable for the synthesis of pyrrolo[3,4-*b*]pyridines (**10**). As a rule, these compounds are synthesized starting from 2,3-disubstituted pyridines (69BCJ2996; 75CB1003; 77CCCC283). Only a

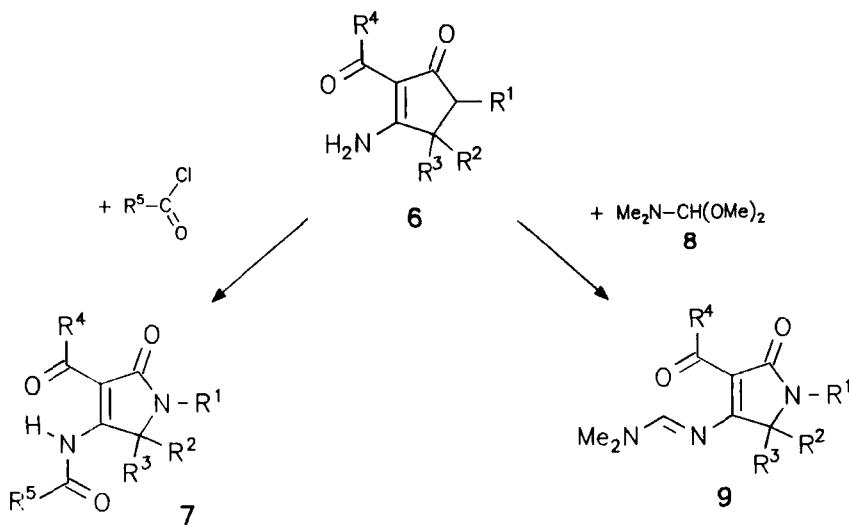
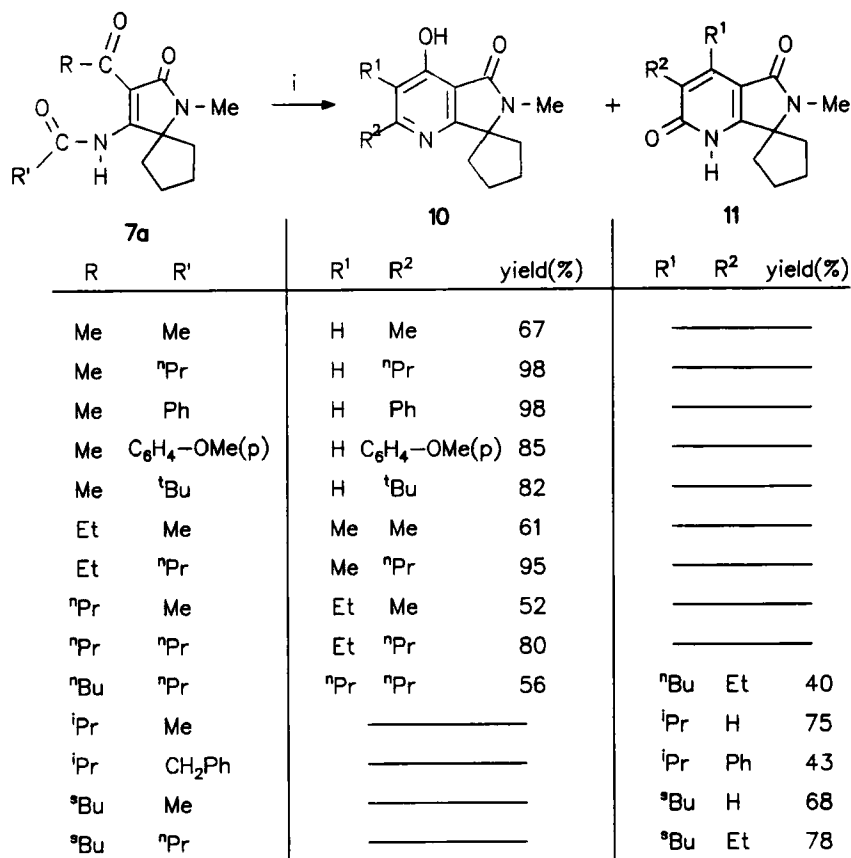


FIG. 3.

few syntheses starting with tetramic acid have been published (74ZN453; 82M475). If R^4 of (7) incorporates a methylene group adjacent to the carbonyl group, the intramolecular cyclization takes place in boiling xylene, in the presence of potassium *tert*-butoxide. In the case where R^4 and R^5 switch their parts (active CH_2 group in R^5) the ring closure leads to the anellated 2-pyridones (11). This may be attributed to the spatial requirement of the substituents. Bulky substituents hinder the formation of (10). Formamides (9) give pyrrolo-[3,4-*b*]pyrid-2-ones (12) under the same conditions (87TH1). (See Figs. 4 and 5.)



i ^tBuOK, Xylene, 140°C

FIG. 4.

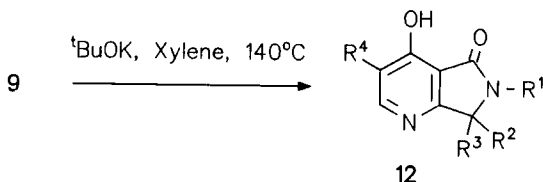


FIG. 5.

2. Hydrolysis

Treatment of the pyrrolones (6) with dilute hydrochloric acid entails loss of the acyl group in position 3. Thus, 4-amino-1,5-dihydro-2-pyrrolones (13) are obtained, suitable as enamines in subsequent syntheses of heterocycles.

As with other enaminones, aqueous KOH effects addition of OH^- to C-4 and subsequent elimination of ammonia involving conversion to 3-acyl tetramic acids (14) (Section III). The reaction pathway, according to this mechanism, depends on the steric requirements of the substituents at C-5. The reaction proceeds rapidly and to completion in the case of $\text{R}^2 = \text{R}^3 = \text{Me}$ and $\text{R}^2\text{—R}^3 = \text{—(CH}_2\text{)}_4\text{—}$. Slightly more sterically hindered substituents like $\text{R}^2 = \text{R}^3 = \text{Et}$ considerably hinder the reaction (87TH2; 89M11). (See Fig. 6.)

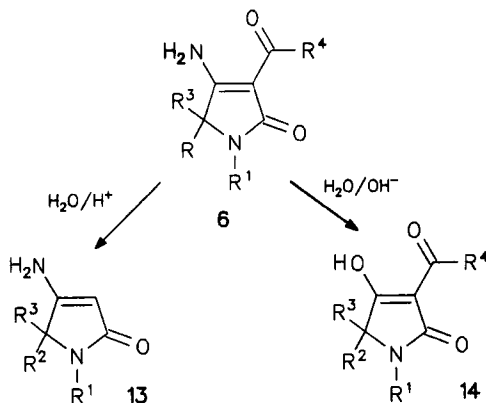


FIG. 6.

3. Reaction with 1,3-Dicarbonyl Compounds

Acid treatment of (6) furnishes products (13) including minor quantities of tricyclic condensation products, which result from the reaction of (13) with excess (6). This side reaction may be extended to become a synthesis of double anellated pyridines when (6) is fused with cyclic 1,3-dicarbonyl compounds. As expected, the spatial requirement of the acyl substituent R affects the yield of (15) (87TH1). (See Fig. 7.) Dipyrrolo[3,4-b:3',4'-e]-pyridinediones of type (15a) were synthesized by Snyder *et al.* starting

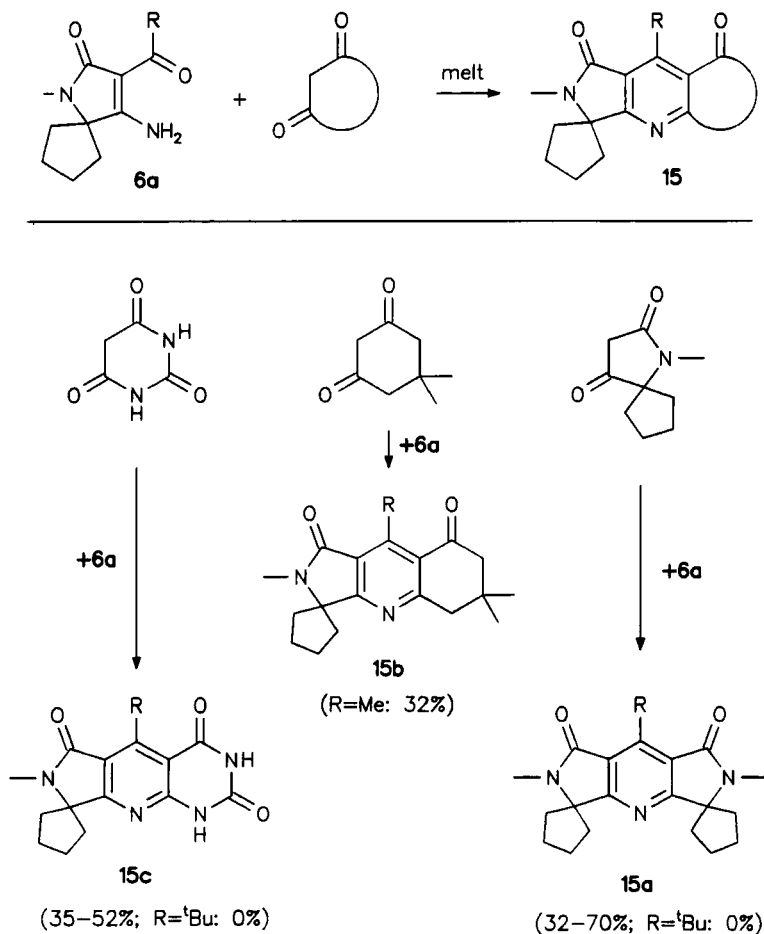


FIG. 7.

from 3-arylmethylidenpyrrolidine-2,3-diones and ammonium formate (82JHC603).

B. 4-AMINO-3-CARBOXY-1,5-DIHYDRO-2-PYRROLONES

1. *Specialty Syntheses*

From retrosynthetic Scheme 1 follows a synthesis of 4-amino-3-carboxy-1,5-dihydro-2-pyrrolones (type **Y**: $R^4 = \text{OH}$ or OR) that needs malonic acid or malonate as starting material. Such reaction is expected to give low yields due to the limited tendency of malonate to undergo enolization (see Table I); yet it is frequently the only solution at hand.

The pathway via Meldrum's acid is not feasible (Section I,B,2) since it requires a more favorable synthesis for 5-alkoxycarbonyl-2,2-dimethyl-1,3-dioxan-4,6-dione. Attempts to synthesize this compound from Meldrum's acid, chloroformate and pyridine give rise to yet another, pyridine-containing product (92LA813).

Several authors preferred a two-step reaction. By reacting monomethyl malonate (83TL4751) or monoethyl malonyl chloride (62BCJ1941; 72JCS(P1)2121; 76CB212; 77HCA660, 77MI1; 78TL3173), they initially prepared the corresponding malonoylamide esters, thereafter cyclized in the presence of base.

4-Amino-1,5-dihydro-3-ethoxycarbonyl-2-pyrrolones (**16**) were obtained in a one-step reaction by heating diethyl malonate and α -aminonitriles in xylene at 130°C with yields of 30–50%. Addition of some potassium *tert*-butoxide may give higher yields (86UP1). Note that products (**16a**), even in the presence of such strong base, do not react further in the manner of an intramolecular ester condensation. By contrast, thermal degradation of amino nitrile $R^1\text{—NH—CMe}_2\text{—CN}$ occurs, resulting in primary amines $R^1\text{—NH}_2$; the latter reacts with malonate to afford its diamide $R^1\text{—NH—CO—CH}_2\text{—NH—R}^1$ (85TH1).

Bis-*p*-nitrophenyl malonate (55M29) reacts with α -alkylamino-isobutyronitriles in xylene to give derivatives (**16b**) of tetramic acids with yields of 30–50% (86UP1; 88UP1). The reaction of derivatized malonic acids with α -amino acid esters to 3-alkoxycarbonyl-1,5-dihydro-4-hydroxy-2-pyrrolones presents the same problems (see Section III). (See Fig. 8.)

2. *Reactions with N-Nucleophiles*

The reactivity of esters (**16**) is comparable with that of esters of anthranilic acid. The low nucleophilicity of the 4-amino group seems noteworthy,

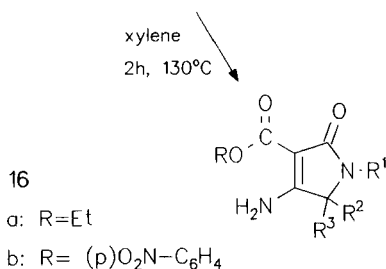


FIG. 8.

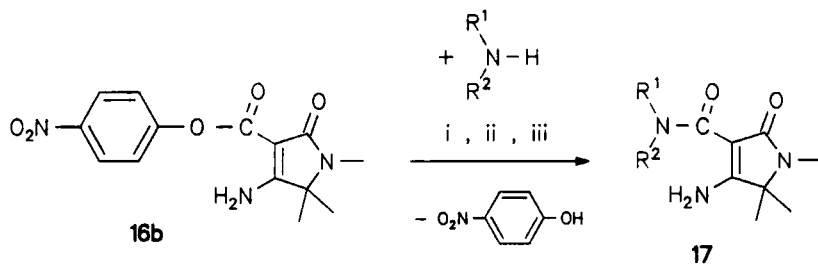
similar to compounds (6). Esters (**16b**) react especially readily with amines to give 3-carbamides (**17**) (86UP1). (See Fig. 9.)

If the *N*-methyl group in (**16b**) is replaced by an *N*-benzyl group, 30 min of reflux in ethanol or *n*-propanol is sufficient to obtain quantitative yields of (**17**) with primary and secondary amines (88UP1).

1,2-Diaminoethane and 1,2-diaminobenzene do not furnish cyclic derivatives of tetramic acid. Independent of the reaction time and the molar ratio of the reactants, the corresponding 3-carboxamides **18** and **19** are the only products [88UP1; cf. 67JCS(C)693]. Heating **19** in a sublimation apparatus to 220–240°C gives benzimidazole **20** in 65% yield (88UP1). (See Fig. 10.)

The following reactions demonstrate that the electrophilic ester carbonyl groups of (**16**) predominantly determine the reactivity: Heating (**16b**) for several hours in ethanol saturated with HCl affords (**16a**) by transesterification. Ester hydrolysis and decarboxylation occur at room temperature in the presence of dilute alkaline hydroxide. Hydrolysis of (**16a**; R¹ = R² = R³ = Me) to 3-carboxy-2-pyrrolone **21** succeeds in the presence of aqueous methanolic KOH at 60°C. Subsequent HCl work-up at 0°C furnishes **21** with 82% yield (86UP1). (See Fig. 11.)

On warming **21** tends to decarboxylate (Section IV) like many β-ketocarboxylic acids. At room temperature **21** can engage in interesting synthetic variations. For example, in the presence of alkyl chloroformates, **21** reacts to new α-aminoacylpenicillins (**22**) (89GEP290424). After addition of KOH, and standing for several days at -5°C, **21** and isoxazolium salt **23** form the pyrrolo [3,4-*d*]pyrimidin-4,5-dione **24** in 21% yield (88ZC334). Similar ring systems were developed by Southwick and Hofmann (63JOC1332) and Cavalla and Willis [67JCS(C)693] using a different approach. (See Fig. 12.)



i: without solvent; r.t.

R ¹	Me	Et	ⁿ Pr	ⁱ Pr	ⁿ Bu	ⁿ Hx	ⁿ Oct	CH ₂ Ph	Et	(CH ₂) ₄	(CH ₂) ₅	(CH ₂) ₂ O (CH ₂) ₂
R ²	H	H	H	H	H	H	H	H	Et			
yield (%)	90	76	68	62	95	70	83	66	83	42	85	36

ii: DMF/HOAc; 80°C

R ¹	(p)MeO-C ₆ H ₄	(p)Me-C ₆ H ₄	Ph	(p)Cl-C ₆ H ₄	(p)O ₂ N-C ₆ H ₄
R ²	H	H	H	H	H
yield (%)	95	89	85	77	73

iii: EtOH; 2h reflux

R ¹	CH ₂ -COOEt
R ²	H
yield (%)	80

FIG. 9.

III. 3-Acyl-1,5-dihydro-4-hydroxy-2-pyrrolones

A. SPECIALTY SYNTHESSES

As demonstrated in Section I, numerous representatives of this type of compounds occur naturally. Such natural substances are commonly characterized by two special features. (a) The C-5 carbon atom of the pyrrolone ring is a stereo center that can be provided by natural derivatives of amino acids. (b) The acyl substituent at C-3 often includes a complex

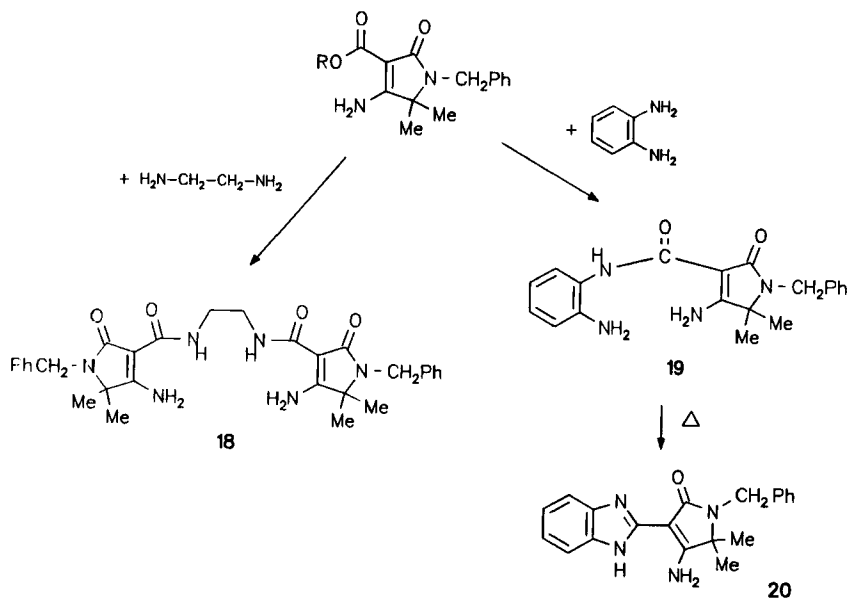
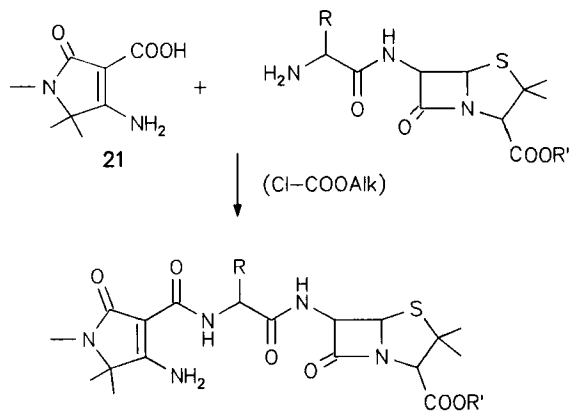


FIG. 10.

unsaturated alkyl group. This fact prompted several authors to focus on interesting specialty syntheses (see, for example, [81JCS(P1)3292]).

Retrosynthetic Scheme 1 shows the general synthetic approach. Under certain conditions, the preparation of the β -ketocarboxylic acids $\text{R}^4\text{-CO-CH}_2\text{-COOH}$ or their esters might become the largest chal-



22
FIG. 11.

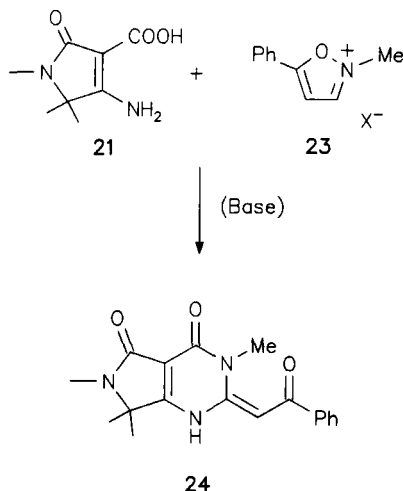


FIG. 12.

lence of the overall synthesis. The general synthesis is frequently based on the C-acylation of ethyl acetoacetate with $R^4\text{—CO—Cl}$. Cleavage of the acetyl group then gives the product, but only in the case of $R^4 = \text{aryl}$ with satisfying yields.

Chances may be better, however, when a cyclic starting material includes the acyl group $R^4\text{—CO}$. Here, the pathway based on Meldrum's acid was proven very useful [87JCS(P1)1177, 87TH1]. De Shong *et al.* started with R^4 -substituted isoxazoles (83JOC1149). The isoxazolium salts, obtained from ethyl bromoacetate, convert into β -ketoamides, where best results were observed in two-phase systems. These β -ketoamides cyclized to 3-acyl-tetramic acids by adding base. (See Fig. 13.)

Tetramic acid derivatives are valuable intermediates in the total synthesis of natural substances; that is why a great number of experiments were carried out to find more convenient pathways to their preparation. In general, there are two different methods to reach this goal.

By deacylating 3-acyltetramic acid, generated by the classic route, 1,5-dihydro-4-hydroxy-2-pyrrolone is initially formed as a basic building block. Acylation at C-3 with carboxylic acid derivatives follows. This reaction step may be carried out in the presence of Lewis acids (73TL163; 78TL3173; 83TL4757), but is not always successful (79H477; 80CPB2494). Under basic conditions O-acylation is favored. Occasionally, the first formed O-acyl compound rearranges, and the substituent at C-5 changes simultaneously (83TL4755).

Jones and Peterson reacted 1,5-dihydro-4-methoxy-2-pyrrolones (26) with *n*-butyl lithium and aldehydes. In this way they introduced an carbinol

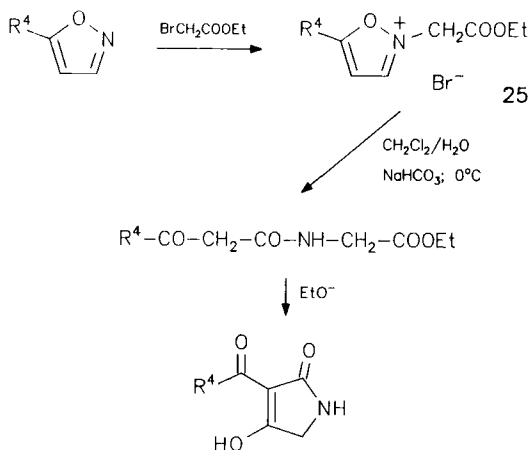


FIG. 13.

substituent into position 3. Oxidation of (27) gave the 3-acyl compound (28). An exchange of methoxy with hydroxy at C-4 was easily achieved using sodium hydroxide at room temperature (83TL4751). This method is useful for the introduction of unsaturated acyl groups (87TL1565). (See Fig. 14.)

Ley *et al.* (88TL5829) followed in principal the classic β -ketoacid pathway (see Scheme 1) in order to synthesize fuligurubin A (87AG597;

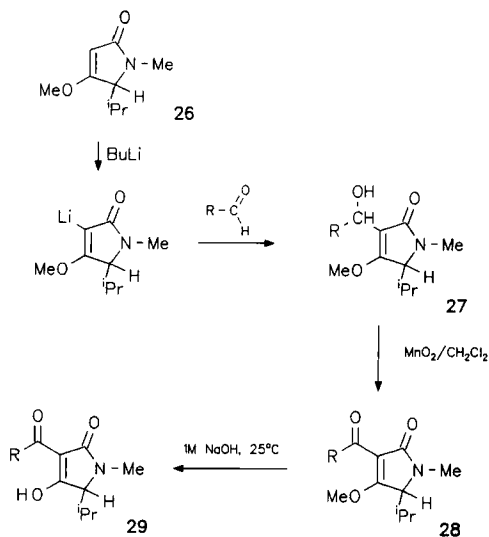


FIG. 14.

89PAC281), a substance found in the fungus *Fuligo septica* (L.) Wiggers [87JCR(S)72]. In accordance with their synthetic goal both reactants were prepared separately. Amino acid component **31** was formed in a three-step reaction, starting from the commercially available (*R*)-glutamic acid derivative **30**. β -Ketoester component **34** is accessible in a Wittig–Horner reaction by reacting β -ketothioester **32** with unsaturated aldehyde **33**. Reaction of **31** with **34** furnished ketoamide **35** that subsequently underwent cyclization to form the tetramic acid derivative **36** under the influence of potassium *tert*-butoxide. Finally, formic acid converted **36** at room temperature into the desired product **37**, which was identical with the natural substance fuligorubin A. (See Fig. 15.)

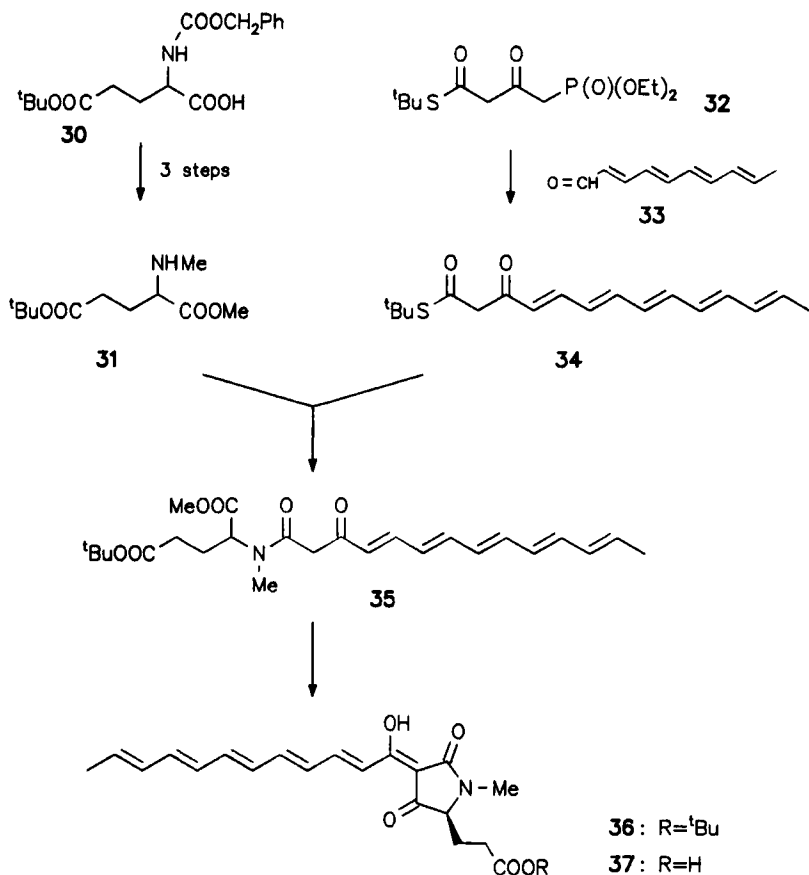


FIG. 15.

Other authors used the same strategy in that they initially synthesized the desired side chain containing the polyene, whereas in a subsequent reaction the tetramic acid ring was closed [89JA8036, 89JA8037, 89JA8231; 90CC765; 91JCS(P1)240].

In the course of the total synthesis of tirandamycin, Schlessinger *et al.* obtained a tetramic acid carrying a phosphonoacetyl residue at C-3. This in fact enabled them to introduce unsaturated residues into the side chain by a Wittig–Horner reaction (85JA1777; see also 82JOC2823; 85JA5219, 85JOC1344; 88JOC1356, 88OS194). (See Fig. 16.)

B. ACIDITY, TAUTOMERISM, COMPLEXES

In their acidity 3-acetyltetramic acids resemble carboxylic acids (Table II).

The relatively high acidity of the acids (**39**) corresponds to the relatively low basicity and the weak nucleophilicity of the corresponding anions (**39**[−]). 3-Acetyltetramic acids cannot be alkylated with reagents of type Alk-X in basic solution, under the usual conditions.

NMR spectra show that (**39**) establish an equilibrium with their tautomers [78TL4707; 80JCS(P1)1057, 80TL4491; 90JPR319]. (See Fig. 17.)

In their SCF MO studies Broughton and Woodward examined the tautomeric geometries of 3-acetyltetramic acids. They found the AM1 and PM3 methods to be satisfactory models for the behavior of these species (90MI1).

3-Acetyltetramic acids form stable complexes with ions of transition metals (79CPB1901; 80CPB2494; 90JPR319, 90MI1). NMR investigations revealed evidence that these complexes are also in equilibrium (92JPR179). (See Fig. 18.)

For some of these complexes interesting applications were suggested, for example, as new antitumor agents (89JAP01/313488; 91JAP02/48591) or as labels in computer tomography.

Jones *et al.* prepared boron complexes and boron compounds of 3-acetyltetramic acid [90JCS(P1)1959].

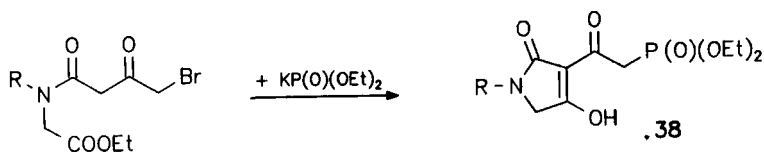
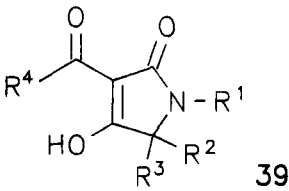


FIG. 16.

TABLE II
pK_a OF SOME 3-ACYL-TETRAMIC ACIDS

					
R ¹	R ²	R ³	R ⁴	pK _a (MeOH:H ₂ O, 1:1)	Reference
Me	H	H	H	2,65	76JHC533
Me	Me	Me	Me	3,40	87TH2
Me	Me	Me	Et	3,65	
Me	Me	Et	Me	3,50	
Me	—(CH ₂) ₄ —		Me	3,75	
Ph	Me	Me	Me	3,05	

C. REACTION WITH ELECTROPHILES

1. Alkylation and Acylation

As shown above, 3-acyltetramic acids (pK_a about 3) form anions whose reactivity toward alkylating agents is low. Successful reaction of 3-acyltetramic acids with carboxylic acid derivatives are scarce in the literature

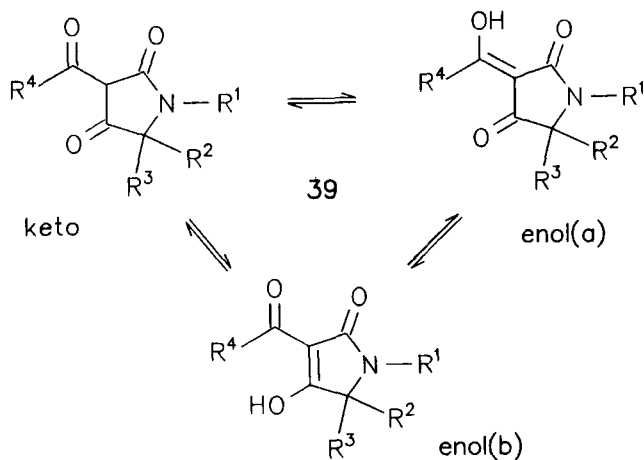


FIG. 17.

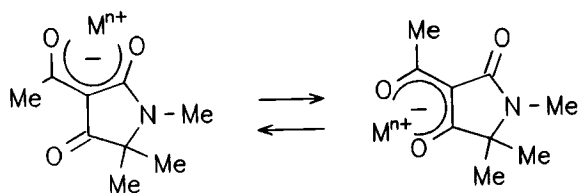


FIG. 18.

(80HCA121). 3-Acetyl-4-hydroxy-1,5,5-trimethyl-2-pyrrolone **39a** gives no acetylated products with either benzoyl chloride or benzoic anhydride, or acetic anhydride. By contrast phase-transfer catalysis ($K_2CO_3/CHCl_3$; r.t.) affords a condensation product, formed from two molecules, **39a**. This product does not bear a benzoyl group (87TH2).

2. Reaction with Aldehydes and DMF-Acetal

Treatment of tricarbonylmethane compounds with acid effects cleavage of the acyl group [59BJ332; 78JA4225; 81ACS(B)667]. Correspondingly, heating of **39a** in the presence of hydrochloric acid provides tetramic acid **40** in quantitative yield after 30 min.

In the presence of aromatic aldehydes, the reaction takes an interesting course. With relatively more strongly electrophilic aldehydes ($Ar = C_6H_5$, $p\text{-Cl}-C_6H_4$, $m\text{-O}_2N-C_6H_4$), hydrolysis to **40** is favored; **40** reacts with these aldehydes subsequently to 3-benzylidenetetramic acids (**41**). However, using *p*-methoxybenzaldehyde gives rise to a proton-catalyzed aldol condensation with formation of 2,4-pyrrolidine **42a** (88PHA473). (See Fig. 19.)

When this reaction is not carried out in an acidic medium, but in ethanol containing some morpholine, aromatic aldehydes furnish chalcone-like (**42**) in 12–17% yield (88PHA473).

In the presence of strong bases, aldol condensation fails. The reason for this lies in the sluggish reactivity of anion (**39⁻**) (Section III,B). When **39a** is substituted by 3-propionyltetramic acid **39c** the yield sags to 0%, obviously an expression for the high steric requirements in the transition state (87TH2).

With DMF-dimethylacetal **8** (61AG493; 84JOC3659), **39a** and **39b** react upon short heating in cyclohexane without catalysis to give compounds

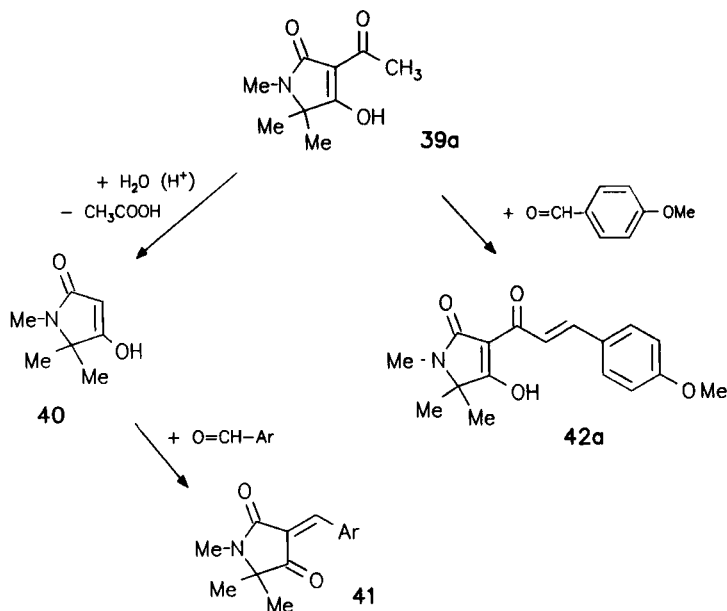


FIG. 19.

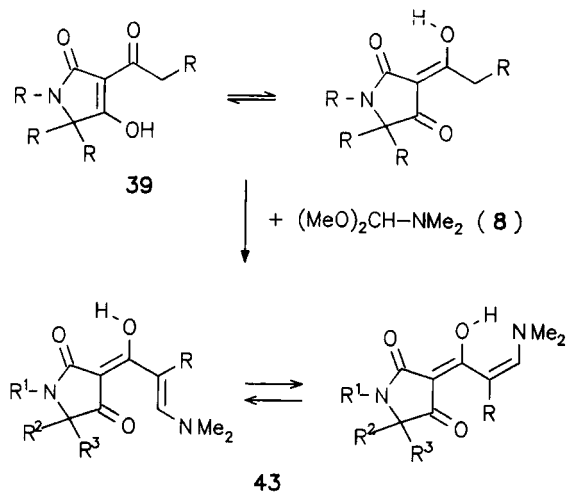
43a and **43b** in good yields. 3-Propionyltetramic acid **39c** requires only a slightly acidic medium to form its product (87TH2). (See Fig. 20.)

D. REACTION WITH N-NUCLEOPHILES

In its reaction with aniline, **43a** reveals its enaminoketone properties: The presence of small quantities of acetic acid initiates an addition/elimination reaction in which the dimethylamino is displaced by the phenylamino group yielding **44** at 72%.

With hydrazines in aqueous ethanolic solution 3-(pyrazol-3-yl)-substituted tetramic acids (**45**) are formed. Hydroxylamine gives the corresponding compound **46** (87TH2). (See Fig. 21.)

3-Acyltetramic acids (**39**) react as expected with primary and secondary amines to yield enamines (**47**) (67CPB727; 72JOC3265; 77G479; 78JA4225; 81CJC763, 81JPJ125; 84CPB4197). In general it is sufficient to reflux in ethanol until (**39**) no longer shows a positive FeCl_3 reaction. With secondary amines, the reaction is best carried out in toluene with simultaneous removal of water (87TH2). (See Fig. 22.)



43	R ¹	R ²	R ³	R	yield(%)
a	Me	Me	Me	H	65
b	Me	-(CH ₂) ₄ -	H	H	41
c	Me	Me	Me	Me	27

FIG. 20.

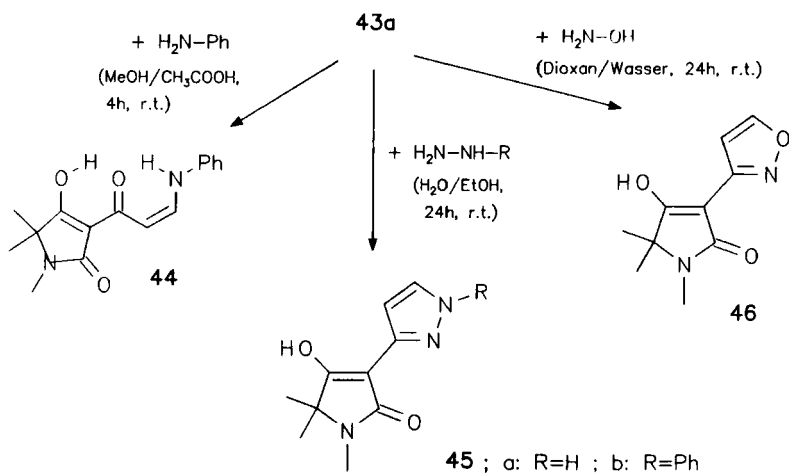
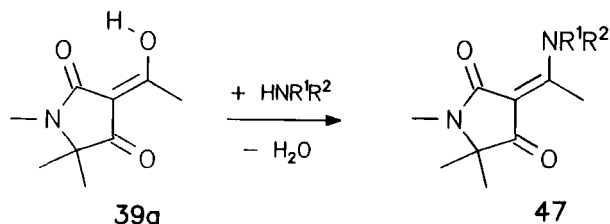


FIG. 21.



47	R ¹	R ²	yield (%)
a	H	Et	82
b	H	ⁿ Pr	95
c	H	Ph	95
d	-(CH ₂) ₂ -O-(CH ₂) ₂ -		86

FIG. 22.

Reaction of (39) with ammonia does not lead to the corresponding enamine, but to the ammonium salt (39⁻ NH₄⁺) that on heating in ethanol or toluene undergoes decomposition into its starting materials. In contrast (47) (R¹ = R² = H) can be obtained in quantitative yield in the reaction of (39) with hexamethyldisilazane in methylene chloride (87TH2).

Compounds (39) are expected to form bicyclic products with hydrazine and diamines. Such cyclizations were recently described for the structurally very similar 4-acyl-3-hydroxyfuranones (91JHC1501). Also, 4-alkoxycarbonyl-1,5-dihydro-3-hydroxypyrrolones give bicyclic products with 1,2-diaminobenzene (91ZOR1951). In the case of 3-acyltetramic acids (39) this is usually not observed in a one-step reaction. But, like other comparable tricarbonylmethane compounds [63MI1; 73JCS(P1)-2697; 75JCS(P1)2435; 82SC431], they furnish hydrazones with hydrazine hydrate and phenylhydrazine. Phenylhydrazones of this type, as well as oximes, semicarbazones, and thiosemicarbazones of 3-acetyl-2,4-pyrrolidinediones, show antiviral activities (67CPB727, 67CPB1107; 71CPB1664). Reacting 1,2-diaminobenzene in ethanol/glacial acetic acid or, even more favorably, in the melt, affords azomethine 48, whereas 49 gives compound 50 (87TH2). (See Fig. 23.)

1,2-Diaminoethane and (39) form azomethines (51) only in trace amounts, but (51) does react with a second mole of (39) to give compounds (52) (87TH2). (See Fig. 24.)

1-Aryl-3-(2-naphthoyl)-4,5-dioxopyrrolidine-2-thione behaves differently. With 1,2-diaminoethane the corresponding pyrrolo[3,4-*e*][1,4]diazepine is generated (89MI3).

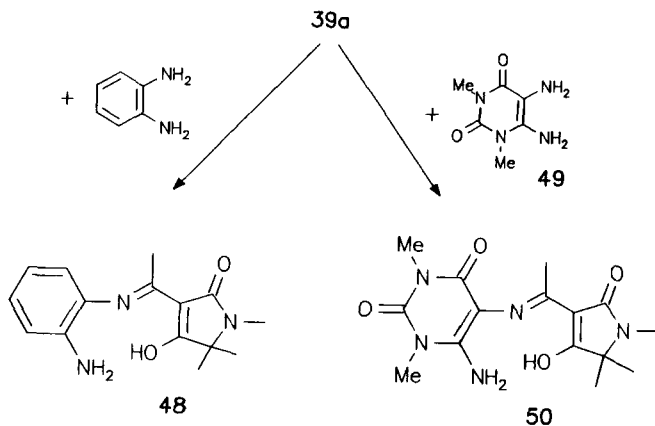


FIG. 23.

Akhrem *et al.* cyclo-condensed 3-acetyltetramic acid (39) with isoquinoline 53 to compounds (55) showing an azasteroid structure (78DOK595; 90ZOR2382). Obviously, referring to (39), an aldol-like reaction, analogous to (39) $\rightarrow$ (42), involving position 1 of the isoquinoline, occurred to give (54).

Intramolecular ring closure between N-2 of the isoquinoline part and C-4 of the tetramic acid moiety followed. This example shows that the 3-acyl group of tetramic acids is not only used for the syntheses of natural

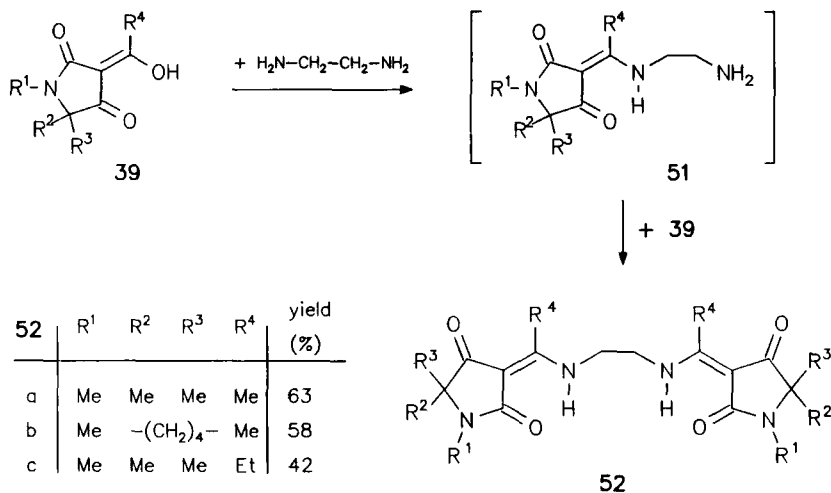


FIG. 24.

compounds with an extended acyl substituent but also for the formation of analogous compounds that incorporate this group in a new ring. (See Fig. 25.)

Refluxing **39a** with formamide furnishes pyrrolo[3,4-*d*]pyrimidin-5-one **56** in 10% yield (87TH2). Reaction of **47** ($R^1 = R^2 = H$) and formamide gives the same compound. This points to a reaction course that was suggested by Brederick *et al.* for analogous pyrimidine syntheses (57CB942). The low yields indicate that the intramolecular reaction of a nucleophilic substituent of the azomethine side chain with the C-4-oxo function obviously requires rather drastic conditions. Experiments on the intramolecular cyclization of azomethines **48** and **50** corroborate this fact. Hydrazones on heating in HCl/EtOH convert to pyrrolo[3,4-*c*]pyrazoles (**57**) in moderate yield (87TH2). This cyclization was observed also with polyphosphoric acid (91MI1). In contrast to azomethine **50**, **48** cyclizes to pyrrolo[3,4-*b*][1,5]benzodiazepine **58a** in the presence of acid (cf. 91JHC1501). (See Figs. 26 and 27.)

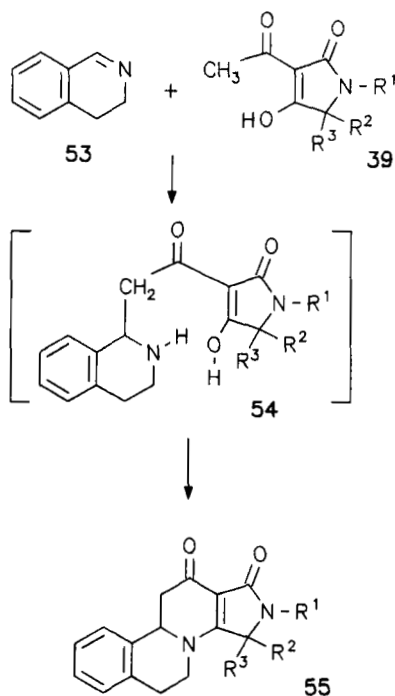


FIG. 25.

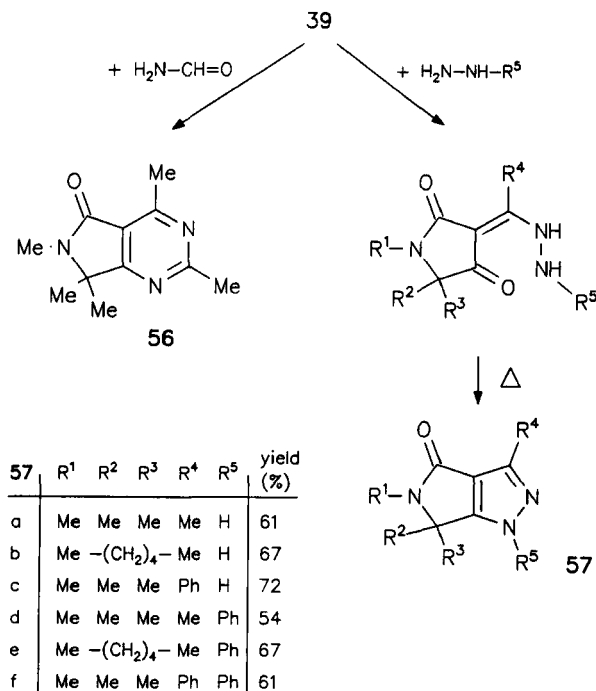


FIG. 26.

E. REACTIONS AT THE EXOCYCLIC DOUBLE BOND

5-Benzylidene-3-dialkylidene-2,4-pyrrolidinediones can be selectively epoxidized at the exocyclic CC double bond [86ZN(B)640]. The products can then undergo further reactions, such as ring enlargement [80ZN(B)724; 90AP381].

3-Acyltetramic acids (**39**) are almost completely enolized in solution as well as in the crystalline state [80JCS(P1)1057], whereby the *exo*-enol form (**a**) is favored. Irradiation of **39a** in peroxide-free cyclohexene leads to [2 + 2]-cycloaddition at the exocyclic double bond. Subsequent thermal reaction opens the four-membered ring of cycloadduct **59**. 3-(2-Acetylcyclohexyl)-1,5,5-trimethyl-2,4-pyrrolidinedione **60** is obtained in 85% yield. In solution, **60** establishes an equilibrium with cyclic hemiacetal **61** (92M93). (See Fig. 28.)

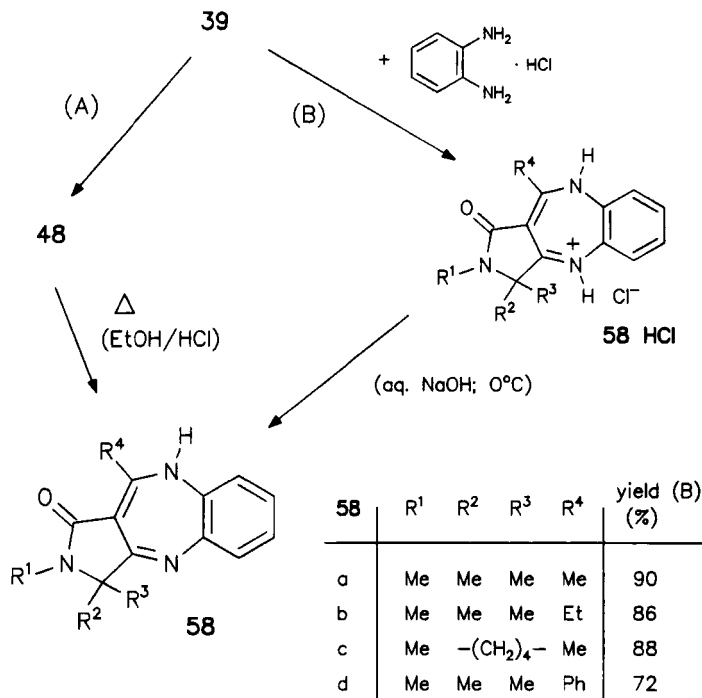


FIG. 27.

IV. 1,5-Dihydro-4-hydroxy-2-pyrrolones (Tetramic Acids)

A. SPECIALTY SYNTHESSES

"Direct synthesis" of tetramic acids (**1/2**) (see retrosynthesis **X**, Scheme 1) starting with an alkanolic acid and an amino acid have rarely been described. One example is a patent of the synthesis of 3,3-dipropyl-2,4-pyrrolidindione formed by bubbling HCl gas through a mixture of valproic acid and glycine in methanol at 25°C (90JAP01/311061).

A reaction by Clough *et al.* comes close to the direct synthesis shown in Scheme 1 (89TL7469). Here amides (**62**) react in a radical mechanism to 4-methylene compounds (**63**) that with O_3/PPh_3 are converted to tetramic acids (**64**). (See Fig. 29.) Several authors, however, prepared esters of 4-amino-3-oxo-butanoic acid, which served as precursors for intramolecular cyclization to tetramic acids (82JHC883). Koehler and Gerlach in an initial stage of a synthesis of dysidine, contained in marine sponge

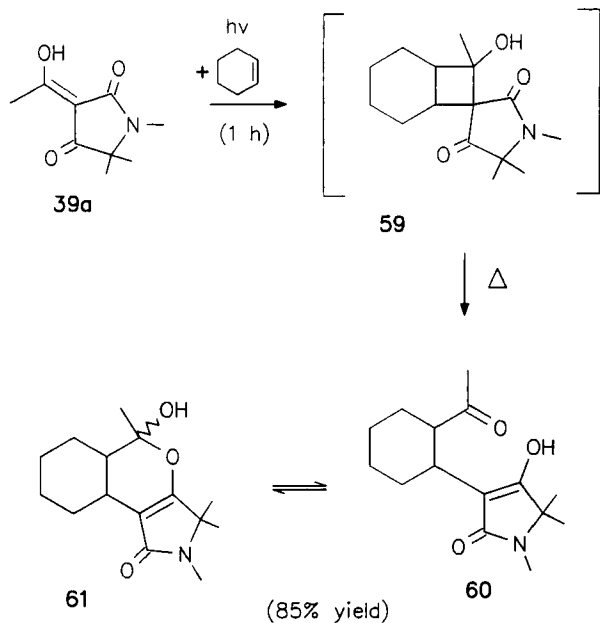
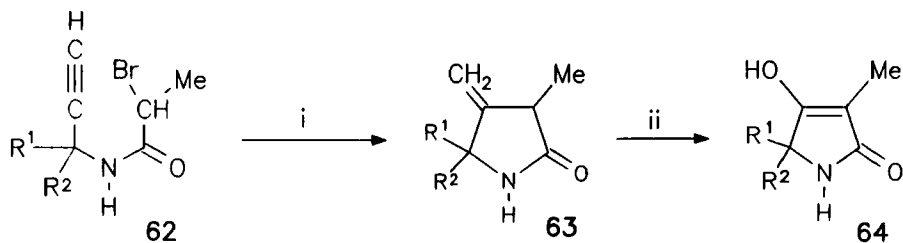


FIG. 28.

Disidea Herbacca, obtained the β -ketoester $\text{H}_2\text{N}-\text{CH}(\text{iPr})-\text{CO}-\text{CH}_2-\text{COOEt}$ from L-valine. The ester was cyclized to 5-isopropyl-tetramic acid in toluene in the presence of potassium 2-methyl-2-butoxide (84HCA1783). In other cases esters of 4-amino-3-oxobutanoic acid, subsequently cyclized in the presence of base, were synthesized using special heterocycles, such as β -lactams (91TL3115), imidazoles (91IZV437) or pyrones (89TL3217). (See Fig. 30.)



i: AIBN/ Bu_3SnH , toluene, reflux; ii: O_3/PPh_3 , MeOH, -78°C

FIG. 29.

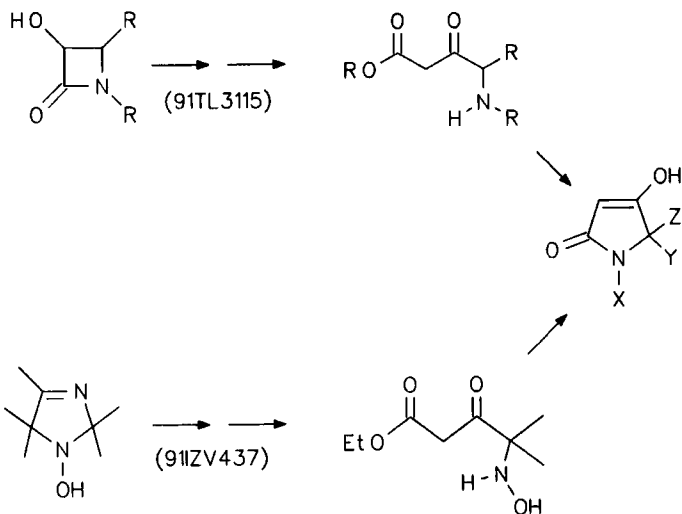


FIG. 30.

The reaction pathway, however, preferred by numerous authors, is a Dieckmann-like cyclization of β -ketoamides corresponding to retrosynthesis **Y** (Scheme 1). This reaction, due to the basic conditions needed, may be accompanied by highly undesirable racemization of a stereo center to be introduced at C-5 [90JCS(P1)611]. To circumvent this complication, many authors resorted to specialty syntheses.

Such syntheses, for example, start from methyl 3-oxo-alkanoates that were initially converted into the enolesters [90JCS(P1)2350], followed by bromination in position 4. Such brominated esters $R-CHBr-C(OMe)=CH-COOMe$ may undergo cyclization either as the 4-phthalimido compounds with hydrazine (63JA1430), or directly with liquid ammonia, or with primary amines into 5-alkyl-1,5-dihydro-4-methoxy-2-pyrrolones (86TL5285). 4-Methoxy compounds including special *N*-acyl groups also occur naturally (86BCJ2185; 89JOC6006; 91JA6692, 91T2087).

A frequently employed route comprises preparation of 3-alkoxycarbonyltetramic acids from malonic acid derivatives and α -aminocarboxylic esters (77MI1; 84CPB3724) or, alternatively, α -aminonitriles (86UP1) followed by hydrolysis and decarboxylation [72JCS(P1)2121; 85AJC1847; 86ZN(B)219].

Similar to other cyclic 1,3-dicarbonyl compounds, tetramic acids in solution predominantly exist in their enol form. As *trans*-configured enols they do not give a color reaction with $FeCl_3$. The pK_a of unsubstituted tetramic acid **2a** was determined to be 6.4 [72JCS(P1)2121].

B. REACTION WITH NUCLEOPHILES

As lactams of 4-amino-3-oxobutanoic acids, tetramic acids react with amines (87JPJ858) and with phenylhydrazine. The latter reaction is catalyzed with *para*-toluenesulfonic acid. Thus, for example, **1/2b** give phenylhydrazone **65** in 80% yield that, in turn, under the conditions of the Fischer indole synthesis, may give rise to pyrrolo[4,3-*b*]indolene **66** (90TH1). (See Fig. 31.)

C. REACTION WITH ELECTROPHILES

1. Alkylation

3-Alkyl- as well as 3-aryl-tetramic acids have interesting biological properties [76AP390; 78AP989; 82AP1020; 84GEP(O)3304485; 90EUP377893, 90JAP01/311061]. Their formation is best carried out starting from the corresponding open-chain amides [87JCR(S)72]. In contrast, the alkylation of tetramic acids under common conditions leads to mixtures of O- and C-alkyl compounds that cannot readily be separated.

2. Reaction with Aldehydes

Aromatic aldehydes react very easily with tetramic acid under acidic conditions to give 3-benzylidene compounds (**41**). The yields are moderate, because often there are subsequent reactions. As α,β -unsaturated carbonyl compounds, (**41**) react in a Michael addition with excess tetramic acid to form (**67**), but it can also react with other acyclic and cyclic 1,3-dicarbonyl compounds. In these reactions the aryl substituents may vary over a wide range. Thus, (**67**) and (**68**) can be cyclized with ammonium acetate to afford pharmacologically interesting compounds (**70**) and (**71**) (90TH1). The latter are dihydropyridines. Curiously, (**69**) does not cyclize under these conditions. (See Fig. 32.)

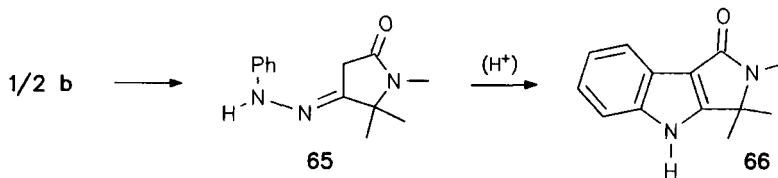


FIG. 31.

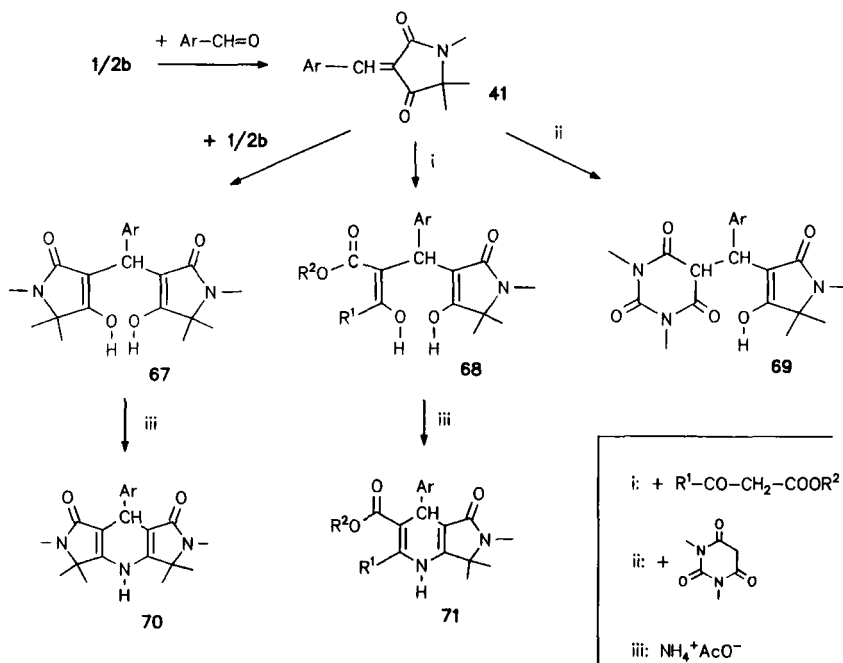


FIG. 32.

The high reactivity of (41) also allows the addition of amines. For example, 41a reacts with 1,2-diamino-benzene to diazepine 72 without isolation of an intermediate in a one-pot reaction (90TH1). (See Fig. 33.)

3. Acylation

As mentioned in Section III, tetramic acids react readily with carboxylic acid chlorides (78TL3173; 83JOC1149; 85JA1777; 86CPB5188; 87CPB4368, 87TL1565). Again, the formation of 4-acyloxy tetramic acids is favored. However, under the conditions of Fries' rearrangement or alternatively, in the presence of triethylamine, conversion to 3-acyltetramic acids is observed (87CPB4368).

An attempt to react 2b with ethyl chloroformate in the presence of pyridine, the Einhorn reaction, gave 73 in low yield and other unknown products. The expected 3-ethoxycarbonyltetramic acid was not isolated (91UP1). An analogous reaction is described for Meldrum's acid (92LA813) (See Fig. 34.)

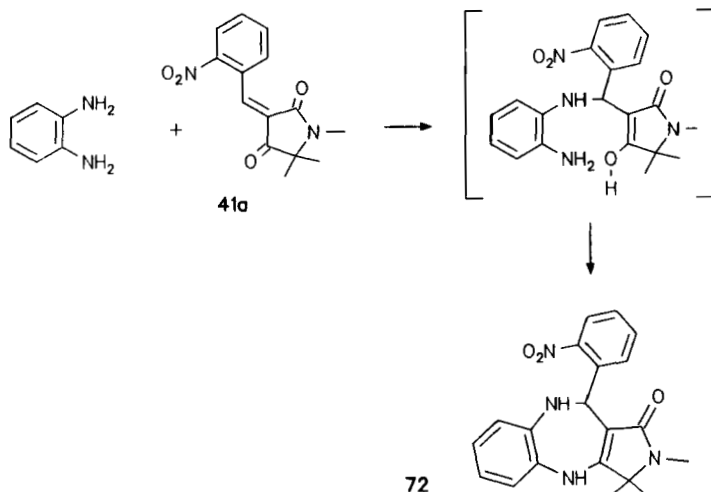


FIG. 33.

With orthoesters, tetramic acid **2b** gives methyldene compounds (**75**) on heating in toluene. With excess triethyl orthoformate as solvent, **2b** forms **75a** in 90% yield. Intermediates (**74**) are not isolable, but react further with an excess of **2b**. Similarly, a high tendency to form **75a** is also reported for the reaction of **2b** with ethoxymethyldene compounds **76a,b** (67M564). In both cases **75a** was furnished in 20% yield. Moreover, **77b** (15%) and **78a** (20%) were obtained (91TH1). According to X-ray

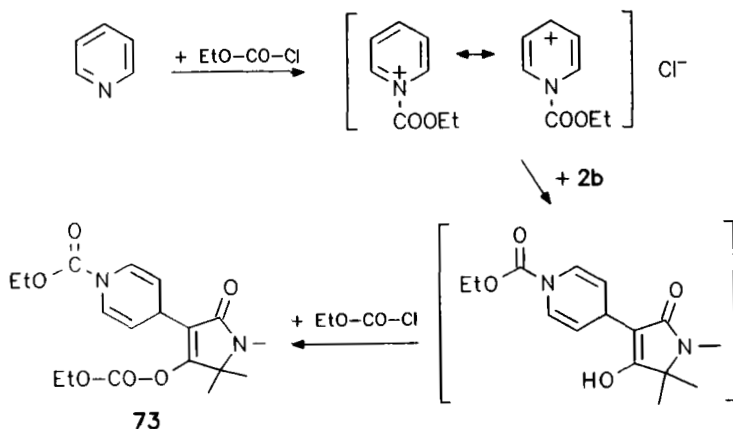


FIG. 34.

analysis, **75a** assumes an almost planar structure with strong intramolecular hydrogen bonds (92UP2). (See Fig. 35.)

As expected, **75a** is converted into **79** upon warming with ammonium formate in ethanol in 81% yield. In the melt **79** forms dipyrrolo[3,4-b:3',4'-e]pyridindione **80** in 90% yield. (See Fig. 36.)

Tetramic acids react with dimethyl orthoformate-*N,N*-dimethylamide **8** to give 3-(*N,N*-dimethylaminomethylidene) tetramic acids in almost quantitative yield. The latter route provides an access to compounds of the same type (**80**) (87TH1). With trimethyl orthoacetoacetate **81**, **2b** forms pyrano[2,3-*c*]pyrrol **82** (91TH1). (See Figs. 37 and 38.)

4. Reaction with *N*-Electrophiles

Nitration of **2b** provides 3-nitropyrrolone **83** (90TH1). In contrast to 3-nitrotetronic acid, **83** is not reduced to the amino compound in Zn/acetic

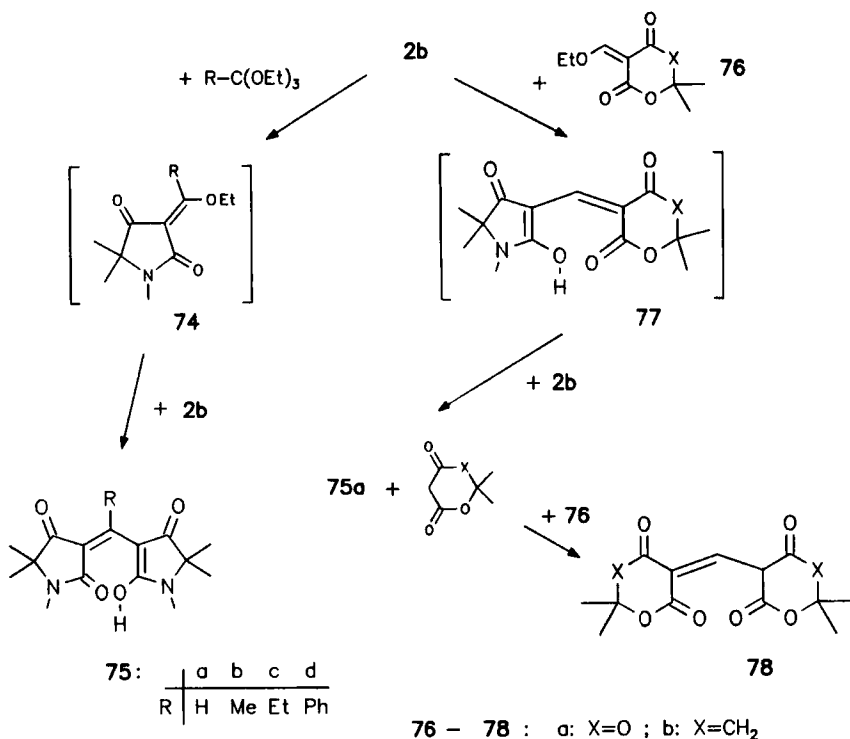


FIG. 35.

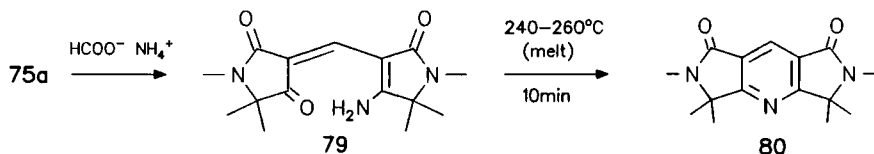


FIG. 36.

acid. Instead, only 3-nitrosotetramic acid **84** was obtained; it immediately rearranged to oxime **85** (90TH1). Even reduction under vigorous conditions did not lead to amine **86**, a reductone-like compound readily reoxidized by air to **85**. Reduction performed in presence of acetic anhydride gives the air-stable *N,O*-diacetyl compound **87**. Electrophilic amination of **2b** also gives oxime **85** rather than **86**. Nitrosation of **2b** at temperatures below 6°C furnishes **85** as well. Due to the acid sensitivity of the oxime **85**, this reaction is preferentially carried out in a basic medium (90TH1). (See Fig. 39.)

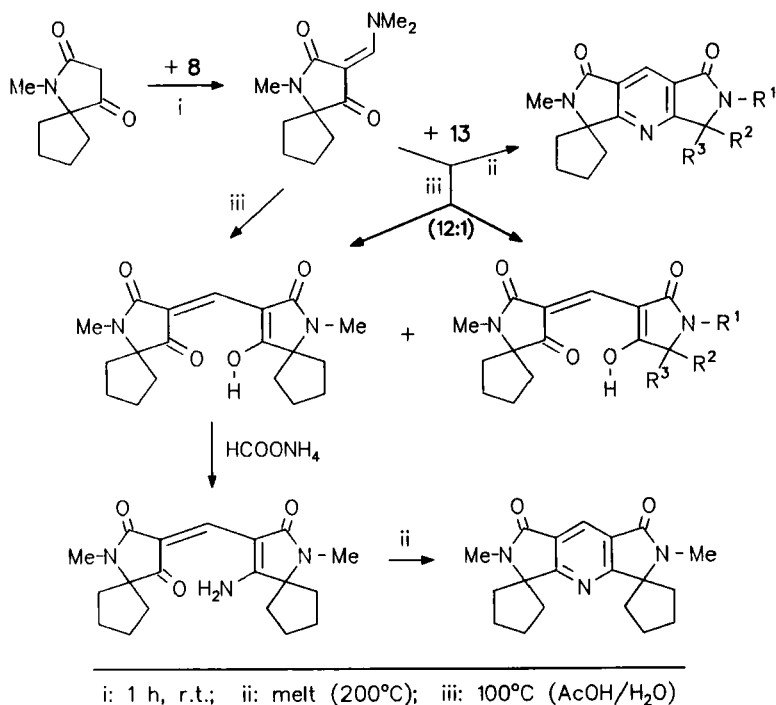


FIG. 37.

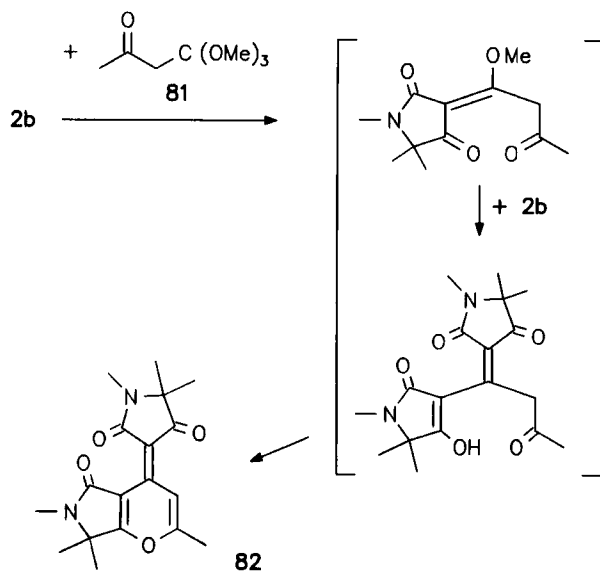


FIG. 38.

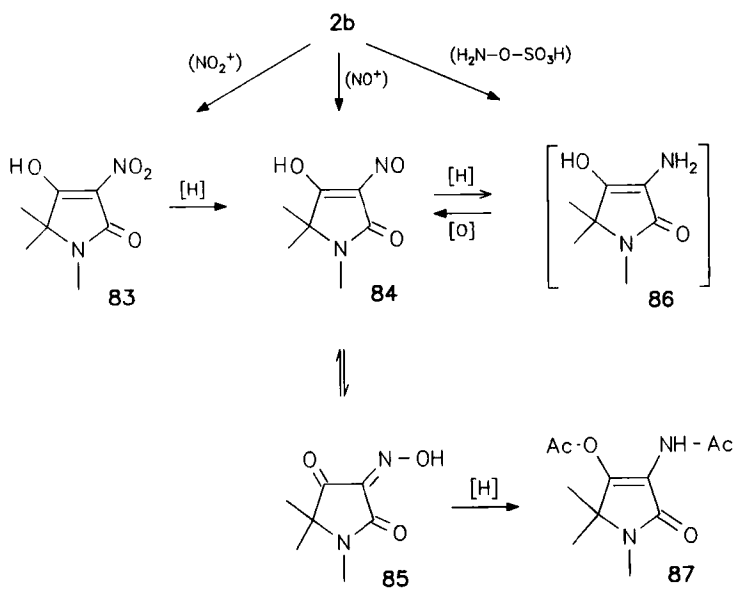
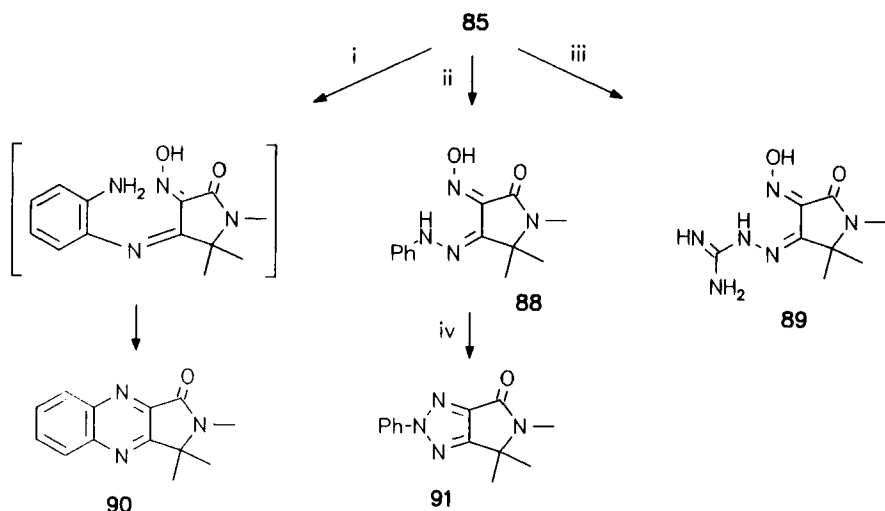


FIG. 39.

Oxime **85** with sodium cobalt nitrite $\text{Na}_3\text{Co}(\text{NO}_2)_6$ forms a poorly water soluble Cobalt(III) complex CoL_3 that, by contrast to **85**, is relatively stable to acids.

Although **85** does not react with aniline under the usual conditions, its 4-oxo group and more strongly nucleophilic hydrazines form the expected condensation products **88** and **89**. The corresponding intermediate with 1,2-diaminobenzene cyclizes immediately with loss of hydroxylamine to give pyrroloquinoxaline **90**. Upon warming, **88** transforms into 1,2,3-triazole **91** (90M671, 90TH1). (See Fig. 40.)

Like other cyclic β -dicarbonyl compounds (61CB929), tetramic acids react with aryl diazonium ions at the α -position. The resultant 2-arylhydrazones of pyrrolidine-2,3,4-trione (**92**) according to IR spectra form an intramolecular hydrogen bond to the amide carbonyl group (90TH1). Like oxime **85**, **92** reacts with 1,2-diaminobenzene on warming in hydrochloric acid to give quinoxaline **90**. With hydroxylamine, **92** forms 3-phenylhydrazone-4-oxime (**93**) (cf. **88**). On heating in acetic anhydride the latter give pyrrolotriazole **91** in nearly quantitative yield. The advantage of the sequence (2)–(**92**)–(**93**)–(**91**) in comparison to



i: 1,2-diaminobenzene, 3*n* HCl, 5h reflux ; ii: Ph–NH–NH₂, toluene, 1h reflux

iii: H₂N–C(=NH)–NH–NH₂·HNO₃, EtOH, 8h, 70°C ; iv: Ac₂O, 0.5h reflux

FIG. 40.

(2)–(85)–(88)–(91) lies in the ease of introduction of aryl substituents. (See Fig. 41.)

As CH-acidic β -dicarbonyl compounds, tetramic acids transform through a transfer of a diazo group with tosyl azide into α -diazoketones (80JHC1195) that may react further (74JA5787; 89AP301).

5. Halogenation

Electrophilic halogenation of β -dicarbonyl compounds causes a reverse polarization at the α -position. Wentrup *et al.* used this fact, for example, in syntheses with Meldrum's acid (84JOC2772).

Under carefully worked out reaction conditions, **2b** can give the 3-bromo compound **94** (CHCl_3 , $0-5^\circ\text{C}$) or the 3,3-dibromo compound **95** (2M NaOH, $0-5^\circ\text{C}$). The reactions of **94** and **95** with N-nucleophiles proceed differently. Refluxing **94** in ethanol gives dimer **96**, which is clearly distinct in structure and properties from other self-condensation products of tetramic acid (85AJC1847). Otherwise, **95** and *N*-methyl-*N*-phenylhydrazine under refluxing in ethanol form 3-hydrazone **92a** in 60% yield (90TH1). (See Fig. 42.)

6. Reaction with Electrophilic N-Heterocycles

Tetramic acid **2b** with ethyl chloroformate in the presence of pyridine give, via *N*-ethoxycarbonylpyridinium cation, compound **73** (Section

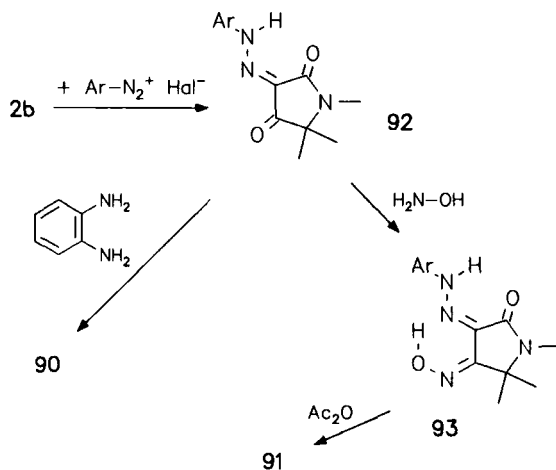


FIG. 41.

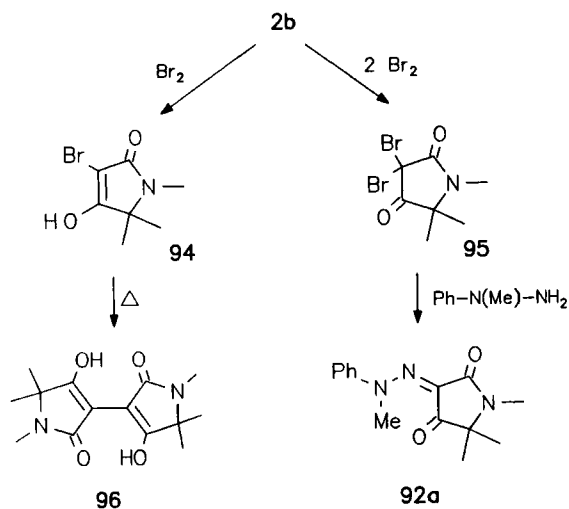


FIG. 42.

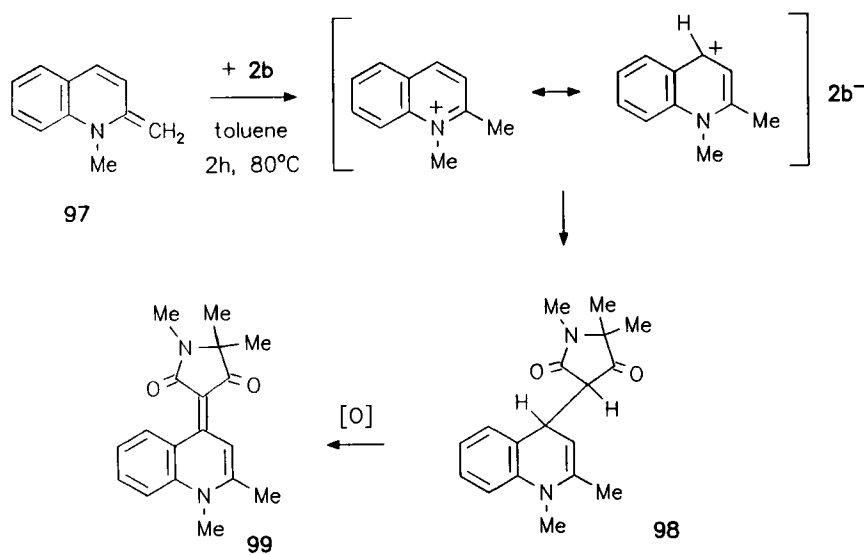
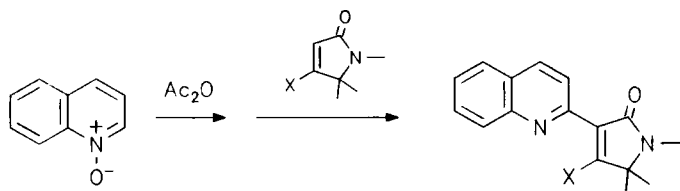
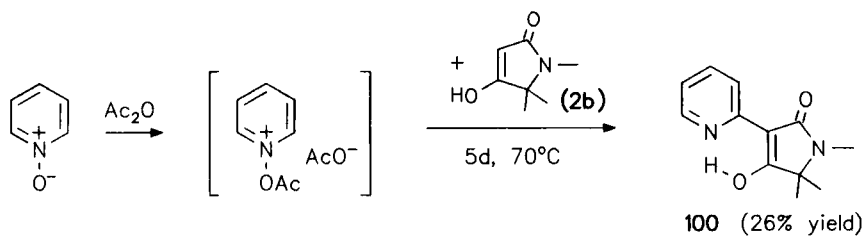
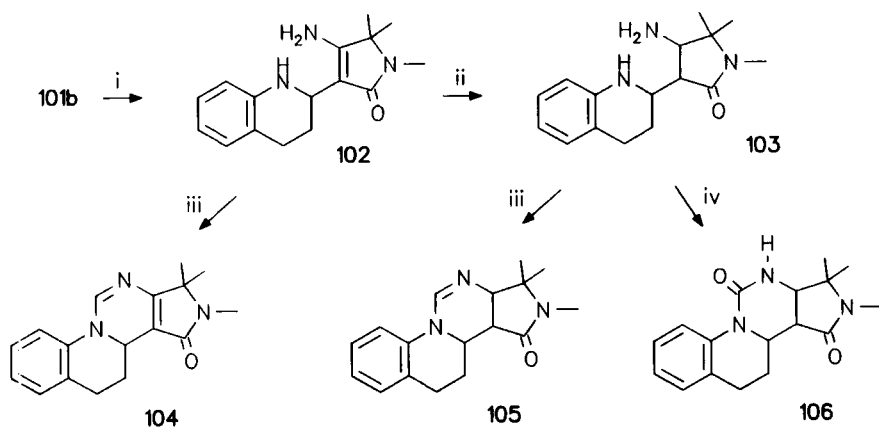


FIG. 43.



101	X		yield(%)
a	HO	15min, 80°C	87
b	H ₂ N	2h, r.t.	32

FIG. 44.



i: H₂/Ra-Ni, 100°C, 150bar ; ii: LiAlH₄ ; iii: HC(OEt)₃ ; iv: Cl-CO-OCCH₃

FIG. 45.

IV,C,8). This gives rise to the question whether in general tetramic acids can be attacked at position 3 by electrophilic N-heterocycles. In connection with investigations on the reactivity of methylene compound **97** it was found that nucleophilic cyclic β -dicarbonyl compounds react at C-4 of the quinoline ring (92UP1). Tetramic acid **2b** follows this pattern and gives the orange-colored enaminedione **99** after oxidation of the primary product **98** with air (92UP2). (See Fig. 43.)

The N-oxides of pyridine and quinoline react in acetic anhydride with β -dicarbonyl compounds to give pyridines and quinolines substituted in position 2 (65CPB918; 81H1083; 82CPB1680, 82CPB2326). Tetramic acids as well as 4-amino-1,5-dihydro-2-pyrrolones can be employed in this reaction. Under mild reaction conditions, **101** can be obtained in good yields (88PHA45). Following stepwise reduction, **101b** may be reacted to give tetracyclic compounds **104–106** with azasteroid skeletons (88PHA45; 89MI2; cf. 78DOK595). (See Figs. 44 and 45.)

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Piperazine-2,5-diones and Related Lactim Ethers

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I. Introduction

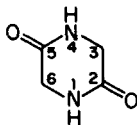
The objective of the present review is to discuss all aspects of the chemistry of piperazine-2,5-diones and their synthesis, physical characteristics, chemical reactivity and applications. Earlier reviews had focused on certain specific topics: thus the review by Sammes (75FOR51) is mainly oriented toward natural products containing the piperazine-2,5-dione ring, whereas the one by Anteunis (78BSB627) deals exhaustively with conformational aspects of the ring, as well as those of the side chains.

The scope of the present review does not permit a detailed account of the isolation and structure of the various natural products containing this moiety. However, inasmuch as the major advances in the synthesis of piperazinediones have been achieved during attempts to meet the challenges posed by these complex natural products, most of these important discoveries have been discussed and highlighted in this review. A fantastic amount of new chemistry has also been generated during studies on the mechanism of action of the antibiotic bicyclomycin. Most of the interesting transformations the molecule undergoes are beyond the purview of this article (91JA6621, and earlier papers; 91JOC5462, and earlier papers).

The other exciting area that has now caught the attention of organic chemists is that of molecular recognition. Cyclodipeptides offer several advantages for the study and application of such phenomena: a relatively rigid framework with the possibility of formation of up to four hydrogen bonds with suitable partners, the possibility of designing piperazinediones with predetermined absolute configuration at two of the ring atoms, and a detailed knowledge of the conformation of the ring and of the side chains.

Throughout this article, the heteroring will be referred to as either piperazine-2,5-dione or occasionally as cyclodipeptide. The earlier practice of referring to the ring as diketopiperazine has been avoided. The numbering of the piperazinedione ring is as shown in (1). In the cyclodipeptide nomenclature, the common three-letter code for the two amino acids, with the necessary prefix to indicate absolute configuration, will be used.

Literature to the end of 1991 is covered in this review (primary journals).



(1)

II. Synthesis of Piperazine-2,5-diones

It is well known that derivatives of α -amino acids, especially the esters, can undergo cyclodimerization to form piperazine-2,5-diones. The stereochemistry of such self-condensation of *dl*-amino acid esters has been investigated [86JCS(P1)1557]. Piperazinediones with a *cis* orientation of substituents were preferentially formed at the initial stages; but increasing amounts of the *trans* product were formed later. The results have been interpreted as reflecting the difference in the rates of cyclization of the two diastereomeric dipeptide esters.

The most common method of synthesizing piperazine-2,5-diones is by cyclizing an appropriate linear dipeptide or its derivative (75FOR51). Sammes has given a good account of the synthetic methods available upto 1973. For cyclization to occur, the existing amide bond must be in the *cis* form. The planar unprotonated peptide bond in open-chain compounds normally exists almost exclusively in the *trans* conformation; the barrier to rotation is around 20 kcal mol^{-1} . In *N*-acyl proline derivatives, however, the *cis* conformation is less unfavorable; *cis* : *trans* ratios of 1 : 7 are normal. This explains the observation that cyclization is especially easy with dipeptide esters having a proline residue or an *N*-methylamino acid at the C-terminus. Interestingly, glycylproline ethyl ester cyclizes much more readily than polyglycine ester [73JCS(P2)1845].

A. SYNTHESIS FROM DIPEPTIDE ESTERS

The earliest method for such a cyclization was that of Fischer, which involves the action of excess ammonia on dipeptide methyl esters (06CB2893). However, this method is known to lead to a considerable amount of racemization.

A significant improvement in the method was developed by Nitecki *et al.* (68JOC864). In this process, *N*-*t*-butoxycarbonyl derivatives of dipeptide esters are deblocked by formic acid (room temperature, 2 h) and the excess formic acid is distilled off. The formate salt of the dipeptide ester left behind is heated with *sec*-butanol and toluene for 2–3 h under azeotropic distillation conditions to form the cyclodipeptide. The yields

range from 50 to 90%. Most of the examples provided are for the cyclization of dipeptides having only hydrocarbon side chains. But the authors have shown the applicability of this method to the synthesis of cyclo (L-Thr- ϵ -cbz-L-Lys) also. No racemization could be detected. It has been suggested that under these conditions the formic acid is removed from the salt as an azeotrope, leaving the residual dipeptide ester to cyclize.

The Nitecki method has been extensively used by several other groups over the last two decades.

Acetic acid-catalyzed intramolecular aminolysis has been recommended as a better procedure by Suzuki (81CPB233). Advantages claimed are shorter reaction time and no racemization. A wide variety of cyclodipeptides have been synthesized by this procedure, including those having sidechain functional groups such as cyclo[Glu(OBzl)-Tyr], cyclo(Gly-Gln), and cyclo[Gln-Arg(NO₂)]. Yields are greater than 80% in the cyclization. Even an acid-labile tryptophan-containing molecule, cyclo(Trp-Leu) could be prepared in good yield by this method.

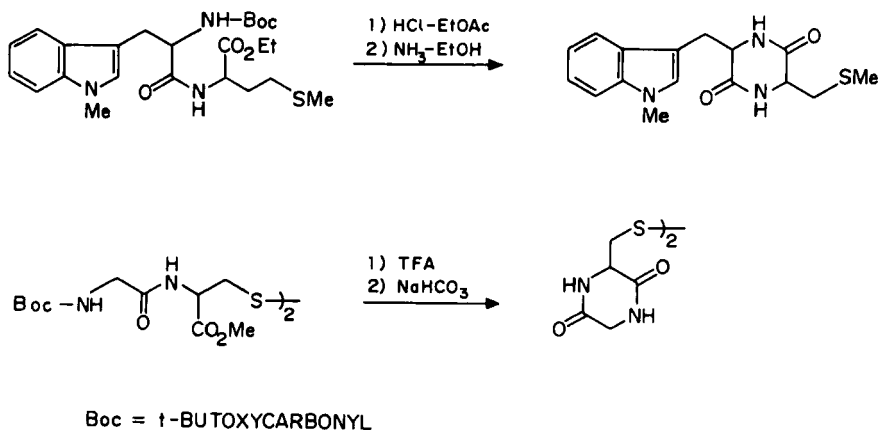
Three methods have thus emerged for the cyclization of dipeptide esters: base-catalyzed cyclization (Fischer); cyclization without any added catalyst, under essentially neutral conditions (autoaminolysis; Nitecki); and acetic acid-catalyzed cyclization (Suzuki).

Despite the known propensity for racemization, base-catalyzed cyclization continues to be used occasionally. Thus a series of cyclodipeptides derived from 1-methyl-L- and D-tryptophans and S-methyl-L- and D-cysteine have been prepared by ammonia-catalyzed cyclization (87JMC1706), (Scheme 1).

An analog of the peptido-leukotriene LTD₄, in which the peptide moiety has been replaced by cyclo (Gly-Cys) has been synthesized. The requisite cyclodipeptide was made by base-catalyzed cyclization of the linear precursor (Scheme 1) (85TL1951). In this case, the cyclization was achieved at pH 8.5 in aqueous sodium bicarbonate.

Cyclization under neutral conditions is still the most popular technique employed for the generation of piperazine-2,5-diones from linear precursors. Some recent representative examples are given below. 6-Demethoxy-fumitremorgin C has been synthesized by Cava, using at the penultimate stage, the cyclization of an N-acylproline ester by refluxing in toluene (Scheme 2) (87TL1131). The same molecule has also been constructed by the attack of a proline NH on a β -carboline ester (Scheme 2) (89TL6421). Cyclization follows automatically on removal of the N-protecting group. Subsequent Swern oxidation gave the ketone in 73% overall yield. This could be converted to the desired product in two simple steps.

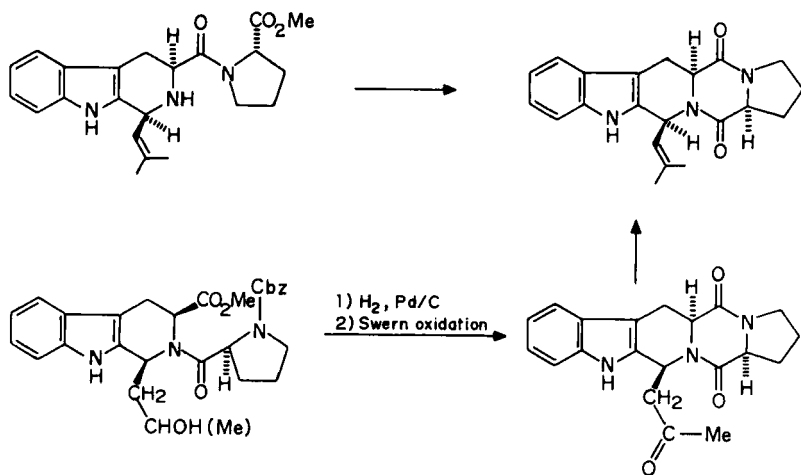
Cyclization to a piperazine-2,5-dione involving an intramolecular attack on a lactone carbonyl has been successfully utilized by Kemp



SCHEME 1

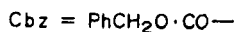
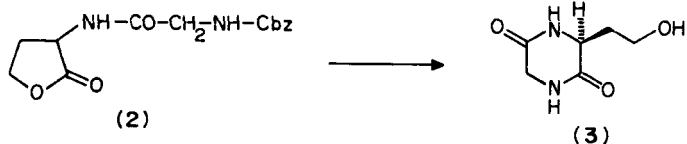
(84JOC2286). Thus, removal of the carbobenzoxy protecting group in (2) by hydrogenolysis in methanol (H_2 , Pd/C) led to spontaneous cyclization to form (3).

A similar lactone ring opening is involved in the asymmetric synthesis of stereospecifically monodeuterated 1-aminocyclopropane-1-carboxylic



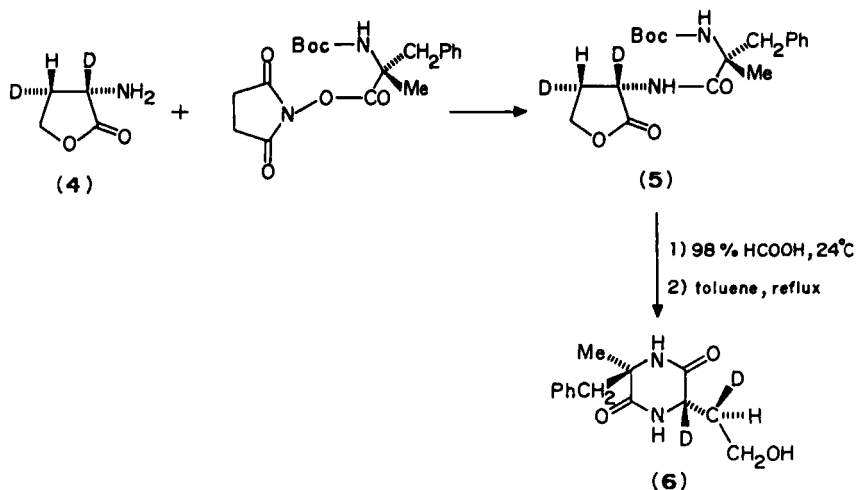
Cbz = CARBOBENZYLOXY

SCHEME 2



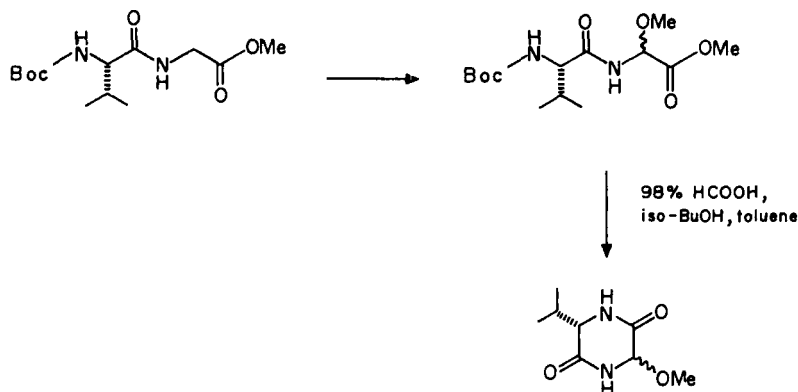
acid (ACC)¹ via cyclo (ACC- α -methyl-Phe) (89JOC270). Cyclization in this case was achieved by the formic acid procedure. For example, the specifically deuterated homoserine lactone (4) was coupled with (2*R*)-*N*-Boc-2-methyl-3-phenylalanine; the dipeptide (5) was deprotected with formic acid and cyclized to the piperazinedione (6) (Scheme 3). Subsequent steps leading to the aminocyclopropane carboxylic acid are discussed in the section on lactim ethers.

3-Methoxypiperazine-2,5-diones have been obtained by the formic acid cyclization of the corresponding linear peptides (91T563). The latter were obtained by electrochemical oxidation of normal dipeptides (Scheme 4). The electrolysis was performed in MeOH-lithium perchlorate (0.1 *M*) containing NaCl at a platinum anode and was found to be totally regioselective.



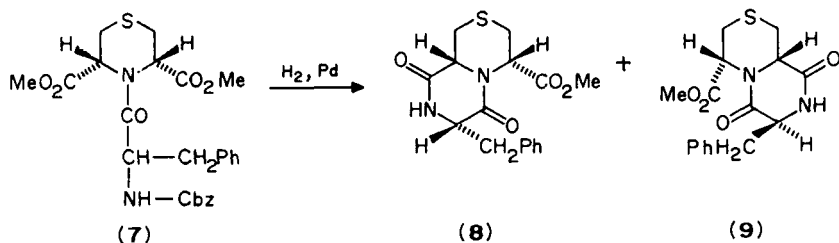
SCHEME 3

¹ ACC: 1-Aminocyclopropane-1-carboxylic acid.



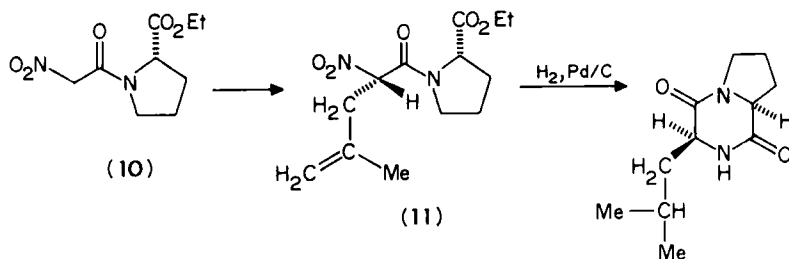
SCHEME 4

An interesting example of the role of solvent in determining the conformation of the linear precursor and hence the relative stereochemistry in the product is provided by the thiamorpholine derivative (7) (90JHC1661). Deprotection of this by catalytic hydrogenolysis leads to cyclization yielding a mixture of (8) and (9). The product ratio depends on the solvent used for the hydrogenolysis. In methanol it is 35 : 54, whereas in dichloromethane–acetic acid (20 : 1) the ratio is 56 : 9. Obviously the rotamer populations are influenced by the solvent chosen.

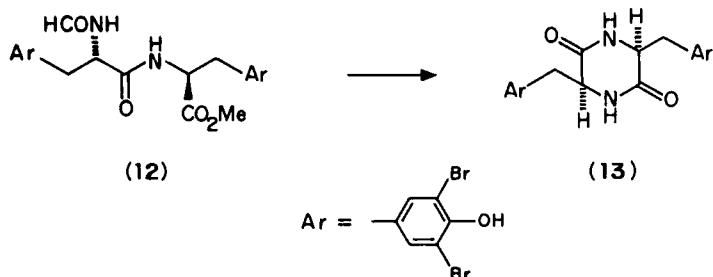


In all the examples cited so far, the NH_2 groups involved in the final cyclization had been liberated at the penultimate stage by an appropriate deprotection step. A novel variant of this has been provided by generating the NH_2 group from an NO_2 group by reduction, leading to cyclization (91CC372). Thus *N*-nitroacetyl L-proline ethyl ester (10) was methallylated at the active methylene to give (11) as the major diastereomer. Catalytic reduction of this (Pd/C, MeOH) led to cyclo-(L-Leu-L-Pro).

The acetic acid-catalyzed cyclization procedure was adopted in a synthesis of the antifungal antibiotic piperazinomycin (86TL4481). The for-

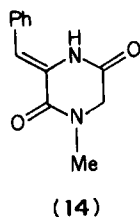


mamide (12) was hydrolyzed by acid (1.5 *M* HCl–MeOH) and the resulting amine hydrochloride was neutralized with *N*-methylmorpholine (1 equivalent) and refluxed with 0.1 *M* acetic acid in 2-butanol; this yielded the piperazinedione (13) in 85% yield.



B. CYCLIZATION OF FREE DIPEPTIDES

Free dipeptides or their hydrobromide salts can be cyclized to the corresponding cyclodipeptides by heating in phenol (68JOC862). No detectable racemization takes place. The versatility of the method is shown by the synthesis of cyclo(Ser–Tyr), cyclo(Met–Tyr), cyclo(Gly–Trp), etc. Very facile cyclization (on warming in water) of sarcosyldehydrophenylalanine to 1-methyl-3-*trans*-benzylidenepiperazine-2,5-dione (14) has been reported [70JCS(C)2530].



C. CYCLIZATION OF DIPEPTIDE AZIRIDIDES

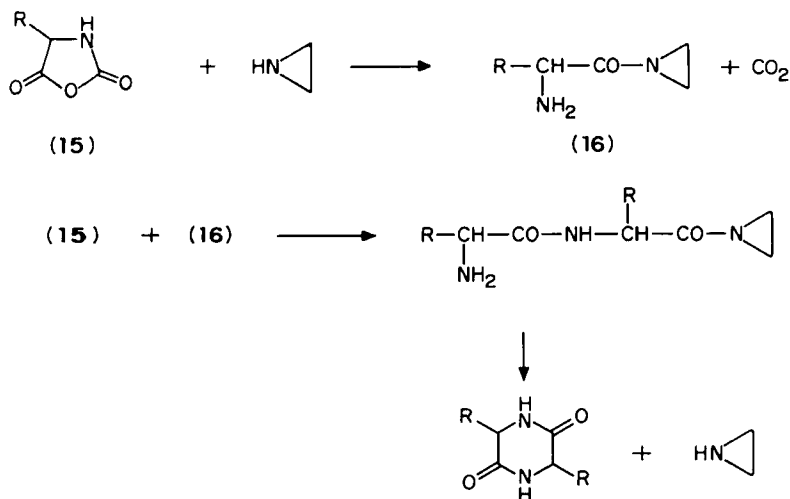
Symmetrical piperazine-2,5-diones have been obtained in good yields by treating Leuchs anhydrides (1,3-oxazolidine-2,5-diones) with aziridine [70AG(E)162]. The reaction apparently proceeds through the formation of dipeptide aziridides (Scheme 5).

D. SYNTHESIS BY INTRAMOLECULAR ATTACK OF AMINES ON OTHER ACTIVATED RING CARBONYL GROUPS

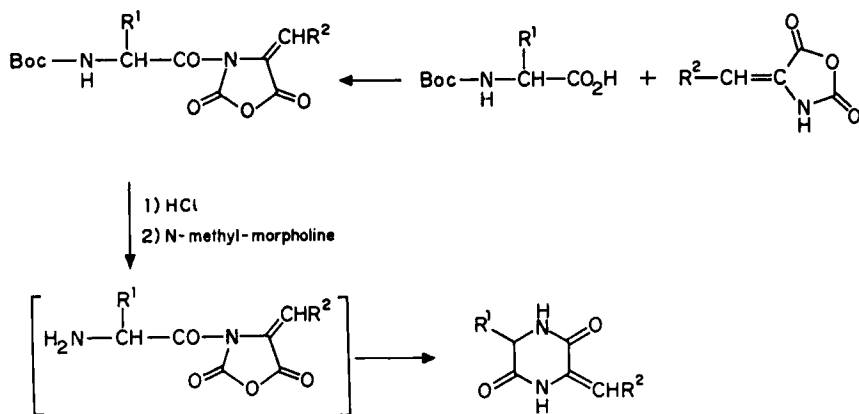
Several 3-alkyldenepiperazine-2,5-diones have been prepared by a novel route involving the prior coupling of a *t*-butoxycarbonyl amino acid with an *N*-carboxydehydro amino acid anhydride, followed by removal of the protecting group (87H2087) (Scheme 6).

Hydrogenolytic N-deprotection of (17) led to piperazinedione (18) by opening the azetidinone ring (84T1039)

The azalactones (19) obtained by the Ugi condensation, on thermolysis, give the piperazinediones (20) in almost quantitative yields [73AG(E)79].



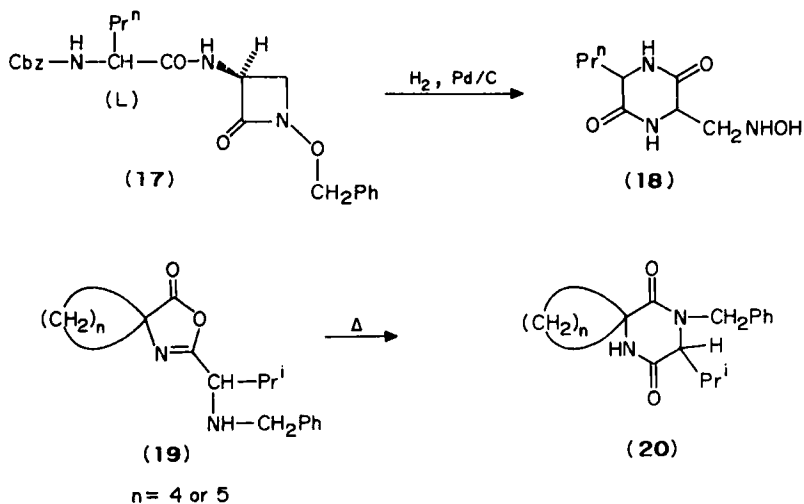
SCHEME 5



SCHEME 6

E. FROM α -HALOACYL DERIVATIVES OF AMINO ACID ESTERS

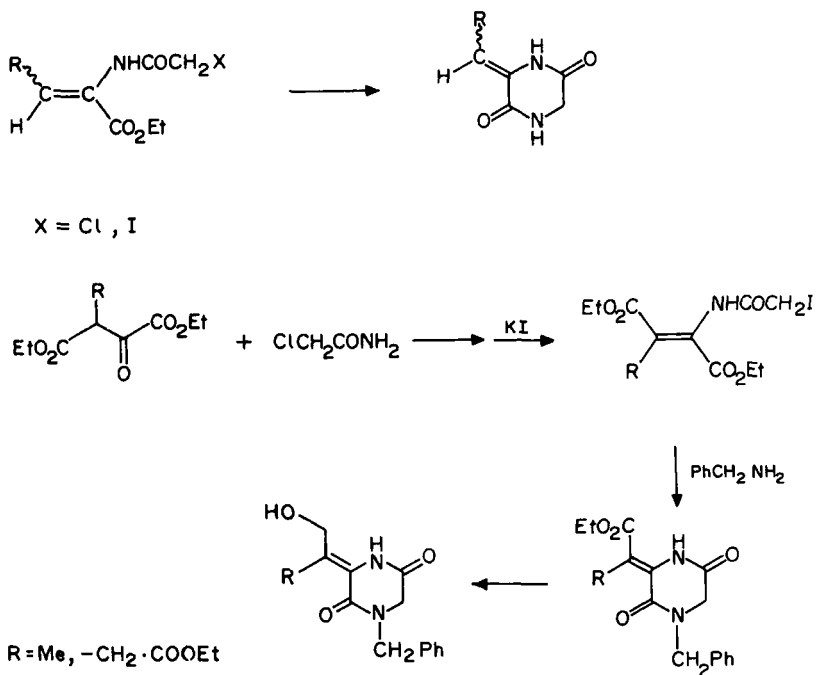
This procedure was originally used by Cook and Slater (56JCS4130); various modifications are still being reported. Thus, a simple method has been described in 1981 for the preparation of 1-methylpiperazine-2,5-dione, which involves treating *N*-chloroacetylsarcosine ethyl ester with ammonia (81JHC423). Shin and his group have made use of this methodology quite extensively. Pure (*E*) and (*Z*) forms of the alkylidene piperazine-



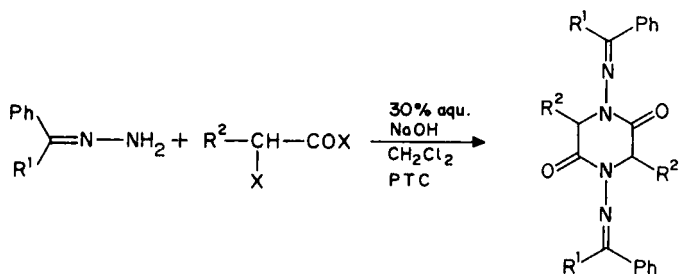
2,5-dione have been obtained by treatment of the corresponding chloroacetyl derivatives with ammonia (Scheme 7) (78BCJ550). Yields in the cyclization are better if the chlorine is first replaced with iodine by treatment with potassium iodide in acetone (87ABC2033). This method has been further extended to generate 3-hydroxyalkylidenepiperazine-2,5-diones; as above, the chlorine is replaced by iodine prior to cyclization, leading to better overall yields. (Scheme 7) (85H2217).

An interesting extension of the reaction is the treatment of hydrazones with α -haloacyl halides under phase-transfer catalysis, when hydrazones of symmetrical 1,4-diaminopiperazine-2,5-diones result (84CPB2426) (Scheme 8).

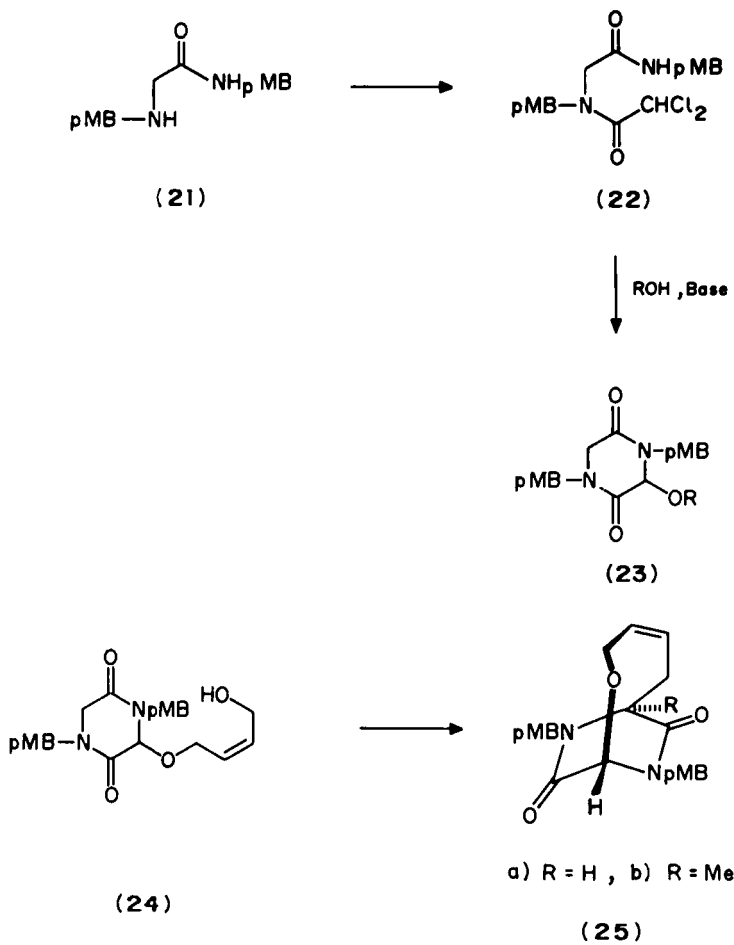
An extremely interesting extension of this method has led to the synthesis of monoethers of piperazinediones (88JOC5785), which are not otherwise easily accessible. The dichloroacetyl derivative (**22**) of the glycina-mide (**21**) undergoes base-catalyzed condensation with alcohols to give the piperazinediones (**23**). This has been used to generate bicyclic [n.2.2] piperazinediones in which the second ring is created by C—C bond formation. Thus, the butenediol derivative (**24**) obtained by the procedure out-



SCHEME 7



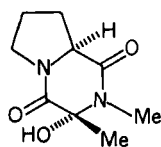
SCHEME 8



lined above could be converted to the allyl chloride and then cyclized to (25a) by treatment with lithium bis(trimethylsilyl) amide in THF at -78°C .

F. BY CYCLIZATION OF *N*-PYRUVOYL AMINO ACID AMIDES

This is a general method, leading to either 3-hydroxypiperazine-2,5-diones, or to the corresponding alkylidene derivatives (74CB2804). Thus *N*-pyruvoylproline methylamide cyclizes in water at pH 7.5 to yield the piperazinedione; the cyclization appears to be highly stereoselective, leading to the kinetically controlled product (26). The scope of the method has been considerably expanded by Dutch workers, who have used it for the synthesis of 1-hydroxypiperazine-2,5-dione derivatives (see Section VI).

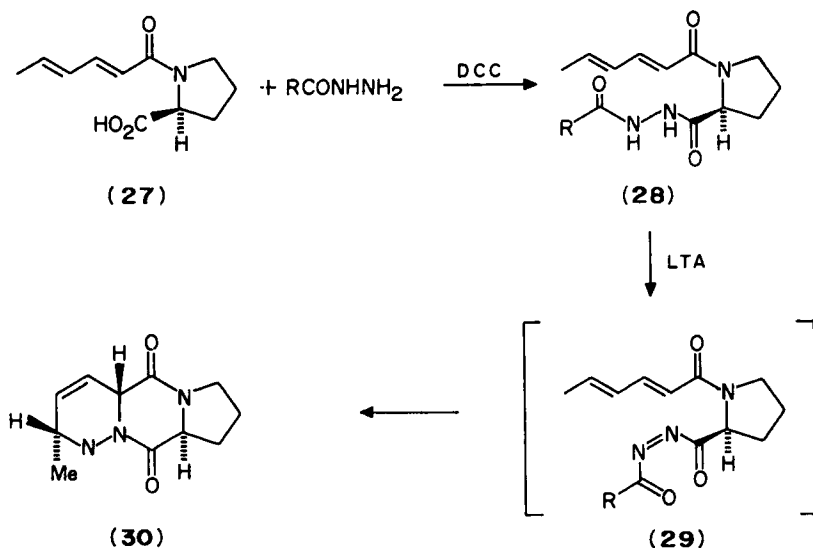


(26)

A modification of this method is to treat the corresponding ester with methylamine (75SC237).

G. BY AN INTRAMOLECULAR DIELS–ALDER REACTION

An extremely interesting and novel method has been described (91TL133). The principle involved is the intramolecular Diels–Alder addition of a 2,4-dienoic acid amide with an azodicarbonyl moiety. *N*-Sorbylproline (27) was condensed with an acylhydrazine to form (28). Oxidation of this with lead tetraacetate (LTA) in boiling benzene resulted in the piperazinedione (30). This must have come about via (29), which could undergo an intramolecular Diels–Alder reaction. The structure and stereochemistry of (30) were confirmed by X-ray crystallography. The two new chiral centers have the *R* configuration as shown in (Scheme 9).



SCHEME 9

III. Structure and Physical Properties

A. SPECTROSCOPY AND CONFORMATION

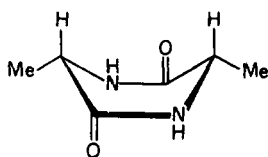
The review by Sammes (75FOR51) has covered the literature in this area thoroughly to 1973. Furthermore, conformational aspects of cyclodipeptides were discussed extensively in a review by Anteunis in 1978 (78BSB627). The material will not therefore be duplicated in the present review; only the important conclusions will be highlighted.

Piperazine-2,5-diones possess two *cis* amide bonds. In the infrared, the CO stretching bands occur at 1670–1690 cm⁻¹ and the NH stretching frequency at 3180–3195 cm⁻¹. More detailed analysis of IR and Raman spectra have been carried out [84SA(A)481, 84SA(A)503].

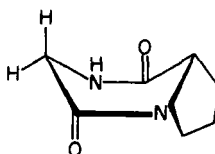
The six-membered ring can exist in either a flat conformation or a slightly puckered boat form. Nuclear magnetic resonance and X-ray diffraction studies have been utilized to assign conformation in solution and the solid state, respectively. Thus, cyclo(L-Ala-L-Ala) has been shown to adopt a boat conformation (31). If another ring is fused to the piperazinedione, as in the case of cyclopeptides containing proline, then the boat conformation (32) is preferred. If an aromatic side chain is present, then the aromatic ring prefers to adopt a folded conformation over the piperazinedione ring

as in (33), resulting in the shielding of the *cis*-disposed glycyl hydrogen atom.

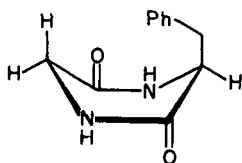
This forms the basis of a strategy to distinguish between the enantiotopic methylene groups of 1-amino-cyclopropane-1-carboxylic acid (ACC) by incorporating this amino acid into a cyclodipeptide (34) along with L-phenylalanine (85JOC4796). The benzyl group does exert a shielding effect on the L-methylene group of ACC. This results in an upfield shift of the relevant hydrogen atoms and a downfield shift in the ^{13}C resonance. Similarly in the α -aminoisobutyric acid-containing cyclodipeptide, cyclo(Aib-L-Phe), the ^1H -NMR spectrum indicates an upfield shift of one of the methyls; the corresponding ^{13}C resonance is shifted down field.



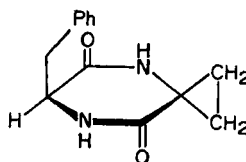
(31)



(32)



(33)



(34)

In cyclo(L-Pro-L-Phe), there could be a conflict between two opposing forces: the attraction between the piperazinedione ring and the phenyl ring, which results in the folding of the aromatic ring over the hetero ring (axial orientation as in 33), and the propensity of the fused bicyclic system to orient the $\text{C}^\alpha\text{—C}^\beta$ bond of the proline residue equatorially as in (32). This dichotomy has been studied in the case of cyclo(D-phenylalanyl-*trans*-4-fluoro-D-prolyl) by X-ray and NMR determinations (90MI2). In the solid state, the molecule adopts a puckered chair form, but in solution, the typical boat conformation with the equatorial $\text{C}^\alpha\text{—C}^\beta$ bonds in both aminoacid residues, precluding the folding of the aromatic residue above the piperazinedione.

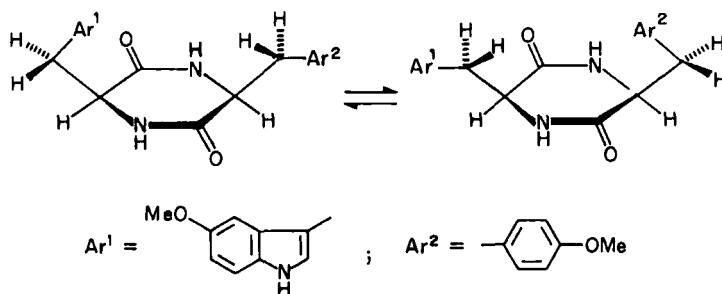
Other cyclodipeptides incorporating a proline and another aliphatic amino acid possessing a *tert*-butyl group have been investigated by Blaha and co-workers (87CCC2295). The *t*-butyl group helps to flatten the boat conformation of the piperazinedione ring.

The conformation of *cis* and *trans* cyclodipeptides incorporating a histidine unit and either leucine or valine has been investigated by NMR and CD spectroscopy. Here the imidazole ring stacks over the piperazinedione ring; in the *trans* cyclodipeptides, cyclo(D-Leu-L-His) and cyclo(D-Val-L-His), the two side chains are on opposite sides of the nearly planar piperazinedione ring. In the *cis* cyclodipeptides, viz, cyclo(L-Leu-L-His) and cyclo(L-Val-L-His), the two side chains compete for the space on the same side of the central boat-like ring (77MI1)

The conformation of cyclodipeptides containing two nonidentical L-aromatic amino acid residues has been addressed recently [90JCS(P2)127]. In such cases, it may be possible to assess the relative strength of the attractive interaction between the piperazinedione ring and the different aromatic groups by NMR studies. On the basis of detailed analyses, the author has concluded that in the case of cyclo[L-5(MeO)Trp-L-Tyr(Me)], a fast conformational equilibrium exists between the two folded-extended conformers (Scheme 10) above room temperature in DMSO and *N,N*-dimethyl formamide (DMF) solutions.

Analogues of cyclo(Phe)₂, with a larger aromatic moiety than phenyl have been prepared and their conformation has been studied. With 1- and 2-naphthyl groups it was found that the central hetero ring was nearly planar and the folded-extended (unsymmetrical) side-chain conformation was the most populated (86BCJ2195). However, when the 9-anthryl analog was studied, it was found that both side chains preferred the extended conformation, probably because of steric bulk (86BCJ3175).

Finally, cyclodipeptides in which both the amino acid units have aliphatic side chains have also been investigated (83BCJ1155). In the case of the *cis* cyclodipeptides, cyclo(L-Val)₂ and cyclo(L-Leu)₂, the hydrophobic interaction between the two side chains may stabilize the planar-axial or the flagpole-boat-type conformation, respectively, in polar solvents.



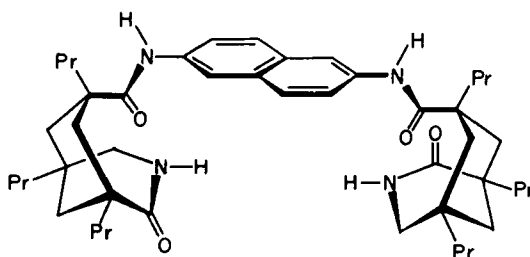
SCHEME 10

The possibility of deriving useful information on the conformation of cyclodipeptides from the coupling constants $^{15}\text{N}-^1\text{H}$, $^{13}\text{C}-^1\text{H}$, and $^{13}\text{C}-^{15}\text{N}$ in isotope-labeled molecules has been discussed (82MI1).

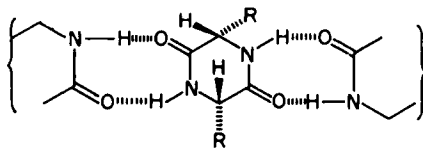
B. HYDROGEN BONDING AND MOLECULAR RECOGNITION

As explained in a later section (Section VII) cyclodipeptides, especially those containing histidine residues, have been used as synthetic enzyme mimics. Three different aspects of the cyclodipeptide molecular architecture have been made use of in achieving those results: (a) H-bond formation with one of the NH groups of the piperazinedione; (b) stacking of the aromatic ring over the hetero ring due to weak attractive forces, and (c) hydrophobic interactions with aliphatic side chains.

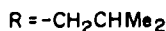
Chiral recognition based on multiple hydrogen bond formation with cyclodipeptides has been most impressively demonstrated by Rebek and his group (90JA6144). The host molecule (35) and its enantiomer were synthesized and their binding with cyclo(L-Leu)₂ was studied. It was found that there was a 100-fold enantiomeric recognition corresponding to a $\Delta\Delta G$ of nearly 2.5 kcal/mol. This enormous difference has been explained as being due to the formation of four hydrogen bonds in the complex (part structure 36).



(35)



(36)



Attempts are also being made to design more efficient recognition systems based on cyclodipeptides. The two different recognition sites of

cyclodextrin and a cyclodipeptide have been assembled together in cyclo(L-His-L-His)-capped β -cyclodextrin (91CC293). The compound was prepared by condensing cyclo (L-His-L-His) with 6-deoxy-6-iodo- β -cyclodextrin. In the resultant product, the piperazinedione ring is placed almost perpendicular to the cyclodextrin cavity. The N-unsubstituted imidazole ring folds over the piperazinedione ring as expected. The ability of this product to coordinate metal ions is being determined.

IV. Reactivity of Piperazine-2,5-diones

A. REACTIVITY AT THE NITROGEN ATOMS

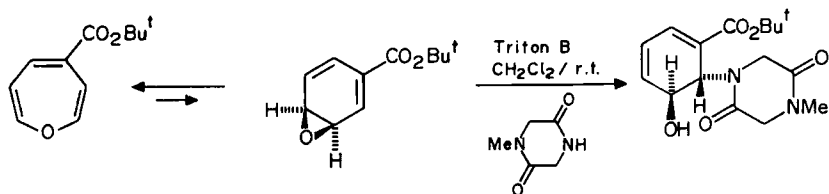
N-alkylation and N-acylation of piperazine-2,5-diones are quite common and have been routinely employed in several synthetic sequences (see Section IV,C). Such operations have also been performed as measures for the temporary protection of the nitrogen during further synthetic maneuvers in other parts of the molecule. Three different alkyl groups have been employed as such protecting groups. Kishi has used the methoxymethyl group for N-protection (potassium *t*-butoxide, chloromethyl methyl ether 0°C, 75% yield). Deprotection was achieved by conc. HCl-ethanol at reflux temperature (81T2045).

Methylthiomethyl has been used as the protecting group in the total synthesis of neoechinulin A (80TL2817). Cyclo(L-Ala-Gly) was treated with sodium hydride in DMF and N-alkylated with chloromethyl methyl thioether at room temperature, to give the bis(methylthiomethyl) derivative. After further chemical transformations, deprotection was achieved by treatment with methyl iodide in the presence of NaHCO₃ at 40°C for 3 days, followed by heating in dioxane at 100°C for 1 h.

Yoshimura has introduced the *p*-methoxybenzyl group for N-protection in piperazine-2,5-diones (83CL1001; 85BCJ1413). The N-alkylation is carried out with sodium hydride and *p*-methoxybenzyl bromide in DMF at room temperature. Deprotection is achieved by ceric ammonium nitrate (CAN) in acetonitrile-water.

N-alkylation by Michael addition followed by ring opening of an epoxide has been used as the strategy for incorporating the dihydrobenzene unit of gliotoxin (81T2045). The trick was to use 4-carbo-*t*-butoxyoxepin as the masked epoxide; the product formed was exclusively the *trans* isomer (Scheme 11).

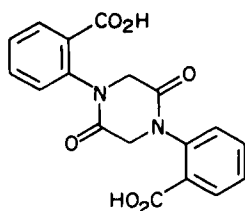
N-arylation has been used as the first step in several syntheses of complex molecules. The Ullmann-type reaction of 2-iodo-3-methoxybenzoic acid with 1-methylpiperazine-2,5-dione forms the basis of Kishi's total synthesis of dehydrogliotoxin (81T2045) (Scheme 12).



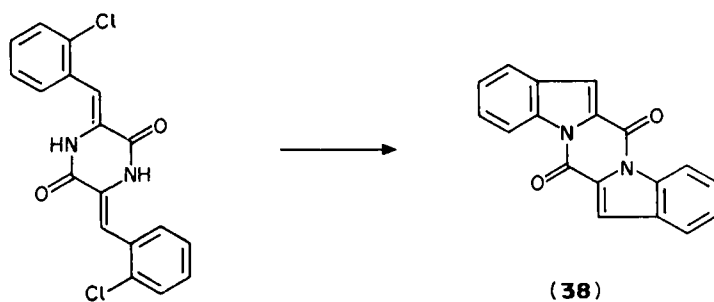
SCHEME 11

N-arylation has also formed the basis of the synthesis of analogs of aranotins (77JOC948). In this case, the *N,N*-bis-arylated product (**37**) has been obtained in 32% yield from piperazine-2,5-dione (Cu_2I_2 , K_2CO_3 , CH_3CN).

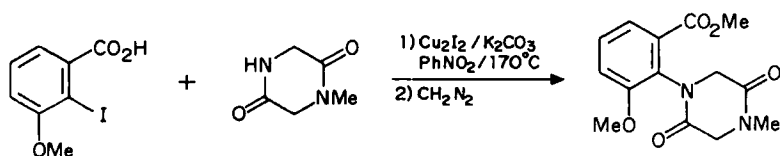
An intramolecular variant of the N-arylation reaction has led to the pentacyclic compound (**38**) (Cu_2Cl_2 , K_2CO_3 , diglyme).



(37)



(38)



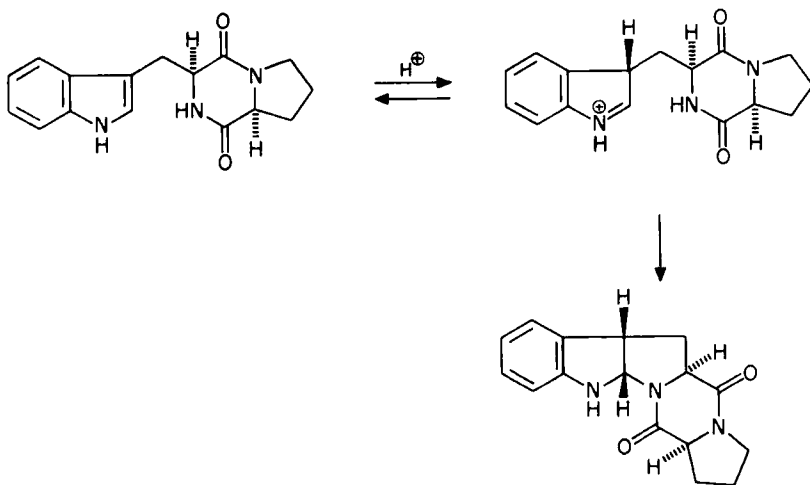
SCHEME 12

Cyclizations involving bond formation between N-1 of the piperazinedione and C-2 of the indole ring of tryptophan have been reported. A few cyclodipeptides incorporating tryptophan have been shown to undergo cyclization in acid medium. The mechanism probably involves initial β -protonation followed by addition of the piperazinedione to the iminium ion (85CPB4783) (Scheme 13).

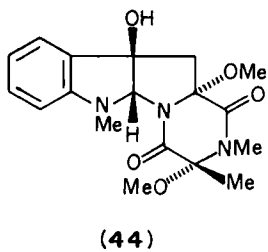
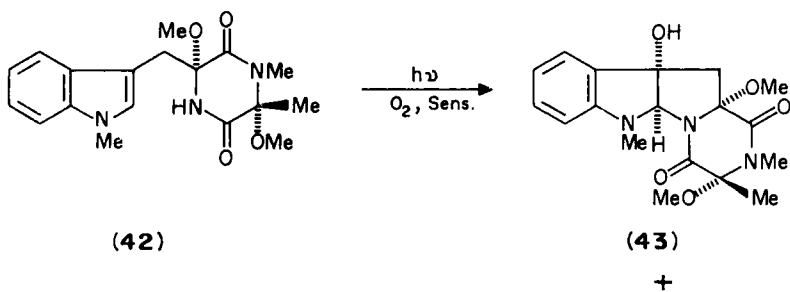
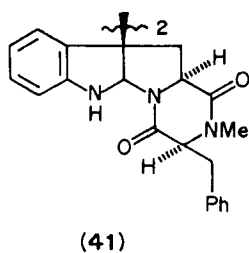
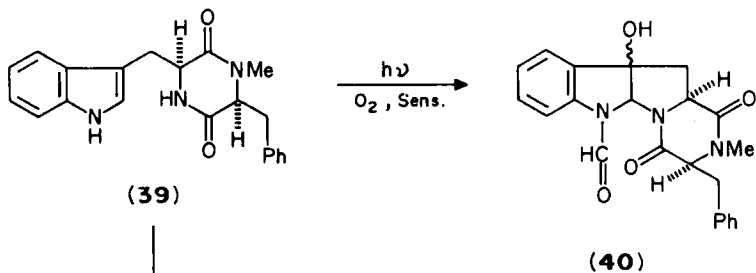
Oxidative cyclizations of cyclodipeptides incorporating tryptophan have also been reported (81TL5323). Thus, irradiation of the piperazinedione (**39**) in formic acid in the presence of a sensitizer such as proflavine or chloranil gave the hydroxypyrroloindole (**40**). Oxidation with thallium (III) trifluoroacetate gave the dimer (**41**) in 3% yield.

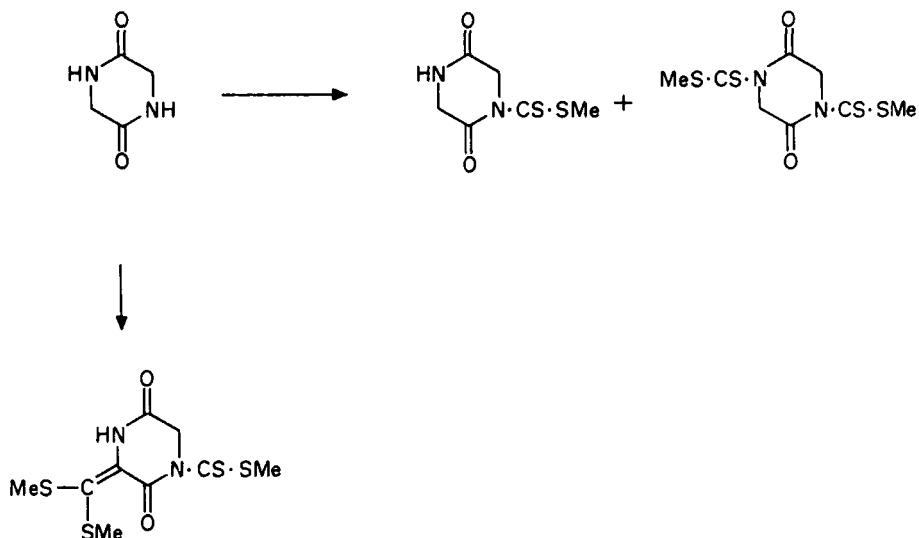
Similar oxidative ring closures by singlet oxygen (methylene blue as sensitizer, -78°C) have also been reported by Dutch workers [87JCS(P1)-2481]. For instance, (**42**) gave a mixture of the two diastereomers (**43**) and (**44**).

In piperazine-2,5-dione itself, both the nitrogen and the carbon C-3 can function as nucleophilic centers. The exact site of the reaction might sometimes depend on the solvent used. Thus treatment with carbon disulfide in dimethylacetamide, followed by methylation, gave only the products of reaction at nitrogen. But in DMSO containing tetrahydrofuran, the C-alkylated product was obtained in 32% yield [79JCS(P1)692] (Scheme 14). Similarly, reaction with 2-formylbenzoic acid has given products (**45**, **46**) by reaction at both nitrogen and carbon (82AJC2567).

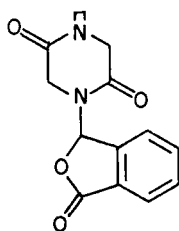


SCHEME 13

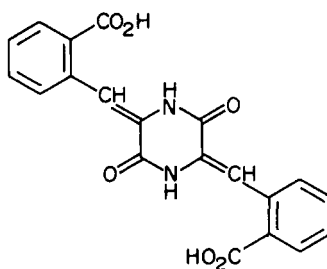




SCHEME 14



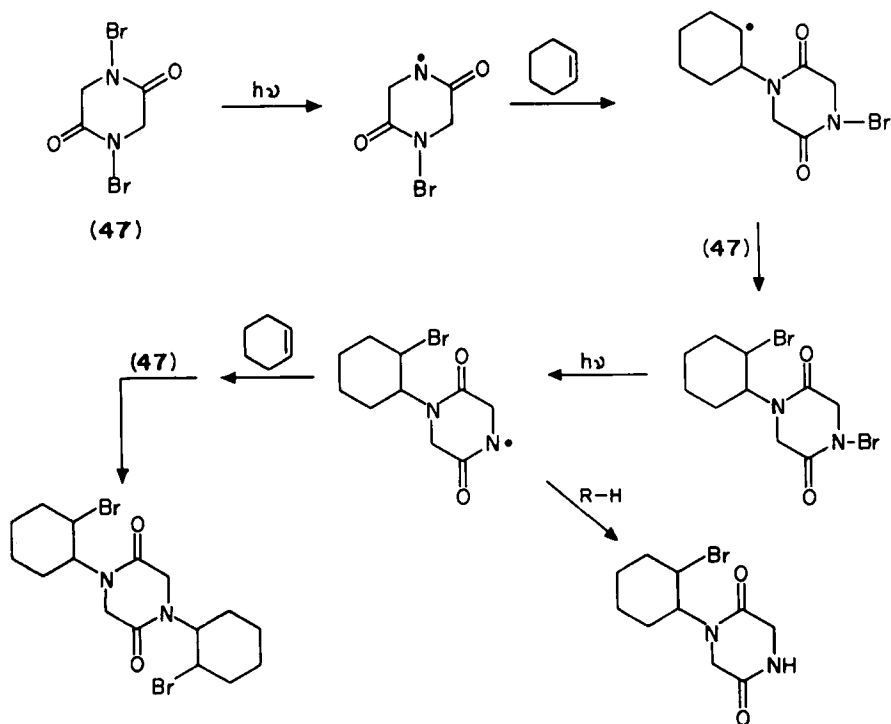
(45)



(46)

The photo-induced addition reaction of 1,4-dibromopiperazine-2,5-dione with several alkenes has been studied (80BCJ219; 83BCJ1705; 86BCJ479). In acetonitrile, the reaction with cyclohexene occurs by a radical chain mechanism as shown in Scheme 15 (in a sequence of reactions).

In the reaction with 3,4-dihydro-2H-pyran, a concomitant ionic process may also be operative.



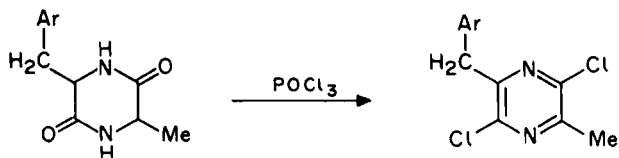
SCHEME 15

B. TRANSFORMATIONS AT C-2 AND C-5

The CO—NH units in piperazine-2,5-diones can be converted to lactim ethers. Such conversions and the reactivity of such lactim ethers are discussed separately in Section V.

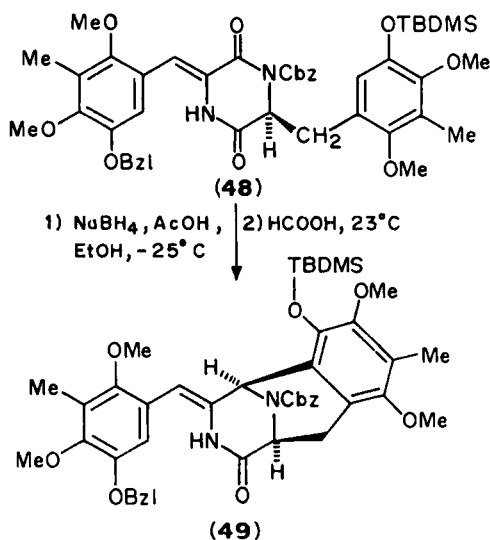
Piperazine-2,5-diones can be converted to the corresponding dithiones by treatment with phosphorus pentasulfide in pyridine. A series of such piperazine-2,5-dithiones has been synthesized and their IR and NMR spectral characteristics have been determined (74BAP115, 74BAP253).

Treatment of piperazine-2,5-diones, unsubstituted on the nitrogen atoms, with phosphorous oxychloride results in chlorination with simultaneous aromatization by loss of two hydrogen atoms [82JCS(P1)953] as shown in Scheme 16.



SCHEME 16

Nucleophilic attack by an electron-rich aromatic ring on an acyliminium ion has been the strategy employed for generating the heterocyclic ring framework of saframycin A and B. The essential principle is to activate the C-2 carbonyl by further acylation of N-1, thus generating an imide system and then to selectively reduce the carbonyl at position 2 to the carbinolamine; subsequent acid treatment leads to the acyliminium ion, which cyclizes spontaneously (82JA4957; 87H1765; 88CPB2607). The reduction can be carried out by lithium tri-*tert*-butoxyaluminumhydride in THF or sodium borohydride in acetic acid. Thus reduction of the 1-benzyloxycarbonyl-3-arylidene-6-arylmethylpiperazine-2,5-dione (**48**) with sodium borohydride in acetic acid and ethanol at -25°C followed by treatment with formic acid generated (**49**) in greater than 75% yield (90JA3712).



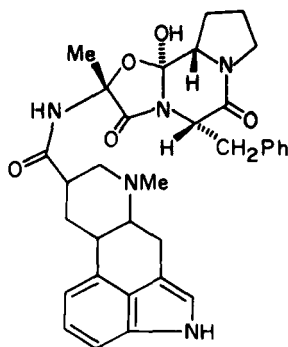
TBDMS = $-\text{SiMe}_2\text{Bu}^t$;

Cbz = $\text{PhCH}_2\text{OCO}-$;

Bzl = PhCH_2-

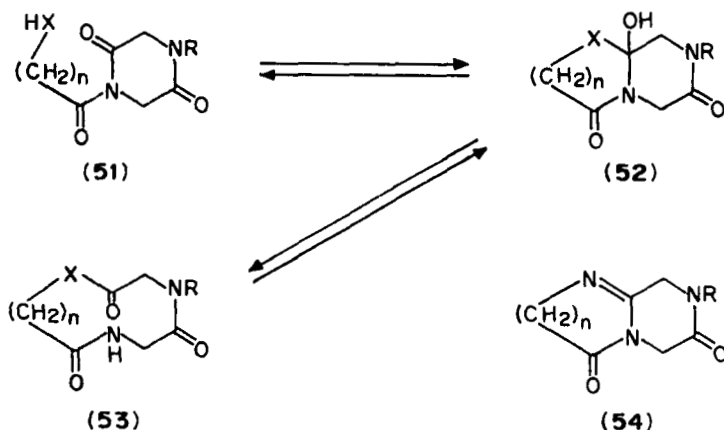
Complete reduction of the carbonyl groups of piperazine-2,5-diones to methylenes has also been reported. This procedure can lead to useful optically active piperazines. Thus, the cyclodipeptide cyclo(L-Phe-L-Phe) was reduced by lithium aluminium hydride (LAH) in ether to (2*S*, 5*S*)-dibenzylpiperazine in 66% yield [81ZN(B)578]. Similarly, the 1,4-dimethyl derivative has also been reduced by LAH (81TL5257). More recently it has been shown that several cyclodipeptides can be cleanly reduced to the corresponding chiral piperazines by an excess of borane/tetrahydrofuran (85JOC4909). Stepwise reduction of the piperazine-2,5-diones has been effected by employing sodium borohydride and acetic acid (1 eq : 1 eq), which led to piperazine-2-one (49%) and piperazine (31%). The structure of the former was confirmed by COSY-NMR (91JHC1219).

Cyclols: Stable molecules obtained by the addition of a heteroatom nucleophile to the carbonyl group of lactams are not very common. The side-chain moiety of the ergot alkaloids (e.g., **50**) is one of the earliest examples of such a cyclolic structure (75FOR51) identified. This has given rise to a number of studies on the synthesis and chemical transformations of such units. The discussion below is confined to cyclols related to or arising from piperazine-2,5-diones.



(50)

The chemistry of cyclols was first investigated systematically by Shemyakin and his group. The concept involved in the synthesis and use of such cyclols has been lucidly discussed by the Russian group in a classic paper (65T3537). The carbonyl group of the piperazinedione moiety can be activated toward nucleophilic attack by N-acylation. If the attacking nucleophile is part of the side chain of the piperazinedione, then a cyclol (**52**) results. This cyclol can then open out to form a macrocyclic peptide, depsipeptide, or thiodepsipeptide (**53**; Scheme 17). When the attacking nucleophile is an NH_2 , the cyclol can also lose water to form an amidine



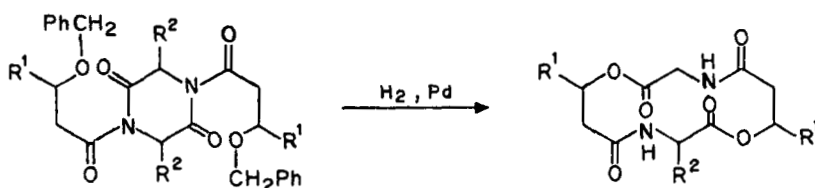
SCHEME 17

(54). The final product isolated or the position of the equilibrium in a particular solvent depends on the length of the side chain, the ring size of the macrocycle, and the polarity of the solvent chosen. Infrared spectroscopy has been extensively used to study this aspect.

Cyclol formation on both carbonyl groups of the piperazinedione has been utilized for the synthesis of cyclotetradepsipeptides (Scheme 18). This strategy has been employed in the synthesis of serratamolide.

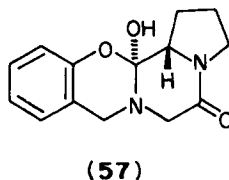
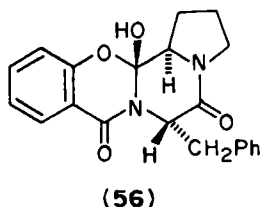
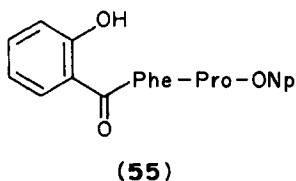
Swiss workers have utilized this methodology for the synthesis of several ergot alkaloids (69HCA1549; 70HCA1278).

Cyclization of the dipeptide and cyclol formation can be carried out in a single step (90M11). The substrate in this case was the *p*-nitrophenyl ester (-ONp) of *N*-salicyloylphenylalanylproline. Treatment of this active ester (55) in benzene solution with DBU gave the oxacyclol (56) in 40% yield. It has been shown that this involves cyclization to the piperazinedione, epimerization of the proline C- α H and then cyclol formation. The ^{13}C -NMR spectrum of the product shows only two carbonyl signals; in addition, there is a signal at 102.3 δ ascribed to the quaternary carbon

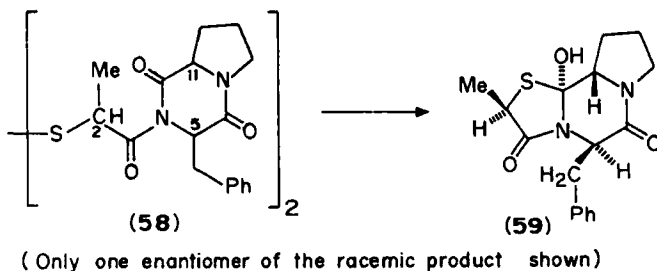


SCHEME 18

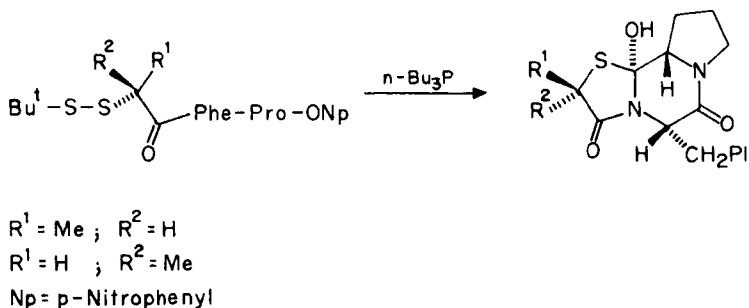
bonded to three heteroatoms. Similar cyclization of salicyloylglycylproline *p*-nitrophenyl ester leads to the formation of the cyclol (**57**) having the *trans* geometry between the C— α H and the C—OH, with partial racemization. The quaternary cyclolic carbon resonates at 102.12 δ in this case. These cyclols do not show any tendency to isomerize to the macrocyclic lactones.



Thiacyclols have been extensively investigated since 1968, when Rothe and Steinberger first demonstrated the formation of such compounds [68AG(E)884]. A thiacyclol related to the peptide portion of the ergot alkaloids (**50**) has been prepared [80JCS(P1)1499]. The disulfide (**58**) (racemic; 2*S*, 5*S*, 11*R* and 2*R*, 5*R*, 11*S*) was reduced with sodium borohydride in DMF at 0°C, to give the racemic thiacyclol (**59**) in good yield.



The proline-containing tricyclic system similar to the unit present in the ergot alkaloids, seems to be particularly efficient in stabilizing the cyclol structure. This is probably due to the conformational rigidity pro-

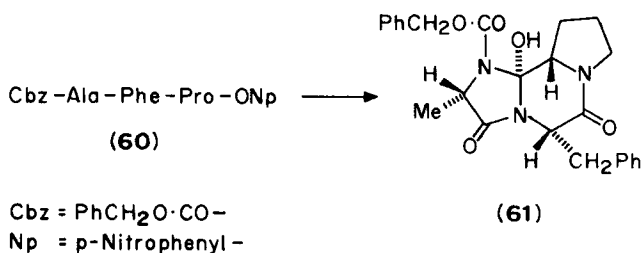


SCHEME 19

vided by the fusion of the three rings. The structure and stereochemistry of (**59**) have been confirmed by an X-ray crystallographic analysis. As expected, the ^{13}C -NMR spectrum showed only two carbonyl signals ($\delta 173.7$ and $\delta 167.2$), but also a singlet at $\delta 91.4$ for the quaternary cyclic carbon atom.

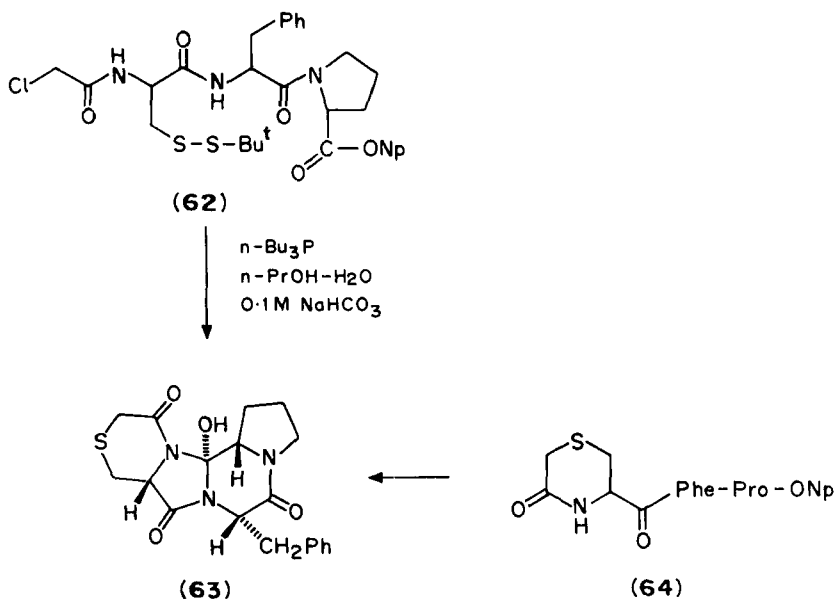
The pure thiacyclopentane incorporating the *cis* cyclodipeptide structure have been subsequently prepared by mild double cyclization of the corresponding linear precursors [84JCS(P1)1153] (Scheme 19).

Azacyclopentane arising from amide–amide interaction have been extensively investigated. The *p*-nitrophenyl ester (**60**) of the linear tripeptide *N*-benzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-proline undergoes a double cyclization when left in an aqueous buffer–dioxane (1 : 1) solution for 1 h, to produce cyclol (**61**) (71CC1605). The hydroxyl group of the cyclol could be converted to the methyl ether by treatment with methyl iodide–silver oxide. The structure of the cyclol (**61**) could be confirmed by X-ray crystallography of the corresponding *p*-bromobenzyloxycarbonyl derivative (71CC1607).

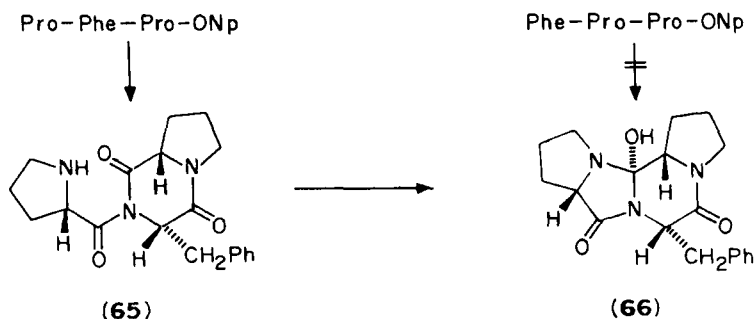


The importance of the rigid tricyclic framework for the formation and stability of the cyclol has been examined by the Italian group. Cyclization of a similar tripeptide derivative containing cysteine as N-terminal residue

has also given a cyclol (85TL5481). Thus, the *N*-chloroacetyl derivative (62) of the *S*-protected tripeptide active ester, on unmasking the thiol function, gave the tetracyclic compound (63). The same cyclol (63) has been obtained in 70% yield by cyclization of the thiamorpholine derivative (64) [88JCS(P1)2647].

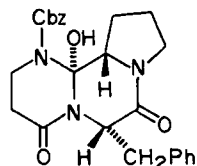


A tetracyclic azacyclol (66) has been obtained from the *p*-nitrophenyl ester of the linear tripeptide prolylphenylalanylproline (81TL3671). However, the tripeptide active ester Phe-Pro-Pro-ONp with an altered sequence did not lead to the cyclol (66). This suggests that in the former reaction the piperazinedione (65) is an intermediate (Scheme 20).



SCHEME 20

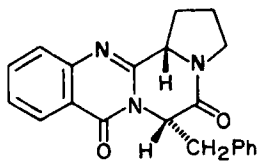
In the above examples, the quaternary cyclolic carbon is located at the junction of a 5-membered and a 6-membered ring. However, when attempts were made to create a stable cyclol with two 6-membered rings [$n = 2$, in structure (52)], the cyclization either did not occur, or led to further transformation products. Thus, cyclol (67) could not be obtained from the *N*-protected linear tripeptide active ester Cbz- β -Ala-Phe-Pro-ONp, incorporating a β -amino acid [82JCS(P1)1311]. Cyclization of the same sequence having a free NH_2 at the *N*-terminus gave the cyclotripeptide (68) with a 10-membered ring.



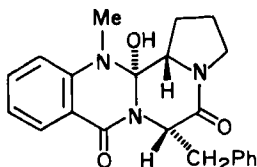
(67)



(68)



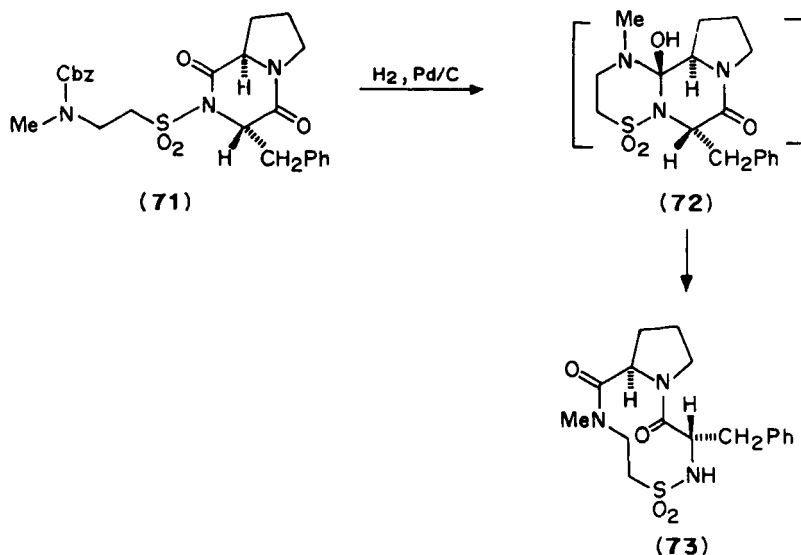
(69)



(70)

Incorporation of anthranilic acid at the *N*-terminus instead of β -alanine, led to the amidine (69). Finally, the cyclol (70) was obtained in 33% yield from the analog having *N*-methylantranilic acid; this reaction also gave the 10-membered cyclotripeptide in 17% yield (84TL5201).

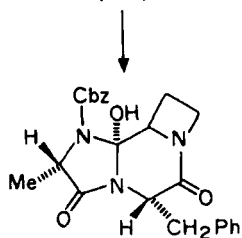
A similar result was obtained when the piperazinedione carried an *N*-sulfonyl group. Thus deprotection of the *N*-carbobenzoxy taurine derivative (71) of cyclo(Phe-D-Pro) led to the 10-membered cyclic compound (73) via the cyclol (72) (89MI1).



In order to check the role of proline at the C-terminus, linear tripeptides with other imino acids at that position have been subjected to cyclization. Both (74) and (76), the former having L-azetidine-2-carboxylic acid, and the latter sarcosine, gave the respective cyclols (75) and (77). The difference is that (75) can be dissolved in alkali and regenerated by acidification, whereas (77) is isomerized to the *N*-acylpiperazinedione and hydrolyzed under these conditions (78TL1009).



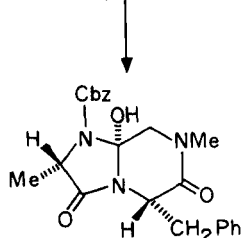
(74)



(75)



(76)



(77)

C. REACTIVITY AT C-3 AND C-6

1. *Base-Catalyzed Equilibration*

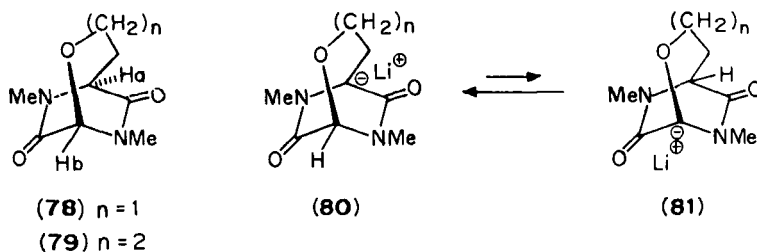
Cyclic dipeptides, especially when N-alkylated, undergo extremely fast epimerization (79JA1885). For example, cyclo(L-Pro-L-Phe) is rapidly converted to its diastereomer, cyclo(D-Pro-L-Phe) (80% conversion), by treatment with 0.5 *N* NaOH at 25°C for 15 min. This diastereomer is the one in which the proline residue has epimerized and not the more activated phenylalanine. CNDO/2 calculations seem to provide a rationale for this. It is not yet completely clear why such base-catalyzed epimerizations of piperazinediones are so easy; the conformation of the molecule may play a role in this (79MI1). It is also worth noting that even in linear peptides, *tert*-amides of *N*-alkyl-amino acids, which consist of *s-trans* and *s-cis* rotamers of almost equal energy, are more prone to racemization than the *sec*-amides, which exist only in the *s-trans* configuration. Of course, the amide functions of piperazine-2,5-diones are obliged to assume the *s-cis* conformation.

Several cyclodipeptides have been subjected to base-catalyzed epimerization (EtOH/NaOEt at 30–75°C) and the ratio of *cis*-to-*trans* isomers at equilibrium has been determined (74JA3985). The results have been correlated with the conformation of the molecules. Thus, cyclo(Pro-Pro) NMR studies (73JA6142) have indicated a boat form in the *cis* and a planar form in the *trans* diastereomer. In the latter, the pyrrolidine rings take up a half-chair conformation, which is greatly strained as long as the amide bonds are planar. This renders the *trans* less stable than the *cis* diastereomer. Consequently, at equilibrium, only *cis* diastereomer is found; the *trans* isomer occurs to the extent of less than 0.5%.

The situation is different with other cyclodipeptides. For cyclo(Pro-Ala), the *trans* isomer is predominant at equilibrium; for cyclo(Ala-Ala) nearly equal amounts of *cis* and *trans* are found. These results have also been sought to be rationalized on the basis of the conformation (78BSB627).

The relative kinetic and thermodynamic acidity of the two bridgehead methine protons of the bicyclic piperazinediones (**78**) and (**79**) has been evaluated (83JA3214). The authors have also addressed the interesting question of the structure of the carbanion formed, since an enolate structure would violate Bredt's rule. The coupling constant $J(^{13}\text{C}-^1\text{H})$ of the bridgehead positions for (**78**) and (**79**) indicate a larger value for C—H_b than for C—H_a. This suggests greater *s*-character for the former and hence greater kinetic acidity. Also, the magnitude of this coupling constant (144 to 169 Hz) indicates about 30% *s*-character, suggesting that this hybridiza-

tion effect may be largely responsible for the acidity of these protons and not the enolate resonance stabilization. However, rapid quenching of the carbanions generated from (78) and (79) by LDA leads to poor regiochemical control. Hence the kinetic acidity of H_a and H_b in these two are similar: in (78) H_a is more kinetically acidic than H_b and in (79), the reverse is the case. However, if quenching is delayed (1 h at -78°C), it is observed that the carbanions equilibrate, the equilibrium favoring the thermodynamically more favored carbanion (80). This effect can be dramatically enlarged by the addition of HMPA. This effect of the oxygen substituent to destabilize the adjacent carbanion in (81) is ascribed to electrostatic repulsion, which is enhanced by the separation of the Li^+ -carbanion ion pair by HMPA.

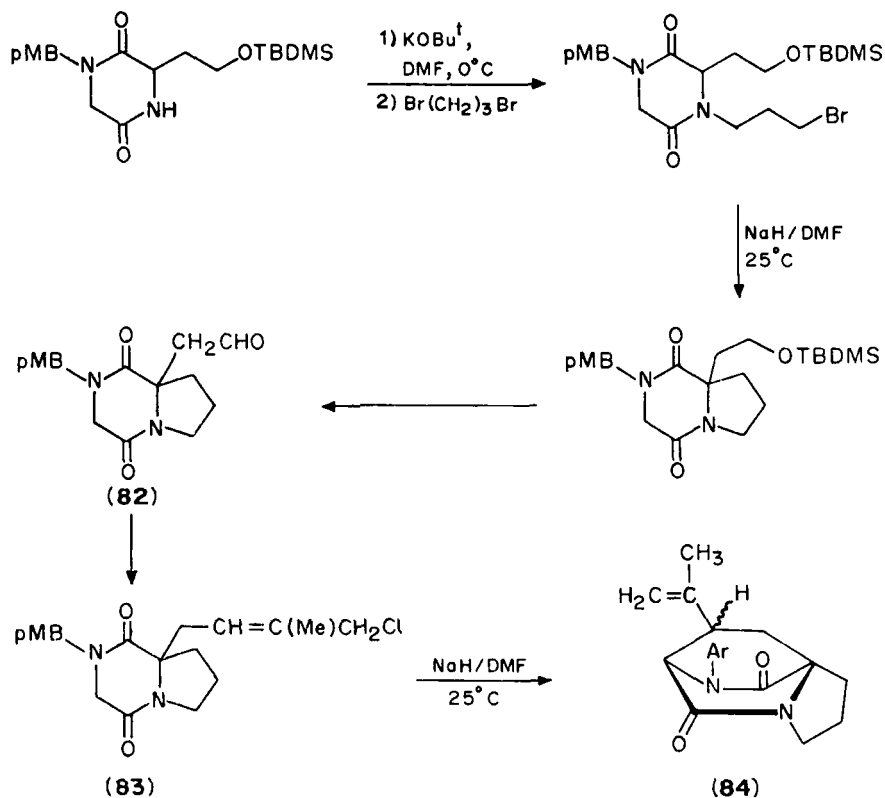


2. Alkylation

Direct alkylation of 1,4-disubstituted piperazine-2-5-diones often leads to poor yields of C-alkylated products (54JA1164). Thus, reaction of the enolate of 1,4-dimethylpiperazine-2,5-dione with α -bromo- γ -butyrolactone gave only a 9% yield of the desired product (85JA3246). However, intramolecular alkylation and alkylation at further activated positions have been successfully achieved and form part of multistep syntheses, such as those of brevianamide B and related molecules (86TL3581; 90JA808); Scheme 21 illustrates the salient alkylations, including the construction of a bicyclo[2.2.2] system involving an $\text{S}_{\text{N}}2'$ attack. The second alkylation leading to cyclization has also been carried out by using a Michael addition. Of the two possible conformers (A) and (B) of (83), (A) seems to be the predominant reactive one.

The alkylation of the remaining bridgehead position on the piperazinedione ring, however, gives rise to problems. Earlier, an intramolecular C-alkylation had been employed by Kishi for the construction of gliotoxin (81T2045). The crucial step is indicated in Scheme 22.

If C-3 on the piperazine-2,5-dione is further activated by another carbonyl group, alkylation can be carried out easily. Kametani has used

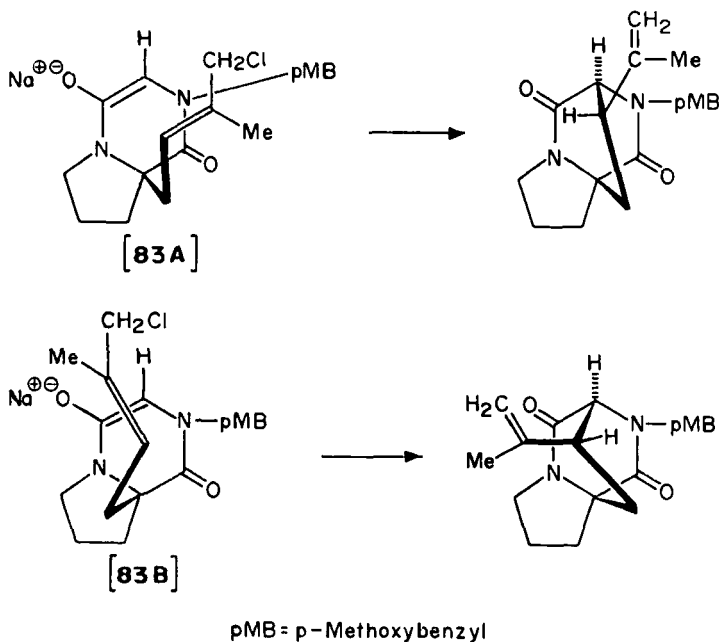


TBDMS = $-\text{SiMe}_2\text{Bu}^\text{t}$

SCHEME 21

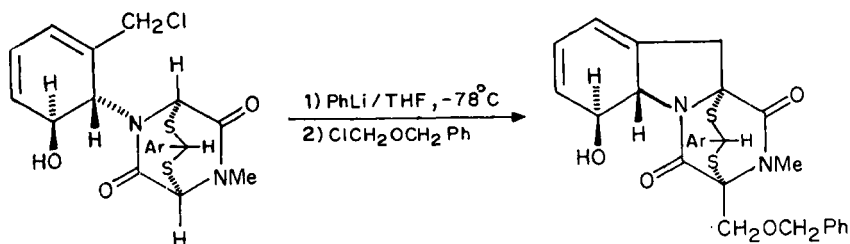
this strategy in his synthesis of deoxybrevianamide E (80JA3974). The electrophile in this case was a suitably substituted gramine. Surprisingly, the C-alkylation was achieved even in the presence of a free NH. The product was hydrolyzed and decarboxylated to give deoxybrevianamide E (Scheme 23).

The same strategy has been used by Williams (90JA808) in his synthesis of brevianamide B. The aldehyde (82), prepared enantioselectively from L-proline, was converted to the silyl ether. Acylation of this (BuLi , ClCO_2Me) gave the carbomethoxy derivative as a mixture of diastereomers, which was alkylated by gramine. As before, an enolate alkylation ($\text{S}_\text{N}2'$) on an allyl chloride derived from the above gave the tricyclic compound, which could be transformed to brevianamide B (Scheme 24).



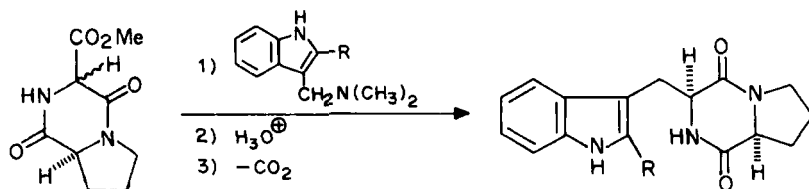
3. Aldol Condensation

The methylene groups at positions 3 and 6 of piperazine-2,5-diones are known to undergo facile condensation with aldehydes to form the corresponding α,β -unsaturated amides. Two earlier reviews have dealt with this subject. (75FOR51; 80FOR251). The review by Sammes covers the literature to 1972 on the synthesis, stereochemistry, and reactivity of



Ar = p-Methoxyphenyl

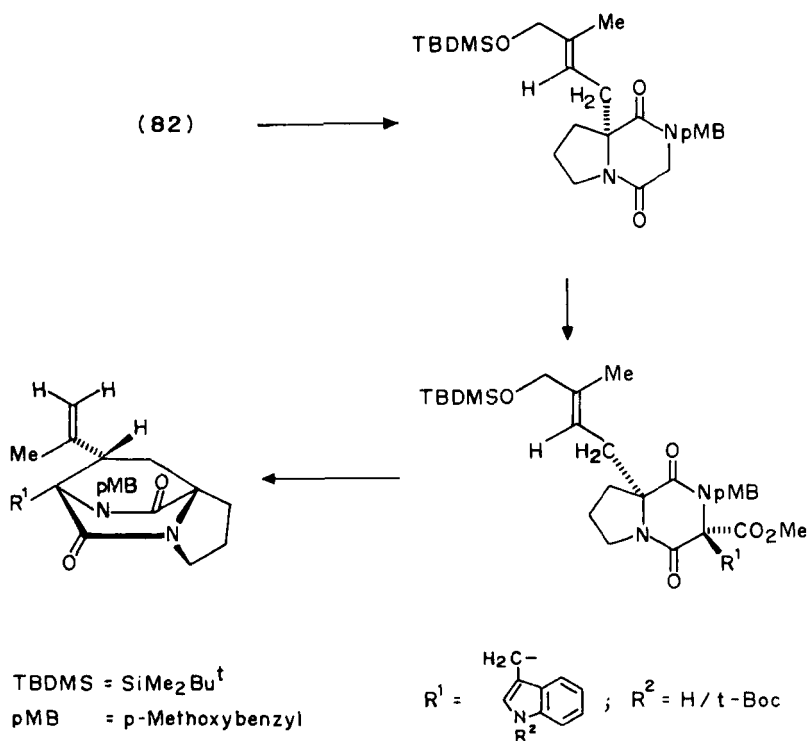
SCHEME 22



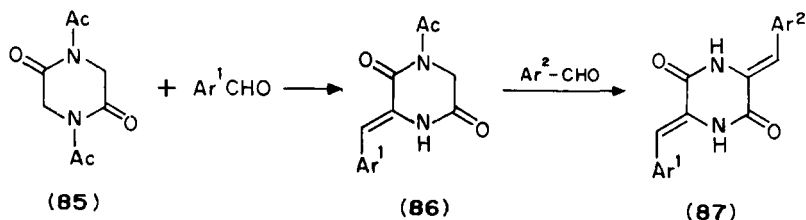
SCHEME 23

3-arylidene and alkylidene, and 3,6-bisarylidene and bisalkylidene derivatives. The second review covers literature to 1978.

It has been known since 1921 that piperazine-2,5-dione can be condensed with benzaldehydes to form benzylidene derivatives (21CB163). However, the reaction needs drastic conditions and fails with aliphatic aldehydes. Gallina and Liberatori have introduced a significant improvement that permits the control of the reaction with aromatic aldehydes to obtain the monoarylidene derivatives; it is also successful with aliphatic



SCHEME 24



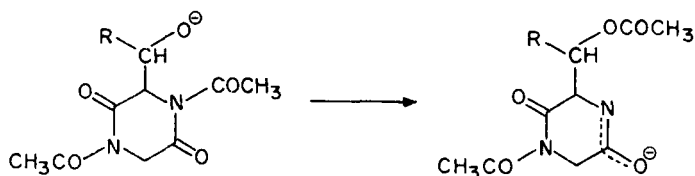
SCHEME 25

aldehydes (74T667). The modification consists in the condensation of aldehydes with 1,4-diacetylpiperazine-2,5-dione (**85**) in presence of a base. With triethylamine as the base, aromatic aldehydes can lead to either 1-acetyl-3-arylidene-4-acetylpiperazine-2,5-diones (**86**) or 3,6-bis-arylidene piperazine-2,5-diones (**87**), depending on the reaction conditions. This permits the synthesis of unsymmetrical bis-arylidene derivatives as shown (Scheme 25).

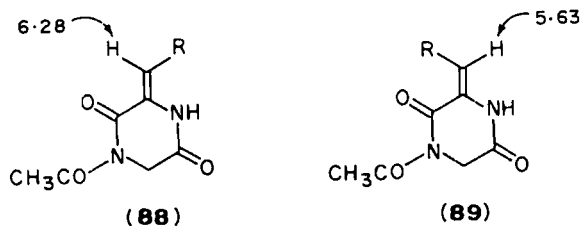
Aliphatic aldehydes react to form monoalkylidene derivatives only in presence of potassium *t*-butoxide. A mechanism has been postulated that also explains the observed N-deacetylation during the formation of the product. The essential step in this is the intramolecular N $\rightarrow$ O acetyl migration in the initially formed aldol. Subsequent protonation and elimination of the acetoxy group lead to the product (Scheme 26).

Earlier work had revealed [70JCS(C)980] that the 3-arylidene derivatives possess the *Z*-configuration. Gallina and Liberatori have confirmed this. In addition, they have isolated both *Z* and *E* alkylidene derivatives from condensation with aliphatic aldehydes. In the $^1\text{H-NMR}$ spectrum, the vinylic proton is deshielded by 0.65 ppm in the *Z* isomer (**88**) compared to the *E* isomer (**89**). Other workers have confirmed these observations [80JCS(P1)419].

It has been reported that KF/alumina is a useful catalyst for the condensation of 1,4-diacetylpiperazine-2,5-dione with aldehydes under microwave irradiation (90SC3325). High yields of the mono- or bis-arylidene derivatives having the *Z*-configuration have been obtained.



SCHEME 26

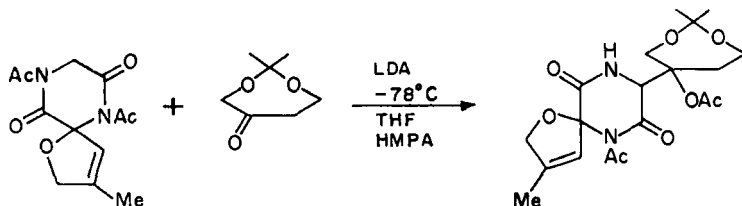


Although ketones are reported to give poor yields in such condensation reactions, Maag and co-workers have used this step in a synthesis of a rearrangement product of bicyclomycin (78JA6786). The route involves two successive aldol condensations, the first with an aldehyde and the second with a ketone; the latter step (Scheme 27) proceeds in 41% yield.

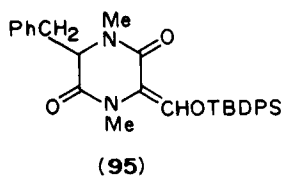
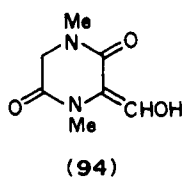
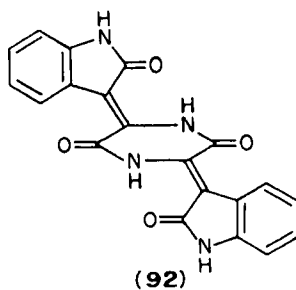
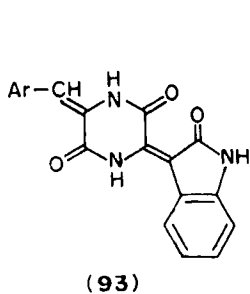
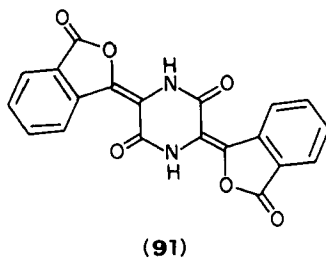
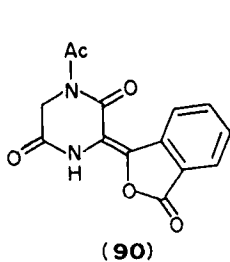
Katritzky and co-workers have made a systematic and thorough study of the reaction of 1,4-diacetyl-2,5-piperazinediones with various carbonyl compounds (88JHC591). The ^1H - and ^{13}C -NMR characteristics of the products have been tabulated. The condensation with aldehydes (DMF, triethylamine) could easily be controlled to occur stepwise; this led to the synthesis of unsymmetrical bisarylidene derivatives from monoarylidene precursors. Phthalic anhydride gave either the mono (90) or the bis condensation product (91), depending on the temperature of the reaction. Most interestingly, 2-chloroindol-3-one reacts with 1,4-diacetyl-2,5-piperazinedione or its monoarylidene derivatives at room temperature to give the indolyl derivatives (92, 93) as purple or red solids. The potential use of a compound of this color is being studied.

Formylation of 1,4-dimethylpiperazine-2,5-dione (ethyl formate, sodium methoxide) proceeds in nearly quantitative yield to give the hydroxymethylene derivative (94) (80JOC2625). The silyl enol ether of this has been benzylated at C-6 to give (95) in 80–97% yield.

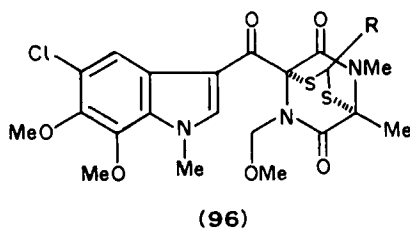
C-acylation with acid chloride has been used by Kishi in the synthesis of sporidesmin A (73JA6493). The carbanion from the appropriate piperazinedione (derived by treatment with butyl lithium) was reacted with the



SCHEME 27

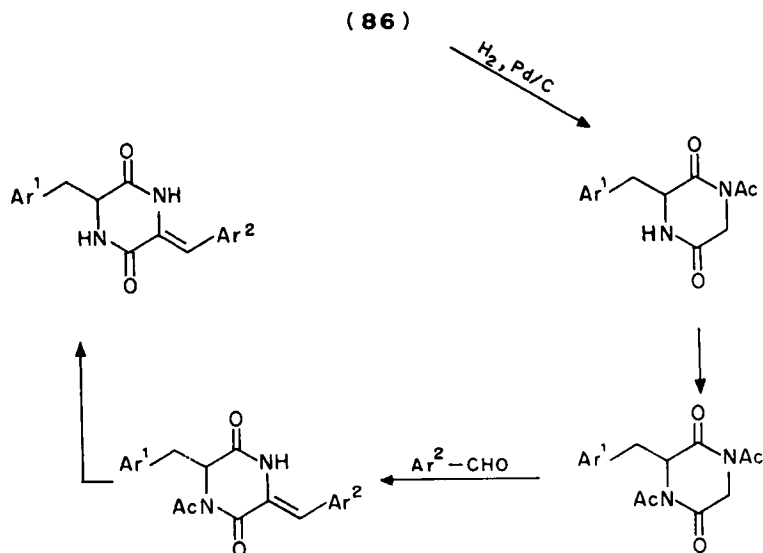


TBDPS = $-\text{SiPh}_2\text{Bu}^t$



substituted indole-3-carboxylic acid chloride at -110°C in THF to yield the acylated product (96) in 61% yield.

Japanese workers have devised a useful strategy for the synthesis of (Z)-3-arylidene-6-arylmethylpiperazine-2,5-diones (87CPB2525). The strategy is illustrated in Scheme 28.

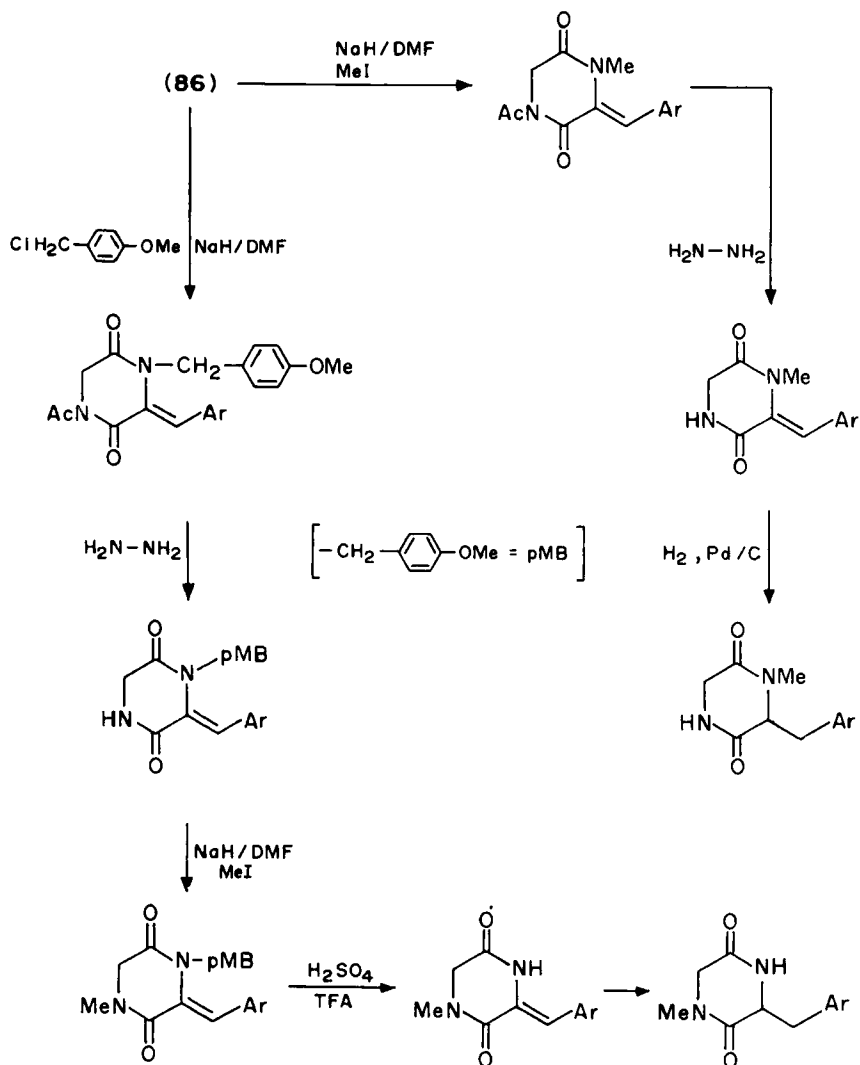


The entire gamut of N-alkylation protection, deprotection, aldol condensation, etc., is nicely brought out in the synthesis of isomeric 1- (or 4)methyl-3-arylmethyl-piperazine-2,5-diones from the same starting material (88CPB2607) (Scheme 29).

A strategy similar to that described above has been used for the total synthesis of saframycin A by Fukuyama and co-workers (90JA3712, 90TL5989). The aldol condensation has been extensively used in the synthesis of bicyclomycin (85JA3253; 83TL5627), neoechinulin A (80TL2817), etc. The X-ray structure and photoelectron spectra of cyclo(dehydro-Ala)₂ have been determined (85T2015).

4. Michael Addition

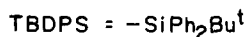
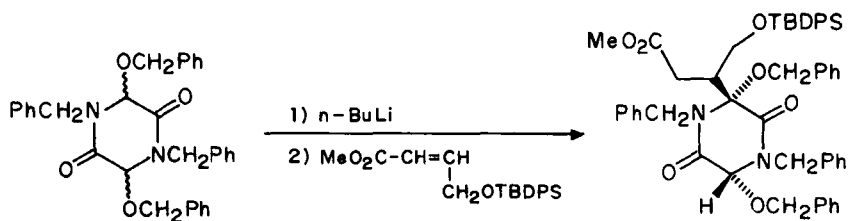
Position 3 of the piperazine-2,5-dione nucleus has been alkylated by Michael addition of the enol to a suitable acceptor. This route has been successfully utilized for the total synthesis of bicyclomycin (83TL5627). The addition proceeded stereospecifically to give only one product (Scheme 30).



SCHEME 29

5. Cyclopropanation

The 3-benzylidenepiperazine-2,5-dione (**97**) derived from L-proline and (Z)-2-methyl-4-benzylideneoxazolone has been converted to a pyrazoline by cycloaddition of diazomethane and then photolyzed to yield a

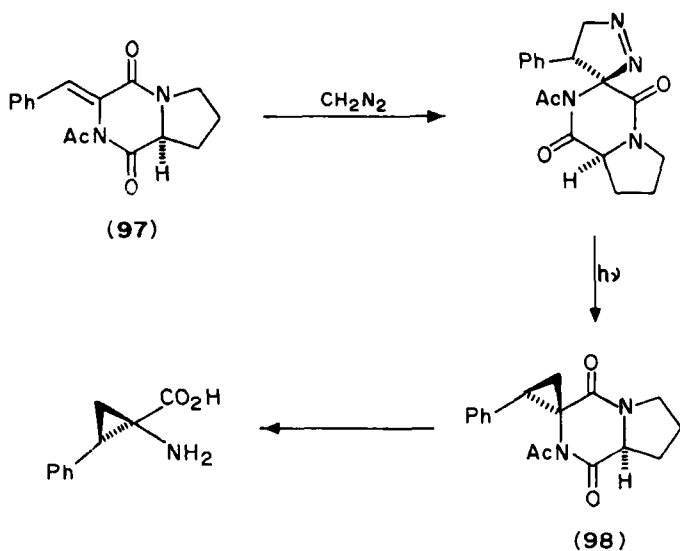


SCHEME 30

spirocyclopropane (**98**). Acid hydrolysis of this yielded (+)-1-amino-2-phenylcyclopropanecarboxylic acid (Scheme 31). Here L-proline acts as a chiral auxiliary, which can be recovered (89TL3101).

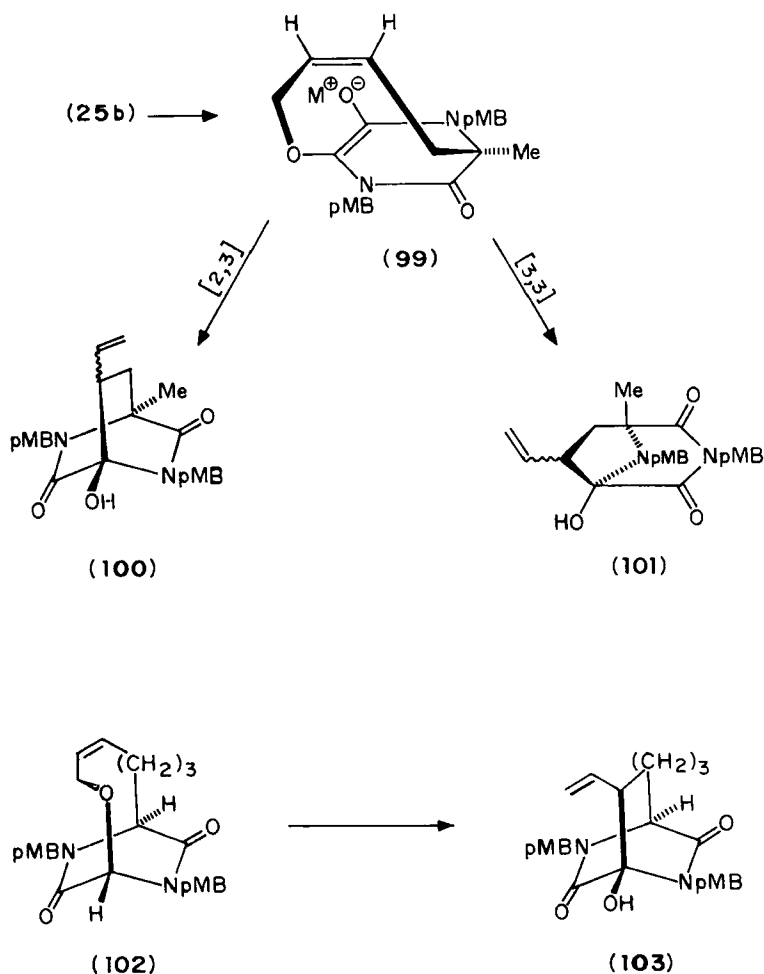
6. Intramolecular Rearrangement

An elegant method has been discovered to generate a bridgehead C—C bond through an intramolecular rearrangement of bicyclo derivatives having a C—O bond at the bridgehead (91JA6621). Generation of the thermo-



SCHEME 31

dynamically more stable bridgehead carbanion from the bicyclo derivative (25a) and methylation gives (25b). Treatment of (25b) in THF with *n*-butyllithium at -100°C followed by quenching with ammonium chloride gave two rearranged products (100) and (101). It has been suggested that the strained enolate (99) is the common intermediate for both: a [2,3] Wittig rearrangement can lead to (100), whereas a [3,3] Claisen rearrangement would give (101). Similarly, a [2,3] Wittig rearrangement on (102) (sodium hydride in dimethoxyethane at room temperature) gave (103) in 60–87% yield (Scheme 32).



SCHEME 32

7. 3-Thia- and 3,6-Dithia-piperazinedione Derivatives

The major impetus for the massive amount of research on the synthesis and reactivity of the 3-thia and 3,6-dithia derivatives of piperazine-2,5-dione has been the discovery of this moiety in several microbial metabolites of the gliotoxin group.

a. *Synthesis.* Three types of reactions have been attempted to introduce a sulfur substituent on the sp^3 carbon atoms of the piperazinedione ring [74JCS(P1)698]:

The nucleophilic route

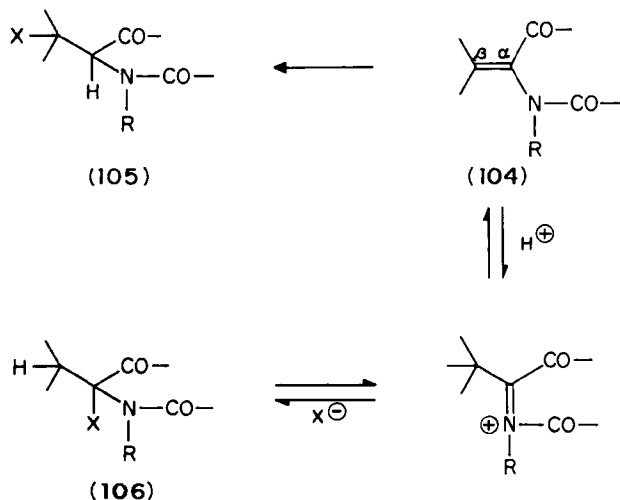
The electrophilic route

Direct cyclization route

Of these, the first two have been successful, whereas the last method has so far failed to lead to the desired product.

The nucleophilic route: In this method a sulfur nucleophile is made to react with an electrophilic species generated by suitable means from the piperazinedione. The method can therefore be subdivided into different classes, depending on the electrophile used.

Addition to iminium species: This constitutes a mild, general method for the introduction of a sulfur substituent [74JCS(P1)698]. The underlying principle is as shown in (Scheme 33). For the *N*-acyldehydro-amino acid system (104), β -addition prevails under weakly acidic, neutral, or basic

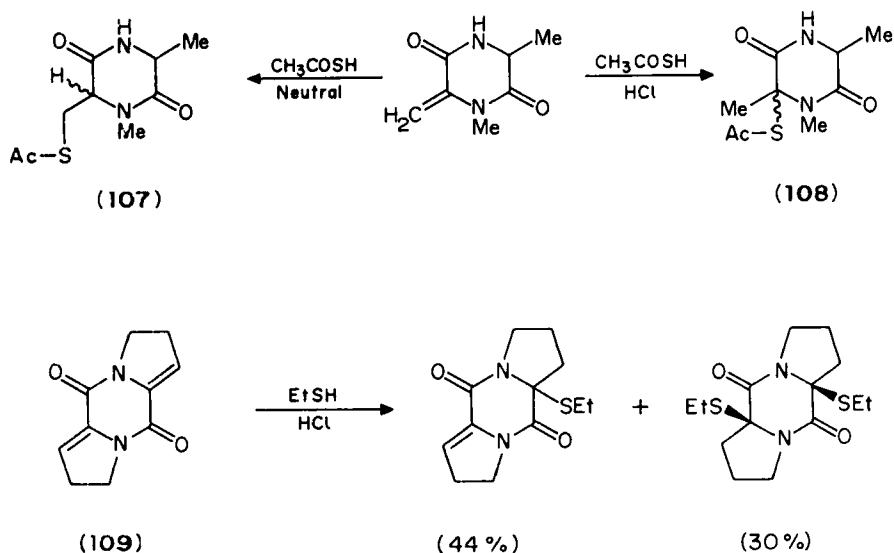


SCHEME 33

conditions, to produce the expected Michael adduct (**105**). In presence of strong acids, however, β -protonation is the first step (weak enaminic character of the enamide is responsible for this); subsequent reaction with nucleophiles leads to α -addition, giving the product (**106**) [73CI(L)324].

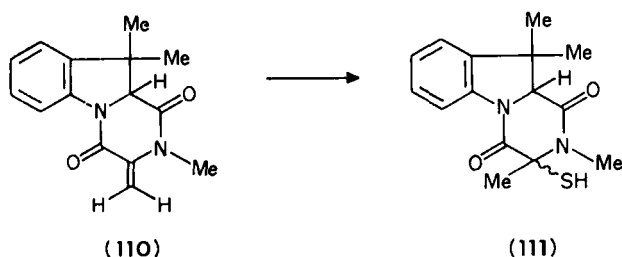
Thus, 1,3-dimethyl-6-methylenepiperazine-2,5-dione, on treatment with thiolacetic acid, gives 100% β -adduct (**107**), but the same reaction in the presence of a small amount of hydrogen chloride gives a quantitative yield of the two α -adducts having the structure (**108**). Even the bis-dehydropiprolone anhydride (**109**) gave similar results (Scheme 34), with both the mono-adduct (44%) and the bis adduct (30%) being formed. The latter had the two ethylthio groups *cis* to each other. The requisite dehydrocyclodipeptides were prepared from the monolactim ether (see Section V).

The basic premise that the sulfur nucleophile would add at the α -position only in the presence of a strong acid was subsequently modified by arguing that H_2S might be converted into a strong enough acid to catalyze this reaction by chelation with transition metal ions. This turned out to be a valid argument and led to the discovery of a versatile method for the synthesis of piperazine-2,5-diones bearing an SH group at position 3. The method involved treatment of the dehydrocyclodipeptide with liquid H_2S in presence of anhydrous ZnCl_2 at room temperature (76JOC3433). An



SCHEME 34

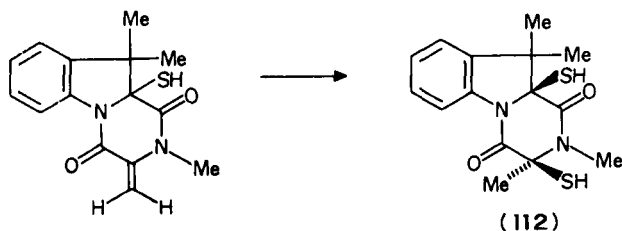
example is the quantitative conversion of (110) to (111) of unknown stereochemistry.



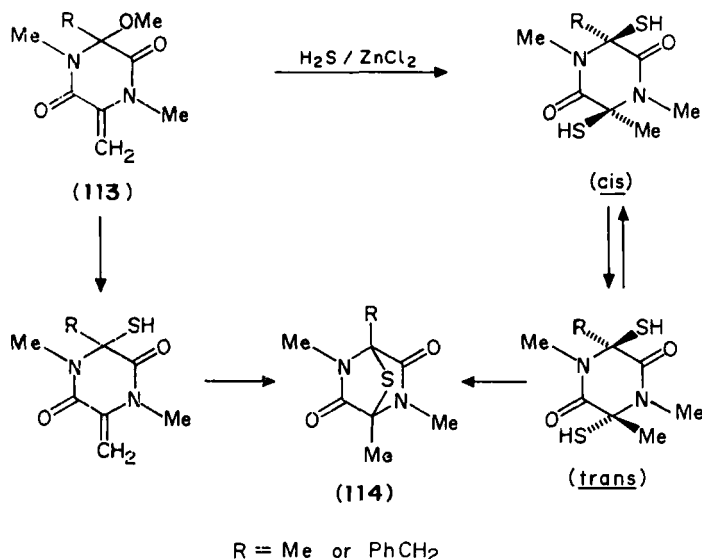
With a preexisting SH group at the 3-position, introduction of the second SH group was diastereoselective, leading only to the *cis* dithiol (Scheme 35). This diastereoselectivity could be caused by complexation of the zinc metal with the thiol group and internal delivery of the second SH. Alternatively, the *cis* configuration may be thermodynamically more stable than the *trans* form. As evidence for the existence of *cis/trans* equilibrium, it has been shown that the optically active form of the *cis* dithiol (112) racemizes when treated with liquid H_2S and ZnCl_2 (80JOC1885).

A consequence of the existence of this equilibrium was the formation of a monosulfide (114) in the reaction of the simple dehydrocyclo dipeptide (113) with an alanine or phenylalanine residue, as shown in Scheme 36. The reaction could have proceeded by replacement of the OMe by SH, followed by protonation of the exocyclic double bond and intramolecular attack by the thiol group. Alternatively, the *cis*-dithiol could have been in equilibrium with the *trans*-dithiol; in the latter, a *trans*-annular attack could have generated the monosulfide.

Nucleophilic displacement of other functionalities: Displacement of bromide by thiolacetate was one of the earliest successful methods for the introduction of a sulfur substituent on the piperazinedione ring (68BBR402). It was subsequently found that treatment of 3,6-dibromo-1,4-dimethylpiperazine-2,5-dione (115) with methanolic methanethiolate



SCHEME 35



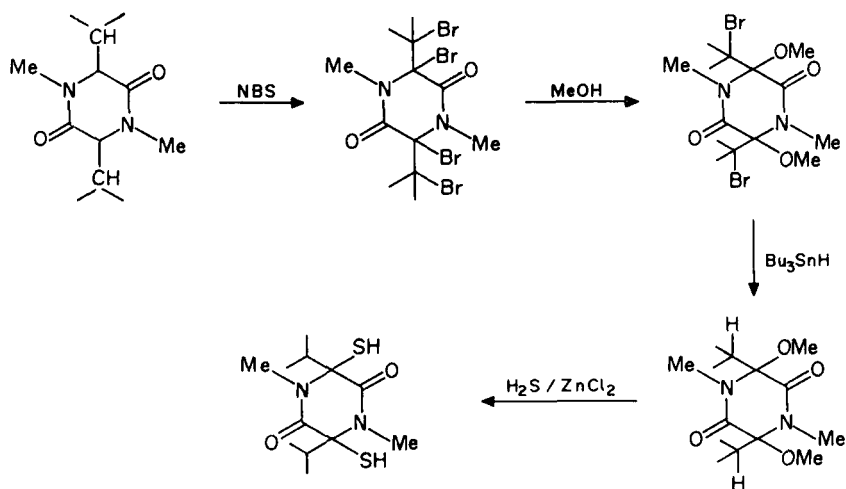
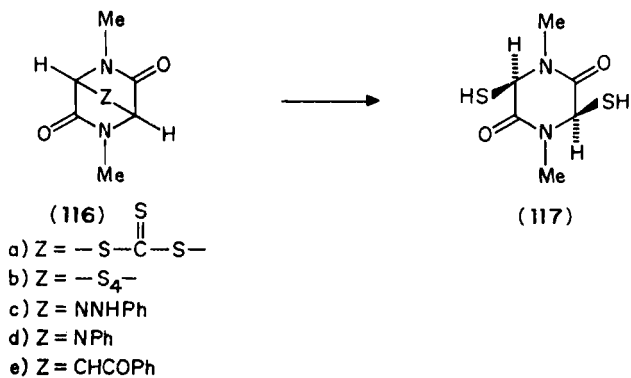
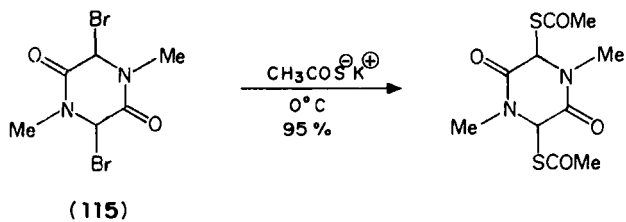
SCHEME 36

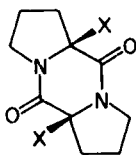
gave a mixture of *cis* and *trans* products. The stereospecific introduction of two sulfur functions, *cis* to each other, was achieved by reacting the dibromo compound with either sodium trithiocarbonate or sodium tetrasulfide to produce the *cis*-bridged structure (116) [71AG(E)130]. The epitetrasulfide (116b), on NaBH_4 reduction, gave the *cis*-dithiol (117) (71CB1714). Other bridging groups have also been utilized subsequently to produce (116) (c,d,e, etc.) (81JHC1545).

In delineating the scope of the bromination–nucleophilic sulfur reaction, two difficulties have been encountered. Bromination with bromine is not successful with tertiary hydrogens such as those present in prolyl derivatives (72CB625). Bromination can be accomplished by means of *N*-bromosuccinimide in presence of 2,2'-azobisisobutyronitrile; however, in this case, 3,6-dialkylpiperazine-2,5-diones yield tetrabromo derivatives. These could be successfully utilized for the required purpose, as shown in Scheme 37. The trick consisted of displacing the bromine atoms attached to the ring by methoxy groups, followed by debromination and thiolation (75BCJ605).

Like the methoxy groups above, hydroxy groups can also be displaced by SH groups. Thus, the *cis* dihydroxy compound (118) leads to the *cis* dithiol (119) (73CB165).

Williams and co-workers (85JA3246) have reported that NBS bromination (CCl_4 reflux) of a series of 1,4-dialkylpiperazine-2,5-diones results in

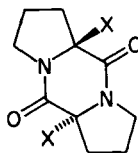




(118) X = OH

(119) X = SH

(120) X = SEt

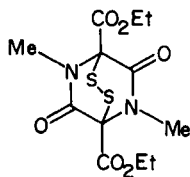


(121) X = OAc

the formation of only the *syn*- dibromides. Reaction of these dibromides with the sodium salt of 2-mercaptopyridine provided the *syn*-bis(sulfides) in high yields. In these compounds, the C-3 methine protons appear as a sharp singlet between $\delta 6.3$ and $\delta 6.8$, confirming the *syn*-assignment. The *anti* diastereomer (prepared in one case from the *anti*-dibromide) exhibited this two-proton singlet at $\delta 5.44$.

Oxidation of cyclo(Pro-Pro) with lead tetraacetate afforded the *trans*-diacetoxy compound (121) in 32% yield. These acetoxy groups could be displaced by sulfur nucleophiles. Thus, with ethanethiol and ZnCl_2 , it gave the *cis*-3,6-bis(ethylthio) derivative (120); solvolysis by dilute aqueous acid followed by treatment with $\text{H}_2\text{S}/\text{ZnCl}_2$ gave the *cis*-dithiol (73CB396), which can be directly oxidized to the episulfide.

The electrophilic route: The underlying principle is to generate a carbanion at position 3 of the piperazine-2,5-dione and react this with an electrophilic sulfur reagent; this could be either S_2Cl_2 or elemental sulfur. Thus, dimerization of diethyl *N*-methylaminomalonate gave 3,6-diethoxycarbonyl-1,4-dimethylpiperazine-2,5-dione (only one isomer). Treatment of this with NaH and freshly purified S_2Cl_2 gave the epidithio compound (122) in 17% yield (71TL3127). Elemental sulfur can also be used as the electrophilic species in this reaction. Thus the monocarbanion generated from cyclo(Pro-Pro) by NaH in DMSO or by NaNH_2 in liquid ammonia reacts with sulfur to form the mercaptide. The second carbanion

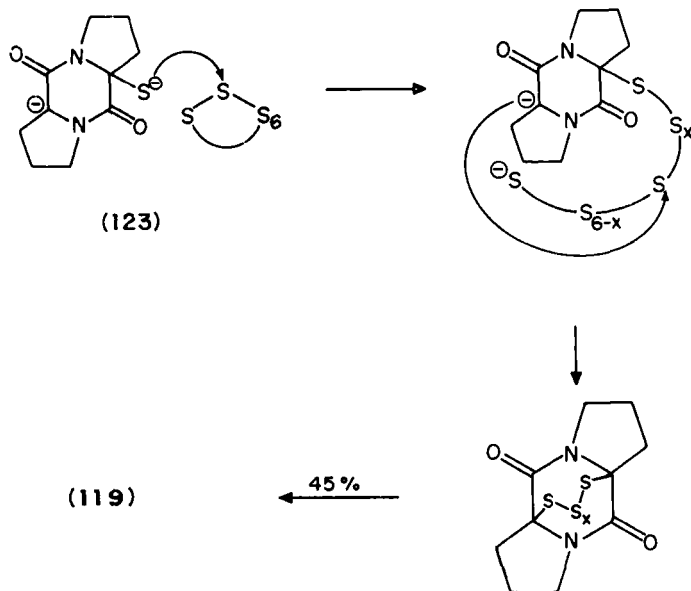


(122)

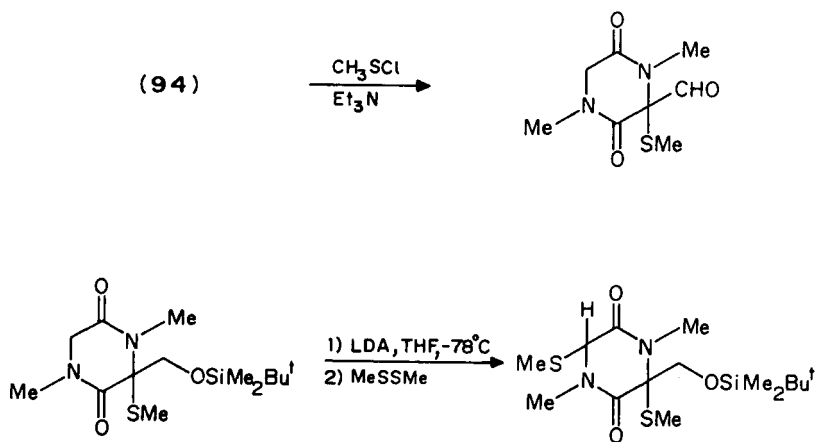
can again be generated by NaNH_2 in liquid NH_3 . Reaction of this with elemental sulfur, followed by methylation gives the bismethylmercapto derivative (19%), which consists of a 3:4 mixture of the *cis* and *trans* isomers (72CB625). However, it was shown that in the reaction of the dianion (**123**) with elemental sulfur (S_8) internal delivery leads to *cis*-epipolysulfide, which could be reduced by NaBH_4 to the *cis* dithiol (45%) (Scheme 38), (72CB635).

Reaction of an enolate derived from piperazine-2,5-dione with an electrophilic sulfur species has been used to synthesize gliovictin and hyalodendrin. Thus, the enol (**94**) can be sulfenylated at low temperatures with sulfenyl chlorides in presence of triethylamine. A second thiomethyl group can be introduced at position 6 by reacting the enolate with dimethyldisulfide as shown in Scheme 39.

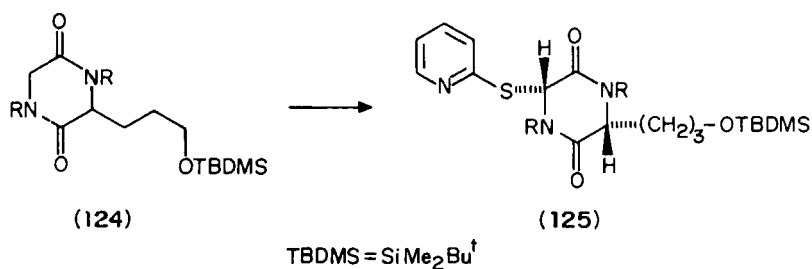
2,2'-Dipyridyldisulfide has been used as the electrophilic reagent by Williams and co-workers in their studies directed toward the synthesis of bicyclomycin (82JA6092). The enolate of (**124**) was generated by means of lithium diisopropyl amide (LDA) in tetrahydrofuran (THF) at -78°C and added to a solution of 2,2'-dipyridyldisulfide. This gave (**125**) as a single regio- and stereoisomer in 80–95% yield. Contrary to expectation, the two side chains of the piperazinedione in (**125**) were disposed *cis* to each other.



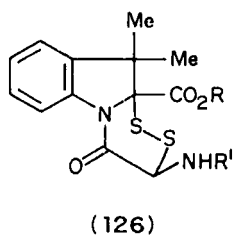
SCHEME 38



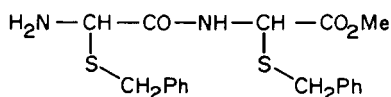
SCHEME 39



The direct cyclization route: So far, attempts at closing the lactam ring from an open-chain precursor carrying appropriate sulfur substituents have not been successful. These include efforts at building a lactam ring from the dithiazine (**126**) (73JA1989) or the open-chain compound (**127**) (73HCA1218).

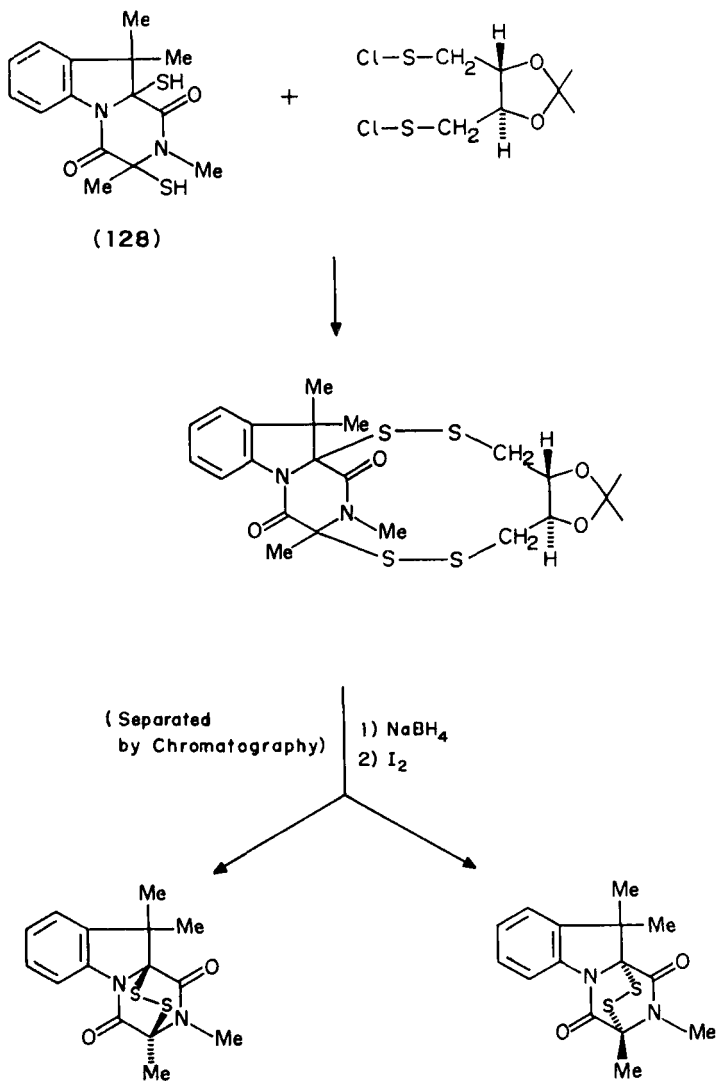


(126)



(127)

Optical resolution of the dithiol: The problem of optical resolution of racemic disulfides has been successfully tackled (77JOC925). The bis-thiol (**128**) was reacted with a chiral bis-sulfenyl chloride, the resultant mixture of diastereomers separated, and the product reconverted to the starting material by NaBH_4 reduction. Subsequent iodine oxidation gave the chiral epidisulfides (Scheme 40).

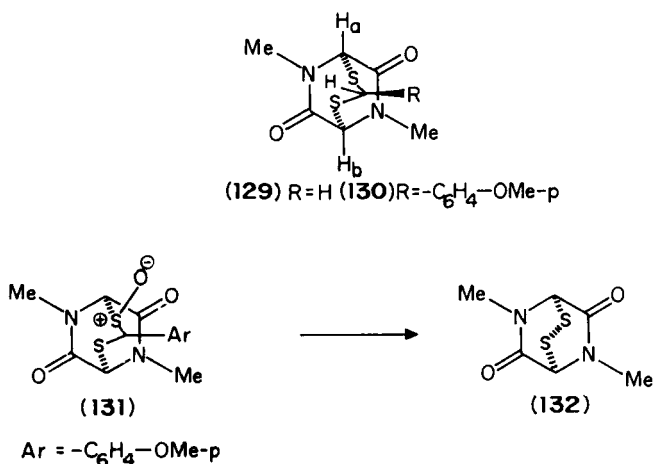


SCHEME 40

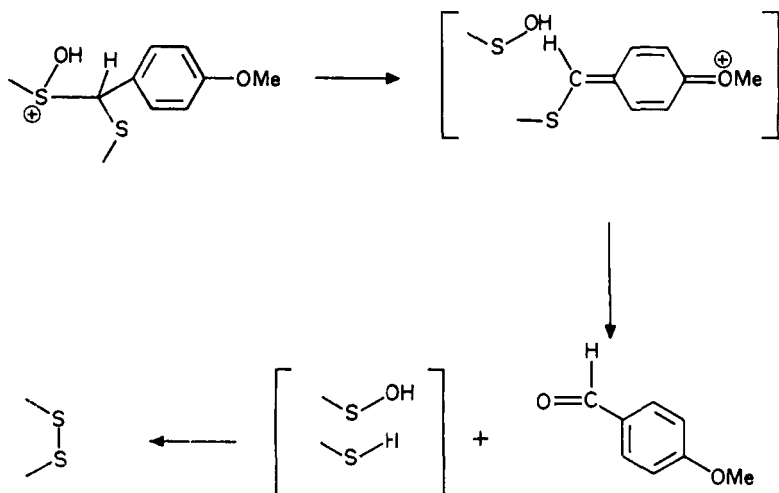
b. *Reactions.* The physical and chemical properties of 3-monothio and 3,6-dithio derivatives of piperazine-2,5-diones have been thoroughly investigated by Kishi and co-workers during the course of their synthetic studies on gliotoxin and related natural products, culminating in the total synthesis of gliotoxin itself (81T2045). The important reactions are summarized below.

Protection and deprotection of the dithiol: The formaldehyde dithioacetal (**129**) could be prepared by reacting the dithiol with diiodomethane and pyridine, but not with paraformaldehyde. Other thioacetals could be prepared by the standard procedure (aldehyde, BF_3 etherate). Interestingly, both *cis* and *trans* dithiols gave the thioacetal, thereby enabling the complete conversion of mixtures of *cis* and *trans* dithiols to the pure *cis* derivative. Several mechanistic explanations are possible for the epimerization at C-6 in the thioacetalization of the *trans* dithiol, but detailed analysis has not been done.

The formaldehyde thioacetal (**129**) was found to be stable to several standard deprotection conditions (conc. HCl , H_2SO_4 , HBr , HgCl_2 , $\text{Hg}(\text{OAc})_2\text{--HCO}_2\text{H}$, AgNO_3 , AgCl--HCl). The thioacetals could be converted to the corresponding monosulfoxides with *m*-chloroperbenzoic acid; these were found to be stereochemically homogeneous. Of the several sulfoxides, the one derived from anisaldehyde (**131**) was the only one susceptible to clean acid cleavage, leading to the epidithiopiperazinedione (**132**).



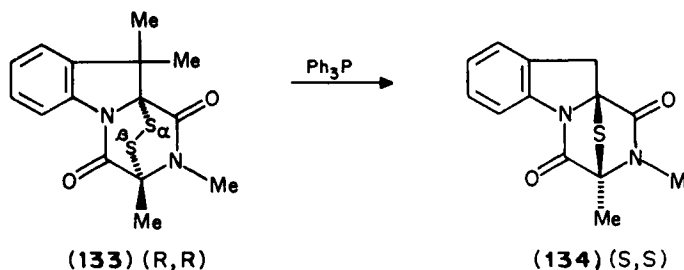
It has been suggested that this easy cleavage of the C—S bond in the case of anisaldehyde dithioacetal might be due to the stabilization of the carbonium ion (Scheme 41).



SCHEME 41

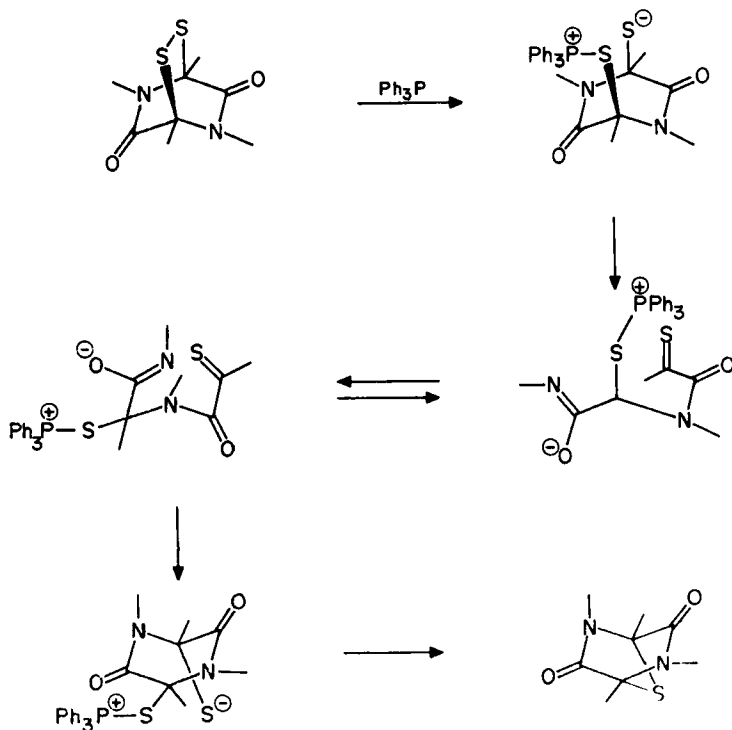
Synthesis of epidithiopiperazinediones and epithiopiperazinediones: The 3,6-dithiol can be easily oxidized to the episulfide by means of iodine. The most common reagents are iodine/potassium iodide [73CB165, 73CB396; 71AG(E)130] and iodine/pyridine (80JOC1880). The epidithiopiperazinediones are extremely labile toward oxidation [*N*-bromosuccinimide (NBS), *m*-chloroperbenzoic acid (mCPBA)]; reduction [lithium aluminum hydride (LAH) and NaBH_4]; and bases (NaOH, NaOMe, Et_3N), but are reasonably stable under acidic conditions (81T2045).

The desulfurization of epidithiopiperazinediones by means of triphenylphosphine to produce the corresponding monosulfides has been known for some time [69CC1466; 71JCS(C)1189; 76JOC3433]. In this conversion Safe and Taylor originally suggested that the configuration at both the bridgehead carbon atoms was inverted; this conclusion was based on the fact that the CD curves of the two compounds showed opposite signs. This unexpected result has been subsequently confirmed and a possible mechanism proposed (79JA1159). When compound (**133**), having the (*R,R*) configuration at the piperazine 3 and 6 carbon atoms, was reacted with triphenylphosphine, the monosulfide (**134**) was formed in 93% yield. This was proved to have the (*S,S*) configuration at the two concerned carbon atoms by an X-ray structure determination. It was also confirmed that there was a change in the sign of the "Cotton effect" on going from the disulfide to the monosulfide. Other interesting results emerging from this study are (*a*) the chiral phosphine (–) Diop reacts faster with the (*S,S*) disulfide than with the (*R,R*) enantiomer; (*b*) chiral shift reagents can be



employed to discriminate between the two enantiomers in their NMR spectra; and (c) the desulfurization seems to be regiospecific, the sulfur atom β being attacked by the phosphine. A possible mechanism has been proposed for the configuration inversion (Scheme 42).

However, the authors have pointed out that this unexpected stereochemical outcome may hold only when the epidithiopiperazinedione nucleus is fused to not more than one ring. In fact, in another related instance,



SCHEME 42

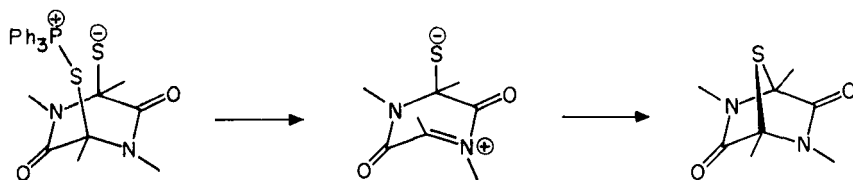
retention of configuration has been proposed (76T507). The mechanism may involve a normal S_N1 -type attack as seen in Scheme 43.

Acidity of the methines: A new method of constructing complex piperazine-2,5-diones with a disulfide bridge was first described by Kishi and co-workers (73JA6490; 81T2045). The key is the introduction of substituents on the piperazinedione ring *after* the sulfur atoms have been installed. Regiospecificity is ensured by the significant difference in the acidities of the two methines.

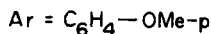
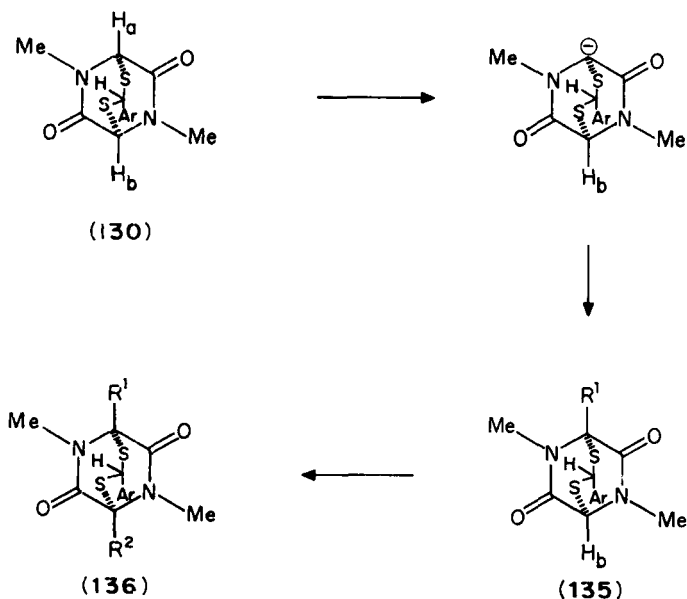
The two bridgehead hydrogens H_a and H_b in the anisaldehyde dithioacetal (**130**) have a large difference in their acidities, as indicated by the NMR chemical-shift difference (4.88 and 5.03 ppm). Preparation of the monocarbanion (1 BuLi in THF at -78°C) and quenching with DCl removed only the higher field hydrogen. The carbanion can be reacted with electrophiles such as primary halides, acid halides, or aldehydes to produce (**135**). Carbanion generation and alkylation can be repeated on (**135**) to yield the disubstituted derivative (**136**) as shown in Scheme 44.

The regiospecificity in the alkylation was demonstrated as follows: The two stereoisomers (**137**) and (**138**) were isolated by fractional crystallization. The stereochemistry of the two diastereomers was assigned on the basis of their NMR spectra. The signal of the proton on the thioacetal bridge of (**137**) was shifted considerably downfield (6.32 ppm) compared to that of (**138**) (5.37 ppm) due to the deshielding effect of the aromatic ring. Treatment of (**137**) with phenyllithium at -78°C in THF led to cyclization, whereas under the same conditions (**138**) did not cyclize. Instead, the latter could be C-alkylated by addition of alkyl halide, and subsequently a second carbanion, generated, then cyclized (Scheme 45). An X-ray crystallographic structure determination of the monoethylated product (**139**) has confirmed the above deductions (75CC542).

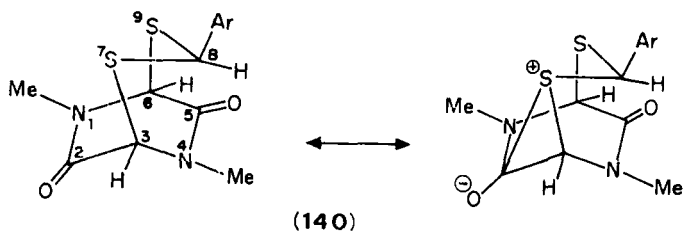
Apparently there is still some doubt regarding the reason for the regiospecificity of the metallation. The most plausible explanation appears to be that this regiospecificity could arise from the difference in the orientation of the lone pair on the two sulfur atoms with respect to the carbonyl group on the same side. In structure (**140**) the lone pair on S(7) is sterically close to C(2); this might make the proton at C(3) more acidic than that at C(6).



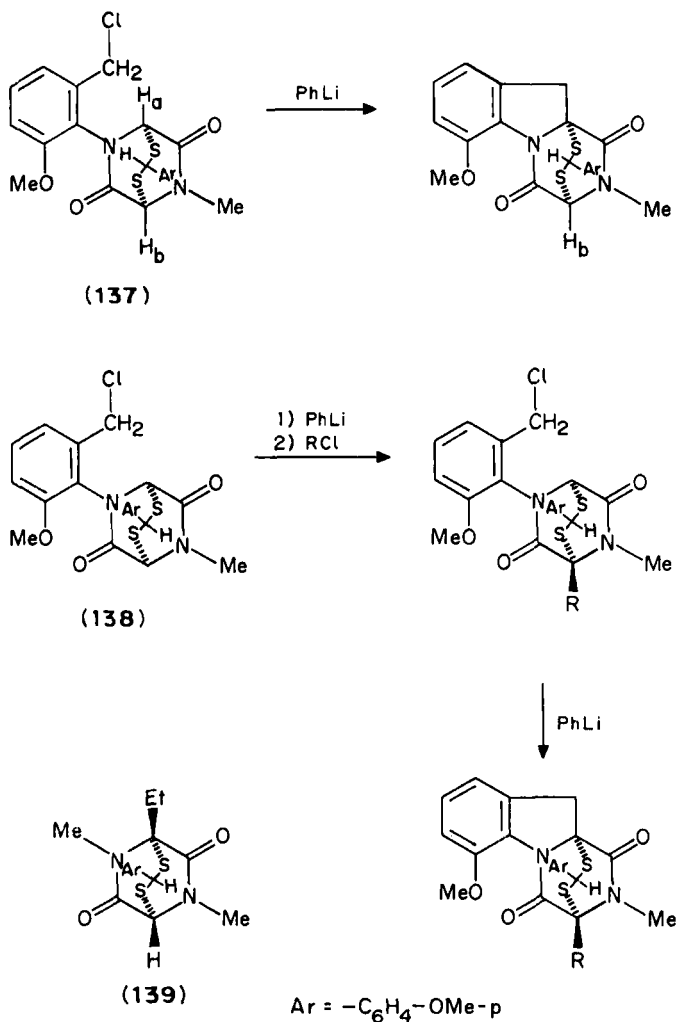
SCHEME 43



SCHEME 44



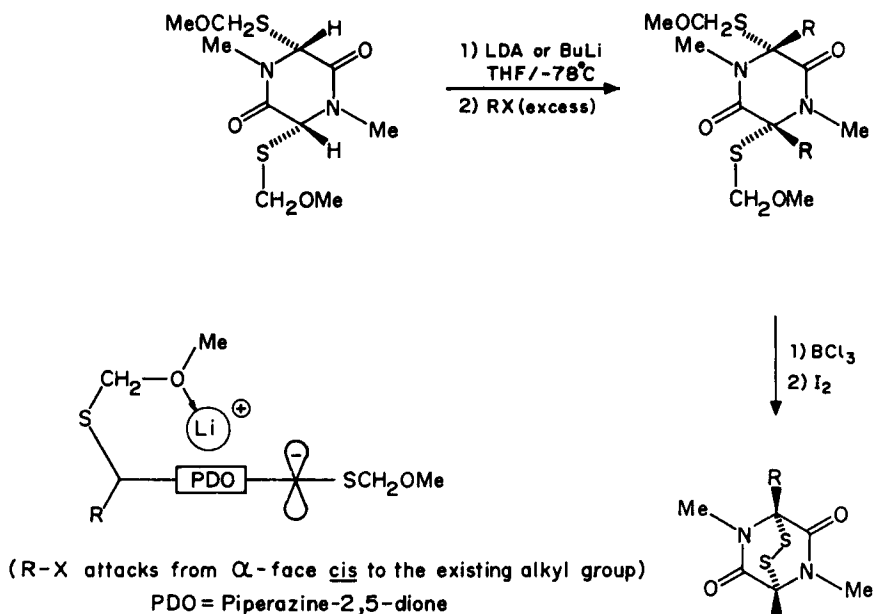
A simpler method of constructing the epidithiopiperazinediones dispenses with the need for protection of the dithiol as anisaldehyde dithioacetal (76TL3393; 81T2045). The sequence is shown in Scheme 46. The route could also be adopted for the synthesis of unsymmetrically alkylated products. The remarkable stereospecificity in the above alkylation can be attributed to steric reasons. In the carbanion derived from the monoalkylated product, coordination of the oxygen lone pairs with the lithium cation would stabilize the conformation as shown. This would make the β -face sterically more crowded for the incoming alkylating agent than the α -face. The method has been used to generate several synthetic analogs of natural products for evaluation as platelet aggregation inhibitors (87CPB3527).



SCHEME 45

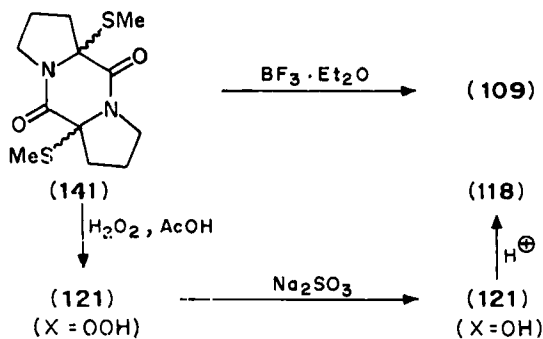
Other Reactions: The alkylthio group attached to the 3 (or 6) position of the piperazinedione can be eliminated or oxidized to the sulfone (73CB165), or displaced by a peroxide group. Some of the transformations are shown in Scheme 47.

Displacement by nucleophiles: C—C Bond formation has been accomplished by coupling the syn-3,6-bis(2'-thiopyridyl)piperazine-2,5-diones with ketene trimethylsilyl acetals in presence of silver triflate. There are several interesting features in this extremely useful reaction. The proce-



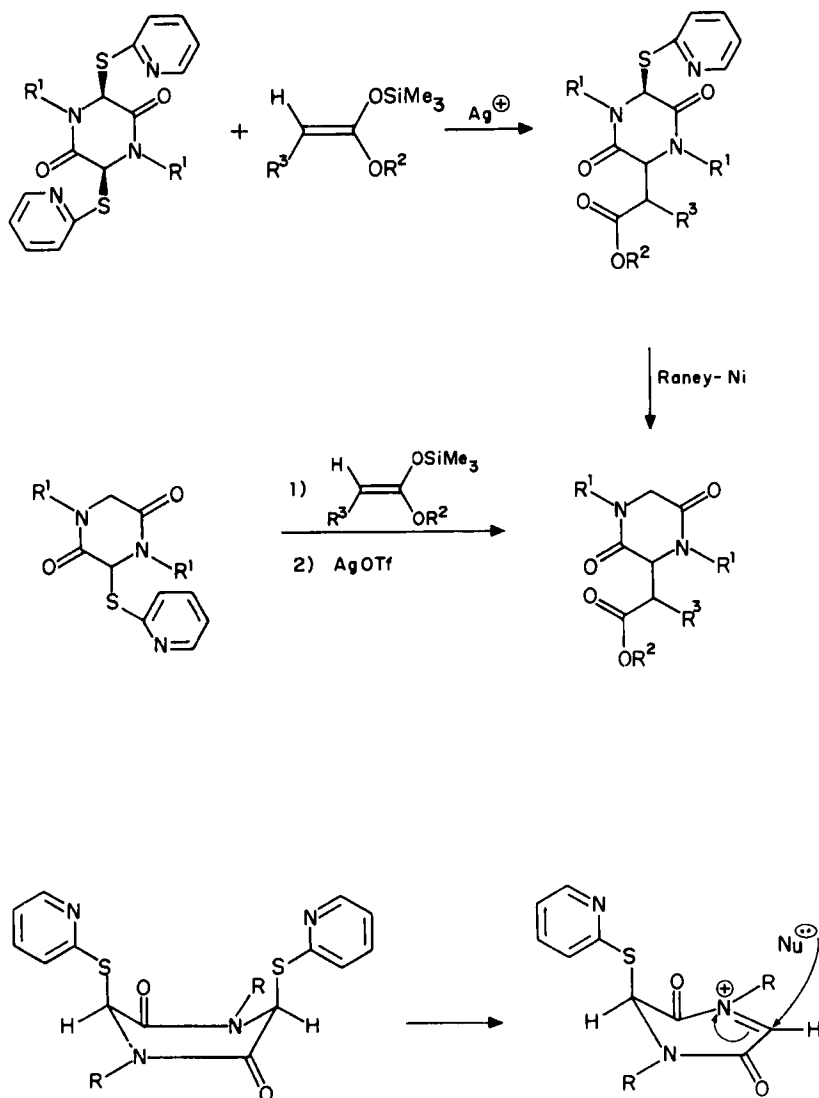
SCHEME 46

ture involves precomplexation of the bis(sulfide) with silver triflate. Only one of the sulfide groups is displaced, leading to the monocoupled products. Even in the presence of excess reactants, the 3,6-bis-coupled products are not observed. If necessary, Raney-nickel desulfurization can remove the remaining pyridinethiol group. The monosulfide, prepared from the monobromide, is not displaced under the same conditions. However, in this case (but not with the bis-sulfide) reaction can be brought

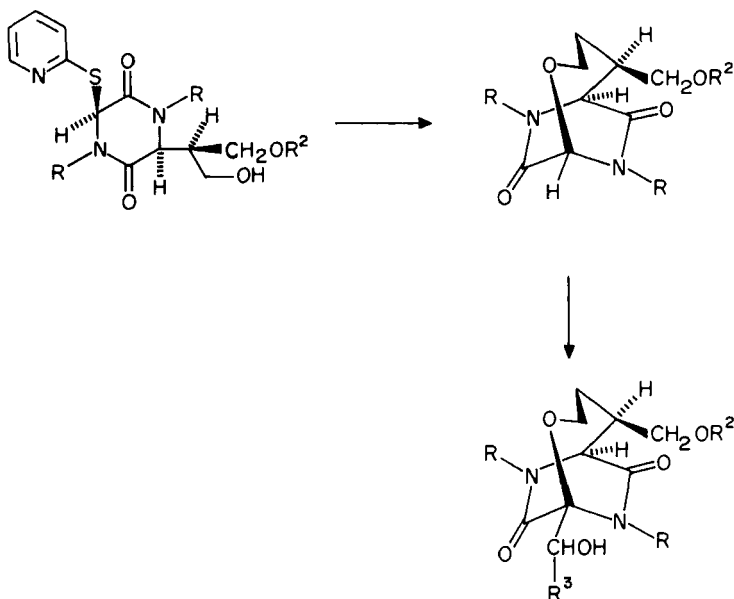


SCHEME 47

about by changing the order of addition of reagents. The stereochemical results indicate that the initially formed Ag^+ complex produces the iminium species, which is predominantly attacked from the same face of the piperazinedione nucleus as the departing thiopyridyl residue, leading to overall retention of stereochemistry (Scheme 48).



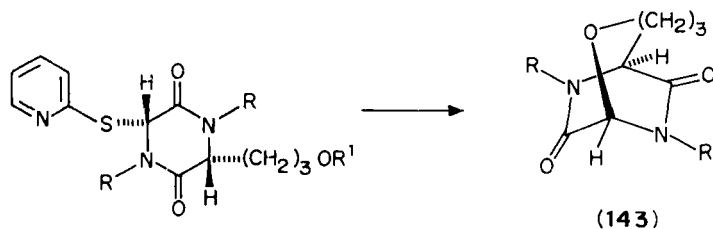
SCHEME 48



SCHEME 49

This strategy has been utilized in a total synthesis of bicyclomycin (85JA3253). The crucial steps were silver triflate-induced cyclization with displacement of the second pyridinethiol group by an oxygen nucleophile, followed by aldol condensation (Scheme 49).

This sequence had earlier been worked out on model substrates (82JA6092). Treatment of (**142**) with 1 eq of silver perchlorate in dichloromethane at room temperature resulted in clean intramolecular cyclization to (**143**) in 60–93% yield. Alternatively, the silyl-protected precursor (**144**) could be directly converted to (**143**) in one step by treatment with phenylmercuric perchlorate for 2–3 min at room temperature.



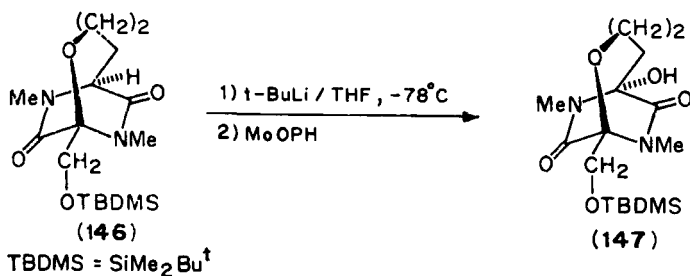
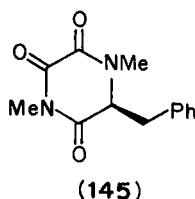
(**142**) $R^1 = H$

(**144**) $R^1 = \text{TBDMS}$

8. Introduction of Oxygen Substituents

a. *Direct Introduction of Oxygen Substituents.* Oxidation of cyclo-(Pro-Pro) with lead tetraacetate affords a 32% yield of the *trans* diacetox compound (**121**; X = OAc) (73CB396). Benzophenone-sensitized photo-oxidation of cyclopeptides has been shown to lead to mono- and bis-hydroperoxides [76AG(E)497; 78CB361]. These have been identified by comparison with the products obtained by nucleophilic displacement of sulfone substituents (73CB165). Similar photochemical oxidation of racemic *cis*- or *trans*-3,6-dibenzyl-1,4-dimethylpiperazine-2,5-dione is reported to give the piperazine-2,3,5-trione (**145**), in high yield, presumably via the hydroperoxide (85AJC343).

A hydroxyl group has been introduced at the bridgehead of the bicyclic compound (**146**) by treating the carbanion with the reagent oxodiperoxy-molybdenum hexamethylphosphoric triamide, pyridine (MoOPH), to give compound (**147**) (81TL2341).



b. *By Displacement of Sulfur Functionalities.* This has been discussed under the reactivity of the sulfur-functionalized derivatives. For instance, the *cis* or *trans* bismethylmercapto derivative (**141**), on treatment with H_2O_2 in acetic acid, mainly produces the *trans* bis-hydroperoxide (**121**; X = —OOH), which is thermodynamically more stable than the *cis* compound (73CB165). The hydroperoxide function can be converted to a

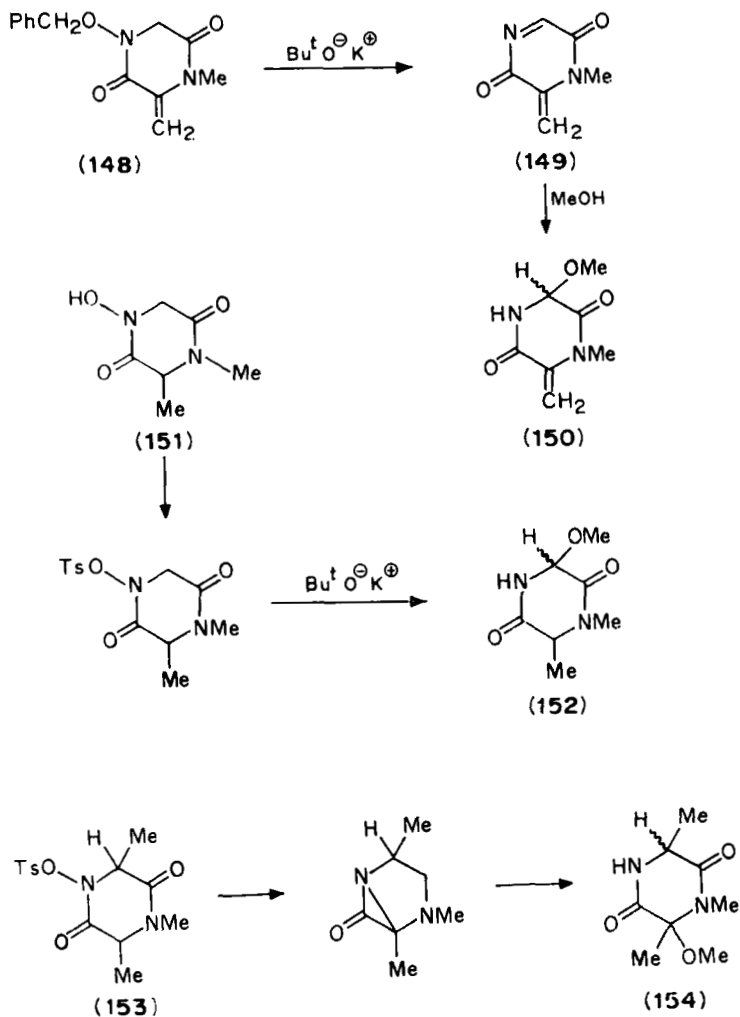
hydroxyl by sulfite reduction. Surprisingly, in the case of the dihydroxy derivative, acid treatment of the *trans* derivative (**121**; X = OH) leads to the thermodynamically more stable *cis* isomer (**118**) (see Scheme 47). (Only relative stereochemistry is indicated and not absolute configuration.)

c. *By Addition of Alcohol to Imines.* Reaction of the *N*-benzyloxy compound (**148**) with 1 eq of potassium-*t*-butoxide in methanol afforded the methoxy derivative (**150**) almost quantitatively. Obviously the imine (**149**) must have been an intermediate, to which methanol has added (80JOC1885). Similarly, the *N*-hydroxypiperazine-2,5-dione (**151**), on tosylation followed by treatment with potassium-*t*-butoxide in methanol, led to the formation of methoxyderivative (**152**) (80JOC1880). With the corresponding alanyl derivative (**153**) an isomeric by-product (**154**) was also isolated, which presumably arose via an α -lactam as shown in Scheme 50.

Studies directed toward the synthesis of bicyclomycin have resulted in the discovery of efficient routes to the construction of the 2-oxa-8,10-diazabicyclo[4.2.2]decane system (**160**). Thus, the monolactim ether (**155**) with a hydroxypropyl side chain at position 3, on oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), gave the product (**156**) in good yield, presumably via an iminium species (Scheme 51). No trace of the spiro compound (**157**) could be detected in this reaction. The formation of (**156**) is probably kinetically controlled. Prior protection of the alcohol as a silyl ether, followed by DDQ oxidation, gave the pyrazinone (**158**); subsequent deprotection and acid treatment gave the thermodynamically preferred spiro compound (**159**). The method has been extended to the synthesis of (**160**), having an exocyclic methylene; this compound is a key intermediate in the total synthesis of bicyclomycin [88JCS(P1)2585].

d. *From 3- (or 6-) Alkylidene Derivative.* Yates has provided an ingenious solution to the problem of introducing a hydroxyl group at position 3 (83CJC1397). This consists in epoxidizing the isopropylidene derivative (**161**) and opening the epoxide with magnesium isopropylcyclohexylamide (Scheme 52).

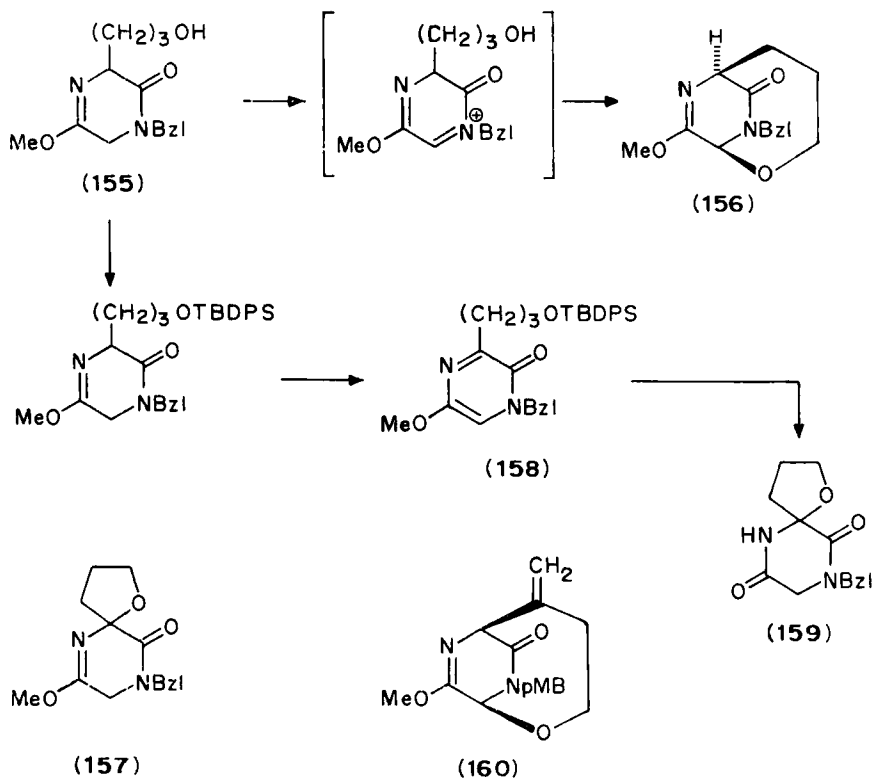
Another method of introducing an oxygen substituent has been explored by Shin and co-workers. This is illustrated in Scheme 53, where reasonably good stereoselectivity has been attained in the introduction of a methoxyl group at position 6 (diastereomeric excess, de 87%) (83H405). The critical step is the reaction of the 6-alkylidene derivative (**162**) with NBS in methanol to give the 6-(2-bromoalkyl)-6-methoxypiperazine-2,5-dione (**163**), which is subsequently debrominated by hydrogenolysis. The starting mate-



SCHEME 50

rial was obtained from cyclo(L-Thr-Gly) by acetylation followed by condensation with benzaldehyde.

This strategy has been extended to generate spiro derivatives from appropriate hydroxyalkylidene precursors (83BCJ2652). The salicylidene derivative (**164**) has also been similarly cyclized (84CL1301) by treatment with *t*-butyl hypochlorite to yield a mixture of diastereomers (Scheme 54).

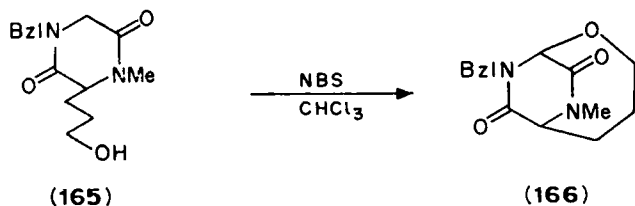


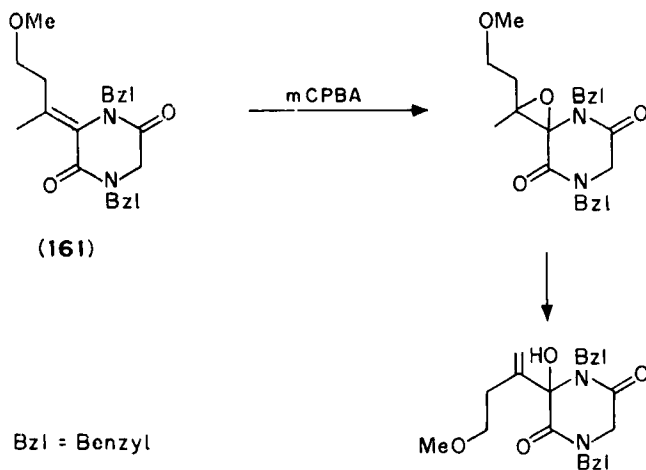
Bzl = Benzyl

pMB = *p*-MethoxybenzylTBDPS = $-\text{SiBu}^t\text{Ph}_2$

SCHEME 51

e. By Displacement of Other Functional Groups. Japanese workers have devised a method for the construction of the bicyclomycin framework, which depends on *in situ* generation of a C-6 bromo derivative (81TL2401). Thus, treatment of (165) with *N*-bromosuccinimide (NBS) in

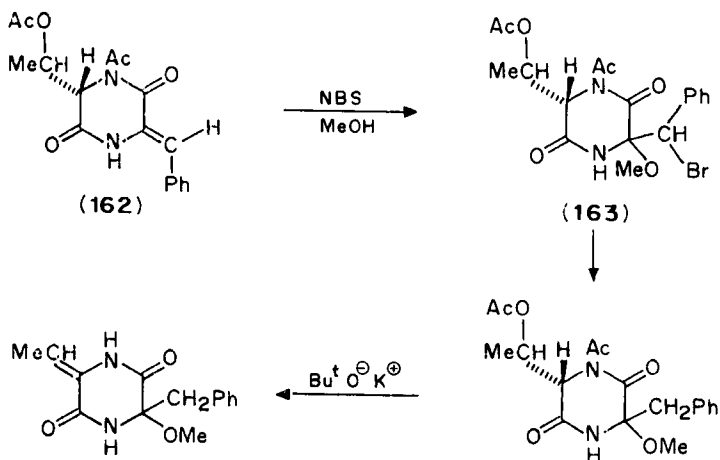




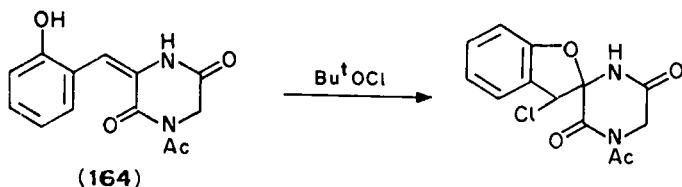
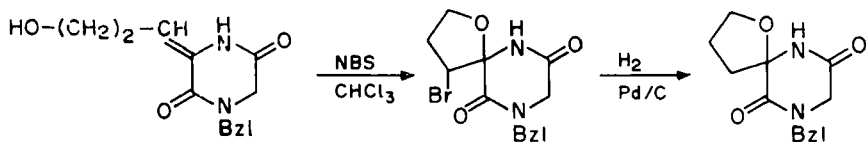
SCHEME 52

chloroform gave **(166)** in 68% yield. This method has been extended to generate a key intermediate for the total synthesis of bicyclomycin (84CL1547).

Finally, in a 3,6-bismethoxy-substituted piperazine-2,5-dione, the problem of selective activation of one of the methoxyl groups has been successfully tackled. Acid-catalyzed cyclization of the alcohol **(167)** gave, as

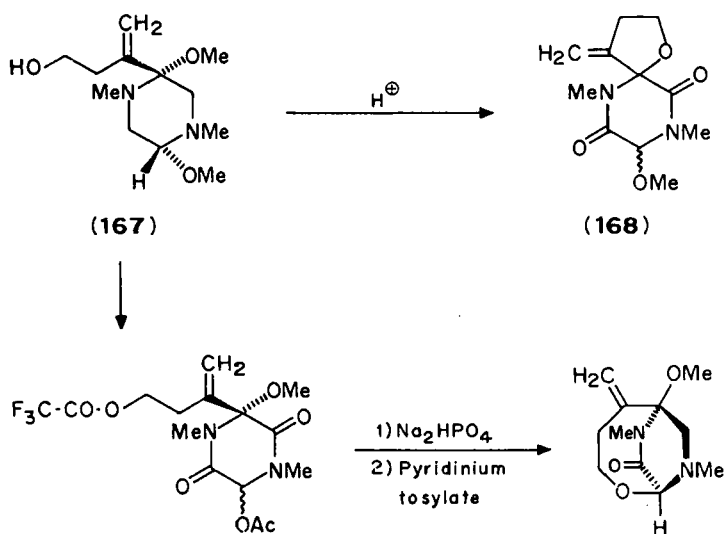


SCHEME 53



SCHEME 54

expected, the unwanted spiro compound (168). In order to circumvent this, the more reactive secondary methoxyl was first converted to an acetoxy group (acetic anhydride, trifluoroacetic acid, 40°C, 2 h), the trifluoroacetyl protecting group removed, and the alcohol cyclized by pyridinium tosylate (80°C, 2 h) to give the desired bicyclic system (Scheme 55) (81TL2009).



SCHEME 55

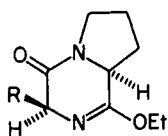
V. Lactim Ethers

A. SYNTHESIS OF LACTIM ETHERS FROM PIPERAZINE-2,5-DIONES

Piperazine-2,5-diones react with trimethyloxonium fluoroborate (Meerwein's reagent) or triethyloxonium fluoroborate to generate the corresponding lactim ethers.

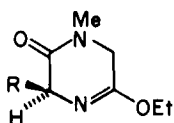
1. Monolactim Ethers

The earliest report on such lactim ether formation was from Sammes [72JCS(P1)2494], who converted piperazine-2,5-dione to 2,5-diethoxy-3,6-dihydropyrazine (**173**) with an excess of triethyloxonium fluoroborate. Subsequently, Rajappa and Advani (73T1299) converted proline-based piperazine-2,5-diones into the corresponding monolactim ethers. The starting material was a piperazinedione in which one of the amino acid units was the secondary amino acid proline, and the other a primary amino acid. This naturally led to the regiospecific formation of a monolactim ether (**169**) (on O-alkylation) from the secondary amide, whereas the tertiary amide remained intact. This was later extended to piperazine-2,5-diones in which the secondary amino acid was sarcosine [74JCS(P1)2122], leading to the monolactim ethers (**170**).



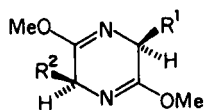
(169)

- a : R = H
- b : R = Me
- c : R = CHMe₂
- d : R = CH₂CHMe₂
- e : R = CHMeEt



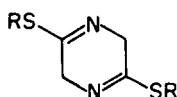
(170)

- a : R = H
- b : R = Me



(171)

- a : $R^1 = R^2 = H$
 b : $R^1 = H$; $R^2 = iPr$
 c : $R^1 = Me$; $R^2 = iPr$
 d : $R^1 = Ph$; $R^2 = iPr$
 e : $R^1 = H$; $R^2 = t-Bu$
 f : $R^1 = R^2 = iBu$
 g : $R^1 = R^2 = Me$



(172)

R = Me, Et

2. Bislactim Ethers

Piperazine-2,5-diones, in which both amino acid units are primary, lead to bislactim ethers on O-alkylation with Meerwein's reagents. No selectivity in this reaction has been demonstrated so far. Such bislactim ethers (171) have been prepared and extensively used by Schöllkopf and his school [79AG(E)863, and later papers]. During the preparation of these bislactim ethers, neutralization of the initially formed bis-tetrafluoroborate salt is carried out with phosphate buffer to avoid racemization.

The methine protons at positions 3 and 6 of the bislactim ether (171g) resonate at 4.04 δ (q) in $CDCl_3$ solution [79AG(E)863].

The 3,6-dioxygenated derivatives of the bislactim ethers have been produced by the reaction of 2,5-diethoxypyrazines with singlet oxygen, followed by sodium borohydride reduction of the endoperoxide [79JCS(P1)1885].

3. Thiolactim Ethers

Gompper [83AG(E)717] has prepared the thiolactim ethers (172) by the action of Meerwein's reagent on the thiolactam.

B. REACTIVITY

Three main types of reactions undergone by these lactim ethers will be discussed in this section. They are (a) hydrolysis, (b) displacement of the alkoxy (or alkylthio) groups by other nucleophiles, and (c) dehydrogenation/aromatization.

The generation of the anions from the lactim ethers and their reaction with electrophiles is deferred to the next section.

1. Hydrolysis

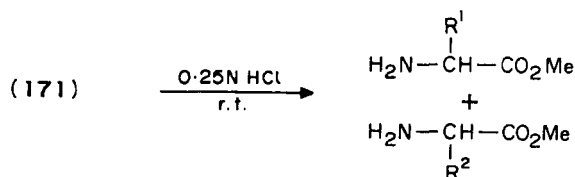
Treatment of the bislactim ethers with two equivalents of 0.25 *N* hydrochloric acid at room temperature leads to their hydrolysis to their constituent amino acid esters under these conditions (Scheme 56). The hydrolysis does not proceed via the piperazine-2,5-dione since the products are the esters and not the free amino acids. The rate of hydrolysis depends on the number and nature of the substituents at the 3 and 6 positions (83CJC1397).

The possibility of selective hydrolysis of one of the imino ether functions in the bislactim ether has been discussed by Schöllkopf (88LA1025). This procedure if accomplished regiospecifically would be extremely useful. Treatment of the bislactim ether with one equivalent of hydrogen chloride in ether does give rise to a monolactam monolactim ether; however, the state of the art at present does not give control over the regioselectivity.

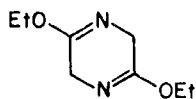
2. Displacement of Alkoxy Groups by Other Nucleophiles

Bislactim ether (173) reacts with secondary amines (such as pyrrolidine, piperidine, and morpholine) to form the diaminodihydropyrazines (174) in good yields [83AG(E)717]. An interesting extension of this reaction is where the nucleophile is anthranilic acid. In this case, a second reaction takes place between the ring nitrogen (acting as the nucleophile) and the carboxylic acid, leading to cyclization which gives (175) [83AG(E)717].

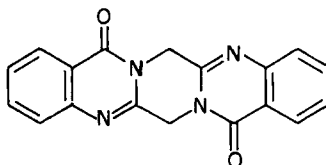
This type of reaction was, in fact, originally described in 1973 for the



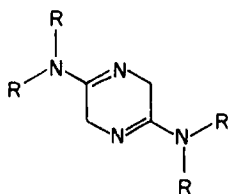
SCHEME 56



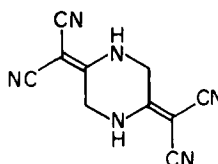
(173)



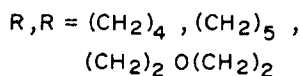
(175)



(174)



(179)

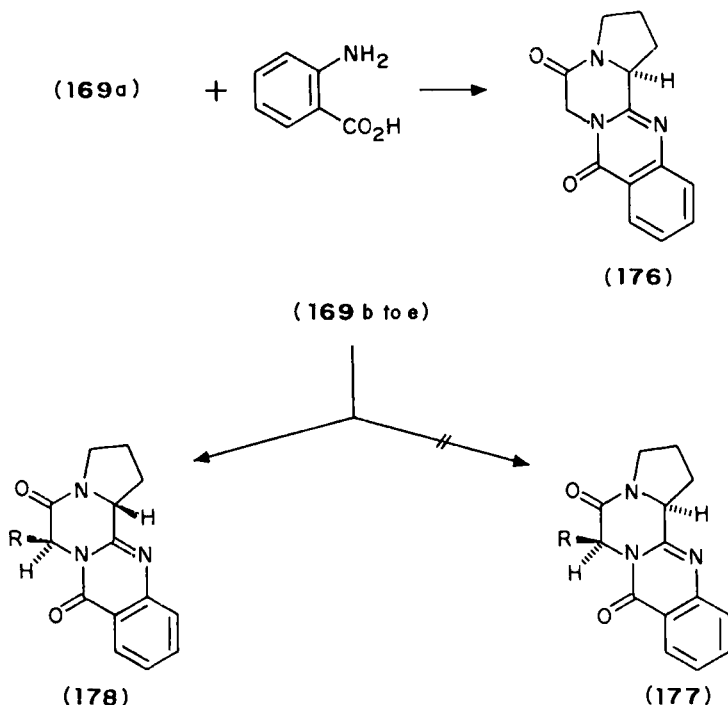


monolactim ethers (73T1299). The iminoether (**169a**) reacts with anthranilic acid to give the tetracyclic quinazolinone (**176**). However, the reaction with other lactim ethers (**169b**) to (**169e**) does not lead to the expected product (**177**) but to the diastereomeric quinazolinone (**178**) in which the proline centre has been epimerized. The structure and stereochemistry have been confirmed by X-ray crystallography [82AX(B)2304]. Such a *trans* stereochemistry of the 3 and 6 methine protons apparently enables the molecule to relieve the steric strain present in the structure (**177**) with the *S,S* configuration.

Gompper has also reported the reaction of the iminoether (**173**) with carbon nucleophiles. Thus malononitrile reacts almost quantitatively to give the product (**179**).

3. Dehydrogenation/Aromatization

Alkoxy-pyrazines are obtained by dehydrogenation of bislactim ethers of piperazine-2,5-diones [72JCS(P1)2494]. Thus, oxidation of (**180**) with dichlorodicyanobenzoquinone (DDQ) gave (**181**) [81JCS(P1)3111]. Similarly, (**182**) on DDQ oxidation gave (**183**) by aromatization followed by intramolecular displacement of the methoxyl group [88JCS(P1)2585]. Of course, if a third double bond is also present in the molecule at a suitable



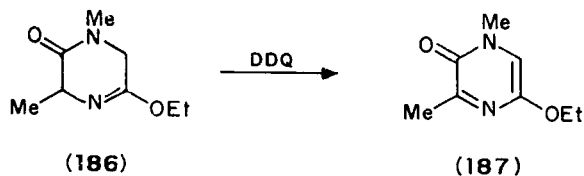
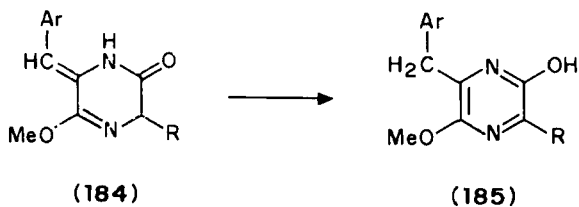
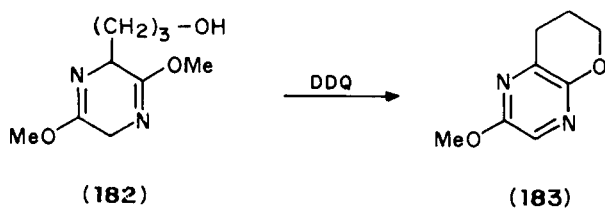
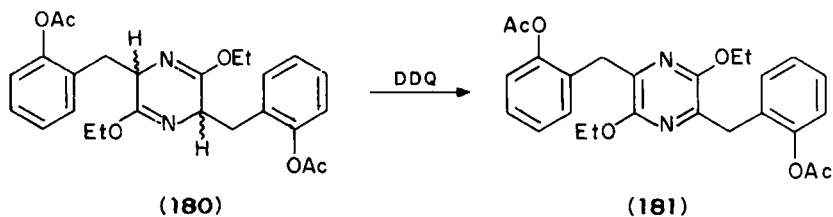
SCHEME 57

location, aromatization is very easy. Thus, the monolactim ether (184) with an exocyclic double bond is converted to the pyrazine (185) on treatment with alkali (82TL5409).

On the other hand, if one of the nitrogen atoms of the piperazinedione carries an extra substituent, dehydrogenation of the derived monolactim ether can lead to a pyrazinone [73JCS(P1)404; 74JCS(P1)698] [e.g., (186) to (187)].

C. APPLICATIONS: SYNTHESIS OF NONPROTEINOGENIC AMINO ACIDS

This section deals mainly with the metalation of lactim ethers and subsequent reaction with electrophiles to generate new C—C bonds at position 3 or 6. Hydrolysis of the products leads to new amino acid esters. The chief attraction of this synthetic route is the high degree of stereoselectivity in the carbon—carbon bond-forming step. It is known as the Schöllkopf method for the chiral synthesis of amino acids.

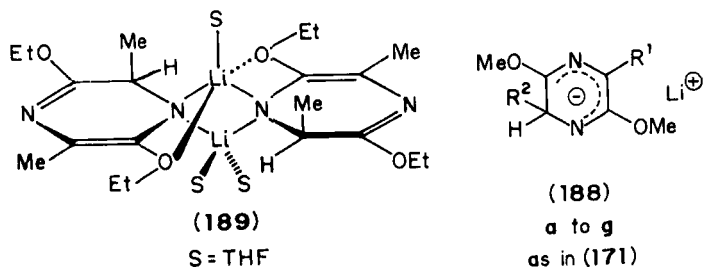


1. Metalation of Bislactim Ether

Bislactim ethers of the general type (171) react with butyl lithium or LDA in THF or glyme at -78°C to give the lithium derivative (188) by the abstraction of a proton from position 3. This incorporates a diazapenta-dienyl anion, which was originally represented as an ion pair (83T2085).

A second metalation at C-6 is very unlikely because it would give an anti-aromatic 8π -electron system (83MI1).

With unsymmetrically substituted bislactim ethers of the type (171b to e), regiospecific deprotonation is feasible. Examples from Schöllkopf's work are given below:

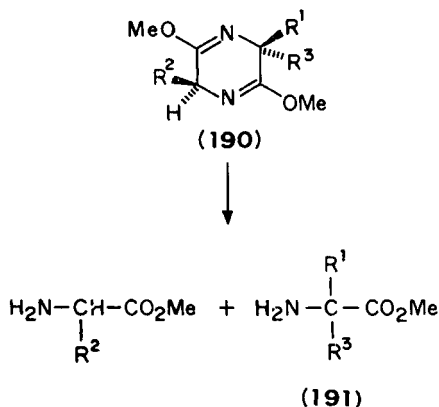


Structure of the lithio derivatives (84CC853): The crystal structure of a THF solvate of the lithium derivative of racemic bislactim ether (derived from two molecules of alanine) has been determined. In the solid state, the lithium derivative exists as a dimer in which the two lithium atoms are nonequivalent (189). The two organic moieties in each dimer are homochiral; this means that the crystal contains equal number of enantiomers. The Li ... Li distance is 2.61 Å. In THF solution at -108°C , the compound seems to exist as an equilibrium mixture of monomer and dimer in the ratio 5:1. It is not clear at the moment whether the reacting species is the monomer or the dimer.

2. C—C Bond Formation via the Bislactim Ether Anion

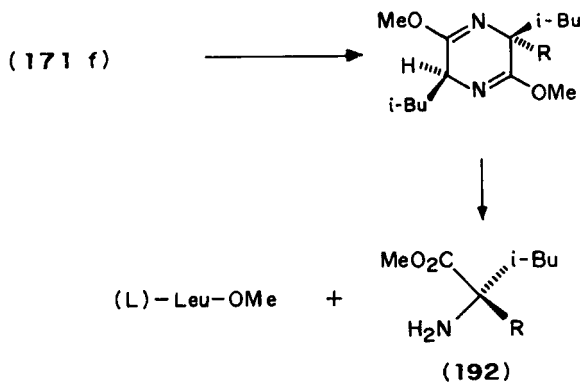
The lithium derivatives described above react with electrophiles such as alkyl halides, carbonyl compounds, and thiocarbonyl compounds, resulting in the corresponding 3-substituted derivatives (190). Hydrolysis of these products by dilute acid as described in Section B,1 gives the new nonproteinogenic amino acid ester (191) along with the original amino acid ester used as the chiral auxiliary. The chemical yields are above 80% (83MI1).

In all the above alkylation reactions, the electrophile enters *trans* to the directing group R^2 . Thus, if the absolute configuration at C-6 is (*S*) (natural amino acid series), the configuration at C-3 becomes (*R*) (assuming R^3 has a higher priority than R^1). The diastereoselectivity is quite high ($>90\%$). The following examples illustrate the use of this method.

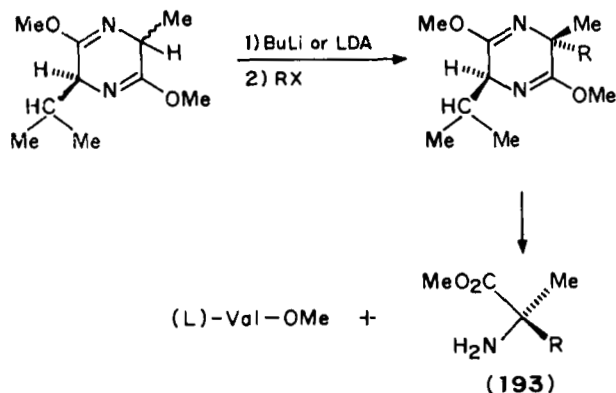


From the symmetrical bislactim ether (**179g**) derived from two molecules of L-alanine, a series of (*R*)- α -methyl amino acid methyl esters having a chiral quaternary carbon have been obtained (83T2085). Similarly, α -alkylleucine methyl esters (**192**) have been obtained from the symmetrical bislactim ether (**171f**) derived from two molecules of L-leucine (84S271) (Scheme 58). In this case, as expected, the final hydrolysis proceeds sluggishly. The de of the products is greater than 85%.

The disadvantage in using such symmetrical bislactim ethers is that half the chiral auxiliary ends up as part of the product molecule; thus only half of the auxiliary can be recovered and reused. This drawback is avoided in the "mixed" bislactim ether prepared from a chiral auxiliary (L-valine) and a *racemic* amino acid (e.g., DL-alanine). Regiospecific deprotonation followed by diastereoselective alkylation leads to the required α -methyl amino acid ester (**193**) (83T2085); the de is >95%. In this method, the chiral auxiliary (L-valine) is recovered intact. (Scheme 59).



SCHEME 58



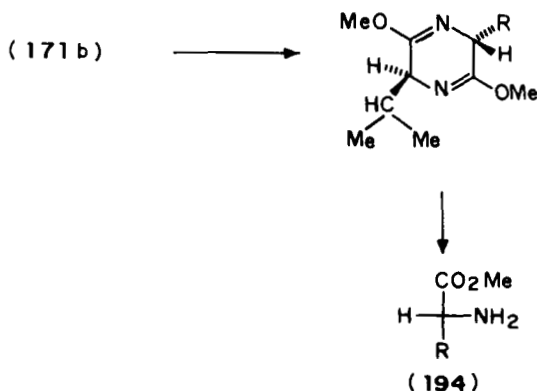
SCHEME 59

An interesting extension of this has led to the synthesis of α -amino-isobutyric acid (Aib), in which one of the prochiral methyl groups, the Pro-(*R*)-methyl, has been labeled with deuterium (85LA1917). In this synthesis the *R* group in structure (193) was CD_3 derived from CD_3I .

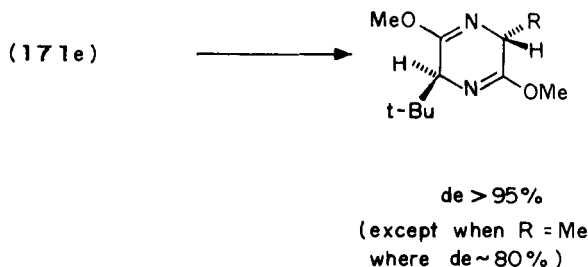
Using the corresponding (6*R*) isomer (from D-valine and DL-alanine), alkylation with 2-chloro-3-methyl quinoxaline followed by further transformation has yielded an aldose reductase inhibitor in optically pure form (90T7745).

An interesting sidelight is that when the methyl group at position 3 of the bislactim ether is replaced by hydrogen, the diastereoselectivity of the alkylation drops to 90–95% (83T2085). The product obtained on acid hydrolysis is an α -unsubstituted amino acid ester (194) (Scheme 60).

The best de values are obtained when the isopropyl is replaced by a *t*-



SCHEME 60

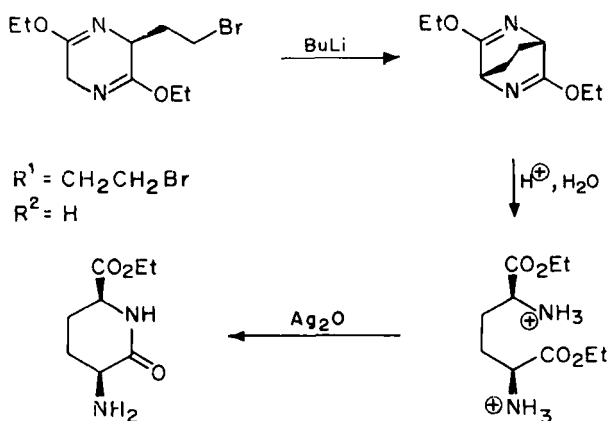


SCHEME 61

butyl group. The drawback, of course, is that the necessary starting material is not a natural amino acid (Scheme 61).

The bislactim ether method has also been applied to an intramolecular alkylation (84JOC2286) to generate stereospecifically the β -turn-inducing element, (LL) 3-amino-2-piperidone-6-carboxylic acid as shown in Scheme 62. The efficiency of chiral induction was in the range 99.5%. It is noteworthy that there is no racemization of the intermediate bromo compound, thus proving the regiospecificity of the deprotonation.

A similar 3-(2-bromoethyl) derivative has been utilized to synthesize 1-aminocyclopropane-1-carboxylic acid by an intramolecular base-catalyzed cyclization. This was possible when position 6 was blocked by the presence of two substituents. Some unexpected stereochemical results also came up in this study (85MI2). The starting material was the piperazine-2,5-dione derived from (*R*)-(+)-2-methyl-3-phenylalanine and glycine. The bislactim ether derived from this, on treatment with butyl lithium in THF at -78°C , gave the lithio derivative. Alkylation of this with 2-haloethyl



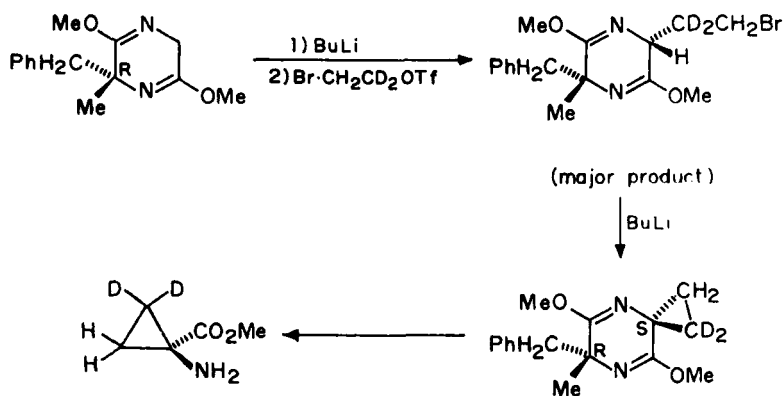
SCHEME 62

triflate gave, as the major product, the diastereomer in which the haloethyl group entered *cis* to the bulky benzyl group at C-6, to give the (*R*) configuration at C-3. The assignment was made on the basis of ^1H -NMR spectra. This violation of Schöllkopf's rules seems to occur only when the leaving group is triflate. (It has been established that it is not due to a preliminary formation of the 2-haloethyl cation in a $\text{S}_{\text{N}}1$ process.) A base-catalyzed intramolecular alkylation on the 2-haloethyl compounds leads to the cyclopropane derivatives. Again the alkylation takes place from the side *cis* to the benzyl group, as shown by deuterium labeling studies. Since in the second alkylation step any stereochemistry at the C-3 position would be lost due to deprotonation and rehybridization from sp^3 to sp^2 , the initial anti-Schöllkopf approach is only of academic interest. Hydrolysis by 0.25 *N* HCl as usual gave the (*S*)-1-amino [2,2- $^2\text{H}_2$]cyclopropane-1-carboxylic acid methyl ester (Scheme 63). The corresponding (*R*) enantiomer was similarly obtained by alkylation with 2-bromo-2,2-dideuterioethyl triflate.

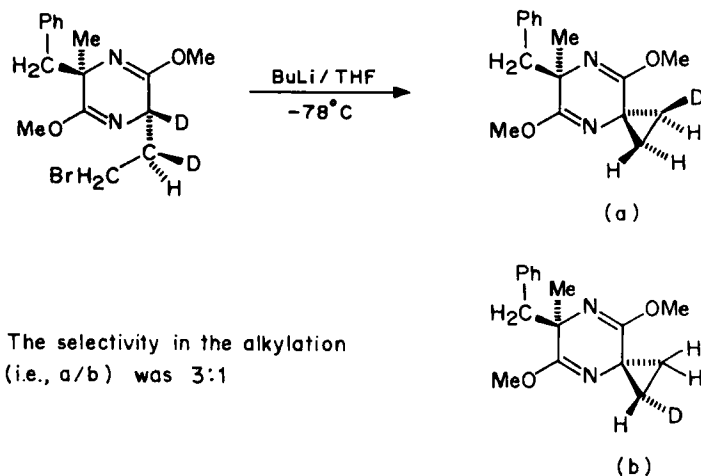
Subsequently, the asymmetric synthesis of stereospecifically monodeuterated 1-aminocyclopropane-1-carboxylic acids (1*S*, 2*R*) and (1*S*, 2*S*) has also been achieved by a modification of the above route (89JOC270). The essential step involves an intramolecular alkylation on a lactim ether anion (Scheme 64).

Another intramolecular cyclization has been reported, giving rise to α -methylproline and related compound [87AG(E)143]. Thermolysis of the bromo compound (195) leads to the cyclization in this case (Scheme 65).

An interesting base-catalyzed ring expansion takes place when there is only one carbon in the side chain containing the nucleofugal leaving group [89AG(E)613] (Scheme 66). Obviously, deprotonation at C-5 is followed by cyclization to form the heteronorcaradiene. Electrocyclic ring-opening



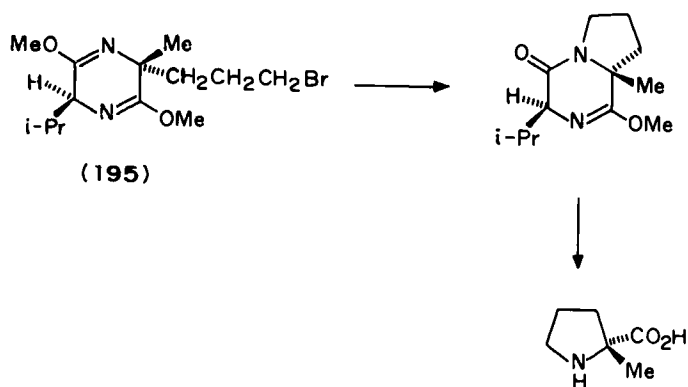
SCHEME 63



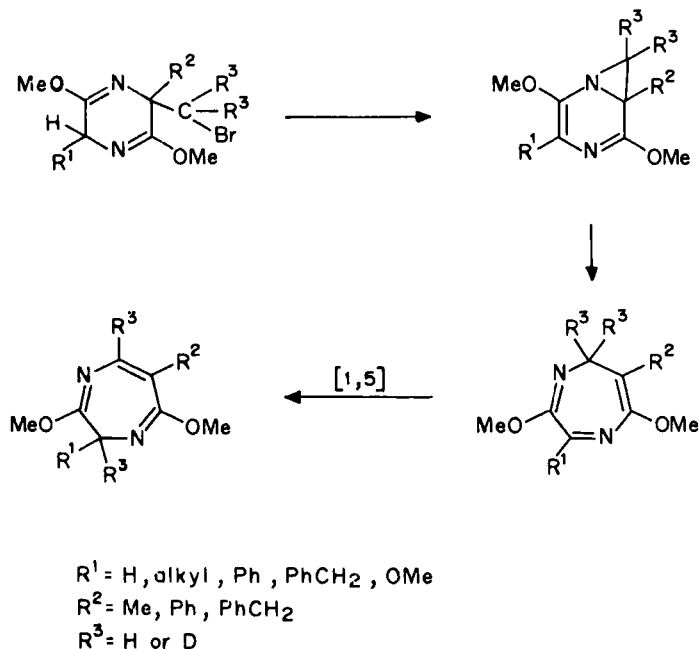
SCHEME 64

of this leads to a 5*H*-1,4-diazepine. This undergoes an extremely fast 1,5-sigmatropic shift to give the final diazepine.

The anion generated from the bislactim ether also reacts diastereoselectively with carbonyl compounds. As usual, the carbonyl compounds enter *trans* to the stereo-controlling substituent at C-6. With aldehydes or unsymmetrical ketones, a new chiral center is created at C-3'. Enantioface selection at the carbonyl group can lead to either the (*S*) or the (*R*) configuration at C-3'. The selectivity varies widely. In general, the C=O group enantioface selection is poorer than the diastereoface selection at the anion (83T2085). The predominant configuration at C-3' is dependent on the substituents, as shown in Scheme 67.

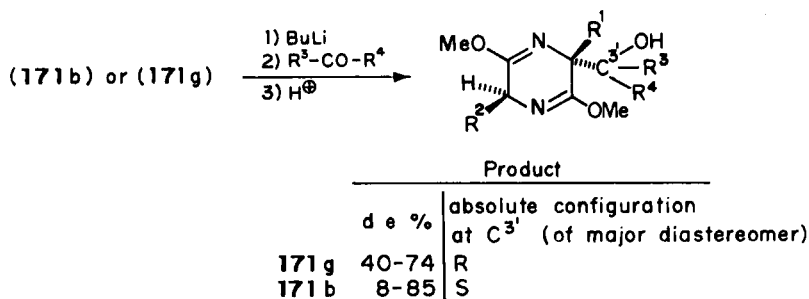


SCHEME 65

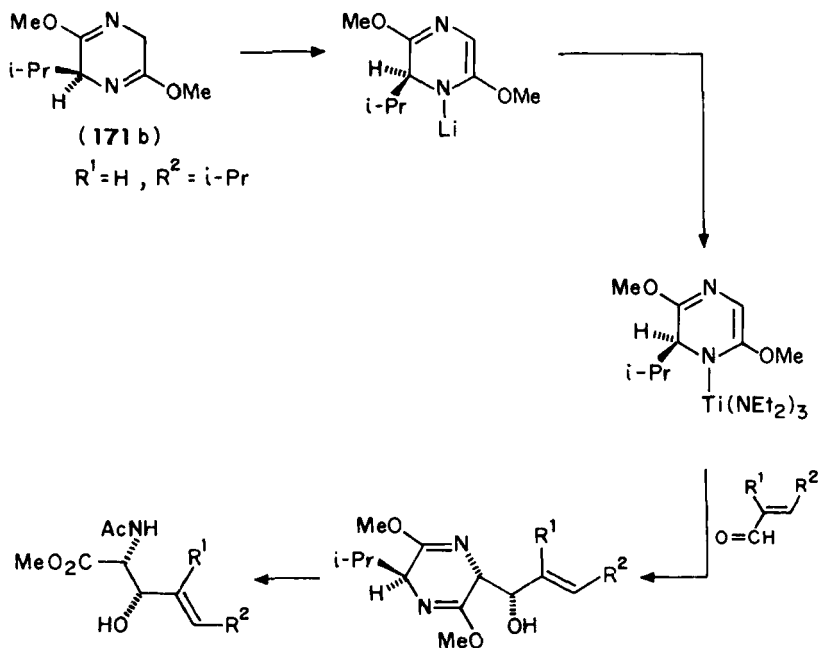


SCHEME 66

The degree of diastereoselectivity in the reaction with carbonyl compounds is raised significantly when the lithium is exchanged for titanium (88T5293). This has been ascribed to the shorter metal—oxygen and metal—nitrogen bonds in the titanium derivatives, which result in more compact transition states [85MI1; 89LA223]. Thus, the threo serine esters can be prepared as shown in Scheme 68. Even an α,β -unsaturated aldehyde can be used as starting material. This leads to the possibility of further



SCHEME 67



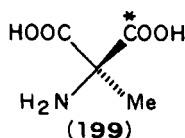
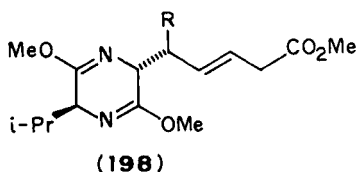
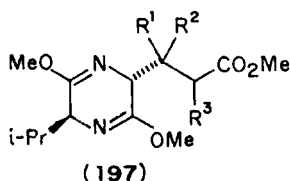
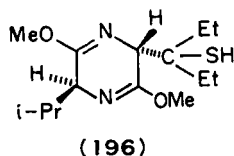
SCHEME 68

synthetic manipulations (epoxidation, cyclopropanation, etc.) (91LA857). With chiral aldehydes, double stereodifferentiation comes into play. (*S*)-Glyceraldehyde reacts with exceedingly high diastereoselectivity to give the product with 3*R*, 1'*R*, 2'*S* configuration.

The anions derived from bislactim ethers have been systematically reacted with several other electrophiles as well, by Schöllkopf and his school. Among these are thioketones (83T2085), acid chlorides (88LA781), and Michael acceptors (86S737; 88LA87). Pettig and Schöllkopf (88S173) report a 1,6 addition to methyl 2,4-pentadienoates. Compounds (196), (197), and (198) are some of the products obtained from (171b). The ^{13}C -labeled C-acetyl derivative obtained from (171c) has been oxidized with potassium hypochlorite to produce the ^{13}C -labeled carboxylic acid and esterified, and the bislactim ether hydrolyzed to produce finally the ^{13}C -labeled 2-amino-2-methylmalonic acid (199) (91T497).

Final hydrolysis of the bislactim ether is best carried out with dilute trifluoroacetic acid (91LA1207).

The lower enantioface selectivity at the carbonyl carbon of (*2E*)-hexadecenal with the lithiated derivative of (171b) (Scheme 67) has been



utilized to obtain the adduct with anti configuration; hydrolysis of this has led to D-erythro-sphingosine (91T2835).

For 1,4 addition to enones, the cuprates of the bislactim ethers have been found to be very useful [88AG(E)1194]. These are made by reacting the lithio derivatives with $\text{CuBr} \cdot \text{SMe}_2$ in the presence of dimethyl sulfide.

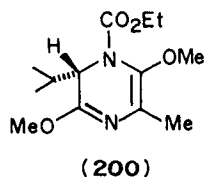
For Michael addition to nitroolefins, the lithio or titanium derivatives have been found to be useful [87AG(E)480]. Hydrolysis gives α -amino- γ -nitrocarboxylate esters (Scheme 69).

Occasionally, N-acylation is the predominant reaction with acyl halides. Thus ethyl chloroformate or diethyl carbonate on reaction with (171c) leads only to the urethane (200) (91T497).

A carbene has been generated at position 3 of the bislactim ether derived from cyclo(L-Val-Gly) via the lithio derivative and the diazo compound. The carbene has been trapped by an acetylene to provide a cyclopropene [88AG(E)433]. Hydrolysis with 0.1 N HCl leads to the cyclopropene aminoacid esters (Scheme 70).



SCHEME 69



3. Alkylation of Monolactim Ethers

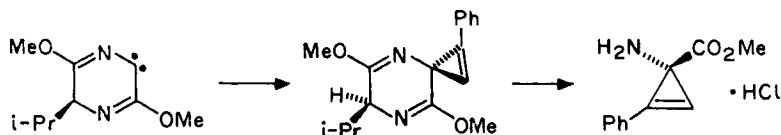
Monolactim ethers have been regio- and stereospecifically alkylated to give predominantly the *trans* products (Scheme 71) (85TL2955).

4. Generation of Chiral Cation from the Bislactim Ether and Its Use for C—C Bond Formation

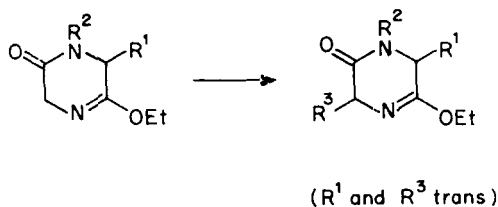
The 3-chloro derivative of the bislactim ether (**171b**) can be obtained by reacting the lithium derivative with hexachloroethane in THF at -78°C [85AG(E)1066]. Surprisingly, the major product of the reaction has the chlorine *cis* to the isopropyl group (*cis* : *trans*, 94 : 6). The chlorine can be displaced by soft nucleophiles in $\text{S}_{\text{N}}2$ reactions, with inversion of configuration. A chiral nonracemic, glycidyl cation equivalent could be generated by reacting the chloro compound with the Lewis acid SnCl_4 . This undergoes a Friedel Crafts reaction with activated arenes to produce the *trans* substituted bislactim ethers. Careful hydrolysis leads to the aryl glycines (Scheme 72) [87AG(E)683].

VI. N-Hydroxypiperazine-2,5-diones

1-Hydroxy- and 1,4-dihydroxypiperazine-2,5-diones belong to the class of cyclic hydroxamic acids. This moiety is known to occur in several natural products, such as mycelianamide. The chemistry of these fungal metabolites has been discussed by Sammes (75FOR51). A more recent review has also covered some synthetic aspects of 1-hydroxypiperazine-2,5-diones (88FOR203).



SCHEME 70



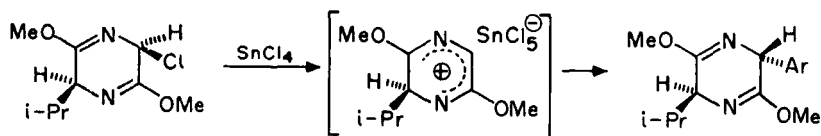
SCHEME 71

Three general methods have been employed for the synthesis of such molecules, all of them depending on cyclization of an appropriate linear precursor.

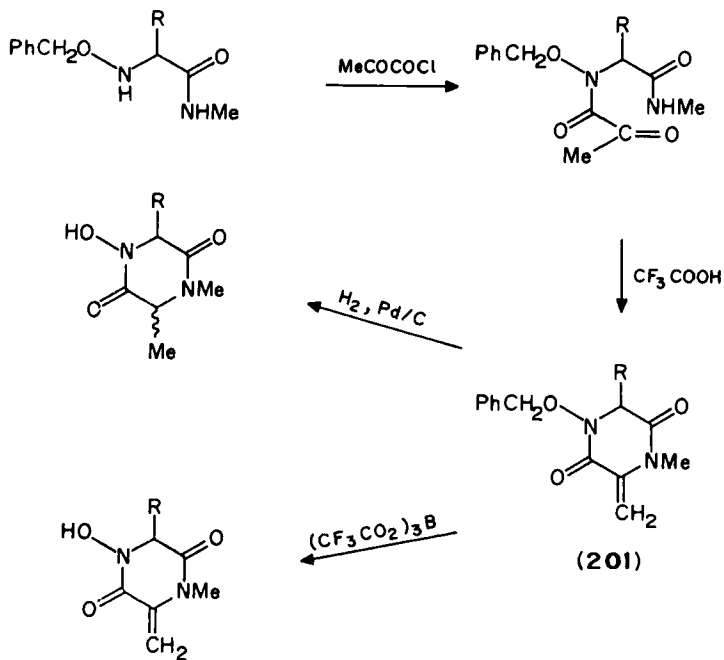
Acid-catalyzed cyclization of *N*-pyruvoyl derivatives of α -hydroxyl-aminocarboxylic acid amides has been extensively used by Dutch workers to generate 1-hydroxypiperazine-2,5-diones (80JOC1880). The requisite starting materials were prepared by reduction of the corresponding oximes with $\text{Me}_3\text{N}-\text{BH}_3$ complex. For subsequent transformations, the hydroxyl group was protected by benzylation. Trifluoroacetic acid-catalyzed ring closure of the derived pyruvamides gave the dehydro derivatives (**201**) in 50–70% yields. These could be converted to the 1-hydroxy-3-methylpiperazine-2,5-diones by catalytic hydrogenolysis. Selective debenylation, without saturating the exocyclic double bond, could be achieved by $(\text{CF}_3\text{CO}_2)_3\text{B}$ (Scheme 73).

The strategy has also been utilized in a synthetic approach to molecules related to neoechinulin and sporide smin (82JOC2147). Interestingly, acid cyclization ($\text{CF}_3\text{CO}_2\text{H}$) of the substrate (**202**) gave the 1-hydroxy-3-methylenepiperazine-2,5-dione (**203**) (50%) as well as a second compound (26% yield) identified as (**204**). Prolonged treatment of (**203**) with $\text{CF}_3\text{CO}_2\text{H}$ or HCl gave, as expected, a quantitative yield of (**204**) by protonation of the methylene, followed by alkylative cyclization on the indole ring (Scheme 74). A second exocyclic double bond could be introduced at position 6 of the piperazinedione ring in (**203**) by tosylation followed by base-catalyzed elimination to give (**205**).

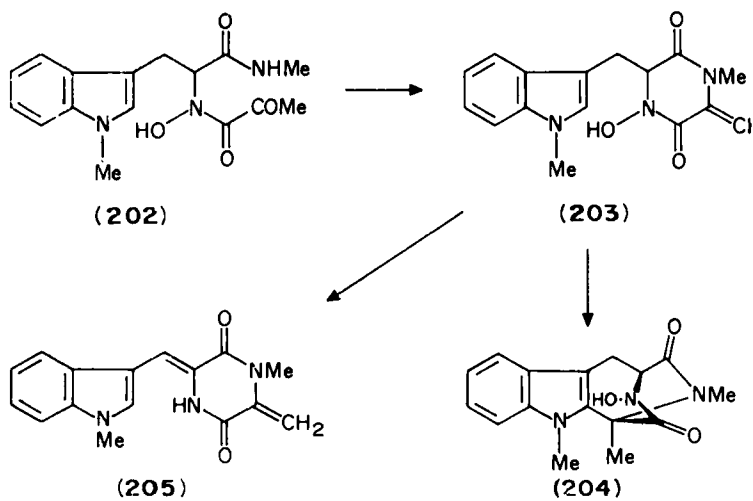
A similar series of reactions has given the *N*-allyl derivative (**206**) of neoechinulin B [87JCS(P1)2473]. However, conversion of this to neoechi-



SCHEME 72



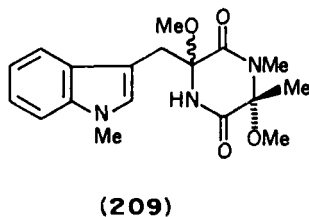
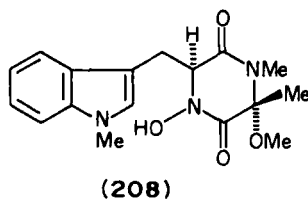
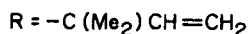
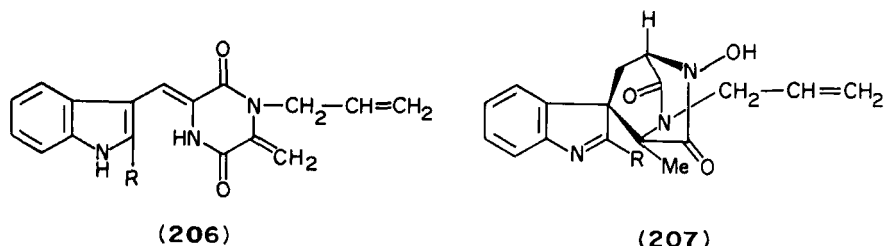
SCHEME 73



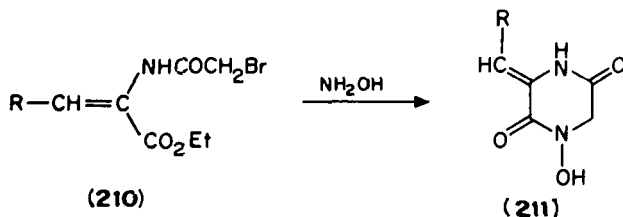
SCHEME 74

nulin B by N-deallylation could not be achieved. In this case also, a by-product was isolated during the acid-catalyzed cyclization, which was identified as the spiroindolenine (**207**). Presumably this also arose by protonation of the exocyclic double bond and then electrophilic attack of the resulting carbocation (or acyliminium ion) on the indole ring. Evidence for this has been provided by trapping the acyliminium ion generated from (**203**) with an external nucleophile-like methanol. The 3-methoxy derivative (**208**) was thus produced in 80% yield and with high stereoselectivity [86CRV697; 87JCS(P1)2481]. A second methoxy group could be introduced at position 6 by O-benzoylation of the above, base-catalyzed elimination and trapping of the acylimine with methanol. The product (**209**) was obtained as a 5 : 3 mixture of two diastereomers.

Some more examples of such α -functionalization are provided in Section IV.C.



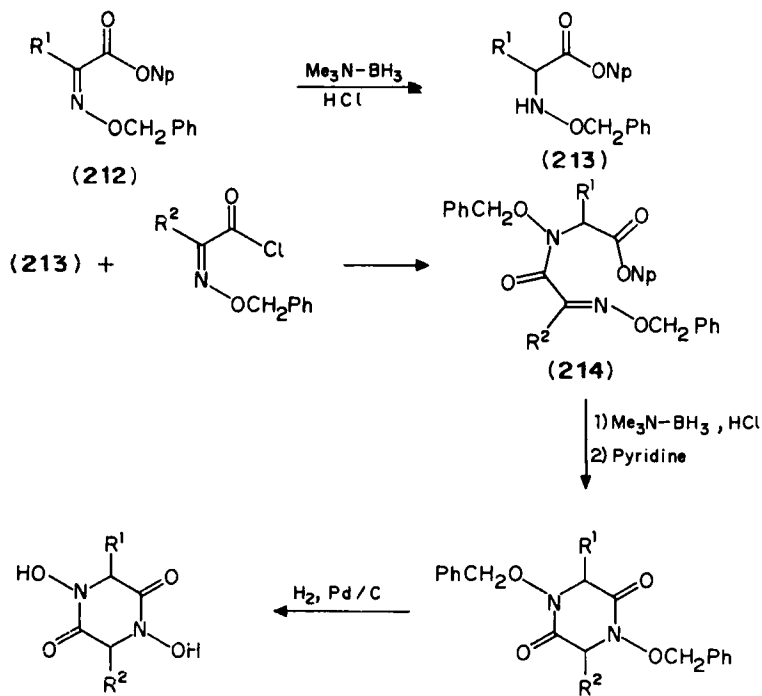
Cyclization of a dipeptide having a hydroxylamine unit at the N-terminus is the second general method for the synthesis of 1-hydroxypiperazine-2,5-diones. Thus, Japanese workers have reported that the *N*-bromoacetyl derivatives (**210**) obtained from the corresponding dehydro amino acid esters, on treatment with hydroxylamine, give low yields of 1-hydroxy-3-alkylidenepiperazine-2,5-diones (**211**) (78BCJ550). The corresponding iodo compounds lead to better yields, whereas the chloroacetyl derivative does not cyclize under these conditions.



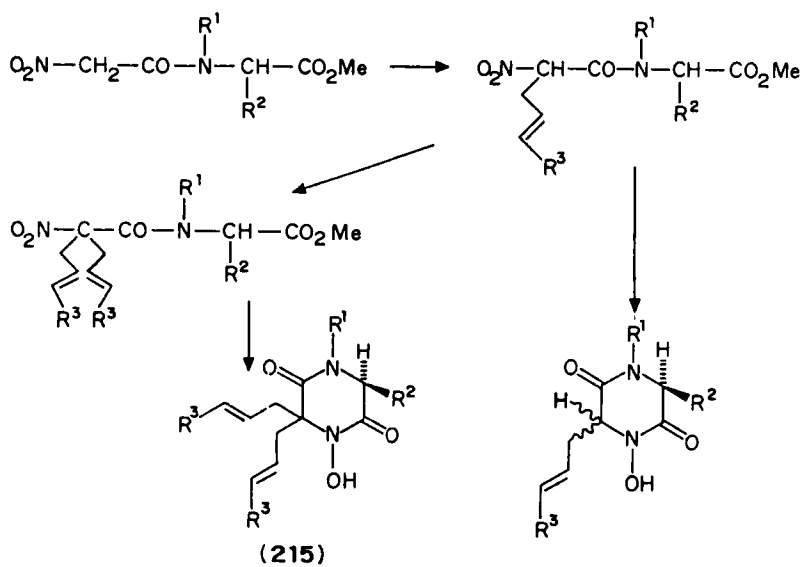
It has been reported that cyclization of a dipeptide ethyl ester having a hydroxylamine unit at the N-terminus is more difficult than that of a normal dipeptide because of the decreased nucleophilicity of the hydroxylamine nitrogen (81JOC3346). However, cyclization could be successfully achieved with a more "active" ester, viz., the *p*-nitrophenyl ester. This strategy is exemplified in the synthesis of several 1,4-dihydroxypiperazine-2,5-diones (Scheme 75). Crucial to this was the discovery that the oximes (**212**) and (**214**) could be reduced to the hydroxylamino esters without affecting the *p*-nitrophenyl group by means of the reagent Me_3N-BH_3 .

The requisite hydroxylamine function for such cyclizations can also be generated from a precursor having a nitro group. This novel route has provided access to hitherto unknown 1-hydroxy-6-allyl-, and -6,6-bisallyl-piperazine-2,5-diones (91UP1). The starting material is an *N*-nitroacetyl amino acid ester that can be either mono- or bis-allylated at the methylene adjacent to the nitro group. Reduction of the NO_2 to $NHOH$ using zinc/ammonium chloride, followed by cyclization, leads to the desired products (Scheme 76). Compound (**215**) is unique in that it possesses a chiral center at C-3 and a quaternary carbon at C-6 on a 1-hydroxypiperazine-2,5-dione system.

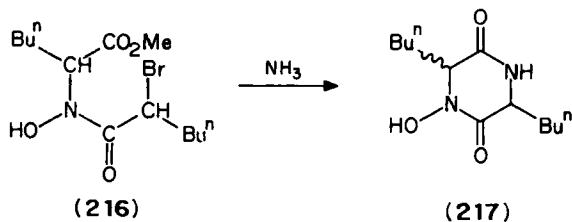
The third general method involves the cyclization of a linear dipeptide in which the C-terminal amino acid carries the *N*-hydroxy unit. This was the basis of a method described as far back as 1956 (56JCS4130), in which the bromoacetyl derivative (**216**) gave the 1-hydroxypiperazinedione (**217**) on treatment with ammonia. They have also described the formation of 1,4-dihydroxypiperazine-2,5-dione by treatment of (**216**) with hydroxylamine.



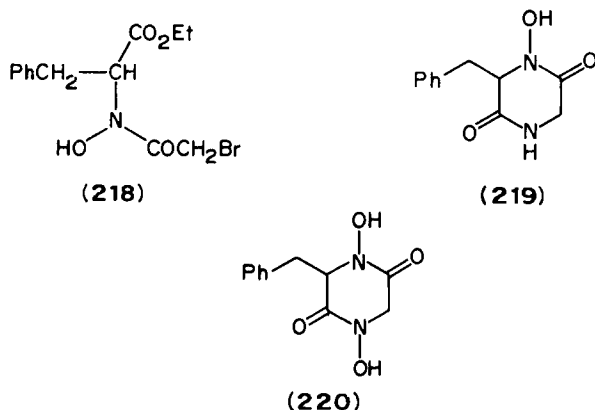
SCHEME 75



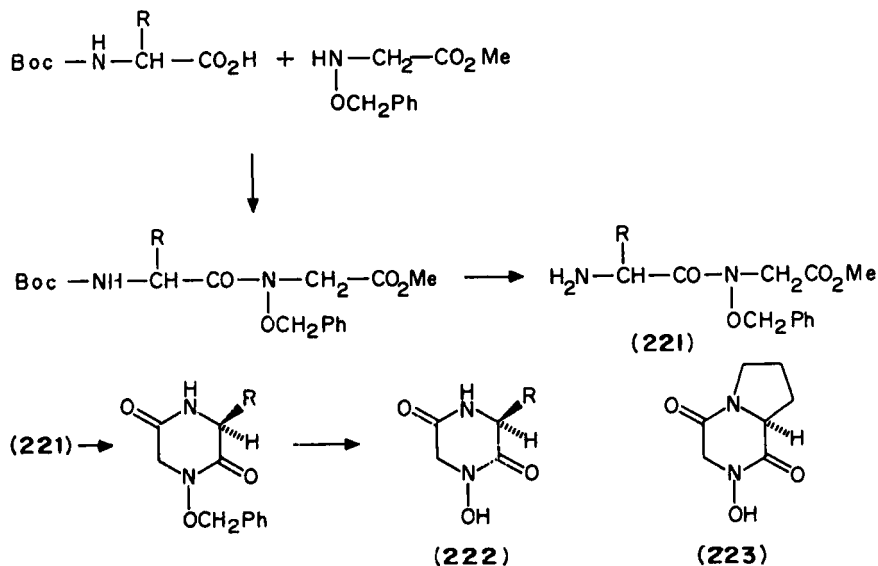
SCHEME 76



The above observations have been confirmed and extended by Japanese workers (75BCJ2584). The *N*-bromoacetyl derivative (**218**) of an α -hydroxylamino ester, on treatment with ammonia in ethanol at room temperature, gave 1-hydroxy-6-benzylpiperazine-2,5-dione (**219**). Under the same conditions, the chloroacetyl derivative gave only the 6-benzylidenepiperazine-2,5-dione by prior elimination and rearrangement. Treatment of (**218**) with hydroxylamine gave the 1,4-dihydroxycompound (**220**).



Chiral 1-hydroxypiperazine-2,5-diones (**222**) have been synthesized and their spectroscopic properties studied in detail recently [89JCS(P1)235]. *N*-Benzyloxyglycine methyl ester was condensed with BOC-L-amino acids using the mixed anhydride method. The resulting dipeptide was deprotected and cyclized by treatment with aqueous 5% NaHCO₃, and finally debenzylated by catalytic hydrogenolysis (H₂, Pd/C) (Scheme 77). Using L-proline, compound (**223**) has also been synthesized similarly. Interestingly, the rate of cyclization of the linear peptide (**221**) with an *N*-hydroxy in the middle of the chain is higher than that of the corresponding normal peptide. This is in contrast to the difficulty of cyclizing dipeptides with an N-terminal hydroxylamine mentioned earlier.



SCHEME 77

Detailed NMR studies have shown that the conformation of these 1-hydroxypiperazinediones is quite similar to that of the corresponding normal (NH) piperazinediones.

VII. Application of Piperazine-2,5-diones

A. CATALYTIC ACTIVITY OF PIPERAZINE-2,5-DIONES

The secondary structure of the polypeptide chain in hydrolytic enzymes ensures the spatial proximity of the necessary functional groups, which are responsible for the observed catalytic effect. In synthetic enzyme mimics, it is possible to bring the requisite functionalities into close juxtaposition only if there is a rigid framework to which these groups are attached. It was thus logical to examine cyclic peptides, especially cyclodipeptides, which bear the necessary functional groups for their catalytic activity in ester hydrolysis.

The efficiency of the catalysis would also depend on the binding of the substrate to the piperazine-2,5-dione by means of weak forces. Imanishi and his group (85BCJ497) have sought to achieve this by means of hydrophobic interactions. They have chosen as substrates *p*-nitrophenyl esters of long-chain fatty acids; the hydrocarbon chain would enter into

an attractive interaction with the hydrophobic part of the side chain of the piperazine-2,5-dione. In order to maximize this interaction, leucine or valine was chosen as one of the amino acids of the piperazine-2,5-dione. The catalytic site was provided by the imidazole unit of a histidine residue.

Both cyclo(D-Leu-L-His) and cyclo(D-Val-L-His) exhibited a high catalytic activity toward $\text{CH}_3-(\text{CH}_2)_{10}-\text{COOC}_6\text{H}_4\text{NO}_2$ at a substrate concentration of $2.0 \times 10^{-6} \text{ mol dm}^{-3}$. The k_{cat} in both cases was higher than with pure imidazole, although the piperazine-2,5-diones are less basic ($\text{p}K_{\text{a}}$ 6.00) than imidazole ($\text{p}K_{\text{a}}$ 7.05). This clearly suggests that the hydrophobic binding is responsible for the increased reaction rate with the cyclic peptides. Interestingly, the k_{cat} values for the two cyclic dipeptides cyclo(L-Leu-L-His) and cyclo(L-Val-L-His) are lower than those for the diastereomers mentioned above. When the hydrophobicity of the substrate was drastically reduced, as in $\text{CH}_3\text{COOC}_6\text{H}_4\text{NO}_2$, imidazole proved to be more effective as a catalyst than the cyclic dipeptides, perhaps because of decreased basicity and increased steric hindrance in the latter. An attempt has also been made to deduce the solution conformation of these cyclodipeptides from their $^1\text{H-NMR}$ spectra. The results suggest that in cyclo(D-Leu-L-His) or cyclo(D-Val-L-His), the backbone is almost planar; the two side chains exist on opposite sides of this plane. In D_2O , the proportion of the folded conformation, with the imidazole side chain of the histidine stacking over the peptide plane, is about 60 to 68%.

The catalytic effect of these cyclodipeptides on substrates having other charged functionalities, in addition to the *p*-nitrophenyl ester, has been studied (83MI2). The authors were unable to detect any specific catalysis of the hydrolysis of such substrates.

B. CHIRAL INDUCTION IN PIPERAZINE-2,5-DIONE-CATALYZED REACTIONS

The addition of hydrogen cyanide to carbonyl compounds to form cyanohydrins is a base-catalyzed reaction. It is also known that the enzyme oxynitrilase catalyzes the addition of HCN to benzaldehyde to give (*R*)-mandelonitrile exclusively. It was therefore logical to explore the possibility of using synthetic enzyme mimics to bring about chiral induction in cyanohydrin formation. Beginning from 1982, Inoue and colleagues (82MI2) have systematically investigated the use of cyclic dipeptides containing a histidine unit as chiral catalysts in this reaction. The imidazole side chain provides the necessary base catalysis. Cyclo[(*S*)-Phe-(*S*)-His] has been found to be excellent for the hydrocyanation of various alde-

hydes. The yields are good and enantiomeric excesses obtained are quite high [81CC229; 86BCJ893; 90JOC181].

Addition of HCN to various aldehydes was carried out by using 2 mol% of the cyclic dipeptide as catalyst and 2 eq of HCN. The reaction was preferably carried out in toluene at -20°C . Under these conditions, benzaldehyde gave (*R*)-mandelonitrile in 97% yield with an enantiomeric excess (ee) of 97%. The use of cyclo[(*R*)-Phe-(*R*)-His] gave (*S*)-mandelonitrile with ee of 93%. The presence of electron-withdrawing groups on the phenyl ring of benzaldehyde led to poor ee values.

Asymmetric induction with aliphatic aldehydes was moderate (18 to 71%). It was also found that the activity of the chiral catalyst was maximum when it was first purified by nonaqueous solvents. Other cyclic dipeptides containing a histidine moiety (e.g., cyclo[(*S*)-Ala-(*S*)-His]; cyclo[(*S*)-His-(*S*)-His]; cyclo[(*S*)-Pro-(*S*)-His]) gave low ee values (0–10%). The linear dipeptide *Z*-(*S*)-Phe-(*S*)-His-OMe showed no asymmetric induction.

On the basis of the above data, a tentative hypothesis has been advanced for the observed asymmetric induction. The carbonyl oxygen of benzaldehyde forms a H-bond with the piperazine ring NH of the histidine, the imidazole is protonated by the HCN, and the resulting cyanide ion attacks the *si* face of the activated carbonyl group since the *re* face is blocked by the phenyl ring of the phenylalanine, as seen in the Fig. 1.

However, recently other intriguing facts have come to light, which makes it obvious that some other factors may also be involved in the enantioselectivity of the addition. When cyclo[(*S*)-Leu-(*S*)-His] is used as the catalyst for the same reaction, (*S*)-mandelonitrile is formed with 55% ee. The best solvent for this reaction was ether (better than toluene). Aliphatic aldehydes generally led to better enantioselectivities (60 to 80% ee). This perhaps suggests some hydrophobic attraction with the leucyl side chain (89CL2119).

Evidence for a preliminary complex formation between the chiral cata-

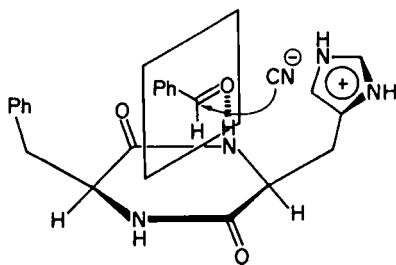


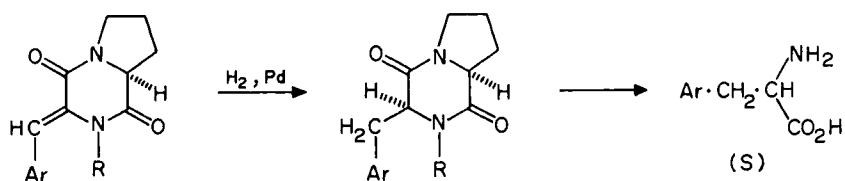
FIG. 1.

lyst, cyclo[(*R*)-Phe-(*R*)-His], and the product, (*S*)-cyanohydrin, has been provided by a detailed study of the addition of HCN to 3-phenoxybenzaldehyde (91JOC6740). This complex seems to promote the asymmetric hydrocyanation and is an example of "enantioselective autoinduction."

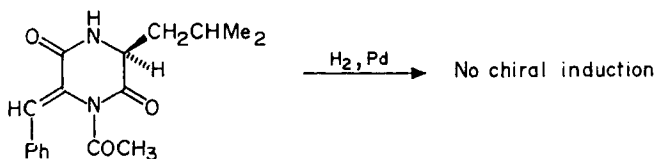
C. SYNTHESIS OF AMINO ACIDS BY ASYMMETRIC HYDROGENATION

Poisel and Schmidt (73CB3408) reported in 1973 that the catalytic hydrogenation of arylidene derivatives of cyclo(Gly-(*L*)-Pro) proceeds with high asymmetric induction. Subsequent acid hydrolysis leads to optically active aromatic amino acids (Scheme 78). The asymmetric induction was as high as 90% and the new chiral center also had the *S*-configuration in the major diastereomer. However, the corresponding alkylidene derivatives did not lead to any asymmetric induction on hydrogenation. They also reported that when *L*-proline was replaced by *L*-leucine, hydrogenation followed by hydrolysis gave only *racemic* phenylalanine.

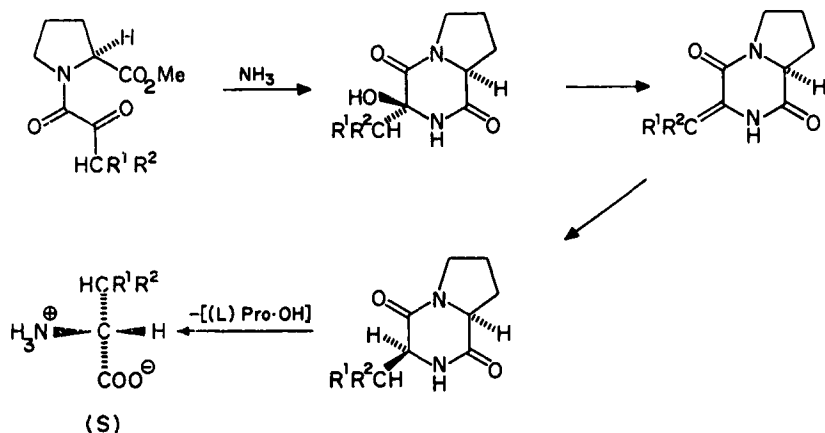
Bycroft and Lee (75CC988) developed this into a general method for the asymmetric synthesis of α -amino acids, wherein the chiral auxiliary (*L*-proline) could be recovered and recycled. Condensation of *L*-proline methyl ester with α -keto acids using DCC, followed by a treatment with anhydrous ammonia at room temperature, gave the 3-hydroxypiperazine-2,5-diones with high stereoselectivity (cf. Scheme 79). These could be



R = H or COMe



SCHEME 78



SCHEME 79

easily converted to the dehydrocyclic peptides (anhyd $\text{CF}_3\text{CO}_2\text{H}$ or SOCl_2/Py). Hydrogenation of these dehydro derivatives (H_2 , 1 atm., EtOH, Adam's catalyst, room temp.) afforded the (*S,S*) cyclodipeptides. The chiral induction was greater than 90%. Acid hydrolysis then yielded L-proline and the other aminoacid with the (*S*)-configuration as shown in (Scheme 79).

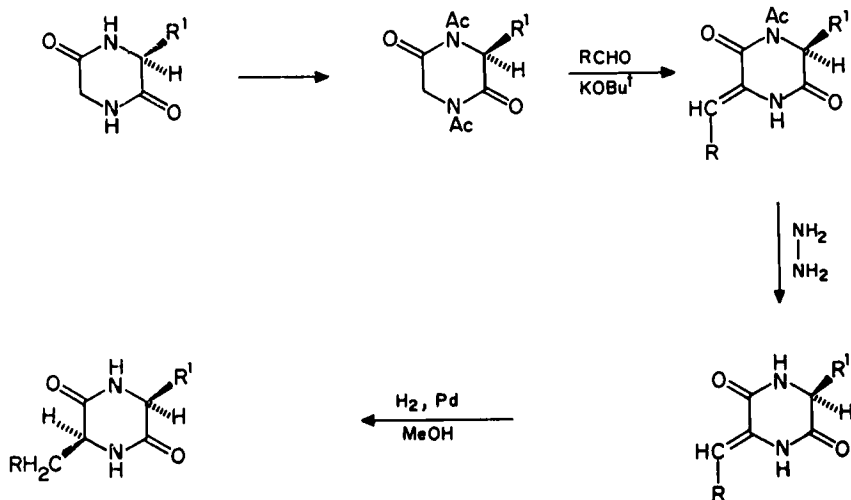
If, in the above sequence, the (*S*)-proline is replaced by (*S*)-Phe or (*S*)-Ala, then the resulting asymmetric induction is considerably diminished.

The above method could be extended to the synthesis of *N*-methyl amino acids by using anhydrous MeNH_2 instead of ammonia for the cyclization to the piperazine derivative.

Izumiya and co-workers (77JA8346) have undertaken a systematic study of the chiral induction on hydrogenation (H_2 , 1 atm., Pd black, MeOH) of a series of cyclodipeptides of the type $\text{cyclo(L-aminoacyl-Dha)}$, where Dha represents dehydroalanine. These were synthesized from the corresponding L-serine derivatives; the final dehydration was accomplished by Photaki's procedure (63JA1123). Contrary to the report of the earlier workers, the de in the product $\text{cyclo(L-aminoacyl-Ala)}$ [(*S,S*) over (*S,R*)] was the highest with valine (98.4%) and the least with proline (84.8%). Leucine gave about 95% de.

In order to prove the importance of the rigid structure, as in the piperazinediones, these authors have carried out similar hydrogenation under identical conditions with the corresponding linear dipeptide derivatives. The ratio of the two diastereomers in the product was 49:51 (77JA8346).

The method has been further extended by Izumiya and co-workers (79TL4483). The starting cyclic dipeptides incorporating a dehydro amino



SCHEME 80

acid (represented as ΔXYZ) were prepared as shown in Scheme 80. In every case the de of the hydrogenated product was estimated. This ranged from 66 to 99%. The lowest de was obtained with cyclo(Δ Trp-L-Leu). This is ascribed to the fact that in this substrate, the piperazine-2,5-dione ring and aromatic side chain are not coplanar.

Pd black was found to be the most effective catalyst for such stereoselective hydrogenation; methanol or dimethyl formamide was the best solvent.

The conditions for the hydrolysis of the final piperazine-2,5-dione have been critically examined. A 1 : 1 mixture of dioxane and aqueous HCl (1 or 0.5 M) was found to be the best. Some unusual amino acids, including those having a basic side chain, have been synthesized by this procedure (86BCJ323; 89BCJ2315).

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Halogenation of Heterocycles:

I. Five-Membered Rings

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I. Introduction

It has been some years since Eisch reviewed heterocyclic halogenation [66AHC(7)1], although there has been more recent coverage of specific aspects of halogenation. The most recent and comprehensive is included in a survey of quantitative aspects of electrophilic substitution of heterocycles [90AHC(47)1], which includes references up to 1986. Halogenation of individual ring systems has been summarized in the various volumes of "Comprehensive Heterocyclic Chemistry" (published in 1984) and in the "Chemistry of Heterocyclic Compounds" series of monographs. The specific sources will be referenced in the appropriate sections of this present review which emphasizes material published since 1978, but also provides a more comprehensive coverage by the inclusion of appropriate earlier material. Although the paucity of information in some sections may be a consequence of the author's selection process, it is more likely to be a reflection of the absence of significant new work within the period surveyed.

Originally conceived as a single review, this work has now been divided into three parts that separate the five-membered rings (Part I), six-membered rings (Part II), and condensed systems (Part III). The section dealing with halogenation methods is introductory to all three parts.

With the exception of ring-synthetic procedures, an effort has been made to include all methods of introduction of halogen atoms into a heterocyclic ring. Thus electrophilic, nucleophilic, and radical processes are covered as well as some rearrangements.

Coverage is restricted to halogenation of conjugated heterocycles. Although not all of these can be classified as aromatic (e.g., pyranones, fulvalenes), there are aspects of their reactivities that have parallels in the series traditionally classified as heteroaromatic. Processes that produce a halogenoaromatic product from a nonaromatic substrate (e.g., quinolone to chloroquinoline) are usually included.

Although physico-chemical aspects and mechanistic features are covered, the emphasis of this review is largely qualitative and does not seek to repeat the treatment of Katritzky and Taylor [90AHC(47)1]. Rather, information is organized to assist researchers wishing to use halogenoheterocycles as reactive intermediates in heterocyclic synthesis. Methods of specific regiochemical introduction of halogen allow the potential incorporation of other substituents whether by way of metallation procedures, by more direct nucleophilic or electrophilic substitution, or by use of the halogen atom to modify reactivity and direct substitution elsewhere in the molecule before removal or replacement.

That fluorination procedures make up an appreciable part of this review reflects the burgeoning interest in fluorinated compounds and the "new chemistry" that results from the incorporation of a fluorine atom into a heterocyclic ring.

II. Halogenation Methods

A. ELECTROPHILIC HALOGENATION

Electrophilic halogenation processes can involve conventional mechanisms with a carbocation intermediate, or pathways that are of the addition-elimination type. Sometimes the process does not go beyond the addition stage; there are also examples of halodehalogenation in which the displaced halogen attaches elsewhere in the ring, as in the chlorination of 3-bromobenzo[*b*]thiophene to give 2-bromo-3-chlorobenzo[*b*]thiophene as one of the products (73IJS233).

The halogenating agents are sometimes conveniently divided into "positive" and "molecular" species, with the former referring to cases where the halogen is nearly fully polarized, and the latter to instances where the molecular halogen only becomes significantly polarized on close approach to the substrate [66AHC(7)1; 90AHC(47)70]. Positive halogenation includes reactions of acidified hypohalous acids and processes involving Friedel-Crafts catalysts. Molecular halogenations apply when halogens dissolved in organic solvents are used, and with *N*-haloamides (which provide a low equilibrium concentration of molecular halogen). Because, however, of the varying degrees of coordination between halogen and solvent there will naturally be a wide spread of reactivities, and classification of many reactions as positive or molecular halogenation can only be speculative. Accordingly, the introductory summary that follows (II,A,1-3) does not attempt to classify all of the processes in this way.

Electrophilic halogenation frequently involves displacement of a substituent other than hydrogen as a result of *ipso* attack, e.g., trimethylsilyl (84JOC4687; 86S757; 91MI1), sulfonic acid (70RCR923; 76MI1, 76SC243), formyl (80BAU778; 86TL5019; 90CHE416), carboxylic acid or ester (59ACS888; 69RTC321; 78CJC2430; 80BAU778), another halogen atom [37LA(527)237], nitro (25RC33; 38JA2906; 70RCR923; 82JGU807), and various metallic species such as magnesium (Grignard) (60BRP826619; 67BSF1294), mercury [75JCS(P2)620; 76MI1; 80JCS(P1)1390; 81JHC885; 82CJC554; 85CHE322; 88MI1], lithium [85H(23)417; 88JOC2740; 90JCS-(P1)1829, 90JOC2993; 91MI2; 92JOC2495], tin [81H(16)1161; 82CPB1731; 86S757; 87TL759], and thallium derivatives [85S353; 86H(24)3065; 87CPB3146; 87H(26)1173, 87H(26)2817]. The improvements in selective

lithiation techniques have opened the way for the simple synthesis of halogenoheterocycles previously accessible only with difficulty.

Because halogens vary so much in size the regiochemistry of attack can vary within the group. It is, for example, more likely that 1,2-dichlorination will occur than 1,2-dibromination or 1,2-diiodination. The larger halogens may also produce a greater proportion of a more abundant isomer in reactions that typically give mixtures, e.g., halogenation of benzo[*b*]thiophene [71JCS(B)79], and there are other examples [81H(15)1285; 90S497].

The great diversity of reactivity in π -excessive and π -deficient heterocycles serves to make halogenation too easy in some instances or quite difficult in others. It is a problem to prepare a monohalogenated pyrrole even in dilute solution with mild reagents and low temperatures (81JOC2221), yet azines are reluctant to submit to electrophilic halogenation, necessitating the use of powerful reagents such as bromine in concentrated sulfuric acid in the presence of silver sulfate, or alternatively a nucleophilic process.

1. Chlorination and Bromination

Electrophilic chlorination has been accomplished by the use of chlorine in the presence of Lewis acid catalysts, e.g., for furans and thiophenes [55JOC657; 72CHE541; 76JHC393; 89EUP340472, 89M65], benzothiazoles (84GEP3234530), and picolines (80JGU354). Similarly bromine in the presence of aluminium chloride for furans and thiophenes (80CHE1195; 84JHC215), thiazoles (86CHE663), and pyrones (85CHE1215), with iron powder for dibenzofurans [82H(19)2349], and other catalysts such as tin(IV) bromide and thionyl chloride have found application [80JCR(S)201; 85CHE458].

Chlorine in concentrated sulfuric acid was successful for 2-aminopyridine (76JOC93) and quinolines [83CHE1093], and with added silver sulfate for quinoxalines [80JCR(S)2823; 84CL323]. Bromination, too, in sulfuric acid or oleum for pyridines (88ZC59; 89ZC287), bromopyridine *N*-oxides (62RTC864, 62T227), and pyrazoles (88CHE703), or in the presence of trifluoroacetic acid for pyrroles (88JOC2796), pyridines [70JCS(B)117, 70RC779], and 1,6-diazaphenylene (82CJC3049) has proved successful. Addition of silver sulfate to the concentrated sulfuric acid (71BAU2687) provided a suitable brominating medium for oxazoles (71JOU1835), benzisothiazoles [80JCR(S)197], benzodiazepinones (84CHE927), and particularly for unreactive azines [62T227; 79JCS(P1)1503; 80CHE275, 80JCR(S)201; 81JAP(K)128762; 89CS309]. Fluoroantimonic acid instead of 97% sulfuric acid has been used in the bromination of indolines (83JHC349).

Positive bromination of thiophene and selenophene [70JCS(B)43], isoxazoles (82MI1), indoles [86H(24)1311], and substituted pyridines (76JOC93) occurs with aqueous hypobromous acid, sometimes containing dioxane. There are numerous examples of the use of hypochlorites, whether in acidic or basic medium, for the chlorination of heterocycles [80JHC409; 81JOC2054; 82JOC1008; 83JHC277, 84JOC4784; 86H(24)1311; 87JOC173; 89SC1505], and *tert*-butyl hypochlorite, too, has been used [80H(14)867, 80JOC76], although this reagent may promote radical chlorination.

Chlorine or bromine in the presence of an alkali, in aqueous or chlorinated hydrocarbon solution, has also been widely used (54ZOB488; 82CHE539, 82S844; 83S932; 85ZPK1185).

Reactions with sulfuryl chloride, phosphoryl chloride, and thionyl chloride may also involve a fairly positive chlorine [67JCS(C)1922; 72JCS(P1)2004; 83CHE1044; 86H(24)2879], and the first named is a very mild reagent for reactive heterocycles such as furans. It has been used in acetic acid (81RCR816), chloroform (84S847), methylene chloride (80JHC1125; 90JHC315), diethyl ether (89CJC433), and dioxan (90M565), or supported on silica [84JCR(S)390; 85JHC281] or alumina (92SC1095).

Interhalogen compounds [e.g., BrF [88JOC1123, 88JOC5545] and BrCl (83G149)] have found increasing application as polarized halogenating agents. The former reagent can be prepared directly from its elements by passing fluorine through a cold suspension of bromine in trichlorofluoromethane. The solution is used without purification, as BrF disproportionates to BrF₃ and Br₂ (88JOC5545), and is particularly effective with deactivated compounds such as pyridines.

A number of N-brominated and N-chlorinated heterocycles also provide sources of electrophilic bromine. Examples include 1-chlorobenzotriazole (82JOC4895; 87JOC173; 88CHE36) and various HBr and Br₂ adducts of pyridines, or pyridine perbromides [84SC939; 85JAP(K)60/87264]. Polymer-supported reagents of this type include 1-cyclohexylpyridinium perbromide linked to polystyrene, effective for the bromination of 1-methylindole, benzo[*b*]furan, and benzo[*b*]thiophene (89T7869).

Related to these reagents are dioxane-dibromide (54ZOB1265; 78JHC123; 82CHE1284; 86CHE806; 89BAU1494; 90CHE416), hexabromocyclopentadiene (91MI4), and halodimethylsulfonium halogenids or the sulfoxonium analogues (e.g., Me₂S⁺Br Br⁻ or Me₂S⁺(O)Cl Cl⁻), which are generated when trimethylsilyl chloride and dimethyl sulfoxide react [80ACR330; 89JCR(S)182]. Solvated halogen molecules or halonium ions are involved as the reactive species. These reagents have been used to chlorinate and brominate indoles and indole alkaloids [89JCR(S)182, 89SC3415]. The same type of species may be the brominating agent generated in a solution of ethyl bromide (65T945) or *t*-butyl bromide (82G535) in dimethyl sulfoxide.

Molecular chlorination has employed solutions of chlorine in water (80JHC1311), alcohols (80CC1139), carbon tetrachloride (82JGU2287; 86CPB4432), carbon disulfide (84G1), acetonitrile (80T2681), and toluene [86JAP(K)61/106563], often with an added base (pyridine or tertiary aliphatic amine) to remove hydrogen chloride.

Bromination using bromine is even more common. It can use bromine alone [80JHC1399; 86H(24)2545] or chloroform [80JCR(S)197; 82CHE268; 84CHE687; 85JHC1537; 86JHC17], methylene chloride [83JCR(S)144, 83JCS(P1)93; 88S950], carbon tetrachloride (83CHE1287, 83JOC1064; 84JHC725), dimethylformamide [72JCS(P1)2567; 92JOC3240], benzene [85CS(25)295], alcohols (80CC1139; 83CJC2171, 83S932; 85TL3039; 90M565], nitrobenzene (83JOC3297), water (82CHE753; 83CJC2171; 84S972), or carbon disulfide (83CJC2171; 84G1), again often in the presence of tertiary amines (81CJC635; 82JHC673; 84CHE713). The solvent can also act as the base to remove hydrogen bromide, e.g., pyridine (88BCJ2690). Bromination in acetic acid is common [80JCR(S)197; 82CHE240, 82CJC1233; 83M425; 84JOC3401; 87H(26)2817; 90AHC(47)70, 90LA1083], and other acidic solvents such as trifluoroacetic acid (88JOC2796) and hydrobromic acid (84SC939; 88SC855, 88SC1763) have been used. Frequently sodium acetate is added to buffer the medium [82BSF(2)89, 82CJC3049, 82JHC407; 83CHE1322; 86JCR(S)122; 88JOC4185; 90H(31)109]. Similarly, chlorinations in acetic acid-sodium acetate mixtures have been reported [83CHE802; 90CHE307, 90H(31)109].

Solutions of bromine in thionyl chloride or sulfonyl chloride may not brominate by the usual electrophilic aromatic substitution process (60JA4430).

Although *N*-haloamides such as *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) can act as sources of halogen radicals under certain conditions, they characteristically provide a low equilibrium concentration of molecular bromine or chlorine and are especially suitable reagents for the halogenation of the more reactive heterocycles. The mechanism of bromination with NBS has been discussed (78ACR381). Both of these reagents have been used frequently in acetic acid [86S555; 87IJC(B)225; 88CPB3838; 89JOC5347; 90JOU1166], trifluoroacetic acid (82CJC3049), sulfuric acid (88CHE892), chloroform (84CHE426; 88TL2405), carbon tetrachloride (80JOC3738; 82CHE307; 88S767; 89SC2721), alcohols [89JCS(P1)2009], tetrahydrofuran [81JOC-2221; 84JOC3239; 88HCA2053; 90JHC1505], dimethylformamide [85MI1; 89JCS(P1)95], and supported on silica gel in methylene chloride (86TL1051; 88MI4; 91MI3). Other analogous *N*-haloamide reagents include *N*-chlorobenzamide (89CC1466), *N*-chloroacetanilide (86CC1585),

N-chloroisatin (82JOC4895), and *N*-halopolymaleimides (81S413). Other related reagents that provide low equilibrium concentrations of molecular bromine probably include the dioxane–bromine complex, 2,4,4,6-tetrabromocyclohexa-2,5-dienone [73JCS(P1)68], hexabromocyclopentadiene (82CC778; 91MI4), and quaternary ammonium perbromides (84BSF157).

Instead of using molecular chlorine or bromine directly, these species can be generated *in situ* by the action of an oxidizing agent on a metal halide or hydrogen halide. Such reagents as sodium or potassium bromate (82BAU2104; 84CHE924; 86MI1), potassium chlorate (90S499), hydrogen peroxide (80CC1139; 88S890; 89BAU1494; 91MI5), and *meta*-chloropero-benzoic acid (81JOC2819) have proved successful, although one suspects that the peroxides may also be generating halogen radicals. The use of copper(II) bromide in acetonitrile for the oxidative bromination of pyrroles is a related reaction (90JHC1209), as are the recent applications of enzymatic methods to heterocyclic halogenations. Chloroperoxidase-catalyzed halogenations of uracil and cytosine to give the 5-chloro- and 5-bromo-derivatives are probably electrophilic processes (87CL2311), and there are other examples (87B282, 87JHC1313; 89MI1).

Other chlorinating and brominating agents that have been used rarely include 1,3-dibromo-5,5-dimethylhydantoin (51MI1), sodium bromide in the presence of antimony pentahalide catalysts (80S345), and benzeneseleninyl chloride with aluminium halide catalysts (90MI1). 5,5-Dibromobarbituric acid effectively brominates anilines, but has yet to be applied to heterocycles (87MI2), and there may be occasions on which phase-transfer catalysis procedures could with profit be applied to heterocyclic halogenation, e.g., an anionic heterocycle with carbon tetrachloride or bromotrichloromethane [81ACS(B)263].

Although some organometallic derivatives of heteroaromatic compounds are made by halogen–metal exchange, there are occasions on which it may be advantageous to prepare a halogenoheterocycle from the metallic derivative, and there are examples of chlorination, bromination, and iodination of lithium derivatives [81CC1095; 83JCS(P1)271, 83SC467; 84JHC785, 84JOC3857; 85H(23)417; 87JCS(P1)1865; 88JOC2740, 88S215; 89SC1047; 90JHC673, 90JOC2993]. Such sequences allow electrophilic halogenation of ring positions often only susceptible to nucleophilic attack. Thus, lithiation of 1,2,3-triazolo[1,5-*a*]pyridine followed by quenching with chlorine, bromine, or halide solvents gave the 7-chloro- and 7-bromoderivatives [82JCS(P1)967].

Amides capable of complexing with bromine (e.g., carboxamides, urea, HMPA) are known to increase yields in the bromination of methyl alkyl ketones (84BAU418), and there may be applications of this in heterocyclic bromination.

2. Iodination

A review of methods of synthesis of aromatic iodo compounds has appeared offering considerable information of potential value to research chemists wishing to prepare iodoheterocycles (84RCR343). Iodination differs from chlorination and bromination in that a much less reactive electrophile (and a much larger one) is involved. The second step of the reaction is usually at least partially rate-determining. Isotope effects are noted in the iodination of indole [68AC(R)1435], and the transition state resembles the Wheland intermediate more than in chlorination and bromination.

Electrophilic iodinations generate hydrogen iodide, which is such a strong acid that it can cause protolytic cleavage of some heterocycles, but the problem can be alleviated by addition of mercury(II) oxide or acetate (86EGP236733). The low electrophilic reactivity of iodine means that drastic conditions have to be employed if the substrate is unreactive. Iodine in concentrated sulfuric acid in the presence of silver sulfate may be necessary for the iodination of resistant species (83CHE1093; 84JHC785; 85CHE1215; 90SC877).

There are, however, many examples of the successful use of iodine in solvents such as chloroform [84H(22)1195], dimethyl sulfoxide [82CHE240; 84H(22)1195], dimethylformamide (82S1096), nitrobenzene (83JOC3297), or aqueous acetic acid [82IJC(A)417]. Basic solvents such as pyridine [82JAP(K)40497], aqueous ammonia (83CHE1008), or aqueous sodium carbonate (90S497) or addition of bases to other reaction solvents [84H(22)1195; 85CPB5147] helps overcome the problem of HI formation. There are examples of the use of iodine in the form I_3^- in neutral [86H(24)2879] or alkaline medium [83JCS(P1)735]. Direct iodination under mild conditions where iodine is in the presence of alumina-supported copper(II) chloride or sulfate has yet to be reported for heteroaromatic compounds (92BCJ306). Frequently, oxidative conditions have been used, either with iodine alone or with iodine-iodide mixtures. Thus, iodine with iodic acid in acetic acid (85MI2; 89CJC433), iodine and periodic acid (84LA31), iodine with acidified permanganate (88CHE1407), and iodine-iodide in the presence of cerium(IV) salts (88TL2855; 90JOC4928) have found applications, although the anodic oxidation conditions successful for iodination of nitrobenzene seem as yet untried [80ACS(B)47].

Iodine monofluoride, prepared *in situ* from the elements, has been recommended for the iodination of deactivated substrates without the need for Friedel-Crafts catalysts (90JOC3553) and may find application with heterocyclic compounds. The corresponding chloride has been used frequently [82CJC554; 83ACS(B)345; 84CHE492, 84MI1; 86JHC1849;

88CPB3838; 90AHC(47)70] and is effective in acidic medium [83ACS(B)345] or in the presence of added triethylamine [85ACS(B)501]. Iodine monobromide has also proved an effective iodinating agent (88CPB3838).

In contrast to NBS and NCS, *N*-iodosuccinimide (NIS) is quite unstable and is not always successful (89MI2), but, if prepared *in situ*, it is a useful reagent in such solvents as acetic acid, ethanol, dimethylformamide, and ethanol–chloroform mixtures [81MI1, 81RTC267; 82CJC3049; 86S555].

Cross-linked polystyrene 4-vinylpyridinium dichloroiodate [89JCS-(P1)2279], sodium dichloroiodide in phosphate buffer (pH 1–3) [85ACS-(B)501], and iodination in the presence of phenyliodosotrifluoroacetate [in which trifluoroacetyl hypoiodite has been proposed as the iodinating agent (80IZV2649; 84RCR343)] are infrequently used in heterocyclic chemistry, as is the process in which chlorine gas is passed through a solution of iodine in dioxane (84S252). Iodine and silver nitrite provide a very mild iodinating agent (89TL3769).

Among the more useful methods of synthesis of iodoheterocycles are those in which a metallic species is displaced. Lithium [81CC1095; 83CPB2164, 83JCS(P1)271; 84JHC785; 85JCS(P1)173, 85JCS(P1)799, 85JHC505; 86S670; 90JHC673], trimethylstannyl [81H(16)1161; 82CPB-1731; 86S757], mercury (82CJC554; 85CHE322; 88MI1), and thallium groups [84H(22)797; 85S353; 86H(24)3065; 87H(26)1173, 87H(26)2817] have all proved useful.

The oxidizing properties of iodine can sometimes lead to unwanted side reactions such as thiol to sulfide (82JOU1630), and methoxy cleavage has also been reported (88SC855).

3. Fluorination

In recent years there has been intense interest in the preparation of fluorinated heterocycles since fluorine atoms confer unique properties on the rings. General discussions of methods of introduction of fluorine to heterorings have appeared [81AHC(28)1; 91MI6], although many of the sequences described are not electrophilic. Nevertheless, the strong impetus provided by potential applications of ^{18}F -labeled pharmaceuticals makes the ability to be able to introduce fluorine in the form of an electrophile to π -excessive compounds imperative. Fluorination processes, however, may be explosive, and the unpleasant natures of the reagents make it essential that procedures are carefully controlled.

Elemental fluorine, commonly diluted with an inert gas (argon, neon, nitrogen), can be used in a variety of solvents. Chlorinated hydrocarbons

are commonly used (86BSF930; 87TL255; 89G203), but these can occasionally lead to unexpected products, as when a chloroisoquinolone was formed on fluorination with fluorine in methylene chloride [82H(17)429]. Fluorine in aqueous solution (in which the reactive species may be HOF and F_2O) (82CPB887; 84TL4885) and in hydrofluoric (77CCC2694), acetic [80TL4605; 82CPB887, 82H(17)429; 83JOU403; 86CJC424], and trifluoroacetic acid [82JAP(K)57/15471; 83TL1055] has been used with varying success.

Fluorine can be "tamed" in the form of acetyl hypofluorite (and related species such as CH_3OF , $\text{CH}_3\text{CO}_2\text{F}$, ClO_3F , CF_3OF) to provide a source of "cationic" fluorine [71AHC(13)235; 79JOU357; 81CPB3181; 84JOC806; 85JOC4152; 86BSF861, 86CJC424, 86JOC1466; 88ACR307; 88JCS(P1)-1203], although whether the fluorination processes are strictly conventional electrophilic aromatic substitutions is uncertain. Radical cation mechanisms may be operating (86JOC1466). Displacement of a mercury group with acetyl hypofluorite in chloroform or acetonitrile provides a regioselective alternative (88TL1501).

Fluorination sometimes occurs preferentially at a hetero-nitrogen atom, and this maybe followed by rearrangement to C-fluorinated derivatives. Certainly *N*-fluoropyridinium (83JOC761; 89JOC1726; 90JA8563; 91BCJ1081, 91JOC5962) and -pyrimidinium (83CC563; 90T3093, 90TL775; 88JAP62/207230) salts are formed when the azines are treated with fluorine (91BCJ1081), hypofluorites (88ACR307), or cesium fluoroxysulfate [83CC563; 88JOC1123; 89H(28)249, 89JOC1726; 90T3093; 90TL775; 91T7447]. This last reagent is reported to be much inferior to elemental fluorine or fluoromethyl hypofluorite, but superior to perchloryl fluoride (FClO_3) (91T7447). The *N*-fluorinated salts can be stabilized by the presence of non- or weakly nucleophilic counteranions (91BCJ1081). Base-catalyzed decomposition of *N*-fluoropyridinium salts leads to 2-fluoropyridines via what may be a carbene mechanism (89JOC1726), but the salts are also potent electrophilic fluorinating agents for aromatic and heteroaromatic compounds (86TL4465; 90JA8563; 91JOC5962). The reaction mechanism has been explained in terms of a one-electron transfer process (90JA8563). Other *N*-fluoroheterocycles can also serve as fluorinating agents, e.g., *N*-fluorophthalimide and *N*-fluorosaccharin (91T7447), and no doubt other examples will be reported in the near future.

Polyfluorination frequently results when pyrroles, pyridines, and quinolines are treated with cobalt(III) fluoride [81JCS(P1)2059; 83JFC287] or cesium tetrafluorocobaltate at elevated temperatures [81AG(E)647; 82JFC413]. Carbonyl difluoride (COF_2) is a reagent that introduces fluorine into molecules by oxidative addition, or by displacement of hydrogen from an NH group (84CC416). It does not appear to have been used in

heterocyclic halogenations; nor has diethylaminosulfur trifluoride in the presence of antimony(III) fluoride (88TL5729). Cesium fluoroxysulfate in acetonitrile at room temperature is capable of replacing a hydroxyalkyl function on an aromatic ring by fluorine, although no heteroaromatic example has yet been cited (92CC274).

Electrophilic halogen exchange to convert chlorinated heterocycles into fluoro analogues has been reported, especially for the synthesis of fluorinated pyridines. Silver or antimony fluorides, or hydrogen fluoride at elevated temperatures and pressures, have been employed [81AHC(28)1]. Benzene derivatives are fluorinated in good yield by an addition-elimination process initiated by silver(II) fluoride. The argentic species acts as an oxidizing agent. No heterocyclic examples of the use of this reagent have been found (80JOC3597). As with the other halogens, fluorinated compounds are accessible via lithiated heterocycles. The process has been applied to the synthesis of fluorothiophenes using perchloryl fluoride as quenching agent [63JOC1420; 68ACS907; 69AK561; 71CS33; 86HC(44-2)159].

B. HOMOLYTIC HALOGENATION

Classification problems are abundant under this heading. It is likely that high temperature halogenations are radical in nature and that processes that involve light catalysis or radical initiators such as peroxides also provide examples with some degree of validity. One can sometimes also infer a homolytic process by the position of substitution, but matters are seldom clear-cut. Instances in which side-chain halogenation accompanies ring-halogenation provide a clue. For example, the chlorination of 2,3-dimethylbenzo[*b*]thiophene gives methyl chlorinated products as a result of homolytic processes [68JCS(B)1397; 76JCS(P2)266], and there are numerous such examples [89H(28)23; 90H(31)1933]. More than one mechanism may be occurring in many instances.

Eisch [66AHC(7)1] considers that the relatively weak bonds in fluorine and iodine predispose these halogens to homolytic processes more than with chlorine and bromine.

There are many examples of high-temperature or vapor phase chlorinations, particularly of pyridine derivatives [81JAP(K)120666, 81JAP(K)120667; 83JAP(K)58/206564; 88USP4785112]. Such reactions will be discussed in more detail in Part II.

Peroxide-initiated reactions include the chlorination of thiazoles using NCS and benzoyl peroxide [89CHE454], and the similar bromination of uracil (80CHE89; 85PHA194, 85SC1001), but there will be many instances

in which peroxides are only acting as oxidizing agents rather than as radical initiators. The selective chlorination at C-5 of 2-methoxycarbonylpyrrole by *t*-butyl hypochlorite may be due to a radical process, as may the indiscriminate attack at the 4- and 5-positions by chlorine and sulfuryl chloride in the presence of peroxides indicate the operation of both polar and radical processes [66AHC(7)1].

A number of photolytic processes have been reported, including the light-catalyzed bromination and chlorination of thiadiazoles (80LA1216; 89CCC2176), and photochlorinations of pyridines in the gas phase [89JAP(K)01/132564] or in solution [88JAP63/156774; 89JAP(K)01/42467]. The photolysis of diazonium fluoroborates devised by Kirk and Cohen for the preparation of fluorinated heterocycles is another radical process [73JA4619; 84JOC1951; 90AHC(48)65].

C. NUCLEOPHILIC HALOGENATION

Probably the most widely used procedures that belong under this heading are the use of phosphorus halides to convert oxy-substituted heterocycles (e.g., pyridones) or heterocyclic *N*-oxides into halogenated derivatives, and the Sandmeyer and Balz–Schiemann reactions of diazonium halides. There are, however, increasing numbers of examples of halogen–halogen and halogen–hydrogen exchange reactions that are also nucleophilic.

When hydroxy heterocycles (or their keto tautomers) are heated with phosphorus oxychloride, often in dimethylformamide (Vilsmeier–Haack conditions), and with added tertiary amine base to react with any hydrogen chloride produced, the hydroxy group is effectively replaced by chlorine [82CPB1947; 84H(22)79, 84S743; 85AJC221; 86M1305; 87JHC205, 87JHC1243, 87JOC1344, 87JPR945; 88M953]. Thionyl chloride [86CHE791; 87CI(L)694] and mixtures of phosphoryl chloride and phosphorus pentachloride [80IJC(B)775; 82JHC1061; 88BSB919] are also effective, whereas bromo analogues are formed using phosphoryl bromide (83TL2973). Phosphoryl chloride alone (82JHC1061; 83T291; 88CPB2244) or with acetic anhydride (82JHC465), or acetyl chloride (88JOU599) converts heterocyclic *N*-oxides into deoxygenated chloroheterocycles in the Meisenheimer reaction.

A simple example of the Balz–Schiemann reaction is the preparation of 2-fluoropyridine by diazotization of 2-aminopyridine in HF–pyridine at 0°C, and then allowing the salt to warm up to 20°C [88JFC(38)435]; there are many other examples [81CJC2608, 81JOC4567; 82JHC1245; 84H(22)1105; 85H(23)1431, 85H(23)1969, 85JHC145; 87LA857]. Chloro,

bromo, and iodo heterocycles are available through Sandmeyer reactions using copper(I) chloride (83CHE91; 85CPB3696; 86CHE1148; 89S905), copper(I) bromide (85CPB3696), or potassium iodide (85CPB3696).

Nucleophilic substitution of one halogen by another is not uncommon, particularly in π -deficient heterocycles or where nucleophilic attack is activated by electron-attracting substituents or quaternization. The processes are frequently of the addition–elimination type. Thus, reaction of chloro-azines or -azoles with a source of fluoride ion gives the fluorinated analogues [70MI2; 73MI1; 76JHC1297; 81AHC(28)1, 81JFC385; 82JFC495, 82JCS(P1)1251; 83GEP3131735, 83JAP(K)58/18360; 88MI2, 88T2583]. Such reactions may be aided by metallic ions (86JHC1079) and suitable crown ethers [85JHC1621; 87H(26)1215]. There are numerous examples in which bromine is replaced by chlorine or vice versa (88MI3), whereas iodide is well known as a good nucleophile under suitable conditions. Other groups such as nitro may also be displaced by halide [72JCS(P1)2671; 73JOC4353; 81AHC(28)1; 82T3277; 83JHC1307; 87MI1; 91T1697].

Aromatic fluorination by the silver ion-promoted decomposition of aryl-diazo sulfides is similar to the Balz–Schiemann process. It provides efficient utilization of stoichiometric levels of fluoride ion, but has yet to be used for heterocyclic synthesis (91JOC4993).

Hydroxyquinolines can be converted into the fluoro derivatives by the action of 2,4,6-trifluoro-1,3,5,-triazine (60BRP845062).

D. OTHER HALOGENATION PROCESSES

No attempt will be made in this chapter to cover methods of preparation of halogenated heterocycles where the halogen is introduced before the ring is formed.

Examples exist of rearrangements in which a halogen atom migrates from annular nitrogen to carbon, or from one ring carbon to another ("halogen-dance" or transmetalation). Such processes occasionally have preparative importance, and they will be covered in the appropriate sections.

Electrochemical halogenations are having increasing preparative value, although early electrochemical perfluorinations of pyridines gave only low yields of saturated products [62JCS3407; 73MI1; 81AHC(28)1] that could be rearomatized by heating with iron (75BRP1392571). Electrochemical fluorination of pyridazines [89JAP(K)01/29366] and pyrazoles [88JFC(39)435; 89JAP(K)01/29364] has also been reported.

III. Halogenation of Five-Membered Heterocycles

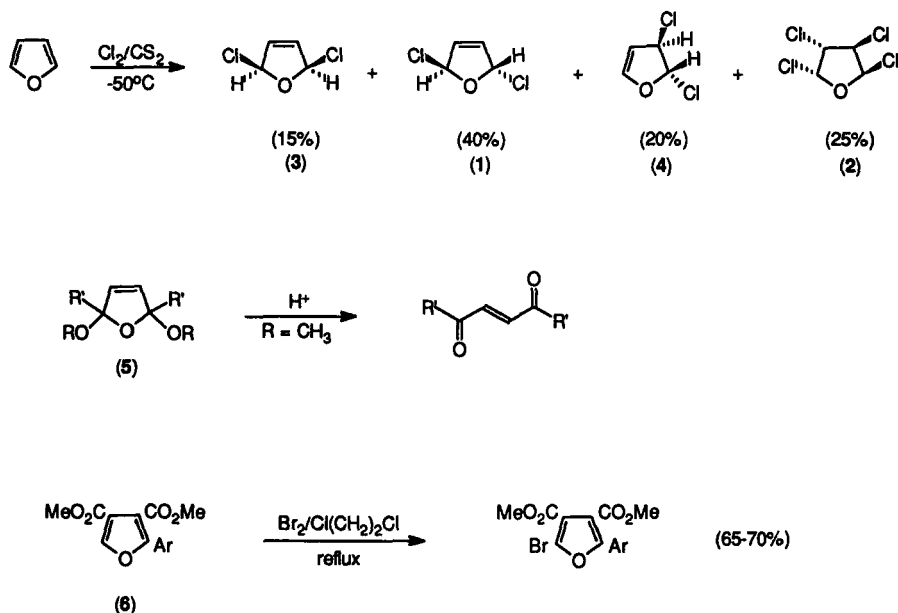
A. FIVE-MEMBERED RINGS WITH ONE HETERO ATOM

Heterocycles of this type are π -excessive molecules that usually react very vigorously with electrophilic halogenating agents. Substitution can occur in both α - and β -positions, with the former the preferred sites, and addition is also frequently observed. The high degree of reactivity makes it difficult to prepare monohalogenated derivatives.

1. *Furan*

Furan is not particularly stable under halogenation conditions since mineral acids such as HBr and HCl generated in the process can cause ring fission. Reactions are frequently too fast to be followed by standard kinetic measurements, and both addition and substitution are observed. Electron-withdrawing substituents decrease reactivity and reduce the tendency to undergo addition, and the products are more stable toward acids [66AHC(7)378; 84MI4; 90AHC(47)98; 90AHC(47)181]. Thus, 2-methoxycarbonyl furan brominated in the 5-position with bromine in acetic acid at 25°C with a partial rate factor (relative to benzene) of 6.1×10^{11} . The comparative factor for analogous chlorination is 1.9×10^9 , and the relative bromination rates for the 2-methoxycarbonyl derivatives of pyrrole, furan, and thiophene are $5.9 \times 10^8 : 120 : 1$ [68JCS(B)392]. Furan is chlorinated about 50 times faster than thiophene (65T843; 70TL1389). The observed kinetic behavior is similar to that exhibited by activated benzene compounds, suggesting that the mechanisms of electrophilic halogenation operating must substantially resemble those of typical aromatic species.

a. *Chlorination.* Low-temperature chlorination of furan with chlorine in carbon disulfide gave a mixture of addition products in which the 2,5-*trans*-dichloro compound (**1**) predominated, although the addition products could not be isolated. A tetrachloro product (**2**), believed to be formed on further chlorination of a 2,3-*cis*-dichloro isomer, was also detected, and in the presence of excess chlorine more than one such tetrachloro derivative was formed. Decomposition of the three dichloro species (**1,3,4**) gave 2-chlorofuran, a rather unstable compound, in 25% yield. The same product is available from chlorination of furan in dichloromethane at -40°C (84G1). Earlier patent literature reported direct chlorination of furan at 50°C and in the range -20 to -40°C with immediate removal of HCl (47USP2430667; 48USP2443493).



SCHEME 1

With 1.6 mol of chlorine, furan gave a mixture of 2-chlorofuran (64%), 2,5-dichlorofuran (29%), and 2,3,5,-trichlorofuran (7%); an even greater excess of chlorine gave 2,2,3,4,5,5-hexachloro-2,5-dihydrofuran and tetrachlorofurans (84G1). It is not clear whether the fully aromatic products are formed entirely by dehydrochlorination of the addition products detected.

Efficient synthesis of 2-chlorofuran is best achieved by decarboxylation of 2-chlorofuran-5-carboxylic acid (63JGU1397) or *via* the lithium derivative of furan. When furan or 3-bromofuran were treated in turn with ethyllithium and hexachloroethane, 2-chlorofuran (48%) or 3-chlorofuran (54%) was formed, uncontaminated by any polychlorinated products (73SC213). Chlorodesilylation of ethyl 5-trimethylsilyl-2-furoate with sulfonyl chloride in acetonitrile gave the 5-chloro ester in $\sim 85\%$ yield (91MI4).

Under the influence of ultraviolet irradiation, chloride displaced the nitro group of 2-(5'-nitro-2'-furanyl)benzothiazole to give a chlorofuran exhibiting intense violet fluorescence. This allowed the reaction to be used as an analytical process for chloride determination (80CPB939).

b. Bromination. The bromination of furan has been studied in much more detail than chlorination. At low temperatures, in carbon disulfide or carbon tetrachloride, bromine converted furan into the 2,5- and 2,3-

dibromo adducts which formed 2-bromofuran when allowed to warm up. Under these conditions it is difficult to prevent multiple bromination, and this trend is even more marked at room temperature (83CJC2171). When alcoholic solvents were used, addition products of type **5** ($R' = H$) formed, presumably from 2,5-dibromo precursors. In aqueous solution ring opening led to the formation of malealdehyde (83CJC2171), and even bromine in methanol can induce such ring fission in 2,5-disubstituted furans, possibly through 2,5-dialkyl analogues of **5** ($R = Me, R' = \text{alkyl}$), which react with the solvent (85TL3039) (Scheme 1).

The 2,5-dibromo addition products (analogous to **1** and **3**) were formed in the ratio 1:3 (67BCJ130). A more recent low-temperature spectroscopic study largely confirmed this result, but also detected around 20% of *trans*-2,3,-dibromo-2,3-dihydrofuran (analogous to **4**) (75CC875). Again it is unclear whether these adducts, which demonstrate competition between 1,4- and 1,2-addition, are intermediates on the pathway to bromine substitution, or whether they are formed in a separate equilibrium as in benzo[*b*]furan [90AHC(47)181].

Good yields of 2-bromofuran using dioxan dibromide at 0°C (50DOK693) could not be confirmed subsequently (90SC3371), but NBS in boiling benzene with a catalytic amount of *p*-toluenesulfonic acid gave a 39% yield (64JOC1991). Addition of bromine to a mixture of furan and trimethylphosphate at 0–10°C gave a 35% yield of 2-bromofuran (76SC621; 90SC3371), but the reagent of choice appears to be bromine in dimethylformamide. The use of one or two molar equivalents of bromine gave 70 and 48% of the 2- and 2,5-dibromofurans, respectively. Any addition products could be removed by shaking with water (90SC3371). Hexabromocyclopentadiene in refluxing acetonitrile gave the same two products (82CC778), but NBS and triethylamine in chloroform at room temperature converted furan into 5,5'-dibromo-2,2'-bifuryl (40%) (79CB1493).

Routes to 2- and 3-bromofurans from the corresponding lithium derivatives (2-bromofuran can be formed in 83% yield in this way) (70BSF1838; 74S443; 89SC1047) would seem to render the approaches through 2-bromofuran-5-carboxylates less important (63JGU1397; 72FRP2097261). Approaches to a variety of bromofurans have been summarized (71BSF990).

Low yields of bromo products were formed when NBS in the presence of peroxides (with or without added azobisisobutyronitrile) reacted with furan and its methyl derivatives. 3-Methylfuran gave the 2-bromo (33%), 2,5-dibromo (38%), 2,4,5,-tribromo, and 2,5-dibromo-3-bromomethyl derivatives under these conditions. The latter two components were obtained in a 1:5 ratio (34% total yield) [64JOC1991; 73TL637; 74CCC3109; 77BSJ1903].

The presence of at least one electron-withdrawing group in the furan ring makes monobromination a much more viable process. Considerable study has been made of the bromination of 2-acylfurans, especially in the presence of Lewis acid catalysts. A kinetic study of the bromination of 2-formylfuran in aqueous medium showed that the reaction is first order in each reactant and pH-independent, and influenced by bromide ion concentration (83MI1). In contrast to the analogous acylthiophenes and acylselenophenes, 2-acetylfuran was hydrolyzed when treated with bromine in the presence of sodium acetate (81SC29).

With bromine and excess aluminium chloride, 2-acetylfuran was converted into a mixture of 2-acetyl-4,5-dibromofuran (major product) and about equal quantities of the 4- and 5-bromo derivatives. The "swamping catalyst effect" is operating here. Coordination of the catalyst with the carbonyl function makes the substituent more electronegative, and in the presence of a large excess of Lewis acid catalyst, positions *ortho* and *para* to the substituent are deactivated more than the *meta*-position [68AG(E)519; 82AHC(30)167]. In terms of a 2-acylfuran, this means that 4-halogenation becomes favored. Even better coordination is possible with 2-formylfuran, which gave mainly the 4-monobromo isomer under swamping catalyst conditions (71BSF238; 71BSF242; 72CHE541; 73BAU2666).

Methyl-2-furoate reacted with one molar equivalent of bromine in the presence of 2.5 equivalents of aluminium chloride to give a mixture of the 5-bromo and 4,5-dibromo products. In chlorinated hydrocarbon solvents there is some bromine-chlorine exchange, possibly as a result of double complexation between aluminium chloride and the carbonyl and annular oxygens. Both methyl 5-chloro-2-furoate and methyl 4-bromo-5-chloro-2-furoate were identified among the products. In the absence of catalyst the major product was the 5-bromo ester [68JCS(B)392; 71BSF238; 73JCS(P1)1766; 75BSF2334]. Similarly, bromination of 3-acetylfuran in the presence of excess aluminium chloride in dichloromethane gave 3-acetyl-5-bromo- and 3-acetyl-5-chloro-furans (80%; 4:1 ratio) (75BSF-2334). 2-Formylfuran gave the 4-bromo-5-chloroaldehyde in the absence of solvent, and the 4,5-dibromo derivative in dichloroethane [73JCS(P1)-1766].

Monobromination of 2-arylfurans *para*-substituted by halogen or nitro gave high yields (75–84%) of 5-bromo products; two molar equivalents of bromine led to 3,5-dibromination (77–96%). Presumably there is better charge delocalization for 3- than for 4-substitution (80CHE334). Ethyl 5-bromo-2-furoate has been made by a bromodesilylation process (91MI1).

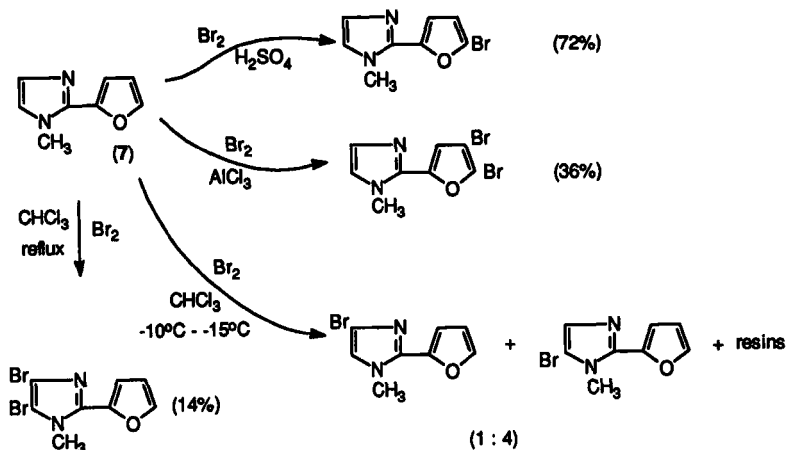
When furan was substituted at C-2 by a pyridine function [e.g., 4'-(2',6'-dimethyl)pyridyl] high yields (>90%) of the 5-bromo derivatives were

obtained (83CHE1287). At room temperature bromine in acetic acid converted *trans*-1-methyl-2-(β -2'-furyl)vinylbenzimidazole into the 5'-product. Apparently the vinyl group decreases the electron-withdrawing effect of the benzimidazole moiety since, without its intervention, temperatures as high as 80°C were needed for 5-bromination (86CHE872). Provided that sufficient heat is applied even highly deactivated furans (e.g., 6) can be brominated efficiently (82CHE337) (Scheme 1).

When 1-methyl-2-(2'-furyl)imidazole (7) was brominated under conditions that either protonate or complex the azole nitrogen, substitution was directed mainly into the furan nucleus. Bromine only enters the imidazole ring in neutral organic solvents (89CHE1168) (Scheme 2) In 6-(2'-furanyl)-imidazo[2,1-*b*]thiazole and some of its methyl derivatives, both furan-5- and imidazole-4-positions were brominated (80MI1).

c. *Iodination.* 2-Iodofuran can be made by treatment of 2-furoic acid with iodine and potassium iodide in aqueous sodium hydroxide (84MI4), and presumably from the 2-lithium derivative (89SC1047). Certainly methyl 4-iodo-3-furoate is readily prepared by such a metal-halogen exchange process [91JCS(P1)2600]. Direct iodination of 2-formylfuran gave 32% of the 5-iodo derivative (55AK87). High yields (82–87%) of the 5-iodo derivatives were obtained by treatment of 5-trimethylsilyl-2-furoates at room temperature with iodine monochloride (91MI4).

d. *Fluorination.* Fluorinated furans have become increasingly accessible in recent years. When 2,5-dibromofuran was treated with HF and sulfur tetrafluoride in the presence of catalytic amounts of bromine



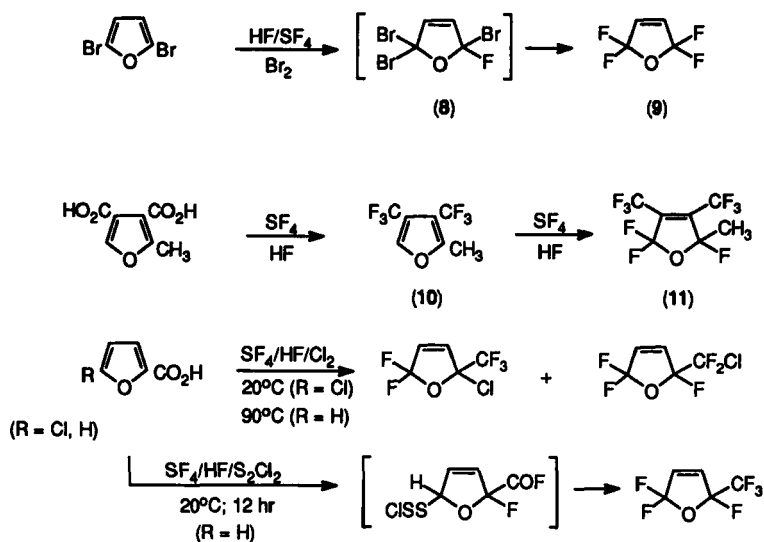
SCHEME 2

the tetrafluoro compound (9) was formed in 90% yield, derived from fluoride ion substitution of the allylic bromine atoms of the intermediate (8) (86JOU1609). The same reagents converted 2-methylfuran-3,4-dicarboxylic acid initially into the 3,4-bis(trifluoromethyl) product (10), and subsequently by 2,4-addition of fluorine into 11. Four moles of sulfur tetrafluoride were consumed in the overall process. (Scheme 3) With 2-trifluoromethylfuran-3,4-dicarboxylic acid as substrate, the 2,3,4-tris(trifluoromethyl) analogue was formed (84JOU709). A related study in which carbonyl- and carboxyl-substituted furans were treated with the fluorinating agents in the presence of chlorinating agents indicated that 2,5-addition is followed by nucleophilic displacement of halogen. The presence of electron-withdrawing chlorine in the α -position assists the reaction (86BSF974). A similar reaction sequence involving 2-bromo-5-furoic acid has been described (81JOU1588).

Polyfluorinated furans have also been prepared by electrochemical methods in which the substrates are treated with CoF_3 (or the less reactive KCoF_4), followed by base-induced elimination of HF [70JCS(C)2146; 73MI1].

2. Thiophene

General discussions of aspects of the halogenation of these compounds have appeared earlier [50MI1; 52MI2; 66AHC(7)1; 74MI2; 79MI1; 84MI5;



SCHEME 3

86HC(44-2)1; 88MI3; 88MI4; 90AHC(47)98]. As with the furans, reaction is so facile that the preparation of monosubstituted derivatives can be a problem unless electron-withdrawing substituents are present. Because of the high degree of bond-fixation (the 2,3-bond order is high), thiophenes are prone to halogen addition, although subsequent dehalogenation or dehydrohalogenation usually leads to aromatic products.

Halogenothiophenes are finding increasing application in the synthesis of pharmaceuticals and plant protection reagents, but efforts to devise methods that specifically introduce a halogen to an α - or a β -position have not always been completely successful.

a. *Chlorination.* Chlorination procedures frequently give rise to mixtures of products that mainly consist of 2-chloro- and 2,5-dichlorothiophenes, along with smaller amounts of the 3-chloro and 2,3-dichloro isomers, and tri- and tetra-chlorinated derivatives. Perchlorination can ultimately result in the formation of chlorinated thiolanes (**12**), or thiolenes (**13**). All of the possible chlorothiophenes are available through chemical or thermolytic dehydrochlorination of these thiolanes (74MI2; 80JOC2151).

Sulfuryl chloride seems to be the best reagent for the preparation of 2- and 2,5-dichlorothiophenes [51JGU1667; 76ACS(B)423]; the former is formed in 43% yield with this reagent (37% with chlorine; 44% with 1,3-dichloro-5,5-dimethylhydantoin), but NCS and hypochlorous acid have also been used with advantage [52HC(3)179; 55JA3410; 76ACS(B)423; 86HC(44-2)159; 90AHC(47)98]. Addition can be minimized by the use of polar solvents such as acetic acid, and by exclusion of light.

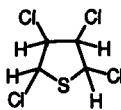
The difficulty experienced in preparation of monochlorothiophenes is a consequence of the fact that once one chlorine has been introduced, a subsequent chlorination is relatively easy because chlorine groups are only weakly deactivating. Di- and tri-substitution can be circumvented to some degree by using a high thiophene-to-chlorine ratio, and a number of patents rely on this concept. Passing chlorine gas over refluxing thiophene gave a 72% yield of 2-chlorothiophene (78GEP2749235). The monochloro product does not reflux under the reaction conditions and never comes into contact with the chlorine.

Most chlorination reactions are highly selective in that only very small quantities (~1%) of 3-chlorothiophene are usually formed, but at elevated temperatures (e.g., 750°C) the proportion of this isomer is greatly increased, as a consequence either of greater thermodynamic stability or a change in reaction mechanism [53JA3517; 70JCS(B)1153].

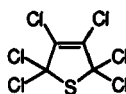
Whereas in benzene chemistry halogen substituents are *ortho-para* directing because of their weak donor effects, in thiophene the +M effect is strongest across the 2,3-bond. This means that a 2-chloro group gives

rise to more 3-substitution than expected and vice versa. The overall directional preferences for 2-halogenothiophenes are $5 > 3 \gg 4$, and for the 3-isomers $2 \gg 5 \approx 4$ [86HC(44-2)1]. Nevertheless, the high $\alpha : \beta$ selectivity means that α -substitution predominates; e.g., 2-chlorothiophene gave 98% of the 2,5-dichloro derivative on further chlorination (50USP2492644). Even electron-donating groups may not alter this strong preference for α -substitution. Sulfuryl chloride converted 2- and 3-methylthiophenes into the 5- and 2-chloro derivatives, respectively (48JA413), and 2-bromo-3-methylthiophene chlorinated at C-5 (74MI3). 3-Alkylthiophenes can react at both the 2- and the 5-positions, with the product ratios dependent on the nature of the electrophile and the size of the alkyl group (79MI1). Benzyltrimethylammonium iodochloride chlorinated 3-methylthiophene to give either 2,5-dichloro or 2,4,5-trichloro derivatives, depending on the mole ratio of the halogenating agent (91BCJ2566). Efficient α -chlorination of both thiophene and its 2-methyl derivative has been accomplished using benzeneseleninyl chloride with aluminium chloride. Yields of the α -chloro products exceeded 75% (even higher yields of the corresponding bromo derivatives were obtained using aluminium bromide). The reaction appears to work also for furan, but not for pyrrole (90MI1).

When 2- or 3-bromo- and the corresponding iodo-thiophenes were



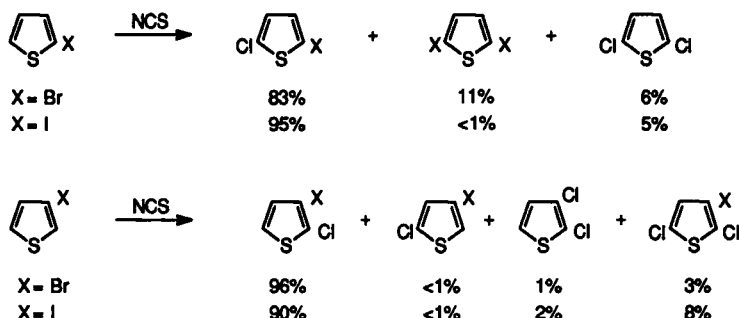
(12)



(13)

treated with NCS the primary 5-chlorination was accompanied by chloro-dehalogenation [76ACS(B)423]. (Scheme 4) Sulfuryl chloride in chloroform converted 3-methoxythiophene into its 2-chloro derivative (53%) (89M65). High yields of 5-chlorinated products were isolated from the reaction of an alcoholic solution of *t*-butyl hypochlorite and 2-chloro-3-methylthiophene (89MI3), and in the copper halide-catalyzed chlorination of 2,2'-bithiophene (89MI4).

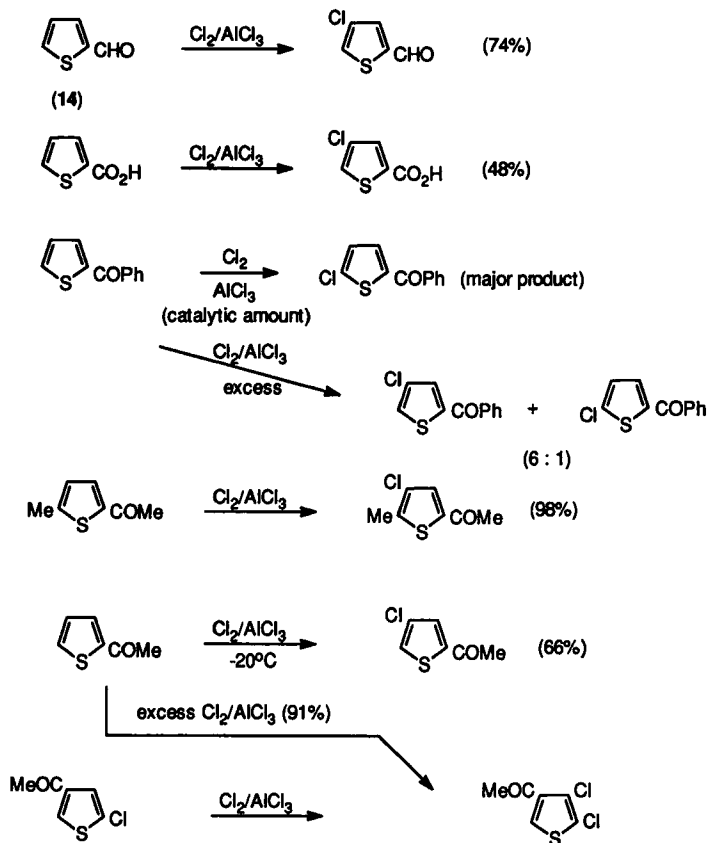
Electron-withdrawing groups can overcome thiophene's high α -selectivity, but the requirement to use a Lewis acid catalyst with these less reactive substrates can complicate matters, since these catalysts may complex with substituent and modify its effect. When there is an excess of Lewis acid catalyst (swamping catalyst effect), or if a substituent complexes very strongly with such a catalyst, a higher proportion of β -substitu-



SCHEME 4

tion is observed [72JA4985; 76JHC393; 78JMC978; 86HC(44-2)159]. Thus, although 2-alkoxycarbonylthiophene-2-chlorosulfonates were mainly 5-chlorinated in the presence of iron powder (89EUP340472), both 2-formylthiophene (**14**) and thiophene-2-carboxylic acid in the presence of aluminium chloride gave the 4-chloro derivatives (**74** and **48%**, respectively) (76JHC393). A formyl group coordinates better than a carboxyl group. Under similar conditions 3-formylthiophene formed the 4,5-dichloro products (83%) and smaller amounts of the 5-chloro, 2,5-dichloro, and 2,4,5-trichloro products (73M920), and the 3-nitro isomer was converted into 2,4,5-trichloro-3-nitrothiophene (75M1103). Some examples are shown in Scheme 5 (70BAU2592; 76JHC393; 89M53; 89M65).

When there is a hydroxy group in the thiophene ring, keto-enol tautomerism becomes a complicating factor. As addition reactions can occur in chlorination, it was not surprising to find that methyl 3-hydroxythiophene-2-carboxylate (**15**; $\text{R} = \text{H}$) gave **16** ($\text{R} = \text{H}$) when treated with one molar equivalent of sulfuryl chloride. Release of HCl by the reagent led to dichloro products [84JCS(P1)2711] (Scheme 6). A reagent such as NCS, which is not a source of HCl, gives only monochlorinated species. A variety of electron-releasing substituents on **15** (Br, I, Me, Ph) promoted the formation of dichlorinated products, with 4-methyl and 4-phenyl compounds adding HCl faster than the others [84JCS(P1)2711; 90JHC315]. When, however, the 5-position of **15** was blocked by methyl or phenyl, only 2-chloro products were obtained (90JHC315). Electron-withdrawing groups (nitro, acyl, ester) in the 4-position appear to enhance the enolic character of the substrate rendering HCl addition negligible and leading only to 2-chlorinated products [86JCR(S)168; 90JHC315]. Thus, methyl 4-hydroxythiophene-3-carboxylate (**17**) was smoothly converted by one molar equivalent of sulfuryl chloride into **18**. Two moles of chlorinating agent gave the dichloro compound (**19**) which isomerized in the

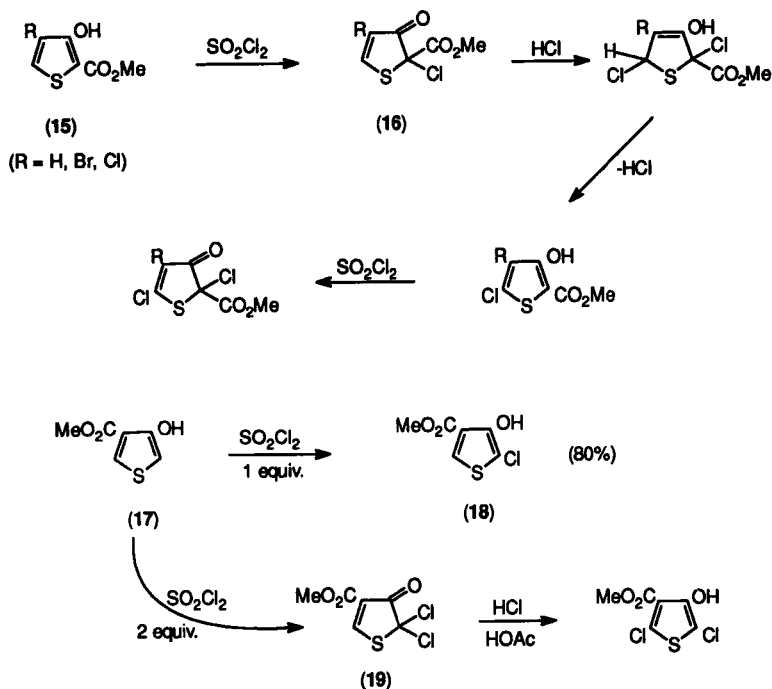


SCHEME 5

presence of HCl in acetic acid into the fully aromatic dichlorothiophene (87CZ15) (Scheme 6).

Methods of synthesis of 3-chloro- and 3,4-dichloro-thiophenes have usually involved tedious procedures in which tri- and tetra-chloro derivatives are dechlorinated by reductive or other methods. Ethanolic potassium hydroxide converted 2,3,4,5-tetrachlorothiophene into a 50:50 mixture of 2,4- and 3,4-dichlorothiophenes; direct heating of the same tetrachloro substrate gave a mixture of 2,3- and 2,4-dichloro isomers (48JA1158). 3,4,5-Trichlorothiophene was readily prepared by the reaction of 1,1,2,3-tetrachloro-1,3-butadiene with sulfur (82JOU348).

Nucleophilic substitution procedures are also of use of the synthesis of β -chlorinated thiophenes. Copper(I) chloride converted 3-bromothiophene into its chloro analogue. Such reactions are best carried out in an



SCHEME 6

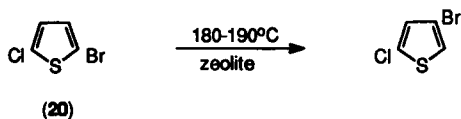
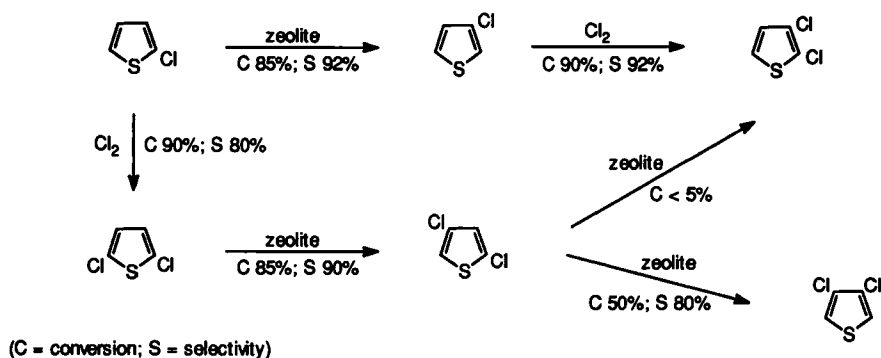
aprotic solvent (e.g., DMF, DMSO) and can give high yields (>80%) [76S412]. 3-Chlorothiophene was prepared in 53% yield by the action of chloride ion on the dithienyliodonium salt (77JHC281). Thienyl-lithium compounds are also suitable substrates for the preparation of chloro derivatives (71CS33; 72JHC725; 77CS57; 78MI2), and displacements of hydroxy or methoxy functions under Vilsmeier–Haack conditions have also been reported (72CHE392; 80CS38; 91JHC1449). Sandmeyer reactions are seldom successful in thiophenes unless the diazonium salts are activated by electron-withdrawing groups elsewhere in the ring [71JHC537; 74CC1044; 85H(23)1431]. A recent survey of nucleophilic substitution reactions reported no generally useful examples in the thiophene series [91HC(44-4)295].

Potentially, the most useful procedure for the preparation of β -halogenated thiophenes is the isomerization of the more readily available α -isomers using silicon-rich zeolite catalysts [87AG(E)468]. Over a period of time at 300–450°C on a H-ZSM-5 fixed-bed catalyst, 2-chlorothiophene was converted into the 3-isomer in 85% yield. When combined with chlori-

nation steps the isomerization is applicable to the synthesis of all of the possible dichlorothiophenes; mixed di- and tri-halogenated compounds can be isomerized selectively. Thus, the bromine atom in 2-bromo-5-chlorothiophene (**20**) migrated in the liquid phase to the thermodynamically more stable 3-position, whereas the less reactive chloride was unaffected. At gas-phase temperatures ($>300^{\circ}\text{C}$) there was about 20% chlorine migration to C-4 [87AG(E)468, 87GEP3537288] (Scheme 7).

b. *Bromination.* Bromination usually occurs even more readily than chlorination; partial rate factors for 2-chlorination with chlorine (3.86×10^7) and 2-bromination with bromine (5.09×10^9) have been reported [90AHC(47)98]. The ρ values for chlorination and bromination of thiophene are -7.8 and -10.0 , respectively [71AHC(13)235].

Molecular bromination of thiophene gave mixtures of 2-mono- and 2,5-dihalogenated products [42JA477; 56AK373; 63AHC(1)1]; at higher temperatures 3-bromothiophene was formed in preference (53JA3517). Addition processes are not a problem in molecular bromination, but multiple bromination is difficult to avoid (61AK267). The use of very dilute solutions can give yields of 2-bromothiophene as high as 78% [45JA2092; 53YZ(73)1023]. Reagents that have been recommended include cyanogen bromide (45% of 2-bromothiophene) [22LA(430)79], potassium bromate with HBr (60%) (82BAU2104), benzyltrimethylammonium tribromide



SCHEME 7

(91BCJ2566), hexabromocyclopentadiene in refluxing acetonitrile (82CC778; 84TL3369; 91MI4), and the dioxan-bromine complex which was reported to give a quantitative yield of 2-bromothiophene (54JGU1251; 79T329). The same product was formed in 84–87% yield when a solution of bromine in HBr was added to thiophene at -20°C , and in 94% yield when hydrogen peroxide was added to a mixture of the heterocycle and 48% HBr in ether (two molar equivalents of HBr led to 2,5-dibromothiophene in greater than 95% yield) (88S890). The use of NBS in acetic acid containing some acetic anhydride gave a higher yield of 2-bromothiophene than in the absence of the anhydride [82CHE28]. A patent has described the low-temperature synthesis of 2-bromothiophene in 98% yield [87JAP(K)62/63562].

Specificity for α -bromination is very high, and there is seldom more than 1% of the 3-bromo isomer produced [70JCS(B)1153] unless the reactions are carried out at high temperatures (53JA3517). This high α/β -specificity has been discussed recently [90AHC(47)98]. In summary, it means that 2-substituted thiophenes are brominated at C-5; those substituted in the 3-position give mainly 2- and 5-bromo products [1886CB644; 37LA(527)237; 52BSF713; 68JOC2902; 72ACS1851; 92SC1095]. 3-Methylthiophene gave mainly the 2-bromo derivative, whereas the 2-methyl isomer gave a mixture of 3- and 5-bromo products with the latter predominating (76JOC2187). In the presence of excess bromine both methylthiophenes were substituted in all vacant ring positions [35LA(515)273]. The more bulky the 2-alkyl group, the greater the ratio of 5-:3-bromination [67ACS1952; 81IJC(A)1183]. Both 3-methyl-2-phenyl- and 2-methyl-3-phenyl-thiophenes gave greater than 90% yields of 5-brominated products [76JCS(P)2355], whereas 3-phenylthiophene gave a mixture of 2- and 5-bromo compounds (67JOC463; 68JOC2902). Despite the steric problems 3-*i*-butylthiophene gave 57% 2-bromination (73BAU2233).

Multiply brominated products can be reduced to 3-bromothiophenes with yields approaching 50% (81SC25), but these methods, which are also used to make 3,4-dibromo derivatives, are tedious. Exhaustive bromination followed by reaction with a Grignard reagent (54AK267), an organolithium compound (56AK373), or reduction with zinc and acetic acid (59ACS1045; 73OSC149; 81SC25) would now appear to be superseded by thermal isomerization, as for the chlorinated analogues [87AG(E)468].

Although sometimes surpassed by other reagents, NBS is the best choice for the preparation of 2,5-dibromothiophene (68JOC2902). The orientation of attack is the same as that for molecular bromine, but HBr formation does not occur with NBS, and there is also a reduction in *trans*-halogenation. A complicating factor with this reagent is the likelihood of side-chain bromination, especially in the presence of peroxides. Ring

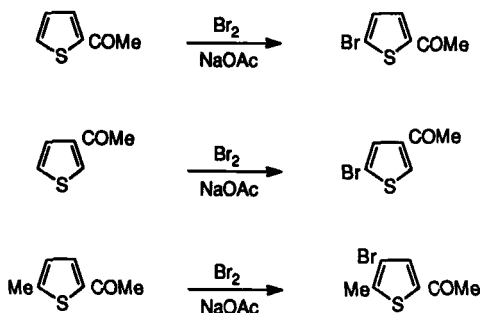
substitution is favored by the use of acetic acid as solvent, or as a cosolvent with chloroform or carbon tetrachloride [68JOC2902; 81H(15)947].

The use of bromine adsorbed on alumina gave 85% bromination of 2-methylthiophene with no obvious benzylic halogenation. After a 1-min stirring at room temperature, an 80:20 mixture of 5-bromo and 3,5-dibromo products was obtained (92SC1095). Benzyltrimethylammonium tribromide converted 3-methylthiophene into its 2,5-dibromo derivative (91BCJ2566).

As mentioned in the chlorination discussion, resonance electron-withdrawing substituents decrease substrate reactivity and affect the α/β -selectivity, particularly when combined with complexing catalysts (75BSF2334; 84JHC215). Whereas bromination of 2-formylthiophene with NBS in acetic acid-acetic anhydride gave the 5-bromo product in 70% yield (73CHE170; 76T1403), bromine in 82% sulfuric acid gave rise to a 1 : 1 ratio of the 4- and 5-bromo isomers in addition to 45% of dibrominated product. The substituent is protonated in the latter medium reducing the electron density in the 5-position. With 100% sulfuric acid the products were 4-bromo-2-formylthiophene (16%), 5-bromo-2-formylthiophene (23%), and 4,5-dibromo-2-formylthiophene (61%). 2-Acetylthiophene behaved similarly (71BAU2687). Thiophene-2-carboxylic acid was converted into a mixture of 5-bromo- and 4,5-dibromo acids along with products of decarboxylation. Silver salts under Hunsdiecker conditions (62BCJ432) and sodium salts with bromine water were also bromodecarboxylated (69RTC321). In contrast thiophene-3-carboxylic acid gave a mixture of 5-bromo-, 2,5-dibromo-, and 2,4,5-tribromo-thiophene-3-carboxylic acids, with no observable decarboxylation (54JA2445; 55AK23). The influence of a boronic acid group at C-2 or C-3 has been explored and shown to be largely *meta*-directing. Despite this, thiophene-2-boronic acid was brominated exclusively at the 5-position [89AHC(46)143]. One or two equivalents of bromine in acetic acid transformed methyl 3-hydroxythiophene-2-carboxylate into the 4-bromo (60%) and 4,5-dibromo (81%) derivatives (84S847).

When 2-nitrothiophene was brominated, a low yield of the 5-bromo derivative was obtained, the reaction being accompanied by some bromodenitration (38JA2906); 3-nitrothiophene gave only 2,5-dibromo-3-nitrothiophene, reflecting the lower reactivity of the 3-position [14LA(403)63].

The swamping catalyst effect can mimic reaction in strong acid and lead to an increased proportion of 4-bromination of 2-acylthiophenes [68AG(E)519]. One frequently observes side-chain bromination in acylthiophenes as a consequence of acid-catalyzed enolization of the acyl substituent (81SC29; 87CHE384), but excess aluminium chloride promotes annular bromination (75BSF2334; 84JHC215), as does reaction in sodium

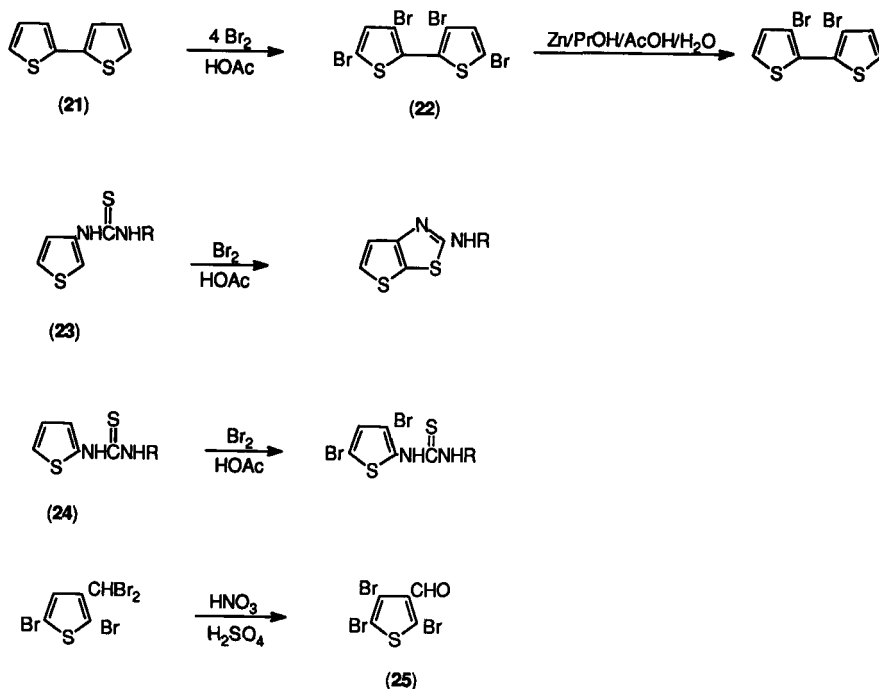


SCHEME 8

acetate solution (81SC29) (Scheme 8). Protection of the acetyl group as its hydrazone achieved the same result with bromine in acetic acid (84BRP2139214).

Inductively electron-withdrawing groups, too, seldom overcome thiophene's tendency to be α -brominated. Two moles of bromine in acetic acid converted thiophene-3-acetic acid into the 2,5-dibromo product; 3 mol of bromine in 48% HBr in ether gave an 83% yield of 2,3,5-tribromothiophene (88SC1763). Both 2- and 3-chlorothiophenes can be tribrominated in 80–90% yields [37LA(532)250]. With NBS, 2- and 3-bromothiophenes were readily monobrominated at the expected sites (64AK201; 68JOC2902). The former substrate has been shown to form a π -complex with bromine (82MI2). Similarly 3-chlorothiophene gave the 2-bromo derivative (81JMC959), the bromo analogue formed the 2,3,5-tribromo product (82%) (76JOC3668), and 3-bromo-2-chlorothiophene was converted into the 2-bromo derivative (90%) with some diiodination being observed [37LA(527)327]. Such bromodeiodination is also a feature of the reaction of 2-iodothiophene. With excess NBS the major product was 2,5-dibromothiophene. Similarly 2,3-diiodothiophene was diiodinated at the more reactive 2-position when 2,4,5-tribromo-3-iodothiophene was prepared from it [37LA(527)327].

Treatment of 2-methoxy-5-methylthiophene with NBS gave a 4 : 1 mixture of 3- and 4-bromo products, with some 3,4-dibromination also evident. The dibromination became more significant when 2 mol of NBS were used. Similarly 2-methoxythiophene gave the 3,5-dibromo derivative (84BAU1447). Bromination of 2-(2'-thienyl)-thiophenes (**21**) and 2-(3'-thienyl)-thiophenes gave the 5- and 2-bromo products in high yield [79CS157; 91H(32)1805]. With four molar equivalents of bromine in acetic acid the tetrabromo derivative (**22**) was obtained in 97% yield. Reduction removed the 5,5'-bromines preferentially [91H(32)1805] (Scheme 9). This



SCHEME 9

behavior parallels other electrophilic substitution behavior of **21** in which the 5,5'-positions are more reactive than the 3,3'-positions [69JOC343; 88AX(C)1800]. The bromine–dioxan complex converted **21** into its hexabromo derivative in 75% yield [81CHE(16)332]. Whereas 1-acyl-3-(3'-thienyl)thioureas (**23**) were oxidatively cyclized by bromine in acetic acid, the corresponding 2'-thienyl compounds (**24**) were brominated [78HC(33)81]. In 2-benzamido-4-phenylthiophene-3-carbonitrile, NBS brominated the remaining ring position in 94% yield (82CPB4396). In contrast, 1-methyl-2-(5'-methyl-2'-thienyl)benzimidazole was mainly brominated in the 5(6)-position of the benzimidazole moiety (87CHE1316).

A study of reactions of NBS in acetic acid and acetic anhydride with thiophenes substituted in the α -position by groups such as 4-thiazolyl or 2-quinolinyl demonstrated that after initial perbromide formation (at around 20°C), slow conversion into C-brominated products followed. Reactions carried out above 40°C with one molar equivalent of NBS gave 5-bromo products only, but introduction of electron-donating groups into the thiazole substituent and excess brominating agent led to some thiazole bromination. With a 2-aminothiazolyl substituent, bromination took place exclu-

sively at C-5 of thiazole (82CHE28). Thienylpyrazoles brominated preferentially in the thiophene ring [79CS157; 80CS(15)10].

During the attempted nitration of 2,5-dibromo-3-dibromomethylthiophene nuclear bromination was observed to give **25**. Presumably the substrate was initially nitrated in the 4-position; then ionization of the dibromomethyl group produced bromide ion, which displaced the nitro function that had activated the molecule for such a nucleophilic displacement. Addition of sodium chloride failed to give the corresponding 4-chloro product, implying that the bromide attack might have taken place within a nonseparated ion pair [84H(22)1175] (Scheme 9).

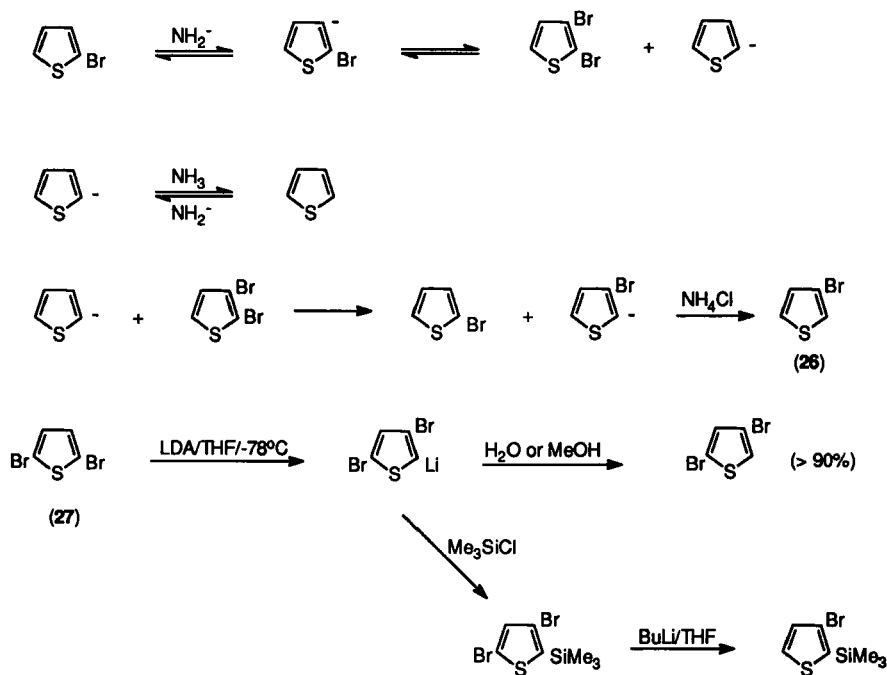
Some examples in which electrophilic bromine replaces a group other than hydrogen have been mentioned above. Others include bromodealkylation [37LA(532)250], bromodeacylation (1893CB2457), *ipso*-substitutions of sulfonamido groups (76SC243), and reactions in which bromine replaces a metallic function. Addition of bromine to thallium acetate and thiophene gave 2-bromothiophene in 82% yield; under the same conditions 2-methylthiophene gave the 5-bromo product (75%), and 3-methylthiophene formed 2-bromo-3-methylthiophene (72%). These reactions involve prior formation of the thallated heterocycles (72JOC88). Bromodemercurations have been reported [29JCS2589; 75JCS(P2)620; 80JCS(P1)1390], as have displacements of trimethylsilyl (54JA1252), methylselenyl (72CHE424), and conversion of Grignard reagents into bromothiophenes (60BRP826619).

The synthesis of bromothiophenes from organometallic derivatives is of limited use for the simpler derivatives since, for example, lithiated substrates are normally made from the bromo precursors. When direct metalation is possible, it is a different matter. A 5-lithio derivative was converted into the 5-bromothiophene by quenching with carbon tetrabromide [74CS217; 82JCS(P2)625]. Selective lithiation of 6,6-bis-(2-thienyl)-pentafulvene followed by reaction with bromine α -brominated the thiophene rings (91MI2). Transmetalation processes have merited some recent attention because of their potential for the synthesis of thiophenes brominated in less accessible positions [71JOC2690; 72JOC4257; 72TL3507; 73RTC(92)245; 73RTC(93)33; 80JHC171; 81H(15)947; 83H(20)2035; 84JOC5250; 89S771]. Large-scale synthesis of 3-bromothiophene (**26**) in 66–72% yield was achieved by a procedure that treated 2-bromothiophene with excess sodamide in liquid ammonia and subsequently quenched the reaction mixture with ammonium chloride (90SC1697). When equal proportions of sodamide and potassium *t*-butoxide were used, disproportionation led mainly to 3,4-dibromothiophene (58–68%) with smaller quantities of thiophene and tri- and tetra-bromothiophenes (90SC2119). Treatment of 2,5-dibromothiophene (**27**) with lithium diethylamide in tetrahydrofuran

at -78°C followed by quenching with electrophiles gave good yields of 2-substituted-3,5-dibromothiophenes (90JOC2993) (Scheme 10). Side-chain bromination predominates when alkyl-substituted thiophenes are treated with a bromine source (especially NBS) in the presence of radical initiators [75TL4705; 84H(22)1175]. Nonpolar solvents also favor this mode of attack (46HCA573; 53OS96).

c. *Iodination.* Iodothiophenes have been made by reaction with iodine in the presence of a variety of co-reagents. Mercuric oxide is a traditional additive that serves to remove HI formed in the reaction, thereby reducing protolytic ring cleavage (43OSC357; 72JOC514). Other co-reagents used have been iodic acid in acetic acid [60LA(634)84; 71BCJ1021], nitric acid [71JCS(B)2264; 74JCS(P2)1214], and silver trifluoromethane sulfonate at 0°C [77JCR(S)215]. Other reagents include iodine monochloride [82IJC(A)417] and benzyltrimethylammonium dichloriodate in acetic acid, sometimes with added zinc chloride (91BCJ2566). Iododeboronation has been reported (38JA111; 65AJC1527).

Yields of 2-iodothiophene lie in the range 70–80% with some 2,5-diiodo



SCHEME 10

product also being formed. Once 2-iodothiophene has been formed, it iodinates more slowly than the parent heterocycle, but high yields of 2,5-diiodo product can be achieved (71MI1). Other 2-halogenothiophenes were similarly iodinated in the 5-position [82IJC(A)417]. Under forcing conditions 2,3,5-triiodothiophene can be made (63AK191).

Kinetic studies have shown that iodination of thiophene by molecular iodine in nitric acid involves the HNO_2I^+ species formed in the rate-determining step. This means that the iodination rate should be independent of thiophene concentration (this has been demonstrated in the case of 2-phenylthiophene) [71JCS(B)2264; 74JCS(P2)1214]. Nitric acid also assists the reaction (as does iodic acid) by oxidizing HI back to iodine. Periodic acid does this even more efficiently, but it is a more expensive reagent (71NKZ1021). The observation that acid catalysts assist some iodinations suggests that iodonium species are implicated as with iodinations using silver sulfate and sulfuric acid (50JCS3694), iodine monochloride with hydrochloric acid (51JA613), and with Lewis acids (71BAU1137).

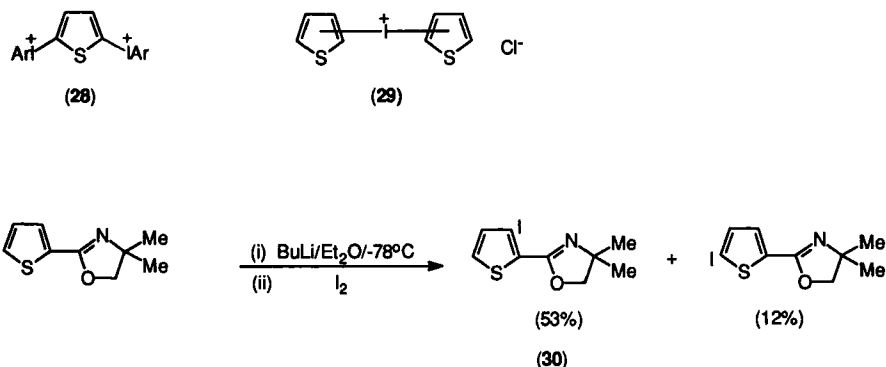
The ^{13}C -NMR spectra of all the possible iodothiophenes have been tabulated and discussed (85M685).

Orientation effects of ring substituents resemble those discussed under chlorination and bromination. Thus 3-methylthiophene was 2,5-diiodinated [80JCS(P1)1390], 2,4-dimethylthiophene gave a 59% yield of the 3,5-diiodo product (73CS220), methylthiophene-2-carboxylate formed a mixture of the 5-iodo (96%) and 4-iodo (4%) products (63AK191), and 2,5-dichlorothiophene was converted into the 3-iodo and 3,4-diiodo derivatives [76ACS(B)439]. Partial rate factors for the 5-iodination of 2-chloro-, 2-bromo-, and 2-iodo-thiophenes have been listed as 0.23, 0.21, and 0.72 [90AHC(47)98]. When 3-iodothiophene was iodinated in 73% yield, the 2- and 4-positions were substituted in the proportions 93:7. Treatment of 2,3,5-triiodothiophene with zinc dust and acetic acid removed the α -iodines preferentially to give a mixture of 3-iodo- and unsubstituted thiophene, but butyl-lithium gave 2,4-diiodothiophene (63%) (63AK191).

In the liquid phase at 100°C 2-iodothiophene isomerized to give the more stable 3-isomer [87AG(E)468].

Thienyliodonium salts (e.g., **28**, **29**) can be made by direct oxidation of thiophene with iodine in either the +5 or the +3 oxidation states (58JA4279), or by iodination of thienyl-lithium species (77JHC281; 80CS(15)135). Such compounds are, however, of limited use only for the synthesis of halogenated thiophenes (Scheme 11).

Access to iodothiophenes through metallic derivatives is quite common. Iododethallation has been employed to prepare 2,5-diiodothiophene (79JOM111) and 2-iodothiophenes (71JA4841), and similar reactions of thienyl-mercury [37LA(527)237; 37LA(532)250] and -copper (70MI4) de-

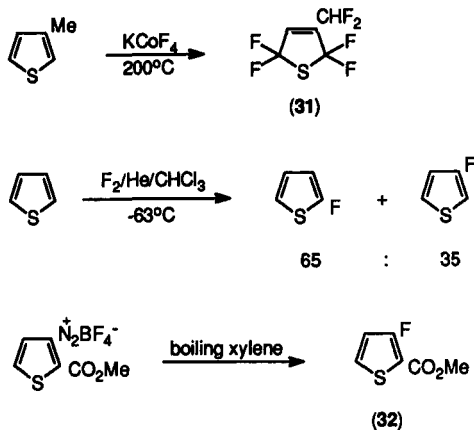


SCHEME 11

rivatives, and Grignard reagents (70MI3) have been reported. Thiophene substituted at C-2 by a 4,4-dimethyloxazolin-2-yl group was mainly 3-lithiated by butyl-lithium. The substituent group controls the regioselectivity and can be converted subsequently into carboxy. Quenching the lithiated species with iodine gave mainly the 3-iodo product (30) [85JCS(P1)173] (Scheme 11).

d. *Fluorination.* Direct fluorination of thiophenes has met with only limited success. Fluorine, diluted with nitrogen, gave mixtures of fluorocarbons and sulfur hexafluoride [86HC(44-2)1]. Polyfluorinated thiophenes can be made, however, by treatment of thiophene with cobalt(III) fluoride or the less reactive potassium tetrafluorocobaltate (KCoF₄), followed by reaction with alkali to remove HF [71JCS(C)352]. The latter reagent converted 3-methylthiophene into a hexafluoro derivative (31) at elevated temperatures [81AG(E)647] (Scheme 12). When low temperatures and very dilute fluorine (5% F₂ diluted with helium in chloroform at -63°C) were used in the absence of light it was possible to introduce a single fluorine into the thiophene ring. The process is probably electrophilic, although the high proportion of 3-fluoro isomer observed in this process would not be expected. Nevertheless, products were relatively tar-free provided that the process was stopped after 5–10% of reaction (89G203).

Access to fluorinated thiophenes from lithiated precursors has been quite promising. Prepared in this way were 3-fluorothiophene (28%) (68ACS907), 2-fluorothiophene (49%) (63JOC1420; 73CS94), and 2,3-difluorothiophene (48%) (69AK561). The most common quenching reagent is FClO₃. In these reactions the major competing process is hydrolysis of the lithiothiophene.



SCHEME 12

A few examples exist in which halogen-halogen exchange gives rise to fluorothiophenes. Both addition and halogen exchange occurred when potassium tetrafluorocobaltate reacted with tetrachloro- or 2-iodothiophene [71JCS(C)346].

Attempts to prepare fluorothiophenes from diazonium salts (the fluoroborate and hexafluorophosphate salts) have met only variable success. Methyl 3-fluorothiophene-2-carboxylate (32) was obtained in 89% yield by this method (Scheme 12), but the 3-diazonium salt of the corresponding 4-ester could not be isolated. Furthermore, the methyl ester of 2-diazothiophene-3-carboxylic acid coupled before decomposition could be attempted [85H(23)1431].

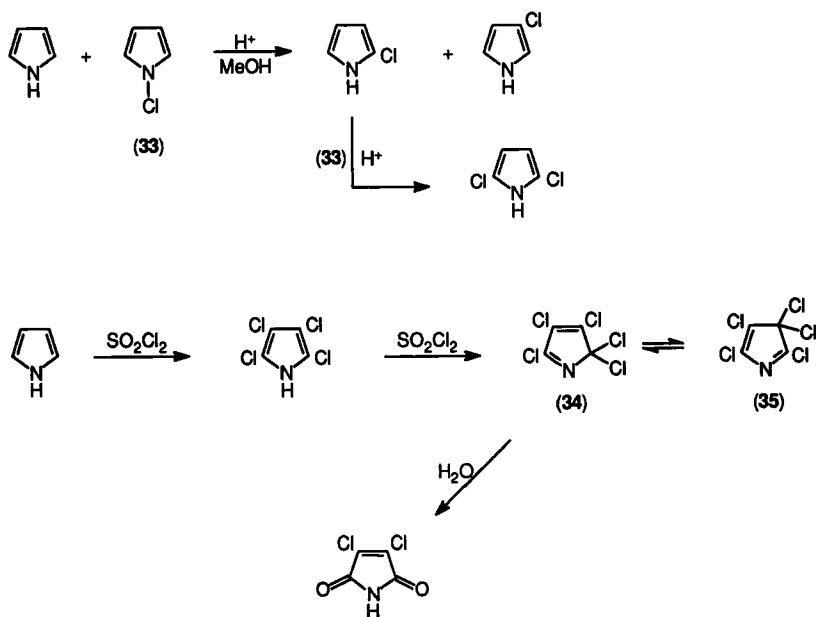
3. Pyrrole

Pyrrole differs from the other five-membered heterocycles discussed thus far in a number of respects. It is the least susceptible to addition reactions, it is frequently the most reactive, it is the least selective for α -halogenation, and N-halogenation becomes a possibility (84MI3). Very recently much of the data concerning theoretical calculations, relative rates, and quantitative aspects of the regiochemistry of halogenation of pyrrole and its derivatives have been tabulated and discussed [90AHC(47)98]. The survey that follows will emphasize qualitative features and approaches to the synthesis of halogenated pyrroles.

a. *Chlorination.* Pyrrole is chlorinated very readily indeed. When treated with aqueous hypochlorite in carbon tetrachloride at 0°C N-chlorination occurred in 65–72% yield. The 1-chloropyrrole (33) re-

arranged when warmed in methanol to yield 2-chloropyrrole, a thermally unstable liquid. Alternatively, acid-catalyzed rearrangement gave a mixture of 2- and 3-chloro- and some 2,5-dichloro-pyrrole. This latter reaction is initiated by nucleophilic attack on the N—Cl bond of **33** as can be demonstrated by reactions with cyanide and thiocyanate ions (82JOC1008) (Scheme 13). Excess hypochlorite was reported to give tetrachloropyrrole [62MI2; 77MI1].

Low-temperature treatment of pyrrole with one molar equivalent of sulfuryl chloride in ether gave a low yield of 2-chloropyrrole. Further chlorination with the same reagent gave di-, tri-, and tetra-chloropyrroles and ultimately 2,2,3,4,5-pentachloro-2*H*-pyrrole (**34**), which is in tautomeric equilibrium with 2,3,3,4,5-pentachloro-3*H*-pyrrole (**35**) (62JOC2585; 77MI1; 80JA7862; 80JOC435; 81JOC3036). The formation of 3,4-dichloro-maleimide when pyrrole is treated with chlorine in warm aqueous alkali is probably a result of hydrolysis of a such a pentachloropyrrole (81JOC435) (Scheme 13). Sulfuryl chloride is, then, capable of chlorinating all vacant pyrrole sites (56G757; 67BSF2796), and its reactions may be partly electrophilic and partly radical processes [62MI2; 65JCS459; 67MI1]. Side-chain chlorination of methylpyrroles can also occur with this reagent with α -methyls being the more reactive. Even in the presence of added benzoyl



SCHEME 13

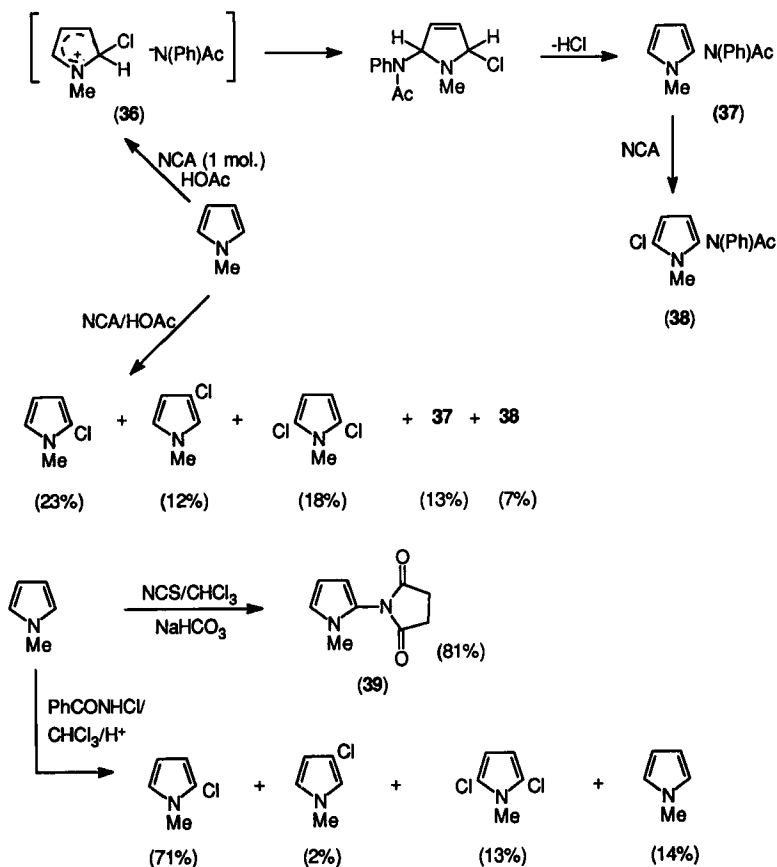
peroxide and AIBN, lateral chlorination does not always take place [62MI2; 74MI2; 92JOC2486].

The observed α -chlorination preference is very much temperature dependent, for a 2-chloro group can migrate to C-3 when warmed, and acid-catalyzed rearrangement also occurs under mild conditions (82JOC3668). Monochloropyrroles are not particularly stable unless there are electron-attracting groups in the ring, and the 2,5-dichloro derivatives are even less stable (although the 3,4-isomers are more readily stored) (75JOC3161).

Although successful with furan and thiophene, benzeneseleninyl chloride in the presence of aluminium chloride failed to chlorinate pyrrole (90MI1).

The most widely studied chlorinating agents for pyrrole are the various *N*-chloroamides [NCS and *N*-chloroacetamide (NCA)]. Using NCS, pyrrole and its 1-methyl, -benzyl, and -phenyl derivatives were converted into the 2-chloro compounds in good yield, although a little less selectively than with NBS. One molar equivalent of NCS gave 2-chloropyrrole (86%) and 2,5-dichloropyrrole (9%) with 5% unchanged starting material. The 1-phenyl compound similarly formed the 2-chloro (69%) and 2,5-dichloro (5%) derivatives (81JOC2221).

Over the past decade De Rosa and co-workers have studied the chlorination of pyrrole with *N*-chloroamides in detail. They have shown that acid-catalyzed chlorination with NCA occurs by direct transfer of Cl^+ to the 2- and 3-positions, with the ratio being 10 : 1 under competitive conditions. In contrast NCS gave no 3-chloropyrrole (82JHC1585). When the annular nitrogen was substituted, NCA gave a variety of products (Scheme 14), among which the *N*-phenylacetyl species (**37** and **38**) are believed to arise through an addition–elimination sequence, perhaps because a tight ion pair (**36**) is formed between the Wheland intermediate and the anion (86CC1585). It is uncommon to find addition–elimination processes in pyrrole chemistry, but with chlorination it appears to predominate over the more usual electrophilic aromatic substitutions. Usually, proton loss from the sigma complex is energetically more favorable than nucleophilic addition, but such addition can be observed in some instances. If there is a π -donor (e.g., halogen) in the 2-position, the diene character of pyrrole is enhanced, and addition becomes competitive when there is a sufficiently nucleophilic anion present (79NJC473). In the presence of sodium bicarbonate, NCS reacted with 1-methylpyrrole in chloroform to give 76% of the sigma substitution product (**39**). Without the bicarbonate the yield of **39** was reduced to 33%, whereas in tetrahydrofuran there was considerable 2-chlorination, demonstrating a solvent effect on product distribution (88TL2405). As with the NCA reaction, formation of **39** may be a consequence of tight ion-pair formation, favored in solvents of medium polarity.



SCHEME 14

Highly polar solvents favor solvent-separated ion pairs that would tend to deprotonate to form chloropyrroles. The observations that NBS and NIS failed to behave in the same way (see 3,b and 3,c) can be attributed to the greater electron-releasing powers of chlorine having a greater effect than bromine or iodine on the aromatic nature of the pyrrole ring, and hence favoring collapse of the ion pair to the 2,5-adduct (88TL2405).

Only *N*-chloroimides appear to promote sigma-substitution, and there is an apparent correlation between the pK_a of the *N*-chloro precursor and the reaction pathway (89JOC5347). Whereas *N*-chlorophthalimide (pK_a 8.3) and NCS (pK_a 9.7) gave 81 and 74% of the sigma-substitution product, respectively, both *N*-chlorobenzimidazole (pK_a 12.9) and NCA (pK_a 15.1) gave none. These pK_a values provide a measure of the "leaving group

ability'' of the nitrogen anion formed. Substituents on the pyrrole nitrogen are also important in defining the reaction process. 1-Acetylpyrrole failed to react with NCS in chloroform in the presence of bicarbonate, but a variety of 1-alkyl and -aryl groups allowed both chlorination and sigma-substitution. Neither 1-tritylpyrrole nor pyrrole itself reacted in this way, and 1-phenylpyrrole reacted sluggishly, but this did not appear to be a steric problem. With pyrrole itself deprotonation is much faster than collapse of the ion pair. Electron-withdrawing groups on pyrrole naturally decrease the rate at which it attacks an *N*-chloroimide, thus explaining the lack of reactivity of 1-acetylpyrrole and the slow reaction of the 1-phenyl derivative (89JOC5347).

Under conditions of acid catalysis 1-methylpyrrole was largely chlorinated by *N*-chlorobenzamide (Scheme 14). There was evidence of an amplified isotope effect ($k_H/k_D = 19.10$ at 40°C), which points to deprotonation of the sigma-complex being rate-determining. Thus, the chlorination process should be reversible (89CC1466). The observed instability of 2-chloropyrrole in acidic medium supports this (75JOC3161). (See also 3,b and 3,c for reactions of *N*-bromo- and *N*-iodo-imides.)

Chloropyrroles have been prepared from organometallic derivatives; indeed, the first synthesis of 2-chloropyrrole was from the reaction of pyrrolylmagnesium bromide with chlorine at -50°C [62MI2; 77MI1], and lithium derivatives with NCS have also been used (84MI3).

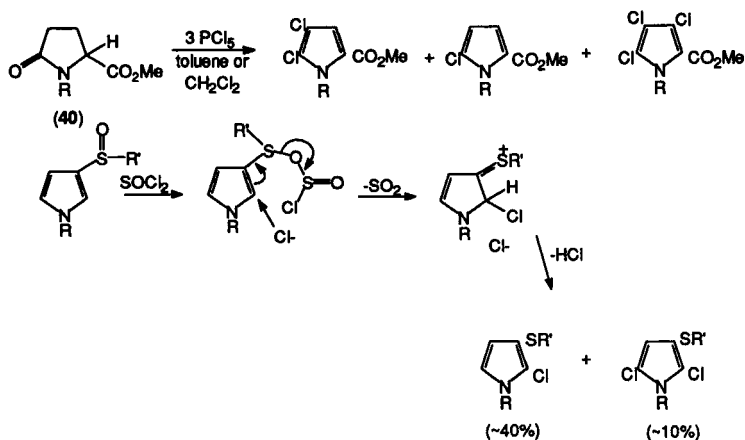
The presence of electron-withdrawing groups in the pyrrole ring makes it easier to prepare mono- and di-chloro derivatives (65JCS459), but deactivates positions *ortho* and *para* to the substituent. Chlorination of 3-nitropyrrole with sulfuryl chloride in acetic acid gave 2,3-dichloro-4-nitropyrrole (13%) [82JAP(K)67557]. The same reagent in ether at 0°C converted 3-benzoylpyrrole into 2-chloro-4-benzoyl pyrrole in 67% yield, with a combination of steric and electronic factors controlling the product orientation (89CJC433). Acyl substituents are, however, prone to α -halogenation by reagents such as copper(II) chloride [85H(23)165] and benzyltrimethylammonium dichloroiodate (90S212), and may even be displaced on sulfuryl chloride treatment (69CPB588). A 2-dimethylsulfonium substituent directed both electrophilic and radical chlorination to carbon-4 (82JOC1682), and strongly electron-withdrawing 1-substituents (e.g., phenylsulfonyl) also favor β -chlorination (81TL4901). Ester functions in the 2-position also direct a proportion of attack into the β -positions. Ethyl 1-phenylpyrrole-2-carboxylate was converted on treatment with chlorine in acetic acid into a mixture containing 5-chloro (20%), 4-chloro (8%), 4,5-dichloro (40%), and 3,4,5-trichloro (25%) derivatives (71CJC136; 71CJC919). A comparative study of halogenation of the methyl ester of pyrrole-2-carboxylic acid using bromine, *t*-butyl hypochlorite, and sulfuryl

chloride demonstrated that chlorine is more reactive and less selective than bromine by forming about equal quantities of 4- and 5-chloro products. Radical chlorination by *t*-butyl hypochlorite went mainly into the 5- and then the 3-position; sulfonyl chloride attacked the 5-position preferentially (65JCS459).

Sulfonyl chloride alone, or in the presence of silicon dioxide or disulfur dichloride-aluminium chloride, gave the 5-chloro derivatives of 2-perhalogenomethylthiopyrroles, along with some di-substituted (3,5- and 4,5-) and tri-substituted (3,4,5-) compounds. Brominating and iodinating agents reacted similarly (85JHC281).

The action of phosphorus halides on pyrrolinones and related compounds offers an alternative route to chloropyrroles. Yields of around 60% of 2,5-dichloropyrroles were obtained in this way from *N*-substituted succinimides (82ZC126). Vilsmeier reaction of *N*-alkylsuccinimides formed chlorinated pyrrole aldehydes in modest yields (90CJC791), and there are other examples [66YZ158; 81H(15)547]. A useful synthesis of chloropyrrole-2-carboxylates employed the action of phosphorus pentachloride on pyrrolidin-2-one-5-carboxylates (**40**) (87CB45) (Scheme 15), and in a Pummerer-type reaction pyrrol-3-yl sulfoxides were transformed by thionyl chloride into chloropyrroles. Yields were increased to >80% by the use of oxalyl chloride (88JOC2634) (Scheme 15).

Polysubstituted 2- or 5-methylpyrroles can be laterally chlorinated through a two-stage process that involves initial *ipso*-chlorination in the β -position, followed by rearrangement into the side chain. Migration is also possible from the vinylogous α' -position (80JA1377).



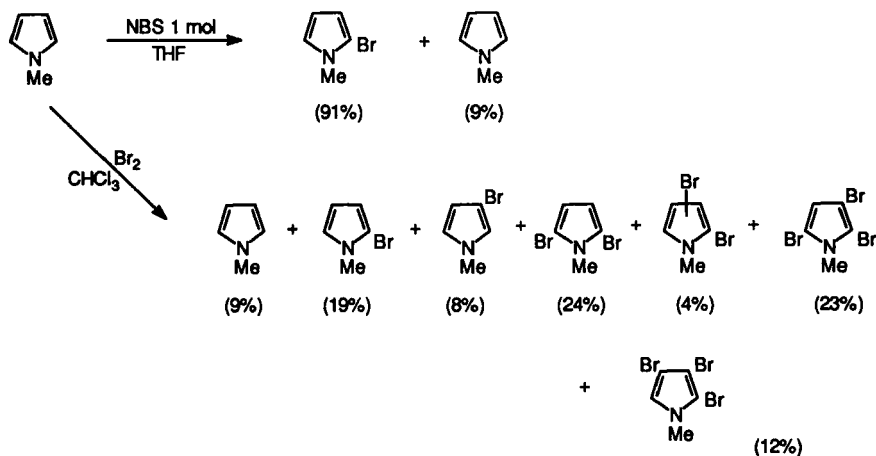
SCHEME 15

b. *Bromination.* When pyrrole was brominated with elemental bromine under alkaline conditions similar to those used for chlorination, the major products were 2,3,4,5-tetrabromopyrrole and 3,4-dibromomaleimide [62M12; 77M11], although bromine in carbon tetrachloride gave 3-bromopyrrole (which is more stable than the kinetic product 2-bromopyrrole) (81JOC221). The 3-isomer is formed in a very facile acid-catalyzed reaction induced by HBr produced in the process. Bromine will halogenate any vacant ring positions in a polysubstituted pyrrole, and various *ipso*-brominations are known (53JA2089, 53JA5295). 1-Benzylpyrrole was converted by bromine in carbon tetrachloride at 0°C into a mixture of 3-bromo (60%) and 2,5-dibromo (30%) products (67CJC2227). Electron-withdrawing substituents stabilize the ring and permit slower, more controllable bromination. Relative rate measurements on molecular bromination of 2-methoxycarbonyl-pyrrole, -furan, and -thiophene (respective values were 5.9×10^8 , 120, 1) indicate just how reactive pyrrole is. The reaction products were the 5-monobromo (23%) and 4-monobromo (77%) isomers [68JCS(B)392]. With the same substrate, Lewis acid catalysis by iron led to a mixture of 4-bromo (48%), 5-bromo (17%) and 4,5-dibromo (5%) products; aluminium chloride was less specific with respective percentage yields being 29, 30, and 6%; pyridinium bromide perbromide favored 4-bromination (49, 2, 5% yields) (65CJC409).

Widespread use of NBS is a result of this reagent not being a source of HBr, which catalyzes rearrangement and debromination of 2-bromopyrroles through disproportionation reactions (81JOC2221; 82JOC3668). When one molar equivalent of this reagent in tetrahydrofuran was used, pyrrole and its 1-methyl, 1-benzyl, and 1-phenyl analogues were regiospecifically 2-brominated in yields of 91, 99, 99, and 49%. Only a small proportion of dibromopyrroles was observed. In contrast, bromination with bromine in chloroform gave variable results (Scheme 16). With two or three equivalents of NBS regiospecific multiple bromination of 1-methylpyrrole gave the 2,5-dibromo (98–100%) and 2,3,5-tribromo (90%) products (81JOC2221). As noted earlier (Section 3,a), NBS does not lead to sigma-substituted products (88TL2405).

When peroxides were present, NBS converted methyl pyrrole-2-carboxylate into a mixture of its 4-bromo (15%), 5-bromo (14%), and 2,5-dibromo (11%) derivatives (65CJC409). Low-temperature treatment of 1-butoxycarbonylpyrrole with NBS gave the 2,5-dibromo derivative in 61% yield (91S613).

Although substituents can exert polar and steric effects, there is always a strong tendency for α -bromination (88HCA2053; 88JOC2796). Hence, 2-alkylpyrroles are brominated mainly in the 5-position, although selectivity is less than with the corresponding furans and thiophenes. A very large group on nitrogen (e.g., trityl) promotes 3- and 3,4-bromination



SCHEME 16

[83JCS(P1)93], and even 1-benzylpyrrole formed mainly the 3-monobromo product before polybrominating (67CJC2227). Similarly 1-triisopropylsilylpyrrole formed the 3-bromo product (in 90% yield) (84JOC3239), as did 2-methyl-5-phenylpyrrole [73AC(R)245]. Reaction of 1,2-dimethyl-3-nitropyrrole with NBS (80CS72), and 2-(2'-pyrrolyl) benzimidazole and its 1-methyl derivative, with bromine in dichloroethane at 0°C (80CHE59) gave the 5-bromo products. At higher temperatures, and in acidic media, both substrates showed evidence of some β -bromination. Similarly only the 5-bromo product was isolated when 3-acetylpyrrole was treated with bromine in acetic acid (67CJC897).

When complexed with a Lewis acid, though, the 5-position of a 2-acylpyrrole becomes more deactivated, and more 4-bromination is observed [71CR(C)276]. There are numerous examples where sufficient electron withdrawal from a 2-substituent promotes 4-substitution. Bromine in carbon tetrachloride at 0°C gave a 30 : 1 mixture of 4- and 5-bromo products from 2-formylpyrrole; at 28°C the ratio became 6 : 1 with some, 4,5-dibromination; at 70°C the ratio of 4-brominated : 5-brominated : 4,5-brominated products was 1.6 : 1.5 : 1. The methyl ester of pyrrole-2-carboxylic acid behaved similarly (65CJC409). Dioxan dibromide in the presence of sufficient alkali to mop up HBr gave a mixture of 4-bromo (20%) and 4,5-dibromo (20%) aldehydes from the same starting material (86CHE806). Bromine in carbon tetrachloride gave more than 90% of 4-bromo-2-nitropyrrole from the nitroheterocycle (70JHC1101).

Side-chain halogenation of alkyl or acyl groups on pyrrole can occur under conditions in which the ring is fully substituted, or when radical promoters are present, especially with NBS as the reagent (89SC2721).

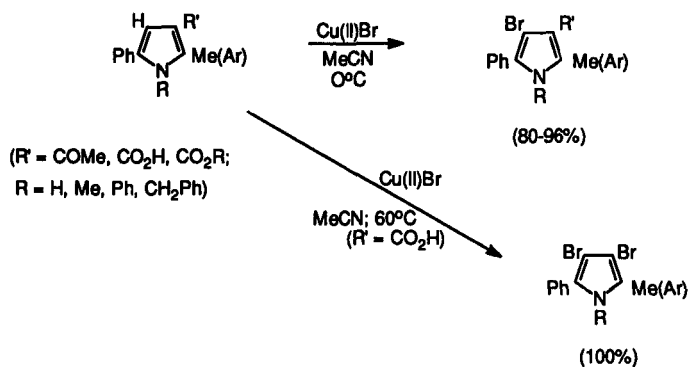
Ester functions in the α -position or alkyl groups in the β -position are especially prone to such reactions (92JOC2486).

By means of oxidation of the initially formed 3,4-disubstituted 5-bromo-2-bromomethylpyrrole, bromine converted 3,4-disubstituted-2-methylpyrroles and their 5-carboxylic acids into 5-bromo-5'-bromomethyl-2,2'-dipyrrolylmethanes. Similar reaction with sulfonyl chloride led to the analogous chloro species (77MI2). Whereas treatment of 2-aryl-1,3-dimethylpyrrole-5-acetic esters with NBS brominated the vacant ring carbon, the related oxalate ester gave the 3-bromomethyl derivative (80JMC98).

Copper(II) bromide polybrominated 1-methylpyrrole (75JOC3161), whereas methyl pyrrole-2-carboxylate gave low yields of the 4- and 5-bromo derivatives with the same reagent (65CJC409). Oxidative brominations of a series of 1-substituted 3-acyl-2-alkyl (or aryl)-5-phenylpyrroles gave high yields of 4-bromo products, and at higher temperatures the acid group was also replaced by bromine (Scheme 17). Replacement of the 5-phenyl group by methyl resulted in complex mixtures and minimal nuclear bromination (90JHC1209, 90JHC1277).

Bromopyrroles are accessible from metallic derivatives quenched with bromine [62MI2; 77MI1].

c. *Iodination.* Iodine with potassium iodide or in alkaline solution converted pyrrole into the light-sensitive tetraiodopyrrole (62MI2). At low temperatures iodine in chloroform formed a 1 : 1 charge-transfer complex with pyrrole (and indole). Collapse of this complex gave the 2- and 3-iodo derivatives [62JA4438; 70MI1; 72HC(25-2)127; 77MI1]. The 2-position of pyrrole is around 26 times more reactive than the 3-position in iodination



SCHEME 17

(49JA159). Iodine and potassium iodide also gave polyiodinated methylpyrroles. Thus, both 2,4- and 2,5-dimethyl isomers were diiodinated, and at -10°C 1,2,5-trimethylpyrrole was converted into the moderately stable 3-iodo derivative, before giving the 3,4-diiodo species at higher temperatures [58LA(614)176]. 1-Methylpyrrole reacted with NIS to give its 2-iodo derivative in 63% yield, along with some 2,5-diiodo (12%) product and traces of sigma-substitution product (88TL2405). Oxidative procedures include potassium iodide with hydrogen peroxide or iodic acid (72JOC925; 73BSF351; 89CJC433), or iodine with acetic or sulfuric acids (89CJC433). Iodinative decarboxylation of pyrrole-2-carboxylic acids is a common reaction, especially when the ring bears other electron-withdrawing groups (63JCS359; 64AJC987; 78CJC2430).

As in other halogenations, electron-withdrawing groups in the 2-position direct iodination to C-4 [70CI(L)156; 72JOC925; 73BSF351]. Both steric and electronic factors combined to direct iodination of 3-benzoylpyrrole into the 5-position (89CJC433). Thallation of 2-formyl-1-methylpyrrole gave the 3,4-dimetallated derivative, which was converted by reaction with iodine into the 3,4-diiodo species in 54% yield (79JHC993; 85S353).

Reductive processes are sometimes useful for conversion of polyiodinated pyrroles into compounds with fewer iodine atoms. Sequential action of butyl-lithium and water reduced tetraiodopyrrole to a mixture of 2,3,4-triiodopyrrole (63%) and 2,3,5-triiodopyrrole (3%). Zinc and acetic acid was able to reduce the tetraiodo compound to 3,4-diiodopyrrole which was converted by butyl-lithium and then dimethylformamide into 3-formyl-4-iodopyrrole (75JHC373).

d. *Fluorination.* Direct fluorination of pyrrole and its simple derivatives gives complex mixtures. When treated with potassium tetrafluorocobaltate and cobalt(III) fluoride 1-methylpyrrole gave a mixture of polyfluorinated 1-methylpyrrolidines [75JCS(P1)781; 77MI1], and even the methyl group was partially fluorinated by these reagents (83JFC287). More careful reaction with fluorine diluted with helium in chloroform at -60°C was successful in monofluorinating 1-methylpyrrole, a mixture of 2-fluoro (20%) and 3-fluoro (80%) isomers being obtained through what is believed to be an electrophilic process (89G203). It is usually more convenient to prepare fluoropyrroles by treating lithiopyrroles with perchloryl fluoride, or by photolysis of a diazonium fluoroborate (85TL4221).

The difficulty of perfluorinating pyrrole is enhanced in the porphyrins, which have reduced π -density on the α -carbons. Although direct fluorination appears promising, it is not yet fully developed [88JCS(P1)1735; 89CL263; 90TL6847]. The use of *N*-fluoropyridinium triflate resulted only in *meso*-fluorination (92TL1069).

4. Selenophene

Comparative studies using the perchloric acid-catalyzed reaction with hypobromous acid at 25°C in 90% aqueous dioxan have shown that selenophene is more reactive than thiophene by a factor of 4.5. Uncatalyzed bromination in acetic acid is 47.5 times faster than thiophene, and chlorination in acetic acid occurs at 6.5 times the rate [70JCS(B)43; 71AHC(13)235]. The reactions are highly specific for the 2-position (less than 1% of the 3-isomer is usually formed) and no addition has been reported. The greater reactivity of selenophenes in both nucleophilic and electrophilic substitution reactions may be a function of the capacity of selenophene to delocalize both positive and negative charges, since selenium is larger and more polarizable than sulfur. It can therefore release *p*-electrons or absorb them into empty *d*-orbitals more easily than sulfur [82AHC(30)127; 84MI6].

a. *Chlorination.* Initial selenophene halogenation is at an α -position, but di-, tri-, and tetra-halogeno compounds can be readily prepared. Sulfuryl chloride converts selenophene into 2-chloroselenophene (60JGU2706), but preparation of both the 2- and the 3-isomers via the lithium derivatives with hexachloroethane seems a more attractive approach, giving yields of around 45% (73SC213). Sodium telluride reduced tetrachloroselenophene to a mixture of 3-chloro and 3,4-dichloro derivatives, again demonstrating the greater reactivity of the α -positions (70FRP1568529).

b. *Bromination.* One mole of NBS in carbon tetrachloride gave a good yield (46%) of 2-bromoselenophene; two or three molar equivalents of molecular bromine in acetic acid gave the 2,5-dibromo (70%) and 2,3,5-tribromo (81%) bromo derivatives, respectively [75CS(7)111]. With excess bromine, tetrabromoselenophene was obtained quantitatively (36BCJ157). Multiply brominated species have been reduced to the 3-bromo compounds using zinc and acetic acid (81SC25).

Presence of electron-withdrawing substituents does not usually prevent α -substitution being favored. Both 2- and 3-acetylselenophenes reacted with bromine in the presence of sodium acetate to give the 5-bromo products in 61 and 58% yields (81SC29). Under mild conditions 1-methyl-2-(2'-selenienyl)benzimidazole was monobrominated in the vacant α -position. More vigorous conditions (bromine-acetic acid) gave the 3',5'-dibromo product, and bromine in polyphosphoric acid at 120°C also introduced bromine into the benzimidazole moiety (83CHE1216). When the 5'-position was blocked by a methyl group, bromine in acetic acid gave 64% of the 4'-bromo derivative. In contrast, bromine in 1,2-dichloroethane led

to products substituted in the benzimidazole 5- and 6-positions. The acetic acid presumably protonates the imidazole nitrogen, rendering the benzimidazole less reactive (87CHE1316).

c. *Iodination.* Iodination of selenophene with iodine and mercuric oxide (56JGU3517), or more conveniently with iodine–iodic acid [75CS(7)111], gave 2-iodoselenophene (25%). The yield was improved to 58% by reaction of 2-selenienyllithium with iodine [75CS(7)111].

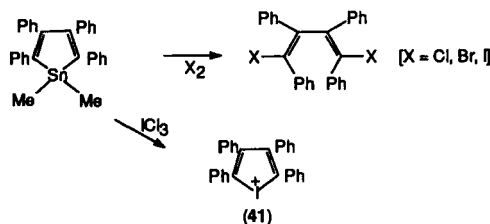
d. *Fluorination.* 2-Fluoroselenophene was formed by the reaction of perchloryl fluoride with the 2-lithium derivative (73CS94), and other halogenated selenophenes have been made in the same general way (72CHE13; 73SC213).

5. Tellurophene

Because it is so sensitive to acids, tellurophene has only a limited range of electrophilic aromatic substitution reactions. both the parent compound and its derivatives tend to form 1,1-addition compounds with halogens at the tellurium atom [66AG(E)896; 72JCS(P1)199; 77AHC(21)119; 84MI6], and the C-monohalogenated species frequently need to be made from the lithium derivatives. This process was successful for making 2-bromo-, 2-chloro-, and 2-iodo-tellurophenes, but failed for the 2-fluoro analogue [76ACS(B)605].

6. Other Five-Membered Rings with One Heteroatom

Little is known about the halogenation properties of other members of this general group (84MI2). Germales and stannoles are cleaved readily by halogens [74JOM(66)321]. The tin compounds gave the cation (41) on treatment with iodine trichloride (81JOC4069) (Scheme 18). Arsoles tend to chlorinate with iodobenzene dichloride at the heteroatom, whereas borole does not appear to have been halogenated (84MI14).



SCHEME 18

B. FIVE-MEMBERED RINGS WITH TWO OR MORE HETEROATOMS

1. *Pyrazoles (1,2-Diazoles)*

Electrophilic halogenations in pyrazole occur initially at carbon-4 with partial rate factor, 7.2×10^6 (cf. imidazole, 9×10^6) [64JA2857; 66AHC(6)391; 78JCS(P2)865; 84MI8]. Localization energy calculations gave a value of -2.10β in accord with this (55AJC100). Other physical aspects of pyrazole halogenation have been discussed recently [90-AHC(47)165]. The compounds are so reactive, however, that it is difficult to achieve monohalogenation by direct methods. Methyl ring substituents increase reactivity even more; 1-methylpyrazole is twice as reactive as pyrazole, and 3,5-dimethylpyrazole is brominated 3700 times more rapidly than the parent (71AJC1413). The individual effects of 3- and 5-methyl groups have been estimated at around 15- and 300-fold, respectively (the bond order effect will make the 4,5-interaction about twice that of the 2,5-interaction in imidazole). Even strongly electron-attracting groups at C-3 do not prevent 4-halogenation; the 3,4-bond order in pyrazole is low (82JGU2291). A 1-phenyl group may be halogenated preferentially. Halogenation still occurs at C-4 in 1-hydroxypyrazole and its 2-oxide even though the oxide function should increase the reactivities of the 3- and 5-positions (80JOC76).

Certainly pyrazole is very much less reactive than pyrrole toward electrophiles. As the neutral molecule it resembles benzene in reactivity; as the anion it is like phenol. Pyrazolium cations are so deactivated that they are reluctant to react with electrophiles.

Although N-halogenated pyrazoles are known, they are quite unstable compounds, increasing in stability from chloro to iodo. They may be implicated in the formation of polyhalogenated derivatives (76MI2). There are many examples of competition between nuclear and side-chain halogenation, particularly when radical species can form (90CHE301).

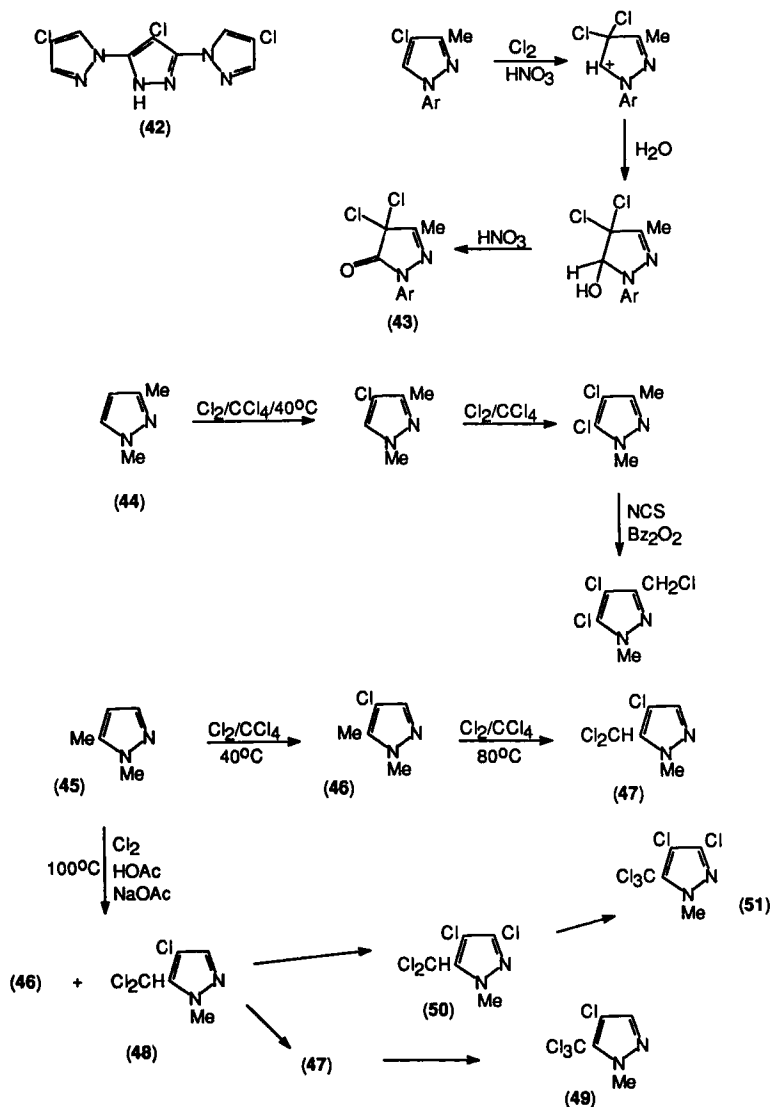
a. *Chlorination.* 4-Chlorination of pyrazoles occurs with reagents as diverse as molecular chlorine in aqueous solution [66AHC(6)391], in carbon tetrachloride (82JGU2287; 90CHE301), in nitric acid (67BSF328), in oleum (88CHE703), or in acetic acid with or without added sodium acetate (83CHE802; 90CHE301); with hypochlorous acid or hypochlorites (80JOC76; 83JHC277), hydrogen chloride with hydrogen peroxide or other oxidizing agents [58LA(618)110; 66AHC(6)391], NCS (80JOC76; 86-JHC459), sulfonyl chloride [66AHC(6)391; 92EUP464736], phosphorus pentachloride [66AHC(6)391]; or using enzymatic methods (87JHC1313). It is frequently difficult to prevent multiple chlorination. Chlorination

of *N*-unsubstituted pyrazoles as the silver salts may have advantages (70CB1942). Some of the above reagents may induce side-chain chlorination, and dimers and trimers (e.g., **42**) are formed on occasion. When chlorination is attempted in nitric acid, pyrazolones may be formed (see below). Tri- and tetra-chloropyrazoles do not appear to be known [56LA(598)186].

In weakly polar solvents, chlorine converted 3-methylpyrazole into 4-chloro-3-methylpyrazole, whereas more vigorous treatment with chlorine in acetic acid gave a mixture of 4,5-dichloro-3-methyl- and 4,5-dichloro-3-trichloromethyl-pyrazoles [56LA(598)186]. Whereas sulfonyl chloride in chloroform 4-chlorinated 1-aryl-3-methylpyrazoles, chlorine in nitric acid led to pyrazolones (**43**) by a process in which electrophilic chlorination was followed by nucleophilic attack by water and subsequent oxidation (67BSF328) (Scheme 19). The latter process appears to require the presence of a strong electron-acceptor in the 1-position, and is common to both chlorination and bromination. When, however, 1,3-dimethylpyrazole was exposed to these conditions the only product isolated was the 4,5-dihalogeno-1,3-dimethylpyrazole (66BSF293). Chlorine in acetic acid-sodium acetate converted 1,3-dimethylpyrazole into the pyrazolone analogous to **43** (83CHE802). Detailed studies of the halogenation of 1,3-dimethylpyrazoles (**44**) and 1,5-dimethylpyrazoles (**45**) have demonstrated clear differences between the reactivities of the 3- and 5-positions during electrophilic halogenation, and between the methyl groups during radical halogenation (80JGU1705; 82JGU2287; 83CHE802; 88CHE33; 90CHE301). This is responsible for the low selectivity of chlorination of **45** compared with **44**. With 1,3-dimethylpyrazole, methyl chlorination only takes place after the 4- and 5-positions have been substituted. In the isomer (**45**) 4-halogenation precedes 5-methyl-halogenation. Chlorination for 1 hr at 100°C gave a mixture of **46**, **47**, **48**, and **50** in the ratio 78 : 12 : 5 : 5. After 2 hr the ratio was 48 : 18 : 5 : 8 along with increasing amounts of **49** and **51** (90CHE301) (Scheme 19).

The other possible isomer, 1,4-dimethylpyrazole (and its other *N*-alkyl and -aryl analogues), reacted with chlorine in dichloroethane at 25–35°C to produce 5-chloro derivatives in around 70% yields (90EUP366329). 5-Aryl-3-methylpyrazoles were chlorinated by NCS at C-4 (86JHC459), as were a range of pyrazoles by chloroperoxidase in the presence of hydrogen peroxide and potassium chloride at pH 2.9. Yields of 68–83% make this latter process an improvement over some traditional chemical methods (87JHC1313).

Substituents can enhance or reduce reactivity, but the usual substituent effects may not always be apparent in cases where the substituent can exist in a tautomeric modification, e.g., hydroxy, thiol, amino. Thus,



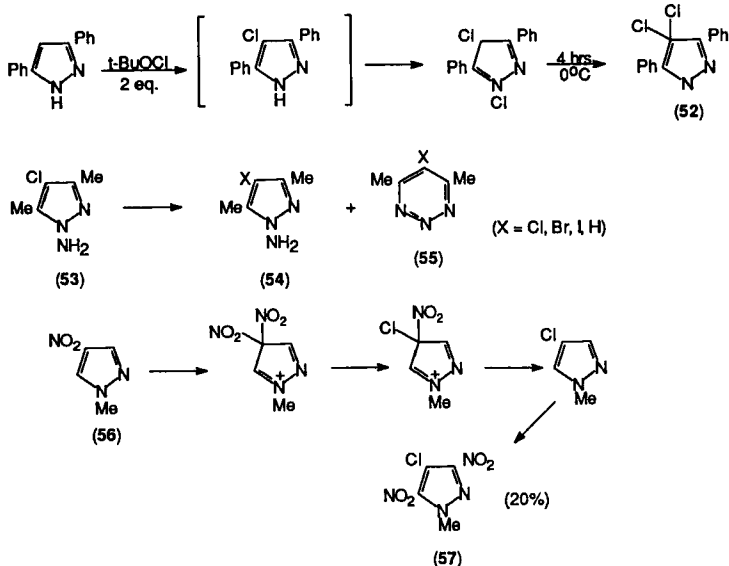
SCHEME 19

3-amino- and 3-hydroxy-pyrazoles, and 3-pyrazolin-5-ones are 4-halogenated, but 2-pyrazolin-5-ones may be 4,4-dichlorinated, although it is frequently possible to reduce out one of the chlorine groups (85S299). Apparently, 4-hydroxypyrazoles are dichlorinated at the 5-position to give 5,5-dichloro-2-pyrazolin-4-ones and, when there is a strong electron-

acceptor in the 1-position, chlorine (or bromine) in nitric acid give the 4,4-dihalogeno-5-pyrazolones (analogous to **43**) when they react with pyrazoles (67BSF328). Sulfuryl chloride converted the iminopyrazolidine into 5-amino-4-chloro-3-methylpyrazole (92EUP464736).

4,4-Dichlorination was also observed when two molar equivalents of NCS or *t*-butyl hypochlorite reacted with 1-hydroxypyrazoles and their 2-oxides. One equivalent of NCS gave only the 4-monochloro derivative in high yield (80JOC76). When there was already a 4-substituent present, as with 3,4,5-trisubstituted pyrazole 2-oxides or 1-hydroxy-3,4,5-trisubstituted pyrazole 2-oxides, the reaction products were 4-chloro-4*H* derivatives (77JOC3721). With 2 mol of *t*-butyl hypochlorite, 3,5-diphenylpyrazole gave the unstable 1,4-dichloro derivative, which rearranged to form 4,4-dichloro-3,5-diphenyl-4*H*-pyrazole (**52**) (80JOC76) (Scheme 20).

A comparison of the effects of a wide variety of halogenating agents on 1-aminopyrazoles (**53**) has shown that although some of the reagents cause preferential oxidation of the amino group and consequent formation of 1,2,3-triazines, others give both 1-amino-4-halogenopyrazoles (**54**) and 5-halogeno-1,2,3-triazines (**55**). The formation of **55** implies that 4-halogenation has preceded oxidation. In some instances oxidation and halogenation appear to have proceeded concurrently since unhalogenated triazines, 1-amino-4-halogenopyrazoles, and 5-halogenotriazines were all formed (see Table I; Scheme 20). The oxidations may have occurred



SCHEME 20

TABLE I
YIELDS OF 1-AMINO-4-HALOGENO-3,5-DIMETHYLPYRAZOLES (54) AND 5-HALOGENO-4,6-DIMETHYL-1,2,3,-TRIAZINES (55) FORMED WHEN 1-AMINO-3,5-DIMETHYLPYRAZOLE IS HALOGENATED (88CPB3838) (SCHEME 20)

Reagent	% (54)	% (55)
Cl ₂	Trace	21
Br ₂	2	75
I ₂	69	Trace
BrCl	16	61
IBr	77	Trace
NCS	21	34
NBS	26	34

by insertion of a nitrene into the pyrazole 1,2-bond, or an intermediate haloamine may be implicated [86JCS(P1)1249; 87CPB3952; 88CPB3838].

Although 4-nitro-1-methylpyrazole (56) could not be chlorinated in oleum, the use of chlorine in concentrated nitric acid containing oleum (20%) was effective. The result could be explained in terms of *ipso*-attack of chlorine at the 4-position to give a 4-chloro-4-nitro cation, which could eliminate a nitro group or rearrange. Subsequent nitration might then give rise to the product isolated (57) (88CHE703) (Scheme 20). Such a process would not occur with bromine because bromine would be preferentially eliminated from any *ipso*-intermediate.

5-Chloropyrazoles (and 5-bromopyrazoles) can be prepared in good yields by 1,3-dipolar addition of 4-halogenosydnone and dimethyl acetylenedicarboxylate (75CJC913). They should also be readily available using lithiation processes specific for C-5 substitution. The traditional nucleophilic reactions in which a 5-pyrazolone is treated with phosphoryl chloride in dimethylformamide, or chloroform with triethylamine are well known. Such reactions are favored by electron-withdrawing substituents elsewhere in the pyrazole ring (81JHC957; 87JPR945). 3-Pyrazolones and the corresponding thiones react similarly (81CPB2871; 90M1023). Sandmeyer processes, too, are sometimes useful. Diazotized 3,5-diaminopyrazole was converted in 75% yield into 3,5-dichloropyrazole [87JAP(K)62/04271]. The same method, however, gave only a 37% yield of 3-chloropyrazole (66CB3350), but with copper(I) chloride rather than HCl the yield could be increased to 57%. Addition of excess sulfur dioxide as catalyst for chlorodediazonization allowed the yield to be maximized to 93%. It is believed that an electron transfer from sulfur dioxide to the diazonium cation occurs in the first step (91JHC1545).

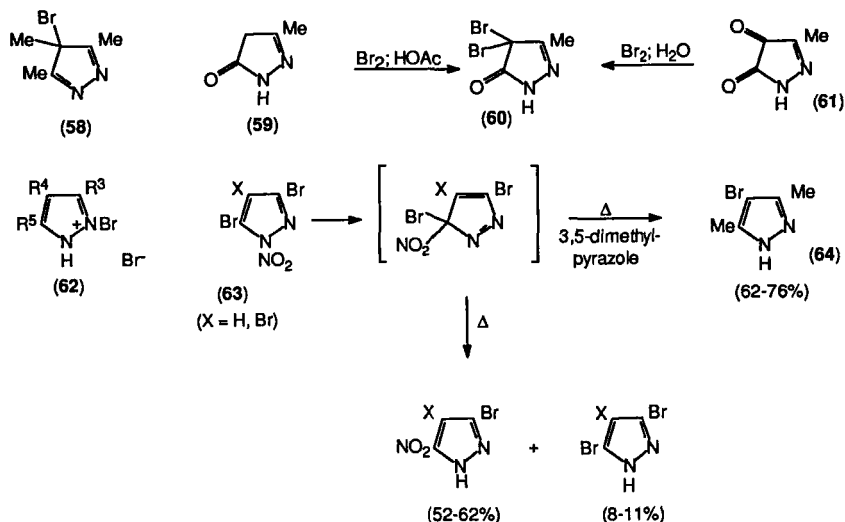
b. *Bromination.* Tribromination of pyrazole is so facile a reaction that it is difficult to achieve 4-monobromination [56LA(598)186; 66AHC(6)391]. Under alkaline conditions (reaction of the anion) yields of 90–96% of 3,4,5-tribromopyrazole have been reported (73OPP141; 74FRP2193823). 1-Methylpyrazole, too, was readily tribrominated, and methyl substituents generally facilitate C-brominations [56LA(598)186; 71AJC1413; 84JOC4687].

The most common reagents employed have been bromine in chloroform or acetic acid, and NBS (82JGU2287; 83JHC277; 84MI8; 86AF419, 86PHA813; 90CHE301), with 4-bromination occurring if at all possible under electrophilic or radical conditions (80JGU1714; 82JGU2287; 82S844; 83BSF(2)5; 83CJC154; 84JHC945; 87JHC689; 87JOC4384) even if a group other than hydrogen needs to be displaced from the 4-position. Bromine in acetic acid gave the 4-bromo derivatives from a number of 1-arylpyrazole-4-carbaldehydes (86PHA813; 87JOC4384). Once the 4-position has been brominated, then 3- and 5-bromination can take place, or side-chain halogenation may eventuate, although in some instances a Lewis acid catalyst might be required to ensure complete polybromination (80JGU1714; 88CHE33).

Careful addition of bromine in acetic acid containing sodium acetate to 1-methylpyrazole gave a 4 : 1 mixture of the 4,5- and 3,4-dibromo isomers (83CHE1322). Exhaustive bromination of **44** gave the 4,5-dibromo product in 2 hr; the isomer (**45**) required 10–12 hr of reaction for complete bromination, reflecting the lower reactivity of the 3- compared with the 5-position (80JGU1714). Using bromine in acetic acid, or NBS or bromine with benzoyl peroxide gave the 4-bromo derivatives of both of the dimethylpyrazoles (**44**, **45**), but once that position was filled radical substitution occurred at a lateral position. This is not universal, however, since 4-chloro-1,3-dimethylpyrazole gave the 5-bromo derivative under similar conditions. Some lateral bromination of 4,5-dichloro-1,3-dimethylpyrazole was evident under radical conditions (82JGU2287; 88CHE33). With five molar equivalents of bromine at 75°C over 8 days 4-bromo-1-methylpyrazole gave a mixture of 3,4,5-tribromo-1-methylpyrazole (34%) and 4,5-dibromo-1-methylpyrazole (46%), again reflecting the lower reactivity of the 3-position (84JOC4687).

When the 1-position is unsubstituted, bromination of 4-methylpyrazoles can form dimers and trimers (cf. chlorination), while 3,4,5-trimethylpyrazole reacts similarly. Possible products may include 4-bromoisopyrazoles (**58**) [69CR(C)(269)570; 70CB1949; 76MI1] (Scheme 21).

The presence of a 3-fluoroalkyl group did not prevent 4-bromination, but extended reaction times were necessary to obtain high yields (80–94%). Under similar conditions 1-substituted-5-fluoroalkyl- and -3,5-



SCHEME 21

bis-fluoroalkyl-pyrazoles failed to react. Although the nature of the 3-fluoroalkyl substituent does not markedly affect reaction rates, the N-substituent does [82BSF(2)89].

Bromination of 1-phenylpyrazoles resembles nitration in that it occurs initially in the benzene ring, and only then in the heterocyclic nucleus to give what is probably 4,5-dibromo-1-(*p*-bromophenyl)pyrazole [61JCS2769; 66AHC(6)391]. 3-Methyl-1-phenylpyrazole was brominated at both C-4 and in the *para*-position (61JCS2769), and there are other examples (83JHC277).

Brominations in nitric acid have received some attention for the preparation of 4,4-dibromo-5-pyrazolones analogous to the chloro compounds (43). Such reactions need strong electron withdrawal in the 1-position, since 4-bromo-1,3-dimethylpyrazole only brominated in the 5-position under the conditions (66BSF293; 67BSF328). Such 4,4-dihalogenated species are frequently the major products of direct halogenation of 2-pyrazolin-5-ones, although one of the halogens may be removed by subsequent reduction (85S299). Thus, 3-methyl-2-pyrazolin-5-one (59) gave the 4,4-dibromo product (60) in 78% yield when treated with bromine in acetic acid. Aqueous bromine gave the same product with the 4,5-dione (61) (81S72; 84S972) (Scheme 21). The 1-phenyl derivative of 61 behaved similarly. When 1-hydroxypyrazoles or their 2-oxides reacted with 2 mol of NBS, the products were 4,4-dibromo-1-oxides or -1,2-dioxides (80JOC76).

1-Bromopyrazoles are quite unstable compounds, but they resemble NBS and may play a role in C-bromination by providing a source of positive bromine. Perbromides, formulated as **62**, have been identified in the bromination of 4-substituted pyrazoles. Dehydrobromination occurs quite readily with the formation of 1-bromopyrazole (76MI2). Polybrominated 1-nitropyrazoles (**63**), too, are potentially valuable brominating agents. When heated with 3,5-dimethylpyrazole, **63** gave a mixture of products including 4-bromo-3,5-dimethylpyrazole (**64**). Heating **63** alone resulted in a proportion of nitrodebromination (86JOC4656) (Scheme 21).

*Ips*o-brominations in these compounds include displacement of formyl, sulfonic acid, mercury groups, and trimethylsilyl (76MI1). In 1-methyl-4,5-bis(trimethylsilyl)pyrazole and its 3,4-isomer, molecular bromine at 0°C selectively brominated the 4-position. Over a longer period at 40°C excess bromine replaced the 3- and 5-trimethylsilyl groups as well (84JOC4687) (see also B,I,c).

Syntheses of 3(5)-halogenated pyrazoles from the lithium derivatives are now available. Organolithium reagents metalate 1-protected pyrazoles in the 5-position, and even N-unsubstituted pyrazoles can be lithiated as long as 2 mol of reagent is used. Metal-halogen exchange further broadens the ring sites which can be lithiated [79OR(26)1; 83T2023]. The preference for 5- over 3-lithiation is a function of the "adjacent lone pair effect" (78JOC3565; 83T4133). Katritzky and co-workers have reviewed the protecting groups available for N-substituted pyrazoles (89T4253), and although such lithiation processes have been seldom used for the preparation of 3- or 5-halogenopyrazoles the potential is evident [90JCS(P1)1829]. One example is the synthesis of 4,5-dibromo-1-phenylsulfonylpyrazole made by low-temperature bromination of 4-bromo-5-lithio-1-phenylsulfonylpyrazole. Over a period of time the initial reaction product isomerized into the more stable 3,4-dibromo isomer [90JCS(P1)1829], a not uncommon transformation [73RTC(92)245].

In pyrazolium salts a ring chlorine can be displaced by the more nucleophilic bromide, and nucleophilic substitutions of diazonium groups by halogen are also relatively common (especially for fluorination) with yields frequently 80% or higher [61CB1036; 66CB3350; 90JAP(K)02/304064].

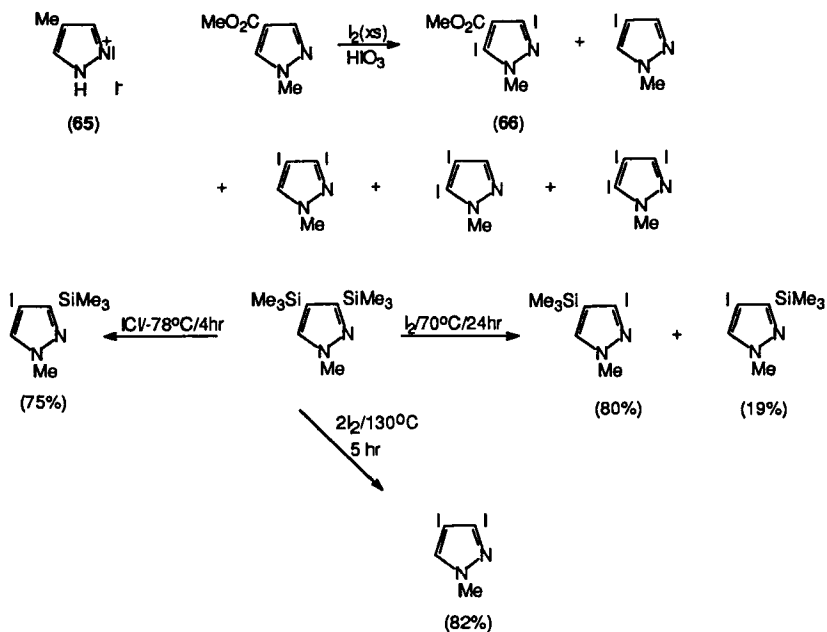
c. *Iodination*. Pyrazole iodination seldom meets with success in the absence of some species which neutralizes the HI formed in the reaction. The problem has been overcome by use of the silver salt of the heterocycle, or by doing the reaction in the presence of alkali or sodium acetate, or with hypoiodous acid [66AHC(6)391]. The anion of pyrazole is more reactive than the neutral molecule by a factor of $10^{9.5-12.8}$ (67JA6218), and there have been a number of kinetic studies of pyrazole iodination [71PMH(4)55;

76MI1; 90AHC(47)165]. Coordination of the heterocycle with nickel(II) in aqueous solution increased iodination rates (72JA2460).

In addition to the reagents mentioned above, iodine monochloride, iodine in nitric acid in the presence of silver nitrate, and iodine in iodic acid have been used [66AHC(6)391]. In polyiodination experiments *N*-iodopyrazoles have been frequently encountered. These are quite stable compounds (70CB1949), but the *N*-iodo function can be reduced by sulfur dioxide or HI treatment, or it can rearrange to give a *C*-iodo product. In this way 1-iodo-3,5-dimethylpyrazole formed the 4-iodo isomer by an electrophilic process [55LA(593)200; 76MI1]. 4-Methylpyrazole reacted with iodine in carbon tetrachloride to form a deep red-colored oil, believed to be **65** (76MI1). Multiple iodination of pyrazoles is possible using iodine or iodine monochloride in aqueous alkali, or in a two-phase system in the presence of an anionic tenside. Under the latter conditions 3-methylpyrazole gave an 85–90% yield of 3,4-diiodo-5-methylpyrazole in contrast to a 50% yield in the absence of tenside (89EGP274419). Micelles of Rodapon N50 or cetyltrimethylammonium Rodaponate in aqueous or alkaline medium were found to assist the iodination of pyrazole and its 3-methyl and 3-carboxy derivatives (89JPR799).

Interhalogen compounds may lead to product mixtures. The products formed when 1-aminopyrazoles were treated with iodine monobromide were a 17 : 73 ratio of 4- and 5-bromo derivatives; with iodine monochloride there was an 81% yield of the 4-iodo product with only traces of the chloro analogue [86JCS(P1)1249].

Among the more recent major studies of pyrazole iodination have been the reactions of 3-, 4-, or 5-substituted 1-methylpyrazoles with iodine in iodic acid. Particular attention was paid to substrates bearing electron-withdrawing substituents. The 4-iodo derivatives were isolated in 78–91% yields on monoiodination of methyl 1-methylpyrazole-3- or 5-carboxylates. Two equivalents of iodine gave around 85% of the 4,5- and 3,4-diiodo products, and even when both 3- and 5-positions were substituted by ethoxycarbonyl groups 75% 4-iodination still took place. Strong electron withdrawal appears unable to prevent or even seriously hinder iodination of the reactive 4-position. Similarly one molar equivalent of iodine led to the 4,5-diiodo product. A 4-substituent, though, has a marked effect on reactivity. Excess iodine converted methyl 1-methylpyrazole-4-carboxylate into a mixture containing some 4-iodinated products (Scheme 22). This observed *ipso*-iodination probably results from reaction of the hydrolyzed ester group since 1-methylpyrazole-4-carboxylic acid gave essentially the same products (except that analogous to **66**). In contrast, the 1-methyl-3- and 5-carboxylic acids reacted like the corresponding esters. With one molar equivalent of iodine, 4-formyl-1,3-dimethylpyrazole formed the 4-iodo derivative mainly, as did the 1,5-



SCHEME 22

dimethyl isomer. Two equivalents of iodine in iodic acid caused diiodination in 70–80% yield (80BAU778). The same reagent also *ipso*-iodinated 1,5-dimethylpyrazole-4-carboxamide, but the 3-amide was conventionally iodinated at C-4. Only when the 3- and 4-positions were blocked by groups resistant to displacement did 5-iodination occur (85MI2).

*Ips*o-iodination was also observed when iodine or iodine monochloride reacted with silylated pyrazoles. Specificity was found to be high for the 4-position, but iodine was apparently less selective than the interhalogen reagent since it could displace a 3- (but not a 5-) trimethylsilyl group (84JOC4687) (Scheme 22).

Reaction with one equivalent of iodine transformed 1-hydroxypyrazoles and their 2-oxides into 4-iodo products (80JOC76). The iodative oxidation of pyrazolones has been discussed (87CC711). A 95% yield of 5-iodo-1-(*p*-tolylsulfonyl)pyrazole was made from the 5-lithium derivative (92PC1).

In pyrazolium salts chlorine can be displaced quite readily by iodide (77BSF171), and Sandmeyer reactions have found application in the preparation of iodopyrazoles from their diazonium salts [90AHC(48)65; 90JAP(K)02/304064].

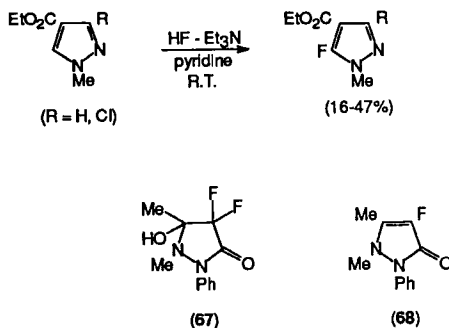
d. *Fluorination*. There are few references to direct fluorination of pyrazoles, and most synthetic procedures involve sequences from diazo-

nium salts or ring synthesis. Fluoropyrazoles appear to be quite stable compounds. Selective electrofluorination of ethyl 1-methylpyrazole-4-carboxylate and its 3-chloro derivative was achieved using the poly-(hydrogen fluoride)–triethylamine complex under electrolytic anodic oxidation conditions [88JFC(39)435] (Scheme 23). The fluorine attached at the 5-position mainly, with some lateral fluorination of the *N*-methyl group (5-F: 1-CH₂F of 83:17) [89JAP(K)01/29364]. Fluorine in acetic acid at 20°C gave 75% of the 4-fluoro derivative of methyl pyrazole-3-carboxylate (83JOU403), although other fluorinating agents were ineffective (77BSF-171). Barton's method (using fluoroxytrifluoromethane) converted antipyrine mainly into the 4,4-difluoro species (**67**) (74MI1). Selective fluorination of antipyrine with acetyl hypofluorite gave an 85% yield of 4-fluoroantipyrine (**68**) in a reaction that is believed to follow an addition–elimination process at the 3,4-bond (86BSF861).

The most universally applied approaches to fluoropyrazoles have used diazonium fluoroborates. Although the Balz–Schiemann method gave rather poor yields of 3(5)-fluoropyrazoles (66CB3350; 77BSF171), the Kirk–Cohen method, which irradiates the salts, was much more successful [73JA4619; 75MI1; 78JHC1447; 79TL3179], having been used to prepare 4-fluoro-3,5-di- and -1,3,5-tri-methylpyrazoles (75MI1). Fluoride does not appear to be capable of displacing chlorine from pyrazolium salts (77BSF171).

2. Imidazoles (1,3-Diazoles)

Electrophilic substitution in imidazole occurs preferentially in the 4(5)-positions (4- and 5-positions in *N*-unsubstituted imidazoles are tautomerically equivalent) with the 2-position being much less reactive [70AHC(12)103; 80AHC(27)241; 84MI7; 90AHC(47)165]. It is usually dif-



SCHEME 23

ficult to prevent polyhalogenation at all vacant ring positions. In 1-substituted imidazoles the 5-position is slightly more reactive than C-4. Partial rate factors have been determined and discussed in detail elsewhere [74AJC2331; 78JCS(P2)865; 80AHC(27)241; 90AHC(47)165]. Although a 1-methyl group is only mildly activating, a 2-methyl substituent increases the bromination rate of imidazole 180-fold (74AJC2331).

While imidazoles form *N*-halogeno derivatives (especially iodo) these are not particularly stable and rearrange to form *C*-halogeno isomers. There is evidence that such *N*-halogeno derivatives are intermediates in some *C*-halogenation processes. In cases where $N \rightarrow C$ rearrangement is not possible (e.g., when bromine in dry ether reacts with the sodium salt of 2,4,5-triphenylimidazole), 1,1'-biimidazoles are formed, suggesting that a radical process is in operation [70AHC(12)103; 84MI7]. Charge transfer complexes between imidazoles and halogens are known [77JOU1872; 85JCS(P2)531; 88JA2586].

a. *Chlorination.* Imidazoles react with sodium hypochlorite or NCS usually to give 4,5-dichloroimidazoles and smaller amounts of 2,4,5-trichlorinated product (74MI2). Thus, imidazole-2-carboxylic acid gave a 52% yield of the 4,5-dichloro product [67JHC399; 77JMC1189; 82AHC-(32)234; 92PIA21], and a range of 2-alkylimidazoles behaved similarly (67JHC399). Control is extremely difficult when chlorine is used; indeed imidazole has been converted into 2,2,4,5-tetrachloro-2*H*-imidazole using this reagent (76CB1625). Nor is sulfonyl chloride useful for producing simple chloroimidazoles. *N*-Chloroimides such as NCS or *N*-chlorophthalimide in refluxing chloroform converted imidazole into a mixture of 4-chloroimidazole (13%) and 4,5-dichloroimidazole (25%). Similar behavior was exhibited by 2-methylimidazole, whereas the 2,4-dimethyl substrate gave a 60% yield of its 5-chloro derivative (76MI1). It is possible that initial reaction with the chloroimides is radical, and electrophilic chlorination only takes over once the process has been initiated. Careful treatment of 1-protected 2,2'-bi-1*H*-imidazoles with NCS introduced a single chlorine into the 4-positions, giving a mixture of 4-chloro (36%) and 4,4'-dichloro (26%) derivatives (87JHC689).

Reactions of a number of 1-phenylimidazole-2-carboxamides with chlorine in acetic acid, NCS, or hypochlorite failed to introduce chlorine into the 4- or 5-positions (80JHC409). Chlorination of a variety of 2,4-disubstituted imidazoles, however, was quite facile. Thus, 2,4-diester [83JCS(P1)809] and 2-amino-4-aryl compounds [80IJC(B)526] were readily 5-chlorinated, and even when both the 4- and the 5-positions were blocked, as in 5-aminoimidazole-4-carboxamide, 2-chlorination with iodine monochloride was possible (89MI5). When all three carbons were substituted (e.g., in 2,4,5-triphenyl-, 2-chloro-4,5-diphenyl-, and 2-trichloromethyl-

4,5-diphenyl-imidazoles) the products included 4-chloro-4*H*-imidazoles [76CB1638; 76GEP2441820]. Chlorination of 1-methyl-2,4,5-trichloroimidazole at 100–200°C induced ring-opening (84MI7).

Clean monochlorination at all possible ring positions can be achieved by use of the appropriate lithiated imidazoles. 1-Benzyl-2-lithioimidazole reacted with hexachloroethane to give 1-benzyl-2-chloroimidazole (86-JHC1257; 90JHC673), and quenching the 2-lithio derivative of 1-tritylimidazole with chlorine, followed by removal of the protecting group gave 2-chloroimidazole in 39% yield (78JOC4381) (see also B,2,b and B,2,c).

Nucleophilic processes that introduce chlorine include displacement of diazonium functions, but these are not well known in the imidazoles because of the instability of many simple aminoimidazoles. In one instance the lack of success may have been a function of the high stability of 5-ethoxycarbonyl-4-diazoimidazole. Other 1-substituted 4-diazonium salts showed expected reactivity, and 1-substituted 5-aminoimidazoles formed sufficiently reactive diazonium salts to give good yields of the 5-chloro compounds [80JCS(P1)2310]. Most of the thrust in this reaction strategy has focused on the preparation of fluoroimidazoles (see B,2,d).

Imidazolones, particularly 2-imidazolones, give the corresponding chloro derivatives when heated with phosphoryl chloride, especially with copper(I) chloride as catalyst [76MI1; 80AJC1545; 90EGP3828208]. The same reagents convert imidazole *N*-oxides into 2-chloroimidazoles [75JCS(P1)275].

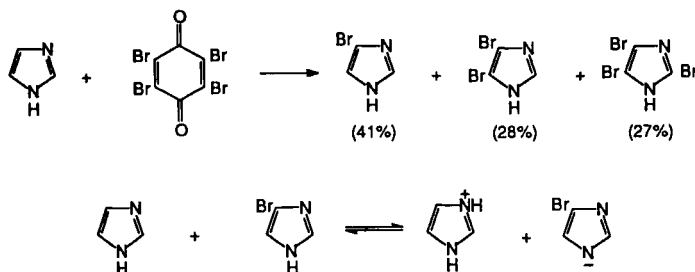
Reactions in which another halogen is displaced by chlorine are quite common. Boiling hydrochloric acid, or lithium chloride in dimethylformamide at 100°C, transformed 2,4,5-tribromoimidazole and 2-bromo-4,5-dichloroimidazole into the 2,4,5-trichloro derivative (69USP3435050). Similar reaction of 2,5-dibromoimidazole-4-carboxylic acid at 150°C gave a mixture. Such nucleophilic substitutions work best when there is an electron-withdrawing group present. 4-Chloro-5-nitroimidazole was readily made from the bromo analogue [92JCS(P1)211]. Halodenitrations can occur with some ease when there is more than one nitro group in the imidazole ring. The displacement order was reported to be 2 > 5 > 4 [77CHE529, 77CHE1332; 80AHC(27)241]. The isolation of 2-chloro-4-nitroimidazole from the reaction of 2,4-dinitroimidazole with 2-chloroethanol, 3-chloropropanol, or 3-chloropropionitrile is in agreement with this order [84IJC(B)363], although the product had earlier been designated as 4-chloro-5-nitroimidazole (79JHC1499). Phosphoryl chloride in pyridine or dimethylformamide converted 2,4,5-trinitroimidazole into 2,5-dichloro-4-nitroimidazole [80AHC(27)241].

Attempted reduction of 1-methyl-4-nitroimidazole with tin(II) chloride and hydrochloric acid produced some 4-chlorinated product as a result of

nucleophilic attack by chloride (87JOC3493), whereas chloride (from sodium chloride) displaced the nitro group from 4-nitroimidazole complexed with cobalt(III) (91IC4374). Reaction of 5-chloro-1-methylimidazole (prepared in 95% yield from dimethyloxamide) with phosphorus chlorides gave 4,5-di- and then 2,4,5-tri-chloro-1-methylimidazole (89IJC391).

b. *Bromination.* Tribrominated imidazole is formed with great facility using reagents such as bromine in acetic acid, often with added sodium acetate (73ACS2179); bromine water (91JA2657); bromine in chloroform (81JOC1781; 89CHE1168), in aqueous sodium hydroxide (82CHE539), and in dimethylformamide with potassium bicarbonate (92JOC3240); and NBS in carbon tetrachloride or dimethylformamide [80IJC(B)526; 87JHC689; 88S767; 89JCS(P1)95]. Even imidazoles with electron-withdrawing groups can still be brominated successfully at vacant sites, e.g., 2,4-diethoxycarbonylimidazole [83JCS(P1)809], 2-ethoxycarbonylimidazole (80JHC409), 4,5-dicyanoimidazole (91JA6178), 2-nitroimidazole [89JCS(P1)95], 2-methyl-4-nitroimidazole (86JHC913), 1-benzyl-2-methyl-4-nitroimidazole (81MI2), 4-bromo-5-methoxycarbonyl-1-methylimidazole (88S767), and 1-ethoxymethyl-5-methylthio-2-phenylthioimidazole (81CC1095). Bromine in aqueous alkali not only brominated the 2-position, but also replaced the carboxyl function in 4-nitroimidazole-5-carboxylic acid in a process similar to the Borodin-Hunsdiecker reaction (82CHE539). Imidazole brominations can be accompanied by some ring degradation, which increases as the pH decreases.

The positional reactivities for bromination in imidazole have been quoted at about 0.45 for the 4(5)-positions and 0.2 for C-2. In 1-methylimidazole the corresponding figures are 2.3 (C-5), 1.7 (C-4), and 0.8 (C-2) [74AJC2331; 78JCS(P2)865]. The ease of 2-bromination of imidazoles is in stark contrast to the nitration behavior and could be a consequence of addition-elimination at the 2,3-bond rather than conventional aromatic substitution [80AHC(27)241]. Imidazole's propensity for polybromination makes the synthesis of monobromo derivatives difficult and frequently tedious. Reduction with sulfite or triphenylphosphine converted the tri-bromo derivative into the 4-mono- or 4,5-di-bromo species (91CB1639). Even very mild bromination at low temperatures does not give monobromo products. One molar proportion of 2,4,4,6-tetrabromocyclohexa-2,5-dienone gave a mixture of mono-, di-, and tri-bromoimidazoles (Scheme 24). The polybrominated compounds are formed as a consequence of an equilibrium set up between imidazole and 4-bromoimidazole, producing a conjugate base species able to be further brominated (Scheme 24). Such an explanation could account for the comparative resistance of 1-methylimidazole to the reagent. With 2 mol of brominating agent the 1-methyl



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substrate gave 5-bromo-1-methylimidazole (60%); 2 mol gave the 4,5-dibromo derivative in 65% yield with only traces of other products [72JCS(P1)2567], but the 2,4,5-tribromo compound can be prepared in good yield (88S767).

Controlled treatment of imidazole with NBS in dimethylformamide gave 4-bromoimidazole (41%), 4,5-dibromoimidazole (6%), and 2,4,5-tribromoimidazole (3%) [89JCS(P1)95]. 1-Methylimidazole gave mainly its 5-bromo derivative under similar conditions (81MI3). This preference for 5-substitution is emphasized by the observation that 1,5-dimethylimidazole is brominated less easily than its 1,4-isomer [72JCS(P1)2567]. When N-protected 2,2'-biimidazole was treated with NBS, a mixture of 4-bromo (43%) and 5-bromo (24%) products were obtained, along with around 17% of products brominated in both rings. The majority attack at C-4 was probably a result of steric control by the N-trimethylsilylethoxy protecting groups (87JHC689). Bromine in chloroform at -10°C converted 4-methylimidazole into a 2:1 mixture of 2,5-dibromo-4-methyl- and 5-bromo-4-methylimidazoles (68JA1307).

Phenyl groups in the 4- or 4,5-positions are not able to prevent bromination of the vacant carbon sites (76MI1). In 1-phenylimidazole the heteroring acts as a weak resonance electron-donor ($\sigma_{\text{Ro}} = -0.15$) and quite a strong inductive electron-acceptor ($\sigma_1 = 0.51$). Any bromination of the substituent, then, should go mainly *para*, especially when the azole is protonated [81JCR(S)364]. Even 2-nitroimidazole proved difficult to monobrominate; NBS treatment gave the 4,5-dibromo derivative which was unable to be selectively debrominated. 1-Methyl-2-nitroimidazole (69), though, gave the 4-bromo product (the nitro group destabilizes the transition state for 5-bromination more than that for 4-bromination [89JCS(P1)95] (Scheme 25). High yields (61-94%) of 1,2-dialkyl-5-bromo-4-nitroimidazoles were obtained in bromination of the 4-nitro precursors with bromine in dimethylformamide containing potassium bicarbonate (92JOC3240). Treatment of 4-nitroimidazoles, substituted in the 1- and 5-



SCHEME 25

positions by cycloalkylthio groups, with bromine in acetic acid gave 36-39% yields of the 2-bromo products (85AJC1873).

Considerable confusion has existed in the literature since the publication of incorrect structural assignments of 4-iodo- and 4,5-diiodo-imidazoles over 60 years ago (28JPR33). Pauly believed these compounds to be the 2- and 2,4-isomers, respectively, and only recently were the assignments finally corrected (81JOC1781; 87AJC1399). Those involved in the field should therefore be wary of many reported structures of bromo- and iodo-imidazoles. For example, 4- (not 2-) iodoimidazole reacted with bromine in chloroform to give 4-bromo-5-iodoimidazole (not the 4-bromo-2-iodo isomer), and there are many other examples (81JOC1781).

A study aimed at comparing the reactivities of furan and 1-methylimidazole brominated 1-methyl-2-(2'-furyl)imidazole under a variety of reaction conditions. In acidic media ($\text{Br}_2/\text{AlCl}_3$ or $\text{Br}_2/\text{H}_2\text{SO}_4$) most substitution occurred in the furan ring (both α - and β -positions); the imidazole ring is protonated under these conditions. In neutral medium ($\text{Br}_2/\text{CHCl}_3$) both rings were brominated (89CHE1168).

Kinetic studies have shown that imidazole is brominated by a rate-determining bimolecular process between the imidazole neutral molecule and bromine, giving a conventional Wheland intermediate. Initial substitution is at the 4(5)-position. The relative rates of successive bromine introductions depend on the pH, suggesting that it may be feasible to design reaction conditions that give optimum yields of partially brominated imidazoles, although these hopes not have been proved to be synthetically viable. The second, much more rapid, bromination may be a function of the lower pK_a of 4-bromoimidazole, which allows rapid formation of the conjugate base. The limited effect of N-methylation (only 4-fold across the 1,2- or 1,5-bonds) contrasts with the larger activating effect of a 2-methyl group (180-fold between C-2 and C-5). These differences emphasize the importance of bond-fixation effects in such heterocycles [74AJC2331; 78JCS(P2)865].

More recent studies of the kinetics of bromination of imidazoles coordinated to cobalt(III) have implied that, in aqueous solution, proton-abstraction from a Wheland intermediate is rate-determining at acidic pH values. In more nearly neutral conditions bromine addition becomes rate-

limiting. Rate constants are sufficiently large to suggest preassociation of the substrate with bromine before proton abstraction (91JA2657). Attempts to prepare the monobromo complexes with bromine in water or dimethyl sulfoxide were unsuccessful; mixtures of the 4,5-di- and 2,4,5-tri-bromo complexes only were obtained because of the rapid bromination of the 4-bromo species. The similar cobalt(III) complex of 1-methylimidazole was able to be 5-monobrominated since reaction was much slower (91JA2656). Site selectivity for the neutral and anionic ligand was found to be $4 > 5 \gg 2$ (86AJC1465; 91JA2656), and it seems that when the pH is greater than 5 the conjugate base of the imidazole complex is involved (this cannot form with the 1-methylimidazole complex) [91AJC981, 91JCS(D)3031]. Under neutral or alkaline conditions, aqueous bromination of imidazole complexes was accompanied by some oxidation (91IC1635).

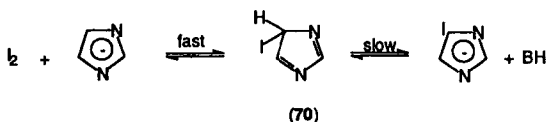
The use of lithiation techniques to introduce a wide range of substituents with specific regiochemistry has greatly improved the accessibility of some bromoimidazoles [85H(23)417]. Lithiation can be directed into the 2- and 5-positions, and lithium-halogen exchange at C-4 is well known. Bromine, NBS, a variety of alkyl bromides, and *N*-bromodiethylamine have all been used as quenching agents to produce bromoimidazoles [69CHE418; 75CC334; 81MI3; 83JCS(P1)271]. The reactions, however, are not always successful. It was not possible to prepare monobromo compounds from the 5-lithio derivative of 1-methyl-2-nitroimidazole [89JCS(P1)95], and transmetalations may complicate matters [69RTC1246; 71RTC594; 79JCS(P1)1132; 88BSB573], as well as serving to extend the applicability of such procedures [85H(23)417]. Iddon and co-workers metalated 1,2-dimethylimidazole with ethereal butyl-lithium at -10°C before quenching with NBS to give a 35% yield of 4,5-dibromo-1,2-dimethylimidazole. There were also polymeric products resulting from laterally brominated species reacting with the nucleophilic ring nitrogen [83JCS(P1)271]. These workers were unable to confirm the isolation of 5-bromo-1,2-dimethylimidazole reported earlier (69CHE418). 1-Methylimidazole, which reacted in turn with butyl-lithium and NBS to give 5-bromo-1-methylimidazole, gave the 2-bromo-1-methyl isomer when quenched with bromine (81MI3). Successive reductions that make use of the reaction of 2,4,5-tribromoimidazole with butyl-lithium followed by treatment of the lithium derivatives with water provide an alternative approach to the synthesis of mono- and dibromoimidazoles. Treatment of 1-substituted 2,4,5-tribromoimidazoles in this way gave mixtures of 1-substituted 4,5- and 2,4-dibromo isomers [87JCS(P1)1445, 87JCS(P1)1453]. The use of more than two molar equivalents of lithiating agents can give 2,5-dilithio derivatives of *N*-protected imidazoles, increasing the versatility of the process (81MI3). Similarly *N*-unsubstituted imidazoles can be *N,C*-dilithiated. Differential reactivities

of bromine atoms at the 4- and 5-positions of imidazoles (and thiazoles, see 9b) have been attributed to "adjacent lone-pair" effects, which destabilize developing negative charge at the 4-position for bromine-lithium exchange. This provides an added useful property for specific orientation of halogenation via lithium compounds. Indeed, bromine atoms in 1-protected 2,4,5-tribromoimidazoles are replaced stepwise in the order $2 > 5 > 4$. Thus, the availability of products with more than one type of halogen substituent is enhanced [85H(23)417; 87JCS(P1)1445, 87JCS(P1)1453; 92JCS(P1)215]. Further coverage of this general topic follows later (B,2,c).

Nucleophilic substitutions that produce bromoimidazoles usually require an electron-withdrawing group to ensure their success. Displacement of iodine by bromide at C-5 is easier than at C-4. With hydrobromic acid, 5-iodo-4-nitroimidazole gave the 5-bromo analogue (81JOC1781). When there is more than one nitro group in the ring, halodenitration becomes possible. Hot 2-bromoethanol or hydrobromic acid converted 2,4-dinitroimidazole into the 2-bromo-4-nitro compound [84IJC(B)363]. The latter reagent also converted 1-methyl-4,5-dinitroimidazole into 5-bromo-1-methyl-4-nitroimidazole [77CHE529, 77CHE1332; 80AHC(27)241].

c. Iodination. As mentioned above, many references to iodoimidazoles must be read with caution because of the historical error of structure assignment of 4,5-diiodoimidazole, which had been designated as the 2,4-isomer. Imidazole can be triiodinated with considerable ease using iodine in aqueous alkali. Some 4,5-diiodoimidazole is the minor product. Even imidazole-4-carboxylic acid was 2,5-diiodinated under these conditions, whereas 4-methylimidazole gave a mixture of 4-iodo-5-methyl and 2,4-diiodo-5-methyl products. In contrast, 1-substituted imidazoles are reluctant to react with molecular iodine, and although aspects of the reaction mechanism remain uncertain, it appears that the rate-determining step is nucleophilic attack by a base on the hydrogen being abstracted from the sigma-complex (**70**) (Scheme 26). The acceleration follows the nucleophilicity of the base rather than its basicity, and the involvement of imidazole anions even at pH 7 accounts for the failure of 1-methylimidazole to react. Rate-limiting proton abstraction from the 4(5)-position was demonstrated by an appreciable isotope effect ($k_H/k_D = 4.5$) with 4,5-di- and 2,4,5-tri-, but not 2-deuterioimidazoles [69JCS(C)1328; 70T2297].

A study of the kinetics of iodination of 2- and 4-methylimidazoles also demonstrated base-catalyzed iodination, but whereas imidazole and its 2-methyl derivative were subject also to uncatalyzed iodination, 4-methylimidazole was not. Relative rates for base-catalyzed iodination (imidazole: 2-methylimidazole: 4-methylimidazole) were 1 : 34 : 667. For uncatalyzed



SCHEME 26

iodination the corresponding rate ratio was 1 : 28 : 0. Further conclusions drawn from this study (80JOC3108) will need to be reassessed in the light of the more recent correction to the identity of "2,4-diiodoimidazole" (81JOC1781). The iodination of nickel(II)-coordinated imidazole was found to be much slower than that for imidazole; the opposite is true for pyrazoles, which form much weaker complexes (66JA5537; 72JA2460).

Involvement of *N*-iodo species in electrophilic C-iodinations needs to be considered since a number of imidazoles are known to form such compounds in basic medium. Charge-transfer complexes, too, are quite well known. They seem to be of the "n"-type through the unshared electron pair at N-3. Equilibrium constants for their formation are known to increase regularly in line with electron-donating powers of substituents (or vice versa). Some K_{CT} values at 20°C (L M⁻¹ are imidazole (200), 1-methylimidazole (333), 1,2-dimethylimidazole (1165), 4-phenylimidazole (152), and 4,5-diphenylimidazole (141) (83BSB923). The charge-transfer complexes formed between iodine and imidazole-2-thiones appear to involve the sulfur atoms (88JA2586).

Overnight stirring with iodine and potassium iodide in aqueous sodium hydroxide gave a 75% yield of 2,4,5-triiodoimidazole from the parent [83JCS(P1)735], but minor changes to the reaction conditions changed the major product to 4,5-diiodoimidazole [91JOC4296; 91JOC5739; 92JCS(P1)211]. The 4-iodo product then becomes available using reductive procedures; e.g., the use of sodium sulfite gave a 67% yield [81JOC1781; 83JCS(P1)735; 91JOC5739]. Although 1-methylimidazole is more difficult to iodinate (it cannot form the anion) it has been converted by iodine and iodic acid in acetic or sulfuric acids or in carbon tetrachloride at elevated temperatures into mixtures containing 4- and 5-mono-, 4,5-di-, and 2,4,5-triiodo derivatives in varying amounts (79BAU1446; 81MI3). A typical product mixture contained 4- (and 5)-iodo-1-methylimidazole (14%), 4,5-diiodo-1-methylimidazole (33%), and 2,4,5-triiodo-1-methylimidazole (2%). The diiodo product is usually the major one, and it can be made in up to 95% yield (81MI3). An *N*-protected 2,2'-bi-1*H*-imidazole could not be iodinated by NIS (87JHC689). Treatment of 5-chloro-1-methylimidazole with iodine in iodic acid gave 4-iodo (28%) and 2,4-diiodo (13%) products (78JOC4381).

As with the bromo and chloro analogues, monoiodoimidazoles are now readily available as a result of lithiation processes. The 2- and 5-iodo compounds have become especially accessible in this way. Lithiation of 1-benzenesulfonylimidazole, quenching with iodine, and deprotonation gave 2-iodoimidazole in 5% yield (77JHC517), which rose to 40% when 1-tritylimidazole was used (78JOC4381). There have been a number of other reports of similar syntheses of 2-iodoimidazoles (73CHE1025; 77JHC517; 79BAU1446; 90JHC673) and 2,4-diiodoimidazoles [79-BAU1446; 85H(23)417]. A 16% yield of 5-iodo-1,2-dimethylimidazole was formed when the appropriate lithium derivative was quenched with iodine [83JCS(P1)271].

When heated with potassium iodide in dimethylformamide, 1-alkyl-4-chloro- (or bromo)-5-nitroimidazoles were converted into the 4-iodo analogues (79JGU1251). One would expect the 5-chloro-4-nitro isomers to be even more susceptible to this replacement (87AJC1399).

d. *Fluorination.* Earliest attempts to prepare fluoroimidazoles focused on the heating or photolysis of diazonium fluoroborates, especially for 2-fluoroimidazoles (71JA3060; 73JA2695; 73JA4619; 77BSF171; 78JOC4381; 84JOC1951). The Balz-Schiemann method gave the best yields (73JA4619), probably because of the unusual thermal stabilities of imidazole diazonium salts. 2,4-Difluoroimidazole (84JOC1951), and a number of 4-fluoro- and 4-fluoro-5-methyl compounds were also prepared by this general sequence (73JOC3647; 75MI1). Yields were frequently only of the order of 30–40% (78JOC4381), but working in fluoroboric acid medium can improve matters (75MI1). A limiting factor is the difficulty of preparing some aminoimidazoles. The 4- and 5-fluoro derivatives are more stable than the 2-isomers.

Other nucleophilic fluorination processes in heterocycles have included displacement of bromine with potassium, cesium, or silver fluorides, but these failed to work for 4-bromo-5-nitroimidazole and ethyl 4-bromoimidazole-5-carboxylate (73JA4619). Xenon hexafluoride was reported to convert 2,4,5-tribromoimidazole into the trifluoro analogue (79JGU1251).

Electrophilic methods do not include direct fluorination, but metallic derivatives can provide anions capable of fluorination. Both 2- and 4-fluoroimidazoles were made when fluorine sources reacted with lithioimidazoles, as when 2-lithio-1-methylimidazole was treated with perchloryl fluoride to give the 2-fluoro derivative in greater than 50% yield (77BSF171; 81MI3). Organotin groups, too, have been replaced by the action of fluorine or cesium fluoroxysulfate (86BSF930). Access to 4- and 5-fluoroimidazoles from the trimethylstannyl derivatives is much more convenient

than earlier lengthy procedures (78JHC1227). Mercury derivatives react in much the same way, but they are more difficult to prepare and purify (86BSF930).

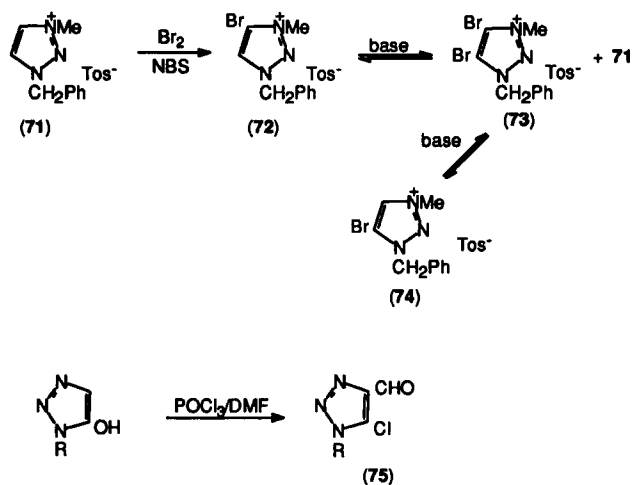
3. 1,2,3-Triazoles

In principle, halogenation could take place at an annular nitrogen or at a carbon, but the heterorings are quite deactivated to electrophilic attack compared with the diazoles (84MI9). Certainly N-halogenated compounds have been isolated, especially as reaction intermediates (70ZC220). The presence of three annular nitrogens increases the likelihood of nucleophilic halogenations.

1,2,3-Triazoles with no N-substituent can be brominated quite readily in the 4- and 5-positions [69ACS(B)2733; 74AHC(16)33; 80HC(39)199; 84MI9]. The parent compound gave the 4,5-dibromo derivative in 90% yield when treated with bromine, and in the presence of excess hypobromite it formed 1,4,5-tribromo-1,2,3-triazole (59ACS888). 2-Methyl-1,2,3-triazole proved to be less reactive, but still gave the 4,5-dibromo derivative with bromine in the presence of iron filings [55LA(593)207]. Even 1,2,3-triazole-4,5-dicarboxylic acid gave the 4,5-dibromo derivative by bromodecarboxylation (59ACS888). 1-Substituted-1,2,3-triazoles, however, do not form the 4,5-dibromo compounds, which have to be made either by alkylation of 4,5-dibromo-1,2,3-triazoles or from lithiated compounds [69ACS(B)2733; 71ACS(B)249]. 2-Phenyl-1,2,3-triazole was brominated by bromine-sulfuric acid-silver sulfate specifically in the *para*-position of the substituent, the acidic conditions presumably generating the unreactive triazolium modification (63CJC2380). The 1-phenyl isomer was also *p*-halogenated [87ACS(B)724].

In view of this apparent resistance of triazolium to bromination with electrophilic bromine, it is interesting to discover that 1,3-dimethyl-1,2,3-triazolium tosylate (**71**) was 4-brominated by bromine and NBS. When the 4-bromo salt (**72**) is dissolved in base, an equilibrium is established containing unbrominated salt (**71**) and 4,5-dibromo salt (**73**). Presumably, base converts **72** into an ylid, which is further brominated by **72**. A similar product mixture was obtained from the isomeric 5-bromo tosylate (**74**) [69ACS(B)2733; 71ACS(B)249] (Scheme 27).

The oxide group mildly activates 3-substituted 1,2,3-triazole 1-oxides to electrophilic attack. Thus, 3-benzyl-1,2,3-triazole 1-oxide reacted much more rapidly than the unoxidized compound in giving the 5-bromo derivative, and there have been a number of other examples of 5-bromination and 5-chlorination of triazole oxides, including that of the 3-phenyl-1-oxide, which was not *para*-halogenated [87ACS(B)724].



SCHEME 27

Strongly activating substituents assist halogenation at the adjacent ring site. When 4-hydroxy-2-phenyl-1,2,3-triazole was treated with bromine, the product was mainly 5-bromo, but a small amount of 2-*p*-bromophenyl product was also observed. The corresponding 1-oxide gave only resins when similarly treated (88JOU599).

When heated, the relatively stable 1-iodo-1,2,3-triazoles rearrange to the 4-isomers (70ZC220).

Under Vilsmeier–Haack conditions 1-substituted 5-hydroxy-1,2,3-triazoles were converted into the chloroaldehydes (75) in 60–90% yields (84JHC1603) (Scheme 27). Phosphorus pentachloride in toluene gave the 5-chloro derivatives from some ethyl 5-hydroxy-1,2,3-triazole-4-carboxylates, but the reaction conditions also proved conducive to Dimroth rearrangement [82JCR(S)292]. When heated with thionyl or acetyl chlorides, 2-phenyl-1,2,3-triazole 1-oxide gave the 5-chloro derivative (88JOU599).

Other nucleophilic processes have included displacements of diazonium salts (66JMC733), and the reactions of potassium fluoride with 1-methoxy-2-phenyl-1,2,3-triazolium salts and their 4-methyl derivatives to give the 5-fluoro products (77BSF171).

4. 1,2,4-Triazoles

As with the 1,2,3-isomers, 1,2,4-triazoles can also be halogenated on N-1 to form reasonably stable products that are then subject to thermal

N $\rightarrow$ C rearrangement. The ring carbons have reduced tendency to be attacked by electrophilic reagents with a corresponding greater reactivity toward nucleophiles (84MI10).

a. *Chlorination.* When 1,2,4-triazole was chlorinated in aqueous bicarbonate solution, the N-chloro derivative was formed. With excess chlorine, 1,3-di- and 1,3,5-tri-chloro derivatives were obtained. Reactivity is quite low at the 3- and 5-positions and becomes even lower in acidic media. When 1-chloro derivatives are heated, they rearrange to give C-substituted products. Prepared in this way have been 3-chloro-, 5-chloro-3-phenyl-, and a variety of 3-alkyl-5-chloro-1,2,4-triazoles (65AG429; 67CB2250, 67ZC184; 69CHE844; 69FRP1536979; 72JPR923; 84MI10). The 1,3-dichloro species have been used to chlorinate other triazoles (69ZC325). Chlorine in aqueous solution failed to chlorinate 1- and 4-methyl; 1,3-, 1,5-, and 4,5-dimethyl-; 1- and 4-phenyl-; 3-methyl-1-phenyl-; 3-methyl-4-phenyl-; and 5-methyl-1-phenyl-1,2,4-triazoles. When NCS was used, however, the 3,4-dimethyl derivative was 5-chlorinated in 25% yield, although the other substrates were unaffected (75BSF647).

Nucleophilic processes that generate chlorotriazoles include reactions of phosphoryl chloride with triazolones. Yields are seldom high, e.g., 3-chloro-1-methyltriazole (20%) and 3-chloro-4-methyl-1,2,4-triazole (25%) (75BSF647). Chloride readily replaced the nitro function in 1-glucosyl-5-nitro-1,2,4-triazole (83JHC1307). Interhalogen exchanges of halogenotriazolones require the presence of mineral acid to increase the cationic nature of the ring, and such substitutions occur most readily at the 5-position (62MI1; 67CB2250).

b. *Bromination.* Bromine enters the 1,2,4-triazole ring more easily than does chlorine, and again N-bromo products are possible, especially when the medium is basic [81HC(37)289]. The 1-bromo derivatives of 3,5-disubstituted triazoles are quite stable, but in other instances the C-brominated species are formed with some facility (67CB2250). 1,2,4-Triazole-3-carboxylic acid was brominated in the 1-position (69ZC300). 1,3,5-Tribromo-1,2,4-triazole has been used to brominate other triazoles (69ZC325). When heated, or allowed to stand for some time, N-bromotriazoles give the C-isomers, which may be the products actually isolated in many instances of triazole bromination. Thus 1,2,4-triazole and some of its 3-substituted derivatives gave 3,5-di- or 5-mono-bromo products in yields of about 80% (65AG429; 67CB2250, 67ZC184). Aqueous bromination of 4-phenyl-1,2,4-triazole initially gave rise to the 2-bromo salt (60%), which decomposed to give 3,5-dibromo-4-phenyl-1,2,4-triazole. No

trace of the 3-monobromo product could be detected. Similarly the ultimate products isolated from 4-methyl-, 4,5-dimethyl-, and 3-methyl-4-phenyl-1,2,4-triazoles were the 3,5-dibromo (18%), 3-bromo (31%), and 5-bromo (63%) derivatives, respectively. Both the 1,3-dimethyl- and the 3-methyl-1-phenyl substrates gave 5-bromo products (28 and 38% yields, respectively), but the 1-methyl-, 1,5-dimethyl-, 1-phenyl-, and 5-methyl-1-phenyl-triazoles formed only hydrobromide salts or unchanged starting material in neutral brominations, and they were unchanged by basic bromination. When NBS was used, the 1-methyl-, 1-methyl-3-phenyl-, 1,3-dimethyl-, 3,4-dimethyl-, and 1-phenyl-triazoles were 5-brominated (yields were between 18 and 37%), and 3,5-dibromo products were formed with 4-methyl- and 4-phenyl-1,2,4-triazoles. These NBS brominations are believed to proceed through *N*-bromotriazolium intermediates (75BSF647).

Heating 1-phenyl- and 5-methyl-1-phenyl-1,2,4-triazol-3-ones with phosphoryl bromide gave 45% yields of the 3-bromo derivatives (75BSF647).

c. *Iodination.* An *N*-iodotriazole was formed when the parent was treated with iodine monochloride in ethanol or aqueous alkali. The product was quite stable and did not rearrange on heating, but it acted as an iodinating agent when warmed with 1,2,4-triazole (69ZC300). Iodination of sodium salts of 5-aryl-1,2,4-triazol-3-thiones was accompanied by the formation of disulfides (84CHE690).

d. *Fluorination.* Only a few examples of nucleophilic displacement by fluoride in nitro- and chloro-triazoles are known. 3-Fluoro-1,2,4-triazole was obtained in 80% yield when the corresponding nitro derivative was heated at 150°C with liquid hydrofluoric acid (73JOC4353; 77BSF171). Photochemical decomposition of the diazonium fluoroborate salt from 3-amino-1,2,4-triazole gave the same 3-fluoro derivative (75MI1).

5. Tetrazoles

Few references to the direct halogenation of tetrazoles exist. The molecules are quite resistant to electrophilic attack, and rather more likely to be subject to nucleophilic reactions. *N*-substituted tetrazoles can, however, be halogenated, and the derivatives formed are subject to halide displacement by a number of nucleophiles [47CRV1; 67HC(8)1; 77AHC(21)323; 84MI11]. 5-Chlorotetrazoles are usually made by ring-synthetic methods (67JOC3580).

Reaction of bromine with 1-phenyltetrazole gave the 5-bromo derivative [67HC(8)1]. In a recent study of direct iodination of 1-alkyltetrazoles

using iodine in the presence of the potassium permanganate–sulfuric acid oxidizing system, maximum yields of 5-iodo-1-methyltetrazoles (75%) and 5-iodo-1-ethyltetrazoles (55%) were obtained when the reaction was carried out in 80% acetic acid. 2-Alkyltetrazoles were unaffected, and 1-phenyltetrazole gave only an intractable mixture (88CHE1407).

Syntheses of 5-halogenotetrazoles from metallic derivatives have met with mixed fortunes. Lithiation of 1-methyltetrazole followed by reaction at -60°C with bromine, iodine, or cyanogen bromide gave the 5-bromo and 5-iodo compounds in 36–55% yields (71CJC2139). 1,2-Disubstituted tetrazolium tetraphenylborates were lithiated in the 5-position, but subsequent reaction with chlorine or bromine failed to trap the anion. Instead, oxidation produced a radical cation, which abstracted a hydrogen atom from the solvent [91AG(E)1162].

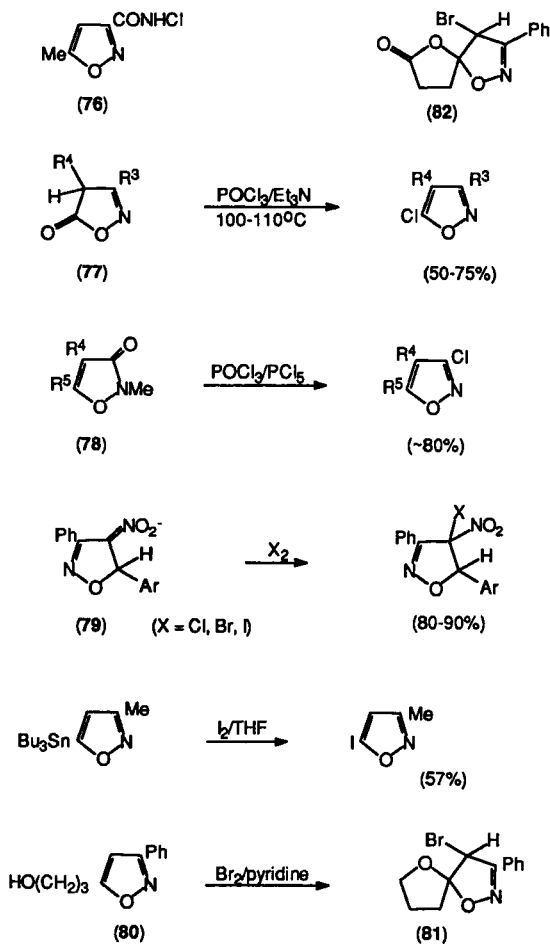
Preparation of 5-halogenated tetrazoles from the diazonium salts is well known [47CRV1; 77AHC(21)323].

6. Isoxazoles (1,2-Oxazoles)

Isoxazoles are more reactive to halogenation than pyridine, but less so than furan and pyrrole. The annular nitrogen is electron-withdrawing; the oxygen is a weak donor. As neutral molecules isoxazoles substitute with electrophiles at the 4-position rather more readily than benzene. Substituent effects can modify this behavior, with 5-substituents apparently having greater activating or deactivating effects than those in the 3-position (84MI12).

a. *Chlorination.* When an isoxazole is treated with chlorine or bromine, coordination compounds may be formed, but when these are heated or exposed to light they rearrange to give 4-halogenoisoxazoles. The 4-chloro derivatives of 3- and 5-methyl-, and 3,5-dimethyl-isoxazole were made in this way. The 4-chloro derivative of 3-amino-5-phenylisoxazole was also made using sulfonyl chloride as the halogenating agent (77JMC934). Chlorine in aqueous chloroform containing 20% hydrogen chloride converted 3-carboxamido-5-methylisoxazole into its 4-chloro derivative, but sodium hypochlorite at $5-10^{\circ}\text{C}$ reacted only at the exocyclic amide site to give **76** (82MI1) (Scheme 28). *N*-Chloroamide reagents were used to prepare the 4-chloro derivatives of a number of 3- and 5-substituted isoxazoles (89MI2).

Nucleophilic displacement of a hydroxy (or keto) function is a common procedure for making chloroisoxazoles. Reaction of 5(4*H*)-isoxazolones (**77**) with phosphoryl chloride in the presence of triethylamine gave the



SCHEME 28

5-chloro compounds (89S275), whereas 2-methyl-4-isoxazolin-3-ones (**78**) gave demethylated 3-chloroisoxazoles. Yields were improved to around 80% when mixtures of phosphoryl chloride and phosphorus pentachloride were used [84ACS(B)815] (Scheme 28).

b. *Bromination.* 4-Bromination is typical of isoxazole and many of its 3- and 5-substituted derivatives [60G356; 63AHC(2)365; 68YZ1289; 84MI12; 89MI2; 90JHC337, 90TL5043] with NBS (89MI2; 90JHC337) and bromine in media such as sulfuric acid (71JOU1835), acetic acid

(75CHE643), nitric acid (60DOK598), carbon tetrachloride or chloroform (90TL5043), and pyridine (74BAU2566), all proving successful.

Kinetic studies on alkyl- and phenyl-isoxazoles in 85% acetic acid at 150°C have shown that isoxazoles are 100–1000 times more reactive than benzene. The relative 4-bromination rates for 5-phenyl-:3,4-diphenyl-:3-methyl-5-phenyl-:5-methyl-3-phenylisoxazoles were 1:3:30:5 (75-CHE643). Under conditions in which the ring is protonated or quaternized, and with 4-phenylisoxazole, bromination occurred almost exclusively in a phenyl *para*-position [67G1604; 71JOU1835; 76CI(M)880]. Homolytic bromination is also directed to C-4 unless the substrate is a 4-methylisoxazole when lateral bromination occurs. Methyl reactivity was found to decrease in the positional order $4 > 5 > 3$ [63AHC(2)365; 74CHE521].

1-Benzyl-5-phenyl-3-isoxazolone was readily transformed by bromine in chloroform into the 4-bromo derivative (38%). Improved yields (81–96%) followed in this and similar operations when the bromine was complexed with a base such as *N,N*-dimethylacetamide, which removes HBr (90TL5043). 5(2*H*)-Isoxazolones were 4-brominated in 81–84% yield by bromine or NBS (90JHC337), as were the anions of 4-nitroisoxazolines (**79**) (87JOU1187) (Scheme 28). Whereas the 4-acetoxymcury derivative of 5-phenylisoxazole was converted into the 4-bromo product (65%) by successive reactions with potassium bromide and bromine, the unsubstituted compound was merely oxidized to the mercury(I) salt (84MI12).

Examples of neighboring group participation in isoxazole bromination have been reported. When the isoxazolypropanol (**80**) was treated with bromine in pyridine, it gave the spiro (furan-2,5-isoxazole) (**81**) (74BAU2566). The corresponding propenoic acid gave **82** [76JCS(P1)1694], whereas a similar process accounts for the reaction of 5-phenacyl-3-phenylisoxazole (*E*)-oxime with NBS [74JCS(P1)679].

c. *Iodination*. Provided that the 4-position is vacant, iodination occurs there using iodine in nitric acid (60DOK598; 68YZ1289). *N*-Haloamides (e.g., NIS) failed to convert 3- and 5-substituted isoxazoles into their iodinated products (89MI2). The 5-tributylstannyl derivatives (prepared by ring-synthesis), however, gave the iodo derivatives when treated with iodine in tetrahydrofuran (91T5111) (Scheme 28).

7. Oxazoles (1,3-Oxazoles)

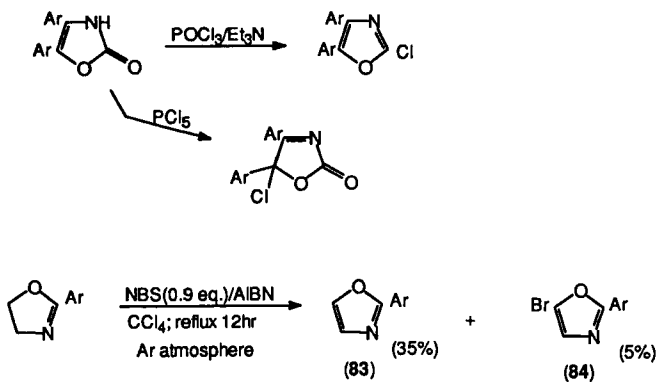
Oxazoles resemble 1-substituted imidazoles in their positional reactivity order for electrophilic substitution, $5 > 4 > 2$ [59LA(626)83, 59LA(626)92; 74AHC(17)99; 84MI29]. The compounds can be regarded as hybrids of

pyridine and furan in which the deactivating effect of the annular nitrogen decreases electrophilic reactivity with the ring. This is accentuated in acidic media, which protonate the nitrogen. The ability of some halogenating agents to also act as oxidizing agents can cause oxazole ring cleavage.

a. *Chlorination.* Among the few references to oxazole chlorination is the 4-chlorination of 4-acetyl-2-phenylisoxazolin-5-one; the product is ring-opened by acid hydrolysis (84BAU418, 84IZV161). Extended treatment of 2-methyl-4,5-diphenyloxazole with chlorine in chloroform gave a 4,5-dichloro-2-trichloromethyl addition product [59LA(626)83].

Whereas neutral oxazolones and the corresponding thiones are not particularly reactive with electrophiles, 2(3*H*)-oxazolones (and benzoxazolones) give the 2-chloro derivatives on heating with phosphoryl chloride [77AHC(21)175]. With phosphorus pentachloride, though, 5-chlorination can occur (87JOU813) (Scheme 29).

b. *Bromination.* Oxazoles have been 5-brominated by bromine in carbon tetrachloride or acetic acid, with NBS and *N*-bromoacetamide, and less effectively with *N*-bromophthalimide or dioxan dibromide [59LA(626)83, 59LA(626)92; 72AP509; 74AHC(17)99]. Yields seldom exceed 50% because the HBr released protonates the substrate, rendering it unreactive. Addition of a suitable base can counter this problem. Thus, with bromine in benzene containing some triethylamine, a 56% yield of 5-bromo-2-phenyloxazole was achieved, and with excess bromine some 4,5-dibromination was observed [84CHE713; 85CS(25)295]. When the bromination was attempted in sulfuric acid, or in the presence of aluminium chloride, most bromine entered the phenyl *meta*-position [85CS(25)295].



SCHEME 29

An earlier report, however, noted that 4,5-diphenyloxazole was not brominated in either benzene ring even in the presence of iron filings, iodine, or ferric chloride (63JCS1363). Normal 5-bromination was observed with bromine or NBS on 2-methyl-4-phenyl- and 4-methyl-2-phenyl-oxazoles; the 2-methyl-5-phenyl isomer was brominated at the 4-position. Amino groups at C-2 and C-4 activate the ring for 5-substitution, but when all ring positions are substituted the ring may be cleaved. Bromine atoms have been introduced into all ring positions by displacement of mercury derivatives (65MI1; 66CHE517; 81JHC885).

A recent approach to the synthesis of 5-bromooxazoles reacted 2-phenyl-4,5-dihydrooxazole with NBS in the presence of α,α -azobisisobutyronitrile (AIBN). The 2-aryloxazole product (**83**) resulted from a bromination-dehydrobromination process. Further bromination then gave **84**. With two equivalents of NBS the yields of **83** and **84** were 45 and 10%, respectively, whereas three equivalents raised the yield of dibromo product to 56% (89S873) (Scheme 29). When treated with bromine in neutral conditions, 2,5-diphenyloxazole formed an *N*-bromo adduct [59LA(626)83].

c. *Iodination*. Iodooxazoles have been made by reaction of iodine with mercury derivatives [65MI1; 66CHE517; 81JHC885, 81JOC1410, 81TL3163] and should be available from lithium derivatives [68T3965; 89H(29)667]. Various 4-substituted 2-aryl (or -alkyl) oxazole-5-thiols were oxidized to the disulfides by iodine (82JOU1630).

8. Isothiazoles (1,2-Thiazoles)

Isothiazole halogenation resembles that of pyrazole, being easier than in benzene and giving 4-substituted products. Yields are frequently poor, perhaps because of the formation of multiply halogenated products [65AHC(4)107; 69FRP1555414; 72AHC(14)1; 79MI2]. There have been relatively few references to halogenation of these compounds in recent years, but reviews have been published [84MI13; 85AHC(38)105].

a. *Chlorination*. The parent compound mainly gave 4-chloroisothiazole (30–40%) with small quantities of dichlorinated products. Under conditions that favor radical attack (high temperatures, irradiation) 4-methylisothiazole gave a mixture of the 3-chloro and 4-chloromethyl derivatives [63AG(E)714]. Activating substituents greatly assist chlorination. Thus, 2-substituted isothiazole-3-ones reacted very readily with chlorine, first to form 4-chloro and 4,5-dichloro compounds. Excess chlorine at 60°C ultimately resulted in chlorine addition at the 4,5-bond to give tetrachloro compounds (**85**) [77JHC627, 77JHC725]. Even when the 4-position is

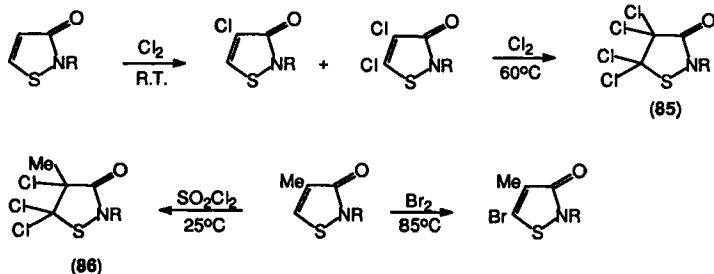
blocked, as in 2-substituted 4-methylisothiazol-3-ones, sulfonyl chloride is still capable of giving an addition product (**86**) (76JHC1321; 77JHC725) (Scheme 30). As the 2-substituent varies from alkyl to aralkyl to cyclohexyl to *p*-chlorophenyl, the chlorination becomes increasingly difficult. So far N-chlorination has been reported only for the reactions of benzisothiazoles. The Sandmeyer reaction was used to make 5-chloro-3-methylisothiazole (74USP3840665).

b. *Bromination.* 4-Bromination of isothiazoles is quite facile, especially when there are activating groups in the 3- and/or 5-positions [63AG(E)714; 64CI(M)207; 72AHC(14)1; 77JHC627, 77JHC725]. Like the chloro compounds, 4-bromoisothiazolones were readily formed from the 2-substituted 3-isothiazolones, but 4,5-dibromination took place only with difficulty. Steric hindrance may retard the second bromination, particularly in view of the short C₄—C₅ bond (77JHC725). Similar considerations may explain the more ready chlorination than bromination of the 4-methyl analogue [90AHC(47)165].

Deactivating substituents do not always prevent 4-bromination, as in 3-methylisothiazole-5-carboxylic acid (63JCS2032), but with 4-phenylisothiazole bromination occurred in the 5-position and *para* in the phenyl ring (69JHC841). Bromo-substituted isothiazoles, especially the 5-bromo compounds, can be made from lithium derivatives [68TL3905; 72AHC(14)1].

9. Thiazoles (1,3-Thiazoles)

Although thiazoles structurally resemble imidazoles and oxazoles, they are less reactive with electrophiles. Calculated π -densities (48BSF1021) and localization energies (61CCC156) largely agree with experimental observations that positional specificities for electrophilic substitution are 5



SCHEME 30

$> 4 \gg 2$. In the benzothiazoles the 2-position is largely unreactive with electrophiles, but nucleophilic substitution occurs there with some facility, especially in acidic medium. The protonated species is about 20 times more reactive than the neutral molecule (70BSF2705). Thiazole halogenation has been touched on in a number of articles in recent years [74MI2; 77BSF171; 79HC(34-1)565; 84MI15; 86CHE663, 86S757; 90AHC(47)165].

a. *Chlorination.* Unsubstituted thiazole would not react with chlorine in an inert solvent, and the chlorothiazoles usually have to be made by ring-synthetic methods, from the amino derivatives, or from thiazolones.

2-Chlorothiazole was readily prepared in high yield (92%) by the action of phosphoryl chloride on 2-thiazolone (80CHE28; 85JHC1621; 91EUP446913), and in 30–70% yields from the diazonium salt [71JCS(B)1373; 85JHC1621]. 2,4-Dichlorothiazole was made similarly in 60–70% yield from the thiazolidinedione [62BSF1735; 92JCS(P1)215] and from the 5-chloro-2-diazo precursor [79HC(34-1)565]. With phosphoryl chloride in dimethylformamide the dione was converted into 2,4-dichlorothiazole-5-carbaldehyde (63%) [92JCS(P1)973].

The 4- and 5-chloro isomers are best made by selective reductive dehalogenation of 2,4- and 2,5-dichlorothiazoles (62BSF1735). 5-Bromo-2-chlorothiazole was made from the 2-amino-5-bromo derivative (45HCA985). Under homolytic conditions (NCS in the presence of dibenzoyl peroxide) 4-methylthiazole gave a mixture of the 5-chloro, 2,5-dichloro, and 2,5-dichloro-4-chloromethyl derivatives (89CHE454).

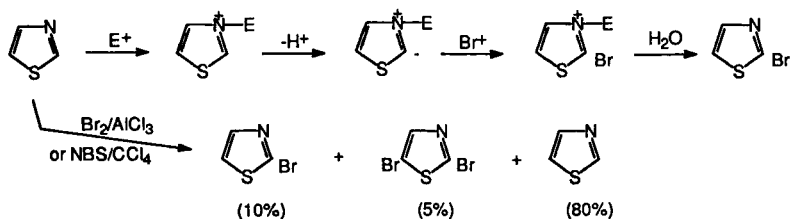
b. *Bromination.* Bromine in chloroform leaves thiazole largely unaffected, but 2-methylthiazole gave the 5-bromo derivative with this reagent [34RTC77; 79HC(34-1)565]. When the 5-position was blocked, however, there was no reaction. All of the mono-, di-, and tri-bromothiazoles are known, having been prepared by combinations of direct bromination, selective reductive bromination, reactions of thiazolones with phosphoryl bromide, and Sandmeyer reactions of the diazonium salts [34RTC77; 45HCA985; 47JCS431; 54HCA2057, 54RTC325; 57JGU799; 62BSF1735, 62BSF2075; 66BSF3524; 71CC1093; 76JHC1297; 81CC655; 85JHC1621; 86S757; 87S998; 88CJC1617, 88JOC1748; 92JCS(P1)215].

Vapor phase bromination of thiazole on pumice at 250–400°C gave 2-bromothiazole (1 : 1 ratio of bromine to thiazole). With excess bromine, 2,5-dibromothiazole was isolated in low yield. The product orientation corresponds with the assumed radical nature of the process for which free valence indices predict a substitution order of $2 > 5 > 4$ for the three available ring positions (34RTC77; 39CB1708; 61CCC156). This contrasts with the homolytic chlorination of 4-methylthiazole discussed above.

Substituents exert their expected effects with activating groups increasing bromination rates (39CB1470; 47JCS431; 54RTC325; 86S757) and electron-withdrawing groups retarding reactivity (72MI1; 76JHC1297). The free base form of 2-phenylthiazole was brominated at the 5-position [85CS(25)295] and 2-aryl groups displayed the usual substituent effects [72MI1; 73ACH107; 85CS(25)295]. With bromine in acetic acid 2,4-dichlorothiazole formed the 5-bromo derivative initially, but subsequent bromodechlorination led in turn to the 2,5-dibromo-4-chloro- and 2,4,5-tribromo-thiazoles. The same reagent readily displaced the 2-chloro group of 2,4,5-trichlorothiazole, followed by the chlorines in the 5- and 4-positions, and it also converted 4,5-dibromothiazole into the tribromo compound in 87% yield (76JHC1297).

When NBS is used, methylthiazoles can react at the substituent, in the ring, or at both sites, depending on the rest of the substitution pattern. An ester group directed attack preferentially into the side chain; phenylthiazoles reacted at both sites (81LA623). When thiazole itself was treated with NBS or with bromine in a neutral solvent (or neat) in the presence of aluminium chloride, a low yield (~10%) of 2-bromothiazole eventuated (57JGU799). This regiochemistry contradicts predictions of traditional electrophilic substitution, and an alternative ylid mechanism has been proposed (86CHE663) (Scheme 31). Yields were low when only catalytic amounts of Lewis acid were used (as in pyridine bromination [81CHE(17)923]). It is known that when 2-methylthiazole was 5-brominated by a solution of bromine in chloroform, the reaction was impeded by aluminium chloride. Presumably the heterocycle is deactivated by complexing at the nitrogen atom, and low yields are probably a function of much of the NBS being consumed in ylid formation. Thus, although NBS in carbon tetrachloride gave only 10% of 2-bromothiazole, excess NBS doubled the yield, but resulted in considerable resin formation (86CHE663).

With 2-methylthiazole as substrate, ylid formation cannot take place, and electrophilic substitution has to follow charge-density calculations.

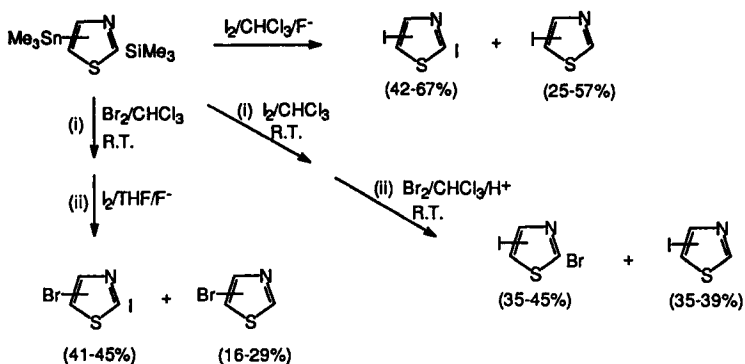


SCHEME 31

Hence bromine in dichloromethane converted 2-methylthiazole into 5-bromo-2-methylthiazole in 48% yield (76JAP76/48655). In this reaction HBr was present as a base acceptor. In its absence the yield was halved, and with an equimolar proportion of aluminium chloride the yield fell to 10%. It is evident that although 2-methylthiazole can be brominated under mild conditions, its activity is sharply reduced by protic or aprotic acids capable of complexing with the annular nitrogen (86CHE663).

A recent modification of the methods found useful in preparing halogeno-pyridines and -quinolines (82CPB1731) has proved its value for thiazoles. Reactions of 2-, 4-, and 5-trimethylstannylthiazoles with brominating (and iodinating) agents led to selective halogenations. With mixed trimethylsilyltrimethylstannyl derivatives the much slower halodesilylations allowed even greater selectivity, but yields failed to exceed 50%. Some protodesilylation at carbon-2 competes with halodesilylation (86S757) (Scheme 32).

Transmetalation was observed when 2,5-dibromo-4-chlorothiazole was treated with 1 mol of butyl-lithium in ether at -78°C before quenching with water. The products after 12 s were 5-bromo-4-chloro-, 2-bromo-4-chloro-, and 4-chloro-thiazole in the ratio 7 : 10 : 0.9. After half an hour the exclusive hydrogen-bearing product was 4-chlorothiazole. In tetrahydrofuran at -90°C the only isolable hydrogen-bearing product was 2-bromo-4-chlorothiazole. One molar equivalent of butyl-lithium in ether, followed by quenching as before, converted 2,4,5-tribromothiazole into a mixture of 2,4-dibromo- and 4-bromo-thiazole (10 : 5.5 after 10 min at -78°C ; 3 : 10 after 30 min at -78°C ; after 10 min at -90°C a mixture of 2,4- and 4,5-dibromo-, and 4-bromo-thiazoles was formed in the ratio 10 : 4.6 : 5.5) [92JCS(P1)215]. Although these processes were not directed toward the synthesis of specifically halogenated thiazoles, the potential is evident.



SCHEME 32

c. *Iodination*. Triiodothiazole can be made by reaction of molecular iodine with the mercury complex of 2-iodothiazole (55G926). The 2-iodo compound is available in 90% yield from the lithium derivative (68ACS1690), with the metallic derivative being prepared by lithium-bromine exchange. Sandmeyer processes have also been successful (85JHC1621). All of the monoiodothiazoles have been made in high yield from the trimethylsilyltrimethylstannyl derivatives (see also 9,b) (86S757) (Scheme 32). Iodination (and bromination) of some 5-thiazolyl derivatives of isoflavones occurred entirely in the phenolic ring (82CHE240).

d. *Fluorination*. Nucleophilic processes offer the best routes to fluorothiazole synthesis. A 38% yield of 2-fluorothiazole was obtained from the action of potassium fluoride on 2-chlorothiazole in the presence of 18-crown-6 in acetonitrile (85JHC1621). Nitro groups may also be displaced by fluoride [72JCS(P)2671; 77BSF171], though yields seldom exceed 20%. Thermal decomposition of the 2-diazonium fluoroborate has also been used (70ZC116), and potassium fluoride in sulfolane converted 2,4,5-tribromo- and 2,5-dibromo-4-chloro-thiazoles into the 2-fluoro derivatives (76JHC1297).

10. *Isoselenazoles (1,2-Selenazoles)*

The 4-position of isoselenazole (1,2-selenazole) resembles those of pyrazole and isothiazole as the most reactive in electrophilic aromatic substitution. Isoselenazole is more reactive than the sulfur analogue. Nevertheless, bromine at room temperature in the dark gave only 8% of the 4-bromo derivative [88H(27)2431]. An earlier report had stated that the ring was partially destroyed during bromination [84H(21)612], despite the 3,5-dialkyl, -diaryl, or -aralkyl derivatives forming 4-bromo products quite readily (35–83% yields) [84H(21)612; 88H(27)2431]. With NBS in acetic acid isoselenazole formed 4-bromoisoselenazole in 48% yield [88H(27)2431].

11. *Selenazoles (1,3-Selenazoles)*

The most reactive ring site for electrophiles in selenazole (1,3-selenazole) is the 5-position (cf. imidazole and thiazole) [75CS(8A)39; 84MI16]. When 2,4-dimethylselenazole was treated with bromine in the cold, an unstable bromo derivative (*N*-bromo?) formed initially eventually gave rise to 5-bromo-2,4-dimethylselenazole hydrobromide [53YZ(68)195; 79HC(34-3)217]. An activating group at C-2 promotes rapid reaction. 2-Amino-4-methylselenazole reacted with bromine in carbon tetrachloride

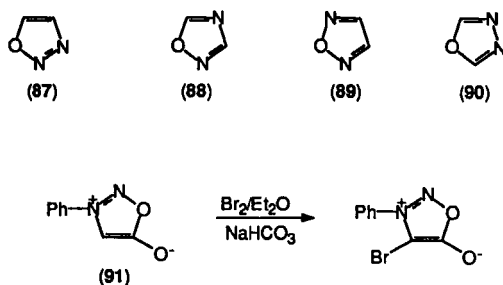
to give the 5-bromo derivative [53YZ(68)195], but excess bromine destroyed the molecule [79HC(34-3)217]. 2-Fluoroselenazoles were made in low yield (~17%) from the diazonium fluoroborates (82JHC1245).

12. Oxadiazoles

Those compounds with three heteroatoms (one oxygen and two nitrogen) are the 1,2,3-oxadiazoles (**87**), 1,2,4-oxadiazoles (**88**), 1,2,5-oxadiazoles (**89**), and 1,3,4-oxadiazoles (**90**) (Scheme 33). The 1,2,5-oxadiazoles are also known as furazans; 1,2,3-oxadiazoles include the sydnones.

a. *1,2,3-Oxadiazoles.* The highest π -density in **87** is at the 4-position. Halogenation should occur there first (64CRV129; 84MI17). The 3-phenylsydnone (**91**) was converted by bromine in acetic anhydride at 0°C, or with NBS in boiling chloroform, into the 4-bromo derivative (68MI1). Even more effective was bromine in diethyl ether with added sodium bicarbonate. There was no phenyl bromination in this compound because of deactivation by the positive nitrogen (83CJC154). A 1-pyrazolyl substituent attached to the *para*-position of the 3-phenyl substituent of **91** provides a suitable molecule in which to compare the relative reactivities of pyrazole and sydnone. The sydnone ring was found to 4-brominate before pyrazole (83CJC154). Further study of 3-arylsydones with electron-donating groups in the aryl ring showed no example of exclusive aryl halogenation; in most instances the heterocyclic ring was halogenated exclusively. Both NBS and NCS in dimethylformamide gave 4-halogenosydones in 75–93% yields (85MI1). This trend has been largely confirmed recently (90JHC1259).

b. *1,2,4-Oxadiazoles.* The π -density at C-3 of 1,2,4-oxadiazole is even lower than that of C-2 in the 1,3,4-isomer (84MI17). It is not unexpected,



SCHEME 33

then, to find that the 5-phenyl and 4-alkyl-3-phenyl derivatives are *meta*-substituted in the aryl group by electrophiles, although only nitration results have been reported (63G1196). Chlorine can displace a mercury chloride group from the 5-position [64HCA838; 76AHC(20)65].

c. *1,2,5-Oxadiazoles*. Reactions of 1,2,5-oxadiazoles (furazans), their *N*-oxides (furoxans), and benzo derivatives have been reviewed [61HC(7)463; 62HC(17)283; 75H(3)651; 81AHC(29)251; 84MI18]. The heterorings are quite resistant to electrophilic attack. 3-Phenyl-1,2,5-oxadiazole could not be 4-brominated, but aryl substituents are prone to halogenation, the substituent entering *ortho* or *para* to the heteroring, which is less activating than the sulfur analogue (78MI1). Methyl substituents may be chlorinated and brominated, especially under free radical conditions (77CHE25; 78JOU1162; 80GEP2919293). The ring is resistant to fluorination, but a 3-amino group can be converted by fluorine, diluted with helium, in acetonitrile with added potassium fluoride into the difluoro-amino derivative (87BAU1901).

d. *1,3,4-Oxadiazoles*. Most electrophilic substitution in 2,5-diphenyl-1,3,4-oxadiazole occurred in the *ortho*- and *para*-positions, with a little *meta*-product. Mixtures are always obtained in nitration [80JCS(P2)773], and in halogenation. Both 2-alkyl- and 2-aryl-1,3,4-oxadiazoles were halogenated at the substituent, with difficulties arising with the more acid-sensitive monoaryl derivatives [66AHC(7)183; 84MI19]. The heterocyclic moiety deactivates any attached homocyclic aromatic rings. Thus 2,4-diaryl derivatives required bromine in oleum or bromine-potassium bromate-sulfuric acid-acetic acid to achieve substantial halogenation. When one of the aryl rings was further deactivated by a *para*-nitro group, bromination became confined to the other aryl ring with *ortho:meta:para* attack in the ratio 2:2:3. Subsequent bromination was directed *ortho* or *para* to the bromine already present [84JCR(S)382].

Benzylic halogenation is a feature of 2-diphenylmethyl-1,3,4-oxadiazole and the ethyl ester of 5-phenyl-1,3,4-oxadiazolyl-2-acetic acid [67AC(P)169].

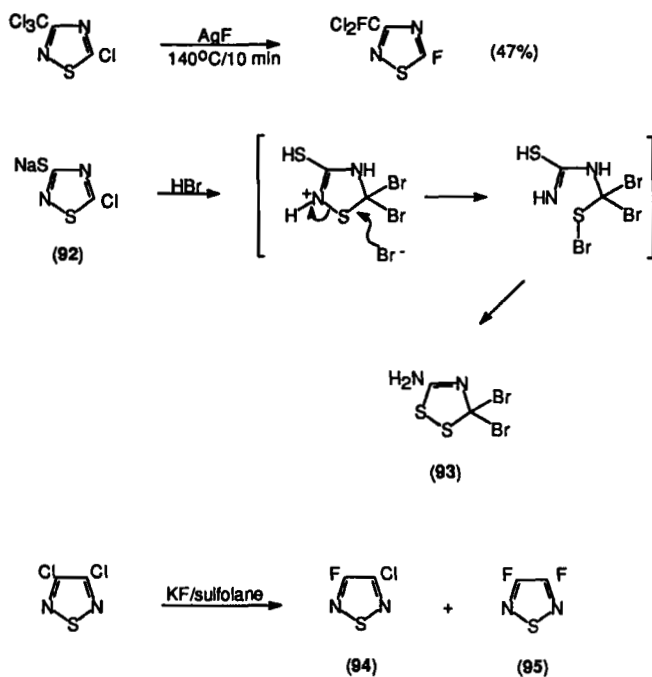
13. *Thiadiazoles*

The title compounds exist in isomeric modifications similar to those of the oxa analogues. Review material has appeared on the 1,2,3-isomers (84MI20; 86CHE811), 1,2,4-isomers [65AHC(5)119; 82AHC(32)285], 1,2,5-isomers [68AHC(9)107; 84MI21; 88AHC(44)133], and 1,3,4-isomers [68AHC(9)165; 84MI22].

a. *1,2,3-Thiadiazoles*. No reports of successful bromination of this nucleus have appeared. The parent compound and its 4-carboxylic acid would not undergo bromination (65JCS5166). The ring is very π -deficient, and NBS only managed to cause side-chain bromination of some mono- and di-alkyl derivatives (80JHC1639; 86CHE811). Ring-synthetic procedures are available for making halogen derivatives (91URP1655963).

b. *1,2,4-Thiadiazoles*. Although electrophilic substitutions in these compounds are virtually unknown, halogenated derivatives are accessible by nucleophilic displacements, particularly in the 5-position. Fluoride displaced a 4-chloro group [65AHC(5)119], but side-chain fluorination also occurred (Scheme 34). Reaction of the sodium derivative of the 3-thiol of 4-chloro-1,2,4-thiadiazole (**92**) gave the dithiazole (**93**) rather than the 5-bromo derivative. This was a consequence of attack on the ring sulfur atoms by the soft nucleophile, bromide [65AHC(5)119].

Sulfur-linked substituents are usually prone to oxidation by halogens. In aqueous solution, chlorine converted 5-amino-3-benzylthio-1,2,4-thiadiazole successively into sulfoxide and sulfone, but in glacial acetic



SCHEME 34

acid the 3-chloro derivative was formed as the benzylthio group was displaced. Other examples exist in which 3,5-dichloro derivatives have been made from the 3,5-dimercapto precursors [65AHC(5)119; 82AHC(32)285].

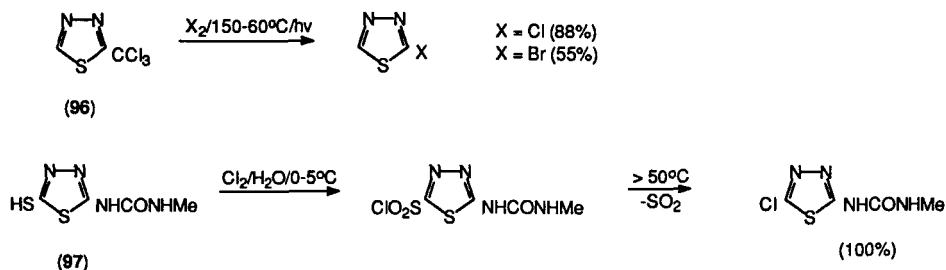
Very reactive diazonium salts can be made from 5-amino-1,2,4-thiadiazoles. These enter the Sandmeyer reactions with great facility to give 5-halogenated derivatives [56CB1033, 56CB1534]. The less reactive 3-amino derivatives give the 3-halogeno compounds with a little more difficulty (60JCS3234; 61CB2043).

c. *1,2,5-Thiadiazoles*. These compounds are resistant to electrophilic halogenation unless an electron-donor is present in the ring. The parent is quite inert to bromine in the presence of Lewis acid catalysts or under ultraviolet irradiation. Light-catalyzed bromination with NBS of 3,4-dimethyl-1,2,5-thiadiazole, however, took place readily at the methyl groups (89CCC2176); the 3-methyl and 3-methyl-5-phenyl derivatives gave bromomethyl products similarly (84JHC1157). Chlorine dissolved in acetonitrile slowly converted 3-methyl-1,2,5-thiadiazole into the 4-chloro derivative, whereas bromine in acetic acid 4-brominated 3-amino-1,2,5-thiadiazole [63BEP629551; 64GEP1175683; 68AHC(9)107; 70RCR923].

The monofluoro (**94**) and difluoro derivatives (**95**) were isolated when a solution of potassium fluoride in sulfolane reacted with 4,5-dichloro-1,2,5-thiadiazole. Careful control of the reaction conditions allowed production of mainly **95**, whereas **94** became the major product when oxidizing fluorinating agents were employed (e.g., XeF₂, BrF₃, AgF₂). Open-chain products were also found (82CB2135) (Scheme 34).

d. *1,3,4-Thiadiazoles*. Unless an electron-donating substituent is present, the ring is reluctant to enter electrophilic substitution reactions [65ACS2434; 68AHC(9)165; 77JHC823; 84MI22]. When treated with bromine in acetic acid with sodium acetate present, 2-amino-1,3,4-thiadiazole gave a high yield of the 5-bromo derivative (77JHC823). Radical bromination and chlorination of a melt of 2-trichloromethyl-1,2,3-thiadiazole (**96**) gave good yields of the 4-halogeno products (80LA1216) (Scheme 35). In the presence of aqueous chlorine, the thiol (**97**) was converted into the 5-sulfonyl chloride, which rapidly extruded sulfur dioxide in a concerted process when heated above 50°C (80JHC1311) (Scheme 35). This type of process is not unique (58JCS1508).

Chloro- and bromo-1,3,4-thiadiazoles are usually prepared by nucleophilic processes, e.g., Sandmeyer reactions of diazonium salts [56CB1534; 68AHC(9)165; 86CHE1148], and reactions of thiadiazolinones with phosphorus halides [68AHC(9)165]. The halogeno derivatives are important



SCHEME 35

reaction intermediates, as the halogens are readily displaced by nucleophiles. One such example, which leads to a halogeno product, is the low-yield conversion of 2-bromo-1,3,4-thiadiazole into the 2-fluoro analogue (62JOC2589; 77BSF171).

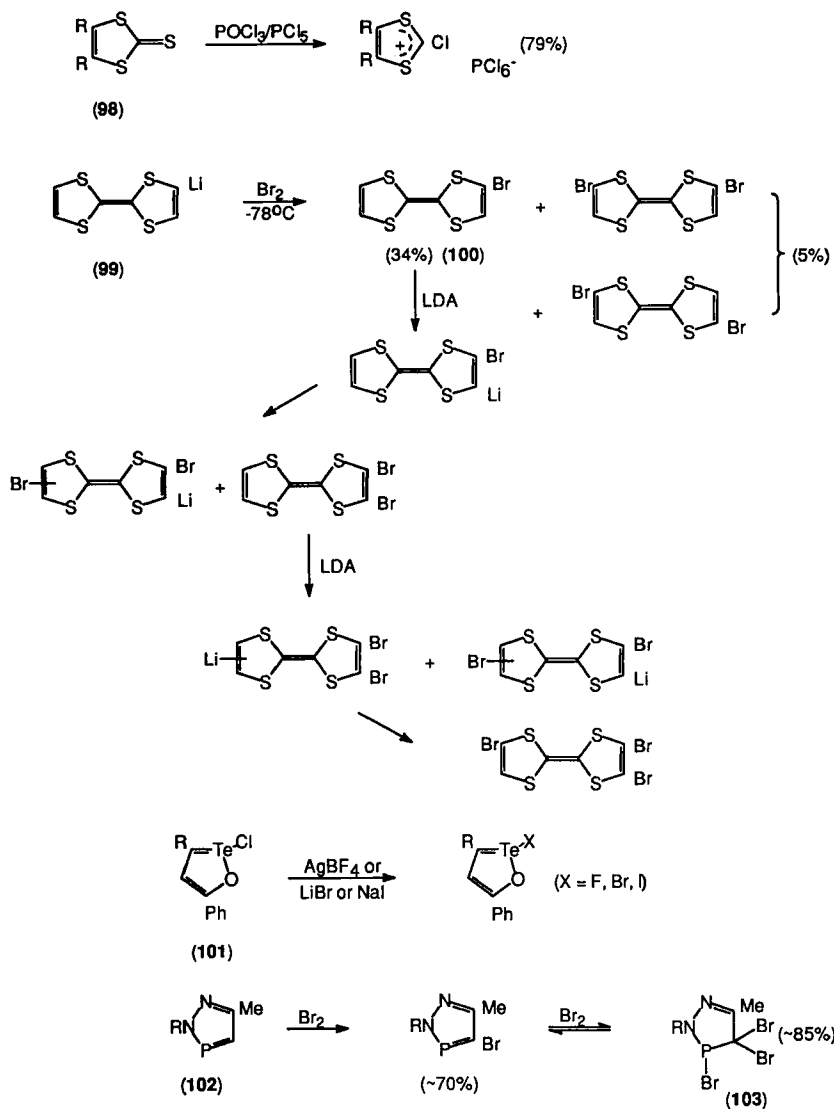
14. Other Unsaturated Five-Membered Heterocycles

This group comprises a wide variety of compounds, few of which are particularly susceptible to direct halogenation. Reactivities of such species have been reviewed in the "Comprehensive Heterocyclic Chemistry" series: dioxoles and oxathioles (84MI24); 1,2- (84MI25) and 1,3-dithioles (84MI26); boroles (84MI2); oxa- and thia-triazoles [76AHC(20)145; 78AHC(22)183; 84MI23]; oxathiazoles, dioxazoles, dithiazoles (84MI28); and trioxoles and trithioles (84MI27). Only recent references are reviewed now.

Reaction of phosphorus pentachloride and phosphoryl chloride with **98** gave the 2-chloro-1,3-dithiolium salt (84S319). The lithium derivative of tetrathiafulvene (**99**) was readily converted into its chloro and bromo derivatives, although base-catalyzed "halogen-dance" reactions complicated the products. 2-Bromotetrathiafulvene (**100**) reacted with lithium diethylamide to give a mixture of unhalogenated product and mono-, di-, and tri-brominated derivatives [86H(24)1145] (Scheme 36). Compound **100** reacted with one molar equivalent of lithium diethylamide, followed by quenching with the appropriate tosyl halide, to give moderate yields of the 2-chloride (48%), 2-bromide (38%), and 2-iodide (34%). With 4.4 equivalents of the lithiating agent and subsequent treatment with tosyl chloride, the tetrachlorotetrathiafulvalene was obtained in 30% yield (91S263).

No halogenation was reported for 1,3- and 1,2-ditelluroles (91CHE235). A variety of nucleophilic substitution reactions with halides took place with 1,2-oxatelluroylium chlorides (**101**) (83JA875).

Rather than oxidizing diazaphospholes (**102**) at the phosphorus atom, bromine converted them into the 4-bromo derivatives in high yields via a



SCHEME 36

combination of addition and elimination reactions. Ultimately the tribromo product (**103**) was obtained (85CB1621) (Scheme 36). With iodine monochloride, a mixture of 5-chloro and 5-iodo derivatives was formed; sulfonyl chloride gave only the former; NBS and cyanogen bromide led to 5-brominated product (84S591).

ACKNOWLEDGMENTS

I am grateful to the University of Otago for the granting of a period of study leave during the latter part of 1991, when much of the material for this review was collected. My task was lightened by the generous way in which The Department of Chemistry and Applied Chemistry at the University of Salford made their facilities so freely available to me during this period. To the staff of that Department, and particularly to Dr Brian Iddon, I owe a debt of gratitude. I must also pay tribute to Diana Walker who undertook the mammoth task of transposing my scribblings into a professional-looking format.

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65JCS5166
65MI1
65T843
65T945
66AG(E)896
66AHC(6)391
66AHC(7)1
66AHC(7)183
66AHC(7)378
66BSF293
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ISBN 0-12-020757-5



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