

1.18

Azetidines, Azetines, and Azetes: Monocyclic

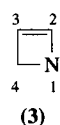
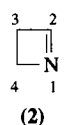
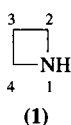
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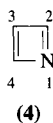
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1.18.1 INTRODUCTION

This chapter deals with the recent aspects on four-membered rings containing one nitrogen atom. This class of compounds has been thoroughly studied in the decade since 1985. While the chemistry of azetidines (**1**) grew steadily, the chemistry of azetidin-2-ones (β -lactams) saw an enormous focus, mainly because of the relation with antibacterial properties of these substances and their derivatives. The chemistry of 1-azetines (**2**) and 2-azetines (**3**) is still underdeveloped due to the unstable nature of these compounds.



The chemistry of azetes (**4**) was almost unknown, but developments in the 1990s on kinetically stabilized azetes filled up this gap.



In view of the uneven attention which azetidines, azetines, and azetes have received and because of their lack of chemical similarity, these compounds are treated separately in this chapter. In addition, because of the increasing interest in azetidin-2-ones, these β -lactams have been dealt with separately, rather than as derivatives of azetidine.

An investigation by a CAS ONLINE computer search for references dealing with monocyclic azetidines revealed 26 328 structures for the period 1983–1993. Careful elimination of some less interesting topics left over 3600 records, published in about 700 articles. It is clear that within the limited page allocation a complete coverage of this material is impossible and a selectivity towards usefulness has been employed. This applies especially for the β -lactam part which has been covered already in several review articles.

1.18.2 AZETIDINES

1.18.2.1 Introduction

Since the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(7)237>, a steady growth of the knowledge of the relative difficulty with which azetidines can be synthesized has occurred, culminating in several novel routes to this class of strained azaheterocycles. In addition, a large number of applications in agrochemistry and in the pharmaceutical field have been reported. Together with CHEC-I, a review in 1983 gave a broad overview of the chemistry of azetidines up to the first years of the 1980s <B-83MI 118-01>. The latter review covers a lot of basic knowledge on azetidines, including information on spectroscopic data, stabilities, etc. Both CHEC-I and <B-83MI 118-01> have to be considered as standard reference works for the period up to 1983.

1.18.2.2 Theoretical Methods

The strain in azetidines influences the tendency for ring formation enormously. Within the homologous series of azaheterocycles, the tendency for cyclization is smallest for the nitrogen-containing four-membered ring ($5 > 3 > 6 > 7 \approx 4$) <85JCS(P2)1345>.

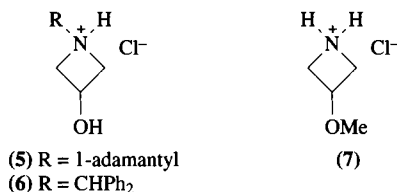
The gas phase proton affinities of azetidine and β -lactams were measured by FTICRMS techniques. Self-consistent field and MP2 calculations at different levels of accuracy have been performed for the neutral and protonated species. Azetidine presents a gas phase basicity practically equal to that of *N*-methyl ethanamine <92JA4728>.

Ab initio UHF calculations predicted the neutral azetidin-1-yl radical to have a puckered ring structure with puckering angles of 12.0° and 15.4° on the STO 3G and 6-31G* levels, respectively. These results were supported by EPR spectroscopy <91JCS(F1)1083>.

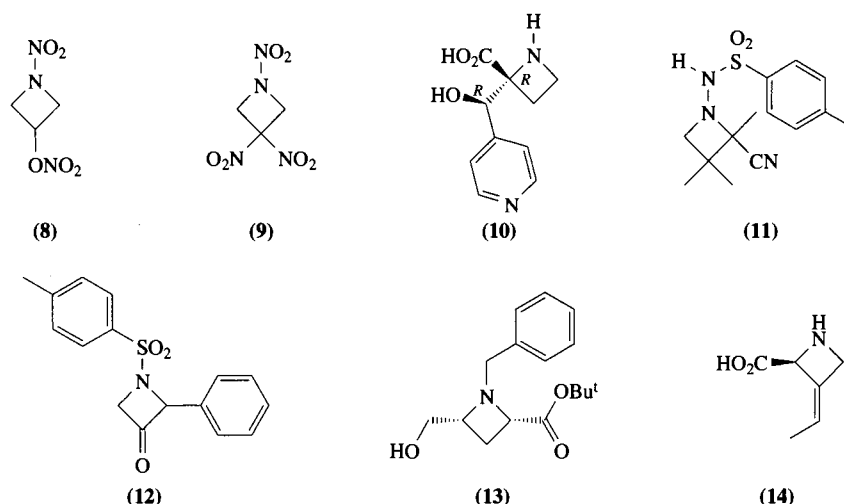
1.18.2.3 Experimental Structural Methods

A whole range of functionalized azetidines have been investigated by x-ray crystallographic analysis. The x-ray analysis of 1-adamantyl-3-hydroxyazetidinium chloride (**5**) revealed that the 1-adamantyl group and the hydroxy function were situated at the same side <89CJC1514>.

The corresponding *N*-benzhydryl derivative (6) had monoclinic crystals. The azetidine ring is buckled 13.0° and the azetidinium moiety is linked to the chloride ion through a hydrogen bond ($\text{OH}\cdots\text{Cl}$ 3.166(5) Å) (84MI 118-01). A similar phenomenon was observed with 3-methoxyazetidinium chloride (7) (93MI 118-01).



The tetragonal 3-nitrato-1-nitroazetidine (8) had a slightly puckered four-membered ring with an angle between the C–C–C and C–N–C planes of 12.7° . The *N*-amino group is pyramidal (92MI 118-01). 1,3,3-Trinitroazetidine (9) has a similarly puckered ring (angle 13.6°) and the nitramino group exhibits an unusually high (39.4°) out-of-plane deformation (90JOC2920). The first x-ray structure of an azetidine-2-carboxylic acid with a carbon substitution at C(2) (10) and an azetidine-2-carbonitrile (11) have been determined (88T3653, 90LA687). Data from x-rays on functionalized azetidines (12), (13), and (14) have been reported (86T4879, 87KGS468, 93TL4153). A comparison of x-ray data of 1-tritylazetidine, 1-tritylazetidinium perchlorate, and azetidinium perchlorate has been made (93JHC1197).



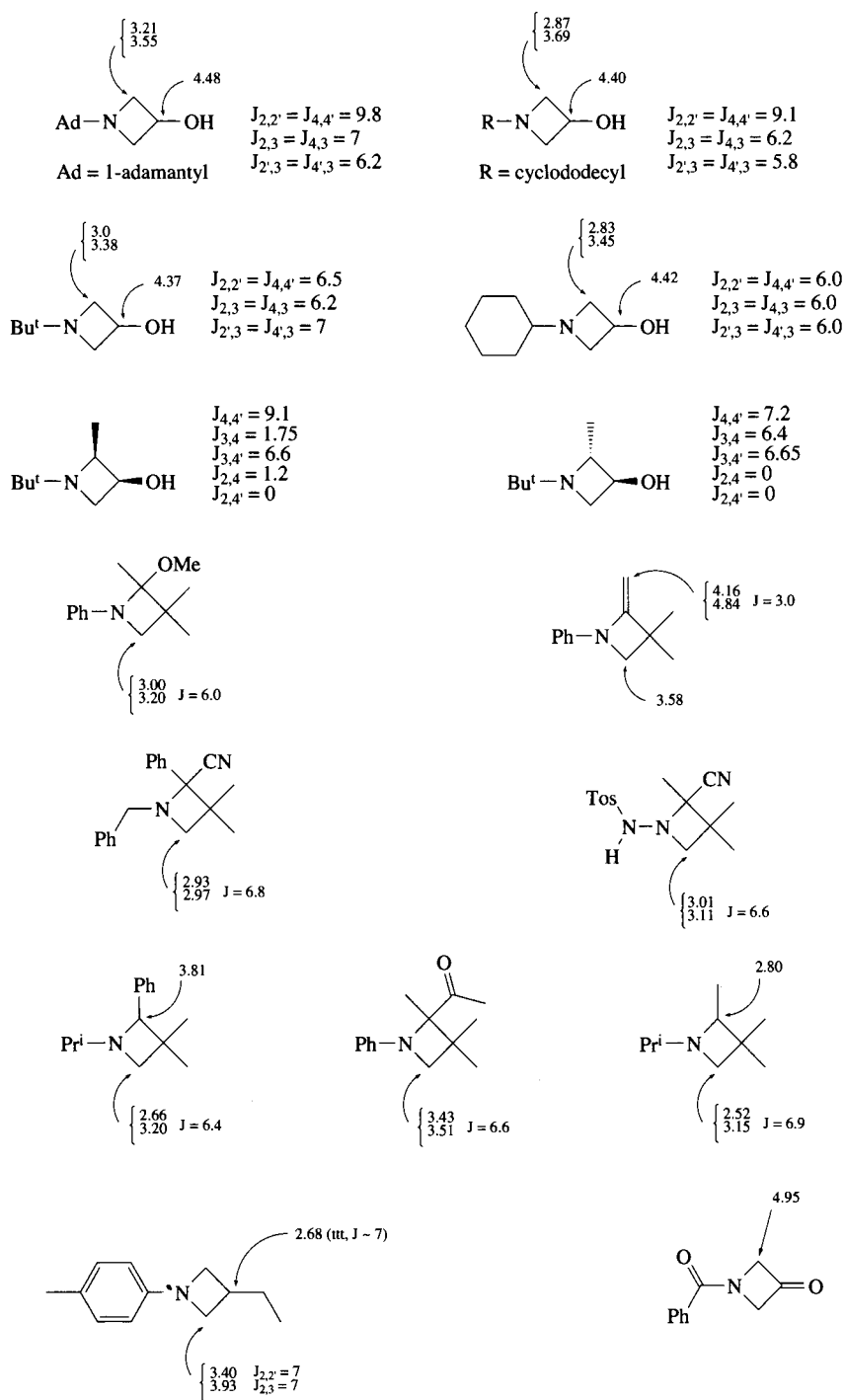
Azetidine has been investigated by high resolution NMR spectroscopy (87MRC101). Enantiomers of *N*-unsubstituted azetidines were investigated by NMR via the use of chiral isocyanates, giving diastereomeric urea derivatives (88JOC3358). Numerous ^1H NMR data and to a minor extent ^{13}C NMR data have been reported, some of which are selectively given here (solvent CDCl_3). One major remark concerns the geminal coupling constants of the methylene group attached to nitrogen. This coupling constant is very variable, depending on the class of azetidine derivatives, on the nitrogen substituent, and presumably on the conformation (89CJC1514).

Selected ^1H NMR data (δ values in ppm; J values in Hz) are shown in Scheme 1 (71JHC961, 71JHC1059, 88HCA1035, 88JOC4462, 88T3653, 89CJC1514, 89T629, 89T1851, 89T2937, 90JMC1561, 93S89).

Selected ^{13}C NMR data (δ values in ppm) are shown in Scheme 2 (88JOC4462, 88T3653, 89T629, 89T1851, 89T2937, 93S89).

The hydrogen-bridge in 3-hydroxyazetidine has been studied by IR and Raman spectroscopy (89SA(A)1157, 90JST(220)43).

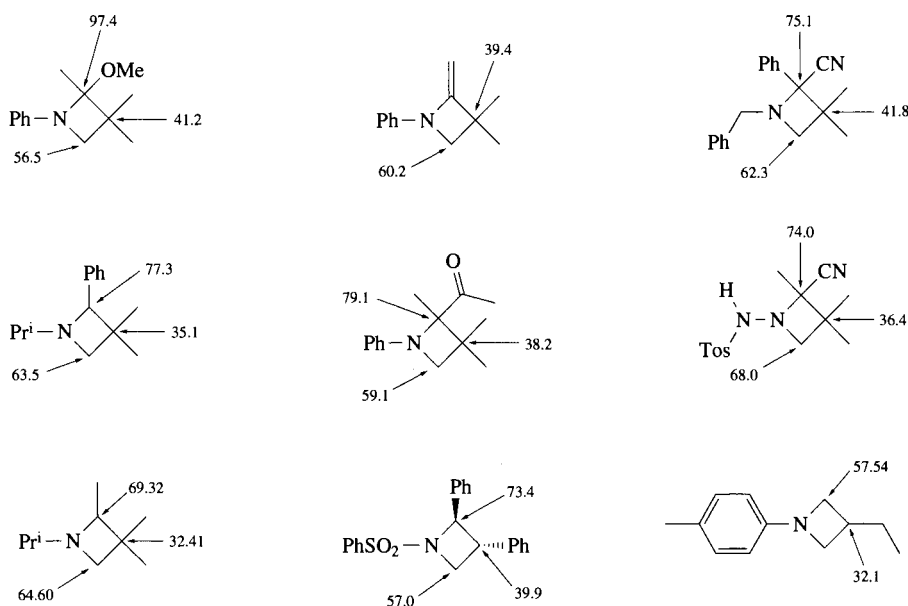
The radical cations from azetidine have been characterized by ESR spectroscopy following their generation in the solid state by γ -irradiation of diluted solutions of the parent compound in a CFCl_3 matrix at 77 K. The ESR parameters are typical of those for a nitrogen-centered amine radical (86JPC2292).



Scheme 1

1.18.2.4 Thermodynamic Aspects

Most azetidines are stable compounds and can be chromatographed, either by gas chromatography or, more recently, by flash chromatography. It is known that 3-azetidinones are labile compounds and usually decompose at room temperature. Decomposition products are, among



Scheme 2

others, aldol-type condensation products. Only crystalline 3-azetidinones, for example, 1-benzhydryl-3-azetidinone, appear to be storeable for prolonged periods <85JOC5223, 88HCA1035>.

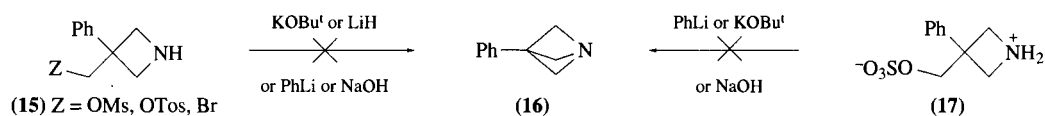
Inversion of the pyramidal nitrogen of azetidines is a major feature of these heterocycles. The $\Delta G^\ddagger$ for the inversion is at best only a few kilocalories (around 10 kcal) per mol <85JA4335>. This estimation is a correction of a literature report <84JA7638>.

The rotational barriers of *N*-nitroso-, *N*-formyl and *N*-(*N,N*-dimethylcarbamoyl)-azetidines, compared with those of analogous acyclic amides, suggest that amide conjugation is weaker when the nitrogen is part of an azetidine ring <87KGS912>.

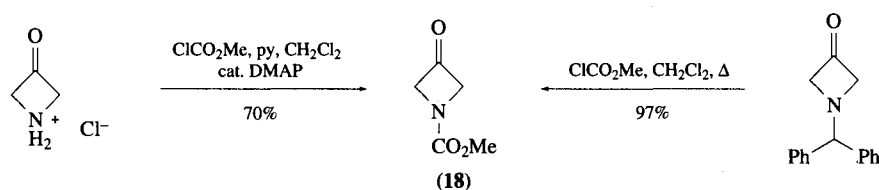
1.18.2.5 Reactivity

1.18.2.5.1 Electrophilic attack at nitrogen

Azetidines are readily alkylated at nitrogen by alkyl halides <86JOC5489>. Intramolecular alkylation of azetidines (**15**) and (**17**), substituted with suitable leaving groups for the synthesis of 1-azabicyclo[1.1.1]pentane (**16**), failed completely after numerous attempts (Scheme 3) <89G81>. The *N*-chlorination of azetidines occurs smoothly with *N*-chlorosuccinimide or *t*-butyl hypochlorite <71JA933, 87CB1971, 88T4447, 89G81>, the resulting *N*-chloroazetidines being suitable substrates for a 1-azetine synthesis. The reaction of *N*-unsubstituted azetidines with chloroformates giving the corresponding carbamates, for example (**18**) contained in Scheme 4, is a major way of *N*-protection <88HCA1035, 92TL7919, 93T8211>.

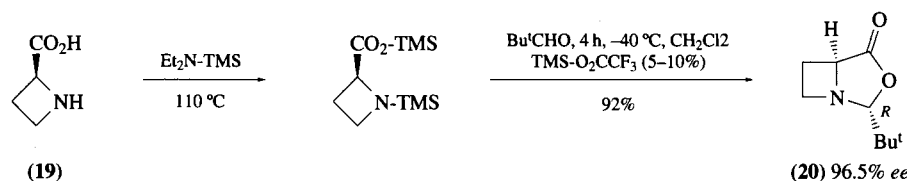


Scheme 3

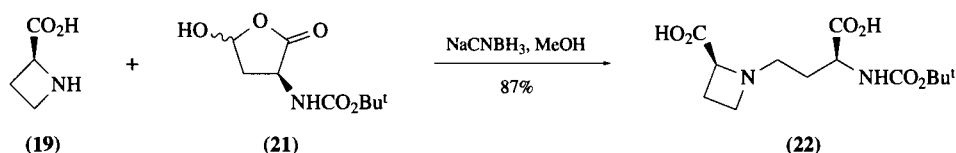


Scheme 4

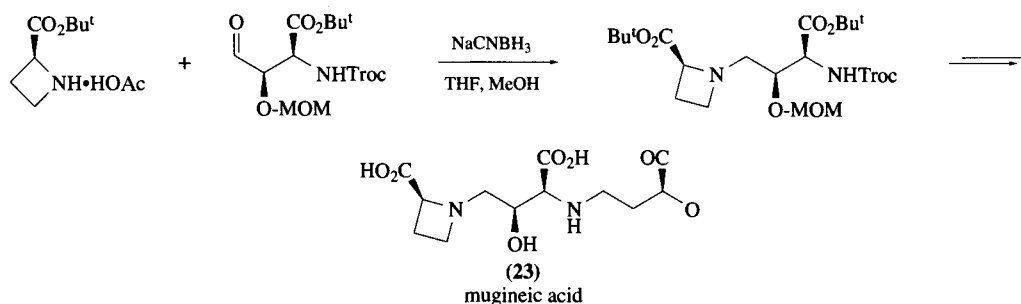
However, *N*-alkylated azetidines, for example, *N*-benzhydryl or *N*-*t*-butyl derivatives, are clearly dealkylated and converted into the carbamates by reaction with chloroformates $\langle 88\text{HCA}1035, 92\text{JHC}1855 \rangle$. Coupling of *N*-unsubstituted azetidines with carboxylic acids in an intramolecular way produces bicyclic azetidines $\langle 85\text{CC}194, 86\text{T}4879 \rangle$. Reaction of *N*-unsubstituted azetidines with aldehydes have been performed through initial *N*-silylation. In the case of (*S*)-azetidine-2-carboxylic acid (19), this allows the synthesis of chiral bicyclic azetidines (20) $\langle 83\text{JA}5390, 90\text{LA}687 \rangle$. The reductive amination of the latent aldehyde (21) produced dipeptide derivative (22) $\langle 83\text{MI}118-02, 84\text{CL}441 \rangle$. The latter reaction has been used for the total synthesis of mugineic acid (23) and 3-*epi*-hydroxymugineic acid (Scheme 7) $\langle 93\text{T}8211, 94\text{T}265 \rangle$. Direct nitrolysis of azetidines with acetyl nitrate, or indirectly, via dealkylative nitrolysis using HNO_3 and acetic anhydride furnished *N*-nitroazetidines (9) and (24) $\langle 90\text{JOC}2920, 90\text{SC}407 \rangle$. The *N*-nitroazetidines and *N*-perchlorylazetidines are formed by reaction of 1-unsubstituted aziridines with N_2O_5 and dichlorine heptoxide (Cl_2O_7), respectively $\langle 87\text{ZAAC}(547)233, 91\text{TL}4985 \rangle$.



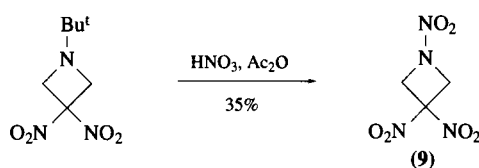
Scheme 5



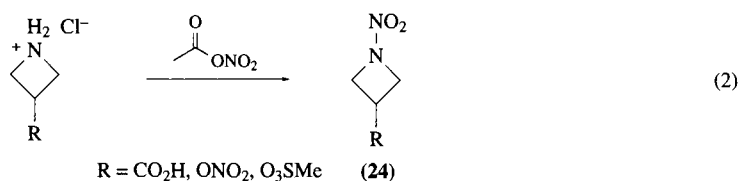
Scheme 6



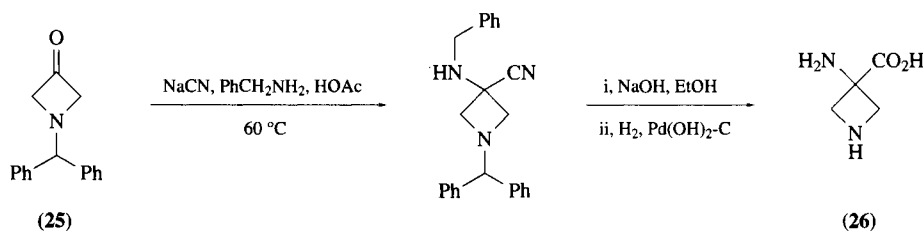
Scheme 7



(1)



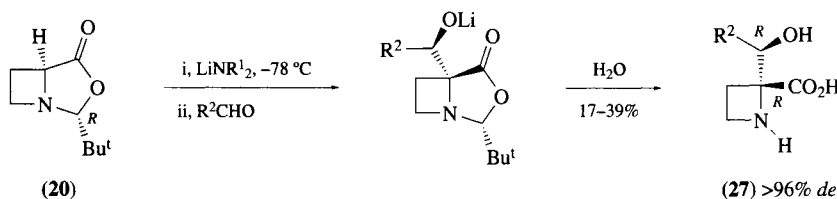
The formation of the α -amino nitrile from 3-azetidinone (**25**), followed by alkaline hydrolysis and hydrogenolysis, gave access to 3-aminoazetidine-3-carboxylic acid (**26**) <91SL783>.



Scheme 8

1.18.2.5.2 Electrophilic attack at carbon

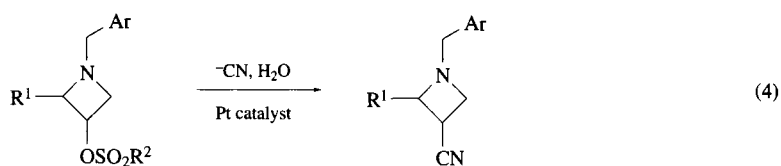
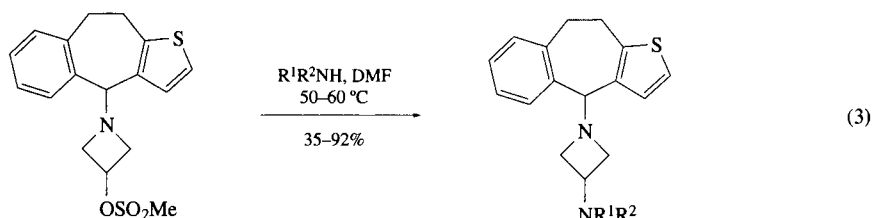
The reaction of the optically active bicyclic azetidine (**20**) with lithium amides, and subsequently with aldehydes, produced amino hydroxy acids (**27**) with high diastereoselectivity (Scheme 9) <90LA687>.

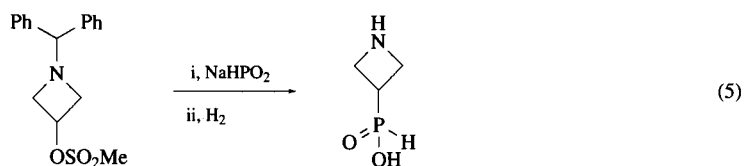


Scheme 9

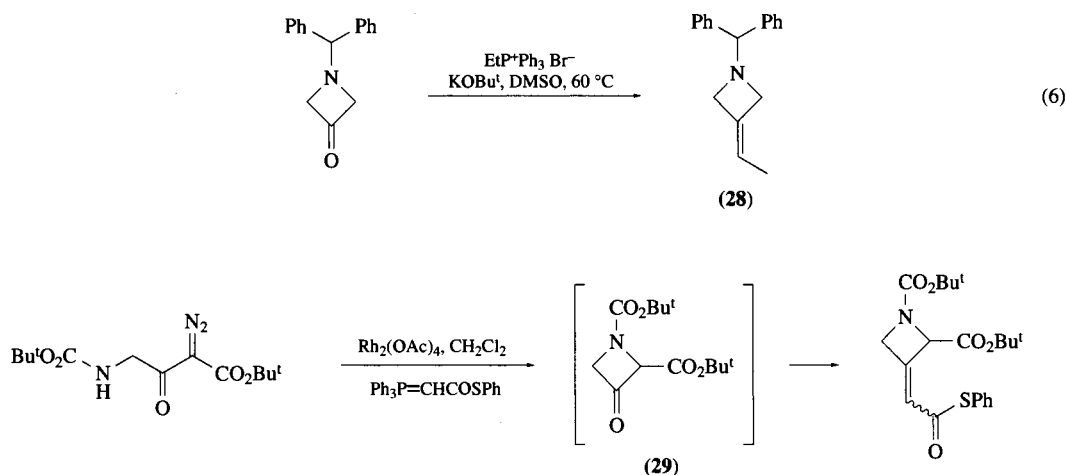
1.18.2.5.3 Nucleophilic attack at carbon

Nucleophilic displacement reactions at the azetidine carbon skeleton are most conveniently executed with mesylate or other sulfonate derivatives and a variety of nucleophiles, including phenols <85EUP131435>, amines (Equation (3)) <86JHC1503, 91EUP406112>, potassium phthalimide (and subsequent hydrazinolysis) <85FRP2560194, 85JHC961>, cyanide (Equation (4)) <86EUP169602, 86EUP169603>, sodium borohydride <86H(24)2467>, sodium nitrite <90JOC2920>, and sodium phosphite (Equation (5)) <91PS(56)1>.

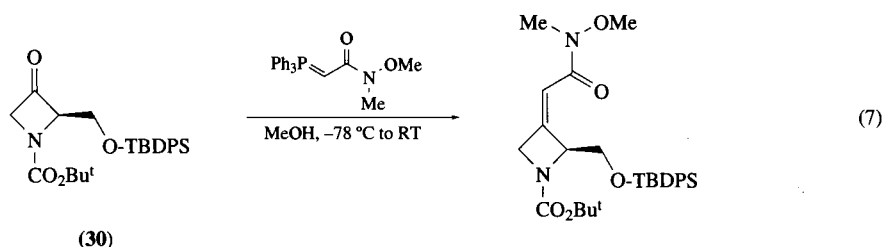




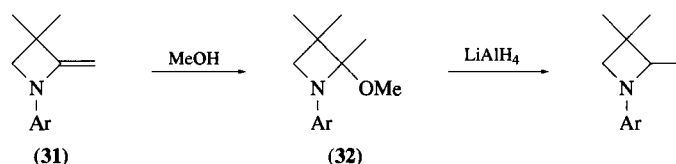
Wittig reactions of 3-azetidinones with ethyltriphenylphosphonium bromide in the presence of base is highly dependent upon the type of *N*-substituent. *N*-Benzhydryl derivatives undergo the Wittig reaction to give 3-ethylideneazetidine (**28**), while *N*-methoxycarbonyl derivatives only give an extremely low yield (3%) <88HCA1035>. The reaction of functionalized Wittig reagents with 3-azetidinones (**29**) and (**30**), generated from rhodium-catalyzed cyclization of α -diazo- β -ketoesters, to give 3-alkylidene-azetidines was applied successfully as a key step in the synthesis of polyoximic acid (**14**) <92T7165, 93TL4157>, see also the revision of the structure of polyoximic acid <93TL4153>.



Scheme 10

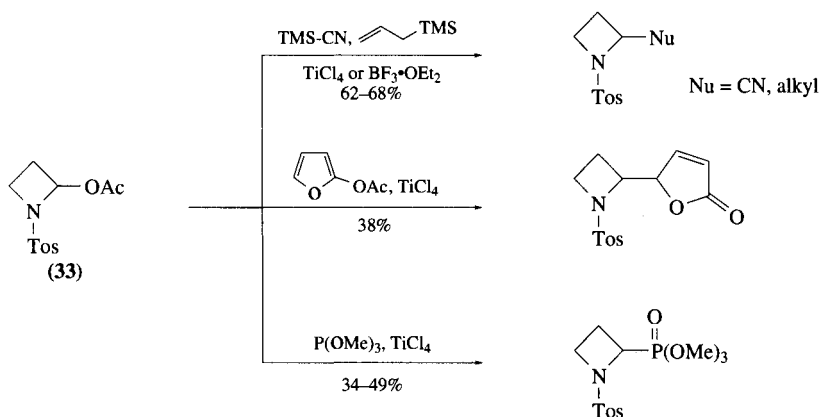


Nucleophilic attack of 2-methyleneazetidines (**31**) by methanol produced 2-methoxyazetidines (**32**), which are suitable building blocks for the synthesis of various azetidines (Scheme 11) <88JOC4462>.



Scheme 11

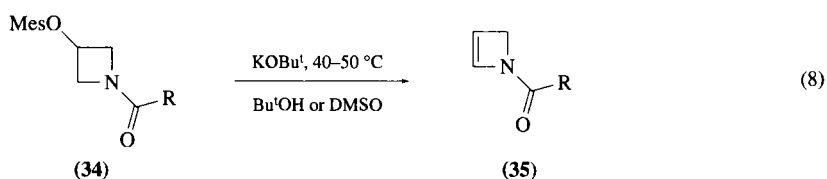
Similar displacements of 2-acetoxiazetidine (**33**) carrying an electron-withdrawing substituent at nitrogen, by carbon and phosphorus nucleophiles have been reported utilizing Lewis acid catalysis (Scheme 12) <88BCJ3029>.



Scheme 12

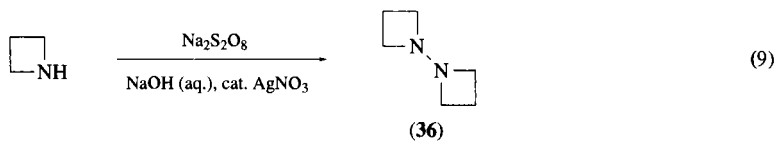
1.18.2.5.4 Nucleophilic attack at H (deprotonation)

Reaction of 1-acyl-3-mesyloxyazetidines (**34**) with potassium *t*-butoxide in *t*-butanol or DMSO led to 1,2-elimination affording 1-acyl-2-azetidines (**35**) in moderate yield (Equation (8)) <91JOC6729>.



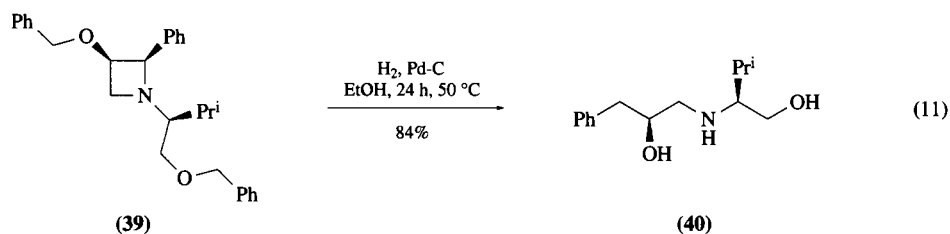
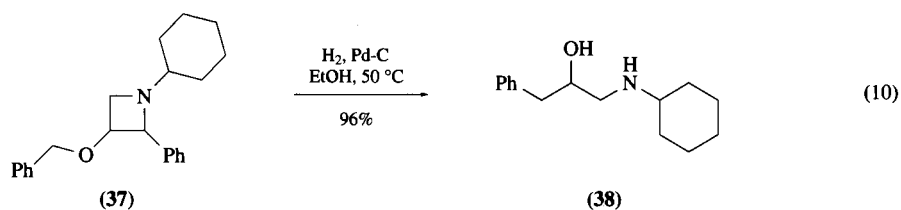
1.18.2.5.5 Radicals

While the oxidation of pyrrolidine with sodium peroxydisulfate under the catalytic influence of silver nitrate produced 1-pyrroline, which trimerized to the corresponding hexahydro-1,3,5-triazine, azetidine was converted in very low yield into the bisazetidine (**36**) (Equation (9)) <82JCS(P1)3031>.

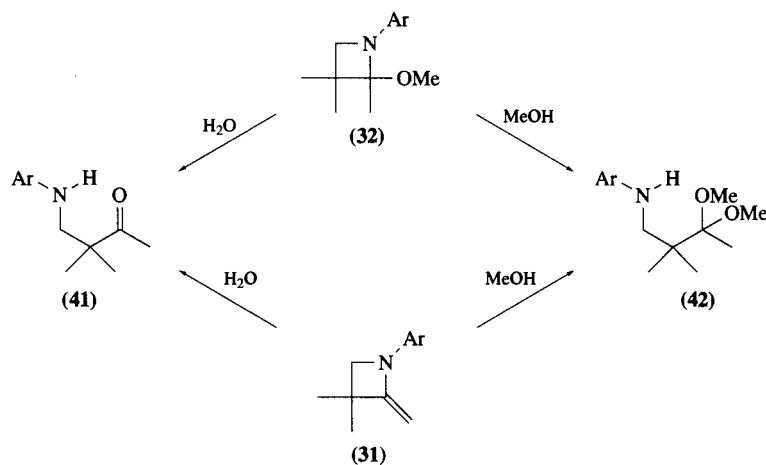


1.18.2.5.6 Ring opening

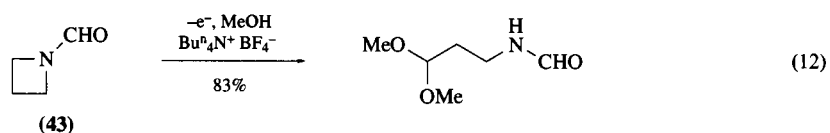
The ring opening of azetidinium ions with bromide <85CC339> and the cleavage of azetidines via specific acid catalysis has been studied <91ZOB1841>. Ring opening of 3-amino-, 3-hydroxy- or 3-alkoxyazetidines (**37**) and (**39**) to give 2-amino- or 2-hydroxyalkylamines (**38**) and (**40**) takes place by catalytic hydrogenation on palladium or Raney nickel (Equations (10) and (11)) <83JA6339, 84JAP59161336, 87BSF649>. It is known that 1-benzoyl-3-azetidinones are opened similarly to β -(*N*-benzoylamino)alcohols <89JMOC81>.



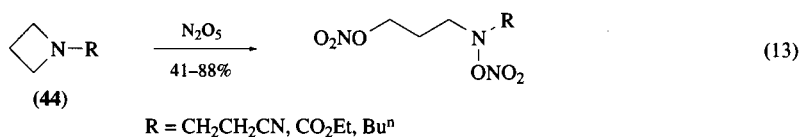
The cleavage of 2-methoxyazetidines ((32)) and 2-methyleneazetidines (31) occurs readily by methanolysis to give β -amino acetals (42). Acid or alkaline hydrolysis of 2-methyleneazetidines and 2-methoxyazetidines affords β -aminoketones (41) in high yield (Scheme 13) <88JOC4462, 89T2937>. The ring opening of 1-formylazetidine (43) by anodic oxidation in methanol is related to these conversions because of the electrolytic generation of the intermediate 1-formyl-2-methoxyazetidine (Equation (12)) <81ACS(B)739>.

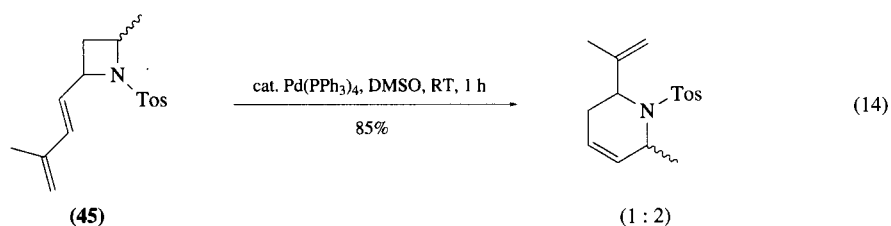


Scheme 13

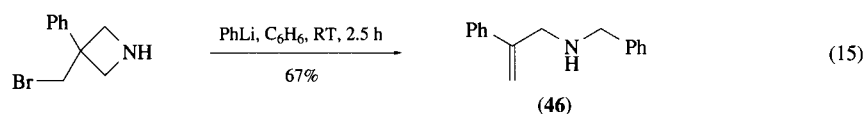


The 1-substituted azetidines (44) yield nitramine nitrates by ring opening with dinitrogen pentoxide (Equation (13)) <88TL2735>. Ring expansion of dienylazetidines (45) into tetrahydropyridines under the influence of palladium complexes has been reported (Equation (14)) <85TL857>.

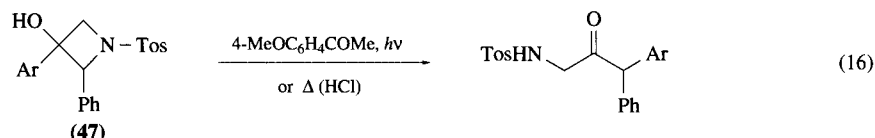




Neighbouring group assisted ring opening of azetidines, bearing a leaving group at the 3-methylene carbon, has been accomplished by phenyllithium, affording allylamine (46). No trace of the desired 1-azabicyclo[1.1.1]pentane was observed <89G81>.

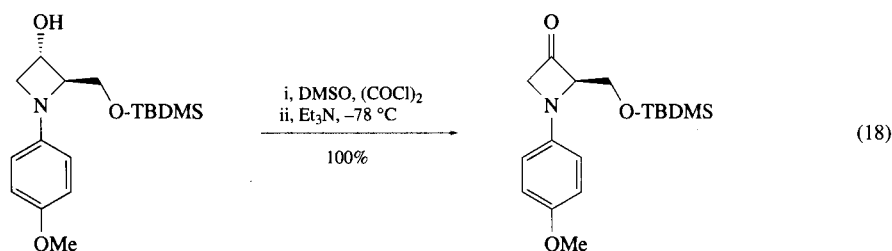
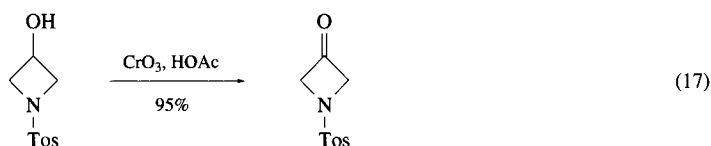


Sensitized photolysis or thermolysis in hydrogen chloride of *N*-tosyl 3-hydroxyazetidines (47) results in ring opening with rearrangement into β -tosylamino ketones, the yield depending on the migratory aptitude of the aryl group (Equation (16)) <83ZC52>. Some activated 3-iminoazetidines show a slow ring opening to give 2-aza-1,3-dienes <83JOC481>. Ring opening of azetidines to give polymers is not covered here. Leading references have been given in the review <92HOU(16C)936>.

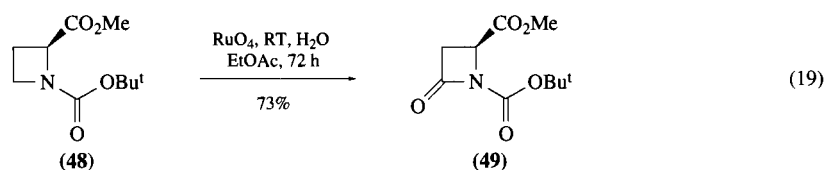


1.18.2.5.7 Oxidation

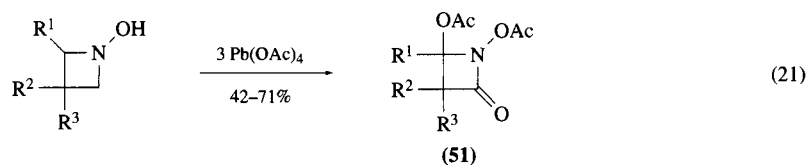
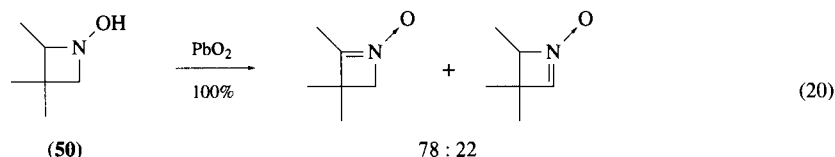
Oxidation of 3-hydroxyazetidines to afford 3-azetidinones is accomplished by chromium trioxide in acetic acid (Equation (17)) <93TL6677> or, under milder conditions, by oxalyl chloride/DMSO (Equation (18)) <91SL783, 93T4201>.



A useful transformation with a great synthetic potential is the oxidative conversion of *N*-*t*-Boc protected azetidines (48) into β -lactams (49) by means of ruthenium tetroxide under two-phase conditions (Equation (19)) <85CPB5515, 86H(24)2539>.

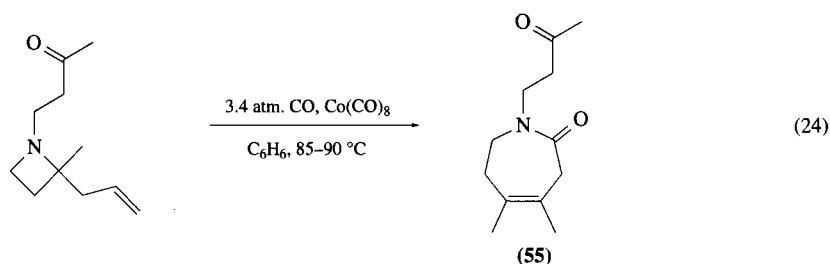
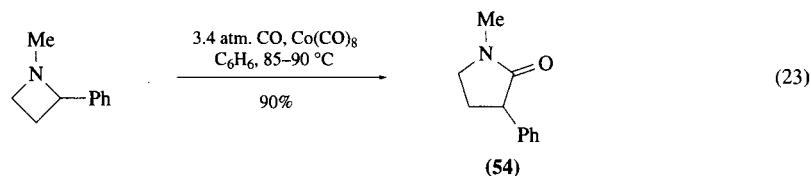
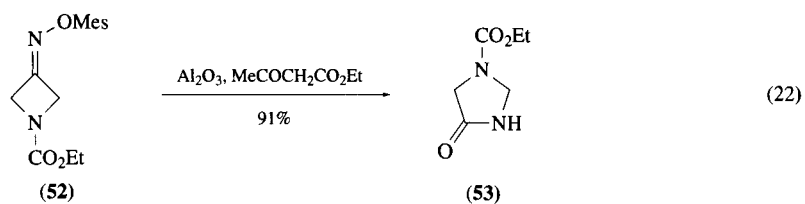


Another type of oxidation concerns the transformation of 1-hydroxyazetidines (**50**) into 1-azetine *N*-oxides by lead(IV) oxide (Equation (20)) <83JOC4043, 83TL825>. When an excess of lead tetraacetate is used as oxidant, 1-hydroxyazetidines are converted into 1,2-diacetoxy-2-azetidinones (**51**) <85TL2809, 87H(26)437>.

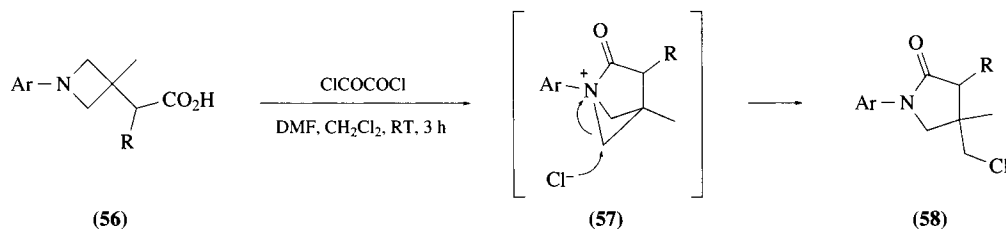


1.18.2.5.8 Miscellaneous reactions

The Beckmann rearrangement of 3-(mesyloxyimino)azetidines (**52**) over alumina gave the imidazolidine-4-one (**53**) in high yield (Equation (22)) <86H(24)25, 86H(24)2467>. The cobalt carbonyl-catalyzed carbonylation of azetidines afforded pyrrolidinones (**54**). For 2-substituted azetidines (2-substituent = alkyl, aryl, CH₂OH, COMe, CH₂Ac, CH₂OMe) the carbonyl insertion occurs into the more or less substituted ring C—N bond, depending on the kind of substituent and on the reaction temperature <89JA7539>. Alkenic double bonds in the side chain can alter the course of the reaction into the direction of tetrahydroazepine derivatives (**55**) <89JA7539>.



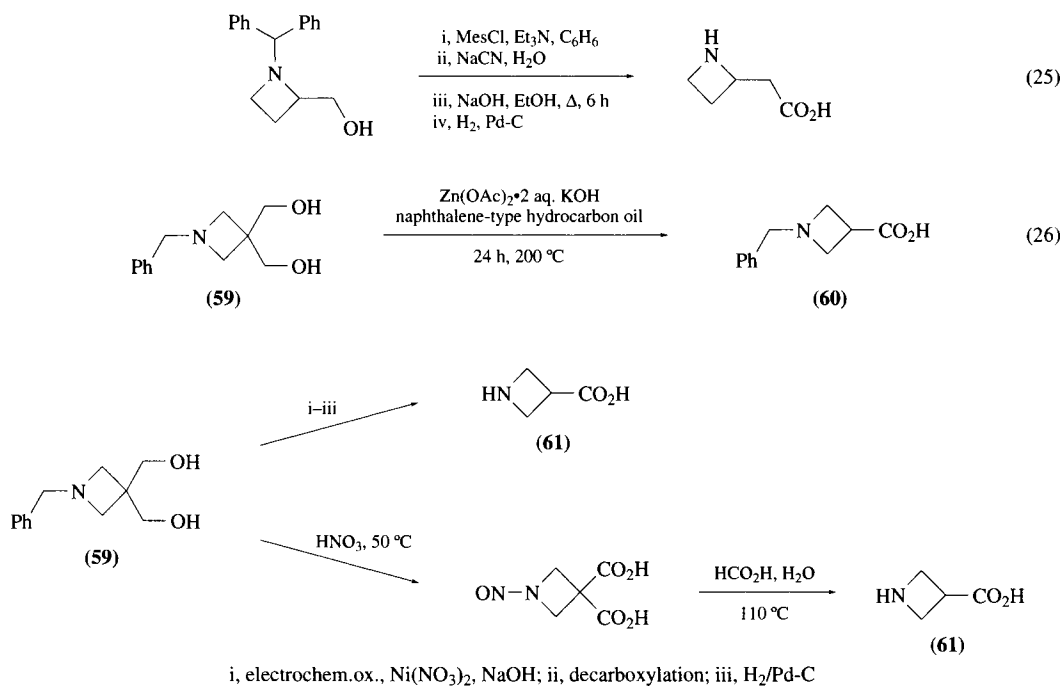
Intramolecular acylation of an azetidine (**56**) via reaction with oxalyl chloride produced a bicyclic intermediate (**57**) which was opened by chloride anion to furnish the *N*-dealkylated end product, which is a 2-pyrrolidone (**58**) <91TL4799>.



Scheme 14

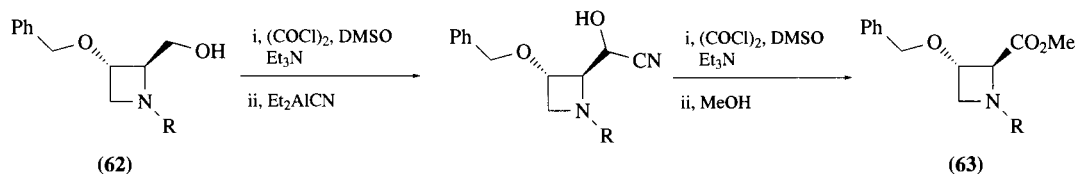
1.18.2.6 Reactivity of Substituents Attached to Ring Carbon Atoms

Nucleophilic substitution at 2-(mesyloxymethyl)- and 3-(chloromethyl)-substituted azetidines by acetate or cyanide has been reported without any indication that the reaction occurs by intramolecular participation of the nitrogen atom <84EUP140437, 86USP4620866>. This type of cyanation has been amply employed for the synthesis of the corresponding carboxylic acids, which have been shown to be useful as male sterilants for plants (Equation (25)) (see the Section 1.18.2.10. on applications). The azetidine-3-carboxylic acids have been prepared by hydrolysis of azetidine-3-carbonitriles <86EUP169602, 86EUP169603>, and by catalytic oxidation of 3-(hydroxymethyl)-2-azetidines and subsequent catalytic reduction <86EUP190786>. Alternatively, azetidine-3-carboxylic acids (**60**) were synthesized by oxidation of 3,3-di(hydroxymethyl)azetidines (**59**) by zinc acetate at 200 °C (Equation (26)) <87JAP6281367>, by HNO₃ at 50 °C and subsequent treatment of the intermediate 1-nitrosoazetidine-3,3-dicarboxylic acid with aqueous formic acid <85EUP165636>, or by electrochemical oxidation and following decarboxylation/hydrogenolysis processes to form (**61**) (Scheme 15) <86EUP199413>.

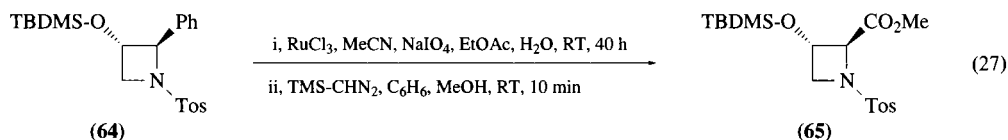


Scheme 15

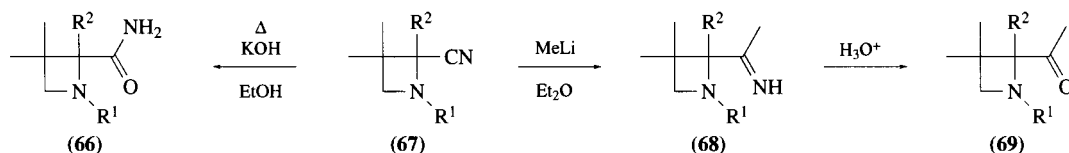
The conversion of 2-(hydroxymethyl)azetidines (**62**) into azetidine-2-carboxylic methyl esters (**63**) has been reported to proceed via Swern oxidation to the aldehyde, cyanation with diethylaluminum cyanide, repeated Swern oxidation, and methanolysis $\langle 93T4201 \rangle$. Alternatively, 2-phenylazetidines (**64**), carrying electron-withdrawing substituents at nitrogen, have been converted directly into the corresponding azetidine-2-carboxylic acid (**65**) by oxidation with ruthenium(III) chloride in the presence of sodium periodate (Equation (27)). Esterification with trimethylsilyldiazomethane finally led to the methoxycarbonyl derivatives $\langle 92TL7921, 94T265 \rangle$.



Scheme 16

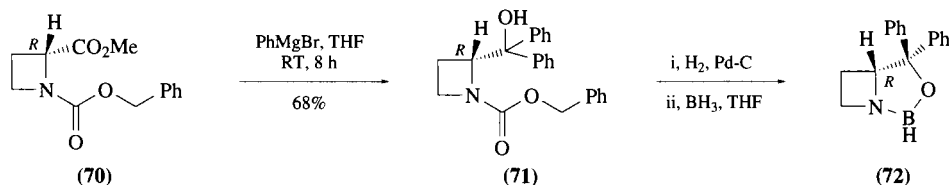


Functional group transformation of azetidine-2-carbonitriles (**67**) is easily accomplished without competitive reactions. Alkaline hydrolysis affords azetidine-2-carboxamides (**66**), while the addition of methyllithium across the nitrile function produces stable 2-acetimidoyl-substituted azetidines (**68**), which are readily hydrolyzed in acid medium to 2-acetylazetidines (**69**) $\langle 85CC715, 88T3653 \rangle$.



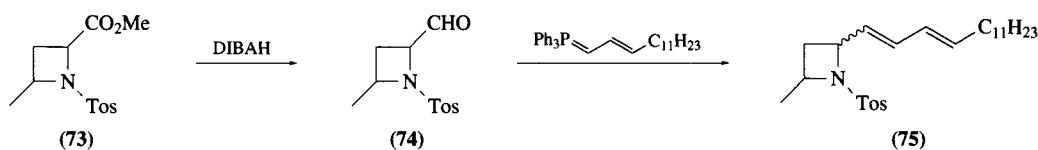
Scheme 17

Other organometallic reagents, such as Grignard reagents, add across the ester moiety of enantiomerically pure azetidine-2-carboxylic methyl ester (**70**) (both pure enantiomers have been used; only the (*R*)-isomer is given in Scheme 18) to give the tertiary alcohol (**71**), which has been converted into oxazaboronolidine (**72**) $\langle 92TA859 \rangle$. The latter compounds have been used for the enantioselective catalytic borane reduction of ketones $\langle 92SC2143, 92TA859, 92TA1475 \rangle$.

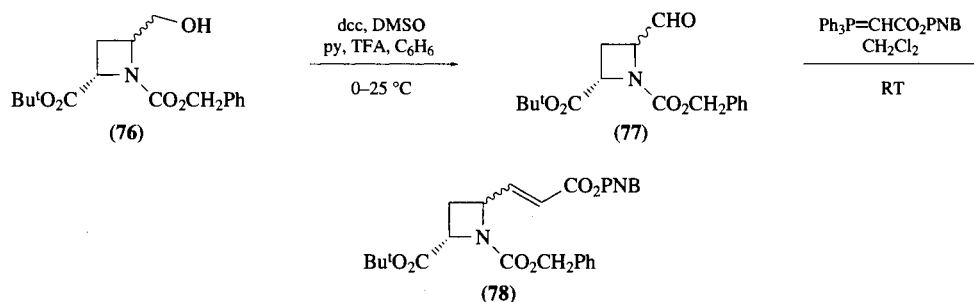


Scheme 18

Azetidine-2-carbaldehydes (**74**) are accessible from azetidine-2-carboxylic esters (**73**) by reaction with diisobutylaluminum hydride (Scheme 19). This conversion is usually followed by a Wittig reaction with a variety of alkylidenephosphoranes to form (**75**) $\langle 85TL857, 89T3089 \rangle$. An alternative procedure to azetidine-2-carbaldehydes (**77**) is the oxidative conversion of 2-hydroxymethyl derivatives (**76**). Again the aldehydes serve as suitable substrates for a Wittig olefination reaction to provide unsaturated azetidines (**78**) $\langle 85CC194 \rangle$.



Scheme 19

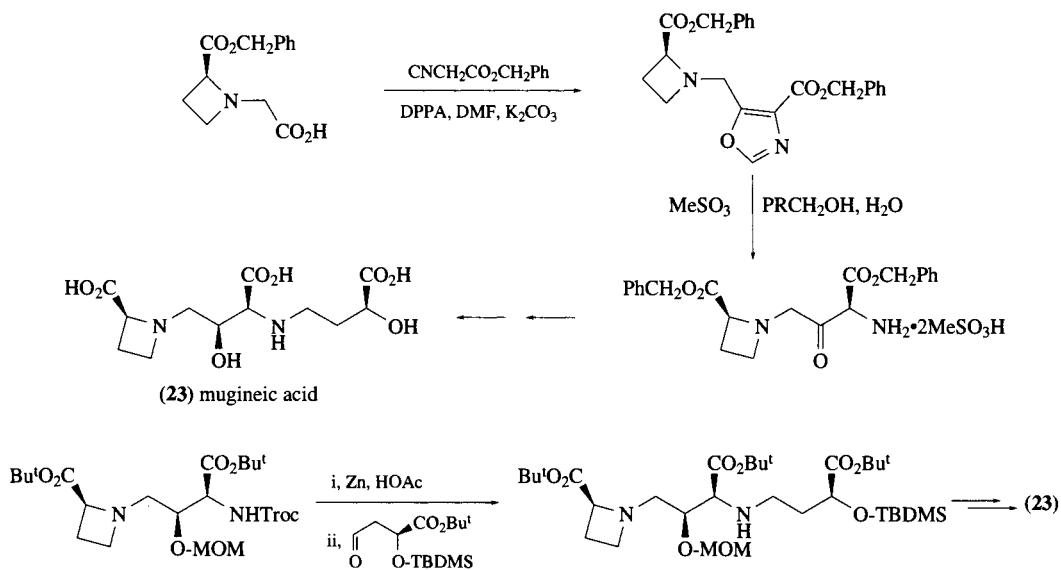


Scheme 20

1.18.2.7 Reactivity of Substituents Attached to Ring Nitrogen Atoms

The classical removal of suitable substituents at nitrogen has been applied routinely with azetidine derivatives. It has been shown that *N*-debenzylation or *N*-debenzhydrylation works well by hydrogenolysis over a palladium catalyst, with or without added hydrogen chloride (85CC194, 85EUP140437, 88HCA1035, 88SC205, 89EUP299513, 90JMC1561). The *N*-benzyloxycarbonyl and Boc groups are easily removed on azetidine derivatives by means of hydrogenolysis and trifluoroacetic acid, respectively (85CC194, 92T7165). Removal of *N*-tosyl groups can be accomplished by alkali metals in an alcoholic solvent (87URP1323557).

The nitrogen substituent of azetidines is often used as an auxiliary to direct certain reactions in the desired way or to protect the nitrogen atom. Accordingly, most of such substituents are removed or replaced in a later stage of the synthetic scheme. There are no specific developments reported, other than those known for pyrrolidines or piperidines. Only in the area of the synthesis of mugineic acid-type derivatives have elaborations of *N*-substituents played a significant role (Scheme 21) (86JOC5489, 86JPR719, 87JPR231, 92SL527, 92TL7917, 92TL7921, 93T8211).



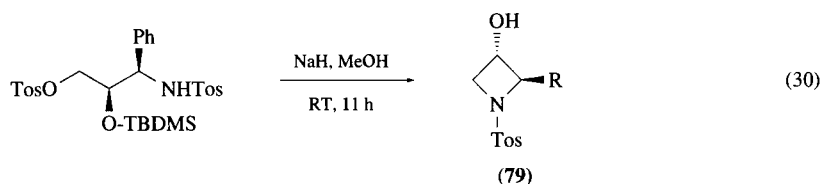
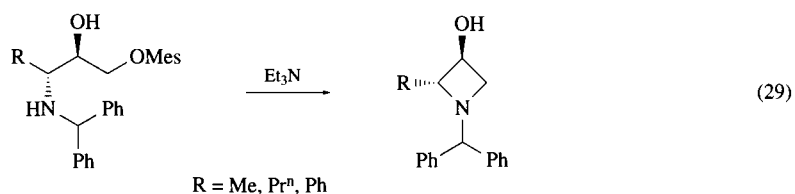
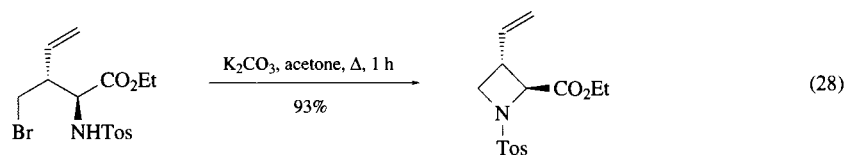
Scheme 21

1.18.2.8 Ring Synthesis

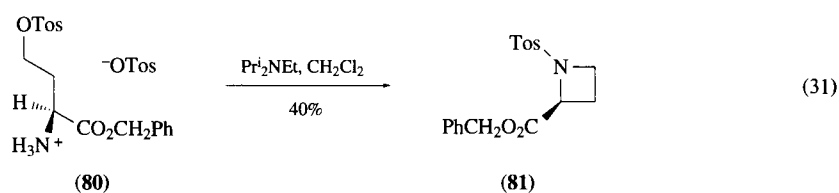
There are a number of classical azetidine syntheses, which have been treated already in CHEC-I. The principle of these reactions will be repeated, but focus will be given to new aspects of these syntheses, for example, improvements of reaction conditions, valuable extensions, side reactions, scope, and limitations, etc.

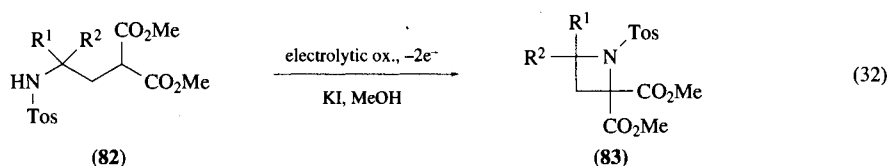
1.18.2.8.1 Ring closure of γ -haloamines

A very powerful method for the synthesis of azetidines is the cyclization of amines, carrying a leaving group at the γ -position (Equation (28)). A kinetic study of the cyclization of γ -chloroamines in aqueous sodium hydroxide revealed a low cyclization ability, due to an entropic factor, as compared to the β -chloroamine cyclization to aziridines <90ZOB625>. Leaving groups, such as bromo, chloro, iodo, tosyloxy, mesyloxy, and trifluoromethanesulfonyloxy, have been used, while the amino group can have substituents such as alkyl, aryl, or tosyl (Equation (29)) <85EUP161722, 87SC469, 88HCA1025, 92MI 118-02, 93JHC1197>. The combination of tosylamides and the tosyloxy leaving group has been found to give good results in the synthesis of azetidines with a desired stereochemistry (79) (Equation (30)) <92TL7921, 93TL6677, 94T265>.

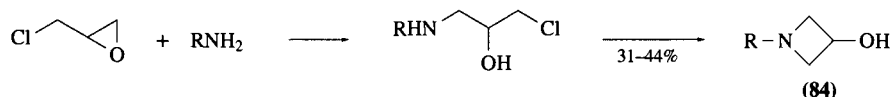


The ammonium salt (80), derived from L-methionine, underwent cyclization with Hünig base to afford *N*-tosyl azetidine ((81) as an unstable oil, and not the expected L-azetidine carboxylic acid benzyl ester (Equation (31)) <88T637>. The electrolytic oxidation of [2-(4-methylbenzenesulfonylamino)alkyl]malonates (82) in the presence of potassium iodide generates a γ -iodosulfonamide which cyclized to the azetidine (83) (Equation (32)) <88CL1065>.

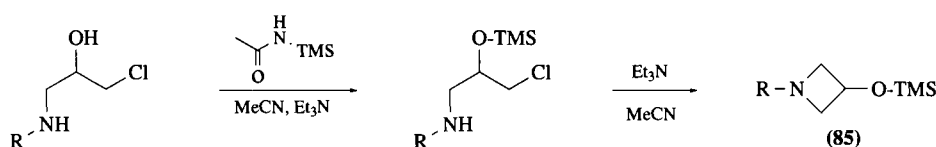




From epihalohydrins γ -halo- β -hydroxyamines are readily accessible. As such the synthesis of 3-hydroxyazetidines (**84**) (3-azetidinols) can be considered as an azetidine synthesis by transformation of another heterocycle, the topic of Section 1.18.2.9.1. However, because of the fact that γ -chloro- β -hydroxyamines are isolable from this reaction <84EUP125714, 87JHC1489>, this conversion is treated in this section. The classical condensation of epichlorohydrin with hindered amines, for example, 1-adamantyl- and 1-cyclododecylamine, to give 3-hydroxyazetidines (**84**) in moderate yields was reinvestigated <89CJC1514>. It is remarkable that this reaction with secondary amines gave complex reaction mixtures, leading to diaminodioxanes, diaminoalcohols, aminoalcohol ethers, etc. The conversion of epichlorohydrin with primary amines, from which the substituent can be removed conveniently (e.g., benzyl-, benzhydrylamine), into 3-azetidinols has been applied several times, despite the sometimes extremely long reaction times <84EUP125714, 86JHC1503, 88JHC383, 90JOC2920, 91JOC6729, 91SL783>. An adaption of this method concerns the use of trimethylsilyl ethers derived from γ -chloro- β -hydroxyamines, giving 3-azetidinol trimethylsilyl ethers (**85**). This method is efficient in circumventing the slow displacement of chloride by amines <87JHC1489, 88JHC383>. There appears to be little or no advantage in the use of trialkylsilyl substituents larger than trimethylsilyl <87JHC1489>.

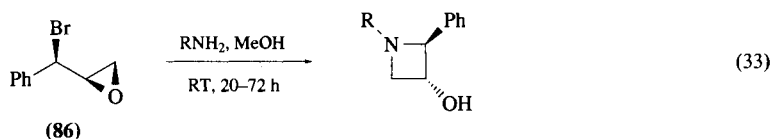


Scheme 22



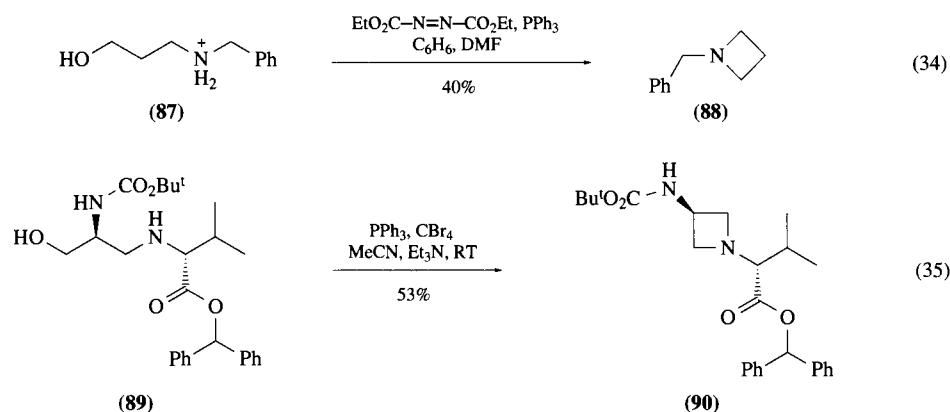
Scheme 23

Higher substituted epihalohydrins, for example, epibromohydrin (**86**), were convenient sources for the construction of the 3-azetidinol skeleton with a defined stereochemistry <92H(33)511>.



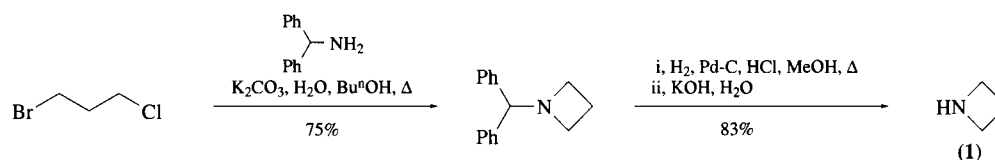
1.18.2.8.2 Ring closure of γ -aminoalcohols

From the cyclization of γ -aminoalcohols or γ -azidoalcohols azetidines can be produced via activation with phosphines <81JOC3562, 84JCS(P1)2415, 85TL2809, 92OPP209>. However, the yields of azetidines are moderate to good as exemplified for the conversion of the hydrobromide of 3-(benzylamino)-1-propanol (**87**) into 1-benzylazetidine (**88**) in 40% yield (Equation (34)) <83CC682, 84JCS(P1)2415>. The transformation of γ -aminoalcohol (**89**) into the protected 3-aminoazetidine (**90**) is accomplished by triphenylphosphine in the presence of tetrabromomethane (Equation (35)). The latter method seems to be mild and effective for the synthesis of simple azetidines, for example, 2-butyl-1-methylazetidine <83CC682, 84JCS(P1)2415>.



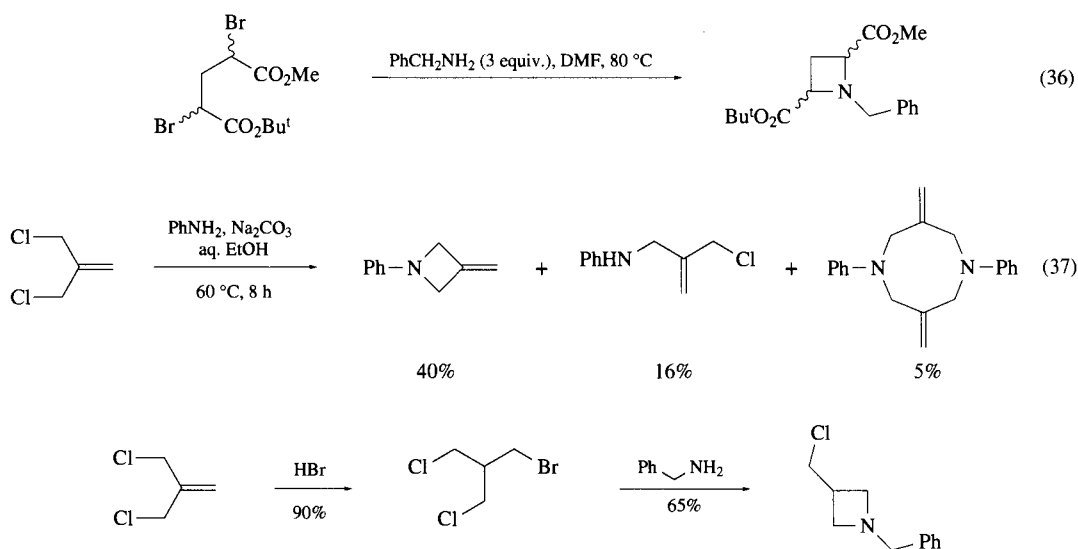
1.18.2.8.3 Ring closure of 1,3-dielectrophiles with primary amines

The difficulties involved in the preparation and isolation of azetidine (1), the parent structure, are out of proportion to its simple structure. A practical synthesis of azetidine on the kilogram scale involved the condensation of 1-bromo-3-chloropropane with benzhydramine to give 1-benzhydrazetidine in 75% yield. After which, hydrogenolysis of the hydrochloride salt and basic workup of the aqueous concentrate of azetidine hydrochloride resulted in azetidine in 83% yield after flash distillation (Scheme 24) <88SC205>.

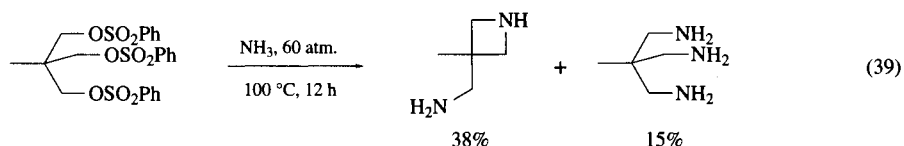
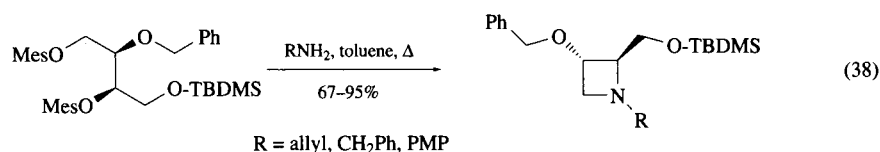


Scheme 24

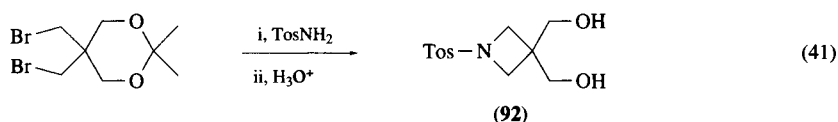
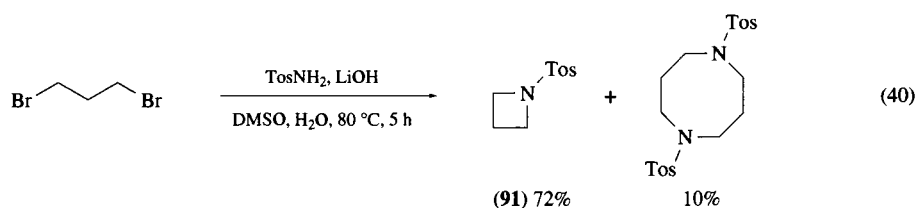
Other 1,3-dielectrophiles that have been reacted with primary amines for azetidine syntheses include 1,3-dibromides (Equation (36)) <85CC194, 89EUP299513, 89T3089, 90JMC1561>, 1,3-dichlorides (Equation (37)) <89T629, 89ZOR2453>, 1-bromo-3-chlorides (Scheme 25) <84EUP140437>, 1,3-dimesylates (Equation (38)) <89T629, 93T4201>, 1,3-benzenesulfonates (Equation (39)) <85IC2559>, and 1,3-ditosylates <89T629>. Several of these 1,3-dielectrophiles were substituted with various functionalities enabling specific constructions of novel target azetidines, some examples of which are given in the accompanying scheme. Some of these transformations suffer from severe competitive reactions.



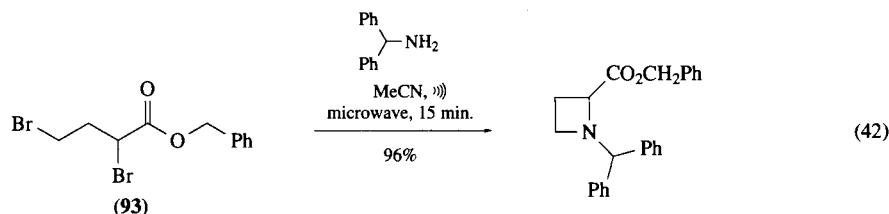
Scheme 25



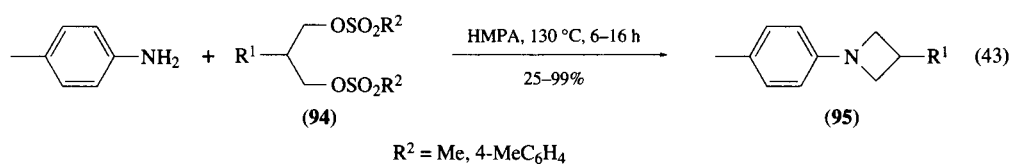
Tosylamide has also been used for the synthesis of *N*-tosylazetidines (**91**) and (**92**) utilizing 1,3-dibromides (Equations (40) and (41)) <84EUP114079, 85MI 118-01>.

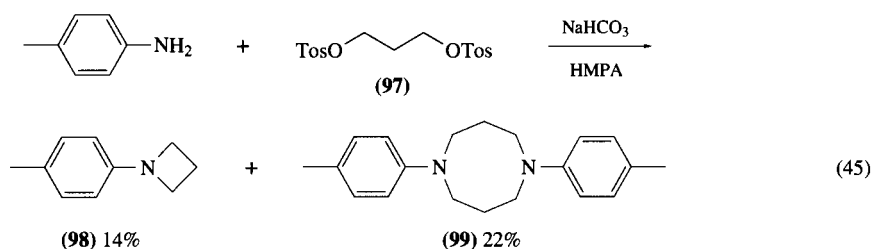
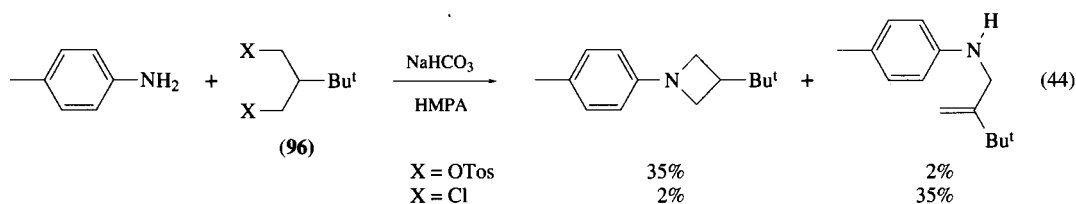


The known reaction of benzyl 2,4-dibromobutanoate (**93**) with benzhydrylamine was reported to require 24 h of reflux in order to get an 82% yield. If microwave irradiation was applied, the reaction was completed in 15 min and furnished a yield of 96% (Equation (42)) <92TA859>.



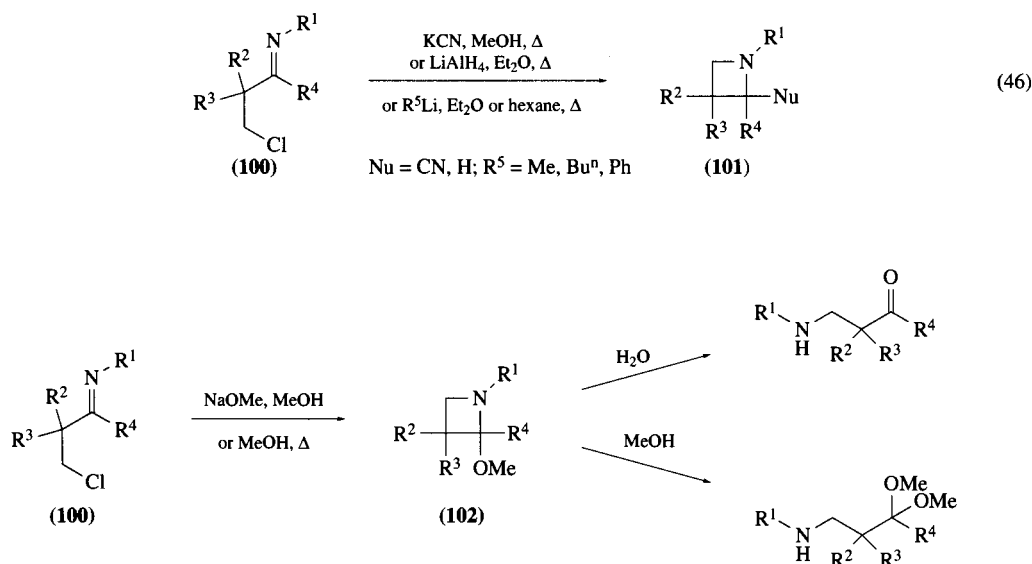
A major drawback of the reaction of 1,3-dielectrophiles with primary amines is the competitive elimination to the corresponding allylamines. Especially, 1,3-dihalides suffer from this disadvantage <84TL3521, 89T629>. The low tendency for cyclization in azetidines is ascribed to the unfavorable activation enthalpy because the activation entropy for aziridines and azetidines is about equal. The condensation of 1,3-dielectrophiles with *p*-toluidine has been investigated in detail <84TL3521, 89T629>. Reaction of 1,3-disulfonates (**94**) with *p*-toluidine in HMPA at 130 °C gives azetidines (Structure (**95**)) in 25–99% yield (Equation (43)). In general, 1,3-dihalides (**96**) afford lower yields due to the above mentioned competitive elimination reaction (Equation (44)). However, even with 1,3-ditosylates, for example, (**97**), the competitive formation of 1,5-diazocines, for example, (**99**), or tetrameric structures cannot be avoided resulting in only very low yields of azetidines, for example, (**98**).





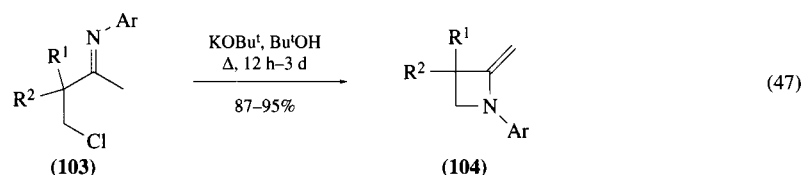
1.18.2.8.4 Ring closure of β -chloroimines

It is known that β -chloroimines are suitable substrates for the synthesis of azetidines without competitive reactions. The addition of nucleophiles, such as cyanide, hydride, or organolithium reagents, to β -chloroimines (**100**) proceeds by nucleophilic addition to give an adduct, such as a γ -chloroamine or γ -chloroamide, which undergoes ring closure in a rate determining step to give azetidines (**101**) [85CC715, 88T3653, 93S89]. On the other hand, the reaction of β -chloroimines (**100**) with sodium methoxide in methanol or methanol alone affords rearranged β -aminoacetals or β -aminoketones via intermediate 2-methoxyazetidines (**102**), which can only be isolated in the case of *N*-aryl derivatives (Scheme 26) [89T2937]. The intermediacy of 2-methoxyazetidines could be proved by trapping experiments with potassium thiocyanate to give perhydropyrimidine-2-thiones [89JOC2587].

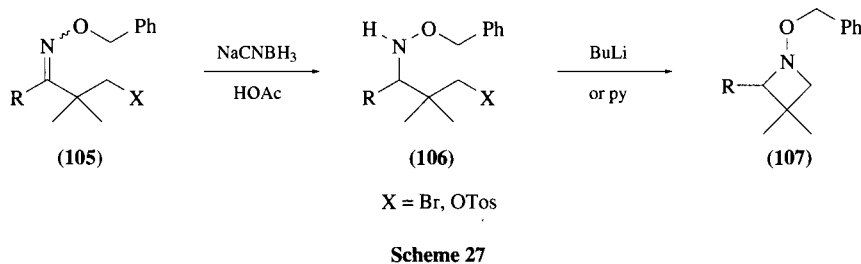


Scheme 26

A convenient way for the synthesis of 2-methyleneazetidines (Structure **104**) involves the reaction of *N*-aryl β -chloroimines (Structure **103**) with potassium *t*-butoxide in *t*-butanol under reflux for an extended period (Equation (47)) [88JOC4462].

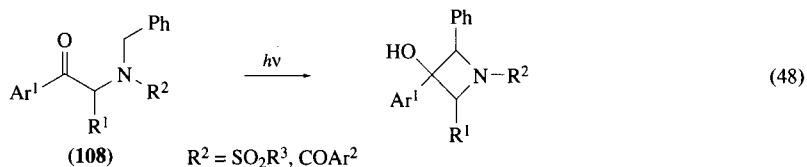


A related synthesis of the azetidine ring consists of the reductive cyclization of β -tosyloxy- or β -bromo-*O*-benzyl oximes (**105**) to 1-benzylazetidines (**107**) via reduction with sodium cyanoborohydride and ring closure of the resulting β -tosyloxy- or β -chlorobenzylamine (**106**) with butyllithium or pyridine (Scheme 27) <83JOC4043>.

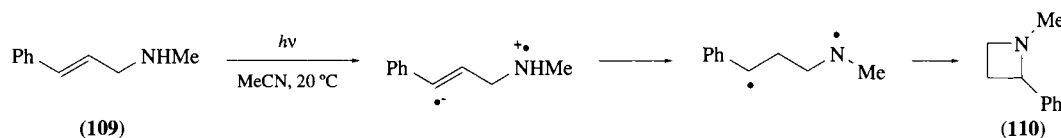


1.18.2.8.5 Photochemical syntheses of azetidines

The previously known photochemical cyclization of β -amino ketones (**108**) to give 3-azetidinols has been applied to various substrates (Equation (48)) <92T6747, 93TL5855>. Some of the photocyclizations of β -amino ketones, for example, phenacylamides, proceeded diastereoselectively <84JPR177>.



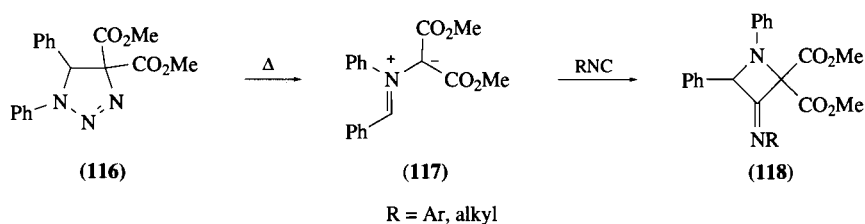
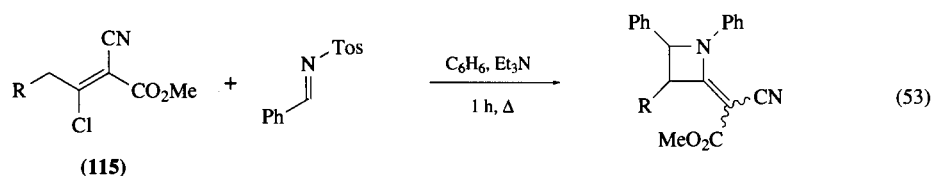
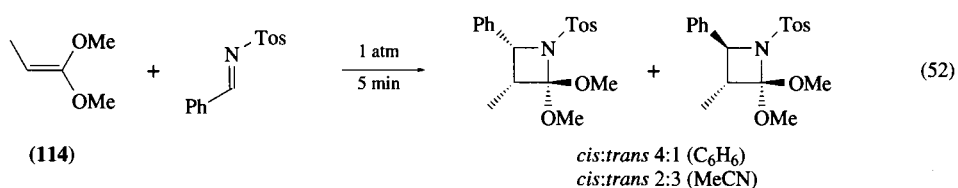
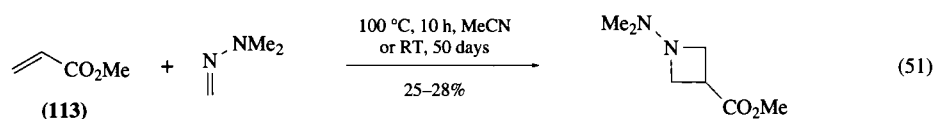
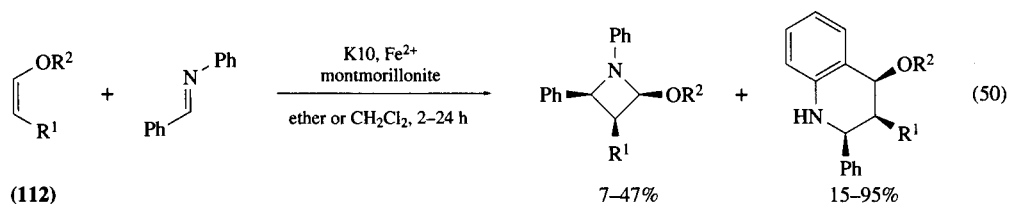
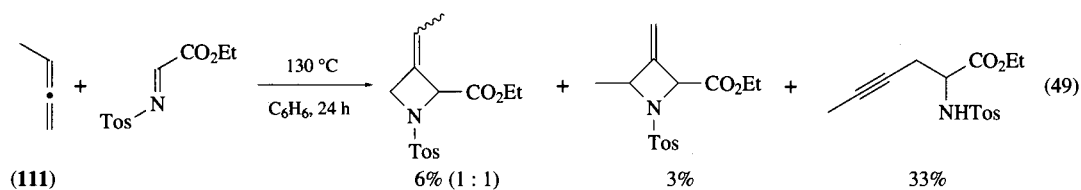
The photochemical reaction of enaminoketonatoboron difluorides with (*E*)-stilbene afforded azetidines and cyclobutanes in a regio- and stereospecific manner <92CC1608>. The solid state photochemical reaction of *N*-acetyl α -cyanocinnamaldimine to give a functionalized azetidine via a [2 + 2] cycloaddition is primarily the result of topochemical control <91JOC6840>. The photochemical cyclization of *N*-methyl cinnamyl amine (**109**) gave 1-methyl-2-phenylazetidine (**110**) in low yield, in which the selectivity for aziridine formation was low (Scheme 28) (azetidine:aziridine > 20:1) <89JA6465>.



1.18.2.8.6 Cycloaddition reactions leading to azetidines

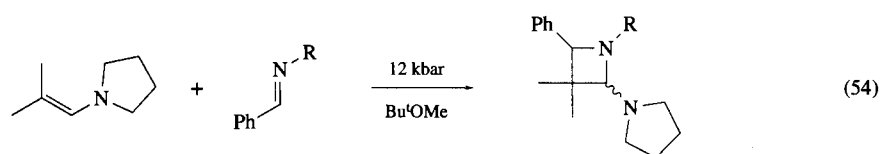
A number of cycloadditions of imines or imino compounds with a variety of alkenes, including allenes (**111**) <88HCA1025>, vinyl ethers (**112**) <88TL547>, methyl acrylate (**113**) <86ZOR636>, ketene acetals (**114**) <87JOC365>, and electrophilic alkenes (**115**) <85T1953> have been reported to afford functionalized azetidines. The [3 + 1] cycloaddition of azomethine ylides, for example, (**117**),

generated from 1,2,3-triazolines or 1-phthalimido-2,3-dicyanoaziridines with isonitriles affords 3-iminoazetidines (**118**) <82JHC1315, 83JOC481>.



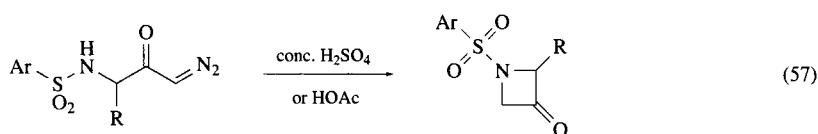
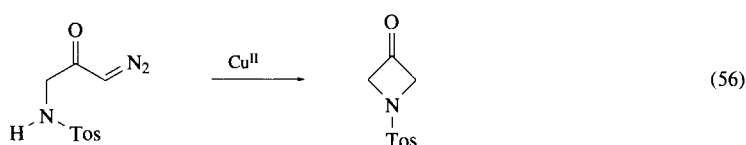
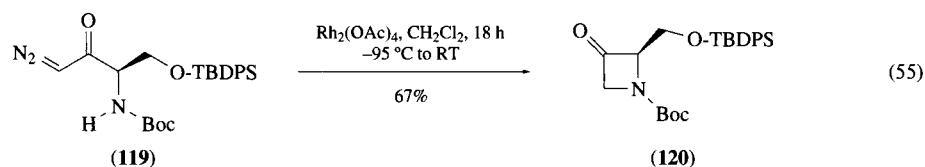
Scheme 29

The high pressure promoted [2 + 2] cycloaddition of imines with electron-rich alkenes, for example, enamines, to give 2-aminoazetidines requires a pressure of 12 Kbar (Equation (54)) <87JOC365>.



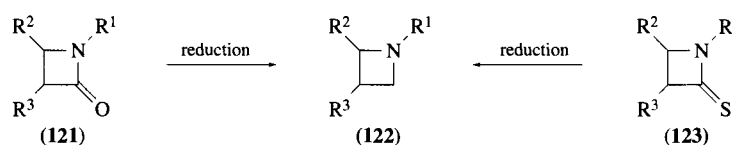
1.18.2.8.7 Metal catalyzed insertion reactions of diazo compounds

A powerful route to functionalized azetidines, for example, (120), is the rhodium-catalyzed insertion of diazo compounds (119), carrying an amino function (Equation (55)) <85JOC5223, 92T7165, 93TL4157>. This reaction was mostly used with 3-amino-2-keto-1-diazo compounds, leading to the corresponding 3-azetidinones. This intramolecular NH insertion can also be carried out under Cu^{II} catalysis (Equation (56)) <93TL6677> or proton catalysis (Equation (57)) <85G33, 87KGS468>.



1.18.2.8.8 Azetidine synthesis by reduction of β-lactams

The reduction of 3-azetidinones (121) to azetidines (122) is a powerful synthetic method (Scheme 30), which is covered in Section 1.18.3.4.6, dealing with the chemical properties of β-lactams. The same applies to β-thiolactams (123) the reduction of which is treated in the same section.

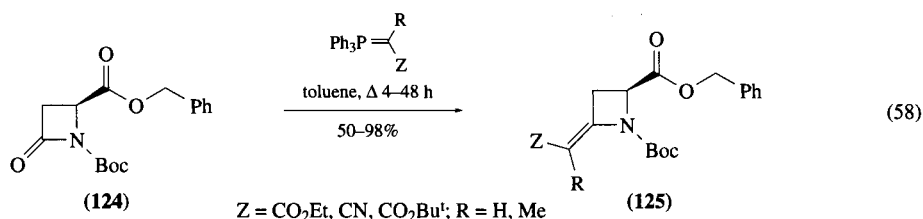


Scheme 30

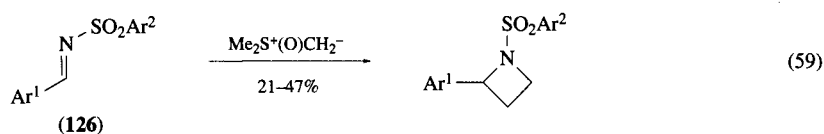
1.18.2.8.9 Miscellaneous syntheses

The aza-Wittig cyclization of β-azidopropiophenone with triphenylphosphine furnishes 2-phenyl-1-azetine, which is reduced *in situ* by hydride to give 2-phenylazetidine in very low yield <87NKK1250>.

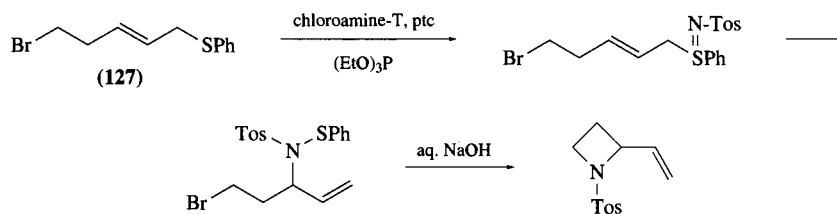
Unstabilized ylides or Horner–Emmons reagents do not afford 2-methyleneazetidines upon reaction with β-lactams. On the other hand, stabilized ylides react with 2-azetidinones (124) to afford 2-methyleneazetidines (125). The Boc protecting group was found to be a suitable *N*-substituent while *N*-silylated β-lactams did not give the Wittig reaction products <93SL49>.



The cycloaddition of *N*-arenesulfonyl arylideneamines (**126**) with dimethyloxosulfoniummethylide led to moderate yields of 1-arenesulfonyl-2-arylazetidines (Equation (59)) <83S554>.

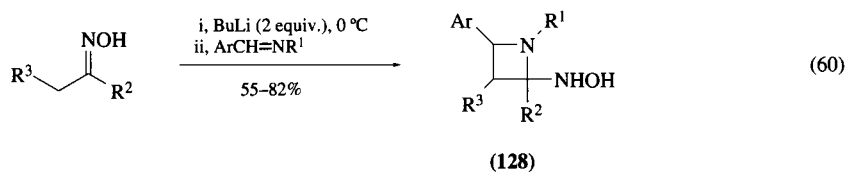


Allylic phenylsulfides (**127**), bearing a bromoethyl substituent, undergo concomitant [2,3]-sigmatropic rearrangement and intramolecular *N*-alkylation upon oxidative conversion to sulfilimines, and treatment with aqueous base (Scheme 31). This method is in fact a general entry into 2-vinylsubstituted cyclic amines <89TL4723>.

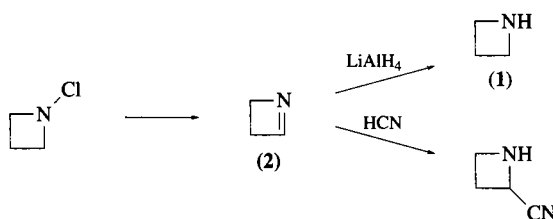


Scheme 31

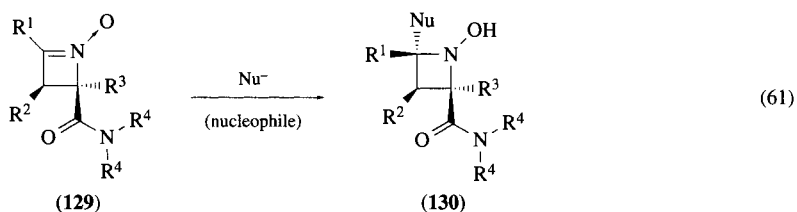
Oxime dianions react with aldimines to produce 2-(hydroxyamino)azetidines (**128**) <83S951>.



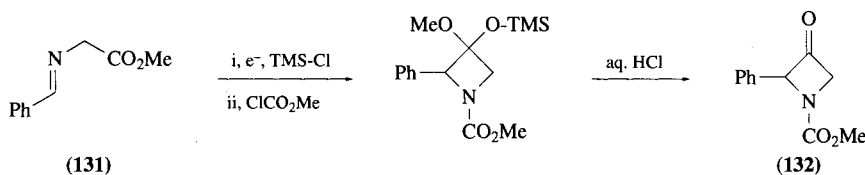
Azetidine (**1**) and azetidine-2-carbonitrile are produced by addition of LiAlH_4 or HCN , respectively, to the labile 1-azetidine (**2**), generated from 1-chloroazetidine *in vacuo* over solid base (Scheme 32) <85S1931>. Similar additions of nucleophiles, for example, cyanide, hydride, or carbanions, across 1-azetidine *N*-oxide (**129**) gave stereoselective addition products, such as 1-hydroxyazetidines (**130**) <88RTC63>.



Scheme 32



The electrochemical conversion of methyl *N*-benzylideneglycinate (131) in the presence of trimethylsilyl chloride affords the silylated hemiacetal of 3-azetidinone (132) <91CL2191>.



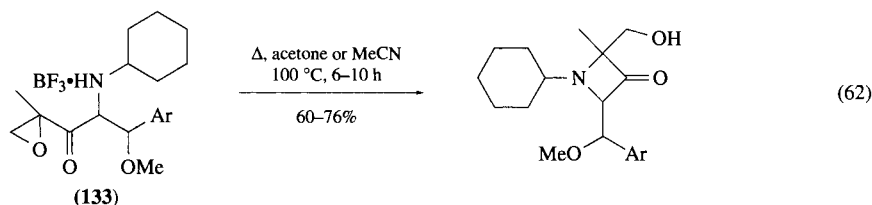
Scheme 33

1.18.2.9 Ring Synthesis by Transformation of Another Ring

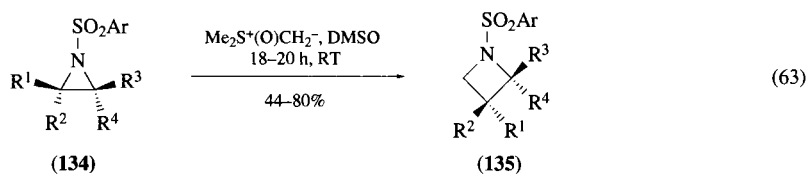
1.18.2.9.1 Ring synthesis by transformation of three-membered rings

The ring transformation of epichlorohydrin with primary amines to 3-azetidinols is treated in Section 1.18.2.8.1.

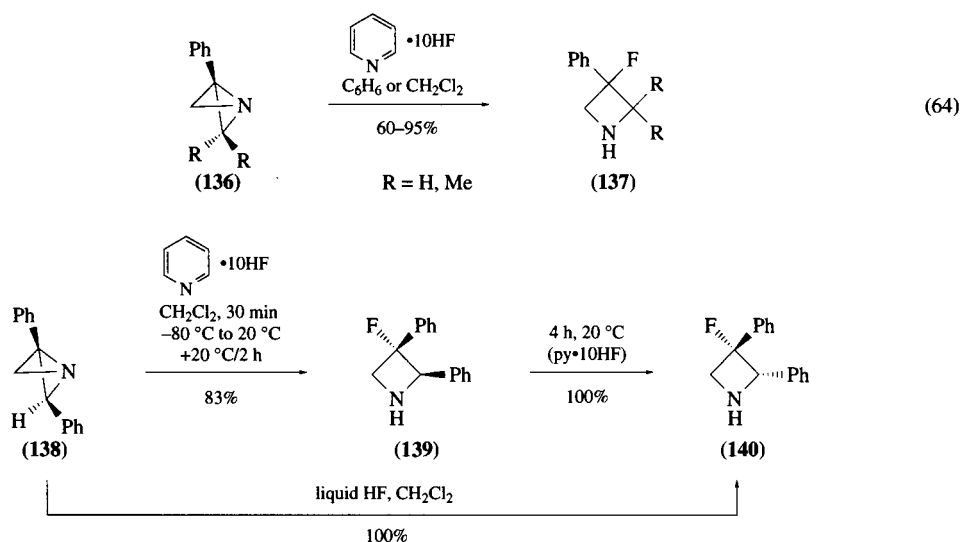
Complexes of BF₃-α-amino-α',β'-epoxyketones (133) rearrange thermally to give 2-(hydroxymethyl)-3-azetidinones via an intramolecular S_N2-reaction (Equation (62)) <88KGS307>. Without complexation, the reaction leads to 3-furanones <88KGS307>.



Ring expansion of *N*-arenesulfonylaziridines (134) occurs with dimethyloxosulfonium methylide to afford *N*-arenesulfonylazetidines (135). *cis*-Aziridines yield *trans*-azetidines and *trans*-aziridines furnish *cis*-azetidines via an S_N2-type reaction and intramolecular nucleophilic substitution <89T1851>.

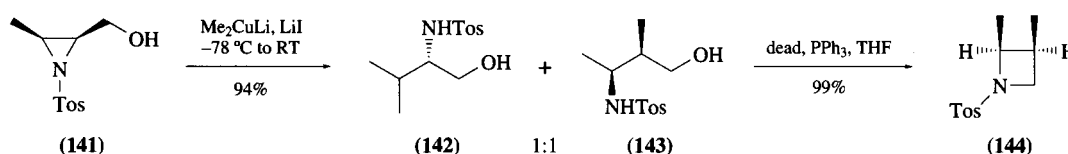


Ring opening of 1-azabicyclo[1.1.0]butanes (136) with Olah's reagent (pyridine, 10HF) gives a ready access to 3-fluoroazetidines (137) <85JFC(29)363>. The diphenyl derivative (138) affords the *cis*-derivative, which could be isomerized quantitatively into the *trans*-derivative (140) (Scheme 34). The latter is also obtained from (138) by liquid hydrogen fluoride <85JFC(29)363>.



Scheme 34

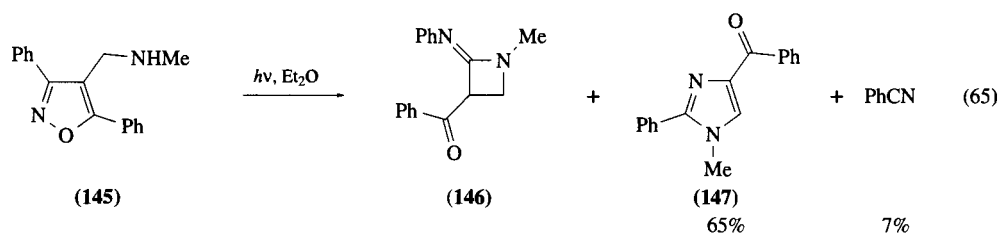
Nonregioselective ring opening of 2-(hydroxymethyl)aziridines (**141**) occurs by lithium dimethylcuprate to give amino alcohols (**142**) and (**143**), the latter being transformed into stereochemically pure azetidine (**144**) by PPh₃/diethyl azodicarboxylate (Scheme 35) <93TL7421>.



Scheme 35

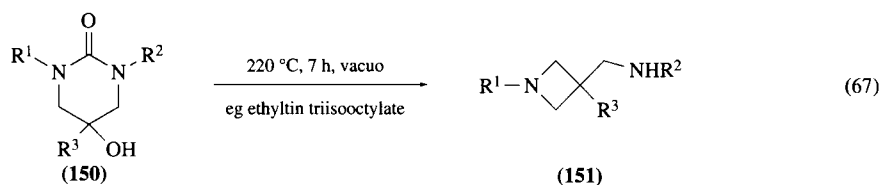
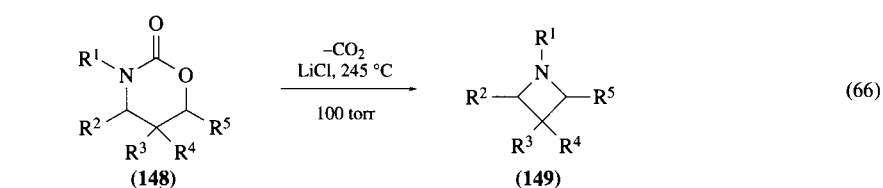
1.18.2.9.2 Ring synthesis by transformation of five-membered rings

Photolysis of isoxazole (**145**) produced 2-iminoazetidines (**146**) via N—O cleavage, phenyl migration to give an intermediate ketenimine, and cyclization, imidazole (**147**) being the major product (Equation (65)) <91G329>.



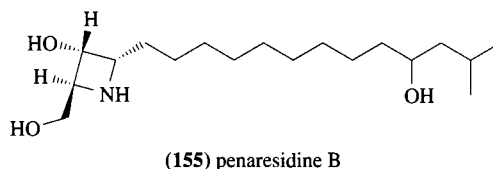
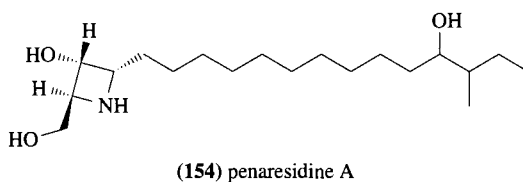
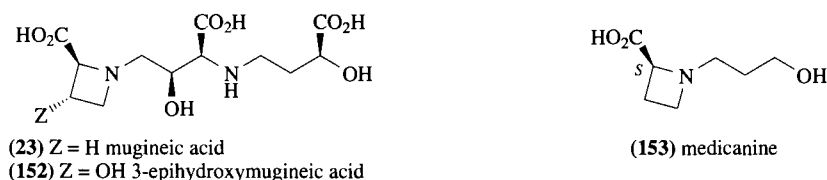
1.18.2.9.3 Ring synthesis by transformation of six-membered rings

Decarboxylation of tetrahydro-1,3-oxazin-2-ones (**148**) at 245 °C under a pressure of 10 torr and in the presence of lithium chloride produced azetidines (**149**), for example, 1-benzyl-3,3-dimethylazetidine in 85% yield <85USP4529544>. The transition metal-catalyzed thermolysis of propyleneureas (**150**) generates 3-(aminomethyl)azetidines (**151**) <88GEP(O)3627246>.



1.18.2.10 Important Compounds and Applications

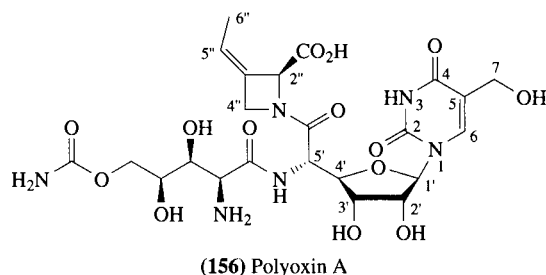
An increased research on phytosiderophores, for example, iron-chelating amino acids, isolated from graminaceous plants, has been noted. Focus was given, among others, to mugineic acid (**23**) and 3-epihydroxymugineic acid (**152**) <86JOC5489, 89JA3436, 92TA1069, 92TL7917, 92TL7921, 93T8211, 94T265>. The most efficient precursor of the mugineic acid family appears to be L-methionine, based on ^{15}N and ^{14}C incorporation studies <93MI 118-02, 93MI 118-03>. Medicanine (**153**) is a natural product isolated from seedlings of *Medicago sativa* <84H(22)1039>. Penaresidine A (**154**) and penaresidine B (**155**) are two functionalized azetidines, isolated from the Okinawan marine sponge *Penares sp.* These sphingosine-derived azetidine alkaloids are potent actomyosin ATPase activators <91JCS(P1)1135>.



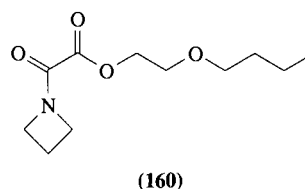
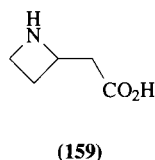
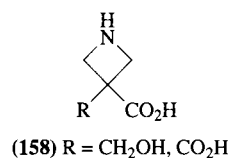
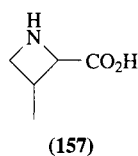
The antifungal antibiotics of the polyoxin group, for example, polyoxin A (**156**), contain polyoximic acid (**14**) as a structural unit <93TL4157>. Polyoxins are peptidyl nucleoside antibiotics isolated from the culture broth of *Streptomyces cacaoi var. asoensis* <69JA7490>.

The stereochemistry of the exocyclic double bond in polyoximic acid has been revised to *cis*-3-ethylidene-L-azetidine-2-carboxylic acid (**14**), based on x-ray analysis, NMR studies of polyoxin A, and synthesis of both *cis*- and *trans*-polyoximic acid <93TL4153, 93TL4157>.

Since 1985 a large number of patents have been taken on agrochemical applications of azetidine derivatives. It is known that azetidine-2-carboxylic acid (Structure (**19**)) acts as a growth regulator



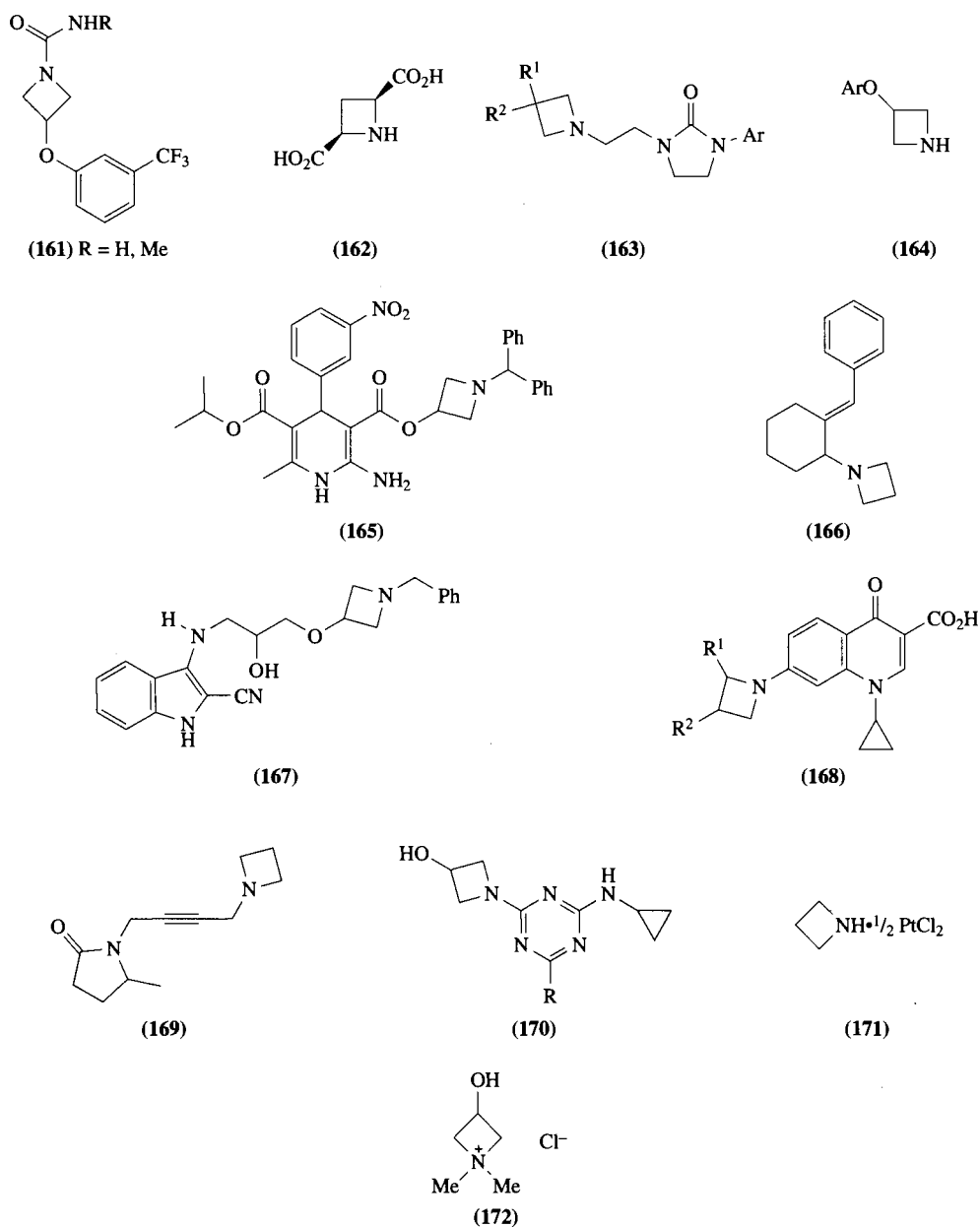
<86MI 118-01, 91P3859> and related amino acids also have potential applications. A use for 3-methylazetidine-2-carboxylic acid (**157**) is as a sterilizing agent for male plants, for example, cereal grains <85USP4560401>. A potential use of azetidine-3-carboxylic acid (**61**) is as a chemical hybridizing agent for wheat <91P3859>. Depending on the application it is referred to as a gametocide <89USP4812581>, sterilant, or plant growth regulator <85EUP140437>. Also *N*-substituted azetidine-3-carboxylic acid (**60**) is a male plant sterilant <87JAP(K)6281367>, while 3-substituted azetidine-3-carboxylic acids (**158**) are reported to be useful as plant breeding chemical hybridizing agents <85EUP165636, 85EUP165637>. Some applications of 2-azetidinylacetic acid (**159**) are as a male sterilant for plants, preventing cross pollination, and in the production of F_1 hybrid seed <84EUP114706, 86USP4620866>. The 2-(1-azetidinyloxy)acetates, for example, (**160**), are plant growth regulators which are superior to *N*-(2-chloroethyl)-*N,N,N*-trimethylammonium chloride for summer wheat, summer barley, and rice <90EUP350693, 92EUP469374>.



There are numerous potential applications of azetidines in the pharmaceutical field. The study of antiepileptic and anticonvulsant properties of azetidines, for example, (**161**), is well documented <83USP4379151, 84EUP102194, 84EUP102740, 86EUP194112, 86USP4571393, 87MI 118-01, 88CBR231, 90MI 118-01, 90USP4956359, 90USP5095014, 92USP5130309, 93USP5183903>. An effect of 3-oxygenated azetidines is as inotropic agents <91BJP193>. It is known that *cis*-azetidine-2,4-dicarboxylic acid (**162**) acts as a neurotransmitter potentiator <89EUP299513, 90JMC1561>, which activates neuronal metabotropic receptors <93MI 118-04>. Azetidines (**163**) are reported as neuroleptic agents <83GEP3307172, 84MI 118-02, 86MI 118-02>. Some azetidines displayed anorexigenic activity (e.g., (**164**)) <83USP4379151>, antihypertensive activity (e.g., (**165**)) <89JAP(K)01139577, 89MI 118-01>, antidepressant activity (e.g., (**166**)) <83EUP85811, 85MIP533463>, cardiovascular activity (e.g., (**167**)) <91GEP(O)4002391>, antibacterial activity (e.g., (**168**)) <89EUP314362, 91AAC442, 93EUP536035>, and analgesic activity <88MI 118-01>.

Other azetidines have been reported to be selective muscarinic agonists (e.g., (**169**)) <88JMC683>, cholinergic, and serotonergic agents (e.g., (**170**)), claimed for treatment of Alzheimer type senile dementia and other memory disorders <93EUP527117>, and calcium blocker <90MI 118-02>. Azetidine-platinum complexes, for example, (**171**), show antitumor activity against P388 leukemia in mice <84MI 118-03, 90JPS750>.

Besides agrochemistry and pharmaceutical applications, azetidines can be used for improved cellulose dyeability via chemical modification with 1,1-dimethyl-3-hydroxyazetidinium chloride (**172**) <89MI 118-02>. Polymerization of azetidines is a peculiar chemical property, which has been covered briefly <92HOU(16C)936>.



1.18.3 AZETIDIN-2-ONES AND RELATED AZETIDINE DERIVATIVES

1.18.3.1 Introduction

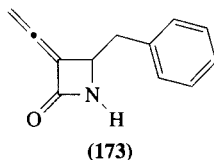
The explosion of literature on β -lactams since 1985 shows the interest in this important class of compounds. The discovery of nonclassical β -lactam antibiotics such as nocardicins and monobactams has stimulated much interest in the synthesis of monocyclic β -lactams and their derivatives. Monocyclic β -lactams frequently serve as precursors for the synthesis of bicyclic β -lactam antibiotics. Pertinent references on various aspects of the chemistry of β -lactams will be provided. More detailed information on specific extended topics is covered in appropriate reviews [B-83MI 118-03, 83PAC1745, 84CHEC-I(7)237, 85AG183, 86ACR49, 87H(26)729, 87H(26)777, 87PAC485, 88MI 118-02, 88T5615, 89CRV1447, 89H(29)2225, 91HOU(16B)31, 91T7503, B-92MI 118-03]. The sections on chemical reactivity and synthesis of 2-azetidinones are extended. However, less emphasis is given to the reactivity of substituents attached to ring carbon and nitrogen atoms. Azetidin-2-thiones and highly functionalized 2-azetidinones, for example, azetidine-2,3-diones, azetidine-2,4-diimines, 4-imino-2-azetidinones, etc., will be covered in a separate section.

1.18.3.2 Theoretical Methods

Gas phase proton affinities of β -lactams have been measured by FTICRMS techniques. Self-consistent field and MP2 calculations at different levels of accuracy have been performed for the neutral and protonated species. In the gas phase, β -lactams are weaker bases than acyclic amides. *Ab initio* calculations show that β -lactams are oxygen bases, but the gap between the oxygen and nitrogen intrinsic basicities is much smaller in the former due to cyclization effects, a result of redistribution due to hybridization changes at the carbonyl carbon <92JA4728>.

1.18.3.3 Experimental Structural Methods

Studies using x-ray crystallography of β -lactams indicate that the ring is planar. Several β -lactam derivatives, for example, a 4-benzylidene-2-iminoazetidine <88JOC18>, an amidinium salt <84HCA927>, α -alkylidene- β -lactams <86MI 118-03, 88MI 118-02>, a 2,3-diiminoazetidine <86BSB97>, and 4-benzyl-3-(ethenylidene)azetidin-2-one (173) <87MI 118-02> have been investigated by x-ray analysis. An x-ray crystallographic analysis of a 1 : 1 inclusion complex of a chiral host, (–)-10,10'-dihydroxy-9,9'-biphenanthryl, and (–)-*N*-(1-*t*-butyl-2-oxoazetidin-3-yl)phthalimide has been performed <93JCS(P1)2357>. The complexation of the racemic β -lactam with the chiral host allowed an optical resolution to optically pure (–)-3-amino-1-*t*-butylazetidine-2-one after hydrazinolysis.

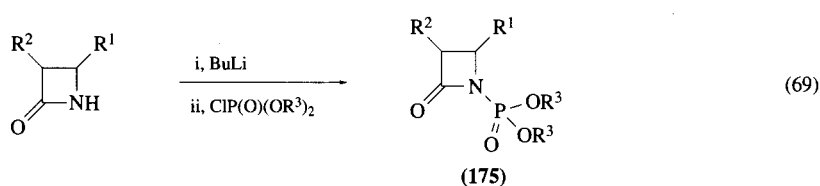
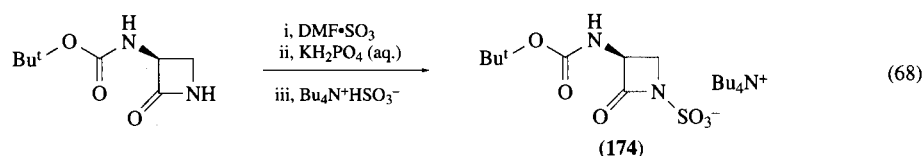


The method most useful for the determination of the relative stereochemistry of 2-azetidinones is ^1H NMR. The coupling constant for vicinal protons at C(3) and C(4) is 4.5–6 Hz for *cis* derivatives and 2–2.5 Hz for *trans* derivatives. The ^{13}C NMR spectra of β -lactams show the typical carbonyl resonance at 160–170 ppm.

1.18.3.4 Reactivity of β -lactams

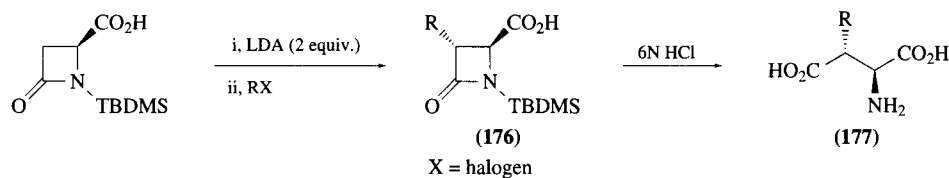
1.18.3.4.1 Electrophilic attack at nitrogen

Representative examples of *N*-alkylations, *N*-acylations, and other reactions of *N*-unsubstituted 2-azetidinones have been given already in CHEC-I. Other specific transformations include the reaction of these β -lactams with sulfur trioxide complexes to give lactam-type structures, for example, (174) <82JOC5160, 83T2577>, the preparation of organophosphorus substituted β -lactams (175) <83JA3743, 83CJC1730>, the reaction of β -lactams with glyoxylic esters <87LA911>, and the intramolecular rhodium-catalyzed insertion of a diazo function into 1-alkoxy- β -lactams <91JOC2688>.

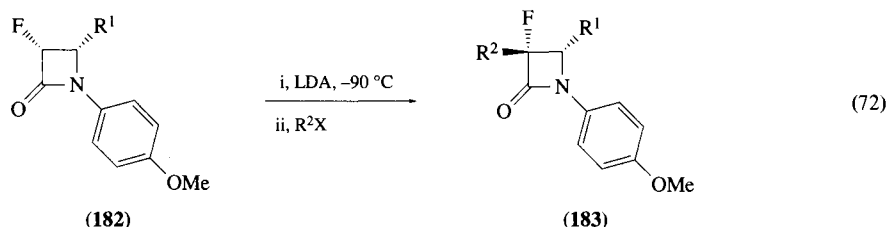
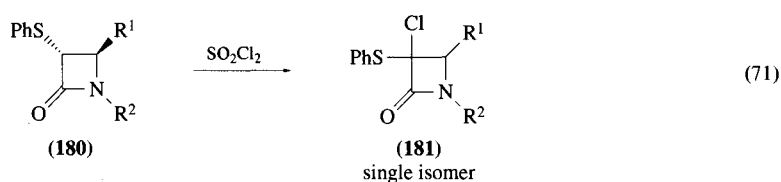
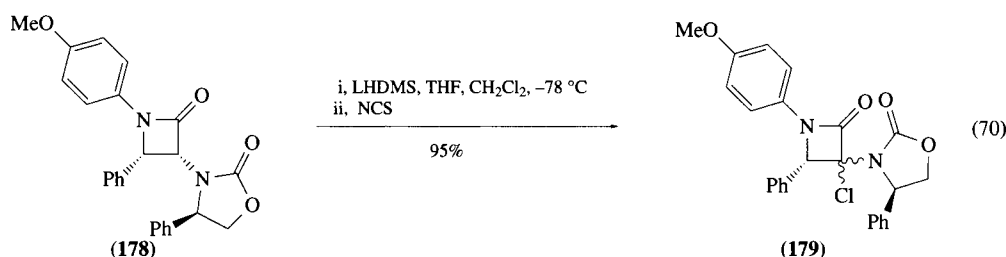


1.18.3.4.2 Electrophilic attack at carbon

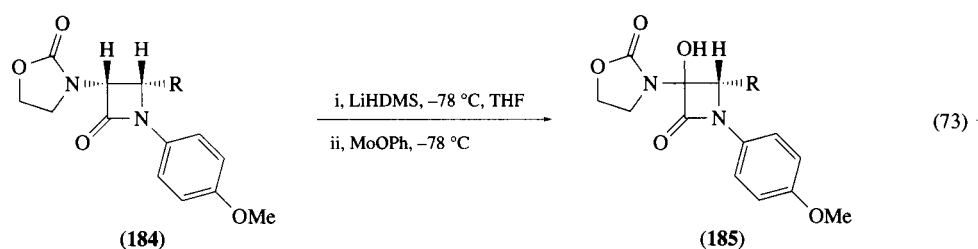
Various substitutions of hydrogen at position three and four in β -lactams have been performed by electrophilic reagents. The 3-position is activated by the carbonyl function, which makes it possible to generate a reactive amide enolate. The asymmetric methylation of 1-[(*S*)-2-phenylethyl]azetidine-2-one occurs with a moderate induction (2:1 diastereomers) <85KGS134>. Alkylation at the 3-position is readily executed via the enolate via reaction with alkyl halides <90T4733>, aldehydes, ketones, carbon dioxide, etc. <83LA1152, 83LA1162, 84H(22)1161, 93JOC245>. The presence of a carboxyl group at C(4) does not interfere as the dilithium salt is alkylated at C(3) with excellent stereocontrol, giving the *trans*-disubstituted lactam (176) <90CC720>. Hydrolysis leads to unprotected β -alkyl aspartates (177) <92SL33>. Alpha-iodination with iodine is similarly performed via the lithio enolate <83CJC411>. The reaction of such amide enolates with alkyl halides or aldehydes has been proven to be very useful when the 3-position carried an additional heteroatom, for example, nitrogen <88JA278, 88T5307, 90JA770, 90TL977, 93BMC2475> (see conversion of (178) to (179) contained in Equation (70)), silicon <84H(22)1161, 88CJC304, 89MI 118-03, 89MI 118-04, 93JCS(P1)1553>, oxygen <90JOC5525>, sulfur (see conversion of (180) to (181) contained in Equation (71)) <89JOC5758>, and fluoro (see conversion of (182) to (183) contained in Equation (72)) <93JOC2454>.



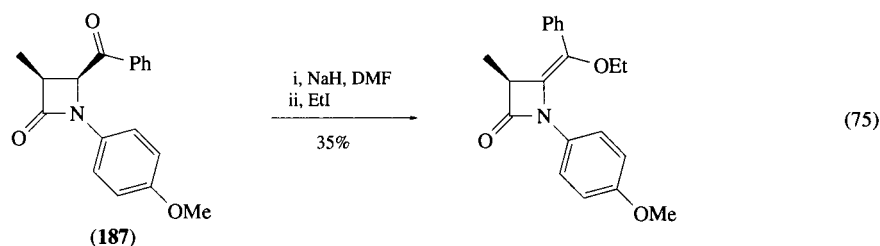
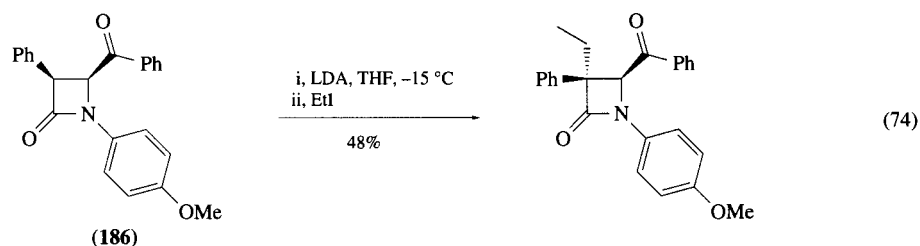
Scheme 36



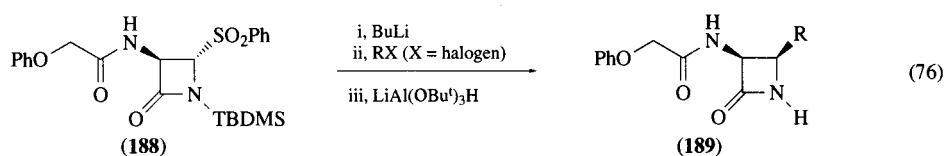
The introduction of heteroatoms at C(3) of β -lactams is also most useful. The C(3) azidation with tosylazide via the enolate is an elegant approach to 3-amino- β -lactams <81JOC2999, 83T2577, 84JOC1430, 84TL765>. 3-Hydroxylations of 2-azetidinones have been executed using the MoOPh reagent (see conversion of (184) to (185) contained in Equation (73)) <93TL6325>, 3-phenyl-1-tosyloxyaziridine <87SC1877>, and diphenoxyoxophosphoric acid tris(dimethylamide)pyridine-molybdenum complex <88CJC304>.



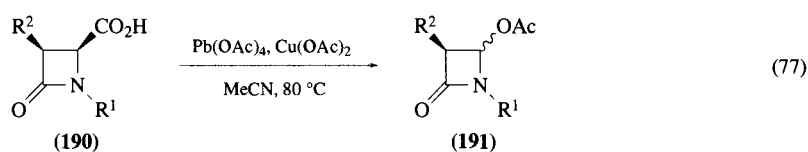
When electron-withdrawing groups, for example, benzoyl, are present at C(4), the C(3) alkylation of (186) via the enolate can be performed with LDA/THF (Equation (74)), but the benzoyl oxygen of (187) is alkylated when NaH/DMF is used (Equation (75)), clearly underlying the importance of anion stabilizing substituents, either at C(3) or C(4), and the base-solvent pair $\langle 89\text{H}(29)719 \rangle$.



Reactions at C(4) of β -lactams require the presence of activating groups. A method for the synthesis of chiral azetidinones (189) with a C—C bond at C(4) consists of the stereoselective alkylation-reduction of a silylated 4-phenylsulfonyl azetidinone (188) $\langle 93\text{TL}3051 \rangle$.



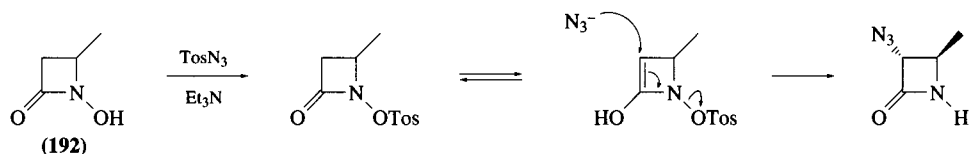
The oxidative decarboxylation of 2-azetidinone-4-carboxylic acids (190) to give 4-acetoxy-2-azetidinones (191) via reaction with lead(IV) acetate is a frequently used procedure in β -lactam chemistry (Equation (77)) $\langle 86\text{JOC}558, 88\text{HCA}395, 88\text{JOC}3784, 90\text{JOC}575, 92\text{JOC}5921 \rangle$. The Baeyer–Villiger type oxidation of 4-acetyl-2-azetidinones to give 4-acetoxy-2-azetidinones using peracids is an alternative $\langle 88\text{JOC}3784, 91\text{TL}2145 \rangle$.



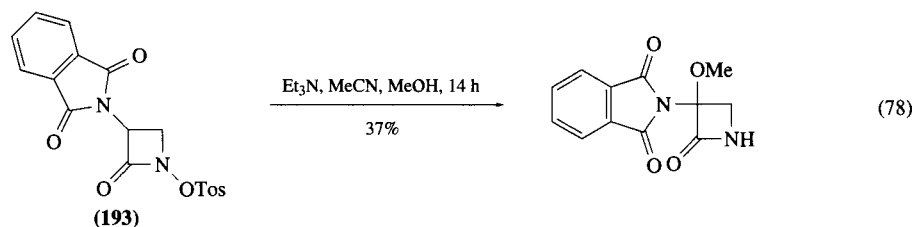
Azetidiniminium salts have been oxidized by bis(trimethylsilyl)peroxide to oxazolidine-2-ones $\langle 87\text{PAC}393 \rangle$.

1.18.3.4.3 Nucleophilic attack at carbon

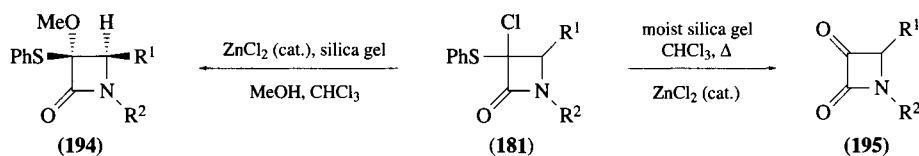
Various nucleophilic attacks at C(3) and C(4) of β -lactams have been employed to introduce desired functionalities. Nucleophilic displacement of a halogen at C(3) by nucleophiles, for example, potassium phthalimide, has been performed $\langle 93\text{JCS(P1)2357} \rangle$. The α -azidation of 1-hydroxy-2-azetidiones, for example, (**192**), with arenesulfonyl azides in the presence of triethylamine affords 3-azido-2-azetidiones via O -tosylation and $\text{S}_{\text{N}}2'$ -type displacement of the tosyloxy group (Scheme 37) $\langle 92\text{JA2741, 93JA548, 93BMC2429} \rangle$. However, the $\text{S}_{\text{N}}2'$ -type displacement of 1-tosyloxy-2-azetidiones, for example, (**193**), with methanol occurs only in low to moderate yield but supports the proposed mechanism (Equation (78)).



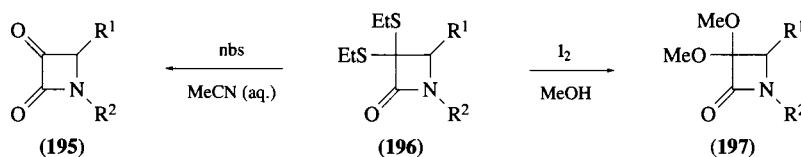
Scheme 37



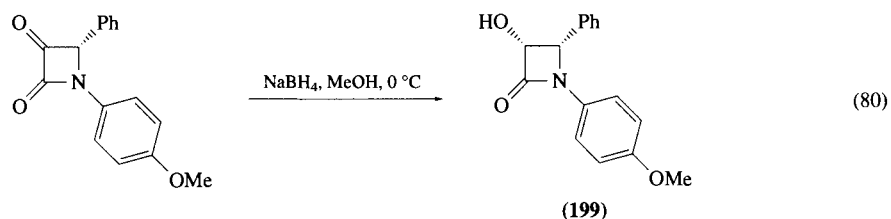
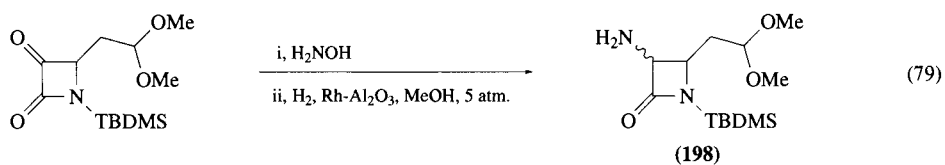
It has been shown that 3-chloro-3-(phenylsulfenyl)-2-azetidiones (**181**) undergo a stereospecific methanolysis in the presence of zinc chloride/silica gel to afford methoxylated β -lactams (**194**), while hydrolysis under similar conditions leads to azetidine-2,3-diones (**195**) $\langle 89\text{JOC5758} \rangle$. Hydrolysis of 3,3-di(ethylthio)-2-azetidiones (**196**) with NBS in aqueous acetonitrile, or with dimethylsulfide dibromide, furnishes azetidine-2,3-diones (**195**), while 3,3-dimethoxy-2-azetidiones (**197**) are formed by iodine induced methanolysis (Scheme 39) $\langle 85\text{TL4239, 87TL1945, 88TL3133, 90JOC2070} \rangle$. Such azetidine-2,3-diones (**195**) are readily attacked by nucleophiles at the 3-position. Oximation and subsequent reduction is a route to 3-amino-2-azetidiones (**198**) $\langle 85\text{H(23)2693} \rangle$, while reduction with sodium borohydride affords 3-hydroxy-2-azetidiones $\langle 83\text{H(20)505, 93BMC2475} \rangle$. The latter reaction was used in the synthesis of *cis*-3(*R*)-hydroxy-4(*S*)-phenyl- β -lactam (**199**), which is a precursor to the taxol side chain (Equation (80)) $\langle 93\text{BMC2475} \rangle$.



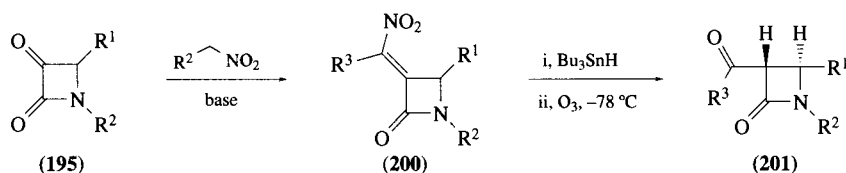
Scheme 38



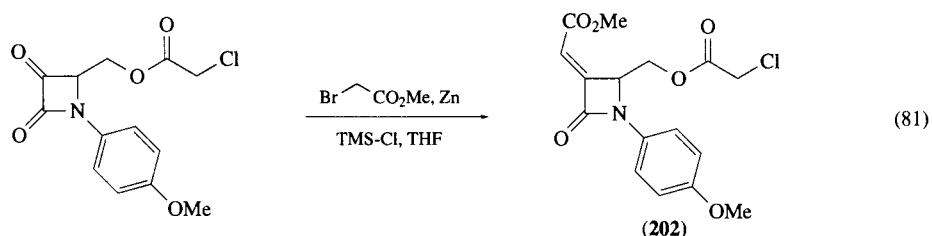
Scheme 39



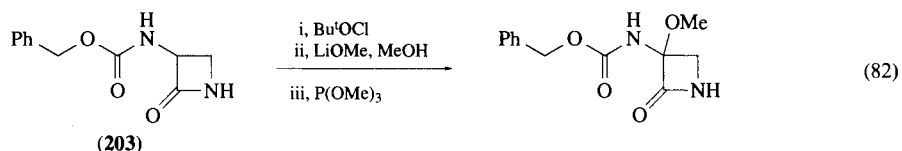
Azetidine-2,3-diones (**195**) undergo a base-induced alkenation reaction with nitroalkanes affording nitroalkenes (**200**), which are reduced and then oxidized to give 3-acyl-2-azetidinones (**201**) $\langle 90\text{JOC}2070 \rangle$. The same substrates suffer alkenation reactions with Reformatsky-type reagents affording 3-methylene-2-azetidinones, for example, (**202**) $\langle 90\text{TL}2205, 90\text{TL}6425 \rangle$. The alkenation of β -lactams is only successful with stabilized ylides and Boc-protected substrates (**124**) and (**125**) (Equation (58)) $\langle 93\text{SL}49 \rangle$.



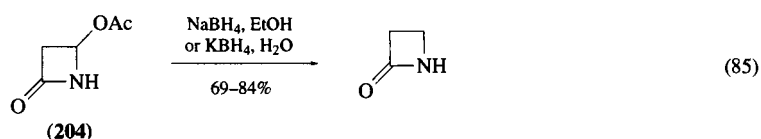
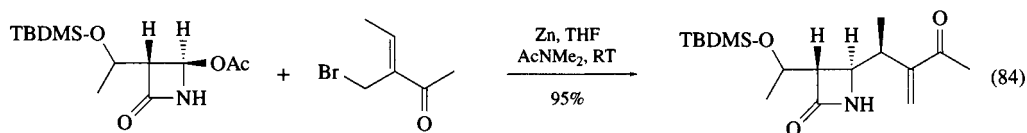
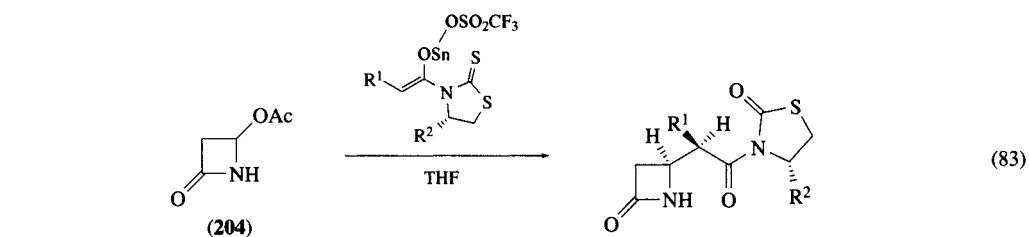
Scheme 40



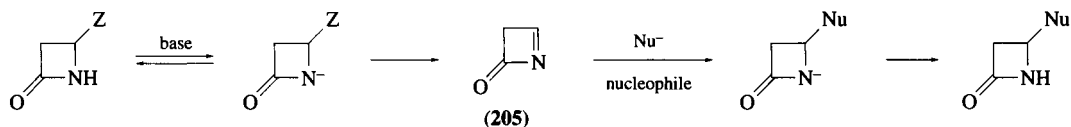
It has been shown that 3-amino-2-azetidinones (**203**), carrying an electron-withdrawing substituent at the 3-amino substituent, are methoxylated at the 3-position by oxidation to the 3-imino-2-azetidinone, and subsequent nucleophilic addition of lithium methoxide (Equation (82)) $\langle 82\text{JOC}179, 84\text{TL}765 \rangle$.



The classical functionalization of 4-acetoxy-2-azetidinones, for example, (**204**), at the 4-position $\langle 84\text{CHEC-I}(7)237 \rangle$ has been exploited several times with a variety of reagents, including a Barbier-type allylation using a Pb/Al bimetal redox system $\langle 88\text{TL}1721 \rangle$, cuprates $\langle 85\text{TL}547, 90\text{JOC}3098 \rangle$, diethyl methylmalonate $\langle 93\text{EUP}546742 \rangle$, tin(II) enolates $\langle 87\text{JOC}5491, 92\text{JOC}4232, 92\text{JOC}4238, 92\text{JOC}4243 \rangle$, allyl tin(IV) reagents $\langle 85\text{JOC}3438 \rangle$, thiols $\langle 90\text{JOC}5110 \rangle$, organozinc reagents (Equation (84)) $\langle 93\text{BMC}2389 \rangle$, and sodium or potassium borohydride (Equation (85)) $\langle 88\text{CJC}304 \rangle$.

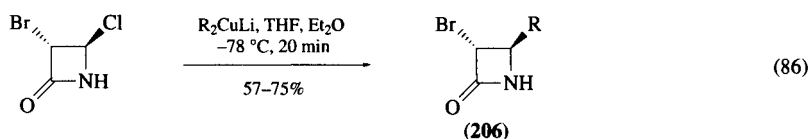


The mechanism of these substitution reactions has been investigated and it was shown that the reactions occur by an E1cB elimination-addition pathway in which a 1-azetin-4-one (**205**) acts as intermediate (Scheme 41) <84JOC5094, 90JOC3244, 90JOC5655>. For *N*-substituted derivatives, substitution at the 4-position involves either elimination-addition via a 4-azetinone intermediate (**205**) or direct displacement by S_N2 or S_N1 mechanisms <90JOC3244>. The intermediacy of 1-azetin-4-one in solution has been demonstrated via polymer-bound 2-azetidinones <90JOC434>.

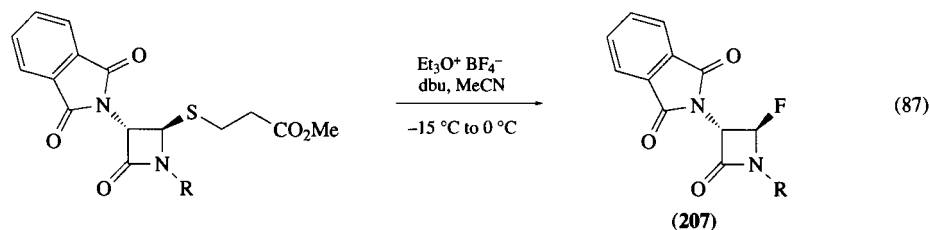


Scheme 41

Not only is the acetoxy group a suitable leaving group at the 4-position of 2-azetidinones, 4-chloro-2-azetidinones can be used as well <85ZN(B)115>, even in the presence of reactive substituents at the 2-position. The latter is illustrated by the synthesis of 4-alkyl-3-bromo-2-azetidinones (**206**) utilizing cuprates (Equation (86)) <83CJC1899>.

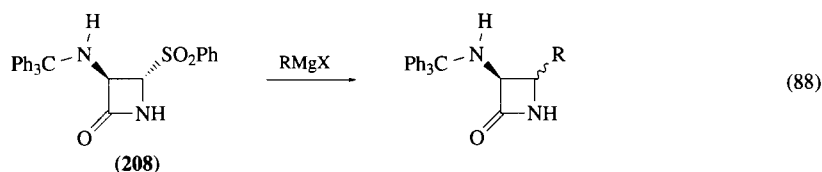


The conversion of 4-sulfinylated 2-azetidinones into 4-fluoroazetidinones (**207**) or 4-chloro-2-azetidinones occurs by reaction with triethyloxonium tetrafluoroborate or chlorine, respectively (Equation (87)) <86TL3199, 87CJC2140>.

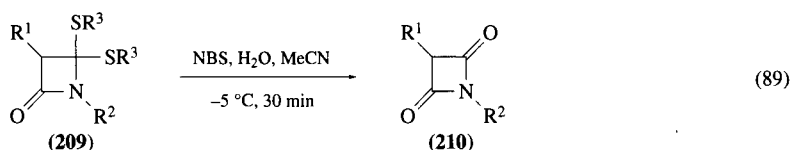


In a similar manner 4-sulfinyl substituted 2-azetidinones react with nucleophiles, for example, organotin(IV) reagents <85JOC3438> or alcohols <83JCS(P1)1157, 81CC959>, to afford 4-substituted 2-

azetidinones. An analogous reaction of 4-sulfonyl substituted 2-azetidinones (**208**) with Grignard reagents has been reported (Equation (88)) <83T2577, 86CPB1423>.



A useful synthesis of azetidine-2,4-diones (**210**) consists of the hydrolysis of 4,4-disulphenylated 2-azetidinones (**209**) with NBS in aqueous acetonitrile (Equation (89)) <92S439>.

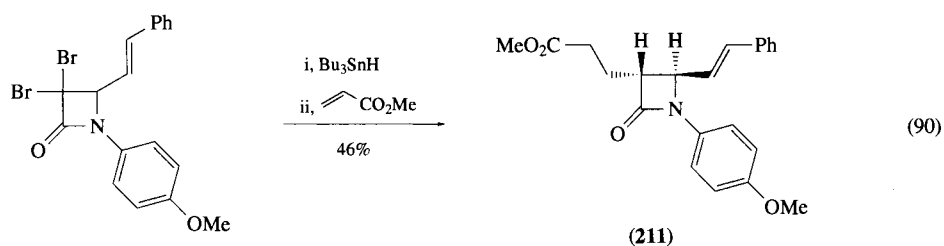


1.18.3.4.4 Nucleophilic attack at hydrogen (deprotonation)

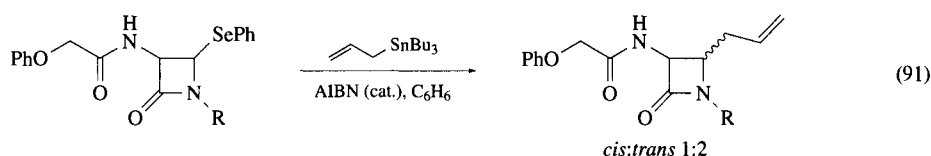
Deprotonation of 2-azetidinones at C(3) or C(4) and following reaction with electrophiles have been treated in Section 1.18.3.4.2. It has been reported that 1,2-elimination reactions of 4-selenoxymethyl-2-azetidinones occur to give 4-methylene-2-azetidinones <91MI 118-01>.

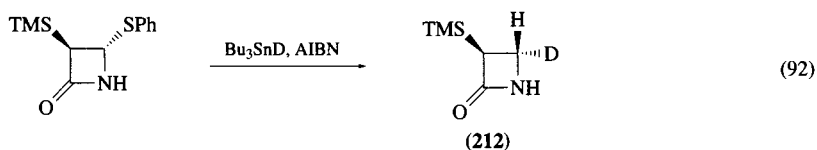
1.18.3.4.5 Radicals and photochemical conversions

Dehalogenation of 3,3-dibromo-2-azetidinones occurs readily with tributyltin hydride <83TL2323>. The intermediate radicals add across methyl acrylate to give highly functionalized β -lactams (**211**) <87JOC3659>.

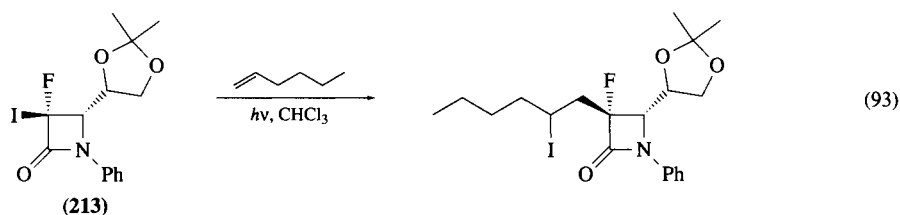


The generation of radicals at C(4) is performed via 4-sulphenylated or 4-selenenylated β -lactams, affording C(4) desulphenylated β -lactams <85JOC4245, 85TL5001>. The C(4) allylated end products are created via interception with allyltin(IV) reagents <90TL5693> or via intramolecular alkene trapping (Equation (91)) <93BMC2369>. Stereospecific synthesis of chiral C(4) deuterated β -lactams (**212**) has been worked out in this way (Equation (92)) <93SC1985>. The reaction of 4-(*t*-butylthio)- β -lactams with tributyltin hydride affords 4-thiol- β -lactams <88JOC4227>.



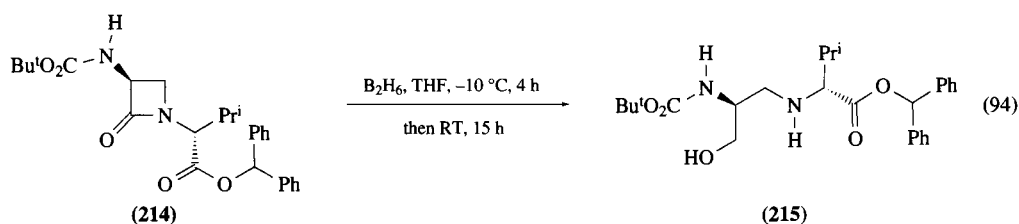


The iodine atom transfer addition reaction of 3-fluoro-3-iodo- β -lactam (**213**) under photolytic conditions is a convenient stereoselective method for the functionalization of β -lactams at the 3-position (Equation (93)) <93TL3087>.

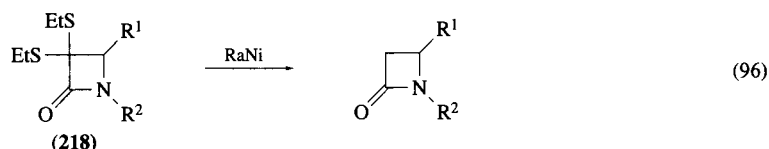
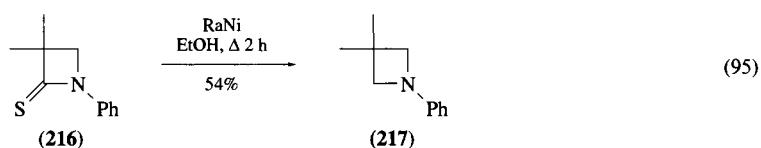


1.18.3.4.6 Reduction

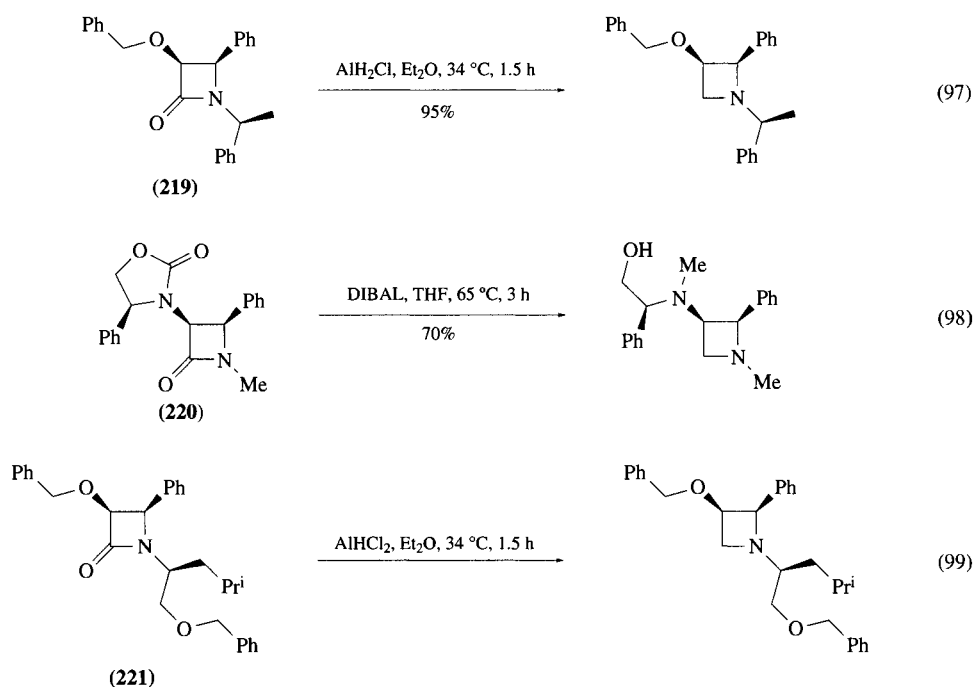
The reduction of β -lactams (**214**) by diborane gives access to γ -amino alcohols (**215**) <84JCS(P1)2415>, while the microwave mediated catalytic transfer hydrogenation by means of ammonium formate and Pd/C has been realized <93SL575>.



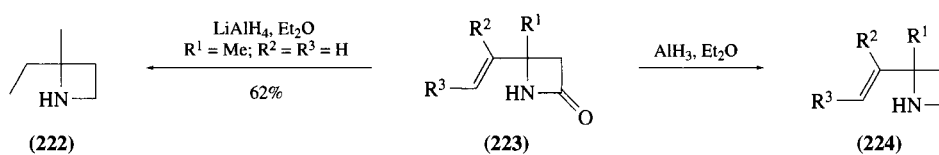
Raney nickel reduces 2-azetidinethiones, for example, (**216**), in ethanol to afford azetidines, for example, (**217**) <85CB653>. Derivatives with 4-phenyl substitutions give only complex reaction mixtures, whereas 3,3-disulfenylated β -lactams (**218**) are readily desulfurized by Raney nickel (Equation (96)) <87TL1945>.



Highly selective reductions of β -lactams to the corresponding azetidines are successfully performed by using diisobutyl aluminum hydride <84JAP(K)59161354, 91JOC5263>, monochlorohydroalane, and dichloroalane as reducing agents <83JA6339, 85TL2035, 87JA1798, 91JOC5263>. Enantiomerically pure azetidines for example, (**219**)–(**221**) are readily synthesized without loss of enantiomeric purity (Equations (97)–(99)) <91JOC5263>.



Aluminum hydride reduces 4-(1-alkenyl)azetidin-2-ones (**223**) to give 2-(1-alkenyl)azetidines (**224**), but the reduction of the same substrates with lithium aluminum hydride also reduces the alkene moiety to afford 2,2-disubstituted azetidines (**222**) <86JOC3652, 87TL683, 87TL4097>.

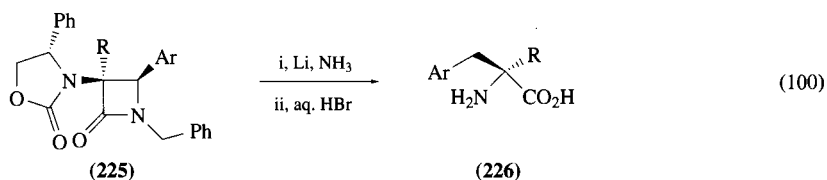


Scheme 42

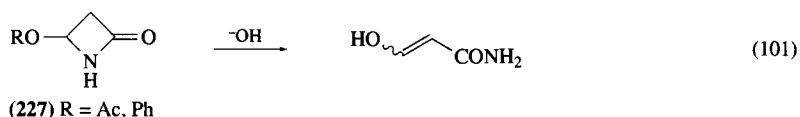
The introduction of an *N*-acetylamino substituent at C(3) via reduction of 3-acetoximino- β -lactams with hydrogen over PtO_2 has been reported <87TL5485>.

1.18.3.4.7 Ring opening

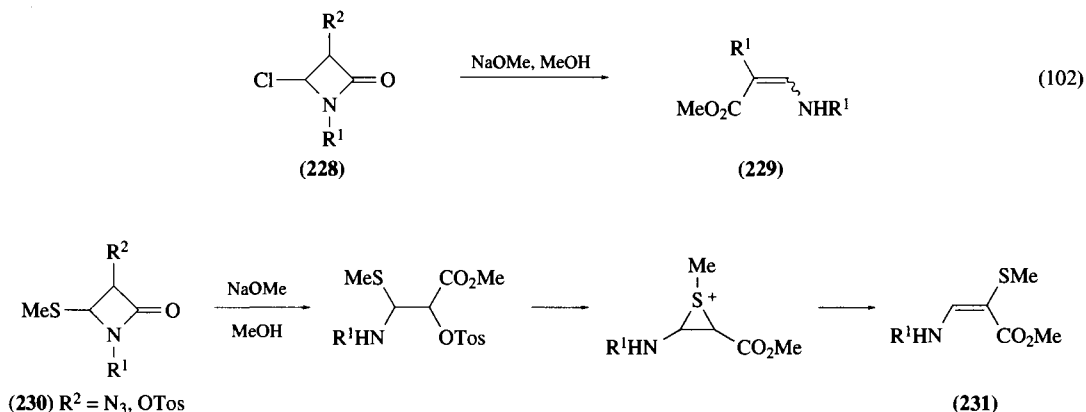
The hydrolysis of chiral β -lactams (**225**), after reductive removal of the *N*-benzyl substituent, in acid medium provides α -alkylated α -amino acids (**226**) in a stereospecific way (Equation (100)) <88JA278, 88T5307, 90JA770>.



Nucleophilic attack upon the β -lactam ring normally occurs at the carbonyl carbon atom and leads to opening of the ring <85TL2809>. When the ring contains a leaving group at the 4-position, nucleophilic displacement can also occur as exemplified by substitutions of 4-acetoxy-2-azetidinones and related substrates (see above). Such 4-acetoxy- and 4-aryloxy-2-azetidinones (**227**) undergo ring opening by aqueous alkaline solutions to give 3-hydroxyacrylamide or α -formylcarboxamides (Equation (101)) <84JOC5094>.

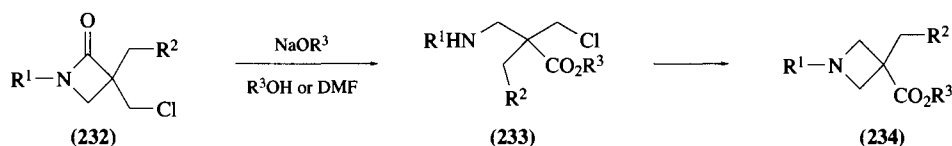


Similarly, the ring opening of 4-chloro- β -lactams (**228**) with sodium methoxide affords enamino esters (**229**) <90JOC3244>. In contrast to the 4-chloro derivatives, the 4-(methylthio)-3-(tosyloxy)- and 3-azidoazetidinones (**230**) in the presence of trimethylamine undergo elimination of tosylate and azide in competition with loss of methanethiol (Scheme 43). The methylthio group rearranges from C(4) to C(3) to afford enamino esters (**231**) <90JOC3244>.



Scheme 43

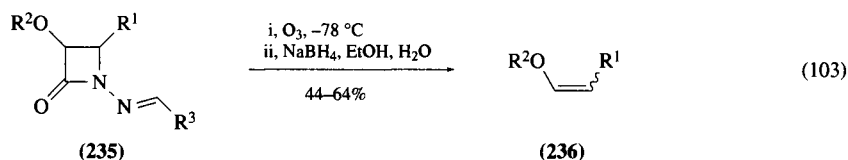
Alkoxides with 3-(chloromethyl)-2-azetidinones (**232**) give ring opening to β -amino esters (**233**) which undergo ring closure to azetidine-3-carboxylic esters (**234**).



Scheme 44

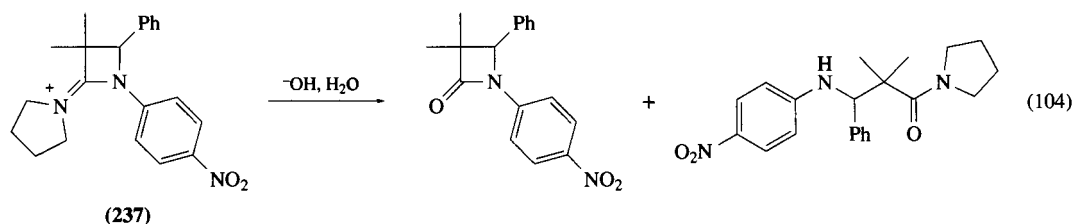
Ring opening of 1,4-diacetoxy- β -lactams occurs with sodium methoxide in ether to afford 3-hydroximino-carboxylic esters <85TL2809>.

Fragmentation of β -lactams (**235**) by ozonolysis, followed by reduction with sodium borohydride provides vinyl ethers (**236**) via intermediate *N*-nitroso- β -lactams (Equation (103)) <93JOC297, 93AQ139>. The alkaline hydrolysis of 1-aryl-3,3-diphenyl-4-(2-pyrrolyl)-2-azetidinones results in 2-(1,1-diphenylethyl)pyrrole in 46% yield, together with diphenylacetic acid, 2-iminopyrroles, and arylamines <88JCS(P2)957>.

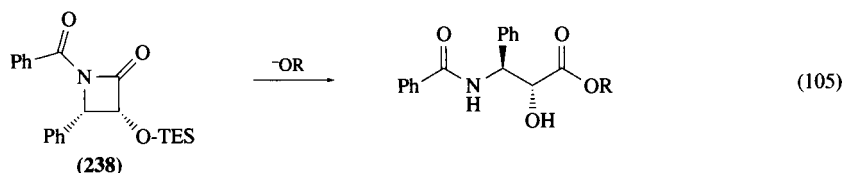


The hydrolysis of 2-azetidinyldeneammonium salts (**237**) in sodium hydroxide and in carbonate buffers yields 2-azetidinones and β -aminocarboxylic amides by competitive endo- and exocyclic C—N bond cleavage, the product ratio being pH and buffer dependent (Equation (104)) <87CC318, 88BSF272, 90JCS(P2)813>. The rate law for hydrolysis shows a third order term that is first order in substrate, hydroxide, and carbonate ions. It is interpreted as kinetically equivalent to general acid-

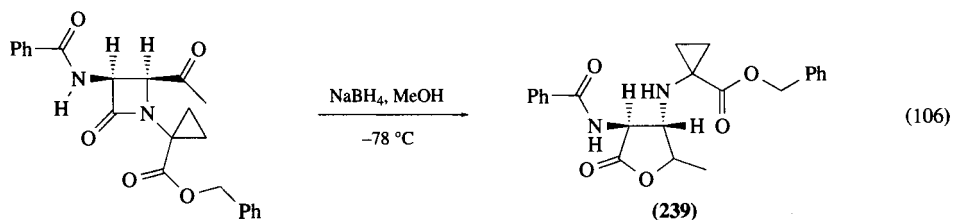
catalyzed breakdown of the ionized tetrahedral intermediate and as evidence for nonfacile C—N bond cleavage in the four-membered ring.



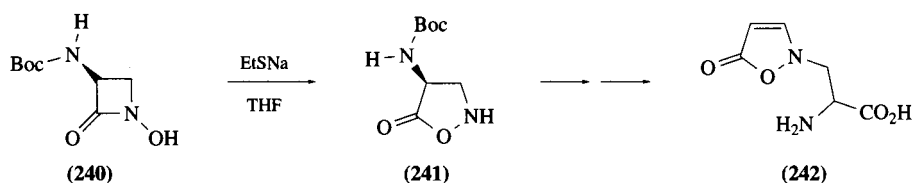
The ring opening of 3-oxygenated-4-phenyl- β -lactams, for example, β -lactam (238), by alkoxides has found an important application in the synthesis of taxol and related substances, delivering the correct stereochemistry of the taxol side chain (Equation (105)) (for some leading references, see <90EUP0400971, 91JOC1681, 91USP5015744, 92T6985, 93BMC2483, 93BMC2467, 93BMC2479, 94JA1599>).



Intramolecular ring opening, via an *in situ* generated alkoxide from reduction of an acetyl moiety by hydride, furnishes ring expansion to lactone (239) <93BMC2423>.



The ring expansion of β -lactam (240) by thiolate to give isoxazolidinone (241) was utilized as a key step in the synthesis of 2-alanyl-3-isoxazolin-5-one (242), a natural product from *Pisum sativum* seedlings (Scheme 45) <85TL5931>.

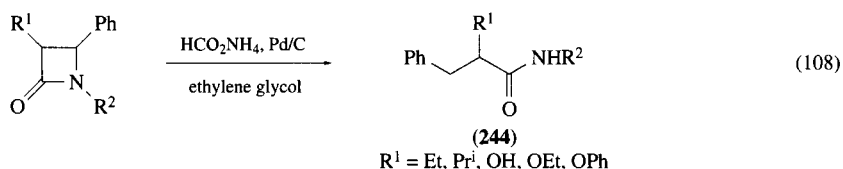
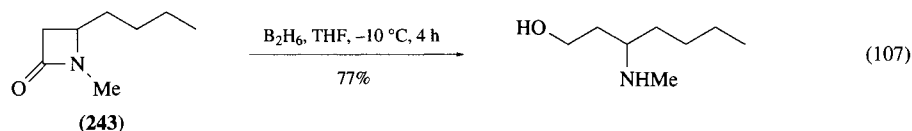


Scheme 45

Under the influence of aqueous tin(II) chloride, 4-acyl- or 4-imidoyl-3,3-dimethyl-2-azetidiones undergo C(3)—C(4) bond breakage and rearrangement affording 2,3-dioxo-1,2,3,4-tetrahydropyrazines or 3,4-dihydro-2,3-dioxo-2H-1,4-oxazines <93JOC4767>. Dimethyloxosulfonium methylide-induced ring opening of *N*-Boc protected β -lactams affords β -ketosulfoxonium ylides <93CC1434>, while 4-vinyl- β -lactams undergo transformation to β,γ -unsaturated carboxylic amides under the influence of palladium-catalyzed organomercurial addition <89TL1897>. Those 4-vinyl- β -lactams suffer palladium-catalyzed cross-coupling of aryl iodides with concomitant ring opening to give 5-aryl- β,γ -unsaturated carboxylic amides <93TL979>.

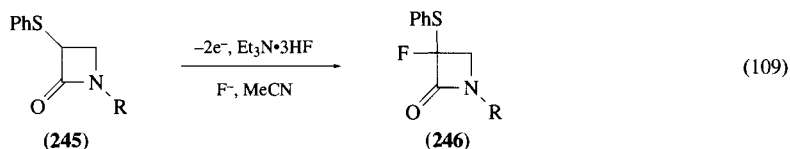
Ring opening of β -lactams, for example, (243), by diborane (Equation (107)) <84JCS(P1)2415>, lithium aluminum hydride, lithium triethylborohydride, and diisobutylaluminum hydride have been described <91JOC5263, 91TL4799>. However, these reducing agents are better known for the conversion

of β -lactams into azetidines. The latter useful transformation is treated in Section 1.18.3.4.6 on reductions of β -lactams. A high temperature catalytic transfer hydrogenation of β -lactams, by means of ammonium formate and Pd/C in ethylene glycol to afford carboxylic amides (**244**), has been realized in a domestic microwave oven <93SL575>.



1.18.3.4.8 Electrochemical transformations

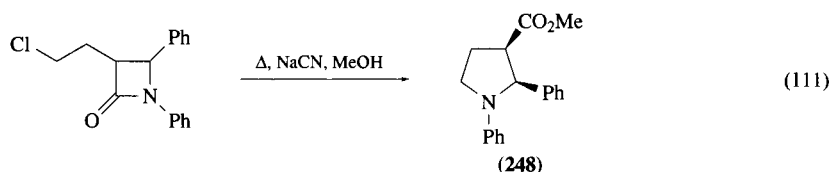
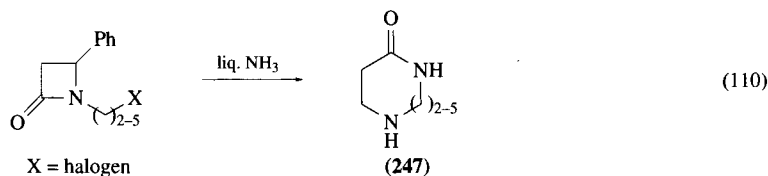
The anodic fluorination of 3-(phenylthio)-2-azetidinones (**245**) is a useful method for the synthesis of 3-fluorinated β -lactams (**246**) <93JOC4200>.



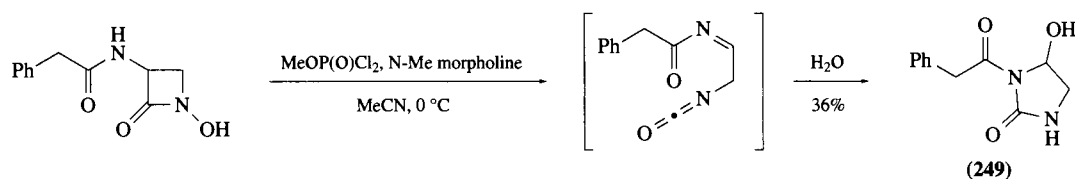
The electrochemical reduction of 3-bromo- or 3-chloro-2-azetidinones to 2-azetidinones <86JCS(P2)419> and the electrochemical 4-acetoxylation of 3-alkylidene-4-(trimethylsilyl)-2-azetidinones <93JCS(P1)1553> have been reported. The introduction of a carboxylate group at the 3-position has been accomplished by electrochemical conversion of 3-halo- β -lactams with carbon dioxide in DMF <86JCS(P2)419, 89T6885>. The electrochemical removal of 4-methoxyphenyl and bis-(4-methoxyphenyl)methyl groups from the nitrogen atom has been covered in Section 1.18.3.6 on nitrogen deprotection.

1.18.3.4.9 Conversions into other heterocycles

Ring expansion of β -lactams, bearing a ω -haloalkyl substituent at the nitrogen atom, occurs with liquid ammonia to heterocycles (**247**) <83CC959, 86TL5147>. A related ring expansion to pyrrolidines occurs with 3-(2-chloroethyl)-2-azetidinones (**248**) <86TL5955>.



Ring expansion of 1-hydroxyazetidine-2-ones produces 2-imidazolidinones (**249**) via activation with MeOP(O)Cl_2 (Scheme 46) <85CC1265>.



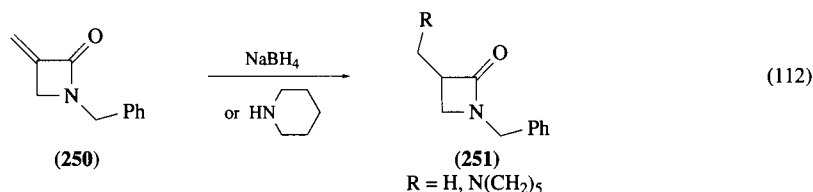
Scheme 46

Base-induced C-4/N-1 ring opening of 1-aryl-4-benzoyl-3,4-diphenylazetidin-2-ones and subsequent alkylation of the ring-closed adduct affords 5-alkoxy-3-pyrrolin-2-ones <87H(26)1461>. Other transformations of β -lactams into other heterocycles, including 3-pyrrolidinones <93CC1434>, isoxazolidin-5-ones <85TL5931>, and 2,3-dioxotetrahydropyrazines <93JOC4767>, have been reported.

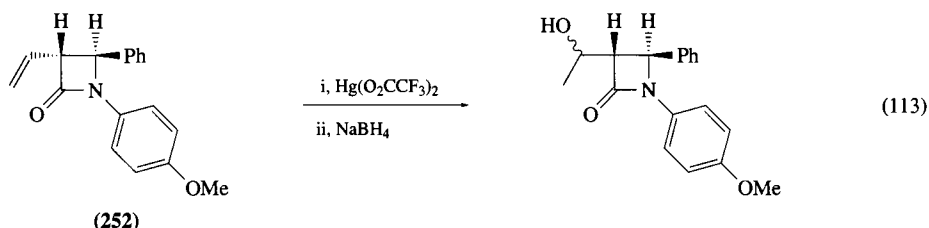
1.18.3.5 Reactivity of Substituents Attached to Ring Carbon Atoms

A brief selection of reactions in which substituents attached to ring carbon atoms are involved in transformations are given. A large number of such reactions has been covered already in the different sections of this chapter.

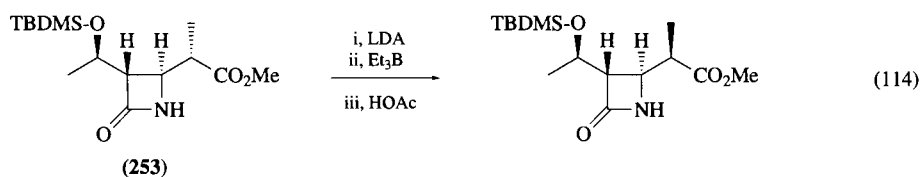
Michael addition of sodium borohydride or piperidine across 3-methyleneazetidin-2-one (**250**) affords the adducts (**251**) <85T375>. It has been shown that 4-(iodomethyl)azetidin-2-one undergoes nucleophilic substitution by sodium azide in DMF to give the azido compound <88JOC4006>.



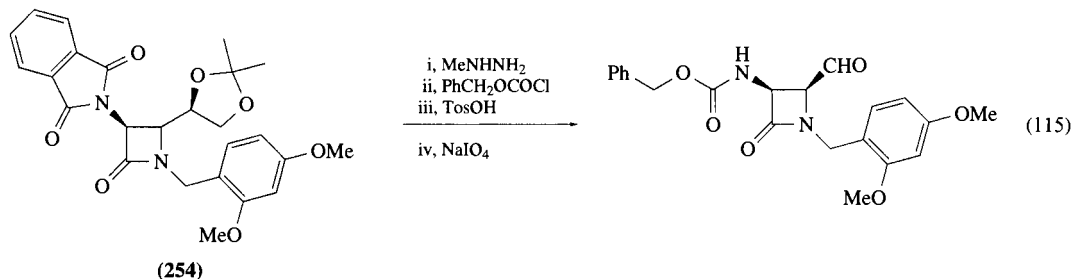
The 3-vinyl substituent of β -lactam (**252**) is converted into a 1-hydroxyethyl group by oxymercuration and reductive demercuration (Equation (113)) <93SL897>. The 1-hydroxyethyl substituent is readily oxidized by the Jones reagent and is further transformed to a hydromethyl substituent by silylation, ozonolysis, oxalyl chloride treatment, and hydride reduction <91JOC3183>.



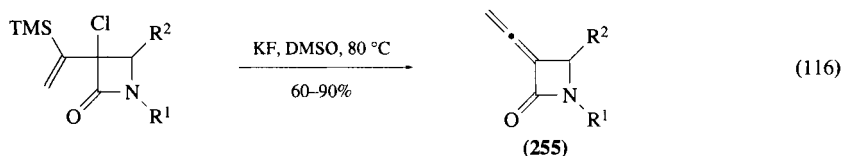
Triethylborane-mediated epimerization of the α -methyl diastereomer (**253**) proceeds with high stereoselectivity (Equation (114)) <92JOC2411>. Enzyme-catalyzed hydrolyses of carboxylic ester groups, localized in the C(2) side chain, have been performed <93JOC4819>. Ozonolysis of 4-(1-alkenyl)substituents is a convenient route towards 4-acyl- β -lactams <89JOC5736>.



The conversion of the C(4) substituent of the chiral β -lactam (**254**) into the important formyl group has been accomplished after changing the C(3) nitrogen protective group (Equation (115)) <83HCA2206>. An analogous conversion of a 4-(2-oxiranyl)-group into a formyl substituent was executed with periodic acid (H_5IO_6) <88TL5065>.



Electrophilic attack at the carbonyl oxygen of β -lactams by triethyloxonium tetrafluoroborate affords 2-ethoxy-1-azetines <93T4383>. The production of 3-ethylidene-2-azetidinones (**255**) is possible from fluoride-mediated desilylation and concomitant chloride elimination (Equation (116)) <87CC735>. The 4-[1-(hydroxymethyl)vinyl]-substituent has been diastereoselectively reduced with hydrogen gas and (*R*)-BINAP- Ru^{II} to give 4-(2-hydroxy-1-(β -methyl)-ethyl)-substituted β -lactams <90TL549>. From 4-benzoyl- β -lactams 4-acyloxy- β -lactams are accessible via Fe_2O_3 -catalyzed aerobic oxidation <92TL7557>.

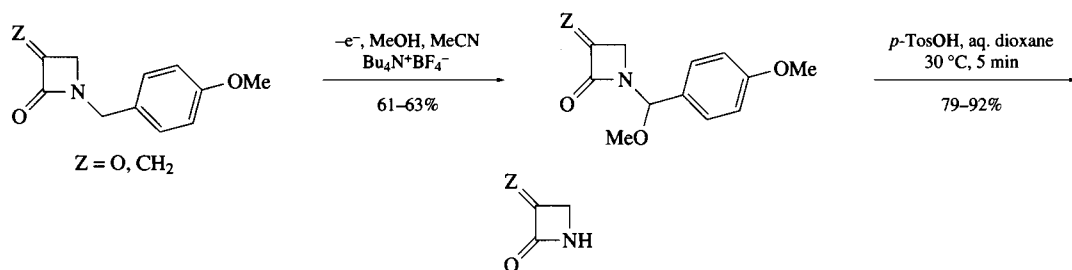
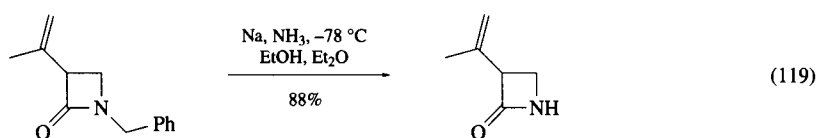
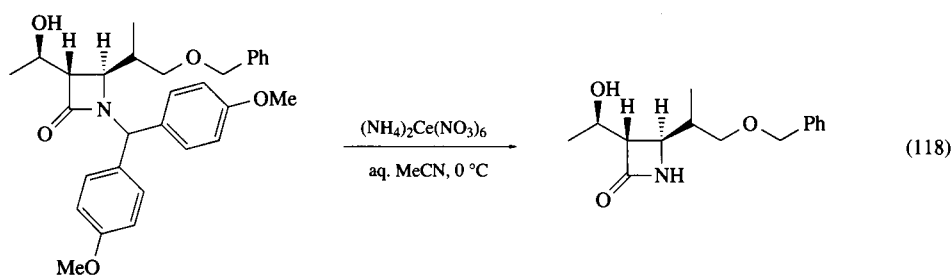
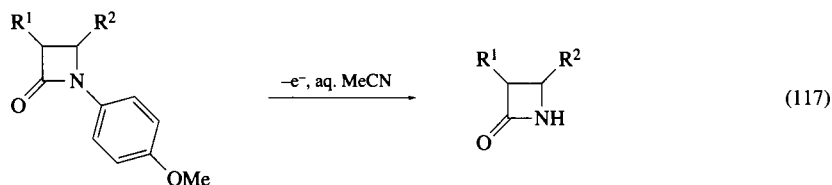


1.18.3.6 Reactivity of Substituents Attached to the Ring Nitrogen Atom

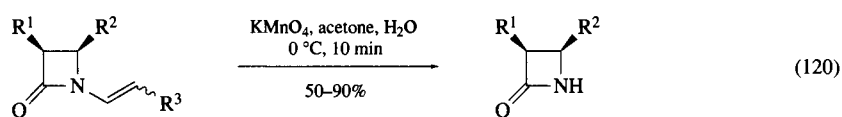
The protection-deprotection procedure of the nitrogen atom of 2-azetidinones holds a prime position in synthetic methodologies leading to functionalized β -lactam derivatives. Some leading references on frequently used protective groups, and their removal from nitrogen, are given below, including some selective examples. In some cases, the *N*-substituent is not necessarily considered as the protective group, for example, 1-hydroxy-2-azetidinones, but removal of this substituent has been investigated.

The *N*-desilylation of 1-trimethylsilyl- or 1-(*t*-butyldimethylsilyl)-2-azetidinones is a commonly used process in 2-azetidinone chemistry <91HOU(16B)551>. The *t*-butoxycarbonyl group is readily removed with trifluoroacetic acid <86H(24)2539>, while the 4-methoxyphenyl protective group (PMP) is conveniently removed by ceric ammonium nitrate (CAN) <82JOC2765, 85CJC3613, 93BMC2471, 93TL6325>, or anodic oxidation (Equation (117)) <88TL1497, 89USP4834846>. The oxidative removal of the di-(*p*-anisyl)methyl group is readily accomplished using ceric ammonium nitrate (Equation (118)) <86TL6241, 88T2149> or peroxodisulfate salts <89JAP(K)01246254>. The deprotection of *N*-benzyl type substituent occurs by sodium in liquid ammonia (Equation (119)) <83JCS(P1)2851, 87TL179, 88JA278, 88T5307, 90JA770>, while the *p*-anisylmethyl group is removed by anodic oxidation and subsequent hydrolysis (Scheme 47) <85H(23)317, 85T375, 88TL1409>. It has been shown that *N*-phenacyl-protected 2-azetidinones are converted in *N*-unsubstituted 2-azetidinones by oxidation with KMnO_4 or via α -bromination and subsequent mercury assisted hydrolysis (Equation (120)) <85TL3041, 85TL4239>. Elegant sources of *N*-unsubstituted 2-azetidinones are *N*-(1-alkenyl)-2-azetidinones via oxidative cleavage with KMnO_4 <87JOC4401, 88TL2409, 90TL451, 93JOC5771>. The allyl group is removed oxidatively in moderate yields <84TL4709> while 2-(2-oxo-1-azetidinyl)carboxylic acids are *N*-deprotected by anodic oxidation <86H(24)2273>. The 2-(trimethylsilyl)ethoxycarbonylamino substituent at position 1 of β -lactams is removable by fluoride-induced carbamate cleavage and subsequent reaction with diphenylnitrosoamine <93BMC 2383>. There are various ways of deprotecting: 1-oxygenated 2-azetidinones including by sodium or lithium in liquid ammonia (1-methoxy derivatives <82JOC5160, 86TL3119>), titanium(III) chloride or manganese(III) acetate (1-hydroxy derivatives

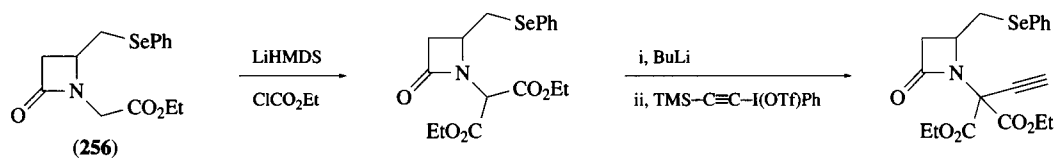
(83JOC3556, 93TL83)). The alternative procedure of *N*-dehydroxylation by tosylazide in the presence of triethylamine also introduces a 3-azido substituent concomitantly (93JA548). The removal of halogens in side chains of β -lactams is conveniently performed by tributyltin hydride reduction (82JA3233).



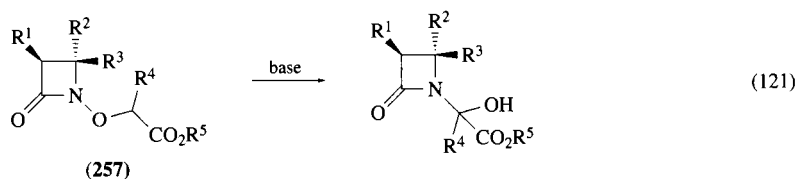
Scheme 47



Other transformations in the *N*-substituent of β -lactams entail the generation of an alkenic double bond at an unactivated position by enzymes, for example, the clavaminic acid synthase (93CC1694), the alkoxyacylation, and alkylation of 1-(ethoxycarbonyl-methyl)- β -lactam (256) (93JOC7923), and the 1,2-anionic rearrangement of substituted *N*-hydroxyazetidinones (257) into carbinolamine-type β -lactams (86JOC106).



Scheme 48

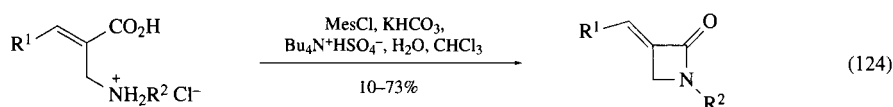
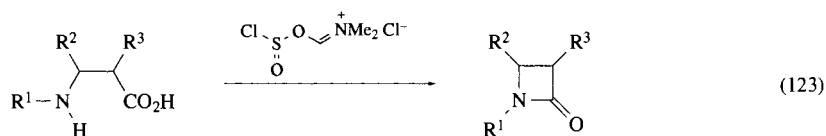
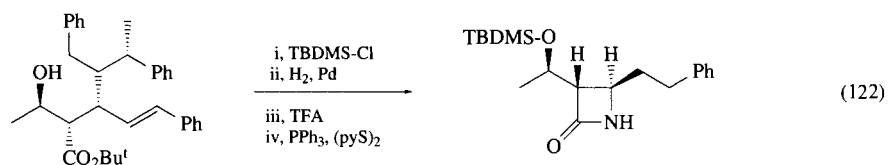


1.18.3.7 β -Lactam Ring Synthesis

A large number of syntheses of the important β -lactams have been developed. All categories of bond formations, such as, N—C(2), N—C(4), C(2)—C(3), and C(3)—C(4), and several types of cycloaddition reactions have been witnessed to have an explosive appearance. The various types of β -lactam syntheses will be discussed, but major synthetic routes, for example, the ester enolate-imine cycloaddition, cannot be covered completely. For more details, readers are advised to consult the reviews on this topic mentioned.

1.18.3.7.1 Cyclization of β -amino acids

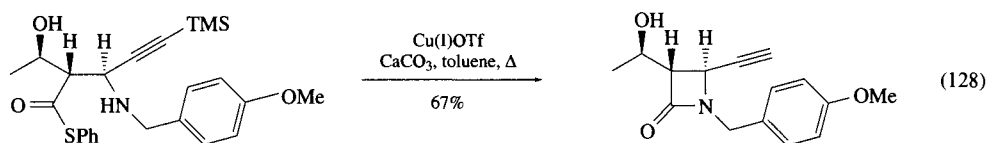
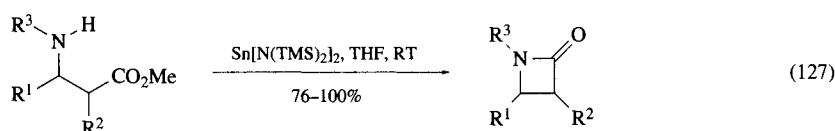
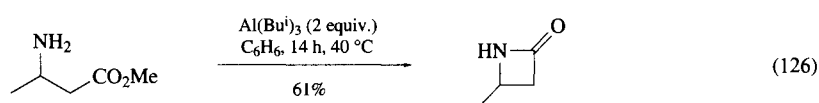
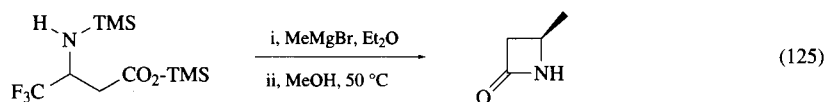
The intramolecular condensation of β -amino acids is accomplished by a large variety of activating agents, including triphenylphosphine/di-2-pyridyldisulfide (Equation (122)) <76AG(E)94, 82CL631, 84CJC1400, 85CPB3046, 85TL1523, 86CPB3020, 86TL2149, 86TL2153, 86TL4961, 87CC1410, 88CC567, 88T4173, 93CC1153, 93CC1660, 93JCS(P1)2247>, triphenylphosphine/ CCl_4 or NBS <88SC247>, triphenylphosphine/ CBr_4 or Br_2 , or I_2 <80M1117>, triphenylphosphine/hexachloroethane <91MI 118-02>, diarylphosphinic acid chloride <88CC1242>, nitropyridylphosphates <93MI 118-05>, phenyl phosphorodichloridate <91JOC2244>, bis(5-nitro-2-pyridyl)-2,2,2-trichloroethyl phosphate <87TL2735>, benzotriazoloxy-tris(dimethylamino)-phosphonium hexafluorophosphate <88MI 118-03>, *N,N*-dimethyl-(chlorosulfinyl)oxyformaliminium chloride (Equation (123)) <93BMC2419>, mesyl chloride/tetrabutylammonium hydrogensulfate (Equation (124)) <91HCA1213>, 2-chloro-1-methylpyridinium chloride <84CL1465>, carbodiimides <84JA6414, 86T2685, 87CPB4672, 88T613, 88T619, 89JOC4649>, triphenylphosphine/diethyl azodicarboxylate <83CL175>, and tosyl chloride/dabco <84TL3849>.



1.18.3.7.2 Cyclization of β -amino esters

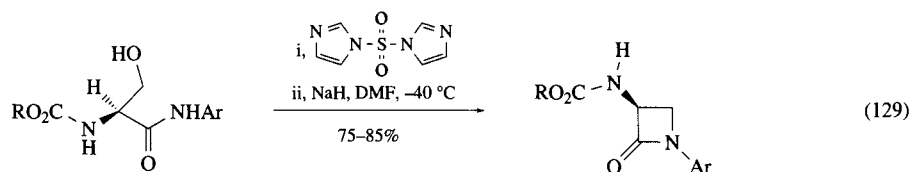
The cyclocondensation of β -amino esters to give β -lactams has been performed in a classical way with Grignard reagents (Breckpot reaction) <84JOC1056>, while in some cases the use of trimethylsilyl esters and amines proved to be much better (Equation (125)) <84JOC1430>. An alternative to the

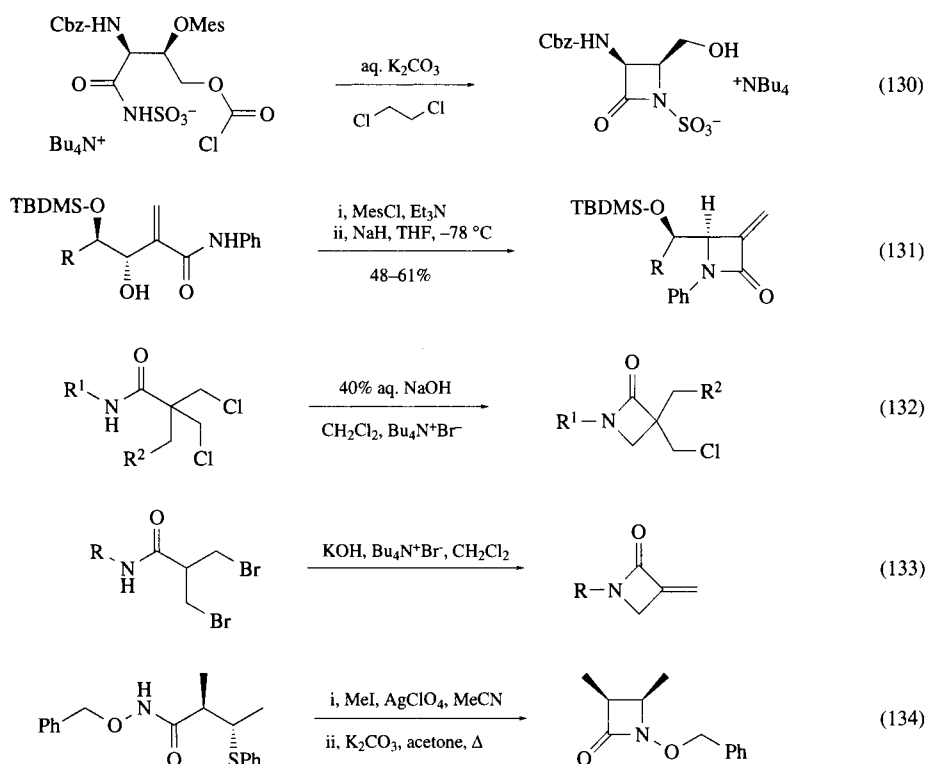
Breckpot reaction is the cyclization mediated by triisobutylaluminium (Equation (126)) <93T1625>. Optically active *t*-butyl 3-amino-2-methyl-3-phenylpropanoates, obtained via stereoselective conjugate addition of lithium (*R*)-(α -methylbenzyl)benzylamide to *t*-butyl cinnamate and its 2-methyl derivative, combined with appropriate sequential elaborations, have been cyclized by LDA to optically active 3-methyl-4-phenyl-2-azetidinones <93CC1153>. The addition of $\text{Sn}[\text{N}(\text{TMS})_2]_2$ to β -amino esters with sterically nondemanding substituents at C(3) or at nitrogen gives β -lactams in 76–100% yield (Equation (127)). More sterically demanding β -amino esters are converted in β -lactams using *in situ* prepared unsymmetrical tin(II) amide reagents <93JA9417>. The conversion of β -amino thioesters to β -lactams occurs without epimerization by reaction with copper(I) triflate (Equation (128)) <89JOC3511, 90JOC1975> or mercury(II) trifluoroacetate <86CL915, 87CL293>.



1.18.3.7.3 Cyclization of β -functionalized amides

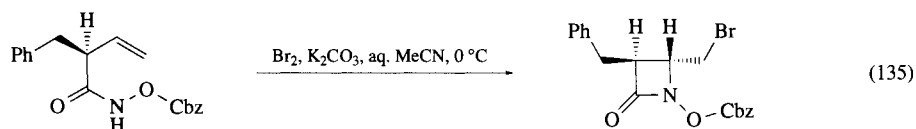
Carboxylic amides or related substrates, for example, hydroxamates, substituted with leaving groups at the β -position, are suitable substrates for β -lactam syntheses. Relatively stable or labile, *in situ* generated, leaving groups can be applied. This cyclocondensation has been performed with β -hydroxy amides utilizing triphenylphosphine/dialkylazodicarboxylates (Mitsunobu conditions) <84CJC2498, 86JAN76, 86T2685, 86TL3819, 87TL1861, 88BSF151, 93BMC2431, 93JOC618>, sulfuric acid diimidazolide (Equation (129)) <85CJC3613> and *p*-toluenesulfonic anhydride <83JCS(P1)605>. The cyclization of β -mesyloxy derivatives proves to be very successful (Equation (130)) <85JOC1126, 87TL1861> and is utilized for the synthesis of more functionalized β -lactams, for example, 3-methylene-2-azetidinones (Equation (131)) <89JOC63>. Both β -chlorocarboxylic amides (Equation (132)) <83H(20)137, 83JA7345, 83S546, 84H(21)413, 84T3223, 91TL4795, 93SC1535> and β -bromo carboxylic amides (Equation (133)) <81CL185, 82CPB1225, 83TL3725, 85TL5385, 86S66, 87JOC4471, 87TL6257> have been utilized to synthesize β -lactams by base-induced cyclization. Sulfonium salts have been utilized as well with success for the synthesis of β -lactams with high stereoselectivity (Equation (134)) <93JCS(P1)2861>. Pummerer-type rearrangements are also useful for the preparation of azetidin-2-ones <85JA5490, 87CC1511, 89JCS(P1)1862>.





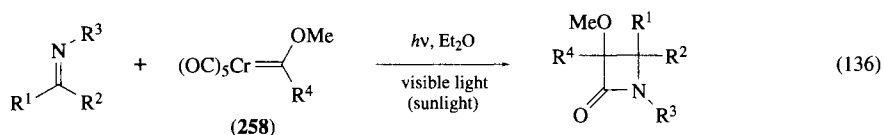
1.18.3.7.4 Cyclization of β,γ -unsaturated carboxylic amides, imidates, and hydroxamates

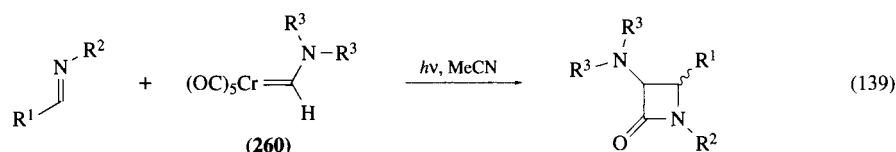
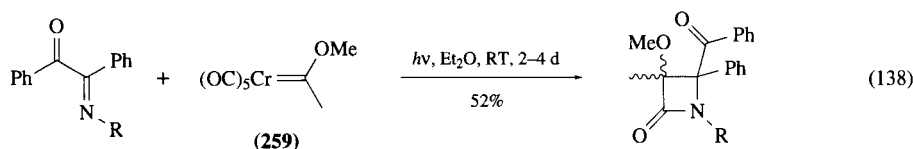
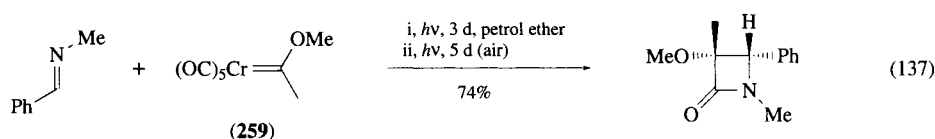
Electrophile-induced cyclization of β,γ -unsaturated carboxylic amides, imidates, hydroxamates, and related substrates, is usually effected by halogens and leads to β -lactams (Equation (135)) <82JA3233, 85TL5385, 87JOC4471, 88JOC4006>. The β -bromo- β,γ -unsaturated carboxylic amides undergo a copper-induced cyclization to 4-methyleneazetidine-2-ones <89TL337>.



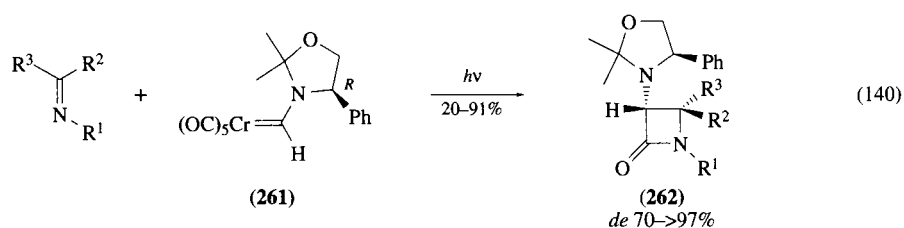
1.18.3.7.5 Cycloaddition of chromium-carbene complexes with imines

The synthesis of β -lactams by cycloaddition of chromium carbene complexes, for example, (258)–(260), with a whole range of imines, including simple imines, α -diimines, α -iminoketones, 2-aza-1,3-dienes, iminodithiocarbonates, etc., is a very powerful and flexible method <82JA5538, 84JA2680, 85T5833, 87JA1101, 92JOC447, 93OSC(8)216>. The [methoxy(methyl)carbene]chromium complex, (259), proved to be an elegant reagent for β -lactam synthesis. Also chromium aminocarbene complexes, for example, (260), have been used with success <87JA1101, 88JOC3113, 91JOM(413)143>.





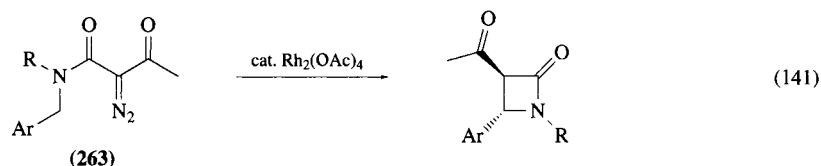
The mechanism of this reaction has been investigated and is thought to involve a reaction of the imine with a photogenerated metal-bound ketene. It involves a two step process that requires an imino nitrogen sufficiently nucleophilic to attack the metal-ketene complex, as well as an imine carbon sufficiently electrophilic to undergo the second step ring closure $\langle 88\text{JOC}3113 \rangle$. Also optically active chromium complexes, for example, (261), have been utilized for the construction of optically active β -lactams (262) $\langle 90\text{JA}1109, 92\text{JOC}5453 \rangle$. Utilizing (*S*)-valine and (*R*)-phenylglycine-derived chiral auxiliaries, good to excellent chemical yields with high diastereoisomeric excess are obtained.

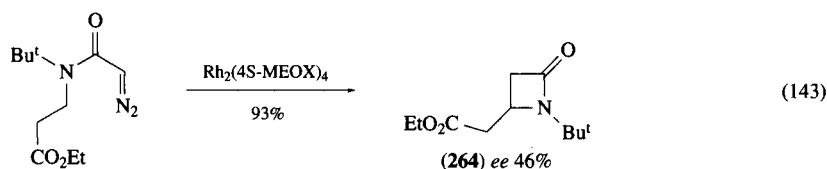
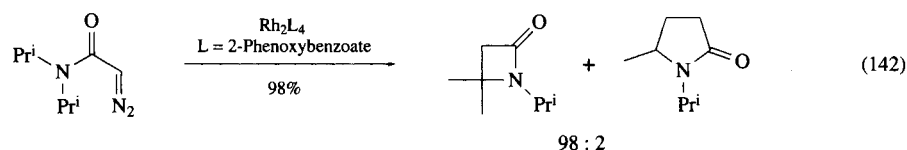


Chromium carbene complexes are useful for the preparation of azetidinyldene complexes, which can be oxidized to β -lactams (see Section 1.18.3.7.15).

1.18.3.7.6 Rhodium(II)-catalyzed insertions of diazo compounds

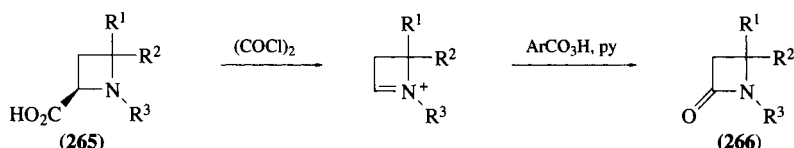
Diazoacetoacetamides (263) and related diazo compounds undergo rhodium(II)-catalyzed decomposition to form β -lactams in high yield and with good stereocontrol $\langle 88\text{JOC}3384, 88\text{TL}2639, 89\text{TL}5397, 91\text{JOC}820, 92\text{JA}1874, 92\text{JOC}4404, 93\text{BMC}2409 \rangle$. It has been shown that 2-phenoxybenzoate is the best ligand (L) for β -lactam synthesis (otherwise more γ -lactam formation) (Equation (142)). Dirhodium(II) catalysts with chiral carboxamide ligands, for example, dirhodium(II)tetrakis(methyl-2-oxazolidinone-4(*S*)-carboxylate) $[\text{Rh}_2(4\text{S-MEOX})_4]$, afford an enantioselective route to β -lactams (264) $\langle 92\text{TL}5983, 93\text{BMC}2409 \rangle$.



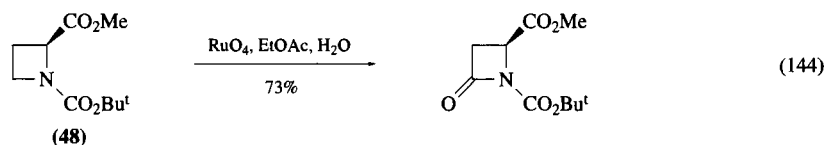


1.18.3.7.7 Oxidation of azetidines to azetidin-2-ones

The conversion of azetidine-2-carboxylic acids (**265**) into β -lactams (**266**) and 3-chloro-2-pyrrolidinones via reaction with oxalyl chloride and peracids has been investigated in detail, revealing that the product ratio and the stereochemistry is highly dependent upon the substituent pattern (Scheme 49) <84TL3111>. Azetidine-2-carboxylic esters (**48**) are oxidized in β -lactams by ruthenium tetroxide (Equation (144)) <85CPB5515, 86H(24)2539>.



Scheme 49

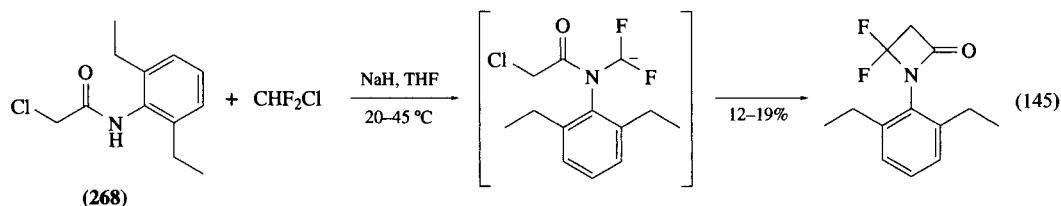


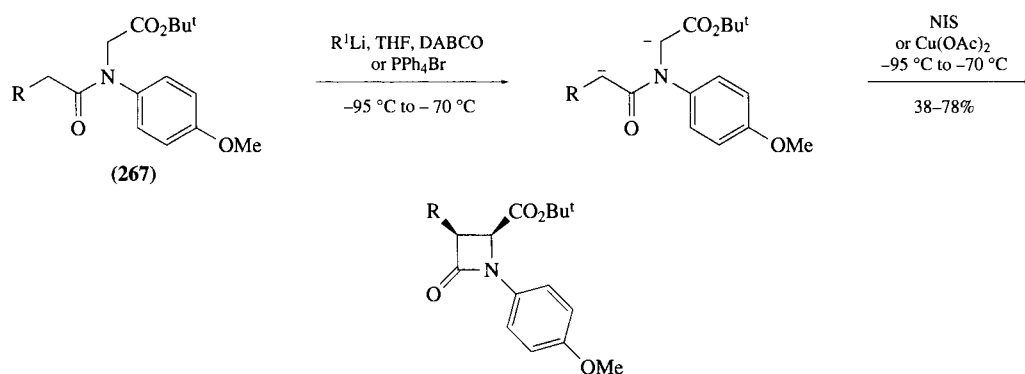
Oxidation of 1-hydroxyazetidines <85TL2809, 87H437> or 1-azetine *N*-oxides <83JOC486> with excess lead(IV) acetate leads to 1-acetoxyazetidine-2-ones.

1.18.3.7.8 Formation of the C(3)—C(4) bonds of β -lactams

Tertiary amides (**267**), bearing an activated methylene function at nitrogen, are converted into the corresponding dianions which are oxidized with NIS or a copper(II) carboxylate to form β -lactams stereoselectively (Scheme 50). It has been demonstrated that NIS is *cis*-selective while copper(II) salts are nonselective <92JOC1864>. The use of this method has become widespread for the synthesis of 3-amino-2-azetidinones <91T7503>.

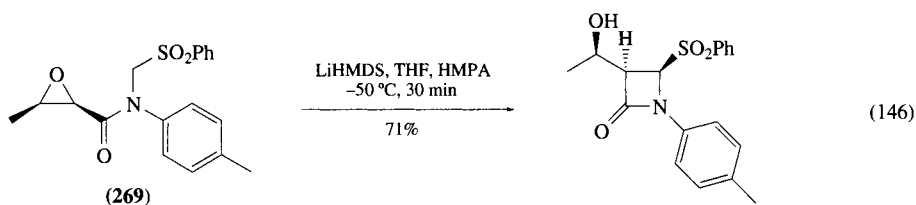
The reaction of *N*-(2,6-diethylphenyl)-2-chloroacetamide (**268**) occurs with chlorodifluoromethane in the presence of sodium hydride to give 4,4-difluoro-2-azetidinones (Equation (145)) <93JOC245>.





Scheme 50

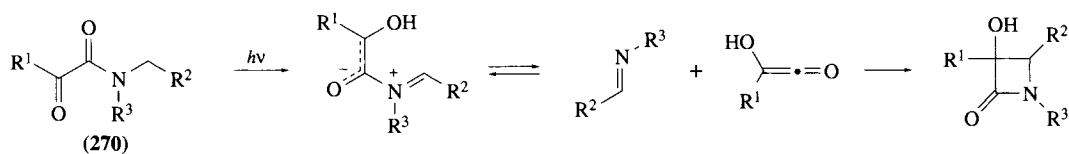
Also α,β -epoxycarboxylic amides (269) with a pendant active methylene function at nitrogen are apt to give base-induced cyclization to β -lactams (Equation (146)) <84H(22)1727, 86H(24)1007, 87BCJ645, 87TL781, 88JHC487, 88TL815>.



1.18.3.7.9 Photochemical synthesis of β -lactams

The photochemical generation of metal-bound ketenes from carbene chromium complexes and the subsequent coupling with imines to give β -lactams is treated separately (Section 1.18.3.7.5).

Photochemical cleavage of α -oxoamides (270) produces imines and hydroxyketene intermediates, which undergo cyclocondensation to β -lactams (Scheme 51) <83JA1958, 87CC1413, 87T1513, 89JA697>. Chiral crystals of *N,N*-diisopropyl arylglyoxylamides were formed which photochemically converted into optically active β -lactams <93JCS(P1)1129>. Cyclization of *N*-thioacyl carboxylic amides also produces 4-sulfonylated β -lactams <85TL4475, 86TL1335, 88JCS(P1)1353, 88JCS(P1)2203>.

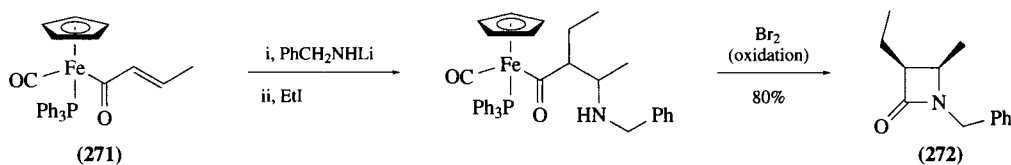


Scheme 51

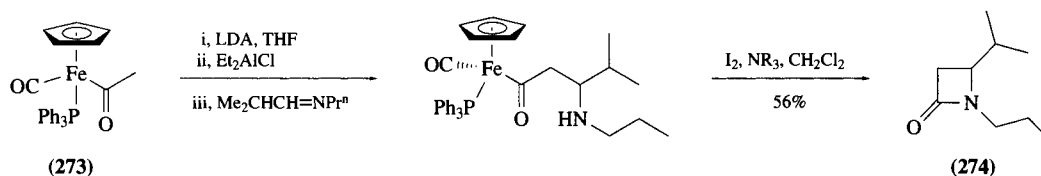
Asymmetric type-II photocyclization of acrylylureas produces β -lactams <92JOC3490>. On the other hand, *N,N*-dibenzyl α,β -unsaturated thioamides undergo photochemical cyclization to yield 2-azetidinethiones <90CC1214>.

1.18.3.7.10 Mediation of β -lactam synthesis by iron and cobalt complexes

Iron complexes (271) and (273), are versatile substrates through which β -lactams, (272) and (274), can be synthesized in an elegant way (Schemes 52 and 53) <84JA441, 85TL3079, 86JA6328>. The required (β -aminoacyl)iron species are formed by a Michael type process or via a metalated acyliron species.

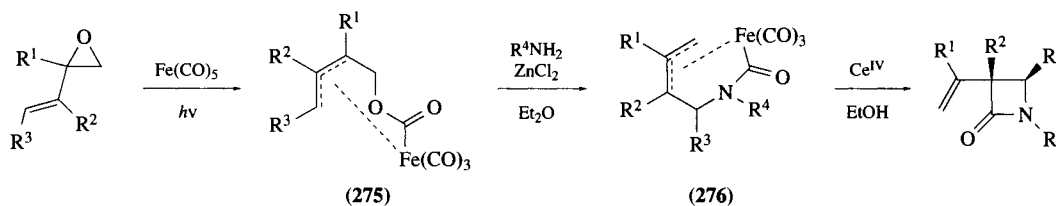


Scheme 52



Scheme 53

The photochemically generated (π -allyloxycarbonyl)tricarbonyl-iron complexes (275) react with amines in the presence of a Lewis acid to give (276), which are oxidatively cyclized by cerium(IV) salts (Scheme 54) <83JCS(P1)2851, 84CC494, 85JCS(P1)2375, 85T5871>. Allylaminocarbonyl-cobalt complexes can be utilized as well <85JCS(P1)2375>.



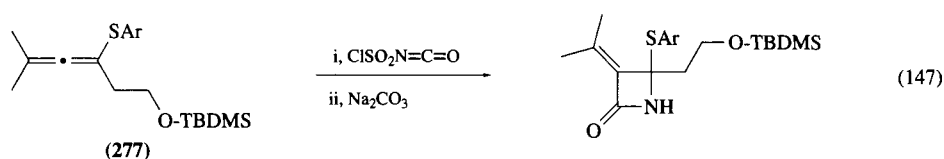
Scheme 54

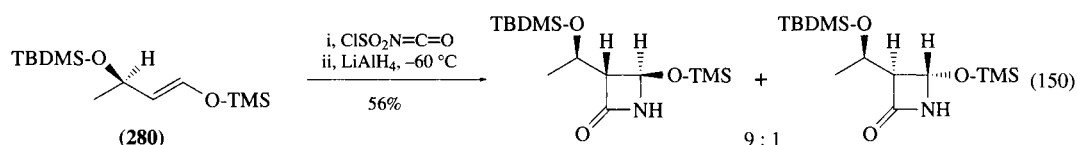
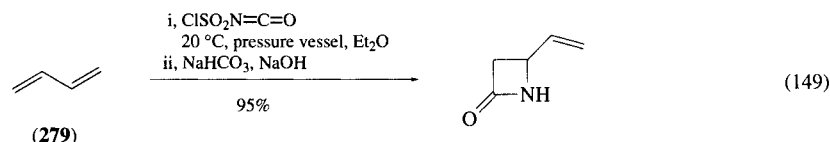
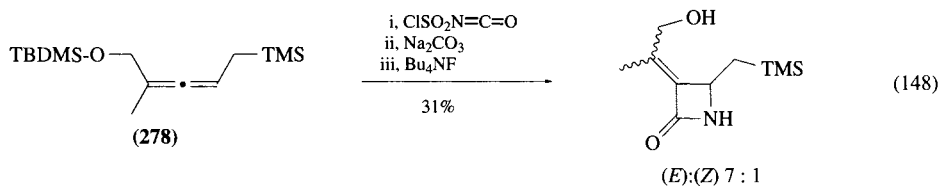
Cationic iron-vinylidene complexes have been used to synthesize β -lactams <87JOC3940>.

1.18.3.7.11 Cycloaddition of isocyanates with alkenes

The reaction of isocyanates with alkenes to give β -lactams requires activation of the former by electron-withdrawing groups or activation of the alkene by electron-donating substituents. *Ab initio* calculations predict that the [2 + 2] reaction takes place through a concerted suprafacial mechanism <93CC1450>.

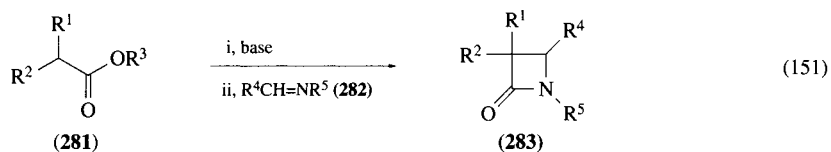
The classical reaction with chlorosulfonyl isocyanate has been extended to allenyl sulfides (277) contained in Equation (147) <85TL5001, 86CC941, 86JOC1571, 87CC735>, allenyl acetates <84CC948, 85JOC4245>, vinyl acetate <93OSC(8)3>, allyl- and (allenylmethyl)trimethylsilanes (278) <90CC1230, 93BMC2405>, 1,3-dienes (279) <86JOC3652, 87S324, 87TL683, 87TL4097>. Optically active trimethylsilyl enol ethers (280), giving a good stereoselectivity, have been used as well (Equation (150)) <86EUP167155>.





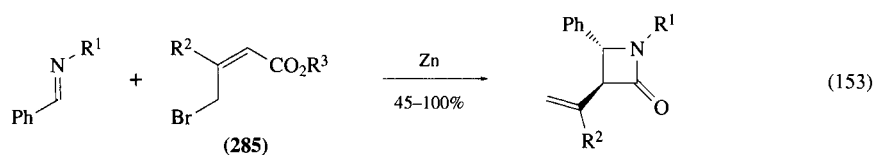
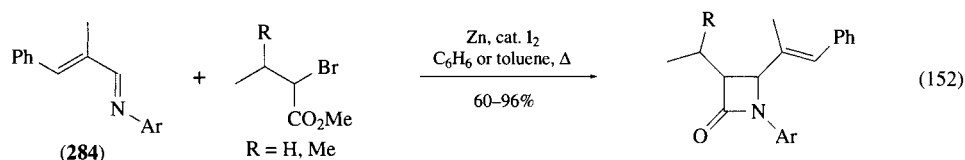
1.18.3.7.12 Ester enolate-imine condensation

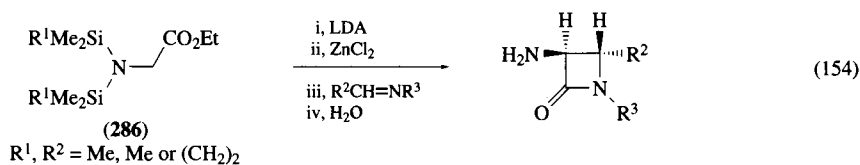
The one-pot condensation of an ester enolate (281) with an imine (282) is a very powerful synthetic procedure for β -lactams (283). The scope and limitations of this reaction have been reviewed [89CRV1447, 91COS(5)85]. The latter reviews cover in detail specific aspects of this cyclocondensation.



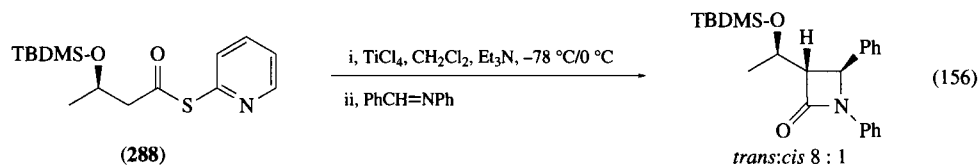
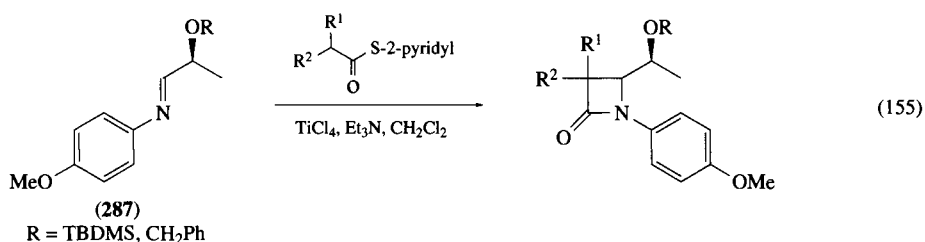
Various ester types and imine types can be utilized. The reaction is mediated by various metals, including zinc, lithium, aluminium, tin, boron, zirconium, and titanium.

The use of zinc enolates, such as Reformatsky reagents, to produce β -lactams can be applied to α,β -unsaturated aldimines (284) [88CC809, 89JOC5736] or γ -bromo- α,β -unsaturated carboxylic esters (285) [88CR(B)1805]. The zinc(II) iodide mediated condensation of silyl ketene acetals with imines to afford β -lactams has been reported [88T4157]. Zinc enolates, generated from lithio salts of *N,N*-diprotected glycine esters (286) and ZnCl_2 , react with 1,4-diaza-1,3-butadiene systems and aldimines selectively affording *trans*-3-amino-4-functionalized 2-azetidinones (Equation (154)) (*de* $\geq 90\%$) [91JOC5868, 93BMC2467].

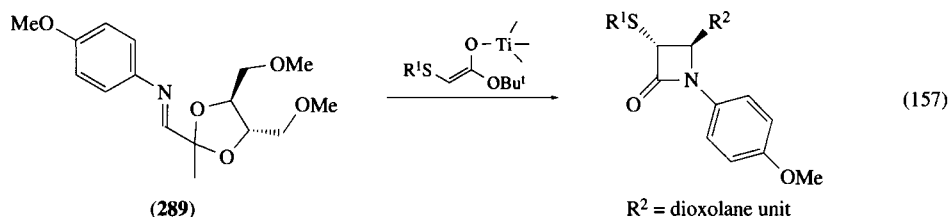




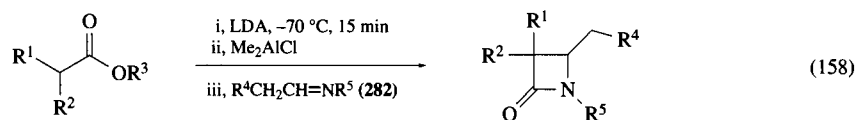
The use of thioesters, instead of carboxylic esters, in the condensation with imines to give β -lactams, allows the avoidance of strong bases for the enolate generation. The enolization is carried out at -78°C and the condensation of 0°C , affording β -lactams in nearly quantitative yield (91T8767). Highly diastereoselective syntheses of β -lactams using titanium enolates, derived from 2-pyridyl thioesters, and chiral imines (287), derived from chiral α -alkoxy aldehydes, have been obtained (Equation (155)) (92TL1113, 93G181, 93JOC4746). Condensations of imines, derived from enantiomerically pure α -alkoxy aldehydes, and titanium-enolates, derived from chiral 3-hydroxybutyrate (2-pyridyl thioester) (288), show high diastereofacial preferences (Equation (156)) (92JOC4155, 93TL6921).



Titanium enolates, generated from α -sulfenylated acetates, react with chiral imines (289) to give (3*R*,4*R*)-substituted 3-sulfenylated azetid-2-ones (Equation (157)) (93BMC2343).

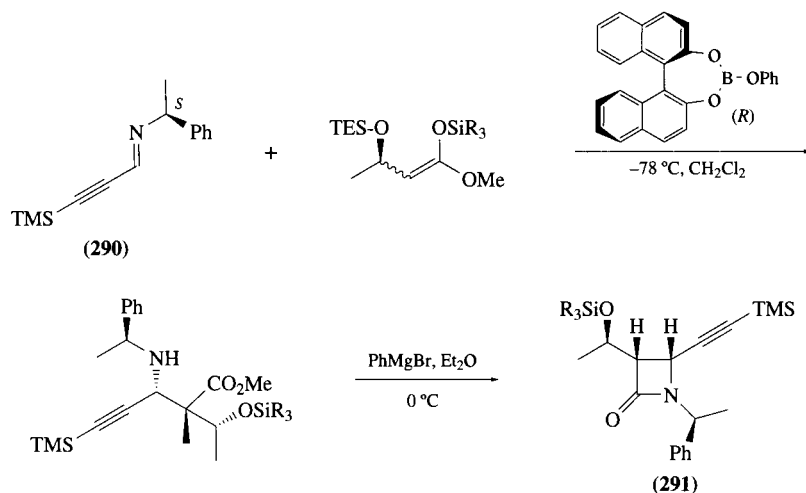


The use of aluminum enolates is valuable when utilizing enolizable *N*-alkyl imines (282), which normally do not give good results in β -lactam syntheses (Equation (158)) (87TL3257, 87TL3377).



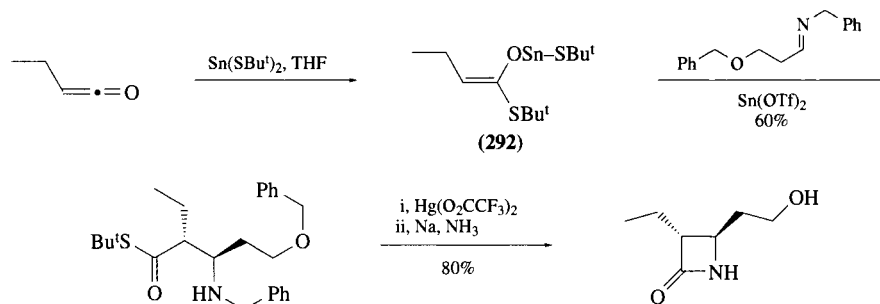
The condensation of zirconium enolates, derived from thioesters, with imines has been reported to afford β -aminothioesters, which are suitable substrates for β -lactams (87TL3257). The phenomenon that some enolate-imine condensations do not directly yield β -lactams is often encountered with boron enolates (85CPB520). The stereochemical course of (vinyl oxy)borane-imine condensations has been examined. Antiaddition products are usually the major compounds, often with good diastereoselectivity (87JOC3489). The asymmetric synthesis of the carbapenem antibiotic (+)-PS-5

has been accomplished utilizing the antiselective boron enolate-imine condensation with very high asymmetric induction <87JOC3488>. The asymmetric reaction of chiral imines (**290**) with silyl ketene acetals, prepared from (3*R*)-hydroxybutyrate, mediated by a boron reagent and leading to β -amino esters with high diastereoselectivity, has been described. Subsequent cyclization with phenylmagnesium bromide leads to β -lactam (**291**) <93BMC2337>.



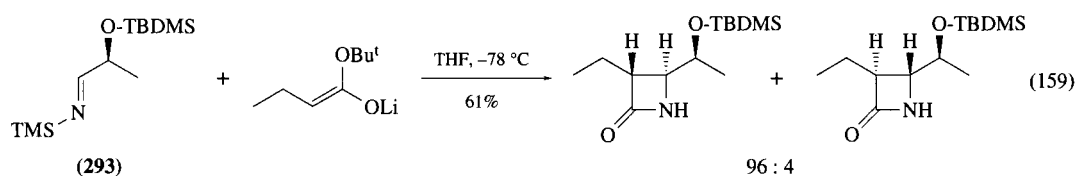
Scheme 55

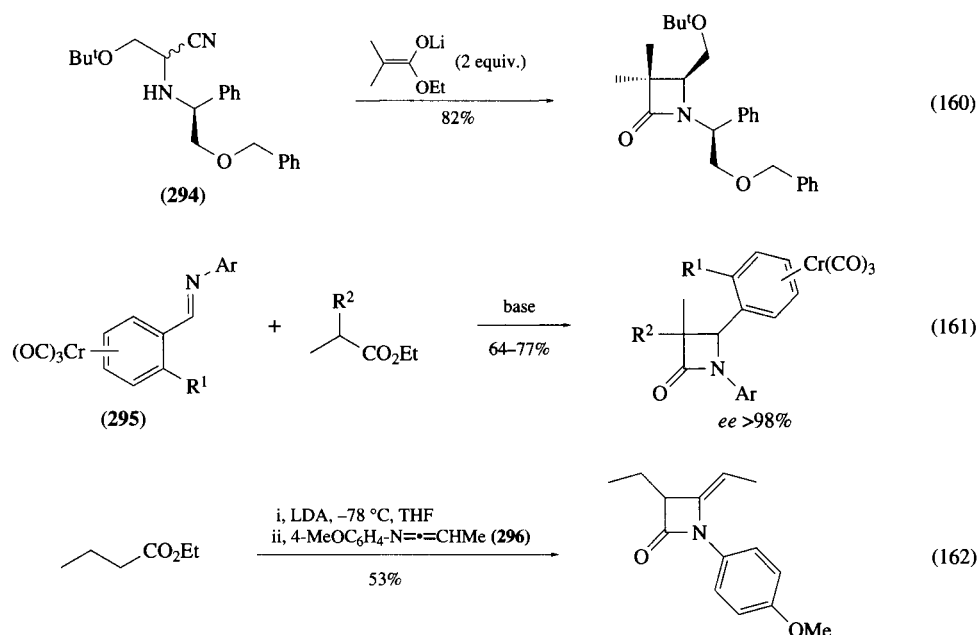
Vinyloxystannanes, for example, (**292**), prepared from ketenes, add across aldimines to produce anti β -amino thioesters, which are easily transformed into β -lactams (Scheme 56) <86CL1013>.



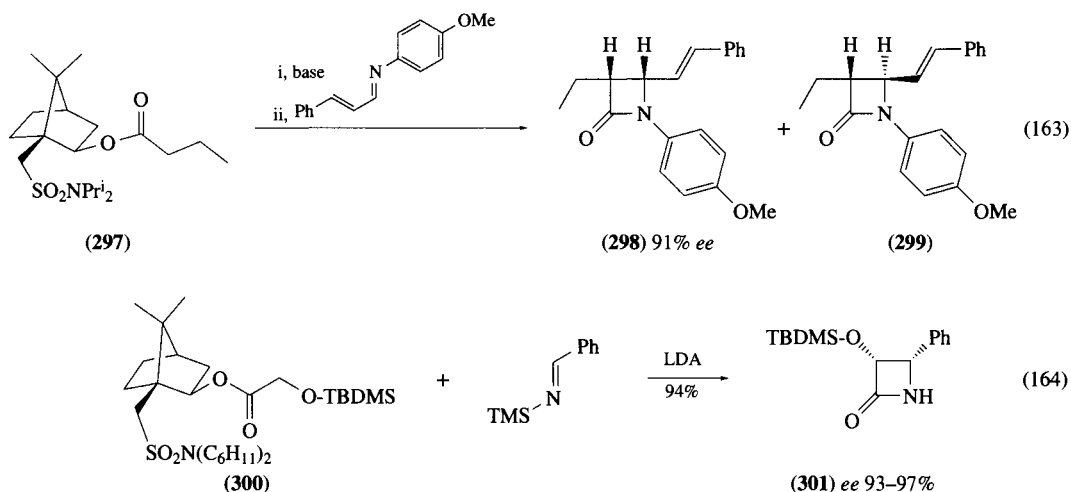
Scheme 56

The majority of condensations have been performed with lithio enolates, probably because of the ease of operation <89CRV1447>. An enormous number of combinations of imino types and enolate types have been described. Imino substrates include aromatic aldimines <92JOC4155>, chiral *N*-trimethylsilyl aldimines, for example, (**293**) <88JA6879, 91JOC5984, 91T9061>, chiral aldimines <92JOC3906, 93BMC2337, 93BMC2343> aliphatic *N*-silylimines <91SL243>, aromatic *N*-silylimines <88T4157, 91JOC1681, 92T6985, 93BMC2467>, *N*-(tritylsulfonyl)imines <86JOC1929>, aliphatic aldimines <87TL3377>, α -diimines <91JOC5868>, *O*-benzyl oximes <84CL369>, chiral α -amino nitriles (aldimine precursor), for example, (**294**) <91JOC1933>, benzylideneaniline–chromium complexes (**295**) <91CC982> and ketenimines (**296**) <87TL4347>.





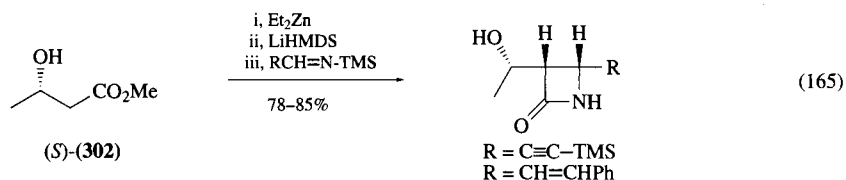
Several types of esters have been used in the condensation reactions, among others carboxylic esters <86JOC1929, 87TL3377, 90TL2493, 91JOC1933, 91JOC5984, 91SL243>, *N,N*-disilyl-protected glycines <91JOC1933, 91JOC5868, 91T7503, 91T9061, 93BMC2351>, 2-pyridyl-thioesters <91T8767, 92TL1113>, chiral 2-pyridylthioesters <92JOC4155>, chiral carboxylic esters <92JOC3906, 93BMC2439, 93BMC2467>, and α -sulfenyl acetates <93BMC2343>. The first examples of asymmetric induction using lithium enolates of α -monosubstituted esters have been reported <86JA6054>. The presumed (*E*)-enolate derived from (297) reacts with a cinnamaldehyde to give β -lactams (298) (74%) and (299) (7%) along with a 95% recovery of the chiral auxiliary (Equation (163)). The major product is formed with 91% *ee*. Another example of the use of chiral carboxylic esters concerns (–)-10-dicyclohexylsulfamoyl-D-isoborneol ester (300), which affords (3*R*, 4*S*)-3-[(*t*-butyldimethylsilyl)oxy]-4-phenyl-2-azetidinone (301) in high enantiomeric purity (Equation (164)). The corresponding 1-benzyl β -lactam has been coupled with 7-(triethylsilyl)baccatin in the presence of sodium hydride to give an efficient taxol semisynthesis <93BMC2467>.



Chiral esters have also been examined in the ketene acetal route to β -amino esters <87TL227, 88T4221>. The use of tin enolates, derived from thioesters, and chiral imines has been found to be successful as a route towards β -lactams <87CL293>.

The use of β -hydroxybutyrate as the ester component leads to β -lactams with a α -hydroxyethyl substituent at C(3), an important substructure of many carbapenem antibiotics. Condensation of

the dianion of β -hydroxybutyrate with aldimines gave rise to β -lactams. The majority of these condensations proceed with good diastereoselectivity at C(3) relative to C(1'), but poor diastereoselectivity at C(4) <84CL1927, 84JA4819, 84TL3779, 85TL3903, 87JA1129, 87JCS(P1)2637, 89T1283>. The overall diastereoselectivity has been improved by silylation of the β -hydroxy moiety <85JOC5120>, or by the sequential treatment of (*S*)- β -hydroxybutyrate (**302**) with diethylzinc, LiHMDS and aldimines (Equation (165)) <88CC1376>. Reactions between imines and vinyloxyboranes derived from thioesters of β -hydroxybutyrate follow a different stereochemical course than reactions of lithium enolates. The major β -amino esters always provide *trans*-3,4-disubstituted β -lactams with a syn C(1')-C(3) relationship <85TL1523, 86TL2149, 86TL2153, 88TL1409>.

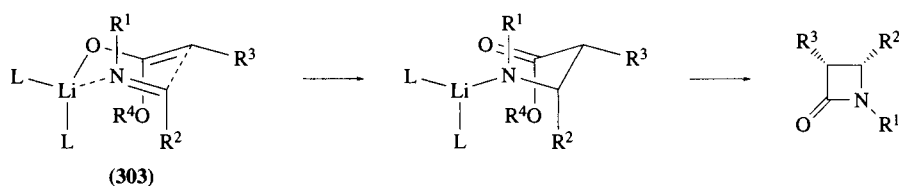


The major product from (*E*)-enolates are *cis* products, while (*Z*)-enolates afford mixtures of *cis* and *trans* β -lactams <84JA4819>. The formation of (*E*)-enolates mostly occurs in THF, while the addition of HMPA gives (*Z*)-enolates <84JA4819, 89CRV1447>.

The 3-amino- β -lactam structure is an important unit in antibacterial β -lactams. The ester enolate-imine condensation is an elegant way to the enantioselective synthesis of 3-amino-2-azetidinones through three approaches, namely (i) the reaction of a chiral ester derivative of *N,N*-diethylglycine, (ii) the use of chiral *N*-(α -methylbenzyl)imines, and (iii) the application of chiral imines, among others, derived from (2*R*)-2,3-*O*-isopropylidene-glyceraldehyde <91T7503, 92JOC3906>.

The transition states for the reactions of α -hydroxy ester lithium enolates with imines to form β -lactams have been located using *ab initio* molecular orbital theory at the RHF/3-21G and RHF/6-31G** levels. Using MP2/6-31G* energy calculations it was indicated that the (*Z*)-isomer of the ester enolates is much more stable than the (*E*)-isomer (5.0–6.9 kcal mol⁻¹), due to coordination of lithium with the α -hydroxyl oxygen. The reaction of the (*Z*)-enolate with an imine proceeds through a boat-like transition state, which is energetically favored over an envelope-like transition state for the reaction of the (*E*)-enolate with an imine <93TL6241>.

The two-step mechanism of the condensation of an ester enolate with an imine proceeds via a six-membered transition state similar to that of the aldol condensation <89CRV1447, 90JOC481, 92JOC3906, 92T6985>. Ketenes are not intermediates in most or all of these reactions. The addition of a lithium (*E*)-enolate to an (*E*)-imine via a chair-like transition state (**303**) affords a *cis*- β -lactam (Scheme 57). The lack of selectivity with lithio-(*Z*)-enolates can be ascribed to additional steric interaction in the transition state <89CRV1447>.



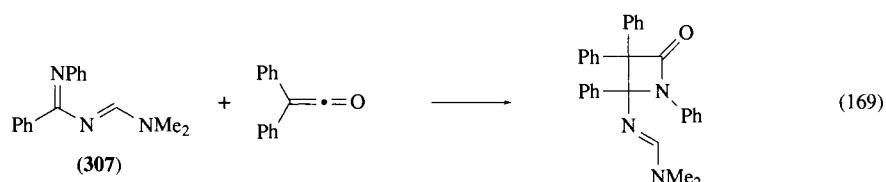
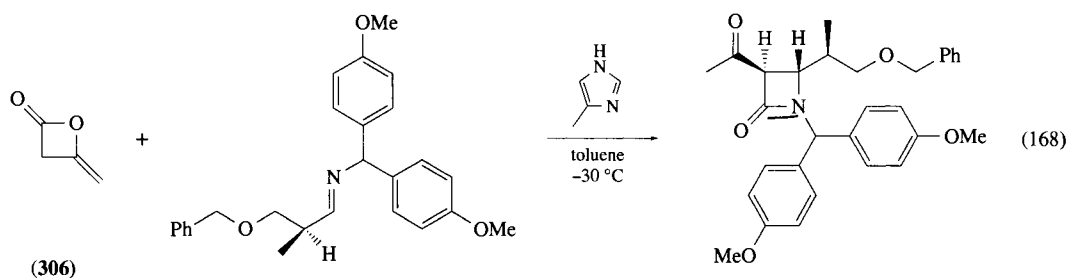
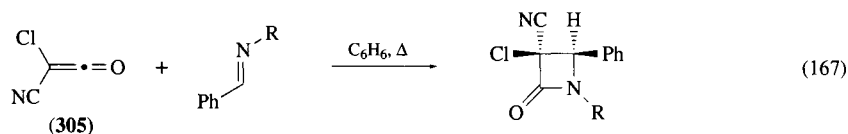
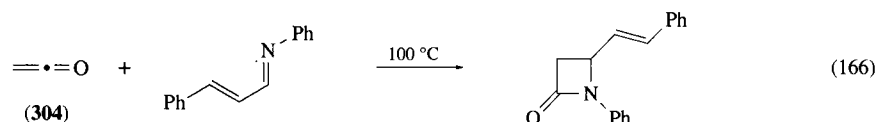
Scheme 57

In addition to the kinetic diastereoselection, the product β -lactams can isomerize under the basic reaction conditions. This latter process seems to be a function of the nitrogen substituent, the C(3) substituents, and the reaction medium. Concerning the use of lithium enolates, the following trends are observed; (i) *N*-aryl β -lactams isomerize more easily than *N*-protio or *N*-silyl β -lactams, (ii) substituents at C(3) that enhance acidity make β -lactams more susceptible to isomerization, (iii) the smaller the C(3) substituent, the faster the rate of isomerization, and (iv) the more polar the solvent, the faster the rate of isomerization <89CRV1447>.

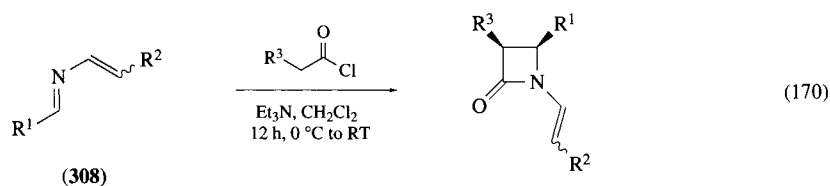
1.18.3.7.13 Cyclocondensation of ketenes and imines

The condensation of ketenes with imines to give β -lactams is a classical reaction known as the Staudinger reaction <91COS(5)85, 91T7503>. This versatile procedure for the stereocontrolled synthesis

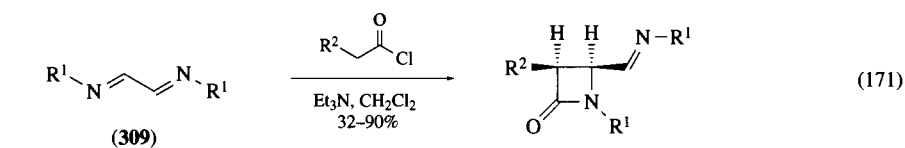
of 2-azetidiones involves a [2 + 2] cycloaddition reaction in which the ketene is mostly generated either from acid chlorides and related derivatives in the presence of tertiary amines, thermally $\langle 85\text{JOC}4231 \rangle$, or photochemically from metal carbenes $\langle 88\text{JOC}3113 \rangle$. Ketenes, for example, ketene (**304**) $\langle 83\text{CPB}538 \rangle$ and cyanoketene (**305**) $\langle 85\text{JOC}4231 \rangle$, react with imines, formimidates, and thioformimidates to give 3-cyano-2-azetidiones with *trans* stereochemistry at C(3) and C(4) (Equations (166) and (167)). Other examples of the reaction of ketenes with imines include the use of (*N*-alkyl-*N*-phenylamino)ketenes $\langle 89\text{JOC}2838, 91\text{JOC}6118 \rangle$, diketene (**306**) $\langle 83\text{CPB}1902, 88\text{T}2149, 89\text{T}5767 \rangle$, and 1,3-diaza-1,3-dienes (**307**) $\langle 86\text{TL}5875 \rangle$.



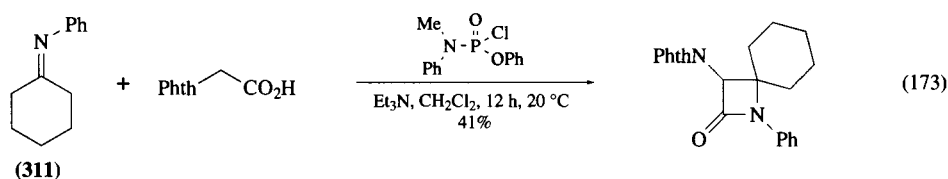
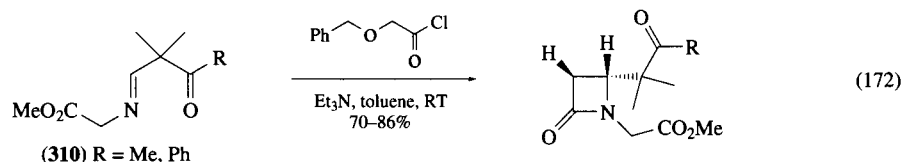
The majority of syntheses of β -lactams via the Staudinger reaction are produced from acid chlorides or other ketene precursors. Various imino substrates have been used, including dithiocarbonate imines $\langle 92\text{S}439, 93\text{BMC}2439 \rangle$, 2-aza-1,3-dienes (**308**) $\langle 88\text{TL}2409, 90\text{TL}451, 93\text{JOC}5771 \rangle$, α,β -unsaturated imines $\langle 89\text{CC}72 \rangle$, 1,4-diaza-1,3-dienes (**309**) $\langle 92\text{JOC}5921 \rangle$, hydrazones $\langle 90\text{JOC}2196 \rangle$, α -fluoro aldimines $\langle 84\text{JOC}1427 \rangle$, 1,2-iminoketones, for example, (**310**) $\langle 89\text{JOC}3792, 93\text{BMC}2369 \rangle$, ketimines, for example, (**311**) $\langle 67\text{T}4769, 84\text{S}846 \rangle$, imidates $\langle 84\text{S}1070, 85\text{SC}1229 \rangle$, and thioimidates $\langle 81\text{SC}1, 85\text{ZN}(\text{B})115 \rangle$.



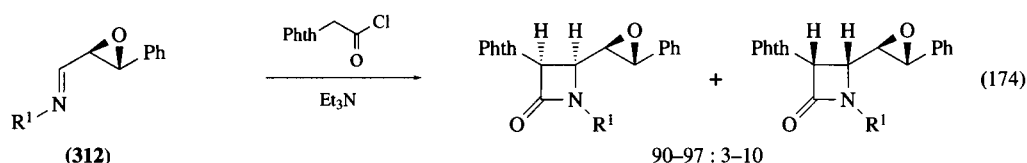
$\text{R}^1 = \text{Ph}, \text{PhCH}=\text{CH}, \text{PhCH}=\text{CMe}, \text{Ph}_2\text{C}=\text{CH}; \text{R}^2 = \text{H}, \text{Me}; \text{R}^3 = \text{PhO}, \text{Phth}$



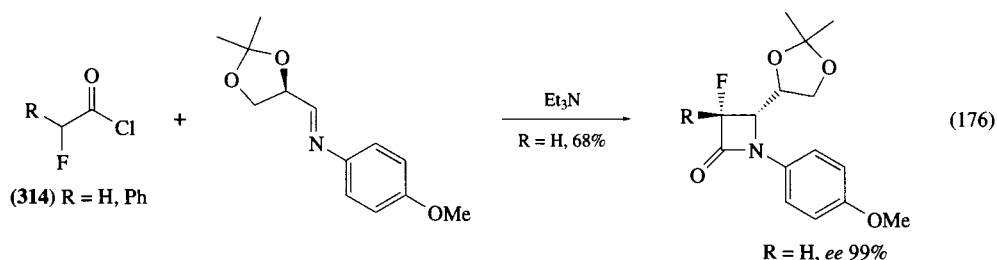
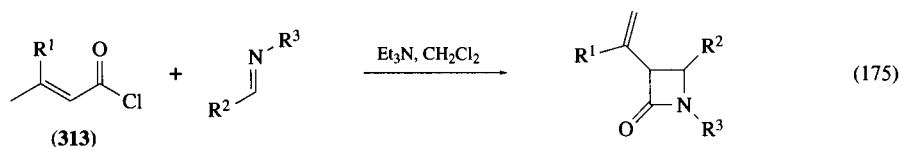
$\text{R}^1 = \text{PMP}$ or $\text{CH}(\text{PMP})_2$; $\text{R}^2 = \text{Ph, Me, PhS, PhCH}_2\text{O, PhO, Et, Pr}^i, \text{Cl, Phth, Br, vinyl}$



Imines derived from chiral α,β -epoxyaldehydes, for example, **(312)**, have been shown to be good chiral glyoxal imine synthons in ketene-imine cycloaddition reaction (Equation (174)). This process, which proceeds with high levels of reaction diastereoselection, affords enantiomerically pure *cis*-substituted 3-amino-4-alkyl-2-azetidiones <88TL5065>.

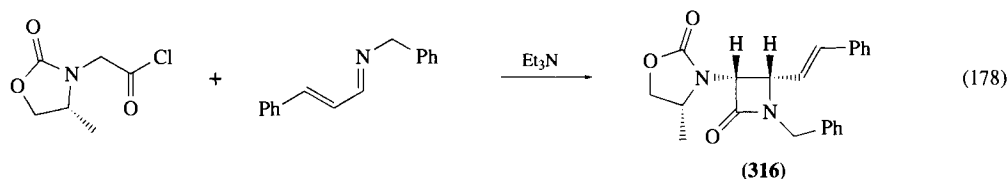
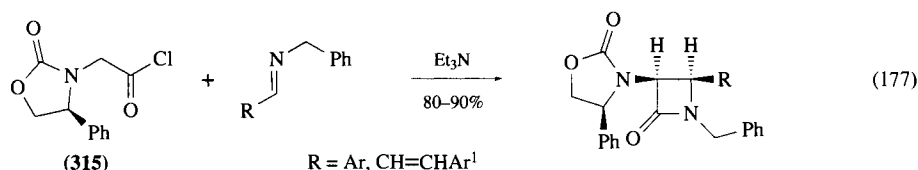


Several types of ketene precursors have been used, including carboxylic acid chlorides <83NJC691, 91COS(5)85, 91T7503>, α,β -unsaturated acid chlorides **(313)** <90JOC575>, α -fluoro acid chlorides **(314)** <93JOC2454>, α -sulfenylated acid chlorides <91JOC4418>, and other α - or β -functionalized carboxylic acid chlorides <91COS(5)85, 91T7503>. Carboxylic acids can be condensed with imines under the influence of trifluoroacetic anhydride, triphenylphosphine dibromide, cyanuric chloride, $\text{Me}_2\text{N-P(O)Cl}_2$, PhOP(O)Cl_2 , and 2-chloro-1-methylpyridinium iodide <83S833, 85JCS(P1)2045, 85T1703, 85TL3041, 87CJC1503, 87TL1945, 89CC72, 91TL581>.



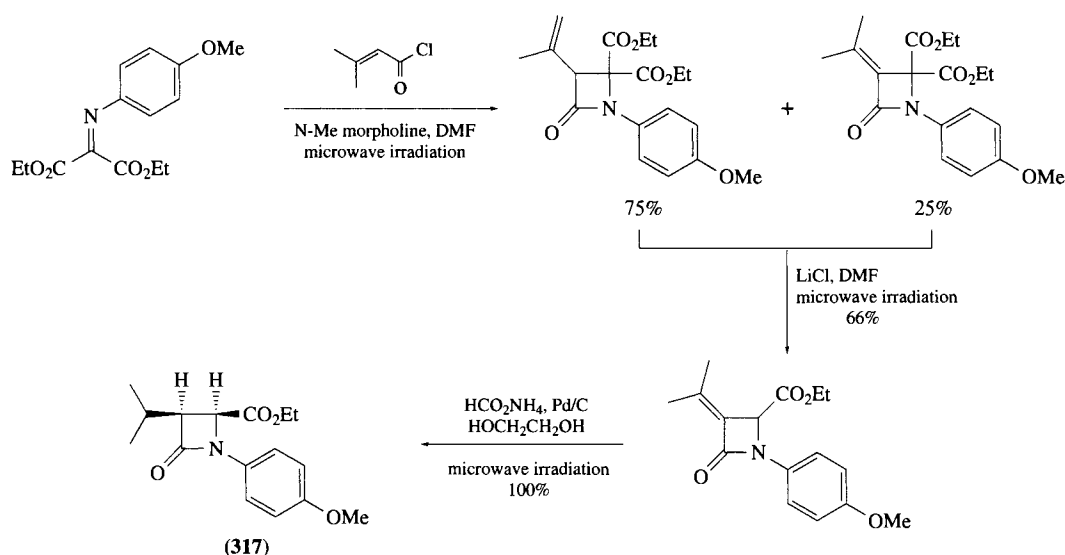
The use of (4*S*)-phenyloxazolidinylacetyl chloride **(315)** has been successful as a homochiral ketene synthon, which reacts with *N*-benzyl imines to give β -lactams with exceptional levels of asymmetric induction (Equation (177)) <85TL3783, 85TL3787>. This process has been utilized for the

synthesis of *cis*-3(*R*)-hydroxyl-4(*S*)-phenyl-1-(4-methoxyphenyl)-2-azetidinone, which is a suitable precursor to the taxol side chain <93BMC2475> and the synthesis of a conformational analog of deoxybouvardin via β -lactam (**316**) <91JOC5385>.



The stereoselectivity of the reaction of benzylideneamines and cinnamaldehydes has been compared <91JA5784> with ketenes. The ketenes include those generated by the reaction of optically active oxazolidinone acid chlorides with triethylamine, and complexed ketenes, generated by photolysis of optically active oxazolidinone–chromium–carbene complexes in the presence of added triethylamine <91JA5784>. The absolute stereochemistry is determined primarily by the structure of the chiral auxiliary. The relative *cis-trans* stereochemistry is determined primarily by the structure of the imine and the free or bound character of the ketene <91JA5784>.

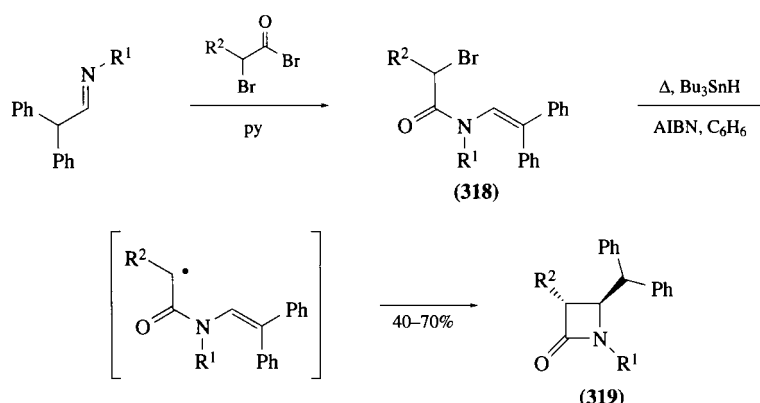
A simplified and stereocontrolled synthesis of β -lactams (**317**) starting from an oxomalonate imine has been achieved in open vessels under microwave irradiation in an unmodified domestic microwave oven (Scheme 58) <93BMC2363>. Also isomerizations of alkenyl groups and reduction of the carbon-carbon double bond occurs efficiently under microwave irradiation <93BMC2363>.



Scheme 58

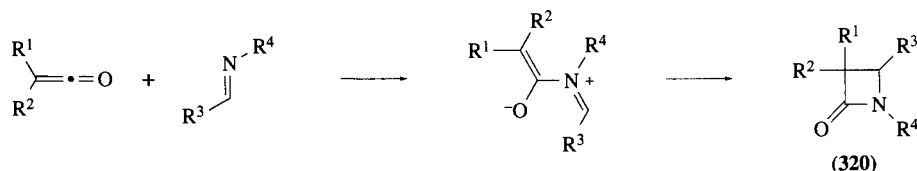
It has been reported that diphenylacetaldehydes react with α -bromo acyl bromides in the presence of pyridine to afford enamides (**318**), which undergo free radical cyclization to form β -lactams (**319**) <91TL2335>.

A semiempirical theoretical study on the formation of β -lactams (**320**) from ketenes and imines has been disclosed (Scheme 60) <93JA995>. The approximate SCF molecular orbital theory calculations



Scheme 59

revealed that the reaction proceeds via a nonconcerted two-step mechanism, in good agreement with related experimental evidence. The first step involves formation of the N(1)—C(2) β -lactam bond leading to a zwitterionic intermediate, and the second step leads to ring closure through formation of the C(3)—C(4) bond. The transition step associated with the latter step has significant biradical character, especially when there is a carbonyl group at the C(4)-position. Further, it has been demonstrated that the experimental stereoselectivity of the reaction is correctly predicted by the calculations. In the second transition state, the substituent at C(4) is inward with respect to the β -lactam ring when an (*E*)-imine is used, whereas when the imine has the (*Z*)-configuration, the disposition is outward. The formation of *cis*- and *trans*- β -lactams depends upon the *endo* and *exo* approaches between the imino nitrogen and the carbonyl group. The *cis-trans* ratio is dependent upon a variety of factors such as structure of the ketene and the imine, solvent, mode of ketene generation, reaction rates, temperature, and order of addition of reagents <93JOC5771>.



Scheme 60

The addition of acid chlorides to imines in the presence of a base results in *cis*- β -lactams, presumably through a process of kinetic control. By changing the order of addition of the reagents, *trans*- β -lactams are produced. This led to *trans*-3-acetoxy-4-phenylazetidinone, a key starting β -lactam for 2'-epitaxol <93BMC 2483>. Electron-rich alkyl- and aryl-substituted acetic chloride, or alkoxy-, or azidoacetic chloride react via ketene adducts, while electron-poor derivatives, for example, dichloroacetyl chloride, acylate the imine first and are deprotonated afterwards <86HCA1424>.

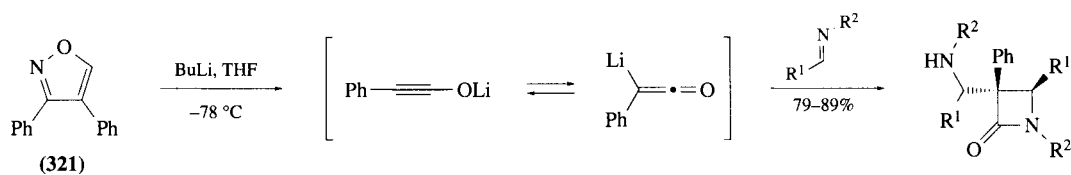
Ab initio calculations at the RHF/6-31G* and MP2/6-31G*/6-31G* theory levels show that the torquoelectronic effect is present in the ketene-imine cycloaddition reactions and that it is an important factor in the control of the reaction stereoselectivity <93JOC7036>. An investigation on the effect of several substituents on the transition structure corresponding to the ring closure step has been reported <93JOC7036>.

The different modes of interaction between achiral ketenes and homochiral aldimines derived from chiral aldehydes to give two possible diastereoisomers of *cis*- β -lactams have been examined using the AM1 method <94JA2085>. The step which determines the final stereochemistry is the conrotatory ring closure between C(3) and C(4) atoms. The predicted high diastereoselectivity is in excellent agreement with available experimental data. The origin of this stereocontrol is rationalized on the basis of the stabilizing interaction between the C-X σ^* orbital (X being an electronegative atom) and the p atomic orbital of the C(3) atom. A similar treatment has been applied to the interaction between achiral imines and homochiral ketenes <94JA2085>. The predicted high diastereomeric excesses were again in good agreement with the experimentally found diastereoselection.

The mechanism of this reaction has been the subject of controversy for several years, but some experimental evidence appears to support a stepwise process rather than a concerted one <82JOC2233>. *Ab initio* calculations show that the [2 + 2] cycloaddition of ketenes and imines takes place in a two-step process, through formation of a zwitterionic intermediate, which undergoes an electronic conrotatory ring closure to give the β -lactam <92JA6249>.

Evidence has been presented by ^1H NMR monitoring that *trans* and *cis*-azetidin-2-ones from phenylacetic chloride and benzyldeneanilines in DMF are formed via two kinds of intermediates, a 2-phenyl-*N*-(α -chlorobenzyl)acetanilide and a *N*-charged adduct <91T7417>. The mechanism of the Staudinger reaction was also investigated by low temperature FT-IR <89JOC3792>.

Lithioketenes, generated from base-induced cleavage of 3,4-diphenylisoxazole (**321**) undergo a cycloaddition with imines to produce β -lactams (Scheme 61) <82JCS(P1)2193>.

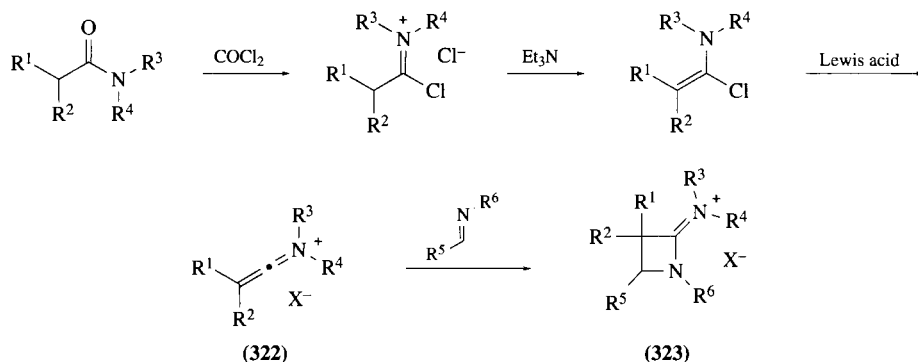


Scheme 61

1.18.3.7.14 Cyclocondensation of ketenimines and keteniminium salts with imines

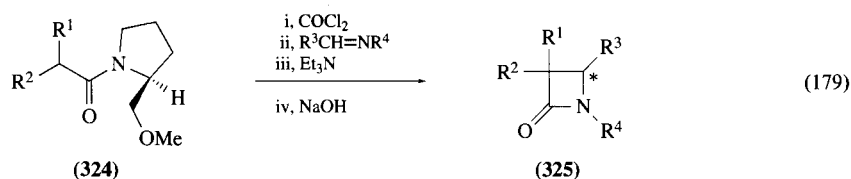
Cycloadditions of ketenimines and imines under Lewis catalysis have been reported <83CBR302>.

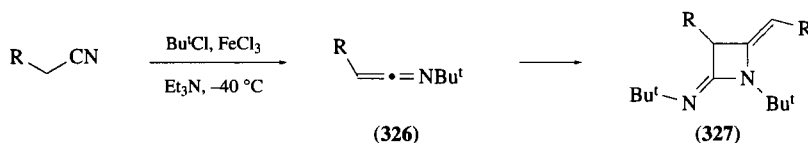
Keteniminium salts (**322**), derived from tertiary carboxamides, undergo cyclocondensation with imines to afford 2-azetidiniminium salts (**323**) with *trans* stereoselectivity (Scheme 62) <83CC818, 91COS(5)85>.



Scheme 62

Asymmetric syntheses of β -lactams (**325**) have been reported using the chiral carboxylic amides (**324**), derived from (2*S*)-(methoxymethyl)pyrrolidine (Equation (179)) <87PAC393>. When $\text{R}^1 = \text{Me}$ and $\text{R}^2 = \text{Me}$ or Ph , β -lactams are obtained in high optical purities ($\geq 95\%$), but the optical purity drops dramatically for $\text{R}^1 = \text{R}^2 = \text{H}$ <87PAC393>. With chiral imines, low diastereoselection of β -lactams was obtained <84JOC1397>. From nitrilium salts, C-monoalkyl ketenimines (**326**) are generated, which undergo self-condensation to 4-alkylidene-2-iminoazetidines (**327**) <84JOC2200, 88JOC18>.

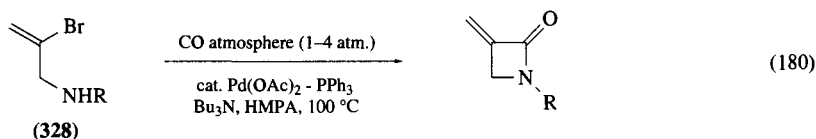




Scheme 63

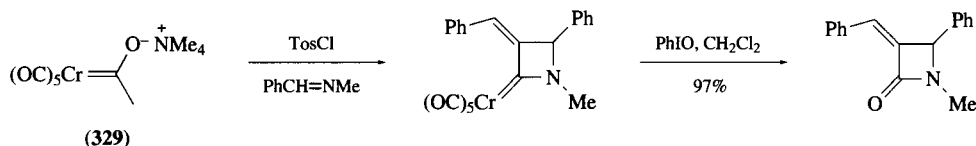
1.18.3.7.15 Miscellaneous β -lactam syntheses

The palladium-catalyzed reaction of 2-bromo-2-propenylamines (328) with carbon monoxide furnishes 2-methylene- β -lactams (Equation (180)) $\langle 85T375, 85T387 \rangle$. Extensions to reactions with higher substituted 2-bromo-2-alkenylamines have been reported $\langle 88TL5601 \rangle$.

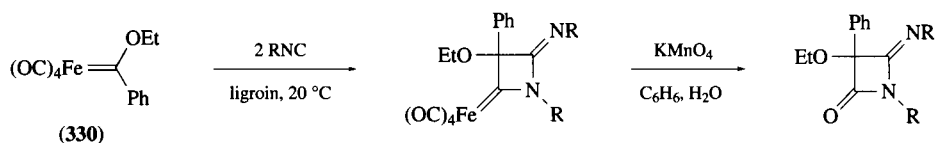


The palladium-catalyzed carbonylation of 4-amino-2-alkynyl carbonates affords 3-alkynyl- or 3-vinylidene- β -lactams $\langle 91TL7683 \rangle$. The silylcarbonylation of propargylamine derivatives proceeds efficiently via rhodium catalysis to give α -trialkylsilylmethylene- β -lactams $\langle 91TL7431 \rangle$. Unsaturated carbamoylcobalt salophens undergo photochemical homolytic cleavage producing carbamoyl radicals which then give cyclization into 2-methylene- β -lactams $\langle 89TL3229 \rangle$. Propargyl carboxylates are carbonylated in the presence of palladium(II) acetate to afford β -lactams $\langle 93EUP523904 \rangle$.

A variety of metal-carbene complexes have been used for the synthesis of metal-azetidynilidene complexes, which are oxidatively converted into β -lactams. Examples include the use of chromium-carbene complexes such as (329) $\langle 85OM1903, 86CB2289, 88CB1739, 88OM2553, 93JOM(454)133 \rangle$, molybdenum-carbene complexes $\langle 86CB2289, 88CB1739 \rangle$, iron-carbene complexes, such as (330) $\langle 86TL3811, 87CB1297, 87JOC3940, 88CB1739 \rangle$, tungsten-carbene complexes $\langle 87AG(E)563, 87CB1939, 88CB1739, 91OM389, 93JOM(454)133 \rangle$, and manganese-carbene complexes $\langle 88CB1085, 88CB1739, 92AG(E)1053 \rangle$.

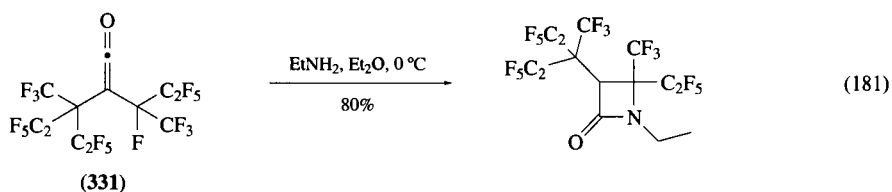


Scheme 64



Scheme 65

Perfluoroketene (331) reacts with ethylamine only to give a β -lactam (Equation (181)), while other amines produce acrylamides $\langle 86JFC(32)151 \rangle$.

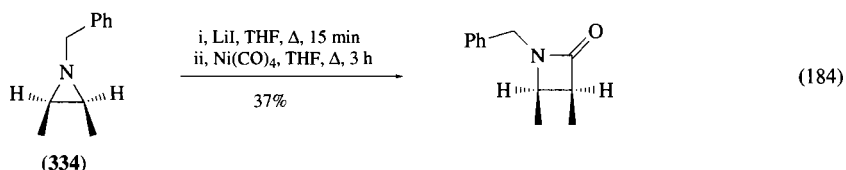
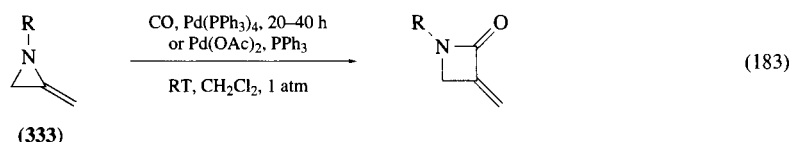
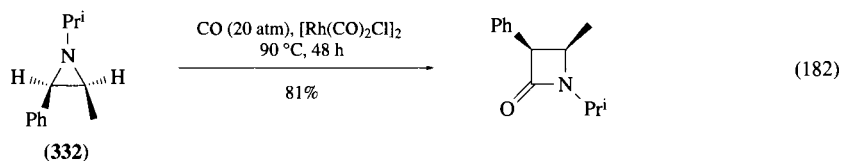


1.18.3.8 β -Lactam Synthesis by Transformation of Another Ring

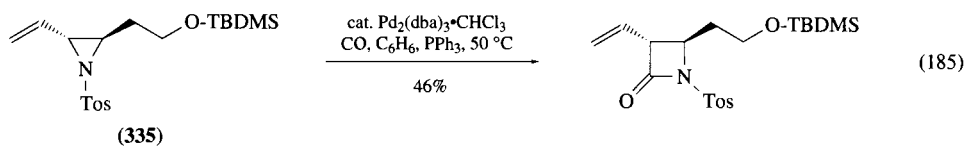
1.18.3.8.1 Transformation of three-membered rings

Ring opening of α,β -epoxycarboxylic acids with α -aminonitriles in the presence of LiHMDS affords 4-cyano-2-azetidinones <84H(22)1725>.

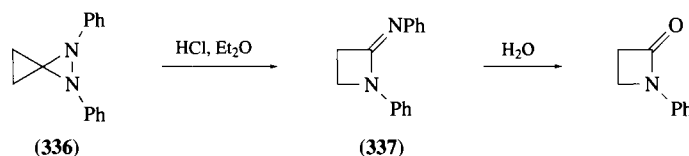
The carbonylation of aziridines, for example, (332), under the influence of rhodium catalysts to give β -lactams occurs with retention of the stereochemistry of the substituent groups (Equation (182)) <83JA6737, 89JA931>. Palladium-catalyzed carbonyl insertion of 2-methylene-aziridines (333) leads to 3-methylene-2-azetidinones (Equation (183)) <87TL3237>, while cobalt- or rhodium-catalyzed carbonylation of aziridinones gives access to azetidin-2,4-diones <84OM1767>. The lithium iodide-induced opening of aziridines (334) and subsequent carbonylation with nickel tetracarbonyl affords β -lactams (Equation (184)) <88CC710, 90JOC2943>.



The regio- and stereoselective carbonylation of optically pure vinylaziridine (335) is catalyzed by the *tris*(dibenzylideneacetone)dipalladium(0)–chloroform complex (Equation (185)) <91SL91, 93BMC 2415>. Analogous conversions via reaction with cuprates, oxidation, and ring closure have been reported for 2-(hydroxymethyl)aziridines <87TL1211, 88T619, 92T6069, 92T6079>.

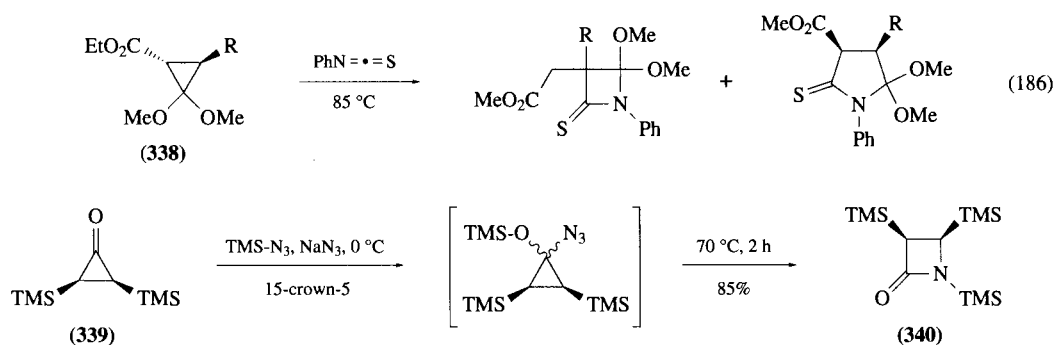


With HCl 1,2-diazaspiro[2.2]pentane (336) has been converted into 4-membered amidine (337), which is hydrolyzed in neutral conditions to give the corresponding β -lactam (Scheme 66) <88MI 118-04>.



Scheme 66

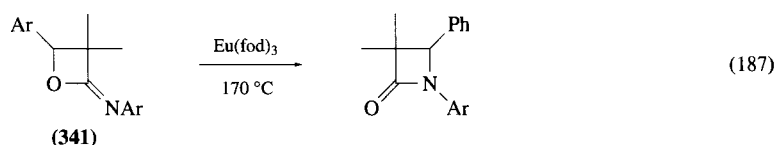
Ring expansion of 2,2-dimethoxycyclopropanecarboxylates (338) occurs with phenylisothiocyanate to labile azetidine-2-thiones and pyrrolidine-2-thiones (Equation (186)) <89JCR(S)42>. The azide adduct to cyclopropanone (339) rearranges to *cis*- β -lactam (340) in a stereospecific manner (Scheme 67) <93JCS(P1)1553>.



Scheme 67

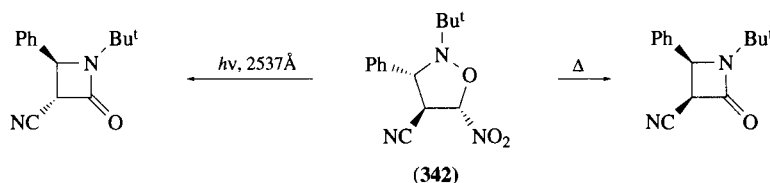
1.18.3.8.2 Transformation of four-membered rings

The thermal rearrangement of 2-iminooxetanes (**341**) in the presence of europium complexes gives 2-azetidinones (Equation (187)) <87TL2995>. The thermolysis of Dewar-4-pyrimidines affords 4-alkylidene-2-azetidinones, in addition to cyclobutenones <87JOC2455>.



1.18.3.8.3 Transformation of five-membered rings

A variety of isoxazolidines have been converted to 2-azetidinones <84JOC282, 85JOC2327, 87TL179, 87TL5481, 93T10965>. By thermolysis or photolysis, 5-nitroisoxazolidines (**342**) are transformed into *cis*- or *trans*- β -lactams, respectively (Scheme 68) <84JOC282>.



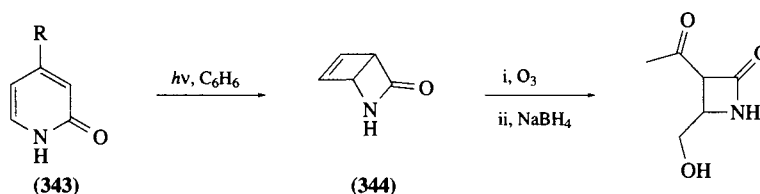
Scheme 68

Other ring contractions of five-membered rings include the oxidative transformation of 1-benzylpyrrolidine-2,3-diones <86EUP190786>, the photolysis of 4-diazopyrrolidine-2,3-diones <83JOC3365>, the rearrangement of 4-hydroxypyrrolidine-2-ones <85T479>, the photolytical or thermal extrusion of SO₂ from 4-oxo-1,3-thiazolidin-*S,S*-dioxides <83JOC494, 92JOC3755>, the photochemically mediated ring contraction of pyrazolidin-3-ones <93BMC 2383>, and the transformation of L-ascorbic acid <85JOC3462>.

1.18.3.8.4 Transformation of six- and seven-membered rings

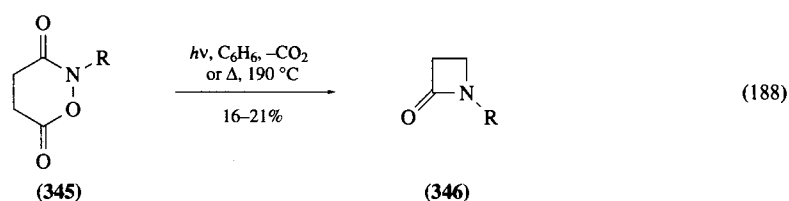
The photochemical conversion of 2-oxo-1,2-dihydropyridines (**343**) affords photopyridones (**344**) which are transformed into functionalized β -lactams by various routes, among others ozonolysis followed by hydride reduction (Scheme 69) <84TL877, 85CC189, 86JCS(P1)1283, 86JCS(P1)1289>.

Similar photocyclizations are known for 4-oxo-3,4-dihydropyrimidines <83JOC2914, 87JOC2455, 88JCS(P1)2653>.



Scheme 69

Photochemical or thermal decarboxylation of 3,6-dioxotetrahydro-1,2-oxazines (345) occurs to give 1-substituted azetidin-2-ones (346) <85TL4107>. The three component reaction utilizing 3-aminopropionic acid, ketones, and isonitriles leads to 1,4-oxazepine derivatives, which rearrange to β -lactams <82AG(E)810, 84H(21)271, 87CC51>. The photochemical reaction of 5-(1-aminoalkyl)-4-oxo-2,4-dihydro-1,3-dioxines produces 3-acetyl- β -lactams <87H(26)2611>.

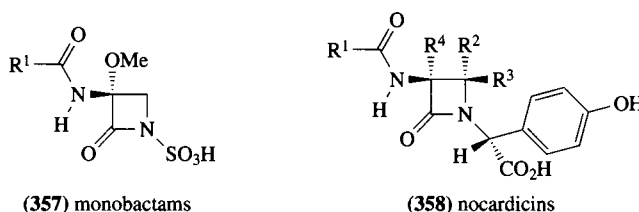


1.18.3.9 Specific Classes of β -Lactam Derivatives

This section gives leading references in Table 1 on specific classes of β -lactam derivatives and focuses on the preparation of these compounds.

1.18.3.10 Applications

The explosive interest in β -lactams and related derivatives stems from the fact that some monocyclic β -lactams exhibit antibacterial activities. Classical examples comprise the naturally occurring monobactams (357) and nocardicins (358) <85AG183>. Contrary to penicillins, cephalosporins, or nocardicins, monobactams are not produced by fungi or actinomycetes, but from bacteria, for example *Bacillus*, *Pseudomonas*, etc. <83CBR302>. Nocardicins proved the relationship with cephalosporins and penicillins via the corresponding β -configuration at C(3), but they have no therapeutic significance.

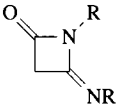
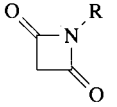
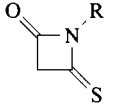
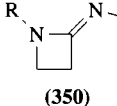
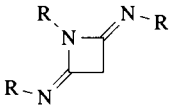
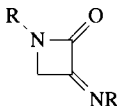
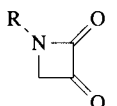
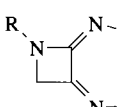
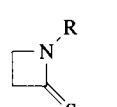
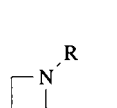


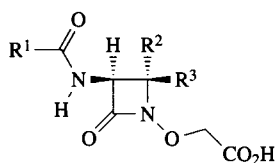
The synthetic oxamazins (359) <84TL3293, 85JMC1447, 85JAN813>, thiamazins (360) <86JOC3133>, and monosulfactams (361) <83T2571> showed some antibacterial activity which raised again a major interest in the area of 2-azetidinone chemistry. Other examples include monophosphams (362) and monocarbams (363) <85AG183>.

The activated β -lactam unit is a salient feature of these antibacterials, but also the nature and sterical arrangement of the substituents play a major role in the antibacterial activity and pharmacokinetics <85AG183>.

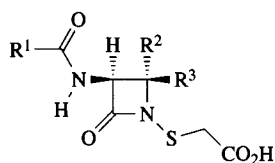
The 3-isopropylidenyl- and 2-isopropyl *N*-acyl-azetidin-2-ones (364) and (365), and further func-

Table 1 Related 2-azetidinone derivatives.

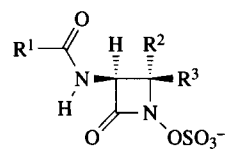
Basic structure	Preparation	Ref.
 (347)	-ketenes + carbodiimides - α -bromo ester + Zn + carbodiimide (Reformatsky) -RNC + Fe- or Mn-carbene complexes + oxidation	87JOC1315, 84LA1193, 85JHC357 81CC41 88CB1085, 87CB1297, 87AG(E)563
 (348)	-Cr-carbene complex + iminodithiocarbonate -RCOCl + iminodithiocarbonate + base -malonic acid mono carboxamide + SOCl ₂ -malonic acid mono carboxamide + Et ₃ Al -aziridinone + Co ₄ (CO) ₁₂	92JOC447 92S439 87TL5481 87TL3593 84OM1767
 (349)	-thioketene + RNCO -malonic acid monothioamide + Et ₃ Al -R ₂ CHCON(R)C(S)OMe + h ν -azetidine-2,4-dione + Lawesson reagent	88CB689 87TL3593 86TL1335, 88JCS(P1)1353 86TL1335, 88JCS(P1)1353
 (350)	-keteniminium salt + imine, then amine -ketenimine + imine	83CC818, 87PAC393 83PJC279
 (351)	-thiazetidine-2,4-diimine + Ph ₃ P=C(Me)COOEt	82TL2909
 (352)	-Mn-carbene complexes + RNC + oxidation - β -lactam + LDA + RONO	88CB1085 86CPB2732
 (353)	-3,3-di(SR)-2-azetidinones + NBS/H ₂ O or I ₂ /H ₂ O -3O,3N-2-azetidinones + H ₂ O/SO ₂ -3Cl,3S-2-azetidinones + H ₂ O/ZnCl ₂ -3-methylene-2-azetidinones + O ₃ -oxidation of 3-hydroxy-2-azetidinones	87TL1945, 90JOC2070 93TL6325, 93BMC2475 89JOC5758, 84TL4733 87TL5481, 85JCS(P1)2375 88TL3133
 (354)	-Cr- or Mo-carbene complexes + ArNC	86CB2289
 (355)	-imine + RC $\equiv$ C-SeLi	92JAP(K)04009366
 (356)	- β -lactam + Lawesson reagent - β -lactam + P ₂ S ₅ -4-membered amidinium salt + NaSH -thermolysis of 1,3,5-dithiazinones -ketene acetal + ArNCS -thioketene + imine -N-benzyl α,β -unsaturated thioamide + h ν	93T4383 92MI 118-04, 85CB653, 83TL3725, 85MI 118-02 83CC818 84CB2205 82CB3340 88CB1165 90CC1214



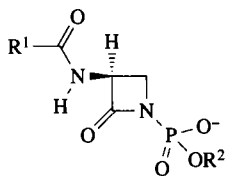
(359) oxamazins



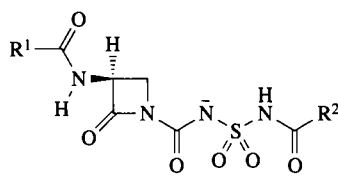
(360) thiamazins



(361) monosulfactams

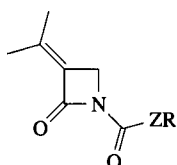
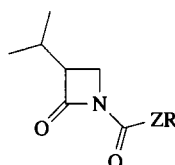


(362) monophosphams

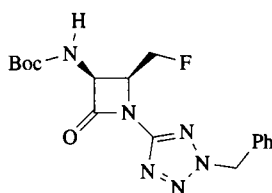


(363) monocarbams

tionalized derivatives are novel synthetic monocyclic β -lactams exhibiting *in vitro* antibacterial activity versus anaerobes and Gram-positive aerobes (87EUP232017, 92JAN213, 93BMC2241). A unique structural aspect differentiating them from other classes of β -lactam antibiotics is the lack of any negatively charged group appended to the lactam nitrogen.

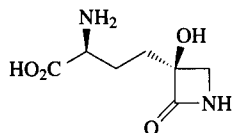
(364) Z = O, CH₂(365) Z = O, CH₂

Analogues of monobactams in which the sulfonic group has been replaced by the isosteric tetrazole, for example, (366), represent a new class of antibacterials (84TL911, 84TL3849, 86JAN215, 93BMC2429).



(366)

The so-called tabtoxinine- β -lactam (367) is considered to be the active form of tabtoxin, a dipeptide exotoxin, produced by *Pseudomonas tabaci*, the organism responsible for the wildfire disease of tobacco plants (86T3097).



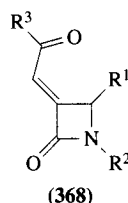
(367)

Antielastase activity of 1,3,4-trisubstituted and 3,4-disubstituted 2-azetidinones has been determined against enzymes, for example, human leucocyte elastase (93BMC2295, 93BMC2547).

An important application of the chemistry of azetidin-2-one is the synthesis of the taxol side

chain (see Section 1.18.3.4.7 on ring opening of β -lactams). Taxol received extraordinary attention because of its exciting *in vivo* antitumor activity.

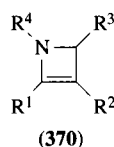
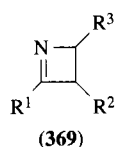
The 3-alkylidene-2-azetidinones, for example, (368), show blood platelet aggregation inhibitory activity <87JAP(K)6287562, 87JAP(K)6287563, 88EUP264231, 88EUP264232, 90CPB393, 91CPB3202>.



1.18.4 AZETINES

1.18.4.1 Introduction

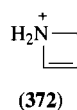
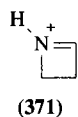
The chemistry of azetines is still underdeveloped, despite the fact that since the early 1980s basic and fundamental information was available for the further unraveling of this class of compounds <84CHEC-I(7)237>. The 1-azetines (369) are very rare compounds except when the α -position is blocked for tautomerism and when the imino function is part of stable functionalities such as imidates, thioimidates, amidines, etc. Relatively few 2-azetines (370) have been reported and examples generally fall into one of two categories. They either contain an electron-withdrawing substituent (COOR, Tos, etc.) on the ring nitrogen, or they possess a conjugating electron-donating substituent (RO, Ph, etc.) at the 2-position and/or a conjugating electron-withdrawing substituent (e.g., CN) at the 3-position.



1.18.4.2 Theoretical Methods

Ab initio calculations of 1-azetine on the 4-31G (N*) set have been performed <89JA906>.

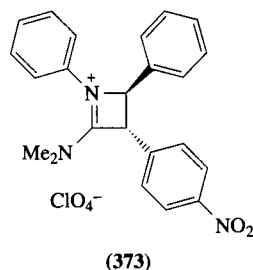
Structures and energies of the cyclic $C_3H_6N^+$ cations have been examined by *ab initio* molecular orbital calculations. The geometries were optimized with the 3-21-G basis set. The iminium ion (371) is the most stable of the four-membered ring isomers. The CH—N bond length is short (1.278 Å), indicating some stabilization of the positive charge by the neighbouring amino group. The enammonium ion (372) is the most stable of the ammonium ions in this series. The C—N bond lengths (1.589 Å and 1.531 Å) are longer than a C—N single bond, as expected for cyclic ions <89JA5560>.



1.18.4.3 Experimental Structural Methods

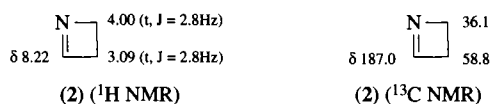
Azetines are considered as planar structures (see CHEC-I). Data from x-ray crystallography on amidinium-type four-membered rings support this fact. The structure of 1-azetinium perchlorate

(373) is a planar ring with an exocyclic C—N linkage with considerable double bond character <88MI 118-05>, as found similarly for related structures <84HCA927>.



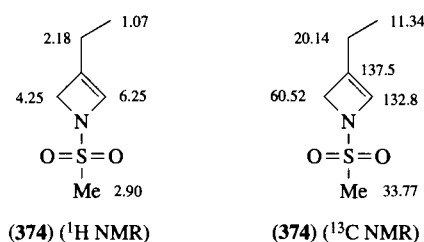
The microwave spectrum of 1-azetine, following pyrolysis and dehydrochlorination of 1-chloroazetidine, has been studied <89JA906>.

Additional NMR data on the parent 1-azetine (2) have been obtained. The compound showed a typical absence of coupling between the aldimine hydrogen and the methylene protons at the 3-position (¹H NMR) <87CB1971, 88T4447>. The C=N bond in the IR spectrum is situated at 1563 cm⁻¹, while the UV absorption is located at 220 nm (ε 80 ± 10) <88T4447>.



Scheme 70

Typical ¹H and ¹³C NMR data (CDCl₃) of 2-azetines have been obtained for the *N*-mesyloxy derivative (374) <94JOC1608> (δ-values given).



Scheme 71

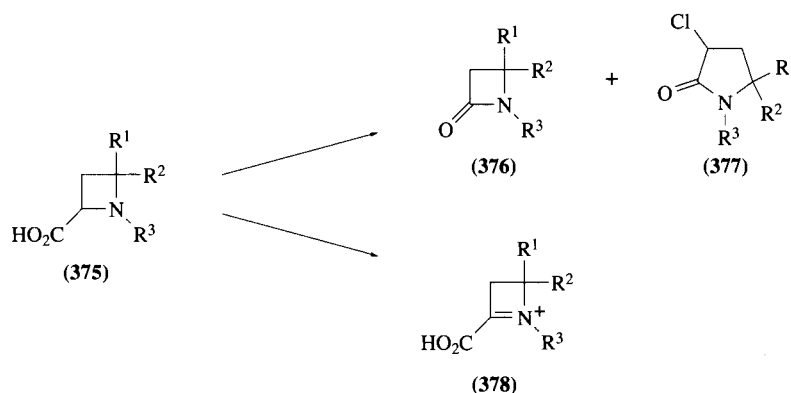
The photoelectron spectrum of 1-azetine has been measured and is composed of seven overlapping bands, whose attribution by Koopmans correlation with MNDO calculations delivered the sequence $n_N < \pi_{CN} < \sigma$ <87CB1971>. Highly sterically hindered 2-azetines, carrying no *N*-substituent, undergo tautomerism into the more stable 1-azetines under acid catalysis <88AG(E)272>.

1.18.4.4 Reactivity

1.18.4.4.1 1-Azetines

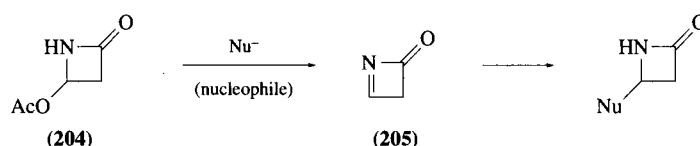
Several 1-azetines and their derivatives were reported as intermediates in reactions. The previously reported conversion of azetidine-2-carboxylic acids (375) into β-lactams (376) via azetinium inter-

mediates (378) has been investigated in detail. Not only β -lactams were formed but also α -chloro- γ -lactams (377), depending on the substituent pattern (Scheme 72) <84TL3111>.

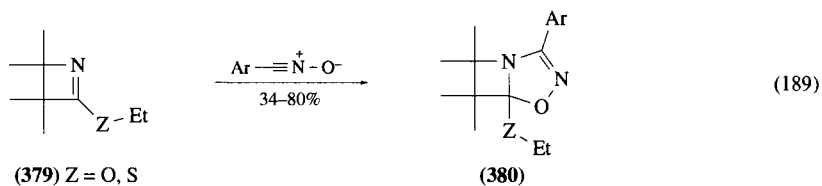


Scheme 72

The intermediacy of 1-azetin-4-ones has been postulated many times in the past (see 2-azetidiones). The reaction of 4-acetoxy- or 4-sulfo-2-azetidinone with nucleophiles in the presence of base to give 4-substituted-2-azetidiones was proven to occur via an elimination-addition process (204). The intermediacy of 1-azetin-4-one (205) in solution was shown. A UV determination of the transient species was performed <88MI 118-06, 90JOC434>. A polymeric phase generated the intermediate, which was trapped by a nucleophilic polymeric agent. Alternatively, the intermediate 1-azetin-4-one was trapped with siloxydienes to afford the cycloaddition products <85TL6309>. Substrates such as 2-ethoxy- and 2-(ethylthio)-1-azetines (379) are suitable for 1,3-dipolar cycloaddition reactions with nitrile oxides giving 1:1 cycloadducts (380). Nitrilimines and nitrile ylides gave similar cycloaddition reactions <90TL123, 93T4383>.

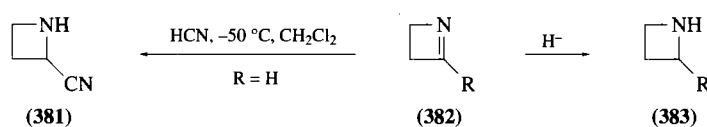


Scheme 73



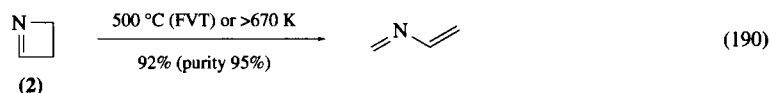
The reduction of 1-azetines (382) occurs easily with sodium borohydride or lithium aluminium hydride to give the corresponding azetidines (383) <85S1131, 88CBR231>.

The 1-azetine ((382), R = H), which polymerizes at 20 °C within a few seconds, undergoes addition of hydrogen cyanide at low temperature to yield the azetidine-2-carbonitrile (381) <85S1131>.



Scheme 74

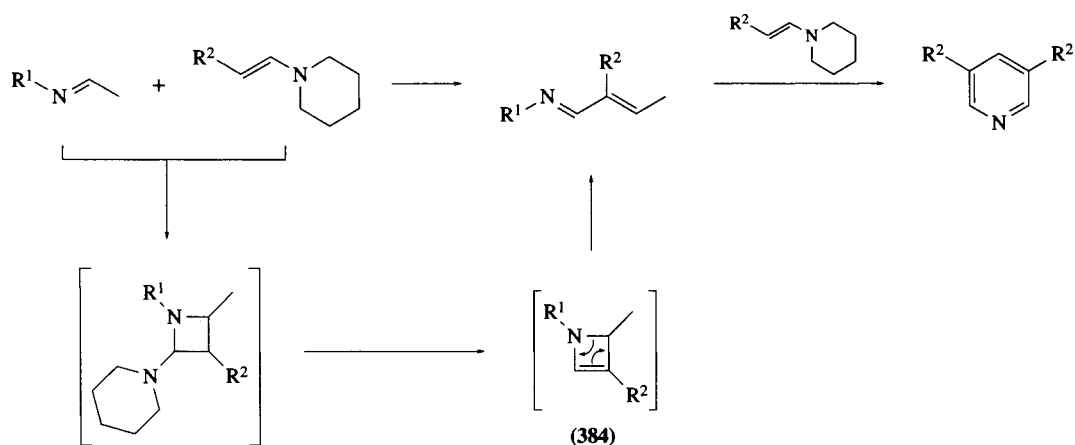
Thermolysis of 1-azetidines results in ring fission to afford 2-aza-1,3-dienes. This process has been studied in detail for the parent 1-azetine (**2**) <87CB1971, 88T4447, 89JA906>. The stereochemical consequences of this process have been studied theoretically <80JOC1341>.



1.18.4.4.2 2-Azetines

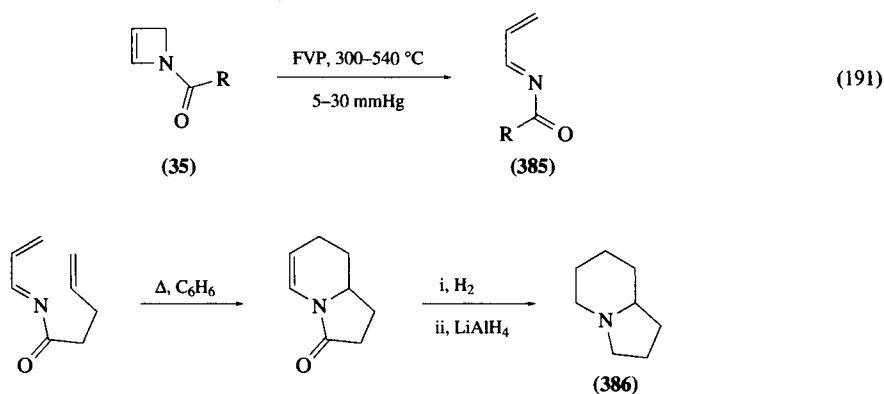
Few reports on the reactivity of 2-azetines have been described due to the unstable nature of these strained species.

The reaction of aldimines with enamines to give pyridines via intermediate 1-aza-1,3-dienes has been explained via the intermediacy and ring opening of 2-azetines (**384**) <84JOC2691, 92MIP9202505>.



Scheme 75

Due to the presence of the less reactive enamide moiety 1-acyl-2-azetidines (**35**) are more stable compounds. These compounds undergo flash-vacuum-pyrolysis into 1-acyl-1-aza-1,3-dienes (**385**). This reaction has been elegantly applied for the synthesis of δ -coniceine (**386**) <91JOC6729>.



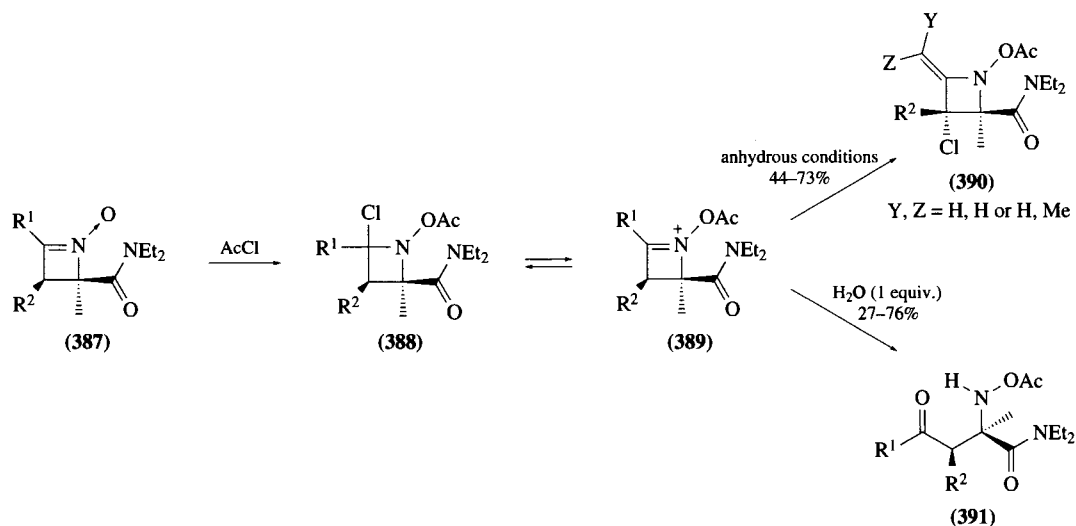
Scheme 76

The use of 2-(trimethylsilyloxy)-2-azetines as intermediates in the epimerization of azetidin-2-ones at C(3) has been demonstrated <85TL4647>.

1.18.4.4.3 1-Azetine N-oxides

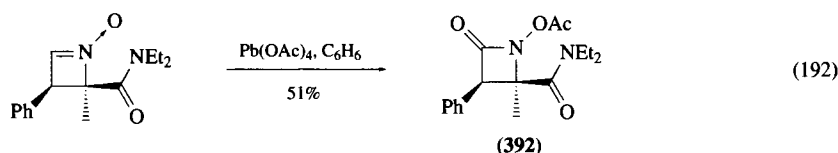
The chemistry of cyclic four-membered nitrones has been developed extensively and, therefore, separate focus is given to this class of compounds (see also the synthesis of these compounds) <90BSF704>.

The reaction of four-membered nitrones (387) with acetyl chloride results in an equilibrium between the *O*-acetylated compounds (388) and the dehydrochlorinated product (389). Ready hydrolysis into (391) takes place, but under prolonged anhydrous conditions an exomethylene derivative (390) is formed via a 1,2-hydrogen shift (Scheme 77) <83JOC486, 88RTC52>.



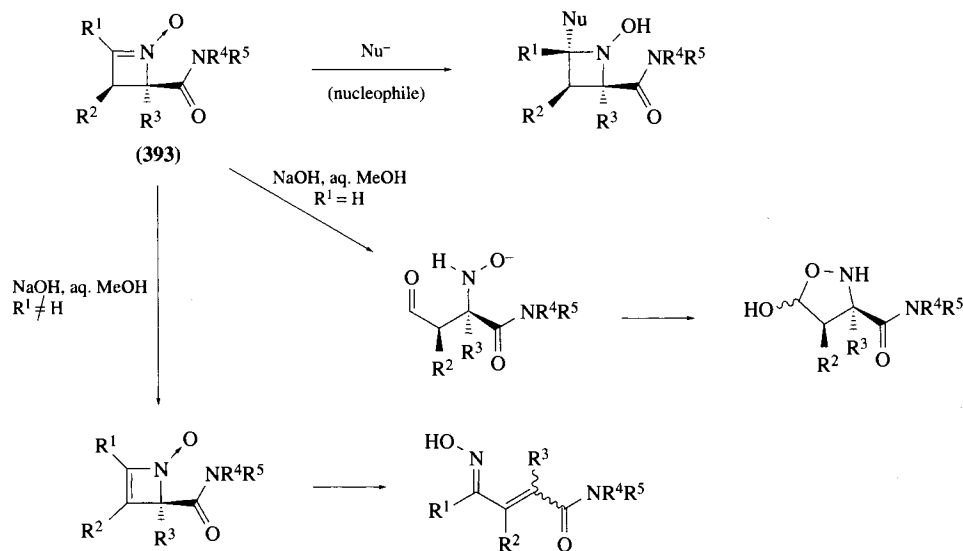
Scheme 77

Oxidation of 1-azetine *N*-oxides with lead tetraacetate gave 1-acetoxyazetidin-2-ones (392) <83JOC486>.

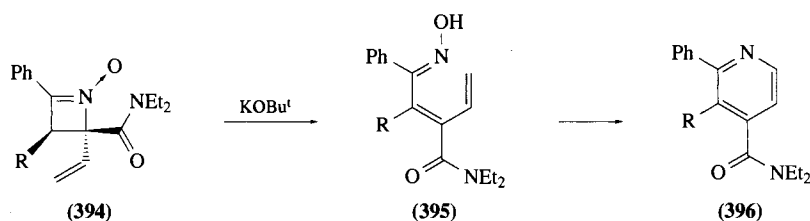


The *cis* and *trans* nitrones (393) react with nucleophiles, for example, cyanide, hydride, carbanions, etc., by stereoselective addition to the nitron moiety to give 1-hydroxyazetidines, whereby addition takes place from the sterically less hindered side (Scheme 78) <88RTC63>. Reaction of the *cis* nitron ((393), ($R^1 = \text{H}$)) with sodium hydroxide in aqueous methanol resulted in ring opening and ring closure in 5-hydroxyisoxazolidines (Scheme 78). However, with $R^1 \neq \text{H}$ tautomerism to 2-azetine *N*-oxide occurred, followed by ring opening to α,β -unsaturated oximes (Scheme 78) <82JOC4419>.

When applied to 2-(1-alkenyl)-substituted nitrones (394), the base-induced reaction led to α,β - γ,δ -unsaturated oximes (395), which cyclized to pyridines (396) <89T3131>.

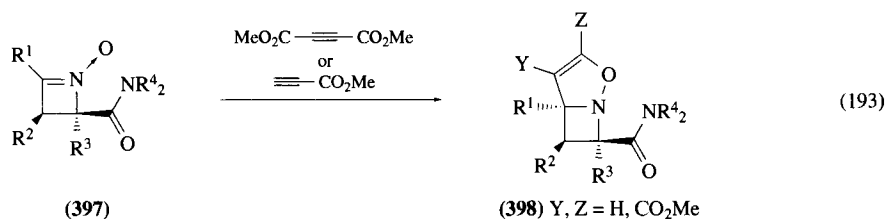


Scheme 78



Scheme 79

Four-membered ring nitrones (397) undergo 1,3-dipolar cycloaddition with electron-deficient alkynes to afford cycloadducts (398) in good yield (Equation (193)) <88RTC142>.

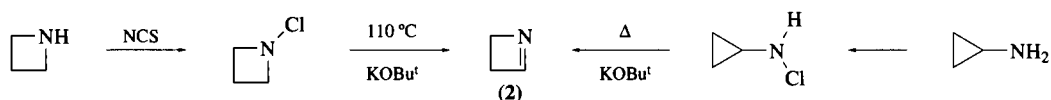


1.18.4.5 Synthesis

1.18.4.5.1 1-Azetines

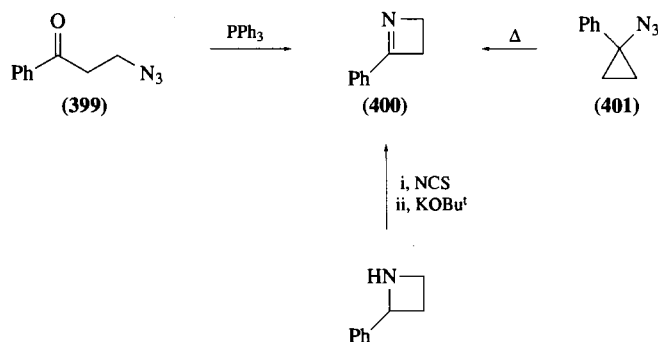
The parent 1-azetine (2) was generated by vacuum dehydrochlorination of 1-chloroazetidene over a solid base such as potassium *t*-butoxide (Scheme 80) <87CB1971, 88T4447>. Subsequently, 1-azetine, which was obtained in 96% yield (purity 97%), rapidly polymerizes at room temperature. A similar approach with rearrangement was described from *N*-chlorocyclopropylamine (Scheme 80) <88T4431>. However, in the latter case, 1-azetine was only the major reaction product in the reaction mixture.

From the corresponding *N*-chloroazetidene derivative 2-phenyl-1-azetine (400) was obtained analogously, while only low yields were obtained from the aza-Wittig reaction of 3-azidopropiophenone (399) or the thermal rearrangement of 1-phenylcyclopropylazide (401)

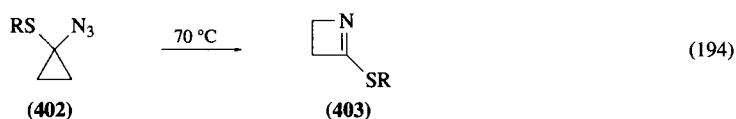


Scheme 80

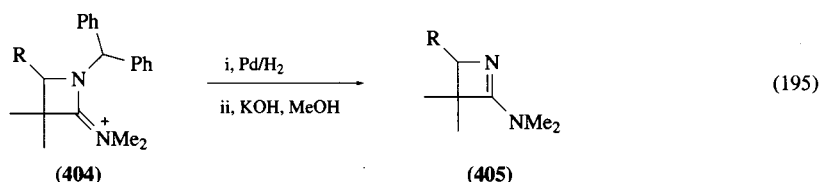
<87NKK1250>. An identical thermal rearrangement of 1-(alkylthio)cyclopropylazides (**402**) led to 2-(alkylthio)-1-azetines (**403**) <81RTC307>.



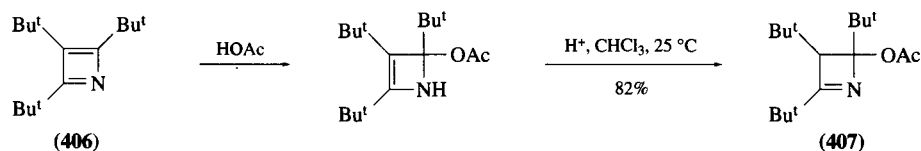
Scheme 81



The preparation of 2-amino-1-azetines (**405**) from the cycloaddition of 1-chloroiminium salts with aldimines occurs in the presence of triethylamine, the resulting amidinium salt (**404**) being *N*-deprotected and treated with base (Equation (195)) <84HCA927>.



A peculiar entry into sterically hindered 1-azetines (**407**) involved the addition of acetic acid across 2,3,4-tri-*t*-butylazete (**406**), followed by acid-catalyzed tautomerism of the initially formed 2-azetene (Scheme 82) <88AG(E)272>.

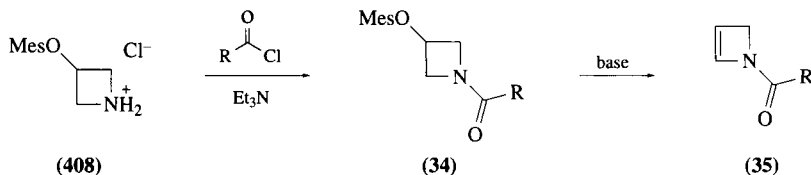


Scheme 82

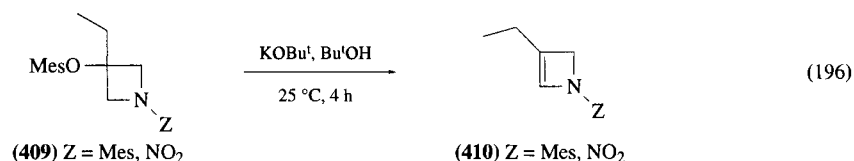
1.18.4.5.2 2-Azetines

The preparation of 1-acyl-2-azetines (**35**) is achieved in a useful but low yield (around 20%) from 3-mesyloxyazetidinium hydrochloride (**408**) by acylation to give (**34**), followed by base-induced elimination of methanesulfonic acid (Scheme 83) <91JOC6729>. A straightforward and high yield

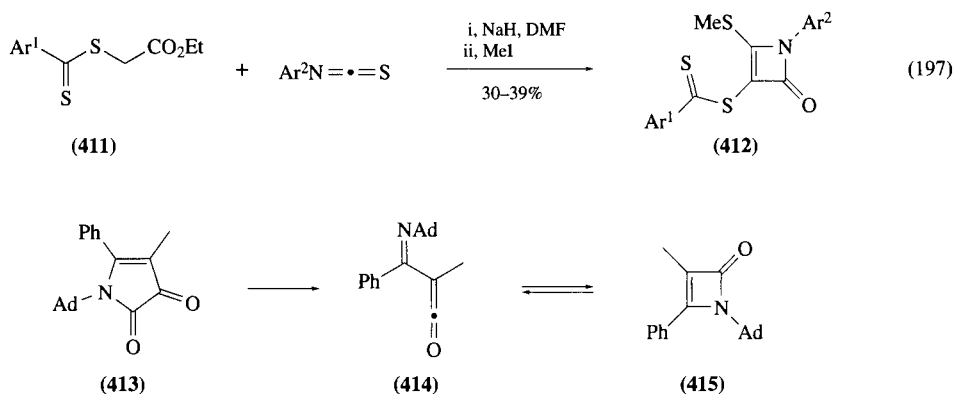
synthesis of 3-ethyl-2-azetines (**410**), carrying electron-withdrawing groups, was developed by a similar elimination of methanesulfonic acid from mesylate (**409**), which were formed by ring opening of 1-aza-3-ethylbicyclo[1.1.0]butane (Equation (196)) <94JOC1608>.



Scheme 83

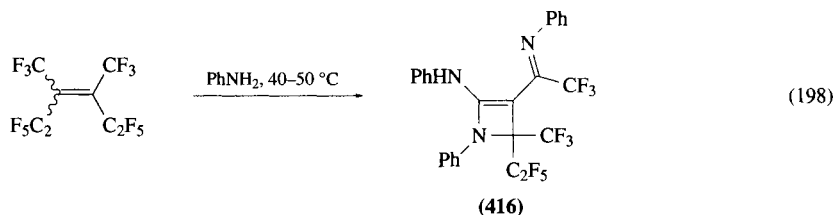


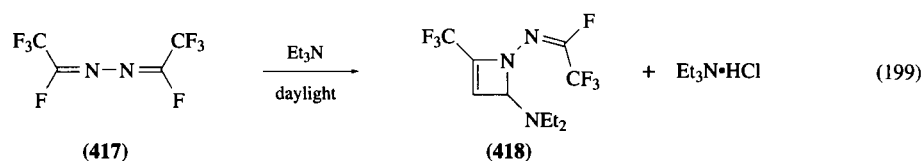
Monocyclic 3-azetin-2-ones are very rare species. Benzoazetidinsones have been known for quite some time. Some tricyclic 1-alkyl-3-azetin-2-ones have been characterized <84JOC2652>. More stable azetinones (**412**) were obtained by condensation of isothiocyanates with activated dithioesters (**411**) <90S621>. It is worth noting that *N*-(1-adamantyl)benzimidoylketene (**414**), produced from pyrroledione (**413**), is in thermal equilibrium with the azetin-2-one (**415**) <92CC488>.



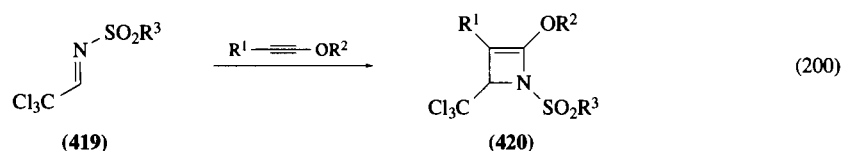
Scheme 84

The 3,4-dioxygenated 3-azetin-2-ones seem to be less stable compounds <86JCS(P2)961>. Per-fluorinated alkenes react with primary amines to give a variety of aminated products, among others fluorinated 2-azetines (**416**) <83MI 118-04, 83MI 118-05, 84MI 118-04>. Exposure of a mixture of azine derivative (**417**) and triethylamine to daylight gave 2-azetine (**418**) as the major reaction product (Equation (199)). Other trialkylamines do not give this reaction <91JFC(51)207>.



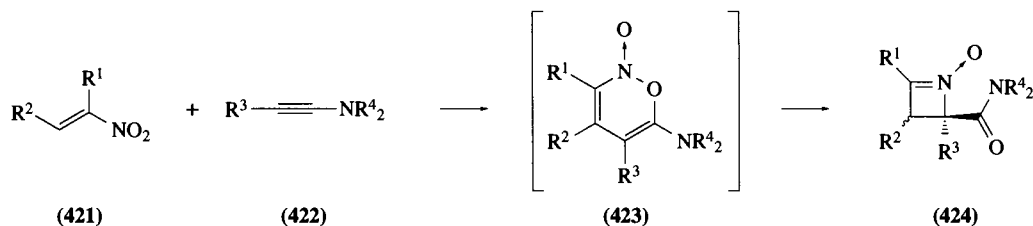


Cycloaddition of *N*-sulfonylimines (419) with alkynyl ethers afforded functionalized 2-azetines (420) in quantitative yield (Equation (200)) <91ZOB1389>.



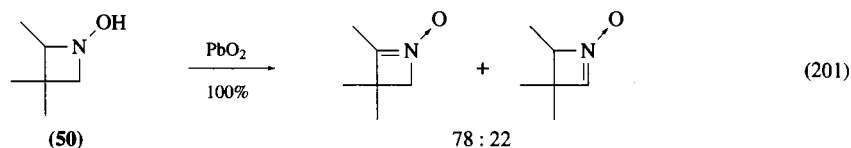
1.18.4.5.3 1-Azetin N-oxides

Reaction of nitroalkenes (421) with ynamines (422) in polar solvents, for example, acetonitrile, afforded four-membered cyclic nitrones (424) by [4 + 2]cycloaddition and ring contraction of intermediate nitronic esters (423), in addition to 3-nitrocyclobutenes by [2 + 2]cycloaddition (Scheme 85) <82JOC1816, 88RTC27, 88RTC40>. In nearly all cases *cis* derivatives were formed, except for the presence of bulky substituents. Some asymmetric induction was observed starting from chiral enamines <87TL6397>.



Scheme 85

Oxidation of 1-hydroxyazetidines (50) with lead dioxide gave a quantitative conversion into regioisomeric nitrones (Equation (201)) <83JOC4043, 83TL825, 86TL2315>. Also mercury(II) oxide was found to be suitable for this oxidation process <83JOC4043>.



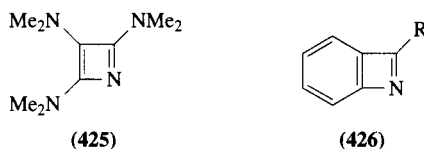
1.18.5 Azetes

1.18.5.1 Introduction

The successful search for cyclobutadienes in the last decades has stimulated efforts to unravel the chemistry of heteroanalogs, for example, azetes or azacyclobutadienes. The experience gathered during the preparation of cyclobutadienes opened routes to relatively simple and efficient syntheses of azetes. Reviews on azetes appeared in the early 1990s <91MI 118-03, 92HOU(16C)936>.

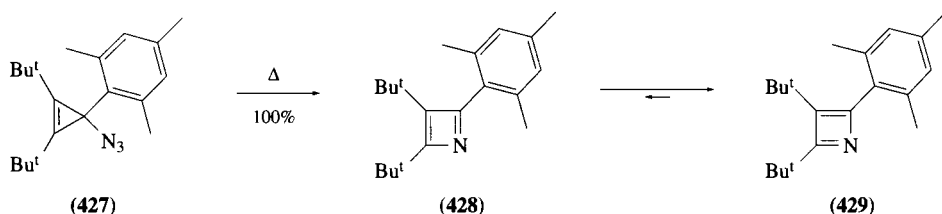
1.18.5.2 Theoretical Methods

Theory predicts that the hitherto unknown unsubstituted azete (**4**) possesses a negative resonance energy of $15.5 \text{ kcal mol}^{-1}$ <70TCA235, 75T295>. This parent molecule is slightly more stable than the carbon analogue, cyclobutadiene <71JA3437>. It should be stressed that previous research <84CHEC-1(7)237> on azetes concentrated on thermodynamically stabilized compounds such as tris(dimethylamino)azete (**425**) <73AG(E)847> and benzo fused azetes (**426**) <73CC19, 75JCS(P1)45>, although the latter compounds do not constitute monocyclic derivatives, the title structures.

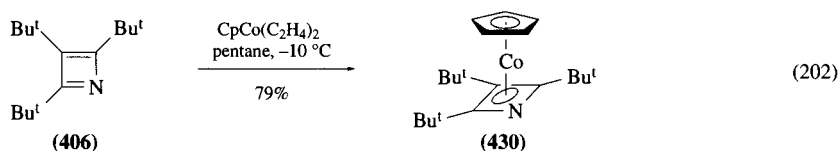


1.18.5.3 Experimental Structural Methods

Thermal rearrangement of 1-azido-1,2-di-*t*-butyl-3-mesitylcyclopropene (**427**) in neat form occurs to afford the corresponding azete (**429**), which is the thermodynamically more stable valence tautomer (Scheme 86). The other isomer (**428**) is not visible and the product crystallizes as 2,3-di-*t*-butyl-4-mesitylazete (**429**). Analysis using x-ray crystallography of Structure (**429**) showed long C(2)—C(3) and long N—C(4) single bonds. In addition, normal double bonds were observed. The angle between the planes of the aromatic ring and the heterocyclic ring is 70° <88AG(E)1559>. The thoroughly investigated 2,3,4-tri-*t*-butylazete (**406**) could not be studied yet by x-ray crystallography. Therefore, a sandwich complex (**430**) with (cyclopentadienyl)-bis(ethylene)-cobalt(I) was made constituting the first metal complex of an azete (Equation (202)) <88AG(E)1559>.

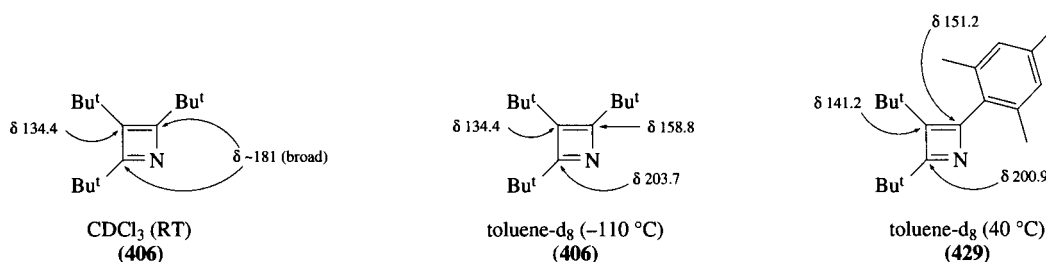


Scheme 86



The crystal structure analysis of the cobalt complex revealed that the bond lengths in the planar four-membered ring became much more similar as a result of electron delocalization ($1.478(3) \text{ \AA}$ and $1.462(3) \text{ \AA}$ for C—C, and $1.424(3) \text{ \AA}$ and $1.433(2) \text{ \AA}$ for N—C).

The ^{13}C NMR spectrum of 2,3,4-tri-*t*-butylazete (**406**) showed it to be close to coalescence at room temperature in CDCl_3 (Scheme 87). By heating in toluene- d_8 , the signal at δ 181 ppm became sharp, while by cooling to -110°C in the same solvent, the system freezes to three resonances at δ 158.8 ppm (C(4)), δ 134.4 ppm (C(3)), and δ 203.7 ppm (C(2)) (Scheme 87) <86AG(E)842>. The ^{13}C NMR spectrum of the mesityl derivative (**429**) at 40°C in toluene- d_8 displayed completely sharp resonance lines for the only visible valence isomer (Scheme 87) <88AG(E)1559>.



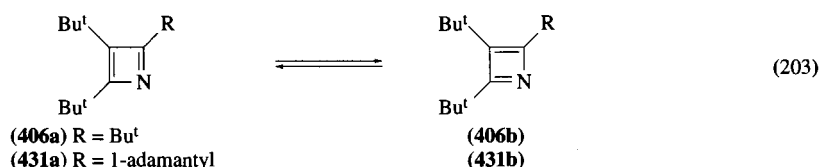
Scheme 87

The IR absorption bands of **(406)** are situated at 2960 cm^{-1} (CH) and 1569 cm^{-1} ($\text{C}=\text{N}/\text{C}=\text{C}$). The mass spectrum of **(406)** showed a small molecular ion (0.7%), the major ion being represented by m/z 57 (Bu^t+). This compound displayed a broad UV absorption band at 320 nm (hexane; ϵ 145).

1.18.5.4 Thermodynamic Aspects

It is known that 2,3,4-tri-*t*-butylazete (**406**) is a remarkably stable strained, kinetically stabilized heterocyclic compound, which can be distilled (Kugelrohr, b.p. 60°C , 0.05 mbar) and has m.p. 37°C <86AG(E)842>. The reddish-brown needles are stable for several days at 100°C , while the compound fragments at 700°C (10^{-6} mbar) into di-*t*-butylacetylene and *t*-butylcyanide.

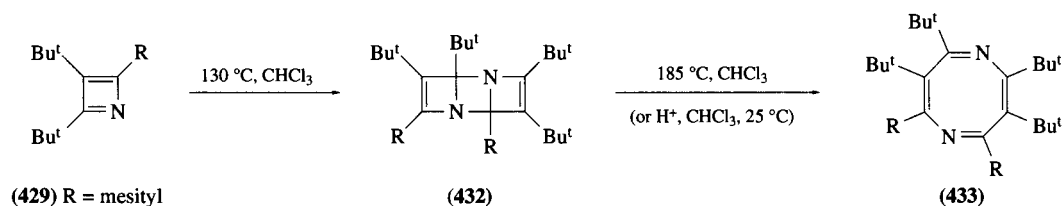
Steric hindrance is of prime importance for azetes as demonstrated by the occurrence of only one valence isomer for the mesityl derivative (**429**). The 1-adamantyl derivative (**431**) can be purified by flash chromatography on silica gel <91MI 118-03>. The valence tautomerism of tri-*t*-butylazete (**406**) and the 1-adamantyl derivative (**431**) has been demonstrated by ^{13}C NMR (Equation (203)).



1.18.5.5 Reactivity

1.18.5.5.1 Dimerization

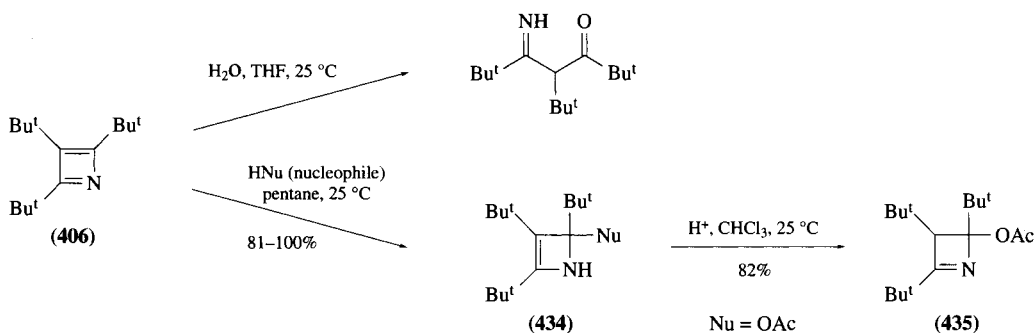
Heating of 2,3-di-*t*-butyl-4-mesitylazete (**429**) in a pressurized vessel at 130°C resulted in dimerization into (**432**), while further heating at 185°C afforded 1,5-diazocin (**433**) <91MI 118-03>.



Scheme 88

1.18.5.5.2 Hydrolysis and nucleophilic addition

Hydrolysis of 2,3,4-tri-*t*-butylazete (Structure (406)) opened up the ring to give a β -iminoketone, while mineral acids, alcohols, and β -dicarbonyl compounds gave 2-azetine adducts (434) <88AG(E)272>. Tautomerism of (434) into 1-azetine (435) occurred with the acetoxy derivative (Scheme 89).

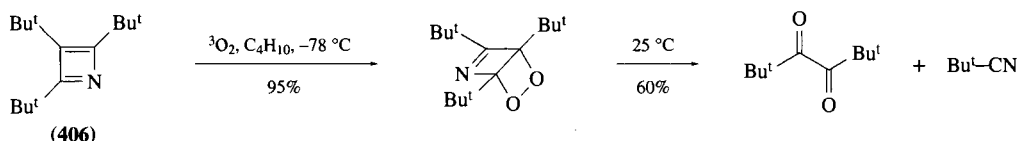


Scheme 89

1.18.5.5.3 Cycloaddition reactions

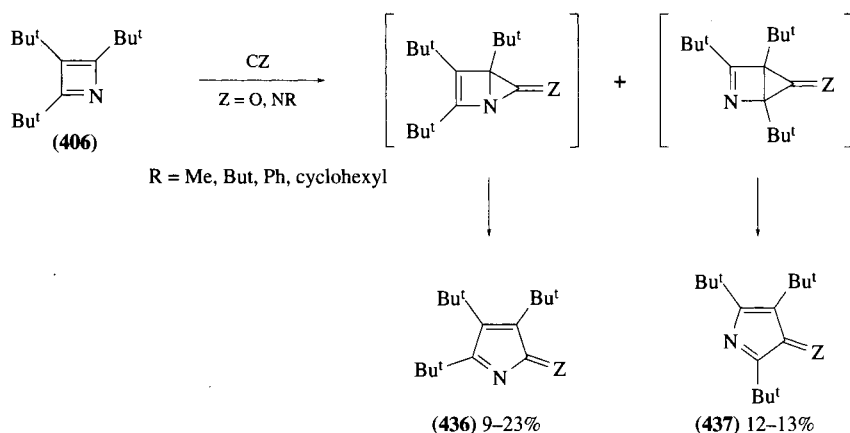
The kinetically stabilized azetes show a high tendency for cycloaddition with a variety of reagents.

Cycloaddition of (406) with triplet oxygen at low temperature produced a fully characterized dioxetan adduct, which decomposed at 25 °C into *t*-butyl cyanide and the α -dione fragment (Scheme 90) <88AG(E)272>.

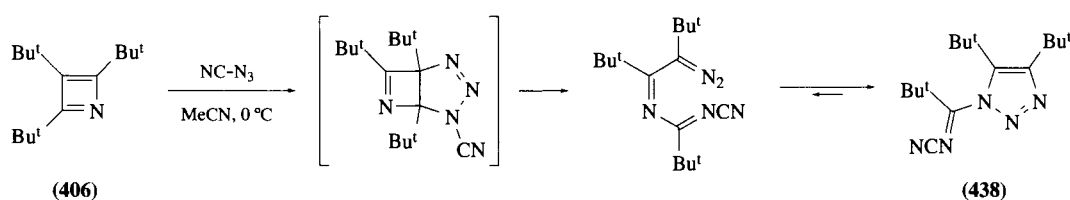


Scheme 90

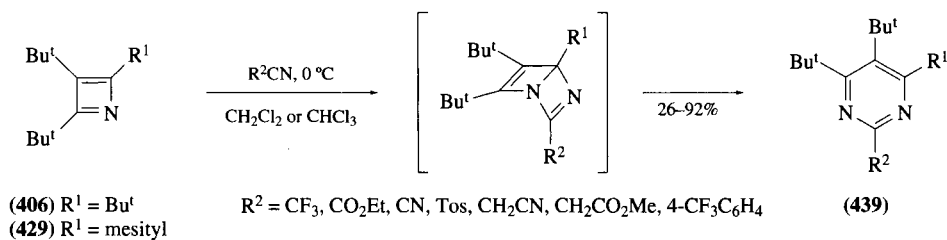
The ready cycloaddition potential is demonstrated by the reactions of 2,3,4-tri-*t*-butylazete (406) and 4-mesityl-2,3-di-*t*-butylazete (429) with isonitriles and carbon monoxide, cyanogen azide, acceptor substituted nitriles, and alkynes to afford the corresponding pyrrolones (436) and iminopyrroles (437), 1,2,3-triazole (438), pyrimidines (439) and pyridines (441) <89T3115, 90S834, 90SL401, 91MI 118-03>.



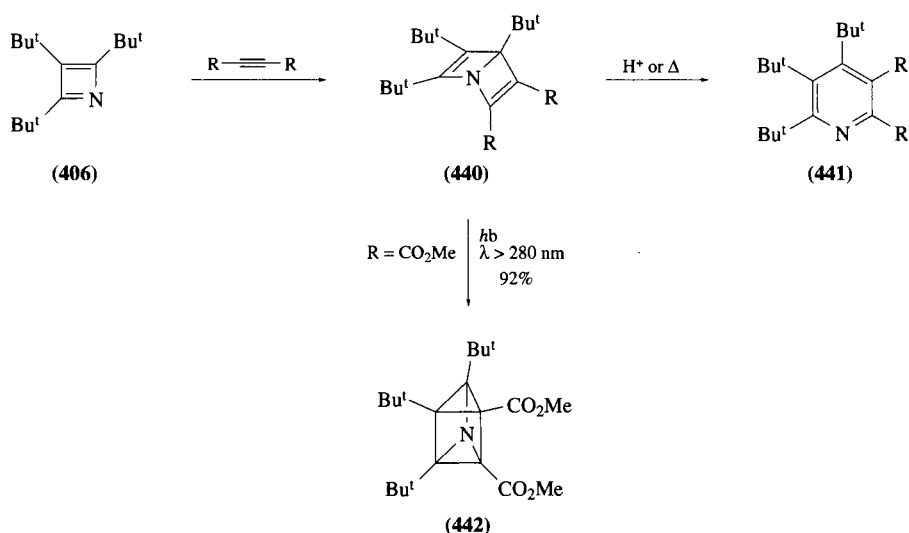
Scheme 91



Scheme 92

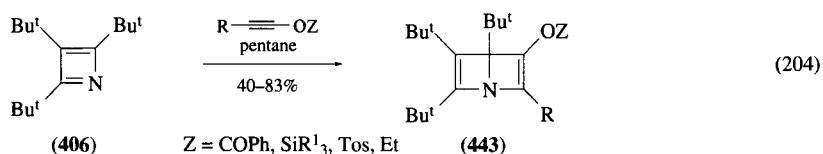


Scheme 93



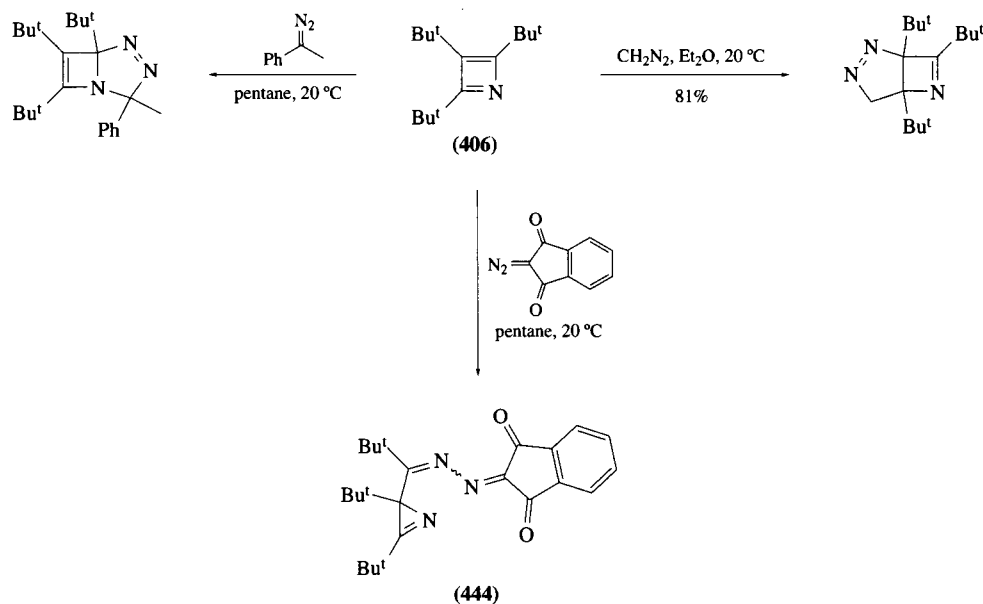
Scheme 94

The intermediate reactive cycloadducts, for example, Dewar pyrimidines, were not isolated but rearranged spontaneously into the final products. Only the 1-Dewar pyridines (**440**) were isolable reaction products, which rearranged thermally or by acid catalysis into pyridines (**441**). The photochemical rearrangement of Dewar pyridines (**440**) led to azaprismane derivative (**442**) ^[89T3115]. On the other hand, azete (**406**) underwent cycloaddition of alkynyl ethers or esters to afford isolable oxygenated 1-Dewar-pyridines (**443**) ^[90CC1456, 91CB1661].

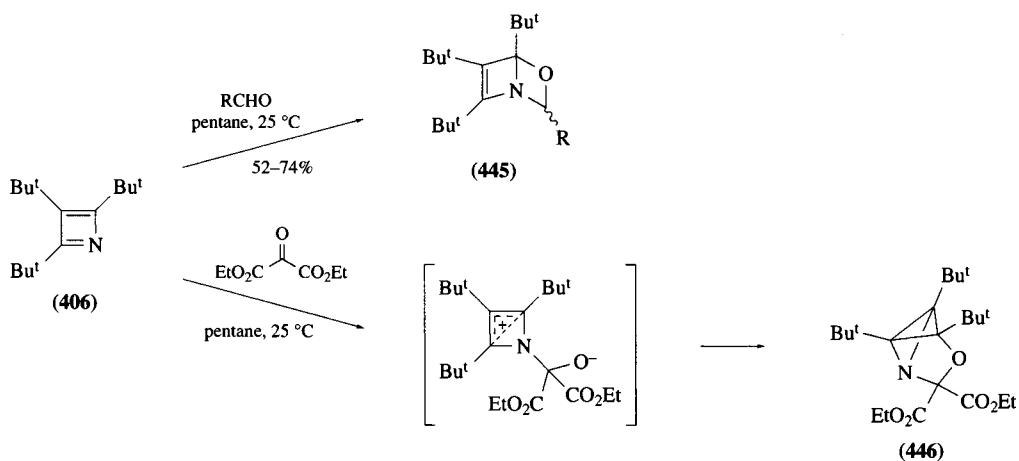


Azete (**406**) showed a remarkable chemical behavior towards diazo compounds, resulting in various adducts ($\text{C}=\text{N}$ or $\text{C}=\text{C}$ adduct) depending on the diazo compound, for example, diazo-

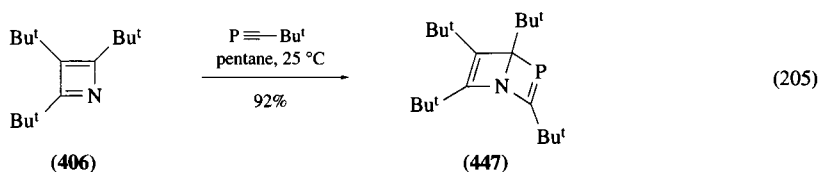
methane or 1-diazo-1-phenylethane <88AG(E)272>. However, 2-diazoindane-1,3-dione furnished a ring contraction into an azirine derivative (**444**) <91MI 118-03>. Nitroarenes gave rise to a [3 + 2] cycloaddition product which rearranged to 1,2,4-oxadiazolines <91MI 118-03>. Azete (**406**) reacted as a 1,3-diene with aldehydes to yield oxazabicyclohexenes (**445**), while mesoxalic ester produced an oxazatricyclohexane (**446**) <91MI 118-03>. Phosphaalkynes, for example, $\text{Bu}^t\text{-C}\equiv\text{P}$, reacted regio-specifically with azete (**406**) to afford Dewar-1,3-azaphosphabenzene (**447**) <88AG(E)272>.



Scheme 95



Scheme 96

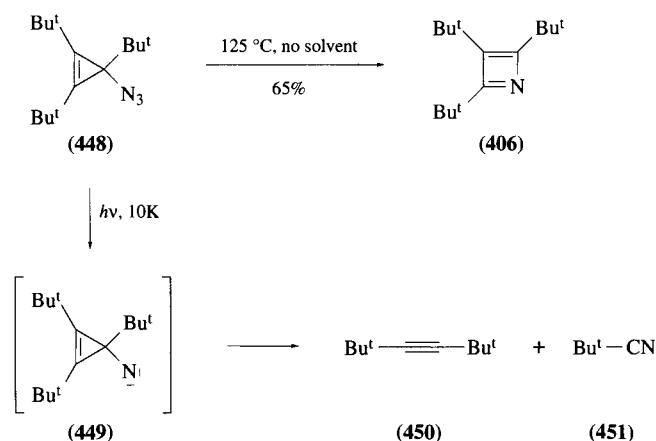


(205)

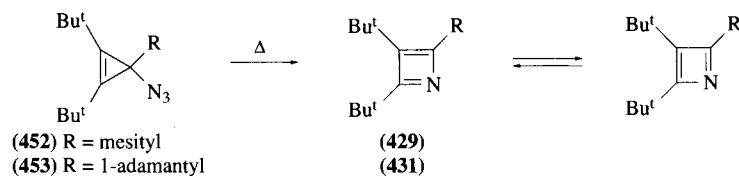
1.18.5.6 Synthesis

1.18.5.6.1 Thermolysis of 3-azidocyclopropenes

Based on the ready accessibility of tri-*t*-butylcyclobutadienes by photolysis of diazo(1,2,3-tri-*t*-butyl-2-cyclopropan-1-yl)acetic esters, the 3-azidocyclopropene (**448**) was selected as precursor of choice for a stable azabutadiene. Irradiation in an argon matrix produced only the fragmentation products (**450**) and (**451**), via an intermediate triplet nitrene (**449**). In order to avoid the nitrene formation, 3-azidocyclopropene (**448**) was heated neat at 125 °C resulting in a concerted N₂ expulsion and 1,2-C shift to afford 2,3,4-tri-*t*-butylazete (**406**) <86AG(E)842>. The 4-(1-adamantyl)- and 4-mesityl-analogs (**429**) and (**431**) were prepared similarly from (**452**) and (**453**) respectively (see valence isomer equilibrium above) (Scheme 98).



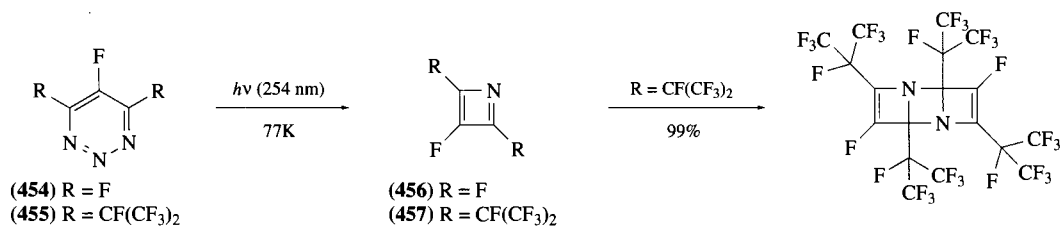
Scheme 97



Scheme 98

1.18.5.6.2 Photolysis of fluorinated 1,2,3-triazines

Photolysis of fluorinated 1,2,3-triazines (**454**) at low temperature resulted in the formation of 2,3,4-trifluoroazete (**456**), which was characterized by IR and mass spectroscopy (Scheme 99). Similar results were obtained with the corresponding bis(perfluoroisopropyl)-derivative (**455**) and (**457**). At higher temperatures, dimerization of the azete took place <87CC1699, 90JCS(P1)975, 90JCS(P1)983>.



Scheme 99

1.19

Cephalosporins

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Lilly Research Laboratories, Indianapolis, IN, USA

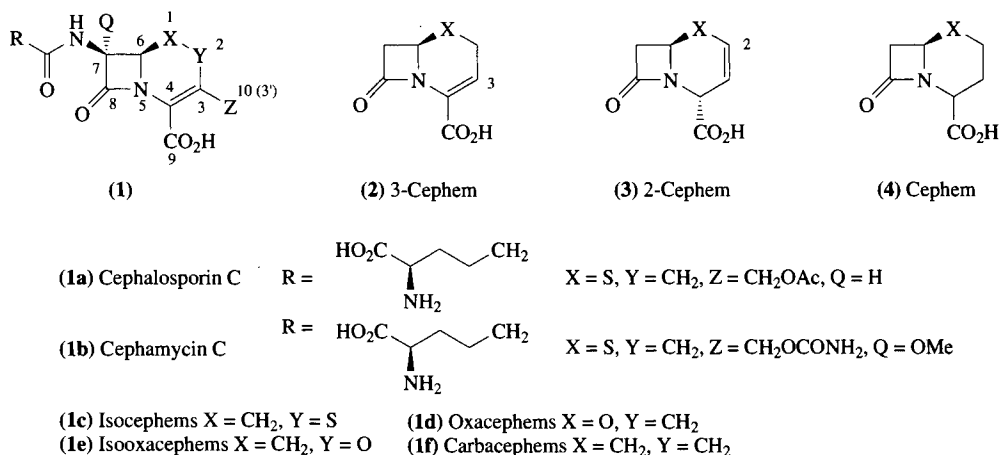
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1.19.1 INTRODUCTION

1.19.1.1 Structural Types and Nomenclature

Traditional cephalosporins refer to a class of dihydrothiazine fused β -lactam antibiotics produced by the fungus families *Cephalosporium* (cephalosporin C) or *Streptomyces* (cephamycins) and derivatives obtained from peripheral modification of these fermentation products. Over the years the term

“ceph” has been extended to include various nuclear analogues of the general structure (1), a number of them exhibiting superior biological activity and chemical stability. The widely accepted conventional nomenclature based on the cepham (4) ring system is used throughout this chapter. The carbon atom attached to C3 has been designated as C10 or C3'. Regioisomers with regard to the double bond are specified as 2/3-cephem, or alternatively as Δ^2/Δ^3 -cephem (2), (3). Stereochemistry at C7 is specified either in absolute terms of *R/S*, or α/β based on whether the substituent (e.g., amino) is attached from below or above the plane, respectively. This conventional system, especially the numbering scheme, should not be confused with the IUPAC sanctioned nomenclature as used by *Chemical Abstracts*. *Chemical Abstracts* designates cephalosporanic acid as (*R*)-3-[(acetyloxy)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.



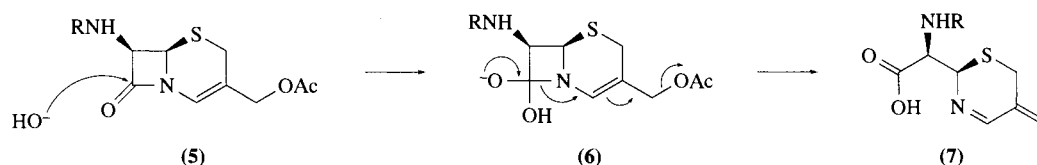
1.19.1.2 General Overview

Cephalosporins continue to dominate other classes of compounds clinically used to treat bacterial infections. Exhaustive structure-activity studies and clinical evaluations conducted by a multitude of laboratories around the world have produced a huge number of compounds that have been introduced to the market place (see Section 1.19.6.1). Nuclear analogues such as 1-oxacephems and 1-carbacephems have been successfully introduced into clinical practice. Advances in the chemistry of cephalosporins are largely driven by their importance as antibacterial agents. Since virtually all cephalosporins that exhibit antibacterial activity possess the natural stereochemistry (6-*R*, 7-*R*), the need for enantioselective synthesis of these compounds has, in no small part, contributed to the rapid advancements in asymmetric synthesis in general. Several excellent monographs [B-82MI 119-01, B-89MI 119-02, B-92MI 119-03, B-93MI 119-03] related to this subject have appeared in the intervening years. Unfortunately, simultaneous with clinical use has come the predictable increase in bacterial resistance to cephalosporins and other β -lactams. It is for this reason that most academic and industrial research laboratories, previously involved in cephalosporin research and development, have refocused their efforts to find antibacterial agents to overcome resistance phenomena or have increased research directed towards other infectious diseases [B-93MI 119-04, B-93MI 119-05].

1.19.2 THEORETICAL METHODS

Extensive theoretical efforts have been directed at the reactivity of the β -lactam ring because nucleophilic cleavage is thought to be related to antibacterial activity [B-82MI 119-02]. Both extended Hückel theory (EH) and complete neglect of differential overlap (CNDO) methods have been used in the calculation of electron density and charge distributions of several cephalosporins, with the latter giving more satisfactory results. CNDO/2 molecular orbital calculations have been used to solve the structural and electronic detail of the β -lactam ring opening of cephalosporin by OH⁻, mimicking the action of the serine hydroxyl group of penicillin binding proteins that are involved in bacterial cell wall synthesis (Scheme 1). Electron density maps indicate that the incoming nucleophile would preferentially approach the ring carbonyl from a conical region nearly perpendicular to the

lactam plane in the α -face, reaching a transition state minimum when OH^- is 1.5 Å away from the carbonyl. *Ab initio*, MO calculation confirmed these results <80CPH291, 80TCA239>. Net energy change from forming such a complex with respect to the energy sum of the two separate reactants as calculated by CNDO/2 is defined as transition state energy (TSE). This is found to be a fairly accurate measurement of the relative ease of ring opening of β -lactam by an external nucleophile <74JMC342, 80JA1812, 83JMC1010>.



Scheme 1

Comprehensive conformational analysis of several cephalosporins has been carried out using semiempirical methods MINDO (modified intermediate neglect of differential overlap), MINDO/3 and AM1 (Austin Method 1). MINDO/3 appears to give better estimations of geometric parameters than MINDO and AM1 as compared to x-ray crystallographic data, even though MINDO is best in characterizing the pyramidal nature of the β -lactam nitrogen. The geometry of several cephalosporins was determined by MINDO/3 <91JST(251)205>. Liability of the tetrahedral intermediate toward cleavage has also been simulated using AM1 MO methods <91MI 119-01, 92BMC485>. Molecular mechanics (MM2 and Amber) optimized geometry of β -lactam antibiotics has been found to be in reasonable agreement with x-ray data <89MI 119-01>.

Boyd and co-workers have also extended the theoretical study to quantitative structure activity relationship (QSAR) of cephalosporins and other antibiotics <84JAN1642>. These include correlation of biological activities with physiochemical properties such as circular dichroism <73JMC1195, 77T711>, ^{13}C NMR chemical shift <84JAN1642> and UV absorption <72JA6513, 79T1499>.

1.19.3 EXPERIMENTAL STRUCTURAL METHODS

1.19.3.1 X-ray Crystallography

Three-dimensional structures of cephalosporins determined by x-ray have served as important tools in drug design and as a benchmark for theoretical calculations. Structures of many cephalosporins and analogues have been determined by x-ray crystallography <70JA5489, B-73MI 119-01, 74JPC2604, 78JCS(P2)1082, 79CSC287, 81CSC259, B-82MI 119-02, 91JST(251)205>.

The strained four-membered ring fused with dihydrothiazine confers little conformational flexibility to the cephalosporin nucleus. The C8—N5 bond length (1.35–1.40 Å) is substantially longer than the free amide (1.33 Å), while the C8—O bond length is shorter than its amide counterpart. This indicates the inhibition of the amide resonance leading to a weaker C—N bond, consequently increasing the charge density on nitrogen relative to an open chain amide. The β -lactam ring is essentially planar even though C6 can be displaced toward S1 by as much as 0.4 nm. Conformational analysis indicated two minima, literally referred to as “S1 up” or “C2 up”, respectively. Except in isolated cases <87JCS(P2)841>, the preferential conformation is that of “S1 up” as indicated by x-ray crystallography, with N5C6—S1C2 dihedral angle between 50 and 60°. Figure 1 illustrates the geometry of cephaloradine (**1e**) as determined by single crystal x-ray <70JA5489>. Theoretical studies using molecular mechanic <B-82MI 119-02>, CNDO <74JMC342>, and MINDO <91JST(251)205> estimated the “S1 up” conformer to be 2–3 kcal mol⁻¹ more stable than that of “C2 up”.

1.19.3.2 Spectroscopic Methods

Spectroscopic methods as applied to cephalosporins have been examined in detail <B-73MI 119-02, 76MI 119-01, 81MI 119-01>. Proton, ^{13}C and ^{15}N NMR spectroscopy have been indispensable in elucidating structures, configuration, and conformations of cephalosporins and derivatives. High field

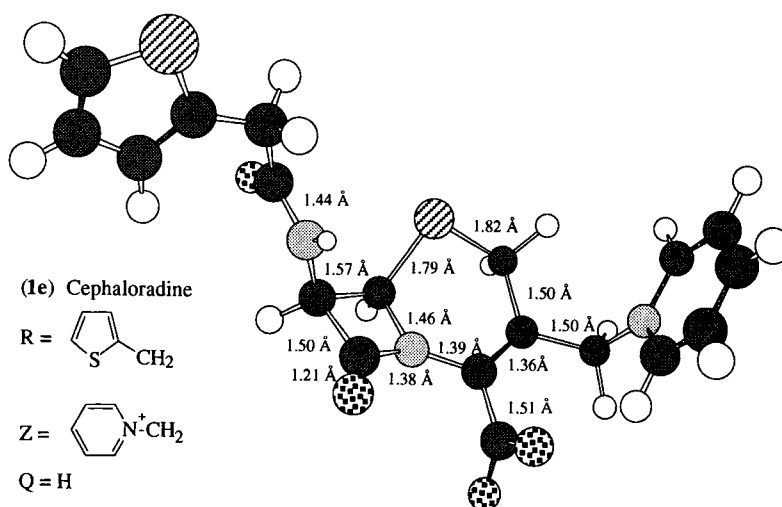


Figure 1 Structure of cephaloradine.

NMR chemical shifts and coupling constants of several important cephalosporins as well as penicillins have been tabulated <77JCS(P2)1749, 78JOC2013, 78OMR(11)638, 79OMR(12)337, 81TL2793, B-82MI 119-02, 87MI 119-01, 88MRC719>. Proton chemical shifts are concentration as well as solvent dependent to various extents, manifesting the degree of self-aggregation at different concentrations and solvents. Studies of relaxation time constant T_1 (spin-lattice) and T_2 (spin-spin) of β -lactam has been very limited and may prove valuable in investigating drug-protein interactions as high field instrumentation and sophisticated pulse sequencing becomes more accessible.

Characteristic of cephems are the distinctively large coupling constants ($^3J = 4-5$ Hz) between resonance of the two *cis* protons on C6 and C7 in the 4.9–5.9 ppm range with a separation of 0.5–0.6 ppm. Another diagnostic feature is the AB doublet pair resulting from resonance of the two protons at C2 in the range of 3.1–3.8 ppm separated by roughly 18 Hz (^2J). Chemical shifts difference between the two β -lactam protons ($\Delta\delta_{6,7}$) is generally greater than that of penicillins ($\Delta\delta_{5,6}$). Due to the stronger deshielding effect of oxygen, the C2 protons of 1-oxacephem such as moxalactam resonate at the lower field (4.3, 4.5 ppm, $^2J = 17.4$ Hz) as expected.

Carbon-13 chemical shifts, especially the differences between C3 and C4 ($\Delta\delta_{4,3}$), have been linked to transition state energy (TSE) and hence antibacterial activity <81JAN1645, 81TL2793>. The presence of an electron-withdrawing group at C10 (i.e., C3') enhances this difference as polarization of π -electron density increases. Carbon-13 and ^{15}N (β -lactam nitrogen) chemical shifts of the cephem nuclei are essentially unsuceptible to structural changes of the C7 amide side chain. The β -lactam carbonyl (C8) resonates in the range of 160–170 ppm. Lack of enamine-type resonance of the β -lactam nitrogen is manifested by the insensitivity of N-5 shifts toward the nature of C3 substituents. Nitrogen-15 resonance of the 7-amido nitrogen hovers over a wide range (8.5 ppm) and serves as a fingerprint for side chain structural variations. Introduction of an α -methoxy group at the 7-position in the cephamycin series causes C6 and C7 to shift downfield by 5 and 35 ppm, respectively, while the C8 signal moves upfield by about 5 ppm.

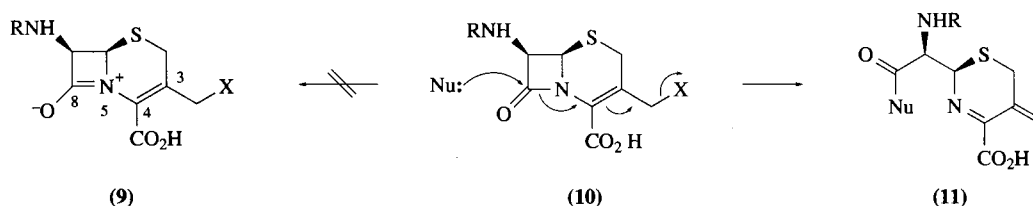
Depending on the nature of C3 substituents, cephalosporins exhibit UV absorption maximum in the 255–273 nm range <81MI 119-01>, accounted for by the unique α -acylamido- α,β -unsaturated carboxyl group chromophore. This band tends to shift to shorter wavelengths when measured in polar media. This phenomenon (blue shift) was explained by the stabilization of the ground state β -lactam nitrogen possessing high electron density. MNDO calculations agree with experimental values in assessing the transition energy <92MI 119-01>. Side chains, especially aromatic ones, may impart additional UV maxima useful for structural identification.

In the infrared region, cephalosporins exhibit absorption bands at 1786–1790 cm^{-1} due to the β -lactam carbonyl and side chain amide bands at around 1680 and 1530 cm^{-1} . The β -lactam carbonyl stretching frequency increases by about 5 cm^{-1} in 1-oxacephems. Attempts have been made to use this frequency as an index for biological activities in SAR (synthetic aperture radar) studies. Free carboxylates or esters show absorption at about 1600–1700 cm^{-1} . Differences in solvation state or crystal polymorphism may complicate the spectroscopic interpretation of these compounds.

1.19.4 REACTIVITY

1.19.4.1 β -Lactam Ring Cleavage

Biological activities of cephalosporins dominate research in this area. Several structural features have been determined to be essential for the desired antibacterial activity. They include the *R*-configuration at C6, amido (RCONH-) substituent at C7 from the β -face, C3=C4 double bond and C4-carboxylic acid (Scheme 2). Perturbation of these positions lead to changes in activity. Unlike other heterocycles, cephalosporins have rarely been used as building blocks for other classes of compounds. The potential of these readily available, enantiopure, highly functionalized bicyclics as a chiral pool for synthesis has yet to be realized.



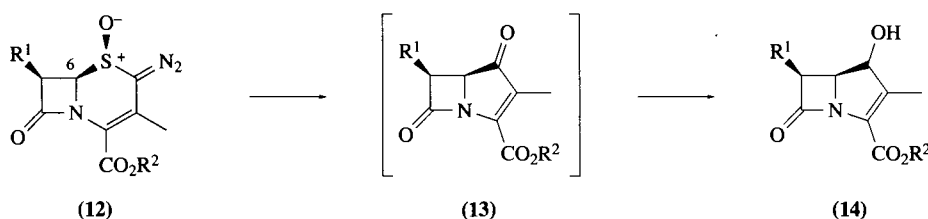
Scheme 2

The reactivity towards nucleophilic cleavage has been the focal point of β -lactam research <B-92MI 119-04>. Since the C8—N5 bond is considerably weakened by the lack of amide resonance due to ring strain as evidenced by the lengthened bond, increased electron density on nitrogen and presence of a leaving group on C10 (C3') or an electron-withdrawing group on C3 serve to enhance the ability of cephalosporins as acylating agents. However, maximum clinical potency can only be achieved when a delicate balance is struck between the reactivity of β -lactam as an acylating agent on the active site of β -lactam binding proteins and its stability against premature ring opening by water and other nucleophiles *en route* to the target enzymes. Contributing to the popularity of cephalosporins in clinical use is their superior chemical stability, especially towards hydrolysis.

1.19.4.2 S1 and C2 Modification

Cephalosporin sulfoxides can easily be obtained by oxidation with peracids, peroxides, and other inorganic oxidants. Chemistry with regard to C2 functionalization has been reviewed quite exhaustively <B-73MI 119-03, B-80MI 119-01, B-93MI 119-06> and in most cases reactions proceeded through a Pummerer-type sulfoxonium ion. The C2 position can also be activated towards a variety of electrophiles in forms of sulfoxide or sulfones undergoing Mannich reactions <92SC2979>, diazo transfer reactions, Michael additions <91JCS(P1)1265>, and alkylations <84JMC1225>. The 2-methylene derivatives obtained from Mannich reactions provide a handle for introducing 2-spirosubstitution through various cycloaddition reactions <84OMR(22)552>.

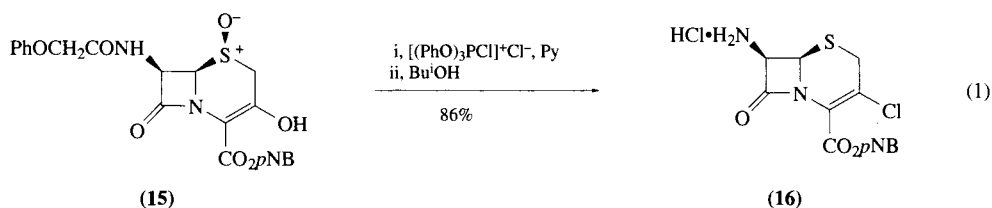
Representing one of the most exciting pieces of cephalosporin chemistry since the early 1980s <84CHEC-I(7)285> is the photo Wolfe rearrangement of 2-diazo sulfoxide ((12), Scheme 3) <82JA4262>. This ring contraction goes with complete retention of chirality at C6 and provides an access to compounds otherwise very difficult to prepare.



Scheme 3

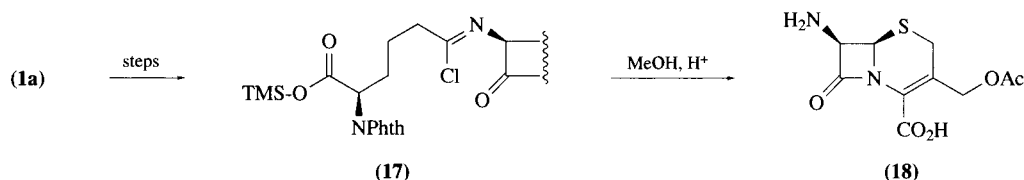
Proper protection of the 4-carboxyl group is crucial in the multistep manipulations of the cephem nucleus. Consideration must be given when the 4-carboxylic acid group is esterified or transformed

since the 3,4-double bond is especially prone to base-catalyzed isomerization <86JOC4723, 92JOC4027>. Other factors to be considered in choosing protecting groups include formation and removal conditions being compatible with the structural integrity (7-epimerization and β -lactam ring cleavage), and the stability of the blocking groups during synthesis. A classical example of incorporating these concerns in the design of a synthesis can be found in the final steps of cefaclor nucleus synthesis (Equation (1)), where one single reagent $[(\text{PhO})_3\text{PCl}]^+\text{Cl}^-$ converted 3-enol into chloride, reduced 1-sulfoxide to sulfide, and deprotected the phenoxyacetamido group through conversion to the imidoyl chloride followed by alcoholysis. As a result, (15) can be converted to (16) in one reaction vessel in 86% overall yield <B-80MI 119-04, B-82MI 119-03>. The *p*-nitrobenzyl (*p*NB) group has been used widely to block 4-carboxyl in cephem production for its robustness, crystallinity, and facile removal (Zn or H_2 reduction). Other ester blocking groups of choice are Bu^t , Cl_3CCH_2 , $\text{Ph}_2\text{CH-TMS}$, and *p*-MeOPhCH₂ (*p*MB). Comprehensive lists of protecting groups for β -lactam chemistry including those for 7-amino, 4-carboxyl, and side chain functionalities have been compiled <B-93MI 119-07>.



1.19.4.3 C7 and 7-Amino Modification

Results from the 1960s indicated that the first cephalosporin isolated, i.e., cephalosporin C, exhibited a broad spectrum of activity; however, its specific activity was low. With the experience and knowledge accumulated with penicillin research, opportunities inherent with C7 amide chain modification were quickly recognized. Morin *et al.* discovered the first practical means of removing the *D*- α -aminoadipyl group by way of iminolactone <62JA3400, 69JA1396>. Later improvements <68HCA1108> include a sequence involving protection of the free carboxylate in the form of silyl ester and the α -amino group in the form of a phthaloyl imide, followed by PCl_5 to give imidoyl chloride (17), which was then hydrolyzed to give 7-ACA (18) (Scheme 4).



Scheme 4

Unlike the penam series, where penicillin amidases have been used to deacylate side chains of fermentation products penicillin G (85; $\text{R} = \text{PhCH}_2\text{CONH}$, $\text{R}' = \text{H}$) or penicillin V (85; $\text{R} = \text{PhOCH}_2\text{CONH}$, $\text{R}' = \text{H}$) to afford 6-aminopenicillanic acid (6-APA) for further modification, no enzyme has been found which is able to deacylate cephalosporin C efficiently. A major breakthrough came when a stepwise enzymatic approach was developed (Scheme 5) <93MI 119-01>. From cephalosporin C, 7- α -ketoadipoyl cephalosporanic acid (19) was obtained either by transamination with glyoxylic acid or enzymatic deamination. Subsequent decarboxylation afforded glutaryl 7-ACA (20) in excess of 95% overall yield. Enzymatic deacylation can be carried out by an immobilized enzyme and 7-ACA (18) was produced routinely in 95% yield. Annual worldwide production of 7-ACA by various methods is estimated to be well over 1000 tonnes, and fermentation continues to be the most economical source of this cephem nucleus.

Penicillin amidase is also capable of catalyzing the hydrolysis of simple side chains of cephalosporins such as cephalixin and cephalothin under slightly alkaline conditions. The same enzyme, under slightly acidic conditions, catalyzes the reverse reaction, i.e., synthesis of these compounds from the corresponding 7-amino moieties. Advantage has also been taken of this mild acylation



(21) racemic
 (2)

(22) Loracarbef, enantiopure

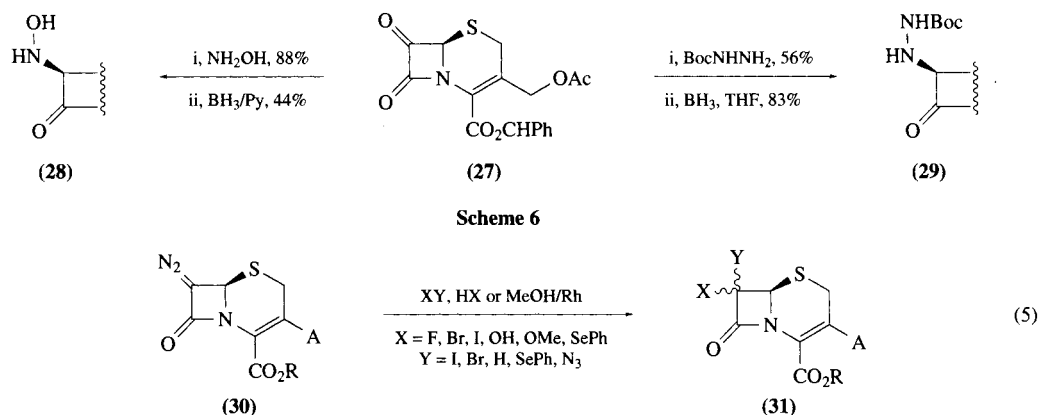
$$\begin{array}{ccc}
 \begin{array}{c} \text{R}^1-\text{N} \\ \diagup \quad \diagdown \\ \text{C}=\text{O} \quad \text{N} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{S} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{C}=\text{O} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{R}^2 \quad \text{CO}_2\text{R}^3 \end{array} & \xrightarrow{\text{X}^-} & \begin{array}{c} \text{X} \\ | \\ \text{R}^1\text{HN} \\ \diagup \quad \diagdown \\ \text{C}=\text{O} \quad \text{N} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{S} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{C}=\text{O} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{R}^2 \quad \text{CO}_2\text{R}^3 \end{array}
 \end{array} \quad (3)$$

(25) $\xrightarrow[\text{ii, E}^+]{\text{i, base}}$ (26)

(4)

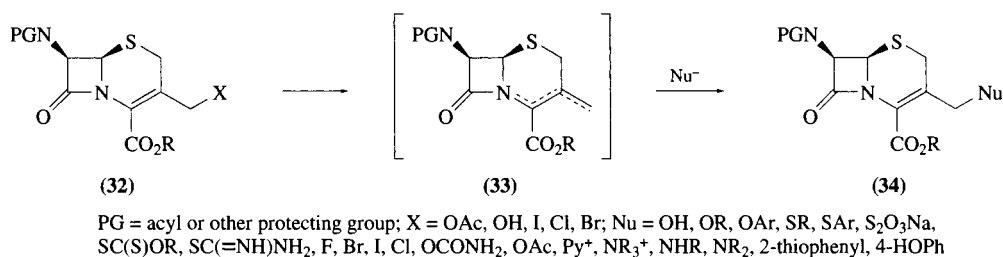
$E^+ = H^+$ and other electrophiles

Structure (29) 7-hydrazino <82H(19)1253>, and 7-hydroxylamino (28) <82CPB3061> cephalosporins are obtainable through the intermediacy of 7-oxo derivative (27) which, among other methods, can be prepared from 7-aminocephem by an enzyme mimicking the transamination reaction with an aromatic aldehyde (Scheme 6) <82JA4446>. 7 α -Alkylthio cephems obtained from these addition reactions can also be transformed into 7-amino analogues by ammonia displacement with Hg²⁺ catalysis <87JCS(P1)45>. 7-Isocyanocephems, easily prepared from a 7-formamido derivative, also provide a convenient anchor for functionalization at C7 and side chain introduction <89TL2375, 91JMC1110>. The 7-diazo derivative (30), readily available from 7-amino compounds by diazotization, transamination, or bistriflate elimination, or by oxidation of the 7-hydroxy analogue, presents a versatile handle for functionalization at the 7-position (Equation (5)). Much of the chemistry developed in the penam series should be applicable for the cephem series as well, and vice versa.



1.19.4.4 C3 and C10 (C3') Modification

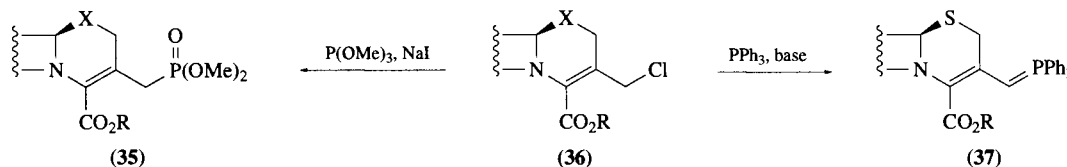
Altering the leaving group at C3' (C10) changes the electron density at the β -lactam nitrogen. This potential for affecting the activity towards ring cleavage is unique to cephalosporins and has been extensively explored in finding clinically useful compounds. Deacylation at C10 can be accomplished by either enzymatic (esterases) or chemical hydrolysis (TMS-I/ $\text{CF}_3\text{COONH}_4$, NaOH, $\text{Ti}(\text{OPr})_4/\text{Pr}^i\text{OH}$, etc.). The resulting allylic alcohol is quite prone to lactonization. The corresponding allylic halide can be obtained from substitution reaction of the alcohol (DAST, PCl_5 , $\text{Cl}_3\text{COCO}_2\text{CCl}_3$) <91JOC7186> or directly from the acetate (TMS-I, BX_3). They can also be prepared by an addition-elimination sequence with the 3-methylenecephem derivative <B-93MI 119-08>. Direct halogenation of 3-methyl-3-cephem gave complicated products, however, photo or radical initiated bromination of 3-methylcephem sulfoxide did give a respectable yield <83T337, 83T461>. Various nucleophiles can be introduced by displacement at the C10 allylic center (Scheme 7). Of particular importance are the heteroarylthiolate (e.g., <85CPB5534, 88JOC983>) and pyridinium substituents which led to a number of clinically successful cephalosporins. Many of these reactions are perceived to have proceeded through a delocalized allylic carbonium ion (33) (or zwitterion in the case of free 4-carboxyl) by an $\text{S}_\text{N}1$ mechanism, especially in neutral or acidic conditions. β -Ketoesters, as well as thiophene and phenol, give rise to C—C bond formation under Lewis acid catalysis <92JMC2631> with the allylic acetates (32; $\text{X} = \text{OAc}$). These allylic acetates also undergo Pd-catalyzed cross coupling reactions with organotin reagents and forms carbon-carbon bonds <88TL5739>. Alternatively,



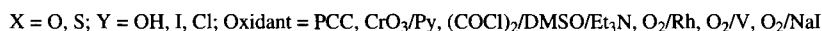
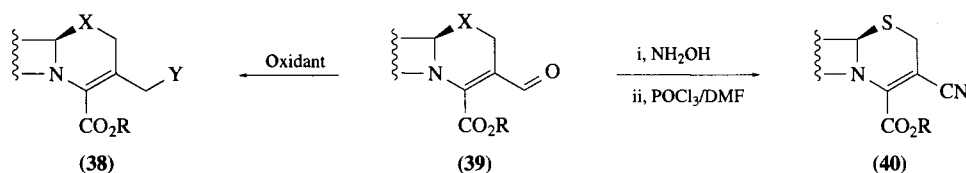
Scheme 7

the 10-phenyl group can be introduced by displacing the 10-bromo compound with phenyl cuprate <83T461>.

10-Phosphinyl cephems (35) <88CPB2354> and phosphonium ylides (37) were obtained from the 10-halo derivatives (36) and coupled with aldehydes or ketones to give 3-alkenyl analogues (Scheme 8) (e.g., <91CPB2433>). Alternatively, allylic alcohols or halides (38) can be oxidized into the corresponding aldehydes (39), which then undergo a Wittig reaction, aminoxidation or nucleophilic additions to give 3-alkenyl, 3-cyano (40), and other derivatives (Scheme 9) <86H(24)1799>.

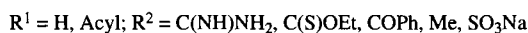
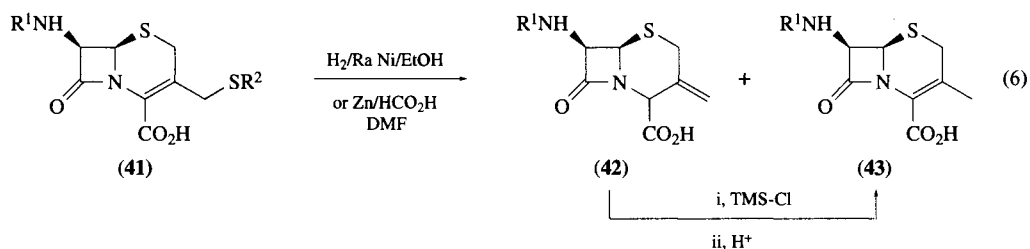


Scheme 8

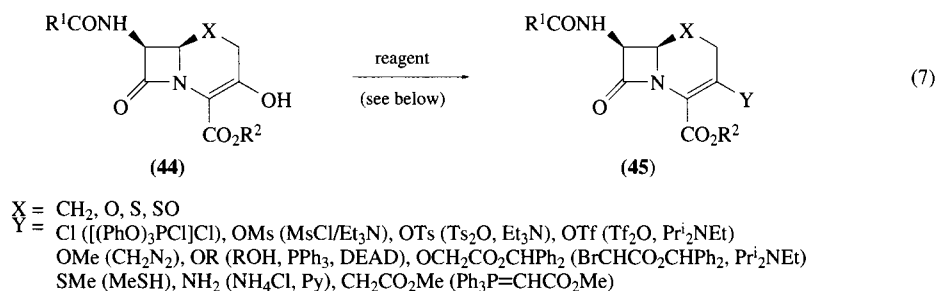


Scheme 9

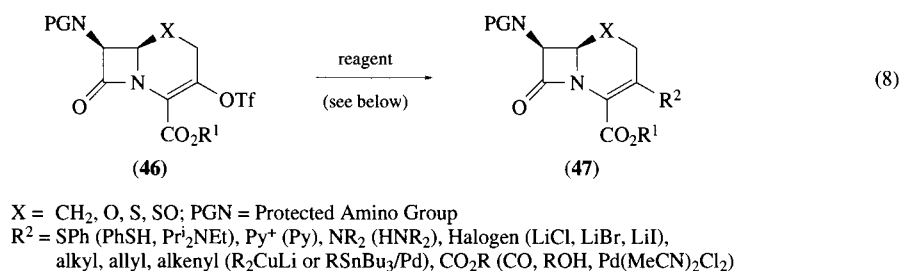
Considerable efforts have been directed at the reduction of the 10-acetoxy group to give 10-deacetoxycephalosporins due to the commercial interest in the synthesis of cephalexin and other 7-ADCA derivatives. Since direct hydrogenolysis required a large amount of Pd catalyst, an alternate route was developed through 10-sulfur derivatives by Raney nickel-catalyzed hydrogenolysis. Electrochemical reduction has also been carried out (Equation (6)) <72TL2341>. Products from the reduction generally consist of a mixture of (43) and (42). The esters of (42) can be isomerized into (43) with a base. Labeling experiments indicated that deuterium on C4 position of 3-methylenecepham (41) was incorporated onto C10 of 3-methylcephem (43). This embodies one of the two practical ways to 3-methylenecepham (42) and 3-methylcephem (43), the other being discussed in Section 1.19.1.2. Direct reduction of 10-acetoxy cephem using SmI₂ occurs with high chemo-, regio-, and stereoselectivity <93SC2977, 93TL6931>.



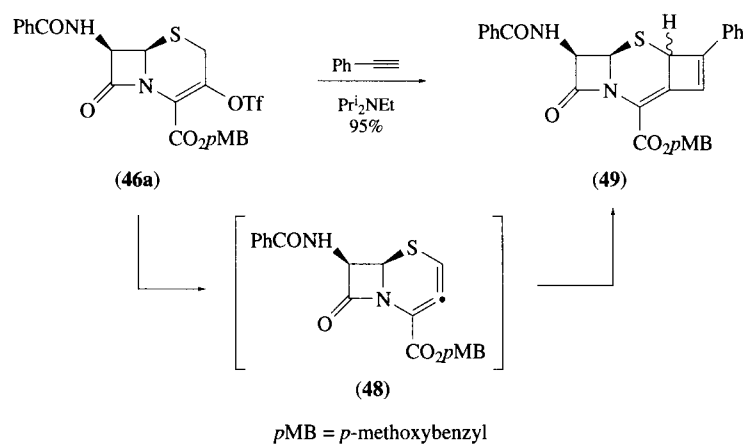
3-Exomethylenecepham (42) not only served as a pivotal intermediate to 3-methyl analogues, but also opened up a whole new horizon for C3 modifications. Ozonolysis of the esters of (42) gave 3-hydroxycephem (44), commonly referred to as cephalosporin enol, proved to be the most useful modification for commercial development. Careful engineering control allows large-scale ozonolysis to be carried out safely and efficiently in hundreds of kilogram scale and accounts for the production of top selling oral antibiotics including cefaclor (45; R = H, R² = PhCHNH₂, X = S, Y = Cl), cefroxadine (45; R = H, R² = 1,4-(cyclohexadienyl)CH(NH₂), X = S, Y = OMe, and ceftibuten (51b) (Equation (7)).



C3 enol exhibits certain ketone characteristics as manifested by its ability to participate in the Wittig reaction. However, in most cases the hydroxyl acts as a leaving group and can be displaced by chlorine, nitrogen, oxygen, and sulfur nucleophiles <89JOC4962, 93JMC2332, B-93MI 119-06>. The hydroxyl group can also be alkylated and sulfonylated. Several of these products are themselves very important intermediates for further transformations. For example, 3-phosphonocarbacephem can be acquired from a 3-chloro derivative and trialkyl phosphite via an Arbuzov-type reaction <93BMC2237>. The 3-azido cephem can be obtained from 3-chloro or 3-tosyloxy analogues which in turn undergo a variety of reactions with Grignard reagent and dipolarophiles <84H(22)2487>. The most useful C3 leaving group, nevertheless, is the triflate (46). These versatile compounds have been instrumental in introducing carbon-carbon linkage at C3 as well as incorporating heterosubstituents (Equation (8)) <93JMC1971>. Representative examples include substitution with low and high order cuprates <90TL3389, 93JOC2296>, palladium-catalyzed Stille coupling of organostannanes <88TL6043, 89JOC5828, 90JOC5833, 90SC2185, 91TL4073>, Pd-catalyzed carbonylation and a variety of heteronucleophile displacement <93JMC1971>.

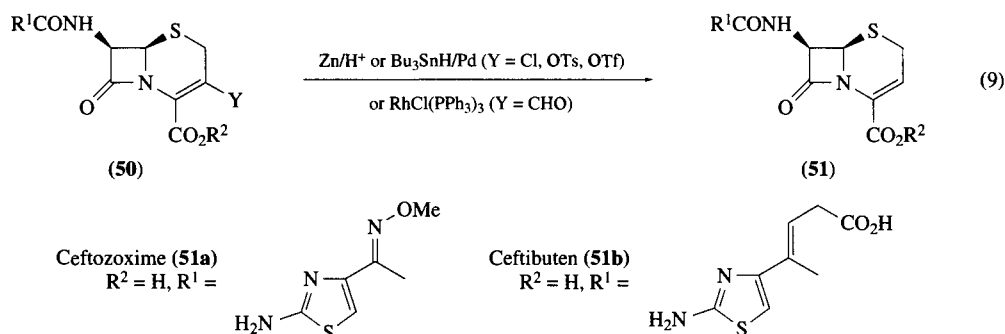


When triflate (46a) was subjected to the Heck coupling conditions, a cyclobutane fused cephalosporin was found to be the major product <93JOC6954>. It was determined that base alone would promote the cyclofusion. This serendipitously discovered [2 + 2] addition of the proposed allenic intermediate (48) with C—C double or triple bond proved to be a very general method for accessing highly strained structures such as (49) (Scheme 10).

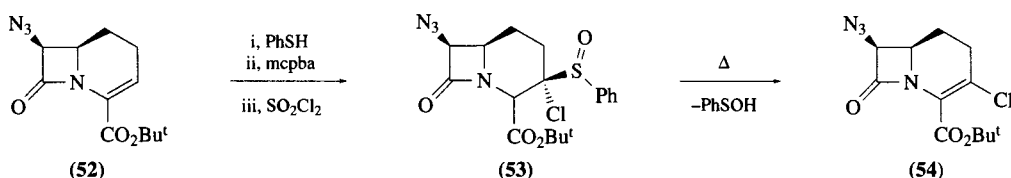


Scheme 10

Reduction of the 3-triflate, mesylate, and chloride or dehydroformylation of 3-carboxyaldehyde gave the 3-hydrido derivatives (**51**, Equation (9) <B-93MI 119-08>). This important class of cephalosporins includes ceftizoxime (**51a**) and ceftibuten (**51b**).



3-Hydridocarbacephems (**52**) can be chlorinated by a sequence involving addition of phenylthiolate, oxidation to sulfoxide, chlorination with SO_2Cl_2 , and elimination of phenyl sulfenic acid (Scheme 11) <82TL2419, 89CPB1239, 94JOC3289>.



Scheme 11

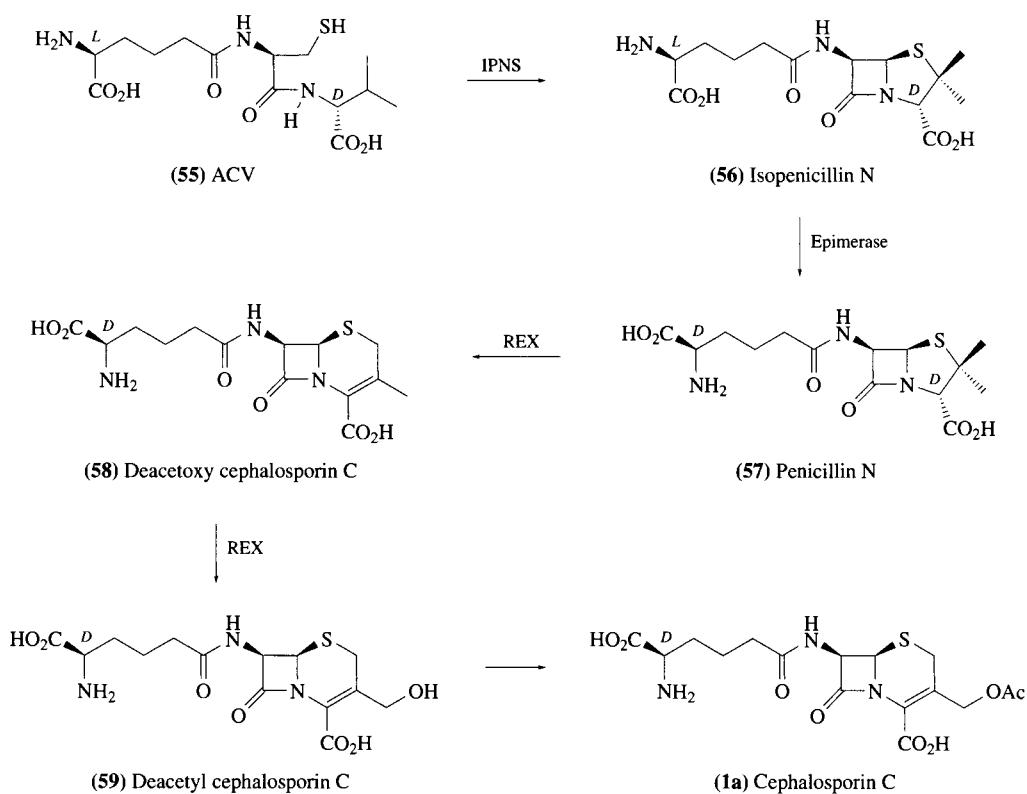
1.19.5 SYNTHESIS

1.19.5.1 Synthesis of Classical Cephalosporins

1.19.5.1.1 Biosynthesis

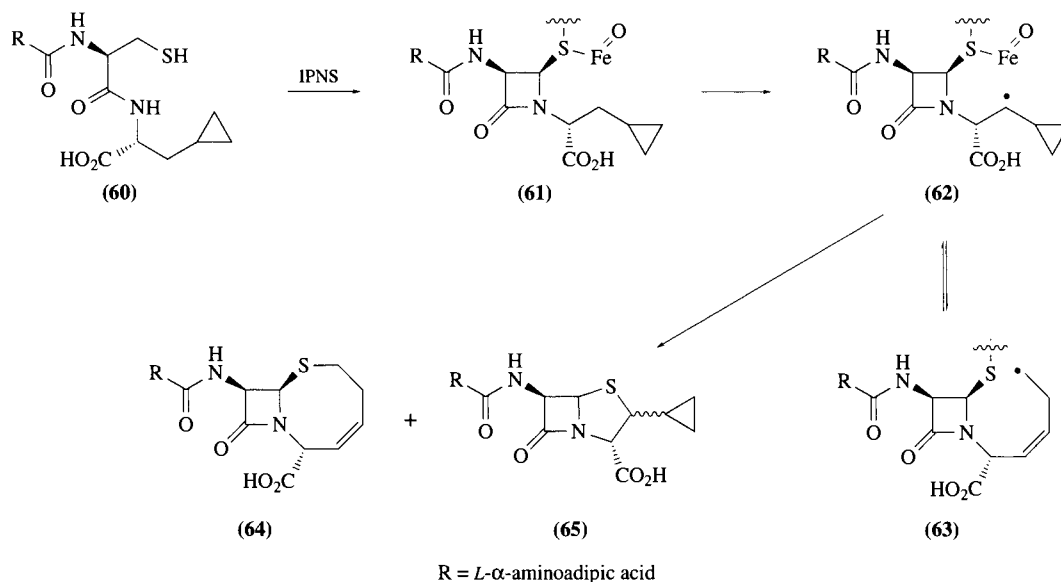
The 1980s witnessed the unraveling of many of the mechanistic details of the biosynthesis of penicillins and cephalosporins <88MI 119-01, 90JHC71>. To a large extent the success of this magnificent effort was due to the isolation, purification, and sequencing of isopenicillin N synthase (IPNS) and ring expansion hydroxylase (REX) enzymes, initially from the eukaryotic organism *Cephalosporium acremonium*, followed by cloning and gene expression in *E. coli*. L-valine, L-cysteine, and L- α -amino adipic acid are assembled into the tripeptide ((**55**) ACV) with valine undergoing epimerization during incorporation (Scheme 12). IPNS converts ACV to isopenicillin N (**56**), requiring ascorbate, Fe^{II} ion, and molecular oxygen. Key to the formation of cephalosporins is the epimerization of the L-amino adipoyl side chain of isopenicillin N to the D-amino adipoyl side chain of penicillin N (**57**) that is the substrate for REX enzyme. The REX enzyme, which requires 2-oxo-glutarate in addition to ascorbate, ferrous ion, and molecular oxygen, then plays the dual role of ring expansion of the penicillin to produce deacetoxy cephalosporin C (**58**) and subsequent oxidation of the 3-methyl group to produce deacetyl cephalosporin C (**59**).

The ready availability of large quantities of recombinant IPNS allowed the evaluation of a huge number of tripeptide substrates <88MI 119-01, 92JMC1897>. While modification of the α -amino adipic acid was restricted to substrates that were very similar to the original ACV (**55**), and C-methylated cysteine could be used, it was modifications of the valine portion that gave the most useful mechanistic information and variety of products from incubation with IPNS. That the radical (**62**) was the intermediate in formation of the thiazolidine ring was demonstrated by use of the cyclopropyl derivative (**60**), among many other compounds. Both the five-membered ring (**65**) and the eight-membered ring (**64**) compounds were produced, the latter resulting from rearrangement of the cyclopropylcarbinyl radical to the homoallyl radical. The precursor to (**62**) is thought to be a high



Scheme 12

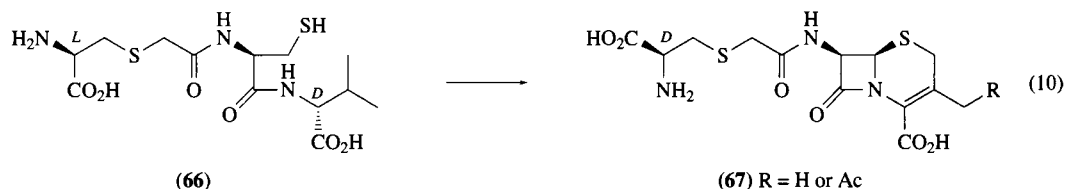
energy iron complex such as (61). Proper choice of valine replacement then can lead to the formation of a multitude of β -lactams fused to five- (penicillins), six- (cephams), seven-, and eight-membered rings (Scheme 13).



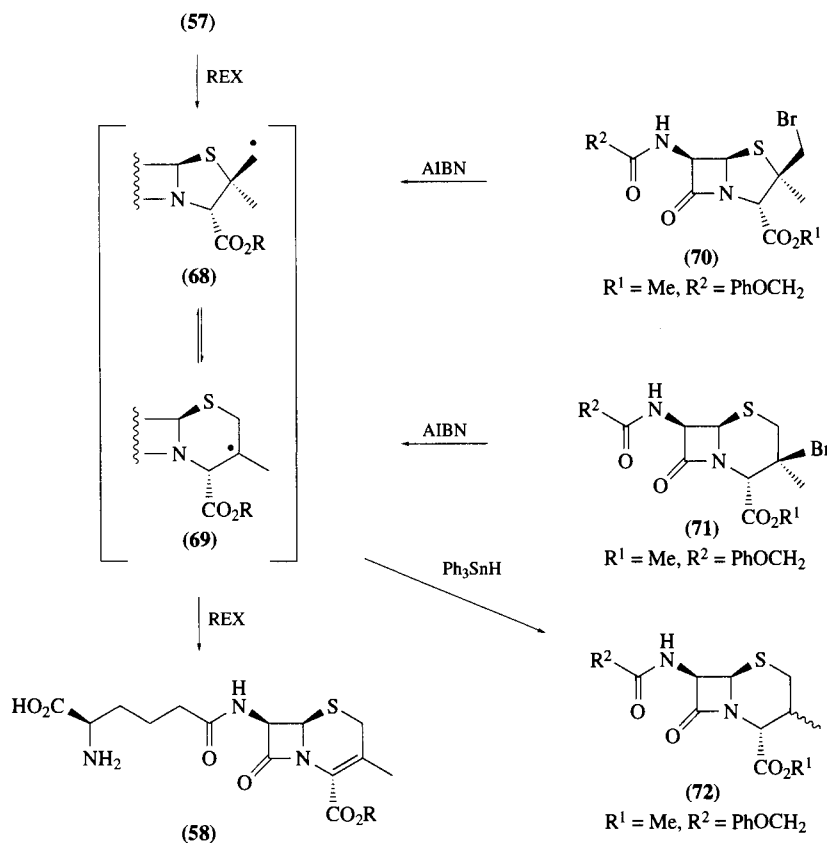
Scheme 13

The enzymes associated with the conversion of ACV to deacetylcephalosporin C have also been isolated from the prokaryotic organism *Streptomyces clavuligerus* (for reviews, see <84SCI1386>). Interestingly these enzymes, including the *epimerase*, are sufficiently stable to be immobilized.

When L-carboxymethylcysteine is used to replace L- α -amino adipic acid in the tripeptide (66), enzymes from both *C. acremonium* and *S. clavuligerus* efficiently convert (66) to the cephalosporin (67) (Equation (10)) (84BBR(120)607, 84HCA870). This observation is important for those interested in studying these conversions since L-carboxymethylcysteine is readily prepared from relatively inexpensive L-cysteine and bromoacetic acid.



The ring expansion of penicillin N (57) to deacetoxy cephalosporin C (58) by the REX enzyme has been studied in some detail (see <90JHC71>), in part because of its similarity to the chemical ring expansion of penicillin sulfoxides to deacetoxy cephalosporins (see Section 1.19.5.1.2). However, it has been demonstrated that neither the α - nor β -sulfoxides of isopenicillin N were substrates for conversion to deacetoxy cephalosporin C (80MI 119-01). The radical (68) has been proposed as the initial intermediate in this transformation (76JA7024, 87CC104), which is in equilibrium with the cepham radical (69). The validity of this mechanism was supported by the chemical conversion of the 2 β -bromomethylpenicillin (70) or 3 β -bromocepham (71) to a mixture of 3 α - and 3 β -methylcepham (72) when treated under radical-chain conditions with AIBN and triphenylstannane (87CC104). The REX enzyme converts the related radical to the 3-cephem (58) (Scheme 14).

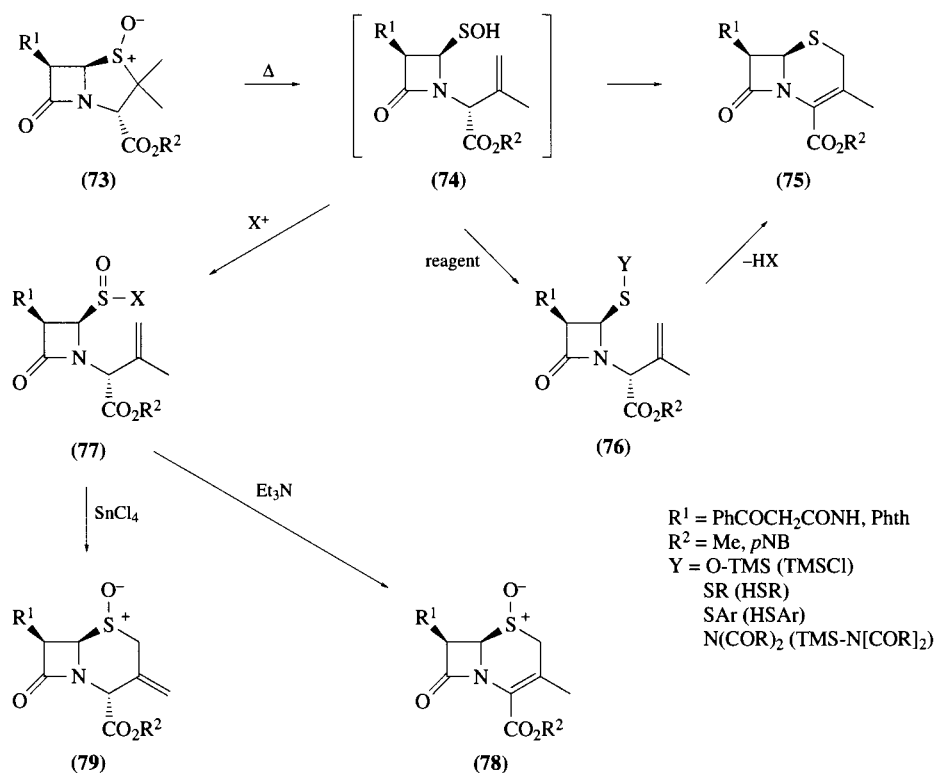


Scheme 14

1.19.5.1.2 Synthesis from penicillins

Initially the presence of the 6 α -amino adipoyl group in cephalosporin C caused low recovery from fermentation broths. Isolation required multistep deblocking procedures to furnish 7-ACA (19) or

7-ADCA (**43**; R = H). On the other hand, penicillin fermentations are high yielding and isolations are very simple, embodying a very inexpensive chiral pool. Since the publication of a seminal paper by the Lilly group <63JA1896> that established the chemical linkage between penicillins and cephalosporins (Scheme 15), synthetic chemists have capitalized on this chemistry and ameliorated it into several robust large-scale industrial processes <B-82MI 119-01, 93RTC66>. In 1995, a large porportion of penicillin produced is used for conversion into cephalosporins.

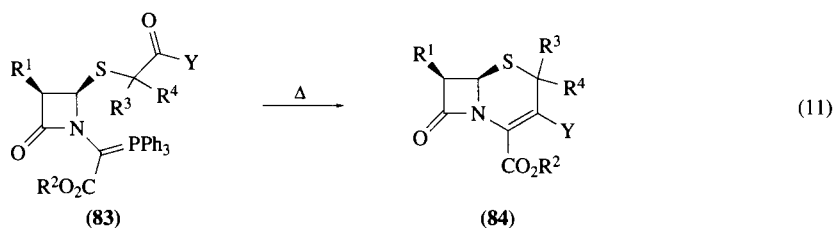


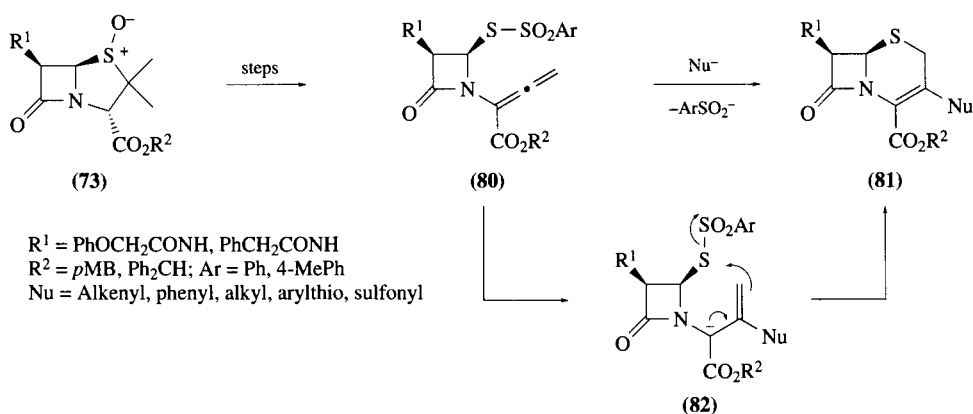
Scheme 15

The intermediate sulfenic acid (**74**) from the penicillin sulfoxide can be trapped with various reagents (e.g., TMS-Cl) and then carefully liberated <74JA1609, 76JA7864>. Reaction of the sulfenic acid (**74**) with a positive halogen source (sulfuryl chloride, NBS, NCS, and *N*-chlorophthalimide) gave the sulfinyl halide (**77**), which upon reaction with base or Lewis acid gave rise to 3-methyl cephem sulfoxide (**78**) or 3-methylene cepham sulfoxide (**79**), respectively. Ozonolysis of compound (**79**) provides a valuable source to 3-enol derivatives <76JA5040>.

Kant and co-workers <92TL3559, 92TL3563, 94JOC4956> at Bristol-Myers Squibb and Torii and co-workers <92TL7029> have reported elegant methodology leading to 3-substituted cephems (Scheme 16), as a logical extension of Torii's earlier cyclosulfenylation reaction <82TL2495, 83BCJ1567, 83BCJ2185, 83JOC3551, 84TL1801, 91BCJ1416>. Penicillin sulfoxide (**73**) was converted into allenic ester (**80**), which underwent a tandem conjugate addition–cyclosulfenylation to afford cephem (**81**).

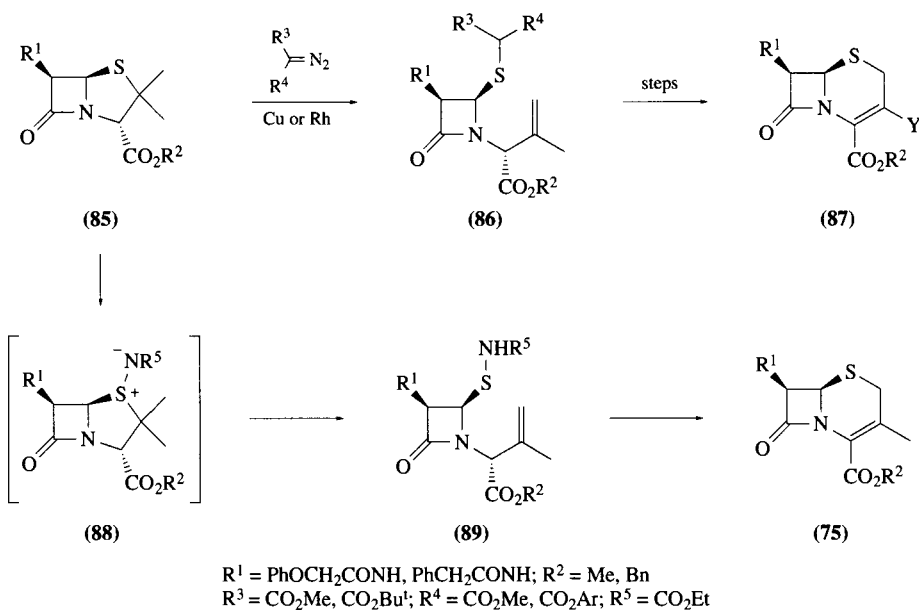
In a fashion similar to that of Woodward's penem and Hoechst's cephem total synthesis <B-92MI 119-04, B-93MI 119-09>, a few groups <79H(13)197, 81T703, 83H(20)435, 83TL1511, 88AJC1591> have utilized phosphoranes (**83**) prepared from penicillin sulfoxides to effect intramolecular condensation, affording cephem (**84**) with various 3-substituents (Equation (11)). The sulfone analogue of (**83**) also underwent similar transformation <85TL497>.





Scheme 16

A sulfonium ylide-mediated penicillin rearrangement opened yet another avenue to cephalosporins (Scheme 17) <72TL4387, 72TL5097>. The resulting sulfenamide (**89**) cyclized *in situ* to give cephem (**75**), while sulfide (**86**) can be converted into 2- or 3-cephem after several synthetic transformations <83H(20)435>. Radical cyclization of the penicillin derived haloalkyne has been shown to proceed to give the 2-cephem <89H(28)47>.



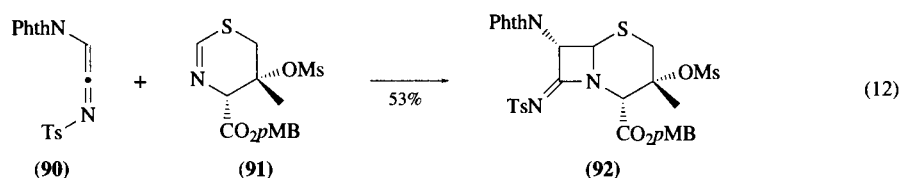
Scheme 17

1.19.5.1.3 Total synthesis

Groups at Roussel and Squibb have adopted Sheehan's penam protocol to achieve synthesis of cephalosporins from cycloacylation of a thiazine amino acid. Strategy featuring the same bond formation using newer cyclodehydrating agents has been utilized in the synthesis of several cephems including 7-methoxy analogues <89JOC2889>; for reviews, see <B-92MI 119-04, B-93MI 119-10, 94MI 119-01>. Woodward's total synthesis of cephalosporin C from L-cysteine is noted for its complete diastereo- and enantiocontrol and marked an important milestone in organic synthesis.

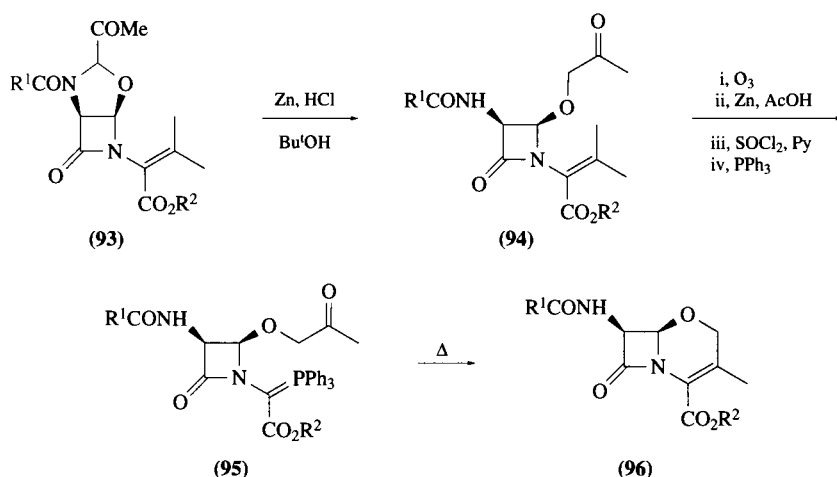
The [2 + 2] Staudinger reaction of cyclic imine such as 1,3-thiazines and dihydro-1,3-thiazines with azidoketene was originally developed by the Merck group. It gave predominantly the *trans* epimer of cepham nucleus which can be isomerized into the desired *cis* epimer at the 7-amino stage

as described in Section 1.19.4.3 <69T1191, 80CPB62, 80CPB2980, B-82MI 119-01>. Similar [2 + 2] additions also took place between imine (90) and ketenimide (92) (Equation (12)) <80TL3081>. For classical cephalosporins, partial synthesis from natural penicillins and cephalosporins is usually superior as far as synthetic efficiency is concerned, and as a consequence most total synthesis endeavors have been devoted to cephem nuclear analogues which are less accessible from these natural products.



1.19.5.2 Synthesis of Oxacephems

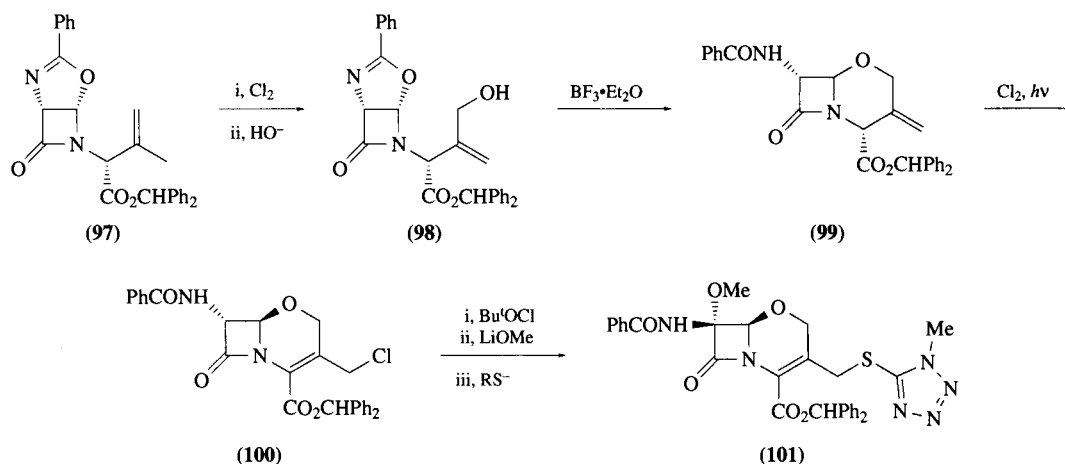
Wolfe *et al.* reported the first synthesis of an oxaceph in 1974 as a methyl ester <74CJC3996>. Biological activity of 1-oxacephalothin synthesized in racemic form by the Merck group in the early 1970s established that the sulfur atom was not essential for antibacterial activities of β -lactams <74JA7582>. Interest in oxacephem was heightened by discoveries at Shionogi that replacement of sulfur with oxygen increased activity by 4–16 fold. Intense synthetic activities ensued following the clinical introduction of moxalactam. Most of the syntheses of 1-oxacephem employed naturally occurring penicillins as starting materials, with varying degrees of stereochemical control at C6 <81MI 119-02, 81MI 119-03>. The most popular way of constructing the 1,3-oxazine ring involved 3,4-double bond formation through phosphorus ylides <B-93MI 119-08>. Establishing a *cis* ether linkage at C6 was crucial. Lewis acid-catalyzed ether formation that was utilized in early synthesis invariably gave *cis/trans* mixtures. A novel solution to this problem was developed by the Shionogi group (Scheme 18). Retaining the stereochemistry of C6, reductive cleavage of oxazolidine (93), which was obtained in a few steps starting from penicillin ring fragmentation, afforded the pivotal intermediate (94), which was further converted into ketophosphorane (95) and cyclized upon heating. Horner–Emmons type phosphoranes can be obtained by reducing azetidinone oxamate esters with phosphites (see also Sections 1.19.5.3 and 1.19.5.4). 2-Oxocephems and 2-oxo-1-oxacephem have also been prepared by similar methodology using *in situ* generated carbonyl precursors <79HCA2681, 80JOC3682, 90H(30)567>. Intramolecular Peterson alkenation provided yet another method of constructing the 3,4-C—C double bond <90TL1921>.



Scheme 18

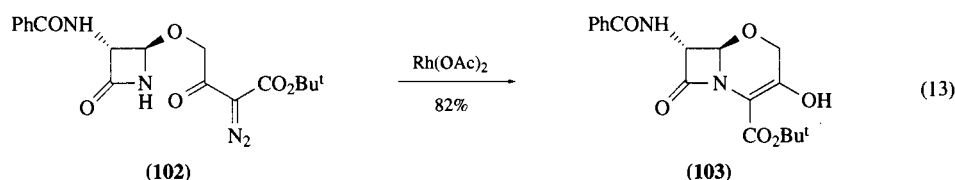
Based on the principle of double epimerization, a synthetic route suitable for the industrial scale production of oxacephem was developed from *epi*-penicillin sulfoxide derived oxazoline (97) (Scheme 19) <80TL351>.

Total synthesis of oxazoline analogous to (97) by a [2 + 2] Staudinger reaction has been reported <89T687, 89T695, 94BCJ1701>. Rhodium-catalyzed carbene insertion furnished a quick entry to 3-



Scheme 19

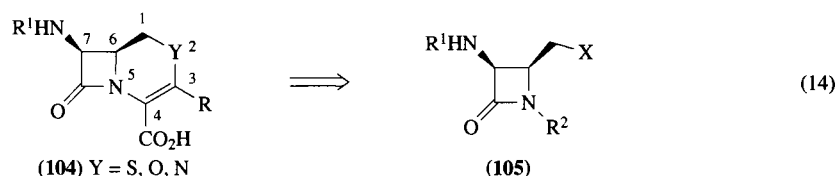
hydroxy-7-epioxacephem (Equation 13) <84T3667, 90H(31)791>. Similar bond formation has been a recurring theme in the synthesis of other 3-cephem analogues.



Intramolecular free radical addition to carbon–carbon multiple bonds of 4-allyloxy or propargyloxy azetidinone is also capable of constructing the C3–C4 bond with varying degrees of *endo/exo* selectivity <83JOC1841, 87TL2637, 89H(28)47, B-89MI 119-05>.

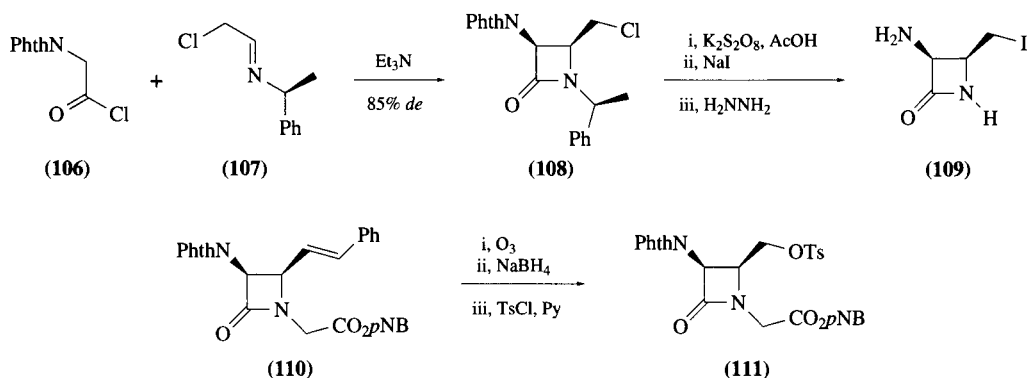
1.19.5.3 Synthesis of Isocephems and Isooxacephems

Most reported cases of isocephem and isooxacephem syntheses <80MI 119-02, B-89MI 119-03> start with a stereodefined monocyclic β -lactam (105), which can be obtained, most conveniently, by a Staudinger reaction (Equation 14) and Scheme 20). Fortuitously, *cis*-selectivity was usually observed for open-chained [2 + 2] Staudinger reaction, and the absolute configuration of C6 and C7 can be induced by the use of imines derived from chiral amine (107) <90T1579>, L-serine <80CJC1605>, or D-glyceraldehyde, and D-glucosamine derived ketene <92TL6641>. Cycloaddition of cinnamaldehyde imine afforded another popular starting β -lactam (110), which could be further transformed into the highly useful hydroxymethyl or tosyloxymethyl derivative (111).

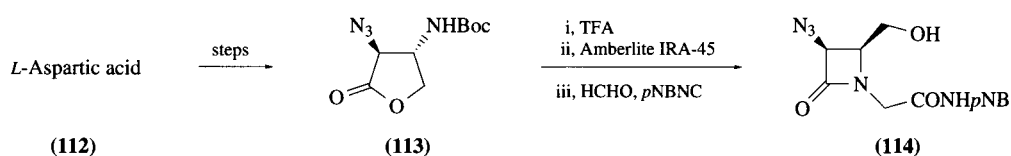


A similar monocyclic β -lactam in enantiopure form has been synthesized from L-aspartic acid through a diastereofacially selective installation of β -amino group followed by the Ugi-type cyclization (Scheme 21) <87CC51, 90JCS(P1)432>. No report on the use of natural β -lactam as starting material has surfaced, presumably due to the difficulties associated with forming an α -hetero C–C bond while preserving the C6 stereogenic center.

The most widely used method in the synthesis of isocephem and isooxacephem centers around formation of either the 1,2- or 2,3-carbon-hetero bond <92TL6641>. The intramolecular Mitsunobu reaction has been the method of choice in a number of isooxacephem syntheses (Scheme 22)

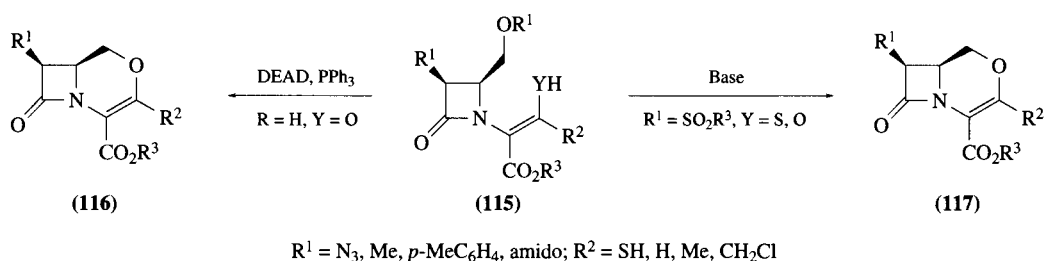


Scheme 20



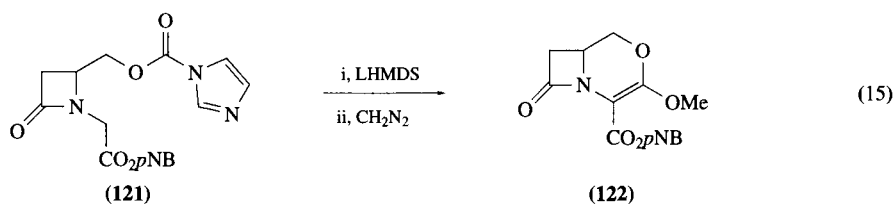
Scheme 21

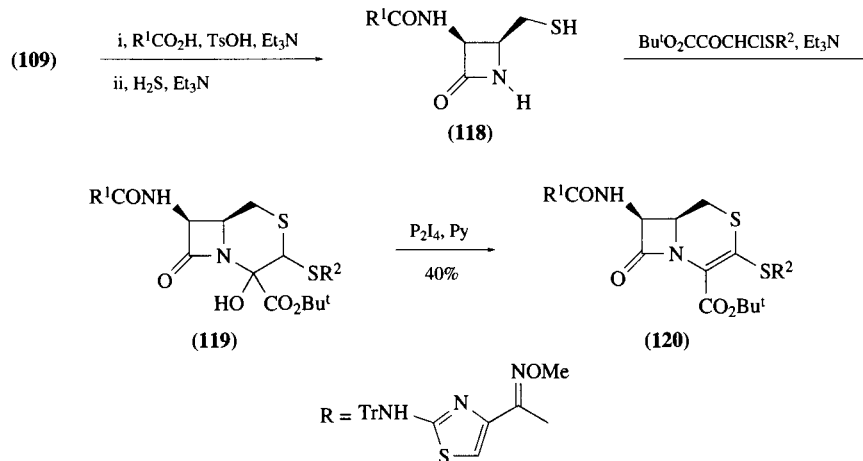
<87CC1283, 87H(26)2393>. Displacement of the sulfonate at 1-position by a heteronucleophile has also been used as the key step in a number of isocephem and isooxacephem syntheses <87CC51, B-93MI 119-08>. The requisite enol or thioenol (**115**) can be obtained by various methods including *in situ* condensation with CS₂ or acylation of the lower glycinate side chain, and carbene insertion of an α -diazo- β -ketoester into the β -lactam NH bond. 3,4-Benzoisooxacephs have also been prepared in a similar fashion <81CJC2981>.



Scheme 22

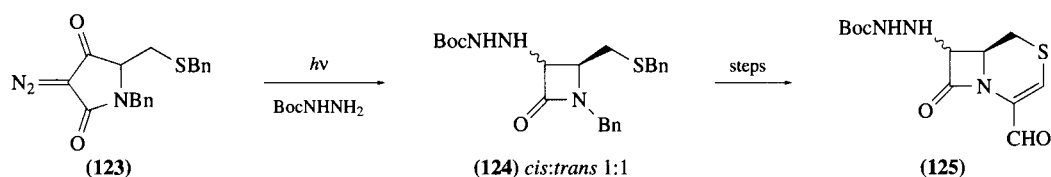
Compound (**109**) was acylated and converted into thiol mercaptan (**118**), which was subjected to simultaneous alkylation on both nitrogen and sulfur, resulting in isocephem (**120**) after dehydration (Scheme 23) <B-89MI 119-03>. Dieckmann condensation of the activated carbamate (**121**) yielded an enol which was methylated *in situ* to give isooxacephem (**122**) (Equation (15)) <90JCS(P1)432>. Isooxacephems and isocephems can also be formed via a triethyl phosphite induced 3,4-double bond formation <86TL305>.





Scheme 23

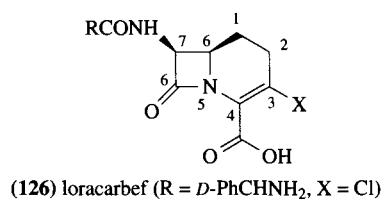
Carbene insertion into the thiazine ring resulted in a mixture of *cis*- and *trans*-isocephem <73JCS(P1)1321>. Rearrangement via carbene photolysis has also been used to generate β -lactam (124) as a precursor to isocephems (Scheme 24) <77JCS(P1)1421>.



Scheme 24

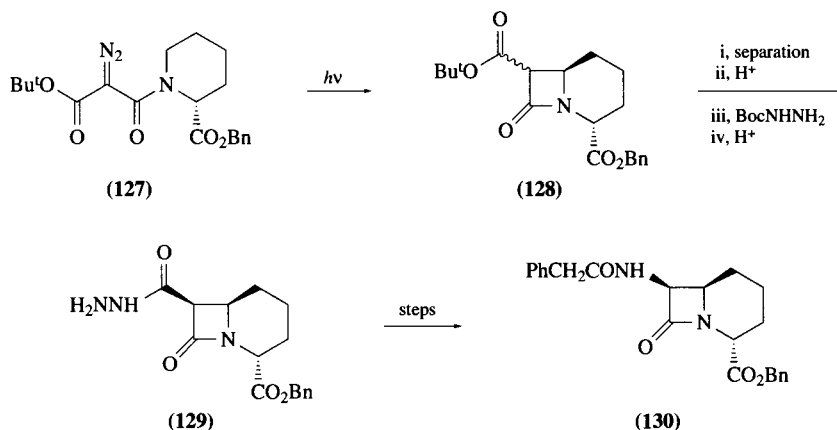
1.19.5.4 Synthesis of Carbacephems

Synthesis of carbacephems (**1f**; X, Y = CH₂) is undoubtedly the most exciting area of cephalosporin research since the 1980s <B-92MI 119-06>. Impetus for the intense research activities can be attributed to the increased stability of carbacephems at physiological pH versus their sulfur analogues. The rate of β -lactam ring cleavage by HO⁻ is 10–50 times slower for carbacephems than their sulfur counterparts <B-92MI 119-05, 94MI 119-04>. This superior stability has allowed the introduction of several substituents at the 3-position and hence new reactivities which were not accessible in the sulfur series. Replacement of the sulfur in cephalosporins by carbon also made 1- and 2-positions available for structural modifications. A wave of intensive synthetic effort in this area proceeded, followed by the introduction of the first carbacephem, loracarbef (**126**; Lorabid) into clinical use as a broad spectrum oral antibiotic in the early 1990s.



1.19.5.4.1 C6—C7 bond formation

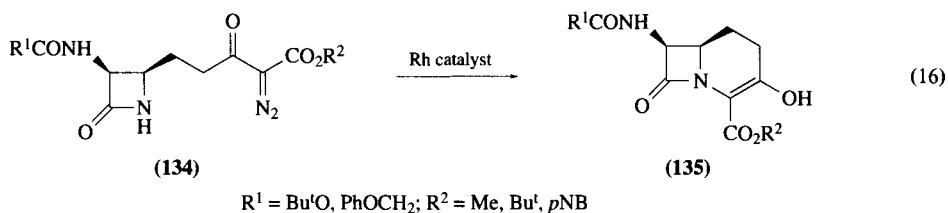
Synthesis of the carbacephem framework was first accomplished through a carbene insertion into an α -C—H bond of piperidine (Scheme 25, see also Section 1.19.5.3) <71JCS(C)3756>. Photolysis of α -diazo malonamide (**127**) gave a 1:2 stereomixture favoring the undesired *trans*-isomer. The *cis*-isomer was separated and subjected to a sequence of transformations to install the C7 amino group with retention of the 7- β configuration.



Scheme 25

1.19.5.4.2 C4—N5 bond formation

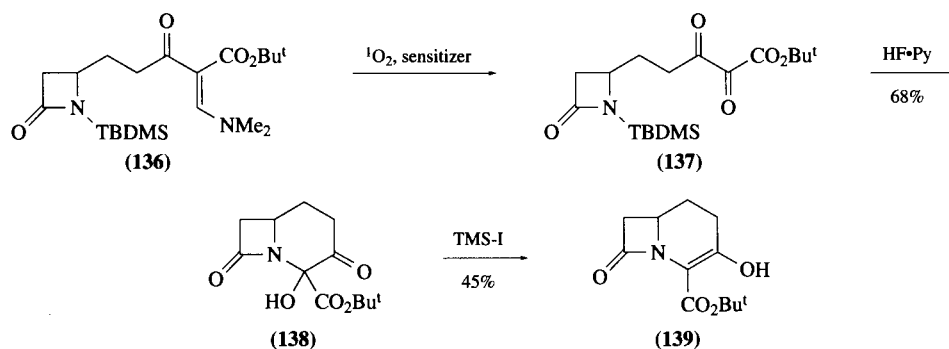
Rhodium-catalyzed carbene insertion of α -diazo β -ketoester into the N—H bond of β -lactams that was employed to synthesize carbapenems has been utilized as a key step in several syntheses of the carbacephem system <85TL3787, 89TL2321, 92CJC2142>. This approach is advantageous in that the product enol can be converted into a wide variety of C3 substituted carbacephems, and the starting diazo group can be readily introduced in high yield, provided the desired relative and absolute stereochemistry around C6 and C7 is established (Equation (16)).



Taking into consideration the substantial nucleophilicity of the β -lactam nitrogen and the supreme electrophilicity of an α,β -diketoester, Wasserman and co-workers <84TL3743, 92JOC3546> devised a novel approach to the enol system (Scheme 26). The requisite precarious tricarbonyl system (**137**) was installed by way of singlet oxygen cleavage of α -enamino- β -ketoester (**136**). *In situ* unmasking of the nitrogen resulted in the formation of 3-keto-4-hydroxy carbacephem (**138**), which was readily reduced to the enol (**139**).

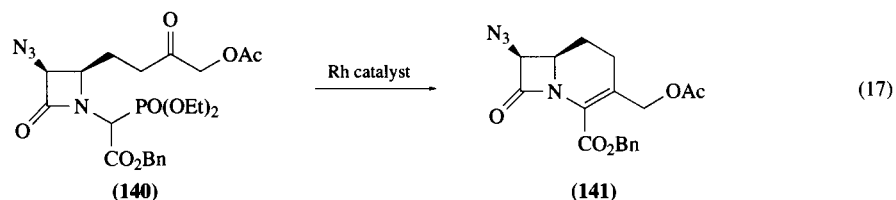
1.19.5.4.3 C3—C4 bond formation

Intramolecular Wittig reaction and other variations (e.g., Horner–Emmons–Wadsworth modification) has been widely employed in forming the 3,4-double bond of carbacephems with oxygen and sulfur analogues. Using this strategy, Christensen and co-workers at Merck reported racemic synthesis of the first carbacephems with antibacterial activities, for example 1-dethia-1-carba analogues of cephalothin, cefoxitin, and cefamandole based upon the common intermediate (**141**)

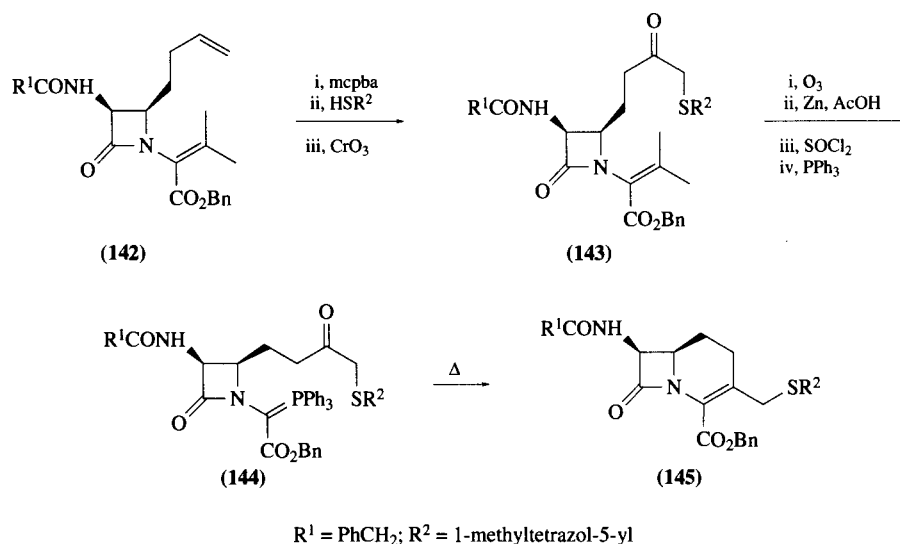


Scheme 26

<74JA7584, 77JMC551>. 1 α -Hydroxy and 2-oxocarbacephem were also prepared in similar protocol from respective phosphoranes (Equation (17)) <81TL5335, 83TL3783>.



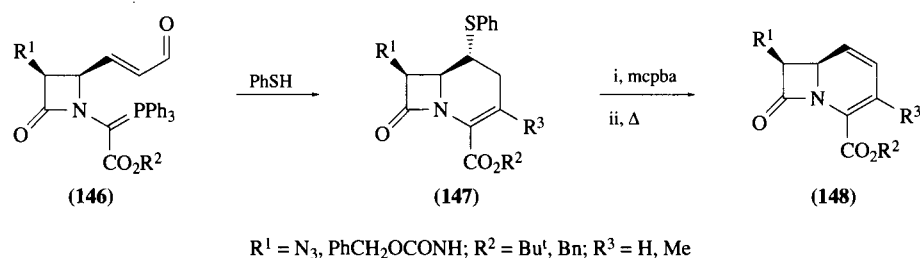
A similar strategy has also been adopted by the Shionogi group for constructing analogous compounds starting from enamide (142) (Scheme 27) <80CPB1563>, and by the Kyowa Hakko group for the synthesis of 3-hydridocarbacephem <89CPB315>. 1-Exomethylene carbacephem has also been accessible via this avenue <86JMC661>.



Scheme 27

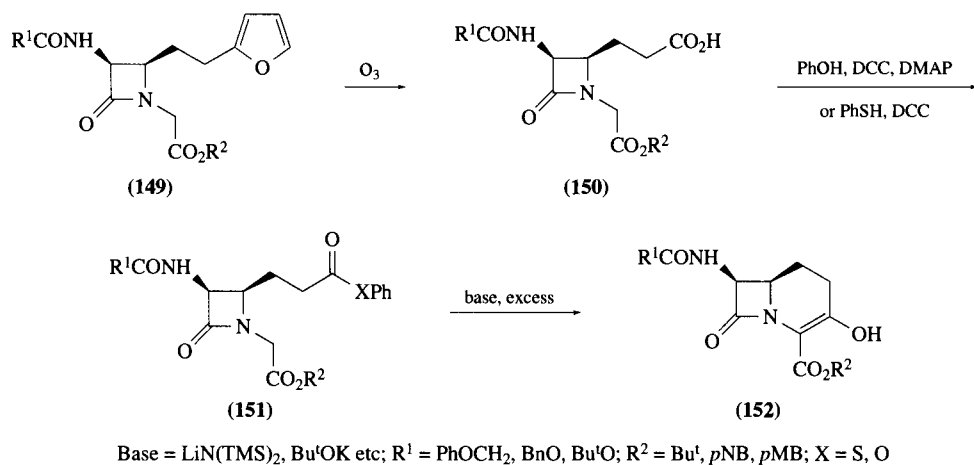
Cyclization of α,β -unsaturated ketone or aldehyde (146) required a little twist as the *trans* double precluded the carbonyl from approaching the phosphorane in an intramolecular fashion. However, the reaction proceeded smoothly when thiophenol was added to the reaction mixture <80CPB1578, 92JAN535>. The benzenethio group can be oxidatively eliminated to give carbacephdiene (148). Selective hydrogenation of the 1,2-double bond afforded 3-carbacephem. When the unsaturation of compound (147) was masked by epoxidation, chlorination, or dihydroxylation, cyclization proceeded smoothly to give rise to 1,2-epoxy, 1,2 dichloro, or 1,2 dihydroxy carbacephem respectively

<89CPB2298>. Direct cyclization can also be achieved by using dabco as a base, presumably through a similar addition–cyclization–elimination scenario (Scheme 28) <89CPB315>.



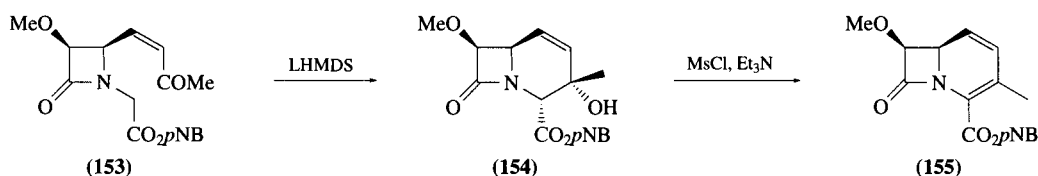
Scheme 28

Another popular approach for establishing the 3,4-double bond is the Dieckmann cyclization giving 3-enol directly <83TL4837>. This has been exemplified in several syntheses of loracarbef (Scheme 29) <84H(22)2227, 87PAC485, 88TL5065, 90TL6317, 91JOC6225, 91S985, 93TL3051>.



Scheme 29

In an analogous manner, intramolecular aldol condensation of (153) yielded 1-cephem (154), which upon dehydration afforded carbacephdiene (155) <81TL2497>. A similar mode of aldol reaction was also used to prepare 3-hydrido carbacephs from the corresponding aldehyde (Scheme 30) <88CPB3642>.

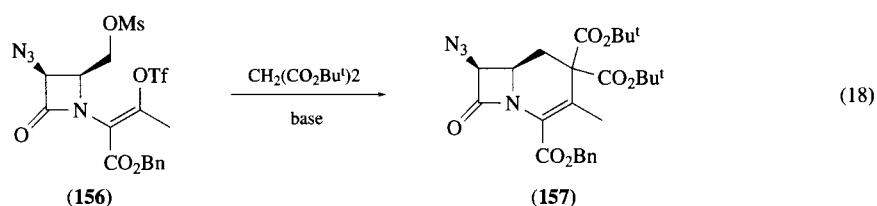


Scheme 30

1.19.5.4.4 C1—C2 and C2—C3 bond formation

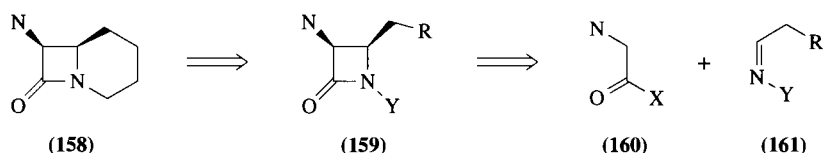
Drawing from the intermediate pool of isooxacephem syntheses, researchers at Bristol-Meyers prepared compound (157) in one step from the readily available biselectrophile (156). Compound

(157) could be decarboxylated and transformed into an array of carbacephem derivatives (Equation (18)) <79CJC227, 79CJC614>.



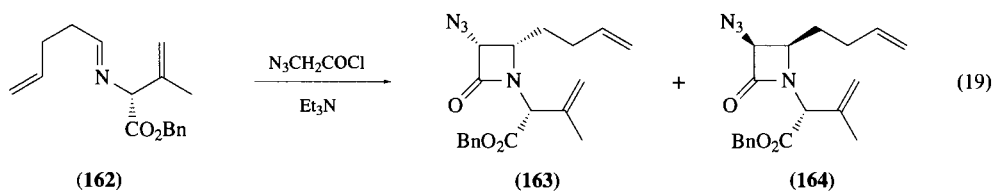
1.19.5.4.5 C6—C7 and N5—C8 bond formation

Essentially all of the foregoing carbacephem syntheses utilized as starting material a β -lactam (159) with two appendages, with *cis* relationship between the C7 and C6 substituents. Again, the preferred method for accessing such intermediates is the Staudinger reaction. The ready availability of glycine derivatives and imines has provided chemists with a convenient tool for building β -lactams with an assortment of functional groups for further modification. While such strategy has been used previously for the synthesis of other cephem nuclei (see Section 1.19.5.3), the synthesis of carbacephems using the Staudinger reaction is distinguished by the fact that tremendous efforts have been directed at chiral induction of C6 and C7 stereogenic centers (Scheme 31).



Scheme 31

Penicillin-derived imine (162) underwent cycloaddition to a ketene formed *in situ* from azidoacetyl chloride, affording a 1 : 1 diastereomixture of (163) and (164). The *cis*-isomer (163) could be separated and converted into phosphorane (146) by double ozonolysis (Equation (19)). Diastereoselectivities with threonine-derived imines were low to moderate.

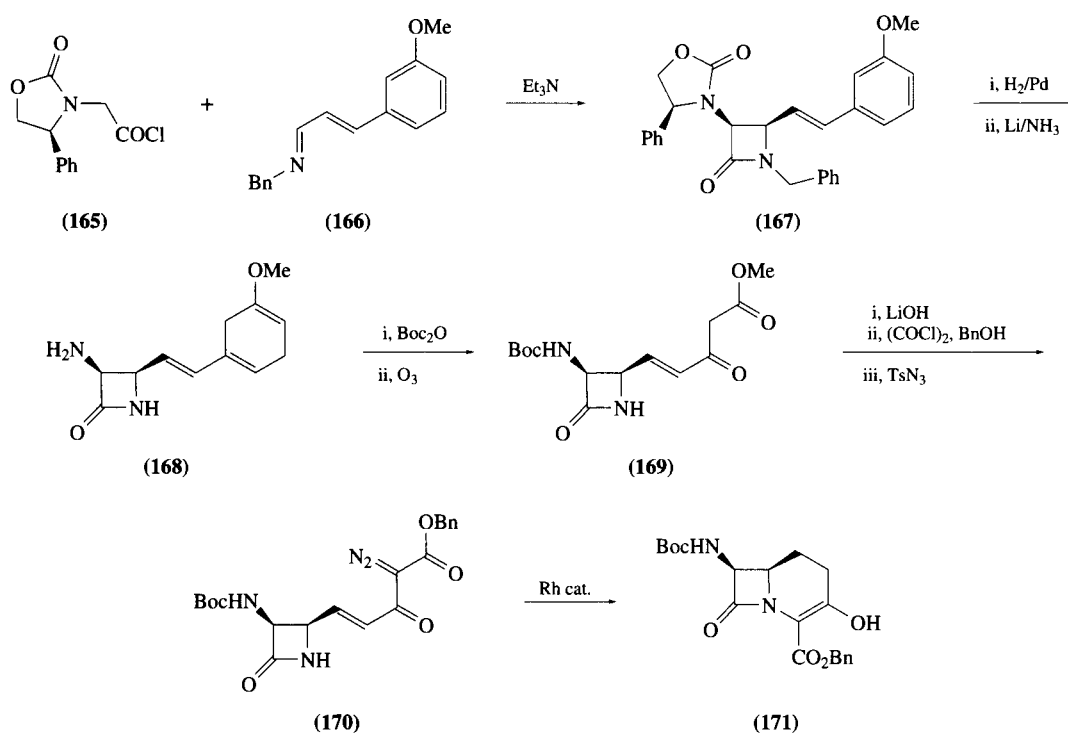


The chiral auxiliary on the ketene precursor has proven to be much more useful at imparting chirality into the cycloaddition process. Evans *et al.* have extended chiral oxazolidinone chemistry to the synthesis of carbacephem, using *m*-methoxycinnamaldehyde imine to furnish the framework of the tetrahydropyridine ring <85TL3787>. The same auxiliary was used by researchers at Lilly in their loracarbef synthesis <89TL2321>. Diastereomeric excesses are in the 90–96% range (Scheme 32).

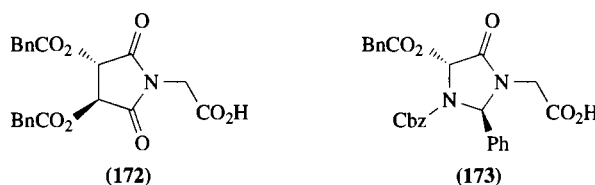
Other 7-amino based chiral auxiliaries employed in carbacephem synthesis include tartarimide (172, 90–95% *de*) <84H(22)2227, 87PAC485> and imidazolone (173, >95% *de*) <B-92MI 119-05>.

Facilities for installing, and more importantly, removing these chiral auxiliaries after the cycloaddition step must be taken into consideration in designing the synthesis, as the resulting β -lactams with *cis* substituents on C6 and C7 are vulnerable to epimerization and ring cleavage. More desirable is a chiral reagent-controlled asymmetric Staudinger cycloaddition of an achiral ketene precursor and an achiral imine, which has been elusive up to mid-1995.

An alternative approach to influence the stereochemical outcome of a Staudinger reaction is to employ an imine derived from a chiral aldehyde. Enantiomerically pure glyceraldehyde imines (174) <83HCA2206> and epoxyaldehyde imine (175) <88TL5065> have been successfully used to effect diastereoselective cycloaddition. Weigel and co-workers have utilized this methodology in con-



Scheme 32

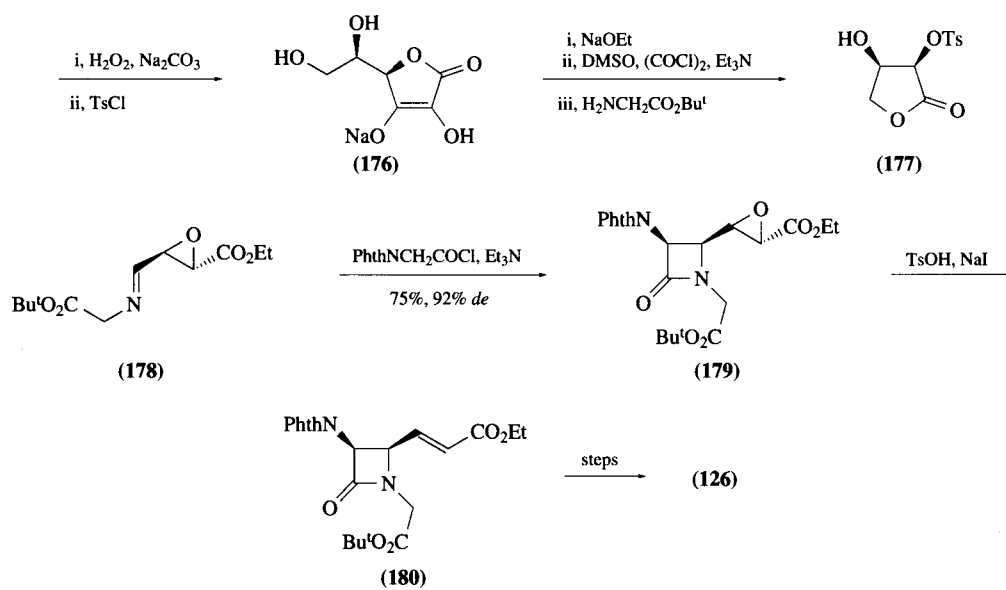


structuring the loracarbef nucleus through the Dieckmann route (Scheme 33) <92TL857>. It is noteworthy that, unlike 7-amino based chiral auxiliaries which have to be cleaved afterwards, the entire backbone of the enantiomerically pure epoxide (179) derived from the very inexpensive sodium erythorbate (176) was incorporated into the tetrahydropyridine ring of carbacephem (126).

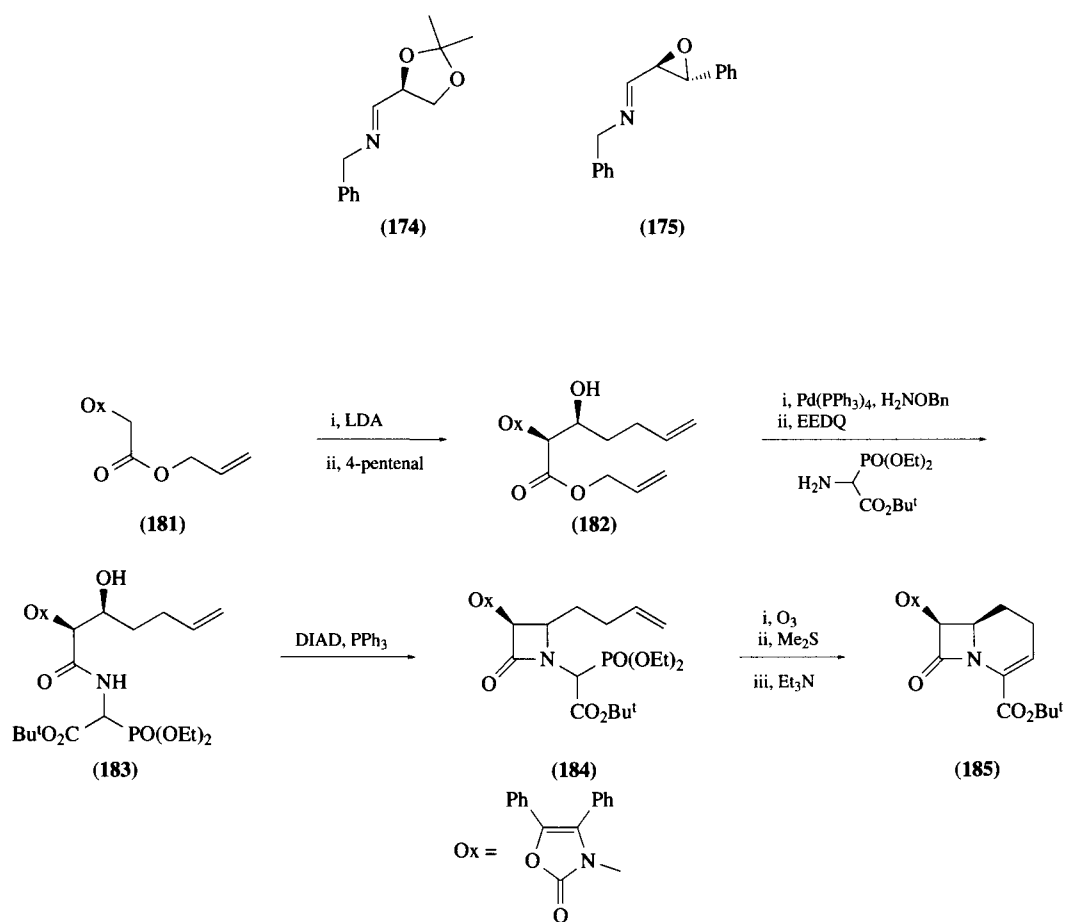
1.19.5.4.6 Synthesis from amino acids

Miller and co-workers have reported cyclic alkylation of amides derived from *erythro* β -hydroxy- α -amino acids under the Mitsunobu conditions <93JOC618>. The requisite starting material was prepared in racemic form by condensation of a protected glycinate and a primary aldehyde. Noteworthy is the use of the "Ox" protecting group, which ensured that aldol condensation would give the desired diastereomer, and the Mitsunobu reaction would proceed uneventfully. The "Ox" group was cleaved in the ozonolysis step (Scheme 34).

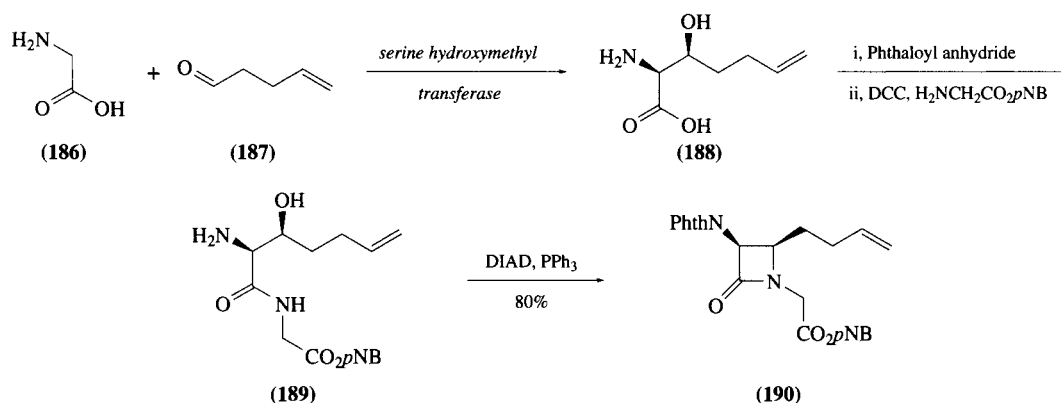
On a similar theme, researchers at Lilly disclosed an enantioselective loracarbef synthesis starting from an enantiopure β -hydroxy- α -amino acid obtained from recombinant enzyme (serine hydroxymethyltransferase)-catalyzed aldol condensation between glycine and pentenal. Replacement of the phthaloyl protecting group in (190) with the phenoxyacetyl group afforded compatibility with later manipulations. The compound was then converted into the loracarbef nucleus by sequential ozonolysis, oxidation, esterification, Dieckmann condensation, and chlorination (Scheme 35) <94MI 119-02>.



Scheme 33



Scheme 34

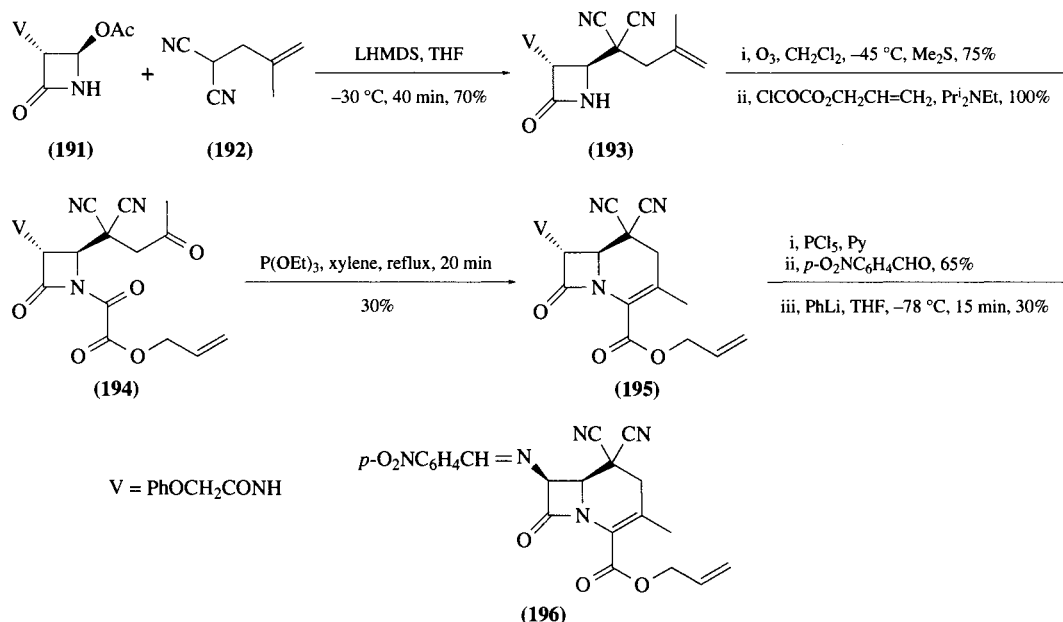


Scheme 35

1.19.5.4.7 C6—C1 bond formation, synthesis from penicillins

The ready availability of natural penicillins and cephalosporins has tempted organic chemists to take advantage of this chiral pool in the synthesis of carbacephems. The critical issue here is forming the C6—C1 bond with *cis*-selectivity. For this reason this bond is usually installed at the early stage of the tetrahydropyridine ring synthesis.

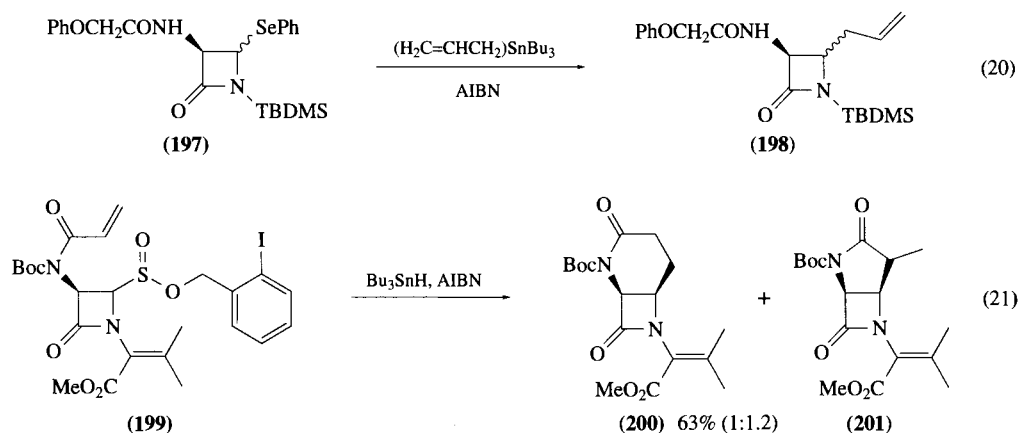
Taking advantage of the fact that nucleophilic displacement at the C6 invariably gives *trans* product, Dunlap *et al.* synthesized carbacephem (103) by the phosphorane route from *epi-seco*-penicillin (191), which was derived from penicillin via epimerization and fragmentation (Scheme 36) <92TL6103>. The desired *cis*-stereochemistry was realized by a second epimerization at C7 position through the use of a Schiff base.



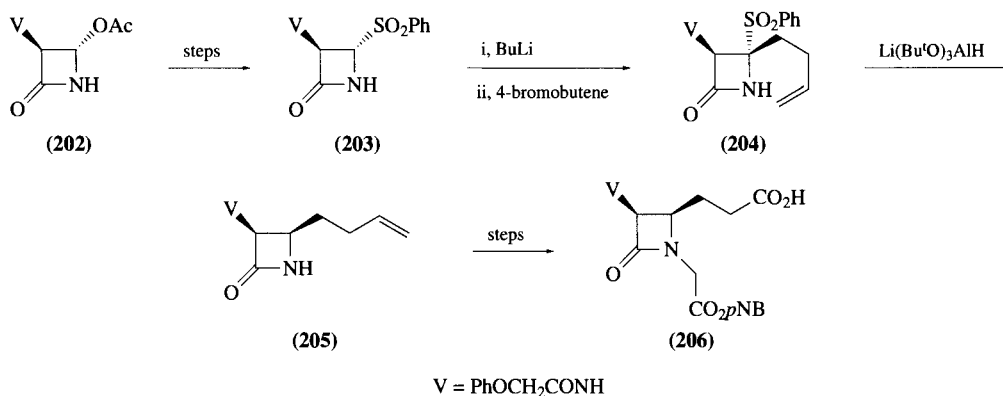
Scheme 36

Radical mediated allylation of *seco*-penicillin (196) afforded a *cis:trans* mixture of azetinone (197) <90TL5693>, which could be separated and converted into (198) via chain elongation and carbene insertion (Equation (20)). A novel stereoselective intramolecular version of this radical based process was also developed <94MI 119-03>. Extrusion of cyclic sulfinate from the radical generated from aryl iodide (199) gave rise to a β -lactam radical, which cyclized with exclusive *cis*

selectivity to afford (**200**) and (**201**) (Equation (21)). Regioisomer (**200**) can be isolated and subjected to selective δ -lactam hydrolysis and further transformed into compound (**126**).



An efficient route from *seco*-penicillin (**202**) was devised by a Lilly group in their synthesis of loracarbef (**126**) (Scheme 37) <93TL3051>. Introduction of the sulfonyl group at C6 served the double role of activating C6 for deprotonation and controlling the diastereofacial selectivity of subsequent alkylation, installing C1—C6 linkage in the desired *cis* relationship with respect to the 7-amino substituent. Key to the success of this approach was the reductive cleavage of the sulfonyl group by a highly hindered $\text{LiAl}(\text{OBu}^t)_3\text{H}$ to give (**205**) with 94% stereoselectivity. *N*-Alkylation followed by conversion of the terminal alkene to a carboxylic ester set the stage for Dieckmann condensation leading to (**126**).

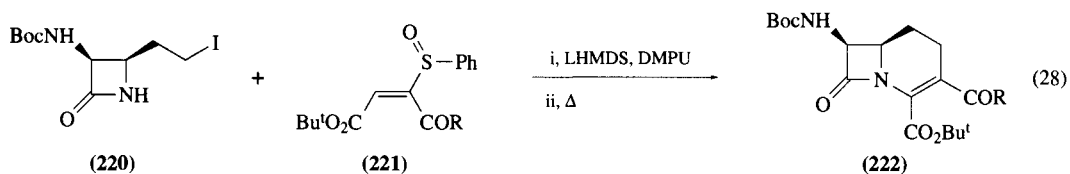
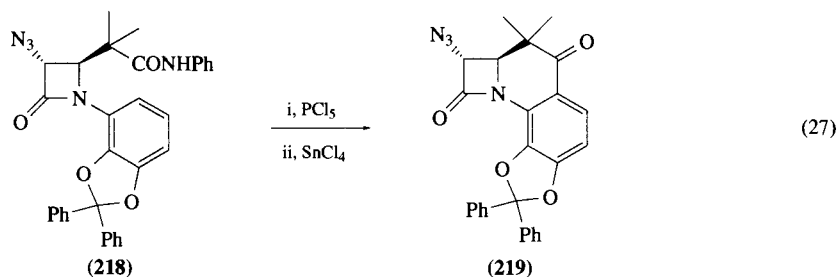
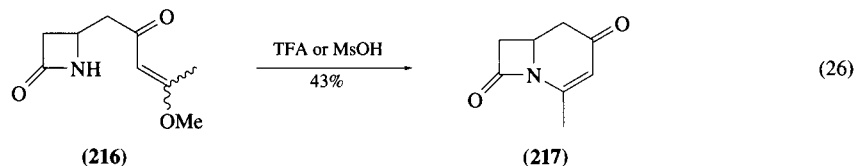
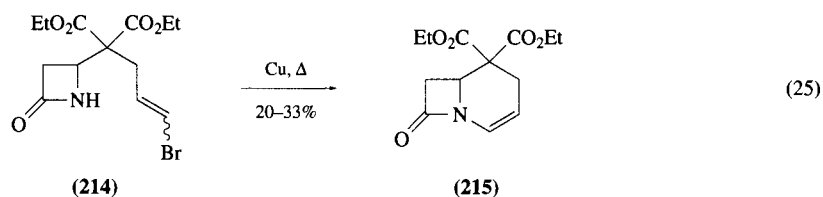
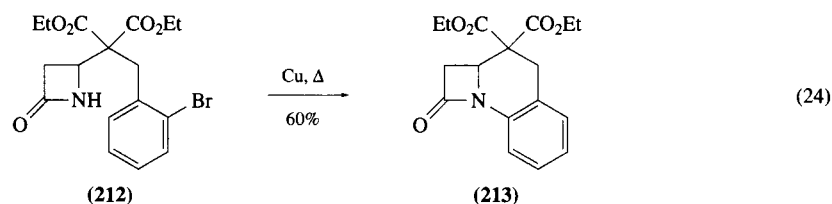
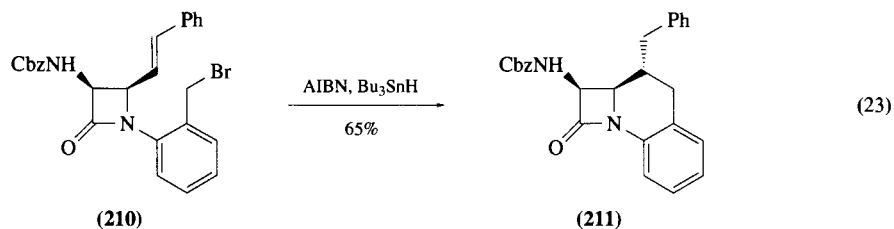
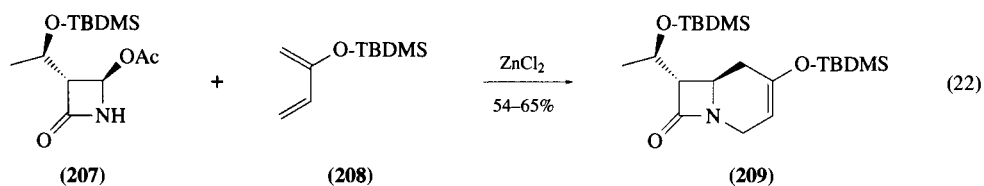


Scheme 37

1.19.5.4.8 Miscellaneous carbacephem synthesis

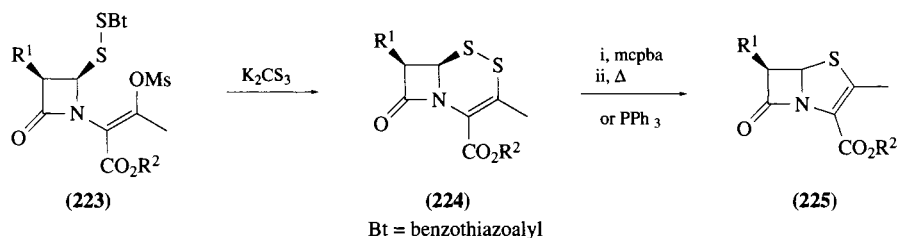
Trans selectivity was observed in the Lewis acid-catalyzed hetero Diels–Alder reaction of silyl dienol ether (**208**) and imine generated *in situ* from azetidinone (**207**). The resulting carbacephem (**209**) was then cleaved and recycled into a carbapenem (Equation (22)) <87TL5103>. Tricyclic carbaceph (**211**) was synthesized by free radical cyclization of benzylic bromide (**210**) (Equation (23)) <87CJC104>. Addition to the alkynes gave 1-exocyclic alkenes which can be converted into 1-oxo compounds by ozonolysis. Numerous single electron processes have been reported to give the carbacephem framework, forming the C1—C6 bond <87TL2637, 88H(27)875, B-89MI 119-05>. 3,4-Benzocarbacephs were obtained through copper-mediated substitution of aryl bromide by the β -lactam nitrogen in an intramolecular manner (Equation (24)) <87JCS(P1)1899>, while alkenyl bromide afforded the 3-cephem (**215**) (Equation (25)) <89TL337>. An intramolecular enamide condensation afforded a similar structure (Equation (26)) <81TL5335>. 3,4-Benzocarbaceph (**219**) was also prepared by a modified Bischler–Napieralski reaction through the intermediacy of the imidoyl chloride

(Equation (27)) <83JCS(P1)1925>. Lilly researchers disclosed an efficient one-pot transformation to carbacephem (**222**) involving a Michael addition, cycloalkylation, and thermal elimination (Equation (28)) <B-89MI 119-04>. Enantioselective carbaceph formation was achieved via photolysis under high pressure when α -oxoamide of piperidine was encased in a chiral crystalline lattice <87T1495>.



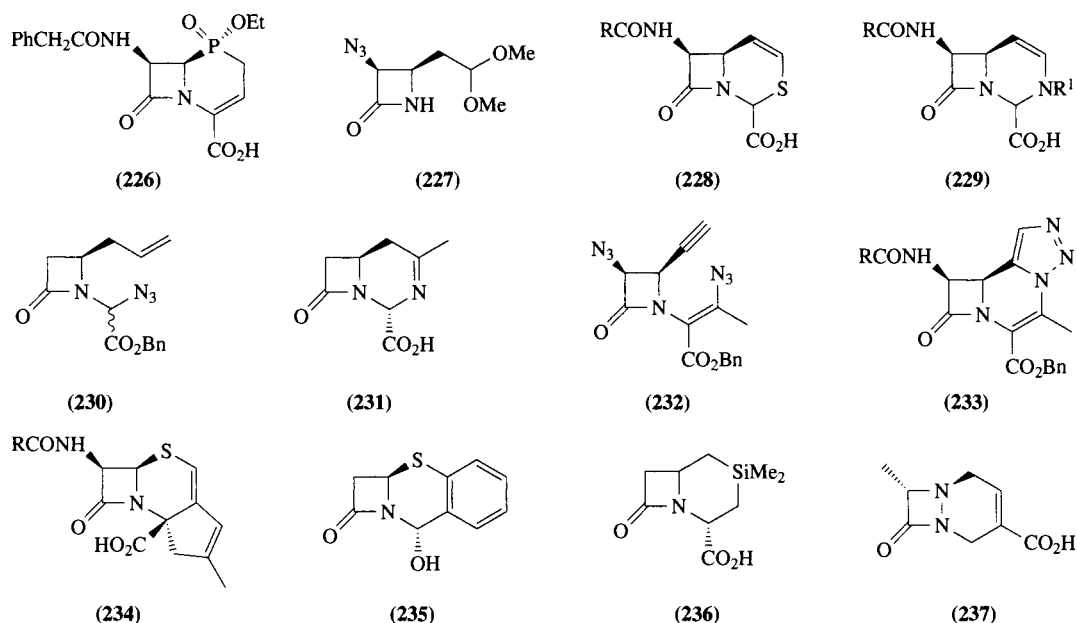
1.19.5.5 Synthesis of Other Nuclear Analogues

A wide variety of nuclear analogues with heteroatoms (N, P, S, Si) substituting S1, C2, C3, or C4 have been prepared and their biological activities tested. Except for a few compounds, most of these analogues exhibited very limited antibacterial activity. Perrone and co-workers have studied 2-thiacephem (224), which can be obtained from *seco*-penicillin (223), in the synthesis of penam via sulfur extrusion (Scheme 38) <83TL1631, 83TL3283, 85MI 119-01, 86JOC3413>.



Scheme 38

1-Phosphacephem (226) and side chain analogues were prepared from *seco*-penicillin (202) and an allylphosphite ester through intramolecular Wittig cyclization <84TL1733, 84TL1737>. 3-Thia-1-dethia-1-cephem (228) and 3-aza-1-dethia-1-cephem (229) were prepared from the common intermediate (227) <80TL3947, 83TL1649>. Thermolysis of azide (230) afforded 3-aza-1-dethia-2-cephem (231) via nitrene insertion <81H(16)1495>. Intramolecular alkyne dipole cycloaddition of (232) afforded structure (233) <82TL4381>. 2,3-Benzocepham (235) and its oxidation derivatives <81H(15)489>, tricyclic 2-cephem (234) <91JCS(P1)1766>, 2-sila-1-carbacephem (236) <94TL2047>, and 6-aza-2-cephem (237) <86JOC1537> are but a few examples of novel cephem ring analogues.



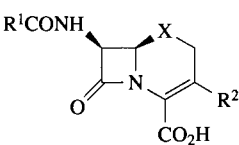
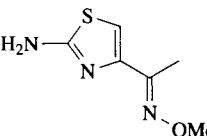
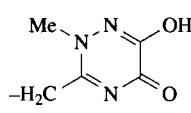
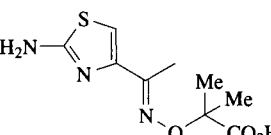
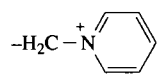
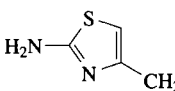
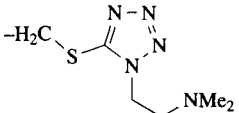
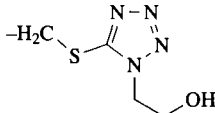
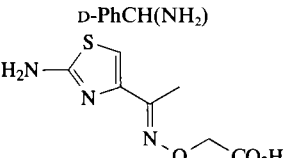
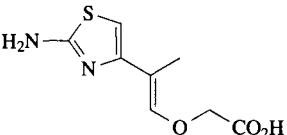
1.19.6 APPLICATIONS

1.19.6.1 Clinically Important Cephalosporins and Analogues

An exceptionally large number of β -lactams have been introduced into the world market <B-86MI 119-01, 92MI 119-02>. These include cephalosporins and nuclear analogues such as 1-oxacephems and

1-carbacephems, as well as penems and monobactams. Cephalosporins constitute the largest share of this market and Table 1 summarizes a few of the most important injectable and oral compounds. These were selected on the basis of clinical use and structural modification. Other clinically important compounds which are not listed include cefoperazone, latamoxef, cefmetazole, cefotetan, ceftizoxime, cefonicid, cefminox, cefuzonam, cefodizime, cefadroxil, and ceftriaxine. While the nuclear analogues (latamoxcef, flomoxef, and loracarbef) currently play an important clinical role, other compounds derived from the 2-isooxacephem <94TA441> appear to have significant activity against resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA). Clinical evaluation of these compounds continues.

Table 1 Injectable and oral cephalosporin antibiotics.

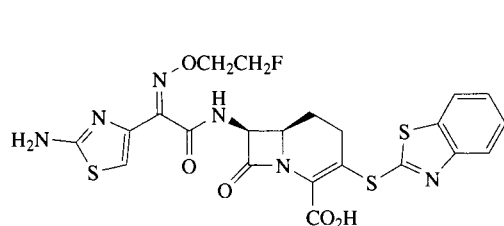
				
Generic name	X	R ¹	R ²	
ceftriaxone	S			
ceftazidime	S			
cefotiam	S			
flomoxef	O	F ₂ CHSCH ₂ - (7-α-OMe)		
cefaclor	S	D-PhCH(NH ₂)	Cl	
cefixime	S		-HC=CH ₂	
ceftibuten	S		H	
loracarbef	CH ₂	D-PhCH(NH ₂)	Cl	
cefprozil	S	D-PhCH(NH ₂)	cis-MeCH=CH-	

1.19.6.2 Mode of Action and Resistance Development

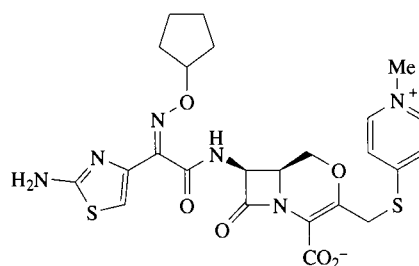
The safety profile for clinical use of cephalosporins and other β -lactams is due to their specificity for interaction with enzymes unique to the bacterial cell. Binding of β -lactams to a variety of

penicillin binding proteins (PBPs) affects the cell in a number of ways that are crucial to normal cell wall synthesis <B-87MI 119-02>. Bacteria produce β -lactamases that bind and hydrolyze β -lactams thus inhibiting the normal action of the antibiotic. The antibacterial activity of a compound is dependent upon its specific affinity for one or more of the PBPs, its stability to β -lactamases, and, of course, its ability to reach the site of action. The increase in resistance to cephalosporins, especially the third-generation compounds, has been alarming <92SCI1064>.

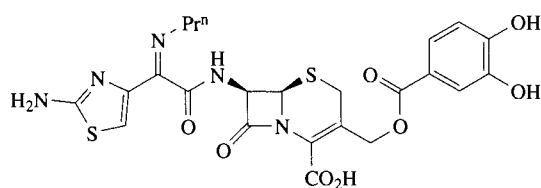
Publications from the late 1980s, early 1990s <89AAC1131, 91AAC1697, 93AAC2045> describe the complex reasons for the emergence of this resistance, from increased production of β -lactamases to alterations in the structure of PBPs. In the late 1990s, much of the chemistry of β -lactams is devoted to finding compounds with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive resistant bacterial strains in general. The carbacephem (238) <93JMC1971> and 2-isooxacephem (239) <94TA441> show excellent activity against MRSA. The catechol or catechol-like derivatives (240) <B-93MI 119-10> and (241) <93JAN833> take advantage of the *ton B*-dependent iron transport system of bacteria and demonstrate excellent activity against gram-negative strains. Common to all of these compounds is the aminothiazole ring which has become important in the medicinal chemistry of cephalosporins.



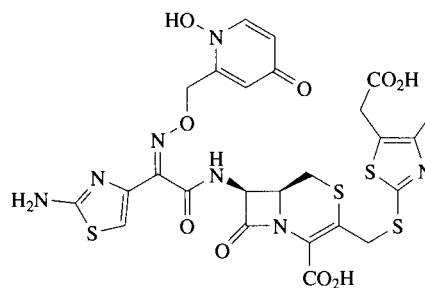
(238)



(239)



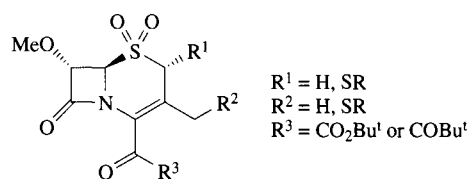
(240)



(241)

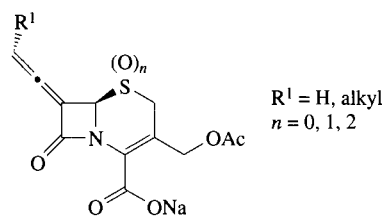
1.19.6.3 Miscellaneous Applications

Cephem sulfones (242) with C2 or C3' heterocyclic thiol groups in which the classical 7 β -acylamino substituent is replaced by a 7 α -methoxy group and in which the C4 carboxylic acid has been modified show potent activity as inhibitors of human leukocyte elastase (HLE), and therefore may show potential for use in a number of connective-tissue diseases <90JMC2529, 91TL6207>. 7-Vinylidenecephem sulfones (243; $n = 2$) have been synthesized from the 7-oxo compounds (27) and proved to be potent β -lactamase inhibitors <94JA10955>.



(242)

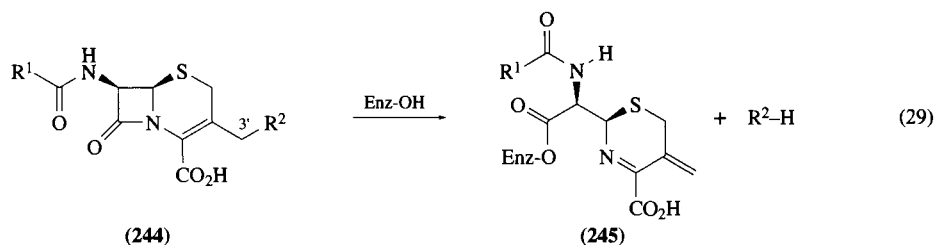
$R^1 = \text{H, SR}$
 $R^2 = \text{H, SR}$
 $R^3 = \text{CO}_2\text{Bu}^t \text{ or } \text{COBu}^t$



(243)

$R^1 = \text{H, alkyl}$
 $n = 0, 1, 2$

Cephalosporins (**244**) have been combined with other agents to take advantage of the release of the C3' substituent during the course of β -lactamase promoted opening of the β -lactam ring. In this manner dipeptides <86JA1685>, quinolone antibacterials <92S1160, 94JMC400>, and vinca alkaloids <92JOC2334> have been conjugated with cephalosporins with linkers at the C3' position and utilized in cancer and infectious disease models (Equation (29)).



R^2 = dipeptide, quinolone antibacterial, or vinca alkaloid

1.20

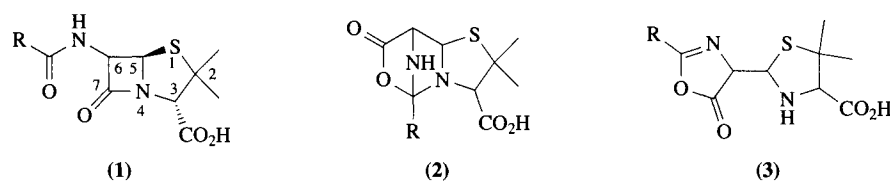
Penicillins

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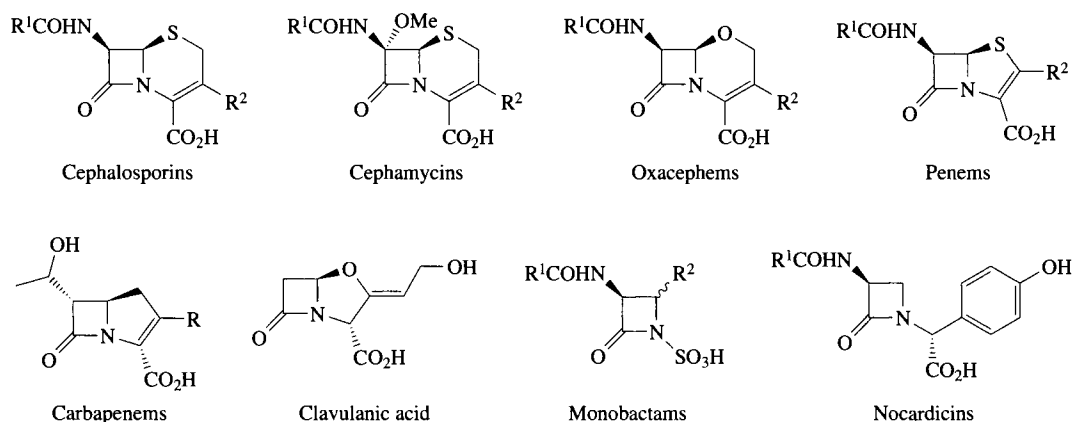
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1.20.1 INTRODUCTION

It was in the late 1920s that Fleming made the serendipitous observation that the growth of staphylococcus colonies was inhibited in the vicinity of *Penicillium notatum* <29MI 120-01>. The antibiotic causing this phenomenon was given the name penicillin. In the early 1940s the therapeutic potentialities of penicillin were recognized, and nowadays penicillin and related compounds (see below) are the most important antibiotics against bacterial infections <B-92MI 120-01, 93MI 120-01>. From earlier structural studies, mainly degradative chemical investigations and IR spectroscopy, three structures (1), (2), and (3) were proposed for penicillin. In 1945, an x-ray crystallographic study of benzylpenicillin revealed unambiguously the structure as shown schematically for (1; R = benzyl) <B-49MI 120-01>.



This molecule belongs to the so-called penams, which contain two fused ring systems: a four-membered β -lactam ring and a five-membered sulfur-containing ring. Penicillin is the first representative of the naturally occurring β -lactam antibiotics. Extensive screening procedures and laboratory syntheses afforded new naturally occurring and synthetic β -lactam antibiotics. According to their structure these compounds can be classified into several groups (Scheme 1): penicillins, cephalosporins (see Chapter 1.19), monobactams and nocardicins (see Chapter 2.02), cephamycins, oxacephems, penems, oxapenams (e.g. clavulanic acid) and carbapenems (the latter compounds are discussed in Chapter 1.21).



Scheme 1

It should be noted that, classically, the β -lactam antibiotics have been named using the ring sulfur atom as position 1 (according to the IUPAC nomenclature the β -lactam nitrogen atom should be assigned position 1). The classical numbering order in (1) is still commonly used in the penicillin literature and will be used in this chapter.

An important feature in the chemistry of penicillins is the absolute configuration of the respective chiral centers in the bicyclic fragment. According to the numbering scheme outlined above, the configuration of the three chiral centers in (1) is 3-(S), 5-(R) and 6-(R).

Although the chemistry of penicillins is relatively old and dates back about fifty years, it is still a subject which is extensively studied. Since the appearance of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), which covers the literature up to about 1982, thousands of papers containing the word penicillin in their title have appeared. A search in the substance index of the *Chemical Abstracts* (period 1982–1994) resulted in 1173 compounds containing the name penicillin. This set was used for a search in the subject index to find all references to these compounds; 22529 references were found. From these hits, only references in the category “Biomolecules and their

synthetic analogues" were selected, which are the interesting ones from a chemical point of view, but still 815 references remained.

Since the amount of relevant literature is so overwhelming, it is obvious that only a selection of important studies have been incorporated in this chapter. The reader is urged to consult the cited references for a more detailed discussion and especially cited books and review articles for further literature citations. Important topics from the older literature, discussed in CHEC-I, are summarized in each section of this chapter including key references to older reviews and books. The latest developments, starting in 1983, in the field of penicillin chemistry are discussed in more detail.

During the 1980s much effort has been spent in the elucidation of the mechanism of the biosynthesis of β -lactams which has led to a much better understanding of the processes involved, (see Section 1.20.6.1). An interesting new application of penicillins (and other β -lactams) is their use as inhibitors of human leukocyte elastase (HLE) (see Section 1.20.7.3).

As mentioned above, the size of the literature dealing with the chemical, biochemical, medical, pharmaceutical, and biotechnological aspects of penicillins and other β -lactam-based antibiotics is overwhelming. The first edition of *Comprehensive Heterocyclic Chemistry* <84CHEC-I(7)299> covers the literature to about 1982. Other important works (earlier and more recent) dealing with the topics mentioned above are: <B-49MI 120-02, B-49MI 120-03, B-71MI 120-01, B-72MI 120-01, B-77MI 120-01, B-77MI 120-02, B-80MI 120-01, B-80MI 120-02, B-80MI 120-03, B-81MI 120-01, B-81MI 120-01, B-84MI 120-01, B-90MI 120-01, B-92MI 120-02, B-93MI 120-02, B-93MI 120-04>. Furthermore, since 1982 the literature on the chemical aspects of penicillins and other β -lactam antibiotics has been surveyed annually <B-86MI 120-01, B-87MI 120-01, B-88MI 120-01, B-89MI 120-01, B-90MI 120-02, B-91MI 120-01, B-92MI 120-03, B-93MI 120-03>.

1.20.2 THEORETICAL METHODS

Earlier computational studies on β -lactam antibiotics were mainly restricted to the extended Hückel method <79T1499, B-82MI 120-02>. It has been well established that the antibacterial activity of penicillins involves the inhibition of a transpeptidase enzyme (see Section 1.20.7) and calculations have shown that a structural similarity exists between penicillins and the tetrahedral intermediate formed during hydrolysis of the amide bond in glycylglycine <79JMC533>. These studies give additional evidence of the concept that penicillins are acting as transition state analogues. CNDO/2 calculations have shown that differences in the antibacterial effectiveness of different β -lactam antibiotics may be a consequence of different binding energies with the inhibited enzyme and variations in the activation energy of acylation <74JMC342>. Semiempirical geometry optimization and a limited *ab initio* study using minimal basis STO-3G calculations with fixed geometries have been reported <80CPH279, 83JMC1010, 91JST(231)109>. It appeared that the calculated STO-3G energy of formamide in a penicillin-like geometry is only 2.8 kcal mol⁻¹ higher than in the planar geometry <83JST(92)19>. Geometry optimization has been performed for penicillin G, ampicillin, amoxycillin, and methicillin by AM1, MNDO, and MINDO/3 calculations <91JST(231)109>. From this study it was concluded that: (i) the MINDO/3 method provides the most reliable results with respect to the geometry of the bicyclic system; (ii) the AM1 method is superior at treating conformations of the thiazolidine ring; and (iii) the MNDO method predicts very well the pyramidity of the β -lactam nitrogen. Finally, it was concluded that the stable conformation depends strongly on the specific type of penicillin.

1.20.3 EXPERIMENTAL STRUCTURAL METHODS

1.20.3.1 X-ray Crystallography

In 1949 the structure of benzylpenicillin was unambiguously proven by an x-ray crystal structure determination <B-49MI 120-01>. According to the *Cambridge Crystallographic Database*, the structures of 32 compounds containing the penicillin skeleton have been elucidated up to 1996. Since CHEC-I, 12 new structures have been reported in the literature: Nafcillin methyl ester <80JMC1283>, Flucloxacillin sodium salt <80JMC1283>, 2,2-dimethyl-3-ureido-6-phenoxyacetamidopenam <81AX(B)2179>, 6-(*N,N*-1,6-hexyleneformamidine)penicillanic acid <81JAN282>, Carfecillin <82AX(B)929>, Penamecillin <87ZN(B)367>, Penamecillin-1 β -sulfoxide <87ZN(B)367>, 3-phenyl-5-methyl-4-isoxazolyl-penicillin sulfone <87MI 120-02>, (3*S*, 6'*S*)-2,2,2-trichloroethyl 3-(4-nitrophenyl)-1-phenylspiro(aziridine-2,6'-penicillate) <86JCS(P1)2195>, calcium bis(phenoxyphenicillin) <87ICA137>.

2 β - acetoxymethyl - 3 α - methoxy - 2 α - methyl - 3 β - (*p* - nitrobenzoyloxymethyl) - 6 β - phenoxyacetamidopenam <87G155> and benzyl 6-methacryloylaminopenicillanate 1-oxide <91AX(C)1338>. Figure 1 shows the structure of benzylpenicillin potassium <78JCS(P1)185> (reconstructed from data of the *Cambridge Crystallographic Database*), and in Table 1 limiting values of some relevant bonding distances and angles of the penicillin skeleton are given.

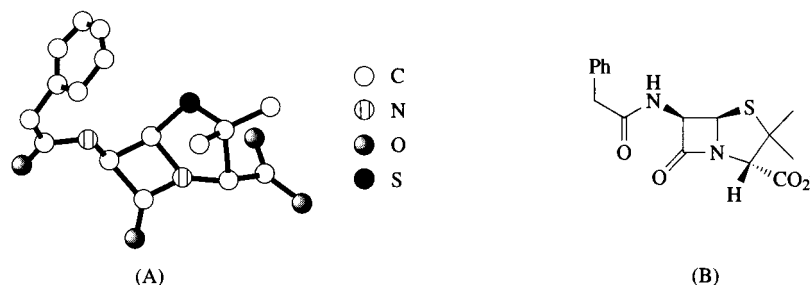


Figure 1 X-ray structure (A) and schematical representation (B) of benzylpenicillin potassium.

Table 1 Limiting values of the bonding distances and angles defining the penicillin skeleton found by x-ray crystallography.

Bond distances (Å)		Bond angles (°)	
S(1)—C(2)	1.84–1.87	C(5)—S(1)—C(2)	90–96
C(2)—C(3)	1.55–1.57	S(1)—C(2)—C(3)	103–105
C(3)—N(4)	1.45–1.47	C(2)—C(3)—N(4)	104–106
N(4)—C(5)	1.45–1.52	C(3)—N(4)—C(5)	117–120
C(5)—S(1)	1.77–1.82	N(4)—C(5)—S(1)	103–104
C(5)—C(6)	1.53–1.58	N(4)—C(5)—C(6)	87–92
C(6)—C(7)	1.51–1.55	C(5)—C(6)—C(7)	83–86
C(7)—N(4)	1.36–1.46	C(6)—C(7)—N(4)	92–96
C(7)—O(8)	1.18–1.21	C(7)—N(4)—C(5)	88–94

From these x-ray crystallographic studies it appeared that the conformation of the thiazolidine ring of the various penicillins is different; this difference has been ascribed to the varying degree of steric repulsion in the 6- β side chain <76AX(B)2279>. Four of the atoms of the thiazolidine ring lie approximately in one plane while the fifth atom is significantly outside this plane. The latter atom may be S(1), C(2) or C(3) depending on the specific compound. In principle, the thiazolidine ring may have two conformations: (i) one in which the α -methyl group is in an equatorial position whereas the β -methyl group and the α -carboxyl are axially positioned, as has been found in benzylpenicillin <78JCS(P1)185>; and (ii) a conformation in which the α -methyl group is in an axial position while the β -methyl group and the α -carboxyl are in equatorial positions.

Furthermore, these studies indicated that the length of the carbonyl bond in β -lactams is significantly shorter (1.18–1.21 Å) than this bond in acyclic amides (1.20–1.23 Å), whereas the C—N bond length is significantly elongated (1.36–1.46 Å against 1.33–1.35 Å). In contrast to the coplanarity of the nitrogen atom with its three substituents in acyclic amides, due to overlap of the filled nitrogen *p*-orbital with the empty carbonyl π^* -orbital, the nitrogen atom in penicillins is pyramidal. This is a consequence of the fused ring structure in penicillins inhibiting such an overlap and is reflected in an enhanced double-bond character of the C=O bond and an increasing single-bond character of the C—N bond. The increase in the double-bond character appears from the observed shift of the C=O stretching frequency to higher wave number as compared to this frequency in normal amides (see Section 1.20.3.4). Moreover, it enhances the susceptibility of the carbonyl carbon center towards nucleophilic attack, which is directly associated with the chemical and biological properties of penicillins.

1.20.3.2 Nuclear Magnetic Resonance

Owing to the more sophisticated NMR techniques which became available during the 1980s, NMR spectroscopy has become one of the most powerful tools in organic chemistry to obtain

structural and conformational information of organic compounds in solution and, more recently, even in the solid state, using a magic-angle spinning technique. In almost all papers concerning synthetic aspects or chemical modifications of penicillins, ^1H and/or ^{13}C NMR data are reported. Already in 1978 the ^{13}C and ^{15}N NMR data of a series of penicillins had been published <78JOC2013, 79JPS64>. Two more reviews report the ^1H and ^{13}C NMR spectral data of 25 penicillin and 15 cephalosporin derivatives and some of their metabolites <86MRC465, 87MI 120-03>. However, when the reader is interested in the ^1H or ^{13}C NMR data of a particular type of penicillin the original papers should be consulted.

Also some more specialized NMR spectroscopic studies on penicillins have been carried out, of which a few are discussed below. A conformational study based on relaxation measurements and lanthanide-induced shifts in the ^1H and ^{13}C NMR spectra of several penicillins in solution indicated that differences in the thiazolidine ring puckering, as observed for ampicillin and penicillin G in the solid state, are not present in solution and that the structure in solution is most likely close to that found for ampicillin in the solid state <75JCS(F2)1145>.

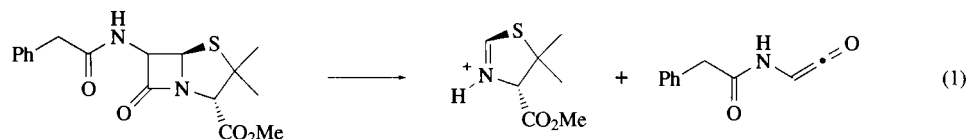
Carbon-13 cross-polarization magic-angle spinning (CP/MAS) NMR spectra have been recorded for a series of penicillins and compared with their solution ^{13}C NMR data <86JCS(P2)1933>. From this study, it was concluded that the differences in ring puckering, either at C(3) or S(1) in the thiazolidine ring as observed in the solid state, are the result of intermolecular interactions. Based on an empirical correlation, predictions could be made with respect to the conformational populations of the thiazolidine ring for penicillins in solution. Finally, the dynamic properties of the phenoxy and benzyl rings in phenoxymethylpenicillin benzyl ester and the corresponding β -sulfoxide were studied in the solid state by variable temperature ^{13}C CP/MAS NMR spectroscopy <88CC786>.

The most significant feature of the ^1H NMR spectra of penicillins is the observation of an AB pattern for the *cis*-positioned H(5) and H(6) protons in the range of 5–6 ppm with $^3J(\text{HH}) = 4\text{--}5$ Hz, whereas in 6-epipenicillins in which H(5) and H(6) are *trans*, the $^3J(\text{HH})$ amounts to 1–2 Hz.

In the ^{13}C NMR spectra of penicillins, the resonances of the four sp^3 carbon atoms C(3), C(5), C(2), and C(6) (see Structure (1)) of the fused-ring system are observed at increasing field, in the ranges of 73–75, 66–69, 64–66, and 57–64 ppm, respectively. These assignments have been based on the magnitude of the $^1J(^{13}\text{C}\text{--}^1\text{H})$ and the multiplicity due to long range $^{13}\text{C}\text{--}^1\text{H}$ couplings <86MRC465>. The chemical shift of the lactam carbonyl carbon atom is found in the range of 167–176 ppm and could be discriminated from the 3-carboxylate and 6-amido carbonyl resonances on the basis of long range $^{13}\text{C}\text{--}^1\text{H}$ couplings. The two 2-methyl resonances are observed at 26.5–28.0 and 29.6–32.5 ppm, respectively: the high field signal was assigned to the α -methyl group and consequently the low field signal to the β -methyl group <70CC1291>. Finally, the ^{15}N chemical shift of the lactam nitrogen atom in penicillins is observed in the range of 134–145 ppm <78JOC2013>.

1.20.3.3 Mass Spectroscopy

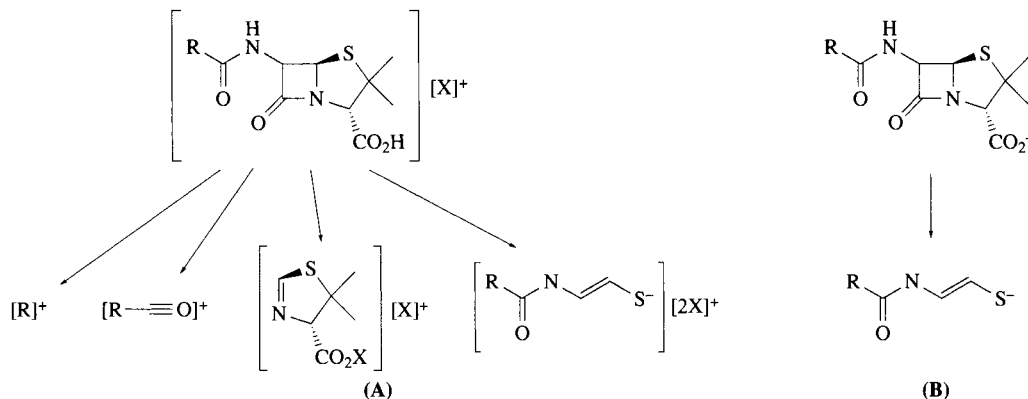
Mass spectroscopic studies of penicillins and other antibiotics were reviewed by Border *et al.* <85MI 120-01>. Earlier studies were carried out with relatively volatile ester derivatives, for example benzylpenicillin methyl ester. Both under electron impact (EI) and chemical ionization (CI) conditions, the primary fragmentation is as outlined in Equation (1).



Desorption chemical ionization has proved to be a valuable technique to obtain both positive and negative ion mass spectra from the free acids of penicillins <81MI 120-02>. It has also been demonstrated that EI spectra of free acids or alkali metal salts of penicillins can be obtained using in-beam electron ionization techniques <83JPS508>. Mass spectroscopic studies carried out on penicillins using fast atom bombardment mass spectroscopy (FAB-MS) <82MI 120-03, 83IJM431> and tandem mass spectroscopy <83MI 120-01> have been reported.

Positive ion FAB-MS spectra of the free acids or alkali metal salts of penicillins show intensive peaks for the protonated molecular ion $[\text{M} + \text{H}]^+$. In addition to the latter ion, the metal salts also show peaks for the metal adduct ions $[\text{M} + \text{X}]^+$, in which X is the alkali metal, as well as peaks of low intensity of the dimeric cluster ions $[2\text{M} + \text{X}]^+$ (Scheme 2(A)). The negative ion FAB-MS

spectra of the free acids or alkali metal salts of penicillins both show $[M-H]^-$ ions, although they are more pronounced for the free acids. On the other hand, the metal salts readily give $[M-X]^-$ ions in addition to dimeric cluster ions $[2M-X]^-$. In Scheme 2 the major fragmentation patterns for both positive FAB-MS and negative FAB-MS are shown.



Scheme 2

The latest development in the field of mass spectroscopic determination of penicillins and their corresponding metabolites is the combination of liquid chromatography with mass spectroscopy (LC-MS) <83IJM157, 89MI 120-02>. This technique which uses thermospray ionization techniques has been reviewed <B-92MI 120-04>.

1.20.3.4 Other Spectroscopic Methods

The most interesting feature of the IR spectra of penicillins is the β -lactam carbonyl stretching frequency at approximately 1780 cm^{-1} . The shift of about 130 cm^{-1} to a higher wave number relative to the carbonyl stretching frequency of acyclic tertiary amides is a consequence of the enhanced double-bond character of the carbonyl bond, as has been explained in Section 1.20.3.1.

A circular dichroism (CD) study of a series of C(10) isomeric pairs of penicillins derived from disubstituted acetic acid, for example phenethicillin, amoxycillin, ampicillin etc., has been reported <82JCS(P1)563>. The strongly positive Cotton effect near 230 nm agrees with earlier reported CD spectra of penicillins. Furthermore, an empirical correlation was found between the configuration at C(10) and the sign of the CD band at 200–210 nm and the chemical shift of H(3) and the methyl protons.

1.20.4 THE ANALYSIS OF PENICILLINS

Since the commercialization of penicillins as antibiotics in 1943, analytical tools have been developed to test the quality and purity of penicillins. Since penicillins are produced by fermentation, the detection of impurities as well as of other microorganisms of which some could be toxic was required. Moreover, there are documented cases of allergic responses of humans to the ingestion of penicillin-contaminated food as a result of the use of penicillins in veterinary medicine for food-producing animals <92JC(624)171>. Therefore, it became necessary to develop methods not only for the analysis of the purity of the produced penicillins itself, but also for the detection of penicillins and their metabolites in biological fluids and animal tissues.

Many procedures for the determination of penicillins are reported in the literature, the most important being: electrophoresis <85MI 120-02>, microbiological analysis <88MI 120-02>, paper chromatography <68MI 120-01>, thin-layer chromatography <69JPS1041, 88MI 120-03>, gas-liquid chromatography (GC) <71ANC1530, 77JC162>, and high performance liquid chromatography (HPLC).

Chromatographical methods are straightforward and give the most reliable results. These methods have been reviewed extensively <92JC171>. Gas chromatographic analysis proceeds quickly, but is restricted to the relatively volatile ester derivatives of penicillins <77JC162>. Nowadays, HPLC is the most powerful method available for the analysis of penicillins and it has been reviewed <89MI 120-

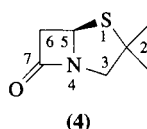
03>. Fast and reproducible methods have been developed which allow analysis of complex mixtures of penicillins within a few minutes <93MI 120-05>. The latest development is the combination of HPLC with mass spectrometry (LC/MS) <86MI 120-02, B-92MI 120-04>, making use of special interfaces for sample introduction, such as moving belt LC/MS <84ANC2632>, direct liquid introduction (DLI) <85MI 120-03>, thermospray <85ANC2373>, or electrospray <85ANC675>.

1.20.5 REACTIVITY

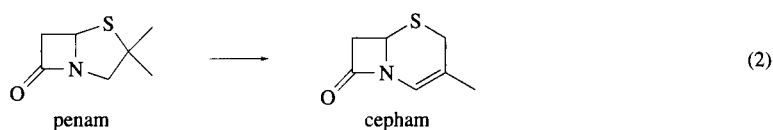
1.20.5.1 Introduction

As mentioned above, a large number of reports have appeared in the literature concerning the chemistry of penicillins and other penams. Many of these are dealing with the introduction and removal of side chains, modification of side chains (this topic has partly been discussed in Section 1.20.6) and reactions of compounds obtained from, for example ring-opened penicillins. Because it is impossible to cover all these topics in this section, only reactions which involve atoms of the penam skeleton will be discussed. Early studies on the chemistry of penicillins and cephalosporins have been reviewed previously <76CRV113>.

A large majority of the reactions reported in the literature are related to modification at the 6-position (4), of penicillins and derivatives like 6-diazo- and 6-halopenicillates. Also reactions at the S(1) atom (e.g. oxidation of sulfur or cleavage of C—S bonds) are of importance, since the compounds so obtained are valuable starting materials for other β -lactam-based antibiotics.



The chemistry involving other positions of the penam moiety is rather less explored with the exception of reactions involving opening of the β -lactam ring (hydrolysis of the amide bond) that are directly associated with the antibacterial activity of penicillins. Last but not least, a reaction involving a rearrangement of the penam skeleton, i.e. conversion of a penam into a cephem (Equation (2)) is of crucial importance, as it offers a way to another important class of β -lactam antibiotics, i.e. the cephalosporins (see Chapter 1.19) via chemical transformation of penicillins.



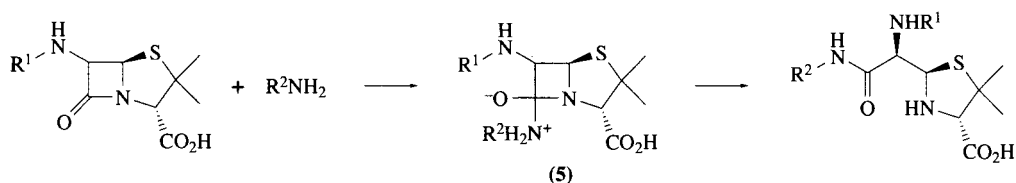
1.20.5.2 Reactivity Associated with the Biological Activity of Penicillins

From a biological and biochemical point of view, reactions involving opening of the four-membered β -lactam ring via aminolysis or hydrolysis of the amide linkage in aqueous media are the most interesting ones. This topic has been reviewed <B-92MI 120-05>.

The aminolysis of penicillins to penicilloyl amides is an important reaction since it has been found that one of the factors responsible for penicillin allergy is that penicilloyl groups get bound via an amide linkage to ϵ -amino groups of lysine moieties in proteins <65MI 120-01>. Moreover, it has been established that another important factor in the mechanism of antibacterial activity of penicillins is inhibition of a transpeptidase enzyme (see Section 1.20.7.1).

Usually, the exchange of amide groups is a difficult process. However, in penicillins this is not the case because breaking of the amide bond is accompanied by a large release of strain energy, which makes this reaction thermodynamically more attractive. The aminolysis of penicillins is catalyzed by buffers because large changes in the basicity and acidity of the reactants occur during

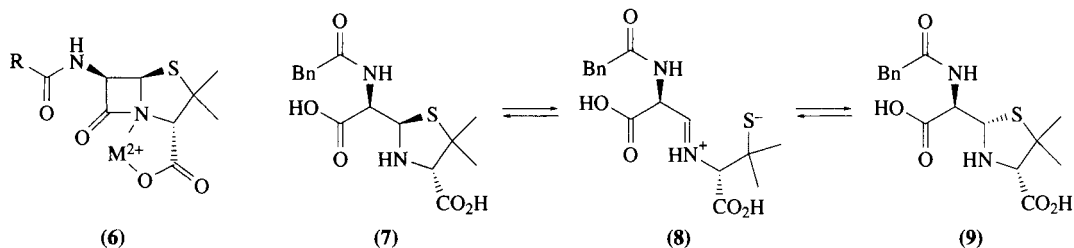
this process. It has been proposed that this process involves an intermediate (5) (Scheme 3) in which the former carbonyl carbon atom becomes tetrahedral <84ACR144>.



Scheme 3

The influence of transition-metal ions (Cu^{2+} , Zn^{2+} , Ni^{2+} and Co^{2+}) on the rate of hydrolysis of penicillins has been studied <69JPS1471, 78JCS(P2)335, 80JCS(P2)1725> which is relevant for understanding the mode of action of metallo-enzymes like β -lactamase II. It appeared that Cu^{2+} enhances the rate of hydrolysis of benzylpenicillin by a factor of 10^8 at pH 7 and decreases its half-life from 11 days to less than 1 second. It has been proposed that the penicillin moiety is chelate bonded via the carboxylate oxygen- and β -lactam nitrogen atom to the metal ion as shown schematically in (6) (Scheme 4) <77JPS533, 80JCS(P2)1725>.

The initial product from the base-catalyzed hydrolysis of benzylpenicillin is 5-(*R*)-6-(*R*)-benzylpenicilloic acid (7), but epimerization then occurs at C(5) to afford a mixture of (7) and 5-(*S*)-6-(*R*)-benzylpenicilloic acid (9) (Scheme 4) <85CC1702>. The iminium ion (8) is proposed to be an intermediate in this epimerization process <91JCS(P2)1219>.



Scheme 4

1.20.5.3 Modification at the S(1) Position

1.20.5.3.1 Oxidation of the S(1) atom

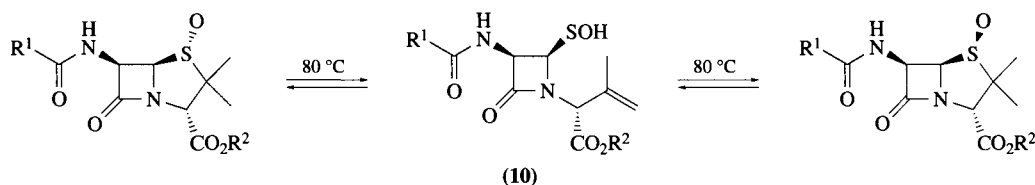
The oxidation of penicillins and other penams to sulfoxides has been studied extensively because these compounds are important intermediates in the conversion of penicillins into other β -lactam-based antibiotics like the cephalosporins (see Section 1.20.5.8). The oxidation reaction can afford either the (*R*)- or (*S*)-sulfoxide (α - or β -, respectively) depending on (i) the substrate, and (ii) the oxidant cf. Table 2 <69JA1528, 74JOC441, 76JCS(P1)1772>. This dependence was discussed in terms of the following factors: (i) hydrogen bonding between a 6- β -amido group and the oxidant giving rise to the formation of β -sulfoxides; (ii) stabilization by hydrogen bonding between a β -sulfoxide and a 6- β -amido group; and (iii) destabilization of β -sulfoxides by bulky 6- β -substituents.

Furthermore, it appeared that these sulfoxides can be epimerized thermally to afford equilibrium mixtures of α - and β -sulfoxides (Scheme 5) in which the position of equilibrium is dependent on the C(6) substituent. Deuterium-labeling studies, and the finding that epimerization at C(2) occurs simultaneously with epimerization of the sulfoxide, support the proposal that sulfenic acid (10) is an intermediate in this epimerization process <71JCS(C)3540>. It should be noted that it is possible to convert the thermodynamically more stable β -sulfoxide into the α -sulfoxide photochemically using UV light <69JA1530>.

Oxidation reactions of penicillins have been reported using the commercially more attractive oxidant H_2O_2 . Yields of up to 98% of penicillin sulfoxide have been reported using the system $\text{H}_2\text{O}_2/\text{HCO}_2\text{H}/\text{polyphosphoric acid}$ <89S197>. Also catalytic processes using tungsten- or molybdenum-based catalysts have been reported for the H_2O_2 oxidation of penicillins to the corresponding

Table 2 Oxidation of penams.

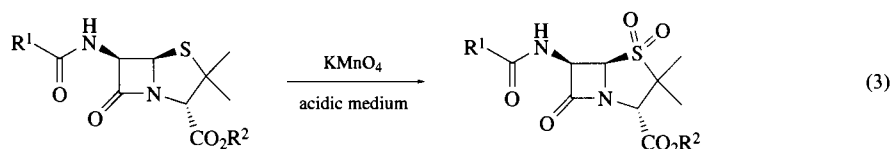
R^1	R^2	Oxidant	β -Sulfoxide	α -Sulfoxide
PhOCH ₂ CONH	H	MCPBA	100	0
		PhICl ₂	20	80
		O ₃	50	50
H	PhOCH ₂ CONH	MCPBA	100	0
		PhICl ₂	0	100
		O ₃	50	50
Phth	H	MCPBA	0	100
H	Phth	MCPBA	80	20
Br	Br	MCPBA	9	91
		NaIO ₄	27	73
H	Br	MCPBA	92	8
H	H	MCPBA	79	21

**Scheme 5**

sulfoxides <86MI 120-03>. Conversions of penicillins into their sulfoxides have been claimed to proceed in yields of about 90% using a two-phase system CH₂Cl₂/aqueous H₂O₂ without a catalyst <86AJC1165>. An interesting approach is the use of an enzymatic process in which an alkanolic acid is oxidized enzymatically by H₂O₂ to an alkanolic peracid that acts as the actual oxidant in a penicillin oxidation process <93RTC462>. Finally, a completely diastereoselective oxidation of 6-halopenicillates to the corresponding sulfoxides has been reported in which dimethyldioxirane (DMDO) was used as the oxidant <93TL7877>.

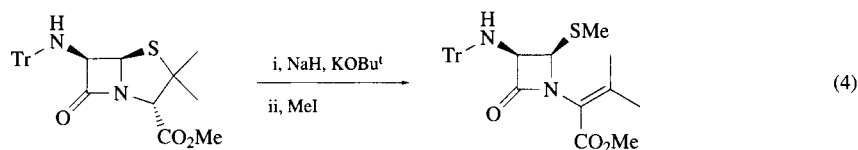
The reduction of penicillin sulfoxides to the corresponding sulfides is quite trivial and P₂S₅ <76TL971>, PCl₃, or PBr₃ <71JCS(C)3540> are used as reducing agents.

Finally, it is also possible to oxidize the sulfur atom of penicillins and other penams to 1,1-dioxides which are of particular interest for the synthesis of β -lactamase inhibitors like sulbactam (see Section 1.20.7.2). An industrial process has been developed by which benzylpenicillin is oxidized in high yield to its 1,1-dioxide by KMnO₄ in acidic media (Equation (3)) <93RTC66 and references cited therein>.

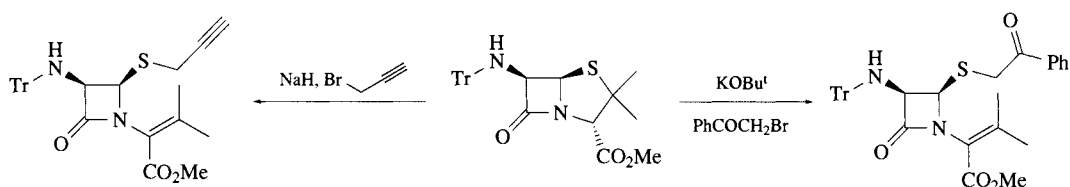


1.20.5.3.2 Reactions involving the S(1)—C(2) bond

In 1971 it was discovered that the reaction of penicillins with a strong base in the presence of an alkylating agent (the Naylor reaction) results in ring opening of the thiazolidine ring of the penicillin under formation of “1,2-secopenicillins” (Equation (4)) <71CC590>.



The use of functionally substituted alkylating agents in this reaction afforded valuable intermediates for other β -lactam-based antibiotics (cephems) (Scheme 6) <76JA7864, 76TL3975>.

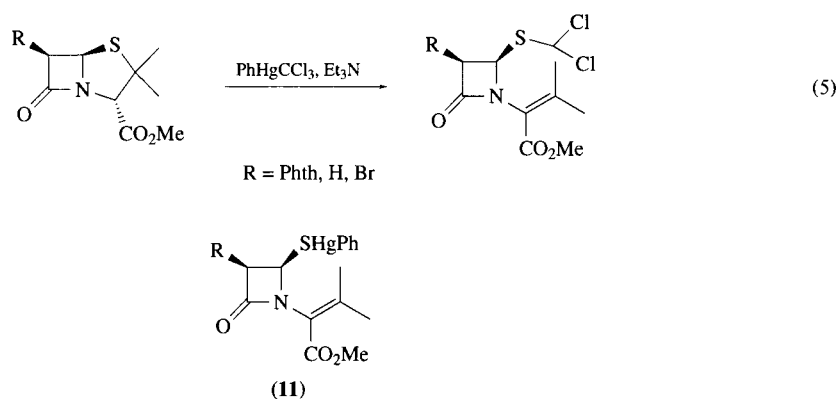


Scheme 6

This reaction has also been applied in the thiazolidine ring opening in 6-halopenicillates and 6-hydroxyalkylpenicillates. A mechanism was proposed involving a thioaldehyde intermediate <85TL1433>.

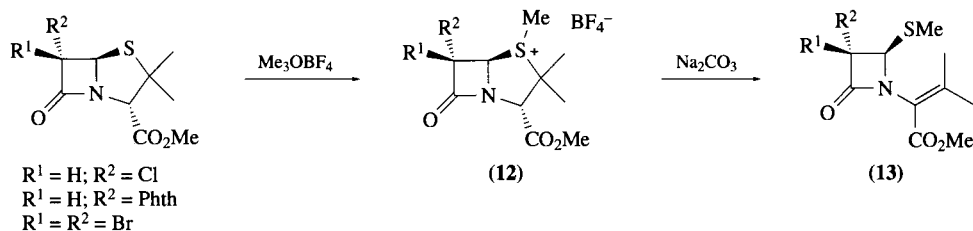
An interesting approach is the use of a strong nonnucleophilic base (DBN) in combination with a thiophilic metal salt (Ag or Hg) to obtain the "1,2-secopenicillins" in high yield <85JA6398, 90H(31)617>. However, the use of stoichiometric amounts of mercury makes this reaction unattractive from an environmental point of view.

Another reaction that uses mercury to cleave the penicillin (S1)—C(2) bond is the reaction of penicillins and derivatives with dichlorocarbene generated from PhHgCCl_3 (Seyferth reagent) (Equation (5)) <89H(29)209>. Surprisingly, when the same reaction is carried out in the presence of NaI in order to generate dichlorocarbene under milder reaction conditions <65JA681>, none of the dichloromethyl derivatives were obtained, but instead the stable phenylmercury mercaptides (**11**) were isolated <90SL611>. It has been suggested that under these conditions reaction of iodide with PhHgCCl_3 affords PhHgI and CCl_3^- . The latter acts as a strong base, giving rise to a "Nayler" type ring opening of penicillin (see above), rather than as a precursor for dichlorocarbene.

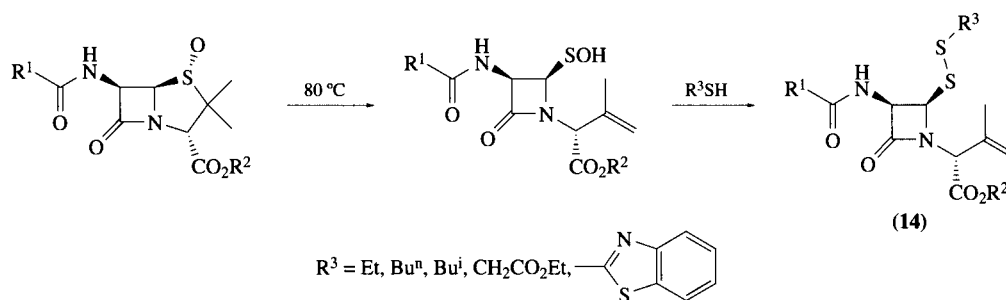


The reaction of very strong alkylating agents such as trimethyloxonium tetrafluoroborate with several penams gives rise to the formation of sulfonium derivatives (**12**) (Scheme 7) that in some cases could be isolated <79JCS(P1)3175>. Upon treatment with a base, these highly reactive compounds undergo cleavage of the S(1)—C(2) bond, giving the 1,2-secopenicillins (**13**).

As has already been mentioned, it is most likely that a sulfenic acid is an intermediate in the thermal epimerization of penicillin sulfoxides. It has been found that these sulfenic acids can be trapped by thiols to give asymmetric disulfides <71CC1137, 73JCS(P1)1182, 73TL3001, 85H(23)325, 85H(23)1403, 85TL3179, 85TL5611> (Scheme 8). These disulfides, in particular (**14**; R = 2-thiol-benzothiazolyl) have found widespread application as precursors for disubstituted penams and other β -lactam-based antibiotics.



Scheme 7



Scheme 8

Another important precursor for other β -lactams is (17) which is obtained by an intramolecular rearrangement of thiocarbamate (15) via the cyclic disulfide (16) <75TL3063, 76TL975, 84TL2017, 88JCS(P1)2813, 91TL7445>.

1.20.5.3.3 Reactions involving the S(1)—C(5) bond

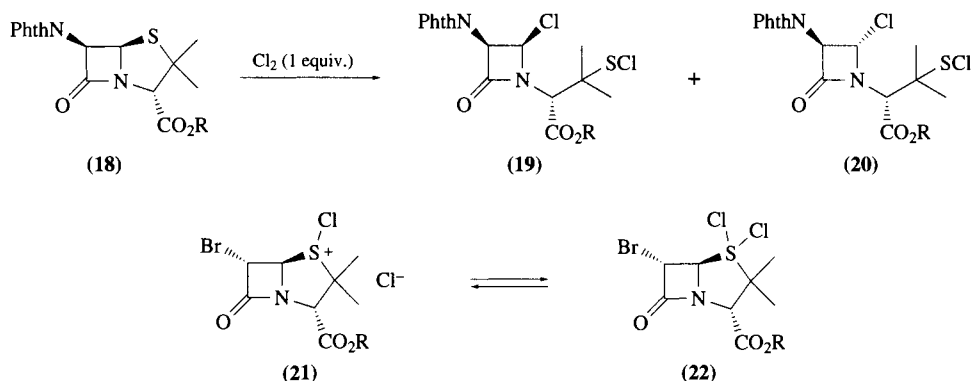
Reaction of penams with chlorine results in cleavage of the S(1)—C(5) bond, for example reaction of (18) with one equivalent of Cl_2 gives a mixture of (19) and (20) (Scheme 9) <71JA6269, 79JCS(P1)3175>. Treatment of the latter compounds with excess Cl_2 or a base affords the corresponding 1,2-seco-penicillates. The formation of either a chlorosulfonium chloride (21) or a sulfurane (22) as initial product during the chlorination of penams was shown by an ^1H NMR study of the chlorination of a 6-bromopenicillate <88T7007>.

Another example of the cleavage of the S(1)—C(5) bond in penams is the reaction of sulfonium ion (23) with methanol giving rise to the formation of (24) (Scheme 10) <79JCS(P1)3175>.

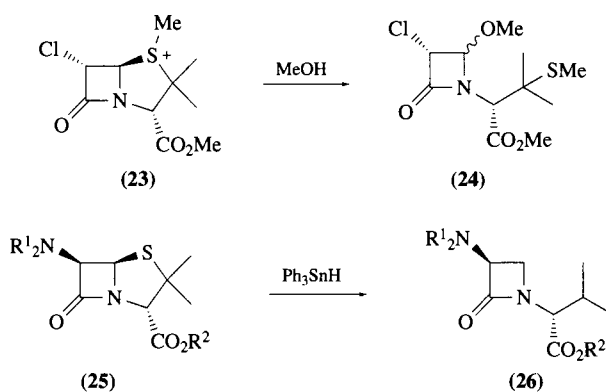
Finally, reduction of penicillins (25) with Ph_3SnH leads to ring opening and a completely desulfurized product (26) (Scheme 10) <89H(28)759>.

1.20.5.4 Modification at the C(3) Position

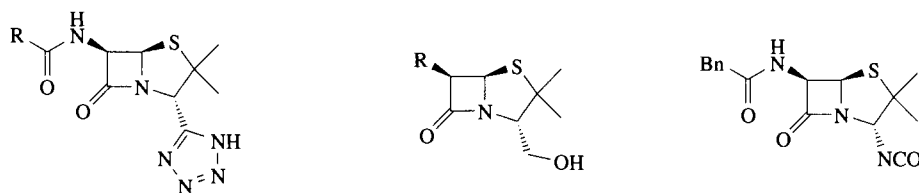
So far, the only transformations at the 3-position of the penam nucleus that have been reported involve the 3-carboxylic functionality <64JMC483, 66JOC1922, 70JMC389, 75MI 120-01, 76HCA2298, B-80MI 120-03>. Some of the compounds prepared are depicted in Scheme 11.



Scheme 9



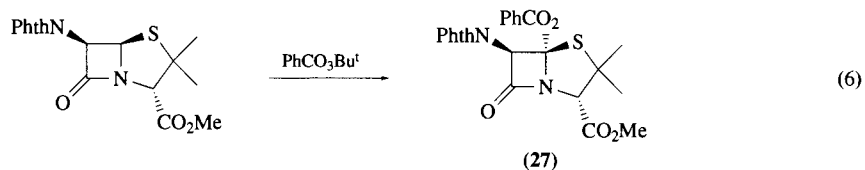
Scheme 10



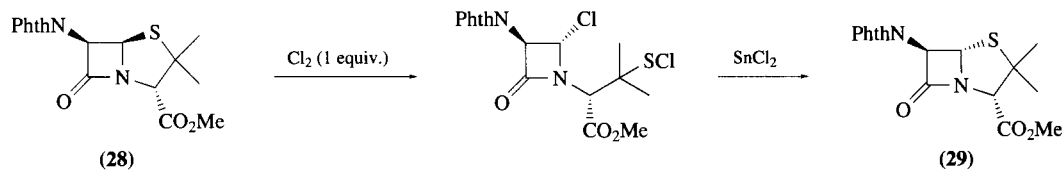
Scheme 11

1.20.5.5 Modification at the C(5) Position

Most of the reactions at the 5-position of penicillins have been discussed in Section 1.20.5.3.3. Only one example of a direct substitution, i.e. a copper-mediated reaction with *t*-butylperbenzoate affording (27) (Equation (6)) has been reported <79CC485>.



Another interesting reaction at the 5-position is the cleavage of the S(1)—C(5) bond in (28) by chlorine and the subsequent tin-mediated ring closure to (29); this reaction sequence makes 5-epipenicillins available (Scheme 12) <76JOC2561>.

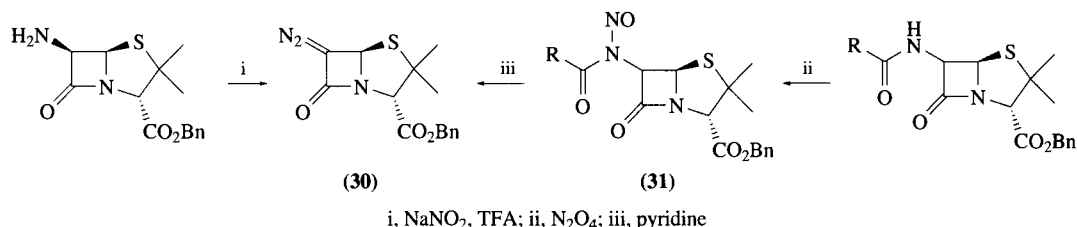


Scheme 12

1.20.5.6 Modification at the C(6) Position

1.20.5.6.1 Synthesis and reactivity of 6-diazopenicillates

The earlier observation that diazotation of 6-APA in the presence of chloride affords 6- α -chloropenicillanic acid was explained by the formation of a diazo intermediate (62JOC2668, 72JCS(P1)895). It appeared to be possible to prepare and isolate esters of this diazo intermediate (Scheme 13), which are valuable starting materials for the synthesis of 6-substituted penicillin derivatives. The diazo ester (30) can be prepared via diazotation of the benzyl ester of 6-APA, or via *N*-nitroso intermediate (31) which is formed by the reaction of phenoxymethylpenicillin with N_2O_4 .

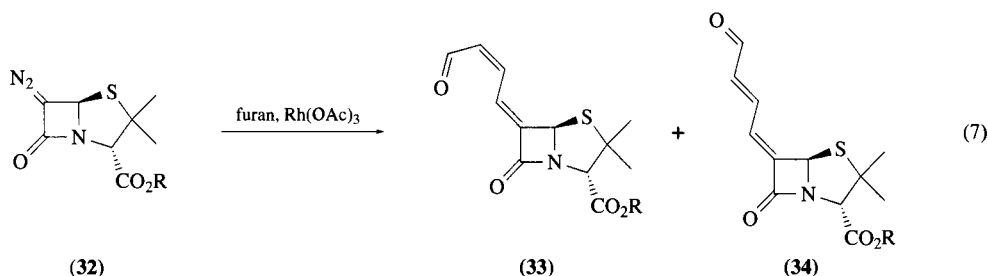


Scheme 13

The most important reactions of the diazo ester of penicillin that have been studied are summarized in Scheme 14. It should be noted that often the trichloroethyl diazo ester ($\text{R} = \text{CH}_2\text{CCl}_3$ in Scheme 14) is used in these reactions and that they are Lewis acid (usually $\text{BF}_3 \cdot \text{OEt}_2$) catalyzed. Substrates that have been used are TsOH , giving rise to the formation of a 6-hydroxypenicillate (67HCA1327, 74JOC1444), thiols (77JOC2224, 78TL995), alcohols (78TL995), ketones (84TL2919, 86JCS(P1)2203), aldehydes (84TL2915, 86JCS(P1)2187), and imines (86CC584, 86JCS(P1)2195). Also, the copper-mediated formation of a penicillin dimer via an exocyclic double bond is noteworthy (86JCS(P1)2213). More detailed information with respect to reaction conditions, stereochemical aspects and mechanistic considerations can be found in the cited literature.

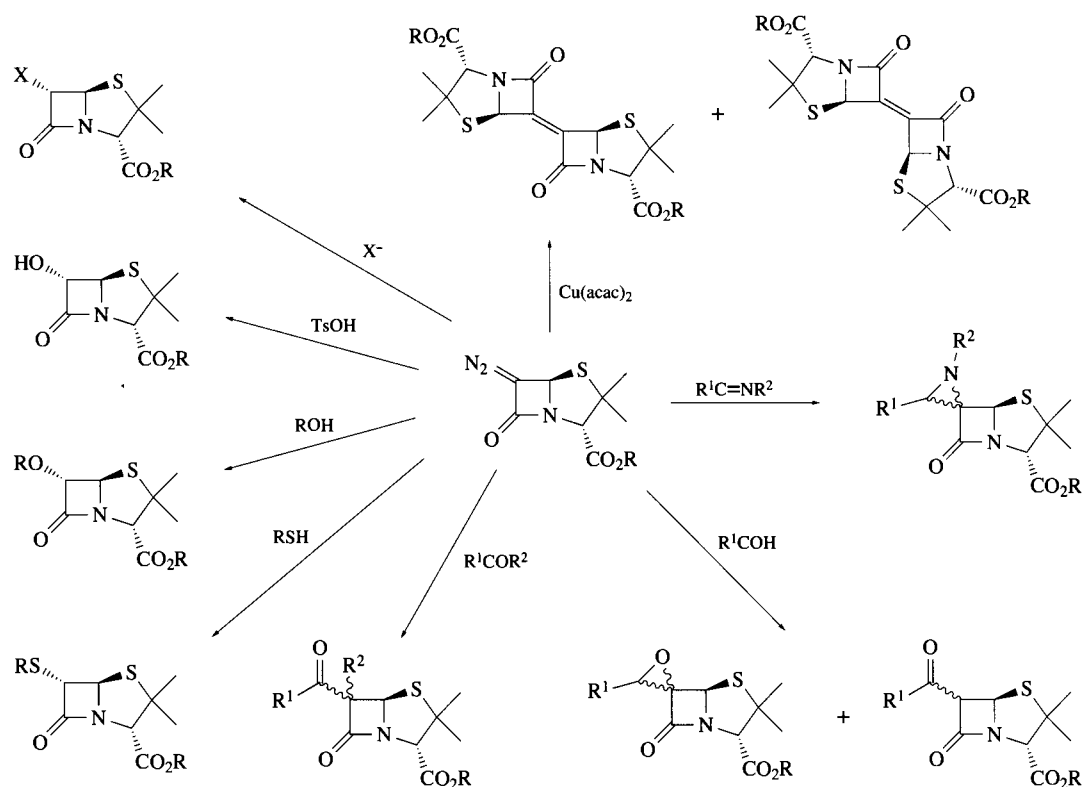
The obvious reaction with halides to give the 6-halopenicillates will be discussed in Section 1.20.5.6.2.

The rhodium-catalyzed reaction of diazopenicillate (32) with furan and substituted furans has been reported that affords the exomethylene penams (33) and (34) (Equation (7)) (90JCS(P1)89).



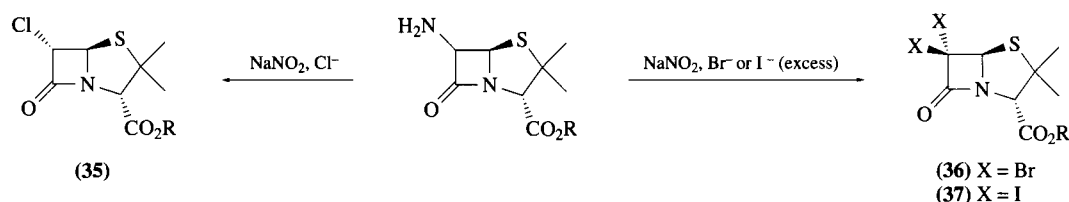
1.20.5.6.2 Synthesis and reactivity of 6-halopenicillates

As already mentioned in the previous section diazotation of 6-APA in the presence of chloride affords 6- α -chloropenicillanic acid (35) (62JOC2668). However, when this reaction is carried out in



Scheme 14

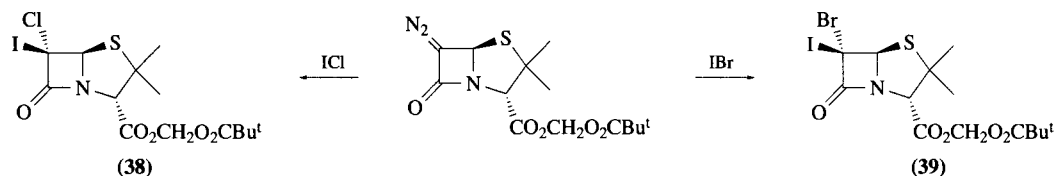
the presence of excess bromide or iodide, the dihalopenicillates (**36**) and (**37**) become the main products <69JCS(C)2123>. It is most likely that (**36**) and (**37**) are formed by the reaction of the initially formed diazo ester with halogen which is formed by oxidation of the halide by nitrous acid.



Scheme 15

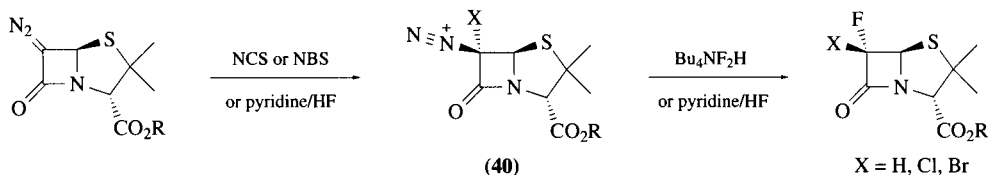
The synthesis and reactivity of some halopenicillanic acid derivatives have been reviewed <67HCA1327, 69JCS(C)2123, 72JA1408, 74JOC1444, 77JOC2960, B-81MI 120-03>. It is noteworthy that 6-halo- and 6,6-dihalopenicillanic acid derivatives do not undergo a normal nucleophilic displacement reaction, but instead nucleophilic attack occurs at the β -lactam carbonyl, followed by a rearrangement <68JCS(C)2533>.

The mixed 6,6-dihalopenicillates (**38**) and (**39**) (Scheme 16) have been prepared from the corresponding diazo ester with ICl or IBr <85CJC3177>. The stereochemistry at C(6) of these compounds was established by x-ray crystal structure determinations.



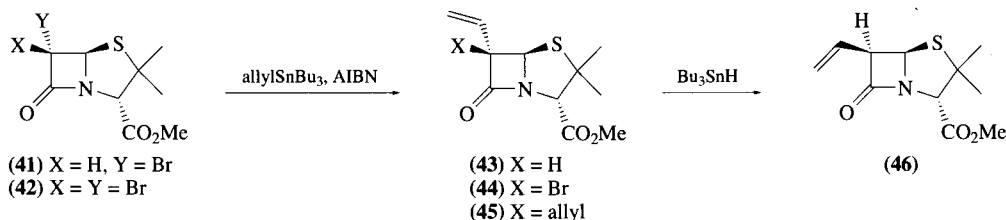
Scheme 16

6-Fluoropenicillates have been prepared via diazonium intermediate (**40**) generated from a diazo ester and NCS, NBS, or pyridinium poly(hydrogenfluoride) (Scheme 17) <88JCS(P1)2059, 90JOC3674>.



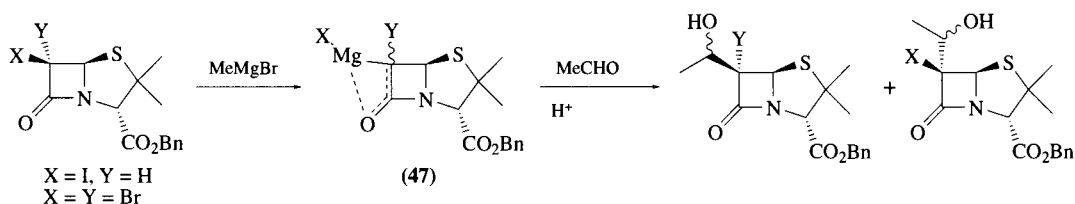
Scheme 17

Allyl groups have been introduced at the 6-position of penicillins by reaction of 6-bromo- (**41**) or 6,6-dibromopenicillates (**42**) with allyltributyltin under radical conditions (Scheme 18) <86TL4857, 89T941>. When excess allyltributyltin is used in the reaction with methyl 6,6-dibromopenicillate the bis-allylated product (**45**) is formed. Finally, the 6-bromo derivative (**44**) could be reduced to (**46**) by Bu_3SnH ; this reduction proceeds with complete inversion of configuration at C(6).



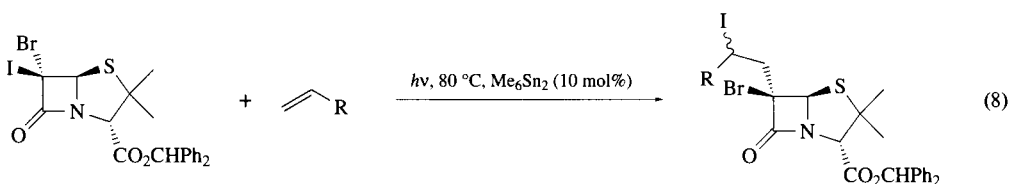
Scheme 18

It has been shown that 6-halo- and 6,6-dihalopenicillates undergo a halogen-metal exchange reaction to afford an enolate-like intermediate (**47**) that reacts with, for example acetaldehyde to 6-(hydroxyethyl)penicillates (Scheme 19) <77JOC2960, 79TL3805>. In general a mixture of diastereoisomers is obtained, the ratio being dependent on the reaction conditions. The 6- α -((*R*)-hydroxyethyl) diastereoisomer is an important precursor to penems and carbapenems. The stereochemistry of this reaction has been studied in more detail, with particular emphasis on the size of the halogen atom, the solvent and the oxidation state of the sulfur <86TL1545>. A similar approach has been used for the synthesis of substituted 6- β -vinylpenicillanic acids by the reaction of (**47**) with acrylates and acrylamides <84JCS(P1)21>.



Scheme 19

Several 6-alkyl substituted penicillates have been prepared, making use of the “iodine atom transfer chemistry” (Equation (8)) <93T3919>, introduced by Curran <88S489>. This methodology allows the use of functionally substituted alkenes that allows further functionalization of the introduced group.

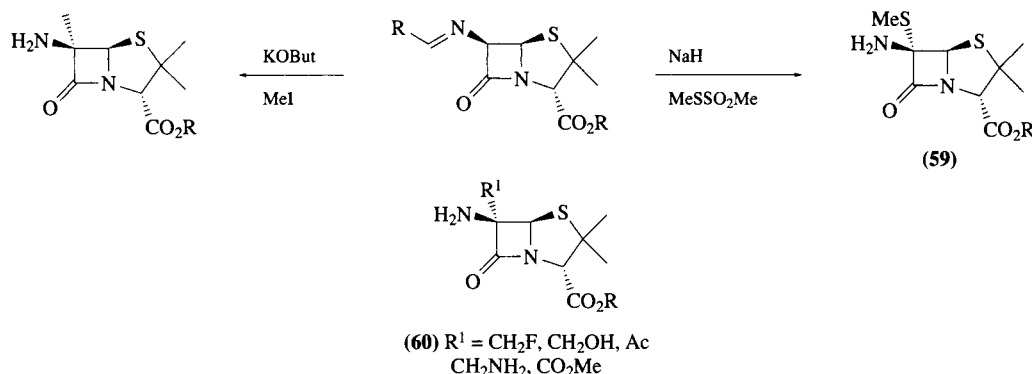


Finally, the reduction of 6-halo- and 6,6-dihalopenicillates is an important synthetic reaction (Scheme 20). The palladium-catalyzed reduction of 6,6-dibromopenicillate (**48**) with H_2 proceeds

Scheme 21

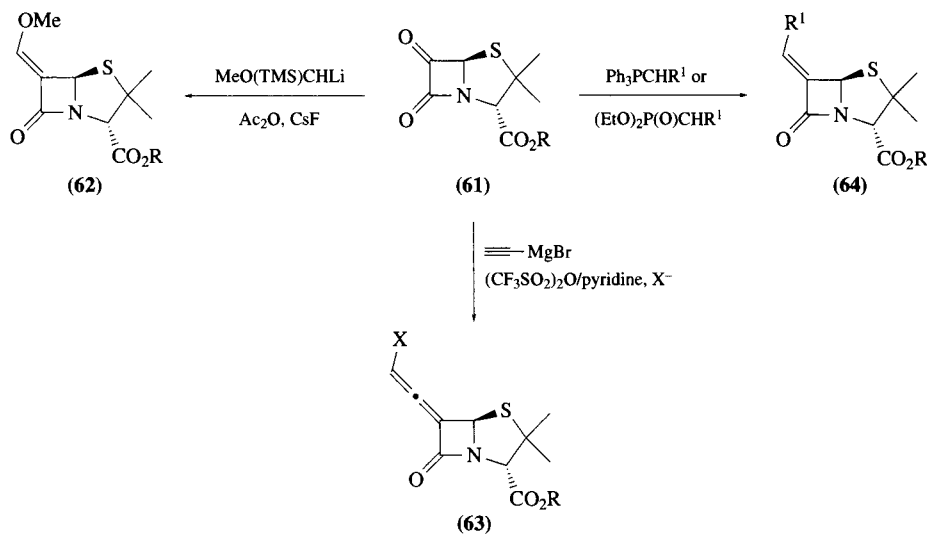
disulfides (Scheme 22) <73JOC2857>, and various other electrophiles giving a variety of 6- α -substituted penicillins (**60**) (Scheme 22) <72TL4917, 73TL145>.

In particular (**59**) has been used as starting material for the introduction of 6- α -formamido- <84CC1335>, 6- α -succinimido-oxy- <86CC401>, 6- α -methoxy- <86CC401>, and 6-spirocyclic- <84JCS(P1)2117> substituents in the penicillin skeleton.



Scheme 22

The 6-oxopenicillate (**61**) <72JA8253, 73JOC2857> could be converted to the 6-(methoxymethylene) derivative (**62**) (Scheme 23) that exhibits interesting anti β -lactamase activity <85JOC18>. Furthermore, 6-vinylidene penams (**63**) were obtained from reaction of (**61**) with $\text{HC}\equiv\text{CMgBr}$ (Scheme 23) <90CC294>. Finally, (**61**) reacts with a variety of Wittig reagents to afford the 6-methylene derivatives (**64**) (Scheme 23) <86H(24)289>.

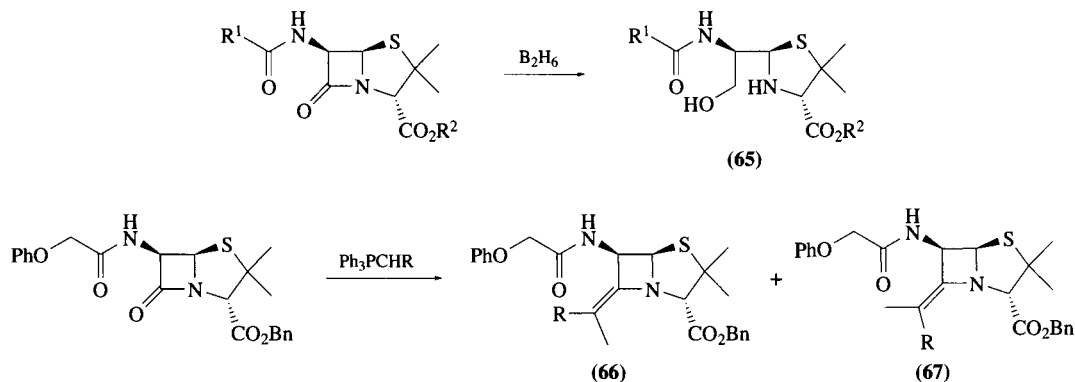


Scheme 23

1.20.5.7 Modification at the C(7) Position

With the exception of the ring-opening reactions discussed in Section 1.20.5.2, modification at the C(7) position has not been studied extensively. In the older literature the replacement of the β -lactam oxygen by sulfur, giving a β -thionolactam in 1% yield, has been reported <75JA5628>. Two more reports concern the diborane reduction of penicillins giving the ring-opened product (**65**)

(Scheme 24) <84JCS(P1)2603>, and the reactivity of Wittig-type reagents towards the β -lactam carbonyl <87JCS(P1)1369>. The latter reaction affords the 7-methylene penams (66) and (67) (Scheme 24) in reasonable yield.

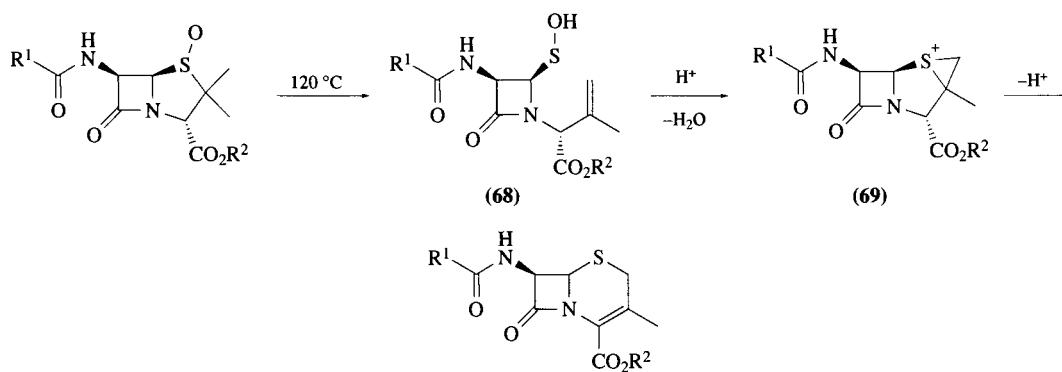


Scheme 24

1.20.5.8 Rearrangement Reactions Involving the Penam Skeleton

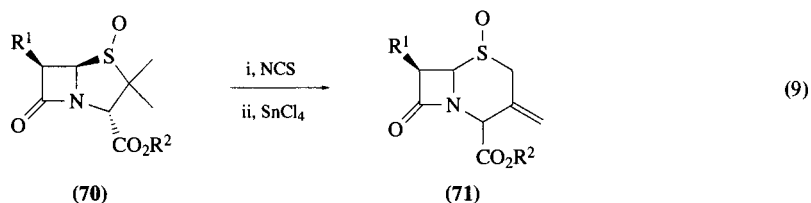
From the time of the discovery that cephalosporins exhibit excellent antibacterial activity, the conversion of penicillins into cephalosporins by ring-enlargement reactions has become a topic that has been studied extensively (see Chapter 1.19). Nowadays this process is very important commercially and is carried out industrially on a large scale <93RTC66>.

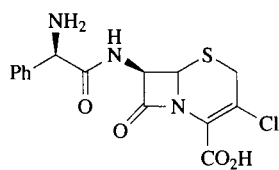
Basically this reaction involves an acid-catalyzed ring enlargement of a penicillin sulfoxide, most likely via sulfenic acid (68) and episulfonium ion (69) (Scheme 25) <93RTC66>.



Scheme 25

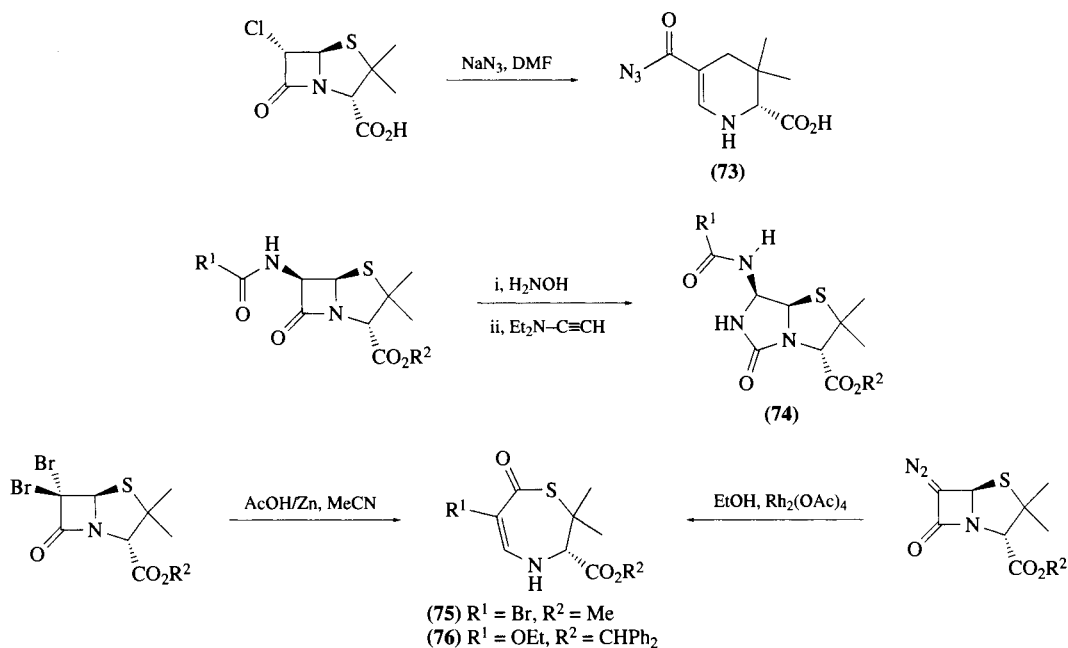
Also the conversion of penicillin sulfoxides into 3-methylene cephalosporins, for example (70) to (71) (Equation (9)) is of prime importance <75JA5583, 81JOC3568> because the products are precursors for the therapeutically important antibiotic Cefaclor (72). In this respect it should be noted that recently a cobalt-mediated ring expansion of 2-iodomethylpenams to 3-methylenecephalosporins has been reported <91TL7093>.





(72)

Some other products **(73)** <68JCS(C)2533>, **(74)** <85BSB1021>, **(75)** <86JOC853>, and **(76)** <80CC798> resulting from rearrangement of the penam skeleton are given in (Scheme 26).



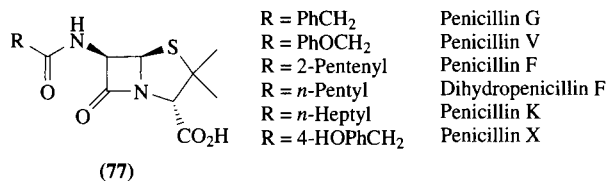
Scheme 26

1.20.6 SYNTHESIS

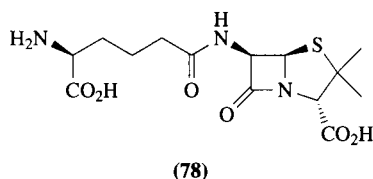
1.20.6.1 Biosynthesis

The production of penicillins on an industrial scale involves aerobic submerged cultivation of microorganisms in an aqueous medium (fermentation), a topic which is discussed only briefly here. Interested readers are referred to more specialized reviews and references cited therein <B-85MI 120-04, B-86MI 120-04>. Penicillins are produced by two types of fermentation. Type 1 fermentation, of which the one involving *Penicillium chrysogenum* is the best known example, results in the formation of penicillins with nonpolar side chains **(77)**. The penicillins are the only β -lactam products formed during this fermentation. It has been recognized at an early stage that the addition of suitable side chain precursors to the fermentation medium allows the formation of specific penicillins.

Type 2 fermentation, of which that involving *Cephalosporium acremonium* is the best investigated



one, produces a penicillin containing a D- α -aminoadipyl side chain (penicillin N) (78) together with other β -lactams such as cephalosporins <B-83MI 120-02>.



The exact technology of the industrial production process of penicillins is still regarded as highly confidential by the commercial penicillin producing firms. Basically, the process involves three important steps: (i) preparation of a shake-flask culture of lyophilized spores of *Penicillium chrysogenum*, followed by inoculation into a seed tank; (ii) the main fermentation process in large fermentators; and (iii) separation of the penicillin from the biomass and purification.

Most production strains of *Penicillium chrysogenum* are derived from the strain Wisconsin NRRL 1951. High-yield strains have been developed by extensive mutation and selection over a long period of time, resulting in an increase of penicillin concentration from about 10 mg l⁻¹ in early strains to about 30 g l⁻¹ nowadays. Details of strain selection and genetics of penicillin production have been reviewed <B-83MI 120-03, B-83MI 120-04>.

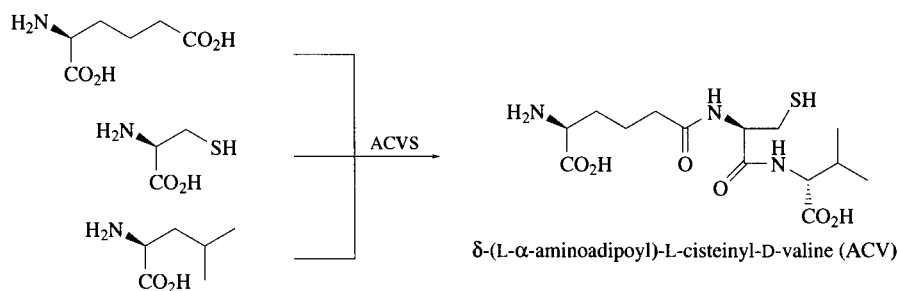
The fermentators, which are the heart of the penicillin production process, usually have a volume of about 300000 l. The main components of the aqueous medium are glucose, sodium phenylacetate, cornsteep liquor, ammonium sulfate, and potassium hydrogen phosphate. During fermentation, the pH of the medium is kept between 6.8 and 7.4 and the temperature is typically 25°C. An important factor of the penicillin fermentation is the aeration process <B-83MI 120-05>. Typically, after 8 to 10 days the maximum concentration of penicillin in the fermentator is reached. As an alternative, fed-batch processes have been developed where nutrients are added continuously.

After fermentation, the whole broth is filtered to remove the mycelium and other solids. The filtrate is acidified to pH 4 and the penicillin is extracted into a solvent like butylacetate. After addition of potassium acetate, potassium penicillin G is precipitated and collected by filtration. The product obtained after purification, for example by recrystallization from isopropyl alcohol can be applied as such or more usually is converted to 6-aminopenicillanic acid (6-APA), see Section 1.20.6.3.1, as starting material for the preparation of semi-synthetic penicillins, see Section 1.20.6.3.2.

1.20.6.2 Mechanism of the biosynthesis of penicillins

During the 1980s much effort has been spent in elucidating the mechanism by which penicillins are formed during the fermentation of *Penicillium chrysogenum* and *Cephalosporium acremonium*. Hundreds of papers covering this topic have been published during that period. Detailed information concerning the mechanistic aspects of the biosynthesis of penicillins and other β -lactam antibiotics can be found in an excellent review by Baldwin and Schofield <B-92MI 120-06>. It has already been suggested earlier that the formation of δ -(L- α -aminoadipoyl)-L-cysteinyl-D-valine (ACV) tripeptide (Scheme 27) is the initial step in this mechanism <62JA4594, 63NAT383>. Additional evidence for this proposal was obtained by the isolation of ACV in minute amounts from *Penicillium chrysogenum* and *Cephalosporium acremonium* <71BJ(123)471, 76B177, 76BJ(157)651>.

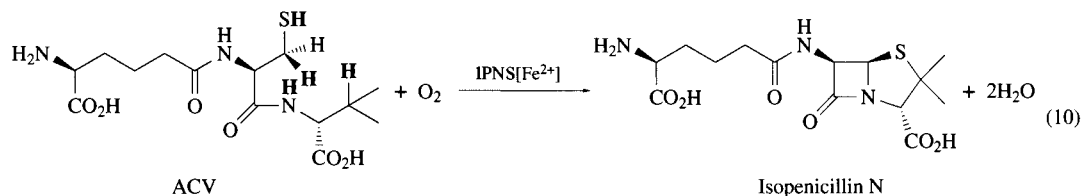
It has been proposed that the ACV biosynthesis is mediated by one multifunctional enzyme,



Scheme 27

i.e. ACV synthetase (ACVS) <87JA2858>. This proposal is supported by the finding that similar multifunctional enzymes are involved in the biosynthesis of other peptide-based antibiotics <B-90MI 120-03, 90MI 120-04>.

The formation of isopenicillin N from ACV is mediated by an enzyme, isopenicillin N synthase (IPNS), which was isolated from *Cephalosporium acremonium*. The purified enzyme was identified as a 38 KDa protein. It appeared that the catalytic activity is strongly enhanced by Fe^{2+} and ascorbic acid, and the enzyme requires O_2 as a cosubstrate (Equation (10)) <84BJ(222)789, 84SCI610>.

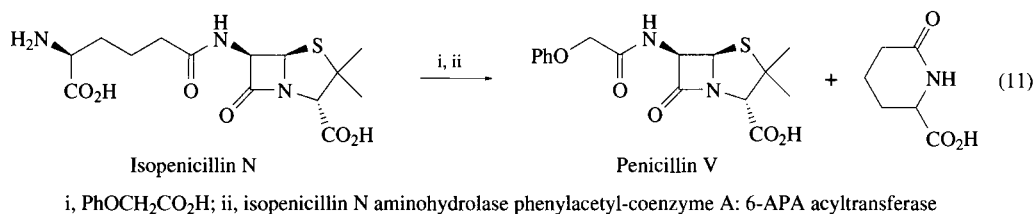


Mechanistic investigations concerning the conversion of ACV into isopenicillin N by IPNS were reviewed <90CRV1079, 90JHC71>. These studies revealed that: (i) Fe^{2+} is essential for activity <90MI 120-05>; (ii) the O_2 consumption has a 1 : 1 molar relation with the amount of isopenicillin N formed (see the bold H atoms in Equation (10) and Scheme 28) <82BJ(203)791>; and (iii) the four hydrogen atoms in ACV are stereospecifically removed and the penam skeleton is formed with retention of configuration (Equation (10)) <85CC1808, 85T3339, 86CC110>. In this respect it should be noted that the complete reduction of O_2 to H_2O represents the most exothermic nonphotochemical reaction available to a biological system. This large driving force is a prerequisite for the formation of the strained penam system. A proposed catalytic cycle for the conversion of ACV into Isopenicillin N mediated by IPNS, based on the latest mechanistic investigations, is presented in Scheme 28.

Additional evidence that a covalent linkage that acts as a conductor for electrons from the peptide to the iron/oxygen redox system is present between the sulfur atom of ACV and the iron atom in the active site of IPNS was obtained from absorption spectroscopy and EXAFS studies <89JBC(264)21677, 90IC1111>.

Finally, during fermentation of *Cephalosporium acremonium*, isopenicillin N is epimerized to penicillin N by a rather unstable epimerase <81BJ(194)645, 81BJ(194)649>.

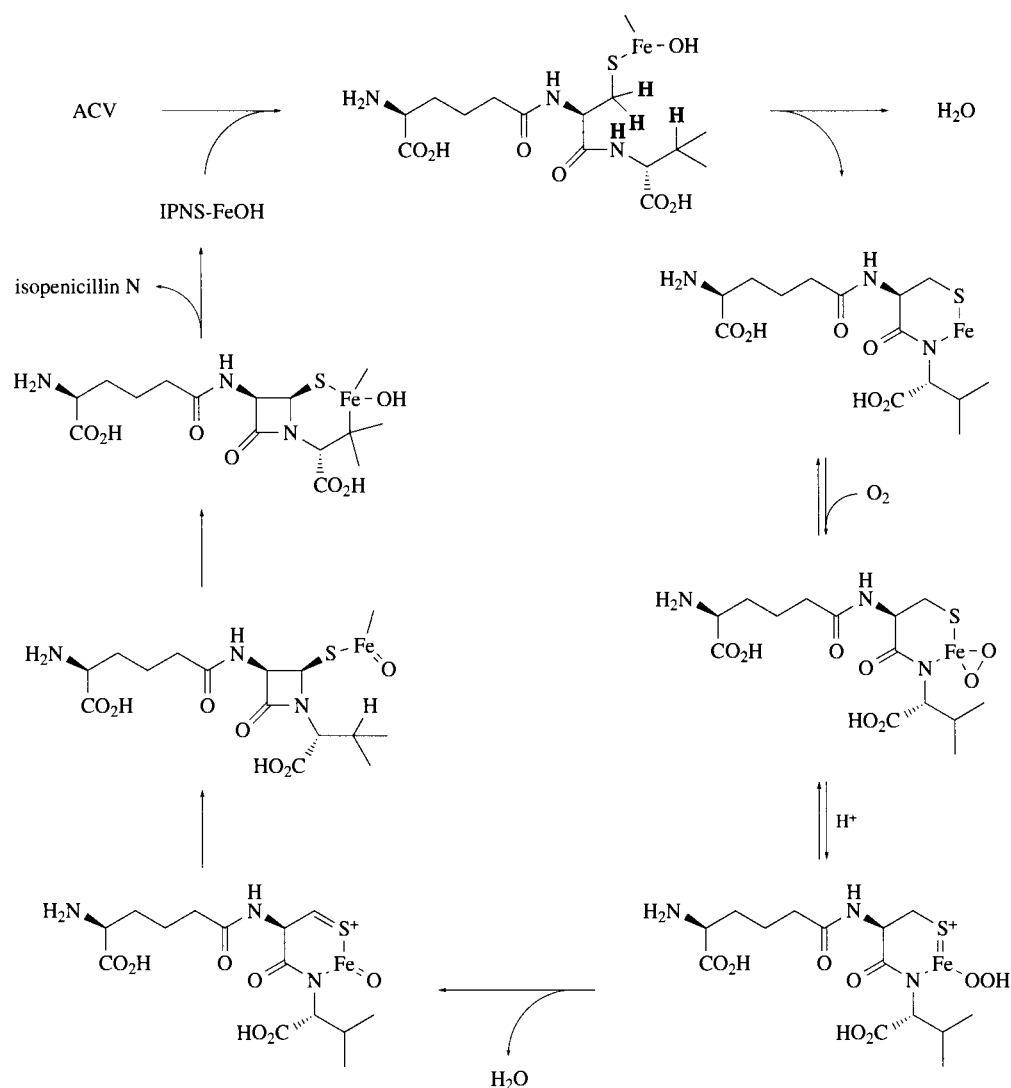
The fact that *Penicillium chrysogenum* produces a variety of penicillins only differing in the 6- β -amino substituent, together with the assumption that ACV is an obligate intermediate in penicillin biosynthesis, indicates that a process involving hydrolysis of the aminoadipoyl group followed by acylation of the formed 6-aminopenicillanic acid must occur <B-92MI 120-06>. Further evidence for such a process was obtained from the observation that *Penicillium chrysogenum* produces 6-oxo-piperidine-2-carboxylic acid, resulting from the aminoadipoyl group (Equation (11)) concomitantly with penicillin V <80JAN1348>.



1.20.6.3 Semisynthetic Penicillins

1.20.6.3.1 Formation of 6-aminopenicillanic acid (6-APA) from natural penicillins

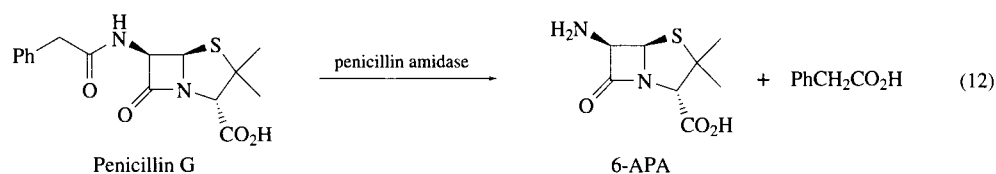
As outlined before, by adding a specific side chain precursor (a substituted acetic acid), to the medium during fermentation of *Penicillium chrysogenum*, penicillins with a specific side chain can be obtained. However, only penicillins with a phenylacetyl (penicillin G) or a phenoxyacetyl (penicillin V) side chain are industrially produced in this way. The isolation of the nucleus of the penicillin molecule, 6-aminopenicillanic acid (6-APA) <59NAT257>, paved the way for the development of the



Scheme 28

synthesis of penicillins containing various 6-amino substituted side chains, the so-called semi-synthetic penicillins.

From earlier studies it had become evident that several microorganisms produce enzymes (amidases) that are capable to hydrolyze selectively the side chain of penicillins produced by fermentation (Equation (12)) <B-72MI 120-02>.



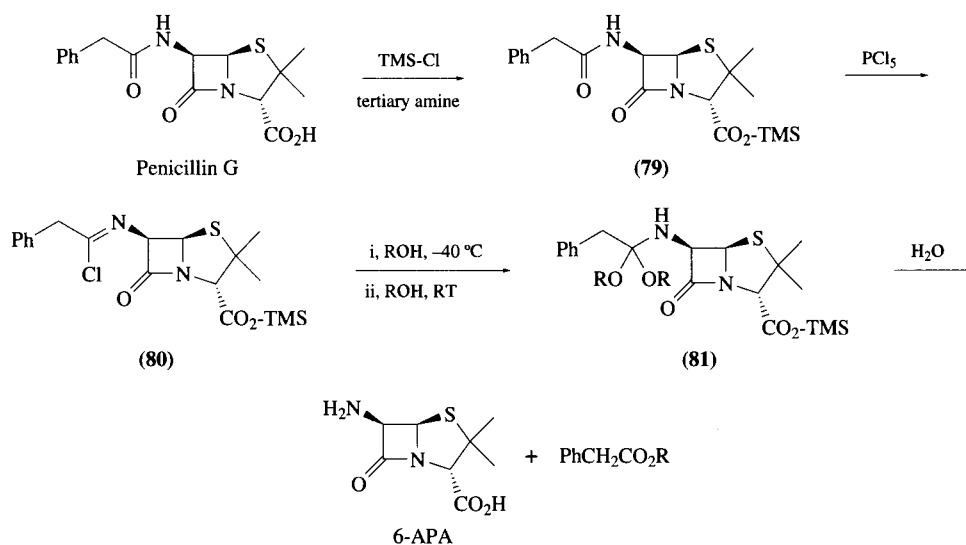
Nowadays 6-APA is produced industrially on a large scale either by enzymatic cleavage or chemical cleavage of penicillin G <93RTC66>. The enzymatic process may be carried out in solution, but the latest development is the use of immobilized enzymes <B-85MI 120-04, B-87MI 120-04, B-87MI 120-05>.

At first glance it seems not to be very easy to cleave the side chain selectively by chemical methods since the side chain amide is relatively stable while the β-lactam amide is rather susceptible towards

hydrolysis. However, by making use of the fact that the side chain amide is a secondary amide while the β -lactam amide is a tertiary one, a chemical route has been developed to cleave the side chain selectively and in high yield (Scheme 29) <70RTC1081>. This process has been carried out industrially as a large-scale one-pot process for the production of 6-APA from penicillin G which is obtained by fermentation <93RTC66>.

Of crucial importance in this procedure is the protection of the 3-carboxylic function as its trimethylsilyl ester (**79**). Reaction of (**79**) with PCl_5 affords the imino chloride (**80**) that after conversion into intermediate (**81**) can be hydrolyzed to 6-APA under very mild conditions.

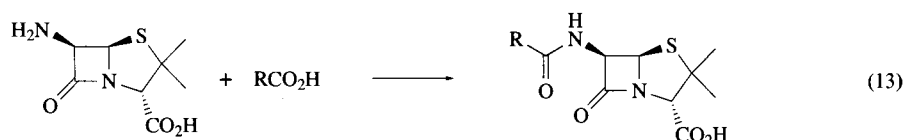
For both environmental (extremely large amounts of phosphorus- and chlorine-containing waste are produced) and economic reasons, nowadays the industrial production of 6-APA involves a highly efficient enzymatic process which is based on an immobilized penicillin amidase (see previous section).



Scheme 29

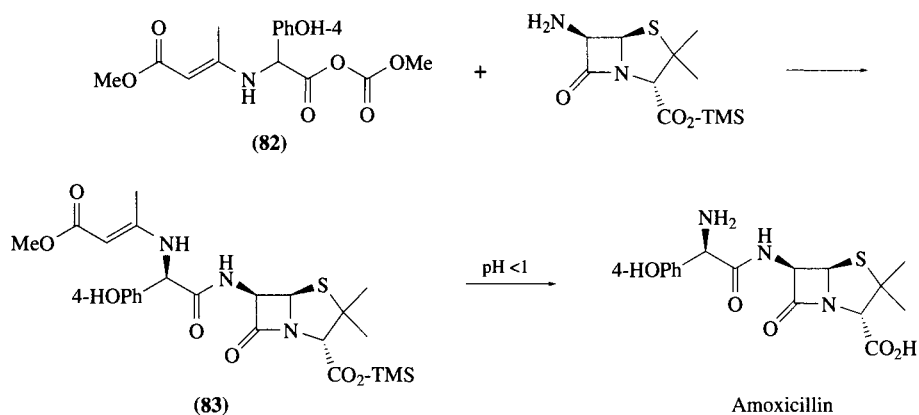
1.20.6.3.2 Acylation of 6-aminopenicillanic acid

The acylation of 6-APA (Equation (13)) is quite easy and has been fully developed <B-72MI 120-03, 74FOR1, 79MI 120-01>. Several methodologies are available that make use of: acid chlorides <60JA3934>, mixed carboxylic carbonic anhydrides <79MI 120-01>, phosphate esters <76T2211>, N,N' -dicyclohexylcarbodiimide <68ACS367>, 1,1'-carbonyldiimidazole <72JMC333>, nitrophenol esters <68JMC70>, and several intramolecular anhydrides <77BSB991>.

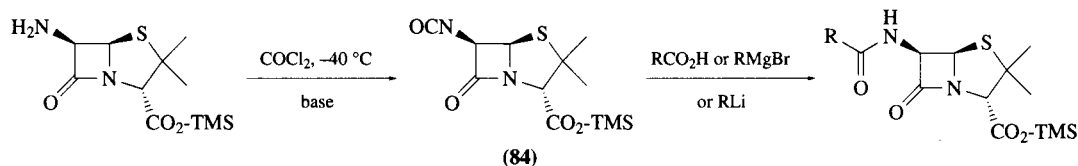


Based on the mixed carboxylic carbonic anhydride route, an industrial process has been developed for the synthesis of amoxicillin starting from cheap starting materials (Scheme 30) <93RTC66>. The mixed anhydride (**82**) is prepared from the Dane salt (obtained from reaction of 4-hydroxyphenylglycine with methyl acetoacetate) by reaction with methyl chloroformate in the presence of a base. Compound (**82**) reacts with trimethylsilyl protected 6-APA to give intermediate (**83**), which after raising the pH to 1 hydrolyzes to amoxicillin. The whole reaction sequence proceeds almost quantitatively.

Another process for the synthesis of semisynthetic penicillins is the reaction of 6-isocyanatopenicillanic acid (**84**), obtained from trimethylsilyl protected 6-APA, with a carboxylic acid or an organometallic reagent (Scheme 31) <69BRP1268536>.



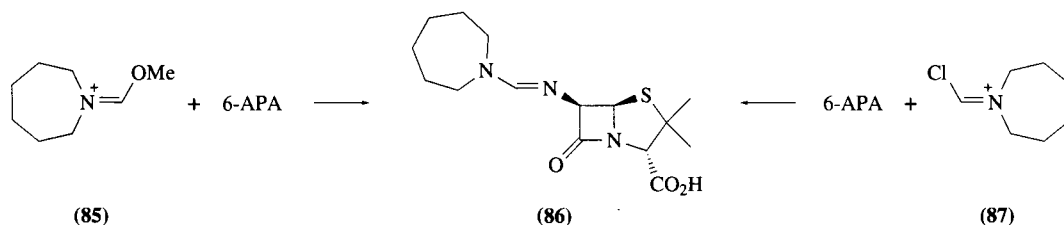
Scheme 30



Scheme 31

The specific procedures for the synthesis of the semisynthetic penicillins mentioned in Tables 3, 4, and 5 in Section 1.20.7 and of other semisynthetic penicillins have been reported extensively <B-77MI 120-01, B-80MI 120-01, B-84MI 120-01, B-90MI 120-01>.

Mecillinam (**86**), which contains an 6- β -formiminoyl group, is prepared by the condensation of 6-APA with either imino chloride (**87**) or imino ether (**85**) (Scheme 32) <72NAT135, 87CPB642>.



Scheme 32

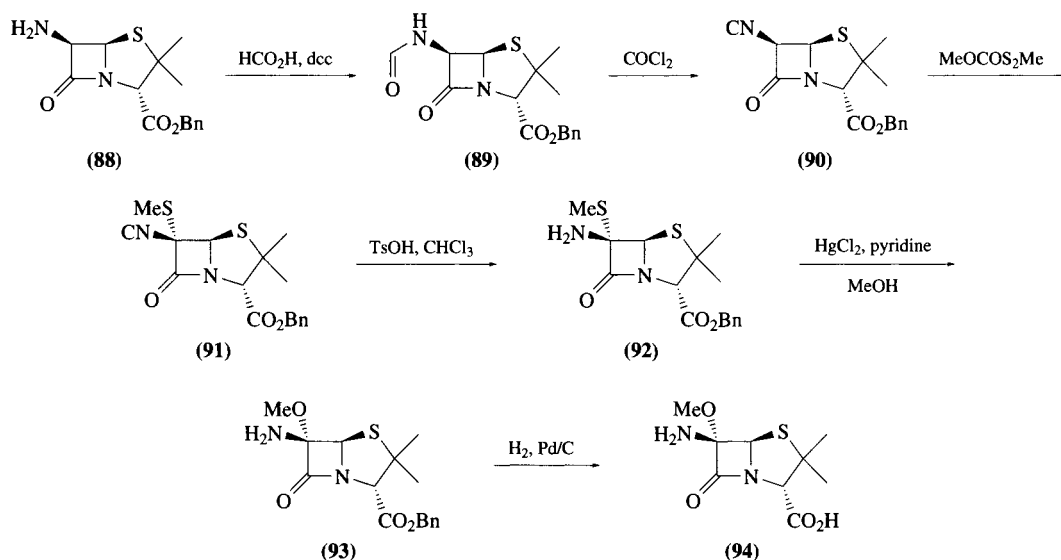
6- α -Methoxy-6- β -aminopenicillanic acid (**94**), the precursor for one of the latest generation semisynthetic penicillins, temocillin (see Table 5 in Section 1.20.7) is prepared starting from the benzyl ester of 6-APA (**88**) (Scheme 33) <79JCS(P1)2455>.

Finally, it should be noted also that enzymatic processes (in solution and immobilized) have been reported to acylate 6-APA <B-87MI 120-05, B-87MI 120-06>. However, these processes usually provide the acylated product in moderate to low yield and therefore this enzymatic route is used only rarely.

1.20.6.4 Total Synthesis of Naturally Occurring Penicillins

Since the discovery of penicillins, it was a challenge for organic chemists to develop a route which would provide these compounds fully synthetically. Furthermore, a total synthetic strategy would provide penicillin analogues that are very difficult to obtain by chemical modification of naturally occurring penicillins <B-72MI 120-02, 76CRV113, 78T1731, B-80MI 120-03>. The earlier attempts to prepare natural penicillins have been reviewed <B-49MI 120-02>.

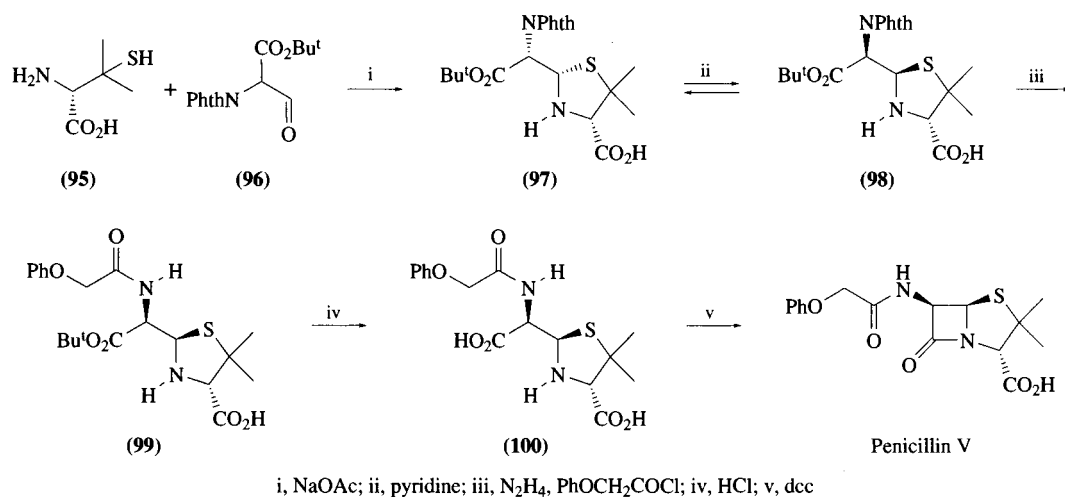
In 1957 the first total synthesis providing a naturally occurring penicillin, i.e. penicillin V,



Scheme 33

in sufficient amount to allow its characterization was reported (Scheme 34) <57JA1262, 59JA3089, 76JOC2556>.

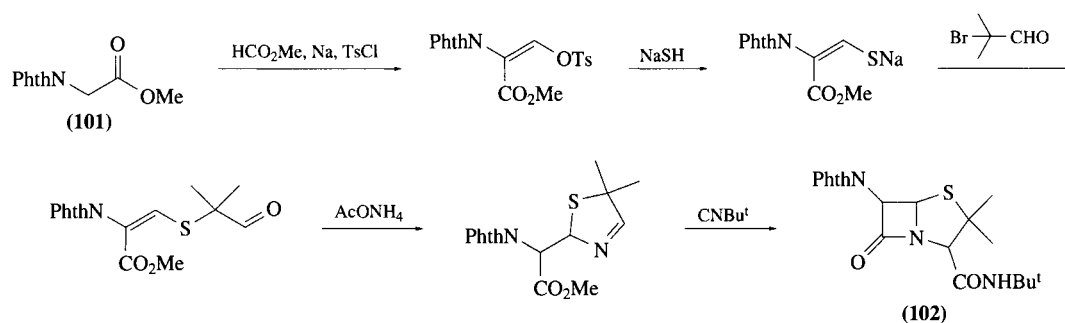
Reaction of D-penicillamine (95) with (96) afforded a mixture of two diastereomeric thiazolidines (97) and (98), respectively, of which (98) corresponds to the configuration in the stereoisomer found in natural penicillins. It appeared to be possible to epimerize (97) into (98) making use of an chiral transformation of the second order. After replacement of the phthalimide function in (98) by a phenoxyacetyl group to give (99) and ensuing hydrolysis of the ester function, diacid (100) was obtained. Ring closure of (100) mediated by dcc afforded penicillin V. Using a similar strategy, in which the trityl group was used to protect the amine in (96), 6-APA has been prepared <62JA2983>.



Scheme 34

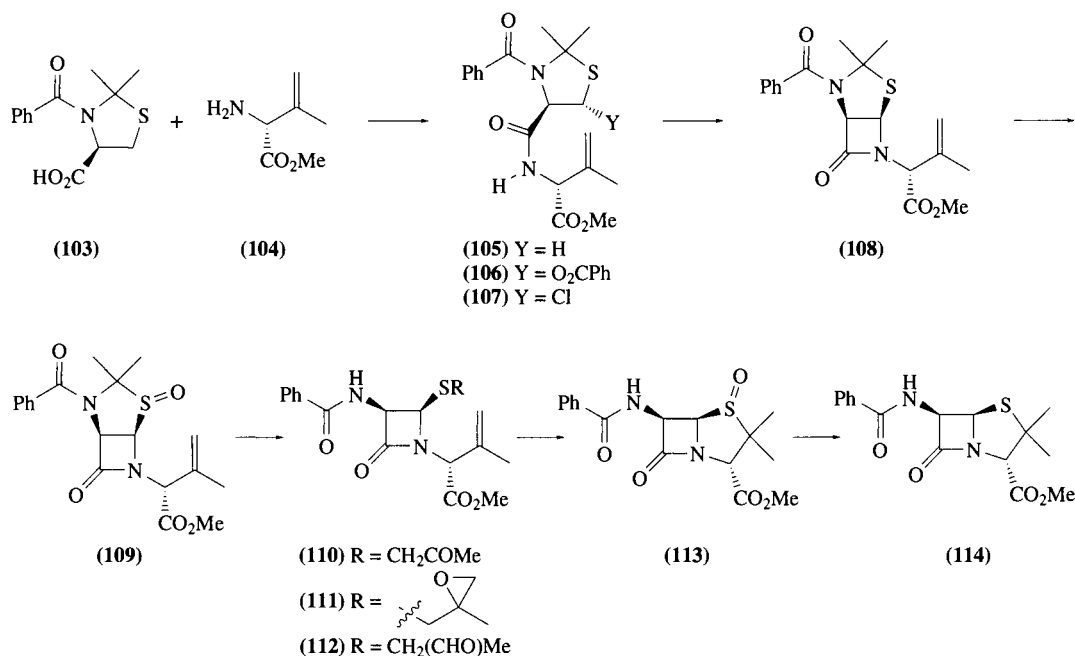
Also the synthesis of a compound which may be regarded as an imide-protected derivative of 6-APA (102) has been described starting from phthaloyl-protected glycine methyl ester (101) (Scheme 35) <79JCR(S)157>. It is most likely that this compound was obtained as a mixture of diastereomers.

In 1976 the first completely stereocontrolled total synthesis of a natural penicillin was reported by Baldwin <76JA3045>.



Scheme 35

This synthesis (Scheme 36) involves an intermediate peptide (105) which is obtained by condensation of protected L-cysteine (103) with D-isodehydrovaline (104). After a multistep synthesis the *N*-benzoyl-protected methyl ester of 6-APA (114) is obtained which has the same absolute stereochemistry as the natural product. Independently a similar route was developed by Kishi for the synthesis of 6- α -methoxy penicillin derivatives <75JA5008>.

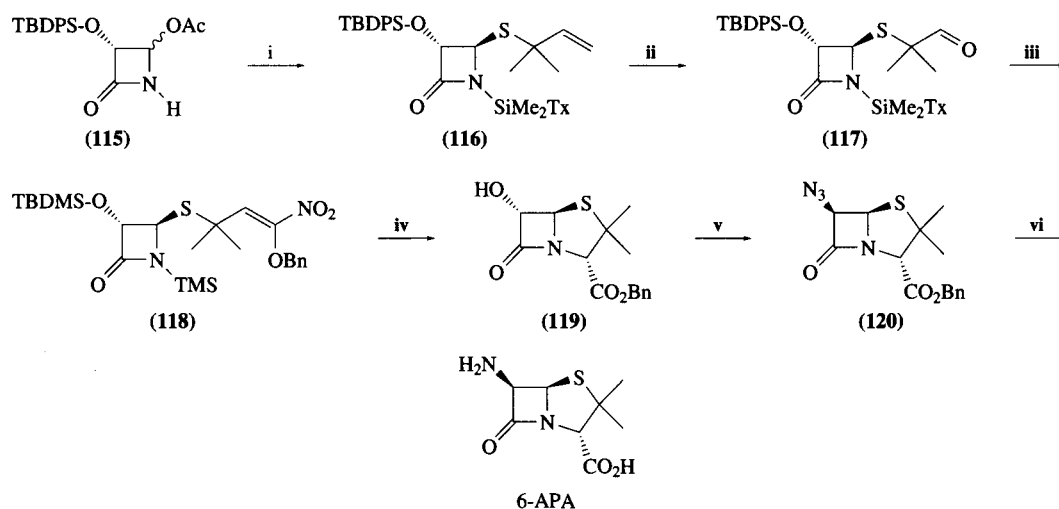


Scheme 36

Reported in 1990 is the total synthesis of 6-APA starting from monocyclic β -lactam (115) (Scheme 37) <90JOC5110>. Reaction of acetyl derivative (115) with 1-methyl-3-butenethiol under basic conditions affords (116) in a completely diastereoselective manner. Compound (118) was obtained after conversion of the alkene functionality into an aldehyde and condensation with benzyloxynitromethane. Further reaction with NH_4F and O_3 afforded smoothly the bicyclic β -lactam (119) together with its 3-epimer. This mixture could be completely epimerized to (119) using DBU in CH_2Cl_2 <85JCS(P1)2235>. Introduction of an azide at the 6-position with inversion of configuration at C(6) (120) and finally reduction and deprotection of the benzyl ester with H_2 and Pd/C afforded 6-APA.

1.20.6.5 Synthesis of Other Compounds Containing the Penam Skeleton

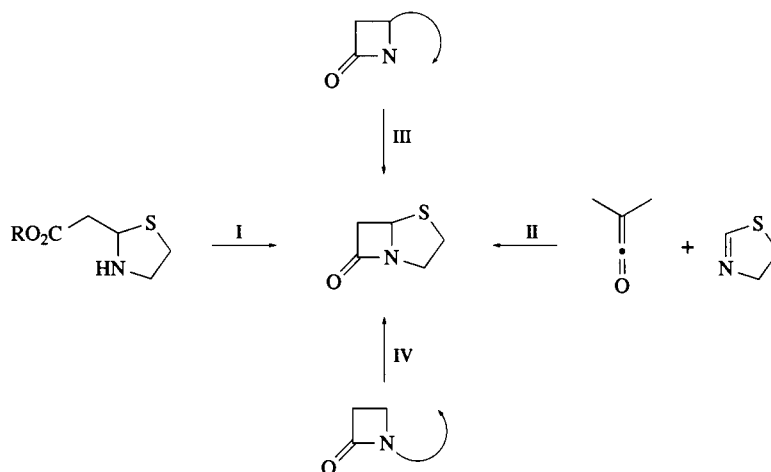
The different strategies (I, II, III, and IV) that have been applied for the synthesis of the penam system, which is the backbone of penicillins, are schematically outlined in Scheme 38.



i, NaOMe, $\text{H}_2\text{C}=\text{CHC}(\text{Me})_2\text{SH}$, $\text{TxMe}_2\text{SiOTf}$; ii, O_3 , Me_2S ; iii, $\text{PhCH}_2\text{OCH}_2\text{NO}_2$, Bu^tOK ; iv, Bu_4NF , O_3 , dbu ; v, TfCl , LiN_3 ; vi, H_2 , Pd/C

Scheme 37

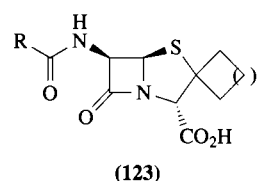
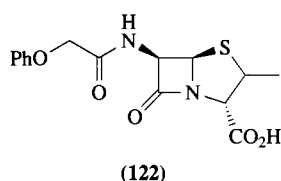
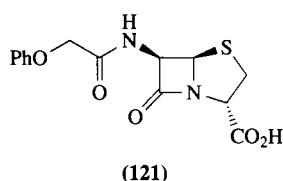
The oldest approach involves intramolecular amide bond formation, i.e. formation of the β -lactam ring, starting from substituted 2-thiazolidineacetic acid (route I). This method has been applied in the final step of the total synthesis of penicillin V (see Section 1.20.6.4). It should be noted that this ring-closure reaction usually proceeds in low yield. The second strategy (II in Scheme 38) involves the cycloaddition reaction of an *in situ* generated ketene with an imine, the well-known Staudinger reaction, which is often applied to the synthesis of monocyclic β -lactams (B-93MI 120-06). More recent are cycloaddition reactions of transition metal alkylidene complexes with imines (see below). Also strategies have been developed that start from monocyclic β -lactams with a proper substituent at either the lactam nitrogen atom (e.g. used in the total synthesis of penicillins developed by Baldwin, (see Section 1.20.6.4, Scheme 36) or the C(4) position (III and IV, respectively, in Scheme 38), that allows ring closure to the penam system.



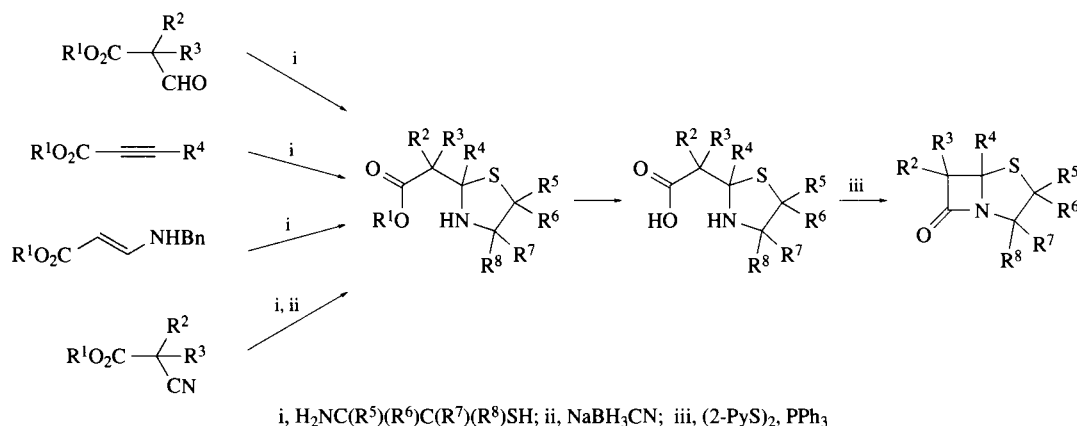
Scheme 38

Bishnorpenicillin V (121) (74JMC389), norpenicillin V (122) (75EJM573) and the 2-spiroderivatives (123; $n = 1-3$) (78CC46) have been prepared using the approach for penicillin V outlined in Scheme 34.

The syntheses of several substituted 2-thiazolidineacetic acids have been reported. These compounds could be prepared in reasonable yield by the condensation of a substituted 2-amino-

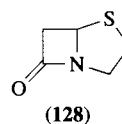
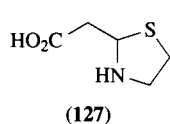
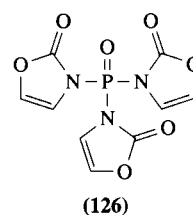
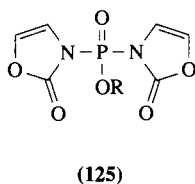
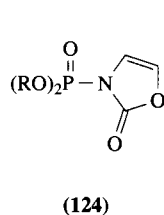


ethanethiol with: (i) formylacetates <87CJC26, 87JCS(P1)1845, 89CPB877>; (ii) propiolates <85CL659, 87JCS(P1)1845>; (iii) enamines <87CJC26>; and (iv) cyanoacetates <85CPB3046> (Scheme 39).



Scheme 39

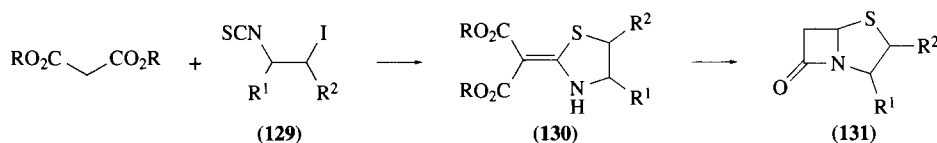
As has been mentioned before, the ring-closure reaction of β -amino acids, i.e. formation of the four-membered β -lactam ring, is the crucial step in the penam synthesis. Several methodologies have been used to perform the ring closure in the 2-thiazolidineacetic acids and ester derivatives depicted in Scheme 39. It appears that Mukaiyama–Ohno's procedure (2,2'-bipyridyl disulfide/triphenylphosphine) <70TL1901, 81JA2406> gives the most consistent yield of the desired penam, but this usually does not exceed 10%. In this respect it should be noted that a model study concerning the intramolecular amide bond formation in β -amino acids mediated by oxazolinyolphosphonate derivatives (**124**), (**125**), and (**126**) afforded β -lactams in high yield <88TL2203>. Using (**126**), 2-thiazolidineacetic acid (**127**) could be cyclized to penam (**128**) (Equation (14)) in yields up to 57%.



(14)

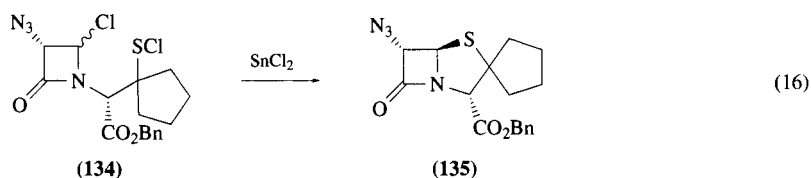
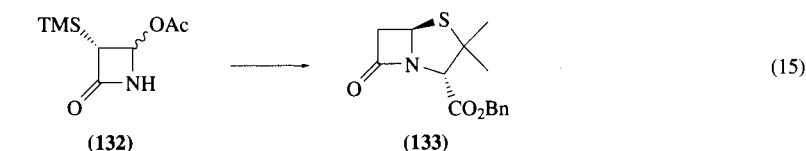
Another interesting approach to the synthesis of penams is depicted in Scheme 40. Reaction of malonate anion with a *vic*-iodoisoithiocyanate (**129**) affords intermediate (**130**) that after decarboxylation, reduction and cyclization gives penam (**131**) <85AJC745>.

Two examples for the construction of penams starting from monocyclic β -lactams are depicted in Equations (15) and (16). Penam (**133**) was prepared completely diastereoselectively starting from monocyclic β -lactam (**132**) using a similar approach as has been applied for 6-APA (see Scheme 37). This method uses the benzyloxynitromethane synthon <89TL2349>. The tin(II)-mediated ring

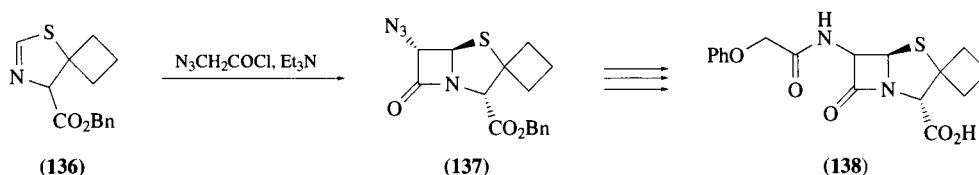


Scheme 40

closure of (134) to afford penam (135) is an example of the use of *N*-substituted monocyclic β -lactams as starting material for penams <80JCS(P1)2228>.

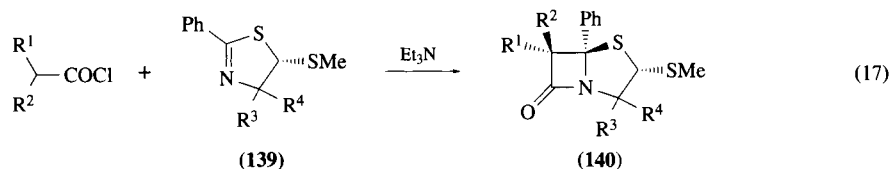


The Staudinger reaction has also been applied to the synthesis of the penam skeleton. Condensation of azidoacetyl chloride with thiazoline (136) afforded azidopenam (137) that in several steps could be converted to (138) (Scheme 41) <77EJM521>.



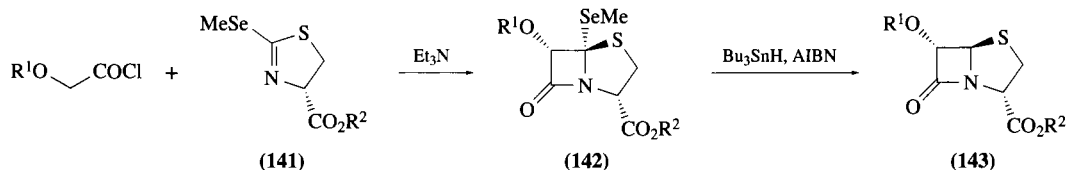
Scheme 41

The Staudinger reaction has been applied to the synthesis of substituted penam derivatives (140) by reaction of either dichloroacetyl chloride ($\text{R}^1 = \text{R}^2 = \text{Cl}$) or azidoacetyl chloride ($\text{R}^1 = \text{N}_3$, $\text{R}^2 = \text{H}$) with a substituted 4,5-dihydro-1,3-thiazole (139) (Equation (17)) <86HCA1424>. In general, the reaction proceeds with high diastereoselectivity, only in one case ($\text{R}^3 = \text{Pr}^i$, $\text{R}^4 = \text{Me}$) a mixture of diastereomers was obtained.



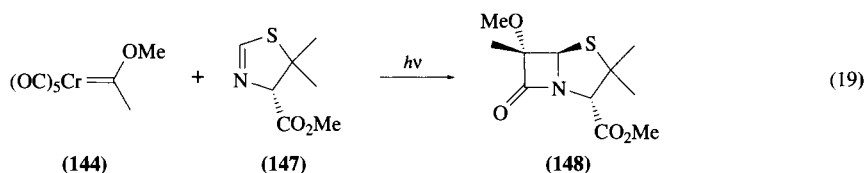
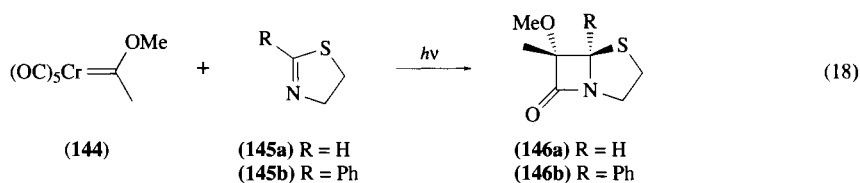
The ketene cycloaddition of several alkoxy-substituted acetyl chlorides with methylseleno derivative (141) affords the methylselenopenams (142) in high yield (Scheme 42) <86JOC4737, 87NKK1447>. Reactions have been carried out with both racemic and enantiomerically pure (141). The latter reactions proceed with an *ee* of 50%. The MeSe group in (142) can easily be removed by reduction with $\text{Bu}_3\text{SnH/AIBN}$ to afford (143).

In 1984, transition-organometallic chemistry was used for the first time in the synthesis of penams. It appeared that under photochemical conditions (visible light) pentacarbonyl[(methoxy)(alkyl)-carbene]chromium(0) undergoes a cycloaddition reaction with imines with concomitant CO insertion to give a β -lactam in high yield <84JA2680>. It was shown that, under these conditions, chromium carbene complex (144) and thiazolines (145) affords penams (146) in high yield (Equation (18)). The



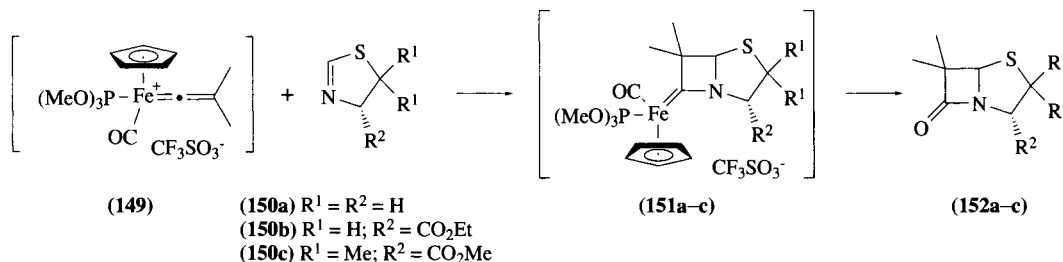
Scheme 42

same reaction carried out with the enantiomerically pure thiazolidine ester (**147**) selectively gave one diastereomer of penam (**148**) (Equation (19)).



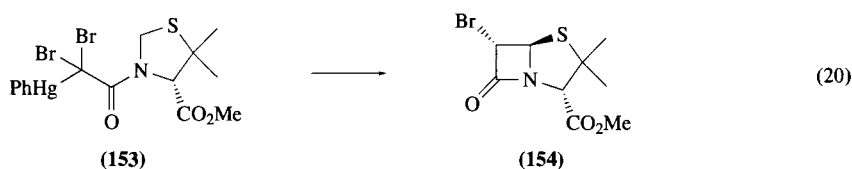
This approach has been extended towards the diastereoselective synthesis of 2-isopropyl-6,6-disubstituted penams starting from pentacarbonyl[(alkoxy)(alkyl)carbene]chromium(0) complexes and (*S*)-(-)-4-isopropyl-2-thiazolidine as the chiral substrate <92JOC1461>.

Similarly, cationic iron(II) vinylidene complexes react with imines to afford β -lactams <87JOC3940, 88OM2553>. Reaction of iron(II) vinylidene complex (**149**) with 2-thiazolidines (**150a**), (**150b**), and (**150c**) affords in high yield the iron alkylidene penams (**151a**), (**151b**), and (**151c**) that after oxidative cleavage of the iron moiety give the penams (**152a**), (**152b**), and (**152c**) (Scheme 43).



Scheme 43

The use of organomercury compound (**153**) to afford penam (**154**) (Equation (20)) has been reported in the older literature <76ACS(B)377>.



1.20.7 APPLICATION

1.20.7.1 Antibacterial Agents

The penicillins, among with other β -lactams, are the most important class of antibiotics which have found a widespread and still growing application against bacterial infections. The amount of

literature concerning the medical, microbiological, pharmacological, toxicological, and biochemical properties of penicillins is overwhelming. These properties are therefore discussed here only very briefly. Interested readers are urged to consult a 1993 review and references cited therein concerning the clinical pharmacology and therapeutic use of penicillins <93MI 120-01>.

1.20.7.1.1 Mechanism of antibacterial activity and resistance

The details of the mechanism by which bacteria are destroyed by penicillins are still unknown. It has been established that the principal antibacterial action is based on inhibition of bacterial cell wall synthesis and on activation of endogenous autolytic mechanisms leading to cell lysis. An essential condition is that the antibiotic must be capable to penetrate the outer spheres of the bacterial cell and then bind in an active form to the target site. The rigidity of bacterial cell walls is maintained by peptidoglycans, which are long polysaccharide chains of *N*-acetylglucosamine and *N*-acetylmuramic acid, cross-linked by shorter peptides. The growth of the bacterial cell wall, i.e., anchoring of new peptidoglycan to old, involves several enzymes (transpeptidases, carboxypeptidases, and endopeptidases). It is believed that specific molecules on the inner membrane of the cell wall, the so called "penicillin-binding proteins" (PBPs) activate specific transpeptidases or other enzymes. The binding of penicillins to these PBPs causes the termination of peptide chain linking and inhibits the formation of a normal peptidoglycan structure. This finally leads to weakening of the bacterial cell wall and lysis <79MI 120-02>. Furthermore, it is believed that inactivation of endogenous inhibitors of bacterial autolysis via penicillin binding to PBPs is a second important mechanism <85MI 120-05>. Especially during the last decade the interaction of β -lactam antibiotics with PBPs has been studied extensively and has been reviewed <B-92MI 120-07 and references cited therein>.

A serious problem in the therapeutic use of penicillins is the phenomenon of resistance to β -lactam antibiotics, which may be intrinsic or acquired. This topic has been reviewed <90MI 120-06, 93MI 120-07>. The three main mechanisms of resistance towards penicillins are: (i) inactivation of the penicillin by bacterially produced enzymes (β -lactamases); (ii) reduction of penicillin permeability of the cell wall; and (iii) alteration of the antibiotic target site (PBPs). The first one, production of β -lactamases by bacteria resulting in cleavage of the β -lactam ring to inactive penicillionic acid derivatives, is the most relevant. Therefore, nowadays certain penicillins are used therapeutically in combination with a β -lactamase inhibitor (see Section 1.20.7.2), for example ticarcillin in combination with clavulanic acid or amoxicillin in combination with sulbactam <89MI 120-04>. These β -lactamase inhibitors may operate by two mechanisms: (i) irreversible binding to, and inactivation of, the β -lactamase; and (ii) potentiation of the activity of the β -lactam, most likely by binding directly to PBPs.

1.20.7.1.2 Therapeutic use

The penicillins cover a wide spectrum of antibacterial activity (for an overview of activity of different penicillins against common pathogenic bacteria see <93MI 120-01>). As outlined before, production of β -lactamases by bacteria is the main mechanism of resistance to β -lactam antibiotics. Therefore, side chain modified penicillins (semisynthetic penicillins) have been developed showing increased β -lactamase stability. Unfortunately, bacteria have countered this by producing more potent and broader spectrum β -lactamases. Nowadays the penicillins that are used therapeutically are classified into six groups <B-92MI 120-01> which are discussed briefly here.

(i) Group 1 penicillins: benzylpenicillin

This compound is the parent compound of the family of penicillins, initially discovered by Fleming. It is highly active against all Gram-positive bacteria, Gram-negative cocci, some actinomycetes, and some spirochaetes. Unfortunately, it is susceptible to all β -lactamase producing organisms. Especially *Staphylococcus aureus* and most Gram-negative bacteria are resistant. Since benzylpenicillin is acid labile and hydrolyzed in the stomach to inactive compounds it is administered via intramuscular or intravenous injections. The other Group 1 penicillins (see Table 3) are insoluble

salts of benzylpenicillin, i.e. benethamine penicillin, benzathine penicillin, and procaine penicillin, and are administered intramuscularly. These compounds slowly release benzylpenicillin and therefore show the same activity spectrum as the parent benzylpenicillin.

Table 3 Group 1 and 2 penicillins.

R^1	R^2	Generic name	R^1	R^2	Generic name
Group 1 penicillins			Group 2 penicillins		
	CO_2H $\text{CO}_2^- \text{ BenethamineH}^+$ $\text{CO}_2^- \text{ BenzathineH}^+$ $\text{CO}_2^- \text{ ProcaineH}^+$	Benzylpenicillin (Pen-G) Benethamine penicillin Benzathine penicillin Procaine penicillin		CO_2H	Phenoxy-methylpenicillin
				CO_2H	Pheneticillin
				CO_2H	Propicillin

(ii) *Group 2 penicillins: oral penicillin derivatives*

These derivatives (see Table 3) have improved stability towards acids and therefore are administered orally. The antibiotic spectrum closely resembles that of benzylpenicillin but there are some minor but significant differences against certain bacterial strains (B-92MI 120-07). Phenoxy-methylpenicillin (penicillin V) is the most widely administered representative of this group.

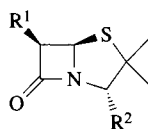
(iii) *Group 3 penicillins: antistaphylococcal penicillins*

Because benzylpenicillin and its derivatives are ineffective against penicillase-producing staphylococci, semisynthetic penicillins (see Table 4) were developed that are stable towards these enzymes. Methicillin was the first compound discovered in this class followed by nafcillin and the isoxazoloyl penicillins. All compounds are intrinsically less active than benzylpenicillin. Because methicillin is not acid resistant and nafcillin is poorly absorbed after oral administration these drugs are given via the intramuscular or intravenous route. The isoxazoloyl penicillins are much better absorbed and are administered orally. In principle the Group 3 penicillins are used in treatment of methicillin sensitive *Staphylococcus aureus* or *Staphylococcus epidermidis* infections.

(iv) *Group 4 penicillins: "broad spectrum" penicillins*

When the aminopenicillins (see Table 5) were introduced, they had reliable antibacterial activity against many common bacterial infections. Nowadays, their usefulness in treating infections is diminished as a consequence of the appearance of bacterial resistance, especially amongst enterobacteria and *H. influenza*. Usually these drugs are administered in combination with a β -lactamase inhibitor, for example ampicillin/sulbactam and amoxicillin/clavulanic acid. The ester derivatives of ampicillin (see Table 5) were developed to increase the oral absorption. These compounds exert their activity by releasing ampicillin through cleavage by tissue esterases. Mecillinam (amidinocillin)

Table 4 Group 3 penicillins.



R^1	R^2	Generic name	R^1	R^2	Generic name
	CO_2H	Oxacillin		CO_2H	Flucloxacillin
	CO_2H	Methicillin		CO_2H	Cloxacillin
	CO_2H	Dicloxacillin		CO_2H	Nafcillin

is structurally different from the other members of this group, as it contains a substituted amidino group. It is very active against Gram-negative organisms but has low activity against Gram-positive strains.

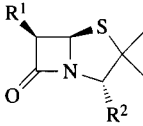
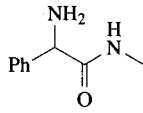
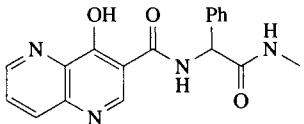
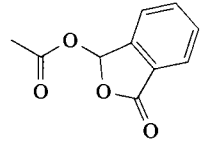
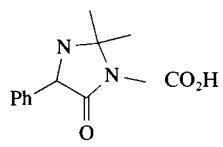
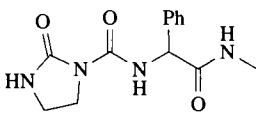
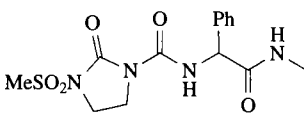
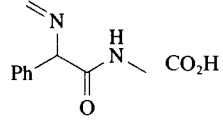
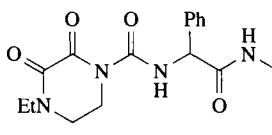
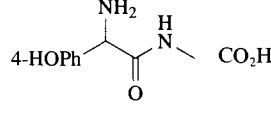
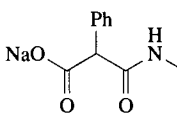
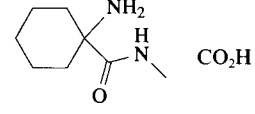
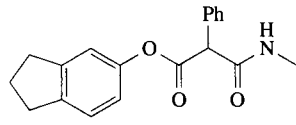
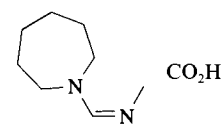
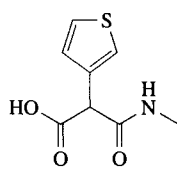
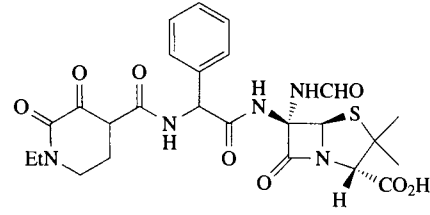
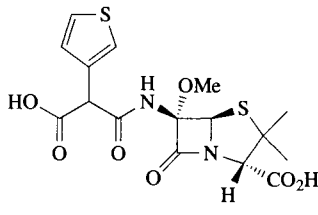
(v) Group 5 penicillins: penicillins active against *P. aeruginosa*

This group consists of carboxypenicillins and acylureidopenicillins (see Table 5). The antibacterial activity of the carboxypenicillins combines the Gram-negative spectrum of ampicillin with activity against *P. aeruginosa*, *Enterobacter*, *Providentia*, and *Morganella*. These compounds are less active than ampicillin against Gram-positive bacteria and have no activity against strains of staphylococci <88MI 120-04>. Ticarcillin in combination with clavulanic acid enhances the activity of ticarcillin to include up to 80% of ticarcillin resistant strains of *Enterobacteriaceae* and all β -lactamase producing strains of *S. aureus*, *H. influenzae*, and bacteroides. The acylureidopenicillins have somewhat better activity against *P. aeruginosa* than the carboxypenicillins, but are susceptible towards many β -lactamases.

(vi) Group 6 penicillins: β -lactamase resistant penicillins

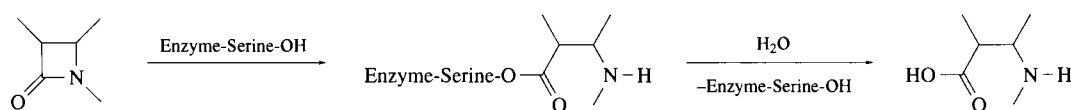
A better understanding of the structure activity relationship of penicillins has led to the development of temocillin and formidacillin (see Table 5). Temocillin is more active than existing carboxypenicillins against most Gram-negative bacteria. Formidacillin is currently under investigation. *In vitro* it is highly active against the *Enterobacteriaceae* family and is more active against *P. aeruginosa* than piperacillin. It is inactive against Gram-positive organisms.

Table 5 Group 4, 5, and 6 penicillins.

					
R^1	R^2	Generic name	R^1	R^2	Generic name
Group 4 penicillins			Group 5 penicillins		
	CO_2H $\text{CO}_2\text{CH}(\text{Me})\text{OCO}_2\text{Et}$ $\text{CO}_2\text{CH}_2\text{OCO}_2\text{Bu}^t$	Ampicillin Bacampicillin Pivampicillin		CO_2H	Apacillin
		Talampicillin			
	CO_2H	Metacillin		CO_2H	Azlocillin
				CO_2H	Mezlocillin
	CO_2H	Metampicillin		CO_2H	Piperacillin
	CO_2H	Amoxicillin		CO_2H	Carbenicillin
	CO_2H	Ciclacillin		CO_2H	Carindacillin
	CO_2H	Mecillinam		CO_2H	Ticarcillin
Group 6 penicillins					
		Formidacillin			Temocillin

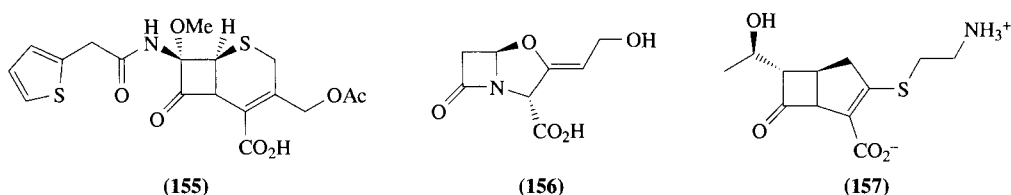
1.20.7.2 β -Lactamase Inhibitors

As has been outlined above, the intrinsic or acquired resistance of several organisms against penicillins and other β -lactam antibiotics is a serious problem in the treatment of bacterial infections. Production of β -lactamases by bacteria, resulting in cleavage of the β -lactam ring to inactive penicillonic acid derivatives is one of the most important mechanisms. It has been suggested that the four types of β -lactamases (A, C, D, and serine β -lactamases), together with bacterial cell wall DD-peptidases, form a family of β -lactam recognizing enzymes that have similar active site structures <89MI 120-05, 86NAT378, 86SCI1429, 88BJ(250)313>. It is believed that a catalytic double displacement mechanism is operative, involving an acyl-enzyme intermediate (Scheme 44) in which the active site nucleophile is a serine hydroxyl group, finally resulting in cleavage of the β -lactam ring. A review has appeared in which the chemical mechanisms responsible for β -lactamase inhibition are discussed <B-92MI 120-08>.



Scheme 44

From earlier studies it appeared that some semisynthetic penicillins, resistant to β -lactamases, potentiated the effects of β -lactamase susceptible penicillins <64NAT867, 64NAT868>. This effect was ascribed to inhibition of the β -lactamase enzymes. Based on these observations extensive research has been carried out on β -lactamase inhibitors. Between 1970 and 1980 it was discovered that cefoxitin (**155**), clavulanic acid (**156**), thienamycin (**157**), and penicillanic acid sulfone (see Scheme 45) are very effective β -lactamase inhibitors. Nowadays, much more compounds are known to be very efficient β -lactamase inhibitors, although almost all are β -lactam based.

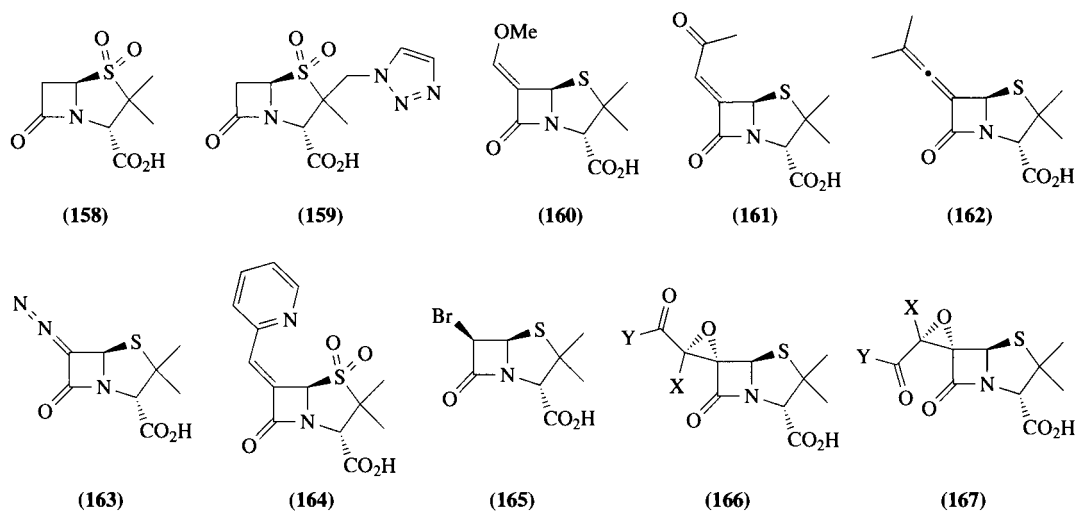


In Scheme 45 the known β -lactamase inhibitors comprising the penicillin skeleton are summarized. As has been mentioned before, penicillanic acid sulfone (sulbactam) (**158**) was the first compound of this family that was discovered. It appeared that the activity towards β -lactamase inhibition could be tuned by varying C(6) <B-85MI 120-06, 89T941> or C(2) substituents <88JAN579>. These investigations resulted in the development of the clinically important β -lactamase inhibitor tazobactam (**159**). It also appeared that some 6-*exo*-methylene penicillins are efficient β -lactamase inhibitors, for example 6-[(*Z*)-methoxymethylene]penicillanic acid (**160**) <84B5839>, acetylmethylene penicillanic acid (**161**) <82JAN1578> and 6-vinylidenepenam (**162**) <88TL5053>. The diazotized 6- β -penicillanic acid (**163**) also exhibits anti β -lactamase activity <83BBA(745)292>.

A combination of a substituted *exo*-methylene penam and a sulfone is found in compound (**164**), which is an excellent inhibitor of both class A and C β -lactamases <87JAN803>. The 6- β -halopenicillanic acids are also efficient β -lactamase inhibitors, of which 6- β -bromopenicillanic acid (**165**) was the first one discovered <78PNA(75)4145, 79BJ(177)365>. The 6-iodo analogue has a comparable activity, but the 6-chloro derivative is less active <80JAN451, 81MI 120-04>. More recent inhibitors are the 6-spiro-epoxides (**166**) and (**167**), in which X and Y are halogens or OMe or NHR groups <88CC274>. Details of the inhibition of *B. cereus* β -lactamase of both (**166**) and (**167**), in which Y = NHPH, have been reported <88CC1610, 91BJ(276)801>.

1.20.7.3 Human Leukocyte Elastase Inhibitors

It is believed that human leukocyte elastase (HLE), a serine protease present in the azurophilic granules of polymorphonuclear leukocytes, is responsible for tissue destruction diseases such as pulmonary emphysema, cystic fibrosis, and rheumatoid arthritis <87MI 120-04>. It has been suggested



Scheme 45

that inhibition of HLE may be therapeutically effective against these diseases. It has been found that several compounds comprising a β -lactam fragment, for example modified cephalosporin antibiotics <86NAT192, 92BMC2259, 92BMC2265>, penem derivatives <92BMC2277>, and monocyclic β -lactams <92BMC2295>, are effective HLE inhibitors. A series of penicillin based inhibitors of HLE have been reported <92BMC2283, 92BMC2289>.

1.20.7.4 Other Applications of Penicillins

An important application of penicillins, in particularly 6-aminopenicillanic acid, is their use as basic starting material for other semisynthetic penicillins and their conversion to cephalosporins. These topics are discussed elsewhere in this chapter. It has been shown that the β -lactam skeleton, especially in monocyclic β -lactams, is a valuable synthon providing chiral intermediates, for example α -aminoacids, oligopeptides, polyamines, polyaminoalcohols, and polyamino ethers <B-92MI 120-09>. It is rather surprising that, although 6-aminopenicillanic acid is readily available on a large scale and relatively cheap, to our knowledge such applications have not yet been exploited.

1.20.8 CONCLUSION

Although penicillins are the longest known β -lactam antibiotics, this class of compounds still finds widespread application against infectious diseases. Also from a scientific point of view, penicillins remain one of the main topics studied in β -lactam chemistry. In particular, the details of the mechanism of the biosynthesis of penicillins are still not very well known and will continue to attract a lot of attention. Investigations into the chemistry of the penicillins nowadays are centered around the conversion of penicillins obtained by a fermentation process into useful intermediates for other β -lactam based antibiotics and β -lactamase inhibitors. Most probably this development will lead to new concepts and methodologies for penicillin and other heterocyclic chemistry in the forthcoming years.

1.21

Other Fused Azetidines, Azetines, and Azetes

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1.21.1 INTRODUCTION

1.21.1.1 Historical Perspectives

Researches continue into the synthesis, reactions, and applications of bicyclic compounds having a four-membered ring containing a nitrogen atom fused to another ring. In the vast majority of examples the bridgehead atoms are at vicinal positions of both rings. Much of this activity is motivated by the requirement to provide an armory for physicians to use in the treatment of bacterial infections and the commercial interest in providing those materials. A great deal of effort is therefore devoted to the chemistry of compounds containing the β -lactam (azetidin-2-one) system. The "classical" β -lactam antibiotics, cephalosporins, and penicillin, are discussed in Chapters 1.19 and 1.20, respectively. These compounds are a reminder that it was not long ago that a sulfur atom in the second ring was thought to be a requirement for useful biological activity in bicyclic β -lactams. The realization that this is not the case opened up new avenues for discovery and development, and much of this chapter is devoted to description of that work. It is difficult to contemplate a world without the future development of novel effective antibiotics and a better understanding and acceptance of the control of their use.

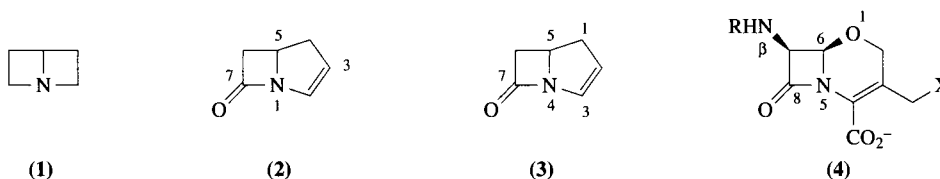
In addition to the β -lactam antibiotics, the scope of the chapter includes the wide range of fused systems having a four-membered ring containing a nitrogen atom. Since the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) there has been steady progress in this area largely in terms of the increased range of ring system types. The majority of compounds discussed have a bridgehead nitrogen atom, but there is a substantial entry for compounds having only carbon atoms at the bridgehead. These two types form a broad division within sections of the chapter. Most of the compounds described are bicyclic, but some more complex systems are also mentioned.

Useful reviews include those in the *Annual Reports on Medicinal Chemistry* (for example, Walsh <88MI 121-01> gives 172 references relating to β -lactam antibiotics) and the Special Publications produced by the Royal Society of Chemistry, London, on β -lactam antibiotics <B-85MI 121-01, B-89MI 121-01> and anti-infective agents <B-93MI 121-01>. Several books are devoted to β -lactam chemistry and biosynthesis <B-82MI 121-01, B-82MI 121-02, B-82MI 121-03, B-90MI 121-01, B-92MI 121-01, B-93MI 121-02>. A part of *Bioorganic and Medicinal Chemistry Letters* was devoted to β -lactam chemistry <93BMC2159>. More specialized reviews on carbapenems <87H(25)729>, thienamycin <90PAC1293>, imipenem <87MI 121-01>, PS-5 and PS-6 carbapenems and related compounds <B-90MI 121-02>, clavulanic acid <B-82MI 121-04, B-85MI 121-02>, oxacephems <91YZ77>, and moxalactam <81MI 121-01> are available. A discussion of bicyclic systems containing 1,3-bridged β -lactams is available <B-89MI 121-02>.

1.21.1.2 Nomenclature

The nomenclature of these bicyclic ring systems can lead to some problems. *Chemical Abstracts* adopts the systematic scheme, in which the total number of ring atoms is counted and the cycloalkane with the same number of carbon atoms is taken as the root of the name. A bridgehead nitrogen atom is assigned number 1 and the ring system is numbered by first including the atoms of the larger ring; for example, (1) is 1-azabicyclo[2.2.0]hexane and (2) is 1-azabicyclo[3.2.0]hept-2-en-7-one. However, there is some possible confusion for compounds containing five- or six-membered rings because workers in the antibiotics field tend to use nomenclature derived from penicillin and cephalosporin naming and numbering systems. In this way (2) becomes carbapenem and is numbered as in (3). Similarly, (4) is a 1-oxacephem derivative. The saturated bicyclic β -lactams analogous to (3) and (4) are carbapenams and 1-oxacephams, respectively. Both systems of nomenclature are used in this account.

The known fused-ring azetines and azetes are many fewer in number than the fused-ring azetidines.



1.21.2 THEORETICAL METHODS

The effect of the β -lactam on the reaction of the alkenic bond in (5) and (6) with nitrenes has been studied both experimentally and by *ab initio* MO calculations <85T1329>. Evidence for the formation of benzoazetine (7) in the flash vacuum thermolysis (FVT) of *o*-aminobenzyl alcohol or the corresponding amine at 923–1073 K (temperature control is crucial) has been provided by a comparison of the results from photoelectron spectroscopy of the pyrolysate and MNDO calculations (see Section 1.21.3.5.) <92TL5753>. The application of AM1 and PM3 methods to the conformational analysis of molecules containing a basic nitrogen atom is not recommended <93AJC547>.



Theoretical methods have been used to study the thermal isomerization of aza- and diaza-bicyclo[2.2.0]hexadienes <80MI 121-01> and the relative stabilities of a series of bisdehydroxyridines <77CC539>.

Theoretical methods have been invoked to probe the potential of bicyclic structures as novel β -lactamase inhibitors (β -lactamases are enzymes which open the β -lactam ring and inactivate antibiotics) <91JST(83)237>. Optical rotatory properties of (5*S*)-1-azabicyclo[3.2.0]heptan-7-one have been calculated using Hückel and CNDO wave functions <79T1499>. An MO-LCAO calculation of electron density in β -lactam antibiotics has been made <83MI 121-02> (see also Section 1.21.3.1).

1.21.3 EXPERIMENTAL STRUCTURAL METHODS

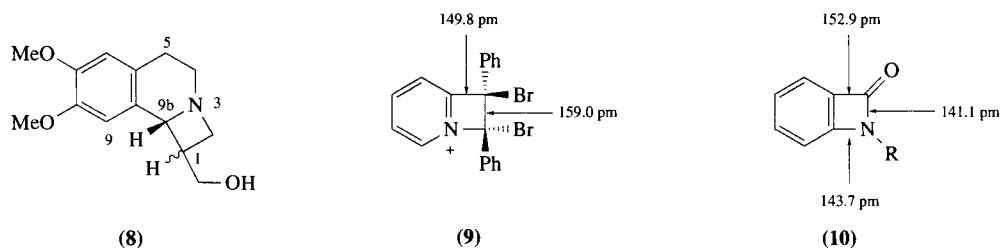
1.21.3.1 X-Ray Diffraction

X-Ray crystallographic methods have become more widely available and the technique has been usefully applied to determine the stereochemistry of bicyclic azetidines and β -lactams in the crystal state. Some of the data have been reviewed <B-82MI 121-02, B-82MI 121-05>. The crystal structure of

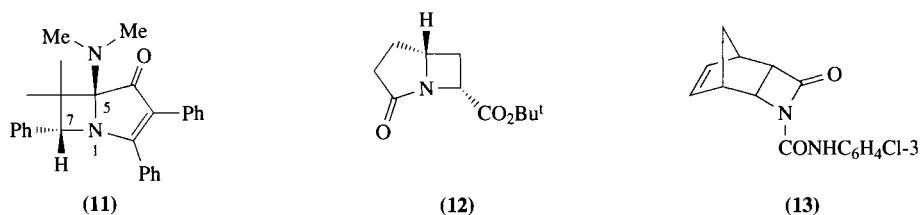
both *cis* and *trans* isomers of (8) are known and show that the N atom has pronounced pyramidality <86T5139>, but the 1,2-dibromo-1,2-diphenyl-1,2-dihydroazeto[1,2-*a*]pyridinium salt (9) is nearly coplanar, with the four-membered ring having one long bond <83JCS(P2)403>.

Few studies are reported for bicyclic azetines, but a palladium complex of 3,5-bis(trifluoromethyl)-2,4,6-trimethyl-1-azabicyclo[2.2.0]hexa-2,5-diene showed each four-membered ring to be planar <76CPB2219>.

The benzoazetidinone (10; R = 1-adamantyl) also has a planar nucleus within experimental error, indicating an sp^2 hybridized nitrogen atom. The x-ray crystallographic data show a higher bond order for the bonds *exo* to or opposite to the four-membered ring compared with other bonds in the benzo nucleus. The differences in bond lengths are less than those found in biphenylene but are in general accord with theoretical predictions <84JOC3367>.



The crystal structure of (11) shows a sum of the bond angles around the bridgehead nitrogen atom of 317.7° , i.e., a highly folded, butterfly-like shape <83HCA1366>. The structures of (12) and its stereoisomers have been confirmed by x-ray diffraction studies <85CC194, 86T4879>. A crystal of (13) has an almost planar azetidinone ring, while the norbornene skeleton has a six-membered ring of almost perfect boat shape <87T1921>.

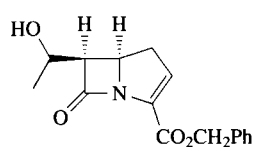


At this point it is appropriate to make some comments about the perceived importance of shape and interatomic distance in the structure-activity relationship (SAR) for the β -lactam antibiotics, which correlates with their biological activity. One such parameter that is of considerable interest is the perpendicular distance h of the nitrogen atom from the plane formed by its immediate substituent atoms, i.e., the pyramidal nature of the bonds from the nitrogen atom. Another measure of this is the sum of the angles between the bonds. In a monocyclic β -lactam $h \approx 0$, whereas in benzylpenicillin $h = 0.4 \text{ \AA}$ and the sum of the angles is 337° . X-Ray diffraction studies play an essential part in determining such parameters. However, the exact significance of these factors in determining the antibacterial activity is open to question <B-92MI 121-02> and other factors, such as the distance between the oxygen of the lactam carbonyl group and the carbon atom of the carboxylate function <83JMC259>, may be of more significance.

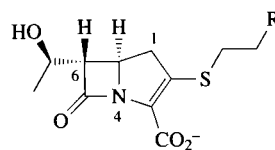
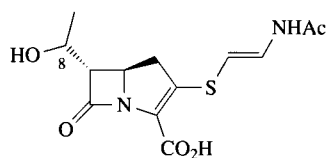
The bond angles and bond lengths for 2,3- <90JCS(P1)1541> and 3,6-disubstituted <92MI 121-04>, 2,3,6-trisubstituted <90JCS(P1)1541>, and 1,2,3,6-tetrasubstituted <89CC821> carbapenams are available. In the carbapenem series, the *cis* isomer (14) has the (5*RS*,6*SR*) stereochemistry as shown by x-ray analysis of crystals of the adduct of thiophenol to the double bond <85JCS(P1)2219>. Thienamycin (15) is an important carbapenem and the stereochemistry of its 1-methyl derivatives <85TL587> and the methyl ester of *N*-acetylthienamycin has been established <78JA6491>. Imipenem (16) is clinically important and is the *N*-formimidoyl derivative of thienamycin. In the crystal state the formimidoyl group has the (*Z*) configuration, but in solution rotational isomers exist <89JOC653>.

The x-ray crystallography of the *p*-nitrobenzyl ester of epithienamycin D (olivanic acid, MM22383) (17) confirmed the *trans* β -lactam substitution pattern and showed C-8 to have the (*S*) configuration, the latter being different from thienamycin (15). The absolute configurations of other epithienamycins (olivanic acids) have been reported <81JAN637>.

The double bond in clavulanic acid (18) is known to have (*Z*) configuration <84JCS(P1)635> and



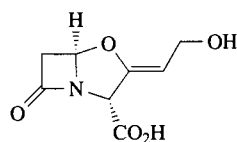
(14)

(15) R = NH₂(16) R = NH—CH=NH₂

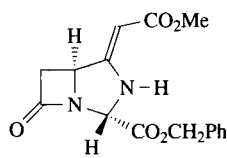
(17)

two crystal structures for antibacterially active 1-oxapenam-3-carboxylates carrying saturated 2-alkyl substituents are established by x-ray techniques <92ZN(B)1037>.

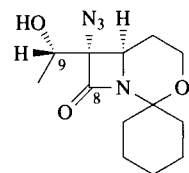
As a general rule, the addition of ketenes to cyclic (*E*)-imines leads to *cis* stereochemistry in the resultant fused-ring β -lactam and this has been explained by a nonconcerted [2 + 2] cycloaddition mechanism (<91HCA767>, but see also <B-93MI 121-03>). X-Ray diffraction studies show that 1-benzoyl-5-methylthio-6-methoxy-1-azapenam prepared by cycloaddition of a ketene is the *cis* isomer and has the (5*R*,6*S*) conformation <92JST(271)191>. The synthetic 2-azapenam (**19**) has (*Z*) stereochemistry <86JCS(P1)1077>. Similar methods show that sodium borohydride reduction of (6*RS*,7*SR*)-7-acetyl-7-azido-8-oxo-3-oxa-1-azacyclo[4.2.0]octane-2-spirocyclohexane gives the (6*RS*,7*SR*,9*SR*)-7-azido-7-(1-hydroxyethyl) derivative (**20**) <92JCS(P1)1305>.



(18)

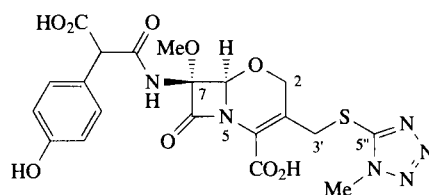


(19)



(20)

The torsional angles C(4)=C(3)—C(3')—S and C(3)—C(3')—S—C(5'') in moxalactam (latamoxef, 6059-S or LY127935) (**21**) and related compounds are approximately $\pm 90^\circ$ <84JAN227>.

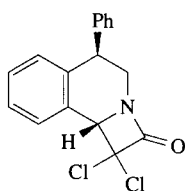


(21)

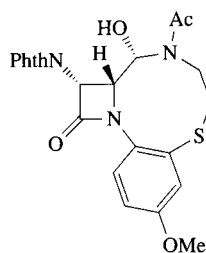
A 1-oxacephem having a C₂H₄ bridge across positions 2 and 7, a thienamycin-type 3-substituent, and a distortion ($h = 0.4 \text{ \AA}$) similar to that in penicillin shows only very weak antibacterial activity <90SL681>. Another tricyclic β -lactam having both a carboxylate carbon-carbonyl group oxygen distance and a torsional angle of the carboxylate group relative to the lactam ring similar to those in the cephalosporins <B-89MI 121-03> is inactive <92JOC2641>. A crystal structure for a 1,3,4-triaza[4.2.0]octan-2,4-dicarboxylate is known <84CC1289>.

X-Ray crystal structures for the tricyclic β -lactams (**22**) <93H(35)1075> and (**23**) <93T7803> are available; the latter on crystallization from dimethylformamide (DMF) gave single crystals containing (**23**) and DMF in the ratio 1 : 1 and these were used for the measurements. Crystal structures

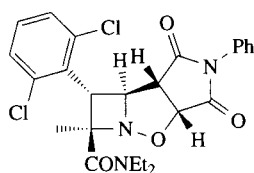
for **(24)** <88RTC142> and **(25)** <92H(33)179> having a bridgehead nitrogen atom in a fused azetidine nucleus are established.



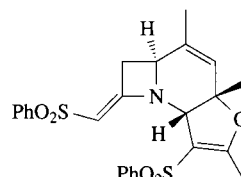
(22)



(23)

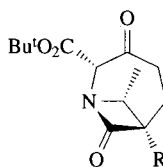


(24)



(25)

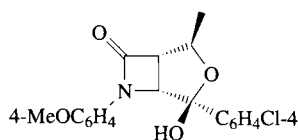
The x-ray crystal structure of the stable “anti-Bredt” compound **(26)**; R = 2-(1,6-dibromonaphthoxy)ethyl) showed the N—CO bond length and the sum of the angles around the nitrogen atom to be similar to those of carbapenems <89JA1073>.



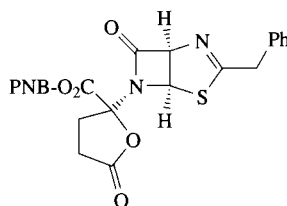
(26)

Compounds containing a fused β -lactam ring but without a bridgehead nitrogen atom for which the crystal structure data are known include **(27)** <90SL431> and the thiazoline **(28)** <91MI 121-01>. The reaction of a thiazoline similar to **(28)**, but with a different *N*-substituent, with ethyl diazoacetate in the presence of dimethyl fumarate, is shown to give the tricyclic β -lactam **(29)** by x-ray crystallography <82JCS(P1)2169>.

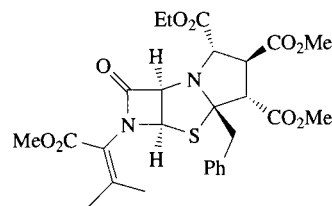
References to single-crystal structure determinations of selected compounds are given in the Tables in Section 1.21.11.



(27)



(28)

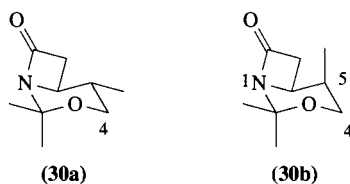


(29)

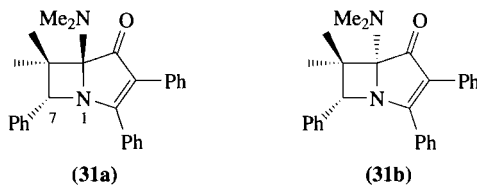
1.21.3.2 NMR Studies

In the 1980s and 1990s reports of the preparation of novel compounds have included a description of the ^1H NMR spectrum as part of the evidence for the molecular structure. Therefore, information about the proton spectra for the compounds mentioned in this chapter is generally contained in the references quoted here or in references therein. Section 1.21.11 of this chapter contains tables giving references to the preparations of a wide range of fused-ring systems containing the azetine, azetidine,

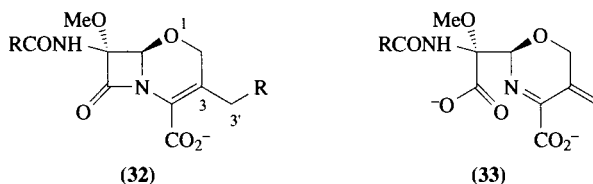
or azetidinone nucleus. In many cases, the ^1H NMR spectrum is discussed in some detail in this chapter in order to utilize differences in the coupling of *cis*- or *trans*-related vicinal protons to establish the relative stereochemistry. Thus, in the case of a structure such as (8), either as the alcohol or a simple derivative, when 1-H or 9b-H are *cis* the coupling constant $J_{1,9b}$ is in the range 7.5–8 Hz, while for the *trans* isomer the value is 2.8–3.5 Hz $\langle 87\text{T1887} \rangle$. In the more complex case of the two isomers (30a) and (30b), only the former shows the large (≈ 12 Hz) vicinal axial–axial coupling between the 4-H and 5-H, while (30b) has $J_{4,5}$ in the range 2–3 Hz owing to the coupling of axial–equatorial and equatorial–equatorial protons $\langle 85\text{TL583} \rangle$. Examples of the use of ^1H NMR spectra in a similar way include $\langle 85\text{T1721}, 87\text{CJC175}, 87\text{T1921}, 89\text{MI 121-04}, 92\text{TL4283} \rangle$. In some cases, the use of lanthanide shift reagents is helpful $\langle 86\text{JCS(P1)973} \rangle$.



Deductions made from consideration of chemical shifts and coupling constants may be reinforced by results from nuclear Overhauser effects (NOE); that is, irradiation at the resonance frequency of one atom or group allows the identification of other atoms or groups in close proximity $\langle 84\text{CJC2440}, 85\text{HCA1359}, 86\text{JCS(P1)973}, 88\text{CJC279}, 89\text{MRC872}, 93\text{H(36)995} \rangle$. A useful shift rule, the benzhydryl shift, for the determination of the configuration of 3-substituents on 1-oxacephem is available $\langle 87\text{H(25)321} \rangle$. Sometimes the effects on the chemical shift of a proton due to the spatial proximity of a heteroatom can be utilized in the assignment of a configuration $\langle 89\text{CPB2298} \rangle$. In these cases it is very desirable to have ^1H NMR data for both isomers. Thus, treatment of (31a) in ether with silica (chromatography) gives an isomeric product. The ^{13}C and ^1H NMR spectra are very similar except for some differences in the δ values for the protons of the 6-methyl substituents, but most marked is the difference in δ for 7-H. For (31a) 7-H has δ 5.01 ppm and the isomeric product (31b) has 7-H at δ 3.88 ppm $\langle 83\text{HCA1366} \rangle$. Sometimes the phenyl group anisotropy can be utilized $\langle 88\text{CJC1546} \rangle$.

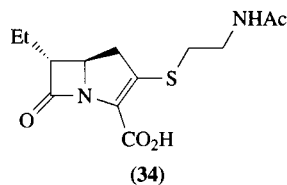


^1H NMR spectroscopy can be used to monitor reaction processes and has been employed to study the opening in alkaline solution of the four-membered ring of oxacephems carrying various substituents at C-3' (32). It is concluded that the leaving group R is not involved in the nucleophilic attack on the β -lactam, though (33) is the product of the reaction $\langle 87\text{JMC523} \rangle$. Earlier studies using ^{13}C NMR and IR spectroscopy on 1-oxa- and 1-thiacephems show the effect of the 1-heteroatom to be significant $\langle 82\text{JAN1724} \rangle$.

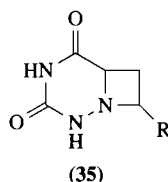


The β -lactam carbonyl group usually shows a signal between 160 ppm and 167 ppm in the ^{13}C NMR spectrum and the resonance frequency of that carbon atom is lower in penicillins than in either the Δ^2 - or Δ^3 -cephalosporins, which have similar chemical shifts. Interestingly, the Δ^2 -cephalosporin series is biologically inactive, but there have been attempts to correlate ^{13}C chemical shifts of the carbonyl carbon atom of other β -lactams with biological activity $\langle \text{B-92MI 121-02} \rangle$. Some examples of the use of ^{13}C NMR in the determination of the molecular structure of bicyclic β -lactams $\langle 84\text{CJC2440}, 85\text{HCA1359}, 87\text{H(25)321}, 87\text{T1921}, 89\text{MI 121-04}, 89\text{MRC872} \rangle$ and fused azetidines $\langle 83\text{HCA1366}, 88\text{RTC142} \rangle$ are available. A comparison of the chemical shifts of the C-1 and C-2 atoms has been

used to assign the *cis* or *trans* geometry to the isomers of (8). This is in line with other evidence and again points to the advantages of having comparable data from all the isomers under consideration <86T5139>. The ^{13}C NMR spectral data of naturally occurring carbapenems (including thienamycin (15), PS-5 (34), and some olivanic acids) have been tabulated and discussed <B-82MI 121-06>.

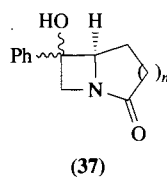
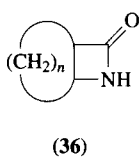


There are far fewer ^{15}N NMR spectra available than ^{13}C spectra. The ^{15}N resonance of most fused-ring β -lactams is generally upfield (≈ 30 Hz) of the value for the planar Δ^2 -cephem resonance, whereas increased conjugation between the amide N atom and carbonyl group is expected to induce a downfield shift <76JOC582>. A few ^{15}N NMR spectra are available for the fused azetidines (35; R = CO_2Me , Ac, CN) <92MI 121-05>.



1.21.3.3 Mass Spectroscopy

The electron impact (EI) mass spectra of a series of fused-ring azetidines <79JCS(P1)1770> and the corresponding azetidinones (36; $n = 3, 4, 5, 6$) are available <86OMS(21)55>. The azetidinones yield a cycloalkene ion as the major fragment by loss of HNCO . The ammonia chemical ionization (CI) spectra of the azetidinones show $(M+1)^+$, $(M+1+\text{NH}_3)^+$ and $(2M+1)^+$ as the major ions <86OMS(21)55>. Hydroxide/negative CI mass spectra of separate isomers of (37; $n = 1, 2, 3$) show that deprotonation of the OH group occurs and that the decomposition of the ion takes place in the second field-free region of the reversed geometry instrument used and is dependent on the stereochemistry <85OMS(20)770>. The mass spectra of some fused-ring azetidines are considered by Porter <B-85MI 121-03>.

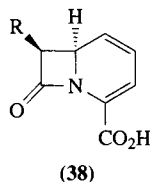


EI tandem mass spectrometry is suggested as a means of class analysis of the β -lactam antibiotics because the major fragment arises from cleavage of the β -lactam ring <83MI 121-01>. A comparison is made of the merits of fast-atom bombardment, field desorption, and desorption-CI techniques when applied to some β -lactam antibiotics <83IJM431>. Studies of EI mass spectra of l-oxacephems <83MI 121-03> and some tricyclic β -lactams derived from benzodiazepines are reported <89OMS(24)276>.

1.21.3.4 Infrared Spectra

These spectra are measured for samples as KBr disks, Nujol mulls, or in solution, and the physical state of the compound under investigation has an effect on the absorption frequencies observed. However, the carbonyl stretching vibration (cm^{-1}) for monocyclic β -lactams occurs in the region between 1730 and 1760, for Δ^3 -cephalosporins in the range 1760–1790, and for penicillins between

1770 and 1790 $\langle$ B-92MI 121-02 $\rangle$. The carbonyl stretching frequency of the β -lactam system in the 1-carbapenem series of epithienamycins (olivanic acids) is in the range 1750–1770 cm^{-1} $\langle$ 77JAN770, 79JAN961 $\rangle$. The compounds (**38**) have $\text{C}=\text{O}$ stretching frequencies equal to or higher than those of the corresponding 1-carbacephems $\langle$ 89CPB275 $\rangle$.



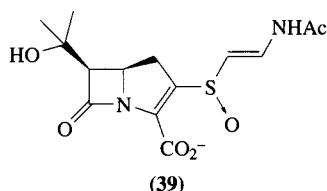
Again attempts have been made to correlate the $\text{C}=\text{O}$ stretching frequency of the antibiotics with their biological activity $\langle$ 82JAN1729, 90SL684 $\rangle$. In the 1,3-bridged β -lactam (**26**; $\text{R} = 2$ -(1,6-dibromonaphthoxy)ethyl) the β -lactam $\text{C}=\text{O}$ stretching frequency is 1785 cm^{-1} , very similar to that of the carbapenems $\langle$ 89JA1073 $\rangle$.

Carbonyl stretching frequencies for simple bicyclic systems containing β -lactam rings fused at the $\text{C}(3)\text{—C}(4)$ bond to cyclobutene $\langle$ 64JA950 $\rangle$, cyclopentene $\langle$ 77JCS(P1)874 $\rangle$, cyclohexane $\langle$ 71TL3721 $\rangle$, cyclononane $\langle$ 73JA4647 $\rangle$, and cyclododecane rings $\langle$ 76JOC3583 $\rangle$ have been reported.

1.21.3.5 Photoelectron Spectra and Circular Dichroism

Photoelectron spectra for (**7**) have been obtained and these correlated with the results from MNDO calculations (see Section 1.21.2). Benzoazetidine (**7**) shows a band in the PE spectrum at 8.3 eV corresponding to the ionization of the electron of the MO combination $\pi_{\text{C}=\text{C}}$ and $n_{\text{N}}\pi$ orbitals. The second band at 9.6 eV is associated with $\pi_{\text{C}=\text{C}}$ orbitals of the aromatic ring, and the band at 10.6 eV is due to the ionization of the $n_{\text{N}}\sigma$ and third π -orbitals $\langle$ 92TL5753 $\rangle$.

The UV and CD spectra of the sulfoxide stereoisomers of (**39**) have been studied. The naturally occurring compound C-19393 has the (*R*) configuration at the sulfoxide and showed a Cotton effect of opposite sign at 260–275 nm from that of the synthetic isomeric sulfoxide. The absorption and Cotton effects may be produced by the chromophore $\text{CHS}(\text{O})\text{CH}=\text{CHNH}$. Compounds produced by reduction of the exocyclic double bond of the natural and synthetic sulfoxides gave a tertiary Cotton effect at 280–300 nm due to the $\text{CH}_2\text{S}(\text{O})\text{C}=\text{CCO}_2^-$ chromophore $\langle$ 83T75 $\rangle$.



Circular dichroism has been used to establish the absolute configuration of the β -lactam ring of certain epithienamycins (olivanic acids) $\langle$ 81JAN637 $\rangle$. The UV $\langle$ 79T1499 $\rangle$ and CD studies $\langle$ 78JOC4438, 79T1499 $\rangle$ of (*5S*)-1-azabicyclo[3.2.0]heptan-7-one have been reported $\langle$ 78JOC4438 $\rangle$.

1.21.4 THERMODYNAMIC ASPECTS

1.21.4.1 Chromatography

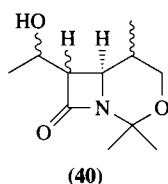
HPLC separation of sulfated olivanic acids is difficult, but reversed-phase procedures on C_{18} silica give a partial resolution. Improved performance is obtained by incorporating ion-pairing agents in the moving phase or by using bonded β -cyclodextrins as the stationary phase $\langle$ B-90MI 121-03 $\rangle$. The degradation of imipenem (**16**) in aqueous solution is studied using HPLC and UV detection and Arrhenius activation energies are derived $\langle$ 91CPB831 $\rangle$. Complex decomposition reaction schemes for imipenem (**16**) have been devised using HPLC analysis and mathematical modeling $\langle$ 90JPS732 $\rangle$.

Clavulanic acid (**18**) is analyzed efficiently using a solid-phase extraction procedure, derivatization,

and a microbore HPLC system fitted with a UV detector <89MI 121-05>. HPLC can be used to study the degradation of the antibiotic in aqueous alkaline solution <83CPB1812, 85CPB218>.

Cephem antibiotics can be analyzed in human blood or urine samples by HPLC <91JC129>. HPLC and thermal gravimetric analysis studies have shown that ready solid-state decarboxylation of the diammonium salt of the 1-oxacephem antibiotic, moxalactam (**21**), occurs after the crystals have lost water of crystallization. In the crystal state, the carboxylate group in the chain is not co-planar with the amide chain and decarboxylation does not occur, but the barrier to rotation towards planarity is relatively small after dehydration of the crystals has occurred <87MI 121-02>. The degradation of this antibiotic in solution has been studied by HPLC <84JPS369, 88MI 121-02>.

The eight isomers of the key synthetic intermediate (**40**) in the synthesis of 1-methylcarbapenem antibiotics were obtained using either HPLC or fractional crystallization of a derivative at some stage in the procedure <85TL583>.



Both GLC and HPLC have been used for the separation of fused-ring β -lactams, but the former suffers from the disadvantage that derivatization is necessary. UV detection has been used in applications of HPLC to these compounds, but either pre- or post-column derivatization with a fluorescent label has also been employed. HPLC methods for the separation of β -lactam antibiotics have been reviewed <85JC361, 89MI 121-06, 90JC509>. An analytical procedure using packed capillary column liquid chromatography with electrospray MS detection has been given <93JC45>.

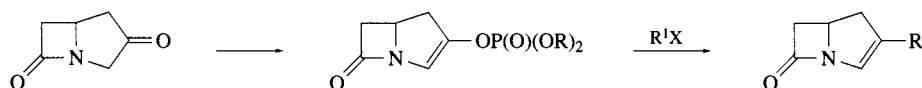
1.21.4.2 Aromaticity

The compounds described in this chapter do not have aromatic character.

1.21.4.3 Conformation and Tautomerism

Some studies of the conformation of fused-ring azetidines have been referred to in discussion of the uses of x-ray crystallography (Section 1.21.3.1) and NMR spectroscopy (Section 1.21.3.2). The conformational flexibility of the methyltetrazolylthiomethyl side chain of antibiotics like (**21**) has been analyzed using x-ray crystallographic data and computer graphics studies <84JAN227>. The conformations of carbapenems, carbacephems, 1-oxapenems, and 1-oxacephems have been studied by *ab initio* calculations, and the conformations and charge distributions have been related to the β -lactamase inhibitory activity <92MI 121-06>.

Perhaps the most significant tautomeric equilibrium in the series of compounds considered here occurs in the 1-carba-2-oxopenam series where the enol tautomer is trapped as a derivative (often a phosphate) (Scheme 1) and then replaced to give 2-substituted 1-carbapenems (see Section 1.21.6.6 for examples).



Scheme 1

1.21.5 REACTIVITY OF FULLY CONJUGATED RINGS

No examples of fully conjugated bicyclic systems have been found.

1.21.6 REACTIVITY OF NONCONJUGATED RINGS

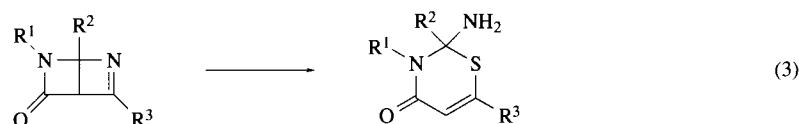
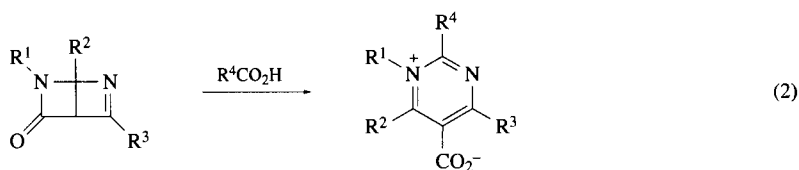
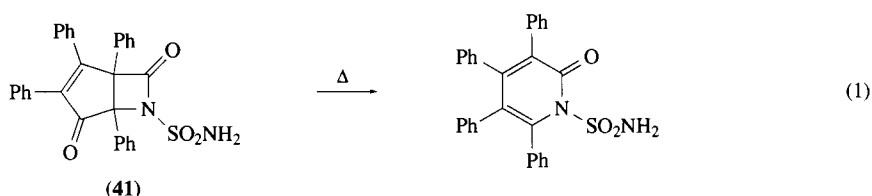
1.21.6.1 Thermal and Photochemical Reactions

The 1-azabicyclo[2.2.0]hexane (**1**) undergoes thermolysis of the N(1)—C(4) and C(1)—C(2) bonds at 80 °C. The more stable 2-azabicyclo[2.2.0]hex-5-ene undergoes thermal cleavage of the C(1)—C(4) bond to give 1,2-dihydropyridines <78JOC944, 79JA6677>.

Thermolysis of (**41**) (obtained by [2 + 2] cycloaddition from tetraphenylcyclopentadienone) gives a pentasubstituted 2-pyridone (Equation (1)) <84IJC(B)1046>.

Irradiation or thermal reactions of Dewar 4-pyrimidinones in aliphatic carboxylic acids (including $R^4 = H$) give the 1,2,4,6-tetraalkylpyrimidinium 5-carboxylates (Equation (2)). The carboxylic acid carbon atom of the aliphatic acid is incorporated into the pyrimidine nucleus at position 2, as indicated by ^{13}C labeling studies. A mechanism involving azetidinyll and acyl cations is proposed <87JOC2455>.

However, Dewar pyrimidinones in water undergo reversible photochemical reactions, but a 1,3-thiazin-4-one is formed in the presence of hydrogen sulfide and when the solvent is acetonitrile (Equation (3)) <89JCS(P1)1231>.

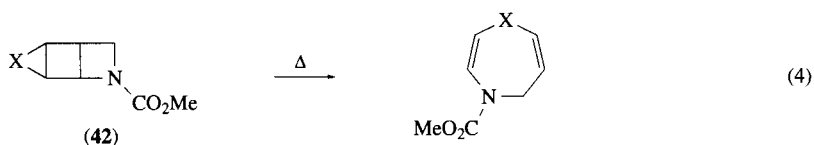


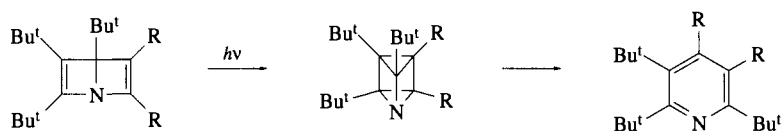
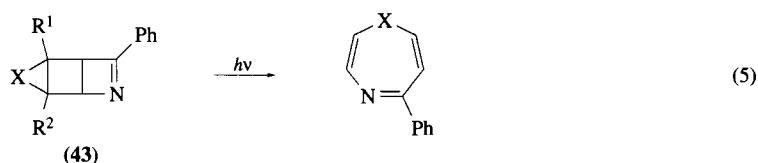
1.21.6.2 Isomerization

Thermolysis of the tricyclic azetidines (**42**; X = O, NCO₂Et, S or CH₂) in solution gives the seven-membered ring heterocycles in high yield (Equation (4)) <83CC941>.

Photochemical valence isomerization of the tricycloheptene system (**43**; X = O or NCO₂Et) provides the 1,4-oxazepines or 1,4-diazepines, respectively, in high yield (Equation (5)) <86CC1188, 87CPB3166>.

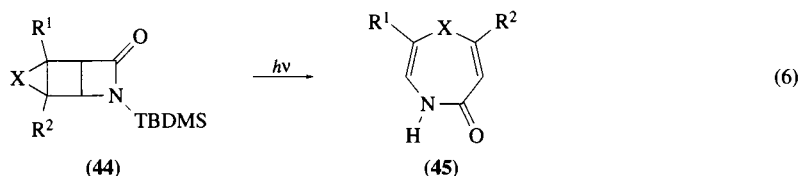
Photolysis of fully substituted Dewar pyridine carrying 2,3,4-tri(*t*-butyl) substituents produces azaprismane, which, on standing or further irradiation, gives the 2,3,6-tri(*t*-butyl)-4,5-disubstituted pyridine (Scheme 2) <89T3115>.





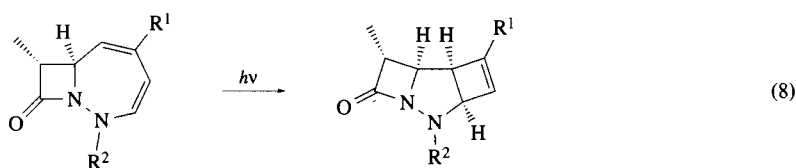
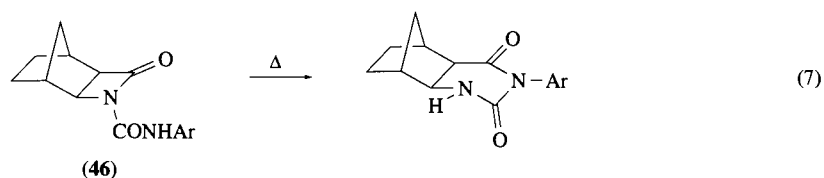
Scheme 2

The tricyclic β -lactams, where the nitrogen is not at a bridgehead, undergo similar ring expansion processes to those noted for the tricyclic azetines (e.g., Equation (5)). Thus, photochemical valence isomerization of (**44**; X = O or NCO₂Et) leads to (**45**; X = O, NCO₂Et) (Equation (6)). Since (**44**) is readily obtained from Dewar 2-pyridone, this constitutes a useful route from the six-membered ring to a seven-membered ring with one more heteroatom <87H(26)3085>.



The β -lactam containing the amide chain (**46**) undergoes ring expansion to the uracil derivative on heating in polyphosphoric acid (Equation (7)). Evidence is presented which indicates that the reaction proceeds by ring opening of the β -lactam and cyclization of the urea <87T1921>.

The azetidinodiazepines having a β -lactam system with the nitrogen atom at a bridgehead and an alkoxy carbonyl substituent on the other nitrogen atom undergo valence isomerization on photolysis to yield the tricyclic 3-azacarbapenam derivatives (Equation (8)) <84CJC2440, 85H(23)2589>.



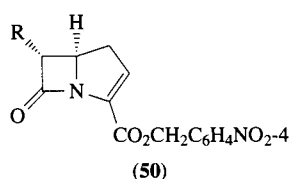
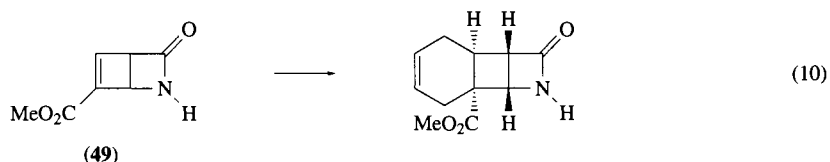
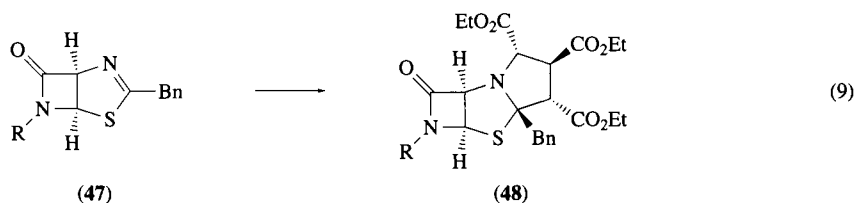
1.21.6.3 Cycloaddition Reactions

The cycloaddition reactions of olivanic acid derivatives are reviewed <B-85MI 121-04>.

The reaction of the thiazoline (**47**) with ethyl diazoacetate in the presence of Cu(acac)₂ at room temperature yields the tricyclic addition product (**48**) (Equation (9)) <82JCS(P1)2169>.

A more usual type of cycloaddition reaction is that of butadiene to the dienophilic alkenic bond in the Dewar 2-pyridone (**49**). High-pressure conditions are required, but the reaction goes with 88% stereoselectivity (Equation (10)) <93CPB1885>.

The *p*-nitrobenzyl ester (**50**) undergoes Diels-Alder and 1,3-dipolar cycloaddition reactions <86JCS(P1)973>.

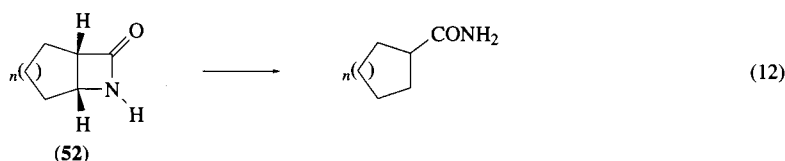
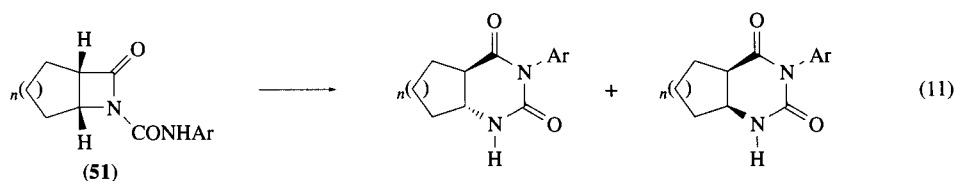


1.21.6.4 Opening of the Four-membered Ring

Bicyclic systems having a β -lactam ring fused at the N(1)—C(4) bond are usually more susceptible to ring opening reactions than the corresponding compounds fused at the C(3)—C(4) bond <72CB2780>.

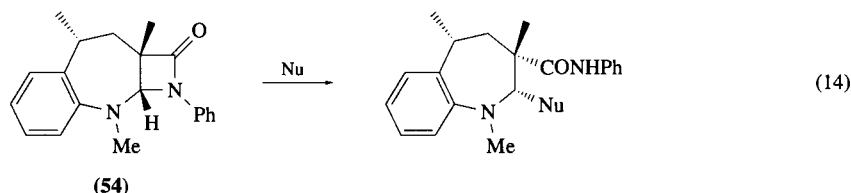
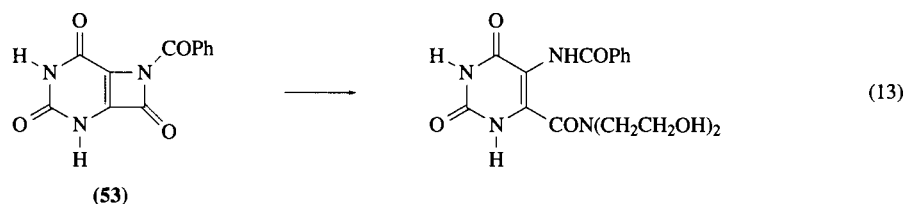
Ureas (51) derived from cyclopentano- or cyclohexano-azetidines undergo a ring expansion reaction in polyphosphoric acid to give the corresponding *cis*- and *trans*-cycloalkanopyrimidindiones (Equation (11)). Presumably the reaction proceeds through a ring opening and subsequent cyclization process <90T1943>.

The corresponding *N*-unsubstituted β -lactams (52; $n = 1-4$) are reduced with lithium aluminum hydride to the azetidine and by catalytic methods in the flow reactor to the cycloalkane amide (Equation (12)) <88JMOC103>.

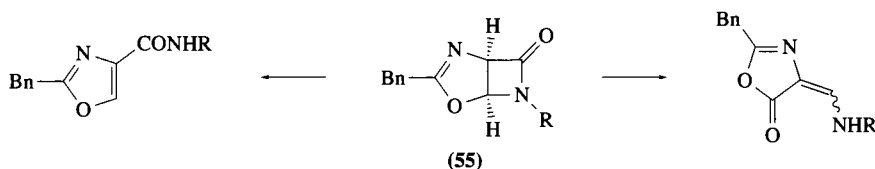


The usual reaction of the β -lactam ring with nucleophiles is by attack at the carbonyl group and opening of the N—CO bond. This process is used to obtain pyrimidine derivatives by reaction of (53) with diethanolamine (Equation (13)) <85FES695>.

The tricyclic azetidinone (54), where a bridgehead carbon atom is bonded to two nitrogen atoms, undergoes nucleophilic attack at that carbon atom with opening of the N(β -lactam)—C(bridgehead) bond (Equation (14)) <91JCR(S)204>.



Similar reactions occur in (55) where the bridgehead carbon atom is bonded to both a nitrogen and oxygen atom, and the product depends on whether the reaction conditions favor fission of the C—N or C—O bond (Scheme 3) <84JCS(P1)1127>. In the latter case, the released alcohol function attacks the β -lactam carbonyl group with formation of a lactone.

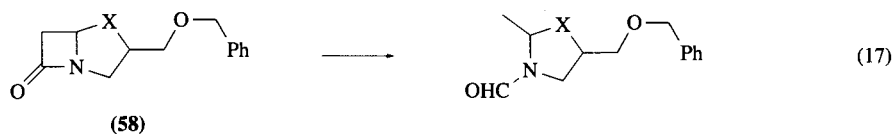
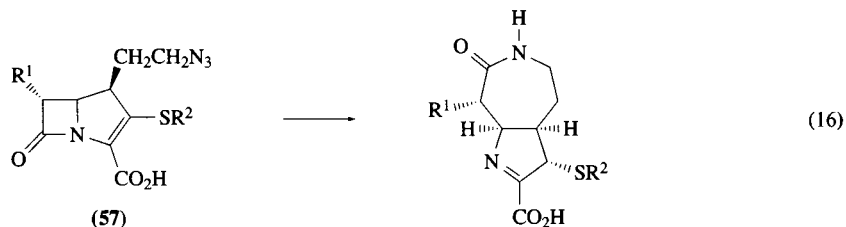
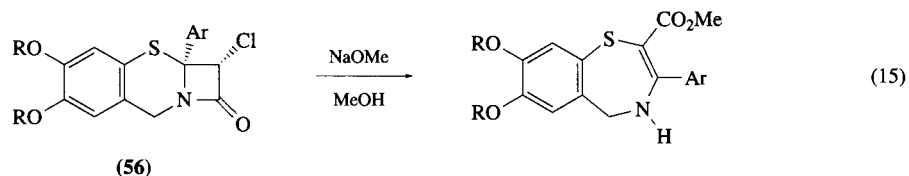


Scheme 3

Opening of the β -lactam ring by nucleophilic attack at the carbonyl group and fission of the N—CO bond is the likely first step in the formation of the seven-membered ring from (56) (Equation (15)) <84T4089>, where the nitrogen atom is at a bridgehead.

Catalytic reduction of the azide (57) generates an amine which then undergoes intramolecular acylation by the β -lactam with fission of the N—CO bond and formation of the seven-membered ring (Equation (16)) <91MI 121-02>.

Reduction of the 1-oxapenam (58; X = O) or the corresponding penam (X = CH₂) in the presence of a palladium catalyst produces hydrogenolytic C—CO bond cleavage (Equation (17)) <92CPB609>.



The action of oxygen nucleophiles on β -lactam antibiotics is important because it is thought to be the process by which the antibiotics exert their lethal effect on bacteria through the reaction with transpeptidase. Also, the alcoholysis of the β -lactam by β -lactamase is the primary process by which bacteria deactivate the antibiotic. It used to be thought that bicyclic β -lactams have exceptional chemical reactivity, but this is now known not to be the case. The high rate of reaction of penicillin with transpeptidase or β -lactamase is due to lowering of the activation energy through favorable nonbonded interactions with the enzymes. Hence, small differences in the substituents may make large differences in the effectiveness as a bactericide and susceptibility to deactivation by β -lactamase.

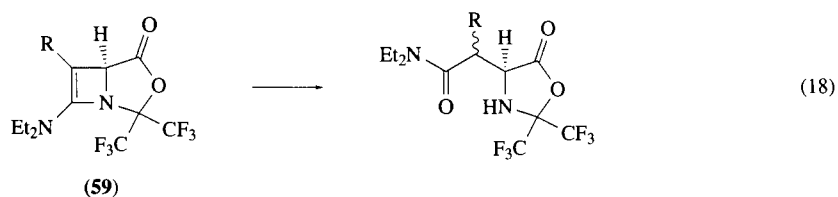
In a purely chemical environment, the effect of replacing the sulfur atom of penicillin by methylene (as in the penams) or oxygen (as in 1-oxapenams) is to increase the rate of the hydroxide ion hydrolysis of the β -lactam by factors of approximately 3 and 5, respectively. A Δ^2 -carbapenem undergoes hydrolysis more rapidly than the corresponding penam. In the cephalosporin series, replacement of the dihydrothiazine sulfur atom by methylene (carbacephem) or oxygen (1-oxacephem) causes a thirty-fold decrease and a six-fold increase, respectively, in the rate of alkaline hydrolysis (90JMC1656).

The effects of substituents on the antibacterial activity and alkaline hydrolysis rates of some cephem antibiotics, including 1-oxacephems, are known, and the effect of the presence of a 7α -OMe substituent in moxolactam (**21**) on its rate of hydrolysis is reported (83JMC1577, 87JMC514). Reaction rate studies of the epimerization in the side chain of (**21**) have shown that the nature of the aryl group and its substituents have a marked effect. Dehydrogenation at the chiral carbon seems to be the rate-determining step (85JPS68).

The hydrolysis of clavulanic acid (**18**) under a variety of conditions of pH has been shown to yield 1-amino-4-hydroxybutan-2-one as one of the major products (84JCS(P1)1345). In the presence of aqueous solutions of amines containing hydroxy groups at pH 8.05–9.8, the aminolysis reaction is pseudo-first-order with respect to the concentration of (**18**). The aminolysis rate constant is related to the sum of terms expressing the uncatalyzed or water-catalyzed reaction, the self-assisted nucleophilic reaction, and the hydroxide ion-catalyzed nucleophilic attack of the amine on the β -lactam function (89JCS(P2)223).

The catalytic effects of metal ions on the hydrolysis of clavulanic acid (**18**) has been studied (86PHA513) and the 1:1 complex has been shown to undergo reaction by hydroxide ion about 2×10^6 times faster than the uncomplexed β -lactam. The reaction was inhibited by the presence of anions which coordinate with the metal or when methyl clavulanate was used (89JCS(P2)227, 90JCS(P2)43). The dehydropeptidase I-catalyzed hydrolysis of imipenem (**16**) and its 3-SMe analogue has been investigated (89JOC653) as has their nonenzymic acid-catalyzed hydrolysis. The 2-pyrroline, formed initially by opening of the β -lactam, isomerized to the 1-pyrroline on neutralization.

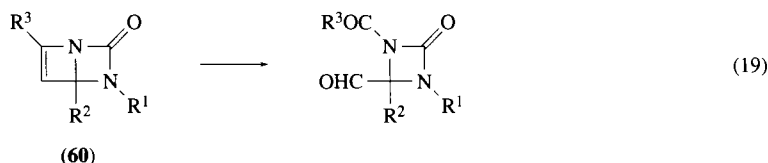
The bicyclic azetine (**59**) readily undergoes hydrolysis in dilute acid at room temperature to a mixture of diastereoisomers by opening of the four-membered ring (Equation (18)) (86CZ422).

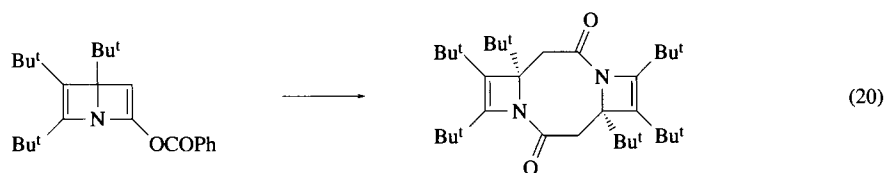


1.21.6.5 Opening of the Fused Ring

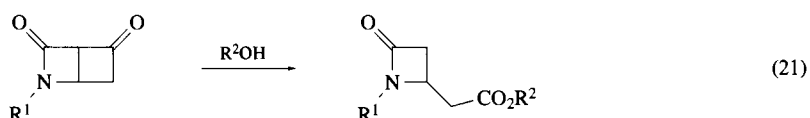
Ozonolysis of the diazabicyclohexene (**60**) (Dewar pyrimidin-2-one) and reductive workup gives the 1,3-diazetid-2-one (Equation (19)) (83H(20)849).

Treatment of the benzoate of a substituted 2-benzoyloxy-1-Dewar pyridine with methyllithium yields a dimeric tricyclic compound (Equation (20)) (91CB1661).



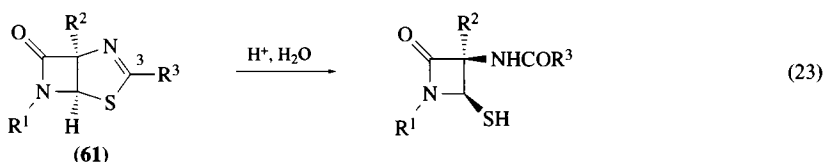
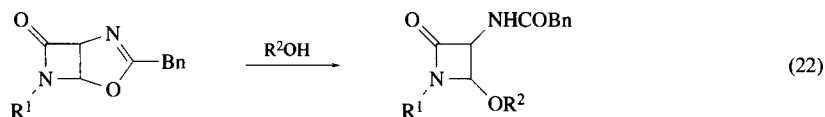


Bicyclic systems containing azetidine or azetidinone rings with a nitrogen atom at the bridgehead or elsewhere form a convenient source of monocyclic four-membered rings when the second ring in the fused system can be degraded readily. For example, a retro-Dieckmann reaction is brought about by the action of nucleophiles on 2-oxocarbapenam esters <85H(23)1081> and the five-membered ring of 2-oxocarbapenam silyl enol ethers is cleaved by ozonolysis <87TL5103>. Hydrolysis of a bicyclic azetidine lactone (2,5-disubstituted 3-oxa-1-azabicyclo[3.2.0]heptane-4-one) yields 2,2-disubstituted azetidines <90LA687>. A variety of oxygen, nitrogen, and sulfur nucleophiles attack 2-substituted 2-azabicyclo[2.2.0]hexane-3,5-diones to give 1,4-disubstituted β -lactams (Equation (21)) <86JCS(P1)1289>.



Some fused bicyclic systems undergo a ring-opening process because a bridgehead carbon atom is attached to both an oxygen and nitrogen atom. Here we are concerned with the case where the oxygen-carbon bond breaks leaving the four-membered nitrogen ring intact. Oxadiazabicycloheptenes undergo ring opening when reacted with oxygen nucleophiles (Equation (22)) or sulfur nucleophiles <84T3667, 84TL4545, 86TL1301>.

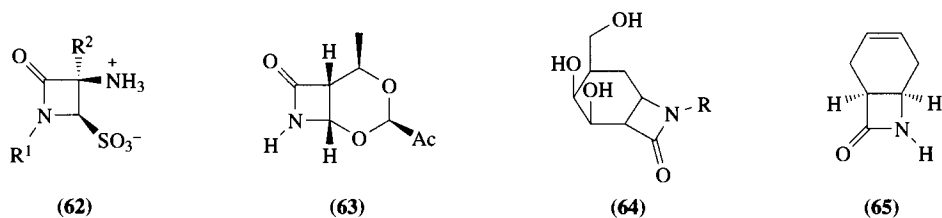
Acidic hydrolysis of the analogous thiodiazabicycloheptene (**61**) proceeds differently and attack occurs at C-3 to yield a β -lactam carrying a 4-thiol substituent (Equation (23)) <83TL2563, 86MI 121-01>.



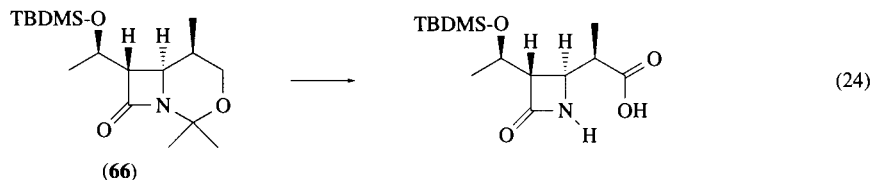
The incorporation of a suitable substituent (**61**; $R^3 = \text{SMe}$) and the use of strongly oxidizing reaction conditions gives the ylide (**62**) <83AG912>. The bicyclic 1,3-dioxin (**63**), obtained by [2 + 2] cycloaddition of chlorosulfonyl isocyanate with a 4*H*-1,3-dioxin derivative, undergoes ring opening at the acetal function <89TL5631>.

Fused bicyclic β -lactams containing a hydroxylated pyran ring (e.g., (**64**)) are readily available by addition of an isocyanate to a protected glycol followed by deprotection. Glycolic cleavage then yields the ring-opened product <87TL3035, 92MI 121-07>.

The simple bicyclic system (**65**) is readily available. The six-membered ring can be benzoyloxylated then opened, and the products can be utilized in approaches to key intermediates in the synthesis of carbapenems <87TL1561, 88TL1057>.

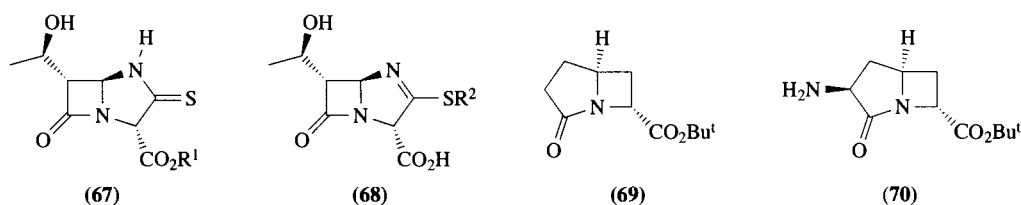


An important series of compounds is the 3-oxa-1-azabicyclo[4.2.0]octanes. For instance, (66) is obtained in a highly stereocontrolled synthesis <87JOC2563> and undergoes a ring opening reaction with Jones reagent (Equation (24)) to yield a key intermediate for the synthesis of 1 β -methyl-thienamycin <88T5965, 90TL271>.



1.21.6.6 Reactions at a Carbonyl or Thiocarbonyl Group of the Fused Ring

Alkylation of the thiolactam (67) and subsequent hydrolysis gives the enethiol (68) <85H(23)3069>. The conversion of (69) to (70) is achieved by amination of the lithium enolate of the former <85CC194>.



Syntheses of carbapenems having a 2-thioether substituent has been facilitated by the use of enol esters derived from 2-oxocarbapenams. The most frequently used ester is the diphenyl phosphate, which is readily displaced by thiols in the presence of Hünig's base at low temperature (Equation (25)) <82TL3105, 82TL4903, 83CJC1996, 83JA7186, 84CC9, 84JA1808, 84TL5075, 85TL587, 86H(24)1331, 86JCS(P1)221, 87JAN1707, 90JAN519, 91JOC3183, 92JAN971, 93JAN1866>.



Some 2-alkyl carbapenems are obtained by the action of a Wittig reagent on the protected 2-oxocarbapenams <84TL5989> and subsequent migration of the double bond into conjugation with the carboxylate group.

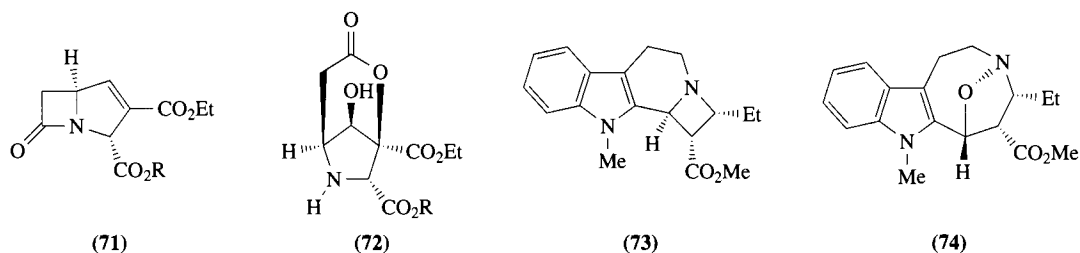
The introduction of an aryl nucleus directly bonded to the 2-position of a carbapenem has been achieved by formation of the triflate from the enol of 2-oxocarbapenem and subsequent displacement of the triflate in a palladium-catalyzed reaction with arylstannanes <90TL2853>. Alternatively, a Suzuki cross-coupling reaction can be used where the triflate is reacted with an arylboronic acid in the presence of a palladium catalyst. This process has the advantage that the highly toxic stannanes are avoided <93TL3211>.

1.21.6.7 Miscellaneous

Methods of introducing a thioether side chain into carbapenem have been noted (Section 1.21.6.6). Another approach is the Michael-type addition of a thiol to a carbapenem <83JA7345> and subsequent reintroduction of the double bond by the reaction of the carbapenem with phenyliododichloride <90JCS(P1)1793>.

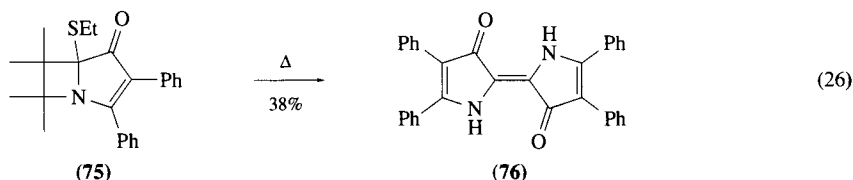
Attempted oxidation of the alkenic bond in (71) with osmium tetroxide yielded the oxazabicyclooctane (72) through an intramolecular esterification of one of the introduced hydroxy groups by the β -lactam carbonyl function <83CC508>. Oxidation of the β -carboline derivative (73)

with *m*-chloroperoxybenzoic acid (MCPBA) followed by a Meissenheimer rearrangement of the *N*-oxide produced a novel ring system (**74**) <91CL1781>.



Thermolysis of (**75**), obtained from 2-ethylthio-3,3,4,4-tetramethylazetidine and 2,3-diphenylcyclopentadienone, gives the unexpected deep-purple bipyrrrolinone (**76**) (Equation (26)) <92TL2231>.

The stereochemistry about the 6-position of a 6-substituted 1-azabicyclo[3.2.0]heptan-7-one can be changed by controlled protonation of the azetidinone enolate <85TL1739>. This is useful in the preparation of *cis*-6-substituted carbapenems.

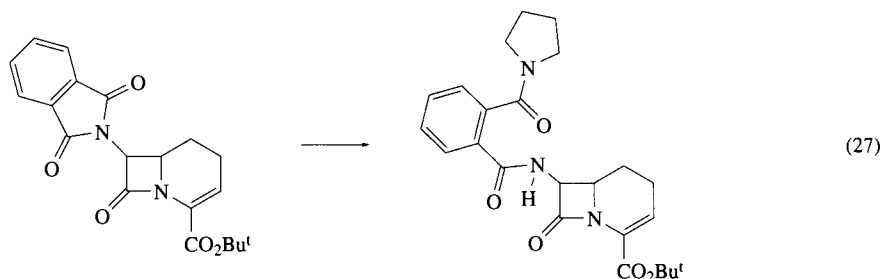


1.21.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The introduction and reactions of functional groups on β -lactams have been reviewed <B-93MI 121-04>.

1.21.7.1 Substituents Attached to the Four-membered Ring

There are many examples of the acylation of amino groups at the 3-position of the β -lactam ring in a bicyclic system and some representative references are given <88JAN332, 88JAN1154, 89CPB275, 89JMC2442, 90JAN357>. The susceptibility of the phthalimido protecting group to basic conditions and unwanted nucleophilic attack has been overcome by deliberately invoking the latter in converting the phthalimide to *o*-(pyrrolidinocarbonyl)benzamide (Equation (27)) <91TL3301>. This protecting group can be converted back to the imide or cleaved to the amine.

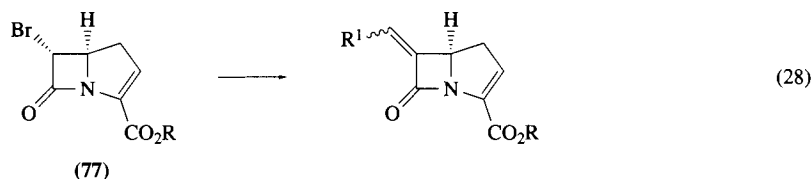


Acylation of the amine group in a carbacephem is utilized in an attempt to develop iron transport-mediated drug delivery with compounds where the side chain includes cyanuric acid-based siderophore analogues <94JOC1020>.

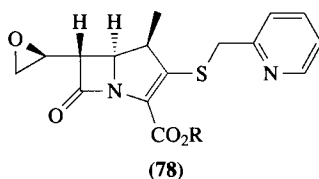
Conversion of 7 α -amino-1-oxacephems to the 7 β -epimer can be achieved by formation of a Schiff base and reduction with borohydride <85TL339>, and 7 β -amino-7 α -methoxy-1-oxacephems can be reduced to 7 β -amino-1-oxacephems with sodium cyanoborohydride <89H(28)687>.

Formation of the anion from (**77**) and its condensation with an aldehyde gives a bromohydrin

which, on reductive elimination, yields a mixture of (*E*)- and (*Z*)-isomers of the 6-alkylidene derivative of the carbapenem (Equation (28)) <91JCS(P1)2699>.

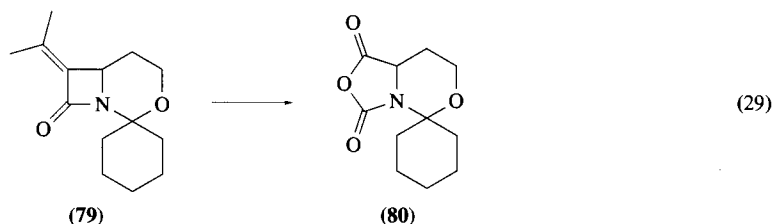


Spirodihydropyrazoles are obtained by the 1,3-dipolar addition of diazomethane to 6-ethylidene-olivanic acid derivatives <86JCS(P1)421>. The epoxide (78) undergoes ring opening to give the 6-(2-hydroxyethylidene) derivatives <91TL10236, 92JAN240>.



Acyl substituents at the 3-position of the β -lactam ring are useful intermediates in the stereospecific formation of the alcohols <86CC1151>; the stereochemistry of the alcohol can be inverted <82JCS(P1)3011> or the epimeric fluoride can be formed <89JAN1520>.

Attempted ozonolysis of the ethylidene (79) and reductive workup conditions unexpectedly gave the anhydride (80) (Equation (29)) <92JCS(P1)1577>.



1.21.7.2 Substituents on the Fused Ring

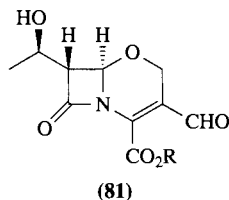
A 2-hydroxycarbapenem can be converted to its methanesulfonate and thence to the carbapen- Δ^2 -em <84CC195>. The introduction of a 3-phenylselenenyl group in a carbapenem followed by treatment with MCPBA also yields the penem <89CC486>. Selenium chemistry can be used to introduce a 3-hydroxy group in place of the ester group in clavulanic acid methyl ester <83JCS(P1)2513>.

Naturally occurring carbapenem antibiotics having a double bond in the side chain can be converted to the (*Z*)-isomers <83JMC271>. The 2-alkylthio substituents in carbapenems can be replaced by other alkylthio groups if the initial substituent is first oxidized to the sulfoxide <83JAN407, 86CPB1089, 92HAC25>. Inversion of configuration occurs when 2-acetoxylation of a 2-alkylthio-substituted carbapenem is caused by lead tetraacetate. The alkylthio substituent can be oxidized by MCPBA, and subsequent treatment of the 2-acetoxy-2-alkylsulfone with 1,5-diazabicyclo-[5.4.0]undec-7-ene (dbu) yields the 2-acetoxycarbapenem <86TL6001, 90JCS(P1)2553>. Replacement of a 2-alkylsulfoxide substituent on a carbapenem occurs with carbon nucleophiles such as the anions from cyanoacetic esters and nitromethane. The 2-nitromethyl substituent is a source of the nitrile oxide which is trapped with 1,3-dipolarophiles, giving carbapenems having a 2-heteroaryl substituent <84CC1513>. Thienamycin sulfone undergoes a Smiles-type rearrangement to give a carbapenem with a substituted 2-amino group <85JOC1996>. A procedure using the Mitsunobu reaction is available for the conversion of a 2-hydroxymethyl substituent on a carbapenem to an amidomethyl, aminomethyl, or heteroarylaminomethyl substituent <92TL7133>.

Replacement of phosphate ester groups at the 2-position of a carbapenem nucleus by thiols <91JAN1172, 92JAN971> has been mentioned earlier (Section 1.21.6.6). The same group or aryl sulfonate enol esters can be replaced by azide, and the azide subsequently reduced to the amine <85TL5407>.

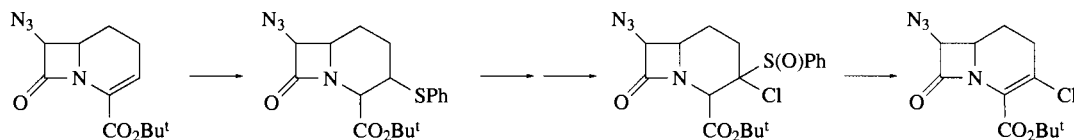
The structure of clavulanic acid (**18**) was established and the 2-(2-hydroxyethylidene) substituent reduced to the ethylidene group or oxidized to a formylmethylene substituent <84JCS(P1)635>. The alcohol group of benzyl clavulanate can be converted to ethers and thioethers in one step, and amines can be obtained <83TL2693>.

Oxidation of 3-hydroxymethyl-1-oxacephems by Swern procedure (DMSO and oxalyl chloride) yields the 3-formyl derivative (**81**) <90H(30)567> and the aldehyde can be modified by standard procedures through the oxime or by reaction with Wittig reagents <89JAN1124>.



A 3-chloromethyl substituent on the 1-oxacephem nucleus is introduced by methanesulfonyl chloride addition to an exocyclic double bond of a 3-methylene substituent and subsequent elimination of the alkylthiol group <83T2515>. The halogen is readily replaced by nucleophiles <85JAN466>.

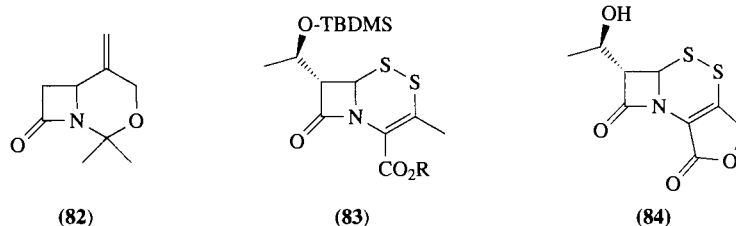
The 3-alkyl- or 3-arylthio substituents are useful in 1-carbacephem chemistry. Addition of thiophenol to the carbacephem, in the presence of an organic base proceeds smoothly to give a single isomer (thought to be 3 α -SPh-4 α -CO₂Bu^t) and this is oxidized to the sulfoxide. Treatment with sulfonyl chloride gives the α -chloro sulfoxide (Scheme 4) <89CPB1239> and mild thermolysis provides the 3-chloro-1-carbacephem.



Scheme 4

Triflates of 3-hydroxy-1-carbacephem can be replaced directly with thiols in the presence of a base <85TL3787, 93JMC1971>. In the presence of a bis(acetonitrile)palladium(II) chloride catalyst, the triflate group may be displaced to yield either 3-alkylcarbacephems by the action of organostannanes or 3-alkoxycarbonyl derivatives in reactions with an alcohol and carbon monoxide <89JOC5828>. A cyclopropane substituent is formed in the addition of carbene to a 3-vinylcarbacephem <89JAN1653>.

Stereoselective reduction of the exocyclic double bond in (**82**) gives the β -methyl derivative <91T7117>. Bromination of the 3-methyl group in (**83**) allows the lactone (**84**) to be obtained <83TL3283>.



1.21.7.3 Deprotection Reactions

The use of protective groups in β -lactam chemistry has been reviewed <B-93MI 121-05>. Only a general outline can be given here and emphasis is placed on the deprotection step.

The benzyl group and its simple derivatives *p*-nitrobenzyl (PNB) and *p*-methoxybenzyl (PMB) are used frequently to protect carboxylic acid functions. In the carbapenem series, hydrogenolysis over a palladium-on-charcoal catalyst is used as the deprotection step to provide carboxylic acids <82JCS(P1)2123, 83JAN1034, 84TL5075, 92JAN971>. Similarly, phosphonic acid derivatives of the car-

bapenem nucleus can be obtained from the phosphonic acid esters <83TL347>. The PNB esters can be cleaved using the same reagent in the carbacephem series <91JAN1172>. With due regard to the nature of other substituents, PNB esters may be cleaved more effectively by dissolving-metal reduction: zinc dust, THF, and aqueous phosphate buffer (pH 6) is a useful system <93H(36)1729>, but zinc dust, DMF, and hydrochloric acid is satisfactory in some cases <93JMC1971>. In the 1-selenapenem series iron powder and aqueous ammonium chloride is used <86TL3041>. Methoxybenzyl esters are cleaved with aluminum chloride in anisole at reduced temperature <84JOC5271>. The reaction can be carried out under nonacidic conditions and is therefore particularly useful in the carbapenem series, which is unstable to acid <84TL2237, 85JAN610>, but is also applicable with the carbacephems <85TL3787>. The reagent also cleaves benzhydryl esters and causes cleavage of methoxybenzyloxycarbonyl groups to yield amines. Tin(IV) chloride is an alternative reagent <85JAN466>. Aluminum chloride liberates carboxylic acids from their PMB esters in the 1-phosphacephem series <84TL1737>.

Allyl esters are efficiently deprotected with pyrrolidine or other organic bases in the presence of catalytic amounts of palladium(0) complexes <87TL4371>. A mixture of palladium tetrakis(triphenylphosphine) and triphenylphosphine has also been used <89H(28)195>. Incorporation of an alkali metal salt of a fatty acid with palladium tetrakis(triphenylphosphine) allows the alkali metal salt of a penem <91JOC3183> or 1-oxapenem 3-carboxylic acid to be isolated <92S1099>. Removal of allyloxy and allyloxycarbonyl protecting groups from an ester and amide, respectively, can be achieved in a one-pot process <88JAN780>.

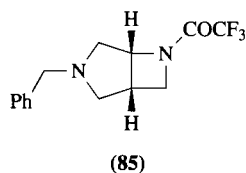
Useful protecting groups for amines include phenoxyacetyl (removed by sequential treatment with phosphorus pentachloride, an alcohol, and water) <93JMC1971>, *t*-butoxycarbonyl (removed by the action of trifluoroacetic acid) <93JMC1971>, phthaloyl (deprotection by treatment with hydrazine and acid) <88CPB3642> (but see Section 1.21.7.1), and the trityl group (cleaved with acid) <87CC1283>. Protection of an amine substituent by incorporation of the nitrogen atom into a 4-phenyl-2-oxazolidinone ring is useful in the carbacephem series <93TL4755>. When the nitrogen atom is part of the second ring, as in a 1,2-diazabicyclo[5.2.0]nona-9-one nucleus, and is protected by either alkoxycarbonyl or benzoyl groups, then methyllithium is a useful deacylating agent even in the presence of the β -lactam ring <90H(30)551>.

1.21.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

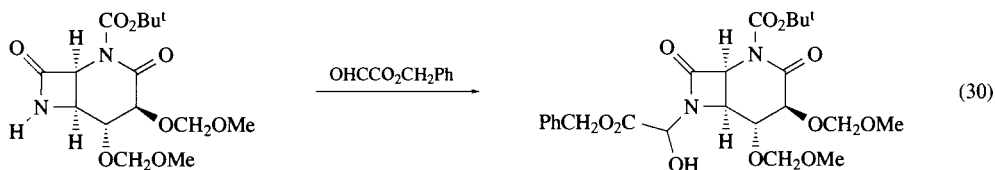
1.21.8.1 At Nitrogen

Some reactions of substituents at the ring nitrogen atom have been considered in Section 1.21.7.3. Other reactions are discussed in Section 1.21.9.

Study of the reductive cleavage of *N*-substituents from 3,6-diazabicyclo[3.2.0]heptane (**85**) shows that either one of the groups or both groups can be cleaved by catalytic hydrogenation if the conditions are carefully controlled <91TL1565>.



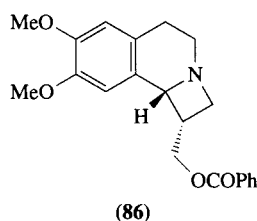
A β -lactam NH group forms an anion which readily reacts with an aldehyde or other electrophile (Equation (30)). The resultant alcohol can be manipulated in the usual ways, such as formation of the corresponding halogen compound <93SL139>.



Electrochemical methods have been used to introduce acetoxy groups into unsaturated

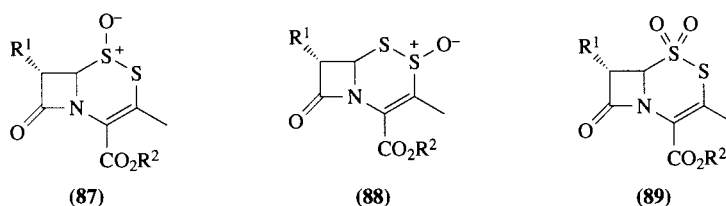
N-substituents of a β -lactam and these products may undergo ready fission of the *N*-substituent bond <90CE873>.

The quaternization of the nitrogen atom of (86) with methyl, benzyl, and allyl halides occurs stereospecifically to give the *N* β -alkylammonium salts <91JHC353> as indicated by ^1H and ^{13}C NMR evidence.



1.21.8.2 At Sulfur

Thermolysis of the thiosulfonates (87) and (88) and thiosulfonate (89) showed that only the last decomposed smoothly to yield penems with retention of stereochemistry at the azetidinone–S junction and the substituent. Strangely, further oxidation of (88) yielded (89) <86JOC3413>.



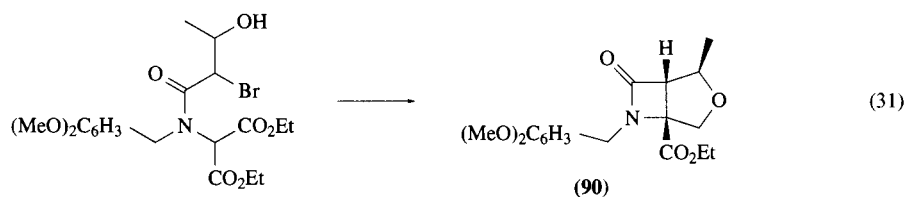
1.21.9 SYNTHESIS OF FUSED SYSTEMS CONTAINING A FOUR-MEMBERED RING

The strategies for the synthesis of bicyclic β -lactams have been reviewed <B-93MI 121-06> as has the application of organometallic reagents in β -lactam chemistry <88T5615>.

1.21.9.1 From Acyclic Compounds

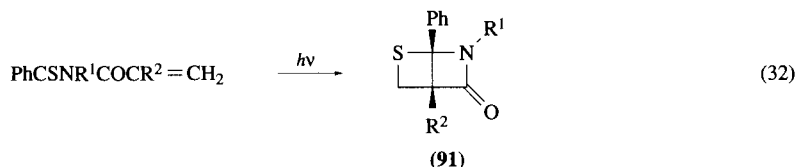
Suitably substituted acyclic amides can be cyclized to bicyclic systems containing a β -lactam system by either chemical or photochemical means. However, this approach is limited in scope.

Treatment of (2*R*,3*R*)-*N*-(2,4-dimethoxybenzyl)-*N*-[bis(ethoxycarbonyl)methyl]-2-bromo-3-hydroxybutyramide with dbu gives (90) (Equation (31)) <84BCJ2135>. Similarly, epoxides can be used in place of the bromohydrin system in the reactant <85JIC891>.



Photochemical cyclization of *N*-(thiobenzoyl)alkyl acrylamides yields 3-oxo-6-thia-2-azabicyclo-[2.2.0]hexanes (91) (Equation (32)) <84JOC396>. This is a convenient route to β -lactams fused to a thietane nucleus; the mechanism has been investigated and shown to proceed by an $n\pi^*$ triplet excited state <91JCS(P1)403>. *N*-(Thiobenzoyl)methacrylanilide crystallizes from hexane as chiral

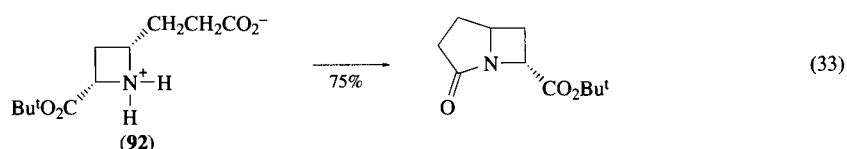
crystals. Photolysis of these chiral crystals in the solid state gives a 75% yield of (**91**; $R^2 = \text{Me}$) with 10% *ee* by a topochemically controlled unimolecular [2 + 2] cycloaddition <93JA818>.



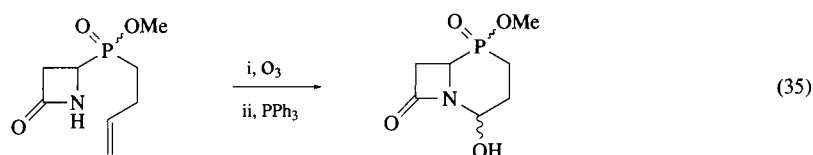
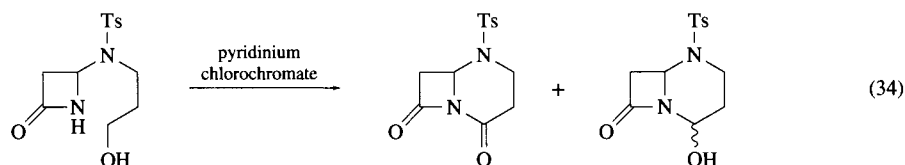
1.21.9.2 Closure to *N*-1 of the Four-membered Ring

Perhaps conceptually the simplest approach, this method may be applied in a number of guises, which are discussed in turn.

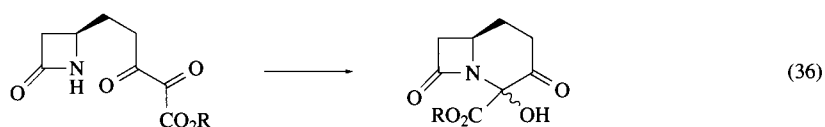
A substituent on the vicinal carbon to the nitrogen atom of the four-membered ring can be cyclized on to the nitrogen atom to yield a lactam. Thus, the azetidine (**92**) yields the endo γ -lactam when treated with Mukaiyama's reagent (2,2'-dipyridylsulfide and triphenylphosphine) (Equation (33)) <86T4879>.



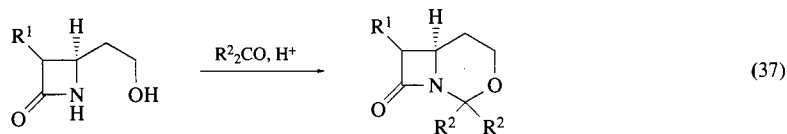
The chain can contain a heteroatom (Equation (34)) <82H(19)1853> and presumably, in this case, the alcohol is produced by attack of the nitrogen anion on the aldehyde formed as an intermediate. A similar reaction of an aldehyde produced in an ozonolysis reaction is known (Equation (35)) <84CC200>.



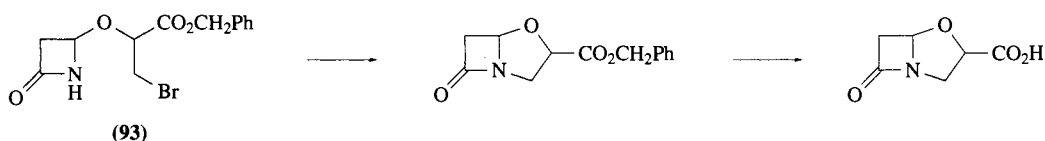
An alternative way in which a carbonyl group in the side chain may be utilized is in the cyclization of α,β -diketoesters, which are available from the corresponding β -ketoesters. The cyclization of the diketoester occurs readily in the presence of molecular sieves (Equation (36)) <84TL3743, 92JOC3546>. An N—C bond formation using an α -ketoester is part of a formal total synthesis of (+)-thienamycin (**15**) <93TL4747>.



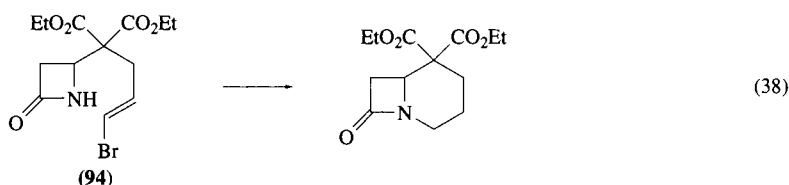
Cyclization of 4-(2-hydroxyethyl)azetidin-2-ones in an intermolecular reaction of both the nitrogen atom and the hydroxyl group with a ketone or ketal is used extensively to prepare 3-oxa-1-azabicyclo[4.2.0]octanones (Equation (37)), which are of value as intermediates in the synthesis of thienamycin (**15**) <86CC941, 86CC1198, 86JOC1571, 88T5965, 90CL531, 90JCR(S)270, 90TL271, 91T7117, 91TA255, 91TL259>.



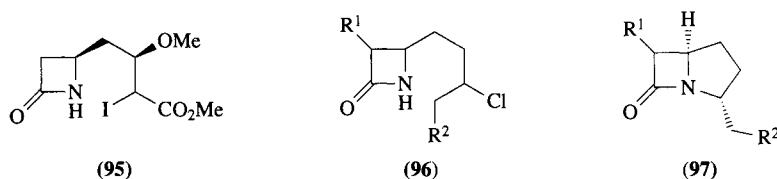
Formation of a fused ring by intramolecular cyclization on to the nitrogen atom of a β -lactam can be achieved by nucleophilic displacement of a suitably sited halogen on a 4-substituent of the azetidin-2-one nucleus. This route is used in the preparation of 4-oxa-1-azabicyclo[3.2.0]heptan-7-ones $\langle 92\text{MI } 121-07 \rangle$. The cyclization of (93) is catalyzed by silver (Scheme 5) $\langle 88\text{TL}1609 \rangle$ but gives a poor yield. In the light of that, it is surprising that nucleophilic attack occurs at the bromovinyl group in (94) to give the carbacephem nucleus (Equation (38)) $\langle 89\text{TL}337 \rangle$.



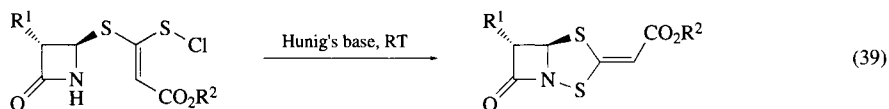
Scheme 5



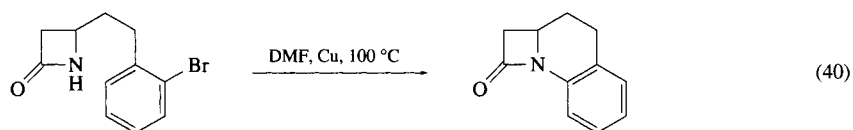
A 4-substituent on the β -lactam carrying an activated halogen (95) cyclizes readily $\langle 86\text{TL}3725 \rangle$, and 4-substituents having a terminal alkenic group are caused to form a bicyclic system after iodination and treatment with a suitable acid scavenger $\langle 87\text{TL}5245, 90\text{T}3321 \rangle$. Activated halogenation at the alkenic site is achieved by the addition of phenylsulfonyl chloride to yield (96; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{SPh}$), which is cyclized to 2-substituted-1-azabicyclo[3.2.0]heptanone (97; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{SPh}$) $\langle 83\text{JA}7345 \rangle$. When the β -lactam has a 3-isopropyl substituent, phenylselenenyl bromide $\langle 86\text{JOC}1724 \rangle$ has been used to obtain (97; $\text{R}^1 = \text{CH}(\text{CH}_3)_2$, $\text{R}^2 = \text{SePh}$). Treatment with Raney nickel then gives 3-methylcarbapenem.



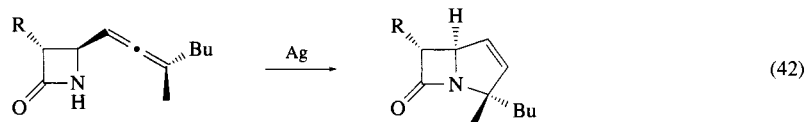
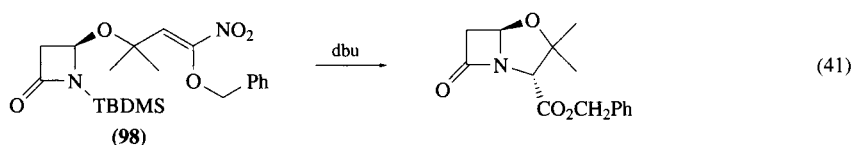
More elaborate bicyclic systems are obtained when the β -lactam substituent contains one or more heteroatoms in the chain (Equation (39)) $\langle 91\text{TL}3771 \rangle$ and in this way 3-hydroxy-2-oxacephems are prepared $\langle 84\text{HCA}18 \rangle$.



Tricyclic systems are produced when the chain contains a suitably sited bromophenyl nucleus. Nucleophilic displacement of the halogen requires much more vigorous conditions, as expected, and is best catalyzed by activated copper powder (Equation (40)) $\langle 83\text{CC}431, 87\text{JCS}(\text{P}1)1899, 88\text{JMC}370 \rangle$.

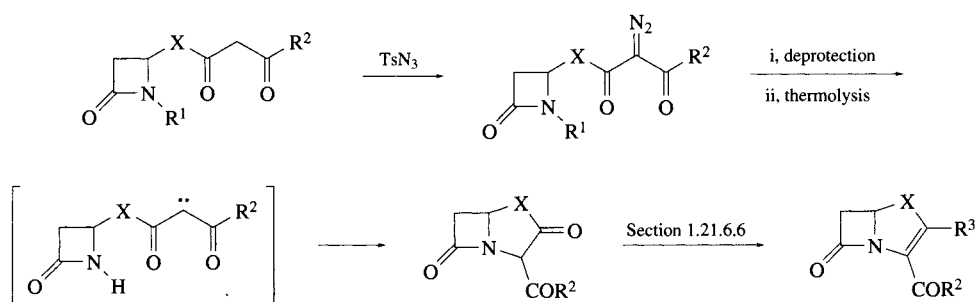


Another way of utilizing the nucleophilicity of the anion sited at the nitrogen atom of the β -lactam is in an attack on a polarized alkenic system as in the Michael reaction <85JOC2603, 87JOC4693>. For example, deprotection of the β -lactam nitrogen atom of (**98**) and treatment with base (dbu) leads to the oxapenam ester (Equation (41)) <89JOC992>. The 4-allenylazetidinone undergoes silver-catalyzed stereospecific cyclization to yield the 1-carbapen-1-em ring system (Equation (42)) <88TL4253>.



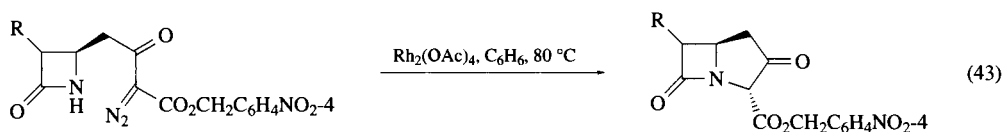
1.2.1.9.3 By a Carbene Insertion Reaction

This is a widely used route to carbapenems and the usual steps in the reaction sequence include the formation of a β -dicarbonyl substituent on a β -lactam, the introduction of the diazo group with tosyl azide, and the thermolysis of the diazo compound with the release of the carbene and its insertion into the N—H bond (Scheme 6, X = CH₂).

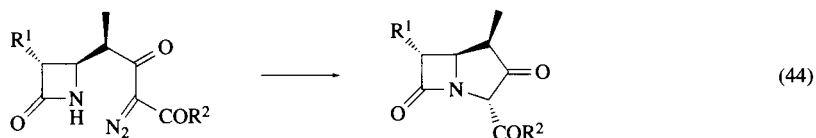


Scheme 6

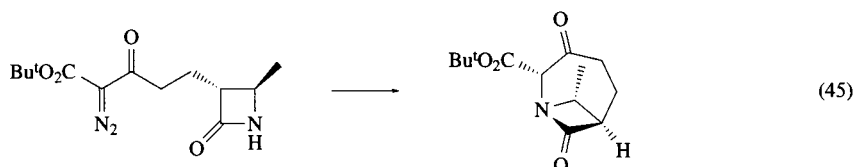
An important development in the usefulness of this approach to the bicyclic systems was the discovery of the catalytic effects of rhodium(II) salts in the formation and reaction of the carbenes <80TL31, 88T5615>. Usually rhodium acetate dimer (Rh₂(OAc)₄) is used, but sometimes rhodium octanoate <87CL2187> is preferred. In the presence of catalyst, the reaction temperatures are about 80 °C and yields are high (Equation (43)) <83CJC1996, 85CPB3299>, but an *N*-benzyloxy protecting group may be removed in the reaction <91JOC2688>. Several reports are available of the application of the reaction when the diazo compound has a 3-alkyl substituent on the β -lactam <82TL3105, 84G225, 85JAN610, 85JCR(S)368, 86JA6054, 86TL3119, 87JAN309, 88JOC692, 91JOC5984>, or a 3-(1-hydroxyethyl) substituent or a protected derivative <83JA1659, 83JAN1034, 83TL3251, 84CC9, 84TL5075, 86CJC2184, 88MI 121-03>. Other 3-substituents on the starting material include (alkoxycarbonyl)hydroxymethyl <87TL781>, 1-hydroxy-1-methylethyl <85H(23)2277>, protected amino <82TL5339, 85TL3787>, substituted ethylidene <83JA7186, 84TL2237, 85JOC4245>, and 2-methyl-1,3-dioxanlan-2-yl <86JCS(P1)221>.



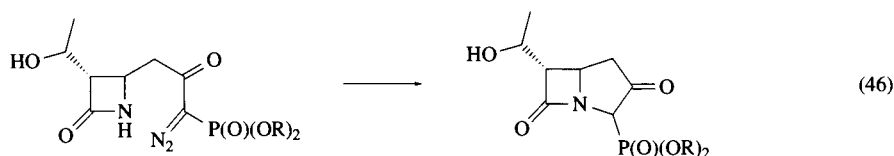
If in Scheme 6, $X = \text{CHCH}_3$ rather than CH_2 as has been assumed thus far, then it is possible to obtain 1 β -methyl carbapenams (readily convertible into carbapenems) by this route provided that a 4-substituent of the correct stereochemistry is present on the β -lactam (Equation (44)). There is much interest in 1 β -methylcarbapenems because some derivatives have excellent antibacterial activity and are resistant to deactivation by renal depeptidase-I (see Section 1.21.12). Also, the carbene route is applicable when a 1-hydroxyethyl substituent (or a protected derivative) at the 3-position of the monocyclic β -lactam is present (84H(21)29, 85TL587, 89JMC601, 91JOC3183, 92JOC4243). A 1 β -methoxycarbapenem has been obtained in a similar way (89CC821). Other 3-substituents present on the β -lactam of the diazo compounds utilized in this way include ethyl (93G509), amido (91H(32)93), 2-oxiranyl (91TL1023), 1-hydroxyprop-2-enyl (92JMC953), and methylthio (92H(33)523) groups.



Several variations on the theme in Scheme 6 are possible. Thus, derivatives of 1-azapenam ($X = \text{NOMe}$ in Scheme 6) (93H(35)1205), 2-oxacephem ($X = \text{CH}_2\text{O}$) (87H(26)2393), and 1-oxacephem ($X = \text{OCH}_2$) (84JCS(P1)1599, 90H(31)791) have been prepared by application of the general procedure. Additional use has been made of the reaction to obtain 1-carbacephem derivatives (Scheme 6, $X = (\text{CH}_2)_2$) (89TL2321, 92CJC2142, 93JMC1971). The general approach has been used in the synthesis of 1,3-bridged β -lactams but here starting with the important substituent on the 3-position of the azetidin-2-one (Equation (45)) (86JA6431, 89JA1073).



For reactions of the type shown in Scheme 6, activation of the methylene group can be achieved by the presence of electron-withdrawing groups other than an ester function. Diesters of a phosphonic acid have been used (83TL347, 84TL595) to produce carbapenam-3-phosphonic esters (Equation (46)). Similarly a 5-tetrazolyl group in place of the ester has given a 3-(5-tetrazolyl)carbapenam derivative (84JA1808).

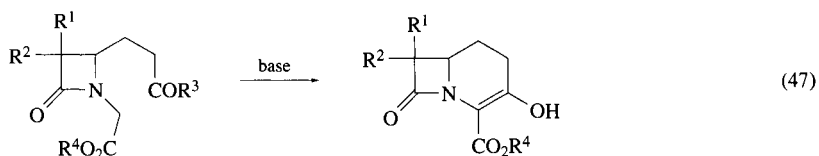


1.21.9.4 From a Disubstituted Four-membered Ring

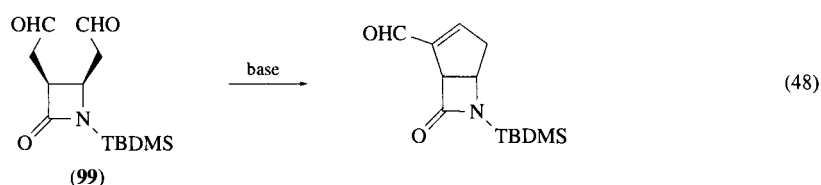
The single most widely used method for the construction of a fused bicyclic β -lactam is from precursors having two substituents on a β -lactam ring. Some aspects of the cyclization reactions are considered here and use of the Wittig reaction is discussed in Section 1.21.9.5.

Intramolecular nucleophilic attack on a carbonyl group is often used to form the fused-ring system and the nucleophile may be formed from an acidic methylene or methine group. This approach is a convenient entry into the 3-hydroxy-1-carbacephem series (Equation (47)) by use of the

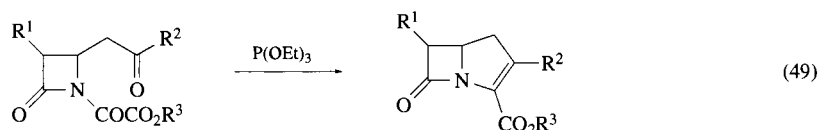
Dieckmann or modified Dieckmann reaction to give the enol of a β -ketoester (83TL4837, 90H(30)863, 90TL6317, 91S743, 92TL857). In a similar way, appropriate diacid derivatives undergo Dieckmann-type cyclization to yield a 1-carbapenam-2-one (82T2659, 84TL2387, 87TL5103). The method has been used to obtain a precursor of 1 β -methyl-1-carbapenam labeled at position 3 with ^{14}C (91MI 121-03). Trialkylsilyl substituents have been used to activate the nitrogen substituents in place of the ester group (Petersen-type alkenation) to yield a 1-carbacephem nucleus without the 4-alkoxycarbonyl group (90TL1921).



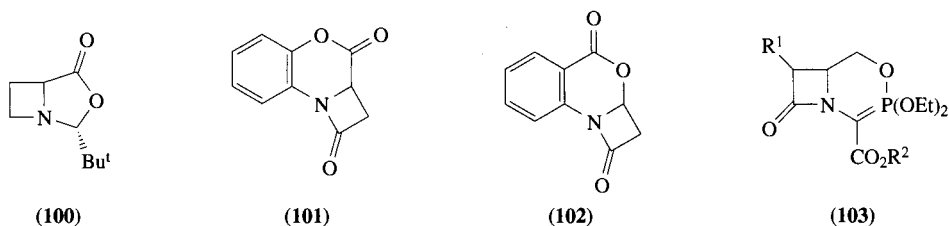
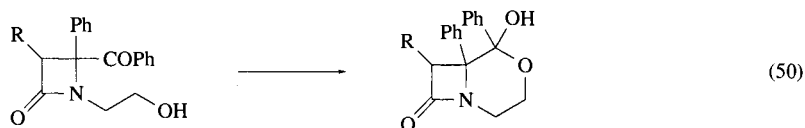
Another modification is the use of intramolecular aldol type cyclization (Equation (48)), this time with a 3,4-disubstituted azetidinone (**99**) and therefore yielding a bicyclic β -lactam not having a bridgehead nitrogen atom (86TL3749).



The reductive coupling of two suitably sited aldehydic or ketonic carbonyl groups to produce an alkenic bond between the carbon atoms is brought about by the action of triethyl phosphite (Equation (49)). This method has been used to obtain 1-carbapenems (85TL4739, 87JAN309, 88CC544, 89JAN374, 89TL2555), their annelated derivatives (94CC441), 1-thiapenems (84TL2395), and 2-oxa- and 2-thiacephem (86TL305).

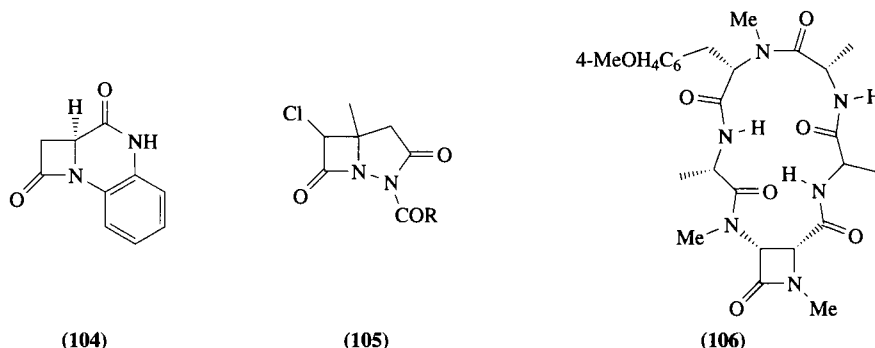


Other ways in which the reactivity of a carbonyl group have been used to form a second ring fused to a four-membered ring include intramolecular hemiketal formation (Equation (50)) (85IJC(B)144); the formation of a cyclic ester from a carboxylic acid to give the lactones (**100**) (90LA687), (**101**) (83AP(316)371), and (**102**) (84M215, 85M979); and also from a phosphorus acid to yield the ester (**103**) (82HCA1359).

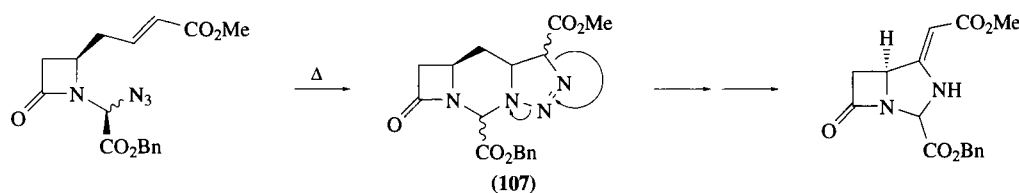


Cyclic amide formation between carboxylic acid functions and suitably sited amine groups (85MI 121-05) and hydrazide groups (89JIC208) has given (**104**) and (**105**), respectively. An imide,

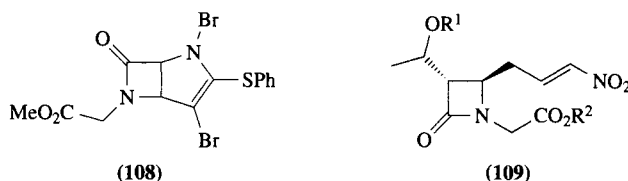
1,3-diazabicyclo[3.2.0]heptan-2,4-dione, has been obtained from a 1-carbamoylazetidine 2-carboxylic acid <72JOC516>. More spectacularly, the last step in the preparation of (106) involved amide formation at the 4-carboxylic acid on the β -lactam ring <91JOC5385>.



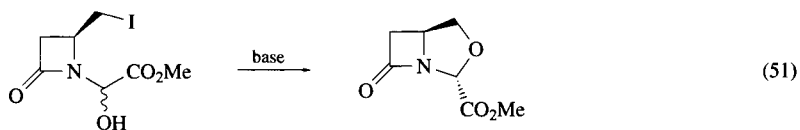
The use of alkenic 4-substituents on an azetidinone to provide an aldehyde by ozonolysis has been mentioned already (Section 1.21.9.4), but the alkenic group may be utilized in other ways to give a fused-ring system. For example, an azide on a 1-substituent of a β -lactam may undergo a thermal intramolecular cycloaddition with an alkenic, or alkynic <85JCS(P1)1491> group in the 4-substituent to yield a triazole derivative (107) which decomposes with loss of dinitrogen to produce a 2-azapenam (Scheme 7) <86JCS(P1)1077>. In a similar way and starting from appropriately substituted β -lactams, 3-aza-1-carbacephams <82TL3003>, 3-aza-1-carbaceph-2-ems <83TL1649>, and 1-thia-3-azaceph-2-ems have been obtained <86JCS(P1)1097>. A more elaborate procedure including bromination by *N*-bromosuccinimide yields (108) <85MI 121-06>.



Scheme 7

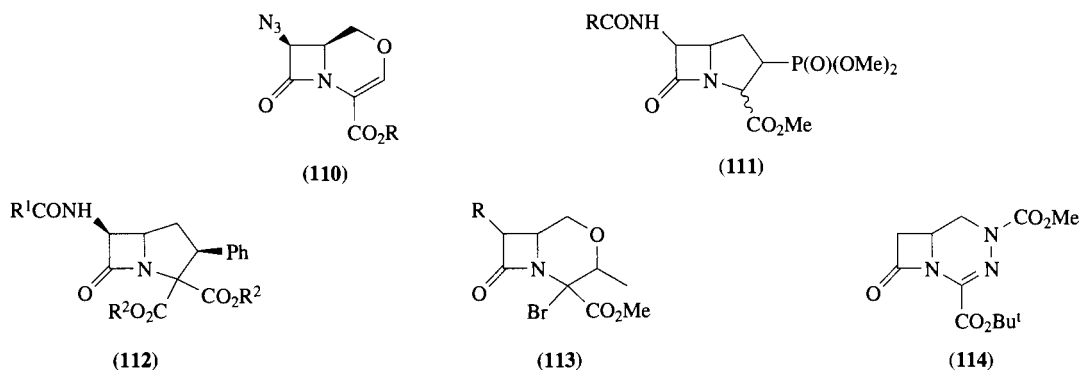


Yet another way in which a bicyclic fused system can be formed from a disubstituted β -lactam occurs when the *N*-substituent carries a nucleophile, or incipient nucleophile, and the 4-substituent includes a suitably sited good leaving group. The simplest examples occur where the 4-substituent is a halogenomethyl group. For example, 2-oxapenams (isoclavan-3-carboxylates) have been obtained by halogen displacement (Equation (51)) <83JCS(P1)649>.

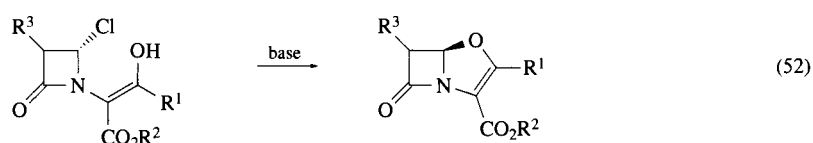


Displacement of sulfur acids from 4-methanesulfonyloxymethyl substituents by oxygen give 2-oxacephems (110) <84HCA902, 87CC51, 90JCR(S)170>. In a similar way, carbon-centered nucleophiles have been used to displace triflate ion to yield the 1-carbapenam (111) <90MI 121-04>. Other activated

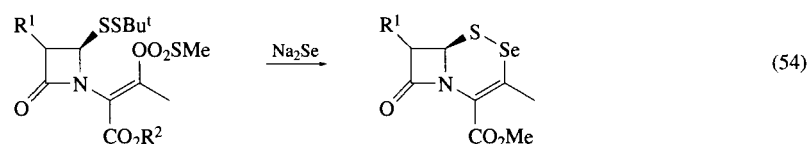
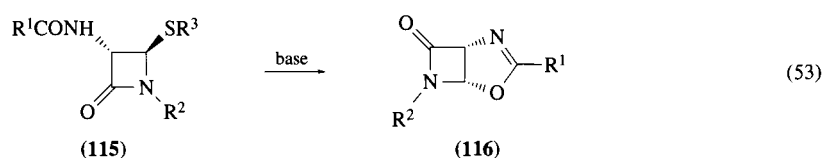
esters can be used in this type of reaction <90JCS(P1)432>. Cyclization at a halogen in a more complex 4-substituent has given other carbapenams (**112**) <82HCA1374>, 2-oxacephems <87CC1283, 88JMC1190>, and 2-oxacephams (**113**) <89HCA1501>. Intramolecular nucleophilic attack of a diazine (produced by oxidation of a hydrazine) yields the 2,3-diazacephem (**114**) <84CC1289, 89JCS(P1)297>.



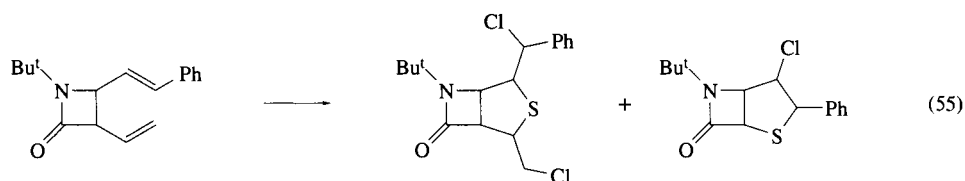
Another approach to fused bicyclic β -lactams is where the 4-substituent on a β -lactam is replaced by nucleophilic attack on the ring by an N - or 3-substituent. The simplest cases are perhaps the replacement of a 4-chlorine substituent by the nucleophilic attack of the oxygen of an enolate to give a 1-oxapenem (Equation (52)) <82T2489, 90JAN1441, 92S1099>. 1-Oxapenems are unstable compounds and yields are generally poor.



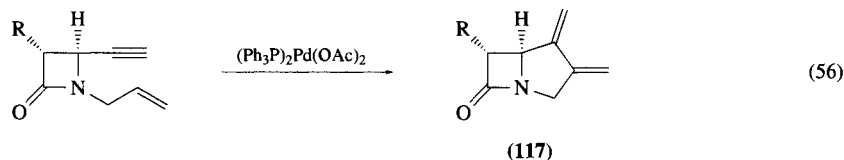
Sulfur-based substituents are good leaving groups when attack is by nucleophiles. Thus 4-methylsulfide (**115**; $\text{R}^3 = \text{Me}$) <89T701>, 4-heteroaryl (**115**; $\text{R}^3 = \text{benzothiazol-2-yl}$) <82TL3379>, 4-heteroarylthio (**115**; $\text{R}^3 = \text{benzothiazole-2-thio}$) <88PJC127>, and 4-sulfinic acid (**115**; $\text{R}^3 = \text{O}_2\text{H}$) <88JCS(P1)2813> are good leaving groups when attack by the enolate of a 3-acylamino substituent occurs (Equation (53)) to give the oxadiazabicycloheptenone (**116**). When a *t*-butyldisulfide substituent is present and an enol is trapped as a methanesulfonate, treatment with sodium selenide yields a 2-selenacephem (Equation (54)) <86TL3041>.



Sulfur dichloride can act as a sulfur transfer agent and a cycloaddition reaction may occur when both substituents on the β -lactam are unsaturated (Equation (55)) <90TL3627>. Bicyclic systems with a bridgehead nitrogen atom have been obtained in a similar way from 1,4-disubstituted β -lactams <91H(32)659>.

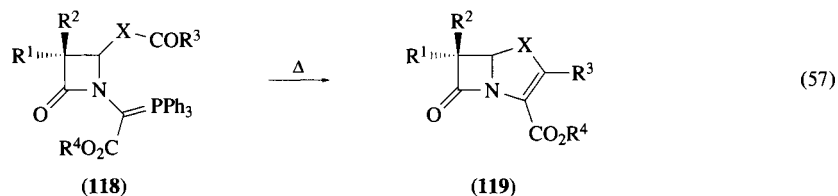


Palladium(0) complexes catalyze the formation of a fused system from certain 1,4-disubstituted β -lactams by ene-halocyclization $\langle 86CC1375 \rangle$, and a Pd(II) complex gives (117) in 50% yield (Equation (56)) $\langle 86JA6053 \rangle$.

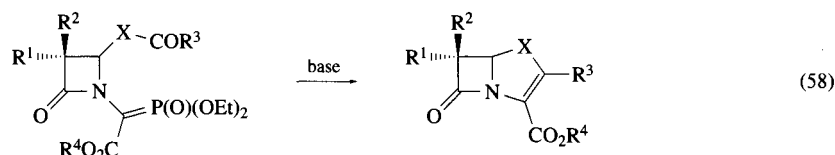


1.21.9.5 By Wittig Reaction

A considerable advantage of this approach is that an alkenic bond is introduced into the second ring at the time of its formation. In addition it is possible to include an ester function to give the 1-carbapenem (119; X = CHR) or 1-oxacephem (119; X = OCHR) system in one cyclization step (Equation (57)) from the readily accessible stabilized phosphoranes. The carbonyl group in the 4-substituent on the β -lactam (118) may be generated by ozonolysis of a suitable alkenic 4-substituent $\langle 82H(19)2099, 85JCS(P1)2219, 85JCS(P1)2235, 89TL3117, 91CPB658 \rangle$. Substituents present in the five-membered ring of carbapen-2-ems produced by the Wittig reaction of a triphenylphosphorane include cyclopropyl, amidoalkyl, halogenoalkyl, hydroxyalkyl, aryl $\langle 83H(20)505, 83T2531, 84TL1639, 85CPB4382, 85H(23)1915, 85TL2765, 87H(25)221, 87H(26)1193, 87JMC871, 88JAN780, 91CPB663, 91JCS(P1)2399, 92JAN940 \rangle$, protected 2-aminoethyl $\langle 86BCJ1363 \rangle$, and heteroarylthiomethyl $\langle 89CPB2338, 92CPB2410 \rangle$. Similarly 1-oxaceph-3-ems have been prepared with various substituents in the six-membered ring $\langle 89JAN1124, 90H(30)567, 90H(31)797 \rangle$.



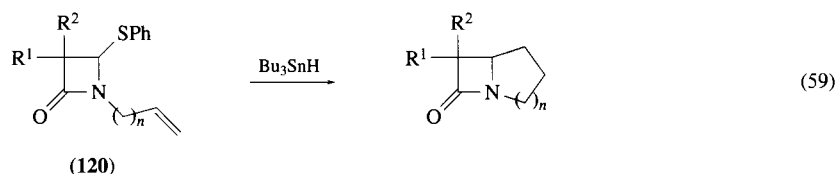
In a similar way, using the appropriate 1,4-disubstituted azetidin-2-ones it has been possible to obtain derivatives of 1-carbapen-1-em $\langle 82JCS(P1)2123, 87JCS(P1)2361 \rangle$, 1-carbacephem $\langle 93SL139 \rangle$, 3-azaceph-2-em $\langle 87LA911 \rangle$, and 1-phosphaceph-3-em $\langle 84TL1737 \rangle$. Sometimes derivatives of the oxyacids of phosphorus have been used in the cyclization step (Horner–Emmons reaction) (e.g., Equation (58)). This approach has been used to obtain derivatives of 1-carbapen-2-em $\langle 83NJC691, 84TL2793, 89H(28)195, 90T8067 \rangle$ and 1-carbaceph-3-em $\langle 83TL3783, 89CPB315, 93JOC618 \rangle$.



1.21.9.6 Radical Cyclization Processes

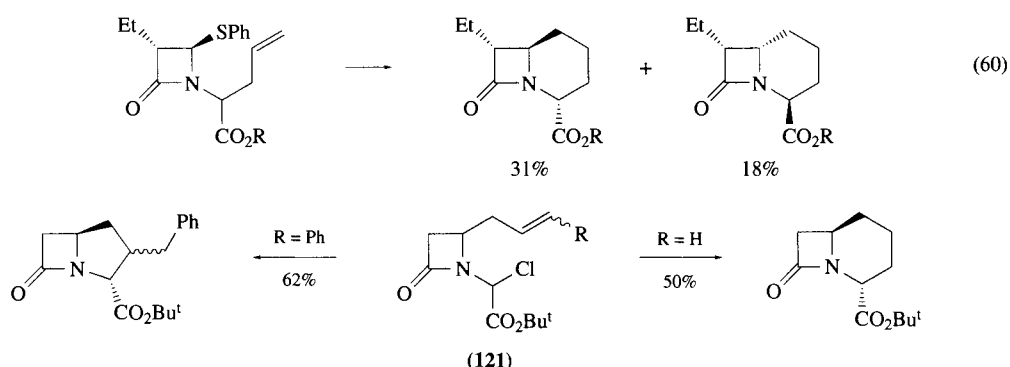
Reviews are available on free-radical routes to bicyclic β -lactams $\langle B-89MI 121-07, B-89MI 121-08 \rangle$.

Azetidinones having a 4-phenylthio substituent and carrying a 1-alkyl chain with a terminal alkenic group (120; $n = 2$) undergo cyclization (Equation (59)) in the presence of tributylstannane and an initiator $\langle 82H(19)1861 \rangle$.



Ring closure by the intramolecular attack of the carbon-centered radical (SH^2 process) does not occur for (120; $n = 1$). A cyclization does occur when the *N*-substituent is *o*-bromophenylmethyl but then the product is a six-membered ring containing sulfur [85TL1761, 88JOC4339]. The approach shown in Equation (59) is applicable to the preparation of carbacephams (Equation (60)) [88H(27)875, 88JOC2683] and to the synthesis of 1-carbacephems if an alkyne replaces the alkene [88H(27)875], or of 1-carbapenamams when suitable substituents are included in the alkyl chain [93AG911].

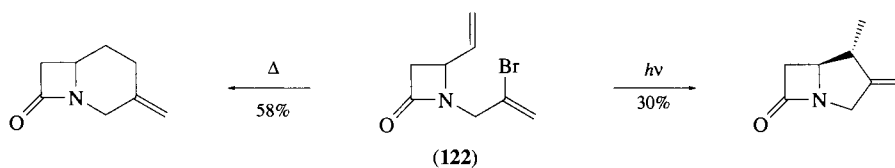
The size of the second ring generated by cyclization of a radical formed at an alkyl halide center on to an alkene depends on the nature of the terminal substituent in (121) (Scheme 8) [87TL2637].



Scheme 8

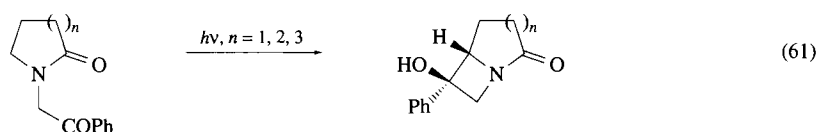
Derivatives of the benzocarbapen-2-em and benzocarbaceph-3-em systems have been obtained from 1-(2-bromophenyl)azetidinones and 1-[2-(bromomethyl)phenyl]azetidinones, respectively [87CJC104].

Cyclization of β -lactams having alkenic substituents at both the 1- and 4-positions, including a vinylic bromine in the 1-substituent (122), give different products in the presence of tributyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) depending on whether thermal or photochemical energy sources are used (Scheme 9) [87JCS(P1)1237]. Useful bicyclic ketones are obtained on ozonolysis of these products.

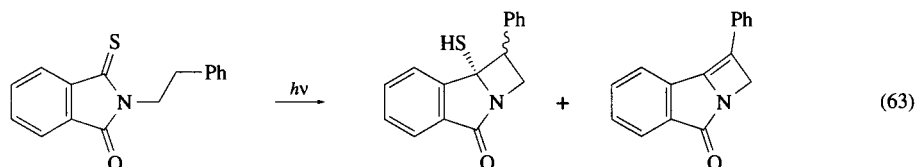
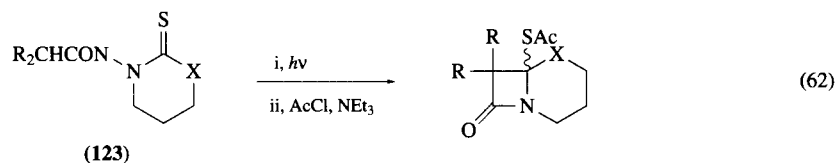


Scheme 9

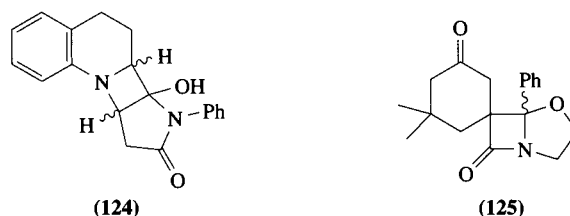
Photocyclization of certain *N*-substituted heterocycles is a means of forming a fused β -lactam system. Thus, *N*-phenacyllactams undergo cyclization in good yield (Equation (61)) [90T7751].



However, the thione group is involved in photocyclizations of *N*-acylthio- (123; $\text{X} = \text{O}$) and *N*-acyldithiocarbamates (123; $\text{X} = \text{S}$) (Equation (62)) [91JCS(P1)2541] and *N*-(2-phenylethyl)thio-phthalimide (Equation (63)) [89CPB642].

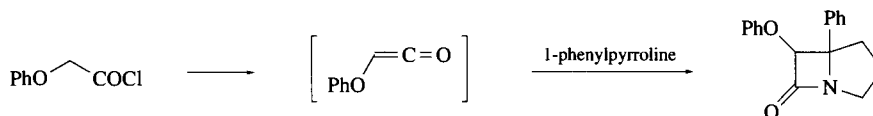


Photochemical cyclizations at the carbonyl group of an imide and at the β -position of an $\alpha\beta$ -unsaturated cyclic ketone have been used to obtain the tetracyclic azetidine (124) <92T6747> and the spiranic oxapenam (125) <92TL1993>.



1.21.9.7 By Cycloaddition Reaction

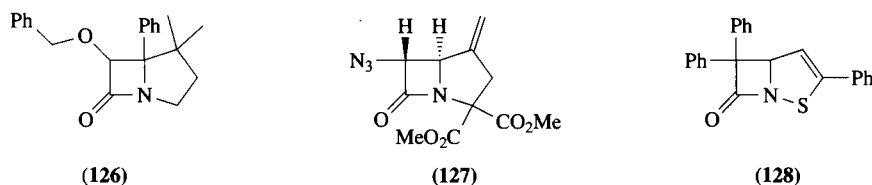
An approach to the bicyclic systems of interest here which provides access to a wide variety of structures is the cycloaddition of a ketene to a cyclic imine (Scheme 10) <88CZ93>. This approach to β -lactams has been reviewed <92BSB541, B-93MI 121-03>.



Scheme 10

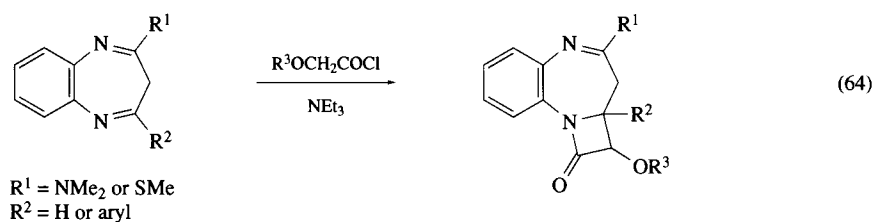
Usually the ketene, which is not isolated, is generated by the action of an organic base on an acid chloride. Sometimes mixed anhydrides formed from the acetic acid and either *p*-toluenesulfonyl chloride <83S833> or phenyl *N*-methyl-*N*-phenylphosphoramidochloridate have been used <84S846>. An alternative is the use of *N*-acyl derivatives of saccharin <84SC353>; for some applications, the potassium salt of *N*-[1-methyl-2-(methoxycarbonyl)vinyl]glycine (Dane salt) is useful <88AP(321)349>. In essence, the method is limited only by the availability of the cyclic imines.

Carbapenams (126) <88AP(321)521> and (127) <82CJC2903> have been prepared from the appropriately substituted pyrrolines. More surprisingly perhaps, isothiazoles undergo an addition reaction with diphenyl ketene to give 3-thiapen-1-em derivatives (128) <85CS239>.

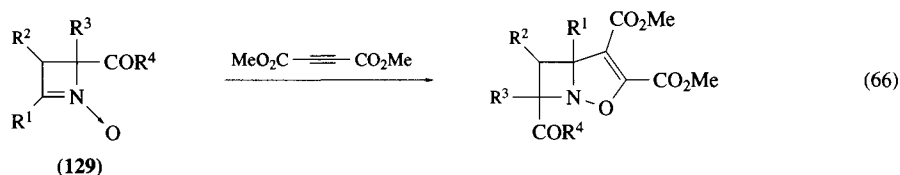
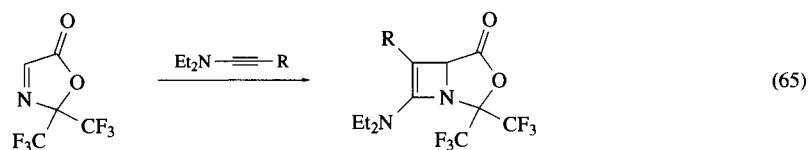


Additions to six-membered rings have been studied for a wider range of imine types including 1,3-oxazines <82IJC(B)1074>. Tricyclic systems have been obtained from 3,4-dihydroisoquinolines <83IJC(B)238, 88IJC(B)494, 93H(35)1075> and 1,3-benzoxazines <89S677, 93H(36)995>, and the stereo-

chemistry of the reactions has been studied. The additions to partially reduced 1,3-thiazines <84IJC(B)857, 85BSB149>, a range of cycloalka[e]-2-phenyl-4*H*-1,3-thiazines <91MRC687>, and isomeric 1,3-benzothiazines <84T4089, 84T4387> have given the expected products. 1-Azacephams are conveniently obtained from partially reduced pyrimidines <84TL1849, 85IJC(B)895, 92BCJ2246> but the presence of a 1-substituent on the pyrimidine is important <92BCJ2246>. Addition of ketene occurs at the double bond not carrying a heteroatom substituent of 1,5-benzodiazepines (Equation (64)) <83JHC161, 89JHC119> and at the imine bond in 1,4-benzodiazepin-2-ones <83ACS(B)75>. Detailed studies have been made of the addition of ketenes to 1-substituted 1*H*-1,2-diazepines <83LA1361, 83LA1374, 83LA1393, 88HCA822, 91HCA767>. Cycloaddition of ketenes to an imine has been used to obtain fused pentacyclic systems <90H(31)1687>.

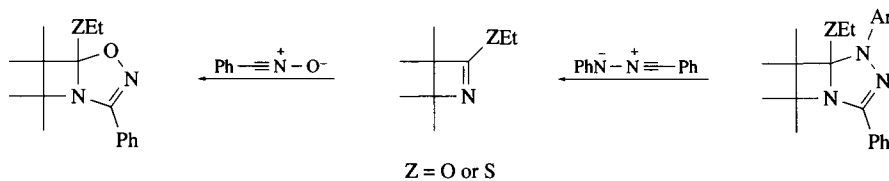


Other species which add to certain activated imines include alkynes. Electron-rich ynamines add to electron-deficient imines to give bicyclic azetines <86CZ422> (Equation (65)) and tricyclic azetines <83JOC1275>. In contrast, the electron-rich cyclic nitron (129) undergoes a 1,3-cycloaddition with dimethyl acetylenedicarboxylate (Equation (66)) <88RTC142>.

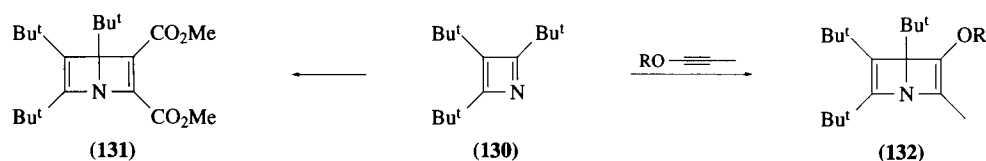


Bicyclic azetidines are also obtained in the 1,3-dipolar cycloaddition reactions of 2-ethoxy- and 2-(ethylthio)-1-azetines with nitrile oxides and diphenylnitrilimines (Scheme 11) <90TL123, 90TL127>.

The kinetically stabilized azete (130) reacts with dimethyl acetylenedicarboxylate <88AG304> and with moderately electron-rich alkynes to give (131) and (132), respectively (Scheme 12) <90CC1456>.

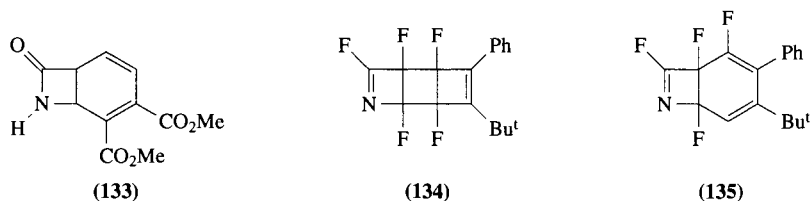


Scheme 11

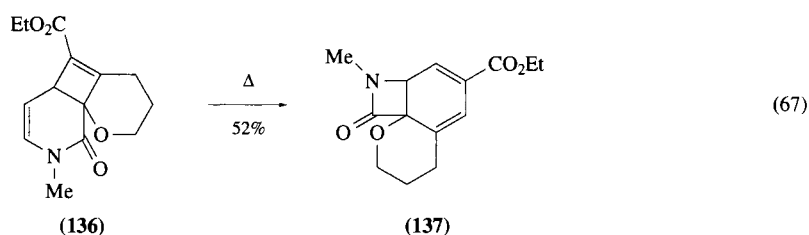


Scheme 12

The [2 + 2] photocycloaddition of dimethyl acetylenedicarboxylate to 2-pyridone is reported to give **(133)** <88JHC731> on thermal rearrangement of the initially formed [2 + 2] cycloaddition product. Reaction of 3,3-dimethyl-1-phenylbutyne and pentafluoropyridine provides the tricyclic **(134)** and the bicyclic azetine **(135)**. A longer reaction time gives 70% yield of **(135)** <89T1755>.

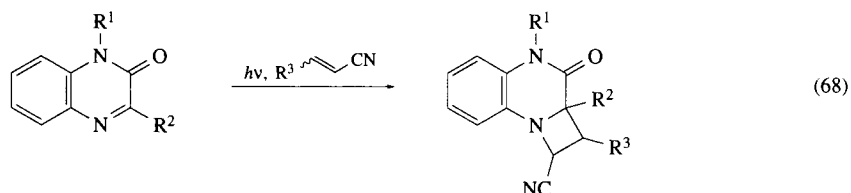


The tricyclic β -lactam **(137)** is obtained on thermal rearrangement of **(136)** (Equation (67)) <91CL2077>.

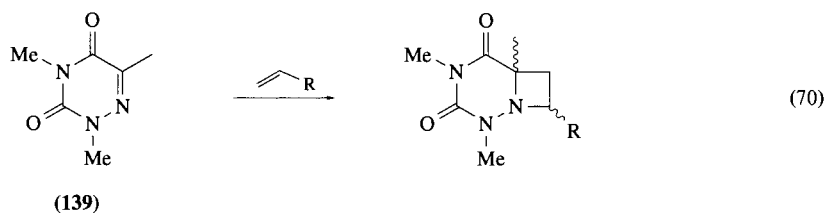
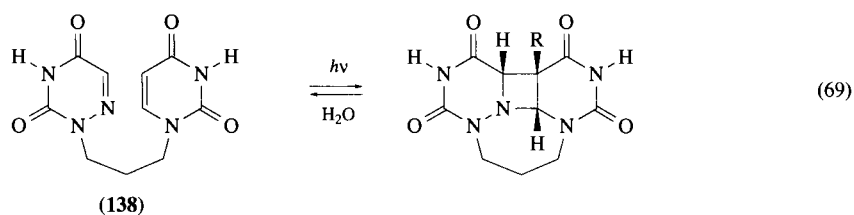


A review of the photocycloadditions to C—N double bonds is available <78TCC65>.

The [2 + 2] photocycloaddition of electron-deficient alkenes to the C—N bond in quinoxalin-2(1*H*)-ones has been studied (Equation (68)) <84JOC827, 86CPB4955, 88LA441, 91HCA225>. Similar reactions occur with 1,4-benzoxazin-2-ones <85JOC1370>.



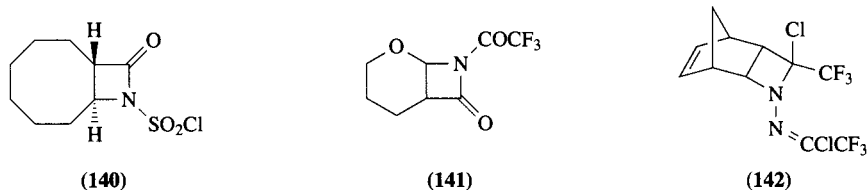
Irradiation of the 6-azapyrimidine–pyrimidine dinucleotide analogue **(138)** caused internal dimerization (Equation (69)) <84H(22)67>. The 6-azapyrimidine **(139)** is closely related to dimethylthymine and readily undergoes addition of alkenes regioselectively (Equation (70)) <86MI 121-02, 87MI 121-03>.



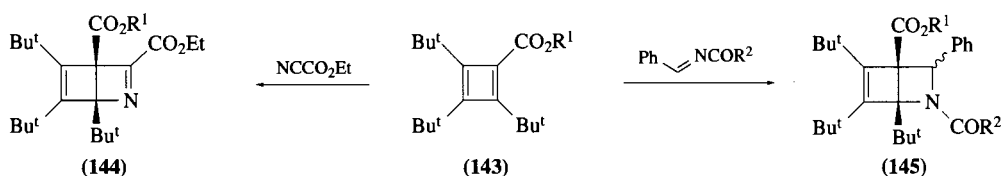
The addition of nitrogen-containing reactants to cyclic alkenes provides another route to the bicyclic systems of interest here. For example, isocyanates react with *trans*-cyclooctene and 2,3-dihydropyran to give the addition products **(140)** <83CB2136> and **(141)**, respectively <83CC299>.

Similar reactions with dihydropyrans derived from naturally occurring monosaccharides yield bicyclic systems with known stereochemistry. Subsequent glycolic cleavage of the *vic* diol gives 3,4-disubstituted monocyclic β -lactams with known configuration $\langle 89T7195 \rangle$. The reaction of chloro-sulfonyl isocyanate with cyclopentadienes $\langle 84H(22)2751 \rangle$ and tetraphenylcyclopentadienone $\langle 84IJC(B)1046 \rangle$ affords bicyclic β -lactams.

A route to fused azetidines by the cycloaddition of reactive alkenes with acyclic unsaturated nitrogen-containing species is demonstrated by the reaction of 2,5-dichloro-1,1,1,6,6,6-hexafluoro-3,4-diazahexa-2,4-diene with quadricyclane to give **(142)** $\langle 93CC9 \rangle$.

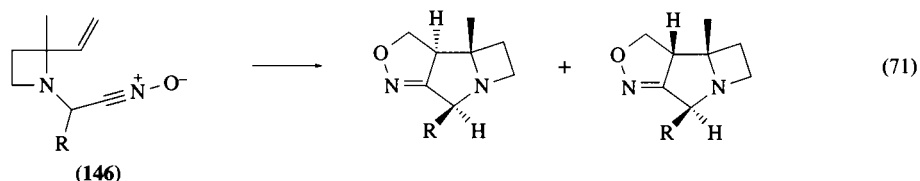


The photoinduced addition of phenyl cyanide to 1,2-dimethylcyclohexene gives a bicyclic azetine $\langle 77JOC4238 \rangle$. Kinetically stabilized cyclobutadienes **(143)** react with certain nitriles and with *N*-acylimines to give the bicyclic azetine **(144)** and azetidine **(145)**, respectively (Scheme 13) $\langle 85TL3315, 86BSF239 \rangle$.

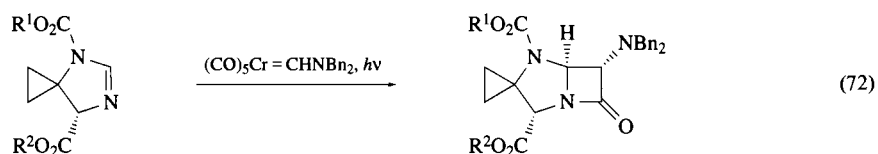


Scheme 13

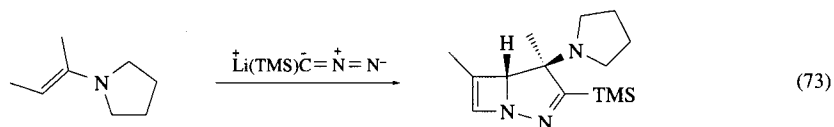
Disubstituted azetidinones or azetidines with a 2-vinyl substituent and a 1,3-dipolar group on the *N*-substituent may undergo an intramolecular 1,3-dipolar cycloaddition to give tricyclic azetidinones $\langle 82TL4381, 87TL97 \rangle$ or azetidines $\langle 87TL683 \rangle$. For example, the nitrile oxide **(146)** undergoes an intramolecular process (Equation (71)) $\langle 87TL4097 \rangle$.



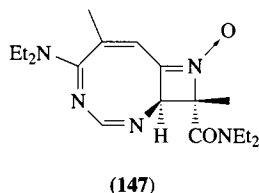
An unusual β -lactam is formed by irradiation of a carbenoid and imidazoline $\langle 93SL57 \rangle$ (Equation (72)), and addition of the Fischer carbene complex $(CO)_5Cr=C(OEt)Me$ to a pyrrolenine is an unusual route to carbapenams $\langle 89T2957 \rangle$. Similarly, 1-oxa-3-azahex-2-ene has yielded a 5-oxa-1-azabicyclo[4.2.0]octan-8-one $\langle 93JOC5918 \rangle$ and imidazolines have afforded 1,4-diazabicyclo[3.2.0]heptan-7-ones in high yields $\langle 92JA5010, 93T5549 \rangle$.



The bicyclic azetine is formed when lithium trimethylsilyldiazomethane undergoes a cycloaddition reaction with β -amino- α,β -unsaturated ketones (Equation (73)) $\langle 93H(35)41 \rangle$.

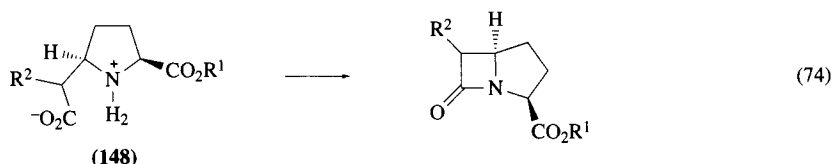


Finally, in this section mention must be made of the cycloaddition of 5-nitropyrimidine with 1-(diethylamino)propyne to yield the bicyclic azetine oxide (**147**) <85JOC270>.

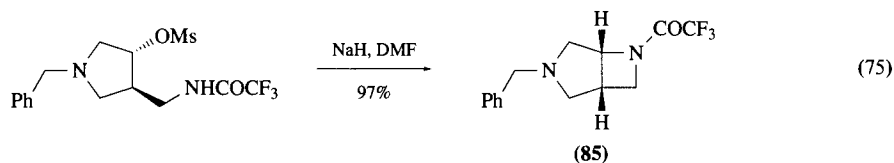


1.21.9.8 From a Five- or Six-membered Ring

The burgeoning interest in the carbapenam and carbapenem antibiotics and the requirement for the development of commercially viable routes makes the accessible 2,5-disubstituted pyrrolidines of interest as starting materials, particularly those containing a 2-alkoxycarbonyl substituent, i.e., compounds related to proline. Compounds of the type (**148**) undergo lactam formation in the presence of a suitable activating reagent (Equation (74)) <83JOC1439>. Dicyclohexylcarbodiimide (dcc) is a useful reagent <86TL4335, 87BCJ2091, 88TL4305, 89CC486, 90TL3209, 92H(33)143>, but 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride has also found favor <83JOC1439> because of its higher solubility in dichloromethane and water.

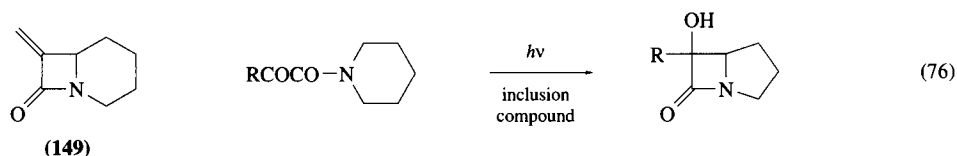


Mukaiyama's reagent (2,2'-dipyridyldisulfide and triphenylphosphine) is also effective in providing penams from pyrrolidines <84CC195, 86H(24)2015, 89CC423>. If the penem is the required target, then the introduction of the phenylselenenyl group (Section 1.21.9.2) followed by an elimination step is useful <87BCJ2091, 88TL4305>, though other approaches are possible <84CC195, 86TL4335>. In addition, the 3,4-disubstituted *N*-protected pyrrolidine yields 3,6-diazabicyclo[3.2.0]heptane (**85**) in an intramolecular cyclization process (Equation (75)) <91TL1565>.

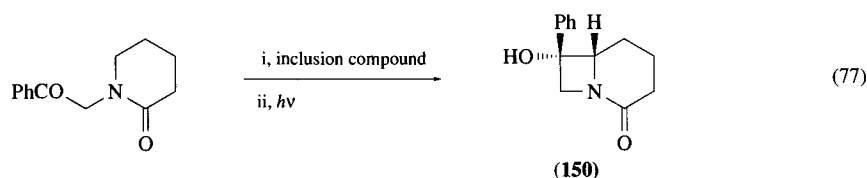


Derivatives of fully reduced or partially reduced azoles can be utilized to give heteroazabicyclo[3.2.0]heptanones, and a review is available <B-85MI 121-07>.

Piperidine derivatives are sources of 1-azabicyclo[4.2.0]octane derivatives. Palladium-catalyzed carbonylation <88T5615> of 2-(1-bromovinyl)piperidine gives a good yield of (**149**) <89H(29)853>, and photochemical cyclization of α -oxoamides as inclusion complexes with desoxycholic acid and other host molecules allows some stereocontrol in the cyclization (Equation (76)) <83CC333, 87T1495, 90MCLC167>.



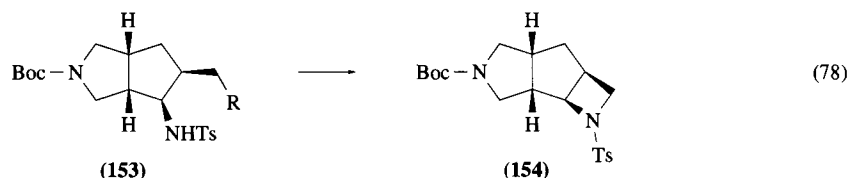
The azetidine (**150**) is obtained in high optical purity by irradiation of a suspension in water of a powdered inclusion compound with an optically active host (Equation (77)) <93JOC3783>.



Photocyclization of 2-(*N*-substituted methylamino)cyclohexanones gives (**151**) <83JCS(P1)573>, and lactam formation from 4-aminocyclohexene-5-carboxylic acid yields (**152**) <85TL5831>.



The tricyclic system (**154**) is formed from (**153**) by the action of lithium triethyl borohydride (Equation (78)) <93T5047>.



1.21.9.9 Biosynthesis

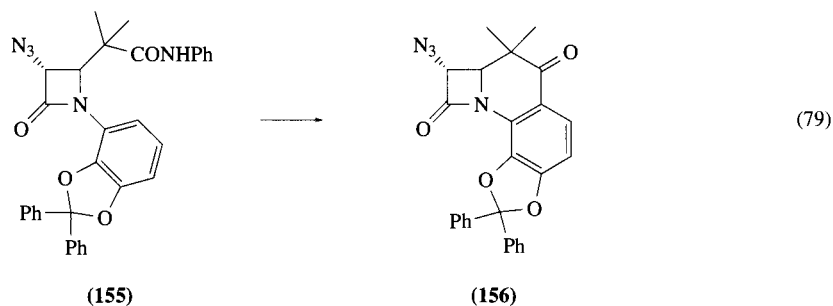
Some penicillins are now readily available as inexpensive chemicals and the fused bicyclic nucleus is obtained by biosynthetic processes (see Chapter 1.20). The biogenetically related cephalosporins are some of the most widely used antibiotics. When the chemistry of the penicillins was first investigated, the quantity of the antibiotic available was very small, but benzylpenicillin became more available through the development of deep-culture techniques and biosynthesis, and through other improvements. The isolation of novel β -lactam antibiotics from fermentation processes has played a major part in the developments of the field in the recent past. This effect has been a source of inspiration to chemists through the recognition of novel ring systems and substituents which produce useful biological effects rather than as a manufacturing and commercial route to new drugs. The yields of the newer antibiotics from fermentation sources are generally, but not always, low.

Some milestones in the discovery of the newer, naturally occurring β -lactam antibiotics include the discovery and determination of the structure of the 1-oxapenam, clavulanic acid (**18**) <76CC266, 76JAN668, 84JCS(P1)635, 87CC86>, the carbapenam, thienamycin (**15**) <79JAN1>, and the epithienamycins (olivanic acids) <77CC523, 77CC953, 77JAN770, 79JAN961, 81JAN628, 81JAN637, 82JAN1394>. More than 50 naturally occurring carbapenems are known.

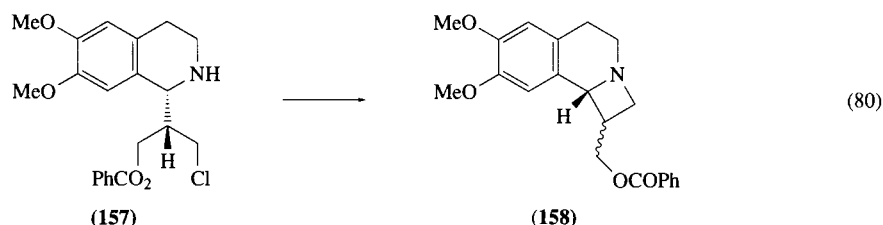
Much effort has gone into revealing the biosynthetic route (biogenesis) to bicyclic β -lactams. Reviews of biogenesis include a wide-ranging coverage of β -lactams <B-92MI 121-08>, and others on the more limited themes of clavulanic acid (**18**) <B-89MI 121-09> and selected carbapenems <B-85MI 121-08, B-89MI 121-10>.

1.21.9.10 Miscellaneous Methods

Tri- and tetracyclic systems containing a β -lactam system have been obtained by use of a modified Bischler–Napieralski synthesis of isoquinolines. The 1,4-disubstituted β -lactam (**155**) is converted to the tetracyclic (**156**) by this route (Equation (79)) <83JCS(P1)1925>.



An alternative route is by cyclization of a 1-substituted 1,2,3,4-tetrahydroisoquinoline derivative <86T5139, 87T1887>. Thus, the tetrahydroisoquinoline (**157**) yields (**158**) (Equation (80)) <86T5139>.

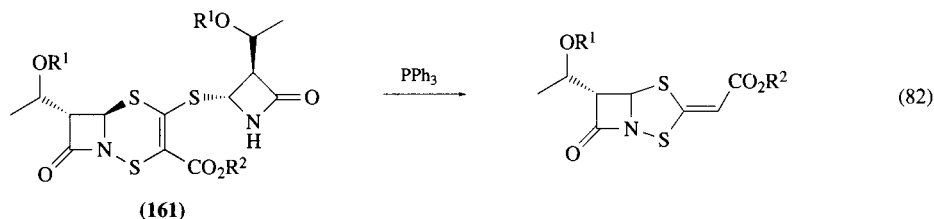
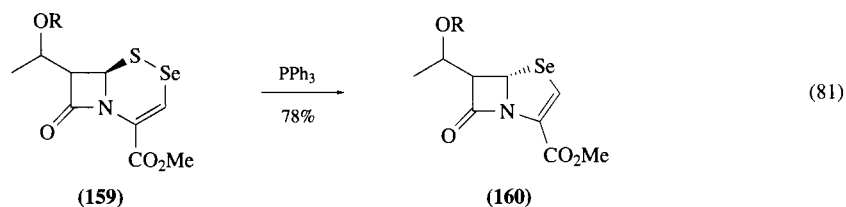


An apparently simple route to carbapenams is the base-promoted addition–cyclization of 4-iodomethyl β -lactams with a Michael acceptor. However, yields are generally low when an alkene is activated by an ester group and a difficulty is to obtain sufficient reactivity in the alkene without making it susceptible to polymerization. Allenes generated *in situ* have been used <85TL4315> and elaboration of the products has produced 1-carbapen-1-ems.

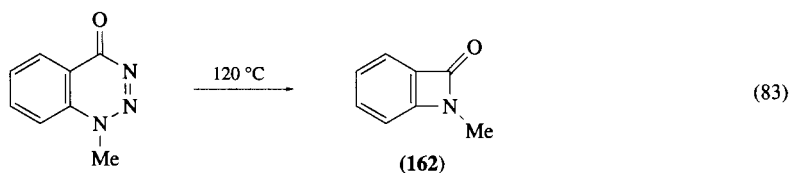
1.21.10 RING SYNTHESSES BY TRANSFORMATION OF ANOTHER RING

1.21.10.1 Ring Contraction Reactions

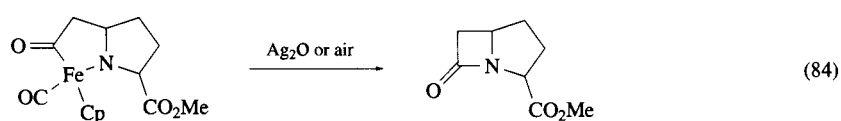
The removal of a sulfur atom from a bicyclic β -lactam by the action of triphenylphosphine produces a ring contraction. Thus, 2-selenocephem (**159**) yields the 1-selenocarbapenem (**160**) (Equation (81)) <86TL3041> and (**161**) gives the 1-aza-2,4-dithiabicyclo[3.2.0]heptanone (Equation (82)) <91TL3771>.



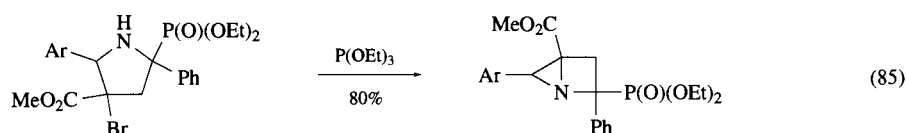
Thermolysis of 1-methyl-1,2,3-benzotriazin-4(1*H*)-one yields 1-methylbenzoazetinone (**162**) (Equation (83)) <89CC1777>.



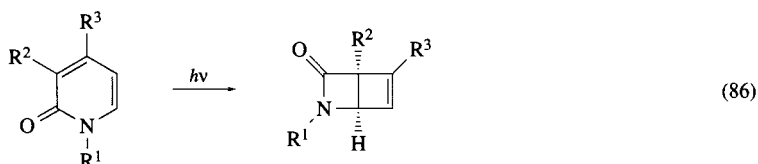
Ring opening followed by cyclization has been used to obtain a four-membered ring. Tricyclic isoazolum salts <84JOC2652> and pyrrolenines <84JCB1184> have yielded fused β -lactam and azetidine derivatives, respectively. Organoiron derivatives of substituted pyrrolidine yield 1-carbapenam on oxidation (Equation (84)) <83JOC158>.



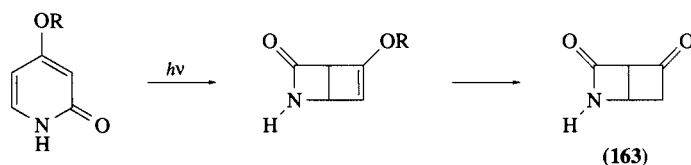
Derivatives of 1-azabicyclo[2.1.0]pentane have been obtained (Equation (85)) <93ZOB1906>.



The photocyclization of 2(1*H*)-pyridones is a useful route to 2-azabicyclo[2.2.0]hex-5-en-3-ones (Dewar pyridones) (Equation (86)) <B-85MI 121-09, 87H(26)1611, 90CPB2911, 92JOC5708, 93CPB1885>. Similarly 2-azabicyclo[2.2.0]hex-5-enes can be obtained from pyridines <85CPB4572>.

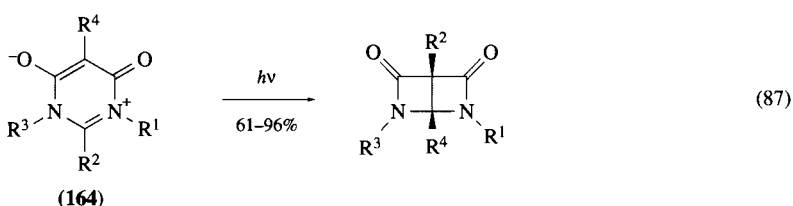


The use of 4-alkoxy- or 4-(trialkylsilyloxy)-2-pyridones in a similar way provides 5-alkoxy- or 5-(trialkylsilyloxy)-2-azabicyclo[2.2.0]hexan-3-ones <84TL5665, 85CC189, 86TL6091, 86JCS(P1)1289> from which the ketone (**163**) can be obtained (Scheme 14) <85CC189, 86JCS(P1)1289>.

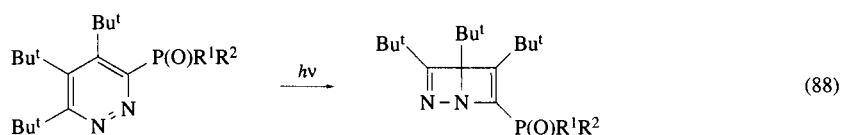


Scheme 14

Photochemical intramolecular cyclization of 4-pyrimidones occurs at low temperature to give 2,6-diazabicyclo[2.2.0]hex-2-en-5-ones <83JOC2914, 85JOC166>, and photolysis of pyrimidiniumolates (**164**) yields bis(β -lactams) (Equation (87)) <86CC687>.

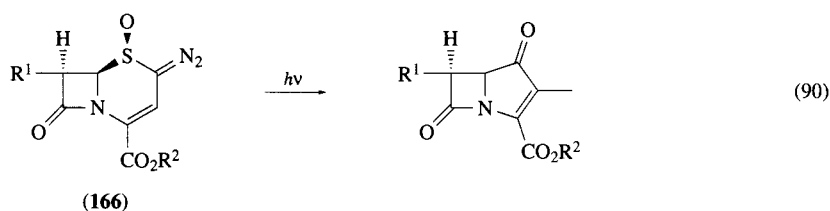
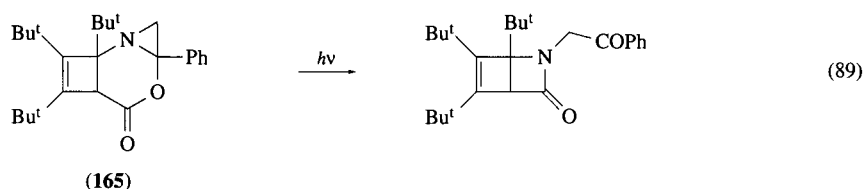


Photochemical formation of a derivative of 1,2-diazabicyclo[2.2.0]hex-2,5-diene (Dewar pyridazine) is achieved by irradiation of a highly substituted pyridazine (Equation (88)) <84CB445>.

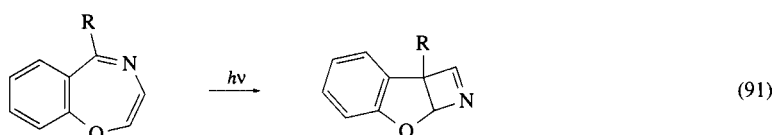


Photochemical isomerization of pentasubstituted 4*H*-1,2-diazepines leads to 2,6-diazabicyclo[3.2.0]hepta-2,6-dienes as intermediates on the way to 6*H*-1,4-diazepines <84TL5627>. Photochemical ring contraction reactions giving 2-azabicyclo[3.2.0]heptanes and 1,2-diazabicyclo[3.2.0]heptanes from dihydroazepines and dihydrodiazepines, respectively, are known <71JOC1934>.

A miscellaneous group of photochemical ring contractions leading to bicyclic systems having the β -lactam or azetidine rings includes the photolysis of the δ -lactone (**165**) to yield a β -lactam (Equation (89)) <90CB927> and the photo-Wolff rearrangement of the diazo derivative of cephalosporin *S*-oxide (**166**) to give the 1-oxo-1-carbapenem (Equation (90)) <90JMC291>.

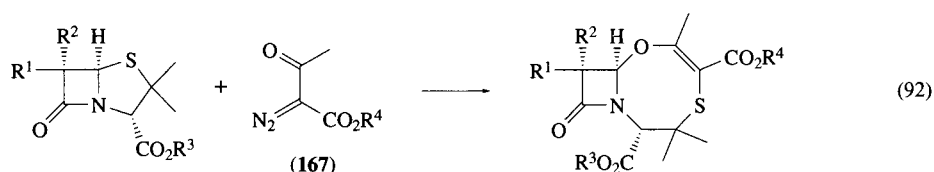


Photoisomerization of 1,4-benzooxazepines yields thermally unstable dihydrobenzofuroazetes (Equation (91)) <90LA917>.

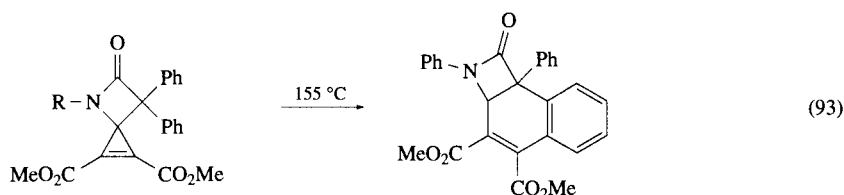


1.21.10.2 Ring Expansion Reactions

One example has been mentioned earlier in the formation of a tricyclic dimer (Equation (20)) <91CB1661>. Diazoacetoacetates (**167**) undergo an insertion reaction with penams in the presence of rhodium acetate to give a bicyclic system containing an eight-membered ring (Equation (92)) <83TL221>. Members of the same family of compounds are obtained by treating penams with iodonium ylides <90SL153>.



Spiro-fused β -lactam cyclopropenes undergo isomerization at 155°C to give naphthoazetidinones, presumably via a vinylcarbene intermediate (Equation (93)) <92CJC2967>.



1.21.11 SYNTHESIS OF AZETIDINES, AZETINES, AND AZETES FUSED TO OTHER RINGS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

No fused-ring systems containing the azete nucleus have been found.

Tables giving references to the preparations of selected compounds and to single-crystal x-ray data are given.

1.21.11.1 Compounds Having a Bridgehead Nitrogen Atom

1.21.11.1.1 No additional heteroatom

See Table 1 for examples.

(i) 1-Azabicyclo[2.1.0]pentane derivatives

The few examples known have been obtained by intramolecular bond formation in 1-unsubstituted 3-bromopyrrolidines (see Table 1).

(ii) 1-Azabicyclo[2.2.0]hexane and unsaturated derivatives

Molecules containing two fused azetine nuclei are obtained by addition of alkynes to kinetically stabilized tri-*t*-butylazete (Scheme 12) <88AG304, 90CC1456>. The initially formed products undergo reactions to give other azetine derivatives (see Table 1). The usual approach to bicyclic systems containing the azetine nucleus is by photochemical isomerization of pyridazines (Equation (88)) and pyrimidinones <80JCS(P1)607>.

(iii) 1-Azabicyclo[3.2.0]heptanes and 1-azabicyclo[3.2.0]heptene derivatives

Much effort has gone into the development of routes to these ring systems because of the interest generated by the discovery of naturally occurring antibiotics having the 1-azabicyclo[3.2.0]hept-2-en-7-one nucleus (1-carbapen-2-ams). Strategies for the synthesis of bicyclic and tetracyclic β -lactams have been reviewed <B-93MI 121-06, B-93MI 121-07>.

A wide variety of routes has been used to obtain 1-carbapenams. Methods which start from a five-membered ring include the addition of ketenes to 1-pyrrolines (Section 1.21.9.7) and lactam formation from a 2-(2-pyrrolidinyl)acetic acid (Section 1.21.9.8). For simple derivatives of the 1-carbapenam nucleus these are probably the best routes.

More heavily substituted 1-carbapenams are usually obtained from appropriately substituted β -lactams. Cyclization of 4-substituted β -lactams to yield a fused bicyclic system occurs when the lactam nitrogen atom acts as a nucleophile to replace a good leaving group in the 4-substituent (Section 1.21.9.2). Alternatively, a carbene center may be generated at the 3-position of the 4-alkyl substituent on the β -lactam so that an insertion reaction yields the carbapenam (Section 1.21.9.3). This is particularly convenient when 3-substituted 1-carbapenam-2-ones are required, usually as intermediates in the preparation of 1-carbapenems. Homolytic cyclizations of 1,4-disubstituted

Table 1 Selected compounds and references related to Section 1.21.11.1.1.

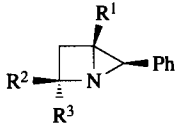
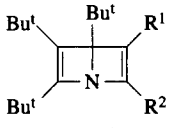
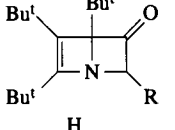
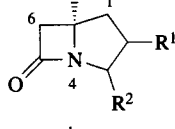
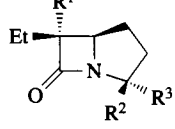
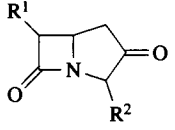
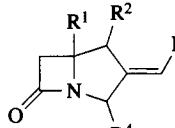
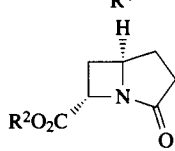
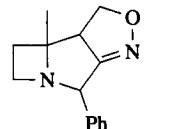
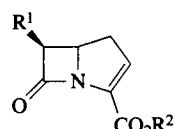
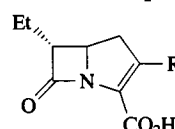
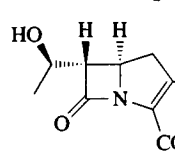
Ring system	Substituents	Ref.
	$R^1 = R^2 = \text{CO}_2\text{Me}$, $R^3 = \text{Me}$	85T2707 ^a , 83AX(C)497 ^b
	$R^1 = R^2 = \text{CO}_2\text{Me}$ $R^1 = R^2 = \text{CN}$ $R^1 = \text{H}$, $R^2 = \text{OCOPh}$ $R^1 = \text{OCOPh}$, $R^2 = \text{H}$	88AG304 ^a 89T3115 ^a 90CC1456 ^a 90CC1456 ^a
	$R = \text{Ph}$ or Bu^t	91CB1661 ^a
	$R^1 = \text{H}$, $R^2 = \beta\text{-CO}_2\text{H}$ $R^1 = \text{H}$, $R^2 = \alpha\text{-CO}_2\text{H}$ $R^1 = \text{H}$, $R^2 = \alpha\text{-CH}_2\text{SPh}$ $R^1 = \text{H}$, $R^2 = \text{CO}_2\text{Me}$	89CC423 ^a 86H(24)2015 ^a 83JA7345 ^a 83JOC158 ^a
	$R^1 = R^3 = \text{H}$, $R^2 = \text{CO}_2\text{PNB}$ $R^1 = \text{CN}$, $R^2 = \text{CO}_2\text{Me}$, $R^3 = \text{SPh}$ $R^1 = \text{H}$, $R^2 = \text{SPh}$, $R^3 = \text{CO}_2\text{Me}$	83JOC1439 ^a 93MI 121-03 ^{a,b} 93MI 121-03 ^{a,b}
	$R^1 = \alpha\text{-Et}$, $R^2 = \text{CO}_2\text{PNB}$ $R^1 = \alpha\text{-CH(OH)Me}$, $R^2 = \alpha\text{-CO}_2\text{PNB}$ $R^1 = \text{H}$, $R^2 = \alpha\text{-CO}_2\text{Me}$	87CL2187 ^a , 88JOC692 ^a 83TL3251 ^a 91JOC2688 ^a
	$R^1 = \alpha\text{-H}$, $R^2 = \text{H}$, $R^3 = \text{Ph}$, $R^4 = \alpha\text{-CO}_2\text{Bu}^t$ $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3 = R^4 = \text{H}$ $R^1 = \alpha\text{-Me}$, $R^2 = \text{Me}$, $R^3 = R^4 = \text{H}$	87TL2887 ^a 87JCS(P1)1237 ^a 87JCS(P1)1237 ^a
	$R^1 = \text{H}$, $R^2 = \text{Bu}^t$ $R^1 = \beta\text{-NHCOCH}_2\text{OPh}$, $R^2 = \text{Bu}^t$	85CC194 ^{a,b} 86T4879 ^a 85CC194 ^{a,b}
		87TL683 ^a
	$R^1 = \text{H}$, $R^2 = \text{Li}$ $R^1 = \text{H}$, $R^2 = \text{CH}_2\text{C}_6\text{H}_4\text{NO}_2\text{-4}$ $R^1 = \text{H}$, $R^2 = \text{Me}$ $R^1 = \text{CH(OH)Me}$, $R^2 = \text{Bn}$	81JCS(P1)3242 ^a 84CC195 ^a 88CC544 ^a 85JCS(P1)2219 ^{a,b}
	$R = \text{SCH}_2\text{CH}_2\text{NHAc}$ (PS-5)	82TL3105 ^a , 86JA6054 ^a 89CC486 ^a , 91TL3105 ^a
	$R = \text{NH}_3^+$ (thienamycin) $R = \text{NHCH=NH}_2^+$ (imipenem)	80JA6161 ^a 80TL2783 ^a B-81MI 121-02 ^a 79JMC1435 ^a 89JOC653 ^b

Table 1 continued

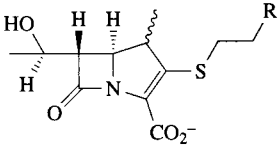
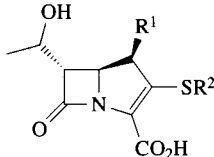
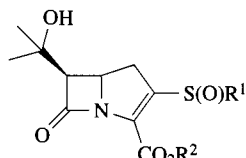
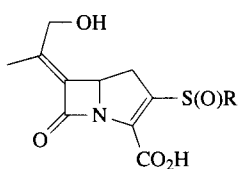
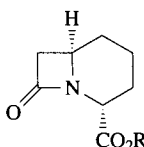
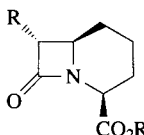
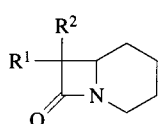
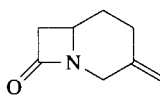
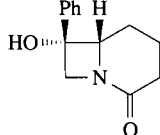
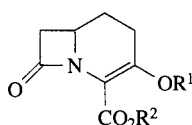
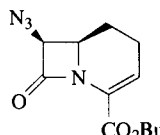
Ring system	Substituents	Ref.
	R = NH ₃ ⁺ (1-methylthienamycin)	85TL587 ^{a,b}
	R ¹ = Me, R ² = 2-pyrimidyl	89CC821 ^{a,b}
	R ¹ = CH=CHNHAc, R ² = H (carpetimycin A) R ¹ = CH=CHNHAc, R ² = CH ₂ C ₆ H ₄ Br-4	83JA1659 ^a 83T75 ^{a,b}
	R = CH=CHNHAc (asparenomyacin C)	83JA7186 ^a
	R = Me R = Bu ^t	82H(19)1861 ^a 87TL2637 ^a
	R = Et	88H(27)875 ^a
	R ¹ = R ² = Me R ¹ = OH, R ² = Ph R ¹ , R ² = CH ₂	85TL1761 ^a 90MCLC167 ^a 89H(29)853 ^a
		86CC78 ^a
		93JOC3783 ^a
	R ¹ = R ² = H R ¹ = H, R ² = Me R ¹ = Ts, R ² = Bu ^t	90H(30)863 ^a 91S743 ^a 84TL3743 ^a
		89CPB315 ^a

Table 1 continued

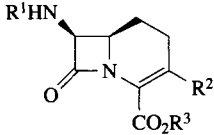
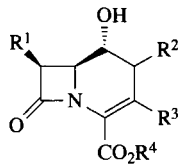
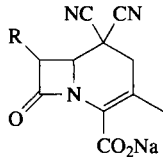
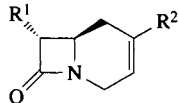
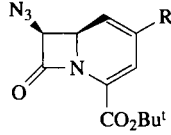
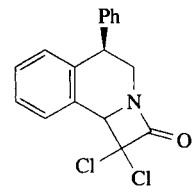
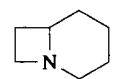
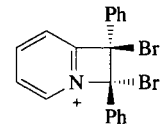
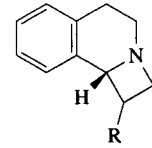
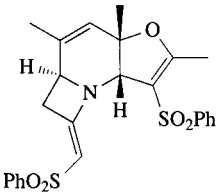
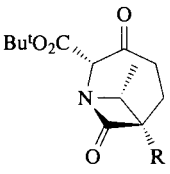
Ring system	Substituents	Ref.
	$R^1 = \text{H}, R^2 = \text{Cl}, R^3 = \text{PNB}$ $R^1 = \text{H}, R^2 = \text{Cl}, R^3 = \text{H}$ $R^1 = \text{PhCH}(\text{NH}_2)\text{CO}, R^2 = \text{Cl}, R^3 = \text{H}$ (loracarbef or carbacefator) $R^1 = \text{PhCO}, R^2 = \text{H}, R^3 = \text{Bu}^t$ $R^1 = \text{PhOCH}_2\text{CO}, R^2 = \text{OSO}_2\text{CF}_3, R^3 = \text{CH}_2\text{CH}=\text{CH}_2$ $R^1 = \text{PhOCH}_2\text{CO}, R^2 = \text{CH}=\text{CH}_2, R^3 = \text{PNB}$ $R^1 = \text{PhOCH}_2\text{CO}, R^2 = \text{SCH}_2\text{CH}_2\text{NH}_2, R^3 = \text{H}$	92TL4283 ^a 89CPB1239 ^a 92TL4283 ^a 93JOC618 ^a 93JMC1971 ^a 89JAN1653 ^a 85TL3787 ^a
	$R^1 = \text{N}_3, R^2 = \beta\text{-OH}, R^3 = \text{H}, R^4 = \text{Bu}^t$ $R^1 = \text{PhOCH}_2\text{CONH}, R^2 = \text{H}, R^3 = \text{Me}, R^4 = \text{Na}$	89CPB2298 ^a 83TL3783 ^a
	$R = \text{PhOCH}_2\text{CONH}$	92TL6103 ^a
	$R^1 = \text{CH}(\text{OSiMe}_2\text{Bu}^t)\text{Me}, R^2 = \text{O-TMS}$	85TL6309 ^a
	$R = \text{H}$ $R = \text{Br}$	89CPB275 ^a 89CPB2298 ^a
		93H(35)1075 ^{a,b}
		60JA2609 ^a
		83JCS(P2)403 ^{a,b}
	$R = \text{CH}_2\text{OH}$ $R = \text{OCOPh}$ $R = \text{Bn}$	86T5139 ^{a,b} 86T5139 ^a 87T1887 ^a

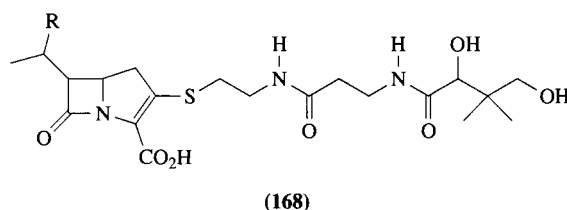
Table 1 continued

Ring system	Substituents	Ref.
		92H(33)179 ^{a,b}
	R = H R = Me R = 2-(1,6-dibromonaphthoxy)ethyl	86JA6431 ^a 89JA1073 ^a 89JA1073 ^{a,b}

^aSynthesis. ^bCrystal structure.

β -lactams by photochemical or chemical methods are useful in the formation of bi- and tricyclic systems (Section 1.21.9.6) (see Table 1).

Judged by the number of publications, by far the most intensively investigated group of compounds of concern in this chapter are the 1-carbapenems. This activity is due largely to the discovery of thienamycin (**15**) and the olivanic acid series of antibiotics followed by the isolation of other naturally occurring carbapenems. Several aspects of carbapenem chemistry have been reviewed. These include a survey of the types of carbapenem antibiotics and methods for enantioselective synthesis <87H(25)729>, discussions of the synthesis and antibacterial activity of asparenomycins <B-85MI 121-10>, 1-substituted carbapenems <B-89MI 121-11>, advances in the synthesis of PS-5 and PS-6 carbapenems and related compounds <B-90MI 121-02>, a review of the OA-6129 group of carbapenems (**168**) <B-85MI 121-08>, and an account of some novel synthetic tetracyclic carbapenems <B-93MI 121-07>. Aspects of the biosynthesis of carbapenems are mentioned in <B-85MI 121-08, B-92MI 121-08>. A description of strategies for the synthesis of bicyclic β -lactams encompasses routes to carbapenems <B-93MI 121-06>.



The two most widely used approaches to carbapenems are from 4-substituted β -lactams by ring closure at *N*-1 (Section 1.21.9.2) or from 1,4-disubstituted β -lactams (Section 1.21.9.4). When a carbapenem is the target, the first method suffers from the potential disadvantage that the initial product is a carbapenam which then has to be modified to yield the unsaturated and suitably substituted derivative. However, the 4-substituents on the β -lactams are generally readily produced, ring closure is efficient (often by the carbene route, Section 1.21.9.3), and modification procedures to introduce the unsaturation and substituents are known (Section 1.21.7.2) and have been reviewed <B-93MI 121-04>. Sometimes the cyclization and elaboration procedures can be carried out in a one-pot process <84H(21)29>.

The second approach, from 1,4-disubstituted β -lactams, has the obvious disadvantage that two different substituents have to be introduced. Efficient cyclization is usually achieved through use of the Wittig reaction or a similar process (Section 1.21.9.5) and has the advantage of introducing the alkenic function at the same time. Two suitable substituents allow other cyclization procedures such as reductive coupling of carbonyl groups in the presence of triethylphosphite (Section 1.21.9.4), and applications of the Michael reaction and the Dieckmann condensation (Section 1.21.9.4). The last two procedures give carbapenams.

A third approach is from a suitably substituted pyrrolidine (Section 1.21.9.8) (see Table 1).

(iv) 1-Azabicyclo[4.2.0]octanes

This too is an area of intense interest and development because of the structural relationship of the 1-azabicyclo[4.2.0]octane (1-carbacepham) and 1-azabicyclo[4.2.0]octene (1-carbacephem) nuclei with compounds of known antibiotic activity. Synthetic routes to carbacephems and their structure-activity relationships have been reviewed <B-92MI 121-09>.

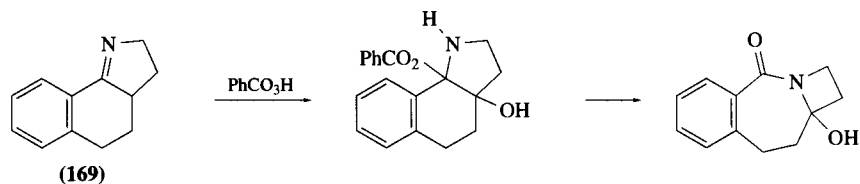
The most popular routes to 1-carbacephams include homolytic cyclization of 1,4-disubstituted β -lactams (Section 1.21.9.6) caused by irradiation or chemical agents, and the cycloaddition of a ketene to a six-membered cyclic imine (Section 1.21.9.7). The last method has been used to obtain bi- and tricyclic systems <88AP(321)349, 93H(35)1075>. Photochemical cyclization of α -oxoamides from piperidine <90MCLC167> and *N*-phenacyl-2(1*H*)-piperidone <93JOC3783>, where the substrates are guest molecules in the crystal lattice of chiral host compounds, is an interesting way of obtaining stereochemical selectivity in the cyclization process.

The Wittig and related reactions provide a useful entry into the 1-carbaceph-3-em series (Section 1.21.9.5) from suitable 1,4-disubstituted β -lactams. Dieckmann-type cyclizations of 1,4-disubstituted β -lactams (Section 1.21.9.4) are also useful because the cyclic β -ketoester exists in the enol form, thus providing the 4-ester function, an alkenic group, and a hydroxy group. The last is readily converted to other substituent groups (Section 1.21.7.2). A similar situation is achieved in a cyclization of an ester of 2-diazo-5-(4-azetidinonyl)-3-oxopentanoate <85TL3787> (Section 1.21.9.3). A detailed consideration of routes to 1-carbacephems is available <B-92MI 121-09>.

Some annelated 1-carbaceph-3-ems have been prepared from substituted azetidinones <83CC431, 83JCS(P1)1925, 87JCS(P1)1899>, as have a group of annelated tri- and tetracyclic 1-carbaceph-1-ems <83IJC(B)238>. Also, tricyclic azetidines have been obtained from 1-substituted 1,2,3,4-tetrahydroisoquinolines <87T1887>.

(v) Seven-membered ring

Oxidation of (169) with perbenzoic acid gives the tricyclic addition product, which undergoes a ring opening and recyclization process to yield the benzazepinone (Scheme 15) <84IJC(B)1184>.



Scheme 15

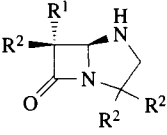
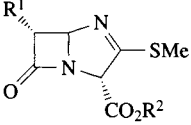
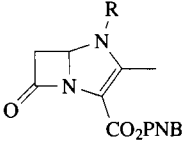
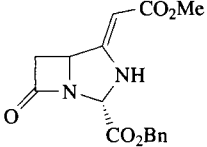
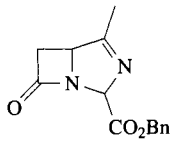
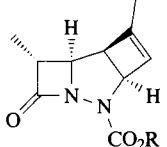
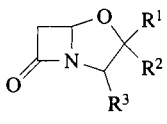
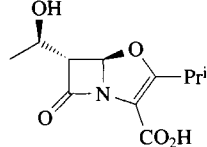
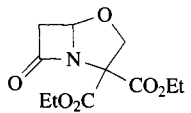
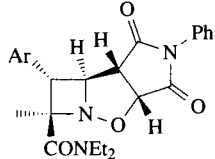
(vi) 1,3-Bridged systems

A small number of β -lactams with 1,3-bridges are known and their chemistry and properties have been reviewed <B-89MI 121-02>. The crucial step in the synthesis is the rhodium(II)-catalyzed carbene insertion into the N—H bond of a 3-substituted β -lactam (Section 1.21.9.3, Equation (45)) <86JA6431, 89JA1073>.

1.21.11.1.2 Compounds having a five-membered ring and additional heteroatoms

Much of the motivation for the chemistry discussed in this section comes from the desire to prepare compounds related to penicillin or clavulanic acid but having other heteroatoms in the five-membered ring. Examples of these ring systems are given in Table 2.

Table 2 Selected compounds and references related to Section 1.21.11.1.2.

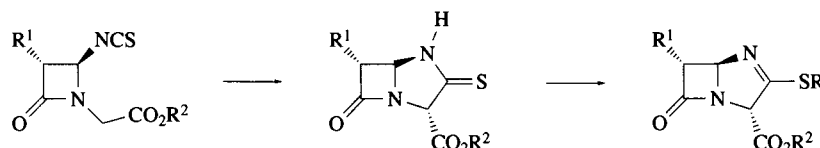
Ring system	Substituents	Ref.
	$R^1 = \text{OMe}, R^2 = \text{Me}$	92JA5010 ^{a,b}
	$R^1 = \text{CH(OH)Me}, R^2 = \text{CH}_2\text{C}_6\text{H}_4\text{NO}_2-4$ $R^1 = \text{H}, R^2 = \text{Me}$	85H(23)3069 ^a 84CC970 ^a
	$R = \text{Ph or Et}$	81CC1269 ^a
		86JCS(P1)1077 ^{a,b}
		81CC946 ^a
	$R = \text{Et or CH}_2\text{CH}_2\text{TMS}$	85H(23)2589 ^a
	$R^1 = \text{CO}_2\text{H}, R^2 = R^3 = \text{H}$ $R^1 = \beta\text{-CH}_2\text{CH}_2\text{OH}, R^2 = R^3 = \text{H}$ $R^1 = R^2 = \text{Me}, R^3 = \text{CO}_2\text{Bn}$ $R^1 = R^2 = \text{Me}, R^3 = \text{COSPh}$	88TL1609 ^a 87T2467 ^a 89JOC992 ^a 85JOC2603 ^a
		90JAN1441 ^a
		86JOC106 ^a
		88RTC142 ^{a,b}

^aSynthesis. ^bCrystal structure.

(i) One nitrogen atom

Examples of 1,4-diazabicyclo[3.2.0]heptane (the 1-azapenam nucleus), 1,3-diazabicyclo[3.2.0]heptane (the 2-azapenam ring), and 1,2-diazabicyclo[3.2.0]heptane (the 3-azapenam system) are known, as are representatives of the corresponding azapenems.

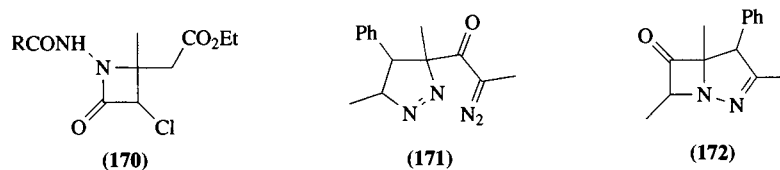
The best route to 1-azapenams appears to be the photolysis of chromium alkoxycarbene complexes with imidazolines <92JA5010, 93SL57> (Section 1.21.9.7, though 1-azapenam-2-thiones have been obtained from 1-alkyl-4-isocyanatoazetidinones (Scheme 16) <84CC970>. Alkylation of the thione yields 2-alkylthio-1-azapenems <85H(23)3069>.



Scheme 16

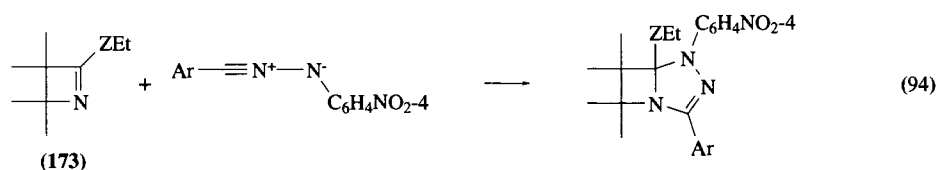
Intramolecular 1,3-dipolar cycloaddition reactions (Section 1.21.9.7) of 1,4-disubstituted β -lactams have been used to obtain 1-alkylidene-2-azapenams <86JCS(P1)1077> and 1-oxo-2-azapenams <82TL2999>. Cycloaddition reactions of highly substituted 1-azetines and nitrile ylides have yielded 1,3-diazabicyclo[3.2.0]hept-2-enes <90TL123>.

The 1,2-diazabicyclo[3.2.0]heptan-3,7-dione (**105**) is reported to be formed from (**170**) <89JIC208>, while a carbene insertion process is used to form the diazabicycloheptenone (**172**) from (**171**) <85JOC2141>.



(ii) Two nitrogen atoms

Certain nitrilimines undergo 1,3-dipolar cycloaddition with ethoxy- (**173**; Z = O) or ethylthio-1-azetines (**173**; Z = S) to yield 1,3,4-triazabicyclo[3.2.0]heptanes (Equation (94)) <90TL127>.



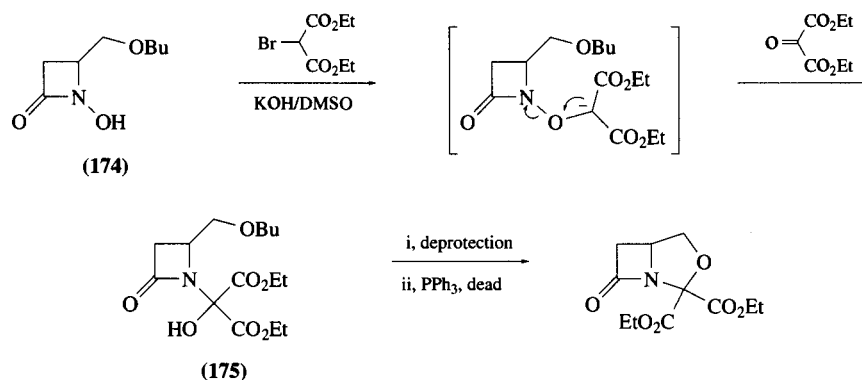
(iii) One oxygen atom

Interest in these ring systems was stimulated by the discovery of clavulanic acid (**18**). The chemistry of clavulanic acid and its derivatives is reviewed <B-85MI 121-02>.

An approach to the synthesis of the 1-oxapenam nucleus is from suitable 4-alkoxyazetidin-2-ones through nucleophilic displacement by the nitrogen atom of a good leaving group in the alkoxy chain. Replacements of bromine <88TL1609> and the methanesulfonyl group <87T2467> have been utilized. Alternatively, nucleophilic addition to an activated terminal alkenic bond in a 4-alkoxy substituent on an azetidinone is a useful way of introducing a 3-carboxylate function into the 1-oxapenam <85JOC2603, 89JOC992>. Photochemical cyclization of *N*-benzyl α,β -unsaturated γ -oxoamides provides a route to 5-phenyl-1-oxapenams with a spiranic substituent at the 6-position <92TL1993>.

Nucleophilic cyclization by attack of an enolate in the 1-substituent on a 3-substituted 4-chloroazetidin-2-one provides routes to 6-alkyl- $\langle 82T2489, 90JAN1441 \rangle$ and 6-alkylidene-1-oxapenems $\langle 92S1099 \rangle$. Oxapenems are obtained in several steps from 3-oxa-6-thia-1-azabicyclo[5.2.0]nonanes $\langle 92S1179 \rangle$.

Preparative routes to 2-oxapenams include cyclization of 4-alkoxymethylazetidinones $\langle 83TL2559 \rangle$ and 1-hydroxymethyl-4-iodomethylazetidinones $\langle 83JCS(P1)649 \rangle$. An interesting development of the latter approach is found in attempts to react diethyl bromomalonate with a 4-substituted 1-hydroxyazetidinone (**174**) with the intention of producing a 1-alkoxyazetidinone. Instead, the alcohol (**175**) forms in a useful yield and deprotection of the alcohol followed by Mitsunobu cyclization yields the 2-oxapenam (Scheme 17) $\langle 86JOC106 \rangle$.



Scheme 17

Cycloaddition reactions of electron-rich ynamines to 2,2-bis(trifluoromethyl)oxazolinone yield 3-oxa-1-azabicyclo[3.2.0]hept-6-en-4-ones $\langle 86CZ422 \rangle$ and the saturated system is represented by the synthesis of 2-*t*-butyl-3-oxa-1-azabicyclo[3.2.0]heptan-4-one $\langle 90LA687 \rangle$.

The 1,3-dipolar cycloaddition of azetine nitrones (**129**) with activated alkynes and alkenes gives 2-oxa-1-azabicyclo[3.2.0]hept-3-enes (Equation (66)) and 2-oxa-1-azabicyclo[3.2.0]heptanes, respectively $\langle 88RTC142 \rangle$. Some stereo- and regioselectivity is observed.

(iv) Two sulfur atoms

The first report of the formation of the 1-aza-2,4-dithiabicyclo[3.2.0]heptane nucleus has been mentioned (Equation (82)) $\langle 91TL3771 \rangle$.

1.21.11.1.3 Compounds having a six-membered ring and additional heteroatoms

Selected compounds are listed in Table 3.

(i) One nitrogen atom

The simplest approach is the annelation of 3,4,5,6-tetrahydropyrimidines by ketenes to give 1,5-diazabicyclo[4.2.0]octanes $\langle 85IJC(B)895 \rangle$ or from 3,4-dihydropyrimidines to give the corresponding bicyclooct-3-enes $\langle 92BCJ2246 \rangle$. Tetracyclic β -lactams have been obtained from 1,2-annelated 1,2-dihydroquinazolines by addition of ketenes $\langle 93IJC(B)517 \rangle$. Irradiation-induced [2 + 2] cycloaddition of alkenes to 1,3-disubstituted quinoxalin-2(1*H*)-ones yields annelated 1,4-diazabicyclo[4.2.0]octan-5-ones $\langle 84JOC827, 88LA441, 91HCA225 \rangle$. Tricyclic derivatives of 1,4-diazabicyclo[4.2.0]octan-8-one are obtained from 4-vinylazetidinones (Section 1.21.9.7) carrying at the 1-position an alkyl chain having a terminal azide group $\langle 82TL4381, 87TL97 \rangle$. Similar methodology can be used to obtain 1,3-diazabicyclo[4.2.0]octan-8-ones $\langle 82TL3003, 83TL1649 \rangle$. This ring system can also be obtained through use of an aza-Wittig reagent $\langle 87LA911 \rangle$. An interesting and efficient reaction of 4-(2-aminoethyl)azetidinones (obtained by reduction of the corresponding azidoethyl compound) with esters

Table 3 Selected compounds and references related to Section 1.21.11.1.3.

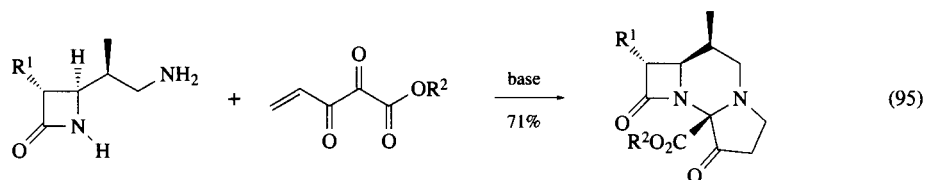
Ring system	Substituents	Ref.
		85JJC(B)895 ^a
	R ¹ = Me, R ² = CN, R ³ = Ph R ¹ = Me, R ² = R ³ = Ph R ¹ = R ² = R ³ = Ph	91HCA225 ^a
	R ¹ = PhOCH ₂ , R ² = Ph, R ³ = Bn R ¹ = PhOCH ₂ , R ² = R ³ = H R ¹ = D-(CH(OH)Ph), R ² = R ³ = H	85JCS(P1)1491 ^a
		92JOC2641 ^{a,b}
		92JCS(P1)3061 ^a
	R ¹ = Me, R ² = Bu	87MI 121-03 ^a
	R = CO ₂ Bu ^t	84CC1289 ^{a,b}
	R ¹ = NHCOPh, R ² = Me, R ³ = OMe, R ⁴ = CO ₂ CHPh ₂	90H(31)791 ^a
	R ¹ = CH(CO ₂ H)C ₆ H ₄ OH-4, R ² = 1-methyltetrazol-5-yl (moxalactam, latamoxef, 6059-S or LY127935)	80TL351 ^a 84JAN227 ^b

Table 3 continued

Ring system	Substituents	Ref.
	$R^1 = \text{SMe}, R^2 = \text{CH}_2\text{CH}=\text{CH}_2$	86TL305 ^a
		91T7117 ^a
	$R^1 = \text{SPh}, R^2 = \text{C}(\text{OH})\text{Me}_2$	83JCS(P1)403 ^{a,b}
		92JCS(P1)1305 ^{a,b}

^aSynthesis. ^bCrystal structure.

of 2,3-dioxopent-4-enoic acid gives a tricyclic β -lactam (Equation (95)) <92JOC2641>. Examples of these ring systems are given in Table 3.



(ii) Two nitrogen atoms

Alkenes undergo cycloaddition with 6-methyl-1,2,4-triazin-3,5(2,4*H*)-diones (6-azathymines) when irradiated (Section 1.21.9.7) to give 1,2,4-triazabicyclo[4.2.0]octan-3,5-diones regioselectively <86MI 121-02, 87MI 121-03>, and ketene similarly adds to 6-trifluoromethyl-1,2,4-triazin-5(2*H*)-ones to give β -lactams <88CPB3354>.

Disubstituted β -lactams (Section 1.21.9.4) are useful starting materials for the synthesis of 2,3-diazaephems <84CC1289, B-85MI 121-07, 89JCS(P1)297> (Table 3).

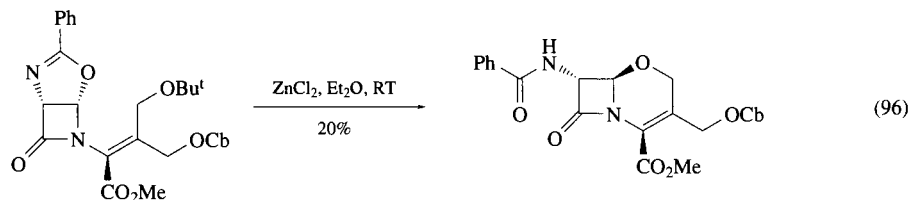
(iii) One oxygen atom

Industrially feasible stereocontrolled synthesis for oxacephems has been reviewed <B-90MI 121-05>.

Favored routes to 1- and 2-oxacephems are from 1,4-disubstituted β -lactams (Section 1.21.9.4), and the route through the Wittig reaction (Section 1.21.9.5) is particularly useful for 1-oxacephems. Enolates from *N*-alkoxycarbonylmethyl substituents produce intramolecular cyclization reactions with suitable 4-substituents on the β -lactam to give 2-oxaceph-3-ems <90JCS(P1)432>.

A useful route to 1-oxacephems is by intramolecular cyclization and ring opening of

oxadiazabicycloheptenones through a suitably sited hydroxy group on an *N*-substituent (Equation (96)) <89T701>.



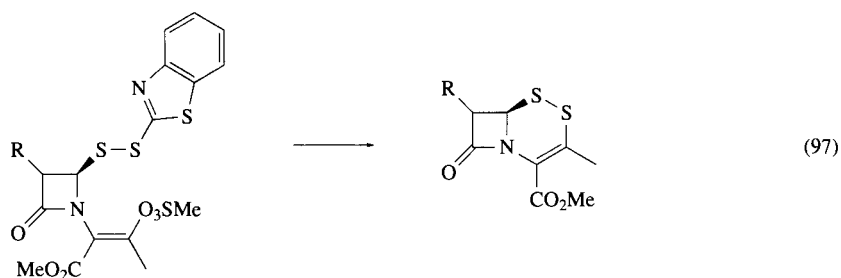
In contrast, 3-oxacephams are usually prepared from 4-(2-hydroxyethyl)azetidinones (Section 1.21.9.2) <91TA255>.

(iv) *One sulfur atom*

These compounds are considered in Chapter 1.20.

(v) *Two sulfur atoms*

Intramolecular cyclization of 4-(heteroaryldithio)-1-substituted β -lactams yields 2-thiacephems (Equation (97)) <83TL1631>.



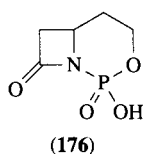
(vi) *One sulfur and one nitrogen atom*

Intramolecular 1,3-dipolar cycloaddition of an azide to an alkene has been utilized (Section 1.21.9.7) <86JCS(P1)1097>.

(vii) *A phosphorus atom or both phosphorus and oxygen atoms*

The Wittig reaction (Section 1.21.9.5) has been used to obtain 1-phosphaceph-3-ems from 1,4-disubstituted β -lactams <84TL1737>. An alternative approach from 4-substituted β -lactams has also been used <84CC200>.

The cyclic derivatives of phosphorus oxyacids (**103**) <82HCA1359> and (**176**) <83CJC1730> are known.

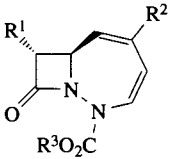
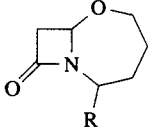
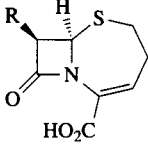
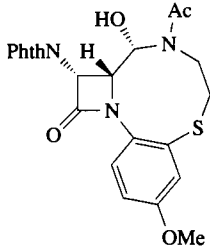


1.21.11.1.4 Compounds having a seven-membered ring and additional heteroatoms

(i) One nitrogen atom

Derivatives of 1,2-diazabicyclo[5.2.0]nona-3,5-diene are obtained by addition of a ketene to a 1-substituted-1,2-diazepine <83LA1361, 83LA1374, 83LA1393, 88HCA822, 91HCA767> (Table 4). In a similar way tricyclic compounds are produced from benzodiazepines (Section 1.21.9.7) <89JHC119>.

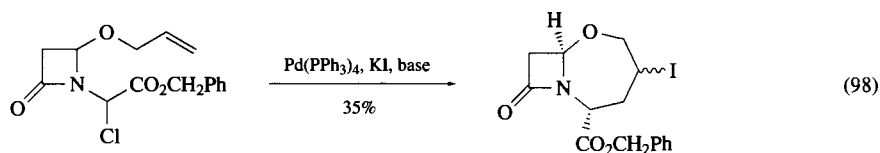
Table 4 Selected compounds and references related to Sections 1.21.11.1.4 and 1.21.11.1.6.

Ring system	Substituents	Ref.
	R ¹ = (4 <i>S</i>)-2-oxo-4-phenyloxazolidin-3-yl, R ² = Me, R ³ = Et	91HCA767 ^{a,b}
	R = H or CO ₂ Bu ^t	81TL2689 ^a
	R = PhCH ₂ CONH	72HCA2567 ^a
		93T7803 ^{a,b}

^aSynthesis. ^bCrystal structure.

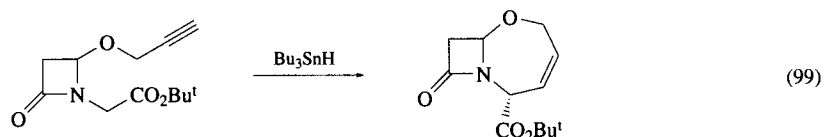
(ii) One oxygen atom

The 6-oxa-1-aza-bicyclo[5.2.0]nonane system has been obtained in a palladium-catalyzed enehalocyclization (Equation (98)) <86CC1375>.



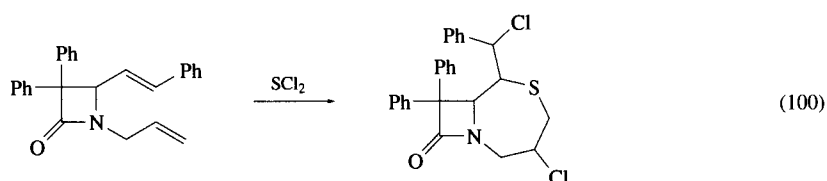
Compounds having one alkenic bond in the seven-membered ring have been obtained from clavulanic acid esters <83JCS(P1)115> and from 1,4-disubstituted β -lactams in a free-radical cyclization process which involves addition of tributyltin radicals to the terminal atom of the alkyne, an intramolecular hydrogen atom transfer to the vinyl radical, intramolecular *endo* addition of the

radical to the vinyltin group, and β -elimination of the tributyltin radical (Equation (99)) <93JOC5581> (Table 4).



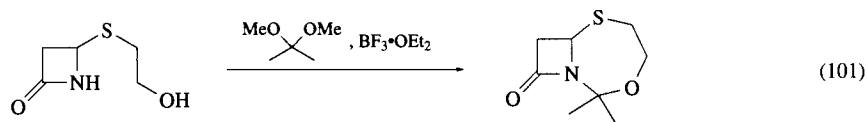
(iii) *One sulfur atom*

The reaction of sulfur dichloride with 1-allyl-4-styryl β -lactam causes ring closure and chlorination (Equation (100)) <91H(32)659>.



(iv) *One oxygen and one sulfur atom*

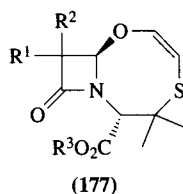
The 4-substituted β -lactams undergo intermolecular cyclization with propanone ketal (Equation (101)) <80JA2039>.



1.21.11.1.5 Compounds having an eight-membered ring and additional heteroatoms

(i) *One oxygen and one sulfur atom*

Derivatives of the ring system (177) have been obtained by rhodium-catalyzed decomposition of diazoketones derived from penicillin <83TL221> and by the action of α -acyl iodonium ylides on penicillins <90SL153>.

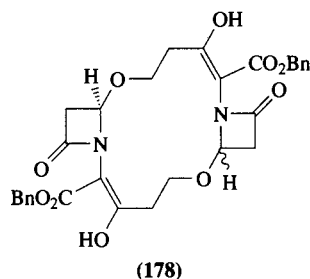


1.21.11.1.6 Miscellaneous compounds

The macrocycle (178) has been obtained from benzyl clavulanate <83JCS(P1)115>.

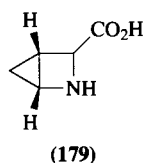
1.21.11.2 Compounds Having Only Carbon Atoms at the Bridgehead

Selected examples are given in Tables 5, 6, and 7.



1.21.11.2.1 Compounds having fused three- and four-membered rings

The naturally occurring antibiotic (179) is known <80ABC73>.

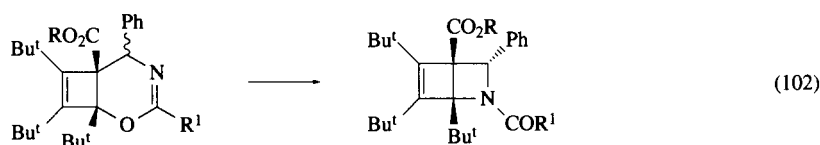


1.21.11.2.2 Compounds having two fused four-membered rings

(i) One nitrogen atom

Bicyclic systems containing the azetine nucleus (144) have been obtained by [4 + 2] cycloaddition of a highly substituted cyclobutadiene with a nitrile (Section 1.21.9.7) <86BSF239>. The fused azetidine 3-aza-7-oxatricyclo[4.1.0.0^{2,5}]hept-3-enes are prepared in three steps from 2-azabicyclo[2.2.0]hex-5-enes <86CC1188>. This last product contains an azetidine nucleus, and such compounds have been obtained by photolysis of pyridine <83CC941, 85CPB4572> and by cycloaddition of *N*-acylimines with cyclobutadienes <85TL3315> (see Table 5).

Thermal (150–170°C) or acid-catalyzed isomerization of 1-oxa-3-azabicyclo[4.2.0]octadienes (obtained from cyclobutadienes and an imine by cycloaddition) yield 2-azabicyclo[2.2.0]hexenes (Equation (102)) <88CB1775>.

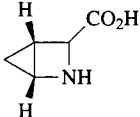
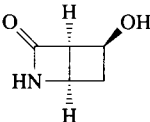
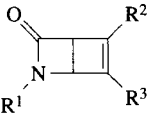
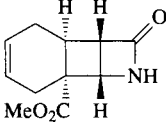
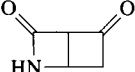
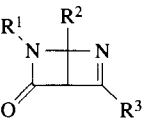
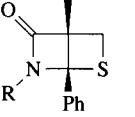


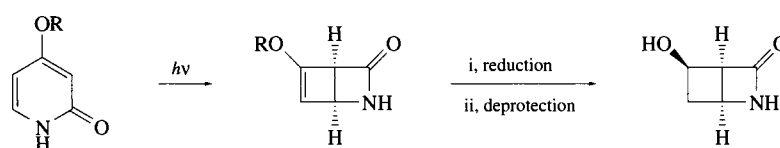
The corresponding β -lactam system, 2-azabicyclo[2.2.0]hex-5-en-3-one, is obtained by photolysis of 1-substituted 2-pyridones (Equation (86)) <87H(26)1611, 90CPB2911, 92JOC5708>. In a similar way, 6-substituted derivatives are formed from 5-substituted pyridones <93CPB1885> in useful yield ($\approx 50\%$) and 4-substituted pyridones give 5-substituted 2-azabicyclo[2.2.0]hexan-3-ones <84TL5665, 85CC189, 86JCS(P1)1289, 86TL6091, 89JCS(P1)663>. When the 4-substituent on the pyridone is a silyloxy or an alkoxy group, the enol in the product may be liberated. This compound exists in the dione form (Scheme 14). Reduction of the alkenic group before deprotection yields the alcohol as a stable crystalline solid (Scheme 18) <84TL5665, 86TL6091>.

(ii) Two nitrogen atoms

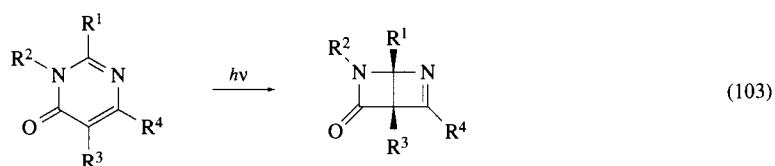
Photolysis of 3-substituted 4(3*H*)-pyrimidinones at low temperature gives 2,6-diazabicyclo[2.2.0]hex-2-en-5-ones, but in poor yield (Equation (103)) <83JOC2914, 85JOC166>, and hydrolysis

Table 5 Selected compounds and references related to Sections 1.21.11.2.1 and 1.21.11.2.2.

Ring system	Substituents	Ref.
		80ABC73 ^{a,b}
		84TL5665 ^c 86TL6091 ^c
	R ¹ = (CH ₂) ₃ CH=CHCO ₂ Et, R ² = R ³ = H R ¹ = Me, R ² = Bu ^t , R ³ = H R ¹ = R ² = H, R ³ = CO ₂ Me R ¹ = Me, R ² = OMe, R ³ = H	92JOC5708 ^c 87H(26)1611 ^c 93CPB1885 ^c 89JCS(P1)663 ^c
		93CPB1885 ^c
		85CC189 ^c 86JCS(P1)1289 ^c
	R ¹ = R ² = R ³ = Me	85JOC166 ^c
	R = alkyl or phenyl	84JOC396 ^c 91JCS(P1)403 ^c 93JA818 ^c

^aNaturally occurring. ^bCrystal structure. ^cSynthesis.**Scheme 18**

occurs when the solvent is water (85TL3247). However, 2,6-diazabicyclo[2.2.0]hexan-3,5-diones are formed in good to excellent yield on photolysis of pyridinium-4-olates (Equation (87)) (86CC687).



(iii) One sulfur and one nitrogen atom

The route to the known compounds (all β -lactams) is by photocyclization of *N*-(thiobenzoyl)-acrylamides (Equation (32)) (84JOC396, 91JCS(P1)403) in solution or in the solid state at -45°C , when topochemical control occurs (Section 1.21.9.1) (93JA818).

1.21.11.2.3 Compounds having four- and five-membered rings

(i) One nitrogen atom

The only bicyclic systems in this category appear to be those derived from (180), which is itself obtained from (65) <88TL1057>. More complex structures such as (13) are obtained by [2 + 2] cycloaddition of norbornadiene and chlorosulfonyl isocyanate followed by acylation of the lactam with an aryl isocyanate <87T1921> (see also Table 6).

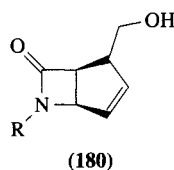


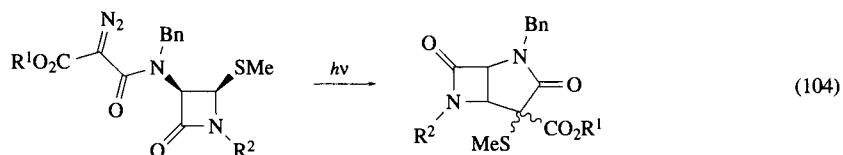
Table 6 Selected compounds and references related to Section 1.21.11.2.3.

Ring system	Substituents	Ref.
	$R^1 = \text{COCF}_3$, $R^2 = \text{Bn}$	91TL1565 ^a
	$R^1 = \text{Me}$, $R^2 = \text{Ph}$	84TL5627 ^a
	$4\text{-MeOC}_6\text{H}_4$, HO , $\text{C}_6\text{H}_4\text{Cl-4}$	90SL431 ^{a,b}
	$R^1 = \text{Bu}^t$, $R^2 = \text{CHClPh}$, $R^3 = \text{CH}_2\text{Cl}$	90TL3627 ^a
	$R^1 = \text{Ph}$, $R^2 = \text{Ac}$	83H(20)1903 ^{a,b}
	$R^1 = \text{CH}(\text{COBu}^t)\text{CO}_2\text{C}_6\text{H}_4\text{NO}_2\text{-4}$, $R^2 = \text{CH}_2\text{OPh}$, $R^1 = \text{C}(\text{CO}_2\text{Me})=\text{CMe}_2$, $R^2 = \text{Bn}$	93TL285 ^a 88JCS(P1)2813 ^a
	$R^1 = \text{COC}_6\text{H}_4\text{Br-4}$, $R^2 = \text{Ts}$	93T5047 ^{a,b}

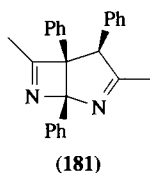
^aSynthesis. ^bCrystal structure.

(ii) Two nitrogen atoms

Trisubstituted β -lactams have been used in syntheses of 2,6-diazabicyclo[3.2.0]heptan-7-one derivatives. A carbene insertion process (Equation (104)) gives a good yield of a diastereomeric mixture of the product $\langle 83H(20)2355 \rangle$. An unusual cyclization is reported to give (**108**) $\langle 85MI 121-06 \rangle$.

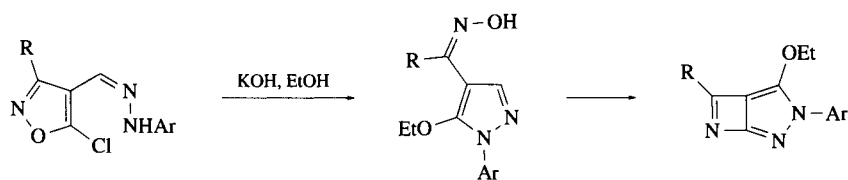


Cyclizations of suitably substituted pyrrolidines (Equation (75)) and phototransformations of 4*H*-1,2-diazepines $\langle 84TL5627 \rangle$ have yielded 3,6-diazabicyclo[3.2.0]heptanes (**85**) $\langle 91TL1565 \rangle$ and 2,6-diaza[3.2.0]hepta-2,6-dienes (**181**) $\langle 84TL5627 \rangle$, respectively.



(iii) Three nitrogen atoms

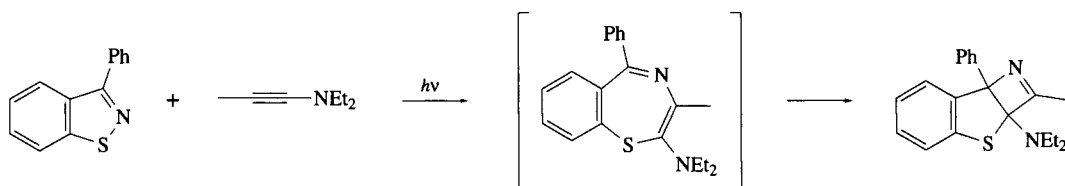
The first example of these systems is reported to be obtained by treatment of 5-chloroisoxazole-4-carbaldehyde arylhydrazones with alcoholic alkali (Scheme 19) $\langle 88JC(B)229 \rangle$.



Scheme 19

(iv) One nitrogen and one or more sulfur atoms

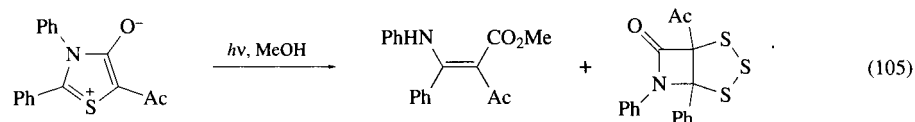
Photocycloaddition reactions of 3-phenylbenzothiazoles and electron-rich alkynes yield annelated 2-thia-6-azabicyclo[3.2.0]heptadienes (Scheme 20), presumably formed by ring contraction of the intermediate benzothiazepines $\langle 83JOC1275 \rangle$.



Scheme 20

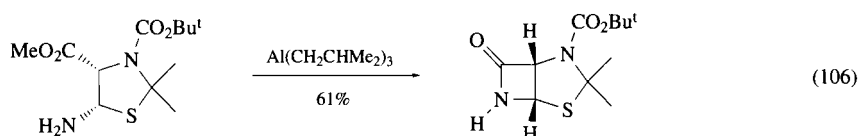
Sulfur dichloride has been utilized as a sulfur transfer agent with 1,3,4-trisubstituted β -lactams (Section 1.21.9.4, Equation (55)). Two consecutive sulfur transfers between radical intermediates

occur on photolysis of mesoionic 5-acetyl-4-thiazolone to give the 2,3,4-trithia-6-azabicyclo[3.2.0]-heptan-7-one (Equation (105)) <83H(20)1903>.



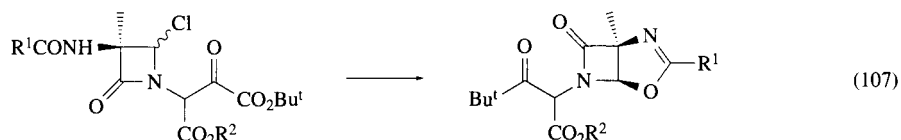
(v) One sulfur and two nitrogen atoms

Aluminum trialkyls have been used to form β -lactams from β -amino esters of thiazolidines (Equation (106)) <93T1625>.



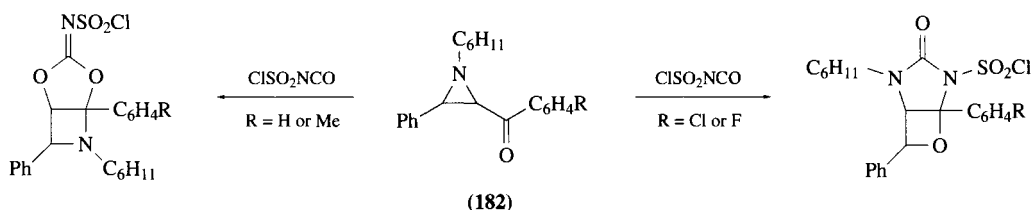
(vi) One oxygen and two nitrogen atoms

Examples of these systems are formed from 3-acylamino β -lactams carrying a good leaving group as a 4-substituent (Equation (53)) <88JCS(P1)2813, 88PJC127> and are obtained in attempts to prepare 6-acylamino-1-oxapenems, which are not isolable (Equation (107)) <93TL285>.



(vii) One nitrogen and two oxygen atoms

The products from the reaction of chlorosulfonyl isocyanate with 2-acylaziridines (**182**) depend on the nature of the substituent on the benzoyl group. When $\text{R} = \text{H}$ or methyl, the product is a 2,4-dioxo-6-azabicyclo[3.2.0]heptane (Scheme 21). However, when $\text{R} = \text{Cl}$ or F , the reaction adopts a different course to yield 6-oxo-2,4-diazabicycloheptanes <84JHC1699>.

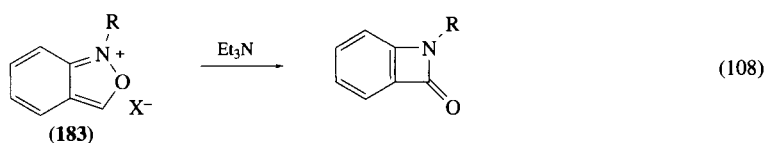


Scheme 21

1.21.11.2.4 Compounds having four- and six-membered rings

(i) One nitrogen atom

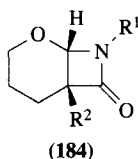
Benzo derivatives of the azetine and azetinone rings are known. The benzoazetine (**7**) is obtained by flash vacuum pyrolysis of *o*-aminobenzyl alcohol under carefully controlled conditions (Section 1.21.2) <92TL5753>. *N*-Alkylbenzoazetinones are formed readily by treatment of anthralinium salts (**183**) with triethylamine (Equation (108)). When the alkyl group is bulky (e.g., *t*-butyl or 1-adamantyl) the compound is stable and, indeed, a single-crystal structure analysis is available for the latter <84JOC3367>.



cis- and *trans*-6-Aza-bicyclo[4.2.0]octanes are known <66JOC1372>. See Table 7 for further examples.

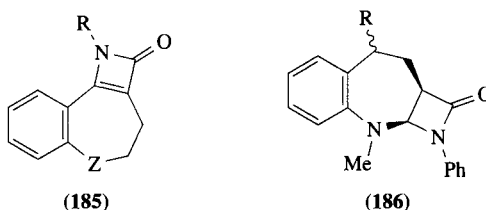
(ii) One nitrogen and one or two oxygen atoms

The [2 + 2] cycloaddition of isocyanates to 2,3-dihydropyran and 4*H*-1,3-dioxin derivatives is an effective route to (**184**) <83CC299> and (**63**) <89TL5631>, respectively.



1.21.11.2.5 Compounds having a four-membered ring fused to either a seven-membered ring or a larger ring

Tricyclic systems (**185**; Z = O or CH₂) and (**186**) appear to be the only representatives of seven-membered ring systems <84JOC2652, 91JCR(S)204>.



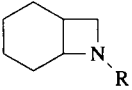
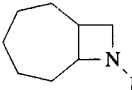
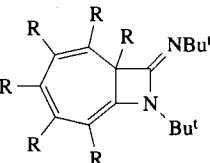
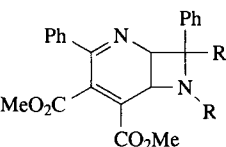
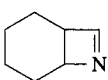
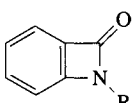
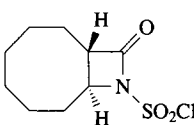
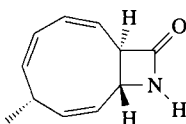
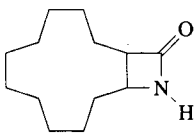
The fused systems with eight-membered rings include (**140**), obtained by cycloaddition to *trans*-cyclooctene <83CB2136>, and (**147**), produced in the reaction of 5-nitropyrimidine and 1-(diethylamino)propyne <86JOC67>. See Table 7 for further examples.

1.21.12 APPLICATIONS

No applications have been established for the compounds not having a bridgehead nitrogen atom. However, the applications of the β -lactams having a bridgehead nitrogen atom as antibacterial agents in medicine are very important (see Chapters 1.21 and 1.20).

For several decades it was thought that the sulfur atom present in both the penicillins and cephalosporins was an essential feature of a bicyclic β -lactam having useful antibacterial activity.

Table 7 Selected compounds and references related to Sections 1.21.11.2.4 and 1.21.11.2.5.

Ring system	Substituents	References
	R = Ts R = H	66JOC1372 ^a 66JOC1372 ^a
		80MI 121-02 ^a
	R = CO ₂ Me	74T2561 ^a
	R = CH(CH ₃)CH ₂ CH ₃	75JOC3363 ^a
		72TL3933 ^a
	R = Bu ^t R = 1-adamantyl	84JOC3367 ^a 84JOC3367 ^{a,b}
		83CB2136 ^a
		73JA4647 ^a
		76JOC3583 ^a

^aSynthesis. ^bCrystal structure.

Then two discoveries were announced in the same year which cast considerable doubt on the hypothesis and opened up a whole new area for investigation (87PAC475). These discoveries were the isolation of the antibiotics olivanic acids (79JAN295, 79JAN1239, 83T2551) and thienamycin (**15**) (79JAN1) from *Streptomyces* derived from soil. All these compounds were members of the 1-azabicyclo[3.2.0]hept-2-en-7-one group having (*R*) absolute stereochemistry at the ring-junction carbon atom and differing mainly in the absolute stereochemistry in the simple 1-hydroxyethyl substituent at C-6. These discoveries emphasized that the presence of a ring sulfur atom was not an essential feature of the β -lactam antibiotics, though the naturally occurring compounds all had a 3-alkylthio or 3-alkenylthio substituent. Since 1979, many more naturally occurring 1-carbapenem antibiotics have been found and structure-activity relationships have been determined (90MI 121-06,

90JAN847). The antibiotics found are grouped into the thienamycins, the olivanic acids, the PS-series (having a 6-isopropyl substituent), the carpetimycins (carrying a 6-(1-hydroxyisopropyl) group), asparenomycins (with a 6-(1-hydroxymethylethylidene)substituent) (B-85MI 121-10), the pluracidomycins (which are sulfates of the 6-(1-hydroxymethyl) group), and the OA-129 series having a range of 6-substituents but carrying a diamide chain on the 3-thio substituent (87H(25)729).

The naturally occurring carbapenems are chemically unstable and are generally obtained in poor yield by fermentation processes. Thus, the syntheses of the 1-carbapenem and related ring systems are important (B-85MI 121-11) and an account of such work forms a considerable part of this chapter. Some consideration has already been given in this chapter to structure-activity relationships (Section 1.21.31, 1.21.34, 1.21.43, and 1.21.6.4). Thienamycin (**15**) does not have sufficient chemical stability to have clinical application. However, the crystalline *N*-formimidoyl derivative imipenem (**16**) is clinically useful as it has enhanced chemical stability and shows activity against a broad spectrum of Gram-positive and Gram-negative aerobic or anaerobic bacteria (85MI 121-12, 88MI 121-04, 91MI 121-04).

Imipenem (**16**) has acceptable stability against β -lactamases, the natural enzymic defenses of bacteria which operate by opening the β -lactam ring of the bicyclic antibiotics (B-85MI 121-13). The development of resistance to carbapenem antibiotics is an increasing problem (92MI 121-10).

Although the carbapenem antibiotics have excellent activity *in vitro*, it soon emerged that performance in clinical situations does not always match expectations. Unlike the penicillins and cephalosporins, the 1-carbapenems are susceptible to degradation by renal dehydropeptidase-I (DHP-I) (90JAN1137). Thus, the use of carbapenems in the treatment of urinary tract infections requires the coadministration of a DHP-I inhibitor such as sodium cilastatin (85MI 121-14, 89JOC653).

The modification of the six-membered ring in the cephalosporin nucleus followed the directions taken with the penams and penems. The 1-carbacephems (89JMC2436) exhibit better chemical stability than the corresponding cephalosporins (89JAN283) but have only recently been introduced into clinical use. Much interest centers around the 3-chloro derivative (loracarbef) (92MI 121-11, 93MI 121-08, 93MI 121-09) and structure-activity relationships for a range of 1-carbacephems have been reported (93JMC1971, 93JMC2332). The stability of carbapenems to renal dehydropeptidase-I is improved by the introduction of a 1 β -methyl substituent, while the antibacterial activity is retained (84H(21)29). Structure-activity relationships have been investigated for unusual 2- (B-93MI 121-07) and 5-substituents (89JAN1100).

Before the discovery of the 1-carbapenem antibiotics, clavulanic acid (**18**), a 1-oxapenam derivative, had been isolated from fermentation media and characterized (76CC266, 84JCS(P1)635). This compound had only weak antibacterial activity and so did not disturb the idea that the presence of sulfur was essential for useful antibacterial activity, but importantly was a strong inhibitor of β -lactamases from both Gram-positive and Gram-negative bacteria (B-85MI 121-02, 93JA4435). Thus, the discovery of novel compounds having β -lactamase inhibitory activity for use as adjuvants in cephalosporin- and particularly penicillin-mediated therapy was initiated (B-85MI 121-02), and not limited to compounds having a 7 α -methoxy substituent (89JAN1100). The synthesis and structure-activity relationships for 2-thia-1-dethiacephems (isocephems) have been investigated (B-89MI 121-12).

The β -lactam antibiotics exert their effects by disrupting the action of D,D-peptidases in catalyzing the peptidoglycan cross-linking in the bacterial cell wall (85AG(E)180).

1.22

Oxetanes and Oxetenes: Monocyclic

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1.22.1 INTRODUCTION

Four-membered cyclic ethers are named oxetanes while the corresponding carbonyl-substituted systems are termed oxetanones. 2-Oxetanones are commonly referred to as β -lactones. Unsaturated oxetanes are named oxetenes. The structure of oxetanes and oxetanones has been the subject of intensive research, and continues to be an active area of investigation for theoretical studies. The chemistry of these oxacyclic species is quite rich and varied. The reactivity of oxetanes and oxetanones stems predominantly from the relatively high degree of ring strain associated with the molecule; however, the basicity of the oxetane ring oxygen also plays a significant role in reactions with electrophilic reagents. Oxetanes have stimulated considerable interest in the pharmaceutical community due to the potent biological activity exhibited by this class. Oxetanones also exhibit a wide range of biological activity, from enzyme inhibition to viral inactivation; however, β -propiolactone (and other β -lactones) have been shown to be carcinogenic and quite toxic. Polymerization reactions of oxetanes and oxetanones continue to be an area of active research. The polymeric materials obtained have many applications ranging from novel composites to high energy explosive materials.

There have been several general reviews of oxetanes and oxetanones since the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) appeared in 1984. Four-membered ring systems were reviewed in 1989 and 1991 <89PHC98, 91PHC58>. The photochemical [2 + 2] cycloaddition route to oxetanes (the Paterno–Buchi reaction) has been reviewed <B-84MI 122-01, B-86MI 122-01, B-89MI 122-01>. The synthesis of oxetanones via reactions of ketenes <81T2949>, synthetic applications of diketene <86CRV241, 93CI(L)173>, the chemistry of β -lactones <93S441>, and the synthesis of the antiviral agent, oxetanocin have also been reviewed <92MI 122-01>. Reviews of oxetane polymers <82KO(18)645, B-87MI 122-01> and cyclooligomerization reactions <93T8707> have been published.

The present review covers the literature predominantly from 1983–1993 and seeks to complement and extend the information presented in Chapter 13, volume 5 of CHEC-I. General comments at the beginning of each section of this review that refer to earlier studies are based on the information given in the first edition.

1.22.2 THEORETICAL METHODS

1.22.2.1 Structure and Synthesis

Theoretical studies of oxetane and oxetanones continue to be an active field. Through the early 1980s, *ab initio* calculations of the barrier to ring planarity for oxetane ($\sim 2\text{--}5\text{ cm}^{-1}$) did not agree with the experimentally determined results (15.5 cm^{-1}). Possible explanations for this discrepancy included the neglect of electron correlation, and vibrational modulation among other factors. A series of papers has been published which address this question using more highly refined basis sets

than those previously applied. An initial study concluded that an adiabatic correction made no contribution to the ring-puckering potential, and that the case of oxetane represented a failure of the Hartree-Fock method (84CPL(108)339). A subsequent study determined the ring-puckering potential by means of a local correlation treatment employing Moller-Plesset (MP) perturbation theory at the 6-31G* and 6-31G** level (86CPL(132)29). Intramolecular nonbonded interactions were identified as the part of the correlation energy that contributed to the barrier in oxetane ring puckering. Due to the fact that very large basis sets are required to describe van der Waals effects, higher level calculations were also undertaken. TZ + nP/MP4 (SDQ) calculations were performed with 6-311G** and 6-311G** basis sets, as well as modified 6-311G** basis sets which included a diffuse set of *d* functions added to all heavy atoms (87JPC4216). The SCF potential did not fully converge as anticipated. The authors concluded that the quadratic contribution to the ring-puckering potential was primarily due to the intramolecular dispersion interactions involving the oxygen lone pairs. An independent analysis of experimental data and *ab initio* calculations led to the conclusion that the isotope dependence of the empirically determined puckering potential had at least two sources: the kinetic anharmonicity affecting primarily the quartic potential term, and the zero-point energy contribution of small amplitude vibrations (87JSP(126)1). However, neither of the corrections taken alone were sufficient to obtain an isotope-invariant potential function, and the ring-puckering potential determined by this method was only $3.3(\pm 0.1) \text{ cm}^{-1}$. An improved method for treating nonperiodic large amplitude internal motions by a Hamiltonian which contained only periodic functions has been developed (90JST(218)327). An excellent correlation of calculated and experimentally determined isotope-dependent ring-puckering barrier heights for oxetane has been obtained by this method (Table 1) (92SA(A)65).

Table 1 Observed and calculated values for oxetane ring puckering.

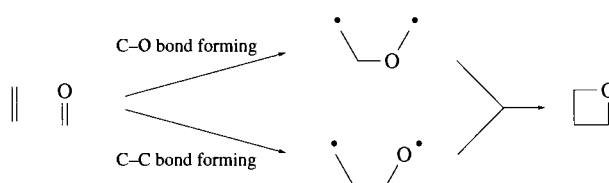
Compound	$V (\text{cm}^{-1}) \text{ exptl}$	$V (\text{cm}^{-1}) \text{ calcd}$
Oxetane	15.3	15.5
Oxetane- β -d ₂	13.9	14.0
Oxetane- α,α' -d ₄	11.8	11.2
Oxetane-d ₆	11.2	11.2

Molecular mechanics (MM2) methods have also been investigated as a means to determine the barriers to planarity for a large number of small rings, including oxetane, 3-oxetanone, and 3-methyleneoxetane (90JPC1830). Although the MM2 program failed to calculate a barrier to planarity for oxetane, the calculated lowest energy conformation of the molecule was in reasonably good agreement with experimental values. Molecular mechanics (MM2) (82PAC2515) and MM3 (92JA6120) analyses of 2-oxetanone have been carried out. The MM3 data are in excellent agreement with experimental values. Bond lengths were $\pm 0.007 \text{ \AA}$, bond angles $\pm 5.6^\circ$, and vibrational frequencies were all within $50\text{--}60 \text{ cm}^{-1}$ with the exception of CH₂ wagging which differed from the experimentally observed value by 106 cm^{-1} . The dipole moment for 2-oxetanone was calculated as 4.28 while the experimental value was 4.17. The heat of formation determined by MM3 was -67.61 kcal/mol , in nearly perfect agreement with the experimental value of $-67.60 (\pm 0.21) \text{ kcal/mol}$. The equilibrium geometry bond lengths of 2-oxetanone determined by a number of molecular mechanics and *ab initio* methods (MM2, MINDO/3, STO-3G, 3-21G, 4-21G, 6-21G, and 6-31G**) have been compared to experimental values obtained from vibrational spectra (91JPC5446). Scaled quantum mechanical vibrational force fields were derived using the 6-31G** and 3-21G basis sets to provide improved agreement of the calculated vibrational frequencies and intensities with the experimental data.

Theoretical studies on the structure of diketene have also provided an equilibrium geometry different from that determined by electron diffraction or x-ray crystallography. An *ab initio* analysis of the three possible isomers of diketene (diketene, 1,3-cyclobutanedione, and 2,4-dimethylene-1,3-dioxetane) determined that the diketene and 1,3-cyclobutanedione structures were essentially degenerate (90JA1493). Molecular structure, harmonic vibrational frequencies, and infrared intensities were evaluated at the self-consistent field (SCF) level of theory with a double zeta plus polarization (DZ + P) basis set, and found to be in only fair agreement with the experimental data. A subsequent study using configuration interaction including single and double excitations (CISD) and the coupled cluster method including single and double excitations (CCSD) (DZd basis set) provided improved agreement of the calculated data with microwave spectroscopy data (92JPC657). These results indicated that the data derived from the previous electron diffraction and x-ray crystal

structure studies were seriously deficient in describing the molecular structure for diketene. The use of larger basis sets at the SCF level of theory, TZ2P/DZP SCF compared to DZP SCF, resulted in a greater discrepancy between theory and experiment.

Theoretical studies on the formation of oxetane and oxetanones are not as common as structural studies. A multiconfiguration self-consistent field (MCSCF/6-31G*) study of the singlet and triplet Paterno–Buchi reaction of formaldehyde and ethylene has been reported (94JA2121). Carbon–carbon and carbon–oxygen bond-forming photochemical mechanisms were both examined (Scheme 1). In the carbon–carbon bond-forming reaction, the singlet mechanism can be nonsynchronous or concerted as the decay to the ground state occurs in a point where the carbon–carbon bond is fully formed. The system can then directly produce oxetane from this decay point, or can produce a transient diradical intermediate. The carbon–oxygen bond-forming mechanism occurs only by a nonconcerted pathway in which the excited state can evolve back to the reactants or produce a carbon–oxygen bonded transient diradical intermediate that may either fragment or form oxetane. The diradical structures derived from the two modes of attack were only 8 kcal/mol apart; however, the singlet excited state to ground state decay point for the carbon–carbon attack pathway was 33 kcal/mol lower than the corresponding point for the carbon–oxygen attack.



Scheme 1

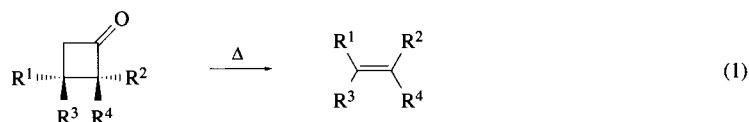
The formation of diketene has been examined by *ab initio* calculations as a test for the existence of the 2S + 2A cycloaddition pathway (91JA5195). According to the Woodward–Hoffman rules, ketene dimerization should occur by a 2S + 2A pathway. The molecular structures for the reactants, transition states, and products for the dimerization reaction were determined at the DZ + P SCF level of theory. The transition state for the dimerization reaction of ketene leading to diketene indicated a nonsynchronous reaction with partial formation of the C-1, C-4 bond and partial breakage of the C-1, O-3 and C-2, C-4 double bonds, followed by formation of the C-2, O-3 bond. The reaction was concerted, but found to be more consistent with the 2S + 2S + 2S pathway than the 2S + 2A pathway. Formation of the 1,3-cyclobutanedione isomer had a barrier height of 36 kcal/mol, while the barrier to the formation of diketene was found to be 32 kcal/mol, providing an explanation for the formation of only the diketene isomer. An independent study using MP2/4-31G level *ab initio* calculations determined the activation barriers for formation of diketene, 1,3-cyclobutanedione, and 2,4-dimethylene-1,3-dioxetane to be 29.8, 35.1, and 61.2 kcal/mol, respectively (88MI 122-01). A frontier–orbital interaction analysis of ketene dimerization has also been published (93BCJ3283), as well as an *ab initio* calculation of secondary deuterium isotope ratios in the formation of diketene (91JA5200).

Theoretical studies on oxetene have been more limited. The formation of oxetene from acrolein has been investigated using complete active space self-consistent field (CASSCF/6-31G*) level calculations (94JA2103). Oxetene formation was found to occur exclusively from the *s-cis* isomer of acrolein by decay from an $S_1^1(n-\pi^*)/S_0$ conical intersection point located 10 kcal/mol above the S_1 minimum. The existence of a barrier to the production of oxetene is in agreement with the observation that oxetene accumulates when acrolein is irradiated at 250 nm, but is not formed upon irradiation of *cis*-acrolein at 300 nm. Multiconfiguration SCF calculations using both unrestricted Hartree–Fock natural orbitals (UHF-NO) and restricted open-shell Hartree–Fock (RHF) molecular orbitals of the ring-opening reaction of oxetene have been carried out (91MI 122-01). A study of electrocyclic isomerization reactions related to the cyclobutene/butadiene reaction examined the ring-opening reaction for oxetene using UHF-NO to define the active space for CASSCF computations (90JA7529). MCSCF, CISD, and MP4SDTQ methods were used to determine the activation barrier and reaction energy. The barrier for oxetene rearranging to *cis*-acrolein calculated by MP4SDTQ/6-31G* (26.6 kcal/mol) was in good agreement with the experimental value (24.1 (± 1.5) kcal/mol). The oxetene to acrolein rearrangement is predicted to be significantly more exothermic than the corresponding cyclobutene to butadiene rearrangement partly due to the difficulty associated with incorporating a strongly electronegative element into the four-membered ring.

1.22.2.2 Stability and Reactivity

There have also been several publications concerning theoretical studies of the stability and reactivity of oxetane and oxetanones. Oxetane and the isoelectronic four-membered ring charged fluoretanium ion were compared using isodesmic reactions to provide empirical estimates of the core ionization energies <90JA1427>. Through-bond and through-space interactions have been compared for a series of four-membered rings, including oxetane, by *ab initio* methods <82JPC3981>.

The thermal decomposition of 2-oxetanones is an example of a [2 + 2] cycloreversion process that occurs with retention of configuration (Equation (1)). A MNDO study concluded that decarboxylation was a one-step process that ensues by successive bond fission through a zwitterionic transition state <83JOC1479>. Two subsequent studies examined substituted 2-oxetanones. A direct correlation was found between the relative thermal stability of the substituted β -lactones and the respective HOMO and LUMO energies <84MI 122-02>. 2-Oxetanones bearing unsaturated substituents at C₄ were thermally less stable than analogous compounds with an alkyl substituent. A more thorough study examined by AM1 methods the enthalpy of activation and reaction for a series of 26 substituted 2-oxetanones <89JOC573>. The variation of ΔH with bond indices in the transition state provided a verification of the Hammond postulate. The conclusions of the study were: that decarboxylation is an asynchronous process that takes place through a planar transition state with a high zwitterionic character, that *trans*-substituted oxetanones will decarboxylate faster than the corresponding *cis* isomer, and that protonated 2-oxetanones decarboxylate through a bisected carbocation intermediate stabilized by hyperconjugation.



The gas-phase basicity of 2-oxetanone has been studied by experimental and theoretical methods <93JA7389>. In general, lactones are more basic than the corresponding acyclic ester. However, 2-oxetanone is less basic (~ 6 kcal/mol) than methyl acetate as a consequence of substantial hybridization changes incurred upon cyclization to the four-membered ring. The effect of cyclization of ethers on basicity is just the opposite, and oxetane is therefore a stronger base than methyl ethyl ether. Lactones and esters normally undergo protonation on the carbonyl oxygen, favored over the ether oxygen by nearly 18 kcal/mol. Since the 2-oxetanone carbonyl is less basic, the energy difference in protonation at the carbonyl oxygen versus protonation at the ether oxygen is substantially reduced to a value of 3 kcal/mol. For this reason, protonation is likely to occur at either the carbonyl oxygen or the ether oxygen. The nucleophilicity of oxetane has also been examined theoretically by an *ab initio* study of the cationic polymerization of oxetane <87IJQ623>.

1.22.3 EXPERIMENTAL STRUCTURAL METHODS

1.22.3.1 Nuclear Magnetic Resonance Spectroscopy

Lead references for the ^1H and ^{13}C NMR chemical shifts for oxetanes and substituted oxetanes prior to 1983 can be found in CHEC-I. Later work in this area has tended to expand upon data already reported in earlier publications. The structural dependence of geminal and vicinal carbon-carbon coupling constants for oxetanone has been determined from the satellites of broad bands or from inadequate experiments <85MRC95>. The dipolar coupling constants of oxetane partially oriented in a nematic solvent have been reported <92MP17>. Oxetane was found to oscillate between two equivalent bent conformations; however, the puckering potential function could not be determined. Additional studies of the anomalously large down field chemical shifts of ^{13}C and other nuclei in four-membered rings have also been completed <83JOC3982>. The ^{13}C NMR chemical shifts of four-membered to seven-membered cyclic ketones, lactams, lactones, and sulfones were plotted against the data from the parent hydrocarbons to illustrate the deviation. An adequate explanation of the anomalous shifts for the four-membered ring compounds could not be offered from the data. Oxygen-17 NMR shifts reported for 2-oxetanone were: carbonyl O, 347 ppm; ether O, 241 ppm; and oxetane ether O, -13 ppm, referenced to water. The ^{17}O NMR chemical shift data for 30 lactones, including some oxetanones, has been compiled <89H(29)301>. The determination of the

enantiomeric purity and absolute configuration of chiral β -propiolactones have been achieved by a ^1H NMR method $\langle 83\text{TL1027} \rangle$. A strongly hydrogen bound complex of the lactone and 2,2,2-trifluoro-1-(9-anthryl)ethanol provides diastereotopic signals that can be easily integrated.

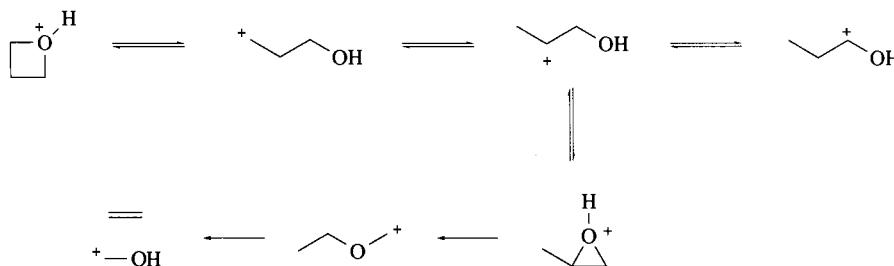
1.22.3.2 Infrared and Ultraviolet Spectroscopy

Few additional fundamental studies involving IR spectroscopy have appeared since 1985. A detailed study of the IR spectrum of 2-oxetanone in various solvent systems has provided an explanation for the observation of three significant bands in the carbonyl stretching region of the IR spectrum $\langle 91\text{MI 122-02} \rangle$. A combined *ab initio* and IR spectroscopic study of 2-methyloxetane and three selectively deuterated isotopomers led to the development of optimized scaling factors for the force field. Calculated and experimental values were then determined for 100 frequencies with a deviation of only $4\text{--}5\text{ cm}^{-1}$ $\langle 89\text{JPC3920} \rangle$. The mid-IR vibrational circular dichroism (VCD) spectrum of 2-methyloxetane indicated that the oxetane ring exists in two distinct puckered conformations designated as axial and equatorial $\langle 90\text{JPC125} \rangle$. The VCD data suggests a preference for the equatorial conformer. Infrared multiple-photon decomposition studies of oxetane $\langle 90\text{BCJ728} \rangle$, and 2-oxetanone $\langle 84\text{JPC2817}, 86\text{BCJ2241} \rangle$ have also been reported.

The toxicity of β -propiolactone (see Section 1.22.12.3) has prompted the development of methods for the detection of this species. An IR spectroscopic method for determining the concentration of β -propiolactone in aqueous solution, including serum, has been described $\langle 90\text{MI 122-01} \rangle$. A UV resonance Raman study of the interaction of β -propiolactone and DNA has determined that alkylation at N-7, N-2, and N-1 of guanine occurs, as well as alkylation at N-1 of adenine $\langle 88\text{MI 122-02} \rangle$.

1.22.3.3 Mass Spectrometry

Mass spectral fragmentation patterns for oxetane and oxetanone were well described in studies prior to 1983. More recent studies have focused on the applications of new techniques for the study of these strained molecules. The mass spectrum of 2-phenyloxetane at 70 eV revealed intense peaks at m/z 104, 105, and 106 $\langle 83\text{OMS(18)443} \rangle$. Mass-analyzed ion kinetic energy spectrometry (MIKE) of these fragments determined that cleavage of the molecule occurs after a rapid exchange of the C-3 and C-4 atoms. Collision-induced (CI) fragmentation (or dissociation CID) has examined metastable $[\text{C}_3\text{H}_7\text{O}]^+$ ions produced by gas-phase protonation of acetone, propanal, propylene oxide, and oxetane $\langle 83\text{OMS(18)517}, 90\text{MI 122-02} \rangle$. Protonated oxetane rearranges to the same intermediates as propanal, but the rearrangement occurs less readily for oxetane. The fragmentation pattern ultimately forms ethylene and formaldehyde through a series of carbocation intermediates (Scheme 2). Collisional activation dissociation mass spectral studies of several oxetanones have also been reported $\langle 84\text{IJM293}, 92\text{MI 122-02} \rangle$.



Scheme 2

Neutralization–reionization mass spectrometry (NRMS) has provided a means to generate the distonic radical cation (**1**) from the diradical (**2**) each of which are postulated as possible intermediates in the thermal decomposition of oxetane $\langle 93\text{JA10849} \rangle$ (see also Section 1.22.4). The bimolecular chemistry of both species has been reviewed $\langle 92\text{CRV1649} \rangle$, but the unimolecular reactions had not been investigated. The NRMS study concluded that the diradical (**2**) dissociated by simple

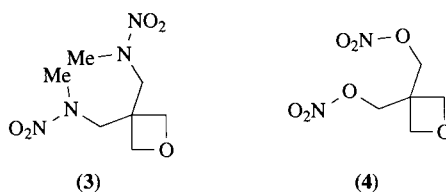
bond cleavage resulting in ethylene and formaldehyde, while the distonic radical cation (1) decomposed by complex rearrangement pathways which do not include the oxetanyl cation as previously assumed.



1.22.3.4 X-ray Crystal Structure

The x-ray crystal structure of oxetane was reported in 1984 <84JA7118>. Crystallographic data, bond lengths, and bond angles were determined at 90 and 140 K. Early spectroscopic studies had indicated that the oxetane ring was planar. Three crystal structures of highly substituted oxetanes were reported prior to 1983, revealing that the ring was not planar, but puckered at an angle ranging from 4.7° to 22.9°. The x-ray crystal structure of the parent oxetane revealed that the ring has exact C_s symmetry and is puckered with an angle of 10.7° at 90 K and 8.7° at 140 K. The carbon–oxygen bond length was unusually large. A comparison of x-ray data for tetrahydrofuran, dioxane, and oxetane reveals carbon–oxygen bond lengths of 1.429(6), 1.433(2), and 1.460(1) Å, respectively.

Several other x-ray crystal structures of substituted oxetanes have also been reported, including two oxetanes important in the production of high energy materials, 3,3-bis(methylnitroamino)methyl)oxetane (3) and 3,3-bis(nitratomethyl)oxetane (4). Interestingly, the oxetane ring of (3) was puckered with an angle of 20.6°, while in (4) the oxetane ring was planar <86AX(C)1161>. X-ray crystal structures have also been reported for E-3-phenylmethylene-2-oxetanone <90S855>, racemic and (–)-4-trichloromethyl-2-oxetanone <91JST(249)127, 93ZN(A)491>.



1.22.3.5 Microwave and Photoelectron Spectroscopy

Microwave spectroscopic studies of oxetanes and oxetanones have been limited since 1985. The equilibrium geometry and barrier to internal rotation of β -butyrolactone has been determined by a combination of microwave data and *ab initio* calculations <90JST(223)365>. Vibration–rotation interactions and ring puckering in 3,3-dimethyloxetane <90JSP(141)231> and 3-methyloxetane <90CPH21> have been examined. The ring puckering for 3,3-dimethyloxetane was determined to be 17.5°, while the 3-methyloxetane ring was effectively planar. Therefore, given the computational and x-ray data discussed above, the structural data available by spectroscopic methods still fails to provide definitive information on ring planarity or puckering in oxetanes.

Photoelectron spectroscopy has also not been as active an area of research since 1985 as in previous years. Earlier studies provided detailed data on the ionization potentials for several substituted oxetanes and 2-oxetanones. Photoelectron spectra data from oxetane, 3-chloromethyl-3-methyloxetane, 3-bromomethyl-3-methyloxetane, and 3-iodomethyl-3-methyloxetane were found to be in good agreement with *ab initio* MRDCI calculations <92JPC7226>.

1.22.4 THERMODYNAMIC ASPECTS

Ring-strain energy for oxetane and oxetanones has been discussed in the previous section on theoretical methods (see Section 1.22.2). Ideal gas thermodynamic properties of oxetane and several other cyclic ethers have been reported <92MI 122-03>. The thermodynamic property contributions due to inversion of the oxetane ring were obtained by direct summation over the energy levels

calculated with the potential function. Extensive data for the ideal gas thermodynamic properties of oxetane are tabulated in the report. The heat capacities for a number of lactones, including 2-oxetanone, have also been reported <83MI 122-01>.

Mechanistic and synthetic studies involving the thermolysis and photolysis of oxetanes and oxetanones are included in Section 1.22.6.2.

1.22.5 REACTIVITY AT FULLY CONJUGATED RINGS

No reports have been published.

1.22.6 REACTIVITY OF NONCONJUGATED RINGS

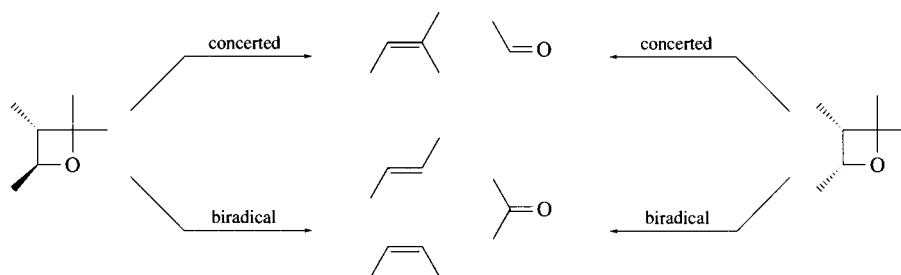
1.22.6.1 General Survey

The reactions of oxetanes and oxetanones range from thermal decomposition to cycloaddition reactions. Oxetanes readily undergo reactions with electrophiles due to the highly basic nature of the ring oxygen. Activation of the ring by Lewis acids can be followed by rearrangements or facile nucleophilic attack at carbon. Oxetanes are also susceptible to reductive ring cleavage and therefore serve as a source of carbanions for subsequent reactions with a variety of electrophiles. Substitution reactions of leaving groups attached to the oxetane ring are possible and comprise a large number of reactions of functionalized oxetanes. The syntheses of several natural products and biologically active oxetane derivatives have been accomplished by substitution reactions. The polymerization of oxetanes can occur by either cationic or anionic processes.

Reactions of oxetanones occur primarily by nucleophilic addition at the carbonyl carbon, yet there are also examples of ring cleavage by attack at the ether carbon-oxygen bond. The high susceptibility of oxetanones to ring cleavage by a variety of nucleophiles limits the extent of synthetic transformations possible on the intact 2-oxetanone ring. 2-Oxetanones also readily lose carbon dioxide upon heating. Several acid-catalyzed transformations of oxetanones are synthetically useful. Oxetanones substituted in the 4-position by alkenyl or alkynyl groups are very reactive towards a number of organometallic species.

1.22.6.2 Thermolysis and Photolysis

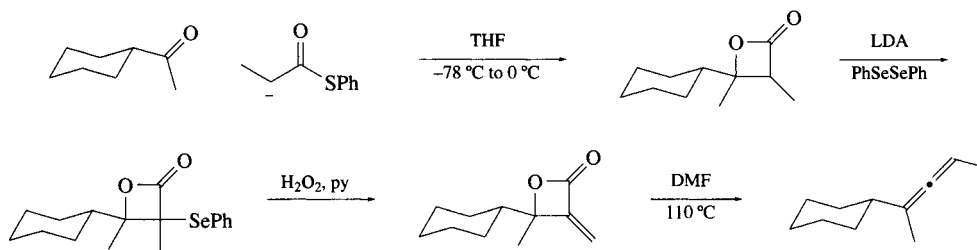
Thermolysis of oxetane derivatives is a well-studied reaction. A considerable number of reports appeared before 1983, indicating that the reaction can occur by two modes leading to multiple products from unsymmetrically substituted oxetanes. The lack of regioselectivity was attributed to the similar bond dissociation energies for the carbon-carbon and carbon-oxygen bonds of the oxetanes. Kinetic and mechanistic studies have determined that a biradical intermediate was involved in the reaction pathway. Rate enhancement was observed for oxetanes bearing a vinyl substituent at C-3, indicating that stabilization of the radical intermediate was advantageous for thermolytic cleavage. Additional studies along the same lines have appeared since 1983. The thermolysis of *cis*- and *trans*-2,2,3,4-tetramethyloxetane was found to occur by parallel unimolecular reactions to produce 2-methyl-2-butene and acetaldehyde, or *cis*- and *trans*-2-butene and acetone <84JCS(F1)691>. The former products were believed to arise by a concerted reaction involving a twisted transition state, while the latter products were derived from a biradical pathway (Scheme 3). Similar studies of the thermolysis of 2-methyloxetane and 3-methyloxetane have also been reported <90JCS(F1)21>.



Scheme 3

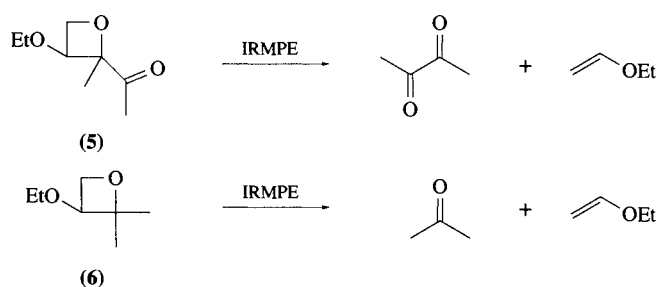
Thermolysis reactions of oxetanones are very commonly employed as a method to generate alkenes stereospecifically. The reaction is high yielding and generally occurs under relatively mild heating. This reaction continues to be the subject of theoretical and synthetic studies. The gas-phase thermal decomposition reaction of 2-oxetanone to ethylene and carbon dioxide was homogeneous and obeyed first-order kinetics (85JCS(F1)1087). The reaction occurred in a concerted fashion through an activated complex with zwitterionic character. The thermal decomposition of 4-methyl-2-oxetanone to propene and carbon dioxide was found to be a true unimolecular process (83JCS(F1)1659). Arrhenius parameters were reported for the reaction into the fall-off region. A comparison of the experimental data with that calculated from RRKM theory was also carried out. The volume of activation for the thermolysis of 3-anisyl-2-butyl-2,3-dimethyloxetane was consistent with the reaction occurring by a two-step process through a highly polar transition state (83TL2897).

Thermolysis of oxetanones has also continued to find synthetic application. Two related methods for the synthesis of allenes involving the [2 + 2] cycloreversion of 2-alkylidene substituted 2-oxetanones have been developed (see also Section 1.22.7.3). In one approach, the 2-oxetanone was directly prepared by the addition of thio ester enolates to ketones and aldehydes (Scheme 4) (93JOC322). The yields of the substituted allenes ranged from 60–84%. The stereospecific decarboxylative thermal elimination reaction of an oxetanone derivative has also provided (3*E*,5*Z*)-1,3,5-undecatriene (92TL2465). An interesting variant of the thermal elimination reaction involved the WOC1₄-catalyzed stereospecific direct conversion of 3-hydroxy carboxylic acids to alkenes (90OM3026). The initial product of the reaction was the 2-oxetanone derivative, which could sometimes be isolated from the reaction mixture in reasonable yield.



Scheme 4

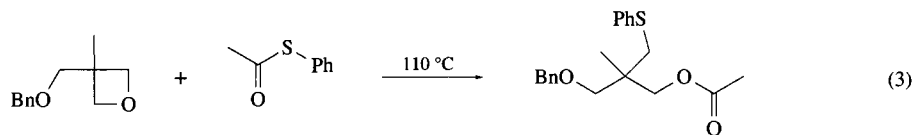
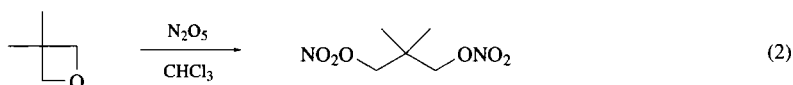
Photolytic fragmentation of oxetanes and oxetanones also leads to alkenes. Photochemical fragmentation of oxetanes are of interest in that the reaction is the formal reverse of the Paterno–Buchi reaction. Infrared multiphoton excitation (IRMPE) of oxetane (5) provided only biacetyl and ethyl vinyl ether with no other significant by-products observed by GC (Scheme 5) (84JA1875). Likewise, oxetane (6) produced only acetone and ethyl vinyl ether. The decomposition of both (5) and (6) occurred with chemiluminescence. Photochemical cleavage of 2,2-diaryloxetanes occurs in the presence of an electron donor to provide 1,1-diaryl-substituted alkenes (89BCJ2733). The regioselectivity of the cleavage reaction was due to the formation of a diaryl-stabilized radical derived from the initial oxetane–donor photocomplex. The quantum yields for the process were moderate, and no photochemical cleavage was observed without the addition of triethylamine as the electron donor. In contrast to the relatively clean photochemical fragmentation reaction described above, mercury- and cadmium-photosensitized reactions of β -propiolactone (86BCJ2559) and β -butyrolactone (89BCJ2235) lead to multiple fragmentation products.



Scheme 5

1.22.6.3 Reactions with Electrophiles

The basicity of the oxetane oxygen has been described in Section 1.22.2.2 and has been the genesis of many of the reactions of oxetanes described prior to 1983. Reactions of oxetanes with strong electrophiles are generally accompanied by ring opening of the strained four-membered ring. Nitration of oxetanes by oxides of nitrogen provides acyclic dinitrate products in reasonable yields (Equation (2)) <88TL2731, 93T7051>. Many cyclic ethers, including oxetane, are cleaved by dimethylboron bromide to afford the corresponding ring opened α,ω -bromoalcohols in very good yield <87JOC1680>. Partially fluorinated oxetanes are susceptible to a similar ring-cleavage reaction upon the addition of aluminum trichloride. The chloro alcohol acyclic product can be obtained in moderate yields <88JFC(40)201>. The reaction of perfluorooxetanes and superacids provides perfluoroalcohols in modest yield <89CJC1724>. A novel nucleophilic addition reaction of an oxetane with a thio ester also results in ring cleavage of the oxetane by initial acylation of the oxetane oxygen (Equation (3)) <91CL697>.

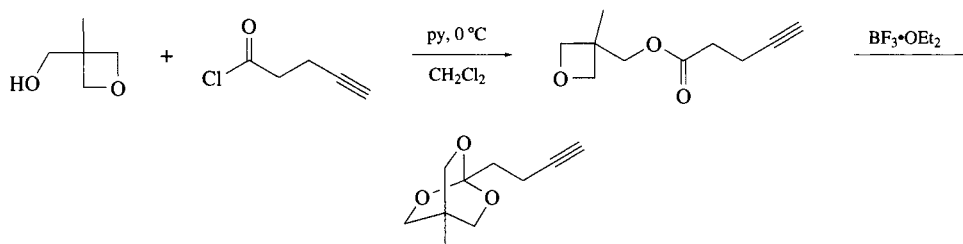


1.22.6.4 Acid-catalyzed Transformations

Earlier studies of acid-catalyzed rearrangements of oxetanes reported ring expansion to tetrahydrofurans, formation of cyclobutanones, and cleavage reactions to acyclic ketones. More recent investigations have expanded upon these observations, and are discussed in Sections 1.22.6.4.1 through 1.22.6.4.5.

1.22.6.4.1 Rearrangements of oxetanes

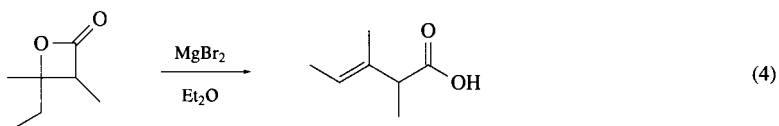
Acylation of 3-methyl-3-(hydroxymethyl)oxetane produced the corresponding oxetane-substituted ester in excellent yields. The oxetane derivatives were found to undergo rearrangement in the presence of boron trifluoride to readily form 2,6,7-trioxabicyclo[2.2.2]octanes, cyclic *ortho*-esters (Scheme 6) <83TL5571>. The cyclic *ortho*-esters, commonly referred to as OBO esters, have found use as a protecting group for the carboxylic acid functional group in many synthetic applications <88JA649, 93JA5021>. Novel trioxabicyclo[2.2.2]octane structures obtained by the rearrangement process have also found application as site-directed affinity ligands for GABA-gated chloride channels <91JMC1531> and as insecticides <85MI 122-01>.



Scheme 6

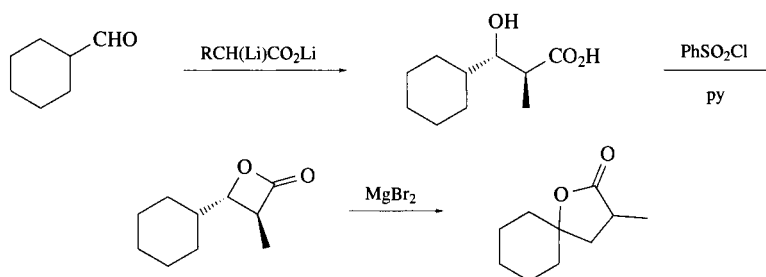
1.22.6.4.2 2-Oxetanone cleavage and elimination

The reaction of substituted oxetanones with magnesium bromide resulted in an ionization/elimination sequence which produced 2,3-dialkyl-3-alkenoic acids that were uncontaminated by the conjugated isomer (Equation (4)) <89SC2885, 90T2307>. However, the alkene stereochemical control was only modest and (*E*)/(*Z*) mixtures were obtained. In some cases, a competing hydride migration resulted in ring expansion and formation of a butanolide (see Section 1.22.6.4.3). The reaction is sensitive to the type of substitution at the C-3 position and electron-withdrawing substituents are not tolerated.

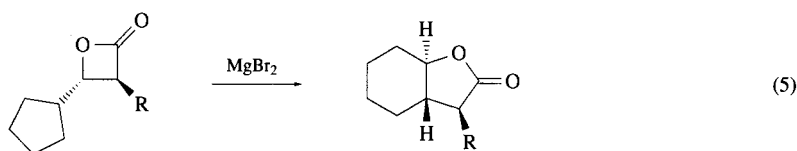


1.22.6.4.3 Ring expansion of 2-oxetanones

Black and co-workers have reported a useful synthesis of butyrolactones from 2-oxetanones by means of a dyotropic rearrangement <87TL4787, 88JOC2371, 88JOC5922, 90SC2959, 90TL6617>. The reaction was quite general and a large number of acid dianion enolates could be employed in the initial condensation step (Scheme 7). The oxetanones were readily formed by lactonization of the 3-hydroxy acid using phenylsulfonyl chloride. Rearrangement was effected by reaction of the oxetanone with magnesium bromide in ether. Spirocyclic-fused butyrolactones were obtained from cyclohexyl-substituted oxetanones, while ring-fused butanolides were obtained from the cyclopentyl-substituted species (Equation (5)). An extension of this chemistry to the synthesis of unsaturated lactones was realized when γ -bromo- β -lactones were treated with silver nitrate. In this case, ring expansion was accompanied by an elimination reaction to provide the butenolide product in reasonable yields <93TL1411>.



Scheme 7



1.22.6.4.4 Cyclooligomerization reactions

Macrocyclic polyethers are of considerable interest, owing to the ability of these compounds to act as selective ion complexation agents. Cyclooligomerization of oxetanes can generate several macrocyclic polyethers, providing the extent of oligomerization can be controlled. The boron trifluoride-catalyzed cyclotrimerization of oxetane provided a synthesis of 12-crown-3 in 40% yield <87CC1391>. An improved yield (73%) of the cyclic trimer was later obtained using phosphorus pentafluoride as the catalyst <91ACS82>. Macrocyclic polylactones derived from cyclooligomerization of oxetanones are also of considerable interest. The tetrameric derivative of (*S*)- β -butyrolactone has

shown antibiotic activity; however, this polylactone is rather difficult to prepare, especially when compared to the cyclooligomerization of β -propiolactone. This synthetic problem led to a detailed study of the thermodynamically controlled cyclooligomerization reactions of each lactone catalyzed by a 2,2-dibutyl-1,3,2-dioxastannolane/dibutyltin dichloride mixed catalyst system <90CC58, 92JOC1472, 93JA3901>. An additional macrocyclic polylactone that acts as a selective iron sequestering agent, enterobactin, has also been prepared by a stannoxane-catalyzed cyclotrimerization <83CC846>.

1.22.6.4.5 Cationic polymerization reactions

The polymerization of oxetanes has been extensively studied. Polymerization is frequently an undesired side reaction in any acid-catalyzed reaction of oxetanes. Specific methods for the controlled polymerization of oxetanes can result in high molecular weight linear polymers. The polymerization of oxetanes is dependent on the substitution pattern of the oxetane ring, as are the properties of the polymers obtained. In many cases, cyclooligomerization is an unwanted side reaction in the formation of high molecular weight polymers. This problem has been carefully studied and is the subject of numerous patents. The mechanism of polymerization has also been studied by a number of methods, including spectroscopic techniques and kinetics. A limited number of references are included herein to indicate developments in this active field. Cationic polymerization of oxetane with triethyloxonium hexafluoroantimonate determined that branched structures were formed in the active solutions by an intermolecular chain transfer reaction to give nonstrained oxonium ions <84MAC249>. The intermolecular reaction was not observed in polymerization reactions of 3,3-dimethyloxetane.

Oxetanones have also been studied extensively in polymerization reactions. An investigation of the triethyloxonium tetrafluoroborate-catalyzed polymerization of β -propiolactone indicated that chain growth occurred by means of carbon-oxygen cleavage of the lactone, resulting in polyesters with alkyl ester end groups <86MAC771>. Polymerization of (*R*)- β -butyrolactone with a variety of tin(IV) catalysts revealed that polymerization predominantly occurs by acyl cleavage, but is accompanied by a significant amount of displacement of the carboxylate with inversion of configuration at the chiral center <93MM6143>.

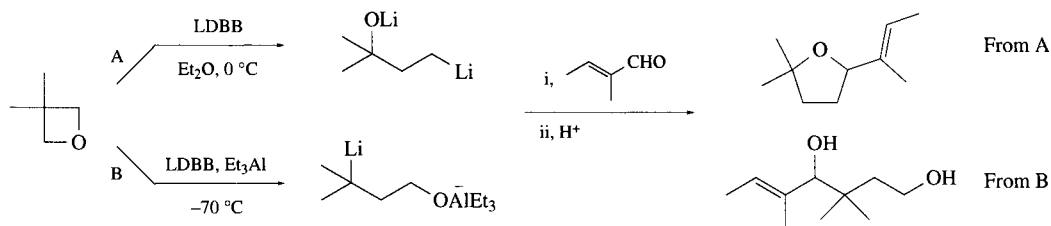
1.22.6.5 Reactions with Nucleophiles

1.22.6.5.1 Reductive ring cleavage of oxetanes

Oxetanes are reduced by strong reducing agents such as lithium aluminum hydride quite readily. Regiochemical issues were addressed in early studies and are not commented on here. More recent reductive cleavage reactions have provided lithioalkoxide ions from oxetanes by reactions with aromatic radical anions <89JOC5657, 91JOC5760>. The lithioalkoxides formed by this reaction are much more stable than the corresponding species formed from oxiranes. In the presence of tri-alkylaluminum reagents the reductive cleavage reaction using lithium 4,4'-di-*t*-butylbiphenylide (LDBB) results in the formation of the most-substituted carbanion while the least-substituted species is formed in the absence of the aluminum additive (Scheme 8). The lithio reagents produced undergo addition reactions with aldehydes and ketones in good overall yields from the oxetane. This methodology has been employed in the generation of homoallylic lithio reagents for the study of 1,2-vinyl rearrangements <93JA3855>. Reaction of the γ -lithioalkoxides with chromium hexacarbonyl results in the formation of pentacarbonyl (2-oxacyclopentylidene)chromium complexes <92CC1623>. Reductive cleavage of oxetane can also be carried out using a potassium/18-crown-6 complex <91CC1513>. An initial electron transfer from potassium to the oxetane provides oxetane radical anion, observed by ESR, which suffers ring cleavage to the alkoxide radical. A subsequent reduction by potassium then provides the alkylpotassium alkoxide product in nearly quantitative yield.

1.22.6.5.2 Reactions with carbon nucleophiles

Oxetanes are not as reactive as oxiranes toward nucleophilic addition, but oxetane ring cleavage by nucleophiles can be easily accomplished in the presence of protic or Lewis acids. Examples of

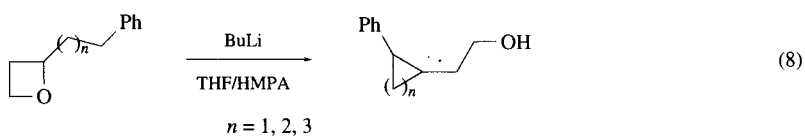
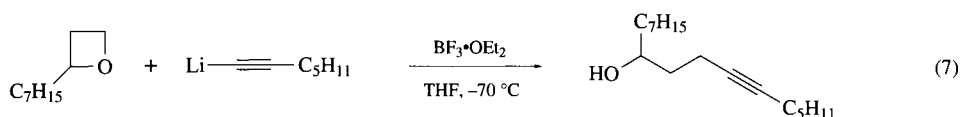
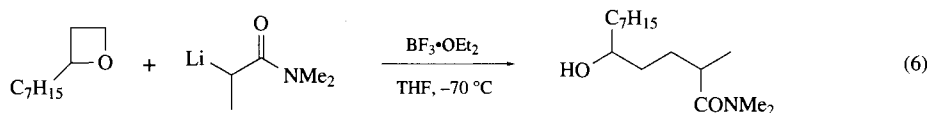


Scheme 8

protic acid-catalyzed reactions are given in Section 1.22.6.5.3 and 1.22.6.4. Lewis acid-catalyzed ring cleavage reactions of oxetanes are also very common. A relatively broad range of nucleophilic species can undergo the addition reaction.

(i) *Enolates and organolithio reagents*

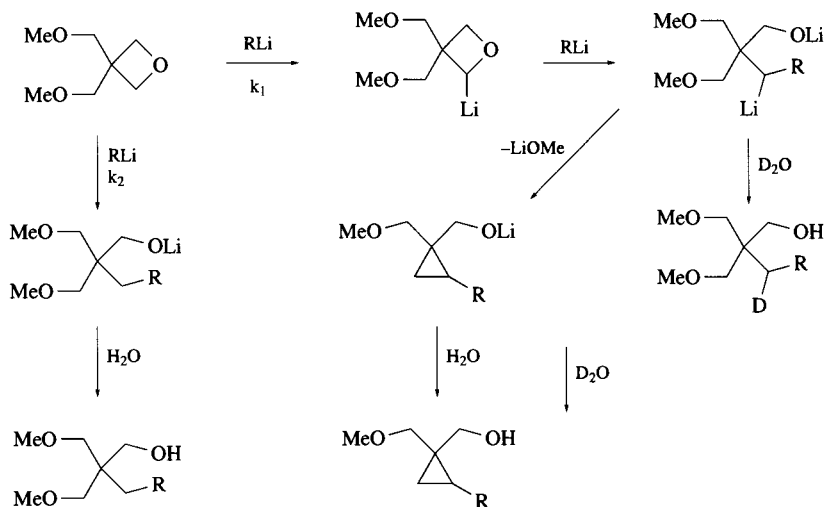
Dithiane anions add to oxetane in the presence of boron trifluoride in >90% yields <88TL5939>. Nucleophilic addition occurs only at the oxetane α -carbon. Ester and amide enolates (Equation (6)) <84TL1159> and lithium acetylides (Equation (7)) <83TL5121, 84T4261> also add to oxetanes in the presence of boron trifluoride. The reaction is regiospecific for addition to the least substituted α -carbon of the oxetane. Without activation by a Lewis acid, substituted oxetanes react with alkyl-lithium reagents quite sluggishly. This feature has provided a method for the novel conversion of oxetanes to cyclopropanes, -pentanes, and -hexanes by an intramolecular nucleophilic attack (Equation (8)) <84TL4549>. Deprotonation occurs selectively alpha to a carbanion-stabilizing substituent to provide benzyl, allyl, propargyl, and thiophenyl stabilized anions. The lithio anion thus obtained then undergoes facile intramolecular nucleophilic addition to the oxetane in good overall yield.



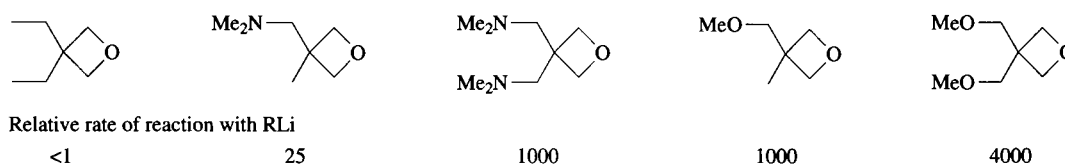
In contrast to the lack of reaction with alkyl-lithium reagents seen for simple oxetanes, 3-(methoxymethyl)- and 3-(dimethylaminomethyl)oxetanes undergo α -lithiation and ring opening reactions (Scheme 9) <87TL5747>. The relative rate of reactivity was found to increase substantially with the degree of (heteroatom)methyl substitution on the ring. The methoxymethyl group was much more effective in this regard than the dimethylamino group (Scheme 10). The α -lithiation of ethers is a common reaction, but had not been observed for oxetanes prior to this study.

(ii) *Al, Cu, and Si reagents*

Boron trifluoride-catalyzed addition of a vinyl alane to oxetane has also been reported <89T6197>. Aluminum acetylides readily add to substituted 2-oxetanones by nucleophilic attack at the ring



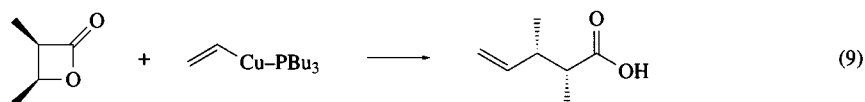
Scheme 9



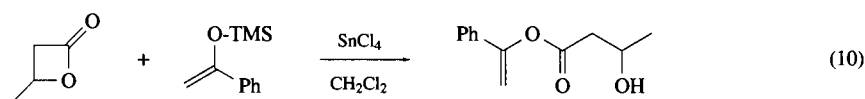
Scheme 10

carbon with concomitant displacement of the carboxylate ^[86TL87]. This regioselectivity is noteworthy since most protic acid-catalyzed nucleophilic addition reactions with oxetanones occur at the acyl carbon.

Regioselective ring opening of 2-oxetanones can also be realized with organocuprates, phosphine-stabilized organocopper reagents, and copper-catalyzed Grignard addition reactions ^[89T403]. Only 3-substituted propionic acid derivatives are obtained in very good yield (Equation (9)). The reaction proceeds by an S_N2 pathway with inversion of configuration at the β -carbon of the lactone. Di-Grignard reagents react with 2-oxetanone to provide α,ω -dicarboxylic acids ^[83BCJ345]. Precursors of the natural products muscone and civitone were prepared by this method.

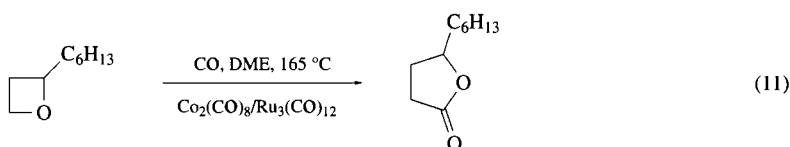


There are few examples of carbon-carbon bond-forming reactions of organosilicon reagents and oxetanes or oxetanones. Allylsilanes add to oxetane in the presence of titanium tetrachloride in moderate to good yields ^[85JOC2782]. The reaction suffers from competitive ring cleavage of the oxetane by titanium tetrachloride. The allylsilane reaction occurred regioselectively at the γ -carbon. Allyl- and alkynyl silanes also react with diketene in the presence of titanium tetrachloride to provide the acetoalkylation product ^[87S1092]. Silyl enol ethers also served as the nucleophile for this reaction leading to the derived 3,5-diketo ester in modest yield. Attempted reaction of 3-methyl-2-oxetanone with the silyl enol ether of acetophenone led only to the *O*-alkylated product in low yield (Equation (10)).

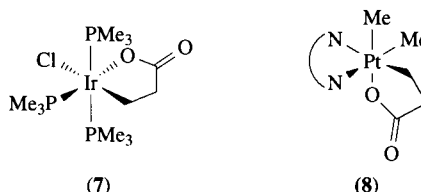


(iii) Co, Pt, Ir insertion/carbonylation reactions

Cobalt-catalyzed silyl-hydroformylation of oxetane to provide 1,4-bis(triethylsiloxy)butane has been accomplished using triethylsilane, carbon monoxide, and dicobalt octacarbonyl as the catalyst <85TL5753, 89JA7938>. The mechanism of the reaction presumed oxetane activation by interaction with the initially formed silacobalt species, $\text{Et}_3\text{SiCo}(\text{CO})_4$. Nucleophilic attack of the cobalt tetracarbonyl anion on the activated oxetane then generated an alkylcobalt intermediate which undergoes CO insertion, hydrosilation, and reductive elimination to give the product. A related reaction of oxetane, *N*-(trimethylsilyl)benzyl amine, and dicobalt octacarbonyl produced *N*-benzyl-4-trimethylsilyloxybutanamide <89CC1253>. The direct carbonylation/ring expansion of substituted oxetanes has been realized at 60 atm of carbon monoxide using a mixture of dicobalt octacarbonyl and tris(ruthenium)dodecacarbonyl (Equation (11)) <89JOC20>. Each catalyst used independently also led to the butyrolactone product, but in lower yields than the combined catalyst system. Insertion of CO was regiospecific for the least substituted α -carbon of the oxetane.



The reaction of oxetanones with dicobalt octacarbonyl and trialkylsilanes has also been examined <86JA7361>. Analogous to the copper-catalyzed reactions discussed above, CO insertion occurs at the ring carbon–oxygen bond with displacement of the carboxylate. Iridium complexes <90OM1300> and platinum complexes <88OM1454> also undergo insertion reactions with 2-oxetanone to provide metal lactone derivatives (7) and (8) (NN = 2,2'-bipyridine), respectively.

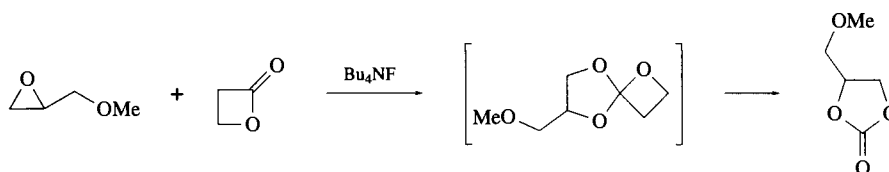


1.22.6.5.3 Reactions with oxygen nucleophiles

The reaction of β -lactones with sodium methoxide in protic solvents was initially investigated in the 1950s. The accepted conclusion at that time was that ring cleavage occurred by means of nucleophilic attack at the acyl CO linkage. This conclusion has been challenged on the basis of data obtained from the reaction of β -propiolactone and potassium methoxide in aprotic (DMF) media indicating that both acyl–oxygen and alkyl–oxygen bond cleavage had occurred <84MAC91>. A subsequent thorough investigation of the reaction of 2-oxetanone and 3-methyl-2-oxetanone with potassium methoxide in aprotic solvents has discarded this possibility and concluded that cleavage only occurs by means of attack at the carbonyl carbon <93JOC4219>. Acid-catalyzed methanolysis of enantiomerically pure 4-(1,1-dichloroalkyl)-2-oxetanones also results in the corresponding 3-hydroxyalkanoate without any racemization <85TL4665>.

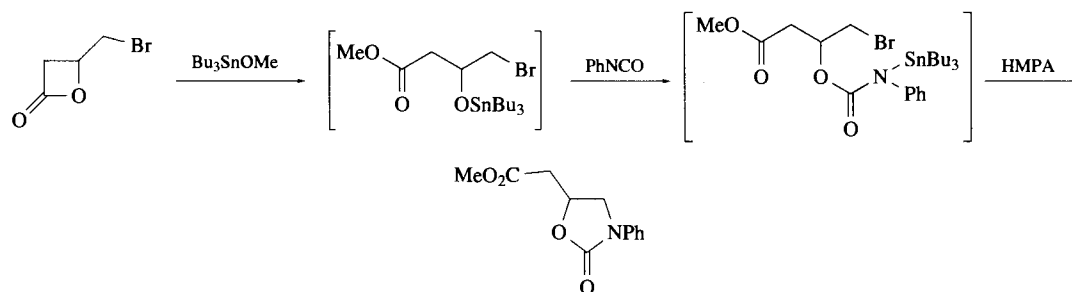
The susceptibility of 2-oxetanones to nucleophilic attack by alkoxides is further illustrated by the generation of cyclic carbonates from the reaction of oxiranes and a number of β -butyrolactones <86TL3741>. The reaction formally involves nucleophilic attack of the oxirane oxygen on the lactone carbonyl, followed by rearrangement to a spirocyclic *ortho*-ester derivative. The carbonate is formed by [2 + 2] cycloreversion of the oxetane portion of the *ortho*-ester (Scheme 11). The use of a 2-oxetanone as an acylating agent provided a means to prepare the lichen metabolite (+)-bourgeanic acid <90JOC5938>.

Nucleophilic attack by tributyltin methoxide can also result in ring cleavage of 3-bromomethyl-2-oxetanone <90JOC2487>. The intermediate trialkyltin ether reacts further with phenyl isocyanate leading to oxazolidinones after an intramolecular alkylation reaction (Scheme 12). The reaction did not require an additional catalyst. A similar reaction of 3-bromoalkyl-2-oxetanones using hexabutyldistannoxane provided butyrolactones stereospecifically in very good yield <91JOC475>.

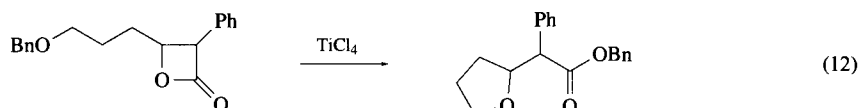


Scheme 11

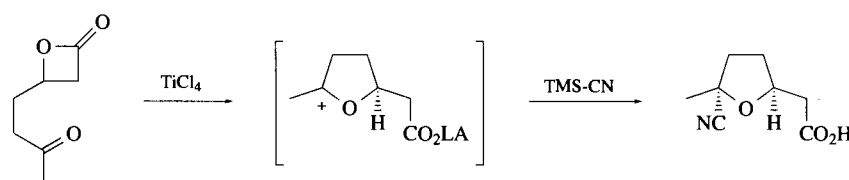
Lewis acid-catalyzed intramolecular nucleophilic addition of ethers (Equation (12)) $\langle 89\text{TL}6829, 90\text{JOC}2991 \rangle$ and ketones $\langle 93\text{TL}6997 \rangle$ to 2-oxetanones provided a method to prepare tetrahydrofurans with good levels of stereoselectivity. The reaction occurs with inversion of configuration at the ring alkyl carbon–oxygen bond. The ketone reaction proceeded through an oxocarbenium ion intermediate which could be trapped by silyl nucleophiles (Scheme 13).



Scheme 12



(12)

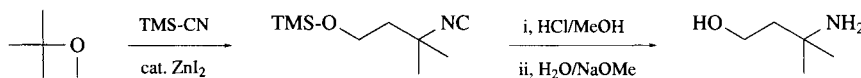


Scheme 13

1.22.6.5.4 Reactions with nitrogen and other heteroatom nucleophiles

The regiospecific ring cleavage of oxiranes, oxetanes, and lactones by the reaction of dialkylaminosilanes and -stannanes provided the dialkylamino alcohols by nitrogen attack at the least substituted α -carbon of the oxetane $\langle 84\text{JCS(P)}12261 \rangle$. The reaction required aluminum chloride and the yields were moderate. Oxetanes were also regiospecifically cleaved by trimethylsilyl cyanide in the presence of zinc chloride $\langle 85\text{SC}775, 85\text{TL}4971 \rangle$. In contrast to the amino silane reactions, reactions of trimethylsilyl cyanide provided the isonitrile product regiospecifically at the most substituted α -carbon of the oxetane. Hydrolysis of the isonitrile provided γ -amino alcohols that were otherwise difficult to obtain in very good overall yields (Scheme 14). Trimethylsilyl isoselenocyanate also reacted with oxetane to provide the selenocyanate in high yield $\langle 90\text{BCJ}825 \rangle$. Nucleophilic addition of phenylselenide, prepared from lithium aluminum hydride reduction of diphenyldiselenide, occurred at the less substituted α -carbon of the oxetane to give the γ -phenylselenyl alcohol $\langle 89\text{S}434 \rangle$.

The ring opening of 2-oxetanones with alkylaminostannanes was found to be a facile reaction that did not require a catalyst. The ω -stannoxyamides were obtained in excellent yield by nucleophilic attack of the amine at the oxetanone carbonyl carbon $\langle 83\text{S}319 \rangle$. In contrast to the acyl attack of the



Scheme 14

aminostannanes, simple thiolate anions cleave 2-oxetanones by nucleophilic displacement of the carboxylate group <87S724>. Nucleophilic addition of sodium phenylthiolate to (*R*) or (*S*) 4-methyl-2-oxetanone resulted in clean inversion of configuration at C-4 of the oxetanone <92S83>.

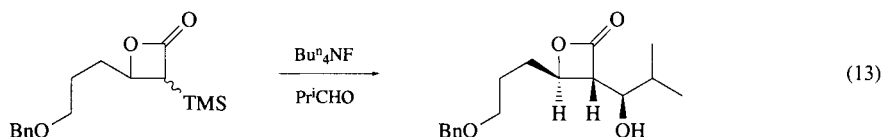
1.22.6.5.5 Anionic polymerization reactions

Polymerization reactions of 2-oxetanone and 4-methyl-2-oxetanone (β -propiolactone and β -butyrolactone, respectively) have been, and continue to be, intensively studied. Many mechanistic studies of anionic polymerization reactions have been reported in the period 1983–1993. Illustrative examples of these investigations are given here. A study of the mechanism of anionic polymerization of β -lactones initiated using potassium alkoxides by end-group analysis and equimolar reactions has been reported <91MM1218, 92MM2017>. The authors concluded that the reaction occurred by a complex mechanism which produced unsaturated esters and potassium hydroxide as the initial products. The potassium hydroxide formed was then the actual initiator of polymerization in the potassium *t*-butoxide/18-crown-6 system.

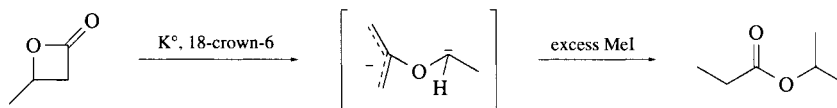
Polymerization by potassium naphthalenide has also been thoroughly studied <89MM3242, 91MM349>. In these reactions both the ring alkyl carbon–oxygen bond and the acyl–oxygen bond were cleaved to form carboxylate and alkoxide active species. The polyesters with low polydispersity formed from these reactions contained unsaturated end groups.

1.22.6.6 Enolates Derived From 2-Oxetanones

The chemistry of 2-oxetanone enolates is quite limited due to the highly reactive nature of the oxetanone ring toward nucleophiles. There are some examples known of enolate formation for 3-alkyl-substituted 2-oxetanones, see Scheme 4, Section 1.22.6.2. Earlier work on 2-oxetanone enolates is cited in a review of β -lactone chemistry, see Section 1.22.1. In Section 1.22.6.5.3, the intramolecular addition of ethers to oxetanones leading to the formation of tetrahydrofurans was discussed. However, several problems were encountered in attempts to extend this chemistry to more substituted oxetanones due to the lack of efficient syntheses of the intermediates. Attempted formation of the enolate of 4-alkyl-2-oxetanones met with little success. The problem was circumvented by generation of the oxetanones using trimethylsilylketene. The enolate of the oxetanone was then easily generated by reaction of the 3-trimethylsilyl-2-oxetanone with tetrabutyl ammonium fluoride <92JOC2511>. Reaction of the enolate with a variety of aldehydes occurred in very good yield with some selectivity for the erythro isomer (Equation (13)).

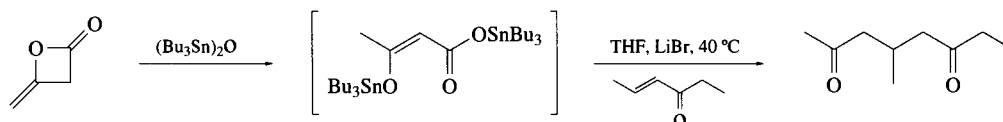


The reaction of 2-oxetanones with potassium metal and 18-crown-6 resulted in the generation of a novel dianion that could undergo dialkylation with alkyl halides (Scheme 15) <88CC1261, 89JOC1500>. The detailed mechanism of this novel reaction was not fully discussed.



Scheme 15

The reaction of diketene with bis(tributyltin)oxide provides the enolate of acetylacetic acid <93CL1219, 93CL1953, 94JOC486>. The enolate was alkylated with a variety of alkyl halides to provide methyl ketones, or undergoes aldol condensation with aldehydes to provide the unsaturated methyl ketone after decarboxylation. The Michael addition of the tin enolate to unsaturated ketones provides a synthesis of 1,5-diketones (Scheme 16) <93CC1067>.



Scheme 16

1.22.6.7 Reactions with Radicals and Carbenes

The reaction of oxetanes with radicals results in a hydrogen abstraction reaction. The reaction of methyl radical and several substituted oxetanes has been examined <84JCS(F1)3391>. Tertiary hydrogen atoms in the 2- or 4-position of oxetane are removed much faster than secondary methylene radicals at any position. A comparison of several cyclic ethers in the reaction with the radical generated from bromotrichloromethane resulted in the relative order of reactivity of oxetane > oxepane > oxetene > tetrahydrofuran <89JPO367>.

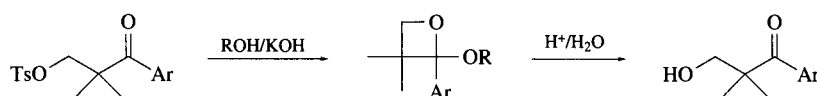
1.22.6.8 Cycloaddition Reactions

The cycloaddition of oxetane and carbon dioxide to form trimethylene carbonate has been reported to occur in excellent yield if tetraphenylstibonium iodide was used as the catalyst <85TL1323>. The reaction proved to be somewhat general in that isocyanates and carbodiimides also undergo cycloaddition to oxetane to provide 1,3-oxazin-2-ones and 1,3-oxazin-2-imines, respectively, in good yields <89JHC1659>. δ -Lactones were obtained upon reaction of oxetane and ketenes in the presence of tetraphenylstibonium iodide <88JOC5974>. Other catalyst systems such as di- or trialkyltin iodide and triphenyl phosphine oxide were not as effective <85TL5167>.

1.22.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

1.22.7.1 Hydrolysis of 2-Oxetanone Derivatives

The mechanism of the acid-catalyzed hydrolysis of a series of oxetane acetals has been investigated <90JCS(P2)825>. The rate determining step for hydrolysis in all of the cases examined was ring cleavage of the oxetane. No general acid catalysis was observed under the reaction conditions. Electron-withdrawing substituents at the 2-position or the substitution of fluorinated alcohols for methanol in the preparation of the acetal resulted in a dramatic kinetic stabilization of the acetal (Scheme 17). The hydrolysis of 2-cyclohexylidene-3,3-dimethoxyoxetane revealed that the oxetane derivative exhibited a rate constant that was an order of magnitude lower than the rate constant for the acyclic analogue <83JOC2627>. The rate retardation was believed to be due to the effect of introducing partial double bond character into the four-membered ring in the rate-determining step of the reaction.

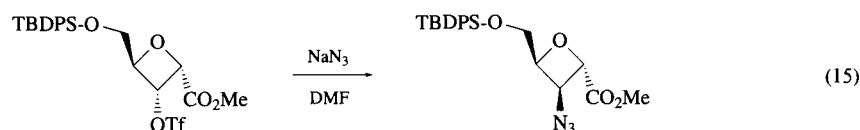
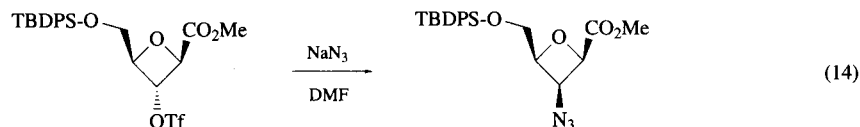


Scheme 17

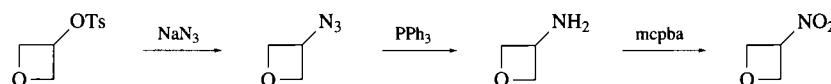
1.22.7.2 Nucleophilic Displacement Reactions

Nucleophilic displacement reactions at ring carbons of oxetanes or oxetanones may be problematic owing to the reactivity of the ring itself. This is especially true for oxetanones, and synthetic manipulations of the substituents on an oxetanone ring are generally not accomplished by nucleophilic substitution reactions. Nucleophilic displacement reactions of functionalized oxetane rings are of considerable interest owing to the number of oxetanes that are of practical interest in the basic chemical, pharmaceutical, and agrochemical industries (see Section 1.22.12). Of particular note is the interest in functionalized oxetane derivatives related to the natural product oxetanocin, a potent antiviral agent. A few examples of nucleophilic substitution reactions are included in this section.

The synthesis of azido- and fluoro-substituted oxetane-containing nucleosides for evaluation as antiviral agents effective against human immunodeficiency virus (HIV) required the need to develop a general method for the preparation of oxetane intermediates containing these functional groups. Nucleophilic substitution of an appropriate triflate derivative proved to be a viable approach $\langle 91\text{TL}1675 \rangle$. The displacement reaction of the triflate with azide occurred in high yield with complete inversion of stereochemistry for two isomers of the oxetane (Equations (14) and (15)). Note that the possible elimination (E_1) of the triflate was not observed in either case. The S_N2 displacement reaction does not appear to be susceptible to steric interactions with the adjacent ring substituents.



Simple oxetanes bearing azide and nitro groups are important as monomers for polymerization. The displacement of 3-tosyloxetane by sodium azide provided the 3-azidooxetane in high yield (Scheme 18) $\langle 83\text{JOC}2953 \rangle$. The azide could be reduced to the amine with triphenylphosphine, and the amine was then oxidized to the nitro derivative in very good overall yield. The Lewis acid-catalyzed polymerization of the 3-azido-, 3-nitro-, and 3,3-bis(dinitro)oxetanes was also carried out.

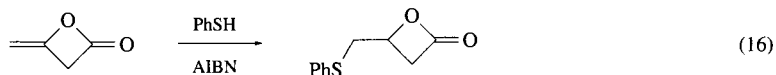


Scheme 18

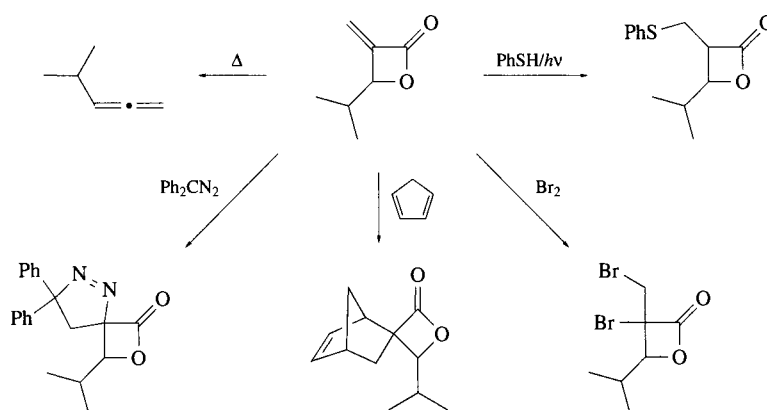
1.22.7.3 Reactions of Methylene-substituted 2-Oxetanones

The reactions of 4-methylene-2-oxetanone, diketene, have been extensively reviewed in 1986 and 1993 (see Section 1.22.1) and will only be discussed briefly here. As with other 2-oxetanones, nucleophilic addition reactions to diketene occur predominantly at the acyl carbon. Thermal decomposition of diketene, unlike other 2-oxetanones (see Section 1.22.6.2), does not lead to allene and carbon dioxide, but rather to ketene by means of a cycloreversion reaction. The reactions of diketene therefore are predominantly involved with the generation and subsequent reactions of ketene. Diketene does undergo radical addition reactions at the exocyclic methylene $\langle 86\text{JCS}(\text{P}1)2081 \rangle$. Alkanethiols and arylthiols add to diketene by free radical processes (AIBN-catalyzed) to give unstable 4-thiomethyl substituted oxetanones (Equation (16)). Oxidation of the sulfur to the sulfoxide or sulfone provided stable solids. Phosphines could also be added, but required harsher reaction conditions using bis(*t*-butylcyclohexyl)peroxydicarbonate (BCHPC). Radical chlorination and the addition of halocarbons to diketene was carried out using BCHPC-catalyzed reactions on scales up to 2 kg. Other reactions at the exocyclic methylene group include hydrogenation. An

asymmetric catalytic hydrogenation using a ruthenium binap complex provided (*R*)-4-methyl-2-oxetanone in 92% *ee* <92CC1725>.



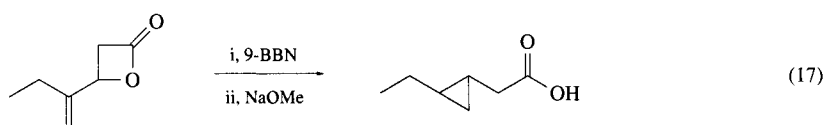
α -Methylene- β -lactones, 3-methylene-2-oxetanones, have been prepared and were shown to undergo a number of useful synthetic transformations (Scheme 19) <91JOC5782, 91TL7033>. As indicated earlier (Section 1.22.6.2), thermolysis of these oxetanones generates an allene by decarboxylation. Photochemical addition of thiophenol occurred at the exocyclic methylene without ring cleavage. Nucleophilic addition reactions of alkoxides or amines, however, occurred only at the carbonyl carbon with concomitant ring cleavage. Cycloaddition products were observed in reactions with dicyclopentadiene and diphenyldiazomethane.



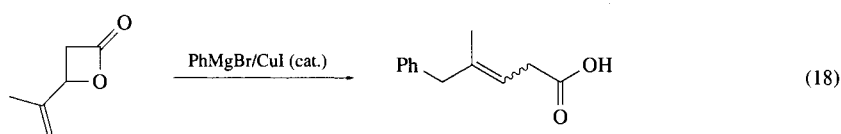
Scheme 19

1.22.7.4 Reactions of Alkenyl-substituted Oxetanes and 2-Oxetanones

A novel synthesis of cyclopropyl acetic acids was realized from 4-alkenyl-2-oxetanones by a hydroboration/methanolysis sequence <83CL1273>. The cyclopropanes are obtained in moderate to good yields as a mixture of *cis* and *trans* isomers (Equation (17)).

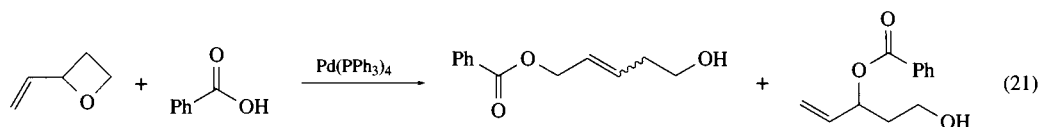
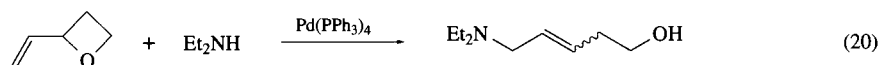
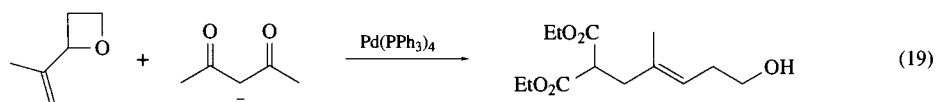


A more common reaction of 4-alkenyl-substituted oxetanones is nucleophilic addition of an organometallic reagent to the alkenyl substituent with displacement of the carboxylate function. This has been an extensively studied reaction and has been applied in the syntheses of several natural products. Cuprate or copper-catalyzed Grignard addition reactions provide the ring-opened β,γ -unsaturated acids in good yields <88BCJ3255, 90SL341>. The reactions are highly regioselective for addition to the alkenyl substituent in preference to direct addition to the carbonyl carbon, but the stereochemistry of the product alkene is generally not controlled (Equation (18)).



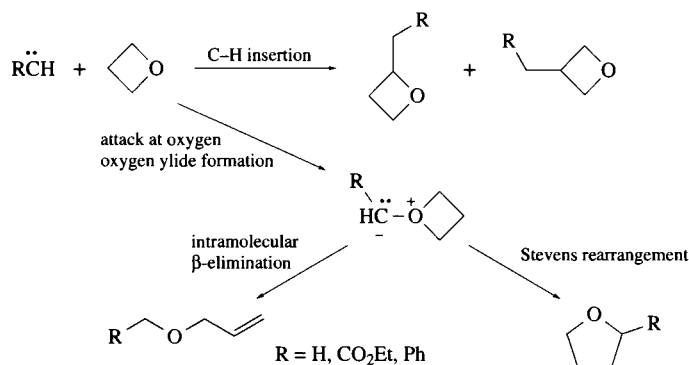
Palladium-catalyzed nucleophilic addition reactions to 2-alkenyloxetanes is a versatile reaction <88TL5069, 89TL3487>. Reactions with dimethylmalonate were very regio- and stereoselective, pro-

viding the (*E*)-homoallylic alcohol as the major product in very good yield (Equation (19)). Amine nucleophiles add regiospecifically, but stereochemical mixtures of the double bond are obtained (Equation (20)). Oxygen nucleophiles are neither regio- nor stereoselective, providing products derived from S_N2 and S_N2' addition (Equation (21)). Palladium-catalyzed cross-coupling reactions of vinyl oxetane with aryl iodides, vinyl iodides, and vinyl triflates have also been reported <93SL145>. The coupling reaction is regiospecific but produces stereochemical mixtures of the alkene in the product.



1.22.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

The reaction of oxetane with carbenes follows two major pathways, carbon–hydrogen insertion or the formation of an oxygen ylide by reaction of the carbene and the oxetane oxygen <85TL193, 85TL197, 91CBI853>. The oxygen ylide species can produce a tetrahydrofuran by a Stevens rearrangement, or generate an allyl ether by an intramolecular β -elimination process. In reactions with methyl carbene, carbon–hydrogen insertion accounts for less than one-half of the products with only a slight preference for insertion at the 2-position of the oxetane. Carboethoxymethyl carbene and phenyl carbene provide less carbon–hydrogen insertion products, but the regioselectivity of insertion was greatly enhanced for the 2-position. However, for each of the latter two carbenes, attack at oxygen was strongly favored over insertion and a substantial increase in the yield of the tetrahydrofuran (Stevens rearrangement) product was observed (Scheme 20). Photolysis of diazomethane in the presence of (*S*)-2-methyloxetane provided a mixture of 2- and 3-methyltetrahydrofuran with 21% retention of configuration, a result in agreement with 1,2-shifts preceded by a sequence of radical dissociation and recombination reactions. The same reaction in the presence of rhodium acetate resulted in exclusive formation of the 3-methyltetrahydrofuran product with nearly complete loss of enantiomeric purity.



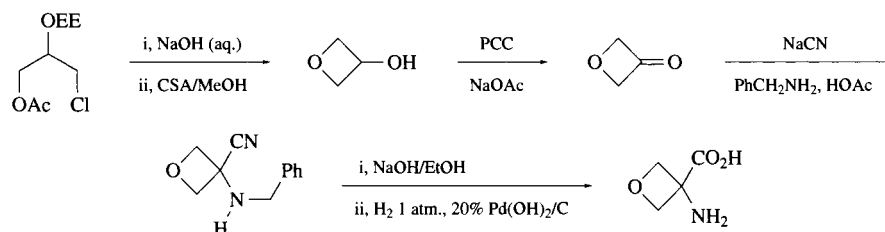
Scheme 20

1.22.9 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS

1.22.9.1 Oxetane Synthesis by Single C—O Bond Formation

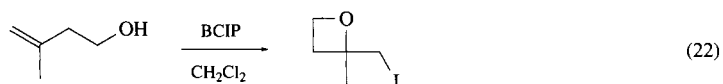
The most common method of obtaining oxetanes involves an intramolecular ether synthesis from a suitably functionalized alcohol. A large variety of leaving groups have been employed for the ring closure, including halides, tosylates, and other ester leaving groups. The base can range from an alkoxide to a nonnucleophilic amine. A competing reaction for strongly basic conditions is fragmentation of the alcohol to formaldehyde and an alkene. These methods continue to be employed and many examples are found in the literature from 1983–1993. Several illustrative examples are given in this section.

An intramolecular ring closure was employed in the synthesis of a novel oxetane amino acid (Scheme 21) <91SL783>. A route to 2-perfluoroalkyloxetanes achieved ring closure of a 1,3-iodohydrin with dbu <93TL5093>. The intramolecular displacement of a halogen using potassium alkoxide as the base has also provided an asymmetric synthesis of 2-aryloxetanes in >80% *ee* <86CC1018>. A novel alkoxide displacement method for oxetane ring closure involved the addition of methoxide to 3-hydroxyvinyl selenones. The selenone intermediate produced then undergoes intramolecular displacement by the 3-alkoxy group to provide the 3-methoxy-2-alkyloxetane <84JOC1230>. The relative stereochemistry of the oxetane substituents was not controlled by the reaction, leading to mixtures of *cis*- and *trans*-substituted oxetanes.



Scheme 21

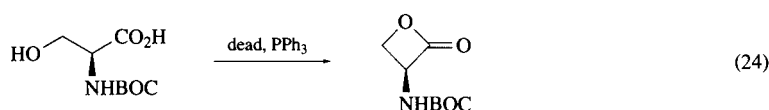
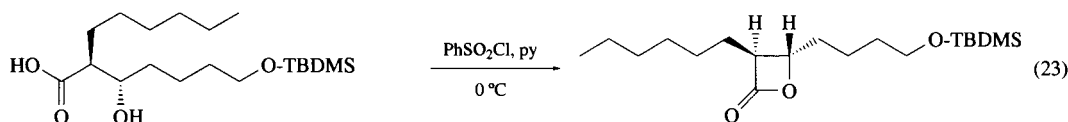
Mildly basic to neutral conditions for the ring closure of 1,3-halohydrins have also been developed. Tetraphenylantimony methoxide was an effective nonbasic reagent for oxetane synthesis from 1,3-bromohydrins <90S106>. The advantages of the antimony reagent over other methods included the fact that ester substituents were stable to the reaction conditions, and the preparation of thermally sensitive oxetanes could be achieved. Another mild reaction sequence for oxetane synthesis achieved *in situ* ring closure by a palladium-catalyzed reaction of dibutylallylstannane with 3-haloketones or -aldehydes <83JOC4629>. In this reaction, the nucleophile is either a stannoxane or an alkoxy-palladium species. Attack of a free alcohol on an electrophilic intermediate has also led to the formation of oxetanes. Reaction of bis(sym-collidine)iodine perchlorate (BCIP) with homoallylic alcohols provided 2-iodoalkyloxetanes in good yields (Equation (22)) <88S862>. Tetrahydrofurans, from endocyclic ring closure, were not observed for homoallylic alcohols; however, 4-pentenol produced a mixture of the oxetane and tetrahydrofuran ring products.



1.22.9.2 2-Oxetanone Synthesis by Lactonization

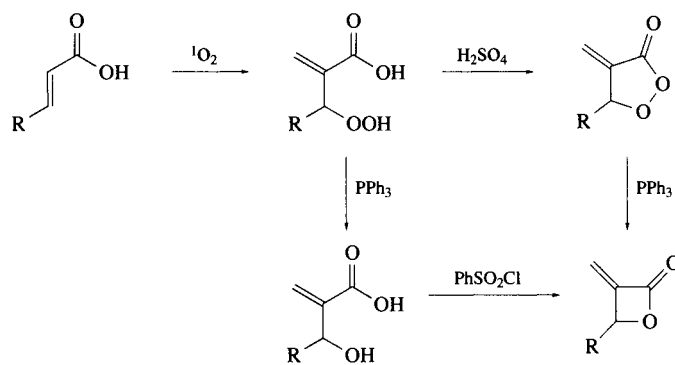
The synthesis of 2-oxetanones was first accomplished by Einhorn in 1883 and has been the subject of several reviews published prior to 1983. The classical routes involved cyclization of β -halocarboxylates. A number of mixed anhydride derivatives have been examined as precursors for 2-oxetanone synthesis; however, the best results are typically obtained with benzenesulfonyl chloride in pyridine. This procedure continues to be commonly employed in the ring closure of 3-hydroxycarboxylates (Equation (23)) <92T5557>. The mixed benzenesulfonic anhydride lactonization procedure has also been employed in the synthesis of the β -lactone derivatives of L-threonine and L-allo-threonine <91JOC1280>. Nevertheless, many 3-hydroxycarboxylates not bearing a substituent

in the 2-position fail to cyclize to the 2-oxetanone, but instead suffer elimination and ketene formation. Therefore, additional methods for the lactonization of 3-hydroxycarboxylates have been developed. Thiopyridyl esters have been shown to cyclize to 4-substituted-2-oxetanones in the presence of mercury(II) salts <93JOC7932>. The β -lactone of serine has been prepared by treating Boc-L-Ser-OH with triphenylphosphine and diethylazodicarboxylate (Mitsunobu conditions) (Equation (24)) <92OS(70)10>. The lactone derivative could then act as a precursor for a variety of novel amino acids by nucleophilic attack at the oxetanone ring carbon–oxygen bond leading to carboxylate displacement. A number of thiol and amino nucleophiles were used <85JA7105, 88JA2237>.

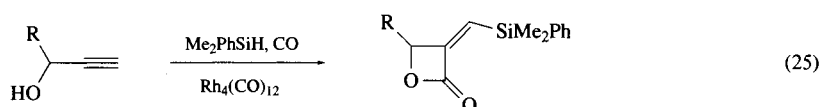


Thiol ester enolate addition to carbonyl compounds results in the spontaneous cyclization of the aldolate intermediate to the 2-oxetanone derivative in excellent overall yields <91JOC1176> (see also Section 1.22.6.2). A wide variety of substituents and substitution patterns are available by this method, perhaps making this method the most useful to date for the synthesis of 2-oxetanones. The aldol reaction of the enolate from acyliron complexes provided the corresponding 3-hydroxy acyliron intermediate which readily undergoes β -lactone formation upon treatment with bromine <91SL779>. Although the yields of oxetanone were very good, the need to prepare the acyliron species limits the general utility of this approach.

α -Methylene- β -lactones have been discussed earlier as useful intermediates (see Sections 1.22.6.2 and 1.22.7.3). This novel class of lactones can be prepared by the deoxygenation of 5-alkyl-4-methylene-1,2-dioxolan-3-ones by reaction with triphenylphosphine, or by lactonization of 3-alkyl-3-peroxy-2-methylene carboxylates using benzenesulfonyl chloride (Scheme 22) <91JOC5778>. α -Methylene- β -lactones are also obtained from the rhodium-catalyzed cyclocarbonylation of substituted propargylic alcohols (Equation (25)) <90JA6120>.



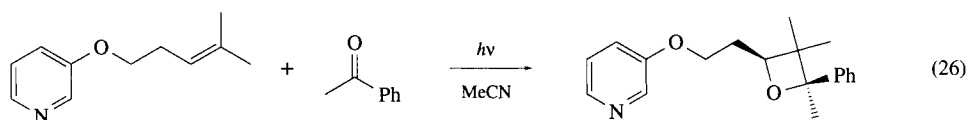
Scheme 22



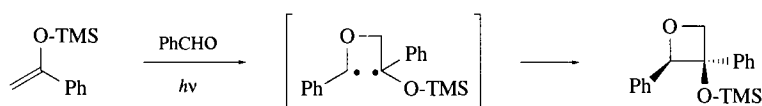
1.22.9.3 Photochemical [2 + 2] Cycloaddition

The photochemical [2 + 2] cycloaddition of an alkene and a carbonyl, known as the Paterno–Buchi reaction, has been one of the most common methods for the preparation of oxetanes

<81MI 122-01> (see Section 1.22.1 for previous reviews). The photochemical cycloaddition reaction occurs readily between electron-rich alkenes and electron-poor carbonyl compounds, but is less likely to provide the oxetane from photolysis of electron-poor alkenes. Although the reaction is not a truly general method due to this limitation, the yields of oxetanes that would be very difficult to produce by any other method can be quite high. The mechanism of the Paterno–Buchi reaction has been investigated by several researchers, and a theoretical investigation was described in Section 1.22.2.1. The regiochemistry of the photocycloaddition can range from high to low and is apparently controlled by the relative stability of diradical intermediates. Alkene stereochemistry is frequently partially lost in the reaction, indicating intermediate radical character, leading to stereochemical mixtures of the oxetane product. For example, photochemical [2 + 2] cycloaddition of 1,1,1-trifluoro-3-decyn-2-one with trisubstituted alkenes led to oxetanes as regiochemical and stereochemical mixtures <86JFC(30)429>. However, regio- and stereoselective photocycloaddition reactions are possible. The photolysis of 3-(4-methyl-3-pentenoxy)pyridine and acetophenone produced an oxetane with high diastereoselectivity (> 30 : 1) (Equation (26)) <90JHC1167>. The regio- and stereoselectivity of the reaction was explained by perpendicular approach of the triplet-excited state of acetophenone to the alkene followed by π – n interaction resulting in carbon–oxygen bond formation and a diradical intermediate. The stereoselectivity observed during carbon–carbon bond formation was then a result of the steric interaction inherent in the perpendicular approach. In contrast, photolysis of more electron-rich alkenes, vinyl methylsulfides, with benzophenone provided oxetanes with excellent regioselectivity, but poor stereoselectivity <87CC964, 91JCS(P1)865>. The 2,2-diphenyl-3-thiomethyl-4-alkyloxetane isomers were obtained nearly exclusively, but only in modest yields. The regioselectivity was due to the formation of the most stable diradical (diphenyl- and thiomethyl-substituted species) after initial carbon–oxygen bond formation.



A similar photochemical reaction of the silyl enol ether of acetophenone and benzaldehyde provided the 2,3-diphenyl-3-trimethylsilyloxyoxetane with excellent regioselectivity (>95 : 5) and diastereoselectivity (>95 : 5) <91TL7037>. In this example, the diastereoselection was explained by anti-approach of the two phenyl groups during the carbon–carbon bond forming step from the diradical intermediate (Scheme 23). Excellent regiochemical control has also been observed in the photochemical reaction of allylsilane and benzophenone <89BCJ336>. In this cycloaddition reaction, regioselective oxetane formation was due to the hyperconjugative stabilization of the β -silyl radical.



Scheme 23

In an interesting comparison study, the stabilizing effect of the silyl group was shown to be less than that of a tertiary radical, leading to a reversal of regioselection in the photocycloaddition of β,β -disubstituted allylsilanes (Scheme 24). Regioselective photocycloaddition of biacetyl to allyl vinyl ethers has also been reported <85TL4407>. The oxetane is formed preferentially at the vinyl ether (more electron-rich alkene), but the yields and stereoselectivity were quite low. The yields of photocycloaddition reactions to produce oxetanes are often compromised by the photodecomposition of the products. For example, in the selective vinyl ether [2 + 2] cycloaddition noted above, photochemical loss of the acetyl group generated a 2-methylene substituent in low yield (Scheme 25).

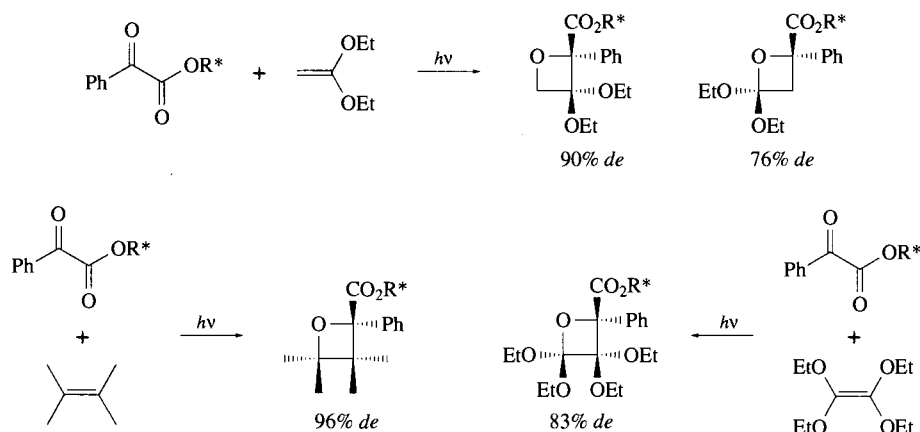
Similarly, the photochemical reaction of methyl benzoate and 2,3-dimethyl-2-butene or 1,1-diethoxyethene results in three types of products: the 2-alkoxyoxetane from direct [2 + 2] cycloaddition, β,γ -unsaturated ketones from allylic hydrogen abstraction by the carbonyl oxygen of the photoexcited ester from the substrate alkene, and alkoxyalkenes from [2 + 2] cycloreversion of the oxetane (Scheme 26) <89JOC135>. Other reactive intermediates may also be generated in the reaction. The photolysis of haloketene acetals and benzophenones results in a mixture of oxetane and tetrahydrofuran products (Equation 27) <87TL4271>. The tetrahydrofuran product is believed to

Scheme 24

Scheme 25

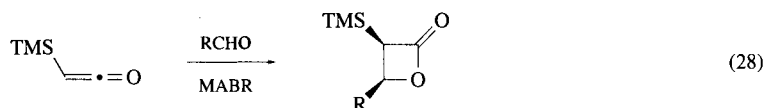
Scheme 26

Ketenes are often associated with the synthesis of cyclobutanones: however, 2-oxetanones are also prepared by [2 + 2] cycloaddition reactions of ketenes and carbonyl compounds. Lewis acid-catalyzed addition of ketenes to aldehydes provides ready access to a variety of β -lactones. Reviews of this chemistry are cited in CHEC-I. Since 1984 work in this area has focused on developing new catalysts for the reaction and on attempts to control the stereochemistry. Cycloaddition reactions of trimethylsilylketene with aliphatic and aryl aldehydes catalyzed by methylaluminum bis(4-bromo-

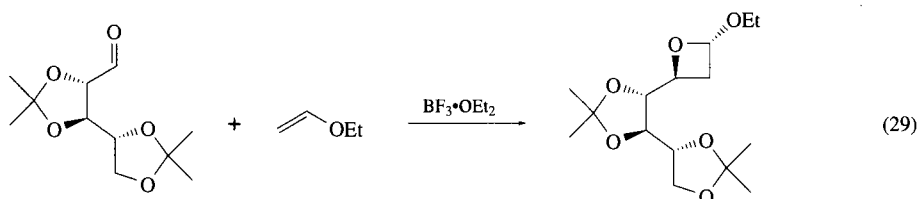


Scheme 27

2,6-di-*t*-butylphenoxide) (MABR) provided exceptionally high levels of stereoselectivity (>90:10) for the *cis*-3,4-disubstituted-2-oxetanone (Equation (28)) (<92SL31>). Trimethylsilylketene cycloaddition reactions with aldehydes have also been employed to prepare 3-trimethylsilyl-2-oxetanones used for the generation of 2-oxetanone enolates (see Section 1.22.6.6) (<88TL6573>). An asymmetric cycloaddition of ketene and chloral has been achieved by using quinidine as a catalyst (<82JA166>). The reaction works well for a number of di- or trichloromethyl aldehydes and ketones, providing the 4-mono- or 4,4-disubstituted 2-oxetanones in 90–98% *ee* (<85JOC1977>). 2-Iminooxetanes are obtained by the reaction of aldehydes and ketene imines in the presence of lanthanide shift reagents (<88JOC5501>). The cycloaddition reaction failed to provide the 2-iminooxetanes under thermal conditions or with other Lewis acid catalysts, and competing Diels–Alder cycloadditions were observed for reactions using unsaturated aldehydes.



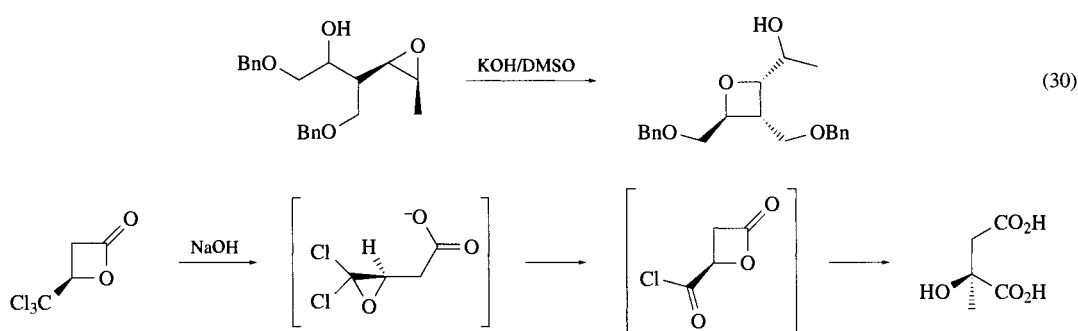
Oxetanes can be prepared by nonphotolytic [2 + 2] cycloaddition reactions of electron-rich alkenes with aldehydes or, to a more limited extent, with ketones. The reaction is catalyzed by Lewis acids and poses some advantages over the photochemical cycloaddition reaction. The regiocontrol of the nonphotolytic reaction is generally high since the reaction proceeds in a stepwise fashion involving nucleophilic attack of the alkene on the carbonyl with subsequent collapse of the zwitterionic intermediate to the oxetane. The stereochemistry of the reaction is not as predictable and depends upon the system under study. The Lewis acid-catalyzed reaction of 1,1-dimethoxypropene with aldehydes illustrates this point (<85JCS(P1)561>). With small aldehydes, no α -substituent, the *cis*-disubstituted oxetane was obtained as the major product, while larger aldehydes provided a stereochemical mixture with a preference for the *trans*-disubstituted oxetane product. The addition reaction of vinyl ethers or vinyl sulfides to aldehydes derived from sugars proceeded with excellent regio- and stereoselectivity (Equation (29)) (<89TL1571>). No catalyst was required if the carbonyl was electron deficient; however, this reaction does not appear to be synthetically useful. For example, biacetyl reacts with 1,1-diethoxyethene to give a low yield of the oxetane accompanied by a large number of side products (<85JOC2815>).



1.22.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

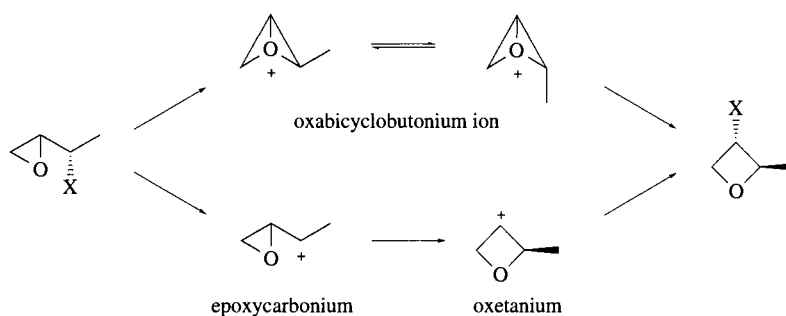
1.22.10.1 Oxirane to Oxetane or Oxetanone Transformations

The synthesis of oxetanes and oxetanones from oxiranes can be accomplished under a variety of conditions. Epoxy alcohols can be treated with base to provide an oxetane by a 4-exo ring closure (Equation (30)) <90T7703, 90TL4777>. There is a strict stereochemical requirement for the 4-exo cyclization reaction to form the oxetane. Only the *cis*-epoxy alcohol forms the oxetane products, while the corresponding *trans*-epoxy alcohol only forms a tetrahydrofuran by a 5-endo cyclization. Basic hydrolysis of (–)-4-trichloromethyl-2-oxetanone provides (*S*)-malic acid through a mechanism involving inversion of configuration at the oxetanone ether carbon–oxygen bond by means of an intramolecular nucleophilic attack of the carboxylate on an intermediate epoxide (Scheme 28) <84CC1181>.



Scheme 28

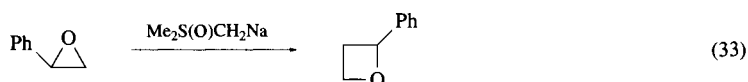
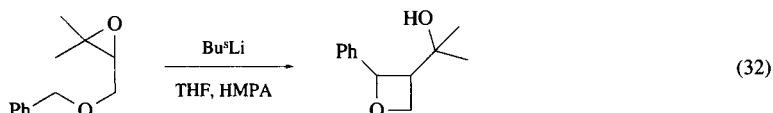
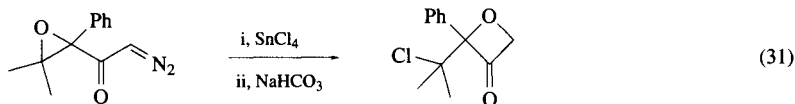
The solvolysis of epoxycarbinol 3,5-dinitrobenzoate esters can lead to oxetanes through the formation of 1-oxabicyclobutonium ions (Scheme 29) <90JA3535>. Computational studies indicated that the oxetanium ion was 20 kcal/mol less stable than any of the other possible cationic intermediates. The exo 1-oxabicyclobutonium ion was 4 kcal/mol more stable than the epoxycarbonium ion. Indeed, the experimental data indicated that the rearrangement was stereospecific, ruling out the epoxycarbonium or oxetanium ion intermediates. Although theoretically interesting, the solvolysis reaction is not really useful for the synthesis of oxetanes.



Scheme 29

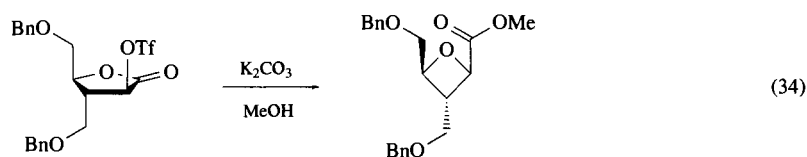
The reaction of α,β -epoxy- α' -diazomethyl ketones with tin tetrachloride produces 2-chloroalkyl-3-oxetanones in modest to good yields (Equation (31)) <92T9985>. The reaction involved an oxonium intermediate formed by carbene addition to the oxirane oxygen. Rearrangement of epoxides into oxetanes by means of anionic carbon–carbon bond forming reactions have also been reported. Similar to the deprotonation/nucleophilic cleavage of oxetanes discussed in Section 1.22.6.5.2, epoxides bearing benzyl ethers can be deprotonated selectively at the benzylic carbon. The benzyl anion then undergoes intramolecular 4-exo cyclization by ring cleavage of the epoxide, generating the oxetane (Equation (32)) <90SC1777>. The reaction of epoxides with sulfur ylides <83JOC5133> or sulfonimidamides <88JOC4190> resulted in the formation of oxetanes in good yields (Equation (33)). A novel synthesis of 2-oxetanones from alkenyl oxiranes has been accomplished by means of a

palladium-catalyzed carbonylation reaction $\langle 93\text{TL}2135 \rangle$. However, the reaction provided oxetanones in poor yields and suffered from a number of limitations.



1.22.10.2 Ring Contraction of Butanolides

The ring contraction of an arabino-lactone triflate derivative to provide an intermediate in the synthesis of noroxetanocin has been examined in some detail (Equation (34)) $\langle 88\text{TL}4743, 90\text{TL}4787, 92\text{JCS(P1)}3003 \rangle$. The yield of oxetane is attenuated by the competing formation of a tetrahydrofuran derivative by loss of one of the benzyl ether protecting groups. In contrast to the arabino-lactone, the ribono-lactone triflate provided the oxetane in better yield without the formation of the tetrahydrofuran product.



1.22.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

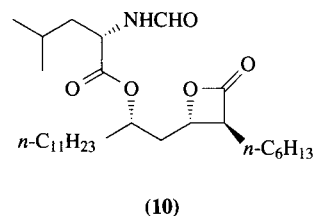
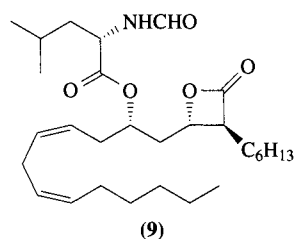
1.22.11.1 Natural Products Containing a 2-Oxetanone Ring

A number of biologically active natural products containing an oxetane or oxetanone ring have been isolated from a variety of sources. Many of the synthetic methods described in the earlier sections of this chapter were developed in response to the need for the efficient regio- and stereo-selective synthesis of functionalized oxetanes and oxetanones related to or intermediates in the synthesis of these natural products. In this section, the syntheses of several of these compounds published in 1983–1993 are highlighted, and alternative approaches are discussed.

1.22.11.1.1 Lipstatin and tetrahydrolipstatin

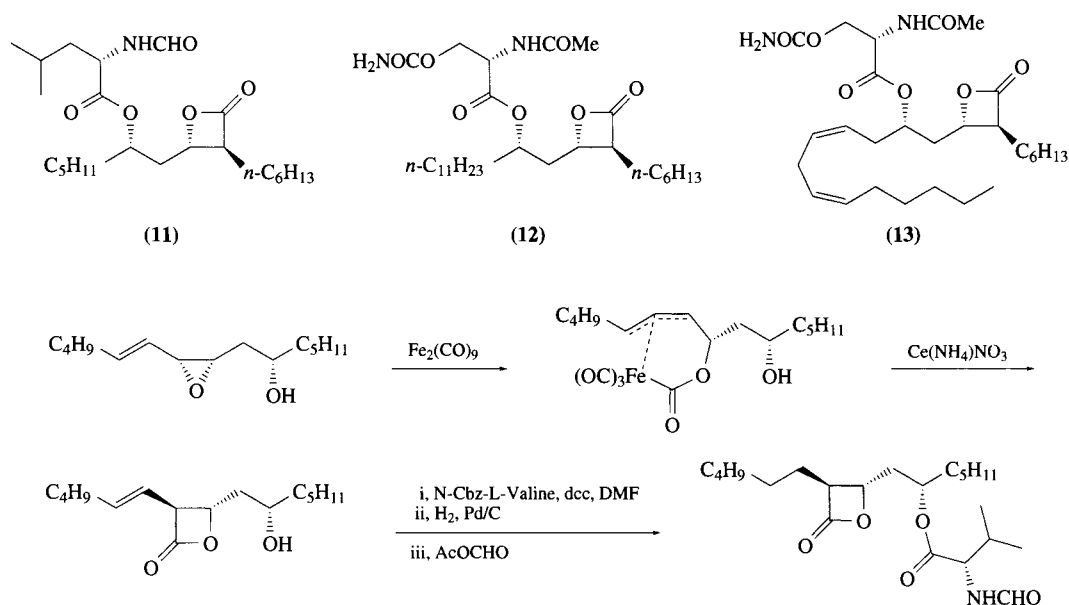
Lipstatin (**9**) and tetrahydrolipstatin (**10**) are potent inhibitors of pancreatic lipase and are of considerable interest due to the potential development of these compounds as antiobesity and cholesterol lowering agents. There have been several syntheses of tetrahydrolipstatin and one report of the synthesis of lipstatin. Nearly all of the approaches to tetrahydrolipstatin form the 2-oxetanone ring from the benzene sulfonyl chloride derived mixed anhydride (see Section 1.22.9.2) $\langle 87\text{HCA}196, 87\text{HCA}1412, 90\text{TL}3645, 91\text{JOC}4714, 93\text{JOC}7768 \rangle$. One example of oxetanone ring closure from a β -hydroxy acyliron intermediate obtained by an aldol reaction has also been reported $\langle 91\text{SL}781 \rangle$. Therefore the key stereochemical questions in these syntheses are controlled by reactions other than oxetanone formation. A single approach to tetrahydrolipstatin by a $[2 + 2]$ cycloaddition of hexyltrimethylsilyl ketene and (*R*)-3-(benzyloxy)tetradecanal achieved partial control of the oxetanone stereochemistry

during the formation of the ring <89TL1833>. The diastereomers were separable by chromatography, allowing for the asymmetric synthesis of the natural product. The asymmetric synthesis of (–)-lipstatin was also completed using a key trimethylsilyl ketene [2 + 2] cycloaddition step <93JCS(P1)1549>.

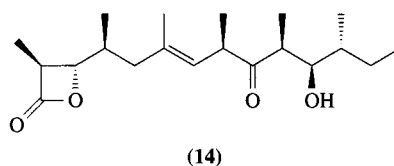


1.22.11.1.2 Valilactone and other β -lactone natural products

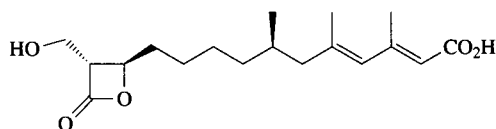
Valilactone (**11**) is an effective esterase inhibitor structurally related to tetrahydrolipstatin and lipstatin, but possesses activity similar to esterastin (**12**) and tetrahydroesterastin (**13**). Valilactone has been synthesized by the reaction of a vinyl epoxide with diiron nonacarbonyl (Scheme 30) <91T9929, 91TL2651>. This approach to the 2-oxetanone ring involves a carbonylation step which provides an acyliron π -complex intermediate. Oxidation of the intermediate with ceric ammonium nitrate directly provides the *trans*-3,4-disubstituted 2-oxetanone in modest yield. Given the low yields obtained by this method, the formation of the 2-oxetanone through a 3-hydroxy acid derivative, as discussed above for tetrahydrolipstatin, may be a more general approach to this class of natural products. The synthesis of ebelactone A (**14**), also an esterase inhibitor, was achieved by the more common method of constructing an acyclic 3-hydroxy acid derivative followed by ring closure of the 2-oxetanone by means of the phenylsulfonyl mixed anhydride lactonization reaction <90TL7513>.



Scheme 30

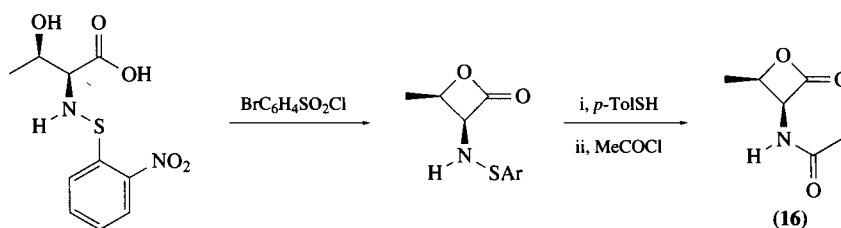


A potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase, a key regulatory enzyme in cholesterol biosynthesis, has been isolated independently from the fermentation broths of *Fusarium* sp. and *Cephalosporin* sp. This natural product is known as L-659, 699, 1233A, and F-(244) (**15**). The synthesis of this compound has also been accomplished by formation of the β -lactone by a lactonization step at a late stage in the synthesis <89JOC5708, 93JOC1610>.



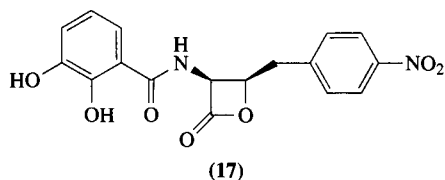
(15)

The need to form the 2-oxetanone ring at a late stage in the syntheses of these natural products is due to the reactivity of the 2-oxetanone, as described in earlier sections of this chapter. The choice of protecting groups is also potentially problematic in the synthesis of compounds containing β -lactones for the same reason. In the syntheses described above, very few synthetic manipulations were carried out once the β -lactone ring was formed. Hydrogenation, ozonolysis, and mild acid-protecting group removal reactions are compatible with the oxetanone. In the synthesis of L-659, 699 <89JOC5708>, a Reformatsky reaction/dehydration sequence was used to obtain the dienyl acid portion of the molecule. The sensitivity of the 2-oxetanone ring is amply illustrated in the synthesis of the antibiotic *N*-acetyl-L-threonine β -lactone (**16**) (Scheme 31) <89JOC2311, 91JOC1280>.

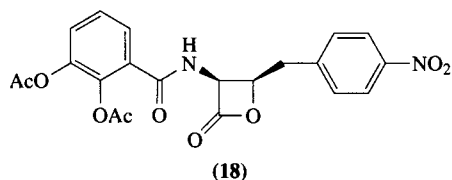


Scheme 31

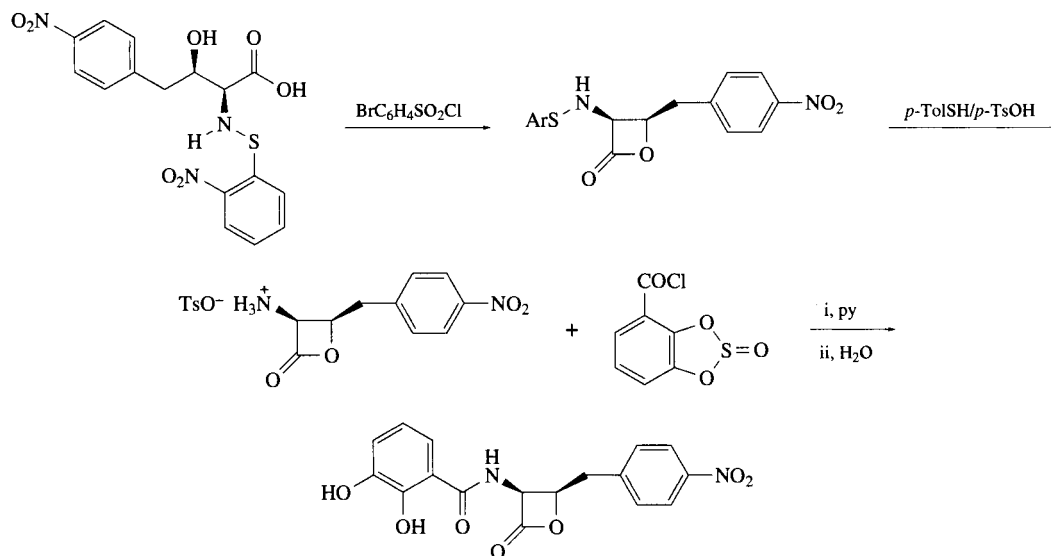
Attempts to cyclize *N*-BOC-L-threonine under Mitsunobu conditions resulted only in decarboxylation rather than lactone formation. Cyclization attempted on any carbonyl-containing *N*-protected threonine derivative led to complex mixtures with little if any of the desired oxetanone product. Although use of a sulfonamide protecting group allowed for cyclization, the harsh acid conditions necessary for the removal of the sulfonamide were incompatible with the oxetanone. During the course of these studies, the cleavage of the 2-oxetanone ring under mildly nucleophilic conditions, such as sodium acetate in acetic acid, was observed. The application of an (*o*-nitrophenyl) sulfonyl protecting group for the nitrogen ultimately provided a protecting group which gave good yields of the β -lactone in the cyclization step (using *p*-bromophenylsulfonyl chloride to form the mixed anhydride) and which could be removed under reaction conditions which did not affect the lactone. The sulfonyl protecting group was removed by the reaction of the protected oxetanone derivative with *p*-thiocresol under acid catalysis. The synthesis of the antibiotic obafluorin (**17**) has also been accomplished using the strategy developed for *N*-acetyl-L-threonine β -lactone <92JOC10>. An earlier synthesis of the diacetyl derivative (**18**) <91CC1007> did not indicate that the acetoxy groups could be removed without cleavage of the oxetanone ring. This problem has been addressed by the use of a cyclic sulfite moiety as the protecting group for the catechol hydroxyl groups (Scheme 32).



(17)



(18)



Scheme 32

1.22.12 IMPORTANT COMPOUNDS AND APPLICATIONS

This chapter has described a number of oxetanes and oxetanones that possess biological activity and are therefore of considerable interest to the pharmaceutical industry. In addition, the polymerization of oxetanes and oxetanones has also been described. There have been a large number of commercial applications of these polymers. The exceptionally large number of patents issued in this area is an indication of the importance of these two classes of polymers. This chapter has focused on literature reports and has not covered the considerable patent literature. Other reviews of oxetane polymers have been listed in Section 1.22.1.

1.22.12.1 Polymers

1.22.12.1.1 Oxetane polymers

A brief survey of the types of oxetane polymers and polymerization reactions reported in the period 1983–1993 is given in this section. This account is by no means exhaustive, but rather representative. Oxetane undergoes oligomerization in the presence of 1,3-propanediol to provide α -hydro- ω -hydroxyoligo(oxytrimethylenes) <89MAC1217>. Polymerization of bis(oxetanes) bearing functional groups at C-3 such as an ester or ketone at the end of a 2-oxapolymethylene spacer provided novel functionalized polymers containing a soft polar polyether network as polymer support <89BCJ1572>.

Copolymerization of oxetanes with a large number of monomers has been investigated. A water soluble copolymer of tetrahydrofuran and 3-(trimethylsilyloxy)oxetane has been synthesized <91JPS(A)1421>. Block copolymerization of oxetanes with a number of other reactive species is also a very active area of investigation. A block copolymer of 1,3-dioxan-2-one and oxetane was prepared using methyl triflate as the catalyst <93MM7106>. A triblock copolymer of tetrahydrofuran and 3,3-bis(chloromethyl)oxetane was formed by a two-end living cationic polymerization reaction <93JPS(A)3371>.

The polymerization of azidomethyl- and nitratomethyl-substituted oxetanes is of great interest due to the use of the derived polymers as energetic binders for solid rocket propellants <93MI 122-01, 93MI 122-02>. Specific homopolymers of these oxetane derivatives have the appropriate acronyms BAMO and AMMO. Triblock copolymers of 3,3-bis(azidomethyl)oxetane and 3-nitratomethyl-3-methyloxetane have been prepared <90JPS(A)2393>. The copolymerization of 3,3-bis(azidomethyl)oxetane and other azide-substituted oxetanes has also been investigated in an attempt to obtain materials for solid propellants that had less of a tendency to crystallize than the homopolymer <91MAC919>.

A number of oxetane derivatives containing mesogenic groups on spacer arms of varying length have been polymerized for potential applications as liquid crystalline materials <91MM4531>. Cyano- and fluoro-substituted biphenyl derivatives were found to be effective mesogens in the derived liquid crystal polymers. Several oxetane polymers containing azobenzene functional groups were also found to exhibit liquid crystal properties <93BCJ1778>.

1.22.12.1.2 Oxetanone polymers

Polymerization of 2-oxetanone, β -propiolactone, has been the subject of many studies. Many catalysts can be employed with metal alkoxides being one of the most common methods <88MM286>. Other metal catalysts include trialkylaluminums <88MM2657>, and nickel carboxylate/phosphine complexes <88MAC717>. The polymerization of optically active monomers has also been actively investigated <88JPS(A)117>. A comparison of the polymerization of optically active and racemic 4-substituted-2-oxetanones indicated that the enantiomeric excess of the monomers employed had a direct influence on the solubility and crystallinity of the polymers. Higher enantiomeric excess monomer feed resulted in insoluble, highly crystalline polymers with a high degree of isotacticity <87JPS(A)1315>.

Polymerization reactions of β -butyrolactones are even more common than those of β -propiolactone due to the fact that the polyester derivatives from β -butyrolactone are often biodegradable. (*R*)-Poly(3-hydroxybutyrate) is a naturally occurring microbial product. An investigation of the depolymerization of homopolymers from (*R*)- β -butyrolactone and (*S*)- β -butyrolactone by *Penicillium funiculosum* revealed that only the (*R*)-polymer was degraded <92MM5927>. The polymerization of racemic β -butyrolactone leads to the production of stereoregular poly(3-hydroxybutyrate). The degree of stereoregularity and the isomorphism of the polymer were dependent on the catalyst system. Triethylaluminum/water as the catalyst produced partially stereoregular isotactic polymers <89MM1656>. In contrast, tributyltin methoxide-catalyzed ring-opening polymerization of racemic β -butyrolactone resulted in a predominantly syndiotactic polymer <93MM1221>. The degree of syndiotacticity was a function of the polymerization conditions, of the catalyst to monomer ratio, and of the reaction temperature. Polymerization of optically active β -butyrolactone by distannoxane catalysts provided a high molecular weight polymer in which ring-opening polymerization had occurred with retention of configuration <93MM5533>. Copolymerization reactions of racemic and optically active β -butyrolactone have also been investigated <89MM1663, 93MM4388>.

1.22.12.2 Toxicity of 2-Oxetanones

2-Oxetanone has been found to be a relatively potent inhalation carcinogen. The carcinogenic potency of 2-oxetanone in rat nasal mucosa was found to be proportional to the rate of hydrolysis <87MI 122-02>. Inhibition of mutagenesis and neoplasia induced by 2-oxetanone in the stomach of mice can be accomplished by reaction of the oxetanone with sodium thiosulfate <87MI 122-03> or 4-thiolbenzenesulfonate <88MI 122-03>. Apparently the reaction of the lactone with a number of nucleophiles removes the carcinogenic effects in a number of tissues. A method for the degradation of 2-oxetanone, and other carcinogenic electrophilic species, using strong base has been reported <90JCE249>.

1.22.12.3 Viral Inactivation by 2-Oxetanone

β -Propiolactone, although toxic itself, has been shown to be a very effective agent for the inactivation of viruses in blood and immunoglobulin. A review of the application of β -propiolactone for inactivation of viruses in blood has been published <83MI 122-02>. More recent work has demonstrated that a large number of viruses can be inactivated by low concentrations of the lactone: human T cell lymphotropic virus (HTLV) (the retrovirus associated with AIDS) <86MI 122-02>; hepatitis non-A and non-B <88MI 122-04>; A/Leningrad/385 and B/Leningrad/489/80 influenza virus <91MI 122-03>; A/WSN/33 influenza virus <93MI 122-03>; human immunodeficiency virus 1 (HIV-1), simian virus 40, equine arteritis virus, and bovine diarrhea virus <93MI 122-04>.

1.22.12.4 Pharmaceutical and Agrochemical Applications

A substantial number of patents have appeared describing the application of oxetane and oxetanone derivatives as pharmaceuticals. Oxetanones are under investigation as pancreatic lipase inhibitors (see Section 1.22.11.1), as antifungal, anti-inflammatory, antiallergic, anticancer, and antiviral agents. Many derivatives of the antiviral natural product oxetanocin have been patented. A large number of patents describing the agrochemical uses of oxetanes has also appeared. Oxetane derivatives are herbicidal, fungicidal, and bactericidal.

1.23

Oxetanes and Oxetenes: Fused-ring Derivatives

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1.23.1 INTRODUCTION

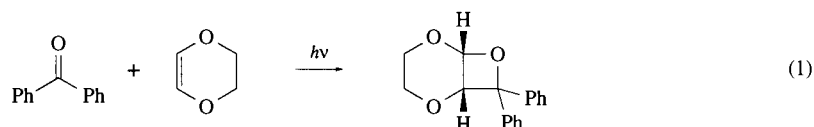
This chapter serves to complement and extend the material covered in Chapter 1.22 on monocyclic oxetanes to fused ring derivatives. Many of the general aspects of oxetane and oxetanone chemistry are not covered in this chapter and the reader is referred to the previous chapter for more details on basic structural investigations, computational studies, experimental structural determinations, and thermodynamic aspects. Some mechanistic studies have been included under the heading of theoretical methods in this chapter, Section 1.23.2; however, theoretical calculations are not covered in this chapter.

A number of reviews of oxetanes and oxetanones are cited in Chapter 1.22. A review on the Paterno–Buchi reaction of aldehydes and furans, and the application of this reaction toward the synthesis of natural products has appeared <85SCI857>. A review on the chemistry of taxol has also appeared <94AG(E)15>. The literature review for this chapter predominantly covers the period 1983–1993 and seeks to extend the information presented in Chapter 5.13 of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I).

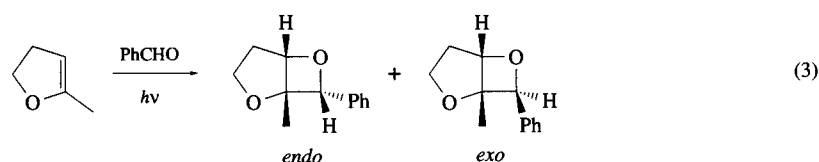
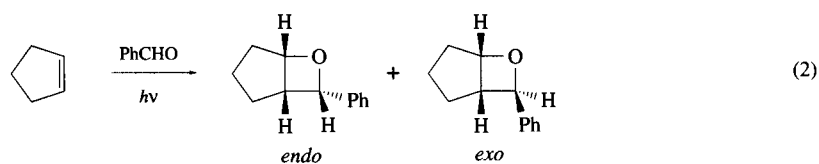
1.23.2 THEORETICAL METHODS

Theoretical studies of the structure and synthesis of oxetane, as well as the stability of this reactive species, are fully discussed in Section 1.22.2. The Paterno–Buchi reaction leading to monocyclic oxetanes is described in detail in Section 1.22.9.3. In this section, mechanistic studies of the Paterno–Buchi reaction leading to fused oxetanes are discussed.

Investigation of the [2 + 2] cycloaddition reaction of benzophenone and dioxene was carried out using picosecond absorption spectroscopy (Equation (1)) <85JA3819>. This study concluded that the mechanism for the reaction is excitation of the ketone to the first excited singlet state followed by rapid intersystem crossing to the lowest triplet state. Attack of the excited state ketone on the alkene then occurs through the electrophilic oxygen atom, resulting in a 1,4-triplet biradical. The intermediate 1,4-biradical lifetime was determined to be in the range of 1–7 ns. Closure of the 1,4-biradical to the oxetane or β -scission to the ground state ketone and alkene must be preceded by intersystem crossing of the triplet state to the singlet state of the 1,4-biradical. The triplet 1,4-biradical can alternatively undergo heterolytic cleavage to form a contact ion pair prior to intersystem crossing. The ion pair may solvent separate, intersystem cross to a singlet pair, or collapse to a singlet biradical. Additional studies of the photocycloaddition reactions of biacetyl, benzil, and benzophenone with cyclic enol ethers concluded that the formation of the radical ion pair is an important pathway if the free enthalpy for electron transfer in the triplet state is smaller than zero <87JA1203>. Aspects of the control of the Paterno–Buchi reaction by means of photoinduced electron transfer have also been reviewed <93CRV99>.

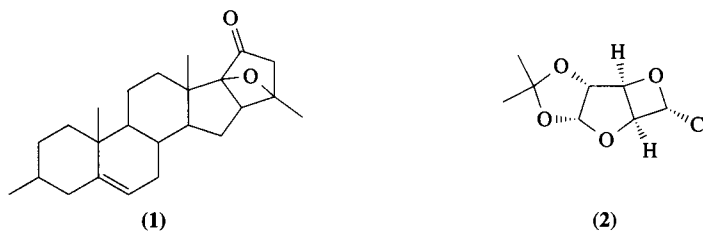


A series of publications has examined the stereoselectivity of the Paterno–Buchi reaction of aromatic aldehydes with cyclic alkenes or cyclic enol ethers <94ACR70>. Triplet biradicals have a much longer lifetime than singlet biradicals and, therefore, photocycloadditions through triplet states can result in nonstereocontrolled reactions. In contrast, singlet biradicals have a very short lifetime and photocyclization proceeding through singlet biradicals generally results in highly stereocontrolled reactions. Spin-orbit coupling is the dominant process for triplet to singlet interactions in biradicals that are relatively close together. Given the long lifetime of triplet biradicals (compared to the singlet species) and the fact that spin-orbit coupling is dependent on the geometry of the triplet biradical, the stereoselectivity of the reaction should be predictable based on a preferred conformation for intersystem crossing to the short lived singlet biradical. The preference for the *endo* oxetane stereoisomer in the reaction of benzaldehyde with a number of cyclic alkenes and cyclic enol ethers was then explained by the establishment of an equilibrium of two triplet biradical conformations in which the least sterically crowded conformer led to the *endo* product (Equation (2)) <90JA1281>. Data in support of this hypothesis was obtained in a subsequent study in which the increasing steric demands of the aldehyde aromatic substituent enhanced the selectivity for the *endo* product <90CB357>. Substituents on the alkene double bond served to decrease the *endo* selectivity of the photocycloaddition <91JA6923>. This stereochemical result is also explained by steric arguments which favor the conformer responsible for intersystem crossing to the singlet state and collapse to the *exo* oxetane. For nonsymmetric cyclic alkenes, mixtures of regioisomers were obtained, while cyclic enol ethers resulted in a single regioisomer (Equation (3)). Aliphatic aldehydes were found to be less stereoselective in the Paterno–Buchi reaction. This observation is explained by the fact that aliphatic carbonyls can react by either the triplet or singlet excited state. Naphthaldehydes also react by a singlet excited state and lead to *exo* oxetanes <91CB407>.



1.23.3 EXPERIMENTAL STRUCTURAL METHODS

Detailed investigations of the structure of oxetanes has been the subject of intensive research that is described in Section 1.22.3. Several x-ray crystal structures of substituted oxetanes have been reported that reveal both puckered and planar rings. Two fused oxetane ring x-ray crystal structures (1) and (2) indicate that the oxetane ring in each structure is planar <86AX(C)1833, 88TL1449>.



Spectral data on fused oxetanes is generally reported within specific manuscripts dealing with other aspects of the chemistry. Compilations of spectral data for this class of compounds are not readily available with the exception of NMR studies of taxane derivatives <83OMR(21)257>. New taxanes containing oxetane rings have also been reported <93JCS(P1)1563>. The structure of oxazolomycin, a novel spiro fused β -lactone containing antibiotic, has been ascertained by spectral studies <85TL1073>.

1.23.4 THERMODYNAMIC ASPECTS

Thermolysis of simple oxetanes and oxetanones are described in Section 1.22.4 and Section 1.22.6.2. Several examples of the thermal decomposition of ring fused oxetanes are also found in Section 1.23.6.

The basicity of oxirane, oxetane, and oxabicycloheptane derivatives have been compared <93JOC2328>. In these examples, the oxetane ring oxygen was found to be the most basic toward protic acids.

1.23.5 REACTIVITY AT FULLY CONJUGATED RINGS

There is no reported data on this subject as of 1995.

1.23.6 REACTIVITY OF NONCONJUGATED RINGS

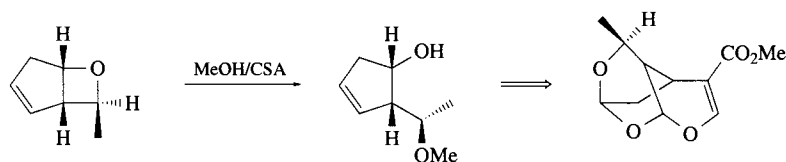
1.23.6.1 General Survey

Oxetanes and oxetanones are susceptible to a range of reactions from thermal decomposition, to electrophilic, or nucleophilic attack. These modes of reaction for nonring fused oxetanes are covered

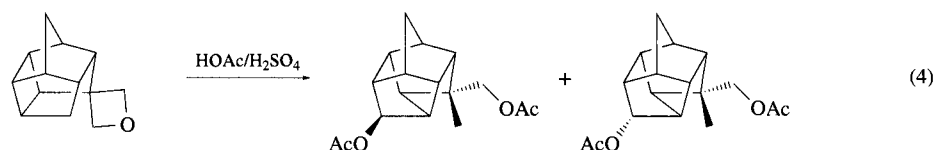
in Section 1.22.6. Ring fused oxetanes and oxetanones are not exceptions and readily undergo the same reactions. Reactions which cleave the four membered ring are detailed in Section 1.23.6, while reactions at substituents which allow the ring to remain intact are covered in Section 1.23.7.

1.23.6.2 Acid-Catalyzed Transformations

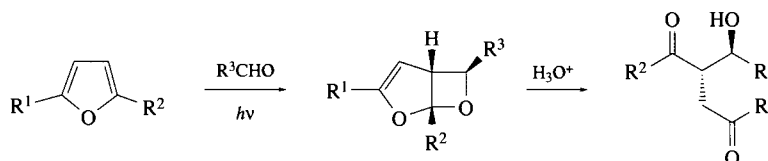
Oxetanes are susceptible to cleavage under acid catalysis. The photocycloaddition reaction of acetaldehyde and cyclopentadiene results in a separable mixture of *endo* and *exo* oxetanes in low yield. The *exo* adduct was then stereospecifically cleaved by reaction with camphorsulfonic acid in methanol to provide a functionalized cyclopentene intermediate for the synthesis of sarracenin (Scheme 1) <89JOC688>. Acid catalyzed ring cleavage of a novel cage spirooxetane resulted in a skeletal rearrangement (Equation (4)) <92TL3983>.



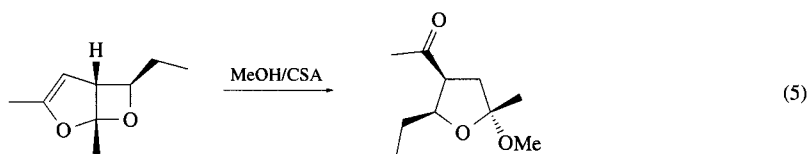
Scheme 1



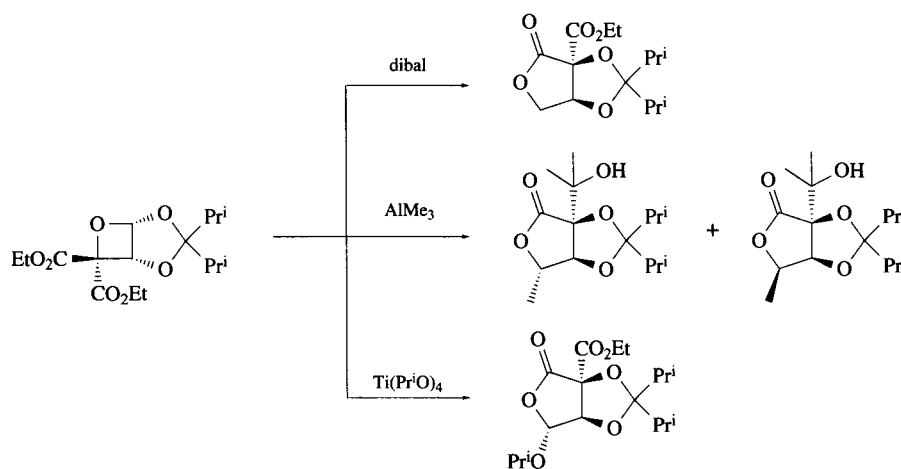
Perhaps one of the most useful reactions of oxetanes formed by the [2 + 2] cycloaddition of aldehydes and furans is the conversion of the photoadduct to the threo aldol product (Scheme 2) <83JA660, 85SCI857>. This extension of the Paterno–Büchi reaction has been applied to a number of syntheses which are described in Section 1.23.12.1. Tetrahydrofuran products can also be obtained by carrying out an acid-catalyzed transacetalization reaction (Equation (5)). It is important to note that the photocycloaddition of aldehydes to furan occurs regioselectively and stereospecifically to provide the *exo* adduct, in contrast to the results of aldehyde [2 + 2] cycloaddition reactions with cyclic enol ethers and cyclic alkenes (Section 1.23.2).



Scheme 2



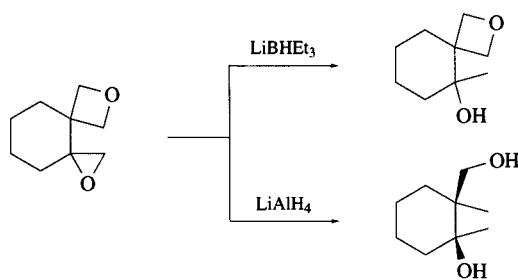
Derivatives of branched (C-2) erythrono-1,4-lactones have been prepared from an oxetane derivative <88HCA981>. The rearrangement can be effected by a number of reaction conditions that lead to different lactone products (Scheme 3). The yields of the reactions were generally low (<25%) with the exception of the trimethylaluminum-catalyzed reaction.



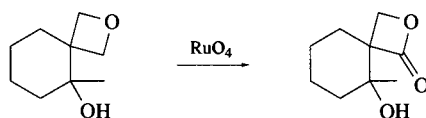
Scheme 3

1.23.6.3 Reactions with Nucleophiles

Oxetanes are very susceptible to reaction with nucleophiles due to the inherent ring strain present in the molecule. In model studies for the synthesis of anisatin, reduction of spiro fused oxetanes and epoxides were directly compared (85CL1785, 86BCJ1647). Lithium triethylborohydride selectively reduced the epoxide, while lithium aluminum hydride reduced both the oxetane and oxirane functional groups (Scheme 4). This study also revealed that the oxetane could be oxidized to an oxetanone using ruthenium tetroxide (Equation (6)). The reduction of a spiro fused oxetane has also been used to accomplish the synthesis of 1,5,9-trioxacyclododecanes bearing methoxymethyl substituents at the 3, 7, and 11 positions (92ACS574).

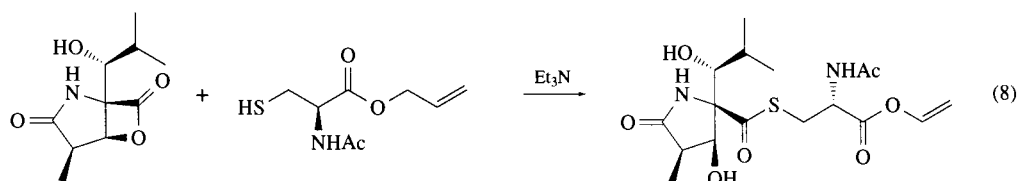
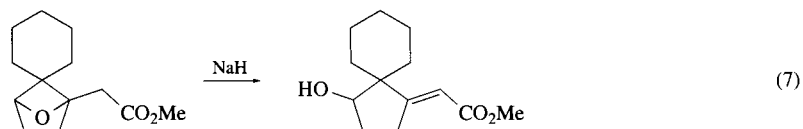


Scheme 4



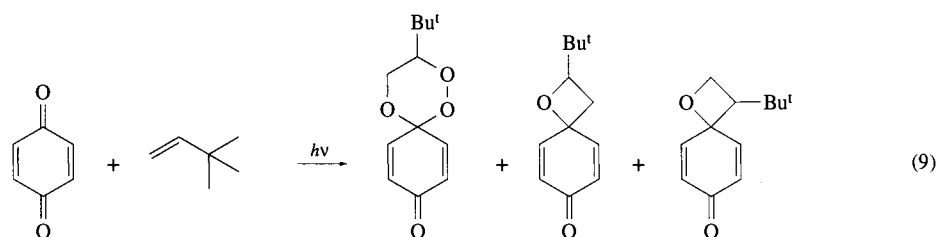
(6)

An analogue of 3'-azido-3'-deoxythymidine (AZT) has been prepared using a nucleophilic ring opening reaction of a nucleosidic oxetane as the key step (89TL2567). The nucleophiles examined included alkyl lithium reagents, lithium hydride, lithium alkoxides, and lithium alkynes. The nucleophilic addition reaction was facilitated by boron trifluoride. Treating bicyclic oxetane derivatives with a nonnucleophilic base has led to a novel method for the synthesis of cyclopentenols and spiro[4.5]decanol derivatives (Equation (7)) (83CL1421). The facile reaction of oxetanones with nucleophiles has also been employed in a synthesis of lactacystin (93TL6977). In this example, formation of a thiol ester proceeded through an intermediate β -lactone (Equation (8)).

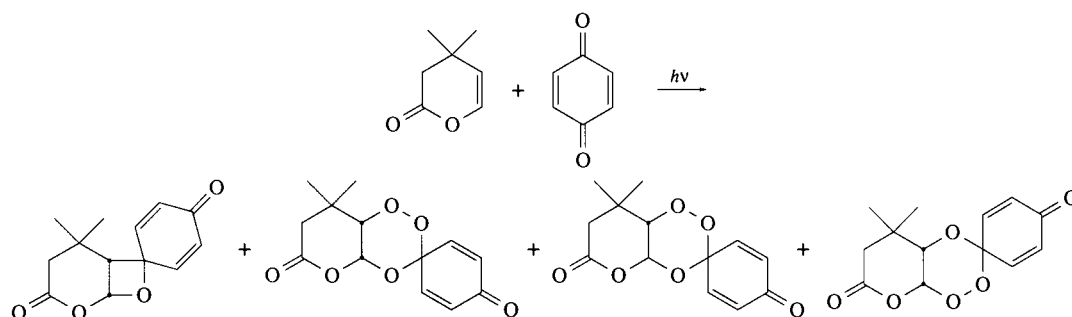


1.23.6.4 Cycloaddition and Cycloreversion Reactions

The Paterno–Buchi intermediate 1,4-biradical species can be trapped by reaction with several electrophilic species. One of the most studied examples of this reaction is the trapping of the biradical by molecular oxygen or sulfur dioxide [82JA4429, 85MI 123-01]. The reaction of benzoquinone and 3,3-dimethylbutene in the presence of oxygen produces a regioisomeric mixture of oxetane products and the 1,2,4-trioxane derivative (Equation (9)).



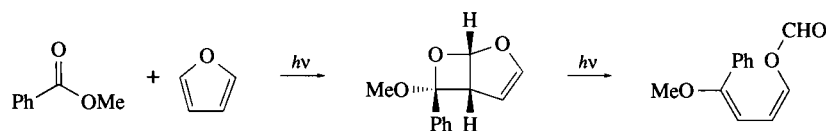
The yields of these reactions are generally quite low due to the fact that the initial adducts are photolabile and undergo secondary reactions leading to a mixture of products. A significant improvement in the yields of the reaction can be obtained if a visible laser (455–515 nm) is used for the reaction [88JOC4986]. The preparative visible laser photocycloaddition studies also determined that the cycloaddition reaction with oxygen is dependent upon the lifetime of the 1,4-biradical intermediate. The reaction of benzoquinone and 3,4-dihydro-4,4-dimethyl-2H-pyran-2-one gave an isomeric mixture of 1,2,4-trioxanes and oxetanes (Scheme 5). In contrast, the same reaction with phenanthraquinone in the presence of oxygen led only to the oxetane regioisomers with no trace of the trioxane products. This data implies that the phenanthraquinone reaction produces a 1,4-biradical preoxetane intermediate that must have a lifetime less than 1 ns.



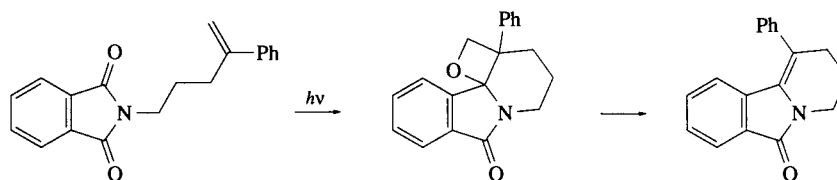
Scheme 5

Cycloreversion of oxetanes formed by the [2 + 2] cycloaddition of esters and furan have been employed to produce dienol esters [89JOC140]. The cycloreversion occurs in the opposite regiochemical orientation to that of the initial cycloaddition reaction (Scheme 6). The reaction products

are dependent on the ester functional group. For example, methyl benzoate and furan produced an unstable oxetane product which underwent cycloreversion upon further photolysis. Methyl naphthoate provided only the dienyl formate product without any trace of the oxetane, while photolysis of methyl furanoate and furan resulted in only the fused oxetane, albeit in low yield. A similar process is observed in the reaction of *N*-methylphthalimide and 2,3-dimethylbutene <83TL143>. The initial Paterno–Buchi product undergoes cycloreversion with loss of acetone to produce a propylidene product. An intramolecular variant of this reaction works very well to provide a single photoadduct after cycloaddition/cycloreversion (Scheme 7).

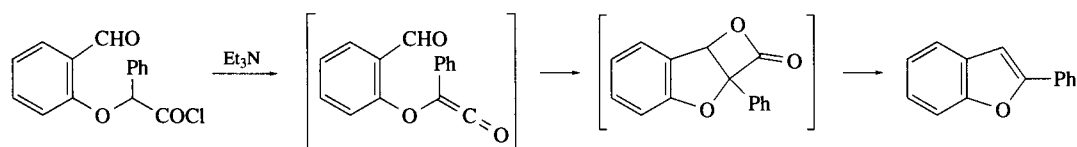


Scheme 6

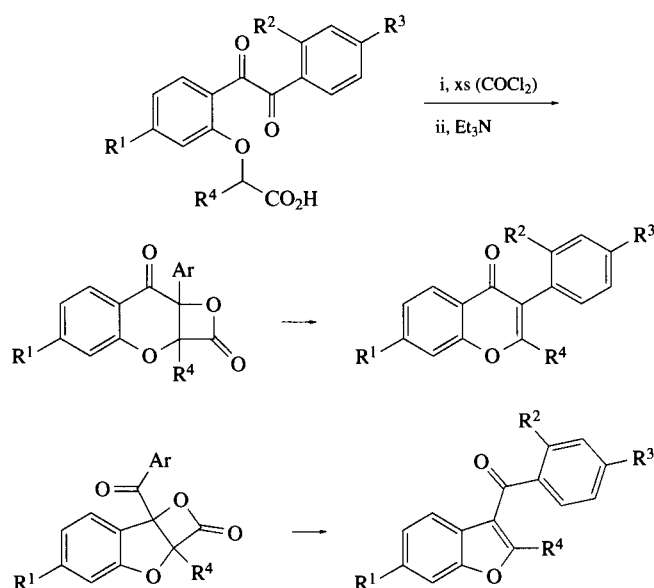


Scheme 7

Intramolecular ketene cycloaddition followed by cycloreversion of the oxetanone with the loss of carbon dioxide has been a strategy that provides benzofurans (Scheme 8) <86JOC2145, 87JOC3457>. An analogous reaction also leads to mixtures of isoflavones and 3-arylbzofurans due to a nonregioselective initial ketene cycloaddition (Scheme 9) <88JOC1353>.



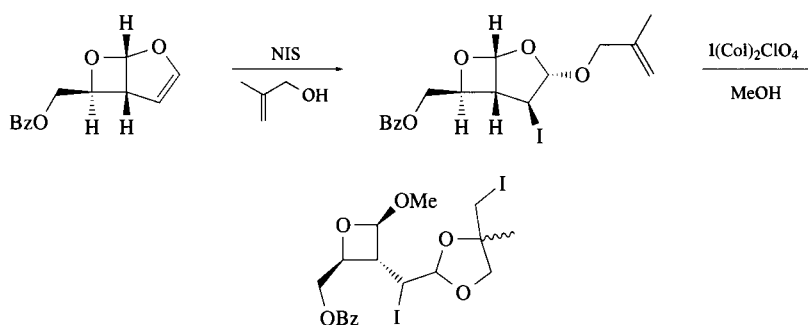
Scheme 8



Scheme 9

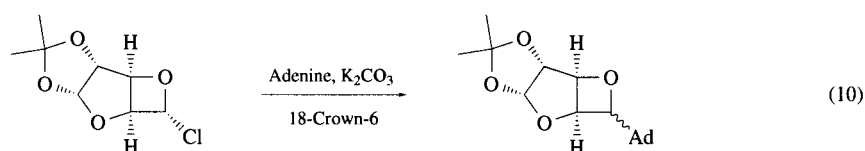
1.23.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The photoadducts obtained from reactions of furan and aldehydes produce ring annulated oxetanes that contain an acetal carbon. The acetal carbon can undergo ring opening reactions that maintain the oxetane ring structure while cleaving the derived tetrahydrofuran portion of the molecule. Trisubstituted oxetanes related to oxetanocin, an antiviral compound discussed in Chapter 1.22, were prepared by an intramolecularly assisted reaction of the acetal carbon with an electrophilic source of iodine (Scheme 10) <90TL4693>. The yields of the ring opened material were only moderate; however, the stereoselectivity of the reaction was excellent, providing for the *cis*-orientation of the C-1 and C-3 substituents.

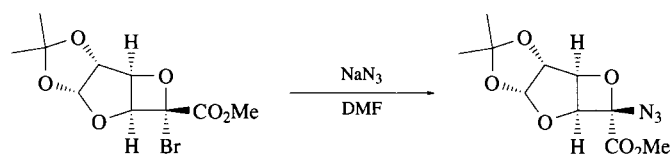


Scheme 10

The synthesis of oxetane nucleosides related to oxetanocin has also been accomplished by the nucleophilic displacement of a stable α -chlorooxetane with adenine (Equation (10)) <88TL1451>. In contrast to the stereocontrolled electrophilic reaction, the nucleophilic displacement reaction of the α -chlorooxetane was stereorandom, producing a 1 : 1 mixture of stereoisomers. Related studies have generated an α -bromooxetane derivative which can undergo nucleophilic displacement reactions with sodium azide (Equation (11)) <91TL3569>. Interestingly, in this example, the displacement reaction was reported to occur stereospecifically.

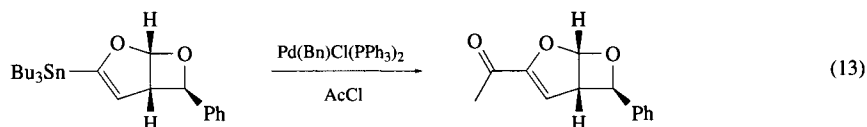
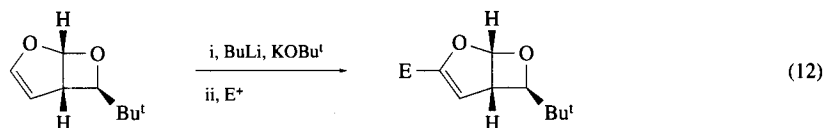


(10)

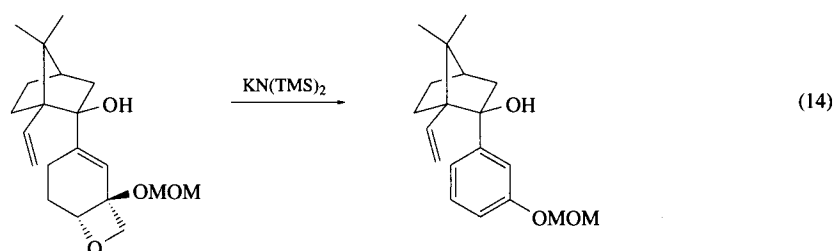
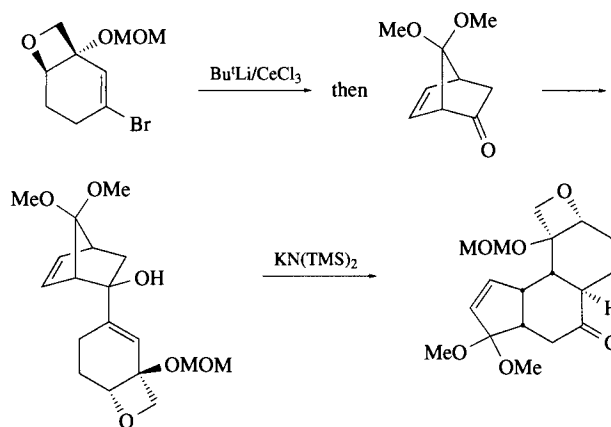


(11)

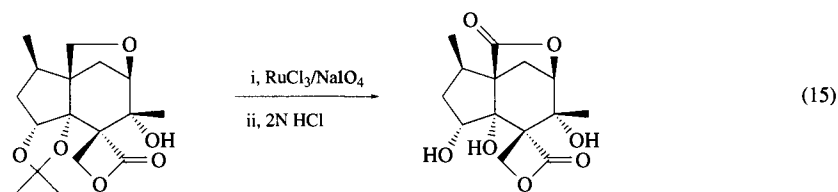
Transformations remote from the oxetane ring have also been reported for fused oxetanes. Given the high reactivity of this class of compounds, the number of synthetic transformations possible might be expected to be low. Nevertheless, a variety of reactions can be accomplished without cleavage of the sensitive oxetane ring. Unsymmetric furans readily undergo photocycloaddition with aldehydes; however, the regiochemistry of this reaction is generally poor (Sections 1.23.2 and 1.23.9). Photoadducts derived from aliphatic aldehydes can be alkylated on the dihydrofuran ring via a vinyl anion intermediate (Equation (12)) <89JOC4721>; however, the photoadducts obtained from aryl aldehydes cannot be deprotonated without decomposition. The substituted fused oxetane product can be obtained by transformation of a tetrabutylstannyl substituted photocycloaddition product. The derivative may be obtained in good overall yields via transmetalation to the lithio species followed by alkylation, or by a palladium-catalyzed coupling reaction (Equation (13)).



It is interesting to note that the photocycloaddition of the tributylstannyl-substituted furan and an aldehyde is regioselective for [2 + 2] cycloaddition at the nonsubstituted double bond of the furan. Fused oxetane structures containing a vinyl bromide have also undergone metal-halogen exchange and subsequent condensation reactions with ketones (Scheme 11) <93JOC4952>. These highly functionalized fused oxetanes were examined as intermediates in a potential route to the CD ring system of taxol. The model system shown in Scheme 11 smoothly rearranged by means of an anionic oxy-Cope mechanism; however, the precursor needed for formation of the taxol CD ring system did not undergo the anionic oxy-Cope rearrangement, but instead suffered loss of the oxetane ring and aromatization (Equation (14)). Attempted thermal rearrangement also resulted in fragmentation of the oxetane ring by an oxy-ene mechanism.



Oxetanones are also an extremely reactive species and are generally only introduced very late in synthetic schemes (Sections 1.22.7 and 1.22.11.1). In the synthesis of (–)-noranisatin, oxidation of a bicyclic ether to the corresponding lactone was achieved by reaction with ruthenium tetroxide (Equation (15)) <91TL1329>. Subsequent hydrolysis of an acetonide in the molecule was also accomplished without cleavage of the oxetanone.



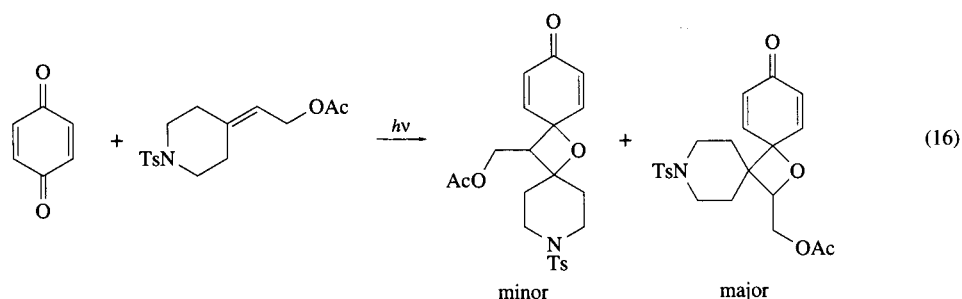
1.23.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

There is no reported data on this subject as of 1995.

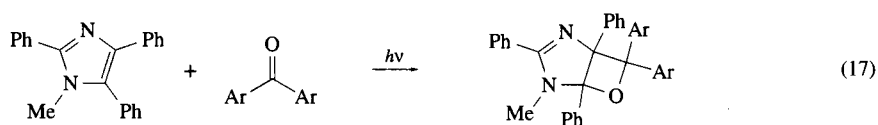
1.23.9 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS

1.23.9.1 Intermolecular [2 + 2] Cycloaddition Reactions

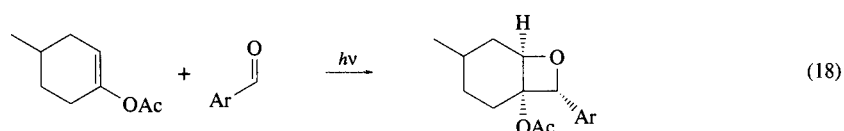
The mechanism of the Paterno–Buchi reaction of quinones was discussed in Section 1.23.2. The ring fused oxetanes obtained from quinones have also proven to be useful synthetic intermediates. Photocycloaddition of benzoquinone and an allylic acetate provided the spiro fused oxetane with very high regioselectivity (Equation (16)) <93TL3505>. The spiro fused oxetane was then subjected to rearrangement and catalyzed by boron trifluoride, to provide a dihydrobenzofuran derivative, a useful building block in the synthesis of opioids.

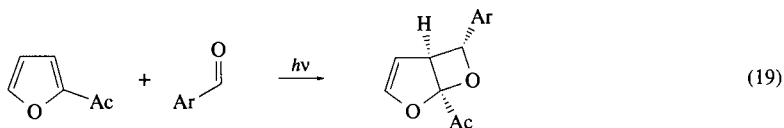


The photocycloaddition reaction of benzophenone with simple imidazoles is not a useful reaction. In contrast, 1-methyl-2,4,5-triphenylimidazole reacts regioselectively in good yields with a variety of benzophenone derivatives (Equation (17)) <85TL2093>. The regioselectivity of the reaction was verified by x-ray crystal structure analysis. Irradiation of the derived fused oxetane products in the solid state results in cycloreversion with very high recovery of the imidazole. The irradiation of benzophenone and allenic esters, on the other hand, was not regioselective, leading to mixtures of monocyclic oxetane and spiro fused oxetane products in low yields <91T2211>.

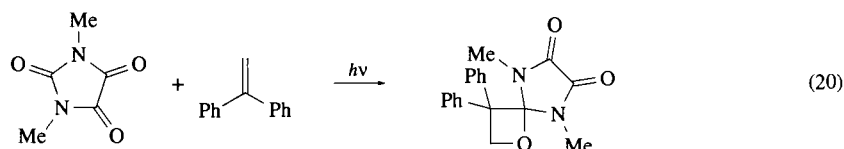


Several other miscellaneous syntheses of ring fused oxetanes by photocycloaddition reactions of aryl aldehydes have also been reported. The Paterno–Buchi reaction of aryl aldehydes and enol acetates occurs with complete regioselectivity, but in low yields (Equation (18)) <94JOC4677>. Paterno–Buchi reactions of acyl nitriles and furan provide the *endo* product predominantly, but also in modest yields <91CB967>. The photocycloaddition reaction of monoalkyl substituted furans and aryl aldehydes occurs with little or no regioselectivity; however, reaction of 2-acetylfuran with a number of aryl aldehydes provided the ring fused oxetane products with regioselectivities greater than 20 : 1 (Equation (19)) <92JCS(P1)1081>. Photocycloaddition reactions of 5-substituted adamantanes with electron-rich or electron-poor alkenes produce a nearly equal mixture of geometric isomers <91JOC5020>. Quadricyclane undergoes thermal or pressure assisted cycloaddition reactions with carbonyl compounds that are activated by an electron-withdrawing group. The yields for this reaction varied from less than 20% to 90% <83CC221>.



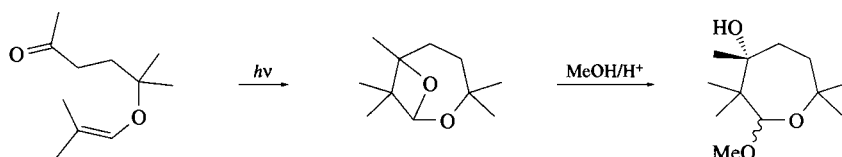


Cyclic imides undergo photocycloaddition reactions with a number of alkenes to provide spiro fused oxetanes. It has been shown that *N,N'*-dimethylimidazolidinetrione reacts with terminal, mono-, di-, and trisubstituted alkenes in very good yields upon irradiation in benzene (Equation (20)) <89JOC2359>. Tetrasubstituted alkenes also react, but the yields of the spirooxetane product are generally quite low. Irradiation of a mixture of 3,4,5,6-tetrafluoro-*N*-methylphthalimide and 1,1-diphenylethene under a nitrogen atmosphere resulted in exclusive formation of the spiro fused oxetane <93BCJ282>. The formation of an oxetane product in the reaction of the fluorinated phthalimide is in marked contrast to the formation of benzophenone in the photochemical reaction of phthalimide and the alkene. The difference in reactivity is attributed to the larger energy difference between n to π^* -S₁ and π to π^* -S₂ of the fluorinated compound compared to the nonfluorinated species. Similar studies of the photochemical reaction of arene dicarboxylic acid anhydrides described a competing oxetane formation and insertion process <86JOC4404, 89CL1639>.

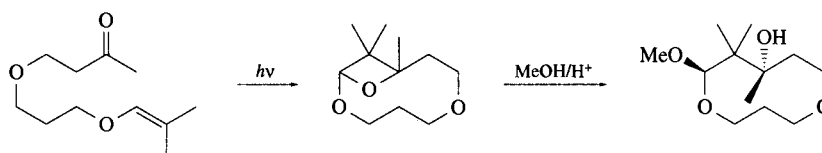


1.23.9.2 Intramolecular [2 + 2] Cycloaddition Reactions

Photocycloaddition of enol ethers has also been accomplished in intramolecular reactions to achieve the synthesis of medium-sized ring ethers. Irradiation of a keto-enol ether led to the formation of a thromboxane A₂ ring analogue in low yield (Scheme 12) <84CC667>. Acetal exchange of the bicyclic ring fused oxetane resulted in the formation of the seven-membered cyclic ether. Larger-sized cyclic ring ethers have also been prepared by the same reaction sequence (Scheme 13) <87TL5933>.

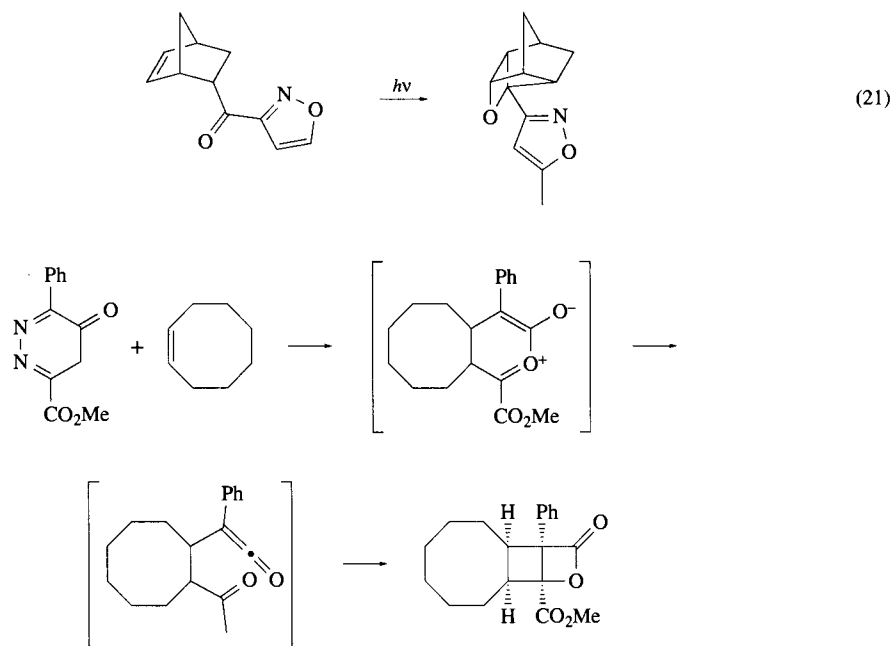


Scheme 12



Scheme 13

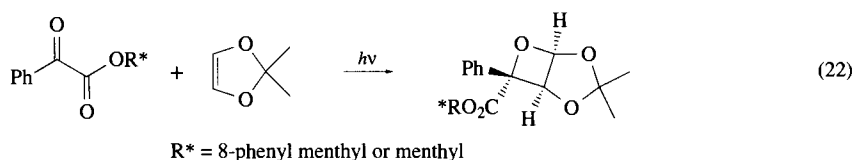
Intramolecular Paterno–Buchi reactions of aryl ketones have also been examined. The isoxazole derivative shown in Equation (21) produced an isolable oxetane product upon irradiation, while the analogous furyl or thiophenyl ketones did not provide the fused oxetane products (Equation (21)) <87JOC5501>. A sequential Diels–Alder/[2 + 2] cycloaddition reaction has been employed in the synthesis of unusual ring fused 2-oxetanones (Scheme 14) <87TL6429>. The initial cycloaddition reaction produces a zwitterionic intermediate upon loss of nitrogen. The zwitterion collapses to a keto-ketene intermediate which provides the cyclobutane/oxetanone product in fair overall yields.



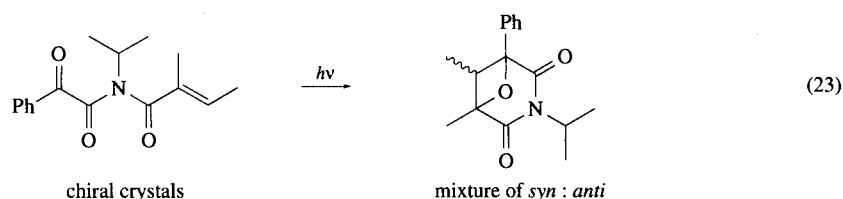
Scheme 14

1.23.9.2.1 Diastereoselective and enantioselective [2 + 2] cycloaddition reactions

Several studies have focused attention on the potential for diastereoselective Paterno–Buchi reactions using chiral ester derivatives of phenyl glyoxalates. Menthyl and 8-phenyl menthyl esters were examined in reactions with a cyclic enol ether (Equation (22)) <85AG(E)877>. The diastereoselectivity of the reaction was best (96% de) for the 8-phenyl menthyl derivative, while the menthyl derivative provided only 57% de. Subsequent reports assessed the conformation of the reactant pair prior to the [2 + 2] cycloaddition reaction <88JCS(P2)49>, the effect of the keto substituent in the α -keto ester derivative <85CB1485>, and the temperature of the reaction <89JA5367>. The conclusions of these investigations were that the diastereoselectivity of the reaction is governed by initial excitation of the ketone carbonyl to an n to π^* singlet state, followed by intersystem crossing to the n to π^* triplet state and the 1,4-biradical intermediate, as indicated by previous mechanistic studies (Section 1.23.2). The 1,4-biradical species can then exist as diastereomeric transition states with collapse to the oxetane favored for one transition state, while the other diastereomeric transition state dissociates to reactants at a faster rate than oxetane formation.

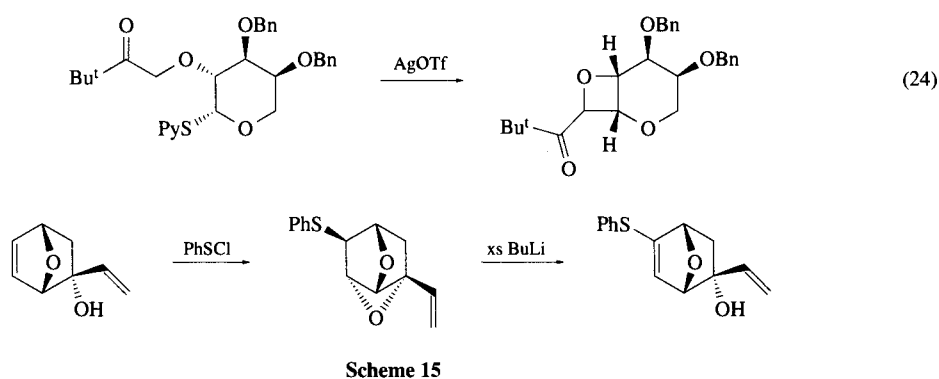


An example of an absolute asymmetric synthesis of an oxetane derivative has been reported <93JOC3476>. Irradiation of chiral crystals of *N*-isopropyl-*N*-tiglylbenzoylformamide in the solid state at 0°C provided an 84% yield (100% conversion) of the intramolecular Paterno–Buchi product as a separable mixture of *syn*- and *anti*-isomers (Equation (23)). The *syn*-isomer exhibited 35% ee while the *anti*-isomer was racemic. The same reaction carried out at –78°C resulted in *syn*-product with >95% ee. The enantioselectivity was determined by NMR methods, but the absolute configuration of the product was not determined.

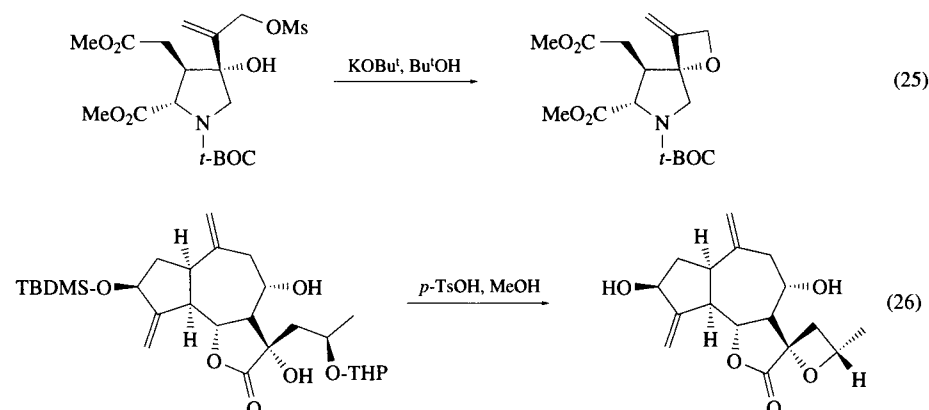


1.23.9.2.2 Intramolecular alkylation approaches to oxetanes and oxetanones

The synthesis of monocyclic oxetanes and oxetanones is commonly achieved by alkylation reactions (Sections 1.22.9.1 and 1.22.9.2). The same is true for the synthesis of fused ring oxetanes. An intramolecular aldol type reaction of a (2-pyridylthio)glycosidic silyl enol ether resulted in a bicyclic keto oxetane product with excellent stereocontrol (Equation (24)) <93CC901>. Formation of a bicyclic oxetane by intramolecular nucleophilic attack of oxygen has also found use in a synthetic method for the synthesis of 7-oxanorbornenic vinyl sulfides (Scheme 15) <92JOC772>.

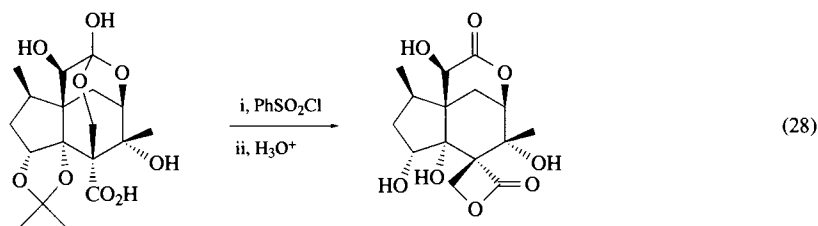
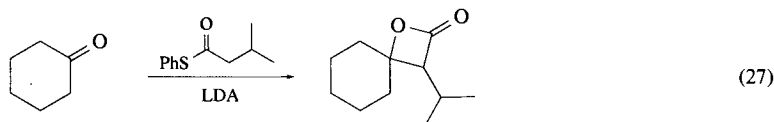


Formation of a fused oxetane by intramolecular C—O bond formation has been accomplished by either basic or acidic conditions. The base-mediated ring formation is illustrated in the synthesis of a rigid analogue of kainic acid (Equation (25)) <90TL2967>. A novel stereoselective cyclization mediated by acid was reported in the synthesis of clementein and clementein B (Equation (26)) <93T2499>. Formation of an oxetane ring under mild acid conditions, analogous to the clementein synthesis, was also reported in the synthesis of subexpinatin C <87JOC3323>.



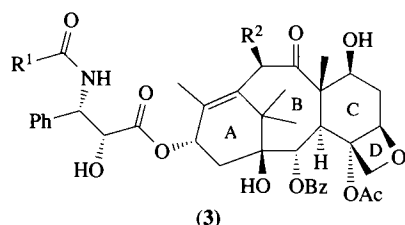
The synthesis of oxetanones by lactonization methods is a common approach for both monocyclic and fused ring oxetanones. Formation of a mixed anhydride using phenylsulfonyl chloride is frequently used as an activation method. A one-step preparation of spiro fused oxetanones not requiring activation has been achieved by condensation of a thioester enolate and a ketone (Equation (27)) <91JOC1176>. The synthesis of anisatin, a neurotoxic sesquiterpenoid containing a spiro fused β -lactone, has been accomplished by means of the mixed anhydride intermediate route (Equation

(28)) <90JA9001>. Similar approaches have also been used in the synthesis of neoanisatin <91CL639> and 8-deoxyanisatin <85JA7184>.

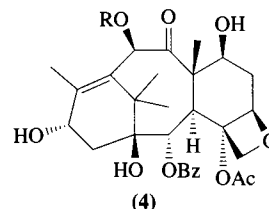


1.23.9.2.3 Oxetane syntheses related to taxol

The total efforts directed toward the preparation of the anticancer agent taxol have required the development of methodology for construction of ring fused oxetanes. The fused oxetane D ring of taxol (Structures (3) and (4)) presents several synthetic challenges in that the synthesis will potentially require selective manipulations of a triol containing a primary, secondary, and tertiary alcohol. Several approaches toward model systems are described in this section. Synthetic manipulation of taxol and taxol derivatives dealing with transformations of the oxetane ring are also described in Section 1.23.11.1. The chemistry of taxol detailed in this review is by no means comprehensive. Readers are referred to lead references in one of the reviews of taxol <94AG(E)15>.



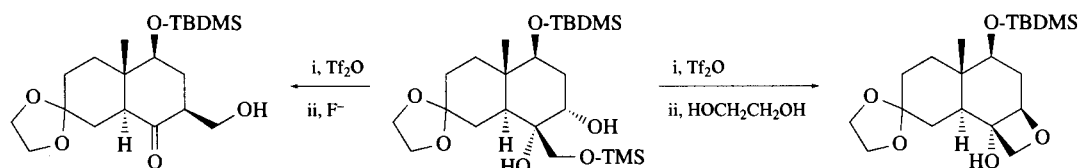
Taxol, $R^1 = \text{Ph}$, $R^2 = \text{OAc}$
Taxotere, $R^1 = \text{Bu}^t\text{O}$, $R^2 = \text{OH}$



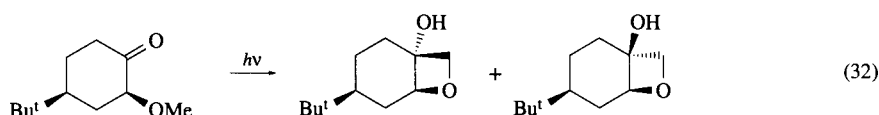
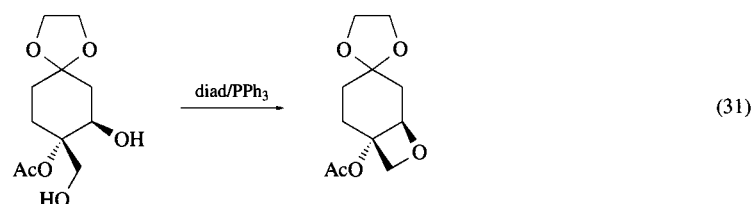
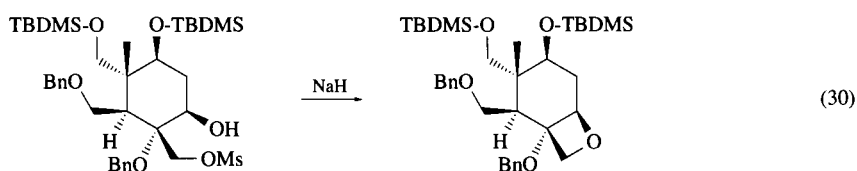
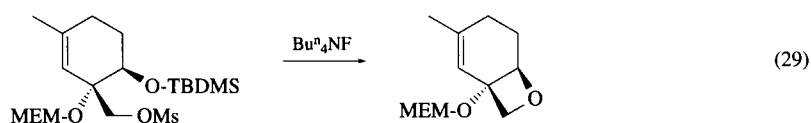
10-Deacetylbaccatin III, $R = \text{H}$
Baccatin III, $R = \text{Ac}$

Intramolecular *O*-alkylation routes for the closure of the oxetane D ring have been reported; however, several problems are associated with alkylation of the alkoxide under basic reaction conditions. Attempted intramolecular displacement of a secondary triflate by a primary alkoxide, generated from fluoride ion removal of a silyl protecting group, resulted in rearrangement rather than oxetane formation (Scheme 16) <92JOC3274>. A similar problem had been reported earlier on an intact taxol ABC ring model system <91T9823>. The fused oxetane was obtained if desilylation was achieved using ethylene glycol. A simpler model system did achieve oxetane ring formation by fluoride ion induced ring closure, but this approach was also problematic if the quaternary hydroxyl group was not protected (Equation (29)) <87JOC3745>. It should be noted that in this synthesis, the secondary alcohol acts as the nucleophile, in contrast to the former approach in which the primary alcohol displaces a secondary triflate. Intramolecular displacement of a primary tosyl group with the sodium alkoxide of a secondary alcohol works quite well <93JOC3938>. This method was successfully employed in the construction of a fully functionalized CD ring system (Equation (30)) <92CC1118>. The problems associated with removal of a protecting group can potentially be circumvented by an application of the Mitsunobu reaction which does not require protecting groups on the primary or secondary alcohols (Equation (31)) <85TL3663, 87JOC1119>. A novel photochemical method has also been reported which involves insertion of an α -methyl ether into a ketone (Equation (32)) <92T7033>.

Unfortunately, the photochemical method is not stereoselective, and the oxetane product is not obtained in good yield.

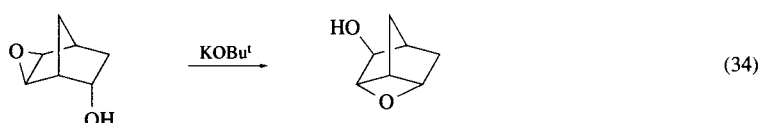


Scheme 16



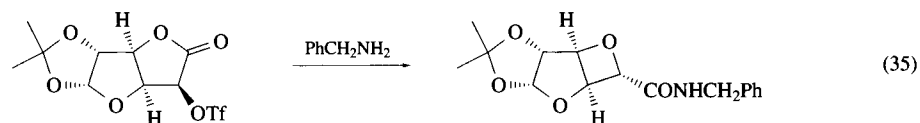
1.23.10 RING SYNTHESIS BY TRANSFORMATIONS OF ANOTHER RING

Epoxides can be transformed into oxetanes by nucleophilic attack of sulfoximine anions (Equation (33)) <83JA252>. The spiro fused oxetane can also be directly obtained from a ketone if an excess of the sodiummethyl sulfoximine reagent is used. Epoxynorbornanols can give rise to oxetanes under either basic (Equation (34)) <84TL4455> or acidic <85TL6277> reaction conditions. Only the *exo*-epoxide, *endo*-alcohol isomer provides the oxetane; other isomers of the norbornane derivatives undergo ring fragmentation reactions.



Ring contraction methods for the synthesis of ring fused oxetanes are less common. Poly-functionalized fused oxetanes can be prepared from sugars by the ring contraction of α -triflyloxy-

γ -lactones (Equation (35)) <87TL4741>. The ring contraction is induced by nucleophilic addition to the lactone carbonyl, followed by intramolecular displacement of the triflate by an alkoxide.

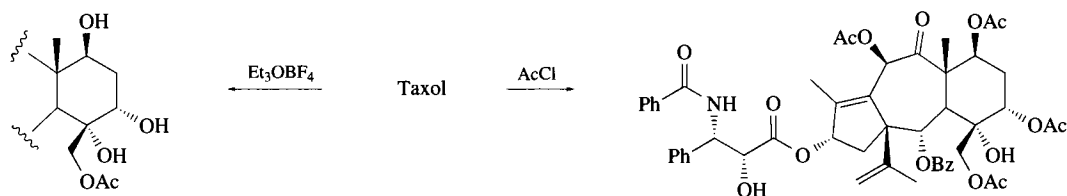


1.23.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

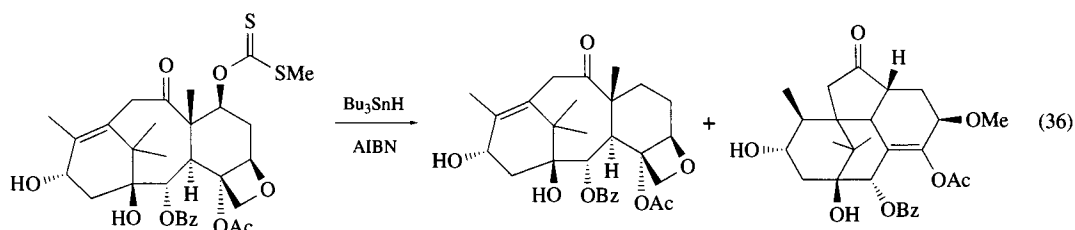
1.23.11.1 Taxol Oxetane Ring Transformations

The highly effective anticancer agent taxol has been the subject of intensive investigation by chemists and biologists. In this section, a few lead references to studies which have examined the stability and/or reactivity of the taxol oxetane D ring to various reagents are discussed. The need to evaluate the minimum structural requirements for biological activity has been one of the driving forces for these investigations. Indeed, the data indicates that the oxetane ring must remain intact for realization of the full biological activity of taxol. In addition, analogue synthesis from the natural material is required due to the limited availability of the compound and the desire to determine simpler synthetic targets for potential therapeutic use. Partial structures of taxol are given in the equations of this section. The reader is referred to structures (3) and (4) for the full structure of taxol and baccatin III.

The oxetane ring of taxol is susceptible to rearrangement and ring cleavage. Several studies of the reaction of taxol with electrophilic reagents have been carried out. No reaction of the oxetane occurs upon treatment of taxol with zinc bromide, however, taxol was converted to 10-deacetyltaxol, 7-epitaxol, and 10-deacetyl-7-epitaxol <91JOC5114>. In contrast, reaction with Meerwein's reagent resulted in a single oxetane rearrangement product (Scheme 17). Reaction with acetyl chloride not only opened the oxetane ring, but also resulted in rearrangement of the A ring as well. Both of the derivatives produced by these reactions were less active than taxol in the tubulin depolymerization assay. Treatment of taxol and baccatin III derivatives with several Lewis acids also resulted in cleavage of the oxetane ring <93T2805>. The ring opening reaction occurs by anchimeric assistance of the C-4 acetate group. A similar mechanism has also been proposed for the reaction of taxol with Meerwein's salt shown in Scheme 17. Attempted debenzoylation of 7,13-diacetylbaccatin III with tributyltin methoxide resulted in cleavage of the oxetane and formation of a tetrahydrofuran by intramolecular attack of the C(2)—OH on the oxetane C-20 <92TL3979>. Deoxygenation of baccatin III using the Barton deoxygenation method ultimately provided a synthesis of both 7-deoxytaxol and 7,10-dideoxytaxol <93JOC5028>. However, the second deoxygenation reaction also produced an unexpected rearrangement product from a complex radical rearrangement cascade (Equation (36)).



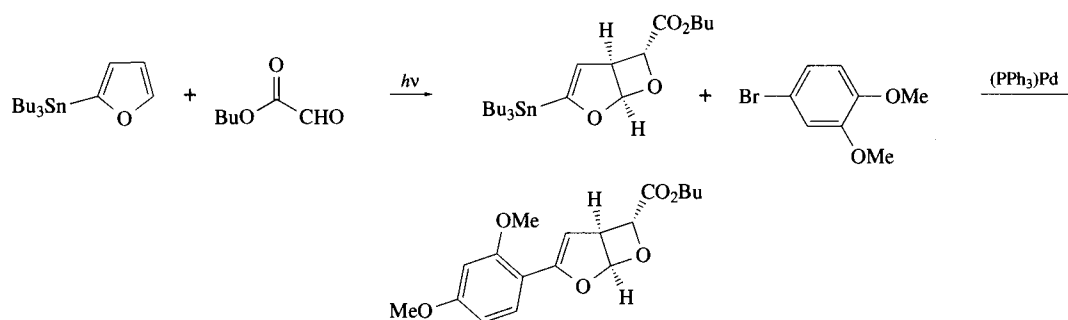
Scheme 17



1.23.12 IMPORTANT COMPOUNDS AND APPLICATIONS

1.23.12.1 Synthetic Applications of the Furan–carbonyl Photocycloaddition Reaction

The Paterno–Buchi reaction of furan and aldehydes and conversion of the photoadduct to a *threo* aldol product (Scheme 2) has been described in Section 1.23.6. This reaction sequence has been employed in the synthesis of several natural products. Given the fact that the stereoselective formation of *threo* aldol products was considered difficult in the 1980s, the photochemical approach provided a very useful alternative method to conventional aldol procedures. Asteltxin has been prepared from the photocycloaddition product of 3,4-dimethylfuran and 3-benzyloxypropanal <83JA6723, 84JA4186>. The photochemical reaction provided a *threo* aldol product containing a quaternary carbon in just three steps with complete stereocontrol. Similarly, avenciolide was obtained from furan and nonanal <84JA7200>. The synthesis of a hybrid structure of ginkgolide B and kadsurenone, effective paf antagonists which competitively inhibit paf binding to the paf receptor, was also achieved starting from a photocycloaddition reaction (Scheme 18) <88TL6689>. In this example, the nonregioselective photocycloaddition of aldehydes and unsymmetric furans was avoided by using a tributylstannyl-substituted furan with subsequent functionalization of the photoadduct using palladium coupling methods. The photocycloaddition reaction of 2-methylfuran or 2-tributylstannylfuran and propionyloxyacetaldehyde has also been employed in the synthesis of oxetanocin <90TL5445>.



Scheme 18

1.24

Thietanes and Thietes: Monocyclic

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1.24.1 INTRODUCTION

In the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) it was noted that thietanes have received somewhat less attention than their synthetically more accessible counterparts with three-, five-, or six-membered rings; that the reactions of thietanes are often dominated by the effects of ring strain (80 kJ mol^{-1}), for example as illustrated by facile base- or electrophile-induced polymerization; that there is a paucity of simple and general methods for preparing diversely substituted thietanes; that, although the ease of ring opening of thietanes has occasionally been exploited, nonetheless very limited use has been made of thietanes in organic synthesis ($\langle 84\text{CHEC-I}(7)403 \rangle$). Ten years later, in the mid-1990s, these points are still valid. Notable advances have appeared in several areas of thietane chemistry. Thus, papers have appeared on the formation and reactivity toward heat, light, and nucleophiles of complexes of thietanes with such metals as Os, Re, Mn, Co, and Ru as prototypes for the study of desulfurization of cyclic sulfides from fuels and as the basis for synthesis of γ -thiobutyrolactones (2-thiolanones) by CO insertion. Chemisorption and reactivity of thietane on single crystal transition-metal surfaces has also been examined as a hydrodesulfurization model. It is noteworthy that while the artificial sweetener alitame (L-aspartyl-D-alanine 2,2,4,4-tetramethylthietanylamide) is about 2000 times as sweet as sucrose, the L,L-isomer of the dipeptide sweetener is bitter while the D,D-isomer is tasteless. The generation and study (e.g. by ESR) of thietane radical cations and their dimers has been reported; ^{33}S NMR data on thietane derivatives has been presented. Use of alkylthietanes as carnivore odors for mammal pest control represents one of the first practical utilizations of mammalian semiochemicals in wildlife management and crop protection. Interest remains strong in the anionic and cationic polymerization of thietanes. A significant number of x-ray structures of thietanes have been published including those of thietane-metal complexes. Many studies have appeared on heat- or light-induced retro $[2 + 2]$ decompositions of thietanes. These reactions have proved useful as a means of generating highly reactive thiocarbonyl compounds for spectroscopic study. Through reaction with alkylating agents or free radicals, thietanes have shown utility as synthetic precursors of 3-halopropyl sulfides.

In addition to the review of thietane chemistry in CHEC-I, an extensive review through mid-1982 of thietanes and related four-membered sulfur heterocycles has appeared ($\langle \text{B-85MI } 124\text{-01} \rangle$). The majority of the references in this chapter are post-1982. A few earlier papers are included if these were omitted in CHEC-I or if they are essential to round out the discussion of later work.

1.24.2 THEORETICAL METHODS

The C—S bond dissociation energy of thietane, thiolane, and thiane have been calculated to be 213.4, 286.2, and $292.5 \text{ kJ mol}^{-1}$, respectively. These values may be described by the equation, $D = 293.3 - E_s$, where E_s is the ring strain energy (79.9 kJ mol^{-1} for thietane) ($\langle 86\text{IZV}1016 \rangle$). The strain energy of thietane has been calculated using the STO-3G minimal basis set ($\langle 89\text{JST}(187)169 \rangle$). The structure and ring puckering vibrations of thietane have been calculated based on NMR dipolar coupling data ($\langle 93\text{MP}1137 \rangle$). A comparison is made of through-space and through-bond 1,3-interactions in thietane and 3-thietanone using *ab initio* methods. It is concluded that through-bond interactions are greater than the through-space interaction energies ($\langle 82\text{JPC}3981 \rangle$). Molecular and electronic structures for the thietane cation radical have been calculated using the MNDO method ($\langle 84\text{JCS}(P2)407 \rangle$). Various calculations have been published of the geometry, spectroscopic, and other properties of thietane ($\langle 81\text{MP}1139$, $82\text{JST}(86)349$, $88\text{JA}8343$, $88\text{JPC}6528$, $91\text{JST}(249)305$, $91\text{JST}(245)315$, $92\text{JST}(271)227 \rangle$, 2- ($\langle 90\text{CJC}90 \rangle$), 3-methylthietane ($\langle 90\text{CPL}(168)564 \rangle$), S-protonated thietane ($\langle 90\text{JST}(205)177 \rangle$),

thietane 1-oxide <88JA8343, 92MI 124-01>, thietane 1,1-dioxide <89JST(183)135>, 4-alkylidenethietane 2-thione <88JOC1239>, 3-alkylidenethietane <84CB310>, and 3-thietanone <84JCP(80)800>.

Molecular orbital calculations have appeared on the chemisorption and reactivity of thietane on the single crystal transition-metal surface ^{110}Mo . The data so obtained has been compared to similar binding in model-discrete Mo complexes. The calculations suggest preferred bonding of thietane on two- or three-fold sites by an S-lone pair donor mechanism. The concerted elimination of cyclopropane is much easier on the surface than in model organometallic molecules <90JA50>.

1.24.3 EXPERIMENTAL STRUCTURAL METHODS

Most papers describing synthesis of thietanes give a variety of spectroscopic data for new compounds including proton and ^{13}C NMR, IR, and mass spectra. Papers cited under synthesis should therefore be consulted for routine spectroscopic information on thietane derivatives.

1.24.3.1 X-ray, Neutron and Electron Diffraction, and Microwave Spectroscopy

Representative bond lengths and bond angles for various monocyclic thietanes and thietes and their derivatives as determined by x-ray crystallography, microwave spectroscopy, and electron diffraction are collected in Table 1. The corresponding table in CHEC-I and the review by Dittmer and Sedergran <B-85MI 124-01> should be consulted for additional structural data. Thietane itself is nonplanar (pucker angle 26°) with a barrier to planarity of 274 cm^{-1} (3.28 kJ mol^{-1}); the $1.847\text{ \AA}$ long C—S bond is $0.008\text{ \AA}$ longer than the comparable C—S bond in unstrained rings while the C—S—C angle of 76.8° is considerably smaller than the corresponding angle in thiolane (93.4°). Thietane 1-oxide is nonplanar with a pucker angle of 34.9° and with oxygen occupying an equatorial position. 2,2-Dimethylthietane 1,1-dioxide is nonplanar with a pucker angle of 22.5° , a C—S—C angle of 80.2° (slightly larger than that of thietane) and C—S bonds of $1.777\text{--}1.807\text{ \AA}$ (somewhat shorter than in thietane). The microwave structure of thiete shows that the molecule is planar with a dipole moment of 1.426 D , and has $\text{CH}_2\text{—S}$ and CH—S bond distances of $1.853\text{ \AA}$ and $1.770\text{ \AA}$, respectively, and a C—S—C angle of 73.7° <84JST(117)141>.

The following post-1982 x-ray structures have appeared: *rel*-(1*R*,2*S*,3*R*,4*R*)-3-hexyl-2-(hydroxymethyl)-4-methylthietane 1-oxide <82JCS(P1)1325>; 3-methyl-3-phenyl-2,2-bis(trifluoromethyl)thietane 1,1-dioxide <87JA4982>; 4,4-dimethyl-3-(2'-methyl-1'-propenyl)-2,2-bis(trifluoromethyl)thietane 1,1-dioxide <87JA4982>; a penicillin thietan-2-one <90JCS(P2)1559>; 2-*n*-propylthiete 1,1-dioxide <93JHC873>; *trans*-2,2-diphenyl-3,4-dichlorothietane <81BCJ3701>; 3-bromothietane 1,1-dioxide <83AX(C)737, 86AX(C)94>; 3-(2-adamantylidene)-2-thietanone <90CB1449>; thietanyl 5-amino-4-carboxamidoimidazole <90TL1373>. The x-ray structures of a number of thietane-metal complexes have also been published: μ -3,3-dimethylthietane- $\text{Os}_3(\text{CO})_{10}$ <91JA1619>; $1,2\text{-Re}_2(\text{CO})_8(\text{S}(\text{CH}_2)_2\text{CMe}_2)_2$, $1,1\text{-Re}_2(\text{CO})_8(\text{S}(\text{CH}_2)_2\text{CMe}_2)_2$, $\text{Re}_2(\text{CO})_8(\text{S}(\text{CH}_2)_2\text{CMe}_2)(\mu\text{-SCH}_2\text{CMe}_2\text{CH}_2)$, $\text{Re}_2(\text{CO})_9(\text{S}(\text{CH}_2)_2\text{CMe}_2)$, *cis*- $\text{ReCl}(\text{CO})(\text{S}(\text{CH}_2)_2\text{CMe}_2)$ <91JA9004>; μ -3,3-dimethylthietane- $\text{Os}_4(\text{CO})_{12}(\mu\text{-CO})$ <92OM3129>; μ -3,3-dimethylthietane- $\text{Os}_4(\text{CO})_{12}$ <92OM2488>; μ -3,3-dimethylthietane- $\text{Re}_3(\text{CO})_{10}(\mu\text{-H})_3$ <92OM3794>; $\text{Mn}_2(\text{CO})_8[\mu\text{-S}(\text{CH}_2)_2\text{CMe}_2]$ and $[\text{Mn}(\text{CO})_3(\text{S}(\text{CH}_2)_2\text{CMe}_2)(\mu\text{-Cl})]_2$ <92OM4104>.

As the structure of 3-bromothietane 1,1-dioxide was determined both by x-ray <83AX(C)737> and by electron diffraction <86AX(C)94> techniques by the same researchers, it is informative to compare the structural information. The electron diffraction data is markedly more accurate. In the free molecule both the C—C and S=O bonds are longer and the OSO and CCC angles are larger than in the crystal. The unusually long C—C bond is consistent with the general observation that four-membered rings tend to have long bonds—longer than, for example, the analogous three- and five-membered molecules. The difference in the observed ring puckering angles as determined by the two techniques is not necessarily significant since the consequences of averaging over intramolecular motion are not the same in the two experiments. Electron diffraction indicates the presence of both equatorial and axial bromine. The ring puckering potential of 3-methylthietane has been evaluated based on microwave and other spectroscopic studies <88JSP(127)450, 91JSP(150)229>. The microwave structure of thietane 1,1-dioxide <88JCP(89)678> and 3-methoxythietane have been determined. In the latter case the oxygen atom is in the equatorial position <91JSP(145)236>. Hydrates of thietane have been characterized using neutron and x-ray diffraction techniques <86MI 124-01>. The electric dipole moment of thietane 1,1-dioxide has been determined by Stark effect measurements <91JST(243)141>.

Table 1 Bond lengths and bond angles for thietane and thiete derivatives.

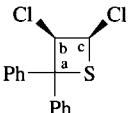
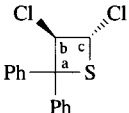
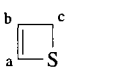
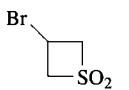
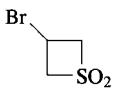
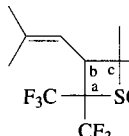
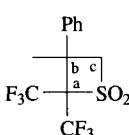
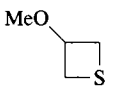
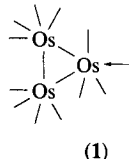
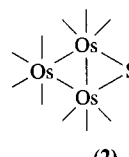
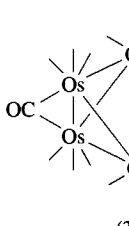
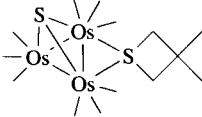
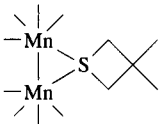
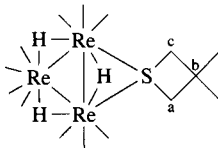
Compound ^a	Bond lengths (Å)	Bond angles (°)	Pucker angle (°)	Method ^b	Ref.
	C _a —S 1.89, C _c —S 1.81, C _a —C _b 1.55, C _b —C _c 1.58	CSC 79.3, CCC 98.1, SC _a C _b 86.7, SC _c C _b 88.8	28.5	X	75BCJ2339
	C _a —S 1.872, C _c —S 1.811, C _a —C _b 1.545, C _b —C _c 1.506	CSC 76.6, CCC 96.9, SC _a C _b 87.6, SC _c C _b 91.0	30	X	81BCJ3701
	C _a —S 1.770, C _c —S 1.853, C _a —C _b 1.350, C _b —C _c 1.501	CSC 73.7, CCC 99.3, SC _a C _b 97.9, SC _c C _b 89.1	(planar)	MW	84JST(117)141
	C—S 1.801, C—C 1.567, S—O 1.442, C—Br 1.933	CSC 80.4, CCC 95.8, CCS 89.2, OSO 121.5	25	ED	86AX(C)94
	C—S 1.793, C—C 1.525, S—O _{av} 1.410, C—Br 1.940	CSC 82.2, CCC 101.3, CCS 87.9, OSO 116.2	9	X	83AX(C)737
	C _a —S 1.844, C _c —S 1.832, C _a —C _b 1.588, C _b —C _c 1.550, S—O _a 1.416, S—O _b 1.443 ^c	C _a SC _c 82.1, C _a C _b C _c 101, SC _a C _b 87.9, SC _c C _b 89.5, OSO 119.1	0.1	X	87JA4982
	C _a —S 1.854, C _c —S 1.759, C _a —C _b 1.612, C _b —C _c 1.557, S—O _a 1.420, S—O _b 1.409 ^c	C _a SC _c 80.0, C _a C _b C _c 94.8, SC _a C _b 87.3, SC _c C _b 92.5, OSO 118.4	25.5	X	87JA4982
	C—S 1.847, C—C 1.549, C—O 1.420	CSC 76.5, CCC 95.2		MW	91JSP(145)236
	C—S 1.83–1.85, Os—C 2.375		28	X	90OM1718
	C _a —S 1.82, C _b —S 1.87, C _a —C _b 1.52, C _b —C _c 1.54	CSC 76, C _a C _b C _c 96	20.6	X	91JA1619
	(C—S) _{av} 1.84, (C—C) _{av} 1.555, (S—Os) _{av} 2.369	CSS 76.5, CCC 95, (SCC) _{av} 92.9	18.2	X	92OM3129

Table 1 (continued)

Compound ^a	Bond lengths (Å)	Bond angles (°)	Pucker angle (°)	Method ^b	Ref.
	(C—S) _{av} 1.835, (C—C) _{av} 1.54, (S—Os) _{av} 2.409	CSS 77.1, CCC 96, (SCC) _{av} 92	18.3	X	92OM2488
	(C—S) _{av} 1.838, (C—C) _{av} 1.546, (S—Mn) _{av} 2.209	CSS 77.2, CCC 95.7, SCC 90.8	24.7	X	92OM4104
	(C—S) _{av} 1.835, (C—C) _{av} 1.53, (S—Re) _{av} 2.409	CSS 77.5, CCC 98, (SCC) _{av} 91.5	12.4	X	92OM3794

^aLines to metal indicate CO ligands. ^bAbbreviations used: X, x-ray crystallography; MW, microwave spectroscopy; ED, electron diffraction. ^cOxygen syn to 2-methyl-1-propenyl or phenyl group.

1.24.3.2 NMR Spectroscopy

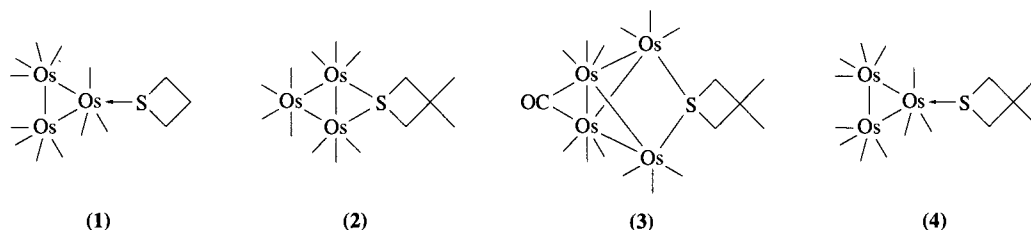
1.24.3.2.1 Proton NMR chemical shifts and coupling constants

Detailed proton NMR spectroscopic data on a variety of monocyclic and fused thietane and thiete derivatives was tabulated in this section of CHEC-I. Therefore, only limited, newer information, is presented here. By way of background data, α -protons of thietanes and their derivatives are deshielded relative to analogous derivatives with larger rings <80JOC4807>. Thus the α -protons of thietane and thietane 1,1-dioxide appear at δ 3.21 and 4.09 ppm, respectively, while the corresponding signals for the α -protons of thiolane and thiolane 1,1-dioxide appear at δ 2.82 and 3.01 ppm, respectively. The four-membered ring deshielding effect is larger in the case of sulfones than the sulfides, an effect which is particularly dramatic with ¹³C NMR spectra. This effect is also seen with ¹⁷O NMR spectra.

Details of the proton NMR spectra, including 2 D and nuclear Overhauser effect (NOE) studies, of penicillin thietan-2-ones have been published <90JCS(P2)1559>. The proton NMR spectra of *cis*- and *trans*-4-methyl-3-(1-(*E*)-propenyl)-2,2-bis(trifluoromethyl)thietane 1,1-dioxide have been analyzed in considerable detail <87JA4982>. In the osmium complex (1), the proton NMR (CDCl₃) spectrum shows the α -CH₂ protons as a triplet at 3.65 ppm (J = 7.9 Hz), while the β -CH₂ protons appear as a broad singlet at 2.84 ppm. At -43 °C in CD₂Cl₂, two multiplets appear at 2.94 and 2.82 ppm while a multiplet appears at 3.61. The temperature-dependent changes are thought to indicate a dynamic process involving intramolecular inversion of configuration at the pyramidal sulfur atom <92OM2281>. In complex (2), the α -CH₂ protons appear as singlets at 4.04 and 3.76 ppm while the methyl groups appear as a singlet at 1.58 ppm. In complex (3), the four α -CH₂ protons appear as a singlet at 4.42 ppm while the methyl groups appear as a singlet at 1.64 ppm <90OM2651>. In complex (4), the four α -CH₂ protons appear as a singlet at 3.44 ppm while the methyl groups appear as a singlet at 1.35 ppm <90OM1718, 91JA1619>. The thietane complex *trans*-PdCl₂(PMe₃)₂[S(CH₂)₂] shows proton NMR (CD₂Cl₂) δ 3.53 (*t*, J = 7.6 Hz, 4 H) and 2.91 ppm (*q*, J = 7.6 Hz, 2 H) <91JA5060>.

1.24.3.2.2 Heteronuclear NMR spectra

The ¹³C NMR chemical shifts have been determined for both the α - and β -carbons in a series of thietanes and their 1-oxides and 1,1-dioxides along with one-bond coupling constants [$J(\text{CH})$] <82OMR(18)82>. The two-bond ¹³C—¹³C coupling constant for ring atoms C(2)—C(4) in 2-benzylthietane 1,1-dioxide is 4.3 Hz <88MRC1103>. Details of the ¹³C NMR spectra, including 2 D and



NOE studies, of penicillin thietan-2-ones have been reported <90JCS(P2)1559>. The ^{13}C NMR chemical shifts for the α - and β -carbons of thietane have been unambiguously assigned as 25.34 and 27.38 ppm, respectively, by using the α,α -dideutero compound. In contrast to larger ring thiacycloalkanes, the α -carbon shift in thietane appears at *higher* field than the β -carbon <88JCP(89)678>. Detailed analyses of the ^{13}C NMR spectra of *cis*- and *trans*-4-methyl-3-(1-(*E*)-propenyl)-2,2-bis(trifluoromethyl)-thietane 1,1-dioxide have appeared <87JA4982>.

The ^{33}S NMR spectra of cyclic sulfides, sulfoxides, and sulfones have been determined; the values of thietane, thietane 1-oxide, and thietane 1,1-dioxide are 31 ($W_{1/2}$ 175), 365 ($W_{1/2}$ 215), and 331 ppm ($W_{1/2}$ 10) <87JOC3857>. The ^{17}O NMR chemical shifts (in CH_2Cl_2) in thietane 1-oxide and 1,1-dioxide of 66 (61 in CHCl_3) and 183 ppm, respectively, agree with earlier data summarized in CHEC-I <82JOC3660>.

1.24.3.3 Mass Spectroscopy

The mass spectral fragmentation patterns of a variety of thietane and thiete derivatives was presented in this section in CHEC-I. Thus, only more recent data is included here. Mass spectra determined by GC-MS are shown, and the fragmentation process analyzed, for a variety of thietanes isolated from the anal sacs of *Mustela* species mammals (ferrets, mink, weasels, etc.) <81CZ273, 83MI 124-01, 83CZ267>. The gas phase heats of formation of several organosulfur cations were determined from thietane by photoionization mass spectrometry <83OMS(18)248, 82JA5016>. The electron impact and chemical ionization mass spectra of 2-methylthietane have been measured and the fragmentation process compared with that of the isomeric $\text{C}_4\text{H}_8\text{S}$ sulfides 2,3-dimethylthiirane, tetrahydrothiophene, and allyl methyl sulfide <89JHC465>. Proton transfer rates for thietane and related heterocycles have been determined using the technique of photoionization mass spectrometry <86JHC1027>. Electron impact induced hydrogen atom loss from C(2) of 2-methylthietane giving the corresponding carbocation is discussed <87JCS(P2)531>.

1.24.3.4 UV, Fluorescence, Electric Dichroism, Vibrational Circular Dichroism, IR, Raman, Photoelectron, and ESR Spectroscopy

Detailed UV and IR spectroscopic data on a variety of monocyclic and fused thietane and thiete derivatives were tabulated in this section of CHEC-I. Therefore only limited, newer information, is presented here. It should be noted that thietanes absorb at somewhat longer wavelengths than larger ring sulfides such as thiolanes (λ_{max} at 270 and 239 nm, respectively).

The puckering absorptions of 3-methylthietane have been studied by means of far-infrared spectroscopy <83JST(102)199>. The charge transfer complexes of thietane with iodine and tetracyanoethylene (TCNE) have been studied using IR/Raman spectroscopy in the former case <84SA(A)351> and UV spectroscopy in the latter case <82CJC862>. The position of the TCNE-thietane CT maximum at 489 nm in CCl_4 is similar to the CT maximum for TCNE-dimethyl sulfide at 482 nm; both compounds also show similar ionization potentials (8.65 and 8.68 eV, respectively). The PE spectrum of thietane *S*-oxide has been determined. The three lowest ionization energies are 8.96 n_s , 10.14 π_{SO} and 12.00 (unassigned) <83CB2374>. For comparison purposes the first ionization potential of thietane appears at 8.67 eV. PE spectra are determined, compared, and interpreted for the following series of thietane 1,1-dioxides and thiete 1,1-dioxides: thietane 1,1-dioxide, 3-chlorothietane 1,1-dioxide, 3,3-dichlorothietane 1,1-dioxide, 2,3-dibromothietane 1,1-dioxide, thiete 1,1-dioxide, 3-chlorothiete 1,1-dioxide, 2-bromothiete 1,1-dioxide, and thiete 1,1-dioxide <86MI 124-02>. The vacuum ultraviolet spectrum (120–230 nm) <89JCP(91)2808> and the electric dichroism

spectroscopy <82JPC1960> of thietane and the vibrational circular dichroism (VCD) spectrum of 2-methylthietane <91CJC345> have been reported.

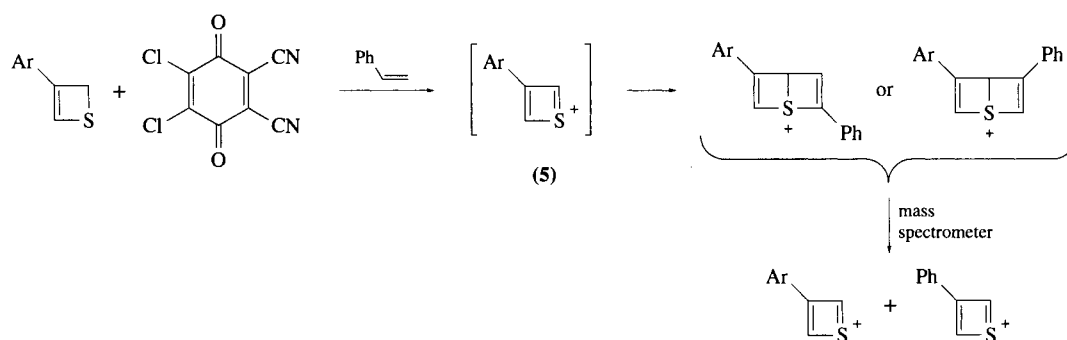
As found by ESR spectroscopy, γ -irradiation of a dilute solution of thietane in a CFCl_3 matrix at 77 K gives the radical cation, which shows normal 31.1 G hyperfine coupling to the four equivalent β -hydrogens and has g_{av} of 2.019 at 90 K. In the more mobile CF_3CCl_3 matrix, thietane dimer radical cations are produced by the combination of a monomer radical cation with a neutral molecule at low temperatures (<100 K). The thietane dimer radical cation shows 8.7 G hyperfine coupling to the eight equivalent β -hydrogens and has g_{av} of 2.012 at 110 K. Centrosymmetric thietane dimer radical cation are coupled by a 3-electron $(\sigma)^2(\sigma^*)^1$ S—S bond. The dimer cation is unstable above 105 K, decomposing to give the 2-thietanyl radical (16.4 (1H) and 29.5 (2H) G hyperfine coupling and g_{av} of 2.0043 in $\text{CFCl}_2\text{CF}_2\text{Cl}$ at 120 K) as a result of hydrogen atom or proton transfer <87JA6778, 87CC257, 84JCS(P2)1681>. ESR spectra obtained by the technique of time-resolved fluorescence-detected magnetic resonance (FDMR) are used to characterize in alkane and aromatic hydrocarbon solvents the thietane radical cation, generated by radiolysis with a van der Graaff accelerator. The monomeric thietane radical cation is stabilized at 205 K at 3 mM concentration in toluene, or other aromatic solvents, giving a signal $a(4\text{H}) = 20.8$ G. The resulting arene-thietane complex radical cation is an example of a mixed complex radical cation involving the interaction between lone pair and π -orbitals. At 290 K and 10 mmol thietane in toluene, only the thietane dimer radical cation signal is seen ($a(8\text{H}) = 9.8$ G). Spectra with monomer and dimer signals superimposed are observed at intermediate temperatures and solute concentrations <91JA4345, 92JPC3640>.

1.24.4 THERMODYNAMIC ASPECTS

Quantitative enantiomer separation has been achieved for *trans*-2,4-dimethylthietane using the technique of complexation gas chromatography with optically active nickel(II) bis[(1*R*)-3-(heptafluorobutyl)camphorate] in squalane coated on a 100 m capillary column <82JA7573>. Enantiomers of *trans*-2,4-dimethylthietane have been partially resolved (*ee* 9%) with tri-*o*-thymotide clathrate crystals <83JA4561>. The optical rotation of (2*S*)-2-propylthietane, a pheromone from the stoat, was determined to be $[\alpha]_{\text{D}}^{20} -147.5^\circ$ <82AJC1945>. Surprisingly, the m.p. of 2-iodothietane 1,1-dioxide, 120–123°C, is considerably higher than that of the higher molecular weight 2-iodothioline 1,1-dioxide, 78–79°C, reflecting the better crystal packing of the more rigid and compact four-membered ring compared to the five-membered ring <85S982>.

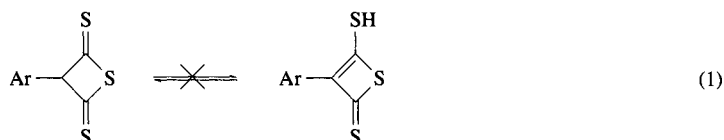
1.24.5 REACTIVITY OF FULLY CONJUGATED RINGS

Thiacyclobutenium ions represent a fully conjugated four-membered ring containing a single sulfur atom. The presence of 4π electrons would render these ions antiaromatic, like cyclobutadiene, making isolation improbable. While these species are seen in the mass spectra of thietes <72JOC1111>, attempts to generate them by removal of a hydride ion from thietes with the triphenylmethyl carbocation or with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) led to intractable solid products which resisted characterization <87H(26)969>. Treatment of 3-*p*-tolyl-2*H*-thiete with DDQ in the presence of phenylacetylene gave an insoluble purple solid whose mass spectrum showed ions at m/e 263, possibly corresponding to the Diels–Alder adduct (5) of the 3-*p*-tolylthiacyclobutenium ion, as well as at m/e 161 and 147, corresponding to 3-*p*-tolyl-2*H*-thiete and 3-phenyl-2*H*-thiete, respectively, possibly formed by two alternative modes of retro-Diels–Alder decomposition of (5) (Scheme 1) <87H(26)969>.



Scheme 1

The enethiol tautomers of thietan-2,4-dithiones represent a second type of fully conjugated four-membered ring containing sulfur with 4π electrons. However, thietan-2,4-dithiones do not undergo methylation, show no SH bands in their IR spectra, and show a singlet integrating for 1 H at δ 9.1 ppm–9.4 ppm, corresponding to the strongly deshielded H-3. Apparently thietan-2,4-dithiones do not tautomerize to the enethiol form to any significant extent (Equation (1)) <82JCR(S)256>.

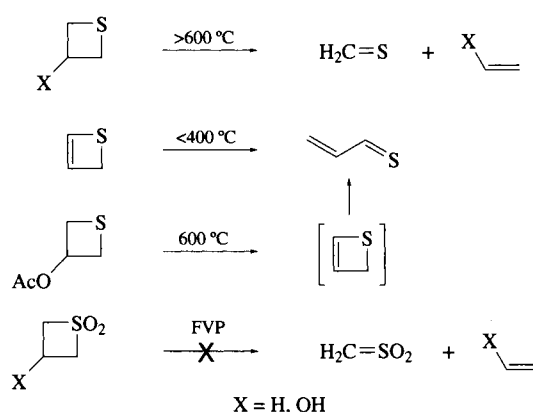


1.24.6 REACTIVITY OF FULLY SATURATED AND PARTIALLY UNSATURATED RINGS

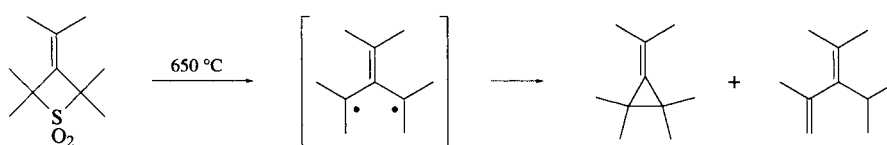
1.24.6.1 Unimolecular Thermal and Photochemical Reactions

1.24.6.1.1 Fragmentations and eliminations

Microwave spectroscopic analysis of the pyrolysis products of thietane, 3-thietanol, 3-acetoxythietane, thiete, thietane 1,1-dioxide, and 3-thietanol 1,1-dioxide showed that three different modes of decomposition occur (Scheme 2). At temperatures above 600 °C, retro [2 + 2] decomposition of thietane gives thioformaldehyde and ethylene. 3-Thietanol gives thioformaldehyde and vinyl alcohol, which rearranges to acetaldehyde. Thiete undergoes electrocyclic ring opening at temperatures below 400 °C to give thioacrolein. Thioacrolein is also formed on pyrolysis of 3-acetoxythietane at 600 °C. Presumably at this temperature 3-acetoxythietane first undergoes elimination to thiete. In the case of thietane 1,1-dioxide and 3-thietanol 1,1-dioxide, sulfene $\text{CH}_2=\text{SO}_2$, the anticipated product of retro [2 + 2] decomposition, could not be found despite a careful search for expected microwave lines, leading to the conclusion that decomposition of these two thietane derivatives involves nonretro [2 + 2] processes, for example loss of SO_2 and cyclopropane <83JST(97)47, 84CHEC-1(7)419>. 3-Isopropylidene-2,2,4,4-tetramethylthietane 1,1-dioxide eliminates SO_2 above 650 °C giving 2,4-dimethyl-3-isopropyl-1,3-pentadiene and 2,2,3,3-tetramethylisopropylidenecyclopropane (Scheme 3) <85JCS(P2)1211>. Decomposition of thietane at 900 K at very low pressure involves the intermediacy of the diradical $\cdot\text{CH}_2\text{CH}_2\text{CH}_2\text{S}\cdot$ <87NKK870>. Thioformaldehyde from pyrolysis of thietane has been trapped with 1,1-dimethylsilaethylene, formed *in situ* by copyrolysis with 1,1-methylsilacyclobutane <84JOM(271)191>.

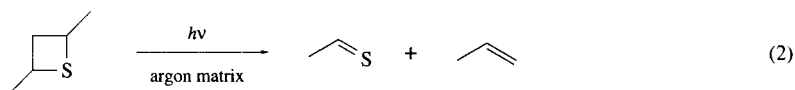


Scheme 2

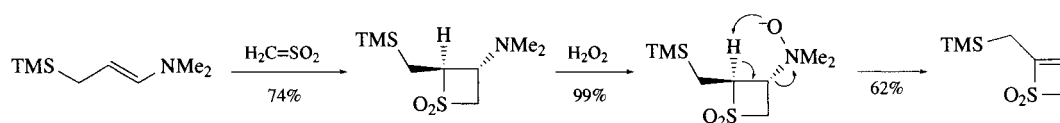


Scheme 3

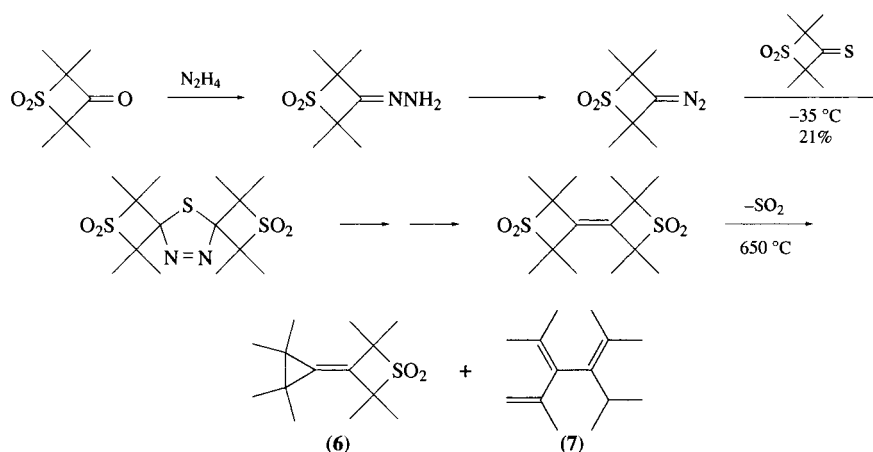
Low temperature photolysis of thietane and thietane- d_2 has been used to generate thioformaldehyde and thioformaldehyde- d_2 , whose IR spectra were determined under matrix-isolation conditions (91BCJ1389). In a similar manner, photolysis of 2-methyl- and 2,4-dimethylthietane in argon matrices affords thioacetaldehyde as one of the products (Equation (2)) (93MI 124-01). 9,10-Dicyanoanthracene (DCA)-photosensitized reaction (at 366 nm) of 3-cyano- or 3-ethoxy-2,2-diarylthietane gave in moderate yield 2-cyano- or 2-ethoxy-1,1-diarylethene, respectively, by extrusion of thioformaldehyde. The ring-splitting reaction proceeds via a one-electron oxidation of the sulfur atom of the thietane ring to the thietane radical cation by photochemical electron transfer to the excited state of DCA. Initial cleavage of the thietane S—C(2) bond is favored over cleavage of the S—C(4) bond due to favorable stabilization of a radical species at C(2). Direct irradiation at 313 nm also resulted in ring-splitting (92BCJ1472). Glassy matrix γ -irradiation of thietane gave the ring-opened “distonic radical anion” (“distonic” refers to a radical ion in which the ionic and radical sites are separated spatially) $\cdot\text{CH}_2\text{CH}_2\text{CH}_2\text{S}^-$ as determined by UV and ESR spectroscopy. The latter species on “photobleaching” with 440–770 nm light gave ethylene and the thioformaldehyde radical anion (90MI 124-01). Ultraviolet irradiation of 2,2,4,4-tetraacylthietane 1-oxides results in loss of sulfur monoxide and formation of the ring-contracted cyclopropanes (90MI 124-02).



3-*N,N*-Dimethylamino-2-(trimethylsilylmethyl)thietane 1,1-dioxide *N*-oxide undergoes Cope elimination affording 4-[(trimethylsilyl)methyl]-2*H*-thiete 1,1-dioxide (Scheme 4) (86CB257); related Cope eliminations have been reported (see Schemes 16, 30) (87JOC695, 93JHC873). Pyrolysis of 2,2,2',2',4,4,4',4'-octamethyl-3,3'-bithietanylidene 1,1,1',1'-tetraoxide gives 2,2,4,4-tetramethyl-3-(2,2,3,3-tetramethylcyclopropylidene)thietane 1,1-dioxide (6) and 4-isopropyl-3-isopropylidene-2,5-dimethylhexa-1,4-diene (7) (Scheme 5) (84JCS(P1)2457).



Scheme 4

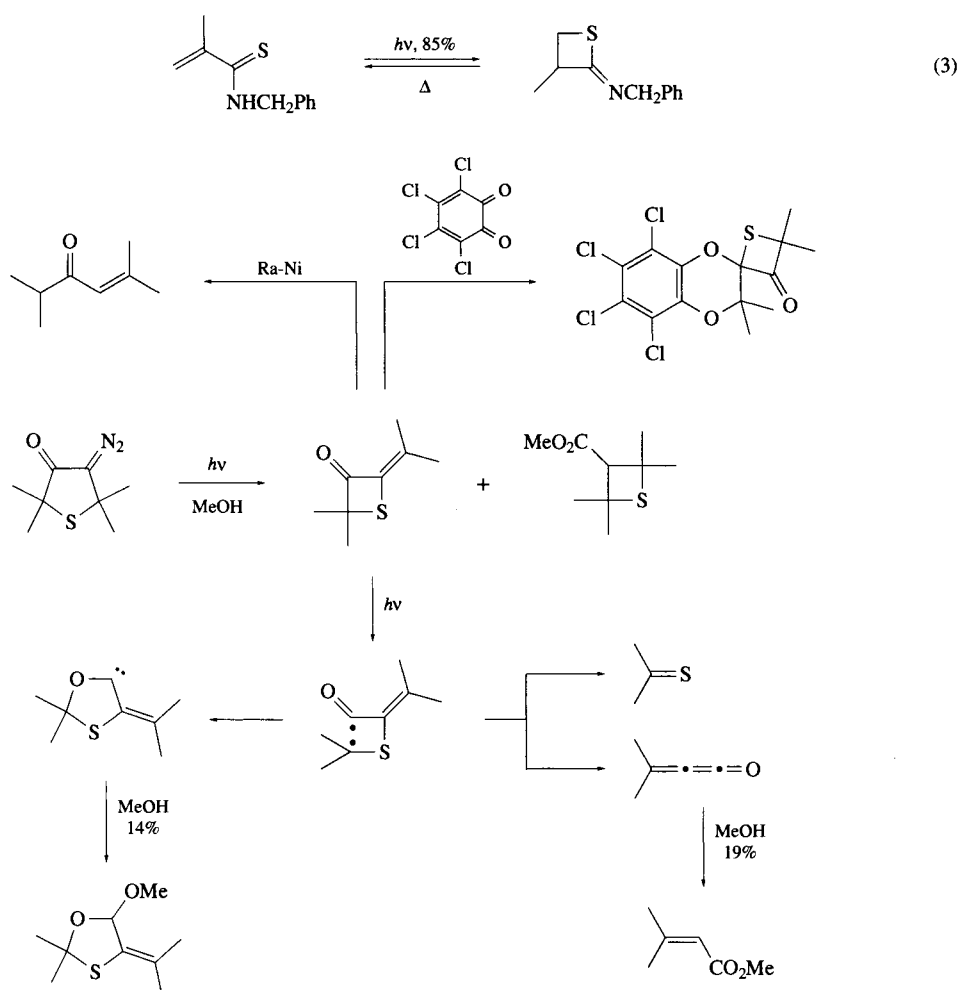


Scheme 5

1.24.6.1.2 Rearrangements

The thermal decomposition of thietane 1-oxide at 400–450 K has been investigated using isotopic labelled samples and the technique of collision activation mass spectrometry. A thietane 1-oxide–1,2-oxathiolane equilibrium precedes rearrangement to 3-thiopropional which then loses hydrogen

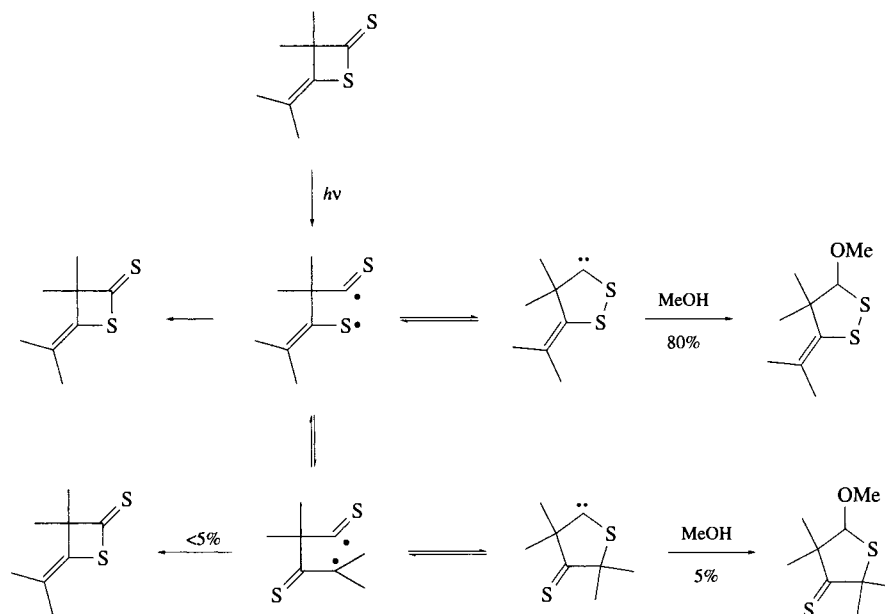
sulfide affording acrolein <84CB1393>. A 2-(1-alkenyl)-3-thietanone 1,1-dioxide is thought to be the intermediate in the rearrangement on oxidation of a 2-(1-alkenyl)-3-thietanone to a 1-oxa-2-thiacyclohep-5-en-4-one 2-oxide <93HCA1251>. Thietane 1-*N*-arylimides, formed by reaction of thietanes with anilines and *t*-butyl hypochlorite, rearrange thermally with ring enlargement to give *N*-aryl-1,2-thiazolidines in high yield <85M1153>. 2-Iminothietanes on heating rearrange to α,β -unsaturated thioamides (Equation (3)) <92JOC2419>. UV irradiation of 2-isopropylidene-4,4-dimethyl-3-thietanone gives 4-isopropylidene-2,2-dimethyl-5-methoxy-1,3-oxathiolane (14%) by rearrangement along with methyl 3-methyl-2-butenate (19%) by a retro-[2 + 2] process (Scheme 6) <82JOC4429>. UV irradiation of 4-isopropylidene-3,3-dimethyl-2-thietanethione in alcohol gives four products by a mechanism suggested to involve ring opening to a 1,4-diradical which can reclose in several ways, including formation of two different carbene intermediates (Scheme 7) <83T2719>. 3-Substituted thietane 1-oxides and 1,1-dioxides can undergo anionic ring opening ("eliminative fission"), for example 3-phenyl-3-hydroxythietane 1,1-dioxide with a base gives $\text{PhC(O)CH}_2\text{SO}_2\text{CH}_3$, probably occurring via anion $\text{PhC(O)CH}_2\text{SO}_2\text{CH}_2^-$ <87CC552, 88BSF317>.



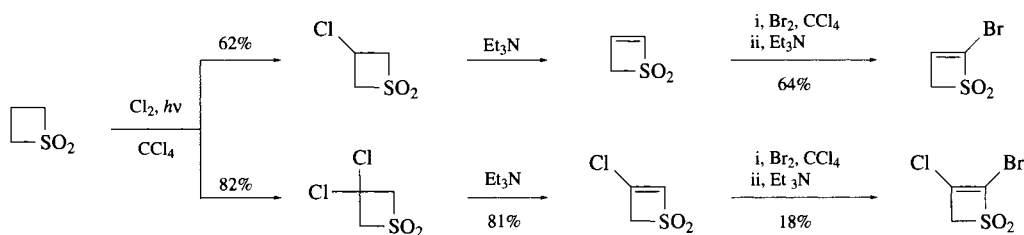
1.24.6.2 Electrophilic Attack

1.24.6.2.1 At carbon

Addition of chlorine and bromine to thiete 1,1-dioxides occurs readily (Scheme 8) <84JOC2408>.



Scheme 7



Scheme 8

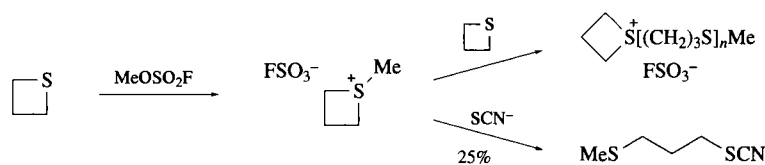
1.24.6.2.2 At sulfur

The kinetics of oxidation of thietane to thietane 1-oxide with sodium metaperiodate in ethanol–water ^[85JCS(P2)683] and of the further oxidation of thietane 1-oxide to thietane 1,1-dioxide by Cr^{VI} in aqueous acetic acid ^[85MI 124-02] is reported. Interestingly, stereoselectivity is seen in the oxidation of several 3-substituted thietane 1-oxides with MCPBA ^[94TL5809]. The oxidation of thietane to thietane 1,1-dioxide with hydrogen peroxide catalyzed by tungstic acid (WO₃·H₂O) is described ^[84JOC2408]. Oxidation of thietane with Davis' *N*-sulfonyloxaziridine gives thietane 1,1-dioxide rather than the 1-oxide ^[88JOC5004]. Thietane 1,1-dioxides are also formed from thietane with KMnO₄ (Scheme 32) ^[92JOC6335]. The interaction of phenols and anilines with thietane and thietane 1-oxide and other cyclic and acyclic sulfides and sulfoxides is examined using IR or UV spectroscopy as a method for assessing basicity ^[82JA4524, 86JCS(P2)1081].

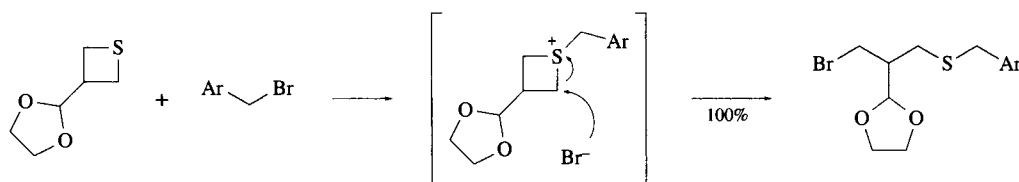
Treatment of 2-thietanones with SO₂Cl₂ gives β,β-dithioalkanoyl dichlorides by a process most likely involving initial attack at sulfur by Cl⁺ ^[83IZV553]. When an excess of SO₂Cl₂ is used together with acetic anhydride, 1,2-oxathiolan-5-one 2-oxides are formed instead ^[92IZV1685]. Electrophilic *S*-chlorination is probably also the first step in the reaction of thietanes with anilines and *t*-butyl hypochlorite forming thietane 1-*N*-arylimides ^[85MI1153].

S-Methylation of thietane with methyl fluorosulfate gives a highly reactive *S*-methylthietanium ion which effects polymerization of unreacted thietane but also is captured by thiocyanate to give 3-(methylthio)propyl thiocyanate (25%) (Scheme 9) ^[86CJC940]. Thietanes can be converted to 3-halopropyl benzyl sulfides in good yield simply through reaction with benzyl halides. Thus, treatment of 3-formylthietane ethylene acetal with *p*-methoxybenzyl bromide gives quantitatively a ring-opened primary bromide by a sequence involving *S*-alkylation of the thietane followed by bromide

ion-induced nucleophilic ring opening (Scheme 10) <83JOC4852, 86JOC846>. Benzyne, generated from 2-carboxybenzenediazonium chloride, reacts with thietane giving 3-chloropropyl phenyl sulfide in 70% yield, most likely via initial *S*-alkylation of the thietane by benzyne <85CL677>.



Scheme 9

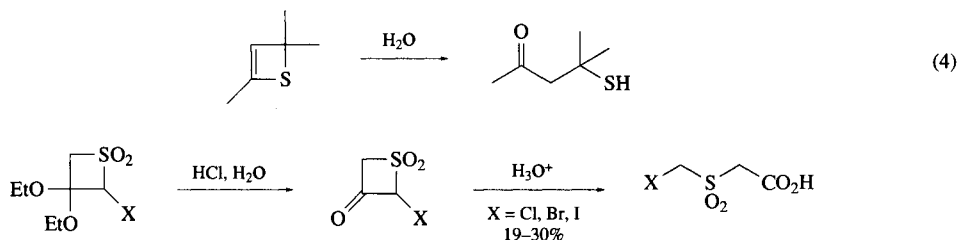


Scheme 10

1.24.6.3 Nucleophilic Attack at Heterocyclic Carbon Atoms

1.24.6.3.1 By oxygen

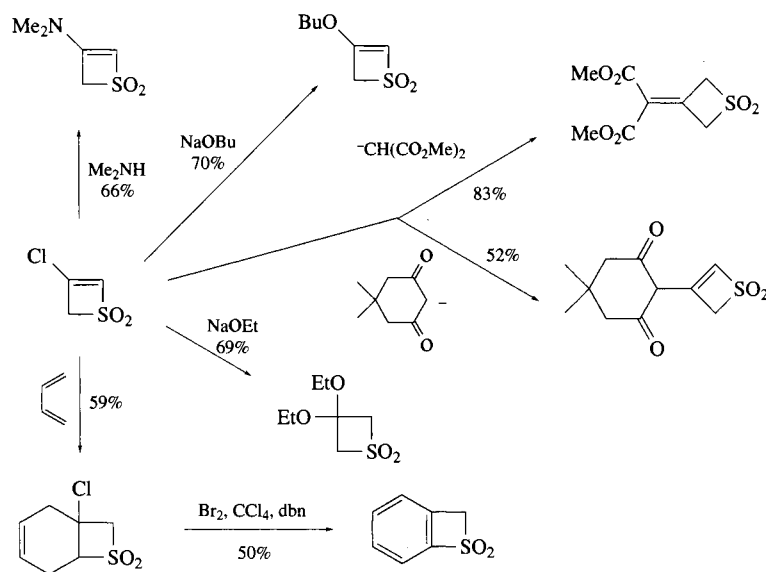
A Fourier transform ion cyclotron resonance (FT-ICR) study has been conducted of the reaction of 3,3-dideuteriothietane with NH_2^- , OH^- (OD^-) and CH_3O^- : with OH^- and CH_3O^- , $\text{S}_\text{N}2$ reactions dominate to the extent of 90–98%; minor amounts (2%) of E_2 elimination occur in the former case while H^- transfer is seen (10%) in the latter case <88JA2066>. Addition of water to 2,4,4-trimethylthiete quantitatively affords 4-thio-4-methylpentan-2-one (Equation (4)) <89AG(E)1499>. Hydrolysis of penicillin-derived 2-thietanones gives 2-amino-2,3-dimethyl-3-thiobutanoic acid salts <83JCS(P1)2259, 84JCS(P2)1127>. Acid hydrolysis of 2-halo-3,3-diethoxythietane 1,1-dioxides gives the corresponding halomethanesulfonyl acetic acids, presumably by acid catalyzed water-induced ring opening of the corresponding 2-halothietanone 1,1-dioxide (Scheme 11) <82SUL79>. Michael addition occurs readily on reaction of 3-chlorothiete 1,1-dioxide with alkoxides resulting in replacement of chlorine by alkoxide. A second addition of alkoxide to 3-alkoxythiete 1,1-dioxide gives 3,3-dialkoxythietane 1,1-dioxides (Scheme 12) <84JOC2408>.



Scheme 11

1.24.6.3.2 By nitrogen

In the reaction of 3,3-dideuteriothietane with NH_2^- , studied by FT-ICR, α -deprotonation is the major process (86%), with minor contributions from E_2 elimination (10%) and even lesser contributions (4%) from $\text{S}_\text{N}2$ promoted ring opening <88JA2066>. Methylamine reacts with 2-thietanones and 3-chloro-2-thietanones giving, respectively, methylamides of β -thiobutyric acids



Scheme 12

<83IZV556> and thiirane-containing methylamides of thioglycidyl acid <85IZV350>. Reaction of 3-chlorothietane 1,1-dioxide with amines results in replacement of chlorine with amine. 3-Thietanone 1,1-dioxide, upon treatment with arylamines affords the corresponding imines, while with alkylamines it gives open chain amides, by ring-opening of the intermediate α -hydroxyamine followed by protonation or nucleophilic attack of the so-formed α -sulfonylcarbanion on a second molecule of 3-thietanone 1,1-dioxide <84JOC2408>. 2,2,4,4-Tetramethyl-3-thietanone 1,1-dioxide gives the corresponding hydrazone <84JCS(P1)2457>; a related reaction is reported for 4,4-dimethyl-2-isopropylidene-3-thietanone (Scheme 5) <86T1989>.

1.24.6.3.3 By hydride

Sodium borohydride reduces thiete 1,1-dioxides to thietane 1,1-dioxides, while lithium aluminum hydride reduces both classes of sulfones to the corresponding thietanes; C—S bond cleavage also occurs on reaction of lithium aluminum hydride with thietanes giving open-chain thiols (Scheme 30) <93JHC873>.

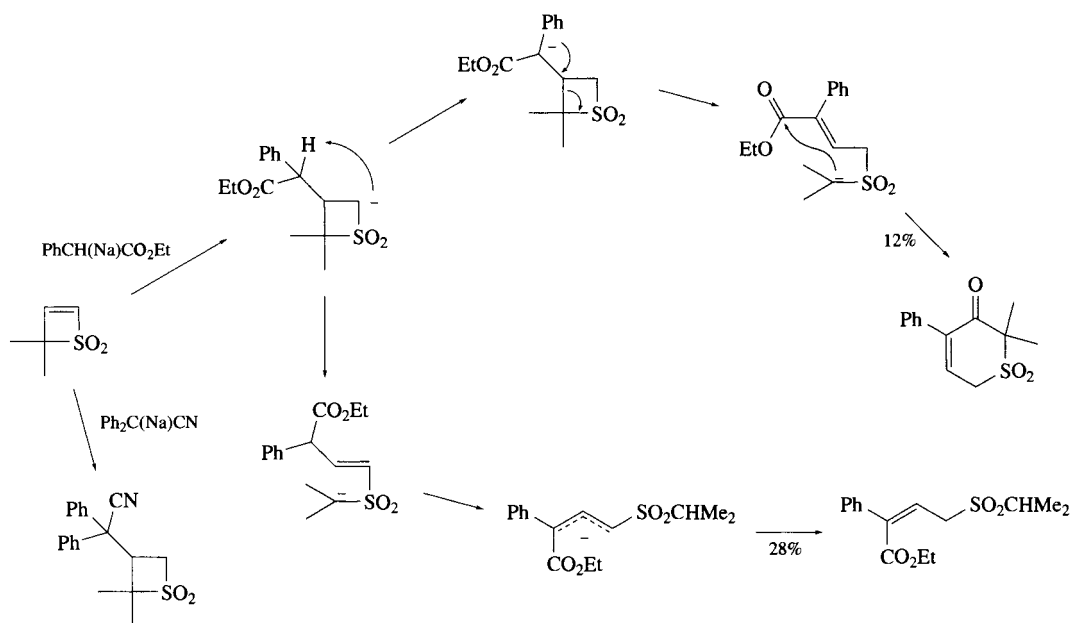
1.24.6.3.4 By sulfur

3-Thietanone 1,1-dioxide reacts with 1,3-propanedithiol in the normal manner to form the 1,3-dithiane derivative, 2,5,9-trithiaspiro[3.5]nonan-2,2-dioxide (Scheme 15) <82SUL79>. Michael addition of thiolates to 3-chlorothietane 1,1-dioxide gives the corresponding 3-alkylthiothietane 1,1-dioxide <84JOC2408>. 4,4-Dimethyl-2-thietanone reacts with $\text{H}_2\text{S}-\text{Et}_3\text{N}$ and then FeCl_3 giving 5,5-dimethyl-1,2-dithiolan-3-one via nucleophilic HS^- attack at the $\text{C}=\text{O}$ group <92JCS(P1)1215>.

1.24.6.3.5 By carbon

2-Thietanones react with stabilized phosphoranes to give the corresponding 2-alkylidenethietanes. 2-Thiolanones are unreactive under the same conditions so it is suggested that the ketonic character of 2-thietanones is enhanced due to ring-strain effects <82CC995>. Michael addition occurs readily on reaction of 3-chlorothietane 1,1-dioxide with carbanions, resulting in replacement of chlorine with

the attacking nucleophile (Scheme 12) <84JOC2408>. Carbanions undergo Michael addition to 4,4-dimethylthiete 1,1-dioxide giving adducts retaining the four-membered ring as well as products resulting from ring opening (Scheme 13) <87NKK1499>.



Scheme 13

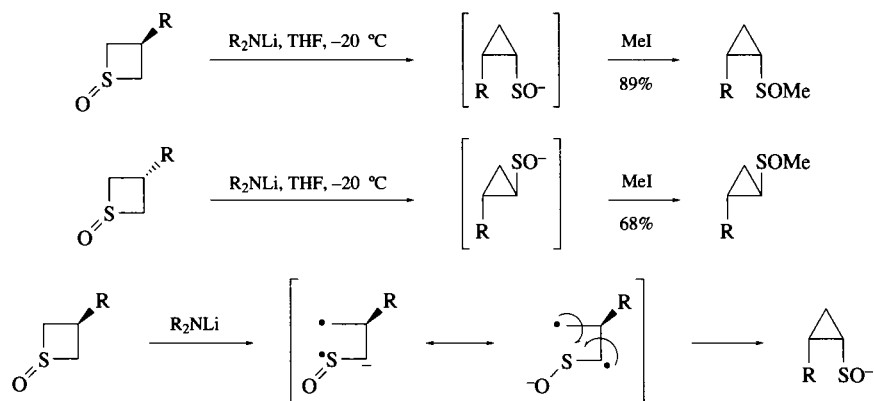
1.24.6.3.6 By other nucleophiles

Reaction of thietane with trimethylstannyl lithium gives a mixture of the product from nucleophilic attack at the α -ring carbon ($\text{Me}_3\text{SnCH}_2\text{CH}_2\text{CH}_2\text{SH}$; 46%) and at sulfur ($\text{Me}_3\text{SnSPr}^n$; 34%) <86G239>. Halide and pseudohalide ions readily effect ring opening of thietanium ions (Schemes 9, 10) <83JOC4852, 86CJC940>.

1.24.6.4 Nucleophilic Attack at Hydrogen Attached to Heterocycle Carbon Atoms (Deprotonation)

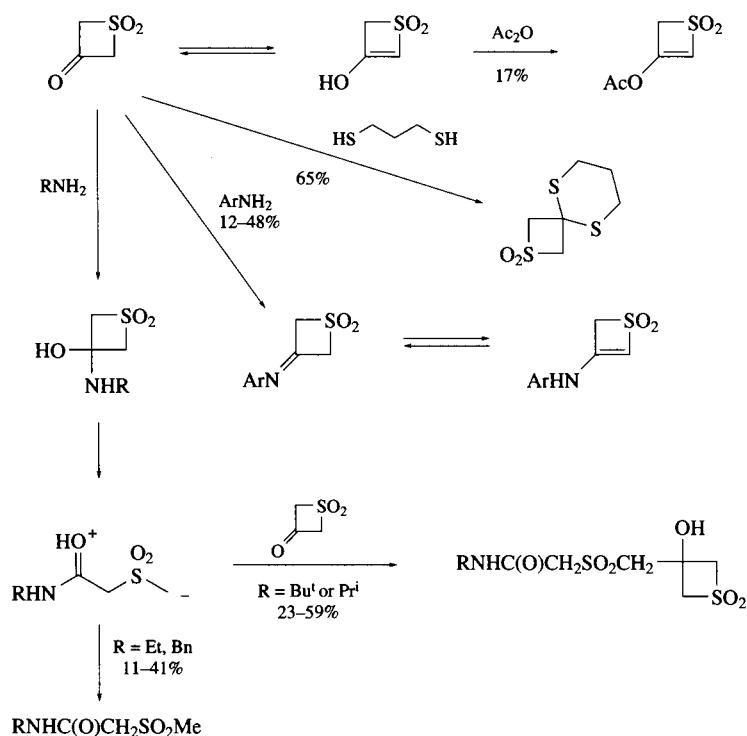
3-Alkyl- and 2,3-dialkylthietane 1-oxides, upon deprotonation α to the sulfinyl group, undergo stereospecific ring contraction giving cyclopropylsulfenates, which react with methyl iodide to give the corresponding cyclopropyl methyl sulfoxides. Deprotonation, achieved with lithium cyclohexylisopropylamide in THF at -20°C , occurs at the α -proton syn to the sulfinyl oxygen. Rearrangement occurs stereospecifically with respect to configuration at sulfur, at the migrating residue (retention), and at the migration terminus (inversion), and is thought to involve either a stereospecific 1,3-diradical formation-ring closure process or an unprecedented concerted anionic 1,2-sigmatropic rearrangement (Scheme 14) <82CC589>.

In the reaction of 3,3-dideuteriothietane with NH_2^- , OH^- (OD^-), and CH_3O^- , studied by FT-ICR, α -deprotonation is the major process (86%) with NH_2^- , with minor contributions from E2 elimination (10%); with OH^- and CH_3O^- , $\text{S}_\text{N}2$ reactions dominate to the extent of 90–98%. Only minor amounts (2%) of E2 elimination occur with OH^- while H^- transfer is seen to the extent of 10% with CH_3O^- <88JA2066>. 3-Thietanone 1,1-dioxide is in equilibrium with its enol form, which can be trapped with Ac_2O in 17% yield. The corresponding 3-iminothietane 1,1-dioxides are also thought to be in equilibrium with the corresponding enamine, 3-amino-2*H*-thiete 1,1-dioxides, based on IR and NMR observation of NH bands (Scheme 15) <82SUL79>. Selective α -iodination of thietane 1,1-dioxide without polyiodination can be achieved by α -lithiation with *n*-butyllithium, conversion of the lithium compound into the alanate by treatment with triethylalane, and finally reaction of

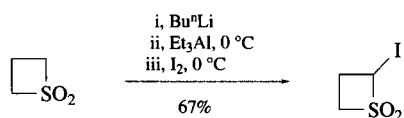


Scheme 14

the alanate with iodine to give α -iodothietane 1,1-dioxide in 67% yield (Equation (5)) $\langle 85S982 \rangle$. Thiete 1,1-dioxides can be prepared via base-induced elimination reactions of 3-halothietane 1,1-dioxides (Scheme 8) $\langle 84JOC2408 \rangle$. 2-Alkyl-2*H*-thiete 1,1-dioxides undergo base-catalyzed rearrangement to 4-alkyl-2*H*-thiete 1,1-dioxides (Scheme 30) $\langle 93JHC873 \rangle$. 3-Ferrocenyl-2*H*-thiete can be prepared in 36% yield by base-induced elimination of the precursor trimethylammonium salt (Scheme 16) $\langle 87JOC695 \rangle$.

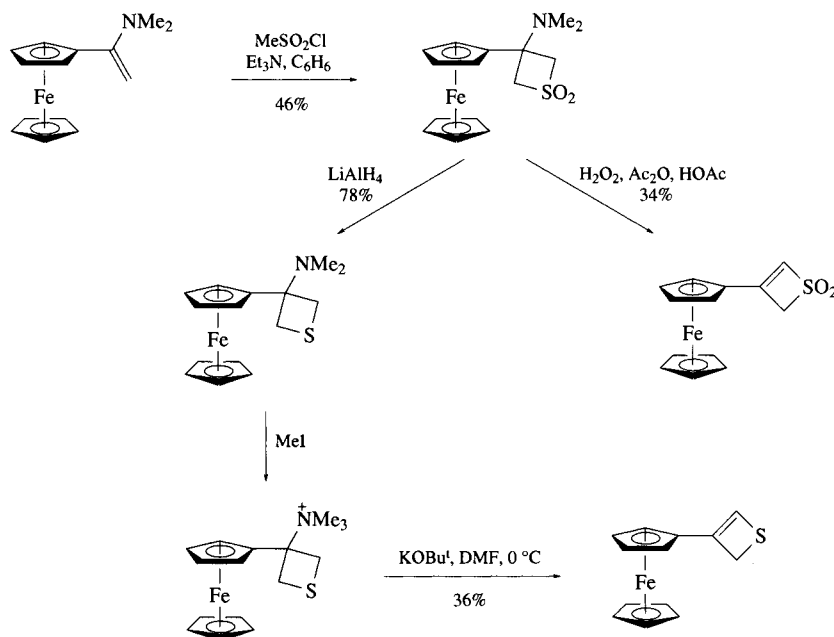


Scheme 15



(5)

4,4-Dimethyl-2-thietanone can be deprotonated with NaH or KH and the resulting carbanion alkylated with MeI or oxygenated with $\text{MoO}_5 \cdot \text{py} \cdot \text{DMPU}$ $\langle 92JCS(P1)1215 \rangle$.

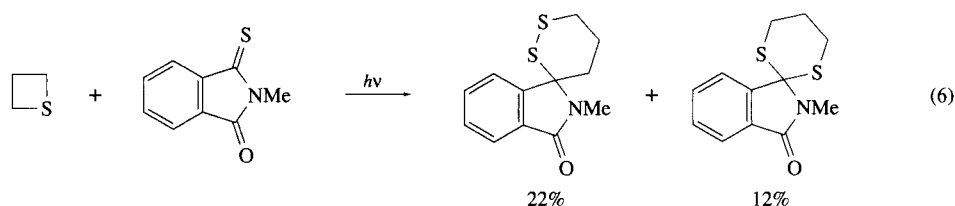


Scheme 16

1.24.6.5 Reaction with Radicals or Electron Deficient Species

1.24.6.5.1 Radical and excited state attack on sulfur

Bromotrichloromethane, with initiation from AIBN at 70 °C, reacts with thietane giving trichloromethyl 3-bromopropyl sulfide by S_H2 attack at sulfur $\langle 89JPO367 \rangle$. Irradiation of a mixture of thietane and *N*-methylmonothioimide gives both a 1,2-dithiane and a 1,3-dithiane (Equation (6)) $\langle 87H(26)147 \rangle$. The gas phase reaction between hydrogen atoms and thietane gives mainly propylene while the analogous reaction with 3,3-dimethylthietane gives isobutene and 1,1-dimethylcyclopropane $\langle 83NKK1481 \rangle$. Atomic sulfur, $S(^1D)$ or $S(^3P)$, reacts with thietane giving 1,2-dithiolane $\langle 84JA6938 \rangle$.



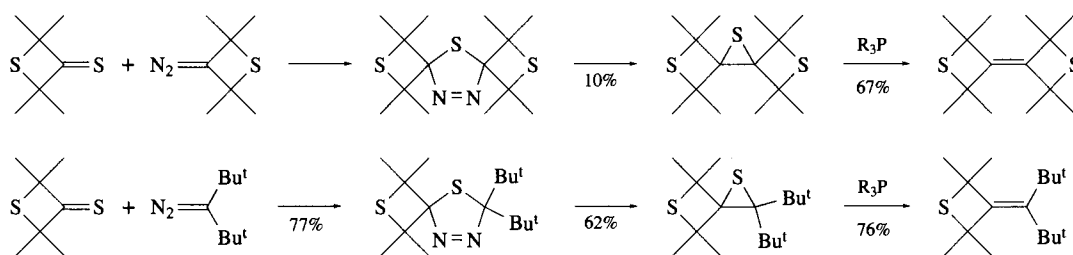
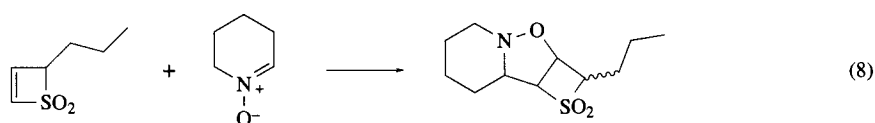
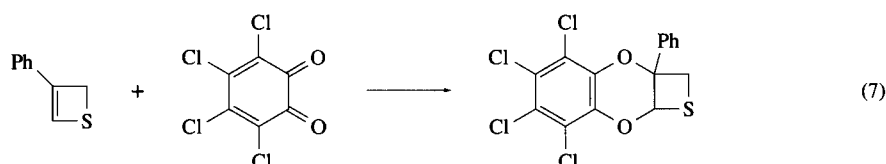
1.24.6.5.2 Radical attack on ring carbon atoms

Free radical chlorination of thietane 1,1-dioxide gives substitution at the 3-position (Scheme 8) $\langle 84JOC2408 \rangle$.

1.24.6.6 Reactions with Cyclic Transition States, Formally Involving a Second Species

2*H*-Thiete undergoes [2 + 2] cycloaddition at room temperature with tetracyanoethylene giving 5,5,6,6-tetracyano-2-thiabicyclo[2.2.0]hexane $\langle 85JOC7799 \rangle$. Thietes also undergo [4 + 2] addition with *o*-chloranil giving dihydrobenzo-1,4-dioxins (Equation (7)) $\langle 87H(26)969 \rangle$. Thiete 1,1-dioxide reacts with nitrile oxides, nitrones, diazoalkanes, and other 1,3-dipoles as well as 1,3-butadiene to form cycloadducts (Equation (8), Scheme 12) $\langle 93JHC873, 82JCS(P2)95, 84JOC2408 \rangle$. 2,2,4,4-Tetramethyl-

thietane-3-thione reacts with 3-diazo-2,2,4,4-tetramethylthietane or 3-diazo-2,2,4,4-tetramethylpentane to give the corresponding thiadiazoline which loses nitrogen to give the corresponding thiirane which in turn is desulfurized with a phosphorus(III) compound giving "tied-back" derivatives of tetra-*t*-butylethene (Scheme 17) <84CB277>. 2,2,4,4-Tetramethyl-3-diazothietane 1,1-dioxide undergoes cycloaddition with 2,2,4,4-tetramethyl-3-thietanethione 1,1-dioxide (Scheme 5) <84JCS(P1)2457>. 2-Isopropylidene-4,4-dimethyl-3-thietanone forms a Diels-Alder adduct with tetrachloro-*o*-quinone (Scheme 6) <82JOC4429>.

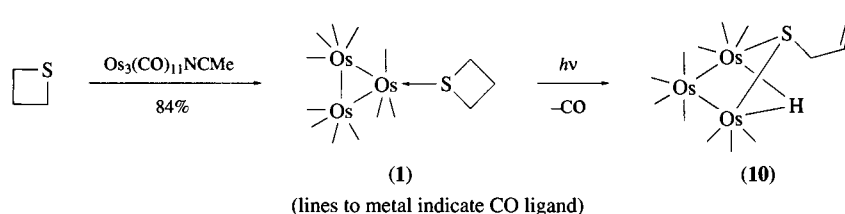


Scheme 17

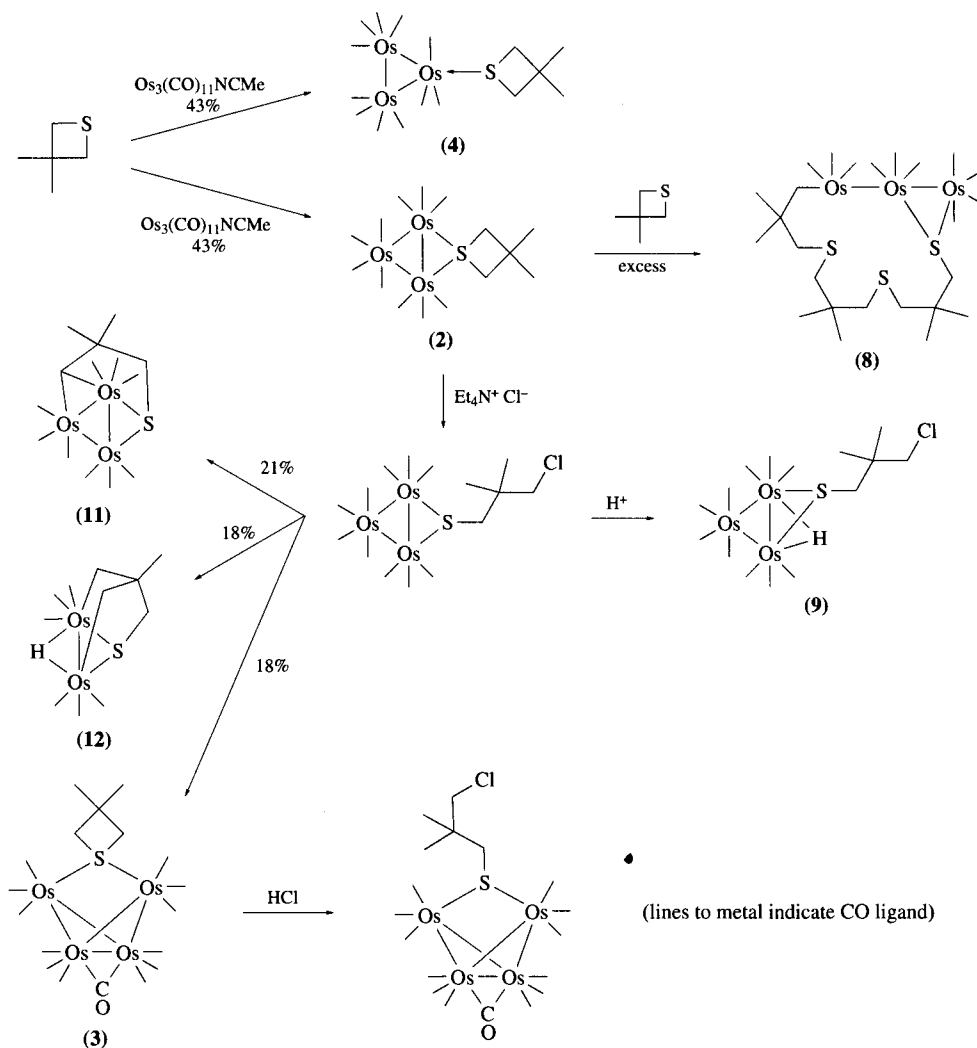
1.24.6.7 Reactions with Metals, Metal Complexes and Surfaces

Ring-opening reactions are thought to be a key step in desulfurization of cyclic thioethers, the principal sulfur-containing contaminants of fossil fuels. These reactions are promoted by metal complexes and molybdenum surfaces. Strained, small-ring thioethers such as thietanes exhibit a greater tendency to undergo ring opening and desulfurization and have therefore been the subject of a number of studies involving metal complexes and surfaces <95CRV2587>. In 1990, the first structural characterization of a thietane-metal complex appeared, namely $\text{Os}_3(\text{CO})_{11}[\text{S}(\text{CH}_2)_3]$ (**1**), formed from reaction of thietane with $\text{Os}_3(\text{CO})_{11}(\text{NCMe})$ (Scheme 18) <90OM1718, 92OM2281>. The ligand occupies an equatorial coordination site in the cluster and is not significantly different from the structure that it exhibits in the gas phase (e.g., a dihedral angle of 28°). 3,3-Dimethylthietane forms a similar complex, $\text{Os}_3(\text{CO})_{11}[\text{S}(\text{CH}_2)_2\text{CMe}_2]$ (**4**) <91JA1619>. When 3,3-dimethylthietane reacts with $\text{Os}_3(\text{CO})_{10}(\text{NCMe})_2$, the μ -bridged thietane complex $\text{Os}_3(\text{CO})_{10}[\mu\text{-S}(\text{CH}_2)_2\text{CMe}_2]$ (**2**) is formed. Here the thietane serves as a bridging ligand donating four electrons, two from each sulfur (Scheme 19) <91JA1619>.

With excess 3,3-dimethylthietane, complex (**2**) forms the trisulfur complex $\text{Os}_3(\text{CO})_{10}[(\mu\text{-}$



Scheme 18

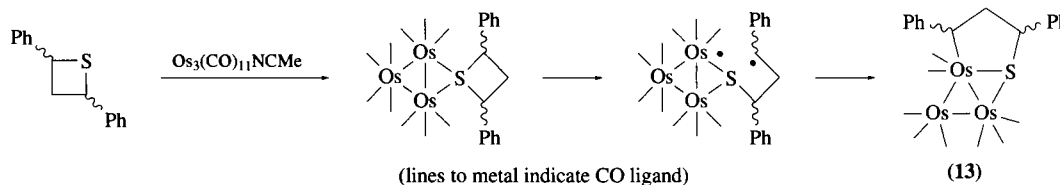


Scheme 19

SCH₂CMe₂CH₂)] (**8**), presumably formed by nucleophilic ring opening of (**2**) <91JA1619>. With [Et₄N]⁺Cl⁻, (**2**) yields after acidification the complex Os₃(CO)₁₀[μ-SCH₂CMe₂CHCl](μ-H) (**9**), which contains a chloroneopentanethiolato ligand thought to be formed by nucleophilic ring opening by chloride ion (Scheme 19). A mixture of 3,3-dimethylthietane and [Et₄N]⁺Cl⁻ showed no observable reaction after 48 h at 25°C. Consequently, the enhancement of the opening of the thietane ring in complex (**2**) can be attributed to the removal of electron density from the sulfur atom via σ-donation of the two lone pairs of electrons to the metal atoms, which in turn makes the adjacent carbon atoms more susceptible to nucleophilic attack (see above examples of ring opening on thietanium ions) <91OM2539>. The thietane complex (**1**) undergoes photoassisted ring opening with loss of CO forming Os₃(CO)₁₀[(μ-SCH₂CH=CH₂)(μ-H)] (**10**), also formed by reaction of Os₃(CO)₁₀(NCMe)₂ with 2-propenethiol (Scheme 18) <90OM1718>.

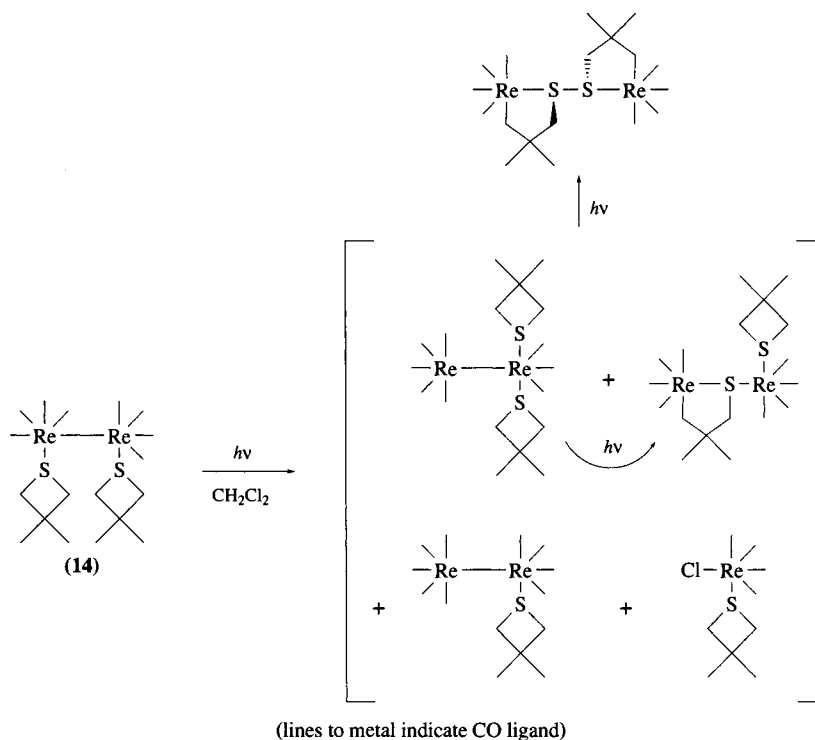
Complex (**2**), upon heating to 97°C, loses CO to give the three complexes Os₃(CO)₉[μ₃-S(CH₂CMe₂CH)](μ-H) (**11**), Os₂(CO)₆[μ-S(CH₂)₃CMe](μ-H) (**12**), and Os₄(CO)₁₂(μ-CO)[μ-S(CH₂)₂CMe₂] (**3**). Decarbonylation followed by C—S and C—H bond cleavage gives (**11**); decarbonylation followed by C—S cleavage and C—H activation and cluster fragmentation gives (**12**); capture of the Os(CO)₃ group by (**2**) gives (**3**). Compound (**3**) undergoes ring opening with hydrogen chloride giving an adduct structurally similar to compound (**9**) (Scheme 19) <90OM2651, 92OM2016, 92OM3129>. With Os₃(CO)₁₁(NCMe), 2,4-diphenylthietane gives a 1:1 mixture of *cis*- and *trans*-Os₃(CO)₁₀[μ-SC(H)PhCH₂C(H)Ph] (**13**), consistent with thermal ring opening with loss of stereochemistry via a diradical process (Scheme 20) <92OM103>. Ring opening of the *trans*-2,4-dimethyl-

thietane complex $\text{Os}_3(\text{CO})_{10}[\mu\text{-trans-SC(H)MeCH}_2\text{C(H)Me}]$ with a variety of nucleophiles gave inversion of stereochemistry at the thietane C2 (or C4), as expected for an $\text{S}_{\text{N}}2$ reaction <92OM1460>.



Scheme 20

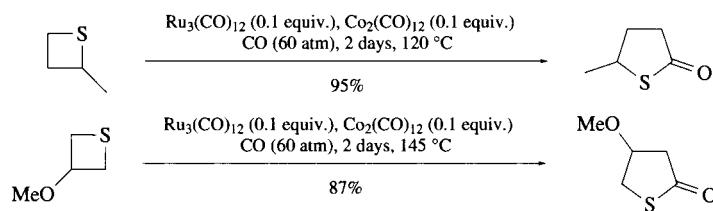
Reactions of thietane and 3,3-dimethylthietane with the rhenium complex $\text{Re}_3(\text{CO})_{10}(\text{NCMe})_2(\mu\text{-H})_3$ are quite similar to the reactions seen with osmium, yielding the complexes $\text{Re}_3(\text{CO})_{10}[\mu\text{-S(CH}_2)_3](\mu\text{-H})_3$ and $\text{Re}_3(\text{CO})_{10}[\mu\text{-S(CH}_2)_2\text{CMe}_2](\mu\text{-H})_3$, respectively <92OM3794>. The latter complex was characterized by x-ray crystallography. This complex reacts with halide ions and trimethylamine to give thietane ring-opened adducts. 3,3-Dimethylthietane reacts with ruthenium carbonyls giving a ruthenium complex structurally similar to tetraosmium complex (3) <90MI 124-03>. Manganese complexes of the type $\text{Mn}_2(\text{CO})_8[\mu\text{-S(CH}_2)_2\text{CMe}_2]$ and $[\text{Mn}(\text{CO})_3(\text{S(CH}_2)_2\text{CMe}_2)(\mu\text{-Cl})]_2$ have been prepared from 3,3-dimethylthietane and have been characterized by x-ray crystallography <92OM4104>. The formation and photochemistry of the dirhenium-thietane complex 1,2- $\text{Re}_2(\text{CO})_8\text{-S(CH}_2)_2\text{CMe}_2$ (14) has been reported (Scheme 21) <91JA9004>.



Scheme 21

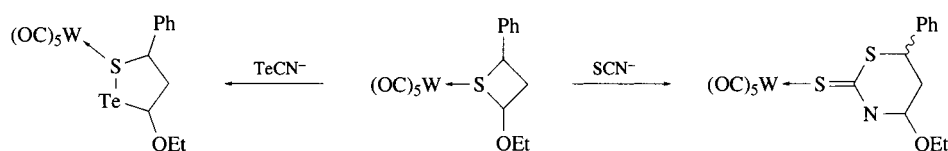
Various rhodium(I) and iridium(I) complexes of thietane have been prepared and characterized <83JOM(241)77, 83JOM(251)369, 84JCS(D)2665, 84MI 124-01, 85JOM(293)115>. Thietane reacts with $\text{Pd}_2(\mu\text{-Cl})_2\text{Cl}_2(\text{PMe}_3)_2$ at room temperature affording adduct *trans*- $\text{Pd}_2\text{Cl}_2(\text{PMe}_3)_2[\text{S(CH}_2)_3]$, which on warming undergoes nucleophilic ring opening giving *cis*- $\text{Pd}_2\text{Cl}_2(\mu\text{-SCH}_2\text{CH}_2\text{CH}_2\text{Cl})(\mu\text{-Cl})(\text{PMe}_3)_2$ in 56% yield <91JA5060>. Thietanes undergo regiospecific carbonylation and ring expansion to γ -thiobutyrolactones (2-thiolanones) with CO in the presence of cobalt and ruthenium carbonyls as catalysts (Scheme 22) <89JOC20, 92OM3422, 94AG(E)1748>. Compounds derived from the reaction of thietanes with osmium carbonyls also yield γ -thiobutyrolactones under forcing conditions <92OM3422>.

Thietanes and Thietes: Monocyclic



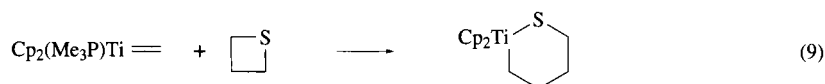
Scheme 22

Pentacarbonyl tungsten coordinated thietanes undergo a number of interesting reactions including insertion of tellurium from TeCN^- to form a tellurathiolane complex $\langle 92\text{CC1050} \rangle$, and insertion of the cyano groups of SCN^- and SeCN^- , ultimately giving a thiazinthione and selenazinthione complex, respectively (Scheme 23) $\langle 93\text{ZN(B)1613} \rangle$. Highly energetic, sterically nondemanding and coordinatively unsaturated atomic molybdenum reacts with thietane to give propylene (45.2%), cyclopropane (3.6%), ethylene (1.4%) and propane (1.7%) $\langle 84\text{JOC4728} \rangle$. The desulfurization of thietane on the single-crystal surface ^{110}Mo has been investigated in detail. Of particular interest is the formation of cyclopropane, which occurs at 190 K with an energy barrier of ca. 13 kcal mol $^{-1}$. In the presence of deuterium atoms on the surface, thietane yields only cyclopropane- d_0 , showing that the cyclopropane is produced in an intramolecular process. Other products formed at higher temperature include propane, propene, and hydrogen. In the case of thiolane, no intramolecular elimination occurs. The desulfurization reactions of thietane are uniformly 18 kcal mol $^{-1}$ more exothermic than the analogous reactions of thiolane, an effect which can be attributed to the enhanced ring strain in thietane of 19 kcal mol $^{-1}$, compared to a ring strain of 2 kcal mol $^{-1}$ in thiolane $\langle 87\text{JA3872}, 88\text{ACR394} \rangle$. Raney nickel desulfurization of 2-isopropylidene-4,4-dimethyl-3-thietanone gives 2,5-dimethylhex-2-en-4-one in low yield $\langle 82\text{JOC4429} \rangle$. Examples of desulfurization of thietane and thiete derivatives with Raney nickel have been summarized in CHEC-I $\langle 84\text{CHEC-I(7)432} \rangle$.



Scheme 23

Titanocene methyldiene trimethylphosphine complex inserts into thietane forming a 2-titanathiane (Equation (9)) $\langle 90\text{OM1650} \rangle$. Germathiones, formed by triethylamine- $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ induced decomposition of cyclogermathianes $(\text{R}_2\text{GeS})_3$, undergo insertion into thietane affording 2-germa-1,3-dithianes $\langle 83\text{JOM(246)227} \rangle$. Ultrasonically dispersed potassium (UDP) cleaves the carbon-sulfur bond of thietane S,S -dioxide and the resulting sulfinate can be alkylated directly with an electrophile such as methyl iodide to give the corresponding open chain sulfone, for example methyl n -propyl sulfone, in good yield $\langle 85\text{TL4495}, 91\text{TL3551} \rangle$.



1.24.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

With concentrated HCl, 3,3-diethoxythietane 1,1-dioxide undergoes hydrolysis to 3-thietanone 1,1-dioxide. The enol form of the latter compound undergoes O -acetylation with acetic anhydride (Scheme 15) $\langle 82\text{SUL79} \rangle$. 3-Aminothietane (RNH_2) reacts with chlorosulfonic acid followed by sodium hydroxide to afford the corresponding sodium sulfamate, RNHSO_3Na $\langle 90\text{AP(323)317} \rangle$. 3- N,N -Dimethylamino-2-(trimethylsilylmethyl)thietane 1,1-dioxide is oxidized at nitrogen with hydrogen peroxide to an amine oxide which on Cope elimination affords 4-[(trimethylsilyl)methyl]-2H-thiete 1,1-dioxide (Scheme 4) $\langle 86\text{CB257} \rangle$; analogous reactions are reported (Scheme 16) $\langle 83\text{JOC4852},$

87JOC695>. Various reactions of 2,2,4,4-tetramethyl-3-thietanone hydrazone 1,1-dioxide, 2,2,4,4-tetramethyl-3-diazothietane 1,1-dioxide and 2,2,4,4-tetramethyl-3-thietanethione 1,1-dioxide are described (Scheme 5) <84JCS(P1)2457> as is the Bamford–Stevens reaction of the tosylhydrazone of 2-isopropylidene-4,4-dimethyl-3-thietanone <86T1989>.

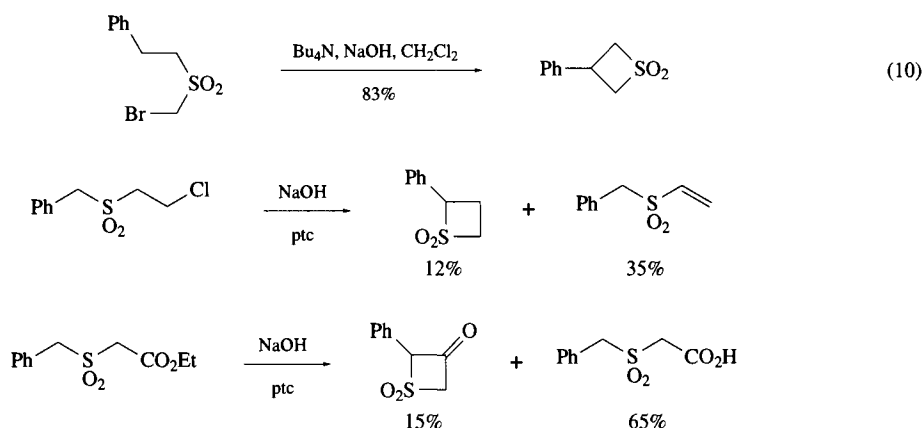
1.24.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING SULFUR ATOMS

Pummerer reactions of 3-thietanone 1-oxides, presumably initiated by electrophilic attack at the sulfoxide oxygen, afford 2-methoxy derivatives, lead to loss of a ring proton to give 2-alkylidene-3-thietanones, or result in ring expansion giving a thiophene derivative <93HCA1251>. The interaction of phenols and anilines with thietane 1-oxide is examined using IR or UV spectroscopy <86JCS(P2)1081>. Thietane 1-oxide is reduced to thietane in 70% yield using a mixture of dichlorodimethylsilane, Me_2SiCl_2 , and zinc dust in dry acetone at 0°C for 10 min <87H(26)2607>. Thietane 1,1-dioxides are reduced to the corresponding thietanes with lithium aluminum hydride (Schemes 16, 30) <83JOC4852, 87JOC695, 93JHC873> or dibal-H <83JOC4852>.

1.24.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

1.24.9.1 Ring Synthesis from Acyclic Precursor of Same Number of Carbons

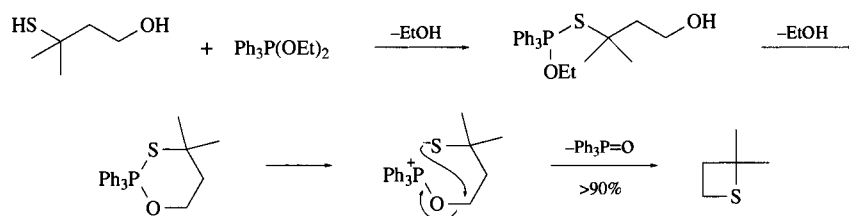
1-Bromomethylsulfonyl 2-phenylethane with the phase transfer catalyst (PTC) 10 mol-% Bu_4NBr , along with 40% NaOH solution, and methylene chloride, gives 3-phenylthietane 1,1-dioxide, via intramolecular cyclization of the benzyl anion rather than the expected Ramberg–Bäcklund product, which would require abstraction adjacent to the sulfonyl group (Equation (10)) <83LA98>. Similarly, benzyl 2-chloroethyl sulfone reacts with 50% aqueous NaOH under PTC conditions giving 2-phenylthietane 1,1-dioxide (12% yield) along with greater amounts of 1,2-elimination product, benzyl vinyl sulfone (35%). In a similar manner, ethyl 2-(α -toluenesulfonyl)acetate gives 2-phenyl-3-thietanone 1,1-dioxide (15%) along with greater amounts of ethyl 2-(α -toluenesulfonyl)acetic acid (65%) (Scheme 24) <91PS(59)149>.



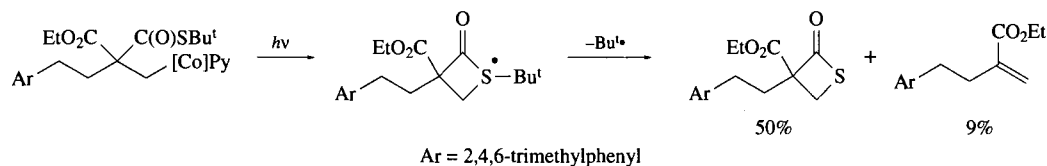
Scheme 24

Diethoxytriphenylphosphorane, at -25°C , converts 4-thio-4-methylbutanol into 2,2-dimethylthietane in >90% yield (Scheme 25) <87PS(31)59>. An alternative reagent that can be used for this purpose is 2,2,2-triphenyl-4,5-(2',2''-biphenylene)-1,3,2-dioxaphospholane <86JOC4473>. Formation of thietanes by ring closure processes involving free radicals is rare. An example of this approach to 2-thietanones has been described wherein a primary radical, generated by irradiation of a cobaloxime, displaces a *t*-butyl radical in a *t*-butylthioester (Scheme 26) <87CL409, 88CL199, 88JA4647>. Irradiation of *N*-monosubstituted α,β -unsaturated thioamides gives iminothietanes via intramolecular cyclization, possibly by way of aminothietes <92JOC2419>. Thietan-2-ones can be prepared by treatment of β -thioacids with $\text{Bu}^t\text{C}(\text{O})\text{Cl}$ <92JCS(P1)1215>, 1,3-dicyclohexylcarbodiimide (DCC)

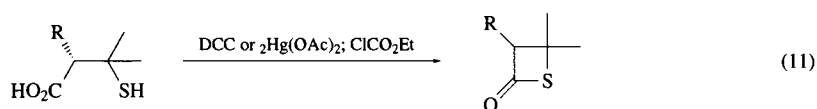
or by treatment of the double mercury salt of β -thioacids with methyl chloroformate (Equation (11)) <90JCS(P2)1559>. Mitsunobu reaction of 2-hydroxythioamides affords β -thioiminolactones in quantitative yield (Equation (12)) <84JA3876>.



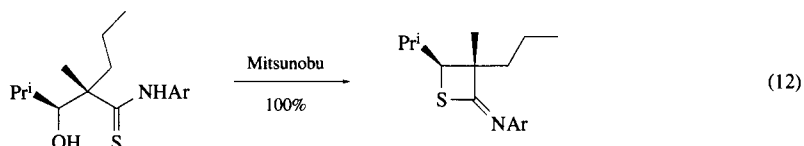
Scheme 25



Scheme 26

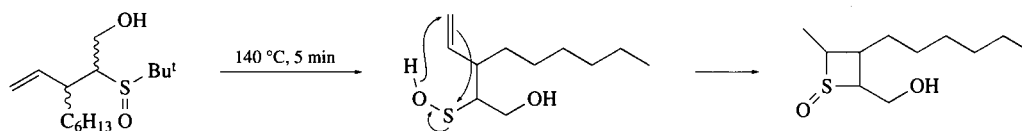


(11)

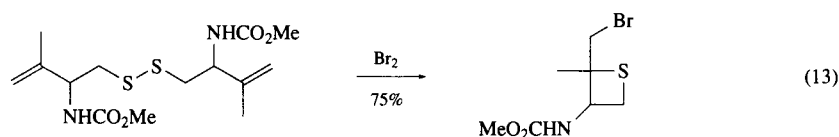


(12)

The conversion of 3-thiopropanal to 2-thietanol in the gas phase or in solution, as previously claimed, has been ruled out based on IR and photoelectron studies of the former molecule <84JCS(P2)609>. The thietane rings in thietanoprostanoids and their precursors have been prepared via intramolecular sulfenic acid-alkene addition. A thietane *S*-oxide is the immediate product of these useful cyclizations (Scheme 27) <82JCS(P1)1325, 82JCS(P1)1333>. A related electrophilic cyclization occurs in the reaction of bis[2-(*N*-carbomethoxy)amino-3-methylbut-3-enyl] disulfide with bromine giving 2-bromomethyl-2-methyl-3-(*N*-carbomethoxy)aminothietane in 75% yield (Equation (13)) <87CC1577>.



Scheme 27

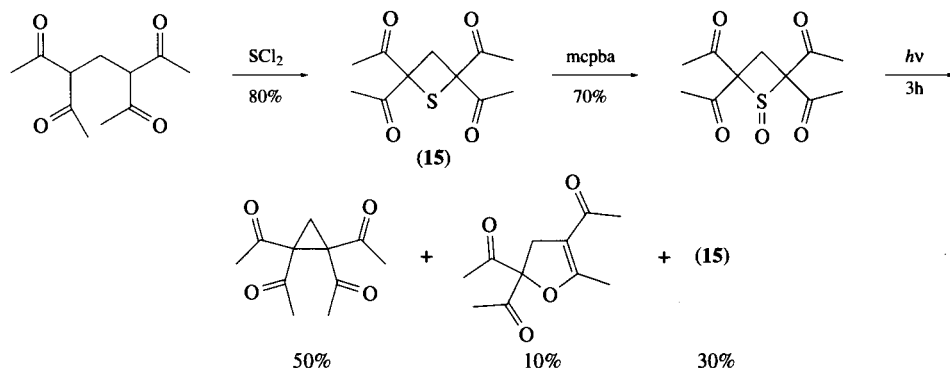
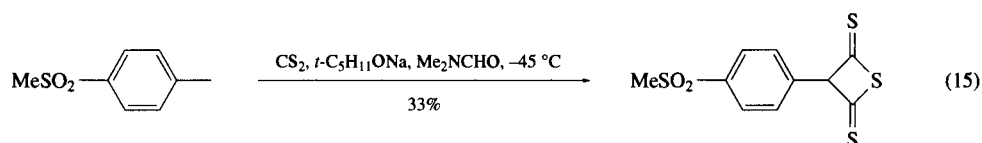
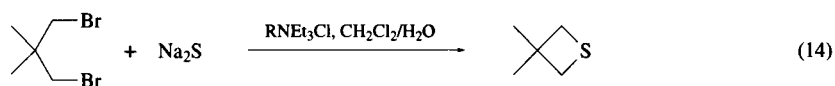


(13)

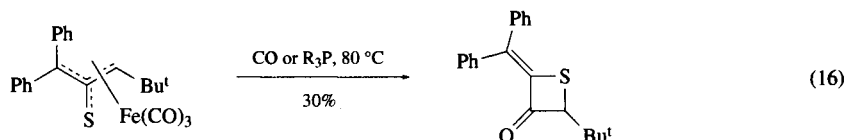
1.24.9.2 Ring Synthesis via Formation of Two Bonds

1.24.9.2.1 From [3 + 1] atom fragments

A number of thietanes, including those ring substituted in the 3-position, are readily prepared by treatment of substituted 1,3-dibromopropanes with sodium sulfide in the presence of a phase transfer catalyst (Equation (14)) <82S582> or by using dimethyl sulfoxide as solvent <85CPB5048>. A novel synthesis has appeared of thietan-2,4-dithiones. These previously unknown compounds are formed when methyl *p*-tolyl sulfone and related *p*-tolyl derivatives are refluxed with excess carbon disulfide in the presence of sodium 1,1-dimethylpropanolate in DMF (Equation (15)) <82JCR(S)256>. 1,1,3,3-Tetraacylpropanes react with sulfur dichloride giving the corresponding 2,2,4,4-tetraacylthietanes (e.g. (15)) in 60–85% yield (Scheme 28) <90MI 124-01, 90MI 124-02>. On thermolysis in the presence of CO, (1-*t*-butyl-3,3-diphenyl-2-thioallyl)iron tricarbonyl gives the carbonyl insertion product 2-*t*-butyl-4-(diphenylmethylidene)thietan-3-one in yields up to 30% (Equation (16)) <92OM1506>. Reaction of methylene-interrupted dienes with MeSSMe/I₂ gives thietanes <94TL5575>.



Scheme 28

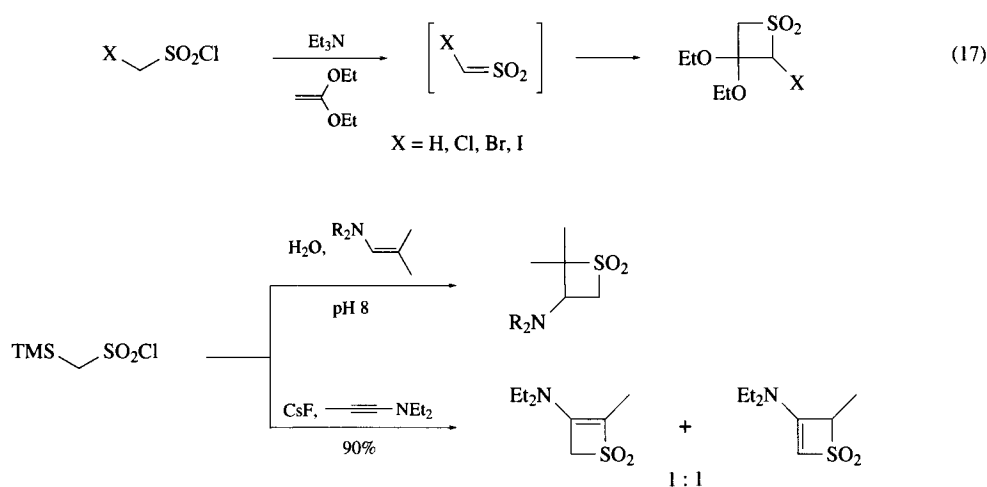


1.24.9.2.2 From [2 + 2] atom fragments

Four-membered rings are routinely prepared by thermal and photochemical cycloaddition reactions of 2π -electron species. Thietane derivatives are formed by [2 + 2] cycloaddition reactions of thioketenes, thioketenes, isothiocyanates, sulfenes and iminosulfenes with alkenes, enamines, allenes, ketenes, keteneacetals, ketenimines, keteniminylidetriphenylphosphoranes, and alkynes.

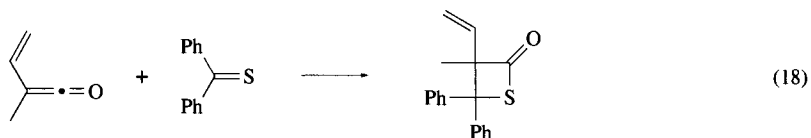
Treatment of a mixture of triethylamine, ketene diethyl acetal and methanesulfonyl chloride or

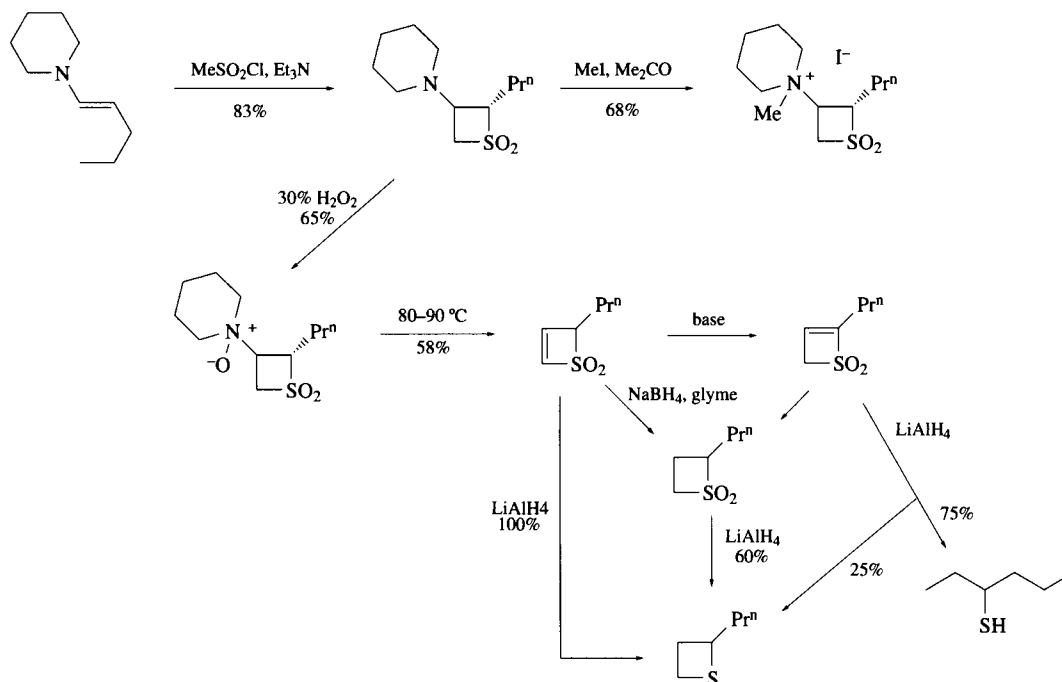
a halomethanesulfonyl chloride ($\text{XCH}_2\text{SO}_2\text{Cl}$, $\text{X} = \text{H}, \text{Cl}, \text{Br}, \text{I}$), affords 3,3-diethoxythietane 1,1-dioxide or 3,3-diethoxy-2-halothietane 1,1-dioxide in 25–83% yield (Equation (12)) $\langle 82\text{SUL}79 \rangle$. Reaction of sulfene with (*E*)-1-(*N,N*-dimethylamino)-3-trimethylsilyl-1-propene affords *N,N*-dimethylamino-2-(trimethylsilylmethyl)thietane 1,1-dioxide (Scheme 4) $\langle 86\text{CB}257 \rangle$. Sulfene smoothly adds to *N,N*-dimethyl-*N*-(1-ferrocenylvinyl)amine giving a thietane which can be converted into 3-ferrocenyl-2*H*-thiete and its 1,1-dioxide (Scheme 16) $\langle 87\text{JOC}695 \rangle$. Sulfene, generated in water from (trimethylsilyl)methanesulfonyl chloride reacts with enamines in the normal manner to give moderate yields of the thietane 1,1-dioxides via the intermediacy of sulfene (Scheme 29) $\langle 93\text{JOC}3429 \rangle$. Sulfene can also be generated from (trimethylsilyl)methanesulfonyl chloride by fluorodesilylation and trapped with enamines or ynamines to give thietane or thiete 1,1-dioxides $\langle 82\text{TL}4203 \rangle$. Bis(trifluoromethyl)sulfene, generated in solution by treating $(\text{Me}_2\text{N})_3\text{S}^+ \text{C}(\text{CF}_3)_2\text{SO}_2\text{F}$ with silicon tetrafluoride or boron trifluoride, undergoes [2 + 2] cycloaddition with moderately electron-rich monoalkenes and dienes ([4 + 2] cycloaddition is also seen in the latter case). The cycloaddition to α -methylstyrene is both regiospecific and stereospecific $\langle 87\text{JA}4982 \rangle$.



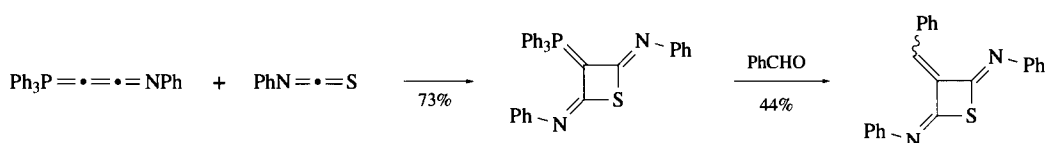
Scheme 29

Thietane 1,1-dioxides from sulfene additions can serve as precursors to reduced thietanes although removal of nitrogen substituents associated with the original enamine starting materials through Hofmann or Cope elimination is usually required (Scheme 30) $\langle 93\text{JHC}873 \rangle$. Addition of thioacetone to *in situ* generated ketene 2-acetoxy-1-propene-1-one (from 2-acetoxypropanoyl chloride and triethylamine) gives 3-hydroxy-3,4,4-trimethylthietan-2-one, also available from photochemical [2 + 2] cycloaddition between thiophosgene ($\text{S}=\text{CCl}_2$) and 3-methyl-2-trimethylsiloxy-2-butene $\langle 91\text{SL}717, 92\text{JCS}(\text{P}1)1215 \rangle$. Thioacetone also gives thietanes with tetracyanoethylene, fumaronitrile, and diethyl fumarate $\langle 86\text{JA}3811 \rangle$. Hexafluorothioacetone adds to perfluoroisobutylene forming 3,3-difluoro-2,2,4,4-tetrakis(trifluoromethyl)thietane $\langle 89\text{IZV}1261 \rangle$. Vinylmethylketene adds to thiobenzophenone in a [2 + 2] process to give a single 2-thietanone (Equation (18)) $\langle 87\text{JOC}3289 \rangle$. On ultraviolet irradiation, thioketones undergo [2 + 2] addition to keteneacetals $\langle 87\text{TL}2701 \rangle$. Allenes react with 2,4,6-tri-(*t*-butyl)thiobenzaldehyde to give 2-alkylidenethietanes in 75–95% yield $\langle 84\text{TL}873 \rangle$. Based upon studies of the reaction of substituted thiobenzophenones with phenylallene it is concluded that the reaction proceeds via a 1,4-diradical-mediated ($\pi 2_s + \pi 2_s + \pi 2_s$)-mechanism $\langle 87\text{JCS}(\text{P}2)907 \rangle$. Isothiocyanates react with ketene acetals to form 2-iminothietanes (Equation (19)) $\langle 82\text{CB}3340 \rangle$ and with keteniminylidenetriphenylphosphoranes to form 2,4-bisiminothietanes (Scheme 31) $\langle 86\text{CL}1529 \rangle$. Thietane complexes are formed from vinyl ethers and pentacarbonyl tungsten coordinated thiobenzaldehyde by regiospecific addition of the $\text{C}=\text{C}$ double bond of the former compound to the $\text{C}=\text{S}$ bond of the latter compound (Equation (20)) $\langle 92\text{CC}563 \rangle$.

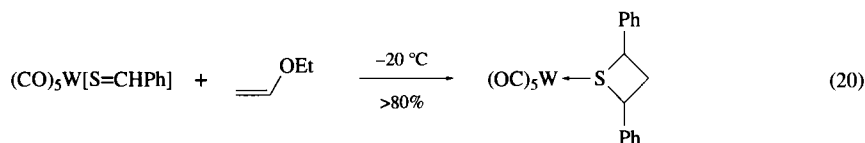
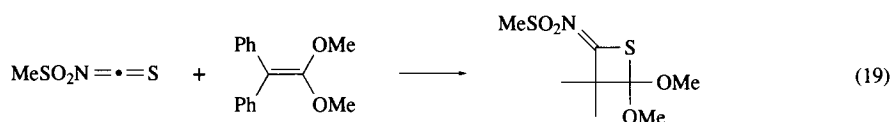




Scheme 30



Scheme 31

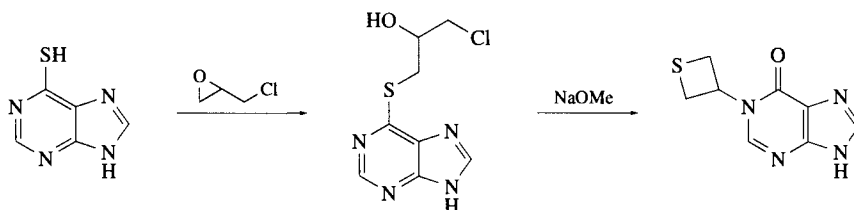
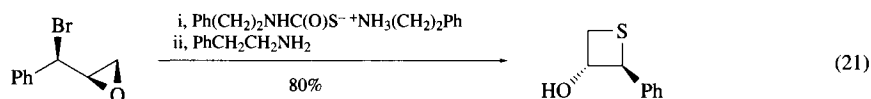


1.24.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

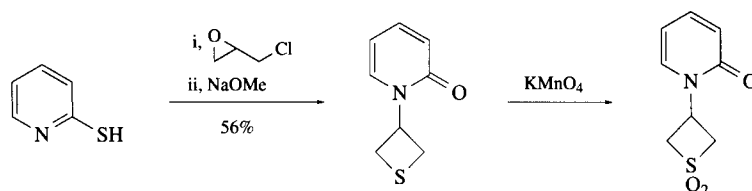
1.24.10.1 Formation from Three-membered Heterocycles

A number of thietane syntheses are based on ring expansion of oxirane or thiirane derivatives. Thus, 2-(1-haloalkyl)oxiranes have been converted into 3-thietanols with monothiocarbamic acid salts (Equation (21)) $\langle 92\text{CL}1655 \rangle$. Reaction of 6-thiopurine with NaHCO_3 and epichlorohydrin followed by treatment of the resulting chlorohydrin derivative with sodium methoxide led to 6-oxo-1-(thietan-3-yl)-purine by an interesting rearrangement (Scheme 32) $\langle 90\text{TL}1373 \rangle$. Related 3-aminothietanes could also be prepared by this method (Scheme 33) $\langle 92\text{JOC}6335 \rangle$. A novel synthesis of thietanes from thiiranes involves use of 3-chloroallyllithium (Equation (22)) $\langle 85\text{S}1069 \rangle$. Ring expansion occurs in the quantitative rearrangement of the *S*-methyl *trans*-2,3-di-*t*-butylthiiranium and di-*t*-butyl thiirenium ions into thietanium and thietium ions, respectively, all in the form of

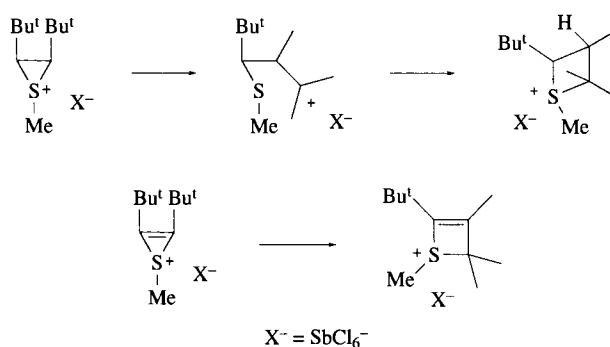
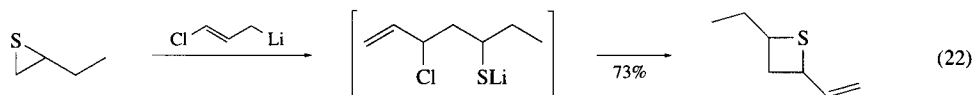
hexachloroantimonate salts. These unusual four-membered ring sulfonium salts are stable and are fully characterized (Scheme 34) <91JA6600, 88JA6900, 93JA4527>. Another example of a ring-expansion synthesis of thietanes is the photochemical conversion of 1,2,3,4-pentatetraene episulfides (**16**) and (**17**) which give 2-cumulenyl-3-thietanethiones (Scheme 35) <89TL4271>.



Scheme 32

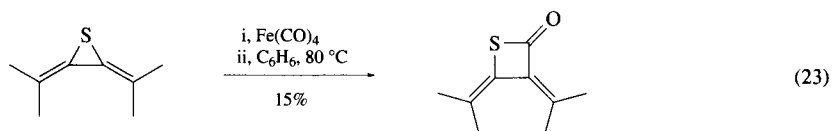


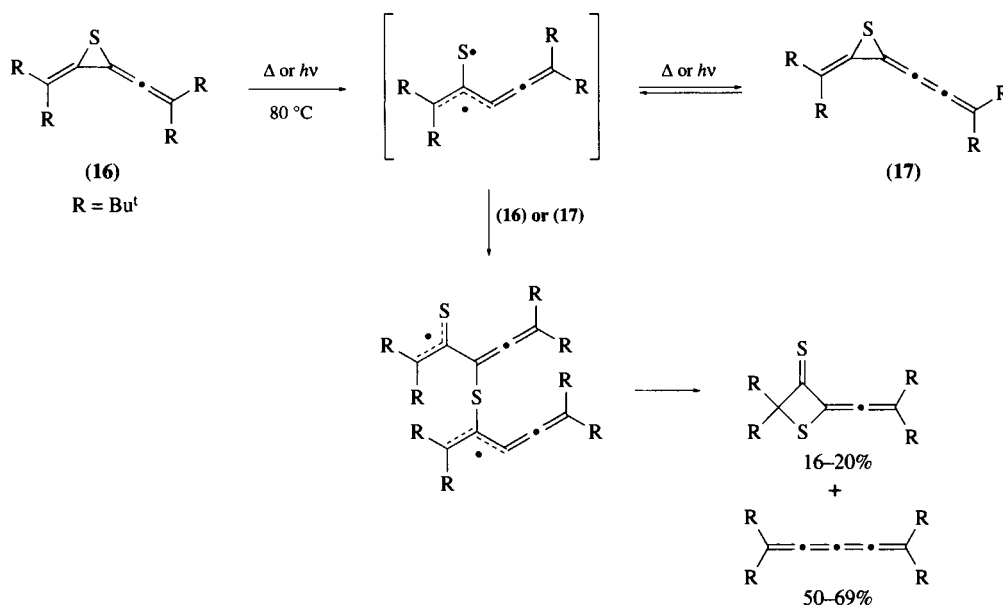
Scheme 33



Scheme 34

Treatment of 2,3-bis(isopropylidene)thiirane with $Fe(CO)_4$ followed by refluxing in benzene affords 3,4-bis(isopropylidene)thietan-2-one (Equation (23)) <94OM741>.

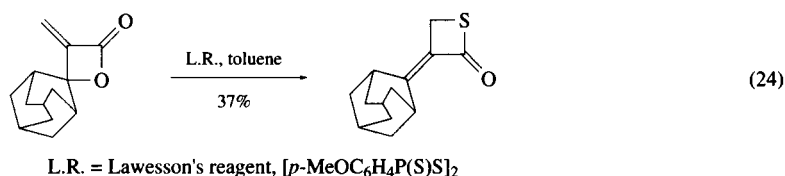




Scheme 35

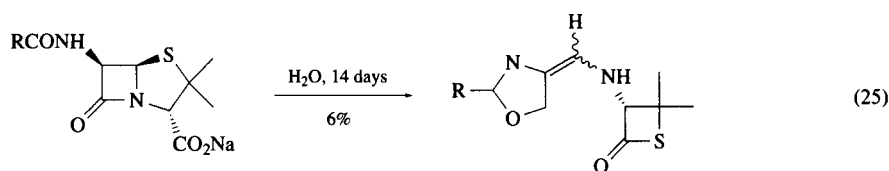
1.24.10.2 Formation from Four-membered Heterocycles

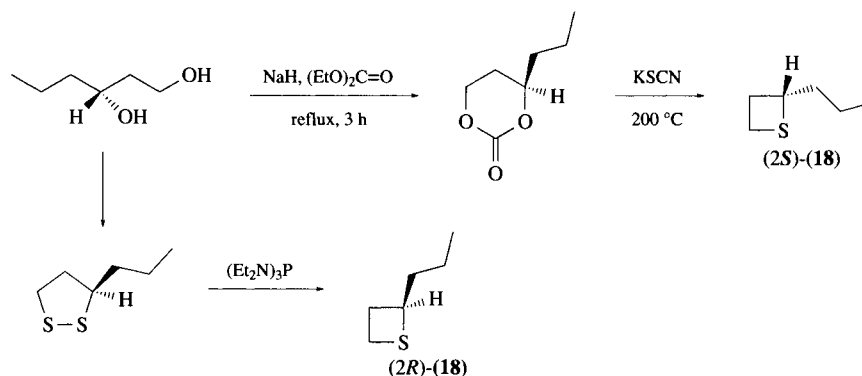
Reaction of α -methylene β -lactones with Lawesson's reagent gives the corresponding α -methylene β -S-thiolactones (α -methylene 2-thietanones; Equation (24)) <90CB1449, 91JOC5782>.



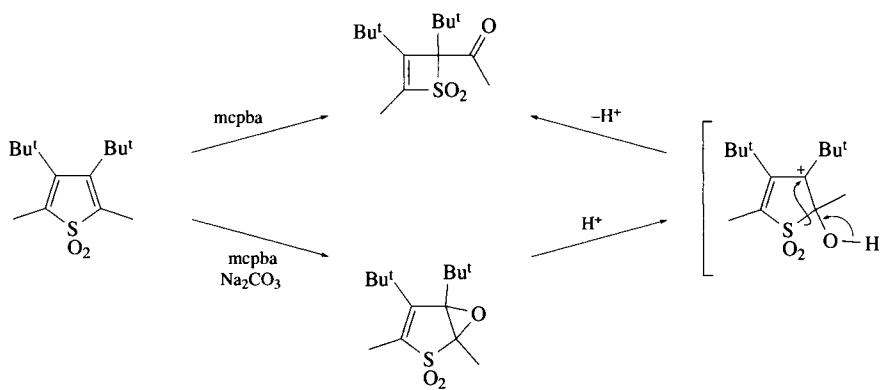
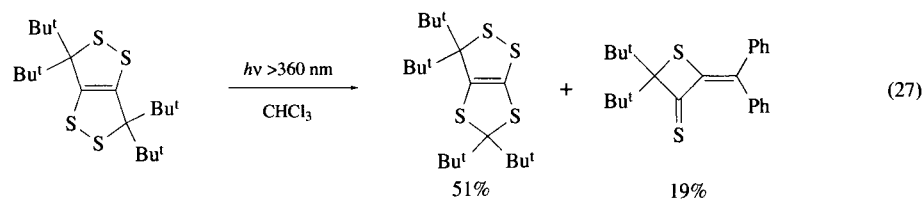
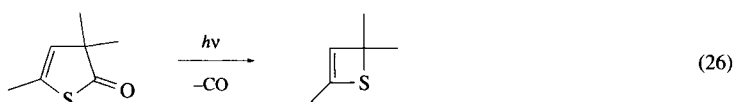
1.24.10.3 Formation from Five-membered Heterocycles

Stereospecific syntheses are reported for (2*R*)- and (2*S*)-2-propylthietane ((2*R*)- and (2*S*)-**(18)**), pheromone of the stoat (*Mustela erminea*). Monodesulfurization of (3*R*)-propyl-1,2-dithiolane, prepared from (3*R*)-hexane-1,3-diol of 85% *ee*, with tris(diethylamino)phosphine gave (2*R*)-**(18)** of 81% optical purity (Scheme 36) <82AJC1945>. Monodesulfurization of 3,3,5,5-tetramethyl-1,2-dithiolane-4-one with carbenes derived from diazo compounds gives 2,2,4,4-tetramethyl-3-thietanone in ca. 30% yield <85TL5187>. Deep-seated rearrangement of penicillin derivatives can afford thietan-2-ones (Equation (25)) <90JCS(P2)1559, 88MI 124-01, 89MI 124-01>. Photodecarbonylation of 3,3,5-trimethyl-2(3*H*)-thiophenone gives 2,4,4-trimethylthiete (Equation (26)) <89AG(E)1499>. An unusual ring contraction synthesis of thiete 1,1-dioxides from sterically congested thiophene 1,1-dioxides is reported by Nakayama and co-workers (Scheme 37) <93HAC445>. The formation of 2-alkylidene-3-thietanones by ring contraction is reported <84CHEC-I(7)423, 86T1989>. A 2-alkylidene-3-thietanethione is formed in a novel photochemical process from the fused 1,2-dithiole, 3,3-di-*t*-butyl-3,3'-diphenyl[1,2]dithiolo[5,4-*d*][1,2]dithiole (Equation (27)) <89TL4825>.





Scheme 36



Scheme 37

1.24.10.4 Formation from Six-membered Heterocycles

Conversion of (3*R*)-hexane-1,3-diol to (4*R*)-4-propyl-1,3-dioxan-2-one with diethyl carbonate followed by fusion of the cyclic carbonate ester with KSCN at 200 °C gave (2*S*)-(18) of 90% *ee*. Based on the above results, (18) isolated from the stoat was determined to have an enantiomeric composition of 63(*S*):37(*R*) (Scheme 36) <82AJC1945>. 2*H*,6*H*-Thiin-3-ones on irradiation (350 nm) afford 3-thietanones in 91–96% yield by a process thought to involve a (9-*S*-3) sulfuranylalkyl biradical (Schemes 38, 39) <92HCA2265, 93HCA1251>.



A ring-contraction sequence starting from photochemically generated 3*H*,7*H*-[1,2]oxathiepin-4-ones gives 3-thietanones (Scheme 38) <93HCA1251>.

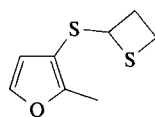
Since the publication of CHEC-I, in 1984, a variety of remarkable new syntheses of thietanes have appeared. However, many of these reactions are of limited general utility. There are a variety of syntheses of thietanes from open chain precursors, most of which are quite specific, as well as numerous syntheses from [2 + 2] processes, which are more general in their utility and scope.

2-*n*-Propylthietane, a volatile malodorous compound in the anal sac secretion of the stoat (*Mustela erminea*) is of interest as a carnivore odor for use in mammal pest control and accordingly its large scale synthesis has been developed. This compound has been found to induce fear responses in some pest herbivores leading to area avoidance and concomitant reduction in damage to vegetation <93JHC873>. A number of publications discuss field trials in controlled-release devices in eliciting avoidance response by gophers, voles, ferrets, and hares. This work represents one of the first

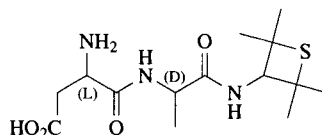
practical utilizations of mammalian semiochemicals in crop protection and wildlife management <84MI 124-02, 88MI 124-02, 89MI 124-02, 90MI 124-04, 90MI 124-05>. A number of other thietanes including *cis*- and *trans*-2,3-dimethylthietane, *cis*- and *trans*-2,4-dimethylthietane, 2-ethylthietane, 2-pentylthietane, *cis*- and *trans*-2-ethyl-3-methylthietane, 2-isopropylthietane, and 2,2-dimethylthietane have all been variously identified in anal gland secretions of the *Mustela* genus mammals, the ferret, polecat, stoat, mink, and weasel <85MI 124-03, 83MI 124-01, 81CZ273, 83CZ267>.

Various thietanoprostanoids have been synthesized and have been found to possess significant thromboxane-like activity on smooth muscle preparations <82JCS(P1)1333>. Dietary administration of thietane significantly increased the styrene oxide hydrolase activity over controls in hepatic microsomes in the liver of the female CD-1 mouse <86MI 124-03>. Among the compounds formed by thermal degradation of thiamin (vitamin B₁) is 2-(2-methyl-3-furylthio)-thietane (**19**), a compound described as having "sulfury, cabbage, meaty, rubbery" sensory properties <B-94MI 124-01>.

Alitame ((**20**), L-aspartyl-D-alanine 2,2,4,4-tetramethylthietanylamide) is patented for use as an artificial sweetener ca. 2000 times as sweet as sucrose. Because of its stability, which is superior to that of the related peptide sweetener aspartame (L-aspartyl-L-phenylalanine methyl ester; 180 times as sweet as sucrose) it is particularly recommended for high-quality reduced calorie sweet baked goods <83USP4411925, 89MI 124-03, B-91MI 124-01>. It is noteworthy that, in contrast to the intense sweetness of L,D-alitame, the L,L-isomer of the dipeptide sweetener is bitter while the D,D-isomer is tasteless. Structure optimization studies showed that the *S*-oxide and *S,S*-dioxide of alitame show reduced sweetness as does the 2,2,4,4-tetramethylcyclobutyl homolog (sweetness relative to sucrose 300–350 ×, 805 ×, and 300 ×, respectively) while the 2,2,4-trimethylthietanylamide shows enhanced sweetness (3900 ×) <B-91MI 124-02>. Both NMR and x-ray crystallography have been used to determine conformations of the alitame isomers which are then related to models used to explain sweetness <91JA3467>. Adaptation (reduction in responsiveness toward a tastant upon repeated exposure) toward alitame is compared to that for other natural and synthetic sweeteners <94MI 124-02>. Methods have been developed for reverse-phase HPLC determination of alitame and other artificial sweeteners in diet food preparations <88MI 124-03>. Another thietane-containing dipeptide sweetener, 300 times as sweet as sucrose, has been described <90JMC1052>.



(19)



(20)

Numerous papers have appeared dealing with aspects of the polymerization of thietane <82MAC2573, 88MAC399, 88MI 124-04>, 3-chlorothietane <82MI 124-01, 83MI 124-02>, 3,3-dimethylthietane <81MAC3371, 84MI 124-03, 88MAC2229, 88MI 124-05, 88MI 124-06, 89MI 124-04, 90MAC1151, 92MI 124-02>, and 3,3-diethylthietane <89MI 124-05>. Polymerization can be achieved under anionic conditions using *n*-butyllithium <84MI 124-03, 88MAC399, 88MAC2229, 89MI 124-04, 89MI 124-05, 90MAC1151>, favoring lower MW polymers ($MW_{av} 6 \times 10^4$), or sodium-naphthalene <82MAC2573, 88MAC399, 88MI 124-04, 88MI 124-05, 89MI 124-04, 89MI 124-05, 90MAC1151>, favoring higher MW polymers ($MW_{av} 1.8 \times 10^5$), or under cationic conditions, using trityl hexafluoroantimonate <81MAC3371>, ethyl trifluoromethanesulfonic anhydride, or boron trifluoride etherate <82MI 124-01>. Triflic acid has been used to initiate polymerization of isobutyl vinyl ether at -40°C in CH_2Cl_2 , the presence of thietane as a nucleophilic moderator leading to formation of star-shaped poly(vinyl ether)-polythietane block copolymers. Thietane has enough ring strain to be polymerized and the activation energy of this polymerization is low enough to allow it to occur at the low temperatures which are generally used for the acid catalyzed vinyl ether polymerizations <94MM1329>. Copolymerization of thietane with the divalent germylene species $\text{Ge}[\text{N}(\text{SiMe}_3)_2]_2$ affords the polymer $-\text{[GeR}_2\text{S}(\text{CH}_2)_3]_n-$, where $\text{R} = \text{N}(\text{SiMe}_3)_2$ <94NKK285>.

ACKNOWLEDGMENT

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1.25

Thietanes and Thietes: Fused-ring Derivatives

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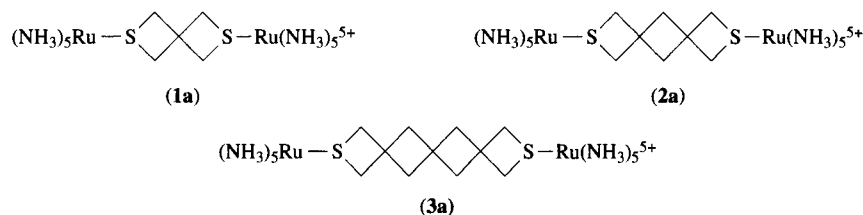
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1.25.1 INTRODUCTION

For the purposes of discussion, “fused” thietanes and thietes include spirocompounds in which the four-membered ring is fused to another ring through a single carbon atom, bridged compounds in which the nonadjacent 2,4-positions of thietane or thiete are bonded to one or more carbon atoms, as well as typical fused rings in which thietane or thiete share their C(2)—C(3) or C(3)—C(4) bond with another ring.

1.25.2 THEORETICAL METHODS

Calculations (CNDO/2) on the ruthenium dinuclear complexes of the dithiaspiro bridging ligands 2,6-dithiaspiro[3.3]heptane (**1**), 2,8-dithiaspiro[3.1.3.1]decane (**2**), and 2,10-dithiaspiro[3.1.1.3.1.1]tridecane (**3**), (**1a**), (**2a**), and (**3a**), respectively, indicate that the highest occupied bonding molecular orbital (HOMO) of each molecule is ideally set up with p_z orbitals on the S and C atoms for “sideways π overlap”, providing a hyperconjugating electron-transfer pathway between the ruthenium atoms bonded to the terminal sulfurs <83IC1124>. The inner-sphere reorganizational energy at zero ionic strength for (**2a**) is 25 kcal mol⁻¹ <89IC3796>. The values of the electron tunneling matrix elements for (**2a**) and (**3a**) have been calculated from Hopfield’s theory <82JA2596>. A semiempirical model approximately reproduces the observed decay of the optical tunneling matrix element with distance in the rigid complexes (**1a**), (**2a**), and (**3a**) <84JA1584>. *Ab initio* SCF calculations using several different basis sets have been carried out on dithiaspiro ligands (**1**), (**2**), and (**3**) and their bis-sulfoxides, affording ionization energies and other calculated values <88JA8343>.



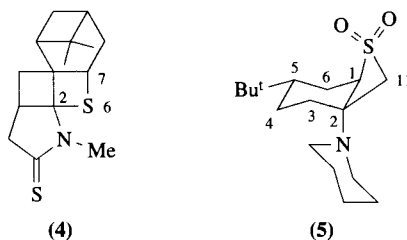
A theoretical and experimental investigation of the cycloaddition of nitrile oxides, nitrones, and diazoalkanes with acyclic vinyl sulfones and thiete 1,1-dioxide has been carried out. The charge-transfer stabilization energy, calculated according to the Klopman–Salem perturbational approach in the CNDO/2 approximation, is able to account for the experimental trends of the isomer ratios <82JCS(P2)95>. Semiempirical SCF–MO calculations, mainly using the MNDO program, have been used to determine the smallest possible change that can be made to the bicyclic ring system of thromboxane A₂ in order to increase its stability. The predicted order of stability is 2,6-dithiabicyclo[3.1.1]heptane > 2-oxa-6-thia-analogue > 6-oxa-2-thia-analogue > 2,6-dioxabicyclo[3.1.1]heptane. This prediction is in qualitative agreement with observations on the stability of synthetic thia analogues of thromboxane A₂ and with the diminished ring strain in thietanes compared to oxetanes <84JCS(P2)1567>. Conformations of 9,11-epithio-11,12-methanothromboxane A₂ in a simulated membrane–water interface have been calculated <89MI 127-01>.

1.25.3 EXPERIMENTAL STRUCTURAL METHODS

1.25.3.1 X-ray Diffraction

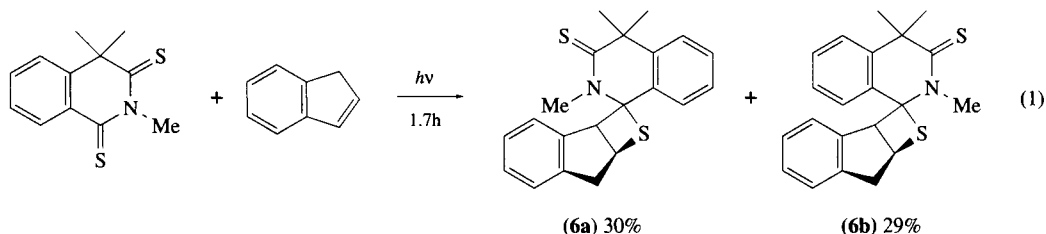
The following x-ray structures have been published: 1-methyl-*exo,exo*-3,5-dichloro-8-thiatricyclo[2.2.1.1.^{2,6}]octane cation <84PS(21)215>; *N*³-[dispiro(fluorene-9,2'-thietane-3',9''-fluorene)-4'-ylidene]-*N*¹,*N*¹-dimethylbenzamidium hexachloroantimonate <91CB2537>; *exo*-7-aza-6-oxa-4-*n*-propyl-3-thiatricyclo[5.4.1.^{1,7}.1^{2,5}]undecane 3,3-dioxide <93JHC873>; and 6,6-diphenyl-4-(mesitylimino)-5-thiaspiro[2.3]hexane <85JOC5368>. X-ray structures are reported for 2-, 3-, and 4-dithiaspirothietane–ruthenium complexes <90JPC2985>. In the crystal structure of highly strained multicyclic fused thietane (**4**) <86CPB1411>, both the five-membered ring containing a nitrogen and the cyclobutane ring fused to the thietane ring are almost planar. In the thietane ring, C(2)—S(6) and S(6)—C(7) bond lengths are 1.83 and 1.88 Å, respectively, while the internal angle C(2)—S(6)—C(7) is 76.7°.

This data is similar to that of a puckered monocyclic thietane. In the crystal structure of 1-(piperidin-1-yl)-4-*t*-butyl-7-thiabicyclo[4.2.0]octane 7,7-dioxide [1α , 4α , 6α] (**5**) the puckering angle, defined as the dihedral angle between the planes C(1)—S—C(11) and C(1)—C(2)—C(11) is 157.7° $\langle 84\text{JHC1065} \rangle$. This value can be compared with the dihedral angles found for monocyclic thietane 1,1-dioxides, which range from 162.1° $\langle 72\text{CSC423} \rangle$ to 170.6° $\langle 73\text{CSC323} \rangle$ to 173.2° $\langle 73\text{CSC499} \rangle$. The cyclohexane ring is considerably flattened along the junction, as shown by the values of the relative torsion angles C(5)—C(6)—C(1)—C(2), 31° , and C(6)—C(1)—C(2)—C(3), 23° .



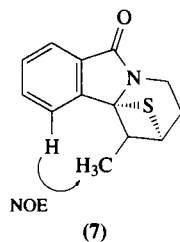
1.25.3.2 NMR Spectroscopy

The ^1H and ^{13}C NMR spectra of the strained bicyclic thietane 5,5,6,6-tetracyano-2-thiabicyclo[2.2.0]hexane has been reported, showing among other features, a long-range proton–proton coupling, $^4J = 1.5 \pm 0.2$ Hz, due to four-bond W-type coupling $\langle 85\text{JOC799} \rangle$. In thiathromboxane A_2 derivatives containing a 2-oxa-6-thiabicyclo[3.1.1]heptane skeleton, bridgehead–bridgehead $^5J = 5$ Hz is seen along with elevated values for bridgehead $^1J_{\text{C-H}}$ of 158–177 Hz $\langle 82\text{TL2883}, 84\text{JOC1554} \rangle$. In *endo*-2-bromo-5-thiabicyclo[2.1.1]hexane and its *S*-oxide and *S,S*-dioxide, the bridgehead–bridgehead proton–proton coupling constants are all in the range of 6.1–6.2 Hz, indicating that the oxidation state of the intervening sulfur is irrelevant in the coupling process. Detailed ^{13}C NMR data is also presented for these compounds $\langle 93\text{HAC33} \rangle$. The 6,6-diphenyl-4-(mesitylimino)-5-thiaspiro[2.3]hexane shows an upfield ^{13}C NMR resonance for C-3 at 47.03 ppm compared to the corresponding value for C-3 at 65.5 ppm in 3,3-dimethyl-4,4-diphenyl-2-(mesitylimino)thietane, consistent with the ring-current model for the anomalous shielding of the cyclopropane moiety $\langle 85\text{JOC5368} \rangle$. The regioisomeric spirothietane products of photocycloaddition of 1,3-dimethyldithiosuccinimide with 2,3-dimethyl-2-butene are distinguished on the basis of their ^{13}C NMR chemical shifts $\langle 86\text{S768} \rangle$. The temperature-dependent ^1H and ^{13}C NMR spectra of 1,4,5,7-tetrahydro-3*H*-2,6-benzodithionin spirothietane are compared to those for spirocyclobutane and oxetane analogues $\langle 91\text{TI417} \rangle$. The stereochemistry of the regioisomeric products (**6a**) and (**6b**) (Equation (1)) from [2 + 2] cycloaddition of 1,2,3,4-tetrahydro-2,4,4-trimethyl-1,3-dithioxoisquinoline with indene are confirmed by analysis of their ^1H NMR spectra.

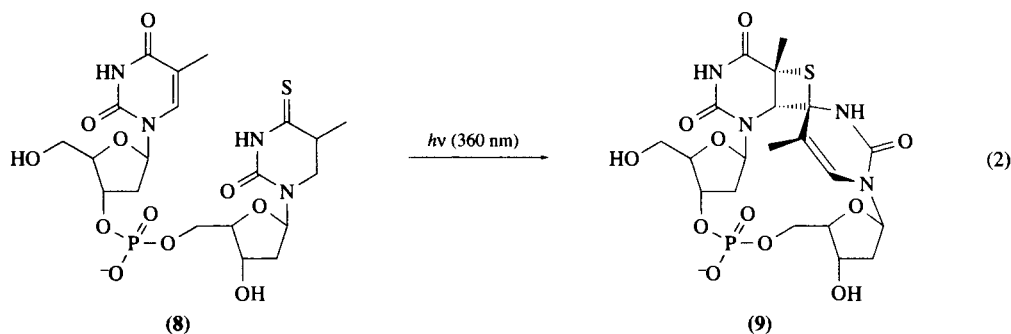


For (**6a**), the *N*-methyl absorption shows an upfield shift at $\delta = 3.36$ ppm compared with that at $\delta = 4.47$ ppm for (**6b**), due to the anisotropic effect of the benzene ring. Furthermore, for the (**6b**) isomer, aromatic protons of the isoquinoline moiety show an upfield shift at $\delta = 6.07$ – 6.90 ppm, indicating that the two benzene rings are close to each other. Thus, (**6a**) is the *anti*-isomer while (**6b**) is the *syn*-isomer $\langle 92\text{S778} \rangle$. The stereochemistry of the intramolecular photocycloaddition product (**7**) of *N*-but-3-enyl thiophthalimide is confirmed on the basis of nuclear Overhauser effect (NOE) analysis $\langle 92\text{CPB585} \rangle$.

The stereochemistry of thietane intermediate (**9**), formed by 360 nm irradiation of thymidyl (3'-5')-4-thiothymidine (**8**) is characterized by 2D phase-sensitive NOESY experiments. The

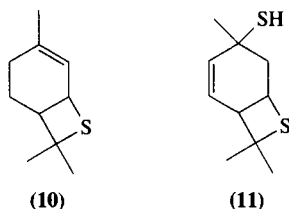


characterization of (9) establishes the stereochemical course of a model reaction leading to (6–4) photoproducts for DNA photodamage mechanistic studies (Equation (2)) <91JA5481>.



1.25.3.3 Mass Spectroscopy

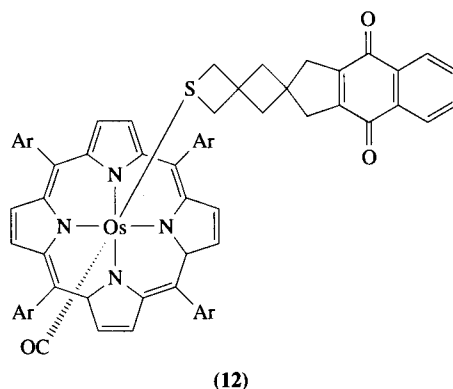
In a GC–MS study of the sulfuration of limonene, the mass spectral fragmentation patterns of bicyclic thietanes (10) and (11), formed by refluxing limonene with elemental sulfur, are reported <86MI 125-01>.



1.25.3.4 UV, Photoelectron, and Pressure Tuning Spectroscopy

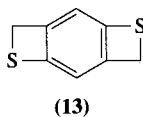
The UV spectrum of 5,5,6,6-tetracyano-2-thiabicyclo[2.2.0]hexane shows a remarkable long wavelength maximum λ_{max} (MeCN) 432 (ϵ 170), 260 (ϵ 158) <85JOC799>. The intervalence transition (IT) bands for the ruthenium spiro binuclears, $(\text{NH}_3)_5\text{Ru}^{\text{II}}-\text{S} \diamond \text{S}-\text{Ru}^{\text{III}}(\text{NH}_3)_5^{5+}$, are at 910 nm (ϵ $43 \pm 2 \text{ M}^{-1} \text{ cm}^{-1}$), 808 nm (ϵ $9 \pm 1 \text{ M}^{-1} \text{ cm}^{-1}$), and 690 nm (ϵ $2.3 \pm 0.7 \text{ M}^{-1} \text{ cm}^{-1}$) for complexes (1a), (2a), and (3a), respectively <82JA2596>. A pressure tuning spectroscopy (PTS) study of the IT band of the ruthenium spiro binuclear (1a), (μ -2,6-dithiaspiro[3.3]heptane)decaamminediruthenium(II, III)hexafluorophosphate in D_2O is reported. A red shift of more than 200 cm^{-1} and a small increase in the oscillator strength of the IT band are observed over a pressure range of 1500 bars <89JA924>. The photoelectron spectra of the series of spiro disulfides (1), (2), and (3), and their disulfoxides have been recorded in order to investigate their electronic structure <83TL2957, 88JA8343>. The ionization potential (in eV) determined for 2,6-dithiaspiro[3.3]heptane (1) are 8.71 (n_s) and 10.04, for the corresponding disulfoxide, 8.75 (n_s), 9.60 (n_s), and 10.45 (π_{SO}), for 2,8-dithiaspiro[3.1.3.1]decane (2), 8.75 (n_s) and 9.45, for the corresponding disulfoxide, 8.78 (n_s), 9.16 (n_s), and 10.10 (π_{SO}), for 2,10-dithiaspiro[3.1.1.3.1.1]tridecane (3), 8.75 (n_s) and 9.45, for the cor-

responding disulfoxide, 8.75 (n_s), 9.00 (n_s), and 10.15 (π_{so}), for thietane, 8.65 (n_s) and 10.7 (n_s), and for thietane 1-oxide, 8.90 (n_s) and 10.1 (π_{so}). It is concluded that, in the disulfoxides, there are substantial through-bond interactions of the sulfur lone pairs, ranging from 0.85 eV for the compound with two rings to 0.25 eV for the compound with four rings. Photoelectron spectra have been obtained for ruthenium dinuclear complexes (**1a**), (**2a**), and (**3a**) (see above) <83IC1124>. Static and time-resolved emission spectroscopy and ultrafast transient absorption measurements have been used to explore the nature of the lowest excited states of the osmium(II) tetratolylporphyrin complex of naphthoquinone–thietane (**12**) <94JA281>.



1.25.4 THERMODYNAMIC ASPECTS

2*H*,5*H*-Benzo[1,2-*b*:4,5-*b'*]bisthiete (4,9-dithiatricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene, (**13**)) functions as a highly reactive bisdiene system, undergoing sequential double ring opening at 90 °C to give diadducts with dienophiles or forming a polymer with a band structure (see below). The carbocyclic system analogous to (**13**), tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene, has a very much higher activation energy for opening the four-membered ring and is therefore unsuitable for repetitive cycloadditions <94AG(E)465>. In predicting the most favorable ring-forming process among several in principle favorable processes using Baldwin's rules, the diminished ring strain of thietanes compared to oxetanes or azetanes has been invoked <76CC734, 76CC736, 85T2737>.

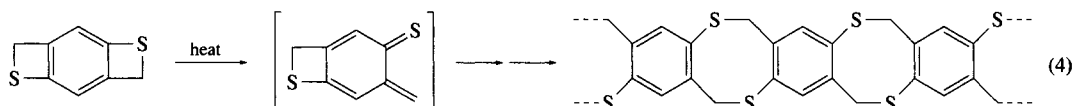
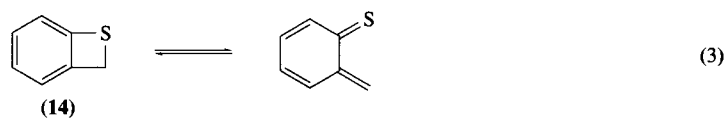


1.25.5 REACTIVITY OF FULLY SATURATED AND PARTIALLY UNSATURATED RINGS

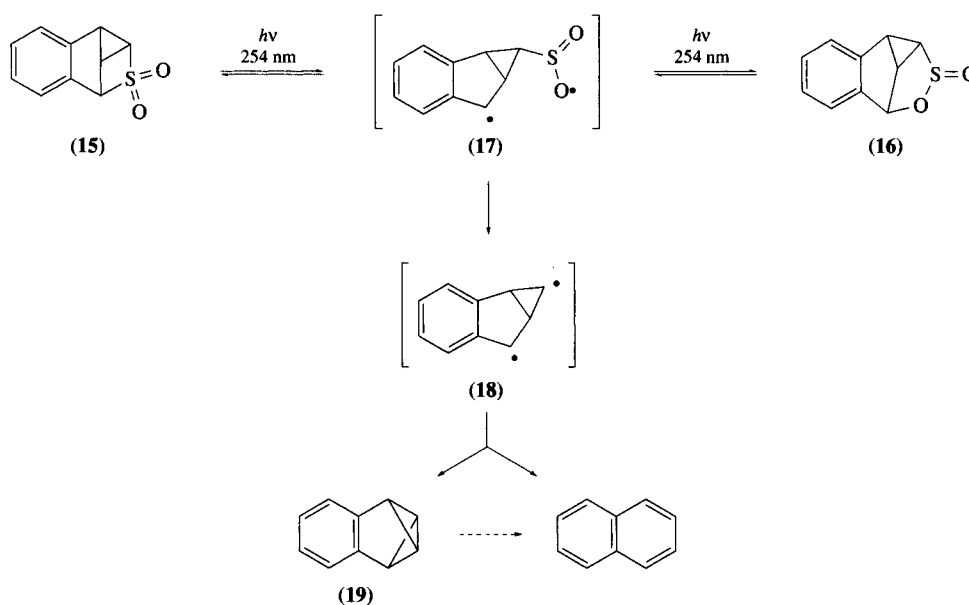
1.25.5.1 Unimolecular Thermal and Photochemical Reactions

1.25.5.1.1 Fragmentations and eliminations

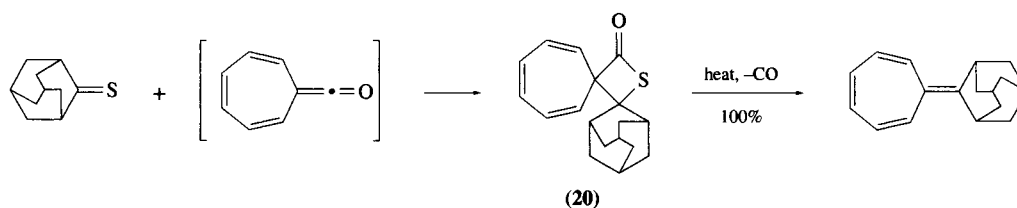
The four-membered ring of 2*H*-benzo[*b*]thiete (**14**) can readily undergo retro [2 + 2] ring opening under thermal or photochemical conditions forming an *ortho*-thiobenzoquinone methide (Equation (3)). This highly reactive 8 π -electron species can participate in cycloaddition reactions with a variety of dienophiles (see below) <93CB775, 94CB955, 94SR23>. Heating 2*H*,5*H*-benzo[1,2-*b*:4,5-*b'*]bisthiete gives a polymer which is suggested to have the structure shown below (Equation (4)) <94AG(E)465>. The polymer is presumed to be formed by sequential (rather than single step) retro [2 + 2] ring opening of the bisthiete.



A strained sulfone (**15**) (Scheme 1) and an isomeric γ -sultine (**16**) can interconvert and eliminate SO_2 photochemically (254 nm). A reversible homolytic cleavage may lead to an intermediate sulfinyloxy biradical (**17**) and subsequent formation of the benzoperfulvene biradical (**18**). The latter in its singlet state undergoes ring closure to (**19**) or opens to give naphthalene $\langle 90\text{HCA}1724, 93\text{PS}(74)417 \rangle$. A similar sequence occurs for other benzvalene derivatives upon heating $\langle 82\text{JA}4889 \rangle$. Spiro thietane (**20**), on heating at ca. 165°C , loses COS giving adamantylenecycloheptatriene in quantitative yield $\langle 84\text{CB}2393 \rangle$. A fused 2-thietanethione loses CS_2 on pyrolysis or irradiation (Scheme 2) $\langle 92\text{TL}4013 \rangle$.



Scheme 1

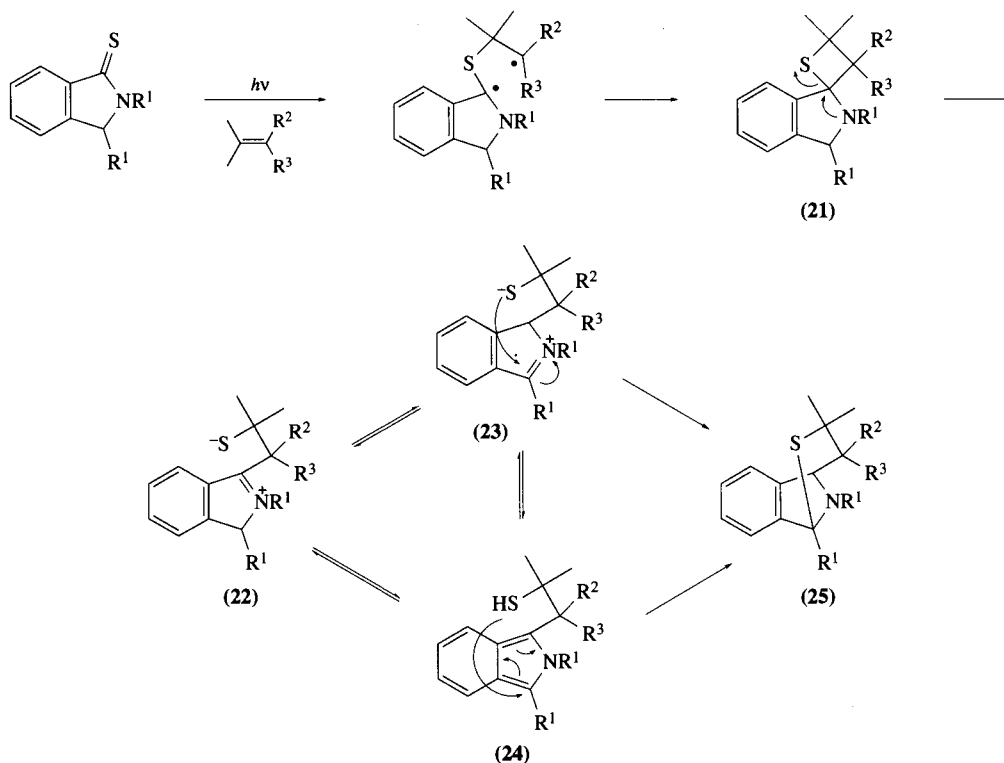


Scheme 2

1.25.5.1.2 Rearrangements

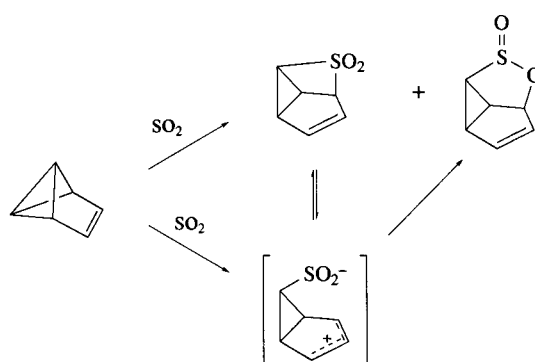
5,5,6,6-Tetracyano-2-thiabicyclo[2.2.0]hexane on refluxing in benzene affords 3-amino-4-cyano-2-(2,2-dicyanovinyl)thiophene via a postulated five-step mechanism $\langle 85\text{JOC}799 \rangle$. A photochemical rearrangement reaction occurs on irradiation of 2-arylisindoline-1-thiones in the presence of alkenes. The [2 + 2] product aminospirothietane (**21**) (Scheme 3) is thought to be formed first, followed by ring cleavage assisted by participation of the nitrogen lone pair electrons forming

zwitterions (**22**), (**23**), or 1-thiolethylisoindole (**24**). Subsequent nucleophilic attack of the thiolate anion on the iminium carbon of (**23**) or attack of the thiol group on C-3 of (**24**) gave the unusual tricyclic isoindolines (**25**) <92JOC4000>.



Scheme 3

In a reaction similar to that shown in Scheme 1, the tetracyclic thietane *S,S*-dioxide from 1,4-addition of SO_2 to the vinylcyclopropane system of benzvalene can undergo reversible ring opening to a zwitterion followed by ring closure to the isomeric γ -sultine (Scheme 4) <82JA4889, 84JA373, 90HCA1724>.

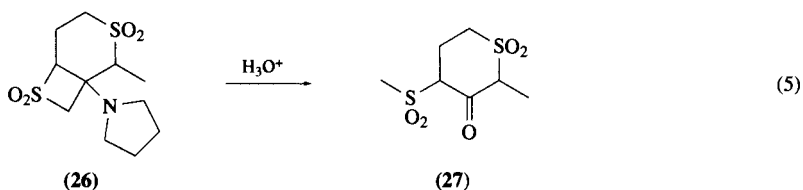


Scheme 4

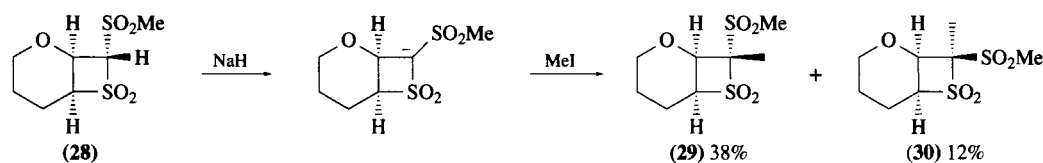
1.25.5.2 Electrophilic Attack

1.25.5.2.1 At carbon

Protonation (with aqueous hydrochloric acid) on the carbon of the fused thietane 1,1-dioxide derivative (**26**) leads to ring fission and subsequent hydrolysis to the ketone (**27**) (Equation (5)) <83JCS(P1)2735>.

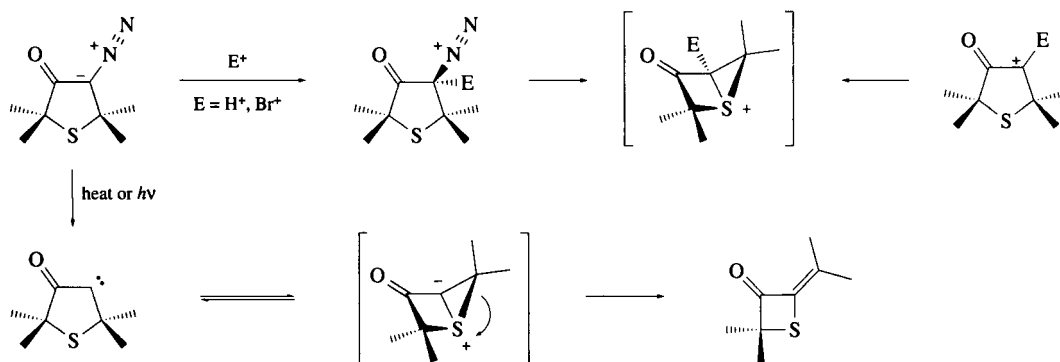


(1*R**,6*S**,8*R**)-8-Methylsulfonyl-2-oxa-7-thiabicyclo[4.2.0]octane 7,7-dioxide (**28**) undergoes alkylation at C(8) in the presence of sodium hydride and alkyl halides, for example methyl iodide, chloromethyl methyl ether, benzyl chloride, *t*-butyl bromoacetate, and allyl bromide, to yield the *endo*- and *exo*-alkyl derivatives (**29**) and (**30**) (Scheme 5) <92JCS(P1)2371>.



Scheme 5

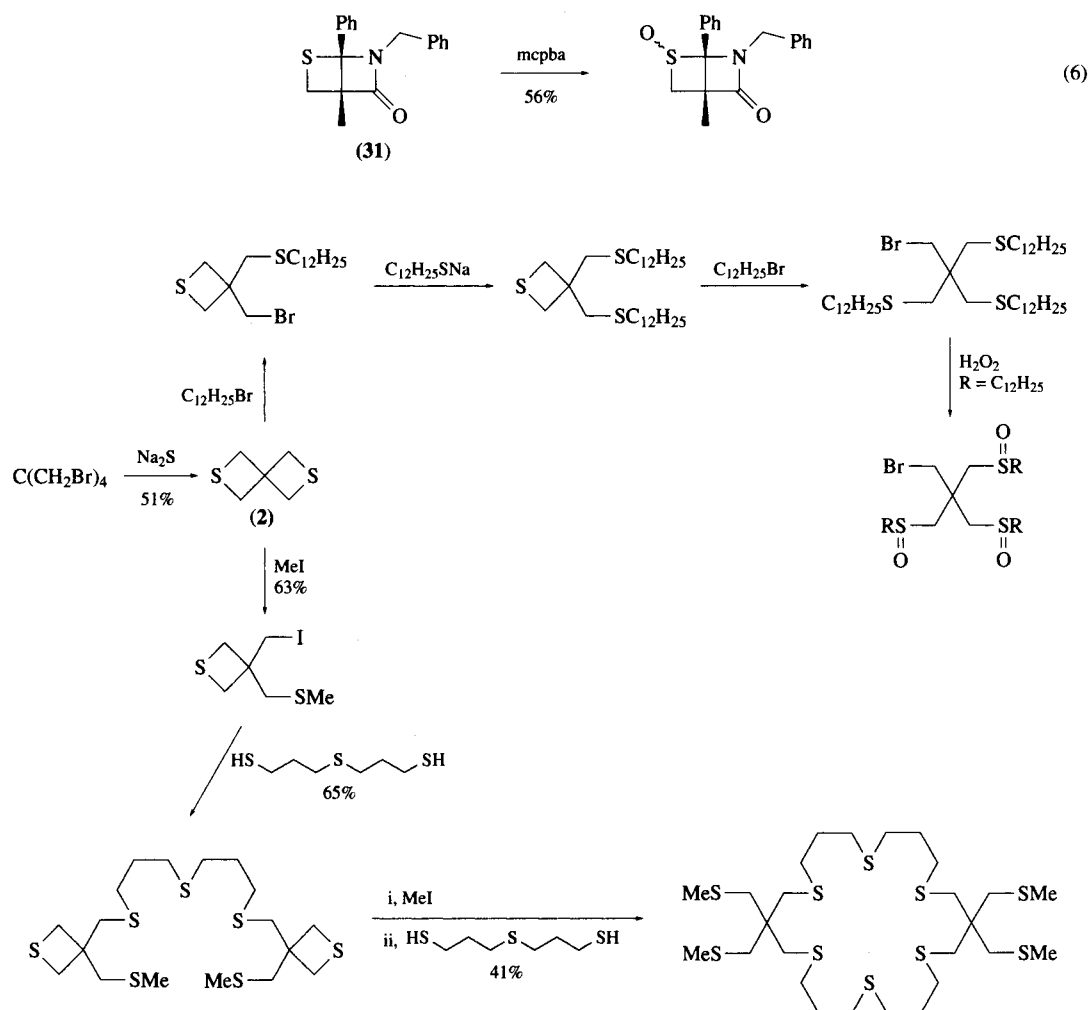
Electrophilic reactions of the α -diazo ketone, 2,2,5,5-tetramethylthiolane-3-diazothiolane-4-dione, via bicyclo[2.1.0]pentyl-1-sulfonium ion intermediates has been examined (Scheme 6) <82JOC4429>.



Scheme 6

1.25.5.2.2 At sulfur

Bicyclic thietane (**31**) undergoes oxidation at sulfur giving a pair of isomeric sulfoxides in 56% yield (Equation (6)) <84JOC396>. Treatment of the fused ring thietane-hexapyranoside methyl 2-*O*-*p*-toluenesulfonyl-4,6-thioanhydro- α -D-gulopyranoside with monoperphthalic acid gives the corresponding sulfone <85T2737>. The sulfoxides and sulfone of 1-(3,5-dideoxy-3,5-epithio- β -D-xylofuranosyl)uracil have been prepared for purposes of characterization <88JCS(P1)2233>. The sulfoxide and sulfone of *endo*-2-bromo-5-thiabicyclo[2.1.1]hexane have been prepared <93HAC33>. The spiro-thietane 2,6-dithiaspiro[3.3]heptane (**2**) undergoes ring opening with an equivalent of methyl iodide to give 3-iodomethyl-3-[(methylthio)methyl]thietane (63%), which is a useful precursor for a thia-crown compound <81H(16)1701, 86JCS(P1)465>, and with dodecyl bromide to give a precursor to an acyclic tris-sulfoxide (Scheme 7) <86JCS(P1)333>. Irradiation of thymidylyl(3'-5')-4-thiothymidine (**32**) leads to the two main products (**33**) and (**34**) (Scheme 8). Compound (**33**) can be protonated giving (**34a**) in a process that is reversible in the presence of H_2O . Electrophilic attack at the sulfur of (**33**) and (**34a**) occurs with methyl methanethiosulfonate to give the methyl disulfide (**34b**) (Scheme 8) <91JA5481>.

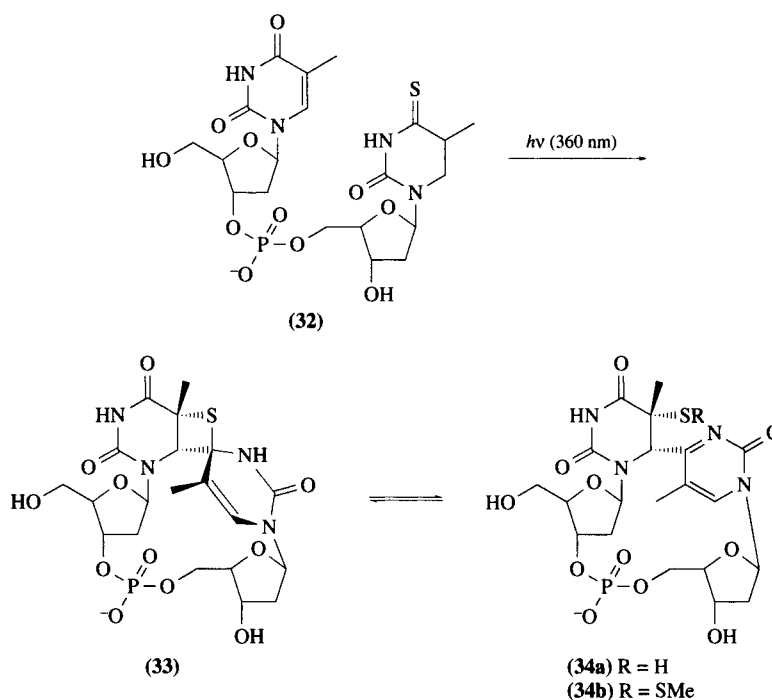


Scheme 7

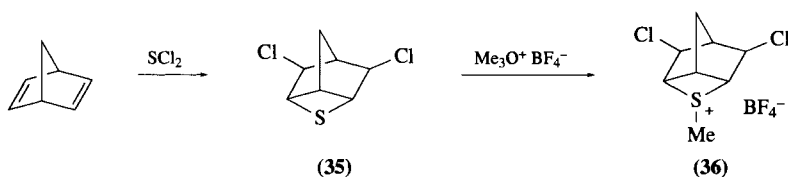
Treatment of *exo,exo*-3,5-dichloro-8-thiatricyclo[2.2.1.1^{2,6}]octane (**35**), prepared from norbornadiene, with trimethyloxonium tetrafluoroborate gives the 1-methyl-*exo,exo*-3,5-dichloro-8-thiatricyclo[2.2.1.1^{2,6}]octane (**36**), characterized by x-ray crystallography (Scheme 9) <66JOC1679, 84PS(21)215>.

1.25.5.3 Nucleophilic Attack at Heterocycle Carbon Atoms

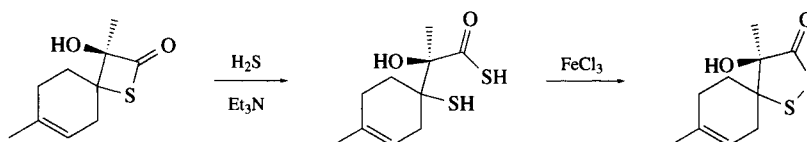
Nucleophilic attack of HS^- (from Na_2S_2) on the thietane CH_2 ring carbon of 1-(3,5-dideoxy-3,5-epithio- β -D-xylofuranosyl)uracil gives, in low yield, 1-(3,5-dideoxy-3,5-epidithio- β -D-xylofuranosyl)uracil, presumably by way of an intermediate dithiol which then undergoes oxidative cyclization <88JCS(P1)2233>. The fused thietane-nucleoside 3',5'-S-cyclouridine undergoes ring opening on treatment with NaSPh <85MI 125-01>. 2,6-Dithiabicyclo[3.1.1]heptane undergoes thietane ring opening with butanethiol <89JOC5821>. In developing synthetic approaches to the fused 1,2-dithiolane antibiotic leinamycin, a spiro 3-oxo-1,2-dithiolane has been synthesized from a spiro 2-thietanone. In the conversion of each diastereoisomer of 3-hydroxy-3,7-dimethyl-1-thiaspiro[3.5]non-6-en-2-one to 2-hydroxy-2-(1-thiol-4-methylcyclohex-3-enyl)propanethioic acid, nucleophilic attack at carbonyl carbon by SH^- is apparently involved. The thiolthioic acid is then converted to 4-hydroxy-4,8-dimethyl-1,2-dithiaspiro[4.5]dec-7-en-3-one in the presence of aqueous ferric chloride (Scheme 10) <92JCS(P1)1215>.



Scheme 8



Scheme 9



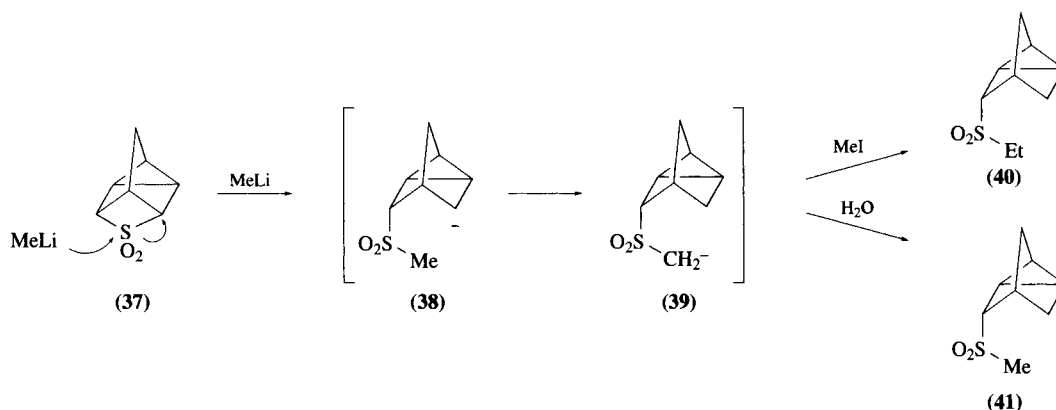
Scheme 10

1.25.5.4 Nucleophilic Attack at the Sulfur Atom

Direct nucleophilic attack on the sulfur atom of norbornadienyl sulfone (37) occurs on treatment with MeLi. Alkylation of the intermediate with MeI affords (40), while treatment with H_2O affords (41) (Scheme 11). The proposed mechanism is shown in Scheme 11 <85JOC4998>. Methyl lithium acts as a nucleophile and attacks the sulfur atom giving the unstable secondary carbanion (38). Rapid proton exchange follows giving sulfone-stabilized primary carbanion (39) which then reacts with either MeI or H_2O to give (40) or (41), respectively.

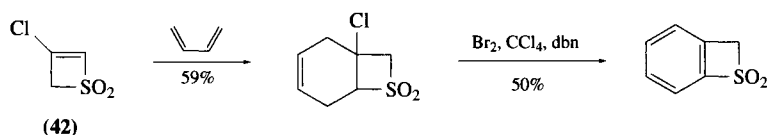
1.25.5.5 Nucleophilic Attack at Hydrogen Attached to Heterocycle Carbon Atoms (Deprotonation)

It has been noted above (Scheme 5) that (1R*,6S*,8R*)-8-methylsulfonyl-2-oxa-7-thiabicyclo-[4.2.0]octane 7,7-dioxide (28) can be deprotonated and subsequently alkylated at C-8 in the presence



Scheme 11

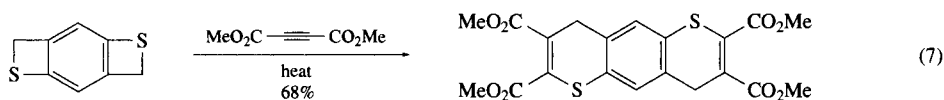
of sodium hydride and alkyl halides <92JCS(P1)2371>. In the conversion of 3-chlorothiete 1,1-dioxide (42) to benzothiete 1,1-dioxide, a key step involves deprotonation of the brominated Diels–Alder adduct of (42) with 1,3-butadiene (Scheme 12) <84JOC2408>.



Scheme 12

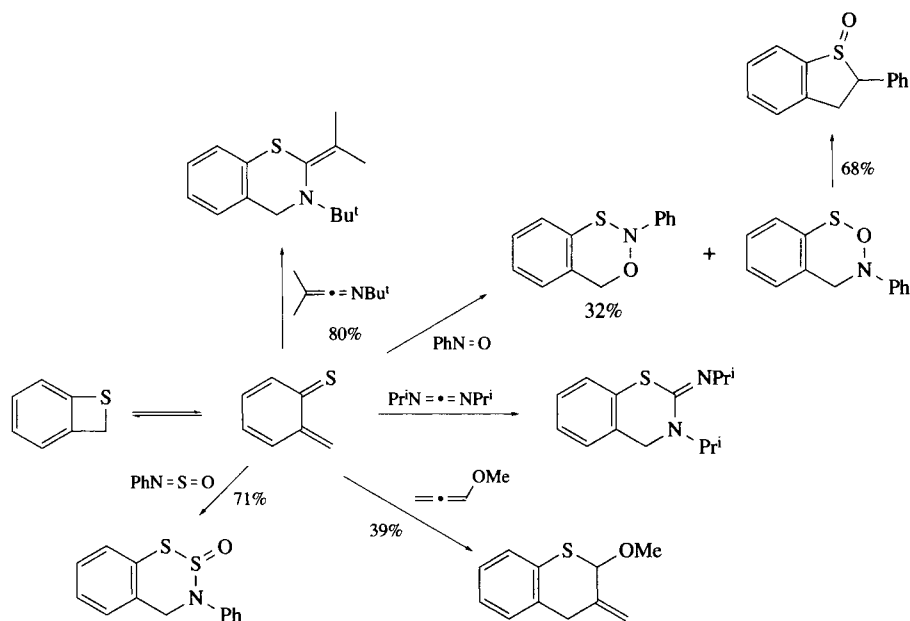
1.25.5.6 Reactions with Cyclic Transition States, Formally Involving a Second Species

2*H*-Benzo[*b*]thiete readily undergoes cycloaddition with nitrosobenzene, allenes, *N*-sulfinylamines, and a number of other dienophiles (Scheme 13) <93CB775, 94CB955>. Heating a mixture of 2*H*,5*H*-benzo[1,2-*b*:4,5-*b'*]bisthiete and dimethylacetylenedicarboxylate affords the 2:1 adduct in 68% yield (Equation (7)) <94AG(E)465>. In a cycloaddition reaction that most likely involves a diradical intermediate, irradiation of a spirothietane and *N*-methylmonothiophthalimide affords a dispiro-1,2-dithiane (Scheme 14) <87H(26)147>.

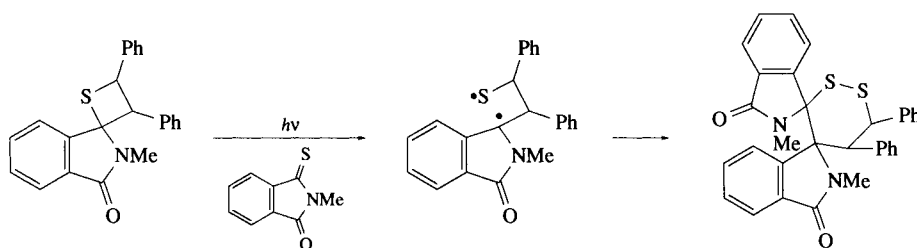


1.25.5.7 Reaction with Metals and Metal Complexes

As already discussed in Sections 1.25.2 and 1.25.3.4, the ruthenium dinuclear complexes (1a), (2a), and (3a) have been synthesized and their spectroscopic properties studied in great detail in order to provide insight into the mechanism by which electrons tunnel through fully saturated systems <82JA2596>. In a related study, an osmium(II) tetratolylporphyrin complex of naphthoquinone–thietane (12) (see Section 1.25.3.4) has been prepared and the photophysics of the charge-transfer states have been studied <94JA281>. Desulfurization of bicyclic thietanes with Raney nickel has been used to prepare 4-spirocyclopropyl β -lactams <93TL5951> and other spirocyclopropanes <86T4691> and to confirm the structure of various thietanes <84JOC396, 85T2737, 92CC891>. Methylation of (CpMo)₂(S₂CH₂)(μ -SMe)₂ gives [(CpMo)₂(S₂CH₂)(μ -SMe)(μ -SMe₂)]X (X = OTf, BF₄), which desulfurizes thietanes, among other compounds <93OM3630>.



Scheme 13



Scheme 14

1.25.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

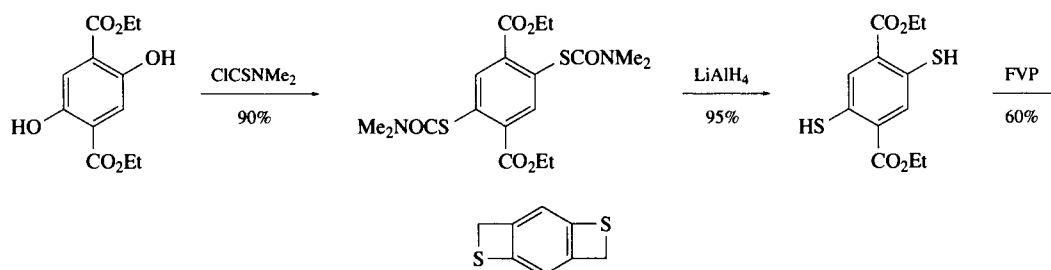
The cycloheptatriene ring of spirothietane (**20**) (see Section 1.25.5.1.1) undergoes photooxygenation giving an *endo*-peroxide and adds 4-methyl-4*H*-1,2,4-triazole-3,5-dione to give the corresponding adduct. Both processes occur in good yield (84CB2393).

1.25.7 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

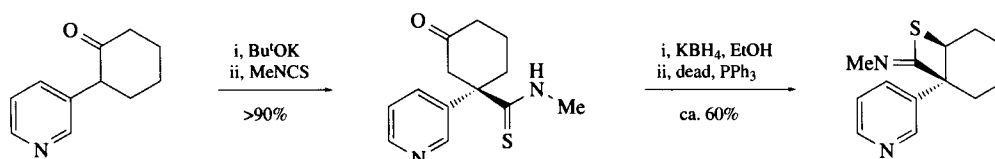
1.25.7.1 Ring Syntheses from Acyclic Precursor of Same Number of Carbons

Flash vacuum pyrolysis (FVP) of 2,5-dithiol-1,4-phenylenedimethanol affords 2*H*,5*H*-benzo[1,2-*b*:4,5-*b'*]bisthiene (4,9-dithiatricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene) (Scheme 15) (94AG(E)465).

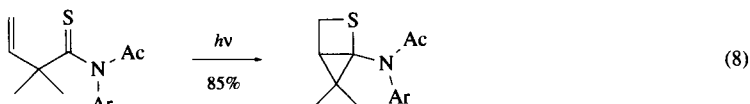
The enolate of 2-(3-pyridyl)cyclohexanone can be trapped with methylisothiocyanate affording racemic ketone thioamide. This was further reduced to the corresponding *trans* and *cis* alcohols in a 9:1 ratio. Under Mitsunobu conditions the *trans* isomer undergoes an intramolecular displacement reaction, forming the thioimide (Scheme 16) (92TL5117). 1-(*N*-acetylanilino)-5,5-dimethyl-2-thiabicyclo[2.1.0]pentanes are prepared by the photolysis of *N*-acetyl-2,2-dimethylbut-3-enethioanilides in high yields via intramolecular [2 + 2] cycloaddition (Equation (8)) (92CC891).



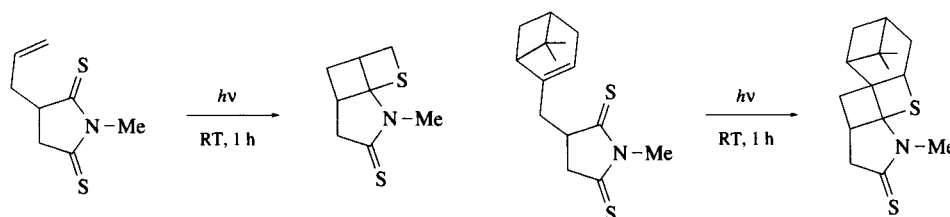
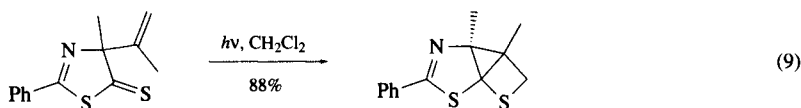
Scheme 15



Scheme 16

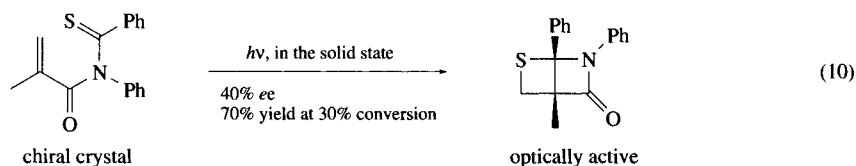


Thietane-fused β -lactams are synthesized in good yields from N -(α,β -unsaturated carbonyl)-thioamides through intramolecular photocycloaddition (84JOC396, 91JCS(P1)403). Similarly, tricyclic thietane derivatives are formed through intramolecular [2 + 2] photocycloaddition of 4-vinyl-1,3-thiazole-5(4*H*)-thiones (Equation (9)) (87HCA992) while related unsaturated systems on irradiation give even more intricate ring systems (Scheme 17) (86CPB1411).

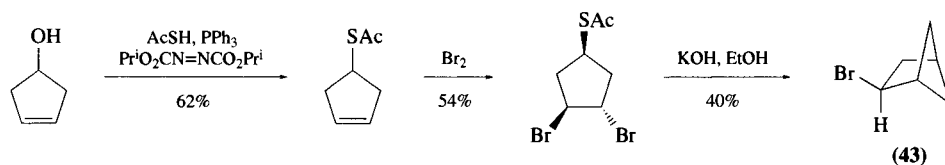


Scheme 17

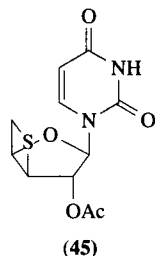
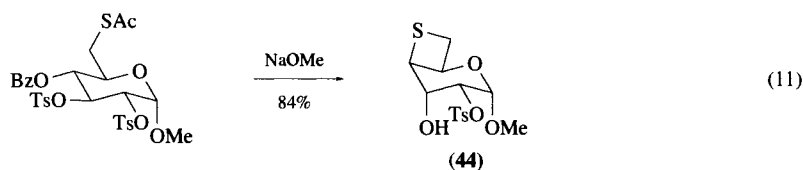
An absolute asymmetric fused thietane synthesis in the solid state involves an intramolecular [2 + 2] photocycloaddition (Equation (10)) (84JOC396, 91JCS(P1)403, 93JA818). In the reactant molecule, N -(thiobenzoyl)methacrylanilide, the distances between the sulfur atom (S) and the alkenyl carbon (C-5) and between the thiocarbonyl carbon (C-1) and the alkenyl carbon (C-2) are 3.59 and 3.11 Å, respectively, according to the x-ray crystallography study. This fact is in agreement with earlier studies which indicate that in an intermolecular [2 + 2] photocycloaddition, the center-to-center distance in substrate molecules should be less than 4.1 Å between the parallel reacting double bonds. Fused thietane formation is postulated to be a topochemically controlled process which occurs stereospecifically in the solid state (93JA818).



Synthesis of the bridged thietane *endo*-2-bromo-5-thiabicyclo[2.1.1]hexane (**43**) has been accomplished in three steps from 3-cyclopentenol, with the final step involving intramolecular nucleophilic attack by thiolate on a C—Br bond (Scheme 18) <93HAC33>. Several sugars and nucleosides possessing a thietane ring fused in the sugar moiety have been synthesized for biological studies, including methyl 2-*O*-*p*-toluenesulfonyl-4,6-thioanhydro- α -D-gulopyranoside (**44**) (Equation (11)) <85T2737>, 3',5'-*S*-cyclouridine (**45**) <85MI 125-01>, and 1-(3,5-dideoxy-3,5-epithio- β -D-xylofuranosyl)uracils <87CC1801, 88JCS(P1)2233>. These novel compounds are synthesized by base treatment of thioacetyl derivatives possessing suitably disposed leaving groups and are characterized by their reactions, such as oxidation or thietane ring opening by thiolate nucleophiles. Unfortunately, none of these unusual fused thietanes displays appreciable biological activity.



Scheme 18

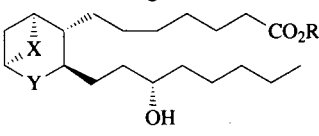


Considerable research activity has occurred in the area of the biologically very potent sulfur analogue of thromboxane A_2 . Several total syntheses, including the synthesis of optically active forms, have been published. Table 1 summarizes the types of compounds prepared. These syntheses typically involve ring closure by intramolecular attack of a thiolate group on a suitably disposed leaving group.

1.25.7.2 Ring Synthesis via Formation of Two Bonds

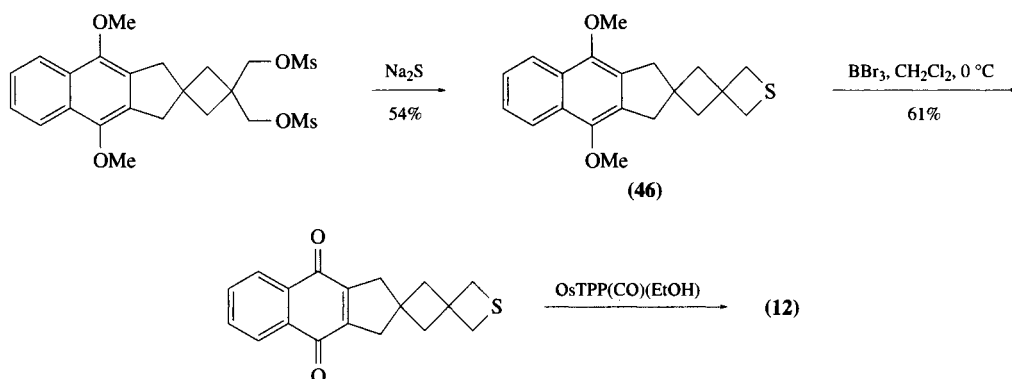
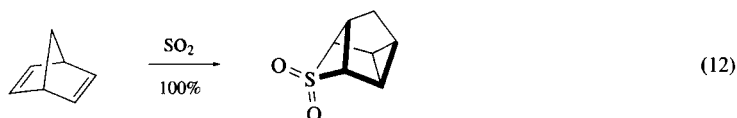
1.25.7.2.1 From 3 + 1 fragments

Spirothietane 2,6-dithiaspiro[3.3]heptane (**1**) (Section 1.25.2) is formed in 61% yield from the reaction of pentaerythrityl bromide ($C(CH_2Br)_4$) with $Na_2S \cdot 9H_2O$ in aqueous ethanol <81H(16)1701, 86JCS(P1)333>. A related procedure is used in the synthesis of a dimethoxynaphthalenethietane (**46**) (Scheme 19) <94JA281>. Benzobenzvalene undergoes formal insertion of sulfur dioxide into one of the lateral bicyclopropane bonds giving a tetracyclic thietane *S,S*-dioxide and the isomeric γ -sultine (see Section 1.25.1.2) <82JA4889, 84JA373, 90HCA1724>. This reaction has been studied over the

Table 1 Sulfur Analogues of Thromboxane A_2 .


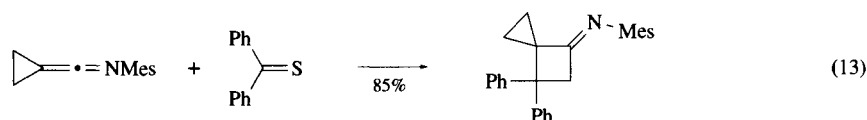
X	Y	R	Ref.
S	CH ₂	H	81TL1349, 83T4263
S	CH ₂	Me	81TL5301, 83T4269
S	O	Me	82TL2883, 84JOC1554
S	S	Na	81JA4597, 83T4273, 86JCS(P1)1397, 89JOC5821
CH ₂	S	H	81TL1345

temperature range -95 to 80°C . Similarly, sulfur dioxide adds in a cheletropic $[\pi 2_s + \pi 2_s + \omega 2_s]$ reaction to norbornadiene giving 4-thiatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4,4-dioxide (Equation (12)), while noncycloaddition products are obtained with cyclohexa-1,4-diene, hexamethyl Dewar benzene and bicyclo[2.2.2]octa-2,5-diene (82CC1105). Norbornadiene reacts with SCl_2 giving *exo*, *exo*-3,5-dichloro-8-thiatricyclo[2.2.1.1^{2,6}]octane (35) (see Section 1.25.3) (66JOC1679, 84PS(21)215). Initial *endo* attack of SCl_2 on norbornadiene presumably gives a bridged sulfonium ion intermediate which undergoes *trans* nucleophilic attack by the liberated chloride anion affording (35). Refluxing limonene with elemental sulfur affords bicyclic thietanes (10) and (11) (see Section 1.25.3.3) (86MI 125-01).

**Scheme 19**

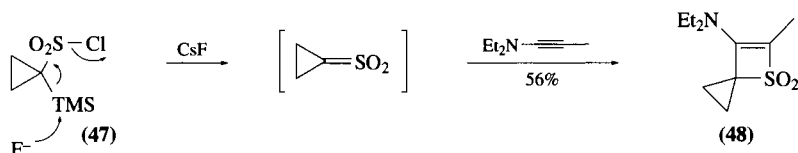
1.25.7.2.2 From 2 + 2 atom fragments

Spirothietanes are formed by 2 + 2 cycloaddition of the $\text{C}=\text{S}$ double bond to the $\text{C}=\text{C}$ double bond in intra- or intermolecular processes. The spirothietane derivative 6,6-diphenyl-4-(mesitylimino)-5-thiaspiro[2.3]hexane is prepared in 85% yield by [2 + 2] cycloaddition of thiobenzophenone with *N*-mesitylcyclopropylideneazomethine (Equation (13)) (85JOC5368).

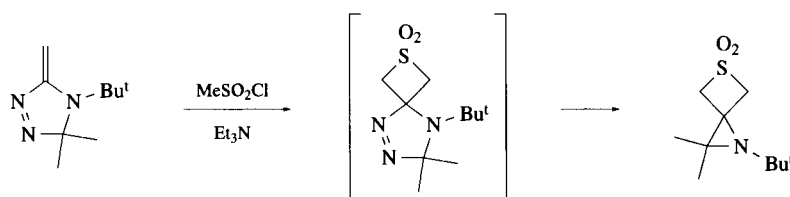


Aromatic thiones such as xanthene-9-thione react with substituted allenes, $\text{XCH}=\text{C}=\text{CH}_2$ ($\text{X} = \text{OR}, \text{SR}, \text{Ph}, \text{NMe}_2$), giving spirothietanes or thiopyran derivatives by [2 + 2] or [4 + 2] cyclo-

additions, respectively, by processes involving radical intermediates (82MI 125-01, 85IJ120, 86MRC616). The spirothietane derivative 4-(*N,N*-diethylamino)-3-methyl-2-thiaspiro[3.2]hex-3-ene 2,2-dioxide (48) can be synthesized in 56% yield through reaction of 1-(trimethylsilyl)cyclopropanesulfonyl chloride (47) with 1-(*N,N*-diethylamino)-1-propyne in the presence of caesium fluoride, which is believed to convert (47) into cyclopropanethione *S,S*-dioxide (Scheme 20) (92JA3492). Sulfene reacts with a 3,4-dihydro-5-methylene-1,2,4-triazole to give a spiroaziridine (Scheme 21) (86CC1721, 88CJC155).

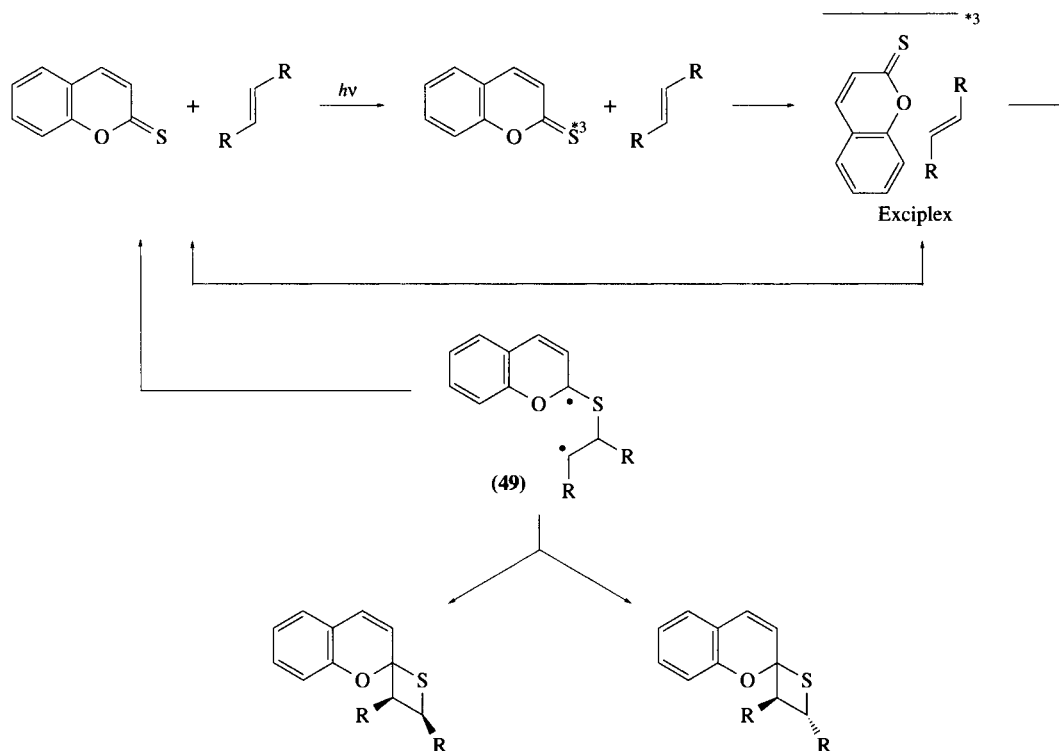


Scheme 20



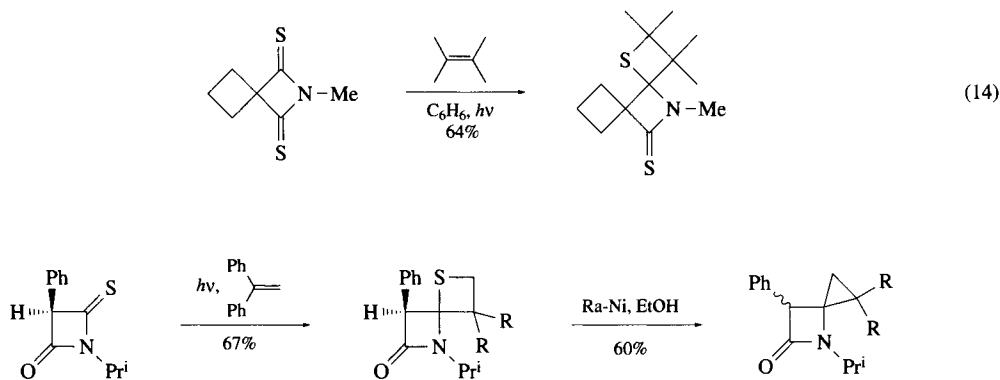
Scheme 21

Spirothietanes have been prepared site- and regiospecifically from reaction of 1,1,3-trimethyl-2-thioxo-1,2-dihydronaphthalene with electron-rich and electron-deficient alkenes upon excitation to either S_2 ($\pi\pi^*$) or S_1 ($n\pi$) states (88JOC327, 88JOC332). Spirothietanes, and in some cases 1,4-dithianes, have been formed upon photolysis of the α,β -unsaturated thione thiocoumarin with both electron-rich and electron-deficient alkenes. The lowest triplet state of thiocoumarin and a 1,4-biradical, 2-thiatetramethylene (49), are thought to be involved in this photocyclization process (Scheme 22) (88JOC741).



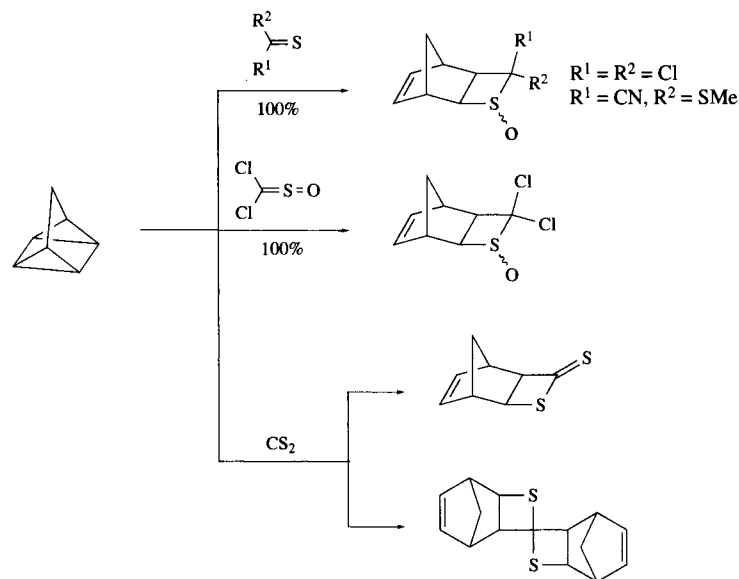
Scheme 22

Many imide-thietanes have been prepared from aliphatic and aromatic mono- and dithioimides with alkenes via both intramolecular <85CPB3552, 89CPB642, 92CC891, 92CPB585> and intermolecular photocycloaddition, as for example the cases shown in Equation (14) <86S768> and Schemes 1 and 23 <93TL5951>, among others <84TL2247, 85H(23)1615, 85JCS(P1)1957, 85JOC1681, 86JCS(P1)2273, 86S768, 86T4691, 89CPB1431>.

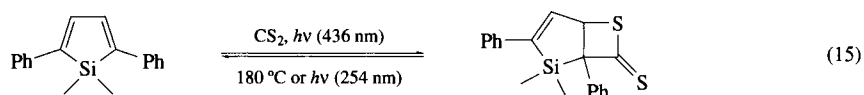


Scheme 23

Spirothietanes ([2 + 2] cycloaddition products), and occasionally thiopyrans ([4 + 2] cycloaddition products), are formed through reaction of substituted allenes with aromatic thiones <82MI 125-01, 85IJ120>. Addition of 2-adamantanethione to *in situ* generated ketene 8-oxoheptafulvene gives spirothietane (**20**) (Scheme 2) <84CB2393>. Mono- and bisadducts are prepared by cycloaddition of quadricyclane with thiocarbonyl derivatives including carbon disulfide, forming a fused 2-thietanethione as well as a spirodithietane (Scheme 24). Products vary with concentration, temperature and pressure <85TL725>. A fused 2-thietanethione is also formed on ultraviolet irradiation (436 nm) of carbon disulfide with 1,1-dimethyl-2,5-diphenylsilacyclopentadiene (Equation (15)). The reaction can be reversed on short wavelength irradiation (254 nm) or pyrolysis <92TL4013>.



Scheme 24

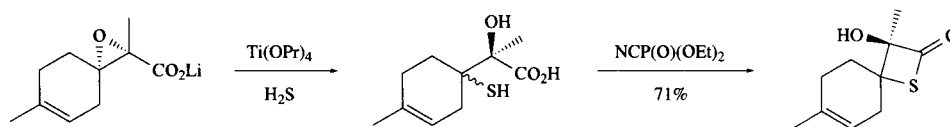
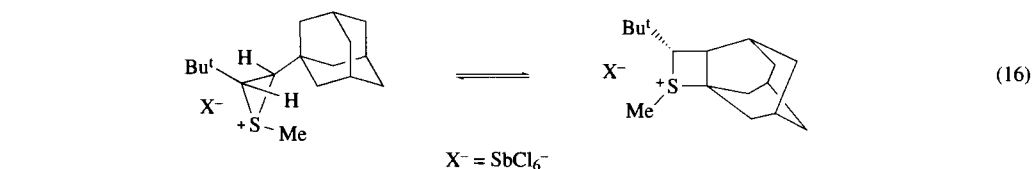


(15)

1.25.8 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

1.25.8.1 Formation from Three-membered Heterocycles

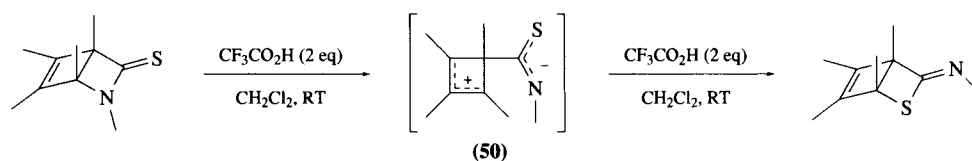
The interconversion of adamantylthiiranium and homoadamantylthietanium ions is reported (Equation (16)) (91JA6600). Lithium glycidate can be converted into 3-hydroxy-3,7-dimethyl-1-thiaspiro[3.5]non-6-en-2-one via the intermediacy of a β -thiolcarboxylic acid (Scheme 25) (92JCS(P1)1215).



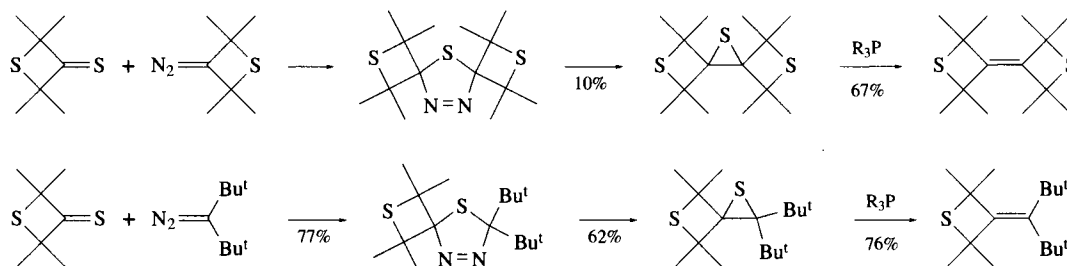
Scheme 25

1.25.8.2 Formation from Four-membered Heterocycles

2*H*-Thiete undergoes a cycloaddition reaction at room temperature with tetracyanoethylene giving 5,5,6,6-tetracyano-2-thiabicyclo[2.2.0]hexane (85JOC799). Benzothiete 1,1-dioxide can be prepared in three steps by cycloaddition of 1,3-butadiene to 3-chlorothiete 1,1-dioxide followed by bromination and treatment with *dbn* (see above) (84JOC2408). In the rearrangement of 1,2,4,5-tetramethyl-2-aza-3-thioxobicyclo[2.2.0]hex-5-ene and 1,2,4,5,6-pentamethyl-2-aza-3-thioxobicyclo[2.2.0]hex-5-ene under the influence of trifluoroacetic acid, dipolar structure (50) (Scheme 26) is believed to be formed first followed by intramolecular electrophilic attack at sulfur prior to nitrogen. The resulting four-membered ring containing a sulfur atom (and an exocyclic C=N) is more stable than one which contains a nitrogen atom (and an exocyclic C=S). This is due to the fact that sulfur is more flexible and induces less strain in a four-membered ring than a nitrogen atom (82JOC1909). Such an explanation has also been given for the atypical behavior of sulfur in ring closures described by Baldwin's rules (76JCC734, 79CC736, 85T2737). Spirothietanes can be prepared through reaction of 3-thietanethione with diazo compounds (Scheme 27) (84CB277).



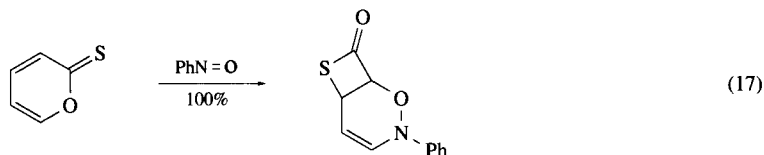
Scheme 26



Scheme 27

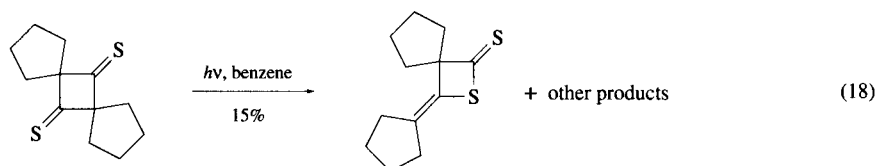
1.25.8.3 Formation from Six-membered Heterocycles

An unusual synthesis of a fused thietanone from pyran-2-thione and nitrosobenzene has been reported (Equation (17)) <85HCA1998>.



1.25.8.4 Formation from Carbocyclic Rings

Cyclobutane-1,3-dithiones such as dispiro[5.1.5.1]tetradecane-7,14-dithione and dispiro[4.1.4.1]dodecane-6,12-dithione on UV irradiation afford dithiolactones among other products (Equation (18)) <83JOC4482>. A similar rearrangement has been previously observed for 2,2,4,4-tetramethyl-1,3-dithione which upon warming to 125°C gives 2,2-dimethyl-4-(dimethyl)methylenethietane-3-thione <67JOC1562>.



1.25.9 IMPORTANT COMPOUNDS AND APPLICATIONS

9,11-Epithio-11,12-methano-thromboxane A₂ (STA₂ or ONO11113, ONO Pharmaceutical Company, Osaka, Japan) is a widely studied stable thromboxane A₂ analogue which induces coronary artery vasoconstriction in the rabbit <86MI 125-02> by increasing transmembrane calcium influx <87MI 125-01>, increases pulmonary microvascular permeability to protein <89MI 125-02>, contracts the ductus venosus sphincter of fetal lambs <85MI 125-02> and canine and monkey cerebral arteries <86MI 125-03>, activates protein-tyrosine kinase p72^{syk} in porcine platelets <93MI 125-01>, and enhances collagen-induced phosphoinositide turnover in human platelets <85MI 125-03>, among other effects.

ACKNOWLEDGMENT

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1.26

Four-membered Rings with One Selenium or Tellurium Atom

MICHAEL R. DETTY

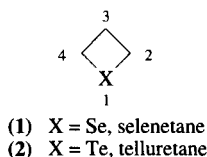
State University of New York at Buffalo, NY, USA

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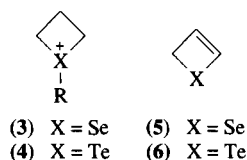
1.26.1 INTRODUCTION

Four-membered heterocyclic compounds containing one selenium atom (selenetane (**1**)) or one tellurium atom (tellurethane (**2**)) are relatively old heterocyclic compounds. Morgan and Burstall first reported selenetane (**1**) in 1930 <30JCS1497> while Farrar and Gulland first reported tellurethane (**2**) in 1945 <45JCS11>. Both materials are reactive species, which form gummy, polymeric materials with heat or react in air to form oxides. A few examples of analogues of these materials, 3-substituted derivatives in particular <86JCS(D)205, 88JOC791, 91ZOR942>, have been described since the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). Transition metal complexes

of (1) have also been described in which the selenium atom functions as a two-electron donor ligand <86JCS(D)205, 92CC563, 92CC1050>.



In addition to the parent compounds (1) and (2), onium salts (3) and (4) can be prepared by alkylation of either selenium or tellurium. Although no compounds of this type have been reported for the selenetane system, one example of the telluretane system (4) has been described <83JCS(D)2143> since the publication of CHEC-I. Unsaturated analogues of (1) and (2) are possible as in compounds (5) and (6) although no examples of molecules of this type have been described since the publication of CHEC-I. It should also be noted that benzo analogues of these materials have not been described since the publication of CHEC-I.



1.26.2 THEORETICAL METHODS

No theoretical investigations of selenetanes or telluretanes have been described, which might give structural information about these systems.

1.26.3 EXPERIMENTAL STRUCTURAL METHODS

1.26.3.1 Nuclear Magnetic Resonance Spectroscopy

In molecules of this class, both proton and carbon NMR spectra have been measured. The chemical shifts reported in this section are in parts per million (ppm) from tetramethylsilane (TMS), where the chemical shift of TMS protons and carbons are $\delta 0.00$. Positive δ values are shifts to lower field while negative δ values are shifts to higher field.

Both selenium and tellurium have NMR-active isotopes with spin 1/2 in fairly high natural abundance (both ^{77}Se and ^{125}Te are found in about 7% natural abundance). Unfortunately, heteronuclear chemical shifts have not been described for the molecules of this chapter.

1.26.3.1.1 Proton NMR spectroscopy

The ^1H NMR spectra of selenetanes (7), (8), and ketone (9) have been described. In compounds (7), which have nonidentical groups R_1 and R_2 , the methylene protons H_A and H_B have different chemical shifts (Table 1) <88JOC791, 91ZOR942>. For selenetanes (8), which are geometrical isomers, the selenetane methylene protons appear as doublets ($J = 17.8$ and 18.0 Hz for (8a) and (8b), respectively) with chemical shifts of $\delta 3.56$ and 3.71 for (8a) and $\delta 3.61$ and 3.85 for (8b) <93BCJ1714>. The remaining methine ring proton appears as a singlet at $\delta 4.61$ in (8a) and $\delta 4.59$ in (8b). In ketoselenetane (9), the methylene protons have identical chemical shifts and appear as a singlet at

δ 4.22 <88JOC791>. The chemical shifts of the methylene protons in compounds (7)–(9) are deshielded by both the four-membered ring structure and by the inductive effect of the selenium atom.

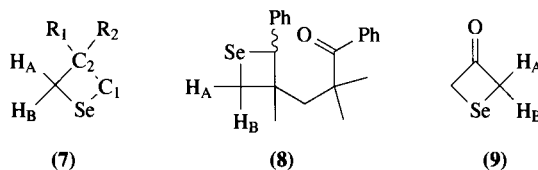


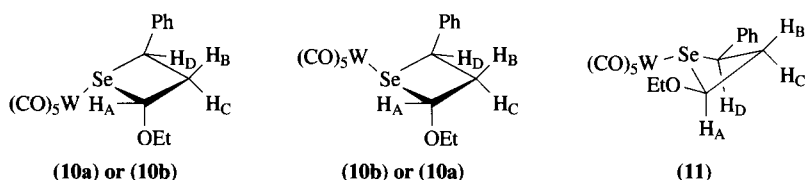
Table 1 Proton NMR and carbon-13 NMR chemical shifts in CDCl_3 for selenetanes (7).

Compound	R_1	R_2	H_A δ	H_B δ	C_1 δ	C_2 δ	Ref.
(7a)	OH	H	3.14	3.25	27.9	68.1	91ZOR942, 88JOC791
(7b)	OH	Ph	3.42	3.48	30.5	79.5	88JOC791
(7c)	OH	4-MeOPh	3.48	3.60	31.0	79.9	88JOC791
(7d)	OH	Et	3.04	3.34			88JOC791
(7e)	H	$\text{O}_2\text{CPh}-3,5-(\text{NO}_2)_2$	3.30	3.71	23.3	70.6	88JOC791
(7f)	OAc	H	3.30	3.43	23.6	68.7	88JOC791

The ^1H NMR chemical shifts of several different metal complexes of selenetanes have been described <86JCS(D)205, 92CC563>, which include three different tungsten carbonyl complexes <92CC563>. With *trans*-2,4-substituents, two different complexes are observed, which implies that there is some geometrical integrity to the selenium–tungsten bond. Chemical shifts, multiplicities, and ^1H – ^1H coupling constants for these two geometrical isomers (10a) and (10b) are compiled in Table 2. Isomers (10) convert thermally to the *cis*-isomer (11), which presumably has the tungsten pentacarbonyl moiety in an ‘equatorial’ position <92CC563>. Chemical shifts, multiplicities, and ^1H – ^1H coupling constants for (11) are also compiled in Table 2.

Table 2 Proton NMR chemical shifts, multiplicities, and H–H coupling constants in CDCl_3 for tungsten–pentacarbonyl complexes of 2-ethoxy-4-phenylselenetanes (10) and (11) <92CC563>.

Compound	Substituents	H_A δ	H_B δ	H_C δ	H_D δ
(10a)	<i>trans</i>	5.93 (d × d) $J = 7.6, 7.0$ Hz			4.60 (d × d) $J = 10.0, 3.6$ Hz
(10b)	<i>trans</i>	5.63 (d × d) $J = 9.4, 9.1$ Hz			5.19 (d × d) $J = 6.7, 2.7$ Hz
(11)	<i>cis</i>	5.57 (d × d) $J = 8.4, 6.5$ Hz	3.54 (d × d × d) $J = 13.9, 11.1, 8.5$ Hz	3.95 (d × d × d)	4.65 (d × d) $J = 11.1, 7.8$ Hz



The palladium complexes (12) have rapidly interconverting ring conformations on the ^1H NMR time scale near ambient temperature <86JCS(D)205>. Proton chemical shifts and the geminal methylene coupling constants are compiled in Table 3. The *trans*-ligand effects of the halides influence the chemical shifts of the selenetane protons.

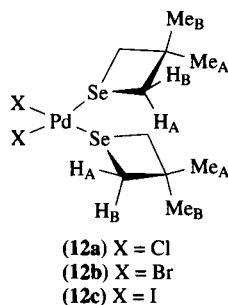


Table 3 Proton NMR chemical shifts and H—H coupling constants for palladium halide complexes of 3,3-dimethylselenetanes (**12**) in $C_6D_5NO_2$ $\langle 86JCS(D)205 \rangle$.

Compound	X	H_A δ	H_B δ	J_{AB} Hz	Me_A δ	Me_B δ
(12a)	Cl	3.66	2.95	−10.3	1.53	1.30
(12b)	Br	3.81	3.05	−10.9	1.51	1.31
(12c)	I	4.06	3.18	−9.8	1.39	1.34

1.26.3.1.2 Carbon-13 NMR spectroscopy

The ^{13}C NMR spectra of selenetanes (**7**) have been described $\langle 88JOC791 \rangle$ and the chemical shifts of the ring carbons are compiled in Table 1. While the ^{13}C NMR spectra of compounds (**8**) are reported, the chemical shift assignments cannot be made unequivocally $\langle 93BCJ1714 \rangle$. The chemical shifts of the α -methylene carbons to selenium are all near $\delta 30$ in selenetanes (**7**). However, in the isomers (**8**), these carbons are in the $\delta 50$ – 61 range. The selenetane methine carbons in isomers (**8**) are found at $\delta 59.5$ in (**8a**) and at $\delta 58.2$ in (**8b**).

1.26.3.2 Mass Spectroscopy

The mass spectra of selenium- and tellurium-containing molecules are characterized by clusters of peaks in the heteroatom-containing fragments. Selenium is composed of isotopes with nominal masses between 74 and 82 while tellurium is composed of isotopes with nominal masses between 120 and 130 $\langle 84CHEC-I(4)942 \rangle$. These isotopes and their relative abundance are compiled in Table 4.

Table 4 Isotope relative abundance for selenium and tellurium $\langle 84CHEC-I(4)942 \rangle$.

Selenium		Tellurium	
Nominal mass	Relative abundance	Nominal mass	Relative abundance
74	1.75	120	0.26
75	0.00	121	0.00
76	18.11	122	7.13
77	15.21	123	2.52
78	47.21	124	13.37
79	0.00	125	20.27
80	100.00	126	54.26
81	0.00	127	0.00
82	18.45	128	92.20
		129	0.00
		130	100.00

The mass spectra of selenetanes (**7**) have been described $\langle 88JOC791 \rangle$. The parent ion is a strong fragment in all six molecules (**7**). For 3-hydroxyselenetane (**7a**), the base peak is the m/z 94 fragment ($^{80}SeCH_2$). This fragment is also significant in (**7b**)–(**7d**). For 3-hydroxy-3-ethyl or -3-aryl substituted

selenetanes (**7b**)–(**7d**), the base peak is the RCO^+ fragment where R is ethyl (m/z 57), phenyl m/z 105), or *p*-methoxyphenyl (m/z 135) from the 3-substituent. In dinitrobenzoate derivative (**7e**), the base peak arises from the $(\text{O}_2\text{N})_2\text{C}_6\text{H}_3\text{CO}$ fragment (m/z 195). In acetate (**7f**), the base peak is the acetyl fragment (m/z 43).

The parent ions of both isomers of (**8**) have been reported. However, relative intensity data and other fragments were not described.

1.26.3.3 Infrared Spectroscopy

Selected bands in the infrared spectra of selenetanes (**7**) have been described, although systematic analyses of the spectra have not <88JOC791>. The hydroxyl stretching frequency in (**7a**)–(**7d**) is “normal” with broad absorption in the $3100\text{--}3600\text{ cm}^{-1}$ range.

1.26.3.4 X-ray Diffraction Studies

X-ray structural data have not been described for these systems.

1.26.4 THERMODYNAMIC ASPECTS

1.26.4.1 Melting Points and Boiling Points

The selenetanes and telluretanes are thermally unstable giving gummy residues, polymers, and decomposition products upon heating. Consequently, few melting points or boiling points are available. 3-Hydroxyselenetane (**7a**) is a fairly volatile material with a boiling range of $60\text{--}62^\circ\text{C}$ at 0.8 torr <88JOC791>. Selenetanes (**8**) are isolated as colorless crystals with melting ranges of $89\text{--}91^\circ\text{C}$ for (**8a**) and $90\text{--}92^\circ\text{C}$ for (**8b**) <93BCJ1714>.

1.26.4.2 Conformational Inversion

Variable temperature ^1H NMR studies have given the activation barriers to ring inversion in transition metal complexes of the selenetanes. For tungsten–pentacarbonyl complexes (**9**) and (**10**), the inversion barrier has been estimated to be $> 58\text{ kJ mol}^{-1}$ <92CC563>. The thermodynamic sink in these systems is the isomer (**11**) with the tungsten–pentacarbonyl group *trans* to the *cis* 2- and 4-substituents since (**9**) and (**10**) isomerize to (**11**) upon heating.

The conformational changes associated with palladium complexes (**12b**) are rapid at room temperature <86JCS(D)205> as determined by ^1H NMR. Cooling the samples allowed the determination of Arrhenius and Eyring activation parameters <86JCS(D)205>. For (**12a**), E_a , $\Delta H^\ddagger$, and $\Delta G_{298}^\ddagger$ are 82.1, 78.6, and 79.2 kJ mol^{-1} , respectively, while $\log_{10} A$ is 13.4 and $\Delta S^\ddagger$ is $2.0\text{ J K}^{-1}\text{ mol}^{-1}$. As the halides increase in size (decrease in electronegativity), values of E_a and $\Delta H^\ddagger$ decrease in energy (76.1 and 73.2 kJ mol^{-1} , respectively, for (**12b**) and 67.8 and 65.0 kJ mol^{-1} , respectively, for (**12c**)) while $\Delta S^\ddagger$ becomes more negative ($-9.3\text{ J K}^{-1}\text{ mol}^{-1}$ for (**12b**) and $-21.4\text{ J K}^{-1}\text{ mol}^{-1}$ for (**12c**)). The net result is that $\Delta G_{298}^\ddagger$ remains fairly constant in the series.

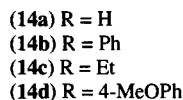
1.26.5 REACTIVITY

1.26.5.1 Reactions with Palladium Dihalides

3,3-Dimethylselenetane (**13**) reacts with palladium dihalides as shown in Equation (1) to give the palladium complexes (**12**) as crystalline solids (mp 136.7°C for (**12a**), 128°C for (**12b**), and 117°C for (**12c**)) in approximately 50% isolated yield <86JCS(D)205>.



When 3-hydroxyselenetanes (**7a**)–(**7d**) are treated with sodium hydroxide, a structural rearrangement accompanied by loss of selenium is observed to give 2-substituted allylic alcohols (**14**) <88JOC791>. A possible mechanism for this reaction is shown in Scheme 1. A similar reaction is observed upon treating 3-hydroxy-3-arylselenetanes (**7b**) and (**7d**) with 4-dimethylaminopyridine in the presence of aroyl halides. The aroyl esters of the rearranged allylic alcohols are the only products isolated.

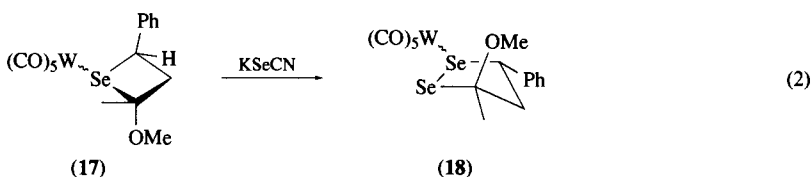


Scheme 1

The tungsten–pentacarbonyl complexes (**9**) and (**10**) react with potassium selenocyanate or potassium tellurocyanate to give ring-expanded products (**15**) and (**16**), respectively (^{92CC1050}), as shown in Scheme 2 and Equation (2). Selenetane–tungsten–pentacarbonyl complex (**17**) also reacts with potassium selenocyanate to give ring expansion and a 1,2-diselenole product (**18**).



Scheme 2



1.26.5.4 Reactions of Substituents

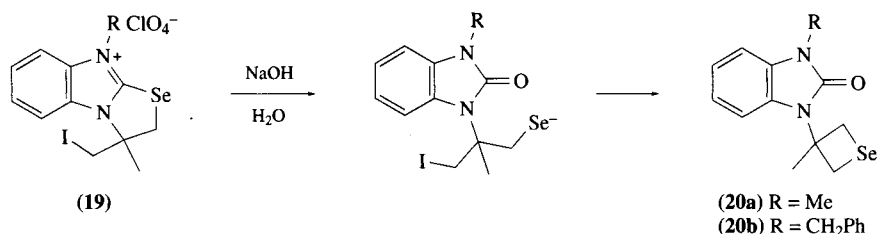
The hydroxyl group of 3-hydroxyselenetane (**7a**) undergoes a variety of reactions typical of a secondary hydroxyl group. Oxidation with the Dess–Martin periodinane in chloroform produces the previously unknown 3-ketoselenetane (**8**) <88JOC791>. The reaction of (**7a**) with acetic anhydride and sodium acetate <88JOC791> or with acetic anhydride and catalytic sulfuric acid in benzene gives acetate (**7f**) <91ZOR942>. In the acetic anhydride/sodium acetate reaction, product yield was 27% following preparative chromatography on silica gel eluted with 30% ether in petroleum ether <88JOC791>. 3-Hydroxyselenetane (**7a**) also reacts with 3,5-dinitrobenzoyl chloride in dry pyridine to give the 3,5-dinitrobenzoate ester (**7e**) in 82% isolated yield.

1.26.6 SYNTHESIS

The selenetanes and telluretanes that have been described in the literature have been constructed via three types of reactions: (i) via a one-component rearrangement–cyclization, (ii) via the reaction of a selenium or tellurium nucleophile with a three-carbon unit, or (iii) via the [2 + 2] cycloaddition reaction of a metal-complexed selenoaldehyde with a two-carbon unit. Substrates for the three-carbon unit include 1,3-dibromopropane derivatives and epichlorohydrin derivatives. Substrates for the two-carbon unit are vinyl ethers.

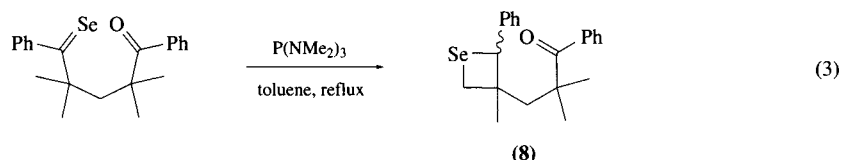
1.26.6.1 One-Component Syntheses

The reaction of 1-alkylbenzimidazoselenazolidinium salts (**19**) with aqueous alkali reportedly gives selenetanes (**20**) as shown in Scheme 3 <91DOK112>. Presumably, hydrolysis of (**19**) generates the urea group and a selenide anion, which displaces iodide intramolecularly to generate selenetanes (**20**). The selenetane derivatives are not characterized sufficiently to assign their structure unequivocally.



Scheme 3

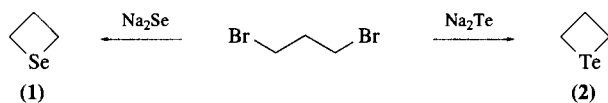
A second, one-component synthesis is illustrated in Equation (3). In this reaction, a selenoketone with *geminal*-methyl substituents on an α -carbon reacts via insertion into a C—H bond to give a mixture of isomers (**8**) <93BCJ1714>. The compounds (**8**) are isolated in low yield (<20%) from two different routes to the selenoketone.



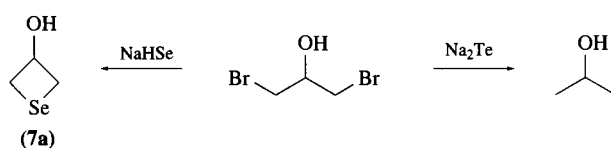
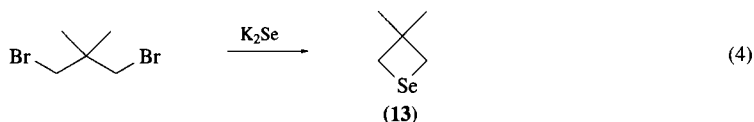
1.26.6.2 [1 + 3] Two-Component Syntheses

The parent selenetane (**1**) <30JCS1497> and telluretane (**2**) <45JCS11> nuclei have been prepared by the addition of the appropriate disodium chalcogenide to 1,3-dibromopropane as shown in Scheme 4, Equation (4), Scheme 5, and Equation (5). Although the selenetane derivative can be isolated in modest yield, the telluretane derivative (**2**) was extremely unstable. Telluretane (**2**) could be extracted

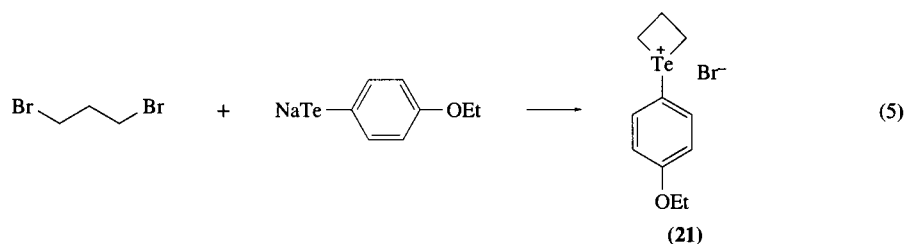
with chloroform although the extract continually formed a yellow gummy solid. Both (1) and (2) polymerize to substances of higher molecular weight.



Scheme 4

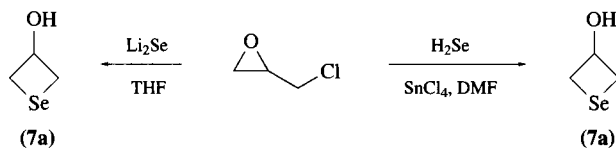


Scheme 5

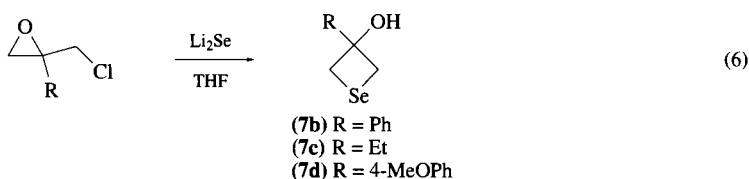


This approach has been extended to include the preparation of 3,3-dimethylselenetane (13) from 1,3-dibromo-2,2-dimethylpropane and dipotassium selenide in 1.7% isolated yield as shown in Equation (4) [86JCS(D)205]. Sodium hydroselenide reacts with 1,3-dibromo-2-propanol to give 3-hydroxyselenetane (7a) in 56% isolated yield [88JOC791], although the reaction of disodium telluride with the same substrate gives 2-propanol as the organic product (Scheme 5). Although the product has not been adequately characterized for unequivocal structural assignment, the addition of sodium 4-ethoxyphenyltelluride to 1,3-dibromopropane most likely generates the telluronium salt (21), which is a telluretane derivative [83JCS(D)2143] as shown in Equation (5).

Epichlorohydrin and epichlorohydrin derivatives serve as useful three-carbon units for the synthesis of 3-hydroxyselenetanes as shown in Scheme 6 and Equation (6). The addition of dilithium selenide, which is prepared by the reduction of selenium metal with lithium triethylborohydride, to epichlorohydrin in THF gives 3-hydroxyselenetane (7a) in 75% isolated yield [88JOC791]. Alternatively, the addition of hydrogen selenide to epichlorohydrin in DMF in the presence of tin(IV) chloride and a catalytic amount of *p*-toluenesulfonic acid also gives (7a) [91ZOR942].



Scheme 6

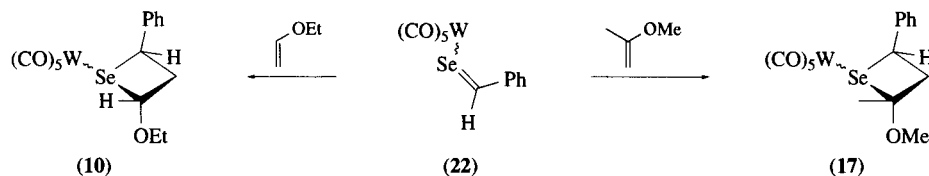


2-Substituted epichlorohydrins also react with dilithium selenide in THF as shown in Scheme 6 and Equation (6) to give 3-substituted-3-hydroxyselenetanes <88JOC791>. 2-Phenylepichlorohydrin gives 3-hydroxy-3-phenylselenetane (**7b**) in 55% isolated yield; 2-ethylepichlorohydrin gives 3-hydroxy-3-ethylselenetane (**7c**) in 58% isolated yield; and 3-(4-methoxyphenyl)epichlorohydrin gives 3-hydroxy-3-(4-methoxyphenyl)selenetane in 67% isolated yield.

The reaction of the epichlorohydrin substrates with disodium telluride does not give telluretane products <88JOC791>. Allylic alcohol derivatives are the isolated products, although one cannot dismiss the possible formation of 3-hydroxytelluretane derivatives as intermediates.

1.26.6.3 [2 + 2] Two-Component Syntheses

The cycloaddition reactions of tungsten–pentacarbonyl complexes of selenobenzaldehyde (**22**) with vinyl ethers give tungsten–pentacarbonyl complexes of selenetanes (**10**) and (**17**) <92CC563, 92CC1050> as shown in Scheme 7. The reaction with ethyl vinyl ether gives a mixture of (**10a**) and (**10b**), which cannot unambiguously be assigned stereochemistry <92CC563>. Thermally, the (**10**) mixture can be isomerized to a single isomer (**11**), which presumably has the stereochemistry shown from ¹H NMR coupling constants <92CC563>. The cycloaddition reaction of selenobenzaldehyde (**22**) with 2-methoxypropene gives a mixture of isomers (**17**) <92CC1050>.



Scheme 7

1.27

Four-membered Rings with One Phosphorus, Arsenic, Antimony, or Bismuth Atom

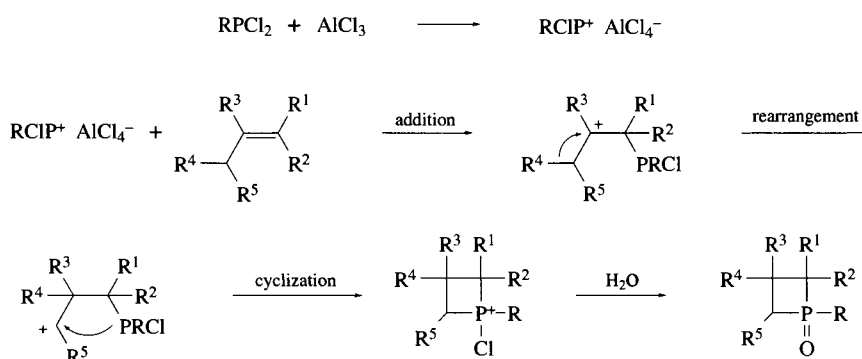
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1.27.1 INTRODUCTION

1.27.1.1 Historical Perspective

Four-membered rings containing one phosphorus, arsenic, antimony, or bismuth atom are pnictogenetanes ($\text{Pn} = \text{P}, \text{As}, \text{Sb}, \text{or Bi}$). Although systematic study has only been carried out using the reaction of phosphorus chlorides with highly substituted alkenes in the presence of aluminum trichloride (Scheme 1), some new approaches to this class of compounds have been developed between 1985 and 1995. A brief review on four-membered rings with one phosphorus atom appeared in <79COC(5)905> together with that on three-membered rings. Since several interesting compounds including the above compounds have also been summarized in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) covering the literature up to about 1982, in the present chapter more recent work published until 1994 has been collected. A new class of compounds, phosphetenes, which have been synthesized since 1983, will also be described in this chapter. Since the first report of four-membered rings containing one arsenic atom <77JCS(D)704> a few new compounds of this class have been synthesized, but four-membered rings with one antimony or bismuth atom are unknown and present an open field of research.



Scheme 1

1.27.1.2 Nomenclature

Four-membered rings containing one phosphorus, arsenic, antimony, or bismuth atom can be classified mainly under three categories.

(i) Phosphetane, arsetane, stibetane or bismetane: Saturated four-membered rings containing one phosphorus atom are named as phosphetane. Arsetane, stibetane, and bismetane are arsenic, antimony, and bismuth analogues of phosphetane, respectively. These compounds can also be named as phospho-, arsa-, stiba-, or bismacyclobutane derivatives.

(ii) Phosphetene, arsetene, stibetene, or bismetene: Four-membered rings with one phosphorus, arsenic, antimony, or bismuth atom and one double bond in the ring are called phosphetene, arsetene, stibetene, or bismetene. These compounds can also be named as phospho-, arsa-, stiba-, or bismacyclobutene derivatives. Two isomers based on the position of the double bond may be named, for example, as Δ^1 -phosphetene and Δ^2 -phosphetene.

(iii) Phosphete, arsete, stibete, or bismete: Four-membered rings with one phosphorus and two double bonds are known as phosphetes. Arsete, stibete, and bismete are named for four-membered rings with one arsenic, antimony, or bismuth and two double bonds. These compounds are also known as phospho-, arsa-, stiba-, and bismacyclobutadiene.

1.27.2 EXPERIMENTAL STRUCTURAL METHODS

Structural elucidation of four-membered rings with one phosphorus atom has been mostly carried out by ^1H , ^{13}C , and ^{31}P NMR spectroscopy. X-ray diffraction has also become a powerful method for structural determination.

1.27.2.1 X-ray Diffraction Studies

X-ray crystallographic analysis has been used to determine the crystal structures of phosphetanes having a trivalent, tetravalent, or pentavalent phosphorus atom. The first x-ray crystallographic analysis was reported by Mazhar-ul-Haque for *trans*-1-chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide (**1**) <70JCS(B)934>. The four-membered ring is significantly puckered, which represents one of the structural features of phosphetanes. Selected bond lengths, bond angles, and dihedral angles of the four-membered ring of phosphetanes are summarized in Table 1 (for structural formulas see Scheme 2). 7-Phosphatricyclo[3.2.0.0^{4,6}]-2-heptene chromium pentacarbonyl complex (**2**) <84NJC453>, 1-*t*-butyl-2,2,3,4,4-pentamethylphosphetane 1-oxide (**3**) <84AX(C)1918>, 2,2,3,4,4-pentamethyl-1-(1-naphthyl)phosphetane 1-oxide (**4**) <85AX(C)975>, 9-chloro-9-diisopropylamino-9-phosphoniatricyclo[5.1.1.0^{4,8}]nonane tetrachloroaluminate (**5**) <86CC1081>, diphosphatricyclo[2.1.0.0^{2,5}]pentane (**6**) <88AG(E)837>, 1,1-di-*t*-butylphosphetanium iodide (**7**) <92CB1987>, *cis*-dichloro-bis(3-*t*-butyl-1-phenylphosphetane)platinum(II) complexes (**8**) and (**9**) <92OM2944>, phosphetane iron complex (**10**) <92JCS(D)1751>, optically active 1-menthylphosphetane (**11**) <93T10291>, and adduct (**12**) of dinuclear iron phosphinidene complex with norbornadiene <93IC5720> were analyzed to show that all four-membered rings are puckered except for (**7**). The longest P—C bond in the ring is 1.950 (3) Å for (**2**) and the shortest one is 1.79 Å for (**7**). Bond angles C—P—C are scattered in the region of 73.6 (4) $^\circ$ (for (**12**)) to 85.9 (11) $^\circ$ (for (**1**)).

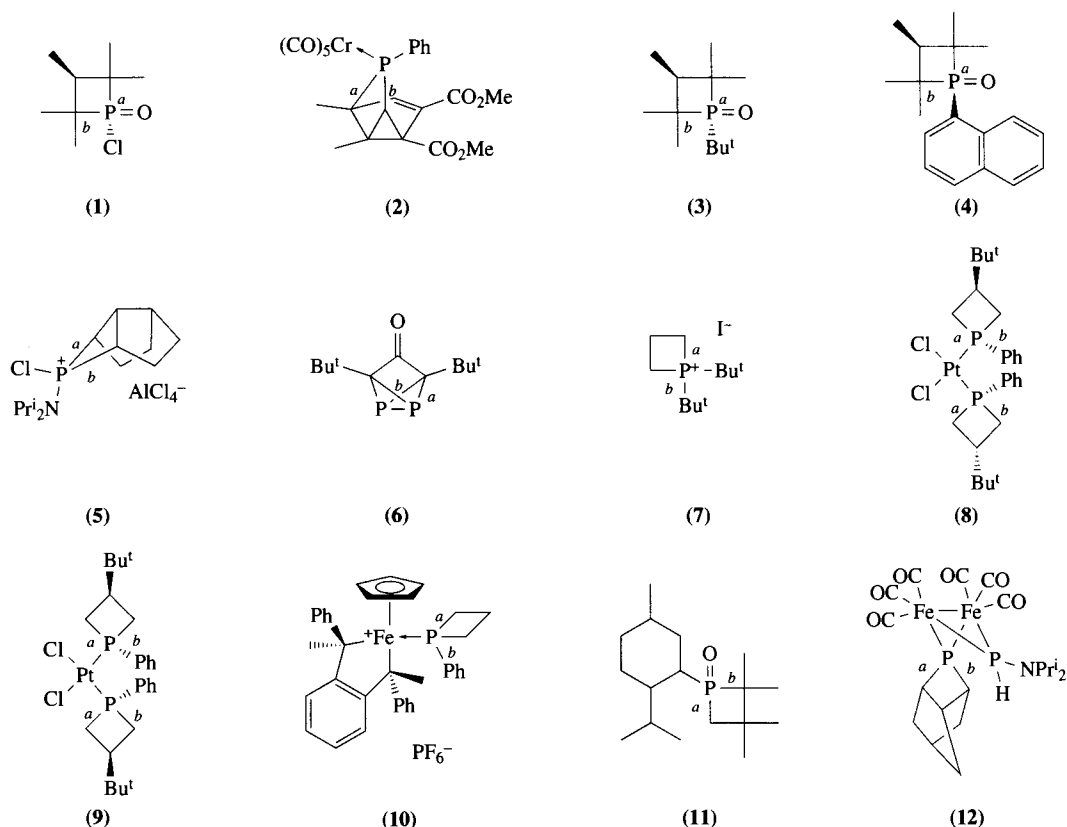
Table 1 Selected bond lengths, bond angles, and dihedral angles of four-membered rings of phosphetanes.

Compound	<i>a</i> (Å)	<i>b</i> (Å)	C—P—C ($^\circ$)	Dihedral angle ^a ($^\circ$)	Ref.
(1)	1.84 (2)	1.83 (3)	85.9 (11)	26.4	70JCS(B)934
(2)	1.950 (3)	1.805 (3)	77.0 (1)	26.3	84NJC453
(3)	1.846 (3)	1.845 (4)	80.7 (2)	19.2	84AX(C)1918
(4)	1.849 (2)	1.838 (2)	81.1 (1)	30.3	85AX(C)975
(5)	1.820 (15)	1.821 (11)	85.2 (6)	22.4	86CC1081
(6)	1.895 (7)	1.897 (8)	—	—	88AG(E)837
(7)	1.80 (1)	1.79 (1)	81.7 (7)	0	92CB1987
	1.83 (1)	—	82.4 (10)	0	
(8) <i>trans</i>	1.824 (7)	1.833 (7)	78.7 (3)	7.98	92OM2944
<i>cis</i>	1.835 (7)	1.830 (7)	78.8 (3)	30.67	
(9) <i>trans</i>	1.829 (8)	1.836 (8)	79.0 (4)	0.77 ^b	92OM2944
<i>trans</i>	1.815 (9)	1.833 (8)	78.2 (2)	20.01	
(10)	1.85 (2)	1.87 (2)	77.6 (8)	14 (2) ^c	92JCS(D)1751
	1.86 (3)	1.90 (2)	77.0 (1)	18 (2) ^c	
(11)	1.806 (5)	1.852 (6)	79.9 (2)	17.6	93T10291
(12)	1.859 (9)	1.83 (1)	73.6 (4)	—	93IC5720

^aDihedral angle between planes C—C—C and C—P—C. ^b ± 10 . ^cDihedral angle P—C—C—C.

X-ray crystallographic analyses carried out for phosphetenone tungsten pentacarbonyl complex (**13**) <85JA5001>, Dewar phosphabenzene (**14**) <86AG(E)280>, phosphetene tungsten pentacarbonyl complex (**15**) <88OM1791>, alkylidenephosphetene oxide platinum complex (**16**) <89OM1007>, free phosphetene (**17**) <89JA9129, 90AG(E)75>, tungsten pentacarbonyl complex (**18**) and HgCl₂ complex (**19**) of (**17**) <91IC3381>, phosphetenium salts (**20**) and (**21**) <93AG(E)1359>, 1-chloro-1,2-dihydrophosphete-4-yl platinum complex (**22**) <93OM4265>, and 1-oxo-1,2-dihydrophosphete-4-yl platinum complex (**23**) <94OM2444> showed that these four-membered rings are almost planar in sharp contrast to those of phosphetanes. Selected bond lengths and bond angles are summarized in Table 2 (for structural formulas see Scheme 3). Single bonds for P—C (*sp*²) are shorter than those for P—C (*sp*³) (see (**15**), (**16**), (**17**), (**18**), (**19**), (**22**), and (**23**)).

Arsetane iron complex (**24**) <92JCS(D)1751>, free arsenetene (**25**) <90AG(E)75>, and arsenetene oxide



Scheme 2

Table 2 Selected bond lengths and bond angles of four-membered rings of phosphetenes.

Compound	<i>a</i> (Å)	<i>b</i> (Å)	<i>c</i> (Å)	C—P—C (°)	Ref.
(13)	1.93 (1)	1.83 (1)	1.36 (1)	71.9 (5)	85JA5001
(14)	1.68 (1) ^a	1.89 (1)	1.54 (1)	79.5 (4)	86AG(E)280
(15)	1.815 (4)	1.902 (5)	1.331 (7)	74.0 (2)	88OM1791
(16)	1.754 (6)	1.766 (6)	1.365 (8)	77.9 (3)	89OM1007
(17)	1.821 (3)	1.886 (4)	1.366 (5)	74.0 (2)	89JA9129
	1.826 (3)	1.872 (4)	1.359 (4)	73.8 (2)	90AG(E)75
(18)	1.816 (19)	1.813 (24)	1.358 (31)	75.4 (10)	91IC3381
(19)	1.80 (1)	1.82 (1)	1.34 (2)	76.8 (6)	91IC3381
	1.80 (1)	1.80 (1)	1.34 (2)	77.9 (6)	
(20)	1.798 (3)	1.856 (3)	1.366 (4)	79.1 (1)	93AG(E)1359
(21)	1.859 (3)	1.781 (3)	1.360 (5)	78.7 (1)	93AG(E)1359
(22)	1.678 (5)	1.911 (6)	1.389 (8)	—	93OM4265
(23)	1.776 (3)	1.844 (10)	1.369 (13)	80.2 (5)	94OM2444

^aC=P double bond.

platinum complex (26) <91OM372>, were analyzed by x-ray diffraction to elucidate that they have similar structures to those of phosphetenes, although bond angles for C—As—C are much smaller than those for C—P—C (see Table 3 and Scheme 4).

1.27.2.2 NMR Studies

1.27.2.2.1 Proton NMR

Although ¹H NMR spectroscopy has been gradually replaced by ¹³C and ³¹P NMR, in terms of their usefulness for the determination of all compounds containing one phosphorus or arsenic

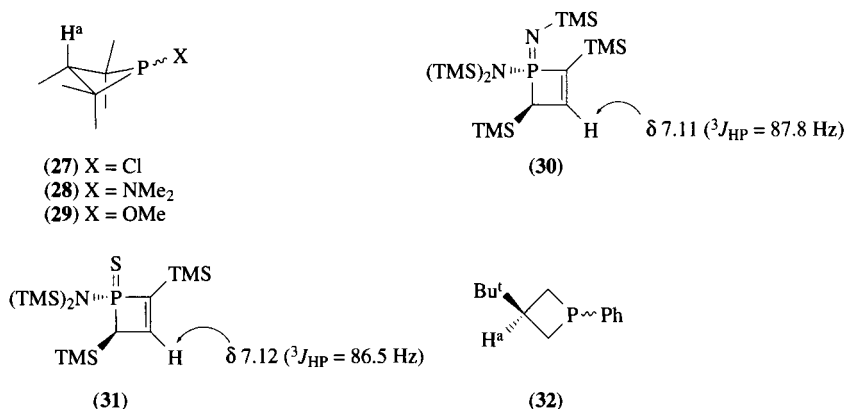


<i>Compound</i>	<i>a</i> (Å)	<i>b</i> (Å)	<i>c</i> (Å)	C—As—C (°)	<i>Ref.</i>
(24) ^a	1.974 (13)	1.953 (12)	—	72.5 (6)	92JCS(D)1751
(25)	1.949 (4)	1.989 (6)	1.358 (6)	69.9 (2)	90AG(E)75
(26)	1.94 (1)	1.89 (1)	1.32 (3)	68.4 (8)	91OM372

^a Dihedral angle As—C—C—C is $-20(1)^\circ$.

atom, it still remains an important method. In the case of trivalent phosphetanes (27)–(29) the stereochemistry of the compounds can be estimated from the coupling constant between the ring proton and ^{31}P nucleus, see Scheme 5. For example, larger coupling constants between a proton on C-3 and ^{31}P were observed for the *cis*-isomers than the *trans*-isomers, as shown in Table 4 (84JCS(P2)553).

An unusually large 3-bond P-H coupling constant ($^3J_{\text{HP}} \approx 87$ Hz) was observed for a proton in the 3-position of 1,2-dihydrophosphetes (**30**) and (**31**), while the $^3J_{\text{HP}}$'s with the *trans*-proton are usually 40–50 Hz, see Scheme 5. The increase of $^3J_{\text{HP}}$ by about 40 Hz can be reasonably explained by the increase in ring strain and a dual pathway for spin–spin coupling in these rings (<7TL6121>).



Scheme 5

Table 4 Selected ^1H NMR spectral data of phosphetanes (27)–(29).

Compounds	δ H^a	$(^3J_{\text{PH}}/\text{Hz})$
(27) <i>trans</i>	2.81	1.3
(27) <i>cis</i>	2.17	2.4
(28) <i>trans</i>	2.65	<0.5
(28) <i>cis</i>	1.64	3.4
(29) <i>trans</i>	2.60	0.6
(29) <i>cis</i>	1.84	2.2

NOESY, a method of two dimensional NMR spectroscopy, has contributed to determine stereochemistry in solution; for example, multiplets at δ 2.81–2.96 and δ 2.41–2.60, whose assignment is otherwise almost impossible because of their very complex signal, can be assigned to *trans*- and *cis*-(32), respectively <92OM2944>, see Scheme 5.

1.27.2.2.2 Carbon-13 NMR

In ^{13}C NMR spectra not only the chemical shifts but also the coupling constants with the ^{31}P nucleus have provided important information about the molecular structure. Tables 5 and 6 summarize the data of chemical shifts and coupling constants for the ring carbons of phosphetanes and dihydrophosphetes and their metal complexes, respectively, along with their ^{31}P chemical shifts. The structural formulas are shown in Schemes 6 and 7.

Selected ^{13}C NMR data for the rhodium π -allyl complex (119) and cobalt π -complex of phosphete (120) are given in Scheme 8.

In the arsenic containing four-membered ring compounds the ^{13}C NMR spectrum has been reported only for dihydroarsete (25) (Scheme 9). The methylene carbon resonates at δ 23.3, which is shifted to a slightly higher field than that of the corresponding dihydrophosphete (17) (δ 28.3), indicating that the shielding effect of arsenic is larger than that of phosphorus.

1.27.2.2.3 Phosphorus-31 NMR

Phosphorus-31 NMR spectroscopy is the most useful for the phosphorus-containing compounds due to its ready measurement emerging from 100% natural abundance and high relative intensity. One of the noteworthy features of ^{31}P NMR is that the chemical shifts directly reflect the structural environment of the phosphorus atom, see Tables 5 and 6. The *trans* isomers at the 1,3 positions of trivalent phosphetanes (Table 7) resonate more downfield than the *cis* isomer in ^{31}P NMR, while the reverse situation is found for pentavalent phosphetanes (Table 8) <84JA7021, 84JCS(P2)553, 87S265, 92JOC511>.

Table 5 Carbon-13 and Phosphorus-31 NMR spectral data of phosphetanes.

Compounds	C-1 (δ ($^1J_{CP}/\text{Hz}$))	C-2 (δ ($^2J_{CP}/\text{Hz}$))	C-3 (δ ($^1J_{CP}/\text{Hz}$))	^{31}P (δ)	Ref.
(33) ^a	39.4(–)	39.8(–) ^b	37.0(9) ^b	17.6 ^a	93T10291
	38.9(–) ^b	41.3(–) ^b	39.9(16.9)	8.7 ^a	93T10291
(34) ^a	36.6(2.5)	43.0(5.3)	42.5(0)	32.1 ^a	93T10291
	36.7(4.6)	44.1(5.7)	43.6(2.9)	26.9 ^a	93T10291
(35) ^a	39.6(2.9)	46.2(9.6)	53.4(9.2)	45.1 ^a	93T10291
(36) ^a	35.4(4.9)	49.5(7.2)	33.8(2.7)	48.6 ^a	93T10291
(37) ^a	40.52(0.0)	47.36(1.9)	C-1 ^c	47.4 ^a	92JOC511
(38) ^a	40.47(6.1)	40.17(14.7)	C-1	39.5 ^a	92JOC511
(6) ^a	178.52(15.1)	b	b	–346.6 ^a	88AG(E)837
(61)	64.8(19.8)	34.6(0)	68.8(0)	–130.2	87AG(E)85
	67.2(11.8)	46.0(0)	68.8(0)		
(62)	17.0(46)	18.6(23)	C-1	74.7 ^d	92CB1987
(63)	16.2(43)	18.4(23)	C-1	80.3 ^d	92CB1987
(64) ^e	33.2(47)	21.3(22)	C-1	41.9 ^d	92CB1987
(39)	44.12(52.3)	40.42(12.4)	C-1	70.4	92JOC511
(40)	43.30(52.8)	40.62(14.2)	C-1	73.4	92JOC511
(41)	45.03(52.7)	40.35(12.7)	C-1	70.1 ^f	92JOC511
(42)	43.95(52.2)	40.58(14.2)	C-1	73.3 ^g	92JOC511
(43)	45.45(52.2)	41.03(13.4)	C-1	70.2	92JOC511
(44)	44.21(52.8)	40.85(14.0)	C-1	73.2	92JOC511
(45)	44.04(56.2)	40.65(13.6)	C-1	69.2	92JOC511
(46)	43.82(56.3)	40.52(13.8)	C-1	–	92JOC511
(47) ^a	52.27(47.9)	38.40(5.2)	C-1	95.7 ^d	92JOC511
(48) ^a	50.04(50.2)	42.83(18.8)	C-1	86.6 ^d	92JOC511
(49) ^a	48.08(63.2)	31.03(7.1)	C-1	55.9	92JOC511
(50) ^a	45.60(63.7)	39.49(20.1)	C-1	76.7	92JOC511
(51) ^a	48.67(65.0)	31.65(6.9)	C-1	48.3	92JOC511
(52) ^a	49.37(52.5)	37.11(8.6)	C-1	74.7	92JOC511
(53) ^a	49.47(52.1)	41.32(13.5)	C-1	83.6	92JOC511
(54) ^a	47.87(47.3)	39.11(9.5)	C-1	63.8	92JOC511
(55) ^a	48.86(47.0)	41.88(11.3)	C-1	67.9	92JOC511
(56) ^d	49.1(72)	36.5(17)	C-1	74.8 ^d	87TL603
(57) ^d	55.1(65)	41.4(11)	C-1	80.1 ^d	87TL603
(58) ^d	48.1(80)	31.9(12)	C-1	55.8 ^d	87TL603
(59) ^d	48.0(79)	32.4(12)	C-1	53.8 ^d	87TL603
(60) ^d	48.2(81)	32.2(11)	C-1	49.6 ^d	87TL603
(10)	49.7(55.1)	36.4(12.3)	41.7(51.1)	62.7 ^a	93T10291
	49.2(58.0)	38.5(14.0)	46.1(47.4)	57.7 ^a	93T10291
(65)	48.5(53.6)	41.8(11.6)	52.7(51.7)	68.8 ^a	93T10291
	48.1(56.2)	42.8(15)	53.4(48.7)	64.5 ^a	93T10291
(66)	48.3(52.6)	44.5(6.7)	51.3(45.6)	64.3 ^a	93T10291
	47.2(56.3)	45.8(7.7)	55.2(40.5)	61.7 ^a	93T10291
trans-(67)	49.3(63.7)	30.0(12.1)	36.5(52.8)	43.4	87S265
trans-(68)	50.2(64.5)	30.8(12.1)	37.2(52.4)	43.6	87S265
trans-(69)	50.8(63.1)	29.6(10.8)	39.9(55.1)	47.7	87S265
(71)	46.7(55.0)	47.4(12.9)	44.0(55.1)	67.9	93T10291
trans-(72)	46.8(58.1)	45.2(5.5)	46.8(58.1)	52.8	87S265
cis-(72)	46.1(59.3)	45.7(–) ^b	46.1(59.3)	55.3	87S265
trans-(73)	46.9(58.2)	45.0(6.6)	46.9(58.2)	52.3	87S265
cis-(73)	46.0(58.2)	45.0(6.6)	46.0(58.2)	55.6	87S265
trans-(74)	47.9(58.2)	45.1(5.5)	47.9(58.2)	52.6	87S265
(76)	52.2(–) ^b	41.4(–) ^b	C-1	64.56	87PS(29)283
(77)	52.8(–) ^b	41.7(–) ^b	C-1	63.4	87PS(29)283
(78)	51.4(78)	27.9(18)	31.3(59)	49.8	88TL1219
(79)	52.7(79)	34.8(14)	46.4(69)	46.4	88TL1219
(80)	58.7(67)	14.3(21)	34.5(61)	48.6	88TL1219
	56.3(63)	19.3(22)	34.0(67)	46.7	88TL1219
(81)	71.9(68)	26.6(22)	33.7(62)	48.4	88TL1219
(82)	46.8(69.7)	7.52(27.2)	C-1	53.2	93JCR(S)268
(83)	36.8(69.7)	7.52(27.2)	C-1	52.6	93JCR(S)268
(84)	37.5(72.0)	7.4(27.6)	C-1	53.2	93JCR(S)268
(10) ^d	25.79(31.9)	23.36(18.5)	C-1	99.47 ^d	92JCS(D)1751
(5)	49.91(14.9)	58.67(58.3)	C-1	79.4 ^d	86CC1081
(85) ^a	39.3(0)	12.8(7)	C-1	–23.7 ^{h,i}	92CB1987
(86) ^a	18.98(0)	17.2(13)	C-1	12.8 ^h	92CB1987
(88) ^a	50.69(23.1)	65.27(–) ^b	41.43(27.2)	37.1 ^a	90CC153
(2)	61.40(25.64)	52.22(9.77)	31.23(50.05)	15.54 ^{a,j}	84NJC453

^aIn C₆D₆. ^bNot assigned or not resolved. ^cC-1 and C-3 are equivalent. ^dIn CH₂Cl₂ or CD₂Cl₂. ^eIn D₂O. ^f $^5J_{\text{PF}} = 6.1$ Hz. ^g $^5J_{\text{PF}} = 6.1$ Hz. ^hIn pentane. ⁱ $^1J_{\text{PF}} = 663$ Hz. ^j $^1J_{\text{PW}} = 239$ Hz.

Table 6 Carbon-13 and Phosphorus-31 NMR spectral data of 1,2-dihydrophosphetes.

Compounds	C-1 (δ ($^1J_{CP}/\text{Hz}$))	C-2 (δ ($^2J_{CP}/\text{Hz}$))	C-3 (δ ($^1J_{CP}/\text{Hz}$))	^{31}P (δ)	Ref.
(17) ^a	b	b	28.3(7.1)	−18.0 ^c	90AG(E)75
(17) ^c	b	b	28.1(7.1)	−16.04 ^a	91IC3381
(91)	177.1(32.6)	139.2(5.0)	47.5(47.6)	−19.0	87AG(E)85
	160.2(21.9)	162.6(15.0)	47.5(47.6)		
(92)	168.6(36.1)	145.7(6.8)	47.92(16.1)	51.2	88OM572
(14)	241.5(33.7)	73.4(6.1)	67.8(17.6)	314 ^a	86AG(E)280
(93)	237.9(33.4)	73.7(3.8)	69.9(19.6)	312 ^a	86AG(E)280
(94)	223.6(36.5)	75.3(−) ^b	71.8(19.5)	314 ^a	86AG(E)280
(95)	239.8(33.5)	73.2(5.9)	67.1(17.7)	315 ^a	86AG(E)280
(96)	242.1(33.4)	73.6(5.5)	67.4(17.9)	315	86AG(E)280
(97)	240.5(31.7)	75.9(5.2)	68.0(17.0)	316	86AG(E)280
(98)	241.7(32.0)	75.8(6.3)	68.6(17.1)	317	86AG(E)280
(99)	242.1(34.5)	75.9(6.0)	68.1(17.3)	316	86AG(E)280
(20)	168.6(36.1)	145.7(6.8)	42.4(46)	81.7	93AG(E)1359
(100)	132.6(26)	172.9(29)	43.8(44)	82.3	93AG(E)1359
(30)	158.73(51.3)	157.21(34.9)	56.58(62.1)	−0.1 ^c	87TL6121
(31)	158.34(36.1)	154.80(32.7)	58.17(41.5)	64.4 ^c	87TL6121
(101)	109.19(120.9)	105.56(15.6)	30.04(99.2)	−13.0 ^c	87TL6121
(102) ^a	b	b	42.7(59.2)	18.4 ^a	91IC3381
(103)	160.2(83.8)	113.57(8.1)	50.82(58.2)	22.95	88OM1791
(104) ^d	67.74(116.2)	b	80.08(116.8)	19.1 ^d	90CC153
(105) ^c	b	b	75.43(40.3)	42.85 ^{c,f,g}	88OM633
(18)	b	b	35.5(38.5)	16.9 ^{a,e}	91IC3381
(19)	b	b	33.9(39.2)	35.45 ^a	91IC3381
(107)	202.13(65.7)	180.35(70.5)	160.46(84.3)	63 ^c	85JA5001
(108)	148.28(50.6)	124.09(10.1)	39.55(31.32)	72.72	89CC788
(109) ^a	95.87(43.3)	151.35(4.3)	77.25(50.8)	−12.5 ^a	90CC153
(110) ^a	93.34(54.3)	149.25(0)	52.14(26.2)	20.2 ^a	90CC153
(111)	b	159.41(10.12)	59.6(35.16)	97.0	90SL171
(112) ^a	b	158.01(7.5)	56.67(32.7)	42.55 ^{a,h}	90OM788
(113) ^a	b	156.32(7.5)	49.46(29.7)	74.39 ^{i,j}	90OM788
(13)	190.72(34.2)	169.5(36.6)	151.7(51.3)	86.9 ^a	85JA5001
(116)	191.42(30.5)	181.30(33)	163.21(48.8)	85.8 ^k	85JA5001
(118)	158.2(36.2)	165.8(15.4)	65.0(60.1)	39.3	87AG(E)85

^aIn C₆D₆. ^bNot assigned or not resolved. ^cIn CH₂Cl₂ or CD₂Cl₂. ^dIn CD₃OD. ^e $^1J_{PW} = 231.4$ Hz. ^f $^1J_{PW} = 244$ Hz. ^gminor diastereomer $\delta_P(\text{CH}_2\text{Cl}_2)$ 47.59. ^h $^1J_{PW} = 239$ Hz. ⁱIn pentane. ^j $^1J_{PW} = 239$ Hz. ^kIn toluene.

The substituents on the phosphorus atom significantly affect the chemical shifts of the ^{31}P NMR. For example, in the trivalent 2,2,3,4,4-pentamethylphosphetanes (27)–(29) the signals may shift downfield in the order $\text{NMe}_2 < \text{Cl} < \text{OMe}$ (OMe being the most downfield) <84JCS(P2)553>, which is simply based on the electronegativity of the nitrogen, chlorine, and oxygen atoms.

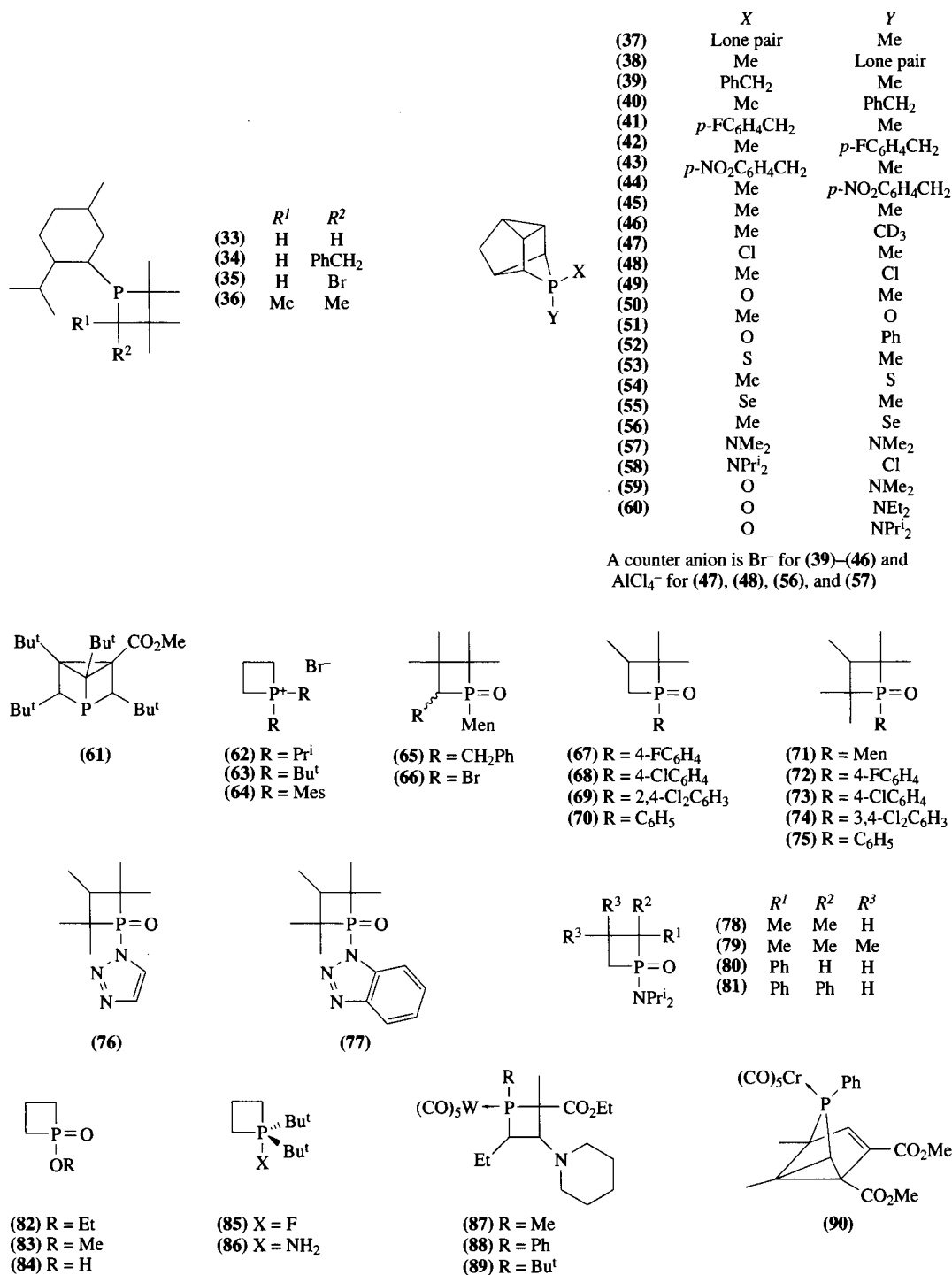
A similar shift is also observed in the tungsten pentacarbonyl complexes of the following phosphetane and 1,2-dihydrophosphetes. In these cases, the compounds resonate downfield in the order $\text{Me} < \text{Ph} < \text{Bu}^t$ (Bu^t being the most downfield), which is attributable to inductive effect (for Me and Ph) and electronic repulsion between bonding electrons (for Bu^t) (Scheme 10) <90CC153, 90OM788>.

Pentacoordinate phosphorus compounds usually resonate at a much higher field than 85% H_3PO_4 external standard (for example (122) <83JOC2621>, (85) <92CB1987>). As shown in Scheme 11 the chemical shifts are strongly sensitive to the coordination number of the phosphorus atom.

The ^{31}P NMR chemical shifts of the metal complexes are also affected by the metal; more downfield shift was observed in the order $\text{W} < \text{Mo} < \text{Cr}$ (chromium causing the most downfield shift) in the cases shown in Scheme 12 <84NJC453, 85JA5001>.

The structures and ^{31}P chemical shifts of other interesting compounds are summarized in Scheme 13. The most upfield shift is $\delta - 346.6$ for (6), which is a reasonable value taking into consideration that the shift is $\delta - 460$ for P_4 . Two Dewar type benzenes (91) and (96) and prismane (61) which are valence isomers of a phosphabenzene were shown to have very different ^{31}P chemical shifts. In the case of (125) the low coordinate λ^3 phosphorus appears at remarkably high field ($\delta - 109$), which points to the high contribution of canonical structure (B) (Scheme 13) <87AG(E)83, 89NJC335>.

The coupling constants of ^{31}P with homo- and heteronuclei provide important structural information and there have been reported several examples for multi-bond through-coupling. The coupling constants with ^{19}F (Scheme 14), ^{183}W (see Schemes 10 and 12), ^{103}Rh (Scheme 16), and ^{185}Pt

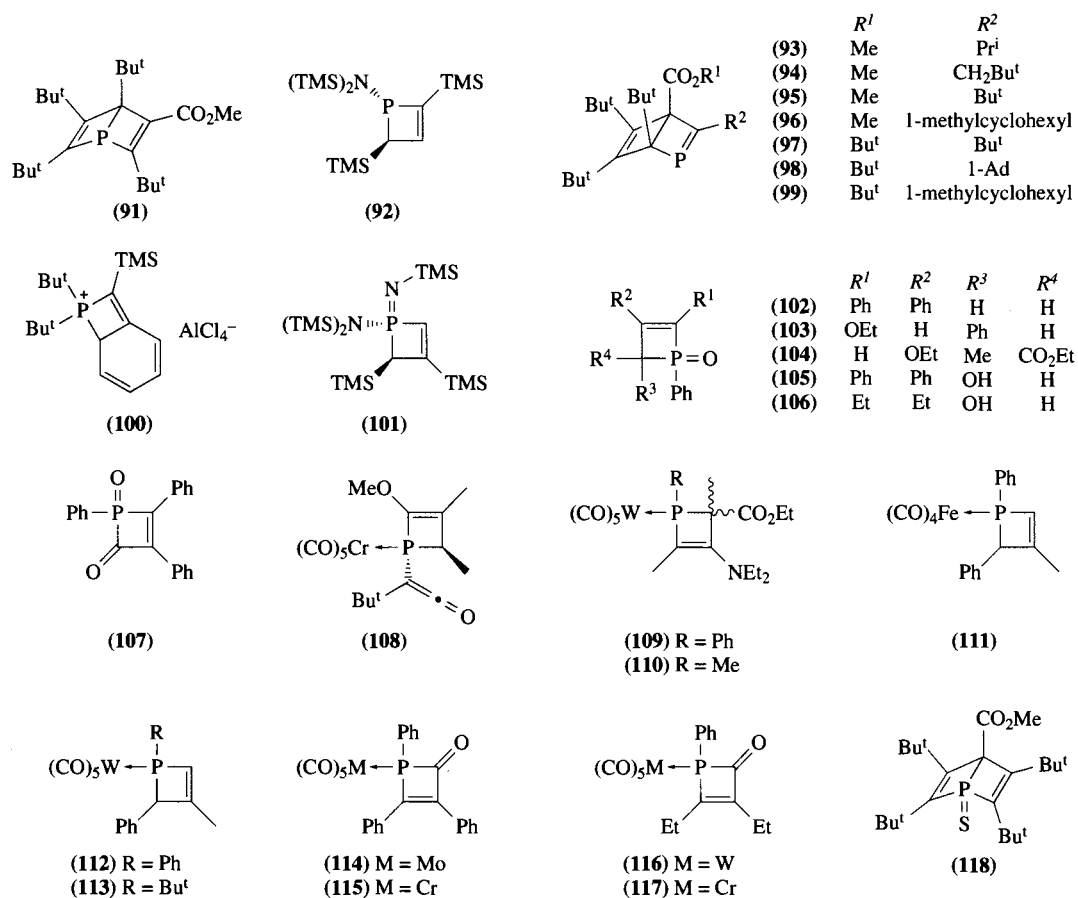


Scheme 6

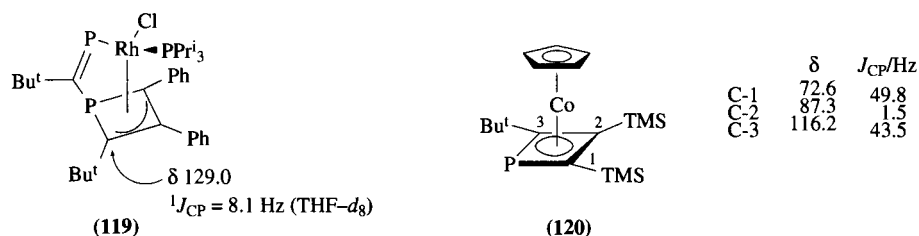
(see Tables 9 and 10) are demonstrated. The J_{PF} values of fluorine-containing compounds (85), (126) <93TL4619>, and (127) <85ZN(B)927> are summarized in Scheme 14. In compound (127) the $^2J_{PF}$ values vary from 8–237 Hz.

The J_{PH} and J_{PP} coupling constants are also demonstrated for compounds (12), (128) <83JA2074>, and (9) as shown in Scheme 15.

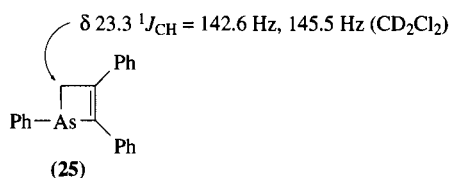
It is interesting to point out that the coupling constants between ^{31}P and ^{103}Rh are 3.4 Hz for the



Scheme 7



Scheme 8



Scheme 9

η^3 complex (119) and 37.3 Hz and 36.5 Hz for η^4 complexes (129) and (130), respectively (Scheme 16).

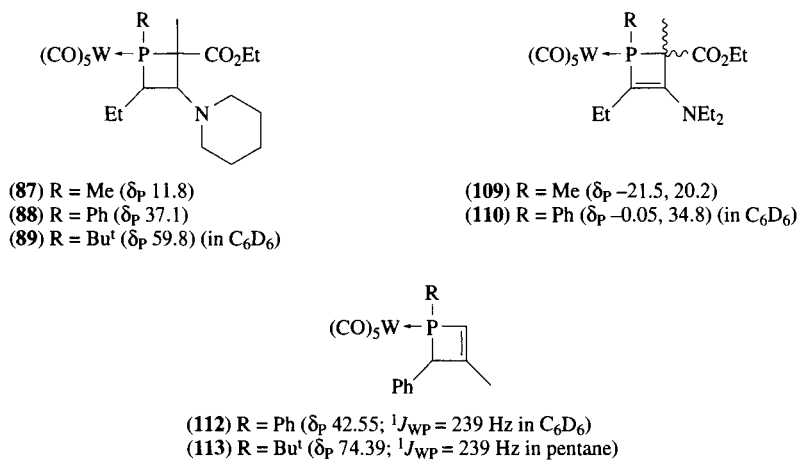
The ^{31}P chemical shifts and coupling constants J_{PP} and J_{PPt} of 1,2-dihydrophosphete platinum complexes (22), (23), and (131)–(135) and the 2-alkylidene-1,2-dihydrophosphete platinum complexes (136)–(139) (Scheme 17) are summarized in Tables 9 and 10.

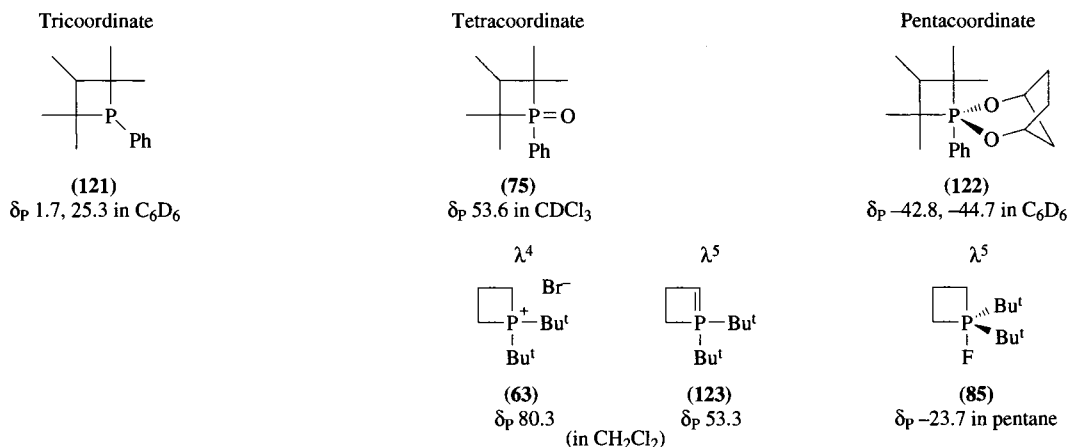
Table 7 Phosphorus-31 NMR spectral data of *trans* and *cis* isomers of trivalent phosphetanes.

Compounds	^{31}P (δ)	Ref.
(27) <i>trans</i>	169.2	84JCS(P2)553
<i>cis</i>	149.0	
(28) <i>trans</i>	127.5	84JCS(P2)553
<i>cis</i>	99.6	
(29) <i>trans</i>	186.6	84JCS(P2)553
<i>cis</i>	169.5	
(32) <i>trans</i>	−6.8	92OM2944
<i>cis</i>	−38.3	
(37) <i>trans</i>	47.4	92JOC511
(38) <i>cis</i>	39.5	92JOC511

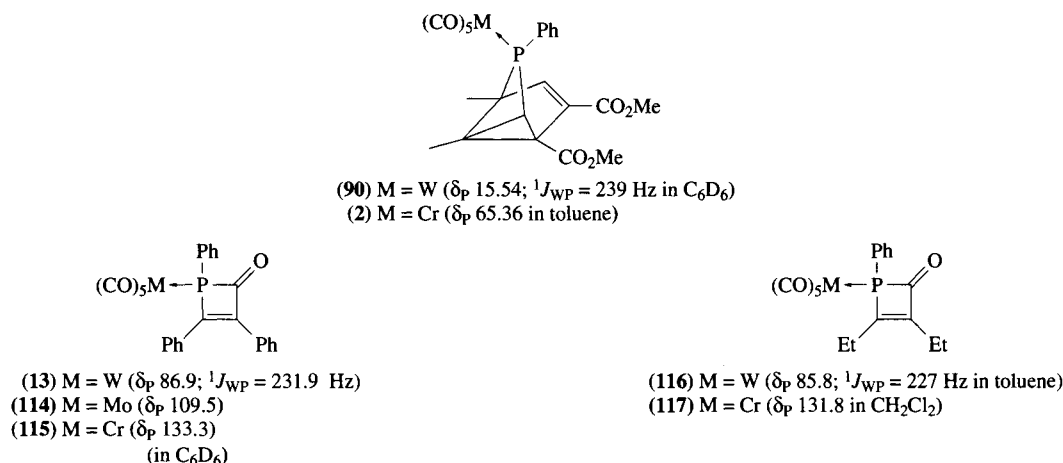
Table 8 Phosphorus-31 NMR spectral data of *trans* and *cis* isomers of pentavalent phosphetanes.

Compounds ^a	^{31}P (δ)	Compounds	^{31}P (δ)
(49) <i>trans</i>	55.9	(70) <i>trans</i>	43.8
(50) <i>cis</i>	76.7	<i>cis</i>	52.2
(52) <i>trans</i>	74.7	(72) <i>trans</i>	52.8
(53) <i>cis</i>	83.6	<i>cis</i>	55.3
(54) <i>trans</i>	63.8	(73) <i>trans</i>	52.3
(55) <i>cis</i>	67.9	<i>cis</i>	55.6
(67) <i>trans</i>	43.4	(74) <i>trans</i>	52.6
<i>cis</i>	51.7	<i>cis</i>	54.5
(68) <i>trans</i>	43.6	(75) <i>trans</i>	53.6
<i>cis</i>	48.6	<i>cis</i>	—
(69) <i>trans</i>	47.7		
<i>cis</i>	—		

^aCompounds (49)–(55): Ref. <92JOC511>; (67)–(75): Ref. <87S265>.**Scheme 10**



Scheme 11



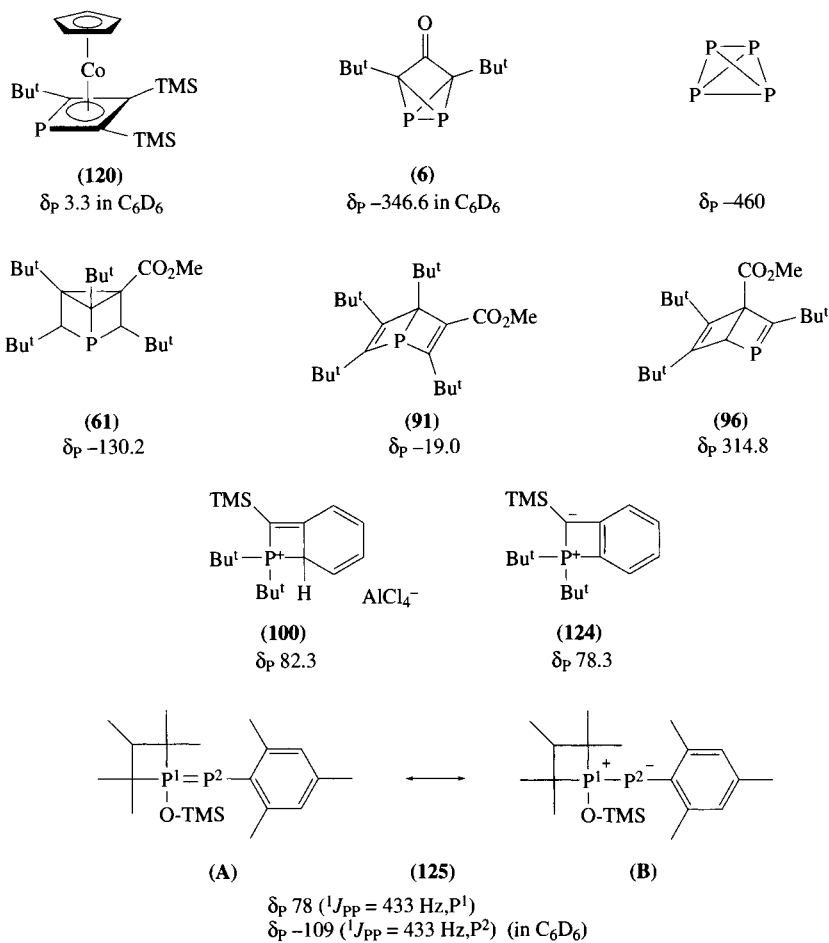
Scheme 12

1.27.2.2.4 Oxygen-17 NMR

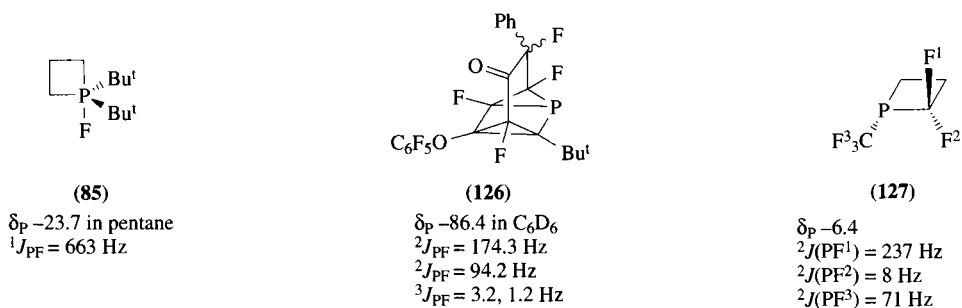
There has been reported only one ^{17}O NMR study on phosphetane 1-oxides (49), (70), and (75) <87MRC271>, in which the ^{17}O NMR chemical shifts are extremely sensitive to structural effects such as ring size and the presence of γ -interactions. The data is shown in Scheme 18. When methyls are placed on the carbons attached to phosphorus, these groups have a gamma relationship to the phosphoryl oxygen and hence the ^{17}O can experience the familiar γ -shielding effect. Therefore, more upfield shift was observed in (75) compared with (70). A comparison of the data for these four-membered heterocycles reveals that still another, stronger effect acts on the ^{17}O shift. The bridged phosphetane (49) with a larger γ -shielding effect resonates at a lower field, by 19 ppm and 34.7 ppm, than (70) and (75), respectively. Although the C—P—C angle of (49) has never been reported, it can be expected to be smaller than that of (70) or (75). Therefore, such a large downfield shift is attributed to the contraction of the C—P—C angle, as has also been noted for cyclic sulfoxides <80JOC4807, 82JOC3660>.

1.27.2.3 Mass Spectrometry

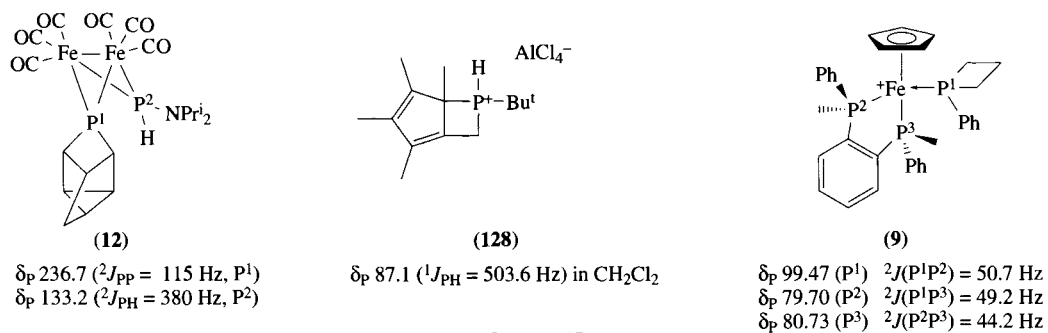
Most of the compounds described in this chapter have their molecular ions in electron impact (EI) or fast atom bombardment (FAB) mass mode. High resolution mass spectra are also useful for determination of element composition of the molecules. In the mass spectra of multicarbonyl complexes a stepwise elimination of carbonyl is an important fragmentation; the fragment ion



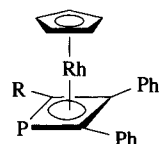
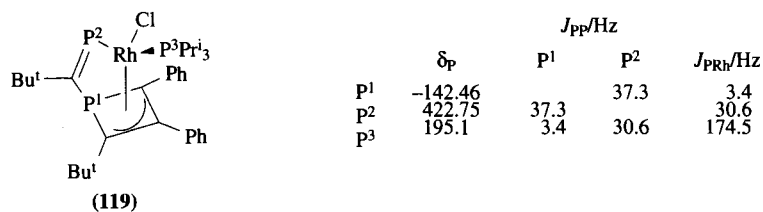
Scheme 13



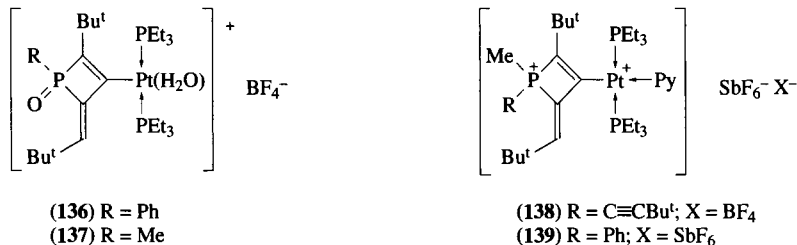
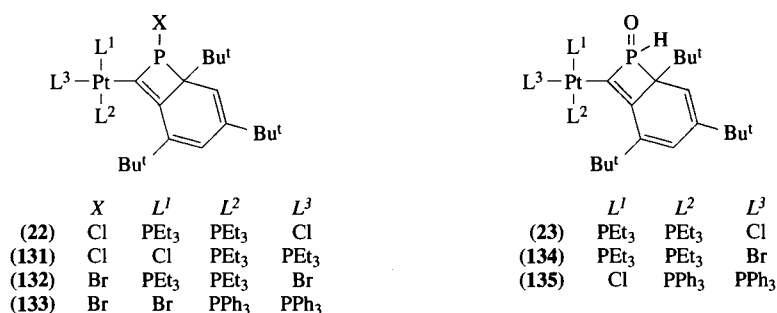
Scheme 14



Scheme 15

(129) R = Bu^t; δ_P -48.75 (J_{PRh} = 37.3 Hz)(130) R = NPrⁱ(TMS); δ_P -26.45 (J_{PRh} = 36.5 Hz)

Scheme 16



Scheme 17

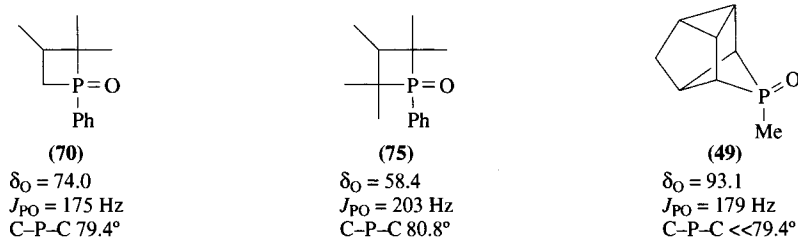
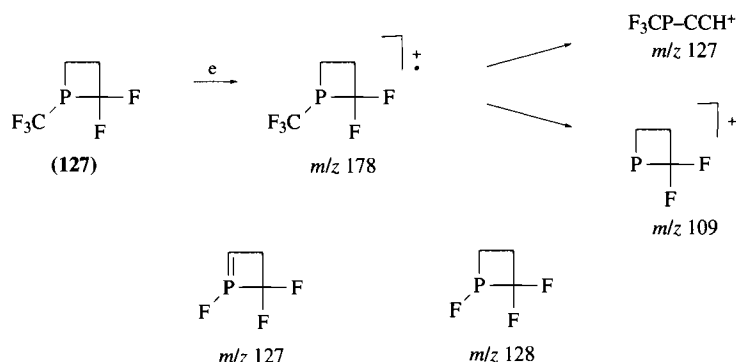
Table 9 Phosphorus-31 chemical shifts and coupling constants (J_{PP} and J_{PPt}) for platinum complexes of 1,2-dihydrophosphetes.

	δ_P				J/Hz						
	P	L ¹	L ²	L ³	P—Pt	L ¹ —Pt	L ² —Pt	L ³ —Pt	P—L ²	P—L ³	L—L
(22)	93.8	12.9	11.2	—	387.7	2737.1	2632.5	—	—	—	—
(131)	88.2	—	9.3	-0.1	190.7	—	1793.0	3970.5	18.3	18.3	18.3
(132)	92.1	7.2	5.3	—	393.8	2714.6	2588.6	—	—	—	—
(133)	88.5	—	13.1	13.8	144.1	—	1762.8	4204.2	19.2	6.4	18.1
(23)	25.9	13.0	11.4	—	147.1	2680.0	2575.0	—	9.6	—	—
(134)	25.5	10.1	8.2	—	145.7	2537.7	2583.0	—	12.4	—	—
(135)	13.1	—	16.4	12.2	20	—	1760	4150	3.2	—	18.1

having no carbonyl ligands is often observed as a base peak. The fragmentation of the pyrolysis product (127) is shown in Scheme 19 <85ZN(B)927> (it was reported originally that the fragment at m/z 127 was CF₃P—CCH⁺, but this is wrong; the fragments of m/z 127 and 128 should be assigned as shown in the scheme).

Table 10 Phosphorus-31 chemical shifts and coupling constants (J_{PP} and J_{PPi}) for platinum complexes of 2-alkylidene-1,2-dihydrophosphetes.

	Solvent	δ_P	δ_{PEt_3}	$^3J_{PPi}/\text{Hz}$	$^1J_{PPi}/\text{Hz}$	$^2J_{PP}/\text{Hz}$
(136)	CD ₃ OD	34.2	14.14, 16.02	652	2678	360
(137)	CDCl ₃	34.2	12.1, 12.9	624	2723	375
(138)	CDCl ₃	12.5	2.85	571	2457	—
(139)	CD ₂ Cl ₂	49.8	7.2	100	2474	—

**Scheme 18****Scheme 19**

1.27.2.4 IR Spectroscopy

IR spectra are still important for the discussion on functionalities such as carbonyl and phosphoryl groups. Stretching frequencies of the carbonyl ligand (ν_{CO}) and the ring carbonyl group ($\nu_{C=O}$) are summarized in Table 11. The values of $\nu_{C=O}$ scatter in the range of 1710–1730 cm^{-1} , indicating that the ring strain of the four-membered ring is not so large, because the P—C bonds are longer than the C—C bonds. Stretching frequencies of the phosphoryl group ($\nu_{P=O}$) are also summarized in Table 12. The stretching frequency $\nu(\text{PO}_2\text{H})$ of the phosphetanic acid (141) (Scheme 20) has been reported to be 1230 cm^{-1} , while its metal salts and ammonium salts have the two frequencies $\nu_{as}(\text{PO}_2^-)$ and $\nu_s(\text{PO}_2^-)$, around 1160–1130 cm^{-1} and 1050–1030 cm^{-1} respectively.

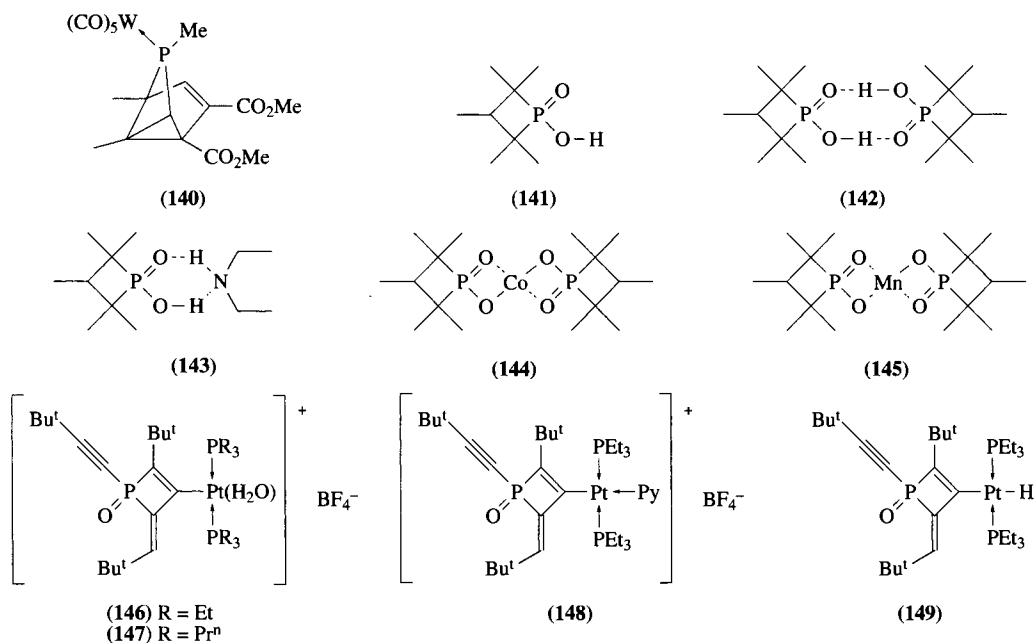
In some respects the behavior of 2,2,3,4,4-pentamethylphosphetanic acid is expected to parallel that of carboxylic acids so that mutual hydrogen bond formation to give cyclic dimers would be anticipated (142). The ν_{OH} peak at around 3500 cm^{-1} is not observed but two very broad and strong peaks at 2250 cm^{-1} and 2600 cm^{-1} can be attributed to $\nu(\text{OH} \cdots \text{O})$ of (142) by analogy with carboxylic acid dimers. Other broad bands at 955 cm^{-1} and 500 cm^{-1} are the corresponding in-plane and out-of-plane $\text{OH} \cdots \text{O}$ bending modes. Dilution of the acid in CCl_4 down to 0.001 M concentration failed to produce a peak in the spectrum at around 3500 cm^{-1} that could arise from the monomeric acid species. This seems to be evidence that the hydrogen bonding of (142) is stronger than that of (RCO_2H) where dilution disturbs the equilibrium towards the monomer sufficiently for the latter's OH bond vibration to be observed.

Table 11 Stretching frequencies of the ring carbonyl group and the carbonyl ligand of pentacarbonyl metal complexes.

Compounds	$\nu_{C=O}$ (cm^{-1})	ν_{CO} (cm^{-1})	Ref.
(2)	—	2075, 1985, 1954, 1944	84NJC453
(90)	—	2065, 1987, 1958, 1945	84NJC453
(140)	—	2070, 1950, 1945	84NJC453
(13)	1710	2074, 1955, 1948	85JA5001
(114)	1725	2072, 1960, 1955	85JA5001
(115)	1710	2067, 1959, 1953	85JA5001
(116)	1723	2072, 1988, 1955, 1943, 1910	85JA5001
(117)	1730	2065, 1990, 1960, 1946	85JA5001
(112)	—	2070, 1950, 1940	90OM788
(113)	—	2070, 1948, 1950, 1944	90OM788
(88)	—	2075, 1955, 1950, 1940	90CC153
(12)	—	2041, 2000, 1970, 1962, 1952	93IC5720

Table 12 Stretching frequencies of the phosphoryl group of 1,2-dihydrophosphetes.

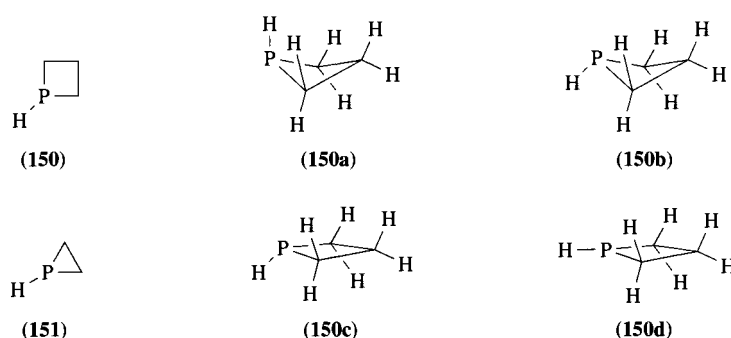
Compounds	$\nu_{P=O}$ (cm^{-1})	Ref.	Compounds	$\nu_{P=O}$ (cm^{-1})	Ref.
(102)	1230	91IC3381	(146)	1172	89OM1007
(107)	1217	85JA5001	(147)	1150	89OM1007
(84)	1205	93JCR(S)268	(148)	1180	89OM1007
(143)	1179, 1037	84POL325	(149)	1177	89OM1007
(144)	1092, 1062	84POL325			
(145)	1089, 1056	84POL325			

**Scheme 20**

1.27.3 THEORETICAL METHODS

1.27.3.1 *Ab Initio* Studies

The optimized structures of phosphetane (**150**) as well as phosphirane (**151**) have been obtained at the HF-SCF level using the 3-21G, 3-21G*, and 6-31G* basis sets <89JPC7780>, see Scheme 21 and Table 13. The lowest energy isomer of phosphetane (**150**) is puckered with the P—H bond being axial (**150a**). The ring strain is estimated as 17.9 kcal mol⁻¹. Optimized transition structures of the ring flip and phosphorus inversion are (**150c**) and (**150d**), respectively. The inversion barrier is 42.65 kcal mol⁻¹ (calculated at MP2/6-31G*//HF/6-31G* with ZPE(3-21G*)). The ring flip barrier is calculated to be 2.45 kcal mol⁻¹.



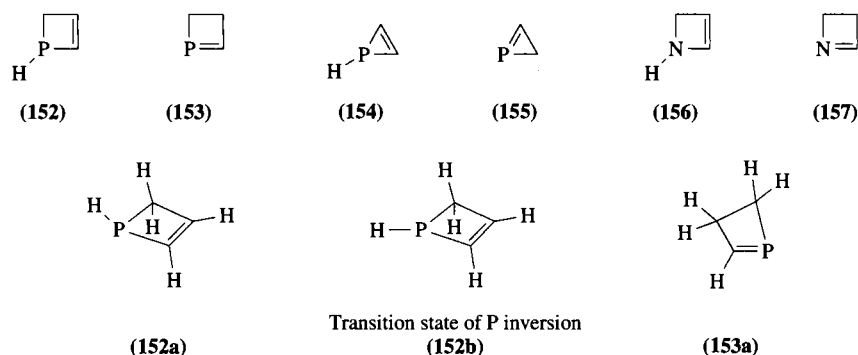
Scheme 21

Table 13 Selected geometric parameters of phosphetanes (**150a**) and (**150b**) and transition states of ring flip (**150c**) and phosphorus inversion (**150d**).

Compound	$r(\text{P}-\text{C})$ (Å)	$r(\text{C}-\text{C})$ (Å)	$\text{C}-\text{P}-\text{C}$ (°)	δ^a (°)	Basis set	Ref.
(150a)	1.9380	1.5618	74.53	156.96	3-21G	89JPC7780
	1.8776	1.5665	76.66	156.62	3-21G*	
	1.8801	1.5444	75.72	155.63	6-31G*	
(150b)	1.9375	1.5651	75.31	155.47	3-21G	89JPC7780
	1.8775	1.5711	77.52	154.68	3-21G*	
	1.8789	1.5474	76.21	151.83	6-31G*	
(150c)	1.8806	1.5518	77.56	172.22	HF/6-31G*/ /HF/6-31G*	89JPC7780
(150d)	1.8365	1.5669	84.23	180.0	HF/6-31G*/ /HF/6-31G*	89JPC7780

^aPucker angle of the four-membered ring.

The geometry of 1,2-dihydrophosphete (**152**) is optimized to be (**152a**) at HF/6-31G* and single-point calculations at MP2 are performed along with 1*H*-phosphirene (**154**) and 2*H*-phosphirene (**155**) <91JOC2205>, see Scheme 22. The transition structure for inversion at phosphorus of (**152**) is also optimized to be (**152b**). The inversion barrier is 46.62 kcal mol⁻¹, see Scheme 22. The allowed conrotatory ring-opening reactions of 1,2-dihydrophosphete (**152**) and 3,4-dihydrophosphete (**153**) are examined together with 1,2-dihydroazete (**156**) and 3,4-dihydroazete (**157**) at the HF/6-31G* and MP2/6-31G* levels <92JOC209>. Reasonable activation barriers are obtained only with the inclusion of electron correlation; however, geometry optimization at MP2 did not significantly change the geometry from those obtained at the HF level. The opening of the dihydrophosphetes (**152**) and (**153**) giving phospho-1,3-butadienes (**158**) or (**159**) and (**160**), respectively, is thermo-neutral or slightly endothermic, while the opening of the dihydroazetes (**156**) and (**157**) is exothermic (Scheme 23 and Table 14). The calculated activation barrier for the opening of (**153**) is 40.76 kcal mol⁻¹. The opening of (**152**) can occur via two diastereomeric pathways. Inward rotation of the heteroatom lone pair is favored for this system; the lower barrier is 24.69 kcal mol⁻¹ for (**152**).

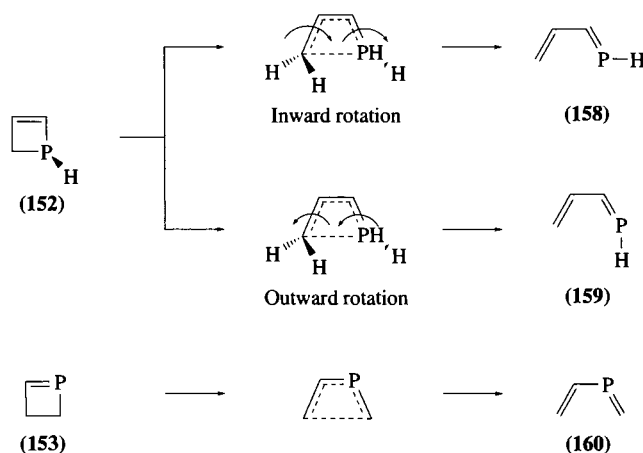


Scheme 22

Table 14 Selected geometric parameters of dihydrophosphetes (152) and (153).

Compounds	$r(P-C1)$ (Å)	$r(P-C4)$ (Å)	$r(C2-C3)$ (Å)	$r(C3-C4)$ (Å)	$C-P-C$ (°)	Ref.
(152a)	1.892	1.834	1.513	1.325	73.63	91JOC2205 ^a
(152a)	1.899	1.832	1.506	1.348	—	92JOC209 ^b
obsd ^c	1.886	1.821	1.517	1.366	74.0	91IC3381
obsd ^c	1.872	1.826	1.510	1.359	73.8	90AG(E)75
(152b) ^d	1.856	1.791	1.526	1.330	77.32	91JOC2205 ^a
(153a)	1.662	1.883	1.507	1.553	77.9	92JOC209 ^a
(153a)	1.691	1.885	1.501	1.551	—	92JOC209 ^b

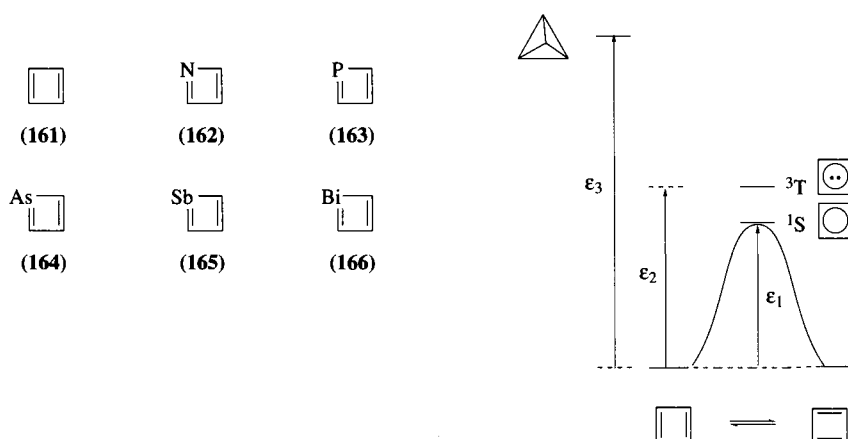
^aHF/6-31G* basis set. ^bMP2/6-31G* basis set. ^cX-ray crystal data of 1,3,4-triphenyl-1,2-dihydrophosphete. ^dTransition state of inversion at P of (152).



Scheme 23

Quantum chemical calculations at the MCSCF level have been reported for phosphete (163) and its valence isomers, which are compared with those for cyclobutadiene (161), aza- (162), 1,3-diaza-

1,3-diphospha-, and tetraphosphacyclobutadienes (93AG(E)617). The relative energy values (in kcal mol⁻¹) are 7.2 (ϵ_1), 7.4 (ϵ_2), 13.6 (ϵ_3), -1.5 (ΔE), where ϵ_1 , ϵ_2 , and ϵ_3 are the energies of singlet and triplet transition states of valence isomerization of (163) and phosphatetrahedrane, respectively, and ΔE is an energy difference for the fragmentation of phosphahedrane into $CH_2=CH_2$ and $HC\equiv P$, see Scheme 24 and Table 15.



Scheme 24

Table 15 Relative energy values (in kcal mol⁻¹) of (161)–(163).

Compounds	Symmetry ^a	ϵ_1	ϵ_2	ϵ_3	ΔE^b
(161)	$D_{2h}(D_{4h})$	8.4	14.8	36.4	-27.2
(162)	$C_2(C_{2v})$	12.1	18.9	30.1	-54.9
(163)	$C_2(C_{2v})$	7.2	7.4	13.6	-1.5

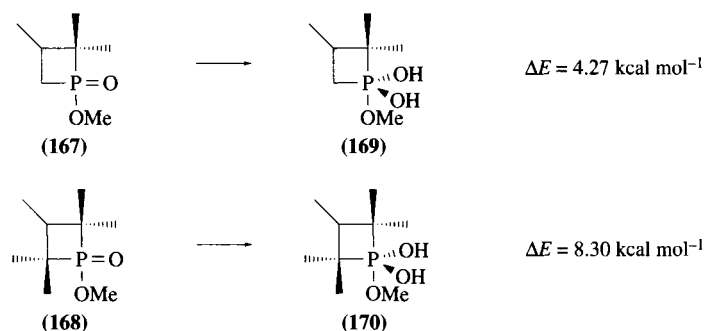
^aSymmetry in parentheses refers to transition state geometries for valence isomerization. ^bValue for fragmentation of the tetrahedranes into (from top to bottom) 2 C₂H₂, C₂H₂ + HCN, C₂H₂ + HCP, respectively.

1.27.3.2 Empirical and Semiempirical Methods

Topological resonance energies (TRE) of heterocyclobutadienes containing one N, P, As, Sb, or Bi have been calculated to evaluate their stability or reactivity. TRE is defined as $TRE = \sum g_j(x_j - x_j^{ac})$ from graph theory <76JA2750, 77JA1692>. However, for open-shell configuration ($g_1 = 2$, $g_2 = g_3 = 1$) TRE values are positive, that is, (162): 0.2236, (163): 0.2132, (164): 0.1856, (165): 0.1376, and (166): 0.0984. Modified TRE*, which can be defined as $TRE^* = \sum g_j|x_j| - |x_j^{ac}|$, is necessary to evaluate their stability correctly <88CPL(151)44>. Their values become around -0.7524 to -0.5936, indicating that they are antiaromatic and antiaromaticity decreases in the order of As > P > N, but the antimony and bismuth derivatives are less antiaromatic. The electron densities for the open-shell configuration are in accordance with ¹³C NMR values. The mobile bond orders suggest a symmetric four-membered ring with strongly distorted diagonal distances for all the molecules. The molecular stability/reactivity has been discussed in the light of HOMO-LUMO separation (ΔE) in the graph spectrum <90JJC(A)370>. The larger gap between HOMO and LUMO makes the molecule more stable. In cyclobutadiene ΔE is zero, and hence the molecule is said to be more reactive and unstable. The values for (161)–(166) are 0, 0.2523, 0.2057, 0.0735, 0.0806, and 0.08616, respectively, indicating that ΔE values decrease in the order (162) > (163) > (165) > (166) > (164) > (161), which is a similar order to that obtained from the TRE calculation. (There are some mistakes, because ΔE values decrease in the order (162) > (163) > (166) > (165) > (164) > (161) and the TRE order is (166) > (165) > (162) > (163) > (164) > (161)).

Hydrolytic reactions of some cyclic esters of phosphorus-based acids have been studied using molecular mechanic calculations (Allinger 1977 force field, MM2 1985) <90JCS(P2)971>. Energy differences between the tetracoordinate starting materials ((167) and (188)) and the pentacoordinate intermediates ((169) and (170)) are 4.27 kcal mol⁻¹ and 8.30 kcal mol⁻¹ for 1-methoxy-2,2,3-trimethyl-1-oxophosphetane (167) and 1-methoxy-2,2,3,4,4-pentamethyl-1-oxophosphetane (168), respectively, see Scheme 25. Therefore, the increase in steric energy caused by two methyl groups in the transition state is 4.03 kcal mol⁻¹. The calculated relative rate of hydrolysis of compounds (167) and (168) is, therefore, 884:1, which is close to the experimental data reported by Hawes *et al.*

<68CC577>. There has not been reported any semiempirical calculation for the molecules dealt with in this session.

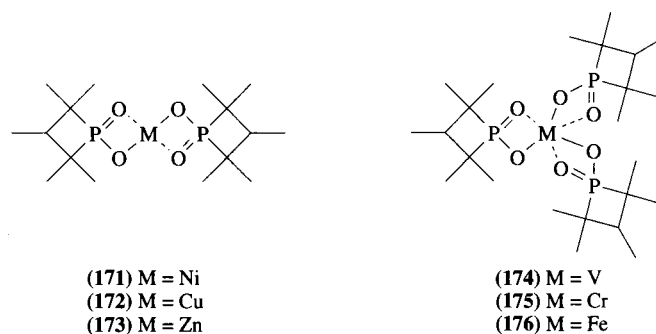


Scheme 25

1.27.4 THERMODYNAMIC ASPECTS

1.27.4.1 Physical Properties and Physical Constants

2,2,3,4,4-Pentamethylphosphetanic acid (**141**) is a fairly strong acid, whose pKa value was reported to be 2.85 <83POL1225>. The melting points, μ_{eff} , and conductances of its transition metal salts (**171**)–(**176**) are summarized in Table 16, see Scheme 26. The conductance of compounds (**62**)–(**64**) <84POL1155> is reported to be about $100 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ <92CB1987>.



Scheme 26

Table 16 The melting points, μ_{eff} , and conductances of selected compounds.

Compounds	mp (°C)	μ_{eff} (BM)	Conductance ($\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$)	Ref.
(174)	98	2.80	—	84POL1155
(175)	125	3.73	—	84POL1155
(145·2H ₂ O)	230	5.87	4.20	84POL1155
(176)	290	5.68	2.8	84POL1155
(171·9H ₂ O)	>360	3.30	252	84POL1155
(172)	>360	1.84	—	84POL1155
(173)	>360	—	—	84POL1155

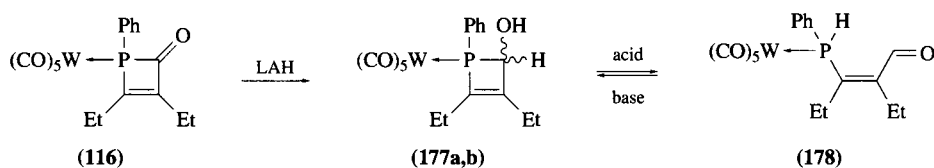
1.27.4.2 Aromaticity

There have been reported three η^4 complexes (**120**), (**129**), and (**130**) of phosphetes, but no research has been done with regard to their aromaticity.

1.27.4.3 Conformational Studies and Tautomerization

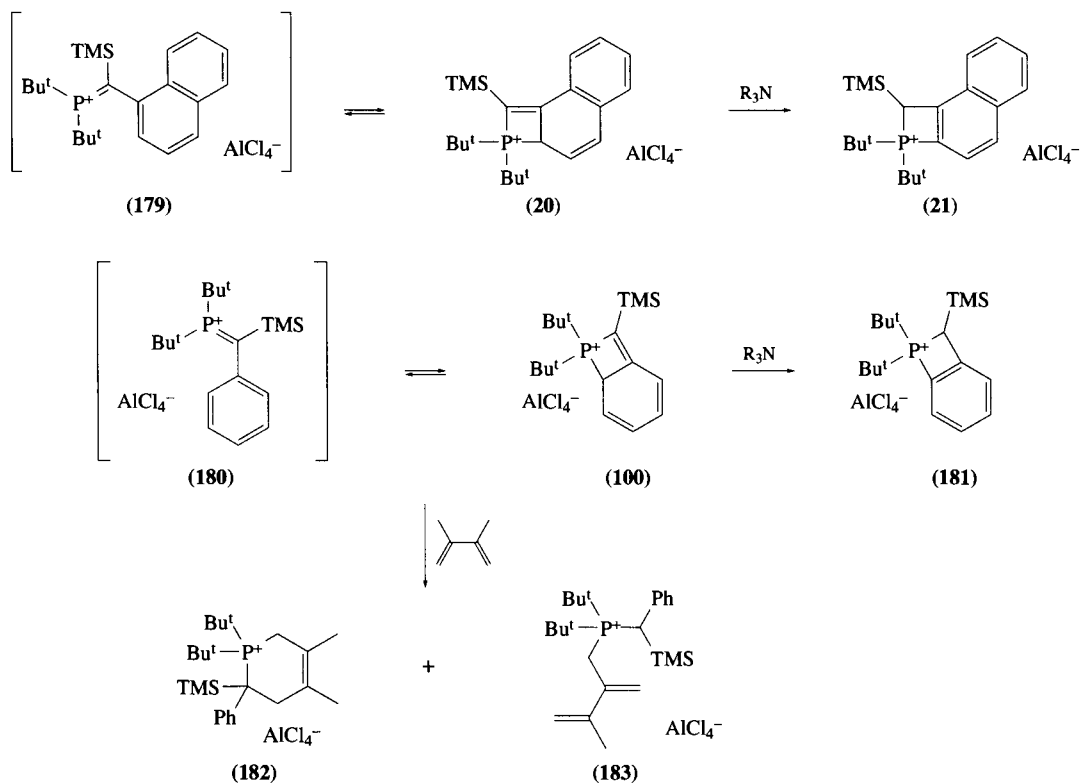
Tungstenpentacarbonyl 2-hydroxy-1,2-dihydrophosphetes (**177a,b**), which were prepared by reduction of the corresponding ketone (**116**) with LiAlH_4 , undergo tautomerization to give the open chain formyl-group containing secondary phosphine complex (**178**). Although (**178**) was not obtained in a pure state, its structure has been strongly supported by the ^1H and ^{31}P NMR spectra ($\delta_{\text{P}} = 24.8$ ($^1J_{\text{PH}} = 356.4$ Hz), $\delta_{\text{H}} = 9.64$ ($-\text{CH}=\text{O}$, $^4J_{\text{HP}} = 1.46$ Hz).

Water and triethylamine may help the closure of (**178**) back to (**177a,b**) while HCl seems to catalyze the opening of (**177a,b**) giving (**178**) and to simultaneously induce an equilibration between (**177a**) and (**177b**) <88OM633>, see Scheme 27.



Scheme 27

Phosphetanium salts (**20**) and (**100**) are prepared by intramolecular electrocyclic ring closure of methylenephosphonium salts (**179**) and (**180**), respectively. This ring closure is reversible, and the methylenephosphonium ion (**180**), which is present at equilibrium in low concentration, reacts with 2,3-dimethylbutadiene (DMB) to give the [2 + 4] cycloadduct (**182**) and an ene reaction product (**183**), though (**180**) could not be spectroscopically detected. On the other hand, (**20**) is stable and does not react with DMB. Upon addition of a tertiary amine base (preferably pyridine) to both (**20**) and (**100**), quantitative tautomerization to phosphetanes (**21**) and (**181**) takes place, which is irreversible because isomers (**21**) and (**181**) are stabilized by aromatization, see Scheme 28 <93AG(E)1359>.



Scheme 28

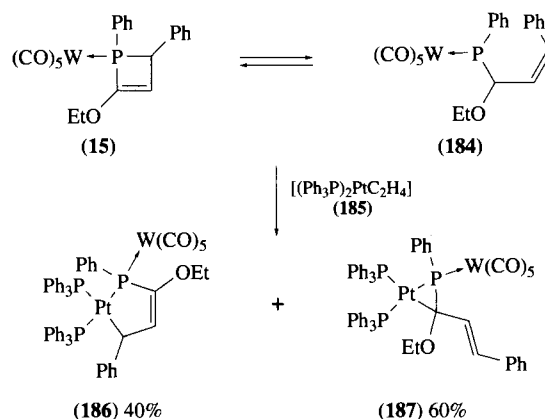
1.27.5 REACTIVITY OF FULLY CONJUGATED RINGS

As described above only three metal complexes (**120**), (**129**), and (**130**) of phosphetes have been synthesized; the *t*-butyl derivative (**129**) of the rhodium complexes was obtained as a yellow crystal which melted at 95°C, while the cobalt complex (**120**) was a red oil. Although all complexes were characterized by ¹H, ¹³C, and ³¹P NMR spectroscopy and mass spectrometry, their reactivity still remains unknown <87JOM(323)C35, 91AG(E)310>.

1.27.6 REACTIVITY OF NONCONJUGATED RINGS

1.27.6.1 Thermal and Photochemical Reactions

Tungstenpentacarbonyl 1,2-dihydrophosphete (**15**) was reacted with bis(triphenylphosphine)-ethene platinum(0) (**185**) to give the five-membered (**186**) and the three-membered (**187**) ring complexes containing phosphorus and platinum, indicating that (**15**) undergoes ring opening to form the 1-phospha-1,3-butadiene complex (**184**) which has both reactivity as an ene and a diene, see Scheme 29 <91JOM(406)C20>.



Scheme 29

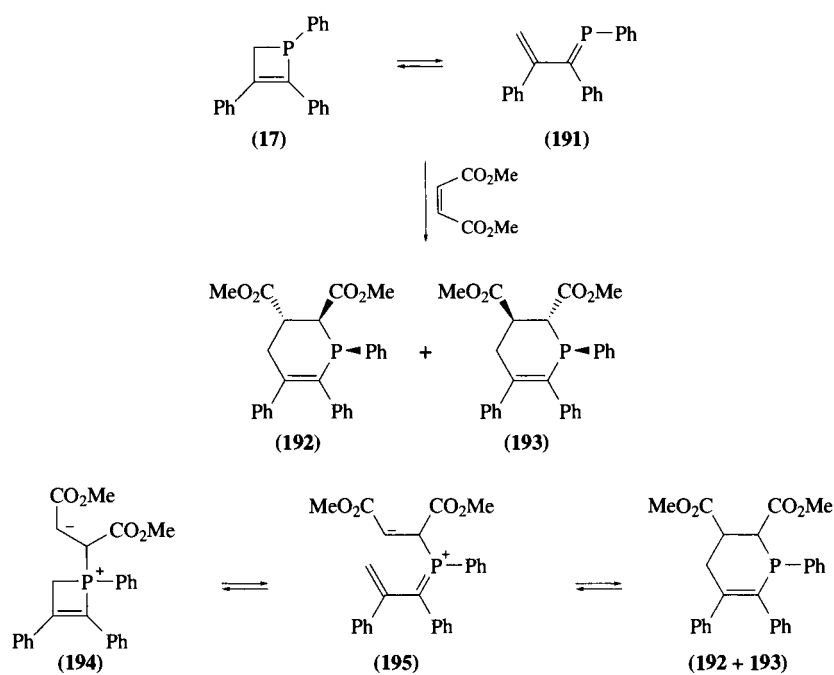
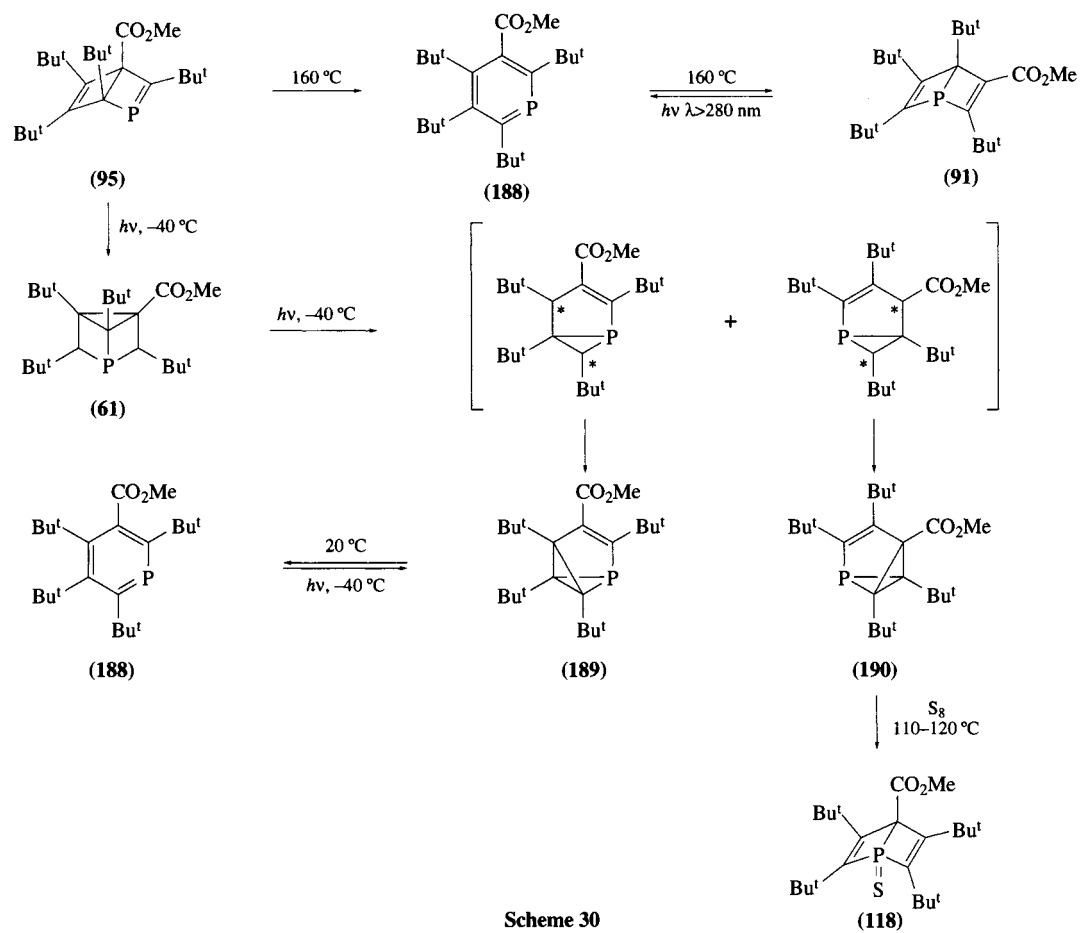
Dewar phosphabenzene (**95**) was heated at 160°C for 4 d to afford Dewar phosphabenzene (**91**) in 44% yield via phosphabenzene (**188**). On the other hand, Dewar phosphabenzene (**91**) was irradiated ($\lambda > 280$ nm) in CDCl₃ to give phosphabenzene (**188**). Irradiation of Dewar phosphabenzene (**95**) for 4 h at -40°C with Pyrex filter results in relatively fast intramolecular [2 + 2] cycloaddition to form, as the main product, the phosphaprismane (**61**) (40%); in addition, phosphabenzene (**188**) formed via phosphabenzbalene (**189**) and phosphabenzbalene (**190**) (each 10%) are formed. The phosphabenzbalene (**190**) was treated with sulfur at 110–120°C for 12 h to afford Dewar phosphabenzene *P*-sulfide (**118**) (65%), see Scheme 30 <87AG(E)85>.

1.27.6.2 Cycloaddition and Retro-cycloaddition Reactions

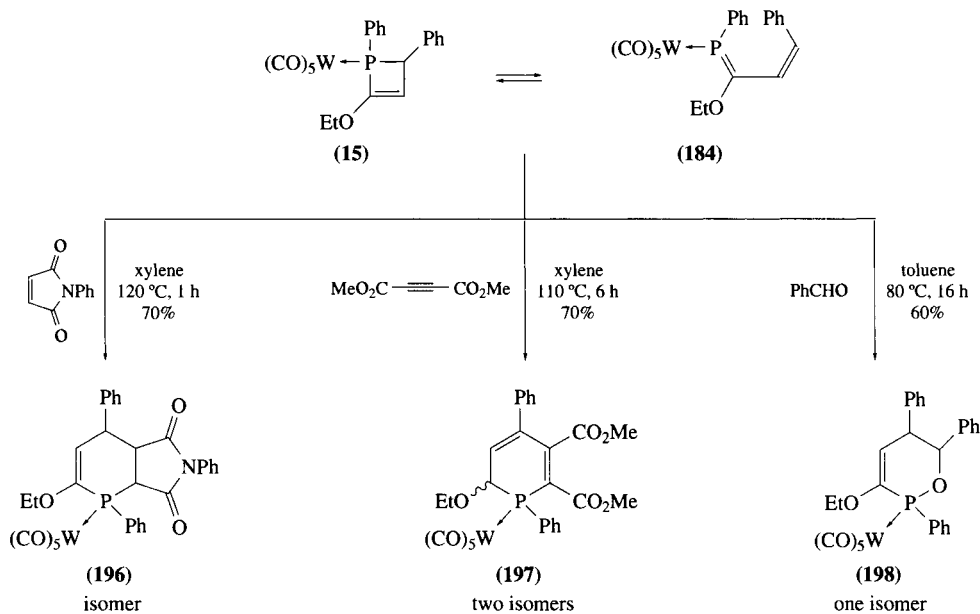
1,3,4-Triphenyl-1,2-dihydrophosphete (**17**) reacts with dimethyl maleate (C₆D₆, 110°C for 14 h) to produce a mixture (3:2) of diastereomeric cycloadducts (**192**) and (**193**), indicating that (**17**) undergoes retro-cycloaddition to give 1-phospha-1,3-butadiene (**191**) under the conditions. Both isomers contain *trans* ester groups, suggesting a nonconcerted pathway via zwitter ionic intermediates (**194**) or (**195**) for the cycloaddition as shown in Scheme 31. This mechanism is supported by the fact that the formation of cycloadducts is faster in (CD₃)₂CO than in C₆D₆.

The same ratio of the diastereomers was obtained from dimethyl fumarate; dimethyl maleate is, however, isomerized to dimethyl fumarate under the reaction conditions. Although a concerted mechanism involving intermediate 1-phospha-1,3-butadiene (**191**) can not be ruled out, the result that the reaction with ethyl acrylate gives a single regioisomer and that no reaction occurs with benzaldehyde suggests a stepwise mechanism <90CC1649>.

Tungstenpentacarbonyl 1,2-dihydrophosphete (**15**) is also in an equilibrium with a retro-cyclo-

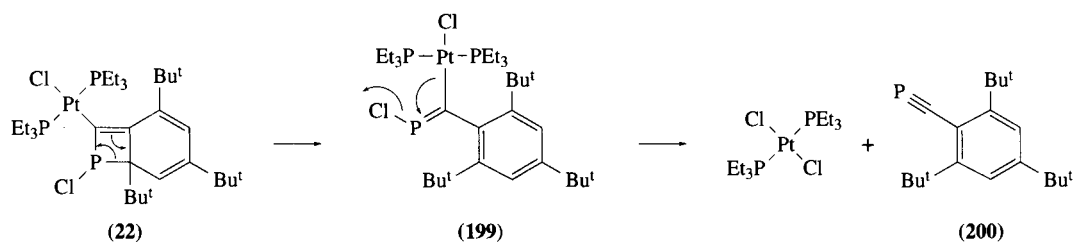


addition product, tungstenpentacarbonyl 1-phospha-1,3-butadiene (**184**), which undergoes a Diels–Alder reaction with dienophiles such as maleimide, ethynedicarboxylate, and benzaldehyde to afford the corresponding cycloadducts (**196**), (**197**), and (**198**), respectively, see Scheme 32 <88TL3077>.



Scheme 32

A solution of platinum phosphite complex (**22**) in dry benzene was placed at room temperature for 6 h to undergo retro-cycloaddition to give the phosphene platinum complex (**199**), which undergoes elimination of *trans*-Cl₂Pt(PEt₃)₂ to afford quantitatively 2,4,6-tri-*t*-butylphenyl-phosphaalkyne (**200**) as shown in Scheme 33 <94OM2444>.



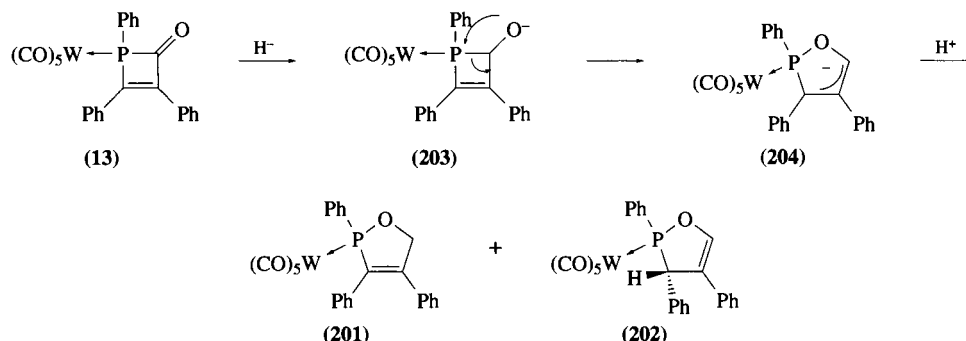
Scheme 33

As shown in Scheme 28, the silylated phosphetanium salt (**100**) undergoes retro-cycloaddition to give the methylenephosphonium salt (**180**) in low concentration, which reacts with 2,3-dimethylbutadiene (DMB) to afford the [2 + 4] cycloadducts (**182**) and ene reaction product (**183**) <93AG(E)1359>.

1.27.6.3 Reactions Involving Rearrangements

1,3,4-Triphenyl-1,2-dihydro-2-oxophosphete tungstenpentacarbonyl (**13**) is reduced by NaBH₄ in dioxane at room temperature to give a mixture of two oxaphospholene complexes (**201**) and (**202**) in a ratio of 3 : 1 (55% yield) instead of the expected 2-hydroxy derivative. The oxaphospholenes

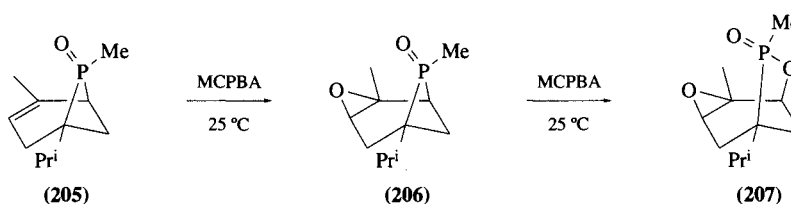
(201) and (202) probably result from the spontaneous rearrangement of the oxyanion (203) to afford the allylic carbanion (204) after the initial attack of H^- on the carbonyl group of (13) as shown in Scheme 34 <88OM633>.



Scheme 34

1.27.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO A RING CARBON ATOM

When bicyclopophosphetane oxide (205) having a $\text{C}=\text{C}$ bond on the bridge has been reacted with MCPBA, both the epoxidation of the double bond and the Baeyer–Villiger reaction take place to give (207) in 52% yield. The former reaction giving (206) seems to be faster than the latter reaction (Scheme 35) <83JOC4466>.

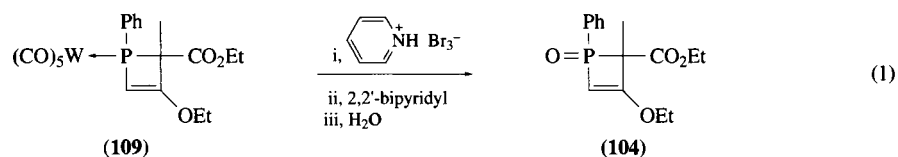


Scheme 35

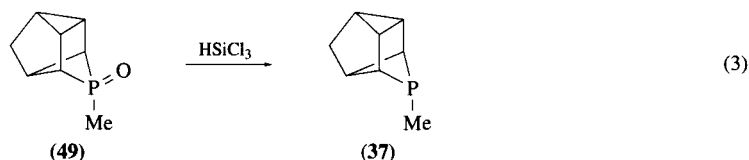
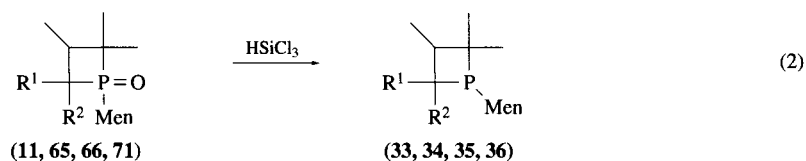
The ligand (H_2O) of the 2-alkylidene-1,2-dihydrophosphete platinum complex (146) can be replaced by pyridine in CH_2Cl_2 to afford (148) in 66% yield (Scheme 20) <89OM1007>.

1.27.8 REACTIVITY OF THE RING PHOSPHORUS ATOM AND SUBSTITUENTS ATTACHED TO THE RING PHOSPHORUS ATOM

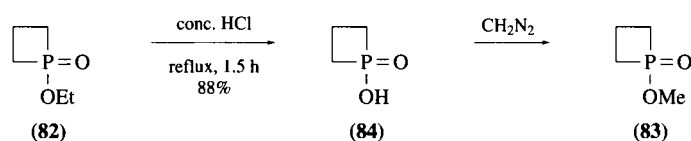
1,3,4-Triphenyl-1,2-dihydrophosphete (17) reacts slowly with oxygen at room temperature or rapidly at 150°C to give the corresponding 1-oxide (102) <91IC3381>. Oxidative decomplexation of 1,2-dihydrophosphete tungstenpentacarbonyl complex (109) with pyridinium perbromide in the presence of 2,2'-bipyridyl gave the corresponding 1-oxide (104) (Equation (1)). Similarly, 1,2-dihydrophosphete oxides (103) and (104) are obtained from (13) and (15), respectively <85JA5001, 88OM1791, 90CC153>.



1-Menthylphosphetane 1-oxides (11), (65), (66), and (71) and tetracyclicphosphetane oxide (49) can be reduced with trichlorosilane to afford the corresponding phosphines (33), (34), (35), (36), and (37), respectively (Equations (2) and (3)) <84JA7021, 93T10291>.

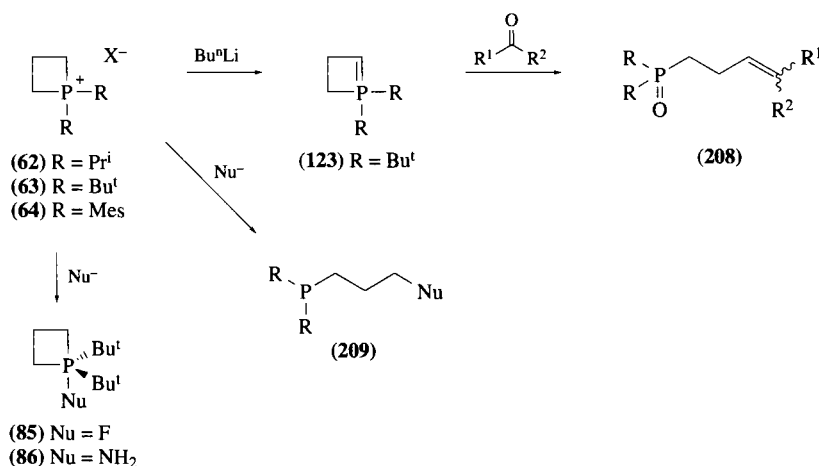


Hydrolysis of ethyl phosphetate (82) and methylation of the phosphetanic acid (84) with diazomethane have been reported (Scheme 36) <93JCR(S)268>.



Scheme 36

Phosphetanium salt (63) has interesting reactivity in the reaction with nucleophiles. For example, α -proton can be removed with a base such as Bu^nLi to afford ylide (123), which undergoes the Wittig reaction with aldehydes and ketones to give the corresponding 4-butenylphosphine oxide (208). Nucleophiles can attack on the phosphorus atom of the phosphonium salts to produce sometimes pentacoordinate phosphetanes (85) or (86), but most of them attack on the carbon attached to the phosphorus atom to form functionalized phosphines (209) accompanied with the C—P bond cleavage, see Scheme 37 <92CB1987>.



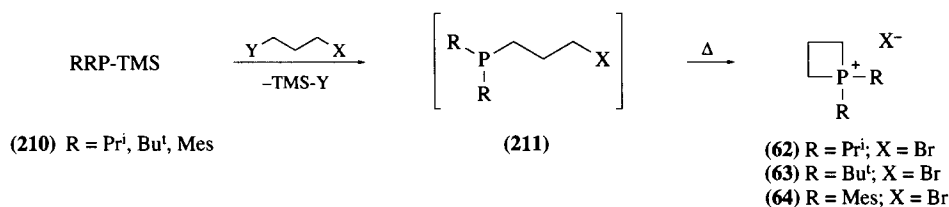
Scheme 37

1.27.9 SYNTHESIS OF FOUR-MEMBERED HETEROCYCLES WITH ONE PHOSPHORUS OR ARSENIC ATOM

1.27.9.1 From Acyclic Compounds by Formation of One Bond to a Phosphorus or an Arsenic Atom

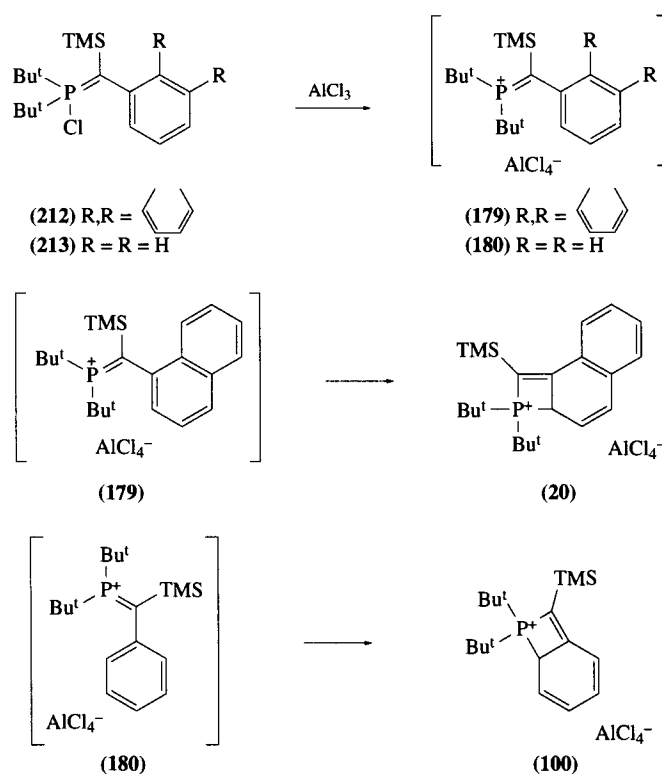
Silylphosphines (210) bearing bulky groups such as isopropyl, *t*-butyl, and mesityl groups react with 1,3-dihalopropane to give intermediary 3-halopropylphosphines (211), which undergo intra-

molecular cyclization to afford the corresponding phosphetanium salts **(62)** (23%), **(63)** (76%), and **(64)** (72%), see Scheme 38 <92CB1987>.



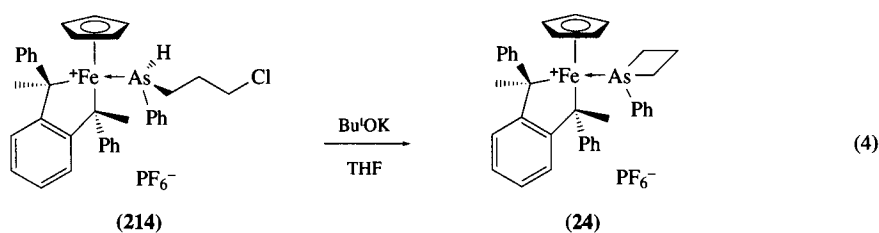
Scheme 38

The phosphonium cations **(179)** and **(180)**, which formed from chlorophosphorus ylides **(212)** and **(213)** by dehalogenation with aluminum chloride, undergo intramolecular cyclization with the benzene ring attached to the ylide carbon to give **(20)** and **(100)** in 80–85% yield, respectively, see Scheme 39.



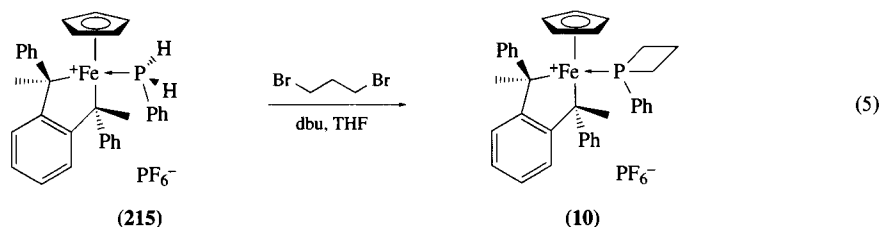
Scheme 39

3-(Chloropropyl)phenylarsine iron complex **(214)** is treated with Bu^tOK in THF to give the corresponding arsetane complex **(24)** in high yield (Equation (4)) <92JCS(D)1751>.

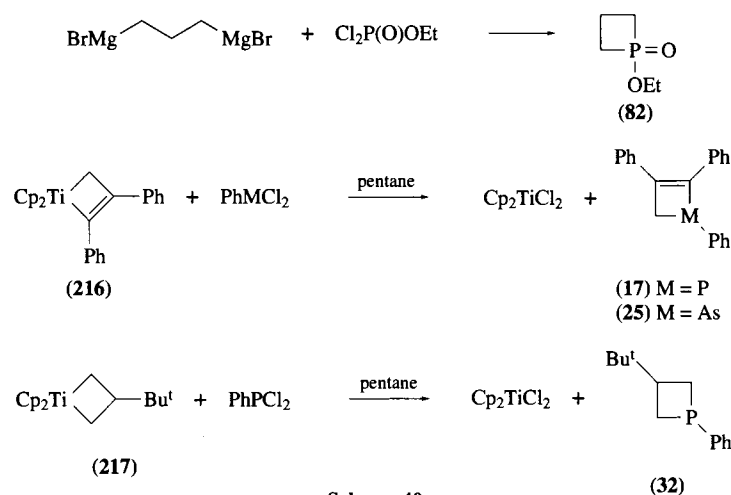


1.27.9.2 Formation of Two C—P or C—As Bonds by Displacement Reactions

As shown in Equation (5), phenylphosphine iron complex (**215**) reacts with 1,3-dibromopropane in the presence of dbu to afford 1-phenylphosphetane complex (**10**) <92JCS(D)1751>.



Propane 1,3-bis(magnesium bromide) reacts with ethyl dichlorophosphate to yield the ethyl ester of phosphetanic acid (**82**). The reaction of titanocene metallacyclobutenes (**216**) and (**217**) with dihalophosphine provides another synthetic route to the 1,2-dihydrophosphete (**17**) and phosphetane (**32**), respectively, where titanocene is replaced by the phosphine moiety. This method was also used for the synthesis of 1,2,3-triphenyl-1,2-dihydroarsete (**25**), see Scheme 40 <89JA9129, 90AG(E)75, 92OM2944>.

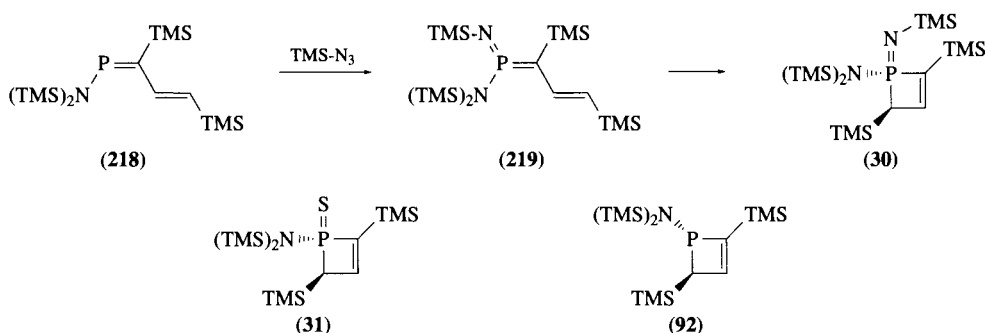


Scheme 40

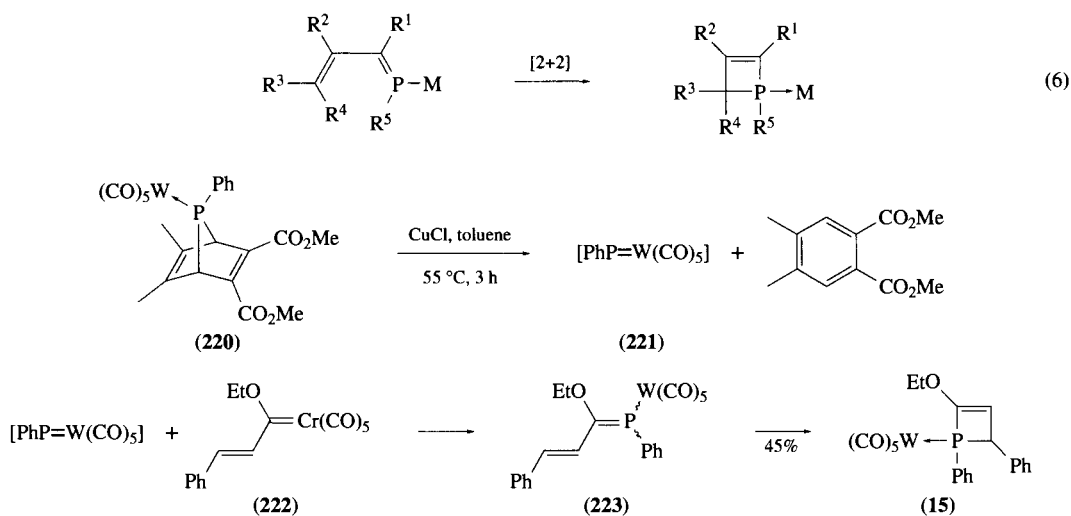
1.27.9.3 Ring Formation by Cycloaddition Reactions

As shown in Scheme 30, phospho-Dewar benzene (**91**) is obtained via phosphabenzene (**188**) from phospho-Dewar benzene (**95**). Irradiation of phosphabenzene (**188**) affords phosphaprismane (**61**) <87AG(E)85>. 1-Bis(trimethylsilylamino)-2,4-bis(trimethylsilyl)-1-phospha-1,3-butadiene (**218**) is reacted with trimethylsilylazide to give the corresponding iminodihydrophosphete (**30**) after the formation of the corresponding iminophosphorane (**219**) and its cyclization. 1-Thioxophosphabutadiene (the 1-sulfide of (**218**)) also readily cyclizes to give 1,2-dihydrophosphete 1-sulfide (**31**), see Scheme 41 <87TL6121>. Similarly, 1-amino-1,2-dihydrophosphete (**92**) is synthesized from the corresponding 1-amino-1-phospha-1,3-butadiene <88OM572>.

Metal complexes of 1-phospha-1,3-butadienes give the corresponding metal complexes of 1,2-dihydrophosphetes (Equation (6)). The reaction of phosphinidene tungstenpentacarbonyl complex (**221**), formed by retro-cycloaddition of 7-phosphanorbornadiene complex (**220**), with carbene chromium pentacarbonyl complex (**222**) was used as a unique generation method of the phosphabutadiene tungsten pentacarbonyl complex (**223**), which cyclizes to give the corresponding 1,2-dihydrophosphete metal complex (**15**) (Scheme 42) <88OM1791, 90SL171>.

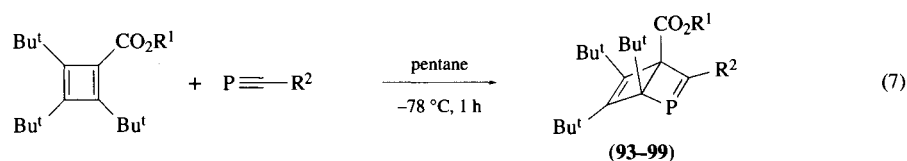


Scheme 41

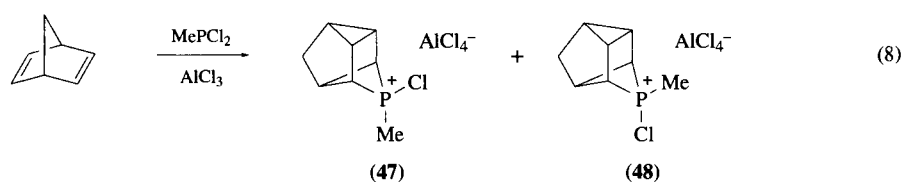


Scheme 42

Dewar benzenes (**93**)–(**99**) were synthesized by the Diels–Alder reaction of phosphalkyne with cyclobutadienes with a high regioselectivity (Equation (7)) <86AG(E)280>.

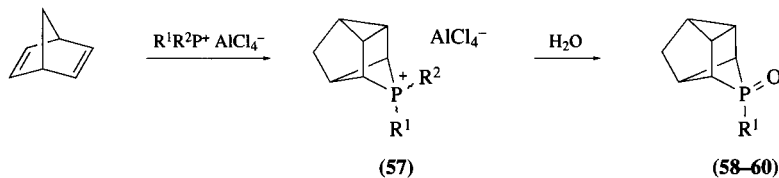


As shown in Equation (8) treatment of norbornadiene with dichloromethylphosphine at 60–80 °C for 1 wk gave a mixture of tetracyclicphosphetanium chlorides in 60–70%, which were readily derivated to their tetrachloroaluminates (**47**) and (**48**) leading to the corresponding phosphine oxides (**49**) and (**50**) after hydrolysis. These oxides were readily reduced with silanes to give the corresponding trivalent phosphines (**37**) and (**38**), which can be converted into several functionalized derivatives (**39**)–(**46**) and (**51**)–(**60**) (Scheme 6) <92JOC511>.



The [1 + 2 + 2] cycloaddition of divalent cation species $\text{R}^1\text{R}^2\text{P}^+$ with norbornadiene and 1,4-cyclohexadiene gave tetracyclicphosphetanium salts (**57**) and (**5**), respectively, the former of which

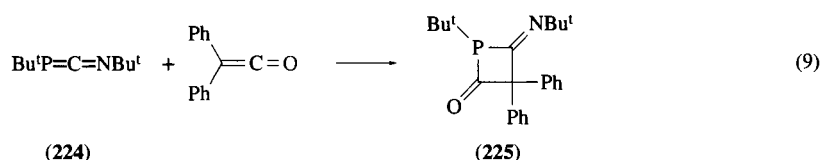
can be converted to the oxides (**58**), (**59**), and (**60**) (Scheme 43) <84TL815, 87TL603>. The phosphinidene dinuclear iron complex similarly reacted with norbornadiene to afford nortricyclan iron complex (**12**) <93IC5720>.



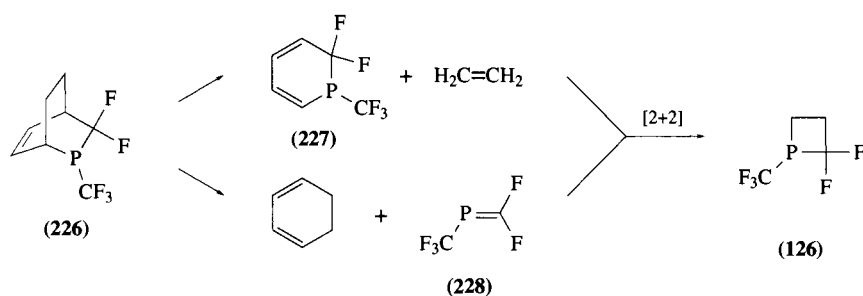
Scheme 43

1.27.9.4 Cycloadditions between Two Fragments Containing C=C and C=P Bonds

P,N-Di-*t*-butylcarboimidophosphene (**224**) reacts with diphenylketene to afford the corresponding 2-oxo-4-iminophosphetane (**225**) (Equation (9)) <83PS(18)39>.

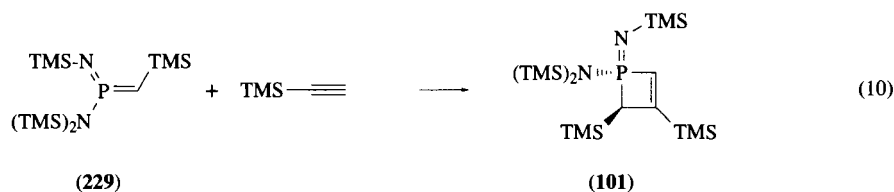


Phosphabicyclo[2.2.2]octene (**226**) undergoes two retro-Diels-Alder reactions to give a mixture of ethylene and phosphacyclohexadiene (**227**) and a mixture of cyclohexadiene and phosphalkene (**228**), respectively. The [2 + 2] cycloaddition between phosphalkene (**228**) and ethylene gives phosphacyclobutane (**126**) (Scheme 44) <85ZN(B)927>.

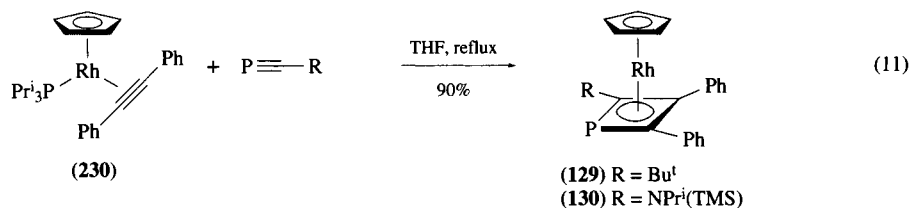


Scheme 44

The [2 + 2] cycloaddition reaction of bis(trimethylsilyl)amino(trimethylsilylimino)(trimethylsilylmethylene)phosphorane (**229**) with trimethylsilylthyne affords the regioisomer (**101**) of (**30**) (Equation (10)) <87TL6121>.



Phosphete complexes (**129**) and (**130**) are synthesized by the [2 + 2] cycloaddition of rhodium alkyne complex (**230**) with phosphalkynes (Equation (11)) <91AG(E)310>.

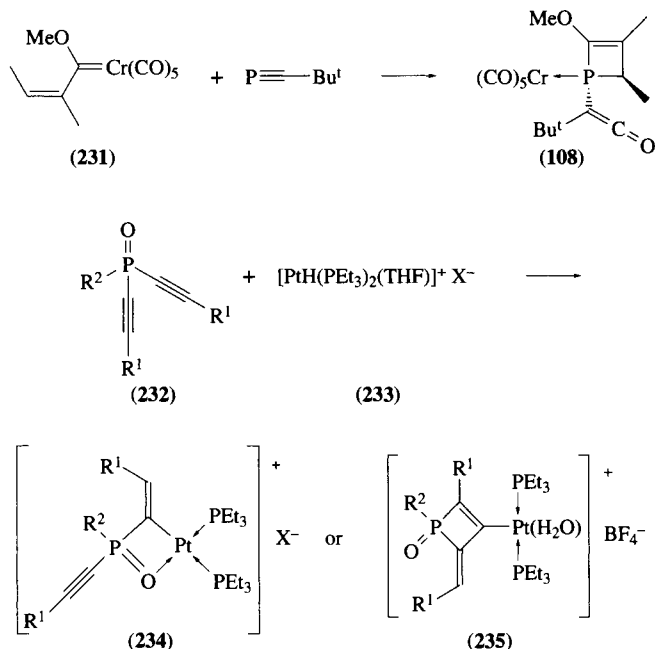


1.27.9.5 Miscellaneous Routes

Reaction of the divalent phosphorus cation species $\text{R}^1\text{R}^2\text{P}^+$ with substituted alkenes gave the corresponding phosphetanium salts through rearrangement of the first formed carbocations. This method is also available for 1,5-cyclooctadiene, see Scheme 1 <87S265, 93T10291>.

Divalent phosphorus cation species $\text{R}^1\text{R}^2\text{P}^+$ reacted with cyclopropanes to give insertion products to the C—C bond between the least and most substituted carbons; this seems to be due to readier electrophilic attack of the phosphorus cation and the higher stabilization of the resulting carbocation <86CC1081>.

Chromium pentacarbonyl carbene complex (**231**) was reacted with phosphalkyne to afford the 1,2-dihydrophosphete complex (**108**) with a ketene moiety (Scheme 45) <89CC788>. Reaction of di- or trialkynylphosphine oxides (**232**) with platinum hydride (**233**) gives either a *Pt,P*- μ -alkylidene product (**234**) or a 2-alkylidene-1,2-dihydrophosphete 1-oxide product (**235**) (Scheme 45). The latter product is favored when a phosphonium salt is used as the substrate instead of a phosphine oxide. Compounds (**136**)–(**139**) can be synthesized by the same method. The mechanism is discussed in detail <89OM1007, 91OM1197>.



Scheme 45

Similarly, trialkynylarsine oxide $(\text{Me}_3\text{CC}\equiv\text{C})_3\text{AsO}$ reacts with 2 equivalents of [*trans*-Pt(H)(PEt₃)₂(THF)]⁺[SbF₆][−] (**233**; X = SbF₆), and subsequently with pyridine to give the corresponding 2-methylene-1,2-dihydroarsenete platinum complex (**26**) (Equation (12)) <91OM372>.



As shown in Scheme 46, diphosphatricyclo[2.1.0.0^{2,5}]pentane (**6**) is obtained by the reaction of $[(\eta^5\text{-C}_5\text{H}_5)_2\text{Ti}(\text{CO})_2]$ with $\text{Bu}^t\text{C}\equiv\text{P}$ via bis(phosphaalkenyl)ketone (**236**) $\langle 88\text{AG(E)837} \rangle$.



Scheme 46

Oxidative addition reactions of $\text{Cl}_2\text{C}=\text{PR}$ ($\text{R} = 2,4,6\text{-tri-}t\text{-butylphenyl}$) (**237**) with $\text{M}(\text{PET}_3)_4$ ($\text{M} = \text{Pt}$ or Pd) initially give the *trans* isomer of square planar (**238**), which rearranges to give the corresponding 1,2-dihydrophosphete (**22**) fused with a benzene ring (Scheme 47). Similarly, the corresponding *cis* complex (**131**) and *trans* dibromo complex (**132**) are synthesized (Scheme 17) <94OM2444>.



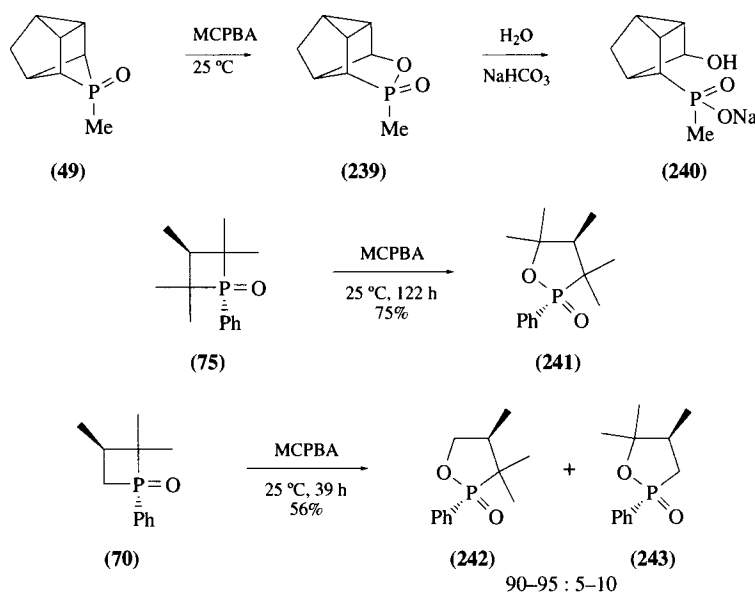
Scheme 47

1.27.10 RING SYNTHESIS BY TRANSFORMATION TO ANOTHER RING

1.27.10.1 By Ring Expansion

Tungstenpentacarbonyl-2-oxo-1,3,4-triphenyl-1,2-dihydrophosphete was treated with NaBH₄ in dioxane to afford oxaphospholene complexes (201) and (202), see Scheme 34 <88OM633>.

The reactivity of the strained four-membered phosphorus-containing ring in the tetracyclic system was demonstrated by the insertion of oxygen into the carbon—phosphorus bond in oxide (49) with trifluoroperoxyacetic acid to give the tetracyclic oxaphospha derivative (239). Use of NaHCO₃ in order to remove *m*-chlorobenzoic acid results in hydrolysis of the product giving (240), which is attributed to its highly strained structure (Scheme 48). *trans*-2,2,3,4,4-Pentamethyl-1-phenylphosphetane 1-oxide (75) is oxidized with MCPBA at 25°C to give the Baeyer–Villiger product (241) in 75% yield. A similar result was obtained for the phosphetane oxide (70). Here the reaction can follow two pathways, but attack occurred primarily at the least substituted carbon to give a mixture (isolated yield 56%) consisting of about 90–95% (242) and 5–10% of (243) (Scheme 48). The opposite orientation would normally be encountered in the Baeyer–Villiger reaction of ketones, however the special steric requirements at phosphorus appear to direct a different course for this and related rearrangement reactions of phosphetanes <83JOC4466>.

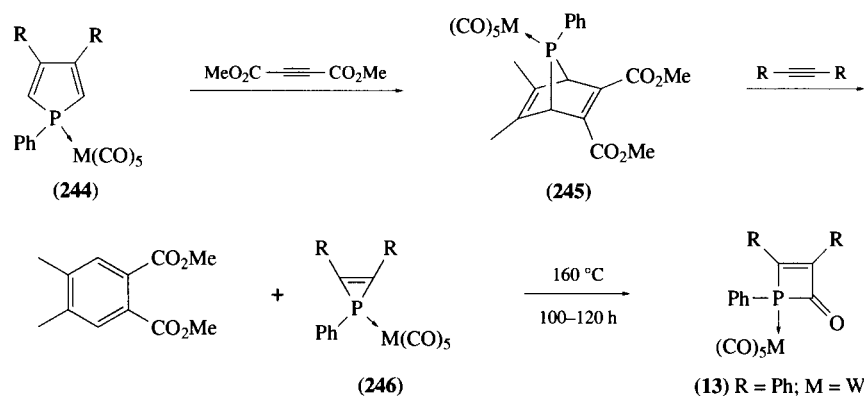


Scheme 48

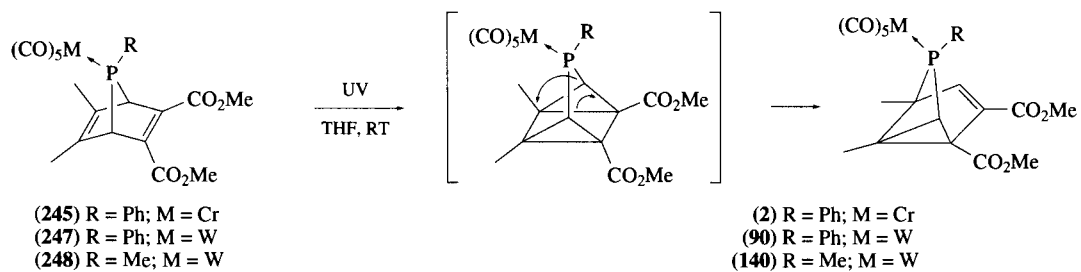
As shown in Scheme 30, Dewar phosphabenzene (95) is heated at 160°C for 4 d to afford Dewar phosphabenzene (91) via phosphabenzene (188). On the other hand, irradiation of Dewar phosphabenzenes (91) and (95) mainly gives phosphabenzene (188) and the phosphaprismane (61), respectively <87AG(E)85>.

1,3,4-Triphenyl-1,2-dihydrophosphete (17) reacts with dimethyl maleate to produce a mixture (3 : 2) of diastereomeric cycloadducts (192) and (193), see Scheme 31 <90CC1649>. The phosphole tungsten pentacarbonyl complex (244) was reacted with dimethyl ethynedicarboxylate to give Diels–Alder adduct (245), which transfers phosphinidene metal complex to diphenylethyne to afford phosphirene tungsten pentacarbonyl complex (246), which was heated at 160°C for 100–120 h to give the corresponding 2-oxo-1,2-dihydrophosphete complex (13). One pot reaction from phosphole metal complex (244) in the presence of dimethyl ethynedicarboxylate and diphenylethyne successfully produces (13) (Scheme 49) <85JA5001, 88OM633>.

7-Phosphanorbornadiene metal complexes (245), (247), and (248) rearrange under UV light for 15 d to give the [2 + 2] cycloadducts (quadricyclane derivatives) which undergo disrotatory opening of one of the two cyclopropane rings to give (2), (90), and (140), respectively. The corresponding tricyclic phosphetane complex (249) is probably formed through 1,3-sigmatropic rearrangement of (140) (Scheme 50) <84NJC453>.



Scheme 49



Scheme 50

1.28

Four-membered Rings with One Silicon, Germanium, Tin, or Lead Atom

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1.28.1 INTRODUCTION

The first silacyclobutane was obtained in 1954 by the cyclization of dimethyl(3-bromopropyl)-chlorosilane in the reaction with magnesium <54JA5002>. The similar reaction of dialkyl(3-chloropropyl)chlorogermenes with sodium has been used for the synthesis of 1,1-dialkyl-1-germacyclobutanes <65CR(260)2255>. Cyclocondensation of dimethyldichlorostannane with 1,3-bis(bromomagnesio)-2,2-dimethylpropane gave the first unstable stannacyclobutane <83JA3336>. The four-membered heterocyclic ring system with lead is unknown. Some reviews on sila- and germacyclobutane chemistry have been published <72MI 128-01, 74IZV1153, 74UK1317>.

1.28.2 STRUCTURE OF FOUR-MEMBERED RINGS WITH ONE SILICON, GERMANIUM, OR TIN ATOM

1.28.2.1 Theoretical Methods

Silacyclobutanes have been studied by various theoretical methods <75JA1311, 79JOM(168)295, 80JOM(190)9, 82JOM(225)131, 87OM1486, 87OM1977, 88JA352, 88JOC5248, 88JPC3037, 90JPC1830, 90JST(218)327, 92JPC4830, 92SA(A)65>. The calculated geometric parameters of silacyclobutanes are given in Table 1. Net atomic charges and bond orders have been obtained from the CNDO/2 method using *sp* and *spd* basis sets (Table 2) <80JOM(190)9>.

Table 1 The calculated geometric parameters of the silacyclobutane ring in compounds.

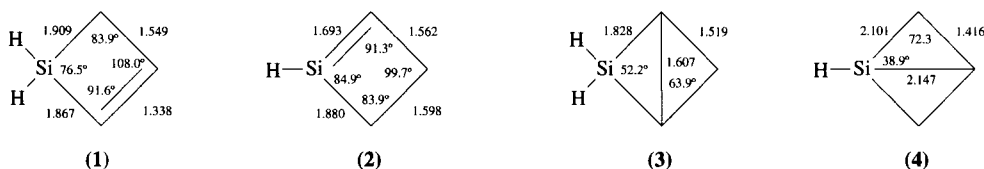
Method	R	r (Å)		Angles (°)		α (°)	Ref.
		Si—C	C—C	$\angle$ CSiC	$\angle$ CCC		
MINDO/2	H	1.891	1.533	78.5	107.0	30 ± 5	75JA1311
	Me	1.890	1.532		102.6		
CNDO/2	Me	1.898					80JOM(190)9
IMOA*	Me	1.902	1.549	78.3	101.6		79JOM(168)295
	RR = (CH ₂) ₃	1.900	1.548	78.8	102.2		
<i>Ab initio</i>	H	1.894	1.586	80.0	100.3		88JA352

* Interactive maximum overlap approximation (IOMA) approach.

Table 2 Net atomic charges and bond order parameters for silacyclobutanes.

R ¹	R ²	spd set			sp set		
		q(Si)	q(C _{2,4})	P _{Si—C}	q(Si)	q(C _{2,4})	P _{Si—C}
H	H	+0.3420	−0.1577	0.2061	+0.5379	−0.1370	0.1991
H	Me	+0.2347	−0.1452	0.2095	+0.5429	−0.1401	0.2009
Me	Me	+0.1563	−0.1405	0.2104	+0.5333	−0.1462	0.1968
Me	Cl	+0.1142	−0.1284	0.2151	+0.6666	−0.1589	0.2010
Cl	Cl	+0.0602	−0.1175	0.2247	+0.8151	−0.1800	0.2096
Me	OH	+0.2369	−0.1412	0.2189	+0.7927	−0.1757	0.2056
OH	OH	+0.3407	−0.1580	0.2287	+1.0209	−0.2105	0.2139
Me	NH ₂	+0.1928	−0.1404	0.2169	+0.6874	−0.1670	0.2029
—CH ₂ CH ₂ CH ₂ —		+0.1421	−0.1373	0.2168	+0.4635	−0.1263	0.2034

Restricted Hartree–Fock *ab initio* calculations have been performed on various isomers of silacyclobutenes (C₃SiH₆) <88JPC3037> and silacyclobutadiene <87OM1977>. Silacyclobutenes (1)–(4) were optimized within C_s symmetry.

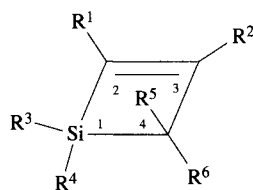


The relative energies of four isomers (1)–(4) indicate structure (1) to be the most stable. This is not unexpected since this isomer avoids the high strain energies associated with (3) and (4), as well as the Si=C double bond of (2). The geometric parameters of silacyclobutadiene have been obtained with different basis sets and vary within the ranges 1.685–1.729 Å (Si=C), 1.884–1.981 Å (Si—C), and 77.4–82.1° ($\angle$ CSiC) <87OM1977>.

1.28.2.2 Electron and X-ray Diffraction

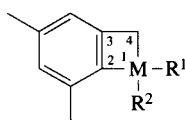
The structures of the simplest members of silacyclobutanes (silacyclobutane, 1,1-dichloro-silacyclobutane, and 4-silaspiro[3.3]heptane) were determined by electron diffraction and microwave spectroscopy. Naphthyl-substituted silacyclobutanes have been investigated by x-ray diffraction. These results were systematized (B-89MI 128-01). Since the publication of these results, further investigations have been made. The molecular structures of 1,1-dimethyl-1-silacyclobutane (91JST(246)229) and 1,1-difluoro-1-silacyclobutane (88ACS(A)352) have been studied by gas phase electron diffraction. The molecule exists in a puckered conformation.

X-ray techniques have been used to examine the molecular structure of some silacyclobutenes (5) (84OM1930, 88JA1315, 89JA7615, 91AG(E)1151, 92OM3088), benzosilacyclobutenes (89JOM(379)217), benzostannacyclobutenes (6) (91JOM(415)343), and fused silacyclobutane (7) (94AG93). The geometric parameters of metallacyclobutenes are presented in Table 3.



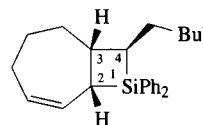
(5)

- (a) $R^1 = R^3 = R^4 = \text{TMS}$; $R^2 = \text{Ph}$; $R^5, R^6 = \text{Ph}(\text{TMS})\text{C}=\text{CH}_2$
 (b) $R^1 = \text{Bu}^t$; $R^2 = [\text{Pt}(\text{PEt}_3)_2(\text{H}_2\text{O})]\text{SbF}_6$; $R^3 = R^4 = \text{Ph}$; $R^5, R^6 = \text{Bu}^t\text{CH}=\text{CH}_2$
 (c) $R^1 = R^2 = R^6 = \text{Bu}^t$, $R^3 = \text{OMe}$, $R^4 = \text{Mes}$, $R^5 = \text{TMS}$
 (d) $R^1 = \text{H}$, $R^2 = R^4 = \text{TMS}$, $R^3 = \text{Mes}$, $R^5 = \text{TMS-O}$, $R^6 = \text{Ad}$
 (e) $R^1 = \text{H}$, $R^2 = \text{Ph}$, $R^3 = \text{Mes}$, $R^4 = \text{TMS}$, $R^5 = \text{TMS-O}$, $R^6 = \text{Ad}$
 (f) $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{TMS}$, $R^5 = \text{TMS-O}$, $R^6 = \text{Bu}^t$
 (g) $R^1 = \text{TMS}$, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{Cl}$, $R^5 = \text{H}$, $R^6 = \text{CH}_2\text{But}$
 Mes = 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$, Ad = 1-adamantyl



(6)

- (a) $M = \text{Si}$, $R^1 = \text{Mes}$, $R^2 = \text{NHSiBu}^t_3$
 (b) $M = \text{Sn}$, $R^1 = 2,4,6\text{-Bu}^t_3\text{C}_6\text{H}_2$, $R^2 = \text{CH}_2\text{CMe}_2\text{C}_6\text{H}_3\text{Bu}^t_{2-3,5}$



(7)

1.28.2.3 Molecular Spectra

1.28.2.3.1 NMR Spectroscopy

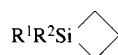
Proton, ^{13}C , and ^{32}Si NMR spectra for different 1,1-disubstituted silacyclobutenes have been studied (80JOM(190)9, 83OMR(21)412) (Table 4). The influence on the ring carbon chemical shifts of substituents on the silicon atom is larger for silacyclobutenes than for silacyclopentanes and acyclic silanes. The δ C-2 and C-3 signals of silacyclobutenes are within the 9.5–27.7 ppm and 11.7–22.7 ppm ranges, respectively.

The measured values of ^{29}Si chemical shifts in silacyclobutenes were correlated with the calculated values of net atomic charges on silicon atoms obtained by the CNDO/2 method in *sp* and *spd* basis sets. The inclusion of *d* orbitals in the calculation gives better agreement between the experimental data and computed values. The upfield shift of the $\delta(^{29}\text{Si})$ signal increases with the positive charge on the silicon atom (80JOM(190)9). The introduction of one or two methyl groups in the β position of the silacyclobutane ring causes the silicon signals to shift upfield, and the $\delta(^{29}\text{Si})$ values for 1,1,3-trimethyl-1-silacyclobutane and 1,1,3,3-tetramethyl-1-silacyclobutane are 5.7 ppm and 2.1 ppm, respectively (80IZV1950).

Chemical shifts and coupling constants for ^{13}C , ^{15}N (at natural abundance), and ^{29}Si are reported

Table 3 Geometric parameters of silacyclobutanes R^1R^2Si , silacyclobutenes (**5**), and benzo-metallacyclobutenes (**6**).

R^1 or structure	R^2	r (Å)				Angles (°)			
		Si—C-2	Si—C-4	C-2—C-9	C-3—C-4	$\angle M$	$\angle C-2$	$\angle C-3$	$\angle C-4$
H	H	1.895(2)		1.607(6)		80.8(5)	85.1(5)	99.7(5)	
Me	Me	1.880		1.565		76.6			
—CH ₂ CH ₂ CH ₂ —		1.898(2)		1.579(3)					
Cl	Cl	1.886(4)		1.544(6)		84.0(6)	79.0(6)	110.7(9)	
F	F	1.836(3)		1.574(8)		82.7(6)	86.8(8)	100.6(8)	
Np ^a	Np ^a	1.894(4)	1.527(6)			81.3(2)	85.3(5)	107.9(3)	
Np ^a	Si(CH ₂) ₃	1.877(3)	1.881(2)	1.475(5)	1.507(8)	78.8(1)	87.8(3)	106.2(4)	86.7(2)
	Np ^a								
Np ^a	OSi(CH ₂) ₃	1.863(2)	1.863(2)	1.537(3)	1.562(4)	79.5(1)	86.8(2)	100.5(2)	86.1(2)
	Np ^a								
(5a)		1.906(8)	1.915(8)	1.367(11)	1.500(11)	74.0(4)	91.9(5)	106.6(7)	87.5(5)
(5b)		1.86(1)	1.88(1)	1.40(1)	1.51(1)	75.3(4)	92.8(6)	103.1(7)	88.7(5)
(5c)		1.837(3)	1.928(3)	1.367(4)	1.599(4)	78.6(3)	91.7(2)	106.9(2)	81.8(2)
(5d)			1.972(7)			71.4(3)	97.7(5)	103.8(5)	86.6(4)
(5e)			1.991(13)			73.8(6)	96.3(4)	106.0(11)	83.9(8)
(5f) ^b			1.981(18)			74.4(8)	95.5(14)	103.9(15)	82.8(10)
			1.983(17)			73.4(8)	94.1(14)	106.2(15)	83.4(10)
(5g)		1.828(1)	1.864(1)	1.354(1)	1.554(1)	80.7(1)	87.8(1)	110.4(1)	
(6a)		1.885(1)	1.938(1)			77.3(5)	89.9(8)	107.3(10)	85.4(7)
(6b)		2.185(5)	2.204(6)	1.417(9)	1.558(8)	67.5(2)	93.5(4)	110.0(6)	89.0(4)
(7)		1.884(1)	1.880(1)	1.564(1)	1.589(1)	79.45(5)	86.44(7)	99.46(9)	85.88(7)

^a1-Naphthyl. ^bFor two independent molecules.**Table 4** NMR Spectroscopic data (¹H, ¹³C, ²⁹Si) for silacyclobutanes.

R^1	R^2	$\delta^1 H$ (ppm)			$\delta^{13}C$ (ppm)		$\delta^{29}Si$ (ppm)
		H-2, H-4	H-3	Me	C-2, C-4 (J(²⁹ Si- ¹³ C) (Hz))	C-3	
H	H	1.1	2.3		9.5 (42)	22.7	−5.0
H	Me	1.03	2.15	0.300	13.3 (42)	20.3	6.0
Me	Me	1.06	2.15	0.258	14.8 (42)	18.1	18.4
Me	Cl	1.4	2.0	0.619	20.9 (45)	15.9	32.5
Cl	Cl	1.95	1.95		27.7 (52)	14.0	18.0
Me	EtO	0.9–2.0		0.238	18.6	13.5	14.1
Me	C ₇ H ₁₅ O			0.23	18.5	14.2	14.5
Me	PhO	1.1–2.0		0.358	19.4 (47)	14.3	17.0
Me	AcO	1.2–2.0		0.383	18.3	15.0	22.7
Me	OSi(CH ₂) ₃	1.1	1.78	0.225	20.6 (48)	13.7	7.0
	Me						
EtO	EtO	1.4	1.4		20.8 (55)	11.7	−17.1
Me	Et ₂ N	0.9–1.9		0.288	19.5 (45)	14.5	7.8
Me	NHSi(CH ₂) ₃	1.0	1.8	0.125	20.4 (45)	14.5	7.6
	Me						
Me	Ph	1.3	2.3	0.513	14.4 (43)	18.3	11.9
Ph	Ph	1.5	2.3		14.0 (44)	18.4	7.0
Ph	Cl				20.4	16.3	21.4
c-C ₆ H ₁₁	c-C ₆ H ₁₁	0.9	2.0		8.8 (41)	18.8	23.8
CH ₂ =CHCH ₂	CH ₂ =CHCH ₂	1.03	2.07		12.2	18.2	17.1
—CH ₂ CH ₂ CH ₂ —		1.25	2.2		18.3 (37)	18.2	37.2

for 1,1-bis(alkylamino)-1-silacyclobutanes $\langle 89\text{SA}(\text{A})1101 \rangle$. The ^{29}Si nuclear shielding of 1,1-bis(isopropylamino)-1-silacyclobutane ($\delta(^{29}\text{Si}) = -10.2$ ppm) and 1,1-bis(*t*-butylamino)-1-silacyclobutane ($\delta(^{29}\text{Si}) = -14.9$ ppm) is increased compared to 1,1-dimethyl-1-silacyclobutane, and the value of $^1J(^{29}\text{Si}-^{15}\text{N})$ for the former compound is smaller (17.2 Hz) than for acyclic bis(alkylamino)silanes.

1.28.2.3.2 IR Spectroscopy

The study of IR spectra of silacyclobutanes indicates that many of the peaks are found in all spectra and can be considered as characteristic of the ring species $\langle 65\text{IZV}1547, 67\text{JA}1144, 77\text{JOM}(139)11, 80\text{JOM}(197)13 \rangle$. There are six ring vibrations expected for a four-membered ring, one of which, ring puckering, has a frequency below 200 cm^{-1} . Three of the silacyclobutane ring modes occur between 850 cm^{-1} and 950 cm^{-1} . Two absorption bands near 1120 cm^{-1} and 1180 cm^{-1} result from vibrations involving methylene groups of the ring $\langle 67\text{JA}1144 \rangle$. IR spectra of silacyclobutane, 1,1-dimethylsilacyclobutane, 1-methyl-1-chlorosilacyclobutane, and 1,1-dichlorosilacyclobutane in inert gas matrixes at 10 K were studied $\langle 80\text{IZV}837 \rangle$. Vibrational frequencies characterizing the silacyclobutane ring at low temperature were determined more precisely.

For 1-silacyclobutane-1- d_1 in the Si—H stretching region, in addition to the fundamental Si—H band at 2148.3 cm^{-1} a second weaker band at 2151.3 cm^{-1} is observed. These two bands arise from the Si—H stretching for the molecule in two different conformations $\langle 82\text{JPC}4335 \rangle$.

According to matrix IR spectroscopy the pyrolysis of dimethyldiallylsilane at $750\text{--}800^\circ\text{C}$ in a vacuum gave propylene and 1-silacyclobut-2-ene. Unstable intermediate compounds with the Si=C bond have not been detected $\langle 85\text{IZV}711 \rangle$.

1.28.2.3.3 UV Spectroscopy

Ultraviolet spectroscopy has been used for the investigation of charge transfer complexes (CTCs) of silacyclobutanes with tetracyanoethylene $\langle 75\text{IZV}1998, 77\text{IZV}1038, 79\text{ZOB}950 \rangle$. The increase in the electron donor ability of alkyl substituents in 1-methyl-1-alkyl-1-silacyclobutanes leads to a bathochromic shift of the CTC band. The first ionization potentials for these compounds were determined from ν_{CTC} values $\langle 77\text{IZV}1038 \rangle$. The comparison of the CTC UV spectra for 1-methyl-1-(*p*-x-phenyl)silacyclobutanes and trimethyl(*p*-x-phenyl)silanes ($\text{X} = \text{H}, \text{Me}, \text{Cl}, \text{CH}_2\text{TMS}, \text{OMe}, \text{NMe}_2$) indicates that both silyl substituents act as electron acceptors with respect to the π -electron system of benzene; this effect is larger for the 1-methyl-1-silacyclobutane group. The calculated σ^+ constants of the TMS and $\text{MeSi}(\text{CH}_2)_3$ groups are -0.22 and -0.20 , respectively $\langle 75\text{IZV}1998 \rangle$.

1.28.2.3.4 EPR Spectroscopy

Silacyclobut-1-yl, 1-methylsilacyclobut-1-yl, and 3-methylsilacyclobut-1-yl radicals were prepared by γ irradiation of the corresponding silanes in adamantane matrixes at 77 K. EPR studies show that the radicals have a nonplanar ring $\langle 88\text{JOM}(341)273 \rangle$. The reduction of phenylsilacyclobutanes with potassium gave anion radicals, and their EPR spectra were recorded at -75°C (Table 5) $\langle 83\text{ZOB}1315 \rangle$.

Table 5 Hyperfine splitting constants of silacyclobutane anion radicals.

$\text{R}^1\text{R}^2\text{Si} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array}$					
R^1	R^2	Hyperfine structure	Hyperfine splitting constants, G		
			a_1	a_2	a_3
Me	Ph	$2 \times 3 \times 3$	7.7	3.3	1.0
Ph	Ph	$2 \times 3 \times 3$	7.6	3.5	1.0
Bu ^t	Ph	$2 \times 3 \times 3$	8.3	3.0	1.1
Me	<i>p</i> -MeC ₆ H ₄	$4 \times 3 \times 3$	9.0	3.4	1.8

1.28.2.3.5 Mass spectrometry

The electron impact fragmentation of silacyclobutane <67JA1144, 76JCS(D)558>, 1,1-dialkylsilacyclobutanes <66ZOB96, 72OMS(6)309, 79ZOB1307, 85JOM(284)5>, 1-alkyl-1-aryl-1-silacyclobutanes <84ZOB1125>, and silacyclobutanes with functional substituents on the silicon atom <76JCS(D)558, 84JOM(277)311> or the methyl group in the 2 or 3 position of the ring <79ZOB1307, 81OMS(16)242, 84JOM(277)311> has been investigated. With rare exceptions silacyclobutanes show intense molecular ion peaks. The main feature of the fragmentation process for the molecular ion of silacyclobutanes is the elimination of ethylene from the heterocycle. The loss of ethylene from these compounds also occurs when they are pyrolyzed in the gas phase. The mass spectrum of 1,1-dimethyl-1-germacyclobutane with respect to the silicon compound is enriched by light fragment ions, and exhibits lower intensities for odd-electron ions. The elimination of C_3H_6 from the molecular ion is more characteristic for germacyclobutane than for silacyclobutane <72OMS(6)309>.

1.28.2.4 Thermodynamic Aspects

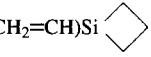
The boiling point (82.75°C) and the heat of evaporation (7.887 kcal mol⁻¹ (33.02 kJ mol⁻¹) at 298 K) of 1,1-dimethylsilacyclobutane have been determined from the results of saturated vapour pressure (P) temperature (t) dependence. The coefficients in the Antoine equation

$$\log P = 7.29978 - 1473.282/(t + 250.640)$$

were obtained from the experimental data <74MI 128-01>.

Enthalpies of combustion for 1-methyl-, 1,1-dimethyl-, 1,1,2- and 1,1,3-trimethyl-, and 1-methyl-1-vinylsilacyclobutanes were determined in a precision isothermal calorimeter. The heats of formation of these compounds in both the liquid and gas phases were calculated at 298.15 K. The calculated energies of monosilacyclobutane ring strain vary within the range 23.8–25.0 kcal mol⁻¹ (107–112 kJ mol⁻¹), increasing with the introduction of substituents to the silicon atom and to the carbon atoms in the ring (Table 6) <91JOM(401)245, 91MI 128-01>. The theoretical heat of formation at 298 K for 1,1-dimethylsilacyclobutane is –23.8 kcal mol⁻¹ (–99.5 kJ mol⁻¹) <89JPC1584>.

Table 6 Enthalpies of combustion, formation, and evaporation, and calculated energies of ring strain for silacyclobutanes (kcal mol⁻¹ (kJ mol⁻¹)) <91JOM(401)245>.

Compound	$-\Delta H_{comb, liq}^\circ$	$-\Delta H_f^\circ$	ΔH_{ev}°	E_{cycle}
MeHSi 	930.2 ± 1.8 (3894.6 ± 7.6)	11.5 ± 1.8 (48.0 ± 7.5)	6.0 ± 1.8 (25.1 ± 7.6)	25.8 (108)
Me ₂ Si 	1076.9 ± 2.1 (4508.8 ± 8.6)	28.2 ± 2.0 (118.1 ± 8.5) ^a	7.9 ± 2.1 (33.1 ± 8.6)	26.0 (109)
Me ₂ Si 	1231.3 ± 1.9 (5155.3 ± 8.0)	34.9 ± 2.0 (146.0 ± 8.5)	8.6 ± 2.0 (36.0 ± 8.4)	26.0 (109)
Me ₂ Si 	1230.7 ± 1.9 (5152.8 ± 8.0)	35.5 ± 2.0 (148.5 ± 8.5)	8.5 ± 2.0 (35.5 ± 8.5)	26.8 (112)
Me(CH ₂ =CH)Si 	1188.1 ± 1.9 (4974.4 ± 8.0)	9.8 ± 2.0 (41.1 ± 8.5)	7.9 ± 2.0 (33.1 ± 8.5)	26.0 (109)

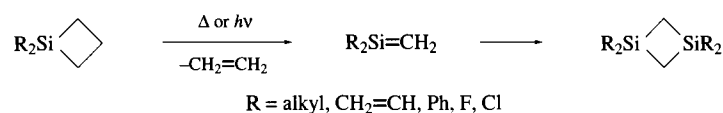
^a27.5 kcal mol⁻¹ (115.0 kJ mol⁻¹) <76IZV2337>.

1.28.3 REACTIVITY OF FOUR-MEMBERED RINGS WITH ONE SILICON, GERMANIUM, OR TIN ATOM

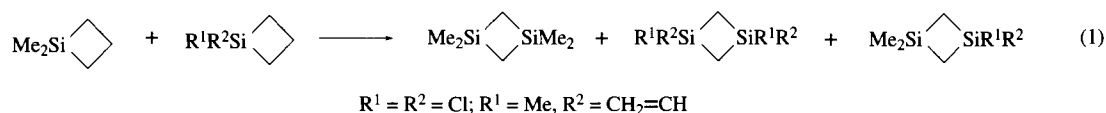
1.28.3.1 Pyrolysis and Photolysis

The first evidence for the existence of compounds containing an Si=C bond was obtained from thermal transformations of silacyclobutanes <B-85MI 128-01>. Pyrolysis of 1,1-disubstituted

silacyclobutanes at 500–700 °C yielded 1,3-disilacyclobutanes, ethylene being the predominant component of the gaseous reaction products (Scheme 1) <66DOK(171)630, 66IZV584>. The investigation of this reaction <68JCS(B)419, 68JCS(B)1396> led to the suggestion that gas phase pyrolysis proceeds via ring cleavage with the formation of alkenes and silaethenes. The subsequent “head-to-tail” dimerization of silaethenes gave disilacyclobutanes <74IZV1153, 75ACR18, 80JOM(188)151, 80JOM(197)13, 80JOM(197)147, 80JOM(202)401, 81JOM(222)33, 82CC806, 82JPC5110, 82ZAAC(485)53, 87BCJ2263, 92JOM(426)23>. Copyrolysis of two different silacyclobutanes produced a mixture of three 1,3-disilacyclobutanes (Equation (1)) <80JOM(188)151, 82CC806>. Gas phase <80JOM(201)363, 83OM39> and laser pulsed photolysis <89JPC8193, 94JOM(466)29> proceed in the same way.



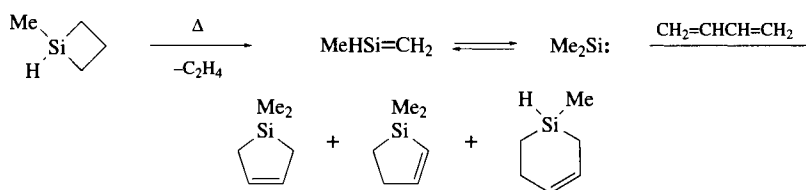
Scheme 1



The formation of silaethenes was confirmed by matrix IR spectroscopy <79IZV2152, 80JOM(201)123, 80JOM(201)137, 82JOM(226)11, 83IZV238, 84JOM(271)55>, electron diffraction <80JA2854>, photoelectron spectroscopy <81JA1212>, and the heat of formation <86JPC389, 91JPC7244>. The chemical evidence for the existence of intermediate silaalkenes was the reaction with H₂O and NH₃ <67CC864, 68JCS(B)419, 68JCS(B)1396>. The formation of 1,3-disilacyclobutanes was completely suppressed. Trimethylsilanol and hexamethyldisiloxane were obtained on reaction with H₂O. Hexamethyldisilazane was isolated from the pyrolysis of 1,1-dimethylsilacyclobutane in the presence of NH₃. The formation of silaalkenes during the pyrolysis of silacyclobutanes also occurs in reactions involving the addition of hydrogen halides <80JOM(188)151, 81CC52>, alcohols and phenols <74JOM(80)37, 78TL2149, 80CC382, 80JOM(202)401, 81CC915, 81T2875, 82NJC381>, halogensilanes <74JA7105, 75JA7371>, acetonitrile <75JA7371>, and hexamethylcyclotrisiloxane <75JA7371> to the Si=C bond.

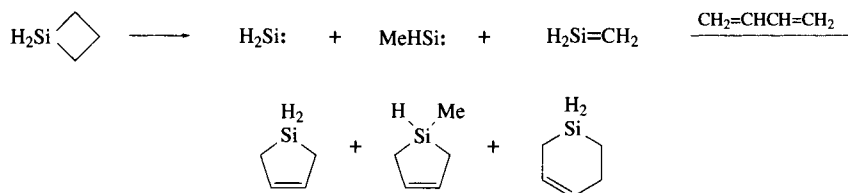
Silaalkenes have been trapped by alkenes, alkynes <71DOK(201)1365, 71IZV1840, 83OM343>, allene <85JA731>, aldehydes and ketones <73CC167, 74JOM(66)29, 75JA7371>, thiobenzophenone <75JOM(101)171>, Schiff bases <74JA614>, oxygen <81CC52>, dimethylsanthione (Me₂Si=S) <84DOK(274)1106, 84JOM(271)191>, and thioformaldehyde (H₂C=S) <83DOK(272)892> in [2 + 2] cycloaddition reactions. During pyrolysis of 1,1-dimethylsilacyclobutane in the presence of a threefold excess of a diene, cyclodimerization was completely suppressed, and the reaction proceeded as a [2 + 4] cycloaddition <71DOK(201)1365>. The products of 1,1-dimethylsilacyclobutane and acrolein copyrolysis can be accounted for in terms of initial [2 + 2] and [2 + 4] competitive addition to the carbonyl group and to the conjugated C=C–C=O system <75JOC229, 75JOM(99)231>.

The cleavage of 1-methyl-1-silacyclobutane by pyrolysis is accompanied by the isomerization of methylsilene to dimethylsilylene (Scheme 2) <81JA1843, 84CC478, 84OM918, 86JA834>. During the pyrolysis of 1-methyl-1-silacyclobutane with a 10-fold excess of butadiene the formation of 1,3-disilacyclobutanes was completely suppressed. The only significant products, other than the decomposition products of butadiene, were the adducts of dimethylsilylene combining with butadiene. The [2 + 4] cycloadduct of methylsilene was a minor product (<1%).



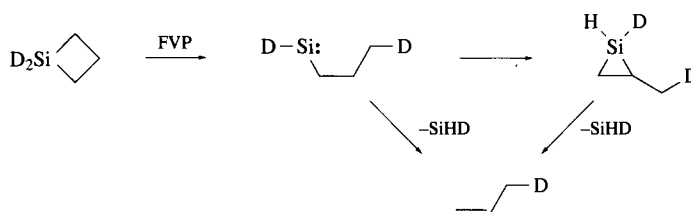
Scheme 2

Silacyclobutane undergoes thermal fragmentation to yield ethene, propene, cyclopropane, and products formed from silylene ($\text{H}_2\text{Si:}$), methylsilylene (MeHSi:), and silene ($\text{H}_2\text{Si}=\text{CH}_2$). Trapping of the three silicon reactive intermediates with butadiene yields five- and six-membered ring compounds (Scheme 3) <83JA618>.



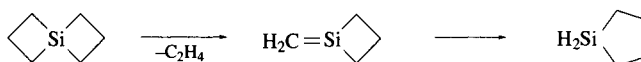
Scheme 3

Flash vacuum pyrolysis (FVP) of 1,1-dideuteriosilacyclobutane proceeds with a low yield (<10%). The products consisted mainly of ethene and propene. The ethene obtained from 1,1- d_2 -silacyclobutane is undeuterated, and approximately 75% of the propene contained at least one deuterium atom. This is consistent with the mechanism for silacyclobutane decomposition initiated by a 1,2-D shift (Scheme 4) <87JA6711>.



Scheme 4

Pyrolysis of 4-silaspiro[3.3]heptane at 500–700°C gave ethene, propene, butadiene, and silacyclopent-3-ene. The last was obtained due to isomerization of the intermediate methylene derivative (Scheme 5) <73DOK(211)106, 83OM8>.

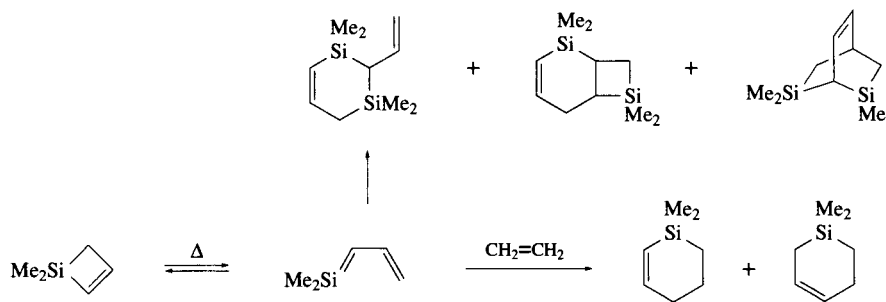


Scheme 5

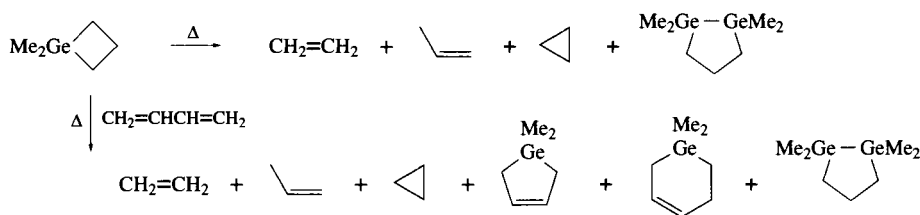
Structural isomerization is known to occur in the pyrolysis of 1,1,3-trimethyl-1-silacyclobutane <70IZV1676> and 1,1,2-trimethyl-1-silacyclobutane <75JOM(85)317>. The migration of a hydrogen from an exocyclic methyl group on a carbon to an α - or β -ring carbon produces trimethylallylsilane (20%) and ethyldimethylvinylsilane (10%), respectively, in addition to disilacyclobutanes. Pyrolysis of (*Z*)- and (*E*)-1,1,2,3-tetramethylsilacyclobutanes at 398.2°C provides the same products but in different amounts <89OM168>.

Gas phase reactions <85IZV711, 88JA3689, 89JOM(376)259> and photolysis <81JOM(219)153, 89OM530> of silacyclobutenes have also been studied (Scheme 6). The pyrolysis of 1,1-dimethyl-1-silacyclobutene under static conditions at 363°C gives three major products which are formal dimers of the starting material or the intermediate isomer—siladiene. In the presence of a 20-fold excess of ethylene the reaction leads cleanly to 1,1-dimethyl-1-silacyclohexenes.

Thermal fragmentation of 1,1-dimethyl-1-germacyclobutane in the gas phase differed significantly from the pyrolysis of its silicon analogue. Examples of these basic differences included the formation of cyclopropane, propene, and 1,2-digermacyclopentane <70DOK(194)1096, 92OM3307>. In the gas phase the carbenoid rupture of dimethylgermylene predominates (Scheme 7). In the presence of a 10-fold excess of butadiene the following products were formed: ethene (17%), propene (16%), cyclopropane (12%), 1,1-dimethylgermacyclopent-3-ene (17%), 1,1-dimethylgermacyclohex-3-ene (34%), and 1,2-digermacyclopentane (16%) (Scheme 7).



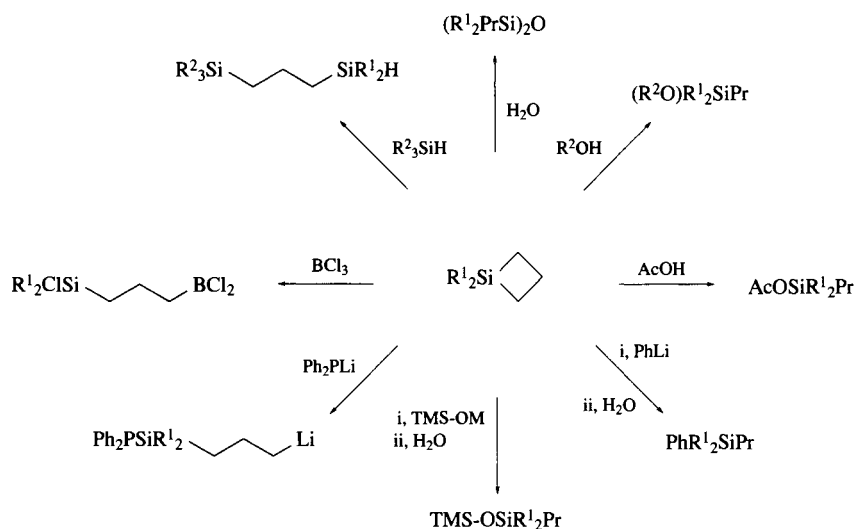
Scheme 6



Scheme 7

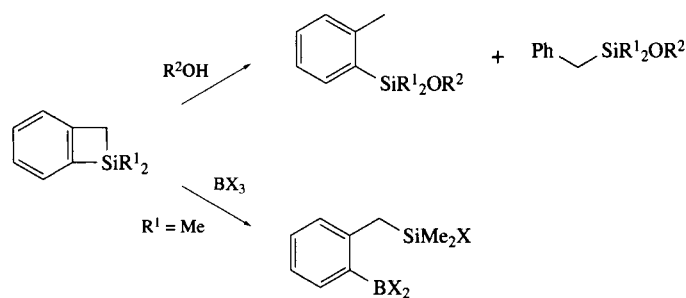
1.28.3.2 Ring-opening Reactions

The highly strained four-membered ring of silacyclobutanes and germacyclobutanes was opened by the action of nucleophilic and electrophilic agents ^{<74IZV1153>}. The reactions of silacyclobutanes with H₂O ^{<71IZV1033, 85IZV1906>}, alcohols ^{<71IZV1033, 85TL4761>}, Hg(NO₃)₂ ^{<75IZV1600>} or KOH in alcohols ^{<54JA5002, 75JOM(96)15>}, acetic acid ^{<73JOM(56)C7, 75JOM(96)15>}, PhLi ^{<65DOK(161)358>}, silanolates ^{<65DOK(161)358, 73IZV1434>}, Ph₂PLi ^{<83IZV2125>}, hydrosilanes ^{<64IZV1133>}, [K 18-crown-6]⁺F⁻ ^{<89IC3182>}, BX₃ (X = Cl, Br, I) ^{<83ZAAC(500)132, 87CB853>}, GeCl₄, and SnCl₄ ^{<80JOM(198)29>} proceeded with the cleavage of the endocyclic Si—C bond (Schemes 8 and 9).



Scheme 8

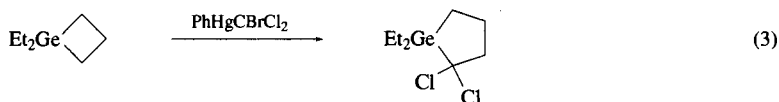
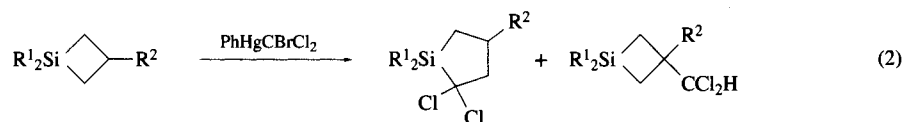
The cleavage of germacyclobutanes with Br₂, HX (X = Cl, Br, I), LiAlH₄ ^{<65CR(260)2255>}, PhLi ^{<68CR(C)1794>}, hydrosilanes, hydrogermanes ^{<67TL255>}, and stannacyclobutanes with MeMgBr ^{<83JA3336>} has also been studied. Ring-opening polymerization of silacyclobutanes proceeds with AlCl₃ ^{<75IZV953>}, platinum ^{<65JOC2618>}, and BuLi ^{<92MM1639, 92MM3834>}.



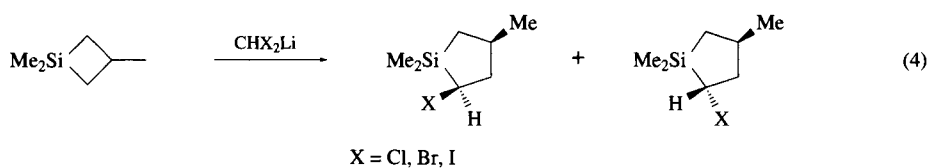
Scheme 9

1.28.3.3 Ring Expansion Reactions

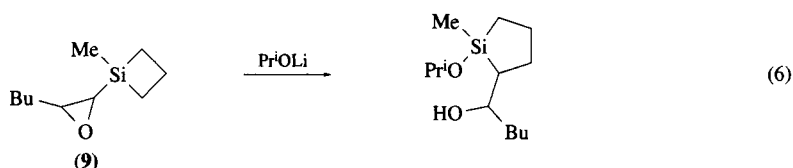
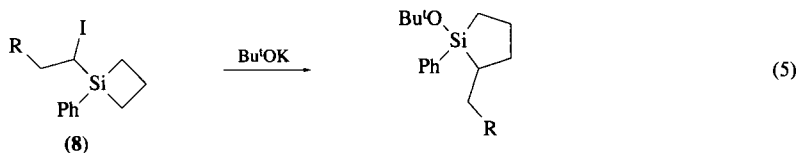
Singlet methylene reacts with 1,1-dimethylsilacyclobutane to yield, besides the expected C—H insertion products, 1,1-dimethylsilacyclopentane formed by insertion into the Si—C bond <89CC284>. The insertion of dichlorocarbene derived from phenyl(bromodichloromethyl)mercury gave ring expansion products with 1,1-dimethyl- <67JA1538, 71JA3709> and 1,3-dimethyl-1-butyl-1-silacyclobutane <73JOM(50)39> as well as with dichloromethyl silacyclobutane derivatives (Equation (2)). 1,1-Diethyl-2,2-dichlorogermacyclopentane was obtained in the same way (Equation (3)) <69JOM(16)503>.



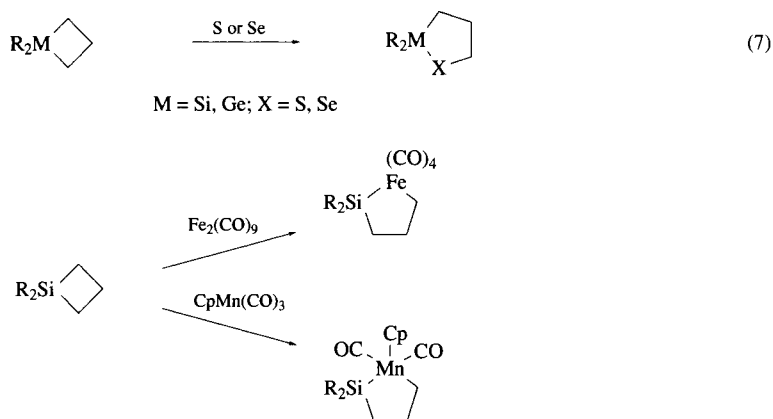
Several silacyclopentanes were prepared by the stereoselective reaction of silacyclobutanes with CHX_2Li (Equation (4)) <90TL6055, 93T8487>.



The treatment of 1-(1-iodoalkyl)-1-silacyclobutanes (8) with Bu^tOK or AgOAc and oxiranyl-silacyclobutane (9) with Pr^iOLi provides silacyclopentanes (Equations (5) and (6)) <91TL4545, 91TL6383>.

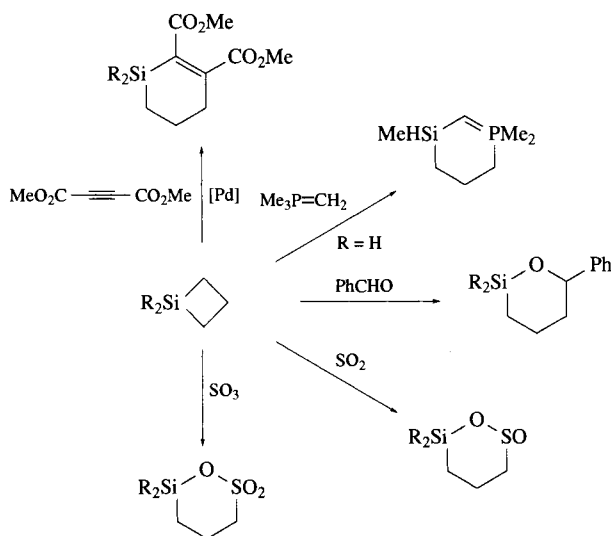


Molecular sulfur and selenium enter into silacyclobutane $\langle 68\text{CR}(\text{C})411 \rangle$ and germacyclobutane rings $\langle 68\text{JOM}(12)143 \rangle$ to give 1-thia(selena)-2-sila(germa)cyclopentanes (Equation (7)). Insertion of a tetracarbonyliron fragment into a strained silacyclobutane ring proceeds smoothly at $6\text{--}20^\circ\text{C}$ in the reaction with $\text{Fe}_2(\text{CO})_9$ $\langle 72\text{CC}445, 76\text{JCS}(\text{D})910, 78\text{JOC}665, 78\text{JOM}(144)317, 79\text{IZV}2815 \rangle$, while irradiation of 1,1-diphenylsilacyclobutane and $\text{CpMn}(\text{CO})_3$ yields 1-sila-2-manganacyclopentane at low temperatures (Scheme 10) $\langle 79\text{JOM}(170)\text{C}37 \rangle$.



Scheme 10

Six-membered heterocycles were obtained by the insertion of alkyne derivatives, in the presence of a palladium catalyst $\langle 75\text{CL}891, 91\text{BCJ}1461 \rangle$, carbonyl compounds $\langle 75\text{TL}2153, 81\text{TL}235, 90\text{TL}6059 \rangle$, phosphorus ylides $\langle 73\text{AG}344, 75\text{CB}2842 \rangle$, SO_2 $\langle 68\text{CR}(\text{C})411, 72\text{JOM}(34)17 \rangle$, and SO_3 $\langle 69\text{BSF}3608, 70\text{JOM}(22)\text{C}7, 70\text{JOM}(25)367, 72\text{CR}(\text{C})1049, 78\text{JOM}(153)289 \rangle$, into the four-membered ring of silacyclobutanes and germacyclobutanes (Scheme 11).



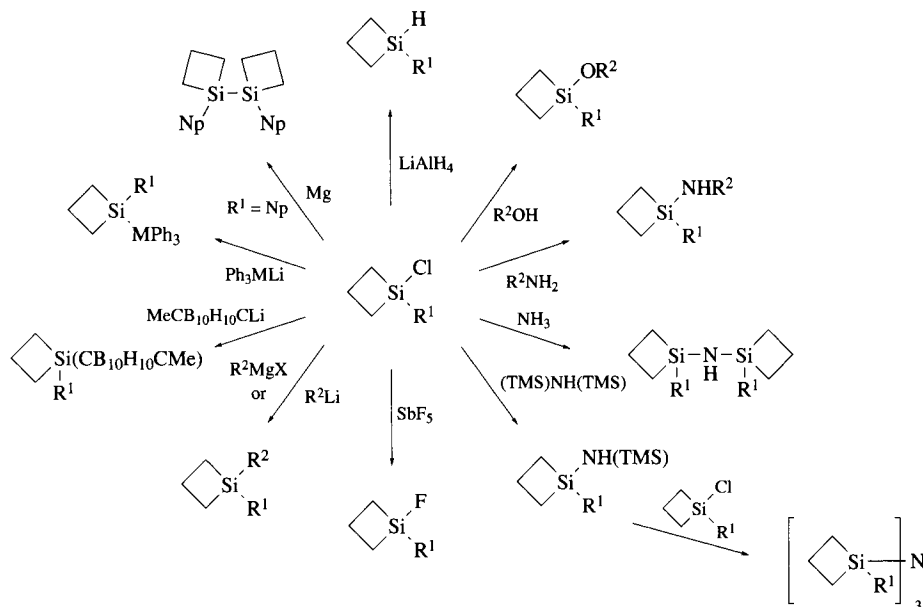
Scheme 11

Dimerization of 1,1-dimethyl-1-silacyclobutane to form disilacyclooctane can be readily achieved by platinum catalysis, but not by rhodium catalysis $\langle 93\text{JOM}(446)183 \rangle$.

1.28.3.4 Reactions of Substituents at the Heteroatom

Chlorine atoms on the silicon of silacyclobutanes easily enter into various exchange reactions (Scheme 12). The reduction with LiAlH_4 $\langle 65\text{DOK}(161)358, 67\text{JA}1144, 74\text{JA}2637 \rangle$ or alkylaluminum hydrides $\langle 90\text{USP}4973723 \rangle$ produces hydrosilacyclobutanes. Alcoholysis $\langle 64\text{DOK}(155)849, 74\text{T}749 \rangle$, ammonolysis $\langle 65\text{KGS}455 \rangle$, aminolysis $\langle 74\text{T}749 \rangle$, acylation $\langle 64\text{DOK}(155)849, 90\text{USP}4965367 \rangle$, fluorination

with SbF_5 <67JA1144>, and alkylation and arylation with different Grignard reagents <61DOK(141)843, 65DOK(161)358, 73IZV135, 74ZOB1970, 77JOM(132)45, 78IZV1686, 86IZV434, 92ZOB1318> or by lithium synthesis <72TL3495, 77JOM(132)45, 77JOM(139)11> gave the products of chlorine substitution. 1-Carboranylsilacyclobutanes were obtained by the treatment of lithiated carboranes with chlorosilacyclobutanes <84ZOB1197>. Metal-substituted silacyclobutanes were prepared in 15%, 55%, and 53% yields by the reaction of 1-methyl-1-chlorosilacyclobutane with Ph_3MLi ($\text{M} = \text{Si}, \text{Ge}, \text{Sn}$) <78IC1092>. Coupling of 1-naphthyl-1-chlorosilacyclobutane with magnesium gave a 45% yield of disilane <83IZV1215>. The reaction of phosphorus ylides and chlorosilacyclobutanes produces silacyclobutyl-substituted ylides <75CB2851>. Trans-silylation of disilazanes with 1-methyl-1-chlorosilacyclobutane has been investigated <67KGS148>.

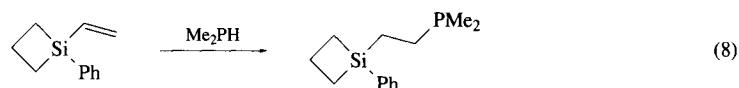


Scheme 12

Silacyclobutanes with hydrogen atoms on the silicon can be used for hydrosilylation of allyl cyanide <65DOK(161)358> or allyl chloride <71DOK(198)112> in the presence of platinum catalysts. The addition of SnCl_4 <68DOK(178)1332> or SnBr_4 <69DOK(185)1056> in Et_2O to silacyclobutane gave 1-chloro- and 1-bromosilacyclobutane, respectively. Using the exchange reaction between 1,2-dimethylsilacyclobutane and Bu_3SnOMe or Me_2NLi , 1-alkoxy- or 1-amino-1,2-dimethylsilacyclobutanes have been obtained <80JOM(197)261>. The platinum complex $\text{Pt}(\text{C}_2\text{H}_4)(\text{PPh}_3)_2$ with 1-methylsilacyclobutane produced a compound in which the silacyclobutane ring is bound to the platinum fragment by an $\text{Si}-\text{Pt}$ bond <78JOM(144)317>. The above-mentioned reactions are shown in Scheme 13.

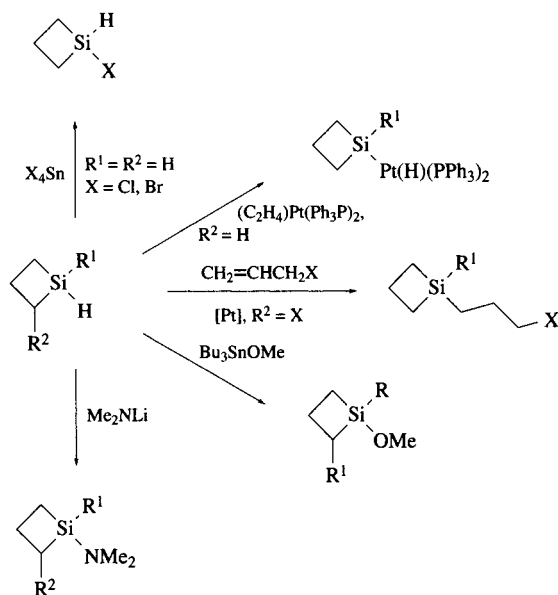
The reaction of alkoxy group substitution in *cis*- and *trans*-1,2-dimethyl-1-alkoxysilacyclobutanes by RMgX and RLi proceeds with the retention of configuration at the silicon <76CR(C)253, 77JOM(139)271>.

The photoaddition of phosphines to 1-phenyl-1-vinylsilacyclobutane gave phosphinoethylsilacyclobutane (Equation (8)) <82ZAAC(489)23>.

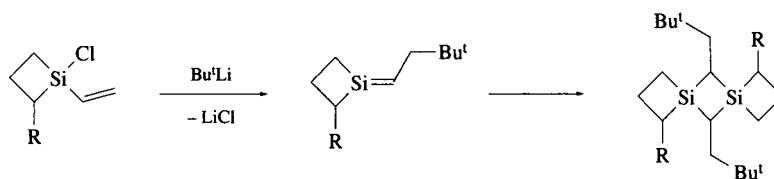


1-Chloro-1-vinylsilacyclobutanes react with Bu^tLi in pentane to yield neopentylsilaethenes, which without a suitable reagent undergo cyclodimerization. In the presence of cyclopentadiene only [2 + 4] products are obtained, with cyclohexa-1,3-diene [2 + 2] and [2 + 4] cycloaddition reactions occur in comparable rates (Scheme 14) <87JOM(336)83>.

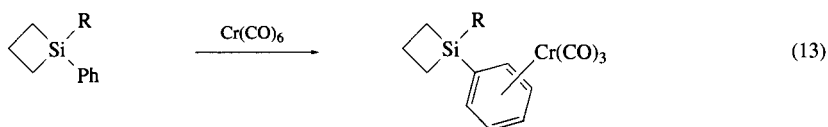
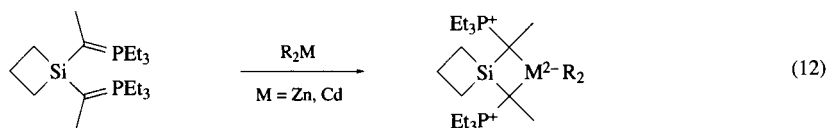
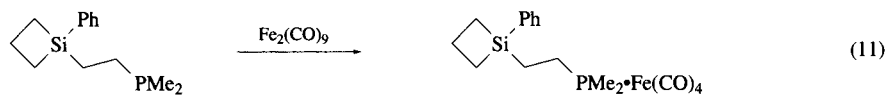
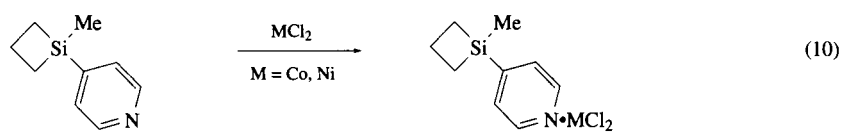
Some silacyclobutanes have been used in complexation reactions (Equations (9)–(13)) <73DOK(208)868, 73IZV135, 73IZV1364, 75CB2851, 82ZAAC(490)38, 85IZV1906>.



Scheme 13

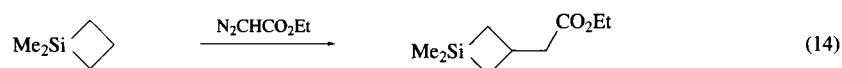


Scheme 14

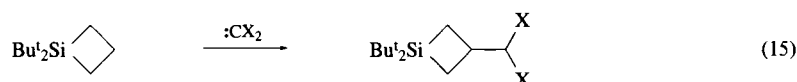


1.28.3.5 Reactions of the Ring Carbons

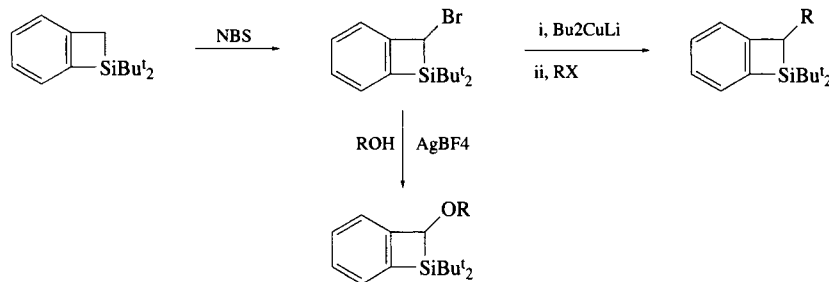
Heating 1,1-dimethylsilacyclobutane with $\text{N}_2\text{CHCO}_2\text{Et}$ in the presence of $\text{Rh}_2(\text{OAc})_4$ gave the product of ethoxycarbonylcarbene incorporation into the C—H bond at the 3 position (Equation (14)) <79ZOB2776>.



The reaction of dichloro- and dibromocarbene with 1,1-di(*t*-butyl)silacyclobutane proceeds exclusively as insertion into the βC —H bonds (Equation (15)) <80JOM(198)29>.

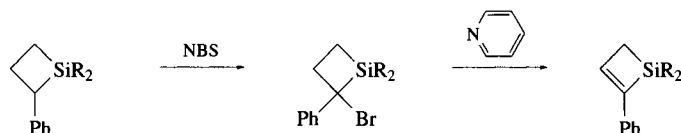


Bromination of 1,1-di(*t*-butyl)-2,3-benzo-1-silacyclobutane with NBS gave the 4-bromo derivative (Scheme 15). Metalation with Bu_2CuLi , followed by alkylation or acylation, generated the corresponding 4-alkyl or acyl compounds. The replacement of the bromine atom with an alkoxy group was achieved by treatment with alcohol in the presence of AgBF_4 <85CL617>.



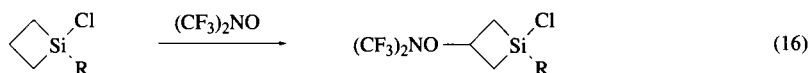
Scheme 15

1,1-Disubstituted 2-phenyl-1-silacyclobut-2-enes were prepared from 2-phenylsilacyclobutanes by bromination and subsequent dehydrohalogenation (Scheme 16) <65JA2678, 75TL2153>.



Scheme 16

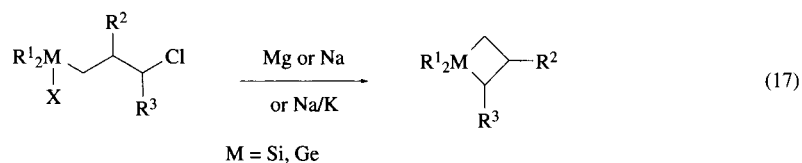
The attack of silacyclobutanes by $(\text{CF}_3)_2\text{NO}$ led to 3-substituted products; 2,3-disubstituted compounds were obtained as minor products (Equation (16)) <94JFC(67)129>.



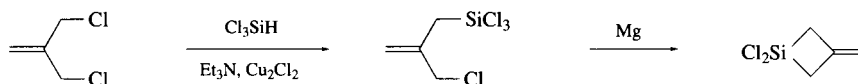
1.28.4 SYNTHESIS

1.28.4.1 Intramolecular Cyclocondensation

The cyclization of chloro-, bromo-, and alkoxy(3-halopropyl)silanes and -germanes with magnesium <54JA5002, 57IZV1206, 61DOK(141)843, 63DOK(150)799, 68KGS565, 71DOK(198)112, 71FRP2069504, 71GEP(O)2053384, 72JOM(43)121, 72TL525, 77JOM(139)11, 80JOM(188)25>, sodium, or sodium/potassium alloy <65CR(260)2255, 66JOM(5)35, 68CR(C)(266)1794, 69IZV976, 85DOK(282)901> was the first method for the synthesis of four-membered heterocycles containing silicon or germanium (Equation (17)).

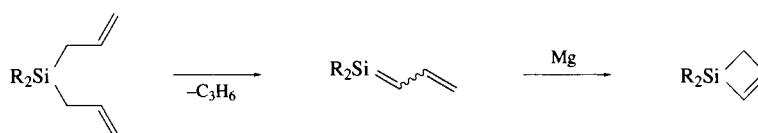


3-Chloro-2-chloromethyl-1-propene reacts with Cl_3SiH in the presence of Et_3N and a catalytic amount of Cu_2Cl_2 to yield 2-chloromethyl-3-trichlorosilylpropene, which undergoes cyclization with magnesium (Scheme 17) <90JOM(391)7>.



Scheme 17

Flash vacuum pyrolysis of allylsilanes has been used for the synthesis of silacyclobutenes <78JA1630, 81JOM(216)C5, 83JA2006>. The main reaction of diallylsilanes is retroene elimination of propene with the formation of silacyclobutene (Scheme 18) <78JA1630, 85OM2210>. Methoxy(allyl)disilanes generated silylenes, which afforded silacyclobutene products (Scheme 19) <83JA2006>.

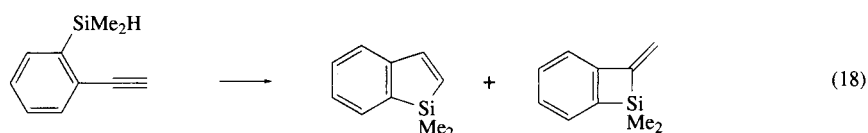


Scheme 18



Scheme 19

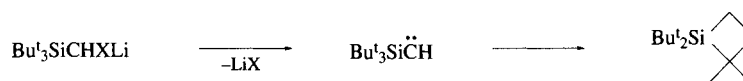
Flash vacuum pyrolysis of [*o*-(dimethylsilyl)phenyl]ethyne at 650°C produced 1,1-dimethyl-1-silaindene and isomeric 1,1-dimethyl-2-methylenebenzo-1-silacyclobutene, arising from an initial 1,5-H shift from silicon (Equation (18)) <85OM575>.



Intramolecular bis-silylation of the $\text{C}=\text{C}$ bond in pentamethyl(4-butenyl)disilane upon treatment with palladium acetate and 1,1,3,3-tetramethylbutylisocyanide in toluene gave 1,1-dimethyl-2-trimethylsilylmethylsilacyclobutane in 83% yield (Equation (19)) <91JA3987>.

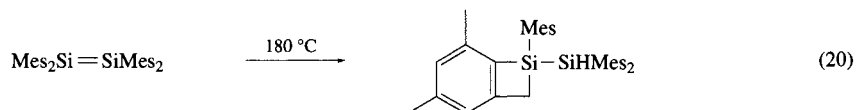


The reaction of tri(*t*-butyl)(dihalomethyl)silanes with organolithium compounds leads to the corresponding carbenoids, which gave carbene by lithium halide elimination. Further intramolecular reaction of the intermediate provides silacyclobutane (Scheme 20) <83ZN(B)1062>.

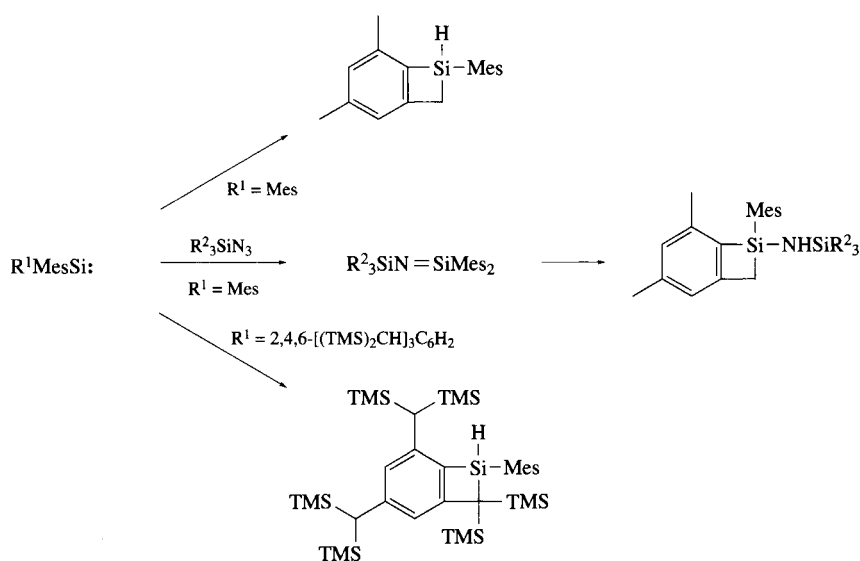


Scheme 20

Many benzosilacyclobutanes have been obtained from mesityl-substituted silanes. Compounds of this type are derived from tetramesityldisilene at a temperature above 180°C (Equation (20)) <83JA1070>.

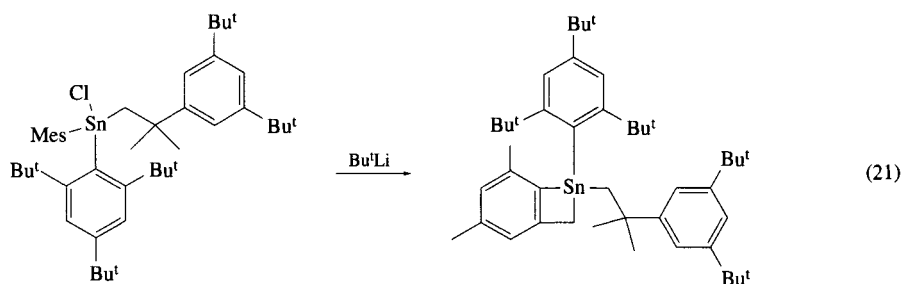


Cyclization of silylenes with sterically hindered substituents gives benzosilacyclobutanes, which most likely result from molecular C—H insertion reactions (Scheme 21) <83CC952, 93JA10428>. Dimesitylsilylene also reacts with R^2_3SiN_3 to produce silaneimine which, however, spontaneously rearranges to form an isomeric benzosilacyclobutane derivative (Scheme 21) <89JOM(379)217>.



Scheme 21

Benzostannacyclobutene was generated from sterically hindered chloro(mesityl)stannane (Equation (21)) <91JOM(415)343>.

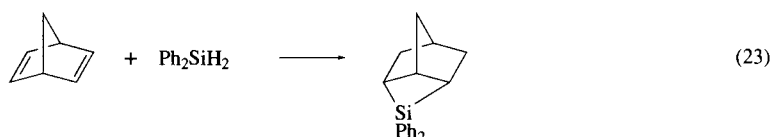


1.28.4.2 [3 + 1] Cyclocondensation

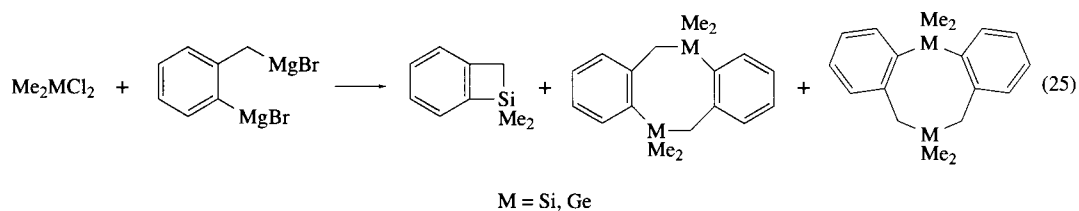
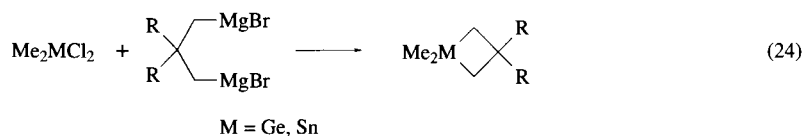
The reaction of the sodium salt of malonic ester with dimethyldichloromethyl- <58JA5414> or dimethyldiodomethylsilane <55JA2339> in EtOH or MeOH, respectively, yielded 1,1-dimethyl-3,3-di(ethoxycarbonyl)-1-silacyclobutane, as well as the linear product (Equation (22)).



The rhodium catalyst $[\text{Rh}(\text{nbd})(\text{DPPE})]\text{PF}_6$ (nbd = norbornadiene) mediates the hydrosilylation of norbornadiene with diphenylsilane to yield 8,8-diphenyl-8-silatricyclo[2.2.1.5]octane (Equation (23)) <91JOM(411)C1>.



The reaction of di-Grignard reagents with Me_2MCl_2 ($\text{M} = \text{Si}, \text{Ge}, \text{Sn}$) is a convenient method for the synthesis of metallacyclobutanes (Equations (24) and (25)) <83JA3336, 84JOM(277)319, 85JOC71, 87JOM(321)291>.



Benzosilacyclobutene and benzogermacyclobutene were formed in high yields, but the tin analogue was not obtained, and the dimeric eight-membered ring species were isolated for all three elements <87JOM(321)291>.

1.28.4.3 [2 + 2] Cycloaddition

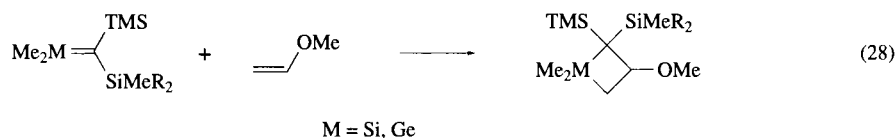
This method includes the reactions of unstable and very reactive silaethenes, containing an $\text{Si}=\text{C}$ bond, with alkenes, dienes, and alkynes. Silaethenes can be conveniently prepared by the reaction of chlorovinylsilanes with Bu^tLi and the subsequent 1,2-elimination of LiCl <77JA8447, 89JOM(377)175, 91AG(E)444, 91AG(E)1151, 92JOM(426)1, 92OM1137, 92OM2494, 93CB2177, 93ZN(B)318>. The trapping of silaethenes with alkenes <93CB2177> or alkynes <91AG(E)1151> yields [2 + 2] cycloadducts (Equation (26) and Scheme 22). In the presence of dienes, [2 + 2] and [2 + 4] cycloadducts are formed in competition (Scheme 22).



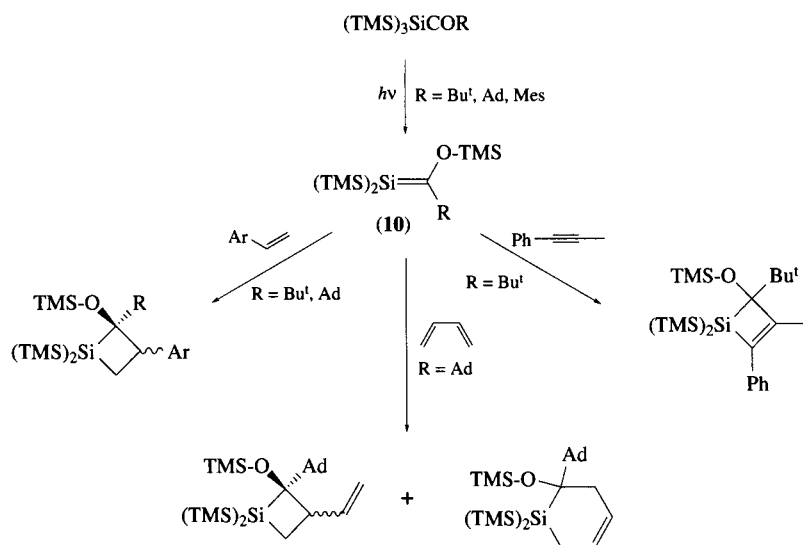
The reaction of dimethylvinylalkoxysilanes with alkyl lithium reagents (Bu^tLi , Bu^sLi , Bu^nLi) in a 2 : 1 ratio at low temperature gives high yields of silacyclobutanes (Equation (27)) <78JOM(159)99>.



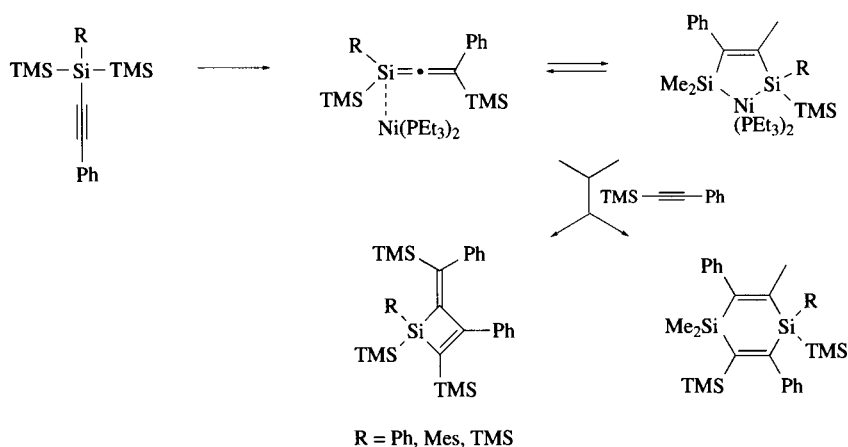
Scheme 22



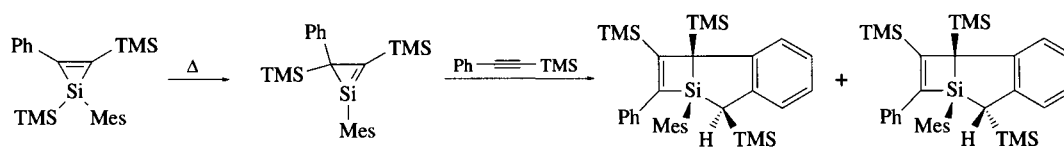
Ring insertion reactions have been used for the synthesis of silacyclobutadiene $\langle 89JA5951 \rangle$ and silacyclobutane $\langle 78JOM(159)137 \rangle$. The photolysis of 2,4,6-triisopropylphenyl(1,2,3-tri-*t*-butylcyclopropenyl)silylene (**11**) in 3-methylpentane glass at 77 K affords the isomeric silacyclobutadiene (**12**) in 68% yield. Compound (**12**) is stable to 140 K. Above 140 K (**12**) cleanly reverts to the silylene (**11**) (Equation (30)) $\langle 89JA5951 \rangle$.



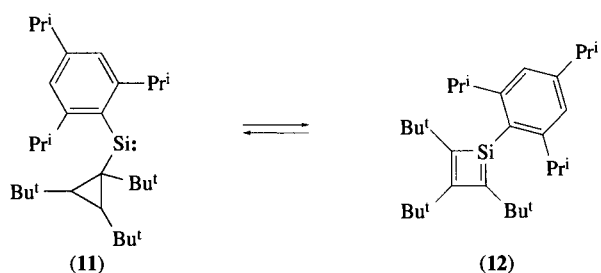
Scheme 23



Scheme 24



Scheme 25

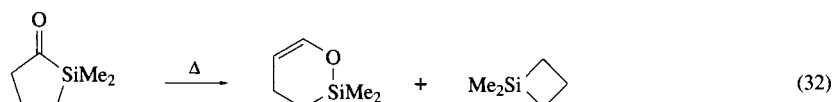


(30)

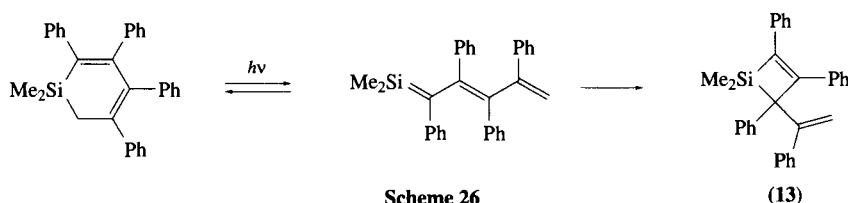
The reaction of hexamethylsilirane with an excess of diazomethane in Et₂O at 0°C resulted in formal CH₂ insertion into the three-membered ring (Equation (31)) <78JOM(159)137>.



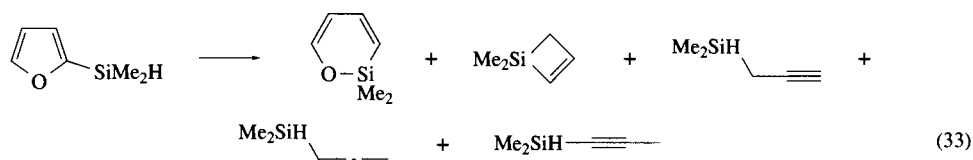
The pyrolysis of 1-silacyclopentan-2-one at 550°C gave a 50 : 50 mixture of silacyclobutane and oxasilacyclohexene (Equation (32)) <80TL429>.



The irradiation of 1,1-dimethyl-2,3,4,5-tetraphenyl-1-sila-2,4-cyclohexadiene generated the silacyclobutene derivative (13) (Scheme 26). The photochemical formation of the silacyclobutene (13) can also be rationalized by the cyclization of silahexatriene <74JA5621>.



The flash vacuum pyrolysis of 2-dimethylsilylfuran at 800°C was performed in an attempt to obtain silapyran. The formation of this product occurred in 15% yield and was accompanied by decarbonylation of the furan to produce dimethylsilacyclobutene and three isomers of Me₂SiHC₃H₄ (Equation (33)) <85JA8297>.



1.28.5 APPLICATIONS

Silacyclobutanes have been widely used for the synthesis of polymeric materials that are useful as intermediates in the preparation of cross-linkable ceramic precursors <88EUP295062, 88EUP295807, 90EUP368535, 90USP4929742, 91EUP423684>. Polymers containing alternating silicon atoms and trimethylene groups in the main chain were obtained by heating silacyclobutanes <62USP3046291, 92IZV223> or by the action of nucleophilic <64IZV203, 92USP5130390> and electrophilic <68BRP1108196> reagents. Laser-induced thermolysis of silacyclobutanes is a highly selective method for the gas phase deposition of organosilicon polymers <88JOM(341)C13, 90JOM(391)275, 94JOM(466)29>.

The formation of continuous coatings of amorphous silicon carbide was achieved by the plasma discharge of silacyclobutanes. The resulting coatings are suitable for use in solar cells and for preventing the corrosion of electronic devices <90EUP392703>.

1.29

Four-membered Rings with One Boron or Other Atom

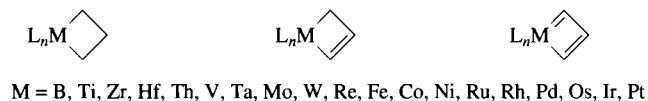
EDMUNDS LUKEVICS and OLGA PUDOVA
Latvian Institute of Organic Synthesis, Riga, Latvia

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1.29.1 INTRODUCTION

The first compound of this type is platinacyclobutane. It was obtained in 1955 by Tipper, who examined the ability of cyclopropane to form complexes with transition metals. He reported <55JCS2045> that cyclopropane reacted with hexachloroplatinic acid in acetic anhydride to give a compound of the empirical formula $[\text{PtCl}_2(\text{C}_3\text{H}_6)]_n$, which he considered to be the cyclopropane complex of platinum chloride analogous to the Zeise's dimer $[\text{PtCl}_2(\text{C}_2\text{H}_4)]_2$. The reinvestigation of this complex allowed it to be suggested <61JCS738> that the cyclopropane ring was opened and recyclized into a four-membered ring containing a platinum atom. The structure of platinacyclobutane was subsequently confirmed by x-ray crystallographic studies <66CC396, 71JOM(33)247>. An excellent review of the experimental data for metallacyclobutanes up until 1980 was published by

Puddephatt <80CCR149>. Interest in the chemistry of these strained-ring compounds has grown steadily since that time. As a result, a variety of bora- and metallacyclobutanes, cyclobutenes, cyclobutadienes, and their fused ring derivatives have been obtained (Scheme 1).

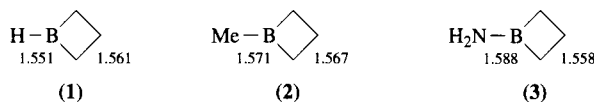


Scheme 1

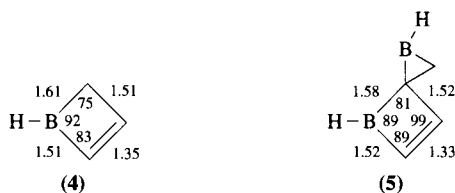
1.29.2 STRUCTURE OF FOUR-MEMBERED RINGS WITH ONE BORON OR OTHER ELEMENT

1.29.2.1 Theoretical Methods

The structure of boracyclobutane and its 1-substituted derivatives have been calculated by *ab initio* methods. The nonplanar bending of boracyclobutane (**1**) is substantial. The puckering angle (53.1°) facilitates transannular interaction between B and C(3) atoms ($r(B-C3) = 1.885 \text{ \AA}$). When electron-donating substituents are present, the nonclassical transannular 1,3-interaction becomes less important; the B-C(3) distances increase from $1.885 \text{ \AA}$ in (**1**) to $1.993 \text{ \AA}$ in 1-methylboracyclobutane (**2**) and to $2.095 \text{ \AA}$ in 1-aminoboracyclobutane (**3**). The last derivative is nearly planar <91JA2466>.



The complete geometric optimization of 1,2-dihydroborete (**4**) performed by the MINDO/3 method leads to the nonplanar form being $6.1 \text{ kcal mol}^{-1}$ more stable than the planar one. Reinvestigation of (**4**) using *ab initio* calculations of Hartree-Fock type gave the puckering angle of 28° . The structural data for 1,2-dihydroboretes (**4**) and (**5**) are presented <84AG(E)370>.



According to an *ab initio* Hartree-Fock study, the titanacyclobutane ring of 1,1-dichlorotitanacyclobutane is planar, but quite floppy with respect to puckering. Using a fixed puckering angle of 10° , the energy of the molecule was increased by only $0.3 \text{ kcal mol}^{-1}$ if compared with that of the optimum planar molecule. The calculated bond lengths and angles of the titanacyclobutane ring are $r(Ti-C) = 2.02 \text{ \AA}$, $r(C-C) = 1.56 \text{ \AA}$, $\angle CTiC = 75.6^\circ$, $\angle CCTi = 89.5^\circ$, $\angle CCC = 105.4^\circ$ <82JA297>.

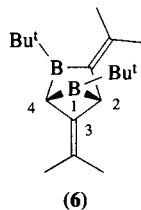
Geometric optimization of the 1,1,1,1-tetrachloromolybdacyclobutane and the 1,1,1-trichloromolybdacyclobutane cation has been made by the *ab initio* method. The metallacycles of these compounds are puckered by 15.24° and 18.15° , respectively. A comparison between the geometric parameters of both derivatives reveals that the addition of the fourth chlorine atom to the cationic complex drastically reduces the endocyclic angle $\angle CMoC$ (from 79.0° to 61.5°) and increases the bond length $Mo-C$ (from $2.07 \text{ \AA}$ to $2.31 \text{ \AA}$) <89OM1550>.

The bonding and energy characteristics in molybdacyclobutadiene are contrasted with those in isomeric molybdetetrahedrane. The complexes differ by 20 kcal mol^{-1} , metallatetrahedran being lower in energy. The resonance stabilization is peculiar to the ring of 1,1,1-trichloromolybdacyclobutadiene. Considering both resonance structures the bond order is 1.5 for $Mo-C$ ($1.85 \text{ \AA}$) and $C-C$ ($1.46 \text{ \AA}$) bonds <88OM98>.

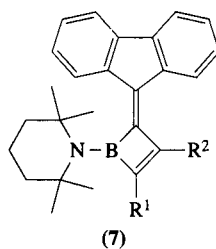
Optimized geometry of palladacyclobutane has been determined using the complete active space SCF (CASSCF) method ($r(\text{Pd}-\text{C}) = 2.14 \text{ \AA}$, $r(\text{C}-\text{C}) = 1.56 \text{ \AA}$, $\angle \text{Pd} = 70^\circ$, $\angle \text{CCC} = 104^\circ$, $\angle \text{PdCC} = 93^\circ$) $\langle 85\text{JA}7408 \rangle$.

1.29.2.2 X-ray Diffraction

The molecular structure of a number of bora- and metallacyclobutanes was determined by x-ray techniques. The strong folding of the borethane ring in 2,5-dibora[2.1.1]bicyclohexane (**6**) leads to the shortening of distance between B(1) and C(3) ($1.749 \text{ \AA}$). The dihedral angle between B(1)C(2)C(4) and C(2)C(3)C(4) planes is 75° $\langle 92\text{AG}(\text{E})606 \rangle$.

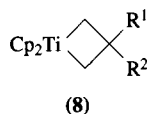


The four-membered ring of 1,2-dihydroboretetes (**7a**, **b**) is also not planar. The heterocycle of compound (**7a**) has the stronger folding ($\alpha = 31.2^\circ$) if compared to (**7b**) ($\alpha = 11.9^\circ$) $\langle 88\text{ZN}(\text{B})275$, $88\text{ZN}(\text{B})449 \rangle$.



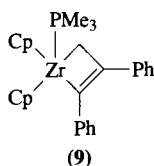
a $\text{R}^1 = \text{R}^2 = \text{Et}$
b $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{NEt}_2$

According to x-ray data $\langle 81\text{JA}7358 \rangle$ the ring of titanacyclobutanes (**8a-c**) is close to planar; the maximum deviation of C(3) from an ideal plane is equal to $0.09 \text{ \AA}$, $0.05 \text{ \AA}$ for (**8a**), (**8b**), and less than $0.01 \text{ \AA}$ for (**8c**). These results are in agreement with the calculated structure of 1,1-dichlorotitanacyclobutane $\langle 82\text{JA}297 \rangle$.



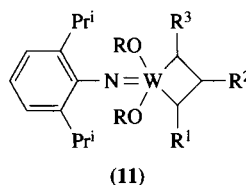
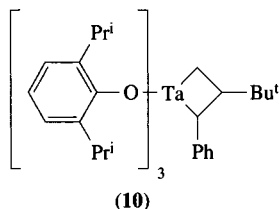
a $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Bu}^t$
b $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$
c $\text{R}^1 = \text{R}^2 = \text{Me}$

The zirconacyclobutene ring of compound (**9**) is not planar but bent in an angle of 21° $\langle 91\text{CB}2165 \rangle$.

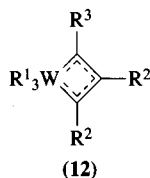


The tantalum atom in complex (**10**) adopts a coordination intermediate between a trigonal bipyramid and square pyramid, the average Ta—C bond length being $2.18 \text{ \AA}$, and the tantalacyclobutane ring being bent ($\alpha = 28^\circ$) $\langle 86\text{OM}2162 \rangle$. The most important feature of tungstacyclobutane

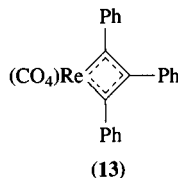
(11a) is an absolute planarity of the four-membered heterocycle <88JA1423>. Substitutions at the carbon atoms of the metallacycle bent the plane, and the puckering angles become 33.8° <89OM2266>, 29.9° <88JA1423>, and 25° <89OM2260> respectively for the compounds (11b), (11c), and (11d). The MC_3 systems of tungstacyclobutadienes (12a–c) <82JA6808, 84OM1554, 84OM1563> and rhenacyclobutadiene (13) <91OM3396> are planar within the limits of experimental error.



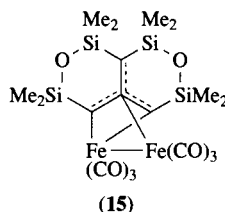
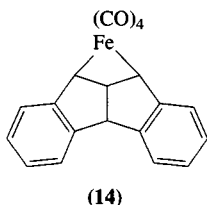
- a $R = C(CF_3)_2C_3F_7$, $R^1 = R^2 = R^3 = H$
 b $R = CMe_2CF_3$, $R^1 = R^3 = H$, $R^2 = Bu^t$
 c $R = CMe(CF_3)_2$, $R^1 = R^2 = TMS$, $R^3 = H$
 d $R = CMe(CF_3)_2$, $R^1 = CO_2Me$, $R^2 = H$, $R^3 = Bu^t$



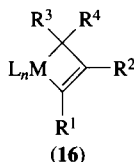
- a $R^1 = OCH(CF_3)_2$, $R^2 = R^3 = Et$
 b $R^1 = OC_6H_3Pr^i_{2-2,6}$, $R^2 = R^3 = Et$
 c $R^1 = Cl$, $R^2 = Me$, $R^3 = Bu^t$



X-ray analysis has been carried out for the four-membered metallacycles containing metals of group 8. According to x-ray data the reaction products of diiron nonacarbonyl with dibenzosemibullvalene <72JA8944> or 2,2,5,5,7,7,10,10-octamethyl-1,6-dioxo-2,5,7,10-tetrasilacyclodeca-3,8-diyne <88CL485> have the structures (14) and (15), respectively, ferracycles being almost planar.

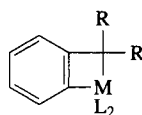


The four-membered rings of cobaltacyclobutenes (16a–d) <85CC35, 93JA1586>, rhodacyclobutene (16e) <85OM421, 86OM1733>, iridacyclobutene (16f) <84OM1223>, and platinumacyclobutene (16g) <88OM2239> appear to be planar as well.



- a $M = Co$, $L_n = Cp(Ph_3P)$, $R^1 = Ph$, $R^2 = CO_2Me$, $R^3R^4 = NC_6H_4Me-4$
 b $M = Co$, $L_n = Cp(Ph_3P)$, $R^1 = Me$, $R^2 = CO_2Me$, $R^3R^4 = NC_6H_4Me-4$
 c $M = Co$, $L_n = Cp(Ph_3P)$, $R^1 = CO_2Me$, $R^2 = Ph$, $R^3R^4 = NC_6H_4Me-4$
 d $M = Co$, $L_n = Cp(Me_3P)$, $R^1 = SO_2Ph$, $R^2 = TMS$, $R^3 = H$, $R^4 = CO_2Et$
 e $M = Rh$, $L_n = [MeC(CH_2PPh_2)_3]Cl$, $R^1 = R^2 = CF_3$, $R^3, R^4 =$
 f $M = Ir$, $L_n = (Me_3P)_3Br$, $R^1 = R^2 = C_6H_4Me-4$, $R^3 = R^4 = H$
 g $M = Pt$, $L_n = (Ph_3P)_2$, $R^1 = R^2 = R^3 = R^4 = F$

The metallacycles are almost coplanar with the benzene ring in nickel $\langle 87\text{CB}471 \rangle$ and platinumacyclobutabenzenes $\langle 89\text{OM}1288 \rangle$ (**17a, b**). The M—C bonds of each compound differ in length, M—C_{sp}² distance being shorter (Ni—C_{sp}² = 1.897 Å, Pt—C_{sp}² = 2.060 Å) than M—C_{sp}³ (Ni—C_{sp}³ = 2.075 Å, Pt—C_{sp}³ = 2.122 Å).

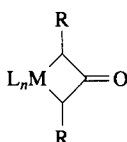


(17)

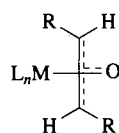
a M = Ni, L₂ = tmeda, R = TMS

b M = Pt, L = Me₃P, R = H

The structure of metallacyclobutan-3-ones (**18a–g**) is characterized by the considerable puckering of heterocycles. The puckering angle in compounds (**18a–g**) varies between 41° for (**18e**) and 53.3° for (**18b**). It is apparent that a bonding description of metallacyclobutan-3-ones should include a contribution from the oxodimethylenemethane structure (**19**) $\langle 78\text{CC}744, 83\text{JOM}(253)\text{C}59, 85\text{JCS}(\text{D})259, 85\text{JCS}(\text{D})549, 86\text{CC}427, 91\text{OM}3344 \rangle$.



(18)



(19)

a M = Ru, L_n = (Me₃P)₄, R = H $\langle 91\text{OM}3344 \rangle$

b M = Pd, L_n = (Ph₃P)₂, R = CO₂Me $\langle 85\text{JCS}(\text{D})259 \rangle$

c M = Pd, L_n = (Ph₃As)₂, R = CO₂Me $\langle 85\text{JCS}(\text{D})259 \rangle$

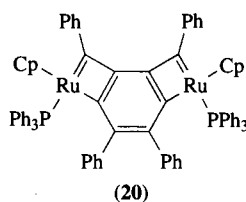
d M = Pd, L_n = bipy, R = CO₂Me $\langle 85\text{JCS}(\text{D})259 \rangle$

e M = Ir, L_n = (Ph₃P)₂(CO)₂, R = H $\langle 86\text{CC}427 \rangle$

f M = Pt, L_n = (Ph₃P)₂, R = CO₂Me $\langle 78\text{CC}744 \rangle$

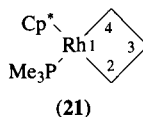
g M = Pt, L_n = (Ph₃P)₂, R = COMe $\langle 83\text{JOM}(253)\text{C}59, 85\text{JCS}(\text{D})549 \rangle$

In complex (**20**) two Ru(PPh₃)Cp moieties are bridged with C₈Ph₄ ligand, being attached to it by Ru—C single bonds from the central six-membered ring, and by Ru—C(carbene) interactions. The Ru₂C₈ skeleton forms a planar 4/6/4-tricyclic unit which can be described as diruthenadicyclobutadiene[a,c]benzene $\langle 91\text{JOM}(420)253 \rangle$.



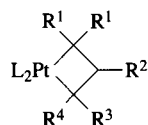
(20)

The metallacyclobutane ring of the rhodium complex (**21**) is essentially planar and symmetrical along the Rh—C(3) axis $\langle 84\text{JA}7272 \rangle$.



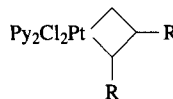
(21)

According to Klingler *et al.* <82JA2147> the platinumacyclobutane ring of the unsubstituted platinum(II) (**22a**) and platinum(IV) (**23a**) complexes is almost planar. The substitution at the carbon atoms of the heterocycle leads to the puckering of the ring ($\alpha = 24.4^\circ$, 28.6° , 29.7° , and 28° for compounds (**22b**, **c,d**) and (**23b**), respectively) <74JOM(70)133, 78JA829>.



(22)

- a** $L_2 = \text{Bipy}$, $R^1 = R^2 = R^3 = R^4 = \text{H}$
b $L = \text{Ph}_3\text{P}$, $R^1 = R^3 = R^4 = \text{CN}$, $R^2 = \text{H}$
c $L = \text{Ph}_3\text{P}$, $R^1 = R^3 = R^4 = \text{CN}$, $R^2 = \text{Ph}$
d $L = \text{Ph}_3\text{P}$, $R^1 = R^3 = \text{CN}$, $R^2 = \text{Ph}$, $R^4 = \text{CO}_2\text{Et}$



(23)

- a** $R = \text{H}$
b $R = \text{Ph}$

The geometrical parameters of the metallacyclobutanes are presented in Table 1.

Table 1 Geometric parameters of four-membered heterocycles.

Compound	r (Å)				angles ($^\circ$)			
	$M-C(2)$	$M-C(4)$	$C(2)-C(3)$	$C(3)-C(4)$	$\angle M$	$\angle C(2)$	$\angle C(3)$	$\angle C(4)$
(6)	1.658(8)	1.595(9)	1.491(7)	1.501(7)	86.1(5)	67.0(4)	95.9(5)	68.5(4)
(7a)	1.527(5)	1.636(4)	1.374(5)	1.531(5)	91.1(4)	82.5(5)	102.0(5)	74.3(4)
(7b)	1.534(3)	1.674(4)	1.357(4)	1.411(3)	88.0(2)	90.3(2)	100.8(2)	79.5(2)
(8a)	2.16	2.14	1.55	1.53	75	84	116	85
(8b)	2.127(3)	2.113(4)	1.546(5)	1.579(5)	75.3(1)	86.0(2)	112.0(3)	85.7(2)
(8c)	2.138(8)	2.152(7)	1.59(1)	1.58(1)	74.8(3)	87.2(4)	110.9(6)	87.0(4)
(9)	2.306(5)	2.386(6)	1.344(8)	1.483(8)	59.6(2)	96.3(4)	111.0(5)	89.3(3)
(10)	2.18(2)							
(11a)	2.064(22)	2.042(20)	1.536(31)	1.584(29)	82.4(8)	78.9(13)	120.1(18)	78.6(12)
(11b)	2.14(1)	2.17(1)	1.55(1)	1.57(1)	63	97	93	95
(11c)	2.066(11)	2.099(11)	1.606(16)	1.584(29)	82.3(4)	78.0(6)	116.1(8)	78.0(6)
(11d)	2.221(8)	2.205(8)	1.54(1)	1.53(1)	65.1(3)	93.1(5)	94.2(5)	101.7(7)
(12a ^a)	1.902(16)	1.864(14)	1.429(18)	1.437(21)	83.6(6)	76.4(9)	122.4(13)	77.5(8)
	1.885(15)	1.860(17)	1.348(27)	1.429(23)	82.8(7)	79.1(10)	121.4(14)	76.7(10)
(12b)	1.949(9)	1.883(10)	1.433(14)	1.467(14)	82.3(4)	77.7(6)	120.8(9)	79.2(6)
(12c)	1.861(9)	1.864(8)	1.455(13)	1.478(12)	85.4(4)	78.2	118.9(8)	77.6
(13)	2.168(7)	2.170(8)			60.5(3)	98.1(5)	103.2(7)	
(14)	2.141	2.137	1.524	1.527				
(15)	1.966	1.981	1.464	1.439	69.6	93.9	101.9	94.1
(16a)	1.968(9)	1.983(3)	1.338(11)	1.504(12)	68.7(3)	97.1(6)	103.1(7)	91.1(5)
(16b)	1.908(7)	1.991(6)	1.357(10)	1.468(10)	68.4(3)	98.5(5)	101.8(5)	91.3(4)
(16c)	1.931(5)	1.980(4)	1.342(6)	1.477(6)	67.3(2)	99.2(3)	100.5(4)	92.5(3)
(16d)	1.918(4)	2.054(4)	1.340(6)	1.523(5)	66.7(2)	99.5(3)	103.0(3)	90.8(2)
(16e)	2.05(3)	2.14(3)	1.30(4)	1.50(4)	63(1)	90(2)	103(3)	102(2)
(16f)	2.134(5)	2.166(6)	1.344(8)	1.525(7)	64.5(2)	98.0(4)	106.1(5)	91.2(3)
(16g)	2.134(5)	2.079(8)	1.351(12)	1.474(12)	65.8(3)	97.5(6)	104.7(7)	92.0(5)
(17a)	1.897(4)	2.075(4)	1.38(1)	1.534(5)	71.7(2)	96.9(3)	106.0(4)	85.3(3)
(17b)	2.060(8)	2.122(7)	1.38(1)	1.52(1)	66.7(4)	97.6(7)	104.6(8)	90.8(7)
(18a)	2.217(4)	2.222(5)	1.468	1.459	65.72(18)	83.5(3)	110.8(4)	83.5(3)
(18b)	2.135(6)	2.165(7)	1.467(9)	1.492(8)	68.4(2)	80.8(3)	109.5(6)	79.2(4)
(18c)	2.125(5)	2.152(5)	1.482(7)	1.473(6)	68.7(2)	80.6(3)	109.5(5)	79.9(3)
(18d)	2.103(3)	2.085(3)	1.471(5)	1.471(5)	68.8(1)	81.2(3)	107.1(3)	81.8(2)
(18e)	2.169(9)	2.184(9)	1.48(2)	1.50(1)	66.5(3)	87.1(6)	106.6(8)	86.0(5)
(18f)	2.149(6)	2.128(6)						
(18g)	2.183(7)	2.153(4)	1.496(9)	1.491(9)	67.3(2)	82.8(4)	107.2(4)	84.0(3)
(20 ^a)	2.062(7)	1.982(7)			64.8(3)			
	2.051(7)	1.997(7)			64.8(3)			
(21)	2.085	2.085	1.527	1.512	67.61	96.24	99.55	96.59
(22a)	2.030(10)	2.037(10)	1.534(14)	1.534(13)	69.9(4)	95.5(6)	98.8(8)	95.8(6)
(22b)	2.137(6)	2.139(6)	1.565		68.4(2)	93.5(4)	100.4(5)	92.3(4)
(22c)	2.137	2.159			67.7	92.3	100.9	91.7
(22d)	2.158	2.200			66.9	90.8	103.2	91.2
(23a)	2.19(5)	2.04(5)	1.52(9)	1.48(8)	74.2(19)	84.3(27)	100.9(38)	99.3(35)
	2.07(4)		1.63(6)		71.9(23)	96.0(30)	96.2(51)	
(23b)	2.06	2.11			70	90	102	91

^aFor two independent molecules.

1.29.2.3 Molecular Spectra

1.29.2.3.1 NMR spectroscopy

The comparison of metallacyclobutane moieties in the platinum(II) $\langle 81JOM(206)C7, 82JA2147 \rangle$ and platinum(IV) complexes $\langle 74JOM(71)145 \rangle$ has been performed using NMR spectroscopy. In the platinum(IV) metallacycles the coupling constants for the α -protons to platinum are 78–88 Hz, with β -coupling constants being unresolved. In most cases the β -coupling constants of the platinum(II) compounds are larger than those for α -protons. The chemical shifts of α - (0.35–1.52 ppm) and β -hydrogen atoms (3.32–4.58 ppm) in the platinum(II) structures differ substantially, but for the platinum(IV) cyclobutanes both α - and β -protons lie in the $\delta = 2.07$ –2.84 ppm range. The comparison of the ^{13}C chemical shifts as well as the ^{195}Pt - ^{13}C coupling constants does not reveal any significant differences between Pt^{II} and Pt^{IV} metallacyclobutanes (Table 2).

The deuterium isotope effects on the carbon chemical shifts have been used as a tool for the determination of titanacyclobutane structure in solution $\langle 81JA7358 \rangle$. If the titanacycles are rapidly equilibrating into alkylidene–alkene complexes, the deuteration at one of the α -carbons should result in a significant shift of the $\delta^{13}C$ signal of the other α -carbons. The resonances C(4) of deuterated titanacyclobutanes appear only 0.045–0.121 ppm downfield from the corresponding signals of nondeuterated complexes (Table 3). These observations are consistent with symmetric but easily distorted metallacyclobutane structures.

The ^1H NMR spectra of pallada- and platinacyclobutan-3-ones (**18b–d,g**), measured at low temperature, showed the expected features for the illustrated static structure with two resonances for the methyl protons of the R group and two signals for the C–H protons, the CH resonance at higher field being assigned to the equatorial hydrogen. Upon warming the signals of Me and CH protons undergo reversible changes. Thus, two Me group signals observed at low temperature collapsed to a singlet, and two CH signals, to a single resonance. These results are in agreement with an inversion of the ring through a planar structure such that there is a rapid interconversion of all equatorial substituents to axial, and all axial ones to equatorial $\langle 85JCS(D)259, 85JCS(D)549 \rangle$.

1.29.2.3.2 IR spectroscopy

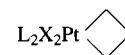
The IR spectra of the palladacyclobutan-3-one complexes (**18c–e**) normally exhibit five peaks in the range 1750–1500 cm^{-1} . The two higher frequencies occur in the regions which can be associated with $\nu(CO)$ of R substituents, and the band in the region 1620–1588 cm^{-1} $\langle 85JCS(D)259 \rangle$ can be assigned to $\nu(CO)$ of the carbonyl ring. In the analogous platinum complexes the frequency of $\nu(CO)$ ring occurs in the region 1648–1617 cm^{-1} $\langle 84JCS(D)1993 \rangle$. Since transannular metal–CO interactions would be expected to weaken the CO bond in the ring and hence lower the values of $\nu(CO)$ ring, the IR data provides further evidence for the stronger metal–CO interactions in palladium complexes, than in platinum complexes as shown by x-ray data.

1.29.2.4 Thermodynamic Aspects

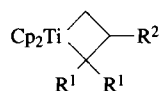
Using *ab initio* calculations the thermochemistry of the reaction between alkylidene complex $Cl_4M=CH_2$ ($M = Cr, Mo, W, Pd$) and ethylene have been studied $\langle 80JA5114, 82JA448, 82NJC337 \rangle$. The process of metallacycle formation for the compounds with $M = Cr, Mo$, or W is not favorable with $\delta G_{300} = +25, +15$, and $+10$ kcal mol^{-1} , respectively $\langle 82JA448 \rangle$. An oxo-alkylidene complex $Cl_2M(O)=CH_2$ would favor the formation of metallacycles due to the conversion of the double-bond oxo-group of alkylidene compound to a triple C–O one in metallacycle. Indeed, the calculations lead to just this result with $\delta G_{300} = -20, -24$, and -18 kcal mol^{-1} for $M = Cr, Mo, W$, respectively $\langle 80JA5114, 82JA448 \rangle$.

According to the calorimetric measurements $\langle 92JMOC(72)1 \rangle$ the heat of molybdenacyclobutane intermediate formation from ethylene and $Mo=CH_2$ carbene complex on the surface of photo-reduced silicomolybdena catalyst was equal to -40 ± 5 kJ mol^{-1} (-9.6 kcal mol^{-1}).

Theoretically extended Hückel study of the substituted metallacyclobutanes ($M = Cr, W$) indicates that the presence of substituents in metallacycle will favor a puckered conformation. The favored conformations with substituents in 2,3- and 2,4-positions of heterocycle are 2e–3e and 2e–4e (e is

Table 2 Proton, ^{13}C , ^{31}P and ^{195}Pt NMR data for platinacyclobutanes.

L_2X_2	Chemical shifts δ , ppm					Coupling constants J, Hz						
	$H(\alpha)$	$H(\beta)$	$C(\alpha)$	$C(\beta)$	P	Pt	$^{195}Pt-H(\alpha)$	$^{195}Pt-H(\beta)$	$H(\alpha)-H(\beta)$	$^{195}Pt-^{13}C(\alpha)$	$^{195}Pt-^{13}C(\beta)$	$^{31}P-^{13}C(\alpha)$
bipy	1.29	3.32					115	110	7			
(Ph ₃ P) ₂	0.37	3.51	-17.61	30.52	26.104		88	112	not resolved	400	150	
(Me ₃ P) ₂	0.47	3.74					82	95				
(Et ₃ P) ₂	0.35	3.75			8.136		80	94	8			
(Bu ^t NC) ₂	1.52	4.58					80	90	8			
(C ₅ H ₅ N) ₂ Cl ₂	2.6	2.6	-15.2	30.0		1342	82		7.5	335	105	80
(C ₅ H ₅ N) ₂ Br ₂	2.80	2.44	-17.9	30.4		827	88		8.0	325	110	
(4-MeC ₅ H ₄ N) ₂ Cl ₂	2.58	2.58	3.77	29.9		1313	83		7.2	338	105	
(4-MeC ₅ H ₄ N) ₂ Br ₂	2.84	2.61	-18.5	30.5		836	88		7.5	323	103	
(NH ₂ CH ₂) ₂ Cl ₂	2.17	2.40	-18.9	29.6			78		7.0	332	108	
(NH ₂ CH ₂) ₂ Br ₂	2.43	2.43	-21.4	30.4			83		7.8	317	105	
(NH ₃) ₂ Cl ₂	2.07	2.40					82		7.0			
(NH ₃) ₂ Br ₂	2.44	2.51					81		8.0			

Table 3 Carbon-13 chemical shifts (ppm) of titanacyclobutanes and their α,α - d_2 labeled compounds.

R^1	R^2	$T^\circ C$	$C(2)$	$C(3)$	$C(4)$	$\Delta C(4)$
H	Bu ^{t*}	25	67.954	18.695	67.954	0.060
D	Bu ^{t*}		67.163	18.452	68.014	
H	Ph ^{**}	-10	73.861	11.708	73.861	0.121
D	Ph ^{**}			11.405	73.982	
H	H ^{**}	0	76.671	-11.633	76.671	0.045
D	H ^{**}		75.913	-11.896	76.716	

* δ relative to C_6D_6 (128.0 ppm). ** δ relative to toluene- d_8 (137.5 ppm).

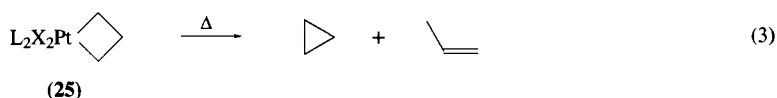
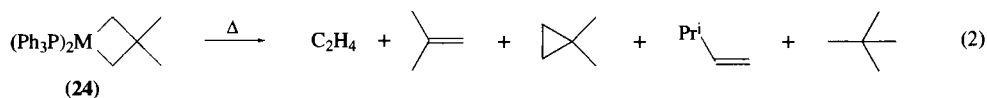
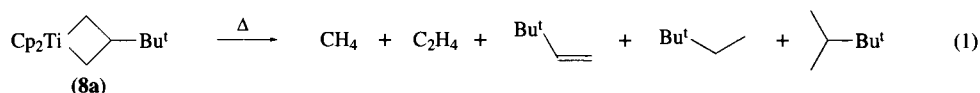
equatorial). The differences in energy between the various conformations of metallacyclobutanes are more pronounced for chromium than for tungsten <83JA2924>.

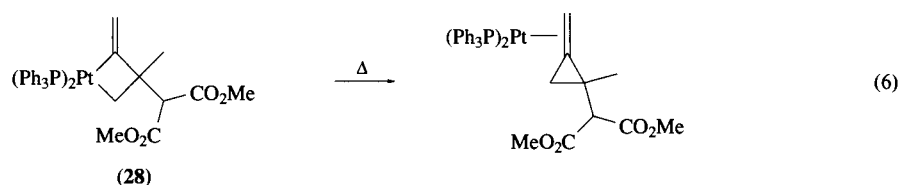
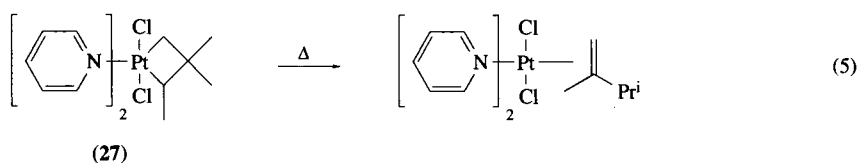
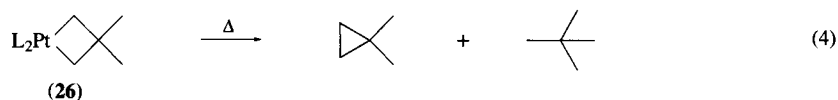
1,1-Dicyclopentadienyl-3,3-dimethylmetallacyclobutanes ($M = Ti, Zr, Hf, V$) have limited stability with a half-life period at $25^\circ C$ of 1, 3, 5, and 4 h, respectively <85JMOC71>.

1.29.3 REACTIVITY OF FOUR-MEMBERED RINGS WITH ONE BORON OR OTHER ELEMENT

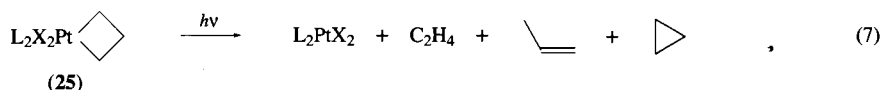
1.29.3.1 Cleavage of the Four-membered Rings

Most reactions of metallacyclobutanes involve the cleavage of the strained MC_3 ring under heating, irradiation, and action of different reagents. The thermal decomposition of titanacyclobutane (**8a**) in toluene at $85^\circ C$ gives a mixture of alkanes and alkenes <80JA6876> (Equation (1)). Nickela- and palladacyclobutanes (**24**) decomposed to ethylene, 2-methylpropene, 1,1-dimethylcyclopropane, 3-methyl-1-butene and 2,2-dimethylpropane (Equation (2)) <81TL1255, 88JOM(338)103>. When complex (**24**; $M = Ni$) was pyrolyzed in the presence of H_2 , methane, 2-methylpropane, 1,1-dimethylcyclopropane and 2,2-dimethylpropane were produced. The reaction of (**24**; $M = Ni$) with CO resulted in the formation of ketene dimer and 2-methylpropene <81TL1255>. The thermolysis of platinacyclobutanes (**25**) in *o*-dichlorobenzene at about $130^\circ C$ proceeds with the loss of the C_3H_6 moiety mostly as cyclopropane (75–85%), the remainder being propene <76JOM(113)91>. The 3,3-dimethylplatinacyclobutanes (**26**) decompose to give 1,1-dimethylcyclopropane (98%) and a small amount of neopentane (Equations (3)–(4)) <82JA3601>. 1,1-Dimethylcyclopropane as a main product was also obtained with the heating of (**26**) in the presence of mercury <78JOM(152)C42>. The thermal isomerization of platinacyclobutanes (**27**) <78JOM(152)C42> and (**28**) <91OM57> gives the platinum complexes of alkenes (Equations (5) and (6)).

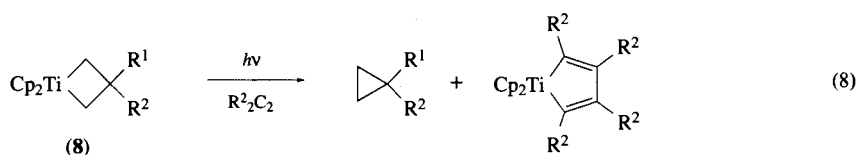




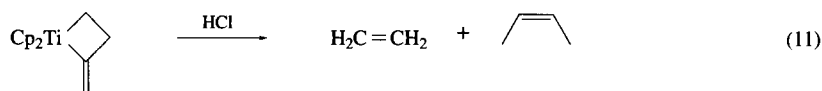
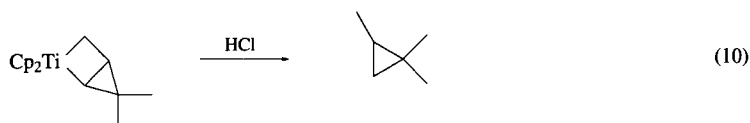
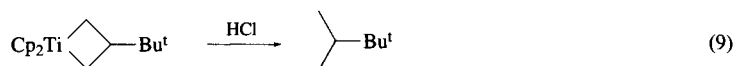
The photolysis of platinacyclobutanes (**25**) gives a mixture of ethylene, propene, and cyclopropane (Equation (7)). The ratio of the volatile products depends considerably on the conditions (solvents, additives) <77JOM(131)467, 78JOM(154)C16, 80JOM(186)419, 80JOM(195)105>. For example, in CH_2Cl_2 propene (95%), cyclopropane (4%), and ethylene (1%) are formed from (**25**; $\text{X} = \text{Cl}$, $\text{L}_2 = \text{phen}$), whereas in DMSO the volatile products were propene (30%), cyclopropane (67%) and ethylene (3%).

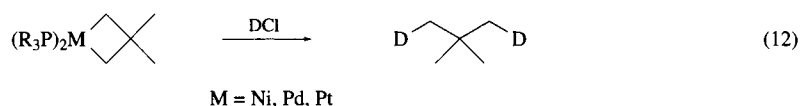


The photochemical decomposition of titanacyclobutanes (**8**) was markedly different from the thermal one. Photochemical activation of (**8**) results in the clean reductive elimination to form cyclopropanes and titanocene which can be trapped by a number of added reagents <87JA6182>. Stereochemical studies strongly suggest a stepwise mechanism in which the primary step involves metal—carbon bond homolysis to produce metal-centered 1,4-biradical intermediate (Equation (8)).

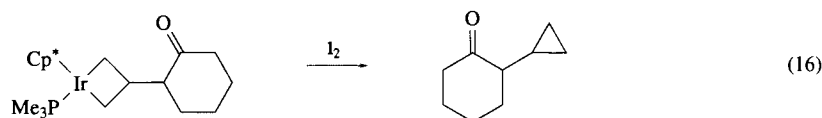
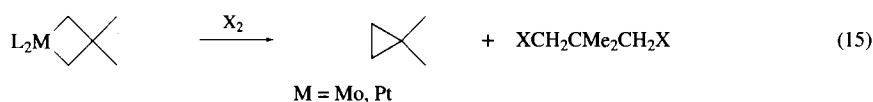
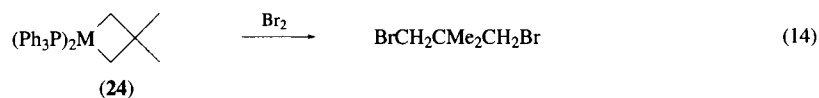
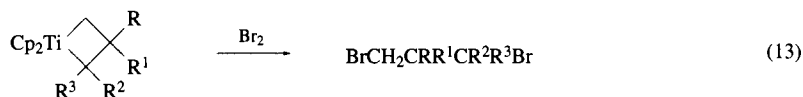


Reactions of titana- <80JA6876, 86OM721, 89JOM(369)43, 93OM4742>, nickela-, pallada- <88JOM(338)103>, and platinacyclobutanes <79JA2732, 80JA6713> with HCl or DCl proceeded with splitting of the $\text{M}-\text{C}$ bonds (Equations (9)–(12)).

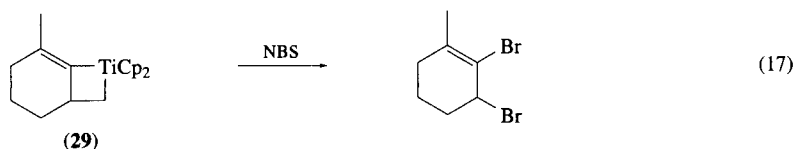




The direction of the reaction of metallacyclobutanes with bromine and iodine is determined by the metal. Thus, titana- <83TL3935>, nickela- and palladacyclobutanes (**24**) <88JOM(338)103> reacted with bromine to give 1,3-dibromopropanes, whereas molybdena- <88JOM(346)197>, irida- <90JA6420>, and platinacyclobutanes <79JA2732, 80JA6713> under halogenation generated cyclopropanes as main products (67–98%) (Equations (13)–(16)).

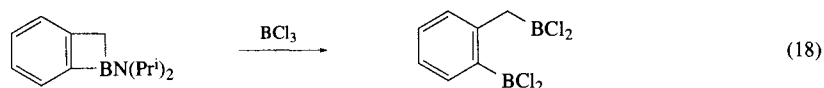


The bromination of the fused titanacyclobutane (**29**) with NBS in THF gave 1-methyl-2,3-dibromocyclohex-1-ene <90CC1060> (Equation (17)).

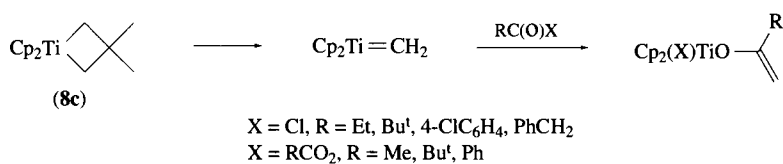


The oxidation of nickela- and palladacyclobutanes (**24**) with oxygen leads to the cleavage of M—C bonds and to the formation of 1,1-dimethylcyclopropane <88JOM(338)103>.

The four-membered ring of dihydrobenzoborete <88JOM(339)33> was opened by the action of electrophile BCl_3 (Equation (18)).

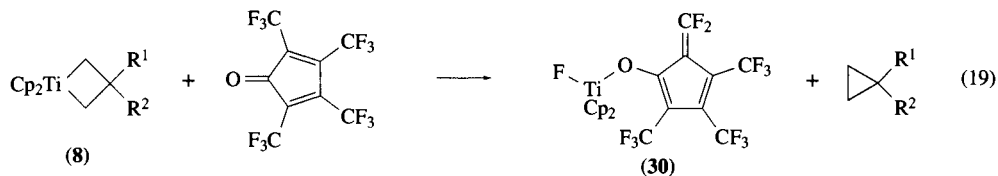


A number of organic compounds react with titanacyclobutanes to produce various ring-opening products with high yields. The titanocene methylidene complex easily generated from titanacyclobutane (**8c**) gives an excellent entry into the most useful enolates by the reaction with acid chlorides <83JA1664> or acid anhydrides (Scheme 2) <85JOC2316>.

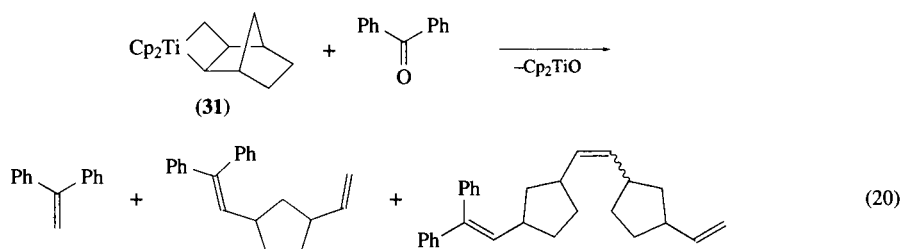


Scheme 2

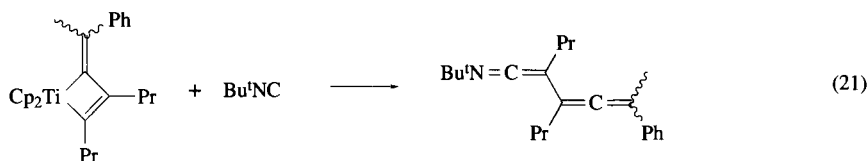
Reaction between titanacyclobutanes (**8**) and tetrakis(trifluoromethyl)cyclopentadienone results in the formal reductive elimination of cyclopropanes and activation of a C—F bond to afford product (**30**) with 80% yield (Equation (19)) <90CC809>.



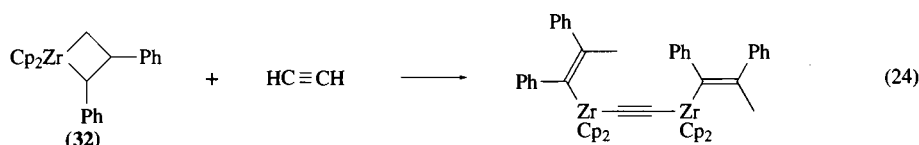
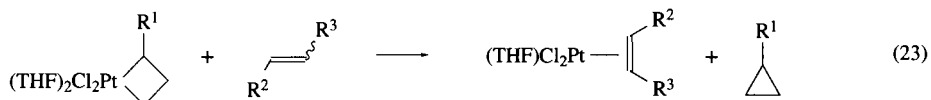
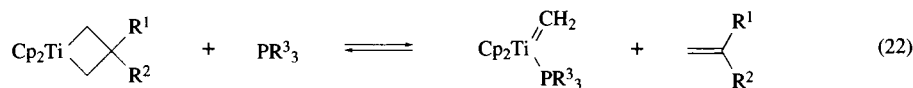
Heating of titanacyclobutanes (**31**) in the presence of benzophenone <86JA733> yields alkenes as major isolable organic products (Equation (20)). When titanacyclobutanes with methylidene groups at C(2) of the ring were treated with ketones for 2–12 h at RT, the substituted allenes were formed in good or excellent yields <83JA5490>.



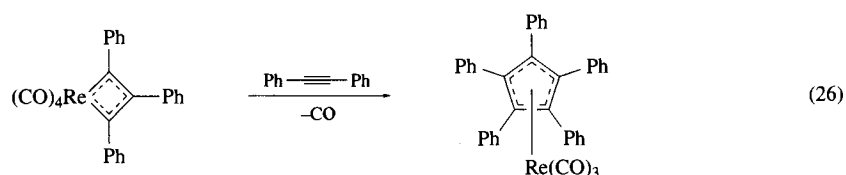
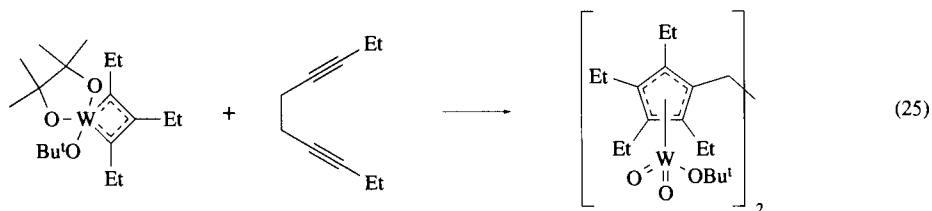
The ring-opening reaction of titanacyclobutenes was also applicable to the synthesis of allenylketenimines (Equation (21)) <92CC35>.



The heterocycle of metallacyclobutanes can be destroyed by the action of different ligands during complexation. Treatment of 3,3-dialkyltitanacyclobutanes with an excess of phosphines yields the corresponding titanocene–methylidene–phosphine complexes in equilibrium with metallacycle. The equilibrium was shifted towards methylidene complex by removal of volatile alkene (Equation (22)) <89OM583>. The reaction of platinacyclobutanes with alkenes proceeds with displacement of cyclopropane to give alkene–platinum complexes. There is little difference in the reaction rates of linear alkenes, but cyclic alkenes and diene compounds react considerably more slowly (Equation (23)) <79JOM(177)403>. The zirconacyclobutene ring of complex (**32**) has been opened by ethyne and its derivatives (Equation (24)) <91CB2165>.

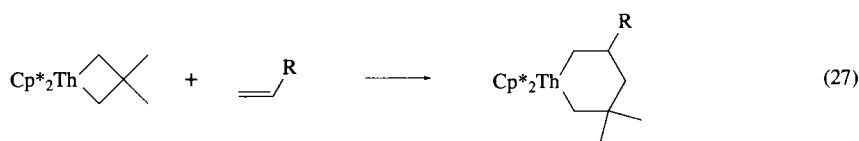


The unusual reactivity of tungsta- <84OM1574, 85OM796> and rhenacyclobutadienes <91OM3396> is demonstrated by the reactions with alkynes, which lead to the substitution of M for C=C fragments and to the formation of cyclopentadienyl compounds (Equations (25) and (26)).

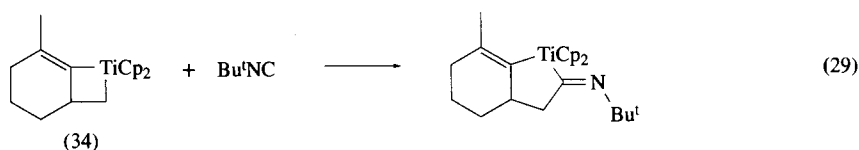


1.29.3.2 Ring Expansion and Ring Contraction Reactions

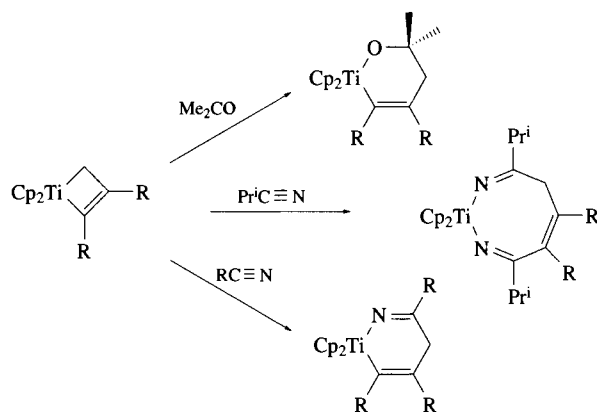
The ring expansion reactions of metallacyclobutanes are the most convenient method for the synthesis of new heterocycles. Thoracyclohexanes were obtained by interaction of thoracyclobutanes with alkenes (Equation (27)) <86JA425>.



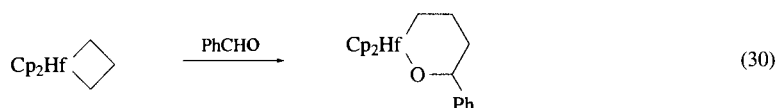
Application of carbonyl complexes $\text{Cr}(\text{CO})_6$, $\text{W}(\text{CO})_6$, or $\text{CpMn}(\text{CO})_3$ in the reaction with titanacyclobutane derivative (33) surprisingly gave Fischer-type carbene complexes with the five-membered 1-oxa-2-titanacyclopentene ring (Equation (28)) <93AG(E)264>. The insertion of *t*-butyl isocyanide into the titanacyclobutane ring of fused compound (34) occurred regioselectively to afford the imino complex (Equation (29)) <90CC1060>. In the first step of the reaction between titanacyclobutenes and aldehydes or ketones the titanium center coordinates with the carbonyl oxygen before ring expansion to the metallaoxacyclohexenes <88BCJ171>. The interaction of titanacyclobutenes with nitriles (1:2) under mild conditions affords diazatitanacyclooctatrienes resulting from nitrile insertion into both Ti—C bonds. Significant steric bulk in either the nitrile or the metallacyclobutene leads to the exclusive formation of the single insertion product, azatitanacyclohexadiene <90OM3012> (Scheme 3).



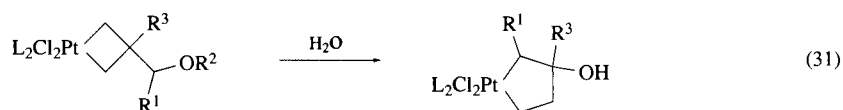
Hafnacyclobutane reacted with benzaldehyde to produce 1-oxa-2-hafnacyclohexane <85OM2059> (Equation (30)).



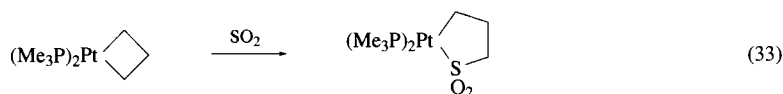
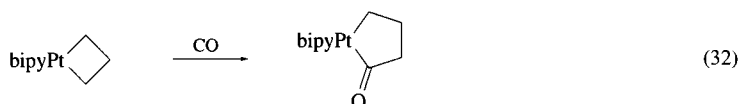
Scheme 3



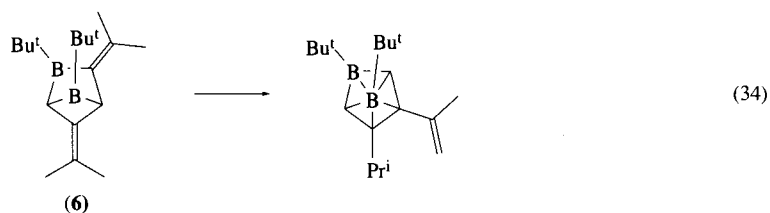
Ring expansion of platinacyclobutanes is a common method for the synthesis of platinacyclopentanes. The solvolysis in aqueous acetone of platinacyclobutanes with a CHR^1OR^2 group in the three position of a heterocycle gives platinacyclopentanol (Equation (31)) <82JA4242, 86OM1312>.



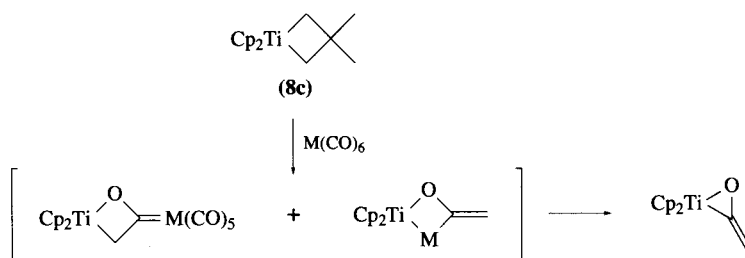
Carbon monoxide and sulfur dioxide are inserted into the $\text{Pt}-\text{C}$ bond of platinacyclobutanes <82JA2147> (Equations (32) and (33)).



Some reactions of metallacyclobutanes lead to smaller ring systems. The strong $\text{B}-\text{C}(3)$ interaction in the boretane cycle of diborabicyclohexane (**6**) results in very easy isomerization to tetracarbahexaborane (Equation (34)) <92AG(E)606, 92CB1981>.

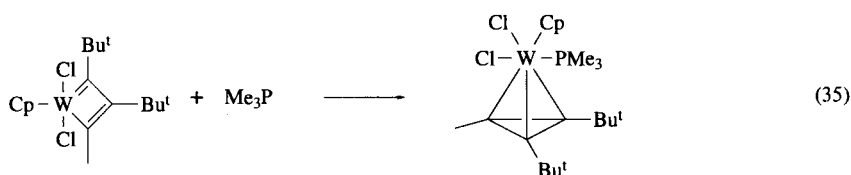


Titanacyclobutane (**8c**) reacts with $\text{Cr}(\text{CO})_6$ and $\text{Mo}(\text{CO})_6$ in toluene to produce a titanocene ketene complex with oxatitanacyclopropane ring. The interaction proceeds via four-membered heterocyclic intermediates (Scheme 4) <88OM2137>.



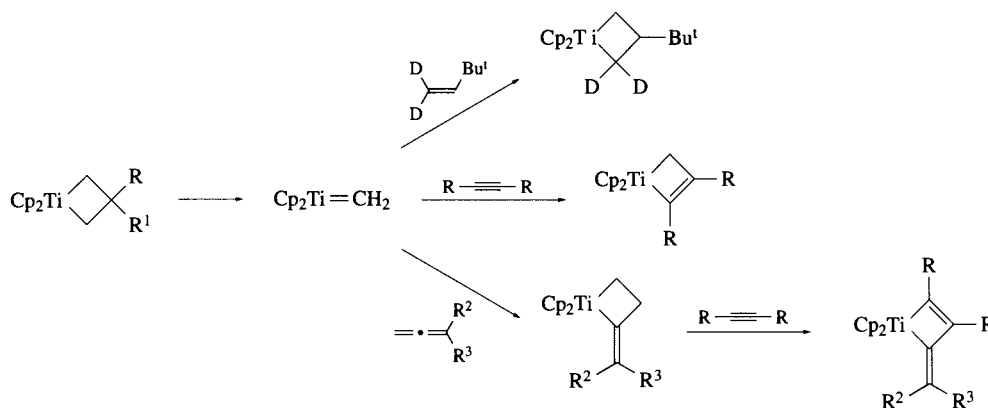
Scheme 4

A compound with a tetrahedral WC₃ core was formed from tungstacyclobutadiene complex via the attack of a phosphorus-donor ligand towards tungsten (Equation (35)) <85JOM(290)375>.



1.29.3.3 Skeletal Transformations of the Heterocycles Carbon Fragment

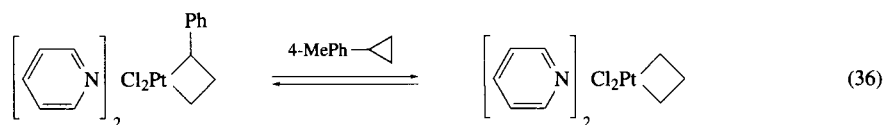
As a rule, the skeletal transformations of the C₃ fragment of titanacyclobutenes proceed through the cleavage of metallacycles to a metal methyldiene species Cp₂Ti=CH₂ <87JA4880>. This mechanism was observed in the isomerization of 3-phenyltitanacyclobutane to 2-phenyltitanacyclobutane <85OM199> and recyclization of titanacyclobutenes in the reactions with alkenes, alkynes <80JA6876, 82JA7491>, and allenes <83JA5490, 88JA2821> (Scheme 5).



Scheme 5

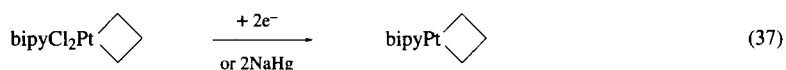
The platinacyclobutane complexes [L₂Cl₂Pt(C₃H₅Me)] exist as a mixture of 2-methyl- and 3-methylplatinacyclobutenes in rapid equilibrium. The ratio of isomers strongly depends on the ligand L, being 1 : 5.9, 1 : 4.0, and 1 : 2.4 for L = pyridine, THF-d₈ and CD₃CN, respectively. The equilibrium is influenced largely by the steric effects. Thus, for butyl- and hexylplatinacyclobutenes, no 2-substituted isomer can be detected when L = pyridine <78JOM(157)C40>. The 2-phenylplatinacyclobutenes isomerized readily to give an equilibrium mixture of 2- and 3-substituted products in ratio 1 : 2.3 (L = pyridine). The 2-phenylplatinacyclobutane complex with L₂ = TMEDA did not isomerize to 3-isomer at 50 °C <76CC626>. The comparison of equilibrium for phenyl- and (2-methylphenyl)platinacyclobutenes (L = pyridine, 4-methylpyridine) indicates the importance of steric effects. In every case the *ortho*-substitution of phenyl groups favors the 3-isomer <79JA364>.

No formation of 2- and 3-(*p*-tolyl)platinacyclobutanes was observed during the rearrangement of 2-phenylplatinacyclobutane in the presence of *p*-tolylcyclopropane (Equation (36)) <79JA4233>.

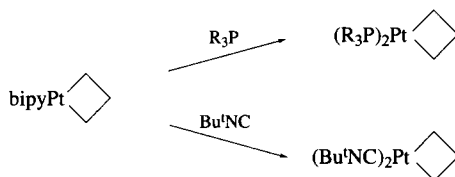


1.29.3.4 Reactions of Substituents Attached to the Heteroatom

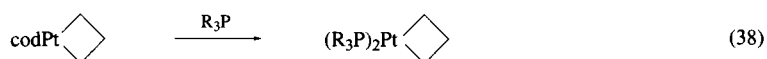
The cathodic or sodium amalgam reduction of the platinum(IV) methallacyclobutane can be used for the synthesis of a platinum(II) analogue (Equation (37)) <81JOM(206)C7, 82JA2147>.



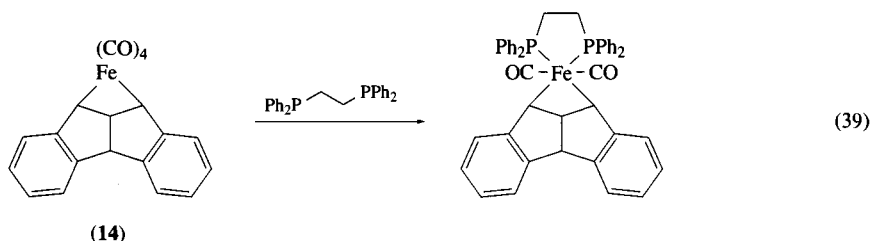
The ligands L on the metals of metallacyclobutanes are found to be replaced by other ligands without changing the (CH₂)₃ moiety. For platinacyclobutanes L₂X₂Pt(CH₂)₃ the increasing order of substitution was THF, pyridine, 4-methylpyridine, ethylenediamine, no reaction with Ph₃P and Ph₃As (L₂ = bipy, ethylenediamine) occurred <75JOM(84)407>. However, platinacyclobutanes of platinum(II) undergo substitution of bipy or cod by phosphines or *t*-butyl isocyanide (Scheme 6 and Equation (38)) <82JA2147, 87JOM(336)447>.



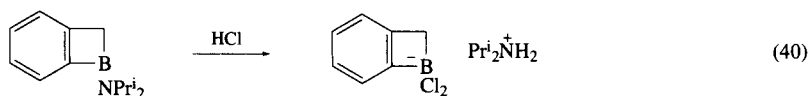
Scheme 6



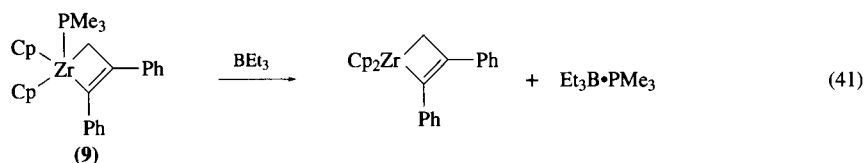
The reaction of iron carbonyl compound (14) with 1,2-bis(diphenylphosphino)ethane leads to the substitution of two carbonyls (Equation (39)) <72JA8944>.



Interaction of dihydroborete with HCl gives a cyclic dichloroborate (Equation (40)) <88JOM(339)33>.

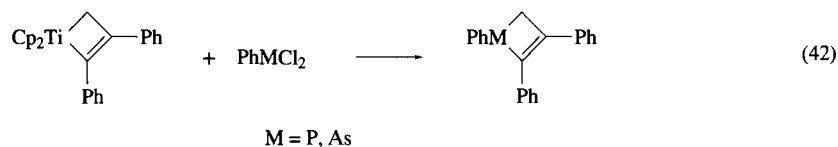


The elimination of the Me_3P group from zirconacyclobutene complex (9) has been achieved by the action of Lewis acid BEt_3 (Equation (41)) <91CB2165>.



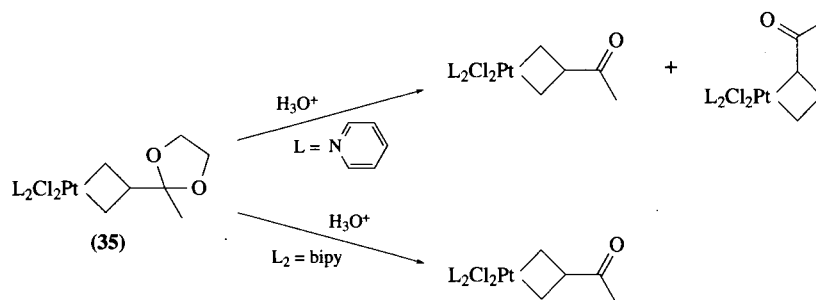
1.29.3.5 Transmetalation

Titanacyclobutenes reacted with phenyldichlorophosphine and -arsine in hydrocarbon solvent to give phospho- and arsacyclobutenes in ~50% yield (Equation (42)) <89JA9129, 90AG89>.



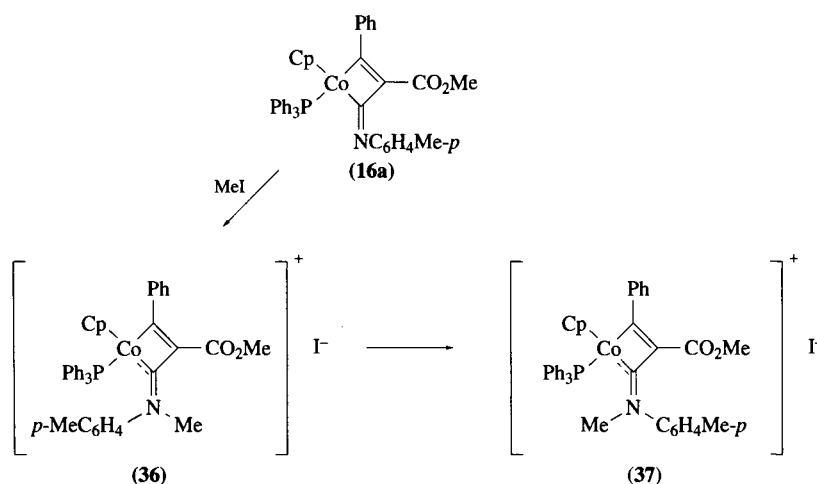
1.29.3.6 Reactions of Functional Groups at the Carbon Atoms

Acetylplatinacyclobutane was obtained from the protected dioxolane compounds using hydrolysis <91OM8>. The pyridine complex (35) gave the mixture of 3- and 2-isomers (ratio 1.5 : 1). The apparent isomerization during the hydrolysis step was prevented by the bipyridine ligand (Scheme 7).



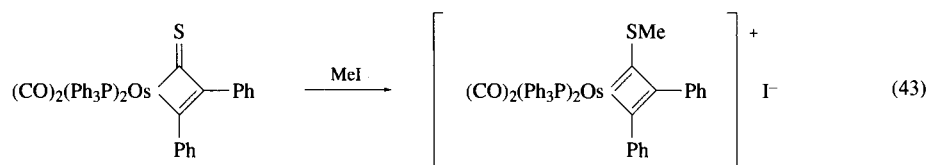
Scheme 7

4-Iminocobaltacyclobutene (16a) reacts with MeI to produce complex (36), which isomerized to metallacycle (37) (Scheme 8) <86JCS(D)1201>.



Scheme 8

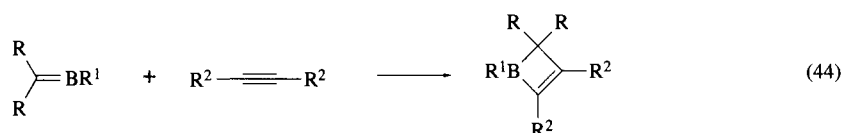
Osmacyclobuten-2-thione was alkylated with MeI at sulfur to give metallacyclobutadiene derivative (Equation (43)) <83JOM(250)C5>.



1.29.4 SYNTHESIS

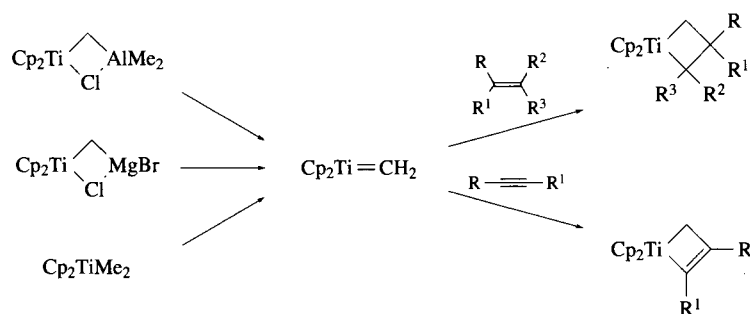
1.29.4.1 [2 + 2] Cycloaddition

This type of cyclization was very fruitful for the synthesis of four-membered heterocycles. All 1,2-dihydroborettes were obtained by trapping of the stable methyleneboranes (e.g., 9-fluorenylidene(tetramethylpiperidino)borane, 2,4-diboramethylenecyclopropane) with alkynes (Equation (44)) <83AG(E)877, 84AG369, 88ZN(B)275, 88ZN(B)449, 90AG438>.

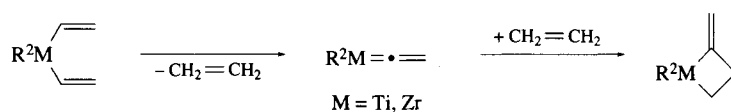


No reaction with alkenes was observed <88ZN(B)449>.

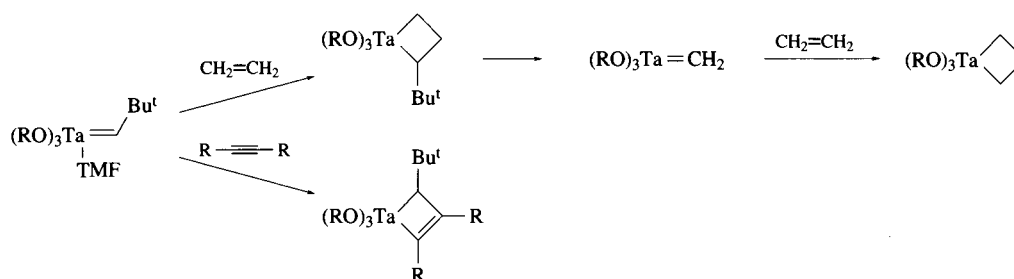
A number of four-membered metallacycles with titanium <79JA5074, 80JA6876, 81JA5922, 81JA7358, 82JA7491, 83TL3935, 86JA733, 86OM721, 89JOM(369)43, 90CC1060, 92CB291, 92OM1793, 93OM3776, 93AG(E)264, 93OM4682>, zirconium <93JOM(452)75>, tantalum <79JA3210, 85OM1847, 86OM2162, 88JA4964, 89OM644>, molybdenum <84JA4067>, tungsten <82JA6808, 84OM1554, 84OM1563, 86JA2771, 88CC1164, 88JA1423>, rhenium <93JA2980, 93JA9986>, rhodium <86OM1733>, and osmium <83JOM(250)C5> were obtained by the interaction of compounds with multiple M—carbon bonds and alkenes or alkynes (Schemes 9–13 and Equations (45) and (46)).



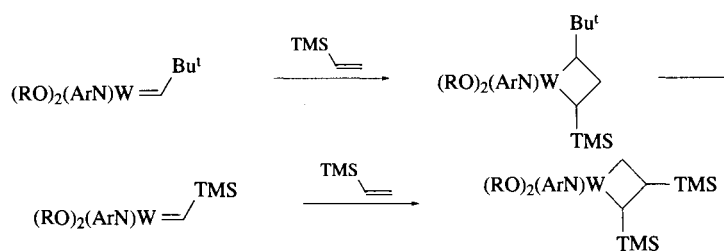
Scheme 9



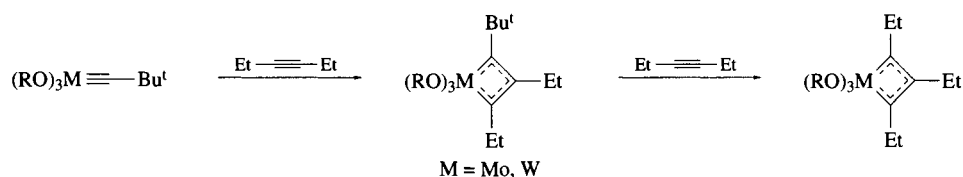
Scheme 10



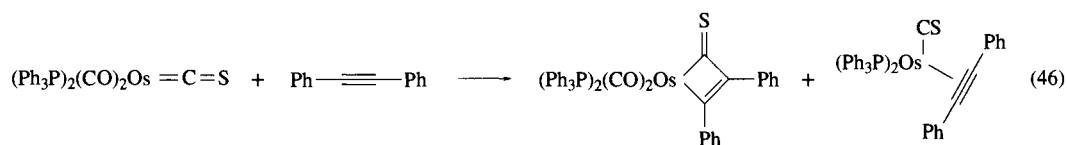
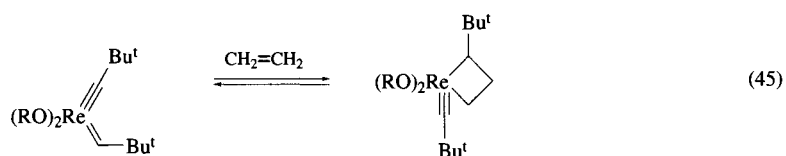
Scheme 11



Scheme 12

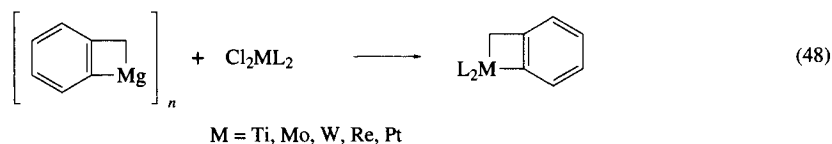
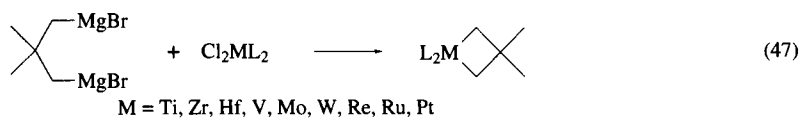


Scheme 13



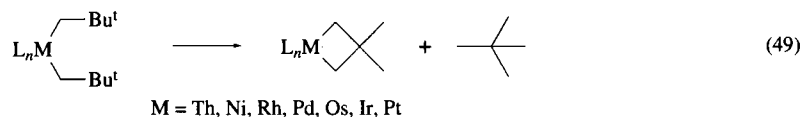
1.29.4.2 Grignard Synthesis

Di-Grignard reagents (1,3-bis(bromomagnesio)-2,2-dimethylpropane <83AG242, 84JOM(275)173, 85JMOC(28)71, 87AG1020, 87AG(E)73, 87JOM(336)447, 88JOM(346)197>, 2-(bromomagnesiomethyl)bromomagnesiobenzene <86AG(E)639>) or oligomeric 1-magnesiacyclobutabenzene <87AG(E)73, 87JOM(321)291, 88JOM(346)197, 89OM1288> with dichlorometal derivatives gave metallacyclobutanes and metallacyclobutabenzenes (Equations (47) and (48)).



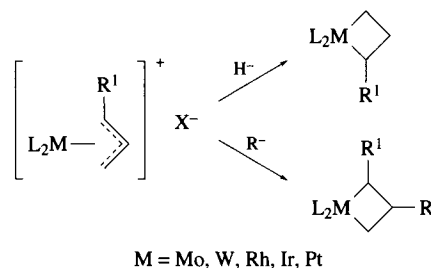
1.29.4.3 Cyclization of Neopentyl Metal Complexes

Intramolecular cyclization of complexes containing neopentyl groups on metal atoms produced thora- <86JA40>, nickela- <88JOM(338)103>, rhoda- <82CC945>, pallada- <88JOM(338)103>, osma- <90JOM(394)481>, irida- <81JA2448>, and platinacyclobutanes <79JA2732, 80JA6713, 81JA948, 82JA3601, 82OM13> with low yields (10–34%) (Equation (49)). Because of the instability of nickelacyclobutanes the reactions with nickel complexes have been carried out below -20°C . In contrast, the palladium complexes were obtained by heating at 60°C .

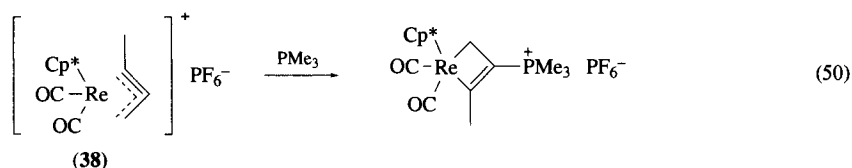


1.29.4.4 Reactions of η^3 -Allyl and η^3 -Propargyl Complexes

Nucleophilic attack by H^- (NaBH_4 , LiAlH_4 , LiBHET_3) or carbon nucleophile (MeLi , $\text{RMeC}\equiv\text{C(OMe)(O-TMS)}$, $\text{MeCH}=\text{C(Ph)(OK)}$, $\text{KCH(CO}_2\text{Me)}_2$) of η^3 -allyl salts occurs on the central carbon atom of the η^3 -allyl group giving metallacyclobutane compounds with $\text{M} = \text{Mo, W}$ <76CC619, 77JCS(D)1131>, Rh <86JA7346, 90JA6420, 92OM16>, Ir <85JA3388, 90JA6420, 93OM600>, and Pt <91OM57, 91OM3956, 93OM3019>. The cationic η^3 -propargyl-rhenium complex (38) reacted with Me_3P , $\text{LiC}\equiv\text{CBu}^t$, $\text{NaCH(CO}_2\text{Et)}_2$ to produce the metallacyclobutene complexes <92JA6597> (Scheme 14 and Equation (50)).

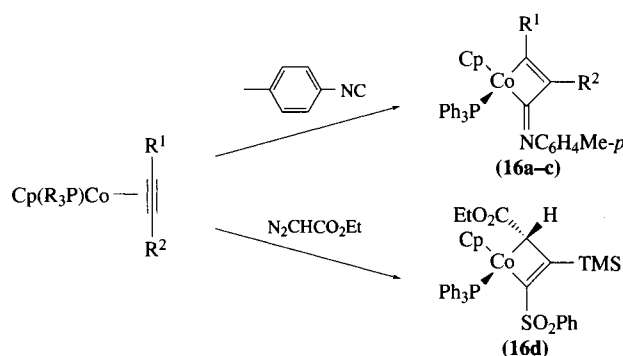


Scheme 14



1.29.4.5 Cyclization of Alkyne Complexes

The cobaltacyclobutenes (**16a–d**) with functional group at the carbon atoms of the cycle were obtained by the reaction of η^2 -alkyne complexes of cobalt with isocyanides <85CC35, 86JCS(D)1201> or ethyl diazoacetate <93JA1586> (Scheme 15).

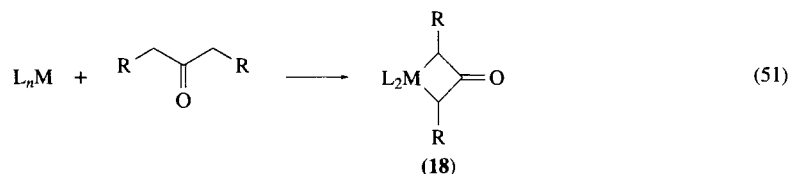


Scheme 15

The (methoxymethyl)iridium–ethyne complex $(\text{Me}_3\text{P})_2\text{Ir}(\text{CH}_2\text{OMe})(p\text{-tol-C}\equiv\text{C-}p\text{-tol})$ with trimethylbromosilane forms the iridacyclobutene complex (**16f**) <84OM1223>.

1.29.4.6 Cyclization of Acetone Derivatives

A common method for the synthesis of metallacyclobutan-3-ones (**18**) is the cyclization of palladium <78CC744, 82CC505, 85JCS(D)259> and platinum <78CC744, 83JOM(253)C59, 84JCS(D)1993, 85JCS(D)549> complexes with 1,3-disubstituted acetones (esters of 3-oxoglutaric acid, heptane-2,4,6-trione) (Equation (51)).



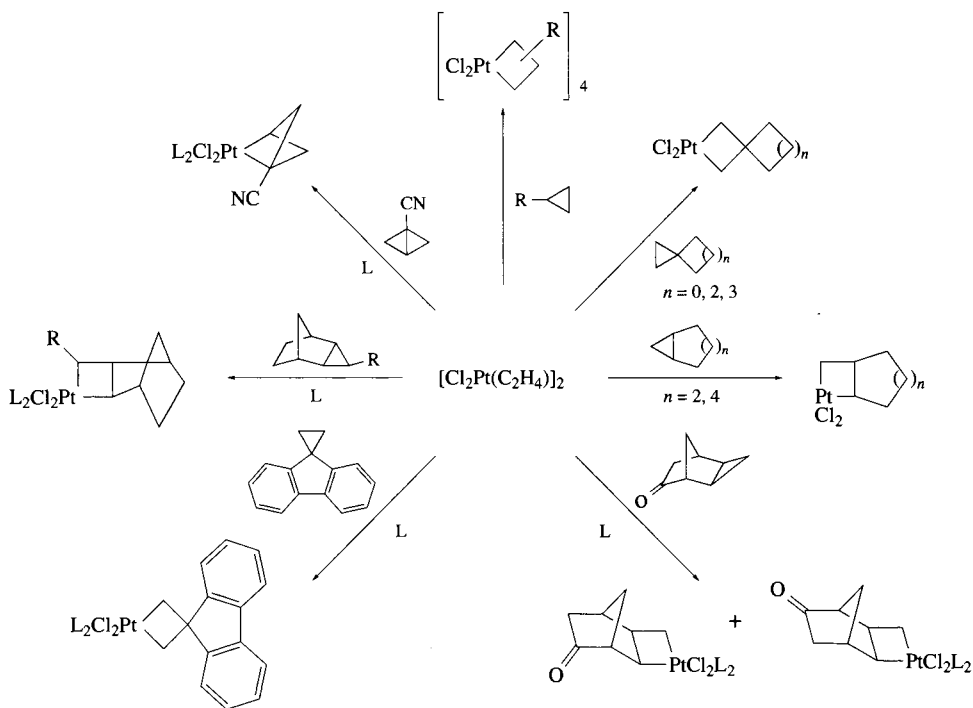
The addition of the potassium enolate of acetone to $(\text{Me}_3\text{P})_4\text{Ru}(\text{OAc})\text{Cl}$ <91OM3326> or silyl ether of chloroacetone to $(\text{Ph}_3\text{P})_3\text{Os}(\text{CO})_2$, $(\text{Ph}_3\text{P})_2\text{Ir}(\text{CO})_2\text{H}$, *trans*- $(\text{Ph}_3\text{P})_2\text{Ir}(\text{CO})\text{Cl}$ and $(\text{Ph}_3\text{P})_2\text{Pt}[(\text{E})-\text{PhCH}=\text{CHPh}]$ <86CC427> gave metallacyclobutan-3-ones.

1.29.4.7 Metal Insertion into Cyclopropane and Cyclopropene Rings

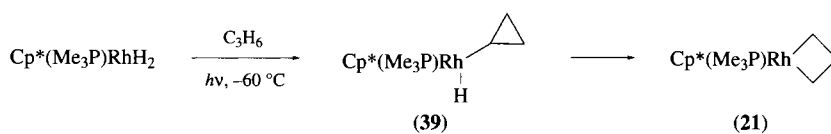
A variety of platinacyclobutanes were successfully prepared by the displacement of ethylene from Zeise's dimer by cyclopropanes (Scheme 16) <72JCS(D)2123, 77JOM(142)117, 78JOM(150)295, 78JOM(152)C42, 78JOM(159)431, 82OM1370, 83OM1487, 83TL2595, 85JOM(281)397, 87JA3973, 87JA5023, 88JA3307, 88OM1435, 91OM8, 93OM4585>.

The interaction of perfluorocyclopropene with $[(\text{R}_3\text{P})_2\text{Pt}(\text{C}_2\text{H}_4)]$ occurred rapidly in toluene at -79°C to afford the tetrafluoroplatinacyclobutene (**16g**) in high yield <88OM2239>. The same reaction was observed for the iridium complex *trans*- $[(\text{R}_3\text{P})_2\text{Ir}(\text{CO})\text{X}]$ <89JA8919>. Metal insertion into the cyclopropane ring condensed with an aromatic system cyclopropane ring has been used for the synthesis of the fused metallacyclobutanes with iron, for example (**14**) <72JA8944>, nickel, for example (**17a**) <86AG(E)640, 87CB471>, rhodium <90OM2149>, or palladium <87AG(E)67> atoms.

Ultraviolet irradiation of $\text{Cp}^*(\text{Me}_3\text{P})\text{RhH}_2$ in liquid cyclopropane at -60°C results in the formation of the hydrido cyclopropyl complex (**39**). Upon further warming of (**39**) in cyclopropane, the apparent rearrangement occurs leading to the C—C insertion product (**21**) in quantitative yield <84JA7272> (Scheme 17).

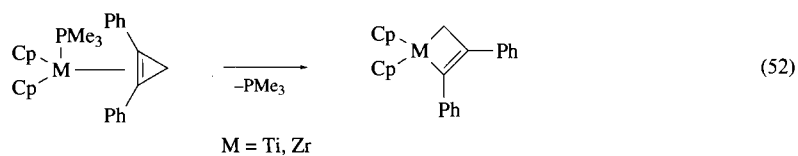


Scheme 16



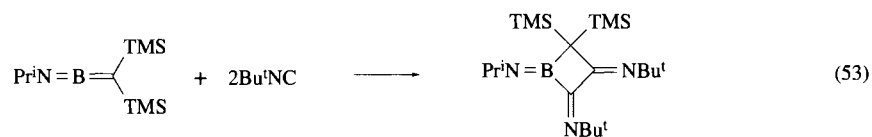
Scheme 17

The η^2 -cyclopropene complexes of titanium and zirconium rearrange smoothly above room temperature to give their metallacyclobutene derivatives (Equation (52)) <91CB2165>.



1.29.4.8 Other Reactions

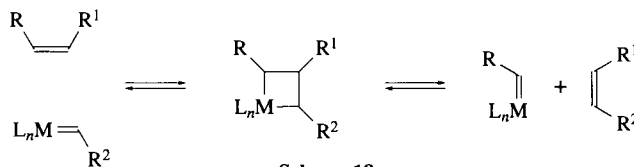
The formation of the boretane cycle was observed in the reaction of alkylideniminoborane with *t*-butyl isocyanide (1 : 2 ratio) (Equation (53)) <89CB595>.



The addition of a pentane solution of $\text{Bu}^t\text{B}(\text{Cl})\text{B}(\text{Cl})\text{Bu}^t$ to an ether solution of the lithium derivative of 1,1-dimethylallene gave 47.6% yield of diborabicyclohexane (**6**) <92AG(E)606, 92CB1981>.

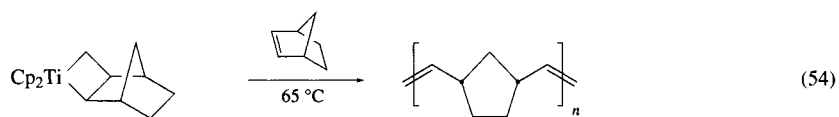
1.29.5 APPLICATIONS

Metallacyclobutanes are commonly recognized as reaction intermediates in different metal-catalyzed reactions. Titana- <85JMOC9>, tantalum- <88JA4964, 89OM644>, molybdenum- <84JA4067>, and tungstacyclobutanes <85JMOC1> can be used as alkene and alkyne metathesis catalysts (Scheme 18).



Scheme 18

Titanacyclobutanes are of current interest for the Wittig-type methylenation of carbonyl compounds (e.g., Equation (20)) <86JA733>, further elaboration to organic products <90CC1060, 92CC35> and ring opening metatheses polymerization of the cyclic alkenes (e.g., norbornene) (Equation (54)) <86JA733>.



(54)

1.30

Four-membered Rings with Two Nitrogen Atoms

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National Chemical Laboratory, Pune, India

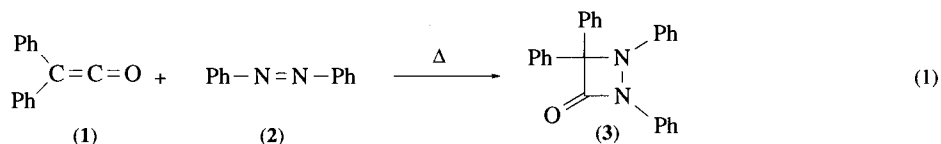
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1.30.1 INTRODUCTION

1.30.1.1 Historical Perspective

Four-membered rings containing two nitrogen atoms are known as diazetidines. Although the claims about the synthesis of this class of compounds date back to the 1850s, most of the earlier reports were later found to be erroneous. The first example of this class of compounds was reported by Hofmann in 1858, when phenyl isocyanate was dimerized in the presence of triphenyl phosphine <1858MI 130-01>. The structure of Hofmann's compound was later proposed by Staudinger as a four-membered ring structure 1,3-diphenyldiazetidine-2,4-dione <B-12MI 130-01>. Staudinger also reported the first synthesis of the 1,2-diazetidine class of compounds, by condensing diphenylketene (1) and azobenzene (2) to yield 1,2,4,4-tetraphenyl-1,2-diazetidine-3-one (Equation (1)).



However, more profound interest in this class of compounds was generated by the serendipitous discovery of penicillin by Fleming in 1929 <29MI 130-01>. Recognition of the therapeutic potential of penicillin and its derivatives gave rise to seemingly ever-increasing interest in this class of molecules, leading to the development of various new synthetic methods. Diazetidines and their derivatives also attract considerable attention from physical chemists, polymer scientists, and theoreticians.

Since this class of compounds has been dealt with briefly in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) and in greater detail by Richter and Ulrich, covering the literature prior to 1980, in the present chapter emphasis is laid on the work published during the period 1980–1994 to highlight the present state of the art <83HC(42)443, 84CHEC-I(5)449>. However, some of the earlier interesting aspects will be included appropriately in order to impart a better understanding and appreciation of the subject by the reader.

1.30.1.2 Structural Types and Nomenclature

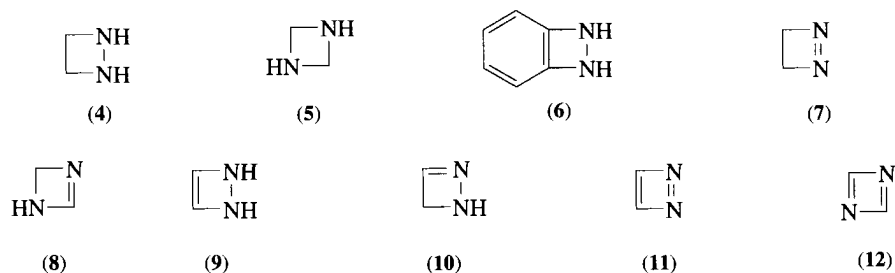
Four-membered rings containing two nitrogen atoms can be classified mainly into three categories, as follows:

(i) *Diazetidines*. A saturated four-membered ring containing two adjacent nitrogen atoms is named as 1,2-diazetidine (4), and when the two nitrogen atoms and the two carbon atoms are alternately placed it is named as 1,3-diazetidine (5). The latter is commonly known as uretidine. Members of this class of compounds are named as diazacyclobutane derivatives in the case of fused

multinuclear heterocyclic systems. For example, 3,4-benzo-1,2-diazetidine is referred to as 1,2-diaza-3,4-benzocyclobutane (**6**).

(ii) *Diazetine*. A four-membered ring with two adjacent nitrogen atoms and one double bond in the ring is called 1,2-diazetine (**7**) or, less commonly, 1,2-diazene. When the two nitrogen atoms are in 1 and 3 positions, the heterocycle is referred to as 1,3-diazetine (**8**) or commonly as uretine. According to the present IUPAC nomenclature, the compound (**7**) is represented as Δ^1 -1,2-diazetine or 3H,4H-diazetine. Similarly, compound (**8**) is named as Δ^2 -1,3-diazetine or 1H,4H-diazetine, whereas compound (**9**) is called Δ^3 -1,2-diazetine or 1H,2H-diazetine and compound (**10**) is called Δ^2 -1,2-diazetine or 1H,4H-diazetine.

(iii) *Diazetes*. A four-membered ring with two nitrogen atoms and two double bonds is referred to as a diazete. In terms of cyclobutadiene derivatives, these compounds are named as 1,2-diazacyclobut-1,3-diene (**11**) or 1,2-diazete and 1,3-diazacyclobut-1,3-diene (**12**) or 1,3-diazete (less commonly as urete). Very little is known about this class of compounds.



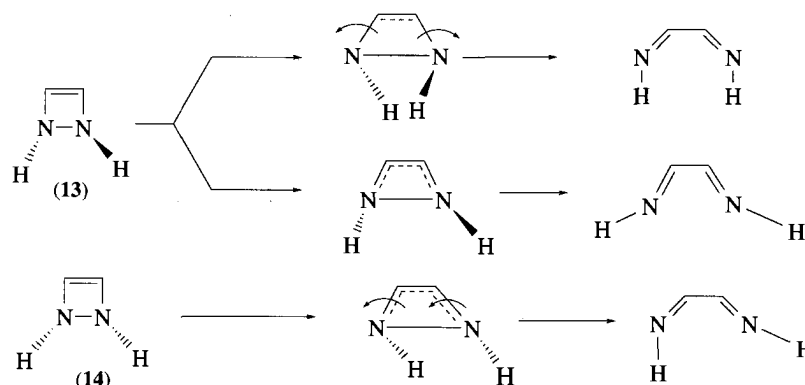
1.30.2 THEORETICAL METHODS

Elucidation of the electronic structure of four-membered heterocycles with two nitrogen atoms has been approached through various theoretical methods. Moffat carried out *ab initio* calculations on the possible formation of diazetidine or diazete by the dimerization of cyanamide <83JST(94)261>. The “nondissociative” dimerization of cyanamide leads to cyclic molecules, all of which are unstable with respect to cyanamide. However, the molecules produced by “dissociative” dimerization are stable relative to the cyanamide. Misra and co-workers <88IJC(A)653> have calculated the topological resonance energy (TRE) for several cyclic compounds and found that increase in TRE value decreases the antiaromaticity and increases the stability of the molecule. These values indicate that 1,2-diazetidine is more stable than 1,3-diazetidine. The TRE value of 0.0831β unit for 1,2-diazetidine reveals that the molecule bears some nonaromatic character.

Politzer and co-workers have also used an *ab initio* SCF molecular orbital approach in conjugation with isodesmic reaction procedure to investigate the anomalous energy effect in strained aza systems and some of their nitro derivatives. The $\Delta E_{\text{isodesmic}}$ values have been found to be $16.7 \text{ kcal mol}^{-1}$ (69.9 kJ mol^{-1}) for 1,3-diazetidine and $25.3 \text{ kcal mol}^{-1}$ ($105.9 \text{ kJ mol}^{-1}$) for 1,2-diazetidine, which clearly suggest that 1,2-diazetidines are more stable than 1,3-diazetidines <90JST(207)193>. These authors have also calculated the energy of isomerization of 1,3-diazete to a highly strained molecule by local density functional theory. The activation energy barrier and total energy change associated with isomerization to diazatetrahedranes were also calculated, for example, the activation energy of 1,3-diazete is 58 kcal mol^{-1} (243 kJ mol^{-1}) whereas for 2,4-dinitro-1,3-diazete it is 86 kcal mol^{-1} . Local density functional theory has been applied to the calculation of the activation barrier for the two symmetry forbidden reactions: i.e., concerted ring decompositions of 1,3-diazacyclobutane and its dinitramine derivatives <91JCP(94)1668>.

The molecular electrostatic potential map of 2,4-dimethyl-1,3-diazete suggests that it is unlikely to be stable and obtainable by cyclodimerization of acetonitrile <92JST(256)17>. The thermally allowed conrotatory ring opening of 1,2-dihydro-1,3-diazete and *trans*- and *cis*-1,2-dihydro-1,2-diazete have been examined, and the products were fully optimized at HF/6-31G* with single-point energy calculation performed at MP2. The calculations have shown the opening of dihydrodiazete to be exothermic. The calculated activation barrier for the opening of *cis*-1,2-dihydro-1,2-diazete (**14**) is $24.58 \text{ kcal mol}^{-1}$ ($102.9 \text{ kJ mol}^{-1}$). The ring opening of the *trans* isomer (**13**) can occur via two diastereomeric pathways. The lower barrier is $22.95 \text{ kcal mol}^{-1}$ (96.1 kJ mol^{-1}). The structural and

energetic differences and trends among these compounds are interpreted in terms of ring strain and orbital interactions (Scheme 1) <92JOC2040>.



Scheme 1

Elguero *et al.* have examined the aromaticity of 1,2- Δ^3 -diazetene <89JST(201)17>. An *ab initio* MO analysis of the correlation diagrams of these systems was made for nitrogen inversion and for the increase in N—N internuclear distance. The ring strain is quite important in determining which NH—NH bond exhibits lone-pair interaction. The existence of ring strain, nitrogen lone-pair interactions, or both seems to be crucial in the absence of aromaticity for this kind of system. The nonaromatic nature of 1,2- Δ^3 -diazetene has been confirmed by resonance energies of opposite sign to that predicted for benzene, as well as by their high barriers to nitrogen inversion. The resonance energy of 1,2- Δ^3 -diazetene was evaluated by means of homodesmotic reaction <76JCS(P2)1222>. The geometries of different conformers of 1,2- Δ^3 -diazetene were fully optimized at the SCF level by using the polarized split valence 6-31G* basis set.

Planar, syn, and anti conformers (15)–(17) were taken into consideration. In addition, in order to obtain the energy curves for nitrogen inversion, the geometries corresponding to values of ϕ and ϕ' between 0° and 80° were also fully optimized (Table 1). From the Table it is clear that going from planar-(15) to anti-(17), the C—C bond length decreases while C—N and N—N bond lengths increase considerably.

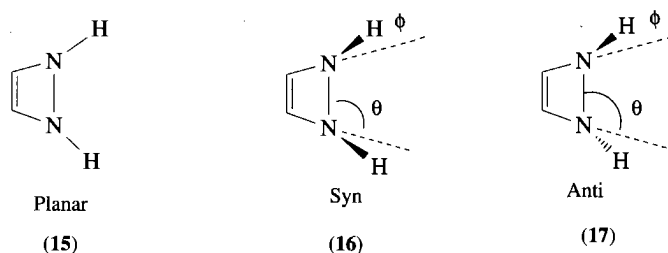


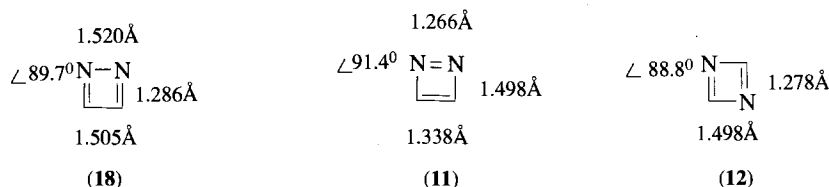
Table 1 Optimized structures: bond length (Å), bond angle (deg.).

Compound	C—N	C—C	N—N	C—H	N—H	$\angle CNN$	$\angle CNN$	$\angle CNN$	$\angle CNN$	ϕ
Planar-(15)	139.4	134.7	138.8	106.6	098.7	89.2	90.8	141.2	128.0	0
Syn-(16)	143.0	132.1	146.0	107.0	100.5	87.2	92.8	132.9	127.8	58.0
Anti-(17)	143.3	132.0	145.5	107.0	100.3	87.3	92.7	129.0	128.0	60.2

Examination of the MO correlation diagram for the 1,2- Δ^3 -diazetene system along the double nitrogen inversion barrier, which connects its *anti* conformation with the totally planar one reveals the following facts: (i) only a few (five) MOs undergo a significant energy change along the barrier; (ii) three of the MOs (π in the planar form) considerably stabilize, whereas the other two (σ in the planar form) considerably destabilize; and (iii) two of the three π -type MOs which stabilize are the HOMOs of the system.

In the early 1990s, Schoeller and Busch calculated bonding parameters and energies at MCSCF

level of the parent 1,2-diazete (**11**) and (**18**) and 1,3-diazete (**12**) $\langle 93\text{AG(E)617} \rangle$. The 1,3-diazete can be considered as “Push–Pull” cyclobutadiene; its singlet ground state is stabilized relative to that of cyclobutadiene. Its valence isomerization proceeds through a planar transition structure with C_2 symmetry. The 1,2-diazetes are higher in energy than their 1,3-isomers. The 1,2-diazete with two $\text{C}=\text{N}$ bonds (**18**) is higher in energy by $12.1 \text{ kcal mol}^{-1}$ (50.7 kJ mol^{-1}), and that with one $\text{N}=\text{N}$ and $\text{C}=\text{C}$ (**11**) by $22.5 \text{ kcal mol}^{-1}$ (94.2 kJ mol^{-1}), than the 1,3-isomer (**12**).



Facelli has also carried out optimization of geometries for 1,2-diazete (**11**) and (**18**) and 1,3-diazete (**12**) using the GAUSSIAN 86 molecular package $\langle 91\text{JST}(236)119 \rangle$. Vibrational frequencies were calculated using fully optimized geometries and the doubly excited configuration interaction (CID) approximation for wave function. For 1,2-diazete (**11**) and (**18**), optimized structures were calculated for both the tautomers, and both optimized geometries exhibited C_{2v} symmetry. IR frequencies were calculated using this symmetry constraint. The fully optimized geometries are given in Table 2.

The MNDO method predicts that the tautomer (**11**) will be more stable in 1,2-diazete, whereas Facelli's calculation suggests that tautomer (**18**) is more stable by $11.8 \text{ kcal mol}^{-1}$ (49.4 kJ mol^{-1}). The IR frequencies and intensities calculated for 1,2-diazete (isomers **11**) and (**18**)) and 1,3-diazete (**12**) are shown in Table 2.

The calculated IR frequencies for (**11**) and (**18**) clearly indicate that the isomers are very different. The most significant difference is the 705 cm^{-1} band present in (**11**) which corresponds to symmetric stretching of $\text{C}-\text{N}$ single bonds, which is absent in the spectrum of (**18**). The prominent bands in the spectrum of (**18**) are 817 cm^{-1} and 1388 cm^{-1} . In the $\text{C}-\text{H}$ stretch region, (**18**) exhibits an intense band at 3327 cm^{-1} and a less intense band at 3345 cm^{-1} , whereas $\text{C}-\text{H}$ stretching is observed at 3326 cm^{-1} and 3369 cm^{-1} for (**11**) with much lower intensity.

The orbital energies of the HOMO and LUMO of (**11**), (**12**), and (**18**), and the π -bond orders, are shown in Table 3; they clearly indicate the antiaromatic character. In several cases, π -bond orders are negative, suggesting that π -electrons tend to destabilize these bonds.

It is interesting to note that nitrogen atoms in 1,3-diazete exhibit the largest electronegativity, probably because the electrostatic repulsion of negative and positive centers is reduced on account of *trans*-configuration. Bonačić-Koutecký *et al.* have calculated the symmetry state and the energy associated with various levels of protonated 1,3-diazacyclobutadiene $\langle 89\text{JA6140} \rangle$.

1.30.3 EXPERIMENTAL STRUCTURAL METHODS

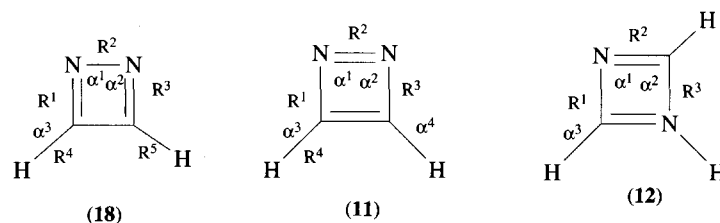
Several methods have been applied to determine the structure, size, shape, and conformation of various four-membered ring compounds containing two nitrogen atoms.

1.30.3.1 X-ray Diffraction Studies

In the late 1980s, several x-ray diffraction studies on four-membered heterocycles with two nitrogen atoms have been reported. The actual conformation and structure of this class of compounds has been questioned; however, the x-ray data have helped to solve these mysteries to a great extent $\langle 87\text{JCS(P1)885} \rangle$.

1.30.3.1.1 1,2-Diazetidine derivatives

Taylor and co-workers reported the x-ray crystallographic structure of α -1-*p*-(bromophenyl)phenyl methylene-3-oxo-1,2-diazetidinium inner salt (**19**), which indicated a shorter distance

Table 2 CID optimized geometry, calculated energy, and vibrational frequencies of the 1,2-diazacyclobutadienes and 1,3-diazacyclobutadienes.

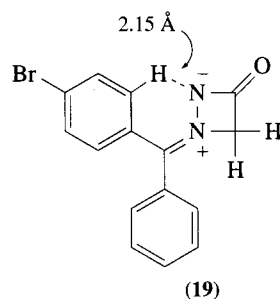
Parameter	Basis set for (18)			Basis set for (11)			Basis set for (12)		
	4-31G*	6-31G*	6-31G**	4-31G*	6-31G*	6-31G**	4-31G*	6-31G*	6-31G**
Bond length (Å)									
R ¹	1.2717	1.2742	1.2738	1.5286	1.5285	1.5277	1.2682	1.2712	1.2712
R ²	1.5900	1.5875	1.5858	1.2445	1.2462	1.2460	1.5106	1.5107	1.5103
R ³	1.2716	1.2742	1.2738	1.5285	1.5285	1.5279	1.0820	1.0834	1.0777
R ⁴	1.0811	1.0824	1.0770	1.0756	1.0774	1.0719			
R ⁵	1.0810	1.0824	1.0770	1.0757	1.0774	1.0719			
Bond angle (°)									
α ₁	87.9376	88.0662	88.1036	91.3379	91.3876	91.3872	80.1827	80.2023	80.1852
α ₂	87.9391	88.0624	88.1057	91.3552	91.3787	91.3872	99.8151	99.7979	99.8111
α ₃	128.3877	128.4446	128.5209	130.6403	130.6304	130.8470	131.6468	131.6450	131.5435
α ₄	128.3738	128.4450	128.5207	130.6537	130.6283	130.8417			
Energy (a.u.)									
HF	−185.4385471	−185.6227608	−185.6267296	−185.4203302	−185.6048394	−185.6090550	−185.4699185	−185.6543874	−185.6583661
MP2	−186.0349244	−186.2188588	−186.2348673	−186.0128661	−186.1968377	−186.2130176	−186.0527050	−186.2367286	−186.2528395
MP3	−186.0460610	−186.2299534	−186.2469756	−186.0265803	−186.2106361	−186.2277746	−186.0642130	−186.2482782	−186.2653814
CID	−185.9652307	−186.1486660	−186.1628995	−185.9460999	−186.1296880	−186.1440457	−185.9884375	−186.1720692	−186.1864578
Symmetry vibrational frequency (cm^{−1})^a									
A ₂	555	552	552	586	585	593	481	474	478
A ₁	712	713	717	996	992	1007	815	818	820
B ₁	811	806	817	648	617	705	895	892	900
A ₂	926	914	927	878	858	922	983	982	984
B ₂	951	949	949	702	705	711	997	991	1004
A ₁	1072	1071	1074	1193	1187	1209	1057	1059	1061
B ₂	1250	1247	1256	1022	1024	1021	1282	1279	1291
A ₁	1381	1378	1388	1691	1680	1682	1309	1306	1318
B ₂	1735	1732	1737	1274	1265	1305	1771	1765	1765
A ₁	1818	1815	1819	1805	1789	1795	1785	1781	1786
B ₂	3294	3298	3327	3367	3404	3326	3305	3308	3336
A ₁	3312	3316	3345	3409	3445	3369	3306	3310	3337

^aSymmetry for compound (12) is different (from Facelli <91JST(236)119>).

Table 3 Comparison of HOMO and LUMO orbital energies for 1,2-diazacyclobutadiene and 1,3-diazacyclobutadiene.

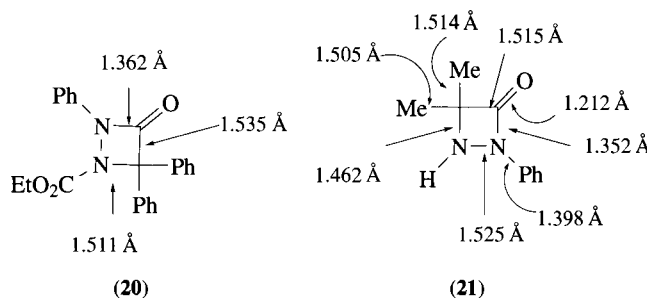
Compound	HOMO	LUMO	$\Delta(\text{HOMO} - \text{LUMO})$
(18)	-0.3782	0.0611	0.4393
(11)	-0.3587	0.0571	0.4157
(12)	-0.3758	0.0659	0.4416

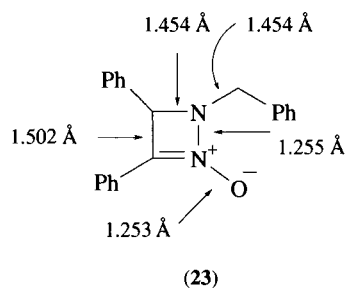
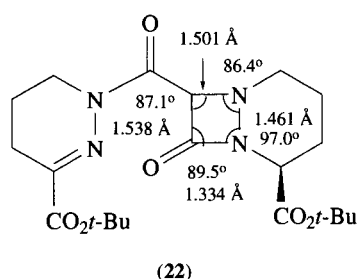
(2.15 Å) between the negatively charged ring nitrogen and aromatic C—H hydrogen than the sum of the Van der Waal's radii (2.7 Å) <68JA5272>. This was interpreted as arising from unusual hydrogen bonding between the aromatic hydrogen and ring nitrogen <68CC917>. This shortening of H—N distance was later attributed to the crystal packing force rather than to hydrogen bonding, on the basis of extensive IR studies <72CC1081, 91JST(236)119>.



Unlike cyclobutane and its derivatives, many of the four-membered heterocycles usually have planar structures. However, diazetidines are slightly nonplanar or puckered. For example, Ruben and co-workers studied the x-ray crystal structure of ethyl 2,4,4-triphenyl-1,2-diazetid-3-one-1-carboxylic acid (20) <74AX(B)1631>. A least-square plane calculated through the four atoms of the ring suggests a deviation of bond angle of N(1), N(2), C(1), and C(2) to form a slightly puckered ring. The N(1)—C(1) bond length is 1.362 Å versus 1.333 Å in amides, and the N(2)—C(2) bond length is 1.511 Å versus 1.472 Å for the N—C bond in alkanes and saturated heterocyclic compounds. The relative orientation to the ring of the three phenyl rings, the ethyl ester, and the oxygen O(1) can be seen to be away from the plane of the ring. The crystallographic structure supports the nonplanarity of the diazetidinone ring. Similarly, Schantl and Decristoforo showed by x-ray analysis of the structure that 4-phenyl-1,2-diazetid-3-one (21) is nonplanar with a folding angle of 6.1° along the N(1)—C(3) axis <87TL6577>. Moody and co-workers discovered the formation of 1,2-diazetid-3-one (22) in a photochemical ring contraction reaction of 4-diazopyrazolidin-3,5-diones, which was confirmed by x-ray diffraction studies <87JCS(P1)885>. None of these 1,2-diazetid-3-ones were found to have planar structures.

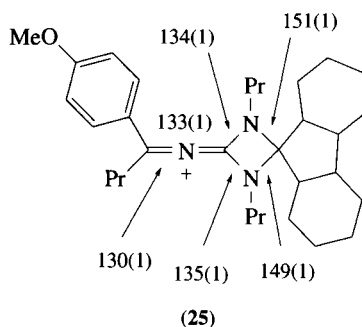
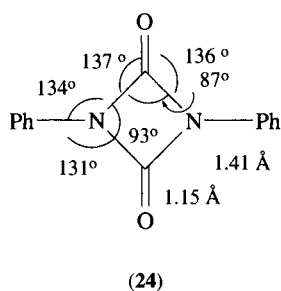
Loeppky and co-workers have confirmed by x-ray crystallography that the structure of the unusual product obtained by aziridine nitrosation is dihydrodiazete N-oxide (23) <91JA2308>.





1.30.3.1.2 1,3-Diazetidines derivatives

The structure of 1,3-diazetidine obtained by dimerization of the phenyl isocyanate (known since 1858) $\langle 1858\text{MI } 130-01 \rangle$ was only verified by x-ray diffraction studies in 1955 $\langle 55\text{JCS}2931 \rangle$. The molecule (24) as a whole has not been found to be planar: although the two phenyl rings and four-membered ring are planar, the $\text{C}=\text{O}$ bond makes an angle of 87.5° . The distortion from planarity of the central ring has been attributed to (i) the close approach of the oxygen atom to the phenyl ring; and (ii) the nitrogen atom of the ring being slightly pyramidal. In contrast to the 1,3-diphenyldiazetidines-2,4-dione, the structure of the 1,3-dimethyldiazetidines-2,4-dione was found to be planar. The two methyl groups are about 22° out of plane, while the oxygen atoms are in the plane $\langle 77\text{CB}1130 \rangle$. In the mid-1980s, Jochims and co-workers determined the crystal structure of the cation of 2-azoniallene derivative (25) and showed that it deviates from planar geometry ($\beta = 119.5^\circ$). The exocyclic $\text{C}=\text{N}=\text{C}$ unit is bent ($\alpha = 127.3^\circ$) $\langle 85\text{T}527, 91\text{CB}2537 \rangle$.

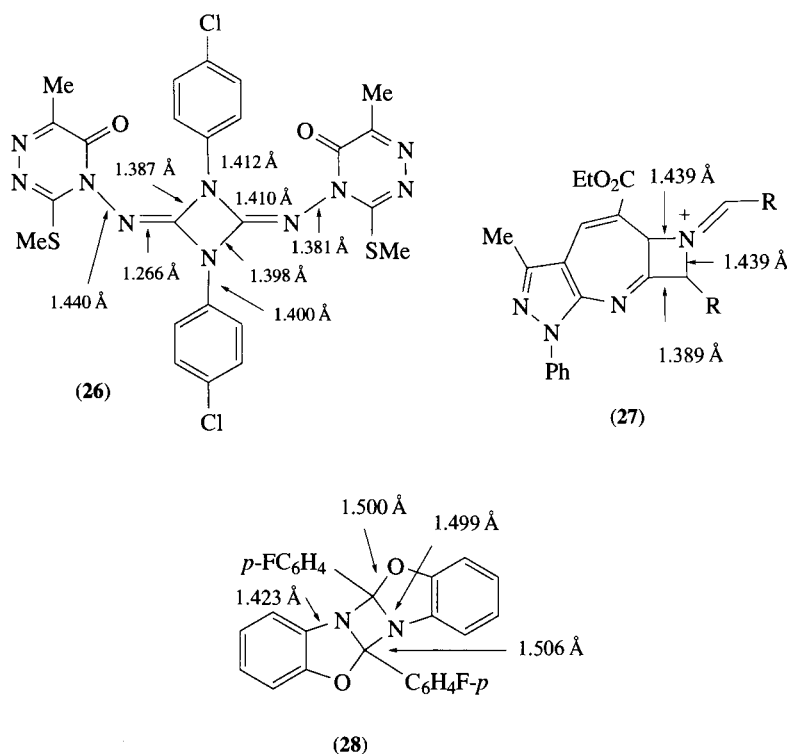


Molina *et al.* have prepared a number of highly substituted 1,3-diazetidines by the reaction of appropriate iminophosphoranes and aryl isocyanates. The structure of these 1,3-diazetidines (26) could only be confirmed by x-ray crystallographic studies $\langle 86\text{JCS(P1)}2037 \rangle$. It has been found that in (26) the two heterocycle substituents exist in *Z,Z*-configuration although it is more crowded than *E,E*-isomer. These authors have also shown by x-ray crystallography that the thermal rearrangement of several betains leads to diazetidines $\langle 92\text{JCS(P1)}199 \rangle$. Similarly, fused 2,4-diimino-1,3-diazetidines (27) obtained by Aza Wittig [2 + 2] cycloaddition of carbodiimide generated in turn from bisiminophosphoranes, were confirmed by x-ray diffraction studies $\langle 92\text{CC}424 \rangle$. Several structural studies of 1,3-diazetidines by crystallographic analysis have been reported by the same research group $\langle 90\text{JCS(P2)}1859 \rangle$. Much of the work by Molina and co-workers is well summarized in a review article $\langle 93\text{JPR}305 \rangle$.

Ulrich *et al.* have reported a [2 + 2] cycloaddition of N-arylcabodiimide with isothiocyanates to give 1,3-diazetidines, the structure of which was confirmed by x-ray crystallography $\langle 87\text{CB}849 \rangle$. An interesting head-to-tail photodimerization of 2-phenylbenzoxazoles leading to a [2 + 2] cycloaddition to furnish 1,3-diazetidines (28) has been studied and the structures finally confirmed by x-ray analysis $\langle 87\text{CC}578 \rangle$.

1.30.3.2 Microwave Spectroscopy

The conformation of 1,2-dimethyl-1,2-diazetidine with a dihedral angle of $154^\circ \pm 10^\circ$ between the nitrogen lone-pair orbitals and with both the methyl groups quasiequatorial has been predicted



<75CB1548, 75CB1557>. This prediction was tested by electron diffraction and microwave studies <80JCS(F2)1293>. Using microwave spectroscopy, rotational constants, quartic centrifugal distortion constants, and quadrupole coupling constants were measured and compared with the calculated values obtained from the force field (Table 4). Rotational and quartic centrifugal distortion constants were fitted by a least-square method. Quadrupole hyperfine interactions were fitted with overall standard deviation of 33 kHz. Splitting of the rotational transition because of internal rotation of methyl groups could not be observed. Assuming the lower limit for the rotational barrier in 1,2-dimethyldiazetidene to be 2.5 kcal mol⁻¹ (10.5 kJ mol⁻¹), the calculation suggests an average splitting of about 50 kHz with maximum splitting of 110 kHz. This suggests that it is not possible to determine the internal rotational barrier by microwave spectra of the vibrational ground state. However, the hyperfine structure of the rotational transition could be explained by nuclear quadrupole interactions.

Table 4 Rotational constants (B), quartic centrifugal distortion (ΔJ , ΔJ_k , ΔK , δJ , δK) and quadrupole coupling constants (χ_{aa} , χ_{bb} , χ_{cc}) of 1,2-dimethyl-1,2-diazetidene.

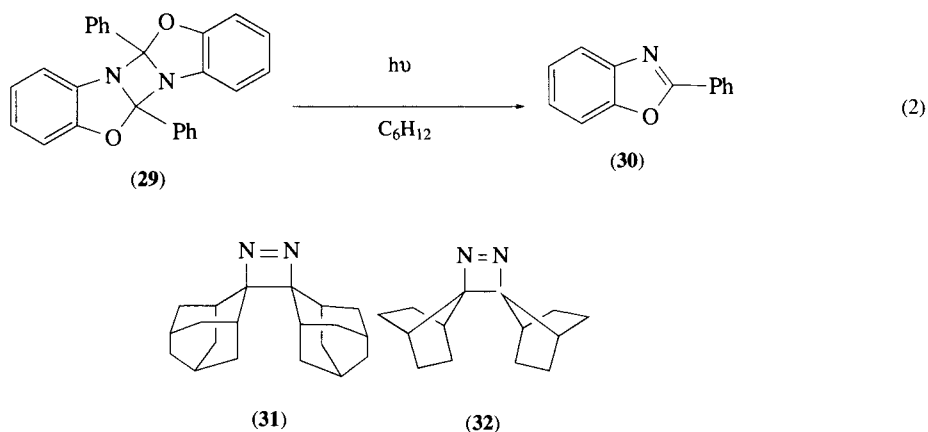
Transition type	Rotational constants (MHz)			Quartic centrifugal distortion constants/Hz				Quartic centrifugal distortion constants (MHz)		
	$B^{(i)}_{(expt)}$	$B_Z^{(i)}_{(expt)}$	$B_Z^{(i)}_{(calc)}$		Expt	Cal ^b		Expt ^a	Cal ^b	
A	5053.003	5055.523	5055.545	ΔJ	907(34)	915	δJ	383(4)	342	χ_{aa} 2.939
B	3801.114	3801.374	3801.378	ΔJ_k	-2249(30)	-1977	δK	168(20)	368	χ_{bb} 1.40
C	2436.404	2436.584	2436.566	ΔK	3842(34)	326				χ_{cc} -4.339

^aValue in GHz (in parenthesis) at which microwave spectra were recorded. ^bCentrifugal distribution constant calculated by force field.

1.30.3.3 UV-Visible Spectroscopy

The UV spectrum of Δ^1 -1,2-diazetidines has been found to give fine structure arising from $n-\pi^*$ transition, unlike other cyclic azo compounds which show broad absorption at 360 nm without any fine structure. For example, 3,3,4,4-tetramethyl- Δ^1 -1,2-diazetine showed highly structured transition at 325 nm, 333 nm, 340 nm, and 356 nm <75JOC1409> whereas 2,3-diazabicyclo[2,2,0]-hex-2-ene

showed $\lambda_{\max}$ at 334 nm, 341 nm, and 350 nm due to $n\text{--}\pi^*$ transition <78TL2469>. The absorption and emission spectra of several 1,2- Δ^1 -diazetidines were studied in various solvents; they showed blue shift of absorption maxima with increasing solvent polarity, which is typical of $n\text{--}\pi^*$ transition <78JA5122, 81JA7743>. The UV spectra of several substituted 1,2-diazetidines have been reported to have fine structural bands at 245 nm and 325 nm <68JA5272>. UV spectroscopy has been used to determine the first-order rate constant of reversion of the photodimer (29) to monomer (30) with an activation energy of $89.9 \pm 6.3 \text{ kJ mol}^{-1}$ (Equation (2)) <83JOC3736>. The $\lambda_{\max}$ of compound (31) has been found to be 358 nm ($\epsilon = 95 \text{ mol}^{-1} \text{ cm}^{-1}$) and 355 nm ($\epsilon = 184 \text{ mol}^{-1} \text{ cm}^{-1}$) whereas, for compound (32), $\lambda_{\max}$ was 345 nm ($\epsilon = 205 \text{ mol}^{-1} \text{ cm}^{-1}$) <93JOC5393>.



1.30.3.4 Photoelectron Spectroscopy

The conformation of molecules containing atoms with electron lone pairs often depends to a large extent on the interaction between these lone pairs and the rest of the molecule. Based on photoelectron spectra, empirical correlation between the interaction energy of the electron lone pairs of the two bonded nitrogen atoms and the dihedral angle between these lone-pair orbitals was found <74TL83>. Rademacher predicted for 1,2-dimethyl-1,2-diazetidine a conformation with dihedral angle of $154^\circ \pm 10^\circ$ between the nitrogen lone-pair orbitals, and thus both methyl groups in quasiequatorial position <75CB1548, 75CB1557>. From the spectra, the negative values of the vertical ionization potentials indicate an increase in the folding of the ring system from diaziridine to 1,2-diazine. By increasing the size of the substituents on 1,2-dialkyl-1,2-diazetidine (Me, Prⁱ), the two substituents *trans* to each other seem to push each other further apart. Thus, the two methyl groups exist exclusively in *trans*-equatorial form (33) whereas, in the case of diisopropyl, both *trans*-equatorial (33) and axial (34) are possible <78JA2806>. Danby's parameter μR was introduced for predicting the ionization potential when alkyl groups are changed <84JOC1891>. It has been found that ring size, alkyl–nitrogen–alkyl angle, alkyl–nitrogen–nitrogen angle, and lone-pair–lone-pair dihedral angle in hydrazine, all affect ionization potential. Values of ionization potential for compounds (35)–(40) are shown in Table 5.

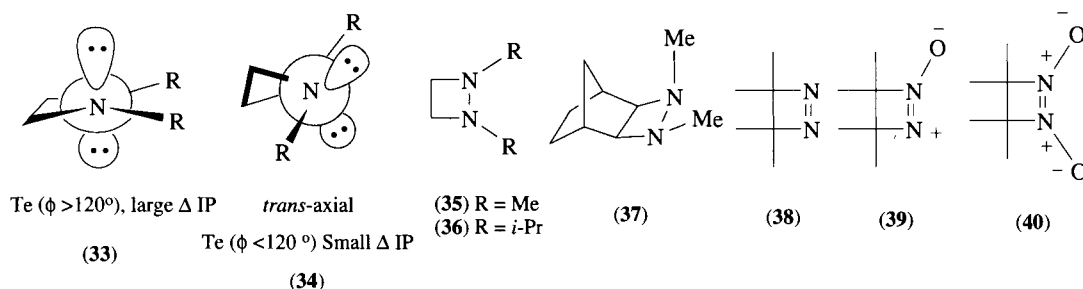


Table 5 Ionization potential (eV) of compounds (35)–(40).

Compound	1st	2nd	3rd	ΔIP	Assignment	Ref.
(35)	8.12	10.16		2.04	<i>Te</i>	78JA2806
(36)	7.6/7.66	8.22/9.69		0.6/2.02	<i>Ta/Te</i>	78JA2806
(37)	7.64	9.52		1.88	<i>Trans</i>	78JA2806
(38)	8.77	10.24	11.5	1.77		77JOC609
(39)		9.82	10.8			77JOC609
(40)	8.52(8.23)	10.7(9.45)	10.6(10.4)			77JOC614

1.30.3.5 IR–Raman Spectroscopy

IR and Raman spectroscopy have been extensively used to determine the cyclic structure of diazetidines and their derivatives. Several studies comparing these cyclic compounds with the related cyclic and acyclic analogues have been reported (62JCS4840). A very few cases of saturated 1,2-diazetidines are reported. For example, dimethyl or diethyl azodiformate form a [2 + 2] 1:1 adduct with methyl or ethyl vinyl ether. The C=O band of ester functionality appeared in the 1600–1800 cm^{-1} region (70JOC1155). Oberhammer and co-workers have carried out detailed IR and Raman spectroscopic studies of 1,2-dimethyl-1,2-diazetidine (80JCS(F2)1293). The IR and far IR spectra were recorded in the ranges 3500–400 cm^{-1} and 50–480 cm^{-1} , respectively. The Raman spectra were recorded in the range 50–3500 cm^{-1} . Frequencies in the range 2700–3000 cm^{-1} can be assigned to the C–H stretching vibrations of methylene and methyl groups. Absorptions around 1450 cm^{-1} are assigned to HCH deformations of methylene and methyl groups. The stretching vibrations of the molecular skeleton are assigned to the absorptions in the range 1100–1220 cm^{-1} . These vibrations are strongly coupled with deformation and rocking vibration of methyl groups. Eight frequencies have been assigned in the lower frequency range. The two absorptions at 216 cm^{-1} and 219 cm^{-1} are assigned to the torsional vibrations of methyl, two are ring deformations (ring scissoring at 653 cm^{-1} and ring puckering at 140 cm^{-1}) and the remaining four frequencies are assigned to the bending vibrations of the methyl group with respect to the ring. Unlike diazetidines, several studies on 1,2-diazetidin-3-ones are reported in which the C=O absorption is in the range 1775–1790 cm^{-1} on account of ring strain which is much higher than observed for β -lactams (1730–1760 cm^{-1}). For example, 1,2-diaryl-1,2-diazetidin-3-one (41) showed an absorption at 1770–1790 cm^{-1} (66TL5245, 67TL161, 74JOC1215) whereas 1,2-di-*tert*-butyl-1,2-diazetidin-3,4-dione (42) showed a C=O absorption at 1813 cm^{-1} (67JOC2360). If a C=O is replaced by C=N, the C=N band is observed at 1705 cm^{-1} (67JHC155). In the case of bicyclic 1,2-diazetidin-3-one, the C=O frequency was observed at 1772 cm^{-1} (79CC568). In contrast to the *N,N*-disubstituted 1,2-diazetidin-3-one, the mono *N*-substituted derivative (44) showed an IR band at 3100 (NH), 1680 (sh), 1720 and 1750 cm^{-1} (C=O) which compares favorably to the β -lactam derivatives (68JA5273). This indicates that the resonance interaction with the nitrogen atom lone pair is lower for aza- β -lactam (76AG(E)432, 81JA7743, 86H(24)885). On the other hand, if an inner salt is produced, two bands in the double bond region at 1740 cm^{-1} and 1775 cm^{-1} are observed as in (45) cf. (68JA5272). The inner salt of the type (19) showed an IR absorption band at 1755–1760 cm^{-1} whereas 1,2-diazetidinium tosylate (46) showed absorption at 1825 cm^{-1} (84JOC4415).

The Δ^1 -1,2-diazetine (47) showed N=N stretching at about 1480 cm^{-1} in 3,3,4,4-tetrafluoro or tetramethyl derivatives. On the other hand, several bands between 1465 cm^{-1} and 1555 cm^{-1} for mono- and dioxides have been observed (72JA3955, 75JOC1409). In the case of 1,3-diazetidiones the C=O band appears somewhat similar to that of the urea carbonyl absorption. Some of the above-mentioned examples are shown in Table 6.

1.30.3.6 Nuclear Magnetic Resonance Studies

Nuclear magnetic resonance (NMR) spectroscopy has been used extensively to study the conformation of a number of diazetidines, their thermodynamic stability, and kinetics of inversion at N-center in addition to the routine structural elucidation.

1.30.3.6.1 Proton NMR

Proton NMR has been quite helpful in structural elucidation of a number of diazetidines, diazetines, and their derivatives. A few examples of chemical shift assignment and their coupling

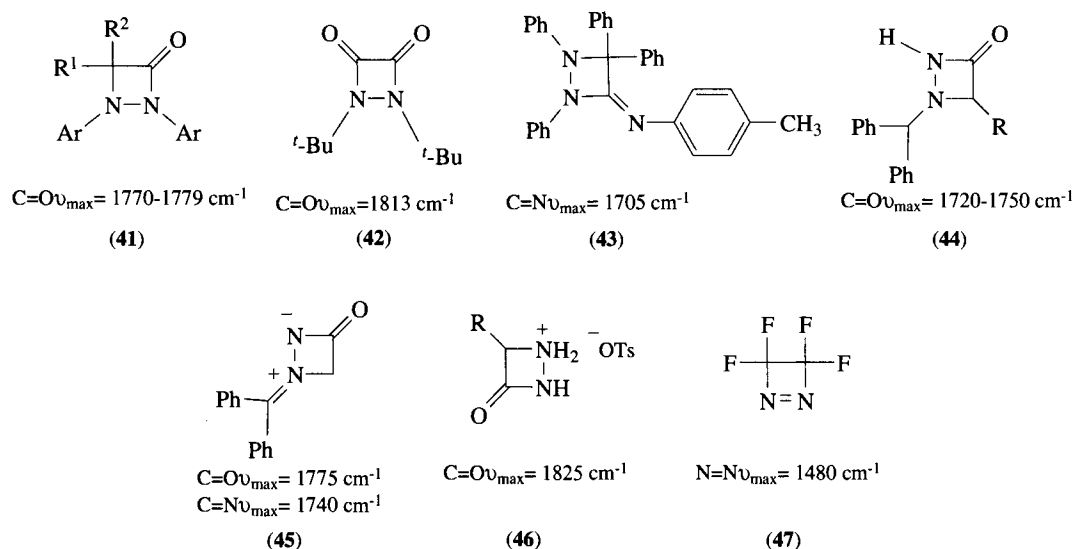


Table 6 IR data for 1,3-diazetidene derivatives.

Compound	Substituents	IR frequencies	Ref.
	R	$C=O$	
	Cl	1819 cm^{-1}	
	C_6F_5	1824 cm^{-1}	83HC(42)443
	Me	1778 cm^{-1}	
	Ph	$C=O \nu_{\max} 1730 \text{ cm}^{-1}$ $C=N \nu_{\max} 1700 \text{ cm}^{-1}$	83HC(42)443
	Ph	$C=N \nu_{\max} 1675-1700 \text{ cm}^{-1}$	83HC(42)443
		$C=O \nu_{\max} 1770-1775 \text{ cm}^{-1}$	90OM762
	X = O	$C=O \nu_{\max} 1725 \text{ cm}^{-1}$	
	X = N-Ph	$C=N \nu_{\max} 1680 \text{ cm}^{-1}$	83JOC1694

constants are summarized in Table 7. Proton NMR has also been an important tool in determining the geometric isomerism of 1,3-diazetidene-2,4-diimines. Several experiments have revealed that although (*Z*, *Z*)-isomer (**48**) is the major isomer, some (*E*, *E*)-isomer (**49**) has also been found (<90JCS(P2)1859>).

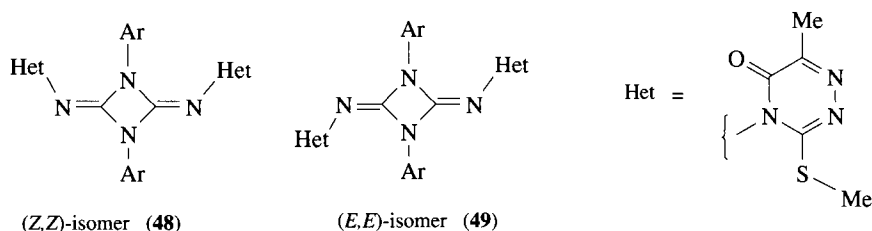
In several cases, the conformational barrier measurements were carried out by ^1H NMR. Three types of conformational changes have been discussed as possible sources for coalescence phenomena observed in such systems: (i) nitrogen inversion; (ii) rotation about the amide bond; (iii) ring flexion. Studies have been reported for each kind of conformational change.

Table 7 ^1H NMR data for 1,2- and 1,3-diazetidine derivatives.

Compound	Chemical shift (δ) and coupling constant (Hz)					Ref.
	5.25 (q, $J = 13$ Hz, H_1) 4.54 (q, $J = 13$ Hz, H_2)					67TL161
	4.18 (q, $\text{CH}_A \text{H}_B$) 3.45 (s, OCH_3) 1.15 (t, OCH_3)					73JOC1605
	4.20 (dd, $J_{AB} = 10.5$ Hz, $J_{AX} = J_{BX} = 7$ Hz, H_B) 4.38 (dd, $J_{AB} = 10.5$ Hz, $J_{AX} = J_{BX} = 7$ Hz, H_A) 3.72 (dd, $J_{AB} = 10.0$ Hz, $J_{AX} = J_{BX} = 7$ Hz, H_A) 3.60 (dd, $J_{AB} = 10.0$ Hz, $J_{AX} = J_{BX} = 7$ Hz, H_B) 1.38 ($J_{AX} = J_{BX} = 7$ Hz, CH_{X3}) 1.11 ($J_{AX} = J_{BX} = 7$ Hz, CH_{X3}) 4.05 (s, OMe) 3.35 (s, OMe) 3.32 (s, OMe) 3.17 (s, OMe)					72CB2437
	4.57–5.48 (H)					87JCS(P1)899
	R = H 5.40 (s, CH_2) R = <i>t</i> -Bu 5.36, 5.28					81JA7743 83JOC4567
	R ¹ = R ² = Ph 4.00 (q, $J = 2.54, 14.0$ Hz)					84CC863
	$\Delta G_N^{100} = 18.6 \text{ kcal mol}^{-1}$ $K = 19.7 \text{ S}^{-1}$ R ¹ = R ² = <i>i</i> -Pr 4.10 (at -20°C) (q, $J = 14.0, 31.0$ Hz) $\Delta G_N^{32} = 15.11 \text{ kcal mol}^{-1}$ $K = 102.6 \text{ S}^{-1}$					
	R ¹ = R ³ = CH_3 , R ² = H, R ⁴ = Ph R ¹ = <i>n</i> -C ₇ H ₁₅ , R ² = H, R ³ = R ⁴ = CH_3					90OM762
	4.20 (t, CH), 2.75 (s, R ³ = R ⁴ = CH_3)					
	H_A	H_X	R ¹	R ²	R ³	
1. R ¹ = H; R ² = Me; R ³ = OMe	4.43 (q, $J_{AB} = 9.5$ Hz)	5.23 (q, $J_{AX} = 6.0$ Hz)	4.01 (q, $J_{BX} = 4.0$ Hz)	3.49(s)	3.83(s), 3.81(s)	
2. R ¹ = H; R ² = Et; R ³ = OEt		5.2 (q, $J_{AX} = 6.0$ Hz)		1.22 (t, $J_{BX} = 4.0$ Hz)	4.18(q), 1.26(t)	
3. R ¹ = H; R ² = Et; R ³ = OMe	4.45 (q, $J_{AB} = 9.5$ Hz)	5.33 (q, $J_{AX} = 6.0$ Hz)	4.05 (q, $J_{BX} = 4.0$ Hz)	3.8(m)	3.83(s), 3.81(s)	
4. R ¹ = D; R ² = Et; R ³ = OMe	4.45 (d, $J_{AX} = 6.0$ Hz)	5.38 (d, $J_{AX} = 6.0$ Hz)		1.27(t) 3.8(m) 1.26(t)	3.83(s), 3.81(s)	
5. R ¹ = OMe; R ² = Me; R ³ = OMe	5.22(s)		3.5(s)		3.54(s) 70JOC1155	

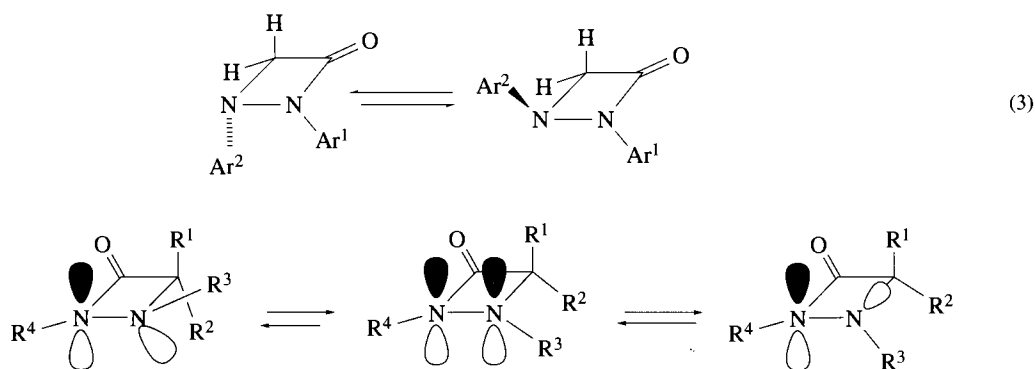
Table 7 Continued.

Compound	Chemical shift (δ) and coupling constant (Hz)			Ref.
	H_X	H_A	H_B	
1. R = Et	5.48 ($J_{AB} = 9.1$ Hz)	4.62 ($J_{AX} = 8.2$ Hz)	4.03 ($J_{BX} = 6.0$ Hz)	
2. R = Ph	5.51 ($J_{AB} = 9.2$ Hz)	4.50 ($J_{AX} = 8.1$ Hz)	3.48 ($J_{BX} = 5.7$ Hz)	
3. R = <i>p</i> -chlorophenyl	5.49 ($J_{AB} = 9.2$ Hz)	4.52 ($J_{AX} = 8.1$ Hz)	3.50 ($J_{BX} = 5.5$ Hz)	



In one of the earliest studies, the free energy of activation of the nitrogen inversion in 1,2-bis(trifluoromethyl)-3,4-tetrafluoro-1,2-diazetidine by ^{19}F NMR analysis was measured to be $7.25 \text{ kcal mol}^{-1}$ (30.3 kJ mol^{-1}). In the case of 1,2-diaryl-1,2-diazetidin-3-one (**41**) in which the amide group is planar, the sharp singlet at 35°C for methylene protons underwent signal splitting of AB type at -50°C with 13 Hz coupling constant $\langle 67\text{TL161} \rangle$.

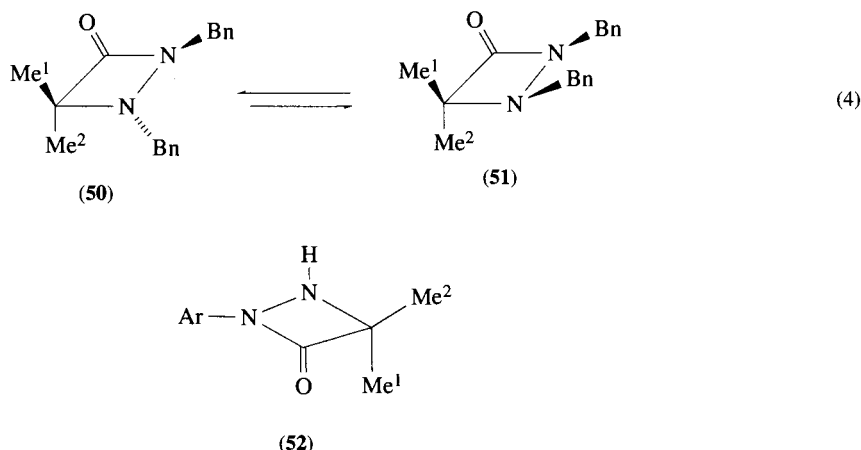
Calculation of $\Delta G^\ddagger$ for inversion at the N^1 center measurement by NMR gave a value of $12.8 \pm 0.3 \text{ kcal mol}^{-1}$ ($53.6 \pm 1.3 \text{ kJ mol}^{-1}$). Similar studies on a number of *N,N*-diaryl or dibenzylsubstituted 1,2-diazetidine-3-one (Equation (3)) have been reported by Fahr *et al.*, and the effect of substituents at C-4 position on the free energy of activation (ΔG) for inversion at nitrogen have been examined. It has been found that the change of substituents at N^1 does not have considerable effect on the free energy of activation ($\Delta G^\ddagger$) of inversion. However, slightly higher (17 kcal mol^{-1} (71 kJ mol^{-1})) values were observed for *N*-benzyl compounds than for *N*-aryl compounds ($14\text{--}15 \text{ kcal mol}^{-1}$ ($59\text{--}63 \text{ kJ mol}^{-1}$)) presumably due to disruption of delocalization of electrons on nitrogen and aryl substituents. Interestingly, the rate of inversion in the case of 1,2-diazetidines was considerably slower than for the analogous azetidines. This has been attributed to the repulsion between the two neighboring nitrogen lone pairs of electrons in the transition state, or to the inductive effects of the adjacent heteroatoms (Scheme 2) $\langle 70\text{TL3605} \rangle$.



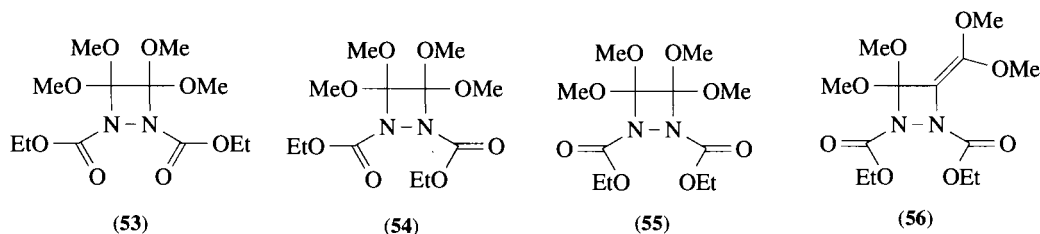
Scheme 2

In the case of 4,4-dimethyl-1,2-dibenzyl-1,2-diazetidine-3-one (**50**) which has an N^1 inversion barrier around $17 \pm 0.2 \text{ kcal mol}^{-1}$ ($71 \pm 0.8 \text{ kJ mol}^{-1}$) $\langle 70\text{TL3605} \rangle$ at 48°C , separate signals for the diastereotopic Me^1 and Me^2 were observed at a lower temperature (-55°C) because of the suppression of inversion at N^1 center. A further splitting of Me^1 ($\delta = 1.15$ and 1.23) and Me^2 ($\delta = 1.40$

and 1.43) signals were observed in the presence of optically active (2*R*,3*R*)-O²,O³-dibenzoyltartaric acid arising from the formation of a diastereomeric association complex <73AG(E)583> between (*R*) and (*S*) enantiomers of diazetidine derivatives (see Equation (4)). In a related ¹H NMR study on 4,4-dimethyl-2-aryl-diazetidin-3-one (**52**), the *gem*-dimethyl group at C-4 were shown to be nonequivalent at 40°C, which was attributed to a comparatively slow inversion of the *sp*³ hybridized N-2 atom <87TL6577>.



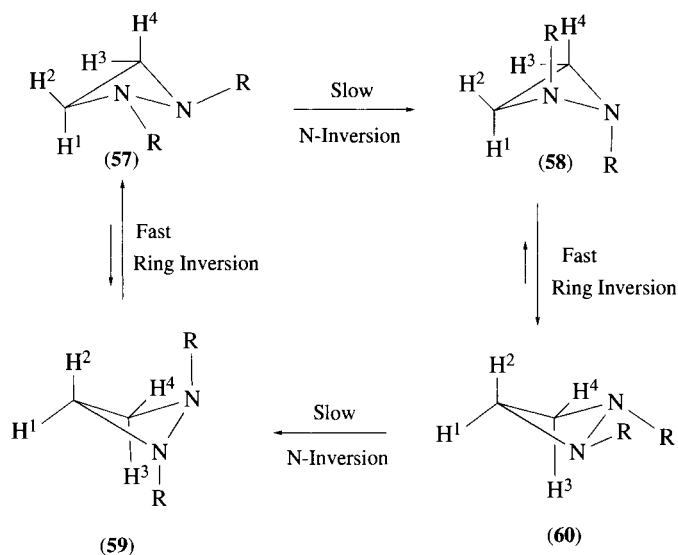
Proton NMR has been used to measure the free energy of the torsional barrier of rotation around the C—N bond. Temperature-dependent studies were carried out to demonstrate the technique in the case of 1,2-bis(ethoxycarbonyl)-3,3,4,4-tetramethoxy-1,2-diazetidine by Raban and co-workers <73JOC1605>. At -65°C , four singlets were observed for the four methoxy groups in acetone-*d*₆-toluene-*d*₈ which coalesce to a singlet when heated to a temperature in the range -40°C to -20°C . This has been attributed to the existence of three isomers at -65°C , (**53**)–(**55**), which undergo rapid interconversion at higher temperatures.



The difference in free energy of formation $\Delta G_{-65^{\circ}\text{C}}((\mathbf{54}) \rightarrow (\mathbf{53})) = 0.3 \text{ kcal mol}^{-1}$ (1.3 kJ mol^{-1}) and $\Delta G_{-65^{\circ}\text{C}}((\mathbf{54}) \rightarrow (\mathbf{55})) = 0.5 \text{ kcal mol}^{-1}$ (2.1 kJ mol^{-1}). The free energy of activation at -27°C was calculated to be $13.6 \text{ kcal mol}^{-1}$ (56.9 kJ mol^{-1}). The torsional barrier was obtained at the coalescence point in acetone-*d*₆ using $K_c = (\pi/1.414)\Delta\nu$; $T_c = -25^{\circ}\text{C}$; $\Delta\nu = 3 \text{ Hz}$, $\Delta G_c^{\ddagger} = 13.8 \text{ kcal mol}^{-1}$ (57.8 kJ mol^{-1}). It is important to point out here that this value of ΔG of activation can be ascribed to the amide torsional barrier and not to the free energy of activation of inversion at N center which has been found to be accidentally similar ($14\text{--}15 \text{ kcal mol}^{-1}$ ($59\text{--}63 \text{ kJ mol}^{-1}$)) in several 1,2-diaryl-1,2-diazetidin-3-ones <70TL3605>. In the related temperature-dependent NMR studies of diethyl 4,4-dimethoxy-3-dimethoxymethylene-1,2-diazetidin-1,2-dicarboxylate (**56**), the free energy of activation ascribed to the amide torsional barrier was found to be more than 20 kcal mol^{-1} (84 kJ mol^{-1}) and the two methoxy signals at C-3 were found to coalesce at 80°C , whereas the coalescence of the remaining two signals requires heating to 180°C due to methoxy at the C-4 position <72CB2437>.

The ¹H NMR line shape analysis has been used to measure the ring and N inversion of diazetidines <78JOC2785>. Proton NMR of several 1,2-dialkyl-1,2-diazetidines showed large differences in $J_{1,4}$ (8.54 to 10.14) and $J_{2,3}$ (2.76 to 4.61) coupling, suggesting a highly puckered ring conformation. As the bulkiness of alkyl groups on N¹ and N² increases (Me, Et, Prⁱ, Buⁱ), the diazetidine ring flattens, as indicated by a decrease in $J_{1,4}$ and an increase in $J_{2,3}$ coupling values. Temperature dependence studies indicate that the nitrogen inversion is slow relative to the ring inversion and occurs at lower temperatures, the concentration of (**58**) and (**59**) being small because of diaxial interaction, especially

when $R = \text{Me}$, Et , or Pr^i (Scheme 3). On the other hand, when $R = \text{Bu}^t$, (58) and (59) predominate because of alkyl group interaction in (57) and (60) and *t*-butyl groups are diaxial as in (58) or (59). In a di-*t*-butyl compound, the methylene protons exhibit an AA'BB' type splitting pattern even at 72 °C, and coalescence is only observed at 155 °C. Temperature-dependent N-inversion studies indicate the relative rates for Me, Et, Pr^i , and Bu^t to be in the ratios $1:0.75:0.51:0.74 \times 10^{-3}$. The activation parameters (ΔH and ΔS) were calculated. The results indicate a relatively small difference between Me, Et, and Pr^i but very restricted inversion for di-*t*-butyl-1,2-diazetidine, which suggests a ring inversion taking place predominantly during heating. The reactions are summarized in Scheme 3. In several cases of 1,2-diazetidines and bicyclic diazetidines, double inversion at N has been observed <78JA2806>.



Scheme 3

1.30.3.6.2 Carbon-13 NMR

Carbon-13 NMR spectra have been routinely recorded for 1,2- and 1,3-diazetidine derivatives for their spectral assignments. Data for a few diazetidines have been collected in Table 8.

1.30.3.7 Mass Spectrometry

The mass spectra of 1,2-diazetidiones show a typical fragmentation pattern consisting of ketene and azo fragments <86H(24)885>. However, 1,3-diazetidiones with a N—Me group normally gave a $(M^+ - \text{MeNCO})^+$ fragment <90OM762>. Results of high-resolution mass spectral studies on several diazetidines matched the calculated values <84JOC4415, 86JOC1530, 87JOC4107>. Chemical ionization mass spectral studies have been used to confirm the dimeric nature of (29) <84CC863>. 1,3-diazetidiones with methyl groups on either or both nitrogen atoms gave a major fragment at m/e 41 due to the loss of methylisocyanide <90OM762>. The presence of a fragment $[\text{Ar}^2\text{N}=\text{C}=\text{N}-\text{Ar}^2]^+ \cdot$ in the mass spectrum from a structure like (48) has led to an assumption that an equilibrium exists with that of the nonsymmetric structure (61), as in Equation (5) <86JCS(P1)2037>.

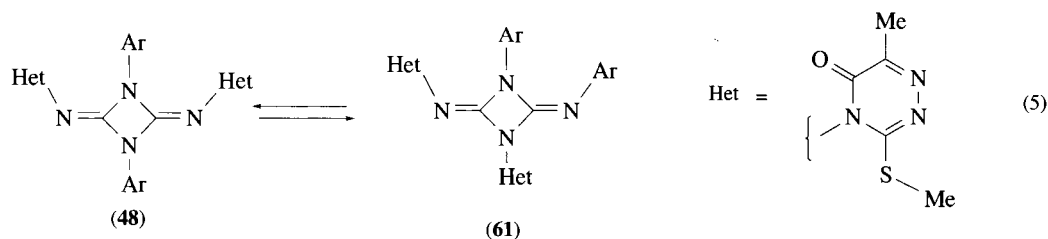
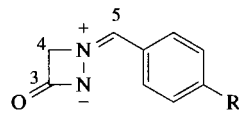
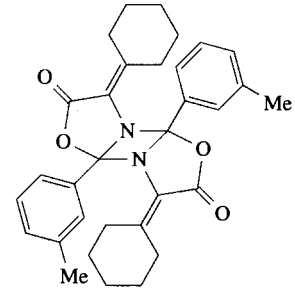
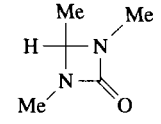
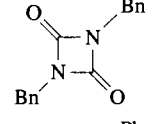
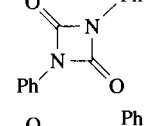
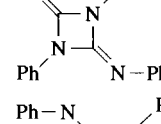
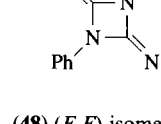
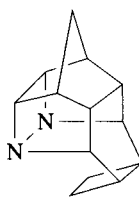


Table 8 Carbon-13 NMR data for some diazetidines.

Compound	Chemical shift (δ)	Ref.
	R = H 171.7(C-3), 74.9(C-4), 142.3(C-5)	72TL4713, 84CC863
	111.8(C-2), 165.3(C-6), 151.4(C-7), 133.5(C-8)	84CC863
	29 (NMe), 76.4(C-4), 160.6(C-2)	90OM762
	156.8(C-2)	
	151.1–151.3(C-2)	
	151.7–153.6(C-2) 140.1–143.1(C-4)	
	144.2–144.6(C-2)	
(48) (<i>E,E</i>)-isomer	155.62(C-2), 123.69(C-5), 126.75(C-6), 114.29(C-7), 159.92(C-8), 55.36(C-9), 148.07(C-10), 153.96(C-11), 157.09(C-12), 17.03(C-13), 14.12(C-14)	
(48) (<i>Z,Z</i>)-isomer	All carbons are magnetically nonequivalent	90JCS(P2)1859

1.30.3.8 Electron Spin Resonance Spectroscopy

The electron spin resonance (ESR) splitting constants for the cations of 1,2-dimethyl and 1,2-diisopropyl diazetidines have been recorded and were compared with cyclic and acyclic hydrazine derivatives <78JA2806>. The ESR spectrum of 3,3,4,4-tetrafluoro- Δ^1 -1,2-diazetidine (**47**) was recorded and compared with acyclic *N,N'*-perfluoroalkylazo compounds. In the radical cation of this heterocycle, the ring seems to be planar or the ring conformations are interconvertible in the ESR scale <70JA2558>. The radical cation of caged diazetidines was generated and was found not to be very long lived. The $\Delta E_0'$ was determined at room temperature by cyclic voltametry to be +13.8 kcal mol⁻¹ (57.8 kJ mol⁻¹). This indicates that (**62**)⁺• is very destabilized compared with the less restricted diazetidine (**35**). This destabilization has been attributed to the incapability of the nitrogen of (**62**)⁺• to flatten very much, due to the caged structure. The nitrogen ESR splitting of (**62**)⁺• is 26.8 G—far larger than for (**35**) (15.0 G). Greater twisting of the radical cation makes the cation lifetime extremely short <79JA1874>.



(62)

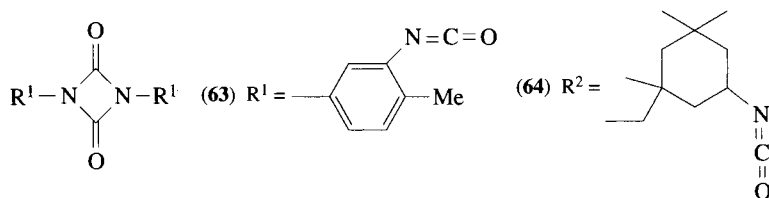
1.30.4 THERMODYNAMIC ASPECTS

1.30.4.1 Physical Properties

1,2- and 1,3-Diazetidines have been found to be mostly solids, except for a few examples where they are in liquid form depending on their substituents. Decomposition has been observed at the melting points of many compounds, especially in the case of 1,3-diazetidines. These compounds are mostly soluble in the usual organic solvents such as ether, chloroform, acetone, etc. However, DMSO has been used to dissolve diazetidinium salts. Diazetidone derivatives are mostly good solids which can be purified by recrystallization. Liquid compounds can be distilled under reduced pressure without decomposition. In a few instances where compounds are obtained as gummy substances, purification is carried out by column chromatography, when recrystallization techniques failed.

1.30.4.2 Chromatography

1,3-Diazetidone-2,4-dione is known to undergo thermal decomposition above 130–150°C. Thus, a 1,3-*N,N*-biaryldiazetidone-2,4-dione (**63**) was subjected to gas chromatographic analysis at 100°C. Only a small amount of impurity eluted after the major product. When the chromatography was carried out at a higher temperature, there was slight decomposition at 150°C, whereas almost complete decomposition occurred at 175°C. The aliphatic 1,3-diazetidone-2,4-diones (**64**) were found to be more unstable, and when they were chromatographed at 50–100°C several peaks were observed <89JC175>.



1.30.4.3 Stability and Heat of Formation, Combustion, and Vaporization

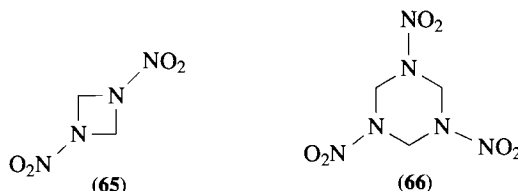
The heat of formation is expressed as:

$$\Delta H_f^\circ = \Delta H_{\text{bond}} + \Delta H_{\text{str}} + \Delta H_{\text{steric}} + \Delta H_{\text{thermo}}$$

where ΔH_{bond} = sum of bond energy contribution, ΔH_{str} = sum of structural energy contribution, ΔH_{steric} = steric energy calculated by program, and ΔH_{thermo} = partition function contribution.

For 3,3,4,4-tetramethyl- Δ^1 -diazetidines (**38**), the experimental and calculated $\Delta H_f^\circ(\text{g})$ and the differences between the experimental and MOMB values were determined. It was found that the calculated MOMB results (36.32 kcal mol⁻¹ (152.0 kJ mol⁻¹)) are in excellent agreement with the experimentally observed value (35.92 kcal mol⁻¹ (150.4 kJ mol⁻¹)). The difference in the ΔH_f° value (0.40 kcal mol⁻¹ (1.67 kJ mol⁻¹)) is within the experimental error <88JA7286>. Politzer *et al.* found the strain energy of 1,3-dinitro-1,3-diazetidone (**65**) to be 8.6 kcal mol⁻¹ (36.0 kJ mol⁻¹), which is in good agreement with the HF/3-21G value of 9.5 kcal mol⁻¹ (39.8 kJ mol⁻¹) <94JCP(100)4706>. The ΔH_f° for (**65**) is 6.2 kcal mol⁻¹ (26.0 kJ mol⁻¹) more than RDX (**66**) (1,3,5-trinitro-1,3,5-

triazacyclohexane), which reflects the strain in the four-membered ring. It is noteworthy that the value of heat of formation of (65) is 351 cal g^{-1} (1469 kJ kg^{-1})—about 70% higher than that of (66), which is 206 cal g^{-1} (862 kJ kg^{-1}); this is the key determinant of the detonation and propellant properties of the energetic materials <68JCP(48)23>. Measurements were also made of the enthalpies of combustion and vaporization for (38); there were found to be $21.04 \pm 0.64 \text{ kcal mol}^{-1}$ ($88.07 \pm 2.68 \text{ kJ mol}^{-1}$) (crystals) and $35.92 \pm 0.69 \text{ kcal mol}^{-1}$ ($150.36 \pm 2.89 \text{ kJ mol}^{-1}$) (gas) <78JCED129>. In the case of 1,3-diazetidine and 1,3-dinitro-1,3-diazetidine, ΔE_{act} (activation energy) and ΔE (dissociation energy) were calculated for the decomposition to methyleneimine and the corresponding nitromethyleneimine, using a local density functional (LDF) method <91JCP(94)1668>.



Vibrational analysis has been used to identify the normal modes that in the extreme limits would correspond to bond rupture and molecular decomposition. The energy requirement for ring fragmentation and N—N bond breaking were computed. It is proposed that N—N bond breaking may be of primary importance for the stability of (65) <90TCA359>. Similar observations have been reported in the case of photodimer (29) of 2-phenylbenzoxazole, which decomposes on heating. The activation energy for the decomposition of dimer was found to be $89.9 \pm 6.3 \text{ kJ mol}^{-1}$ <83JOC3736>. Nangia calculated the heat of formation (H_f) and atomic energies (q) for a number of 1,3-diazetidines and suggested that bicyclic 1,3-diazetidines should be stable enough and may act as β -lactamase inhibitor <91JST(251)237, 93PIA131>.

1.30.4.4 Dipole Moment

No systematic studies on dipole moment have been reported on this class of heterocycles. Theoretical calculation in certain tetrazacubane and 1,3-dimethyl-1,3-diazete indicated the dipole moment to be 0.0 debye <92JST(256)17>.

1.30.4.5 Aromaticity

According to the Hückel $(4n + 2)/(4n)$ rule, four-membered ring compounds should be aromatic with 2 or 6 π -electrons, and antiaromatic with $4n$ -electrons. Despite these predictions, a few four-membered rings with 6π systems are known. The instability of 6π electron, four-membered systems has been attributed to large 1,3-repulsive interactions in the π system <85JOC5869>. The repulsive interactions in the structures of 1,3-diazetidine, 1,2-diazetidine and related systems are less and might be expected to be favorable.

Based on MO calculations, the details of electron density distributions in these molecules were analysed. The 1,2-diazetidines have completely localized C=C bonds and normal C—N and N—N single bonds. The conrotatory ring opening to α -diimine is highly exothermic and has lower activation energies than a similar conversion of cyclobutane to butadiene. Theoretical calculations have shown that the reversible disrotatory cyclization of α -diimine to diazacyclobutane is unlikely to occur even though very similar and well documented closure of butadiene to cyclobutene is known <77JA1949>. In the case of 1,3-diazetidines, there are two possible electronic configurations differing in the occupation numbers of the π -orbitals π_1 – π_4 . The aromatic occupation $\pi_1^2, \pi_2^2, \pi_3^2$ produces a nearly square structure, but these show no evidence of strong C—N π -bonding. For diazetidines, the ring opening has considerable activation energy, hence 1,3-diazetidines, although highly reactive and nonaromatic are experimentally possible to synthesize. The other configuration is $\pi_1^2, \pi_2^2, \pi_4^2$ which produces highly strained diazabicyclobutanes with unusually short C—C bonds, and appreciable π -complex character <87JA6290, 90JA4155>. The aromatic character was recently measured in terms of absolute hardness and relative hardness <89JA7371>. The value of HOMO – LUMO is taken as a good measure of aromaticity, and this is correlated with absolute hardness. Based on these values, relative hardness of 1,3-diazetidines has been reported. Jug has established a correlation between the

magnetic ring current and the weakest bond in the ring. The weakest bond was characterized by its bond order, for example in diazetidine, the bond order is 1.395—i.e., moderately aromatic—and the compound has nonplanar C_{2v} symmetry. The C—C bond order is -0.42 , and N—N bond order is -0.29 . Higher bond order is considered as highly aromatic, whereas bond order less than 1.15 is considered antiaromatic <84JOC4475>.

1.30.4.6 Conformational Studies

A number of studies have been reported for the conformational analysis of 1,2- and 1,3-diazetidines and diazete derivatives using IR–Raman (see Section 1.30.3.5), ^1H and ^{13}C NMR (see Section 1.30.3.6) and photoelectron spectroscopy (see Section 1.30.3.4). The conformational changes may take place as a result of inversion at the nitrogen center or due to the flexibility of the ring. In certain cases, various conformational isomers were also observed which arose from N—CO bond rotation in *N,N*-disubstituted biscarbamates <73JOC1605>. A number of molecular orbital calculations suggest that one conformer predominates over the others. Catalán and co-workers have carried out an *ab initio* calculation at the 4-31G level to study the structure and stability of the possible conformers of 1,3-diazetidines. They have found two stable forms: an equatorial–equatorial (*E,E*) form with a puckered conformation, and an equatorial–axial (*E,A*) form which is planar. A nitrogen inversion barrier of $4.1 \text{ kcal mol}^{-1}$ (17.2 kJ mol^{-1}) <84JST(106)251> possibly connects these two stable forms. The variation in the ring puckering is supposed to be of a topological character rather than an electronic one. Further studies using an INDO method predict that in 1,3-diazetidines, the nitrogen inversion barrier connecting both the *E,E* and *E,A* forms is of the order of $6.5 \text{ kcal mol}^{-1}$ (27.2 kJ mol^{-1}). At the semiempirical level, the *E,E* form has been found to be more stable by $1.2 \text{ kcal mol}^{-1}$ (5.0 kJ mol^{-1}) <84JST(107)269>. The population analysis of the conformers was feasible by ^1H NMR (see Section 1.30.3.6) studies at different temperatures. Conformational changes arising from *cis*–*trans* isomerization in 1,3-diazetidines-2,4-diones have also been observed <90JCS(P2)1859>.

1.30.5 REACTIVITY

Four-membered heterocycles with two nitrogen atoms are expected to show two different kinds of reactivity: one arising from the ring strain and the other from the presence of heteroatoms. In many respects, the chemistry of diazetidines and related systems resemble their closest cousins—the β -lactams, which at present are the best studied four-membered heterocycles (Chapter 1.20). The general electrophilic reagents are expected to attack on nitrogen. Several theoretical calculations have explained the reactivity of the ring towards the nucleophilic, electrophilic, and radical reactions. The quaternary inner salt shows greater reactivity towards the nucleophiles. The reactivities of several diazetidines and diazetes are summarized in the following sections.

1.30.5.1 Reactivity of Fully Conjugated Rings

The reactivity of 1,2- and 1,3-diazetes and their derivatives falls under the class of fully conjugated ring systems. Although sporadic interest has been generated by theoretical calculations, it has not been possible to prepare this class of compounds. Because of their high energy, as shown by HF/6-31G* theoretical calculations, neither 1,2-diazetes (total energy = -185.62430 a.u. ; relative energy = $79.12 \text{ kcal mol}^{-1}$ ($331.2 \text{ kJ mol}^{-1}$); see Table 2) nor 1,3-diazetes (total energy = -185.65532 a.u. ; relative energy = $59.65 \text{ kcal mol}^{-1}$ ($249.7 \text{ kJ mol}^{-1}$); see Table 2) were found to be stable <91JST(236)119>.

1.30.5.2 Reactivity of Nonconjugated Rings

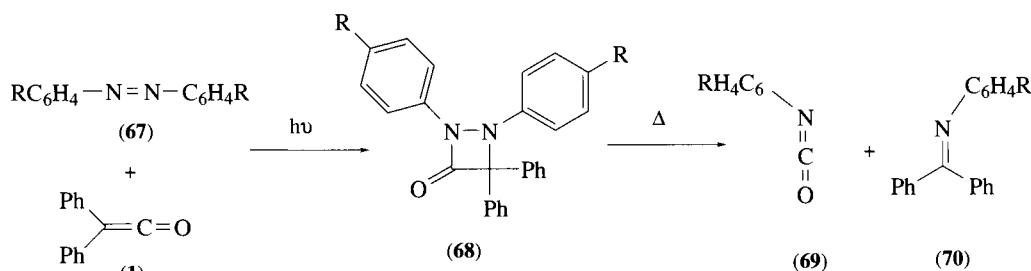
The reactivity of 1,2- and 1,3-diazetidines and their derivatives falls under the class of non-conjugated ring systems.

1.30.5.2.1 Thermal and photochemical transformations

Diazetidines and diazetines undergo facile thermal decomposition by a [2 + 2] cycloreversion pathway either leading back to their parent precursors or to new products. A number of such fragmentation reactions have been compiled by Richter and Ulrich (83HC(42)443).

(i) 1,2-Diazetidine derivatives

Substituted tetraphenyl-1,2-diazetidione (68) has been found to give a mixture of products (69) and (70) resulting from the [2 + 2] cycloreversion upon heating, in addition to a small amount of the azocompound (67) and diphenyl ketene (1), although the diazetidinones (68) were synthesized by irradiating diphenyl ketene (1) with diazocompound (67) (Scheme 4). Table 9 indicates a number of such examples (66JOC1079, 74JOC1215).

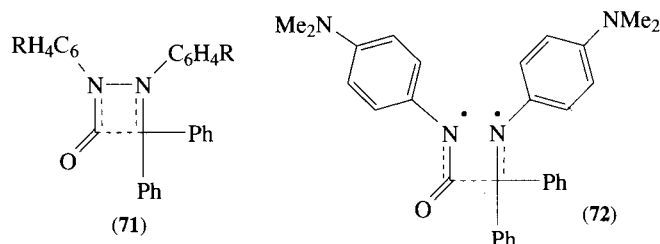


Scheme 4

Table 9 Formation and decomposition of tetrasubstituted 1,2-diazetidiones (Scheme 4).

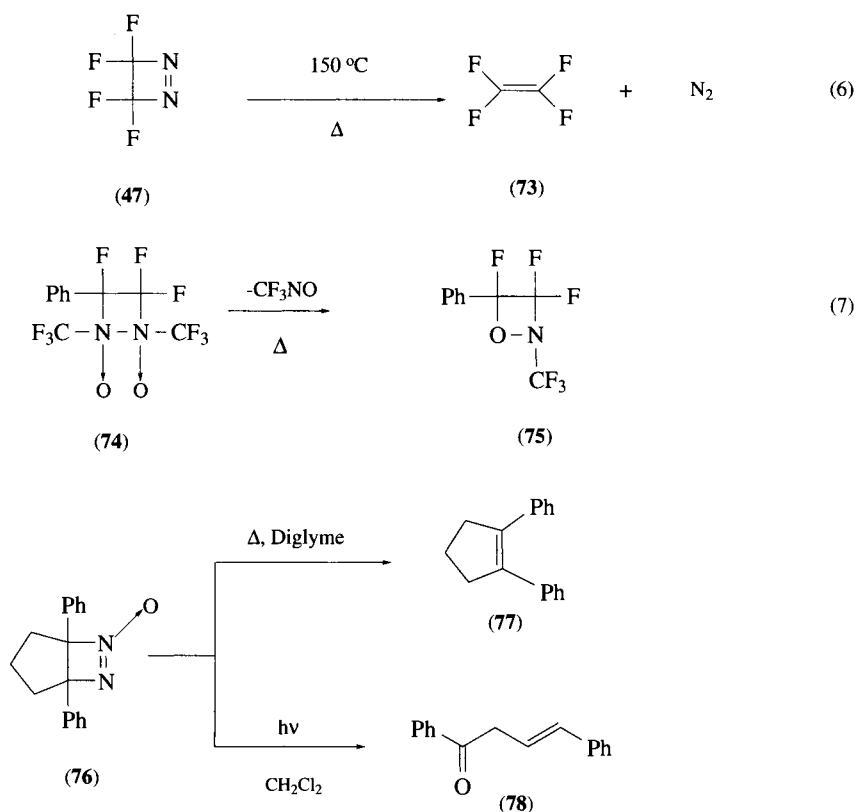
Entry	R	Irradiation time (h)	Solvent	Yield (%)	Decomp. temp. (°C)	Entry	R	Irradiation time (h)	Solvent	Yield (%)	Decomp. temp. (°C)
1	<i>o</i> -Cl	4	Ether	91	139	7	<i>o</i> -OMe	1.5	Benzene	19	133
2	<i>m</i> -Cl	7	Ether	55	177	8	<i>m</i> -OMe	0.3	Benzene	69	160
3	<i>p</i> -Cl	16	Benzene	17		9	<i>p</i> -OMe	8	Ether	71	133
4	<i>o</i> -NO ₂	14	Benzene	20		10	<i>p</i> -COOEt	1.7	Benzene	33	186
5	<i>m</i> -NO ₂	7	Benzene	37	186	11	<i>p</i> -NMe ₂	16	Benzene	0	
6	<i>p</i> -NO ₂	28	Benzene	0		12	H	1.5	Ether	71	165

It has been found that the diazetidinones decompose instantaneously when R is an electron-donating group like NMe₂ (Table 9, entry 11). A transition state (71) resembling the products is normally expected for a concerted decomposition process. Therefore, electron-withdrawing groups should stabilize this transition state. However, electron-donating groups on N-1 and N-2 have been found to accelerate the homolytic cleavage of a relatively weak N—N bond—as in the case of tetraphenyl hydrazines where electron-donating substituents stabilize the imino radicals (72) (41JA3232). Some of the 1,2-diazetidine derivatives are thermally so labile that they instantaneously decompose under the conditions of their formation (Table 9, entries 6,11) (65TL1627, 66JOC1079, 72JHC169, 74JOC1215).



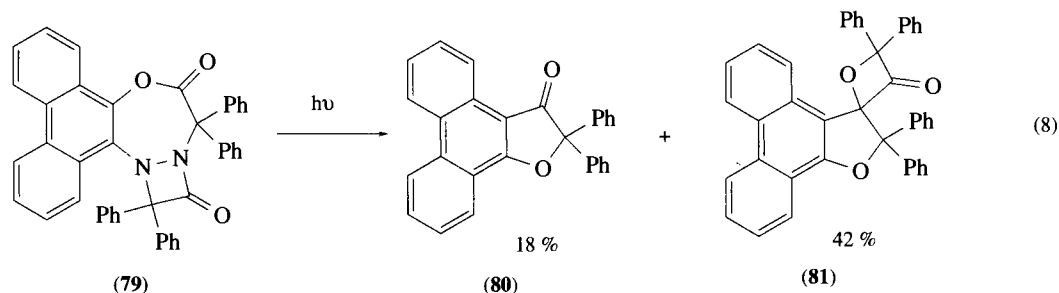
When 3,3,4,4-tetrafluoro- or 3,3,4,4-tetramethyl- Δ^1 -1,2-diazetene (47) was heated above 150°C, tetramethylethylene and tetrafluoroethylene (73) were formed with the extrusion of nitrogen (Equa-

tion (6)) <62JCS3276, 73JCS(F1)1817>. The activation parameters for tetramethyl and tetrafluoro- Δ^1 -1,2-diazetidine are $\Delta H^\ddagger = 132.7 \text{ kJ mol}^{-1}$ and 159 kJ mol^{-1} and $\Delta S^\ddagger = 1.3 \text{ kJ mol}^{-1}$ and 51.8 kJ mol^{-1} , respectively <78JA1876>. However, the thermolysis of 1,2-diazetidino-1,2-dioxide (74) gave rise to an oxazetidine derivative (75) with the loss of trifluoronitroso methane (Equation (7)) <63DOK(152)1104, 65ZOB851>. In certain cases, entirely different products are obtained by thermal and photochemical pathways, for example, 1,4-diphenyl-2,3-diazabicyclo [3.2.0] hept-2-ene-2-oxide (76) upon photolysis gives 1,4-diphenyl-3-buten-1-one (78) whereas, under thermal conditions, it yields 1,2-diphenyl-1-cyclopentene (77) (Scheme 5).

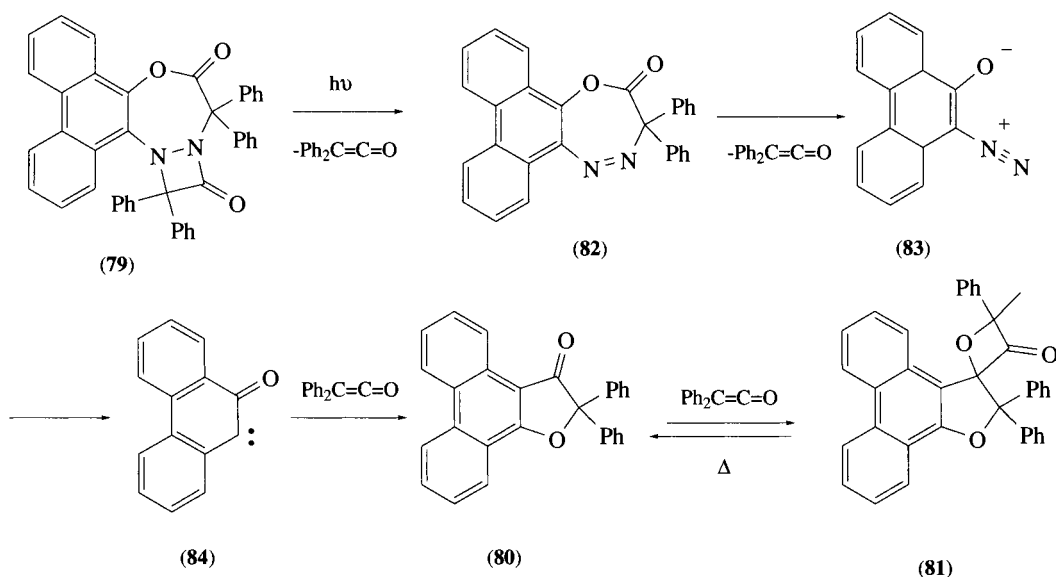


Scheme 5

Lohray and George have reported the photochemical transformations of 2,5-dioxo-1,1,4,4-tetra-phenylphenanthro[9,10-*b*]-diazetidino-[1,2-*d*]perhydro-1,4,5-oxadiazepinone (79) which afforded (80) and (81) upon irradiation in benzene for 8 h (Equation (8)) <90MI 130-01>. One of the plausible pathways (Scheme 6) involves the photofragmentation of (79) with the loss of diphenyl ketene to furnish (82), which in turn can undergo further loss of diphenyl ketene to give (83). The ketocarbene (84) resulting from subsequent loss of nitrogen from (83), upon cycloaddition with diphenyl ketene gives (80). The spiro compound (81) is obtained from the photoaddition of diphenyl ketene to (80).

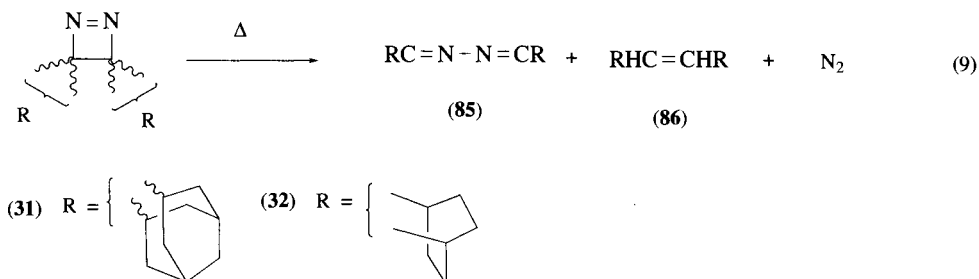


In the early 1990s, elaborate studies on thermal decomposition of Δ^1 -1,2-diazetidine derivatives were reported (Equation (9)) <93JOC5393>. When diazetine (31) was heated at 150 °C, azine (85) and



Scheme 6

alkene (**86**) were formed. Formation of azine has been found to be favored over that of alkene. The ratio of azine to alkene has been found to be solvent and temperature dependent; for example, the ratio of azine versus alkene was found to be 2.9 in THF at 150°C, 2.3 in THF at 185°C, 3.0 in benzene at 150°C, 2.4 in benzene at 185°C, 3.8 in acetonitrile at 150°C, 4.2 in acetonitrile at 185°C, 9.5 in EtOH at 150°C, and 6.1 in EtOH at 185°C. In the case of diazetine (**32**) the ratio of azine to alkene is 1 : 14 at 137°C in dodecane.



Diazetines (**31**) and (**32**) may undergo thermal decomposition either by C—C bond cleavage or C—N bond cleavage. Interestingly, the $K_{\text{C—C}}/K_{\text{C—N}}$ is about 9/1 at 120°C, ring strain being the cause of central C—C bond cleavage. It has been observed in earlier studies <78JA6760>, that diazetines normally undergo clean *cis* loss of N₂ which is accelerated by the presence of aryl substituents. The relative rate of decomposition and $\Delta G^\ddagger$ varies considerably depending on the substitution pattern (Table 10). However, in the case of diazetidine (**37**) no evidence of C—N bond cleavage is observed. From the condition of decomposition of the compound (**37**) one can estimate the $\Delta G^\ddagger$ at 400°C as 40 kcal mol⁻¹ (167 kJ mol⁻¹), which is ca. 10 kcal mol⁻¹ (42 kJ mol⁻¹) higher than for entry 5 (see Table 10). The vacuum flash pyrolysis of both saturated (entry 5) and unsaturated (entry 6) analogues lead to the formation of corresponding diimine (**87**) which arises through a diradical intermediate (Equation (10)). The symmetry allowed [$\sigma^2s + \sigma^2a$] is a less likely route because of steric requirements <80JA837>.

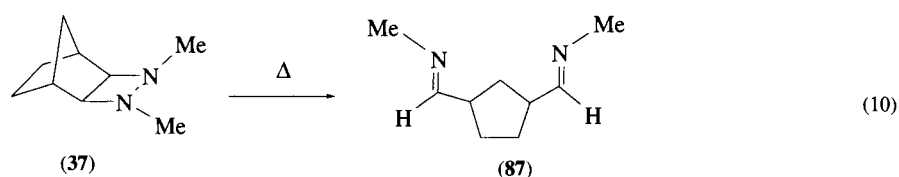
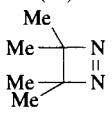
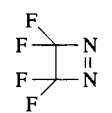
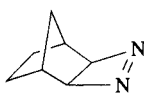
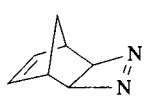
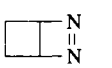
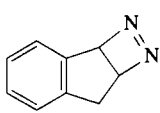
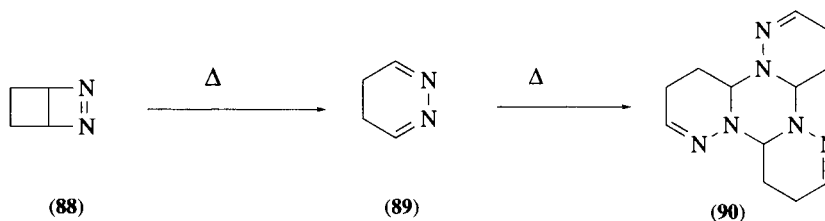


Table 10 Thermal decomposition of 1,2-diazetidines.

Entry	Structure	rel k_{137}	$\Delta G^\ddagger$ (137°C) (kcal mol ⁻¹)	Ref.
1	(31)	1	32.5	93JOC5393
2	(32)	0.03	35.2	93JOC5393
3		3	31.6	78JA1876
4		1	32.5	73JCS(F1)1817
5		0.8	32.7	82JA6836
6		7	30.9	69JA5668
7		3	31.6	80JA7994
8		8×10^5	21.4	80TL3251

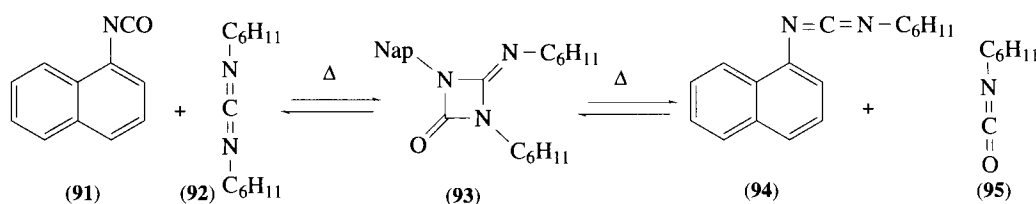
An interesting bicyclic diazetine (**88**) undergoes valence tautomerization to dihydropyridazine (**89**) which subsequently trimerizes to give (**90**) (Scheme 7) <80JA7994>. Some of the thermal reactions followed by rearrangements are outlined in Section 1.30.5.3.3.

**Scheme 7**

(ii) 1,3-Diazetidine derivatives

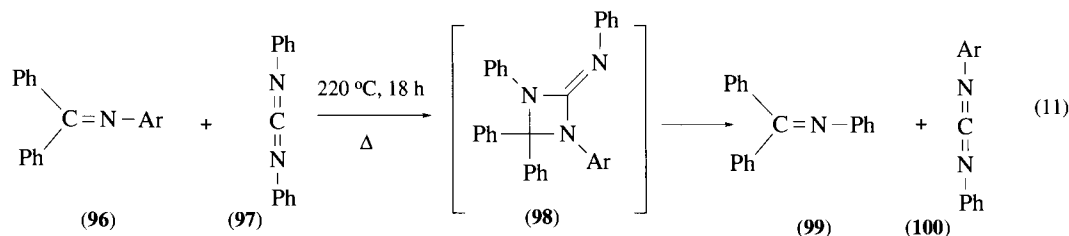
The 1,3-diazetidine derivatives are most commonly synthesized by the dimerization of heterocumulenes. At elevated temperatures, they undergo dissociation and are in equilibrium with their monomers, for example, 1,3-diazetidine (**93**) formed by the reaction of α -naphthyl isocyanate (**91**) with dicyclohexylcarbodiimide (**92**), upon thermal dissociation, furnished an exchanged product of its [2 + 2] cycloreversion reaction—i.e., cyclohexyl isocyanate (**95**)—and α -naphthylcyclohexylcarbodiimide (**94**) (Scheme 8) <62AG(E)621>.

Politzer and co-workers have carried out computational analysis of unimolecular thermal decomposition of 1,3-diazetidine and 1,3-dinitramine derivative <90TCA359>. Vibrational analysis was carried out to identify normal modes that in the extreme limits would correspond to bond rupture and molecular decomposition. It was concluded that ring fragmentation is a probable initial step in the decomposition of the unsubstituted molecule, and it roughly competes with N—N bond



Scheme 8

scission for dinitramine. It is proposed that N—N bond breaking may be of primary importance for nitramine stability. The dissociation of these cycloadducts has been found to be in equilibrium with the fragments. The forward reaction has been found to be of first order while the reverse reaction is of second order <68JOC1913>. Eisch and Dluzniewski have proposed an anil metathesis through the intermediacy of 1,3-diazetidinium ions during the course of their mechanistic investigation of Skraup–Doebner–Miller quinoline synthesis <89JOC1269>. Although 1,3-diazetidine was not isolated in the [2 + 2] cycloaddition reaction of anil (**96**) and diphenyl carbodiimide (**97**), the product distribution clearly indicates the involvement of such an intermediate (Equation (11)) <72JHC169>.



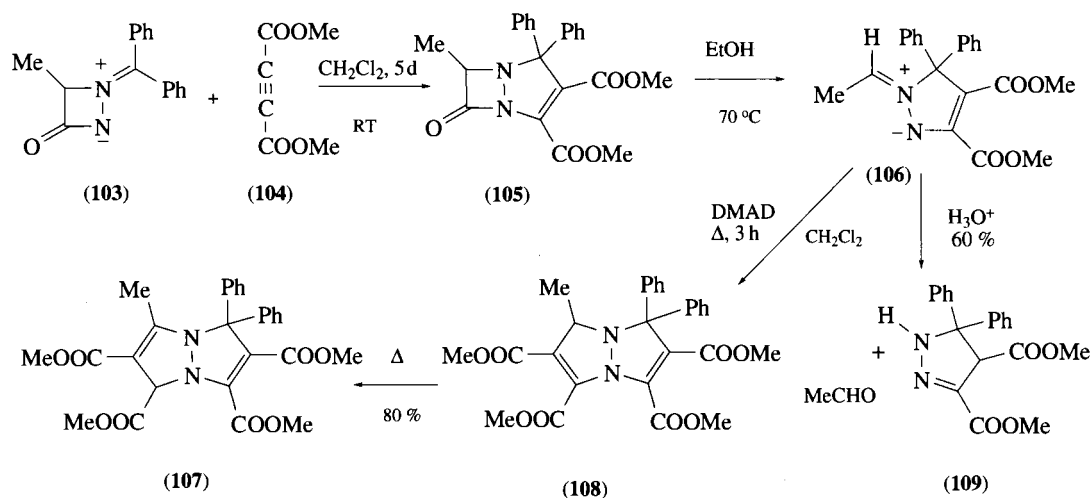
1.30.5.2.2 Cycloaddition reactions

Cyclic azomethine ylides (**101**) are useful intermediates in constructing a variety of heterocycles containing bridgehead nitrogen atoms. The lower homologue (**102**) containing two nitrogen atoms has been shown to be a good 1,3-dipole in cycloaddition reactions <81JA7659, 81JA7660, 81JA7743>.



It has been found that 3-oxo-1,2-diazetidinium ylide (**103**) is unreactive towards several dipolarophiles such as norbornene, methyl propiolate, dimethyl maleate, phenyl isocyanate, and diethylazodicarboxylate. In contrast, reaction with dimethyl acetylenedicarboxylate (DMAD) (**104**) resulted in the formation of a 1:1 cycloadduct (**105**) which isomerized to (**109**) upon melting <81JA7743>. The proposed mechanistic pathway is outlined in Scheme 9. The initial cycloadduct (**105**) gave Δ^2 -pyrazoline (**109**) upon heating at 70°C. A new ylide (**106**) seems to be forming from (**105**) by the loss of a CO molecule. This was confirmed by the reaction of (**106**) with a second equivalent of DMAD which resulted in (**108**) in quantitative yield. Compound (**108**) isomerized to (**107**) during recrystallization.

When the inner salt, 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium hydroxide (**110**) reacted with benzene diazonium-2-carboxylate (**111**) in THF at 40°C, the benzyne adduct (**112**) was obtained in variable yields depending on the substituents (Equation (12)) <91T9599>. The low yield in the case of entry 4 in Table 11, has been found to be due to decomposition during isolation whereas, in the case of entry 6, the product has been found to decompose over a period of time, although it does



Scheme 9

form. The cycloadduct in entry 7 is extremely unstable. On the other hand, the failure in the case of entry 8 has been attributed to its insolubility in THF.

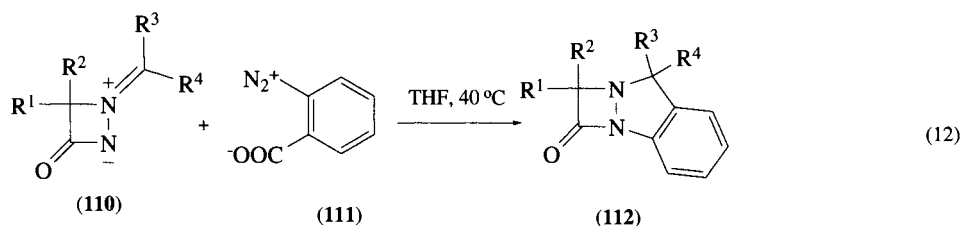
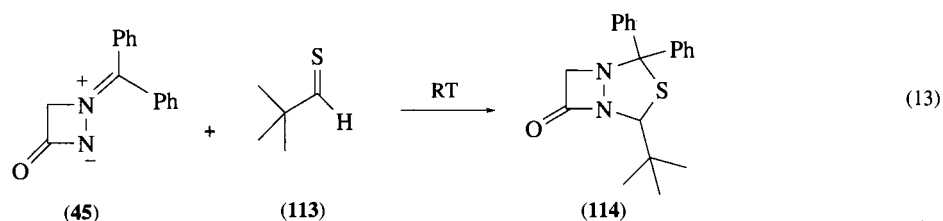


Table 11 Formation of (112) by cycloaddition reaction (Equation (12)).

Entry	R^1	R^2	R^3	R^4	Yield (%)
1	H	H	Ph	Ph	74
2	H	Me	Ph	Ph	55
3	Me	Me	H	Ph	48
4	H	H	$p\text{-ClC}_6\text{H}_4\text{-}$	$p\text{-ClC}_6\text{H}_4\text{-}$	8
5	H	H	$p\text{-MeOC}_6\text{H}_4\text{-}$	$p\text{-MeOC}_6\text{H}_4\text{-}$	51
6	H	Me	H	Styryl	0
7	H	Me	Me	Me	0
8	H	H	H	$p\text{-MeOC}_6\text{H}_4\text{-}$	0

The diazetidione dipole (45) undergoes [2 + 3] dipolar cycloaddition with thiopivalaldehyde (113) to afford the corresponding adduct (114) (Equation (13)). The adduct (114) has been found to be a mixture of two diastereomers at pyramidal nitrogen which interconvert slowly on NMR time scale but too rapidly to allow separation [86JOC117].

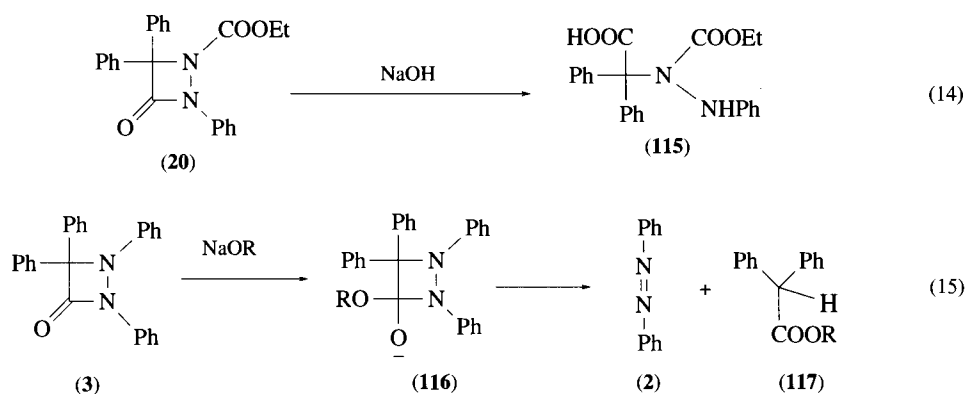


1.30.5.3 Reactivity of Substituents Attached to Ring Carbon Atoms

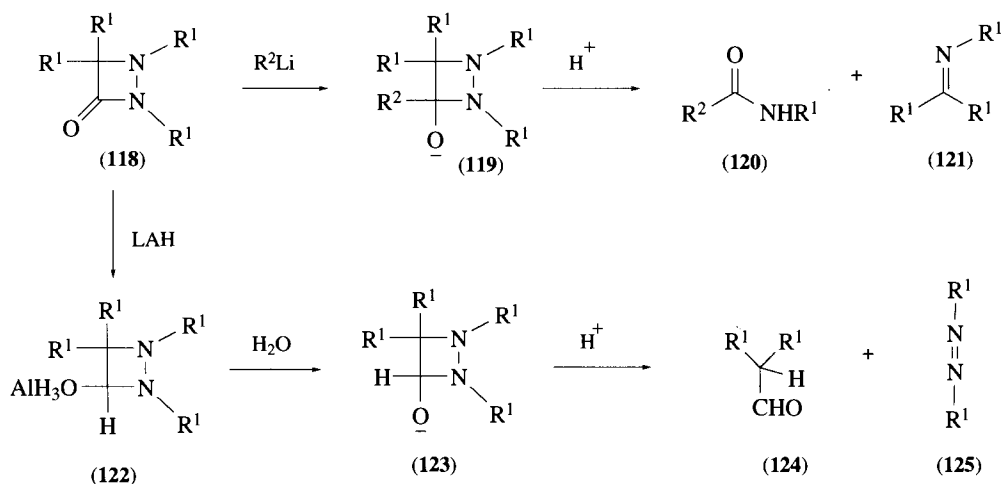
The reactions follow their normal course in most of the cases on the substituents attached to the ring carbon atoms.

1.30.5.3.1 1,2-Diazetidine derivatives

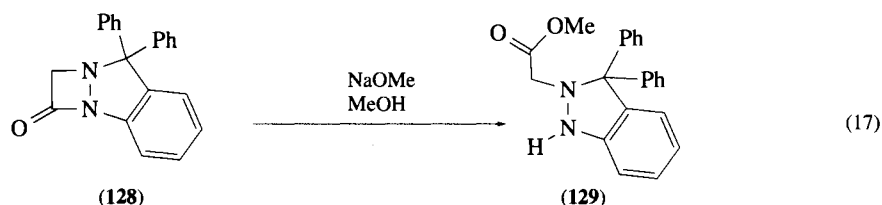
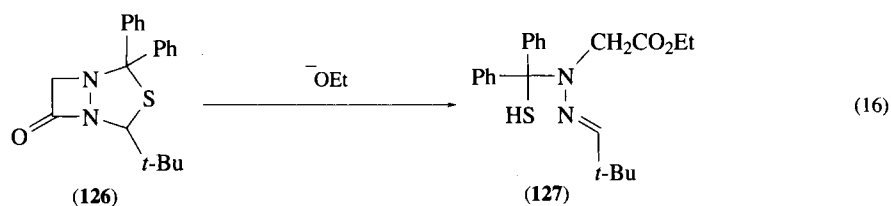
The carbonyl group of the 1,2-diazetidinones resembles in reactivity that of the β -lactam carbonyl group. The four-membered ring opens up when a nucleophile attacks the carbonyl group <83HC(42)443>. For example, the cyclic amide N—CO bond cleavage takes place in the case of ethyl 2,4,4-triphenyl-1,2-diazetidin-3-one-1-carboxylate (**20**) when treated with dilute ethanolic sodium hydroxide to afford hydrazinodiphenyl acetic acid derivative (**115**) (Equation (14)) <63JCS674>. In contrast, 1,2,4,4-tetraphenyl-1,2-diazetidinone (**3**) is attacked by sodium hydroxide only upon prolonged heating to give diphenylacetic acid (**117**) and azobenzene (**2**) (Equation (15)) <56CB2765>. However, the same products are obtained in good yield when refluxed with sodium alkoxides <64JOC3188>.



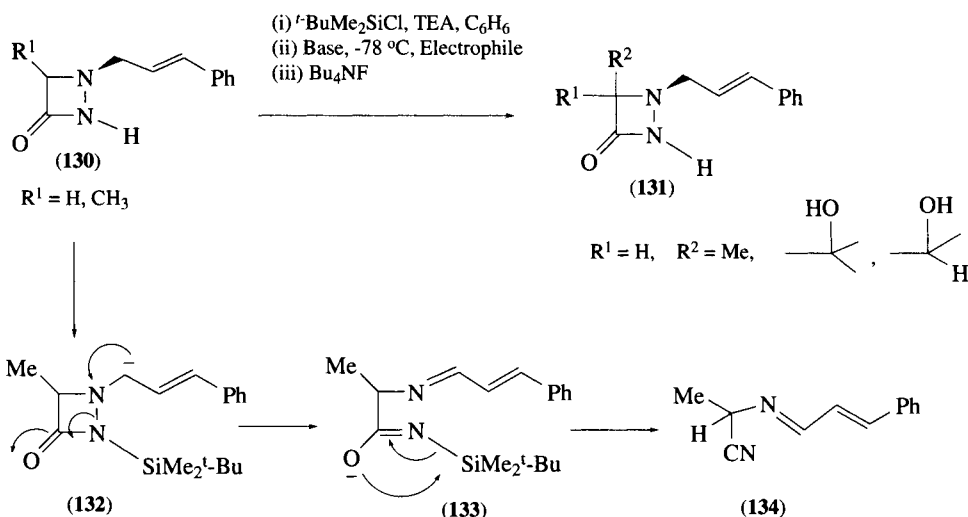
When (**3**) is treated with MeLi or PhLi, addition of organolithium on the C=O bond takes place which finally undergoes ring rupture to furnish amide (**120**) and imine (**121**). On the other hand, diazetidinone, upon LAH reduction, although it seems to proceed through a similar intermediate, furnished a different set of products: namely, an aldehyde (**124**) and diazocompound (**125**) (Scheme 10) <64JOC3188>. Ring cleavage was also observed when the bicyclic diazetidinone (**126**) or tricyclic fused diazetidinone (**128**) were treated with ethoxide ion (Equations (16) and (17)) <86JOC117, 91T9599>.



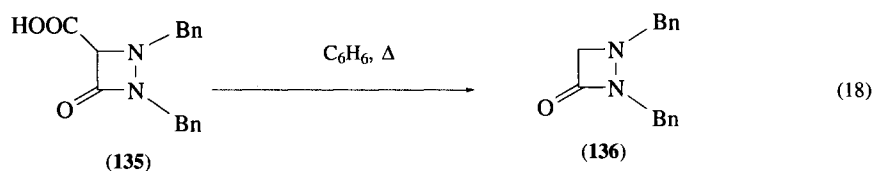
Scheme 10



1,2-Diazetidinones undergo several reactions analogous to those of β -lactams [83TL1403]. Thus, the *N*-silylated 1,2-diazetidinones obtained from (130) when treated with a base followed by electrophiles like MeI, acetaldehyde, or acetone, furnished 3-substituted 1,2-diazetidinone (131). In the case of 3-methyl 1,2-diazetidinone (132), treatment with a base leads to N—N bond cleavage which undergoes rearrangement to give a nitrile (134) (Scheme 11) [84JOC4415]. 3-Carboxyl-substituted 1,2-diazetidinone (135) undergoes a facile decarboxylation on heating, furnishing a nearly quantitative yield of 3-unsubstituted 1,2-diazetidinone (136) (Equation (18)) [84CC754].



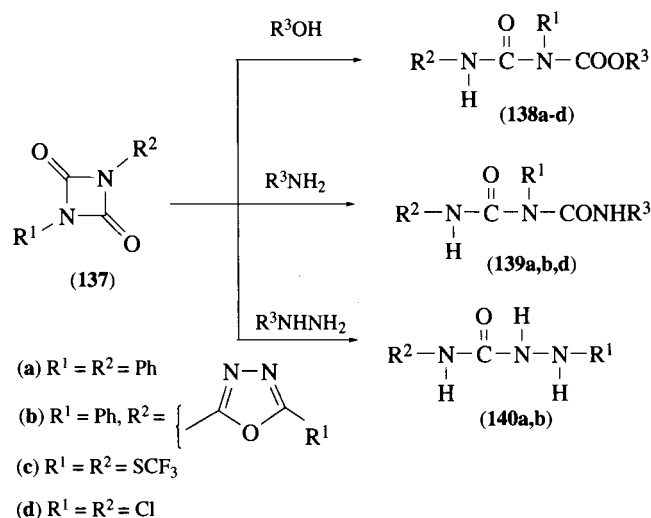
Scheme 11



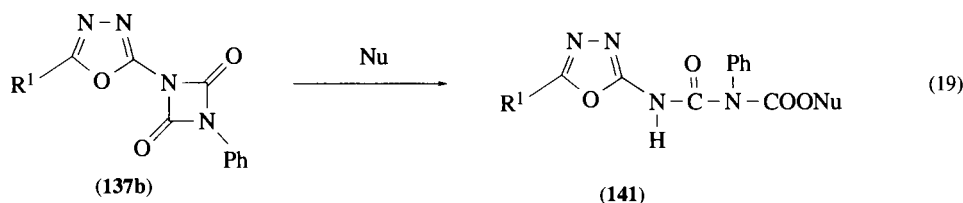
1.30.5.3.2 1,3-Diazetidine derivatives

The most common member of this class of compound is 1,3-diazetidin-2,4-dione. Diazetidin-2,4-diones readily react with a variety of oxygen and nitrogen nucleophiles, leading to the ring-opening products as shown in Scheme 12. The ring opening preferentially takes place from the side of the bulkier substituent, for example, 1,3-diphenyl-1,3-diazetidin-2,4-dione (137a) reacts with R^3OH , R^3NH_2 , or R^3NHNH_2 to furnish ester, amide and hydrazide, respectively [83HC(42)443]. In the case

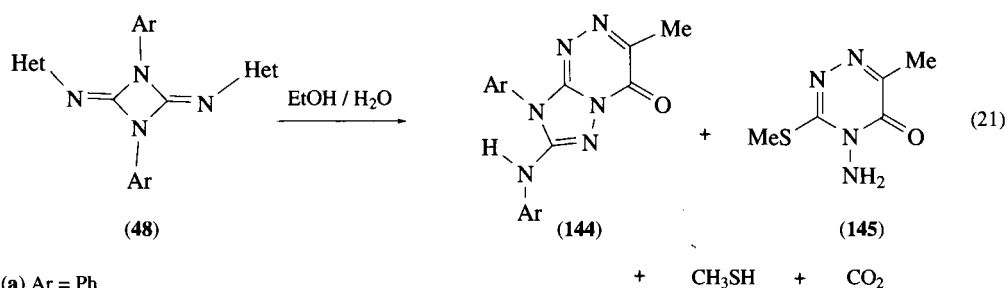
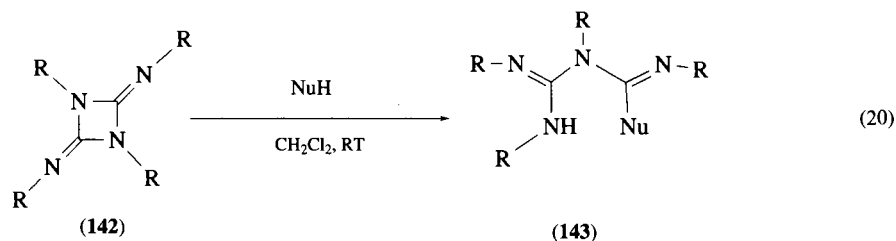
of unsymmetrically substituted 1,3-diazetidines (137b), nucleophiles are found to open up the heterocycles at the N—C bond having a bulkier substituent (Equation (19)) <66LA(692)151, 72JHC459>.



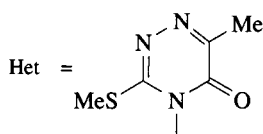
Scheme 12

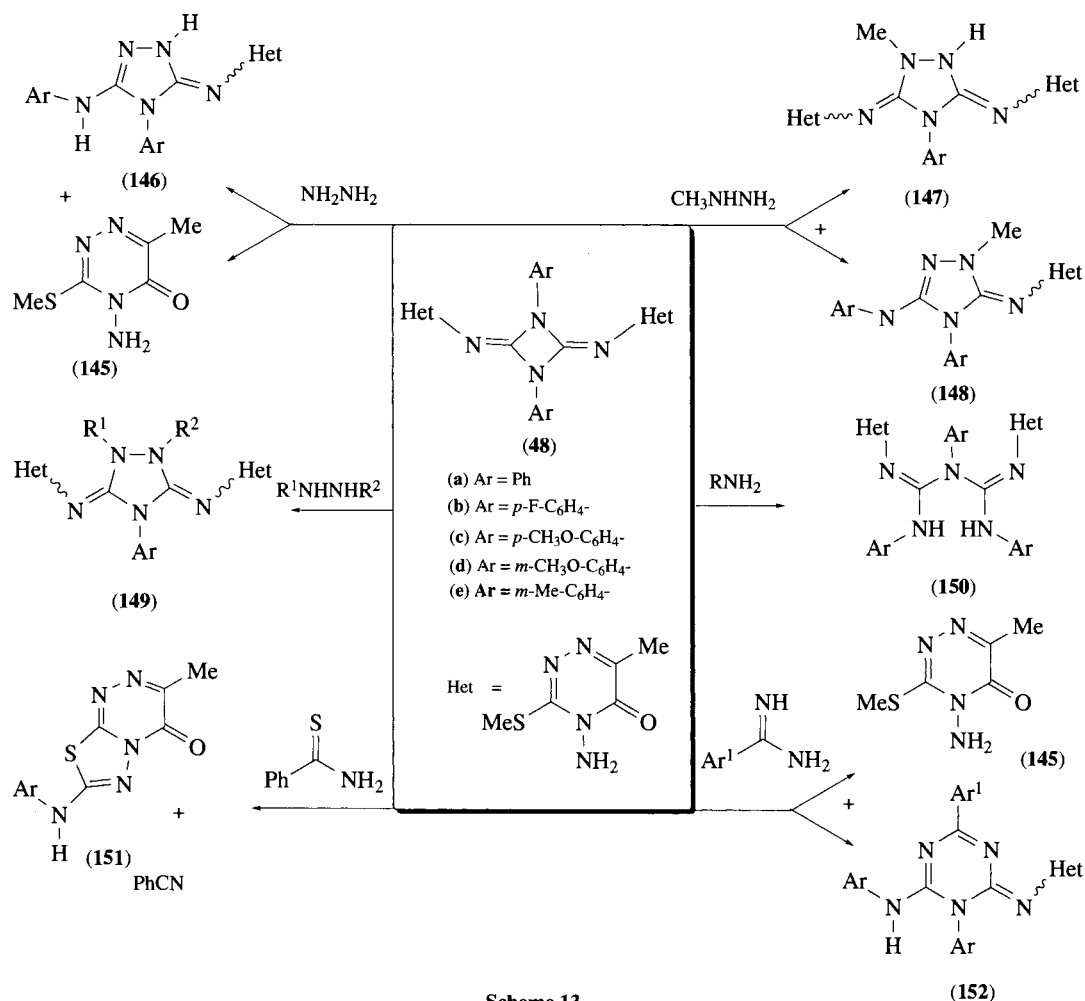


The reactivity of 2,4-diimino-1,3-diazetidines (142) has been extensively studied and reviewed by Molina and co-workers <93JPR305>. The electrophilic carbon center has been found to be readily attacked by nucleophiles, leading to ring-opening products (Equation (20)). 2,4-Diimino-diazetidines (48) yields (144) and (145) when treated with aqueous ethanol (Equation (21)). The reactions of other nucleophiles are summarized in Scheme 13 <86JCS(P1)2037, 87T791, 88S150, 89JCR(S)140, 89JOC1264>.



- (a) Ar = Ph
 (b) Ar = *p*-FC₆H₄
 (c) Ar = *p*-CH₃OC₆H₄
 (d) Ar = *m*-CH₃OC₆H₄
 (e) Ar = *m*-CH₃C₆H₄





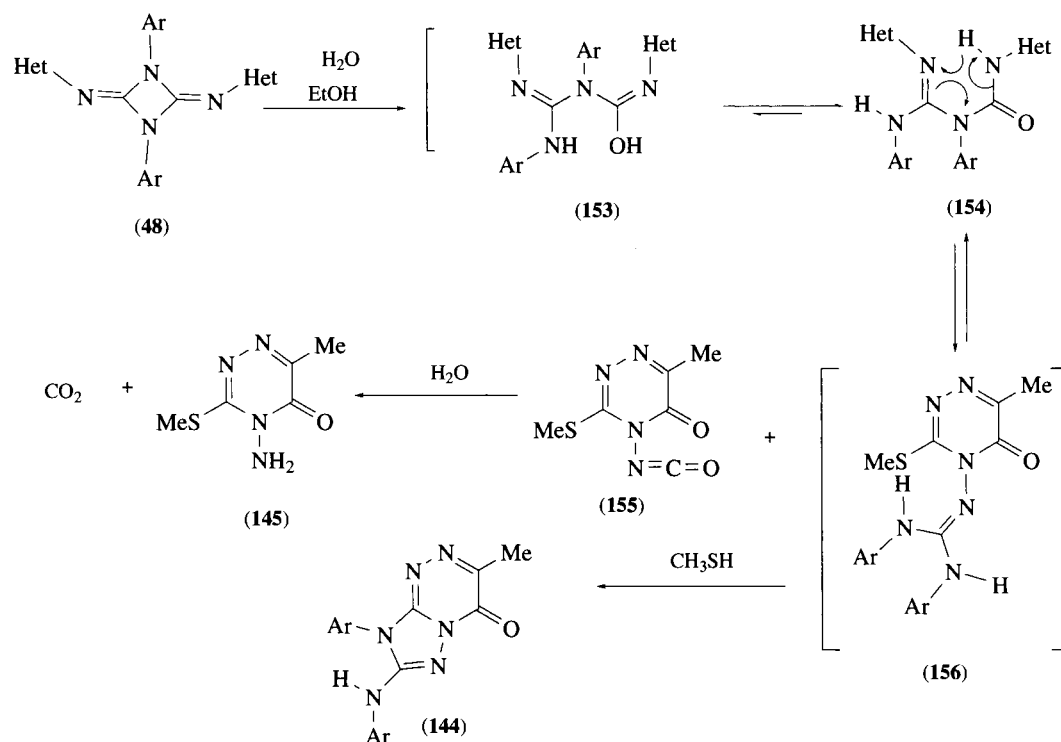
Scheme 13

The mechanism of reaction of (48) with nucleophiles is depicted in Scheme 14. The reaction of *N,N'*-substituted hydrazine gave an entirely different set of products, which has been rationalized in terms of the pathway shown in Scheme 15.

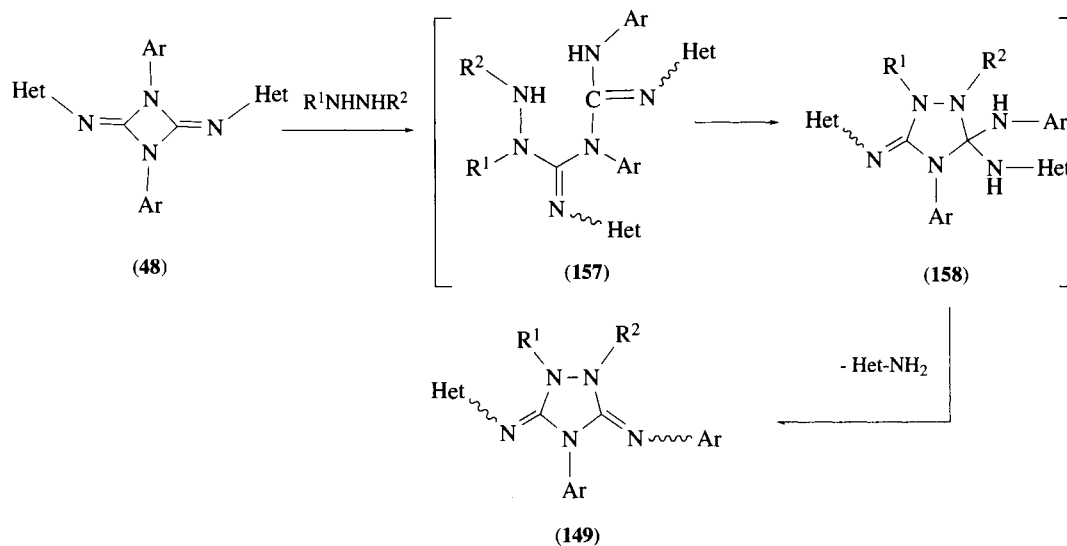
Fused diazetidines (159), when treated with methanolic KOH, gives pyrazole 1,3-diazepine (160) at room temperature by opening of the diazetidine ring. In contrast, methyl amine which initially reacts to give a ring rupture intermediate (161) undergoes rapid cyclization to imidazole derivative (162) (Scheme 16).

1.30.5.3.3 Reactions involving rearrangements

Several reactions involving molecular rearrangements are known in the case of 1,2-diazetidine derivatives. They are often acid catalyzed or thermal reactions. Surprisingly, similar reactions in the 1,3-diazetidine systems are scarce [83HC(42)443]. When 1,2-diazetidinone (163) is treated with acidic ethanol, products resulting from molecular rearrangement are obtained. The formation of oxindole (166) or oxadiazene (167) is believed to arise via the carbonium ion (164) formed by the initial protonation of N-2 or the acyl group on N-2 followed by fission of the 2,3-bond. This carbonium

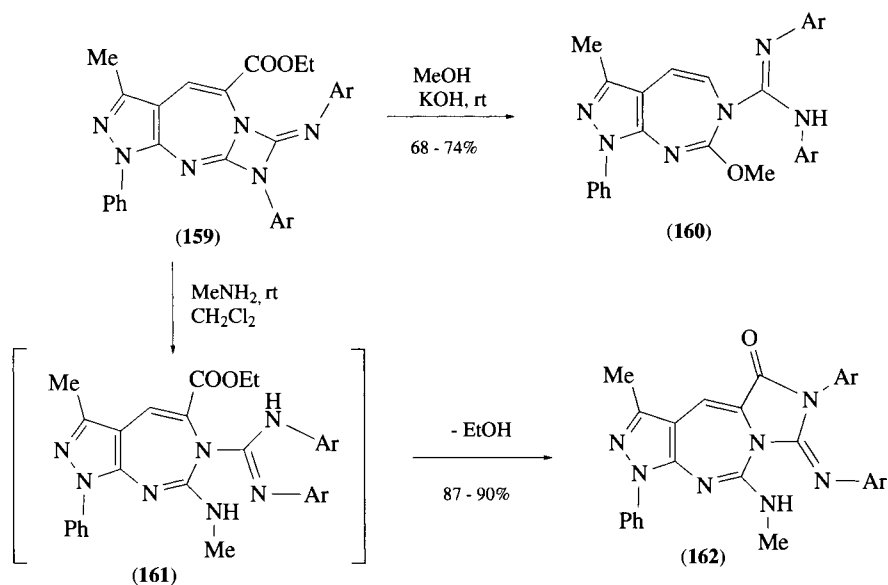


Scheme 14

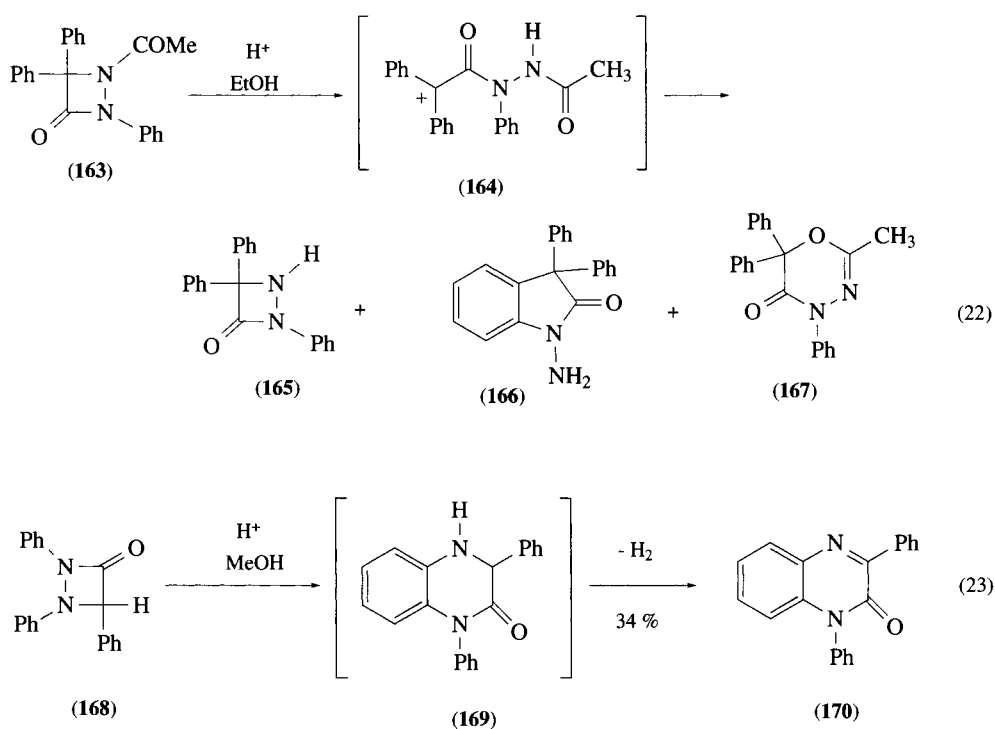


Scheme 15

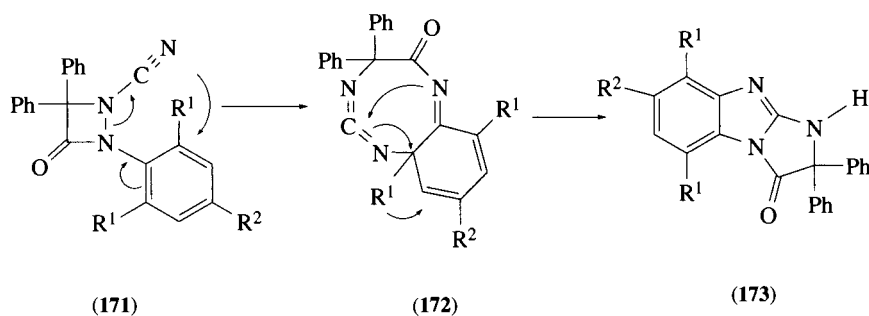
ion would further attack the N-phenyl or acetyl group leading to the observed products (Equation (22)) <63JCS674>. By contrast, 1,2,4-triaryl-1,2-diazetidinone (**168**) undergoes facile orthosemidine type rearrangement leading to quinoxaline derivative (**170**) probably via (**169**) (Equation (23)) <67AG(E)630>.



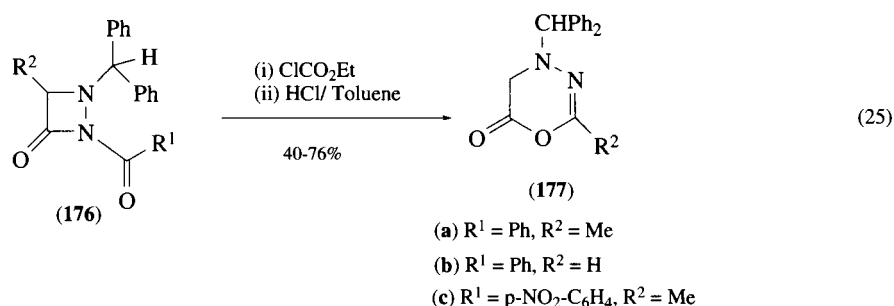
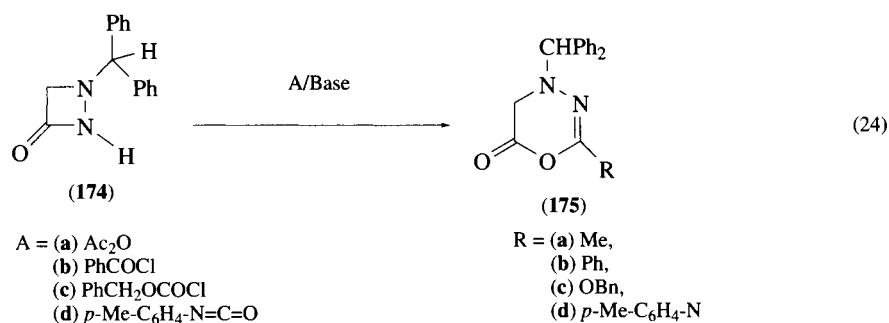
Scheme 16



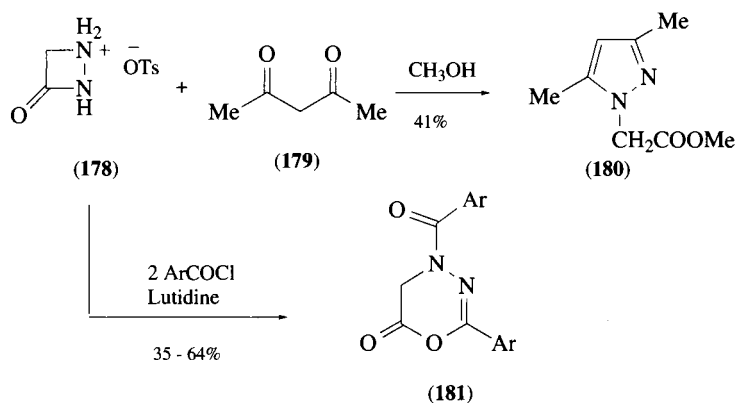
Interesting rearrangement products have been obtained in the case of 1,2-diazetidinones where N-1 has a cyano substituent and N-2 has an aryl group. Thus, the compound (171) undergoes sigmatropic rearrangement to yield (173) in refluxing xylene (Scheme 17) <64JCS5284>. 1,2-Halogen migration has been found to accompany sigmatropic rearrangements, where R¹ or R² or both are halogens. Ring expansion reaction has been observed during acylation of 1,2-diazetidinones (174) using benzoyl chloride, benzyl chloroformate, or *p*-tolylisocyanate (Equation (24)) <81JA7659>. Analogous products were obtained when fully substituted 1,2-diazetidinone (176) was treated with ethyl chloroformate or with hydrogen chloride gas in toluene (Equation (25)) <84JOC2204>.



Scheme 17



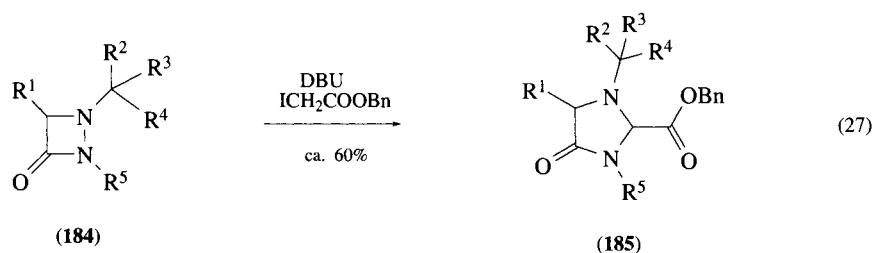
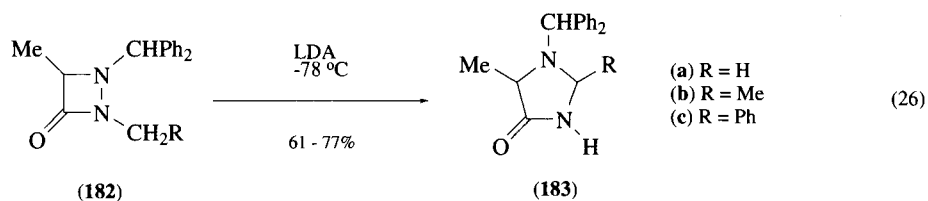
Unsubstituted 3-oxo-1,2-diazetidinium tosylate (**178**), when reacted with acetylacetone (**179**) in methanol at room temperature, gave methyl 3,5-dimethylpyrazole-1-acetate (**180**) <81JA7660>. In contrast, with two equivalents of aroyl chloride in the presence of 2,6-lutidine as a base, (**181**) was obtained due to ring expansion (Scheme 18).



Scheme 18

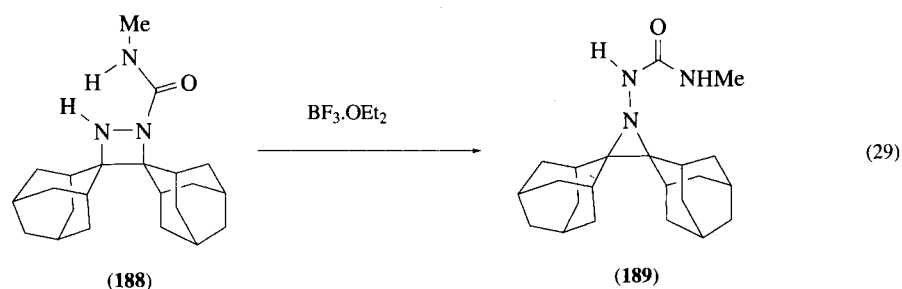
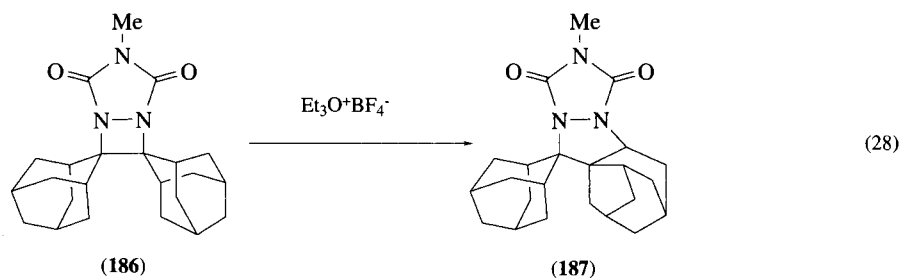
Instantaneous ring expansion to imidazolidinone (**183**) has been observed when 1,2-diazetidinone (**182**) was treated with one equivalent of LDA in anhydrous THF at -78°C (Equation (26))

<81JA7659>. The ease of this reaction is attributed to the formation of a dipole-stabilized anion formed by the deprotonation of the methylene group attached to N-2. The 1,2-diazetidone (184) in which no proton is attached to substituents on ring nitrogen, undergoes ring expansion to imidazolidone (185) when treated with electrophiles like benzyl iodoacetate in the presence of a strong base like DBU, possibly because of proton abstraction from carbon α to N-2 (Equation (27)) <86JOC1530>.



- (a) $\text{R}^1 = \text{R}^5 = \text{H}$, $\text{R}^2 = \text{R}^4 = \text{Me}$, $\text{R}^3 = \text{CH}=\text{CH}_2$
 (b) $\text{R}^1 = \text{R}^4 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{Ph}$, $\text{R}^5 = \text{CH}_2\text{COOCH}_2\text{Ph}$
 (c) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{Ph}$, $\text{R}^4 = \text{CH}=\text{CH}_2$, $\text{R}^5 = \text{CH}_2\text{COOCH}_2\text{Ph}$
 (d) $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$, $\text{R}^4 = \text{CH}=\text{CH}_2$, $\text{R}^5 = \text{H}$
 (e) $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$, $\text{R}^4 = \text{CH}=\text{CH}_2$, $\text{R}^5 = \text{CH}_2\text{COOCH}_2\text{Ph}$

Expansion of 1,2-diazetidone rings has been observed by the reaction of Lewis acids. 1,2-Diazetidone (186) rearranges to an isomer (187) by the action of triethyl oxonium tetrafluoroborate (Equation (28)). On the other hand, ring contraction is observed when the 1,2-diazetidone semicarbazide (188) is treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Equation (29)) <93JOC5393>.

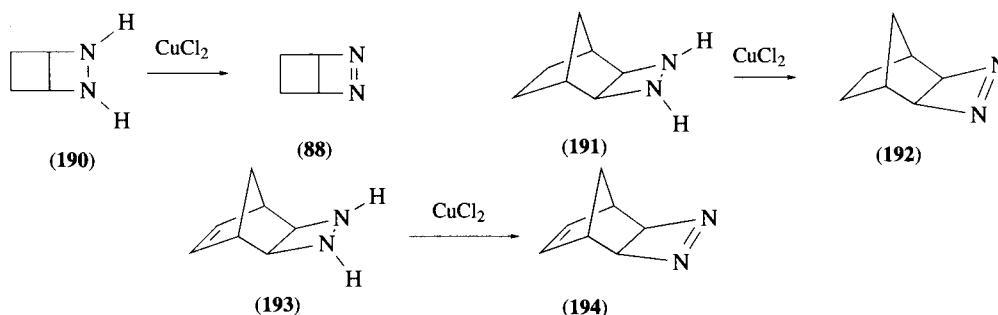


Some of the reactions involving rearrangements are categorized into a different class depending on where the nucleophile initially attacks, to bring about a cascade of transformations leading to rearrangement products (see below).

1.30.5.4 Reactivity of Ring Nitrogen and Substituents Attached to Ring Nitrogen Atoms

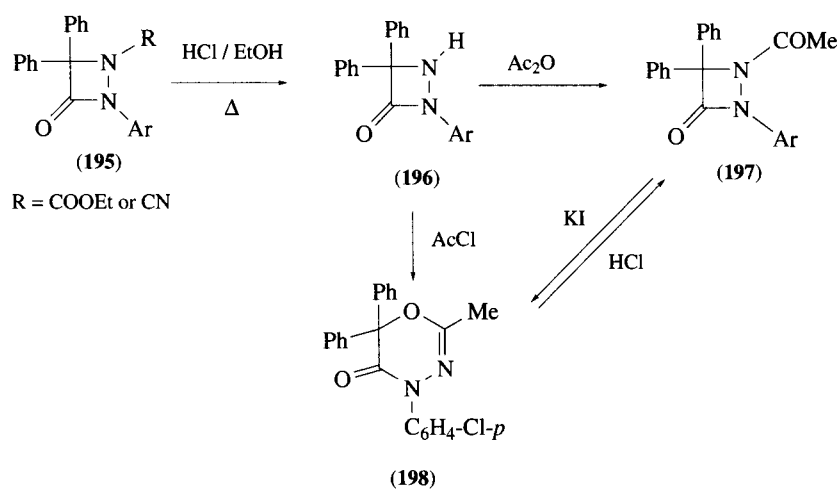
1.30.5.4.1 Reactivity of ring nitrogen atoms

There are a few important reactions which are carried out directly at heteroatoms of diazetidines and their derivatives. For example, several bicyclic 1,2-diazetidines undergo dehydrogenation with cupric chloride and sodium sulfite to afford Δ^1 -1,2-diazetidines (Scheme 19) <69JA5668, 78TL2469>. Tetramethyl- Δ^1 -1,2-diazetine-1,2-dioxides can also be deoxygenated to monoxide and/or 3,3,4,4-tetramethyl- Δ^1 -1,2-diazetine <75JOC1409>.



Scheme 19

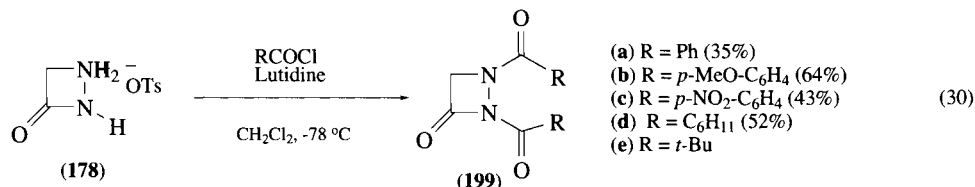
Several 1-aryl-3,3-diphenyl-1,2-diazetid-4-ones (195), having an ethoxycarbonyl or nitrile group on N-2 undergo hydrolytic removal of the group on acid treatment (HCl-ethanol, Δ), furnishing the N-2 unsubstituted 1,2-diazetid-4-one (196). Interestingly, (196) upon treatment with acetic anhydride gave N-2 acetylated-1,2-diazetid-4-one (197) while acetyl chloride treatment produced rearranged product (198). The rearranged product (198) can also be obtained by heating (197) in xylene in the presence of a catalytic amount of KI. The dihydrooxadiazinone (198) can be reversed back to (197) by treatment with concentrated hydrochloric acid (Scheme 20) <63JCS674, 64JCS5284>.



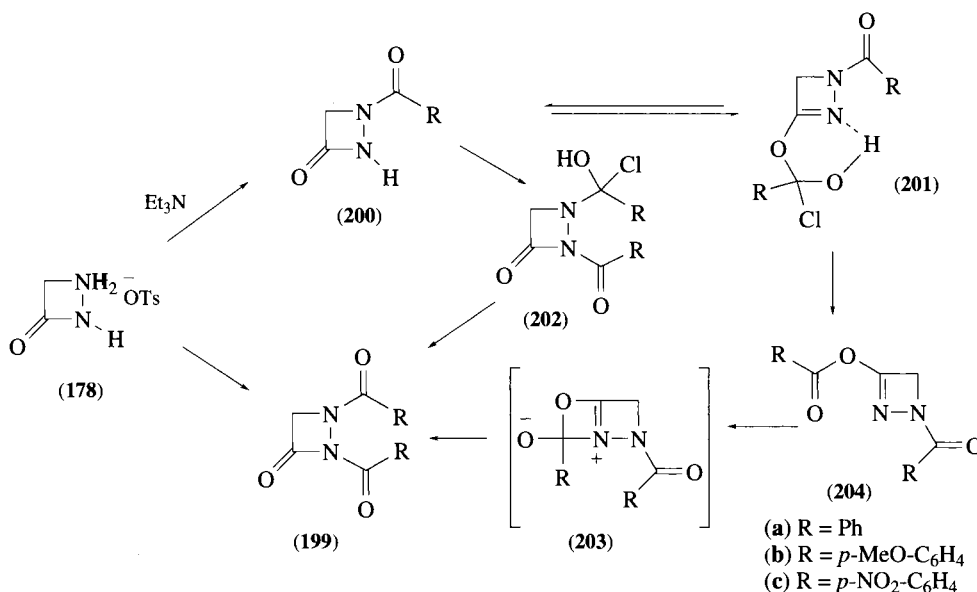
Scheme 20

Unlike the removal of a functional group from a nitrogen atom, substitution at a nitrogen atom has been more difficult. Attempts to monoacylate 1,2-diazetid-4-ones gave only polymeric material; however, diacyl derivatives were isolated in modest yield at -78°C when treated with two equivalents of acyl chloride in the presence of three equivalents of 2,6-lutidine as a base <84JOC2204>. Thus, 3-oxo-1,2-diazetidinium tosylate (178) gives 1,2-dibenzoyl-1,2-diazetid-3-one (199a) in

35% yield when reacted with two equivalents of benzoyl chloride and three equivalents of 2,6-lutidine in CH_2Cl_2 at -78°C (Equation (30)).

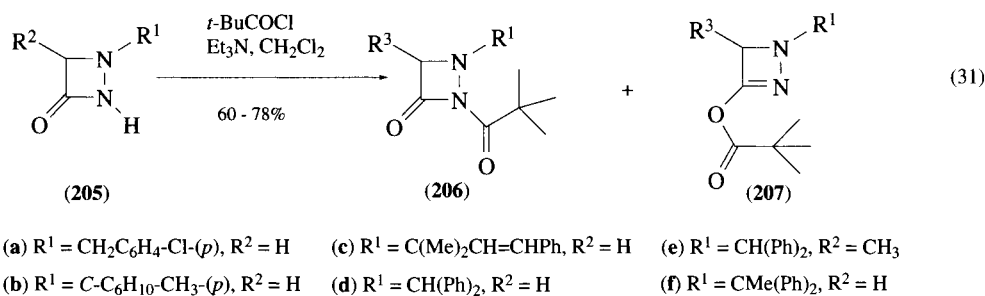


Interestingly, the free base 1,2-diazetididinone seems to be unstable since only polymeric material is obtained during acylation of (178) with less electrophilic acylating agents such as acetic anhydride, which is unable to react instantaneously with the free base generated in the reaction. This reaction has also been found to be dependent on the nature of the base used to generate 1,2-diazetididinone from the salt (178). Thus, when pyridine is used instead of 2,6-lutidine, the heterocycle undergoes ring rupture, presumably because of the predominantly nucleophilic character of the base. By contrast, use of triethylamine exclusively furnished *O*-acylated derivative (204). Therefore, it is reasonable to assume that after the initial acylation at the more nucleophilic and basic N-1, kinetic acylation occurs at the oxygen of the carbonyl functionality, resulting in the formation of (204) in the presence of triethylamine (Scheme 21) <84JOC2204>.

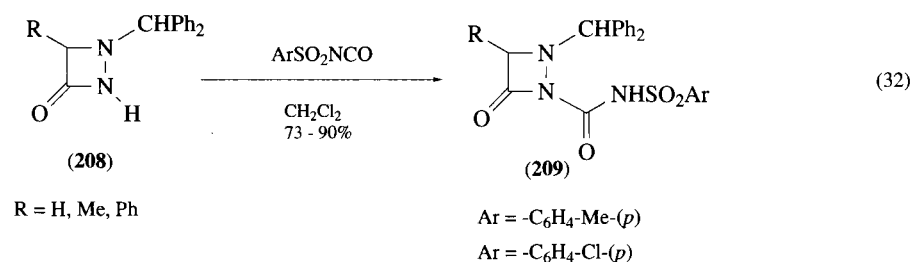


Scheme 21

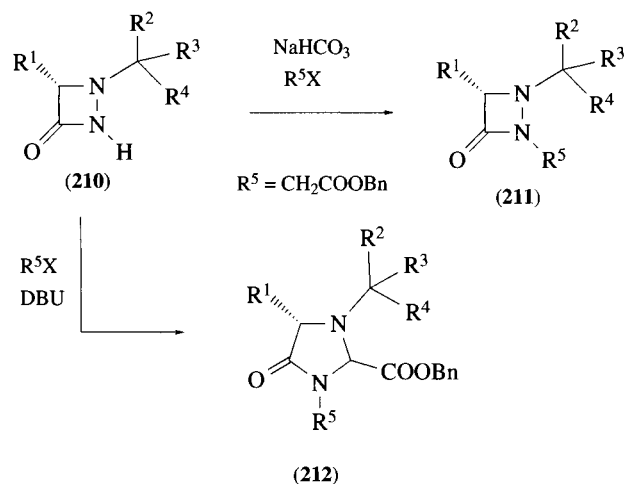
In contrast, under thermodynamically favored conditions ((200) $\rightarrow$ (202) $\rightarrow$ (199)), (199) is the predominant product. The stability of both (199) and (204) is solvent dependent, for example, both (199b) and (204b) decompose readily in DMSO-d_6 , whereas they are stable in acetone- d_6 . In contrast, (204c) rearranges to (199c) in acetone- d_6 within 24 h. The *N,O*-dianisoyl derivative (204b) has been found to be stable for over 2 years at room temperature. It is important to mention that only thermodynamically favored *N*-acylated products are obtained even in the presence of triethylamine, for instance in the case of 1-substituted 1,2-diazetidiones when treated with acylating agents such as anhydrides, acid chlorides, benzyl chloroformate, etc. An exception to this, is the reaction of pivoloxy chloride, which exclusively furnished *O*-pivoloxy derivatives as shown in the case of (205a-f) (Equation (31)) <84JOC2204>.



During the investigation of antibacterial efficacy of aza analogues of β -lactams, Skotnicki has prepared N-2 substituted diazetidinones (**209**) by the reaction of diazetidinones (**208**) with *p*-toluenesulfonyl isocyanate (Equation (32)) <86JAN471>.



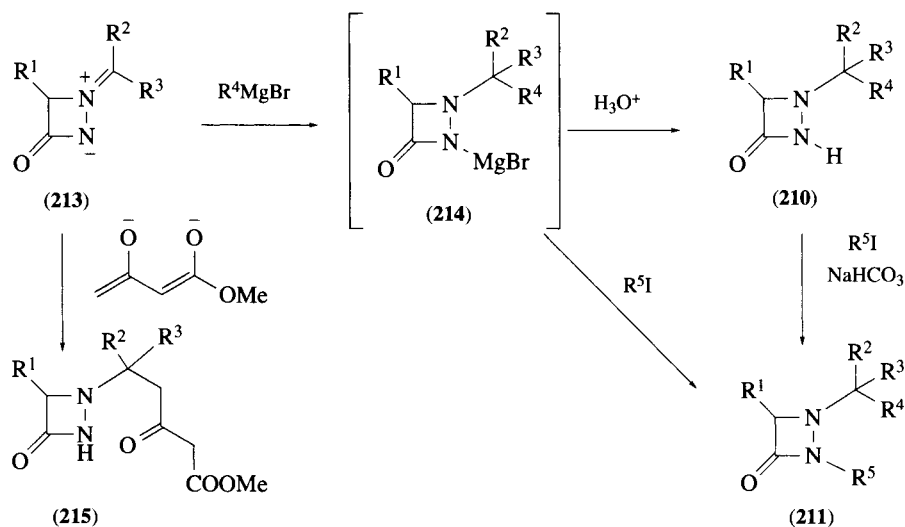
Taylor and Davies have reported an extensive polymerization of 3-oxo-1,2-diazetidinium salt (**178**) during alkylation reactions with a variety of alkyl halides <84JOC4415>. However, using benzyl iodoacetate, N-2 alkylation of (**210**) was possible in the presence of a weak base such as sodium bicarbonate, while use of a stronger base like DBU afforded a rearranged product (**212**) (Scheme 22) <86JOC1530>.



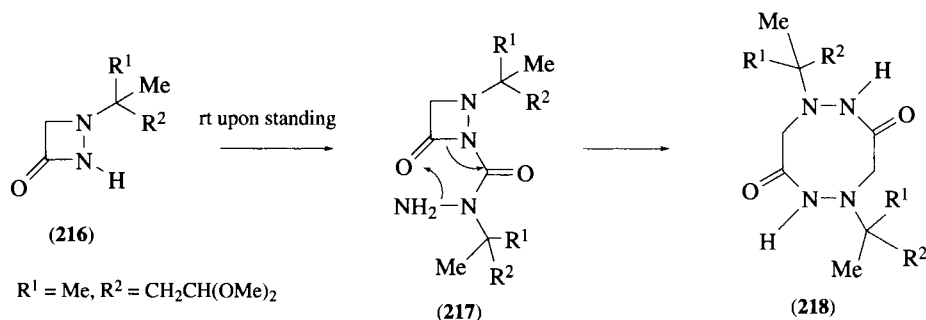
Scheme 22

The presence of bulky substituents at the N-1 position of the heterocycle has been found to have beneficial effect on the yield of N-2 alkylation products. Taylor and co-workers have synthesized several 1,2-diazetid-3-ones (**216**) by the addition of Grignard reagents on the ylide (**213**) <84JOC4415, 86JOC1530>. It has been found that (**211**) is obtained in excellent yields from (**213**) in a one-pot reaction rather than via isolation of (**210**) followed by alkylation. The dianion of methyl acetoacetate similarly adds to the iminium bonds of (**213**) to give (**215**) (Scheme 23).

Taylor and co-workers have also reported an unusual dimerization of aza- β -lactam upon standing at room temperature for a long period, furnishing an eight-membered heterocycle via the pathway shown in Scheme 24 <84JOC4415>. A similar ring expansion from four-membered to eight-membered ring heterocycles is commonly observed in β -lactam chemistry <82TL465>.



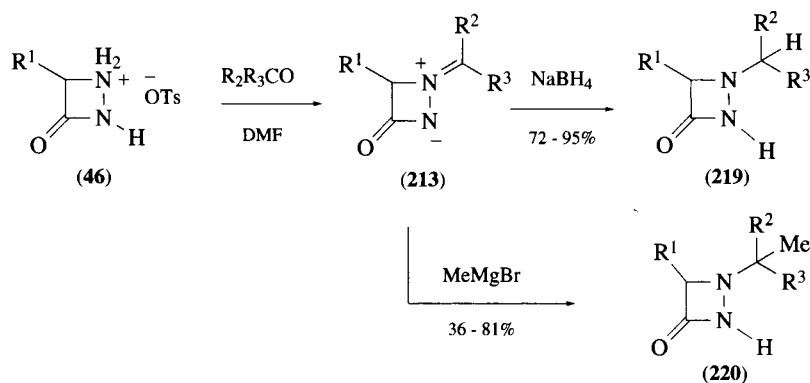
Scheme 23



Scheme 24

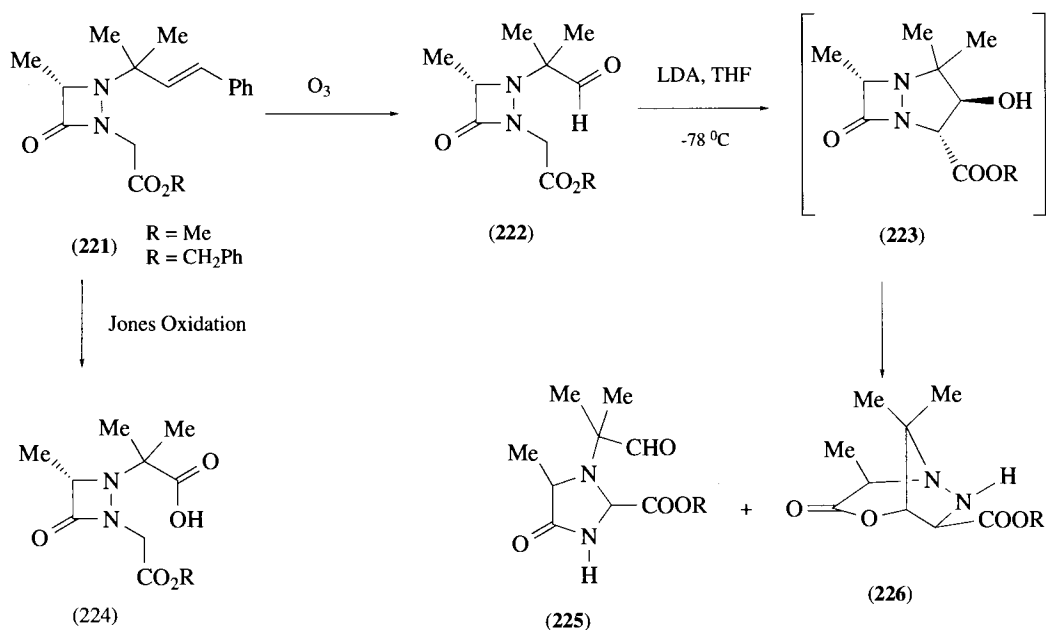
1.30.5.4.2 Reactivity of side chain attached to ring nitrogen atoms

Interest in the development of new carbapenem analogues of the potent β -lactam antibiotics initiated major efforts towards the aza analogues of carbapenem derivatives. Taylor and co-workers carried out reactions to attach a suitable side chain at nitrogen, which subsequently may be cyclized to give aza analogues of bicyclic β -lactam antibiotics. Thus, the readily available inner salt 1,1-disubstituted-3-oxo-1,2-diazetidinium tosylate (213) could be selectively reduced at the side chain attached to N-1 of (213) by sodium borohydride; or alkylate selectively at the side chain by the reaction of (213) with Grignard reagent (Scheme 25) (84JOC4415).



Scheme 25

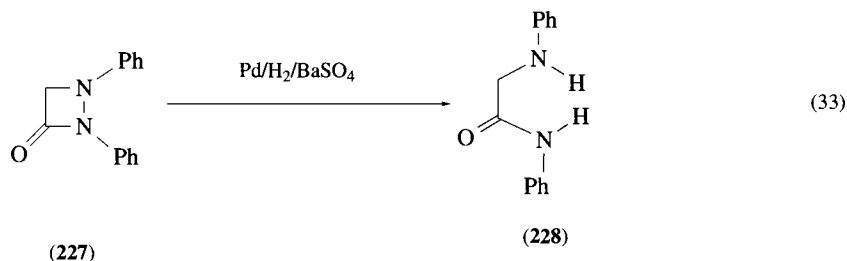
Substituents on the nitrogen exhibit the usual reactivity pattern, for example, the C=C bond on the side chain of (221) could be cleaved by ozonolysis to give aldehyde (222). Taylor and co-workers attempted to synthesize aza carbapenem derivative (223) by intramolecular aldol condensation of (222) using LDA as a deprotonation agent. Instead of (223) an unexpected bicyclic compound (226) was isolated in addition to imidazolidinone (225) (Scheme 26). The formation of (226) could be explained by the intramolecular ring opening of the aza- β -lactam by the secondary hydroxyl group. Numerous attempts to effect intramolecular condensation of (223) and (224) obtained by Jones oxidation of (221), were not successful [86JOC1530].



Scheme 26

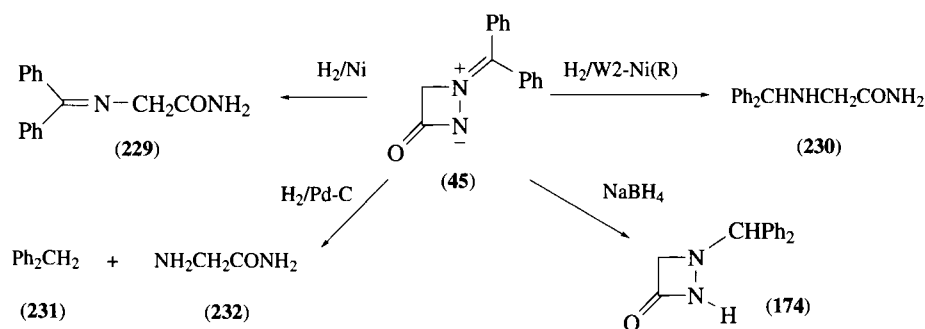
1.30.5.4.3 Reactions with reducing agents

The nitrogen–nitrogen bond in 1,2-diazetidin-3-ones and related systems can be cleaved using a number of reducing agents under mild conditions, owing to the ring strain in the molecule, for example 1,2-diaryl-1,2-diazetidin-3-ones (227) underwent N–N bond scission using Pd catalyst in the presence of hydrogen to give amide (228) (Equation (33)) [56AG71].

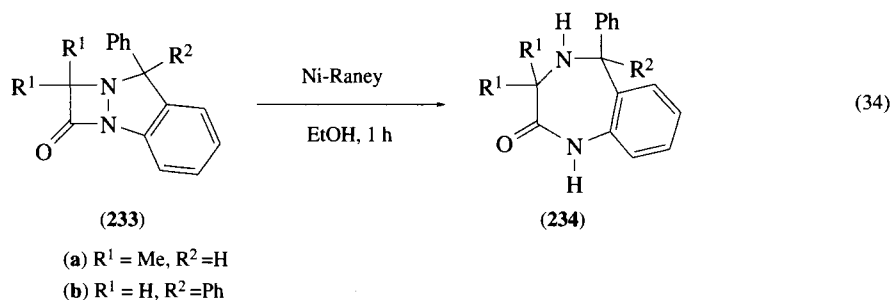


Taylor *et al.* have investigated the effect of various reducing agents on the inner salt (45). Depending on the nature of the reducing agents and catalyst, different products were isolated [81JA7743], for example, reduction of (45) with hydrogen in the presence of deactivated Raney nickel afforded benzophenone imine of amino acetamide (229) while W-2 Raney nickel furnished α -diphenylmethylaminoacetamide (230). In contrast, reduction of (45) with hydrogen in the presence of Pd–C afforded diphenylmethane (231) and aminoacetamide (232) as the exclusive products. On the other hand, treatment with sodium borohydride selectively reduced the iminium bond with retention of diazetidinium ring to give (174) (Scheme 27). The cleavage of the N–N bond was also

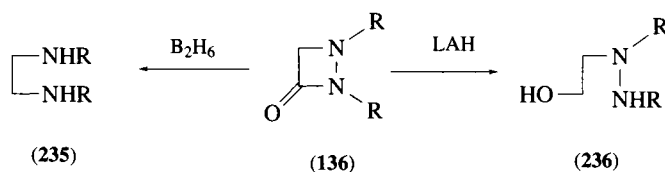
observed in the case of bicyclobenzodiazepinone (**233**) in the presence of W-2 Raney nickel in refluxing ethanol leading to the formation of 1,4-benzodiazepinone (**234**) (Equation (34)). Attempted hydrogenation of (**233**) with hydrogen in the presence of Pd-C or Pd-BaSO₄ did not furnish (**234**) <91T9599>.



Scheme 27



Moody and co-workers have reported an interesting reduction of 1,2-dibenzyl-1,2-diazetidin-3-one (**136**) with diborane in THF and with lithium aluminum hydride in refluxing THF. Whereas in the former case, reduction of both the N—N bond and C=O was observed, in the latter case an unexpected cleavage of a C—N bond was noted. Thus, reduction of (**136**) with diborane gave *N,N*-dibenzyl ethylene diamine (**235**), whereas (**236**) was obtained when (**136**) was refluxed with LAH (Scheme 28) <84CC754, 87JCS(P1)877>.

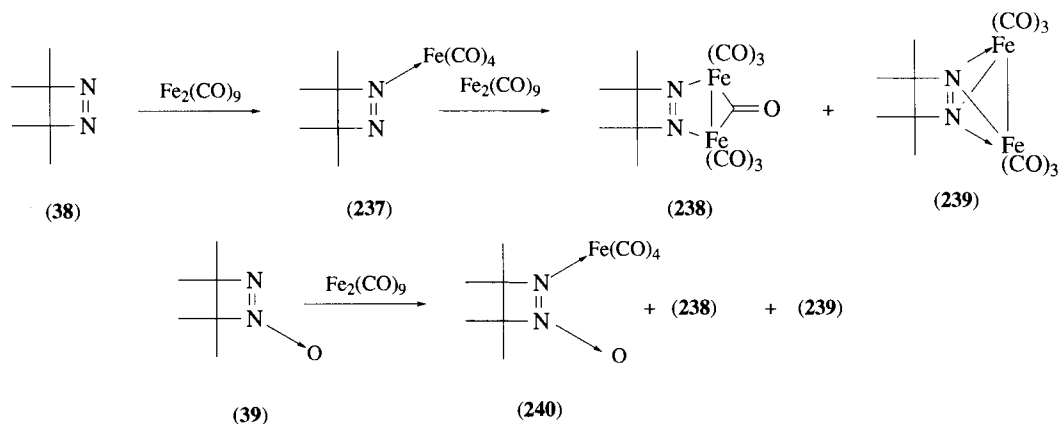


Scheme 28

1.30.5.4.4 Reactions with metal carbonyls

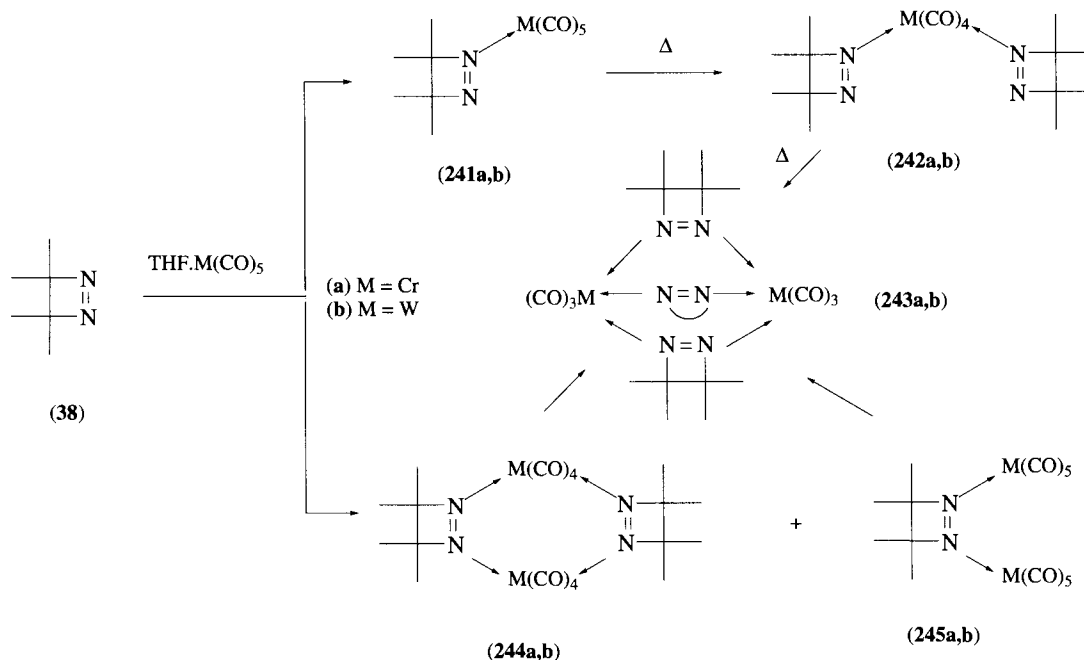
Cyclic diazo compounds are known to form mononuclear σ -complexes with iron carbonyl compounds, which further react to give more stable binuclear complexes containing an Fe—Fe bond <76TCC105>; however, such complexes are rare in the case of cyclic four-membered diazo compounds, for example, reaction of 3,3,4,4-tetrafluoro-1,2-diazetidine (**47**) with iron pentacarbonyl at 180°C only led to decomposition <71JOU2710>, but tetramethyl-1,2-diazetidine (**38**) reacted with iron pentacarbonyl to afford iron complex (**238**) and (**239**). The 3,3,4,4-tetramethyl-1,2-diazetidine-*N*-oxide (**39**) furnished a mixture of products consisting of (**238**), (**239**), and the *N*-oxide (**240**). Solvents have been found to influence the yield of products considerably. The reaction of (**38**) with Fe(CO)₅ in cyclohexane gave (**239**) as the major product (50%) along with 33% of (**238**), whereas, in THF, 88% of (**238**) was isolated along with a minor amount (7%) of (**239**). In contrast, (**240**) is always

the predominant product in both the solvents in the reaction of (39) with $\text{Fe}(\text{CO})_5$; however, the yield of (240) (67%) is higher in THF, with a small amount of (238) (2%) and (239) (5%). In cyclohexane, a mixture of (238) (2%), (239) (39%), and (240) (58%) was obtained $\langle {}^{82}\text{Zn}(\text{B})463 \rangle$. These reactions are shown in Scheme 29.



Scheme 29

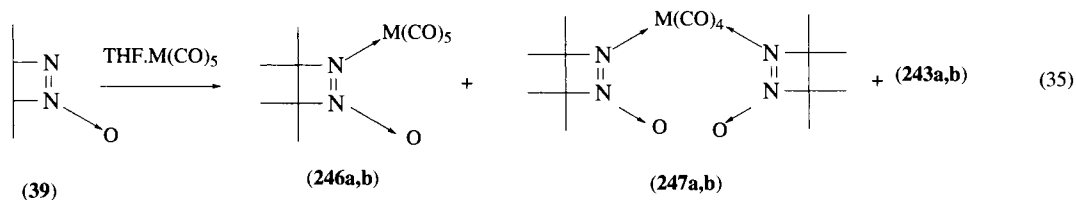
The reaction of diazetine (38) and the *N*-oxide (39) follow a very different reaction pattern. For example, (38) reacts with $(\text{THF})\text{Cr}(\text{CO})_5$ in THF to form exclusively a mononuclear complex (241a), which upon boiling in concentrated solution in benzene furnished a new *cis*-bisdiazetine–chromium carbonyl complex (242a). The latter complex is identical with the product obtained by the reaction of (38) with (norbornadiene) $\text{Cr}(\text{CO})_4$. Heating of (242a) afforded a binuclear trisdiazetine complex (245a), the most stable complex in the series. The complex (243a) is also obtained from (241a) on heating (Scheme 30).



Scheme 30

A similar reaction with tungsten carbonyl $(\text{THF})\text{W}(\text{CO})_5$ resulted in mononuclear (241b) as well as binuclear single-bridge metal carbonyl complex (245b). The reaction of (norbornadiene) $\text{W}(\text{CO})_4$ with (38) not only gave (242b) but also (244b). All the tungsten complexes are stable at room temperature; however they are all converted into triple-bridge complex (243b) upon melting (Scheme 30). The reaction of tetramethyl diazetine-*N*-oxide (39) with $(\text{THF})\text{Cr}(\text{CO})_5$ forms mono and

bis(diazetidine *N*-oxide) complex (**246a**) and (**247a**), respectively, along with a minor amount of (**241a**). At higher temperatures, the deoxygenation becomes predominant and only the most stable complex (**243a**) is obtained (Equation (35)). Similar product distribution is observed using tungsten complex, though in lower yield $\langle 82\text{ZN(B)}468 \rangle$.

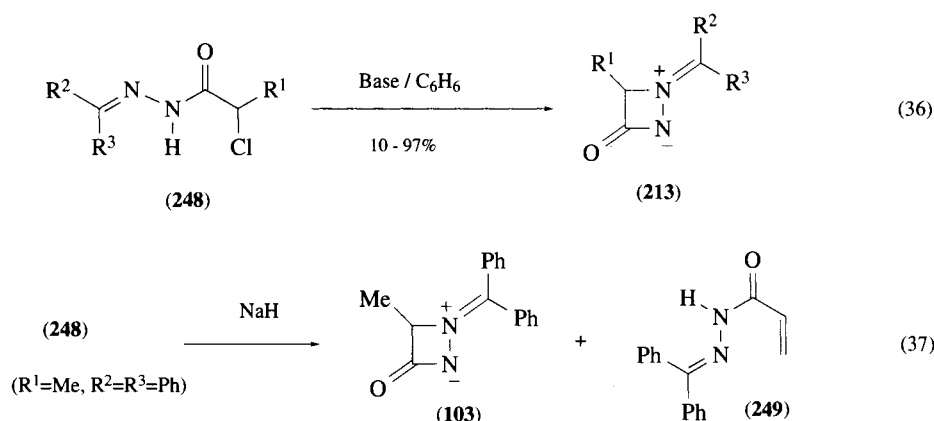


1.30.6 SYNTHESIS OF FOUR-MEMBERED HETEROCYCLES WITH TWO NITROGEN ATOMS

Syntheses of diazetidines are very well documented in the literature. One of the earliest methods to prepare diazetidines involves [2 + 2] cycloaddition of alkenic compounds with azo compounds. A consolidated account of these strategies have been described by Richter and Ulrich $\langle 83\text{HC}(42)443 \rangle$. In CHEC-I, Timberlake and Elder reported a few selected examples $\langle 84\text{CHEC-I}(5)449 \rangle$. The present volume, compiles new synthetic methods examples and covers a few important synthetic strategies reported in the earlier literature.

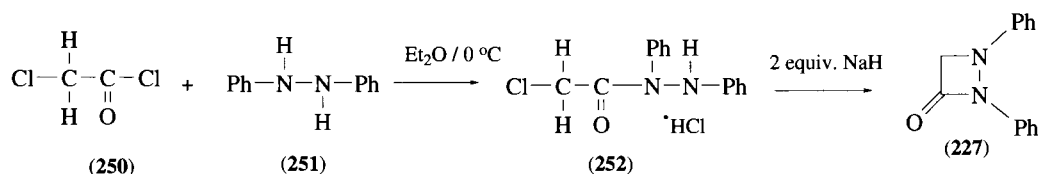
1.30.6.1 Synthesis From Acyclic Compounds via Formation of One Bond to a Nitrogen Atom

Synthesis from acyclic compounds via formation of one bond to a nitrogen atom is most widely applicable to the synthesis of 1,2-diazetidines. Much of the interest in this class of compounds has been stimulated by their biological relevance as aza analogues of carbapenem and carbapenem β -lactam antibiotics. The most general method of synthesis of 1,2-diazetidines has been through the initial formation of diazetidinyl ylides obtained by intramolecular dehydrohalogenation of chloroacetylhydrazone of benzophenone with a strong nonnucleophilic base such as sodium hydride or potassium *t*-butoxide in THF (Equation (36)) $\langle 81\text{JA}7743 \rangle$. Use of other bases such as triethylamine, Triton B or *n*-BuLi has been found to be ineffective. Interestingly, when R^2 or R^3 are H, Me, or CF_3 groups, the hydrazone (**248**) does not undergo cyclization. Also, increase in the size of the substituents at the α -carbon atom leads to the formation of side products, originating from the dehydrohalogenation of the side chain (Equation (37)) $\langle 81\text{JA}7743 \rangle$.

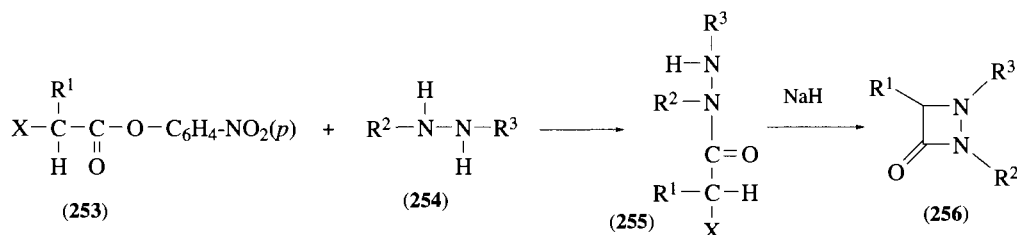


1,2-Diazetidione (**227**) was obtained when 1,2-diphenylhydrazine (**251**) was stirred with chloroacetyl chloride in ether at 0°C in the absence of a base to furnish hydrochloride salt (**252**), followed by intramolecular alkylation by treatment with two equivalents of sodium hydride (Scheme 31) $\langle 87\text{JOC}4107 \rangle$. This methodology is useful for synthesizing N-1-, N-2- and/or C-4-substituted diazetidinones, since it was found difficult to introduce substituents at appropriate positions in 1,2-

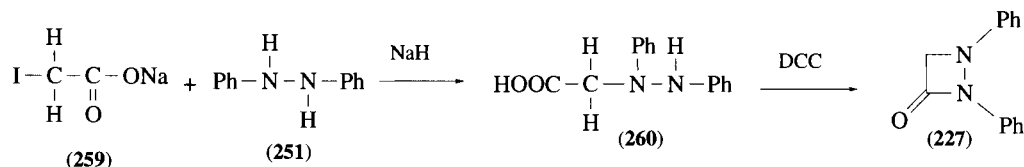
diazetidinones. Use of bromoacetyl bromide resulted in higher overall yield but, however, this was not found to be general in nature. In a modified method, Taylor and Hinkle used α -halo- β -nitrophenyl ester (**253**) instead of haloacetyl halide with a number of hydrazines, and the resulting hydrazides were cyclized to 1,2-diazetidinones (**256**) by sodium hydride ^{<87JOC4107>}. In an alternative strategy, α -haloacyl hydrazides (**258**) could be prepared by DCC coupling of 1,2-diphenylhydrazine (**251**) and iodoacetic acid (**257**). A subsequent intramolecular alkylation step proceeded in a better yield with an iodo intermediate than with bromo or chloro compounds to provide 1,2-diphenyl-1,2-diazetidinone (**227**) (Scheme 32). These authors have also used a reverse sequence of reactions involving initial alkylation of 1,2-diphenylhydrazine with iodoacetic acid followed by DCC dehydrative cyclization (Scheme 33). This strategy led to the successful preparation of 1-acetyl-2-phenyl-1,2-diazetidin-3-one which was difficult to obtain by other methods. Both the latter strategies were successfully applied to the preparation of bicyclic diazetidinones (Scheme 34).



Scheme 31



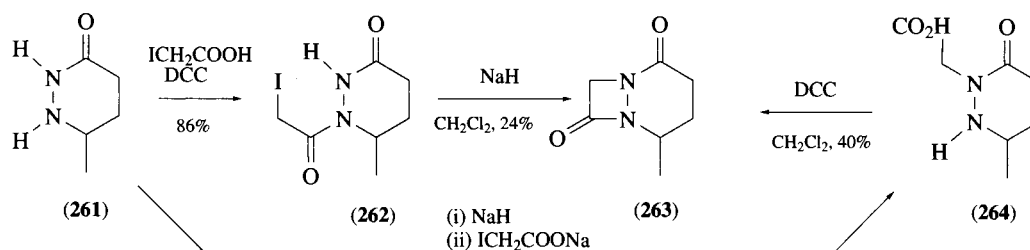
Scheme 32



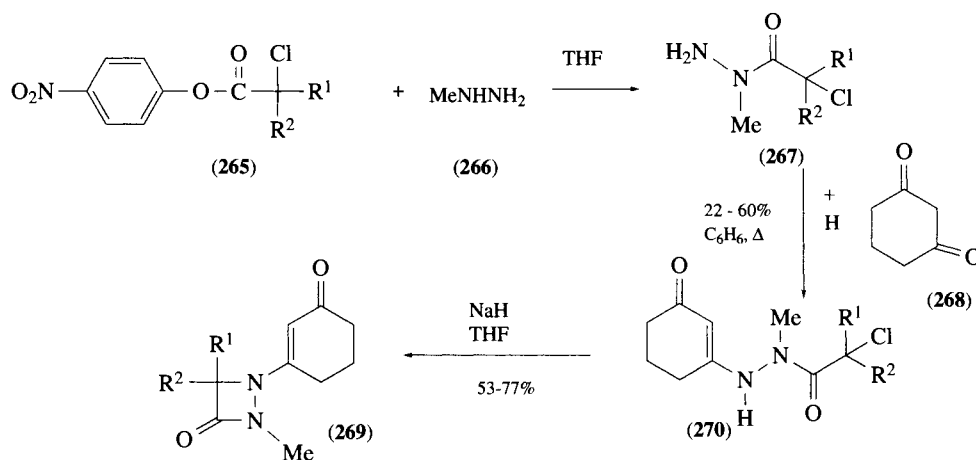
Scheme 33

A different strategy was designed to prepare enaminones (**270**) which undergo ring closure to diazetidin-4-ones (**269**) by heating with sodium hydride in THF ^{<91H(32)2417>} (Scheme 35).

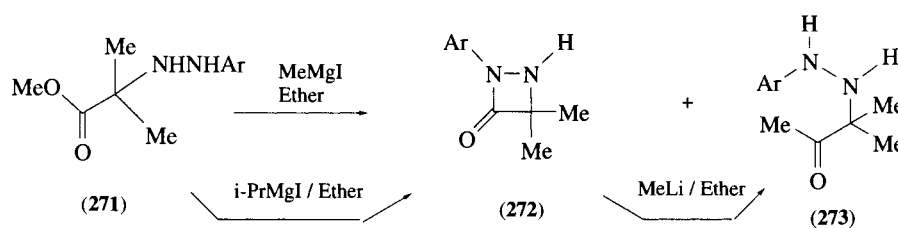
2-Aryl-1,2-diazetidinones (**272**) could be obtained in good yield by the reaction of α -(2-arylhydrazine) ester (**271**) with isopropyl magnesium iodide. Use of methyl magnesium iodide lead also to the formation of ketone (**273**) in addition to the desired diazetidinone (**272**) (Scheme 36) ^{<87TL6577>}. 1,2-Diazetidinone can also be synthesized by the decomposition of diazohydrazide (**276**) in boiling benzene in the presence of a catalytic amount of rhodium acetate ^{<87JCS(P1)899>}. Rhodium-carbenoid-mediated cyclization of diazohydrazides has also been used for the synthesis of aza- β -lactams (Scheme 37) ^{<85TL3171>}.



Scheme 34



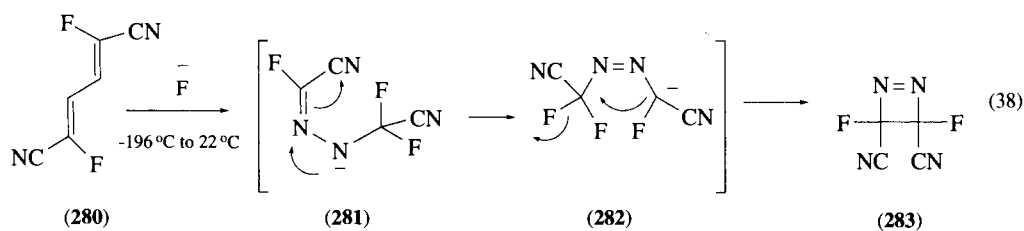
Scheme 35

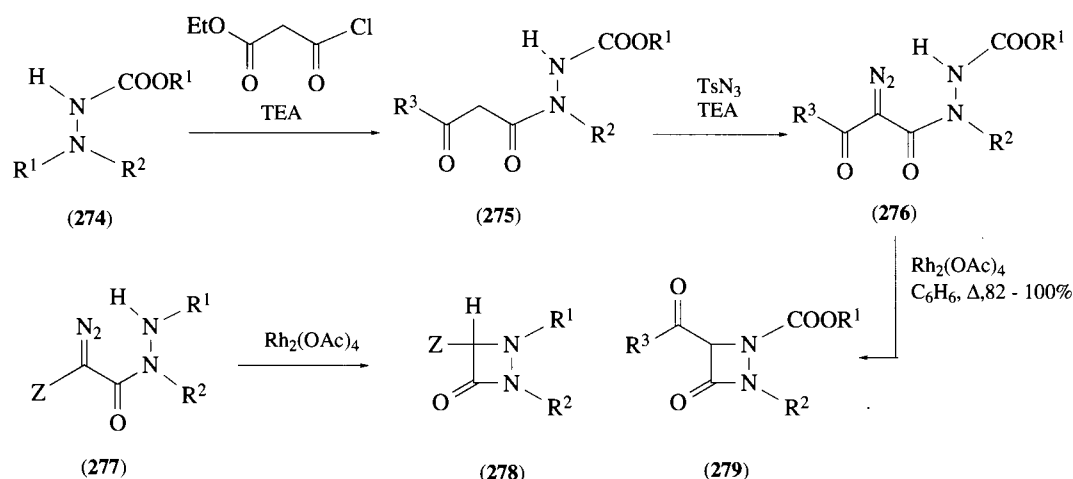


Scheme 36

1.30.6.2 Synthesis From Acyclic Compounds via Formation of One C—C Bond

Synthesis of four-membered heterocycles with two nitrogen atoms by C—C bond formation is very rare. The only example of serendipitous discovery has been reported in the early 1990s as taking place via caesium-fluoride-mediated cyclization of azine (282) (Equation (38)) <9HC535>.

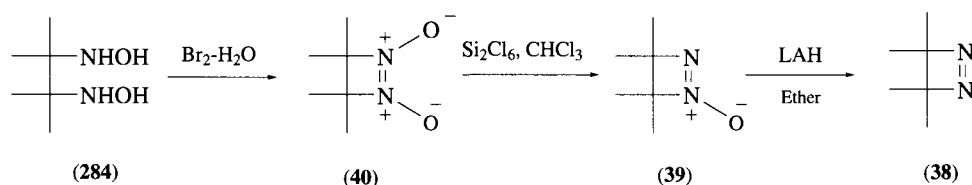




Scheme 37

1.30.6.3 Synthesis From Acyclic Compounds via Formation of One N—N Bond

Very few examples are known of the synthesis of this class of heterocycles using N—N bond formation. Jean and Devaquet calculated by an all-electron “*ab initio*” SCF-CI method for the ground state and the lowest excited state, the potential energy surface for the linear reaction path of the disrotatory cyclization of α -diimine to diazacyclobutene and they showed that although very similar to the allowed and well-documented ring closure of butadiene into cyclobutene, the cyclization of diimine is unlikely to occur [77JA1949]. Oxidation of 2,3-dimethylbutane-2,3-bis-hydroxylamines (284) with bromine or sodium periodate in aqueous solution at room temperature yielded 3,3,4,4-tetramethyl- Δ^1 -1,2-diazetene-1,2-dioxide (40) [72JA5077, 75JOC1409]. The dioxide could be further deoxygenated to monoxide (39) by Si_2Cl_6 and finally to Δ^1 -1,2-diazetene (38) with lithium aluminum hydride. Volodarskii and co-workers have reported the synthesis of 1,2-diazete-1,2-dioxide (40) from the corresponding bishydroxylamine using sodium hypobromide [75KGS748] or sodium hypobromite (Scheme 38) [92MC29, 93IZV896].



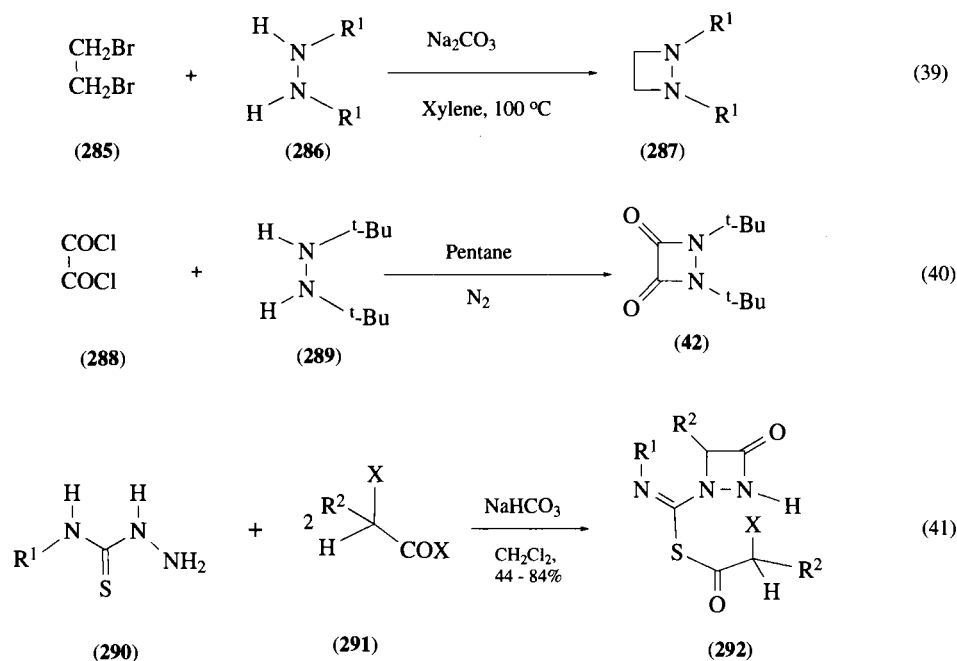
Scheme 38

1.30.6.4 Formation of Four-membered Rings from [2 + 2] Atom Fragments

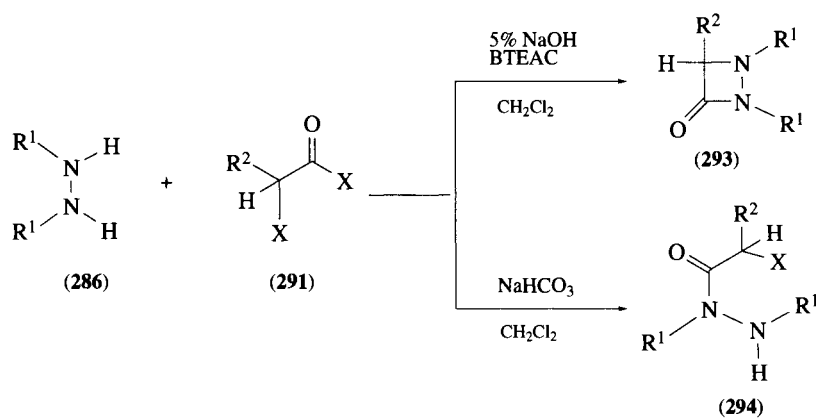
This is the most successful method which is popularly used in the synthesis of the four-membered heterocycles with two nitrogen atoms.

1.30.6.4.1 Formation of two C—N bonds by displacement reactions

1,2-Dialkyl-1,2-diazetidines (287) can be prepared by heating substituted hydrazines (286) with 1,2-dihaloalkanes (285) in the presence of sodium carbonate (Equation (39)) [78JA2806, 78JOC2785]. 1,2-Diazetidine-3,4-dione (42) can be obtained by a double displacement reaction when oxalyl chloride (288) is treated with di-*t*-butylhydrazine (289) (Equation (40)) [67JOC2360]. Furukawa and co-workers have synthesized aza- β -lactams by the reaction of carbazides with α -haloacyl halides (Equation (41)) [86H(24)885].

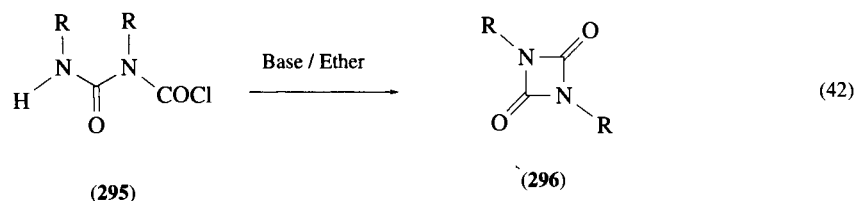


When 1,2-disubstituted hydrazines (286) react with α -haloacyl chlorides in the presence of a phase transfer catalyst like benzyltriethylammonium chloride in 5% NaOH-CH₂Cl₂, 1,2-diazetidin-3-ones (293) were obtained in 20–45% yield. However, only acylation occurred to give (294) in the absence of phase transfer catalyst (Scheme 39) <87JCR(S)254>.



Scheme 39

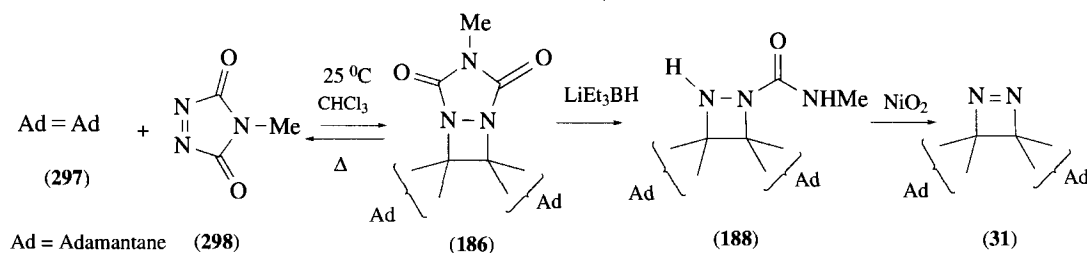
Treatment of allophanoyl chloride (295) with a base such as triethylene diamine led to the formation of 1,3-diazetidine diones (296) (Equation (42)) <78JOC4530>.



1.30.6.4.2 Formation of two C—N bonds by cycloaddition reaction between C=C and N=N fragments

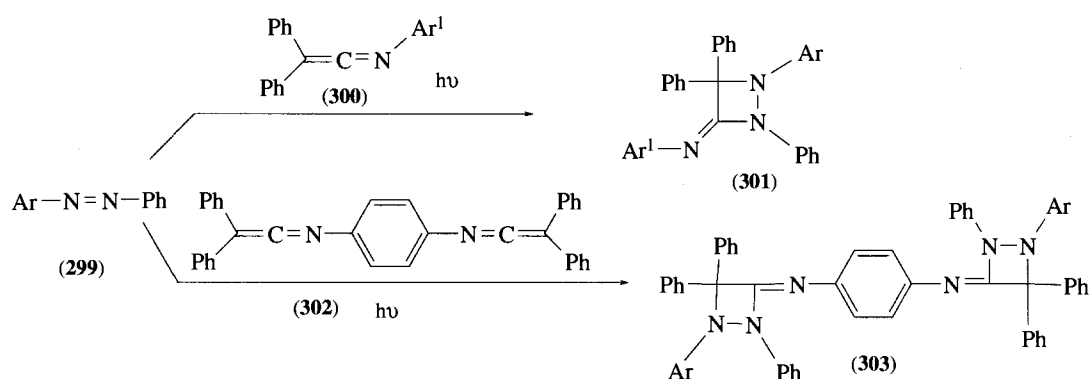
Formation of the diazetidine type of heterocycles by making two bonds from [2 + 2] atom fragments could also be achieved by a thermal or photoinduced [2 + 2] cycloaddition reaction. The

reaction may proceed either by stepwise, zwitterionic, dipolar, or radical intermediates. Since the actual mechanism is not well understood in each case, they will be dealt with through individual examples. A large number of 1,2-diazetidines have been prepared by [2 + 2] cycloaddition of C=C of an alkene and N=N of an azo compound. This type of reaction requires activation of one of the fragments by either electron-donating or electron-withdrawing groups. A large number of syntheses involving these types of fragments have been compiled by Richter and Ulrich <83HC(42)443> and also by Timberlake and Elder <84CHEC-I(5)449>. Most of these reactions use azodicarboxylates as one of the partners. Hogenkamp and Greene have synthesized substituted diazetines by the reaction of *N*-methyltriazolinedione (**298**) with adamantylidene adamantane (**297**) to give (**186**) (Scheme 40) <93JOC5393>. Semicarbazide (**188**) was formed by the reaction of (**186**) with lithium borohydride. Diazetine (**31**) was afforded by the reaction of (**188**) with nickel peroxide (Scheme 40). Diazetine (**32**) has also been synthesized by a similar strategy.

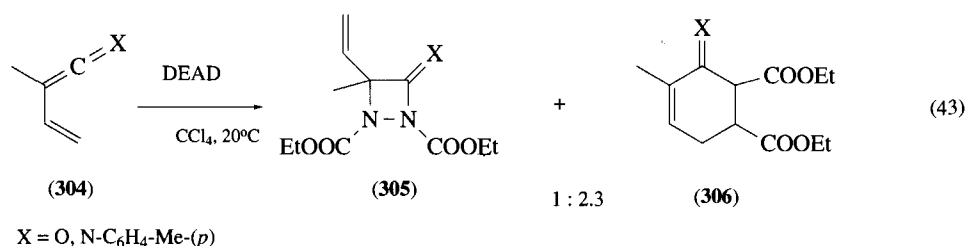


Scheme 40

Another important method is via cycloaddition reaction of azocompounds with ketenes and ketenimines <83HC(42)443, 84CHEC-I(5)449>. The early reaction between azobenzene and diphenyl ketene (Equation (1)) reported by Staudinger in 1912 was later assigned an erroneous structure by Ingold and Weaver in 1925 <25JCS378>. Much later, in the mid-1970s, it was found by Kerber *et al.* that *trans*-azobenzene undergoes photochemical isomerization to *cis*-isomer, which reacts with diphenylketene to give 1,2-diazetidines <74JOC1215>. They also found that irrespective of the nature of the substituents (electron-withdrawing or electron-donating), the cycloaddition followed a concerted pathway. Ketenimine (**300**) or (**302**) also reacts with *cis*-azobenzene (**299**) to give reasonably good yield of 1,2-diazetidines as shown in Scheme 41 <72JHC555, 74JHC409>. 1,2-Diazetidine derivative is formed as a minor product in the reaction of ketene or ketenimine with diethyl azodicarboxylate (Equation (43)) <87JOC3289>.

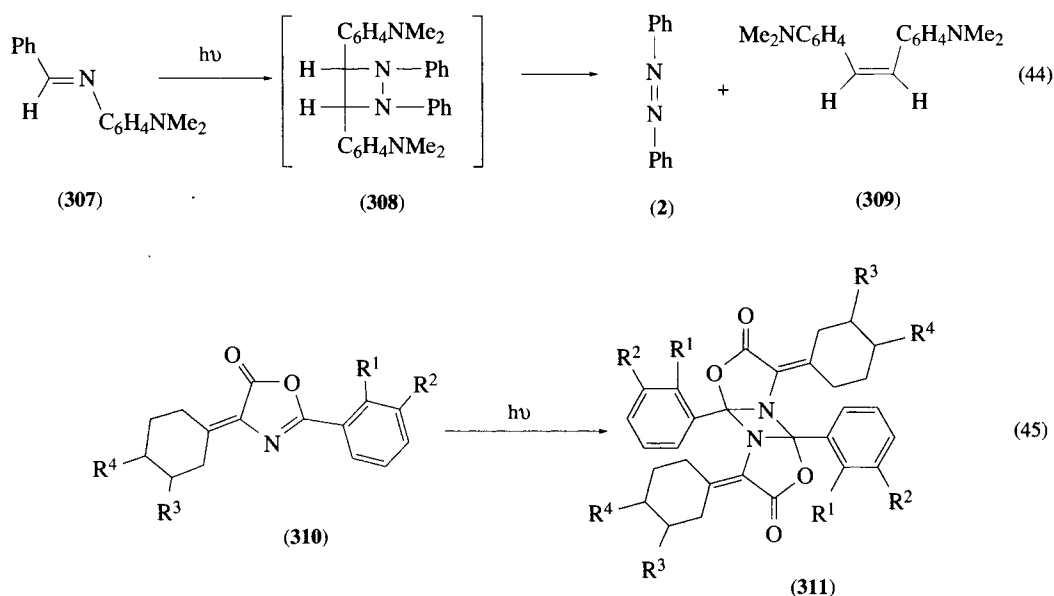


Scheme 41



1.30.6.4.3 Formation of two C—N bonds by cycloaddition reaction between two fragments containing C=N

One of the early examples invoking the intermediacy of 1,2-diazetidines was proposed in the mid-1960s by the photochemical dimerization of imines, for example, 4-*N*-dimethylamino benzylideneaniline (**307**) on photolysis gave diazobenzene (**2**) and 4,4'-bis(dimethylamino)stilbene (**309**) in which substituted 1,2-diazetidine (**308**) has been proposed as an intermediate (Equation (44)) <65TL1627>. The reaction is also photoreversible. A similar photodimerization of 2-phenylbenzoxazole to furnish a 1,3-diazetidine system is reported (Equation (2)) <82CC380, 83JOC3736, 86JOC672>. The dimer has been found to be stable in solid state but to undergo cycloreversion in solution rapidly, especially in the presence of acid. The dimeric structure has been established by x-ray diffraction studies <87CC578>. Formation of 1,3-diazetidines is also achieved by dimerization of imines <84HC(42)443>. Cyclodimerization of 4-cycloalkylideneoxazol-5(4H)-one (**310**) resulted in the formation of 1,3-diazetidine (**311**) (Equation (45)) <84CC863>. The stability of the dimer is dependent on the nature of the substituents.



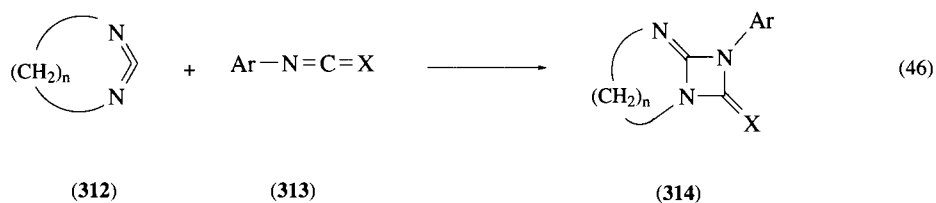
Although imines are not good substrates for photodimerization, the presence of double bonds adjacent to C=N facilitates the cyclodimerization reaction <68JA1666>.

(i) Dimerization of isocyanates

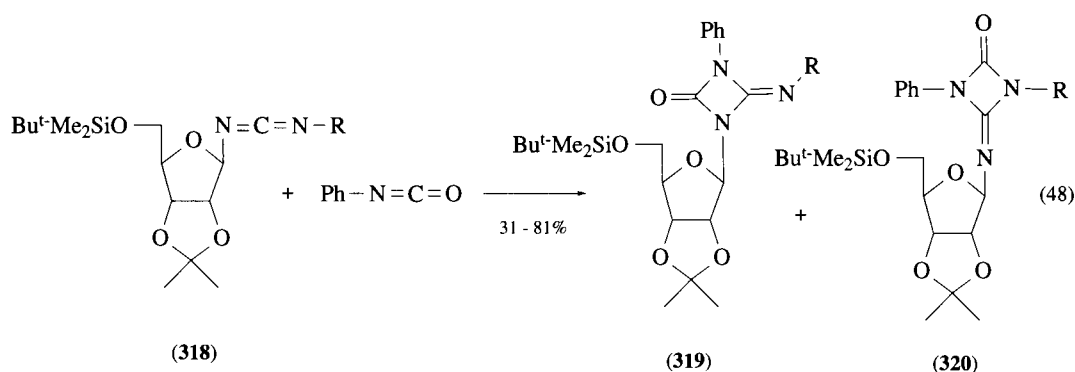
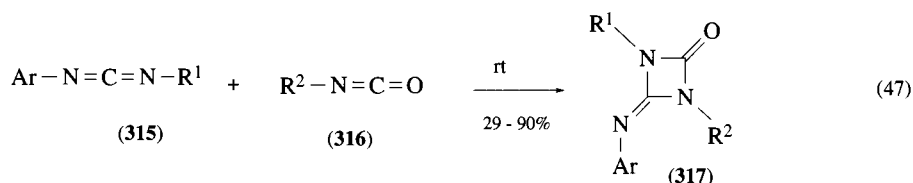
The dimerization of arylisocyanate to 1,3-diaryldiazetidin-2,4-dione is one of the classical methods of synthesis of 1,3-diazetidinone. In a few cases, a catalytic amount of trialkylphosphine, 1,2-dimethylimidazole or pyridine has been used as a catalyst. A comprehensive treaty on this strategy has been summarized by Richter and Ulrich <83HC(42)443>. In 1993, trimerization of phenylisocyanate catalyzed by fluoride ion was also reported, in which a small amount of 1,3-diazetidin-2,4-dione was obtained at room temperature <93JOC1932>.

(ii) Cycloaddition of isocyanates with carbodiimides

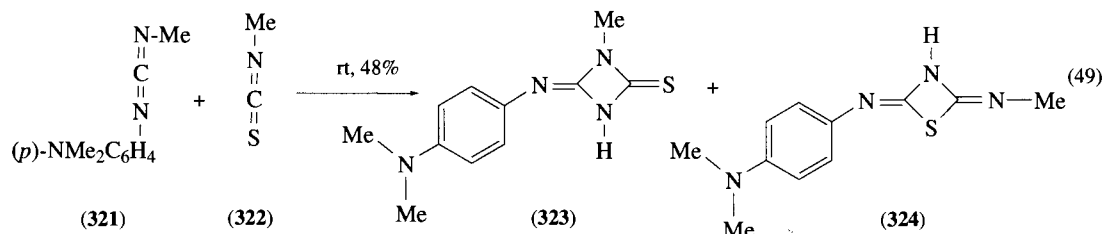
Formation of 1,3-diazetidine derivatives by the cycloaddition reaction of isocyanates with carbodiimides has been known since 1957 <57GEP1012601>. Ulrich and co-workers have studied the effect of substituents on the carbodiimides in the cycloaddition reaction. When an equimolar amount of arylisocyanate or *N,N'*-diphenylcarbodiimide (**97**) was mixed with cyclic carbodiimide (**312**), a bicyclic 2-imino-1,3-diazetidin-4-one (**314**) was formed within a few minutes. On the other hand, the adducts with *N,N'*-diphenyl carbodiimide are formed much more slowly with larger ring carbodiimides (Equation (46)) (*n* = 11 or 12) <83JOC1694>.



It has been found that *N*-alkyl-*N'*-arylcarbodiimides (315) react with alkyl and arylisocyanates (316) to give 4-arylimino-1,3-diazetidines-2-ones (317) due to regioselective cycloaddition with isocyanates. The more nucleophilic nitrogen in the carbodiimide attacks the electrophilic carbon center in the isocyanate group, giving rise to the formation of only one cycloadduct (Equation (47)) <87JHC1121>. Even with sterically hindered *N*-*t*-butyl-*N'*-phenylcarbodiimide, the reaction took place only across the C=N bond. It was observed that the substituents on the aromatic ring and steric factors retard or accelerate the reaction by increasing the size of the substituent on carbodiimide. Aliphatic isocyanates react considerably more slowly than aromatic isocyanates. A similar strategy has been utilized to synthesize uretidine nucleosides, as shown in Equation (48); a mixture of regioisomers (319) and (320) was formed. When R is CH₂=CH-CH₂ only one regioisomer (320) is formed <86MI 130-01>.



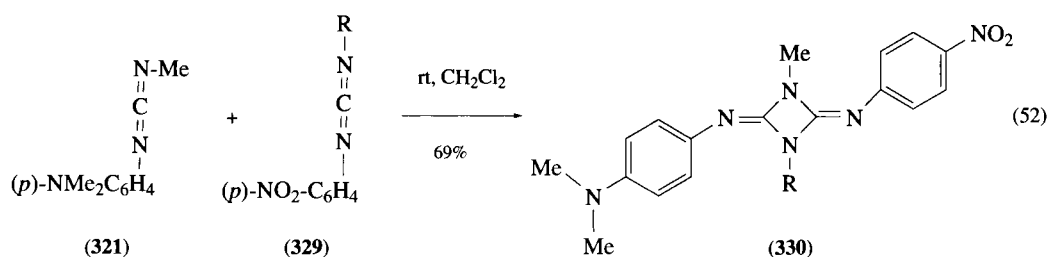
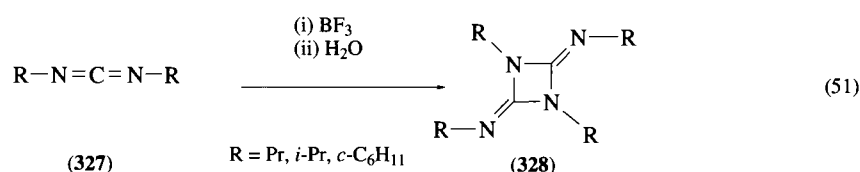
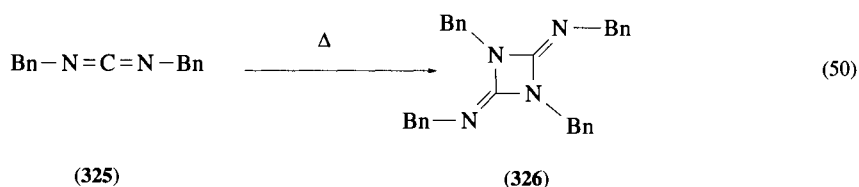
1,3-Diazetidines can also be synthesized by cycloaddition reactions of carbodiimides with isothiocyanates (322) which yielded a mixture of isomeric adducts (323) and (324) in 58:42 ratio (Equation (49)) <87CB849>.



(iii) Cycloaddition between carbodiimide moieties

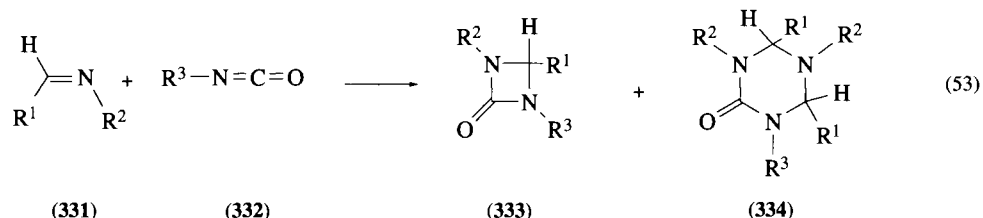
Carbodiimides undergo [2 + 2] cycloaddition reactions to furnish 1,3-disubstituted 2,4-bisalkyl or arylimino-1,3-diazetidines, for example, dibenzyl carbodiimides undergo dimerization to yield

1,3-diazetidine-2,4-diimine (326) on heating. The reaction can be catalyzed by addition of 1% of tributylphosphine (Equation (50)) <40CB1114, 68CB174>. The reaction of dialkylcarbodiimides (327) can also be catalyzed with boron trifluoride to produce 1,3-diazetidin-4-yl iminium salt which undergoes ready hydrolysis to furnish a good yield of bisalkylimino-1,3-bisalkyldiazetidines (328) (Equation (51)) <72LA(762)167>. Ulrich *et al.* have studied the cycloaddition reaction of two unsymmetrically substituted carbodiimides with inverse electron demand to produce only one cycloadduct (330) in 69% yield (Equation (52)) <87JHC1121>.



(iv) Cycloaddition of isocyanates with imines

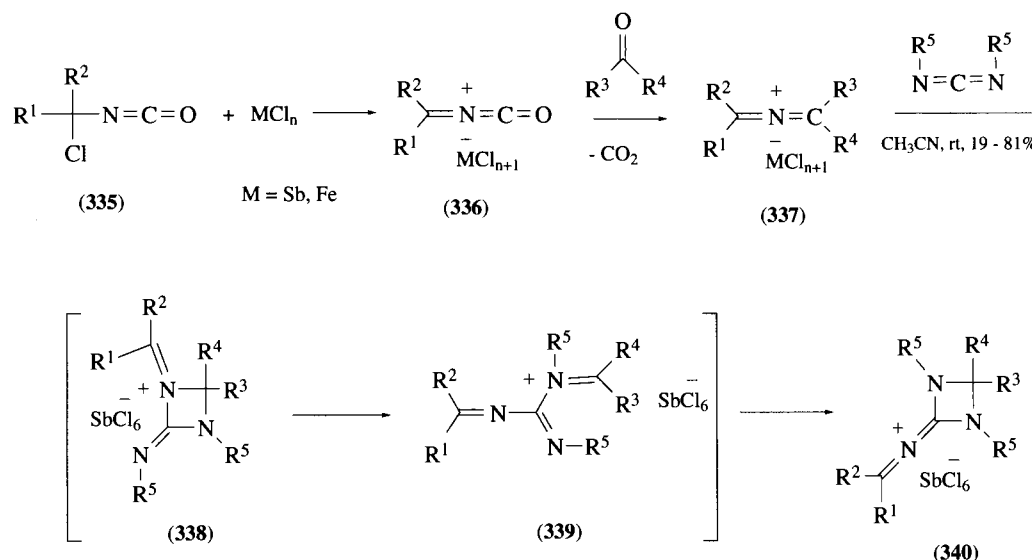
Aromatic substituted imines, especially those having electron-donating groups in the *para* position, undergo a [2 + 2] cycloaddition reaction with aryl isocyanates <69CB938, 78T101>. In the presence of excess of azomethine, six-membered triazine derivative (334) is the exclusive product (Equation (53)) <70MI 130-01>. The reaction is expected to proceed by a polar transition state. This strategy has not been used to synthesize 1,3-diazetidines since the early 1980s; however a comprehensive treaty has been given by Richter and Ulrich <83HC(42)443>.



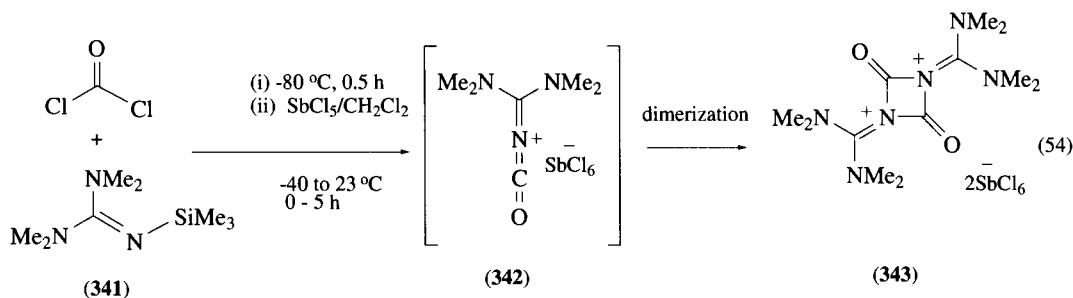
(v) Cycloaddition of carbodiimides with azaallenium salts

1,3-Diazetidinium salts (340) have been synthesized by the reaction of 2-azaallenium salt (337) with diisopropyl carbodiimide <85T527>. The formation of 1,3-diazetidinium salt (340) can be rationalized by assuming a [2 + 2] cycloaddition of carbodiimide to the 2-azaallenium salt (337) to give a diazetidinium intermediate (338) which in turn rearranges to the final product (340) through an intermediate (339) (Scheme 42). 1,3-Diazetidine-2,4-dione (343) can also be obtained by the

reaction of phosgene with silylated guanidine (**341**) in the presence of antimony pentachloride (Equation (54)). The cumulene (**342**) has been found to undergo spontaneous dimerization to 1,3-diazetidinium salt (**343**) <89S400>.



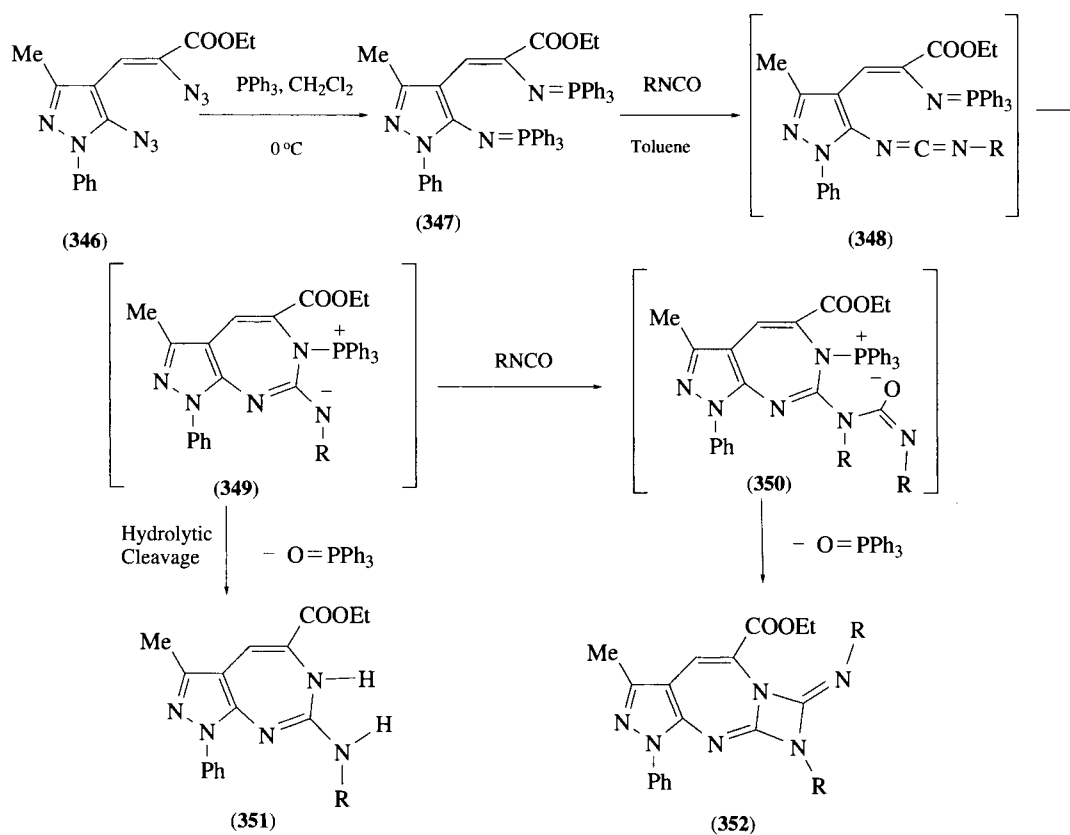
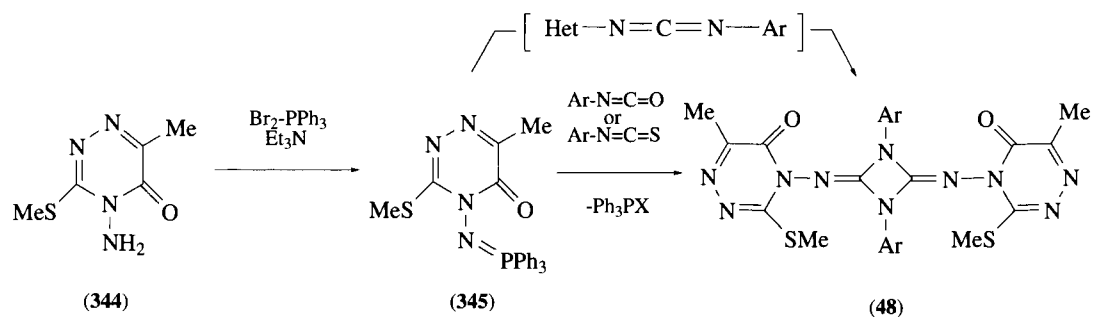
Scheme 42



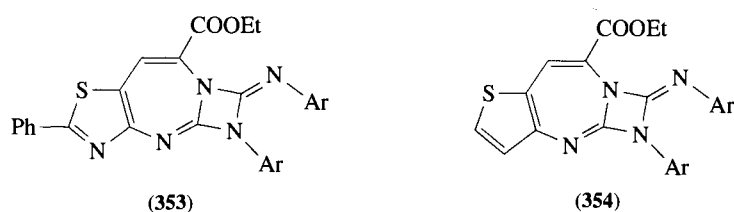
(vi) Cycloaddition of iminophosphoranes with isocyanates

Molina and co-workers have developed the synthesis of 2,4-diimino-1,3-diazetidines (**48**) by the reaction of iminophosphoranes (**345**) with aryl isocyanates <86JCS(P1)2037, 90JCS(P2)1859>. The diazetidines were also obtained by employing aryl isothiocyanates. The reaction is expected to proceed via aza-Wittig reaction between aryl isocyanate and iminophosphorane to give an intermediate carbodiimide which undergoes dimerization to afford the 2,4-diimino-1,3-diazetidines (**48**) (Scheme 43) <86JCS(P1)2037, 90JCS(P2)1859>. These authors have also studied the stability of various geometric isomers possible in the reaction by theoretical calculation <92JCS(P2)299> and the mechanistic routes through which the diazetidines might be arising <92JCS(P1)199>. In the early 1990s, Molina and co-workers examined the formation of diazetidine via an intramolecular aza-Wittig reaction as shown in Scheme 44 <93JOC5264>.

This lead to the formation of fused 2,4-diimino-1,3-diazetidines (**351**). The carbodiimide (**348**) formed by the reaction of iminophosphoranes (**347**) with one equivalent of isocyanate, undergoes cyclization by nucleophilic attack of the nitrogen atom of the styryliminophosphorane-like moiety on the central carbon atom of the carbodiimide group to give a zwitterionic compound (**349**). This undergoes hydrolytic cleavage during work-up to give diazepin (**351**), or reacts with the second equivalent of isocyanate across the negative exocyclic nitrogen atom to give (**350**) which, with concomitant ring closure with the loss of triphenyl phosphine oxide, affords fused tricyclic compound (**352**). Although in a 1992 report, a biscarbodiimide intermediate was proposed <92CC424> followed by a [2 + 2] cycloaddition of carbodiimide process to give the product (**352**), isolation of zwitterionic

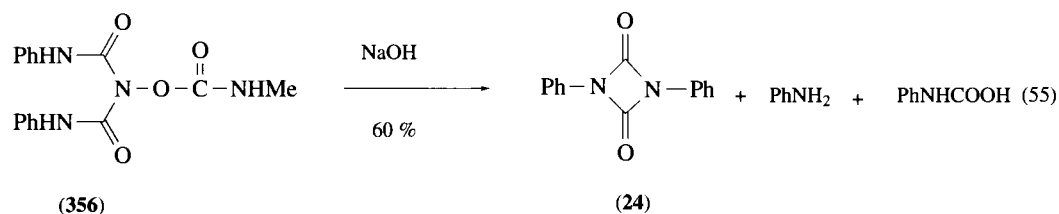


intermediate (348) clearly ruled out the possibility of a biscarbodiimide [2 + 2] cycloaddition process. The isolated compound (348) was treated with one equivalent of the same or different isocyanate or isothiocyanate to give the fused tricyclic compound. A similar strategy yielded tricyclic compounds (353) and (354).



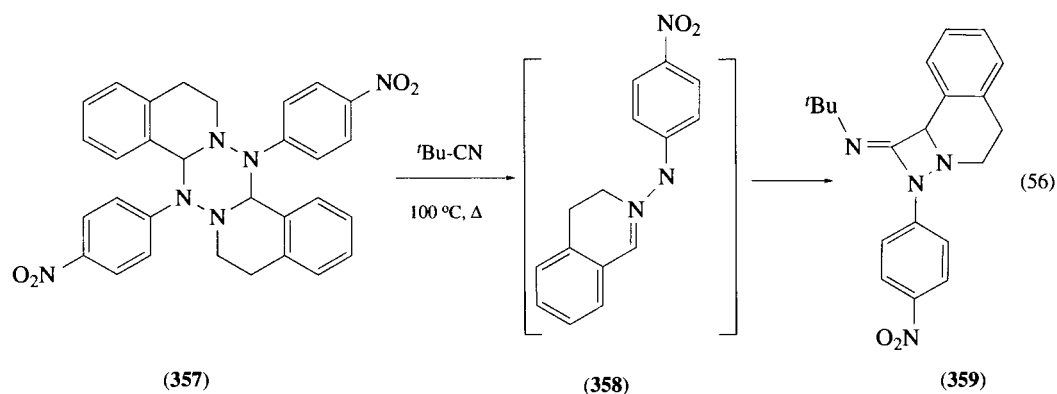
1.30.6.4 Miscellaneous methods

1,3-Diazetidin-2,4-dione derivatives are also obtained by the alkali treatment of 1,5-diphenyl-3-arylcarbamoyloxybiuret derivatives (**356**) (Equation (55)) <83HCA1011>. The latter compound (**356**) is prepared by the reaction of hydroxylamine with excess of isocyanate.



1.30.6.5 Formation of Four-membered Rings Making Two Bonds from [3 + 1] Atom Fragments

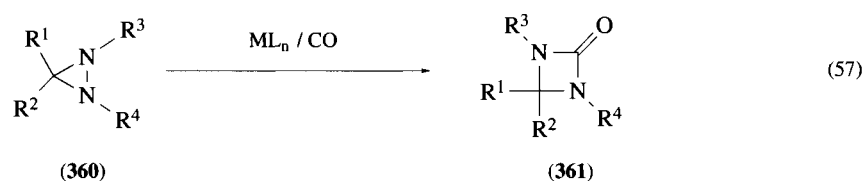
The synthesis of diazetidines by formation of four-membered rings making two bonds from [3 + 1] atom fragments is rare. One example, from the early 1970s, which might be categorized under this heading is the reaction of *t*-butylisocyanide with azomethine imine (**358**) generated *in situ* by the thermal decomposition of hexahydro-1,2,4,5-tetrazine (**357**) (Equation (56)) <71TL2191>.



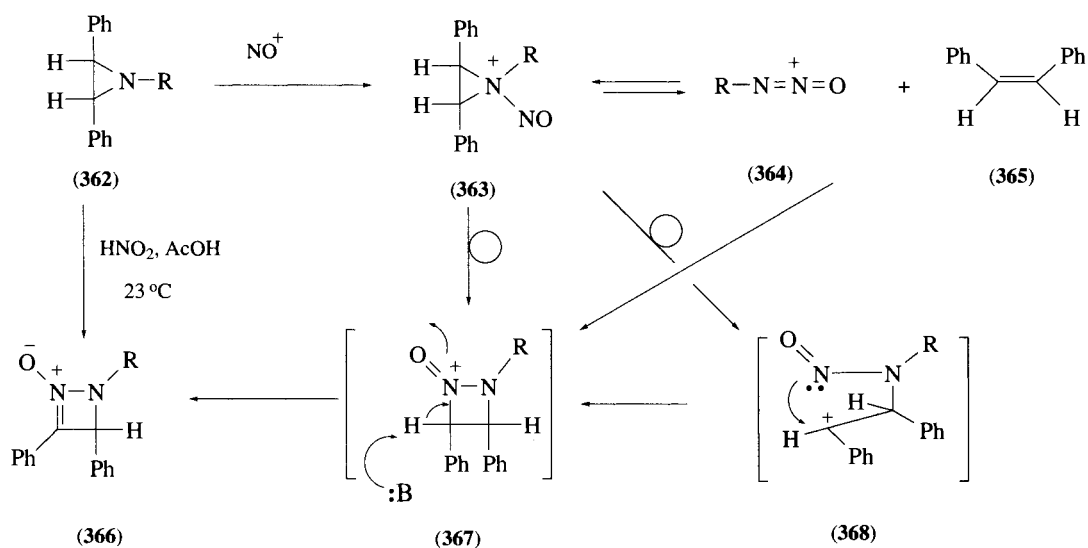
1.30.6.6 Ring Synthesis by Transformation of Another Ring

1.30.6.6.1 Synthesis of heterocycle by ring expansion of another ring

Diazetidines have been synthesized by the ring enlargement of aziridines and diaziridines. Alper *et al.* prepared 1,3-diazetidinone by bis(dibenzylideneacetone)palladium(0)-catalyzed carbonylation of diaziridines (**360**) <90OM762>. Several 1,3-diazetidinones (**361**) with substituents on ring carbon have also been synthesized. Cobalt carbonyl can be used in stoichiometric amounts for the ring expansion reaction of diaziridines (Equation (57)). Although two classes of aza- β -lactams are possible by the insertion of carbon monoxide into one of the two ring C—N bonds, it has been found that carbon monoxide gets inserted only into the N—N bond. The most suitable catalyst was found to be bis(dibenzylideneacetone) palladium (0) in DMF as a solvent <90OM762>.



The dihydrodiazete *N*-oxide (366) was prepared by Loeppky and co-workers by the ring expansion of *N*-nitrosoaziridine (363) <91JA2308>. The formation of dihydrodiazete *N*-oxide is expected to take place by an isomerization of *N*-nitrosoaziridinium ion (363) as shown in Scheme 45. The *N*-nitrosoaziridinium ion (363) can undergo ring opening to give benzylic carbocation (368) which undergoes intramolecular attack by the lone pair of electrons of the NO nitrogen to produce the intermediate (367). The latter undergoes loss of H^+ to give the dihydrodiazete (366). Alternatively, (363) can undergo isomerization to (367) or a chelotropic ring opening ((363) $\rightarrow$ (364) + (365)) followed by $[2\pi_s + 2\pi_a]$ cycloaddition to give (367). An *ab initio* calculation of rotomers of (368) and the cations (363), (366) and (367) has shown (368) to be unstable and hence to spontaneously close to (363) or (367). The energy calculation (MP₂/6-31G*/RHF/3-21G) studies predict the production of (367) via the cycloaddition reaction of (364) and (365) to be disfavored compared with that via the isomerization of (363) to (367).

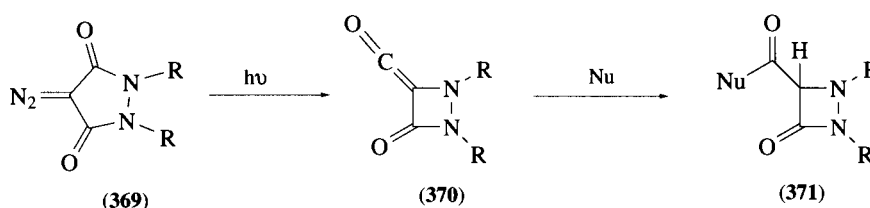


Scheme 45

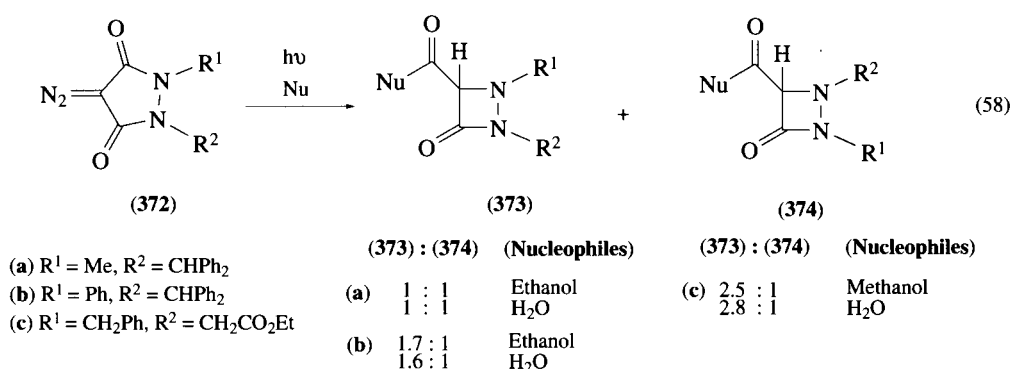
1.30.6.6.2 Synthesis of heterocycle by ring contraction of another ring

Large ring heterocycles containing two properly situated double bonds may undergo ring contraction reaction to give diazetidines, for example dimethyl 1,2-dihydropyridazine-1,2-dicarboxylate, which undergoes an intramolecular $[2 + 2]$ cycloaddition reaction to form 2,3-diazabicyclo [2,2,0]hex-5-ene on irradiation with a high-pressure mercury lamp <68CC686>. Several such examples have been compiled by Richter and Ulrich <83HC(42)443>. More recently in the mid-1980s Moody and co-workers extensively investigated the photochemical Wolff rearrangement of 4-diazopyrazolidine-3,5-diones (369), which undergo efficient ring contraction to 1,2-diazetidinones <84CC754, 87JCS(P1)877>.

When the diazocompound (369) is irradiated in ether containing ethanol, diethylamine, or water, the aza- β -lactam (371) is isolated as a result of a ring contraction reaction (Scheme 46). Nucleophiles such as ethanol act as ketene traps. The effects of several solvents and substituents have been examined. It is interesting to note that although the nitrogen lone pair participates in the amide resonance, the nitrogen atom migrates to the electron-deficient center to effect the observed ring contraction. Unsymmetrical *N,N*-disubstituted 4-diazopyrazolidine-3,5-diones yields a mixture of regioisomeric diazetidinones, depending on the migratory aptitudes of *N*-substituents. It has been observed that the *N*-alkyl group, bearing an electron-withdrawing group like an ester, shows reluctance to migrate (Equation (58)) <85TL3167, 87JCS(P1)885>. The relative migratory aptitudes of nitrogen groups follow the following order: $NPh > NCHPh_2 \approx NCH_2Ph \approx NMe > NCH_2COOEt$.



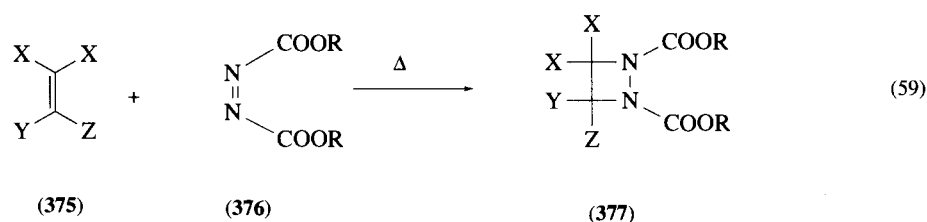
Scheme 46



1.30.6.7 Critical Comparison of Various Synthetic Routes

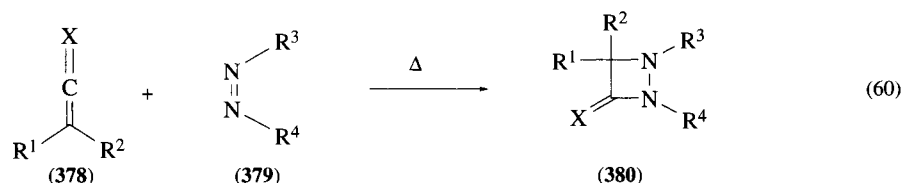
1.30.6.7.1 Synthesis of 1,2-diazetidines

1,2-Diazetidine derivatives are best prepared by [2 + 2] cycloaddition of alkenic with diazo compounds. The cycloaddition reaction proceeds smoothly when one of the components is activated either by electron-donating or electron-withdrawing groups, for example, a C=C bond substituted with electron-donating groups such as OR or NR_2 and an azo group by electron-withdrawing functionality (COR, COOR, CONH_2 , etc.) are suitable substrates for cycloaddition reaction (see, for example, Equation (59)). A number of such examples have been compiled by Richter and Ulrich <83HC(42)443>. The only alternative route to 1,2-diazetidine derivatives is by direct double alkylation of substituted hydrazines with 1,2-dihaloalkanes (Equation (39)) <78JA2806, 78JOC2785>.

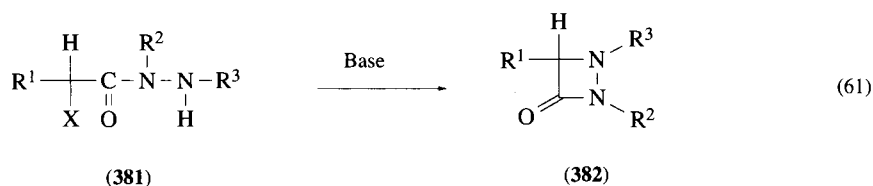


1.30.6.7.2 Synthesis of 1,2-diazetidinones

1,2-Diazetidinone is the most common derivative of 1,2-diazetidines and was the first isolated derivative of four-membered heterocycles with two nitrogen atoms. This class of compounds is prepared by the thermal [2 + 2] cycloaddition of ketene with diazo compounds (Equation (1)). A large number of derivatives of 1,2-diazetidinones prepared by this method have been collected by Richter and Ulrich <83HC(42)443>. Use of ketenimines instead of ketene furnished imino derivatives as shown in Equation (60) <67JHC155>, (see Section 1.30.6.4.2).



A less common but an elegant approach of carbenoid-mediated cyclization of diazohydrazides has been reported by Moody and co-workers (85TL3171, 87JCS(P1)899). These authors have achieved the synthesis of diazetidinones by a photochemical Wolff rearrangement of 4-diazopyrazolidine-3,5-dione Scheme 46 and Equation (58). A large number of diazetidinones have also been synthesized by an intramolecular cyclization of haloacetylhydrazones with suitable bases (Equation (61)) (see Section 1.30.6.1).



1.30.6.7.3 Synthesis of 1,2-diazetines

Δ^1 -1,2-Diazetines are best synthesized by low-temperature photochemical ring contraction reaction of either five-membered (68JA173) or seven-membered diazo heterocycles (72CC827, 76JCS(P1)362). Diazepines are also known to photoisomerize to substituted Δ^1 -1,2-diazetines (76TL305). In 1984 Δ^1 -1,2-diazetine derivatives have been isolated from the reaction of 1,2-diazetidione with pivoloxy chloride in the presence of a base (Equation (31)). 1,2-Diazetines with N=N are rather unstable and rarely isolated, for example 3,4-difluoro-3,4-dicyano-1,2-diazetine has been synthesized (see Equation (38)); however, the best method to prepare this class of compound is by oxidative cyclization of 1,2-bishydroxylamine to 1,2-diazetine-1,2-dioxide (Scheme 38) followed by deoxygenation to give tetramethyl-1,2-diazetine. The most stable compounds in this class, (31) and (32), are prepared by the method shown in Scheme 40.

1.30.6.7.4 Synthesis of 1,3-diazetidines

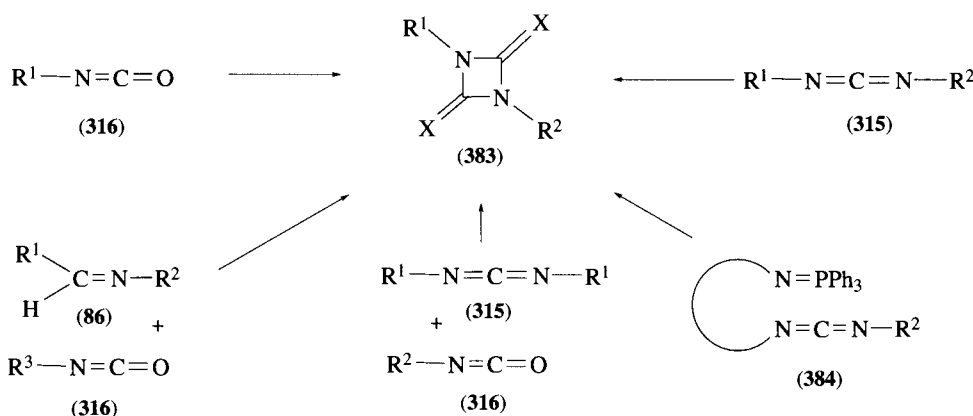
The most general method of synthesis of 1,3-diazetidines involves [2 + 2] cycloaddition reaction of C=N-containing substrates (Scheme 47). Dimerization of azomethines can afford 1,3-diazetidines. Thus, dimerization of imines and isocyanates furnishes substituted 1,3-diazetidines (see Sections 1.30.6.4.3(i) and (iii)). Cycloaddition of isocyanates to carbodiimides (see Section 1.30.6.4.3(ii)) and isocyanates with imines (Section 1.30.6.4.3(iv)) are alternative methods of syntheses. More recently in the late 1980s, Molina and co-workers have developed a new route via cycloaddition of imino-phosphoranes with carbodiimides and isocyanates (see Section 1.30.6.4.3(vi)) (86JCS(P1)2037, 90JCS(P2)1859).

1.30.7 APPLICATIONS IN RESEARCH AND INDUSTRY

Four-membered heterocycles with two nitrogen atoms are widely used in research, in particular because of their structural analogy with β -lactam antibiotics. Numerous examples of 1,3-diazetidines are known to be extensively used in the polymer industries.

1.30.7.1 1,2-Diazetidone Derivatives

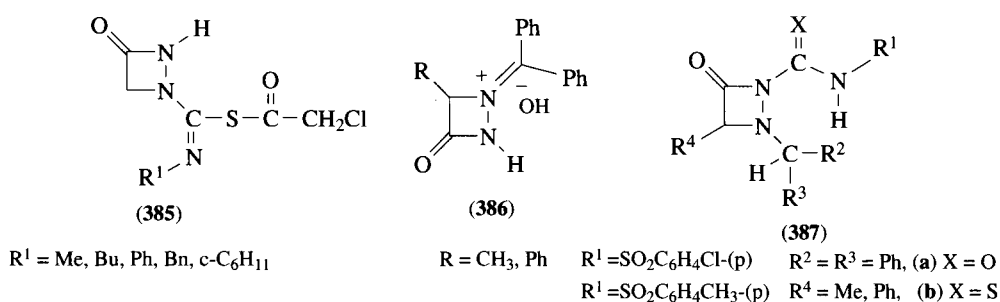
1,2-Diazetidones have been extensively studied by Taylor and co-workers on account of their close structural similarities to the highly potent β -lactam and related antibiotics such as carba-penems, theinamycin, etc. (83JOC4567, 84JOC113, 84JOC2204, 84JOC4415, 86JOC1530, 86JOC1537, 87JOC4107). Moody and co-workers have carried out extensive studies of the aza analogues of β -lactam-derived antiviral agents like penicillin and cephalosporins. The pioneering work of Greene and Gilbert was



Scheme 47

associated with the possible chemiluminescence studies of 3,3,4,4-tetramethyl- Δ^1 -1,2-diazetidene (38), which in principle bears structural similarity to tetramethyldioxetane <75JOC1409>. Although tetramethyl-1,2-diazetidene has strain energy of 102.5 kJ mol⁻¹ and high activation energy for the loss of nitrogen ($\Delta H^\ddagger = 132.6$ kJ mol⁻¹) and heat of exothermic thermolysis reaction (209 kJ mol⁻¹), it does not produce a singlet excited state but has sufficient energy to produce a triplet excited state of tetramethylethylene <75JA1875> and hence could not produce chemiluminescence. Tetramethyl-1,2-diazetidene-1,2-dioxide (40) acts as an efficient triplet state quencher of tetramethylethylene <72JA5077>.

Some of the interesting derivatives of aza- β -lactams (385) have been found to induce differentiation of Friend leukemia cells <86ABC1757>, whereas some other derivatives of diazetidines (385) are antineoplastic agents <85JAP(K)60239420>. 1,2-Diazetidinium inner salts (386) and 1,2-diazetidene-1-carboxamides (387a) have been found to be good medical fungicides <89USP4826971>. 1,2-Diazetidene-1-carbothiamide derivatives (387b) have been shown to possess herbicidal properties <77JAP(K)77110825>. The 4*H*-1,2,4-triazole-4-acetic acid derivative of 1,2-diazetidene has been found to release a development inhibitor with improved abilities in silver halide color photography <92EUP514896>. Interestingly, in 1993, it was shown that some of the 1,2-diazetidene-1,2-dioxide derivatives show vasodilatory activity. They were found to be capable of nonenzymatic generation of nitric oxide at physiological pH and exhibited spasmolytic and antihypertensive activities. Among several examples studied, 3-bromo-4-methyl-3,4-tetramethylenediazetidene-1,2-dioxide was found to possess spasmolytic effect commensurable with glyceryl trinitrate <93MI 130-01>.



1.30.7.2 1,3-Diazetidene Derivatives

The derivatives of 1,3-diazetidines have found wide application in the polymer industry. 1,3-Dicyclohexyl-1,3-diazetidene and 1,3-diphenyl-1,3-diazetidene have been found to inhibit the growth of six different strains of *Mycobacterium tuberculosis* <78MIP175226, 80MIP181447>. The corresponding dihydrochlorides have also shown antitubercular activity <82MIP191757>.

4-Oxo-2-aryl-3-amino-1-sulfonyl-1,3-diazetidene-2-carboxylic acid sulfonamides are used as virucides and bactericides <85EGP221735>. Some other derivatives of 1,3-diazetene have been found to

possess antiinflammatory and antidegenerative activities <88GEP(O)3820420>. The polymers derived from 1,3-diazetid-2,4-dione and aromatic amines are used for cross-linking in polyurethane synthesis <84GEP(O)3232736>. 1,3-Diazetid-2,4-dione derivatives are also used in making cross-linking agents which, when used with epoxyresins, give good electrophoretic coating material <90EUP349873, 91EUP449072>, cross-linker for electrodeposition coatings with yellowing resistance <87EUP293088>. These compounds are also used in cross-linking agents for powder coating <82MI 130-01>, cross-linked insulations <81EUP41192, 82JAP(K)8282981, 82JAP(K)8282983, 82JAP(K)8282984>, polyurethane thermal conductors <83JAP(K)58122913>, epoxy resins for thermosetting <81JAP(K)81110759>, heat-hardenable resins for electrical and electronic insertions <82JAP(K)57187313>, and in sheathing of optical fibers <82JAP(K)8281207, 82JAP(K)8281209>. They are also used in blends suitable for automobile interiors <90GEP(O)3839856> and for coatings and sealing agents with good solvent resistance <92GEP(O)4101527>. 1,3-Diazetid-2,4-dione-derived polymers are also used in adhesives for plastic, metals, ceramics, and cellulose <84JAP(K)5998180>; for polyalkene resin or rubber articles <86GEP(O)3601272>; for glass and thermoplastics <81MI 130-01>; adhesions to plastic surfaces <83USP4397707>, with peeling strength and heat resistance <83JAP(K)5816588>; in storage-stable, heat-activable, polyurethane adhesives <85GEP(O)3325735, 85GEP(O)3403499, 90EUP402726, 90EUP402728, 91EUP417540, 92EUP508259, 92EUP512198>; in aqueous adhesives <86GEP(O)3521618>; adhesions capable of bonding metals to plastic with temperature resistance <88JAP(K)63256675>; in adhesion improvers on textiles <89EUP327047>, and for fastness of colors <87GEP(O)3529530>. Use of 1,3-diazetid-2,4-dione derivative gives spandex fibers of good spinnability <82JAP(K)82101016>. They are also used in coatings and adhesives with satisfactory impact strength and resistance to chemicals, water and weather <92EUP495307, 92JAP(K)04275359>. 1,3-Diazetidone derivatives are also used in polyester-polyurethane moldings which offer good abrasion resistance and which make good shoe soles <91GEP(O)3939698>. They are useful in compositions used in semiconductor devices with heat resistance <83JAP(K)5802456, 86JAP(K)61265847, 89JAP(K)0156720, 89JAP(K)0174214, 89JAP(K)0185215, 90JAP(K)0245519>. Some of the derivatives of 1,3-diazetid-2,4-diones are also used in the conducting layer of electrostatic recording material <83GEP(O)3227088>.

1,3-Diazetid-2,4-dione derivatives are used for storage-stable, heat-curable thermosetting mixtures <84GEP(O)3228670, 84GEP(O)3228723, 84GEP(O)3228724, 84JAP(K)59166525, 85EUP145995, 85GEP(O)3343124, 86GEP(O)3517333, 89GEP(O)3820705, 91EUP431414> and in reducing water permeability of underground caverns for the storage of purified natural gas or other fuel gases <84EUP103204>. They also find use in rubber manufacture: for example, in the manufacture of polyurethane elastomers and polymerization inhibitors <85GEP(O)3403500>. They are used in making thermoplastic polyurethane elastomers <83JAP(K)58157814>, microcapsules useful in copying-paper <85EUP162938>, aqueous dispersion binders for particle boards <85USP4496684>, and photographic development inhibitors <92EUP514896>. They are useful in the manufacture of electrophotographic printing plates with high printing resistance and image quality <91USP5069992> and are used as surfactant for dispersing of magnetic powders on tapes and discs <84JAP(K)59129937>. They are used in photosensitive compositions for presensitized lithographic plates <87GEP(O)3716607, 87JAP(K)62175734, 88GEP(O)3738669, 88JAP(K)63287947, 89JAP(K)01134354, 92JAP(K)04276753, 92JAP(K)0485542>. They are also used in the manufacture of storage-stable, heat-curable powders for polyurethanes <91EUP431413>, cold-curable compositions for polyurethanes <87GEP(O)3529251> and in orthopedic casts <87MIP561738>. 1,3-Diazetid-2,4-dione derivatives are useful in cleaning, passivating, and inhibiting agents for corroded metallic materials <88MIP252378>. 1,3-Diazetid-2,4-dione derivatives find application in coating materials of wide variety <90GEP(O)3829587, 91EUP461500, 92EUP481318, 92EUP496205> and in reaction injection molding compositions <86GEP(O)3516730>. They are also used in vulcanizing agents for rubbers: for example, to impart good gasoline resistance to nitrile rubber <83RC853>, for natural rubber <83MI 130-01>, chloroprene rubber <84MI 130-01>, liquid rubber used in insulator materials <81JAP(K)81133326>, and various diene rubbers <81EUP25355>.

ACKNOWLEDGEMENT

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1.31

Four-membered Rings with One Oxygen and One Nitrogen Atom

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1.31.1 STRUCTURES

1.31.1.1 Types, Nomenclature, and Numbering

Heterocycles containing one nitrogen atom and one oxygen atom in a four-membered ring belong to the oxazetidine family of compounds. The 1,2- and 1,3-oxazetidines and their derivatives are the most common, but a significant number of unsaturated analogues, the 1,2- and 1,3-oxazetes, are known. Some generalized structures (R = any atom or group) are depicted in Figure 1, including neutral species, anions, cations, carbenes, and radicals. Not all types have been reported and those that are unknown but included (somewhat arbitrarily) in the list are marked with an asterisk following the name.

1.31.1.2 Background

The chemistry of four-membered heterocycles with one nitrogen and one oxygen atom in the ring was reviewed in 1984 by Timberlake and Elder as part of a chapter on four-membered heterocyclic rings with two or more heteroatoms (84CHEC-I(7)449). Moderhack reviewed 1,2-oxazetidines with imino substituents within a broader context in 1985, and both imino- and oxo-substituted 1,2-oxazetidines in 1993 (85S1083, 93JHC579).

In order to provide for continuity, this chapter includes some material already covered in previous reviews, as well as some of the primary references cited there. Readers should understand that, while reading this review will give them an overview of the field, the background will be distorted because of the necessity for selection. In particular, many of the early contributors to the field will be inadequately recognized unless the prior reviews and the primary references are consulted also.

1.31.1.3 Theoretical Methods

Several computational studies of the potential energy surfaces of oxazetidines and related compounds have been published. Fabian examined the possible cycloaddition reactions between acrolein and ketenimine (92ACH347). Two of the twelve possible products of [4 + 2] and [2 + 2] cycloaddition

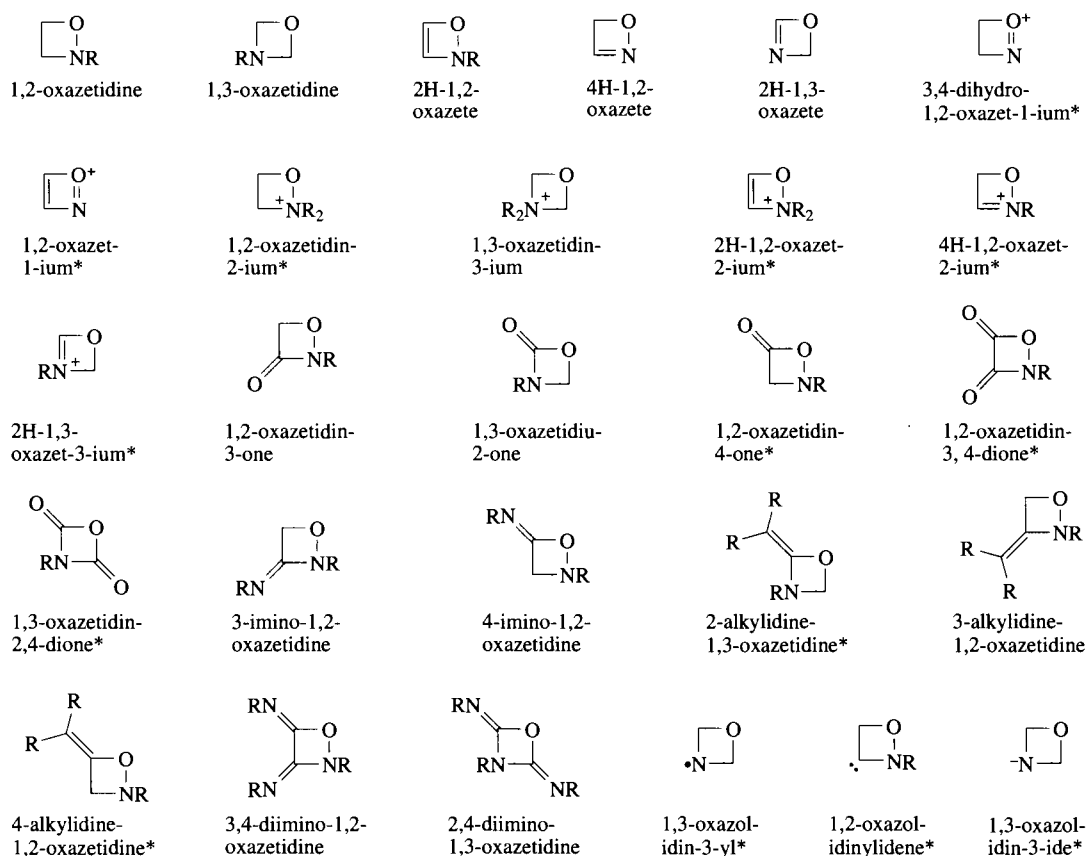
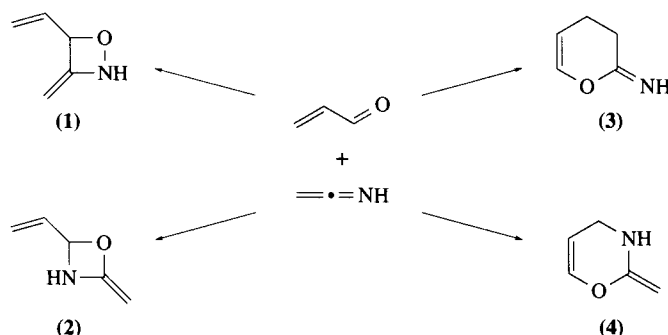


Figure 1 Generalized structures. Unknown types are indicated with an asterisk.

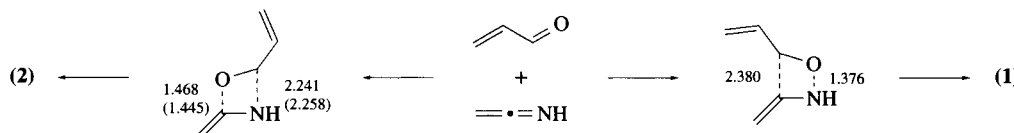
products are oxazetidines (1) and (2) (Scheme 1). The reaction enthalpies by AM1 and PM3 (bracketed numbers) were found to be 41.3 (23.5) kcal mol⁻¹ for formation of the 1,2-oxazetidine (1) and 12.0 (−13.5) for the 1,3-oxazetidine (2), suggesting that the 1,3-isomer is more stable by about 33 kcal mol⁻¹. The activation energies for formation of the 1,2- and 1,3-isomers, 102.3 and 67.5 kcal mol⁻¹ (AM1), respectively, nearly reflected the difference in calculated stabilities of the products. However, two [4 + 2] cycloadditions, to form (3) and (4), were found to be favored over [2 + 2] cycloadditions.



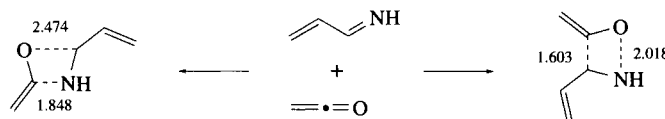
Scheme 1

Schemes 2 and 3 show the bond lengths in the transition state for the formation of (1) and (2) by the [2 + 2] cycloaddition mechanism. In both cases, bonding to oxygen of acrolein (N—O and C—O bond formation in (1) and (2), respectively) is most advanced in the transition state. While neither

oxazetidine is the preferred [2 + 2] product, a direct comparison of all the data concerning (1) and (2) would suggest that 1,3-oxazetidine formation is clearly favored over 1,2-oxazetidine formation <92ACH347>.



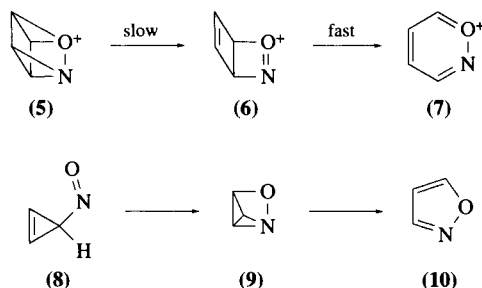
Scheme 2



Scheme 3

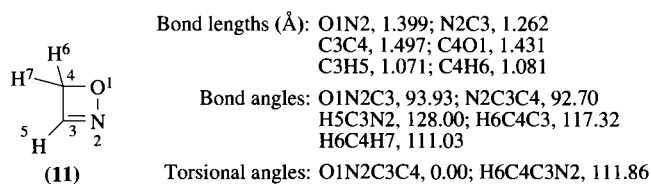
A related study addresses the [2 + 2] and [4 + 2] cycloaddition transition states for reaction of ketene with 1-azabutadiene, as calculated by AM1 methods <94JPO1>. The AM1 transition state bond lengths are also shown in Schemes 2 and 3. The 1,3-oxazetidine derivative is both the thermodynamically and the kinetically favored product; the reaction enthalpies for the 1,3- and 1,2-systems were 10.3 and 44.8 kcal mol⁻¹, respectively while the activation energies were 17.5 and 105.6 kcal mol⁻¹, respectively. Indeed, formation of the 1,3-oxazetidine system has one of the lowest activation barriers for all of the cycloadditions studied <94JPO1>.

Minken *et al.* have studied the valence isomers of the nitrosocyclobutyl cation by the MINDO/3 and *ab initio* (STO-3G) methods <87ZOR717>. Two of those isomers have oxazetidine or oxazete skeletons, corresponding to prismane and Dewar benzene, respectively (Scheme 4). They concluded that the heteroprismene cation (5) may exist in a relatively deep well but that the hetero Dewar benzene cation (6) is very unstable kinetically, relaxing over a very low barrier to the 2-azapyrylium cation (7). The same authors also investigated the potential energy surface of nitrosocyclopropene <86ZOR19>. They found that the most stable structures are (8) and the 1,2-oxazetidine (9). The latter was found to have the lower heat of formation (70.2 vs. 71.5 kcal mol⁻¹) by the MINDO/3 method. Both are unstable relative to isoxazole (10).

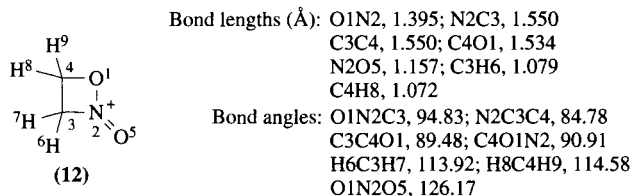


Scheme 4

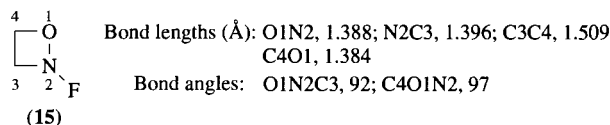
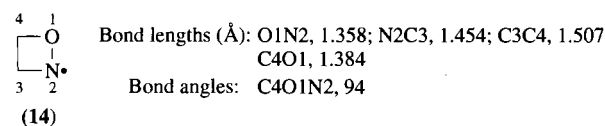
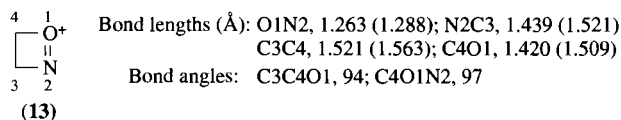
The structure of 4H-1,2-oxazete (11) has also been deduced computationally <92JST(258)167>. Its geometry is optimized at the HF/6-31G* level and its C=N stretching frequency, calculated at the same level of theory, was predicted to be 1697 cm⁻¹. Relative to *cisoid* nitrosoethylene, the oxazete is stabilized by 2.68 kcal mol⁻¹. Transition states for ring opening to nitrosoethylene, and for fragmentation to formaldehyde and HCN, lie 51.6 and 73.9 kcal mol⁻¹ above the oxazete, respectively, suggesting that the oxazete should have considerable kinetic stability.



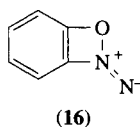
A similar study of the energy surface for ethylene plus NO_2^+ , based on Gaussian 80 and 83, led to the geometry below for the 1,2-oxazetidin-2-onyl cation (**12**), which corresponds to one energy minimum on that surface <84JA1074>. Relative to the components, NO_2^+ plus ethylene, the species is stabilized by 80.9 (3-21 G//3-21 G), or 52.6 kcal mol⁻¹ (6-31 G*//3-21 G).



Minyaev *et al.* studied the gas-phase reactions of nitrosyl fluoride with ethylene by computational methods. Ionic, radical, and concerted mechanisms were considered <87ZOR2508>. The ionic and radical mechanisms involve 1,2-oxazet-1-ium (**13**) and 1,2-oxazetidin-2-yl (**14**) intermediates, respectively. Calculated geometries (bond lengths in Å) for the cation, by MINDO/3 and *ab initio* (brackets) methods are shown in (**13**)–(**15**). Those for the radical came from use of UMINDO/3 while those of the oxazetidine product were obtained with use of MINDO/3. It was found that there are barrier-free paths to either 1-fluoro-2-nitrosoethane or to 2-fluoro-1,2-oxazetidine (**15**) but the former is preferred on the basis of the energetics.



Structure (**16**) was ruled out as an intermediate in the photoisomerization of 1,2,3-benzoxadiazole, in part because of its calculated enthalpy of formation, 124 kcal mol⁻¹, by MNDO <84AG(E)509>.



The geometry of a series of conjugated carbonyl and thiocarbonyl systems has been calculated using MNDO geometry optimizations in an effort to evaluate geometry changes brought about by negative hyperconjugative interactions. Two compounds, 1,3-oxazetidin-2-one (**17**) and 1,3-oxazetidin-2-thione (**18**) were a part of the study and Table 1 gives some molecular bond angles obtained. In each molecule, the exocyclic C=X unit shows a twist toward the oxygen. This interaction is attributed to a favorable negative hyperconjugation of the lone pairs of the X atom with the σ^* orbital of the C—O bond of the ring. The amount of twist in (**17**) and (**18**) (tilt angle: defined as $\angle \text{XCN} - \angle \text{XCO}$) was small compared to the tilt angles in other four-membered heterocycles which possessed more varied heteroatoms <89JST(194)135>.

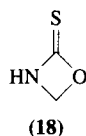
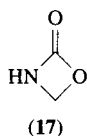


Table 1 Calculated bond angles (MNDO) of 1,3-oxazetidin-2-one and 1,3-oxazetidin-2-thione.

	$\angle NCO$	$\angle XCN$	$\angle XCO$	Tilt angle ^a
17 (X = O)	92.7°	136.8°	130.8°	6.2°
18 (X = S)	92.6°	134.9°	132.4°	2.5°

^aTilt angle = $\angle XCN - \angle XCO$.

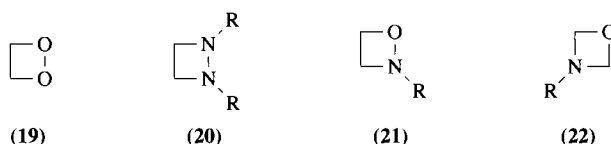
1.31.1.4 Molecular Dimensions

A search of the Cambridge Crystallographic Database (updated October 1995), provided no structures containing the 1,2- or 1,3-oxazete or oxazetidine skeleton. Molecular dimensions of small molecules can be deduced from microwave spectra in favorable cases. That technique has apparently not been applied to oxazetidines and related compounds.

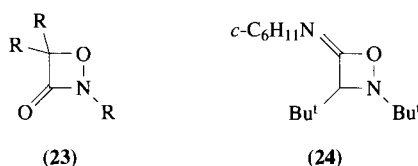
1.31.1.5 Spectroscopy

1.31.1.5.1 Ultraviolet spectroscopy

Reasonable models for 1,2-oxazetidines are the 1,2-dioxetanes (**19**) and 1,2-diazetidines (**20**). The former generally have $\lambda_{\max}$ near 280 nm, with a band width that makes some of them yellow <75CJC1103, 85HC(42)351, 92CB235>. The latter are colorless and absorb very weakly, if at all, in the ultraviolet. It is not clear whether or not the 1,2-oxazetidines (**21**) absorb significantly at wavelengths above 200 nm, since the absorptions shown by some members of the family can be attributed to the substituents rather than to the basic framework. 1,3-Oxazetidines (**22**) without ultraviolet-active substituents are probably transparent in the 200–400 nm region of the electronic spectrum. Ultraviolet spectra of saturated 1,2- and 1,3-oxazetidines were not found.



Unsaturated analogues, the 1,2-oxazetidinones and corresponding imines, as well as the various oxazetes, are expected to have $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ transitions that should be in the readily accessible ultraviolet region. Some of them are not easily observable because of very small extinction coefficients. Electronic spectra of simple 1,2-oxazetidin-3-ones were not found and the absorptions of those with aryl substituents can probably be attributed to those substituents. Several 1,2-oxazetidin-3-ones (**23**) are described as colorless oils or solids <82CZ442, 90AP(323)967, 93PHA669>. 2,3-di-*t*-Butyl-4-cyclohexylimino-1,2-oxazetidine (**24**) is yellow <77CC831>. A 4H-1,2-oxazete is colorless <80TL2025>. Some 3-alkylidene-1-oxetan-2-ones, that may serve as models for particular oxazetidinones, are yellow or even red <93JOC322>. A 4H-1,2-oxazete-2-oxide has $\lambda_{\max} = 222$ nm, $\epsilon = 7.4 \times 10^3$ <68AG(E)637>. The ultraviolet spectra of nitrones are similar <84CHEC-I(7)449>.



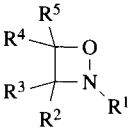
1.31.1.5.2 Photoelectron spectroscopy

Photoelectron spectra of the 1,2- or 1,3-oxazetidines and their derivatives were not found.

1.31.1.5.3 Infrared and Raman spectroscopy

Infrared spectra of 1,2-oxazetidines include a band in the range 1350–1410 cm^{-1} that has been ascribed to a ring motion. Falk and Readio reported the vibrational spectra of ten perfluoro-1,2-oxazetidines, in which the average frequency for that band was 1390 cm^{-1} and the range was 1366–1422 cm^{-1} [69JOC4088]. 2-Cyano-3,3,4,4-tetramethyl-1,2-oxazetidine absorbs at 1360 cm^{-1} [90MI 131-01]. The NH band of 3,3,4-trifluoro-4-X-1,2-oxazetidines (X = F, Cl, Br) appears at 3226 cm^{-1} [69JOC4088]. The NH band for 4-(chlorodialkoxycarbonyl)-methyl-4-trichloromethyl-1,3-oxazetidin-2-ones was measured at 3370–3380 cm^{-1} [80S571]. Some infrared data for 1,2-oxazetidines are gathered in Table 2.

Table 2 Infrared data for 1,2-oxazetidines.

	IR (cm^{-1})		Ref.
	Ring	Substituent	
R ¹ = H R ² –R ⁵ = F	1408 ^a	3226 (NH)	69JOC4088
R ¹ = $\text{c-C}_4\text{F}_7$ R ² –R ⁵ = F	1415 ^b		84IC3654
R ¹ = $\text{c-C}_5\text{F}_9$ R ² –R ⁵ = F	1425 ^b		84IC3654
R ¹ = CN R ² –R ⁵ = Me	1360	2260 (CN)	90MI 131-01

^aAverage ring frequency, ten compounds with various R¹, 1390 cm^{-1} . ^bAssigned to N—O motion.

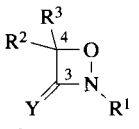
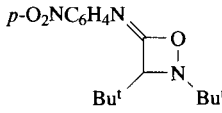
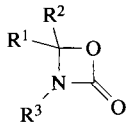
Infrared data can be a diagnostic tool for the identification of 1,2- and 1,3-oxazetidines and related species when the heterocycle bears exocyclic unsaturation. 1,2-Oxazetidin-3-ones have carbonyl stretching frequencies more reminiscent of 1,2-diazetidinones than of β -lactams. Burchardt and Geffken reported carbonyl frequencies between 1765 and 1790 cm^{-1} for 20 1,2-oxazetidin-3-ones [90AP(323)967, 93PHA669]. Lauterbach and Geffken found 1780 cm^{-1} as the average carbonyl frequency for thirteen 1,2-oxazetidin-3-ones [86LA1478]. Moderhack and Stolz reported 1760 and 1780 cm^{-1} , respectively, for 4-*t*-butyl-2-phenyl-1,2-oxazetidin-3-one and for the 2,4-di-*t*-butyl analogue [90CZ5]. 1,2-Diazetidinones absorb in the range 1780–1790 cm^{-1} whereas typical monocyclic β -lactams have carbonyl frequencies between 1730 and 1760 cm^{-1} [84CHEC-I(7)237, 84CHEC-I(7)449]. Examples of infrared characteristics of the 1,2- and 1,3-oxazetidinones are in Table 3.

1,2-Oxazetidin-4-ones are unstable (loss of CO₂) and their CO frequencies have apparently not been reported. Given that β -lactones have carbonyl frequencies in the range 1800–1835 cm^{-1} , those oxazetidinones probably absorb at higher frequencies than corresponding 1,2-oxazetidin-3-ones.

3-Imino-1,2-oxazetidines have strong C=N stretching bands in the infrared, between 1700 and 1715 cm^{-1} [86CB3411, 93JHC579]. In the case of 2,4-di-*t*-butyl-3-arylimino-1,2-oxazetidines, that band moves to 1725 cm^{-1} when the aryl group is 2,6-Me₂C₆H₃, suggesting some loss of conjugation between aryl and imine functional groups from steric hindrance in a coplanar conformation. In 4-imino-1,2-oxazetidines the C=N frequency is higher; in the range 1740–1758 cm^{-1} (Table 3) [77CC831, 79CZ268, 80AG(E)45, 84LA1685, 93JHC579]. This feature can be taken as support for the expectation noted above, that the unstable 1,2-oxazetidin-4-ones probably have higher carbonyl frequencies than 3-one analogues.

The carbonyl stretching frequency of 1,3-oxazetidin-2-ones can be observed in the 1815–1850 cm^{-1} range [67TL3637, 80S571, 81IZV758, 84JA7996]. For instance *N*-phenyl-1,3-oxazetidin-2-one has a carbonyl stretching frequency at 1818 cm^{-1} [67TL3637]. For highly fluorinated analogues, carbonyl

Table 3 Infrared spectra of oxazetidinones and iminoxazetidines.

Compound	Infrared (cm^{-1})	Ref.
		
$\text{R}^1 = \text{CH}_2\text{Ph}$, $\text{Y} = \text{O}$ $\text{R}^2 = \text{Me}$, $\text{R}^3 = 4\text{-MeOC}_6\text{H}_4$	1775(KBr) ^a	90AP(323)967
$\text{Y} = \text{O}$, various $\text{R}^1\text{-R}^3$	1775–1790 ^b	82CZ442
$\text{R}^1 = \text{Me}$, $\text{Y} = \text{O}$ $\text{R}^2 = \text{H}$, $\text{R}^3 = 3\text{-thienyl}$	1770(KBr) ^c	84CZ293
$\text{R}^1 = \text{Me}_2\text{CC(Ph) = NOH}$ $\text{Y} = \text{O}$, $\text{R}^2 = \text{R}^3 = \text{H}$	1474(KBr)	84KGS115
$\text{R}^1 = \text{CH}_2\text{Ph}$, $\text{Y} = \text{O}$ $\text{R}^2 = \text{R}^3 = 2\text{-thienyl}$	1800 ^d	84LA894
$\text{R}^1 = \text{R}^2 = \text{Me}$ $\text{Y} = \text{O}$, $\text{R}^3 = 4\text{-FC}_6\text{H}_4$	1780 (film)	93PHA669
$\text{R}^1 = \text{Ph}$, $\text{Y} = \text{O}$ $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Bu}^t$	1760 (KBr)	90CZ5
$\text{R}^1 = \text{c-C}_6\text{H}_{11}$, $\text{Y} = \text{O}$ $\text{R}^2 = \text{R}^3 = \text{Ph}$	1785 (KBr) ^e	86LA1478
$\text{R}^1 = \text{R}^2 = \text{Bu}^t$, $\text{R}^3 = \text{H}$ $\text{Y} = 2,6\text{-Me}_2\text{C}_6\text{H}_3\text{N}$	1725 (KBr) ^f	86CB3411
	1730 (KBr) ^g	84LA1685
		
$\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$	1818 (KBr)	67TL3637
$\text{R}^1 = \text{C(Cl)(CO}_2\text{Et)}_2$, $\text{R}^2 = \text{CCl}_3$, $\text{R}^3 = \text{H}$	1850 (CH_2Cl_2)	80S571
$\text{R}^1 = \text{NMe}_2$, $\text{R}^2 = 3\text{-pyridyl}$ $\text{R}^3 = \text{C(O)CCl}_3$	1830 ^h	81IZV758

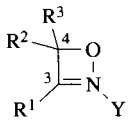
^aThe range for twenty 1,2-oxazetidine-3-ones was 1765–1790 cm^{-1} . Spectra were obtained with KBr discs or from liquid films (90AP(323)967). ^bRange for six 1,2-oxazetidine-3-ones 1775–1790 cm^{-1} ; KBr or film (82CZ442). ^c $\text{R}^1 = \text{benzyl}$, 1770 cm^{-1} (KBr) (84CZ293). ^dFor twelve 4-(2-thienyl) or 4,4-di(2-thienyl) analogues, the range was 1775–1800 cm^{-1} ; KBr or film (84LA894). ^eRange for thirteen 1,2-oxazetidine-3-ones, 1760–1790 cm^{-1} ; KBr or film (86LA1478). ^fRange, depending on arylimino group, between 1710 and 1725 cm^{-1} for six compounds. The highest frequency, for the compound in the table, presumably reflects decreased conjugation between the aryl group and the double bond. ^gFor 3-*t*-butyl-4-cyclohexylimino-2-methyl-1,2-oxazetidine, 1775 cm^{-1} (CCl_4) (77CC831). ^hMode of infrared acquisition not explicitly given.

frequencies are found in the 1860–1930 cm^{-1} range, and they may appear as a doublet (67JOC2960, 80DOK(253)886). 2-Benzoylimino-3-methyl-1,3-oxazetidin-4-*t*-butylimine showed two strong bands at 1689 and 1634 cm^{-1} (72JA3484). A transient highly fluorinated 1,3-oxazetidine bearing an exocyclic imino group has a $\text{C}=\text{N}$ stretching band at 1790 cm^{-1} (83JOC1694).

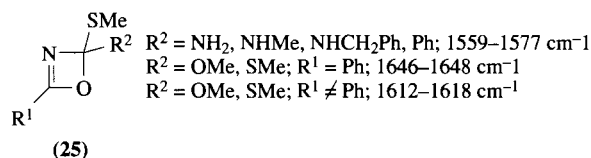
Infrared data was not reported for the only known 3,4-diimino-1,2-oxazetidine (62DOK(142)596). Only one 3-methylene-1,2-oxazetidine has been reported, without identification of the frequency of the exocyclic $\text{C}=\text{C}$ stretching motion (65JCS5602).

An imino double bond in the ring, as in the 4H-1,2-oxazetes, gives rise to a band at 1585 cm^{-1} (80TL2025). That frequency for $\text{C}=\text{N}$ stretching is in keeping with $\nu_{\text{C}=\text{N}}$ of 1-azetine at 1570 cm^{-1} (81JA468). The net effect of the ring oxygen is to increase the $\text{C}=\text{N}$ frequency slightly, relative to that of the carbon analogue (Table 4). The $\text{C}=\text{N}$ stretching frequency of 2H-1,3-oxazetes (**25**) has been shown to be between 1559 and 1648 cm^{-1} . Depending on substituents, this range can be further broken down (79CCC1324). Raman spectra of the various oxazetidines were not found.

Table 4 Infrared data for oxazetes and oxazete-*N*-oxides.

	cm^{-1}	Ref.
$\text{R}^1 = \text{H}, \text{Y} = :$ $\text{R}^2 = \text{R}^3 = \text{Bu}^t$	1595 (CCl_4)	75AG(E)70
$\text{R}^1 = \text{Bu}^t$ $\text{R}^2 = \text{R}^3 = \text{SMe}$	1585 (neat)	80TL2025
$\text{R}^1 = \text{COCl}, \text{Y} = \text{O}$ $\text{R}^2 = \text{R}^3 = \text{Bu}^t$	1680 (CCl_4) ^a	75AG(E)69
$\text{R}^1 = \text{CH}_2\text{NO}_2, \text{Y} = \text{O}$ $\text{R}^2 = \text{R}^3 = \text{Bu}^t$	1690 (CCl_4) ^b	75AG(E)69
$\text{R}^1 = \text{Me}, \text{Y} = \text{O}$ $\text{R}^2 = \text{R}^3 = \text{Bu}^t$	1698 (CCl_4)	68AG(E)637

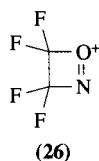
^aCarbonyl frequency 1730 cm^{-1} . ^bNitro group, 1570 cm^{-1} . Compounds with CH(R)NO_2 groups are reported in the same reference.



1.31.1.5.4 Mass spectrometry

Electron impact mass spectra of 1,2-oxazetidines include relatively weak parent ion signals. For example, 4-chloro-3,3,4-trifluoro-1,2-oxazetidine gave intensities of 0.72 and 1.9% for the parent ions with ^{37}Cl and ^{35}Cl , respectively ($\langle 69\text{JOC}4088 \rangle$). 2-Cyano-3,3,4,4-tetramethyl-1,2-oxazetidine gave a parent ion signal of 2.5% intensity ($\langle 90\text{MI } 131\text{-}01 \rangle$) while 7.8% was reported for 3,3,4,4-tetrafluoro-1,2-oxazetidine ($\langle 69\text{JOC}4088 \rangle$). A curious feature in the mass spectrum of the 2-cyano compound is the base peak at $m/z = 110$, corresponding to $\text{M}-2\text{Me}$. The base peak in the mass spectra of perfluoro-1,2-oxazetidines ($m/z = 47$) corresponds to $(\text{COF})^+$ and a weak signal at $m/z = 100$, corresponding to $[\text{C}_2\text{F}_4]^+$, is common ($\langle 69\text{JOC}4088 \rangle$). 2-Perfluorocyclobutyl-3,3,4,4-tetrafluoro-1,2-oxazetidine gives a parent ion signal ($m/z = 311$, $(\text{C}_6\text{F}_{11}\text{NO})^+$) as well as prominent peaks for $[2+2]$ fragmentation to $(\text{CF}_2\text{O})^+$ ($m/z = 66$) and $(\text{C}_5\text{F}_9\text{N})^+$ ($m/z = 245$). Fragmentation of the oxazetidine ring in the other sense, to $(\text{C}_2\text{F}_4)^+$ ($m/z = 100$) and to $(\text{C}_4\text{F}_7\text{NO})^+$ ($m/z = 211$) was also observed. The mass spectrum of the 2-perfluorocyclopentyl analogue showed a similar pattern ($\langle 84\text{IC}3654 \rangle$).

4H-1,2-Oxazetes can show quite substantial parent ion signals in the electron impact mass (EI) spectra. 3-*t*-Butyl-4,4-bis(methylthio)-1,2-oxazete gave $m/z = 205$ (M^+ , 36%), 122 ($((\text{MeS})_2\text{CO})^+$, 24%), 75 ($(\text{CHS}_2)^+$, 100%), 57 ($t\text{-Bu}^+$, 100%) and some other interesting signals but not 83 ($(\text{Me}_3\text{CCN})^+$) ($\langle 80\text{TL}2025 \rangle$). The perfluoro-1,2-oxazetidine with substituent $\text{CF}_2\text{CF}_2\text{C}(\text{CF}_3)_3$ at N2 affords a parent ion signal, as well as signals for loss of F, CF_3 , C_4F_9 , and C_6F_{13} (the substituent at N). The latter loss formally leads to the 3,3,4,4-tetrafluoro-3,4-dihydro-1,2-oxazet-1-ium ion (26) although one cannot be sure of the connectivity, of course ($\langle 82\text{MI } 131\text{-}01 \rangle$).



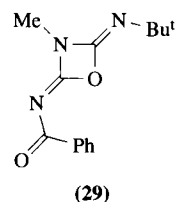
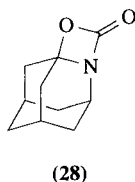
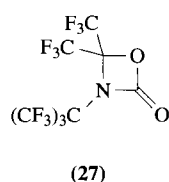
2-Phenyl-4-*t*-butyl-1,2-oxazetidin-3-one gave a parent ion signal ($m/z = 205$) that was 5% of the intensity of the base peak ($m/z = 91$). Loss of 28 mass units (6%) presumably indicates loss of CO. Strong signals for $(\text{PhNCO})^+$ ($m/z = 119$, 91%), for $(\text{Me}_3\text{CCHO})^+$ ($m/z = 86$, 43%), and for Me_3C^+

($m/z = 57$, 81%) suggest ring fractures in the retro-[2 + 2] sense as major pathways <90AP(323)967>. The base peak at $m/z = 91$ corresponds to $(C_6H_5N)^+$, which is presumably the azepine skeleton.

2,4-di-*t*-Butyl-1,2-oxazetidin-3-one gave a more pronounced parent signal ($m/z = 185$, 33%), as well as a stronger M-28 signal (12%). Loss of C_4H_8 gave $m/z = 129$ (85%) and both ketene and isocyanate signals ($(Me_3CCH=C=O)^+$, $m/z = 98$, 42%; $(Me_3CN=C=O)^+$, $m/z = 99$, 38%) were strong, suggesting again that formal [2 + 2] cycloreversions play an important role <90AP(323)967>. Some β -lactams also give rise to isocyanate fragments in their electron impact mass spectra <B-71MI 131-01, 86OMS(21)55>.

3-Imino-1,2-oxazetidines give rise to parent ion signals that are 25–75% of the base peak intensities. 3-Arylimino-2,4-di-*t*-butyl-1,2-oxazetidines show, as major fragmentation patterns, the formation of ketenimine ($(ArN=C=CHCMe_3)^+$) and carbodiimide ($(ArN=C=NCMe_3)^+$). The base peak is generally that corresponding to loss of CH_3 from the ketenimine fragment, to form $(ArN=C=CHCMe_2)^+$, but that property may be conferred by the *t*-butyl substituent <86CB3411>.

Mass spectrometry has also been a key tool for the confirmation of structural assignment of several 1,3-oxazetidine-based heterocycles. A common mode of breakdown of 1,3-oxazetidin-2-ones and 2-imines under mass spectrometric conditions is retro-[2 + 2] cycloaddition. Thus for 1,3-oxazetidin-2-one (**27**), m/z fragments corresponding to $(CF_3C\equiv NC(CF_3)_3)^+$ and $((CF_3)_2C=O)^+$ are observed, while for (**28**) $(M-CO_2)^+$ is an identifiable fragment <80DOK(253)886, 84JA7996>. Lowe *et al.* noticed that the extent of retro-[2 + 2] fragmentation of *N*-phenyl-1,3-oxazetidin-2-one was dependent on the temperature of the inlet system for introducing the sample into the mass spectrometer <76BBR(73)465>. At low temperature, a significant molecular ion ($m/z = 149$) was recorded, but when the sample was introduced at 127°C, the fragment for $(CO_2)^+$ was more intense. Bis(imino) species (**29**) shows fragments consistent with the ions $(PhC(O)N=C=O)^+$ and $(MeN=C=NBu^t)^+$ <72JA3484>. In all of these examples, there are also fragmentation patterns arising from the substituents of the heterocycle.



Mass spectrometry was one of the tools used to assign the oxazete ring structure to compounds (**25**). Kristian *et al.* show a clear chart demonstrating the most common fates of oxazetes (**25**) under mass spectrometric conditions. The molecular ion peak tends to be rather strong (95–100%) while $(RCO)^+$ and $(M-SMe)^+$ are among the more important fragments <79CCC1324>.

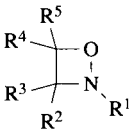
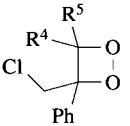
1.31.1.5.5 NMR spectroscopy

In this section those spectroscopic features that could be helpful for the identification of oxazetidines and/or for assessment of their geometries are emphasized and routine features, such as chemical shifts and coupling constants concerning substituent groups remote from the ring are omitted.

(i) Proton NMR spectroscopy

Protons at ring atoms of oxazetidines are not commonplace and not enough compounds were found for examples of all the various values of ^2J , $^3J_{cis}$, and $^3J_{trans}$ of 1,2-oxazetidines. The available data is in Table 5, together with ^1H chemical shift of the CH_2 group of a 1,2-dioxetane model. Proton NMR data for 3-imino-1,2-oxazetidines, 1,2-oxazetidin-3-ones and 1,3-oxazetidin-2-ones are in Table 6, which also holds some data for oxazetes. The ring structure of 1,3-oxazetidin-2-ones precludes the existence of hydrogen relationships leading to $^3J_{cis}$ and $^3J_{trans}$ coupling constants.

Table 5 Proton NMR data for 1,2-oxazetidines and models.

Compound	R^1	R^2R^3	R^4R^5	Ref.
				
$R^1 = H, R^2-R^5 = F$	7.73			69JOC4088
$R^1 = R^2 = \text{carbonyl}^a$			4.89 (R^4) ^b	86ABC357
$R^3 = R^4 = H$ (<i>trans</i>)			$J = 3.6 \text{ Hz}^b$	84TL423
$R^5 = NH_2$			4.90 (R^4) ^c	
			$J = 5.4 \text{ Hz}^c$	
$R^1 = Bu^t$	1.15	3.78–5.19	3.78–5.19	71JA4082
$R^2-R^5 = H$				
				
$R^4 = R^5 = H$			5.51 (br s)	92CB235

^aPart of neopeptin macrocycle, see ref. ^bMajor conformer. ^cMinor conformer.

(ii) Carbon-13 NMR spectroscopy

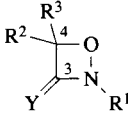
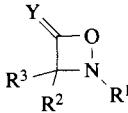
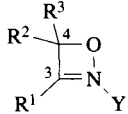
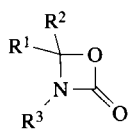
Carbon-13 NMR spectra of 1,2-oxazetidines have not been reported routinely and those for 1,3-oxazetidines are extremely rare (84JA7996, 92MI 131-01). The chemical shifts of the ring carbons are of greater interest than those of carbon atoms of substituents and a comparison of the former with the relevant data for other four-membered rings is appropriate. Table 7 lists, as reference structures, compounds chosen from the azetidine, oxetane, 1,2-diazetidine, and 1,2-dioxetane skeletons. Reference compounds are numbered to conform to the oxazetidine numbering system. There are strong similarities among the ^{13}C shifts of oxazetidine systems and those of model compounds, suggesting that reasonable predictions of the chemical shifts of ring carbons of new 1,2-oxazetidines should be possible.

(iii) Fluorine-19 NMR spectroscopy

Fluorine-19 NMR data is more plentiful than those for any other oxazetidine substituent. Some structural information can be gleaned from such spectra, but it is not clear to what extent extrapolation to properties of nonfluorinated oxazetidines would be valid. Some of the available data is gathered in Table 8 from which it is clear that NCF_2 (ring) signals are about 10 ppm upfield from OCF_2 . The former are generally AB quartets, indicating that inversion at nitrogen is slow on the NMR time scale. The geminal coupling constant (^2J , NCF_2) tends to be between 100 and 200 Hz. It is noteworthy that the OCF_2 signal, which might also be a multiplet for the same reason, can be a singlet. Clearly ^2J in OCF_2 groups and ^3J ($\text{OCF}-\text{NCF}$) can be small. Three entries in Table 8 show some values of $^2J_{\text{F}-\text{F}}$, $^3J_{\text{H}-\text{F}}$, and $^3J_{\text{F}-\text{F}}$ (90IZV1851). Unfortunately, the stereochemistry was not specified in the original article, the values of ^3J are probably for *cis*-related substituents. The last two entries permit direct comparison of the ^{19}F NMR properties of a perfluoro-1,2-oxazetidine with those of perfluorocyclobutane and cyclopentane rings, when the latter are substituents at N of the former. It is clear that both O and N, relative to CF_2 , deshield an attached CF_2 group.

Fluorine-19 NMR spectra of 3,3-difluoroazetidin-2-ones, which could possibly serve as models for ^{19}F NMR spectra of 1,2-oxazetidin-3-ones, were reported by Baldwin *et al.* (92T9085).

Table 6 Proton NMR data for imino-1,2-oxazetidines, 1,2-oxazetidin-3-ones, 1,3-oxazetidin-2-ones, and oxazetes^a.

Compound	¹ H NMR of R ³ (R ¹)	Ref.
		
R ¹ = R ² = Bu ^t R ³ = H, Y = C ₆ H ₅ N	5.18	86CB3411
R ¹ = R ² = Bu ^t R ³ = H, Y = 2,6-Me ₂ C ₆ H ₃ N	4.73	86CB3411
R ¹ = PhCH ₂ , Y = O R ² = R ³ = 4-MeC ₆ H ₄	(4.80)	86LA1478
R ¹ = Pr ⁱ , Y = O R ² = R ³ = 4-MeOC ₆ H ₄	(3.80–4.20)	86LA1478
R ¹ = R ² = Bu ^t R ³ = H, Y = O	4.78	90CZ5
R ¹ = Me ₂ CCH = N(OH)Ph R ² = R ³ = H, Y = O	5.21	84KGS115
R ¹ = Ph, R ³ = Bu ^t R ³ = H, Y = O	5.10	90CZ5
R ¹ = R ³ = Me, Y = O R ² = 4-MeOC ₆ H ₄	1.90(3.30)	90AP(323)967
R ¹ = Me, R ² = 4-MeOC ₆ H ₄ R ³ = CH ₂ Ph, Y = O	3.23 d, <i>J</i> = 1.8 Hz (2.70) ^b	90AP(323)967
R ¹ = CH ₂ Ph, R ³ = Me R ² = 4-MeOC ₆ H ₄ , Y = O	1.67(4.63)	90AP(323)967
R ¹ = Me, R ² = R ³ = C ₆ H ₅ Y = O	(3.32)	82CZ442
		
R ¹ = Me, R ² = Bu ^t R ³ = H, Y = NC ₆ H ₁₁	3.68(2.98)	77CC831
R ¹ = R ² = Bu ^t , R ³ = H Y = 4-O ₂ NC ₆ H ₄ N	4.11	84LA1685
		
R ¹ = Me, R ² = R ³ = Bu ^t , Y = :	1.15(1.95) ^b	75AG(E)70
R ¹ = H, R ² = R ³ = Bu ^t , Y = :	1.18(8.0) ^b	75AG(E)70
R ¹ = Me, R ² = R ³ = Bu ^t , Y = O	1.2(2.1)	68AG(E)637
		
R ¹ = R ² = H, R ³ = Ph	(5.27)	67TL3637
R ¹ = C(Cl)(CO ₂ alk) ₂ , R ² = CCl ₃ , R ³ = H	8.81–9.02 ^{b,c,d}	80S571

^aSome additional data in the primary references and/or in a review by Moderhack (93JHC579). ^bCCl₄. ^c(TMS)₂NH was internal standard. ^dChemical shift for three different compounds falls into the range given.

Table 7 Carbon-13 NMR data for 1,2-oxazetidines, oxazetes, and models^a.

Compound	¹³ C NMR		Ref.
	C3	C4	
 $R^1 = R^2 = Bu^t$ $R^3 = H, Y = C_6H_5N$ $R^1 = R^2 = Bu^t$ $R^3 = H, Y = 2,6-Me_2C_6H_3N$ $R^1 = R^2 = Bu^t$ $R^3 = H, Y = O$ $R^1 = Ph, R^2 = Bu^t$ $R^3 = H, Y = O$	162.7	93.9	86CB3411
 $Y = 4-O_2NC_6H_4N$	76.0	160.4	84LA1685
	183.5	107.7	80TL2025
 $J_{C3,H3} = 182 \text{ Hz}$	187.0		81JA468
	79.7	78.6	85JA410
	46.8		B-87MI 131-01
	164.0		78CB661

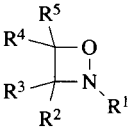
^aSome additional data in the primary references and in a review by Moderhack (93JHC579). The numbering of the models was arbitrarily changed to reduce the number of columns in the Table.

1.31.1.6 Thermodynamic Factors

1.31.1.6.1 Intermolecular forces

There is very little information about intermolecular forces in the 1,2- and 1,3-oxazetidine families. Vapor pressure–temperature relationships have not been reported nor is there any systematic data concerning their solubilities in a series of solvents. Boiling and melting points of oxazetidines appear to be similar to those of model compounds. For example, 20 1,2-oxazetidin-3-ones reported by Burchardt and Geffken are oils or solids with low melting points (90AP(323)967). Two others reported by Moderhack and Stolz have similar properties (90CZ5). Six 3-arylimino-1,2-oxazetidines reported by the latter authors have melting points between 63°C and 107°C (86CB3411). A collection of 17 4-methylthio-2*H*-1,3-oxazetes synthesized by Kristian *et al.* were all solids and were crystallized

Table 8 Fluorine-19 NMR data for 1,2-oxazetidines.

	¹⁹ F NMR Shifts ^{a,b}			Standard	Ref.
	R ¹	R ² R ³	R ⁴ R ⁵		
R ¹ -R ⁵ = F ^c	25.3 (br s)	-105.0, -106.9 <i>J</i> _{2,3} = 140 Hz	-78.4, -80.1 <i>J</i> _{4,5} = 89 Hz	CFCl ₃	70JOC927
R ¹ = H, R ² -R ⁵ = F		-97.8 (br s)	-81.4 (br s)	CFCl ₃	69JOC4088
R ¹ = H, R ² -R ⁴ = F R ⁵ = Cl ^c		-95.5, -100.2 <i>J</i> _{2,3} = 122 Hz	-78.0, -81.6 <i>J</i> _{4,5} = 89 Hz	CFCl ₃	70JOC927
R ¹ = CF ₂ CF(Cl)OEt R ² -R ⁵ = F	-101.9, -105.6, -106.2, -109.8, (complex q)	-94.2, -96.6, -97.6, -100.1 (AB q)	-84.5 (s)	CFCl ₃	69JOC4088
R ¹ = CF ₂ CF ₂ C(CF ₃) ₃ R ² -R ⁵ = F	28.67	20.33	7.56	CF ₃ CO ₂ H	82MI 131-01
R ¹ = H, R ² -R ⁴ = F, R ⁵ = Br		-80.9, -83.2, -93.9, -96.2 (AB q)	-53.4 (s)	CFCl ₃	69JOC4088
R ¹ = CF ₂ CO ₂ Et R ² -R ⁵ = F	-93.7 (br s)	-97.3 (br s)	-83.1 (s)	CFCl ₃	69JOC4088
R ¹ = Cl, R ² -R ⁵ = F	-	-94.2, -96.4, -99.3, -101.5 (AB q)	-77.2, -78.7, -81.1, -82.7 (AB q)	CFCl ₃	69JOC4088
R ¹ = COF, R ² -R ⁵ = F	-5.8 (br s)	-95.1 (s)	-84.4 (s)	CFCl ₃	69JOC4088
R ¹ = CHF ₂ OSO ₂ CF ₃ R ² = H, R ³ -R ⁵ = F	68.2	75.3 <i>J</i> _{2,4} = 5.0 Hz	7.0 <i>J</i> _{3,4} = 5.0 Hz	CF ₃ CO ₂ H	90IZV1851
R ¹ = CFClCFClOSO ₂ CF ₃ R ³ = R ⁵ = Cl, R ² -R ⁴ = F	34.2	12.4 <i>J</i> _{2,4} = 10 Hz	-13.4	CF ₃ CO ₂ H	90IZV1851
R ¹ = CFClCF ₂ OSO ₂ CF ₃	28.5	11.4	-14.8	CF ₃ CO ₂ H	90IZV1851
R ¹ = CF ₂ CF ₂ OSO ₂ CF ₃ R ² -R ⁵ = F	33.2	21.2 <i>J</i> _{2,4} = 1.7 Hz	6.3, 6.4 <i>J</i> _{4,5} = 8.4 Hz <i>J</i> _{3,4} = 1.7 Hz	CF ₃ CO ₂ H	90IZV1851
R ¹ = CF ₂ CF ₂ OSOF R ² -R ⁵ = F	34.08	20.05	6.74, 6.62 <i>J</i> _{4,5} = 8.5 Hz <i>J</i> _{3,4} = 1.8 Hz <i>J</i> _{1,2} = 11.3 Hz	CF ₃ CO ₂ H	82IZV2838
R ¹ = CF ₂ CF(OCF ₃)OSO ₂ F R ² = R ³ = R ⁴ = F R ⁵ = OCF ₃	31.55 <i>J</i> _{1,2} n.r.	17.20 <i>J</i> _{2,3} n.r. ^d	8.14(R4), -21.89(R5) <i>J</i> _{4,5} = 9.0 Hz <i>J</i> _{3,4} n.r. ^d <i>J</i> _{3,5} = 1.7 Hz	CF ₃ CO ₂ H	82IZV2838
R ¹ = CF(Cl)CF ₂ OSO ₂ F R ² -R ⁵ = F	36.21 <i>J</i> _{1,2} = <i>J</i> _{1,3} = 19.8 Hz	18.69, 24.96 <i>J</i> _{2,3} = 204 Hz	-3.13, 4.76 <i>J</i> _{4,5} = 156 Hz <i>J</i> _{2,4} = 11.2 Hz <i>J</i> _{2,5} = 4.0 Hz	CF ₃ CO ₂ H	82IZV2838
R ¹ = <i>c</i> -C ₄ F ₇ ^e R ² -R ⁵ = F	-167.5	-98.5	-83.4	CFCl ₃	84IC3654
R ¹ = <i>c</i> -C ₅ F ₉ ^f	-163	-96 <i>J</i> _{1,2} = 19.5 Hz	-84 (s)	CFCl ₃	84IC3654

^aFor R¹, only the signal from the atom or fragment nearest the N atom is listed. Signs of chemical shifts reported in pre-1980 papers have been changed. ^bRing NCF₂ signal was a quartet in many cases, with *J*_{gem} about 130 Hz. ^cMost stable of two conformations, 24°C. ^dThe symbol n.r. (for not reported) may mean that the value was zero or near zero. ^eCyclobutyl ring: δ C2 -127.3 and -133.1, *J*_{gem} 226 Hz; C3 -129.6 and -167.5, couplings n.r. ^fCyclopentyl ring: δ C2 -134 (s); C3 -126 (s).

from a variety of solvents ranging in polarity from cyclohexane to DMF/water <79CCCC1324>. The fact that unsubstituted skeletons are not known means that the contributions of the four-membered heterocyclic rings to the observed physical properties (vapour pressure, lattice energy, etc.) are not clear.

1.31.1.6.2 Thermodynamic stability

With one exception, the literature appears to be devoid of experimental data such as heats of combustion, isomerization, fragmentation, or hydrogenation of oxazetidines or their derivatives.

Estimates of the ring strain have not been reported nor were equilibrium constants (pK_B or pK_{BH^+}) found for protonation of the basic nitrogen atom. Computed values of the stabilities of some oxazetidine systems, relative to those of component parts, are reviewed under Section 1.31.1.3.

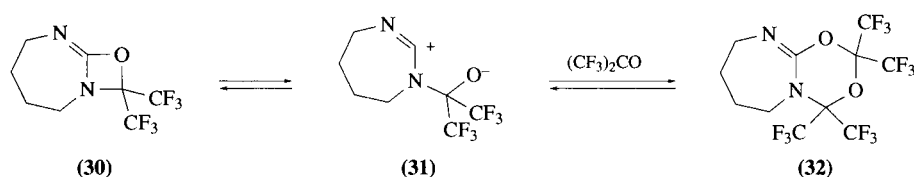
Some 1,2- and 1,3-oxazetidines with exocyclic unsaturation are thermally labile towards $[2 + 2]$ cycloreversion. This chemistry is presented in more detail in Section 1.31.2.1.2. One case worth mentioning at this point is 3-phenyl-1,3-oxazetidin-2-one which extrudes CO_2 via the $[2 + 2]$ cycloreversion. The enthalpy of activation was found to be $30.8 \text{ kcal mol}^{-1}$ $\langle 76BBR(73)465 \rangle$. 1,2-Oxazetidin-4-ones lose CO_2 too readily to permit their isolation.

1.31.1.6.3 Ring-chain and other isomerism

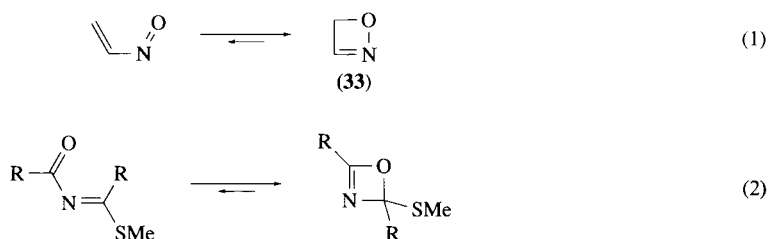
Structures of tricoordinate, neutral *N*-heterocycles can range from pyramidal to planar (at N) depending on the substituents. For pyramidal systems, the barriers to inversion depend upon properties such as electronegativity of substituents and bond angles at N. A small angle, such as that enforced in aziridines, leads to an enhanced inversion barrier. The shapes of oxazetidine rings are therefore of interest.

Relatively little is known about the barriers to inversion at N of 1,2-oxazetidines. For pentafluoro-1,2-oxazetidine, the minimum barrier to N-inversion is available from the temperature dependence of the ^{19}F NMR spectrum $\langle 70JOC927, 84CHEC-I(7)449 \rangle$. That barrier, although not known exactly, must be near 17 kcal mol^{-1} . It is not clear to what extent the barrier is associated with the substituents. It is probably safe to assume that barriers are relatively low, in general, because no instances have yet been reported of diastereomeric 1,2-oxazetidines in which one stereocenter is the ring nitrogen, nor have racemic mixtures been resolved into enantiomers differing only in configuration at N.

Acyclic isomers are not equilibrated with 1,2- and 1,3-oxazetidines. However, 1,3-oxazetidin-2-one (**30**) is suggested as a transient intermediate that is in equilibrium with its ring-opened form, zwitterion (**31**). It is proposed that (**31**) undergoes chemistry with hexafluoroacetone to afford the eventual thermodynamic product, a six-membered ring (**32**) as shown in Scheme 5. The suggestion of (**30**) as an intermediate is based on the observation of a strong band in the infrared at 1790 cm^{-1} $\langle 83JOC1694 \rangle$. In the case of 4H-1,2-oxazetes (**33**), which can be formed by electrocyclic ring closure of α,β -unsaturated nitroso compounds, the equilibrium constant is too large to make the acyclic isomer detectable at room temperature (Equation (1)). Similarly, in the synthesis of 1,3-oxazetes, heterodienes are proposed as intermediates along the pathway to the oxazetes (**25**) (Equation (2)). The heterodienes and the oxazetes are potentially interconvertible by electrocyclic reactions, but it appears that the ring closed form is the thermodynamic sink for this system $\langle 79CCC1324 \rangle$.

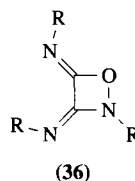
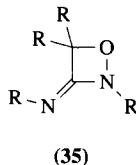
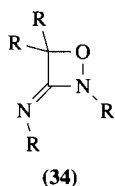


Scheme 5

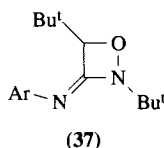


E,Z-Isomerism is possible in imino- and diminoxazetidines. That aspect of their properties was not considered in an otherwise excellent review by Moderhack $\langle 93JHC579 \rangle$. There are two possibilities for the 3- and 4-imino-1,2-oxazetidines (one pair (**34**) and (**35**) illustrated) and four possibilities (one

illustrated as (36)) for 3,4-diimino-1,2-oxazetidines. In the case of the latter, with $R \neq H$, the 3*E*,4*Z*-isomer (36) is presumably the least hindered.



There is good information, pointing to the *E*-isomer, for one set of 3-imino-1,2-oxazetidines <86CB3411>. In the ^1H NMR spectra of (37), the chemical shift of C4-H is 4.73 ppm for $\text{Ar} = 2,6\text{-Me}_2\text{C}_6\text{H}_3$, but between 5.16 and 5.22 ppm for $\text{Ar} = \text{C}_6\text{H}_5$, *p*- $\text{C}_6\text{H}_4\text{Me}$, *p*- $\text{C}_6\text{H}_4\text{OMe}$, *p*- $\text{C}_6\text{H}_4\text{Cl}$, and *p*- $\text{C}_6\text{H}_4\text{NO}_2$. The position of the signal from the NCMe_3 group was independent of Ar. Although the authors did not interpret those features, they can be understood best in terms of the *E*-isomer, with out-of-plane twisting of Ar when it is 2,6- $\text{Me}_2\text{C}_6\text{H}_3$. While evidence that *E*-isomers are more stable than their *Z*-counterparts is lacking, the *E*-isomer places the substituent at the imino group between those at C4 and away from that at N2. Inversion of N2 would necessarily involve an eclipsing interaction in a *Z*-isomer. Infrared data (see Section 1.31.1.5.3) is in agreement with the *E*-isomer assignment.



1.31.2 REACTIVITIES OF OXAZETIDINES AND RELATED COMPOUNDS

1.31.2.1 Reactions of Unsaturated Rings

1.31.2.1.1 Survey of reaction types

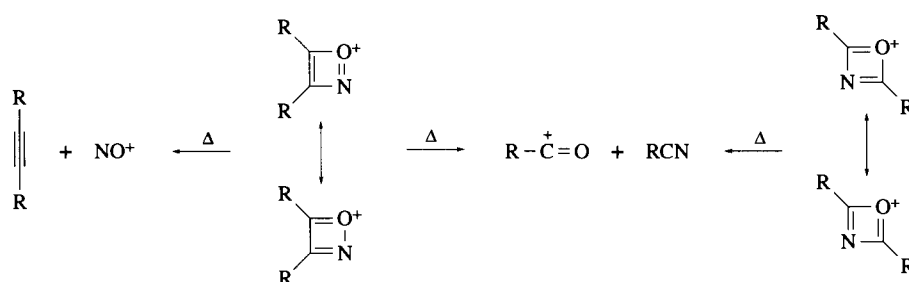
Oxazetes are analogues of cyclobutene, in the broadest sense, or of 1-azetine or 2-azetine. Their general structure leads to the expectation of thermal electrocyclic ring opening similar to the allowed (conrotatory) ring opening of cyclobutene. Moreover, the $\text{C}=\text{N}$ or $\text{C}=\text{C}$ double bond superimposes imine or enamine (and enol ether) character. Oxazetidinones can be expected to show some of the properties of β -lactams and iminoxazetidines might have some resemblance to amidines or imidates. Oxazete *N*-oxides are four π -electron systems that should be capable of $[3 + 2]$ cycloadditions. Finally, a 1,2-oxazet-1-ium ion is a four π -electron analogue of cyclobutadiene. The heteroatoms presumably remove the degeneracy of π -levels of square planar cyclobutadiene and distortion to avoid diradical character may not be necessary.

The reactions of 1,3-oxazetidin-2-ones, the most common member of the 1,3-oxazetidine family, are based for the most part on the release of strain from the four-membered ring. There are instances of thermal unimolecular reactions leading to acyclic products, while other ring-opening reactions tend to proceed through nucleophilic attack at the carbonyl carbon. In general, reactions of these compounds have been performed as either a means of gathering support for their assigned structure or for probing the general chemical and thermal stabilities of the compounds.

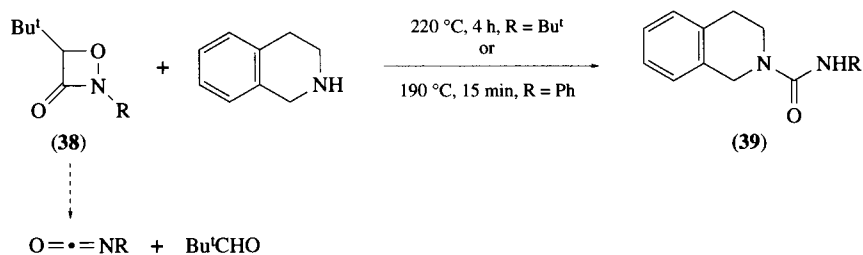
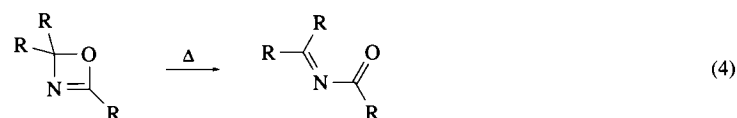
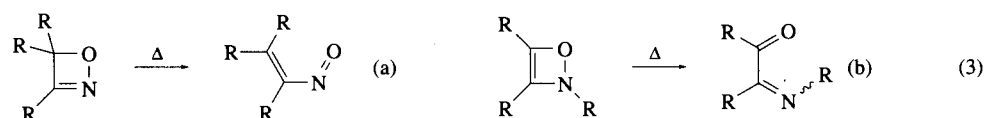
A number of examples were found regarding electrophilic attack at ring heteroatoms, but there do not seem to be any reports of nucleophilic attacks at these atoms.

1.31.2.1.2 Unimolecular reactions from ground states

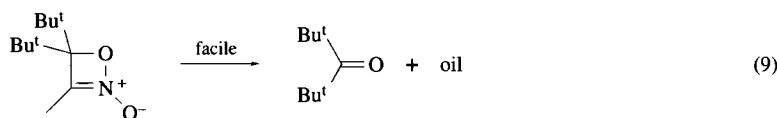
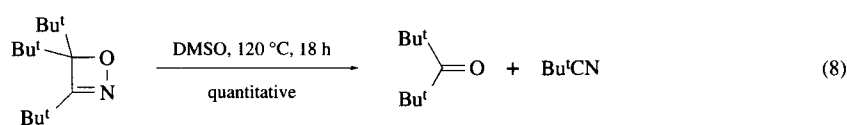
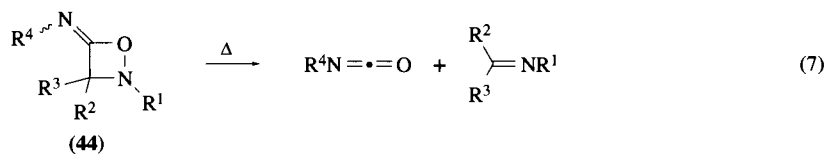
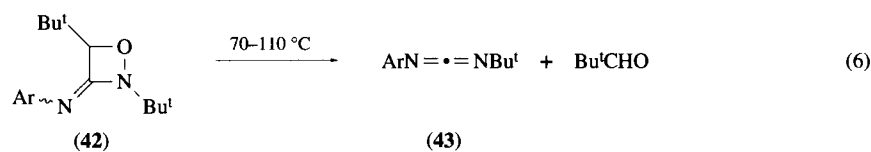
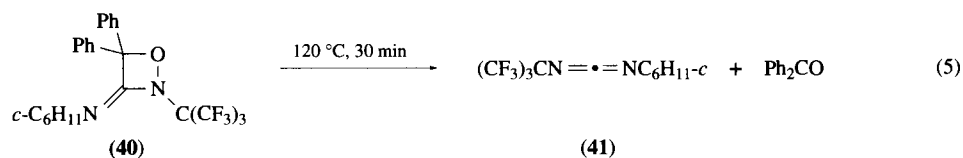
Some potential thermal reactions of unsaturated oxazetidine systems are illustrated in Schemes 6 and 7 and Equations (3)–(9). Some of them are unknown as of 1995.



Scheme 6



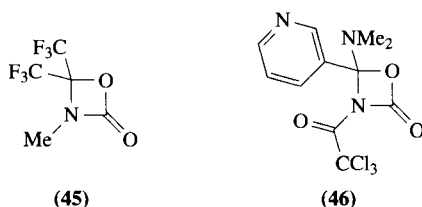
Scheme 7



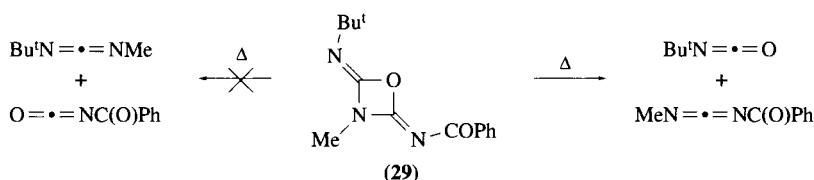
Various ring-opening reactions of 1,2-oxazetidin-3-ones and of 3-imino-1,2-oxazetidines have been reported. One example involves reactions of oxazetidin-3-ones (**38**) with tetrahydroisoquinoline to afford (**39**) (Scheme 7). Those reactions presumably involve initial cycloreversion to pivalaldehyde and isocyanate, the latter reacting with the amine (Scheme 7). The qualitative substituent effects on rates have not been explained <90CZ5>.

Section 1.31.1.6.2, regarding thermodynamic stability, has already indicated an important type of thermal chemistry of unsaturated 1,2- and 1,3-oxazetidinones. The 3-cyclohexylimino compound (**40**) decomposed during 30 min at 120°C to ketenimine (**41**) and benzophenone as in Equation (5) <85S1083>. Similarly, 2,4-di-*t*-butyl-3-arylimino-1,2-oxazetidines (**42**) decompose in the temperature range 70–110°C to afford ketenimines (**43**) and pivalaldehyde (Equation (6)). Substituents in the aryl group have large effects on the rates, in the sense 4-MeO $\gg$ 4-NO₂ <86CB3411>. 4-Imino-1,2-oxazetidines (**44**) fragment thermally to isocyanates and imines (Equation (7)) <93JHC579>.

The mode of [2 + 2] cycloreversion of 1,3-oxazetidin-2-ones is dependent on the substituents of the individual materials. Thus thermal decomposition may proceed in one sense affording CO₂ or by another mode to yield a carbonyl compound. For instance, 1,3-oxazetidin-2-one (**45**) is thermally stable to its boiling point, 102°C, while oxazetidinone (**46**), which can be formed at –120°C, decomposes above –10°C <67JOC2960, 81IZV758>. The decomposition mode in each case as stated is via a retro-[2 + 2] reaction, to afford CO₂ and an amidine from (**46**) and a ketone and an isocyanate from (**45**).



The selectivity of the [2 + 2] cycloreversion of bis(imino)-1,3-oxazetidine (**29**) is also noteworthy <72JA3484>. Under thermal conditions, the ring may fragment by either of two nearly equivalent pathways. However, only a lone reaction course is followed, that which produces *t*-butyl isocyanate and a benzoylated carbodiimide rather than a doubly alkylated isocyanate and benzoyl isocyanate (Scheme 8) <72JA3484>. There was no explanation offered for the selectivity of this cycloreversion.



Scheme 8

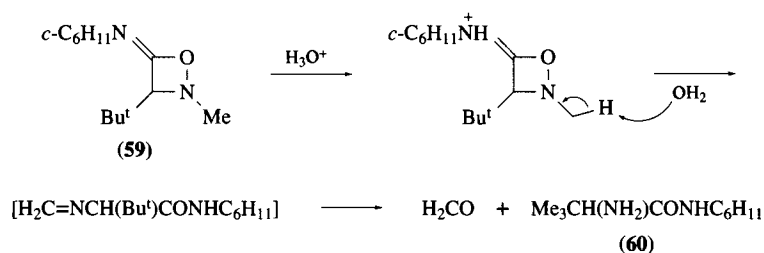
Oxazetes and oxazete *N*-oxides undergo thermal cycloreversions as shown in Equations (8) and (9) <75AG(E)70, 80TL2025>. Evidence for similar cycloreversions of corresponding radical cations, in the gas phase, is included under Section 1.31.1.5.4.

1.31.2.1.3 Electrophilic attack at nitrogen or at oxygen

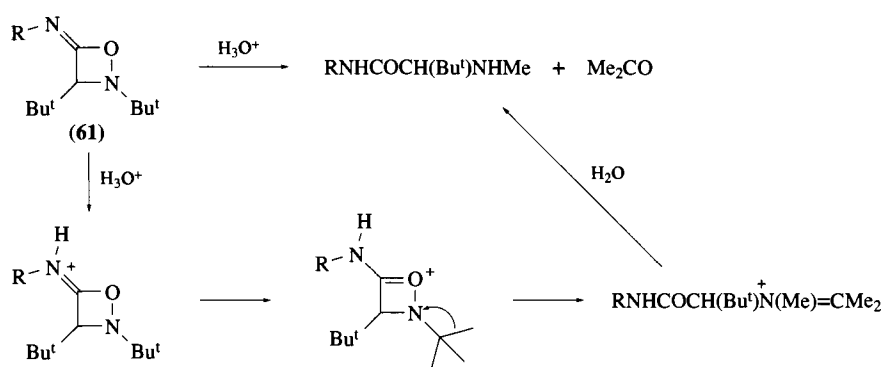
In this section, all compounds having one or more unsaturated ring atoms are included. The site of attack at N could therefore be N2 or an imino nitrogen. Similarly attack at O could involve O1 or the carbonyl oxygen of an oxazetidinone.

Tikhonov *et al.* found that (**47**) decomposed on storage to produce benzonitrile and an oxime ether of acetone <84KGS115>. The process may involve hydration of the amide by adventitious water- and acid-catalyzed dehydration/fragmentation of the initial hydration product, Scheme 9, although the authors did not propose that mechanism. Geffken and Burchardt cleaved oxazetidinone (**48**) with gaseous HCl to (**49**), which could be dehydrochlorinated on Kieselgel to regenerate (**48**). In

the substituent at N is *t*-butyl (**61**) a methyl group migrates to N (Scheme 12) <84LA1685>. Additional examples are in a review by Moderhack <93JHC579>.



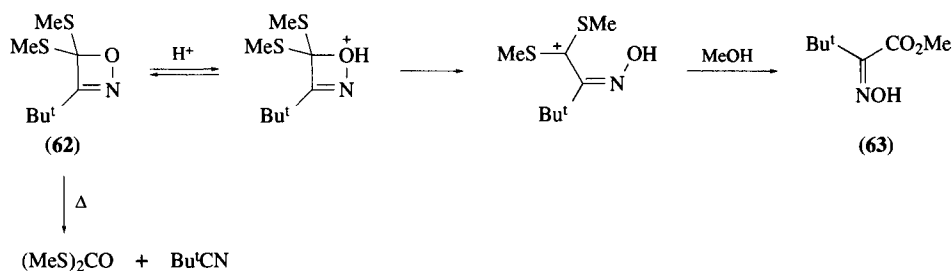
Scheme 11



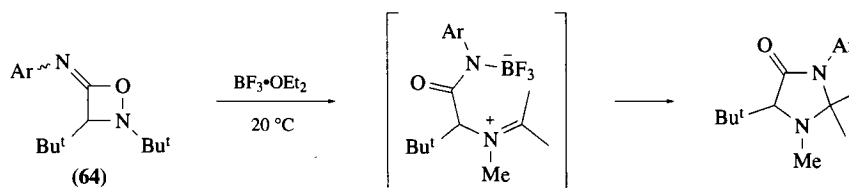
Scheme 12

Acid-catalyzed methanolysis of 4H-oxazete (**62**) afforded oxime (**63**), presumably by C4—O bond cleavage aided by the thiomethyl groups at C4 (Scheme 13) <80TL2025>. A 4-imino-1,2-oxazetidine (**64**) undergoes an isomerization, with ring expansion, on treatment with $\text{BF}_3 \cdot \text{OEt}_2$ <84LA1685>. The process is easily rationalized in terms of an intermediate such as that shown in Scheme 14, but the mechanistic details have not been reported.

The lone reported electrophilic attack by a 1,3-oxazetidin-2-one is shown in Equation (14). The

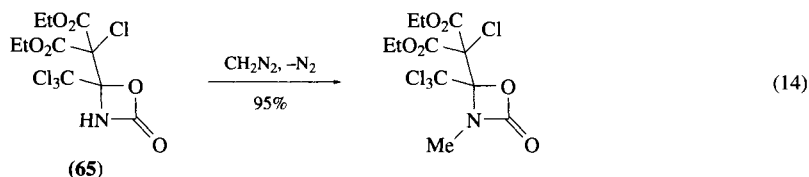


Scheme 13



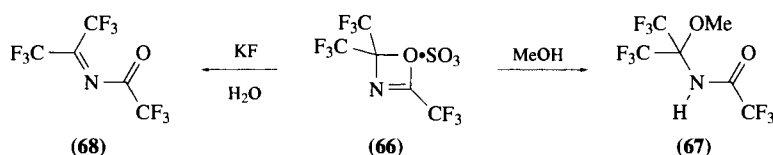
Scheme 14

reaction of 1,3-oxazetidinone (**65**) with diazomethane affords the *N*-methylated version of the compound in excellent yield (80S571).



1.31.2.1.4 Electrophilic attack at carbon

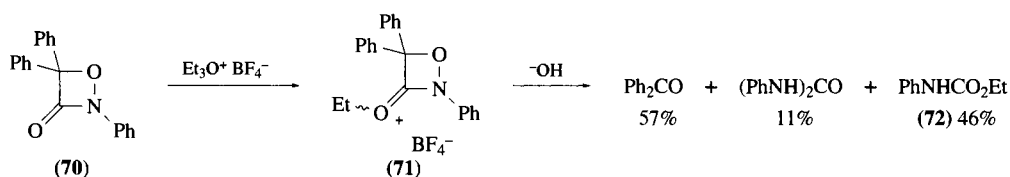
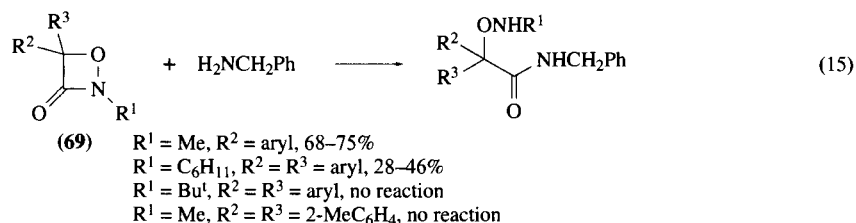
A uniquely stabilized 1,3-oxazete (**66**) reacts with methanol at its sp^3 hybridized ring carbon to afford the ring-opened *N*-substituted trifluoroacetamide (**67**). Nucleophilic attack by fluoride releases the SO_3 from the complex and the ring then falls to acyl imine (**68**) as shown in Scheme 15 (84JOU1213).



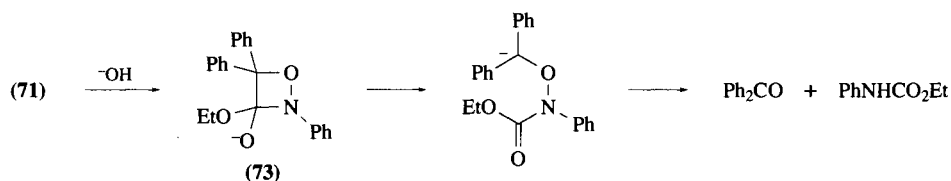
Scheme 15

1.31.2.1.5 Nucleophilic attack at carbon

Aminolysis of 1,2-oxazetidin-3-ones (**69**) with benzyl amine appears to involve normal formation of a tetrahedral intermediate and subsequent C—N bond cleavage, as suggested by the dependence of yields on steric hindrance from R^1 and/or R^2 , R^3 (Equation (15)) (86LA1478). Isopropyl amine cleaves 1,2-oxazetidin-3-ones in the same way, in nearly quantitative yields (84LA894). However, not all 1,2-oxazetidin-3-ones react in that way (Schemes 16 and 17). As early as 1911, it was shown that 2,4,4-triphenyl-1,2-oxazetidin-3-one (**70**) reacts with aniline to afford benzophenone and diphenyl urea (11CB365). It can be ethylated with triethyloxonium tetrafluoroborate to the salt (**71**) which, upon treatment with aqueous base, affords benzophenone, urethane (**72**), and diphenyl urea (74ZN(B)231). It is not clear how the N—O bond cleavage takes place but a reasonable mechanism involves formation of a tetrahedral intermediate (**73**) and ring opening by C—C bond cleavage (Schemes 16 and 17).

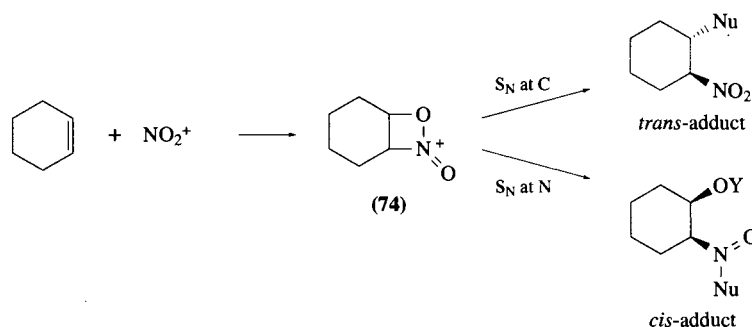


Scheme 16

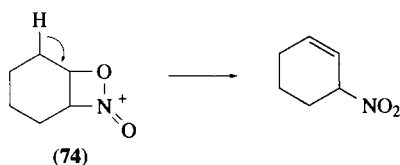


Scheme 17

Ring opening by nucleophilic attack at carbon, in competition with attack at nitrogen, accounts for the *trans*- and *cis*-adducts from reaction of cycloalkenes with NO_2^+ (Scheme 18). The postulated intermediate (74) can account for allylic nitro compounds also, through a reaction resembling the E-2 process (Equation (16)) <84JA1074>.



Scheme 18



(16)

Fluoride-induced ring opening of oxazetidin-2-ones (45) and (75) affords a zwitterionic intermediate that can add either ketone or methyl isocyanate to afford dioxazine (76) or oxadiazine (77), respectively (Scheme 19) <67JOC2960>. The ketone and the isocyanate are the starting materials in the fluoride-catalyzed formation of the oxazetidinone. In the most practical synthesis of the six-membered heterocycles, the oxazetidinones are not isolated, longer reaction time provides the larger rings. The products of the attack of benzylamine at the carbonyl carbon of oxazetidin-2-one (27) are due to breakdown in two directions <80DOK(253)886>.

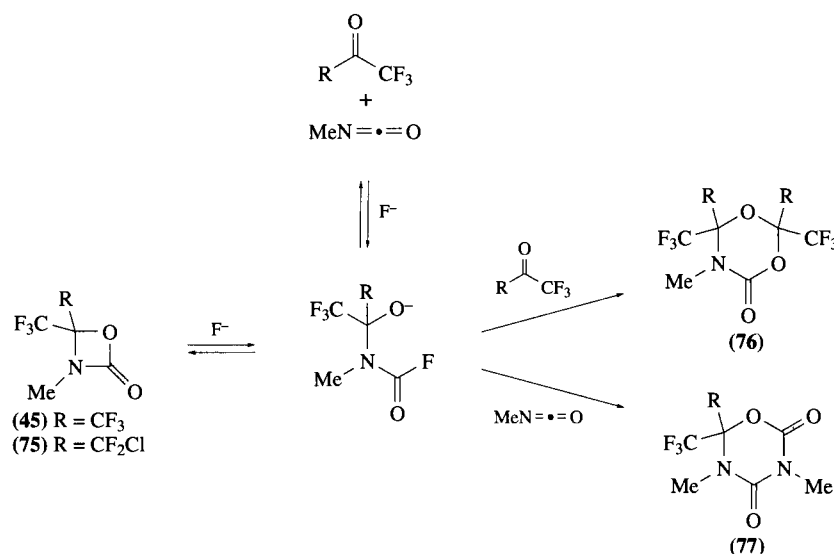
When the oxazetidine does not bear a carbonyl group, but an exocyclic imino group or an electron-poor double bond, the system is still prone to double-bond attack. For instance, methanolysis of (29) affords a ring-opened product while oxazetidine (78) undergoes methanolysis by initial attack at the unsaturated ring carbon (Scheme 20) <72JA3484, 75TL1405>.

1.31.2.1.6 Reactions with carbenes, nitrenes, and radicals

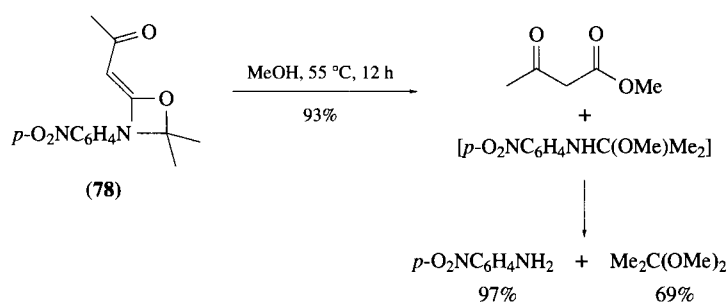
Although saturated oxazetidine systems would presumably react with electrophilic carbenes and nitrenes, examples were not found. The formal insertion of a methylene unit into an N—H bond of a 1,3-oxazetidin-2-one is described in Section 1.31.2.1.3.

1.31.2.1.7 Heterogeneous reactions

1,2-Oxazetidin-3-ones are reduced with H_2 on Pd/C, to products of C—O bond cleavage or N—O bond cleavage, respectively, when the substituent at N is alkyl or aryl <68JOC3619, 84CHEC-I(7)449>. 4,4-Di-*t*-butyl-3-methyl-1,2-oxazete-2-oxide is reduced on Raney nickel with O1—N2 bond cleavage <68AG(E)637>.



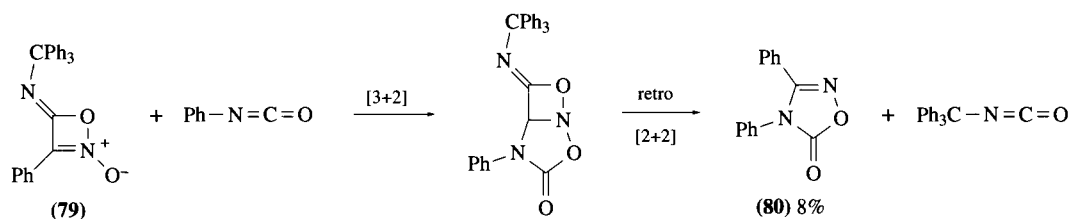
Scheme 19



Scheme 20

1.31.2.1.8 Bimolecular reactions through cyclic transition states

Oxazete *N*-oxides, as 1,3-dipoles, appear to undergo cycloadditions to 2π -electron systems. Boyer *et al.* reported some chemistry that can be rationalized in that way (Scheme 21). 3-Phenyl-4-triphenylmethylimino-4H-1,2-oxazete-2-oxide (79) reacts with phenylisocyanate to afford the oxadiazolone (80) (8%) (<87JCS(P1)2163>).



Scheme 21

1.31.2.2 Reactions of Saturated Rings

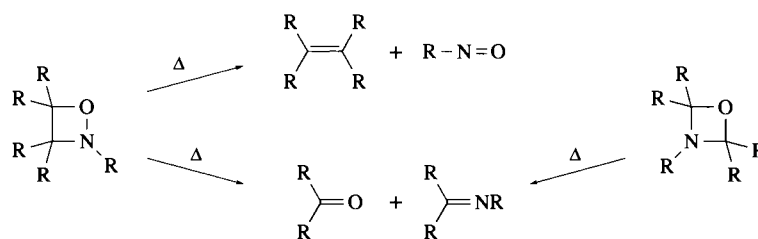
1.31.2.2.1 Survey of reaction types

Oxazetidines are hetero analogues of cyclobutane and to some extent the unimolecular thermal reactions of the all-carbon system may serve as a model for those of the heteroatom counterparts. In other aspects, relationships are more remote or nonexistent.

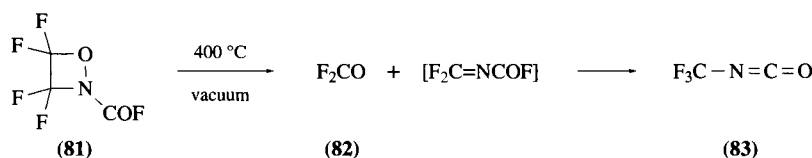
A number of reactions describing electrophilic or nucleophilic attack at the oxygen or nitrogen atom, and of nucleophilic attack at carbon of 1,2-oxazetidines, are presented in the following subsections. There are no reports of electrophilic attack at carbon nor are there reports of the treatment of the heterocycles with reactive intermediates such as carbenes.

1.31.2.2.2 Unimolecular reactions from the ground state

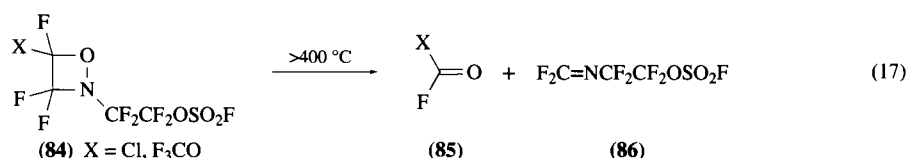
A priori, one might anticipate thermal cycloreversions of 1,2- and 1,3-oxazetidines, as illustrated in Scheme 22. They would have to proceed with ($\pi 2s + \pi 2a$) symmetry if concerted but the geometric distortion associated with that mode could be avoided with a stepwise mechanism. A dipolar intermediate of a two-step mechanism is more likely with heteroatoms present than it is in the case of a cyclobutane. Examples of known types are shown in Scheme 23 and Equation (17). Thus, oxazetidine (81) cleaves thermally to (82) and (83) (Scheme 23) <90IZV1851>. Similarly (84) undergoes thermal cycloreversion to (85) and (86) (Equation (17)) <82IZV2838>. Analogous thermal processes have been reported earlier <65JCS5602, 69JOC4088, 71JA4082, 84CHEC-I(7)449>.



Scheme 22

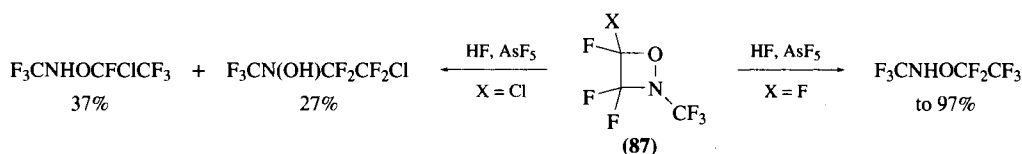


Scheme 23



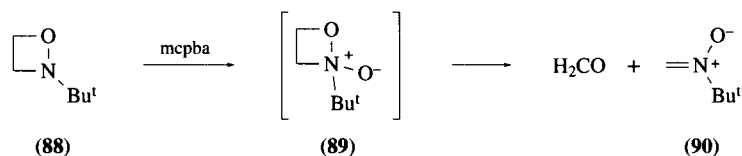
1.31.2.2.3 Electrophilic attack at nitrogen or at oxygen

Electrophilic attack at heteroatoms of 1,2-oxazetidines occurs even in the cases of weakly basic perfluoro species. Super acids, HF/AsF₅ or HF/SbF₅, in liquid HF protonate 3,3,4,4-tetrafluoro-2-trifluoromethyl-1,2-oxazetidine (87) at nitrogen (Scheme 24). The corresponding 3-chloroperfluoro compound protonated competitively at nitrogen and at oxygen as inferred from the products <89CJC1724>. The mechanism proposed by the authors involves ring opening of the appropriate conjugate acid in concert with transfer of fluoride, from F—H---(F—AsF₅)[−], to ring carbon (Scheme 24).



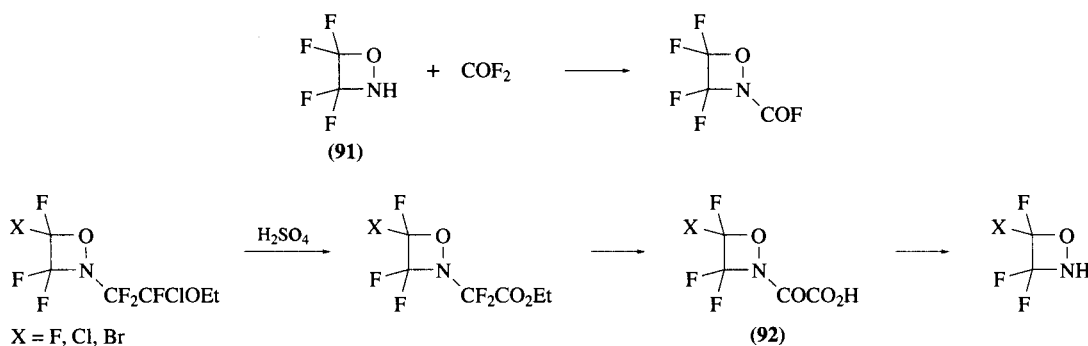
Scheme 24

Another example of electrophilic attack at nitrogen is the oxidation, by *m*-chloroperbenzoic acid, of 2-*t*-butyl-1,2-oxazetidine (**88**) through the presumed intermediate oxazetidine *N*-oxide (**89**) to afford formaldehyde and (probably) nitrene (**90**) (Scheme 25) <71JA4082>.



Scheme 25

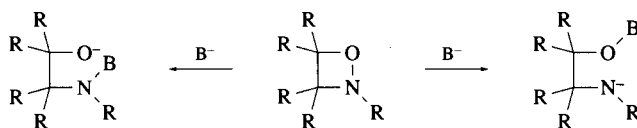
Acylation at nitrogen of 1,2-oxazetidine (**91**) is known and acid-catalyzed deacylation has also been reported. The presumed mechanism involves hydrolysis to the oxalic acid monoamide (**92**), which undergoes decarbonylation and decarboxylation (Scheme 26) <69JOC4088>. Some reactions of the conjugate acids of oxazetidines with nucleophiles are treated under Sections 1.31.2.2.4 and 1.31.2.2.5.



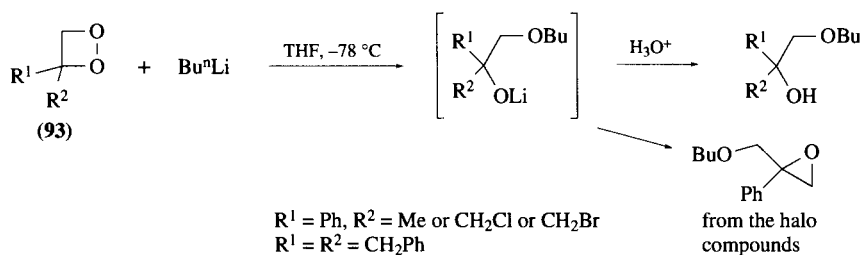
Scheme 26

1.31.2.2.4 Nucleophilic attack at nitrogen or at oxygen

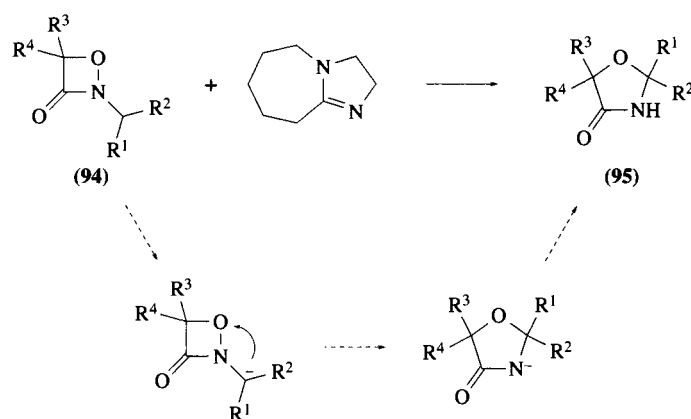
Nucleophilic substitution at nitrogen, or at oxygen, of 1,2-oxazetidines (Scheme 27) would be analogous to that observed by Adam and Heil in the case of 1,2-dioxetanes (**93**) (Scheme 28) <92CB235>. An intramolecular analogue of such a substitution, at oxygen of a 1,2-oxazetidin-3-one, may be the reaction of (**94**) with DBU to afford (**95**) (Scheme 29) <86CZ459>.



Scheme 27



Scheme 28

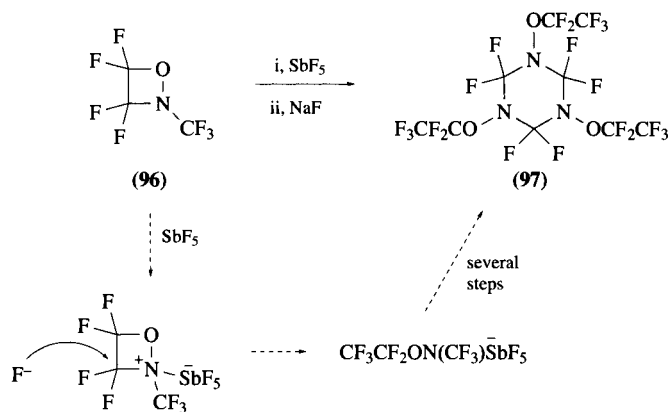


Scheme 29

Lithium aluminum hydride cleaves the ON bond of 2-*t*-butyl-1,2-oxazetidine <71JA4082, 84CHEC-1(7)449>. Although the end result is compatible with attack at oxygen or at nitrogen, the latter atom is neopentyl and therefore attack at oxygen is more likely.

1.31.2.2.5 Nucleophilic attack at carbon

Various apparent substitutions on the conjugate acids of oxazetidine systems are known. For example, the perfluorooxazetidine (96), upon sequential treatment with SbF₅ and NaF, affords the cyclic trimer (97) <90EUP350042>. That reaction presumably involves coordination of the oxazetidine to SbF₅ followed, perhaps, by nucleophilic attack by F⁻ at C3 to generate the OCF₂CF₃ portion of the product (Scheme 30).



Scheme 30

1.31.2.3 Reactions of Substituents at Ring Carbon

1.31.2.3.1 Survey of atoms or groups at ring carbon

Most of the substituents at ring carbon fall into three categories, alkyl, aryl, and halogen. In the last category, fluorine is the most prevalent.

1.31.2.3.2 Hydrogen

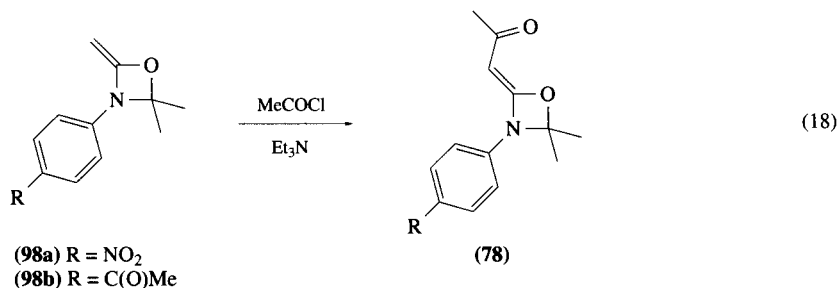
There is very little known chemistry of hydrogen at ring carbons. Halogenations, for example, appear to be unknown and catalytic dehydrogenation or oxidative removal to introduce a double bond were not found nor was deprotonation from a ring carbon encountered.

1.31.2.3.3 Halogen

Halogen can presumably be removed from carbon and a contiguous atom by 1,2-elimination, but this has been demonstrated only for a perfluoro system (see Section 1.31.3.3).

1.31.2.3.4 Alkyl and aryl groups

Alkyl and aryl groups at carbon have served primarily as spectator substituents. Transient oxazetidines (**98**), which possess a ketene *O,N*-acetal within the molecule, can undergo acetylation in the presence of base to yield more stabilized systems such as (**78**) (Equation (18)) <75TL1405>

**1.31.2.3.5 Carbonyl, nitrile, and nitro groups**

There is a carbonyl group at carbon in the neopeptins (see Section 1.31.4) but its function, if any, in determining their properties is not established.

1.31.2.3.6 Hydroxyl, alkoxyl, and thiol groups

Hydroxyl, alkoxyl, and thiol groups are rare C-substituents of oxazetidines. Reactions of (**62**) (see Section 1.31.3.4.1) do not appear to involve the thiomethyl groups as the site of primary attack.

1.31.2.4 Reactions of Substituents at Nitrogen or Oxygen**1.31.2.4.1 Survey of atoms or groups at ring heteroatom**

The types of heterocycles in this family severely limit the number of systems with substituents on oxygen and there are no reports on the chemistry of these substituents. On the other hand, there are several 1,2-oxazetidines that bear a hydrogen or a fluorine atom at nitrogen, yet there are no reports of the removal of these atoms, either by ionic or radical methods. Systems where the nitrogen bears a lone atom, such as one of the other halogens, were not encountered. The chemistry of alkyl, aryl, and some unsaturated groups is summarized in Section 1.31.2.4.2.

1.31.2.4.2 Alkyl and aryl groups

Reactions at *N*-alkyl groups appear to be secondary, as in the methyl group migration of Scheme 14, except for the deprotonation/expansion sequence of Scheme 29. Reactions on *N*-aryl groups, such as electrophilic substitution, were not encountered.

1.31.2.4.3 Carbonyl, nitrile, and nitro groups

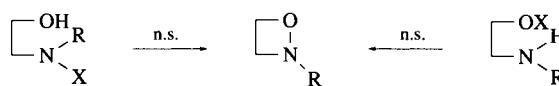
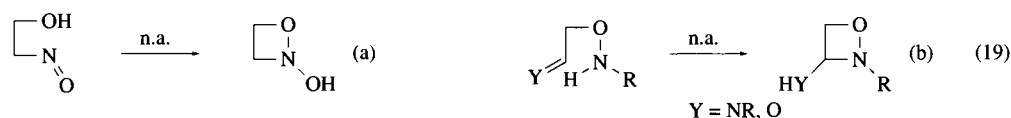
The nitrile group of 2-cyano-3,3,4,4-tetramethyl-1,2-oxazetidine may cause it to polymerize (90MI 131-01). Neopeptins (Section 1.31.4) have a carbonyl group at N2.

1.31.3 SYNTHESSES

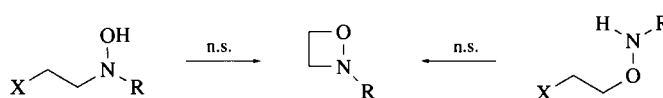
1.31.3.1 1,2-Oxazetidines and Derivatives

1.31.3.1.1 Ring closure of a single component

Selection for this category is somewhat arbitrary because the single component that actually cyclizes could be seen as a reactive intermediate or as a relatively long-lived precursor. The latter approach has been taken because carbenes, nitrenes, and radicals are considered explicitly in Section 1.31.3.1.2. There are basically three types of closures to consider, namely nucleophilic addition (n.a.), nucleophilic substitution (n.s.), and electrocyclic closures (e.c.). The generic types are all illustrated, with those abbreviations, in Equations (19a) and (19b) and Schemes 31–33.



Scheme 31

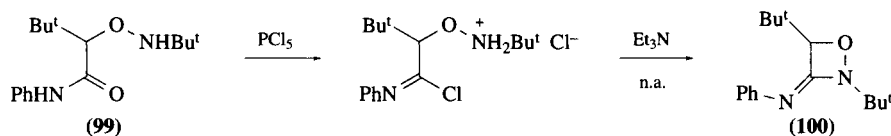


Scheme 32

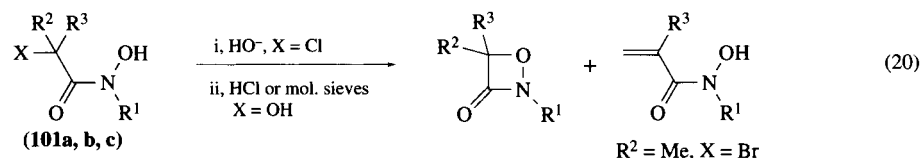


Scheme 33

Examples of nucleophilic addition by hydroxyl to the nitroso group were not found. One example of ring formation by N-to-C addition appears to be the conversion of (99) to (100), Scheme 34 (86CB3411). Nucleophilic substitutions by oxygen at nitrogen or by nitrogen at oxygen, to afford 1,2-oxazetidines from ethanolamine derivatives, were not encountered but cyclizations by O-at-C substitution have been used extensively. For example, α -chlorohydroxamic acids (101a) and α -hydroxyhydroxamic acids (101b) cyclize to 1,2-oxazetidin-3-ones (Equation (20)) (68JOC3619, 84KGS115, 86CZ459, 86ZN(B)1186, 93JHC579). The α -halohydroxamic acids are generated *in situ* and a bromo compound (101c) reacted by 1,2- rather than 1,4-elimination (68JOC3619). This topic was reviewed by Moderhack (93JHC579).

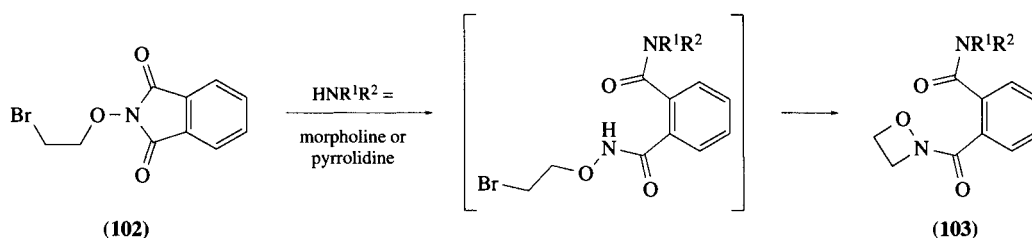


Scheme 34

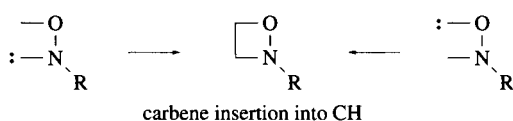


Scheme 35

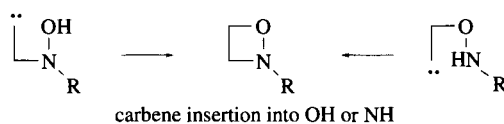
An example of probable substitution by nitrogen at carbon is contained in a patent by Foguet Ambros *et al.* who treated *N*-(2-bromoethoxy)phthalimide (**102**) with pyrrolidine or morpholine to obtain 1,2-oxazetidines (**103**) (Scheme 35) <84MIP519297>.



Scheme 36



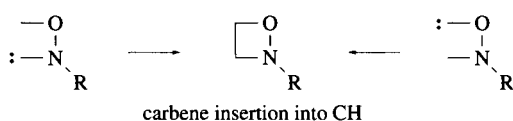
Scheme 37



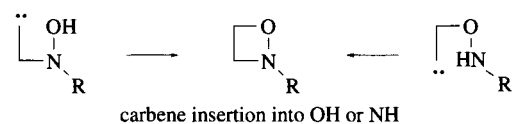
Scheme 38

1.31.3.1.2 Intramolecular reaction of a carbene, nitrene, or radical

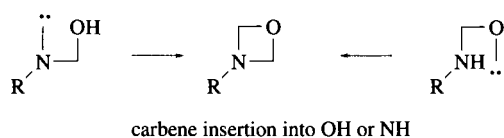
Oxazetidines might be prepared, in principle, by intramolecular ring-forming insertions of carbenes or nitrenes. Some types that can be imagined are illustrated in Schemes 36–38 and Equations (21a) and (21b) in terms of insertion into CH, NH, or OH bonds. The last has a greater likelihood of success than the others, assuming that the carbenes or nitrenes drawn could be generated. Examples of oxazetidine syntheses by such approaches were not found.



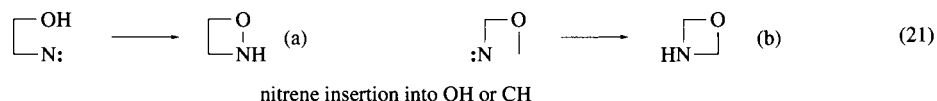
Scheme 36



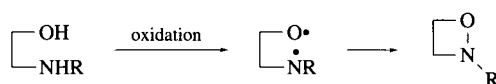
Scheme 37



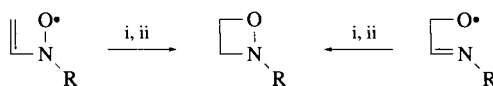
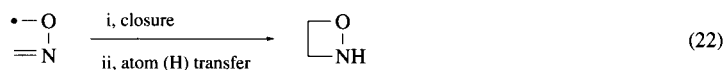
Scheme 38



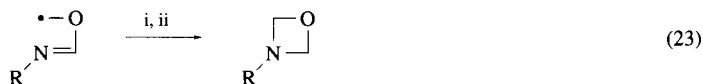
Free-radical processes effecting ring closure would have to be formal diradical couplings or additions followed by atom transfers. The most likely option for the former is an oxidation of an amino alcohol, probably through radical ion intermediates. The depicted diradical is a formality (Scheme 39). Radical cyclizations of the type homoallyl $\rightarrow$ cyclobutyl are generally prevented by the much faster homoallyl $\rightarrow$ cyclopropylmethyl closure. Nevertheless, cyclizations to four-membered rings have not been ruled out in the enamine and imine systems depicted (Equation (22), Scheme 40, Equations (23) and (24)). Oxazetidine syntheses that are clearly recognizable as involving intramolecular radical cyclization were not found.



Scheme 39



Scheme 40

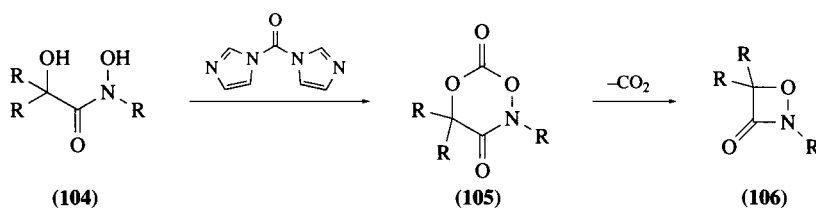


1.31.3.1.3 Transformation of another ring

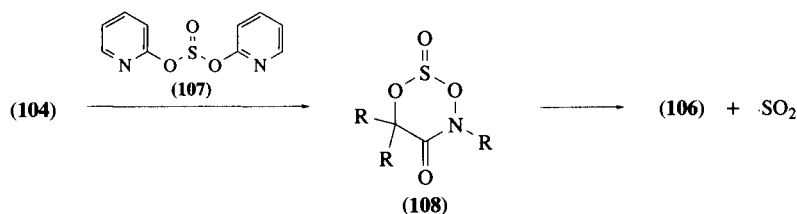
The more obvious reactions of this type include change of the oxidation state of a four-membered ring, to convert an oxazetidine to an oxazete or vice versa, and changes of a larger or smaller ring to a four-membered ring. Examples of the first type include a defluorination <72ZOR186> and the transformation of a 3-methylene-1,2-oxazetidine to a 4-imino-1,2-oxazetidine on heating with $\text{CF}_3\text{N}=\text{O}$ <65JCS5602>.

(i) Contraction of six-membered or larger rings

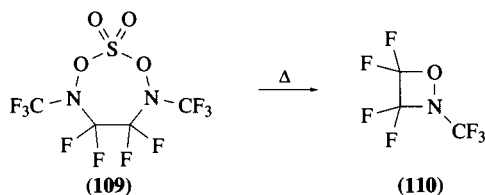
Very good methods, based on thermal extrusion of CO_2 or SO_2 from six-membered rings, have been developed for the synthesis of oxazetidinones. The approach involves reaction of an α -hydroxyhydroxamic acid (**104**) with 1,1'-carbonyldiimidazole (Scheme 41) to afford (**105**). The latter can be isolated in good yield in many instances and a common feature is their thermal decomposition to 1,2-oxazetidin-3-ones (**106**). An alternative method involves the use of 2,2'-dipyridyl sulfite (**107**) to convert (**104**) to (**108**) which loses SO_2 to afford (**106**) (Scheme 41). These approaches, attributed to Geffken and co-workers <82CZ442, 84CZ293, 84LA894, 86ZN(B)1186, 86LA1478, 90AP(323)967> have produced a large number of 1,2-oxazetidin-3-ones. A good review by Moderhack includes many additional references and details <93JHC579>. The one example of contraction of a seven-membered ring (**109**) involves a thermolysis at 350°C (1 mmHg) that produces oxazetidine (**110**) as one component of a complex mixture of products (Equation (25)) <84JCS(P1)1791>.



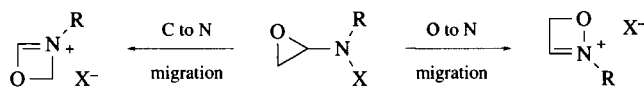
Scheme 41



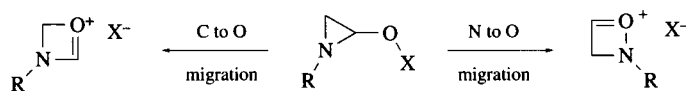
Scheme 42

*(ii) Expansion of three-membered rings*

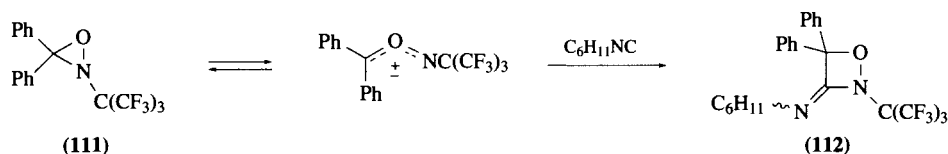
Examples of this approach, illustrated below in terms of some of the potential options (Schemes 43 and 44) are scarce. An oxaziridine (**111**) reacts with cyclohexyl isocyanide to form a 3-imino-1,2-oxazetidine (**112**) <79IZV1788, 93JHC579>. The latter reaction is probably a [1 + 3] cycloaddition (Scheme 45).



Scheme 43



Scheme 44

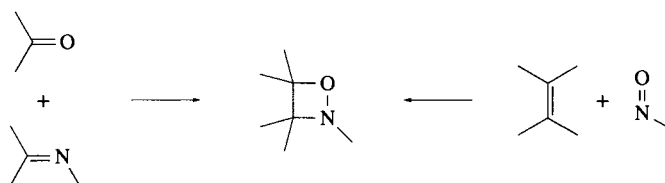


Scheme 45

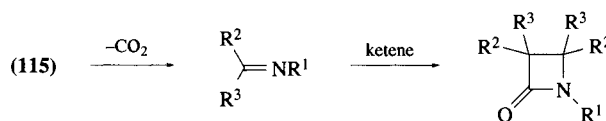
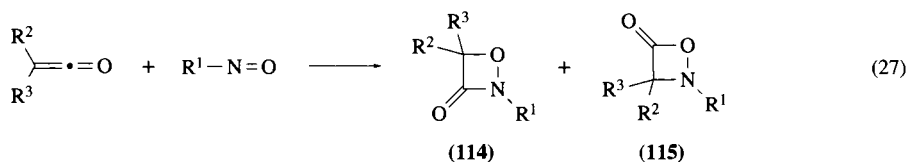
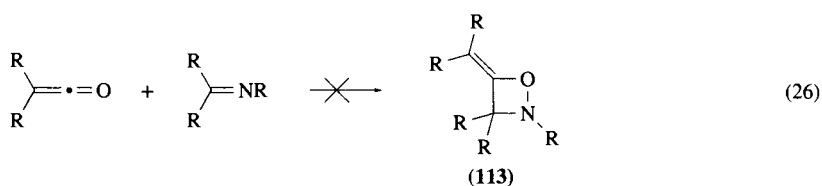
1.31.3.1.4 Ring formation from two components

(i) [2 + 2] Cycloaddition

[2 + 2] Cycloaddition is the most common source of 1,2-oxazetidine rings. For the oxazetidines themselves, only ketone plus imine and alkene plus nitroso compound are possible (Scheme 46). Examples of the former approach were not found but the latter is well represented <84CHEC-I(7)449>. Imines react with ketenes to form β -lactams rather than oxazetidines (**113**) (Equation (26)) but nitroso compounds and ketenes afford products from both (usually) regiochemistries of cycloaddition: the 1,2-oxazetidin-3-ones (**114**) and 1,2-oxazetidin-4-ones (**115**). The latter lose CO₂ spontaneously, however, and the imine so formed attacks ketene still present to form β -lactam (Equation (27) and Scheme 47) <74JOC2552, 93JHC579>. Two 1,2-oxazetidin-3-ones were prepared by the ketene/nitroso compound route <90CZ5>.

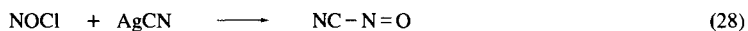


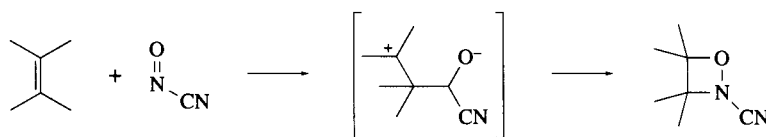
Scheme 46



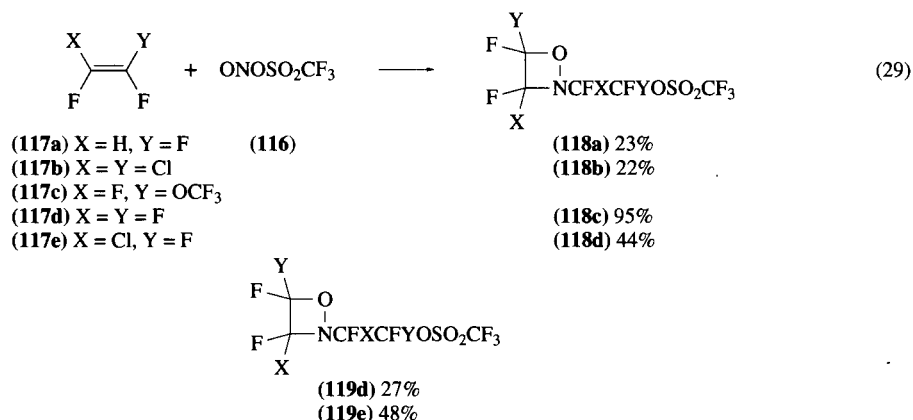
Scheme 47

Treatment of nitrosyl chloride with silver cyanide in CH₂Cl₂ at -30°C, followed by addition of 2,3-dimethyl-2-butene afforded 3,3,4,4-tetramethyl-2-cyano-1,2-oxazetidine (Equation (28) and Scheme 48) <90MI 131-01>. Although the authors proposed a reaction involving electrophilic attack by NO⁺ on the alkene, the process can also be considered as a [2 + 2] cycloaddition, either concerted with $\pi 2s + \pi 2a$ geometry, or in two steps as shown. Similarly, nitroso compounds (**116**) reacted with perfluoroethenes (**117**) to afford oxazetes (**118**) and (**119**), as well as polymeric products as shown in Equation (29) <82IZV2838, 86IZV891>. Numerous other highly fluorinated oxazetidines were made by cycloaddition of other nitroso compounds to fluorinated ethenes <69JOC4088, 90IZV1851>. Perfluoroallene reacts analogously with nitrosotrifluoromethane to afford the only known 3-methylene-1,2-oxazetidine <65JCS5602>.





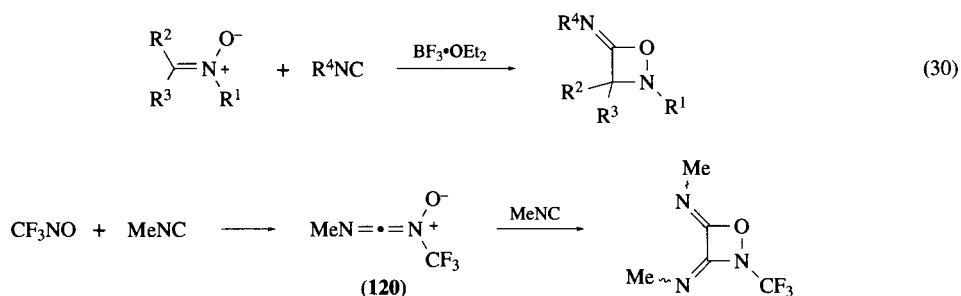
Scheme 48



Reactions of cyclic alkenes with acetyl nitrate presumably afford transient oxazetidine systems by [2 + 2] cycloaddition with NO_2^+ (Scheme 18) <84JA1074>.

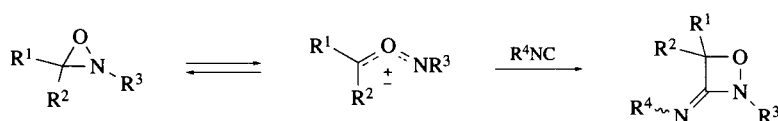
(ii) [1 + 3] Cycloaddition

Nitrones add to isocyanides to afford 4-imino-1,2-oxazetidines (Equation (30)) <85S1083>. The scope and limitations of the approach have been reviewed <93JHC579>. Again, information about stereochemistry at the imino group was not available. An analogous cycloaddition, formally of the [1 + 1 + 2] type is that of Scheme 49 in which a nitron-like intermediate (120) may be involved <62DOK(142)596, 93JHC579>.



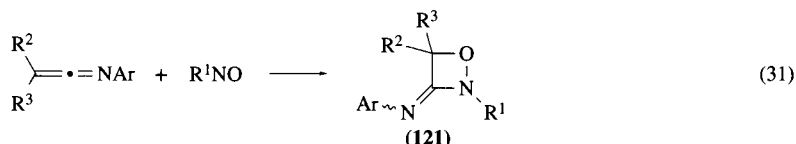
Scheme 49

Isocyanides and carbonyl imines (from oxaziridines) could conceivably undergo [1 + 3] cycloaddition to afford 3-imino-1,2-oxazetidines (Scheme 50). This approach has seen limited applicability (R^4 = cyclohexyl, R^3 = $\text{C}(\text{CF}_3)_3$, $\text{R}^2 = \text{R}^1 = \text{Ph}$) because oxaziridines generally open by C—O or N—O bond cleavage <79IZV1788, 84CHEC-1(7)449>.



Scheme 50

Nitroso compounds add regiospecifically to *N*-aryl ketenimines to afford 3-imino-1,2-oxazetidines, (**121**) (Equation (31)) <70JHC1203, 72JHC77, 74JHC633, 86CB3411>. Unfortunately, there is not any information about the stereochemistry, other than that which can be inferred from NMR spectroscopy (see Section 1.31.1.5.5) which suggests the *E*-configuration for a limited number of 3-imino-1,2-oxazetidines. Implications of the regiospecificity to the mechanism of cyclization were discussed by Moderhack <93JHC579>.



1.31.3.2 1,3-Oxazetidines and Derivatives

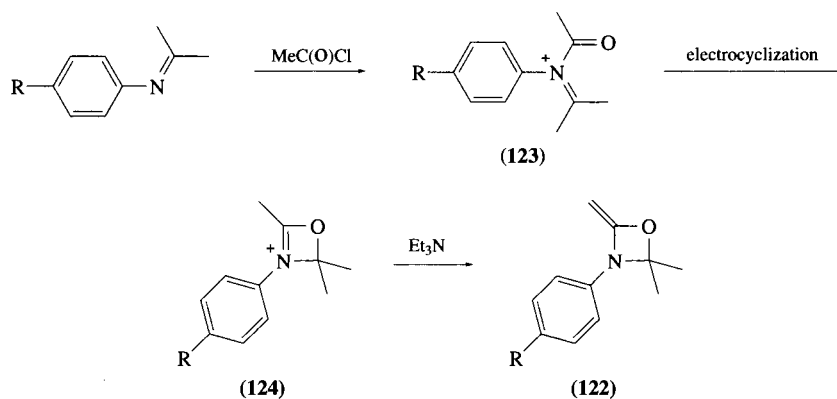
1.31.3.2.1 Ring closure of a single component

(i) Reactions between electrophilic and nucleophilic centres

1,3-Oxazetidin-2-ones have been prepared by the cyclization of *N*-substituted carbamic acid derivatives as outlined previously <80S571, 84CHEC-I(7)449>.

(ii) Electrocyclic reactions

Methylene oxazetidines (**122**) were prepared by the reaction of *N*-aryl acetone imines with acetyl chloride. A proposed acetyl iminium ion (**123**) is believed to undergo an electrocyclic ring closure to (**124**) which leads to the methylene substituted heterocycle after deprotonation. Other products were obtained in the reaction mixtures; yields of compounds (**122**) were not listed (Scheme 51) <75TL1405>.

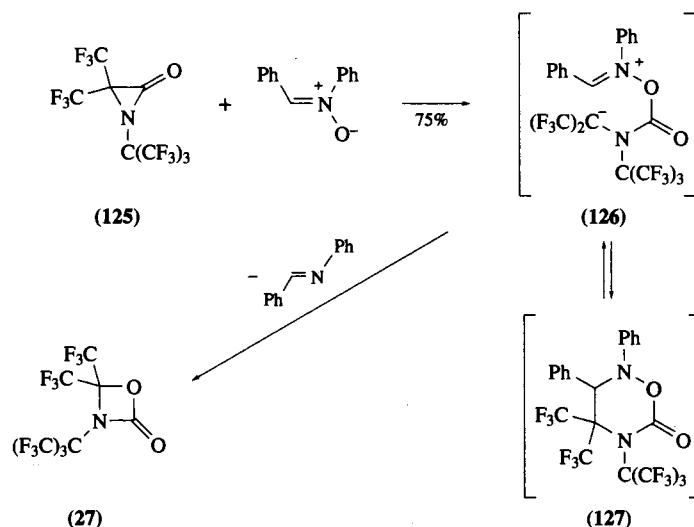


Scheme 51

(iii) Ring expansions

The attack of nitrones on α -lactam (**125**) results in C—C bond cleavage and eventual incorporation of the nitrone oxygen into the ring system <80DOK(253)886>. It is proposed that the ring-opened intermediate (**126**) is in equilibrium with six-membered ring (**127**), but O—N bond breakage in (**126**)

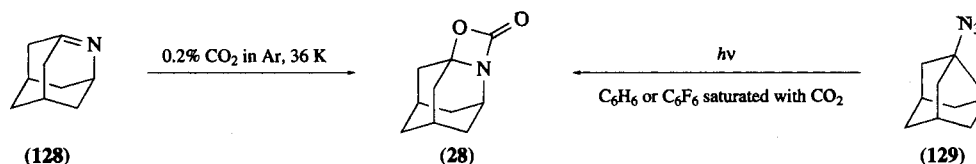
provides perfluorinated oxazetidin-2-one (**27**) (Scheme 52). Reactions of (**125**) with *C,N*-diphenyl nitron afforded (**27**) in 75% yield while triphenyl nitron and pyridine *N*-oxide were less efficient, affording (**27**) in 53% and 58% yields, respectively <80DOK(253)886>.



Scheme 52

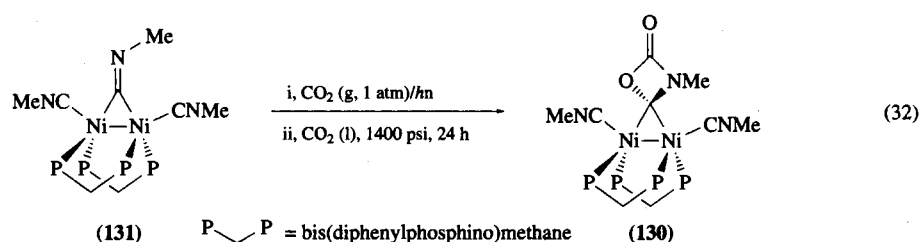
1.31.3.2.2 Ring formation from two components

[2 + 2] Cycloadditions are the most common method for the generation of 1,3-oxazetidin-2-ones as outlined previously <68JOC3088, 84CHEC-I(7)449>. Two new, unique examples involving carbon dioxide are outlined here. 2-Azaadamant-1-ene (**128**) is matrix-isolable material which reacts with dilute CO₂ (0.2% in Ar) at 36 K to yield oxazetidin-2-one (**28**). Scheme 53 also shows that heterocycle (**28**) can be formed directly by the irradiation of the precursor of (**128**), 3-azidonoradamantane (**129**). Imine (**128**) is highly strained and clearly reacts rapidly with carbon dioxide <84JA7996>.



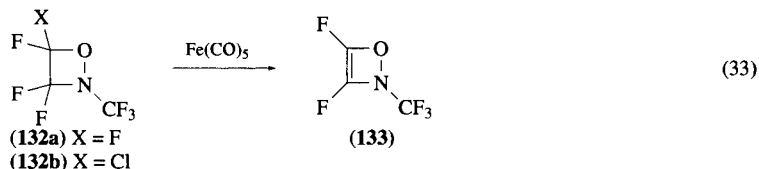
Scheme 53

Unusual organometallic 1,3-oxazetidinone (**130**) has been prepared by Kubiak and co-workers by both photochemical and thermal reactions of imino compound (**131**). The photochemical transformation which is reported to be the first example of a bimolecular association of CO₂ with a transition-metal complex proceeds with a quantum yield of 0.05 at 355 nm (Equation (32)) <88JA6904>. The thermal cycloaddition proceeds either with liquid CO₂ at 1400 psi or in a THF solution saturated with CO₂ and also containing NaPF₆ <87CC1412, 87JA754>.



1.31.3.3 2H-1,2-Oxazetes and Derivatives

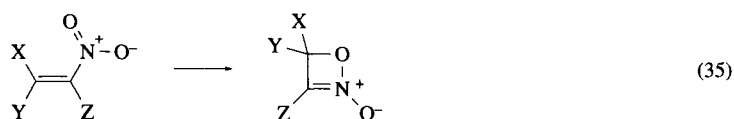
2H-1,2-Oxazetes are rare, only one having been prepared apparently, by elimination of vicinal halogens. Treatment of (132) with $\text{Fe}(\text{CO})_5$ afforded (133) (Equation (33)) <72ZOR186>.



1.31.3.4 4H-1,2-Oxazetes and Derivatives

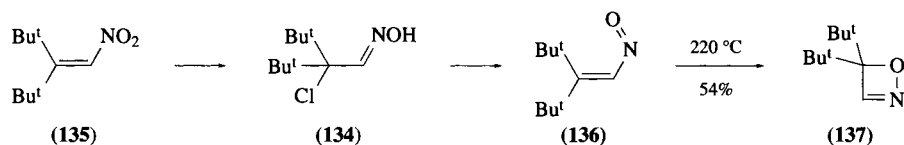
1.31.3.4.1 Electrocyclic reactions

A general approach to the 4H-1,2-oxazete ring system involves electrocyclization of an α,β -unsaturated nitroso or nitro compound (Equations (34) and (35)). Such cyclizations can be thermal or photochemical <73TL4057> but oxazetes have not been isolated from the latter approach. Large groups, X and Y, afford some steric protection of the product against bimolecular reactions.

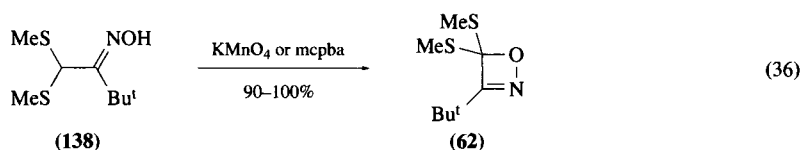


(i) Nitroso precursors

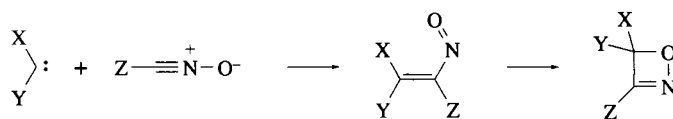
The requisite starting materials have been prepared by 1,4-elimination reactions on oximes or by oxidation of oximes. Wieser and Berndt prepared chloro oxime (134) from nitro alkene (135) and, by hydrohalogenation of the oxime, obtained the first stable nitroso alkene (136) <69AG(E)613, 75AG(E)70>. At 220 °C, in a flow system, (136) afforded oxazete (137) as shown in Scheme 54. In a formally equivalent process, oxidation of (138) at 0 °C, with MCPBA or KMnO_4 , gave oxazete (62) in excellent yield, presumably through electrocyclic ring closure of a nitroso alkene intermediate (Equation (36)) <80TL2025, 84CHEC-1(7)449>.



Scheme 54



An attractive route to α,β -unsaturated nitroso compounds, and hence to 4H-1,2-oxazetes, is shown with Scheme 55, in which a carbene reacts with a nitrile oxide to afford an α,β -unsaturated nitroso intermediate. Examples of this approach were not found.

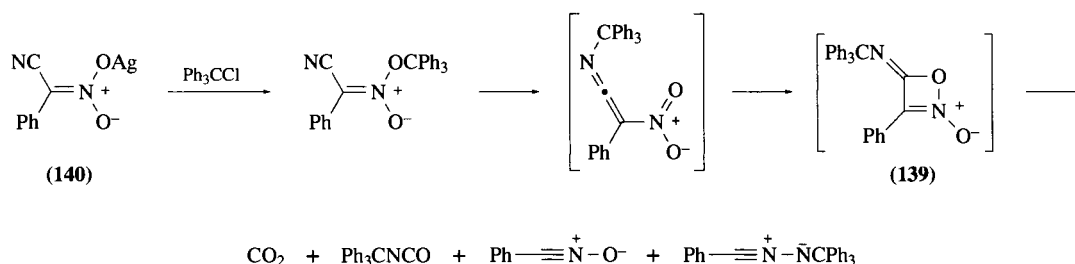


Scheme 55

(ii) Nitro precursors

Various approaches to isolable or transient 1,2-oxazete *N*-oxides from nitro alkenes have been published <68AG(E)637, 70JOC1771, 75AG(E)69, 84CHEC-I(7)449>.

Boyer *et al.* probably generated a 4-imino-1,2-oxazete *N*-oxide (**140**) as a transient during the reaction of (**139**) with trityl chloride <86H(24)2813, 87JCS(P1)2163, 88JCS(P1)2137>. Their rationale for the formation of the observed products is reproduced (in part) in Scheme 56.



Scheme 56

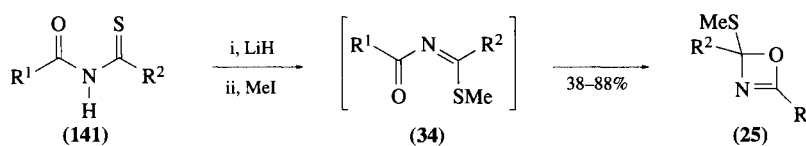
1.31.3.5 2H-1,3-Oxazetes and Derivatives

There are three papers reporting synthetic procedures for 2H-1,3-oxazetes, with only one of the papers demonstrating a general approach <79CCC1324>.

1.31.3.5.1 Electrocyclic reactions

(i) Thiocarbonyl precursors

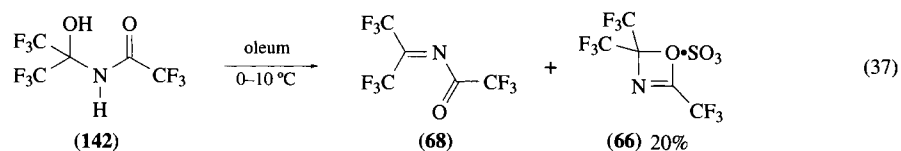
Several *N*-acyl thiocarbonyl compounds (**141**) where $\text{R}^1 = \text{NR}_2$, Ph, OMe, or SMe were deprotonated at nitrogen and then methylated at sulfur to afford the proposed intermediate *N*-acyl thioimidates (**34**). As illustrated in Scheme 57, the thioimidates are proposed to undergo electrocyclic ring closure to methylthio substituted 1,3-oxazetes (**25**). The reaction is fairly general in that it will accommodate various groups R^1 and R^2 . The R^1 groups include methyl, phenyl, and β -styryl <79CCC1324>.



Scheme 57

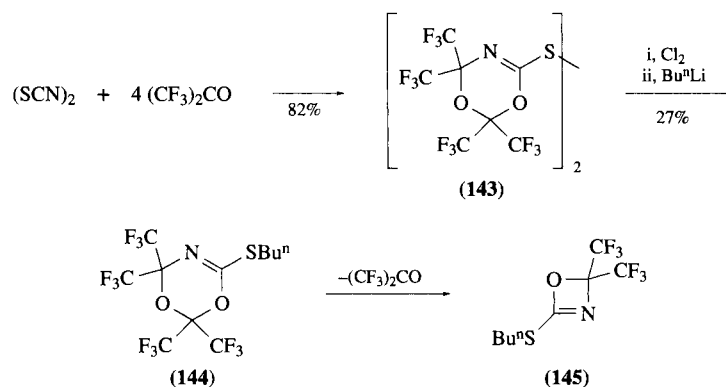
(ii) Hydroxyamide precursors

An unusual 1,3-oxazete complexed to SO_3 was isolated when the oleum mediated dehydration of hydroxyamide (**142**) was attempted. Equation (37) shows two products, the desired acylimine (**68**) which was obtained in 54% yield and complex (**66**) (20%) <84JOU1213>.



(iii) Contraction of six-membered rings

The reaction of thiocyanogen with four equivalents of hexafluoroacetone affords disulfide (**143**), the disulfide bond of which can be cleaved and alkylated as shown in Scheme 58. Heating (**144**) prompts loss of one unit of hexafluoroacetone and results in 1,3-oxazete (**145**) <86ZAAC(532)131>.

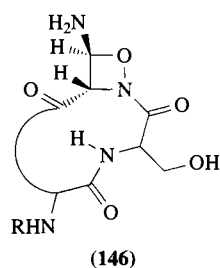


Scheme 58

1.31.4 IMPORTANT COMPOUNDS AND APPLICATIONS

1.31.4.1 Natural Products

The antifungal antibiotics called neopeptin A, B, and C, are macrocyclic lipopeptides in which a 1,2-oxazetidine ring is fused, through N-2 and C-3, to the large ring <86ABC357>. These compounds, isolable from the culture filtrate of *Streptomyces* sp., are depicted (in part) as formulae (**146**). The *trans* substitution pattern of the oxazetidine ring is inferred from the coupling constants between vicinal hydrogens in two conformations, as noted in Table 5.



The arc represents 18 more atoms of a macrocyclic ring. *trans*-Diastereomer inferred from ^1H NMR coupling constants.
 Neopeptin A: $\text{R} = \text{CO}(\text{CH}_2)_{10}\text{CHMe}_2$
 B: $\text{R} = \text{CO}(\text{CH}_2)_{10}\text{CH}(\text{Me})\text{Et}$
 C: $\text{R} = \text{CO}(\text{CH}_2)_9\text{CHMe}_2$

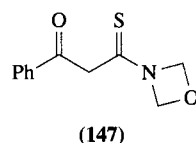
1.31.4.2 Veterinary and Other Medical Applications

3,3,4,4-Tetrafluoro-2-trifluoromethyl-1,2-oxazetidine (**40**) is the source of triazene (**41**), (Scheme 14) the properties of which suggest applications as lubricants, heat-transfer media, and as test fluids for electronic components <90EUP350042>.

1,2-Oxazetidines (**103**), Scheme 35, show therapeutic properties and have medical applications, as in veterinary medicine for example <84MIP519297>.

1.31.4.3 Agricultural Applications

Neopeptins A and B (**146**) have antifungal activity against plant pathogens and inhibit the activity of cell wall-synthesizing enzymes 1,3-glucan synthetase, proteoheteroglycan synthetase and peptidoglycan synthetase <82ABC2621>. Thioamide (**147**) and related compounds bearing other nitrogen substituents were found to have fungicidal activity <80EGP140838>.



1.31.4.4 Polymerization Catalysts

Oxazetidine (**87**) (Scheme 24) was treated with HF and AsF₅ to generate CF₃NHOCF₂CF₃ which was *N*-fluorinated to produce a catalyst for polymerization of C₂F₄. Other *N*-fluoro (fluoroalkyl) fluoroalkoxyamines were also prepared from oxazetidines <90EUP353721>.

1.31.4.5 Miscellaneous Applications

N-Phenyl-1,3-oxazetidin-2-one was employed as a model compound for insight into the bacterial luciferase mechanism <76BBR(73)465>. Its measurable instability toward [2 + 2] cycloreversion (see Section 1.31.1.6.2) prompted the authors to invoke the intermediacy of a similar oxazetidine in the bacterial luciferase mechanism.

1.32

Four-membered Rings with One Sulfur and One Nitrogen Atom

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1.32.1 INTRODUCTION

Four-membered rings containing one sulfur and one nitrogen atom can be classified under two categories: (i) 2*H*-1,2-Thiazetes (**1**), 2*H*-1,3-thiazetes (**2**), and 4*H*-1,2-thiazetes (**3**) contain one nitrogen atom, one sulfur atom, and one double bond in the ring. They are unstable and thus not well known in the literature.



(1)



(2)



(3)

(ii) Thiazetidines are saturated four-membered rings containing one sulfur and one nitrogen atom, and can be subdivided into 1,2-thiazetidines (**4**) and 1,3-thiazetidines (**5**). 1,2-Thiazetidine 1,1-dioxides (**6**) are also known by their trivial name of β -sultams.



(4)



(5)



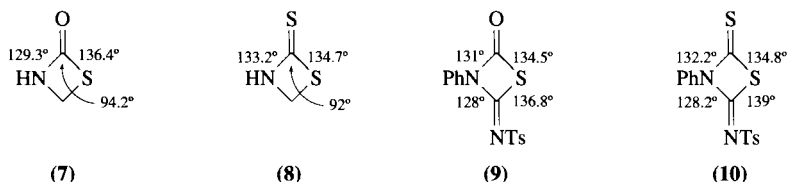
(6)

Two reviews which include four-membered rings containing one sulfur and one nitrogen atom were published in the early 1980s <84AHC(35)199, 84CHEC-1(7)449>. More specifically, the synthesis and reactivity of β -sultams has been reviewed by Chanet-Ray and Vessière <86OPP159>.

1.32.2 THEORETICAL METHODS

Semiempirical MNDO geometry optimizations were carried out on the 1,3-thiazetidine-2-one (**7**) and 2-thione (**8**) ring systems, and the carbonyl group, and to a lesser extent the thiocarbonyl group, were predicted to possess significant tilts towards the nitrogen atom <89JST(194)135>. This was accounted for as an attempt to maximize stabilization from a two-electron interaction between

the carbonyl n orbital and the C—N σ^* orbital (negative hyperconjugation). Comparison can be made with the bond angles obtained from the x-ray crystal structures of 3-phenyl-4-tosylamino-1,3-thiazetidine-2-one (**9**) and 2-thione (**10**) which confirm that there are small tilts towards the nitrogen in such rings systems, although van der Waals repulsion from the adjacent sulfur atom was cited as being the cause by King *et al.* <82BSB729, 83BSB495>.



1.32.3 EXPERIMENTAL STRUCTURAL METHODS

1.32.3.1 X-ray Crystallography

Information on the geometry of the four-membered thiazetidine ring has been determined mainly by single crystal x-ray diffraction.

1.32.3.1.1 1,2-Thiazetidines

Representative bond lengths and angles for the reported x-ray crystal structures of β -sultams are collected in Table 1. The bond distances are similar to those found in N,N -disubstituted sulfonamides, with S—C, S—N, C—C, and N—C lengths of around 1.78, 1.67, 1.55, and 1.49 Å, respectively. The N—S—C bond angle is compressed to about 80° , whilst the C—N—S and N—C—C bond angles are enlarged to 95° . The ring is normally puckered to varying degrees from 10.7° <89LA975>, through 12.9° <85TL5689>, 14.7° <85AX(C)1265>, and up to 23° for 2,3-disubstituted- β -sultams <85LA802>. Of those reported, only the N -carbanoyl- β -sultam <85M493> is planar, which may be explained by the nonpyramidal geometry of the sp^2 hybridized sultam nitrogen due to orbital overlap with the carbonyl group, combined with the absence of substituents at C-3 and C-4.

1.32.3.1.2 1,3-Thiazetidines

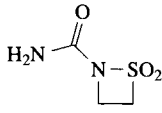
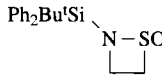
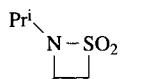
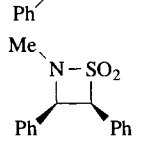
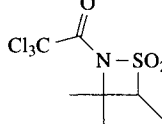
Bond angles and distances from x-ray crystal structures of 1,3-thiazetidines are shown in Table 2. The four-membered ring is more elongated than the 1,2-thiazetidine ring having S—C and N—C bond lengths of ca. 1.80 and 1.39 Å, respectively; with contracted C—S—C bond angles of about 73° and C—N—C angles enlarged to around 101° . The ring is only slightly twisted, consisting of two planes (C(2)—S(1)—C(4) and C(2)—N(3)—C(4)) which intersect at the line S—N with dihedral angles of between 1.4° <82BSB729>, 4.0° <83BSB495>, and 7° <81BSB1185>. Although the nitrogen has an sp^2 configuration, the N—C bond lengths suggest there is limited resonance interaction of the nitrogen electron pair with adjacent unsaturated substituents at C-2 and C-4. Substituents at C-2 and C-4 are bent towards the nitrogen reportedly because of van der Waals repulsion or negative hyperconjugation.

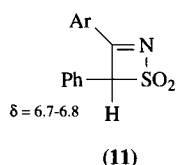
1.32.3.2 Proton NMR spectroscopy

1.32.3.2.1 Thiazetes

3,4-Diaryl-4*H*-1,2-thiazete-1,1-dioxides (**11**) have a single methine proton at C-4 which appears as a downfield singlet, deshielded by the adjacent phenyl and sulfonyl groups <91T1937>.

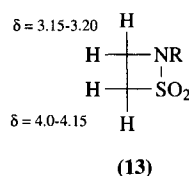
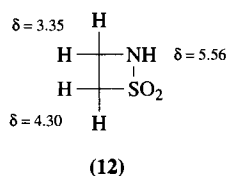
Table 1 X-ray structures of 1,2-thiazetidines.

Compound	Bond length (Å)				Bond angle (°)					Ref.
	S—N	C—N	C—S	C—C	C—N—S	N—S—C	S—C—C	N—C—C	O—S—O	
	1.651	1.470	1.780	1.547	96.8	80.1	89.0	94.1	116.4	85M493
	1.642	1.498	1.779	1.523	94.0	81.5	87.9	95.5	116.0	89LA975
	1.661	1.491	1.761	1.541	93.6	80.0	88.1	93.2	116.4	85LA802
	1.643	1.487	1.806	1.578	95.1	81.9	85.9	95.2	116.4	85AX(C)1265
	1.698	1.512	1.784	1.551	95.1	79.6	90.4	93.5		85TL5689



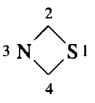
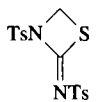
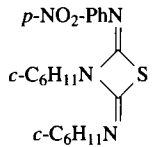
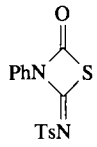
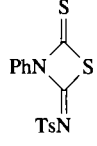
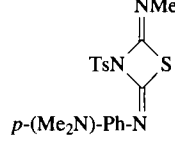
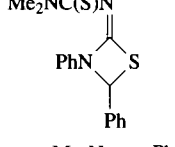
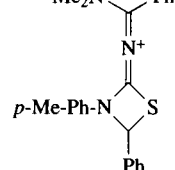
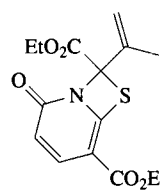
1.32.3.2.2 1,2-Thiazetidines

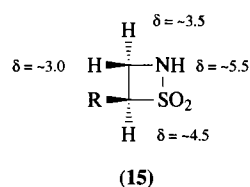
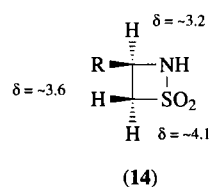
There is available substantial ^1H NMR data on β -sultams. The spectra of ethanesultam (12), the parent compound, was reported by Le Berre and Petit (72TL213) and shows two multiplets, which appear as triplets in D_2O , with the C-4 hydrogens deshielded by around 1 ppm with respect to the C-3 hydrogens, and a broad exchangeable singlet for the N—H. A similar pattern was observed in a series of *N*-alkylated β -sultams (13), as detailed by Vessière and co-workers where both signals appear as triplets (85BSF463).



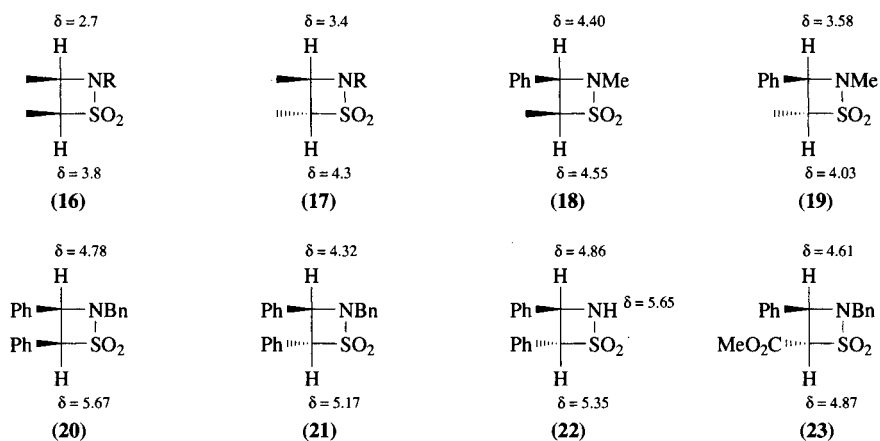
Ring hydrogens of 3-monosubstituted β -sultams (14) appear as double doublets showing an ABX pattern, with the hydrogen at C-3 coupling with 8 and 6 Hz to the *cis*- and *trans*-hydrogens of C-4, respectively (91MI 132-01). The larger geminal coupling of the C-4 hydrogens is around 12 Hz. The more common 4-monosubstituted β -sultams (15) also show ABX double doublets, with the C-4 hydrogen having similar coupling constants of 8 and 6 Hz with the *cis*- and *trans*- C-3 hydrogens, respectively. The hydrogens at C-3 have smaller geminal coupling constants of between 4.5 and 6.1 Hz (85BSF463, 89TL2873, 92LA687).

Table 2 X-ray structures of 1,3-thiazetidines.

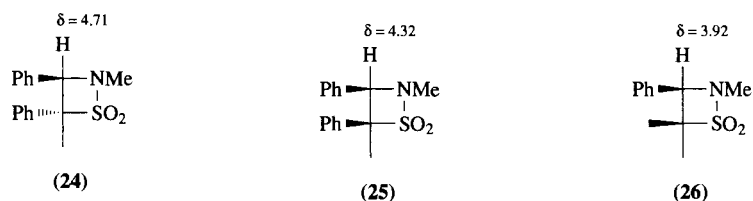
Compound		Bond length (Å)				Bond angle (°)				Ref.
		S1—C2	C2—N3	N3—C4	C4—S1	C—S—C	N—C2—S	C—N—C	N—C4—S	
		1.86	1.49	1.39	1.77	75.2	88.6	101.0	95.5	77RTC263
		1.81	1.36	1.43		72.0	95.6	102.0	90.2	81BSB1185
		1.81	1.40	1.39	1.79	71.9	94.1	98.9	95.0	82BSB729
		1.80	1.39	1.40	1.80	73.1	93.0	101.0	92.8	83BSB495
		1.81	1.39	1.39	1.81	71.4	94.2	100.2	94.2	87CB849
		1.762	1.356	1.474	1.880	73.9	96.6	101.5	87.8	90CL1423
		1.73	1.29	1.45	1.82	74.0	97.0	102.0	88.0	90CB499
		1.942	1.454	1.340	1.752	72.4	86.3	102.9	98.1	92JCS(P1)621



The ring proton spectra of 3,4-disubstituted β -sultams consists of two doublets with the *cis*-diastereoisomer showing larger coupling constants (ca. 8–10 Hz) compared to those of the *trans*-diastereoisomer (ca. 6–7 Hz). Chemical shifts for representative examples are displayed ((16)–(23)) <85BSF463, 89S135, 89TL2869, 91AP(324)15, 91TL751>.

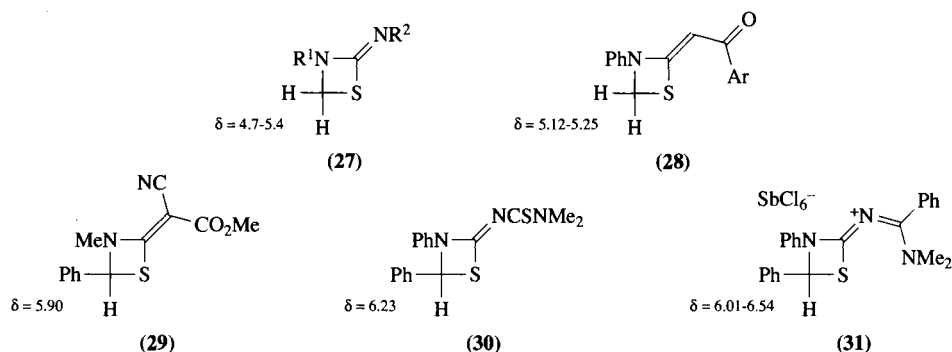


For the trisubstituted β -sultam ring, as exemplified in (24)–(26), a singlet is observed for the single ring methine proton <89JHC1781, 91AP(324)15>.



1.32.3.2.3 1,3-Thiazetidines

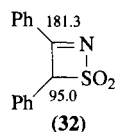
The proton spectra of the 1,3-thiazetidine ring is relatively simple due to the absence of coupling between ring protons ((27)–(31)). An unsubstituted methylene group adjacent to nitrogen and sulfur appears as a singlet at about $\delta = 5$ ppm. If there is a phenyl group at this position, this singlet is shifted downfield by about 1 ppm <84BSB405, 87CS473, 90CB499, 90CL1423, 91JHC177>.



1.32.3.3 Carbon-13 NMR Spectroscopy

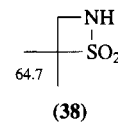
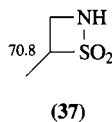
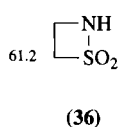
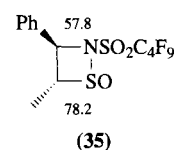
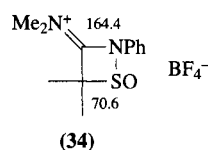
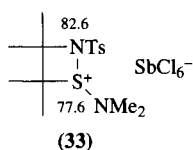
1.32.3.3.1 Thiazetes

3,4-Diaryl-4*H*-1,2-thiazete-1,1-dioxides (32) show two downfield ring ^{13}C NMR resonances for the carbons at C3 and C4 <91T1937>.



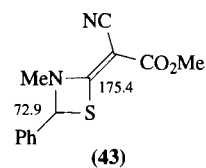
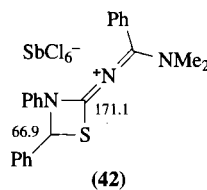
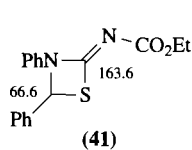
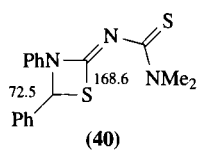
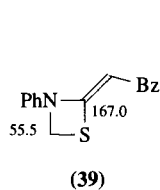
1.32.3.3.2 1,2-Thiazetidines

Carbon-13 NMR chemical shifts for various 1,2-thiazetidinium salts and 1,2-thiazetidin-1-oxides are shown in (33)–(38). The ^{13}C NMR spectra of β -sultams are reported <83TL2131> to show an unusually high α -carbon deshielding effect, which is characteristic of four-membered ring sulfonyl compounds <80JOC4807>. Surprisingly little data has been published in this area <82LA545, 83TL2131, 86LA32, 87LA527>.

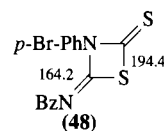
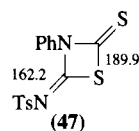
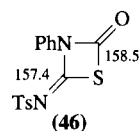
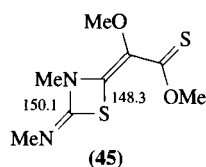
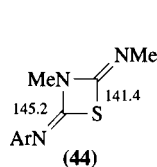


1.32.3.3.3 1,3-Thiazetidines

An unsubstituted carbon adjacent to the nitrogen and sulfur in a 1,3-thiazetidine ring appears at around 56 ppm, whilst substitution by a phenyl group deshields this carbon signal by between 10 and 17 ppm, as illustrated in (39)–(43) <83CB1297, 84BSB405, 87CS473, 90CB499, 90CL1423>.



Chemical shifts for unsaturated carbons as part of imino, carbonyl, and thiocarbonyl groups are seen at around 145–155, 160, and 190 ppm, respectively ((44)–(48)) <82BSB243, 82CB3107, 83BSB61, 87CB849, 93JPR381>.

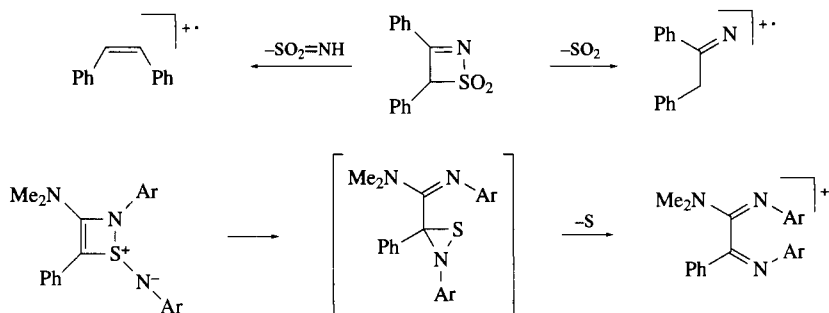


1.32.3.4 Mass Spectrometry

The four-membered ring often undergoes four-center cleavage in the mass spectrometer giving rise to base peaks from retro-cycloaddition.

1.32.3.4.1 Thiazetes

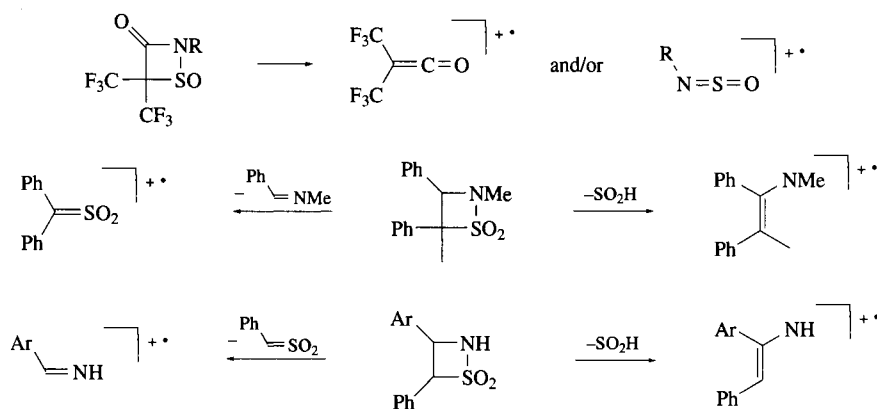
4*H*-1,2-Thiazete-1,1-dioxides fragment with loss of SO₂ and sulfimide <91T1937>; whereas 2*H*-1,2-thiazete salts show a molecular ion corresponding to loss of sulfur, which can occur via a thiaziridine intermediate as shown in Scheme 1 <87CB751>.



Scheme 1

1.32.3.4.2 1,2-Thiazetidines

1,2-Thiazetidine-3-one-1-oxides show base peaks due to retro-cycloaddition <86CB1127>. β -Sultams similarly undergo four-center fragmentations leading to either imine or sulfene molecular ions, as well as loss of SO₂H (cf. Scheme 2) <86CB1127, 89JHC1781, 91TL751>.



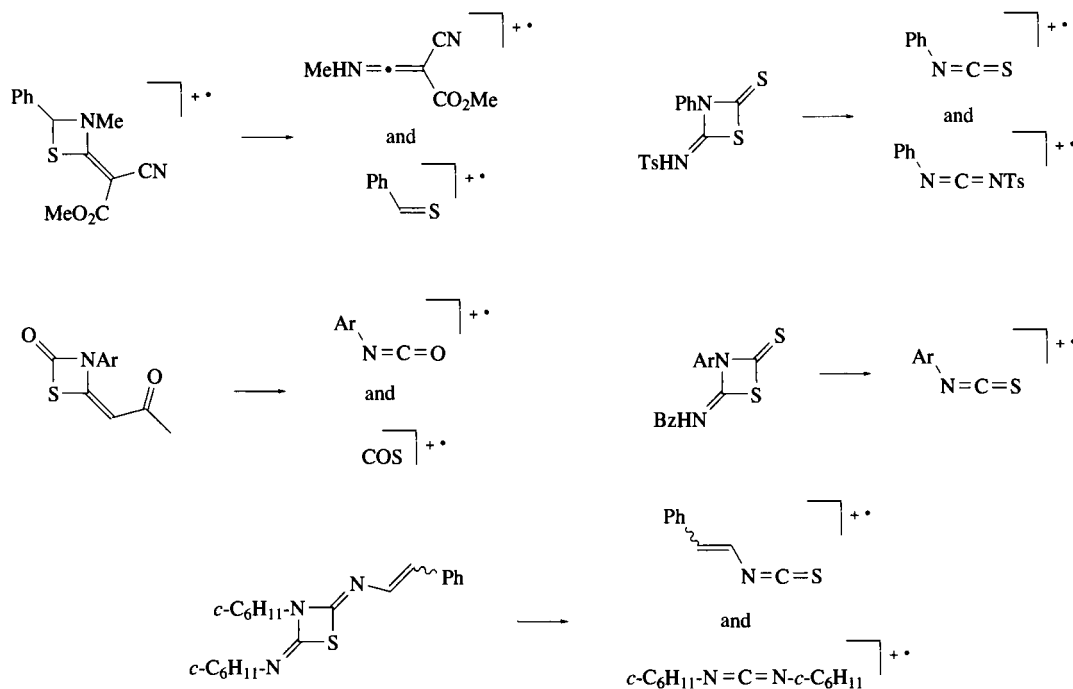
Scheme 2

1.32.3.4.3 1,3-Thiazetidines

1,3-Thiazetidines also produce molecular ions arising from retro-cycloaddition <82CB3107, 84BSB405>. Common fragments are isocyanates <88JPR795>, isothiocyanates <93JPR381>, and carbodiimides <83BSB61>, and these can represent a reversal of the synthesis of the thiazetidine ring <83CCC1745>. Representative fragmentations are shown in Scheme 3.

1.32.3.5 UV Spectroscopy

β -Sultams have small absorptions in the UV spectrum as typified by those of *N*-bromo-3,3-dimethyl- β -sultam at 296 nm (ϵ 240) <83JOC537> and *N*-*t*-butyl-3-phenyl- β -sultam at 260 nm (ϵ 350) <88MI 132-01>.



Scheme 3

1.32.3.6 IR Spectroscopy

1.32.3.6.1 Thiazetes

2*H*-1,3-Thiazetes have stretching frequencies in the IR for the C=N bond at around 1560–1585 cm^{-1} <77CB2114>, whereas 4*H*-1,2-thiazete-1,1-dioxides show a characteristic C=N band at 1520 cm^{-1} <91T1937>.

1.32.3.6.2 1,2-Thiazetidines

Many examples of IR spectra of β -sultams are reported <72TL213, 83AP(316)281, 84JOC1700, 85LA802, 85M493, 85TL5689, 86LA32, 87CB751, 87LA527, 89AP(322)515, 89JHC1781, 89LA975, 89S135, 91AP(324)15, 91AP(324)773, 91LA171, 91TL751, 92LA687>. The sulfonyl group exhibits symmetrical stretching at around 1150 cm^{-1} and unsymmetrical stretching at about 1300 cm^{-1} ; whilst the NH stretching is at 3310 cm^{-1} .

1.32.3.6.3 1,3-Thiazetidines

The IR spectra of 1,3-thiazetidines is determined by the nature of the substituents at C-2 and C-4. Functional groups such as imines and carbonyls at these positions show the most characteristic adsorption bands. The strained 1,3-thiazetidine-2-one ring system can show carbonyl absorption at the unusually high frequency of 1780–1825 cm^{-1} <82BSB243, 86CB1127>, although others are found at the more typical C=O stretching vibration of around 1720 cm^{-1} <88JPR795>. 2-Imino-1,3-thiazetidines show a characteristic strong C=N stretching frequency at 1620–1665 cm^{-1} <82CCC1229,

83CCC1745, 84BSB405, 91JHC177, 93JPR381) and the 2,4-bis(imino)1,3-thiazetidine ring has two bands at 1660 and 1680 cm^{-1} for the exocyclic $\text{C}=\text{N}$ bonds (87CB849).

1.32.4 THERMODYNAMIC ASPECTS

1.32.4.1 Stability

1.32.4.1.1 Thiazetes

Thiazetes are inherently unstable as the sp^2 carbon bond angles are considerably deformed from the ideal angle of 120° . They are synthesized in low yields and as mixtures with other products (87CB751, 91T1937). 2*H*-1,3-Thiazetes were obtained utilizing stabilizing trifluoromethyl groups as substituents (77CB2114, 82T287).

1.32.4.1.2 Thiazetidines

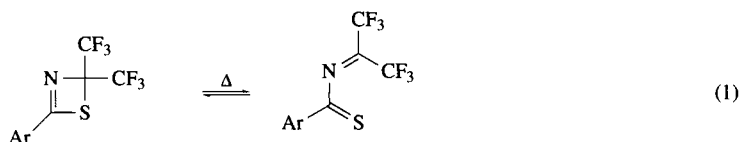
Although 1,2-thiazetidines are more stable than thiazetes since they possess less ring-strain, they are less stable than 1,3-thiazetidines since there is lone-pair-lone-pair repulsion at the $\text{N}-\text{S}$ bond. This is alleviated by oxidation at the sulfur heteroatom, but β -sultams still slowly decompose at room temperature, although they can be stored cold for several weeks (83TL2131). Ethanesultam undergoes hydrolytic ring-opening to taurine in the presence of a trace of water (see Section 1.32.5.2.4) (72TL213, 89AP(322)515). The stability may be improved by bulky substituents at the nitrogen which prevent attack of nucleophiles at the sulfonyl group (89AP(322)515).

1.32.4.2 Conformations

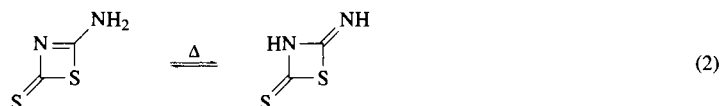
The four-membered ring of 1,2-thiazetidines is twisted out of planarity with puckering angles of up to 23° for the 2,3-disubstituted derivative (85LA802) as determined from their x-ray crystal structures. 1,3-Thiazetidines are closer to planarity with dihedral angles between the two planes of around 4.0° (81BSB1185, 83BSB495).

1.32.4.3 Tautomerism

2,2-Bis(trifluoromethyl)-2*H*-1,3-thiazetes are in thermal mobile equilibrium with the open-chain valence tautomer shown in Equation (1) (77CB2114). This was demonstrated by trapping of the hetero-1,3-diene tautomer with a variety of dienophiles (see Section 1.32.5.1.2) (82T287).



4-Amino-1,3-thiazete-2-thione was reported to exist as a mixture with its imino tautomer (Equation (2)) (77ZAAC(434)110).

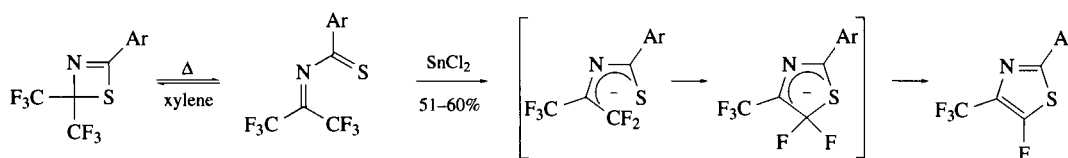


1.32.5 REACTIVITY OF NONCONJUGATED RINGS

1.32.5.1 Thiazetes

1.32.5.1.1 Thermal reactions (unimolecular)

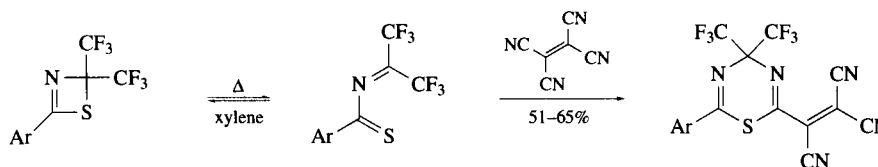
2,2-Bis(trifluoromethyl)-2*H*-1,3-thiazetes have been investigated by Burger *et al.* and were found to undergo ring enlargement in refluxing xylene with tin(II) chloride to give 5-fluoro-4-trifluoromethyl-thiazoles <82CB2494>. The reaction is thought to proceed via the open-chain thiocarboxamide tautomer (Scheme 4).



Scheme 4

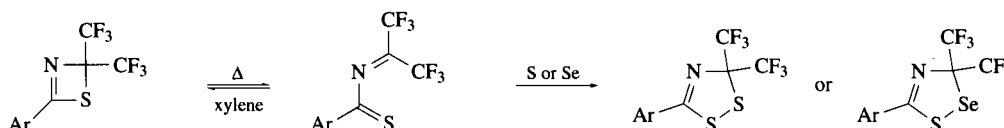
1.32.5.1.2 Cyclic transition state reactions

This 1,3-thiazete-thiocarboxamide thermal tautomerism was further evidenced by trapping of the hetero-1,3-diene tautomer by a Diels–Alder reaction with tetracyanoethene in refluxing xylene (Scheme 5). A minor product was identified as the symmetrical [2:1] adduct formed by cycloadditions at two *trans*-cyano groups on the dienophile <81CZ380, 82T287>.



Scheme 5

In related reactions, the 1,3-thiazete undergoes cycloadditions via the 1,3 heterodiene with either elemental sulfur or selenium to give five-membered ring heterocycles, as illustrated in Scheme 6 <86CZ87>.



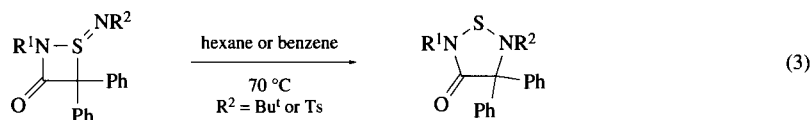
Scheme 6

1.32.5.2 1,2-Thiazetidines

The reactivity of β -sultams is dominated by electrophilic attack at the nitrogen and deprotonated C-4 carbon. A variety of alkylations, acylations, silylations, Mannich, and Aldol-type reactions have been studied, principally by Otto and co-workers <91AP(324)15, 91LA171, 93AP(326)437>. Relief of ring strain facilitates ring-opening hydrolysis and ring-expansion reactions.

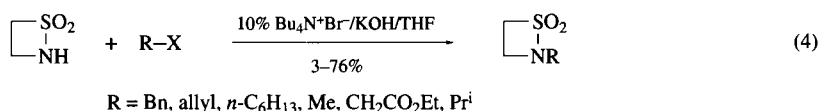
1.32.5.2.1 Thermal reactions (unimolecular)

1-Imino-1,2-thiazetidine-3-ones, isolated from low temperature cycloaddition of sulfur diimides with diphenylketene, readily undergo ring-expansion to give 1,2,5-thiadiazolidine-3-ones in refluxing hexane or benzene (Equation (3)) <70TL1427, 72JOC3810, 83H(20)187>.

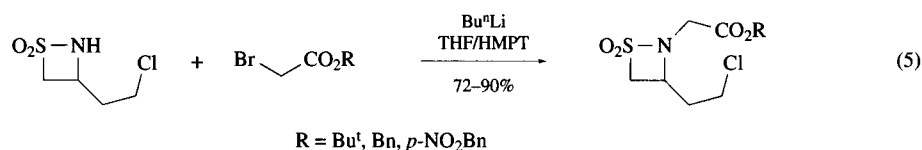


1.32.5.2.2 Electrophilic attack at nitrogen

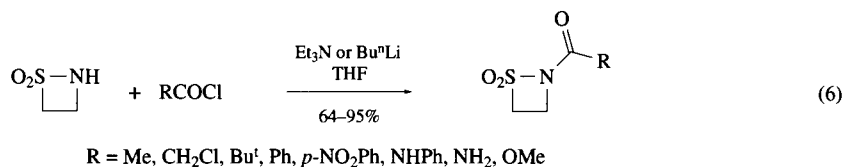
β -Sultams can be *N*-alkylated using the phase-transfer conditions developed for β -lactams (Equation (4)). The reaction works well for activated alkyl halides, such as allyl and benzyl bromides, less so for bromoacetic esters which undergo partial hydrolysis, and poorly for secondary halides <83TL2131>.



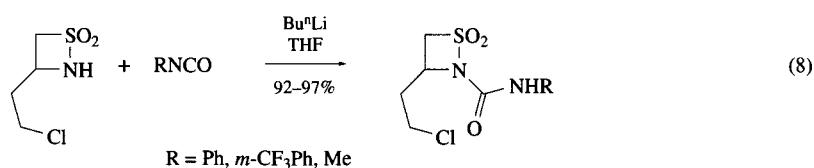
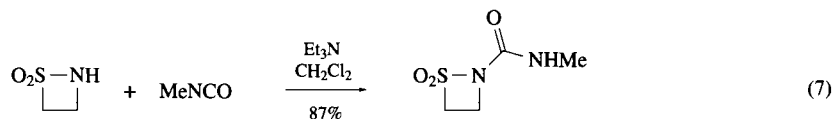
Alkylation with bromoesters is reportedly better accomplished using *n*-butyllithium in THF with a small amount of HMPT added, as demonstrated in the example shown in Equation (5) <93AP(326)437>.



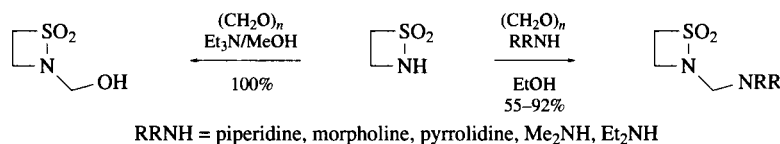
N-Acylation of ethanesultam is achieved by reaction with the acyl chloride in THF using either triethylamine or *n*-butyllithium as base (Equation (6)) <85M493>. Under similar conditions, reaction with oxalyl chloride leads to the oxalyl-bis(sultam) derivative <85M493> and treatment with methyl chloroformate yields the carbamate <83TL2131>.



β -Sultams form unsymmetrical ureas in high yields on reaction with both aliphatic <83TL2131> and aromatic <93AP(326)437> isocyanates (Equations (7) and (8)).

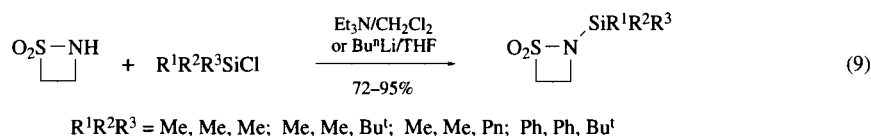


Reaction of ethanesultam with paraformaldehyde gives the amino alcohol <83TL2131>; and with a secondary amine also present aminomethylation occurs via a Mannich reaction (Scheme 7) <89AP(322)515>.



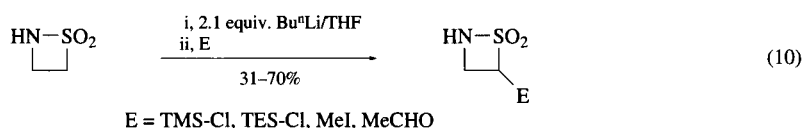
Scheme 7

N-Silylation of ethanesultam was achieved using the appropriate chlorosilane with either triethylamine <83TL2131> or one equivalent of *n*-butyllithium as base (Equation (9)) <89LA975>. Use of excess butyllithium results in additional silylation at C-4.

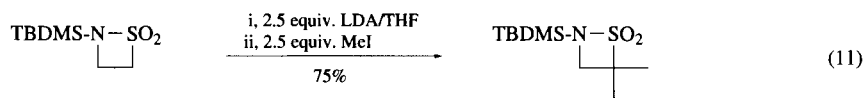


1.32.5.2.3 Electrophilic attack at carbon adjacent to the sulfonyl group

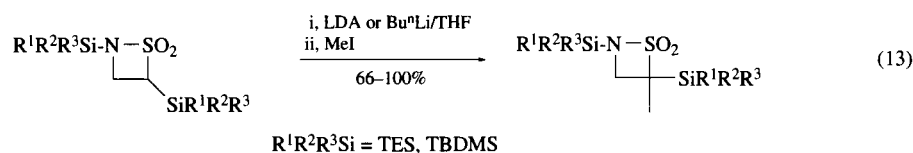
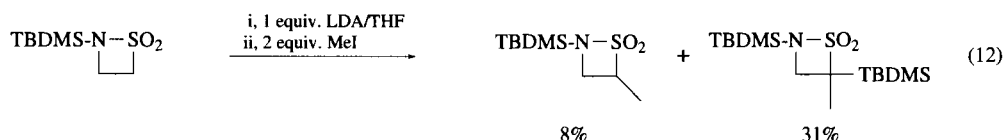
The C-4 hydrogen is relatively acidic since the resulting anion is stabilized by delocalization with the adjacent sulfonyl group. If ethanesultam is doubly deprotonated with *n*-butyllithium, selective C-4 monoalkylation can be achieved using a slight excess of electrophile (Equation (10)) <89TL2873>. A large excess of electrophile and prolonged reaction times leads to additional alkylation at the weaker nucleophilic sulfonamide nitrogen.



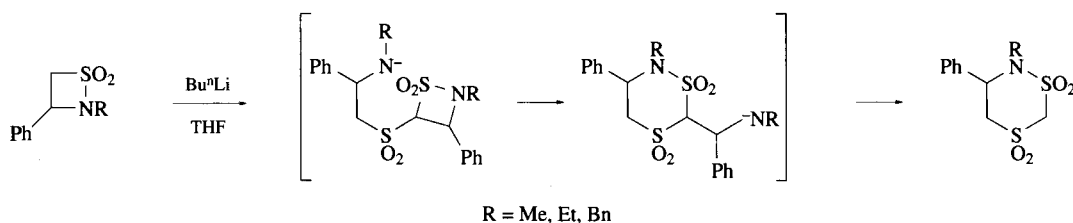
N-Silyl protection of ethanesultam allows for smooth dimethylation at the 4-position using an excess of LDA (Equation (11)) <91AP(324)15>.



Attempts to limit the methylation using one equivalent of LDA lead to contamination with cross-silylation occurring from the nitrogen to C-4 (Equations (12) and (13)) <91AP(324)15>. Monomethylation at C-4 is better accomplished when one of the hydrogens at this site is substituted by a silyl group <89TL2873, 91AP(324)15>.

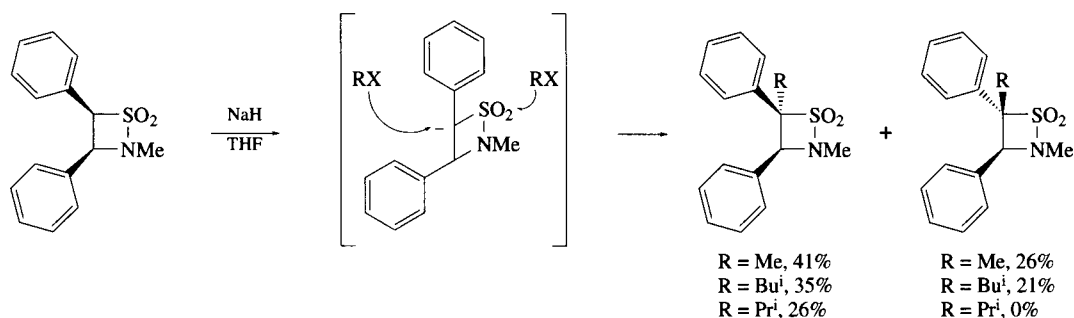


2,3-Disubstituted β -sultams, deprotonated with *n*-butyllithium, are known to undergo self-condensation to give 2,4,1-dithiazine tetroxides [84CC1084, 89AP(322)17]. The postulated mechanism, outlined in Scheme 8, involves an initial dimerization with the anion causing ring-opening of another β -sultam sulfonamide, followed by ring closure and finally a retro-Mannich reaction. When the β -sultam nitrogen has an isopropyl group attached, the initial addition dimer is isolated.



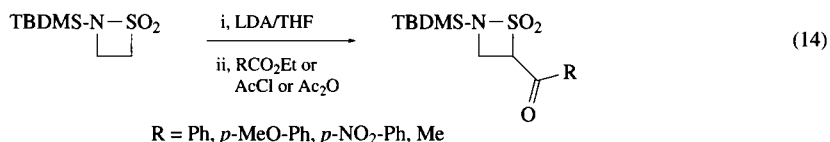
Scheme 8

Alkylation of *N*-methyl-3,4-diphenyl- β -sultam with various alkyl halides leads to 4-alkylation with predominantly the *cis* configuration as expected from approach of the electrophile from the less hindered face of the anion (Scheme 9) [89JHC1781]. Alkyl bromides were found to be better alkylating agents than the corresponding iodides, which, with the exception of methyl iodide, were too bulky to approach the congested reaction site.

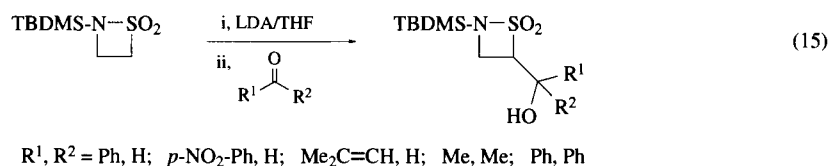


Scheme 9

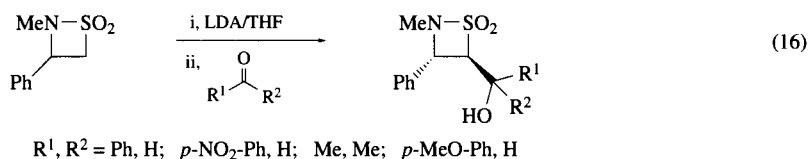
Deprotonation of *N*-silylated β -sultams with LDA and subsequent treatment with alkyl benzoates gives the corresponding 4-acyl- β -sultams (Equation (14)). However, attempted acylation with ethyl acetate gives a mixture of products and was better accomplished using acetic anhydride or acetyl chloride [91LA171].



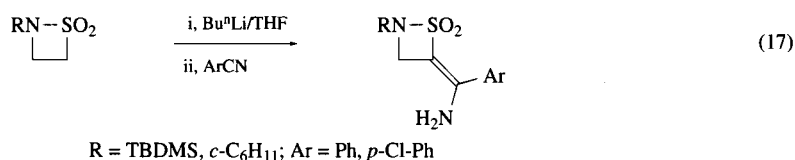
The same β -sultams also undergo aldol-type condensations with either benzaldehydes, acetophenone or benzophenone (Equation (15)). The aldols were obtained as 1 : 1 mixtures of diastereoisomers [91AP(324)773].



N-Methyl-3-phenyl- β -sultam was reported to undergo condensation with carbonyl compounds to give exclusively the *trans* C-4 aldol isomer (Equation (16)) [91AP(324)773].

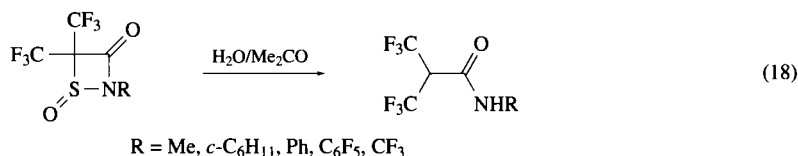


β -Sultams undergo a similar condensation with benzonitriles to give enamines with the *trans* configuration as shown in Equation (17). The enamine predominates in acetone solution, but the imine tautomer was reported to be preferred in chloroform $\langle 93\text{H}(35)193 \rangle$.

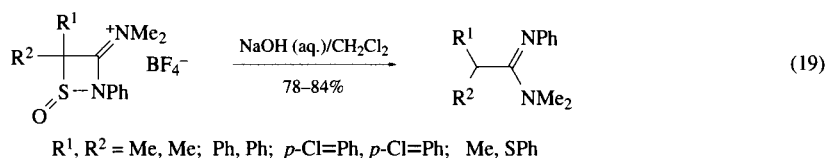


1.32.5.2.4 Nucleophilic attack at sulfur with cleavage of the N—S bond

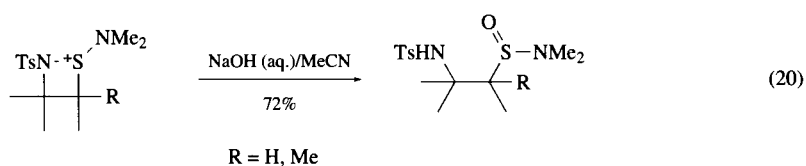
1,2-Thiazetidine-3-one-1-oxides undergo room temperature hydrolysis in acetone/water to give secondary amides (Equation (18)) $\langle 86\text{CB}1127 \rangle$.



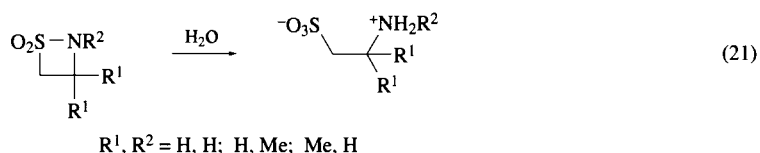
3-Iminothiazetidine-1-oxides readily ring-open with base hydrolysis to give the corresponding trisubstituted amidines (Equation (19)) $\langle 87\text{LA}527 \rangle$.



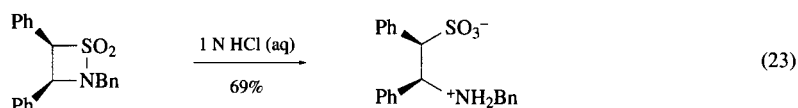
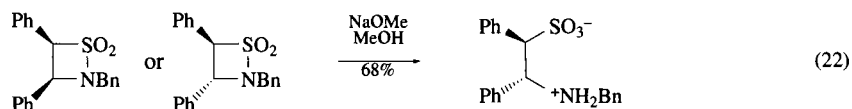
Similarly, thiazetidinium salts are also hydrolyzed by base to give the corresponding sulfinic acid amides (Equation (20)) $\langle 86\text{LA}32 \rangle$.



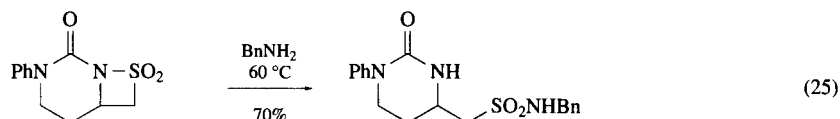
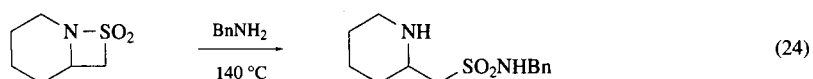
β -Sultams slowly undergo hydrolytic ring-opening to taurines (Equation (21)); for example, an aqueous solution of ethanesultam at 40 °C has a half-life of 30 hours $\langle 72\text{TL}213 \rangle$. The rate of hydrolysis of ethanesultam is faster in alkali, with a half-life at pH = 13 of 6 hours at 30 °C $\langle 83\text{TL}2131 \rangle$. Substitution affects the rate in varying ways; in alkali 3,3-dimethyl- β -sultam is more stable ($t_{1/2} > 9$ days), whereas *N*-methyl- β -sultam hydrolyses faster ($t_{1/2} = 45$ min). The hydrolysis rate increases in acidic conditions as exemplified by *N*-methyl- β -sultam (at pH = 2.3, $t_{1/2} = 12$ min).



N-Benzyl-2,3-diphenyl- β -sultam undergoes ring-opening hydrolysis in either acid or base (Equations (22) and (23)). Both *cis*- and *trans*-isomers give *threo* 1,2-diphenyltaurine on treatment with sodium methoxide due to initial base-catalyzed epimerization of the less stable *cis*-isomer. The *erythro* isomer can only be obtained from the *cis*- β -sultam using hydrochloric acid (<89S135>).

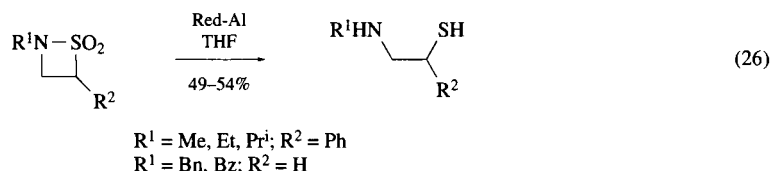


β -Sultams are stable towards amines in aprotic solvents at room temperature, but some bicyclic β -sultams do undergo ring opening to sulfonamides on heating in benzylamine (Equations (24) and (25)) (<83TL2131, 93AP(326)437>).



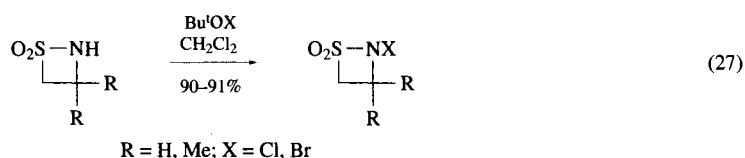
1.32.5.2.5 Reduction

The reduction of β -sultams to 1,2-aminothiols can be accomplished using sodium bis(2-methoxyethoxy)aluminum hydride (Equation (26)) (<87AP(320)571>).



1.32.5.2.6 Radical reactions

The nitrogen of ethanesultam can be halogenated in high yield by treatment with free radical halogenating agents such as *t*-butyl hypochlorite or hypobromite (Equation (27)) (<83JOC537>).

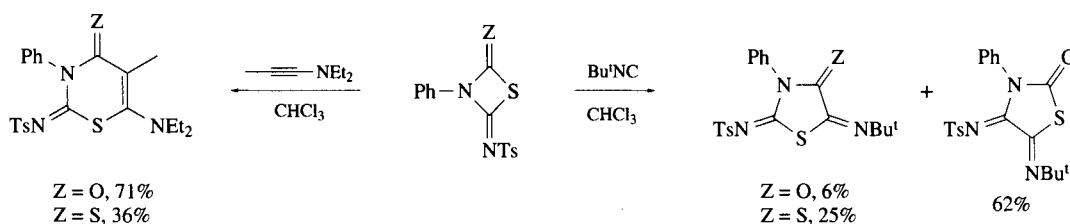


1.32.5.3 1,3-Thiazetidines

Reactivity of 1,3-thiazetidines involves nucleophilic addition at carbonyl, thiocarbonyl, and imino functions at C-2 and C-4, often with concomitant ring opening and reclosure to a larger heterocycle.

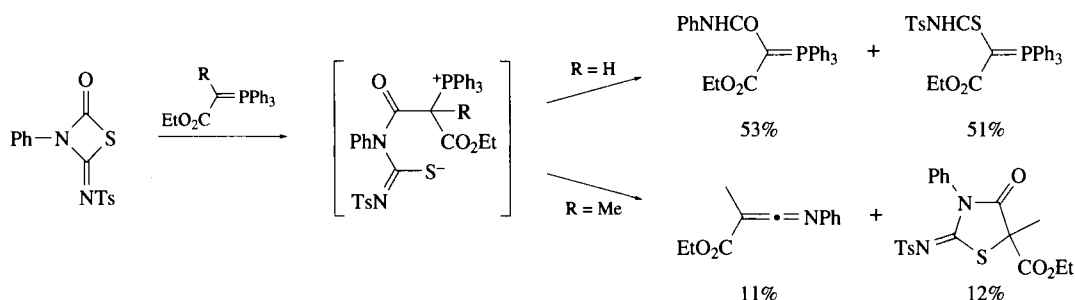
1.32.5.3.1 Reactions at carbon with carbon nucleophiles

The reactivity of both 3-phenyl-4-tosylimino-1,3-thiazetidine-2-one and thione towards nucleophiles was studied by L'abbé *et al.* (82BSB243, 83BSB61). Addition of *t*-butyl isonitrile and *N,N*-diethylaminopropyne resulted in incorporation of one and two carbon fragments to give five- and six-membered ring heterocycles (Scheme 10). Although the thiazetidines possess two electrophilic centers at the C-2 carbonyl/thiocarbonyl and C-4 imine functions, reactions are regiospecific to C-2 except in the case of isocyanate addition to the thiazetidine-2-one which occurs primarily at C-4.



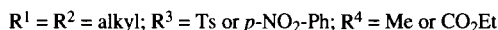
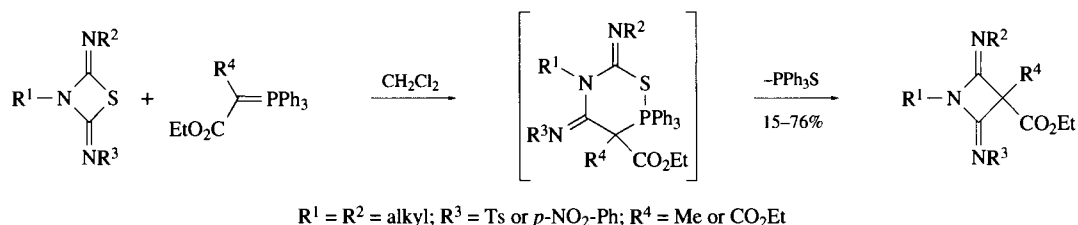
Scheme 10

The 1,3-thiazetidine-2-one also undergoes nucleophilic addition of phosphorane esters at C-2 to give a zwitterion intermediate (Scheme 11), which can undergo hydrogen migration accompanied by elimination of tosyl isothiocyanate. When this is inhibited, recyclization to a five-membered ring heterocycle with elimination of triphenylphosphine, or elimination of both tosyl isothiocyanate and triphenylphosphine oxide, takes place (82BSB243).



Scheme 11

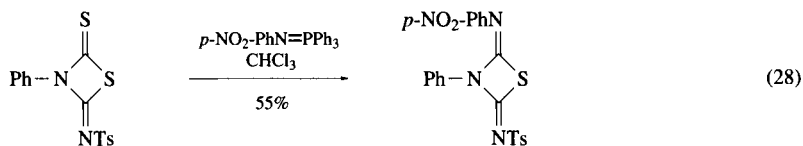
Bis(imino)1,3-thiazetidines undergo reaction at the most electrophilic imino group with ester phosphoranes to yield 2,4-bis(imino)azetidines (82TL2909). A possible mechanism involves formation of the six-membered phosphorus heterocycle (Scheme 12), which ring contracts with extrusion of triphenylphosphine sulfide. This ring transformation is not successful when R^4 is hydrogen, since the resulting heterocycles contain acidic hydrogens which can be abstracted under the basic reaction conditions leading to ring fragmentation and producing open-chain phosphoranes.



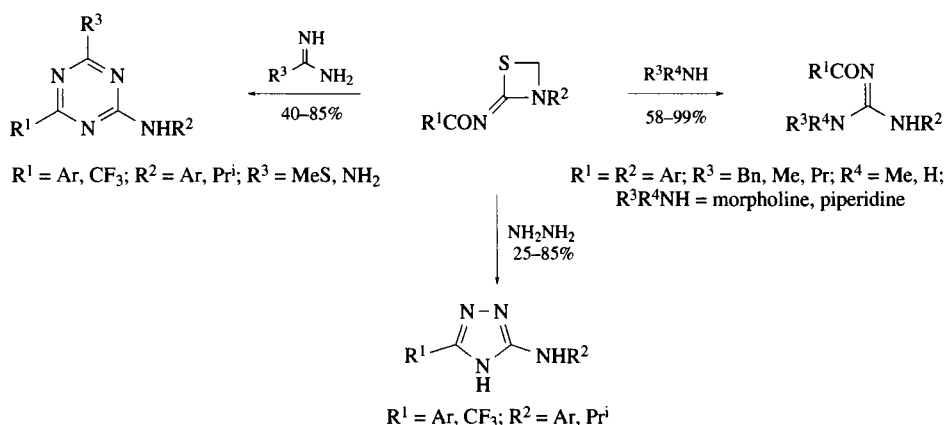
Scheme 12

1.32.5.3.2 Reactions at carbon with nitrogen nucleophiles

3-Phenyl-4-tosylimino-1,3-thiazetidine-2-thione was found to undergo a nucleophilic addition of aryliminophosphorane at the thiocarbonyl group, followed by elimination of triphenylphosphine sulfide, to give the bis(imino)thiazetidine (Equation (28)) (83BSB61).



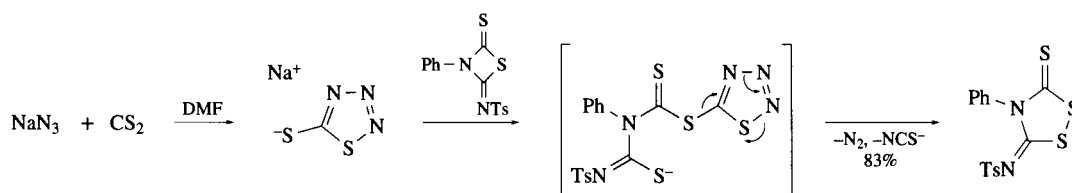
The reactions of 2-benzoylimino-1,3-thiazetidines with a variety of nitrogen nucleophiles involving ring-opening at the C-2 imino group were studied by Okajima *et al.* (Scheme 13) <91JHC177>. The addition of amines leads to *N*-acylguanidines, whilst ring closure at the acyl carbonyl occurs after either hydrazine addition to give 1,2,4-triazoles, or guanidine/isothiourea to give 1,3,5-triazines.



Scheme 13

1.32.5.3.3 Reactions at carbon with sulfur nucleophiles

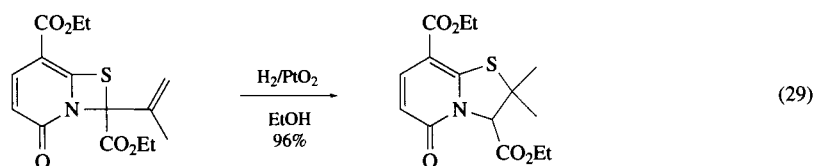
Ring enlargement of the thiazetidine ring by introduction of a sulfur atom was achieved by reaction with sodium azide/carbon disulfide <83BSB61>. This two-component system is known to form the 1,2,3,4-thiatriazolinethione salt (Scheme 14), which can add to the thiocarbonyl of the thiazetidine, and ring closure proceeds with elimination of nitrogen and thiocyanate ion.



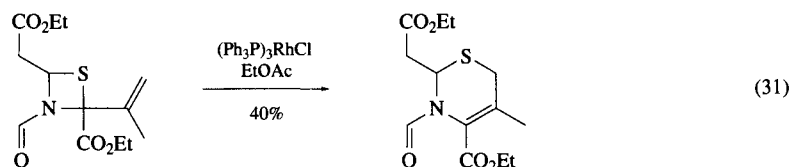
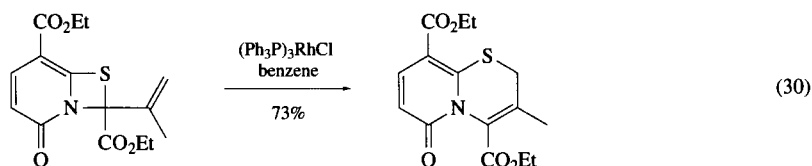
Scheme 14

1.32.5.3.4 Reductive/catalytic rearrangements

2-Isopropenyl-1,3-thiazetidines undergo a novel reductive rearrangement on hydrogenation with Adams' catalyst to give a thiazolidine ring (Equation (29)). Isotopic incorporation indicated about a 2 : 1 preference for *anti*-addition of hydrogen, although specificity was lost on switching to 10% palladium on charcoal as catalyst <84TL4157, 92T10149>.



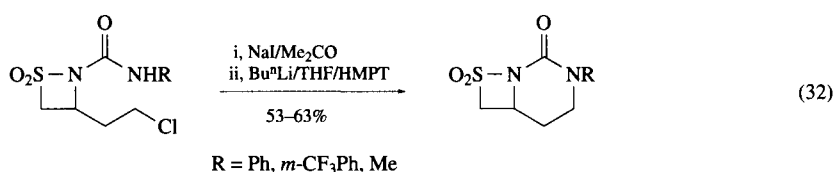
Use of the homogeneous catalyst tris(triphenylphosphine) rhodium(I) chloride resulted in an entirely different rearrangement of the 2-vinyl-1,3-thiazetidine to yield thiazines (Equations (30) and (31)). An explanation of this difference in reactivity may lie in the tendency for the “softer” Rh^I to complex with sulfur pulling electrons away from the alkene and generating the six-membered ring. By contrast, the platinum catalyst would be expected to initially undergo complexation to the alkene, which would then allow for a 1,2-shift of sulfur generating the thiazolidine.



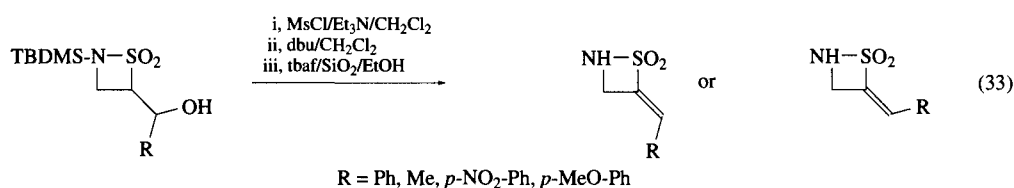
1.32.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

1.32.6.1 1,2-Thiazetidines

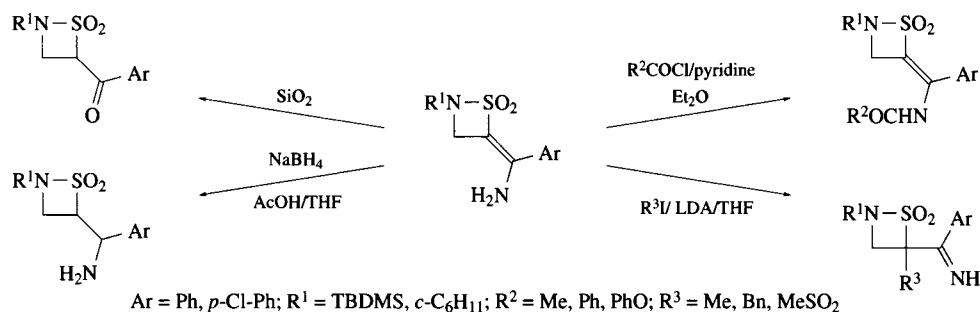
N-Amido- β -sultams possessing a β -chloroethyl moiety at the 3-position can be elaborated to the bicyclic sultam by conversion to the iodide and treatment with *n*-butyllithium (Equation (32)). The bicyclic system can also be obtained in a one-pot reaction from β -iodoethyl- β -sultam by isocyanate addition <93AP(326)437>.



4-Hydroxyalkyl- β -sultams, obtained via aldol condensations, can be converted to 4-alkylidene- β -sultams by successive mesylation, elimination, and desilylation, as detailed in (Equation (33)). The elimination is stereospecific, requiring an anti-periplanar configuration, and either the *cis*- or *trans*-isomer is obtained depending on which diastereoisomer is employed <92LA687>.



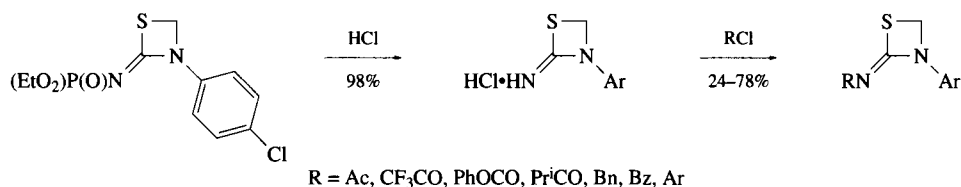
4-Enamino- β -sultams were reported to undergo a variety of reactions including hydrolysis, reduction, and acylation at the enamine nitrogen and alkylation at C-4 (Scheme 15) <93H(35)193>.



Scheme 15

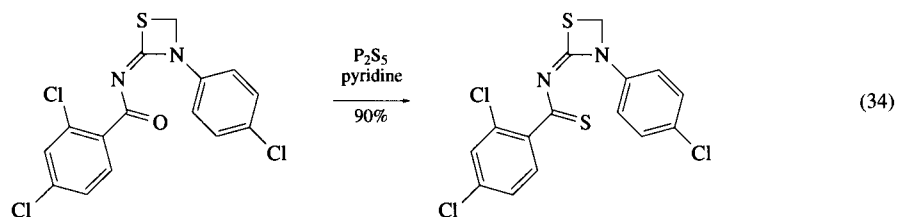
1.32.6.2 1,3-Thiazetidines

2-Imino-1,3-thiazetidines, obtained by hydrolysis of the 2-ethoxyphosphinylimino-1,3-thiazetidine derivative, can be acylated or alkylated by acid chlorides, anhydrides, and either benzyl or benzoyl chloride in the presence of base (Scheme 16) (91JHC177).



Scheme 16

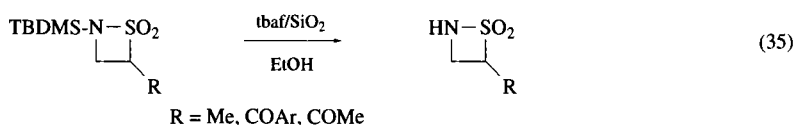
Thionation of a 2-benzoylimino-1,3-thiazetidine was demonstrated to occur with phosphorus pentasulfide in high yield to give the 2-arylthioacylimino-1,3-thiazetidine (Equation (34)) (91JHC177).



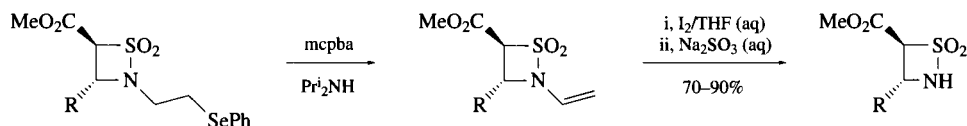
1.32.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO THE RING NITROGEN

1.32.7.1 1,2-Thiazetidines

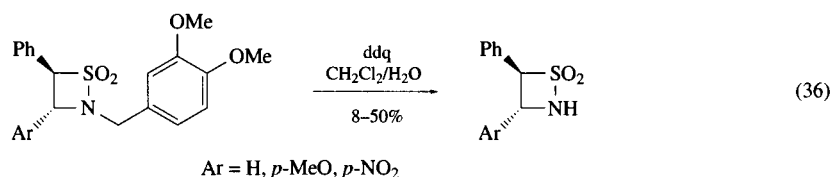
N-Silylated β -sultams are readily deprotected using standard conditions such as tbaF on silica gel (Equation (35)) (91AP(324)15, 91AP(324)773, 91LA171).



β -Sultam synthesis via sulfene/imine cycloadditions can employ phenylselenylethyl <89TL2869> and 3,4-dimethoxybenzyl <91TL751> nitrogen-protecting groups, which can be subsequently cleaved to expose the sultam nitrogen by the oxidative conditions outlined in Scheme 17 and Equation (36).



Scheme 17

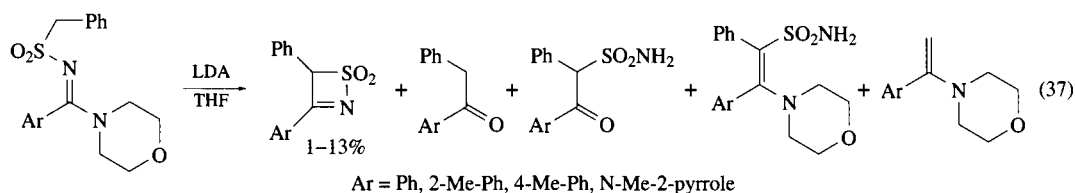


1.32.8 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

1.32.8.1 Thiazetes

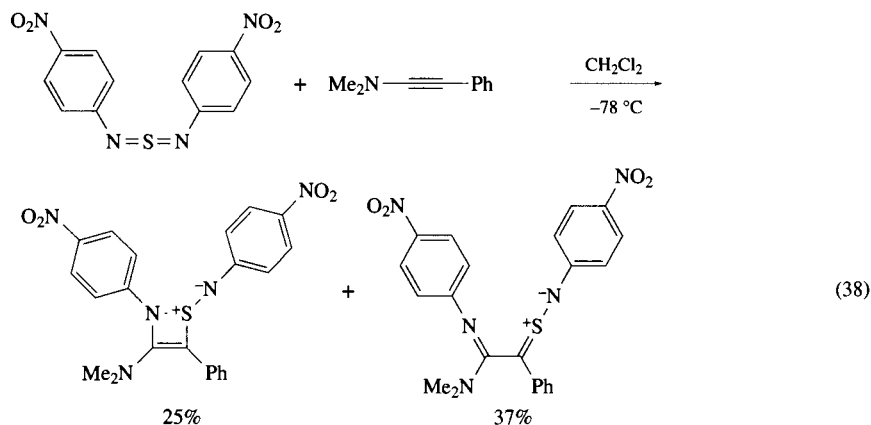
1.32.8.1.1 By cyclization with formation of the C—C Bond

4*H*-1,2-Thiazete-1,1-dioxides are obtained from *N*-benzylsulfonylamidines by generation of the carbanion adjacent to the sulfonyl group and intramolecular cyclization at the amidine carbon <91T1937>. The thiazetes are isolated by chromatography, albeit in low yields, from a variety of other products such as enamines and β -aminosulfonyl-amines (Equation (37)).



1.32.8.1.2 Ring formation by [2 + 2] cycloaddition reactions

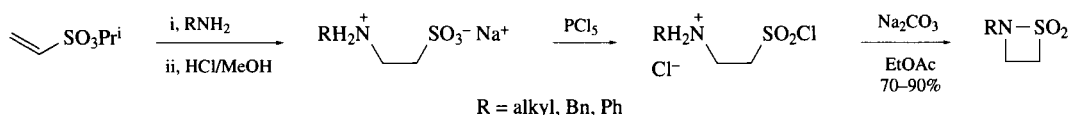
The low temperature cycloaddition of bis(*p*-nitrophenyl)sulfur diimide with an ynamine was reported to result in formation of a 1,2-thiazete salt, along with its isomeric ring-opened amidine (Equation (38)) <87CB751>. The reaction is not general; at higher temperatures or with other substituents the thiazete is not isolated, but reacts further to give various acyclic amidines.



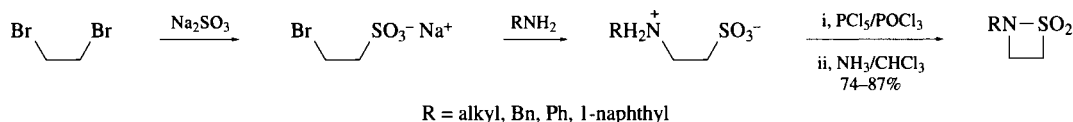
1.32.8.2 1,2-Thiazetidines

1.32.8.2.1 By cyclization with formation of the N—S Bond

Taurines (2-aminoethanesulfonic acids) can be cyclized to β -sultams by chlorination to the corresponding β -aminosulfonyl chloride hydrochloride followed by treatment with base. The taurine can be obtained either by sulfoethylation of primary amines <85BSF463>, or by sodium sulfite treatment of 1,2-dibromoethane and subsequent treatment with a primary amine (Schemes 18 and 19) <83AP(316)281>.

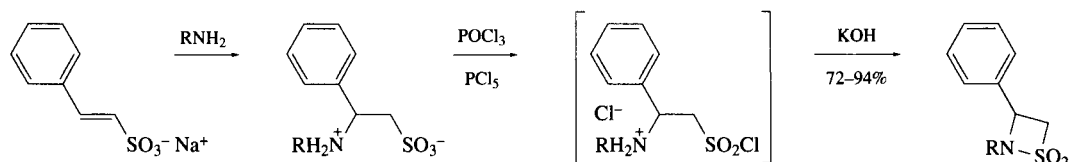


Scheme 18



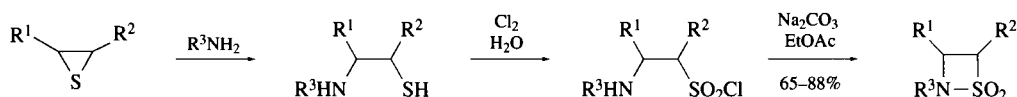
Scheme 19

2-Amino-2-phenylethanesulfonic acids are obtained by addition of primary amines to sodium 2-phenylethanesulfonate and converted to 3-phenyl- β -sultams without isolation of the intermediate sulfonyl chlorides (Scheme 20) <85LA802>.



Scheme 20

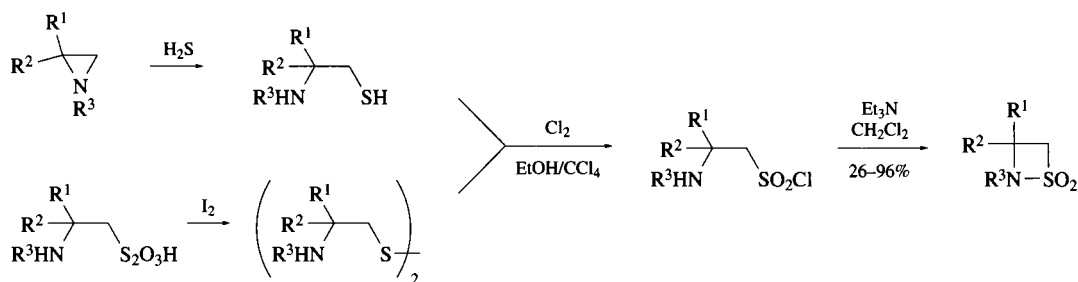
β -Aminosulfonyl chloride hydrochlorides can also be prepared by chlorination of aminothiols or aminodisulfides. The precursor aminothiols are obtained either by the addition of primary amines to thiiranes <85BSF463> or hydrogen sulfide to aziridines <83TL2131>; whereas aminodisulfides result from reaction of aminothiosulfates with iodine <83TL2131>. The various routes are summarized in Schemes 21 and 22.



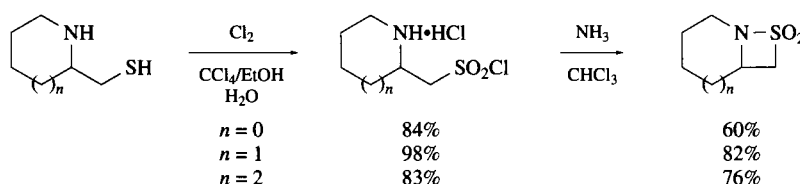
Scheme 21

Bicyclic β -sultams can also be accessed by a similar methodology involving oxidative chlorination of a 2-methylthiol nitrogen heterocycle to the sulfonyl chloride, followed by base-catalyzed cyclization with ammonia (Scheme 23) <82AG(E)548, 82TL5389, 90AP(323)93>.

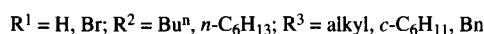
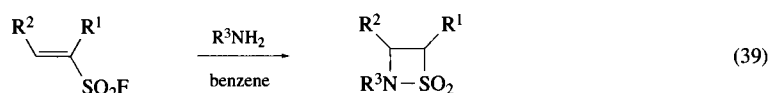
Treatment of substituted alkene-sulfonyl fluorides with two equivalents of a primary amine gave the corresponding β -sultam without isolation of the intermediate 1-fluorosulfonyl-2-aminoethane (Equation (39)) <85BSF463>. The analogous sulfonyl chlorides do not react under these conditions <91MI 132-01>.



Scheme 22

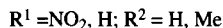
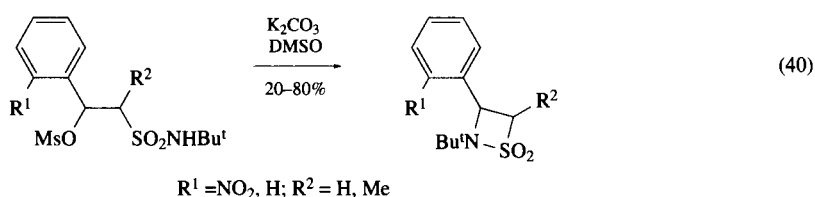


Scheme 23

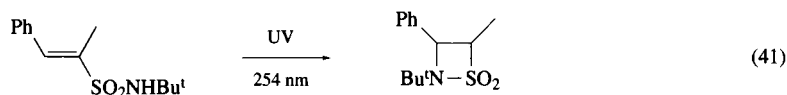


1.32.8.2.2 By cyclization with formation of the C—N Bond

Although a less common approach, β -sultams can also be prepared via C—N bond formation. One method involves a 2-hydroxyethanesulfonamide, which, on conversion to its mesylate, subsequently undergoes intramolecular displacement by the amide nitrogen on treatment with base (Equation (40)) <84JOC1700, 88MI 132-01>.



α,β -Unsaturated sulfonamides can undergo photocyclization to β -sultams when exposed to ultraviolet light; however the reaction does not appear to be general and only one successful example has been reported (Equation (41)) <88MI 132-01>.



1.32.8.2.3 Ring formation by [2 + 2] cycloaddition reactions

Two [2 + 2] cycloaddition approaches to 1,2-thiazetidines have been employed involving either formation of the S—N and C—C bonds or formation of S—C and N—C bonds.

Highly reactive sulfenes ($\text{RCH}=\text{SO}_2$), generated *in situ* from the corresponding sulfonyl chloride by treatment with an organic base, undergo cycloaddition with imines (Schiff bases) to give β -sultams (Scheme 24). In general, the sulfene requires stabilization by either a benzoyl <70BCJ3543>, phenyl <75BCJ480>, or ester group <89TL2869>; whereas the cycloaddition with an imine works better if the imine is derived from a benzaldehyde, presumably to avoid isomerization to an enamine.



$\text{Ph-CH}_2\text{-SO}_2\text{Cl} + \text{R}^2\text{-C}_6\text{H}_4\text{-CH=NR}^1 \xrightarrow[\text{THF}]{\text{Et}_3\text{N}}$

$\text{R}^1 = \text{Bn}, \text{R}^2 = \text{H};$
 $\text{R}^1 = \text{Me}, \text{R}^2 = \text{H, Cl, MeO, NO}_2;$
 $\text{R}^1 = \text{CH}_2\text{CO}_2\text{Et}, \text{R}^2 = \text{Me, MeO}$

(42)

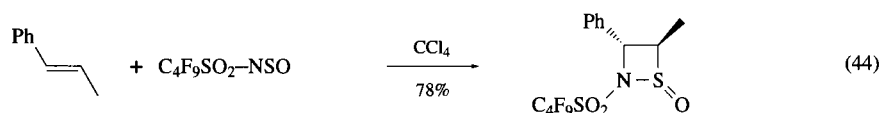
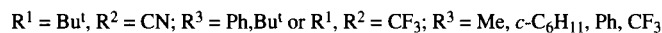
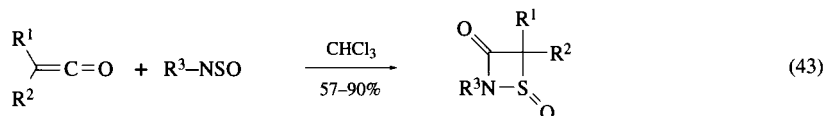
$$\text{MeO}_2\text{C}-\text{CH}_2-\text{SO}_2\text{Cl} + \text{R}^1-\text{CH}=\text{NR}^2 \xrightarrow[\text{THF}]{\text{pyridine}}$$

$\text{R}^1 = \text{Ph}, 2\text{-furyl}, \text{cinnamyl}, \text{alkyl}, \text{TBDMS-OCH}_2\text{CH}_2; \text{R}^2 = \text{Bn}, \text{MeO-Ph}, \text{PhSeCH}_2\text{CH}_2$

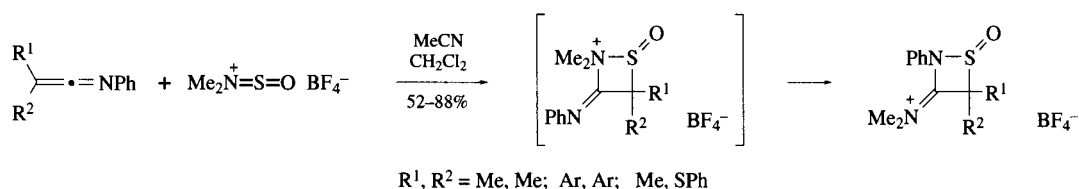
Scheme 25

A variety of [2 + 2] cyclizations have been reported that lead to 1,2-thiazetidines via S—C and N—C bond formation (Equations (43) and (44)). *N*-Sulfinyl amines (R—NSO) undergo cyclization

with ketenes to give 1,2-thiazetidine-3-one-1-oxides <83H(20)187, 86CB1127>; whereas activated *N*-sulfinyl amines, such as the fluorinated sulfonamide derivative, can react with regular alkenes to give 1,2-thiazetidine-1-oxides <82LA545>.

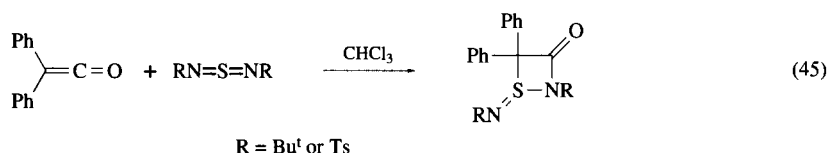


N-Sulfinyldimethylamine tetrafluoroborate and ketenimines undergo an initial [2 + 2] cyclization, followed by Dimroth rearrangement to give the more stable 3-dimethylimino-thiazetidine-1-oxide regioisomer (Scheme 26) <87LA527>.

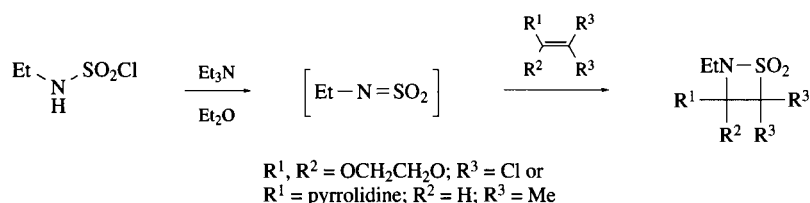


Scheme 26

1-Imino-1,2-thiazetidine-3-ones can be isolated from low temperature cycloaddition of either ditosyl or dibutylsulfur diimides with diphenylketene (Equation (45)) <70TL1427, 72JOC3810, 83H(20)187>.



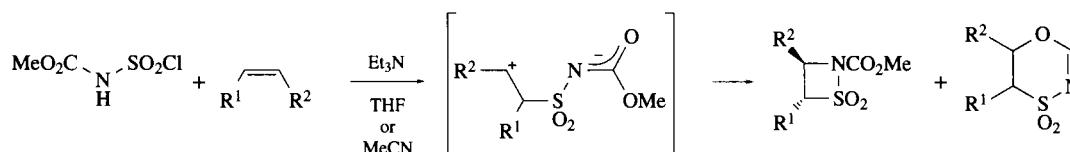
N-Sulfonylamines ($\text{R}-\text{N}=\text{SO}_2$), like the isoelectronic sulfenes, are unstable species and are prepared *in situ* by reaction of a sulfamoyl chloride with an organic base. They are known to interact with nucleophilic alkenes, such as enamines and dioxolanes, to give β -sultams (Scheme 27) <72JA6135>.



Scheme 27

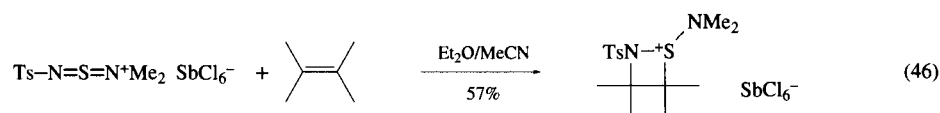
N-Carbomethoxysulfonylamine reacts with substituted alkenes to give *trans*- β -sultams and a second cycloadduct, 1,4,5-oxathiazines, by [2 + 4] cycloaddition <72JA4386>. The ratio of products depends on the solvent polarity, suggesting that the reaction mechanism, as postulated in Scheme 28, like that for carbomethoxysulfene, is nonconcerted and involves a zwitterionic intermediate.

Further support for this mechanism was shown by the fact that enamines possessing either a methylene at the α -carbon or a hydrogen at the β -carbon do not give β -sultams, but can rearrange at the zwitterion stage to give acyclic products <79BCJ1102>.



Scheme 28

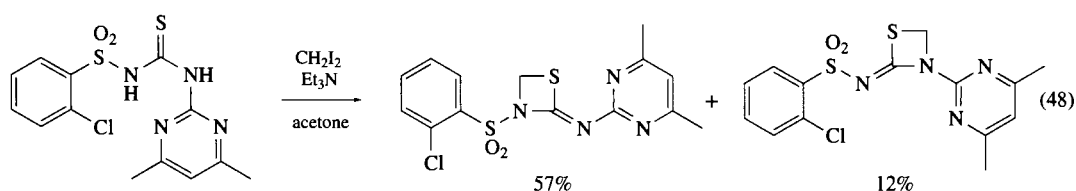
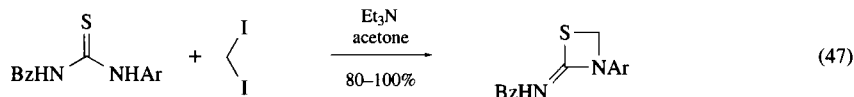
Unsymmetrical sulfur diimide cations undergo a regioselective [2 + 2] cycloaddition with alkenes to give 1,2-thiazetidine antimony hexachloride salts (Equation (46)) <86LA32>.



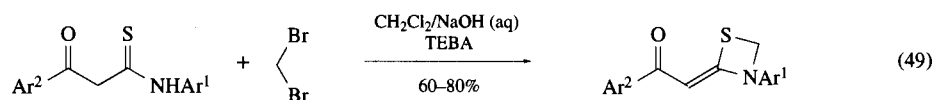
1.32.8.3 1,3-Thiazetidines

1.32.8.3.1 Ring formation by [3 + 1] cyclization reactions

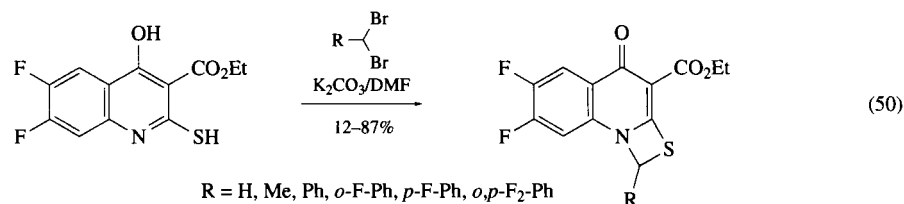
The 1,3-thiazetidine ring can be obtained by cycloaddition of a thioamide unit with a carbon bearing two displaceable geminal halogens. An example is the reaction of a *N*-benzoyl-*N'*-arylthiourea with diiodomethane in the presence of triethylamine to give the corresponding 2-benzoylimino-1,3-thiazetidine in high yield <91JHC177>. The addition to unsymmetrical thioureas can sometimes lead to mixtures of regioisomers (Equations (47) and (48)) <90JAP(K)2160785>.



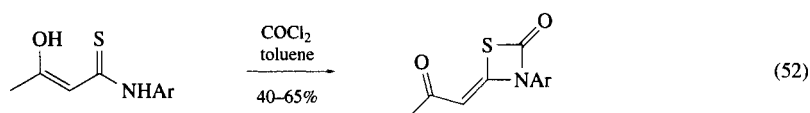
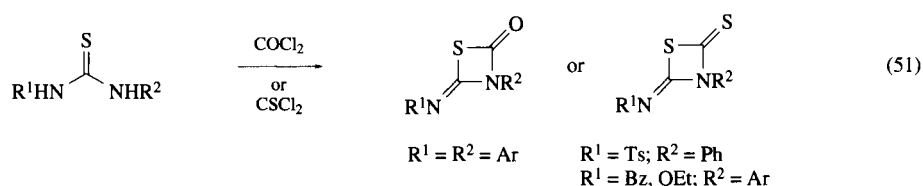
In a similar fashion (Equation (49)), benzoylthioacetanilides react with dibromomethane in a dichloromethane/aqueous sodium hydroxide two-phase medium in the presence of a phase-transfer catalyst to give 1,3-thiazetidines <87CS473>.



Cyclization of 2-thiolquinolines with a variety of substituted geminal dibromoalkanes allows for fusion of a 1,3-thiazetidine moiety onto the quinoline at the N-1 and C-2 positions (Equation (50)) <92JMC4727>.

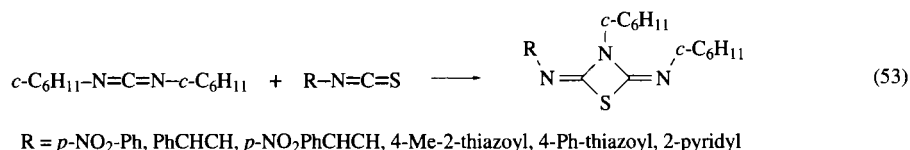


Condensation of thioureas with either phosgene or thiophosgene allows for formation of 4-imino-1,3-thiazetidine-2-ones <64CB1232, 66AG(E)704> and 2-thiones (Equations (51) and (52)) <83BSB61, 93JPR381>. A similar reaction occurs with acetylthioacetanilides activated by a halogen at the *para* position of the anilide portion <88JPR795>.

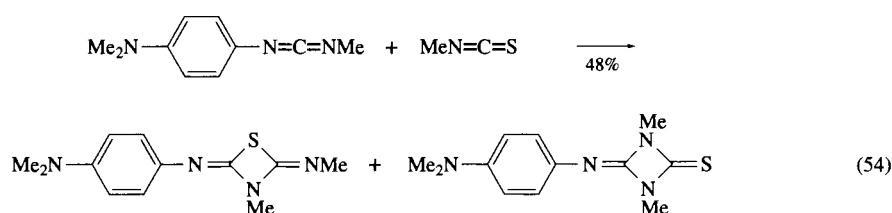


1.32.8.3.2 Ring formation by [2 + 2] cycloaddition reactions

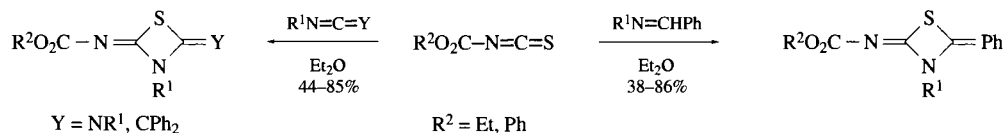
2,4-Bis(imino)-1,3-thiazetidines are obtained by a [2 + 2] cycloaddition of carbodiimides across the C=S bond of isothiocyanates. Examples using DCC are shown in Equation (53) <81BSB1185, 81CCC2557, 82CCC1229, 83CCC1745>. The kinetic data, along with the failure to trap any open-chain intermediates, favors a concerted mechanism in which the carbodiimide is the suprafacial and the isothiocyanate the antarafacial component. The x-ray crystal structure of the *para*-nitrophenyl isothiocyanate adduct showed that the *cis,cis* configuration is adopted in the solid state <81BSB1185>.



The cycloaddition is not always regiospecific, as demonstrated by addition of the *N*-alkyl-*N*-arylcabodiimides to methyl isothiocyanate which gave the 1,3-thiazetidine, along with an isomeric 1,3-diazetidine adduct derived from addition to the C=N bond of the isothiocyanate, in a 42:58 ratio (Equation (54)) <87CB849>.

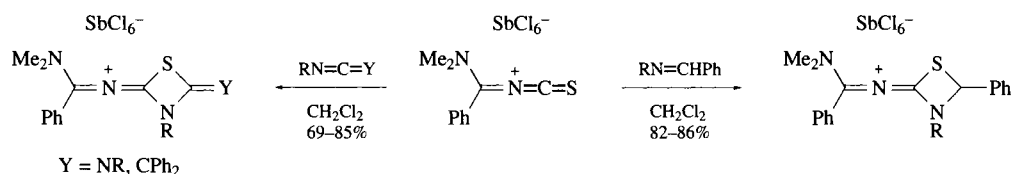


The reactive ethoxy and phenoxycarbonyl isothiocyanates undergo cycloaddition with the C=N bonds of benzaldimines, diphenylketenimines, as well as carbodiimides, to give various 1,3-thiazetidines (Scheme 29) <83CB1297>.



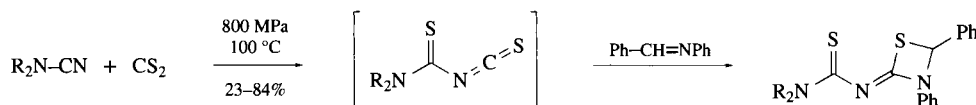
Scheme 29

1-Thia-3-azoniabutatriene salts undergo an analogous set of cycloadditions to those of isothiocyanates with benzaldimines, diphenylketenimines, and carbodiimides to give 1,3-thiazetidines (Scheme 30) <90CB499>.



Scheme 30

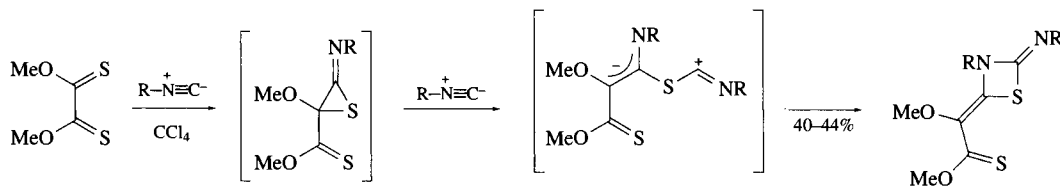
The isothiocyanate-imine cycloaddition can be carried out under high pressure starting from carbon disulfide, dialkylcyanamide, and benzyldeneaniline to give 2-imino-1,3-thiazetidines in one pot <90CL1423>. The rate-determining step for the reaction is the formation of the intermediate dialkylthiocarbamoyl isothiocyanate as shown in Scheme 31 and high pressure is crucial for good yields. Other aldimines tested were not successful.



Scheme 31

1.32.8.3.3 Miscellaneous routes

1,3-Thiazetidines are the main products from reaction of *O,O*-dimethyl dithiooxalate with two equivalents of an isocyanide <82CB3107>. A postulated mechanism (Scheme 32) involves initial addition of isocyanide to give an iminothiirane, followed by ring-opening with the second isocyanide and reclosure of the resulting zwitterion to a thiazetidine. Two other products identified as 2-iminoazetididine-4-thiones and 3,3-biazetididine-2,2-dithiones were also produced.



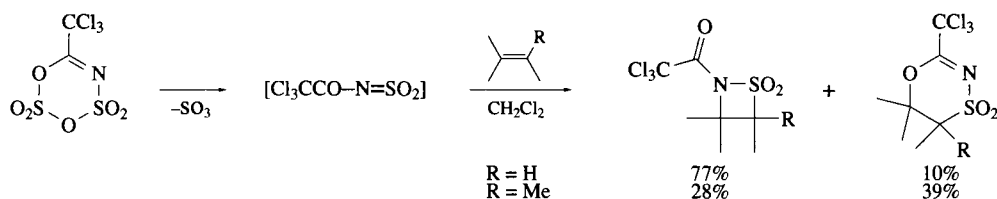
Scheme 32

1.32.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

1.32.9.1 1,2-Thiazetidines

The heterocycle 1,3,2,4,5-dioxadithiazine tetroxide undergoes ring transformation on interaction with alkenes to give mixtures of *N*-acyl- β -sultams and 1,4,5-oxathiazine dioxides <85TL5689>.

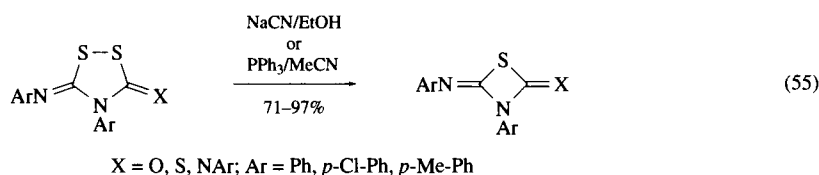
88ZOR1978). The reaction is thought to proceed (Scheme 33), by initial elimination of sulfur trioxide to give the reactive *N*-sulfonylamine species, which are known to undergo both [2 + 2] and [2 + 4] cycloadditions with alkenes (see Section 1.32.8.2.3).



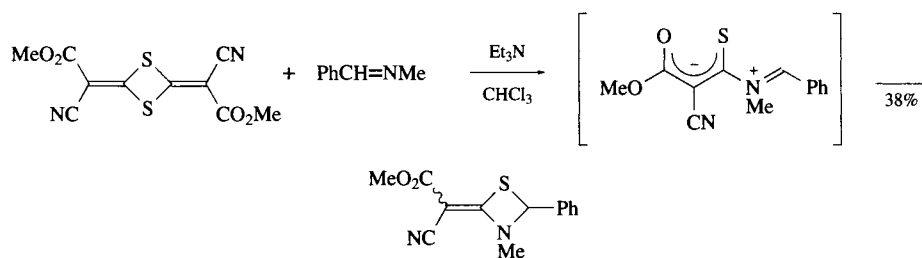
Scheme 33

1.32.9.2 1,3-Thiazetidines

4-Imino-1,3-thiazetidine-2-one, 2-thione and 2-imines can be obtained by ring contraction of the corresponding five-membered 1,2,4-dithiazoline ring, which occurs on treatment with either sodium cyanide in ethanol or triphenylphosphine in acetonitrile (Equation (55)) (87ZC142).

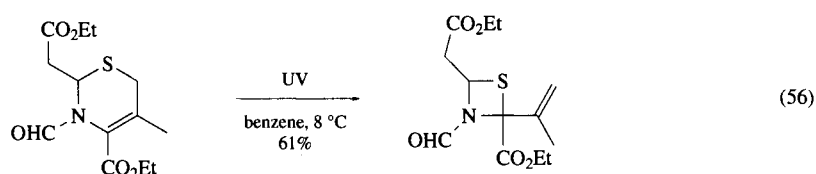


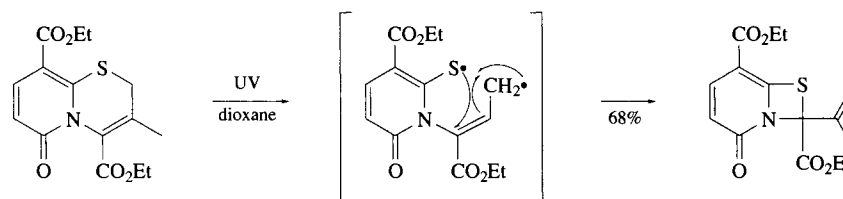
The desaurin 2,4-bis(cyanomethoxycarbonylmethylene)-1,3-dithietane is reported to act as a thioketene equivalent and undergoes cycloaddition to *N*-methyl benzaldimine to give a 1,3-thiazetidine, possibly via the stabilized zwitterionic intermediate shown (Scheme 34) (84BSB405).



Scheme 34

Photochemical rearrangement of *N*-acylthiazines leads to both fused and monocyclic 2-isopropenyl-1,3-thiazetidines (Scheme 35 and Equation (56)) (92JCS(P1)621). As shown for the pyrido[2,1-*b*]thiazine, a diradical resulting from fission of the allylic CH₂—S bond is a possible intermediate.





Scheme 35

1.32.10 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

1.32.10.1 1,2-Thiazetidines

β -Sultams are accessed principally by two routes; one of which involves intramolecular cyclization of β -aminosulfonyl chlorides (see Section 1.32.8.2.1) and the other [2 + 2] cyclizations of sulfenes with imines or *N*-sulfonylamines with alkenes (see Section 1.32.8.2.3). The cyclization of β -aminosulfonyl chlorides would appear to be the more general method, being applicable to the synthesis of β -sultams with a variety of substitution patterns, although several steps are required to prepare the precursors. The [2 + 2] cyclization is more direct but limited to 3,4-disubstituted β -sultams, since the reactive sulfenes require stabilization by electron-withdrawing groups, and the imine is often derived from a benzaldehyde, whereas the sulfonylamine cyclization works better with nucleophilic alkenes such as enamines and dioxolanes.

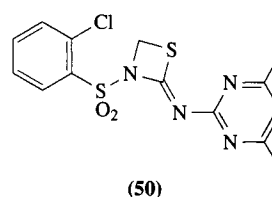
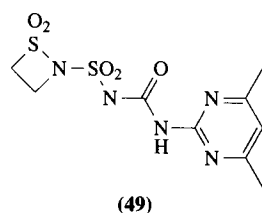
1.32.10.2 1,3-Thiazetidines

For the 1,3-thiazetidine ring the two common approaches involve [3 + 1] cyclization of a thioamide with a geminal dihaloalkane or phosgene (see Section 1.32.8.3.1), or [2 + 2] cyclization of carbodiimides with isothiocyanates (see Section 1.32.8.3.2). The cyclization of a thiourea with a dihaloalkane to give 2-imino-1,3-thiazetidines is high yielding, but requires at least one electron-withdrawing aromatic or benzoyl substituent to activate the thiocarbonyl group. The carbodiimide–isothiocyanate cyclization to give 2,4-bis(imino)-1,3-thiazetidines can suffer from a lack of regioselectivity and works best for isothiocyanates activated by electron-withdrawing aromatic, ethoxy and phenoxy carbonyl groups.

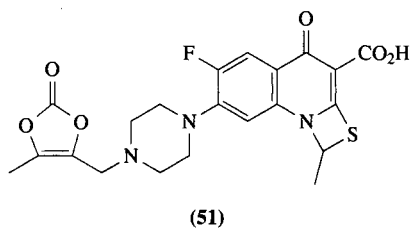
1.32.11 IMPORTANT COMPOUNDS AND APPLICATIONS

The increased interest in the synthesis and reactivity of the β -sultam ring system has been due to their potential use as bioisosteres of β -lactams. Since the sultam ring has a greater chemical reactivity than the lactam, the possibility of β -sultams acting as good β -lactam-like antibiotics in acylation of bacterial cell wall enzymes seems promising. Thus far the β -sultams studied have shown disappointingly weak β -lactamase inhibition activity <82AG(E)548, 84EJM569, 93AP(326)437>, although with the synthetic capability improving rapidly, this may change as more diverse analogues are tested.

Ethanesultam connected through a sulfonyl group to a dimethylpyrimidinyl-urea (**49**) is reported to be useful as a plant growth regulator and broad-spectrum herbicide <89GEP3736959>. Similarly, the 1,3-thiazetidine ring connected through nitrogen to a dimethylpyrimidine ring (**50**) was shown to have herbicidal activity <90JAP(K)2160785>.



A series of 1,3-thiazeto[3,2-*a*]quinoline-3-carboxylic acids were prepared and evaluated for antibacterial activity <89EUP315828, 92JMC4727>. The selected compound (**51**) was found to possess both broad and potent *in vitro* activity against gram-positive and gram negative bacteria, good oral efficacy against *E. coli* infections in mice ($ED_{50} = 0.35$ mg/kg) and low toxicity, and was subsequently submitted for clinical studies.



1.33

Four-membered Rings with Two Oxygen Atoms

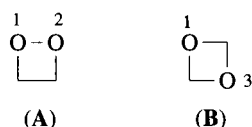
CHANTU R. SAHA-MÖLLER and WALDEMAR ADAM
University of Würzburg, Germany

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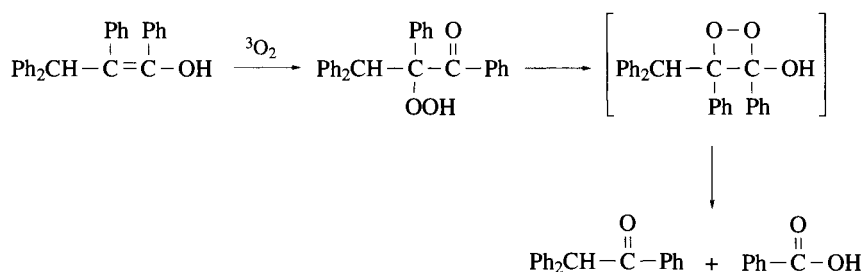
1.33.1 INTRODUCTION

1.33.1.1 Historical Perspective and Scope

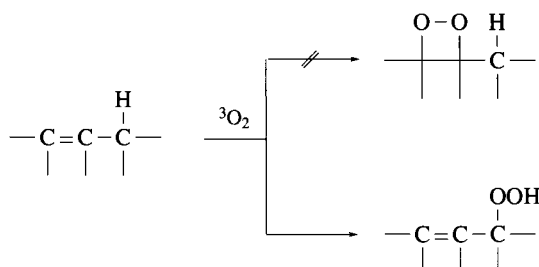
Four-membered rings with two oxygen atoms are known as dioxetanes. Two different isomers of dioxetane, namely 1,2-dioxetane (**A**) and 1,3-dioxetane (**B**), are conceivable. While the first stable 1,2-dioxetane was successfully synthesized in 1969 <69CJC709> and the first dioxetanone (α -peroxy lactone) in 1972 <72JA2894>, to our knowledge there is no convincing report on an authentic 1,3-dioxetane to date. Consequently, in this chapter, dioxetane stands for 1,2-dioxetane.



The intermediacy of dioxetane was first proposed <06JA177> about 90 years ago in the autoxidative cleavage of the stable enol of 1,2,3,3-tetraphenyl-1-propanone (Scheme 1). Around the 1930s, the dioxetanes were postulated as stable autoxidation products in the reaction of alkenes with molecular oxygen <28JA568, 30CB2362, 36AG565>; however, a thorough mechanistic investigation revealed <36LA(522)75, 39CB1799> that the true products of these autoxidations were allylic hydroperoxides (Scheme 2). Nevertheless, in the 1960s, plausible evidence for the intervention of dioxetanes as intermediates in numerous chemiluminescent reactions which involve the autoxidation of electron-rich alkenes was documented <64JA5686, 64TL3167, 65MI 133-01, 66CC522>. Dioxetanones (α -peroxy lactones) were also postulated <25CB1079> as labile reaction intermediates, for example in the autoxidation of ketenes (Scheme 3), long before the preparation of the first stable, authentic entity <72JA2894>.

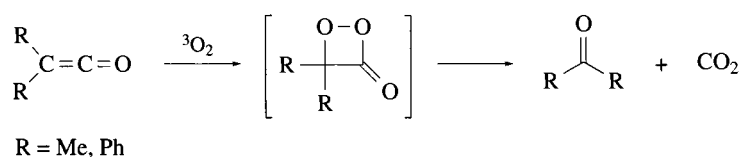


Scheme 1



Scheme 2

Because of the unique property of the energy-rich dioxetanes to generate electronically excited carbonyl products on thermolysis, they are novel tools for photochemical and photobiological transformations in the *dark* and have received much attention during the last two decades. In the



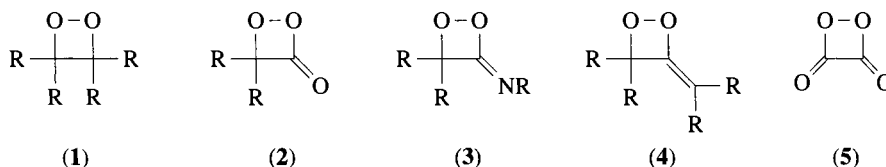
Scheme 3

1990s, a great deal of fundamental and industrial research has been invested to make use of the unique chemiluminescence property of dioxetane in bioanalytical and clinical chemistry (see Section 1.33.10), in particular for immunoassays <90ANC2258, B-92MI 133-01>.

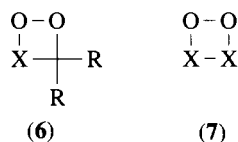
Numerous reviews have appeared on dioxetanes during the last decade <83AG(E)529, B-83MI 133-01, B-85MI 133-01, B-85MI 133-02, 88HOU(E13)401, B-88MI 133-01, 88MI 133-02, B-89MI 133-01, 90MI 133-01, B-92MI 133-02, 92MI 133-03, 92MI 133-04> and a monograph was also published <B-82MI 133-01>. Since in the first edition of *Comprehensive Heterocyclic Chemistry* <84CHEC-I(7)449> dioxetanes were treated only marginally, in this chapter an overview of the important aspects of dioxetanes is given and developments since the early 1980s are highlighted.

1.33.1.2 Structural Types and Nomenclature

Five different types of four-membered ring structures which contain two oxygen atoms are known, (1)–(5). Of these, the 1,2-dioxetanes (1), the 1,2-dioxetanones (2), also known as α -peroxy lactones, and the dioxetanamines (3) are stable entities. The methylene-1,2-dioxetanes (4) do not thermally persist and their formation as reaction intermediates in the photooxygenation of cumulenes at 10 K in an Ar matrix was postulated <87AG(E)475>. It was reported <89BCJ1367> that the observed chemiluminescence in the photooxygenation of allenes originates from the intermediate methylene dioxetanes. On the other hand, the dioxetanedione (5) has been postulated as an intermediate in the oxidation of oxalates with hydrogen peroxide <69ACR80, 92MI 133-04>; however, no spectral nor chemical evidence exists to support this highly strained structure <73JA7050, 90MI 133-02>.



Although four-membered ring peroxides with one or two other heteroatoms (N, P, S, Si, Ge), which are termed heterodioxetanes, (6), (7), were postulated as intermediates in the reaction of singlet oxygen with alkenes containing heteroatoms (see Section 1.33.9) and some thermally persistent heterodioxetanes were isolated since the early 1980s (see Section 1.33.9), this type of dioxetanes was not explicitly covered in previous reviews. Therefore, in this chapter such heterodioxetanes are included.

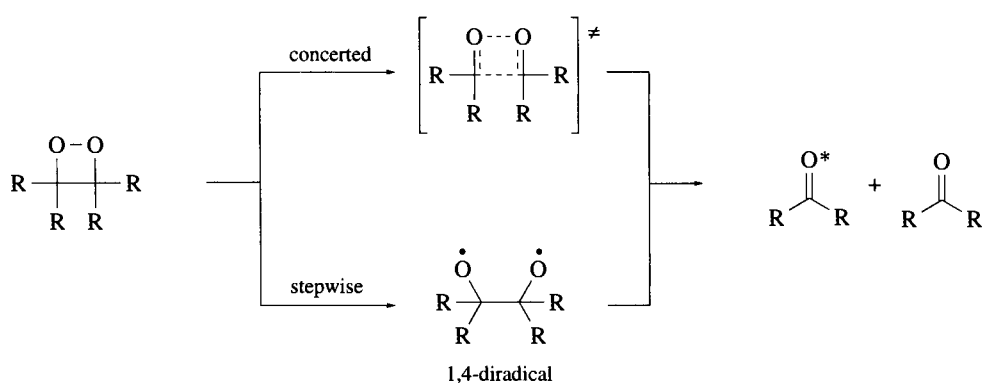


1.33.2 THEORETICAL CONSIDERATIONS

The thermal fragmentation of dioxetanes into two carbonyl products is unique in two ways: (a) one of the carbonyl fragments is electronically excited, i.e. an excited state product is generated thermally which may manifest itself by light emission (chemiluminescence); and (b) the excited state product is formed preferentially in its triplet state, particularly ${}^3n,\pi^*$ excited states. These unusual facts have provided much food for thought for the experimentalists and especially theoreticians.

The earliest theoretical analysis on the basis of orbital symmetry arguments came from McCapra

<68CC155> in terms of a forbidden concerted [2 + 2] cycloreversion (Scheme 4); however, it was Kearns <69JA6554> who through an incisive theoretical analysis predicted that preferentially n,π^* triplet states should be produced, as was subsequently confirmed experimentally <74ACR97>. Yet the most complete analysis, which incorporated the phenomenon of spin-orbit coupling in this thermal intersystem crossing process, was provided by Turro and Devaquet <75JA3859>. Their results are reproduced in Figure 1 in terms of the qualitative potential energy surface crossing for this nonadiabatic transformation. Initial O—O bond loosening on the ground state singlet surface S_0 brings the thermally activated dioxetane molecule near the first crossing point A of the S_0 and T_1 energy surfaces; effective spin-orbit coupling serves for the avoided crossing, and the fragmenting species continues on the triplet surface T_1 by subsequent C—C bond scission. At the second crossing point B, some of the activated complex proceeds to the n,π -excited triplet carbonyl product; most of it crosses back to the ground state singlet surface S_0 and winds up as ground state carbonyl fragments. The fact that the singlet-excited state surface S_1 intersects the ground state surface S_0 at higher points than the triplet surface T_1 , provides a convincing rationale why preferentially triplet- rather than singlet-excited states are produced.



Scheme 4

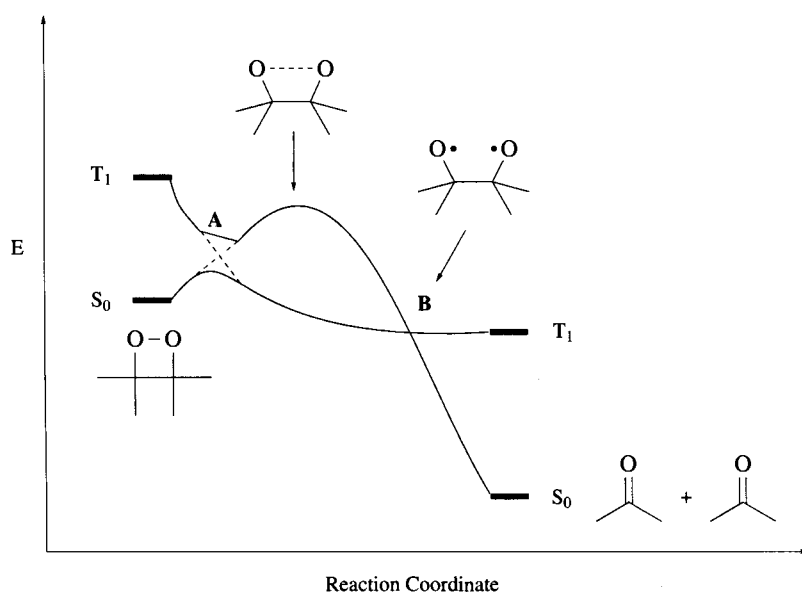


Figure 1 Turro-Devaquet diagram for the merged mechanism of dioxetane fragmentation <75JA3859>.

On the basis of thermochemical considerations, Richardson <72JA8665> proposed a stepwise diradical mechanism (Scheme 4), which adequately rationalizes the kinetic aspects of the dioxetane thermolysis. A molecular mechanics treatment <89JOC4677> confirmed the *merged mechanism* <85JA410>, in which the complex decomposition coordinate displays stepwise (kinetic features) as

well as concerted (excitation properties) character akin to the original Turro–Devaquet rationale (Figure 1).

Most semiempirical theoretical treatments <73CPL(22)461, 73CPL(22)499, 74CC683, 74CJC3837, 74JA7578, 74JA7579, 75TCA113, 76CPL(42)347, 77IJ283, 78CB1413, 78IJQ289, 81JA1292> are in general accord with this mechanistic picture, in that the rupture of the O—O bond is initiated through puckering of the dioxetane skeleton on thermal activation and subsequently cleavage of the C—C bond ensues. Whether a *bona fide* 1,4-diradical is produced is, however, still under intensive debate <94JA5674>. Suffice it to say that such a diradical has to date not been *directly* observed and is merely inferred through indirect evidence.

At the nonempirical level, the first *ab initio* GVB calculations were made by Goddard <77JA4520>, who concluded that the diradical constitutes an authentic intermediate on the thermal decomposition coordinate. The activation energy (22 kcal mol⁻¹ for the parent dioxetane) derives from O—O bond scission. Most surprising is, therefore, the most recent and elaborate *ab initio* MC-SCF/MP2 study in 1991 by Robb <91JA1566>. The triplet 1,4-diradical is, indeed, confirmed as a *bona fide* intermediate, but its formation by O—O bond rupture requires only about 2 kcal mol⁻¹. Intersystem crossing through spin-orbit coupling for this nonadiabatic transformation occurs prior to reaching the diradical species. The activation energy of about 22 kcal mol⁻¹ for the parent dioxetane derives from subsequent C—C rupture in the triplet diradical to produce the triplet-excited carbonyl fragment. The expected temperature dependence on the yield of triplet-excited carbonyl product is, however, not experimentally confirmed <B-82MI 133-02>. If this theoretical conclusion is valid, it is surprising that experimentalists have so far failed to provide direct spectral or indirect chemical evidence for the intermediary triplet diradical, which rests in an energy well of about 20 kcal mol⁻¹. Be this as it may, the last word on the complex thermal decomposition coordinate of dioxetanes has yet to be spoken, from both the theoretical and experimental perspectives.

1.33.3 EXPERIMENTAL STRUCTURAL METHODS

1.33.3.1 Spectroscopic Methods

1.33.3.1.1 IR spectroscopy

Infrared (IR) spectroscopy is not characteristically definitive for the identification and structural proof of dioxetanes <B-82MI 133-03>. The weak O—O stretching frequencies at 845–895 cm⁻¹ <75JA7110> of peroxides is also exhibited by dioxetanes, but is not sufficient for reliable structural proof. On the other hand, the dioxetanones (α -peroxy lactones) display very characteristic signals for the carbonyl stretching frequencies at 1850–1875 cm⁻¹ <B-85MI 133-02>.

1.33.3.1.2 UV-vis spectroscopy

Dioxetanes are generally yellow solids or oils, except spiroadamantyl dioxetanes, which are colorless solids <90JOC6225>. The absorption maximum (λ_{max}) of dioxetanes <75CJC1103> occurs at around 280–300 nm ($\epsilon < 30$) with very weak tailing up to 450 nm, which is responsible for the yellow color. Unfortunately, the UV spectral data of most of the isolated dioxetanes have not been reported.

1.33.3.1.3 Photoelectron spectra

For 3,3,4,4-tetramethyl-1,2-dioxetane the vertical ionization potentials (8.98, 10.98, 11.41, and 12.90 eV) were determined by photoelectron spectroscopy <75CJC3439>. The lowest ionization potential (8.98 eV) involves removal of an electron from the π_y^* HOMO <75CJC3439>.

1.33.3.1.4 NMR studies

NMR spectroscopy is undoubtedly the most useful and general analytical method for the characterization of dioxetanes. Particularly low-temperature NMR spectroscopy is valuable for the identi-

fication of thermally labile derivatives. For the majority of dioxetanes, which were isolated or identified as intermediates during the last decade, both the ^1H and ^{13}C NMR spectra were reported (for references see Sections 1.33.7 and 1.33.8). In general, the signals for quarternary carbon atoms of the dioxetane ring, if not substituted by heteroatoms, are observed at δ 87–90 (B-85MI 133-02). Heteroatom-substituted (O, N, S) quaternary carbon atoms show resonances at δ 106–118 (91JOC4027, 91LA33, 93AG(E)80, 93JOC5524).

The proton resonances directly attached to the dioxetane ring are also very characteristic and they are valuable for the identification of dioxetanes. The signals of these protons appear for alkyl-substituted dioxetanes at δ 4.9–5.2. Alkenic, aryl, and alkoxy substituents at the carbon atom shift the dioxetane proton resonances to δ 5.6–6.0 (B-85MI 133-02). Thus, NMR spectroscopy is the most convenient and definitive tool for the structural determination of dioxetanes.

1.33.3.1.5 Mass spectroscopy

Mass spectroscopy is of limited use for the characterization of dioxetanes, since these labile peroxides usually decompose under the analysis conditions. However, mass spectroscopic data of numerous dioxetanes have been reported (87CB1565, 87JOC3059, 90LA1227, 93JOC47) and in optimal cases even the parent ions of dioxetanes were detected.

1.33.3.1.6 X-ray diffraction

The x-ray diffraction of crystalline materials is the most direct and reliable method for structure proof. Unfortunately, the determination of the crystal structures of dioxetanes by x-ray analysis is difficult, because in most cases these thermally and photochemically labile materials do not survive the strong irradiation. Furthermore, it is quite cumbersome to grow appropriate single crystals for x-ray diffraction. Nevertheless, crystal structures of a limited number of dioxetanes have been successfully determined (Table 1).

The dioxetane ring torsion angles range from 20° for derivatives like bisadamantylidene-1,2-dioxetane (72TL169) to 0° for dioxetanes (84JOC3920) derived from benzo-1,4-dioxene. The comparatively large torsion angle for bisadamantylidene-1,2-dioxetane is presumably due to nonbonding repulsions between the tertiary hydrogen atoms on the two spiroadamantyl moieties. Conclusions as to the structural features of simple alkyl- or aryl-substituted dioxetanes are difficult to draw from the available structural data.

1.33.3.2 Chemical Methods

Because dioxetanes decompose thermally to the corresponding carbonyl fragments, determination of their elemental composition by the combustion analysis may, in general, not be applicable, although numerous satisfactory CH analyses have been reported. Iodometric titration was frequently employed to determine the percentage of active oxygen content in dioxetane and hence its purity (75CJC1103). The quantitative reduction of dioxetanes by lithium aluminum hydride at low temperature to the corresponding 1,2-diols (see Section 1.33.5.3) can be used for their chemical characterization. The deoxygenation of dioxetanes by trivalent phosphorus compounds to epoxides (see Section 1.33.5.3) constitutes another chemical method for the structural determination of dioxetanes.

1.33.4 THERMOCHEMISTRY AND KINETIC ASPECTS OF THE THERMAL DECOMPOSITION OF DIOXETANES

1.33.4.1 Thermochemistry

The emission of light on thermolysis is the most characteristic property of dioxetanes (B-89MI 133-01). The chemical energy stored in these energy-rich molecules is converted mainly into vibrational and to some extent electronic energy; the latter is released in the form of light. The fundamental steps of this process are detailed in Scheme 5. Thus, the ground state reactant R_0 (dioxetane) acquires sufficient thermal energy on heating to form the activated complex $\neq$. This activated

Table 1 X-ray structural data on dioxetanes.

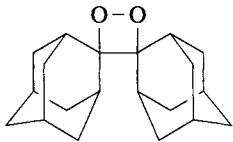
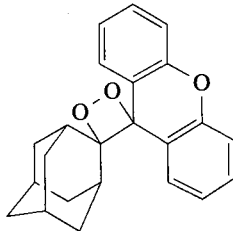
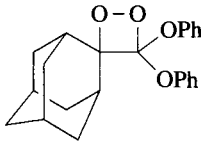
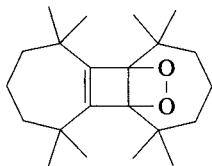
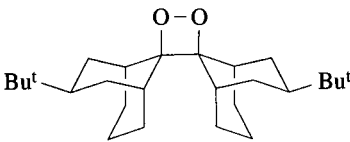
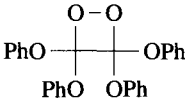
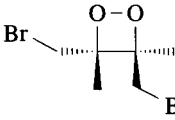
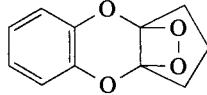
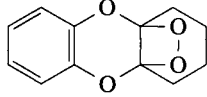
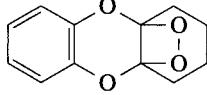
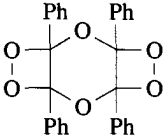
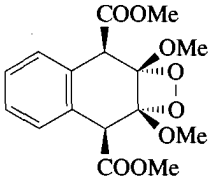
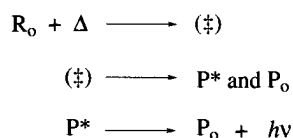
Dioxetane	Torsion angle ^a (°)	Bond distances (pm)			Ref.
		O—O	C—C	C—O	
	21.3	148.0	155.0	147.5	72TL169
	14.8	151.0	157.0	146.0	88TL3137
	11.7	147.0	149.0	149.0, 151.0	82TL3251
	0	149.0	155.0	149.0	80TL3171
	21.9	150.7	153.3	148.2	84JA8174
	9.6	150.5	155.0	148.0, 143.0	82TL3251
	15.3	144.0	151.0	148.0, 149.0	82TL3251
	0	158.0	158.0	144.0	84JOC3920
	0	149.0	151.0	144.0	84JOC3920
	1.0	155.0	161.0	144.0	84JOC3920

Table 1 Continued.

Dioxetane	Torsion angle ^a (°)	Bond distances (pm)			Ref.
		O—O	C—C	C—O	
	16.3	150.0	155.5	144.1, 143.5	83AG(E)546
	2.5	153.0	156.0	145.0	94T9009

^aTorsion angle in dioxetane ring.

complex may dissociate into the electronically excited product P* (the carbonyl fragment). The last step is very unusual since a crossover from a ground state energy surface to an excited state surface, a nonadiabatic path, has taken place. Subsequently, the electronically excited product rids itself of the excess energy by exhibiting chemiluminescence, fluorescence in the case of singlet-excited product ^sP*, and phosphorescence in the case of the triplet-excited one ^tP*. The reaction profile for a general chemiluminescent reaction is shown in Figure 2.



Scheme 5

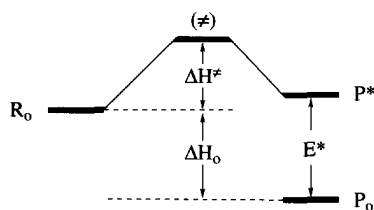


Figure 2 Energy diagram for a chemiluminescent decomposition (ΔH_o = reaction enthalpy, $\Delta H^\ddagger$ = activation enthalpy, E^* = excitation energy).

One of the most important criteria for a chemiluminescent process is that of energy sufficiency. The sum of the activation enthalpy ($\Delta H^\ddagger$) and the reaction enthalpy (ΔH_o) must be greater than the excitation energy (E^*) of the electronically excited product (Equation (1)). A substance that conforms to this energy condition, is designated as energy sufficient. Since the energy of the lowest excited states, namely the n, π^* states, of simple carbonyl compounds such as aldehydes and ketones falls in the range 75–85 kcal mol⁻¹ for singlet excitation and 60–78 kcal mol⁻¹ for triplet excitation, the energy sufficiency criterion demands that at least 70–85 kcal mol⁻¹ of energy must be made available in the transition state during the decomposition to generate one of the carbonyl fragments in its n, π^* -excited state.

$$\Delta H^\ddagger + \Delta H_r > E^* \quad (1)$$

This energy sufficiency criterion is usually fulfilled for dioxetanes and dioxetanones (α -peroxy lactones). Typically, the activation enthalpies ($\Delta H^\ddagger$), determined by isothermal kinetic methods,

range between 20 and 30 kcal mol⁻¹ and the heats of reaction (ΔH_r), estimated from thermochemical calculations <70JA6553, 72JA8665>, vary between 60 and 90 kcal mol⁻¹. Thus, sufficient energy is being released in the thermolysis of dioxetanes to energize singlet and/or triplet carbonyl products (see Figure 2).

1.33.4.2 Activation Parameters (Kinetics) of the Thermal Decomposition

The kinetics of the thermal decomposition of dioxetanes and dioxetanones (α -peroxy lactones) are first order. A variety of experimental methods can be used to determine the rates, which can be classified in isothermal or nonisothermal methods, and chemiluminescent or nonchemiluminescent ones. These include <B-82MI 133-01> direct chemiluminescence of the excited carbonyl product, energy transfer chemiluminescence of the chemienergized, excited carbonyl product to an efficient fluorescer, dioxetane consumption or carbonyl product formation by NMR spectroscopy, iodometry of the cyclic peroxide, and infrared spectroscopy of dioxetanone consumption or appearance of the carbonyl product. Of these kinetic methods, the chemiluminescence techniques are by far the most convenient and sensitive ones.

Most activation parameters of dioxetanes or dioxetanones have been determined by kinetic analysis under isothermal conditions with chemiluminescence methods. The light emission is followed by photometry. Either the fluorescence or phosphorescence intensity of the excited carbonyl fragment is directly monitored or that of an efficient fluorescer, which is excited by energy transfer from the chemienergized carbonyl product to an appropriate fluorophor. The rate constants of the thermolysis should be measured over as wide as possible (at least 30°C) temperature range. The activation parameters are determined by the Arrhenius (Equation (2)) or the Eyring methods (Equation (3)). Unfortunately, dark catalysis can be a problem in these techniques.

$$\ln k = \ln A - E_a/RT \quad (2)$$

$$\ln (k/T) = \ln k/h + \Delta S^\ddagger/R - \Delta H^\ddagger/RT \quad (3)$$

Besides isothermal kinetics, a number of nonisothermal techniques have been developed. The temperature drop method <71JA4126> is advantageous since one can determine the activation energy (E_a) exclusively for the chemiluminescent process and thereby obviate problems of dark catalysis <B-73MI 133-01>. In this case, the chemiluminescence intensity I_1 is monitored at a constant temperature T_1 , the reaction mixture is abruptly dropped by about 15°C to a lower temperature T_2 , maintained at this temperature, and the chemiluminescence intensity I_2 is again recorded. From the temperature dependence, the activation energy E_a is calculated according to Equation (4).

$$E_a = \frac{R \ln(I_1/I_2)}{(1/T_2) - (1/T_1)} \quad (4)$$

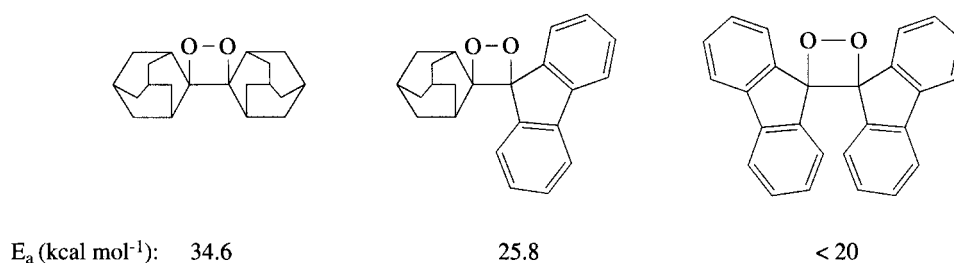
The major advantage of this nonisothermal method, besides convenience, is that in view of the high sensitivity of modern photometric equipment to monitor chemiluminescence emissions, a negligible fraction of the dioxetane or dioxetanone is consumed during the time period of decomposition rather than bulk consumption, as is necessarily the case in isothermal methods. Consequently, only the light-producing process is monitored, which avoids thereby the problems of dark catalysis.

This convenient method has been modified in the form of the so-called step function analysis at various temperatures and continuous temperature variation <74JA282, 79MI 133-01>. In the former <74JA282>, multiple temperature changes are employed; in the latter <79MI 133-01> the temperature is continuously varied in a linear fashion with time. Finally, differential thermal analysis <75CB1198, 76CB2862> has also been utilized to assess activation parameters. In contrast to the above nonisothermal methods, in the latter the peroxide is completely consumed and instead of initial rates one measures total rates. The advantage of minimizing dark catalysis is therefore lost.

When properly carried out, the activation parameters for the thermolysis of dioxetanes or dioxetanones obtained by the various described techniques agree well within the experimental error. Since an excellent updated collection of activation parameters is available in reviews on dioxetanes <B-82MI 133-02, B-82MI 133-04, B-88MI 133-01, B-89MI 133-01>, only some selected typical examples are listed in Table 2. The activation enthalpies ($\Delta H^\ddagger$) fall in the range of 13–36 kcal mol⁻¹; most values

cluster around 26 kcal mol^{-1} . The activation entropies ($\Delta S^\ddagger$) range within $0 \pm 5 \text{ e.u.}$, but when they drop much below -5 e.u. , catalytic dark decomposition should be suspected.

Only limited information can usually be read out of these thermal stability data in terms of structural features and substitution patterns, but some general trends are apparent (for details see <B-82MI 133-04>). Easily oxidized substituents directly attached to the dioxetane ring lower the thermal stability (e.g. CIEEL, see Section 1.33.6.2). Moreover, it has been recognized <B-89MI 133-01> that the more conformationally rigid the dioxetane ring is towards puckering, the higher its thermal stability. Increased steric interactions at geminal positions of the four-membered peroxide ring lead to high $\Delta H^\ddagger$ values with little effect on $\Delta S^\ddagger$. A dramatic case is the dioxetane of bisadamantylidene, the most persistent dioxetane known to date with an E_a value of 35 kcal mol^{-1} (m. p. $174\text{--}176^\circ\text{C}$ without decomposition). Such spiroadamantyl stabilization has been exploited for the preparation of dioxetanes sufficiently persistent for commercial applications <B-91MI 133-01>. This concept of stabilization is illustrated in the series of dioxetanes below (Scheme 6). While the bisfluorenylidene dioxetane is too labile even for spectral detection, replacement of one of the spirofluorenyl moieties with a spiroadamantyl unit provides a persistent derivative at room temperature.



Scheme 6

The bulk of the thermal stability data <B-88MI 133-01> support the diradical mechanism, but for ring-fused dioxetanes the concerted mechanism <75JA3859> provides a more consistent explanation (Scheme 4). However, when the activation data (rate-determining step) is considered together with the excitation yields (product-determining step), the best compromise between these two mechanistic extremes is the *merged mechanism*. This is brought out definitively by the complete series of methyl-substituted dioxetane derivatives <85JA410>. However, a theoretical study <91JA1566> (see Section 1.33.2) suggests that the cleavage of the peroxide bond in dioxetanes requires negligible energy to produce the 1,4-dioxy diradical. The observed thermal activation <85JA410> derives from cleavage of the dioxetane C—C bond in the triplet diradical to afford triplet-excited carbonyl product.

1.33.4.3 Excitation Parameters

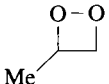
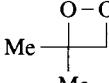
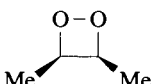
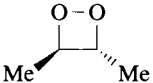
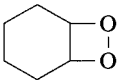
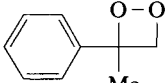
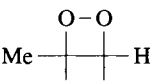
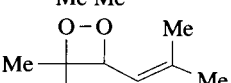
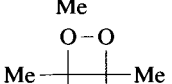
The thermal decomposition of dioxetanes and dioxetanones generates sufficient energy for the formation of one electronically excited carbonyl product, which manifests itself by light emission. The values of the singlet excitation yields (Φ^S), triplet excitation yields (Φ^T), and the spin state selectivity (Φ^T/Φ^S) characterize a particular dioxetane <B-89MI 133-01>. Excitation parameters of selected derivatives are listed in Table 2. Chemiluminescent techniques and photochemical transformations constitute the two most important experimental methods for the determination of chemiexcitation yields.

In the photophysical techniques, the physical properties of the electronically excited state are utilized, specifically its luminescence. If for the excited state product its fluorescence quantum yield (Φ^f), in the case of singlet-excited state, and its phosphorescence quantum yield (Φ^{ph}), in the case of triplet-excited state, are known, the determination of the direct chemiluminescence quantum yield (Φ^{DC}) allows us to calculate <B-89MI 133-01> the desired $\Phi^{S/T}$ parameters (Equation (5)).

$$\Phi^{DC} = \Phi^{S/T} \Phi^{f/ph} \quad (5)$$

The experimental definition of the direct chemiluminescence quantum yield (Φ^{DC}) is given by Equation (6), in which the initial rate of photon production (I_o^{DC}) and the rate of dioxetane decomposition ($k[C_o]$) must be measured. With a suitable photometer or photon-counting apparatus

Table 2 Activation parameters and excitation yields of selected dioxetanes.

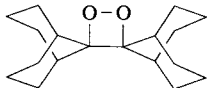
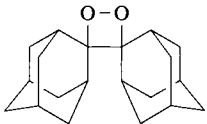
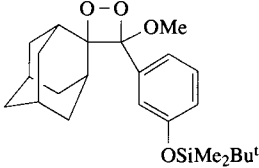
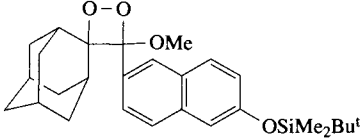
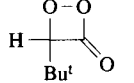
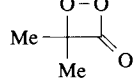
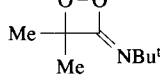
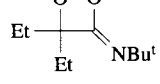
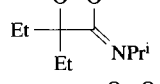
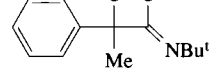
Dioxetane	Activation parameters ^a			Excitation yields ^b		Ref.
	E_A (kcal mol ⁻¹)	$\Delta H^\ddagger$ (kcal mol ⁻¹)	$\Delta S^\ddagger$ (e.u.)	Φ^S (%)	Φ^T (%)	
	c	18.9 ± 0.8	-12.6 ± 0.4	0.00031 ± 0.00006	0.24 ± 0.60	85JA410
	c	21.5 ± 0.5	-5.5 ± 1.1	0.0033 ± 0.0007	4.3 ± 1.3	85JA410
	c	22.5 ± 0.2	-5.1 ± 0.4	0.018 ± 0.002	7.8 ± 1.9	85JA410
	c	21.6 ± 0.6	-7.6 ± 1.6	0.018 ± 0.002	12 ± 2	85JA410
	c	21.5 ± 0.5	-7.4 ± 1.3	0.017 ± 0.004	13 ± 2	85JA410
	22.5 ± 0.3	c	c	c	c	79TL2569
	21.2 ± 0.1	20.5 ± 0.1	-9.7 ± 0.4	0.095	14	75JA2819, 78JA7596
	c	23.4 ± 0.3	-4.7 ± 0.8	0.1 ± 0.01	25 ± 5	85JA410
	22.3 ± 0.3	21.6 ± 0.5	-7.6 ± 0.9	0.0039	0.28 ± 0.03	81ZN(B)1653
	c	24.9 ± 0.7	-2.8 ± 2.3	0.25 ± 0.05	35 ± 7	85JA410

Four-membered Rings with Two Oxygen Atoms

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Table 2 Continued.

Dioxetane	Activation parameters ^a			Excitation yields ^b		Ref.
	E_A (kcal mol ⁻¹)	$\Delta H^\ddagger$ (kcal mol ⁻¹)	$\Delta S^\ddagger$ (e.u.)	Φ^S (%)	Φ^T (%)	
	25.1 ± 0.5	23.4 ± 0.2	-6.3 ± 0.3	0.11 ± 0.05	14 ± 3	90JPR161
	27.6 ± 0.2	26.9 ± 0.2	+2.5 ± 1.0	0.0057 ± 0.0007	0.071 ± 0.006	79MI 133-01, B-89MI 133-01
	28.6 ± 1	c	c	1.0 ± 0.5	10 ± 5	76JA1086
	c	28.2 ± 1.1	+0.3 ± 3.0	0.39 ± 0.06	3.2 ± 0.5	B-89MI 133-01
	24.2 ± 0.3	22.6 ± 0.3	-5.7 ± 0.1	0.011 ± 0.002	3 ± 1	90JPR161
	13.4	c	11.0	c	c	82JA3504
	19.7	19.1	-7.2	22	c	78JA4916
	19.7	c	c	25	c	77CC944

	35.6 ± 0.5	c	c	c	c	76CB2862
	34.6 ± 1.5	33.8	$+2.9 \pm 2.0$	2 ± 1	15 ± 8	75JA7110
	28.4	c	c	45	c	87TL1155
	27.0	c	c	0.11	c	87TL1155
	c	20.5 ± 2.2	-2.7 ± 0.8	0.038 ± 0.003	0.23 ± 0.009	80MI 133-02
	22.3 ± 0.3	21.7	0 ± 1	0.1	1.5	78JA5559
	17.6 ± 2	17.1 ± 2	$+2.7 \pm 1.0$	0.0000052	0.0034	79JA7105
	16.7	c	c	c	0.016	80CC898
	18.3	c	c	c	0.014	80CC898
	15.4 ± 2	c	c	c	0.031	80CC898

^aMost of the activation parameters were determined by measuring the direct or enhanced chemiluminescence with isothermal kinetics. ^bMost of the excitation yields were determined by using energy transfer chemiluminescence with DBA and DPA as fluorophors. ^cNot known.

these values are readily assessed. Once the direct chemiluminescence quantum yield (Φ^{DC}) has been acquired experimentally, the singlet and triplet excitation yields ($\Phi^{\text{S/T}}$) can be computed from Equation (5).

$$\Phi^{\text{DC}} = I_0^{\text{DC}}/k[C_0] \quad (6)$$

Most chemiluminescence yields have been determined by energy transfer to suitable fluorophors and subsequent measurement of the enhanced chemiluminescence quantum yield (Φ^{EC}). One distinguishes between enhanced luminescence chemienergized by singlet–singlet energy transfer (SS) and by triplet–singlet energy transfer (TS). The former permits the determination of singlet (Φ^{S}), the latter triplet excitation yields (Φ^{T}). The chosen fluorophors are generally polycyclic aromatic compounds whose photophysical properties are known <70MI 133-01>.

The fluorescer of choice in the singlet–singlet energy transfer process is 9,10-diphenylanthracene (DPA) in organic solvents and its sulfonate derivative DPAS in aqueous media. By means of steady-state kinetics, the expression in Equation (7) for the DPA-enhanced chemiluminescence quantum yield (Φ_{DPA}) is obtained in terms of the singlet excitation yield (Φ^{S}), the efficiency of singlet–singlet energy transfer (Φ_{ET}), and the DPA fluorescence quantum yield ($\Phi_{\text{DPA}}^{\text{f}}$). At infinite concentration of DPA, i.e. $[\text{DPA}]_{\infty}$, the Φ_{ET} term is unity. One measures the DPA-enhanced chemiluminescence intensity (I_{DPA}) as a function of DPA concentration and constructs a plot of $1/I_{\text{DPA}}$ against $1/[\text{DPA}]$. The intercept of such a double reciprocal plot represents the DPA-enhanced chemiluminescence intensity at infinite DPA concentration ($I_{[\text{DPA}]\infty}^{\text{EC}}$). The experimental definition of the DPA-enhanced chemiluminescence quantum yield ($\Phi_{\text{DPA}}^{\text{EC}}$) is given in Equation (8).

$$\Phi_{\text{DPA}}^{\text{EC}} = \Phi^{\text{S}}\Phi_{\text{ET}}^{\text{SS}}\Phi_{\text{DPA}}^{\text{f}} \quad (7)$$

$$\Phi_{\text{DPA}}^{\text{EC}} = I_{[\text{DPA}]\infty}^{\text{EC}}/k[C_0] \quad (8)$$

The determination of the triplet excitation yields requires 9,10-dibromoanthracene (DBA) or other heavy atom-containing fluorophors, which involve triplet–singlet energy transfer with triplet-excited carbonyl products <80MI 133-01>. Steady-state kinetics affords the expression given in Equation (9) for the DBA-enhanced chemiluminescence quantum yield ($\Phi_{\text{DBA}}^{\text{EC}}$). As with DPA-enhanced chemiluminescence, to ensure that all chemienergized carbonyl triplets are intercepted by DBA in the triplet–singlet energy transfer, the DBA-enhanced chemiluminescence intensity (I_{DBA}) is determined at infinite DBA concentration, i.e. $[\text{DBA}]_{\infty}$, by constructing a double reciprocal plot of $1/I_{\text{DBA}}$ against $1/[\text{DBA}]$. By using Equation (10), analogous to the singlet excitation yield (Φ^{S}), the corresponding triplet excitation yield (Φ^{T}) is calculated. Note that these expressions neglect the contribution of energy transfer by singlet-excited product to DBA. This is usually a valid assumption since for simple dioxetanes and α -peroxy lactones the Φ^{S} values (DPA method) are generally at least two orders of magnitude smaller than the corresponding Φ^{T} values (DBA method).

$$\Phi_{\text{DBA}}^{\text{EC}} = \Phi^{\text{T}}\Phi_{\text{ET}}^{\text{TS}}\Phi_{\text{DBA}}^{\text{f}} \quad (9)$$

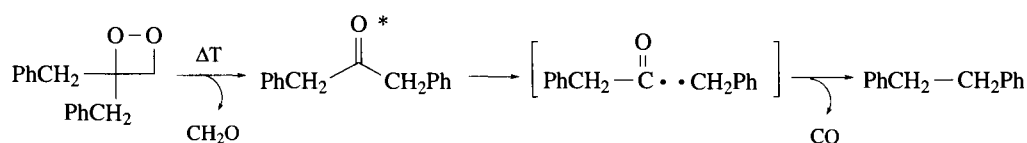
$$\Phi_{\text{DBA}}^{\text{EC}} = I_{[\text{DBA}]\infty}^{\text{EC}}/k[C_0] \quad (10)$$

Nonchemiluminescent methods for the determination of excitation yields involve photochemical transformations <B-83MI 133-01>. Since simple alkyl- or aryl-substituted dioxetanes or dioxetanones (α -peroxy lactones) produce very low yields of excited singlets, this method is not usually sufficiently sensitive to allow accurate determinations of $\Phi^{\text{S/T}}$. If the quantum yield for the photochemical reaction (Φ_{photo}) is known and the relative yield of the photochemical product (Φ_{chem}) determined experimentally, the yield of excited states ($\Phi^{\text{S/T}}$) can be calculated according to Equation (11). Representative transformations include Norrish Type I (Scheme 7) and Type II (Scheme 8) cleavages, and cyclohexadienone (Scheme 9) and cyclopentyl ketone rearrangements (Scheme 10).

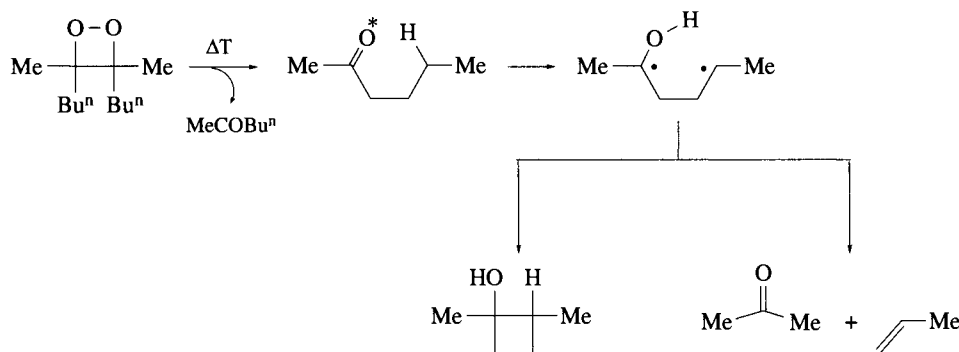
$$\Phi_{\text{chem}} = \Phi^{\text{S/T}}\Phi_{\text{photo}} \quad (11)$$

$$\Phi_{\text{chem}} = \Phi^{\text{S/T}}\Phi_{\text{ET}}\Phi_{\text{photo}} \quad (12)$$

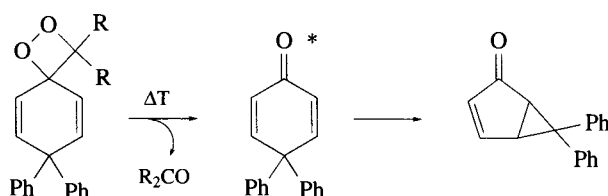
More convenient is intermolecular energy transfer to a photolabile reactant for the determination of chemiexcitation yields in the thermolysis of four-membered ring cyclic peroxides, because a particular 1,2-dioxetane or α -peroxy lactone need not to be tailor-made for the chemical transformation in question. Compared to intramolecular reactions (Equation (11)), one has to know additionally the efficiency of energy transfer (Φ_{ET}) of the excited carbonyl fragment to the photolabile reactant (Equation (12)). Again, recourse is taken in a double reciprocal plot of the yield of photoproduct against the concentration of the photolabile substrate. A variety of photochemical transformations have been carried out in this way (B-83MI 133-01), which include *cis/trans* isomerization of alkenes (Scheme 11), alkene dimerization (Scheme 12), oxetane formation (Scheme 13), the di- π -methane (Scheme 14) and dienone rearrangements (Scheme 15), hydrogen abstraction, azoalkane denitrogenation (Scheme 16), and photocyclizations (Scheme 17).



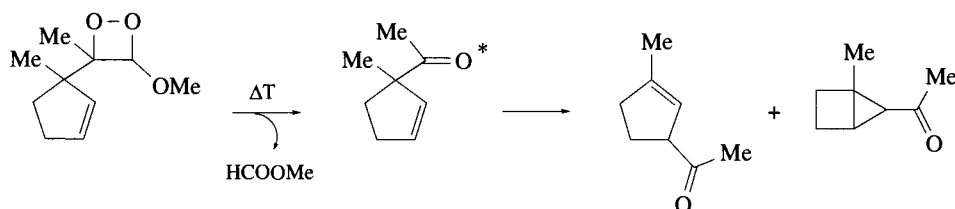
Scheme 7



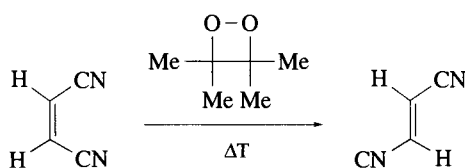
Scheme 8



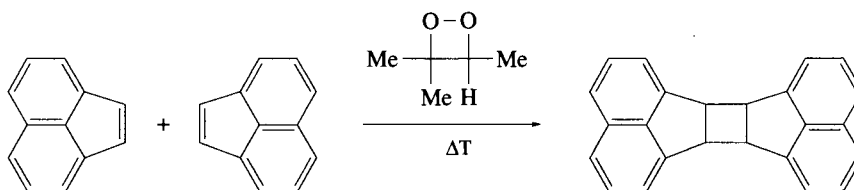
Scheme 9



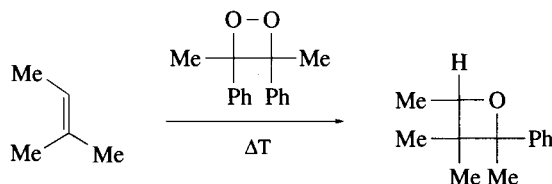
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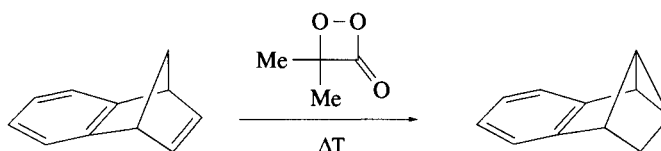
Scheme 11



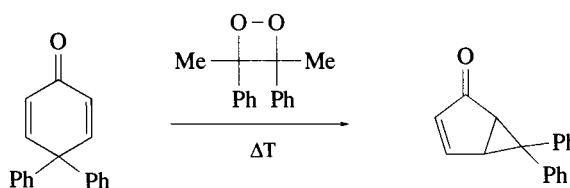
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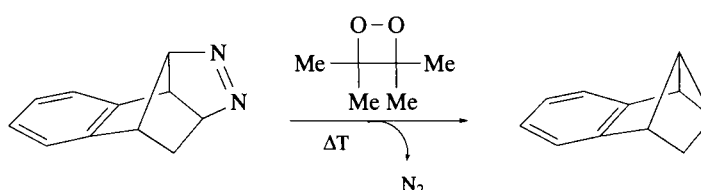
Scheme 13



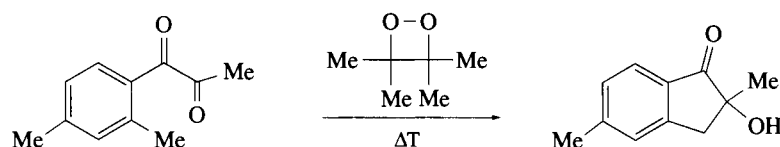
Scheme 14



Scheme 15



Scheme 16



Scheme 17

For symmetrically substituted 1,2-dioxetanes, only one electronically excited product fragment is possible. However, in unsymmetrical dioxetanes, two different electronically excited carbonyl fragments can be formed and the identification of both excited states is a major problem. Such detailed information about energy partitioning between the two possible excited carbonyl products is rare (78JA6649), although this data would provide valuable mechanistic insight.

In general, it is not straightforward to draw definitive conclusions about what concerns the dependence between the excitation parameters and structural variations of the dioxetanes, but some interesting empirical trends can be recognized (B-82MI 133-01, B-83MI 133-01) (for details see (B-89MI 133-01)). For dioxetanes that chemienergize n,π^* excited states of carbonyl products, the triplet yields are high ($\Phi^T > 10\%$) and the singlet yields low ($\Phi^S < 1\%$). On the other hand, in the case of dioxetanes which chemienergize π,π^* or charge transfer excited states, for example, by the intramolecular CIEEL mechanism (see Section 1.33.6.2), the singlet excitation yields are quite high ($\Phi^S > 10\%$) compared to the n,π^* chemienergizers. Although the triplet yields are generally not reported for these systems (triplet yields are difficult to measure when the singlet yields are high), it should be apparent from the relatively large Φ^S values that the Φ^T values are quite low.

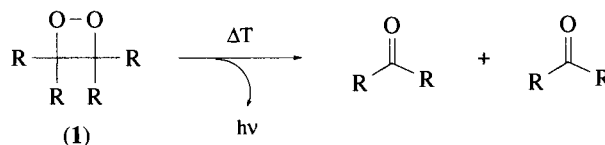
Provided the dioxetane is energy-sufficient to chemienergize a particular carbonyl product, empirically no definitive correlation between excited state energy of the product and excitation yield can be discerned. The effects are small and are buried within the experimental error. Generally speaking, n,π^* triplet states are preferred over π,π^* , even if the latter are of lower excitation energy (Scheme 9) (76JA5574). This trend does not apply to π,π^* singlet-excited states, which are produced by the intramolecular electron exchange mechanism (CIEEL). In the case of unsymmetrical 1,2-dioxetanes, a correlation of the partitioning of the available energy between the two possible fragments was attempted (79JA4683). Although there exist some exceptions, it has been concluded that the lower-energy n,π^* triplet states are formed preferentially.

An impressive contrast exists between the 3,3,4,4-tetramethyl-1,2-dioxetane (**1a**) and the α -dimethylperoxy lactone (**2a**), which both produce excited acetone. The total efficiency of excited state production drops from 35 to 1.5% (see Table 2) for the α -peroxy lactone. It should be noted that this decrease is exclusively in the triplet yield, since the singlet excitation yields are essentially negligible compared to the triplet yields (Table 2). Although the decomposition of the dioxetanone is about 22 kcal mol⁻¹ more exothermic than that of the tetramethyldioxetane (Figure 3), the former is the less efficient system to produce excited acetone. Consequently, the available energy of these reactions does not necessarily parallel the observed chemienergization efficiencies.

1.33.5 REACTIONS OF DIOXETANES

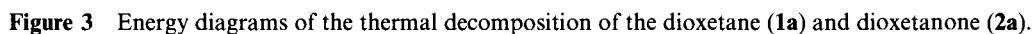
1.33.5.1 Thermal and Photochemical Reactions

Thermolysis of simple alkyl- or aryl-substituted dioxetanes (**1**) leads to carbonyl fragments by O—O and C—C bond cleavage with concomitant light emission (Scheme 18) (B-88MI 133-01, B-89MI 133-01). As already stated (see Section 1.33.2) for the decomposition of dioxetanes, both concerted and diradical (stepwise) mechanisms have been argued (Scheme 4) (B-82MI 133-01, B-88MI 133-01). A merged mechanism, in which the kinetic features reflect diradical character and the excited state products display the concerted nature along the complex reaction coordinate, was proposed to reconcile best the available experimental data on the two extreme mechanistic views (74ACR97, 75JA3859, 85JA410).

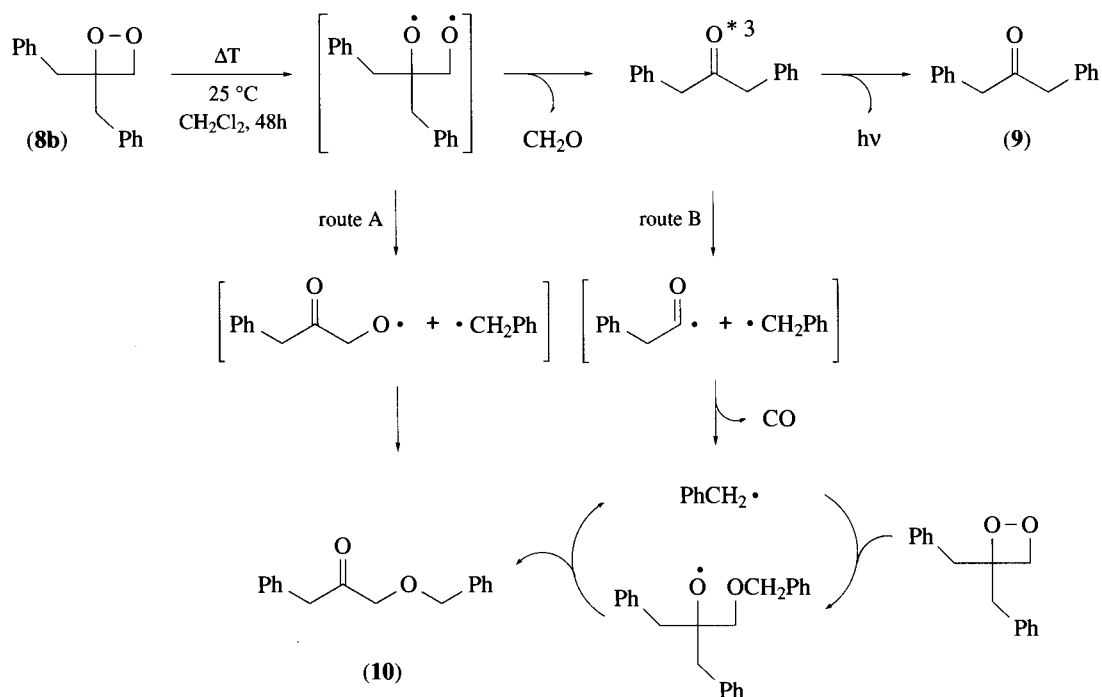


Scheme 18

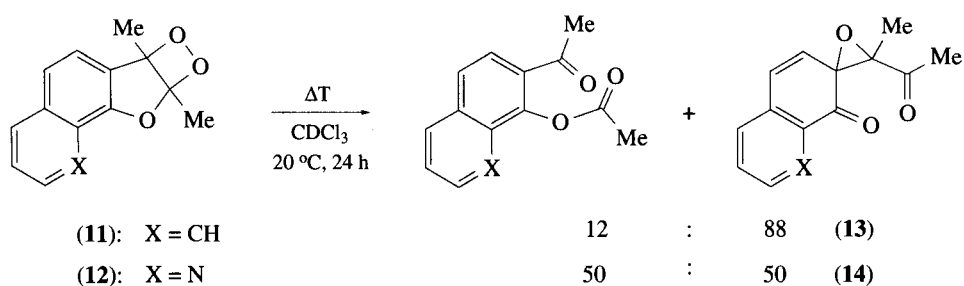
Experimental evidence was provided in favor of the diradical mechanism. For example, the thermolysis of 3,3-dimethyl-1,2-dioxetane (**8a**) in cyclohexa-1,4-diene as solvent afforded the 1,2-diol (Scheme 19) by trapping of the intermediate 1,4-dioxy diradical (89JOC3523). Furthermore, the thermal decomposition of 3,3-dibenzyl-1,2-dioxetane (**8b**) gave, besides the expected decomposition product 1,3-diphenyl-2-propanone (**9**), the rearrangement ketone 1-(benzyloxy)-3-phenyl-2-propanone (**10**) (see Scheme 20). It was postulated that the ketone (**10**) was formed by β cleavage (route A in Scheme 20) of the benzyl group in the intermediate 1,4-dioxy diradical and in-cage combination of the resulting radicals (92JA8807). However, a more detailed examination (94JA5674) confirmed induced decomposition (route B in Scheme 20) to be the dominant source for this unusual rearrangement ketone.



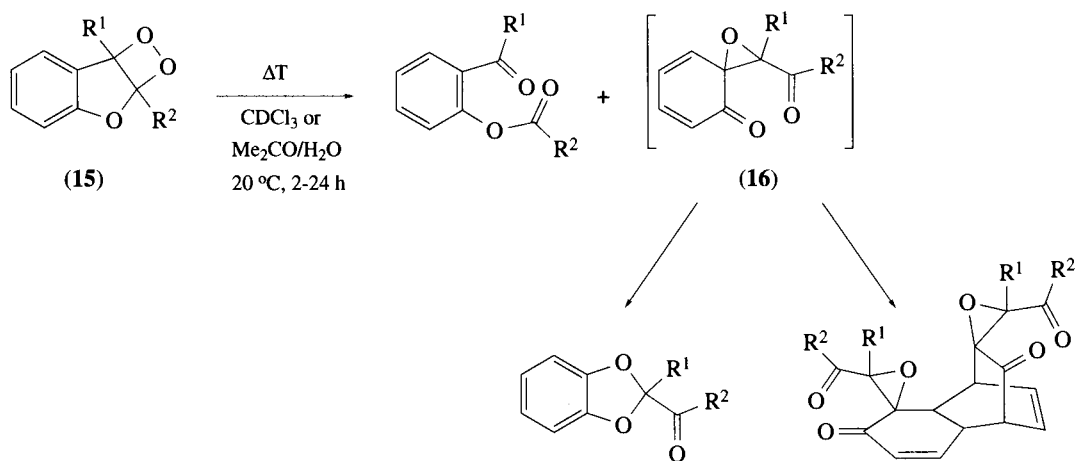
Although thermolysis of simple alkyl- or aryl-substituted dioxetanes entails exclusively C—C cleavage (Scheme 18), other products were also observed in the thermolysis of specific dioxetanes. For example, treatment of the thermally labile naphthofuran dioxetane (**11**) and furoquinoline dioxetane (**12**) at 20 °C in CDCl₃ (Scheme 21) gave, besides the usual cleavage products, also the novel spiroepoxides (**13**) and (**14**) by rearrangement ^{<90LA1227>}. A similar thermal rearrangement was also observed for the benzofuran dioxetanes (**15**); however, the spiroepoxides (**16**) are thermally labile and underwent rearrangement to the dioxoles or dimerization (Scheme 22) ^{<91JA8005, 94JA6713>}. The rearrangement of benzofuran dioxetanes to spiroepoxides can be conveniently induced by bromide ions at subambient temperatures ^{<94JA6713>}.



Scheme 20

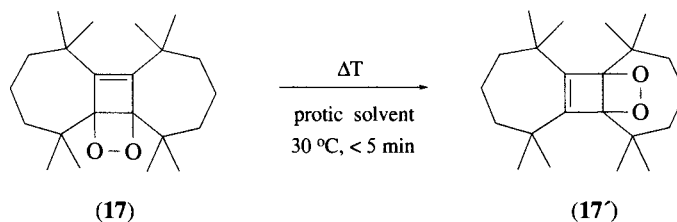


Scheme 21

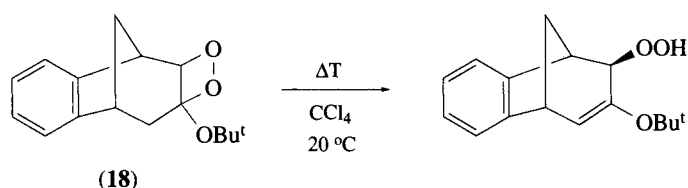


Scheme 22

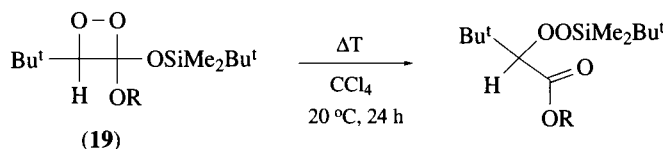
In contrast to the dioxetanes, (11), (12), and (15), the cyclobutadiene dioxetane (17) was isomerized on heating exclusively to its regioisomer (17') (see Scheme 23) <80TL3171>, whereas the alkoxy-substituted dioxetane (18) rearranged by C—O bond cleavage into the corresponding allylic hydroperoxide (Scheme 24) <89TL3339>. Furthermore, silyl migration of dioxetane (19) occurred at room temperature in benzene (Scheme 25) <90TL2259, 91JOC4737>.



Scheme 23

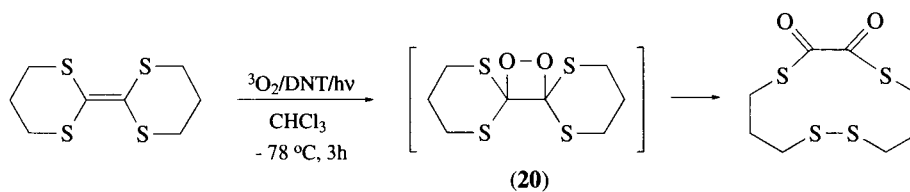


Scheme 24



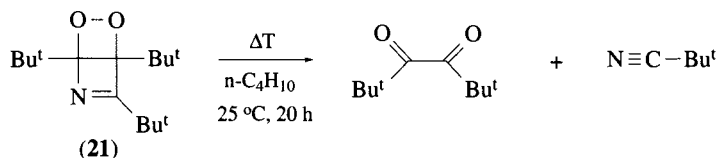
Scheme 25

On thermolysis, not only the peroxide and C—C bond of the dioxetane ring can be cleaved, but also the two vicinal substituent bonds can be broken with preservation of the dioxetane ring C—C bond. An early case was the decomposition of the tetrathioetene acetal dioxetane (20) into the cyclic oxalate in Scheme 26 <72CC73>. Another example is the cleavage of the azacyclobutadiene dioxetane (21) into the α -dione and pivalonitrile (Scheme 27) <88AG(E)272>.



DNT = dinaphthylthiophene

Scheme 26

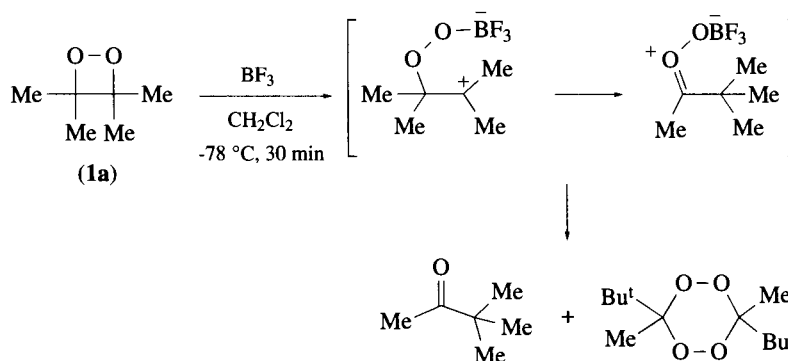


Scheme 27

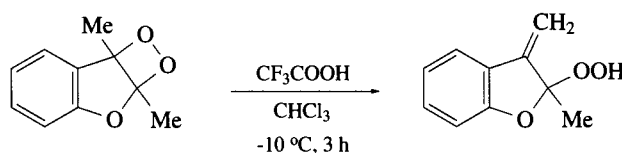
The photolysis of dioxetanes has been studied much less extensively in comparison to their thermal reactions <B-88MI 133-01, B-89MI 133-01, B-92MI 133-02>. Thus, since the mid-1980s no significant contributions on this subject have been reported. Some investigations on the photolysis of dioxetanes were made in the 1970s, which were summarized in a review <77AHC(21)437>. As with the thermolysis, the direct photolysis of dioxetanes generates electronically excited carbonyl compounds <73JA2035, 75CB3159>; however, the triplet spin selectivity (ratio of triplet- and singlet-excited species) in the photolysis is ca. 25-fold lower than in the thermal process <73JA2035>.

1.33.5.2 Electrophilic Attack at Ring Heteroatoms

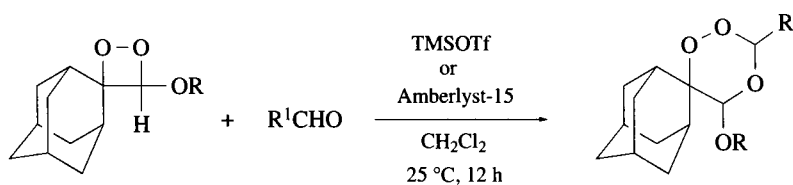
Very few reactions of dioxetanes with electrophiles are known. The electrophilic attack of boron trifluoride, a strong Lewis acid, at the peroxide oxygen atom of the tetramethyl-1,2-dioxetane (**1a**) leads to pinacolone and the 1,2,4,5-tetroxane (Scheme 28) <77JA1890>. Brønsted acids such as $\text{CF}_3\text{CO}_2\text{H}$ catalyze rearrangement of the dioxetanes to allylic hydroperoxides (Scheme 29), but this transformation is limited to the easily opened benzofuran dioxetanes <91JA8005>. Under Lewis or Brønsted catalysis, aldehydes add to dioxetanes with α -alkoxy or aryloxy substituents to give 1,2,4-trioxanes (Scheme 30) <83HCA2615, 85T2081>. The latter transformation has been utilized extensively for the preparation of model compounds for the natural product *Artemisinin*, a Chinese folk medicine to treat malaria <94ACR211>.



Scheme 28



Scheme 29

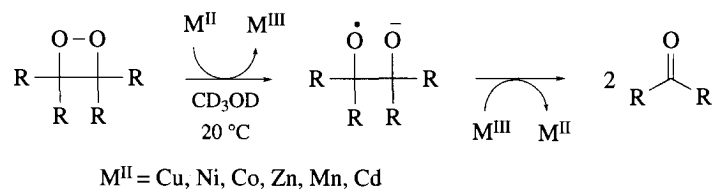


Scheme 30

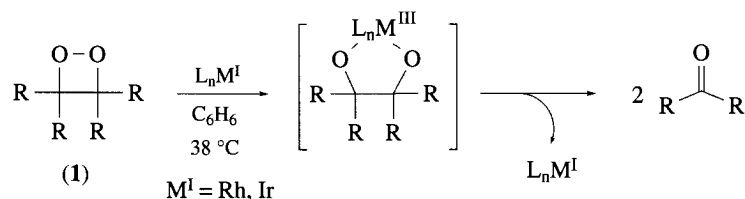
The reaction of divalent transition metals such as copper, nickel, cobalt, zinc, manganese, and cadmium with dioxetanes leads to catalytic decomposition into carbonyl fragments (Scheme 31). An electron-transfer mechanism has been proposed for this dark decomposition route <74JA5557>. In contrast, univalent rhodium and iridium complexes react with dioxetanes by insertion of the metal into the peroxide bond and subsequent cleavage of the metallacycle releases the carboxyl fragments and the metal complex (Scheme 32) <77JA5334>.

1.33.5.3 Nucleophilic Attack at Ring Heteroatoms

Extensive studies have been made on the reaction of dioxetanes with nucleophiles <B-92M1 133-02>. Fragmentation, reduction, deoxygenation, and adduct formation were observed in such $\text{S}_{\text{N}}2$ type nucleophilic substitutions on dioxetanes.



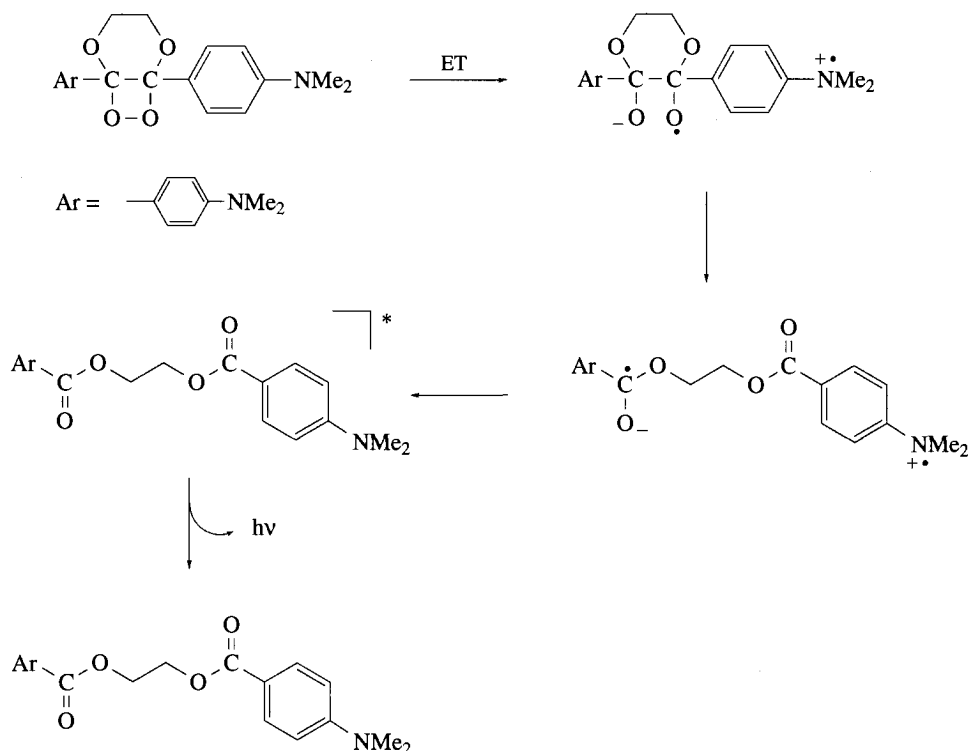
Scheme 31



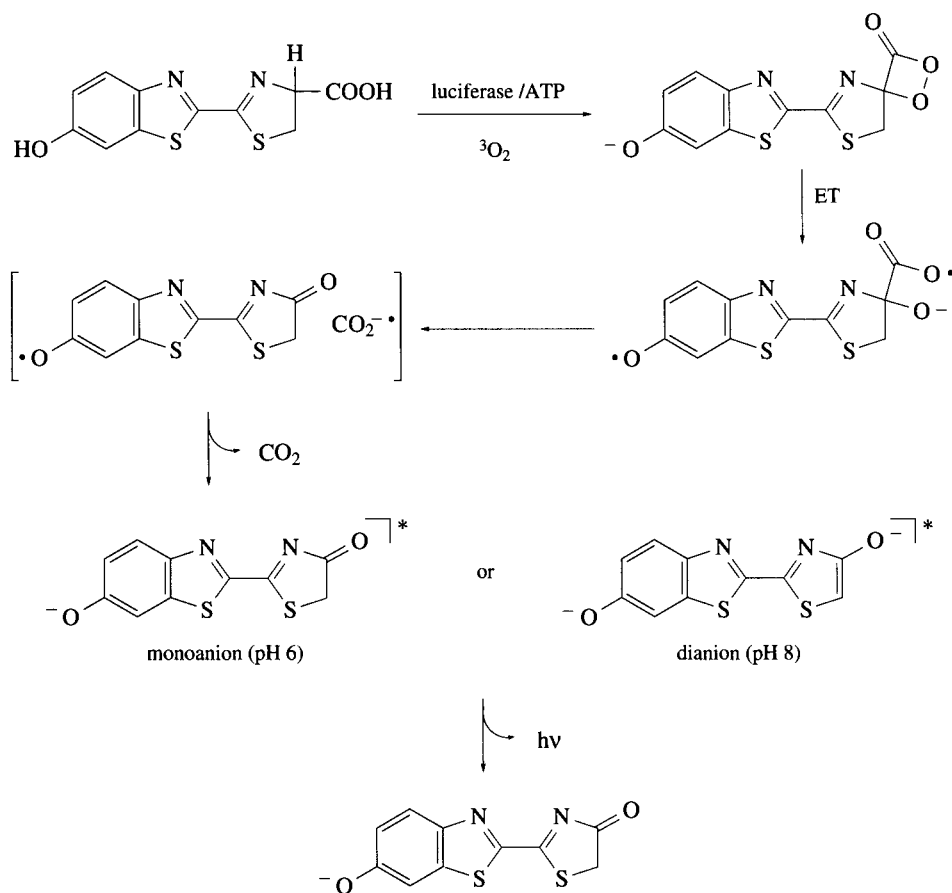
Scheme 32

Simple alkyl-substituted dioxetanes react with nucleophiles such as enol ethers, amines (B-73MI 133-01), and easily oxidized electron-rich arenes (79JA7097, 80JA5279) to undergo fragmentation into carbonyl products with or without light emission. Dioxetanones (α -peroxy lactones) also undergo chemiluminescent decomposition with electron-rich arenes such as rubrene (78JA2587). For these chemiluminescent decomposition reactions (B-73MI 133-01) an intermolecular electron-transfer mechanism operates (79JA7097).

Intramolecular electron transfer from an electron-donating substituent to the dioxetane moiety affords the corresponding carbonyl products (Scheme 33) with the emission of intensive chemiluminescence (79MI 133-02, 79MI 133-03). This phenomenon is known as chemically initiated electron exchange luminescence (CIEEL) (79ACR366) and is of general scope. The primordial case is that of the firefly shown in Scheme 34 (78PNA(75)30). The CIEEL decomposition of thermally stable dioxetanes by enzymatic triggering is the basis for the chemiluminescence immunoassay (B-92MI 133-01) (see Section 1.33.10), which is modeled after the bioluminescence of the firefly (B-88MI 133-03).

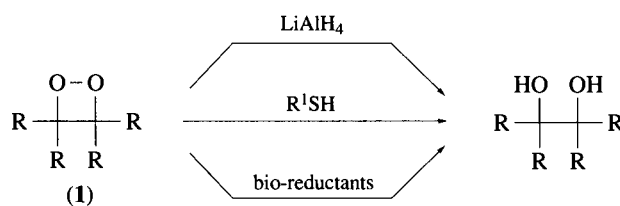


Scheme 33



Scheme 34

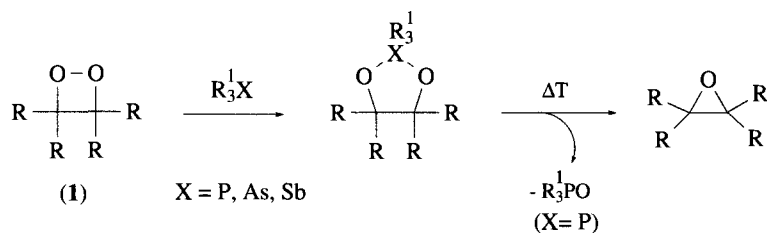
Dioxetanes are readily reduced to 1,2-diols (Scheme 35) by lithium aluminum hydride $\langle 75CJC1103 \rangle$, thiols $\langle 88AG(E)429 \rangle$, and biologically important reductants $\langle 89MI 133-02 \rangle$ such as ascorbic acid, tocopherol, dihydronicotinamide adenine dinucleotide (NADH), and riboflavin adenosine diphosphate (FADH₂). Thiols as well as the biological reductants also catalyze the dark decomposition of dioxetanes.



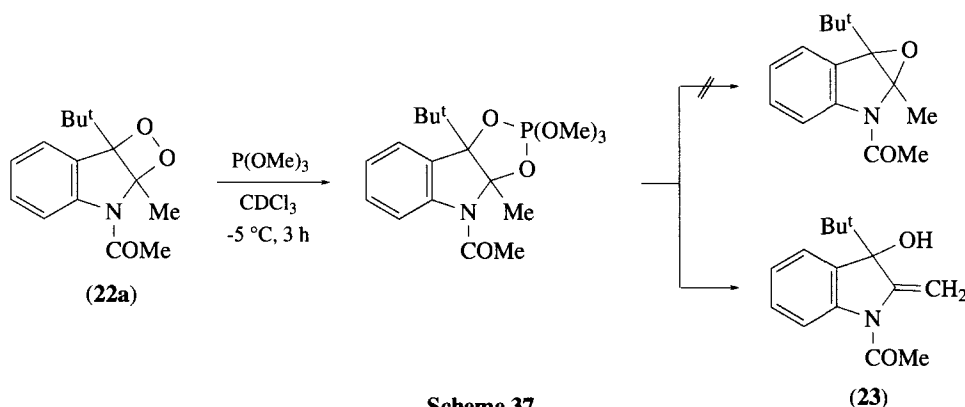
Scheme 35

One of the earliest reactions of dioxetanes with nucleophiles was their deoxygenation to the corresponding epoxides by phosphorus nucleophiles $\langle 73JA6486 \rangle$. The trivalent phosphines, phosphites or phosphinates first insert into the peroxide bond of the dioxetanes to afford a phosphorane intermediate, which in favorably persistent cases has been spectrally detected $\langle 74JA5267, 77JOC1661, 94TL6063 \rangle$. On warming, the phosphorane eliminates phosphine oxide to yield the epoxide (Scheme 36).

It has been reported $\langle 93JOC47 \rangle$ that the reaction of the indol dioxetane (**22a**) with trimethyl phosphite gave the indoline (**23**) instead of indol epoxide (Scheme 37). Presumably the labile indol epoxide $\langle 94JOC2733 \rangle$ served as precursor by ring opening.

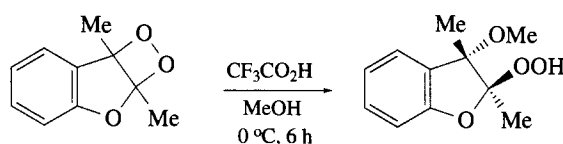


Scheme 36

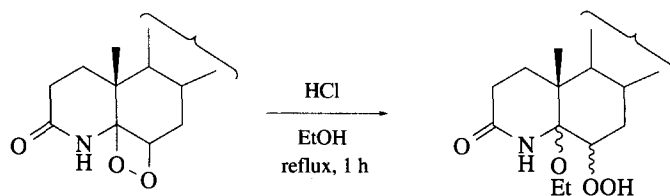


Scheme 37

Analogous to the trivalent phosphorus compounds, triphenylarsine and triphenylstibine undergo biphilic insertions with dioxetanes to form stable arsenic(V) and antimony(V) adducts (Scheme 36), which are sufficiently persistent for isolation [79JOC4251]. Divalent sulfur compounds also react with dioxetanes to afford the corresponding epoxides [75JA3850, 91AG(E)200, 91JA8005, 94JOC2733]. For dialkoxysulfides the intermediary sulfuranes were spectrally observed [75JA3850]. Protic nucleophiles, for example alcohols, react with α -heteroatom-substituted dioxetanes to form labile β -alkoxy hydroperoxides (Schemes 38 and 39) [75HCA2549, 91AG(E)200].



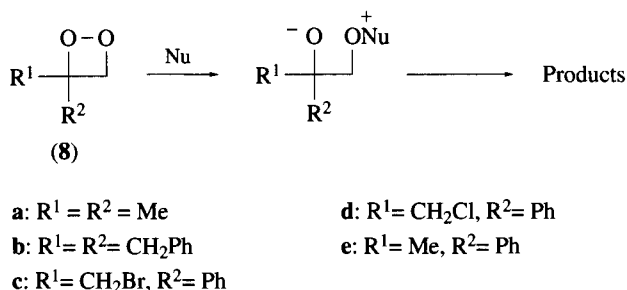
Scheme 38



Scheme 39

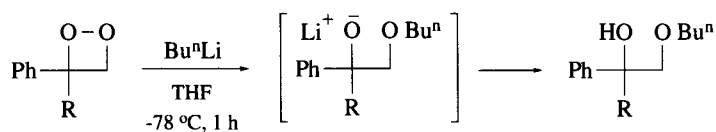
It has been demonstrated that 3,3-disubstituted dioxetanes (8) are much more reactive towards nucleophiles than the tri- or tetrasubstituted derivatives and they exhibit S_N2-type reactivity [B-92MI 133-01]. Carbanions [92CB235], diazoalkanes [94JOC840], alkylidenephosphoranes [94JA7581], and

π nucleophiles, for example electron-rich alkenes <91AG(E)1365> and enamines <92JOC2680>, as well as heteroatom nucleophiles <92JA5591>, all undergo nucleophilic substitution at the sterically more exposed site of the peroxide bond in the 3,3-disubstituted dioxetanes. A variety of products derived from the intermediary nucleophile-dioxetane adducts are obtained (Scheme 40).

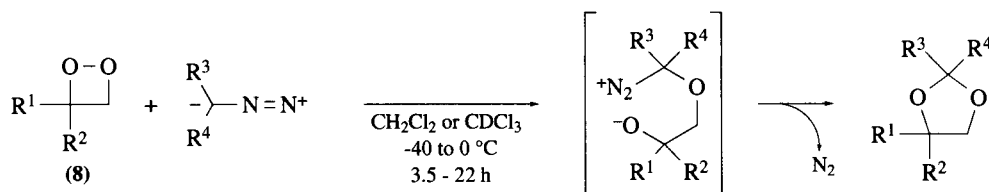


Scheme 40

The nucleophilic attack of carbanions, for example *n*-butyllithium, on the dioxetane peroxide bond leads to the β -hydroxy ether in Scheme 41 <92CB235>. On the other hand, the nucleophilic attack by the negatively charged carbon pole of the diazoalkane on the peroxide bond afforded the 1,3-dioxolane (Scheme 42) after cyclization with denitrogenation of the resulting O,N dipole (Scheme 42) <94JOC840>.

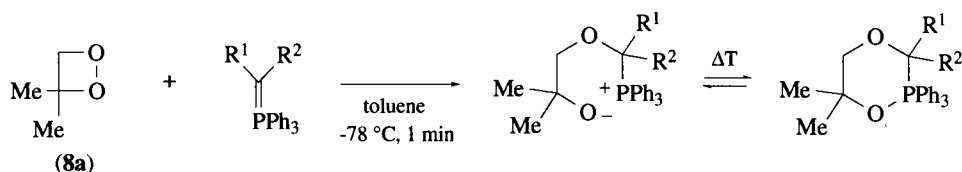


Scheme 41



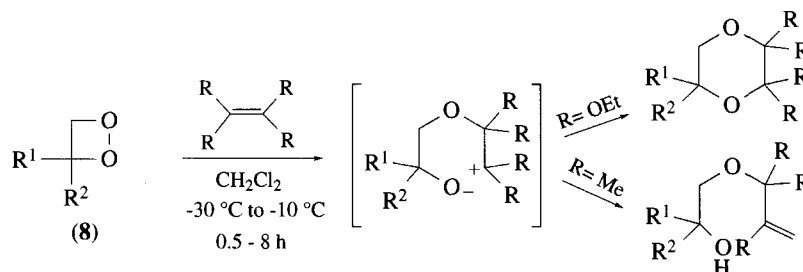
Scheme 42

The reaction of 3,3-dimethyl-1,2-dioxetane (**8a**) with triphenylalkylidenephosphoranes gave the dipolar phosphonium alkoxides. These are in equilibrium with the ring-closed 1,4-dioxaphosphorinanes (Scheme 43) <94JA7581>.

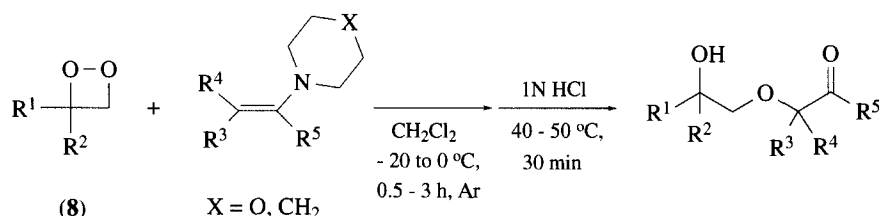


Scheme 43

The S_N2 attack of the alkenic π bond on the dioxetane peroxide linkage results in an intermediate dipolar ion (Scheme 44), which can form the 1,4-dioxane by ring closure or the β -hydroxy ether by intramolecular proton abstraction <91AG(E)1365>. Analogously, the reaction of 3,3-disubstituted dioxetanes (**8**) with enamines afforded β -hydroxy β' -keto ethers after hydrolysis of the intermediate adducts (Scheme 45) <92JOC2680>.



Scheme 44

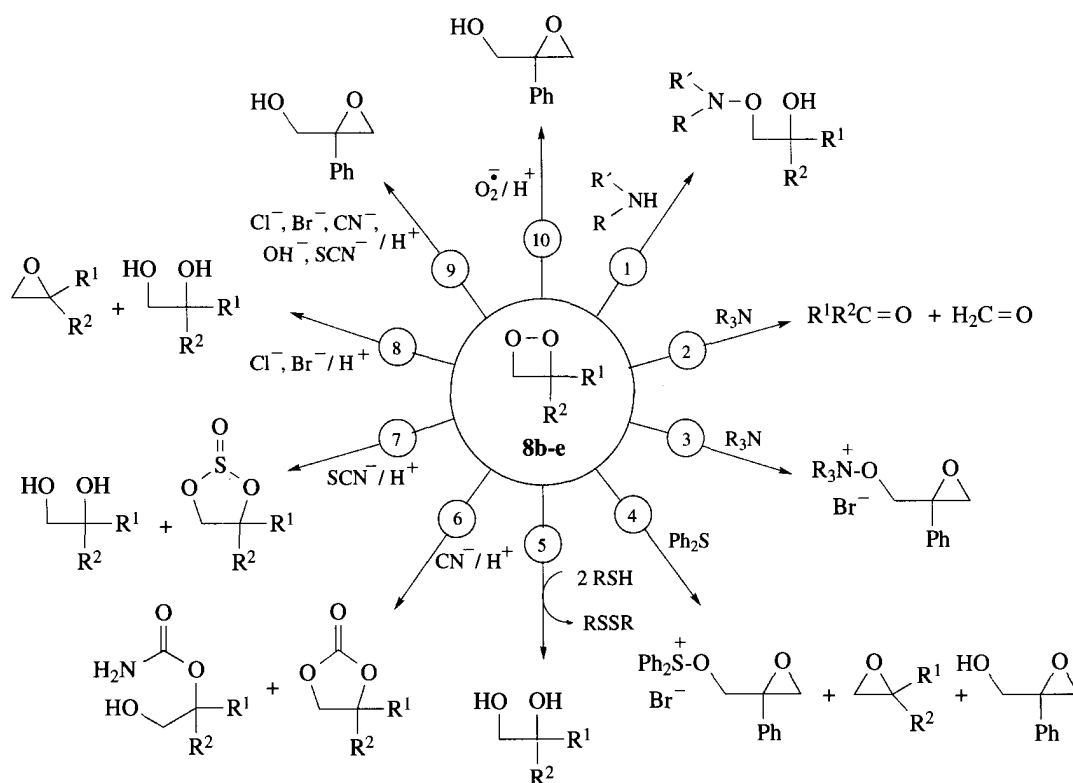


Scheme 45

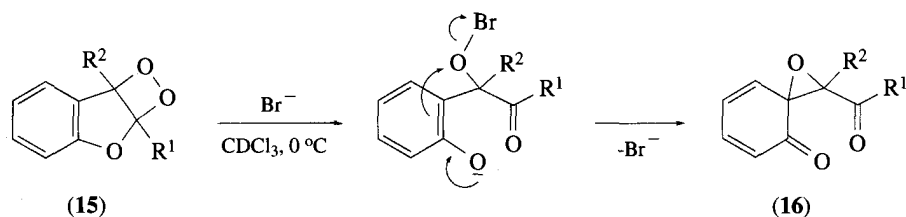
As already mentioned, the early reports on the transformation of dioxetanes with heteroatom nucleophiles such as phosphines <77JOC1661> and sulfides <75JA3850> were restricted to the tetrasubstituted dioxetanes, for which deoxygenation by these nucleophiles was observed. The S_N2 reactivity of dioxetanes has been established in the reaction of 3,3-disubstituted dioxetanes (**8b-e**) with a large number of heteroatom nucleophiles, which include secondary and tertiary amines, sulfur derivatives, and anions such as CN^- , SCN^- , X^- (Cl, Br), HO^- and the superoxide anion ($O_2^{\cdot-}$) <92JA5591>. The multitude of products in the reaction of these nucleophiles with the 3,3-disubstituted dioxetanes (**8b-e**) are presented in the rosette of Scheme 46.

While hydroxylamine derivatives were formed in the reaction of secondary amines (transformation 1 in Scheme 46), tertiary amines, for example triethylamine and DABCO, gave with dioxetanes (**8b,e**) exclusively cleavage products (transformation 2). On the other hand, with the same tertiary amines, the bromomethyl-substituted dioxetane (**8c**) afforded only alkoxyammonium epoxides (transformation 3). The same type of adduct, namely a labile alkoxy-sulfonium epoxide, was detected with diphenyl sulfide, besides the deoxygenation product of the dioxetane (**8c**) (transformation 4). Like tetrasubstituted dioxetanes <88AG(E)272>, the 3,3-disubstituted derivatives were reduced by thiols to 1,2-diol (transformation 5). In the reactions of the cyanide (transformation 6) and thiocyanate ions (transformation 7) with (**8c**), five-membered ring insertion products, namely carbonates and cyclic sulfites, were isolated. The halide ions Cl^- and Br^- (transformation 8) reduced the dioxetane (**8c**) to the corresponding 1,2-diol. Moreover, appreciable amounts of 2,3-epoxy-2-phenyl-1-propanol were obtained in the reactions of dioxetane (**8c**) with anionic nucleophiles (transformation 9). With HO^- and $O_2^{\cdot-}$, the epoxy alcohol was formed essentially exclusively (transformation 10).

While the 3,3-disubstituted dioxetanes (**8**) were reduced by Br^- to 1,2-diols (Scheme 46, transformation 8) as stated already, the benzofuran dioxetanes (**15**) rearranged to the spiroepoxide (**16**) under bromide ion catalysis (Scheme 47) <94JA6713>. For this unprecedented bromide ion-catalyzed rearrangement, an S_N2 attack of Br^- at the O-3 oxygen atom of the peroxide bond of benzofuran dioxetane was proposed <94JA6713>. The resulting hypobromite intermediate (Scheme 47) rearranges to the spiroepoxide (**16**) by opening of the furan ring and expulsion of the bromide ion through intramolecular nucleophilic attack of the phenolate ion on the O—Br bond (Scheme 47).



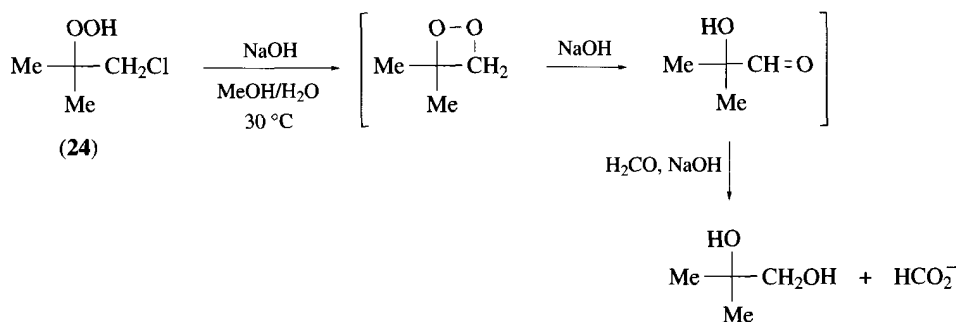
Scheme 46



Scheme 47

1.33.5.4 Base Attack at Hydrogen Attached to Carbon

Deprotonation at the dioxetane carbon atom by bases represents an unusual transformation in that the dioxetane C—C bond is conserved. Thus, amines ^{<75JA5028, 75TL1735>} and sodium hydroxide ^{<71JA3996>} convert such dioxetanes by the so-called Kornblum–De La Mare reaction ^{<51JA880>} into α -hydroxy carbonyl products. For example, the reaction of *t*-butyl- β -chlorohydroperoxide (**24**) with sodium hydroxide in aqueous methanol afforded the 2-methylpropane-1,2-diol (Scheme 48). This transformation was mechanistically rationalized in terms of deprotonation by sodium hydroxide of the intermediate dioxetane with concomitant O—O bond cleavage to form α -hydroxyisobutyraldehyde. The latter is converted into the 1,2-diol by a crossed-Cannizzaro reaction with formaldehyde, which is produced *in situ* by dioxetane cleavage. However, it has been confirmed ^{<92JA5591>} that nucleophilic attack of the hydroxide ion on the dioxetane peroxide bond is preferred over the Kornblum–De La Mare reaction, at least for 3,3-disubstituted dioxetanes (see transformation 9 in Scheme 46).



Scheme 48

1.33.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

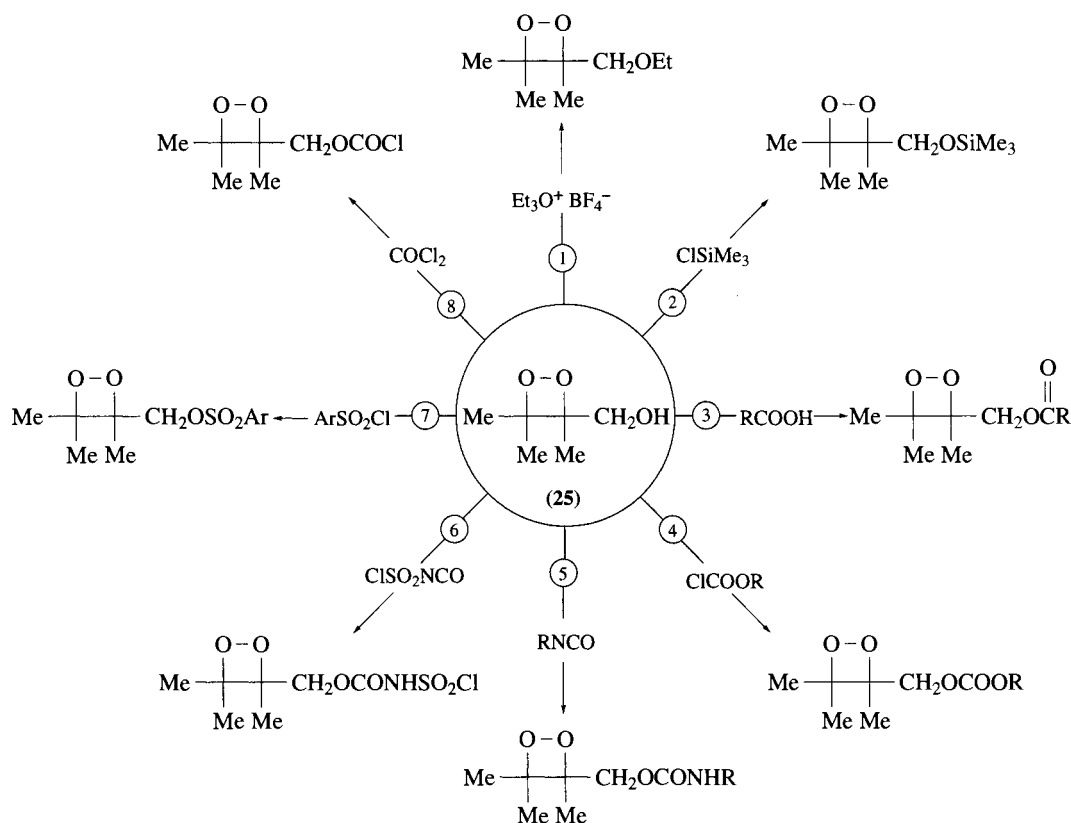
1.33.6.1 Reaction of Hydroxymethyl-substituted Dioxetanes

The hydroxymethyl-substituted dioxetanes, particularly the 3-hydroxymethyl-3,4,4-trimethyl-1,2-dioxetane or HTMD (**25**), can be transformed with a variety of electrophiles such as trialkyloxonium salts, trialkylsilyl chlorides, carboxylic acids, chloroformates, isocyanates, sulfonyl chlorides, and phosgene or its equivalent, as shown in the rosette of Scheme 49 <88HOU(E13)401>. Thus, the etherification of dioxetane (**25**) with triethyloxonium salt (Scheme 49, transformation 1) in dichloromethane at 20°C afforded the ethoxymethyl-substituted dioxetane in moderate yield <87JOC3059>, while the silylation of (**25**) with trimethylsilyl chloride in the presence of pyridine as base catalyst in diethyl ether at 0°C gave the silyl ether-functionalized dioxetane in high yield (transformation 2) <87JOC3059>. By means of a modified Mitsunobu procedure <81S1>, HTMD was esterified with carboxylic acids to the corresponding carboxylates (transformation 3) <84ZN(B)679, 87JOC3059>. Also the carbonate-functionalized dioxetanes may be obtained readily by the reaction of the corresponding chloroformates (transformation 4) with the dioxetane (**25**) <87JOC3059>. In the reaction of isocyanates (transformations 5 and 6), the corresponding carbonates were isolated in very good yields <86S330, 87JOC3059>. Sulfonate-functionalized dioxetanes were prepared by esterification of HTMD (transformation 7) with sulfonyl chloride in the presence of pyridine <84ZN(B)679>. The nucleophilic hydroxy functionality in the dioxetane (**25**) was converted into its chlorocarbonyl derivative (**26**) <86S330, 87CB1565> by means of phosgene (transformation 8). Derivative (**26**) was successfully utilized as vehicle for the functionalization of dioxetanes with nucleophilic biomolecules such as cholesterol, xanthotoxol, glycine, phenylalanine ester, and a dipeptide (Scheme 50).

The cholesterol-functionalized dioxetane (Scheme 50, transformation 1) was obtained in moderate yield by nucleophilic substitution of the electrophilic chlorocarbonyl dioxetane (**26**) with potassium alcoholate of cholesterol, which was prepared *in situ* from potassium hydride and cholesterol <87CB1565>. The reaction of 8-hydroxypsoralen (xanthotoxol) with dioxetane (**26**) in the presence of triethylamine in dichloromethane at 0°C (transformation 2) afforded the psoralen-functionalized dioxetane <87AG(E)796>, which is an efficient DNA-photobinding reagent in the dark <91MI 133-02>. The functionalization of glycine and ethyl phenylalanate with the electrophilic dioxetane (**26**) was achieved (transformations 3 and 4) by using aqueous NaOH as base and CH₂Cl₂/H₂O as biphasic medium <87CB1565>, while L-phenylalanyl-L-leucine was converted into the corresponding dipeptide-substituted dioxetane (Scheme 50, transformation 5) in good yield by the same method <87CB1565>.

1.33.6.2 Deprotonation of Hydroxyaryl-substituted Dioxetanes (CIEEL Triggering)

The thermal decomposition of dioxetanes leads preferentially to triplet-excited carbonyl compounds (see Section 1.33.5.1). In contrast, with electron-donor substituents, dioxetanes display chemically initiated electron exchange luminescence (CIEEL) <79ACR366, B-82MI 133-05>. This is akin to the electron-transfer mechanism observed first for the diphenoyl peroxide <77JA6107>, in which singlet-excited species play the major role. Thermally persistent aryl ether- or ester-substituted dioxetanes undergo rapid CIEEL decomposition <86USP889823> by chemical or enzymatic deprotonation of the hydroxyaryl group.



Scheme 49

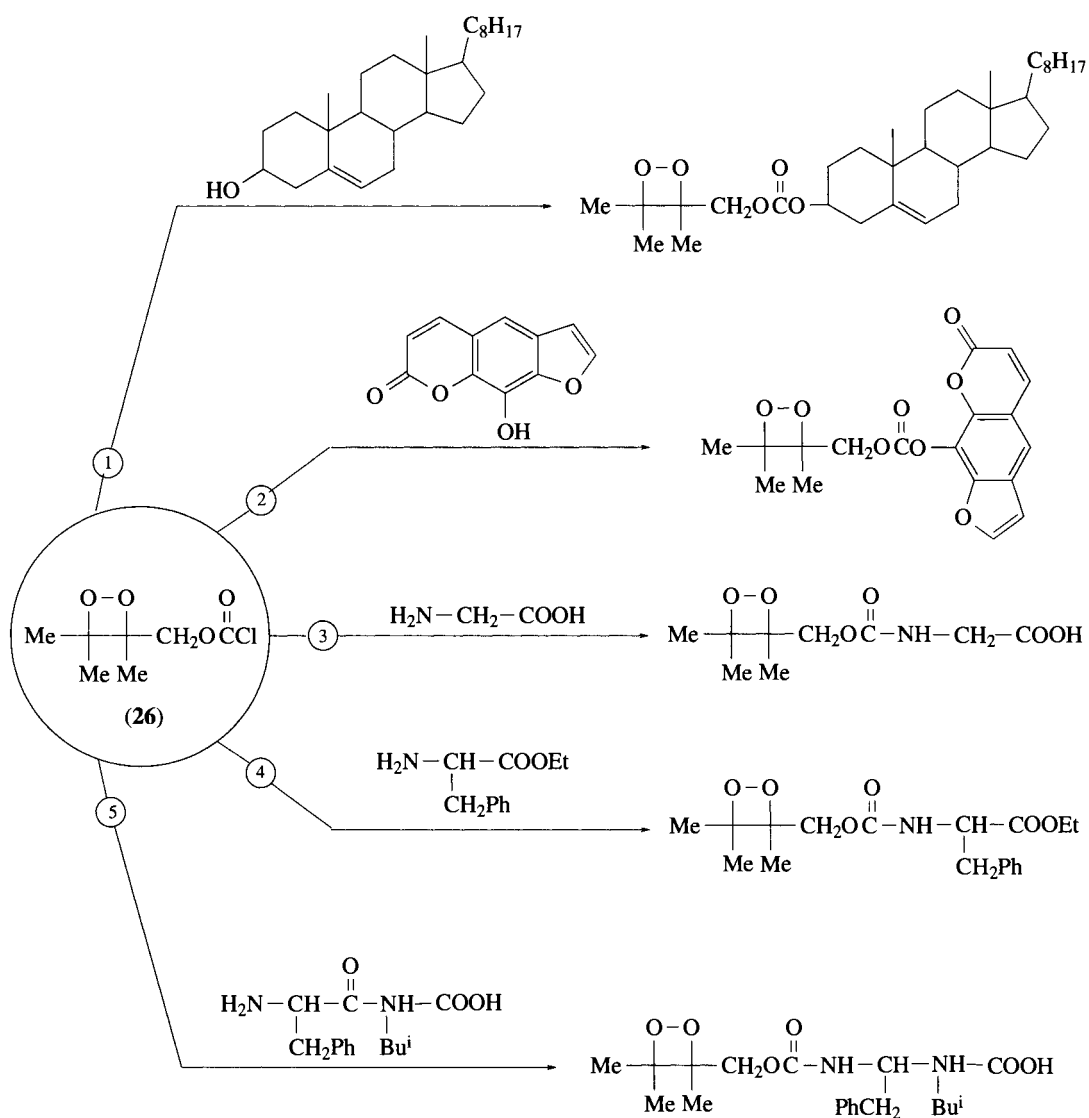
The deprotonation of the thermally stable ($t_{1/2} = 17$ y at -30°C) phenol-substituted dioxetane (**27a**) by means of the bulky base $(\text{TMS})_2\text{MeCONa}$ released the phenoxide-substituted dioxetane (**27b**) (see Scheme 51) which decomposed 4.4×10^6 times faster than the protonated form $\langle 82\text{JA}3504 \rangle$ with a flash of bluish luminescence. Furthermore, the thermally very stable silyloxyaryl-functionalized spiroadamantyl dioxetane (**28a**) was deprotected by fluoride ion to the unstable, chemiluminescent aryloxide-substituted dioxetane (**28c**), as shown in Scheme 52. Rapid CIEEL decomposition with high chemiluminescence quantum yields ensued $\langle 87\text{TL}1155 \rangle$. The enzymatic triggering (Scheme 53) of the phosphoryloxy-substituted dioxetane (**28b**) with alkaline phosphatase released also the CIEEL-active phenolate-substituted dioxetane (**28c**) $\langle 89\text{MI} 133-03 \rangle$. The enzymatically triggerable CIEEL-active dioxetanes are a valuable tool in biomedical analyses, particularly in chemiluminescence immunoassay (see Section 1.33.10).

A new type of CIEEL-active dioxetanes, namely the phenyl-substituted benzofuran dioxetanes (**15b-c**), has been introduced $\langle 92\text{CB}2455, 93\text{T}2227 \rangle$, which undergoes base- or fluoride ion-triggered decomposition with light emission (Scheme 54). However, their chemiluminescence efficiency is much inferior to that of the phenyl-substituted spiroadamantyl dioxetanes (**28a,b**).

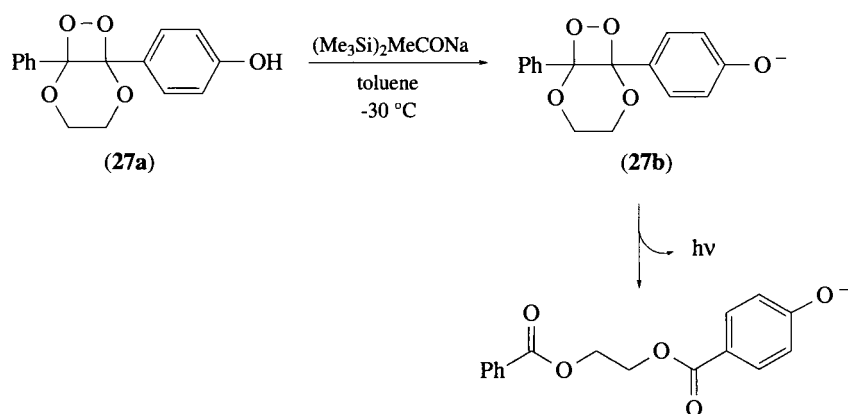
1.33.6.3 Deprotection of *N*-Acylamino-substituted Dioxetanes

As mentioned in Section 1.33.7.1.2, relatively persistent *N*-acylated indole dioxetanes are accessible by photooxygenation of the corresponding indol. Indol dioxetanes (**22b-c**) with chemically triggerable functionalities were prepared (Scheme 55) and their CIEEL activity was determined $\langle 94\text{JCS(P}2)1503 \rangle$. The deprotection of the silyl-substituted indol dioxetane (**22c**) with fluoride ion sets free the corresponding indolyl anion (Scheme 56), which decomposes rapidly by the CIEEL mechanism and the desired flash of light $\langle 94\text{JCS(P}2)1503 \rangle$.

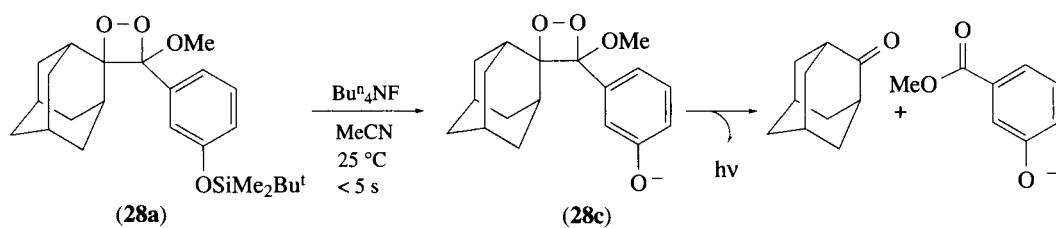
In early reports $\langle 64\text{TL}657, 66\text{TL}5169 \rangle$, the intermediacy of dioxetanimine anion (Scheme 57) has



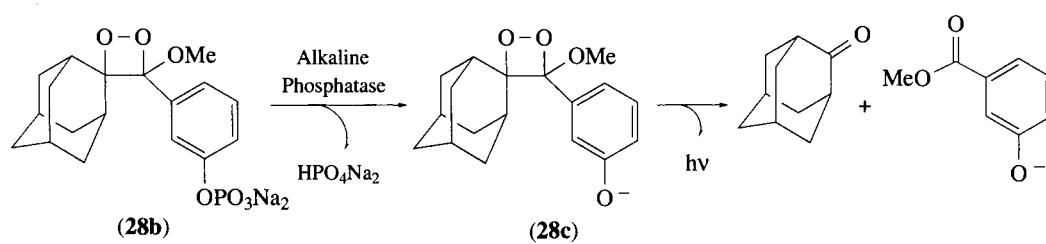
Scheme 50



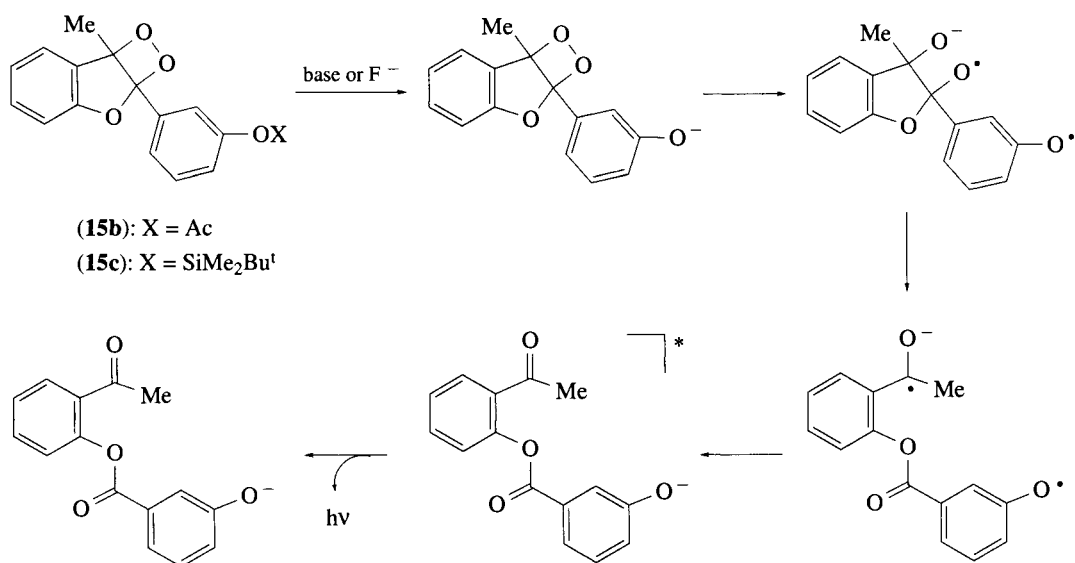
Scheme 51



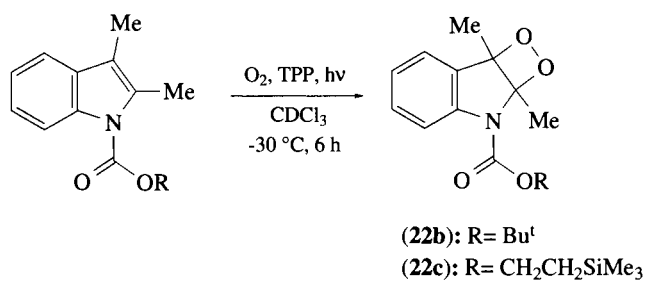
Scheme 52



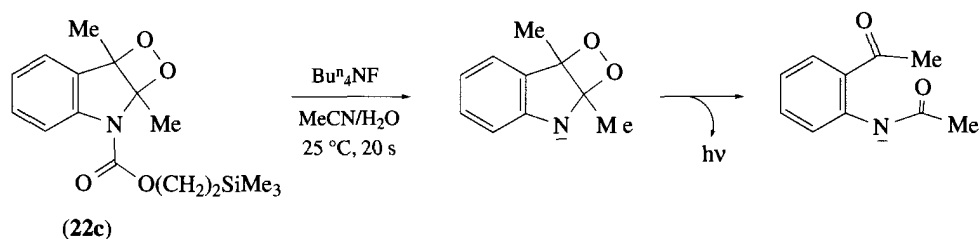
Scheme 53



Scheme 54

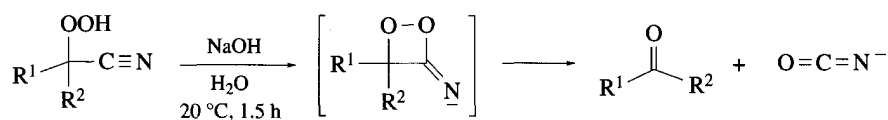


Scheme 55

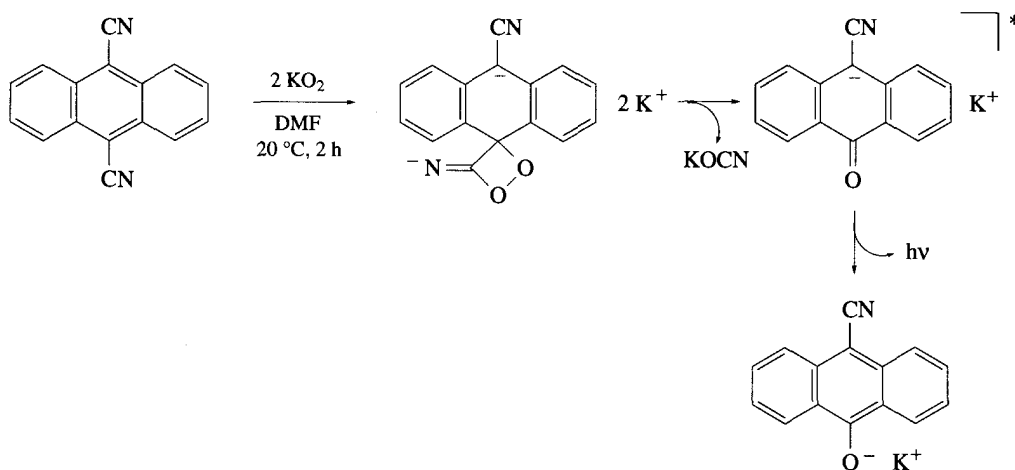


Scheme 56

been postulated in the base-catalyzed chemiluminescent decomposition of α -cyano hydroperoxides (Scheme 57). Evidence has been provided ^[93JA11716] for the dioxetanimine dianion intermediate (Scheme 58) in the chemiluminescent reaction of 9,10-dicyanoanthracene with potassium superoxide.



Scheme 57



Scheme 58

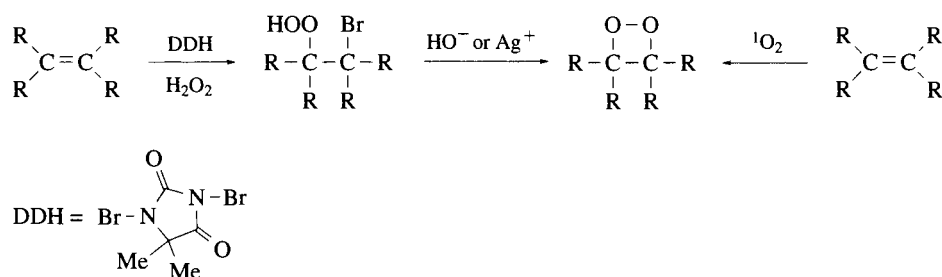
1.33.7 SYNTHESIS OF FOUR-MEMBERED RING HETEROCYCLES WITH TWO OXYGEN ATOMS

1.33.7.1 Dioxetanes

Since dioxetanes are thermally labile compounds and prone to respond to redox chemistry, the methods for the preparation of dioxetanes are rather limited. Only the β -halo hydroperoxide cyclization (Kopecky method) ^[75CJC1103] and singlet oxygen ($^1\text{O}_2$) cycloaddition to electron-rich alkenes have general applicability for the synthesis of these labile four-membered ring cyclic peroxides (Scheme 59).

1.33.7.1.1 The Kopecky method

The dehydrohalogenation of β -halo hydroperoxides to the dioxetanes by means of a base or silver ion is known as the Kopecky method ^[75CJC1103], which is given in general terms in Scheme 59.



Scheme 59

β -Bromo hydroperoxides are normally used in this reaction, but in some cases the β -chloro and β -iodo hydroperoxides are also employed. The β -bromo hydroperoxides are usually prepared by bromination of suitable alkenes with 1,3-dibromo-5,5-dimethylhydantoin (DDH) in the presence of conc. (ca. 85%) hydrogen peroxide. The Kopecky method has been used for the preparation of numerous dioxetanes. In previous reviews <B-82MI 133-03, B-85MI 133-02, B-88MI 133-01, B-92MI 133-02> the more typical derivatives are listed. Some representative derivatives are featured in Table 3.

Table 3 1,2-Dioxetanes prepared by dehydrohalogenation of β -halo hydroperoxide.

				Yield (%)	<i>m.p.</i> (°C)	Ref.
<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴			
Me	Me	Me	Me	30	76–77	75CJC1103
Me	Me	Me	H	ca. 30	5–7	75CJC1103
Me	Me	H	H	26	6	73JA7050
Me	H	Me	H	27	^a	73JA7050
Me	H	H	Me	39	^a	75JA3850
Me	H	H	H	3	^b	85JA410
H	H	H	H	ca. 1	^b	85JA410
Bz	Bz	H	H	38	60–61	74JA7525
Ph	Ph	H	H	21	^b	74JA7525
				12.5	–11	80JA3644
				11	ca. 20	81CJC851

^aLiquid. ^bIsolated as a solution in the stated organic solvent.

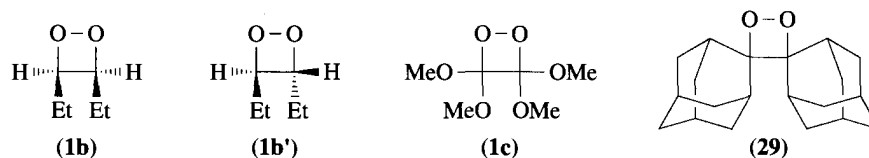
The primary and secondary β -bromo hydroperoxides can be cyclized to the dioxetanes by base (HO^- , RO^-), while for the tertiary bromides silver oxide, acetate, and particularly succinimide work better <B-92MI 133-02>. The silver salts must be freshly prepared because the metallic silver, formed through light exposure, catalyzes decomposition of the dioxetane.

The cyclization reactions must be carried out at low temperatures (-30 to 10°C), but in the case of the thermally more stable dioxetanes, temperatures up to 30°C can be tolerated. In the silver ion-promoted cyclizations, solvents such as alkanes (pentane, hexane, cyclohexane) and haloalkanes (carbon tetrachloride, methylene chloride, dichlorodifluoromethane) are advantageous. In the reactions with base, protic solvents (water and/or methanol, ethanol) are employed; however, two-phase solvent systems such as aqueous methanol and pentane are also useful. Under the latter conditions the base-catalyzed decomposition of the dioxetane can be suppressed.

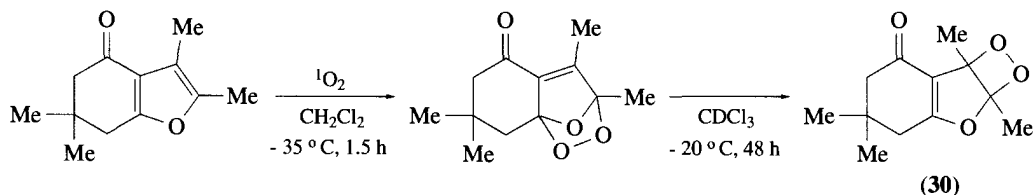
1.33.7.1.2 Singlet oxygen cycloaddition

The $[2 + 2]$ cycloaddition of singlet oxygen (${}^1\text{O}_2$) with electron-rich alkenes is the most convenient and versatile method for the preparation of dioxetanes. Shortly after the successful synthesis of the

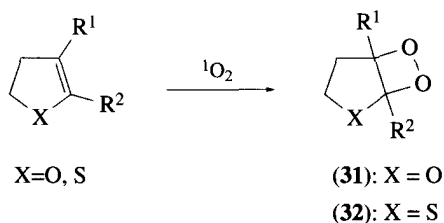
first stable dioxetane by Kopecky <69CJC709> in 1969, the preparation of dioxetanes **(1b)**, **(1b')** <70JA3223>, **(1c)** <70JA3225>, and **(29)** <72TL169> by the $^1\text{O}_2$ route was reported. Since that time a large number of dioxetanes, which are not accessible by the Kopecky method, were synthesized by $^1\text{O}_2$ cycloaddition. Selective examples are given in Table 4.



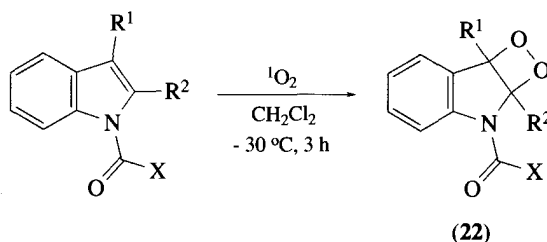
Although the reactions of $^1\text{O}_2$ with furans, which lead to thermally labile furan endoperoxides, have been known for a long time <60JA2086, 70CR(C)461> and their chemistry has been studied intensively <85T2057, 91CC1061, 92JCS(P1)1855>, the first isolable furan dioxetane **(30)** was synthesized only in 1993 <93AG(E)80> by the $^1\text{O}_2$ route (Scheme 60). In contrast, dihydrofuran **(31)** <91JOC4017> and dihydrothiophene dioxetanes **(32)** <91JOC4027> are easily accessible by [2 + 2] cycloaddition of $^1\text{O}_2$ with the corresponding dihydro compounds (Scheme 61). Similarly, stable indol dioxetanes **(22)** (see Scheme 62) have been made available from *N*-acylated indols <93JOC47, 93JOC5524, 94JCS(P2)1503, 94JOC2733>.



Scheme 60



Scheme 61

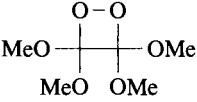
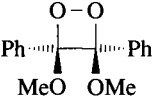
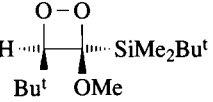
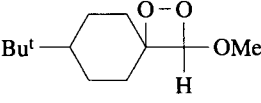
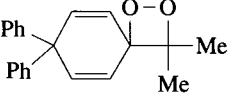
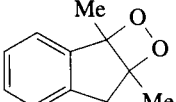
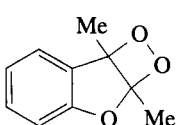
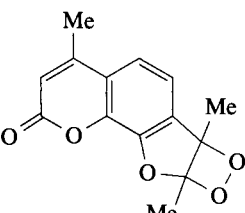
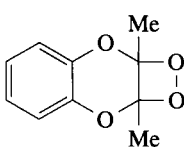
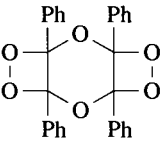
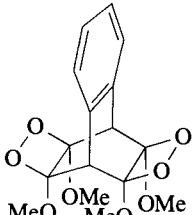


Scheme 62

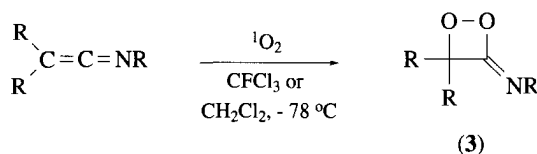
Not only electron-rich alkenes but also cumulenes, for example ketene imines, can be converted to the persistent dioxetanimes **(3)** by singlet oxygen (Scheme 63) <79AG(E)788, 79JA7105, 80CC898>. In contrast to the extensively investigated dioxetanes and dioxetanones <B-92MI 133-02>, the closely related isoelectronic dioxetanimes **(3)** have received little attention <93JA11716>.

Singlet oxygen can be generated either by photosensitization of triplet dioxygen or chemically. The former method is the more common and convenient procedure. The sensitizer-solvent systems which are frequently used are: tetraphenylporphyrin (TPP) in dichloromethane, Rose Bengal in methanol, polymer-bound Rose Bengal (Sensitox) <75JA3741> in acetone, and methylene blue in methanol. Of these alternatives, the TPP/ CH_2Cl_2 combination is the cleanest because type I photo-oxygenation <91MI 133-03> is minimized.

Table 4 1,2-Dioxetanes prepared by $^1\text{O}_2$ cycloaddition.

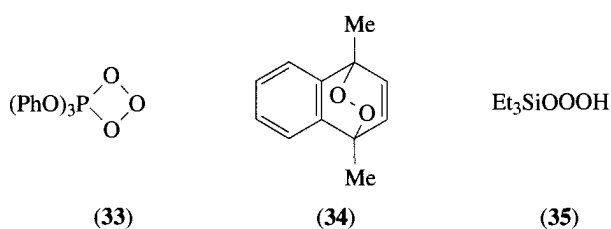
Dioxetane	Yield (%)	m.p. ($^{\circ}\text{C}$)	Ref.
	94	^a	76JA1086
	80	67–68	72BSF822
	97	^a	B-92MI 133-02
	60	^b	80JA3644
	82	72–74	76JA5574
	39	40–41	86TL6153, B-92MI 133-02
	53	53–54	91LA33
	44	100–101	90LA1227
	33	118–122	81AG(E)1031
	22	111	79JA4735
	48	130–132	94T9009

^aLiquid. ^bIsolated as solution in the stated solvent.



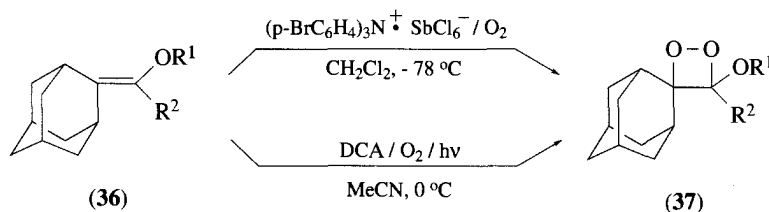
Scheme 63

Excellent chemical sources of $^1\text{O}_2$ are triphenylphosphite ozonide (**33**) <69JA5358> and the 1,4-dimethylnaphthalene endoperoxide (**34**) <72CC253>. Triethylsilyl hydrotrioxide (**35**) has been introduced as an $^1\text{O}_2$ source <86JA2472>. Interestingly, like triphenylphosphite ozonide, the hydrotrioxide also reacts directly with alkenes to give dioxetanes <89JOC3252, 91TL4235>.



1.33.7.1.3 Other methods

Besides the Kopecky method and the $^1\text{O}_2$ route, diverse other preparations of dioxetanes have been reported. The single electron transfer (SET) process has been successfully employed for the preparation of thermally stable dioxetanes <87TL5319, 91TL117, 92T7321>. Thus, the reaction of alkyl- or aryloxymethylideneadamantanes (**36**) in oxygen-saturated dichloromethane with catalytic amounts of one-electron oxidizing agents such as tris-*p*-bromophenyl ammoniumyl hexachloroantimonates at -78°C afforded the spirodioxetanes (**37**) almost quantitatively (Scheme 64) <87TL5319, 92T7321>. A radical cation chain oxidation mechanism has been postulated for this reaction <87TL5319>. The spirodioxetanes (**37**) can also be prepared (Scheme 64) by 9,10-dicyanoanthracene (DCA)-sensitized electron-transfer photooxygenation <89TL485>.

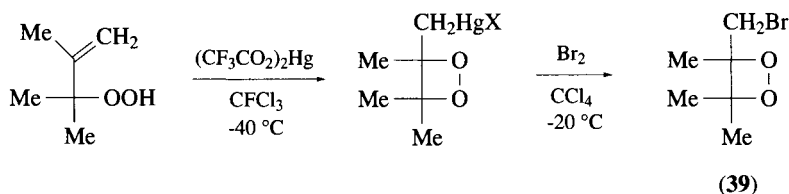
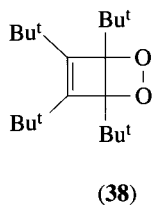


Scheme 64

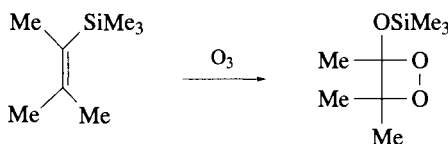
Triplet dioxygen also reacts with sterically hindered tetrasubstituted alkenes, for example bisadamantylidene, in the presence of one-electron oxidants to give the corresponding dioxetanes <81JA2096>. Autoxidation of isolable cyclobutadienes leads in excellent yields to the persistent dioxetanes (**38**) <80AG(E)211>, (**17'**) <80TL3171>, and (**21**) <88AG(E)272>.

Bromomethyl-substituted dioxetanes (**39**) were obtained in acceptable yields by intramolecular peroxymercuration of allylic hydroperoxides <78JA3935> with mercury(II) trifluoroacetate and subsequent reaction with molecular bromine at low temperature (Scheme 65). This halogen-functionalized dioxetane is not accessible either by the Kopecky method or the $^1\text{O}_2$ cycloaddition.

The ozonolysis of vinyl silanes (Scheme 66) affords dioxetanes as well <78JA294>. This potentially useful method has <90TL1799> been employed in the synthesis of *Qinghaosu* analogues, the naturally occurring antimalaria agent.



Scheme 65

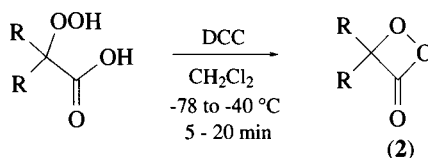


Scheme 66

1.33.7.2 Dioxetanones (α -Peroxy Lactones)

1.33.7.2.1 Cyclization of α -hydroperoxy acids

The cyclization of α -hydroperoxy acids (Scheme 67) by means of the mild dehydration agent dicyclohexylcarbodiimide (DCC) constitutes a general method for the synthesis of dioxetanones, which are also known as α -peroxy lactones (**2**) <72JA2894, 77JA5768>. The α -peroxy lactones which were synthesized by this route are featured in Table 5.



Scheme 67

1.33.7.2.2 Singlet oxygen cycloaddition

The [2 + 2] cycloaddition of $^1\text{O}_2$ (generated chemically) with ketenes (Scheme 68) is the most direct method for the preparation of dioxetanones. A few dioxetanones were prepared by this method <77JA5836> (Table 5). Apparently, ene reaction and [4 + 2] cycloaddition are not serious side reactions since ketenes which bear allylic hydrogen atoms and/or aryl substituents afford the desired α -peroxy lactones in fair yields.

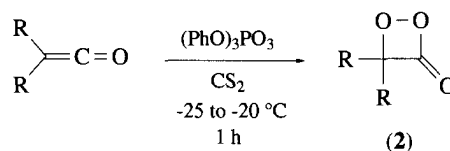
1.33.8 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

1.33.8.1 Transformation of Epoxy Hydroperoxides to Hydroxymethyl-substituted Dioxetanes

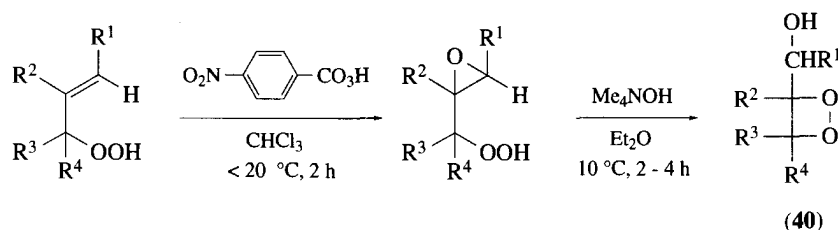
As already mentioned (Section 1.33.7), only two general methods with considerable scope are available for the synthesis of dioxetanes. Besides these synthetic routes, some other preparations

Table 5 Dioxetanones (α -peroxy lactones) prepared by carbodiimide cyclization of α -hydroperoxy acids or photooxygenation of ketenes.

$\begin{array}{c} \text{O}-\text{O} \\ \quad \\ \text{R}^1-\text{C}-\text{C} \\ \quad \\ \text{R}^2 \quad \text{O} \end{array}$		Method ^a	Yield (%)	m.p. (°C)	Ref.
R ¹	R ²				
Me	Me	A	68	10	77JA5768
		B	40		
CF ₃	CF ₃	B		^b	77JA5836
Bu ^t	H	A,B	50	2	77JA5836
Pr ⁿ	Me	B	20	^b	77JA5836
Bu ^t	Bu ^t	A	35	5	77JA5768
Ph	Bu ⁿ	B	14	^b	80JA5058
Ph	Ph	B	10	^b	80JA5058

^aMethod A, dehydration of α -hydroperoxy acids; method B, photooxygenation of ketenes.^bNot isolated.**Scheme 68**

of dioxetanes have been reported, which are the methods of choice, particularly for the synthesis of substituted dioxetanes. For example, the hydroxymethyl-substituted dioxetanes (**40**) can be synthesized <82S778, 87JOC3059> in good yields by base-catalyzed ring closure of the epoxy hydroperoxides (Scheme 69). The latter are easily accessible by peracid epoxidation of the corresponding allylic hydroperoxides (Scheme 69) <82S778>, which in turn are ene products in the photooxygenation of alkenes. Another example for the synthesis of dioxetanes by ring transformation was reported <78JA6649> for 3-acetyl-substituted dioxetanes, which is of limited scope. Nonetheless, the hydroxymethyl-substituted dioxetanes, which serve as versatile substrates for the preparation of functionalized dioxetanes (see Section 1.33.6.1) of photobiological interest, can only be prepared by this ring transformation method.

**Scheme 69**

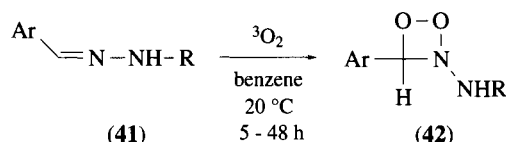
1.33.9 SYNTHESIS OF PARTICULAR CLASS OF COMPOUNDS

1.33.9.1 Synthesis of Heterodioxetanes

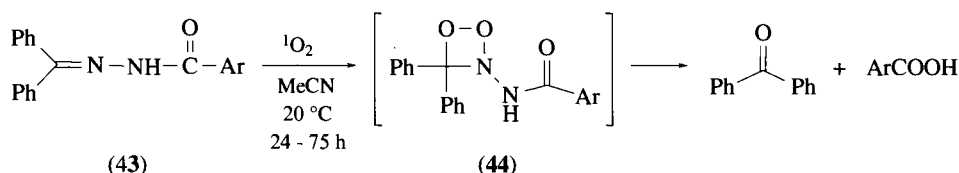
Four-membered rings which contain two adjacent oxygen atoms and one or two other heteroatoms, for example N, P, S, Si, or Ge, are designated as heterodioxetanes. Although, dioxetanes have been studied extensively since the mid-1970s <B-92MI 133-02>, the chemistry of dioxetanes with heteroatoms constitutes a little investigated area.

In earlier reports <14CB3277, 27JPR216> it was mentioned that autoxidation of hydrazones (**41**) (see

Scheme 70) leads to peroxidic compounds, which were tentatively assigned as nitrogen-containing heterodioxetanes (**42**). However, neither spectral nor chemical evidence have been provided in support of the dioxetane structure. It has been reported $\langle 93\text{JCR}(\text{S})278 \rangle$ that benzophenone arroylhydrazones (**43**) were oxidatively cleaved on photooxygenation to benzophenone and the substituted benzoic acids through the intermediary heterodioxetane (**44**), as shown in Scheme 71. It was postulated that the benzoic acids were formed from the intermediary *N*-nitroso amides, the cleavage products of the dioxetanes (**44**).

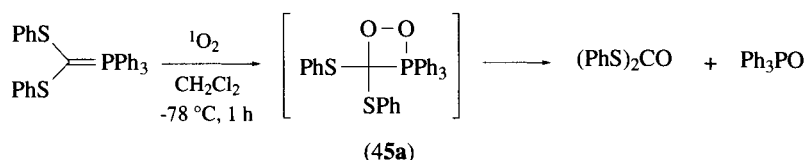


Scheme 70

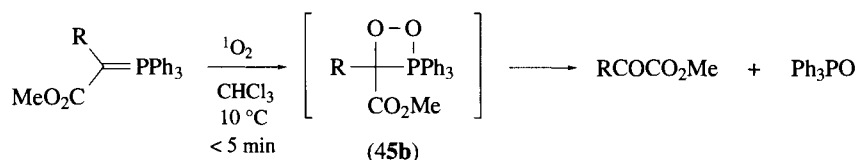


Scheme 71

Four-membered ring peroxides with one phosphorus atom (**45a,b**) were postulated $\langle 72\text{JA}1206, 77\text{TL}4531 \rangle$ as intermediates in the singlet oxygen reaction of phosphonium ylides (Schemes 72 and 73). On the other hand, the photooxygenation of the phosphazines (**46**) gave the corresponding 3-phospha-1,2-dioxo-4,5-diazines (**47**), which decomposed thermally with light emission $\langle 80\text{TL}2313 \rangle$; the phospho-1,2-dioxetane (**48**) was proposed as chemiluminescent intermediate (Scheme 74). Indeed, direct evidence was provided $\langle 85\text{JA}5539 \rangle$ for the formation of phospho-1,2-dioxetane (**48a**) in the photooxygenation of triphenylphosphazine (**46a**) by high-field ^{31}P NMR analysis (Scheme 75). The heterodioxetane with two phosphorus atoms (**49**) was proposed in the singlet oxygen reaction of the corresponding diphosphene (Scheme 76), which persists for several days at -78°C $\langle 87\text{PS}(30)425 \rangle$.

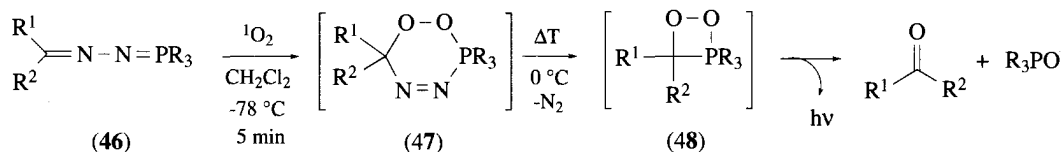


Scheme 72

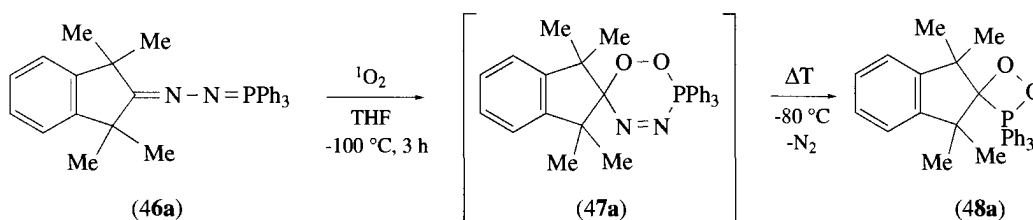


Scheme 73

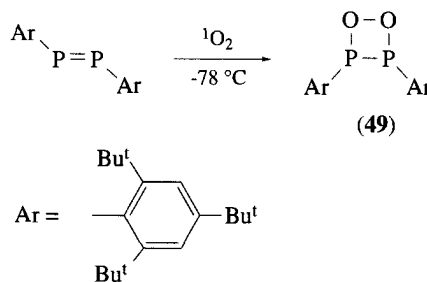
The intermediacy of sulfur-containing heterodioxetanes (**50**), which are also named 1,2,3-dioxathietanes, has been postulated $\langle 82\text{BCJ}3351, 82\text{JOC}3550, 83\text{JOC}214 \rangle$ in the photooxygenation of thioketones (Scheme 77). Theoretical calculations also suggest that the reaction of a thioketone with singlet oxygen proceeds through the 1,2,3-dioxathietane (**50**) intermediate $\langle 80\text{JCS}(\text{P}2)188 \rangle$. The photooxygenation reactions of sulfoxes $\langle 70\text{TL}4683 \rangle$, *O*-alkyl thioesters $\langle 79\text{TL}4635 \rangle$, and sulfur ylides $\langle 79\text{MI}133-04 \rangle$ were also claimed to proceed through similar heterodioxetane intermediates. However, no



Scheme 74

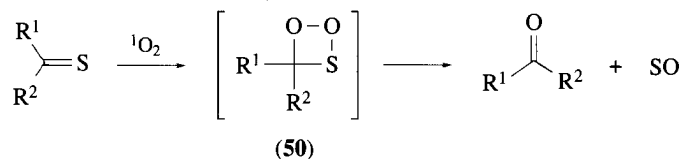


Scheme 75



Scheme 76

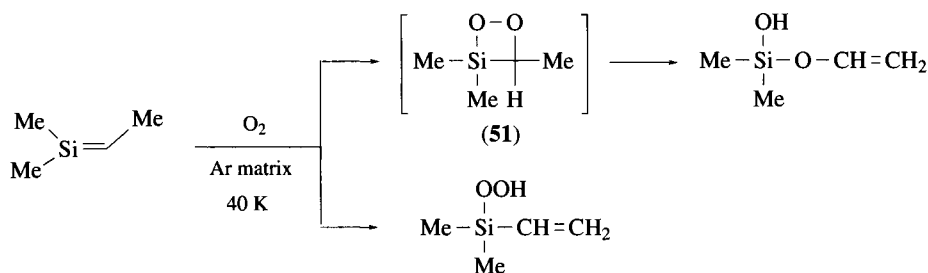
direct chemical or spectral evidence exists for the intermediary dioxathietane (50) in the photo-oxygenation of these sulfur compounds.



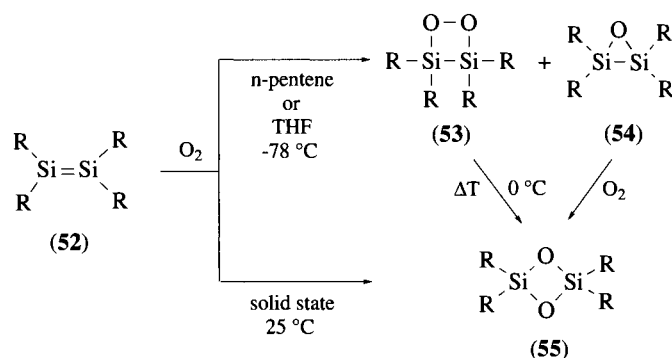
Scheme 77

Four-membered ring peroxide with one silicon atom (51) was postulated <92CB2813> as intermediate in the oxidation of trimethylsilene by molecular oxygen in an argon matrix (Scheme 78). On the other hand, the oxidation of disilenes has been studied extensively <91AG(E)902> and its high reactivity towards dioxygen has been established. Thus, disilenes (52) react with molecular oxygen in organic solvents such as pentane or tetrahydrofuran to give the 1,2-disiladioxetane (53) and the disilaoxirane (54) (Scheme 79) <84CC1525, 89PS(41)3>. The heterodioxetanes (53) rearrange readily to the 1,3-cyclodisiloxanes (55), which are also produced from the silaoxiranes (54) by further oxidation. In contrast, the oxidation of disilenes in the solid state <91AG(E)902> lead directly to 1,3-cyclodisiloxanes (55) (Scheme 79). However, tetrakis (2,4,6-triisopropylphenyl)disilene (52a) reacts with molecular oxygen to give the rearrangement product (56) (see Scheme 80) presumably through the intermediary disiladioxetane (53a) <88CL1343>.

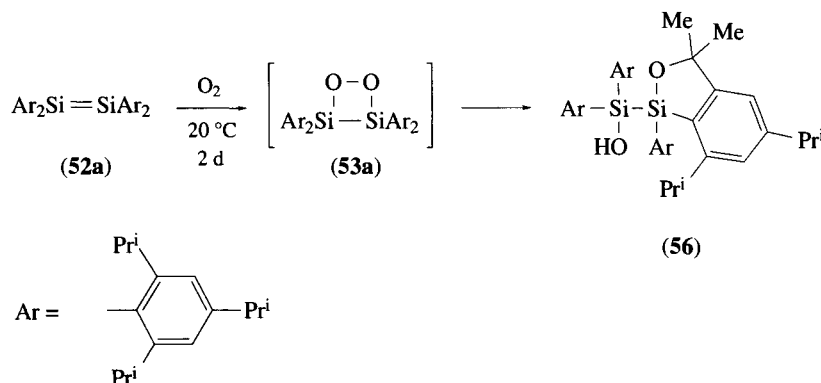
Like the disilenes (52), the digermanes (57) also react with dioxygen to afford the corresponding 1,2-digermadioxetanes (58), which are persistent at room temperature (Scheme 81) <89JA1888>. On thermolysis, the heterodioxetanes (58) led to the rearranged products (59), while photolysis <89JA1888> gave the 1,3-cyclodigermoxanes (60).



Scheme 78



Scheme 79



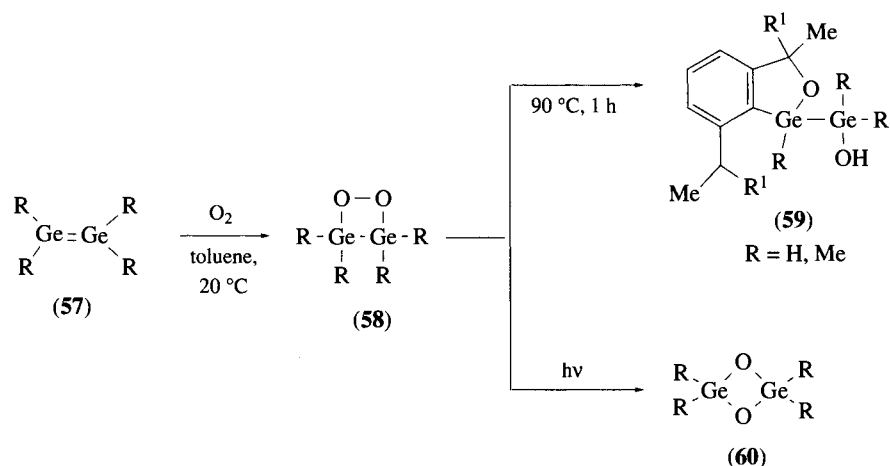
Scheme 80

1.33.10 IMPORTANT COMPOUNDS AND APPLICATIONS

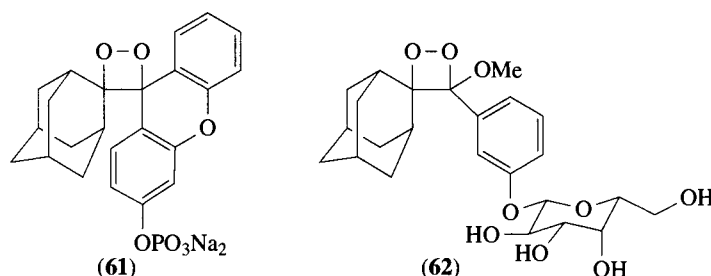
1.33.10.1 Application of Spiroadamantyl Dioxetanes for Bioanalysis: The Chemiluminescence Immunoassay

Intensive research work has been invested to develop bioanalytical methods by employing CIEEL-active dioxetanes (90ANC2258, B-92MI 133-01). The enzymatically triggerable and thermally persistent chemiluminescent dioxetanes (28b), (61), and (62) have proven to be very useful tools in a variety of bioanalytical applications, particularly for medical diagnostic tests (94MI 133-01). Examples include immunoassays for the qualitative and quantitative determination of biomolecules (B-90MI 133-03, B-91MI 133-01), DNA fingerprinting and sequencing (93MI 133-01), reporter gene assays (91MI 133-04), Southern and Northern blotting (B-91MI 133-05), virus detection and microbe screening (B-90MI 133-03).

The phosphate-substituted adamantyl-1,2-dioxetane (AMPPD, (28b)) is an excellent substrate for the alkaline phosphatase enzyme, which is one of the most widely used labels in enzyme-based immunoassays and nucleic acid analysis (B-91MI 133-05). Phosphatase-catalyzed dephosphorylation of the phosphate-substituted adamantyl dioxetane (28b) produces the deprotected electron-rich



Scheme 81



phenolate-functionalized dioxetane (**28c**), which undergoes rapid CIEEL decomposition to afford the long-lived emission at $\lambda_{\text{max}} = 477\text{ nm}$ in aqueous buffer solution (Scheme 53) <89MI 133-03>. Thus, extremely minute levels of alkaline phosphatase enzyme may be detected with chemiluminescent dioxetanes, which enables the quantitation of phosphatase-labeled substances such as proteins and nucleic acids with a sensitivity as low as ca. 10^{-20} mol .

The enzymatic chemiluminescence immunoassay is not limited to alkaline phosphatase-labeled substrates. The β -D-galactoside-substituted dioxetane (**62**) was also used as a highly luminescent detection method with the β -galactosidase enzyme <88TL3137>. It is anticipated that the use of thermally persistent CIEEL-active dioxetanes with enzyme-triggerable protecting groups will offer new perspectives in bioanalytical chemistry through the use of chemiluminescence <94MI 133-01>.

1.34

Four-membered Rings with One Oxygen and One Sulfur Atom

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1.34.1 INTRODUCTION

The four-membered ring structures containing one oxygen and one sulfur atom fall into two classes: the 1,2-oxathietanes and the 1,3-oxathietanes. The oxathietanes in general have been included in Davis's review of small ring compounds of sulfur and selenium <79SST187> and, along with other small rings, by Timberlake and Elder in the first edition of *Comprehensive Heterocyclic Chemistry* <84CHEC-I(7)449>.

By far the most commonly encountered examples of these compounds are the 2,2-dioxide derivatives of 1,2-oxathietanes, better known in the literature as β -sultones. They can also be regarded as internal esters of β -hydroxy sulfonic acids and hence as the sulfur equivalent of β -lactones. An alternative naming system calls for numbering the carbon atom bonded to sulfur, then the adjacent carbon attached to oxygen, in the longest carbon chain containing both. This gives rise to names like 1,2-sultone, 2,1-sultone, or sometimes just ethane sultone.

Roberts and Williams review on sultone chemistry includes information on β -sultones <87T1027>, as does the review of Buglass and Tillett on sultones and sultams <B-91MI 134-01>. The unsubstituted β -sultones are unstable, but the fluorinated derivatives are better known and have been the subject of several extensive review articles, including the early one of Knunyants and Sokol'skii <72AG(E)583> and the later review of Mohtasham and Gard <92CCR47>.

The 1,2-oxathietane 2-oxides can be regarded as internal esters of β -hydroxy sulfinic acids and are commonly known as β -sultines. They are even less stable than the β -sultones as a whole and have been included in reviews on cyclic sulfinic acid derivatives <69MI 134-01, B-90MI 134-01>.

Figure 1 shows the more likely parent systems. Only derivatives of 1,2-oxathietane (1), its 2-oxide or β -sultine (3) and its 2,2-dioxide or β -sultone (4) have been prepared and properly characterized, although there are a few reports of 1,2-oxathiete systems (2), including S-oxides. Also (2) and 1,3-oxathietane systems (5) have been the subjects of theoretical studies.

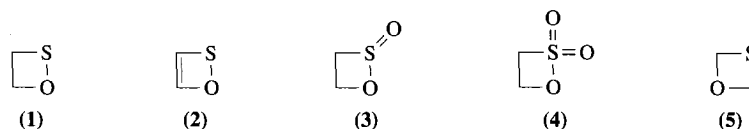


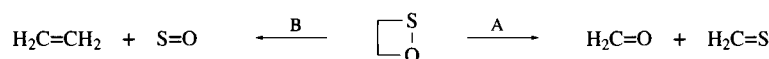
Figure 1 Basic skeletons of four-membered heterocycles containing one oxygen and one sulfur atom.

1.34.2 THEORETICAL METHODS

Surprisingly scant attention has been paid to theoretical aspects of 1,2- and 1,3-oxathietanes and derivatives of these molecules since the mid-1980s. Only one reference is quoted in CHEC-I <84CHEC-I(7)449>, where CNDO calculations were performed on the parent 1,2-oxathietane (1) <77JA2931>.

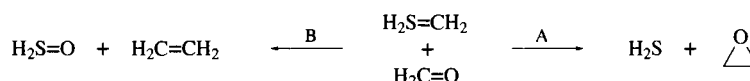
1.34.2.1 1,2-Oxathietanes

There are two reports of *ab initio* treatments of 1,2-oxathietanes <87JA1, 88CJC1890>. Lown and co-workers have used calculations at the level of 3-21G* SCF and MP3/3-21G* on (1) and its formal [$\sigma 2s + \sigma 2a$] cycloreversion products <88CJC1890>. Similarly, Hartree–Fock calculations were used for (*E*)- and (*Z*)-3,4-dimethyl-1,2-oxathietane and their cycloreversion products. In all three cases, in accord with experimental findings <86JA3811>, energy differences between the heterocycle and the various possible cycloreversion fragments favour production of carbonyl and thiocarbonyl species (route A, Scheme 1). Moreover, cycloreversion is postulated to proceed via a biradical mechanism to give ground state products, in agreement with the fact that chemiluminescence has not been observed for this process <83JA126, 86JA3811, 86JOC2116>. See Sections 1.34.4.3.2 and 1.34.6.1 for further details of the cycloreversion process.



Scheme 1

Volatron and Eisenstein <87JA1> have used SCF calculations with the 4-31G* and 4-31G** basis sets to explain why reaction between a sulfonium ylide and a carbonyl function nearly always proceeds by the Corey–Chaykovsky route (A) rather than the Wittig route (B) (Scheme 2). The unfavored Wittig route was computed to go through two located extrema, one of which was 2,2-dihydro-1,2-oxathietane (6) and this corresponded to a minimum on the energy profile. The optimized geometries for all the 1,2-oxathietane calculations, including the intermediate (6), are summarized in Figure 2.



Scheme 2

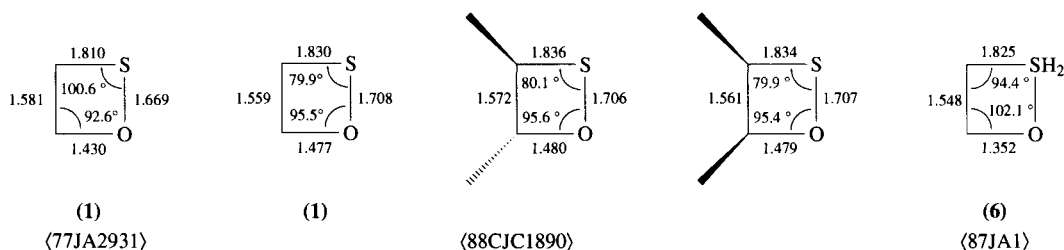


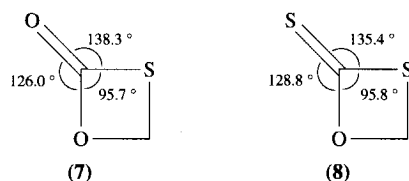
Figure 2 Optimized geometries for some 1,2-oxathietanes (bond lengths in Å).

1.34.2.2 1,3-Oxathietanes

The only theoretical treatment of 1,3-oxathietanes is that of Pasto *et al.* <82JPC3981>, although there is a theoretical thermochemical treatment <92JA1456> which is dealt with in Section 1.34.4.3. Pasto *et al.* used *ab initio* methods to calculate through-space $\text{S} \cdots \text{O}$ interaction energies in the parent 1,3-oxathietane (5). These were based on a planar molecule (C_{2v} symmetry), the optimized geometry for which was $r(\text{S}-\text{C}) = 1.795 \text{ \AA}$, $r(\text{C}-\text{O}) = 1.476 \text{ \AA}$, $\angle \text{CSC} = 74.02^\circ$, $\angle \text{COC} = 94.22^\circ$, $\angle \text{SOC} = 95.85^\circ$. Through-space interactions were separated from through-bond interactions by performing parallel calculations in the presence and absence of CH_2 groups that indirectly bond together the O and S functions. The through-space interaction energy was estimated to be much lower than the through-bond interaction energy.

MNDO geometry optimizations have been carried out on a series of acyclic and cyclic ketones and thioketones and related compounds, including 1,3-oxathietanone (7) and 1,3-oxathietanethione (8) <89JST(194)135>. The optimized bond angles suggest a definite distortion ("tilt") of the carbonyl group (and to a lesser extent the thiocarbonyl group) which was attributed to maximization of

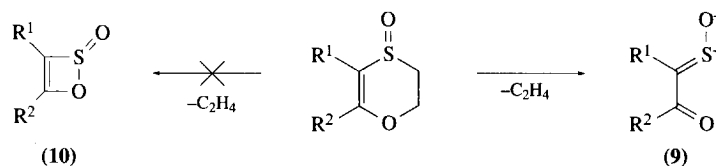
favorable $n\text{-}\sigma^*$ interaction (negative hyperconjugation). Although such distortions have been observed in the crystal structures of thiazetidinethiones <83BSB495>, there is to date no empirical structural information on either 1,3-oxathietanones or 1,3-oxathietanethiones.



1.34.2.3 1,2-Oxathietes and 1,2-Oxathiete 2-Oxides

Ab initio calculations have been performed on benzoxathiete (**28**) and its monothio-*o*-benzoquinone open-chain tautomer (**29**), their S-oxides and other postulated intermediates in the homolytic diazotization of 2-sulfinyl anilines <89JA258, 90CJC1950>. The calculations used the 3-21G* and 6-31G* basis sets within the Hartree-Fock approximation, but the MP2/3-21G* method was also used. Benzoxathiete (**28**) was found to be less stable than its open-chain tautomer (**29**), and it was also found that, like 1,2-oxathietanes <88CJC1890>, this interconversion process was much more energetically favorable than the SO extrusion process. Similar conclusions were drawn for the S-oxides of (**28**) and (**29**). These reactions are discussed further in Sections 1.34.4.3.4 and 1.34.6.1.2.

Ripoll and co-workers <91NJC533> have studied the flash vacuum thermolysis (FVT) of 2,3-dihydro-1,4-oxathiin S-oxides and have shown, by a combination of IR and photoelectron spectroscopy and MNDO calculations, that the products are thioalkanal S-oxides (**9**) rather than the ring tautomers 1,2-oxathiete 2-oxides (**10**) (Scheme 3). For a further example of ring-chain tautomerism involving 1,2-oxathietes, see Section 1.34.4.3.4. The optimum geometry calculated for (**10**) ($R^1 = R^2 = H$) using the AMPAC program with a reduced configuration interaction method is $r(\text{O}(\text{exocyclic})\text{—S}) = 1.488\text{\AA}$, $r(\text{S—C}) = 1.769\text{\AA}$, $r(\text{C—O}) = 1.367\text{\AA}$, $r(\text{C=C}) = 1.382\text{\AA}$, $\angle \text{CSO}(\text{exocyclic}) = 109.4^\circ$, $\angle \text{CCS} = 90.32^\circ$, $\angle \text{CCO} = 101.1^\circ$.



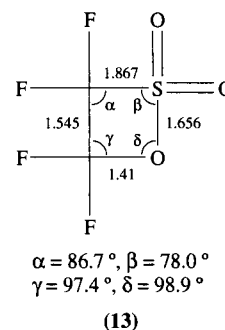
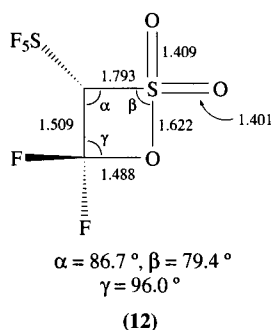
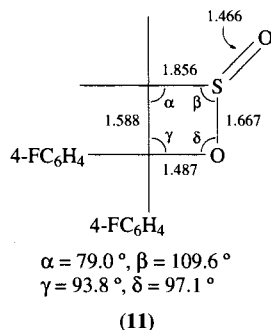
Scheme 3

1.34.3 STRUCTURAL METHODS

1.34.3.1 X-ray Diffraction and Electron Diffraction

As a result of the general low stability of oxathietane ring systems, combined with difficulties in obtaining crystalline samples, x-ray crystallographic information is still scarce. In fact there are only four reports in the literature: one for the β -sultine (**11**) <81JCS(P1)1826>, and three for β -sultones <88SUL55, 90IC3058, 92RTC478>. Additionally, there is one report which includes x-ray structure analysis of the S-fluorinated 1,2-oxathiete, 2-tetrafluoro-4-phenyl-3,4-dihydro-1,2-oxathietane <90AG(E)1128>. Bond lengths ($\text{\AA}$) and bond angles ($^\circ$) are summarized for the β -sultine (**11**) and for the fluorinated β -sultone (**12**) in the relevant structure diagrams <90IC3058>. Agreement is good for the three β -sultones, and in all the cases the rings are nonplanar with dihedral angles of 20.3° for (**11**) and 14.0° , 13.7° for (**12**), for example. In the early 1990s, the gas phase structure of 3,3,4,4-tetrafluoro-1,2-oxathietane 2,2-dioxide (**13**) was determined using electron diffraction analysis <94IC1273>, as summarized below. The most interesting feature of (**13**) is the planar β -sultone ring; in all previous examples of β -sultone structures, and also for β -sultine (**11**), the ring is distinctly puckered. The planarity of the ring in (**13**) is explained using the argument that full fluorination at the carbon atoms increases the angle strain with respect to other β -sultones and hence favors the

planar conformer. Also, other factors may influence the ring conformation in the crystalline state, especially with regard to intermolecular hydrogen bonding which plays an important role in the crystal structure of (12), see Section 1.34.4.1.1.



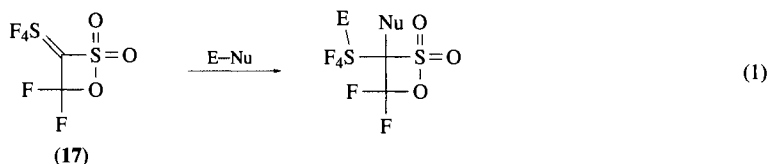
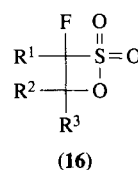
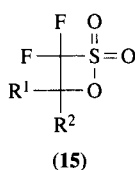
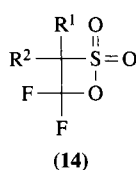
1.34.3.2 NMR Spectra

1.34.3.2.1 Fluorinated β -sultones

(i) Fluorine-19 spectra

Mohtasham and Gard's review <92CCR47> gives an exhaustive list of ^{19}F NMR chemical shifts and $^2J_{\text{FF}}$ coupling constants for the ring $\text{CF}_2(\text{O})$ group, as in (14), nearly always lies within the range -70 ppm to -100 ppm (w.r.t. CCl_3F), and $^2J_{\text{FF}}$ coupling constants are in the range 100 – 110 Hz, again with few exceptions. Interestingly, although the chemical shifts of the relatively few cases with $\text{CF}_2(\text{S})$ groups, as in (15), are in the same range as above, the values of $^2J_{\text{FF}}$ are generally much larger. They are typically in the region of 150 Hz <90JFC(49)349>, although values of 119 Hz for (15; $\text{R}^1 = \text{F}$, $\text{R}^2 = \text{Cl}$) <74SA(A)511> and 173 Hz for (15; $\text{R}^1 = \text{OEt}$, $\text{R}^2 = \text{CF}_3$) <77JA1214> have been observed.

Single fluorine atoms at ring position 3, as in (16), appear to have a much wider range of chemical shifts, depending on the nature of R^1 . The range extends from -170.2 ppm ($\text{R}^1 = \text{H}$) <92CCR47> to -79.5 ppm ($\text{R}^1 = \text{CF}_2\text{O}(\text{CF}_2)_2\text{OCF}_3$) <89JFC(43)349>. However, the majority of resonances for this group lie close to -150 ppm. Gard and co-worker have also used ^{19}F NMR spectroscopy to characterize addition products of (17) (Equation (1)) <91JFC(52)57>. See Section 1.34.7 for further details of this reaction.

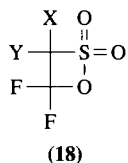


(ii) Carbon-13 spectra

The available ^{13}C NMR data for fluorinated β -sultones are discussed in Mohtasham and Gard's review <92CCR47>, where ^{13}C chemical shifts are listed along with $^1J_{\text{CF}}$ coupling constants. The chemical shift of the α -(or 3-) ring carbon atom is related to the shielding effect of the α -substituents, X and Y, as summarized in Table 1 for (18) <90MRC998>. The effects of α -(3-) substituents on the

chemical shift of the β (4-) ^{13}C nucleus appear to be small <90MRC998>. The $^1J_{\text{CF}}$ coupling constants at the ring α -carbon atom are observed to vary within the range 270–330 Hz. Furthermore, the magnitude of this coupling constant is noted as increasing with increase in the electron-withdrawing character of the α -substituent <90MRC998>.

Table 1 Carbon-13 chemical shifts of α -C in fluorinated β -sultones (18).

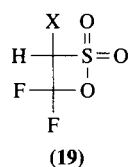


<i>X</i>	<i>Y</i>	δ (α - ^{13}C)
CF_3	H	79.3
$\text{F}_4\text{S}=\text{C}$	H	80.7
CF_3	F	112.5
F	F	126.0
F_5S	F	128.3

(iii) Proton spectra

There are relatively few fluorinated β -sultones with ring hydrogens, and these appear to be restricted to those with just a single hydrogen at the α (3-) position, as summarized in Table 2 for (19) <92CCR47>. Although there are no systematic attempts at chemical shift–structure correlation in the literature, it appears that through-space shielding effects may need consideration along with through-bond deshielding effects.

Table 2 Proton chemical shifts of α -H in fluorinated β -sultones (19).



<i>X</i>	δ (α - ^1H)
ClF_4S	7.10
F_5S	6.58
F	6.40
CF_3	5.60
FO_2S	4.42

1.34.3.2.2 Nonfluorinated β -sultones: ^1H and ^{13}C spectra

Since the nonfluorinated β -sultones are generally less stable than their fluorinated analogues, the majority of ^1H and ^{13}C data are derived from the analysis of alkene sulfonation mixtures at low temperatures, rather than from analyses of pure isolated compounds <87TL1699, 87TL3383, 89JOC1680, 91MI 134-02, 92RTC49, 92RTC389, 93RTC201, 93RTC247>. Although, in many cases, ring ^1H chemical shifts and exocyclic ^{13}C chemical shifts have been discussed in terms of shielding effects, there still appears to be scope for more systematic NMR study. Proton and ^{13}C chemical shift data for ring atoms

from the late 1980s and early 1990s can be found in Figure 3 <87TL1699, 87TL3383, 92RTC49, 92RTC188, 92RTC478, 93RTC201, 93RTC247>. For spectral data from the late 1970s see <77JCS(P1)247, 78JCR(S)484, 81JA5976>.

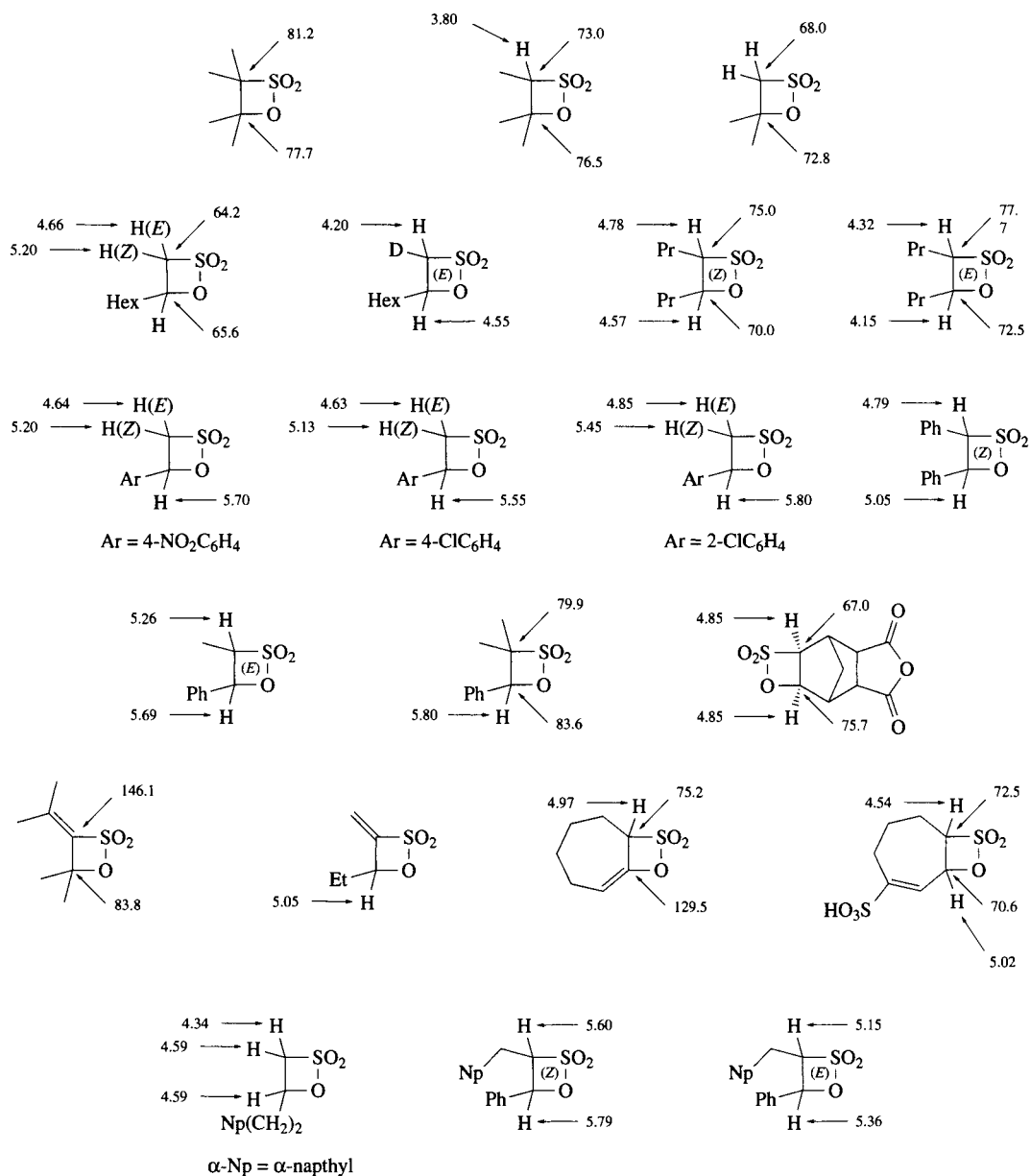
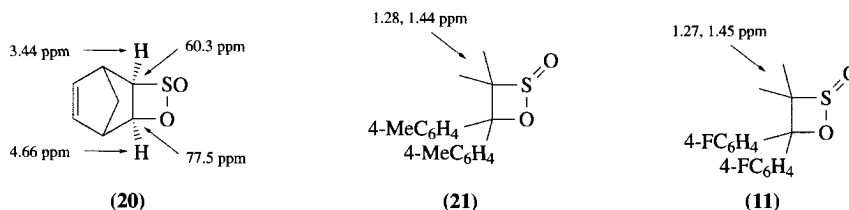


Figure 3 ^1H and ^{13}C chemical shifts of β -sultone ring atoms (ppm w.r.t. TMS).

1.34.3.2.3 β -Sultines

The β -sultines are, in general, less stable than their β -sultone analogues, with the fully substituted versions having the greatest stability. Consequently there is a scarcity of NMR data, with only one report of ring ^1H and ^{13}C resonances for compound (20) <82CC464>. The $^3J_{\text{HH}}$ coupling constant for the β -sultine ring protons in (20) is 4.7 Hz, which is typical of *endo-endo* vicinal coupling constants in norbornanes. The only other ^1H spectra were reported for β -sultine ring methyl substituents of (21) and (11) by Durst and co-workers <75CC724, 81JCS(P1)1826>. The two distinct methyl resonances in each case presumably reflect the nonplanar conformation of the β -sultine ring.



1.34.3.2.4 1,2-Oxathietanes and 1,2-oxathietes

The only oxathietane NMR spectrum reported up to 1995 is the 100 MHz ^1H spectrum of 3,3,4,4-tetramethyl-1,2-oxathietane, whose methyl protons at position 3 ($\text{S}-\text{CMe}_2$) and those at position 4 ($\text{O}-\text{CMe}_2$) resonate at 0.98 ppm and 1.18 ppm respectively [86JA3811]. A single line for each pair of geminal methyl protons is indicative of either the existence of a planar conformation for the 1,2-oxathietane ring or of a system in rapid conformational isomerism. Unfortunately, there is no further NMR information in the literature to shed light on the subject.

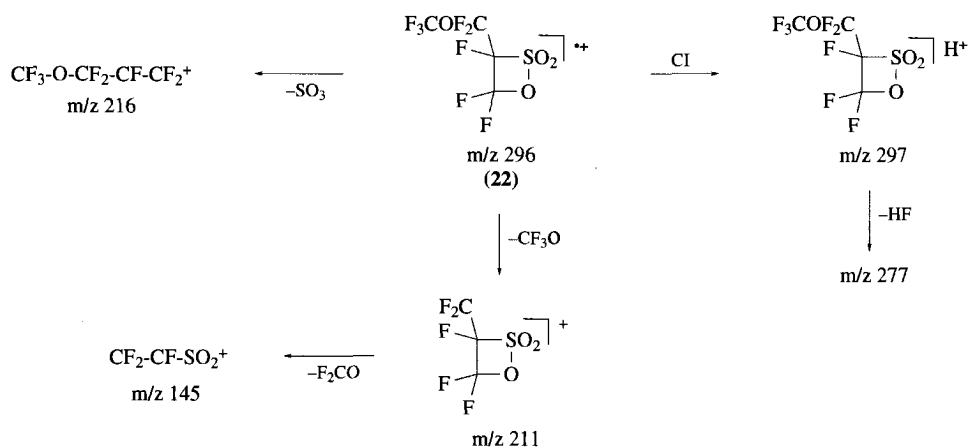
The ^{19}F NMR spectrum of S-tetrafluorooxathiete (30) is typical of an A_2BC system, in agreement with the x-ray structural data [90AG(E)1128].

1.34.3.3 Mass Spectrometry

1.34.3.3.1 Fluorinated β -sultones

The relatively abundant mass spectral data for these compounds have been tabulated in Mohtasham and Gard's review [92CCR47]. All reported mass spectra have been obtained by EIMS or CIMS modes using 70 eV electron beams. Most are positive-ion spectra [84IC4403, 89JFC(42)119, 89JFC(43)349, 90JFC(49)349, 90JFC(50)31, 91JFC(52)57], but negative-ion spectra have also been reported [88IC2916, 91JFC(52)57].

The positive-ion EIMS and CIMS fragmentation patterns are complex, but a common route for most fluorinated β -sultones involves the early loss of SO_3 . However, there are many fragmentation routes which do not initially feature rupture of the β -sultone ring, but instead involve early loss of HF , $\text{F}^\bullet$, $\text{CF}_3\text{O}^\bullet$ (from fluorinated ether side chains), or $\text{Cl}^\bullet$ (from chlorinated side chains). Rearrangements also appear to be a common feature. Molecular ions are generally observed, but often as MH^+ species in CIMS. Scheme 4 highlights some of the general fragmentation modes for fluorinated β -sultones, by illustrating those for compound (22) [89JFC(43)349]. Although internal standards are often used (see e.g. [89JFC(43)349]), only low-resolution m/z values are usually quoted and there appear to be no reports of metastable ions.

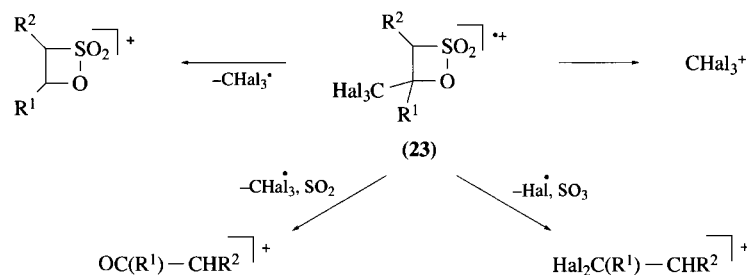


CI = chemical ionization

Scheme 4

1.34.3.3.2 Other β -sultones

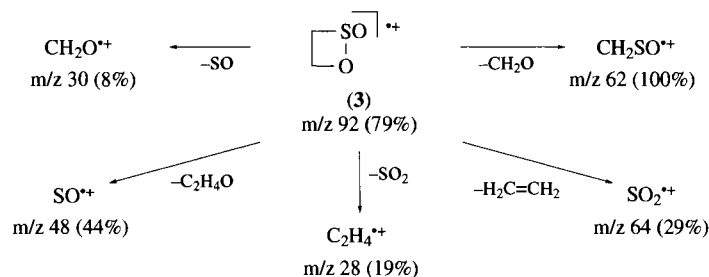
The only nonfluorinated β -sultones to be studied in detail by mass spectrometry are the trihalomethyl derivatives (**23**) <77OMS(12)467>. Preferential fragmentation does not occur at the β -sultone ring, but rather at the C—CHal₃ bond, as illustrated for (**23**) in Scheme 5. Thus, in all but one case (**23**; R¹ = H, R² = Me, Hal = Cl), the ion CHal₃⁺ gives rise to the base peak. Metastable ions were used to confirm fragmentation routes. Molecular ions were absent.



Scheme 5

1.34.3.3.3 β -Sultines

Interestingly, the only mass spectrum reported for a β -sultine is the EI spectrum of the parent heterocycle (**3**), which was identified as a product of the solid state photolysis of sulfolane <81JPC3603>. An abundant molecular ion (79%) was reported. The major fragmentation routes are summarized in Scheme 6. Other β -sultines have been synthesized and characterized by spectroscopic methods (see Sections 1.34.3.2 and 1.34.3.4) but not by mass spectrometry.



Scheme 6

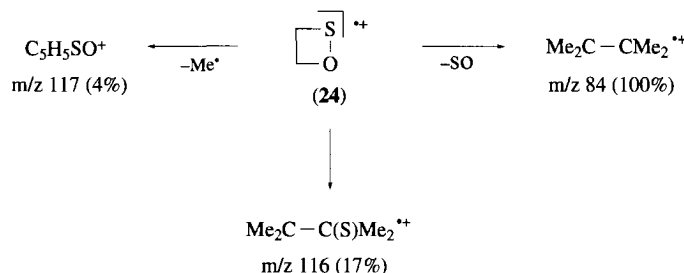
1.34.3.3.4 Oxathietanes and oxathietes

The high-resolution 70 eV EI spectrum of the 1,2-oxathietane (**24**) has been recorded using a double-focus instrument and with an internal standard for accurate mass measurement <86JA3811>. The results are summarized in Scheme 7, where it can be seen that loss of SO is the preferred fragmentation mode, in contrast to the cycloreversion process (Section 1.34.6.1.1). A further peak is assigned to Me₂C=S⁺ (m/z = 74, 8%), but it is unclear how it arises, as there are no metastable ion data; it may be produced by cycloreversion.

The 80 eV EI spectrum of 2-tetrafluoro-3-bromo-4-phenyl-3,4-dehydro-1,2-oxathietane has been reported and includes a molecular ion (m/z = 304, 306, 21%) <90AG(E)1128>.

1.34.3.4 IR and UV Spectra

There is a considerable amount of routine IR data on a number of the four-membered ring systems containing one oxygen and one sulfur atom. Not surprisingly, the greatest number of spectra



Scheme 7

have been recorded for fluorinated β -sultones and have been summarized in reviews $\langle 67\text{DOK}(172)1327, 92\text{CCR}47 \rangle$. The asymmetric SO_2 stretching mode is found in the region $1440\text{--}1465\text{ cm}^{-1}$ whereas the symmetric mode appears in the region of 1200 cm^{-1} . They are both strong bands, but assignment can sometimes be confused by the existence of $\text{C}\text{--}\text{F}$ absorptions in the same regions $\langle 84\text{IC}4403 \rangle$.

Other β -sultones, including highly halogenated derivatives, have SO_2 asymmetric and symmetric stretching modes at rather lower (ca. 1400 cm^{-1}) and higher (ca. 1230 cm^{-1}) values, respectively, compared with their fluorinated analogues $\langle 67\text{DOK}(172)1327, 81\text{AP}(314)799 \rangle$. The SO stretching mode of β -sultones appears at about 1150 cm^{-1} $\langle 75\text{CC}724, 78\text{CC}1020, 81\text{JCS}(\text{P}1)1826, 82\text{CC}464, 84\text{JCS}(\text{P}2)2079 \rangle$. This includes data for a pair of diastereoisomeric 1,2-oxathietanone 2-oxides with SO stretching bands at 1160 and 1185 cm^{-1} $\langle 84\text{JCS}(\text{P}2)2079 \rangle$, see Section 1.34.4.3.5.

Oxathietanes with no $\text{S}=\text{O}$ bonds do not have such characteristic IR absorption bands, but limited data is available for 3,3,4,4-tetramethyl-1,2-oxathietane (**24**) $\langle 86\text{JA}3811 \rangle$. Interestingly, there is a band quoted at 1720 cm^{-1} , which may be the sign of some cycloreversion product acetone.

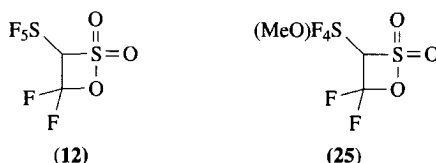
All the literature IR data is basically routine in nature; evidence for structural assignment. With virtually no exception (e.g. $\langle 84\text{JCS}(\text{P}2)2079 \rangle$), there are no systematic IR studies. This may be a productive area of study in the future, considering the great versatility and wide application of modern FTIR instruments. UV-visible spectrometric data is very scarce: 1,2-oxathietane (**24**) was found to have absorption maxima (CCl_4) at 258, 265, and 320 nm $\langle 86\text{JA}3811 \rangle$. Unlike 1,2-dioxetanes, compound (**24**) exhibits no chemiluminescence during its cycloreversion process $\langle 86\text{JA}3811, 88\text{CJC}1890 \rangle$.

1.34.4 THERMODYNAMIC ASPECTS

1.34.4.1 Physical Data

1.34.4.1.1 Fluorinated β -sultones

A comprehensive tabulation of boiling and melting points of these compounds can be found in Mohtasham and Gard's review $\langle 92\text{CCR}47 \rangle$. Sokol'skii and co-workers also quote densities and refractive indices for a number of fluorinated β -sultones $\langle 86\text{JOU}1653 \rangle$. All but two, (**12**) and (**25**), are colorless liquids. Intermolecular hydrogen bonding most likely plays an important role in the crystalline phase of (**12**) and (**25**). Indeed the crystal structure of (**12**) has been determined by x-ray diffraction analysis (see Section 1.34.3.1), and hydrogen bonding between the exocyclic oxygens and the ring hydrogen of different molecules does appear to be largely responsible for the crystal packing $\langle 90\text{IC}3058 \rangle$. It is unclear why the hydrogen bond distances ($3.177\text{ \AA}$ and $3.230\text{ \AA}$) appear to be longer than standard $\text{O}\cdots\text{H}$ hydrogen bond lengths ($2.3\text{--}2.8\text{ \AA}$).



1.34.4.1.2 Other β -sultones, β -sultines, and 1,2-oxathietanes

Physical data is available only for a small number of β -sultones <77JCS(P1)247, 77OMS(12)467, 78JCR(S)484, 81AP(314)799, 81JA5976>. These are often colorless crystalline solids and 4-tribromomethyl-3-chloro-1,2-oxathietane 2,2-dioxide <81AP(314)799> probably has the highest m.p. for a β -sultone (151°C). Two other nonfluorinated β -sultones are known to be solids, but no physical data are given <88SUL55, 92RTC478>.

The limited information available for β -sultines is summarized in Table 3. There is only one report for 1,2-oxathietanes; compound (**24**) is described as a pale yellow oil, but no b.p. is given <86JA3811>.

Table 3 Physical data for β -sultines.

Compound	Physical state	Ref.
(11) $R^1 = R^2 = \text{Me}$ $R^3 = R^4 = 4\text{-FC}_6\text{H}_4$	Solid, m.p. 102–104°C	81JCS(P1)1826
(20) $R^1 = R^3 = \text{H}$ $R^2 = R^4 =$	Oil (no data)	82CC464
(21) $R^1 = R^2 = \text{Me}$ $R^3 = R^4 = 4\text{-MeC}_6\text{H}_4$	Solid (no data)	81JCS(P1)1826
(26) $R^1 = R^2 = \text{Me}$ $R^3 = R^4 = \text{Ph}$	Solid, m.p. 97–99°C	75CC724

1.34.4.2 Solubilities and Chromatographic Behavior

The fluorinated and polyhalogenated β -sultones are generally soluble in a wide range of organic solvents, including chlorinated solvents, ethers (including dioxan) and hydrocarbons <92CCR47, 81AP(314)799, 78JCR(S)484>. There is very little information on pure isolated nonhalogenated β -sultones, but 3-(1,1-diphenylethyl)-3-methyl-1,2-oxathietane 2,2-dioxide has been recrystallized from ethanol <77JCS(P1)247>. Nonhalogenated β -sultones, present in the sulfonation mixtures of alkenes, although not normally isolated, are evidently soluble in the medium, typically dichloromethane/dioxan.

The few β -sultines that have been prepared appear to have solubilities similar to those of the β -sultones <81JCS(P1)1826, 82CC464>.

The only isolated 1,2-oxathietane, the 3,3,4,4-tetramethyl derivative (**24**), is reported to be soluble in ether <86JA3811>, and S-tetrafluorooxathiete (**30**) is reported to be soluble in pentane and is recrystallized from ether <90AG(E)1128>.

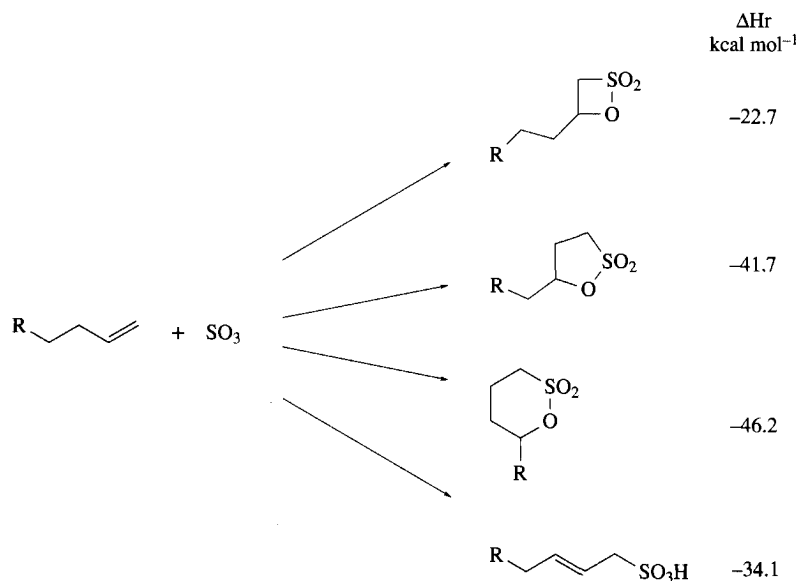
There appears to be virtually no detailed chromatographic information; purification by vacuum distillation or crystallization (often at low temperatures) being generally preferred. Owing to a likelihood of thermal instability, analysis by GLC could well be problematic, but nevertheless has been reported for (**24**) using a 10% carbowax column with helium carrier gas (22 ml/min) at 60°C, where the retention time was 5.3 min <86JA3811>. There are no reports of column chromatographic, TLC, HPLC, or SFC separations.

1.34.4.3 Stability and Thermochemical Aspects

1.34.4.3.1 Isomerization of β -sultones

Fluorinated and polyhalogenated β -sultones are well known to be relatively thermally stable compounds. Nonfluorinated β -sultones, on the other hand, tend to undergo facile isomerization to the larger ring γ - and δ -sultones and to alkenesulfonic acids, a subject which has been previously reviewed (87T1027, B-91MI 134-01). These reactions are discussed in Section 1.34.6.1.2.

Canselier and co-workers, using a combination of product distribution analysis, thermochemical calculations, and kinetic methods in the study of alkene sulfonation, concluded that β -sultones (Scheme 8) are kinetic products (84PS(20)259). Contributing bond energies and conventional ring strain energies were used to estimate enthalpies of reaction (ΔH_r , Scheme 8) and these clearly show the β -sultone to be the thermochemically least favored product.



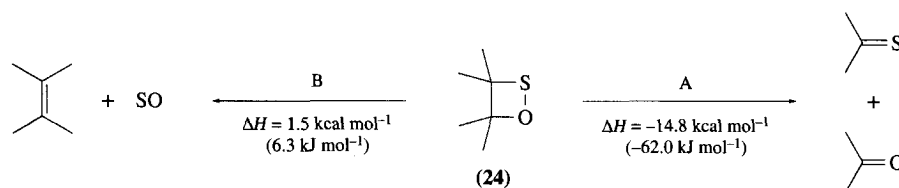
Scheme 8

1.34.4.3.2 Cycloreversion reactions

Nonfluorinated β -sultones are generally prone to cycloreversion (*retro* sulfonation) (89TL5451), although it has been argued that the energy of activation of this process is higher than those for the various isomerization processes discussed in Section 1.34.4.3.1 (92RTC389).

Beta-sultones are known to decompose readily by extrusion of SO_2 , although there is no thermochemical or theoretical information on the subject (75CC724, 81JCS(P1)1826, 82CC464). Cycloreversion of β -sultones is discussed in Section 1.34.6.1.1.

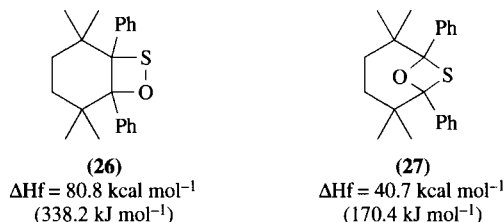
Cycloreversion of 1,2-oxathietanes has been studied by Steliou *et al.*, using their own computer-aided evaluation of enthalpic differences method to predict that the favored cycloreversion pathway is the one which produces carbonyl and thiocarbonyl fragments rather than the SO extrusion pathway (Scheme 9, routes A and B, respectively) (92JA1456). The same appears to be true of benzoxathiete (28) and its S-oxide (89JA258, 90CJC1950), although the S-tetrafluorinated oxathiete (30) undergoes thermal extrusion of $SF_4=O$ and does not show tendency to isomerize (90AG(E)1128).



Scheme 9

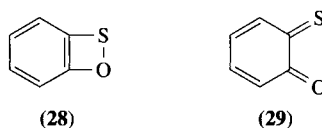
1.34.4.3.3 Relative stability of 1,2- and 1,3-oxathietanes

Steliou *et al.* used their computer-aided enthalpic differences method to assess enthalpic stability differences between isomeric 1,2- and 1,3-oxathietanes. The former were generally predicted to be slightly more stable, with the exception of (26) and (27) <92JA1456>.



1.34.4.3.4 Isomerization of 1,2-oxathietes

Benzoxathiete (28) has been shown to be of higher energy than the open-chain monothio-*o*-benzoquinone (29) <81AG(E)570>, although Lown and co-workers, whilst agreeing with this conclusion, have shown that the conversion of (28) to (29) is thermally disallowed <89JA258, 90CJC1950>. Furthermore, these workers give experimental evidence for the participation of (28) and its S-oxide in the decomposition of 2-sulfinyl- and 2-sulfenyl-anilines (respectively) under homolytic (aprotic) conditions. Attempts to displace the position of tautomeric equilibrium toward the cyclic tautomer have not been very successful, although there is an early report of photolytic conversion in an ethanol glass at 77 K <71CC383>.

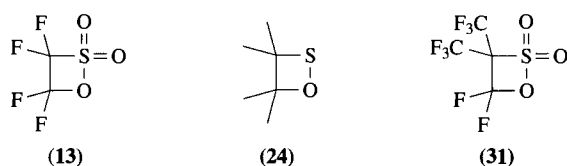


There appear to be only two cases where the open-chain/ring isomerization involving 1,2-oxathietes favors the ring tautomer, and that is 2,2,2,2-tetrafluoro-4-phenyl-3,4-dehydro-1,2-oxathietane (30) and its 3-bromo derivative (see Equation (2), Section 1.34.5) <90AG(E)1128>.

1.34.4.3.5 Stereoisomerization

X-ray diffraction evidence so far indicates favored nonplanar conformers for β -sultones <88SUL55, 90IC3058, 92RTC478> and a β -sultine <81JCS(P1)1826>. It has been observed in the NMR spectra of symmetrically substituted β -sultines and β -sultones that *gem*-methyl groups are magnetically nonequivalent <81JCS(P1)1826, 87TL3383>. This suggests that either a nonplanar conformer has overriding stability, or that the conformation isomerism process is essentially “frozen”, on the NMR time scale. On the other hand, no such nonequivalence has been reported for the ring ¹⁹F nuclei of the fluorinated β -sultones (31) <72IZV2441> and (13) <91IC4821> and the methyl substituents of 1,2-oxathietane (24) <86JA3811>. Furthermore, the gas phase structure of (13) has been shown by electron diffraction analysis to be planar <94IC1273>. Thus in view of the lack of systematic dynamic NMR information, the situation regarding conformation isomerism remains unclear. However, Sutcliffe and co-workers have reported on preferred conformers of fluorinated β -sultones by studying *gem* and *vic* ¹⁹F coupling constants <74SA(A)511>.

(*Z*) and (*E*) isomers of β -sultones have been prepared but no interconversion has been observed

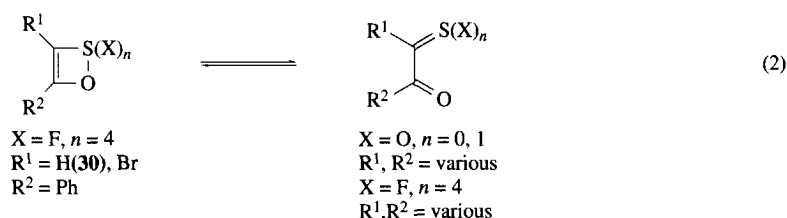


<87TL1699, 89TL5451>, although a (*Z*)/(*E*) isomerization process may be involved in the reaction of some β -sultones with SO_3 to form carbyl sulfates <92RTC49>, see Section 1.34.6.4.

The (*Z*) and (*E*) isomers of 3-methyl-1,2-oxathietan-4-one have been prepared (as a mixture) in low-temperature matrices, but there is no evidence of any interconversion process <84JCS(P)2079>.

1.34.5 REACTIVITY OF FULLY CONJUGATED RINGS

Fully conjugated examples (i.e. with all ring carbon atoms sp^2 hybridized) of these small heterocyclic systems are rare; in the majority of cases it seems that the open-chain isomers are thermodynamically favored, as illustrated in Equation (2) <81AG(E)570, 89JA258, 90AG(E)1128, 90CJC1950, 91NJC533>. The few reactions performed on isolated 1,2-oxathiete (**30**) suggest normal behaviour of the C—C bond <90AG(E)1128>. Thus (**30**) undergoes addition reactions with HBr and Br_2 (see Section 1.34.9), and also thermal polymerization with elimination of $\text{SF}_4=\text{O}$. Hydrolysis of (**30**) gives $\text{PhCOCH}_2\text{SO}_2\text{F}$, but the mechanism of this reaction is unclear.

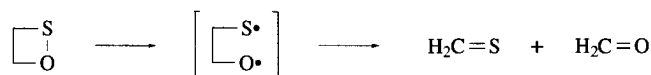


1.34.6 REACTIVITY OF NONCONJUGATED RINGS

1.34.6.1 Thermal and Photochemical Processes

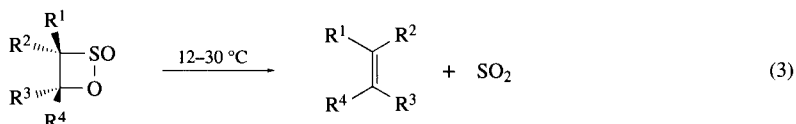
1.34.6.1.1 Cycloreversion

Cycloreversion can be described as the reversal of cycloaddition, i.e. conversion of a cyclic compound to its acyclic constituents, from which it is (at least formally) derived. It is a thermal process. Of the well-characterized four-membered rings with one oxygen and one sulfur atom, only the 1,2-oxathietanes and their 2-oxides (the β -sultines) show a marked tendency to cycloreversion, although some β -sultones also show a certain tendency. The oxathietane (**24**) (Scheme 1) undergoes cycloreversion to acetone and thioacetone, even at -20°C <86JA3811>. The reactive thioacetone was trapped by [2 + 2] cycloaddition reactions using reagents such as tetracyanoethene and fumaronitrile and by $[\pi 4s + \pi 2s]$ cycloadditions using anthracene derivatives. Furthermore, the UV spectrum of (**24**) (see Section 1.34.3.4) showed the gradual appearance of a peak at 430 nm which was tentatively assigned to thioacetone. Carbonyl and thiocarbonyl compounds have been determined by GC/MS and attributed to cycloreversion of even less stable 1,2-oxathietanes than (**24**), which have been postulated as intermediates in the decomposition of antileukaemic 2-chloroethylnitrosoureas (CENUs) <80JMC798, 83JA126, 86JA3811, 86JOC2116>. Alkene decomposition products were also seen (in small yield), but these were not definitely attributed to cycloreversion by the alternative SO extrusion pathway (Scheme 1). In the late 1980s, *ab initio* studies suggested the cycloreversion of 1,2-oxathietanes such as (**1**) proceeds via a biradical intermediate (Scheme 10) to give ground state products, in accord with the lack of chemiluminescence accompanying the decomposition <88CJC1890>. Benzoxathiete (**28**) and its S-oxide appear to undergo a similar reaction <89JA258, 90CJC1950>.

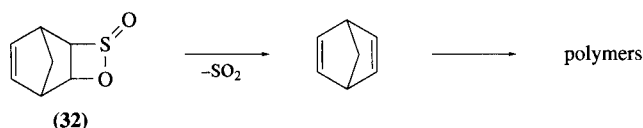


Scheme 10

β -Sultines readily undergo thermal cycloreversion to give alkene products, with the extrusion of SO_2 (Equation (3)) <73JA3420, 75CC724, 78IZV142, 81JCS(P1)1826>. The fact that the process occurs with retention of configuration suggests that it is concerted. Also the insensitivity of the rate of decomposition to medium changes suggests that the mechanism does not involve biradical or zwitterionic intermediates. Indeed CNDO-MO studies indicate that the cycloreversion is a [2 + 2] process which occurs via a suprafacial-antarafacial pathway <77TL2045>.

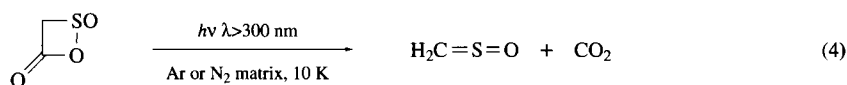


It is possible that the decomposition of the norbornene β -sultine (**32**) to give polymeric materials occurs via cycloreversion (Scheme 11) <82CC464>.

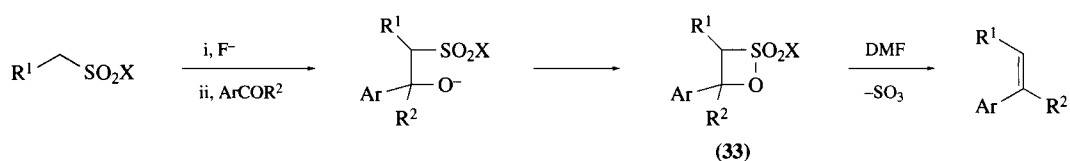
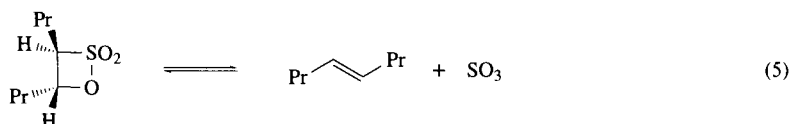


Scheme 11

The only example of a photochemical decomposition of β -sultines is that of 1,2-oxathietan-4-one 2-oxide, which extrudes CO_2 rather than SO_2 (Equation (4)) <78CC1020>.



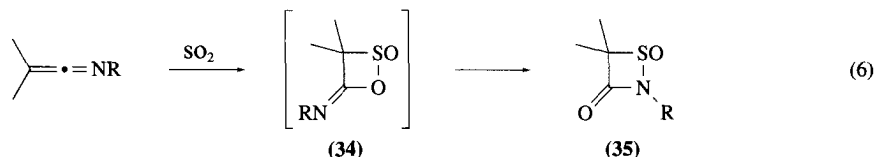
On the whole, β -sultones do not show a great tendency toward desulfonation, instead there are many reactions which compete successfully. These include rearrangements/isomerizations (see Section 1.34.6.1.2) and reactions involving nucleophilic attack at ring sulfur (see Section 1.34.6.2) and ring carbon (see Section 1.34.6.3). However 3,4-disubstituted nonhalogenated β -sultones <89JOC1680, 89TL5451, 91MI 134-02> and fluorinated β -sultones <92CCR47> show evidence of desulfonation, probably because of their superior stability with regard to attack by nucleophiles. The rate of desulfonation, however, appears to be very slow <89TL5451, 91MI 134-02>. Cerfontain and his group have provided good evidence that desulfonation occurs via stereoselective retro-sulfonation (i.e. cycloreversion (Equation (5)) <89TL5451>). Furthermore, retro-sulfonation followed by resulfonation has been implicated in certain isomerizations, probably occurring via alkene- SO_3 π complexes <92RTC389>. In 1994, cycloreversion of a β -sultone intermediate (**33**) was proposed as the final step in the formation of alkenes by the reaction between electron-deficient aryl ketones and alkane-sulfonyl halides (Scheme 12) <94JOC2898>.



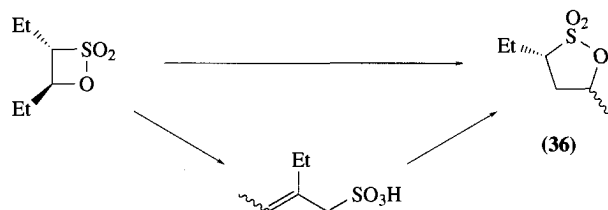
Scheme 12

1.34.6.1.2 Rearrangements/isomerizations

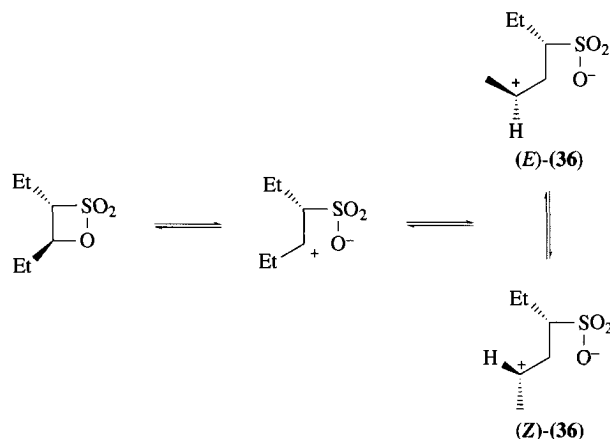
Very little is known of the rearrangement/isomerization reactions of either 1,2-oxathietanes or β -sultines. It is likely that the formation of compound (35) (Equation (6)) occurs via formation of, and subsequent isomerization of, β -sultimine (34) <81CC350>. For a theoretical thermochemical account of 1,2-/1,3-oxathietane isomerization, see Section 1.34.4.3.3.



Nonfluorinated β -sultones undergo a multitude of isomerizations, which have been reviewed <87T1027, B-91MI 134-01>. The most common isomerizations are those involving either ring expansion to γ - and δ -sultones, or ring opening to form alkenesulfonic acids (Scheme 13). The majority of reports on these reactions come from Bakker and Cerfontain's group <87TL1699, 89JOC1680, 89TL5451, 92RTC49, 93RTC201, 93RTC247>, but other workers, notably Roberts and co-workers <87TL3383>, Boyer *et al.* <84PS(20)259>, Thaler and du Breuil <84MI 134-01>, Storey and Lee <90MI 134-01>, and Yoshimura *et al.* <91MI 134-02, 92MI 134-01> also report β -sultone isomerizations. The mechanism of these isomerizations most likely involves the formation of zwitterionic intermediates via C—O bond rupture, followed by a 1,2-hydride shift (or in some cases a 1,2-methide or other shift) <84PS(20)259, 87TL3383, 93RTC247>. This certainly explains the nonstereoselective nature of the isomerizations to γ -sultones (e.g. (36)) (Schemes 13 and 14).



Scheme 13



Scheme 14

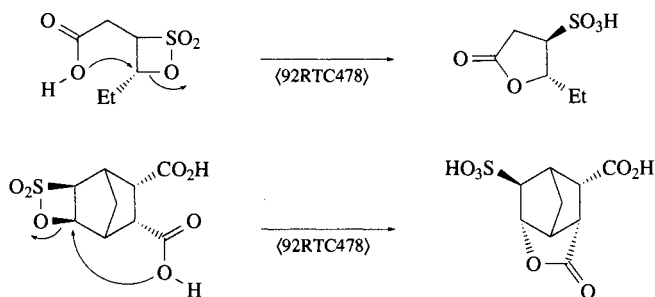
Isomerizations of β -sultones to alkenesulfonic acids have been explained by intramolecular (C $\rightarrow$ O) proton transfer in the zwitterionic intermediates derived from ring opening of β -sultones (Scheme 15) <84PS(20)259, 92RTC49>. This accounts for the fact that formation of alkenesulfonic acids is difficult when there is no proton available on a neutral β - or δ -carbon of the zwitterion: other products such as δ -sultones tend to be formed instead <84PS(20)259, 87TL3383, 92RTC49>. The intramolecular mechanism also explains why 2-alkene-sulfonic acids are formed in preference to other alkene-

sulfonic acids, although the whole story is complicated by the fact that alkenesulfonic acids can be formed directly from alkene sulfonation and can also be produced by isomerization of γ - and δ -sultones $\langle 84PS(20)259, 89TL5451 \rangle$ as well as by decomposition of β -pyrosultones (or carbyl sulfates) which can also be formed during alkene sulfonations $\langle 87TL3383, 89JOC1680, 92RTC49, 93RTC201 \rangle$.

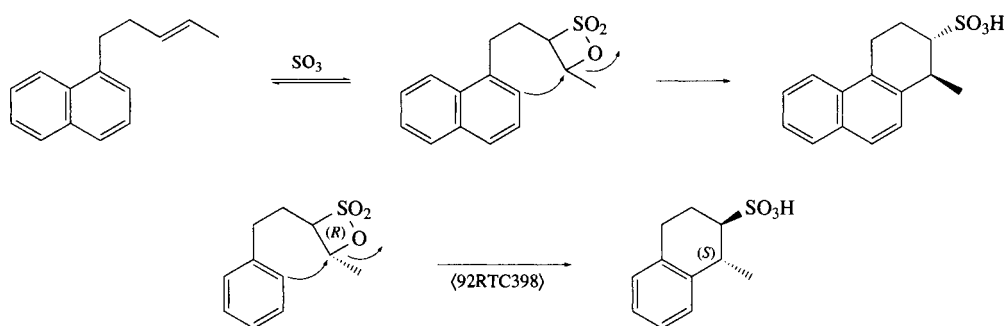


Scheme 15

Cerfontain and co-workers have reported a number of β -sultone isomerizations which involve the formation of cyclic sulfonic acids which are produced during the sulfonation of alkenoic acids $\langle 92RTC478 \rangle$ and ω -arylalkenes $\langle 92RTC389, 93RTC247 \rangle$, as a result of internal attack at C-4 by oxygen and carbon nucleophiles, respectively (Schemes 16 and 17).

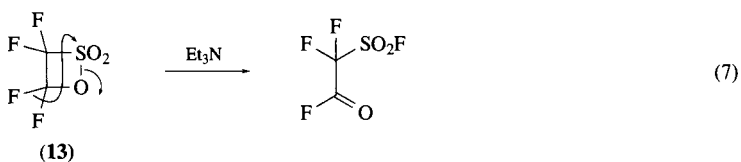


Scheme 16



Scheme 17

Rearrangement of fluorinated β -sultones to isomeric acyclic α -fluorosulfonyl polyfluorocarbonyl fluorides has been known for some time, and is assisted by nucleophiles, even in catalytic amounts, as illustrated for (13) with catalysis by triethylamine (Equation (7) $\langle 60JA6181 \rangle$). Rearrangement of (13), apparently in the absence of a nucleophile, when considered with a theoretical estimate of its molecular geometry, led Sokol'skii and Knunyants to suggest an intramolecular pathway (Equation (8)) $\langle 71IZV964 \rangle$. However, Gard *et al.* have shown from electron diffraction analysis that the molecular geometry of (13) is not ideal for intramolecular rearrangement $\langle 94IC1273 \rangle$, thus supporting an intermolecular mechanism proposed earlier by the same group (Scheme 18) $\langle 84IC4403 \rangle$. It can be seen that the latter mechanism involves nucleophilic attack at ring sulfur; there is further discussion on this type of reaction in Section 1.34.6.2.



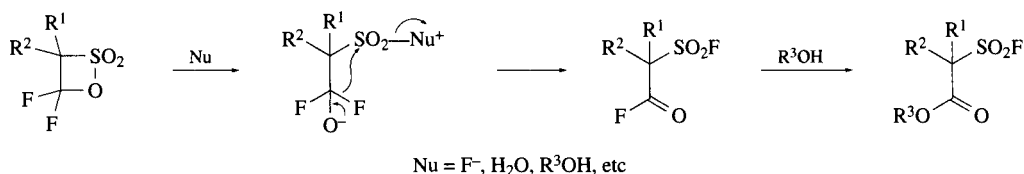


There appears to be no information on simple oxathietanes, but the oxides and dioxides of 1,2-oxathietanes (the β -sultines and β -sultones, respectively) are susceptible to nucleophilic attack at sulfur.

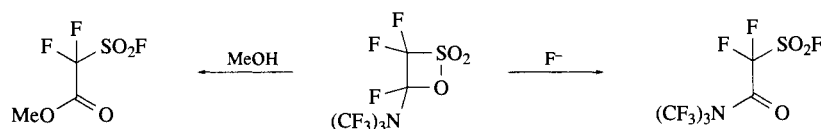
Fluorinated β -sultones and polyhalogenated β -sultones generally react readily with a wide variety of nucleophiles, including NH_3 , amines, H_2O , metal hydroxides, alcohols, metal alkoxides, and metal fluorides. These reactions have been the subject of reviews ^{<72AG(E)583, 92CCR47>} and are summarized in Scheme 19. Some of these reactions have found industrial application and is dealt with in Section 1.34.11.



The favored mechanism for these reactions appears to involve an initial nucleophilic attack at ring sulfur, with ring opening caused by S—O bond cleavage. Rearrangement of this product then occurs, followed by attack of the reagent on the reactive COF group (Scheme 20) <92CCR47>. Nitrogen substituted β -fluorosultones also appear to react in a similar manner (Scheme 21) <94IC628>.



Scheme 20

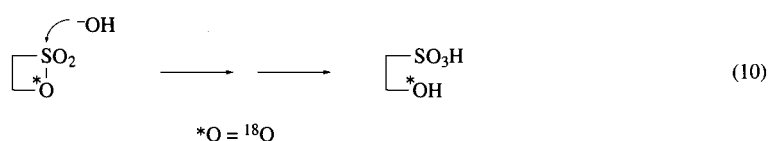
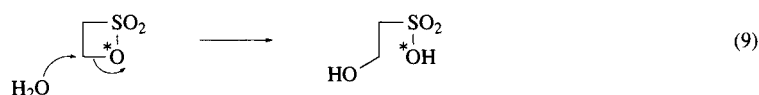


Scheme 21

Like their fluorinated cousins, polyhalogenated β -sultones react readily with a number of nucleophiles, including amines, amidines, guanidines, and hydrazine, via nucleophilic attack at sulfur <78AP(311)698, 81AP(314)799>.

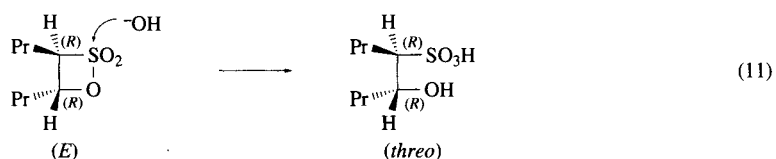
1.34.6.2.2 Nonfluorinated β -sultones

Unlike β -fluorosultones, these ring systems are ambivalent in their reactions with nucleophiles. Ring opening under acidic or neutral conditions tends to occur via nucleophilic attack at ring carbon (Section 1.34.6.3) with C—O bond cleavage whereas, less commonly, under alkaline conditions, nucleophilic attack occurs preferentially at ring sulfur with S—O bond cleavage <88CC415, 89CJC2162, 92RTC188>. King and Hillhouse have shown that ethanesultone (**4**) is an intermediate in the hydrolysis of 2-hydroxyethane sulfonyl chloride <83CJC1583>. Isotopic (¹⁸O) labelling experiments and further kinetic investigations have led to the proposed mechanism shown in Equations (9) and (10) <88CC415, 89CJC2162>.



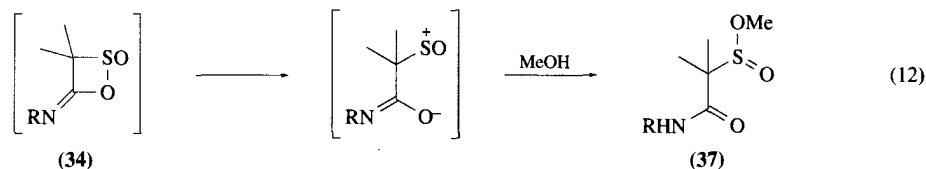
The explanation offered after a careful study of C—S—O—C dihedral angles in sulfonic esters (using crystallographic data) is that the favored conformation of (**4**) possesses a C—S—O—C dihedral angle ($\sim 75^\circ$) which endows the ring sulfur with near maximum electrophilicity by limiting delocalization of the type C—SO₂—O—C $\leftrightarrow$ C— $\dot{S}$ O₂— $\ddot{O}$ —C.

Bakker *et al.* have shown that hydrolysis of 4,5-octanesultone also occurs by nucleophilic attack at carbon under acidic conditions and via attack at sulfur under basic conditions <92RTC188>. The latter was shown to occur with retention of configuration (Equation (11)).



1.34.6.2.3 Reactions of β -sultines

Relatively little has been reported for β -sultines, but the β -sultinimine (**34**) proposed as a reaction intermediate (and not isolated) may be the source of product (**37**) formed in methanol, via nucleophilic attack at ring sulfur, although a dissociative mechanism is suggested (Equation (12)) <81CC350>.



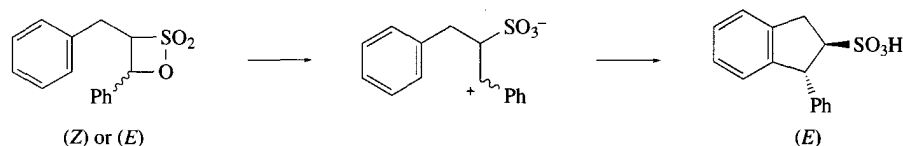
1.34.6.3 Nucleophilic Attack at Ring Carbon

The ring carbon bonded to oxygen in nonfluorinated β -sultones is susceptible to nucleophilic attack, and many examples have been reported in the literature. Nucleophiles include alkoxides <84PS(20)259>, carboxylic acids <84MI 134-01, 92RTC478>, amines <84MI 134-01>, water <88CC415, 89CJC2162, 92RTC188>, halide <89CJC2162> and various carbon nucleophiles (but see Section 1.34.6.5 for reactions with organometallic compounds) <92RTC188, 92RTC389, 93RTC247>. Much of the evidence for the C—O bond cleavage pathway via nucleophilic attack at ring carbon comes from isotopic labelling and stereochemical studies. King *et al.* have found that ethane sultone (**4**), formed as an intermediate in the hydrolysis at pH 6 of 2-[^{18}O]-hydroxyethane sulfonyl chloride, gives hydrolysis products with 90% of the ^{18}O label attached to the sulfur atom (see Equation (10)) <88CC415>.

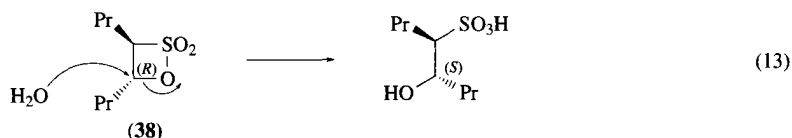
Cerfontain and co-workers have studied a number of reactions which involve intramolecular nucleophilic attack at ring carbon <92RTC188, 92RTC389, 93RTC247>. Since these are really rearrangement/isomerization reactions, they are discussed in Section 1.34.6.1 and consideration here is limited to mechanistic criteria. It has been observed that these intramolecular reactions mainly proceed with inversion of configuration at ring carbon, strongly suggesting an $\text{S}_{\text{N}}2$ pathway (Schemes 16 and 17). It is of interest to note that some of these reactions may be assisted by sulfonation of the β -sultone ring oxygen, as described in Section 1.34.6.4.

Other reactions of this type are nonstereoselective and probably proceed via an $\text{S}_{\text{N}}1$ process which involves unimolecular ring opening, followed by internal nucleophilic attack to give the thermodynamically more favored (*E*) product (Scheme 22) <92RTC389>.

Cerfontain and co-workers have studied the hydrolysis and methanolysis of octane- β -sultones and have shown that reactions are stereoselective, involving $\text{S}_{\text{N}}2$ attack at ring carbon <92RTC188>. Thus hydrolysis of racemic (**38**) leads to the racemic *erythro* product under acidic conditions (Equation (13)).



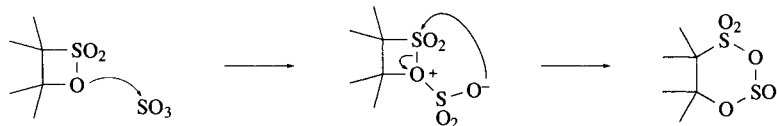
Scheme 22



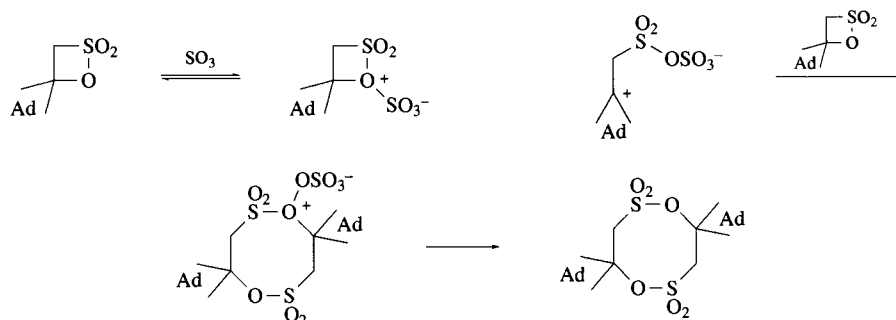
1.34.6.4 Electrophilic Attack at Ring Oxygen

Nonfluorinated β -sultones readily form cyclic pyrosulfates, commonly known as carbyl sulfates, in the presence of excess SO_3 <57JA5000, 65BSF787, 75JOC1179, 87TL1703, 89JOC1680>. Bakker and co-workers have proposed that these reactions proceed by electrophilic attack at the ring oxygen of

the β -sultone, with SO_3 behaving as a Lewis acid (Scheme 23) <87TL1703, 89JOC1680>. It has been proposed that attack of SO_3 at ring oxygen also occurs in some isomerizations <92RTC389> as well as being an important step in the cyclic dimerization of certain β -sultones (Scheme 24) <89JOC1680>.



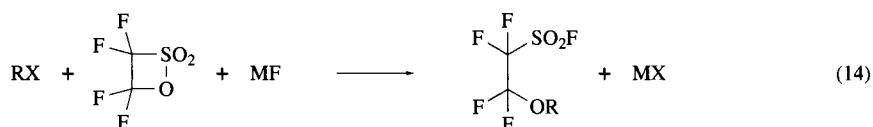
Scheme 23



Ad = adamantyl

Scheme 24

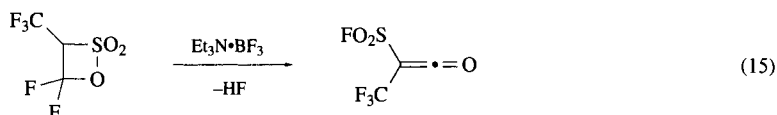
In the case of fluorinated β -sultones, reactions which may at first sight appear to involve electrophilic attack at ring oxygen are more likely to proceed via the usual rearrangement to the corresponding α -fluorosulphonylalkanoyle fluorides followed by formation of the metal alkoxide which then undergoes an $\text{S}_{\text{N}}2$ reaction with RX , for example (Equation (14)) <90JFC(46)21, 93JFC(64)11>.

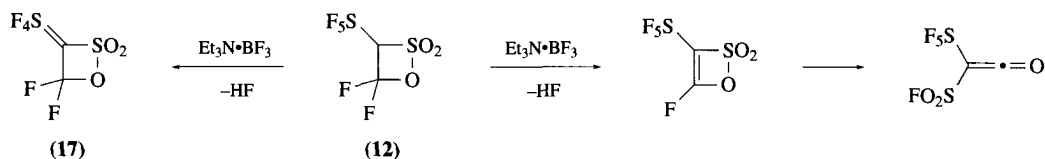


1.34.6.5 Miscellaneous Reactions

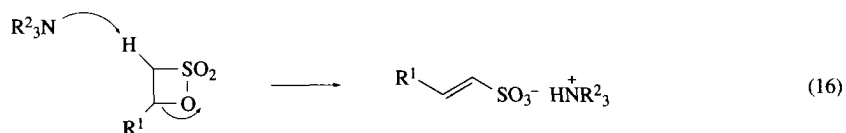
1.34.6.5.1 Elimination reactions

Fluorinated β -sultones with a hydrogen at the ring 3-position undergo dehydrofluorination in the presence of an amine- BF_3 complex to give the corresponding ketene (Equation (15)) <78MI 134-01>. The pentafluorosulfonyl β -sultone (**12**), however, undergoes dehydrofluorination by two routes, one of which leads to the interesting and useful unsaturated β -sultone (**17**) (Scheme 25) <89IC3766>. Nonfluorinated β -sultones react with tertiary amines to form ammonium alkenesulfonates (Equation (16)) <72AG(E)583>.



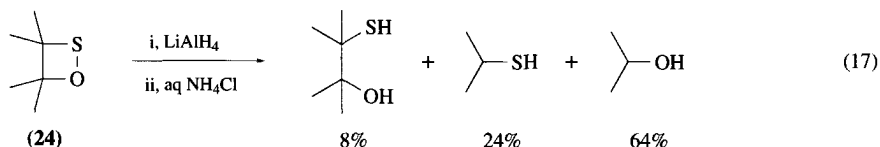


Scheme 25

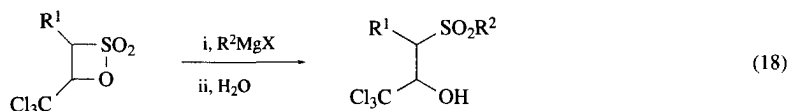


1.34.6.5.2 Other reactions

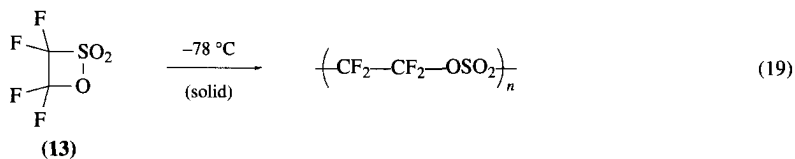
The 1,2-oxathietane (**24**) is reduced by lithium aluminum hydride to give a variety of products (Equation (17)) <86JA3811>.



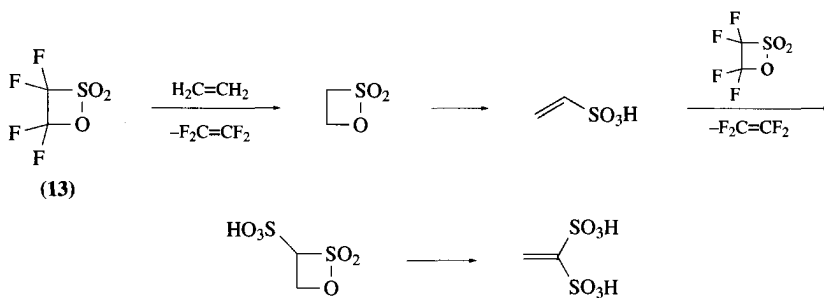
Chlorinated β -sultones are reduced by Grignard reagents, presumably by nucleophilic attack at ring sulfur (Equation (18)) <81S229>.



The only self-polymerization of these small ring compounds to be reported is that of the fluorinated β -sultone (**13**) in the solid phase (Equation (19)) <72AG(E)583>



An interesting reaction of (**13**) with ethene to produce the bisulfonic acid can be explained by successive transsulfonations and isomerizations (Scheme 26) although no mechanistic details are available <70IZV625>.



Scheme 26

1.34.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON

There is limited information on the reactions of ring substituents at carbon, other than single atoms such as hydrogen or fluorine, or nucleophilic groups which participate in isomerizations (see Section 1.34.6.3). Indeed the only detailed reports involve the reactivity of exocyclic double bonds in β -fluorosultones. Thus compound (**38**) readily adds HCl, HF, and ClF to its S—C bond <89IC3766>. It also reacts with alcohols, although the addition product has only been properly characterized for R—Me (see Scheme 29) <91JFC(52)57>.

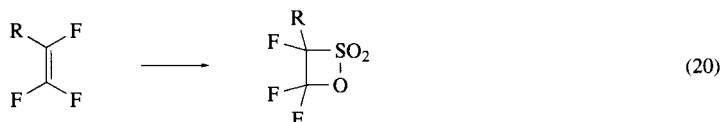
1.34.8 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

1.34.8.1 Cyclizations of Two-atom Components

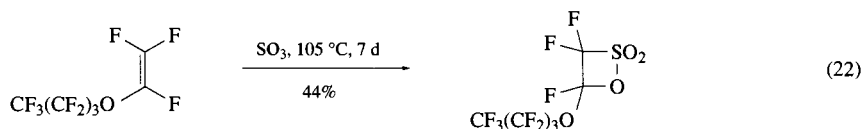
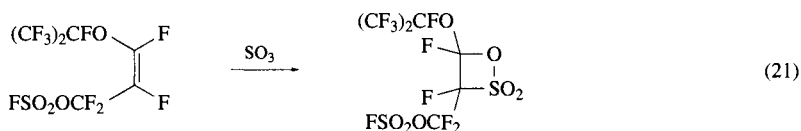
1.34.8.1.1 Cyclizations involving S—C and O—C bond formation

Cycloadditions of SO₃ and C=C (i.e. alkene sulfonations) are the most investigated and exploited routes to β -sultones in general, and synthesis of some β -sultines via SO₂ and C=C cycloadditions (alkene sulfinations) have also been reported. However, there are no reports of cycloadditions leading to simple oxathietane systems. Sulfonation of fluoroalkenes offers the best route to fluorinated β -sultones, and many such compounds have been synthesized in this way <72AG(E)583, 92CCR47>. Sulfonation is carried out under a variety of conditions, but pure, freshly distilled SO₃ is essential, either prepared from the trimer or generated *in situ* <84IC4403, 89JFC(42)119>. Trimeric SO₃ is not as reactive as the monomer, but can be used to prepare certain β -fluorosultones <92IS33>. Formation of β -sultones is inhibited by the presence of B₂O₃, various open chain products such as fluoroalkenyl fluorosulfates being produced instead <82IZV2468>. Sulfonation of fluorinated alkenes is generally carried out at high temperatures, typically higher than 100°C, often using a Carius tube with a Kontes teflon valve.

β -Fluorosultones with simple fluorinated or chlorinated side chains have been prepared from the corresponding alkene (Equation (20)) <86JOU1653, 90JFC(46)491, 90JFC(50)31>.



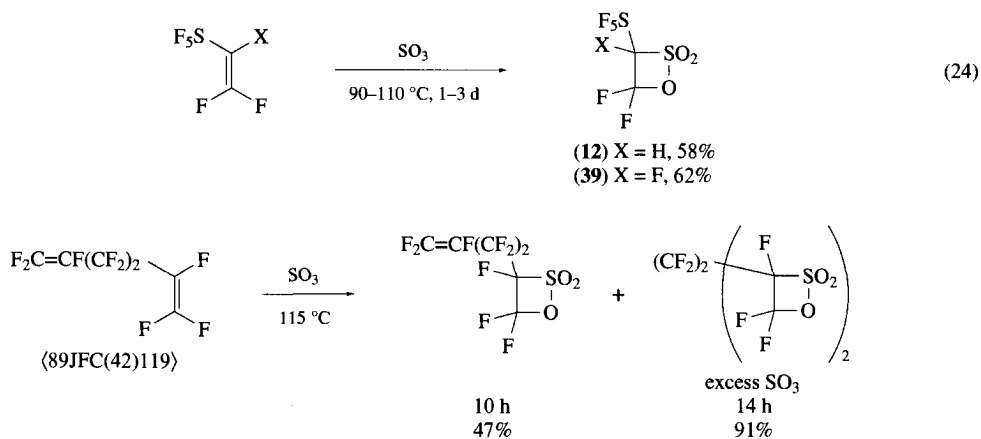
Typical reaction conditions were 120°C (8 h) for the β -sultones with fluorinated side chains <86JOU1653, 90JFC(46)491> and 0°C to 50°C (up to 7 days) for those with chlorinated side chains <90JFC(50)31>. Compounds with oxygenated fluorocarbon side chains have been made in a similar way <89JFC(43)349> but, if an oxygen atom is attached to an alkene carbon atom, reverse addition of SO₃ occurs (Equations (21) and (22)) <86JOC4460, 90JFC(50)31>.



The synthesis of the first β -fluorosultones with nitrogen-containing side chains has been reported, again with reverse addition of SO₃ (Equation (23)) <94IC628>.



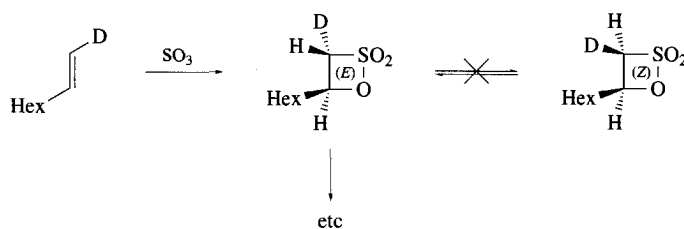
Synthesis of pentafluorosulfur derivatives of fluorinated β -sultones from pentasulfuryl alkenes has been of considerable value since the mid-1980s, on account of potential industrial applications (see Section 1.34.11) (Equation (24)) $\langle 84\text{IC}4403, 88\text{IC}2916 \rangle$. Seppelt and co-workers have reported the formation of 1,2,4-oxadithietanes as by-products in this reaction $\langle 92\text{CB}557 \rangle$. Nonconjugated (typically α, ω -) perfluorodienes can also be sulfonated to give the mono β -sultone, or with excess SO_3 , the bis β -sultone (Scheme 27) $\langle 82\text{IZV}2230, 89\text{JFC}(42)119 \rangle$.



Scheme 27

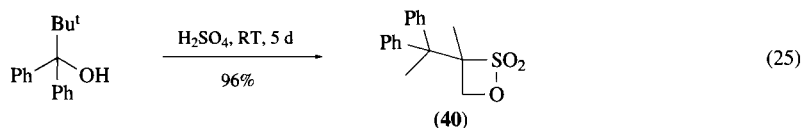
Sulfotrioxidation of nonfluorinated alkenes has been studied for some time, initially by Bordwell and co-workers, who were interested in other aspects of alkene sulfonation (59JA2000, B-91MI 134-01). Since the late 1980s, the subject has received considerable attention from Bakker, Cerfontain, and co-workers (87TL1699, 87TL1703, 89TL5451, 89JOC1680, 92RTC49, 92RTC188, 92RTC389, 92RTC478, 93RTC201, 93RTC247), Roberts and co-workers (85JCS(P)2389, 87TL3383), and other workers (84MI 134-01, 84PS(20)259, 90MI 134-01, 91MI 134-01). The SO_3 reagent is usually used in the form of its Lewis acid–base complex with dioxane or pyridine (87TL3383) in order to moderate its reactivity, but gaseous SO_3 (75GEP(O)2362536) and chemisorbed SO_3 have also been used (85MI 134-01). Also acetyl sulfate has been used as the sulfotrioxidation agent (84MI 134-01, 90MI 134-01). Reactions are generally performed at low temperatures (typically -20°C) in respect of the greater reactivity of non-fluorinated alkenes. Also, unlike the β -fluorosultones, nonfluorinated β -sultones have only rarely been isolated (88SUL55, 92RTC478), on account of their predisposition toward rearrangement and other reactions (see Sections 1.34.6.1.2 and 1.34.6.3) at higher temperatures. However, good solution yields of β -sultones have been observed when sulfotrioxidation has been monitored by NMR spectroscopy (87TL1699, 89TL5451, 91MI 134-02). There is now very good evidence that addition of SO_3 to $\text{C}=\text{C}$ is a thermally allowed concerted $[\pi\ 2s + \pi\ 2s]$ process, especially in view of the observed stereoselective formation of β -sultones (Scheme 28) (87TL1699, 87TL1703, 87TL3383).

Dehydration of 2,2-dimethyl-1,1-diphenylpropan-1-ol by concentrated H_2SO_4 produced the

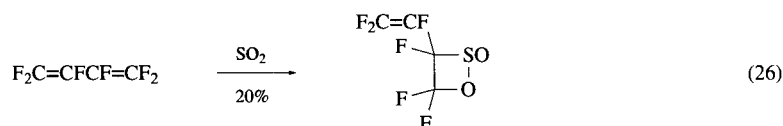


Scheme 28

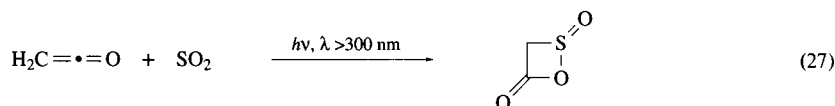
β -sultone (**40**) (Equation (25)) <77JCS(P1)247>. The mechanism suggested involves dehydration and re-arrangement to 2,3-dimethyl-3,3-diphenylprop-1-ene, followed by addition of the elements of SO_3 .



Some of the earliest reports of β -sultone synthesis involved the addition of SO_2 to polyhalogenated (mainly fluorinated) alkenes, although often in low yield (Equation (26)) <60JA6181, 66JCS(C)1171, 78IZV142, 79IZV106>.

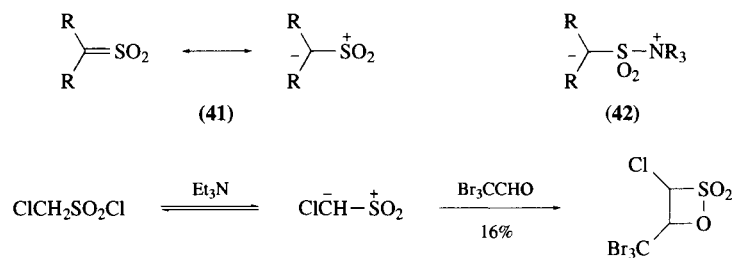


Additionally, Dunkin and MacDonald were able to identify the 1,2-oxathietan-4-one 2-oxide, a product of the photochemical addition of SO_2 to keten in an argon or nitrogen matrix at 10–20 K (Equation (27)) <78CC1020, 84JCS(P2)2079>. Also the norbornenyl sultone (**32**) was synthesized (though not in pure form) by the addition of SO_2 to quadricyclane at low temperatures <82CC464>.



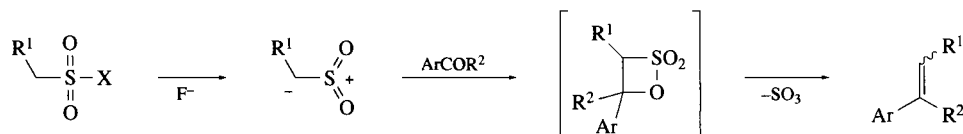
1.34.8.1.2 Cyclization involving S—O and C—C bond formation

The most widely reported reactions of this type are those between sulfenes (**41**) or their zwitterionic analogues (**42**) and carbonyl compounds, mostly halogenated derivatives, to give polyhalogenated β -sultones (Scheme 29) <66CB1245, 66GEP1227890, 69CI(L)457, 78JCR(S)484, 81AP(314)799>.



Scheme 29

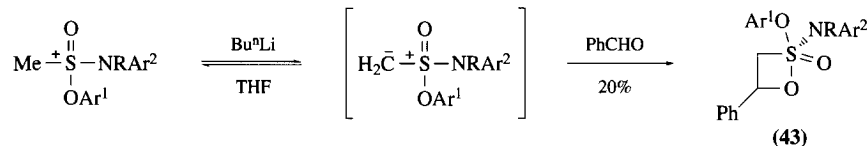
Since the mid-1980s, β -sultones have been implicated in reactions between sulfenes and 1,2,3-tricarbonyl compounds, but not actually isolated <88AP(321)85>. Similarly β -sultones formed in this way have been postulated as intermediates in alkenation reactions of ketones, but again none has been isolated <94JOC2898>. The sulfenes here are unique in being generated by fluoride-catalyzed dehydrohalogenation of the alkanesulfonyl halide (Scheme 30).



Scheme 30

Syntheses of fluorinated β -sultones from $\text{CF}_3\text{CFHSO}_2\text{F}/\text{Me}_3\text{N}-\text{SiF}_4$ and $(\text{CF}_3)_2\text{CO}$ have been reported <92CCR47>, but this appears to be the only report of its kind for β -fluorosultones. Formation

of an unusual 1,2-oxathietane derivative (**43**) from a sulfene and benzaldehyde has been reported <81JA5976>. The sulfene is generated by reaction of the aminoaryloxyoxosulfonium salt (**44**) with butyllithium (Scheme 31). There appear to be no other reports of this type of reaction.

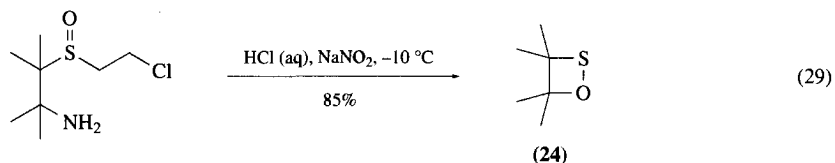
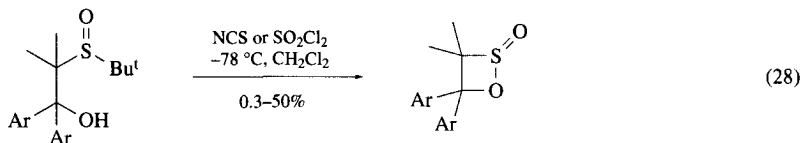


Scheme 31

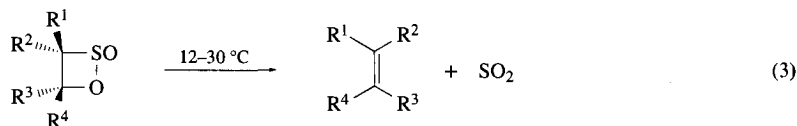
1.34.8.2 Cyclization of a Single Four-atom Component

Intramolecular cyclizations are important in the synthesis of a number of 1,2-oxathietane systems, especially simple 1,2-oxathietane and β -sultines, but a small number of β -sultones have been synthesized this way too, as intermediates.

A significant number of β -sultines have been prepared by the cyclization of 2-hydroxy sulfoxides in the presence of sulfonyl chloride or *N*-chlorosuccinimide (Equation (28)) <75CC724, 81JCS(P1)1826>. The postulated mechanism involves transfer of Cl^+ from NCS or sulfonyl chloride to form a chloro oxosulfonium intermediate which then undergoes ring closure to produce the β -sultine, with elimination of Bu^tCl . Lown and Koganty have succeeded in preparing the sole example of a simple 1,2-oxathietane (**24**) by diazotization of (**43**) (Equation (29)) <86JA3811>. Unfortunately this remains the only example of its kind.



S-fluorinated oxathietes (e.g. (**30**)) have been prepared by the isomerization of benzoylalkylidene sulfur tetrafluorides as outlined in Equation (30)) <90AG(E)1128>.

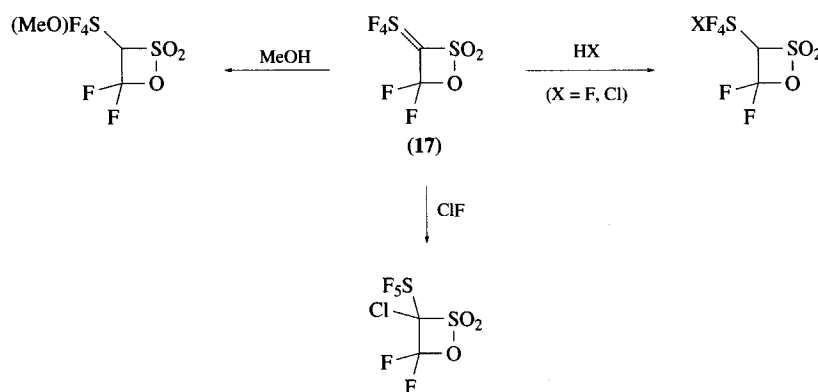


β -Sultones have been postulated as intermediates in the hydrolysis of 2-hydroxyalkanesulfonyl chlorides, but have not been isolated (see Section 1.34.6.2.2) <87PS(31)161, 88CC415, 89CJC2162>.

1.34.9 OTHER SYNTHESSES

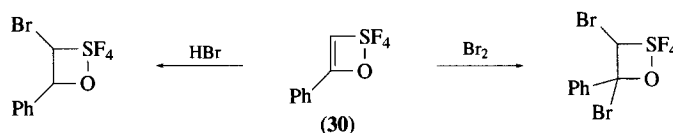
There are few syntheses outside the reaction categories discussed in the previous sections. In particular there appear to be no reports of syntheses by transformations of other rings, either by ring contraction or expansion.

Saturated fluorinated β -sultones have been prepared by addition to the $\text{S}=\text{C}$ bond of compound (**17**) (Scheme 32) <89IC3766, 91JFC(52)57>.



Scheme 32

Saturated S-tetrafluoro-1,2-oxathietanes have been reported as being the products of addition to the ring double bond of (30) (Scheme 33) <90AG(E)1128>.



Scheme 33

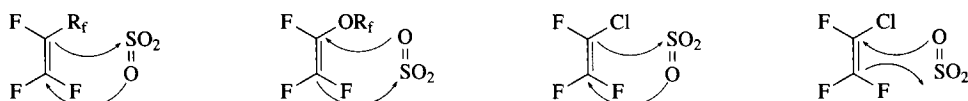
1.34.10 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND A CRITICAL COMPARISON OF AVAILABLE ROUTES

1.34.10.1 Fluorinated β -Sultones

The sulfotrioxidation of (fluorinated) alkenes route ($[2 + 2]$ addition; $\text{S}-\text{C} + \text{O}-\text{C}$ bond formation) to this important class of compounds is easily the most common one and has been much exploited and refined since the earliest reports by England, Knunyants, Sokol'skii, and their co-workers in the 1950s and 1960s. Many β -fluorosultones (well over 50) have been prepared in usually high yields (certainly often better than 50%), provided freshly distilled SO_3 is used in conjunction with apparatus designed to accommodate the reaction at high temperatures (100°C or higher), which are required to effect reaction. Two typical examples are given in detail in reference <92IS33>.

The major limitation of the method is the type of alkene that can be sulfotrioxidized: partially fluorinated alkenes generally give low yields of β -sultones because of successful side reactions. Also fluoroalkenes with nonfluorinated side chains must be treated at lower temperatures to prevent or minimize side chain sulfonation.

The direction of SO_3 addition to $\text{C}-\text{C}$ is usually well defined; nucleophilic oxygen bonds to the alkene carbon which is better able to support a positive (or partial positive) charge (the more electrophilic carbon, usually CF_2). "Reverse" addition occurs if the other alkene carbon atom is bonded to a stronger electron donor (e.g. fluoroalkoxy, R_fO). In cases of carbon atoms with similar electrophilicity, both additions can occur (Scheme 34).



Scheme 34

1.34.10.2 Nonfluorinated β -Sultones

The sulfotrioxidation of nonhalogenated alkenes can often produce high yields of β -sultones in solution, according to NMR evidence, but only rarely have β -sultones been isolated by this means. However, formation of other products via the β -sultones is often sterically controlled, and hence this procedure is of considerable synthetic value. The reactions are carried out at low temperatures (typically -70°C) to minimize side reactions, often using SO_3 dioxane complex, typically in dichloromethane, to moderate SO_3 reactivity and to reduce charring.

Of greater use in the preparation of pure samples of β -sultones is the carbonyl-sulfene cyclo-addition route ($[2 + 2]$ addition; $\text{S}=\text{O} + \text{C}=\text{C}$ bond formation). However, this method appears to be limited to halogenated aldehydes and ketones, such as $\text{Cl}_3\text{C}\cdot\text{CHO}$, possibly because of the superior reactivity (electrophilicity) of their carbonyl carbon atoms. Intramolecular cyclization routes have not been extensively investigated, except in mechanistic studies where there is good evidence for the formation of β -sultones, despite the strained nature of the transition state in the cyclization step.

1.34.10.3 β -Sultines, 1,2-Oxathietanes

The most widely reported route to β -sultines is by the intramolecular cyclization route via $\text{O}=\text{S}$ bond formation in 2-hydroxysulfoxides. The method appears to be limited to β -sultines with fully substituted carbons.

Sulfodioxidation of halogenated alkenes ($[2 + 2]$ addition; $\text{S}=\text{C}$ and $\text{O}=\text{C}$ bond formation) is reported to be useful in the synthesis of a limited number of β -sultines, and sulfodioxidation of quadricyclane has produced a β -sultine with only two ring carbon substituents. These routes have not been significantly extended since the mid-1980s. Intramolecular cyclization routes are the only ones reported for the synthesis of 1,2-oxathietanes and 1,2-oxathietes, there being only a handful of properly characterized examples.

1.34.11 IMPORTANT COMPOUNDS AND APPLICATIONS

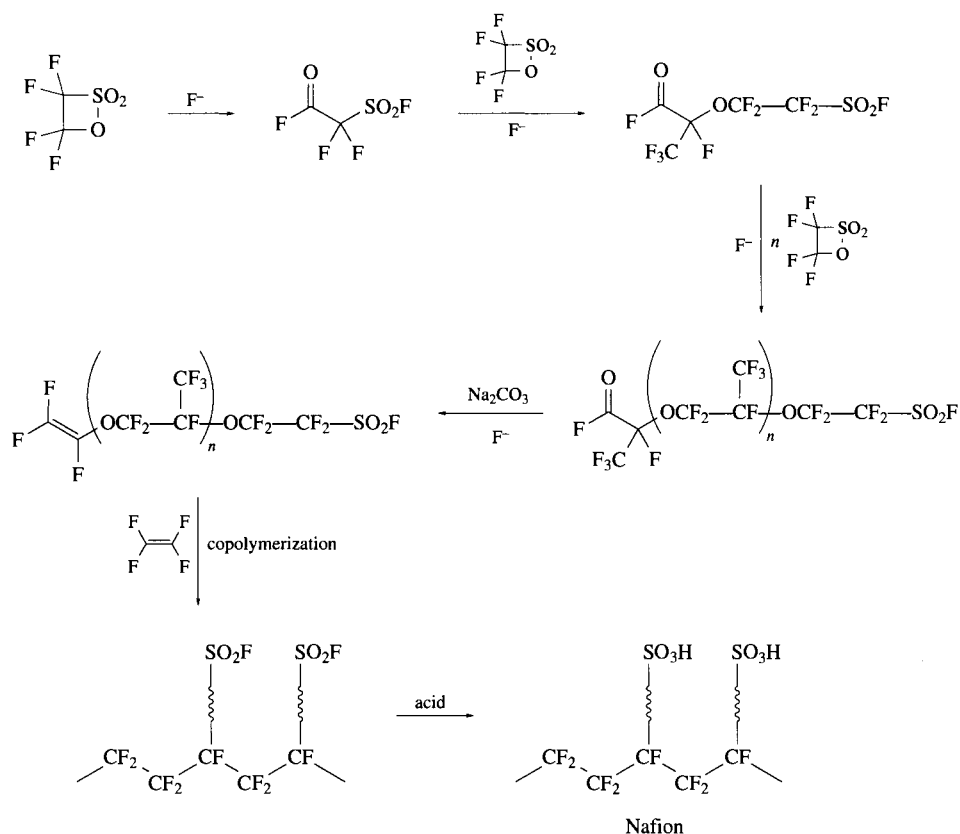
The most important oxathietane derivatives are the fluorinated β -sultones, mainly because the α -fluorosulfonyl polyfluoro-carbonyl fluorides rearrangement products (Section 1.34.6.1.2) can be converted to fluorinated polymers which have found use as ion exchange resins, fuel cell electrolytes, and catalysts in organic synthesis. Of particular interest is the polymeric sulfonic acid called Nafion (Du Pont), which is prepared as outlined in Scheme 35 <86MI 134-01>. Nafion has been used as a polymer supported superacid <86S513>, a fuel cell electrolyte, and a membrane-ion separator <58USP2852554, 66USP3282875, 86MI 134-01, 92CCR47>.

A fluorinated ion exchange copolymer was prepared as long ago as 1960 <60USP3041317>, but in the late 1980s, Gard and co-workers prepared several potential ion exchange resins by reaction of β -fluorosultones (**12**) and (**13**) with polyvinyl alcohol. Similarly, β -fluorosultones (**12**), (**13**), (**18**), and (**38**) were reacted with allyl alcohol in the presence of fluoride to produce fluorosulfonyl alkenes which were then polymerized with UV light (Scheme 36) <88JFC(38)3>. A similar reaction sequence has been performed on fluorinated β -sultones with fluoroether side chains <89JFC(43)349> and on mono- and bis β -sultones derived from perfluorohexa-1,5-diene <89JFC(42)119>. Additionally, the bis β -sultone of $\text{CF}_2=\text{CFCF}_2\text{O}(\text{CF}_2)_5\text{OCF}_2\text{CF}=\text{CF}_2$ has been prepared as an intermediate for monomers <88JAP(K)63039873>.

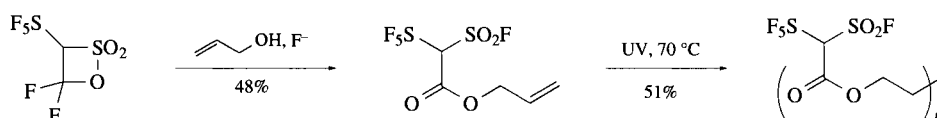
Potentially useful ion exchange resins have been prepared by the reaction of polyanions from poly(benzimidazoles) with β -sultones. In the early 1990s, monomers derived from perhalogenated β -sultones were used to synthesize an ionically conducting cross-linked copolymer <92FRP9316988>.

Fluorinated β -sultones are also useful precursors of surfactant materials, as shown by Bargigia *et al.* who converted (**13**) into anionic surfactant (**45**) by the sequence of reactions in Scheme 37 <82JFC(19)403>. Surfactant (**45**) is reported to be very stable to heat as well as to aggressive reagents such as CrO_3 and strong acids. Application of pattern recognition and linear programming has resulted in the optimization of yields of (**45**) (Scheme 37) <90MI 134-03, 91MI 134-02>.

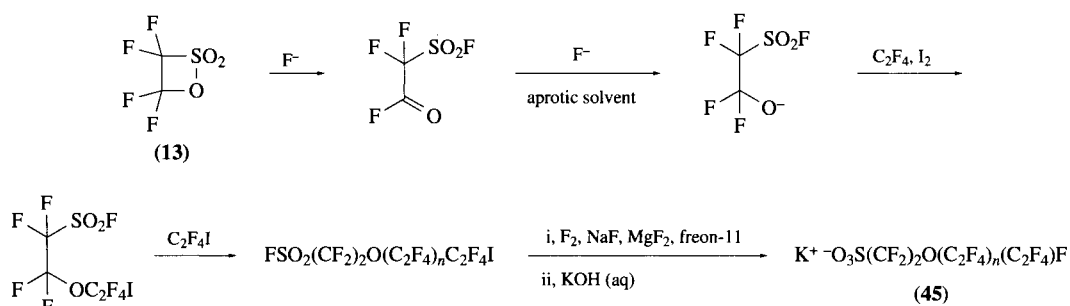
Of particular interest is the use of sulfobetaine derivatives of tri-2-pyridylphosphine as surfactant ligands in the Rh-catalyzed micellar biphasic hydroformylation of 1-tetra-decene <91JMOC143>. The surfactant ligands were prepared by reaction (sulfoalkylation) of the phosphine derivative with β -sultones. A number of sulfonic acids (e.g. $\text{SF}_3\text{CF}_2\text{SO}_3\text{H}$, $(\text{HO})_2\text{P}(\text{O})\text{CF}_2\text{SO}_3\text{H}$) have been prepared



Scheme 35



Scheme 36



Scheme 37

from β -sulfones <89CJC1795, 89JA1773, 90USP9007513>, as has a potentially useful fluorinating agent <90EUP384261>.

Although relatively few nonfluorinated β -sulfones have actually been isolated, they are nevertheless important precursors of sulfonic acids, which are themselves valuable precursors of surfactants. An understanding of the chemistry of β -sulfones has helped in the optimization of sulfonic acid production. Thus Yoshimura *et al.* were able to minimize cycloreversion of β -sulfones, produced by sulfotrioxidation of nonterminal alkenes, while maximizing sulfonic acid yields <91MI 134-02,

92MI 134-01>. This was done by performing the hydrolysis of the β -sultones in two steps: firstly at 35°C to eliminate cycloreversion competition, and secondly at above 100°C to convert all γ -sultones and other rings (formed from β -sultones earlier) to the 2-alkenesulfonic acids.

ACKNOWLEDGEMENT

The author is indebted to Jack Timberlake and Eleanor Elder for supplying much useful information.

1.35

Four-membered Rings with Two Sulfur Atoms

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1.35.1 INTRODUCTION

1.35.1.1 Historical and Future Perspectives

Small rings and the associated concepts of distorted hybridization and strain have fascinated organic chemists for more than a century and this interest shows no sign of abating; if anything, it is growing <89CRV973>. Indeed, three- and four-membered rings, over the years, have received great attention from both experimental and theoretical perspectives. However, the consequences of replacing one or more of the cyclic carbon atoms in these systems by heteroatoms, on bonding and structure, strain energies, chemical reactivity, and reaction mechanisms are still being extensively explored in an attempt to bridge the gap between theoretical predictions and experimental tests <94JA9311, B-94MI 135-01>.

Although no three-membered rings with two heteroatoms were prepared before 1950, several

isolable compounds incorporating two heteroatoms, one or both sulfur, are known to date (B-83MI 135-01, 93JA4914). Similarly, examples of virtually all four-membered rings with two heteroatoms, including those with two sulfur atoms, have been prepared (84CHEC-I(7)449). In this series, however, four-membered rings containing two sulfur atoms such as derivatives of the 1,3-dithietane system (2) have been known for over 120 years (1872CB970).

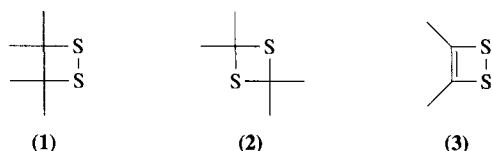
It is well established that the introduction of heteroatoms into small rings produces significant variations in the molecular geometry which reflect the changes in covalent radii, electronegativity, charge distribution, and effective hybridization. Consequently, there are changes in the bonding of these heterocyclic systems compared to that of the hydrocarbon analogues. Indeed, the carbon-heteroatom bond length shows an effective increase with increasing heteroatom electronegativity, in line with potential facile ring opening involving the carbon-heteroatom bonds. This, coupled with the ring strain, makes the three- and four-membered rings containing two heteroatoms thermally unstable and highly reactive: carbon-heteroatom and heteroatom-heteroatom bonds are weak compared to the corresponding bonds in unstrained systems. Indeed, small-ring heterocycles are the foremost chemically reactive among the class of small-ring compounds, making these molecules intriguing for preparation and study. In view of the above, it is no wonder that the parent compounds in three-membered ring systems containing two heteroatoms, at least one of which is sulfur, are not known thus far. Also the parent compound of the four-membered 1,2-dithietane system (1) has until now remained unknown. The parent compound of the 1,3-dithietane system (2) was first prepared in 1976 (76JA5715) whereas that of the 1,2-dithiete system (3) is thermally stable only within low temperature matrix conditions (89JA7651).

Extensive research since 1980 has established that theory, in particular molecular orbital *ab initio* calculations, is an extremely useful and reliable source of fundamental chemical information (such as molecular structure, thermodynamic data, and electronic structure) for a wide variety of molecules (B-86MI 135-01). On the other hand, gas-phase ion-molecule investigations have been demonstrated to be very useful for probing intrinsic reactivities even for reactive intermediates such as small-strained rings and heterocycles (both neutral and ionic), which are difficult to examine in solution. Since the experimental results of gas-phase studies are directly comparable to *ab initio* molecular orbital calculations, these two complementing strategies appear to be the combined methods of choice for the future study of four-membered rings containing two sulfur atoms. Indeed, by adding a second set of both *d*- and *f*-type polarization functions, *ab initio* quantum mechanical calculations at the MP2/6-31G (2*d*2*f*) level of theory predicted the parent compound of the 1,2-dithiete heterocyclic system (3) to have higher thermodynamical stability than its ring-opened isomer (1,2-dithioglyoxal), in full agreement with experimental results (91CPL(177)175).

Thus, the combination of these two methodologies with the development of synthetic methodologies for the preparation of thermodynamically and kinetically stable four-membered ring systems of types (1)–(3), via appropriate (bulky) substitution and/or their inclusion within appropriate stabilizing systems, will facilitate answers to the still open questions related to this class of intriguing compounds.

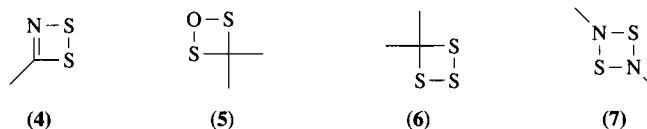
1.35.1.2 Structural Types, Nomenclature, and Scope

The International Union of Pure and Applied Chemistry (IUPAC) uses the name “thietane” and “thiete” for the saturated and unsaturated four-membered ring systems (1), (2), and (3), respectively containing two sulfur atoms within the cyclic array. Thus, the 1,2-dithietanes (1), 1,3-dithietanes (2) and the 1,2-dithietes (3) constitute the focus of this chapter.



The related four-membered ring systems containing three heteroatoms, at least two of which are sulfur atoms, are dealt with briefly to do justice to the subject of this chapter: “Four-membered Rings with Two Sulfur Atoms”. This refers to the 1,2,3-dithiazetidines (4), 1,2,4-oxadithietanes (5), 1,2,3-trithietanes (6), and 1,3,2,4-dithiadiazetidines (7). There are relatively few reports of such four-

membered heterocycles <84CHEC-I(7)449> and still more study is required for structural substantiation of the early assignments made.



Up to 1995, all of the above systems, albeit not necessarily the parent compound (e.g. the unsubstituted (1), or the neutral species (e.g. (4)) have been synthesized. While the chemistry of the first three is well established, this is not the case concerning the last four as well as additional closely related systems such as the yet unknown 1,2,4,3-oxadithiazetidine.

Four-membered heterocycles containing two sulfur atoms were initially reviewed in 1976 <76RCR639> and within a comprehensive review on four-membered sulfur heterocycles summarizing the relevant literature up to mid-1982 <B-83MI 135-02>. A review within this series <84CHEC-I(7)449> provides the state of the art concerning the systems (1)–(7) up to the early 1980s.

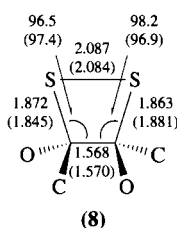
The relevant literature since 1984 reviewed here includes the literature pertaining to the first three: 1,2-dithietane, 1,3-dithietane, and 1,2-dithiete systems ((1)–(3)) cited in *Chemical Abstracts* to about mid-1994 and in the *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Journal of the Chemical Society*, *Tetrahedron*, and *Tetrahedron Letters*, also up to about the same date. However, this chapter is not exhaustive nor inclusive: the criterion for the inclusion of or dealing with any topic, item, data, or issue related to four-membered rings containing two sulfur atoms was the potential contribution of each of the former to the understanding of the structure–reactivity relationships in these systems and their mapping within the class of small-ring heterocycles. The preparation and study of uniquely substituted compounds of the titled series is not only challenging, but also promising, owing to their potential for providing a deeper insight into the unique structural features and chemical behavior of these intriguing systems.

1.35.2 STRUCTURE OF DITHIETANES AND DITHIETES

1.35.2.1 Theoretical Methods

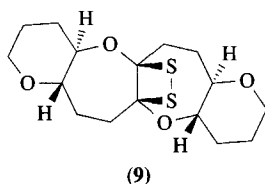
Very few theoretical studies on the saturated dithietane systems (1) and (2) were reported until the 1990s. Thus, with respect to the 1,2-dithiane (1), theoretical calculations (CBDO/B) have suggested optimized geometries of 2.146 and 1.835 Å for the S—S and S—C bonds, and 99.1° and 80.9° for the S—C—S and C—S—S angles, respectively. Frontier orbital energies were calculated to be –0.07 and –10.1 eV and the spectrum lines 396, 242, 224, 201, and 186 nm <77JA2931>. The contribution of the sulfur 3d orbitals in the lowest unoccupied molecular orbital was estimated as 45% which is quite substantial. Previous CNDO calculations have matched the observed λ_{max} positions in the UV spectrum to the corresponding molecular orbitals <84CHEC-I(7)456>.

The isolation of the first stable 1,2-dithietane compound dithiatopazine in the late 1980s <87JA3801> made it possible to compare theoretical predictions based on sophisticated programs for *ab initio* molecular structure and quantum mechanical calculations with actual experimental results. Thus, MM2 force field parameterization for the oxygen-substituted 1,2-dithietane system (i.e. that of the dithiatopazine) provided optimized structures superpositioned with those of the x-rays as shown in (8). Application of the enhanced force field to the x-ray conformation of the thithiatopazine showed that the four-membered dithietane ring geometry is well described in this framework <90JA3029>. As one can see, there is an excellent match between the calculated and experimental values (in parenthesis) of bond lengths and angles.



The corresponding values calculated (6-31G*SCF) for the parent 1,2-dithiete (**12**; R = H) are 2.094, 1.765, 1.324 Å for the S—S, S—C and C—C bonds, and 102.60° for the S—C—C angle, respectively <87MI 135-01>. Significantly, the S—S bond lengths in (**8**) and (**12**) are essentially the same.

The above-mentioned mechanics evaluation, as well as additional quantum mechanical (PRDDO) calculations for various dithietane systems, led to the conclusion that dithiatopazine is a remarkably rigid structure experiencing little conformational mobility and that its singular stability arises from a combination of thermodynamic factors and internal energy distribution <90JA3029>. Strain and resonance effects can be expected to play a reduced role in the parent and simply substituted dithietane systems (i.e. (**1**)). Similarly, the ability of the latter to distribute their internal vibrational energy to regions of the molecule uncoupled to the thermally labile C—S bond <86JCP(84)4710> is significantly less than that of the fused system of the dithiatopazine (**9**). The thermal instability of the four-membered dithietane ring systems, particularly via the extrusion of the singlet S₂ moiety with the concomitant formation of the corresponding alkene, is thus explained: even though the barrier to S₂ extrusion for simple (**1**) may be somewhat higher than for (**9**), the probability for traversing it is higher too, resulting in a decreased thermal stability.



Ab initio calculations with geometries fully optimized (within the appropriate point group) at the UHF/6-31G* and UMP2/6-31G* levels showed the total energies for the four-membered ring 1,2-dithietane and 1,3-dithietane radical cations ((**10**) and (**11**)) to be (for a C_{2v} symmetry) -872.783 43, -873.274 85 (ZPE = 165.1), and -872.754 53, -873.255 56 (ZPE = 163.1) hartrees, respectively. The bond lengths in the former were calculated to be 1.541, 1.838, and 1.979 Å for the C—C, C—S, and S—S bonds, respectively in (**10**). The S₂C₂H₄^{•+} species was detected under chemical ion conditions (*m/z* 92) at low temperature and high pressures <93JA12510>.



Molecular orbital calculations have been performed on 1,2-dithiete systems throughout the 1960s and the 1970s <B-83MI 135-02>, primarily with respect to the equilibrium of the cyclic 1,2-dithiete with its 1,2-dithioglyoxal (or 1,2-dithione) valence tautomer (Scheme 1).



Scheme 1

Electron-releasing substituents were calculated to favor the ring-opened 1,2-dithione tautomer (**12b,c**) whereas electron-withdrawing substituents favor the cyclic dithiete structure, the S—S bond order increases with increasing electronegativity of the substituent <80JA6687>. *Ab initio* STO-3G calculations through energy minimization for the open ring form of the parent compound (**12c**; R = H, *syn*, C_{2v}-symmetry) provided the results of r(C—C) = 1.489 Å, r(C=S) = 1.591 Å, r(C—H) = 1.092 Å, ∠ C—C—H = 112.4°, and ∠ C—C—S = 126.4° compared with r(C—C) = 1.319 Å, r(C—S) = 1.769 Å, r(S—S) = 2.099 Å, r(C—H) = 1.080 Å, and ∠ C—C—H = 131.1° for the cyclic form (**12a**; R = H, C_{2v}-symmetry <83HCA801>). The then available experimental data for (**12a**) and (**12c**) were: r(S—S) = 2.10–2.12 Å, r(C—C) = 1.34–1.35 Å, and r(C—S) = 1.78–1.79 Å for the former and r(C—S) = 1.65 Å, r(C—C) = 1.47 Å for the latter. The opened-chain tautomer thus appears to dominate in the case of the parent 1,2-dithiete system. In most cases studied, the two highest occupied molecular orbitals were found to be b₂(π) and a₂(π) separated by about 2 eV from a third band (a₁(σ_{S,S})⁻¹) due to electron ejection from an orbital

which is essentially that of the S,S, σ -bond. These results, which are supported by the photoelectron (PE) spectral data of substituted 1,2-dithietes, led to the conclusion that the closed, four-membered ring moiety is present in all the 1,2-dithietes investigated <83HCA801>.

Quantum chemical calculations on the total energies of the various valence isomers (**12a–d**) did not yield unambiguous results concerning their relative stability <75JCS(P2)559, 83JA4519, 85ZC50>. However, the most elaborate calculations (optimization on the 6-31G* SCF level, addition of 3-21G*SCF zero-point vibrational, and MP4SDQ electron correlation energies to the energy minima obtained) determined the *trans* form (**12b**) to be more stable than the *cis* (**12c**) and the ring (**12a**) forms by ~ 4 and ~ 7 kcal mol $^{-1}$, respectively <87MI 135-01>. Further calculations at the MP2/6-31G* level of approximation resulted with a total energy minima of $-872.392\,60$, $-872.401\,31$, and $-872.394\,54$ AU for (**12a**), (**12b**), and (**12d**), respectively. These results indicate that the *trans* form (**12b**) is somewhat more stable than the *gauche* (**12d**) and the ring (**12a**) forms which lie higher in energy by 4.2 and 5.5 kcal mol $^{-1}$, respectively, in accord with the MP4/6-31G* (7.8), CCD/6-31G* (5.4), and MP2/6-311G* (6.6) energy differences between the more stable (**12b**) and (**12a**) <89JA7651>. In contrast to the IR data which unequivocally suggest the 1,2-dithiete as the most stable isomer, the computed total energies indicate the *trans* form (**12b**) to be the most stable thermodynamically. The orbital energies calculated for (**12a–c**) and the orbital correlation diagram for the PE spectra of a series of available 1,2-dithietes <83HCA801> confirmed earlier results <82JOC1979> according to which the ring-closed structure of the 1,2-dithiete is indeed the most stable.

The barrier for parent dithiete to ring open to dithioglyoxal has been calculated to be 32.1 kcal mol $^{-1}$ (3-21G* SCF) or 35.5 kcal mol $^{-1}$ (6-31G* SCF) with a predicted activation energy of 21.9 kcal mol $^{-1}$ (6-31G* MP4SDTQ). Thus, there is a substantial barrier to the isomerization of dithiete to *gauche*-dithioglyoxal which is very close in energy (within 3 kcal mol $^{-1}$) at the SCF or Moller-Plesset levels <90JA7529>. This result is consistent with the previously established lower stability of (**12d**) compared with that of (**12b**) by about 4–5 kcal mol $^{-1}$ <87MI 135-01, 89JA7651>.

The addition of polarization functions in the *ab initio* quantum-mechanical calculations at the MP2/6-31G(*d–3d*) levels of theory was found to be critically important for calculating the energy differences between the various valence isomers of the unsubstituted (**12**) <91CPL(177)175>. In these calculations the theoretically predicted geometries for (**12a,b,d**) at the MP2/6–31G(*d*) level <90ZC176> have been used. The predicted values are given in Table 1.

Table 1 Theoretically predicted geometries for the cyclic (**12a**), *trans* (**12b**), and *gauche* (**12c**) forms of the parent 1,2-dithiete.

	Bond lengths (Å)				Angles (°)		
	C—C	C—H	C—S	S—S	HCS	CCS	r(SCCS)
(12a)	1.352	1.083	1.755	2.112	125.2	102.5	0.0
(12b)	1.460	1.093	1.631		121.1	123.3	180.0
(12d)	1.474	1.094	1.627		119.5	126.1	23.0

Thus, with standard exponents for the *d*-functions, the *trans* form (**12b**) was calculated as more stable than the cyclic form (**12a**) by 5.00, 2.30, and 3.48 kcal mol $^{-1}$ at HF/6–31G(*d*), (*2d*), and (*3d*) levels, respectively. With inclusion of correlation energy at the MP2 levels, these values change to 5.46, 0.71, and 3.40 kcal mol $^{-1}$, respectively in favor of (**12b**). Based on the experimental results: $r(\text{C—C}) = 1.350$ Å, $r(\text{C—H}) = 1.080$ Å, $r(\text{C—S}) = 1.753$ Å, $r(\text{S—S}) = 2.096$ Å, $\angle \text{HCS} = 126.7^\circ$, and $\angle \text{CCS} = 102.3^\circ$ <85CPL(114)575>; the correct stability order ((**12a**) > (**12b**)) is obtained only when a set of *f*-functions is added. Then (**12a**) is calculated to be more stable than (**12b**) by 6.8 and 5.36 kcal mol $^{-1}$ at the MP2/6–31G(*2df*), and (*3df*) theoretical levels, respectively <91CPL(177)175>.

Much earlier, the strain of the parent 1,2 dithiete (**12a**) was calculated as 43 kcal mol $^{-1}$ and the π delocalization energy as 92 kcal mol $^{-1}$ <62AK(19)265>. The 1,2-dithiete dianion has also been discussed theoretically <62JA4756>.

1.35.2.2 Experimental Structural Methods

The x-ray diffraction technique proved to be the method of choice for structure–molecular dimensions determination of four-membered rings containing two sulfur atoms particularly, of

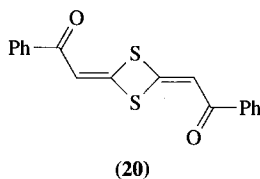
course, of those having a crystalline structure and are stable enough thermally. Also electron diffraction, photoelectron, microwave, and infrared spectroscopy proved to be very useful in establishing the geometries and related structural features and properties of the 1,2- and 1,3-dithietanes, 1,2-dithietes, and related four-membered ring systems. Available experimentally determined bond lengths, angles and additional structurally related spectral data of selected representative dithietanes and dithietes are given in Table 2.

Only two 1,2-dithietanes systems are well characterized experimentally: the isolated stable dithiatopazine (**9**) <87JA3801> and its α -methyl and α,α -dimethyl-substituted derivatives <90JA3029>, and the first isolable 3,4-diethyl-1,1-dioxide derivative (**13**) <80JA2490>. The detailed spectroscopic data of these compounds (i.e. UV, IR, NMR, and more) are available in the original papers.

Although several 1,2-dithietanes have been postulated as unstable intermediates en route to the corresponding alkenes and sulfur <75CB630, 85JOC1550, 87JA926> or in the reaction of sulfur and sulfur-rich compounds with fluorinated and unfluorinated alkenes <57USP2793999, 62JOC3995, 65JOC4188>, only in a few cases are such suggestions supported by spectroscopic data. Thus, an ion corresponding to 3,3,4,4-tetrafluoro-1,2 dithietane is observed in the mass spectrum of a volatile material derived from a copolymer of sulfur and tetrafluoroethylene <65JOC4188>, and a 1,2-dithietanyl radical is a plausible intermediate in the photolysis of 2,2-diphenyl-4*H*-pyran-4-thione <81CJC2612>.

1,2-Dithietane radical cations of type (**18**) could be detected via the hyperfine splittings by hydrogen atoms α to the sulfur atoms with unpaired spin density in the ESR ($a^H = 3.7(4H)G$; $g = 2.0193$) upon treatment of 1,2-ethanedithiol with concentrated H_2SO_4 at $25^\circ C$. Dithiete radical cations, generated through the treatment of dithioenes and 1,2-dithiols with H_2SO_4 and $H_2SO_4/K_2S_2O_8$, respectively, were detected too by ESR ($a^H = 3.04$; $g = 2.0155$ and $a^H = 2.75$; $g = 2.0144$, respectively) <85JA4175>.

Representative experimental data of the 1,3-dithietane series is given in Table 2 ((**14**)–(**16**)). The ^{19}F NMR, IR, and Raman spectroscopic data of tetrafluoro-1,3-dithietane are consistent with a planar ring with D_{2h} symmetry. The tetrachloro analogue is also of the same point group. Other simple 1,3-dithietanes have been characterized by ^1H , ^{19}F , and ^{13}C NMR, mass spectrometry and UV <84CHEC-I(7)449>. The parent 1,3-dithietane tetraoxide (**16**) and its tetrahalo derivatives have all had their x-ray structure determined and the UV, IR, and the NMR spectral data are available for these planar, almost square rings. Desaurin (**20**) was shown by x-ray to have the *trans* structure with the unsaturated carbonyl portions and the two sulfur atoms being co-planar. The longer than normal α,β -unsaturated carbonyl absorption (1650 cm^{-1}) suggests the sulfur-carbonyl through space or the π system interaction. The UV, IR spectra, and the MS base peak (molecular ion) are consistent with this conclusion <84CHEC-I(7)449>.



The position of the equilibrium between 1,2-diethietes and 1,2-dithiones (**12a**)–(**12b-d**), which was shown to be substituent dependent, is the structure-related feature most extensively studied experimentally. The four-membered cyclic (**12a**) is obtained if the substituents R are either strongly electron withdrawing as in (**17**) (see Table 2) <61JA3434, 76JA899> or bulky alkyl (e.g. Bu^t and structurally related) groups as in (**21**) <79H(12)1153, 82JCR(S)314>, or an annellated aromatic 6π -electron system <75CC756, 82JOC1979, 84PS(19)131>, an illustrative example of which is (**22**) <77JCS(P1)515>.

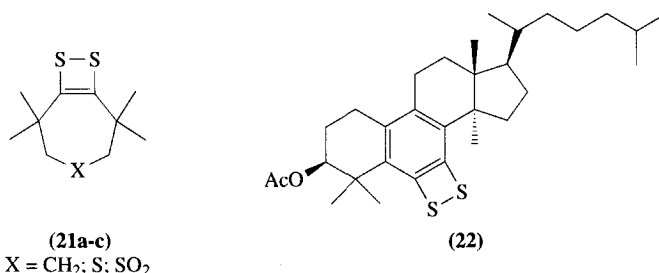
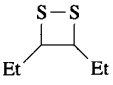
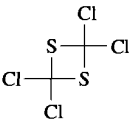
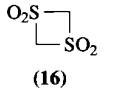
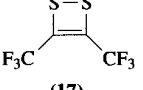
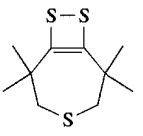


Table 2 Bond lengths (Å), angles (°) and selected spectroscopic data of dithietanes and dithietes.

Compound	$r(C-C)$	$r(C-S)$	$r(S-S)$	$\angle(C-C-S)$ or $\angle(S-C-S)$	$\angle(C-S-S)$ or $\angle(C-S-C)$	Method
 (13)						¹³ C-NMR ¹⁷ O-NMR
Dithiatopazine  (14a)	1.571	1.844, 1.881	2.084	97.4, 96.8 ^b	82.2, 80.7 ^b	x-rays Raman ^c
 (15)		1.81, 1.82, 1.473	2.600	81.7 ^f	ab.91.2 ^f	¹³ C-NMR MS x-rays
 (16)		1.813, 1.804		88.5 ^g	91.5 ^g	x-rays
 (17)	1.40	1.73	2.05	100.8	89.5	ED
 (18)	1.346	1.775 ^h	2.079			x-rays PE
 (19)						MS

^aIn acetone, relative to water. ^bDihedral angle between planes = 11.0°. ^cSolid laser 514 nm, Ar radiation. ^dPlanar with D_{2v} symmetry. ^eIn $CDCl_3$. ^fPuckered ring 39.3°. ^gPositions of the band maxima (the negative ionization energies).

The experimental techniques most used for establishing the dominance (or the sole existence) of the cyclic structure of the 1,2-dithiete system were the electron diffraction (ED) applied, for example for (17) <76JA899>, the photoelectron (PE) method applied, for example for (21a-c) <83HCA801> and the infrared (IR) spectroscopy, mainly at low temperature (10 K) matrix conditions, applied, for example for the parent compound (12; R = H).

An agreement between the calculated spacing of the energy levels (assuming the cyclic form and a C_{2v} symmetry in cases of a similar substitution) on both (C_3 and C_4 ring positions) and the spacing between the negative positions of the band maxima I_f^m in the actual PE spectrum of the 1,2-dithiete, confirms the ring structure of the latter. Thus, the observed PE data of (17) and (21a-c) were found to be in excellent agreement with the calculated (STO-36) ~ 2 eV separation between the energies of the first two coincident bands maxima [$b_2(\pi)^{-1}$, $a_2(\pi)^{-1}$] and that of the third [$a_1(\sigma_{s,s})^{-1}$] <83HCA801>.

A similar methodology, a combined experimental and theoretical approach, was used to determine the higher stability of the 1,2-dithiete (12a) over that of the 1,2-dithioglyoxal (12b-d) using IR spectroscopy <89JA7651>. The calculated (MP2/6-316*) (scaled) frequencies as well as the integrated absorption coefficients were found to be in excellent agreement with the observed (Ar matrix-isolated reaction mixture at 10 K), and the following interpretations were suggested for (12a) ν SS (494), δ ring (566), γ CH (637), ν asCS (791), ν s (798), δ_s SCH (1049), δ_s SCH (1215), and ν CC (1501) <89JA7651>. The existence of the parent, 1,2-dithiete system was thus established. In contrast, in a study <91CC358> which reported the first isolated example of a $RCSxCR^{++}$ cation ($x = 3$ in this case), a claim was made that the ESR spectra previously assigned to 1,2-dithiete radical cations which have been extensively investigated by ESR spectroscopy were, in fact, the similar five-membered 1,2,3-trithiolium cations.

X-ray analysis and electron diffraction PE appear to be the methods of choice for the experimental structure determination of the 1,3-dithietane system (see Table 2). ^{13}C NMR and mass spectrum are very useful complementary experimental techniques for the structure determination of this class of compounds, particularly in the absence of hydrogen atoms in the ring skeleton (e.g. (14a)). In particular cases, the use of chemical shift reagents, for example Eu(fod)₃, and aromatic solvent-induced shift studies are of particular importance. Such determinations facilitated the structure elucidation of *endo-exo*, *endo*, *exo* and *exo, exo*-1,3-dithietane S-oxides and S-dioxides <92BCJ3343>.

The gas-phase structure of 1,3-dithietane 1-oxide (15) has been determined from its microwave spectrum and the spectra of eight isotopic modifications <82JA3119>. The ring is puckered, the angle between the two CSC planes being 39.3° with the oxygen equatorial. The oxide displays short nonbonded sulfur-sulfur and carbon-carbon distances (2.600 and 2.372 Å, respectively). None the less, the sulfur-oxygen bond (1.473 Å) and the angle of pucker appear to be normal compared to the corresponding data for the thietane oxides <B-94MI 135-01, B-94MI 135-02>.

The structure of 1,3-dithietane tetroxide (16) has been shown by x-ray diffraction methods to be planar and almost square <82JA3119>, the molecule being located on a crystallographically required center of symmetry at the center of the four-membered ring, with the planes of the SO₂ and CH₂ groups essentially perpendicular to the plane of the four-atom ring (89.9° and 85° , respectively). Again, these results are in accord with previous studies that established the planarity (or near planarity) of the analogous thietane dioxides <75JMR(17)219>. It appears that the inclusion of a second sulfur atom, a sulfoxide, or a sulfone group in the four-membered ring thietane oxides and dioxides (in a 1,3 relationship) does not alter the conformational preferences of the latter, nor does it cause any unusual anomalies as far as the particular geometrical parameters (e.g. bond lengths and angles) of these molecules are concerned.

The PE spectrum of 1,3-dithietane 1-oxide (15) is best discussed by comparisons with the thietane oxide, since the large perturbation $S \rightarrow SO$ can be replaced by the isovalent and electronic one, $CH_2 \rightarrow S$ <82JA3119>.

The three highest occupied orbitals of sulfoxides are the lone pairs n_s and n_o , as well as the π_{so} bond <74CB68, 74CB2299>. The 1,3-dithietane 1-oxide adds a "lone-pair" ionization and destabilizes the n_o and π_{so} radical-cation states compared with thietane oxide. According to a hyperconjugative MO model, the n_s^+ combination in 1,3-dithietane is destabilized by about 1 eV relative to the basis orbital energy $\alpha(n_s)$ due to the combination with the $\sigma CH_2(b_{2u})$ orbital <74CB68>. In the 1,3-dithietane 1-oxide, both sulfur "lone pair" ionizations are further increased by the oxygen substitution. In thietane oxide both n_o and π_{so} ionizations are lowered by the $S \rightarrow CH_2$ substitution, whereas a $CH_2 \rightarrow SO$ replacement splits the n_o and π_{so} ionizations and increases their center of gravity. The radical-cation-state correlation shown in Figure 1 <82JA3119> is supported both by EHMO and modified CNDO calculations based on the known structural parameters <76JA5715>. Similar considerations

and interpretations have been applied for the PE spectra of 1,3-dithietane dioxide (**15**) and 1,3-dithietane tetroxide (**16**) and their assignments.

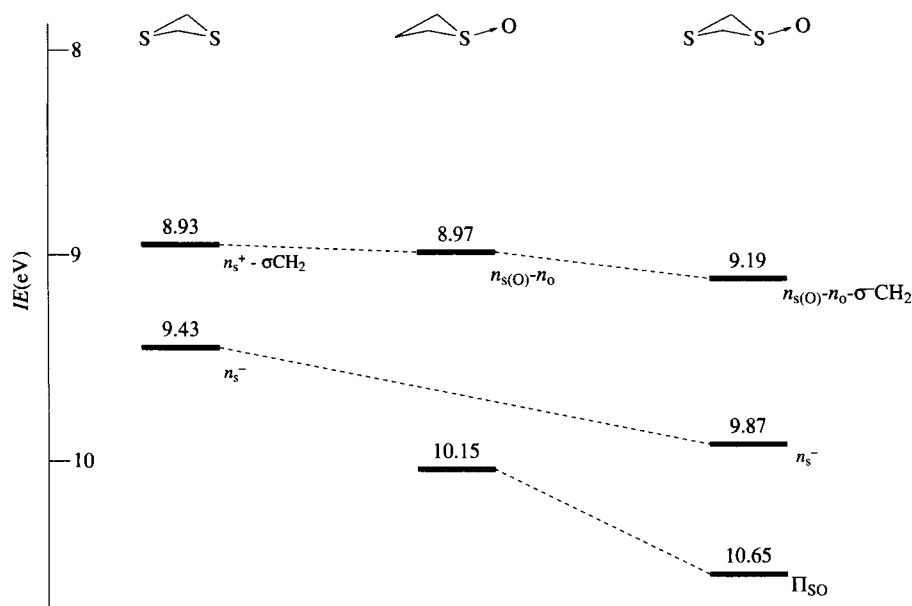


Figure 1 Sulfur lone-pair and π_{SO} ionization patterns in 1,3-dithietane, thietane oxide, and 1,3-dithietane oxide <82JA3110, B-94MI 135-01>.

Proton and ^{13}C NMR spectroscopy are the techniques most often applied to the study and characterization of four-membered ring sulfoxides and sulfones <B-94MI 135-01>. Chemical shifts and coupling constants have been used for structural, conformational, and stereochemical assignments and preferences and for the establishment of the four-membered ring sulfone effect <82OMR(18)82>. ^1H and ^{13}C chemical shifts and coupling constants of some selected representative 1,3-dithietane sulfoxides and sulfones are given in Table 3 <82JA3119>.

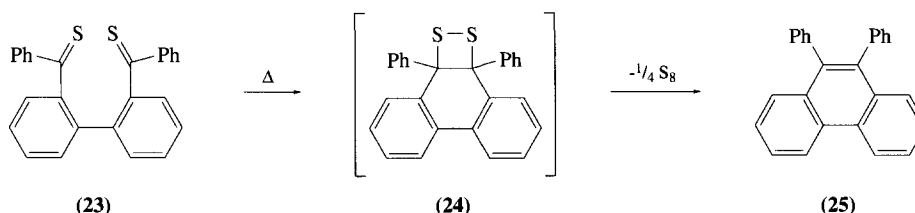
Table 3 Proton and ^{13}C NMR chemical shifts and coupling constants of 1,3-dithietane sulfoxides and sulfones <B-94MI 135-01>.

	Chemical shifts δ		Coupling constants			
	^1H	^{13}C	gem- H^3H^4	trans- H^3H^6	cis- H^4H^6	cis- H^3H^5
	4.23 ^a , 3.37, 3.73 ^b	53.1	-7.53 ^c	0.73 ^d	5.56	0.005 ^d
	5.27 ^{f,j}	68.4				
 (cis-)	4.78, 5.72 ^c	69.1	-13.40 ^c	1 ^d	3.76 ^d	1 ^d
 (trans-)	4.97 ^c	69				
	6.40 ^c	92.1				

^aIn $(\text{CD}_3)_2\text{SO}$. ^bIn C_6D_6 . ^cNegative sign assumed. ^dSign unknown. ^eIn CF_3COOH .

1.35.2.3 Thermodynamic Aspects

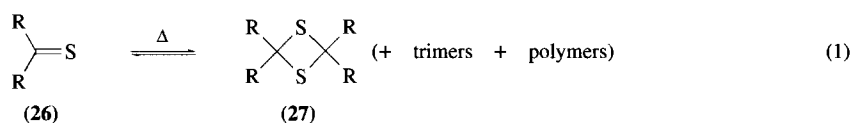
While the four-membered 1,3-dithietanes (**2**) are readily available, thermodynamically stable (in most cases) compounds to work with, not many stable 1,2-dithietes (**3**) are known and, practically speaking, only one stable 1,2-dithietane system (**1**) (dithiatopazine (**9**)) has been isolated and its chemistry established to date <87JA926>. Stability and stabilization are of vital importance as far as the 1,2-dithietes and 1,2-dithianes are concerned, the latter in particular. A number of 1,2-dithietanes have been postulated as transient intermediates along the reaction coordinates of various chemical transformations <70CC371, 75CB630, B-83MI 135-02, 84CHEC-I(7)449, 85JOC1550, 87JA926>. The unstable nature of this type of intermediate has been largely attributed to the expected destabilizing repulsion between the lone pairs of electrons on the adjacent sulfur atoms imposed by the geometrical constraints of the four-membered thietane ring and to related thermochemical calculated (MINDO/3) factors (i.e. heats of formation). Consequently, the 1,2-dithietanes once formed (e.g. (**24**)) will undergo a facile loss of elementary sulfur with the concomitant formation of the corresponding alkenes as depicted in Scheme 2 <87JA926>.



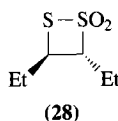
Scheme 2

A ΔH of $-37.09 \text{ kcal mol}^{-1}$ was estimated by molecular modeling-based calculations for the conversion of (**23**) to (**25**). Surprisingly, the postulated 1,2-dithietane intermediate (**24**) calculates to virtually the same ΔH as its precursor (**23**) <87JA926>. Aromization, however, as a driving force for the (**24**) $\rightarrow$ (**25**) transformation should not be underestimated.

The destabilizing repulsion between the lone pairs of electrons on adjacent sulfur atoms in a four-membered ring cluster appears to be a valid rationale for the thermodynamic instability of the 1,2-dithietanes. In accord, non-enolizable thiones, thioaldehydes in particular, thermally undergo reversible dimerization (or trimerization) in a "head-to-tail" fashion (Equation (1)) <79COC(3)373, 85JOC1107, 86JOC1556>. The opposite "head-to-head" thermal condensations are not known to take place <46CRV1, 74JOC2509, 78S713>.



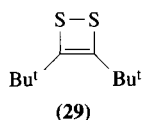
Substitution of the two lone pairs on one of the sulfur atoms by oxygen atoms via oxidation provided the first isolable 1,2-dithietane-1,1-dioxide (**28**) <80JA2490>.



Photolytic or thermal decomposition of dithiatopazine (**9**) led, as expected, to the corresponding alkene via the loss of diatomic sulfur which could be trapped with suitable acceptors. The activation energy for the thermolysis was calculated to be $26.3 \text{ kcal mol}^{-1}$ based on kinetic studies <90JA3029>. MM2 parameterization for this 1,2-dithietane system and subsequent molecular mechanics evaluation led to the conclusion that (**9**) has a remarkably rigid structure experiencing little conformational mobility. The global minimum, the all-chair x-ray conformation, comprises 99.5% of the conformer

mix based on a Boltzman distribution of the MM2 relative energies meaning, essentially, a single chair–chair conformation with respect to the four oxygen-containing rings. Yet the molecule experiences a mobile dithietane breathing motion for small values of ϕ (C—S—S—C). Further quantum mechanical (PRDDO) calculations for various dithietane systems suggest the combination of thermodynamic factors and possibilities of internal energy redistribution to account for the dithiatopazine singular stability <90JA3029>.

Similar to the situation in the 1,2-dithietane series, most of the 1,2-dithietes are highly reactive and elude isolation at room temperature. The facile tautomerization to the corresponding 1,2-dithiones (i.e. **(12a)** $\rightarrow$ **(12b–d)**, Scheme 1) must be, at least in part, responsible for their instability <74JA3502, 93BCJ623>. As was discussed before (see Section 1.35.2.1), theoretical calculations on the total energies of the various valence isomers (**(12a–d)**) support the above explanation, indicating the *trans* form (**(12b)**) to be the most stable thermodynamically. Strongly electron-withdrawing groups, highly bulky (and structurally related) groups and aromatic 6π -electron systems make the isolation of the 1,2-dithietes possible; for example **(17)**, **(29)**, and **(21a–c)** and **(22)**, respectively. The question whether the relative stability of these 1,2-dithietes reflects the greater difficulty of their uniquely substituted four-membered ring to undergo the thermally allowed, concerted conrotatory ring opening <65JA395> necessary for the dithiete–dithione tautomerization <90JA7529> to take place, remains open.



1.35.3 REACTIVITY OF DITHIETANES AND DITHIETES

1.35.3.1 Reactivity of 1,2-Dithietanes

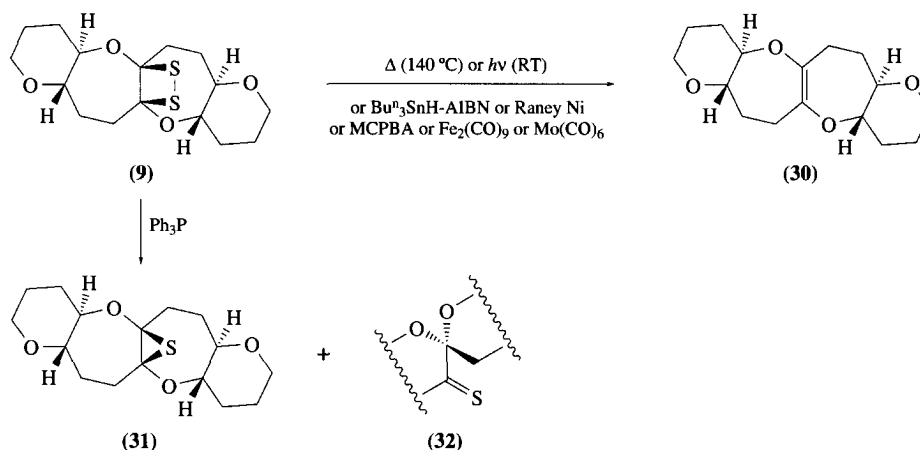
The four-membered ring structure of the 1,2-dithietanes (**(1)**) within which the disulfide —S—S moiety is incorporated, suggests high reactivity and, simultaneously, an intriguing chemistry. In view of their transient nature due, apparently, to the loss of sulfur leading to the corresponding alkene and the availability of only one isolable stable 1,2-dithietane (i.e. **(9)**), it is the chemistry of the latter <87JA3801, 88JA4868, 90JA3029> as a representative of this class of compounds that is reviewed and discussed. Significantly, however, several isolable 1,2-dioxetanes <B-79MI 135-01> and 1,2-oxathietane <86JA3811> have been reported.

Compared with the 1,2-dithietes and the isomeric 1,3-dithietanes, the 1,2-dithietanes are the most reactive thermally, photolytically, nucleophilically, and electrophilically.

Thermolysis and photolysis of dithiatopazine (**(9)**) resulted in desulfurization, leading within an hour or less and in very high yields (90–95%), to the corresponding alkene (**(30)**). The same results, within shorter periods of time were obtained in exposing **(9)** to radical or oxidative conditions. However, the successful removal of the sulfur atoms from **(9)** to give **(30)** in high yield by taking the advantage of the thiophilic properties of $\text{Fe}_2(\text{CO})_9$ and $\text{Mo}(\text{CO})_6$ which were also employed, may be applicable only in systems similar to that of the dithiatopazine; namely, that the “pull” from the metal coupled with the “push” from the ring oxygens facilitates this facile transformation rather than the formation of a stable metal–dithiane complex (Scheme 3) <90JA3029>.

The reaction of **(9)** with the nucleophilic phosphine Ph_3P led to the isolation in equal amounts (~45%) of the corresponding thiirane (**(31)**) and a rearranged thione-spiro ketal (**(32)**) (directly related to the specific structure of the entire dithiatopazine molecule) both via the abstraction of one of the sulfur atoms of the included 1,2-dithietane system. The transformation **(31)** $\rightarrow$ **(30)** could be materialized easily via thermolysis V(160°C, 88%), Bu^n_3S_n —AIBN (110°C, 93%), or exposure to Et_3P (110°C, 94%). The reaction of **(31)** with MCPBA provided the ketone analogue of the thione-spiro ketal (**(32)**). A plausible mechanism according to which the initial attack of the phosphine on one of the sulfur atoms of the 1,2-dithietane ring of **(9)** to form a ring-opened S-radical species, i.e. **(33)** has been advocated to account for the above results <90JA3029>. Similar (mechanistically) ring opening was observed in reacting **(9)** with the thiophenoxide ion.

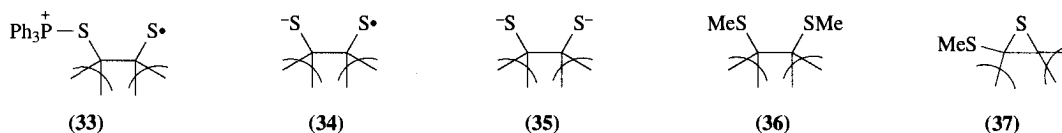
The reduction of dithiatopazine with sodium naphthalide at -78°C gives, upon quenching with MeI and warming to room temperature, the expected corresponding bis(methylthio) ether (**(36)**) as



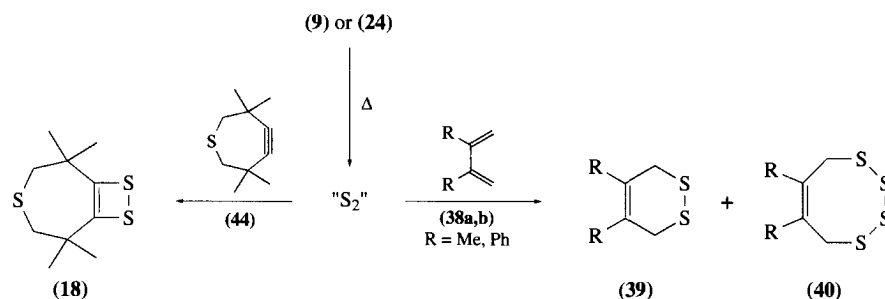
Scheme 3

the main ruptured disulfide linkage product, most probably via the initially formed radical anion (34).

The reaction of (9) with NaBH_4 results in the initial reductive cleavage of the S—S bond leading, after quenching with MeI, to the MeS-substituted thiirane (37), apparently via the intermediacy of the dianion (35). Reduction of (28) with NaBH_4 afforded the DL-hexane-3,4-dithiol <80JA2490>. Reaction of (9) with excess Et_3SiH in the presence of AgBF_4 resulted in the obtaining of a skeletal rearrangement product which contained no sulfur atoms. The initial rupture of the 1,2-dithietane ring moiety by the silver ions followed, in a later step, by the loss of the Ag—S—S^- species, is proposed to account for the observed product <90JA3029>.



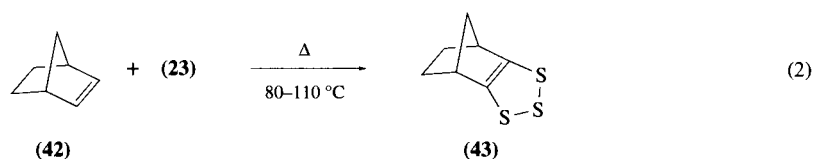
The ability of 1,2-dithietanes to donate their sulfur atoms as reactive diatomic sulfur species (S_2) on thermolysis was demonstrated in [2 + 4] Diels–Alder type [2 + 2] and, what appears to be [2 + 2 + 4] cycloadditions. Thus, the dithione (23), via the intermediacy of the 1,2-dithietane (24), and dithiatopazine (9) provide S_2 which is trapped by suitable dienes (38), serving as the acceptors to form the Diels–Alder cycloadducts (39) <87JA926, 90JA3029>. Also the formation of an eight-membered tetrasulfide ring system (i.e. (40)) in this cycloaddition reaction as well as the formation of four-membered 1,2-dithiete rings (e.g. (18)) in the presence of bulky groups, disubstituted alkynes (e.g. (41)) has been demonstrated (Scheme 4) <90JA3029>.



Scheme 4

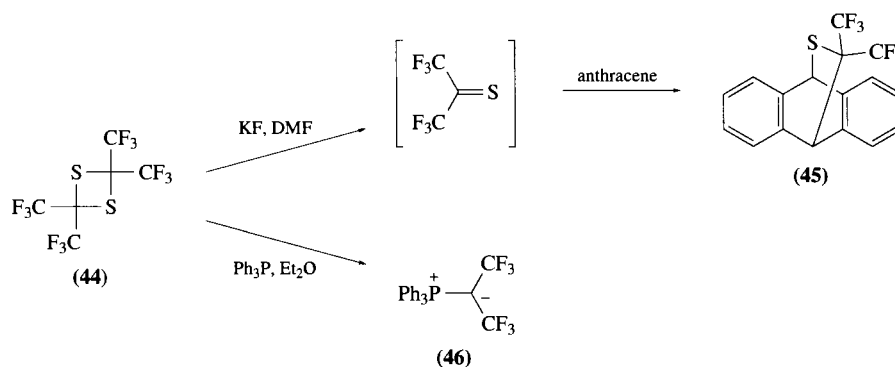
1-2-Dithietanes can therefore, be regarded as diatomic sulfur transfer reagents. However, while cyclic trisulfides (e.g. (43), Equation (2)) were smoothly obtained in high yields on thermolysis of 1,2-dithietane (24) at higher temperatures (80–110 °C) in the presence of norbornene and norbor-

nadiene, no trace of the possible [4 + 2]-type adduct (the “analogue” of, e.g. (40)) was noted <87JA926>.



1.35.3.2 Reactivity of 1,3-Dithietanes

The 1,3-dithietanes are chemically less reactive than the 1,2-dithietanes. Yet, they decompose to thiocarbonyl compounds (thiones) thermally <81JOC153, 82CB492, 82JA3119, 82JOC377, B-83MI 135-02> and photochemically <73BCJ2253, 79CC899, 80CPH159, B-83MI 135-02>. The fluoroalkyl-1,3-dithietanes decompose in the presence of nucleophiles or bases <76BCJ2491, 78TL877, 82JOC377>. While the fluoride ion produces the monomer, anilines give imines and phenylhydrazine gives hydrazone <B-83MI 135-02>. The thiones formed in the above de-dimerization reactions (i.e. the reverse of (Equation (1)) can be trapped by nucleophiles, dienes, and alkenes <B-83MI 135-02>, an illustrative example of which is given in Scheme 5 <73CL267>:



Scheme 5

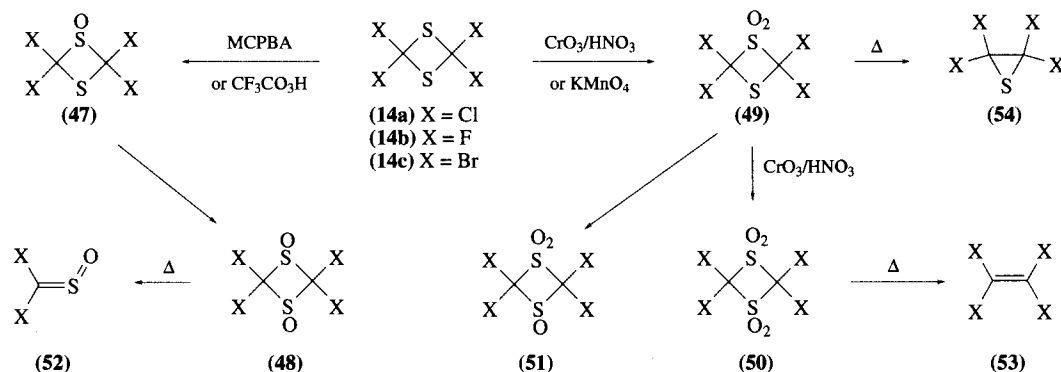
Several alternative ring-cleavage reactions of the 1,3-dithietanes are known <B-83MI 135-02> one of which is that conducted with triphenylphosphine to give phosphonium yield (i.e. (46)), which can be trapped by aldehydes, apparently following the initial desulfurization by the thiophilic nucleophilic reagent <79TL3397>.

Bis-alkylidene and perfluoromethylated 1,3-dithietanes (e.g. (20) and (44), respectively), are generally stable thermodynamically, and only decompose at temperatures exceeding 500 °C to give the corresponding thioketene and thione “monomers” <84CHEC-I(7)449>.

1,3-Dithietanes are best stabilized by electron-withdrawing groups on the ring. The perhalodimers, which are readily available from the corresponding monomers (e.g. thiophosgene $\text{Cl}_2\text{C}=\text{S}$; see Section 1.35.4.2: synthesis of 1,3-dithietanes) will undergo thermolytic ring opening to the corresponding thiones or sulfines/sulfenes (in the case of oxidized sulfur ring atoms to the corresponding oxides and dioxides) only at high temperatures (400–600 °C).

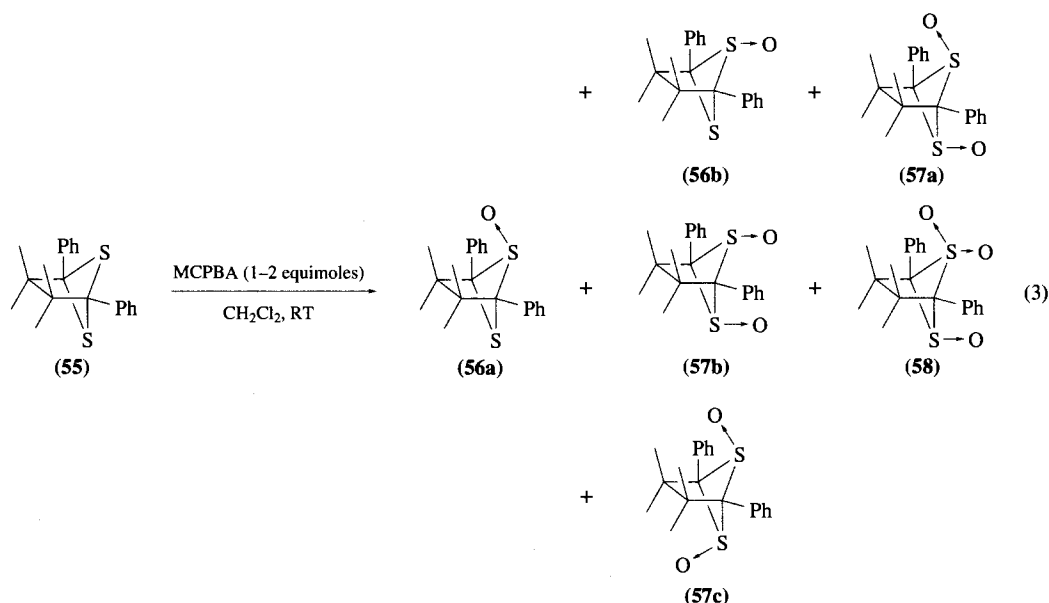
Oxidation of the sulfur atoms in 1,3-dithietanes gives both sulfoxides and sulfones with the classical oxidizing agents MCPBA, KMnO_4 , CrO_3 , $\text{CF}_3\text{CO}_3\text{H}$, and $\text{CrO}_3/\text{HNO}_3$ <85CB1415, 88S349>. The reagent of choice appears to be MCPBA whenever the S-oxides are required and $\text{CrO}_3/\text{HNO}_3$ is preferred whenever the S,S-tetroxides are required. In certain cases (e.g. $\text{X} = \text{F}$), the formation of the 1,3-dioxides (e.g. (48)) or of the 1,1,3-trioxides (e.g. (51)) is only possible through the use of the trifluoromethane persulfonic acid <83CB1623> (Scheme 6).

Oxidation of the bicyclo-1,3-dithietane (55) with MCPBA gives two isomeric *endo*- (56a) and *exo*-sulfoxides (56b), three S,S-dioxides (*endo*, *exo* (57a), *exo*, *exo* (57b), and *endo*, *endo* (57c)), and an S,S-trioxide (58). The relative reactivity to further oxidation is (56b) > (56a) and (57b) > (57a), suggesting the attractive 1,3-transannular interaction to be operative in the 1,3-dithietane part of

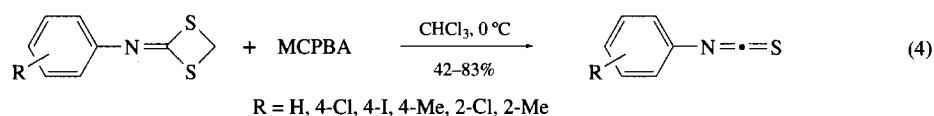


Scheme 6

(56a) and (57a) and thus to be responsible for the decrease in their reactivity (Equation (3)) <92BCJ3343>.

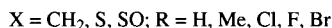


It is interesting to note that the oxidation of the 2-phenyl- (and other 2-substituted-) phenylimino-1,3-dithietanes with MCPBA under similar reaction conditions afforded the corresponding isothiocyanate derivatives (Equation (4)). Since 2-phenylimino-1,3-dithiolane was not converted to phenylisothiocyanate on reaction with MCPBA, it was suggested that the strain in the four-membered ring of the 1,3-dithietane is responsible for the ease of the ring rupture (and loss of the "C=S=O" moiety?) and the consequent formation of the isothiocyanates <91JHC177>. This is in analogy to the formation of sulfene from 3-hydroxythietane-1,1-dioxide <69CJC4509>.



Thermolysis of the perhalogenated 1,3-dithietanes S,S-dioxides (e.g. (48)) provides quantitatively the corresponding perhalogenated sulfines (52), whereas that of the perhalogenated S,S-tetraoxides (e.g. (50)) leads exclusively to the corresponding alkenes (i.e. (53)) via the extrusion of both SO₂ moieties from the four-membered ring. The loss of sulfur dioxide from the S,S-dioxides (e.g. (49)) on thermolysis constitutes a convenient entry into the perhalogenated thiirane series <88S349>. The corresponding thiirane is also obtained when (49) (X = CF₃) undergoes thermolysis <80JCS(P1)487>.

In contrast, thermolyses of the four-membered ring sulfoxides do not eliminate sulfur monoxide, but undergo, almost exclusively, a retro [2 + 2] decomposition (simultaneous for a concerted ($\sigma_a^2 + \sigma_s^2$) process or stepwise for a process involving 1,4-diradical) leading to the generation of sulfines (Equation (5)) [⟨76JA1264, 82JA3119, 83CB1623, 88S349⟩](#). The formation of these low-molecular weight, reactive, short-lived species can be detected by either mass spectrometry, microwave, or photoelectron spectroscopy techniques [⟨82JA3119⟩](#), or through the actual trapping, isolation, and identification of the final products.



Most thioketones are known to exist as dimers in solution ^[65JCS5953] including the closely related α -thioketo esters ^[78TL2289]. Such a dimer, the thiobenzylimine-1,3-dithietane (**59**) was shown to reversibly afford the original monomer on thermolysis (Equation (6)) ^[85JOC1107].

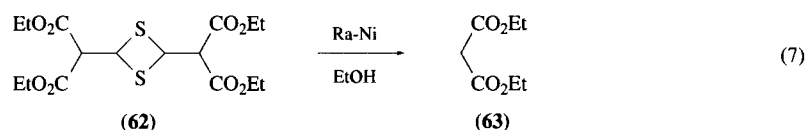


Acid hydrolysis of the perhalogenated 1,3-dithietanes provides the 2-dihalo-1,3-dithietane-4-one $\langle 33\text{CB}567, 85\text{CB}1415 \rangle$ whereas the treatment of their tetraoxides (e.g. **(14c)**) with silver nitrate in aqueous methanolic solution gives the 2,4-dihalo-1,3-dithietane-S-S-tetroxides with the concomitant immediate formation of the silver bromide quantitatively $\langle 85\text{CB}2208 \rangle$. Halogen exchange occurs on treatment of the tetrachloro-1,3-dithietane (**14a**) with antimony trifluoride. Two or more chlorine atoms can be replaced by fluorine atoms $\langle 65\text{JOC}1375, 78\text{IJ}100 \rangle$, whereas treatment with aniline gives a 2-imine (Scheme 7) $\langle 33\text{CB}567 \rangle$.



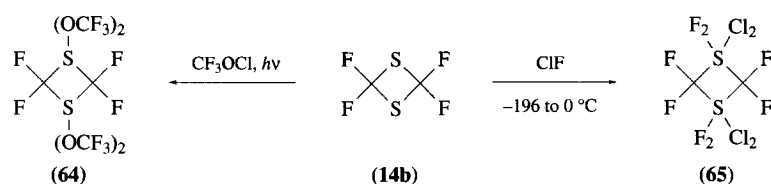
Scheme 7

Desulfurization of the 1,3-dithietanes can be accomplished not only by the classical desulfurization reagents such as phosphines, but also with Raney nickel, an example of which is shown in Equation (7) ^{68JOC3642}.



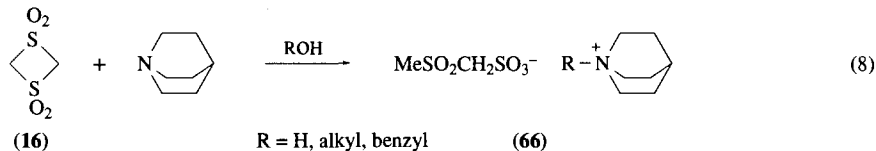
Treatment of the tetrafluoro-1,3-dithietane (**14b**) with the fluoro-containing electrophilic reagents such as trifluoromethyl hypochlorite <79JA5949> results in the formation of the hyper-4-valent and hyper-6-valent sulfur-1,3-dithietanes <78IJ1, 81JA406>. Fluorination of the divalent-sulfur of the S,S-dioxide (**49a**) with F₂ leads to the corresponding hyper-4-valent 1,3-dithietane system <85CB1415>. The S^{iv} difluorides thus obtained react with silica (SiO₂) to give the corresponding sulfoxides (Scheme 8) <88S349>.

These reactions and the chemistry of the hypervalent sulfur products have been reviewed elsewhere <78IJ1, B-83MI 135-02>.

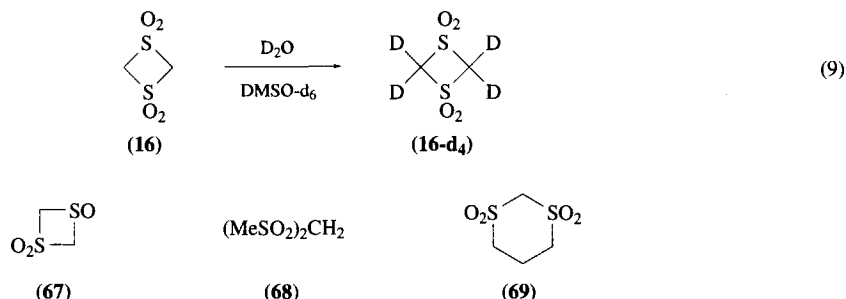


Scheme 8

Water and some alcohols react with the 1,3-dithietane-S,S-tetraoxide (**16**) in the presence of quinuclidine to give the corresponding (alkyl) chinuclidinium methanesulfonyl methanesulfonates (i.e., (**66**)) <90CB1687>. Since these reactions are conducted under reflux conditions (~80°C) the intermediacy of the sulfene "CH₂=SO₂" trapped by the nucleophile used (ROH; R = H or alkyl) adequately accounts for the actually isolated product (i.e. (**66**), Equation (8)).



Ring-strain effects are known to enhance the acidity of hydrogens in α positions to functional groups capable of stabilizing a negative charge <67JA4651>. A comparison of the pK_a values <82JA3119> (in DMSO, Equation (9)) of the sulfoxide-sulfone (**67**) and the disulfone (**16**), 13.8, and 12.5 ± 0.08 respectively, with 15.0 ± 0.02, for (**68**) and 15.5 for (**69**) <80JOC3305>, demonstrates that similar effects are most probably operative in the cyclic thietane sulfoxide and sulfone systems. Both the 1,3-dithietane oxide (**15**) <82JA3119> and the tetraoxide (**16**) <69AG(E)73> have shown to undergo ready H/D exchange with NaOD/D₂O.



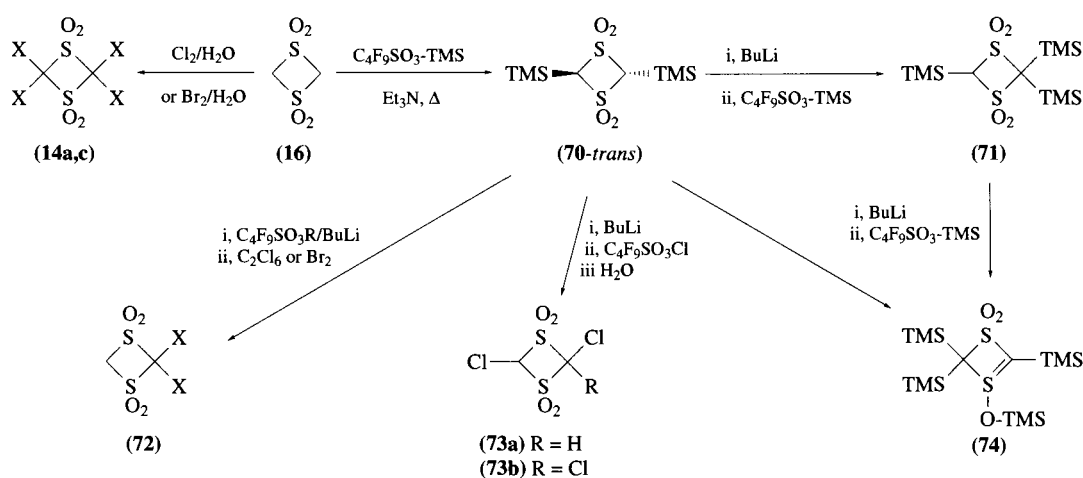
Analysis of deuterated (**15**) indicates a 6 : 1 preference of "axial" monodeuteration over "equatorial" monodeuteration, in contrast to the predictions of the "gauche effect theory" of greater reactivity for the quasiequatorial protons *gauche* to both the S—O bond and the lone pair of sulfur <75JA5883>.

Both thermal- and acid-induced equilibrations of 3,3-disubstituted thietane oxides were very slow ($K_{\text{eq}} \sim 10^{-5} \text{ s}^{-1}$) <78JOC3827>. The results suggest that thietane oxides are similar to the various

acyclic sulfoxides with respect to the rates of thermally induced pyramidal inversion at sulfur <68JA4854>, and that this inversion process therefore, does not interfere significantly in the above exchange/racemization studies.

It is noteworthy that, in spite of the demonstrated acidity of the α -hydrogens in 1,3-dithietane oxides and dioxides, attempted mono- or dialkylations of these systems have been unsuccessful up to 1993 when the S,S-tetraoxide (**16**) was shown to undergo alkylation on treatment with sodium hydride and alkylhalide <93CB537>.

The 1,3-dithietane tetraoxides (**16**) readily undergo tetra α -halogenation <83CB1285> with either Br_2 or Cl_2 , but not with I_2 . Partial α -halogenation in this series can be accomplished indirectly by starting from either 2,4-bis(trimethylsilyl)- or 2,4-bis(*t*-butyldimethylsilyl)-1,3-dithietane tetroxides (**70**) as shown in Scheme 9 <81CB3378, 83CB1285, 88S349>. In all of the above reactions advantage is taken of the highly acidic α -hydrogens and, consequently, the facile *in situ* formation of the reactive α -sulfonyl carbanions. Of particular interest is the first "enol ether" of sulfone (i.e. (**74**)) which could be obtained from either (**70**) or (**71**) in using the same reagents and methodology <88S349>.



Scheme 9

1.35.3.2.1 Reactivity of methylene- and imino-1,3-dithietanes

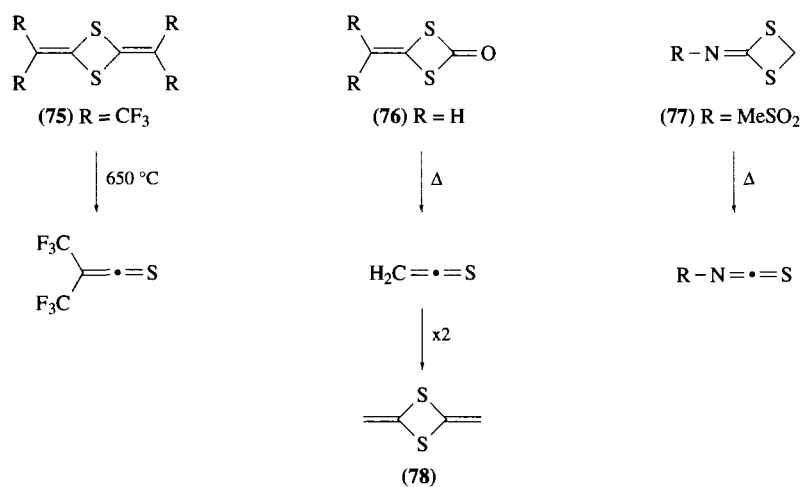
Methylene-1,3-dithietanes (**75**), methylene-1,3-dithietane-2-ones (**76**), and imino-1,3-dithietanes (**77**) decompose thermally via a formally $[2 + 2]$ π retrocycloaddition process (Scheme 10) <65AG(E)430, 70JOC3470, 77CB1225, 79LA1715, 82CB492, B-83MI 135-02>.

Small-ring heterocyclic compounds are known to be susceptible to ring opening due to their ring strain <B-83MI 135-02, B-94MI 135-01>. It is not surprising, therefore, that ring opening of the various 1,3-dithietane systems occurs not only under thermolytic conditions, but also as a result of their reactions with a variety of nitrogen (e.g. amines), oxygen (e.g. alcoholates), and sulfur (e.g. thiolates) nucleophiles as well as with nucleophilic thiophiles such as phosphines <B-83MI 135-02, 84CHEC-I(7)449>. Thus, the apparent initial Michael addition of the nucleophile to the electron-deficient double bond in the methylene group of 2,4-bis(methylene)-1,3-dithietanes (i.e. (**75**)), which is the most common reaction of this class of compounds with nucleophiles, is followed by a nucleophilic ring opening induced by the adjacent carbanion formed (Scheme 11) <76S386>.

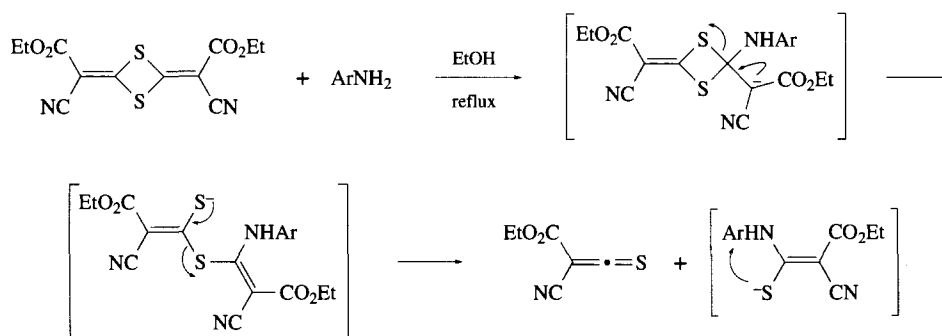
In the above case, the thioketene (**80a**) and the intermediate (**80b**) are sufficiently reactive to undergo further transformations the particulars of which are dependent on the specific reaction conditions employed.

The reaction of electron-withdrawing groups substituted methylene-1,3-dithietanes (i.e. (**81**)) were shown to react with amines (N-nucleophiles), alcoholates (O-nucleophiles) and thiolates (S-nucleophiles) <90JHC567> in an analogous manner to the reaction of the bis(methylene)-1,3-dithietanes with amines hydrazines, hydrazides, and azide ions (Scheme 12) <76JPR939, 79JPR205, 81ZC102, B-83MI 135-02>.

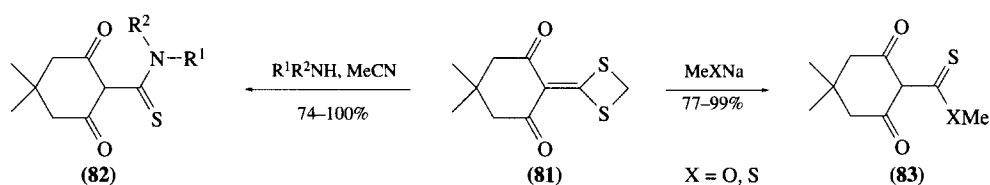
The reaction of several methylene-1,3-dithietane-2-ones with secondary amines appears to proceed



Scheme 10

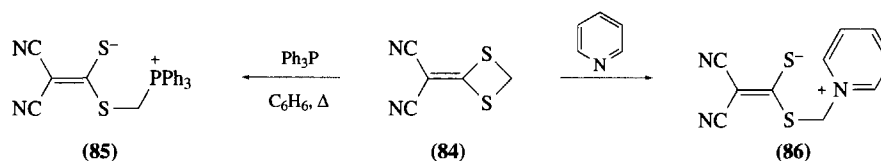


Scheme 11



Scheme 12

via loss of carbon oxysulfide followed by the addition of the amine to the thioketene formed $\langle 79LA1715 \rangle$. In contrast to the above nucleophile-induced ring opening reactions, reactions of the imino nitrogen atom of several imino-1,3-dithietanes have been observed, leaving the thietane ring unaffected $\langle B-83MI\ 135-02 \rangle$. However, several cases have been reported in which the carbon atom of the four-membered ring 1,3-dithietane was attacked. In these cases, one of the two ring carbon-sulfur bonds is cleaved, but both sulfur atoms are retained in the products (Scheme 13) $\langle 64JOC497 \rangle$.

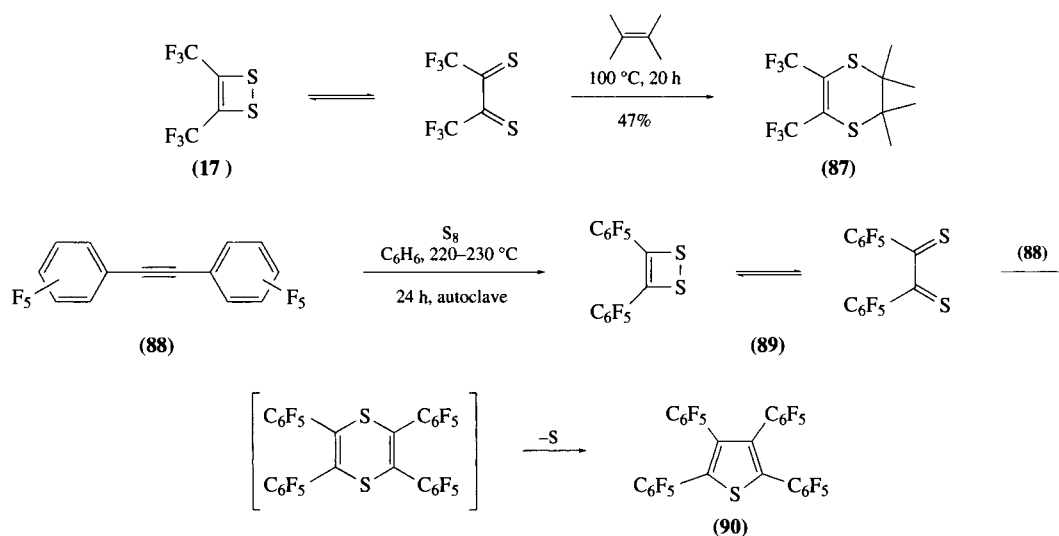


Scheme 13

Tri(*n*-butyl) phosphine, Raney nickel, and zinc-desulfurized 1,4-bis(methylene)-1,3-dithietanes and a mixture of nitric and sulfuric acids leads to oxidized products. Treatment of (75)–(77) with P_4S_{10} leads to extensive rearrangement with incorporation of additional sulfur atom in the products. Other reactions in which the products are dependent on the particular structure and functionality of the 1,3-dithietane employed are known and have been reviewed <B-83MI 135-02>.

1.35.3.3 Reactivity of 1,2-Dithietes

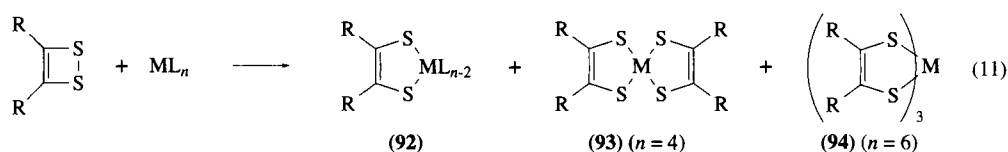
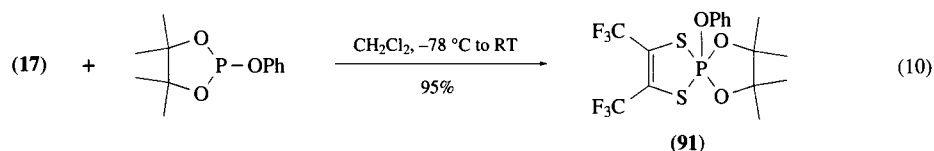
The dominance of the 1,2-dithiete $\rightleftharpoons$ 1,2-dithione equilibrium (Scheme 1) in the chemistry of the 1,2-dithietes is reflected in their facile undergoing Diels–Alder-type cycloadditions in which the cisoid dithione (i.e. (12c)) serves as the diene. This pattern is illustrated in Scheme 14 for two relatively stable (electron-withdrawing group substituents) 1,2-dithietes <60JA1515, 93BCJ623>.



Scheme 14

Without the stabilizing effect of either (a) electron-withdrawing substituents (e.g. (17)), most probably by decreasing the interaction between the two lone pairs of electrons on the two adjacent sulfur atoms of the dithiete ring, or (b) the buttressing effect of highly bulky groups, which makes the tautomerism 1,2-dithiete $\rightarrow$ 1,2-dithione unfavorable (e.g. (18)), most of the 1,2-dithietes are highly reactive and elude isolation at room temperature. Occasionally, even their cycloadducts are thermally unstable under the reaction conditions employed, particularly if a driving force towards the formation of a more stable product (e.g. aromatization) is operative (see the formation of (90) in Scheme 14).

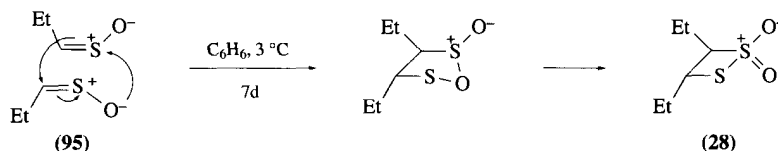
Ring opening of the strained, four-membered dithiete ring occurs with trivalent phosphorus derivatives <78JA7300> as well as with a wide spectrum of metal complexes (i.e. V, In, Cr, Mo, W, Mn, Fe, Ru, Co, Rh, Ir, Pd, Pt, Au, and U) to form stable complexes (Equations (10) and (11)) <73JOM(51)113, B-83MI 135-02, 84CHEC-I(7)449>.



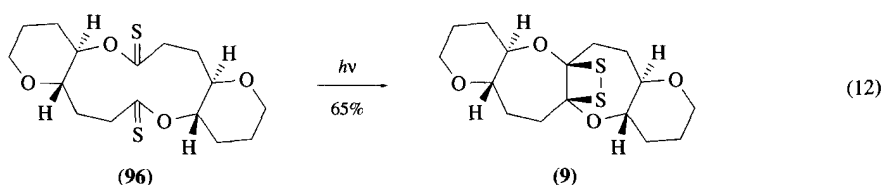
1.35.4 SYNTHESIS OF DITHIETANES AND DITHIETES

1.35.4.1 Synthesis of 1,2-Dithietanes

Although the intermediacy of 1,2-dithietanes has been proposed in several chemical transformations <B-83MI 135-02, 85JOC1550, 87JA926>; there are only two isolable, stable, and well-characterized 1,2-dithietane systems known thus far: the 1,1-dioxide (**28**) <80JA2490> and the dithiatopazine (**9**). In both cases, the key step in the synthesis is the cycloaddition reaction, $[2 + 3]\pi$ thermally and $[2 + 2]\pi$ photochemically, for (**28**) and (**9**), respectively (Scheme 15, Equation (12)).



Scheme 15



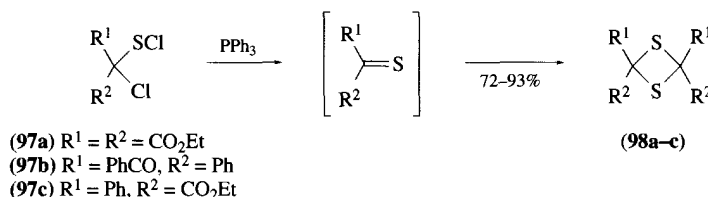
Thus, the "head-to-head" orientation and proximity between two " $C=S$ " moieties contained in the precursor compound constitute a necessary precondition for a successful realization of the 1,2-dithietane synthesis. The specific structural features, substitution pattern, stereochemistry, and availability of favorable thermal decomposition energy surface of the formed 1,2-dithietanes determine their relative stability and consequently isolability <87JA926>.

The structure of both 1,2-dithietanes (**28**) <80JA2490> and (**9**) <90JA3029> was unequivocally determined spectroscopically (IR, ^1H and ^{13}C -NMR, UV, MS) and confirmed by x-ray crystallographic analysis for the latter <87JA3801>.

1.35.4.2 Synthesis of 1,3-Dithietanes

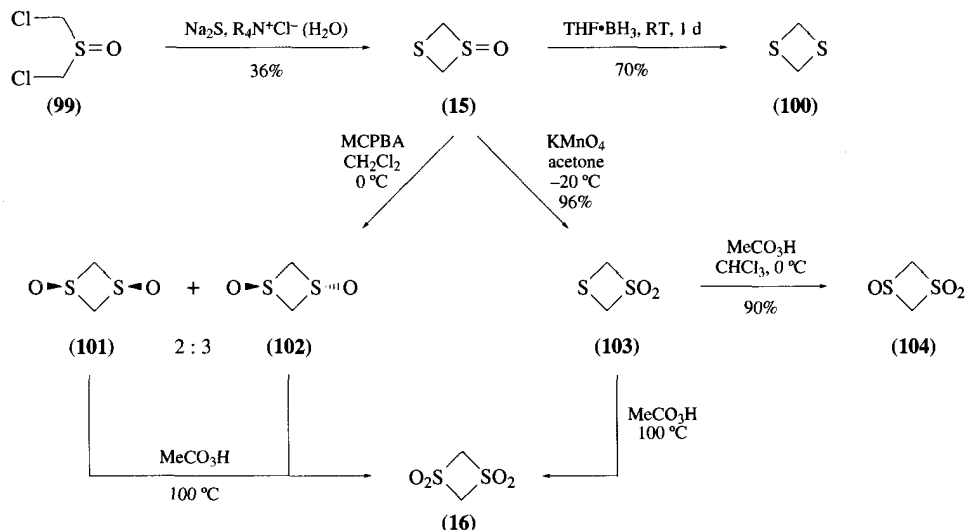
"Head-to-tail" dimerization of thiocarbonyl compounds to 1,3-dithietanes occurs thermally <33CB567, 77JOC2345, 78T2289>, photochemically <73BCJ2253, 79CC899, 81JOC3911>, in the presence of a trace of a base <65JOC1375, 73T2759>, in the presence of a sulfonic acid <70CJC3530>, or of a complex of MnO <82JOM(224)C31>. Although diaryl thioketones are resistant to dimerization, and steric factors may inhibit dimerization of other thiocarbonyl compounds, this straightforward construction of the four-membered 1,3-dithietane ring (i.e. Equation (1)) is the method of choice for the synthesis of substituted 1,3-dithietanes <B-83MI 135-02>.

Other reactions leading to 1,3-dithietanes are known. However, thiones formed *in situ* are, most probably, involved as intermediates <B-83MI 135-02>. Such examples are the reactions of (a) elemental sulfur <73T2759> or other sulfur transfer agents with fluoroalkenes often accompanied by the production of 1,3-dithiolenes <82CL201>; (b) carbon suboxide with sulfur dichloride <68JOC3642>; (c) carbon disulfide with thioureas <78TL3823>; (d) triphenylphosphine with α -chlorosulfonyl chlorides <79JOC1736> and several others (Scheme 16) <B-83MI 135-02>.



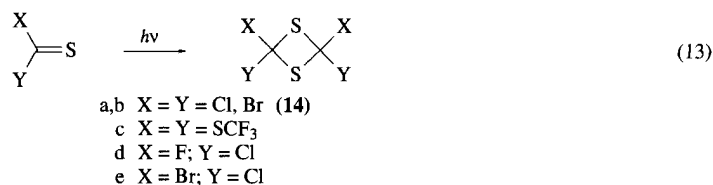
Scheme 16

Although substituted derivatives of 1,3-dithietanes have been known since the mid-1870s <1872CB970>, the parent compound 1,3-dithietane as well as its S-oxides, S,S-dioxides, S-dioxides, S,S-trioxides, and tetraoxides were successfully prepared only in the mid-1970s according to Scheme 17 <76JA5715, 82JA3119>.



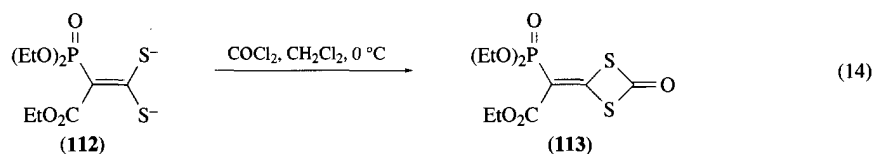
Scheme 17

The disulfone (16) is readily available via the dimerization of the parent sulfene ($\text{CH}_2=\text{SO}_2$) <69AG(E)73> and so are the perhalogenated 1,3-dithietanes via the photolytic dimerization of the corresponding thiophosgene monomers <33CB567, 77CB916, 85CB1415>. Recrystallization from organic solvents (e.g. ether) provides the pure solid products, the *cis-trans* isomers in the case of mixed substituted thiophosgenes (Equation (13)) <77CB916>.



Treatment of the tetrachloro-1,3-dithietane with SbF_3 provides a mixture of the mixed fluoro-chloro-1,3-dithietanes which can be separated by distillation under reduced pressure <85CB1415>. Oxidation of the various perhalogenated 1,3-dithietanes (14) leads directly to the corresponding S- and S,S-oxides, dioxides, trioxides and tetraoxides <85CB1415> depending on the particular oxidizing agent used and the reaction conditions employed as previously described (see Scheme 6). An analogous entry into the tetra-trifluoromethyl series is shown in Scheme 18 <85CB116>.

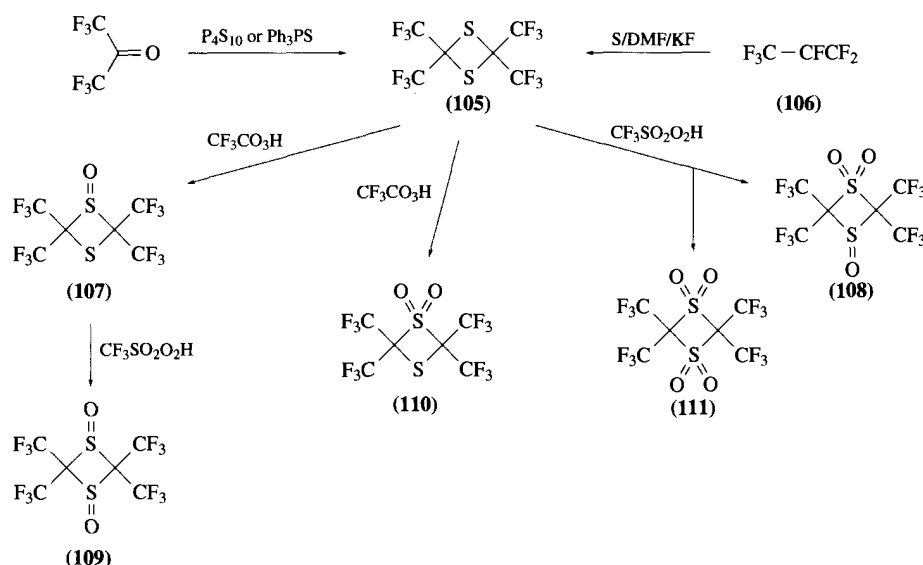
Acid hydrolysis ($\text{CH}_3\text{CO}_2\text{H}$) of the perhalo-1,3-dithietanes or 2,2-bis(trifluoromethyl)thio-1,3-dithietanes yields the corresponding carbonyl derivatives <33CB567, 77CB916, B-83MI 135-02>. The reaction of phosgene with salts of 1,1-dithiolethylene derivatives such as (112) also yields 1,3-dithietane-2-ones (Equation (14)).



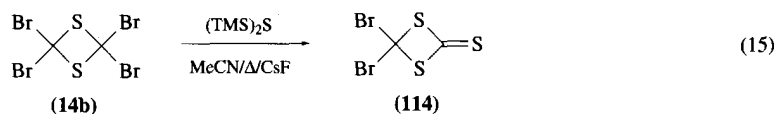
The parent 1,3-dithietane-2-thione can be obtained, albeit in low yield, by the treatment of diiodomethane with K_2CS_3 <70ZAAC(376)73>.

2,2-Dichloro-1,3-dithietane-4-thione is prepared by interaction of perchloro-1,3-dithietane (14a) with trithiacarbonic acid ($\text{S}=\text{C}(\text{SH})_2$) <70ZAAC(376)64>. The corresponding 2,2-dibromo-4-thione

Four-membered Rings with Two Sulfur Atoms



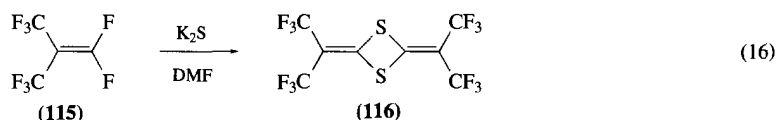
(i.e. **(114)**) is readily accessible via the reaction of the sulfur transfer agent bis(trimethylsilyl) sulfide with the perbromo-1,3-dithietane (**(14b)**) (Equation (15)) <94UP 135-01>.



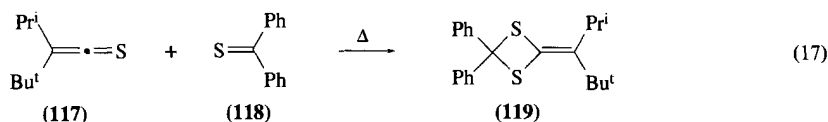
Oxidation of the parent 1,3-dithietane-2-thione with nitric acid and of the 2,2-dichloro-1,3-dithietane-2-thione with KMnO_4 gives the corresponding 1,3-dithietane-2-ones <70ZAAC(376)64, 70ZAAC(376)73>.

1,3-Dithietane tetracarboxylic esters are obtained by treatment of the α -chlorosulfonyl chloride of diethylmalonate with sodium dimethyl- (or diethyl-) malonate followed by treatment with potassium *t*-butoxide at -78°C <80TL3579>. The preparation of the silylated 1,3-dithietane-S,S-tetraoxides (e.g. **(70)**, **(71)**) have already been described <88S349> and miscellaneous methods for the preparation of specific 1,3-dithietane-centered species (occasionally just as intermediates) have been reviewed previously <B-83MI 135-02>.

The most common method of synthesis of methylene-1,3-dithietanes is the “head-to-tail” [2 + 2] cycloadditions of thioketenes <75ZC91, B-83MI 135-02>, particularly the bis(trimethylsilyl), although alkyl-, aryl-, and ester-substituted derivatives also dimerize (Equation (16)) <68JOC1850, 71BAU2386, 78IJ100, 79LA1715, B-83MI 135-02, 84CHEC-I(7)449>.

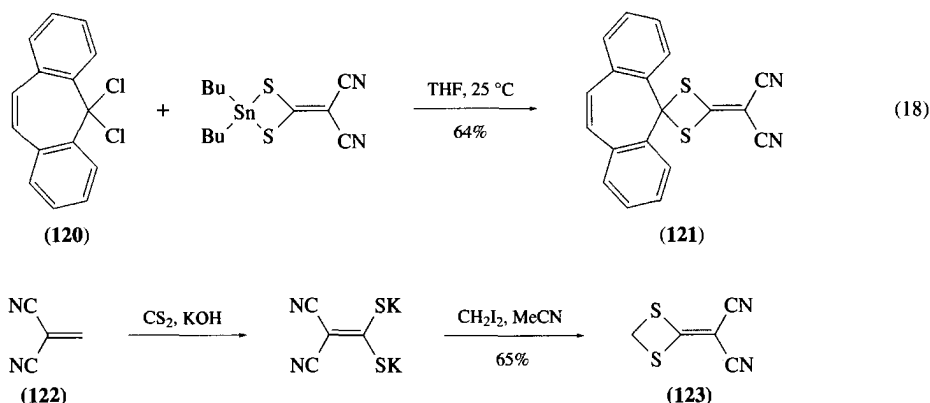


The bis(trimethylsilyl)thioketene undergoes numerous cycloadditions with other thiocarbonyl compounds to give methylenedithietanes <76CB906> as shown in Equation (17). Many other compounds yield on thermolysis methylene-1,3-dithietanes, possibly via thioketenes <B-83MI 135-02>.



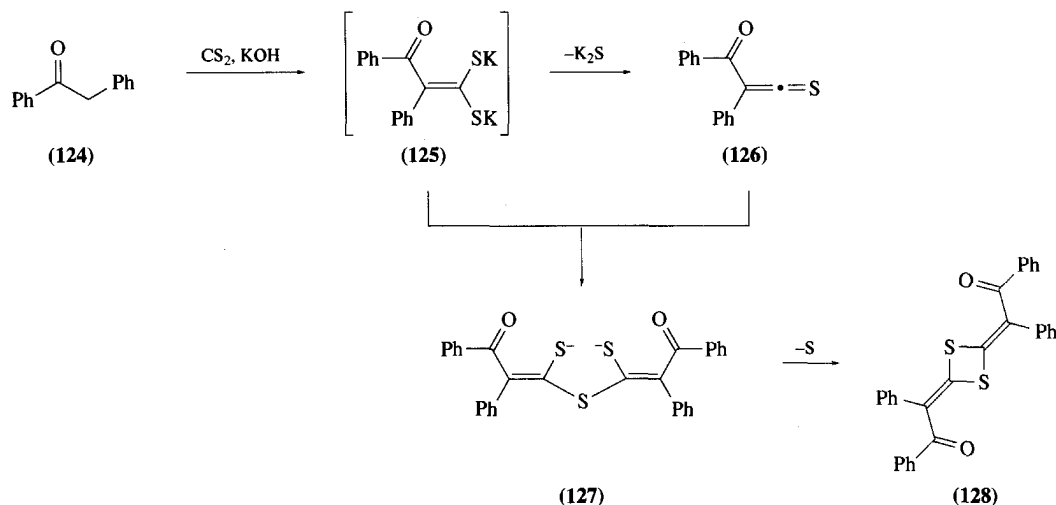
The other common method for the preparation of the methylene-1,3-dithietanes is the reaction of 1,1-dihalides or their equivalents with salts of 1,1-dithiolalkenes <B-83MI 135-02> an example of which is Equation (18) <82S227>.

Monomethylene-1,3-dithietanes such as (123) can similarly be obtained <64JOC497> (Scheme 19).



Scheme 19

The synthesis of “desaurins” may be accomplished by means of the two a.m. cycloaddition methodologies <B-83MI 135-02, 84CHEC-I(7)449>. However, their formation from ketones, carbon disulfide, and base is believed to involve nucleophilic attack on a thioketene by the dianion of 1,1-dithiolalkene as illustrated in the synthesis of desaurin 129 (Scheme 20) <71CJC1456>.



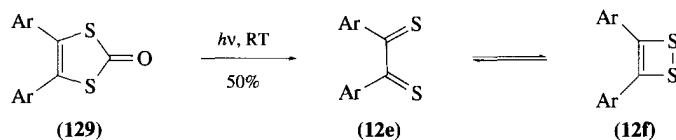
Scheme 20

Related synthesis involves the use of thiophosgene instead of carbon disulfide and the use of diazoalkanes <77H(7)961> or phosphonium <76JCS(P1)692>, and sulfonium ylides <71TL1781> instead of a ketone and base. It has been shown that 1,2-dithiole-3-thiones with a methylthio substituent in the 5-position give the corresponding desaurin by its reaction with phosphites (e.g. (CH₃O)₃P) <88BSF101>. In many other reactions, the transitory involvement of thioketenes is responsible for the ultimate formation of 1,3-dithietanes.

1.35.4.3 Synthesis of 1,2-Dithietes

Although the study of the equilibrium between substituted 1,2-dithietes and 1,2- (or α -) dithiones (i.e. (12a) $\rightleftharpoons$ (12b-d)) led to the conclusion that the closed, four-membered ring moiety of the former

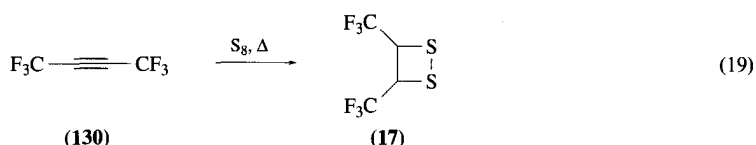
is present in all the 1,2-dithietes investigated <82JOC1979, 83HCA801>, all attempts to synthesize the latter failed until about 20 years ago when the first stable 1,2-dithione (**12e**) was prepared (Scheme 21) <73JA2383>.



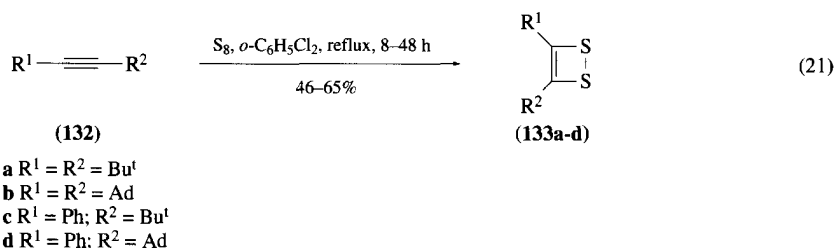
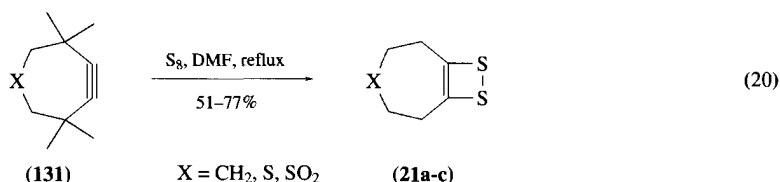
Scheme 21

The steroid dithiete (**22**) was also prepared photolitically via ring contraction of its precursor <77JCS(P1)515>. Although benzodithiete can be obtained by thermolysis of benzodithiocarbonate or its SO-analogue, the thermal instability of the product (up to 180 K) makes this method synthetically impractical <82JOC1979>.

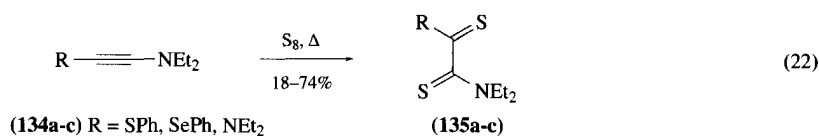
The first stable 1,2-dithiete, however, the 3,4-bis(trifluoromethyl)-1,2-dithiete (**17**) was reported already in 1960 as a result of the reaction of hexafluoro-2-butyne with boiling sulfur <60JA1515, 61JA3434>. Other fluorinated derivatives were also prepared via the same route (Equation (19)) <B-83MI 135-02>.



Since it was later demonstrated, both theoretically and experimentally, that the four-membered cyclic thietes are obtained if the substituents are either strongly electron withdrawing (e.g. (**17**)) or bulky (e.g. (**21a-c**)), or an annellated aromatic 6 π -electron systems (e.g. (**22**)) <76JA899, 82JCR(S)314, 82JOC1979>, the sulfurization of appropriately substituted alkynes by elemental sulfur has been evolved as the method of choice for the synthesis of stable 1,2-dithietes (Equations (20) and (21)) <79H(12)1153, 93BCJ623, 93TL115>.



The treatment of ynamines (i.e. (**134**)) with elemental sulfur under somewhat milder conditions affords the corresponding *trans*-1,2-dithiones (**135a-c**) (Equation 22) <93TL115>.

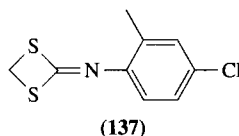
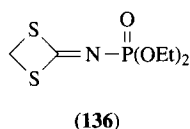


The only thus far known stable 1,2-dithietane, dithiatopazine (**9**), when heated with the highly strained alkynic compound (**131**; $X = S$) provides the 1,2-dithiete (**21**; $X = S$) in 65% <90JA3029>. This perhaps opens the gate for the synthesis of 1,2-dithietes by reacting substituted alkynes with other sulfur (i.e. "S₂") transfer agents.

1.35.5 IMPORTANT ASPECTS AND APPLICATIONS

1,2-Dithietanes are of fundamental theoretical, chemical, and biological interest <81JA159, 90JA3029> particularly as far as the disulfide linkage within cyclic arrays are concerned. Cephamycin or cephalosporin derivatives that incorporate a 1,3-dithietane ring are highly bacterial and inhibit hydrolysis by the cephalosporinases of various bacteria <82AAC613, B-83MI 135-02>. Several 1,3-dithietane derivatives are used as plasticizers in the production of polyvinyl chloride or as monomers in the preparation of polyester coatings <B-83MI 135-02>. Various methylene 1,3-dithietanes are antibiotics active against gram-negative bacteria <80CPB2629> whereas others are claimed to be antibacterial, plant viricides, fungicides, insecticides, drugs that decrease blood alcohol concentration (hyperglycemia), and useful in the prevention and treatment of liver diseases <B-83MI 135-02>. Imino-1,3-dithietanes are very useful systematic pesticides, insecticides, fungicides, nematocides, and molluscicides, two specific compounds of which, i.e. AC64475, Nematac, Fosthietane (**136**) and Nimadane (**137**) are shown below <B-83MI 135-02>.

It appears that, so far, the theoretical aspects, already discussed, are the most important as far as the 1,2-dithietes are concerned.

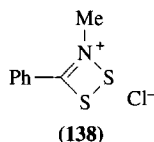


1.35.6 RELATED FOUR-MEMBERED RINGS WITH THREE HETEROATOMS

There are relatively few reports of four-membered heterocycles containing three heteroatoms, at least two of which are sulfur atoms. A few selected examples of such systems are mentioned briefly here. Their provided structure should be taken as tentative, since more study is required for structural substantiation of the early assignments made <84CHEC-I(7)449>.

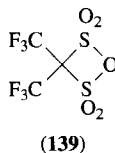
1.35.6.1 1,2,3-Dithiazetidinium Derivatives

The reaction of thiobenzamide with sulfur dichloride was reported to give the 3-methyl-4-phenyl-1,2-dithiazetidinium chloride (**138**). Convincing structural proof for (**138**) is not provided.



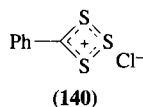
1.35.6.2 1,2,4-Oxadithietane Derivatives

Heating of hexafluoroisopropylidene-1,3,2-dioxathietane-2,2-dioxide yields 3,3-bis(trifluoromethyl)-1,2,4-oxadithietano-2,2,4,4-tetroxide (**139**), the only reported derivative of this ring system.

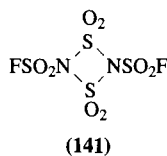


1.35.6.3 1,2,3-Trithietane Derivatives

The reaction of dithiobenzoic acid with sulfur dichloride yields the thietanylium ion, the proposed structure of which is (140).

**1.35.6.4 1,3,2,4-Dithiadiazetidine Derivatives**

This class of compounds is the best characterized of all the four-membered rings with more than two heteroatoms <84CHEC-I(7)449>. Apart from the S_4N_4 obtained from the reaction of ammonia and sulfur dichloride, several other compounds of this class with sulfur in a higher oxidation state such as (141) are known. They are reactive towards pyridine and form six-membered adducts with benzonitrile.



1.36

Four-membered Rings with Two or More Heteroatoms including Selenium or Tellurium

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1.36.1 INTRODUCTION

Four-membered heterocyclic compounds containing two or more heteroatoms including at least one selenium or tellurium atom have been known in the literature since the first preparation of a 1,3-diselenetane by Morgan and Drew in 1920 in their studies of chalcogen derivatives of 1,3-diketones <20JCS1456, 21JCS610, 22JCS922, 22JCS2432>. Most of the molecules of this classification that have been described since the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-1) have been 1,3-diselenetane derivatives (1) with only a few examples of the

corresponding 1,3-ditellurethane derivatives **(2)** <89JA8749, 91CC1378, 92C78> and only one example of a 1,3-selenatellurethane derivative **(3)** <91CC1378> having been described. Other permutations of the 1,3-diheteroatom structure include one example of a 1,3-azaselenetane **(4)** <93JPR381> and one example of a 1,3-oxaselenetane **(5)** <93BCJ1714>.



- (1) X = Y = Se
 (2) X = Y = Te
 (3) X = Se, Y = Te
 (4) X = NR, Y = Se
 (5) X = O, Y = Se

A few new examples of the 1,2-diheteroatom structures have been described since the publication of CHEC-I. A bis(selenonium) salt of a 1,2-diselenetane **(6)** has been described <93T1605>. Several 1,2-diheteroete structures have also been described. In addition to the 1,2-diselenete ring **(7)** <87AG(E)343, 88IC1474>, which was first described in 1970 <70IC1820>, examples of the 1,2-thiaselenete **(8)** <87AG(E)343> and 1,2-stannaselenete **(9)** <93CC407> rings have been described.



(6) X = Y = Se



- (7) X = Y = Se
 (8) X = S, Y = Se
 (9) X = R₂Sn, Y = Se

Four examples of four-membered rings containing three heteroatoms including one selenium or tellurium atom have been described since the publication of CHEC-I. One example of the 1-aza-2-bora-3-selenetane ring **(10)** has been described <85CB3748>, as well as one example of the 2,4-digermana-1-selenetane ring **(11)** <88OM1882, 90OM2061>. Tellurium-containing derivatives include one example of the 2,4-diaza-1-tellurethane ring **(12)** <91JOM(418)339> and one example of the 2,3-diaza-1-tellurethane ring **(13)** <93CL1047>.

Examples of four-membered rings containing four heteroatoms including one selenium or tellurium atom include the 2-aza-1,4-digermana-1-selenetane **(14)** <90OM2061> and 2,4-dibora-1,3-diselenetane **(15)** <85CB3748> ring systems.



- (10) X = NR, Y = Br, Z = Se
 (11) X = Z = GeR₂, Y = Se
 (12) X = Z = NR, Y = Te
 (13) X, Y = N=N, Z = Te



- (14) W = Y = GeR₂, X = NR, Z = Se
 (15) W = Y = BR, X = Z = Se

Organoselenium and organotellurium compounds are characterized by a rich chemistry that involves both the +2 and +4 oxidation states. The inorganic aspects of the chemistry of ligand exchange in selenium(IV) and tellurium(IV) compounds is important as well. For the four-membered heterocyclic compounds containing two or more heteroatoms including at least one selenium atom or tellurium atom described in this chapter, the +4 oxidation state has been described for relatively few compounds and the inorganic chemistry associated with reactions at the selenium or tellurium atoms of these compounds is limited to oxidative addition across the diselenide bond of 1,2-diselenetes <88IC1474>.

1.36.2 THEORETICAL METHODS

For the molecules of this chapter, no theoretical studies have been described since the publication of CHEC-I. At least part of this absence can be attributed to the difficulty of obtaining good parameter sets for the heavy atoms selenium and tellurium with filled *d*-shells.

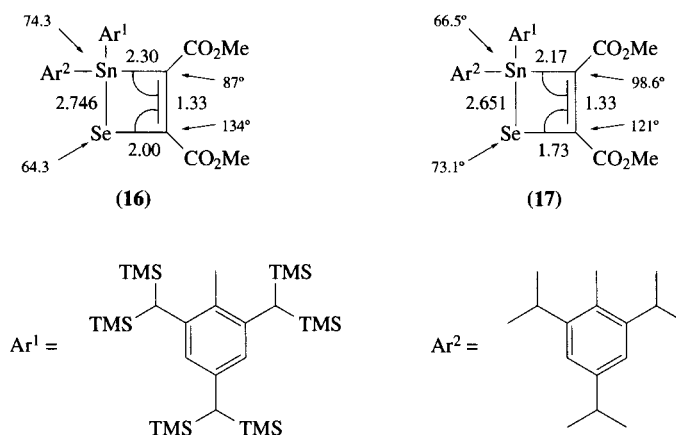
1.36.3 EXPERIMENTAL STRUCTURAL METHODS

1.36.3.1 X-ray Diffraction Studies

X-ray crystal structures have been determined for a number of 1,3-diselenetane derivatives, one 1,3-ditellurethane derivative, and one 1-diarylstanna-2-selenete derivative. For all of the 1,3-diselenetane and 1,3-ditellurethane molecules, the four-membered ring is planar and the bond angles with the heteroatom as central element are all less than 90° [86ACS(B)98, 89JOM(359)33, 90AG(E)1067, 91CC1378, 91ZN(B)157].

The 1-diarylstanna-2-selenete derivative (**16**) is nonplanar with a dihedral angle of 10.7° between the planes on either side of the Se—C4 axis [93CC407]. This dihedral angle is slightly larger than the dihedral angle of 7.3° observed in 1-diarylstanna-2-thiete derivative (**17**) along the S—C4 axis [93CC407].

The bond lengths and angles for the four-membered ring in 1-diarylstanna-2-selenete (**16**) are shown in Scheme 1 [93CC407]. These values can be compared with those for 1-diarylstanna-2-thiete (**17**), which are also shown in Scheme 1. The substitution of selenium for sulfur markedly changes the geometry about the ring in these two molecules. While the carbon–carbon double bond length is the same in the two molecules at 1.33 Å, the tin–carbon bond length is 0.13 Å longer in selenete (**16**) relative to that in thiete (**17**). The longer selenium–carbon and selenium–tin bond lengths relative to the corresponding sulfur–carbon and sulfur–tin bond lengths lead to a larger tin–selenium–carbon bond angle in (**16**) relative to the tin–sulfur–carbon bond angle in (**17**) and lead to a larger selenium–tin–carbon bond angle relative to the corresponding sulfur–tin–carbon bond angle. The other ramifications of the heteroatom change with respect to structure are observed in an increase in the tin–carbon–carbon angle of 12° and a decrease in the chalcogen–carbon–carbon angle of 13° in (**16**) relative to the corresponding angles in (**17**). These structural changes have yet to be associated with any differences in chemical reactivity.



Scheme 1

The crystal structures of the 1,3-diselenetanes (**18**)–(**22**) show similar bond lengths and angles for the 1,3-diselenetane ring. The carbon–selenium bond lengths, selenium–selenium intramolecular distances, selenium–carbon–selenium angles, and carbon–selenium–carbon angles are compiled in Table 1 [76JST(35)253, 86ACS(B)98, 89JOM(359)33, 90AG(E)1067, 91CB51, 91ZN(B)157]. These values can be compared to the corresponding values for tetrafluoro-1,3-ditellurethane (**23**) [91CC1378]. The longer tellurium–carbon bond lengths relative to the selenium–carbon bond lengths and the short tellurium–tellurium intramolecular contact (3.385 Å) lead to compression of the carbon–tellurium–carbon angle in (**23**) relative to the corresponding carbon–selenium–carbon angles in (**18**)–(**22**) with corresponding expansion of the tellurium–carbon–tellurium angle in (**23**).

In all of these molecules, the intramolecular distance between the two ring heteroatoms is much less than the sum of Van der Waals radii (4.40 Å for tellurium, 4.00 Å for selenium [64JPC441]) and is much closer to the sum of covalent radii (2.72 Å for tellurium, 2.32 Å for selenium). While both the 1,3-diselenetanes and 1,3-ditelluretanes appear to be “normal” four-membered rings in terms of covalent bonding, the interactions between the 1,3-oriented heteroatoms might become important in reactions involving one-electron oxidations of one or both selenium or tellurium atoms.

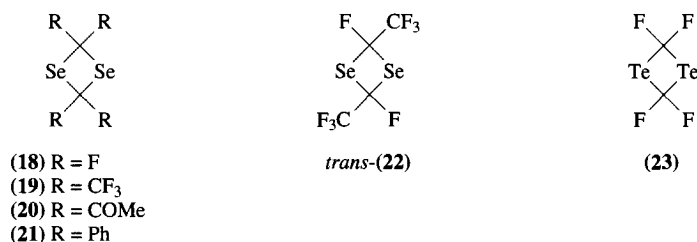


Table 1 Bond lengths (Å) and bond angles (°) as determined by x-ray crystal structures for 1,3-diselenetanes (18)–(22).

Compound	(18)	(19)	(20)	(21)	<i>trans</i> -(22)
Se—C	1.968	1.971	1.965, (1.970)	2.002	1.955
Se...Se	2.981	2.931	2.907	2.901	2.943
C—Se—C	81.5	83.6	85.4, (85.0)	87.2	82.3
Se—C—Se	98.5	96.4	94.6, (95.0)	92.9	97.7
Ref.	<76JST(35)253>	<91ZN(B)157>	<86ACS(B)98, 89JOM(359)33>	<90AG(E)1067>	<91CB51>

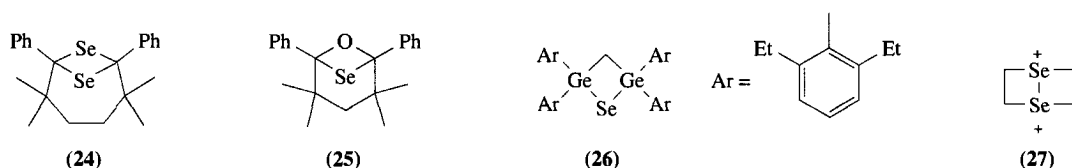
The tetraacetyl-1,3-diselenetane derivative (20) has the two selenium atoms in distorted octahedral environments. Two intermolecular selenium–oxygen contacts of 3.051 Å and two intramolecular selenium–oxygen contacts of 3.036 Å complete the octahedral coordination. The selenium–oxygen contacts are less than the sum of Van der Waals radii for the two atoms of 3.42 Å <64JPC441>, which is indicative of secondary-bonding interactions. The secondary-bonding interactions lead to a linear polymer along the *c*-axis of the crystal <86ACS(B)98, 89JOM(359)33>.

1.36.3.2 Nuclear Magnetic Resonance Spectroscopy

The 1,3-diselenetane and 1,3-ditelluretane derivatives of this chapter have been well characterized by NMR spectroscopy. The chemical shifts reported in this section for ¹H and ¹³C nuclei are in parts per million (ppm) from tetramethylsilane (TMS), where the chemical shift of TMS protons and carbons are δ0.00. Positive δ values are shifts to lower field while negative δ values are shifts to higher field. In addition to ¹H and ¹³C NMR spectroscopy, ⁷⁷Se and ¹²⁵Te NMR chemical shifts have been determined in a number of derivatives. Both selenium and tellurium have NMR-active isotopes with spin 1/2 in fairly high natural abundance (both ⁷⁷Se and ¹²⁵Te are found in about 7% natural abundance). Both ⁷⁷Se and ¹²⁵Te chemical shifts are given in ppm with the heteroatom chemical shift of Me₂Se and Me₂Te, respectively, as references set as δ0.00. A number of ¹⁹F NMR chemical shifts in ppm are also given for ring substituents with CFCl₃ as reference with a chemical shift of δ0.00. A few ¹¹B NMR chemical shifts in ppm from boron trifluoride etherate are listed for boron-containing four-membered selenium heterocycles.

1.36.3.2.1 Proton NMR spectroscopy

In terms of characterizing the ring, ¹H NMR spectroscopy has been of little utility. None of the 1,3-diselenetane or 1,3-ditelluretane molecules of this chapter possess protons directly attached to an atom of the ring. Tetraphenyl-1,3-diselenetane (21) has normal phenyl chemical shifts for its substituents as do the phenyl substituents of 1,3-diselenetane (24) <92CL2289> and 1,3-oxaselenetane (25) <93BCJ1714>. The 1,3-digermana-2-selenetane (26) displays a two-proton singlet at δ3.27 for the ring methylene (with normal aryl chemical shifts) <90OM2061>. The 1,2-diselenetane bis(selenonium) salt (27) displays a broadened eight-proton singlet at δ4.25.

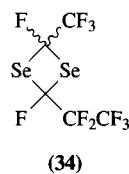
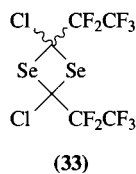
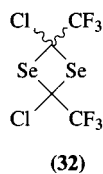
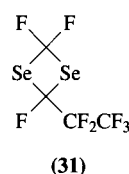
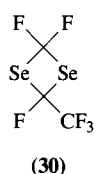
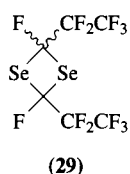
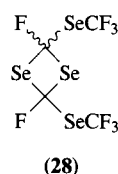


1.36.3.2.2 Carbon-13 NMR spectroscopy

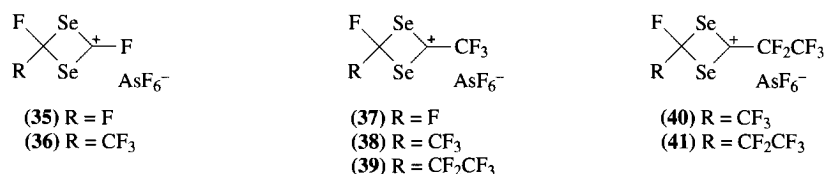
Carbon-13 NMR spectroscopy has been utilized extensively for the characterization of 1,3-diselenetane and 1,3-ditellurethane derivatives. The chemical shift range is large and ^{13}C NMR chemical shifts of the ring carbons are compiled in Table 2 for neutral 1,3-diselenetane derivatives and in Table 3 for 1,3-diselenetan-2-ylum hexafluoroarsenate derivatives. Among the neutral molecules, the range varies from $\delta 15$ for tetra(trifluoromethyl)-1,3-diselenetane (**19**) <91JFC(53)71, 91ZN(B)157> to $\delta 129.4$ for tetraphenyl-1,3-diselenetane (**21**) <90AG(E)1067>. The effects of substituents on ^{13}C NMR chemical shifts as compiled in the chemical-shift values of Table 2 are typical of substituent effects in other acyclic, cyclic, and heterocyclic systems.

Table 2 Carbon-13, Selenium-77, and fluorine-19 NMR chemical shifts for the ring atoms of 1,3-diselenetanes.

Compound	^{13}C NMR δ	^{77}Se NMR δ	^{19}F NMR δ	Ref.
(18)	87			76JST(35)253
(19)	15.0	667.6		91ZN(B)157
(19)	14.8	666.6		91JFC71
(21)	129.4			90AG(E)1067
cis-(22)	66.8	874.6	−129	88C265
trans-(22)	67.9	875.3	−141	88C265
(24)	42.3			92CL2289
cis-(28)	55.7	1214.5	−54.9	88C265
trans-(28)	58.8	1198.2	−72.2	88C265
cis-(29)	70.3	888	−125.5	91CB51
trans-(29)	81.3	892	−138.1	91CB51
(30)	86.9 (CF_2), 68.5	1039	[−35.1, −47.0 (CF_2)], −137.1	91CB51
(31)	87.9 (CF_2), 71.8	1047	[−34.7, −47.7 (CF_2)], −136.0	91CB51
cis-(32)	31.4	982		91CB51
trans-(32)	30.9	988		91CB51
cis-(33)	32.1	1009		91CB51
trans-(33)	31.7	1013		91CB51
cis-(34)		881	−126.5, −128.3 (CFCF_3)	91CB51
trans-(34)	31.7	1013	−138.1, −141.2 (CFCF_3)	91CB51

**Table 3** Carbon-13, Selenium-77, and fluorine-19 NMR chemical shifts for the ring atoms of 1,3-diselenetan-2-ylum hexafluoroarsenates.

Compound	^{13}C NMR δ	^{77}Se NMR δ	^{19}F NMR δ
(35)		1334	+102 (C^+F), −67 (CF_2)
(36)	245.7 (C^+F)	1240	+118.3 (C^+F), −157.2 (CFCF_3)
(37)	87.5 (CF_2), 251.8 (C^+CF_3)	1447	−67.2 (CF_2)
(38)	78.0 (CFCF_3), 255.6 (C^+CF_3)	1327	−145.0 (CFCF_3)
(39)		1334	
(40)	78.7 (CFCF_3), 256.1 ($\text{C}^+\text{C}_2\text{F}_5$)	1358	−142.6 (CFCF_3)
(41)	80.0 (CFC_2F_3), 245.9 ($\text{C}^+\text{C}_2\text{F}_5$)	1365	−139.8 (CFCF_3)



The ^{13}C NMR chemical shift of tetrafluoro-1,3-ditellurethane (**23**) of $\delta 45.3$ is significantly upfield of the CF_2 chemical shifts of 1,3-diselenetanes in Table 2 ($\langle 91\text{CC1378} \rangle$) which are in the $\delta 80$ – 90 range. This chemical shift difference is most readily attributed to greater shielding from the adjacent tellurium nuclei.

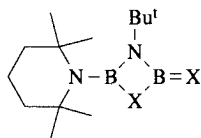
The ^{13}C NMR chemical shift of 1,3-oxaselenetane (**25**) of $\delta 92.6$ ($\langle 93\text{BCJ1714} \rangle$) is significantly downfield of the value of $\delta 42.3$ observed for 1,3-diselenetane (**24**) with an identical hydrocarbon framework ($\langle 92\text{CL2289} \rangle$). This difference is again most readily attributed to increased shielding from the selenium nuclei relative to oxygen nuclei.

The 1,3-digermana-2-selenetane (**26**) displays a ^{13}C NMR chemical shift of $\delta 40.8$ for the 4-carbon ($\langle 90\text{OM2061} \rangle$). The carbon in this molecule is not flanked by selenium or tellurium nuclei, but is flanked by two diarylgermanium nuclei.

The 1,2-diselenetane nucleus found in the bis-selenonium salt (**27**) displays a ^{13}C NMR chemical shift of $\delta 47.0$ ($\langle 93\text{T1605} \rangle$). The cationic character of the selenium atoms of this molecule has little effect on the observed chemical shifts of the adjacent carbon atoms. In 1,4-diselenacyclohexane, which is the neutral precursor to (**26**), the ring carbons are observed at $\delta 20.4$ ($\langle 93\text{T1605} \rangle$).

The ^{13}C NMR chemical shifts of the neutral ring carbon (C4) of the 1,3-diselenetane-2-ylum hexafluoroarsenates (**35**)–(**41**) fall in the range observed for the neutral 1,3-diselenetanes of Table 2 ($\delta 78.0$ – 87.5) ($\langle 91\text{CB51} \rangle$). The ylium carbon (C2) is found at much lower field ($\delta 245.7$ – 256.1), which is indicative that the carbon atoms of these molecules bear a large portion of the positive charge. The fluoro, trifluoromethyl, and pentafluoroethyl substituents have little effect on the ^{13}C NMR chemical shifts of the ring carbons in these molecules.

In the ^{13}C NMR spectrum of 2-bora-1,3-azaselenetane (**42**), the ring carbon appears at $\delta 198.5$ ($\langle 85\text{CB3748} \rangle$). The chemical shift of the diselenocarbamate carbon is similar to the chemical shift of the dithiocarbamate carbon of 2-bora-1,3-azathietane (**43**) ($\delta 203.6$) but is significantly downfield of the carbamate carbon of the corresponding 2-bora-1,3-oxetane (**44**) ($\delta 155.8$) ($\langle 85\text{CB3748} \rangle$).



- (42) X = Se
(43) X = S
(44) X = O

1.36.3.2.3 Selenium-77 NMR spectroscopy

Selenium-77 NMR spectroscopy has been utilized to characterize many of the selenetane and diselenetane molecules described in this chapter. For the neutral molecules, the chemical shift range is large, varying from $\delta 667$ for 1,3-diselenetane (**19**) (Table 2) to $\delta 1220.1$ for tetrafluoro-1,3-selenatellurethane ((**45**), Table 4). The ^{77}Se NMR chemical shifts for the 1,3-diselenetanes are compiled in Table 2. The 1,2-diselenetane bis-selenonium salt (**27**) displays a ^{77}Se NMR chemical shift of $\delta 1202.0$ ($\langle 93\text{T1605} \rangle$). In the 1,3-diselenetane molecules, electron-withdrawing substituents attached to the ring carbons (F, Cl) give downfield shifts relative to other substituents, which are more electron donating (perfluoroalkyl, Ph). The one interesting observation in the effects of substituents is the replacement of a selenium atom in the ring with a tellurium atom in (**45**), which leads to a several hundred ppm downfield shift in the ^{77}Se NMR chemical shift of the remaining selenium atom.

In 2,4-perfluoroalkyl-substituted 1,3-diselenetanes (**22**), (**28**), (**29**), (**32**), and (**33**), very little difference in ^{77}Se chemical shifts is observed between *cis*- and *trans*-isomers (Table 2). Exceptions to this observation are *cis*- and *trans*-(**34**), which differ by 132 ppm ($\langle 91\text{CB51} \rangle$).

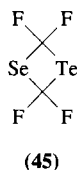
In the 1,3-diselenetane-2-ylum salts (35)–(41), the ^{77}Se NMR chemical shifts (Table 3) are found in a fairly broad range from $\delta 1240$ to $\delta 1447$, which is indicative of fairly pronounced substituent effects in the fluoro, trifluoromethyl, and pentafluoroethyl substituents of these molecules <91CB51>. The range of chemical shifts is much larger in the ^{77}Se NMR spectra of these molecules relative to the observed range of chemical shifts in the ^{13}C NMR spectra of these molecules (Table 3).

1.36.3.2.4 Tellurium-125 NMR spectroscopy

Tellurium-125 NMR chemical shifts have been described for tetrafluoro-1,3-ditelluretane (23) and for tetrafluoro-1,3-selenatelluretane (45). The chemical shift values for these two molecules are $\delta 2321.7$ for (23) and $\delta 2272.8$ for (45) and are compiled in Table 4 <91CC1378>. It is interesting to note that the substitution of one selenium atom for a tellurium atom in the ring of (23) gives a 49 ppm upfield shift in the ^{125}Te signal of (45) relative to that of (23). This upfield shift is much smaller in magnitude than the downfield shift observed in ^{77}Se NMR chemical shifts upon substitution of tellurium for selenium in 1,3-diselenetanes.

Table 4 Carbon-13, Selenium-77, and fluorine-19 NMR chemical shifts for the ring atoms of 1,3-ditelluretane (23) and 1,3-selenatelluretane (45) <91CC1378>.

Compound	^{13}C NMR δ	^{77}Se NMR δ	^{125}Te NMR δ	^{19}F NMR δ
(23)	45.3		2321.7	– 38.8
(45)		1220.1	2272.8	– 42.0



1.36.3.2.5 Fluorine-19 NMR spectroscopy

Fluorine-19 NMR chemical shifts have been described for tetrafluoro-1,3-ditelluretane (23), tetrafluoro-1,3-selenatelluretane (45), 1,3-diselenetanes (22), (28), (29), and (32)–(34), and 1,3-diselenetane-2-ylum salts (35)–(41) (Tables 2–4). The ^{19}F NMR chemical shifts for the ring CF_2 groups found in the tellurium-containing molecules (23) and (45) ($\delta -38.8$ and $\delta -42.0$, respectively) are between the ^{19}F NMR chemical shifts for the nonequivalent fluorine atoms of ring CF_2 groups in 1,3-diselenetanes (30) and (31) ($\delta -35.1$ and -7.0 for (30) and $\delta -34.7$ and -47.7 for (31)) <91CB51>. The ^{19}F NMR chemical shift of the ring CF_2 group in 1,3-diselenetane-2-ylum salt (37) is found at higher field ($\delta -67$) relative to the neutral molecules <91CB51>.

The ^{19}F NMR chemical shift of the fluorine attached to the 2-ylum carbon in (35) and (36) is found at $\delta +102$ and $+118.3$, respectively. These values reflect the deshielding from the adjacent positive charge <91CB51>.

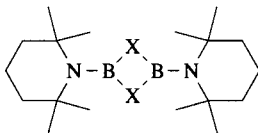
The replacement of a fluorine atom with a trifluoromethyl or pentafluoroethyl group on a CF_2 group leads to pronounced shift to higher field in the ^{19}F NMR spectra of (22), (29)–(31), and (34) (Table 2). The magnitude of the shift is roughly 80–100 ppm. A similar shift with trifluoromethyl or pentafluoroethyl substitution for fluorine is observed with 1,3-diselenetane-2-ylum salts (36) and (38)–(41) <91CB51>.

1.36.3.2.6 Boron-11 NMR spectroscopy

In the ^{11}B NMR spectrum of 2-bora-1,3-azaselenetane (42), the boron nucleus appears at $\delta 44.2$ (with borontrifluoride etherate as $\delta 0.00$) <85CB3748>. The chemical shift of the 2-bora-1,3-aza-

selenetane boron is nearly identical to the chemical shift of the boron nucleus of 2-bora-1,3-azathietane (**43**) ($\delta 44.8$) but is significantly downfield of the boron nucleus of the corresponding 2-bora-1,3-oxetane (**44**) ($\delta 27.9$) $\langle 85CB3748 \rangle$.

In the 2,4-dibora-1,3-dichalcogenetane series (**46**)–(**48**), the ordering is somewhat different $\langle 85CB3748 \rangle$. The ^{11}B NMR chemical shift of 2,4-dibora-1,3-diselenetane (**46**) ($\delta 34.9$) is intermediate between the ^{11}B NMR chemical shifts of $\delta 40.0$ for 2,4-dibora-1,3-dithietane (**47**) and $\delta 28.2$ for 2,4-dibora-1,3-dioxetane (**48**).



(**46**) X = Se

(**47**) X = S

(**48**) X = O

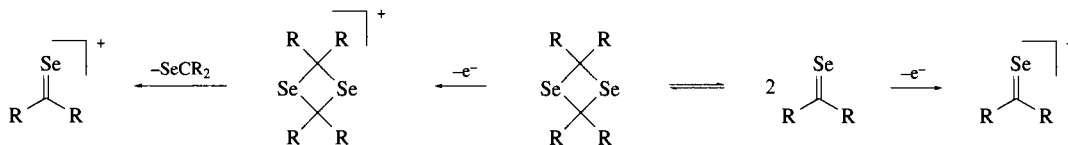
1.36.3.3 Mass Spectroscopy

The mass spectra of selenium- and tellurium-containing molecules are characterized by clusters of peaks in the heteroatom-containing fragments. Selenium is composed of isotopes with nominal masses between 74 and 82 while tellurium is composed of isotopes with nominal masses between 120 and 130 $\langle 84CHEC-I(4)956 \rangle$. These isotopes and their relative abundances are compiled in Table 5.

Table 5 Isotope relative abundance for selenium and tellurium $\langle 84CHEC-I(4)956 \rangle$.

Nominal mass	Selenium Relative abundance	Nominal mass	Tellurium Relative abundance
74	1.75	120	0.26
75	0.00	121	0.00
76	18.11	122	7.13
77	15.21	123	2.52
78	47.21	124	13.37
79	0.00	125	20.27
80	100.00	126	54.26
81	0.00	127	0.00
82	18.45	128	92.20
		129	0.00
		130	100.00

The mass spectra for many of the molecules of this chapter have been described. The parent ion is a major fragment for 1,3-diselenetanes (**22**) and (**28**)–(**34**), which has aided in their characterization $\langle 91CB51 \rangle$. Another major fragment in these molecules is shown in Scheme 2 as the selenoketone cation radical. This fragment might arise from either loss of a neutral fragment from the parent ion or from ionization of the selenoketone in equilibrium with the 1,3-diselenetane. 1,3-Diselenetane (**24**) $\langle 92CL2289 \rangle$ and 1,3-oxaselenetane (**25**) $\langle 93BCJ1714 \rangle$ also display strong parent ions, but seleno-carbonyl fragments are tethered intramolecularly to the other half of the molecule.



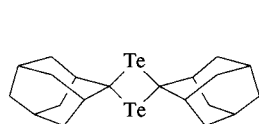
Scheme 2

Similar behavior is observed in 1,3-ditellurethane (**23**) and 1,3-selenatellurethane (**45**). Both the parent ion and fragments corresponding to the difluorotellurocarbonyl and/or difluoro-selenocarbonyl cations are observed $\langle 91CC1378 \rangle$. 1,3-Ditellurethane (**49**) has only been characterized

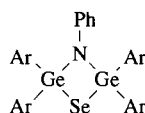
by its mass spectrum, which was indicative of the molecular ion and the expected isotope pattern for Te_2 <89JA8749>.

1,3-Digermana-2-selenetane (**26**) and 4-aza-1,3-digermana-2-selenetane (**50**) display parent ions of somewhat lesser intensity <90OM2061>. The 1,3-diaza-2-telluretan-4-one (**51**) also gives a parent ion <91JOM(418)339>.

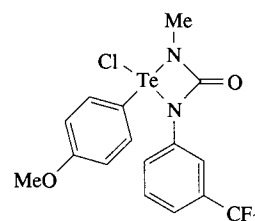
1,2-Diselenete (**7**) and 1,2-thiaselenete (**8**) are characterized by strong parent ions as the base peak <87AG(E)343>. The Se_2^+ and SSe^+ fragments are also large in (**7**) and (**8**), respectively.



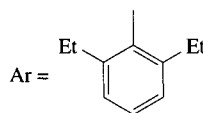
(49)



(50)



(51)



Ar =

1.36.3.4 Infrared Spectroscopy

Selected bands in the infrared spectra of 1,3-oxaselenetanes, 1,3-diselenetanes, 1,3-selenatelluretanes, and 1,3-ditelluretanes have been described although systematic analyses of the spectra have not <91CB51, 91CC1378, 92CL2289, 93BCJ1714>. The carbonyl stretching frequency of 1,3-diaza-2-telluretan-4-one (**51**) is observed at 1668 cm^{-1} <91JOM(418)339>.

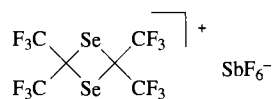
The infrared spectra in the series of 1,2-diselenete (**7**), 1,2-thiaselenete (**8**), and 1,2-dithiete (**52**) have been examined in somewhat greater detail <83JA4519, 87AG(E)343>. An intense band for the carbon-hydrogen out-of-plane vibration is observed at nearly the same frequency (734 cm^{-1} for (**7**) and (**8**) and 735 cm^{-1} for (**52**)) in all three molecules, which is indicative that the heteroatom is exerting minimal influence on this vibration.



(52) X = Y = S

1.36.3.5 Electron Paramagnetic Resonance Spectroscopy

Tetra(trifluoromethyl)-1,3-diselenetane (**19**) has been oxidized to the radical cation (**53**) with antimony pentafluoride <91JFC(53)71>. The EPR spectrum of (**53**) displays a broad, unresolved signal (width at half-height of 30 G) with a g factor ($g = 2.01515$) significantly different than that of the free electron.



(53)

1.36.3.6 Photoelectron Spectroscopy

The photoelectron (PE) spectrum of tetrafluoro-1,3-diselenetane (**18**) has been described although the band assignments have not been described <84CB187>. The lower-energy bands in the PE spectrum of (**18**) are observed at 9.9, 11.0, 12.2, and 14.3 eV.

The PE spectra of 1,2-diselenete (**7**), 1,2-thiaselenete (**8**), and 1,2-dithiete (**52**) have been measured and compared <83JA4519, 87AG(E)343>. The lower-energy bands for these molecules, which are compiled in Table 6, are quite similar. Presumably, the small electronegativity difference between sulfur and selenium leads to the similarity in the PE spectra of the three molecules <87AG(E)343>. However, a monotonic increase in ionization energy for each band is observed upon replacement of a selenium atom with a sulfur atom in this series, which one would expect from the slightly more electropositive character of selenium relative to sulfur.

Table 6 Photoelectron spectra of 1,2-diselenete (**7**), 1,2-thiaselenete (**8**), and 1,2-dithiete (**52**).

Compound	Band 1	Band 2	Band 3	Band 4	Ref.
(7)	8.71	8.82	11.18	11.64	87AG(E)343
(8)	8.87	9.13	11.46	11.97	87AG(E)343
(52)	9.05	9.36	11.83	12.31	83JA4519

1.36.4 THERMODYNAMIC ASPECTS

1.36.4.1 Melting Points

Nearly all of the molecules of this chapter are crystalline compounds. What is somewhat surprising is the relatively low melting points associated with most of the 1,2-selenete, 1,3-diselenetane, 1,3-ditellurethane, 1,3-oxaselenetane, and 1,3-selenatellurethane derivatives. The low melting points suggest that intermolecular selenium–selenium or tellurium–tellurium interactions are not strong in the crystalline state of these molecules, which is reflected in the x-ray structural data for 1,2-stannaselenete (**16**) <93CC407>, 1,3-diselenetanes (**18**) <76JST(35)253>, (**19**) <91ZN(B)157>, (**21**) <90AG(E)1067>, and (**22**) <91CB51>, and 1,3-ditellurethane (**23**) <91CC1378>. Intermolecular selenium–selenium and tellurium–tellurium distances are not particularly short.

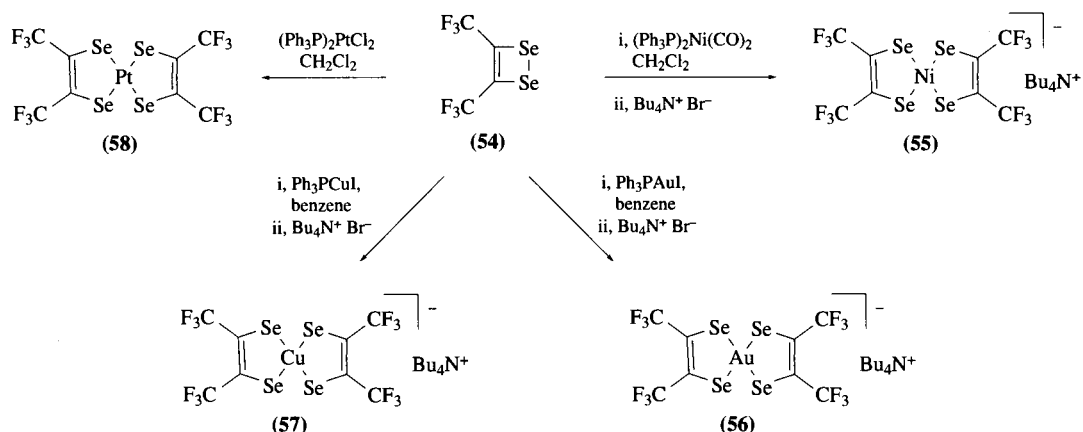
The melting point of tetraacetyl-1,3-diselenetane (**20**) is somewhat higher (m.p. 183–185°C <89JOM(359)33>). The higher melting point reflects the intermolecular interactions in this molecule from acetyl–oxygen coordination to a selenium atom of a neighboring molecule, which lead to a polymeric chain in the crystal.

1.36.5 REACTIVITY

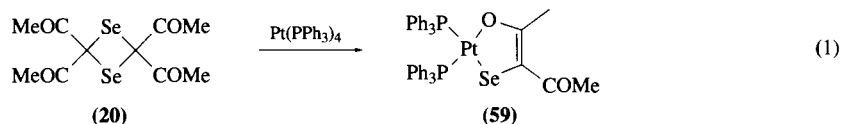
1.36.5.1 Oxidative Addition Reactions with Metals

Bis(trifluoromethyl)-1,2-diselenete (**54**) undergoes oxidative addition reactions with a variety of different transition metal complexes to give metal diselenolate complexes (**55**)–(**58**) as crystalline solids in 43–90% isolated yields as shown in Scheme 3 <88IC1474>. In these reactions, the selenium–selenium bond of (**54**) is cleaved by the metal and each metal center reacts with two molecules of (**54**) suggesting two oxidative addition reactions. Some of these reactions were described much earlier <67CC670, 70IC1820>, but the 1988 review describes some novel complexes as well as improved procedures with higher yields for the known complexes.

Platinum tetrakis(triphenylphosphine) reacts via an oxidative addition reaction with tetraacetyl-1,3-diselenetane (**20**) to give complex (**59**) (Equation (1)) <91CL1299>. In this reaction, the 1,3-diselenetane ring must be destroyed prior to the oxidative addition step, either by cycloreversion to two molecules of selenoketone or by formation of a diselenide from ring-opening attack of the metal.



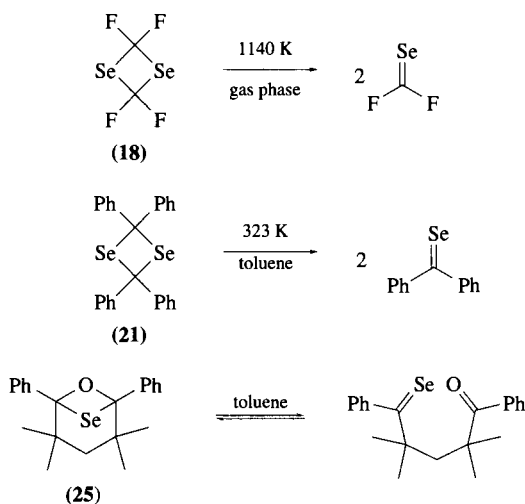
Scheme 3



1.36.5.2 Cycloreversion Reactions

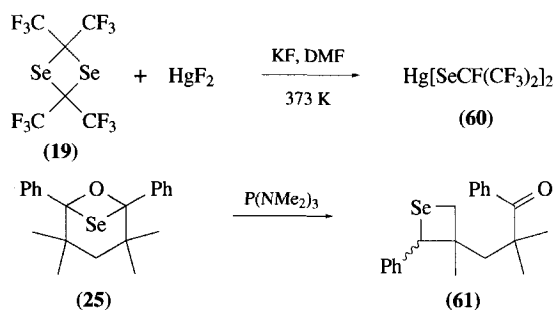
Although the dimerization reactions of selenocarbonyl and/or tellurocarbonyl compounds have been the primary synthetic routes to 1,3-diselenetane, 1,3-selenatelluretane, and 1,3-ditelluretane nuclei, the cycloreversion reactions of these molecules have been observed in both the gas phase and in solution. The thermal cycloreversion of the 1,3-diselenetane nucleus to two molecules of selenocarbonyl compound as illustrated in Scheme 4 has been well characterized in the gas phase at 1140 K for tetrafluoro-1,3-diselenetane (**18**) <84CB187> and in solution for tetraphenyl-1,3-diselenetane (**21**) <90AG(E)1067>. The observation of ions for the selenocarbonyl and tellurocarbonyl fragments of 1,3-diselenetane, 1,3-selenatelluretane, and 1,3-ditelluretane nuclei in the mass spectra of these molecules also suggests the cycloreversion reaction in the gas phase (Scheme 2). In benzene solution, the thermal cycloreversion of (**21**) proceeds with a first-order rate constant, k , of $1.73 \times 10^{-4} \text{ s}^{-1}$ and with an Eyring free energy of activation, $\delta G^\ddagger$, of $24.4 \pm 0.3 \text{ kcal mol}^{-1}$ at 323 K <90AG(E)1067>.

Similar cycloreversion chemistry has been observed with 1,3-oxaselenetane (**25**). 1,3-Oxaselenetane (**25**) is in equilibrium in toluene solution with its ring-opened ketone-selenoketone form as shown in Scheme 4 <93BCJ1714>. Rate data was not described for this reaction, however.

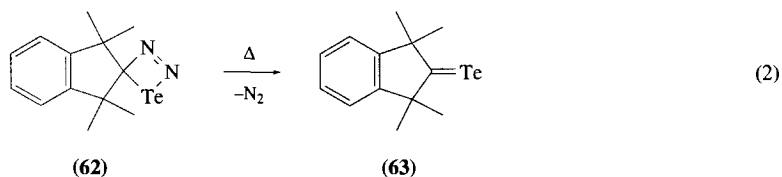


Scheme 4

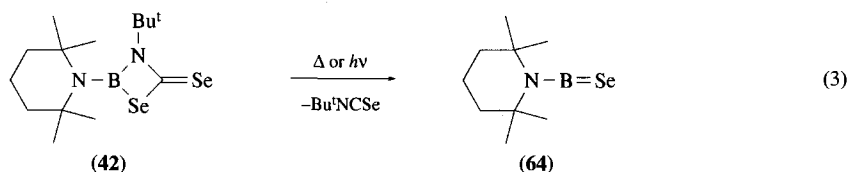
The equilibrium between the selenocarbonyl compound and the 1,3-diselenetane favors the 1,3-diselenetane in solution. Similarly, the equilibrium of 1,3-oxaselenetane (**25**) and its ring-opened form favors the 1,3-oxaselenetane. However, thermal reactions of the 1,3-diselenetane and 1,3-oxaselenetane can be driven to completion by selective reaction of the selenocarbonyl. Two examples are shown in Scheme 5. In the presence of mercury(II) fluoride and potassium fluoride in DMF, the thermal reaction of 1,3-diselenetane (**19**) gives mercury complex (**60**) in 35% isolated yield, presumably via the initial formation of bis(trifluoromethyl)selenocarbonyl, which then reacts with the mercury salt <91CB423>. 1,3-Oxaselenetane (**25**) in refluxing toluene in the presence of hexamethylphosphortriamine gives a mixture of selenetanes (**61**) in 19% isolated yield, presumably from reaction of the selenoketone in the ring-opened form <93BCJ1714>.



2,3-Diazotelluretane (**62**) loses nitrogen thermally to give telluroketone (**63**) as shown in Equation (2) <93CL1047>. Compound (**62**) is formed *in situ* and has not been isolated. Consequently, rate data is lacking for the specific reaction of Equation (2).



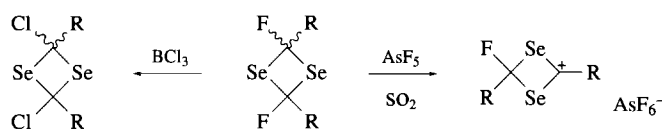
3-Aza-2-bora-1-selenetane (**42**) undergoes a thermal loss of *t*-butyl isoselenocyanate in the solid state under vacuum at 323 K to give (**64**) as shown in Equation (3) <85CB3748>. This reaction also proceeds photochemically in benzene solution.



1.36.5.3 Reactions with Lewis Acids

1,3-Diselenetanes with a 2-fluoro substituent react with Lewis acids to give 1,3-diselenetan-2-ylum species from ionic cleavage of a fluorine-carbon bond <91CB51>. When the Lewis acid is arsenic pentafluoride in sulfur dioxide, the hexafluoroarsenate salts (**35**)–(**41**) are isolated as crystalline solids from the appropriate 1,3-diselenetane precursor (**18**), (**22**), (**29**), (**30**), or (**34**) as shown in Scheme 6. When the Lewis acid is boron trichloride, ionization of (**22**) or (**29**) to the corresponding 1,3-diselenetan-2-ylum salt is followed by nucleophilic capture of chloride. Repetition of the process gives 2,4-dichloro-1,3-diselenetanes (**32**) and (**33**).

In the absence of an ionizable carbon-fluorine bond on the 1,3-diselenetane ring, a different chemistry is observed. Tetra(trifluoromethyl)-1,3-diselenetane (**19**) is oxidized by the Lewis acid antimony pentafluoride to give the selenium-centered radical cation (**53**) as a deep blue solution <91JFC(53)71>.



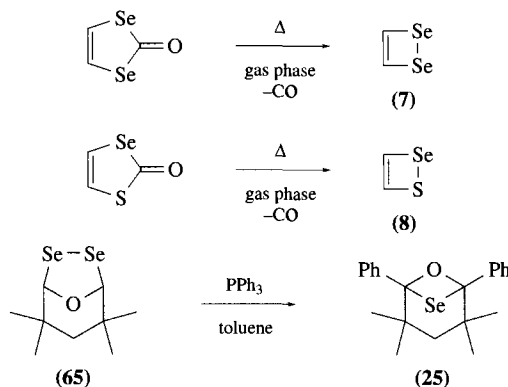
Scheme 6

1.36.6 SYNTHESIS

The molecules of this chapter have been synthesized via a number of different routes. One-component syntheses include the thermal extrusion of an atom or small molecule from another heterocyclic system, the intramolecular formation of a selenium–selenium bond via an oxidative process, and the intramolecular [2 + 2] cyclization of two selenocarbonyl groups. Thermal [2 + 2] two-component syntheses have been utilized for the construction of all examples of 1,3-oxaselenetane, 1,3-diselenetane, 1,3-selenatelluretane, and 1,3-ditelluretane nuclei. 1,2-Stannaselenetes, 2,4-dibora-1,3-diselenetanes, and 3-aza-2-bora-1-selenetanes have been constructed by thermal [2 + 2] two-component syntheses as well. Several different [3 + 1] two-component syntheses have been utilized for the construction of various diazatelluretanes, azaselenetanes, digermanaselenetanes, and azadigermanaselenetanes.

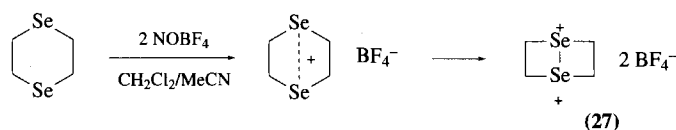
1.36.6.1 One-component Synthesis

Several heterocyclic systems have served as precursors to four-ring heterocycles with one or more selenium or other heteroatoms. As shown in Scheme 7, the thermal extrusion of carbon monoxide from 1,3-diselenol-2-one and 1,3-thiaselenol-2-one gives 1,2-diselenete (**7**) and 1,2-thiaselenete (**8**), respectively <87AG(E)343>. The triphenylphosphine-induced extrusion of selenium from 3,4-diselenafuran (**65**) gives 1,3-oxaselenetane (**25**) as shown in Scheme 7 <93BCJ1714>.



Scheme 7

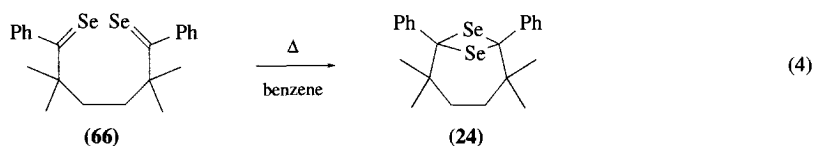
The oxidation of 1,4-diselenacyclohexane with two equivalents of nitrosyl tetrafluoroborate gives the bicyclic compound (**27**) as shown in Scheme 8 <93T1605>. The first selenium–selenium bond in this molecule is probably formed with the oxidation of the first selenium-centered radical cation. A transannular selenium–selenium interaction then forms a two-center, three-electron bond. The removal of the second electron then gives a stronger selenium–selenium bond.



Scheme 8

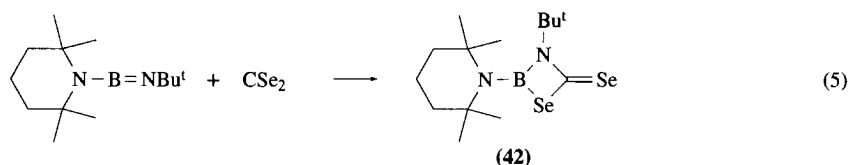
The bis(selenocarbonyl) species (**66**) undergoes an intramolecular [2 + 2] cycloaddition reaction to give 1,3-diselenetane (**24**) as shown in Equation (4) <92CL2289>. The intermolecular version of the

[2 + 2] reaction has been the major synthetic route to 1,3-diselenetanes and 1,3-ditelluretanes as described in the next section.

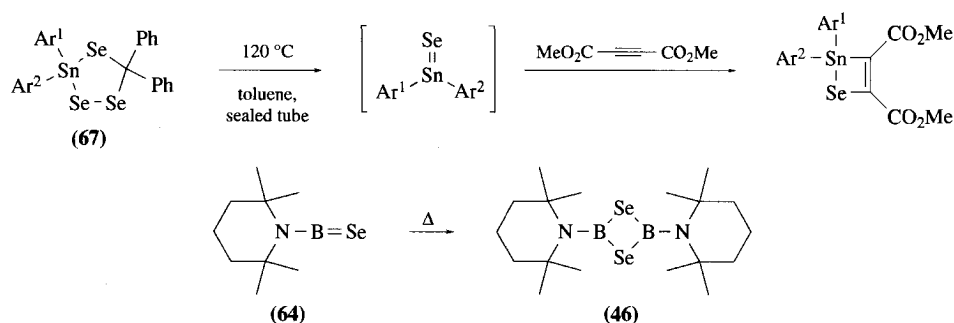


1.36.6.2 [2 + 2] Two-component Synthesis

As shown in Equation (5), carbon diselenide reacts with a boraimine to give 3-aza-2-bora-1-selenetane (**42**) via a two-component [2 + 2] reaction <85CB3748>. The reaction conditions and yield with carbon diselenide are similar to those with carbon disulfide for the construction of the thiatane analogue (**43**).



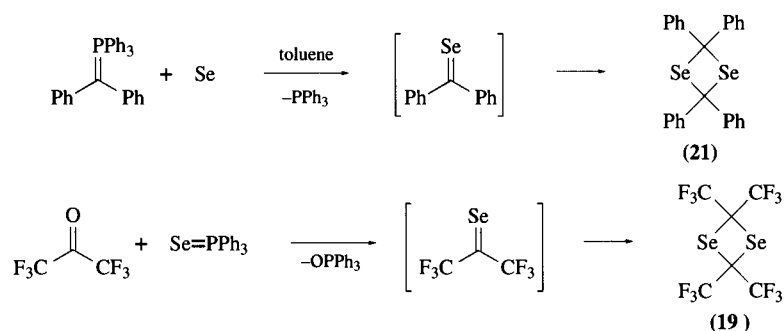
The reaction of a heteroatom-selenium double bond with another two-atom component has been utilized for the synthesis of 1,2-stannaselenete (**16**) and 2,4-dibora-1,3-diselenetane (**46**) as shown in Scheme 9. In the synthesis of (**16**), trisena compound (**67**) is heated at 120 °C in a sealed tube to give the diarylstannaselenide, which then reacts with dimethyl acetylenedicarboxylate <93CC407>. The boraselenide (**64**) of Scheme 9, which is prepared by thermal loss of *t*-butyl isoselenocyanate from (**42**), dimerizes to give the 2,4-dibora-1,3-diselenetane (**46**) <85CB3748>.



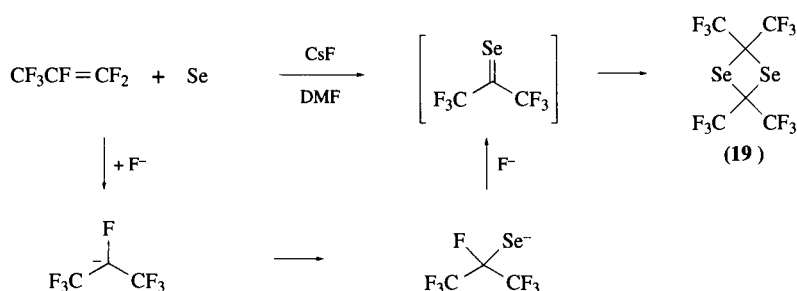
Scheme 9

The dimerization of selenocarbonyl compounds has been the exclusive route to 1,3-diselenetane compounds since the publication of CHEC-I. This two-component [2 + 2] approach can be subdivided into methods of preparation of the selenocarbonyl species. In Scheme 10, two approaches to selenocarbonyls are illustrated, which utilize triphenylphosphine. In the preparation of (**21**), the phosphonium ylide reacts with two equivalents of selenium to give the selenocarbonyl species and triphenylphosphine selenide <90AG(E)1067>. The dimerization of the selenoketone then gives (**21**). In the second approach, the transfer of selenium from triphenylphosphine selenide to hexafluoroacetone with formation of triphenylphosphine oxide gives bis(trifluoromethyl)selenocarbonyl, which dimerizes to give (**19**) <80JOC3517, 91CB423, 91ZN(B)157>.

Bis(trifluoromethyl)selenocarbonyl has also been prepared from perfluoropropene as shown in Scheme 11 <91JFC(53)71>. The addition of fluoride to perfluoropropene in DMF generates the 2-perfluoropropyl anion, which can then react with selenium metal to form the selenide anion. Although the perfluoroisopropylselenide anion is stable in the presence of mercury(II) (Equation (2)), the caesium salt undergoes intramolecular elimination of fluoride generating the selenocarbonyl, which dimerizes to give (**19**). This reaction is catalytic in caesium fluoride.

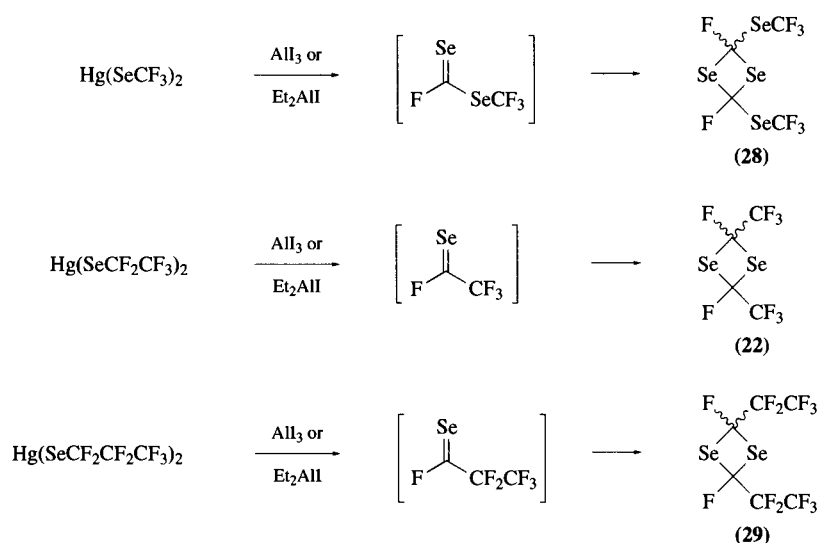


Scheme 10



Scheme 11

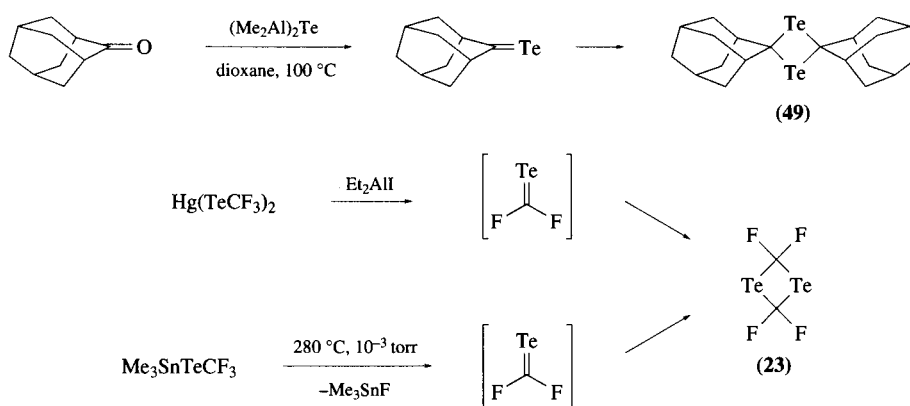
Mercury–selenide complexes have also been utilized as precursors to selenocarbonyl compounds as shown in Scheme 12 (88C265, 91CB51). In the presence of aluminum triiodide or diethylaluminum iodide, the mercury(II) complexes of Scheme 12 lose fluoride from the carbon α to the selenium to generate the corresponding selenocarbonyl compound, which then dimerizes to give the 1,3-diselenetanes (22), (28), and (29). The mechanism of this process appears to be somewhat complex from the formation of (28). In the case of the mercury–trifluoromethylselenide complex, difluoro-selenocarbonyl derived tetrafluoro-1,3-diselenetane (18) is not observed. Instead, 1,3-diselenetane (28) is derived from fluoro(trifluoroseleno)selenocarbonyl, which is a dimeric product of two difluoroselenocarbonyl units.



Scheme 12

1,3-Ditellurethane derivatives have only been prepared by [2 + 2] dimerizations of tellurocarbonyl compounds as shown in Scheme 13. The telluroketone of adamantane was prepared by the reaction of bis(dimethylaluminum)telluride with adamantaneone <89JA8749>. The resulting tellurocarbonyl compound dimerized to give the 1,3-ditellurethane (**49**).

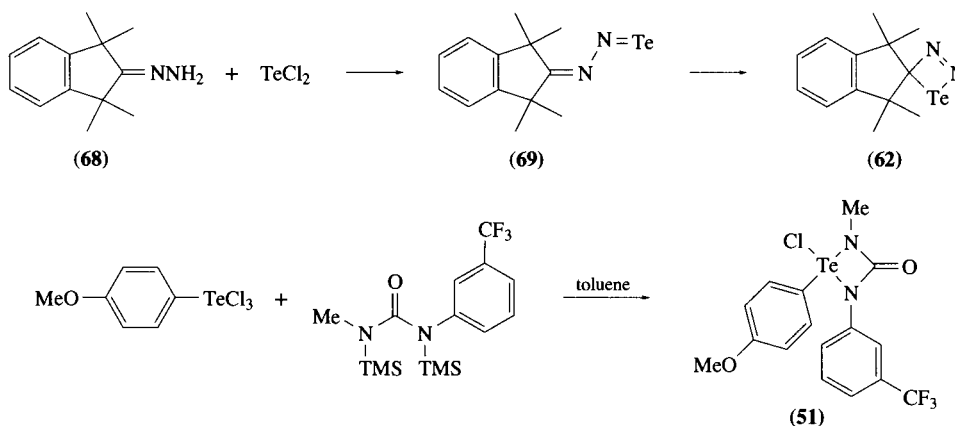
Difluorotellurocarbonyl has been prepared from mercury bis(trifluoromethyl)telluride and diethylaluminum iodide <91CC1378> and from trimethylstannyltrifluoromethyltelluride <92C78>. Tetrafluoro-1,3-ditellurethane (**23**) was isolated from the dimerization of the tellurocarbonyl. The chemistry of the mercury complex differs from that observed with mercury bis(trifluoromethyl)selenide as shown in Scheme 12. When the tellurocarbonyl is generated in the presence of an excess of difluoroselenocarbonyl, tetrafluoro-1,3-selenatellurethane (**45**) is isolated.



Scheme 13

1.36.6.3 [3 + 1] Two-component Synthesis

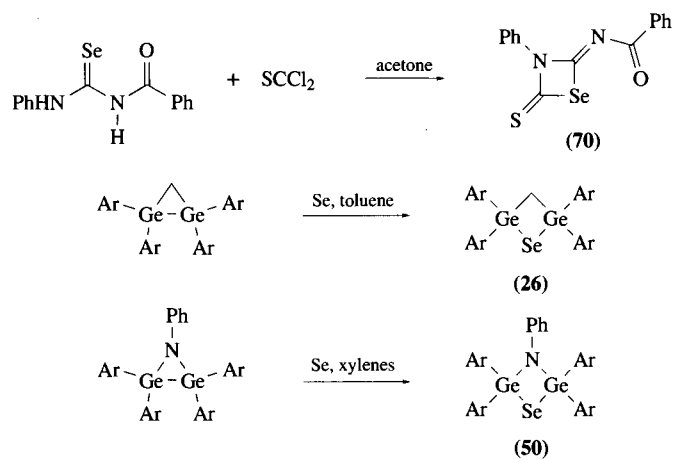
Two different [3 + 1] two-component syntheses of diazotellurethane derivatives have been reported in which a reactive tellurium species combines with a three-atom substrate containing two nitrogen atoms. These routes are illustrated in Scheme 14. The reaction of tellurium dichloride with hydrazone (**68**) leads presumably to diazatelluride (**69**), which then cyclizes to diazotellurethane (**62**) <93CL1047>. The addition of *p*-anisyltellurium trichloride to the bis(trimethylsilyl)urea of Scheme 14 gives diazatellurethane (**51**) via the loss of two equivalents of chlorotrimethylsilane <91JOM(418)339>.



Scheme 14

Several selenetane derivatives have been prepared by [3 + 1] two-component syntheses as shown in Scheme 15. The addition of thiophosgene to a selenourea gives azaselenetane (**70**) via reaction at nitrogen and selenium atoms <93JPR381>. Selenium adds oxidatively across the germanium-

germanium bonds of digermanacyclopropanes and (digermana)aziranes to give (26) and (50), respectively (88OM1882, 90OM2061).



Scheme 15

1.37

Four-membered Rings with Two Heteroatoms including Phosphorus to Bismuth

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University of Erlangen-Nürnberg, Germany

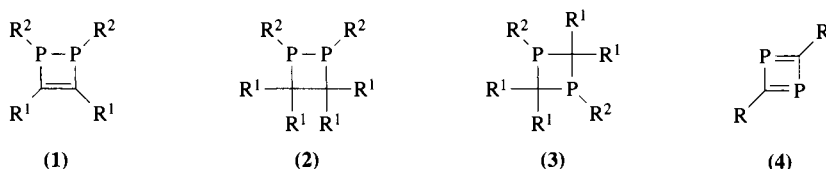
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1.37.1 INTRODUCTION

1.37.1.1 Historical Perspective

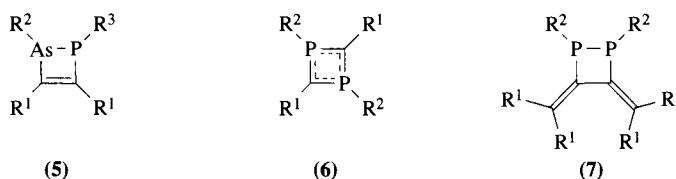
The first example of a four-membered heterocycle with two group 15 heteroatoms excluding nitrogen was reported in 1964 by Mahler <64JA2306>, who prepared a 1,2-diphosphetene derivative (1). The saturated 1,2- and 1,3-diphosphetane (Structures (2) and (3)) rings followed in 1976 when Becker started developing the chemistry of phosphalkenes, as the head-to-head and head-to-tail cyclodimerization gave access to both rings <76ZAAC(432)242>. A transition metal-mediated [2 + 2]-cyclodimerization of phosphalkynes leads to the formation of the fully unsaturated diphosphetes (4), which are stable only as η^4 -ligands. Free diphosphetes are highly reactive, but may be used as interesting intermediates for the synthesis of organophosphorus cage compounds.



Corresponding phospharsa and diarsa four-membered rings have been synthesized and still play a marginal role. The heavier analogues are still to be made. Only theoretical calculations on these species exist.

1.37.1.2 Structural Types and Nomenclature

No trivial names exist in this field of chemistry. The combination of elements this chapter deals with allows 1,2- and 1,3-heterocycles and the rings may include no, one or two double bonds. The hetero elements within the rings may be three, four, or five-valent (λ^X) and two to five coordinated (σ^X). Following the IUPAC recommended Hantzsch–Widman system, the fully unsaturated rings are characterized by the suffix -ete and the completely saturated ones by -etane. Thus the phosphorus-rings are named diphosphetes and diphosphetanes, respectively. The names of partly unsaturated rings may be derived from the fully unsaturated ones by formal hydrogenation at the appropriate positions, which is indicated by the prefix hydro. Alternatively, use can be made of the name of the saturated species as the basis and indicating the unsaturated bond by the prefix dehydro, but this is rarely used. A convenient third option for rings with one double bond uses the suffix -etene. Thus, for example, ring (5) may be called a 1,2-dihydro-1-arsa-2-phosphete or 1-arsa-2-phosphet-3-ene. This latter approach is in line with the so-called replacement names, which use corresponding hydrocarbons as their basis. Thus heterocycle (6) may be named 1,3-dihydro-1,3-diphosphete, 1,3-diphosphacyclobutane-2,4-diyl or 2,4-dehydro-1,3-diphosphetane. If an unsaturated part of the heterocycle forms exocyclic double bonds, this is indicated by the connected carbenoid group and the corresponding suffix of the saturated ring. As a consequence, 1,2-diphosphet-3-enes have the same valence electron count within the ring as 3,4-dimethylene-1,2-diphosphetanes (7).



1.37.1.3 Reviews

Fluck and Neumüller reviewed the phosphorus-heterocycles covering the literature up to 1988 <B-89MI 137-01>. Synthesis, NMR spectroscopic results, and structural data are mainly presented. Synthesis and properties of diphosphetanes are summarized by Afarinkia <92H(34)369> and those of 1,2-diphosphetenes by Mathey *et al.* <92MI 137-01>. The extraordinary synthetic potential of phosphalkynes as precursors of unsaturated phosphorus heterocycles and of polycyclic compounds is described by Regitz <B-93MI 137-07>.

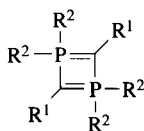
1.37.1.4 Theoretical Methods

Theoretical calculations utilizing *ab initio* and semi-empirical methods have been applied to all principal ring structures. According to MCSCF (multi configuration self-consistent field) *ab initio* molecular orbital calculations <93AG(E)617> the highly reactive λ^3, λ^3 -1,2- and 1,3-diphosphetes have a singlet ground state with a triplet state close by. Their principal structures are a trapezoid (1,2) and a parallelogram (1,3). 1,2-Diphosphete is 44 kJ mol⁻¹ more stable than its 1,3-isomer, which in turn is less stable than the corresponding diphosphatetrahedrane. In contrast to the free rings, π -complexed 1,3-diphosphetes have been prepared and the PES (photoelectron spectroscopy) spectra of an irontricarbonyl and a cyclopentadienyl cobalt complex were correlated to INDO SCF calculations <92OM177>. Both metals interact strongly with this planar π -ligand, which shows no sign of localization of π -electrons, thus drastic reaction conditions are required for decomplexation <96UP 137-01>. *Ab initio* calculations on the 1,3-diphosphete dianion C₂H₂P₂²⁻ reveal a D_{2h} symmetry, close to that found for the π -complexed 1,3-diphosphete ligand of cobalt <93JPC6384>. The HOMO–LUMO separation has been estimated on the basis of graph theory for completely unsaturated PAs, PSb, AsAs, AsBi, and SbSb 1,3-rings <90IJC(A)370>. Ring opening of 1,2- and 1,3-diphosphetenes have been studied by *ab initio* methods <92JOC2040>. Ring strain energies of possible isomers of 1,3-diphosphetanes were compared with that of a tetraphosphacubane derivative which is composed of 1,3-diphosphetane units. Both are less strained than the corresponding carbon hydrides. The ring strain energy of tetraphosphacubane is 264 kJ mol⁻¹ <93TL6365>.

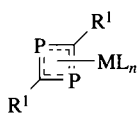
1.37.2 EXPERIMENTAL STRUCTURAL METHODS

1.37.2.1 X-ray and Electron Diffraction Studies

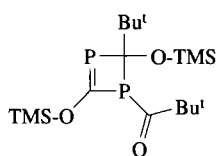
1 $\lambda^5, 3\lambda^5$ -Diphosphetes (**8**) are practically planar with intra-ring P—C bond distances in the range 172–177 pm and P—C—P as well as C—P—C bond angles between 88° and 92° <B-89MI 137-01>. Structural information of 1 $\lambda^3, 3\lambda^3$ -diphosphetes is accessible only for π -coordinated species (**9**). Published data are available for complexes with the transition metals Co, Ir, Fe, Mo, Ni, and Rh. The first examples were with cobalt <86AG(E)644, 86CC737, 88CB637>. Part of this field was reviewed by Nixon <88CRV1327>. The coordinated rings are always close to a planar square. Depending on the metals, the P—C bond length ranges from 174–186 pm; most of them are close to 180 pm. The structural data of the trapezoid 1,2-diphosphet-3-enes, including λ^3, λ^3 , λ^3, λ^5 , and σ -complexed λ^3, λ^3 -species are summarized by Mathey *et al.* <92MI 137-01>. Most λ^3 —P—C_{ring} bond distances are 184 ± 1 pm. An example for 1,3-diphosphet-2-enes is given by (**10**) <83CB938>. The ring is slightly puckered (dihedral angle 7.5°) and the P=C double bond is significantly shortened in respect to the P—C single bonds (168 pm versus 179, 189, and 191 pm). 1 $\lambda^3, 3\lambda^5$ -Diphosphetenes (**11**), also have a localized P=C double bond <86CB535>.



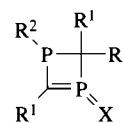
(8)



(9)

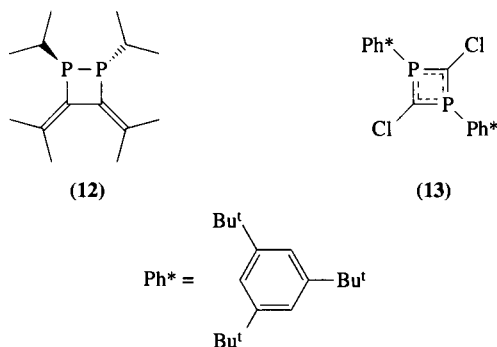


(10)

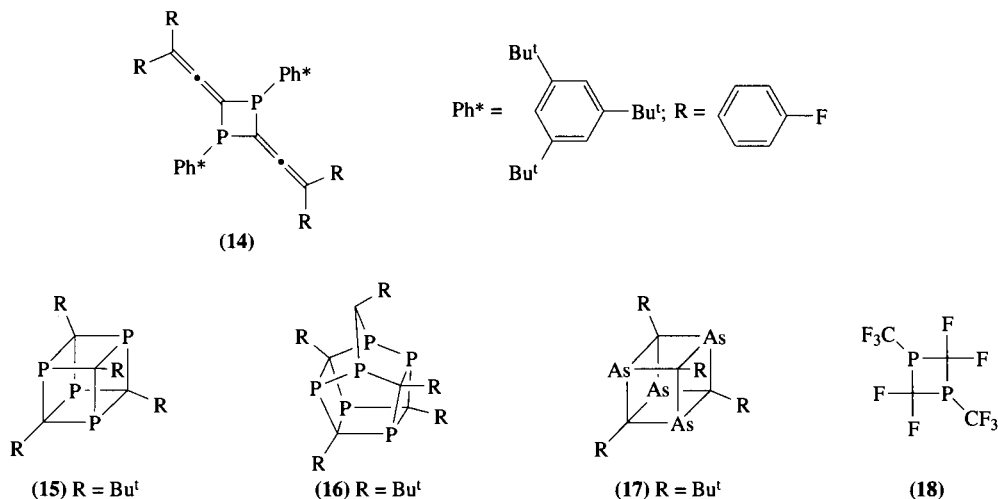


(11)

3,4-Diisopropylidene-1,2-diphosphetane (**12**) is puckered with a dihedral angle of 15.3° and the P—C single bonds within the ring are 184 pm long $\langle 93\text{CB}845 \rangle$. In contrast, 1,3-dihydro-1,3-diphosphete (**13**) is planar with P—C_{ring} distances of 175 pm $\langle 95\text{AG(E)}555 \rangle$. In principle, (**13**) has the same π -electron count in the ring as the diphosphetenes and (**12**); however, the shortened P—C bond distance and *ab initio* molecular orbital calculations clearly indicate a strong interaction of the two carbon π -electrons and the phosphorus lone pairs, (**13**) is thus better described as a delocalized π^6 -electron system.

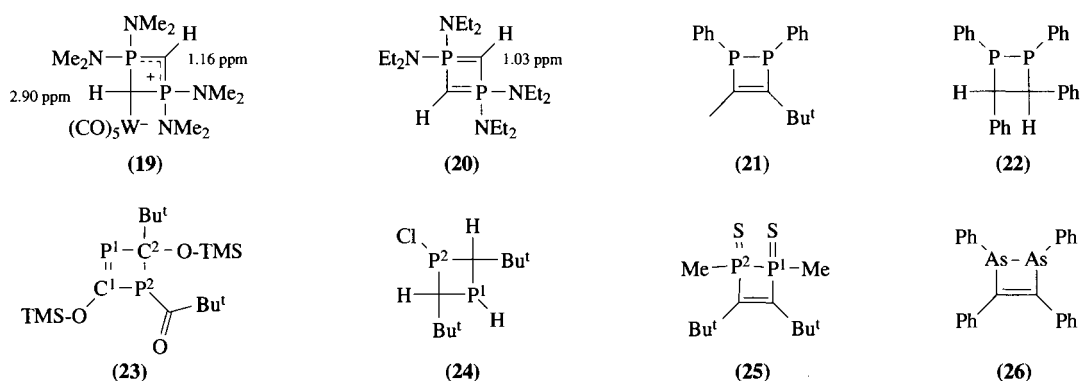


2,4-Diallylenyl-1,3-diphosphetane (**14**), a representative of the 2,4-dimethylene-1,3-diphosphetanes, is a nearly planar (bent by 3.1°) parallelogram with P—C single-bond distances in the normal range (181–186 pm) $\langle 90\text{TL}4429 \rangle$. 1,2-Diphosphetanes, as well as 1,3-diphosphetanes, are folded molecules with regular to slightly elongated P—C bonding distances (187–195 pm) $\langle 79\text{AG(E)}872, 82\text{ZAA}(485)23, 90\text{CB}733 \rangle$. However, if the 1,3-diphosphetane unit is part of a polycyclic system, as for example in tetraphosphacubane (**15**), $\langle 89\text{AG(E)}1013 \rangle$ or in hexaphosphahomopentaprismane (**16**) $\langle 89\text{AG(E)}900 \rangle$, the rings might be close to planarity with P—C distances from 186–191 pm. Structural parameters of diarsa or arsaphospha four rings are available in much smaller amounts. The structures of a complete series of tetraphenyl-substituted 1,2-diphosphet-3-ene $\langle 81\text{JOC}3 \rangle$, 1,2-diarset-3-ene $\langle 83\text{OM}298 \rangle$, and 1-arsa-2-phosphet-3-ene $\langle 93\text{BSF}521 \rangle$ were investigated. There are no principal differences in the ring structures. The As—As bond of the diarsete with its length of 247 pm is regarded as relatively long and the arsaphosphetene mediates between the two symmetrical species. In line with this finding, tetraarsacubane (**17**) is closely related with (**15**) (bonding angles, deviation from a regular cube; As—C = 201 pm on average) $\langle 93\text{AG(E)}103 \rangle$. A gas-phase electron-diffraction study on the perfluorinated 1,3-diphosphetane derivative (**18**) confirms the x-ray results on this class of compounds. The ring is significantly puckered (dihedral angle 35.4°) and the C—P—C angle within the ring is very small (77.6°) $\langle 86\text{IC}3177 \rangle$.



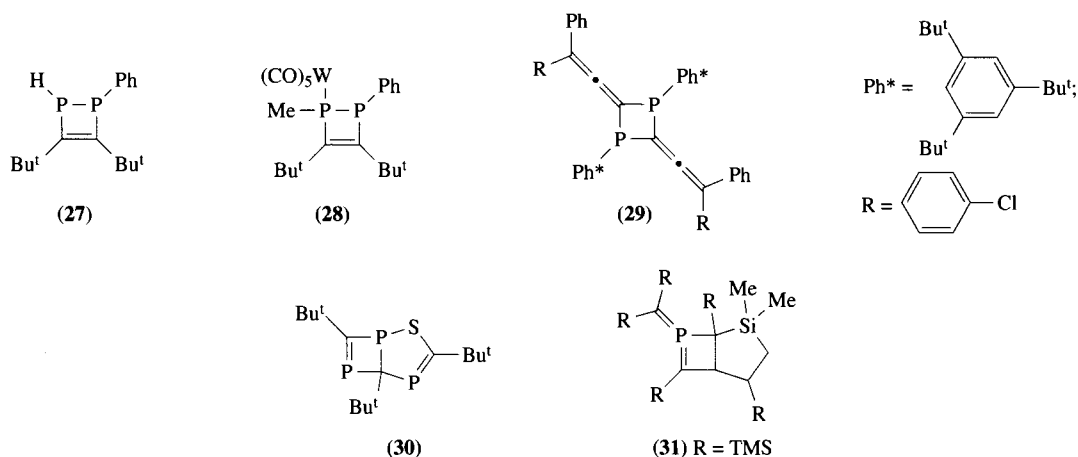
1.37.2.2 NMR Studies

Proton, ^{13}C , and ^{31}P NMR Spectroscopy play a very important role for the characterization of the compounds. A survey on the ^{31}P NMR spectroscopy of low coordinated phosphorus compounds with P-element multiple bonds was given by Karaghiosoff <B-90MI 137-01>. Proton NMR data are of special interest only if ring protons are present; however, only few of the many known compounds fulfill this condition. Therefore, no clear trends for the proton chemical shifts or coupling constants can be deduced from the data for different bonding situations within the rings. Saturated C—H units in phosphetanes which are not influenced by polar groups or transition metals close by, absorb in the range 1–2.2 ppm <84TL1963, 91AG(E)207>. Unfortunately, the C—H protons of the unsaturated compounds (19) <92ZAAC(612)56> and (20) <89ZAAC(576)81> are found in the same region (Structures (19)–(26)). Carbon-13 NMR Spectroscopy is plagued by the same problem. The chemical shift ranges of sp^2 - and sp^3 -carbons partly overlap. This is mainly due to charges and substituents, the group 15 element plays a lesser role (As vs. P). Carbon-13 and ^{31}P NMR Data for $1\lambda^5, 3\lambda^5$ -diphosphetes of the type (8; $\text{R}^1 = \text{H}, \text{Me}, \text{Ph}$; $\text{R}^2 = \text{NMe}_2, \text{NEt}_2$) have been summarized <89ZAAC(576)81>. Some selected NMR data is presented in Table 1.

Table 1 Selected ^{13}C and ^{31}P NMR data.

Compound	(^{31}P)	J_{PP} (Hz)	(^{13}C)	J_{PC} (Hz)	Ref.
(21)	–35.9 (P1) –35.7 (P2)	64	159.1 144.0		86OM623
(22)	–21.3 –14.7		43.3 42.9	23.7 25.7	92HAC395
(23)	279.1 (P1) 104.1 (P2)	16.2	223.2 (C1) 79.9 (C2)	53.2 (J_{P1C}) 11.6 (J_{P2C}) 27.2 (J_{P1C}) 1.3 (J_{P2C})	83CB938
(24)	24.1 (P2) –133.6 (P1)	22.8	46.4	31.9 12.5	91AG(E)207
(25)	56.29 (P1) 54.26 (P2)	41.8	157.7 157.45		86OM623
(20)	43.4		19.8		89ZAAC(576)81
(26)			151.5		83OM298
(17)			–46.5		93AG(E)103
(15)	257.4	8.52	–29.1	13.43	89AG(E)1013

Even for ^{31}P NMR, an overlap of chemical shift and coupling constant ranges is observed. Not surprisingly $^2J_{\text{PP}}$ values in 1,3-ring systems are found to be smaller (5.5–35 Hz) than the $^1J_{\text{PP}}$ values for 1,2-rings (60–130 Hz) in most cases. But some rings definitely violate this rule. Extraordinarily small P–P coupling is found for the 1,2-diphosphetenes (27) ($^1J_{\text{PP}} = 29.3$ Hz) <86OM623> and (28) ($^1J_{\text{PP}} = 36.5$ Hz) <92BSF76>. Due to the metal coordination of one of the phosphorus atoms in (28), a reduction of the coupling constant from the 61.0 Hz found for the free ring is not difficult to understand, but similar arguments are not available for (27). Remarkably large $^2J_{\text{PP}}$ values are found for (29) (45.7 Hz) <90TL4429>, (30) (54.0 Hz) <93AG(E)1424>, and (31) (89.0 Hz) <86CB535>.



1.37.2.3 Mass Spectroscopy

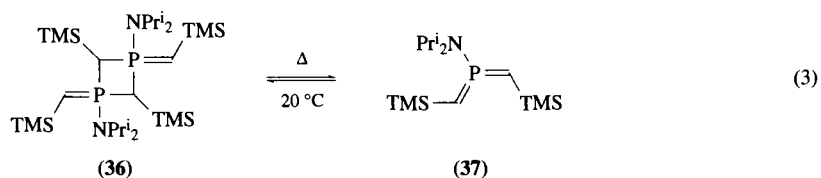
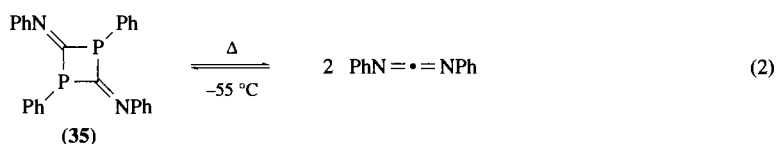
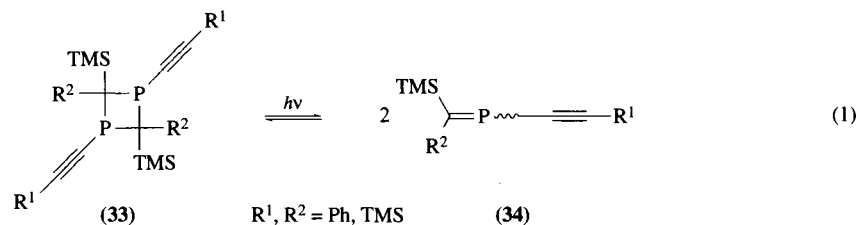
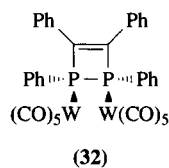
Mass spectroscopy is used in most cases to characterize ring systems, molecular peaks are regularly observed for neutral species. Under the conditions of the mass spectroscopic experiment, diphosphetanes may undergo a [2 + 2]-cycloreversion reaction, yielding phosphalkenes, but this is not the favored route of degradation in general <85PS(21)349, 85PS(25)345>.

1.37.2.4 Infrared, Raman, Electron Spin Resonance, and Photoelectron Spectroscopy

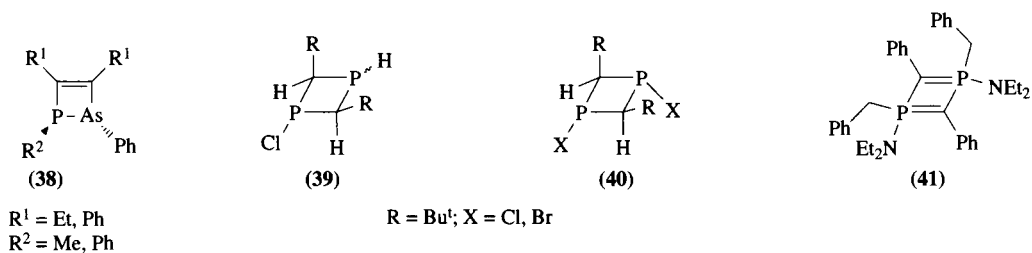
Infrared spectroscopy is used predominantly to generate fingerprint spectra. Decisive information is obtained, however, if stretching modes of polar groups connected to the rings are observable, for example, C=N or C=O. Helium(I) photoelectron spectra have been interpreted with the help of semiempirical or *ab initio* molecular orbital calculations. The two highest occupied molecular orbitals of 1,3,3,3-tetrakisubstituted-1,3-diphosphetanes of the type (8; R = H, Ph; R' = NEt₂) are π -ring orbitals <88CB2071>. Metal-complexed 1,3,3,3-tetrakisubstituted-1,3-diphosphetanes interact significantly more with cobalt(I) and iron(0) than their carbacyclic analogue cyclobutadiene <92OM177>. According to its high symmetry, tetraphosphacubane (15) exhibits a triply degenerated delocalized state as HOMO. The first ionization takes place predominantly in the vicinity of the phosphorus atoms <90CB757>. Electron spin resonance data are only available from the redox products of (η^6 -toluene)(η^4 -di-*t*-butyl-1,3-diphosphete)iron <87JOM(334)C35>. Evidence is found for a LUMO which consists of a combination of iron d-functions and π -orbitals of the diphosphete ligand, whereas the HOMO is located at the iron atom only.

1.37.3 THERMODYNAMIC ASPECTS

Melting points and chromatographic properties are dominated by substitution effects, as the heterocyclic rings themselves are often smaller than the rest of the molecules. The same is true for distillation properties. All types of rings have been crystallized successfully and recrystallization is the most popular route to purify the compounds. Column chromatography on silica gel is an alternative which helps in other cases. A number of polycyclic polyphosphorus hydrocarbons including (16) and some metal-containing species were purified upon medium-pressure liquid chromatography on water-deactivated (5%) silica <89AG(E)900>. Tetraphosphacubane (15) was distilled under reduced pressure (10⁻¹ mbar, 155°C) <89AG(E)1013>. The existence of an equilibrium between 1,2-diphosphetene and its 1,4-diphosphabutadiene open-chain isomer was proved only for the bistrungsten complex (32) <90POL1363>. The free ring shows no such activity <92JOC2040>. Evidence for a dimerization equilibrium between phosphalkene and a 1,3-diphosphetane was found for the ethynyl compounds (Equation (1)). The dimerization of (34) is a slow reaction at room temperature; daylight regenerates the monomer <84CB2693>. Flash vacuum pyrolysis of the iminodiphosphetane (35) (Equation (2)) gave access to the open-chain monomer <83JA7194>. In contrast to this, even slight heating of 1,2,3,4-tetrakisubstituted-1,2-diphosphetane (36) yields the bis(methylene)phosphorane (37) (Equation (3)) <92CB771>.



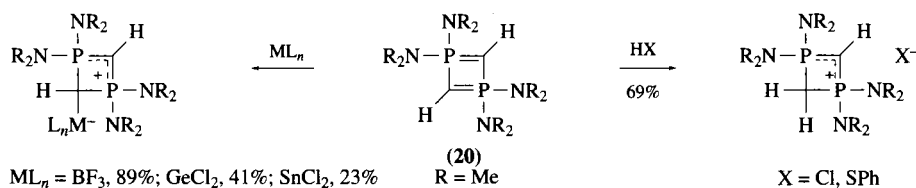
Stereoisomerism in respect to the heteroelements is reported frequently. Two σ^3, λ^3 -group 15 element atoms in a four ring principally leads to *cis* and *trans* isomers. 1,2-Diphosphetenes $\langle 91\text{AG(E)207} \rangle$ or the 1-arsa-2-phosphet-3-enes (38) $\langle 93\text{BSF521} \rangle$ strongly favor the *trans*-configuration. 1,3-Rings do not discriminate as clearly between the two possibilities, thus (39) forms a *cis/trans* mixture (1 : 2) whereas (40) consists of the *cis* isomer only $\langle 91\text{AG(E)207} \rangle$. The same situation is created in λ^5, λ^5 -rings if different substituents are attached to the heteroelement. Surprisingly, the *cis* isomer is found only for (41) $\langle 92\text{ZAAC(609)99} \rangle$.



1.37.4 REACTIVITY OF FULLY CONJUGATED RINGS

1.37.4.1 Reactivity of $1\lambda^5, 3\lambda^5$ -Diphosphetes

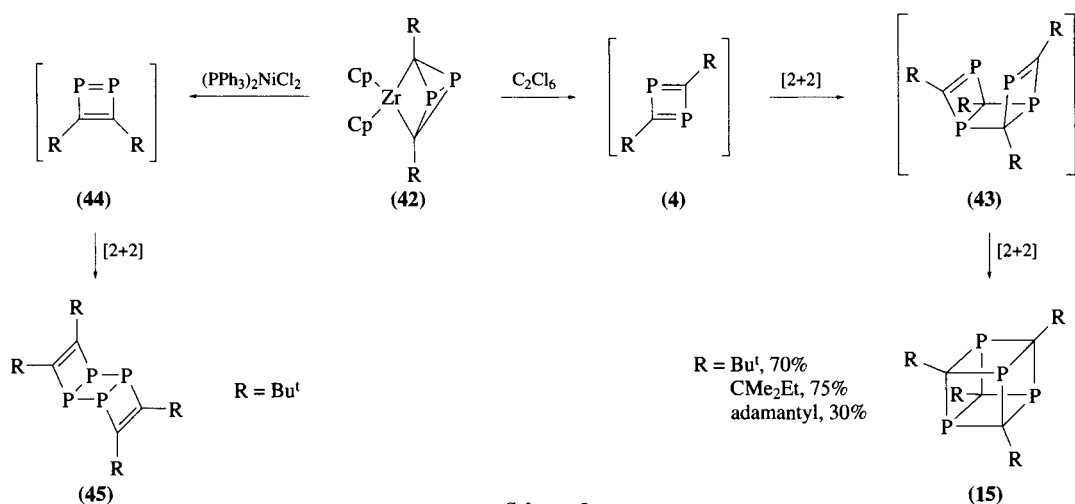
The reactivity of $1\lambda^5, 3\lambda^5$ -diphosphetes (20) (Scheme 1) has been reviewed $\langle 94\text{RHA65} \rangle$. Electrophiles like proton active compounds, BF_3 , GeCl_2 , SnCl_2 , W(CO)_5 , and Fe(CO)_4 add to one of the ring carbon atoms of the diphosphetes and salts are formed $\langle 86\text{PS(29)23, 92ZAAC(612)56, 93ZAAC(619)1551} \rangle$.



Scheme 1

1.37.4.2 Cyclic Addition Reactions of λ^3, λ^3 -Diphosphetes

Oxidative decomplexation of the diphosphabicyclobutanediyl ligand of the zirconium complex (**42**) yields 1,3- or 1,2-diphosphetes as reactive intermediates, depending on the agents used. The 1,3-isomer effectively forms tetraphosphacubanes (**15**) upon double [2 + 2]-cyclic addition via tricyclic (**43**) (Scheme 2) (<92AG(E)758>. 1,2-Diphosphete (**44**) shows one [2 + 2]-cyclic addition step only and a tricyclic (**45**) is formed as the stable product (<95AG(E)484>. Both, highly reactive (**43**), and stable (**45**) have a saturated central ring connecting two diphosphetenes. The second cyclic addition step, however, is impossible for (**45**), as the unsaturated rings occupy different sides of the central one. A corresponding structure to (**45**) for the dimer of 1,3-diphosphete (**4**) is strongly disfavored, because of sterical interactions of the bulky substituents. In contrast, (**44**) cannot form a dimer of type (**43**) as the main product, again because of strong repulsion of substituents.



Scheme 2

1.37.4.3 Addition Reactions of λ^3, λ^3 -Diphosphetes

If **(42)** is degraded in the presence of transition metal carbonyl complexes or halogenating agents, dimerization of **(4)** is prevented and complexes of the type **(9)** ($\text{ML}_n = \text{Fe}(\text{CO})_3$) and phosphorus-halogenated diphosphetenes or diphosphetanes **(39)** and **(40)** are formed (Scheme 2), $\langle 91\text{AG(E)207} \rangle$.

1.37.5 REACTIVITY OF NONCONJUGATED RINGS

Treatment of 3-alkynyl-1 λ^5 ,2 λ^5 -diphosphet-3-enes with iminophosphanes leads to a bicyclic ring expansion product $\langle 94CB313 \rangle$. The diphosphetene ring is transformed into a 1,2-diphosphacyclopent-3-ene which is condensed to a phosphetene.

Bis(tungstenpentacarbonyl) complexes of 1,2-diphosphetenes and 1-arsa-2-phosphetenes exhibit

a formal ring expansion reaction with electron-poor dienophiles. 1,4-Dielement cyclohexenes or cyclohexadienes are formed. This reaction was interpreted in terms of a [4 + 2]-cyclic addition reaction of the open-chain dielementbutadienes (see Section 1.37.3) <90POL1363, 93BSF521>.

1.37.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO THE RING CARBON ATOMS

To our knowledge, no systematic studies concerning this point have appeared in the literature.

1.37.7 REACTIVITY OF RING HETEROATOMS AND SUBSTITUENTS ATTACHED TO RING HETEROATOMS

1.37.7.1 Protonation and Reactions with Organic Electrophiles

Mono- or diprotonation of tetraphosphacubane with superacids and monoalkylation or alkylation with strong electrophiles leads to stable phosphonium salts of the cage compounds <93JOC4105>.

1.37.7.2 σ -Complexation of Transition Metals

λ^3 -heteroatoms as parts of rings may function as σ -donor ligands of transition metals in many examples. Such metal–ligand units may remain intact over several reaction steps, including open-chain educts and products <88IC2269, 88OM1791, 92BSF76>. If $\text{W}(\text{CO})_5\text{THF}$ is reacted with the mixed-element As—P species (38) the arsenic atom is the preferred ligand <93BSF521>. π -Coordinated diphosphetes still exhibit ligand properties through the lone pairs of the phosphorus atoms. One or two transition metals may be bonded this way <86AG(E)644, 91HAC253>.

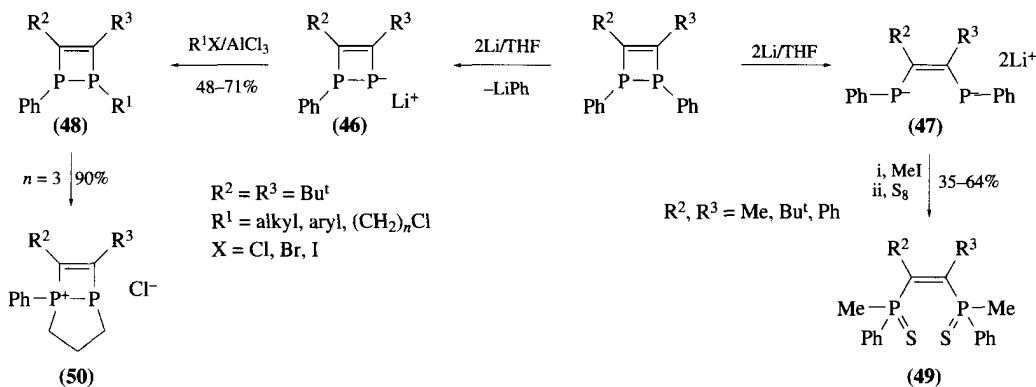
1.37.7.3 Oxidation of Ring Heteroatoms

The phosphorus atoms of tetraphosphacubane (15) may be oxidized stepwise without disruption of the cage. Oxidizing agents that can be used are; tetrachloroorthochinone, CH_3N_3 , diazoalkanes, Se_8 , and $[(\text{CH}_3)_3\text{Si}]_2\text{O}_2$, <92AG(E)879>. Phosphorus oxidation is possible for 1,2-diphosphetenes as well by using S_8 <86OM623>.

1.37.7.4 Reactions with Reducing Agents

Alkali metals and lithium alkyls are able to cleave the P—P bond of 1,2-diphosphetenes or one substituent of a phosphorus may be removed as well <84CC1707>. The resulting mono- and dianion lithium salts, (46) and (47) (Scheme 3), respectively, give access to many new 1,2-diphosphetenes (48) and open-chain *cis*-diphosphaethene derivatives (49). If the incoming group R^1 of (48) is an ω -chloroalkyl, self-quarternization leads to bicyclic (50) and related compounds <86OM623>. The reaction of dianion (47) with organodihalides leads to diphosphacyclopentene derivatives, Me_2SiCl_2 yields siladiphosphacyclopentenes <92OM459>, methylene dichloride diphosphacyclopentenes <92POL601> and C_2Cl_4 tetraphosphafulvalene <88AG(E)950>, respectively. The cleavage of the P—As

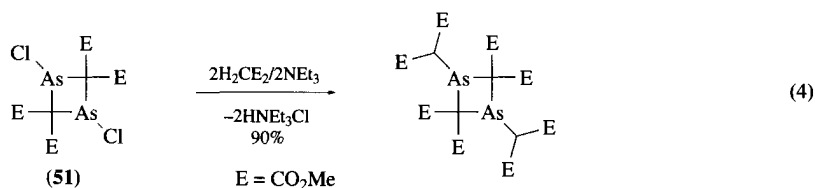
bond in 1-arsa-2-phosphetene (**38**) again yields an open-chain dianion which can be condensed with carbon disulfide and methyl iodide or with methylene dichloride to yield 1-arsa-3-phosphacyclopentene derivatives <93BSF521>.



Scheme 3

1.37.7.5 Other Reactions

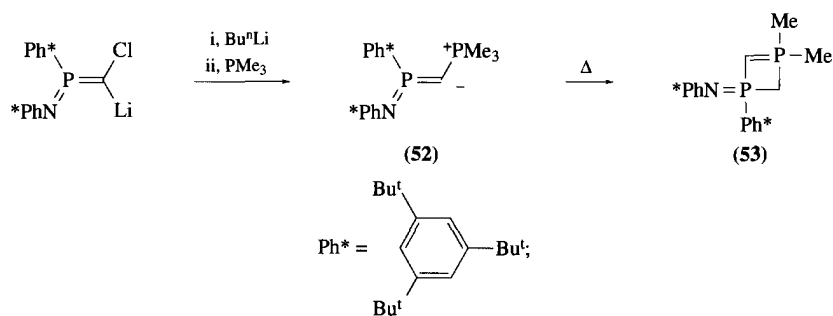
The chlorine atoms of 1,3-dichloro-1,3-diarsetane (**51**) may be replaced by an organic group upon reaction with methyl malonic ester in the presence of triethylamine (Equation (4)) <78JCR(M)3363, 78JCR(S)252>. Chlorine iodine exchange reaction on 3-chloro-1,3-diphosphet-1-ene was furnished with I-TMS <93BSF642>.



1.37.8 SYNTHESIS OF FOUR-MEMBERED HETEROCYCLES WITH TWO PHOSPHORUS ATOMS

1.37.8.1 From Acyclic Compounds by Formation of One Bond to a Phosphorus Atom

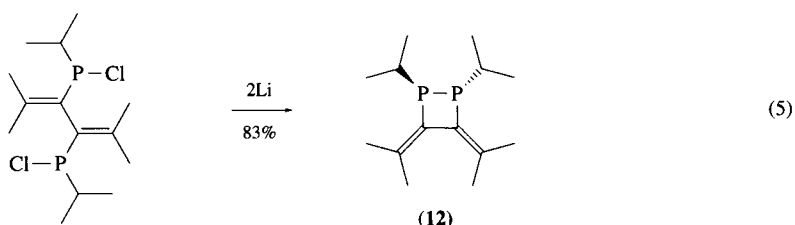
One of the rare examples falling into this category was found by Niecke *et al.* <94AG(E)982> when they prepared 1λ⁵,3λ⁵-diphosphet-2-ene (**53**) (Section 1.37.12.4). The final step starts with a 1,3-H-shift from a methyl group to the negatively charged carbon in (**52**) and the ring is closed. The authors prefer a polar formulation for (**53**) (Scheme 4).



Scheme 4

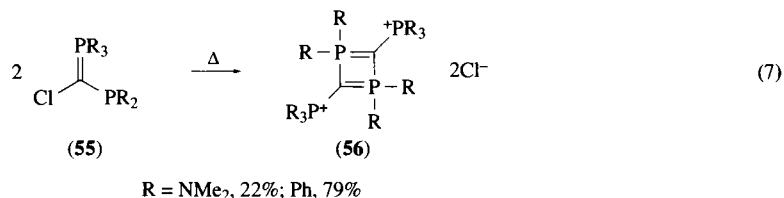
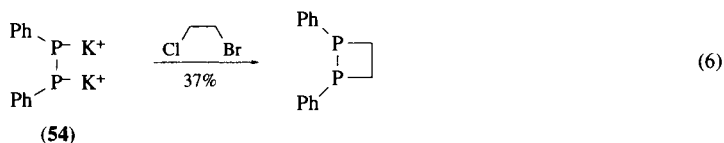
1.37.8.2 From Acyclic Compounds by Formation of One P—P Bond

A high-yield route to *trans*-3,4-diisopropyliden-1,2-diphosphetane (**12**) utilizes reductive coupling of a bis(chlorophosphane) (Equation (5)) <93CB845>.



1.37.8.3 Formation of Two C—P Bonds by Displacement Reactions

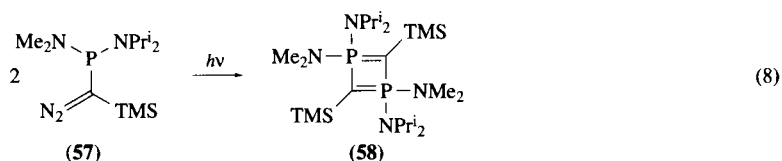
Dipotassium diphosphide (**54**) and 1-chloro-2-bromoethane form 1,2-diphosphetanes in a nucleophilic substitution reaction (Equation (6)) <84TL1963>. In a 1,3-cyclosubstitution reaction of phosphalkene (**55**), the lone pairs of the λ^3 -P-atoms attack the carbon atoms of the other molecule and chloride is eliminated (Equation (7)). The λ^5, λ^5 -diphosphete diphosphonium salt (**56**) is very stable and exhibits no ylide reactivity <77AG(E)402>. $(\text{NMe}_2)_3\text{P}=\text{CCl}_2$ is an alternative duct for salts of the type (**56**) ($\text{R}=\text{NMe}_2$) <83CB2275>.

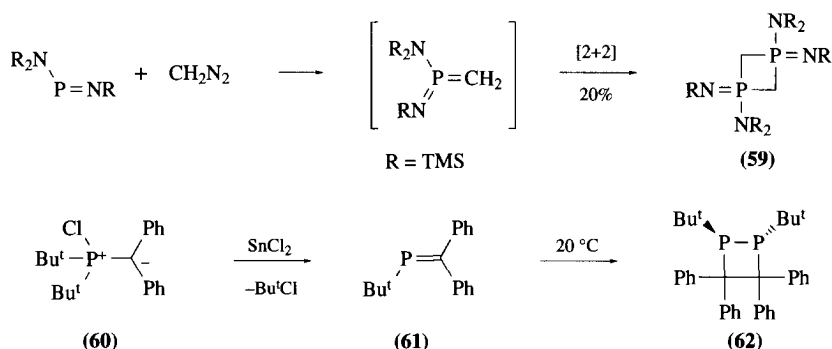


1.37.8.4 Ring Formation by Organic Cyclic Addition Reactions

Cyclic addition reactions of unsaturated phosphorus and arsenic organic compounds are the most prominent route to four-ring heterocycles containing two group 15 elements.

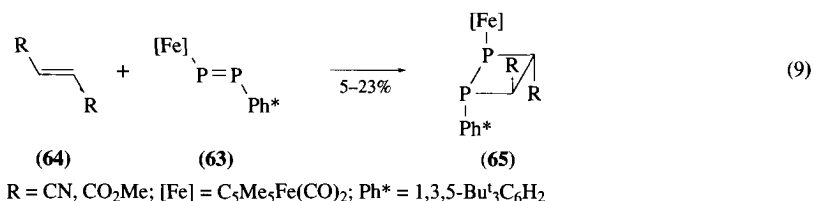
λ^5 -Phosphaalkyne is formed as a reactive intermediate by photolysis of diazo compound (**57**). It dimerizes spontaneously, yielding $1\lambda^5, 3\lambda^5$ -diphosphete (**58**) (Equation (8)) <90AG(E)1429>. $1\lambda^5, 3\lambda^5$ -Diphosphetanes (**36**) and (**59**) (*cis* and *trans* isomers) are formed by a head to tail [2 + 2]-cyclic addition reaction of the formal C=P double bonds of bis(methylene)- or iminomethylenephosphoranes (Scheme 5) (see Section 1.37.3) <80CB1549, 92CB771>.





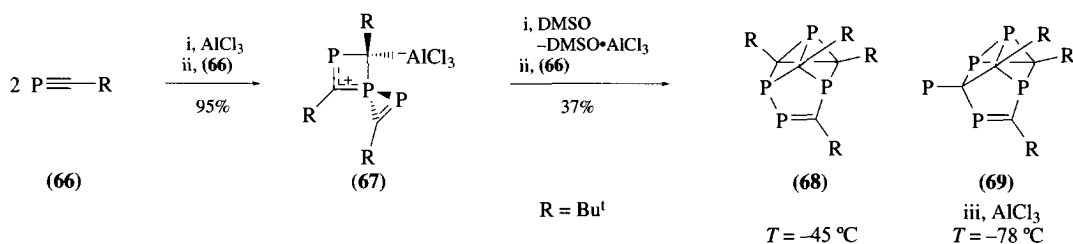
Scheme 5

The preparative potential of phosphalkenes was explored soon after the first access to this class of compound and an early review of Appel *et al.* outlines the most important facts (81AG(E)731). The preferred route of cyclodimerization is head-to-tail, which yields 1,3-diphosphetanes (80ZAAC(462)130, 84ZAAC(517)75, 85PS(25)345, 91CB2843). The same is true for the perfluorinated species $\text{CF}_3\text{P}=\text{CF}_2$ (20°C; 94% *trans*) (86IC3177, 92ZN(B)321). Phosphacumulenes $\text{RP}=\text{C}=\text{X}$ ($\text{X} = \text{CR}_2$, NR , O) are often shown to be reactive intermediates, exhibiting the same reactivity as phosphalkenes. They lead to 2,4-dimethylene-1,3-diphosphetane derivatives (compare Section 1.37.3 for $\text{X} = \text{NR}$) (80TL2497, 83TL2639, 86CB2466, 86ZAAC(534)31, 90TL4429). The alternative head-to-head cyclo dimerization leads to 1,2-diphosphetanes (84CB3151, 86CB2915). An interesting example was given by Grützmaier and Pritzkow. Reactive phosphalkene (61) is formed by catalytic alkane chloride abstraction of the phosphorus-chlorinated ylide (60). At room temperature it dimerizes, yielding the *trans*-1,2-diphosphetane (62) (92AG(E)99 (according to a personal communication, the diphosphetane is a 1,2-species, not a 1,3-one)). [2 + 2]-Cyclic addition of an alkene with a diphosphene results in the formation of 1,2-diphosphetanes exclusively. Metallated diphosphene (63) and electron-poor alkenes like (64) exhibit similar reactivity, leading to *trans*-1,2-diphosphetane (65) (Equation (9)) (90CB733).



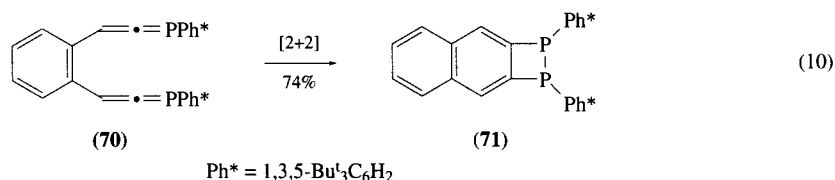
Tetraphosphacubane (15) is formed in small amounts by the thermal cyclooligomerization of neat phosphalkyne (66) (89AG(E)1013). Much higher yields of (15) are obtained by using 1,3-diphosphete as a reactive intermediate (Section 1.37.4.2).

The reaction of aluminum trichloride with three λ^3 -phosphalkyne molecules leads almost quantitatively to the spirocyclic inner salt (67). Bases like DMSO remove AlCl_3 from (67). Repetitive cyclic addition reactions of the intermediate and another phosphalkyne, give the tetraphosphatetracycles (68) or (69) (Scheme 6) (92AG(E)1055).



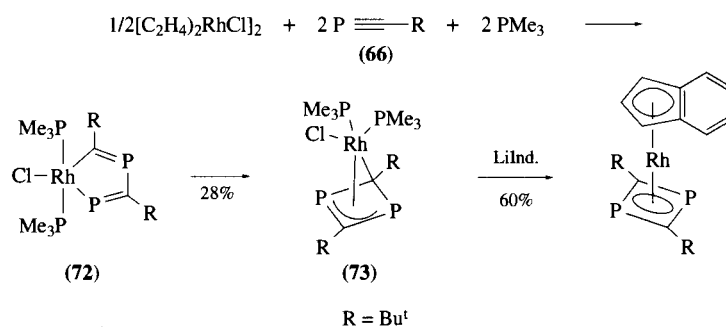
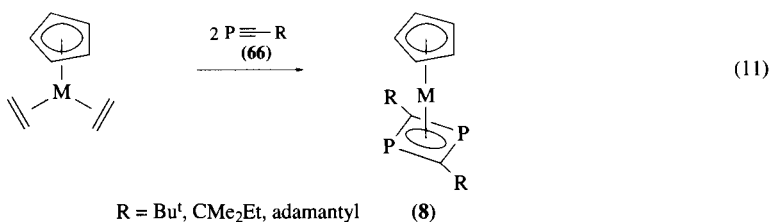
Scheme 6

A 1,2-diphosphetane as part of a hexacyclic diphospha hydrocarbon was made photochemically <83JA6871>. Bisphosphallene (70) is a spectroscopically observable intermediate, which undergoes an intramolecular [2 + 2]-cyclic addition reaction at room temperature forming 3-naphtho-1,2-diphosphetene (71) effectively (Equation (10)) <96UP 137-02>.

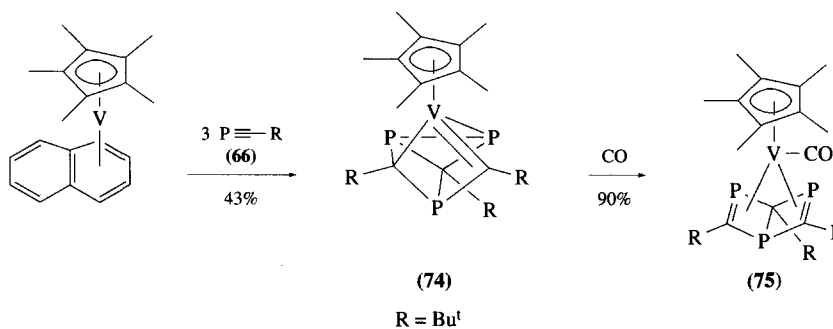
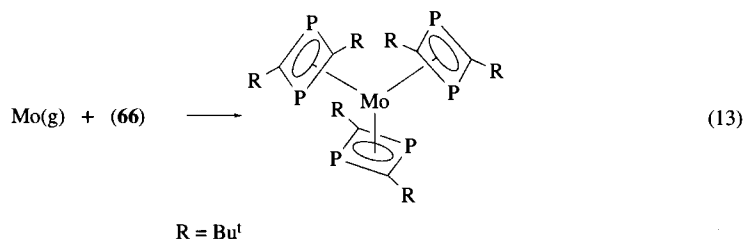
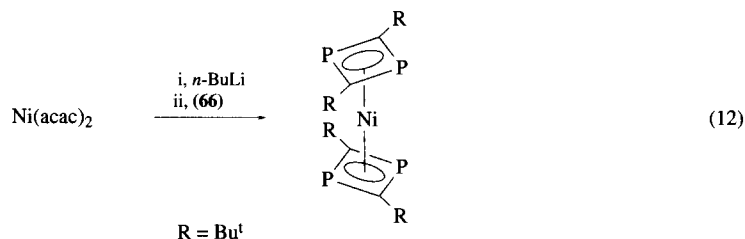


1.37.8.5 Ring Formation by Cyclic Addition Reactions in the Coordination Sphere of a Transition Metal

t-Butylphosphaalkyne (66) can be used very successfully for the synthesis of transition-metal coordinated 2,4-di-*t*-butyl-1,3-diphosphete in complexes of type (8) (Equation (11)). This field was opened by Binger *et al.* <86AG(E)644, 86CC737>. Some reviews reveal the most important facts <88AG(E)1484, 88CRV1327, B-90MI 137-02>. Examples of transition-metal complexes used for this purpose are CpM(C₂H₄)₂ (Cp = cyclopentadienyl derivatives including indenyl, dicarbollide; M = Co, Rh, Ir), Fe₂(CO)₉ and (η⁶-toluene)FeL₂ (L = C₂H₄, L₂ = η⁴-1-methylnaphthalene) <89CC1409, 95AG(E)198>. From the reaction of [(C₂H₄)₂RhCl]₂ with (66) some mechanistical insight in these cyclic addition reactions was acquired. The two intermediates (72) and (73) have been fully characterized <88AG(E)1157>. Homoleptic 2,4-di-*t*-butyl-1,3-diphosphete complexes are formed in the reaction of (acac)₂Ni with BuⁿLi and (66) (Equations (12) and (13)) <90CC1541>, and in the metal vapour reaction of molybdenum (g) with (66) (Scheme 7) <94CC489>. The only cyclotrimers of (66) characterized unambiguously are formed at a vanadium(I) center. The triphospha ligands of (74) and (75) are isomers of the yet unknown 1λ³,3λ³,5λ³-triphosphabenzene (Scheme 8) <87AG(E)908>. The cyclotrimer of (66) has not been decomplexed without decomposition yet. Decomplexation of the 1,3-diphosphete leads to 1,2-diphosphetene (Fe) and 1,3-diphosphetane (Co), respectively <96UP 137-01>. Structure (66) may add to complex cluster structures under formation of cyclic C₂P₂ substructures as well. A good example was given by Imhof and Huttner <93JOM(447)31>.



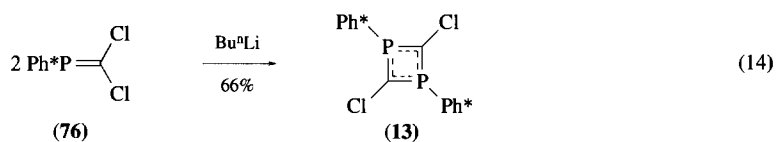
Scheme 7



Scheme 8

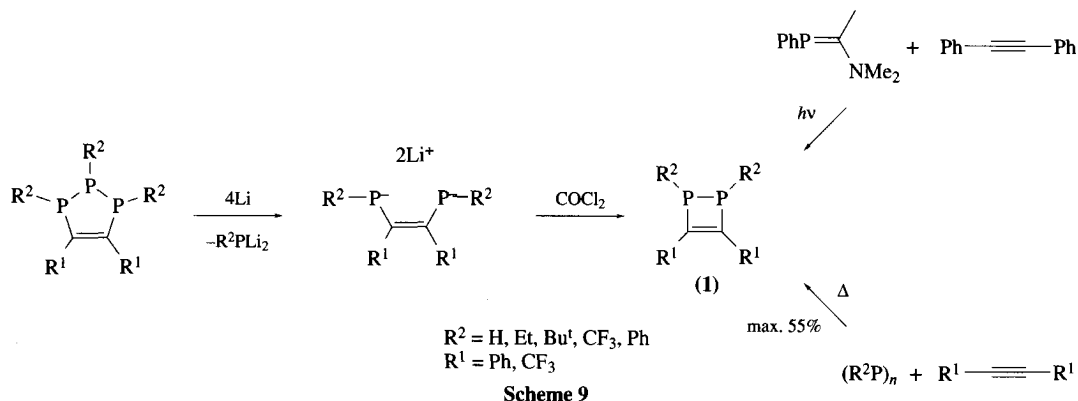
1.37.8.6 Various Routes

Dehalogenation of phosphorus-fluorinated λ^5 -phosphaalkenes is a useful route for the preparation of $1\lambda^5,3\lambda^5$ -diphosphetes <B-89MI 137-01, 90ZAAC(588)147>. 1,3-Dihydro-1,3-diphosphete (13) was found to be the final product of the chlorine abstraction of phosphaalkene (76) with Bu^nLi (Equation (14)) <95AG(E)555>. The first and simplest route (Scheme 9) to 1,2-diphosphetenes (1) utilizes cyclopolyphosphines and alkynes (max. 55% yield) <64JA2306, 86OM623>. The photocleavage of a phosphorus-phenylphosphaalkene in the presence of toluene <83TL1975> and the ring contraction of the readily available 1,2,3-triphospholenes <81JOC3>.

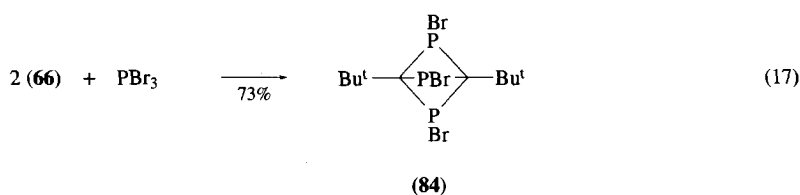
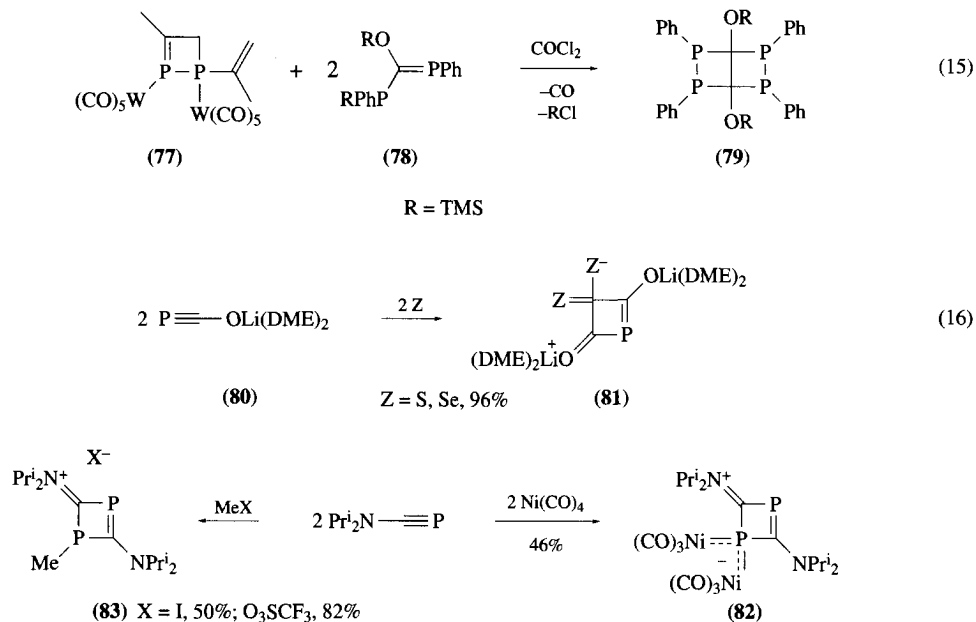


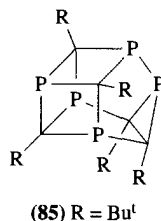
Alkylbis(trimethylsilyl)phosphanes and oxalylchloride yield 1,2-diphosphetenes as well <80TL1923>. The only access known to a 1,2-diphosphet-2-ene like (77) is based on a complex reaction sequence, starting with a phosphole derivative <91OM3958>.

Phosphaalkene (78) is desilylated by phosgene (Equation (15)). A proposed bisphosphaalkene intermediate undergoes intramolecular cyclic addition and bicyclic 1,2-diphosphetane (79) is formed as the stable product <79AG(E)872>. A head-to-head dimerization of a C-dichloro-phosphaalkene under reducing conditions leads to a 3,4-dichloro-1,2-diphosphetane <91MI 137-07>. Oxidation of phosphaalkyne (80) with gray selenium or sulfur leads to $1\lambda^3,3\lambda^5$ -heterocycle (81) (Equation (16)) <96UP 137-03>. Structure (81) is isolobal with the transition metal-stabilized species (82), which is accessible via an aminophosphaalkyne (Scheme 10) <92AG(E)95>. The same aminophosphaalkyne leads to salt (83) in good yields upon reacting with methyl iodide or triflate (Scheme 10) <94HAC337>.



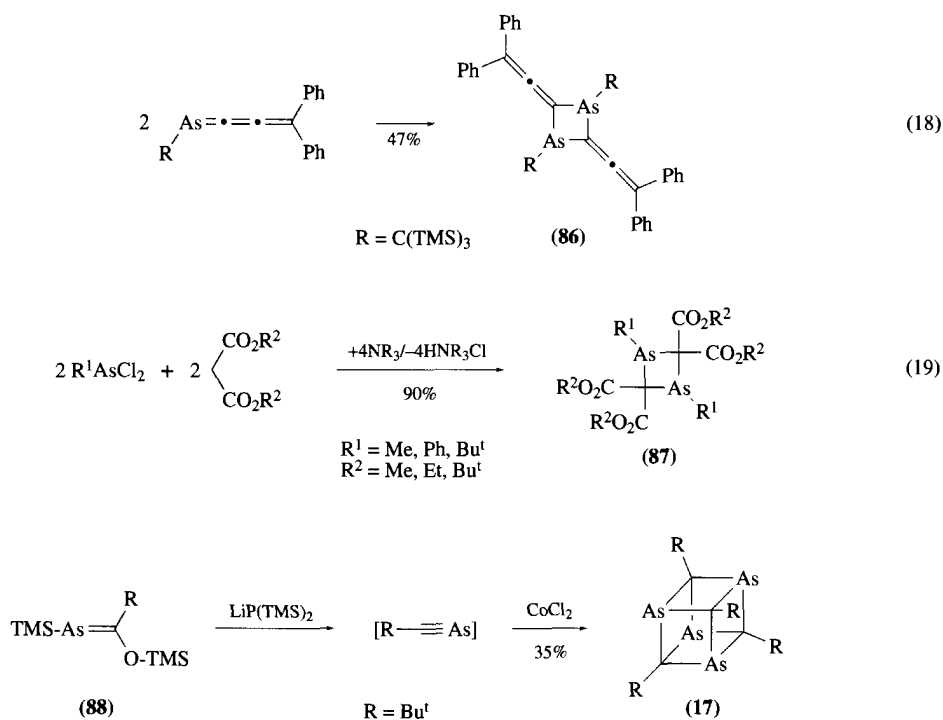
Structures **(82)** and **(83)** are planar rings; their π -electrons and charges are delocalized. Addition of PBr_3 to phosphalkyne **(66)** leads to bicyclic triphospha[1.1.1]pentane **(84)** in good yield (Equation (17)) <85MI 137-01>. An access to a 1,2-diphosphetane not utilizing a $[2 + 2]$ -cyclic addition reaction of phosphalkenes was found by Regitz and co-workers <94JOM(464)41>. 1,3-Diphosphetanes as part of polycyclic polyphosphorus hydrocarbons have been observed for the first time by reacting **(66)** with the Lewis acid TaCl_5 . An ionic product was isolated, $(\text{Me}_3\text{CCP})_6\text{P}^+\text{TaCl}_6^-$. Oxidation of a reactive intermediate of the reaction leads to a tricyclic product <85MI 137-01>. Several different metal-containing or metal-free cages can be made in small yields by reacting **(66)** with reactive arene iron(0) complexes. Examples are the pentamer **(85)** and the hexaphosphahomopentaprismene **(16)**. Better yields for **(85)** are obtained by two alternative routes; reduction of **(66)** at a potassium mirror and oxidation of the mixture by air <93PS(77)5> or oxidation of mixtures of di and triphospholyl anions <89JOM(375)C31>. Based on **(66)** the K/air route gives the better yields; however, they differ from run to run.





1.37.9 SYNTHESIS OF FOUR-MEMBERED HETEROCYCLES WITH TWO AS (SB, BI) ATOMS

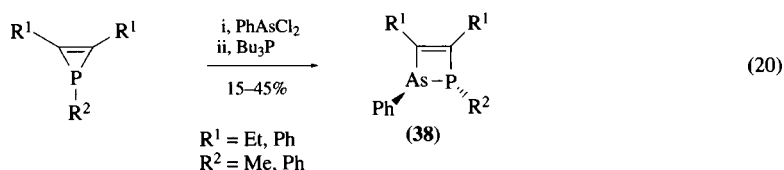
By analogy to the corresponding phosphorus-heterocycle, tetraphenyl-1,2-diarsetene is formed from (AsPh)₆ and toluene at elevated temperatures <83OM298>. 2,4-Diallenyl-1,3-diarsetanes (**86**) are formed in a spontaneous cyclic dimerization of corresponding arsaaccumulenes (Equation (18)) <90TL6331>. Aryl- and alkylarsenic dichlorides react with malonic esters under formation of 1,3-diarsetanes (**87**) (Equation (19)) <78JCR(M)3363, 78JCR(S)252>. Arsaalkenes cyclodimerize photochemically to form 1,3-diarsetanes or 1,2-diarsetanes, respectively <80ZAAC(470)144, 84ZAAC(517)75>. Perfluorinated arsaalkene CF₃As=CF₂ is more reactive, 1,2- and 1,3-perfluorodiarsetanes are obtained at low temperature in 90% yield <84AG(E)710>. Arsaalkene (**88**), LiP(TMS)₂ and CoCl₂ are the adducts for the synthesis of tetraarsacubane (**17**) in surprisingly good 35% yield (Scheme 11). An unstable arsaalkyne is believed to be an intermediate in the reaction <93AG(E)103>.



Scheme 11

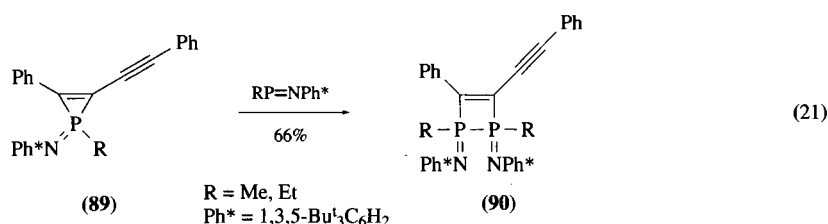
1.37.10 SYNTHESIS OF FOUR-MEMBERED HETEROCYCLES WITH TWO DIFFERENT HETEROATOMS

By analogy to the synthesis of 1,2-diphosphetenes (see Section 1.37.11) dichloroarsine and phosphirenes form 1-arsa-2-phosphetenes (**38**). Only the *trans* isomer is found (Equation (20)) <93BSF521>.

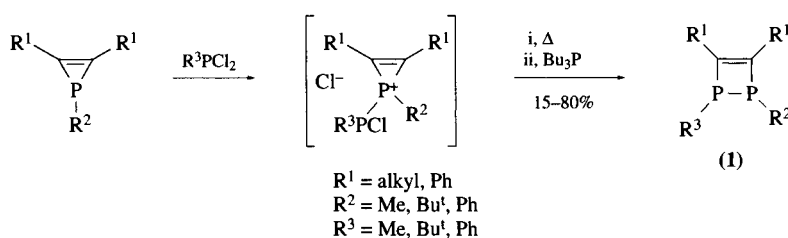


1.37.11 RING SYNTHESIS BY TRANSFORMATION TO ANOTHER RING

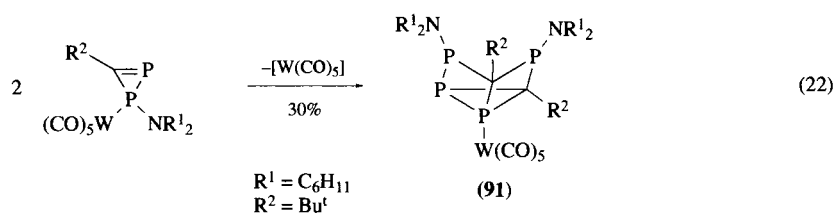
1 λ^5 ,2 λ^5 -Diphosphet-3-enes (**90**) are formed upon insertion of iminophosphanes into the P—C bond of λ^5 -phosphirenes (**89**) in good yield (Equation (21)) <94CB313>.



Phosphinidene insertion into a phosphirene ring is a general route to 1,2-diphosphetenes (**1**) (Scheme 12) <87(AG(E)548>. Ring opening and dimerization of a 1*H*-diphosphirene tungsten complex under mild conditions yields a tricyclic species (**91**) (Equation (22)) with a diphosphetane substructure <91CC1305>.



Scheme 12



1.37.12 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

All relevant reactions leading to the heterocycles are described in Sections 1.37.8 to 1.37.11. This section points out only the most useful preparative routes to the ring compounds.

1.37.12.1 1,2- and 1,3-Diphosphetes

1 λ^5 ,3 λ^5 -Diphosphetes can be made most successfully from C—Cl—phosphaalkenes (**55**) (Section 1.37.8.3) or C-diazo diaminophosphane precursors (**57**) (Section 1.37.8.4). Free 1 λ^3 ,3 λ^3 -diphos-

phetes (**4**) as well as $1\lambda^3,2\lambda^3$ -diphosphetes (**44**) are accessible as reactive intermediates only by oxidative degradation of the zirconium complex (**42**) (Section 1.37.4.2). η^4 -Complexed $1\lambda^3,3\lambda^3$ -diphosphetes are made easily from phosphalkynes (**66**) (Section 1.37.8.5).

1.37.12.2 1,3-Dihydro-1,3-Diphosphetes

1,3-Dihydro-1,3-diphosphete (**13**) can be made by chlorine abstraction of $C-Cl_2$ -phosphalkene (**76**) (Section 1.37.8.6).

1.37.12.3 1,2-Diphosphetenes

$1\lambda^5,2\lambda^5$ -Diphosphet-3-enes (**90**) are made from λ^5 -phosphirenes in good yield (Section 1.37.11). The chemistry of $1\lambda^3,2\lambda^3$ -diphosphet-3-enes (**1**) was reviewed including all relevant syntheses <92MI 137-01>. Favorable reactions yielding (**1**) are; ring contraction of 1,2,3-triphospholenes (15–43%), cyclopolyphosphines plus alkynes (max. 55%, difficult workup) (see Section 1.37.8.6), and phosphiniden insertion into phosphirenes (30–80%) (Section 1.37.11). Tricyclic (**45**) includes two 1,2-diphosphetene rings. It is formed upon cyclodimerization of reactive 1,2-diphosphete (**44**) (see Section 1.37.4.2). The only access known to a 1,2-diphosphet-2-ene (**77**) is starting with a phosphole derivative (Section 1.37.8.6).

1.37.12.4 1,3-Diphosphetenes

An iminophosphane leads to $1\lambda^5,3\lambda^5$ -diphosphet-2-ene (**53**) (see Section 1.37.8.1). $1\lambda^5,3\lambda^3$ -Diphosphet-2-ene (**81**) and $1\lambda^3,3\lambda^3$ -diphosphet-2-enes (**82**) and (**83**) are made in good yield from nitrogen and oxygen substituted phosphalkynes (Section 1.37.8.6). $1\lambda^3,3\lambda^3$ -Diphosphet-2-ene (**10**) is synthesized in 75% yield by reacting a phosphalkene with phosgene <83CB938>.

1.37.12.5 1,2- and 1,3-Diphosphetanes

$1\lambda^5,3\lambda^5$ -Diphosphetanes (**59**) are formed in moderate yield by a cyclic addition reaction of bis(methylene)- or iminomethylenephosphoranes (Section 1.37.8.4). λ^3 -Phosphalkenes are excellent precursors for many different λ^3,λ^3 -diphosphetanes. Head-to-head cyclic addition leads to 1,2-diphosphetanes and the preferred head-to-tail dimerization to 1,3-diphosphetanes (Section 1.37.8.4). This principal route has been reviewed <92H(34)369>.

trans-3,4-Dipropyliden-1,2-diphosphetane is accessible in 83% yield by a reductive coupling reaction (See Section 1.37.8.2).

1.37.12.6 Diphosphetanes as Parts of Cage Compounds

Tetraphosphacubanes (**15**) are preferably made (30–75%) by using zirconium complexes (**42**) as ducts (Section 1.37.4.2). Tetracyclic tetramers of phosphalkyne (**66**), which include 1,3- as well as 1,2-diphosphetane subunits, are made in a reaction of (**66**) with $AlCl_3$ (Section 1.37.8.4). Pentamers of (**66**) and other $P-C$ cage compounds can be made in poor to moderate yields by reductive routes (Section 1.37.8.6).

1.37.12.7 Mono and Diarsa Four-Membered Rings

These are summarized in Sections 1.37.9 and 1.37.10.

1.38

Four-membered Rings with Two Heteroatoms including Silicon to Lead

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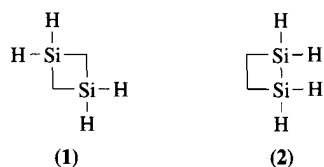
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1.38.1 INTRODUCTION

This chapter deals with saturated and unsaturated cyclobutane ring systems containing two heteroatoms. One or two of these heteroatoms are from group 14. Heterocyclic systems containing silicon, germanium, tin, or lead have been described previously by Armitage <84CHEC-I(1)573>.

1.38.2 THEORETICAL METHODS

SCF methods were used to calculate infrared ring-puckering vibrations of 1,3-disilacyclobutane (**1**) <85CPH311>. HF/3-21G and MNDO calculations have found (**1**) to be 19.9 kcal mol⁻¹ (83.3 kJ mol⁻¹) more stable than its 1,2-disilacyclobutane isomer (**2**) <89JST(194)183>.



The effect of ring atom substitution by silicon has been studied theoretically and experimentally (see Table 1). The barrier to ring inversion decreases with silicon substitution. Thus, the barrier to inversion decreases as follows: cyclobutane > (**3**) > (**1**). Strain energies, however, are relatively unaffected (the low experimental value for (**3**) has been questioned <90JA3408>). The degree of ring puckering which is expressed by the dihedral angle (0° is planar) decreases as follows: (**3**) > cyclobutane > (**1**).

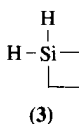


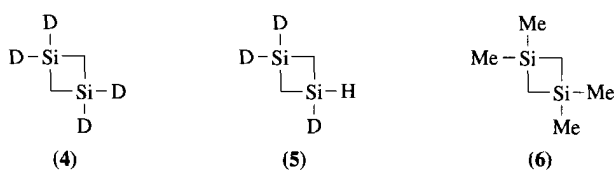
Table 1 Comparison of inversion barriers and dihedral angles of four-membered rings.

Compound	Inversion barrier		Strain energy		Dihedral angle (°)	Ref.
	kcal mol ⁻¹	kJ mol ⁻¹	kcal mol ⁻¹	kJ mol ⁻¹		
Cyclobutane	1.47 (0.92)	6.15 (3.85)	26.5 (26.2)	110.0 (109.7)	29 (28)	90JA3408, 90JPC1830
(3)	1.26 (1.24)	5.28 (5.19)	16.8 (23.3)	70.3 (97.6)	36 (32)	90JA3408, 90JPC1830
(1)	0.25 (0.25)	1.05 (1.05)	24.6 (20.6)	103.0 (86.2)	24 (24)	90JA3408, 90JPC1830

Calculated values are in parentheses. Experimental values are from (a) electron diffraction and (b) infrared and Raman spectroscopy.

1.38.3 EXPERIMENTAL STRUCTURAL METHODS

The structural aspects of the disilacyclobutane (**1**) have been studied extensively using various experimental methods. Infrared (IR) and Raman techniques have been used for disilacyclobutanes (**1**), (**4**), and (**5**) <77JA3273, 78JPC2845, 78JSP(70)307, B-78MI 138-01, 80JSP(84)139, 82JCP(76)3890>. Other experimental methods include: microwave spectroscopy <88JSP(128)250> and electron diffraction <88ACS(A)352>. Photoelectron spectroscopy <73JOM(51)99> and gas phase electron diffraction <91JST(246)229> have been used to study disilacyclobutane (**6**).



1.38.4 THERMODYNAMIC ASPECTS

Some conformational and energy aspects of disilacyclobutanes have already been discussed in Section 1.38.2. Table 2 compares experimental and theoretical data for (1), (6), and (7).

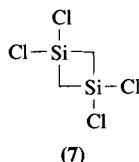


Table 2 Geometry conformation data for 1,3-disilylbutanes.

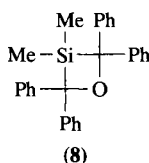
Compound	Phase	Bond length, Si—C (Å)	Ring angle (°)		Dihedral angle (°)	Barrier		Ref.
			C—Si—C	Si—C—Si		kcal mol ⁻¹	kJ mol ⁻¹	
(1)		(1.900)	(96.1)	(81.7)	(24)	(0.25)	(1.05)	90JPC1830
(1)		1.923 (1.912)						90JA3408
(1)	Gas ^a	1.888 (1.899)	90.6 (91.0)	86.8 (88.0)	25 (15)			88ACS(A)352
(1)	Gas ^b				24	0.25	1.05	77JA3273
(6)	Gas ^a	1.884	90.1	90.1	22.1			91JST(246)229
(6)						0.24	1.00	82JCP(76)3890
(7)	Gas and solid ^b	1.86	93.50	86.50	0			85JST(127)1
(7)	Gas ^a	1.89	89		14			B-72MI 138-01

Calculated values are in parentheses. Experimental values are from (a) electron diffraction and (b) infrared and Raman spectroscopy.

The conformation and energy of disilacyclobutane (1) can be compared to the tetraethyl (6) and tetrachloro (7) derivatives. The similar degree of puckering for (1) and (6) suggests the methyl groups have little effect on this 1,3-disilacyclobutane system. Interestingly, (1) changes from a puckered conformation in the gas phase to a planar structure in the solid state <77JA3273, 78JPC(70)2845>.

The short Si—Si nonbonding distance (2.592 Å) in (1) compared to its C—C transannular distance (2.684 Å) has been explained by Si—C bond lengths and antibonding Si—Si interactions <87JCS(D)271>.

The cyclosiloxane (8) exhibits unusually strong fluorescence in the visible region. This phenomena has been attributed to silicon–oxygen hyperconjugation and ring structural requirements <81JOM(215)373>.



1.38.5 REACTIVITY OF NONCONJUGATED RINGS

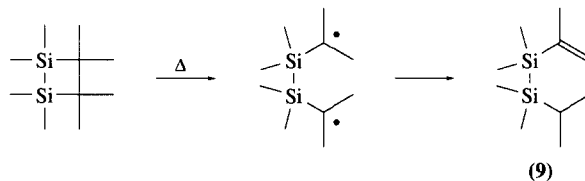
A characteristic reaction of most 1,2-dimetallo-cyclobutanes is that they are reactive to molecular oxygen. In cases where the substituents are small (e.g., methyl), they are also sensitive to trace amounts of water. Strained siletanes containing a good leaving group within the ring are especially sensitive to bimolecular ring-opening processes catalyzed by surface moisture.

1.38.5.1 Thermal and Photochemical Reactions

The general patterns of thermal unimolecular reactions are considered here. In principal, cyclo-reversions are important, and a large variety are possible. However, in cases where the reaction is

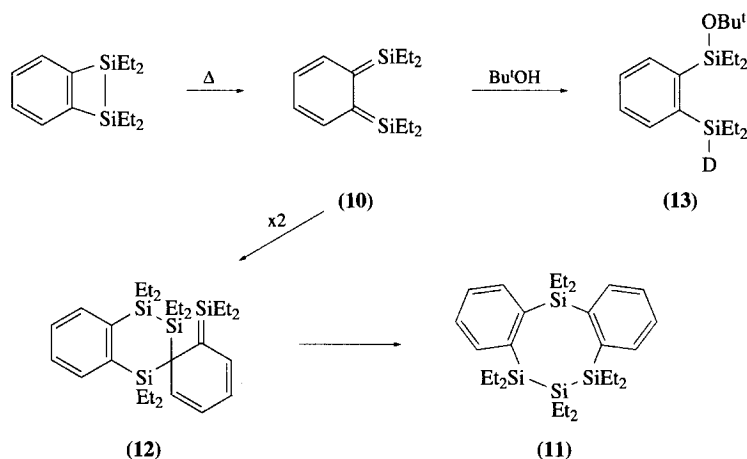
very endothermic with a good migratory group on silicon, such as hydrogen or silicon, atom shifts to or from the ring silicon atom can occur with ring opening.

The thermal rearrangement of octamethyl-1,2-disiletane (Scheme 1) to the ring-opened product (9) presumably occurs by disproportionation of the 1,4-diradical intermediate <80JOM(187)297>.



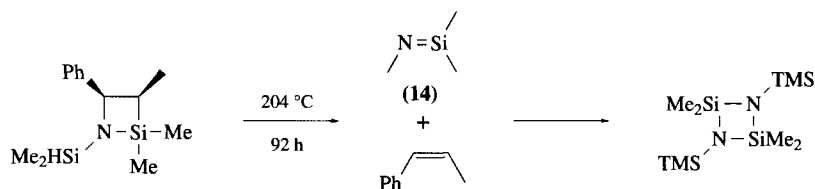
Scheme 1

Thermolysis of 3,4-benzo-1,1,2,2-tetraethylsiletene (Scheme 2) at 250°C produces the reactive intermediate *o*-quinodisilane (10), as suggested by the formation of (11) through the [4 + 2] dimer (12). Additional trapping experiments with Bu^tOH (to form (13)), alkynes, and aldehydes also support formation of (10) <91OM3173>.



Scheme 2

Thermal fragmentation in solution of a variety of azasiletanes are reported to provide the silanimine (14) and the corresponding alkene by a [2s + 2a] concerted pathway (Scheme 3) <92JA218>. These reactive species then couple in a head-to-tail fashion. When the carbon substituents on C-3 are large (e.g., neopentyl and phenyl) the fragmentation is believed to involve a zwitterionic species <93CB581>. Other fragmentation patterns are also seen in the gas phase at higher temperatures <94JOM(484)89>.

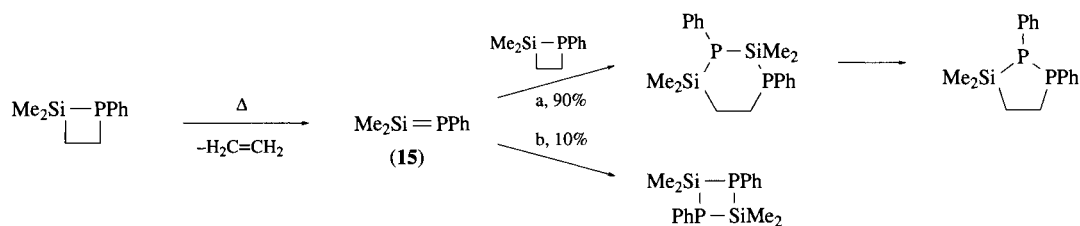


Scheme 3

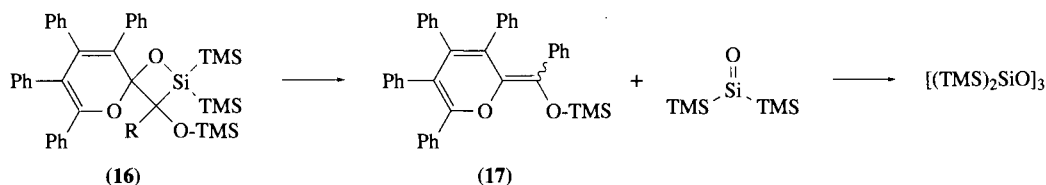
Phosphasiletanes thermally decompose at reduced pressure to transient species (15) via [2 + 2] cycloreversion (Scheme 4). The major products are formed by the recombination of (15) with starting material <79JOM(182)9>.

The silaoxetane (16) undergoes fragmentation to the cyclotriene (17) (Scheme 5) <83OM692, 83TL1477>.

It is believed that the silathietane (18) thermally decomposes to a transient species containing a

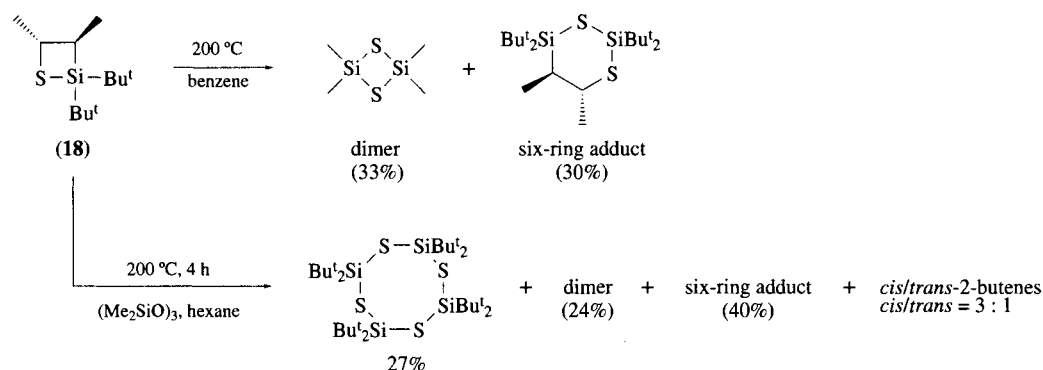


Scheme 4



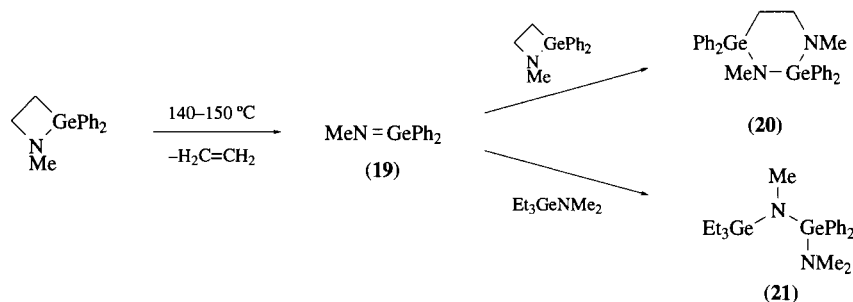
Scheme 5

silicon-sulfur π bond ($\text{R}_2\text{Si}=\text{S}$). Evidence of this includes formation of a dimer and its disappearance in the presence of trapping agents (Scheme 6) <90OM2205>.



Scheme 6

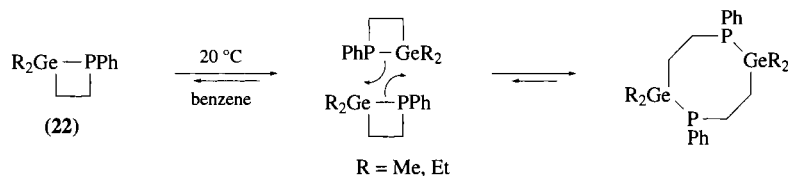
Thermal decomposition of germanium-nitrogen heterocycles are reported to occur cleanly to ethylene and the reactive germaine (19). Chemical trapping of the transient species with azagermetane (starting material) or dimethylamino(triethyl)germane, to form (20) and (21), respectively, provides evidence for the $[2 + 2]$ fragmentation (Scheme 7) <78JOM(154)C23>.



Scheme 7

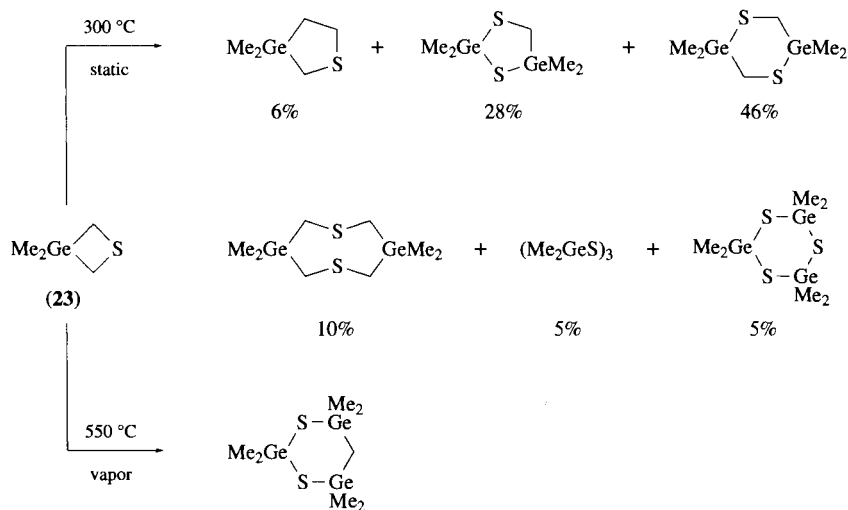
In the condensed phase 1,2-phosphagermetanes (22) undergo dimerization to the corresponding ring-expanded products (Scheme 8). The reaction is an example of an isodesmic process in which

the number and type of bonds (Ge—C, Ge—P, and P—C) do not change, and the thermodynamic driving force is formation of a relatively strain-free eight-membered ring $\langle 82\text{OM}1261 \rangle$.



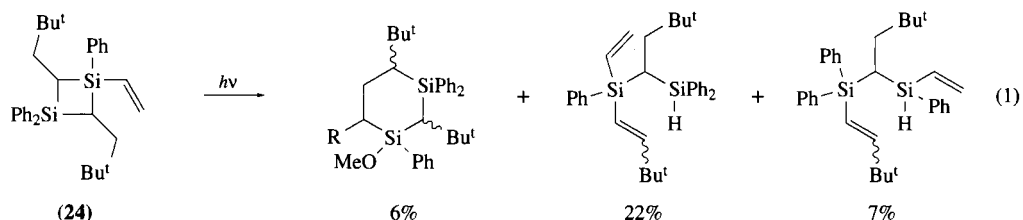
Scheme 8

Liquid-phase thermal decomposition of the 3-thiagermetane (**23**) at 300 °C or in the vapor phase at 550 °C yields cyclic molecules containing Ge—S bonds (Scheme 9). It appears that the decomposition of the ring initially proceeds by formation of a dimethylgermene ($\text{R}_2\text{Ge}=\text{CH}_2$) and subsequently requires formation of the germathione ($\text{R}_2\text{Ge}=\text{S}$) $\langle 88\text{JOM}(345)39 \rangle$.



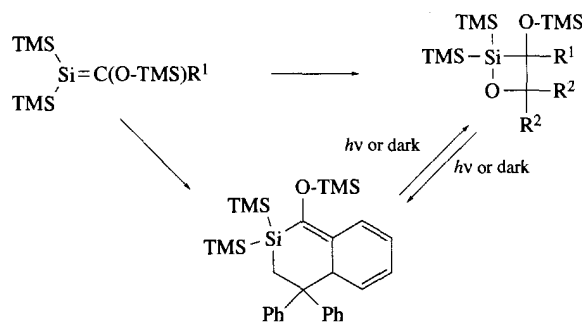
Scheme 9

Examples of photochemical reactions for 1,3-disiletanes are rare although such processes have been observed when the silicon atom carries phenyl groups $\langle 80\text{JOM}(202)401 \rangle$. Photolyzed ring expansion of the 1,3-disiletane (**24**) gives the products presumably via a 1,4-diradical intermediate (Equation (1)) $\langle 92\text{OM}1626 \rangle$.

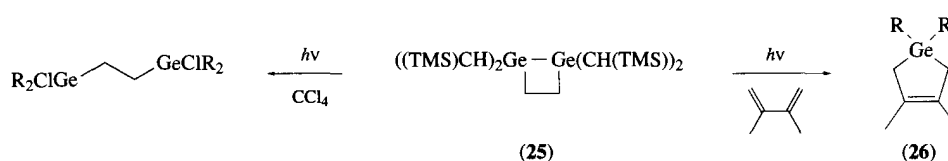


A characteristic reaction of the 1,2-silaoxetanes with aryl groups on the ring carbons is ring expansion (Scheme 10). The reverse process can be done photochemically $\langle 87\text{OM}1246 \rangle$.

Irradiation of highly substituted digermetanes, such as (**25**), yields reactive germylene species that add to butadiene, giving the corresponding pentacyclogermiranes (**26**), or abstract a chlorine atom from carbon tetrachloride (Scheme 11) $\langle 95\text{OM}2139 \rangle$.



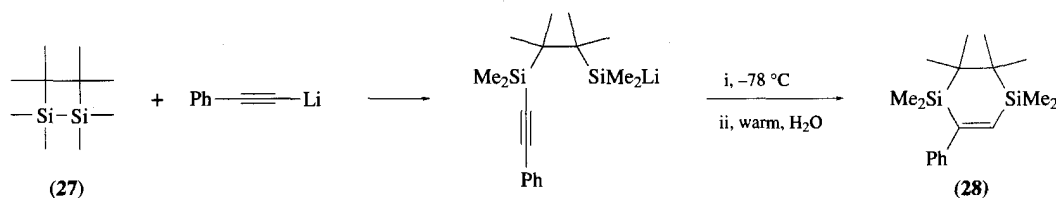
Scheme 10



Scheme 11

1.38.5.2 Reactivity Toward Nucleophiles

Processes with polar or ionic reactants lead to ring-opened products in which the more electro-negative end of the of the reagent becomes bonded to silicon. Therefore, phenylethynyllithium adds across the silicon–silicon bond of octamethyldisiletane (27) giving the 1,4-disilacyclohexene (28) in 30% yield (Scheme 12). A variety of different alkynes (R^1 , $\text{R}^2 = \text{Ph}$, H ; H , H ; H , CO_2Me ; H , $\text{C}(\text{O})\text{Me}$; $n\text{-C}_5\text{H}_{11}$, H ; Me , H ; $\text{CH}_2=\text{CHMe}$, H ; MeO_2C , MeO_2C ; Me , $\text{C}(\text{O})\text{Me}$) can insert into 1,2-disiletanes via a palladium ($(\text{Ph}_3)\text{PdCl}_2$)-catalyzed process, reaching 70–90% yields. Palladium and nickel complexes also catalyzed reactions with butadiene and isoprene at 100°C , leading to a mixture of 12-membered ring products $\langle 84\text{JOM}(271)337 \rangle$.



Scheme 12

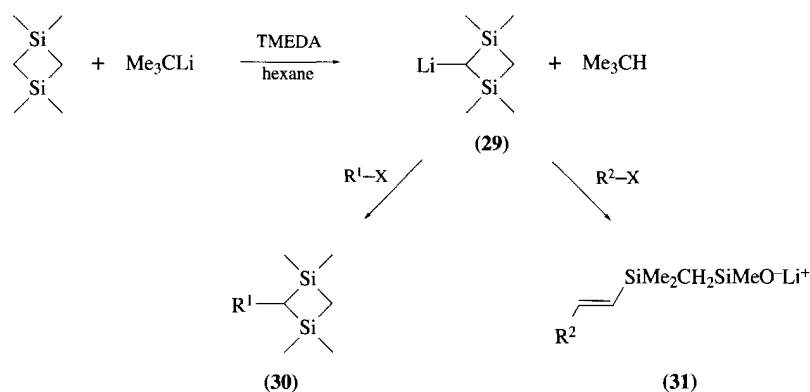
1.38.5.3 Reactivity Toward Electrophiles

A large number of reactions from the disiletane anion (29) have been reported $\langle 90\text{OM}2677 \rangle$. Reactions with various electrophiles lead to ring carbon-substituted products (30) or ring-opened compounds (31) with aqueous workup (Scheme 13).

1.38.6 SYNTHESIS OF 1,2-DIHETEROBUTANE SYSTEMS

1.38.6.1 Saturated Rings

Thermal [2 + 2] cycloaddition reactions between disilenes ($\text{R}_2\text{Si}=\text{SiR}_2$) and alkenes may appear to be a direct route to 1,2-disiletanes, but this approach has met with limited success. The disilenes that were first reported ($\text{R} = \text{hydrogen}$ $\langle 75\text{JOM}(86)347 \rangle$, methyl $\langle 78\text{JA}6236 \rangle$, or silyl $\langle 83\text{OM}1484$,

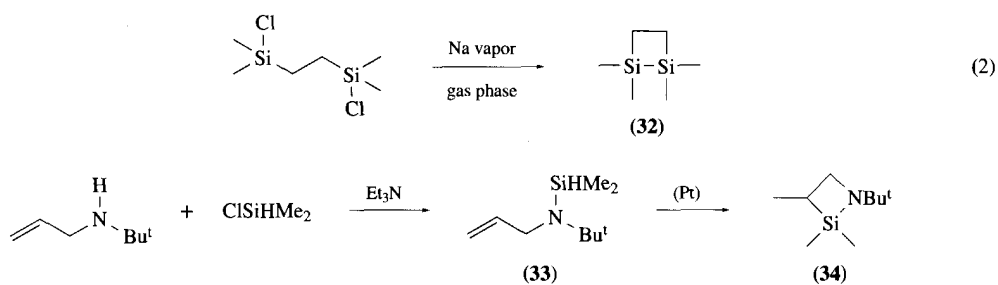


Scheme 13

94AG(E)1489)) were usually formed as reactive intermediates at the higher temperature ($> 300^\circ\text{C}$). They subsequently rearrange by reversible 1,2 shift to the isomeric silylenes. These phenomena have been explored by both kinetics (84JOM(271)249) and theory (84CC1392). Even exceptionally stable disilenes (81SCI1343, 82JA1150, 87AG(E)1201) undergo a diverse variety of unimolecular isomerizations and possibly bimolecular rearrangements prior to reaction (86JA4239). The chemist's intuition developed from the lighter elements can become misleading as one proceeds down the periodic table and the bonding becomes more delocalized. A difluorosilylene ($\text{F}_2\text{Si}=\text{CR}_2$), on the other hand, can be used to synthesize 1,1,2,2-tetrafluoro-1,2-disiletane in low yields (72CJC459, 81JOM(214)31).

1.38.6.1.1 Formation by one bond

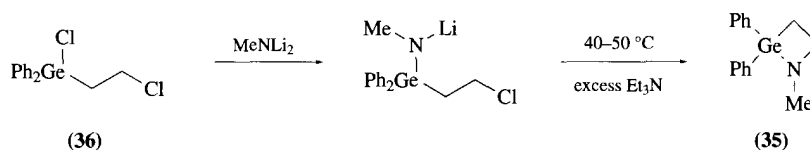
Various methods have been developed to effect ring closure to prepare 1,2-diheterocyclobutane systems. In the gas phase, an intermolecular Wurtz reaction was used to prepare the 1,2-disiletane (32) in high yield (Equation (2)) (80DOK(253)1387). Platinum catalyzes the ring closure of *N*-silylalkenes (33), giving the azasiletanes (34) via intramolecular hydrosilylation (Scheme 14) (90JOC3438, 94JOM(484)89).



Scheme 14

The moderately stable azagermetane (35) is produced, in 60–70% yield, by amination of the germyl chloride (36) followed by ring closure (Scheme 15) (78JOM(154)C23). A less stable 2,2-diethylazagermetane has also been prepared by this method.

Phosphogermetanes, such as (37), are key precursors for the preparation of phosphagermetanes



Scheme 15

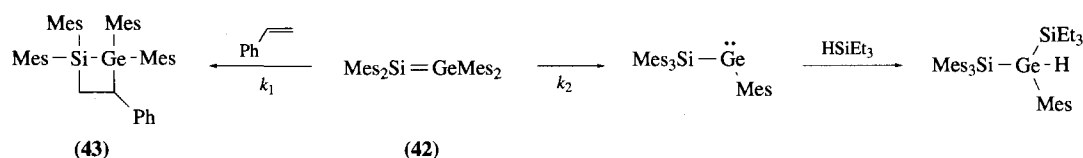
$$\begin{array}{ccccc}
 \begin{array}{c} \text{Br} \\ | \\ \text{R}_2\text{Ge}-\text{CH}_2-\text{CH}_2-\text{P}(\text{H})(\text{Ph}) \end{array} & \xrightarrow[\text{-(Me}_2\text{NH}_2^+)\text{Br}^-]{2\text{ Me}_2\text{NH}} & \begin{array}{c} \text{NMe}_2 \\ | \\ \text{R}_2\text{Ge}-\text{CH}_2-\text{CH}_2-\text{P}(\text{H})(\text{Ph}) \end{array} & \xrightarrow[\text{-Me}_2\text{NH}]{20^\circ\text{C}} & \begin{array}{c} \text{R}_2\text{Ge}-\text{PPh} \\ | \\ \text{PPh} \end{array} \\
 (38) & & (37) & & (39)
 \end{array}$$

Scheme 16

(i) *[2 + 2] Coupling with alkenes*

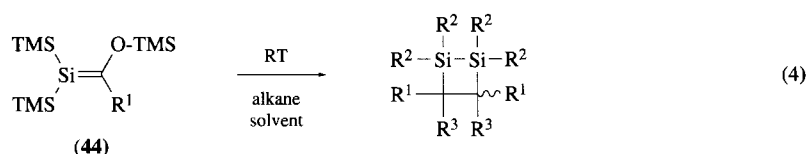
$$\begin{array}{c} \text{Bu}^t \\ | \\ \text{Si} \\ | \\ \text{Bu}^t - \text{Si} - \text{Si} - \text{Bu}^t \\ | \quad | \\ \text{Bu}^t \quad \text{Bu}^t \end{array} + \text{C}_6\text{H}_4(\text{CH}_3)\text{CH=CH}_2 \xrightarrow{h\nu} \begin{array}{c} \text{Bu}^t \quad \text{Bu}^t \\ \diagdown \quad \diagup \\ \text{Si} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ | \quad | \\ \text{C}_6\text{H}_4(\text{CH}_3) \quad \text{o-Tol} \end{array} + \begin{array}{c} \text{C}_6\text{H}_4(\text{CH}_3) \quad \text{o-Tol} \\ \diagdown \quad \diagup \\ \text{Si} - \text{Si} \\ | \quad | \\ \text{Bu}^t \quad \text{Bu}^t \end{array} \quad (3)$$

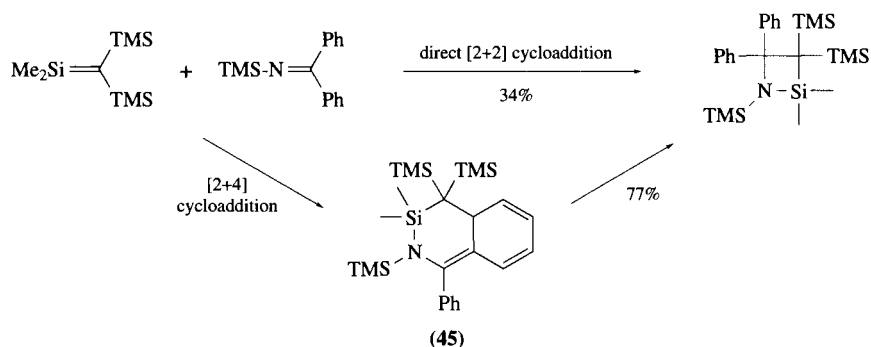
(40) 44% (41) 66%



Scheme 17

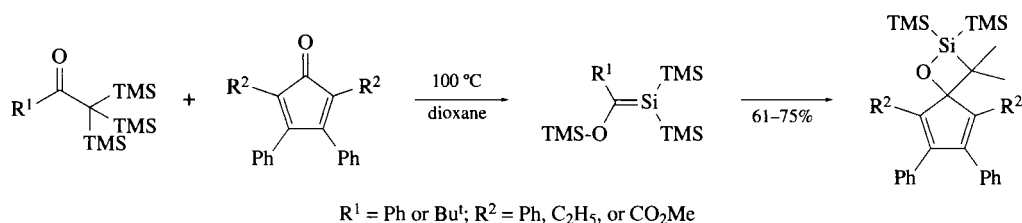
Silenes bearing an electron-donating group on carbon, such as the 2-siloxysilene (**44**), dimerize in head-to-head fashion to give 1,2-disilylcyclobutanes (Equation (4)) $\langle 79JA83, 92OM2317 \rangle$. In a similar manner, azasiletanes can be prepared via direct coupling or via isomerization of the [2 + 4] adducts, such as (**45**) (Scheme 18) $\langle 81CB3518, 88CB1407 \rangle$.


$$R^1 = \text{Ar, Bu}^t, \text{Pr}^i, \text{Bn, (2.2.2)-octyl}; R^2 = \text{TMS}; R^3 = \text{O-TMS}$$



Scheme 18

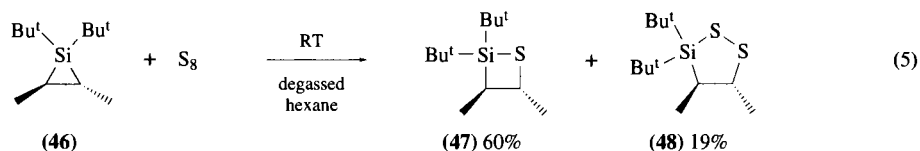
Synthesis of silaoxetanes involves the addition of a reactive silene, generated thermally or photochemically, to highly a substituted ketone (Scheme 19) <81CB3518, 83OM692, 83TL1477, 84JOM(273)141, 85CRV419, 87OM1246>.



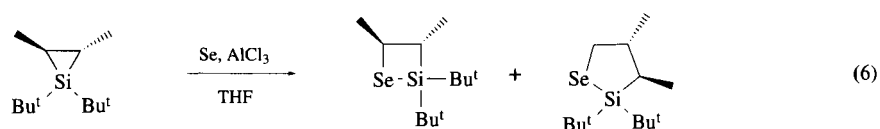
Scheme 19

1.38.6.1.3 Formation from other ring systems

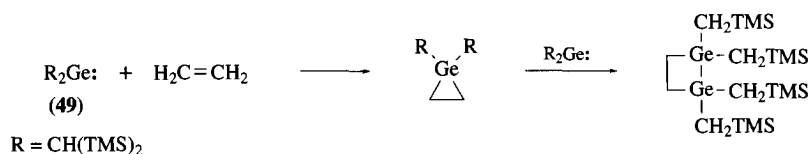
The thermolysis of silylcyclopropane rings generates dimethylsilylene ((CH₃)₂Si:), which inserts into the strained Si—C bond of the starting material to yield permethyl-1,2-disiletanes in good yields <75JA7162>. Similarly, a single sulfur atom can be inserted into *trans*-1,1-di-*t*-butyl-2,3-dimethylsilirane (46) at ambient temperature, yielding one major product (47). Also formed are minor amounts of the S₂ insertion product (48) (Equation (5)).



Reaction of several siliranes with selenium powder in the presence of lithium chloride leads rapidly to products from insertion of one or more selenium atoms into the three-membered ring, typically in greater than 70% yield (Equation (6)). The relative instability of the ring system has prevented its isolation <94OM3715>.



Stable germynes, such as (49), add to ethylene over 24 hours to form 1,2-digermetanes in good yields (Scheme 20) <95OM2139>.

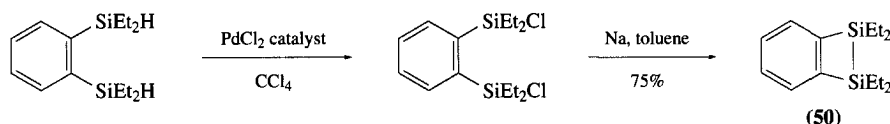


Scheme 20

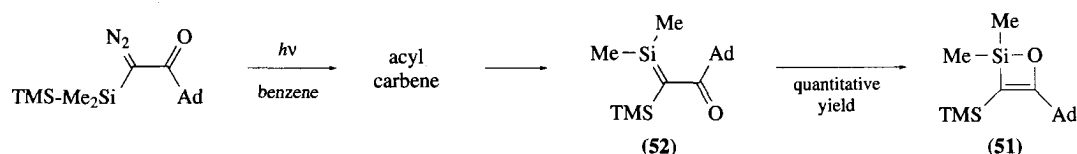
1.38.6.2 Unsaturated Rings

1.38.6.2.1 Formation of one bond

Alkylidene-1,2-disilanes (**50**) have been prepared by sodium-induced coupling of dichlorosilane substrates (Scheme 21) <86JOM(310)C57, 92JOM(427)C26, 93CL985>. Synthesis of the 1,2-silaoxene (**51**) utilizes photochemically induced carbene formation to generate the silene (**52**), which ring closes to (**51**) (Scheme 22) <84JA1486>.



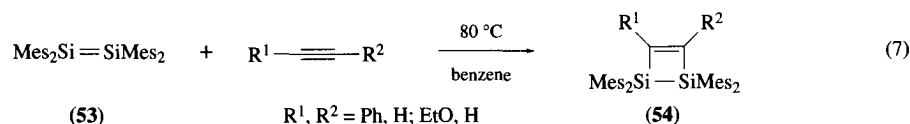
Scheme 21



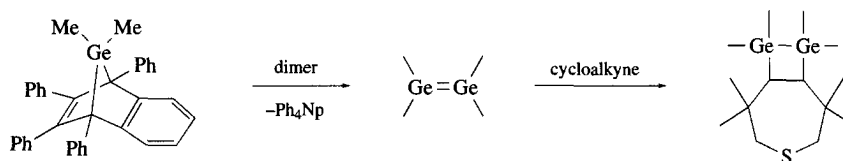
Scheme 22

1.38.6.2.2 Formation of two bonds: [2 + 2] coupling with alkynes

Tetramesityldisilene (**53**) reacts thermally at 300°C or at 80°C in benzene with various alkynes, giving silylcyclobutenes (**54**) (Equation (7)). The reduction or complete loss of retention of stereochemistry in the products suggests the involvement of a diradical intermediate <85CL643, 85JOM(282)305, 86CL883>.



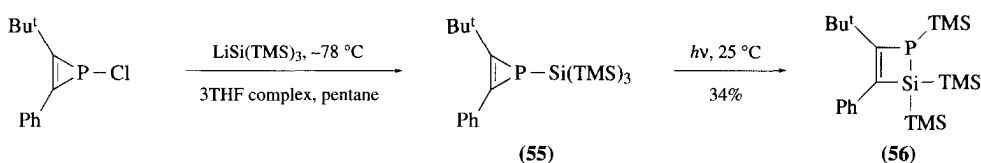
Germynes ($\text{R}_2\text{Ge}=\text{GeR}_2$), generated thermally or photolytically, are known to react with different alkynes, even those fused to a large ring (Scheme 23) <82JA6136, 86JOM(301)C21, 88TL3383, 89CC770>.



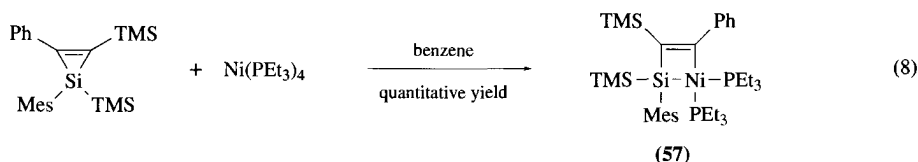
Scheme 23

1.38.6.2.3 Formation from other ring systems

The synthetic method used to prepare these highly strained structures usually involves a key photochemical process, for example irradiation of the cyclopropene (**55**), provides the 1,2-silaphosphetene (**56**) in moderate yields (Scheme 24) <90AG(E)1436>. Reactive metals are known to insert into the Si—C bond of strained silirenes, thus providing a synthetic route for silametalloacyles. Equation (8) demonstrates this strategy for the preparation of the nickelasiletane (**57**) <86JA7417>.

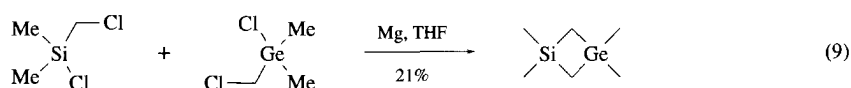


Scheme 24

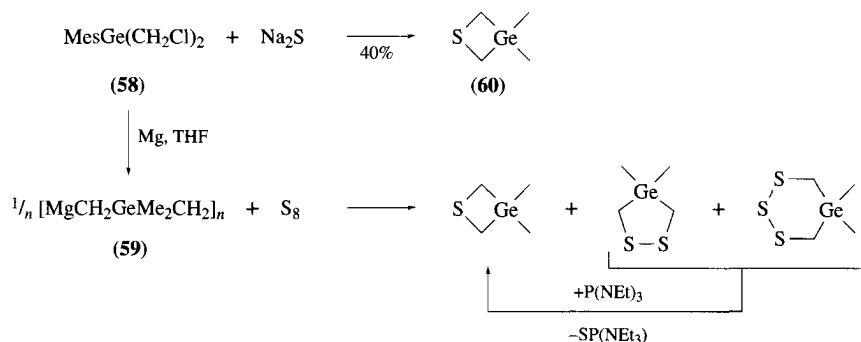


1.38.7 SYNTHESIS OF 1,3-DIHETEROBUTANES: [2 + 2] HEAD TO TAIL COUPLING

Historically, practical synthesis of 1,3-disilanes has relied on magnesium-induced dimerization of halomethylsilyl halides ($\text{XCH}_2\text{Si}(\text{CH}_3)_2\text{X}$), probably via coupling of silylene ($\text{R}_2\text{Si}=\text{CH}_2$). This has been extensively covered elsewhere <84CHEC-1(1)573>. Upon pyrolysis, siletanes quantitatively yield 1,3-disiletanes. Formation of this ring is often cited as critical evidence for the involvement of a silylene <77DOK(235)1086, 77JA7452, 92JA3643>. Magnesium has also been used to prepare 1,3-silagermetanes by cross-coupling chloromethylgermylchlorides ($\text{ClCH}_2\text{Ge}(\text{CH}_3)_2\text{Cl}$) and chloromethylsilyl chlorides ($\text{ClCH}_2\text{Si}(\text{CH}_3)_2\text{Cl}$), again $\text{R}_2\text{Ge}=\text{CR}_2$ and $\text{R}_2\text{Si}=\text{CR}_2$ are suspected intermediates (Equation (9)) <70JOM(21)103>. In the early 1990s, butyllithium-generated silylenes have produced 1,3-disilanes <90SL344>.



Synthesis of the 3-thiagermatane ring is achieved by a reaction sequence beginning from bis(chloromethyl)dimethylgermane (**58**) (Scheme 25) <84SRI21>. Reaction of the dichloride with



Scheme 25

magnesium in THF produces a polymeric Grignard reagent (**59**) that upon reaction with S₈ affords 3-thiagermetane (**60**) along with minor amounts of di- and trisulfide adducts. The additional sulfur atoms of the polysulfides can be removed by the reaction of the mixture with triethylamino-phosphene. The overall yield leading to the four-membered ring is 40%. The ring sulfur atom of (**60**) can be oxidized by ozone to yield a sulfonylthiagermatane <83JOM(252)C73, 88JOM(345)39>.

1.39

Four-membered Rings with Three Heteroatoms

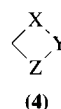
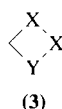
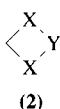
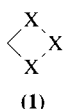
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1.39.1 INTRODUCTION

All four-membered heterocycles with three heteroatoms can be classified into four types: the insufficiently studied compounds with three similar heteroatoms (**1**; X = Si, P, Se), the symmetrical (**2**) and unsymmetrical (**3**) heterocycles with two different heteroatoms, and derivatives with three different heteroatoms (**4**).

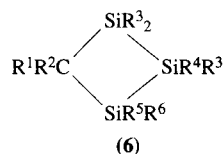
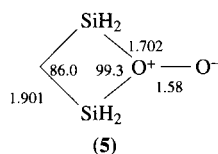


1.39.2 STRUCTURE OF FOUR-MEMBERED RINGS WITH THREE HETEROATOMS

1.39.2.1 Theoretical Methods

The structure of the trisilacyclobutane molecule was studied by *ab initio* quantum mechanical techniques <87JA6577>. The planar four-membered ring does not exhibit any specific structural features. The optimized geometric parameters are $r(\text{Si—Si}) = 2.363 \text{ \AA}$, $r(\text{Si—C}) = 1.914 \text{ \AA}$, $r(\text{Si—H}) = 1.471\text{--}1.472 \text{ \AA}$, $\angle \text{SiCSi} = 101.4^\circ$.

The structure of peroxonium ion (5) with a 1,2,4-oxadisiletane ring was calculated by *ab initio* MO method <93OM1514>. The most stable conformation has C_s symmetry with the pendant oxygen bending out of the 1,2,4-oxadisiletane plane by 150.2° . The characteristic feature of (5) is the long O—O bond ($1.58 \text{ \AA}$).



	R^1	R^2	R^3	R^4	R^5	R^6
(a)	H	Ad	TMS	TMS	TMS	Et_3GeO
(b)	$2,6\text{-Pr}_2\text{C}_6\text{H}_3\text{N=}$		Bu^t	Bu^t	Bu^t	Bu^t
(c)	$\alpha\text{-C}_{10}\text{H}_7\text{N=}$		Bu^t	H	Bu^t	Bu^t

Ad = adamantyl

1.39.2.2 X-ray Diffraction

The molecular structure of compounds with trisilacyclobutane ((6a), (6b), and (6c)) <92JOM(441)185, 93JOM(446)123>, triphosphacyclobutane (7) <91CC1305> and triselenacyclobutane (8) <84ACS(A)289> heterocycles was determined by x-ray techniques. The four-membered rings with three heteroatoms of compounds (6a) and (7) are slightly puckered, while the heterocycles of trisilacyclobutanimes ((6b) and (6c)) and triselenacyclobutane (8) are strictly planar. The planarity of the molecule (8) leads to short intramolecular contacts between $\text{Se}(1)\text{—Br}(1)$ and $\text{Se}(3)\text{—Br}(2)$ ($3.056 \text{ \AA}$ and $3.015 \text{ \AA}$) atoms. The bond lengths and angles for (1) type heterocycles are presented in Table 1.

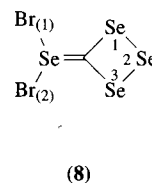
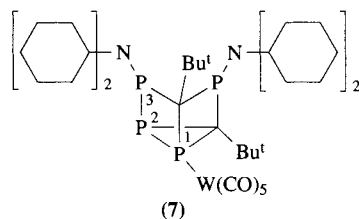
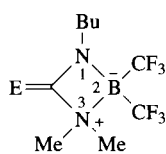


Table 1 Geometric parameters of type (1) heterocycles.

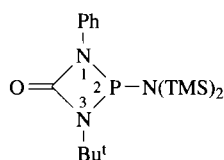
Compound	$r \text{ (\AA)}$				Angles ($^\circ$)			
	$X(1)\text{--}X(2)$	$X(2)\text{--}X(3)$	$X(1)\text{--}C$	$X(3)\text{--}C$	$\angle X(1)$	$\angle X(2)$	$\angle X(3)$	$\angle C$
(6a)	2.391(2)	2.389(2)	1.948(5)	1.924(4)	89.8(1)	90.4(1)	90.4(1)	100.8(2)
(6b)	2.477(2)	2.497(2)	1.955(3)	2.010(3)	85.7(1)	87.4(1)	87.4(1)	107.1(1)
(6c)	2.373(1)	2.405(1)	1.942(2)	1.992(2)	82.9(1)	84.1(1)	84.1(1)	107.0(1)
(7)	2.188(2)	2.229(2)	1.900(6)	1.892(6)	82.8(8)	84.8(2)	84.8(2)	100.8(3)
(8)	2.373(2)	2.376(2)	1.844(0)	1.826(10)	79.44(6)	84.7(3)	84.7(3)	111.5(3)

The molecular structures (9a) and (9b) are very similar, each heterocycle lies in a crystallographic mirror plane <91JOM(407)283>. The four-membered ring of 1,3-diaza-2-phosphetidinone (10) is puck-

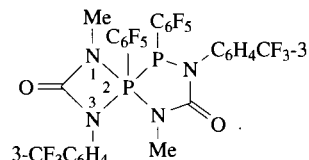
ered ($\alpha = 16.5^\circ$) $\langle 83ZOB525 \rangle$. The phosphorus atoms of compounds ((11)–(13)) display the distorted trigonal bipyramidal geometry typical of the related phosphoranes. As expected, the axial bonds P—N are longer than the equatorial ones $\langle 79CB1365, 83ZN(B)702, 86ZN(B)207, 87CB1713, 88AG(E)1562 \rangle$. The 1,3-diaza-2-phosphetidine and 1,2,4-azadiphosphetidine rings $\langle 86ZOB1988 \rangle$ of heterocyclic derivatives ((11)–(14)) are nearly, but not completely planar. The molecule of compound (15) with its 1,2,4-thiadiphosphetane skeleton has a puckered form. The dihedral angle between the PSC planes is 19.2° $\langle 90CL643 \rangle$. Puckering of the 1,2,4-azadisiletidine cycle of the compound (16a) is slight, the two half-rings are folded along the Si—Si diagonal, forming a dihedral angle of 2.2° $\langle 89CC1494 \rangle$. The four-ring atoms of compound (16b) lie exactly in a plane $\langle 90CB1795 \rangle$.



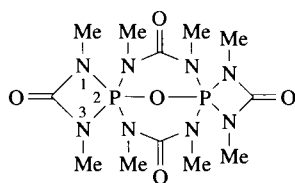
(9)
(a) E = O
(b) E = S



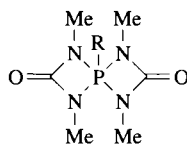
(10)



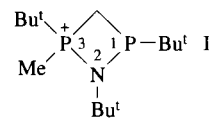
(11)



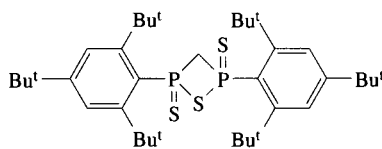
(12)



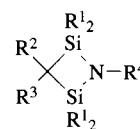
(13)
(a) R = PPh₂
(b) R = I
(c) R = Cl
(d) R = NMe₂
(e) R = N₃



(14)



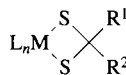
(15)



(16)

	R ¹	R ²	R ³	R ⁴
(a)	Me	PhMe ₂ Si	PhMe ₂ Si	2,6-Me ₂ C ₆ H ₃
(b)	Bu ^t	[c-C ₆ H ₁₁ N=]		c-C ₆ H ₁₁

According to x-ray analysis, dithiolate complexes of iron $\langle 81JOM(218)81 \rangle$, cobalt $\langle 82AG(E)197 \rangle$, rhodium $\langle 92OM889 \rangle$, and iridium $\langle 90JA2022 \rangle$ have the structure (17) with its four-membered heterocycle. The geometric parameters of type (2) heterocycles are given in Table 2.



(17)

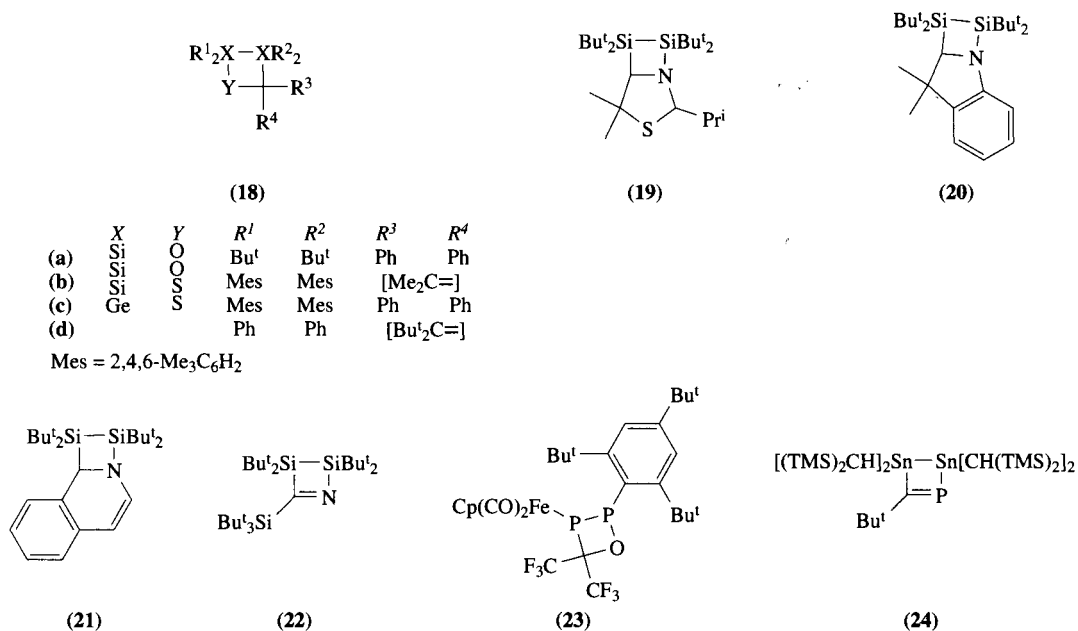
	M	L _n	R ¹	R ²
(a)	Co	MeC(CH ₂ PPh ₂) ₃	[O=]	
(b)	Rh	Cp*(Me ₃ P)	H	H
(c)	Ir	Cp*(Me ₃ P)	Me	Me

The structures of compounds (18)–(24) with unsymmetrical heterocycles were confirmed by x-ray crystallography. 1,2,3-Oxadisiletanes ((18a) and (18b)) $\langle 85JOM(282)305, 93OM2177 \rangle$ reveal an almost planar ring, whereas in 1,2,3-thiadisiletane (18c) $\langle 91OM827 \rangle$ it is highly puckered with a dihedral angle of 45.6° between the SiSiC and SiSC planes. The puckering of 1,2,3-thiadigermetane

Table 2 Geometric parameters of type (2) heterocycles.

Compound	<i>r</i> (Å)				Angles (°)			
	<i>X</i> (1)- <i>Y</i>	<i>X</i> (3)- <i>Y</i>	<i>X</i> (1)- <i>C</i>	<i>X</i> (3)- <i>C</i>	∠ <i>X</i> (1)	∠ <i>X</i> (3)	∠ <i>Y</i>	∠ <i>C</i>
(9a)	1.535(8)	1.635(8)	1.314(8)	1.525(8)	95.8(4)	84.1(4)	83.8(4)	96.3(5)
(9b)	1.520(1)	1.610(1)	1.328(9)	1.510(1)	95.0(7)	84.8(6)	84.5(6)	95.7(7)
(10)	1.760(2)	1.751(2)	1.406(4)	1.374(4)	92.5(2)	94.0(2)	73.4(1)	98.0(2)
(11)	1.668(3)	1.867(3)	1.400(4)	1.374(5)	98.5(2)	90.6(2)	72.6(1)	98.3(3)
(12)	1.676(1)	1.867(3)	1.395(3)	1.360(2)			73.7(1)	98.5(1)
	1.674(2)	1.812(2)	1.402(3)	1.352(2)	96.7(1)	92.4(1)	73.0(1)	97.9(2)
(13a)	1.674(2)	1.803(2)	1.398(4)	1.357(4)				
	1.676(2)	1.790(2)	1.409(4)	1.351(4)				
(13b)	1.670(8)	1.760(9)	1.399(15)	1.397(14)	95.5(7)	91.6(7)	75.4(4)	97.2(8)
	1.676(9)	1.753(10)	1.415(15)	1.396(15)	94.6(7)	92.0(7)	75.9(5)	97.3(9)
(13c)	1.677(4)	1.755(4)	1.408(6)	1.386(6)	94.7(3)	92.1(3)	75.5(2)	
	1.660(4)	1.755(4)	1.400(6)	1.380(6)	95.4(3)	92.1(3)	75.2(2)	
(13d)	1.690(2)	1.771(2)	1.394(3)	1.359(3)	95.2(1)	92.9(2)	73.8(1)	
	1.692(2)	1.773(2)	1.402(3)	1.357(4)	95.1(2)	93.2(2)	73.7(1)	
(13e)	1.659(2)	1.763(2)	1.403(3)	1.369(3)	95.7(1)	92.4(1)	74.7(1)	
	1.676(2)	1.745(2)	1.409(3)	1.369(3)		92.8(1)	75.3(1)	
(14)	1.779(4)	1.632(4)	1.869(6)	1.768(5)	80.4(2)	87.6(2)	100.0(2)	91.9(2)
(15)	2.120(3)	2.127(3)	1.872(8)	1.867(7)	88.1(2)	88.0(3)	83.0(3)	97.6(4)
(16a)	1.733(3)	1.746(3)	1.925(3)	1.913(3)	89.4(1)	89.5(1)	96.2(1)	84.9(1)
(16b)	1.772(2)	1.775(2)	1.904(3)	1.944(3)	84.1(1)	82.9(1)	101.7(1)	91.2(1)
(17a)	2.260(7)	2.250(6)	1.700(3)	1.690(3)			75.5(3)	109.1(16)
(17b)	2.361(1)	2.376(2)	1.832(4)	1.821(4)	90.9(1)	90.7(1)	73.58(5)	101.9(2)

heterocycle (18d) <86TL5105> is smaller ($\alpha = 15.4^\circ$). The Si—Si bond lengths of 1,2,3-oxa(thia)-disiletanes ((18a) and (18c)) and 1,2,3-azadisiletidines ((19) and (21)) <88JOM(338)C1, 92JOM(423)329> are abnormally long (2.409–2.460 Å) (Table 3). In complex (23) the Cp(CO)₂Fe fragment is linked via an Fe—P single bond with an essentially planar 1,2,3-oxadiphosphetane ring <92QM2351>. The 1,2,3-phosphadistannetene heterocycle (24) with C=P double bond is planar within the experimental error <88AG(E)838>.



A variety of (4) type compounds ((25)–(37)) containing four-membered heterocycles with three different heteroatoms have been studied by x-ray analysis <80CB55, 82AG(E)136, 83OM16, 83OM1675,

Table 3 Geometric parameters of type (3) heterocycles.

Compound	<i>r</i> (Å)				Angles (°)			
	<i>X-X</i>	<i>X-Y</i>	<i>C-X</i>	<i>C-Y</i>	∠ <i>CXX</i>	∠ <i>XXY</i>	∠ <i>Y</i>	∠ <i>C</i>
(18a)	2.409(2)	1.681(3)	2.028(4)	1.461(5)	71.6(1)	78.4(1)	112.5(2)	97.4(2)
(18b)	2.373(2)	1.693(4)	1.886(5)	1.428(7)	71.1(2)	78.2(1)	106.6(3)	103.5(3)
(18c)	2.443(2)	2.177(3)	1.994(6)	1.870(6)	81.9(2)	74.5(1)	92.3(2)	93.0(3)
(18d)	2.406(2)	2.242(6)	2.020(15)	1.847(16)	85.6(4)	78.7(2)	94.8(5)	99.3(7)
(19)	2.445(1)	1.771(1)	1.944(2)	1.487(2)	72.5(1)	76.1(0)	107.0(1)	100.4(1)
(20)	2.460(1)	1.745(2)	1.937(3)	1.494(5)	72.4(1)	74.9(1)	108.3(2)	98.7(2)
(21)	2.436(4)	1.743(5)	1.944(7)	1.494(8)	73.7(2)	75.6(2)	110.0(4)	98.5(4)
(22)		1.996(3)	1.996(3)	1.304(3)	69.5(1)	75.8(1)	109.7(2)	104.8(2)
(23)	2.249(5)	1.722(8)	1.927(13)	1.409(13)	72.3(4)	81.3(3)	104.2(7)	105.9(4)
(24)	2.878(1)	2.544(4)	2.203(13)	1.712(15)	76.1(4)	74.78(9)	94.5(4)	114.5(6)

85CB922, 85CB3748, 89HCA139, 90CB485, 91JOM(407)283, 92AG(E)316, 92JA9691, 92OM15, 93OM752). In most cases the four atoms of rings are coplanar or almost coplanar. The puckering was observed only for compounds (31) and (37) along the As—O axis (11.7°) and Ta—B axis (36.9°), respectively (Table 4).

Table 4 Geometric parameters of type (4) heterocycles.

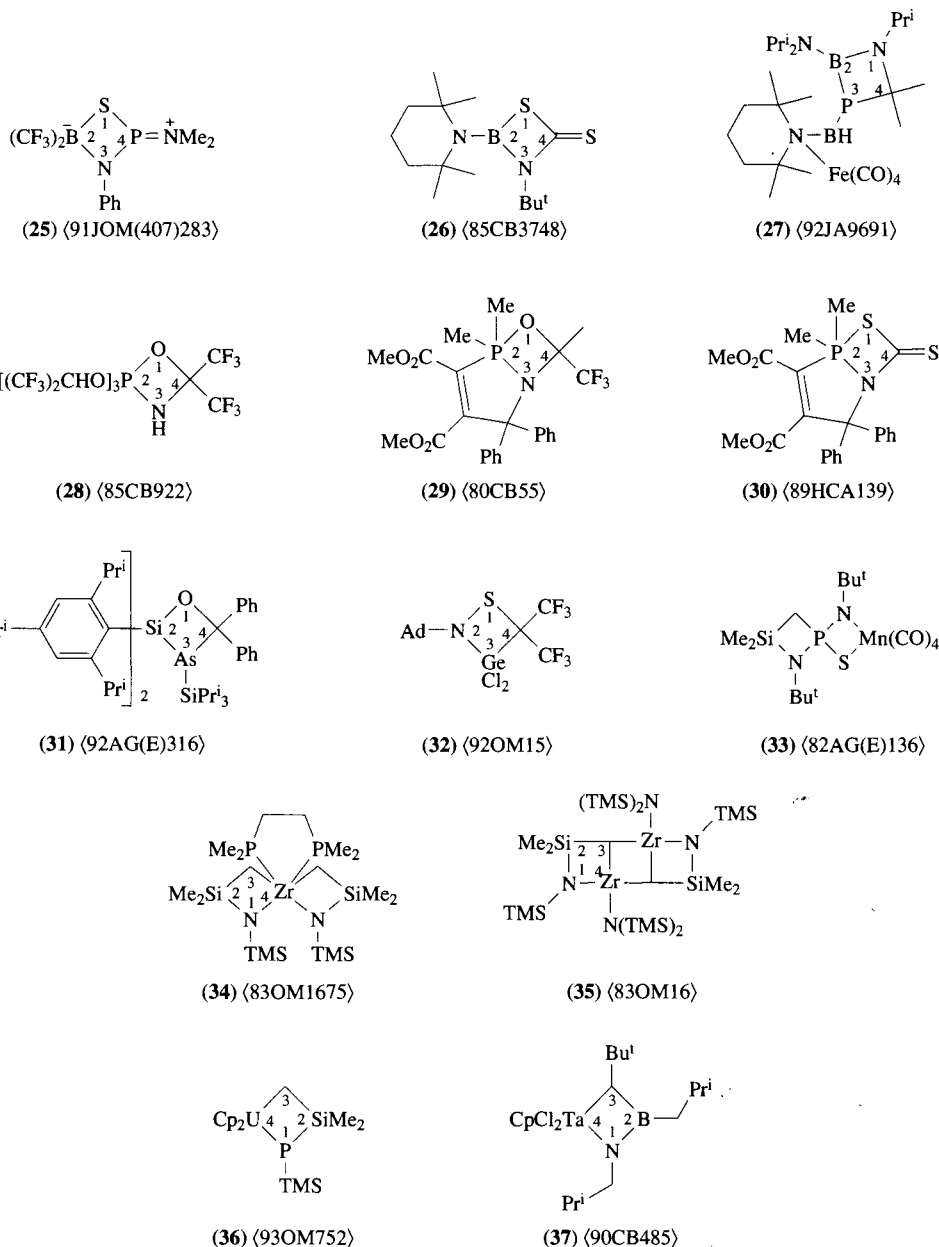
Compound	<i>r</i> (Å)				Angles (°)			
	(1-2)	(2-3)	(3-4)	(1-4)	∠ 1	∠ 2	∠ 3	∠ 4
(25)	1.963(8)	1.557(9)	1.325(8)	1.747(7)	72.3(4)	85.8(4)	99.0(5)	102.8(5)
(26)	1.894(3)	1.452(3)	1.391(3)	1.777(3)	71.3(1)	91.9(1)	97.7(1)	99.2(1)
(27)	1.417(10)	1.964(8)	1.900(7)	1.493(9)				
(28)	1.710(3)	1.647(4)	1.411(6)	1.411(6)	93.7(2)	75.8(2)	96.3(3)	94.1(3)
(29)	1.811(3)	1.684(3)	1.482(6)	1.413(5)	94.3(2)	74.2(1)	97.2(2)	93.5(2)
(30)	2.531(1)	1.689(3)	1.397(4)	1.727(3)	71.9(1)	69.15(9)	113.4(2)	105.4(2)
(31)	1.688(4)	2.382(2)	2.057(7)	1.450(8)	105.8(3)	82.5(1)	68.6(2)	101.0(4)
(32)	1.787(4)	1.813(3)		1.819(4)	89.3(2)	96.9(2)	82.9(2)	89.4(2)
(34)	1.749(2)	1.843(3)	2.324(3)	2.091(2)				76.30(10)
	1.741(2)	1.835(3)	2.309(3)	2.084(2)				76.27(9)
(35)	1.790(1)	1.870(2)	2.160(2)	2.040(1)	92.9(6)	98.1(6)	87.0(6)	81.9(5)
	1.760(1)	1.880(2)	2.160(2)	2.070(1)	92.6(4)	99.0(6)	86.6(5)	81.6(4)
(36)	2.234(9)	1.888(22)	2.415(20)	2.656(6)	82.2(3)	102.4(7)		78.7(5)
(37)	1.481(24)	1.583(26)	2.081(11)	2.159(12)	87.7(8)	103.1(9)	87.9(8)	68.9(4)

1.39.2.3 Molecular Spectra

1.39.2.3.1 NMR Spectroscopy

The general character of the 1,3,2-diazaphosphetidine derivatives has been studied (<87CB1713, 89PS(41)419>). For compounds (13) only one doublet is observed in the region 2.53–2.73 ppm for the ¹H resonances of the methyl groups at room temperature. This fact is the result of the rapid exchange of the axial and equatorial positions on the NMR time scale. The ³¹P chemical shifts of phosphoranes (13) are within the 56–71 ppm interval. Only for iodophosphorane (13b) is the δ³¹P signal markedly displaced upfield if compared with that of the chloro derivative (13c). This is in agreement with the findings for other iodophosphoranes (Table 5). The ¹H NMR spectral data of dispirocyclic cyclodiphosphazanes (38) are presented in Table 6.

In the ²⁹Si NMR spectra, the asymmetrical 1,2,3-oxadisiletanes showed two resonances, both falling between –7 ppm and 34 ppm (<91OM3466, 93OM2177>). For a compound with R¹ = R² = Me having ²⁹Si resonances at 17.08 ppm and 19.88 ppm a two-dimensional ²⁹Si-¹H correlation experiment was performed. It has been shown that the more downfield resonance was due to the silicon adjacent



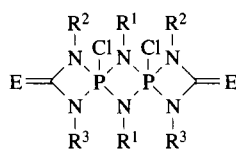
to the oxygen atom. The $^1J(^{29}\text{Si}-^{29}\text{Si})$ values are closer to the corresponding values of organodisilanes, than of three- and four-membered heterocycles derived from tetramesityldisilene (Table 7).

The ^1H , ^{19}F , and ^{31}P NMR data of 1-oxa-2 λ^5 -phospha-3-azetidines are given in Table 8. Due to a slow ligand exchange at the phosphorus atom the ^{19}F NMR spectrum of spiro-compound with dioxaphospholane ring exhibits eight magnetically nonequivalent CF_3 groups $\langle 81CB3609 \rangle$. At the same time for compounds with $\text{R}^2 = \text{F}$, $\text{OCH}(\text{CF}_3)_2$ the axial and equatorial positions are not distinguished at room temperature $\langle 85CB922 \rangle$.

The formation of 1-aza-2-bora-4-tantalet-3-ines from 1-aza-2-bora-4-tantaletidines by means of HCl elimination was confirmed by the comparison of ^1H , ^{11}B and ^{13}C NMR data (Table 9) $\langle 90CB485$, $93CB1571 \rangle$. The signal of the ring proton appears only in 1-aza-2-bora-4-tantaletidine spectra. The chemical shift of the ring carbon is transformed from a doublet to a singlet and shifted downfield by 140–150 ppm passing from the saturated compound to the carbene-tantalum cyclic complex. The double character of the $\text{Ta}=\text{C}$ bond was confirmed also by the upfield shifts of Cp -group $\delta^{13}\text{C}$ and $\delta^{11}\text{B}$ signals in NMR spectra of azaboratantalet-3-ines.

Table 5 Proton and ^{31}P NMR and IR data of 4-R-1,3,5,7-tetramethyl-1,3,5,7-tetraaza-4 λ^5 -phosphaspiro[3.3]heptane-2,6-diones (**13**).

<i>R</i>	$\delta^1\text{H}$ (ppm)	$\delta^{31}\text{P}$ (ppm)	^3J (<i>P—H</i>) (Hz)	$\nu_{\text{C=O}}$ (cm^{-1})
Cl	2.67	−56.0	17.0(NMe)	1770
I	2.70	−119.1	16.7(NMe)	1770
OMe	2.60	−57.0	15.5(NMe)	1765
	3.58		19.6(OMe)	
OPh	2.64	−61.1	15.5(NMe)	1760
	7.21			
SMe	2.70	−56.0	13.5(NMe)	1773
	2.15		19.9(SMe)	
SPh	2.56	−59.0	12.4(NMe)	1760
	7.29			
NMe ₂	2.53	−57.5	12.8(NMe)	1743
	2.48		13.0(NMe ₂)	
N ₃	2.73	−66.2	15.0(NMe)	1769
N=PMe ₃	2.61	−71	14.8(NMe)	1727
	1.55	+15	14.8(PMe ₃)	

Table 6 Proton NMR and IR data of cyclodiphosphazanes.

(38)

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>E</i>	$\delta^1\text{H}$ (ppm)			Stretching frequencies (cm^{-1})		
				<i>Me</i>	<i>Arom.</i>	<i>NH</i>	<i>C=X</i>	<i>P—Cl</i>	<i>P—N—H</i>
Ph	Ph	Ph	O		7.3		1775	515	
<i>p</i> -ClC ₆ H ₄	Ph	Ph	O		7.6		1775	515	
<i>p</i> -MeC ₆ H ₄	Ph	Ph	O	2.2	7.7		1775	515	
<i>p</i> -MeOC ₆ H ₄	Ph	Ph	O	3.5	6.9		1780	515	
Ph	Ph	Ph	S		7.2		1130	515	
<i>o</i> -ClC ₆ H ₄	Ph	Ph	S		7.4		1125	525	
<i>p</i> -ClC ₆ H ₄	Ph	Ph	S		7.3		1125	515	
<i>p</i> -MeC ₆ H ₄	Ph	Ph	S	2.5	7.5		1125	515	
<i>p</i> -MeOC ₆ H ₄	Ph	Ph	S	3.6	7.0		1130	500	
Ph	H	H	S		7.2	9.5	1075	500	2600
<i>o</i> -MeC ₆ H ₄	H	H	S	2.0	7.2	8.0	1110	500	2550
<i>p</i> -ClC ₆ H ₄	H	H	S		7.2	9.3	1095	500	2600
<i>p</i> -MeOC ₆ H ₄	H	H	S	3.7	7.0	7.8	1160	500	2550
Ph	H	Ph	S		7.2	6.8	1170	500	2600
<i>o</i> -ClC ₆ H ₄	H	Ph	S		7.3	8.6	1170	530	2600

1.39.2.3.2 IR Spectroscopy

Among the four-membered heterocyclic compounds with three heteroatoms in the ring special IR spectroscopic investigations have been performed for cyclization products of urea and thiourea derivatives with phosphorus compounds, 1,3,2-diazaphosphetidines <87CB1713, 89PS(41)419, 91ZOB638>. The stretching $\nu_{\text{C=O}}$ frequencies of 1,3,5,7-tetramethyl-1,3,5,7-tetraaza-4 λ^5 -phosphaspiro[3.3]heptane-2,6-diones are within the 1770–1727 cm^{-1} region (Table 5) <87CB1713>. The characteristic absorption bands of cyclodiphosphazanes (**38**) are summarized in Table 6. Some problems of the chlorotropic tautomerism of 2,2,2,4-tetrachloro-1,3,2-diazaphosphetidines have been studied using IR spectroscopy <91ZOB638>.

Table 7 Silicon-29 NMR spectra of 1,2,3-oxadisiletanes.

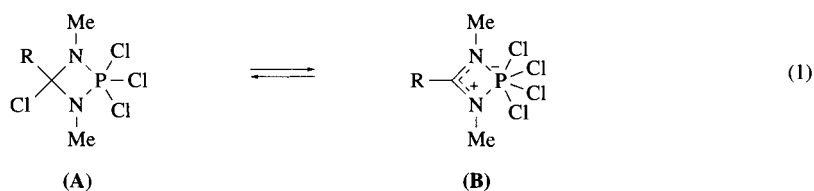
R^1	R^2	$\delta^{29}\text{Si}$, ppm	
Me	Me	17.08 (Si—C)	19.88 (Si—O)
		$J(^{29}\text{Si}-^{29}\text{Si}) = 84 \text{ Hz}$	
Et	Et	21.25	21.03
Pr ⁱ	Pr ⁱ	17.05	34.08
Ph	Ph	22.93	23.61
Bu ⁿ	H	14.55	24.86
Ph	H	15.69	22.52
CH ₂ =CH	H	14.41	25.59
CH ₂ =CH	Me	21.07	23.99
CH ₂ =CH	Et	21.68	25.19
<ULE ID = 001>	Me	14.99	24.37
H ₂ C=		-2.37	23.96
Me ₂ C=		-7.37	22.19
		$J(^{29}\text{Si}-^{29}\text{Si}) = 86 \text{ Hz}$	
Ph ₂ C=		-0.67	26.06
<ULE ID = 002>		0.21	25.80
<ULE ID = 003>		20.25	24.08
		$J(^{29}\text{Si}-^{29}\text{Si}) = 89 \text{ Hz}$	

Table 8 Proton, ¹⁹F, and ³¹P NMR data of 1-oxa-2λ⁵-phospha-3-azetidines.

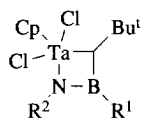
R^1	R^2	$\delta^1\text{H}$ (ppm)		$\delta^{19}\text{F}$ (ppm)		$\delta^{31}\text{P}$ (ppm)
		$R^1\text{N}$	OCH	$\text{OCH}(\text{CF}_3)_2$	$\text{C}(\text{CF}_3)_2$	
H	$\text{OCH}(\text{CF}_3)_2$	7.52	5.94	-76.00	-81.20	-60.8
Me	F	2.78	5.04	-76.96	-79.42	-57.5
Me	$\text{OCH}(\text{CF}_3)_2$	3.80	6.55	-74.57	-77.67	-58.9
Bu ⁱ	F	1.21	4.86	-76.23	-76.23	-62.3
H	$R^2R^2 = \text{<ULE ID = 001>}$	7.40	5.18	-73.86	-78.58	-40.3

1.39.2.4 Chlorotropic Tautomerism

The chlorotropic tautomerism in 1,3,2-diazaphosphetidines has been studied by IR <91ZOB638>, UV <91ZOB638>, ¹³C and ³¹P NMR <83ZOB932, 84ZOB2207, 84ZOB2477>, ³⁵Cl nuclear quadrupole resonance <89MI 139-01> spectroscopy (Equation (1)).



In the ¹³C and ³¹P NMR spectra of compounds with R = CF₃, CCl₃ two signals of phosphorus atoms (penta- and hexacoordinated) and two signals of carbon atoms (C_{sp^3} and C_{sp^2}) were observed.

Table 9 Proton, ^{11}B , and ^{13}C NMR data for 1-aza-2-bora-4-tantaletidines.

R^1	R^2	δ^1H (ppm)			$\delta^{11}B$ (ppm)	$\delta^{13}C$ (ppm)		
		3-H	3-Bu ^t	Cp		3-C	3-Bu ^t	Cp
Et	Bu ^t	2.59	1.22	6.04	43.6		31.6; 37.6	115.6
Et ^a	Bu ^t	—	1.23	5.90	30.9	244.8	33.1; 46.5	105.4
Pr	Bu ^t	2.81	1.13	6.26	36.8	100.2	31.3; 37.4	117.6
Pr ^a	Bu ^t	—	1.25	5.84	32.6	246.4	33.6; 46.3	105.3
Bu	Bu ^t	2.65	1.26	6.06	44.2	100.3	31.4; 37.5	117.6
Bu ^a	Bu ^t	—	1.27	5.84	31.7	244.9	33.1; 46.4	105.4
Pr ⁱ	Bu ^t	2.56	1.24	6.06	42.4	98.1	36.8; 40.2	117.8
Pr ^{ia}	Bu ^t	—	1.29	5.83	30.7	250.1	33.3; 46.5	105.4
Ph	Bu ^t	2.91	1.10	6.09	45.0	98.7	31.6; 37.3	118.1
Ph ^a	Bu ^t	—	1.00	5.86	33.4	246.1	33.1; 46.4	105.6
Pr ⁱ	Pr ⁱ	3.28	1.29	5.89	38.5	105.1	34.3; 40.2	114.5
Pr ^{ia}	Pr ⁱ	—	1.31	5.82	29.3		33.7; 46.2	105.4
Bu ⁱ	Bu ⁱ	2.54	1.13	6.66	40.9	100.3	31.4; 37.5	117.6
Bu ^{ia}	Bu ⁱ	—	1.35	5.77	31.3	239.7	33.9; 45.3	105.5
Bu ^t CH ₂	Bu ^t CH ₂	2.54	1.29	6.10	40.1	100.1	34.9; 37.4	118.4
Bu ^t CH ₂ ^a	Bu ^t CH ₂	—	1.30	6.12	29.3	241.6	33.8; 45.3	105.7
TMS-CH ₂	TMS-CH ₂	2.59	1.17	6.59	35.9	107.9	33.7; 38.9	115.6
Bu ^t	Me	4.28	1.12	6.41	38.7	135.6	34.2; 43.6	114.6
Bu ^t	Pr ⁱ	4.52	1.34	5.77	39.3	106.8	33.3; 44.2	114.3
Bu ^t	TMS	4.36	1.17	5.90	51.1	107.0	34.2; 44.8	115.4

^aFor 1- R^2 -2- R^1 -3-(*t*-butyl)-4-chloro-4-cyclopentadienyl-1-aza-2-bora-4-tantalet-3-ine.

The position of the equilibrium would be shifted towards (A) when the electron-acceptor ability of R is increased ($\text{CCl}_3 < \text{CF}_3$) <83ZOB932>. According to IR and UV data the compound with R = Ph in solid state and in solution ($\text{ClCH}_2\text{CH}_2\text{Cl}$, MeCN) has a system (B) with hexacoordinated phosphorus <91ZOB638>. Polar solvents favor the formation of tautomer (B), for example the (A):(B) ratio for compound with R = CCl_3 is 60:40 in CD_3CN , 84:16 in $\text{C}_6\text{H}_4\text{Cl}_2$ -*o*, 87:13 in C_6D_6 , and 97:3 in *c*- C_6D_{12} , all at 30°C. The increase in temperature shifts the equilibrium in solution towards the (A) form. The (A):(B) ratio is 66:34 in CD_3CN at 50°C (R = CCl_3) <83ZOB932>.

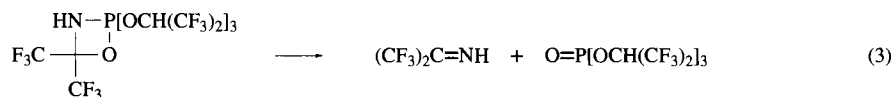
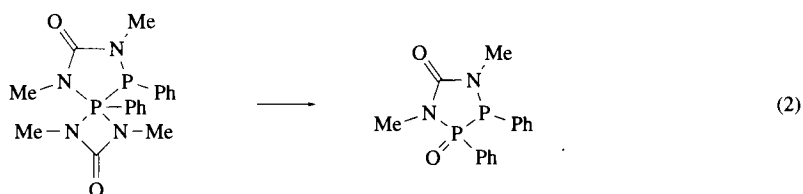
1,3-Dimethyl-2,2,2,4-tetrachloro-4-trichloromethyl-1,3,2-diazaphosphetidine (A; R = CCl_3) is stable at 77 K in crystalline state. The elevation of temperature leads to chlorotropic transformation and the coexistence of (A) and (B) forms in crystal <89MI 139-01>.

1.39.3 REACTIVITY OF FOUR-MEMBERED RINGS WITH THREE HETEROATOMS

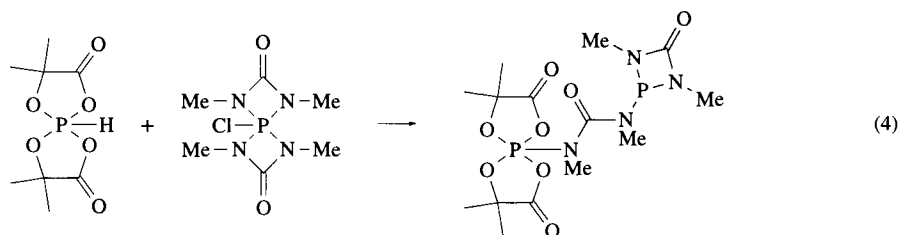
1.39.3.1 Cleavage of Four-membered Rings with Three Heteroatoms

2,2,4,4-Tetramethyl-1,2,4-oxadigermetane and its thia analogue <85JOM(282)315, 87OM659> are relatively stable in solution at room temperature, but easily dissociate upon heating. The decomposition reaction proceeds with the formation of dimethylgermanone (or thione) $\text{Me}_2\text{Ge}=\text{Y}$ and dimethylgermaethylene $\text{Me}_2\text{Ge}=\text{CH}_2$ intermediates. Photolysis of 1,2,3-oxa- and 1,2,3-thiadisiletanes in the presence of ethanol gives the trapped products corresponding to silenes $\text{R}^1_2\text{Si}=\text{CR}^2\text{R}^3$ and silanones (silanthiones), which have been postulated to arise from retro [2 + 2] cleavage of the rings <91OM827, 91OM3466>. 1-Oxa-2-sila-3-arsetane (31) under drastic conditions (160°C, 10 h) also decomposes into silanone and arsaethylene <92AG(E)316>.

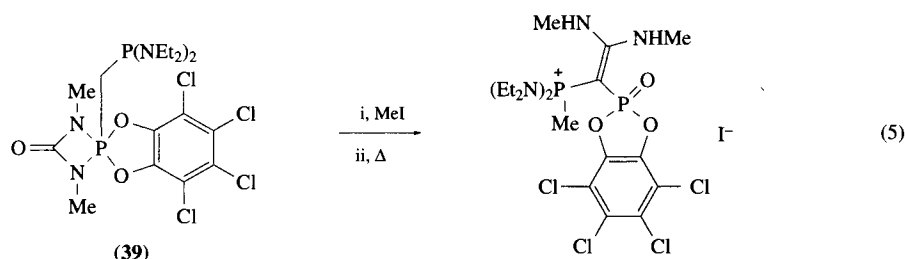
1,3-Diaza-2-phosphetidine <81CB2132> and 1-oxa-2-phospha-3-azetidine <85CB922> rings have also been decomposed thermally (Equations (2) and (3)).



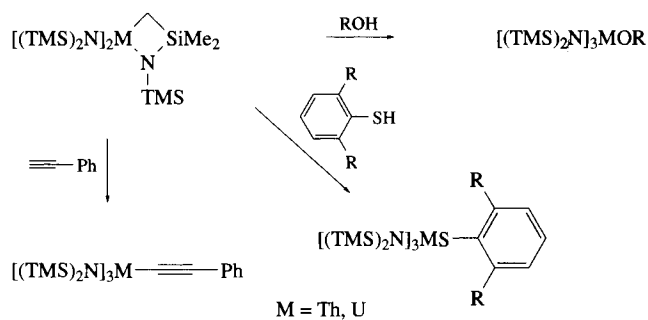
Reaction of hydridophosphorane with 4-chloro-1,3,5,7-tetramethyl-1,3,5,7-tetraaza-4 λ^5 -phosphaspiro[3.3]heptane-2,6-dione in the presence of Et₃N gave the compound with a urea bridge between two phosphorus atoms (Equation (4)) <90T3527>.



The methylenephosphinophosphorane (**39**) was methylated by MeI, forming the stable phosphonium salt in crystalline form which rearranges under heating with cleavage of the four-membered heterocycle (Equation (5)) <93POL435>.



The metal—carbon bond of the 1-aza-2-sila-4-metalletidines (M = Th, U) reacts with alcohols <85CC914, 86TL1497>, phenols <85CC914>, thiophenols <93IC772> and alkynes <85CC914> under mild conditions to produce the ring-opened compounds (Scheme 1).

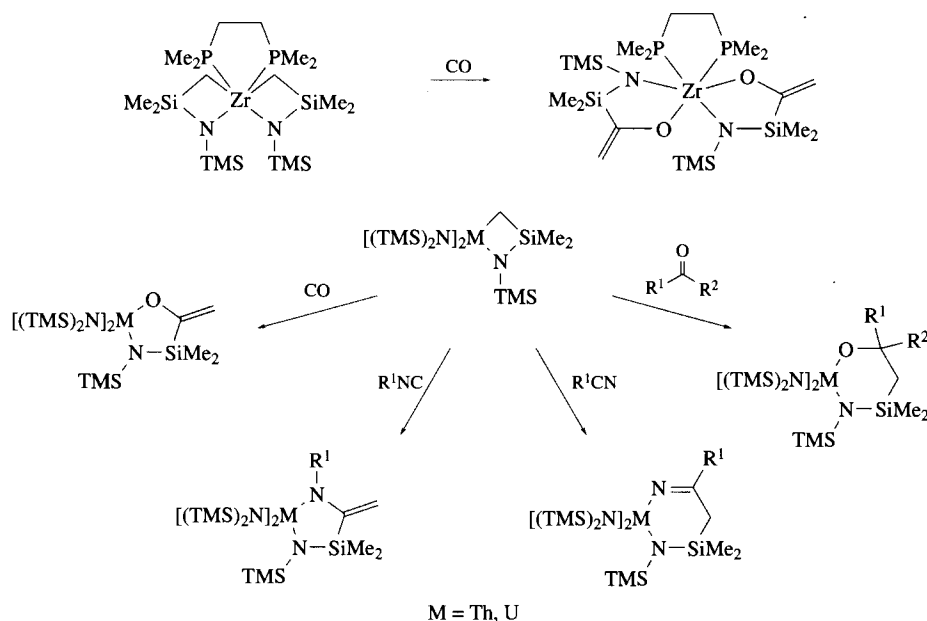


Scheme 1

1.39.3.2 Ring Expansion and Ring Contraction Reactions

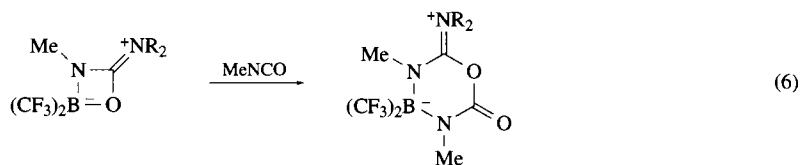
The polarity of the actinide—carbon bond and the ring strain inherent in the four-membered ring of 1-aza-2-sila-4-metalletidines enhance significantly their reactivity in ring expansion reactions

<87ICA(139)171>. Carbon monoxide <81JA4063, 83OM1675> and isocyanides <81JA4063, 85CC914> insert easily into the M—CH₂ bond to give five-membered heterocycles (Scheme 2). A fast and quantitative insertion of aldehydes, ketones or cyanides <81JA4063, 85JOM(288)C1, 89JOM(369)171> proceeds with the formation of six-membered heterocycles (Scheme 2).

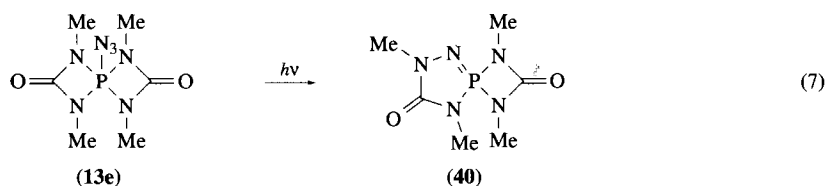


Scheme 2

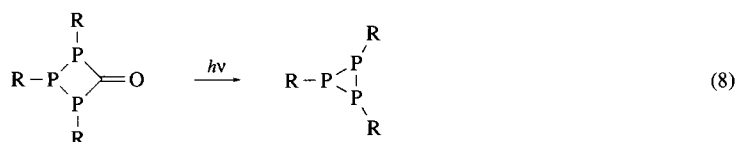
1-Oxa-2-bora-3-azetidines with an imonium group on the carbon atom of the heterocycle incorporate methylisocyanate to form six-membered heterocycles (Equation (6)) <91JOM(407)283>.



Photolysis of phosphorane azide (**13e**) led to the nitrogen insertion into one of the 1,3,2-diazaphosphetidine rings to give intermediate product (**40**), which dimerized (Equation (7)) <83PS(18)221>.



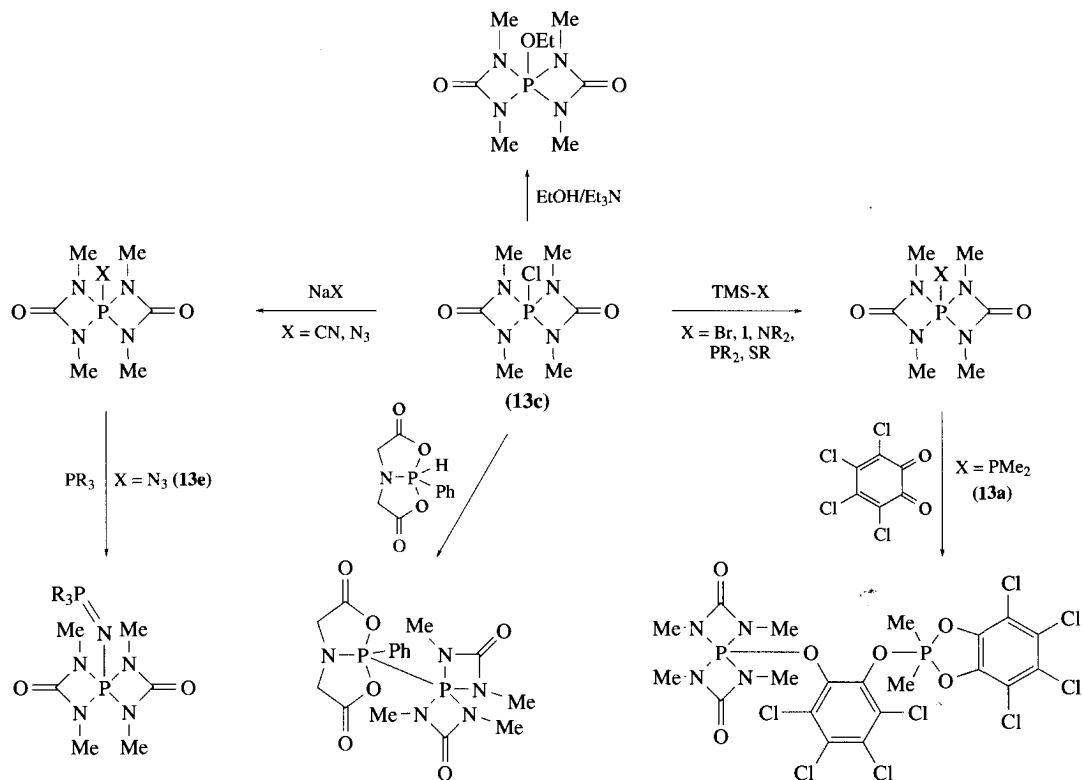
Tris(*t*-butyl)triphosphetanone was decarbonylated with sunlight (Equation (8)) <83CB2371>.



1.39.3.3 Reactions of Heteroatoms and Substituents on Heteroatoms

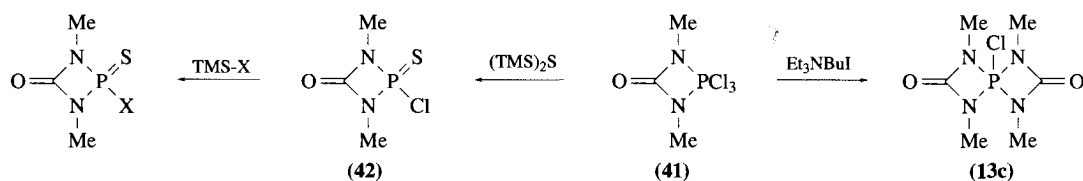
The chloride atom at the phosphorus in phosphorane (**13c**) easily enters into various exchange reactions with NaCN <91PS(62)139>, NaN₃ <87CB1713>, TMS-Br <91PS(62)139>, TMS-I <88AG(E)1562>.

91PS(62)139), TMS-NR₂, TMS-SR <87CB1713>, TMS-PR₂ <83ZN(B)702>, EtOH/Et₃N <87CB1713> or hydridophosphorane <90T3527>. The azide group of (13e) undergoes a Staudinger-type reaction with R₃P to give the product with an N=PR₃ group at the phosphorus atom <86PS(26)193, 87CB1713>. The reaction of compound (13a) containing the λ⁵P—λ³P bond with tetrachloro-*o*-quinone leads not only to the oxidative addition of the *o*-quinone to λ³P, but also to the insertion of the second *o*-quinone molecule into the P—P bond as well (Scheme 3) <90ZN(B)1177>.



Scheme 3

1,3-Dimethyl-2,2,2-trichloro-1,3-diaza-2-phosphetidinone (41) reacted with Et₃NBuI in benzene to produce the spiro compound (13c) in 90% yield <87ZOB2397>. The reaction of (TMS)₂S with trichlorophosphorane (41) gave the thio derivative (42), its chlorine atom was substituted by the action of TMS-X (X = NR₂, OMe, SMe) (Scheme 4) <90ZN(B)1398>.

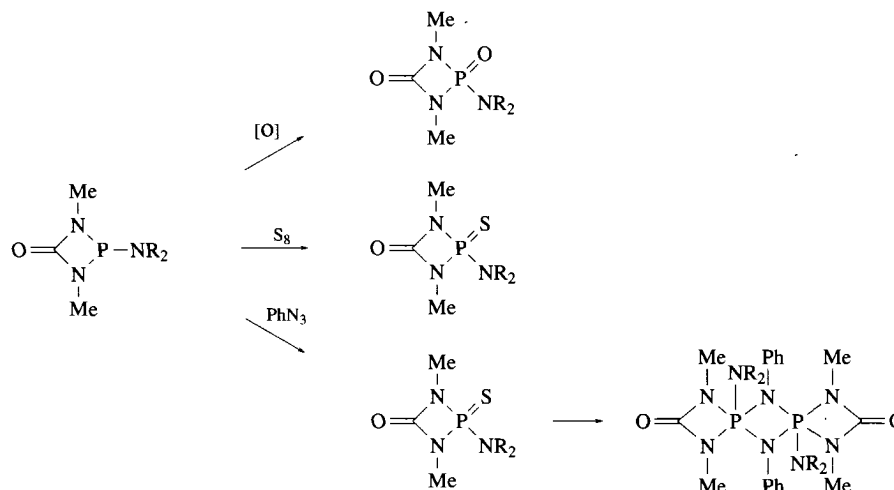


Scheme 4

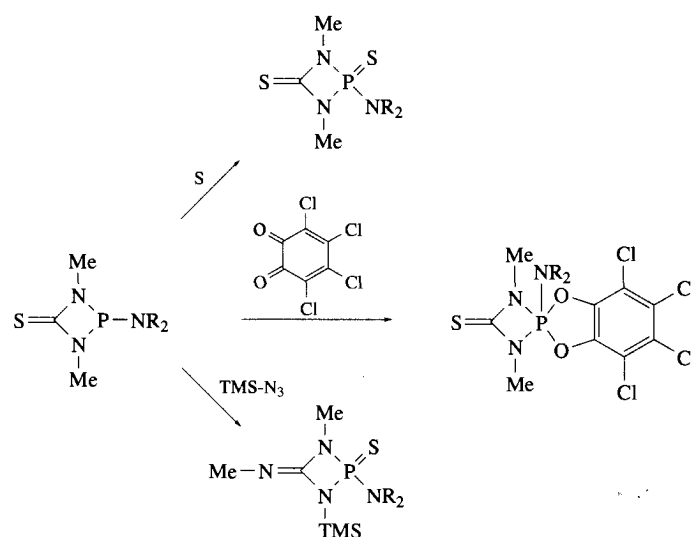
The reaction of diaza-λ³-phosphetidinones with NO₂, (TMS-O)₂ <90CB1307>, S₈ <90ZN(B)1398>, and PhN₃ <90PS(53)193> proceeded as the oxidation of the phosphorus atom. 2-Phenylimino-diazaphosphetidinones, excepting the bulky dicyclohexylamino derivative, are unstable, and dimerize rapidly (Scheme 5).

1,3-Diaza-2-phosphetidine-4-thione derivatives undergo oxidation with TMS-N₃, tetrachloro-*o*-benzoquinone and elemental sulfur. With TMS-N₃ a rearrangement was observed in addition to the thionation of the phosphorus atom (Scheme 6) <90CB289, 92PS(73)195>.

The treatment of 2,4-diamino-1,2λ³,4λ³-azadiphosphetidines (43) with one or five equivalents of MeI gave mono- and diphosphonium salts, respectively <86ZOB221, 86ZOB1988>. The latter with NaH in CH₂Cl₂ yielded iminophosphonium iodide. The chlorination of (43) with AcCl gave unstable 2,4-



Scheme 5



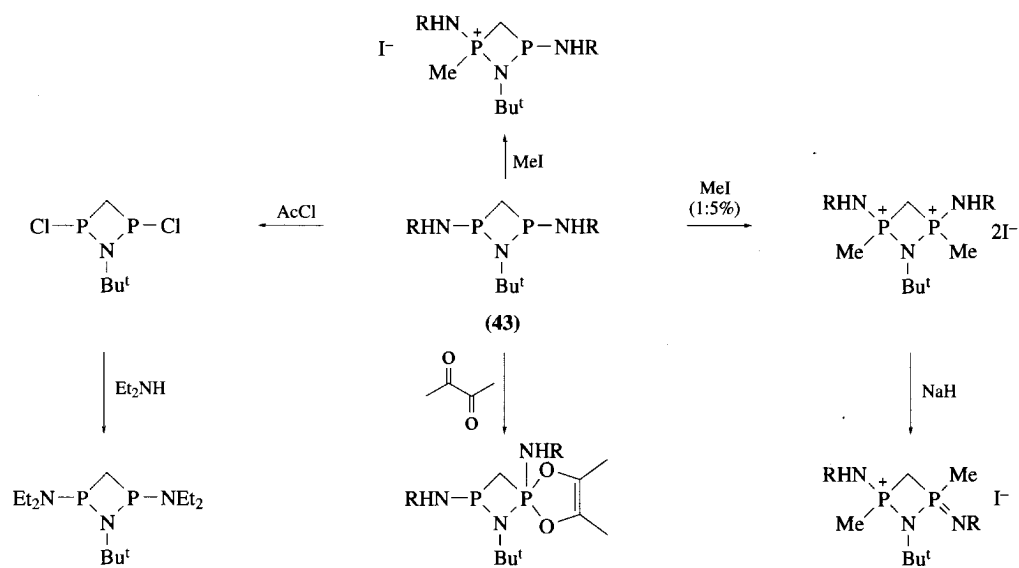
Scheme 6

dichloro-1,2 λ^3 ,4 λ^3 -azadiphosphetidine, which was aminated with Et₂NH $\langle$ 85ZOB1199 $\rangle$. The oxidation of the phosphorus atom was observed in the reaction with diacetyl (Scheme 7) $\langle$ 85ZOB2618 $\rangle$.

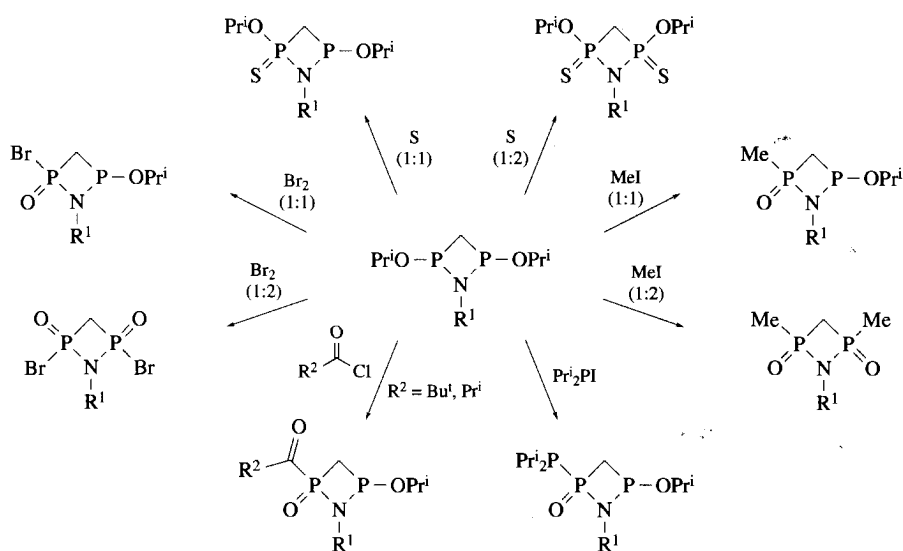
1,2,4-Azadiphosphetidines containing one or two tetracoordinated phosphorus atoms were obtained by alkylation, acylation, bromination, phosphorylation, and thionation of 2,4-dialkoxy-1,2 λ^3 ,4 λ^3 -azadiphosphetidines (Scheme 8) $\langle$ 86ZOB269 $\rangle$.

The availability of the four-membered azadiphosphetine ring (**44**) offers a rare opportunity to study the relative donor properties of the two- and three-coordinated phosphorus atoms within the same ring system $\langle$ 93JOM(461)61 $\rangle$. The reaction of platinum(0) (R₃P)₂Pt(C₂H₄), tungsten(0) W(CO)₅(THF), and rhodium(I) (Ph₃P)₃RhCl complexes with (**44**) afforded the compounds, in which the azadiphosphetine ring is η^1 -bonded to metal through the two-coordinated phosphorus atom. In contrast to the above reactions, the treatment of two equivalents of (**44**) with dinuclear complexes [(Et₃P)₂M₂Cl₄] (M = Pd, Pt) gave the compounds involving an M—P bond on the three-coordinated phosphorus atom. Both phosphorus atoms have been coordinated to the platinum atoms by interaction of (**44**) with Pt₂Cl₄(PEt₃)₂ in a 1 : 1 ratio (Scheme 9).

The dimeric unit in (**35**) and its hafnium analogue are not cleaved by pyridine, as this Lewis base gives a 1 : 2 coordination complex. The diphosphine Me₂PCH₂CH₂PMe₂, however, reacts with the dimeric complexes at room temperature to give the spiro-compounds (Scheme 10) $\langle$ 83OM1675 $\rangle$.



Scheme 7

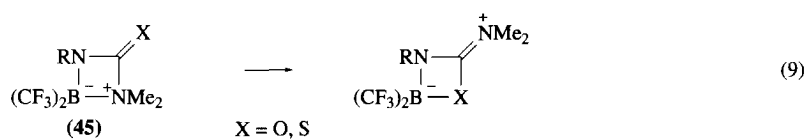


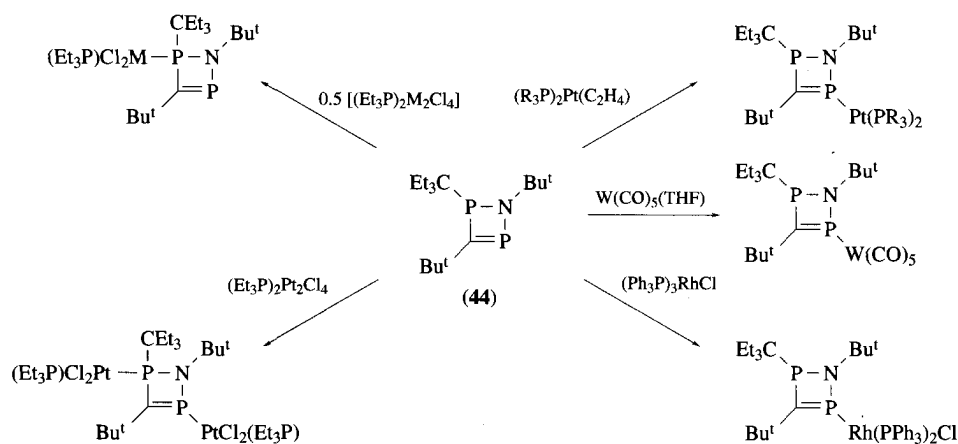
Scheme 8

Bis(trimethylsilyl)amino groups at the thorium and uranium atoms of 1-aza-2-sila-4-metalletidines were substituted by the action of cyclopentadienes $\langle 85CC914 \rangle$, the reaction with TMS-N_3 proceeds as an addition (Scheme 11) $\langle 81JA4063, 85CC914 \rangle$.

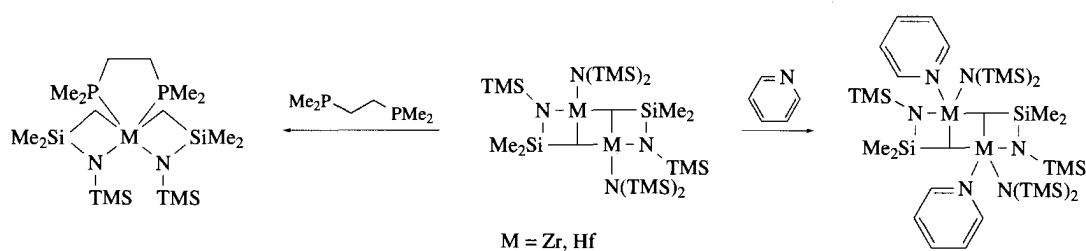
1.39.3.4 Rearrangement of the Ring

$[2 + 2]$ Cycloaddition products (45) rearrange at $\approx 60^\circ\text{C}$ to form imoniumoxa(thia)azaboretidines (Equation (9)) $\langle 91JOM(407)283 \rangle$.

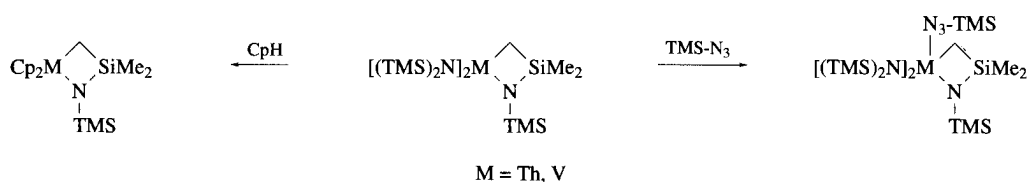




Scheme 9

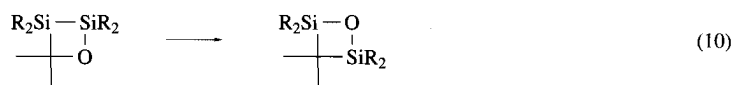


Scheme 10

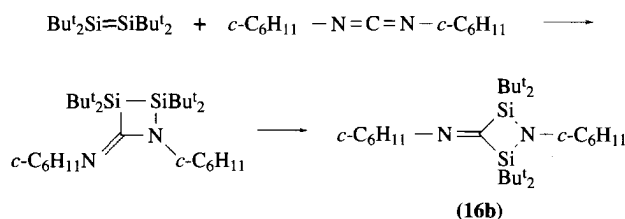


Scheme 11

The acetone adduct to disilene rearranges to 1-oxa-2,4-disiletane isomer under photolysis. This rearrangement may take place through the cleavage of the 1,2,3-oxadisiletane ring to silanone and silene followed by the ring closure in the opposite direction (Equation (10)) <83JA1070>.



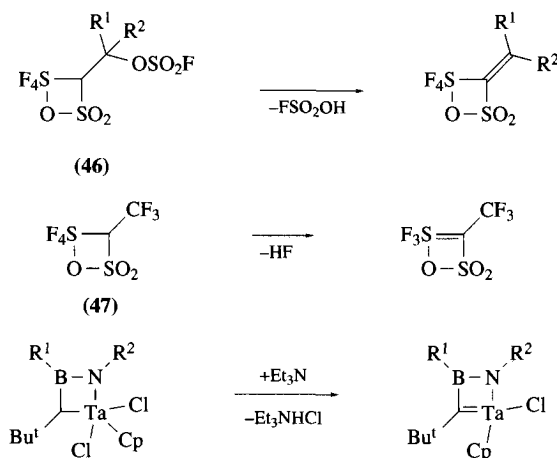
Photolysis of hexa-*t*-butyltrisilacyclopropane in the presence of dcc yields the 1,2,4-azadisiletidine (**16b**), presumably formed by the rearrangement of the [2 + 2] cycloaddition product of disilene to the C=N double bond of dcc (Scheme 12) <90CB1795>.



Scheme 12

1.39.3.5 Elimination Reactions

Elimination of FSO_2OH from oxadithietanes (**46**) affords 3-methylene-1,2,4-oxadithietanes $\langle 92\text{CB}557 \rangle$. HF elimination from oxadithietane (**47**) $\langle 92\text{CB}577 \rangle$ and HCl elimination from 4,4-dichloro-1-aza-2-bora-4-tantalidines $\langle 93\text{CB}1571 \rangle$ occurred within the four-membered ring (Scheme 13).



Scheme 13

1.39.4 SYNTHESIS

1.39.4.1 [2 + 2] Cycloaddition

The [2 + 2] cycloaddition reaction appears to be quite a general method for the construction of four-membered (1–4) type heterocycles. This method is applicable to the synthesis of symmetrical 1,2,4-oxadithietanes $\langle 92\text{CB}557 \rangle$, 1,2,4-thiadiazetidines $\langle 78\text{AG}722, 84\text{ZAAC}(518)197 \rangle$, 1,3,2-diazaboretidines $\langle 91\text{JOM}(407)283 \rangle$, 1,3,2-diazaphosphetidines $\langle 76\text{JOM}(116)\text{C}13, 77\text{ZN}(\text{B})845, 83\text{ZOB}525 \rangle$, 1,3,2-dioxasiletanes $\langle 89\text{AG}(\text{E})762 \rangle$, 1,3,2-dithiastannetanes $\langle 93\text{JA}2065 \rangle$, and 1,2,4-thiadisiletanes (Scheme 14) $\langle 84\text{DOK}(274)1106 \rangle$.

Disilenes undergo the cycloaddition reactions with substrates containing $\text{C}=\text{O}$ $\langle 83\text{JA}1070, 85\text{JOM}(282)305, 91\text{OM}3466, 93\text{OM}2177 \rangle$, $\text{C}=\text{S}$ $\langle 91\text{OM}827 \rangle$, $\text{C}=\text{N}$ $\langle 88\text{JOM}(338)\text{C}1, 90\text{CB}1795, 92\text{JOM}(423)329 \rangle$, and $\text{C}\equiv\text{N}$ $\langle 89\text{AG}(\text{E})95 \rangle$ bonds to afford novel 1,2,3-oxadisiletane, 1,2,3-thiadisiletane, 1,2,3-azadisiletidine and 1,2,3-azadisiletine compounds with two silicon atoms in the cycle (Scheme 15).

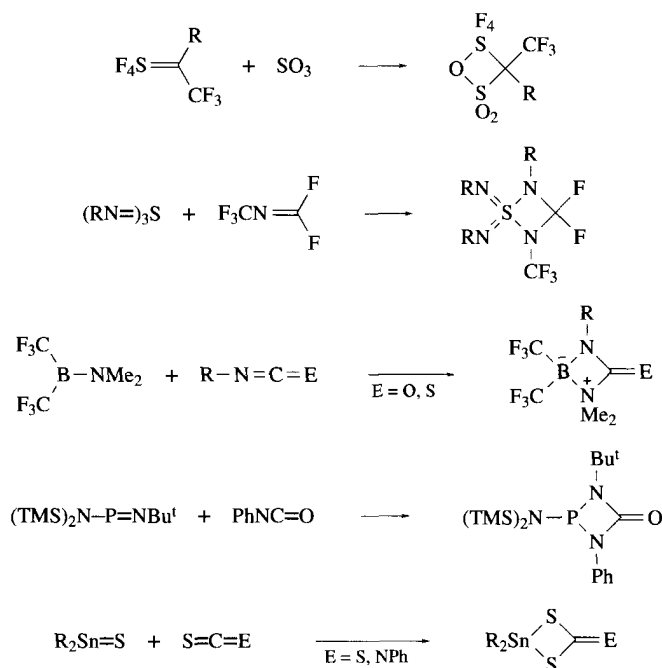
The interaction of Brook's acylsilane (**48**) with a twofold excess of Et_3GeLi in THF gives a 1 : 2 mixture of trisilacyclobutane (**6a**) and adamantoyladamantyl carbinol. It is suggested that the trisilacyclobutane skeleton is formed by the cycloaddition reaction between silene (**49**) and disilene (**50**) (Scheme 16) $\langle 93\text{JOM}(446)123 \rangle$.

Intermediate $\text{Me}_2\text{Si}=\text{C}(\text{TMS})_2$ with an $\text{Si}=\text{C}$ double bond reacts with azotrimethylsilane to produce 1,2,3-diazasiletidine (Equation (11)) $\langle 77\text{AG}343 \rangle$.

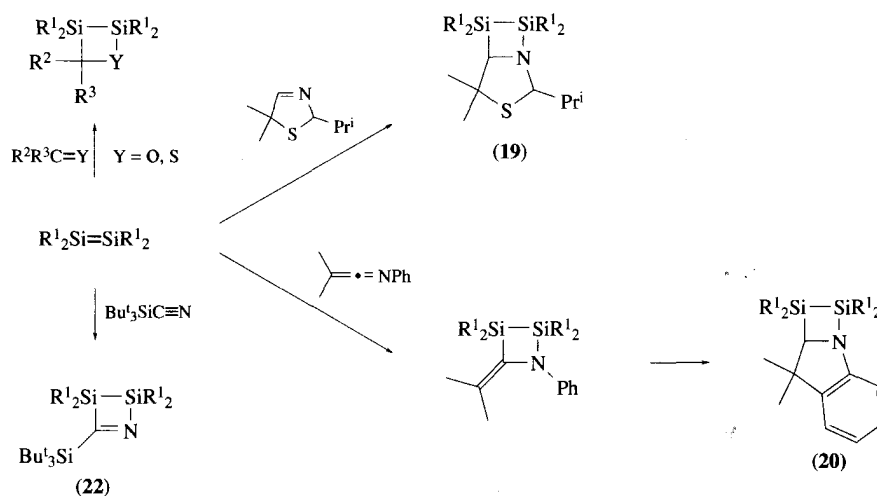


1,2,3-Oxadiphosphetane (**23**) is apparently formed from the formal [2 + 2] cycloaddition between the diphosphenyl complex of iron and hexafluoroacetone, but really the reaction proceeds via [2 + 3] cycloaddition and the subsequent rearrangement to a four-membered ring at -40°C (Scheme 17) $\langle 92\text{OM}2351, 94\text{OM}2194 \rangle$.

1,2,3-Phosphadistannetane (**24**) was obtained by cyclization of distannene with phosphalkyne $\text{Bu}^t\text{C}\equiv\text{P}$ $\langle 88\text{AG}(\text{E})838 \rangle$.



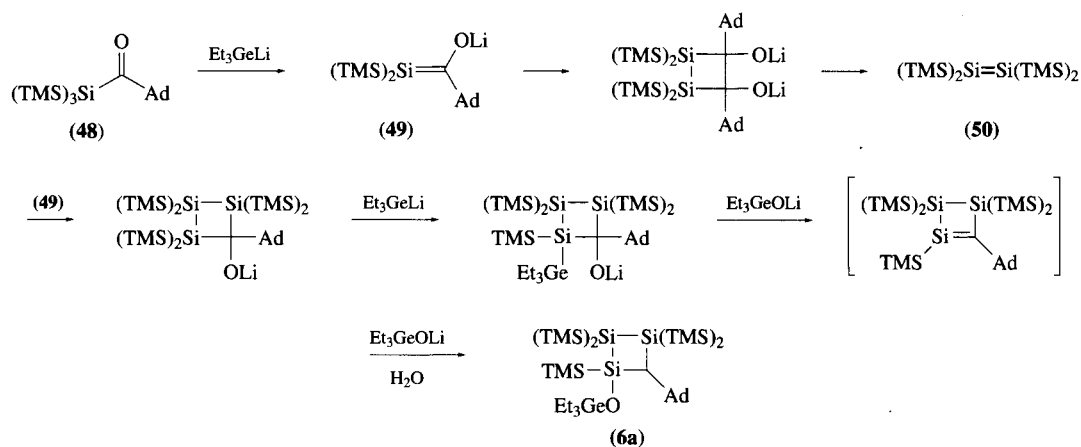
Scheme 14



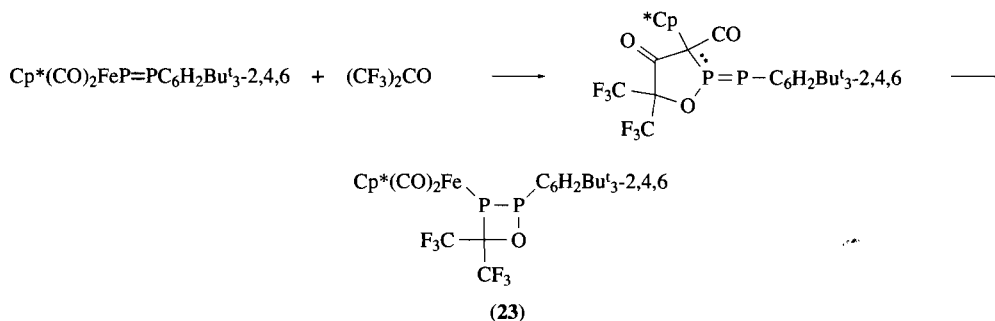
Scheme 15

Cycloaddition reactions of compounds containing the $N=Y$ double bond ($Y = S$ <84ZAAC(518)197>, $Y = P$ <78CB3747, 80CB55, 85CC1050, 89HCA139, 89ZOB278>, $Y = Si$ <91ZN(B)709>, $Y = B$ <85CB1724, 85CB3205, 85CB3748, 87CB863, 90CB485, 93CB1571>) with CO_2 , COS, CS_2 , CSe_2 , aldehydes, ketones, and methylene complexes of titanium and tantalum ($L_nM=CHR^3$) gave a variety of four-membered heterocycles with three different heteroatoms (Scheme 18).

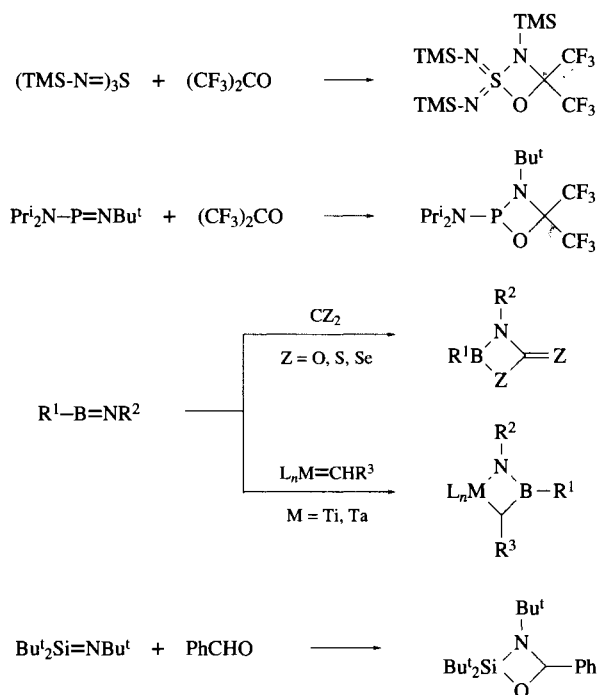
Similar reactions occur between arsanilidenesilene (2,4,6-Pr₃C₆H₂)₂Si=AsSi(Pr)₃ <92AG(E)316> or germaphosphenes Mes₂Ge=PR <91JOM(415)327> with aldehydes and ketones PhRC=O to give 1,2,3-oxasilarsetane (31) and 1,2,3-oxagermaphosphetanes, respectively. Oxo-complexes of molybdenum <87CC1610, 90OM2333>, tungsten <90OM2333>, rhenium <86AG(E)817, 86JOM(311)163>, and thio-complexes of tantalum <93CC851> and molybdenum <93IC3799> undergo net [2 + 2] cycloaddition of the M=O and M=S bonds across the C=N double bonds of PhNCO and tol-N=C=N-tol to produce 1-oxa(thia)-2-metalla-3-azetidines.



Scheme 16



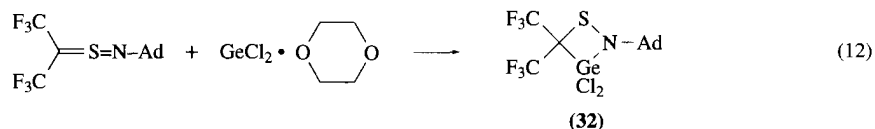
Scheme 17



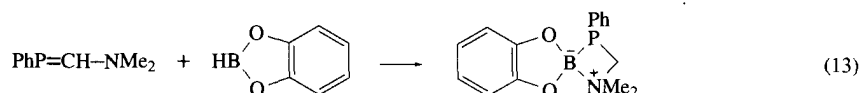
Scheme 18

1.39.4.2 [3 + 1] Cycloaddition

Germylation of compounds containing the fragment $C=S=N$ with dichlorogermylene at room temperature proceeds as [3 + 1] cycloaddition. The yield of 1-thia-2-aza-3-germetidine (**32**) is 42% (Equation (12)) <92OM15>.

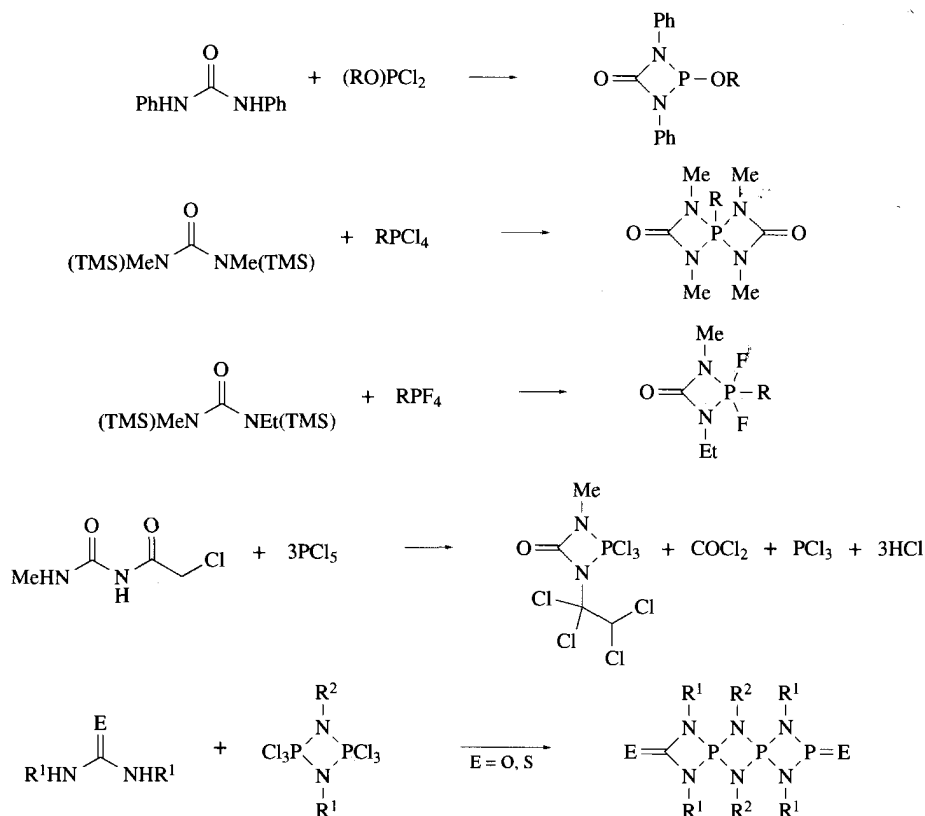


Hydroboration of [(dimethylamino)methylene]phenylphosphine $P=C$ double bond with boron derivative of pyrocatechol yields the four-membered ring (Equation (13)) <87IZV232>.



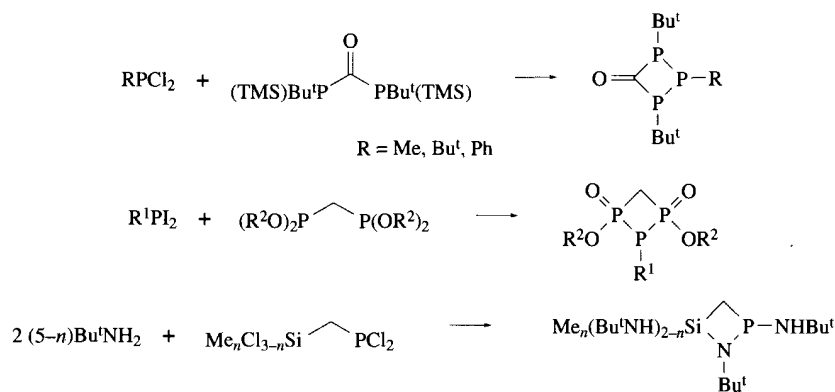
1.39.4.3 [3 + 1] Cyclocondensation

This method appeared to be the most fruitful for synthesis of (**2**) type compounds by the reaction between disubstituted methanes $R_2C(XE)_2$ with active E groups at heteroatoms X and primary amines, phosphorus compounds, Na_2S , metal derivatives (Me_2GeCl_2 , $\text{Fe}(\text{CO})_5$, $\text{Ru}_3(\text{CO})_{12}$, $(\text{Ph}_3\text{P})_2\text{PtC}_2\text{H}_4$). As a rule, 1,3,2-diazaphosphetidines were obtained by cyclization of the urea derivatives with RPhCl_2 <79CB1365>, $(\text{RO})\text{PCl}_2$ <81IZV2796>, R_2NPhCl_2 <92PS(73)195>, $(\text{Et}_2\text{N})_3\text{P}$ <83CB610>, Me_2PCl_3 <76CB3581>, RPF_4 <81PS(10)87>, RPhCl_4 <90ZN(B)1407>, PCl_5 <89ZOB715, 91IZV187, 92ZOB306>, and hexachlorocyclodiphosphazanes <87PS(29)239, 89PS(41)419> (Scheme 19).



Scheme 19

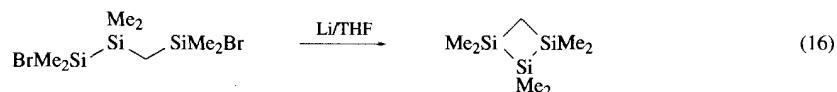
<80ZOB228, 83CB2371>) and (4) type (1-aza-2-phospha-4-siletidines <93IZV990>) compounds (Scheme 22).



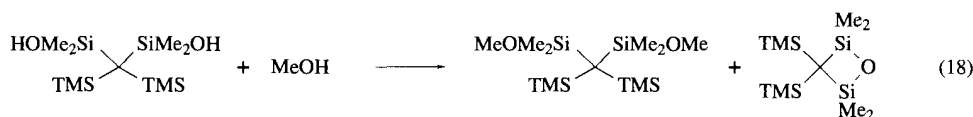
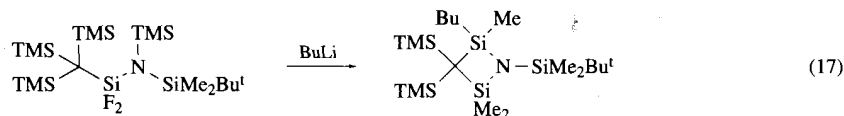
Scheme 22

1.39.4.4 Intramolecular Cyclocondensation

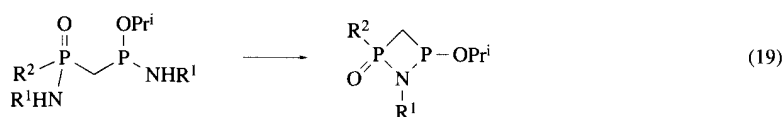
The trisiletane heterocycle was obtained by adding THF to a suspension of lithium in 1,1,2,2-tetramethyl-1-bromo-2-(dimethylbromosilylmethyl)disilane at 25°C (Equation (16)). Hexamethyltrisiletane was unstable and decomposed on isolation <81ZAAC(473)59>.



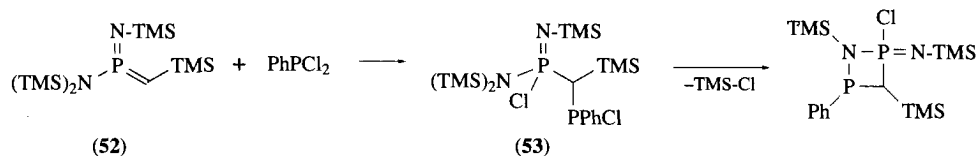
Treatment of difluoro(tris(trimethylsilyl)methyl)(trimethylsilyl)(*t*-butyldimethylsilyl)amino silane with BuLi produced an 82% yield of 1,2,4-azadisiletidine (Equation (17)) <85JOM(291)277>. Disilanol $(\text{TMS})_2\text{C}(\text{SiMe}_2\text{OH})_2$ with methanol gives a mixture of di(methoxysilyl)methane and cyclic 1-oxa-2,4-disiletane (Equation (18)) <88JOM(340)283>.



1,2,4-Azadiphosphetidines were also synthesized by intramolecular cyclization of the bis(alkylamides) of phosphorus-containing acids (Equation (19)) <85ZOB331, 87ZOB949>.

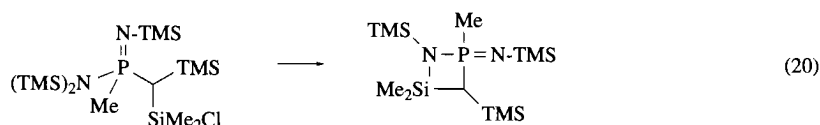


The treatment of (amino)(imino)(methylene)phosphorane (**52**) with dichlorophenylphosphine gave the P^V-C-P^{III} system via addition over the $P=C$ bond. The linear compound (**53**) eliminated $TMS-Cl$ to afford the cyclic product with the $P^V-NP^{III}-C$ ring structure (Scheme 23) <89IC899>.

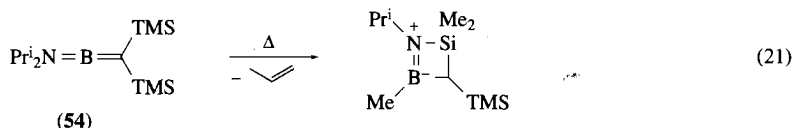


Scheme 23

The heating of (amino)(imino)(methyl)((chlorosilyl)methyl)phosphorane proceeds with the loss of $TMS-Cl$ and cyclization to afford the four-membered azaphosphasiletidine (Equation (20)) <89IC899>.



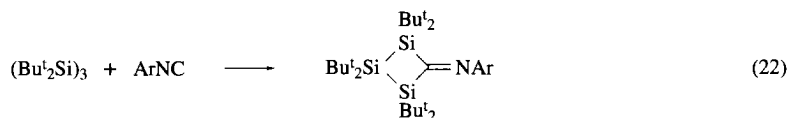
The alkylidenaminoborane (**54**) was transformed to azasilaboretidine by the thermal elimination of propene and migration of a methyl group at $500-600^\circ C$ (Equation (21)) <89CB595>.



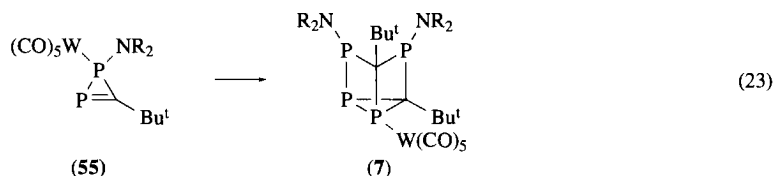
A number of 1-aza-2-sila-metallatetridines with tin <87JOM(321)Cl, 88ZN(B)707>, titanium <90POL1423>, zirconium <83OM16, 90POL1423>, hafnium <83OM16>, thorium and uranium <81IC2991> can be conveniently prepared by the thermal or photolytic intramolecular cyclocondensation of trimethylsilylaminometal derivatives (Scheme 24). The same heterocycles have been obtained by the interaction of *N*-lithio- and *N*-sodiohexamethyldisilazane with chlorides of titanium <81IC3627>, zirconium <85IJC(A)37>, thorium, and uranium <85JOM(288)Cl>. The heating of bis(pentamethylcyclopentadienyl)[bis(trimethylsilyl)phosphino]methyluranium and thorium at $120^\circ C$ for 3 h results in their quantitative conversion to 1-phospha-2-sila-4-metallatanes (Scheme 24) <93OM752>.

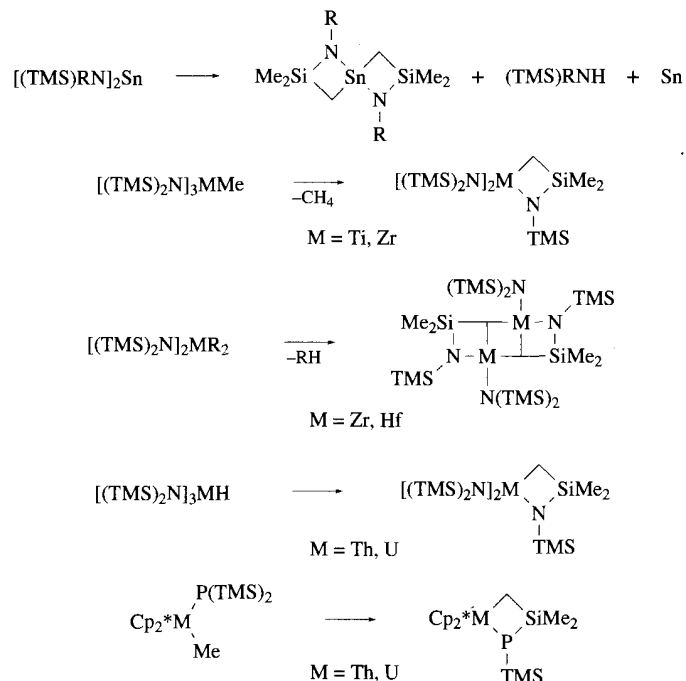
1.39.4.5 Ring Insertion Reactions

Treatment of hexa-*t*-butylcyclotrisilane with several aryl isocyanides bearing a bulky substituent at the nitrogen atom gives the ring-enlarged trisilacyclobutanamines (Equation (22)) <92CB1043, 92JOM(441)185>.



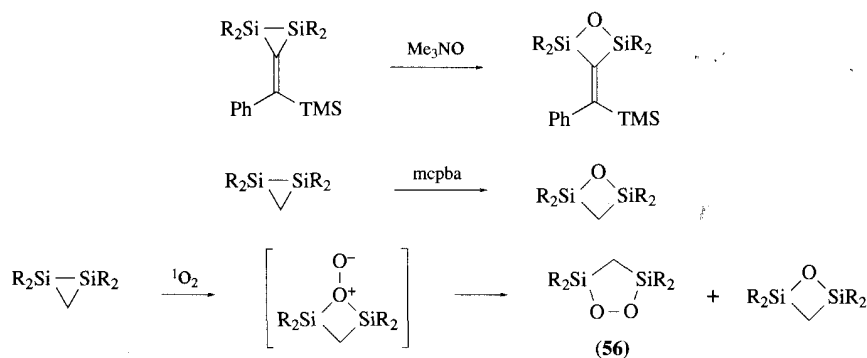
The diphosphirene complex of tungsten (**55**) undergoes dimerization with elimination of a $W(CO)_5$ fragment to give the tricyclotetraphosphahexane (**7**) in a 30% yield (Equation (23)) <91CC1305>.





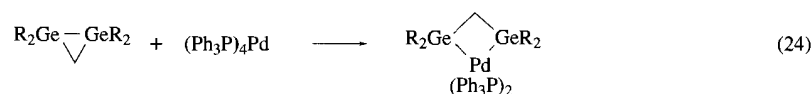
Scheme 24

The oxidation of disiliranes with MCPBA (<83JA7776, 93OM1514> or trimethylamine *N*-oxide (<85JA7706>) proceeds with the insertion of oxygen into the Si—Si bond of the three-membered cycle (Scheme 25). Singlet oxygen oxidation of tetramesityldisilirane in benzene in the presence of tetraphenylporphine afforded the corresponding 1,2,3,5-dioxadisilolane (**56**). In the presence of sulfoxides, photooxidation of tetramesityldisilirane gave 1,2,4-oxadisiletane (10–25%) along with the five-membered heterocyclic compound (**56**) (Scheme 25) (<93OM1514>).

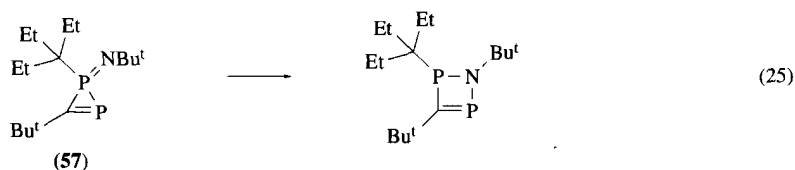


Scheme 25

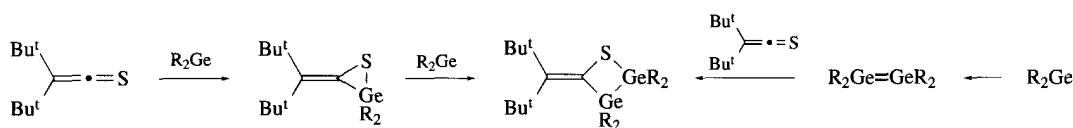
Interaction of digermiranes with $(\text{Ph}_3\text{P})_4\text{Pd}$ produced 45% 1,3,2-digermapalladetane (Equation (24)) $\langle 89\text{OM}2286 \rangle$.



The diphosphirene compound (**57**) with an imino group on the phosphorus atom rearranges into 1,2,4-azadiphosphetene by intramolecular *N*-insertion (Equation (25)) ^{<89TL459>}.



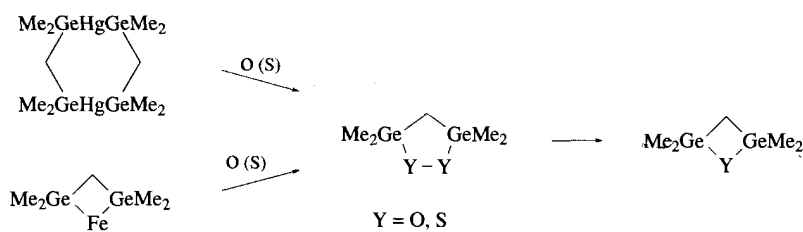
Dimethyl-, diphenyl-, and dimesitylgermylenes react with di-*t*-butyl-thioketene <86TL5105, 89OM1467> at 70°C to give alkylidenethiadigermetanes. The same heterocycle was obtained by flow copolyrlysis of dimethylgermylene with adamantanethione at 250°C <85TL4523>. These compounds appear to be derived from either insertion of germylenes into alkylidenethiagermiranes or a [2 + 2] cycloaddition of the thio derivatives with digermenes, the products of germylene dimerization (Scheme 26).



Scheme 26

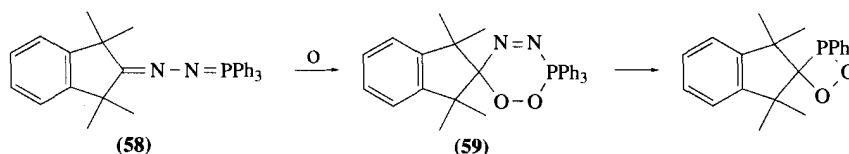
1.39.4.6 Ring Contraction Reactions

Thionation (or oxidation) of 1,3,5,7-tetragerma-2,6-dimercurocane <87OM659> or 1,3-digerma-2-ferretane <89OM1585> leads first to a dithia- or dioxadigermolane, and then by loss of sulfur or oxygen to the thia(oxa)digermetane (Scheme 27).



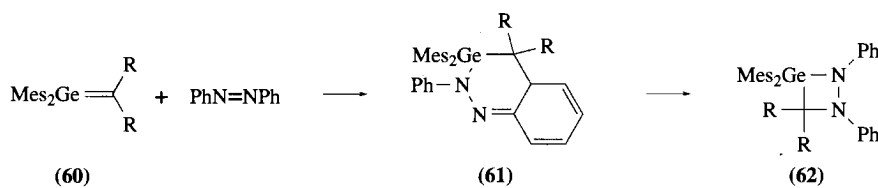
Scheme 27

Photooxidation of phosphazine (58) by singlet oxygen at -100°C gave cyclic diazine (59), which upon warming lost N₂ to produce 1,2,3-dioxaphosphetane (Scheme 28) <85JA5539>.



Scheme 28

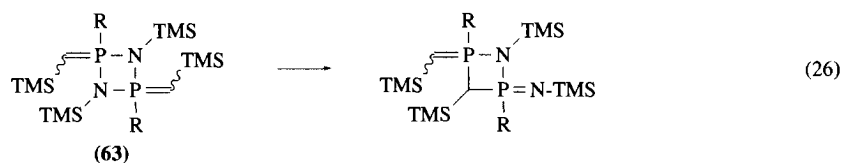
A [2 + 2] cycloaddition of dimesitylfluorenylidengermane (60) is observed with azobenzene leading to the six-membered compound (61). Heating of (61) in a sealed tube at 100°C for 4 h results in isomerization to 1,2-aza-3-germetidine (62) (Scheme 29) <91OM1140>. Although (62) has not been isolated in a pure state, its formation was proved by NMR spectroscopy and by its decomposition products.



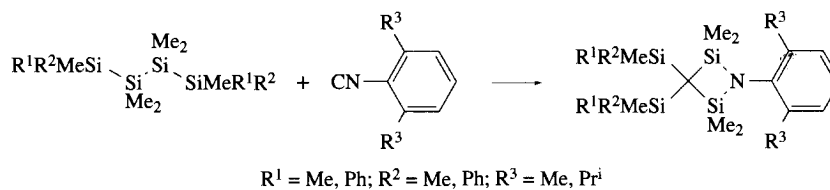
Scheme 29

1.39.4.7 Other Reactions

The diazadiphosphetidine compound (**63**; $\text{R} = \text{Mes}$), with trimethylsilylmethylene groups on the phosphorus atoms, was isomerized, under heating, into 1,2,4-azadiphosphetidine (Equation (26)) <83OM1406>.



The new skeletal rearrangement of tetrasilanes in the palladium catalyzed reactions with aryl isocyanides forms 1,2,4-azadisiletidine derivatives (Scheme 30) <89CC1494, 91JA8899>.



Scheme 30

References

EXPLANATION OF THE REFERENCE SYSTEM

Throughout this work, references are designated by a number–lettering coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted; the advantages of this system are outlined in the Introduction. The system has been used previously in the first edition of *Comprehensive Heterocyclic Chemistry*, eds A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984 and is based on that used in the following two monographs: (a) A. R. Katritzky and J. M. Lagowski, “Chemistry of the Heterocyclic N-Oxides,” Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, “The Tautomerism of Heterocycles,” in “Advances in Heterocyclic Chemistry,” Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer, is given immediately following these notes. Journal names are abbreviated throughout using the CASSI (Chemical Abstracts Service Source Index) system.
2. Each volume contains all the references cited *in that volume*; no separate lists are given for individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For nontwentieth-century references the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are *not* included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code “MI” for miscellaneous with the whole code for books prefixed by the letter “B-”.
11. Where journals have changed names, the same code is used throughout, e.g. CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

Journal Codes

AAC	Antimicrob. Agents Chemother.
ABC	Agric. Biol. Chem.
AC	Appl. Catal.
AC(P)	Ann. Chim. (Paris)
AC(R)	Ann. Chim. (Rome)
ACH	Acta Chim. Acad. Sci. Hung.

ACR	Acc. Chem. Res.
ACS	Acta Chem. Scand.
ACS(A)	Acta Chem. Scand., Ser. A
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AFC	Adv. Fluorine Chem.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AHCS	Adv. Heterocycl. Chem. Supplement
AI	Anal. Instrum.
AJC	Aust. J. Chem.
AK	Ark. Kemi
AKZ	Arm. Khim. Zh.
AM	Adv. Mater. (Weinheim, Ger.)
AMLS	Adv. Mol. Spectrosc.
AMS	Adv. Mass. Spectrom.
ANC	Anal. Chem.
ANL	Accad. Naz. Lincei
ANY	Ann. N. Y. Acad. Sci.
AOC	Adv. Organomet. Chem.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AQ	An. Quim.
AR	Annu. Rep. Prog. Chem.
AR(A)	Annu. Rep. Prog. Chem., Sect. A
AR(B)	Annu. Rep. Prog. Chem., Sect. B
ARP	Annu. Rev. Phys. Chem.
ASI	Acta Chim. Sin. Engl. Ed.
ASIN	Acta Chim. Sin.
AX	Acta Crystallogr.
AX(A)	Acta Crystallogr., Part A
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chim. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochim. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BMC	Bioorg. Med. Chem. Lett.
BP	Biochem. Biopharmacol.
BPJ	Br. Polym. J.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CAN	Cancer
CAR	Carbohydr. Res.
CAT	Chim. Acta Turc.
CB	Chem. Ber.

CBR	Chem. Br.
CC	J. Chem. Soc., Chem. Commun.
CCA	Croat. Chem. Acta
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CE	Chem. Express
CEN	Chem. Eng. News
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CHEC-I	Comp. Heterocycl. Chem., 1st edn.
CI(L)	Chem. Ind. (London)
CI(M)	Chem. Ind. (Milan)
CJC	Can. J. Chem.
CJS	Can. J. Spectrosc.
CL	Chem. Lett.
CLY	Chem. Listy
CM	Chem. Mater.
CMC	Comp. Med. Chem.
COC	Comp. Org. Chem.
COMC-I	Comp. Organomet. Chem., 1st edn.
COS	Comp. Org. Synth.
CP	Can. Pat.
CPB	Chem. Pharm. Bull.
CPH	Chem. Phys.
CPL	Chem. Phys. Lett.
CR	C. R. Hebd. Seances Acad. Sci.
CR(A)	C. R. Hebd. Seances Acad. Sci., Ser. A
CR(B)	C. R. Hebd. Seances Acad. Sci., Ser. B
CR(C)	C. R. Hebd. Seances Acad. Sci., Ser. C
CRAC	Crit. Rev. Anal. Chem.
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CT	Chem. Tech.
CZ	Chem.-Ztg.
CZP	Czech. Pat.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B.
DOK	Dokl. Akad. Nauk SSSR
DP	Dyes Pigm.
E	Experientia
EC	Educ. Chem.
EF	Energy Fuels
EGP	Ger. (East) Pat.
EJM	Eur. J. Med. Chem.
EUP	Eur. Pat.
FCF	Forstchr. Chem. Forsch.
FCR	Fluorine Chem. Rev.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GAK	Gummi Asbest Kunstst.
GEP	Ger. Pat.
GEP(O)	Ger. Pat. Offen.

GSM	Gen. Synth. Methods
H	Heterocycles
HAC	Heteroatom Chem.
HC	Chem. Heterocycl. Compd.
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
HP	Hydrocarbon Process
IC	Inorg. Chem.
ICA	Inorg. Chim. Acta
IEC	Ind. Eng. Chem. Res.
IJ	Isr. J. Chem.
IJC	Indian J. Chem.
IJC(A)	Indian J. Chem., Sect. A
IJC(B)	Indian J. Chem., Sect. B
IJM	Int. J. Mass Spectrom. Ion Phys.
IJQ	Int. J. Quantum Chem.
IJS	Int. J. Sulfur Chem.
IJS(A)	Int. J. Sulfur Chem., Part A
IJS(B)	Int. J. Sulfur Chem., Part B
IS	Inorg. Synth.
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAN	J. Antibiot.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JC	J. Chromatogr.
JCC	J. Coord. Chem.
JCE	J. Chem. Ed.
JCED	J. Chem. Eng. Data
JCI	J. Chem. Inf. Comput. Sci.
JCP	J. Chem. Phys.
JCPB	J. Chim. Phys. Physico-Chim. Biol.
JCR(M)	J. Chem. Res. (M)
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(A)	J. Chem. Soc. (A)
JCS(B)	J. Chem. Soc. (B)
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(F2)	J. Chem. Soc., Faraday Trans. 2
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JCS(S2)	J. Chem. Soc. (Suppl. 2)
JEC	J. Electroanal. Chem. Interfacial Electrochem.
JEM	J. Energ. Mater.
JES	J. Electron. Spectrosc.
JFA	J. Sci. Food. Agri.
JFC	J. Fluorine Chem.
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JINC	J. Inorg. Nucl. Chem.
JLC	J. Liq. Chromatogr.

JMAS	J. Mat. Sci.
JMC	J. Med. Chem.
JMOC	J. Mol. Catal.
JMR	J. Magn. Reson.
JMS	J. Mol. Sci.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
JPJ	J. Pharm. Soc. Jpn.
JPO	J. Phys. Org. Chem.
JPP	J. Pharm. Pharmacol.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JPS(A)	J. Polym. Sci., Polym. Chem., Part A
JPU	J. Phys. Chem. USSR (Engl. Transl.)
JSC	J. Serbochem. Soc.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KFZ	Khim. Farm. Zh.
KGS	Khim. Geterotsikl. Soedin.
KO	Kirk-Othmer Encyc.
KPS	Khim. Prir. Soedin.
L	Langmuir
LA	Liebigs Ann. Chem.
LC	Liq. Cryst.
LS	Life Sci.
M	Monatsh. Chem.
MAC	Macromol. Chem.
MC	Mendeleev Chem. J. (Engl. Transl.)
MCLC	Mol. Cryst. Liq. Cryst.
MI	Miscellaneous [book/journal]
MIP	Miscellaneous Pat.
MM	Macromolecules
MP	Mol. Phys.
MRC	Magn. Reson. Chem.
N	Naturwissenschaften
NAT	Nature
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)
NKZ	Nippon Kagaku Zasshi
NZJ	N. Z. J. Sci. Technol.
OCS	Organomet. Synth.
OM	Organometallics
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PA	Polym. Age
PAC	Pure Appl. Chem.

PAS	Pol. Acad. Sci.
PB	Polym. Bull.
PC	Personal Communication
PCS	Proc. Chem. Soc.
PHA	Pharmazi
PHC	Prog. Heterocycl. Chem.
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PJC	Pol. J. Chem.
PJS	Pak. J. Sci. Ind. Res.
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
POL	Polyhedron
PP	Polym. Prepr.
PRS	Proceed. Roy. Soc.
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
QRS	Quart. Rep. Sulfur. Chem.
QSAR	Quant. Struct. Act. Relat. Pharmacol. Chem. Biol.
RC	Rubber Chem. Technol.
RCM	Rapid Commun. Mass Spectrom.
RCP	Rec. Chem. Prog.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RHA	Rev. Heteroatom Chem.
RJ	Rubber J.
RP	Rev. Polarogr.
RRC	Rev. Roum. Chim.
RS	Ric. Sci.
RTC	Recl. Trav. Chim. Pays-Bas
RZC	Rocz. Chem.
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SCI	Science
SL	Synlett
SM	Synth. Met.
SR	Sulfur Reports
SRI	Synth. React. Inorg. Metal-Org. Chem.
SS	Sch. Sci. Rev.
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
SUL	Sulfur Letters
SZP	Swiss Pat.
T	Tetrahedron
T(S)	Tetrahedron, Suppl.
TA	Tetrahedron Asymmetry
TAL	Talanta
TCA	Theor. Chim. Acta
TCC	Top. Curr. Chem.
TCM	Tetrahedron, Comp. Method.
TFS	Trans. Faraday Soc.
TH	Thesis
TL	Tetrahedron Lett.
TS	Top. Stereochem.

UK	Usp. Khim.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
URP	USSR Pat.
USP	US Pat.
WCH	Wiadom. Chem.
YGK	Yuki Gosei Kagaku Kyokaishi
YZ	Yakugaku Zasshi (J. Pharm. Soc. Jpn.)
ZAAC	Z. Anorg. Allg. Chem.
ZAK	Zh. Anal. Khim.
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(A)	Z. Naturforsch., Teil A
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe-Seyler's Z. Physiol. Chem.
ZPK	Zh. Prikl. Khim.

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