SMALL RING HETEROCYCLES - PART 1

This is the Forty-Second Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

SMALL RING HETEROCYCLES

Part 1

Aziridines, Azirines, Thiiranes, Thiirenes

Edited by

Alfred Hassner

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF NEW YORK AT BINGHAMTON

AN INTERSCIENCE® PUBLICATION

JOHN WILEY AND SONS
NEW YORK · CHICHESTER · BRISBANE · TORONTO · SINGAPORE

An Interscience® Publication

Library of Congress Cataloging in Publication Data:

Main entry under title:
Small ring heterocycles.

(The Chemistry of heterocyclic compounds, ISSN 0069-3154; v. 42, pt. 1-)
"An Interscience publication."
Includes indexes.
1. Heterocyclic compounds. 2. Ring formation (Chemistry) I. Hassner, Alfred, 1930-
II. Series: Chemistry of heterocyclic compounds; v. 42, pt. 1, etc.

QD400.S5115 547'.59 82-4790
ISBN 0-471-05626-X AACR2
ISBN 13: 978-0-471-05626-3

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Preface

The chemistry of small ring compounds (three- and four-membered rings) has played a considerable role in the development of modern organic chemistry. Foremost among these reactive molecules are the small ring heterocycles. The presence of one or more heteroatoms in these strained rings imparts a measurable dipole moment to such molecules. It also adds a new dimension of intrinsic difficulty concerning the synthesis and stability of such heterocyclic analogs of cyclopropanes and cyclobutanes. If one considers the compressed bond angles (near 60° in three-membered rings and near 90° in four-membered rings), the mere synthetic challenge, especially for the unsaturated analogs of these heterocycles, seems enormous. Indeed, the small ring heterocycles possess much greater reactivity toward a variety of reagents than do their five- or six-membered ring analogs.

It is only since the mid-1960s that an explosive expansion in the chemistry of some of these heterocycles has taken place. In 1964, when the first volume of this series on three- and four-membered heterocycles was published, three pages were devoted to azirines, the unsaturated analogs of aziridines; in this volume the subject occupies an entire chapter. Similarly, while the chemistry of the saturated three-membered rings containing sulfur (e.g., thiiranes) has been relatively well established for some time, the analogous unsaturated compounds (thiirenes, thiirene oxides, etc.) have been known for only 10 years. A number of three-membered rings incorporating two or more heteroatoms still constitute essentially unexplored territory. Therefore the field of small ring heterocycles not only holds current intense interest but also provides a challenge for further investigations.

Because of the overwhelming amount of material to be covered, more than two volumes in this series are necessary. The first is devoted to three-membered rings containing nitrogen and sulfur. It also covers the 3-membered rings containing Sulfur and another hetero atom, such as Thiaziridine-dioxide. It consists of three chapters: Aziridines, Azirines, and Three-Membered Rings Containing Sulfur. This is an area in which considerable progress has been made over the past 18 years and which is of importance, not only from the synthetic and mechanistic points of view, but also from considerations of theoretical calculations and orbital symmetry considerations. For instance, there has been a great deal of recent progress on regio- and stereoselectivity, as well as on photochemistry of these three-membered rings. What is even more intriguing is their use as synthons for other functional groups as well as for larger ring heterocycles. Furthermore, there has been increasing interest in the biological properties and polymerization behavior of such molecules.

Editing this volume is especially meaningful to me, because I had the privilege of being involved firsthand in the exciting explorations of some of these heterocycles (in particular of azirines) during the past 20 years.

An effort was made to update the chapters since the appearance of the last review in this series edited by Weissberger in 1964. Hence, this volume cannot

possibly be all-inclusive but must be selective. Each chapter attempts to build on a previous chapter or review on this subject but from that point stands on its own.

I am grateful to the authors of the chapters for their splendid cooperation and to my secretary, Joyce Scotto, for her help and encouragements.

Most of all, this book is devoted to my family with love and appreciation and to the memory of our 16-year-old daughter Erica, who was torn from us so prematurely during the time this volume was being completed.

ALFRED HASSNER

Binghamton, New York
January 1983

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Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner

CHAPTER I

Aziridines

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I. INTRODUCTION

Eighteen years have elapsed between the original aziridine review in this series and the publication of this book.[1] During this time span the quantity and diversity of aziridine chemistry underwent enormous expansion. Synthetic approaches to the aziridine ring, modifications of functionalized aziridines, and the reactions of aziridines have received particular attention. As a result, applications of aziridine chemistry to synthesis, mechanistic studies, and biological investigations have become increasingly numerous. Space restrictions have made it impossible to include all publications or to cover all areas in optimum depth. It is hoped, however, that the most useful and promising developments are covered.

A number of reviews have appeared during this period. The most important is the comprehensive book by Dermer and Ham published in 1969.[2] Synthesis of aziridines were summarized in 1967.[3] A particularly useful review of aziridine polymers[4] appeared in 1976, and that subject is not discussed here. Two reviews of the Russian literature have appeared.[5,6] The rearrangements of aziridines have been discussed in detail in 1971[7] and in an earlier reference.[8] Other more specialized reviews are mentioned in subsequent sections.

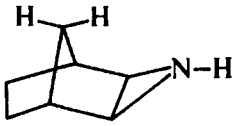
This chapter is organized along lines parallel to the original chapter. A discussion of physical properties is followed by aziridine syntheses and aziridine transformations (with and without ring destruction). Subsequent sections treat aziridinium salts, α-lactams, methyleneaziridines, biological applications, and so on.

II. PHYSICAL PROPERTIES

1. Nuclear Magnetic Resonance Spectroscopy: Structure and Stereochemistry at Carbon

Applications of proton nuclear magnetic resonance ^{1}H nmr spectroscopy have been especially useful in aziridine structure and stereochemical assignments. A particularly useful review summarizes pertinent work through 1969.[9] The large (5–9 Hz) coupling constant for the coplanar vicinal *cis* hydrogens compared to the smaller (2–6 Hz) *trans* value allows configurational assignment to many aziridines.[9–16] The geminal coupling constant decreases from approximately 2 to − 7 Hz as the electronegativity of the aziridine substituents increases.[12]

The aziridine ring exerts anisotropic effects on adjacent groups.[17–19] The chemical shifts (relative to the corresponding alkene) of **1** and **2** are indicative of shifts caused by the aziridine ring. A detailed theoretical study of these effects and their origin has been published.[20] The effect seems to be the result of anisotropy of the nitrogen atom.



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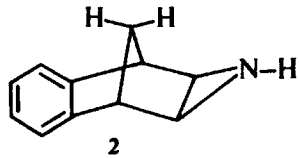
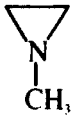


2

Applications of ^{13}C nmr to aziridines have become more frequent. An extensive study of diverse *N*-unsubstituted structures has allowed development of an empirical formula for shift prediction.[21] Three bond $^{13}J_{CH}$ coupling constants have been determined for aziridines[10] and the *s* character of C in **3** (30%) and **4** (34%) assigned from ^{13}C–H coupling constants.[22] A complete ^{13}C analysis of mitomycin C (**5**) has been published.[23]



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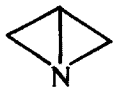

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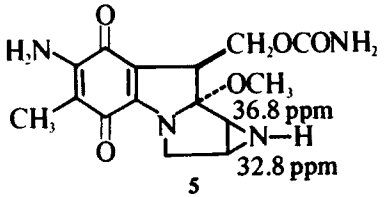
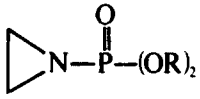


5

Mitomycin C

A variety of aziridines with general structure **6** have been examined by ^{1}H[193] as well as by ^{15}N nmr spectroscopy[24] and ^{15}N–^{13}C coupling constants have been correlated with stereochemistry in aroylaziridines.[25] The ^{13}C nmr spectra of various *cis*- and *trans*-aziridines (**7** and **8**) have revealed important differences between the chemical shifts of the two ring carbons.[26]



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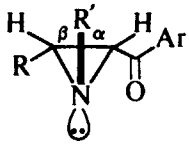

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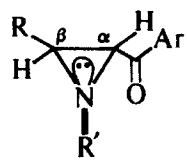
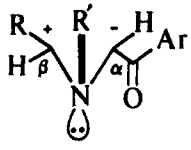


8

In the former case, the α-carbon is more deshielded than the β. In the isomer, **8**, the reverse is true. This difference is explained on the basis of hyperconjugative delocalization between the aziridine ring and the carbonyl (structure **9**) for the *trans* isomer. Apparently, the *trans* isomer allows a bisected geometrical relationship between carbonyl and ring that is favorable to structure **9**. In contrast, steric constraints force the carbonyl of **7** into a conformation that prohibits such delocalization. Similar conclusions about *cis* vs. *trans* differences had previously been identified via infrared (ir) and ultraviolet (uv) spectroscopy (see Section II, 3).[27]



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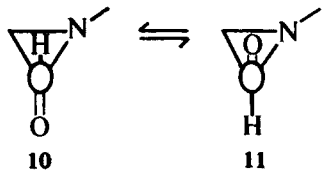
Although less reliable than coupling constants, chemical shifts have also generated useful structural data. In one such study, solvent effects were employed to measure electronic transmission by the aziridine ring.[28] It was concluded that the aziridine ring was *less* effective in such transmissions than cyclopropane and epoxide rings. Other studies on chemical shifts vs. structure[29] and solvent effects[30] have been published.

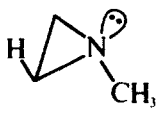
2. Nuclear Magnetic Resonance Spectroscopy: Conformation and Nitrogen Configuration

In addition to structural-stereochemical assignments, nmr spectroscopy has been able to address intriguing questions of side chain conformation and nitrogen stereochemistry. Both considerations are important because of their relationships to the chemical properties of aziridines.

The conformations of some aziridine aldehydes have been studied, and *trans* conformation **10** is both less polar and more stable than the *s-cis* form **11**. The former is favored (based on coupling constant analysis) by a 75:25 ratio.[31] Long-range coupling between the *N*-methyl group and the *trans* hydrogen of **12** is larger than with the *cis* hydrogen and, as a result, the former is broader.[32] Studies on ^{15}N–^{1}H coupling in structures of type **13** have revealed that the coupling constants are dependent on the orientation of the lone pair.[33] Similar effects have been noted in *N*-chloroaziridines.[34]



10 **11**



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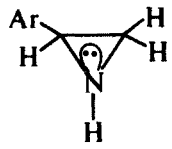
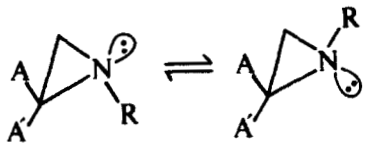


13

In contrast to most amines, the bonding constraints of the aziridine ring usually depress inversion rates until they are at least observable by nmr spectroscopy. When the substituent bulk of A and A′ (Eq. 1) is unequal, the population of the two configurations is different. This fact has been used in an ingenious manner to differentiate between *cis* and *trans* isomers. The *trans* isomer (**14**) displays a more complex spectrum at low temperatures because of slow interconversion between the two configurations. In contrast, the *cis* isomer (**15**) spectrum is essentially temperature invariant because the all-*cis* configuration is so unfavorable.[35]



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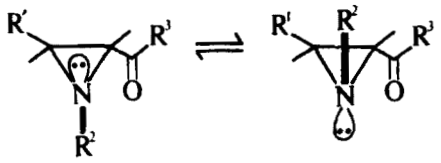

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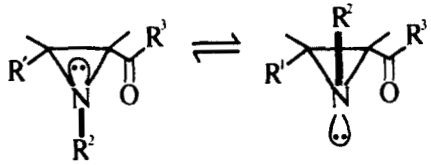


15

When A = A′ (as in Eq. 1), the analysis of the nmr spectra, the extraction of rate constants, and the determination of energies of activation are relatively straightforward. In general, conjugative effects (**16** and **17**) stabilize the transition state and accelerate inversion. Electron-withdrawing groups on nitrogen hinder rehybridization (**18**), and bulky groups on nitrogen and on the ring (**19**) facilitate inversion.[36–39]

16

17

18

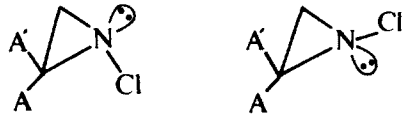
19

Subsequent work has added numerous examples of these principles.[13, 15, 34, 40–47]

3. Configurational Stability at Nitrogen: Optically Active Aziridines

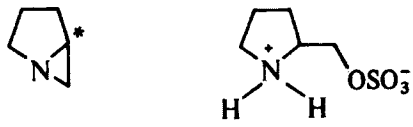
The results described in the preceding section suggested the possibility that configuration stability at nitrogen might be attainable. In fact, a number of isomeric

pairs of type **20** have been separated[48–53] and a $\Delta F^{\ddagger}$ for inversion in excess of 21 kcal/mole has been estimated.[38]

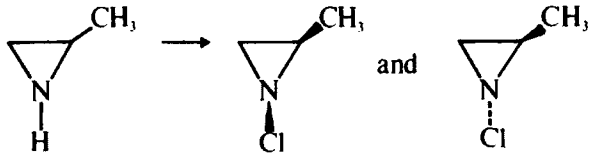


20

Configuration has also been imposed on an aziridine nitrogen by incorporation of the ring into bicyclic structure **21**.[54] Since **21** was formed from an optically active precursor (**22**), its optical rotatory dispersion (ORD) spectrum could be used to assign configuration to the *N*-chlorocompounds **23** and **24**, which were, in turn, separable by gas-liquid chromatography (glc).[55–57]

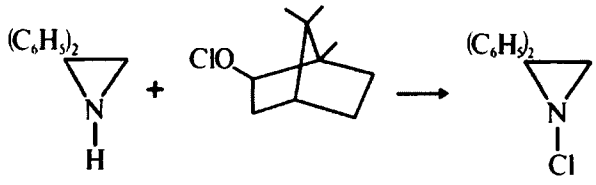


21 **22**



23 **24**

Finally, it has been possible to achieve synthesis of optically active aziridines in which nitrogen is the only chiral center. Chlorination of an aziridine with an optically active hypochlorite yielded aziridine **25**. This aziridine racemized in 4 days at 0°.[58] It has also been possible to prepare optically active **26** either by resolution of the half-ester with subsequent esterification[59, 60] or by partial destruction of one antipode via aminolyses with l-ephedrine.[61]



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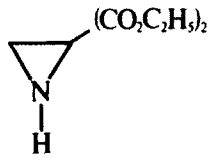
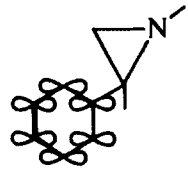


26

4. Ultraviolet Spectroscopy

It has been known for a long time that *cis*-aziridinyl ketones (7) have uv maxima at shorter wavelengths and lower extinction coefficient ϵ than their *trans* analogs (8).[27, 62, 63] Even with the advent of sterochemical assignments by nmr spectroscopy, this application of uv spectroscopy remains useful.[64] More recently, semiempirical calculations have confirmed that the preferred conformation of aryl- (and presumably carbonyl-) substituted aziridines is the bisected conformation 27.[65] As previously mentioned, steric factors prohibit this conformation in the *cis* isomer.



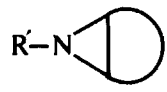
27

5. Mass Spectroscopy

Although routine mass spectra are common in most recent publications, the technique has not been especially important in structural assignment. Not surprisingly, little difference exists between *cis* and *trans* isomers.[66] A few additional studies contain useful information.[67, 68]

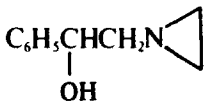
6. X-ray Crystallography

A significant number of aziridines with general structure 28 have been analyzed by x-ray crystallographic techniques.[69–75] In all cases the nitrogen is pyrimidal. Bond lengths of 1.48 Å (C–N) and 1.46 Å (C–C) are typical. Other structures determined include 29,[76] 30,[77] 31,[78] and mitomycin A, 32.[79]



28

R = Ar, $ArSO_2$



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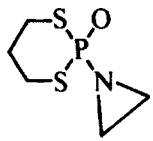

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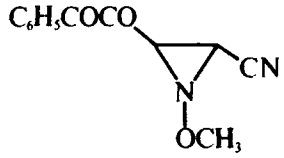

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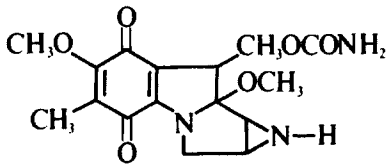
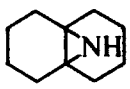


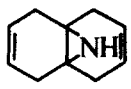
32
Mitomycin A

7. pK_a

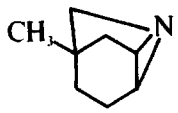
The originally cited range (8–9.5) for aziridine pK_a's[80] was based on relatively simple aziridine structures. A number of more complex systems have been studied and they also fall within this range. The pK_a's of structures **33**,[81] **34**,[81] and **35**[82] illustrate this point. Compound **36**[82] is only slightly outside this range.



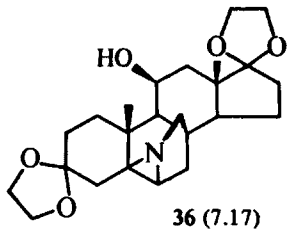
33 (8.59)



34 (8.14)

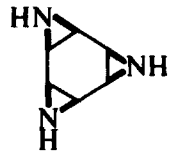


35 (8.50)

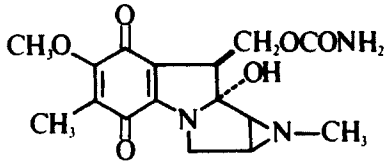


36 (7.17)

The novel triimine **37**, however, falls outside this range for all three of its pK_a's (6.42, 2.71, and *ca.* −1.0). These values, however, are within good agreement of those calculated on the basis of inductive effects.[83] Somewhat less obvious are the pK_a's of mitomycins. Values of 3.2[84] for mitomycin C (**5**) and 4.3 for mitomycin B (**38**)[85] have been reported. It does not seem that inductive factors alone could be responsible for this effect. The answer is worth seeking, since the bioalkylating ability of the mitomycin aziridine rings is preserved under physiological conditions by these low pK_a's.[86]



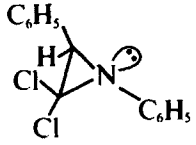
37 (6.42, 2.71)



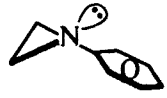
38
Mitomycin B (4.3)

8. Other Physical Studies

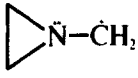
A dipole moment study has allowed assignment of the *trans* configuration to the phenyl groups of **39**.[87] Dipole moment studies[88] and electron diffraction[89] demonstrated that the *N*-phenyl group assumes the orientation of **40**. This conformation is also found in crystallographic studies. Electron spin resonance (esr) spectroscopy studies of **41** have shown conformations **41a**[90] and **41b**[91] to be the most stable for these radicals.



39



40

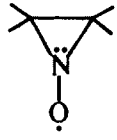


41

41a

41b

The structure **42**, which was assigned on the basis of esr spectral evidence,[92] has been shown to be incorrect.[93, 94]

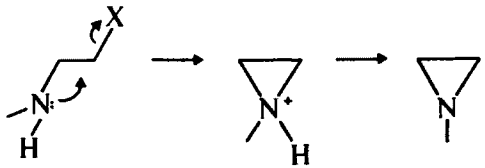


42

III. SYNTHESIS OF AZIRIDINES

1. Aziridines via Intramolecular Cyclization

The most obvious and oldest approach to aziridine synthesis involves internal (neighboring group) cyclization of an amino group situated beta to a leaving group. The best known of these procedures are the so-called Gabriel and Wenker synthesis (Eq. 2).



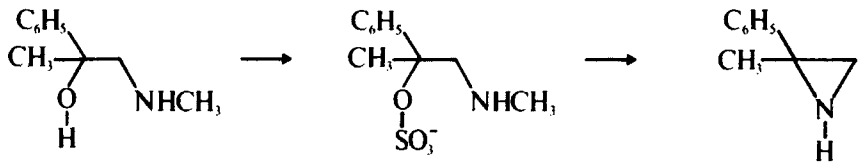
(2)

X = Br, Cl, I (Gabriel)
X = OSO_3^- (Wenker)

Such reactions show the expected stereospecificity and generally fail when the appropriate *trans* coplanar geometry cannot be assumed.[95,96] Side reactions include dimerization, polymerization, and elimination. Most of the recent developments in this synthetic approach have been in the routes to the cyclization precursor (new reagents, higher yields, greater stereospecificity, more convenient techniques, etc.) and in the cyclization step (ease of isolation, milder conditions, etc.). The sections that follow are organized on the basis of the precursor employed for cyclization.

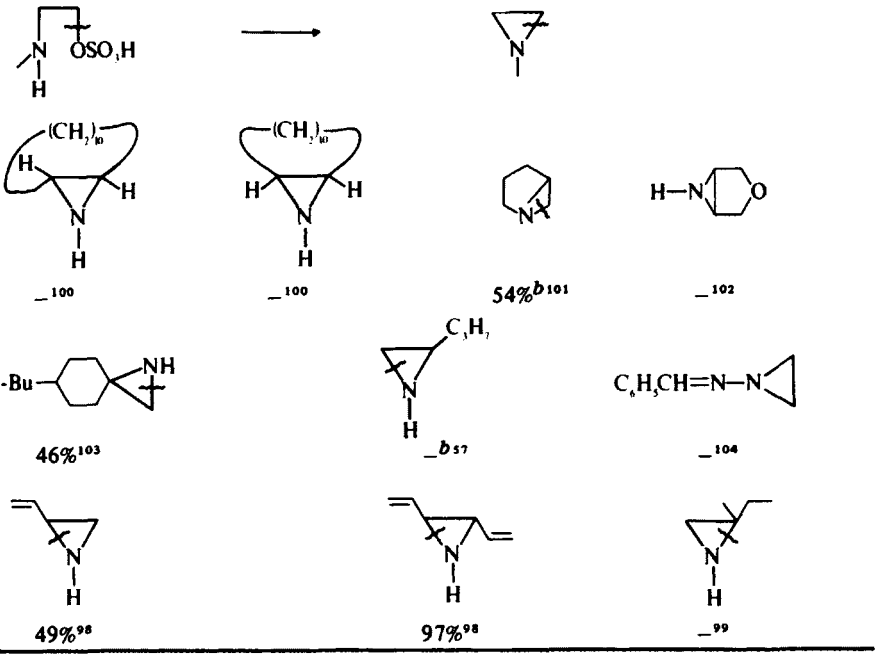
A. *Aziridines from Amino Alcohols*

Amino alcohols suitable for aziridine synthesis are readily available from epoxides and occasionally from the reduction of α-amino ketones. The Wenker procedure for converting amino alcohols to aziridines has been reviewed thoroughly.[95,96] Early workers utilized sulfuric acid to form the hydrogen sulfate ester. This approach remains applicable for a remarkable number of systems. The alternative use of $ClSO_3H$ offers advantages with more sensitive systems.[97–99] Some of the more interesting structures prepared by this method are found in Table 1. The Wenker-type synthesis has even been identified in the enzymatic synthesis of aziridine **43**. Apparently the enzymatic synthesis of the hydrogen sulfate ester is followed by nonenzymatic cyclization.[105]



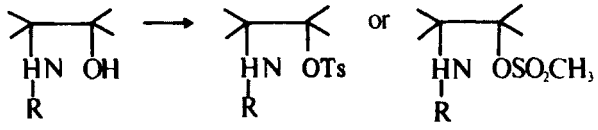
43

TABLE 1. AZIRIDINES FROM AMINO HYDROGEN SULFATE CYCLIZATIONS[a]

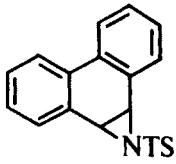


[a] Wavy line indicates the new C–N bond formed in the cyclization step.
[b] Optically active.

It is also possible to convert an amino alcohol to the corresponding tosylate or methanesulfonate ester (Eq. 3). This variation has most often been applied to compounds that have bulky or electron-attracting groups on nitrogen because such groups inhibit reaction on nitrogen. Some representative structures and yields are found in Table 2. This approach has been applied to the synthesis of **44**[109] and to a wide variety of epimino sugars.[110–119]

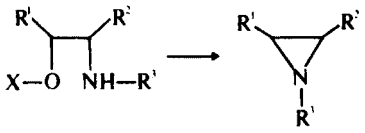


(3)



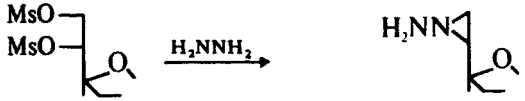
44

TABLE 2. AZIRIDINES FROM AMINO TOSYLATE CYCLIZATION



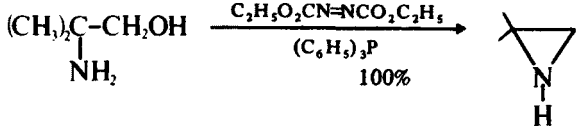
X	R^1	R^2	R^3	Yield (%)	Ref.
Ts	H	$CO_2C_2H_5$	Ts	90	106
Ts	H	$CO_2C_2H_5$	$COCH_2C_6H_5$	63	106
Ts	H	$CO_2C_2H_5$	$COCH_2NHCO_2CH_2C_6H_5$	95	106
Ts	H	$CONHCH_2CO_2C_2H_5$	$COCH_2NHCO_2CH_2C_6H_5$	67	106
Ts	CH_3	$CO_2C_2H_5$	Ts	29	106
Ts	CH_3	$CO_2C_2H_5$	$COCH_2NHCO_2CH_2C_6H_5$	88	106
Ts	CH_3	$CONHCH_2CO_2C_6H_5$	$COCH_2NHCO_2CH_2C_6H_5$	94	107
CH_3SO_2	H	CH_2Cl	*t*-Bu	55	108
CH_3SO_2	H	$CH_2O_2CCH_3$	*t*-Bu	32	108

Reaction of dimesylates with hydrazine has been used to make 1-aminoaziridine sugar derivatives (Eq. 4).[120, 121]

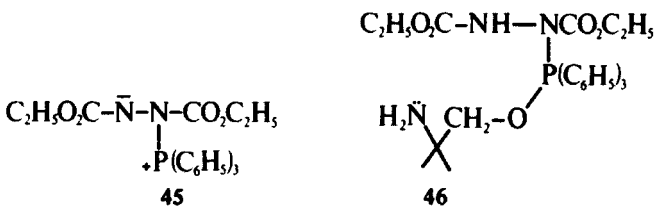


(4)

Several more recent publications have resulted in a superior route from amino alcohols to aziridines based on the driving force furnished by the strength of the phosphorus-oxygen bond. These reactions utilize reagents formed from $(C_6H_5)_3P$ and Br_2, Cl_2, or CCl_4 in the presence of base. Examples of the products formed are listed in Table 3. As can be seen, the reactions are general and the yields are high. The reactions often proceed below 0° and are stereospecific (ring closure with inversion). The final step probably involves nitrogen assisted C–O rupture with formation of the P–O bond. A similar reaction (Eq. 5) may also become useful.[130] Intermediates **45** and **46** were postulated

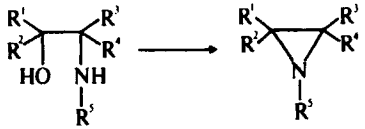


(5)

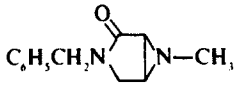


45 **46**

TABLE 3. AZIRIDINES FROM PHOSPHINE–HALIDE-MEDIATED RING CLOSURE OF AMINO ALCOHOLS

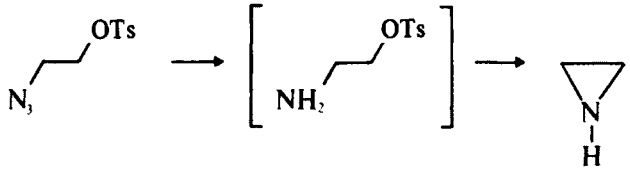


R^1	R^2	R^3	R^4	R^5	Reagent	Yield (%)	Ref.
C_6H_5	H	H	H	*n*-C_4H_9	$(C_6H_5)_3PBr_2$	60	122
C_6H_5	H	H	H	*t*-Bu	$(C_6H_5)_3PBr_2$	66	122
C_6H_5	H	H	H	C_6H_{11}	$(C_6H_5)_3PBr_2$	50	122
C_6H_5	H	H	H	$C_6H_5CH_2$	$(C_6H_5)_3PBr_2$	54	122
CH_3	H	H	H	C_6H_{11}	$(C_6H_5)_3PBr_2$	11	122
CH_3	H	H	H	$C_6H_5CH_2$	$(C_6H_5)_3PBr_2$	51	122
C_2H_5	H	H	H	$C_6H_5CH_2$	$(C_6H_5)_3PBr_2$	51	122
C_6H_5	H	H	CH_3	CH_3	$(C_6H_5)_3PBr_2$	74	122
CH_3	CH_3	H	CO_2CH_3	$CH_2C_6H_5$	$(C_6H_5)_3PBr_2$	76	123
$CH_2=C(CH_3)$	H	H	CH_3	C_6H_5	$(C_6H_5)_3PBr_2$	50–60	124, 125
$CH_2=C(H)$	H	H	CH_3	C_6H_5	$(C_6H_5)_3PBr_2$	50–60	124, 125
$CH_2=C(CH_3)$	H	H	C_2H_5	C_6H_5	$(C_6H_5)_3PBr_2$	50–60	124, 125
$CH_2=C(C_2H_5)$	H	H	H	C_6H_5	$(C_6H_5)_3PBr_2$	50–60	124, 125
$CH_2=C(CH_3)$	H	H	CH_3	$CH_2C_6H_5$	$(C_6H_5)_3PBr_2$	50–60	124, 125
$CH_2=C(CH_3)$	H	H	CH_3	C_2H_5	$(C_6H_5)_3PBr_2$	50–60	124, 125
CH_2=CH–	H	CH_2=CH	H	CH_3	$(C_6H_5)_3PBr_2$	–	126
H	H	H	H	H	$(C_6H_5)_3PCCl_4$	52	127
H	H	H	H	C_6H_{11}	$(C_6H_5)_3PCCl_4$	58	127
H	H	H	H	$CH_2C_6H_5$	$(C_6H_5)_3PCCl_4$	66	127
CH_3	H	H	H	$CH_2C_6H_5$	$(C_6H_5)_3PCCl_4$	80	127
CH_3	H	H	H	C_6H_{11}	$(C_6H_5)_3PCCl_4$	68	127
C_2H_5	H	H	H	$CH_2C_6H_5$	$(C_6H_5)_3PCCl_4$	73	127
C_6H_5	H	H	H	*t*-Bu	$(C_6H_5)_3PCCl_4$	86	127
C_6H_5	H	H	H	$CH_2C_6H_5$	$(C_6H_5)_3PCCl_4$	91	127
H	$(CH_2)_4$		H	*n*-Bu	$(C_6H_5)_3PCCl_4$	74	127
H	$(CH_2)_4$		H	$CH_2C_6H_5$	$(C_6H_5)_3PCCl_4$	89	127
CH_2=CH	–	C≡CH	–	*t*-Bu	$(C_6H_5)_3PCl_2$	31	128



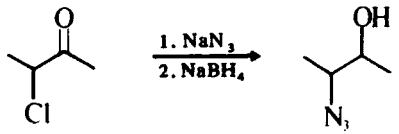
76% ($[C_6H_5]_3P$, CCl_4)[129]

The reduction of azidotosylates or methanesulfonates under conditions that cause immediate cyclization (Eq. 6) has been used to advantage in certain cases.



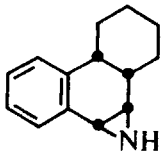
(6)

This approach is particularly useful for *N*-unsubstituted aziridines, where selective esterification of the amino alcohol would not be possible. The azidoalcohols are available from the corresponding epoxide or via the sequence of Eq. 7. The latter route has been used to synthesize epimino derivatives of the juvenile hormone.[131]



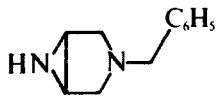
(7)

Although $NaBH_4$ is the usual reducing agent for azidotosylates, nickel-catalyzed hydrogenations have also been employed.[132–134] This type of aziridine synthesis has been utilized in the preparation of epimino sugars and sugar derivatives.[134–137] Structures **47**,[133] **48**,[138] **49**,[139] **50**,[83] and **51**[140] are among the more interesting molecules made by these reductive cyclizations.

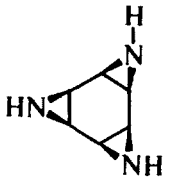


47 (80%)

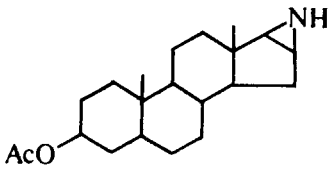
48 (25%)



49

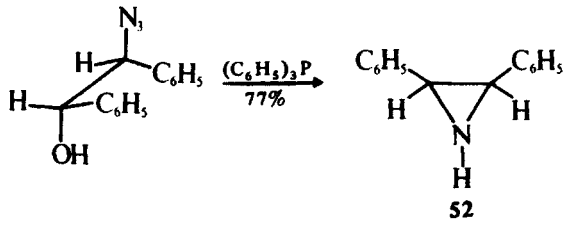


50 (45%)

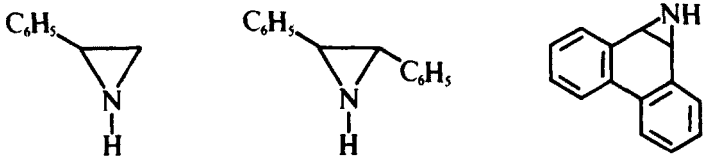


51

A new route to aziridines from azidoalcohols has been developed recently. In this reaction the azidoalcohol is reacted with triphenylphosphine. The reaction is stereospecific, as exemplified by the formation of **52**.[141] The details of the reaction mechanism are unclear. The yields of **53**, **54**, **55**,[141] **56**, and **57**[142] are good.



52



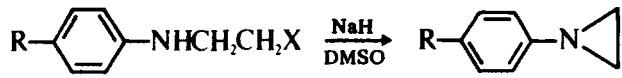
53 (72%) 54 (68%) 55 (72%)

56 (78%) 57 (90%)

A related reaction has been employed in the recent, total synthesis of *dl*-porfiromycin.[143]

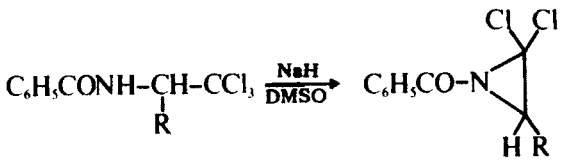
B. *Aziridines from β-Haloamines*

The synthesis of aziridines from β-haloamines (Gabriel synthesis) is very general and has been used extensively. The following discussion emphasizes some of the more interesting recent examples. The preparation of various *N*-arylaziridines (Eq. 8) via NaH-DMSO treatment takes place in approximately 80% yield.[144]



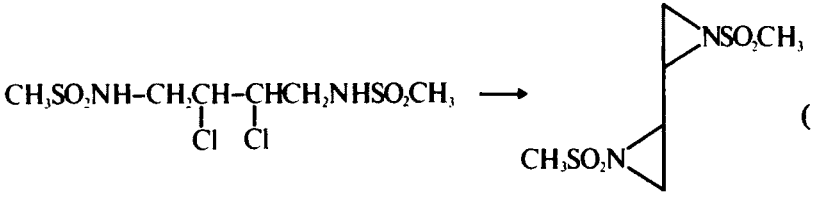
(8)

Dihaloaziridines (Eq. 9) can also be prepared by this approach when the nitrogen substituent is strongly electron attracting.[145] A novel biaziridine has been obtained (both *dl* and *meso* forms) as shown in Eq. 10.[146] Aziridines with a functional group on nitrogen (Eq. 11) result from the appropriate dihalide.[147] A different type of dihalide provides a useful route to the bicyclic aziridines 58 (Eq. 12).[148]

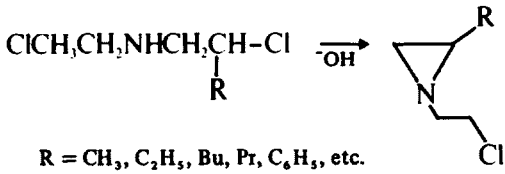


(9)

R = CH_3 (52%)
R = C_6H_5 (62%)
R = $C(CH_3)_2CHO$ (45%)

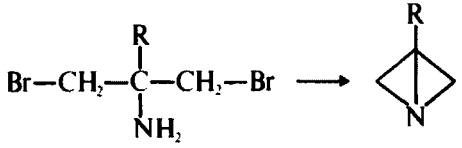


(10)



(11)

R = CH_3, C_2H_5, Bu, Pr, C_6H_5, etc.

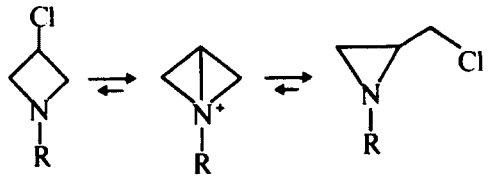


58

R = H (7%)
R = CH_3 (42%)
R = C_2H_5 (75%)

(12)

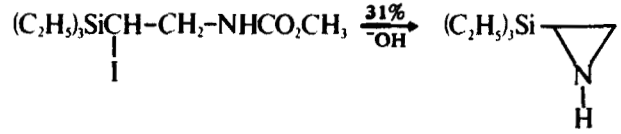
Intramolecular alkylation (Eq. 13) results in aziridine synthesis via ring contraction.[149] Presumably a bicyclic intermediate **59** is formed.



59

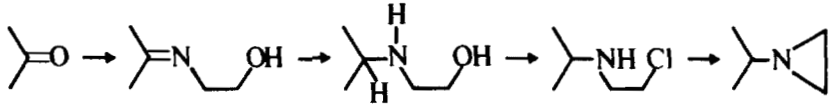
(13)

The synthesis of a silicon derivative of an aziridine has been achieved via a Gabriel-type reaction (Eq. 14).[150]

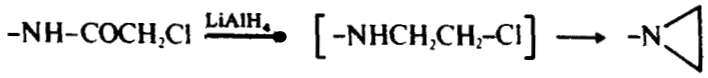


(14)

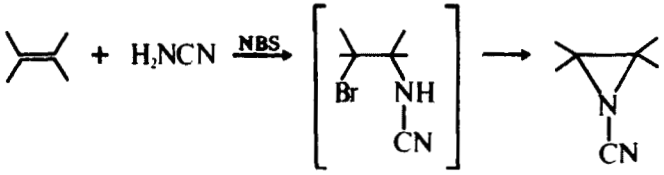
Steroids bearing an aziridine ring have potential biological activity. In addition to cyclization of steroidal iodoamines,[151] Eqs. 15,[152] 16,[152] and 17[153] have been successful procedures for attaching the aziridine ring to the steroid nucleus.



(15)

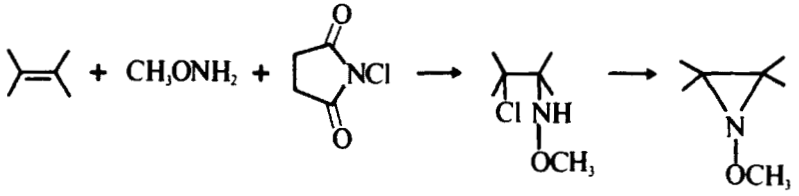


(16)

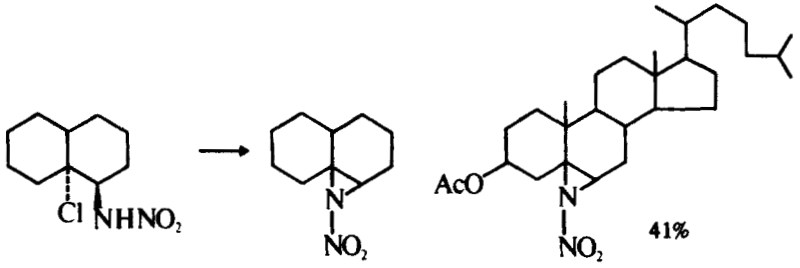


(17)

A number of unusual bicyclic aziridines have been prepared from amino halides. These are summarized in Table 4. Cyclization is also possible when the nitrogen has a heteroatom substituent. Examples are depicted in Eq. 18[160] and Eq. 19.[161]



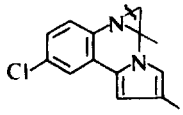
(18)



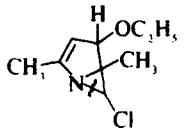
(19)

TABLE 4. BICYCLIC AZIRIDINES PREPARED VIA AMINO HALIDE CYCLIZATION[a]

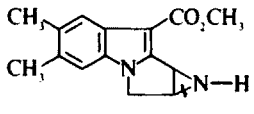
20%[154]



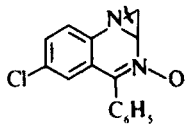
_155



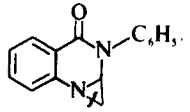
_156



_157



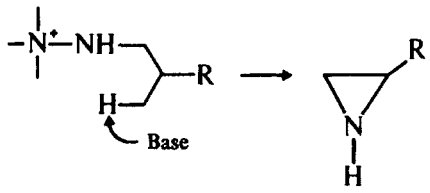
_158



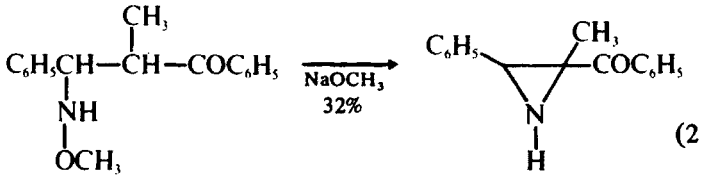
42%[159]

[a] Wavy line indicates bond generated via cyclization.

The cyclizations described so far have been displacements by nitrogen on carbon. This can be reversed with appropriate substituents on nitrogen as depicted in Eqs. 20 and 21.[162] Specific examples of Eq. 20 are located in Table 5.



(20)

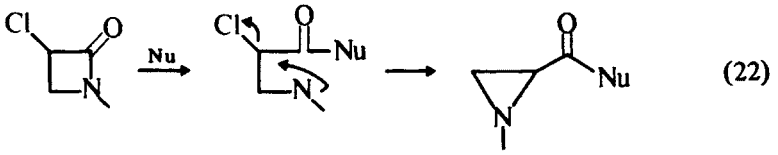


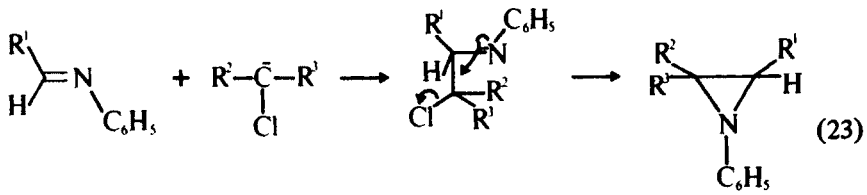
(21)

TABLE 5. AZIRIDINE VIA DISPLACEMENT ON NITROGEN

R	Yield (%)	Ref.
$CON(i\text{-}Pr)C_6H_5$	57	163
$CON(CH_3)C_6H_5$	35	163
$CO_2C_2H_5$	5	164
CO_2CH_3	30	164
$CON(C_2H_5)_2$	56	164
CN	5	164

The contraction of α-chloro-β-lactams to aziridines by certain nucleophiles (Nu) has been reported (Eq. 22). The conversion is stereospecific, and although more exotic mechanisms can be considered, the intermediate shown is more reasonable. These reactions are found in Table 6. The extension of the Darzen's synthesis to aldimines produces aziridines (Eq. 23) and is mechanistically similar to the ring closures of this section. The reaction requires low temperatures and aprotic solvents. The stereochemical course of the reaction depends on the substituents and the base-cation pair employed. Although attempts have been made to rationalize the stereochemical outcome on the basis of these parameters, it is not clear that a satisfactory explanation is available. These results are given in Table 7.

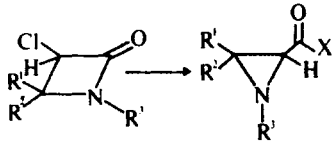




C. *Aziridines from Latent β-Amino Halides*

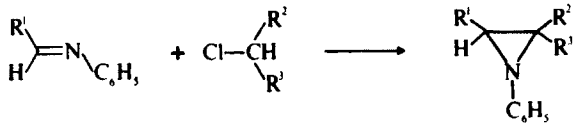
Although the direct closure of β-haloamines usually proceeds without problems, attempts to prepare and purify these precursors can prove to be unsatisfactory. For this reason a number of alternative approaches have been developed in which

TABLE 6. AZIRIDINE VIA β-LACTAM CONTRACTION



R^1	R^2	R^3	X	Yield (%)	Ref.
H	H	*t*-Bu	O^-	94	165, 166
CH_3	H	*t*-Bu	O^-	83	165, 166
H	CH_3	*t*-Bu	O^-	30	165, 166
H	C_6H_5	C_6H_5	NC_5H_{10}	100	167
H	C_6H_5	C_6H_5	NC_4H_8	90	167
H	C_6H_5	C_6H_5	$N(CH_2CH_2)_2O$	20	167
H	*p*-$CH_3OC_6H_4$	C_6H_5	$C_5H_{10}N$	62	167
H	*p*-$CH_3OC_6H_4$	C_6H_5	C_4H_8N	37	167

TABLE 7. DARZEN'S AZIRIDINE SYNTHESES



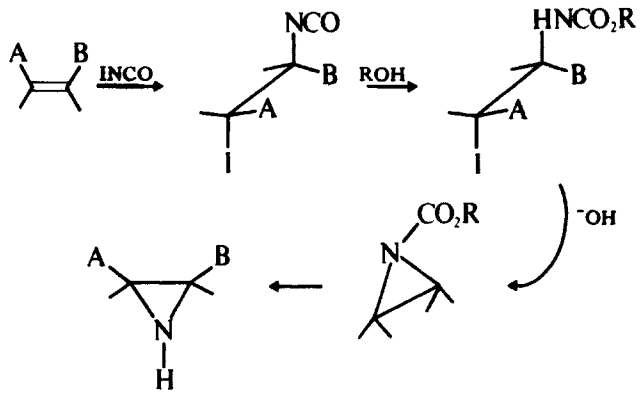
R^1	R^2	R^3	Base	Yield (%)[a]	Ref.
C_6H_5	H	$CO_2C_2H_5$	KO*t*-Bu	29	168
C_6H_5	$CON(C_2H_5)_2$	H	KO*t*-Bu	65	168
C_6H_5	H	CO_2t-Bu	KO*t*-Bu	85	169
C_6H_5	CO_2t-Bu	H	$[(CH_3)_3Si]_2NLi$	–	169
C_6H_5	CN	H	KO*t*-Bu	100	169
C_6H_5	CH_3	CO_2t-Bu	KO*t*-Bu	60	169
C_6H_5	CH_3	CN	KO*t*-Bu	90	169

[a] Total yield with structure shown of predominant isomer.

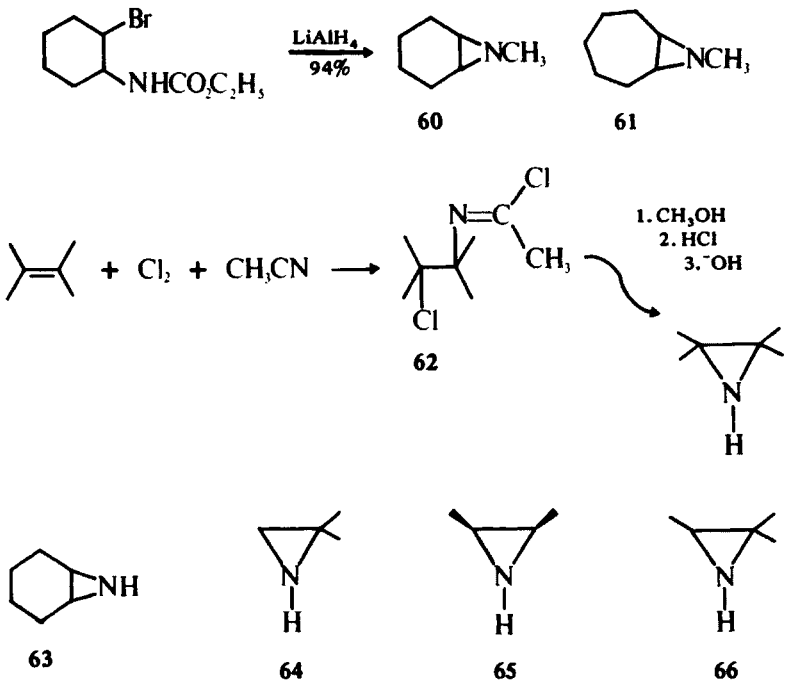
the amino function is generated during the course of the reaction and then, without isolation, converted to the aziridine.

D. *Aziridines from β-Iodoisocyanates*

Iodoisocyanates (generated, e.g., from silver cyanate and I_2) add stereospecifically (*trans*), regiospecifically, and selectively to alkenes. The conditions are mild and the yields high (Eq. 24). The aziridines are produced by subsequent addition of alcohol, followed by cyclization and hydrolysis. Although the urethane intermediate can be bypassed, its formation appears to be advantageous in many instances. The scope and synthetic utility of this route to aziridines has been discussed in detail.[170] The utility of this procedure is indicated in Tables 8 and 9. Use of $LiAlH_4$ instead of alkoxide or hydroxide produces the *N*-methylaziridines **60** and **61**.[183, 184] An alternative to the latent functionality of the isocyanate groups has been proposed. Chlorination of alkenes in acetonitrile yields intermediate **62**, which can be converted to aziridines **63** to **66** in yields of approximately 45%.[185]



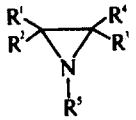
(24)



E. *Reductive Cyclization Routes to Aziridines*

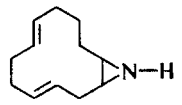
The stability of the aziridine ring toward many reducing agents allows reductive generation of β-amino halides and, without intermediate isolation, direct cyclization to the aziridine. The most useful examples of this approach are found in the hydride

TABLE 8. AZIRIDINES FROM IODOISOCYANATE CYCLIZATIONS

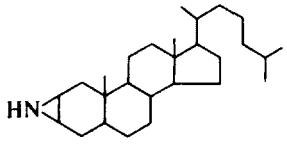


R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	$(CH_2)_4$		H	H	56	170
$(CH_2)_4$		H	H	H	60	170
C_6H_5	H	H	D	H	98	171
$CH_3(CH_2)_7$	H	H	$(CH_2)_7CO_2K$	H	97	101
$CH_3(CH_2)_7$	H	H	$(CH_2)_7CH_2OH$	H	70	101
$CH_3(CH_2)_7$	H	$(CH_2)_7CH_2OH$	H	H	58	101
$CH_3(CH_2)_7$	H	H	$(CH_2)_7CH_3$	H	47	101
$CH_3(CH_2)_7$	H	$(CH_2)_7CH_3$	H	H	19	101
CH_3	*i*-Pr	H	H	$CO_2C_2H_5$	44	99
C_6H_5	H	H	H	H	–	172
C_6H_5	$(CH_2)_4$		H	H	–	173

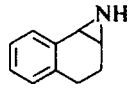
TABLE 9. AZIRIDINES FROM IODOISOCYANATES CYCLIZATIONS



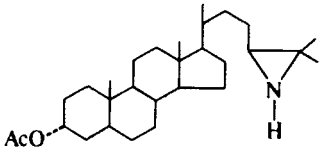
—[170]



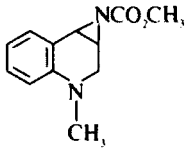
88%[174]



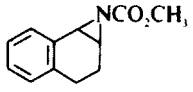
70%[175, 176]



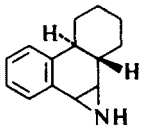
80%[177]



77%[178]



56%[179]



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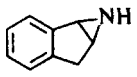
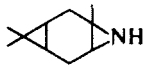
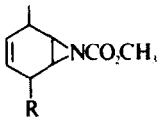


65%[176]



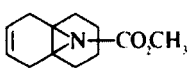
—[181]



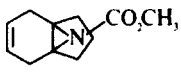
R = H (57%)[182]
R = CH_3 (88%)[182]

92%[182]

95%[182]

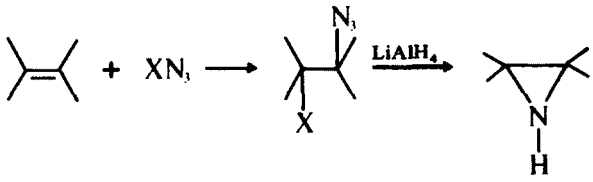


92%[182]



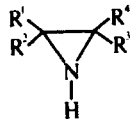
—[182]

reductions of haloazides.[186] These haloazides are accessible via stereospecific addition of halogen azides (Hassner reaction). Haloazides are more reactive toward styrenes and trisubstituted alkenes.[186] Haloazides can be generated from ICl and NaN_3[187] or NBS and NaN_3.[188] The overall scheme is indicated in Eq. 25. $LiAlH_4$ seems to be the reducing reagent of choice. Other reagents that have been used include B_2H_6–^-OH[186] and Pd–C or Pd–H_2.[189] Examples of these reductive cyclizations are found in Tables 10 and 11.



(25)

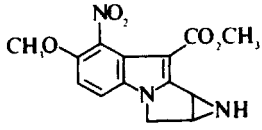
TABLE 10. AZIRIDINES FROM HALOAZIDE REDUCTIONS



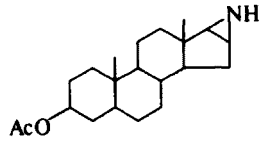
R^1	R^2	R^3	R^4	Reducing Agent	Yield (%)	Ref.
C_6H_5	H	H	H	$LiAlH_4$	–	186
n-C_4H_9	H	H	H	$LiAlH_4$	–	186
$C_6H_5CH_2$	H	H	H	B_2H_6	–	186
t-Bu	H	H	H	$LiAlH_4$	–	186
C_6H_5	H	C_6H_5	H	B_2H_6	87	186
C_6H_5	H	H	C_6H_5	$LiAlH_4$	53	186
CH_3	H	CH_3	H	$LiAlH_4$	100	186
CH_3	H	H	CH_3	$LiAlH_4$	100	186
C_2H_5	H	C_2H_5	H	$LiAlH_4$	100	186
i-Pr	H	i-Pr	H	$LiAlH_4$	95	186
C_6H_5	H	CH_3	H	$LiAlH_4$	95	186
H	$(CH_2)_3$		H	$LiAlH_4$	100	186
H	$(CH_2)_4$		H	$LiAlH_4$	100	186
H	$(CH_2)_5$		H	$LiAlH_4$	100	186
H	$(CH_2)_6$		H	$LiAlH_4$	100	186
$(CH_2)_5$		H	H	$LiAlH_4$	100	186
C_6H_5	C_6H_5	H	H	$LiAlH_4$	–	186
CH_3	CH_3	H	H	$LiAlH_4$	–	186
C_6H_5	CH_3	H	H	$LiAlH_4$	–	186
C_6H_5	C_6H_5	H	H	$LiAlH_4$	–	186
CH_3	$(CH_2)_4$		H	$LiAlH_4$	81	186
C_6H_5	$(CH_2)_4$		H	$LiAlH_4$	Low	186
CH_3	CH_3	CH_3	H	$LiAlH_4$	45	186
CH_3	CH_3	C_2H_5	H	$LiAlH_4$	60	186
CH_3	CH_3	CH_3	CH_3	$LiAlH_4$	56	186
CH_3	CH_3	H	$(CH_2)_2CH(CH_2)_2OAc$ (CH$_3$ on CH)	$LiAlH_4$	65	188
CH_3	H	C_2H_5	CH_3	$LiAlH_4$	55	188
CH_3	H	CH_3	C_2H_5	$LiAlH_4$	55	188
CH_3	H	CH_3	n-C_5H_{11}	$LiAlH_4$	65	188
CH_3	H	n-C_5H_{11}	H	$LiAlH_4$	13	188
H	H	H	n-C_6H_{13}	$LiAlH_4$	13	188
$(CH_3)_3Si$	H	H	H	$LiAlH_4$	–	190
$(CH_3)_3Si$	H	H	C_6H_5	$LiAlH_4$	–	190

The reaction between iodoazides and trivalent phosphorus compounds also leads to aziridines (Eq. 26).[194] Other mechanisms for this conversion may be proposed. The utility of this reaction stems from the fact that phosphorus substituents can be removed in high yield by $LiAlH_4$ reduction. In a few cases this approach offers advantage over the direct $LiAlH_4$ reductive cyclization of halo azides. Specific examples of Eq. 26 are found in Table 12.

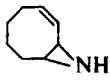
TABLE 11. AZIRIDINES FROM HALOAZIDE REDUCTIONS



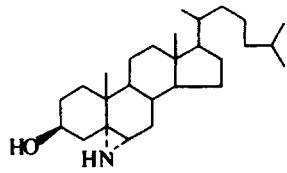
60% (Pd–C, H_2)[189]



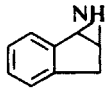
– ($LiAlH_4$)[140]



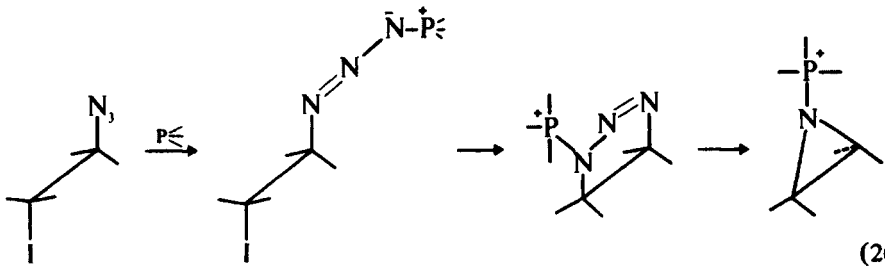
49% ($LiAlH_4$)[187]



90% ($LiAlH_4$)[191]

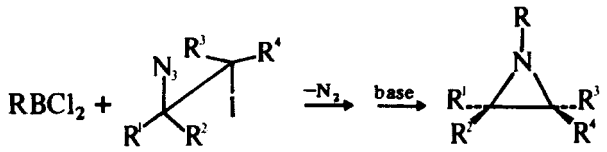


90% ($LiAlH_4$)[192]



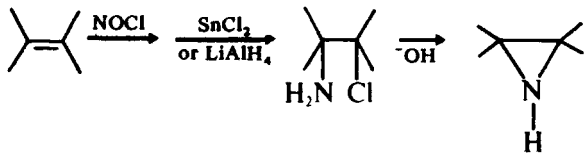
(26)

An especially interesting variation of this synthesis is Eq. 27.[195] This sequence offers a new route to *N*-substituted aziridines as indicated in Table 13.



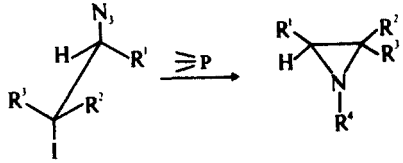
(27)

Alkenes that are especially reactive toward electrophilic attack add NOCl. The product can be reduced and cyclized to give aziridines (Eq. 28).



(28)

TABLE 12. IODOAZIDE TO AZIRIDINE CONVERSIONS BY PHOSPHINE AND PHOSPHITES



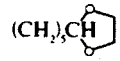
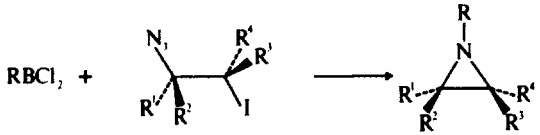
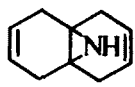
R^1	R^2	R^3	R^4	Yield (%)	Ref.
CH_3	CH_3	H	$\overset{+}{P}(C_6H_5)_3$	91	193
CH_3	CH_3	H	$PO(OCH_3)_2$	90	193
CH_3	CH_3	H	$PO(OC_2H_5)_2$	95	193
CH_3	H	CH_3	$\overset{+}{P}(C_6H_5)_3$	91	193
CH_3	H	CH_3	$PO(OCH_3)_2$	89	193
CH_3	H	CH_3	$PO(OC_2H_5)_2$	100	193
C_6H_5	H	C_6H_5	$PO(OCH_3)_2$	93	193
CH_3	H	$CO_2C_2H_5$	$PO(OCH_3)_2$	80	193
CH_3	H	C_6H_5	$\overset{+}{P}(C_6H_5)_3$	86	193
CH_3	H	C_6H_5	$PO(OCH_3)_2$	76	193
$(CH_2)_4$		H	$\overset{+}{P}(C_6H_5)_3$	100	193
$(CH_2)_6$		H	$\overset{+}{P}(C_6H_5)_3$	71	193
C_6H_5	H	H	$\overset{+}{P}(C_6H_5)_3$	95	193
C_6H_5	H	H	$PO(OCH_3)_2$	87	193
n-Bu	H	H	$PO(OCH_3)_2$	94	193
$(CH_2)_3$		H	$PO(OCH_3)_2$	95	193
$(CH_2)_4$		H	$PO(OC_2H_5)_2$	95	193
CH_3	H		$PO(OC_2H_5)_2$	–	194

TABLE 13. AZIRIDINES FROM IODOAZIDES AND IODOBORANES[195]



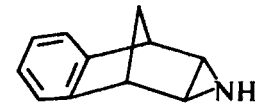
R^1	R^2	R^3	R^4	R	Yield (%)
CH_3	H	CH_3	H	$CH_3(CH_2)_5$	92
H	$(CH_2)_4$		H	$CH_3(CH_2)_5$	94
$CH_3(CH_2)_3$	H	H	H	$CH_3(CH_2)_5$	91
H	$(CH_2)_4$		H	$CH_3(CH_2)_2C(CH_3)CH_2$	87
H	$(CH_2)_4$		H	$CH_3(CH_2)_2CH(C_2H_5)$	86
H	$(CH_2)_4$		H	$(CH_2)_4CH$	94
H	$(CH_2)_4$		H	C_6H_{11}	86
H	H	H	H	C_6H_5	73
H	$(CH_2)_4$		H	C_6H_5	73
CH_3	H	H	CH_3	C_6H_5	83
CH_3	H	CH_3	H	C_6H_5	76

Aziridines **67**,[196] **68**,[81] and **69**[197] were synthesized by this procedure.



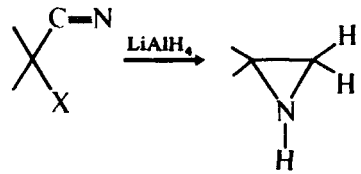
67

68



69

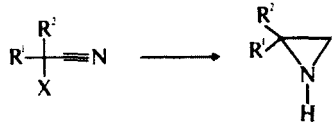
The reductive cyclization of nitriles bearing a chloro or tosylate in the α-position has become a very useful and generally applied procedure (Eq. 29).



X = OTs, Cl, etc. (29)

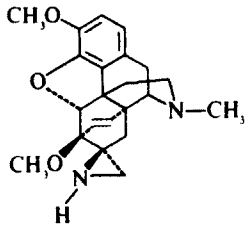
The precursors are, in turn, usually available via the addition of HCN to the appropriate ketone or aldehyde. Examples of aziridines synthesized in this manner are found in Tables 14 and 15. Several mechanisms may be written. Although it is possible that an azirine intermediate is involved (by analogy to $LiAlH_4$ and RMgX reactions with oximes that yield aziridines via azirines), it is also possible that the aziridine is formed in a direct, simple nucleophilic ring closure after reduction of the nitrile group. In support of the second possibility is the observation that α-halo- and α,α-dihaloimines also yield aziridines (Eq. 30). In these cases (Tables 16 and 17) azirine intermediates seem much less likely.

TABLE 14. AZIRIDINES FROM $LiAlH_4$ REDUCTIONS OF NITRILE DERIVATIVES

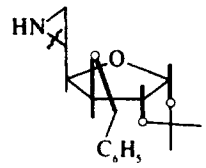


R^1	R^2	X	Yield (%)	Ref.
n-C_3H_7	H	Cl	82	198
i-C_3H_7	H	Cl	72	198
n-C_6H_{13}	H	Cl	67	198
$C_6H_5CH_2$	H	Cl	58	198
C_6H_5	H	Cl	46	198
$(CH_2)_5$		Cl	68	199
C_6H_{11}	H	Cl	83	200
	H	OTs	54	201

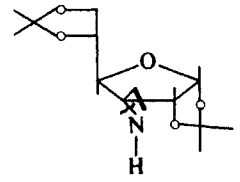
TABLE 15. AZIRIDINES FROM $LiAlH_4$ REDUCTIONS OF NITRILE DERIVATIVES[a]



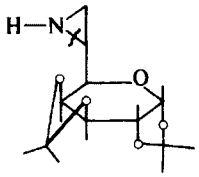
202



33%[201]

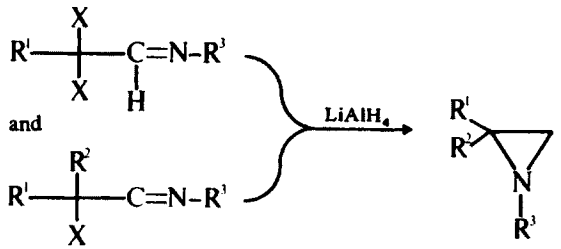


75%[203, 204]



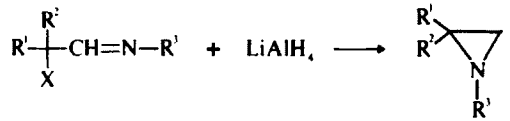
72%[205]

[a] Wavy line indicates the new C–N bond.



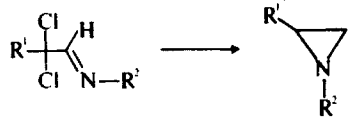
(30)

TABLE 16. AZIRIDINES FROM α-HALOIMINE REDUCTIONS WITH $LiAlH_4$



R^1	R^2	X	R^3	Yield (%)	Ref.
C_2H_5	H	Cl	$CH_2CH{=}CH_2$	55	206
H	H	Br	C_6H_{11}	44	206
H	H	Br	*t*-Bu	60	206
i-Pr	H	Br	*t*-Bu	47	206
t-Bu	H	Br	CH_3	48	206
CH_3	CH_3	Cl	*t*-Bu	0	207
CH_3	CH_3	Cl	C_6H_{11}	90	207
CH_3	CH_3	Cl	$CH_2C_6H_5$	39	207
CH_3	CH_3	Cl	*i*-Pr	78	207
C_2H_5	C_2H_5	Cl	C_6H_{11}	85	207
$(CH_2)_5$		Cl	*t*-Bu	26	207
$(CH_2)_5$		Cl	C_6H_{11}	90	207
CH_3	CH_3	Cl	CH_3	90	207

TABLE 17. AZIRIDINES FROM α,α-DIHALOIMINE REDUCTIONS WITH $LiAlH_4$

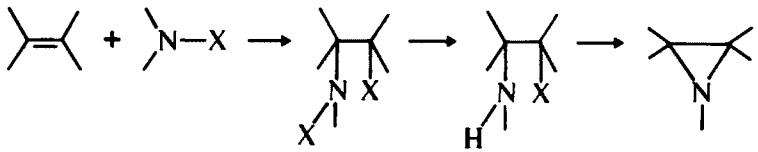


R^1	R^2	Yield (%)	Ref.
i-Bu	C_6H_{11}	86	208
n-Pr	C_6H_{11}	70	208
neo-Pent	C_6H_{11}	98	208
t-Bu	C_6H_{11}	65	208
CH_3	*t*-Bu	90	209
C_2H_5	*t*-Bu	90	209
n-Pr	*t*-Bu	80	209
i-Pr	*t*-Bu	80	209
n-Bu	*t*-Bu	84	209
s-Bu	*t*-Bu	84	209
n-Pr	$COCH_3/C_2H_5$	89	210
n-Bu	$COCH_3/C_2H_5$	95	210
n-Pent	$COCH_3/C_2H_5$	55	210

F. *Aziridines from N-halo- and N,N-dihaloamines*

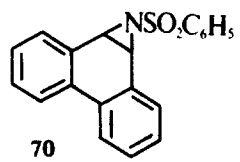
Amines that bear suitable substituents can be converted to their mono- or dihalo derivatives. These derivatives can undergo nucleophilic addition to electrophilic alkenes (Eq. 31)[211] with subsequent cyclization (Eq. 32).

(31)



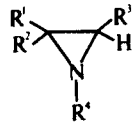
(32)

In some cases the intermediate *N*-halo compound is reduced in a separate step. In others, the base used for cyclization also serves as the dehalogenating agent. Examples of aziridines prepared by this route are illustrated in Table 18 and by structure **70**.[220]



70

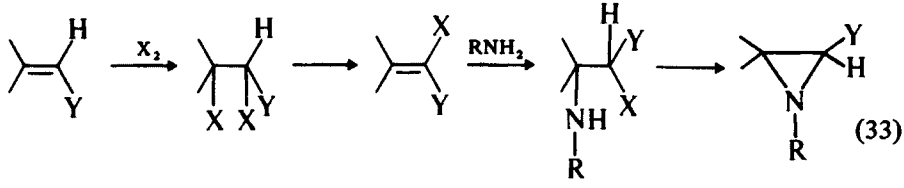
TABLE 18. AZIRIDINES FROM *N,N*-DIHALOAMINE ADDITIONS



R^1	R^2	R^3	R^4	Yield (%)	Ref.
C_6H_5	H	H	$CO_2C_2H_5$	60	212
C_8H_{17}	H	H	$CO_2C_2H_5$	75	212
$C_{10}H_{21}$	H	H	$CO_2C_2H_5$	65	212
C_6H_5	H	H	$PO(C_2H_5)_2$	72	213
CH_3	CH_3	H	$PO(C_2H_5)_2$	67	213
CO_2CH_3	H	H	$PO(C_2H_5)_2$	28	213
CO_2CH_3	CH_3	H	$PO(C_2H_5)_2$	24	213
C_3H_7	H	H	$PO(C_2H_5)_2$	60	214
C_4H_9	H	H	$PO(C_2H_5)_2$	65	214
C_5H_{11}	H	H	$PO(C_2H_5)_2$	80	214
C_7H_{15}	H	H	$PO(C_2H_5)_2$	80	214
C_4H_9	C_2H_5	H	$PO(C_2H_5)_2$	90	214
CH_3	CH_3	CH_3	$PO(C_2H_5)_2$	70	214
C_6H_5	H	H	$PO(C_2H_5)_2$	82	215
C_6H_5	H	H	$SO_2CH_2C_6H_5$	–	216
CH_2Cl	H	H	*p*-$ClC_6H_4SO_2$	72	217
CH_2Cl	CH_3	H	*p*-$ClC_6H_4SO_2$	84	217
CCl_3	H	H	*p*-$ClC_6H_4SO_2$	92	218
CCl_3	H	H	$C_6H_5SO_2$	90	218
H	H	H	*p*-$ClC_6H_4SO_2$	82	219
C_6H_5	H	H	*p*-$ClC_6H_4SO_2$	80	219
CN	H	H	*p*-$ClC_6H_4SO_2$	50	219

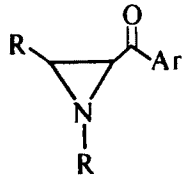
G. *Aziridines via Nucleophilic Addition to Vinyl Halides*

Most of the previously discussed approaches were of greatest use for the synthesis of aziridines lacking electron-withdrawing substituents since most of the precursors were prepared via electrophilic attack on alkenes. The reactions described in this section involve nucleophilic attack on vinyl halides. Such reactions are facilitated by electron-attracting substituents. This strategy thus provides a complement to the other methods. The overall scheme is depicted in Eq. 33 (when Y is an electron-attracting group).

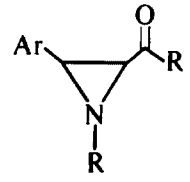


(33)

There are many variations on this theme. Either the vinyl halide or the dihalide (which can be dehydrohalogenated by excess amine) can be used. The reaction of the vinyl group with amine and halogen (usually I_2) can allow direct formation of the desired aziridine. The stereochemical course (*cis-trans* mixtures almost always result), factors that alter the stereochemical course of the reaction, structural assignment, and so on, have been summarized elsewhere.[221-223] Some of the more interesting recent applications of this synthesis are now reviewed.

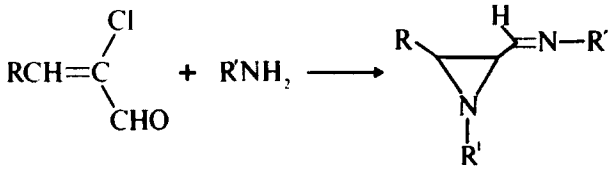


71



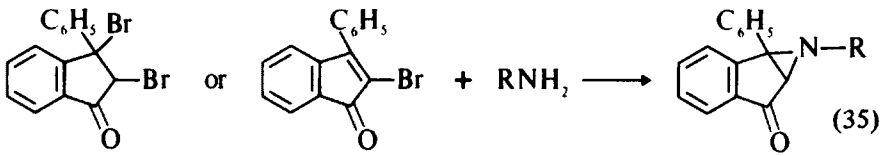
72

The use of this approach for the synthesis of ketones with general structures 71 and 72 continues because of the interesting chemistry manifested by such functionally substituted aziridines.[64, 224-227] Aldehydes give both aziridines and imines (Eq. 34).[228] A similar reaction of two functional groups has been noted in cyclic, unsaturated ketones (Eq. 35).[229] An extension of this approach to the use of diamines resulted in the formation of an additional ring. This is illustrated by Eqs. 36,[230] 37,[230] and 38.[231]



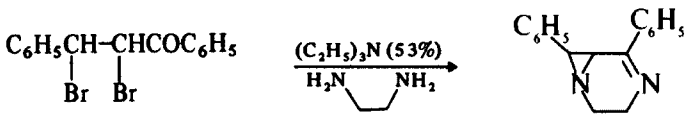
(34)

R	R′	Yield (%)
H	*i*-Pr	38
H	*t*-Bu	21
CH_3	C_2H_5	38
CH_3	*i*-Pr	53
CH_3	*t*-Bu	58

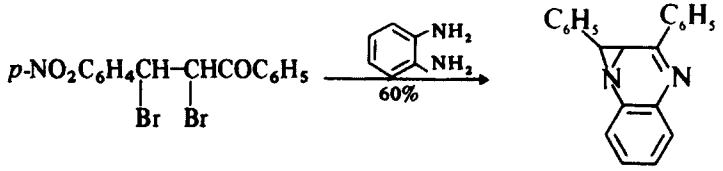


$R = C_6H_{11}$ (98%)
$R = CH_3$ (70%)

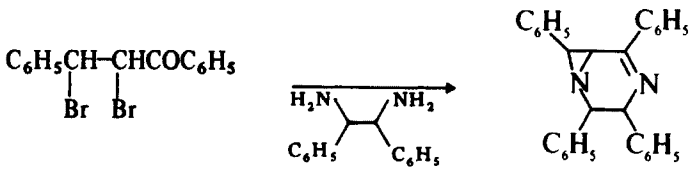
(35)



(36)



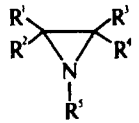
(37)



(38)

Analogous nucleophilic additions have been very useful in the synthesis of aziridine esters (Table 19) and nitriles (Table 20) as well as structures **73** (90%)[238] and **74** (76%).[241]

TABLE 19. AZIRIDINE ESTERS AND AMIDES VIA NUCLEOPHILIC ADDITION



R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
p-$C_6H_5C_6H_4$	H	H	CO_2CH_3	C_6H_{11}	–	232
$CO_2C_2H_5$	H	H	$CO_2C_2H_5$	H	–	233
H	H	H	$CO_2C_2H_5$	H	38	234
H	H	H	CO_2Pr	H	25	234
H	H	H	CO_2-*i*-Pr	H	76	234
H	H	H	CO_2Bu	H	44	234
H	H	H	CO_2CH_3	CH_3O	46	235
H	H	H	CO_2CH_3	C_2H_5O	55	235
H	H	H	CO_2CH_3	*i*-PrO	79	235
H	H	H	CO_2CH_3	$C_6H_5CH_2O$	63	235
H	H	CO_2CH_3	CO_2CH_3	CH_3O	74	235
H	H	$CO_2C_2H_5$	$CO_2C_2H_5$	CH_3O	53	235
H	H	$CO_2C_2H_5$	$CO_2C_2H_5$	C_2H_5O	43	235
H	H	H	CO_2-l-Menthyl	CH_3O	60	236
H	H	H	$CONH_2$	CH_3O	98	236
H	H	H	$CONH_2$	C_2H_5O	86	236
H	H	H	$CONH_2$	*i*-PrO	94	236
H	H	H	$CONH_2$	$C_6H_5CH_2O$	100	236
X[a]	H	H	$CO_2C_2H_5$	$C_6H_5CH_2$	25	237

[a] X =

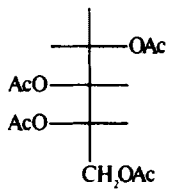
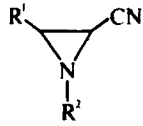
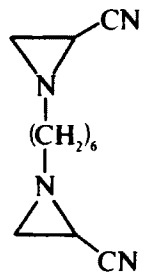


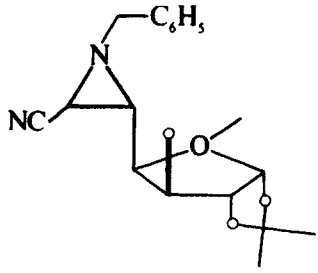
TABLE 20. AZIRIDINE NITRILES VIA NUCLEOPHILIC ADDITION



R^1	R^2	Yield (%)	Ref.
H	CH_3	82	238
H	C_3H_7	90	238
H	$CH(CH_3)_2$	93	238
H	*t*-Bu	93	238
H	C_5H_{11}	95	238
H	C_6H_{13}	95	238
H	*p*-$ClC_6H_4CH_2$	98	238
H	*p*-$CH_3OC_6H_4CH_2$	92	238
H	$CH(C_6H_5)_2$	90	238
H	C_6H_5	86	238
CH_3	$C_6H_5CH_2$	85	238
CH_3	*p*-$CH_3OC_6H_4CH_2$	84	238
CH_3	*p*-$ClC_6H_4CH_2$	85	238
C_6H_5	$C_6H_5CH_2$	87	238
C_6H_5	*p*-$ClC_6H_4CH_2$	91	238
H	H	65	239
CH_3 or H	Alkyl	–	240

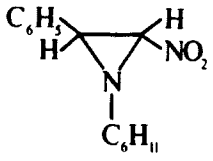


73

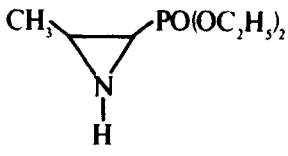


74

Nucleophilic addition has also been successfully applied to nitroaziridines (75),[242] aziridine phosphonates (76),[243] and sulfonyl aziridines (Table 21).

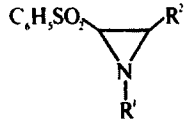


75



76

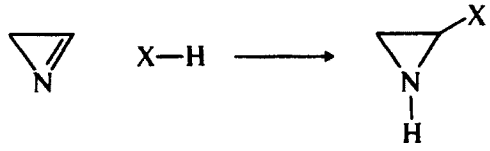
TABLE 21. PHENYLSULFONYL AZIRIDINES VIA NUCLEOPHILIC ADDITION[244]



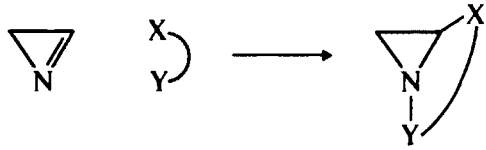
R^1	R^2	Yield (%)
CH_3	H	25
C_2H_5	H	35
i-Pr	H	56
t-Bu	H	81
C_6H_{11}	H	63
C_2H_5	CH_3	38
i-Pr	CH_3	71
n-Pr	CH_3	63
t-Pr	CH_3	14
C_6H_{11}	CH_3	72
$C_6H_5CH_2$	CH_3	66

2. Aziridines from Azirines

Since synthetic approaches to azirines have grown more sophisticated and numerous, azirines themselves have become useful precursors of aziridines. The sections that follow arbitrarily separate additions to azirines that produce N–H groups (Eq. 39) and cycloadditions (Eq. 40).



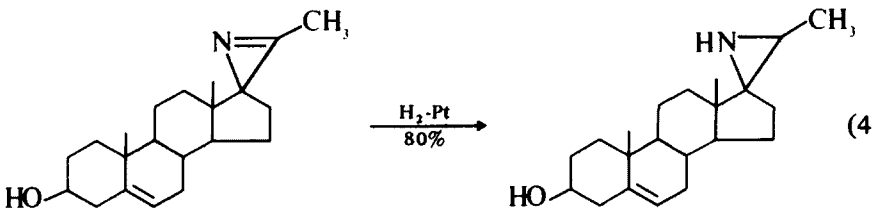
(39)



(40)

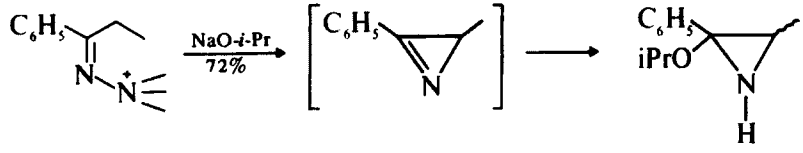
A. *Conversion of Azirines to Aziridines*

Selective catalytic reduction of azirines has been reported (Eq. 41).[245,246] More numerous are examples of azirine reduction by $LiAlH_4$ to give the corresponding aziridines in good yield, as shown in Table 22.[247,248] The reduction proceeds with good stereospecificity.[248] Other reducing agents such as $NaBH_4$ and $NaAlH(OCH_2CH_2OCH_3)_2$ have been used.[249]

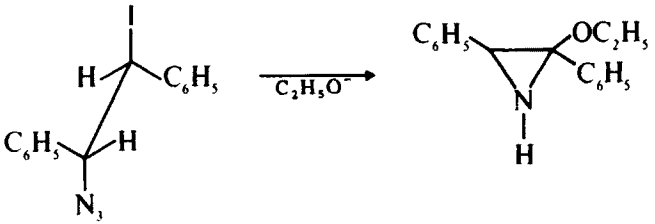


(41)

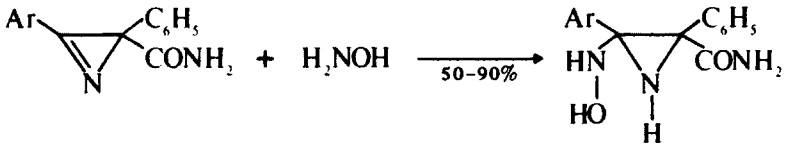
The addition of sodium isopropoxide to an azirine (unisolated) has been shown to give *cis* and *trans* isomers (Eqs. 42[250] and 43[251]). Hydroxylamine[252] and hydrazine[253] add to azirines as indicated in Eqs. 44 and 45, respectively.



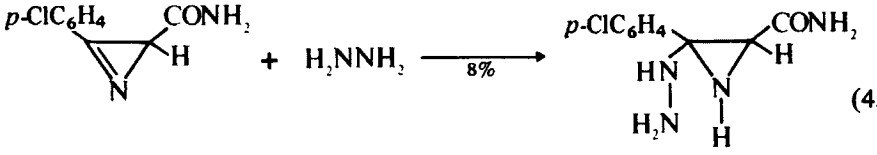
(42)



(43)

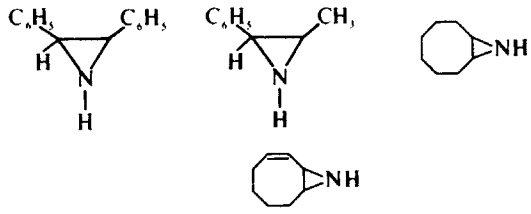


(44)

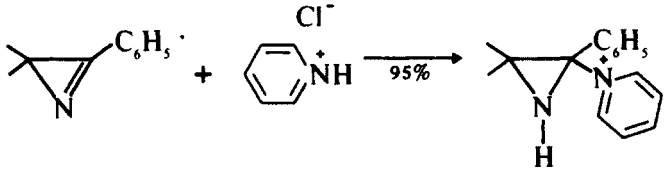


(45)

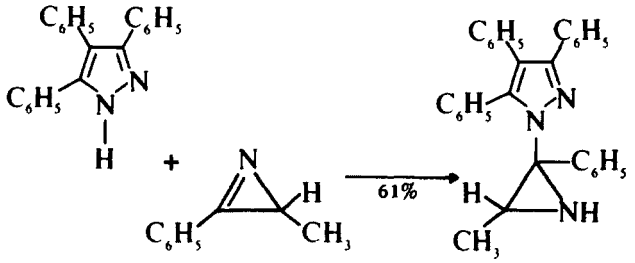
TABLE 22. AZIRIDINES FROM AZIRINES VIA HYDRIDE REDUCTION[248]



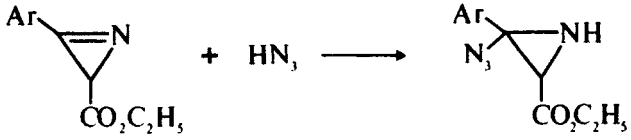
In both cases additional (nmr) spectral and chemical data would have supported the structural-stereochemical assignments. Addition of pyridine hydrochloride has produced the surprisingly stable salt indicated in Eq. 46.[254] The addition of a pyrazole goes as shown in Eq. 47, instead of producing the originally postulated structure.[255] Addition of hydrazoic acid takes place stereoselectively (stereochemistry unknown) as indicated in Eq. 48.[256] The bisaziridine 77 is presumably the result of addition to an unisolated azirine.[257]



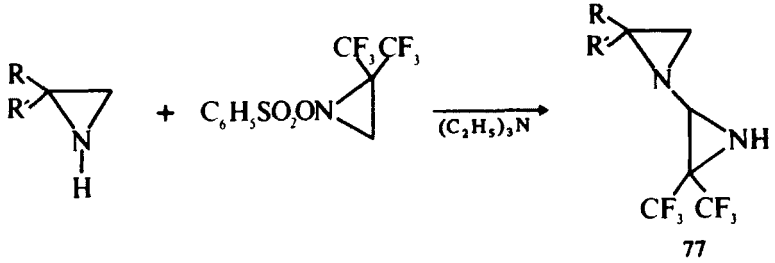
(46)



(47)

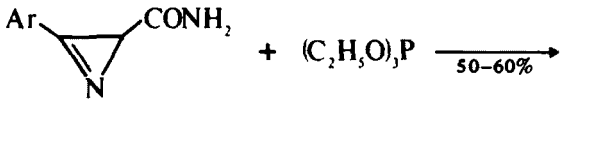


(48)

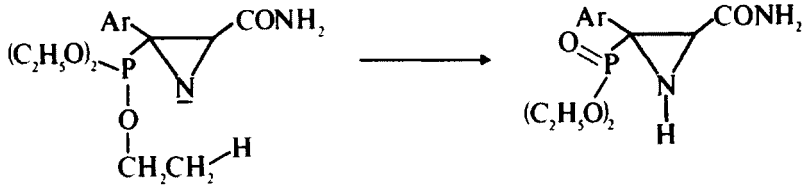


77

Novel aziridinyl phosphonates are formed from the reaction of certain azirines with trialkyl phosphites (Eq. 49).[258] Presumably an intermediate formed by nucleophilic attack on the imine undergoes inter- or intramolecular elimination (Eq. 50).

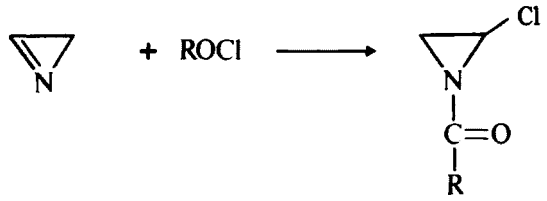


(49)

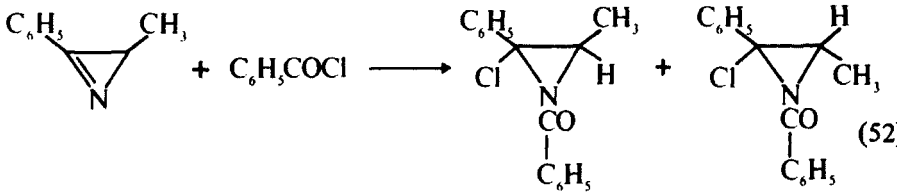


(50)

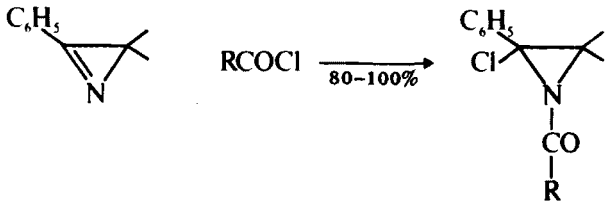
Besides the preceding examples in which atoms other than carbon become joined to the azirine ring, a variety of carbon-carbon bond-forming reactions have been reported. Both acyl and aroyl halides add across the imine bond of azirines to produce stable aziridinyl halides (Eq. 51).[259-261] The yields are generally high. The products apparently owe their stability to electron delocalization by the amide carbonyl. Typical examples of these addition products are given by Eqs. 52,[259] 53,[260] and 54.[261]



(51)

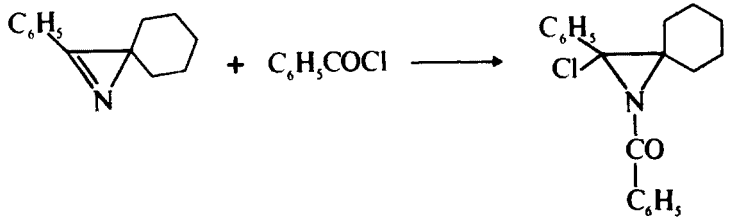


(52)



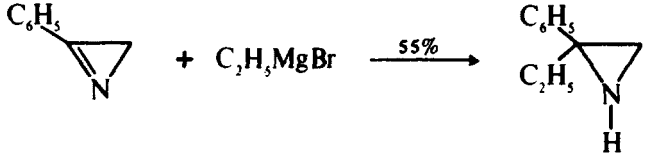
(53)

R = CH_3, $C_6H_5CH_2$, *t*-Bu, C_6H_5, CH_2=CH, CH_2=CH–CH_2, CCl_3, etc.

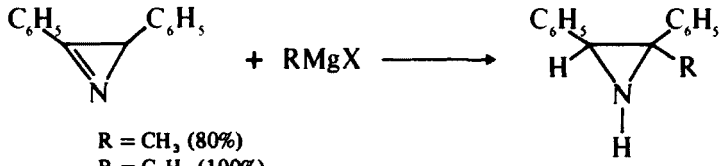


(54)

Addition of organometallic reagents to the strained imine bond of azirines should be a facile process, and a number of stable aziridines have been isolated in this manner. Equations 55,[262] 56,[200] and 57[263] illustrate the addition of Grignard and organolithium reagents. The addition shown in Eq. 58 is particularly significant because it allows introduction of a pendant functional group.[264] A related Reformatsky reaction (Eq. 59) yields the analogous esters.[265]

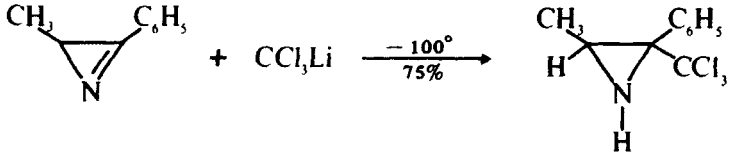


(55)

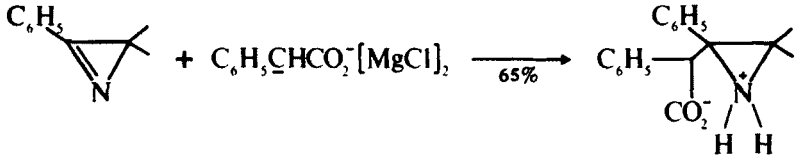


$R = CH_3$ (80%)
$R = C_2H_5$ (100%)
$R = C_6H_5$ (100%)

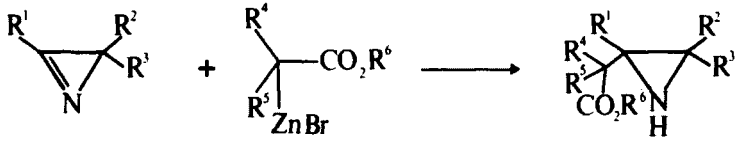
(56)



(57)

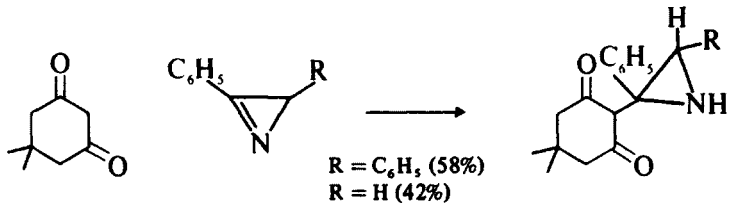


(58)



(59)

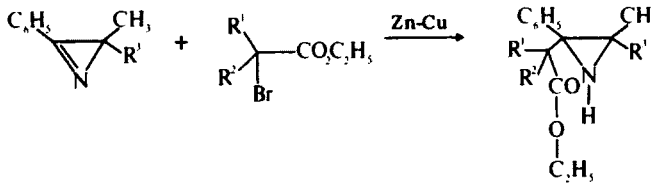
The generality of this reaction is indicated in Table 23. Aldol-type condensations have also been reported (Eqs. 60 and 61).[266]



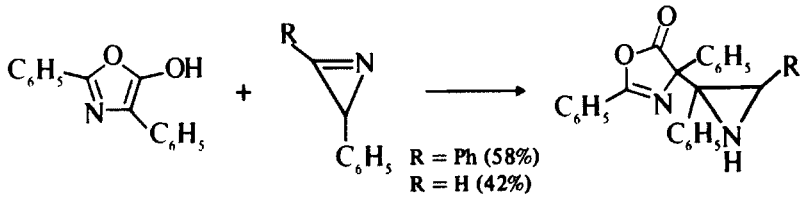
$R = C_6H_5$ (58%)
$R = H$ (42%)

(60)

TABLE 23. AZIRIDINES FROM REFORMATSKY-TYPE ADDITIONS TO AZIRINES[265]



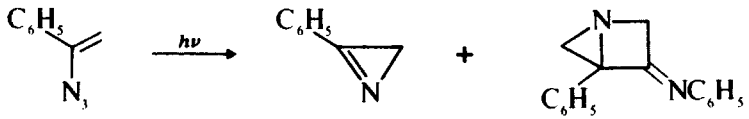
R^1	R^2	R^3	Yield (%)
H	H	CH_3	65
H	CH_3	CH_3	81
CH_3	CH_3	CH_3	66
H	H	H	37
H	CH_3	H	59
CH_3	CH_3	H	56



R = Ph (58%)
R = H (42%)

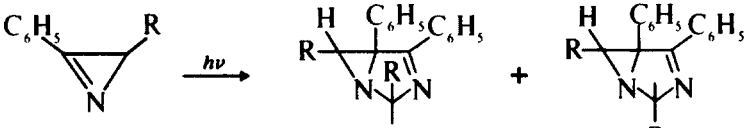
(61)

Cycloadditions to azirines also yield aziridines. An initial report[267] that the bicyclic structure **78** resulted from vinyl azide photolysis (via the expected intermediate azirine) has been shown to be incorrect.[268–270]



78

Photolysis of a variety of azirines (Eq. 62) has been shown to yield products of structures **79** and **80**. Apparently the azirine undergoes photochemical ring opening to a nitrile ylid which, in turn, undergoes (thermal) 1,3-dipolar cycloaddition to a second molecule of azirine (Eq. 63). In support of this suggestion, it has been found that chemical generation of nitrile ylids yield similar structures (Eq. 64).[266] Azomethine ylids (generated from aziridines) also have been added to azirines.[271] The products (**81**) are summarized in Table 24.

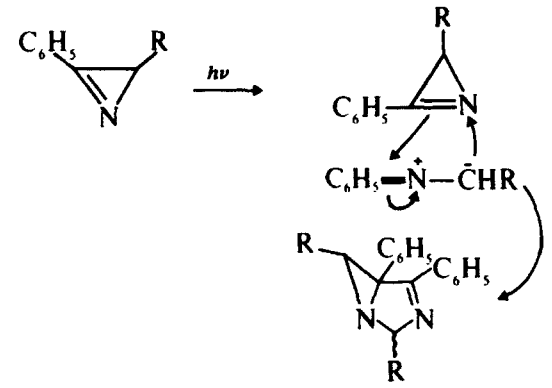


79

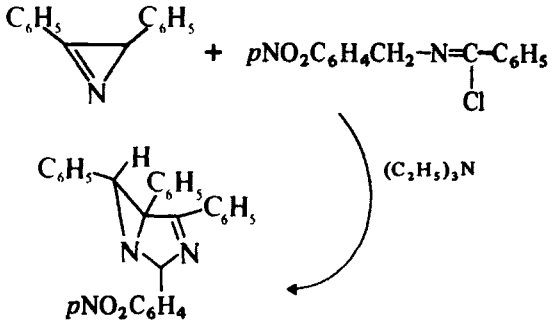
R = H, CH_3, C_6H_5

80

(62)



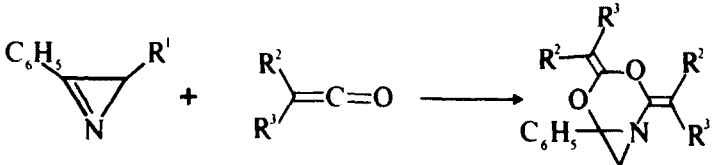
(63)



(64)

81

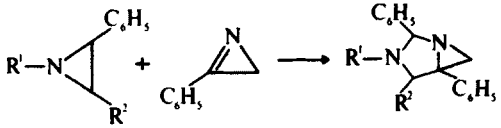
Additions of ketenes (Eq. 65)[272, 273] and phenyl isocyanate (Eq. 66)[274] yield similar heterocyclic structures. In the latter case the reaction is reversible. Presumably intermediates of structure 82 are formed and undergo stepwise cyclization to the observed products. The reaction between a ketenimine and an azirine (Eq. 67) takes an unusual course.[273] Although the reaction probably yields intermediate 83, subsequent steps and the timing of the oxidation step have not been established. Two reports of apparent (not necessarily concerted) [4 + 2] cycloadditions on azirines have appeared (Eqs. 68,[275] 69,[276] and 70.[276]



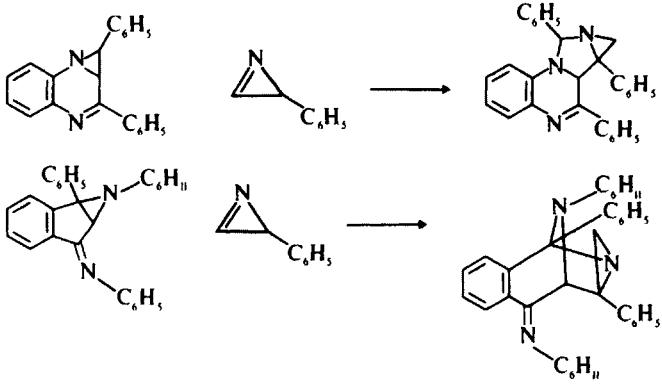
(65)

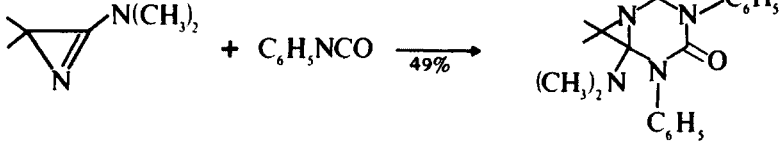
$R^1 = H; R^2, R^3 = C_6H_5$ (60%)
$R^1 = CH_3; R^2, R^3 = C_6H_5$ (65%)
$R^1 = H; R^2 = t\text{-Bu}; R^3 = CN$

TABLE 24. AZIRIDINES FROM ADDITION OF AZOMETHINE YLIDS TO AZIRINES[271]

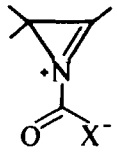


R^1	R^2	Yield (%)
C_6H_{11}	*p*-$CH_3OC_6H_4CO$	81
C_6H_{11}	*p*-$CH_3C_6H_4CO$	73
C_6H_{11}	C_6H_5CO	77
C_6H_{11}	*p*-ClC_6H_4CO	80
C_6H_{11}	*p*-$NO_2C_6H_4CO$	74
$C_6H_5CH_2$	C_6H_5	78

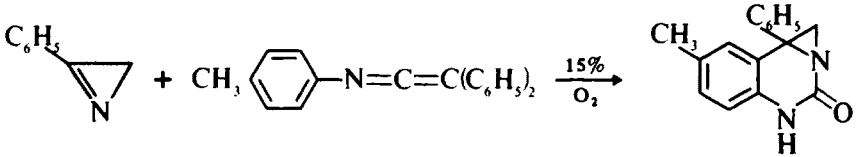




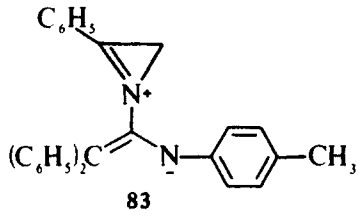
(66)



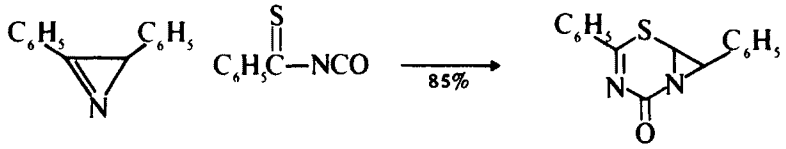
82



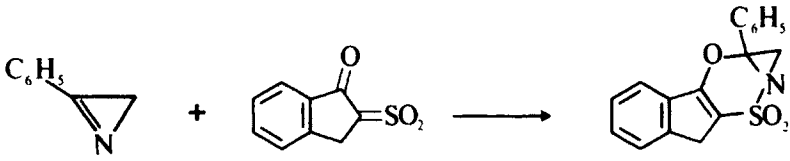
(67)



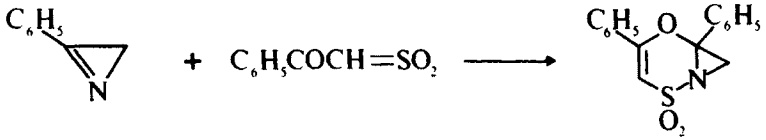
83



(68)



(69)

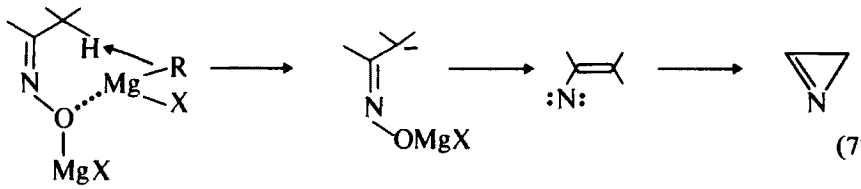


(70)

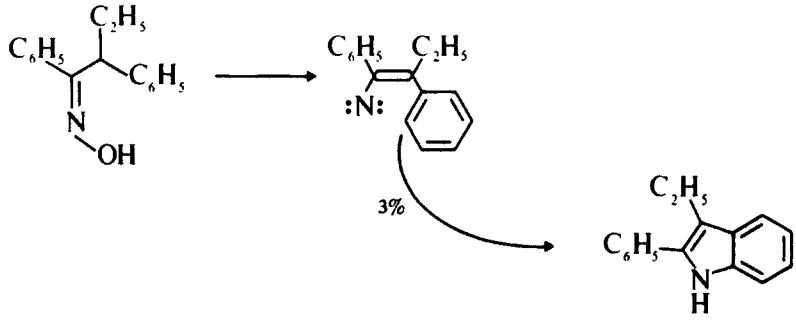
B. *Aziridines from Oximes and Related Reactions*

The reaction between oximes and Grignard reagents (Hoch-Campbell synthesis, Eq. 71) has been the subject of continued study. The best evidence suggests that the hydrogen is abstracted *cis* to the oxime oxygen as shown in Eq. 71.[277] The specificity of this first step is solvent dependent.[277] Subsequent steps include nitrene formation and cyclization to an intermediate azirine.[262] The azirine intermediate has been isolated from the reaction under carefully controlled conditions.[262] Support for the nitrene intermediate is found in the isolation of an indole (84) as a minor product (Eq. 72).[278, 279]

(71)

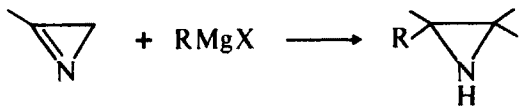


(72)

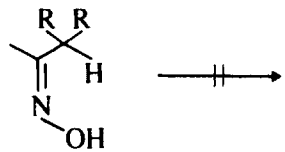


84

Under normal reaction conditions, the excess Grignard reagent adds to the azirine intermediate to produce an aziridine (Eq. 73). The addition reaction is relatively stereoselective, and this selectivity is a complex function of azirine substituents and the Grignard reagent.[278] The reaction is not satisfactory when there are two alkyl groups on the *cis*-α carbon (Eq. 74).[262] The utility of this reaction is indicated by the entries in Tables 25 and 26. The reaction has also been extended to steroidal side chain modifications.[289]



(73)

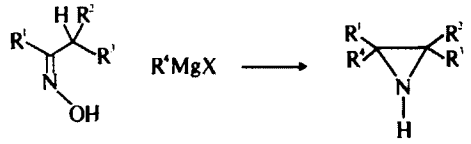


(74)

A related aziridine synthesis that has been published recently appears to offer, in certain cases, advantages over the oxime reduction (Eq. 75).

(75)

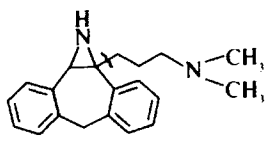
TABLE 25. AZIRIDINES FROM GRIGNARD ADDITIONS TO OXIMES



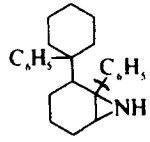
R^1	R^2	R^3	R^4	Yield (%)	Ref.
C_6H_5	CH_3	H	CH_3	41	277
H	C_6H_5	CH_3	CH_3	20	277
C_6H_5	C_6H_5	H	CH_3	49	277
C_6H_5	C_6H_5	CH_3	CH_3	23	277
$C_6H_5CH_2$	H	H	C_6H_5	22	262
$C_6H_5CHCH_3$	H	H	C_6H_5	67	262
$C_6H_5C(CH_3)_2$	H	H	C_6H_5	70	262
i-Pr	H	H	C_6H_5	75	262
t-Bu	H	H	C_6H_5	90	262
C_6H_5	C_6H_5	C_2H_5	CH_3	30[a]	278,279
$(CH_2)_4$		H	CH_3	22	280
$(CH_2)_4$		H	C_2H_5	36	280
C_6H_5	CH_3	H	$CH{=}CH_2$	73	281
C_6H_5	CH_3	CH_3	$CH{=}CH_2$	46	281
$(CH_2)_4$		H	$CH{=}CH_2$	54	281
C_6H_5	CH_3	H	*i*-Pr	40	282
C_6H_5	C_6H_5	H	*i*-Pr	40	282
$C_6H_5(CH_3)CH$	H	H	C_6H_5	–	283
$C_6H_5CH_2$	C_6H_5	H	$(CH_3)_2CHCH_2$	47	284
C_6H_5	C_6H_5	H	$(CH_3)_2CHCH_2$	49	284

[a] Stereochemical mixture.

TABLE 26. OTHER AZIRIDINES FROM GRIGNARD ADDITIONS TO OXIMES[a]

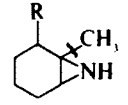


46%[285]



16%[287]

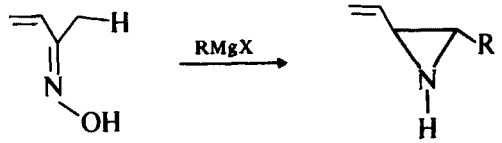
R = CH_3 (21%)
R = C_2H_5 (75%)[286]
R = C_6H_5 (22%)



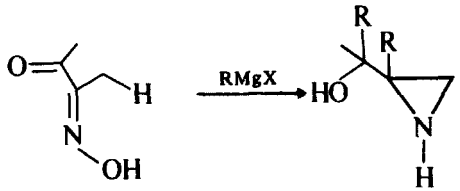
R = C_6H_5 (53%)[b, 288]
R = CH_3 (43%)[b, 288]

[a] Wavy line indicates the atoms introduced by the Grignard reagent.
[b] Stereochemical mixture.

Examples of the reaction are located in Table 27. The Hoch-Campbell synthetic approach has been extended to α,β-unsaturated oximes (Eq. 76),[280, 291] α-keto-oximes (Eq. 77),[292, 293] and α-hydroxyoximes (Eq. 78).[293] These reactions are summarized in Tables 28 to 30.

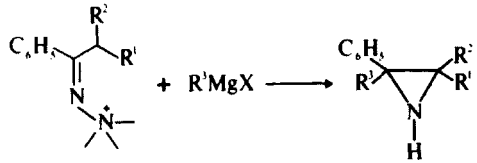


(76)



(77)

TABLE 27. AZIRIDINES FORMED BY REACTIONS OF HYDRAZONE DERIVATIVES WITH GRIGNARD REAGENTS



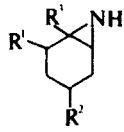
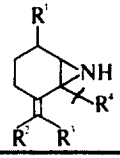
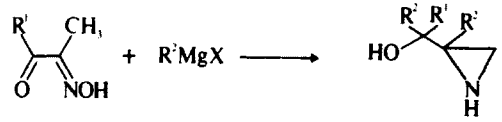
R^1	R^2	R^3	Yield (%)	Ref.
H	H	C_6H_5	76	290
H	CH_3	C_6H_5	80	290
H	CH_3	CH_3	57	290
CH_3	CH_3	CH_3	40	290
CH_3	CH_3	C_6H_5	40	290
H	CH_3	$CH=CH_2$	75	280
CH_3	CH_3	$CH=CH_2$	46	280
				
C_6H_5	H	CH_3	93	290
H	*t*-Bu	CH_3	72	290
H	H	C_6H_5	54	290
H	H	$CH=CH_2$	54	280
C_6H_5	H	$CH=CH_2$	61	280
H	*t*-Bu	$CH=CH_2$	66	280
H	$(CH_3)_2$	C_6H_5	64	280
H	$(CH_3)_2$	CH_3	46	280
H	$(CH_3)_2$	$CH=CH_2$	20	280

TABLE 28. VINYLAZIRIDINES FROM α,β-UNSATURATED OXIMES



R^1	R^2	R^3	R^4	Yield (%)
H	C_6H_5	H	C_6H_5	70
H	C_6H_5	H	CH_3	47
CH_3	CH_3	CH_3	C_6H_5	24

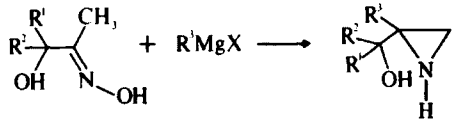
TABLE 29. ADDITION OF GRIGNARD REAGENTS TO α-OXOOXIMES



R^1	R^2	Yield (%)	Ref.
CH_3	C_6H_5	41[a]	292
CH_3	C_2H_5	30[a]	292
C_6H_5	*i*-Bu	50[a]	292
C_6H_5	C_2H_5	64[a]	292
C_6H_5	C_2H_5	70[a]	292
C_6H_5	C_6H_5	90	293
C_6H_5	C_2H_5	64[a]	293
CH_3	C_2H_5	30[a]	293

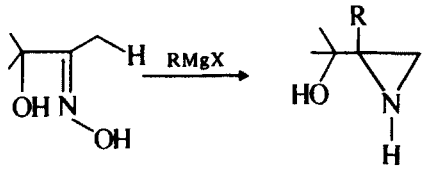
[a] Stereochemical mixture.

TABLE 30. AZIRIDINES FROM THE ADDITION OF GRIGNARD REAGENTS TO α-HYDROXY-OXIMES[293]



R^1	R^2	R^3	Yield (%)
C_6H_5	C_6H_5	C_2H_5	50
C_6H_5	H	C_6H_5	64[a]
C_6H_5	H	C_2H_5	50[a]
C_6H_5	C_2H_5	C_6H_5	70
CH_3	H	C_6H_5	57[a]

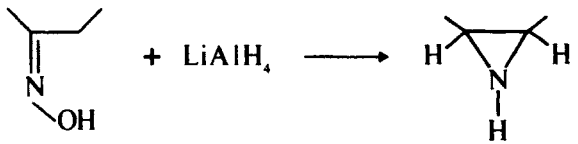
[a] Stereochemical mixture.



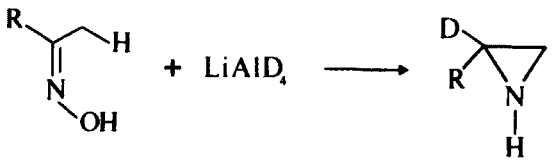
(78)

C. *The Reaction of Oximes with Hydrides*

The reduction of oximes with $LiAlH_4$ yields, in certain cases, aziridines instead of the expected amine (Eq. 79). The reaction is stereoselective in that only *cis*-aziridine is formed.[294] The ring closure takes place preferentially with loss of the *α-cis* (*syn*) hydrogen.[294–296] Loss of benzyl hydrogens is preferred to loss of aliphatic hydrogens.[294] The use of $LiAlD_4$ reveals that only one of the deuterium atoms is incorporated into the product and that it is located on the original imine carbon (Eq. 80).[297]



(79)



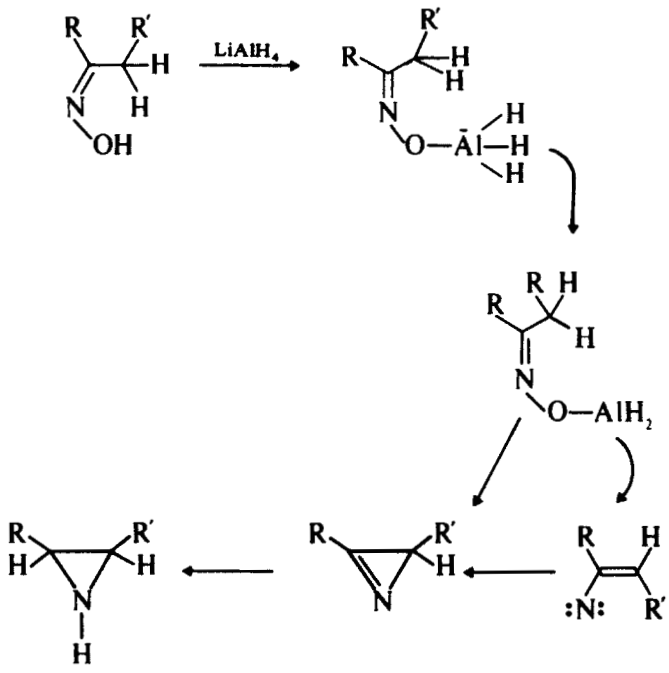
(80)

The proposed mechanism (Eq. 81)[294] is thus extremely similar to that evolved for the previously discussed Hoch-Campbell reaction. It is not clear whether nitrene intermediate or direct closure accounts for the intermediate azirine.

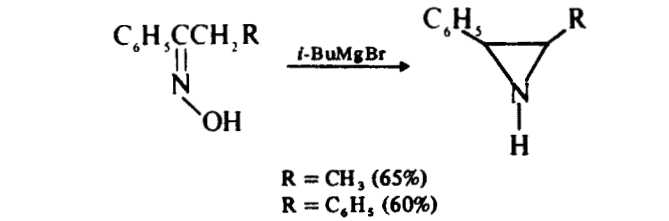
Investigation of the role of solvent reveals that THF is a superior choice and that normal (amine) reduction products predominate in ether and dioxane.[298, 299] These aziridine-forming reductions are summarized in Tables 31 and 32.

Other reagents besides $LiAlH_4$ seem to be capable of affecting this transformation. The use of $NaAlH_2(OCH_2CH_2{-}OCH_3)$ in THF produces the results shown in Table 33.[304] The same reagent has been used to reduce hydrazone salts as shown in Table 34.[305] Certain Grignard reagents also result in reduction,[306] as indicated in Eqs. 82 and 83.

The $LiAlH_4$ reduction of 2-isoxazolines also produces aziridines (Eq. 84).[307, 308] The mechanism is unproved but undoubtedly resembles the oxime reductions. The heterocyclic precursors appears to offer no advantages over the oximes (Table 35).

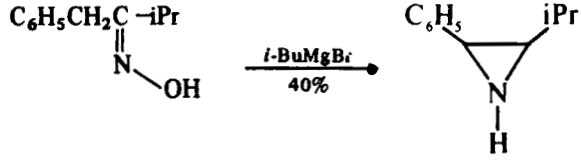


(81)

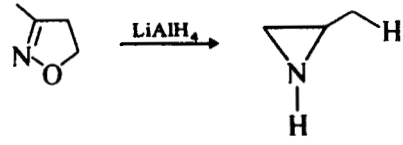


R = CH_3 (65%)
R = C_6H_5 (60%)

(82)

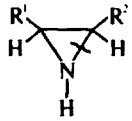


(83)



(84)

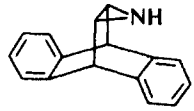
TABLE 31. AZIRIDINES VIA $LiAlH_4$ REDUCTION OF OXIMES[a]



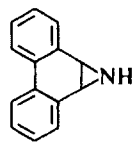
R^1	R^2	Yield (%)	Ref.
β-$C_{10}H_7$	CH_3	25	300
β-$C_{10}H_7CH_2$	H	7	300
C_6H_5	C_2H_5	24	300
$C_6H_5CH_2$	C_6H_5	77	300
C_6H_5	C_6H_5	25	300
C_5H_4N	C_6H_5	22	300
C_6H_5	H	17	300
p-ClC_6H_4	H	11	300
p-$CH_3OC_6H_4$	H	16	300
C_6H_5	CH_3	3; 34	300
α-$C_{10}H_7$	H	64	300
β-$C_{10}H_7$	H	16	300
$C_6H_5CHCCH_3$	H	40	245

[a] Wavy lines indicates the new N–C bond.

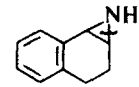
TABLE 32. AZIRIDINES FROM $LiAlH_4$ REDUCTION OF OXIMES



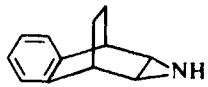
27%[301]



70%[301]

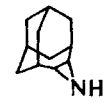


40%[300]

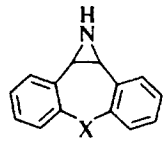


46%[301]

3%[301]

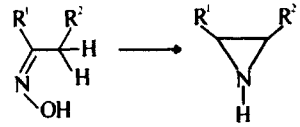


85%[302]



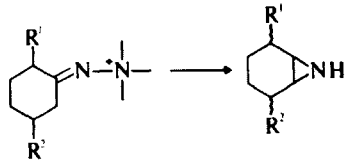
X = CH_2 (80%)[303]
X = S (77%)[303]
X = O (65%)[303]
X = CHOH (70%)[161]

TABLE 33. OXIME REDUCTIONS WITH $NaAlH_2(OCH_2CH_2OCH_3)$[304]



R^1	R^2	Yield (%)
C_6H_5	H	52
p-ClC_6H_4	H	45
α-$C_{10}H$	H	75
$C_6H_5CH_2$	C_6H_5	91
C_6H_5	C_6H_5	88
C_6H_5	CH_2CH_3	15

TABLE 34. HYDRAZONE SALT REDUCTIONS WITH $NaAlH_2(OCH_2CH_2OCH_3)$[305]

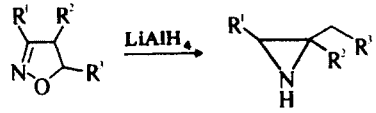


R^1	R^2	Yield (%)
H	H	55
CH_3	H	55[a]
CH_3	*i*-Pr (*trans*)	50[a]
i-Pr	CH_3 (*cis*)	46[a]
i-Pr	CH_3 (*cis*)	86[a]

70%

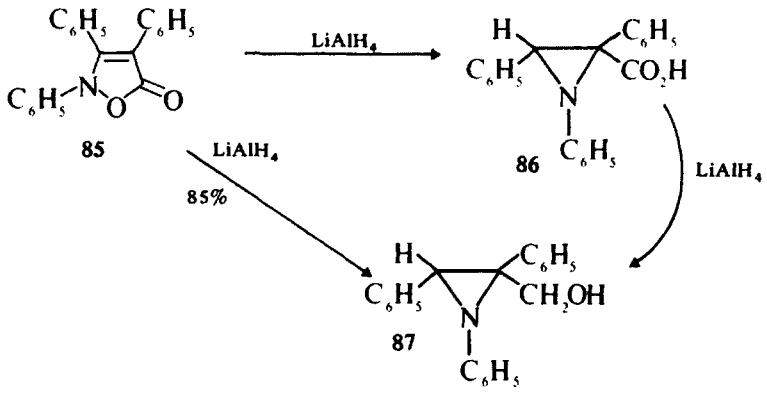
[a] *syn-anti* Mix.

TABLE 35. AZIRIDINES FROM 2-ISOXAZOLINES[308]

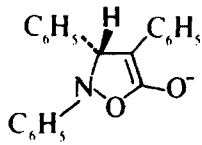


R^1	R^2	R^3	Yield (%)
C_6H_5	H	C_6H_5	31
C_6H_5	H	H	36
C_6H_5	C_6H_5	C_6H_5	83
CH_3	C_6H_5	C_6H_5	70

The heterocycle **85** is converted to aziridine **86** or **87**.

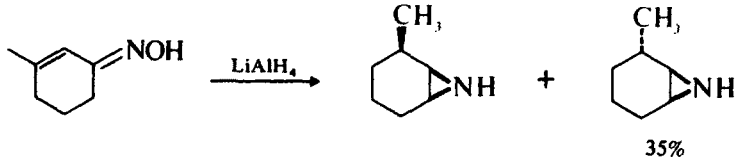


The latter results when excess $LiAlH_4$ is used. Intermediate **88** is initially formed and undergoes a stereospecific 1,3-sigmatropic shift, which produces **86**.[309]



88

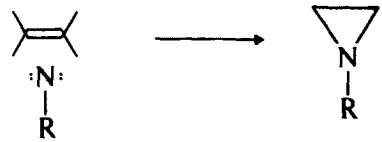
The reduction of α,β-unsaturated oximes also leads to aziridines, but the products are often mixtures.[310–314] An example of this reduction is shown in Eq. 85,[315] and some selected others are listed in Table 36.



(85)

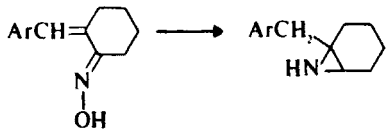
3. Aziridines via Cycloadditions to Alkenes

In principle, there are two approaches to aziridine synthesis via cycloaddition to alkenes. The most direct approach is the addition of nitrenes (or "nitrenoids") to alkenes (Eq. 86).

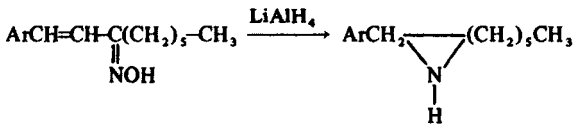


(86)

TABLE 36. AZIRIDINES FROM α,β-UNSATURATED OXIME REDUCTIONS

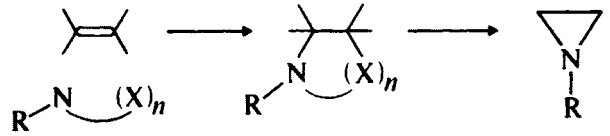


Ar	Yield (%)	Ref.
C_6H_5	92	316
O-Cl-C_6H_4	91	316
p-ClC_6H_4	89	316
$(p\text{-}CH_3)_2NC_6H_4$	–	316



Ar	Yield (%)	Ref.
C_6H_5	13	317
O-ClC_6H_4	12	317
p-ClC_6H_4	76	317
3,4-$Cl_2C_6H_3$	74	317

The alternative is indirect in that the cycloaddition first results in a larger heterocycle, and subsequent expulsion of part of the ring produces the desired aziridine (Eq. 87).

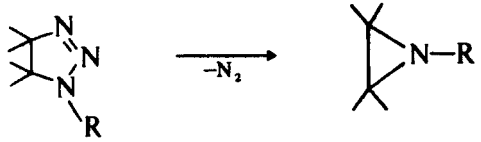


(87)

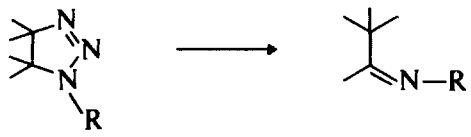
The latter approach, best exemplified by triazoline formation and decomposition, is discussed first.

A. *Aziridine Synthesis via Triazolines*

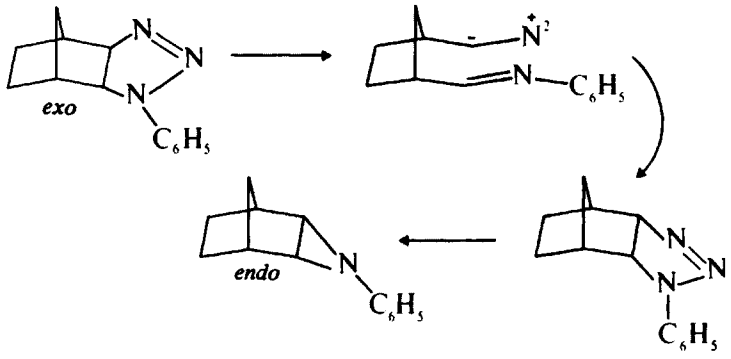
The formation of aziridines from triazolines (Eq. 88) is not a new reaction. Originally the conversion was accomplished under thermal (usually $> 100°$) conditions. Side reactions include imine formation (Eq. 89), isomerization of the triazoline before decomposition (Eq. 90),[318, 319] isomerization of the aziridine once formed (Eq. 91),[320] and tar formation.



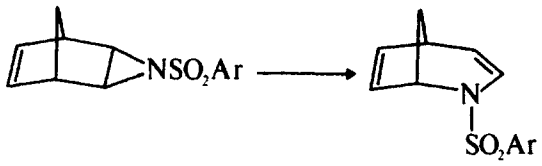
(88)



(89)



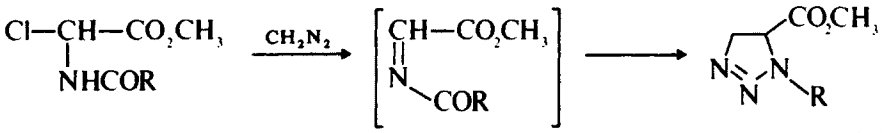
(90)



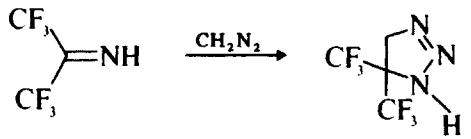
(91)

More recently the photochemical decomposition of triazolines has been touted as a cleaner reaction with fewer of the side reactions above.[318, 321] Neither approach, however, is necessarily stereospecific.[322, 323]

Triazolines are, in turn, most often prepared by 1,3-dipolar cycloaddition to alkenes. Addition is thus favored by alkene angle strain, conjugation, and so on.[324, 325] Occasionally triazolines may be formed from diazomethane addition to imines bearing electronegative substituents on carbon.[45, 326–330] Typical examples are found in Eqs. 92[326] and 93.[327]



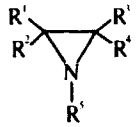
(92)



(93)

More often, however, diazomethane addition to imines does not initiate a useful route to aziridines.[331]

TABLE 37. MONOCYCLIC AZIRIDINES FROM TRIAZOLINE PHOTOLYSES AND THERMOLYSES



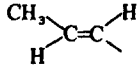
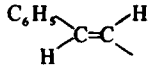
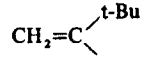
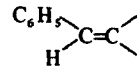
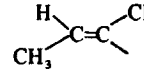
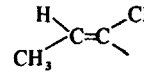
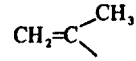
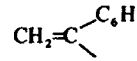
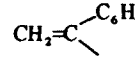
R^1	R^2	R^3	R^4	R^5	Method[a]	Yield (%)	Ref.
CF_3	CF_3	H	H	H	Δ	84	327
CO_2CH_3	H	H	H	COC_6H_5	Δ	15	326
CO_2CH_3	H	H	H	CO_2CH_3	Δ	34	326
CO_2CH_3	H	H	H	$CO_2CH_2C_6H_5$	Δ	33	326
C≡N	H	H	H	*n*-Bu	Δ	8	332
$NC(CH_2)_2$	CN	H	H	*n*-Bu	Δ	72	332
CH_3	CH_3	H	$(CH_3)_2N$	C_6H_5	Δ	50	333
CH_3	C_6H_5	H	$(CH_3)_2N$	C_6H_5	Δ	25	333
$(CH_3O)_2PO$	H	H	H	C_6H_5	Δ	–	334
CO_2CH_3	CH_3	H	H	C_6H_5	Δ	75	335
CO_2CH_3	H	H	CO_2CH_3	*p*-$CH_3OC_6H_4$	Δ	–	336
$CONH_2$	H	H	H	C_6H_5	*hν*	–	337
$-C(CH_3)=CH_2$	H	H	H	*p*-BrC_6H_4	*hν*	96	338
C_6H_5	H	H	CH_3	C_6H_5	*hν*	–	322,323
CH_3	CH_3	H	H	CN	Δ	34	339
CF_3	CF_3	H	H	CH_3CO_2	–	44	328
CF_3	CF_3	H	H	$C_2H_5CO_2$	–	95	328
CF_3	CF_3	H	H	$C_6H_5CO_2$	–	66	328
CF_3	CF_3	H	H	$C_6H_5SO_2$	–	79	328
CF_3	CF_3	CH_3	H	$C_6H_5SO_2$	–	50	328
CO_2CH_3	CO_2CH_3	H	H	*p*-$CH_3CH_4SO_2$	–	12	328
$(CH_3)_3Si$	H	H	H	*p*-BrC_6H_4	Δ	55	340
$(CH_3)_3Si$	H	H	H	*p*-BrC_6H_5	Δ	55	340
$CH_3(CH_2)_5$	H	H	H	C_6H_5	Δ	63	341
CF_3	CF_3	H	CN	C_6H_5	*hν*	100	330
CF_3	CF_3	H	$CO_2C_2H_5$	C_6H_5	*hν*	88	329
CF_3	CF_3	H	COC_6H_5	C_6H_5	*hν*	60	329
CH_3	CH_3	CH_3O	CH_3O	C_6H_5	*hν*	–	342
CO_2CH_3	H	H	H	C_6H_5	Δ	95	343
CO_2CH_3	H	H	H	*p*-$CH_3OC_6H_4$	Δ	–	343
CO_2CH_3	H	H	H	*p*-$CH_3C_6H_4$	Δ	–	343
CO_2CH_3	H	H	H	*p*-ClC_6H_4	Δ	–	343
CO_2CH_3	H	H	H	C_6H_5CO	Δ	–	343
CO_2CH_3	H	H	H	*p*-$NO_2C_6H_4$	Δ	–	343
CO_2CH_3	CH_3	H	H	C_6H_5	Δ	–	343
CO_2CH_3	H	H	CH_3	H	Δ	–	343
CO_2CH_3	CO_2CH_3	H	H	C_6H_5	Δ	100	344
CO_2CH_3	CO_2CH_3	C_6H_5	H	C_6H_5	Δ	–	344
CF_3	CF_3	H	H	$(CH_3)_2C=CH-$	–	95	345a
CF_3	CF_3	H	H		–	90	345a
CF_3	CF_3	H	H		–	85	345a

TABLE 37 CONTINUED

R^1	R^2	R^3	R^4	R^5	Method[a]	Yield (%)	Ref.
H	H	H	H		Δ	94	345b
CN	H	H	H		Δ	35	346
CO_2CH_3	H	H	H		Δ	56	346
CN	H	H	H		Δ	73	346
CO_2CH_3	H	H	H		Δ	83	346
CN	H	H	H		Δ	45	346
CO_2CH_3	H	H	H		Δ	68	346
	H	H	H	*p*-BrC_6H_4	*hν*	–	337
F	F	H	H	CF_3	Δ	64	347
Cl	CF_3	H	H	SF_5	Δ	20	347
CH_2Cl	CF_3	H	H	SF_5	Δ	76	347
N_3	CF_3	H	H	SF_5	Δ	40	347
CF_3	CF_3	H	H	CH_3	*hν*	23	45
CF_3	CF_3	H	H	Ph	*hν*	30	45
CF_3	CF_3	H	H	F	Δ	38	45
CF_3	CF_2NF_2	H	H	F	Δ	43	330
CF_3	CF_3	H	H	*p*-$CH_3C_6H_4SO_2$	Δ	25	348
C_6H_5	H	H	CN	*p*-$NO_2C_6H_4$	Δ	28	349
CH_3	CH_3	CH_3O	CH_3O	$CO_2C_2H_5$	Δ	–	350

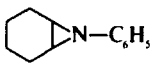
[a] Δ = heat treatment; *hν* = photolytic reaction.

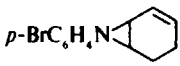
Tables 37–42 list some of the aziridines prepared from triazolines since publication of the original review. In some cases the triazolines were not isolated and/or nitrene intermediates were claimed. For reasons to be suggested later, the triazoline intermediacy seems to be the most probable.

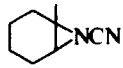
B. *Aziridines Formed via Nitrene Additions to Alkenes*

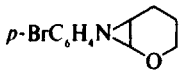
Direct formation of aziridines from the addition of nitrenes to alkenes has been discussed extensively from the mechanistic and theoretical perspectives in a recent review.[387] The general approaches to nitrene generation include azide decomposition, primary amine oxidation, and α-elimination. When azides serve as precursors, the alternative of 1,3-dipolar cycloaddition must be excluded for every case in which nitrene intermediates are proposed. Since the rate-determining

TABLE 38. BICYCLIC AZIRIDINES FROM TRIAZOLINES

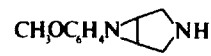

79% (Δ)[337, 341]

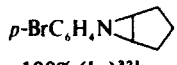

– (*hν*)[337]

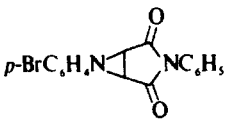

46% (Δ)[339]

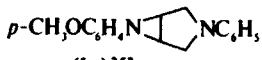

67% (*hν*)[351]

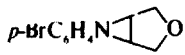

87% (*hν*; Cu^{2+})[352]

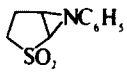

98% (*hν*; Cu^{2+})[352]

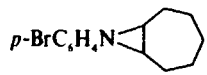

100% (*hν*)[321]

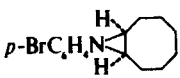

– (*hν*)[322]

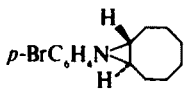

– (*hν*)[353]

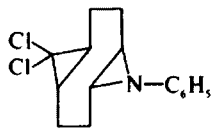

100% (*hν*)[337]

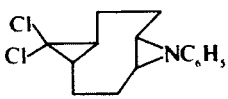

– (Δ)[354]

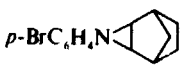

– (*hν*)[337]


– (*hν*)[337, 355]

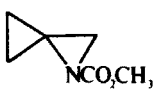

– (*hν*)[355]

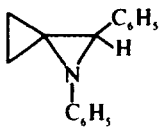

– (*hν*)[356]

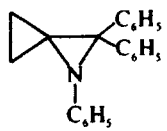

– (*hν*)[356]


– (*hν*)[337]


90% (*hν*)[357, 358]


3% (*hν*)[357]


99% (*hν*)[358]


91% (*hν*)[358]

step should be nitrene formation, reaction rates should be independent of acceptor concentration if nitrenes are actually involved. Nitrenes are also implicated when azides and other nitrene sources show similar selectivity ratios toward various alkenes.

Even when the method of nitrene formation yields a singlet, intersystem crossing eventually may produce the triplet configuration. The propensity for intersystem crossing depends on the nitrogen substituent, and both electron donors and acceptors appear to stabilize the singlet.[387] The singlet is more likely to yield aziridine adducts and the triplet to display diradical character.

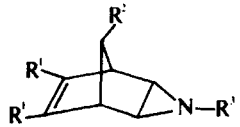
TABLE 39. AZIRIDINE DERIVATIVES OF THE UNSUBSTITUTED 2,2,1-BICYCLOHEPTANE SYSTEM FROM TRIAZOLINES

R	Method[a]	Yield (%)	Ref.
CO_2CH_3	$h\nu$	94	321
p-BrC_6H_4	$h\nu$	86	321
$C_6H_5CH_2$	Δ	88	359,360
C_6H_5CO	Δ	92	360
p-NO_2–C_6H_4	Δ	94	360
C_6H_5	$\frac{\Delta}{h\nu}$	$\frac{55}{100}$	318,360
p-$CH_3C_6H_4$	Δ	92	360
m-ClC_6H_4	Δ	92	360
p-$CH_3C_6H_4SO_2$	Δ	97	360
CN	Δ	41	361
2,4,6-$(NO_2)_3$–C_6H_3	Δ	90	362
$C_6H_5SO_2$	Δ	–	363
C_6H_5	Δ	65	364
p-$CH_3C_6H_4OSO_2$	Δ	65	364
p-$ClC_6H_4OSO_2$	Δ	75	364
p-$C_6H_5C_6H_4OSO_2$	Δ	98	364
$(C_2H_5O)_2PO$	$h\nu$	90	365

[a] $h\nu$ = photolytic reaction; Δ = heat treatment.

In the case of intermolecular additions, only nitrenes attached to oxygen (89), nitrogen (90), and carbonyl (91) groups appear to have general synthetic utility. Aliphatic groups prefer rearrangement (Eq. 94) to additions. Arylnitrenes from various sources yield a wealth of interesting chemistry that does not usually include

TABLE 40. OTHER AZIRIDINE DERIVATES BASED ON THE 2,2,1-BICYCLOHEPTANE SYSTEMS FROM TRIAZOLINES

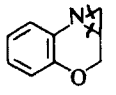


R^1	R^2	R^3	Stereochemistry	Method[a]	Yield (%)	Ref.
H	H	CN	*exo*	Δ	–	361
H	H	CO_2CH_3	*exo*	$\frac{\Delta}{h\nu}$	$\frac{60}{93}$	366,367
H	H	C_6H_5	*exo*	$h\nu$	97	367
H	H	C_6H_5	*endo*	$h\nu$	91	367
H	*O*-*t*-Bu	C_6H_5	*endo*	$h\nu$	96	367
CO_2CH_3	H	C_6H_5	*exo*	$h\nu$	40	367

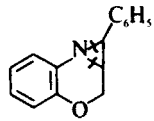
[a] Δ = heat treatment; $h\nu$ = photolytic reaction.

TABLE 41. AZIRIDINES FROM INTRAMOLECULAR CYCLIZATION OF AZIDES[a]

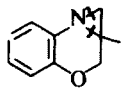
3.2% ($h\nu$)[368]



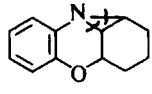
58% (Δ)[369]



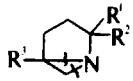
70% (Δ)[369, 370]



69% (Δ)[369]



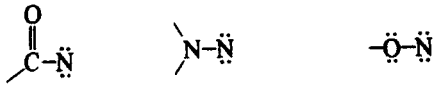
94% (Δ)[370]



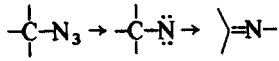
R^1	R^2	R^3	Method	Yield (%)	Ref.
CH_3	CH_3	H	Δ	21	371
CH_3	H	H	Δ	14	371
H	H	H	Δ	9	371
CH_3	H	CH_3	Δ	9	371

[a] Wavy line indicate the new bonds.

the formation of stable aziridines.[387] Sulfonylnitrenes (**92**) are also not useful in aziridine synthesis.



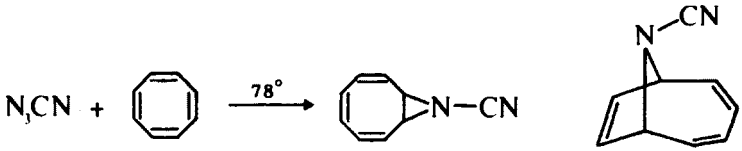
89 **90** **91**



(94)

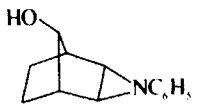
92

The reaction of cyanogen azide, however, with cyclooctatetrene gives a mixture of **93** and **94**.[388]

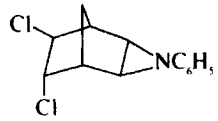


93 (50%) **94** (14%)

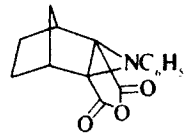
TABLE 42. OTHER AZIRIDINES FORMED FROM TRIAZOLINES



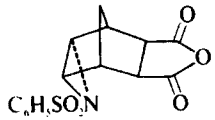
95% (Δ)[372]



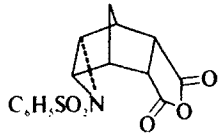
98% (Δ)[372]



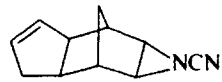
– (*hν*)[326]



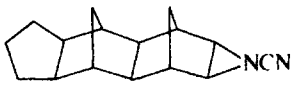
74% (Δ)[373]



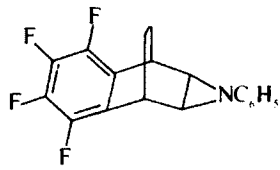
60% (Δ)[373]



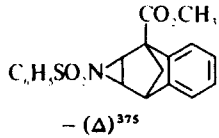
86% (Δ)[339]



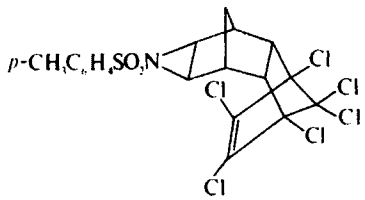
91% (Δ)[339]



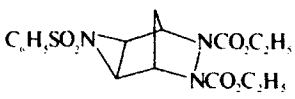
– (Δ)[374]



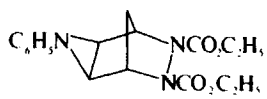
– (Δ)[375]



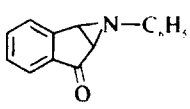
48% (Δ)[376]



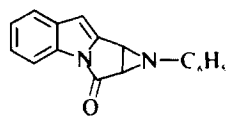
97% (Δ)[377]



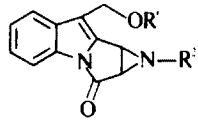
99% (*hν*)[378]



65% (*hν*)[379]

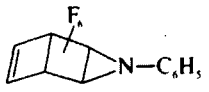


99.5% (*hν*)[380]

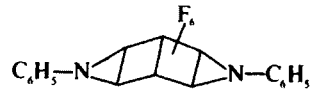


R¹	R²	Method	Yield (%)	Ref.
CH_3	C_6H_5	*hν*	50	381
CH_3	$CH_2C_6H_5$	*hν*	18	381
$CH_2C_6H_5$	$CH_2C_6H_5$	*hν*	5	381

TABLE 42 CONTINUED

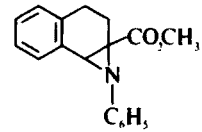


56% ($h\nu$)[382]

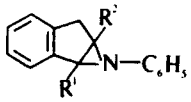


73% ($h\nu$)[382]

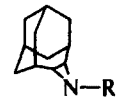
– ($h\nu$)[383]



100% (Δ)[384]

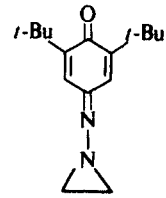


R^1	R^2	Yield (%)	Method	Ref.
CO_2CH_3	H	30	Δ	384
H	CO_2CH_3	85	Δ	384



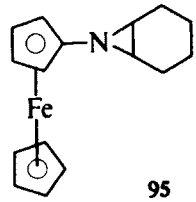
R	Yield (%)	Method	Ref.
Ph	49	Δ	286
1-Ada	36	Δ	286
p-$CH_3C_6H_4SO_2$	6	Δ	286

– (Δ)[385]



72% (Δ)[386]

The novel product **95** has been claimed to be the result of thermal or photochemical addition to cyclohexene in low (4%) yield.[389]

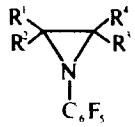


95

Perfluoroarylnitrenes add to alkenes in reasonable yields. One method of generation involves the reaction of the corresponding nitroso compound with triethyl phosphite (Eq. 95).[390, 391] The other method utilizes photolysis of the corresponding azide.[391] These reactions are summarized in Table 43.

$$C_6F_5NO + (C_2H_5O)_3P \rightarrow C_6F_5\ddot{N} \qquad (95)$$

TABLE 43. AZIRIDINES FROM PENTAFLUOROPHENYL NITRENE

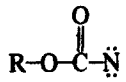


R^1	R^2	R^3	R^4	Method[a]	Yield (%)	Ref.
CH_3	CH_3	CH_3	CH_3	C / $h\nu$	31 / 60	390,391
CH_3	H	CH_3	H	C / $h\nu$	18 / 18	390,391
CH_3	H	H	CH_3	C	17 / 18	390,391
C_6H_5	H	C_6H_5	H	C	26	390
H	$(CH_2)_4$		H	C / $h\nu$	35 / 39	390 / 391
H			H	C	35	390
H	Cl	Cl	H	$h\nu$	21	391
Cl	H	Cl	H	$h\nu$	27	391
CH_3	$(CH_2)_4$		CH_3	$h\nu$	11	391
CH_3	H	*i*-Pr	H	$h\nu$	20	391

[a] C = ArNO + $(EtO)_3P$; $h\nu$ = Ar-N_3 + $h\nu$.

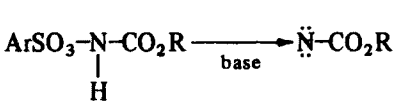
a. AZIRIDINES FROM CARBONYL NITRENE

Carbalkoxyaziridines (**96**) have been generated by photochemical, thermal, and α-elimination routes.[387]



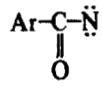
96

In the latter case, reactions of carbamates **97** with base are successful for the synthesis of aziridines via nitrenes.[392]



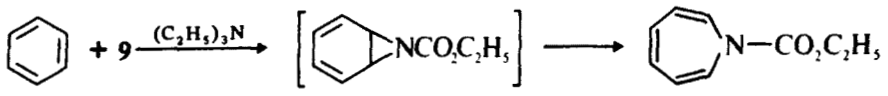
97

In general the selectivities shown by the photochemical process are different from the other two. This has resulted in the suggestion that the photochemical route leads predominantly to triplet.[387] Aroylnitrenes (**98**) have been formed from the photochemical decomposition of the corresponding azides. No additions have been reported for the alkanoyl analogs.

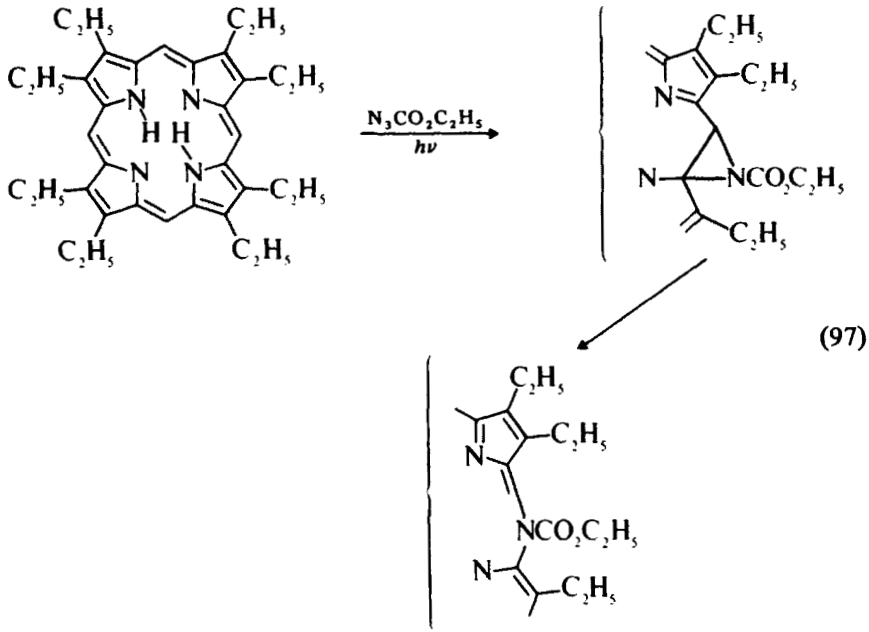


98

In a few cases the formation of aziridines must be inferred, since these compounds are converted to other products under reaction conditions. Examples include benzene (Eq. 96)[392] and a porphyrin (Eq. 97).[393] Aziridine syntheses via carbonyl nitrenes are found in Tables 44 and 45. As can be noted, the reactions are usually not stereospecific and the yields often low. Although usually not the method of choice, many interesting structures appear only accessible in this way. The stereo- and regioselectivity of carboethyoxynitrene toward steroidal systems has been noted.[394, 395]



(96)

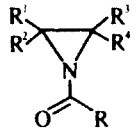


(97)

b. AZIRIDINES FROM AMINONITRENE ADDITIONS TO ALKENE

The lead tetraacetate oxidation of 1,1-disubstituted hydrazine derivatives can, in certain cases, yield nitrenes that are efficiently trapped via intramolecular addition to alkenes (Eq. 98).[414, 415]

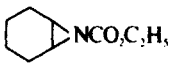
TABLE 44. MONOCYCLIC AZIRIDINES FROM CARBONYL NITRENES



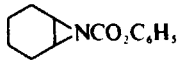
R	R^1	R^2	R^3	R^4	Method[a]	Stereochemistry	Yield (%)	Ref.
OC_2H_5	CH_3	H	H	*i*-Pr	C	Mixed	57	393
OC_2H_5	CH_3	$CH{=}CH_2$	H	H	*hν*	–	41	99
OC_2H_5	H	$C(Cl_3){=}CH_2$	H	H	*hν*	–	44	99
OCH_3	CH_3	H	H	CH_3	*hν*	Mixed	70	396
OC_2H_5	CH_3	CH_3	H	$COCH_3$	Δ	–	56	397
OCH_3	CH_3	CH_3	H	CO_2CH_3	Δ	–	72	397
OC_2H_5	Ph	H	H	CH_3	Δ	Mixed	–	398
OC_2H_5	CH_3CO_2	CH_3	H	H	*hν*	–	–	399
OCH_3	CH_3	CH_3	H	$CH{=}C(CH_3)_2$	*hν*	–	60	400
OC_2H_5	CH_3	CH_3	H	$CH{=}C(CH_3)_2$	*hν*	–	60	400
$OCH_2{-}CH{=}CH_2$	CH_3	CH_3	H	$CH{=}C(CH_3)_2$	*hν*	–	60	400
OCH_3	CH_3	CH_3	H	CO_2CH_3	*hν*	–	60	400
OCH_3	CH_3	CH_3	H	$CO_2C_2H_5$	*hν*	–	60	400
OC_2H_5	CH_3	CH_3	H	CO_2CH_3	*hν*	–	60	400
OC_2H_5	CH_3	CH_3	H	$CO_2C_2H_5$	*hν*	–	60	400
p-Cl–C_6H_4			CH_3; H; etc.		*hν*	–	–	401
C_6H_5	CH_3	H	*i*-Pr	H	*hν*	*cis*	26	402
t-Bu	CH_3	H	*i*-Pr	H	*hν*	*cis*	31	402
C_6H_5	CH_3CH_3	H	CH_3CH_2	H	*hν*	*cis*	34	402

[a] C = α-elimination; Δ = heat treatment; *hν* = photochemical reaction.

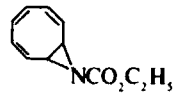
TABLE 45. OTHER AZIRIDINES FROM NITRENES[a]



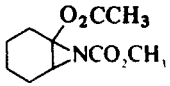
60% (C)[403]



62% (*hν*)[401]

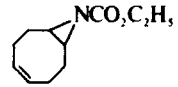


37% (C)[404]



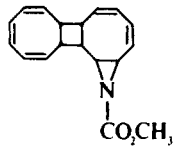
– (*hν*)[399]

56% (*hν*)[405]

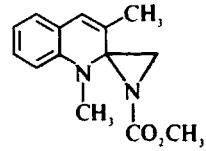


65% (*hν*)[405]

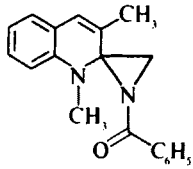
35% (*hν*)[406]



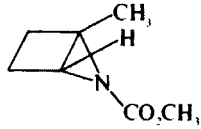
20% (*hν*)[407]



74% (*hν*)[408]

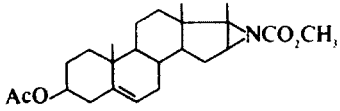


60% (*hν*)[408]

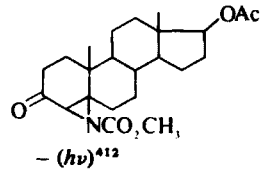


65% (*hν*)[409,410]

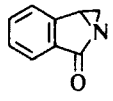
– (*hν*)[411]



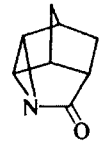
– (*hν*)[395]



– (*hν*)[412]



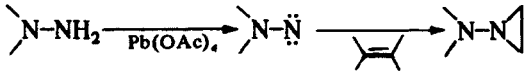
– (*hν*)[413]



– (*hν*)[413]

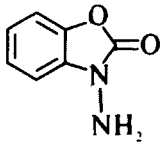
– (*hν*)[413]

[a] C = α-elimination; *hν* = photochemical reaction.

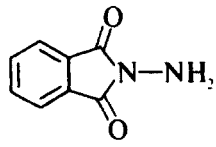


(98)

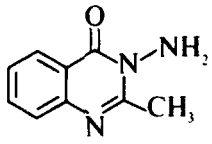
The amino group apparently stabilizes the singlet state. The nature of the substituent is critical. Compounds **99–102** examplify the compounds found useful in aziridine synthesis.[416]



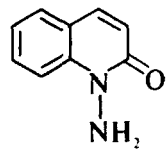
99



100

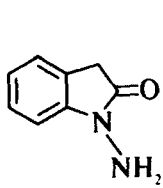


101

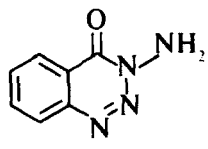


102

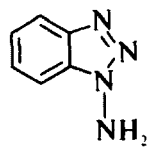
In contrast, structures **103–106** undergo extrusion and/or rearrangement and do not lead to interceptable nitrenes.[416] The successful additions are stereospecific. The yields and generality of the method are indicated in Tables 46–52.



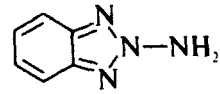
103



104



105



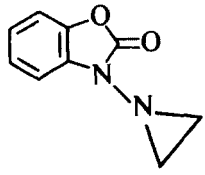
106

Although the lead tetraacetate oxidation is mild (room temperature) and quick (< 30 min), other oxidation routes have been observed. Electrochemical oxidation of **107** gave stereospecific addition of the corresponding nitrene to *cis*- and *trans*-

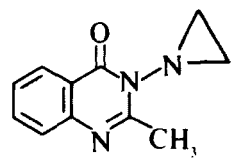
$(C_6H_5)_2NNH_2$

107

2-butene.[435, 436] Photochemical decomposition of **108** and **109** gave nitrenes, as evidenced by the stereospecific formation of new aziridines from added alkenes.[418] Yields of aziridines were fair, and the photochemical route offered no advantages over lead tetraacetate. Finally, thermolysis of **110** yielded nitrene **111**, which in turn added to alkenes.[437]

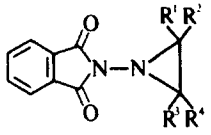


108



109

TABLE 46. PHTHALIMIDOAZIRIDINES FROM NITRENES

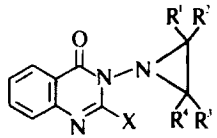


R^1	R^2	R^3	R^4	Yield (%)	Ref.
H		$(CH_2)_4$	H	40	416,417
$(CH_3)_3$	H	CH_3	CH_3	61	416
C_6H_5	H	H	H	42	416
CH_3	H	H	CH_3	19; 53	416,417
CH_3	H	CH_3	H	36; 51	416,417
$COCH_3$	H	CH_3	CH_3	88	416
CO_2CH_3	H	CH_3	CH_3	75	416
CO_2CH_3	H	H	H	73	416
$CO_2C_2H_5$	H	H	H	65	416
$CO_2C_2H_5$	H	$CO_2C_2H_5$	H	20	416
CO_2CH_3	CH_3	H	H	100	416
CO_2CH_3	H	CH_3	H	90	416
Cl	H	Cl	H	60	416
Cl	Cl	Cl	H	90	416
$CH(CH_3)_2$	H	CH_3	H	–	418
$CH(CH_3)_2$	H	H	CH_3	–	418
C_6H_5	H	C_2H_5	H	50	419
H			H	6.2 (*exo*–*endo* mixture)	420
H	$-(CH_2)_2-CH=CH$		H	12	415
H			H	52 *exo*–3.5 *endo*	415
p-CH_3O–C_6H_4	H	CO_2CH_3	CN	35	421
C_6H_5	H	CO_2CH_3	CN	73	421
p-Cl–C_6H_4	H	CO_2CH_3	CN	83	421
p-NO_2–C_6H_4	H	CO_2CH_3	CN	95	421
p-CH_3O–C_6H_4	H	$CONH_2$	CN	17	421
m-$CH_3OC_6H_4$	H	$CONH_2$	CN	74	421
C_6H_5	H	$CONH_2$	CN	81	421
p-Cl–C_6H_4	H	$CONH_2$	CN	90	421
p-NO_2–C_6H_4	H	$CONH_2$	CN	83	421
p-$CH_3OC_6H_4$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	40	421
C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	98	421
p-NO_2–C_6H_4	H	$CO_2C_2H_5$	$CO_2C_2H_5$	96	421
p-$CH_3OC_6H_4$	H	NO_2	C_2H_5	50	421
C_6H_5	H	NO_2	C_2H_5	50	421
p-Cl–C_6H_4	H	NO_2	C_2H_5	62	421
p-NO_2–C_6H_4	H	NO_2	C_2H_5	70	421
C_6H_5	H	$PO(OC_2H_5)_2$	CN	18	421
p-NO_2–C_6H_4	H	$PO(OC_2H_5)_2$	CN	50	421
p-NO_2–C_6H_4	H	*p*-CH_3–$C_6H_4SO_2$	CN	20	421
p-$CH_3OC_6H_4$	H	C_6H_5	CN	25	421
C_6H_5	H	C_6H_5	CN	43	421
C_6H_5	H	CO_2CH_3	H	75	421
C_6H_5	H	COC_6H_5	H	70	426

TABLE 46 CONTINUED

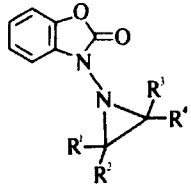
R^1	R^2	R^3	R^4	Yield (%)	Ref.
C_6H_5	H	CHO	H	50	426
C_6H_5	H	CN	H	35	426
H	$-CH=CH-CH_2-$		H	69	422
H	$-CH=CH-CH_2-CH_2-$		H	49	422
H	$-(CH=CH)_3-$		H	40	422
H	$-CH_2-CH=CH-CH_2-$		H	35	422
H	$(CH_2)_6$		H	40	417
H	$-(CH_2)_2CH=CH-(CH_2)_2-$		H	50	417
CO_2CH_3	$(CH_2)_2$		CO_2CH_3	35	423
C_6H_5	H	NO_2	H	90	424
p-ClC_6H_4	H	NO_2	H	62	424
CH_3	H	NO_2	H	72	424
C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	26	425
C_6H_5	H	CO_2CH_3	CN	60	425
p-ClC_6H_4	H	CO_2CH_3	$COCH_3$	40	425
p-ClC_6H_4	H	CO_2CH_3	CO_2CH_3	55	425
CH_3	CO_2CH_3	H	H	100	426
C_6H_5	C_6H_5	H	H	32	427
H	$(CH_2)_3$		H	49	428
H	$(CH_2)_5$		H	27	428
CH_3	$-C\equiv C-t$-Bu	H	H	35	429

TABLE 47. 3,4-DIHYDRO-4-OXOQUINAZOLIN-3-YLAZIRIDINES FROM NITRENES

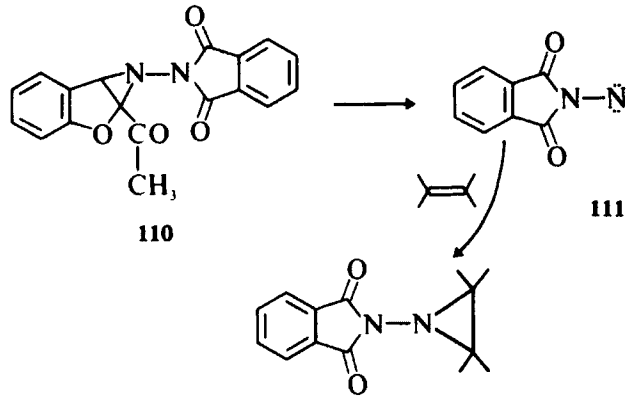


X	R^1	R^2	R^3	R^4	Yield (%)	Ref.
CH_3	$CH:CH_2$	H	H	H	81	416
CH_3	H	$(CH_2)_4$		H	53	416
CH_3	H	$(CH_2)_6$		H	43	416
CH_3	C_6H_5	H	H	H	64	416
CH_3	H	CH_2 	CH_2	H	41	416
CH_3	Me	H	H	CH_3	48	416
CH_3	Me	H	CH_3	H	46	416
CH_3	CO_2Me	H	H	H	30	416
CH_3	CO_2Me	Me	H	H	36	416
CH_3	CO_2Me	H	CH_3	H	32	416
CH_3	Cl	H	Cl	H	60	416
H	$CH=CH_2$	H	H	H	14	430
C_6H_5	$CH=CH_2$	H	H	H	69	430
CH_3	$CH=CH_2$	H	H	CH_3	13	430
CH_3	$CH=CH_2$	H	CH_3	H	23	430
CH_3		H	H	H	27	430
CH_3		H	H	H	10	430

TABLE 48. 2,3-DIHYDRO-2-OXOBENZOXAZOLIN-3-YLAZIRIDINES FROM NITRENES



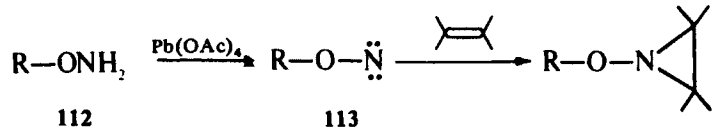
R^1	R^2	R^3	R^4	Yield (%)	Ref.
CO_2CH_3	CH_3	H	H	61	416
CO_2CH_3	H	H	H	96	416
$C(=CH_2)CH_3$	CH_3	H	H	42	431
$CH{=}C(CH_3)_2$	H	CH_3	CH_3	35	431
$CH{=}CH_2$	CH_3	H	H	21	431
$CH(CH{=}CH_2)CH_3$	H	H	H	15	431
$CH{=}CH_2$	H	H	H	71	431
$(CH_2)_5CH_3$	H	H	H	10	431
CH_3	H	H	CH_3	67	431
CH_3	H	CH_3	H	60	431



110 111

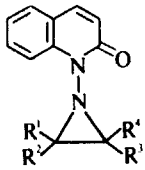
c. AZIRIDINES FROM OXYNITRENE ADDITION TO ALKENES

Although the yields are not as high and the reaction not as thoroughly investigated, the oxidation of alkoxyamines (112) with lead tetraacetate results in nitrene (113) formation and subsequent addition to alkenes.[160, 438–441] The reaction is not completely stereospecific, and the nitrene formulation may be an oversimplification. Table 53 depicts typical examples of this procedure.



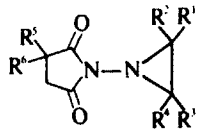
112 113

TABLE 49. 1,2-DIHYDRO-2-OXOQUINOLIN-1-YLAZIRIDINES FROM NITRENES



R^1	R^2	R^3	R^4	Yield (%)	Ref.
H	$(CH_2)_4$		H	20	416
CO_2Me	H	H	H	29	416
CO_2Me	Me	H	H	40	416

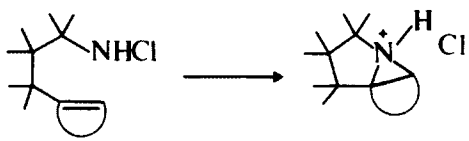
TABLE 50. SUCCIMIDOAZIRIDINES FROM NITRENES



R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	Ref.
C_6H_5	H	CN	CO_2CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	67	425
C_6H_5	H	CN	CO_2CH_3	C_6H_5	C_6H_5	40	425
p-ClC_6H_4	H	CO_2CH_3	$COCH_3$	C_6H_5	C_6H_5	55	425
C_6H_5	H	CH_3	NO_2	C_6H_5	C_6H_5	60	424
C_6H_5	H	H	NO_2	$C_6H_5CH_2$	$C_6H_5CH_2$	70	424
p-$CH_3OC_6H_5$	H	H	NO_2	$C_6H_5CH_2$	$C_6H_5CH_2$	41	424
CO_2CH_3	H	H	H	C_6H_5	H	42	432
CO_2CH_3	H	H	H	C_6H_5	C_6H_5	42	432
CO_2CH_3	H	H	H	C_6H_5	CH_3	48	432
CO_2CH_3	H	H	H	C_6H_5	$C_6H_5CH_2$	65	432
CO_2CH_3	H	H	H	$C_6H_5CH_2$	$C_6H_5CH_2$	71	432

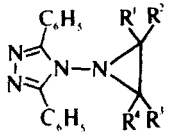
d. INTRAMOLECULAR ADDITION OF UNSTABILIZED NITRENES

Although attempts to add alkyl nitrenes to alkenes are usually not successful, the analogous intramolecular reaction is an extremely useful reaction. Two procedures have been reported. The first utilizes lead tetraacetate oxidation and the second the rearrangement of *N*-chloroamines (Eq. 99).[442, 443]



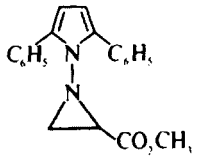
(99)

TABLE 51. AZIRIDINATRIAZOLES FROM NITRENES

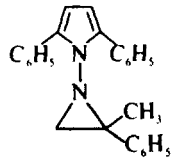


R^1	R^2	R^3	R^4	Yield (%)	Ref.
C_6H_5	H	H	H	35	433
C_6H_5	H	CH_3	H	73	433
H	$(CH_2)_4$		H	31	433
H	$(CH_2)_3$		H	48	433
CH_3	CH_3	H	$COCH_3$	26	433

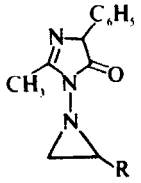
TABLE 52. MISCELLANEOUS AMINOAZIRIDINES FROM NITRENES



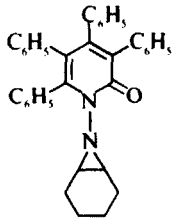
91%[433]



89%[433]

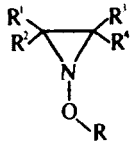


R = C_6H_5 (72%)[433]
R = CO_2CH_3 (86%)[433]



25%[434]

TABLE 53. AZIRIDINES VIA OXYAMINE OXIDATION

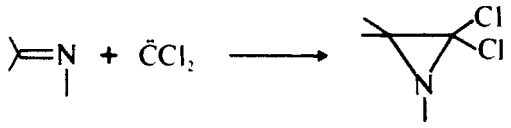


R	R^1	R^2	R^3	R^4	Yield (%)	Ref.
CH_3	CH_3	CH_3	CH_3	CH_3	30	160
CH_3	H	H	H	CH_3	–	439
C_2H_5	CH_3	H	CH_3	H	–	439
i-C_3H_7	CH_3	CH_3	H	H	–	439

The latter are stable below $-10°$, but rearrangement occurs above 0°. The lead tetraacetate oxidation appears to be superior in most cases. The double bond must be part of a ring system and in the δ-ϵ position.[443] The products are extremely unstable and often polymerize rapidly. Fortunately, the salts are (surprisingly) stable. The mechanism is unclear, but it may resemble the familiar carbenoid routes to cycloalkanes. Thus, the rate of oxidation has been found to be dependent on presence of a suitably located double bond. Examples of this reaction are found in Table 54.

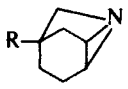
4. Aziridines from Carbenoid Addition to Imines

Since the original description of dichlorocarbene addition to imines (Eq. 100) in 1959,[446] many additional related examples have been reported.

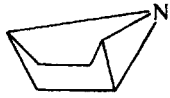


(100)

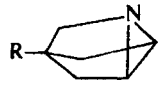
TABLE 54. AZIRIDINES FROM INTRAMOLECULAR NITRENE ADDITIONS[a]



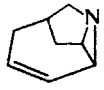
R = H (45%; P)[442]
R = CH_3 (60%; P)[442]



90% (P)[443]

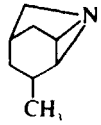


R = H (45%; P)[443]
R = C_6H_5 (57%; P)[443]



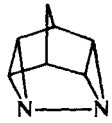
90% (P)[443]

60% (P)[442]

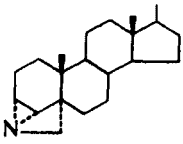


– (P)[445]

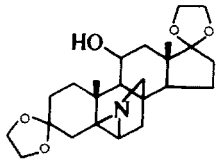
64% (P)[417]



82% (P)[417]



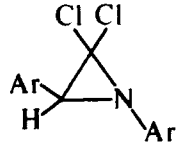
90% (C)[442]
100% (P)[442]



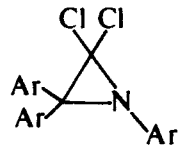
71% (C)[442]
80% (P)[442]

[a] P = $Pb(OAc)_4$ oxidation; C = rearrangement of N–Cl-amine.

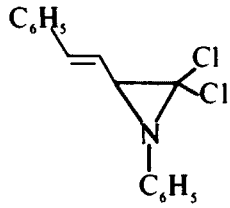
Dichlorocarbene has produced a multitude of aziridines (**114** and **115**) from the corresponding diarylaldimines and triarylketimines.[447–452] The unusual vinylaziridine **116** has been obtained in 64% yield.[452]



114

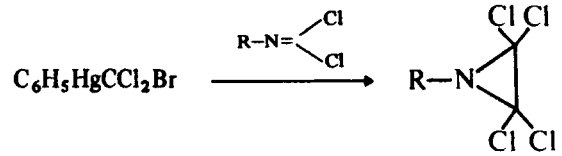


115



116

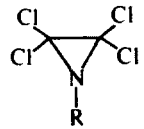
The use of phase transfer catalysis in the generation of dichlorocarbene appears to offer superior yields.[453, 454] There are limitations on the synthesis. For example, replacement of the nitrogen substituent with alkyl groups is unsuccessful because of the product lability. The presence of enolizable hydrogen atoms on the ketone or aldehyde is incompatible with the strongly basic conditions.



(101)

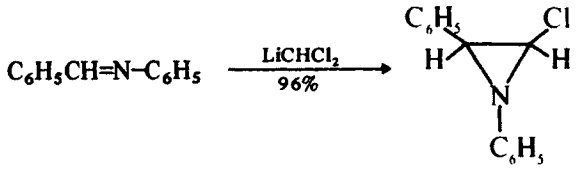
Addition of dichlorocarbene generated from organomercury reagents (Eq. 101) has resulted in a number of novel tetrachloroaziridines (Table 55).

TABLE 55. TETRACHLOROAZIRIDINES FROM ORGANOMERCURY REAGENTS



R	Yield (%)	Ref.
C_6H_5	53	455,457
C_6H_{11}	26	455,457
i-Pr	43	455,457
$[C_2H_5O_2C]_2N$	–	456
p-$CH_3C_6H_4$	78	457
p-ClC_6H_{11}	54	457

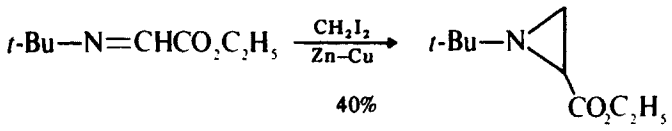
The addition of a monochlorocarbene to an imine (Eq. 102) has been described.[458]



(102)

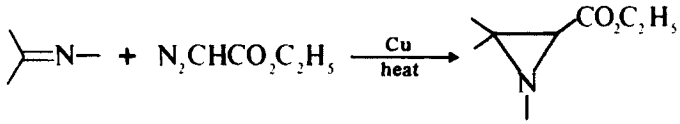
Other dihalocarbenes have been added to imines. Dibromo,[452, 459–462] chlorobromo,[459, 460] fluorochloro,[452, 459, 460] and fluorobromo[452, 460] all add in reasonable yields. The mixed halogens present structural assignment problems that are difficult to resolve with confidence.

The Simmons-Smith procedure, although highly successful in alicyclic three-membered ring synthesis, has not been of similar utility in aziridine synthesis. A number of failures and one success (Eq. 103) have been reported.[463]



(103)

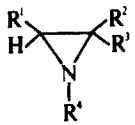
The copper-catalyzed addition of diazo compounds to imines (Eq. 104) has also been of limited success,[464] as indicated in Table 56.



(104)

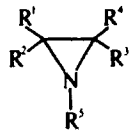
Certain one-carbon transfer agents have also been employed in aziridine syntheses from imines. In each case the negative charge on carbon is stabilized by an adjacent sulfur (Table 57). The most novel use of these reagents is in the synthesis of strained heterocycle **117** as shown in Eq. 105.[263, 473]

TABLE 56. DIAZOACETATE ADDITIONS TO IMINES

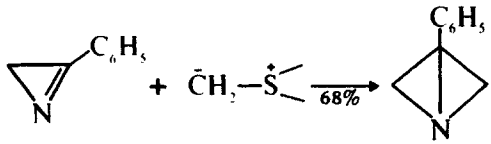


R^1	R^2	R^3	R^4	Yield (%)	Ref.
t-Bu	$CO_2C_2H_5$	H	*t*-Bu	15	464
C_6H_5	$CO_2C_2H_5$	H	*t*-Bu	30	464
C_6H_5	H	$CO_2C_2H_5$	C_6H_5	15	464

TABLE 57. AZIRIDINES FROM THE ADDITION OF YLIDS TO IMINES



R^1	R^2	R^3	R^4	R^5	Reagent	Yield (%)	Ref.
C_6H_5	H	H	H	C_6H_5	$(CH_3)_2SO\bar{C}H_2$	44	465
C_6H_5	H	H	H	C_6H_5	$(CH_3)_2SO\bar{C}H_2$	–	466
C_6H_5	H	H	H	$C_6H_5CH{=}N$	$(CH_3)_2SO\bar{C}H_2$	–	466
C_6H_5	H	H	H	C_6H_5	$(CH_3)_2S\bar{C}H_2$	81	467
C_6H_5	H	H	H	p-$CH_3OC_6H_4$	$(CH_3)_2S\bar{C}H_2$	76	467
C_6H_5	H	H	CH_3	C_6H_5	$Ar{-}S(=N(CH_3)_2)O{-}\bar{C}HCH_3$	35	468
C_6H_5	H	H	H	C_6H_5	$C_6H_5S(=N{-}SO_2C_6H_5)O\bar{C}H_2$	86	469
C_6H_5	H	H	H	C_6H_5	$C_6H_5S(=N(CH_3)_2)O\bar{C}H_2$	23	470
Ar	H	H	H	Ar	$(CH_3)_2\overset{+}{S}{-}\bar{C}H_2$	> 50	471
p-FC_6H_4	H	H	H	p-$FC_6H_4CH{=}N$	$(CH_3)_2\overset{+}{S}\bar{C}H_2$	58	472
p-ClC_6H_4	H	H	H	p-$ClC_6H_4CH{=}N$	$(CH_3)_2\overset{+}{S}\bar{C}H_2$	54	472
p-BrC_6H_4	H	H	H	p-$BrC_6H_4CH{=}N$	$(CH_3)_2\overset{+}{S}\bar{C}H_2$	61	472
p-$CH_3OC_6H_4$	H	H	H	p-$CH_3OC_6H_4CH{=}N$	$(CH_3)_2\overset{+}{S}\bar{C}H_2$	64	472



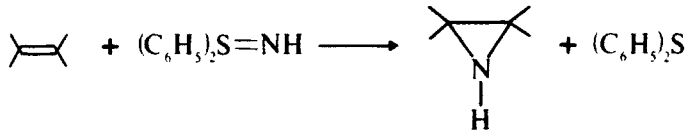
(105)

117

5. Other Aziridine Syntheses

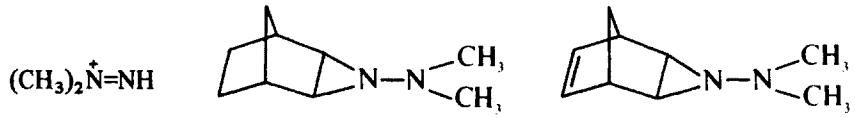
The syntheses of aziridines described here do not fit neatly into the rather arbitrary groups of the previous sections. Most of these reactions are less general and have been less widely applied, moreover, their mechanistic details are often obscure. They are no less important, however, and many contain the seeds of new research areas.

Direct epimination of alkenes has been affected by several reagents. Electron-deficient alkenes react with diphenylsulfilimine to yield aziridines (Eq. 106). The mechanism appears to involve nucleophilic attack by nitrogen and subsequent ring closure.

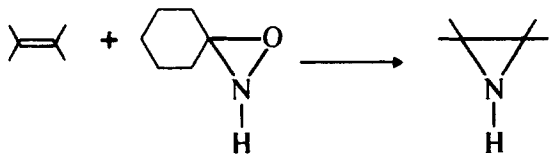


(106)

The reaction is not stereospecific. Some examples of this reaction are found in Table 58. The reaction of 1,1-dimethyldiazenium bromide (**118**) with alkenes is apparently electrophilic. Norbenene and norbornadiene give **119** (59%) and **120** (20%), respectively.[477] The reaction mixtures are complex. A novel reaction of oxaziridines with alkenes (Eq. 107) yields aziridines.[478]



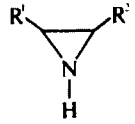
118 **119** **120**

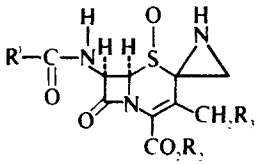


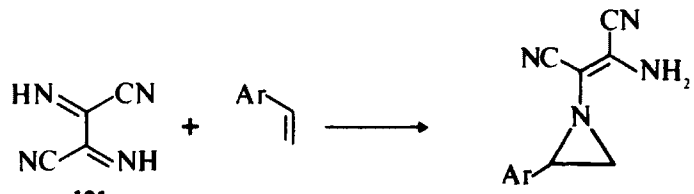
(107)

The mechanism is unclear and warrants further study. The epimination of electron-deficient alkenes by diiminosuccinonitrile (**121**) gives aziridines (Eq. 108) in reasonable yields.[479]

TABLE 58. AZIRIDINES FROM ALKENE-SULFILIMINE REACTIONS



R^1	R^2	Yield (%)	Ref.
C_6H_5CO	COC_6H_5	50	474
CH_3O_2C	CO_2CH_3	46	474
C_6H_5CO	C_6H_5	73	474
C_6H_5	$COCH_3$	23	475
		50–60	476

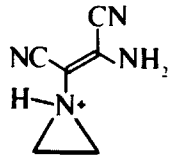


(108)

121

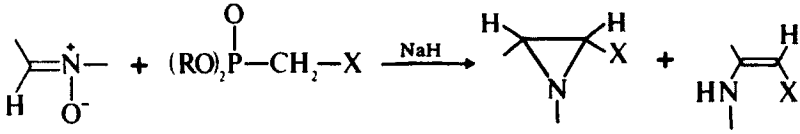
Ar	Yield (%)
C_6H_5	58
p-ClC_6H_4	51
p-FC_6H_4	79
p-$CH_3C_6H_4$	62

Intermediate **122** has been suggested. Electron-rich alkenes give [4 + 2] cycloaddition.



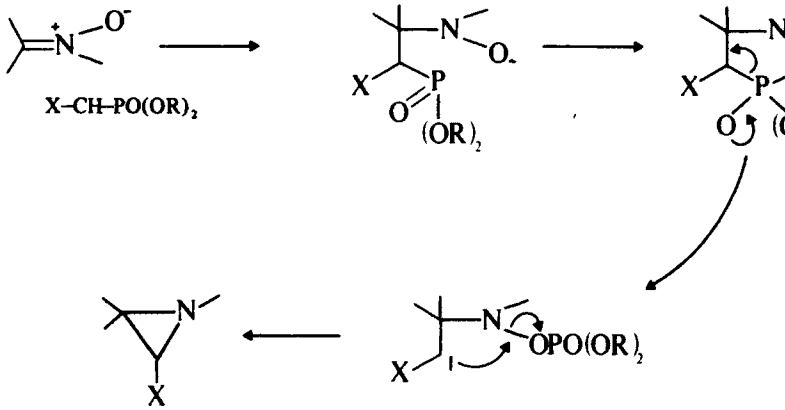
122

The reaction of phosphonate sodium salts with nitrones yields aziridines (Eq. 109) and has been studied in detail.[480]



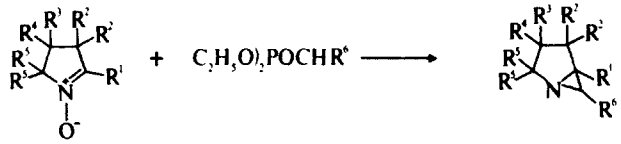
(109)

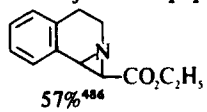
The enamine by-product (as well as stereochemistry, etc.) is solvent dependent.[481,482] The mechanism depicted in Eq. 110 seems to be the one most consistent with the available data.



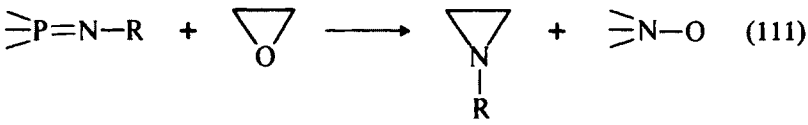
(110)

TABLE 59. AZIRIDINES FROM PHOSPHONATE ESTERS



R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	Ref.
H	H	H	H	CH_3	CN	59	483
H	H	H	H	CH_3	$CO_2C_2H_5$	75	483–485
H	CH_3	H	H	CH_3	$CO_2C_2H_5$	52	484, 485
					 57%[486]		

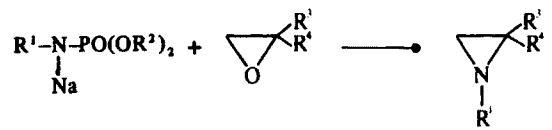
Compounds prepared via this reaction are listed in Table 59. In related reactions, amidophosphates and iminophosphoranes react with epoxides to yield aziridines (Eq. 111). These reactions are summarized in Tables 60 and 61.



(111)

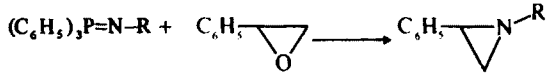
Isoxazolines undergo ring contraction to aziridines (Eq. 112). Although in many cases the aziridines are unstable and rearrange further (Eq. 112), certain nitrogen and ring substituents allow aziridine isolation under favorable experimental conditions.[489] Electron-withdrawing substituents on nitrogen and lack of C-3 substituents favor aziridine stability. In some cases, the isoxazole (formed from alkyne and nitrone) is not isolable and spontaneously rearranges to an aziridine. Aziridines prepared in this manner are listed in Table 62.

TABLE 60. AZIRIDINES FROM AMIDOPHOSPHATES[487]

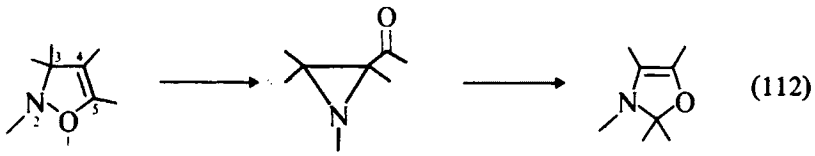


R^1	R^2	R^3	R^4	Yield (%)
C_6H_5	C_2H_5	C_6H_5	H	38
$C_6H_5CH_2$	C_2H_5	C_6H_5	H	58
$C_6H_5CH_2$	C_2H_5	C_6H_5	H	10
t-Bu	C_6H_5	C_6H_5	H	30
C_6H_5	C_2H_5	C_6H_5	CH_3	21

TABLE 61. AZIRIDINES FROM INIMOPHOSPHORANES[488]

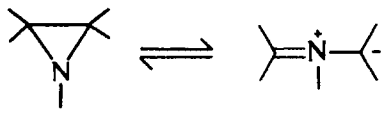


R	Yield (%)
CH_3	72
C_2H_5	67
$CH(CH_3)_2$	49
C_6H_5	47



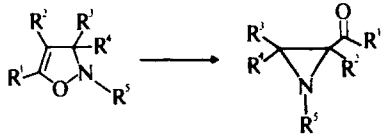
(112)

Thermal and photochemical ring opening of aziridines produces azomethine ylids (Eq. 113). The subsequent chemical interception of these intermediates is discussed later. Generation of these ylids in the absence of an intercepting agent should allow aziridine synthesis.



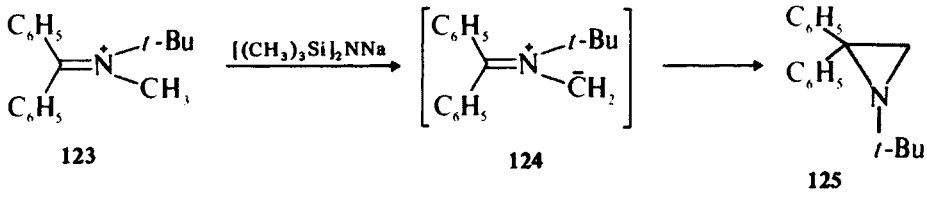
(113)

TABLE 62. AZIRIDINES FROM ISOXAZOLINES



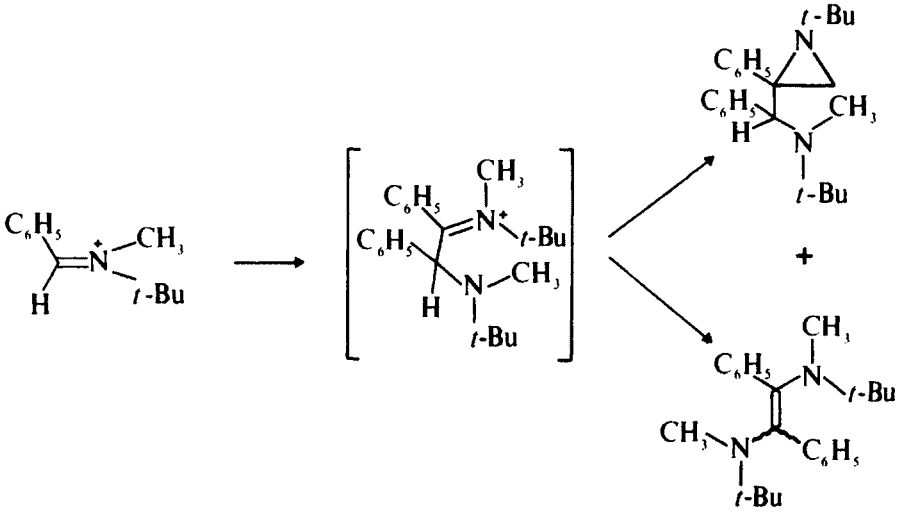
R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
CO_2CH_3	CO_2CH_3	H	H	*t*-Bu	–	489
$(CH_3)_2C(OH)$	H	H	H	*t*-Bu	–	489
C_6H_5	H	H	H	CH_3	65	490
C_6H_5	H	H	H	*t*-Bu	60	490
C_6H_5	CH_3	H	H	C_6H_5	93	490
CO_2CH_3	H	H	CN	OCH_3	–	491
COC_6H_5	H	H	CN	OCH_3	100	492
C_6H_5	H	H	CO_2CH_3	OCH_3	46	493
$HOCH_2$	H	H	CO_2CH_3	OCH_3	52	493
$ClCH_2$	H	H	CO_2CH_3	OCH_3	55	493
CO_2CH_3	H	H	CO_2CH_3	OCH_3	74	493
CH_3CO	H	H	CO_2CH_3	OCH_3	82	493
CO_2CH_3	CH_3	H	CO_2CH_3	OCH_3	15	493,494

A few examples of this approach can be found in the literature. The reaction of the ketiminium salt **123** results in a quantitative yield of **125** via the azomethine ylid **124**.[495] The reaction is not general, however.



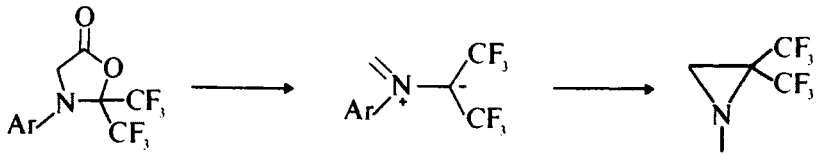
123 **124** **125**

Aldiminium salts give more complex products (Eq. 114).[495, 496]



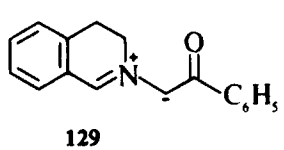
(114)

1,3-Oxazolidin-5-one (**126**) yields aziridine **128** via intermediate **127**.[497]

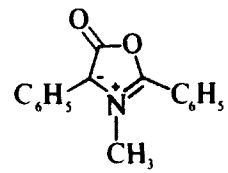


126 **127** **128**

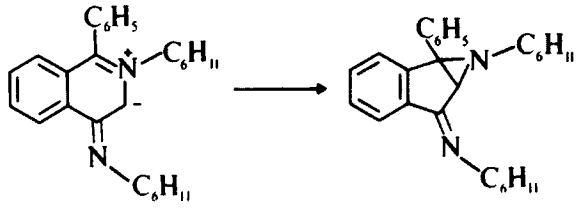
Some azomethine ylids (e.g., **129**[498] and **130**[499]) fail to undergo apparent ring closure because of their stability or aziridine instability. The cyclization of **131** to **132** has been reported to take place under thermal and photochemical conditions.[500]



129

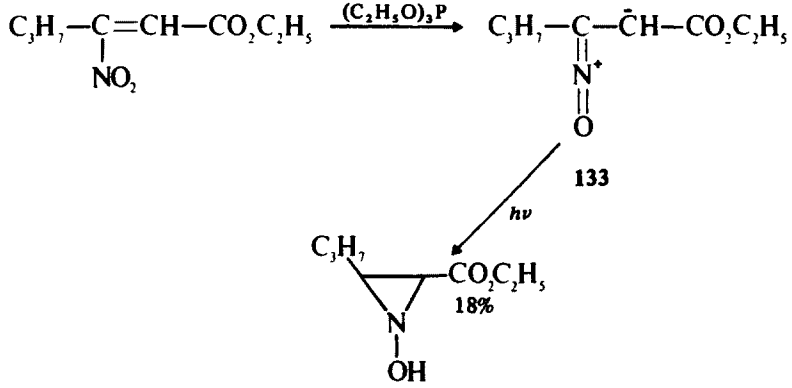


130



131 132

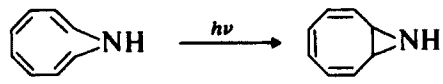
Photochemical ring closure of azomethine ylid **133** has resulted in the formation of aziridine **134**.[501]



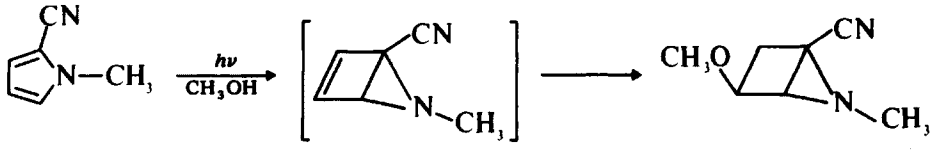
133

134

Photochemically induced valence tautomerism has produced the novel structures **135**[502] and **136**.[503]

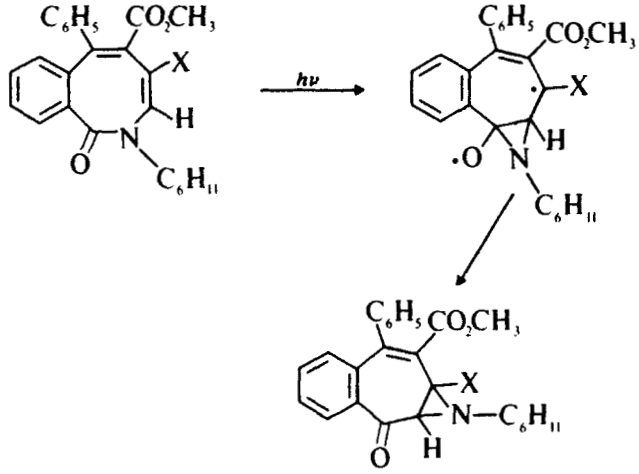


135



136

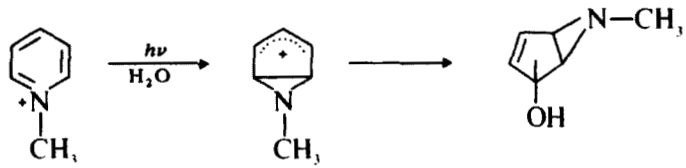
More complex photochemical aziridine syntheses have also been described. The mechanism of Eq. 115 has been suggested to account for aziridine formation.[500]



(115)

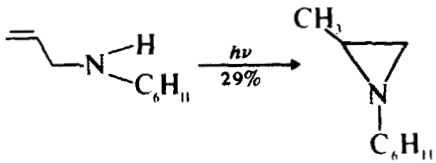
X = H (61%)
X = CO_2CH_3 (43%)

The photolysis of pyridinium salts allows entry into the 6-aza[3.1.0]bicyclic aziridine system.[504] The reactions are complex because labeling demonstrates that the initial bicyclic intermediate undergoes isomerization (via tricyclic intermediates or sigmatropic shifts) before solvent capture (Eq. 116).



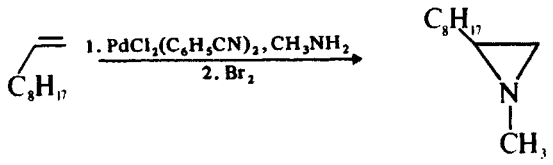
(116)

Aliphatic allylamines can be photochemically cyclized to aziridines (Eq. 117).[505]

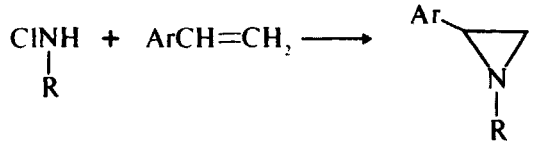


(117)

An interesting new approach to aziridine synthesis via transition metal complex oxidation (with bromine) has been published.[506] The reaction is not stereospecific. The mechanism and generality of the reaction (Eq. 118) are unknown. A report has appeared concerning the addition of *N*-haloamines to styrene derivatives (Eq. 119).

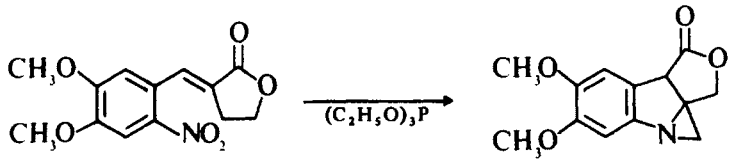


(118)

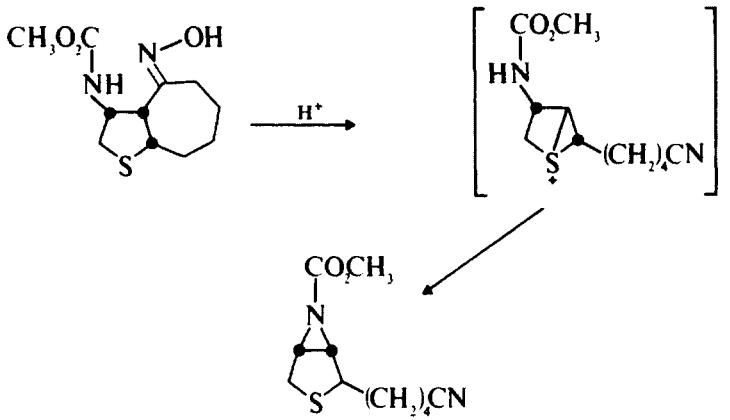


(119)

The reaction appears to involve a radical chain addition of the haloamine to the alkene and subsequent ring closure of the intermediate β-haloamine.[507] The reactions depicted in Eqs. 120[508] and 121[509] represent novel approaches to otherwise unattainable aziridine derivatives.

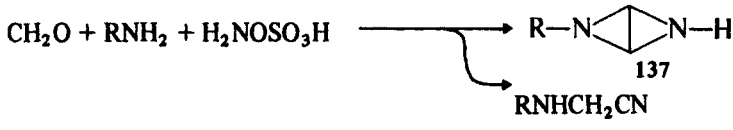


(120)



(121)

Finally, the novel bicyclobutane derivative first shown as **137**[510] has been shown to have structure **138** instead.[511] Structures of type **137** are thus still unknown.



IV. REACTIONS OF AZIRIDINES

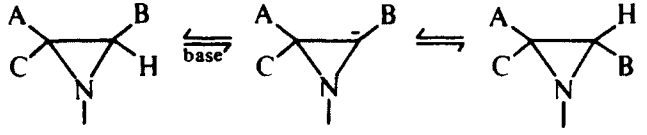
The reactions of aziridines can be divided into those in which the aziridine ring retains its integrity and those in which the ring is enlarged or opened. This is an arbitrary distinction because such classification often is a function of aziridine substituents and/or reaction conditions. In spite of such difficulties, this organization is particularly appropriate for emphasizing synthetic applications of aziridine chemistry.

1. Reactions in Which the Aziridine Ring is Retained

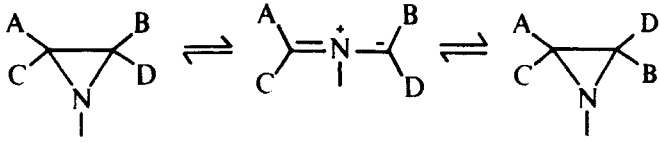
Section IV, 1 has five subsections. The first deals with stereochemical isomerization of aziridines and the sometimes attendant proton exchange. The second covers reactions in which exocyclic bonds to the nitrogen atom are formed or broken. The third deals with modifications of the nitrogen substituent. The fourth is concerned with reactions at one of the ring carbons. The last subsection treats reactions on side chains that are attached to the annular carbon atoms.

A. *cis-trans Aziridine Isomerization*

There are at least two mechanisms available for aziridine *cis-trans* isomerism. The first is base catalyzed and proceeds via an intermediate anion. Concomitant isotopic exchange is indicative of this pathway (Eq. 122). The second mechanism can be either thermally or photochemically initiated and proceeds by way of an intermediate azomethine ylid. Absence of catalysis and interception of the intermediate provide support for this route (Eq. 123).

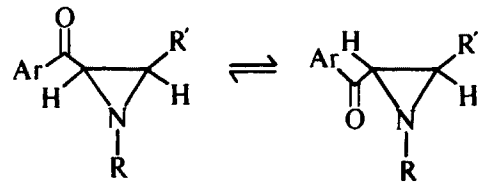


(122)

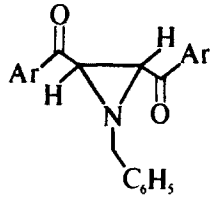


(123)

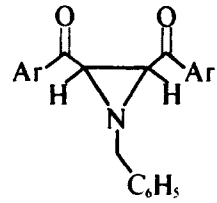
A variety of aziridinylketones (Eq. 124) have been subject to base-catalyzed equilibration.[62,64,225,512–516] In most of these cases, the *cis* isomer is more stable than the *trans* form. Particularly revealing is the effect of solvent on the *cis-trans* equilibrium of **139** and **140**.[512]



(124)

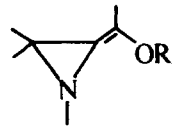


139



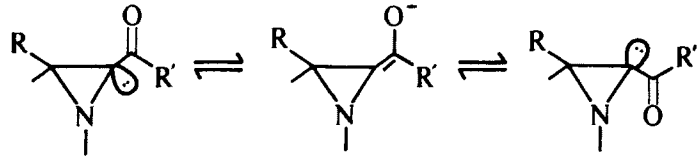
140

For this pair, the equilibrium percentage of *cis* ranged from 84% *cis* in polar solvents (DMSO) to 24% in apolar (*t*-BuOH) solvents. The reason for greater *cis*-isomer stability is not readily obvious, and since energy differences between the two isomers are small (*ca.* 1 kcal or less), speculation may not be fruitful. Although the enolate anions have been isolated via isotope incorporation, they have not apparently been converted to enol ethers (**141**) or esters. Such products should have chemical properties analogous to those of methylene aziridines.



141

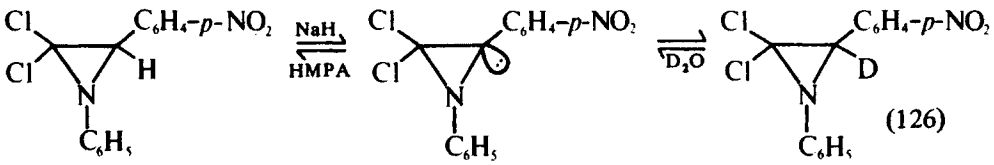
Other chemistry of these anions is both unexplored and potentially useful. The structure of the enolate anions is not totally clear. The observation that exchange rates exceed epimerization rates has led to a postulate of three intermediates,[513] as shown in (Eq. 125). Structure **143** is quite analogous to α-lactam structures established by x-ray crystallographic studies.



(125)

142 143 144

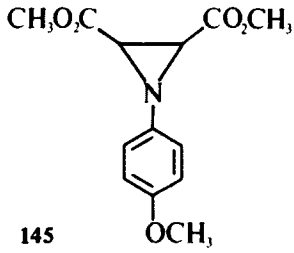
It is likely that **142** and **144** are unnecessary and that the data are better explained by invoking **143** and familiar ion-pairing arguments. Base-catalyzed isotope exchange has also been observed in at least one molecule that lacks a stabilizing carbonyl group (Eq. 126).[517]



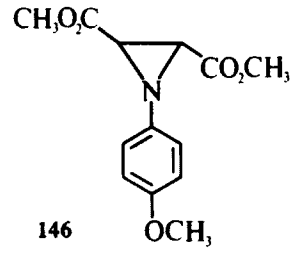
(126)

It is interesting to note that elimination to give a 2-azirine structure was not observed.

Equilibration of aziridines via azomethine ylids (Eq. 123) has been reported for a variety of structures.[168,518-525] Here also solvent effects have been noted. Thus, the percentage of *cis* (**145**) in the **145**-to-**146** interconversion has ranged from 22% (CCl_4) to 47% (1,3-dioxolan-2-one).[519]



145



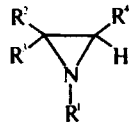
146

Most other aziridines equilibrated by this method show greater *cis* stability. An energy barrier has been detected between the two isomeric azomethine ylids (Eq. 123).[519]

B. *Formation and Cleavage of Bonds to the Aziridine Nitrogen*

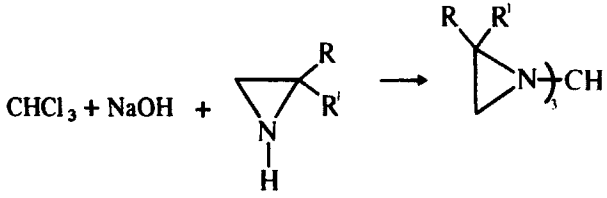
Nucleophilic attack by the aziridine nitrogen on aliphatic halides is a useful, familiar, and extensively reviewed reaction.[526,527] A few new examples deserve mention. The use of phase transfer conditions (Table 63) can give superior yields

TABLE 63. AZIRIDINE ALKYLATION UNDER PHASE TRANSFER CONDITIONS[528]



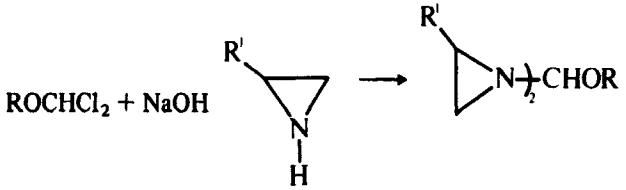
R^1	R^2	R^3	R^4	Yield (%)
n-Bu	H	H	H	100
i-Pr	H	H	H	30
i-Bu	H	H	H	10
$C_6H_5CH_2$	H	H	H	100
C_6H_5	H	H	H	10–15
n-Bu	C_6H_5	CH_3	CH_3	5
$C_6H_5CH_2$	C_6H_5	CH_3	CH_3	80

in direct alkylation reactions.[528] Reaction of chloroform with aziridines yields trisubstituted products (Eq. 127).[529] Dihalides give similar results (Eq. 128).[529]



(127)

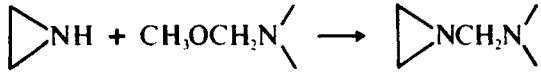
R	R^1	Yield (%)
H	H	100
CH_3	H	43
CH_3	CH_3	30



(128)

R	R^1	Yield (%)
CH_3	H	70
C_2H_5	H	50
$(CH_3)_2CHCH_2CH_2$	H	82
CH_3	CH_3	57

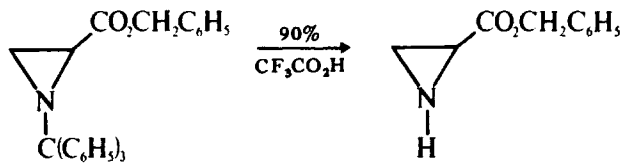
Aziridines have been alkylated by amino ethers (Eq. 129).[530,531]



(129)

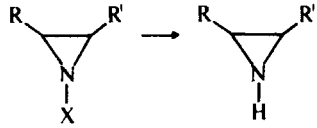
The reaction depicted in Eq. 130 also belongs in this category.[532] One dealkylation (Eq. 131) is significant because it demonstrates that the acid sensitivity of the aziridine ring can be overemphasized.[533]

(130)



(131)

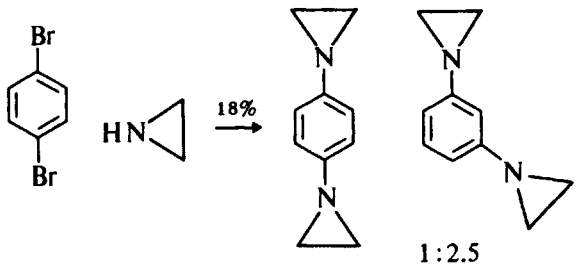
TABLE 64. $LiAlH_4$ CLEAVAGE OF PHOSPHORUS-AZIRIDINE BONDS[193]



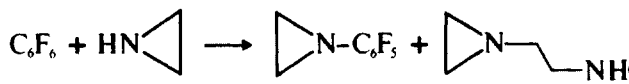
R	R^1	X	Yield (%)
C_6H_5	H	$(C_6H_5)_3\overset{+}{P}$	16
C_6H_5	H	$(RO)_2PO$	88
C_6H_5	CH_3	$(C_6H_5)_3\overset{+}{P}$	90
C_6H_5	CH_3	$(RO)_2PO$	76
CH_3	CH_3	$(C_6H_5)_3\overset{+}{P}$	46
$(CH_2)_6$		$(C_6H_5)_3\overset{+}{P}$	50
C_6H_5	C_6H_5	$(RO)_2PO$	93

Phosphorylated aziridines are readily prepared from aziridines and the appropriate phosphorous halides. These phosphorylated aziridines have interesting biological properties and thus continue to attract interest. A few new reactions[534–538] should be added to previously cited references.[539,540] The direct conversion of phosphorylated aziridines to their selenium derivatives have been achieved.[541] The reductive cleavage of the nitrogen-phosphorus bonds (Table 64) proceeds in high yield.[193] This procedure has been used in a key step of a mitomycin total synthesis.[143] Formation of N–Si[542,543] and N–halogen bonds warrants no additional discussion.[544] The reductive ($NaBH_4$) removal of an N–Cl group has been described.[52]

A few new examples of aziridine arylation are of interest. The reaction of 1,4-dibromobenzene with a metallated aziridine (Eq. 132) yields products indicative of a benzyne pathway (545). The reaction of perfluorobenzene with ethylenimine results in arylation (Eq. 133) along with side reactions.[546]

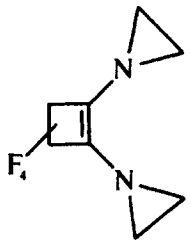


(132)

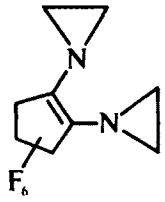


(133)

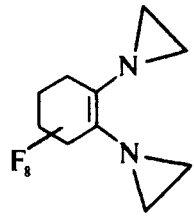
Nucleophilic displacement of vinyl derivatives can lead to interesting products. Perfluorocycloalkenes yield **147–151**. Ketene dithioacetal undergoes a single displacement (Eq. 134).[548]



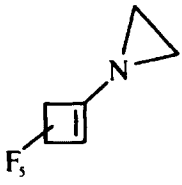
147[546,547]



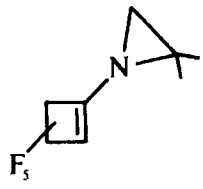
148[546]



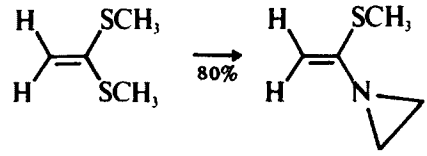
149[546]



150[547]

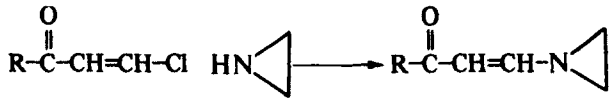


151[547]



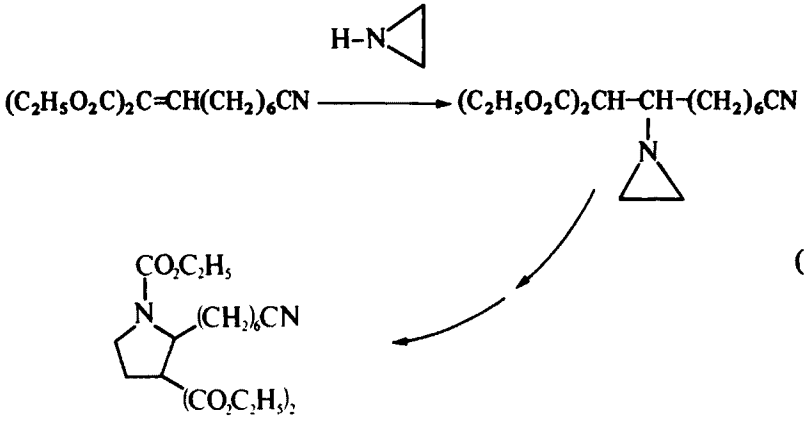
(134)

The preparation of acylvinylaziridines is accomplished in high yield (Eq. 135).[549]



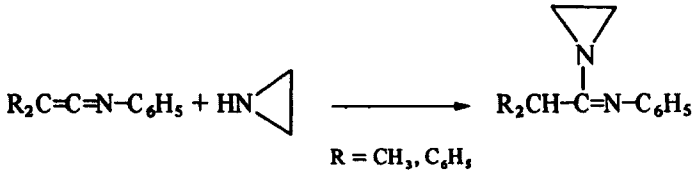
(135)

Michael-type additions of aziridines to alkenes and alkynes constitute general approaches to aziridine derivatives.[526,550,551] A variety of new additions to conjugated[552–555] and fluorinated[556] alkenes have been described. One particularly interesting application depicted in Eq. 136 constituted a key step in the synthesis of a 9-azaprostaglandin analog.[557]

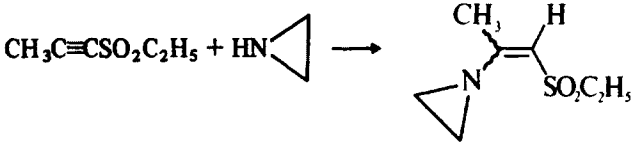


(136)

Ketenimines readily add ethylenimine (Eq. 137).[558] The addition of ethylenimine to nonterminal acetylenes gives a stereochemical mixture of conjugated adducts,[559,560] as shown in Eq. 138.

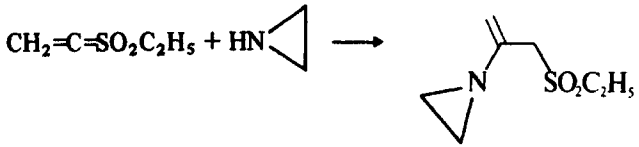


(137)



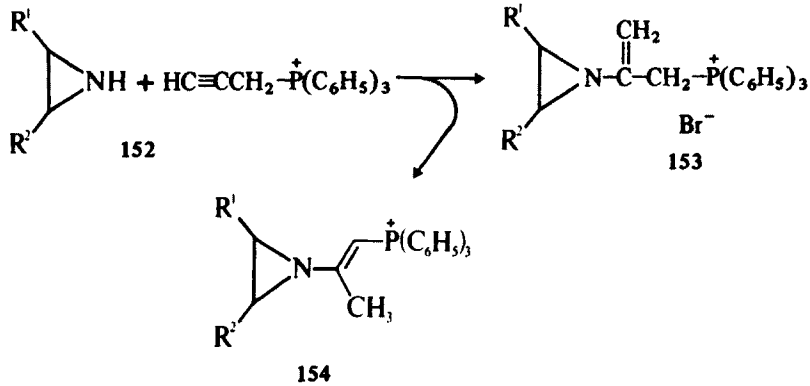
(138)

Under the same conditions the corresponding allenes give nonconjugated products (Eq. 139).

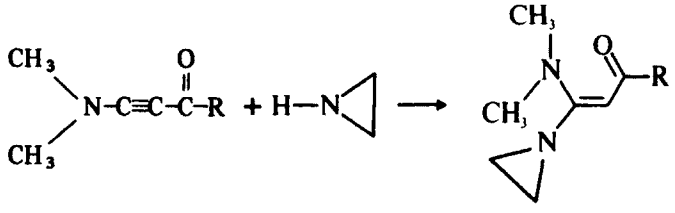


(139)

Aziridine additions to alkyne **152** can give either **153** (kinetic) or **154** (thermodynamic) depending on conditions.[561] The addition of ethylenimine to **155** gives **156** in high yields.[562]

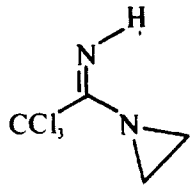


Acylations of aziridines are well documented.[563,564] To the list may be added acylations with diketene.[565] A useful study of deacylation reactions[566] concluded that deacylation (attack on the carbonyl) was favored when good nucleophiles were used; poorer nucleophiles were found to be more prone to attack the ring.

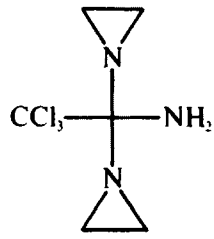


155 R = H (95%) R = CH_3 (90%) R = OCH_3 (97%) 156

Nitriles and nitrile derivatives are quite reactive toward aziridines. Trichloroacetonitrile can yield either **157** or **158** depending on reaction conditions.[567]



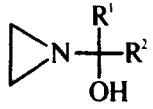
157



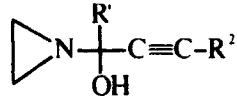
158

Nitrile oxides,[568-570] isocyanide dichlorides,[571,572] and imino ethers[573] all readily add the aziridine moiety.

In contrast to most other secondary amines, aziridines react with aldehydes to give compounds of structures **159**[530,574] and **160**[575-578] in good yields.

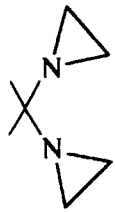


159

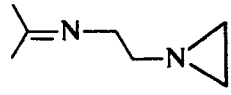


160

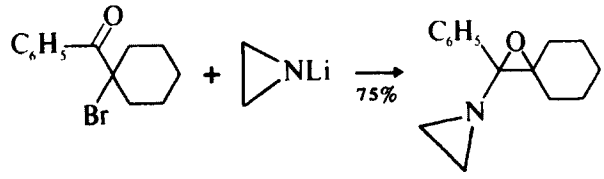
These structures are attainable because of the combined good nucleophile-poor π-donor properties of the aziridine ring. Titanium tetrachloride catalyzed addition of ethylenimine to carbonyl groups provides access to compounds of structure **161** as well as by-product **162**.[579] Other novel structures attainable with aziridines are illustrated by Eqs. 140,[580,581] 141,[582] and 142.[161]



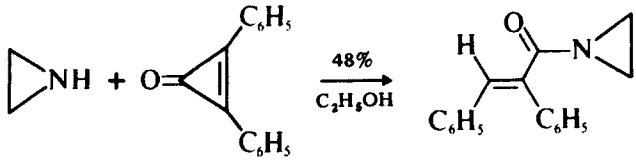
161



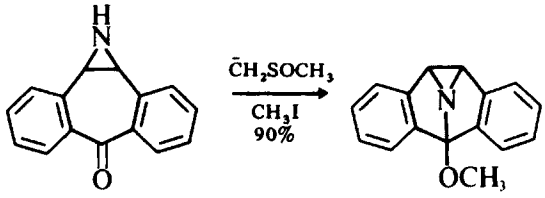
162



(140)



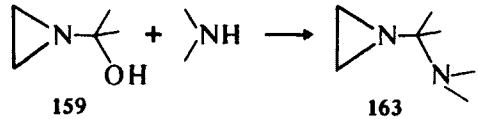
(141)



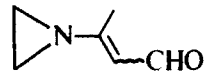
(142)

C. *Modifications of the Nitrogen Substituent*

Although relatively little has been done on the chemistry of the nitrogen substituent, some results are indicative of the potential in this area. The previously described aldehyde adducts (**159**) react with amines to give **163** (cf. Eq. 129).[530,531,574] Compounds with structure **160** (R^2 = H) spontaneously isomerize at 20° to **164**.[578]

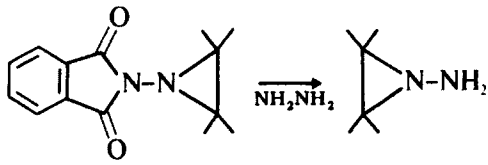


159 **163**



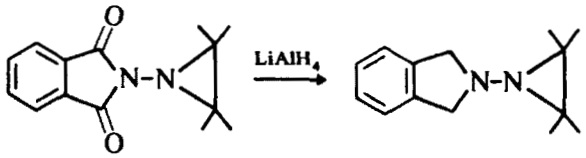
164

The phthalimido group (introduced via nitrene addition) can be cleaved without damage to the aziridine ring (Eq. 143).[419,583]

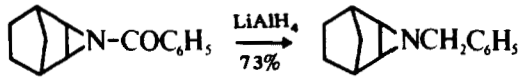


(143)

Reduction of the phthalimido ring with $LiAlH_4$ (Eq. 144) is also feasible.[418] Although acylethylenimines are cleaved by $LiAlH_4$ to the corresponding aldehyde, this reaction appears to follow a different course for more complex aziridine derivatives (e.g., Eq. 145).[138,360]

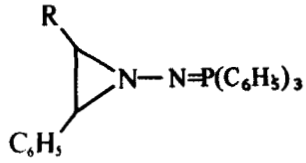


(144)



(145)

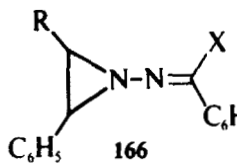
The conversion of *N*-aminoaziridines to the corresponding hydrazones proceeds in high yield.[120,584,585] A series of intriguing reactions has been found with ylids of structure **165**.



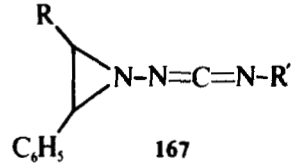
165

R = C_6H_5; H

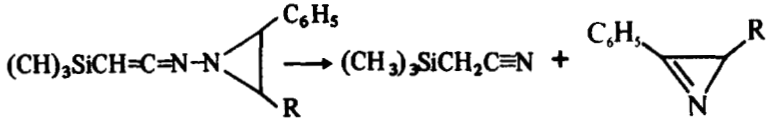
These compounds react with C_6H_5COX (X = CN, Br, N_3) and R'N=C=O to give **166** and **167**, respectively, in good to excellent yields.[586] Reaction of **165** with $(CH_3)_3SiCH{=}C{=}O$ gives **168**.[587] The latter is unstable and spontaneously undergoes retroene formation of **169** and **170**. Diphenylketene gives an analogous initial adduct that undergoes a 1,3-sigmatropic shift (Eq. 146).[588]



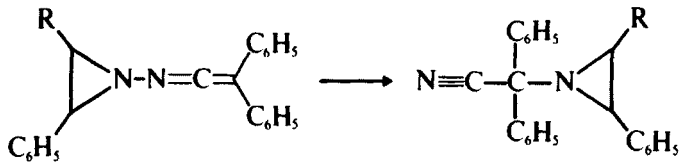
166



167

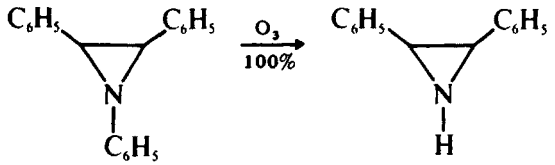


168 **169** **170**



(146)

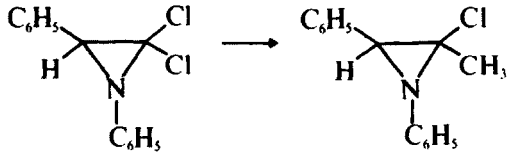
The aziridine ring is surprisingly stable toward ozonolysis, as demonstrated in Eq. 147.[589] Other reactions that involve both the N–H and a carbon side chain are discussed in Section III, 1, E.



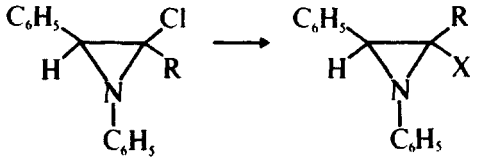
(147)

D. *Reactions on the Aziridine Ring Carbons*

Since cyclopropyl halides are relatively inert and α-haloamines are usually unstable (relative to the iminium form), the 2-haloaziridines might be expected to show intermediate behavior. This expectation has been fulfilled in the cases of a variety of substituted 2-haloaziridines for which chemical interconversions can be observed without ring opening. Displacement, as depicted in Eqs. 148 and 149, appears to involve intermediate **171** in spite of the observed inversion.[590]



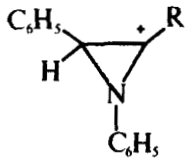
(148)



(149)

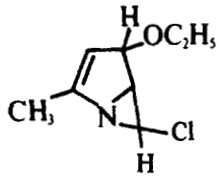
R	X	Yield (%)
H	$CH_3(Li)$	88
H	$CH_3O(Na)$	82
H	$C_6H_5S(Na)$	–
CH_3	CN(K)	–
CH_3	$C_6H_5S(Na)$	95
CH_3	$H(AlH_3Li)$	89

The displacements followed first-order kinetics, and faster rates were noted with **171** if $R = CH_3$ than with $R = H$. The observed inversion was ascribed to ion pairing and/or stereoselectivity. When $R = Cl$, the intermediate is less stable and undergoes ring opening in preference to interception (see Section IV, 2, I).

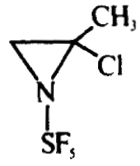


171

The stability of **172**[156] and **173**[347] suggests that **171** is probably planar and that charge stabilization by the unshared pair plays a crucial role in reactivity.

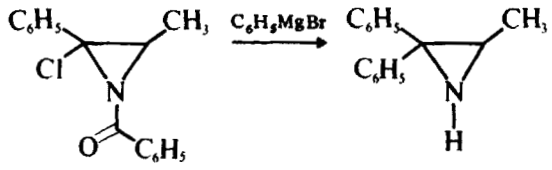


172

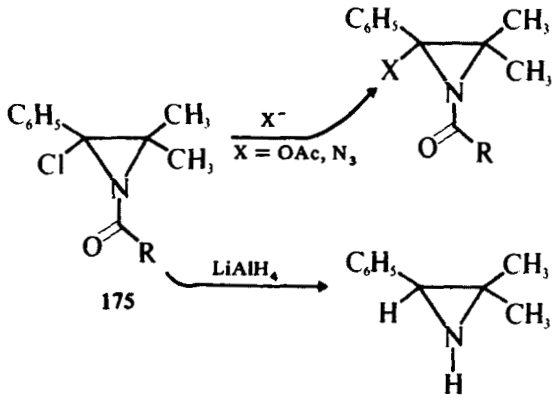


173

Similar conclusions follow from the *N*-acylaziridine analogs **174** and **175**, which undergo the indicated displacements with ring retention.[259, 260]

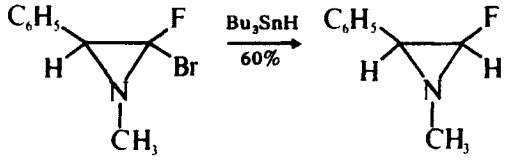


174

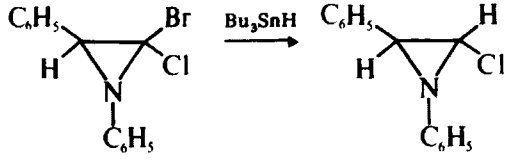


175

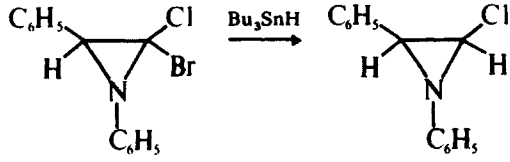
The Bu_3SnH reduction of dihaloaziridines exemplifies another approach to substitution on the aziridine ring carbons (Eqs. 150–152).



(150)



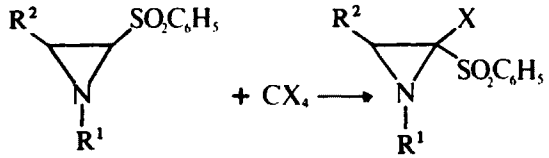
(151)



(152)

Especially noteworthy is the retained configuration in all three cases. This behavior differs from the cyclopropyl analog and was explained on the basis of increased *s* character in the exocyclic bond caused by the nitrogen atom. This interesting observation probably warrants additional study.

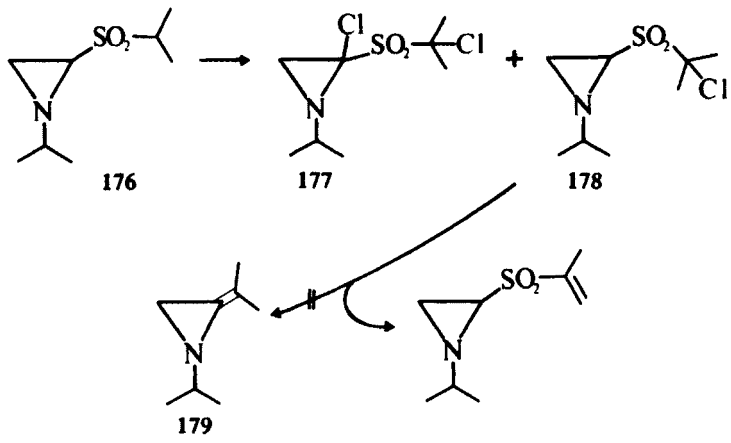
A final approach to aziridine substitution is found in the halogenation of 2-sulfonylaziridines (Eq. 153).[591] Attempted elimination of HX with methoxide from the products regenerated 2-sulfonylaziridine.



(153)

R^1	R^2	X	Yield (%)
t-Bu	H	Cl	70
t-Bu	H	Br	75
C_2H_5	C_6H_5	Br	75

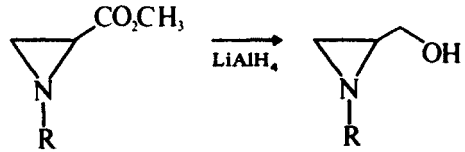
Other nucleophiles produced the same results. A similar halogenation of **176** gave mixtures of **177** and **178**. The latter failed to form **179** upon dehydrohalogenation.



176 177 178 179

E. *Reactions on the Aziridine Side Chain*

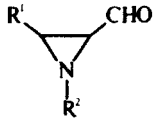
The aziridine ring is quite stable toward metal hydrides, organometallics, and other similar reagents. As a result, a large number of useful side chain modifications can be accomplished. Aziridine esters may be either totally reduced to the corresponding primary alcohol (Eq. 154)[592] or partially reduced to the aldehyde (Table 65).



(154)

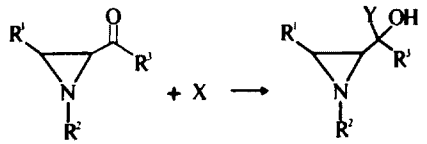
The latter reduction requires milder conditions and/or reagents. The reactions of other ketones and aldehydes with various reagents are summarized in Table 66.

TABLE 65. SYNTHESIS OF AZIRIDINE ALDEHYDES



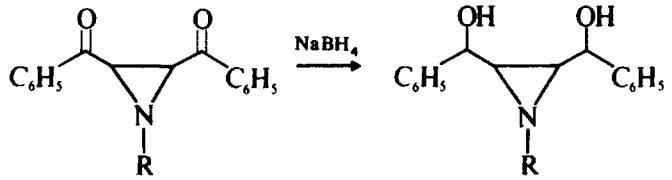
R^1	R^2	Reagent	Yield (%)	Ref.
H	*i*-Pr	$LiAlH_4$ (−70°)	*ca.* 30	593
H	*t*-Bu	$LiAlH_4$ (−70°)	*ca.* 30	593
H	*t*-Bu	HAl (*i*-Bu)$_2$	73	594
H	C_6H_{11}	$LiAlH_4$ (−70°)	*ca.* 30	593
H	$C_6H_5CH_2$	$LiAlH_4$ (−70°)	*ca.* 30	593
CH_3	CH_3	HAl (*i*-Bu)$_2$ (−65°)	85	595
CH_3	*i*-Pr	HAl (*i*-Bu)$_2$ (−105°)	45	595
CH_3	*t*-Bu	HAl (*i*-Bu)$_2$ (−80°)	90	595

TABLE 66. ADDITIONS TO AZIRIDINE SIDE CHAIN CARBONYL GROUPS



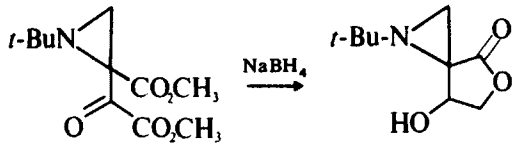
R^1	R^2	R^3	X	Y	Yield (%)	Ref.
H	*t*-Bu	OCH_3	C_6H_5MgBr	C_6H_5	73	592
H	*t*-Bu	H	CH_3MgBr	CH_3	55	595
H	*t*-Bu	H	C_6H_5MgBr	C_6H_5	70	595
C_6H_5	C_6H_{11}	C_6H_5	$LiAlH_4$, $NaBH_4$	H	–	596
H	*t*-Bu	CH_3	$LiAlH_4$	H	–	597
H	*t*-Bu	C_6H_5	$LiAlH_4$	H	93	592
H	*t*-Bu	C_6H_5	$NaBH_4$	H	62	592
H	*t*-Bu	H	CH_3Li	CH_3	–	597
t-Bu	CH_3	CH_3 (*cis*)	$LiAlH_4$	H	–	597
t-Bu	CH_3	CH_3 (*trans*)	$LiAlH_4$	H	–	597

A mixture of diastereomers is usually encountered when a new chiral carbon is generated. The unambiguous assignment of structures to these isomers poses some problems, although one procedure (Section IV, 2, A) has been successfully applied.[597,598] A variety of factors have roles in determining the stereochemical course of the reaction.[593,595-600] Diketones (Eq. 155) have also been reduced to the corresponding diastereomeric diols.[601]



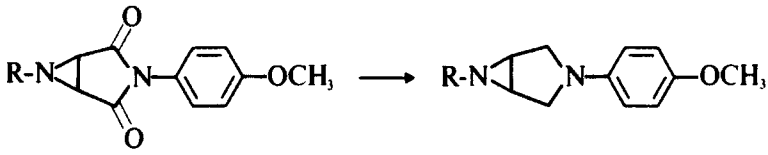
(155)

A number of other side chain reductions are also of interest. Reduction of **180** yielded spirolactone **181**.[489]



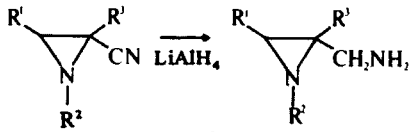
180 **181**

Reduction of **182** by $LiAlH_4$ resulted in bicyclic structure **183**.[138,602]



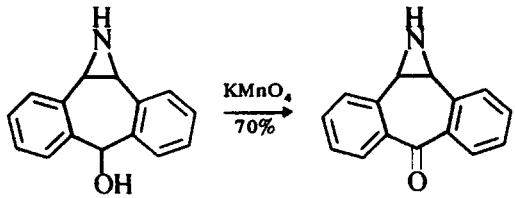
182 **183**

TABLE 67. FORMATION OF 2-AMINOMETHYLAZIRIDINES VIA $LiAlH_4$ NITRILE REDUCTION[603]

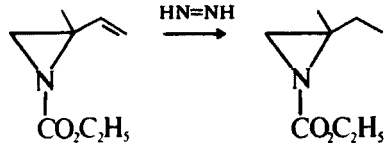


R^1	R^3	R^2	Yield (%)
H	H	C_6H_5	60
H	H	$C_6H_5CH_2$	68
H	CH_3	C_6H_5	75
H	CH_3	$C_6H_5CH_2$	87
H	CH_3	CH_2=CH–CH_2	63
H	CH_3	$CH_3(CH_2)_7$	90
H	CH_3	$C_6H_5CHCH_3$	75
H	CH_3	$(CH_3)_2CH$	72
H	$CH_3CH_2CH_2$	$C_6H_5CH_2$	86
H	CH_3	*t*-Bu	78
$(CH_2)_3$		$C_6H_5CH_2$	79

Reduction of side chain nitriles has been used to synthesize the corresponding side chain amines (Table 67). Although side chain alcohol oxidations are rare, one example suggests that this would be a useful reaction (Eq. 156).[161] Diimide reduction of the side chain proceeds without destruction of the aziridine ring (Eq. 157).[99]

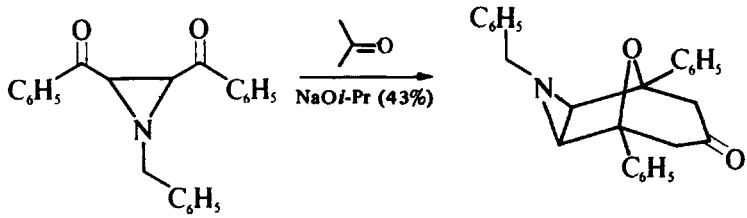


(156)



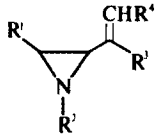
(157)

These readily accessible side chain ketones have been subjected to a variety of interesting chemical reactions. For example, additions of Wittig reagents produced the corresponding alkenes without disruption of the aziridine ring (Table 68). The aldol condensation (Eq. 158) forms a novel tricyclic aziridinylketone.[601]



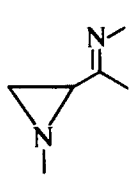
(158)

TABLE 68. VINYLAZIRIDINES VIA THE WITTIG REACTION[604,605]

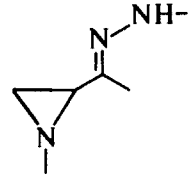


R^1	R^2	R^3	R^4	Yield (%)
H	*t*-Bu	CH_3	H	60
H	*t*-Bu	C_6H_5	H	50
H	$C_6H_5CH_2$	C_6H_5	H	33
H	*t*-Bu	H	$CO_2C_2H_5$	77
CH_3	$C_6H_5CH_2$	C_6H_5	H	50
C_6H_5	$(CH_3)_2CH$	CH_3	H	12
C_6H_5	C_6H_{11}	C_6H_5	H	60
C_6H_5	$(CH_3)_2CH$	C_6H_5	H	56
C_6H_5	$C_6H_5CH_2$	C_6H_5	H	48
C_6H_5	$C_6H_5CH_2$	C_6H_5	Cl	30
C_6H_5	$C_6H_5CH_2$	C_6H_5	C_6H_5	36
C_6H_5	$C_6H_5CH_2$	C_6H_5	CH_3	41

Conversion of aziridinylketones to imines **(184)**[593,606] and hydrazones **(185)**[162] has been reported.

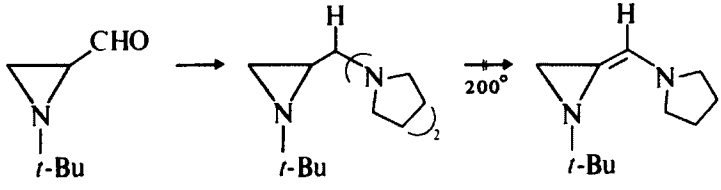


184



185

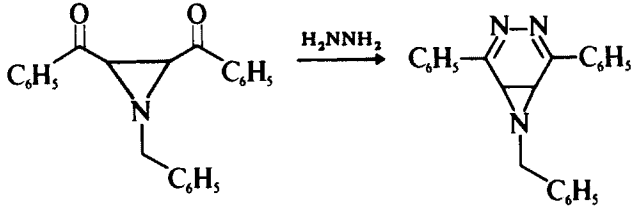
The adduct **187** from **186** fails to yield the interesting enamine **188**.[593]



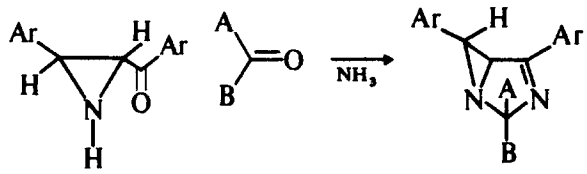
186 187 188

Diketone **189** reacts with hydrazine to yield the cyclic azine **190**.[516]

Aziridinylketones unsubstituted on nitrogen condense with aldehydes or ketones and ammonia to give the interesting bicyclic system **191**,[607] as summarized in Table 69.

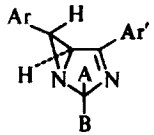


189 190



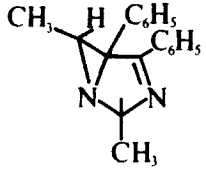
191

TABLE 69. SYNTHESIS OF 1,3-DIAZOBICYCLO[3.1.0]HEX-3-ENES[607]

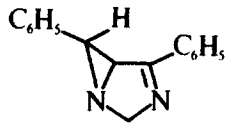


Ar	Ar'	A	B	Yield (%)
p-$NO_2C_6H_4$	C_6H_5	H	H	97
p-$NO_2C_6H_4$	C_6H_5	CH_3	CH_3	82
C_6H_5	*p*-$O_2NC_6H_4$	CH_3	CH_3	90
p-ClC_6H_4	C_6H_5	CH_3	CH_3	–
p-$NO_2C_6H_4$	C_6H_5	C_2H_5	C_2H_5	74
m-$NO_2C_6H_4$	C_6H_5	C_2H_5	C_2H_5	78
p-$NO_2C_6H_4$	C_6H_5	$(CH_2)_2CH$	$(CH_2)_2CH$	30
p-$NO_2C_6H_4$	C_6H_5	$(CH_2)_4$		45
p-$NO_2C_6H_4$	C_6H_5	$(CH_2)_5$		95
p-$NO_2C_6H_5$	C_6H_5	$(CH_2)_6$		63
p-$NO_2C_6H_4$	C_6H_5	$(CH_2)_7$		69
p-$NO_2C_6H_4$	C_6H_5	$(CH_2)_4CH(CH_3)$		55
p-$NO_2C_6H_4$	C_6H_5	$(CH_2)_2CHCH_3(CH_2)_2$		69
p-$NO_2C_6H_4$	C_6H_5	C_6H_5	C_6H_5	40
p-$NO_2C_6H_4$	C_6H_5	H	CH_3	74
p-$NO_2C_6H_4$	C_6H_5	H	*n*-C_3H_7	59
p-$NO_2C_6H_4$	C_6H_5	H	*i*-C_3H_7	46
p-$NO_2C_6H_4$	C_6H_5	H	C_6H_5	92
m-$NO_2C_6H_4$	C_6H_5	H	C_6H_5	83
C_6H_5	C_6H_5	H	C_6H_5	60
C_6H_5	*p*-$NO_2C_6H_4$	H	C_6H_5	59
p-$NO_2C_6H_4$	C_6H_5	H	*p*-$NO_2C_6H_4$	48
p-$NO_2C_6H_4$	C_6H_5	H	*p*-$CH_3C_6H_4$	53
p-$NO_2C_6H_4$	C_6H_5	H	*o*-$CH_3C_6H_4$	78

In some cases more than one isomer is formed (with respect to configuration of A and B) and structure-chemical assignments have been made.[608] Other examples of these condensation reactions include **192**[269] and **193**.[268]

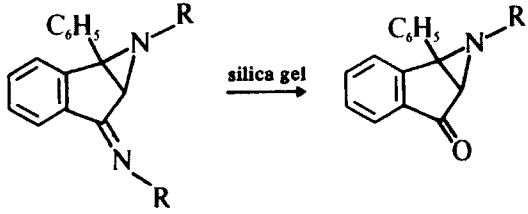


192



193

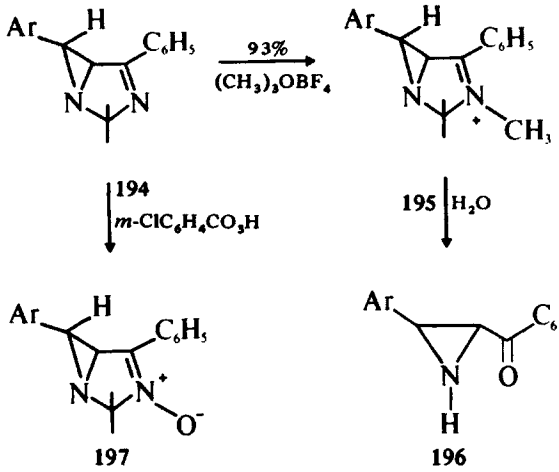
In almost all cases hydrolysis to the original aziridinylketones is readily accomplished in high yield. An interesting example of selective imine hydrolysis without affecting the aziridine ring is found in Eq. 159.[609]



(159)

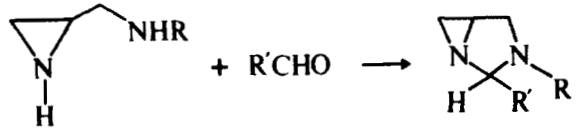
R = CH_3CH_2 (97%)
R = C_6H_{11} (95%)
R = CH_3 (60%)

The chemistry of **192** provides further insight into the selectivity possible with aziridine rings. Alkylation of **194** yields **195** as the exclusive product.[610]



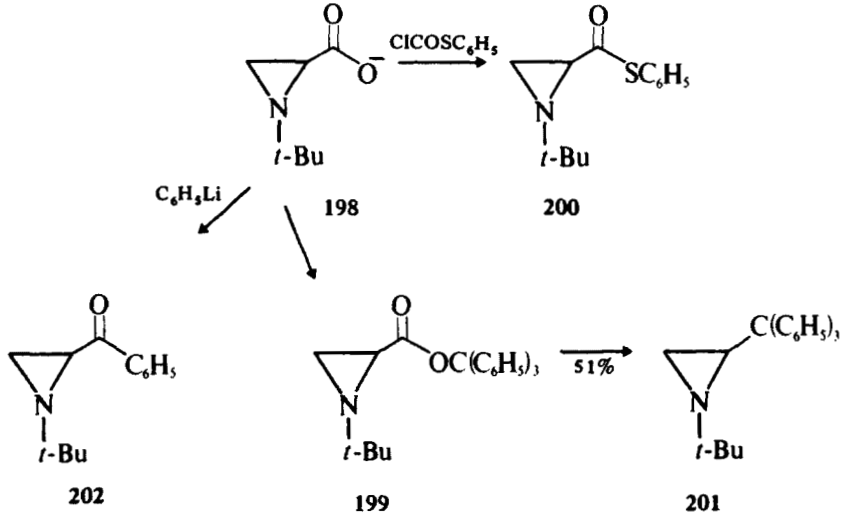
197 **196**

Hydrolysis of **195** yields the original precursor aziridine (**196**). Oxidation of **194** is also selective for the imine nitrogen (see **197**). The saturated analogs of **191** are available from side chain amine-aldehyde condensations (Eq. 160).[611,612]



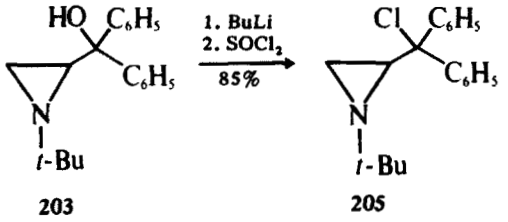
(160)

Aziridine esters are easily converted by hydrolysis to the corresponding salts.[533,592] In a few cases where electron-withdrawing groups were located on nitrogen, the acid itself has been isolated.[59,60,613] The acids have been reesterified by diazoalkanes,[60] and one salt (**198**) has been converted to its trityl ester (**199**) with trityl bromide.[614] The same salt (**198**) forms thioester **200**.[615]

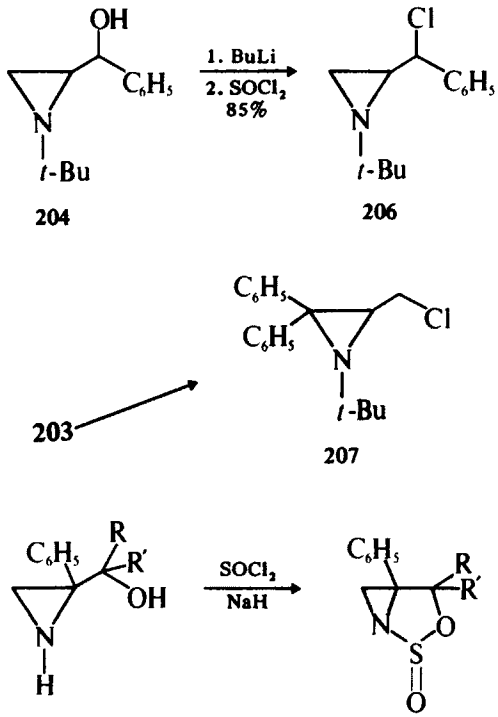


Trityl ester **199** decarboxylates at 180°C to give **201**.[614] It is not clear whether the process is homo- or heterolytic. Salt **198** also can be converted to the ketone **202** with C_6H_5Li.[592]

The aziridinemethanolates derived from **203** and **204** react with thionyl chloride to give chlorides **205** and **206**, respectively.[598]



Rearranged chloride **207** is produced from **203** when NaH is used as a base. This reaction proceeds via a ring-opened intermediate.[598] In the absence of nitrogen substituents, bicyclic oxaisothiazolidin-2-ones are formed (Eq. 161).[616]

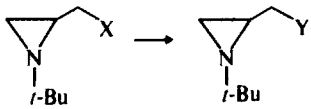


(161)

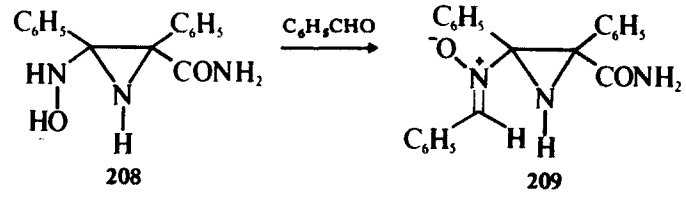
Primary aziridine methanols are also easily converted to their tosylate derivatives.[617] The aziridinemethyl bromides, chlorides, and tosylates undergo nucleophilic displacement in high yield when reacted with good nucleophiles under poor ionizing conditions (Table 70). It should be noted that side reactions (polymerization, etc.) increase and yields diminish as the bulk of the nitrogen substituent shrinks.

Several other unrelated reactions warrant brief mention. Hydroxylamine **208** forms nitrone **209** in 57% yield.[252]

TABLE 70. DISPLACEMENTS OF THE AZIRIDINE METHYL DERIVATIVES

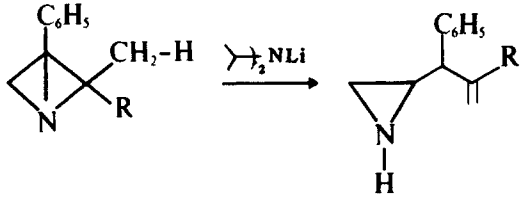


X	Nucleophile	Y	Yield (%)	Ref.
OTs	$NaOC_2H_5$	OC_2H_5	100	617
OTs	Bu_4NBr	Br	100	617
Cl	*t*-BuSNa	*S*-*t*-Bu	73	108
Cl	*t*-BuOK	*O*-*t*-Bu	49	108
Cl	CH_3ONa	OCH_3	88	108
OTs	Bu_4NBr	Br	36	592
OTs	CH_3ONa	OCH_3	65	592



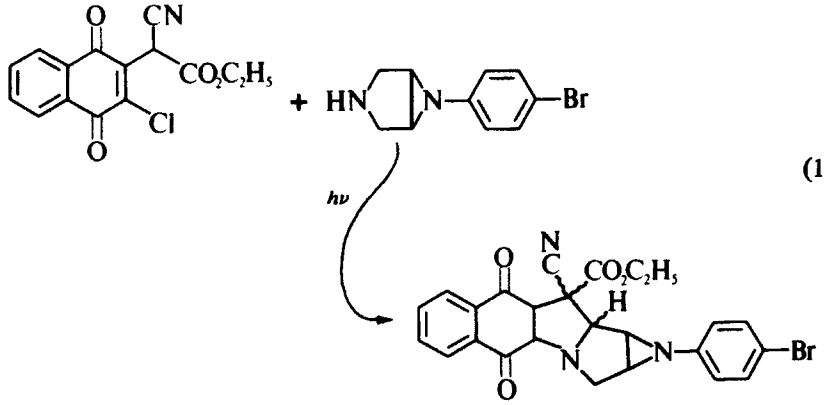
208 209

Bicyclic aziridine **210** is partially cleaved by strong base.[618] A photosynthetic approach to the mitomycin skeleton (Eq. 162) has been described.[619]



210

R = H (48%)
R = CH_3 (52%)



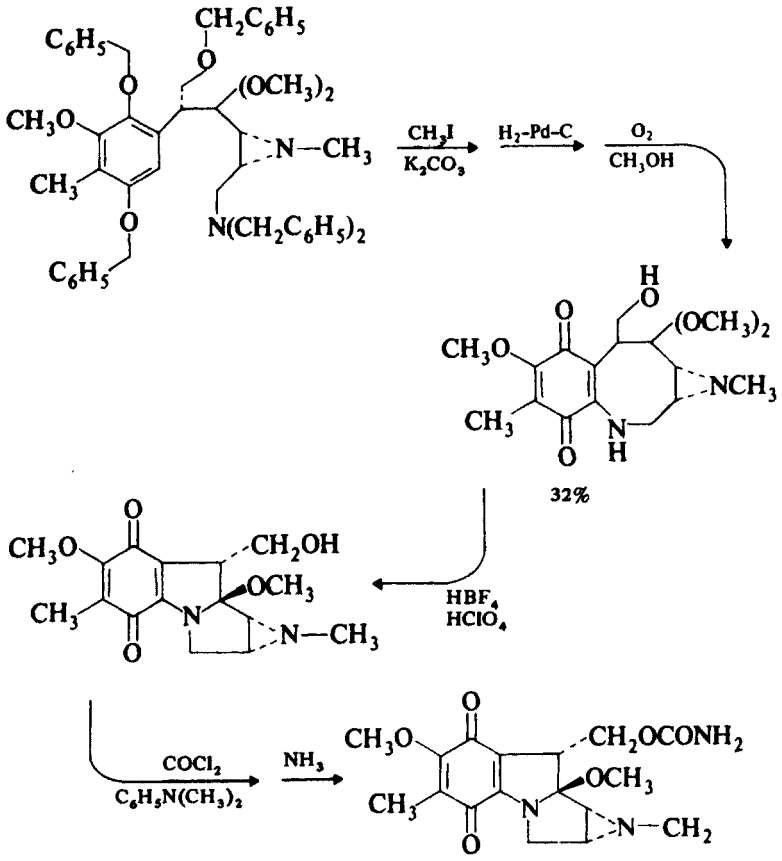
(162)

A final lesson in the stability of the aziridine ring toward ring opening is found in the brilliantly conceived and executed multistep synthesis of a porfiromycin precursor.[143] The latter compound is closely related to the mitomycins, and its synthesis constitutes the first entry to this medicinally important natural product (Scheme 1).

2. Reactions in Which the Aziridine Ring Is Destroyed

Reactions in which the aziridine ring is opened or enlarged comprise some of the most useful examples in aziridine chemistry. Classification of these reactions is,

Scheme 1



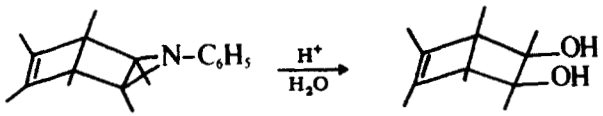
of necessity, rather arbitrary. We first deal with acid-catalyzed and nucleophilic ring openings that do not result in isomerization. Subsequent subsections discuss isomerizations and other ring-destroying reactions.

A. *Lewis Acid Initiated Ring Openings (Without Isomerization)*

The mechanistic details of acid-catalyzed ring openings have been reviewed.[620–622] Bimolecular ring opening can be governed either by steric factors or, where electron-releasing groups are attached to carbon, by positive charge development in the transition state. First-order ring opening has also been observed. Some of the more interesting developments since the earlier reviews are noted below.

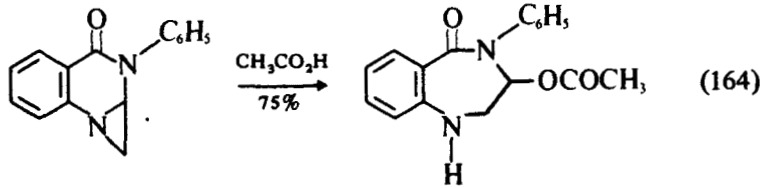
Acid-catalyzed ring opening of rigid steroidal aziridines results in *trans*-diaxial ring opening (toward acetate and azide nucleophiles).[174,623] Comparisons of acid-catalyzed ring opening of epoxides and aziridines led to the conclusion that aziridines were more likely to give *trans* opening.[624] A number of recent papers

have discussed those factors affecting regio- and stereospecificity of aziridine ring openings with different proton-nucleophile combinations.[398,625-628] Although usually only one carbon-nitrogen bond severed, in one unusual structure hydrolysis breaks both bonds (Eq. 163).[383]

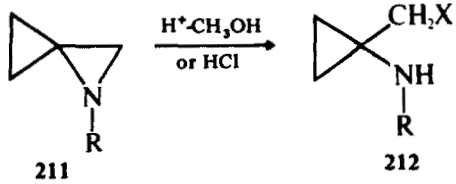


(163)

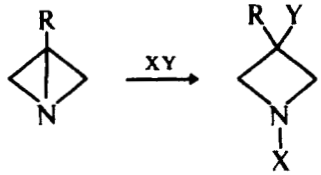
Other acid hydrolyses of note include a study of aziridine ring opening of the mitomycins[85,629-631] and the expansion depicted in Eq. 164.[159] Spiroaziridine **211** yields **212** in good yields.[357,358] Bicyclic aziridines also undergo facile rupture of the central bond (Eq. 165).[632-634]



(164)

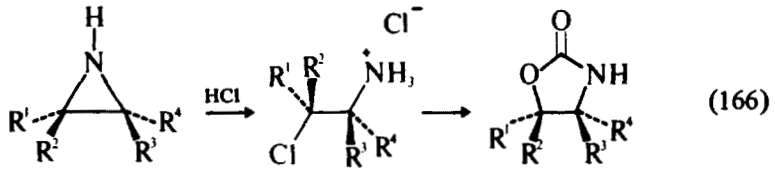


R = C_6H_5, CO_2CH_3
X = Cl, OCH_3

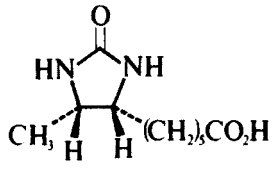


(165)

The potential synthetic utility of such ring openings is illustrated by the stereospecific synthesis of Eq. 166 (635) and (±)-dethiobiotin (**213**).

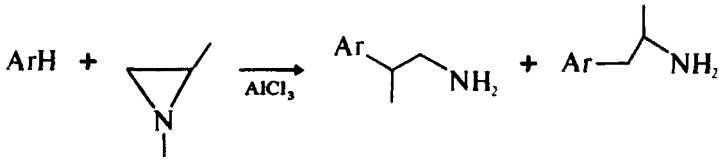


(166)



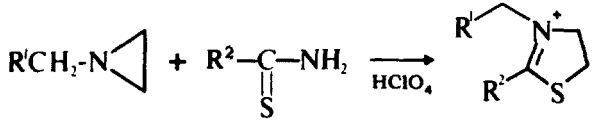
213

The key step in the latter example is the acid-catalyzed ring opening of an aziridine in the presence of azide ion.[194] The aluminum chloride catalyzed alkylation of benzene derivatives has been reported to give regioisomeric mixtures (Eq. 167).[636]

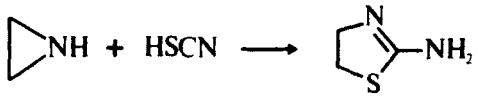


(167)

Certain bifunctional nucleophiles allow cyclization after ring opening. Formation of 2-thiazolium salts (Eq. 168)[637] and the analogous production of 2-amino-2-thiazolines from aziridines and thiocyanic acid (Eq. 169)[638,639] fall in this category.

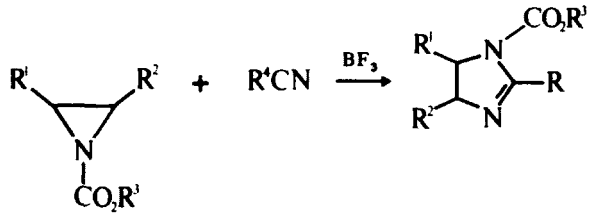


(168)



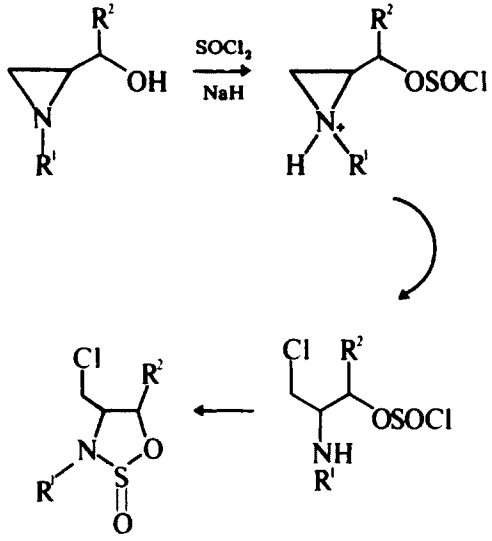
(169)

A similar heterocyclic synthesis utilized nitriles (Eq. 170).[640] The reaction of thionyl chloride with aziridinemethanols also belongs in this class (Eq. 171).

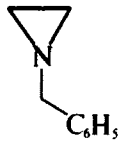


(170)

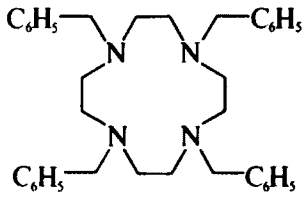
This reaction is noteworthy because two isomers are formed (because of asymmetry at the sulfur) with retained configuration of the two ring carbons.[598] The latter property allows spectral assignment of configuration to R^2.[597,598] In contrast to similar aziridines, *N*-benzylethylenimine (**214**) yields the novel tetramer **215** in 95% yield.[641–643]



(171)

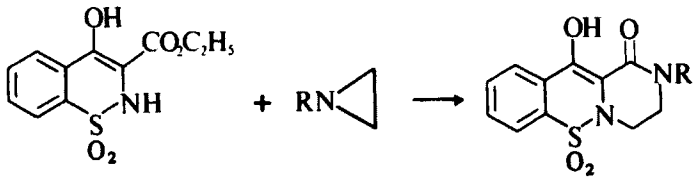


214



215

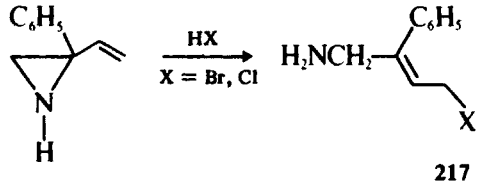
A final example of bifunctional attack on a protonated aziridine is found in Eq. 172.[644]



(172)

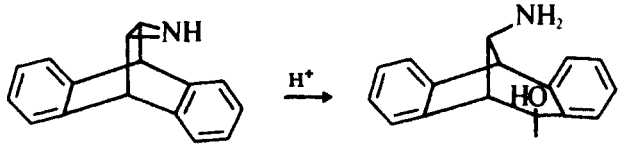
R	Yield (%)
H	60
C_2H_5	41
$(CH_2)_2CN$	95
$(CH_2)C_6H_5$	43
$(CH_2)OH$	

When acid-catalyzed ring opening is not synchronous with nucleophilic attack, the intermediate carbonium ion can undergo rearrangement. Acid-catalyzed ring opening of **216** produces allylic isomer **217**.[618]

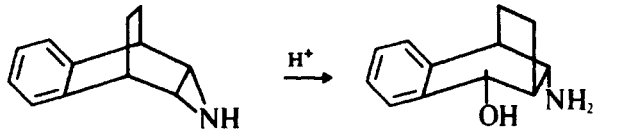


216 217

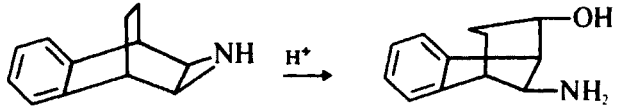
Rearranged products **218** to **220** indicate the novel structures available from these reactions.[645]



218

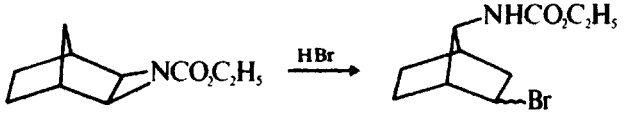


219

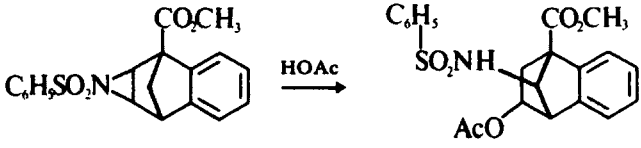


220

Rearrangements of the type illustrated by Eqs. 173[366] and 174[375] have proved to be useful routes to 7-aminonorbornyl systems and diterpene alkaloid precursors, respectively.



(173)

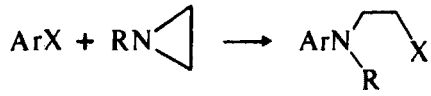


(174)

Although alkylation of aziridines leads, in some selected cases, to stable aziridinium salts, ring opening is more frequently observed. High yields of dimeric structures (Eq. 175) have been obtained under controlled conditions.[646]

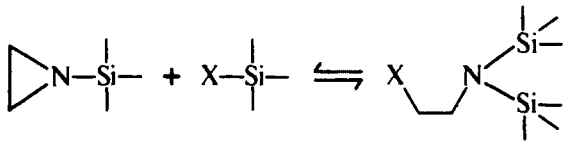
(175)

Aryl halides that bear appropriate activating substituents readily react with simple aziridine structures (Eq. 176).[647]

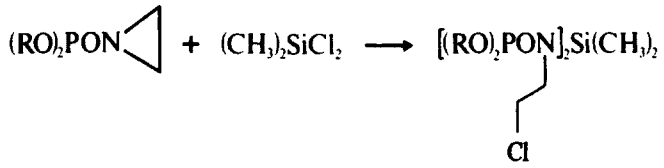


(176)

Silyl halides also have opened aziridine rings (Eqs. 177 and 178).[648,649]

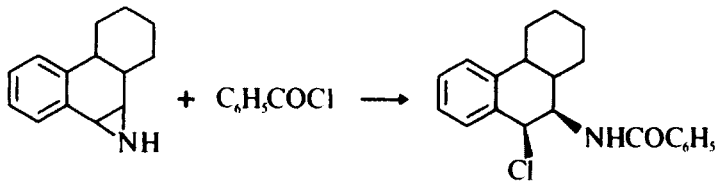


(177)

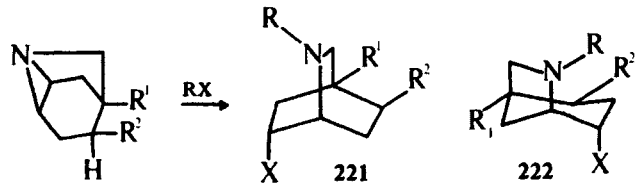


(178)

Ring openings with acid halides are general and often useful reactions.[650] Several *cis* ring openings have been noted (Eq. 179).[133,180] The most interesting recent reaction of this type is illustrated in Eq. 180. Under controlled conditions, the isoquinuclidine structure **221** predominated over the [3,2,1]azabicyclopentane system (**222**) by approximately 3 : 1.[442]



(179)



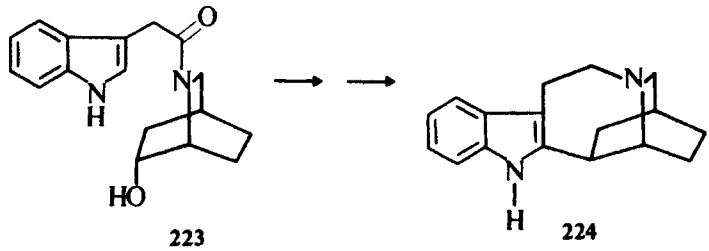
(180)

$R^1 = R^2 = H$
$R = CH_3; R^2 = H$
$R^1 = R^2 = (CH_2)_4$

$R = C_6H_5CO$
$R = p\text{-}CH_3C_6H_4SO_2$
$R = RCO_2$

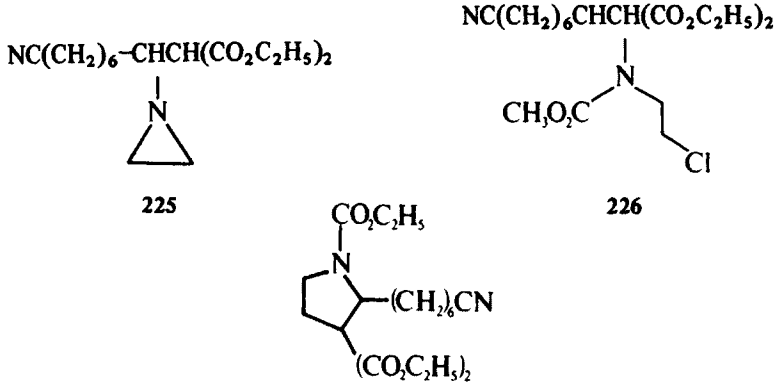
$X = Cl$
$X = Cl$
$X = O_2CR$

Use of indoleacetic anhydride allowed synthesis of **223** and eventually desethylibogamine (**224**). Extension of this strategy led to the synthesis of ibogamine,[445] coronaridine, and velbanamine.[651]



223 224

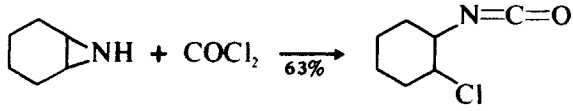
In another interesting application aziridine **225** was opened with ethyl chloroformate to give **226**. The latter was ultimately converted to a 9-azaprostaglandin analog **227**.[557]



225 226

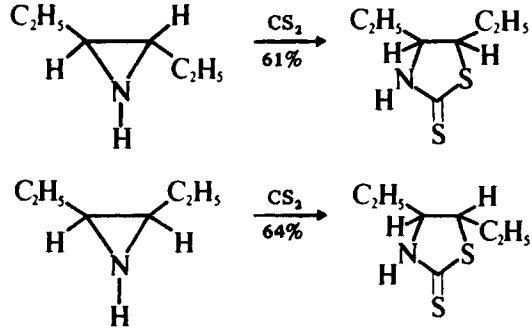
227

Thionyl chloride,[649,652] thiophosgene,[652] and phosgene[652,653] open the aziridine ring. The latter reaction allows synthesis of chloroisocyanates (Eq. 181).



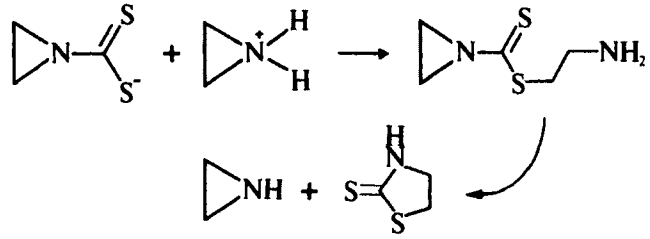
(181)

Carbon disulfide expands the aziridine ring to thiazolidinethiones. The stereochemical consequence of this reaction (Eq. 182) led to the mechanism



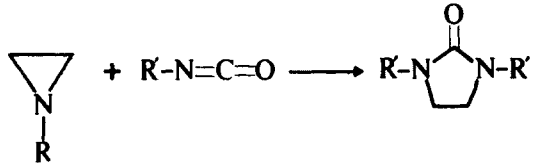
(182)

proposed in Eq. 183.[654] This expansion also appears to take place with *N*-substituted aziridines.[655]



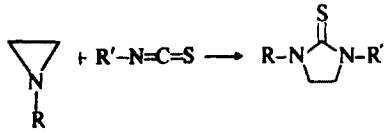
(183)

Isocyanates (Eq. 184), isothiocyanates, trichloroacetaldehyde, and COS effect similar expansions as summarized in Tables 71–73.



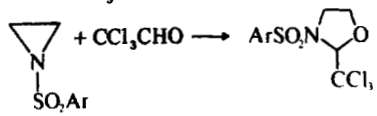
(184)

TABLE 71. EXPANSION OF AZIRIDINES WITH ISOCYANATES



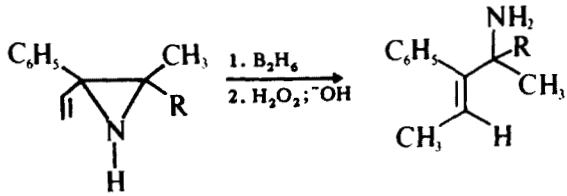
R	R′	X	Yield (%)	Ref.
C_6H_5CO	C_6H_5	O	46	656
p-$NO_2C_6H_4$	C_6H_5	O	57	656
$OCOC_2H_5$	C_6H_{11}	O	60	656
$OCOC_2H_5$	C_6H_5	O	30	656
$C_6H_5CH_2CH_2$	C_6H_5	O	83	656
C_6H_5CO	C_6H_5CO	O	46	656
p-$NO_2C_6H_4$	C_6H_5CO	O	36	656
$C_6H_5CH_2CH_2$	C_6H_5CO	O	59	656
$C_6H_5CH_2CH_2$	$C_6H_5SO_2$	O	92	656
C_6H_5CO	*p*-$CH_3C_6H_4SO_2$	O	85	656
$C_6H_{11}CO$	*p*-$CH_3C_6H_4SO_2$	O	75	656
C_6H_5CO	*p*-$ClC_6H_4SO_2$	O	79	656
p-$CH_3C_6H_4SO_2$	C_6H_5	O	93	657
p-$ClC_6H_4SO_2$	C_6H_5	O	92	657
p-$CH_3OCONHC_6H_4SO_2$	C_6H_5	O	95	657
p-$CH_3C_6H_4SO_2$	C_6H_5	S	96	657
p-$CH_3OCONHC_6H_4SO_2$	C_6H_5	S	99	657
p-$CH_3OCONHC_6H_4SO_2$	$CH_2CH{=}CH_2$	S	99	657
p-$CH_3OCONHC_6H_4SO_2$	$CH_2C(CH_3){=}CH_2$	S	68	657
p-$CH_3C_6H_4SO_2$	CH_3	S	76	657
p-$ClC_6H_4SO_2$	C_6H_5	S	99	657
p-$ClC_6H_4SO_2$	$CH_2CH{=}CH_2$	S	76	657
p-$ClC_6H_4SO_2$	$CH_2C(CH_3){=}CH_2$	S	72	657
p-$CH_3C_6H_4SO_2$	$CH_2C(CH_3){=}CH_2$	S	66	657

TABLE 72. EXPANSION OF AZIRIDINES WITH CCl_3CHO[657]



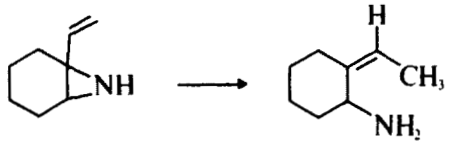
Ar	Yield (%)
p-$CH_3C_6H_4$	99
p-ClC_6H_4	75
p-$CH_3OCONHC_6H_4$	66

Diborane converts vinylaziridines in a stereospecific manner to primary allylic amines (Eqs. 185).



(185a)

$R = CH_3$ (75%)
$R = H$ (79%)

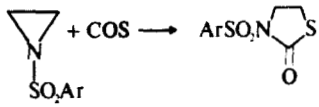


(185b)

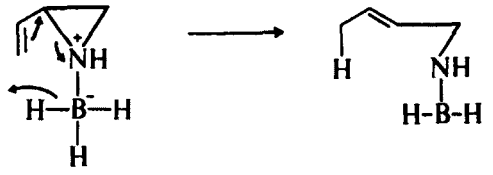
The key step in this reaction is thought to proceed as shown in Eq. 186.[658a] Another interesting ring opening of vinylaziridines is shown in Eq. 187. Depending on the substituent X, ring opened products or tetrahydroazepines result.[658b]

Cyclooctene aziridines are opened by mercuric salts (Eq. 188). Intermediates **228** and **229** have been proposed.[659]

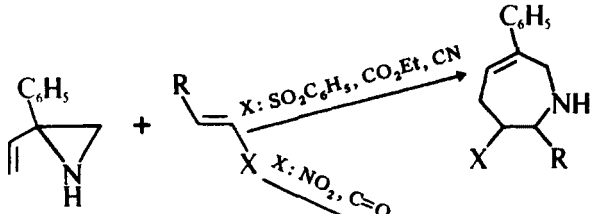
TABLE 73. EXPANSION OF AZIRIDINES WITH COS[657]



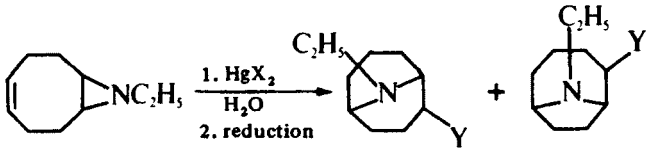
Ar	Yield (%)
p-$CH_3C_6H_4$	93
p-$CH_3OCONHC_6H_4$	92
p-ClC_6H_4	95



(186)



(187)

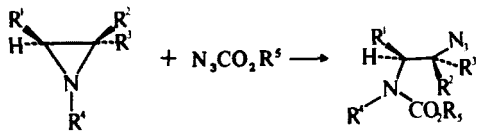


(188)

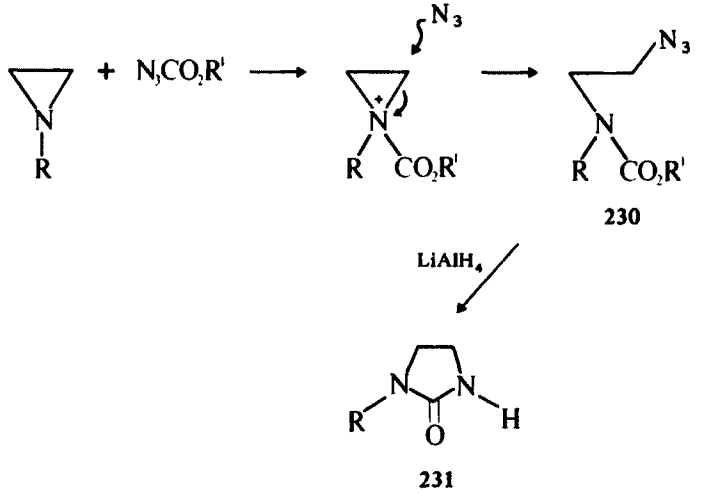
228 229

Another intriguing expansion results from the reaction of azidoformates with aziridines (Eq. 189). Yields in this reaction are indicated in Table 74. The reaction is stereospecific. The potential synthetic utility of this reaction stems from the fact that $LiAlH_4$ reduction of **230** yields **231**.[660]

TABLE 74. REACTIONS OF AZIRIDINES WITH AZIDOFORMATES[660]



R^1	R^2	R^3	R^4	R^5	Yield (%)
H	H	H	$CH_2CH_2C_6H_5$	C_2H_5	100
H	H	H	$CH_2C_6H_5$	CH_3	71
CH_3	H	CH_3	$CH_2C_6H_5$	C_2H_5	75
CH_3	CH_3	H	$CH_2C_6H_5$	C_2H_5	92

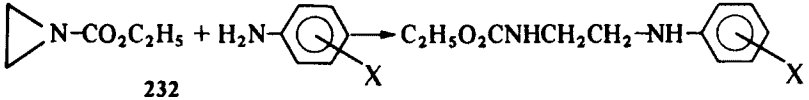


(189)

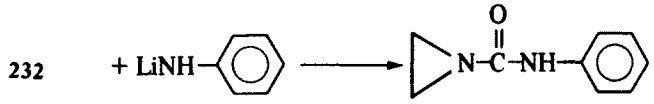
B. *Nucleophilic Ring Opening (Without Resultant Isomerization)*

Most of the aziridines that undergo direct nucleophilic ring opening bear strong electron-accepting groups (RCO, RSO_2, CN, Ar, etc.) on nitrogen. The aziridines that do not bear such substituents require very strong nucleophiles or vigorous reaction conditions for ring opening. It is possible that some of the latter examples actually involve general acid catalysis. Actual proof of bimolecular ring opening has been based, in one instance, on Hammett σ-ρ correlations and kinetic evidence.[661]

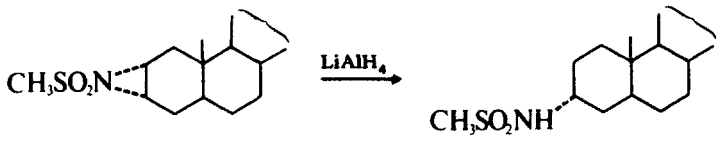
Competition occurs between attack on the ring and carbonyl carbon of **232**, and thus presents a complication in the synthetic utilization of such reactions. It has been shown that the poorer nucleophiles are more likely to open the ring (Eq. 190).[566] Trityl lithium behaves like aniline, while benzyl or t-butyl lithium acts like the lithium anilide.[566]



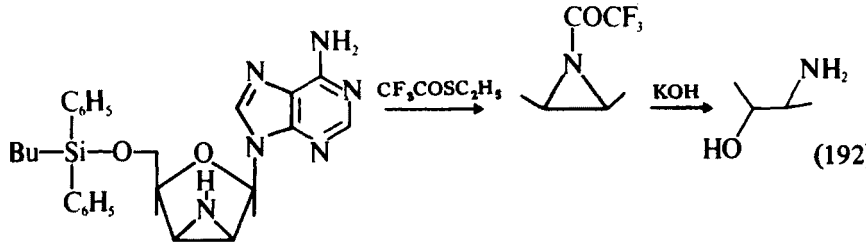
232 (190)



Various nucleophiles open *N*-cyanosteroidal aziridines.[662] $LiAlH_4$ has been shown to cleave an activated steroidal aziridine (Eq. 191).[663] The *trans* ring opening of **233** is best accomplished via the indirect procedure of Eq. 192.[664]



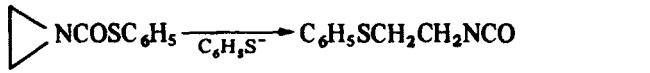
(191)



(192)

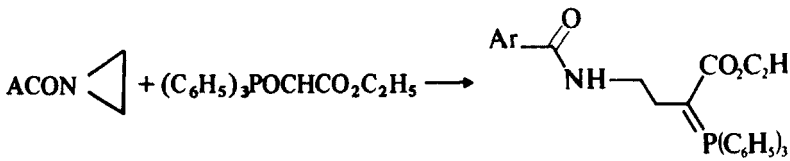
233

Activated aziridines have been opened by thiosulfate[665] and thiophenoxide.[666] In the latter case elimination results in isocyanate formation (Eq. 193).



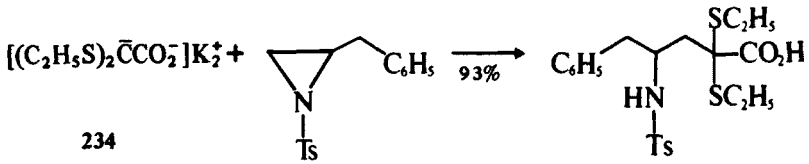
(193)

A number of nitrogen nucleophiles such as NaN_3[667] and aniline[561] open aziridines. Some of the most interesting and potentially useful reactions of this type involve carbon nucleophiles. Certain ylides attack activated aziridines as indicated in Eq. 194.[668]



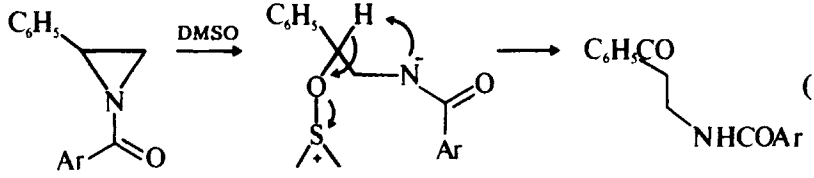
(194)

Attacks by dianion **234**[669] and by various other stabilized anions[670–672] give good yields of opened products.



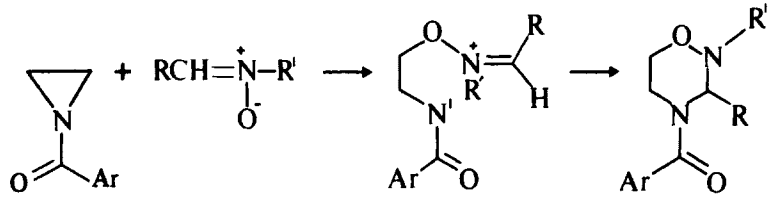
234

Nucleophilic ring opening of aziridines by dimethylsulfoxide[405,673,674] results in the oxidation of one ring carbon (Eq. 195).[673]



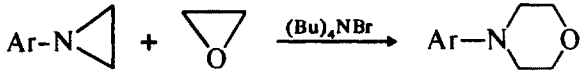
(195)

Synthesis of larger heterocycles can result when bifunctional nucleophiles open the aziridine ring and subsequently recyclize. The reaction of nitrones with aziridines (Eq. 196) as summarized in Table 75 falls into this category.

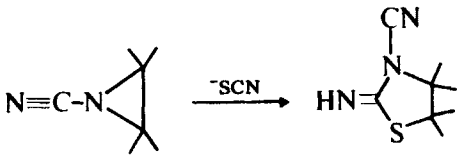


(196)

Also noteworthy is the high yield reaction of *N*-arylaziridines with ethylene oxide (Eq. 197).[676] An *N*-cyano steroidal aziridine has been converted to **235** by ^{-}SCN.[662]

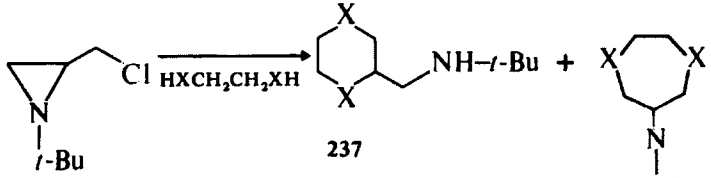


(197)



235

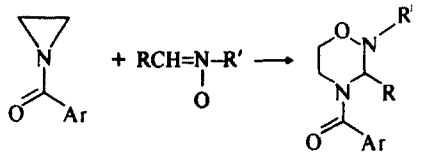
Aziridine **236** is converted to mixtures of **237** ("abnormal") and **238** ("normal") by different difunctional nucleophiles.[677]



236 **237** **238**

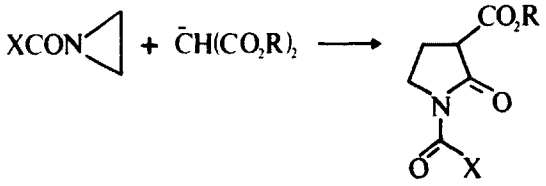
X = S; CH_3N

TABLE 75. REACTION OF NITRONES WITH AZIRIDINES[675]



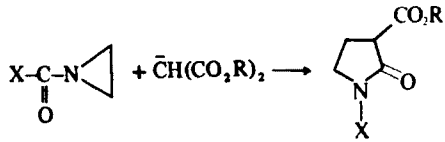
R	R¹	Ar	Yield (%)
C_6H_5	C_6H_5	p-$NO_2C_6H_4$	51
C_6H_5	p-$CH_3C_6H_4$	p-$NO_2C_6H_4$	88
C_6H_5	p-$CH_3C_6H_4$	3,5-$(NO_2)_2C_6H_3$	99
C_6H_5	CH_3	3,5-$(NO_2)_2C_6H_3$	73
CH_3	C_6H_{11}	3,5-$(NO_2)_2C_6H_3$	27
C_6H_5	$(CH_3)_3C$	p-$NO_2C_6H_4$	44
C_6H_5	p-$CH_3C_6H_4$	3,4-$(Cl)_2C_6H_5$	78
p-ClC_6H_4	p-$CH_3C_6H_4$	3,5-$(NO_2)_2C_6H_3$	84
C_6H_5	p-$C_2H_5C_6H_4$	3,5-$(NO_2)_2C_6H_3$	66
C_6H_5	CH_3	p-$NO_2C_6H_4$	66

The most useful reactions combine carbanion nucleophiles with activated aziridines. The ring expansion of Eq. 198 typifies the heterocyclic synthesis that is possible (Table 76). The conversion is quite general, since many analogous transformations have been observed in which different carbanion-stabilizing substituents were employed.[679-682]



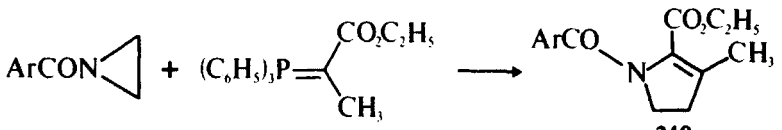
(198)

TABLE 76. RING OPENING OF AZIRIDINES BY MALONATE SALTS[678]



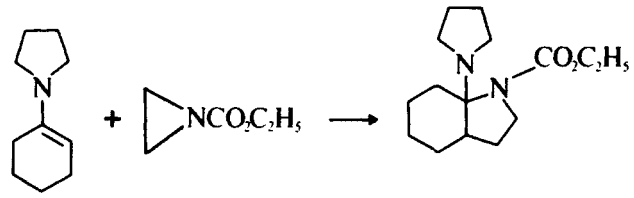
X	R	Yield (%)
OC_2H_5	C_2H_5	55
OC_2H_5	t-Bu	18
C_6H_5NH	CH_3	35
C_6H_5NH	C_2H_5	58
C_6H_5NH	t-Bu	76
p-ClC_6H_4NH	C_2H_5	49
p-ClC_6H_4NH	t-Bu	47
$(C_6H_5)_2N$	C_2H_5	24
$(C_6H_5)_2N$	t-Bu	18

Ylid **239** yields **240** in several steps.[668]



239 **240**

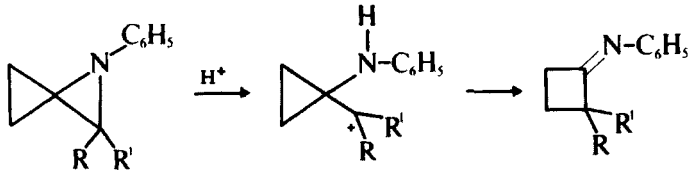
An enamine has also been utilized as the nucleophile (Eq. 199).[683]



(199)

C. *Acid-Catalyzed Rearrangement of Aziridines*

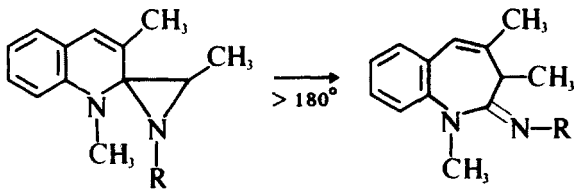
In contrast to cases of R = R′ = H (Section IV, 2, A), **241** undergoes ring expansion when R = R′ = C_6H_5 or R = H, R′ = C_6H_5 (Eq. 200).[358]



(200)

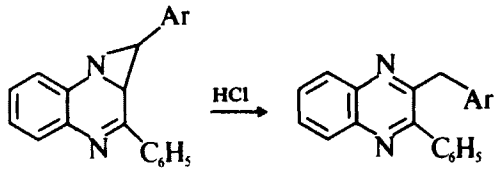
241

A similar ring expansion is probably responsible for the isomerization of spiroaziridine **242**.[408] Proton migration (Eq. 201)[230] and elimination (Eq. 202)[435,436] are other typical fates of ring-opened cations.

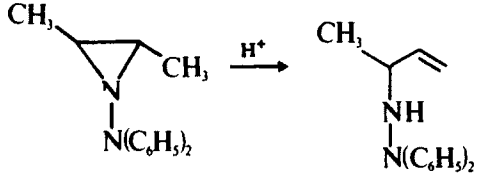


242

R = CO_2CH_3 (90%)
R = C_6H_5 (98%)
R = C_6H_5CO (91%)

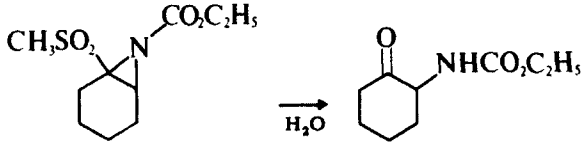


(201)

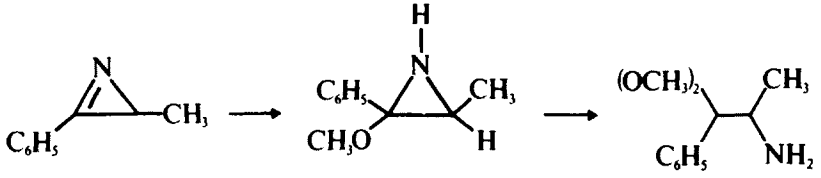


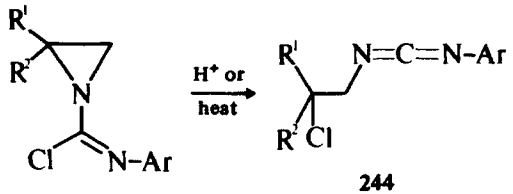
(202)

Although the mechanistic details are unspecified, ring openings of the type illustrated in Eq. 203[248, 399] are probably also analogous to Eq. 202. The acid-catalyzed isomerization of **243** to **244** yields a product with potential synthetic utility.[571]



(203)

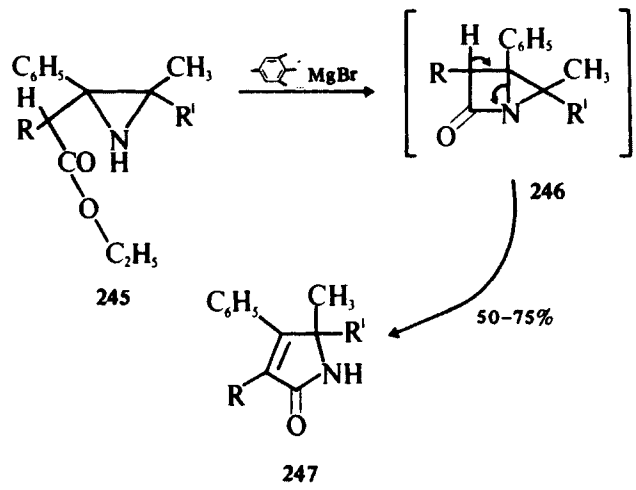




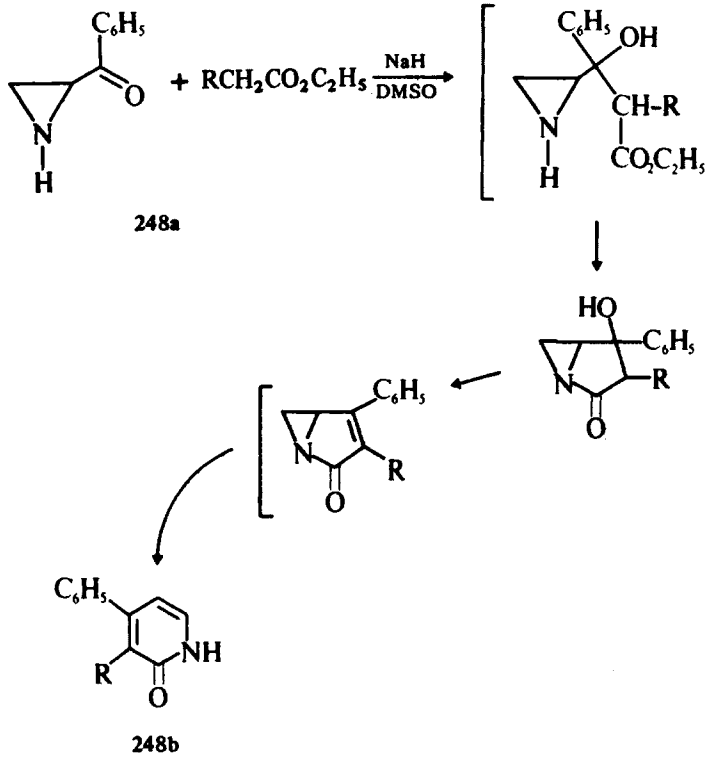
243 **244**

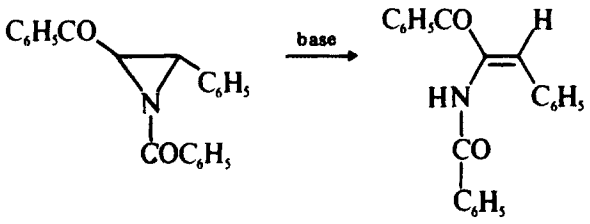
D. *Base-Catalyzed Rearrangements and Other Reactions of Aziridines*

The unusual rearrangement of **245** to **247** is believed to go via ring opening of intermediate **246**.[265]

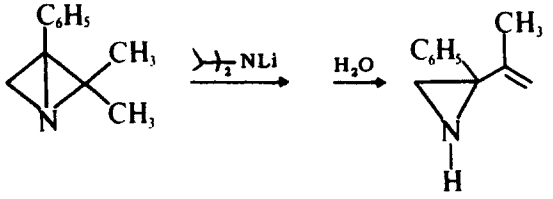


A similar intermediate was postulated in the conversion of **248a** to **248b**.[684] In spite of the potential acidity of aziridine ring hydrogens, there are only a few reports of reactions initiated by deprotonation. Equations 204[685] and 205[618] are among the more interesting examples.



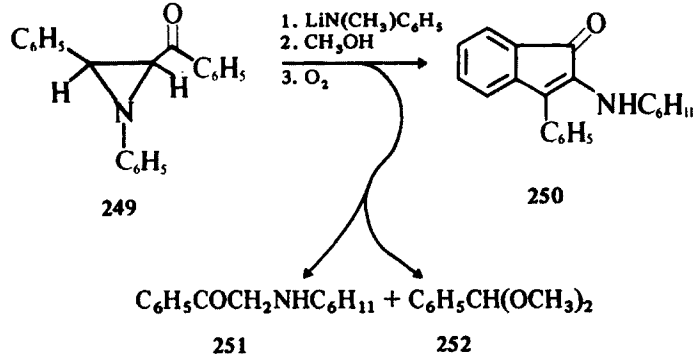


(204)



(205)

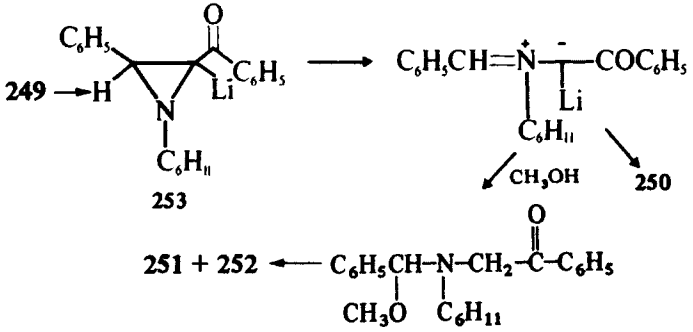
One of the most unusual base-catalyzed reactions is the oxidative rearrangement of Eq. 206.[515,686,687] The mechanism shown in Eq. 207 has been proposed to account for the experimental observations. It is known that **249** is thermally stable toward azomethine ylid formation under the reaction conditions. It is not clear why **253** would be less stable.



249 **250**

251 (52%) **252**

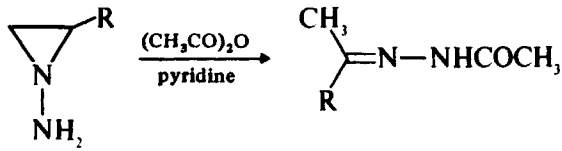
(206)



(207)

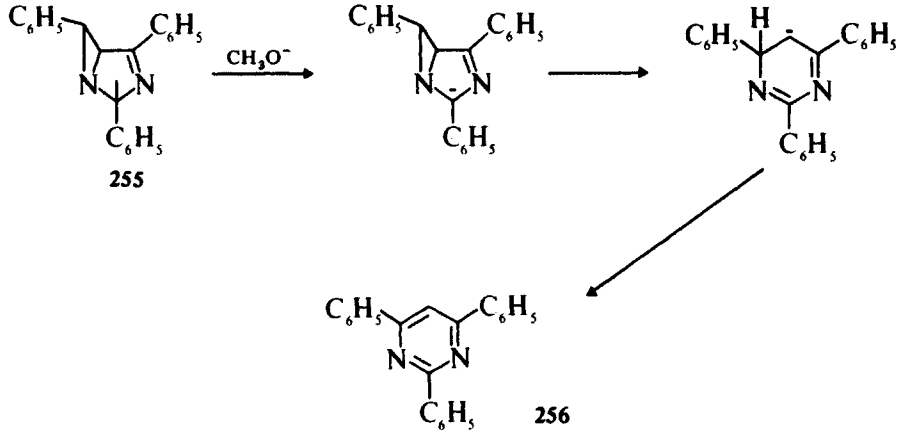
253

Ring-opening isomerization of compounds of general structure **254** upon acetylation is probably base catalyzed.[120,121]



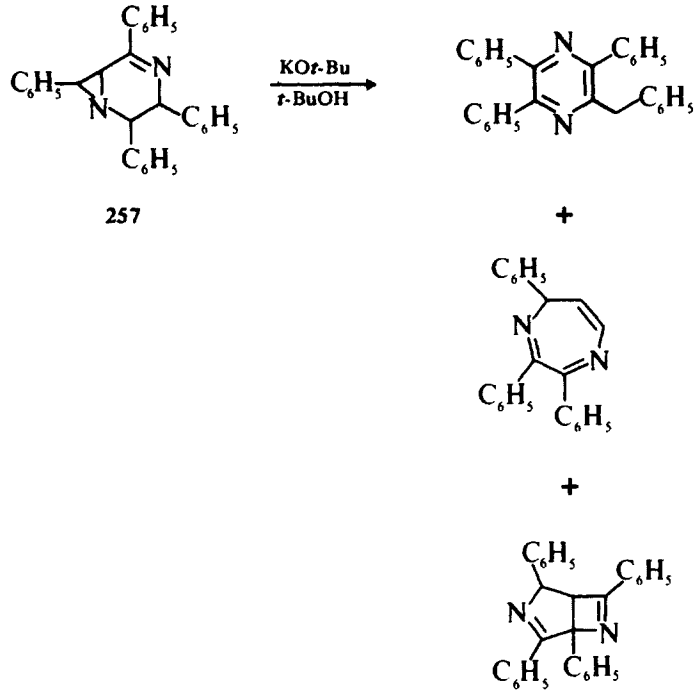
254

Bicyclic aziridine **255** is oxidatively ring opened to **256**.[607]



255 256

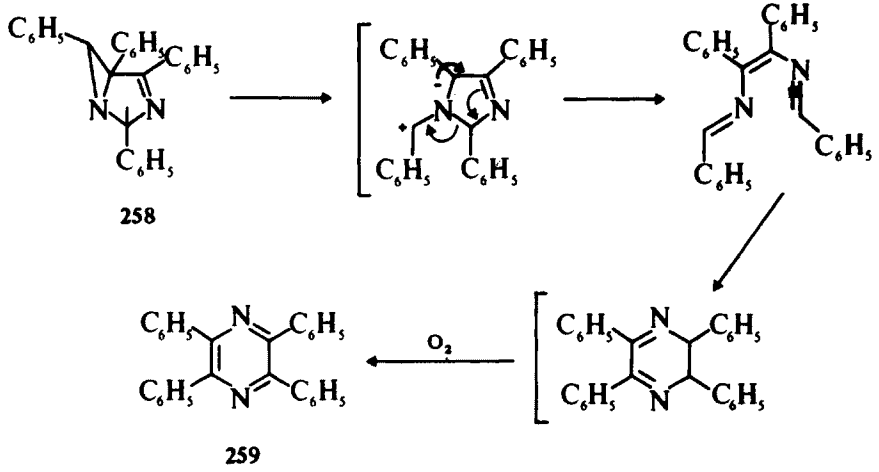
Analog **257** yields a variety of products derived from initial deprotonation.[231]



257

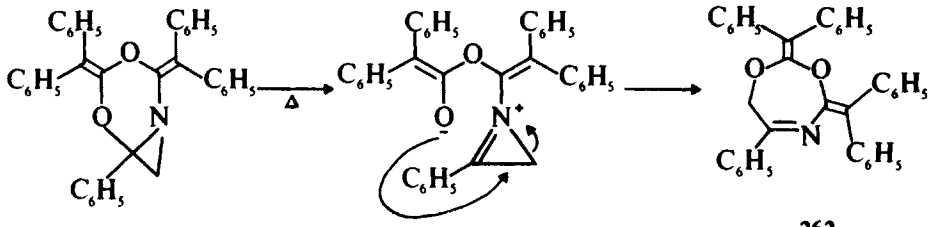
E. *Thermal Aziridine Decomposition*

A number of thermal aziridine decompositions have been reported that do not appear to be concerted. Pyrolysis of **258** gives **259**. This reaction is in contrast to the base-catalyzed transformation **255** → **256**.



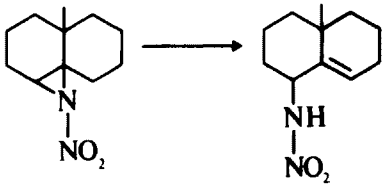
258 **259**

Bicyclic aziridine **260** is thermally converted to **262**. Intermediate **261** has been proposed.[688]

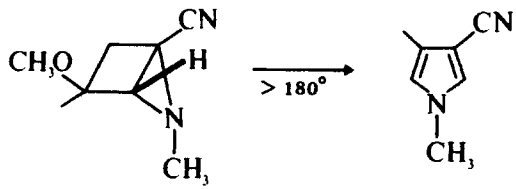


260 **261** **262**

N-Nitroaziridine **263** is converted thermally to **264**.[689] No explanation exists for the unusual thermolysis of Eq. 208,[503] which probably proceeds via methanol elimination to a Dewar-pyrrole.



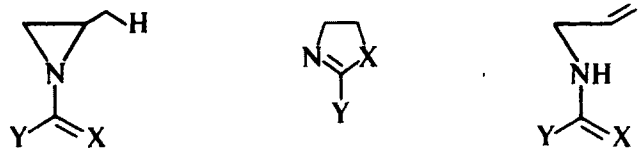
263 **264**



(208)

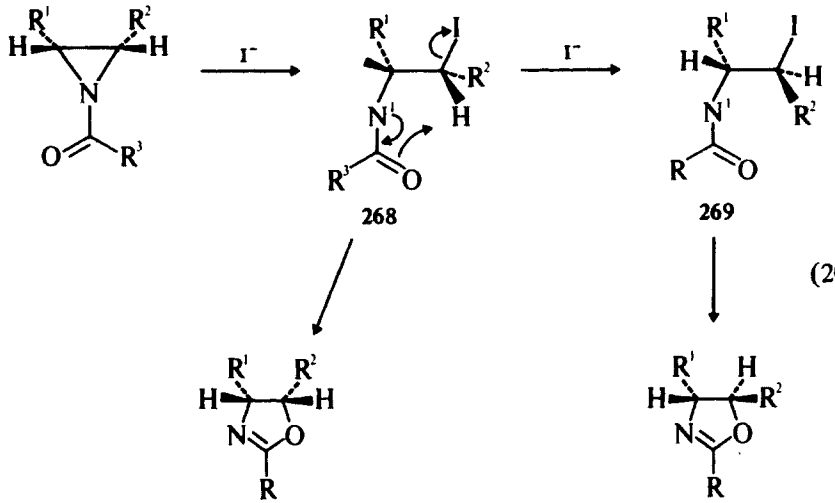
F. *Isomerizations of* $\triangleright N\text{–}X\text{=}Y$ *Derivatives*

Aziridines bearing unsaturation on nitrogen rearrange under various conditions. These rearrangements have been alluded to in two reviews.[690,691] A particularly useful chapter on aziridine rearrangements, published in 1971, contains excellent additional coverage.[7] Some of the most important isomerizations include the conversion of partial structure **265** to **266** and/or **267**. The former occurs under acidic or nucleophilic conditions as well as thermally. Formation of **267** is usually encountered under thermal conditions.



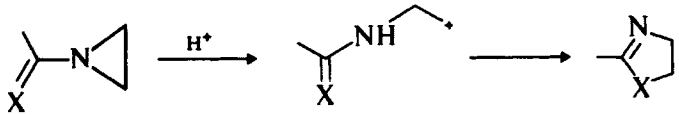
265 **266** **267**

Iodide is often used as a nucleophilic catalyst for the **265** → **266** isomerization.[692] The initial displacement (Eq. 209) yields **268**, which can cyclize to a 2-oxazoline. Under certain conditions and substituent patterns, a second displacement by I^- yields **269**, which can then close to the thermodynamically favored isomer.[693,694]

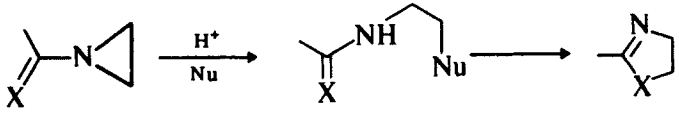


(209)

Acid-catalyzed isomerization can lead to a variety of stereochemical results. S_N1 (Eq. 210), S_N2 (Eq. 211) as well as S_Ni processes have been considered.[695] The S_N1 process would lead to stereochemical scrambling, whereas the double inversion implicit in the S_N2 pathway would give retention. The S_Ni route would be equivalent to a tight ion-pair mechanism and would also result in retention.

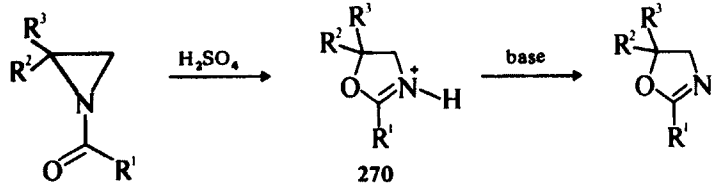


(210)



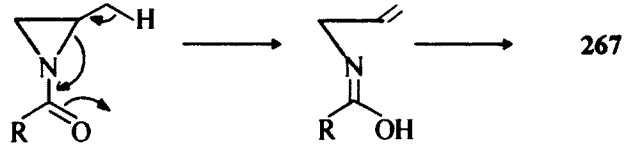
(211)

Orientation and substituent effects on these different processes have been studied and found to be consistent with the proposed mechanisms.[696,697] Isomerizations in sulfuric acid have been examined,[698] and intermediate **270** has been detected by nmr spectroscopy.[699]



270

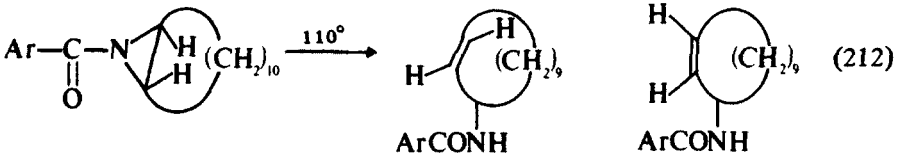
The thermolysis of 1-acyl-2-alkylaziridines generally results in the formation of *N*-allylamides (**267**). Considerable evidence has been accumulated in support of a concerted six-center transition state (**271**). First-order kinetics and a high entropy of activation are consistent with **271**.[700] The lack of a solvent effect along with a Hammett equation indicative of negative charge accumulation on nitrogen also support the postulate of **271**.[701]



267

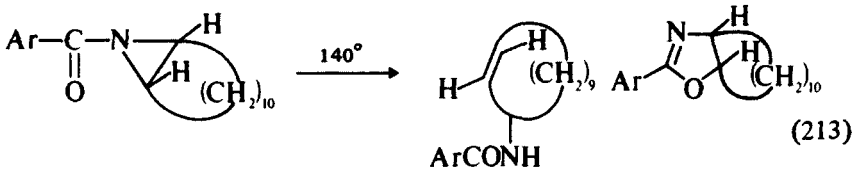
271

Particularly revealing are the pyrolyses of Eqs. 212 and 213.[702] The difference is explainable only in terms of conformational accessibility of the respective side chain hydrogens.



(212)

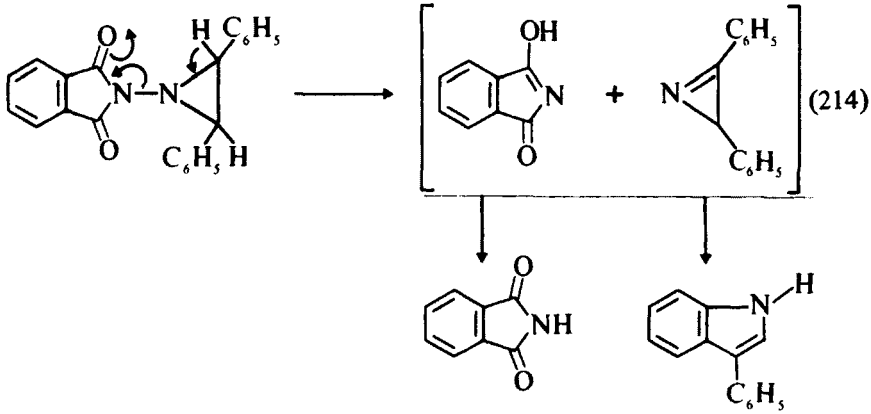
2:1



(213)

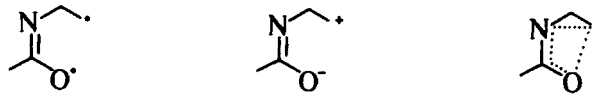
7:1

A different type of six-center transition state is depicted in Eq. 214.[430]



(214)

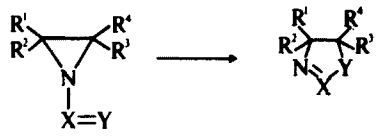
Other thermolyses of **265** in which the side chain is absent provide a stereospecific route to 2-oxazolines. Diradical **272**, dipole **273**, and concerted transition states (**274**) have been proposed.



272 **273** **274**

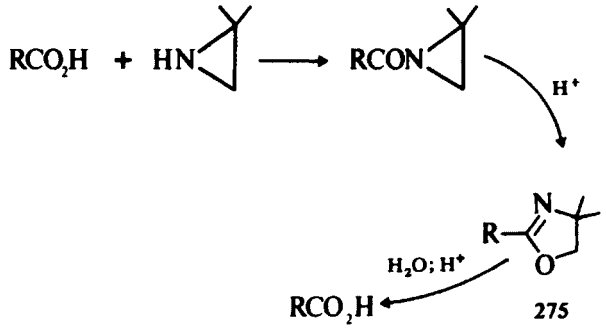
Although some abbreviated substituent effect observations are indicative of a transition state with negative charge on nitrogen,[692] more complete mechanistic studies are needed. It should be noted that acid and nucleophilic catalysis must be excluded in such studies and that **274** is formally disallowed.[703, 704] Table 77 summarizes recent thermal, acidic, and nucleophilic isomerization of the type **265** → **266**.

TABLE 77. ISOMERIZATION OF AZIRIDINES TO FIVE-MEMBERED RINGS



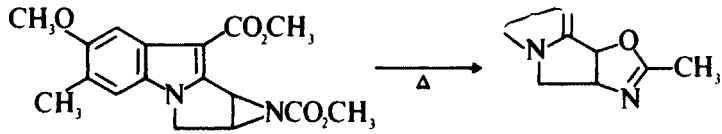
R^1	R^2	R^3	R^4	X	Y	Agent	Yield (%)	Ref.
H	H	H	H	CH_3C	O	H^+	61	698
CH_3	H	H	H	CH_3C	O	H^+	53	698
CH_3	CH_3	H	H	CH_3C	O	H^+	66	698
H	H	H	H	C_6H_5C	O	H^+	68	698
CH_3	H	H	H	C_6H_5C	O	H^+	71	698
H	H	H	$CH=CH_2$	p-$NO_2C_6H_4$	O	I^-	–	705
H	H	H	$CH=CH_2$	p-$NO_2C_6H_4$	O	^-SCN	97	706
H	CH_2–O–CH_2		H	C_6H_5C	O	I^-	79	102
H	CH_2–O–CH_2		H	C_6H_5C	O	Heat	33	102
CH_3	H	CH_3	H	p-$NO_2C_6H_4C$	O	I^-	96	4
CH_3	H	H	CH_3	p-$NO_2C_6H_4C$	O	I^-	96	4
C_6H_5	H	C_6H_5	H	p-$NO_2C_6H_4C$	O	I^-	85	4
CH_3	CH_3	OCH_3	OCH_3	OC_2H_5	O	Heat	–	350
C_6H_5CO	H	C_6H_5	H	C_6H_5C	O	I^-	97	685
CH_3	CH_3	CH_3	CH_3	p-ClC_6H_4C	O	H^+	11	707
CH_3	CH_3	CH_3	CH_3	2,4-$Cl_2C_6H_4$	O	H^+	11	707
CH_3	CH_3	CH_3	CH_3	p-$CH_3OC_6H_4$	O	H^+	11	707
CH_3	CH_3	H	H	$CH_3COCH_2CH_2O$	O	H^+	80	708
CH_3	CH_3	H	H	$CH_3O_2C(CH_2)_4C$	O	H^+	80	708
CH_3	CH_3	H	H	p-NNC_6H_4C	O	H^+	75	708
CH_3	CH_3	H	H	3-Pyridyl-C	O	H^+	50	708
H	$(CH_2)_3$		H	p-$NO_2C_6H_4C$	O	I^-	100	709
H	$(CH_2)_3$		H	p-$NO_2C_6H_4C$	O	Heat	34	709
H	H	H	H		O	I^-	79	710
C_6H_5	H	H	H	p-$NO_2C_6H_4C$	O	I^-	98	711
C_6H_5	H	H	C_6H_5	p-$NO_2C_6H_4C$	O	Heat	80	711
C_6H_5	H	C_6H_5	H	p-$NO_2C_6H_4C$	O	Heat	70	711
H	H	H	H	C_2H_5C	S	Heat	69	712
H	H	H	H	$C_6H_5CH_2C$	S	Heat	68	712
H	H	H	H	α-Naphthyl	S	Heat	69	712
CH_3	H	H	H	CH_3C	S	Heat	65	712
CH_3	H	H	H	$C_6H_5CH_2C$	S	Heat	60	712
CH_3	H	H	H	C_6H_5C	S	Heat	70	712
H	H	H	H	ArC	S	Heat	–	713
H	H	H	H	p-ClC_6H_4	S	H^+	70	714
H	H	H	H	p-$CH_3C_6H_4$	S	H^+	92	714
H	H	H	H	p-$CH_3OC_6H_4$	S	H^+	91	714
H	H	H	H	$(CH_3)_2CHC$	NC_6H_5	H^+	–	558

One of the most useful applications of these rearrangements utilizes the sequence of Eq. 215. The utility of the sequence stems from the inertness of **275** toward such reagents as R'MgX and $LiAlH_4$.[715] Since **275** is readily hydrolyzed by aqueous acid, the entire sequence represents a convenient protecting group for carboxylic acids.



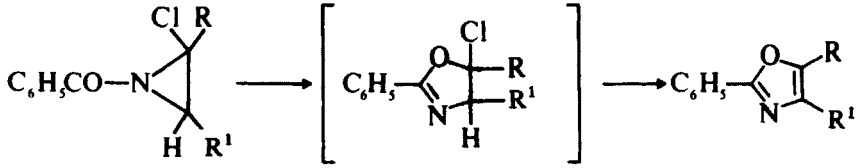
(215)

The rearrangements described in this section have been applied to a number of more complex systems. For example, thermolysis of mitomycin analog **276** yields **277**.[157]



276 **277**

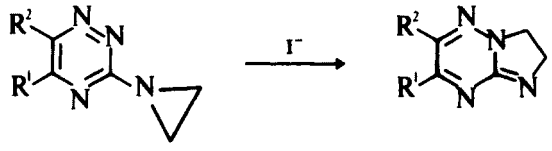
In another related example, *N*-acylhaloaziridine **278** yielded oxazole **280** via **279**.[145,259]



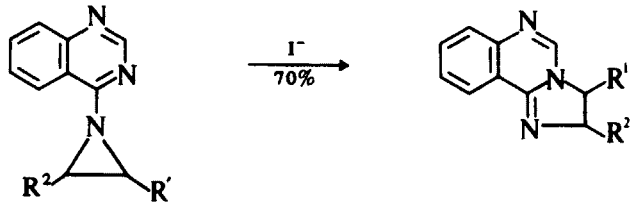
278 **279** **280**

R = C_6H_5; R¹ = CH_3[259]
R¹ = C_6H_5; R = Cl[145]

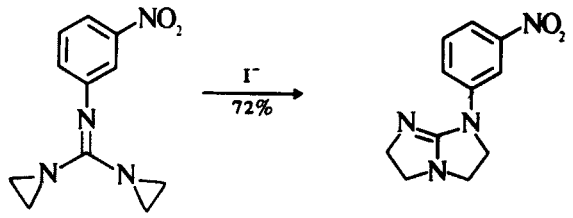
These rearrangements have been also especially useful in the synthesis of complex heterocycles. Typical examples are given by Eqs. 216,[716] 217,[717,718] 218,[572] 219,[532] and 220.[573] Two related rearrangements that yield six-membered rings are found in Eqs. 221[719] and 222.[568,569]



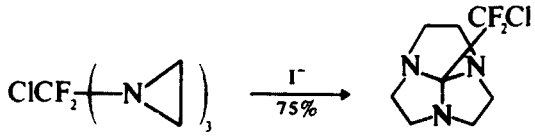
(216)



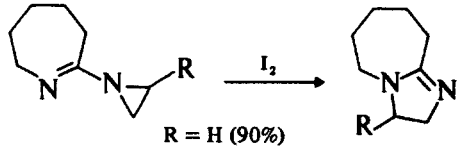
(217)



(218)

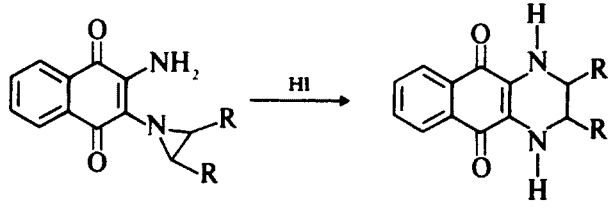


(219)

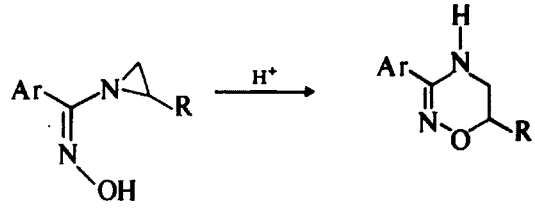


R = H (90%)
R = CH_3 (89%)

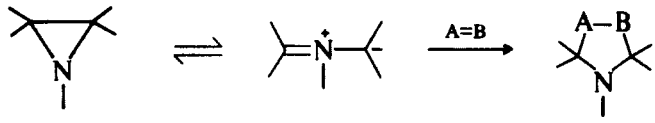
(220)



(221)



(222)



(223)

G. *Azomethine Ylids from Aziridines*

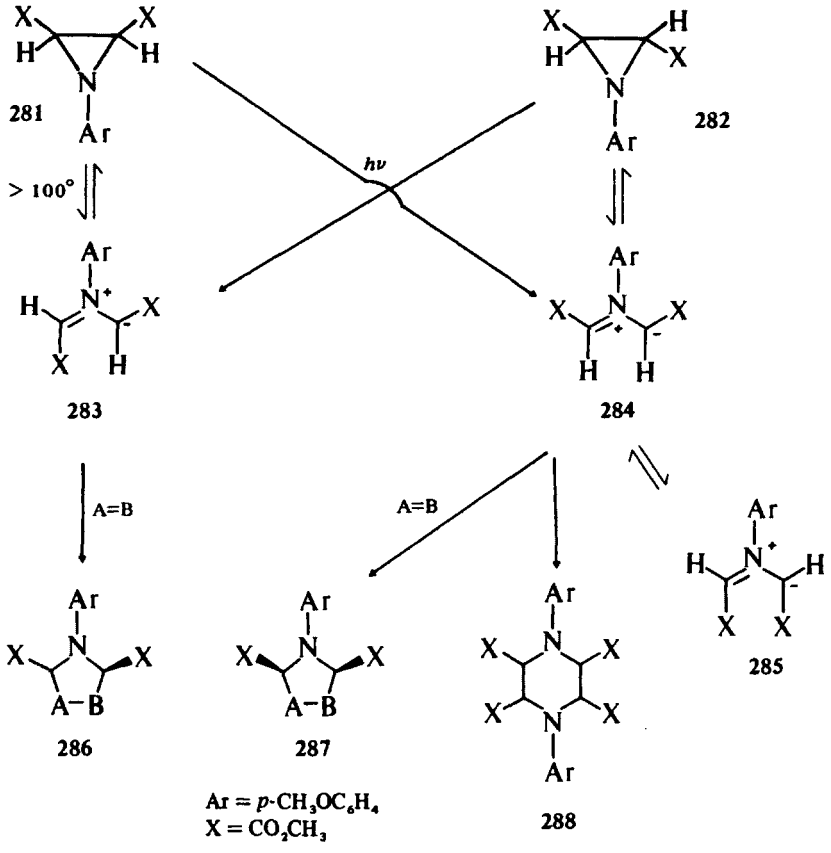
a. INTRODUCTION

One of the major discoveries made since the last review is the equilibrium that exists between aziridines and azomethine ylids (Eq. 223).

The latter undergo facile dipolar additions to a dipolarophile (A=B). The net result is a versatile synthesis of five-membered heterocycles.

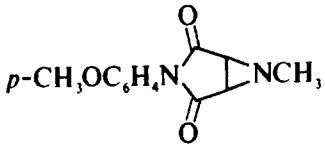
b. MECHANISTIC ASPECTS

The isomeric aziridine esters **281** and **282** have been studied in great detail.[518] The chemistry of these aziridines provides some of the most elegant support for the tenets of orbital symmetry. The stereochemical outcome of the thermal ring opening is defined as conrotatory by the stereospecific interception of ylids **283** and **284** by dipolarophiles. In the absences of dipolarophiles, however, **281** and **282** equilibrate via **283** and **284**. Formation of dimers (e.g., **288**) also occurs when dipolarophiles are absent.[366] Photochemical ring opening of the 2–3 bond proceeds via a disrotatory process.

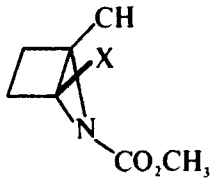


Thus, **281** yields **284** and **282** produces **283**. The photochemical reactions of **281**, however, were less stereospecific because of apparent competing photochemical interconversion of **283** and **284**. Even the thermal process is not always stereospecific. Stereochemical mixtures are often encountered with the less reactive dipolarophiles since interconversions of the **283** ⇌ **284** type then become competitive.[519] It has also been noted that the additions of **283** are faster than those of **284**.[519] Aromatic nitrogen substituents appear more likely to give stereospecific addition than aliphatic nitrogen substituents. *Exo* adducts result from additions to norbornene derivatives.[523,524] The energetics of these interconversions have been deduced from a series of carefully designed experiments.[521,720] Activation energies of approximately 29 and 22 kcal/mole are required for the **281** → **283** and **282** → **284** interconversions, respectively.

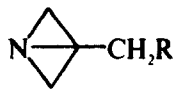
In contrast to **283**, two ylids, configurations **284** and **285**, must be considered for the thermal product from **282**. It has been concluded that in at least one case, **284** is more reactive in addition reactions.[721] Aziridines that are *cis* fused in a bicyclic system are precluded by geometrical considerations from conrotatory opening. Examples include **289**,[721] **290**,[409] and **291**.[634]



289

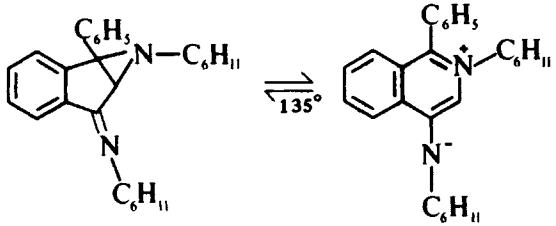


290



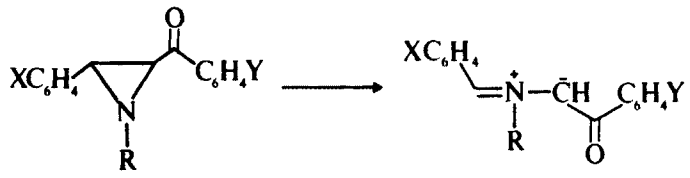
291

In one case, **289**, photochemical opening proceeded without difficulty. When the resultant ylid is the recipient of sufficient delocalization, forbidden disrotatory opening is possible (Eq. 224).[722,723]



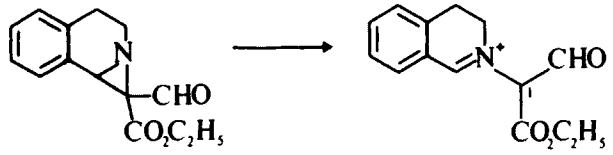
(224)

A variety of additional evidence has been amassed for the intermediacy of azomethine ylids. These ylids have been synthesized by other methods and are allowed to close[495] or to be trapped.[724] The most significant evidence comes from observations of photochromism in aziridines.[725] Flash photolysis of **281** and **282** produces a yellow color that fades slowly on warming (reversion to **281** and **282**) or instantly on addition of a good dipolarophile.[726] Similar observations have been made in a detailed study of **292**.



292 293

When X = *p*-CH_3O and Y = NO_2, charge stabilization in **293** is so great that it is visible and stable at room temperature.[725] Another extreme example of such stabilization is found in **294**, which exists only in the ylid form **295**.[726]



294 295

Similar photochromism is also observable in bicyclic aziridines (**296**).[607, 725] Sensitivity to substituent and strain effects followed expected patterns.[725]

297 296

c. SYNTHETIC APPLICATIONS: FIVE-MEMBERED HETEROCYCLES

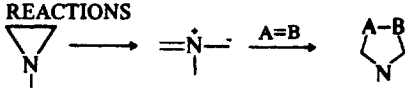
The addition of azomethine ylids to various dipolarophiles is an experimentally simple reaction. Such additions constitute a versatile route to a wide variety of five-membered heterocycles. A useful review has appeared.[727] Some of the possible permutations and combinations are depicted in Table 78. Although many of these additions are probably concerted, it is possible that some occur in stepwise fashion.

d. OTHER CHEMISTRY OF AZIRIDINE-DERIVED AZOMETHINE YLIDS

In some cases, particularly when alkynes are used as dipolarophiles, aromatization and/or isomerization of the double bond occurs. A typical example is shown in Eq. 225.[486, 758]

A number of other similar oxidative dimerizations have been noted.[748, 754, 755, 759] Aromatization via HCN loss (Eq. 226),[760] decarbonylation (Eq. 227),[227] and combinations of both[761] results in novel heterocyclic syntheses. A particularly interesting postaddition rearrangement is depicted in Eq. 228.[353, 762] The major product arises via a 1,3-shift.

TABLE 78. HETEROCYCLES FROM AZOMETHINE YLID: DIPOLAROPHILE REACTIONS



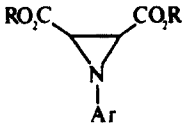
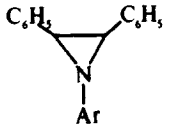
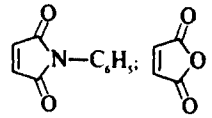
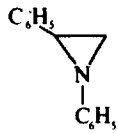
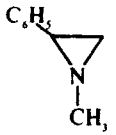
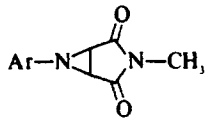
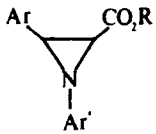
Aziridine	Dipolarophile[a]	Ref.
	$R'O_2CC{\equiv}C{-}CO_2R$	518
	$R'O_2CHC{=}CHCO_2R'$	336
	Norbornene	336
	$C_6H_5COC{\equiv}CC_6H_5$	336
	$O{=}C[CO_2R']_2$	519
	$R'O_2CN{=}NCO_2R'$	519
	$C_6H_5N{=}NCO_2R'$	728
	C_6H_5CHO	729
	$C_6H_5CH{=}N{-}CH_3$	729
	$C_6H_5N{\ddagger}C{=}O$	729
	Phenanthrene, anthracene	730
	$RO_2CC{\equiv}CCO_2R$	523, 524, 731
	$RO_2CCH{=}CHCO_2R$	523, 524, 731
		731
	Norbornene	731
	$RO_2CN{=}NCO_2R$	731
	$C_6H_5COCH{=}CHCOC_6H_5$	731
	Cyclohexene	731
	$C_6H_5COCH{=}CHCOC_6H_5$	336
	$CH_2{=}CHCN$; $CH_2{=}CHCO_2CH_3$	733
	Norbornene ($h\nu$)	721
	$R'O_2CC{\equiv}CO_2R'$	168
	NCCH=CHCN	734
	$CH_2{=}CHCN$	734
	$CH_2{=}CHCO_2R'$	734
	$C_6H_5CH{=}CHCOCH_3$	734
	$Ar''N{\ddagger}C{=}O$	735
	$ArN{\ddagger}C{=}S$	

TABLE 78. CONTINUED

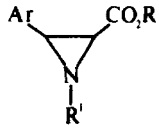
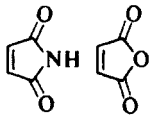
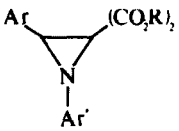
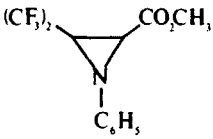
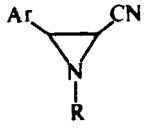
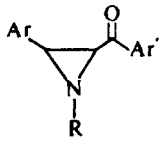
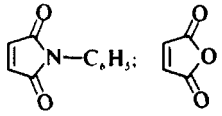
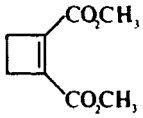
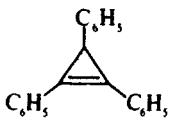
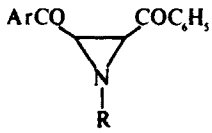
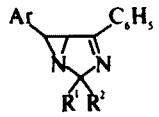
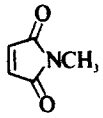
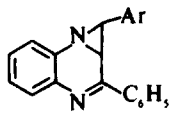
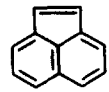
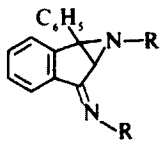
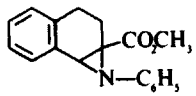
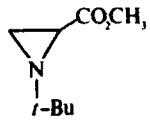
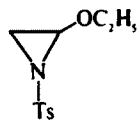
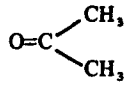
Aziridine	Dipolarophile[a]	Ref.
	$R''O_2CN{=}NCO_2R''$	736
	$R''O_2CCH{=}CHCO_2R''$	520
	$R'O_2CC{\equiv}CCO_2R''$	520
		520
	$C_6H_5CH{=}C[CO_2R']_2$	737
	$R''CHO$	738
	$R''C{\equiv}CR''$, $R''CH{=}CHR''$	739–742
	$(C_6H_5)_2C{=}C{=}O$; $CH{=}C{=}O$	743
	$H{-}N{=}C{=}O$, $H{-}N{=}C{=}S$, $H{-}N{=}C{=}S$	744
	$Ar''{-}N{=}C{=}O$	735
	$CH_3O_2CC{\equiv}CCO_2CH_3$	329
	$R'{-}C{\equiv}C{-}R'$	525
	$R''O_2CCH{=}CHCO_2R'$	525
	$Ar''SO_2N{=}CHAr'''$	745
		227
	$R'O_2CCH{=}CHCO_2R'$	227
		746–748
	$R'O_2CN{=}NCO_2R'$	736, 748
	$Ar''CH{=}CHCOC_6H_5$	749
	$C_6H_5COCH{=}CHCOC_6H_5$	749, 750
	$N{=}CCOC_6H_5$	750
		751
		271
		752

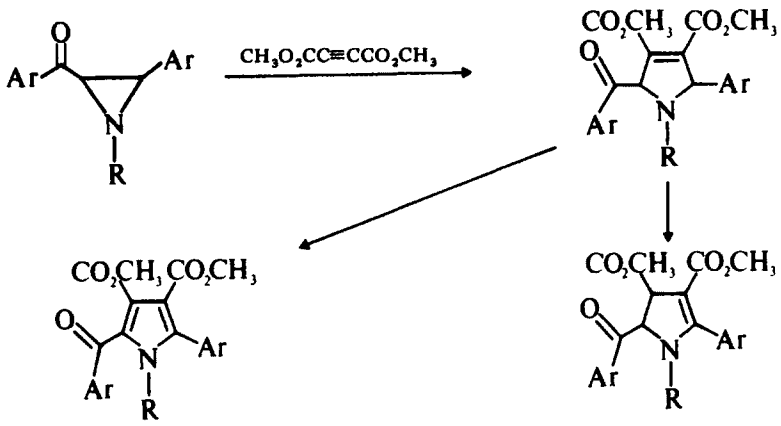
TABLE 78. CONTINUED

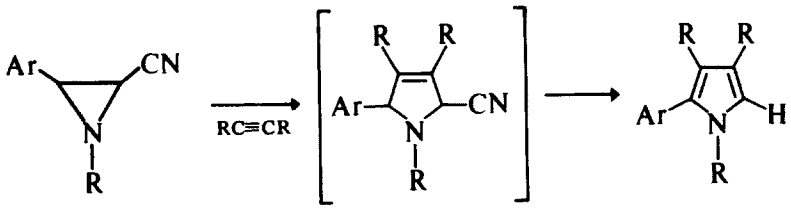
Aziridine	Dipolarophile[a]	Ref.
	$C_6H_5COCH{=}CHCOC_6H_5$	336, 749
	$R'O_2CC{\equiv}CCO_2R'$	749, 753
	$R'O_2CN{=}NCO_2R'$	753
	$R'O_2CCH{=}CHCO_2R'$	753
	$R^3O_2CCH{=}CHCO_2R^3$	754
	$R^3O_2CN{=}NCO_2R^3$	754
		754
	$R^3O_2CC{\equiv}CCO_2R^3$ ($h\nu$)	755
	C_6H_5CHO	230
		230
	$C_2H_5O_2CN{=}NCO_2C_2H_5$	230
	$H{-}C{\equiv}CCO_2CH_3$	500
	$CH_3O_2CC{\equiv}CCO_2CH_3$	500
	Norbornene	723, 777
	$R'O_2CCH{=}CHCO_2R'$	723, 777
	$CH_3O_2CC{\equiv}CO_2CH_3$	384
	$CF_3CF{=}CFCF_3$	756
		757

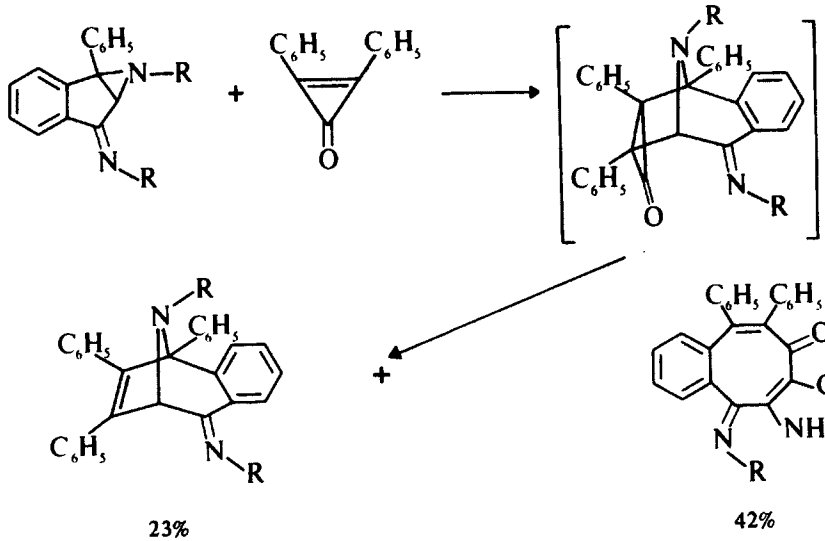
[a] $h\nu$ = photochemical reaction; wavy line indicates bond added to in cumulative system.

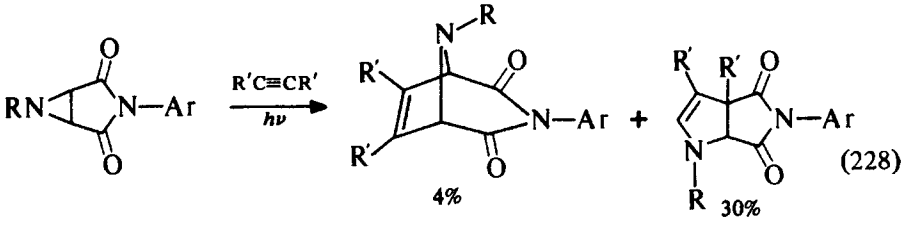
The azomethine ylid is often intercepted via concerted electrophilic attack. A typical example is shown in Eq. 229.[344]

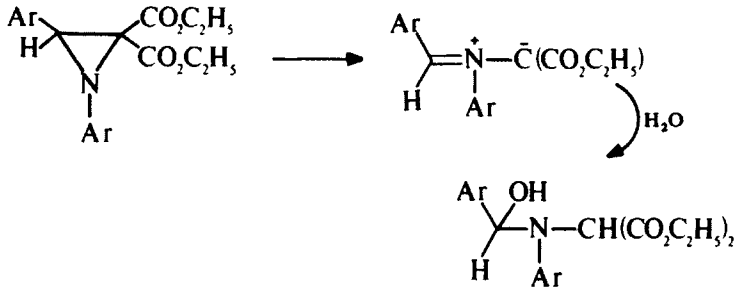
Similar reactions of the dipole intermediate with water,[232, 763] alcohols,[732, 764] amines,[765] and carboxylic acids[764] have been described. A particularly significant result occurs when the ylids are trapped with $LiClO_4$.[766]


Ar
O
N
R
CH3O2CC≡CCO2CH3
CO2CH3 CO2CH3
Ar
(225)


Ar
CN
N
R
RC≡CR
R R
(226)

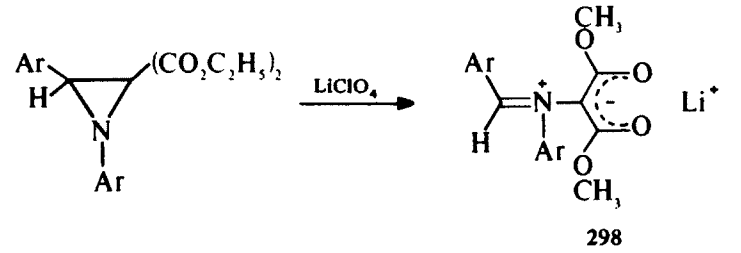

C6H5
N–R
+
O
(227)
23%
42%
NHR


RN
N–Ar
O
R'C≡CR'
hν
R'
4%
30%
(228)

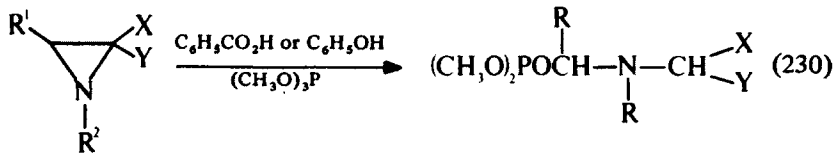


(229)

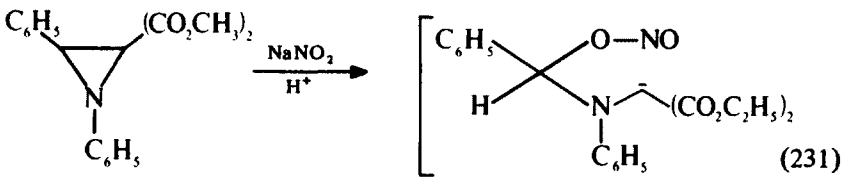
The resultant salt (**298**) has been observed by nmr spectroscopy and reacted under mild conditions with various reagents (e.g., H_2O, KCN). Other noteworthy interceptions of these ylids are found in Eqs. 230[767] and 231.[768]



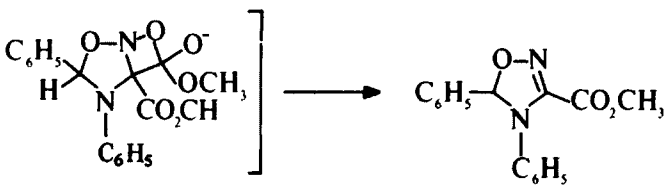
298



(230)



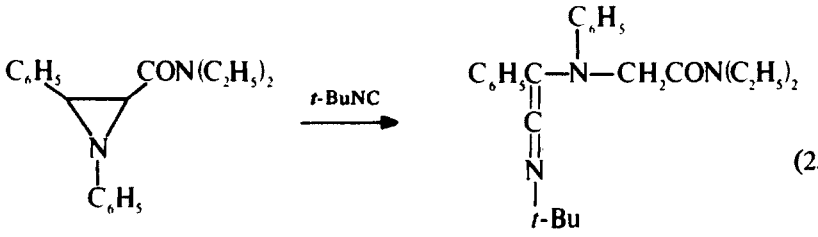
(231)



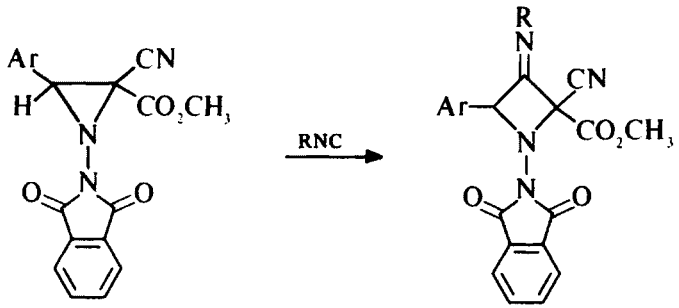
The azomethine ylid has been shown to react with aldehydes formed via hydrolysis[732,769] and to undergo Stevens rearrangements.[232,770-772]

A large number of other reactants have been subjected to azomethine ylids. Many of these give interesting but complex chemistry. These reactants include

cyclopropenone imines,[773] cyclopropenones,[774,775] phosphorous ylids,[776] sulfonium ylids,[777,778] nitroso compounds,[779–783] and oxygen.[784,785] Isonitriles react with aziridine generated azomethine ylids to give both open (Eq. 232)[786] and cyclic (Eq. 233)[787] products. The former process is acid catalyzed. The concertedness of the latter is unknown.



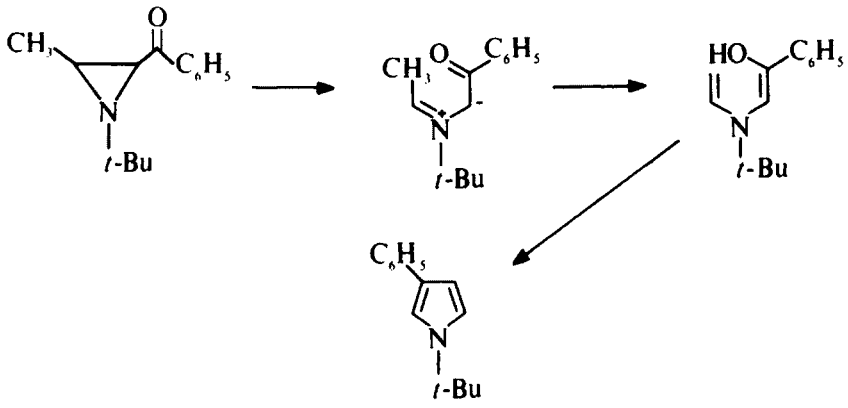
(232)



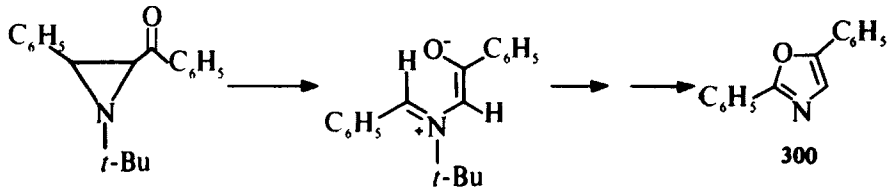
(233)

e. AZIRIDINE ISOMERIZATIONS AND RELATED REACTIONS VIA AZOMETHINE YLIDS

Formation of both **299**[514] and **300**[788] is initiated by ring-closing isomerization of an azomethine ylid.

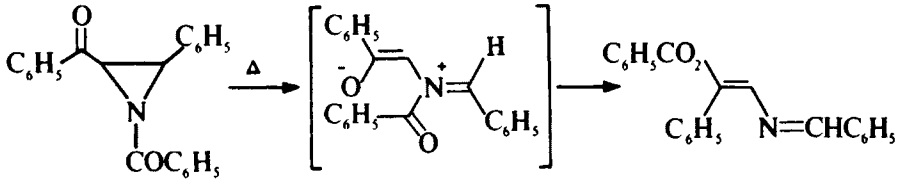


299

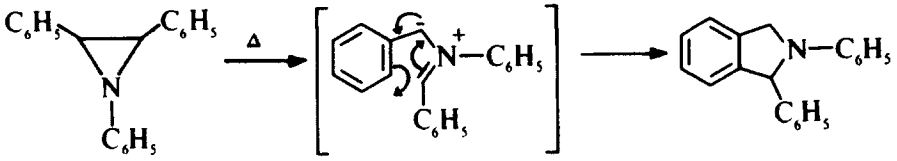


300

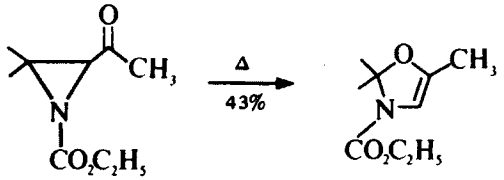
The final products then result from aromatization of these precursors. The isomerizations of **301**,[789] **302**,[790] **303**,[397] **304**,[256] **305**,[791] and **306**[489] proceed via azomethine ylids.



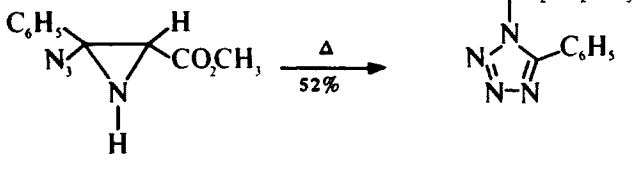
301



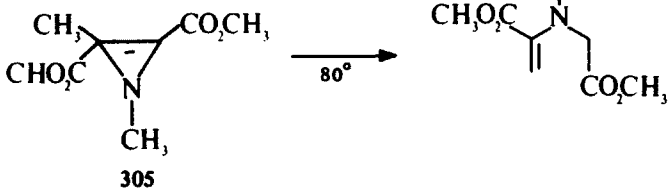
302



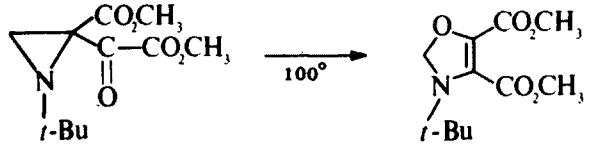
303



304

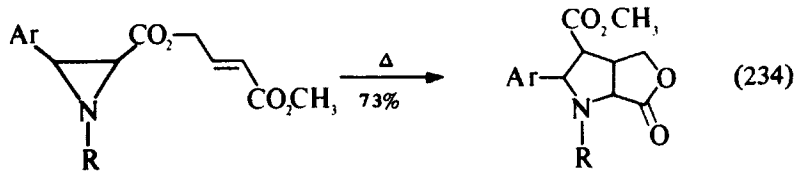


305

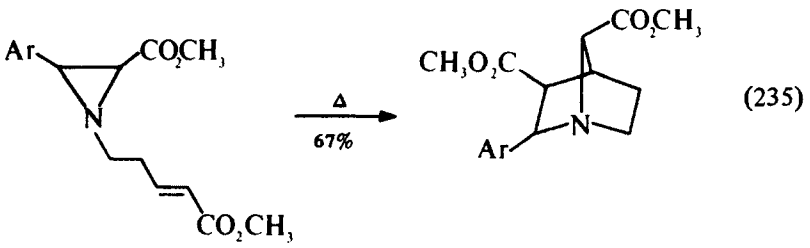


306

The intramolecular cyclization of azomethine ylids represents a recently tested route to novel bicyclic structures (Eqs. 234 and 235).[792] Other azomethine ylid-type rearrangements are covered later in the discussion of vinylaziridines.



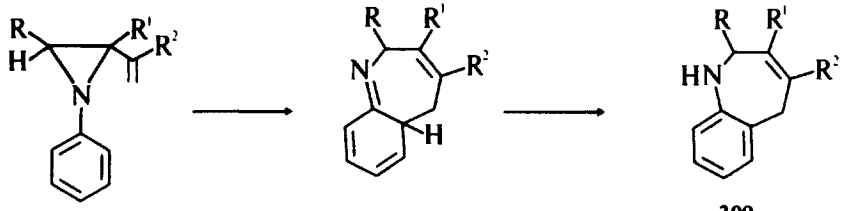
(234)



(235)

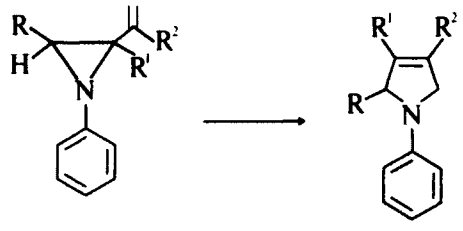
H. *Thermal Rearrangements of Vinyl- and Allylaziridines*

Aziridines bearing pendant unsaturation display especially interesting and diverse chemistry. The actual reaction course depends on the geometry and nature of the substituents. Thermolysis of compounds with structure **307** yield **308**.[124,125,338] In contrast, isomers of structure **310** give 3-pyrrolines (**311**) on heating.



307 308 309

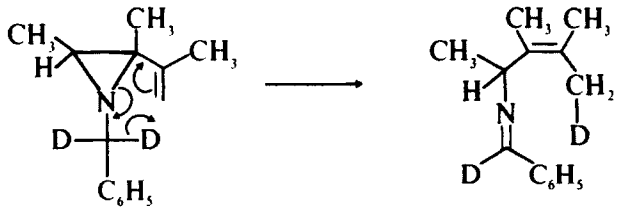
Similar 3-pyrroline formation has been noted with carbethoxy,[99] phthalimidyl,[430] and other related[431,793] electron-delocalizing nitrogen substituents. The importance of the relative geometry (*cis*) for the vinyl and phenyl groups in the formation of



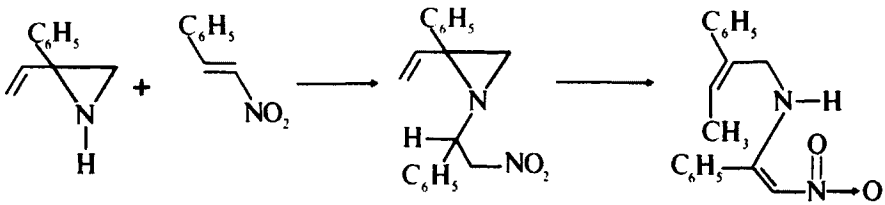
310 311

309 has been noted.[124,125] Although either concerted or diradical mechanisms may be written, the lack of crossover between **307** and **310** decompositions suggests a concerted type of mechanism. On the other hand, the large effect of $R' = CH_3$ for both **307** and **310** (rearrangement is spontaneous at room temperature) requires explanation. Further studies of substituent electronic and steric effects would shed additional light on these interesting reactions.

A second pattern is exhibited by the spontaneous rearrangement of **312** and **314**.[124,658b]

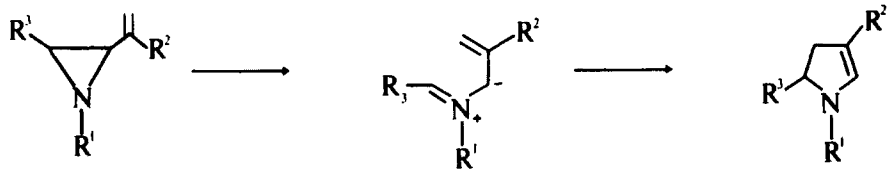


312 313



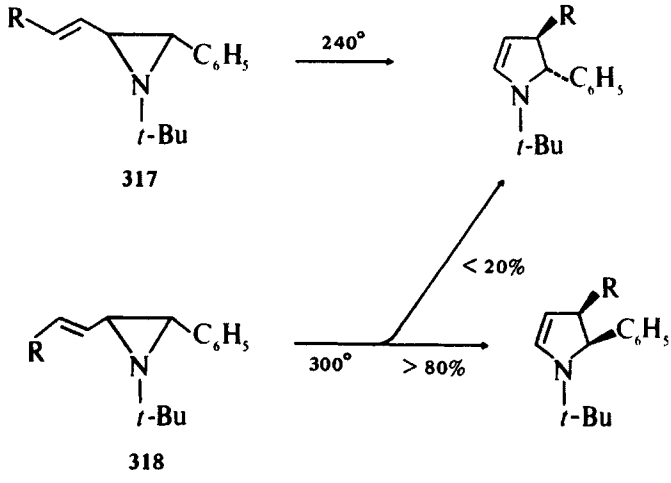
314

Isomer **315** yields a mixture of 2- and 3-pyrrolines. Other *N*-alkylaziridines (**315**) have been noted to give 2-pyrrolines (**316**) and structures related to **313**.[605,606]

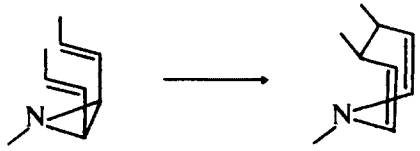


315 316

Further information on the latter type isomerization is provided by the *cis* and *trans* aziridines **317** and **318**.[794] These authors favor an azomethine ylid intermediate but note that concerted pathways cannot be excluded.

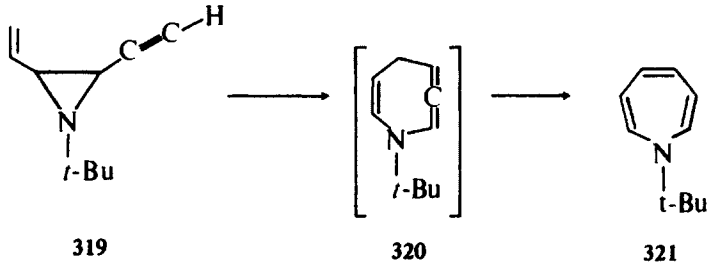


Cis- and *trans*-2,3-divinylaziridines have been studied by various laboratories.[97,126,794] The *cis* isomers undergo extremely rapid room temperature Cope rearrangement (Eq. 236).

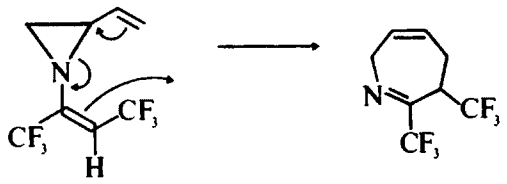


(236)

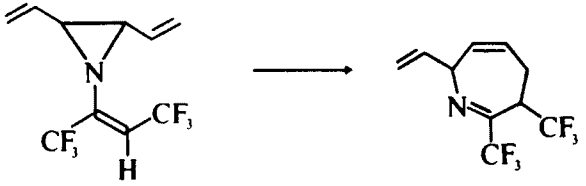
By contrast, the *trans* analogs require higher temperatures (300°). Although the stereochemistry of the latter was not defined, an azomethine ylid probably was involved.[794] The acetylenic analog **319** rearranges to **321** via **320**.[128,795]



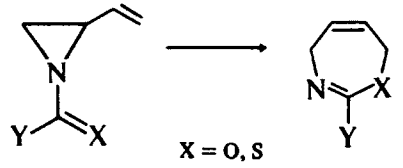
Thermal Cope-type rearrangements between *C*-vinyl and nitrogen substituents bearing appropriately located unsaturation are also known. These are depicted in Eqs. 237,[98] 238,[98] and 239.[796]



(237)

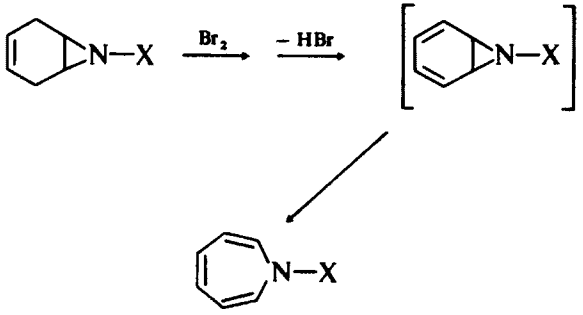


(238)

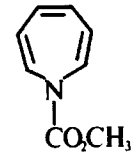


(239)

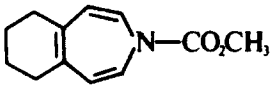
Synthesis of azepine derivatives via the valence tautomerism approach of Eq. 240 has been particularly useful. Some examples of this synthesis include **322**,[186] **323**,[186] **324**,[186] and **325**.[81,797]



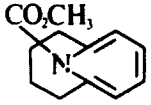
(240)



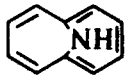
322



323

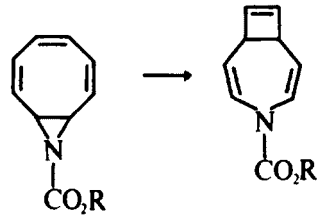


324

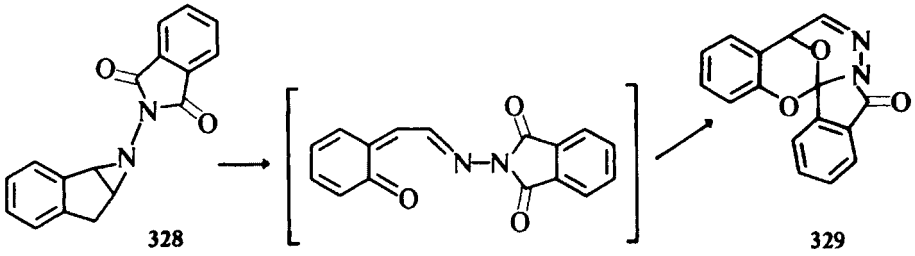


325

A related tautomerism has been applied to a porphyrin.[393] The conversions of **326** to **327**[404,798] and of **328** to **329**[799] represent other valence tautomerism routes to novel heterocyclic systems.

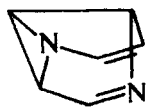


326 **327**



328 **329**

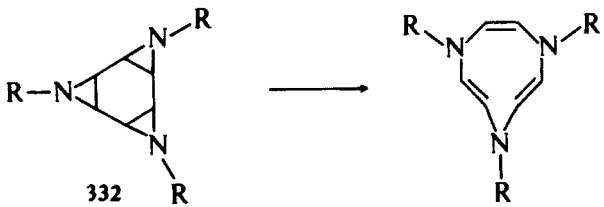
The most intriguing valence tautomerism of an aziridine derivative remains to be demonstrated. Calculations have predicted that aziridine derivative **330** would be a nonclassical molecule because its ground state would be characterized by degenerate isomerism without activation.[800] This molecule has not yet been synthesized.



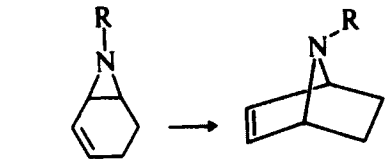
330

Isomerism of **331** and **332** allows entry into medium-sized heterocycles.[801,802] It is not known whether these reactions are stepwise or concerted. Sigmatropic-type rearrangements of **334** and **335** lead to useful bicyclic heterocycles.[422]

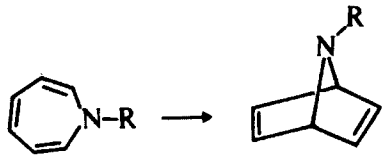
331



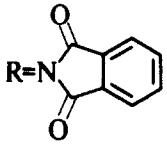
332



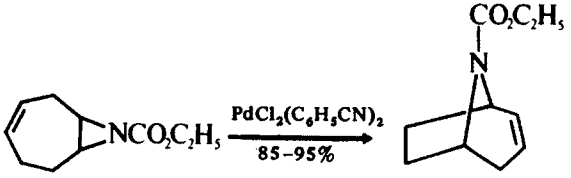
333



334

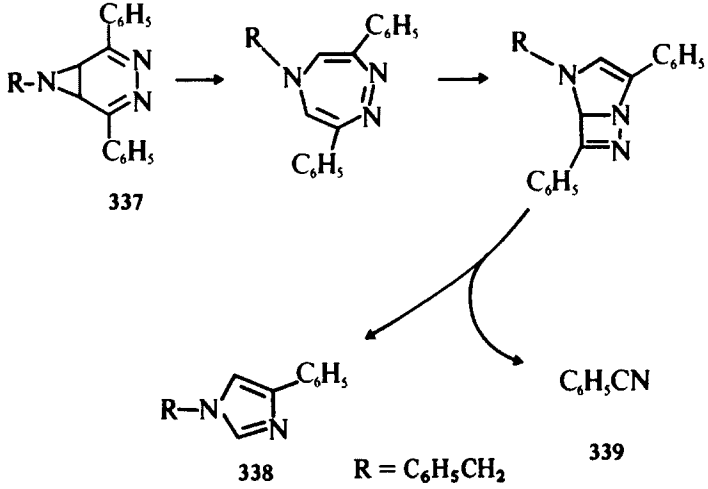


A palladium derivative efficiently converts **335** to **336**.[406]



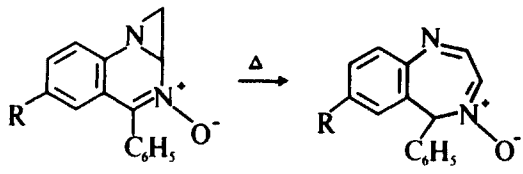
335 336

Heteroanalogs of vinylaziridines have also been studied. Under mild conditions **337** rearranges to **338** and **339** via the sequence of Eq. 241.[803a] An analog behaves similarly.[803b]

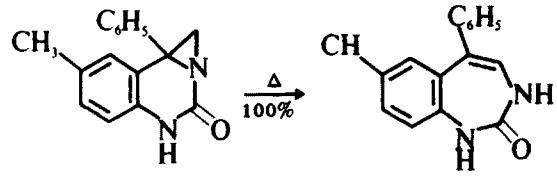


(241)

The ring expansions of **340**[158,446] and **341**[273] also deserve mention in this section.

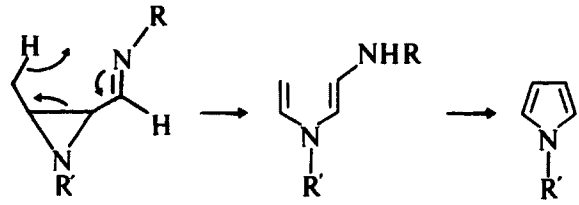


340 R = H, Cl

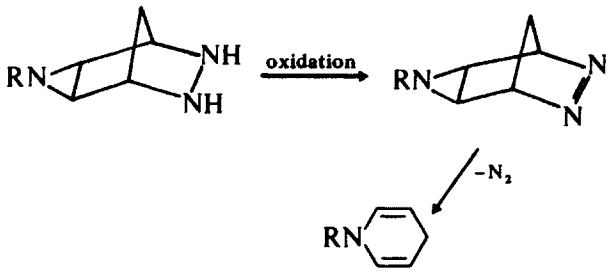


341

Pyrroles result from thermolysis (see Eq. 242)[228] and dihydropyridines from the sequence of Eq. 243.[377,378]

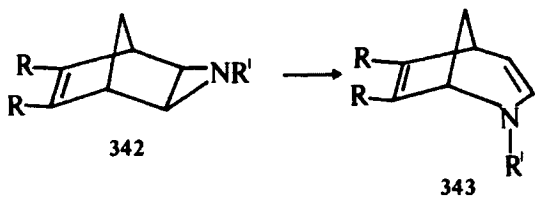


(242)

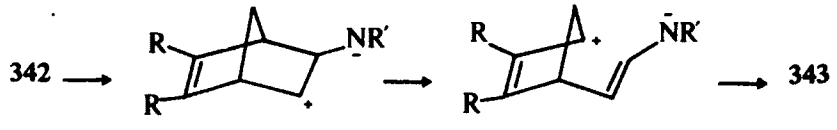


(243)

Numerous compounds of general structure **342** expand to **343**.[320,361,415,804-806] A solvent effect suggested a polar nonconcerted mechanism (Eq. 224).[804]



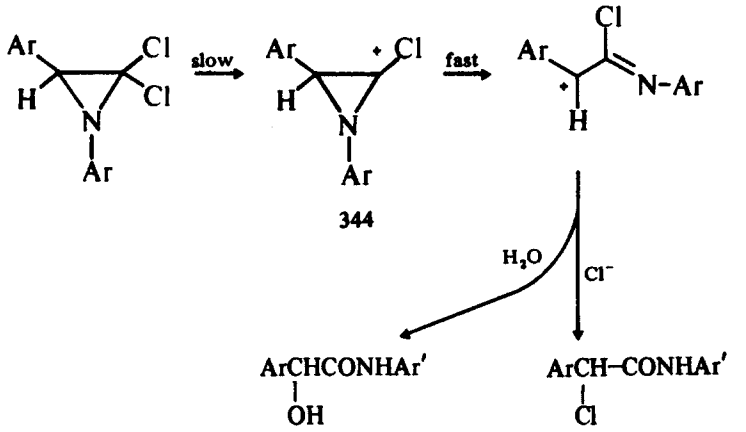
342 **343**



(244)

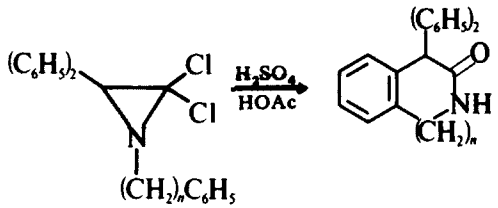
I. *Rearrangements and Other Ring-Opening Reactions of 2-Haloaziridines*

A detailed mechanistic analysis of the hydrolysis of 2,2-dichloroaziridines has provided evidence for the process shown in Eq. 245.[447] Additional support for the intermediacy of **344** has been derived from a study of the analogous monochloroaziridines.[590]



(245)

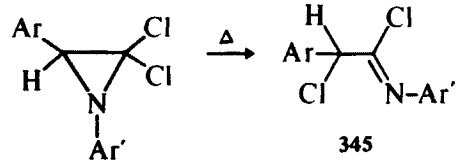
Numerous subsequent studies have extended the scope and added confirmation for the proposed mechanism.[448,461,807] Carbonium ion **344** has also been intercepted via intramolecular electrophilic aromatic substitution as indicated in Eq. 246.[808]



(246)

$n = 0$ (96%)
$n = 1$ (80%)
$n = 2$ (67%)

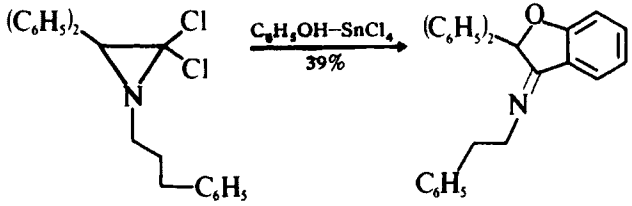
Thermolysis of dihaloaziridines, in an apparently analogous reaction, produces α-haloimidoyl halides (Eq. 247).[460,809,810] Although it has been claimed that **345** is formed directly in a concerted electrocyclic ring opening, the evidence for this assertion may not be adequate.



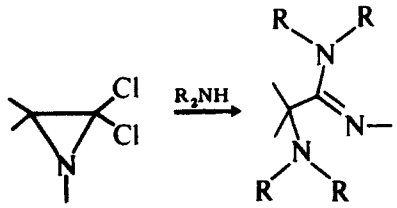
(247)

345

Analogy with the more easily studied hydrolysis suggests that **344** is also involved in the thermal reaction. The ring-opened carbonium ion has been intercepted as shown in Eqs. 248[811] and 249.[812]

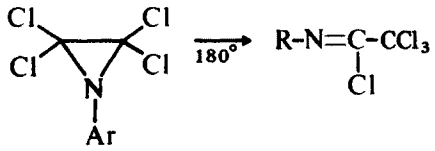


(248)

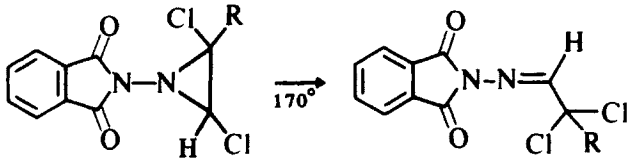


(249)

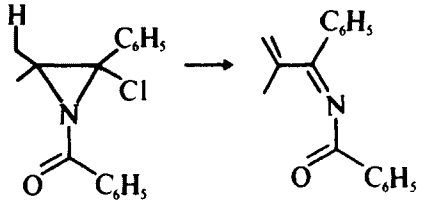
Equations 250,[455,457] 251,[416] and 252[260] demonstrate that such ring openings are not limited to 2,2-dihaloaziridines.



(250)

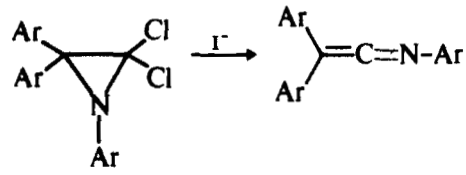


(251



(25

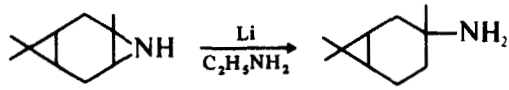
Closely related to the preceding reactions is the high yield conversion of 2,2-dihaloaziridines to ketinimines (Eq. 253).[260,449,450]



(253)

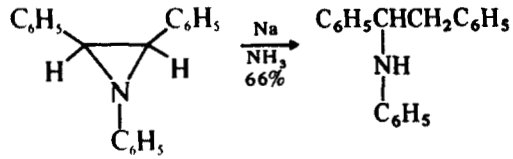
J. *Hydrogenolysis of the Aziridine Ring*

The aziridine is relatively inert toward ring-opening hydrogenolysis[813] (Section III, 2, A). Lithium in ethylamine affects the conversion of **346** to **347**.[181]

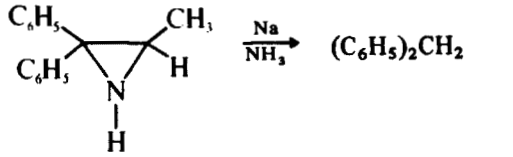


346 **347**

Sodium in liquid ammonia has been reported to give the results of Eqs. 254 and 255.[814] The origin of the product in the latter case is unclear.

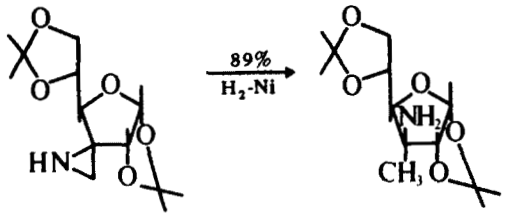


(254)

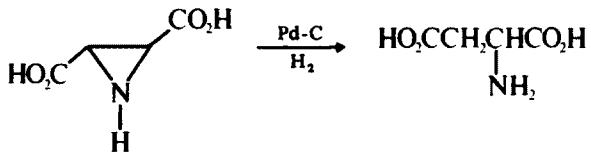


(255)

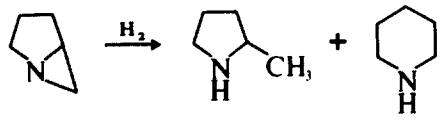
The catalytic reductions of Eqs. 256,[204] 257,[815] 258,[54] and 259[158] illustrate some of the published catalytic hydrogenolytic ring openings.



(256)

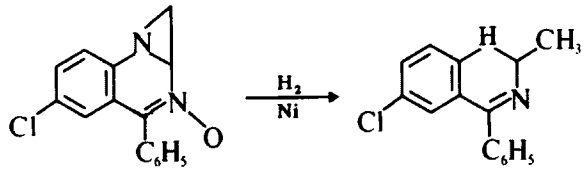


(257)



2:1

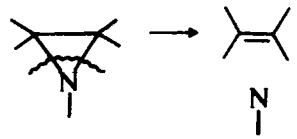
(258)



(259)

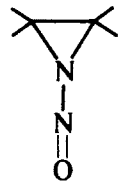
K. *Deamination of Aziridines*

The deamination of aziridines includes reactions in which the aziridine nitrogen is removed and an alkene formed (Eq. 260).[816] Although such reactions were initially studied for mechanistic reasons, they have come to be employed for structural purposes. More recently, such reactions have also become known as useful synthetic routes to unsaturation.



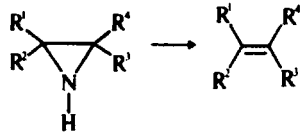
(260)

The deamination of unsubstituted aziridines is summarized in Tables 79 and 80. Some of the entries marked as stereospecific may be stereoselective. It is also possible that strongly electron-donating or -attracting groups might reduce stereospecificity. Nitrosyl chloride presumably forms an intermediate **348**, which has been detected in one case.[817]



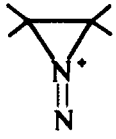
348

TABLE 79. DEAMINATION OF 1-UNSUBSTITUTED AZIRIDINES



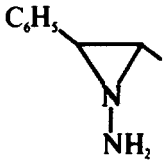
R^1	R^2	R^3	R^4	Stereo specificity	Reagent	Yield (%)	Ref.
H	H	H	H	–	NOCl	40	817
H	H	H	H	–	HNF_2	80	818
CH_3	H	H	H	–	NOCl	57	817
C_2H_5	H	H	H	–	NOCl	53	817
CH_3	H	H	CH_3	Yes	NOCl	43	817
CH_3	H	H	CH_3	Yes	HNF_2	–	819
CH_3	H	CH_3	H	Yes	NOCl	52	817
CH_3	H	CH_3	H	Yes	HNF_2	–	819
CH_3	CH_3	CH_3	CH_3	–	NOCl	27	817
C_6H_5	H	p-C_6H_5–C_6H_4CO	CH_3	Yes	NOCl	22	162
C_6H_5	H	C_6H_5	CH_3	Yes	NOCl	32	162
CH_3	H	C_5H_{11}	H	Yes	n-BuONO	92	200
C_6H_{11}	H	H	H	–	n-BuONO	100	200
$C_6H_5CH_2$	H	H	H	–	n-BuONO	86	200
C_6H_5	H	H	C_6H_5	Yes	n-BuONO	58	200
C_6H_5	H	CH_3	C_6H_5	Yes	n-BuONO	87	200
C_6H_5	H	C_2H_5	CH	Yes	n-BuONO	83	200
C_6H_5	H	C_6H_5	C_6H_5	–	n-BuONO	73	200
$CO_2C_2H_5$	H	$CO_2C_2H_5$	H	Yes	NOCl	–	233

The stereospecificity suggests a concerted loss of N_2O. Although nitrosyl chloride was the early reagent of choice,[162,233] most recent publications have described the use of HNO_2, BuONO, $NOBF_4$, and other diazotizing agents.[132,142,200,303,802] The intermediate **348** also decomposes in a concerted, stereospecific manner. Another reagent, HNF_2, has also been used to generate **349**.[817,818]

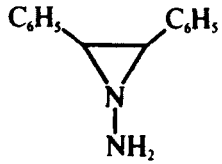


349

Oxidation of **350** and **351** with MnO_2 may also proceed via **349**. The reaction, however, is not stereospecific.[419]

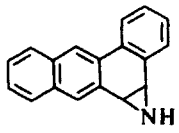


350

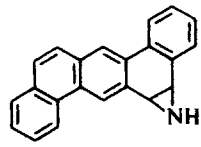


351

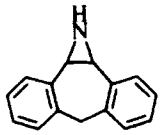
TABLE 80. DEAMINATION OF 1-UNSUBSTITUTED AZIRIDINES



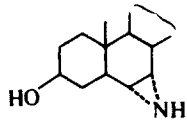
78% (isoamyl-NO)[142]



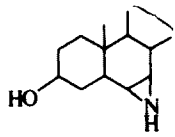
90% (isoamyl-NO)[142]



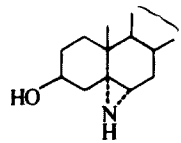
89% (HNO_2)[303]



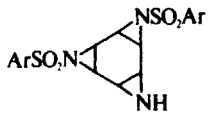
– (HNO_2)[132]



– (HNO_2)[132]

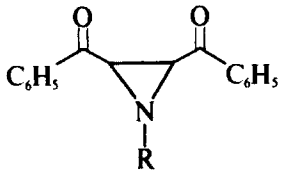


– (HNO_2)[132]

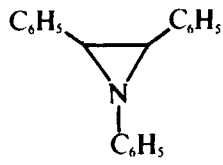


70% ($NOBF_4$)[802]

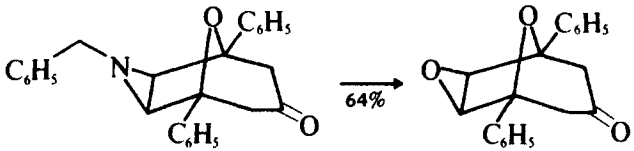
Oxidation of aziridines with peracids has been studied by several laboratories. The deamination of **352** appears stereospecific in 85–90% yield.[820] The corresponding peracid oxidations of **353** are not stereospecific.[63,820] In one case (Eq. 261) the intermediate alkene undergoes epoxidation.[820]



352



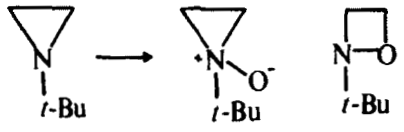
353



(261)

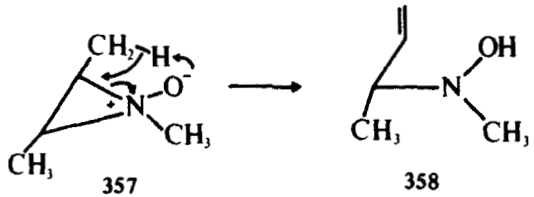
Ozonolysis of **354** results in deamination. The *N*-oxide intermediate was spectrally identified, although it was unstable above 0°.[821] It was also demonstrated that

independently synthesized 1,2-oxazetidine **356** was stable under the reaction conditions, hence **355** must decompose directly to products.



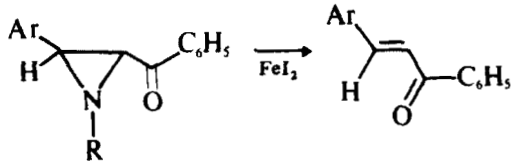
354 **355** **356**

N-Oxide **357** yielded **358** instead of the deamination product. *N*-Oxides have also been postulated in the low yield liver microsomal deamination of aziridines.[822]

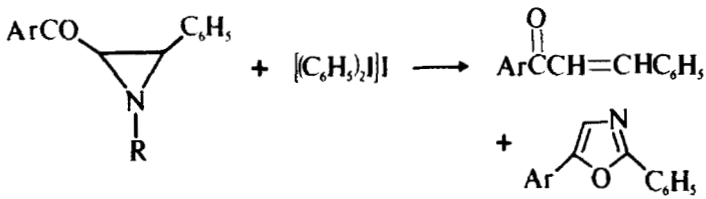


357 **358**

Ferrous iodide deaminates aziridines (Eq. 262) in high (nonstereospecific) yield.[823] Similarly, *N*-alkyl-substituted aziridines are deaminated by the process shown in Eq. 263.[824] Oxazoles are often formed as a by-product.

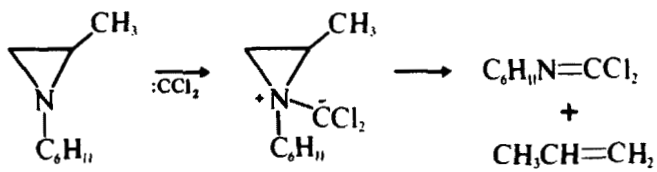


(262)

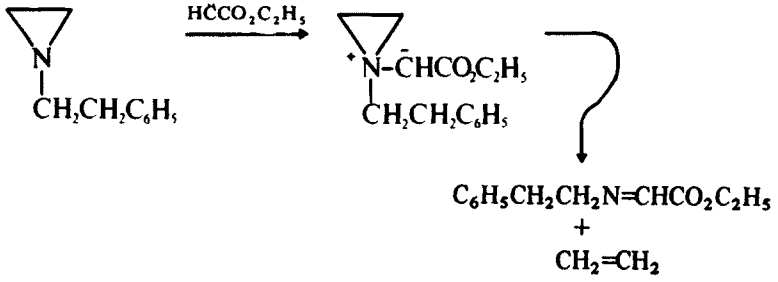


(263)

Other nonoxidative procedures have been used. Aziridines react with carbenes to yield ylids, which subsequently decompose to the alkene. Dichlorocarbenes (from chloroform) and carbethoxycarbene (from ethyl diazoacetate and Cu^{2+}) have served as the carbene sources. The former gives dichloroisocyanides as by-products,[825,826] (Eq. 264) and the latter yields imines[827] (Eq. 265).



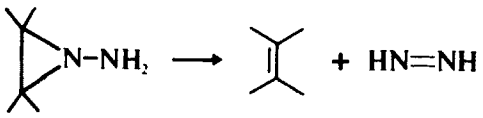
(264)



(265)

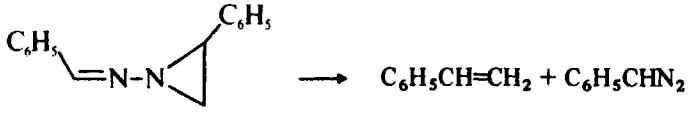
The procedure has also been applied to aziridines unsubstituted on nitrogen.[825] The decomposition step is not totally stereospecific.

Certain *N*-substituted aziridines are particularly labile toward deamination. *N*-aminoaziridines decompose with high stereospecificity to alkenes and diimide (Eq. 266) between 20° and 60° in good yield.[98,583] *N*-Aroylazoamines also decompose stereospecifically to alkenes and *N*-aroylazides.[828-830]

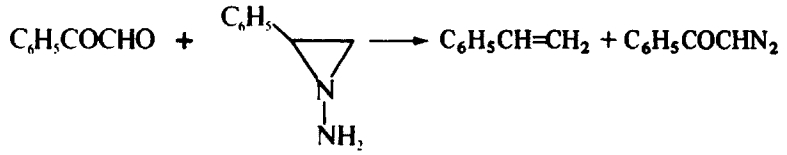


(266)

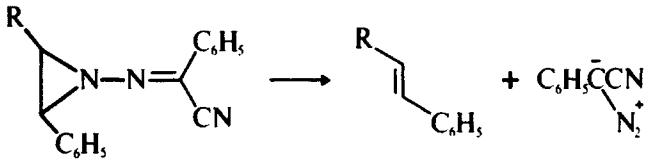
Aziridinyl hydrazones function as masked diazocompounds. Temperatures of approximately 150° are required. Examples of the prototype reaction are found in Eqs. 267,[828] 268,[831] and 260.[586] The most important application of this procedure has been to cyclic α,β-epoxyketones (Eq. 270).[832]



(267)

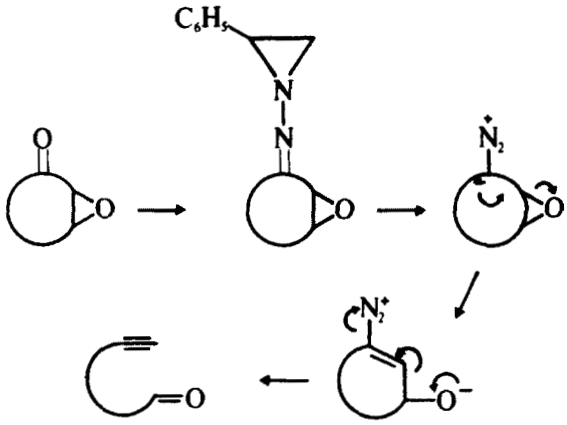


(268)



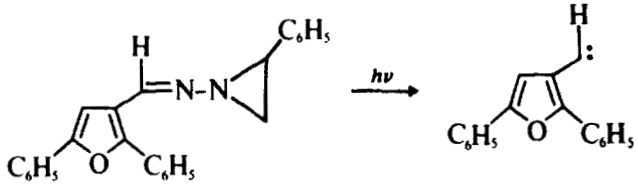
(269)

Although temperatures of about 150° are required, the product is removed by distillation as it is formed. This procedure, which has been particularly useful in vitamin B_{12} syntheses, is summarized in Table 81. Photochemical decomposition



(270)

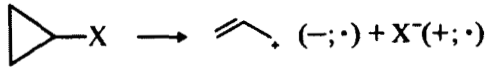
has been employed with good success.[835] Photochemical decomposition of **359** has been employed in the study of carbene **360**.[836]



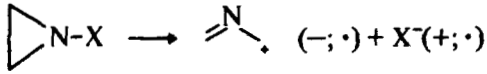
359 **360**

L. *Ring Opening of Aziridines to Azaallyl Intermediates*

Interest in the ring opening of the cyclopropyl ring to allyl systems (Eq. 271) sparked similar studies on the aziridine rings bearing appropriate nitrogen substituents (Eq. 272).

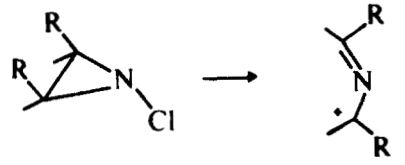


(271)



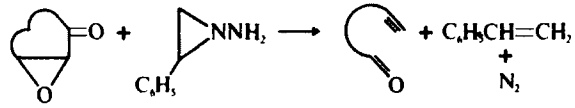
(272)

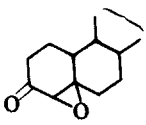
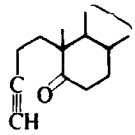
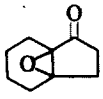
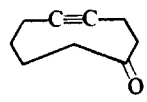
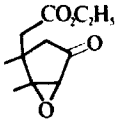
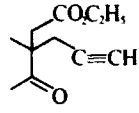
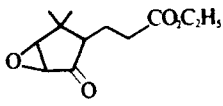
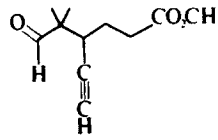
The solvolysis of carbon-substituted *N*-chloroaziridines has demonstrated that nitrogen-chlorine and carbon-carbon cleavages occur simultaneously in a disrotatory fashion (Eq. 273).[48,49,837] For example, **361** is labile where **362** is stable.[48] The relative rates of **363**, **364**, and **365** also support this conclusion.[837]

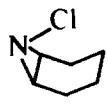


(273)

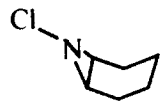
TABLE 81. ACETYLENIC KETONES AND ALDEHYDES FROM AZIRIDINE THERMOLYSIS



			Ref.
	78%	$CH_3C{\equiv}C(CH_2)_3CHO$	586
	94%	$CH_3C{\equiv}C(CH_2)_3CHO$	586
	64%	$HC{\equiv}C(CH_2)_3CHO$	586
	87%		586
	38%		832
	62%		833
	63%		834



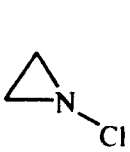
361



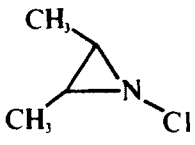
362

The stability of **366** thus must also be due to a substituent effect[52].

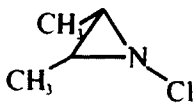
The conversion of **367** to **368** may also be explained in these terms (Eq. 274).[192] The novel transformation of Eq. 275 constitutes still another example.[256]



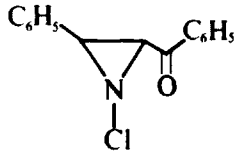
363 (1)



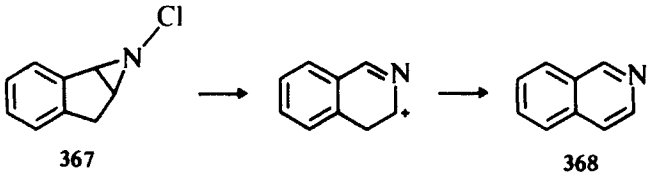
364 (1500)



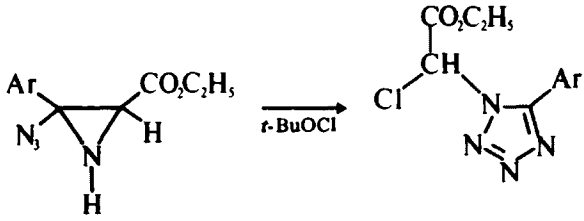
365 (150,000)



366

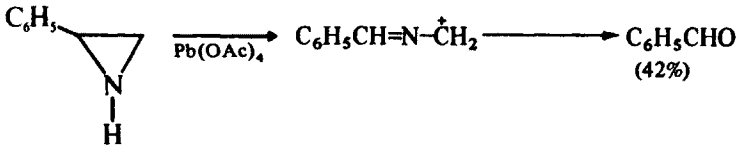


367 368 (274)

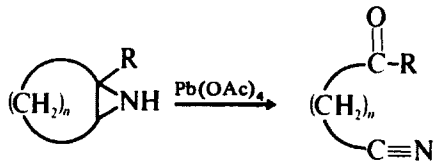


(275)

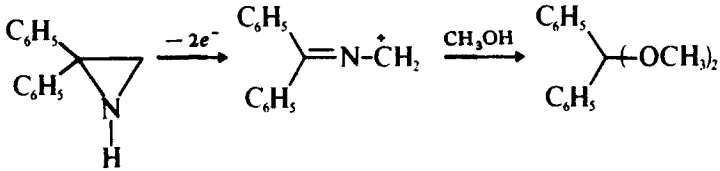
Other approaches to the generation of the azaallyl cation have been found. One of the most useful involves the use of $Pb(OAc)_4$.[838,839] The results of Eqs. 276 and 277 are illustrative of this procedure. Specific examples of Eq. 277 are found in Table 82. Aniodic oxidation of aziridines also leads to the azallyl cation intermediate (Eq. 278).[840]



(276)

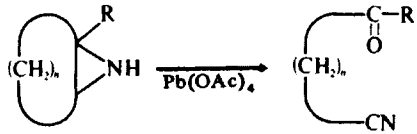


(277)



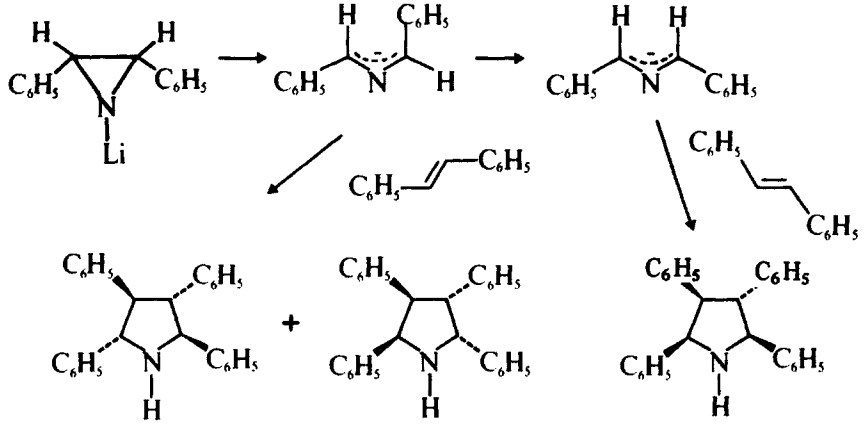
(278)

TABLE 82. LEAD TETRAACETATE OXIDATION OF AZIRIDINES[839]

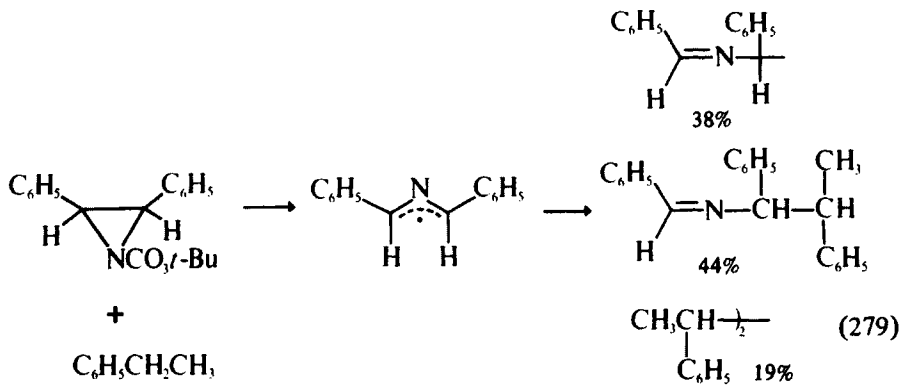


R	*n*	Yield (%)
CH_3	10	82
C_6H_5	10	85
H	10	58
CH_3	6	58
C_6H_5	6	46
H	6	29
CH_3	9	82

The anionic version of these ring openings is also known.[841-843] The key findings are found in Scheme 2.[841] The corresponding radical has been found by thermolysis of the appropriate perester (Eq. 279).[844]



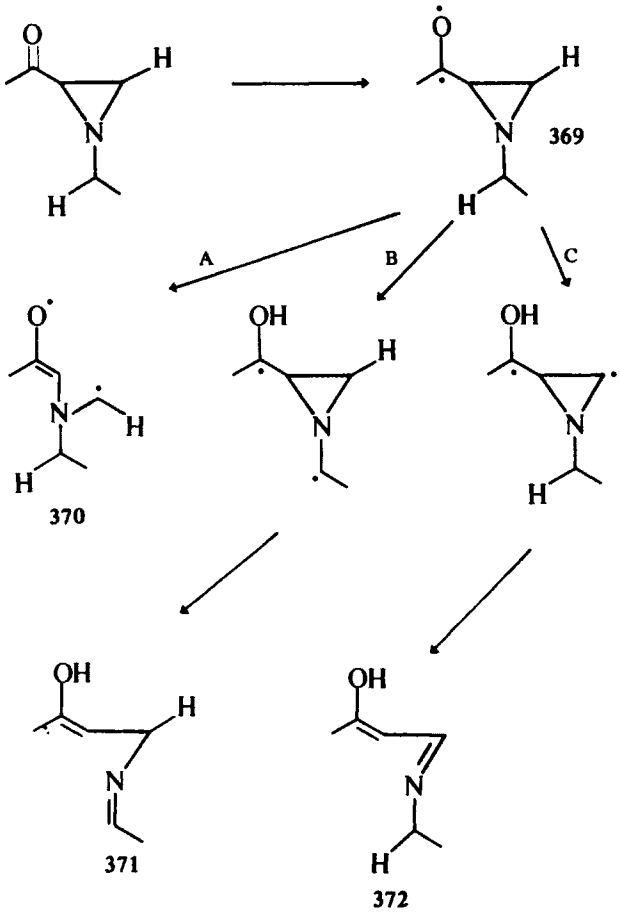
Scheme 2



(279)

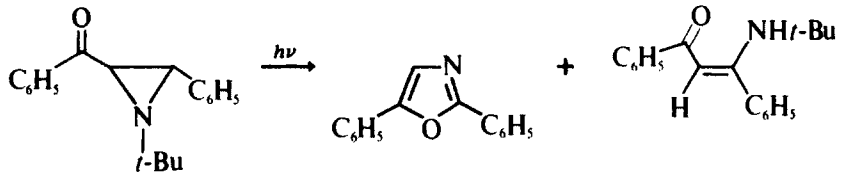
M. *Photochemistry of Aziridines*

General aspects of aziridine photochemistry have been reviewed.[845] The photochemistry of aziridinylketones has been extensively studied.[64,225,270,845-848] Initial $n \rightarrow \pi^*$ excitation of the ketone produces an excited state (depicted for convenience as **369**), which can partition itself in at least three ways (Scheme 3).

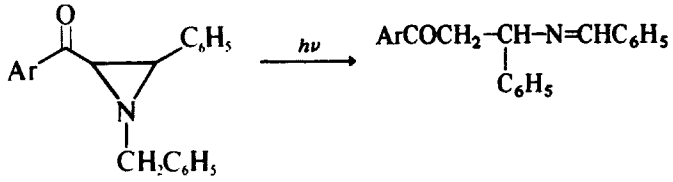


Scheme 3

For example, photolysis of **373** leads to **374** and **375**.[225,845] Product **375** is readily obtainable from **372** (path C). Cyclization of **370** and subsequent aromatization could account for **374** (path A). Photolysis of **376** yields **377** via structure **371** (path B).[347] The preceding is, of necessity, an abbreviated summary of the observed results.



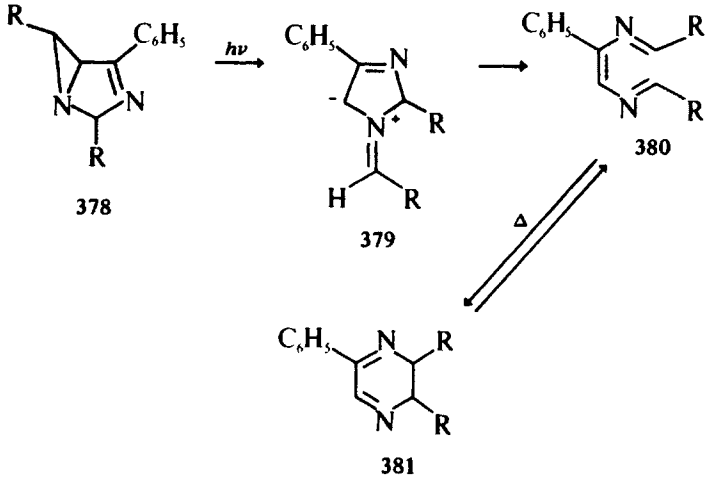
373 374 375



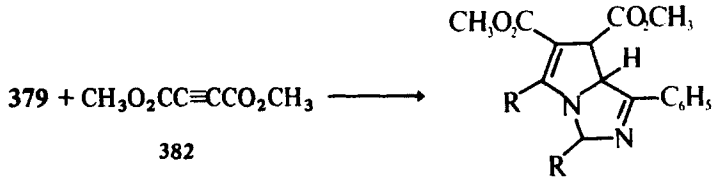
376 377

Stereochemistry of the aziridine and the nature of the solvent play critical roles in product distribution. Studies are further complicated by secondary thermal and photochemical reactions.

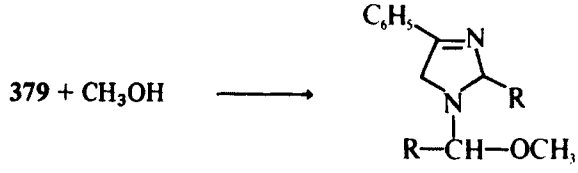
The photochemical behavior of some bicyclic aziridines of structure **378** is relatively well understood (Scheme 4).[269,270,608,755,759,849] Dipolar intermediate **379** has been trapped by **382** and by methanol to yield **383**.[608,755,759] Other products derived from **379–381** are also obtained.



378 379 380 381



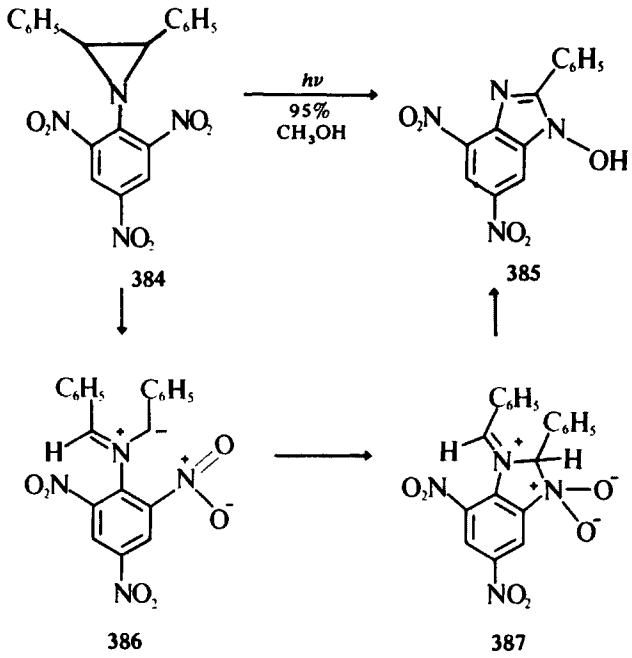
382



383

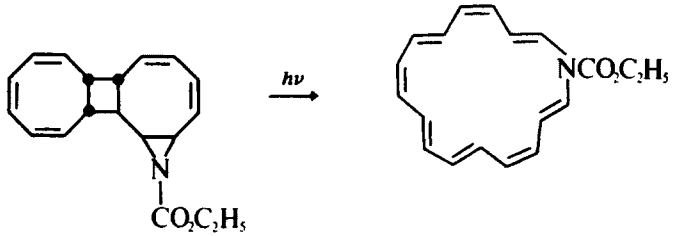
Scheme 4

A novel photochemical transformation of **384** has been observed.[850] Several mechanisms may be postulated, but intramolecular attack on azomethine ylid **386** might give **387**, which could in turn form **385**.

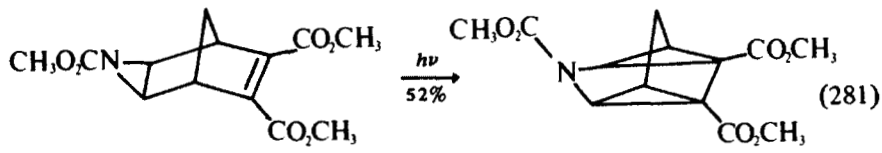


384 **385** **386** **387**

Several photochemical valence tautomerisms that involve the aziridine ring have been observed. Two of the more interesting are depicted in Eqs. 280 and 281.[805]



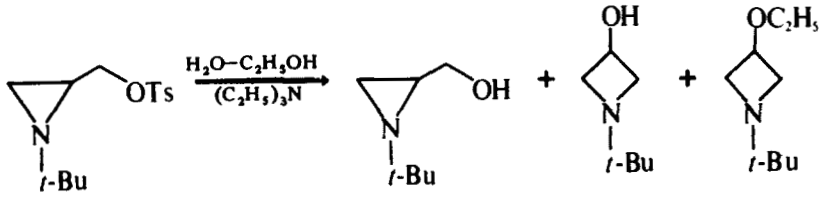
(280)



(281)

N. *Other Ring-Opening Reactions and Rearrangements*

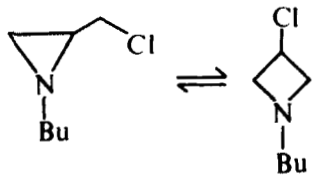
Solvolysis of tosylate **388** yields, in addition to aziridinyl alcohol (**389**), ring-expanded products **390** and **391**.[617] These products and the observed rates were explained in terms of the bicyclic intermediate **392**.



388 **389** **390** **391**

392

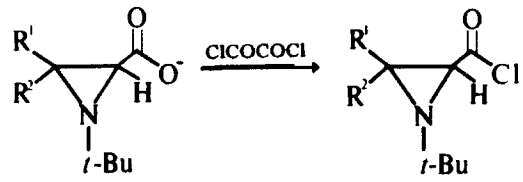
Equilibration of **393** and **394** in acetic acid has also been observed.[149]

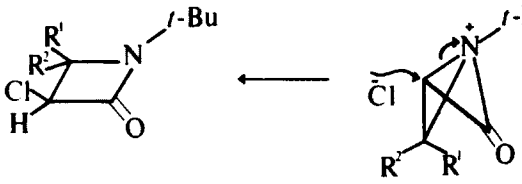


393 **394**

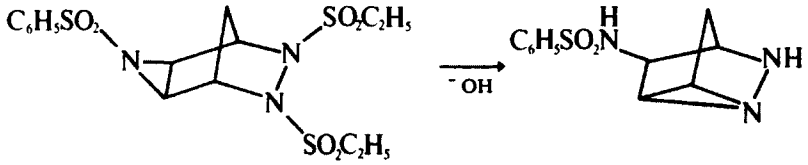
A nonclassical ion was proposed to account for the results. Intervention of **392** and/or ring-opened intermediates (in the acidic medium) were not excluded. An intermediate resembling **392** has been postulated in the ring expansion of aziridine carboxylates (Eq. 282). Evidence for the intermediate included the overall stereospecificity of the conversion.[165,166]

The aziridine ring itself is particularly susceptible to ring opening by internal nucleophiles. Among the more interesting examples are those illustrated in Eqs. 283[377] and 284.[601]

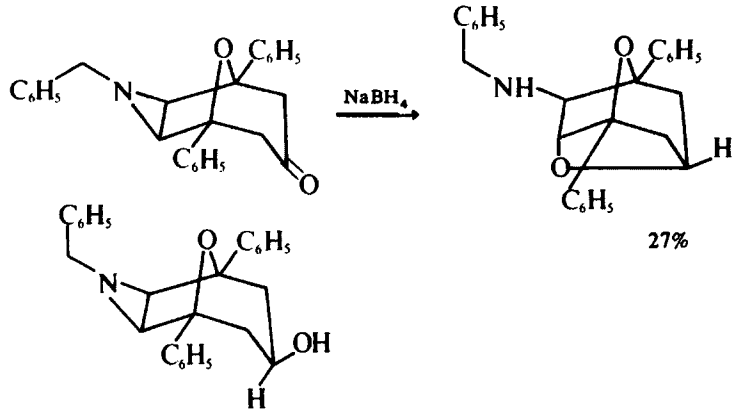




(282)

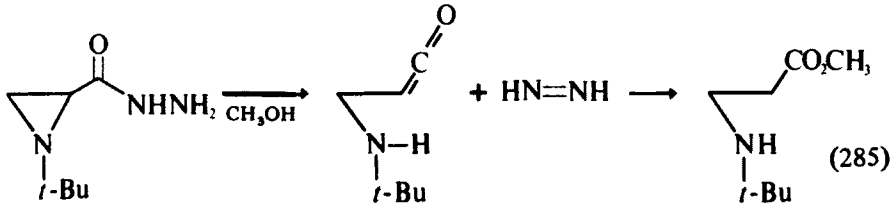


(283)



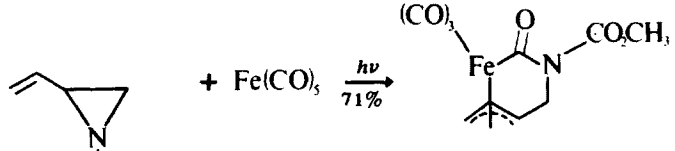
(284)

Neighboring group participation by hydrazones leads to pyrazole formation.[851] Several new examples have been reported.[162, 593] Aziridine hydrazides undergo an interesting fragmentation reaction that results in ring opening and diimide formation (Eq. 285).[852, 853]

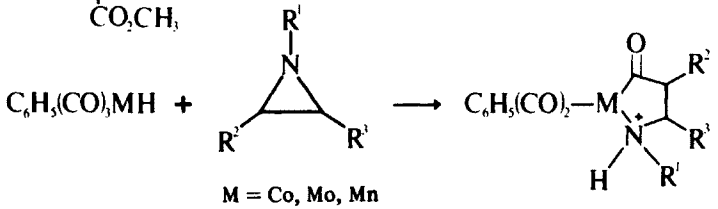


(285)

Transition metals have been inserted into the aziridine ring. Photochemical addition of $Fe(CO)_5$ takes the course indicated in Eq. 286.[854] Certain transition metal hydrides also insert into the aziridine ring (Eq. 287).[855, 856]



(286)

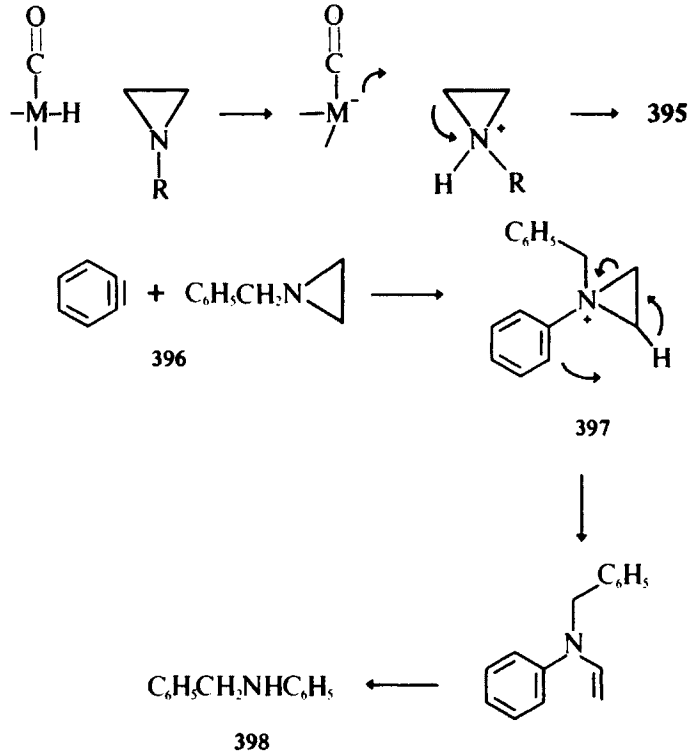


M = Co, Mo, Mn
$R^1 = CH_3$, H, *t*-Bu
$R^2 = C_6H_5$, CH_3, H

395

(287)

Stereochemical studies suggest that transfer of a proton is followed by bimolecular (inversion) attack on the ring with subsequent closure on the carbonyl (Eq. 288). Reaction of benzyne with **396** yields **398** via **397**.[857]



396

397

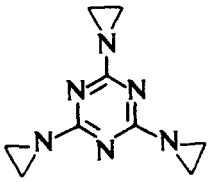
398

(288)

V. AZIRIDINES WITH BIOLOGICAL ACTIVITY

The strain and reactivity of the aziridine ring has led to the hope that these properties might be translated into useful biological activity. Efforts in this area have been summarized through 1969.[858] Most of the interest in the biological activity of aziridines has focused on those that chemically modify DNA. Aziridines that have this characteristic have been investigated for potential antitumor and insect chemosterilant activity.

Structures **399** (TEM), **400**, **401** (Trenimon), **402** (TEPA), **403** (Thio-TEPA), and **404** are among the synthetic compounds with useful antitumor activity.[352]



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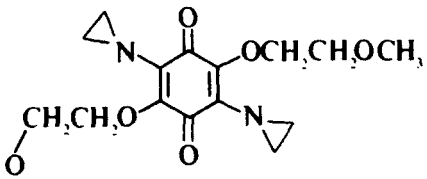
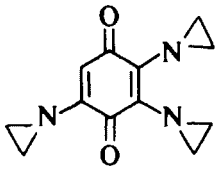
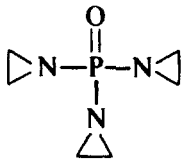


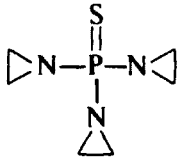
400



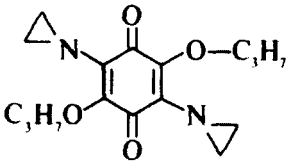
401



402

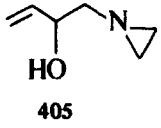


403

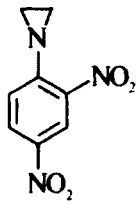


404

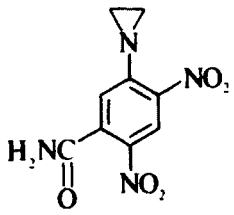
All these compounds possess two or more aziridine rings and are thus polyalkylating agents. It has been proposed that these compounds may owe their activity to their ability to cross-link DNA. It has also been suggested that the compounds with quinone rings may generate oxidizing agents (e.g., H_2O_2, O_2^-, $\cdot OH$) that degrade DNA. Some other active synthetic agents possess but a single aziridine moiety. Among these are **405** (Tetramin), **406** and **407**.[859]



405



406

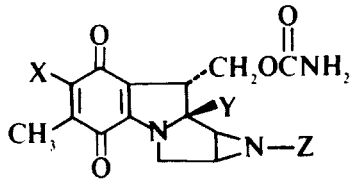


407

Some evidence suggests that these compounds are metabolically converted to dialkylating agents.[859] A large number of diaziridinyl quinones (related to **400**) have been reported.[352, 360–364] Other monoaziridines (related to **406** and **407**)

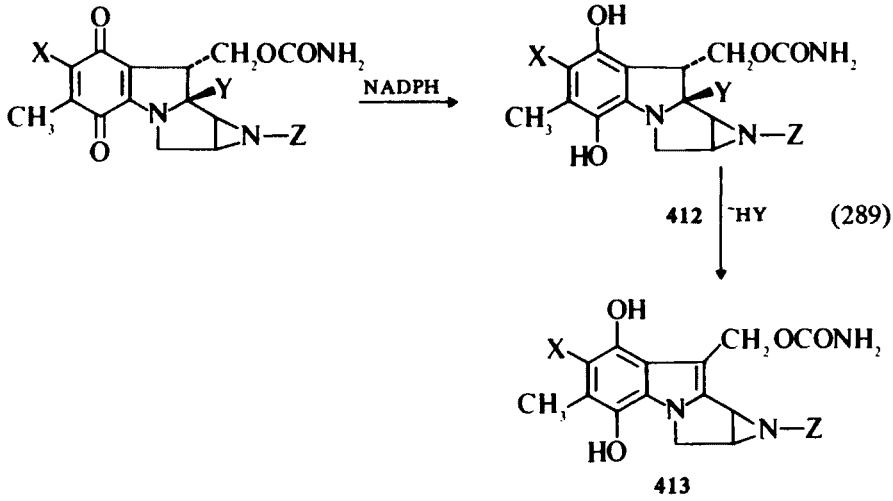
have been prepared and tested.[865, 866] Phosphorus-aziridinyl compounds have been the subject of several studies.[534-536, 538]

The naturally occurring mitosanes (**408–411**) show both antibiotic and antitumor activity.[867]



	X	Y	Z
408 (mitomycin A)	CH_3O	OCH_3	H
409 (mitomycin B)	CH_3O	OH	CH_3
410 (mitomycin C)	H_2N	OCH_3	H
411 (porfiromycin)	H_2N	OCH_3	CH_3

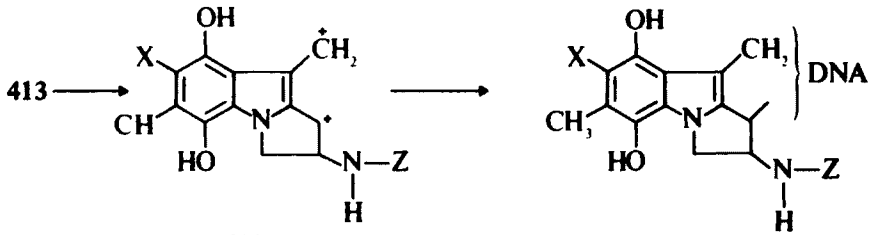
The mitosanes appear to be reductively converted to bifunctional alkylating agents (Eq. 289).[86, 868] The eliminated intermediate, **413**, can yield stabilized cations at two sites (**414**). Presumably the two positive charges of **414** are formed and consumed consecutively, not simultaneously.



(289)

In this manner cross-linking of DNA is possible (**415**). Ring opening via nucleophiles of unreduced mitosanes has also been demonstrated.[85] The generation of hydroxyl radicals from **412** has been proposed (Eq. 289).[869]

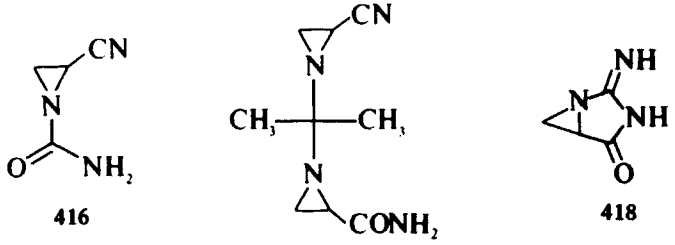
Support for this proposal was found in the inhibition of DNA cleavage by superoxide dimutase, catalase, and free-radical scavengers. It is interesting to note that other antitumor antibiotics (e.g., daunorubicin and adriamycin) appear to utilize pathways similar to Eq. 290.[870]



414 415

$$\begin{aligned} 412 + O_2 &\rightarrow 408\,H\cdot + HO_2\cdot \\ HO_2\cdot &\rightarrow H^+ + O_2^-\cdot \\ 2HO_2\cdot &\rightarrow H_2O_2 + O_2 \\ O_2^-\cdot + H_2O_2 &\rightarrow \cdot OH + O_2^- \end{aligned} \qquad (290)$$

Aziridine derivatives have attracted attention as potential insect chemosterilants.[858, 871] Applications to the boll weevil have been reviewed.[872] Recent research has revealed the immunomodulating characteristics of **416**[873] and **417**[874] as well as the immunostimulant tumour suppressant properties of **418**.[875]



416 417 418

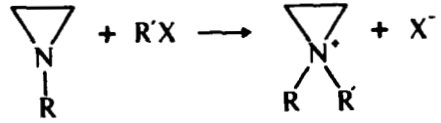
VI. AZIRIDINIUM SALTS

1. Introduction

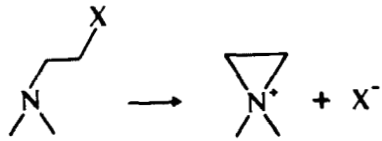
The lability of the aziridinium ion toward ring opening does not preclude isolation of aziridinium salts under the proper conditions. As noted in a review (1969),[876] isolation is facilitated by use of weakly nucleophilic anions (e.g., ClO_4^-, BF_4^-), mild conditions, and appropriate substituents. Aziridinium salts can be distinguished from ring-opened and dimeric salts by nmr spectroscopy and their reaction with $Na_2S_2O_3$. The latter reagent is specific for aziridinium salts[877–879] and forms the basis for quantitative analysis of the aziridinium ring. The nmr spectra of numerous aziridinium salts have been reported and the ring protons are upfield relative to comparable larger cyclic and acyclic protons.[876, 877, 880]

2. Synthesis

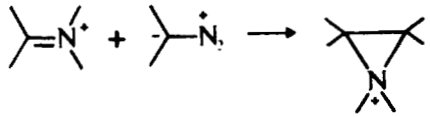
Three approaches to the synthesis of relatively stable aziridinium salts have proved to be fruitful. Direct protonation or alkylation is potentially the most versatile when the reaction conditions are mild (Eq. 291). Gabriel-type cyclization of β-tertiary amino halides has been utilized frequently (Eq. 292). The third procedure, additions of diazomethane to an iminium salt, is successful in many instances (Eq. 293).



(291)

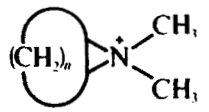


(292)



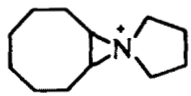
(293)

Direct alkylation and protonation has resulted in the monocyclic salts listed in Table 83 and in a recent reference.[884] Most alkylations have utilized CH_3I or the most reactive "magic" methyl (CH_3OSO_2F). A large number of bicyclic salts (**419**) have been prepared and have received x-ray crystallographic structural confirmation.[100, 102, 885-889] The interesting spiro salt **420** has been prepared from the aziridine and 1,4-diiodobutane.[885] The stereochemistry of aziridine alkylation has been the subject of a recent extensive discussion.[884]



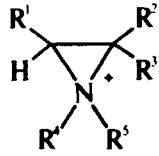
419

$n = 5, 6, 8, 10$, etc.



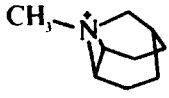
420

TABLE 83. AZIRIDINIUM SALTS PREPARED FROM AZIRIDINES VIA ALKYLATION

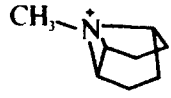


R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
i-Pr	CH_3	H	CH_3	CH_3	50	878
CH_3	CH_3	H	CH_3	CH_3	–	881
CH_3	CH_3	H	CH_3	CH_3	> 90	879
C_2H_5	CH_3	H	CH_3	CH_3	> 90	879
i-C_3H_7	CH_3	H	CH_3	CH_3	> 90	879
t-Bu	CH_3	H	CH_3	CH_3	> 90	879
CH_3	H	CH_3	CH_3	CH_3	> 90	879
C_2H_5	H	CH_3	CH_3	CH_3	> 90	879
i-C_3H_7	H	CH_3	CH_3	CH_3	> 90	879
t-Bu	H	CH_3	CH_3	CH_3	> 90	879
CH_3	H	CH_3	CH_3	H	> 90	879
C_2H_5	H	CH_3	C_2H_5	H	> 90	879
i-C_3H_7	H	CH_3	*i*-C_3H_7	H	> 90	879
t-Bu	H	CH_3	*t*-Bu	H	> 90	879
m-BrC_6H_4	H	H	CH_3	CH_3	82	882
p-BrC_6H_4	H	H	CH_3	CH_3	88	882
C_6H_5	H	H	CH_3	CH_3	89	882
p-$CH_3C_6H_4$	H	H	CH_3	CH_3	91	882
$CO_2C_2H_5$	H	H	CH_3	CH_3	90	883
$CO_2C_2H_5$	H	H	*t*-Bu	CH_3	95	883
CO_2CH_3	CH_3	H	CH_3	CH_3	90	883
CO_2CH_3	H	CH_3	CH_3	CH_3	90	883
CN	H	H	CH_3	CH_3	60	883
COC_6H_5	H	H	CH_3	CH_3	90	883
CH_2OH	H	H	*t*-Bu	CH_3	85	883

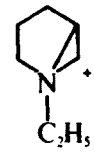
The tricyclic salts **421**[890] and **422**[444] are readily prepared by aziridine alkylation with methyl iodide. These salts are unexpectedly stable. Alkylation with $EtClO_4$ yielded strained aziridinium salt **423**.[891, 892]



421



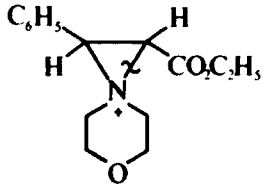
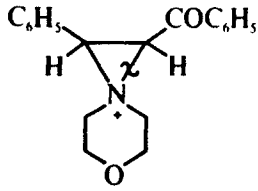
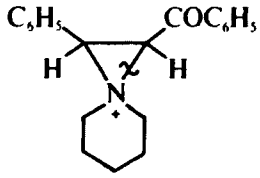
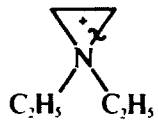
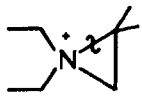
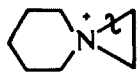
422



423

Many aziridinium salts have been synthesized in good yields from the internal alkylation of amines in the presence of $AgClO_4$. The entries in Table 84 indicate the scope of this method. The same aziridinium ion (**424**) was isolated from the reaction of two allylic isomers.[895]

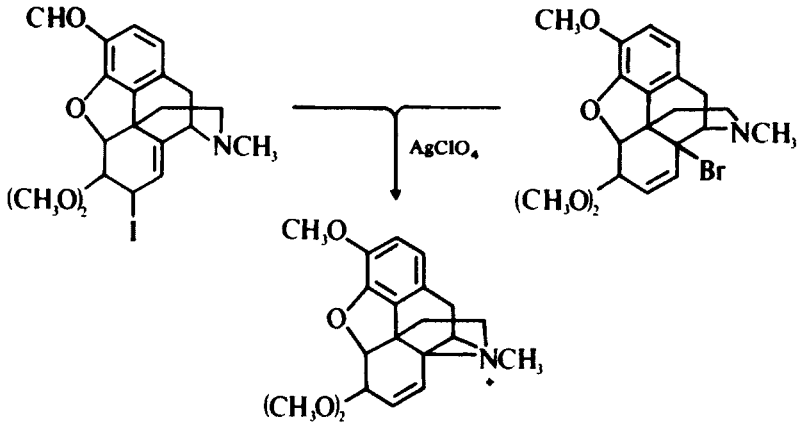
TABLE 84. AZIRIDINIUM SALTS VIA INTERNAL ALKYLATION[a]

Salt	Yield (%)	Ref.
	88	893
	79	893
	61	893
	94	894
	98	894
	73	894
	–	894

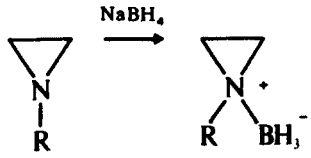
[a] The anion, in each case, is ClO_4^-. The wavy lines indicate the bonds closed in the alkylation step.

Reaction of simple aziridines with $NaBH_4$ has been shown to result in nitrogen-boron bond formation (Eq. 294).[896]

Addition of diazoalkanes is the newest of the three approaches.[876] The procedure is simple and the reactions are usually very clean. The reaction apparently proceeds in two steps (Eq. 295).

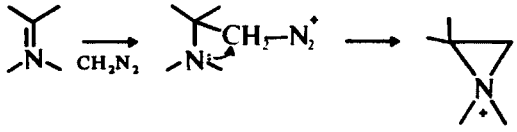


424



(294)

R = H, CH_3 (42%)

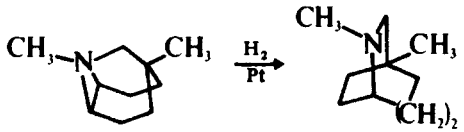


(295)

The precursor iminium salts are readily available and often can be prepared from direct reaction of ammonium salt and carbonyl compound. The compounds prepared by this method are found in Table 85. The method is limited to simple diazoalkanes, and in some cases the product reactivity precludes isolation.[902]

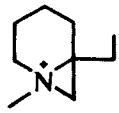
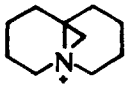
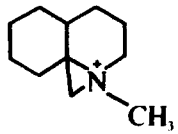
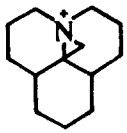
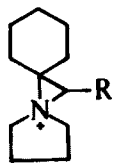
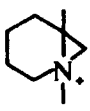
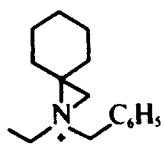
3. Reactions

Isolation of aziridinium salts permits the introduction of additional reagents and observation of chemistry not possible when they are unisolated reaction intermediates. Hydrogenation of aziridinium salts has been reported in several instances (425–428).

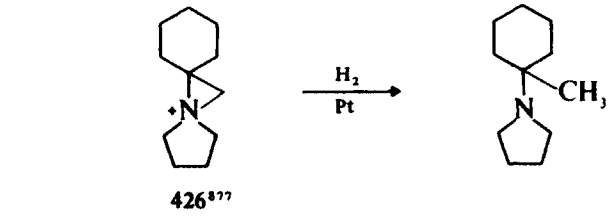


425[442]

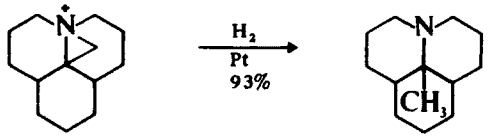
TABLE 85. AZIRIDINIUM SALTS FROM DIAZOALKANE ADDITION TO IMINIUM SALTS

Salt	Yield (%)	Ref.
	93	897
	87	898
	90	898
	90	898
	72	898
	93 (R = H) 40 (R = CH_3) 52 (R = C_2H_5)	877 877 877
	84	899
	90	900
	–	901

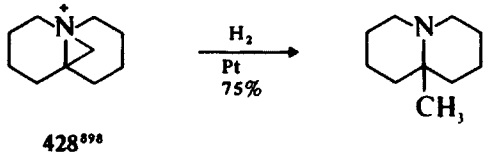
A large number of aziridinium salts have been subjected to direct nucleophilic displacement with concomitant ring opening.[876, 877, 898, 903] The potential complexity of the reaction is illustrated by the following example (Eq. 296).[876]



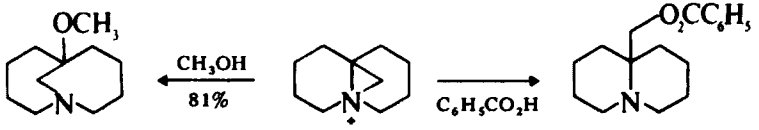
426[877]



427[898]

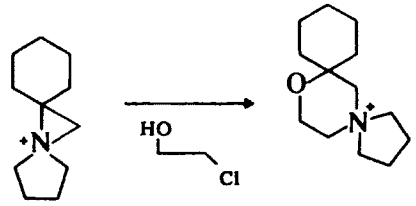


428[898]



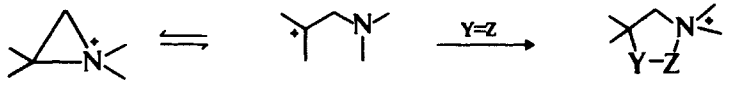
(296)

The dichotomy is reminiscent of S_N1 vs. S_N2 displacements and probably has a similar explanation. Bifunctional reagents can lead to novel heterocycles (Eq. 297).[877]



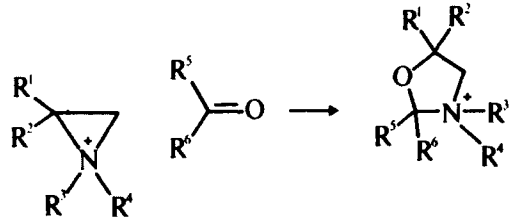
(297)

The aziridinium salt is apparently in equilibrium with an amino carbonium ion under the reaction conditions. This ion is captured by the oxygen before nucleophilic attack by the nitrogen on carbon (Eq. 298).[904] This two-step ring opening–



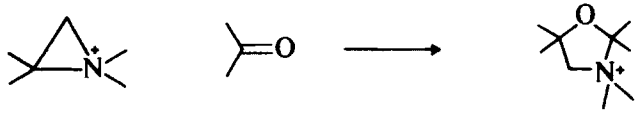
(298)

TABLE 86. REACTION OF AZIRIDINIUM SALTS WITH KETONES AND ALDEHYDES



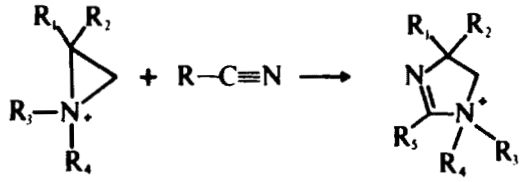
R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	Ref.
CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	55	897
CH_3	CH_3	CH_3	CH_3	$(CH_2)_4$		60	897
CH_3	CH_3	CH_3	CH_3	$(CH_2)_5$		52	897
CH_3	CH_3	CH_3	CH_3		$(CH_2)_2$	60	897
CH_3	CH_3	CH_3	CH_3	C_6H_5	CH_3	27	897
CH_3	CH_3	CH_3	CH_3	$(CH_2)_2$		73	897
CH_3	CH_3	CH_3	CH_3	CH_3	CH	47	897
$(CH_2)_5$		$(CH_2)_4$		CH_3	CH_3	81	897
$(CH_2)_5$		$(CH_2)_4$		$(CH_2)_2$		52	897
$(CH_2)_5$		$CH_2C_6H_5$	CH_2CH_3	CH_3	CH_3	40	897
$(CH_2)_5$		$CH_2C_6H_5$	CH_2CH_3	$(CH_2)_4$		32	897
$(CH_2)_5$		$CH_2C_6H_5$	CH_2CH_3	$(CH_2)_5$		44	897
CH_3	CH_3	CH_3	CH_3	C_6H_5	H	57	899
CH_3	$(CH_2)_4$		CH_3	C_6H_5	H	59	899
CH_3	$(CH_2)_4$		CH_3	CH_3	CH_3	12	899
p-BrC_6H_4	H	CH_3	CH_3	C_6H_5	H	70	904
p-ClC_6H_4	H	CH_3	CH_3	C_6H_5	H	74	904
p-$CH_3C_6H_4$	H	CH_3	CH_3	C_6H_5	H	78	904
$(CH_2)_5$		$(CH_2)_5$		C_6H_5	H	54	905
$(CH_2)_5$		C_3H_7	C_3H_7	C_6H_5	H	66	905
$(CH_2)_5$		C_2H_5	$CH_2C_6H_5$	C_6H_5	H	47	905
$(CH_2)_5$		$(CH_2)_4$		C_6H_5	H	55	905
$(CH_2)_5$		$(CH_2)_4$		C_6H_5	H	55	905
$(CH_2)_5$		$(CH_2)_4$		p-$CH_3C_6H_4$	H	67	905
$(CH_2)_5$		$(CH_2)_4$		p-$CH_3OC_6H_4$	H	44	905
$(CH_2)_5$		$(CH_2)_4$		o-$CH_3OC_6H_4$	H	40	905
$(CH_2)_5$		$(CH_2)_4$		p-$(CH_3)_2NC_6H_4$	H	67	905
$(CH_2)_5$		$(CH_2)_4$		p-BrC_6H_4	H	68	905
$(CH_2)_5$		$(CH_2)_4$		2,6-Cl_2-C_6H_3	H	13	905
$(CH_2)_5$		$(CH_2)_4$		2,3-$(CH_3O)_2C_6H_3$	H	55	905
$(CH_2)_5$		$(CH_2)_4$		2-C_4H_3O	H	59	905

ring closure procedure is quite general and useful. Reactions involving ketones, aldehydes (Eq. 299),[897, 899, 904, 905] nitriles (Eq. 300),[899, 900, 906] and nitrones (Eq. 301)[899, 907] have also been described (Tables 86, 87, and 88, respectively).

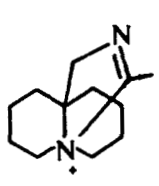


(299)

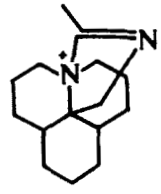
TABLE 87. REACTION OF AZIRIDINIUM SALTS WITH NITRILES



R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
$(CH_2)_5$		C_2H_5	$CH_2C_6H_5$	CH_3	57	900
$(CH_2)_5$		C_2H_5	$CH_2C_6H_5$	C_2H_5	43	900
CH_3	CH_3	CH_3	CH_3	CH_3	37	899
CH_3	$(CH_2)_4$		CH_3	CH_3	49	899



22%[899]

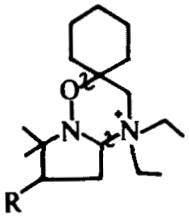


58%[899]

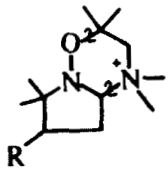
One of the most useful reactions of aziridinium ions is illustrated in Eq. 302.[901]

The decomposition of the ylid is analogous to other aziridine-to-alkene decompositions. The overall sequence converts a ketone to a methylene group. All the steps go in high yield, and in some cases results superior to those obtained by the

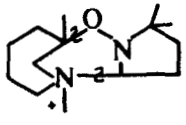
TABLE 88. REACTION OF AZIRIDINIUM SALTS WITH NITRONES



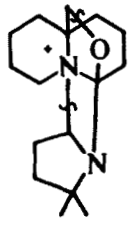
$R = CH_3$ (84%)[907]
$R = H$ (89%)[907]



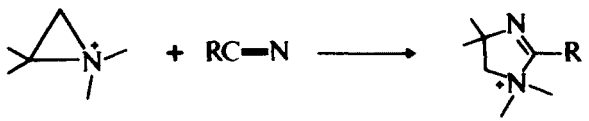
76%[883,907]
80%[907]



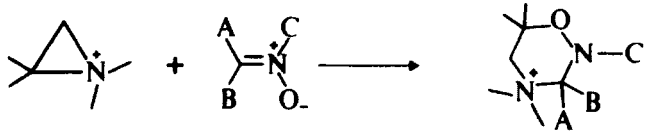
68%[899]



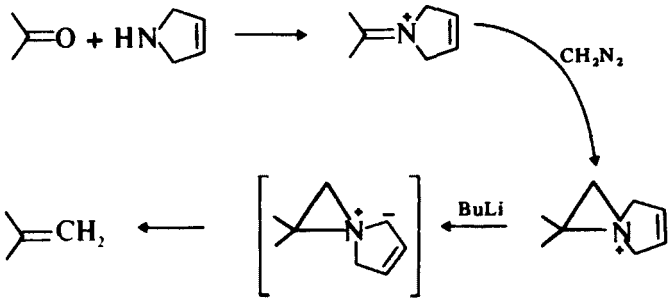
58%[899]



(300)



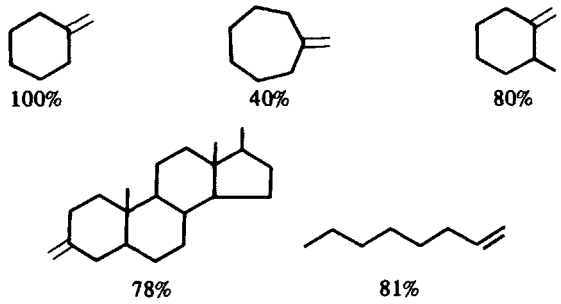
(301)



(302)

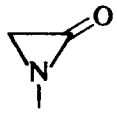
Wittig reactions have been reported. It is interesting that the aziridinium ring does not suffer competitive deprotonation. The yields for the deprotonation of the spiro salts are shown in Table 89.

TABLE 89. YIELDS OF METHYLENE COMPOUNDS FROM SPIRO-UNSATURATED AZIRIDINIUM IONS[901]



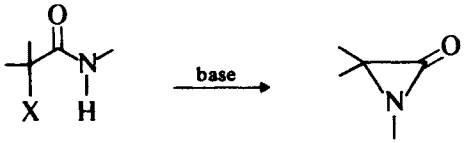
VII. α-LACTAMS (AZIRINONES)

The structural features of α-lactams **(429)** have stimulated considerable synthetic and chemical activity. In principle there are two obvious routes to this ring system based on "Favorskii-type" reactions.[908]

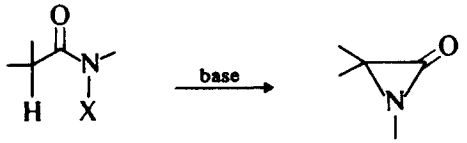


429

The approach of Eq. 303 has predominated over that of Eq. 304 in all the recent literature. Apparently the milder conditions required for deprotonation in the former make it the method of choice.

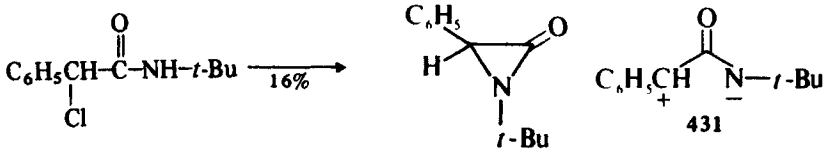


(303)



(304)

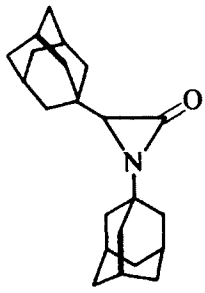
The routine assignment of structures to α-lactams is based on the infrared absorption of the carbonyl group between 1830 and 1850 cm^{-1}.[909–911] The optical activity of α-lactam **430** excludes mesoionic formulation **431** as a precursor or as a readily accessible intermediate.[912]



(optically active) (optically active)

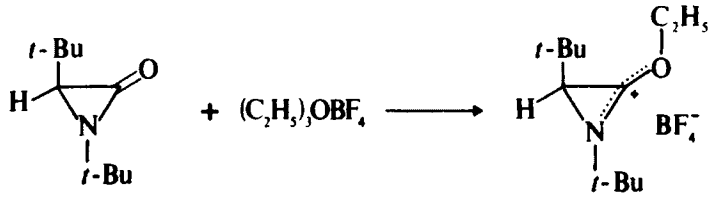
430 431

An x-ray structure analysis of **432** revealed a number of interesting features.[913] In contrast to β- and larger lactams, the nitrogen atom was found to be pyramidal, not planar.



432

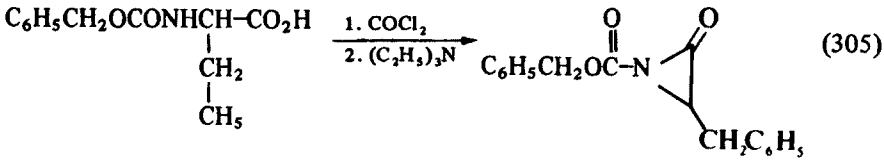
In spite of this, the N_1-C_2 bond length was indicative of some double bond character. As would be expected, the two bulky groups were *trans* to each other. Salts of α-lactams have been prepared and assigned structure **433**.[914] The salts were extremely unstable and the evidence (ir spectra) does not rule out acyclic alternatives.



433

The topic of α-lactam stability has been the subject of some speculation. For example, a review article has pointed out that bulky substituents at C-1 and N-3 impart stability.[915] This is at least partly due to steric inhibition of nucleophilic attack on the carbonyl by the bulky substituents. Both *t*-butyl and adamantyl groups have been favorite substituents. Tables 90 and 91 summarize some of the recently synthesized α-lactams.

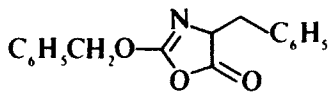
At least one proposed α-lactam structure has not withstood chemical and spectral scrutiny. The reaction depicted in Eq. 305 resulted in a product to which structure **434** was assigned.[930–932]



(305)

434

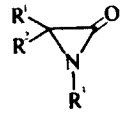
The ir absorption at 1840 cm^{-1} and the retained optical activity were offered in support of this structure. Application of ^{13}C nmr on unlabeled and ^{15}N-labeled compounds conclusively excluded **434** and supported structure **435**.[933]



435

The thermal chemistry of α-lactams has been a source of considerable interest because of the apparent relationship to methylene cyclopropene. The thermal products (Eq. 306) include an aldehyde or ketone plus an isocyanide.[910, 917, 925, 926, 934, 935]

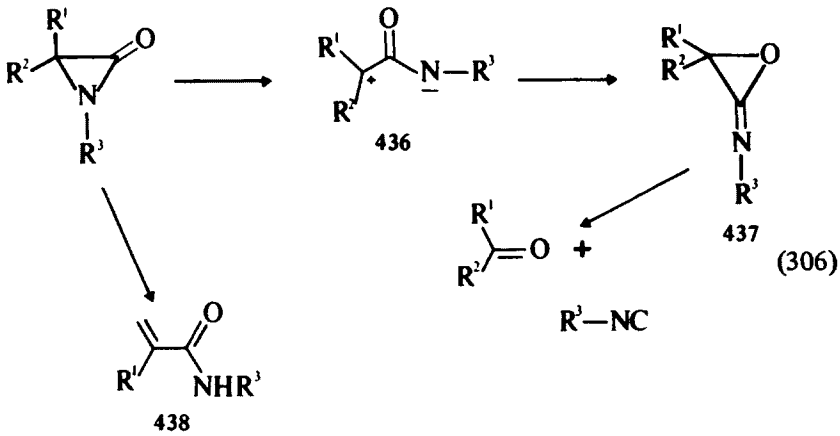
TABLE 90. α-LACTAMS[a]



R^1	R^2	R^3	Yield (%)	Ref.
C_6H_5	H	*t*-Bu	31	909
t-Bu	H	*t*-Bu	68	910
1-Ada	H	1-Ada	90	911
t-Bu	H	1-Ada	65	916
1-Ada	H	*t*-Bu	96	917
1-(3-CH_3-Ada)	H	*t*-Bu	97	917
1-(3,5-di-CH_3-Ada)	H	*t*-Bu	97	917
1-(3,5,7-tri-CH_3-Ada)	H	*t*-Bu	98	917
2-Ada		*t*-Bu	–	98
2-Ada		1-Ada	–	98
1-Ada	H	1-Ada	–	919
C_6H_5	CF_3	*t*-Bu	–[d]	920
C_6H_5	*t*-Bu	*t*-Bu	52	921
C_6H_5	H	2-Ada	50	922
C_6H_5	H	1-Ada	55	922
1-CH_3-1-c-pent[b]	H	*t*-Bu	77	923
1-CH_3-1-c-hex[c]	H	*t*-Bu	91	923
$(CH_2)_5$		*t*-Bu	80	924
$(CH_2)_8$		*t*-Bu	21	924
CH_3	CH_3	*t*-Bu	45	925
p-$CH_3C_6H_4$	H	*t*-Bu	–	926

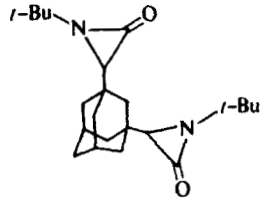
[a] 1-Ada = 1-adamantyl, etc.
[b] c-pent = cyclopentyl.
[c] c-hex = cyclohexyl.
[d] From *N*-haloamide.

When R^2 contains a β-hydrogen, elimination to give products of structure **438** have been observed.[925] It is not known whether **437** is produced directly or via

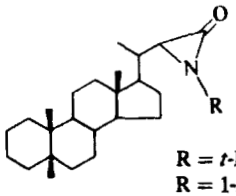


(306)

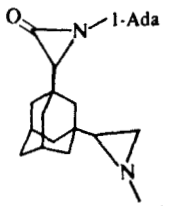
TABLE 91. α-LACTAMS



76%[927,928]

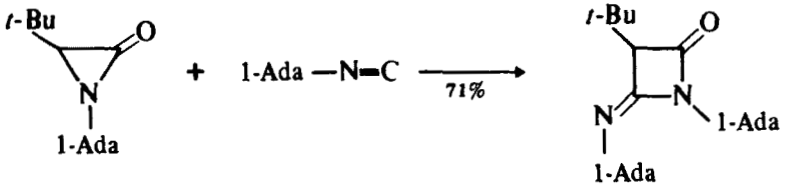


R = t-Bu (80%)[929]
R = 1-Ada (45%)[929]



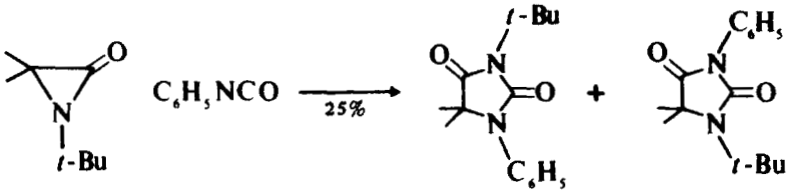
60%[928]

436. The fact that a [3 + 1] cycloaddition product is formed in Eq. 307 suggests that **436** is attainable.

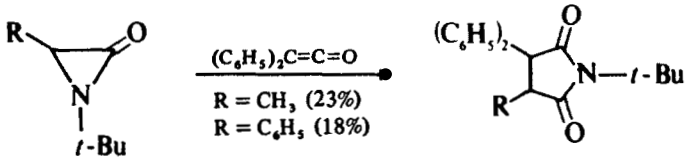


(307)

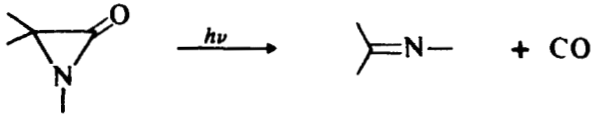
Thermal cycloadditions of the sorts exemplified by Eqs. 308[930] and 309[937] also support the concept of an interceptable **436**. Photolyses of α-lactams take a different course in that decarbonylation occurs without molecular reorganization (Eq. 310).[923,938]



(308)

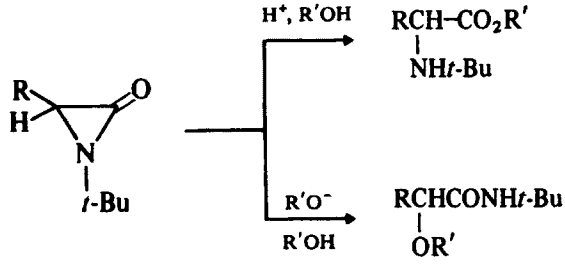


(309)



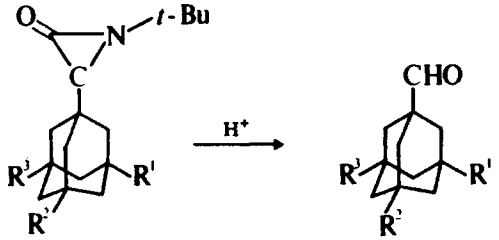
(310)

Acid- or base-catalyzed ring opening of α-lactams can give results that are highly dependent on conditions and α-lactam structure. The reactions of Eq. 311 are illustrative.[909,910]



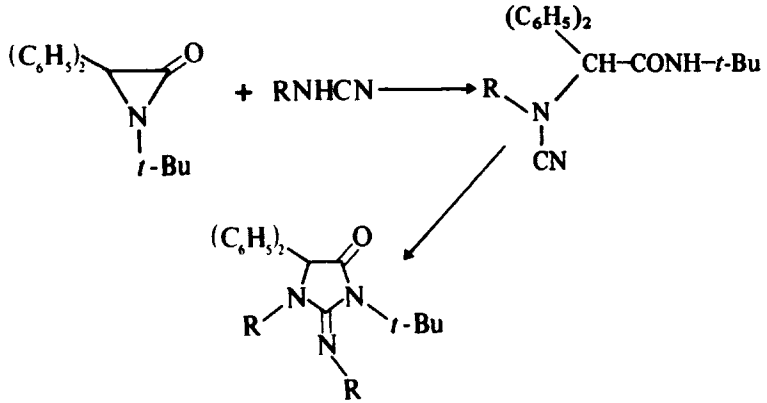
(311)

The difference in reaction course appears to depend on whether the first step is nucleophilic attack on the carbonyl group or proton-catalyzed ring opening. In contrast, the compounds of Eq. 312 give aldehydes in high yield.[917,934,939]



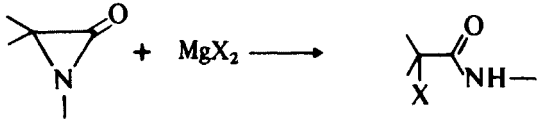
(312)

The reactions proceed via hydrolysis of an initially formed (by loss of CO) imine. The difference between the reactions of Eqs. 311 and 312 probably stems from the bulk and the modest electron-releasing ability of the adamantane ring. An interesting application of the α-lactam reactivity to heterocyclic synthesis is found in Eq. 313.[940]



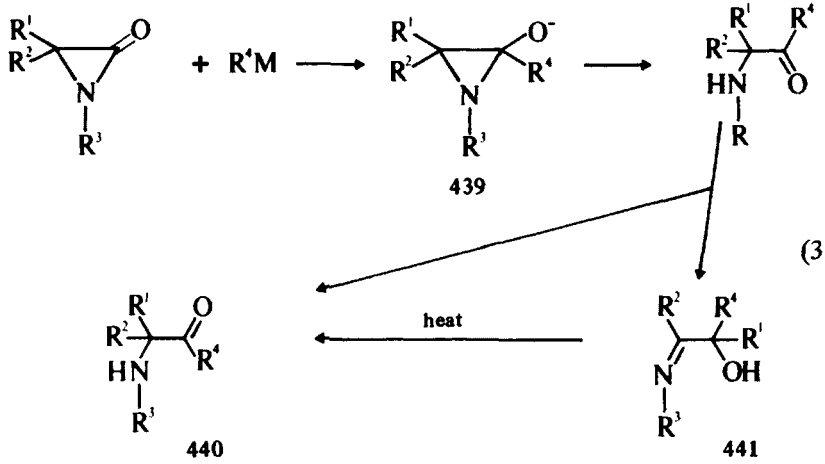
(313)

The initially formed product undergoes spontaneous or base-catalyzed cyclization. The yields are quite satisfactory. The one reported reaction of an α-lactam with $LiAlH_4$ proceeds as shown in Eq. 314.[941]



(314)

Perhaps the most confusing part of all literature on α-lactam chemistry concerns the reactions of these compounds with organometallics. The definitive paper in this area delineates the areas of conflict and their resolution.[942] In brief, α-lactams may undergo prior ring opening (Eq. 314) by metal halides present in the reaction.[942–945] Thus, some of the chemistry reported may be due to reactions with these haloamides. The initial adduct **439** can yield a product capable of following at least two paths (Eq. 315).



(315)

The product can thus often be determined by reaction conditions, ratios of reactants, and method of isolation. The final products are capable of interconverting during isolation (**441** → **440**). Spectral structural assignment to these closely related compounds is fraught with ambiguity.

Finally, some products reported[946] do not equate with those isolated from repeated reactions[942] and/or independent synthesis.[947] When the ring opening by halide (Eq. 314) is suppressed, formation of **440** and/or **441** predominates. Organometallic additions of α-lactams are summarized in Table 92.

A recently reported reaction of α-lactams that has theoretical interest is the reaction of an α-lactam with *m*-chloroperbenzoic acid, resulting in the quantitative production of an oxaziridine (**442**). The *N*-oxide **443** has been suggested as an intermediate, but the details of the subsequent conversion to **442** are obscure.[951]

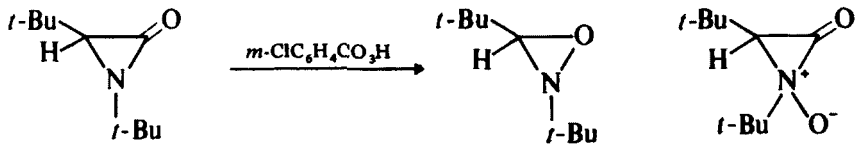
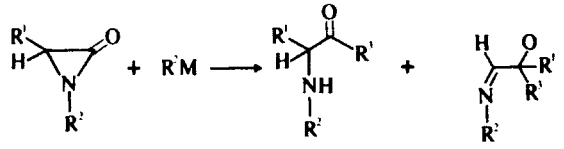


TABLE 92. REACTIONS OF α-LACTAMS WITH ORGANOMETALLIC REAGENTS

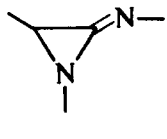


				Yield (%)			
R^1	R^2	R^3	M	A	B	Note[a]	Ref.
t-Bu	*t*-Bu	C_6H_5	MgBr	–	100		942
t-Bu	*t*-Bu	C_6H_5	Li	67	33	(Excess RM)	942
1-Ada	*t*-Bu	*t*-Bu	Li	–	77		948
t-Bu	1-Ada	*t*-Bu	Li	–	> 75		948
t-Bu	*t*-Bu	*t*-Bu	Li	–	> 75		948
1-Ada	1-Ada	*t*-Bu	Li	–	> 75		948
1-Ada	1-Ada	CH_3	Li	67	–	low T	949
1-Ada	1-Ada	*i*-Pr	Li	72	–	low T	949
1-Ada	1-Ada	*t*-Bu	Li	80	–	low T	949
1-Ada	1-Ada	C_6H_5	Li	64	–	low T	949
i-Bu	1-Ada	CH_3	Li	65	–	low T	949
t-Bu	1-Ada	*i*-Pr	Li	92	–	low T	949
t-Bu	1-Ada	*t*-Bu	Li	69	–	low T	949
t-Bu	1-Ada	C_6H_5	MgBr	Major	–		950

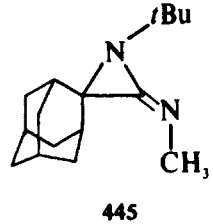
[a] T = temperature.

VIII. AZIRIDINE IMINES

The analogous aziridine imines (**444**) are a recent addition to heterocyclic literature. One such compound (**445**) has been studied by x-ray crystallography and found to also have a pyrimidal nitrogen.[952]

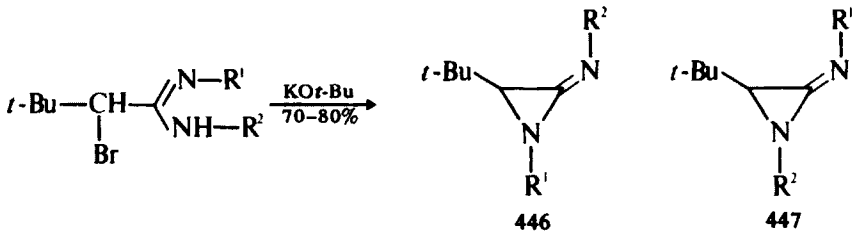


444



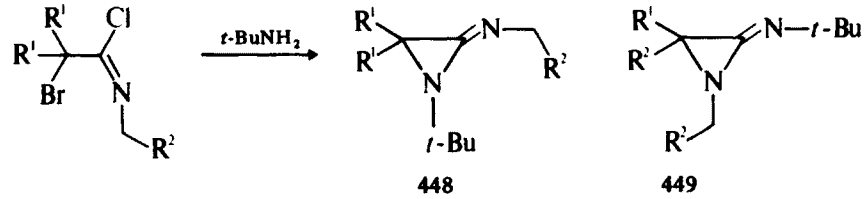
445

The first reported synthesis (Eq. 316) utilized an approach analogous to that which has been so successful with α-lactam preparations.[953] In all cases mixtures of isomers (**446** and **447**) were obtained.



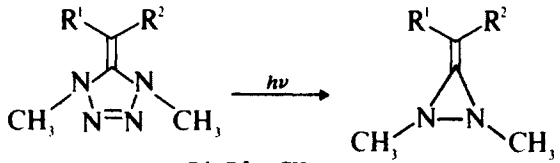
a. $R^1 = R^2 = CH_3$
b. $R^1 = CH_3$; $R^2 = t$-Bu
c. $R^2 = t$-Bu; $R = CH_3$ (316)

Interconversion of these isomers was observed as well as thermal decomposition (> 50°) to imines and isocyanide. No products were obtained that were suggestive of valence tautomerism. In contrast to these results, a later publication of a modified synthetic approach yielded products **448** and **449**.[954]

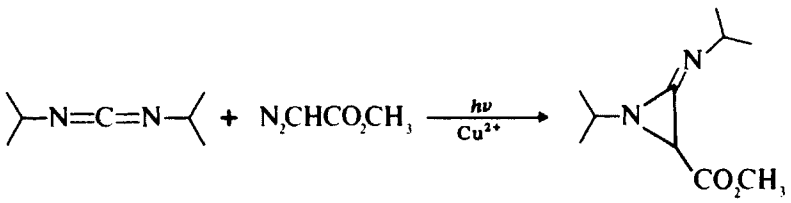


	R^1	R^2	Yield (%)	Ratio of 448 to 449
a	H	CH_3	71	92:8
b	*t*-Bu	CH_3	90	40:60
c	H		80	– :100

Subsequent thermolysis of **448a** and **448b** gave, besides $R'CH_2N{\equiv}C$, some products from the decomposition of **449a** and **449b**. This result indicates that valence tautomerism between the two structures can take place at a rate that is competitive with decomposition. The reverse (**449** → **448**) was not observed. More work is needed to reach an understanding of the structural features required for such isomerizations. Two photochemical routes to aziridine imines have also been reported. The first involves photolysis of methylene tetrazolines (Eq. 317).[955] The second route involves the addition of a carbene to a diimide (Eq. 318).[956]



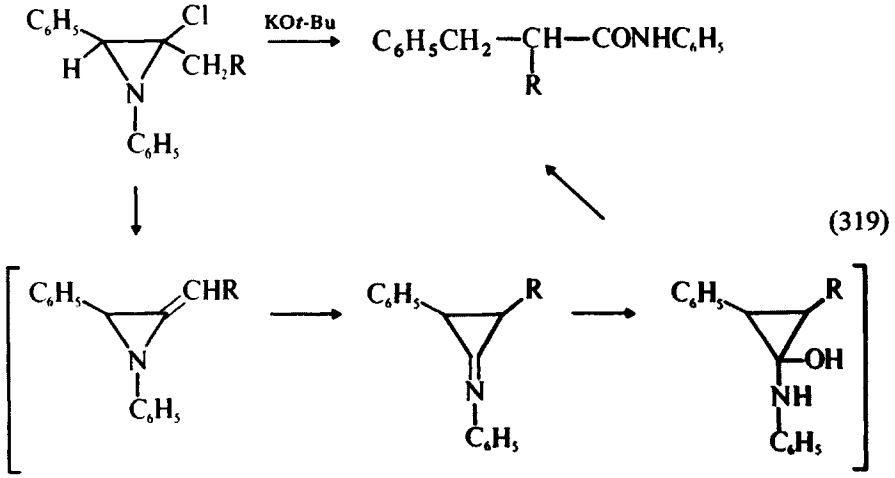
$R^1, R^2 = CH_3$
$R^1 = CH_3$
$R^2 = t$-Bu (317)



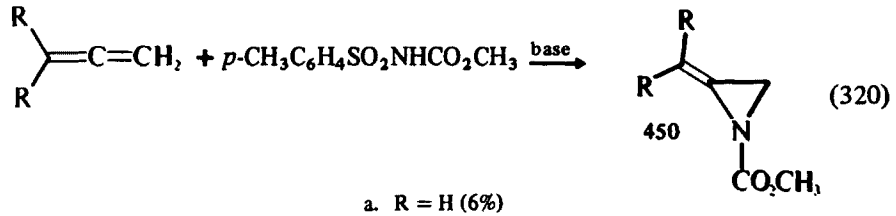
(318)

IX. METHYLENE AZIRIDINES

The publication of the reaction and proposed mechanism shown in Eq. 319 stimulated a search for other substituted methylene aziridines.[957] Addition of a nitrene to allenes produced the results shown in Eq. 320.[958]



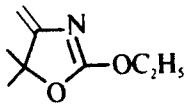
(319)



(320)

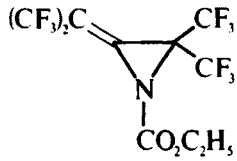
a. R = H (6%)
b. R = CH_3 (8%)

The enlarged heterocycle **451** was sole product of thermolysis of **450b**. No valence tautomerism was observed.



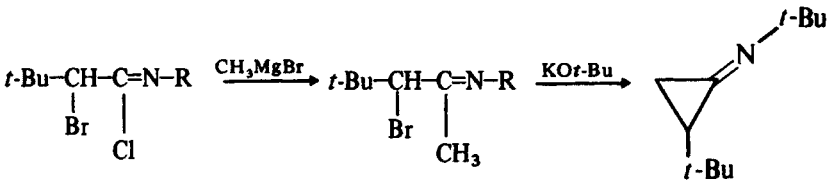
451

Similar addition of carbethoxynitrene to a fluorinated allene produced **452**.[959] Tetramethylallene does not, however, undergo such addition.[958]



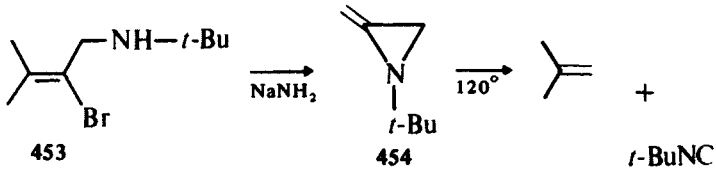
452

Two synthetic routes to iminocyclopropenones are shown in Eq. 321.[960] Again, no valence tautomerism of this product to a methylene aziridine was observed.



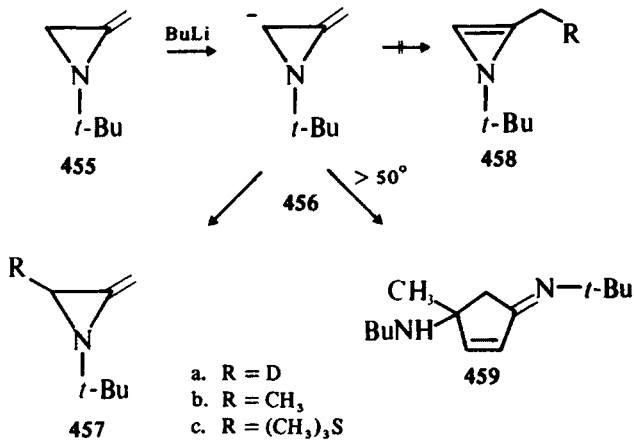
(321)

In contrast, the methylene aziridine **454** did yield decomposition products indicative of valence tautomerism.[961]



453 **454**

The reaction of methylene aziridine **455** with BuLi yielded the anion **456** at $-78°$.[962] This anion reacts at $-78°$ with various electrophiles to give high yields of **457a–457c**. No products of the antiaromatic type **458** were detected. Above 50° the product **459** is produced in 36% yield, and a reasonable but complex multistep mechanism for its formation was proposed.

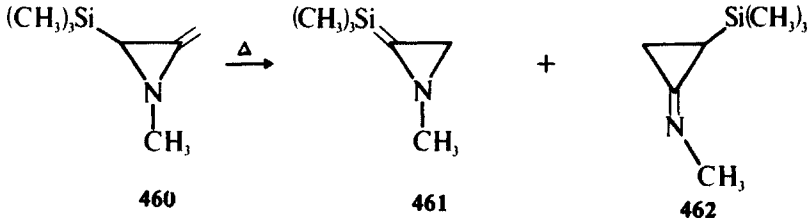


455 **458** **456** **459**

457

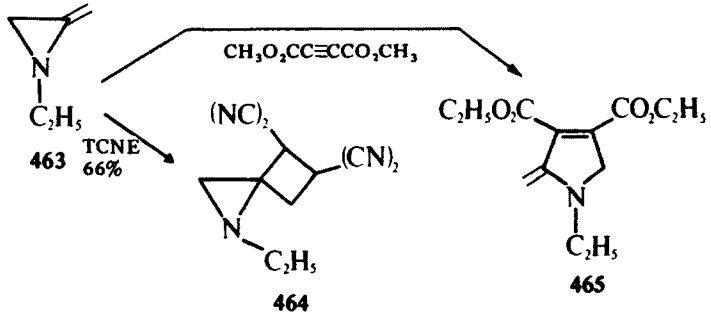
a. R = D
b. R = CH_3
c. R = $(CH_3)_3S$

Product **460** was produced in optically active form when a chiral amine was used in the deprotonation step.[963] Thermolysis of **460** resulted in the valence tautomers **461** and **462**.



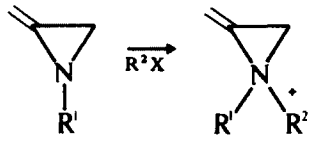
460 **461** **462**

A detailed kinetic analysis of these reactions was presented, and high stereospecificity in the formation of **462** noted.



463 **464** **465**

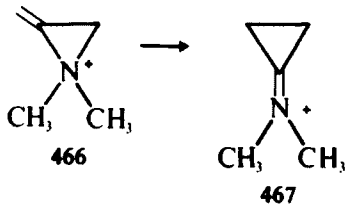
Addition of tetracyanoethylene to a methylene aziridine **463** yielded the spiro product **464**.[964] The addition of an alkyne produces a product of less certain mechanistic origin. Methylene aziridines have been protonated and alkylated (Eq. 322).[965]



(322)

$R^1 = CH_3$, $C_6H_5CH_2$, cyclopropyl
$R^2 = H$; $X = FSO_3^-$
$R = CH_3$; $X = CH_3Cl$

The products are surprisingly stable. At 115° **466** rearranges to **467**.[966]



466 **467**

X. REFERENCES

1. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings, Part 1*, A. Weissberger, Ed., Wiley-Interscience, New York, 1964, p. 524.
2. O. C. Dermer and G. E. Ham, *Ethylenimine and Other Aziridines*, Academic Press, New York, 1969.
3. L. L. Muller and J. Hamer, *1,2-Cycloaddition Reactions*, Wiley-Interscience, New York, 1967, Chap. 2.
4. G. E. Ham, *Encyclopedia of Polymer Science, Technological Supplement* 1, Wiley, New York, 1976, p. 25.
5. P. A. Gembitskii, N. M. Loim, and D. S. Zhuk, *Russ. Chem. Rev.*, **35**, 105 (1966).
6. F. N. Gladysheva, A. P. Sineokov, and V. S. Etlis, *Russ. Chem. Rev.*, **39**, 118 (1970).
7. H. W. Heine, "Rearrangements of Aziridines," in *Mechanisms of Molecular Migration*, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, 1971, pp. 145–176.
8. H. W. Heine, *Angew. Chem., Int. Ed. Engl.*, **1**, 528 (1962).
9. H. Booth, in *Progress in Nuclear Magnetic Resonance Spectroscopy*, Vol. 5, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Eds., Pergamon Press, Oxford, 1969, p. 186.
10. C. A. Kingsbury, D. L. Durham, and R. Hutton, *J. Org. Chem.*, **43**, 4696 (1978).
11. S. J. Brois and G. P. Beardsley, *Tetrahedron Lett.*, 5113 (1966).
12. A. A. Fomichev and R. G. Kostyanovskii, *Dokl. Phys. Chem.*, **199**, 713 (1971).
13. G. Bouteville, Y. Gelas-Mialhe, and R. Vessiere, *C.R. Acad. Sci., Paris, Ser. C*, **271**, 1606 (1971).
14. T. Yonezawa and I. Morishima, *J. Mol. Spectrosc.*, **27**, 210 (1968).
15. J. -L. Pierre, P. Baret, and P. Arnaud, *Bull. Soc. Chim. Fr.*, 3619 (1971).
16. S. L. Mannat, D. D. Elleman, and S. J. Brois, *J. Am. Chem. Soc.*, **87**, 2220 (1965).
17. K. Tori, K. Aono, K. Kitahonoki, R. Muneyuki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Lett.*, 2921 (1966).
18. K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Lett.*, 869 (1965).
19. J. -L. Pierre and P. Baret, *C.R. Acad. Sci., Paris, Ser. C*, **272**, 2069 (1971).
20. H. Saitô, K. Nukada, T. Kobayashi, and K. Morita, *J. Am. Chem. Soc.*, **89**, 6605 (1967).
21. P. Mison, R. Chaabouni, Y. Diab, R. Martino, A. Lopez, A. Lattes, F. W. Wehrli, and T. Wirthlin, *Org. Magn. Reson.*, **8**, 79 (1976).
22. D. H. Aue, H. M. Webb, and M. T. Bowers, *J. Am. Chem. Soc.*, **97**, 4137 (1975).
23. J. W. Lown and A. Begleiter, *Can. J. Chem.*, **52**, 2331 (1974).
24. G. A. Gray, G. W. Buchanan, and F. G. Morin, *J. Org. Chem.*, **44**, 1768 (1979).
25. P. Tarburton, J. P. Edasery, C. A. Kingsbury, A. E. Sopchik, and N. H. Cromwell, *J. Org. Chem.*, **44**, 2042 (1979).
26. P. Tarburton, C. A. Kingsbury, A. E. Sopchik, and N. H. Cromwell, *J. Org. Chem.*, **43**, 1350 (1978).
27. N. H. Cromwell and M. A. Graff, *J. Org. Chem.*, **17**, 414 (1952).
28. A. B. Turner, R. E. Lutz, N. S. McFarlane, and D. W. Boykin, Jr., *J. Org. Chem.*, **36**, 1107 (1971).
29. D. W. Boykin, Jr., A. B. Turner, and R. E. Lutz, *Tetrahedron Lett.*, 817 (1967).
30. T. Yonezawa, I. Morishima, and K. Fukuta, *Bull. Chem. Soc., Jpn.*, **41**, 2297 (1968).
31. J. -L. Pierre, H. Handel, and P. Baret, *Org. Magn. Reson.*, **4**, 703 (1972).

32. M. Ohtsuru and K. Tori, *J. Mol. Spectrosc.*, **27**, 296 (1968).
33. M. Ohtsuru and K. Tori, *Tetrahedron Lett.*, 4043 (1970).
34. H. Paulsen and W. Greve, *Chem. Ber.*, **103**, 486 (1970).
35. D. L. Nagel, P. B. Woller, and N. H. Cromwell, *J. Org. Chem.*, **36**, 3911 (1971).
36. F. A. L. Anet and J. M. Osyany, *J. Am. Chem. Soc.*, **89**, 352 (1967).
37. F. A. L. Anet, R. D. Trepka, and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 357 (1967).
38. S. J. Brois, *Trans. N.Y. Acad. Sci.*, (2)**31**, 931 (1969).
39. A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, **9**, 400 (1970).
40. R. S. Atkinson, *J. Chem. Soc., Chem. Commun.*, 676 (1968).
41. R. G. Kostyanovsky, Z. E. Samojlova, and I. I. Tchervin, *Tetrahedron Lett.*, 3025 (1968).
42. J.-M. Lehn and J. Wagner, *J. Chem. Soc., Chem. Commun.*, 148 (1968).
43. J. D. Andose, J. -M. Lehn, K. Mislow, and J. Wagner, *J. Am. Chem. Soc.*, **92**, 4050 (1970).
44. R. S. Atkinson and C. W. Rees, *J. Chem. Soc., C*, 772 (1969).
45. R. G. Kostyanovsky, I. I. Tchervin. A. A. Fomichov, Z. E. Samojlova, C. N. Makarov, Y. V. Ziefman, and B. L. Dyatkin, *Tetrahedron Lett.*, 4021 (1969).
46. D. J. Anderson and T. L. Gilchrist, *J. Chem. Soc., C*, 2273 (1971).
47. R. S. Atkinson and J. R. Malpass, *J. Chem. Soc., Perkin Trans. 1*, 2242 (1977).
48. D. Felix and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, **7**, 224 (1968).
49. P. G. Gassman and D. K. Dygos, *J. Am. Chem. Soc.*, **91**, 1543 (1969).
50. S. J. Brois, *J. Am. Chem. Soc.*, **90**, 506 (1968).
51. S. J. Brois, *J. Am. Chem. Soc.*, **90**, 508 (1968).
52. A. Padwa and A. Battisti, *J. Org. Chem.*, **36**, 230 (1971).
53. P. Baret, M. Bourgeois, C. Gey, and J. -L. Pierre, *Tetrahedron*, **35**, 189 (1979).
54. P. G. Gassman and A. Fentiman, *J. Org. Chem.*, **32**, 2388 (1967).
55. R. G. Kostyanovskii and Z. E. Samojlova, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 665 (1969).
56. R. G. Kostyanovsky, V. I. Markov, and I. M. Gella, *Tetrahedron Lett.*, 1301 (1972).
57. R. G. Kostyanovskii, Z. E. Samojlova, and I. I. Tchervin, *Tetrahedron Lett.*, 719 (1969).
58. R. Annunziata, R. Fornasier, and F. Montanari, *J. Chem. Soc., Chem. Commun.*, 1133 (1972).
59. R. G. Kostyanovskii, V. F. Rudchenko, and V. I. Markov, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 2515 (1975).
60. R. G. Kostyanovskii and V. F. Rudchenko, *Dokl. Chem.*, **231**, 713 (1976).
61. R. G. Kostyanovskii, V. F. Rudchenko, and V. I. Markov, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1581 (1975).
62. A. E. Pohland, R. C. Badger, and N. H. Cromwell, *Tetrahedron Lett.*, 4369 (1965).
63. A. Padwa and L. Hamilton, *J. Org. Chem.*, **31**, 1995 (1966).
64. A. Padwa, D. Dean, and T. Oine, *J. Am. Chem. Soc.*, **97**, 2822 (1975).
65. S. Sorriso, F. Stefani, E. Semprini, and A. Flamini, *J. Chem. Soc., Perkin Trans. 2*, 374 (1976).
66. N. H. Cromwell, P. B. Woller, H. E. Baumgarten, R. G. Parker, and D. L. von Minden, *J. Heterocycl. Chem.*, **9**, 587 (1972).
67. Q. N. Porter and R. J. Spear, *Org. Mass Spectrom.*, **3**, 1259 (1970).
68. I. Lengyel, D. B. Uliss, and F. D. Greene, *J. Chem. Soc., Perkin Trans. 2*, 1415 (1972).
69. M. Zacharis and L. M. Trefonas, *J. Heterocycl. Chem.*, **5**, 343 (1968).

70. M. Zacharis and L. M. Trefonas, *J. Heterocycl. Chem.*, 7, 755 (1970).
71. M. Zacharis and L. M. Trefonas, *J. Heterocycl. Chem.*, 7, 1301 (1970).
72. J. N. Brown, R. L. R. Towns, and L. M. Trefonas, *J. Heterocycl. Chem.*, 7, 1321 (1970).
73. L. M. Trefonas and R. Majeste, *J. Heterocycl. Chem.*, 2, 80 (1965).
74. L. M. Trefonas and T. Sato, *J. Heterocycl. Chem.*, 3, 404 (1966).
75. E. M. Gopalakrishna, *Acta Crystallogr., Sect. B*, **28**, 2754 (1972).
76. T. -M. Ko, L. Olansky, and J. W. Moncrief, *Acta Crystallogr., Sect. B*, **31**, 1875 (1975).
77. A. Grand, J. B. Robert, and A. Filhol, *Acta Crystallogr., Sect. B*, **33**, 1526 (1977).
78. Y. Delugeard, M. Vaultier, and J. Meinnel, *Acta Crystallogr., Sect. B*, **31**, 2885 (1975).
79. A. Tulinsky, *J. Am. Chem. Soc.*, **84**, 3188 (1962).
80. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 527.
81. G. L. Grunewald, A. M. Warner, S. J. Hays, R. H. Bussell, and M. K. Seals, *J. Med. Chem.*, **15**, 747 (1972).
82. W. Nagata, S. Hirai, K. Kawata, and T. Aoki, *J. Am. Chem. Soc.*, **89**, 5045 (1967).
83. R. Schwesinger and H. Prinzbach, *Angew. Chem., Int. Ed. Engl.*, **12**, 989 (1973).
84. C. L. Stevens, K. G. Taylor, M. E. Munk, W. S. Marshall, K. Noll, G. D. Shah, and K. Uzu, *J. Med. Chem.*, **8**, 1 (1965).
85. M. Tomasz and R. Lipman, *J. Am. Chem. Soc.*, **101**, 6063 (1979).
86. J. W. Lown and G. Weir, *Can. J. Biochem.*, **56**, 296 (1978).
87. B. A. Arbuzov, S. G. Vul'fson, R. R. Kostikov, L. A. Monetina, A. F. Khlebnikov, and A. N. Vereshchagin, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1199 (1975).
88. R. S. Armstrong, M. J. Aroney, R. J. W. LeFevre, H. J. Stootman, and W. Lüttke, *J. Chem. Soc., B*, 2104 (1971).
89. V. A. Naumov, *Dokl. Chem.*, **169**, 748 (1966).
90. W. C. Danen and C. T. West, *J. Am. Chem. Soc.*, **96**, 2447 (1974).
91. W. C. Danen and T. T. Kensler, *Tetrahedron Lett.*, 2247 (1971).
92. G. R. Luckhurst and F. Sundholm, *Tetrahedron Lett.*, 675 (1971).
93. P. Singh, D. G. B. Boocock, and E. F. Ullman, *Tetrahedron Lett.*, 3935 (1971).
94. J. F. W. Keana, R. J. Dinerstein, and D. P. Dolata, *Tetrahedron Lett.*, 119 (1972).
95. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 528.
96. O. C. Dermer and G. E. Ham, Ref. 2, p. 2.
97. E. L. Stogryn and S. J. Brois, *J. Org. Chem.*, **30**, 88 (1965).
98. E. L. Stogryn and S. J. Brois, *J. Am. Chem. Soc.*, **89**, 605 (1967).
99. A. Mishra, S. N. Rice, and W. Lwowski, *J. Org. Chem.*, **33**, 481 (1968).
100. P. E. Fanta, R. Golden, and H. -J. Su, *J. Chem. Eng. Data*, **9**, 246 (1964).
101. C. G. Gebelein, G. Swift, and D. Swern, *J. Org. Chem.*, **32**, 3314 (1967).
102. P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, **31**, 59 (1966).
103. R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, A. C. Richards, and R. Scattergood, *J. Chem. Soc., Perkin Trans. 2*, 41 (1972).
104. S. Hillers, A. V. Eremeev, M. Lidaks, and V. A. Kholodnikov, *Khim. Geterotsikl. Soedin.*, 466 (1970); *Chem. Abstr.*, **73**, 045227 (1970).
105. U. Bicker and W. Fischer, *Nature (London)*, **249**, 344 (1974).
106. Y. Nakagawa, T. Tsuno, K. Nakajima, M. Iwai, H. Kawai, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **45**, 1162 (1972).
107. K. Okawa, Japan Kokai, 73/36158; *Chem. Abstr.*, **79**, 42848 (1973).
108. V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970).

109. K. Shudo and T. Okamoto, *Chem. Pharm. Bull. (Jpn.)*, **24**, 1013 (1976).
110. D. H. Buss, L. Hough, and A. C. Robinson, *J. Chem. Soc.*, 5295 (1963).
111. W. Meyer Zu Reckendorf, *Chem. Ber.*, **97**, 325 (1964).
112. B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1047 (1964).
113. B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1051 (1964).
114. B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1057 (1964).
115. B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1063 (1964).
116. B. R. Baker and T. L. Hullar, *J. Org. Chem.*, **30**, 4038 (1965).
117. B. R. Baker and T. L. Hullar, *J. Org. Chem.*, **30**, 4049 (1965).
118. B. R. Baker and T. L. Hullar, *J. Org. Chem.*, **30**, 4053 (1965).
119. M. Cerney, T. Elbert, and J. Pacak, *Collect. Czech. Chem. Commun.*, **39**, 1752 (1974).
120. H. Paulsen and D. Stoye, *Angew. Chem., Int. Ed. Engl.*, **7**, 134 (1968).
121. H. Paulsen and M. Budzis, *Chem. Ber.*, **103**, 3794 (1970).
122. I. Okada, K. Ichimura, and R. Sudo, *Bull. Chem. Soc. Jpn.*, **43**, 1185 (1970).
123. C. Berse and P. Bessette, *Can. J. Chem.*, **50**, 4061 (1972).
124. (a) A. Sauleau, J. Sauleau, H. Bourget, and J. Huet, *C.R. Acad. Sci., Paris, Ser. C*, **279**, 473 (1974); (b) J. Sauleau, A. Sauleau, and J. Huet, *Bull. Soc. Chim. Fr. Part II*, 97 (1978).
125. H. P. Figeys and R. Jammar, *Tetrahedron Lett.*, 637 (1981).
126. J. C. Pommelet and J. Chuche, *Tetrahedron Lett.*, 3897 (1974).
127. R. Appel and R. Kleinstück, *Chem. Ber.*, **107**, 5 (1974).
128. N. Manisse and J. Chuche, *J. Am. Chem. Soc.*, **99**, 1272 (1977).
129. T. Kametani, Y. Kigawa, and M. Ihara, *Tetrahedron*, **35**, 313 (1979).
130. J. T. Carlock and M. P. Mack, *Tetrahedron Lett.*, 5153 (1978).
131. R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Org. Chem.*, **37**, 1266 (1972).
132. K. Ponsold, *Chem. Ber.*, **97**, 3524 (1964).
133. W. L. Nelson and B. E. Sherwood, *J. Org. Chem.*, **39**, 66 (1974).
134. M. J. Robins, S. D. Hawrelak, T. Kanai, J. -M. Siefert, and R. Mengel, *J. Org. Chem.*, **44**, 1317 (1979).
135. J. Cleóphax, S. D. Géro, and J. Hildesheim, *J. Chem. Soc., Chem. Commun.*, 94 (1968).
136. A. D. Barford and A. C. Richardson, *Carbohyd. Res.*, **14**, 217 (1970); *Chem. Abstr.*, **73**, 88105 (1970).
137. J. S. Brimacombe, N. F. Hunedy, and M. Stacey, *Carbohydr. Res.*, **13**, 447 (1970); *Chem. Abstr.*, **74**, 13353 (1971).
138. S. Oida and E. Ohki, *Chem. Pharm. Bull. (Jpn.)*, **17**, 939 (1969).
139. S. Oida and E. Ohki, *Chem. Pharm. Bull. (Jpn.)*, **17**, 980 (1969).
140. G. J. Matthews and A. Hassner, *Tetrahedron Lett.*, 1833 (1969).
141. Y. Ittah, Y. Sasson, I. Shahak, S. Tsaroom, and J. Blum, *J. Org. Chem.*, **43**, 4271 (1978).
142. J. Blum, I. Yona, S. Tsaroom, and Y. Sasson, *J. Org. Chem.*, **44**, 4178 (1979).
143. F. Nakatsubo, T. Fukuyama, A. J. Cocuzza, and Y. Kishi, *J. Am. Chem. Soc.*, **99**, 8115 (1977).
144. J. T. Rudeshill, R. F. Severson, and J. G. Pomonis, *J. Org. Chem.*, **36**, 3071 (1971).
145. H. E. Zaugg and R. W. DeNet, *J. Org. Chem.*, **36**, 1937 (1971).
146. P. W. Feit and O. T. Neilsen, *J. Med. Chem.*, **13**, 447 (1970).
147. M. G. Avetyan, O. S. Tsatinyan, and S. G. Matsoyan, *Arm. Khim. Zh.*, **27**, 576 (1974); *Chem. Abstr.*, **82**, 16626 (1974).

148. W. Funke, *Angew. Chem., Int. Ed. Engl.*, **8**, 70 (1969).
149. V. R. Gaertner, *Tetrahedron Lett.*, 5919 (1968).
150. L. P. Vakhrushev, E. F. Filippov, N. F. Chernov, and V. P. Ageev, *J. Gen. Chem. USSR*, **45**, 1878 (1975).
151. A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).
152. Y. Langlois, C. Poupat, H. -P. Husson, and P. Potier, *Tetrahedron*, **26**, 1967 (1970).
153. K. Ponsold and W. Ihn, *Tetrahedron Lett.*, 1125 (1970).
154. R. Buyle, *Chem. Ind.*, 195 (1966).
155. G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 2968 (1971).
156. R. Nicoletti and M. L. Forcellese, *Tetrahedron Lett.*, 153 (1965).
157. T. Hirata, Y. Yamada, and M. Matsui, *Tetrahedron Lett.*, 4107 (1969).
158. G. F. Field, W. J. Zally, and L. H. Sternbach, *Tetrahedron Lett.*, 2609 (1966).
159. Y. Yamada, T. Oine, and I. Inoue, *Chem. Pharm. Bull. (Jpn.)*, **22**, 601 (1974).
160. S. J. Brois, *J. Am. Chem. Soc.*, **92**, 1079 (1970).
161. M. J. Haire, *J. Org. Chem.*, **45**, 1310 (1980).
162. D. L. Nagel and N. H. Cromwell, *J. Heterocycl. Chem.*, **11**, 1093 (1974).
163. G. R. Harvey, *J. Org. Chem.*, **33**, 887 (1968).
164. S. Hillers, A. V. Eremeev, I. Kalvins, E. Liepins, and V. G. Semenikhina, *Khim. Geterotsikl. Soedin.*, 1625 (1975); *Chem. Abstr.*, **85**, 20962 (1976).
165. J. A. Deyrup and S. C. Clough, *J. Org. Chem.*, **39**, 902 (1974).
166. J. A. Deyrup and S. C. Clough, *J. Am. Chem. Soc.*, **91**, 4591 (1969).
167. D. Johnson and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1062 (1976).
168. J. A. Deyrup, *J. Org. Chem.*, **34**, 2724 (1969).
169. L. Wartski, *J. Chem. Soc., Chem. Commun.*, 602 (1977).
170. A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).
171. A. Hassner and C. C. Heathcock, *Tetrahedron Lett.*, 1125 (1964).
172. S. Fujita, K. Imamura, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **44**, 1975 (1971).
173. C. Anselmi and G. Camici, *Gazz. Chim. Ital.*, **102**, 1129 (1972); *Chem. Abstr.*, **79**, 41785 (1972).
174. A. Hassner and C. C. Heathcock, *Tetrahedron Lett.*, 393 (1963).
175. G. Drefahl and K. Ponsold, *Chem. Ber.*, **93**, 519 (1960).
176. A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).
177. R. Ikan, A. Markus, and Z. Goldschmidt, *J. Org. Chem.*, **37**, 1892 (1972).
178. T. Greibrokk, *Acta Chem. Scand.*, **26**, 3305 (1972).
179. A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 3640 (1964).
180. W. L. Nelson and D. D. Miller, *J. Org. Chem.*, **35**, 1185 (1970).
181. A. Kubik, K. Piatkowski, and H. Kuczynski, *Rocz. Chem.*, **48**, 1225 (1974).
182. L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, **34**, 2866 (1969).
183. O. Cervinka, V. Dudek, and V. Senft, *Z. Chem.*, **13**, 176 (1973).
184. J. Beger and W. Hoebold, *J. Prakt. Chem.*, **311**, 760 (1969); *Chem. Abstr.*, **72**, 12448 (1969).
185. G. Lamaty, A. Delbord, and W. Werner, *Justus Liebigs Ann. Chem.*, **726**, 77 (1969).
186. A. Hassner, G. J. Matthews, and F. W. Fowler, *J. Am. Chem. Soc.*, **91**, 5046 (1969).
187. F. W. Fowler, A. Hassner, and L. A. Levy, *J. Am. Chem. Soc.*, **89**, 2077 (1967).
188. D. Van Ende and A. Krief, *Angew. Chem., Int. Ed. Engl.*, **13**, 279 (1974).

189. T. Hirata, Y. Yamada, and M. Matsui, *Tetrahedron Lett.*, 19 (1969).
190. F. Duboudin, *J. Organomet. Chem.*, **156**, C25 (1978).
191. Y. Houminer, *J. Chem. Soc., Perkin Trans. 1*, 1037 (1976).
192. D. C. Horwell and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1428 (1969).
193. A. Hassner and J. E. Galle, *J. Am. Chem. Soc.*, **92**, 3733 (1970); *J. Org. Chem.*, **41**, 2102 (1976).
194. R. J. Parry, M. G. Kunitani, and O. Viele, III, *J. Chem. Soc., Chem. Commun.*, 321 (1975).
195. A. B. Levy and H. C. Brown, *J. Am. Chem. Soc.*, **95**, 4067 (1973).
196. E. Vogel, M. Biskup, W. Pretzer, and W. A. Böll, *Angew. Chem., Int. Ed. Engl.*, **3**, 642 (1964).
197. S. J. Dominianni, U.S. Patent, 3715262/1973; *Chem. Abstr.*, **78**, 136040 (1973).
198. K. Ichimura and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 432 (1967).
199. K. Ichimura and M. Ohta, *Bull. Chem. Soc., Jpn.*, **43**, 1443 (1970).
200. R. M. Carlson and S. Y. Lee, *Tetrahedron Lett.*, 4001 (1969).
201. K. Ichimura, *Bull. Chem. Soc. Jpn.*, **43**, 2501 (1970).
202. J. W. Lewis, M. J. Readhead, I. A. Selby, A. C. B. Smith, and C. A. Young, *J. Chem. Soc., C*, 1158 (1971).
203. J. -M. Bourgeois, *Helv. Chim. Acta*, **57**, 2553 (1974).
204. J. -M. Bourgeois, *Helv. Chim. Acta*, **59**, 2114 (1976).
205. H. Saeki and E. Ohki, *Chem. Pharm. Bull. (Jpn.)*, **18**, 789 (1970).
206. L. Duhamel and J. -Y. Valnot, *Tetrahedron Lett.*, 3167 (1974).
207. N. DeKimpe, R. Verhe, L. DeBuyck, and N. Schamp, *Rec. Trav. Chim. Pays-Bas*, **96**, 242 (1977).
208. N. DeKimpe, N. Schamp, and R. Verhe, *Synth. Commun.*, **5**, 403 (1975).
209. N. DeKimpe, R. Verhe, L. DeBuyck, and N. Schamp, *Synth. Commun.*, **5**, 269 (1975).
210. N. DeKimpe, R. Verhe, L. DeBuyck, W. Dejonghe, and N. Schamp, *Bull. Soc. Chim. Belg.*, **85**, 763 (1976).
211. Y. V. Zeifman, S. O. Koshtoyan, and I. L. Knunyants, *Dokl. Chem.*, **195**, 783 (1970).
212. T. A. Foglia and D. Swern, *J. Org. Chem.*, **32**, 75 (1967).
213. A. Zwierzak and S. Zawadzki, *Synthesis*, 416 (1972).
214. A. M. Pinchuk, T. V. Kovalevskaya, and G. K. Bespal'ko, *J. Gen. Chem. USSR*, **45**, 1219 (1975).
215. A. M. Pinchuk, L. N. Markovskii, and T. V. Kovalevskaya, *J. Gen. Chem. USSR*, **39**, 2094 (1969).
216. H. Terauchi, S. Takemura, and Y. Ueno, *Chem. Pharm. Bull. (Jpn.)*, **23**, 640 (1975).
217. V. I. Markov, V. A. Doroshenko, O. I. Klimenko, and G. P. Sachko, *J. Org. Chem. USSR*, **8**, 1754 (1972).
218. N. A. Rybakova, N. A. Pochkailo, and L. N. Kiseleva, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 2728 (1973).
219. N. A. Rybakova, L. G. Sharonova, and R. K. Freidlina, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1313 (1973).
220. V. F. Baranovskaya and M. M. Kremlev, *Vopr. Khim. Khim. Tekhnol.*, **36**, 120 (1974); *Chem. Abstr.*, **82**, 155947 (1975).
221. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 535.
222. O. C. Dermer and G. E. Ham, Ref. 2, p. 27.
223. P. Tarburton, P. B. Woller, R. C. Badger, E. Doomes, and N. H. Cromwell, *J. Heterocycl. Chem.*, **14**, 459 (1977).

224. P. Tarburton, L. J. Wolpa, R. K. Loerch, T. L. Folsom, and N. H. Cromwell, *J. Heterocycl. Chem.*, **14**, 1203 (1977).
225. A. Padwa and W. Eisenhardt, *J. Am. Chem. Soc.*, **93**, 1400 (1971).
226. R. Bognar, G. Litkei, and P. Szigeti, *Acta Chim. (Budapest)*, **68**, 421 (1971); *Chem. Abstr.*, **75**, 35620 (1971).
227. J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **48**, 2215 (1970).
228. Y. Gelas-Mialhe, R. Hierle, and R. Vessiere, *J. Heterocycl. Chem.*, **11**, 347 (1974).
229. N. H. Cromwell and M. C. McMaster, *J. Org. Chem.*, **32**, 2145 (1967).
230. H. W. Heine and R. Henzel, *J. Org. Chem.*, **34**, 171 (1969).
231. A. Padwa, L. Gehrlein, and R. B. Kinnel, *J. Org. Chem.*, **40**, 1683 (1975).
232. P. B. Woller and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 579 (1968).
233. K. D. Berlin, L. G. Williams, and O. C. Dermer, *Tetrahedron Lett.*, 873 (1968).
234. E. Kyburz, H. Els, St. Majnoni, G. Englert, C. von Planta, A. Fürst, and P. A. Plattner, *Helv. Chim. Acta*, **49**, 359 (1966).
235. R. G. Kostyanovskii, A. V. Prosyanik, and V. I. Markov, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 453 (1974).
236. R. G. Kostyanovskii, A. V. Prosyanik, V. I. Markov, I. A. Zon, and A. E. Polyakov, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1481 (1976).
237. B. A. Dmitriev, N. E. Bairamova, and N. K. Kochetkov, *Bull. Acad. Sci. USSR Chem. Sci.*, 2564 (1967).
238. K. -D. Gundermann, K. Burzin, F. -J. Sprenger, and H. Schulze, *Chem. Ber.*, **105**, 312 (1972).
239. K. Burzin and K. Enderer, *Angew. Chem., Int. Ed. Engl.*, **11**, 151 (1972).
240. G. Bouteville, Y. Gelas-Mialhe, and R. Vessiere, *Bull. Soc. Chim. Fr.*, 3264 (1971).
241. J. M. J. Tronchnet and O. R. Martin, *Helv. Chim. Acta*, **59**, 945 (1976).
242. J. P. Edasery and N. H. Cromwell, *J. Heterocycl. Chem.*, **16**, 831 (1979).
243. K. D. Berlin and S. Rengaraju, *Proc. Okla. Acad. Sci.*, **53**, 73 (1973); *Chem. Abstr.*, **79**, 136918 (1973).
244. P. Carlier, Y. Gelas-Mialhe, and R. Vessiere, *Can. J. Chem.*, **55**, 3190 (1977).
245. D. F. Morrow and M. E. Butler, *J. Heterocycl. Chem.*, **1**, 53 (1964).
246. D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 579 (1965).
247. A. Hassner and F. W. Fowler, *Tetrahedron Lett.*, 1545 (1967).
248. A. Hassner and F. W. Fowler, *J. Am. Chem. Soc.*, **90**, 2869 (1968).
249. T. Nishiwaki and F. Fujiyama, *Synthesis*, 569 (1972).
250. S. Sato, *Bull. Chem. Soc. Jpn.*, **41**, 1440 (1968).
251. A. Hassner and L. A. Levy, *J. Am. Chem. Soc.*, **87**, 4203 (1965).
252. T. Nishiwaki and S. Onomura, *J. Chem. Soc. C*, 3026 (1971).
253. T. Nishiwaki and T. Saito, *J. Chem. Soc. C*, 2648 (1971).
254. N. J. Leonard and B. Zwanenburg, *J. Am. Chem. Soc.*, **89**, 4456 (1967).
255. R. E. Moerck and M. A. Battiste, *J. Chem. Soc., Chem. Commun.*, 782 (1974).
256. G. Szeimies, K. Mannhardt, and W. Mickler, *Chem. Ber.*, **110**, 2922 (1977).
257. R. G. Kostyanovskii, G. K. Kadorkina, I. I. Chervin, M. O. Isobaev, and E. N. Voznesenskii, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 2239 (1976).
258. T. Nishiwaki and T. Saito, *J. Chem. Soc., C*, 3021 (1971).
259. F. W. Fowler and A. Hassner, *J. Am. Chem. Soc.*, **90**, 2875 (1968).
260. A. Hassner, S. S. Burke, and J. Cheng-fan I, *J. Am. Chem. Soc.*, **97**, 4692 (1975).
261. S. Sato, *Nippon Kagaku Zasshi*, **90**, 113 (1969); *Chem. Abstr.*, **70**, 96501 (1969).

262. G. Alvernhe and A. Laurent, *J. Chem. Res. (S)*, 28 (1978).
263. A. Hassner, J. O. Currie, Jr., A. S. Steinfeld, and R. F. Atkinson, *J. Am. Chem. Soc.*, **95**, 2982 (1973).
264. B. Blagoev and S. Novkova, *C.R. Acad. Sci. Paris, Ser. C*, **288**, 281 (1979).
265. B. Kryczka, A. Laurent, and B. Marquet, *Tetrahedron*, **34**, 3291 (1978).
266. N. S. Narasimhan, N. Heimgartner, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 1351 (1973).
267. F. P. Woerner, H. Reimlinger, and D. R. Arnold, *Angew. Chem., Int. Ed. Engl.*, **7**, 130 (1968).
268. A. Padwa, S. Clough, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **94**, 1395 (1972).
269. N. Gakis, M. Märky, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 748 (1972).
270. A. Padwa, J. Smolanoff, and S. I. Wetmore, Jr., *J. Chem. Soc., Chem. Commun.*, 409 (1972).
271. K. Matsumoto and K. Maruyama, *Chem. Lett.*, 759 (1973).
272. A. Hassner, A. S. Miller, and M. J. Haddadin, *Tetrahedron Lett.*, 1353 (1972).
273. F. P. Woerner, H. Reimlinger, and R. Merenyi, *Chem. Ber.*, **104**, 2786 (1971).
274. E. Schaumann, E. Kausch, and W. Walter, *Chem. Ber.*, **107**, 3574 (1974).
275. V. Nair and K. H. Kim, *Tetrahedron Lett.*, 1487 (1974).
276. O. Tsuge and M. Noguchi, *Heterocycles*, **9**, 423 (1978); *Chem. Abstr.*, **89**, 43335 (1978).
277. G. Alvernhe and A. Laurent, *Bull. Soc. Chim. Fr.*, 3003 (1970).
278. R. Bartnik and A. Laurent, *C.R. Acad. Sci. Paris, Ser. C*, **279**, 289 (1974).
279. R. Bartnik and A. Laurent, *Bull. Soc. Chim. Fr.*, 173 (1975).
280. R. Chaabouni and A. Laurent, *Bull. Soc. Chim. Fr.*, 2680 (1973).
281. R. Chaabouni and A. Laurent, *Synthesis*, 464 (1975).
282. Y. Diab, A. Laurent, and P. Mison, *Bull. Soc. Chim. Fr.*, 2202 (1974).
283. G. Alvernhe and A. Laurent, *Tetrahedron Lett.*, 1913 (1971).
284. K. Imai, Y. Kawazoe, and T. Taguchi, *Chem. Pharm. Bull. (Jpn.)*, **24**, 1083 (1976).
285. V. Seidlova and M. Protiva, *Collect. Czech. Chem. Commun.*, **32**, 1747 (1967).
286. T. Sasaki, S. Eguchi, and S. Hattori, *Heterocycles*, **11**, 235 (1978).
287. K. Miyano and T. Taguchi, *Chem. Pharm. Bull. (Jpn.)*, **18**, 1806 (1970).
288. R. Chaabouni, A. Laurent, and P. Mison, *Tetrahedron Lett.*, 1343 (1973).
289. A. Tzikas, C. Tamm, A. Boller, and A. Fürst, *Helv. Chim. Acta*, **59**, 1850 (1976).
290. G. Alvernhe, S. Arsenyiadis, R. Chaabouni, and A. Laurent, *Tetrahedron Lett.*, 355 (1975).
291. G. Ricart and D. Couturier, *C.R. Acad. Sci. Paris, Ser. C*, **284**, 191 (1977).
292. R. Bartnik and A. Laurent, *Tetrahedron Lett.*, 3869 (1974).
293. R. Bartnik, Y. Diab, and A. Laurent, *Tetrahedron*, **33**, 1279 (1977).
294. H. Tanida, T. Okada, and K. Kotera, *Bull. Chem. Soc. Jpn.*, **46**, 934 (1973).
295. K. Kotera, T. Okada, and S. Miyazaki, *Tetrahedron*, **24**, 5677 (1968).
296. J. C. Philips and C. Perianayagam, *Tetrahedron Lett.*, 3263 (1975).
297. K. Kotera, Y. Matsukawa, H. Takahashi, T. Okada, and K. Kitahonoki, *Tetrahedron*, **24**, 6177 (1968).
298. J. Humbert and A. Laurent, *C.R. Acad. Sci. Paris, Ser. C*, **272**, 1165 (1971).
299. K. Kotera and K. Kitahonoki, *Org. Prep. Proced.*, **1**, 305 (1969); *Chem. Abstr.*, **72**, 55111 (1969).

300. K. Kotera, S. Miyazaki, H. Takahashi, T. Okada, and K. Kitahonoki, *Tetrahedron*, **24**, 3681 (1968).
301. K. Kitahonoki, K. Kotera, Y. Matsukawa, S. Miyazaki, T. Okada, H. Takahashi, and Y. Takano, *Tetrahedron Lett.*, 1059 (1965).
302. J. L. M. A. Schlactmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26**, 949 (1970).
303. J. Fouché, *Bull. Soc. Chim. Fr.*, 1376 (1970).
304. S. R. Landor, O. O. Sonola, and A. R. Tatchell, *J. Chem. Soc., Perkin Trans. 1*, 1294 (1974).
305. Y. Girault, M. Decouzon, and M. Azzaro, *Tetrahedron Lett.*, 1175 (1976).
306. Y. Diab, A. Laurent, and P. Mison, *Tetrahedron Lett.*, 1605 (1974).
307. K. Kotera, Y. Takano, A. Matsuura, and K. Kitahonoki, *Tetrahedron*, **26**, 539 (1970).
308. K. Kotera, Y. Takano, A. Matsuura, and K. Kitahonoki, *Tetrahedron Lett.*, 5759 (1968).
309. G. Chidichimo, G. Cum, F. Lelj, G. Sindona, and N. Ucella, *J. Am. Chem. Soc.*, **102**, 1372 (1980).
310. G. Ricart, D. Couturier, and C. Glacet, *C.R. Acad. Sci. Paris, Ser. C*, **277**, 519 (1973).
311. L. Ferrero, S. Geribaldi, M. Rouillard, and M. Azzaro, *Can. J. Chem.*, **53**, 3227 (1975).
312. F. Ferrero, M. Rouillard, M. Decouzon, and M. Azzaro, *Tetrahedron Lett.*, 131 (1974).
313. G. Ricart, *Bull. Soc. Chim. Fr.*, 2607 (1974).
314. M. Y. Shandale, M. D. Solomon, and E. S. Waight, *J. Chem. Soc.*, 892 (1965).
315. L. Ferrero, M. Decouzon, and M. Azzaro, *Tetrahedron Lett.*, 4151 (1973).
316. J. R. Dimmock, W. A. Turner, P. J. Smith, and R. G. Sutherland, *Can. J. Chem.*, **51**, 427 (1973).
317. J. R. Dimmock, P. J. Smith, L. M. Noble, and W. J. Pannekoek, *J. Pharm. Sci.*, **67**, 1536 (1978).
318. R. S. McDaniel and A. C. Oehlschlager, *Tetrahedron*, **25**, 1381 (1969).
319. R. L. Hale and L. H. Zalkow, *Tetrahedron*, **25**, 1393 (1969).
320. A. C. Oehlschlager and L. H. Zalkow, *J. Chem. Soc., Chem. Commun.*, 70 (1965).
321. P. Scheiner, *J. Org. Chem.*, **30**, 7 (1965).
322. P. Scheiner, *J. Am. Chem. Soc.*, **90**, 988 (1968).
323. P. Scheiner, *J. Am. Chem. Soc.*, **88**, 4759 (1966).
324. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
325. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).
326. Z. Bernstein and D. Ben-Ishai, *Tetrahedron*, **33**, 881 (1977).
327. I. L. Knunyants and Y. V. Zeifman, *Bull. Acad. Sci. USSR Chem.*, 695 (1967).
328. R. G. Kostyanovskii, G. K. Kadorkina, G. V. Shustov, and K. S. Zakharov, *Dokl. Phys. Chem.*, **221**, 242 (1975).
329. Y. M. Saunier, R. Danion-Bougot, and R. Carrie, *Tetrahedron*, **32**, 1995 (1976).
330. B. L. Dyatkin, K. N. Makarov, and I. L. Knunyants, *Tetrahedron*, **27**, 51 (1971).
331. See P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 12.
332. W. Broeckx, N. Overbergh, C. Samyn, G. Smets, and G. L. l'Abbé, *Tetrahedron*, **27**, 3527 (1971).
333. M. DePoortere and F. C. DeSchryver, *Tetrahedron Lett.*, 3949 (1970).
334. N. G. Kusainova, Z. A. Bredikhina, F. K. Karataeva, T. I. Bychkova, and A. N. Pudovik, *J. Gen. Chem., USSR*, **46**, 1665 (1976).
335. R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **99**, 475 (1966).
336. R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Lett.*, 397 (1966).
337. P. Scheiner, *Tetrahedron*, **24**, 2757 (1968).

338. P. Scheiner, *J. Org. Chem.*, **32**, 2628 (1967).
339. M. E. Hermes and F. D. Marsh, *J. Org. Chem.*, **37**, 2969 (1972).
340. A. R. Bassindale, A. G. Brook, P. F. Jones, and J. A. G. Stewart, *J. Organomet. Chem.*, **152**, C25 (1978).
341. K. R. Henery-Logan and R. A. Clark, *Tetrahedron Lett.*, 801 (1968).
342. R. Scarpati, M. L. Graziano, and R. A. Nicolaus, *Gazz. Chim. Ital.*, **100**, 665 (1970); *Chem. Abstr.*, **74**, 13073 (1971).
343. G. Szeimies and K. Mannhardt, *Chem. Ber.*, **110**, 2939 (1977).
344. F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 4119 (1971).
345. (a) K. Burger and J. Fehn, *Justus Liebigs Ann. Chem.*, 757, 9 (1972). (b) A. Hassner, B. A. Belinka, M. Haber and P. Munger, *Tetrahedron Letters*, 1863 (1981).
346. Y. Nomura, N. Hatanaka, and Y. Takeuchi, *Chem. Lett.*, 901 (1976).
347. A. I. Logothetis, *J. Org. Chem.*, **29**, 3049 (1964).
348. R. G. Kostyanovskii, G. K. Kadorkina, and A. A. Fomichev, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1623 (1972).
349. F. Roelants and A. Bruylants, *Tetrahedron*, **34**, 2229 (1978).
350. M. L. Graziano and R. Scarpati, *J. Heterocycl. Chem.*, **13**, 205 (1976).
351. P. Scheiner, *J. Org. Chem.*, **32**, 2022 (1967).
352. M. H. Akhtar, A. Begleiter, D. Johnson, J. W. Lown, L. McLaughlin, and S. -K. Sim, *Can. J. Chem.*, **53**, 2891 (1975).
353. S. Oida and E. Ohki, *Chem. Pharm. Bull. (Jpn.)*, **16**, 764 (1968).
354. P. G. Dul'nev, T. S. Lutsii, and T. E. Bezmenova, *Ukr. Khim. Zh. (Russ. Ed.)*, **40**, 433 (1974); *Chem. Abstr.*, **81**, 13470 (1974).
355. T. Aratani, Y. Nakanisi, and H. Nozaki, *Tetrahedron*, **26**, 4339 (1970).
356. J. A. Deyrup and M. F. Betkouski, *J. Org. Chem.*, **40**, 284 (1975).
357. D. H. Aue, R. B. Lorens, and G. S. Helwig, *Tetrahedron Lett.*, 4795 (1973).
358. J. K. Crandall and W. W. Conover, *J. Org. Chem.*, **39**, 63 (1974).
359. L. H. Zalkow, A. C. Oehlschlager, G. A. Cabot, and R. L. Hale, *Chem. Ind., (London)*, 1556 (1964).
360. R. Huisgen, L. Möbius, G. Müller, H. Stangl, G. Szeimes, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965).
361. A. G. Anastassiou and H. E. Simmons, *J. Am. Chem. Soc.*, **89**, 3117 (1967).
362. A. S. Bailey and J. J. Wedgewood, *J. Chem. Soc., C*, 682 (1968).
363. J. E. Franz, C. Osuch, and M. W. Dietrich, *J. Org. Chem.*, **29**, 2922 (1964).
364. M. Hedayatullah and A. Guy, *J. Heterocycl. Chem.*, **16**, 201 (1979).
365. R. S. McDaniel and A. C. Oehlschlager, *Can. J. Chem.*, **46**, 2316 (1968).
366. H. Tanida, T. Tsuji, and T. Irie, *J. Org. Chem.*, **31**, 3941 (1966).
367. B. Halton and A. D. Woolhouse, *Aust. J. Chem.*, **26**, 619 (1973).
368. A. G. Hortman and J. E. Martinelli, *Tetrahedron Lett.*, 6205 (1968).
369. R. Fusco, L. Garanti, and G. Zecchi, *J. Org. Chem.*, **40**, 1906 (1975).
370. O. Tsuge, K. Ueno, and A. Inaba, *Heterocycles*, **4**, 1 (1976); *Chem. Abstr.*, **84**, 105510 (1976).
371. A. L. Logothetis, *J. Am. Chem. Soc.*, **87**, 749 (1965).
372. B. Halton and A. D. Woolhouse, *Aust. J. Chem.*, **26**, 1373 (1973).
373. A. C. Oehlschlager and L. H. Zalkow, *J. Chem. Soc., Chem. Commun.*, 5 (1966).
374. I. N. Vorozhtsov, N. N. Povolotskaya, A. K. Petrov, and V. A. Barkhash, *J. Gen. Chem., USSR*, **38**, 2049 (1968).

375. K. Wiesner, P.-T. Ho, R. C. Jain, S. F. Lee, S. Oida, and A. Philipp, *Can. J. Chem.*, **51**, 1448 (1973).
376. R. J. Stedman, A. C. Swift, and J. R. E. Hoover, *Tetrahedron Lett.*, 2525 (1965).
377. A. I. Meyers, D. M. Stout, and T. Takaya, *J. Chem. Soc., Chem. Commun.*, 1260 (1972).
378. D. C. Horwell and J. A. Deyrup, *J. Chem. Soc., Chem. Commun.*, 485 (1972).
379. P. E. Hansen and K. Undheim, *Acta Chem. Scand.*, **27**, 1112 (1973).
380. R. W. Franck and J. Auerbach, *J. Org. Chem.*, **36**, 31 (1971).
381. G. J. Siuta, R. W. Franck, and R. J. Kempton, *J. Org. Chem.*, **39**, 3739 (1974).
382. M. G. Barlow, R. N. Haszeldine, and W. D. Morton, *J. Chem. Soc., Chem. Commun.*, 931 (1969).
383. L. A. Paquette, R. J. Haluska, M. R. Short, L. K. Read, and J. Clardy, *J. Am. Chem. Soc.*, **94**, 529 (1972).
384. J. Vebrel, E. Cerutti, and R. Carrie, *C.R. Acad. Sci. Paris, Ser. C*, **288**, 351 (1979).
385. P. L. Coe and A. G. Holton, *J. Fluorine Chem.*, **10**, 553 (1977).
386. G. F. Bannikov, M. G. Luchinskaya, G. A. Nikiforov, and V. V. Ershov, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 2007 (1976).
387. W. Lwowski, Ed., *Nitrenes*, Wiley-Interscience, New York, 1970.
388. A. G. Anastassiou, *J. Am. Chem. Soc.*, **90**, 1527 (1968).
389. R. A. Abramovich, C. I. Azogu, and R. G. Sutherland, *J. Chem. Soc., Chem. Commun.*, 134 (1971).
390. R. A. Abramovitch and S. R. Challand, *J. Chem. Soc., Chem. Commun.*, 1160 (1972).
391. R. A. Abramovitch, S. R. Challand, and Y. Yamada, *J. Org. Chem.*, **40**, 1541 (1975).
392. W. Lwowski and T. J. Maricich, *J. Am. Chem. Soc.*, **87**, 3630 (1965).
393. R. Grigg, *J. Chem. Soc., Chem. Commun.*, 1238 (1967).
394. A. V. Kamernitskii, Z. I. Istomina, E. P. Serebrayakov, and A. M. Turuta, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 186 (1979).
395. R. P. Gandhi, M. Singh, and T. D. Sharma, *Indian J. Chem.*, **12**, 117 (1974); *Chem. Abstr.*, **81**, 105796 (1974).
396. K. Hafner, W. Kaiser, and R. Puttner, *Tetrahedron Lett.*, 3953 (1964).
397. T. Hiyama, H. Taguchi, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **47**, 2909 (1974).
398. H. Nozaki, T. Okuyama, and S. Fujita, *Can. J. Chem.*, **46**, 3333 (1968).
399. J. F. W. Keana, S. B. Keana, and D. Beetham, *J. Org. Chem.*, **32**, 3057 (1967).
400. M. P. Sammes and A. Rahman, *J. Chem. Soc., Perkin Trans. 1*, 344 (1972).
401. V. P. Semenov, A. N. Studenikov, A. P. Prosypkina, and K. A. Ogloblin, *J. Org. Chem. USSR*, **13**, 2056 (1977).
402. Y. Hayashi and D. Swern, *J. Am. Chem. Soc.*, **95**, 5205 (1973).
403. W. Lwowski and J. S. McConaghy, Jr., *J. Am. Chem. Soc.*, **87**, 5490 (1965).
404. S. Masamune and N. T. Castellucci, *Angew. Chem., Int. Ed. Engl.*, **3**, 582 (1964).
405. S. Fujita, T. Hiyama, and H. Nozaki, *Tetrahedron*, **26**, 4347 (1970).
406. G. R. Wiger and M. F. Rettig, *J. Am. Chem. Soc.*, **98**, 4168 (1976).
407. H. Röttele, G. Heil, and G. Schröder, *Chem. Ber.*, **111**, 84 (1978).
408. Y. Sato, H. Kojima, and H. Shirai, *J. Org. Chem.*, **41**, 3325 (1976).
409. D. Aue, H. Iwahashi, and D. F. Shellhamer, *Tetrahedron Lett.*, 3719 (1973).
410. J. N. Labows, Jr., and D. Swern, *Tetrahedron Lett.*, 4523 (1971).
411. I. Brown and O. E. Edwards, *Can. J. Chem.*, **43**, 1266 (1965).
412. R. P. Gandhi and M. Singh, *Indian J. Chem.*, **8**, 485 (1970); *Chem. Abstr.*, **73**, 56298 (1970).

413. I. Brown, O. E. Edwards, J. M. McIntosh, and D. Vocelle, *Can. J. Chem.*, **47**, 2751 (1969).
414. D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 146 (1969).
415. L. Hoesch and A. S. Dreiding, *Chimia*, **23**, 405 (1969).
416. D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *J. Chem. Soc., C*, 576 (1970).
417. L. Hoesch, N. Egger, and A. S. Dreiding, *Helv. Chim. Acta*, **61**, 795 (1978).
418. T. L. Gilchrist, C. W. Rees, and E. Stanton, *J. Chem. Soc., C*, 988 (1971).
419. L. A. Carpino and R. K. Kirkley, *J. Am. Chem. Soc.*, **92**, 1784 (1970).
420. A. G. Anderson, Jr., and D. R. Fagerburg, *J. Heterocycl. Chem.*, **6**, 987 (1969).
421. H. Person, F. Tonnard, A. Foucaud, and C. Fayat, *Tetrahedron Lett.*, 2495 (1973).
422. L. Hoesch and A. S. Dreiding, *Chimia*, **26**, 629 (1972).
423. G. R. Meyer and J. Stafinoha, Jr., *J. Heterocycl. Chem.*, **12**, 1085 (1975).
424. H. Person and A. Foucaud, *Bull. Soc. Chim. Fr.*, 1119 (1976).
425. A. Foucaud and M. Baudru, *C.R. Acad. Sci. Paris, Ser. C*, **271**, 1613 (1970).
426. D. J. Anderson, D. C. Horwell, and R. S. Atkinson, *J. Chem. Soc., C*, 624 (1971).
427. R. Annunziata, R. Fornasier, and F. Montanari, *J. Org. Chem.*, **39**, 3195 (1974).
428. A. G. Anderson, Jr., and D. R. Fagerburg, *Tetrahedron*, **29**, 2973 (1973).
429. D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 550 (1973).
430. T. L. Gilchrist, C. W. Rees, and E. Stanton, *J. Chem. Soc., C*, 3036 (1971).
431. R. S. Atkinson and C. W. Rees, *J. Chem. Soc., C*, 778 (1969).
432. M. Baudru and A. Foucaud, *C.R. Acad. Sci. Paris, Ser. C*, **270**, 104 (1970).
433. K. K. Mayer, F. Schröppel, and J. Sauer, *Tetrahedron Lett.*, 2899 (1972).
434. C. W. Rees and M. Yelland, *J. Chem. Soc., Chem. Commun.*, 377 (1969).
435. C. Cauguis and M. Genies, *Tetrahedron Lett.*, 3959 (1971).
436. C. Cauguis, B. Chabaud, and M. Genies, *Bull. Soc. Chim. Fr.*, 3487 (1973).
437. D. W. Jones, *J. Chem. Soc., Chem. Commun.*, 884 (1972).
438. F. A. Carey and L. J. Hayes, *J. Org. Chem.*, **38**, 3107 (1973).
439. B. V. Ioffe and E. V. Koroleva, *Tetrahedron Lett.*, 619 (1973).
440. B. V. Ioffe, Y. P. Artsybasheva, and I. G. Zenkovich, *Dokl. Chem.*, **231**, 742 (1976).
441. B. V. Ioffe and E. V. Koroleva, *J. Org. Chem. USSR*, **8**, 1581 (1972).
442. W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *J. Am. Chem. Soc.*, **89**, 5046 (1967).
443. W. Nagata, *Lect. Heterocycl. Chem.*, **1**, 29 (1972).
444. P. S. Portoghese and D. T. Sepp, *Tetrahedron*, **29**, 2253 (1973).
445. W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *J. Am. Chem. Soc.*, **90**, 1650 (1968).
446. G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Am. Chem. Soc.*, **89**, 332 (1967).
447. R. E. Brooks, J. O. Edwards, G. E. Levy, and F. Smyth, *Tetrahedron*, **22**, 1279 (1966).
448. M. Abou-Gharbia and M. M. Joullie, *J. Pharm. Sci.*, **66**, 1653 (1977).
449. K. Ichimura and M. Ohta, *Tetrahedron Lett.*, 807 (1966).
450. K. Ichimura and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 1933 (1967).
451. R. R. Kostikov, A. F. Khlebnikov, and K. A. Ogloblin, *J. Org. Chem. USSR*, **9**, 2360 (1973).
452. R. R. Kostikov, A. F. Khlebnikov, and K. A. Ogloblin, *J. Org. Chem. USSR*, **13**, 1721 (1977).
453. J. Graefe, *Z. Chem.*, **14**, 469 (1974).

454. M. K. Meilahn, D. K. Olsen, W. J. Brittain, and R. T. Anders, *J. Org. Chem.*, **43**, 1346 (1978).
455. D. Seyferth and W. Tronich, *J. Organomet. Chem.*, **21**, P3 (1970).
456. D. Seyferth and H. Shih, *J. Am. Chem. Soc.*, **97**, 2508 (1972).
457. J. Seyferth, W. Tronich, and H. Shih, *J. Org. Chem.*, **39**, 158 (1974).
458. J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 321 (1965).
459. H. Yamanaka, J. Kikui, K. Teramura, and T. Ando, *J. Org. Chem.*, **41**, 3794 (1976).
460. R. R. Kostikov, A. F. Khlebnikov, and K. A. Ogloblin, *Dokl. Chem.*, **223**, 507 (1975).
461. N. S. Kozlov, V. D. Pak, and V. V. Mashevskii, *Khim. Geterotsikl. Soedin.*, 84 (1974); *Chem. Abstr.*, **80**, 120656 (1974).
462. N. S. Kozlov, V. D. Pak, and V. V. Mashevskii, *Dokl. Akad. Nauk Beloruss. SSR*, **16**, 1020 (1972); *Chem. Abstr.*, **78**, 29516 (1973).
463. P. Baret, H. Buffet, and J. L. Pierre, *Bull. Soc. Chim. Fr.*, 825 (1972).
464. P. Baret, H. Buffet, and J. L. Pierre, *Bull. Soc. Chim. Fr.*, 2493 (1972).
465. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
466. V. H. Metzger and K. Seelert, *Z. Naturforsch. B.*, **18**, 336 (1963).
467. V. Franzen and H. -E. Driesen, *Chem. Ber.*, **96**, 1881 (1963).
468. C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, **95**, 7692 (1973).
469. C. R. Johnson, R. A. Kirchhoff, R. J. Reischer, and G. F. Katekar, *J. Am. Chem. Soc.*, **95**, 4287 (1973).
470. C. R. Johnson, M. Haake, and C. W. Schroeck, *J. Am. Chem. Soc.*, **92**, 6594 (1970).
471. E. Liepins, V. A. Pestunovich, A. V. Eremeev, D. A. Tikhomirov, and N. P. Gaidarova, *Khim. Geterotsikl. Soedin.*, 906 (1977); *Chem. Abstr.*, **87**, 183795 (1977).
472. S. Hillers, A. V. Eremeev, D. A. Tikhomirov, and E. Liepins, *Khim. Geterotsikl. Soedin.*, 426 (1975); *Chem. Abstr.*, **83**, 28023 (1975).
473. A. G. Hortmann and D. A. Robertson, *J. Am. Chem. Soc.*, **89**, 5974 (1967).
474. N. Furukawa, S. Oae, and T. Yoshimura, *Synthesis*, 30 (1976).
475. T. Yoshimura, T. Akasaka, N. Furukawa, and S. Oae, *Heterocycles*, **7**, 287 (1977).
476. D. O. Spry, *Tetrahedron Lett.*, 3611 (1977).
477. W. H. Urry, Z. L. F. Gaibel, J. C. Duggan, and S. S. Teng, *J. Am. Chem. Soc.*, **95**, 4338 (1973).
478. E. Schmitz and K. Joehnisch, *Khim. Geterotsikl. Soedin.*, 1629 (1974); *Chem. Abstr.*, **82**, 111859 (1975).
479. T. Fukunaga, *J. Am. Chem. Soc.*, **94**, 3242 (1972).
480. E. Bruer and I. Ronen-Braunstein, *J. Chem. Soc., Chem. Commun.*, 949 (1974).
481. E. Bruer, S. Zbaida, J. Pesso, and S. Levi, *Tetrahedron Lett.*, 3103 (1975).
482. S. Zbaida and E. Bruer, *Tetrahedron*, **34**, 1241 (1978).
483. E. Breuer and S. Zbaida, *J. Org. Chem.*, **42**, 1904 (1977).
484. D. St. C. Black and V. C. Davies, *J. Chem. Soc., Chem. Commun.*, 416 (1975).
485. D. St. C. Black and V. C. Davies, *Aust. J. Chem.*, **29**, 1735 (1976).
486. E. Bruer, S. Zbaida, J. Pesso, and I. Ronen-Braunstein, *Tetrahedron*, **33**, 1145 (1977).
487. I. Shahak, Y. Ittah, and J. Blum, *Tetrahedron Lett.*, 4003 (1976).
488. R. Appel and M. Halstenberg, *Chem. Ber.*, **109**, 814 (1976).
489. J. E. Baldwin, R. G. Pudussery, A. K. Qureshi, and B. Sklarz, *J. Am. Chem. Soc.*, **90**, 5325 (1968).
490. I. Adashi, R. Miyazaki, and H. Kano, *Chem. Pharm. Bull. (Jpn.)*, **22**, 70 (1974).
491. R. Gree and R. Carrie, *J. Am. Chem. Soc.*, **99**, 6667 (1977).

492. R. Gree and R. Carrie, *J. Chem. Soc., Chem. Commun.*, 112 (1975).
493. V. A. Tartakovskii, O. A. Luk'yanov, and S. S. Novikov, *Dokl. Chem.*, **178**, 21 (1968).
494. V. A. Tartakovskii, O. A. Luk'yanov, and S. S. Novikov, *Bull. Acad. Sci. USSR Chem. Sci.*, 2186 (1966).
495. J. A. Deyrup and W. A. Szabo, *J. Org. Chem.*, **40**, 2048 (1975).
496. C. L. Deyrup, J. A. Deyrup, and M. Hamilton, *Tetrahedron Lett.*, 3437 (1977).
497. K. Burger, A. Meffert, and S. Bauer, *J. Fluorine Chem.*, **10**, 57 (1977).
498. R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).
499. R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Angew. Chem., Int. Ed. Engl.*, **3**, 136 (1964).
500. A. Padwa and E. Vega, *J. Org. Chem.*, **40**, 175 (1975).
501. C. Shin. Y. Yonezawa, and J. Yoshimura, *Tetrahedron Lett.*, 3995 (1972).
502. A. G. Anastassiou, S. W. Eachus, R. L. Elliott, and E. Yakali, *J. Chem. Soc., Chem. Commun.*, 531 (1972).
503. H. Hiraoka, *J. Chem. Soc., Chem. Commun.*, 1610 (1971).
504. L. Kaplan, J. W. Paulik, and K. E. Wilzbach, *J. Am. Chem. Soc.*, **94**, 3283 (1972).
505. S. J. Cristol, T. D. Ziebarth, and G. A. Lee, *J. Am. Chem. Soc.*, **96**, 7844 (1974).
506. J. A. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 413 (1977).
507. E. Schmitz, U. Bicker, S. Schramm, and K. P. Dietz, *J. Prakt. Chem.*, **320**, 413 (1978).
508. T. Kametani, F. F. Ebetino, K. Fukumoto, and A. I. Myers, *Heterocycles*, **2**, 559 (1974); *Chem. Abstr.*, **82**, 43294 (1975).
509. P. N. Confalone, E. D. Lollar, G. Pizzolato, and M. Uskokovic, *J. Am. Chem. Soc.*, **100**, 6291 (1978).
510. A. A. Dudinskaya, L. I. Khmelnitsky, I. D. Petrova, E. B. Barnyshnikoya, and S. S. Novikov, *Tetrahedron*, **27**, 4053 (1971).
511. A. H. Lawrence, D. R. Arnold, J. B. Stothers, and P. Lapouyade, *Tetrahedron Lett.*, 2025 (1972).
512. R. E. Lutz and A. B. Turner, *J. Org. Chem.*, **33**, 516 (1968).
513. P. Tarburton, A. Chung, R. C. Badger, and N. H. Cromwell, *J. Heterocycl. Chem.*, **13**, 295 (1976).
514. A. Padwa, D. Dean, A. Mazzu, and E. Vega, *J. Am. Chem. Soc.*, **95**, 7168 (1973).
515. P. Tarburton, D. K. Wall, and N. H. Cromwell, *J. Heterocycl. Chem.*, **15**, 1281 (1978).
516. A. B. Turner, H. W. Heine, J. Irving, and J. B. Bush, Jr., *J. Am. Chem. Soc.*, **87**, 1050 (1965).
517. G. M. Rubottom, G. R. Stevenson, J. C. Chabala, and V. Pascucci, *Tetrahedron Lett.*, 3591 (1972).
518. R. Huisgen, W. Scheer, and H. Huber, *J. Am. Chem. Soc.*, **89**, 1753 (1967).
519. R. Huisgen, W. Scheer, and H. Mäder, *Angew. Chem., Int. Ed. Engl.*, **8**, 602 (1969).
520. P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, **35**, 888 (1970).
521. H. Hermann, R. Huisgen, and H. Mäder, *J. Am. Chem. Soc.*, **93**, 1779 (1971).
522. J. H. Hall, R. Huisgen, C. H. Ross, and W. Scheer, *J. Chem. Soc., Chem. Commun.*, 1188 (1971).
523. J. H. Hall and R. Huisgen, *J. Chem. Soc., Chem. Commun.*, 1187 (1971).
524. A. G. Anastassiou and R. B. Hammer, *J. Am. Chem. Soc.*, **94**, 303 (1972).
525. F. Texier, J. Guenzet, and B. Merah, *C.R. Acad. Sci. Paris, Ser. C*, **277**, 1371 (1973).
526. P. F. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 542.

527. O. C. Dermer and G. E. Ham, Ref. 2, p. 121.
528. M. -T. Maurette, A. Lopez, R. Martino, and A. Lattes, *C.R. Acad. Sci. Paris, Ser. C*, **282**, 599 (1976).
529. W. Funke, *Justus Liebigs Ann. Chem.*, **725**, 15 (1969).
530. R. G. Kostyanovskii, D. A. Pan'shin, and T. Z. Papoyan, *Dokl. Chem.*, **177**, 1160 (1967).
531. R. G. Kostyanovskii, O. A. Pan'shin, and V. F. Bystrov, *Bull. Acad. Sci. USSR*, 869 (1962).
532. F. Lautenschlaeger, *J. Heterocycl. Chem.*, **7**, 1413 (1970).
533. K. Nakajima, F. Takai, T. Tanaka, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **51**, 1577 (1978).
534. E. D. Bergmann, Z. Goldschmidt, J. Migron, and J. Dancona, *J. Polym. Sci.*, Part C, **31**, 375 (1970).
535. E. J. Lien and G. L. Tong, *Cancer Chemother. Rep.*, Part 1, **57**, 251 (1973).
536. Y. Y. Hsiao, T. J. Bardos, G. L. Wampler, and W. Regelson, *J. Med. Chem.*, **18**, 195 (1975).
537. G. Zon, W. Egan, and J. B. Stokes, *Biochem. Pharmacol.*, **25**, 989 (1976).
538. K. C. Tsou, D. Bender, N. Santora, L. David, S. Damle, and A. B. Borkovec, *J. Med. Chem.*, **19**, 806 (1976).
539. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 547.
540. O. C. Dermer and G. E. Ham, Ref. 2, p. 172.
541. G. Sosnovsky and M. Konieczny, *Synthesis*, 583 (1978).
542. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 548.
543. O. C. Dermer and G. E. Ham, Ref. 2, p. 194.
544. O. C. Dermer and G. E. Ham, Ref. 2, p. 200.
545. R. G. Kostyanovskii, Y. I. Elnatanov, and K. Khafizov, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1815 (1970).
546. F. Lautenschlaeger, M. Myhre, F. Hopton, and J. Wilson, *J. Heterocycl. Chem.*, **8**, 241 (1971).
547. Z. E. Samojlova and R. G. Kostyanovskii, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 974 (1970).
548. A. Kumar, H. Ila, and H. Junjappa, *J. Chem. Soc., Chem. Commun.*, 592 (1976).
549. N. F. Savenkov, P. S. Khokhlov, S. G. Zhemchuzhin, and G. A. Lapitskii, *J. Org. Chem. USSR*, **6**, 710 (1970).
550. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 545.
551. O. C. Dermer and G. E. Ham, Ref. 2, p. 136.
552. G. Manecke and H. -J. Kretzschmar, *Makromol. Chem.*, **169**, 15 (1973).
553. P. Joseph-Nathan, V. Mendoza, and E. Garcia G., *J. Org. Chem.*, **37**, 3950 (1972).
554. G. Ricart, D. Couturier, and C. Glacet, *C.R. Acad. Sci. Paris, Ser. C*, **280**, 953 (1975).
555. F. V. Shomina, V. S. Etlis, and A. P. Sineokov, *Khim. Geterotsikl. Soedin.*, 1216 (1973); *Chem. Abstr.*, **79**, 146447 (1973).
556. K. F. Thom, N. P. Sweeny, and J. J. McBrady, *J. Heterocycl. Chem.*, **6**, 667 (1969).
557. G. P. Rozing, T. J. H. Moinat, H. DeKoning, and H. O. Huisman, *Heterocycles*, **4**, 719 (1976); *Chem. Abstr.*, **85**, 20998 (1976).
558. N. Murai, M. Komatsu, T. Yagii, H. Nishihara, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, **42**, 847 (1977).

559. W. E. Truce and D. W. Onken, *J. Org. Chem.*, **40**, 3200 (1975).
560. W. E. Truce and L. D. Markley, *J. Org. Chem.*, **35**, 3275 (1970).
561. M. A. Calcagno and E. E. Schweizer, *J. C.*, *. Chem.*, **43**, 4207 (1978).
562. A. Niederhauser, A. Frey, and M. Neuenschwander, *Helv. Chim. Acta*, **56**, 944 (1973).
563. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 546.
564. O. C. Dermer and G. E. Ham, Ref. 2, p. 160.
565. T. Kato, Y. Yamamoto, and M. Sato, *Yakugaku Zasshi*, **91**, 384 (1971); *Chem. Abstr.*, **75**, 20058 (1971).
566. A. Hassner and A. Kascheres, *Tetrahedron Lett.*, 4623 (1970).
567. F. Lautenschlaeger, *J. Heterocycl. Chem.*, **7**, 1283 (1970).
568. R. Rajagopalan and C. N. Talaty, *J. Am. Chem. Soc.*, **88**, 5048 (1966).
569. T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.*, **42**, 556 (1969).
570. T. Sasaki, T. Yoshioka, and Y. Suzuki, *Bull. Chem. Soc. Jpn.*, **44**, 185 (1971).
571. D. A. Tomalia, T. J. Giacobbe, and W. A. Sprenger, *J. Org. Chem.*, **36**, 2142 (1971).
572. E. V. Dehmlow and H. -J. Westendorf, *Z. Naturforsch. B*, **25**, 1191 (1970).
573. D. Bormann, *Angew. Chem., Int. Ed. Engl.*, **12**, 768 (1973).
574. G. Zinner and W. Kilwing, *Chem. -Ztg.*, **97**, 156 (1973); *Chem. Abstr.*, **79**, 5186 (1973).
575. A. V. Eremeev, D. A. Tikhomirov, V. A. Tyusheva, and E. Liepins, *Khim. Geterotsikl. Soedin.*, 753 (1978); *Chem. Abstr.*, **89**, 146873 (1978).
576. A. V. Eremeev, D. A. Tikhomirov, V. A. Tyusheva, and E. Liepins, *Khim. Geterotsikl. Soedin.*, 483 (1978); *Chem. Abstr.*, **89**, 59808 (1978).
577. Y. Oshiro, K. Yamamoto, and S. Komori, *Yuki Gosei Kagaku Kyokai Shi*, **24**, 945 (1966); *Chem. Abstr.*, **66**, 37706 (1967).
578. A. V. Eremeev, D. A. Tikhomirov, and E. Liepins, *Khim. Geterotsikl. Soedin.*, 207 (1977); *Chem. Abstr.*, **87**, 5737 (1977).
579. S. C. Kuo and W. H. Daly, *J. Org. Chem.*, **35**, 1861 (1970).
580. C. L. Stevens and P. M. Pillai, *J. Org. Chem.*, **37**, 173 (1972).
581. C. L. Stevens, J. M. Cahoon, T. R. Potts, and P. M. Pillai, *J. Org. Chem.*, **37**, 3130 (1972).
582. E. V. Dehmlow, *Chem. Ber.*, **102**, 3863 (1969).
583. R. K. Müller, D. Felix, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 1479 (1970).
584. S. Hillers, A. V. Eremeev, M. Lidaks, and V. A. Kholodnikov, *Khim. Geterotsikl. Soedin.*, 472 (1970); *Chem. Abstr.*, **73**, 45228 (1970).
585. S. Hillers, A. V. Eremeev, and M. Lidaks, *Khim. Geterotsikl. Soedin.*, 1 (1970); *Chem. Abstr.*, **72**, 100390 (1970).
586. E. Keschmann and E. Zbiral, *Tetrahedron*, **31**, 1817 (1975).
587. J. Schweng and E. Zbiral, *Monatsh. Chem.*, **107**, 537 (1976).
588. J. Schweng and E. Zbiral, *Tetrahedron*, **31**, 1823 (1975).
589. Y. Ito, H. Ida, and T. Matsuura, *Tetrahedron Lett.*, 3119 (1978).
590. J. A. Deyrup and R. B. Greenwald, *J. Am. Chem. Soc.*, **87**, 4538 (1965).
591. J. M. Gaillot, Y. Gelas-Mialhe, and R. Vessiere, *Can. J. Chem.*, **57**, 1958 (1979).
592. J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **35**, 3424 (1970).
593. L. Wartski, C. Wakselman, and A. S. Escudero, *Tetrahedron Lett.*, 4193 (1970).
594. L. Duhamel, P. Duhamel, and P. Siret, *Bull. Soc. Chim. Fr.*, 2460 (1973).
595. L. Wartski, *Bull. Soc. Chim. Fr.*, 1663 (1975).

596. D. K. Wall, J. -L. Imbach, A. E. Pohland, R. C. Badger, and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 77 (1968).
597. J. L. Pierre, H. Handel, and P. Baret, *J. Chem. Soc., Chem. Commun.*, 551 (1972).
598. J. A. Deyrup, C. L. Moyer, and P. S. Dreifus, *J. Org. Chem.*, **35**, 3428 (1970).
599. J. L. Pierre, H. Handel, and P. Baret, *Tetrahedron*, **30**, 3213 (1974).
600. H. Handel and J. L. Pierre, *Tetrahedron*, **31**, 997 (1975).
601. A. B. Turner and R. E. Lutz, *J. Heterocycl. Chem.*, **5**, 437 (1968).
602. S. Oida, H. Kuwano, Y. Ohashi, and E. Ohki, *Chem. Pharm. Bull. (Jpn.)*, **18**, 2478 (1970).
603. G. Szeimies, *Chem. Ber.*, **106**, 3695 (1973).
604. D. Borel, Y. Gelas-Mialhe, and R. Vessiere, *C.R. Acad. Sci. Paris, Ser. C*, 1393 (1974).
605. D. Borel, Y. Gelas-Mialhe, and R. Vessiere, *Can. J. Chem.*, **54**, 1582 (1976).
606. L. Wartski and A. Sierra-Escudero, *C.R. Acad. Sci. Paris, Ser. C*, **279**, 149 (1974).
607. H. W. Heine, R. H. Weese, R. A. Cooper, and A. J. Durbetaki, *J. Org. Chem.*, **32**, 2708 (1967).
608. A. Padwa and E. Glazer, *J. Am. Chem. Soc.*, **94**, 7788 (1972).
609. D. I. Garling and N. H. Cromwell, *J. Org. Chem.*, **38**, 654 (1973).
610. H. W. Heine, T. A. Newton, G. J. Blosick, K. C. Irving, C. Meyer, and G. B. Corcoran, III, *J. Org. Chem.*, **38**, 651 (1973).
611. S. Hillers, A. V. Eremeev, V. A. Kholodnikov, and E. Liepins, *Khim. Geterotsikl. Soedin.*, 1212 (1975); *Chem. Abstr.*, **84**, 17032 (1976).
612. A. V. Eremeev, V. A. Kholodnikov, D. A. Tikhomirov, and E. Liepins, *Khim. Geterotsikl. Soedin.*, 758 (1977); *Chem. Abstr.*, **87**, 201407 (1977).
613. R. G. Kostyanovskii, V. F. Rudchenko, A. V. Prosyanik, M. D. Isobaev, I. I. Chervin, and V. I. Markov, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 565 (1977).
614. J. A. Deyrup and S. C. Clough, *J. Chem. Soc., Chem. Commun.*, 1620 (1970).
615. R. A. Gorski, D. J. Dagli, V. A. Patronik, and J. Wemple, *Synthesis*, 811 (1974).
616. Y. Diab, J. C. Duplan, and A. Laurent, *Tetrahedron Lett.*, 1093 (1976).
617. J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).
618. A. G. Hortmann and J. Koo, *J. Org. Chem.*, **39**, 3781 (1974).
619. M. Akiba and T. Takada, *Heterocycles*, **6**, 1861 (1977); *Chem. Abstr.*, **88**, 89549 (1977).
620. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 551.
621. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 558.
622. O. C. Dermer and G. E. Ham, Ref. 2, p. 206.
623. K. Ponsold and D. Klemm, *Chem. Ber.*, **105**, 2654 (1972).
624. G. Berti, G. Camici, B. Macchia, F. Macchia, and L. Monti, *Tetrahedron Lett.*, 2591 (1972).
625. U. Harder, E. Pfeil, and K. -F. Zenner, *Chem. Ber.*, **97**, 510 (1964).
626. L. Wartski and C. Wakselman, *Bull. Soc. Chim. Fr.*, 1478 (1972).
627. A. Hassner and J. E. Galle, *J. Org. Chem.*, **41**, 2273 (1976).
628. G. Alvernhe, E. Kozlowska-Gramsz, S. Lacombe-Ber, and A. Laurent, *Tetrahedron Lett.*, 5203 (1978).
629. D. V. Lefemine, M. Dann, F. Barbatschi, W. K. Hausmann, V. Zbinovsky, P. Monnikendam, J. Adam, and N. Bohonos, *J. Am. Chem. Soc.*, **84**, 3184 (1962).
630. J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer,

R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidnacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84**, 3185 (1962).

631. J. S. Webb, D. B. Consulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidnacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84**, 3187 (1962).
632. J. L. Kurz, B. K. Gillard, D. A. Robertson, and A. G. Hortmann, *J. Am. Chem. Soc.*, **92**, 5008 (1970).
633. A. G. Hortmann and D. A. Robertson, *J. Am. Chem. Soc.*, **94**, 2758 (1972).
634. W. Funke, *Chem. Ber.*, **102**, 3148 (1969).
635. A. Hassner and S. S. Burke, *Tetrahedron*, **30**, 2613 (1974).
636. N. Milstein, *J. Heterocycl. Chem.*, **5**, 339 (1968).
637. R. D. Westland, M. H. Lin, and J. M. Vandenbelt, *J. Heterocycl. Chem.*, **8**, 405 (1971).
638. D. Kalsines, A. V. Kamernitskii, and A. M. Turuta, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1735 (1976).
639. R. A. Wohl and D. F. Headley, *J. Org. Chem.*, **37**, 4401 (1972).
640. T. Hiyama, H. Koide, S. Fujita, and H. Nozaki, *Tetrahedron*, **29**, 3137 (1973).
641. G. R. Hansen and T. E. Burg, *J. Heterocycl. Chem.*, **5**, 305 (1968).
642. S. Tsuboyama, K. Tsuboyama, I. Higashi, and M. Yanagita, *Tetrahedron Lett.*, 1367 (1970).
643. K. Tsuboyama, S. Tsuboyama, J. Uzawa, K. Kobayashi, and T. Sakurai, *Tetrahedron Lett.*, 4603 (1977).
644. C. R. Rasmussen and D. L. Shaw, *J. Org. Chem.*, **39**, 1560 (1974).
645. K. Kitamogi and Y. Takano, Japanese Patent 68 03, 185; *Chem. Abstr.*, **69**, 96348 (1968).
646. C. R. Dick, *J. Org. Chem.*, **32**, 72 (1967).
647. H. J. Nestler and H. Bestian, *Justus Liebigs Ann. Chem.*, 460 (1974).
648. F. Piper and K. Rühlmann, *J. Organomet. Chem.*, **121**, 149 (1976).
649. E. S. Gubnitskaya, A. M. Pinchuk, and L. A. Zolotareva, *J. Gen. Chem. USSR*, **45**, 1226 (1975).
650. I. Okada, T. Takahama, and R. Sudo, *Bull. Chem. Soc. Jpn.*, **43**, 2591 (1970).
651. M. Narisada, F. Wanatabe, and W. Nagata, *Tetrahedron Lett.*, 3681 (1971).
652. D. A. Tomalia, *Tetrahedron Lett.*, 2559 (1967).
653. C. K. Johnson, *J. Org. Chem.*, **32**, 1508 (1967).
654. T. A. Foglia, L. M. Gregory, G. Maerker, and S. F. Osman, *J. Org. Chem.*, **36**, 1068 (1971).
655. H. Stamm, *Pharm. Zent.*, **107**, 440 (1968).
656. E. Gulbins, R. Morlock, and K. Hamann, *Justus Liebigs Ann. Chem.*, **698**, 180 (1966).
657. V. I. Markov and D. A. Danileiko, *Zh. Org. Khim.* (Engl. trans.), **10**, 1269 (1974).
658. (a) R. Chaabouni, A. Laurent, and B. Marquet, *Tetrahedron Lett.*, 757 (1976); (b) A. Hassner, R. D'Costa, A. T. McPhail, and W. Butler, *Tetrahedron Lett.*, 3691 (1981).
659. M. Barrelle and M. Apparu, *Tetrahedron*, **33**, 1309 (1977).
660. Y. Hata and M. Watanabe, *Tetrahedron*, **30**, 3569 (1974).
661. G. E. Ham, *J. Org. Chem.*, **29**, 3052 (1964).
662. K. Ponsold and W. Ihn, *Tetrahedron Lett.*, 4121 (1972).
663. K. Ponsold and D. Klemm, *Chem. Ber.*, **99**, 1502 (1966).
664. M. J. Robins and S. D. Hawrelak, *Tetrahedron Lett.*, 3653 (1978).
665. R. N. Castle and S. Takano, *J. Heterocycl. Chem.*, **5**, 113 (1968).
666. D. A. Tomalia, D. P. Sheetz, and G. E. Ham, *J. Org. Chem.*, **35**, 47 (1970).

667. R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 3828 (1965).
668. H. W. Heine, G. B. Lowrie, III, and K. C. Irving, *J. Org. Chem.*, **35**, 444 (1970).
669. G. S. Bates, *J. Chem. Soc., Chem. Commun.*, 161 (1979).
670. H. Stamm and W. Wiesert, *Chem. Ber.*, **111**, 502 (1978).
671. H. Stamm, L. Schneider, and J. Budny, *Chem. Ber.*, **109**, 2005 (1976).
672. H. Stamm and W. Wiesert, *Chem. Ber.*, **111**, 2665 (1978).
673. H. W. Heine and T. Newton, *Tetrahedron Lett.*, 1859 (1967).
674. S. Fujita, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, 1677 (1969).
675. M. A. Calcagno, H. W. Heine, C. Kruse, and W. A. Kofke, *J. Org. Chem.*, **39**, 162 (1974).
676. A. P. Sineokov, F. N. Gladysheva, V. S. Etlis, and V. S. Kutyreva, *Khim. Geterotsikl. Soedin.*, 475 (1970); *Chem. Abstr.*, **73**, 45229 (1970).
677. V. R. Gaertner, *J. Heterocycl. Chem.*, **8**, 519 (1971).
678. H. Stamm and L. Schneider, *Chem. Ber.*, **108**, 500 (1975).
679. T. Kametani and M. Ihara, *Chem. Pharm. Bull. (Jpn.)*, **19**, 2256 (1971).
680. J. Lehmann and H. Wamhoff, *Synthesis*, 546 (1973).
681. W. Klötzer, *Monatsh. Chem.*, **101**, 1841 (1970).
682. H. Stamm, *Tetrahedron Lett.*, 1205 (1971).
683. J. E. Dolfini and J. D. Simpson, *J. Am. Chem. Soc.*, **87**, 4381 (1965).
684. R. Bartnik, A. Laurent, and S. Lesniak, *C.R. Acad. Sci. Paris, Ser. C*, **288**, 505 (1979).
685. A. Padwa and W. Eisenhardt, *J. Org. Chem.*, **35**, 2472 (1970).
686. A. E. Pohland, M. C. McMaster, R. C. Badger, and N. H. Cromwell, *J. Am. Chem. Soc.*, **87**, 2510 (1965).
687. P. Tarburton, D. K. Wall, and N. H. Cromwell, *J. Heterocycl. Chem.*, **13**, 411 (1976).
688. M. J. Haddadin and A. Hassner, *J. Org. Chem.*, **38**, 3466 (1973).
689. M. J. Haire and G. A. Boswell, Jr., *J. Org. Chem.*, **42**, 4251 (1977).
690. P. E. Fanta, in *Heterocyclic Compounds with Three- and Four-Membered Rings* (Ref. 1), p. 556.
691. O. C. Dermer and G. E. Ham, Ref. 2, p. 280.
692. H. W. Heine, "Rearrangements of Aziridines," in *Mechanisms of Molecular Migrations*, Vol. 3, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, 1971, p. 159.
693. H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31**, 2662 (1966).
694. T. A. Foglia, L. M. Gregory, and G. Maerker, *J. Org. Chem.*, **35**, 3779 (1970).
695. T. Nishiguchi, H. Tochio, A. Nabeya, and Y. Iwakura, *J. Am. Chem. Soc.*, **91**, 5835 (1969).
696. T. Nishiguchi, H. Tochio, A. Nabeya, and Y. Iwakura, *J. Am. Chem. Soc.*, **91**, 5841 (1969).
697. A. Nabeya, T. Shigemoto, and Y. Iwakura, *J. Org. Chem.*, **40**, 3536 (1975).
698. S. P. McManus, R. A. Hearn, and C. U. Pittman, Jr., *J. Org. Chem.*, **41**, 1895 (1976).
699. C. U. Pittman, Jr., and S. P. McManus, *J. Org. Chem.*, **35**, 1187 (1970).
700. P. E. Fanta and M. K. Kathan, *J. Heterocycl. Chem.*, **1**, 293 (1964).
701. C. H. Chang and P. E. Fanta, *J. Org. Chem.*, **36**, 3907 (1971).
702. I. J. Burnstein, P. E. Fanta, and B. S. Green, *J. Org. Chem.*, **35**, 4085 (1970).
703. R. Hoffmann and R. B. Woodward, *Acc. Chem. Res.*, **1**, 17 (1968).
704. J. A. Berson and L. Salem, *J. Am. Chem. Soc.*, **94**, 8917 (1972).
705. P. G. Mente, H. W. Heine, and G. R. Scharoubim, *J. Org. Chem.*, **33**, 4547 (1968).
706. H. W. Heine and G. D. Wachob, *J. Org. Chem.*, **37**, 1049 (1972).

707. V. P. Semenov, A. P. Prosypkina, O. F. Gavrilova, and K. A. Ogloblin, *Khim. Geterotsikl. Soedin.*, 464 (1977); *Chem. Abstr.*, **87**, 68211 (1977).
708. D. Haidukewych and A. I. Meyers, *Tetrahedron Lett.*, 3031 (1972).
709. P. E. Fanta, R. J. Smat, and J. P. Krikau, *J. Heterocycl. Chem.*, **5**, 419 (1968).
710. D. A. Tomalia, N. D. Ojha, and B. P. Thill, *J. Org. Chem.*, **34**, 1400 (1969).
711. H. W. Heine and M. S. Kaplan, *J. Org. Chem.*, **32**, 3069 (1967).
712. P. Reynaud, R. C. Moreau, and P. Fodor, *C.R. Acad. Sci. Paris, Ser. C*, **266**, 632 (1968).
713. F. A. Vingiello, M. P. Rorer, and M. A. Ogliaruso, *J. Chem. Soc., Chem. Commun.*, 329 (1971).
714. Y. Iwakura, A. Nabeya, and T. Nishiguchi, *J. Org. Chem.*, **32**, 2362 (1967).
715. A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).
716. B. T. Keen, D. K. Krass, and W. W. Paudler, *J. Heterocycl. Chem.*, **13**, 807 (1976).
717. F. Claudi, P. Franchetti, M. Grifantini, and S. Martelli, *J. Org. Chem.*, **39**, 3508 (1974).
718. G. E. Hardtmann and H. Ott, *J. Org. Chem.*, **39**, 3599 (1974).
719. G. Casini, F. Claudi, M. Grifantini, and S. Martelli, *J. Heterocycl. Chem.*, **11**, 377 (1974).
720. R. Huisgen and H. Mäder, *J. Am. Chem. Soc.*, **93**, 1777 (1971).
721. R. Huisgen and H. Mäder, *Angew. Chem., Int. Ed. Engl.*, **8**, 604 (1969).
722. J. W. Lown and K. Matsumoto, *J. Org. Chem.*, **36**, 1405 (1971).
723. J. W. Lown and K. Matsumoto, *J. Chem. Soc., Chem. Commun.*, 692 (1970).
724. J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **50**, 534 (1972).
725. A. M. Trozzolo, T. M. Leslie, A. S. Sarpotdar, R. D. Small, G. J. Ferraudi, T. DoMinh, and R. L. Hartless, *Pure Appl. Chem.*, **51**, 261 (1979).
726. H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.*, **102**, 904 (1969).
727. J. W. Lown, *Rec. Chem. Prog.*, **32**, 51 (1971).
728. E. Brunn and R. Huisgen, *Tetrahedron Lett.*, 473 (1971).
729. R. Huisgen, V. Martin-Ramos, and W. Scheer, *Tetrahedron Lett.*, 477 (1971).
730. R. Huisgen and W. Scheer, *Tetrahedron Lett.*, 481 (1971).
731. H. W. Heine, R. Peavy, and A. J. Durbetaki, *J. Org. Chem.*, **31**, 3924 (1966).
732. H. Nozaki, S. Fujita, and R. Noyori, *Tetrahedron*, **24**, 2193 (1968).
733. H. Matsushita and M. Noguchi, *Agric. Biol. Chem.*, **39**, 2079 (1975); *Chem. Abstr.*, **84**, 43745 (1976).
734. F. Texier, J. Jaz, and R. Carrie, *C.R. Acad. Sci. Paris, Ser. C*, **269**, 646 (1969).
735. H. Benhaoua, F. Texier, P. Guenot, J. Martelli, and R. Carrie, *Tetrahedron*, **34**, 1153 (1978).
736. J. W. Lown and M. H. Akhtar, *Can. J. Chem.*, **50**, 2236 (1972).
737. F. Texier and R. Carrie, *C.R. Acad. Sci. Paris, Ser. C*, **268**, 1396 (1969).
738. F. Texier and R. Carrie, *C.R. Acad. Sci. Paris, Ser. C*, **269**, 709 (1969).
739. F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 2373 (1972).
740. F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 3642 (1971).
741. F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 2381 (1972).
742. F. Texier and R. Carrie, *Tetrahedron Lett.*, 823 (1969).
743. F. Texier, R. Carrie, and J. Jaz, *J. Chem. Soc., Chem. Commun.*, 199 (1972).
744. M. Vaultier and R. Carrie, *Tetrahedron*, **32**, 2525 (1976).
745. J. W. Lown, J. P. Moser, and R. Westwood, *Can. J. Chem.*, **47**, 4335 (1969).
746. G. Dallas, J. W. Lown, and J. P. Moser, *J. Chem. Soc., C*, 2383 (1970).

747. G. Dallas, J. W. Lown, and J. P. Moser, *J. Chem. Soc., Chem. Commun.*, 278 (1970).
748. J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **48**, 3399 (1970).
749. J. W. Lown and B. E. Landberg, *Can. J. Chem.*, **52**, 798 (1974).
750. B. E. Landberg and J. W. Lown, *J. Chem. Soc., Perkin Trans. 1*, 1326 (1975).
751. K. Matsumoto, T. Uchida, and K. Maruyama, *Chem. Lett.*, 327 (1974).
752. T. Uchida, *J. Chem. Soc., Perkin Trans. 1*, 1315 (1978).
753. H. Duewell, *Aust. J. Chem.*, **30**, 1367 (1977).
754. H. W. Heine, A. B. Smith, III, and J. D. Bower, *J. Org. Chem.*, **33**, 1097 (1968).
755. T. DoMinh and A. M. Trozzolo, *J. Am. Chem. Soc.*, **92**, 6997 (1970).
756. J. Leroy and C. Wakselman, *Can. J. Chem.*, **54**, 218 (1976).
757. V. P. Semenov, I. K. Zhurkovich, I. M. Stroiman, and K. A. Ogloblin, *J. Org. Chem. USSR*, **10**, 139 (1974).
758. A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965).
759. T. DoMinh and A. M. Trozzolo, *J. Am. Chem. Soc.*, **94**, 4046 (1972).
760. T. Uchida, *J. Heterocycl. Chem.*, **15**, 241 (1978).
761. J. W. Lown, T. W. Maloney, and G. Dallas, *Can. J. Chem.*, **48**, 584 (1970).
762. S. Oida and E. Ohki, *Chem. Pharm. Bull. (Jpn.)*, **17**, 2461 (1969).
763. Y. Gelas-Mialhe, R. Hierle, and R. Vessiere, *Bull. Soc. Chim. Fr.*, 709 (1974).
764. M. Vaultier, R. Danion-Bougot, D. Danion, J. Hamelin, and R. Carrie, *Tetrahedron Lett.*, 2883 (1973).
765. F. Texier and P. Corbier, *C.R. Acad. Sci. Paris, Ser. C*, **275**, 1443 (1972).
766. M. Vaultier and R. Carrie, *Tetrahedron Lett.*, 1195 (1978).
767. M. Vaultier, R. Danion-Bougot, D. Danion, J. Hamelin, and R. Carrie, *C.R. Acad. Sci. Paris, Ser. C*, **280**, 213 (1975).
768. M. Vaultier and R. Carrie, *J. Chem. Soc., Chem. Commun.*, 356 (1978).
769. G. Subrahmanyam, *Indian J. Chem.*, **11**, 1049 (1973); *Chem. Abstr.*, **80**, 81780 (1973).
770. J. W. Lown, G. Dallas, and T. W. Maloney, *Can. J. Chem.*, **47**, 3557 (1969).
771. H. Person, A. Foucaud, K. Luanglath, and C. Fayat, *J. Org. Chem.*, **41**, 2141 (1976).
772. H. Person, C. Fayat, and A. Foucaud, *Tetrahedron Lett.*, 1943 (1974).
773. J. W. Lown, R. Westwood, and J. P. Moser, *Can. J. Chem.*, **48**, 1682 (1970).
774. J. W. Lown, R. K. Smalley, and G. Dallas, *J. Chem. Soc., Chem. Commun.*, 1543 (1968).
775. J. W. Lown, R. K. Smalley, G. Dallas, and T. W. Maloney, *Can. J. Chem.*, **48**, 89 (1970).
776. F. Texier and R. Carrie, *Tetrahedron Lett.*, 4163 (1971).
777. M. Vaultier, R. Danion-Bougot, D. Danion, J. Hamelin, and R. Carrie, *Tetrahedron Lett.*, 1923 (1973).
778. M. Vaultier, R. Danion-Bougot, D. Danion, J. Hamelin, and R. Carrie, *J. Org. Chem.*, **40**, 2990 (1975).
779. J. W. Lown and M. H. Akhtar, *J. Chem. Soc., Perkin Trans. 1*, 1459 (1972).
780. J. W. Lown and J. P. Moser, *J. Chem. Soc., Chem. Commun.*, 247 (1970).
781. J. W. Lown and J. P. Moser, *Can. J. Chem.*, **48**, 2227 (1970).
782. J. W. Lown and M. H. Akhtar, *Can. J. Chem.*, **49**, 1610 (1971).
783. J. W. Lown and J. P. Moser, *Tetrahedron Lett.*, 3019 (1970).
784. V. Bhat and M. V. George, *Tetrahedron Lett.*, 4133 (1977).
785. V. Bhat and M. V. George, *J. Org. Chem.*, **44**, 3288 (1979).
786. J. A. Deyrup and G. S. Kuta, *J. Chem. Soc., Chem. Commun.*, 34 (1975).
787. J. Charrier, H. Person, and A. Foucaud, *Tetrahedron Lett.*, 1381 (1979).

788. A. Padwa and W. Eisenhardt, *J. Chem. Soc., Chem. Commun.*, 380 (1968).
789. A. Padwa and W. Eisenhardt, *J. Chem. Soc., Chem. Commun.*, 1215 (1969).
790. H. W. Heine and F. Scholer, *Tetrahedron Lett.*, 3667 (1964).
791. P. Dowd and K. Kang, *J. Chem. Soc., Chem. Commun.*, 258 (1974).
792. A. Padwa and H. Ku, *J. Org. Chem.*, **44**, 255 (1979).
793. T. L. Gilchrist, C. W. Rees, and E. Stanton, *J. Chem. Soc., C*, 3036 (1971).
794. J. C. Pommelet and J. Chuche, *Can. J. Chem.*, **54**, 1571 (1976).
795. N. Manisse and J. Chuche, *Tetrahedron*, **33**, 2399 (1977).
796. P. G. Mente and H. W. Heine, *J. Org. Chem.*, **36**, 3076 (1971).
797. E. Vogel, W. Pretzer, and W. A. Böll, *Tetrahedron Lett.*, 3613 (1965).
798. A. G. Anastassiou, R. L. Elliott, and A. Lichtenfeld, *Tetrahedron Lett.*, 4569 (1972).
799. D. W. Jones, *J. Chem. Soc., Perkin Trans. 1*, 225 (1972).
800. M. J. S. Dewar, Z. Nahlovska, and B. D. Nahlovsky, *J. Chem. Soc., Chem. Commun.*, 1377 (1971).
801. H. Prinzbach, M. Breuninger, B. Gallenkamp, R. Schwesinger, and D. Hunkler, *Angew. Chem., Int. Ed. Engl.*, **14**, 348 (1975).
802. H. Prinzbach, R. Schwesinger, M. Breuninger, B. Gallenkamp, and D. Hunkler, *Angew. Chem., Int. Ed. Engl.*, **14**, 347 (1975).
803. (a) H. W. Heine and J. Irving, *Tetrahderon Lett.*, 4767 (1967). (b) D. J. Anderson and A. Hassner, *J. Chem. Soc. Chem. Commun.*, 45 (1974).
804. A. G. Anastassiou, *J. Org. Chem.*, **31**, 1131 (1966).
805. M. Klaus and H. Prinzbach, *Angew. Chem., Int. Ed. Engl.*, **10**, 273 (1971).
806. K. Umano, H. Taniguchi, H. Inoue, and E. Imoto, *Tetrahedron Lett.*, 247 (1979).
807. N. S. Kozlov, V. D. Pak, and V. V. Mashevskii, *Khim. Khim. Tekhnol.*, **2**, 67 (1973); *Chem. Abstr.*, **82**, 85703 (1975).
808. M. Seno, S. Shiraishi, Y. Suzuki, and T. Asahara, *Bull. Chem. Soc. Jpn.*, **49**, 1893 (1976).
809. R. R. Kostikov, A. F. Khlebnikov, and K. A. Ogloblin, *J. Org. Chem. USSR*, **11**, 583 (1975).
810. R. R. Kostikov, A. F. Khlebnikov, and K. A. Ogloblin, *Khim. Geterotsikl. Soedin.*, 48 (1978); *Chem. Abstr.*, **88**, 169358 (1978).
811. M. Seno, S. Shiraishi, H. Kise, and Y. Suzuki, *J. Org. Chem.*, **43**, 3402 (1978).
812. M. K. Meilahn, L. L. Augenstein, and J. L. McManaman, *J. Org. Chem.*, **36**, 3627 (1971).
813. O. C. Dermer and G. E. Ham, Ref. 2, p. 296.
814. E. M. Kaiser, G. S. Edmonds, S. D. Grubb, J. W. Smith, and D. Tramp, *J. Org. Chem.*, **36**, 330 (1971).
815. H. Naganawa, N. Usui, T. Takita, M. Hamada, and H. Umezawa, *J. Antibiot.*, **28**, 828 (1975).
816. O. C. Dermer and G. E. Ham, Ref. 2, p. 291.
817. R. D. Clark and G. K. Helmkamp, *J. Org. Chem.*, **29**, 1316 (1964).
818. C. L. Bumgardner, K. J. Martin, and J. P. Freeman, *J. Am. Chem. Soc.*, **85**, 97 (1963).
819. J. P. Freeman and W. H. Graham, *J. Am. Chem. Soc.*, **89**, 1761 (1967).
820. H. W. Heine, J. D. Myers, and E. T. Peltzer, III, *Angew. Chem., Int. Ed. Engl.*, **9**, 374 (1970).
821. J. E. Baldwin, A. K. Bhatnagar, S. C. Choi, and T. J. Shortridge, *J. Am. Chem. Soc.*, **93**, 4082 (1971).
822. Y. Hata, M. Watanabe, T. Matsubara, and A. Touchi, *J. Am. Chem. Soc.*, **98**, 6033 (1976).
823. I. Imamoto and Y. Yukawa, *Chem. Lett.*, 165 (1974).
824. A. Padwa, D. Eastman, and L. Hamilton, *J. Org. Chem.*, **33**, 1317 (1968).

825. Y. Hata and M. Watanabe, *Tetrahedron Lett.*, 3827 (1972).
826. V. I. Markov and A. E. Polyakov, *J. Org. Chem. USSR*, **9**, 1786 (1973).
827. Y. Hata and M. Watanabe, *Tetrahedron Lett.*, 4659 (1972).
828. R. Huisgen, R. Sustmann, and K. Bunge, *Tetrahedron Lett.*, 3603 (1966).
829. M. H. Akhtar and A. C. Oehschlager, *Tetrahedron*, **26**, 3245 (1970).
830. R. E. Clark and R. D. Clark, *J. Org. Chem.*, **42**, 1136 (1977).
831. D. Felix, J. Schreiber, K. Piers, U. Horn, and A. Eschenmoser, *Helv. Chim. Acta*, **51**, 1461 (1968).
832. D. Felix, R. K. Müller, U. Horn, R. Joos, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 1276 (1972).
833. R. V. Stevens, J. M. Fitzpatrick, P. B. Germeraad, B. L. Harrison, and R. Lapalme, *J. Am. Chem. Soc.*, **98**, 6313 (1976).
834. R. V. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai, and R. Lapalme, *J. Am. Chem. Soc.*, **98**, 6317 (1976).
835. A. Pfaltz, B. Hardegger, P. M. Müller, S. Faroug, B. Kräutler, and A. Eschenmoser, *Helv. Chim. Acta*, **58**, 1444 (1975).
836. T. L. Gilchrist and D. P. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1257 (1976).
837. P. G. Gassman, D. K. Dygos, and J. E. Trent, *J. Am. Chem. Soc.*, **92**, 2084 (1970).
838. T. Hiyama, H. Koide, and H. Nozaki, *Tetrahedron Lett.*, 2143 (1973).
839. T. Hiyama, H. Koide, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **48**, 2918 (1975).
840. P. G. Gassman, I. Nishiguchi, and H. Yamamoto, *J. Am. Chem. Soc.*, **97**, 1600 (1975).
841. T. Kauffmann, K. Habersaat, and E. Köppelmann, *Angew. Chem., Int. Ed. Engl.*, **11**, 291 (1972).
842. T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **13**, 627 (1974).
843. T. Kauffmann and R. Eidenschink, *Chem. Ber.*, **110**, 651 (1977).
844. S. Sustmann, R. Sustmann, and C. Rüchardt, *Chem. Ber.*, **108**, 1527 (1975).
845. N. R. Bertoniere and G. W. Griffin, *Org. Photochem.*, **3**, 115 (1973).
846. A. Padwa and L. Hamilton, *J. Am. Chem. Soc.*, **87**, 1821 (1965).
847. A. Padwa and L. Hamilton, *J. Am. Chem. Soc.*, **89**, 102 (1967).
848. A. Padwa and W. Eisenhardt, *J. Am. Chem. Soc.*, **90**, 2442 (1968).
849. A. Padwa, S. Clough, and E. Glazer, *J. Am. Chem. Soc.*, **92**, 1778 (1970).
850. H. W. Heine, G. J. Blosick, and G. B. Lowrie, III, *Tetrahedron Lett.*, 4801 (1968).
851. O. C. Dermer and G. E. Ham, Ref. 2, p. 239.
852. J. A. Deyrup and S. C. Clough, *J. Am. Chem. Soc.*, **90**, 3592 (1968).
853. G. Szeimies and R. Huisgen, *Chem. Ber.*, **99**, 491 (1966).
854. R. Aumann, K. Fröhlich, and H. Ring, *Angew. Chem., Int. Ed. Engl.*, **13**, 275 (1974).
855. W. Beck, W. Danzer, and R. Höfer, *Angew. Chem., Int. Ed. Engl.*, **12**, 77 (1973).
856. W. Beck, W. Danzer, A. T. Liu, and G. Huttner, *Angew. Chem., Int. Ed. Engl.*, **15**, 495 (1976).
857. A. G. Giumanini, *J. Org. Chem.*, **37**, 513 (1972).
858. O. C. Dermer and G. E. Ham, Ref. 2, p. 394.
859. T. A. Connors and D. H. Melzack, *Int. J. Cancer*, **7**, 86 (1971).
860. H. Nakao and M. Arakawa, *Chem. Pharm. Bull. (Jpn.)*, **20**, 1962 (1972).
861. H. Nakao, M. Arakawa, T. Nakamura, and M. Fukushima, *Chem. Pharm. Bull. (Jpn.)*, **20**, 1968 (1972).
862. F. -T. Chou, A. H. Khan, and J. S. Driscoll, *J. Med. Chem.*, **19**, 1302 (1976).
863. J. S. Driscoll, L. Dudeck, G. Congleton, and R. I. Geran, *J. Pharm. Sci.*, **68**, 185 (1979).

864. A. H. Khan and J. S. Driscoll, *J. Med. Chem.*, **19**, 313 (1976).
865. G. A. M. Butchart, M. F. G. Stevens, and B. C. Gunn, *J. Chem. Soc., Perkin Trans. 1*, 956 (1975).
866. T. A. Connors, J. A. Hickman, M. Jarman, D. H. Melzack, and W. C. J. Ross, *Biochem. Pharmacol.*, **24**, 1665 (1975).
867. O. C. Dermer and G. E. Ham, Ref. 2, p. 403.
868. V. N. Iyer and W. Szybalski, *Science*, **145**, 55 (1964).
869. J. W. Lown, A. Begleiter, D. Johnson, and A. R. Morgan, *Can. J. Biochem.*, **54**, 110 (1976).
870. J. W. Lown, S. -K. Sim, K. C. Majumdar, and R. -Y. Chang, *Biochem. Biophys. Res. Commun.*, **76**, 705 (1977).
871. J. W. Haynes, E. Mattix, N. Mitlin, A. B. Borkovec, and O. H. Lindig, *U.S. Agric. Res. Serv., South. Reg. (Rep.)*, 30 (1976).
872. A. B. Borkovec and C. W. Woods, *Irs. J. Entomol.*, **11**, 53 (1976).
873. M. Von Ardenne and P. G. Reitnauer, *Arzneimitt. -Forsch.*, **27**, 1701 (1977).
874. U. Bicker, *Fortsch. Med.*, **96**, 661 (1978).
875. Boehringer Mannheim GmbH Belg. Pat. 843803; *Chem. Abstr.*, **87**, 194233 (1977).
876. D. R. Crist and N. J. Leonard, *Angew. Chem., Int. Ed. Engl.*, **8**, 962 (1969).
877. N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, **84**, 4806 (1962).
878. A. T. Bottini and R. L. Van Etten, *J. Org. Chem.*, **30**, 575 (1965).
879. A. T. Bottini, L. R. Sousa, and B. F. Dowden, *J. Org. Chem.*, **39**, 355 (1974).
880. G. A. Olah and P. J. Szilagyi, *J. Am. Chem. Soc.*, **91**, 2949 (1969).
881. G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *J. Org. Chem.*, **30**, 666 (1965).
882. A. P. Borsetti and D. R. Crist, *J. Heterocycl. Chem.*, **12**, 1287 (1975).
883. J. -L. Pierre, P. Baret, and E. -M. Rivoirard, *J. Heterocycl. Chem.*, **15**, 817 (1978).
884. E. -M. Rivoirard, P. Baret, A. Boucherle, C. Gey, and J. -L. Pierre, *J. Heterocycl. Chem.*, **16**, 327 (1979).
885. P. E. Fanta, L. J. Pandya, W. R. Groskopf, and H. J. Su, *J. Org. Chem.*, **28**, 413 (1963).
886. L. Trefonas, R. Towns, and R. Majeste, *J. Heterocycl. Chem.*, **4**, 511 (1967).
887. L. M. Trefonas and R. Majeste, *Tetrahedron*, **19**, 929 (1963).
888. L. M. Trefonas and R. Towns, *J. Heterocycl. Chem.*, **1**, 19 (1964).
889. L. Trefonas and J. Couvillion, *J. Am. Chem. Soc.*, **85**, 3184 (1963).
890. W. Nagata, T. Wakabayashi, and N. Haga, *Synth. Commun.*, **2**, 11 (1972).
891. C. F. Hammer, S. R. Heller, and J. H. Craig, *Tetrahedron*, **28**, 239 (1972).
892. C. F. Hammer and S. R. Heller, *J. Chem. Soc., Chem. Commun.*, 919 (1966).
893. N. J. Leonard, R. Y. Ning, and R. L. Booth, *J. Org. Chem.*, **30**, 4357 (1964).
894. N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **30**, 821 (1965).
895. R. M. Allen and G. W. Kirby, *J. Chem. Soc., Chem. Commun.*, 1121 (1971).
896. B. P. Robinson and K. A. H. Adams, *Tetrahedron Lett.*, 6169 (1968).
897. N. J. Leonard, J. V. Paukstelis, and L. E. Brady, *J. Org. Chem.*, **29**, 3383 (1964).
898. N. J. Leonard, K. J. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963).
899. N. J. Leonard, D. B. Dixon, and T. R. Keenan, *J. Org. Chem.*, **35**, 3488 (1970).
900. N. J. Leonard and L. E. Brady, *J. Org. Chem.*, **30**, 817 (1965).
901. Y. Hata and M. Watanabe, *J. Am. Chem. Soc.*, **95**, 8450 (1973).
902. N. J. Leonard and J. A. Klainer, *J. Heterocycl. Chem.*, **8**, 215 (1971).

903. N. J. Leonard and D. B. Dixon, *J. Org. Chem.*, **35**, 3483 (1970).
904. T. R. Keenan and N. J. Leonard, *J. Am. Chem. Soc.*, **93**, 6567 (1971).
905. N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1971).
906. K. Werner and E. Fischer, *J. Prakt. Chem.*, **316**, 223 (1974); *Chem. Abstr.*, **81**, 91425 (1974).
907. N. J. Leonard, D. A. Durand, and F. Uchimaru, *J. Org. Chem.*, **32**, 3607 (1967).
908. O. C. Dermer and G. E. Ham, Ref. 2, p. 60.
909. H. E. Baumgarten, *J. Am. Chem. Soc.*, **84**, 4975 (1962).
910. J. C. Sheehan and J. H. Beeson, *J. Am. Chem. Soc.*, **89**, 362 (1967).
911. E. R. Talaty, A. E. DePuy, Jr., and A. E. Cancienne, Jr., *J. Heterocycl. Chem.*, **4**, 657 (1967).
912. H. E. Baumgarten, J. J. Fuerholzer, R. D. Clark, and R. D. Thompson, *J. Am. Chem. Soc.*, **85**, 3303 (1963).
913. A. H.-J. Wang, I. C. Paul, E. R. Talaty, and A. E. DePuy, Jr., *J. Chem. Soc., Chem. Commun.*, 43 (1972).
914. J. C. Sheehan and M. M. Nafissi-V, *J. Org. Chem.*, **35**, 4246 (1970).
915. I. Lengyel and J. C. Sheehan, *Angew. Chem., Int. Ed. Engl.*, **7**, 25 (1968).
916. I. Lengyel and D. B. Uliss, *J. Chem. Soc., Chem. Commun.*, 1621 (1968).
917. K. Bott, *Justus Liebigs Ann. Chem.*, **755**, 58 (1972).
918. E. R. Talaty and A. E. DePuy, Jr., *J. Chem. Soc., Chem. Commun.*, 790 (1968).
919. E. R. Talaty, J. P. Madden, and L. H. Stekoll, *Angew. Chem., Int. Ed. Engl.*, **10**, 753 (1971).
920. E. R. Talaty and C. M. Utermoehlen, *Tetrahedron Lett.*, 3321 (1970).
921. E. R. Talaty and C. M. Utermoehlen, *J. Chem. Soc., Chem. Commun.*, 473 (1970).
922. E. R. Talaty, C. M. Utermoehlen, and L. H. Stekoll, *Synthesis*, 543 (1971).
923. J. C. Sheehan and M. M. Nafissi-V, *J. Am. Chem. Soc.*, **91**, 1176 (1969).
924. J. C. Sheehan and J. H. Beeson, *J. Am. Chem. Soc.*, **89**, 366 (1967).
925. J. C. Sheehan and I. Lengyel, *J. Am. Chem. Soc.*, **86**, 1356 (1964).
926. J. C. Sheehan and R. R. Kurtz, *J. Am. Chem. Soc.*, **95**, 3415 (1973).
927. I. Lengyel, D. B. Uliss, and R. V. Mark, *J. Org. Chem.*, **35**, 4077 (1970).
928. E. R. Talaty and A. E. DePuy, Jr., *J. Med. Chem.*, **13**, 1021 (1970).
929. S. Sarel, B. A. Weissman, and Y. Stein, *Tetrahedron Lett.*, 373 (1971).
930. M. Miyoshi, *Bull. Chem. Soc. Jpn.*, **43**, 3321 (1970).
931. M. Miyoshi, *Bull. Chem. Soc. Jpn.*, **46**, 212 (1973).
932. M. Miyoshi, *Bull. Chem. Soc. Jpn.*, **46**, 1489 (1973).
933. J. H. Jones and M. J. Witty, *J. Chem. Soc., Chem. Commun.*, 281 (1977).
934. E. R. Talaty, A. E. DePuy, Jr., C. M. Utermoehlen, and L. H. Stekoll, *J. Chem. Soc., Chem. Commun.*, 48 (1973).
935. K. Bott, *Tetrahedron Lett.*, 3323 (1968).
936. M. Kakimoto, S. Kajigaeshi, and S. Kanemasa, *Chem. Lett.*, 47 (1976).
937. G. l'Abbé, A. Van Asch, and S. Toppet, *Bull. Soc. Chim. Belg.*, **87**, 929 (1978).
938. E. R. Talaty, A. E. DePuy, Jr., and T. H. Golson, *J. Chem. Soc., Chem. Commun.*, 49 (1969).
939. K. Bott, *Angew. Chem., Int. Ed. Engl.*, **7**, 894 (1968).
940. G. Simig, K. Lempert, J. Tamas, and G. Czira, *Tetrahedron*, **31**, 1195 (1975).
941. J. C. Sheehan and I. Lengyel, *J. Org. Chem.*, **31**, 4244 (1966).

942. H. E. Baumgarten, D. G. McMahan, V. J. Elia, B. I. Gold, V. W. Day, and R. O. Day, *J. Org. Chem.*, **41**, 3798 (1976).

943. E. R. Talaty, A. E. DePuy, Jr., and C. M. Utermoehlen, *J. Chem. Soc., Chem. Commun.*, 16 (1971).

944. E. R. Talaty, A. E. DePuy, Jr., C. K. Johnson, T. P. Pirotte, W. A. Fletcher, and R. E. Thompson, *Tetrahedron Lett.*, 4435 (1970).

945. I. Lengyel, R. V. Mark, and C. A. Troise, *Synth. Commun.*, **1**, 153 (1971).

946. J. C. Sheehan and M. M. Nafissi-V, *J. Am. Chem. Soc.*, **91**, 4596 (1969).

947. E. R. Talaty, L. M. Pankow, M. N. Deshpande, K. E. Garrett, and A. L. Edwards, *Tetrahedron Lett.*, 3665 (1978).

948. E. R. Talaty and C. M. Utermoehlen, *J. Chem. Soc., Chem. Commun.*, 204 (1974).

949. E. R. Talaty, L. M. Pankow, D. D. Delling, and C. M. Utermoehlen, *Synth. Commun.*, **4**, 143 (1974).

950. E. R. Talaty, L. M. Pankow, K. E. Garrett, C. M. Utermoehlen, and K. W. Knutson, *Tetrahedron Lett.*, 4797 (1976).

951. Y. Hata and M. Watanabe, *J. Am. Chem. Soc.*, **101**, 1323 (1979).

952. H. Quast, personal communication.

953. H. Quast and E. Schmitt, *Angew. Chem., Int. Ed. Engl.*, **9**, 381 (1970).

954. H. Quast and P. Schäfer, *Tetrahedron Lett.*, 1057 (1977).

955. H. Quast and L. Bieber, *Angew. Chem., Int. Ed. Engl.*, **14**, 428 (1975).

956. A. J. Hubert, A. Feron, R. Warin, and P. Teyssie, *Tetrahedron Lett.*, 1317 (1976).

957. J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 5091 (1966).

958. E. M. Bingham and J. C. Gilbert, *J. Org. Chem.*, **40**, 224 (1975).

959. Y. V. Zeifman, E. M. Rokhlin, U. Utebaev, and I. L. Knunyants, *Dokl. Chem.*, **226**, 149 (1976).

960. H. Quast, E. Schmitt, and R. Frank, *Angew. Chem., Int. Ed. Engl.*, **10**, 651 (1971).

961. H. Quast and W. Risler, *Angew. Chem., Int. Ed. Engl.*, **12**, 414 (1973).

962. H. Quast and C. A. W. Velez, *Angew. Chem., Int. Ed. Engl.*, **13**, 342 (1974).

963. H. Quast and C. A. W. Velez, *Angew. Chem., Int. Ed. Engl.*, **17**, 213 (1978).

964. R. C. Cookson, B. Halton, I. D. R. Stevens, and C. T. Watts, *J. Chem. Soc. C*, 928 (1967).

965. E. Jongejan, H. Steinberg, and T. J. de Boer, *Rec. Trav. Chim. Pays-Bas*, **97**, 145 (1978).

966. E. Jongejan, H. Steinberg, and T. J. de Boer, *Rec. Trav. Chim. Pays-Bas*, **98**, 66 (1979).

Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner

CHAPTER II

Azirines

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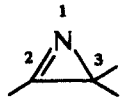
I. INTRODUCTION

The chemistry of the small ring heterocycle, azirine, has fluorished with considerable intensity in the past decade or so because of its theoretical, mechanistic, and synthetic applications. The theoretical and mechanistic interests are associated with the structure, stability, and inherent strain energy of the azirines, and the ability of the system to participate in and direct in several distinct ways the course of many mechanistically significant reactions. The synthetic potential for their transformations into other heterocyclic systems and for incorporation into compounds containing certain desirable functions is impressive.

There are two isomeric azirines **1** and **2**, and these are referred to as 1-azirine and 2-azirine, respectively, in this chapter. The 2-azirine ring system is of interest theoretically. It represents a cyclic conjugated system with 4π electrons and according to Hückel's rule would not be predicted to be stabilized by electron delocalization. Simple molecular orbital (MO) calculations on the parent 2-azirine system shows $DE_\pi \simeq 0.00\beta$ ($\alpha_N = \alpha_C + 1.5\beta$; $\beta_{C-N} = \beta_{C-C}$).[1,2] The corresponding uncyclized enamine has $DE_\pi \simeq 0.30\beta$, suggesting that cyclic conjugation results in destabilization. Therefore the 2-azirine system has been classified as antiaromatic.[3] Although the intermediacy of 2-azirines has been invoked in several attempts at their synthesis, this ring system, because of its inherent instability, has eluded isolation until 1981. For this reason this chapter on azirines will be devoted almost entirely to the chemistry of 1-azirines except for a brief mention of the attempted synthesis of the isomeric ring system. A number of reviews on azirines have appeared during the past few years.[4,42,50,53,172,212]



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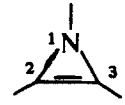

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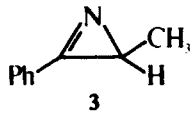
This chapter discusses nomenclature, physical properties, spectroscopic data, and particularly syntheses and reactions of 1-azirines. Tables of all known 1-azirines together with their melting points or boiling points and literative citation are also included. The references at the end of the chapter cover mainly the literature to 1981. In general, only literature references directly covering aspects of 1-azirine chemistry are cited.

II. NOMENCLATURE

The two isomeric azirine ring systems (**1** and **2**) have been designated as 2*H*- and 1*H*-azirine, respectively, by the Ring Index of the American Chemical Society[5] and *Chemical Abstracts*. For example, the azirine **3** is named 2-methyl-3-phenyl-2*H*-

azirine. In a system of nomenclature that has been used more frequently, the position of the double bond is designated: thus **1** and **2** are referred to as 1-azirine and 2-azirine, respectively. Compound **3** then is named 3-methyl-2-phenyl-1-azirine, and this nomenclature is employed throughout the chapter. In compounds **4–7**, however, both nomenclatures are shown for completeness. The stereochemistry at C-3 of the azirines is not implied necessarily by the structural representations.



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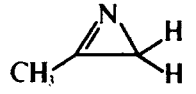

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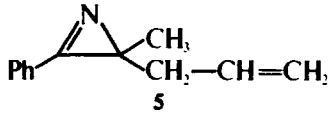
2-Methyl-1-azirine
[3-Methyl-2*H*-azirine]



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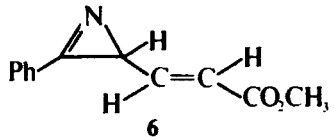
3-Allyl-3-methyl-2-phenyl-1-azirine
[2-Allyl-2-methyl-3-phenyl-2*H*-azirine]



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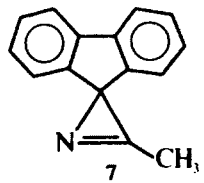
Methyl (E)-2-phenyl-1-azirine-3-acrylate
[Methyl (E)-3-phenyl-2*H*-azirine-2-acrylate]



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3,3-(2,2'-Biphenylene)-2-methyl-1-azirine
[2,2-(2,2'-Biphenylene)-3-methyl-2*H*-azirine]

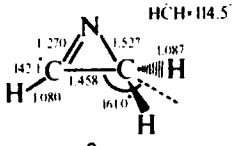
III. PHYSICAL PROPERTIES AND SPECTROSCOPIC DATA

1. Theoretical Calculations

Pople et al.[6] have carried out calculations on the parent 1-azirine (**8**) and 2-azirine (**9**) systems. For 1-azirine (**8**), an overall C_s symmetry was assumed. The structure showed a C–C bond shorter and a C–N bond longer than in acyclic molecules. For 2-azirine (**9**), when nonplanarity at nitrogen and a C_s symmetry are considered, the C–N bond again is found to be slightly lengthened, while the C=C bond is somewhat shorter than in cyclopropene.[6] The angle between the plane of the N–H bond and the ring plane is 72.1°. When compared to aziridines, this HN̂p1 angle is found to be larger. Calculations carried out by Clark[7] showed a similar effect. Clark rationalized this result by suggesting that in its planar form the 2-azirine (**9**) is unstable because

of antiaromaticity arising from the delocalization of its 4π- electrons. Clark[7] calculated the inversion barrier in 2-azirine to be 35 kcal/mole, some 20 kcal/mole higher than the inversion barrier in aziridines, again supporting the idea of the instability of the planar antiaromatic form. Pople and his co-workers[6] calculated the ground state energy of 1-azirine and found it to be 40.5 kcal/mole less than that of 2-azirine, whereas Clark[7] obtained 27 kcal/mole for this difference. Apparently, 2-azirine is unstable, both because of ring strain and an energetically unfavorable π-electron structure.

Bond lengths and bond angles for an azirine and its palladium complex have been measured by Hassner and his coworkers[260] from X-ray data, and by Taniguchi and his coworkers[275] from X-ray data.



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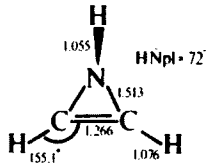

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2. Physical Characteristics

1-Azirines crystallize as colorless or pale yellow crystals. The lower molecular weight azirines are colorless or pale yellow liquids that can be purified relatively easily by fractional distillation under reduced pressures. 1-Azirines have sharp unpleasant odors and are skin irritants.

3. Infrared Spectral Data

2-Aryl-1-azirines show in the ir spectrum a strong C=N stretching absorption at about 1740 cm^{-1}. 2-Alkyl-substituted 1-azirines show this absorption at about 1775 cm^{-1}. Both absorptions are about 100 cm^{-1} higher than those observed for aromatic and aliphatic Schiff bases.[10] The spectra of 1-azirines with a hydrogen at the 2-position exhibit markedly different C=N absorptions compared to 2-substituted 1-azirines, with values around 1650 cm^{-1}. Typical C=N stretching frequencies of some representative 1-azirines are shown in Table 1.

4. Electronic Absorption Spectra of 1-Azirines

Table 2 summarizes the uv absorption spectra of some selected 1-azirines. 2-Alkylated 1-azirines show only a weak uv peak at about 230 nm. 2-Arylazirines exhibit an intense uv absorption peak at about 240 nm ($\epsilon > 13{,}000$). There is an inflection on the long wavelength side of the principal absorption band in these

TABLE 1. IR SPECTRAL DATA (NEAT) FOR SELECTED 1-AZIRINES[8,9]

R_1	R_2	R_3	C=N Absorption (cm^{-1})
Ph	H	H	1740
Ph	CH_3	H	1740
$PhCH_2$	H	H	1780
n-Bu	H	H	1776
H	$CH_3CH_2CH_2$	H	1650
H	Ph	H	1655
H	C_2H_5	C_2H_5	1665

compounds (*ca.* 285 nm). This weak band shifts to shorter wavelengths (blue shift) with increasing polarity of the medium, suggesting that it is associated with an $n\pi^*$ transition.

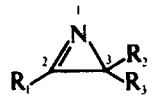
5. Nuclear Magnetic Resonance Spectral Data

Both ^1H and ^{13}C nmr data have been utilized extensively in 1-azirine chemistry. ^{13}C nmr spectroscopy can be particularly useful, not only for determining the structural characteristics of 1-azirines, but also for working out the structures of

TABLE 2. UV ABSORPTION SPECTRA OF SOME 1-AZIRINES[11-13]

R_1	R_2	R_3	Solvent	λ_{max} (nm)	ϵ
n-Bu	H	H	Ethanol	229	112
Ph	H	H	Ethanol	242	13,000
				287	1,000
Ph	Ph	H	Ethanol	245	23,600
				285	1,500
				305	1,050
Ph	CH_3	CH_3	Ethanol	245	15,200
				277	1,500
				286	1,040
Ph	Ph	Ph	Ethanol	250	24,500
				285	1,400
				310	1,100
Ph	PhCO	H	Ether	247	30,000
				324	165

TABLE 3. ^{13}C CHEMICAL SHIFTS OF 1-AZIRINES[15, 16]



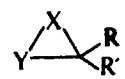
			Chemical shift, δ (ppm), TMS as internal standard			
R_1	R_2	R_3	C_2	C_3	CH_3	Phenyl carbons
Ph	H	H	165.7	19.6	–	126.0, 129.2, 129.5, 132.8
Ph	CH_3	H	172.4	27.5	18.9	126.2, 129.2, 132.7
Ph	Ph	H	163.8	34.6	–	124.6, 127.1, 128.4, 129.2, 129.3, 129.8, 133.1, 141.1
Ph	Ph	CH_3	169.2	39.1	21.0	124.3, 127.8, 128.2, 129.3, 129.4, 129.5, 132.9, 144.0
Ph	Ph	Ph	166.7	44.7	–	124.0, 127.2, 128.2, 128.3, 129.4, 129.7, 133.4, 141.8
CH_3	Ph	Ph	167.3	42.6	12.5	126.8, 127.9, 128.3, 142.1
CH_3	CH_3	Ph	169.9	35.6	12.1, 20.9	125.6, 126.2, 128.1, 144.3
CH_3	H	Ph	164.2	33.3	12.5	125.5, 126.6, 128.1, 141.2
H	Ph	Ph	163.2	39.3	–	127.3, 128.2, 128.4, 141.8
H	CH_3	Ph	165.9	31.9	21.7	126.0, 126.6, 128.1, 144.1
H	H	Ph	160.6	28.7	–	125.6, 127.0, 127.9, 140.4

its reaction products. The ^{13}C nmr chemical shifts of some representative azirines reported by Nair[15] and by Taniguchi et al.[16] are presented in Table 3.

The chemical shift of carbon-3 is in the range of ~ 19 to ~ 45 ppm; Table 4 compares this chemical shift with those of other three-membered cyclic compounds. Carbon-3 of 1-azirines resonates at a higher field than the ring carbons of oxiranes and aziridines but at a lower field than those of cyclopropanes.

A striking difference in chemical shift exists between the heterocyclic ring carbons 2 and 3 of 1-azirines. Carbon-2 appears in the imine region of the ^{13}C spectrum (i.e., 160–170 ppm). For example, the imino carbons of acetophenone methylimine and benzalaniline occur at 166.7 and 159.5 ppm, respectively.[16]

TABLE 4. ^{13}C CHEMICAL SHIFTS OF AZIRINE RING CARBONS COMPARED TO OTHER THREE-MEMBERED CYCLIC RING CARBONS[16–19]



			Chemical shift, δ (ppm) –X–Y–		
R	R′	–CH=N–	$-CH_2-CH_2-$	$-CH_2-O-$	$-CH_2-NH-$
H	H	–	−2.6	40.8	–
Ph	H	28.7	15.9	52.2	–
Ph	CH_3	31.9	–	56.7	36.3
Ph	Ph	39.3	30.3	61.7	44.0

Examination of ^{13}C–^{1}H coupling constants allows an approximate determination of the percentage of *s* character in the exocyclic orbitals of small ring systems.[2, 20–22] For 1-azirines J (C_3–H) of 186–187 Hz have been observed, which indicate about 37% *s* character in the exocylic σ bonds. This is consistent with the expected greater amount of *p* character of the endocyclic orbitals.[23] In 3-phenyl-1-azirine, the C_2–H coupling constant is 242.5 Hz, which corresponds to about 49% *s* character of the C–H bond.[16] Even if the effect of an electronegative nitrogen atom is taken into account, the *sp*-like hybridization of the exocyclic orbital of carbon-2 is still appreciable. Collectively, these data also suggest that the nitrogen hybridization approaches *sp* in character.[2]

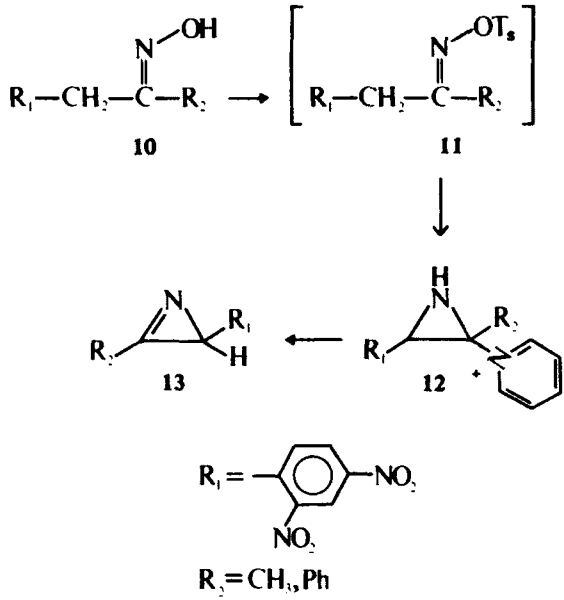
IV. SYNTHESIS OF 1-AZIRINES

A number of general methods are available for the synthesis of 1-azirines. These include the modified Neber reaction, thermolysis and photolysis of vinyl azides and isoxazoles, and thermolysis of oxazaphospholines. All these methods are discussed in this section, and representative examples to illustrate each procedure are mentioned. Tables 11–15 at the end of the chapter present specific examples of 1-azirines that have been synthesized, together with the literature citations of the procedures used. Perusal of these tables will show that 1-azirines with many diverse substitution patterns are known. Substitutions at the 2-position include examples with aryl and alkyl groups, vinyl groups, amino groups, and fluoro groups. Numerous examples of 3-substituted azirines have been synthesized, including such groups as aryl, alkyl, aralkyl, vinyl, allyl, akenyl, hydroxymethyl, halogeno, carboxylic ester, aldehydo, keto, imino, and phthalimido. Spiro- and ring-fused azirines also are known. A number of 2-unsubstituted azirines have been synthesized. It is clear that choice of the method to be used for synthesis of a particular azirine is dependent on the structural characteristics of the azirine and the availability of precursor compounds.

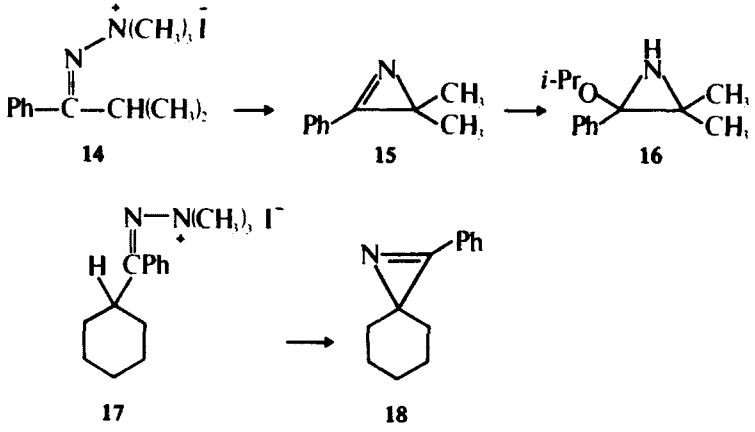
1. Neber and Related Reactions

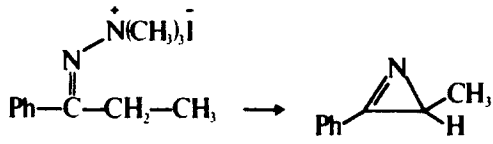
In 1932 Neber and his co-workers suggested for the first time the intermediate formation of a 1-azirine in the conversion of oxime *p*-toluene-sulfonates **11** to aminoketones with base.[25, 26] The structure of the 1-azirine intermediate was confirmed by Cram and Hatch in 1953.[27] They found that in the presence of tosyl chloride and pyridine, the oxime **10** is converted via **11** into aziridines **12**, and 1-azirines **13** could then be prepared by treating **12** with sodium carbonate.

However, the Neber reaction lacked generality, and several modified Neber reactions have been developed during more recent years. For example, the synthesis of 3,3-dimethyl-2-phenyl-1-azirine (**15**) was carried out by the reaction of the dimethylhydrazone methiodide (**14**) with sodium isopropoxide in isopropanol.[28]

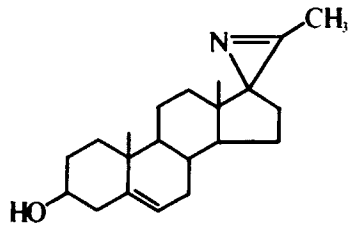


This method was applied successfully to the preparation of certain spiroazirines. For example, Sato[24] found that treatment of **17** with sodium isopropoxide resulted in an 80% yield of the spiro-1-azirine **18**. However, because of the formation of alkoxyaziridine during the reaction with sodium isopropoxide, only poor yields of the azirine **20** were obtained by this method. A more practical synthesis was developed[30–32] using dimethylsulfinyl carbanion as the base and dimethylsulfoxide as solvent. Using this modified Neber reaction, Nair[30] prepared pure 3-methyl-2-phenyl-1-azirine (**3**) in 63% yield from propiophenone dimethylhydrazone methiodide (**19**). Synthesis of the steroidal spiroazirine (**20**) using this method also has been reported.[31,32] Padwa and Carlsen recently reported the preparation of a series of 3-allyl-substituted 1-azirines (**21**) by a modified Neber reaction.[29,33] Acetylenic 1-azirines (e.g., **22**) also have been reported.[33]



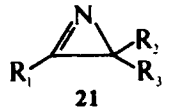


19 3



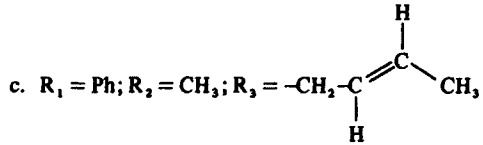
20

However, these modified Neber reactions do not always ensure the preparation of 1-azirines.[24,34] For example, attempts by Sato[24] to prepare 2-phenyl-1-azirine from acetophenone dimethylhydrazone methiodide resulted in the formation of 2,4-diphenylpyrrole. But the isolation of 2-phenyl-1-azirine in low yields by this method confirms the intermediate formation of the azirine in this preparation.[41]

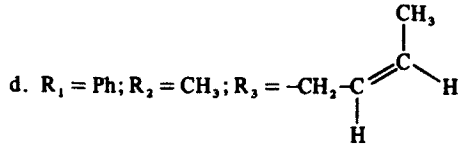


21

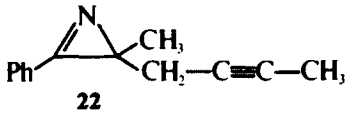
a. $R_1 = Ph; R_2 = CH_3; R_3 = -CH_2-CH=CH_2$ (5)
b. $R_1 = CH_3; R_2 = Ph; R_3 = -CH_2-CH=CH_2$



c. $R_1 = Ph; R_2 = CH_3; R_3 =$



d. $R_1 = Ph; R_2 = CH_3; R_3 =$



22

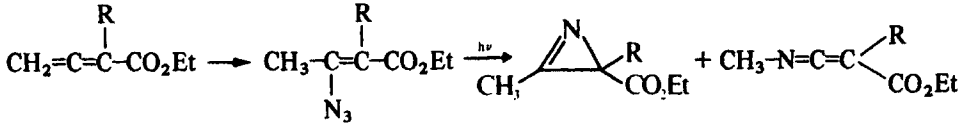
2. Thermolysis and Photolysis of Vinyl Azides

In 1961 Smolinsky reported the first general synthesis of 1-azirines by the vapor phase thermolysis of vinyl azides (23).[35,36] Moderate yields (50–60%) of the 1-azirines **24** were obtained together with small amounts (5%) of the ketenimines **25**. The latter appear to be formed by migration of the group that is alpha to the azido function in a Curtius-type rearrangement.

23 **24** **25**

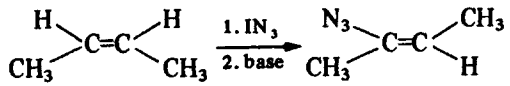
a. R = Ph
b. R = *o*-$CH_3C_6H_4$
c. R = *n*-C_4H_9

The photolysis of vinyl azides also produces azirines. Harvey and Ratts[37] reported the synthesis of 1-azirines (**28**) through photolysis of β-azidocrotonates (**27**). The vinyl azides **27** were prepared by the addition of sodium azide in THF-H_2O to the allenic esters **26**. Ketenimines (**29**) were produced also in the photolysis step.



26 **27** **28** **29**

Advances in the preparation of vinyl azides[38–40] have made the thermolysis or photolysis of vinyl azides the preferred general method for the synthesis of 1-azirines (see, e.g., references 8, 9, 35–37, 42–49). Hassner and his co-workers discovered[39,40] that iodine azide, generated from iodine monochloride and sodium azide, adds regiospecifically[51] to many olefins to give high yields of β-iodoazides (Hassner reaction). Elimination of hydrogen iodide from the iodoazide with base occurs preferentially in the direction of the azide function to give good yields of vinyl azides. Thus, a terminal olefin such as 1-hexene gave 2-azidohexene rather than the isomeric 1-azidohexene. A vicinally disubstituted olefin such as *cis*-2-butene (**30**) resulted in stereospecific formation of *trans*-2-azido-2-butene (**31**). A conjugated olefin such as *trans*-methyl cinnamate (**32**) gave *cis*-azidocinnamate **33**. Steric effects in some cases may be dominant in determining the position of the azido group. For example, the *t*-butylethylene **34** gave the vinyl azide **35** rather than the vinyl



30 **31**

$$\underset{\textit{trans}\text{-}32}{PhCH{=}CHCO_2CH_3} \xrightarrow[2.\ base]{1.\ IN_3} \underset{\textit{cis}\text{-}33}{Ph{-}\overset{\displaystyle N_3}{\overset{|}{C}}{=}CHCO_2CH_3}$$

azide **36**, the expected, electronically favored product. Cyclic olefins such as indene, 1,2-dihydronaphthalene, and cyclooctene gave the corresponding vinyl azides. However, the iodine azide adducts from cyclopentene and cyclohexene produced allyl azides. Trisubstituted olefins reacted with iodine azide regiospecifically so that the azido function occupied the tertiary position. The absence of a hydrogen geminal to the azido group precluded the synthesis of vinyl azides from these adducts.

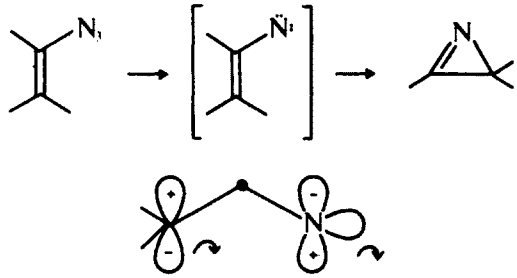
$$\underset{\mathbf{34}}{t\text{-}BuCH{=}CH_2} \qquad \underset{\mathbf{35}}{t\text{-}BuCH{=}CHN_3} \qquad \underset{\mathbf{36}}{t\text{-}Bu\overset{\displaystyle N_3}{\overset{|}{C}}{=}CH_2}$$

Vinyl azides such as 1-azidostyrenes are conveniently prepared by bromine addition to the styrenes followed by azide ion displacement and elimination of hydrogen bromide.[43] This method is particularly useful for the synthesis for 2-phenyl-1-azirines.

Free-radical addition of bromine azide complements the iodine azide method for the synthesis of some vinyl azides. Thus, 2-azidostyrene can be conveniently prepared through free-radical addition of bromine azide to styrene followed by base treatment of the resulting bromoazide.[52]

Vinyl azides can be prepared by a number of other methods. For example, treatment of epoxides with azide ions and dehydration of the resulting azido-alcohols gives vinyl azides. The β-hydroxyazide precursors can also be prepared by the reduction of α-azidoketones with sodium borohydride.[53] The displacement of activated vinyl halides and sulfinates has been utilized for the synthesis of some vinyl azides.[54-56] As mentioned previously, treatment of allenic esters with sodium azides gives vinyl azides.[37] When hydrazoic acid is added to conjugated acetylenes, vinyl azides are formed.[57] The base-catalyzed reaction of α-azido esters and ketones with aromatic aldehydes has been developed as a good method for the synthesis of some vinyl azides.[58-60]

Several mechanisms can be postulated for the formation of 1-azirines from the thermolysis or photolysis of vinyl azides.[8,54] One attractive pathway involves formation of a transient vinyl nitrene species by loss of molecular nitrogen from the thermally or photolytically excited vinyl azide.[61] If the 1-azirine is formed from singlet vinyl nitrene, this conversion is a symmetry-allowed conrotatory electrocyclization (Scheme 1).[62] Although evidence for the intermediacy of a nitrene in the formation of 1-azirines is not available, the formation of certain side products provides some support for the transient existence of this fugitive species. For example, the formation of ketenimine, indole, and dihydropyrazine can be reason-



Scheme 1 A possible mechanism for the synthesis of 1-azirines from vinyl azides.

ably assumed to arise from intermediate nitrene species.[54] Two further studies relevant to this should be mentioned. Nair and Kim[67] reported that the vinyl azide **37** decomposes spontaneously and exothermically at room temperature to give intractable polymers and two crystalline compounds (**40** and **43**). The formation of both compounds can be rationalized as occurring through the intermediacy of the vinyl nitrene **38**. A thermally allowed [4 + 2] capture of this fugitive species by the vinyl azide **37** may lead to a pyrroline **39** which on subsequent elimination of hydrogen azide would furnish **40**. Dimerization of the vinyl nitrene and electrocyclization of the resulting triene **41** would give **42**, which would undergo rapid air oxidation to the aromatic compound **43**. α-Azidostyrene also decomposes on storage and produces 2-phenyl-1-azirine, 3,6-diphenylpyridazine, and 2,5-diphenylpyrrole.[68]

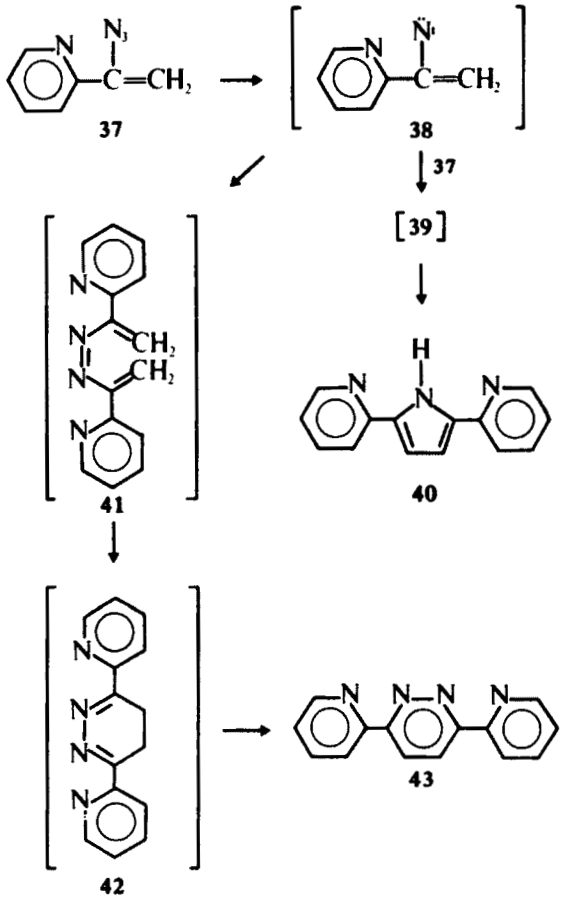
The thermolysis and photolysis of vinyl azides have been utilized extensively for the preparation of 1-azirines, and some representative examples are discussed below.

Preparation of the parent 1-azirine **8** by flash-vacuum pyrolysis of vinyl azide has been reported.[63] The azirine was characterized by its rotational spectrum. It can be trapped at liquid nitrogen temperatures but decomposes at higher temperature to acetonitrile.

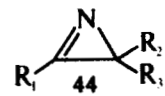
Hassner and Fowler[8] have reported the preparation of a number of 1-azirines (**44**) in good to excellent yields by photolysis of the corresponding vinyl azides at 3500 Å. 2,3-Diphenyl-1-azirine is conveniently prepared by the thermolysis of 1-azido-1,2-diphenylethylene.[39] Hassner and Fowler[8] also prepared the first ring-fused 1-azirines. For example, photolysis of 1-azidocyclooctene gave 9-azabicyclo[6.1.0]non-1(9)-ene (**45**) in 93% yield.

Smolinsky and Pryde[54] prepared the spiroazirine **47a** by thermolysis of 9-(1-azidoethylidene)fluorene (**46a**). However, the related azirine **47b** unsubstituted at the 2-position could be obtained only by irradiation of the vinyl azide **46b** at $-15°$.[48] Other spiroazirines also have been synthesized and are mentioned in Table 15.

Perfluoro-2-azidopropene (**49**) prepared from perfluoropropene (**48**) undergoes thermolysis to give the perfluoroazirine **50**.[64-66] In the presence of catalytic amounts of HF, this azirine is converted to the thermodynamically more stable isomer **51**.

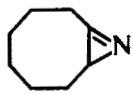


37 38 [39] 40 41 42 43

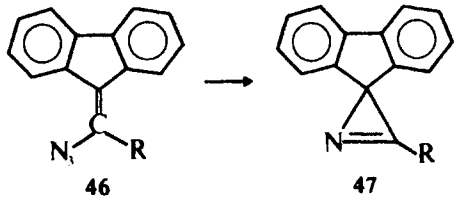


44

a. $R_1 = Ph; R_2 = H; R_3 = H$ **(24a)**
b. $R_1 = Ph; R_2 = CH_3; R_3 = H$ **(3)**
c. $R_1 = n\text{-}Bu; R_2 = H; R_3 = H$
d. $R_1 = C_2H_5; R_2 = C_2H_5; R_3 = H$
e. $R_1 = PhCH_2; R_2 = H; R_3 = H$
f. $R_1 = PhCHCH_2; R_2 = H; R_3 = H$
g. $R_1 = Ph; R_2 = CO_2Me; R_3 = H$
h. $R_1 = Ph; R_2 = Ph; R_3 = H$

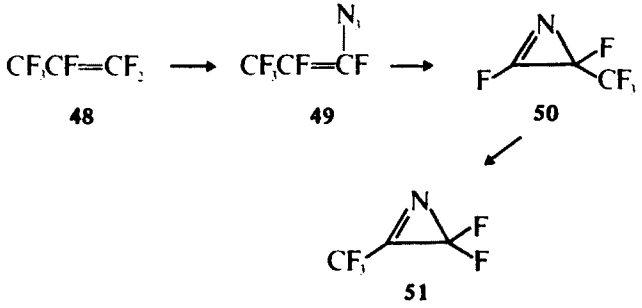


45



46
a. R = CH_3
b. R = H

47
a. R = CH_3
b. R = H



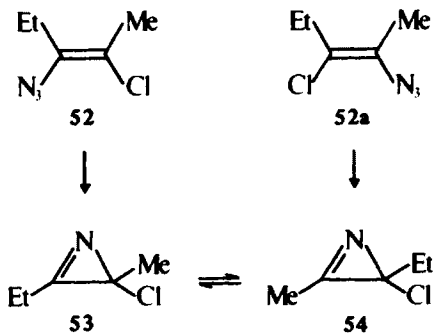
48 49 50

51

It was originally believed that thermolysis or photolysis of terminal vinyl azides did not give azirines.[54] However, the intermediacy of the 2-unsubstituted 1-azirines was implied in a number of studies of decomposition of terminal vinyl azides.[8, 54, 69] It was later reported that both photolysis and pyrolysis of terminal vinyl azides can result in the formation and isolation of 1-azirines.[9, 49] 2-Unsubstituted 1-azirines are thermally unstable, and their preparation and isolation generally requires photolysis at low temperatures.

The preparation of some fatty acid azirines has been reported.[70]

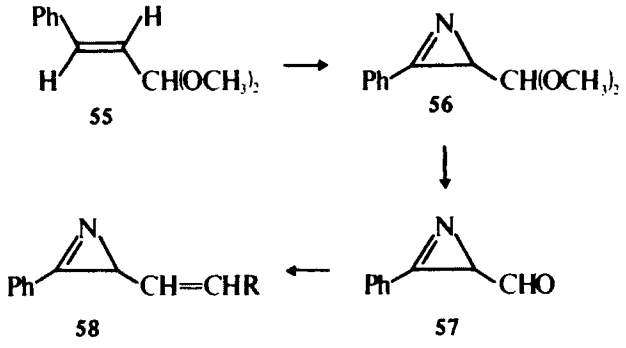
Ciabattoni and Cabell reported the synthesis and thermal isomerization of 3-chloro-1-azirines.[71] When a solution of **52** was photolyzed at 3500 Å at −40°, the 1-azirine **53** was formed exclusively as evidenced by nmr spectral data. When the solution of **53** was warmed in the nmr probe, the appearance and growth of new peaks corresponding to **54** was noted. Similarly, the vinyl azide **52a** gave the 1-azirine **54**, which underwent interconversion to **53**. The activation energy E_a for the isomerization of **53** → **54** was 15 kcal/mole with $\Delta S^{\ddagger}$ (−15°) = −15 eu.



52 52a

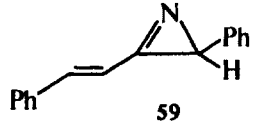
53 ⇌ 54

Padwa and his co-workers[72–74] synthesized the azirine **57** containing a carboxaldehyde at the 3-position. Cinnamaldehyde dimethylacetal (**55**), when treated with iodine azide followed by dehydrohalogenation, thermolysis, and aqueous hydrolysis, gave **57**. Azirine **57** served as a convenient starting material for the synthesis of a series of vinyl-substituted azirines **58**.[73] For example, when **57** was treated with the Wittig reagent, carbomethoxymethylenetriphenylphosphorane in benzene, methyl (E)-2-phenyl-1-azirine-3-acrylate (**58a**) was formed in quantitative yield. A similar set of Wittig reactions gave azirines the **58b–58e**.



a. R = CO_2CH_3
b. R = CN
c. R = C–Ph (‖ O)
d. R = CHO
e. R = Ph

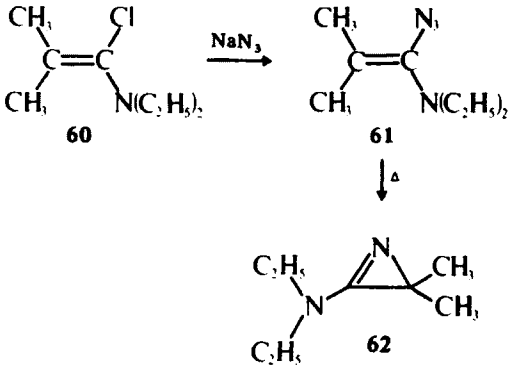
Hassner and Keogh[75] prepared the 2-vinyl-substituted azirine **59** by addition of IN_3 to diphenylbutadiene followed by HN_3 elimination and thermolysis.



Another interesting class of azirines, 2-amino-1-azirines, has been reported by Ghosez and his co-workers.[76–78] These compounds were prepared from α-chloroenamines by reaction with sodium azide as shown here for **62**.

Synthesis of a bisazirine by the vinyl azide route has been reported.[96]

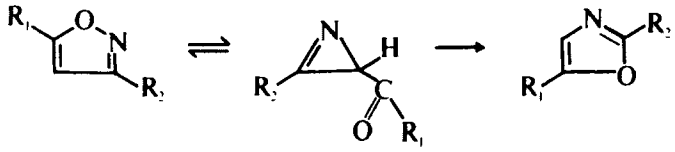
Although the thermolysis or photolysis of vinyl azides offers a convenient entry to many 1-azirines, the yields in these transformations are not always good. In some cases, catalysis by tertiary amines gives higher yields. For example, it has been reported that diazabicyclo[2.2.2]octane (DABCO) not only accelerates the conversion of vinyl azides to 1-azirines, but also inhibits the formation of some of the by-products of the reaction.[79]



60 61 62

3. Photolysis and Thermolysis of Isoxazoles

In some very elegant photochemical work, Ullman and Singh reported that 1-azirines could be generated from isoxazoles.[13, 80, 81] Irradiation of 3,5-diphenylisoxazole (**64a**) (λ_{max}^{ether} 245 nm, ϵ 22,000; 265 nm, ϵ 24,000) in ether solution with 2537 Å light led to the formation of 2,5-diphenyloxazole (**65a**) (λ_{max}^{ether} 302 nm, ϵ 30,000; 315 nm, ϵ 27,600). However, when the reaction was interrupted before completion, an intermediate whose structure proved to be the azirine **63a** (λ_{max}^{ether} 247 nm, ϵ 24,300; 350 nm, ϵ 150) was isolated. Investigation of the effect of wavelength revealed a striking dependence of photochemistry on wavelength. Irradiation of **64** at 2537 Å produced the 1-azirines **63**, which rearranged to the oxazoles **65**, whereas irradiation of the 1-azirines **63** with 3340 Å light resulted in their conversion to the isoxazoles **64**. It has also been observed that photolysis of 3,4,5-triphenylisoxazole gives 3-benzoyl-2,3-diphenyl-1-azirine, 2,4,5-triphenyloxazole, and *N*-phenylbenzoylphenylketenimine.[83] Further mechanistic aspects of isoxazole photochemistry have been reported.[86, 87]

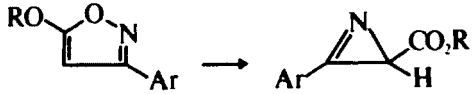


64 63 65

a. $R_1 = R_2 = Ph$
b. $R_1 = Ph; R_2 = p\text{-}C_6H_4\text{-}OCH_3$
c. $R_1 = Ph; R_2 = CH_3$
d. $R_1 = CH_3; R_2 = Ph$

At relatively high temperatures (~ 200°), Singh and Ullman[13] found that 3-benzoyl-2-phenyl-1-azirine (**63a**) can be converted to 3,5-diphenylisoxazole (**64a**). It is likely that at these temperatures the azirine and isoxazole are in equilibrium,

as evidenced by the preparation of several 1-azirine 3-carboxylates (**67**) from the corresponding isoxazoles by Nishiwaki and his co-workers.[84,85] 2-Amino-1-azirines can be prepared by the thermolysis or photolysis of amino-substituted isoxazoles.[92]

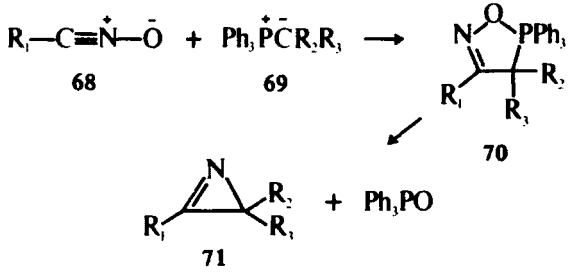


66 **67**

a. Ar = Ph; R = CH_3
b. Ar = Ph; R = C_2H_5
c. Ar = Ph; R = *n*-Bu
d. Ar = *p*-C_6H_4–CH_3; R = CH_3
e. Ar = *p*-C_6H_4–Cl; R = CH_3
f. Ar = *p*-C_6H_4–OCH_3; R = CH_3
g. Ar = *p*-C_6H_4–NO_2; R = CH_3

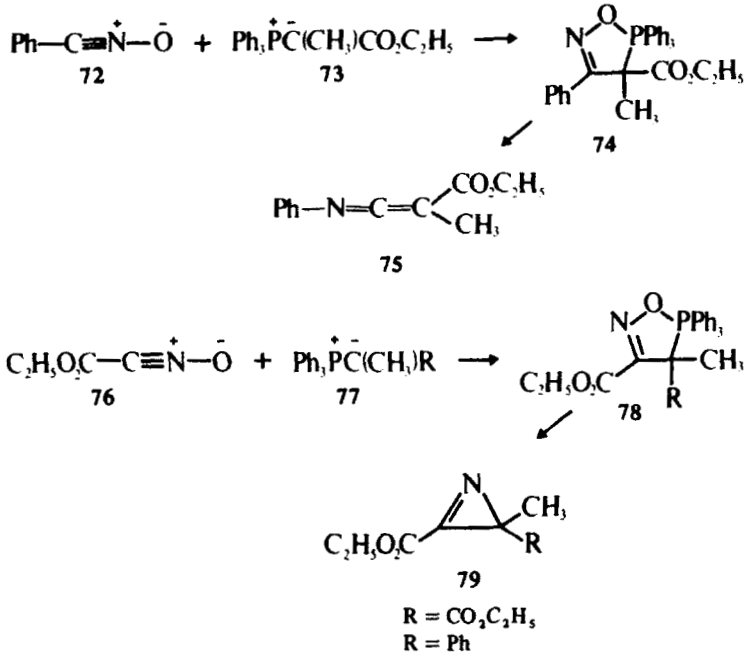
4. Thermolysis of Oxazaphospholines

Huisgen and Wulff,[88,89] and Bestmann and Kunstmann[90,91] discovered that nitrile oxides add smoothly to phosphorous ylides to gives oxazaphospholines **70**. Thermolysis of **70** results in elimination of triphenylphosphine oxide and formation of 1-azirines (**71**). The method is dependent on the availability and structure of both the nitrile oxide and the phosphorous ylide. Electron-withdrawing groups on the phosphorous ylide (e.g., carbomethoxy in **73**) give rise to unstable oxazaphospholines (**74**), which convert to the ketenimine **75** at the expense of 1-azirine formation. The presence of electron-withdrawing groups on the nitrile oxide (e.g., **76**) also results in unstable oxazaphospholines (**78**), but these do convert to 1-azirines (**79**), albeit in low yields.

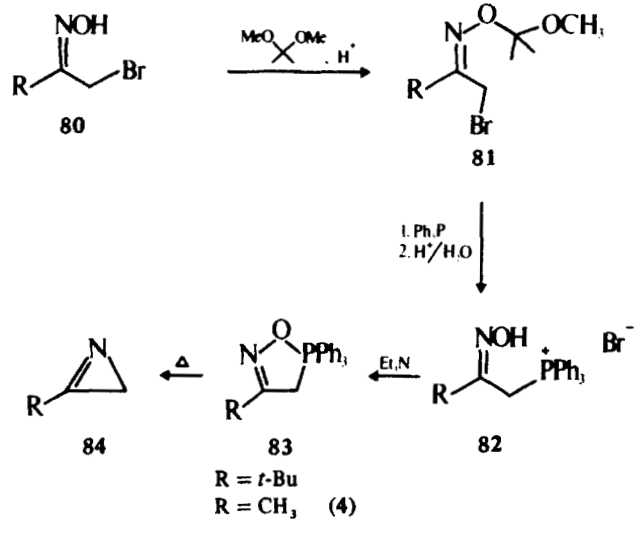


68 **69** **70** **71**

R_1 = Ph; R_2 = R_3 = H **(24a)**
R_1 = Ph; R_2 = CH_3; R_3 = CH_3 **(15)**
R_1 = Ph; R_2 = CH_3; R_3 = C_2H_5
R_1 = Ph; R_2 = CH_3; R_3 = H **(3)**
R_1 = *p*-C_6H_4–Cl; R_2 = CH_3; R_3 = H
R_1 = Ph; R_2 = CH_3; R_3 = Ph

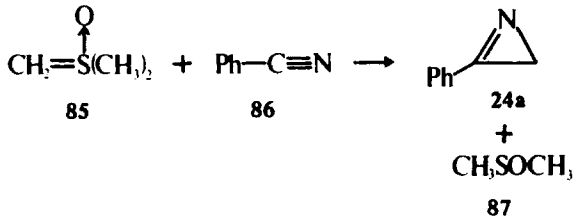


Hassner and Alexanian[82] used α-bromoketoximes (**80**) to prepare oxazaphospholines (**83**). They applied their procedure for the synthesis of azirines that are not easily accessible via the more general vinyl azide procedure (e.g., 2-*t*-butylazirine **84**). This method also avoids the necessity of handling potentially explosive low molecular weight vinyl azides in the synthesis of simpler 1-azirines. It also allows the preparation of 1-azirines with specific labeling (e.g., deuterium) at the 3-position.[82]



5. Addition of Methylene to Nitriles

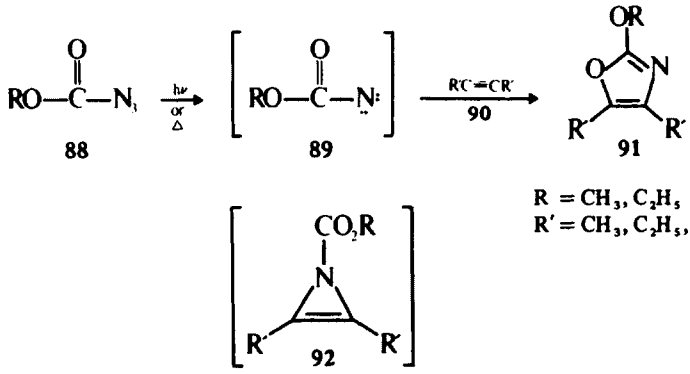
The reaction of "methylene transfer" reagents with nitriles offers a simple and direct approach to the synthesis of 1-azirines. However, very little work has been done in this area. There is one report of the reaction of dimethyloxosulfonium methylide (**85**) with benzonitrile (**86**) to give 2-phenyl-1-azirine (**87**) in low yield.[93]



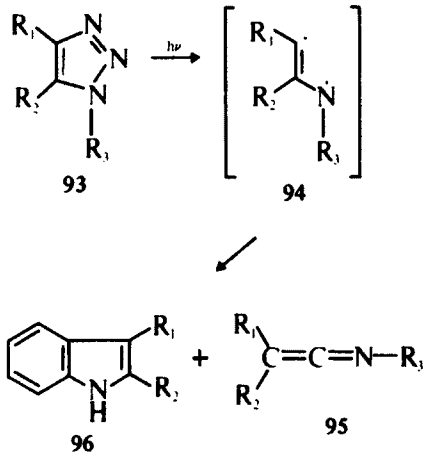
V. ATTEMPTED APPROACHES TO 2-AZIRINES

Although the 2-azirine ring system has been invoked as a transient intermediate in a number of studies directed towards its synthesis, it has been detected only recently and has not yet been isolated. Yamada, Mizoguchi, and Ayata[94] originally suggested that treatment of *1H*-1,2,3-triazole-4,5-dicarboxylic acid with acetic anhydride resulted in a 2-azirine system. However, further investigation of this reaction by Anderson, Gilchrist, and Rees[95] showed the product of this reaction to be an oxazole.

Huisgen and Blaschke[97] and Meinwald and Aue[98] studied the addition of nitrenes to acetylenes as an approach to obtaining 2-azirines. However, the addition of carbethoxy or carbomethoxy nitrene (**89**), generated thermally or photochemically from the corresponding azidoformate **88**, to acetylenes **90**, resulted in isolation of oxazoles **91**. The latter could arise by one or more of several pathways including one that involves addition of the nitrene **89** to **90** to produce the transient 2-azirine intermediate **92**.



Another direct route to 2-azirines by photolytic decomposition of *vic*-triazoles was examined by Burgess and his co-workers.[99] They envisioned that the 1,3-diradical **94** (or the related carbene) resulting from photochemical loss of nitrogen from **93** might undergo ring closure to a 2-azirine. However, irradiation of the triazoles **93** resulted in isolation of the ketenimine **95** and the indole **96**.



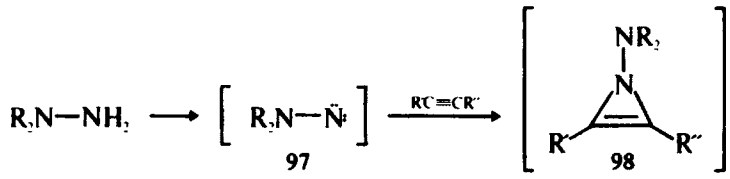
$R_1 = R_2 = R_3 = C_6H_5$
$R_1 = H; R_2 = R_3 = C_6H_5$
$R_1 = R_3 = C_6H_5; R_2 = H$

Fowler and Hassner[2] attempted the dehydrohalogenation of chloroaziridines as a method of generating 2-azirines but succeeded only in isolating oxazoles.

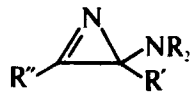
Phthalimidonitrene (**97**), generated by lead tetraacetate oxidation of *N*-aminophthalimide, reacts with acetylenes to give the 1-azirines **99**. This work provides good evidence of the probable intermediate formation of a 2-azirine system, **98**. Rees and his co-workers provided even more compelling evidence for the generation of the 2-azirine intermediate by examining the pyrolysis of 4-methyl-5-phenyl-1-phthalimido-1,2,3-triazole and 5-methyl-4-phenyl-1-phthalimido-1,2,3-triazole.[101] Both triazoles gave identical mixtures of 1-azirines and their pyrolysis products, indicating that the products are formed from a common intermediate (i.e., 2-methyl-3-phenyl-1-phthalimido-2-azirine).

The failure in all these studies to isolate the 2-azirine system is in complete agreement with theory, which predicts that the 2-azirine ring system is unstable because of ring strain and an electronically unfavorable structure. MO calculations show 2-azirine to be approx. 30 kcal less stable than 1-azirine.[102]

Taking advantage of donor-acceptor substituent stabilization, Regitz and co-workers[106] were able to detect the presence of 2-azirine **101** by the photoirradiation of α-diazoimine **100** in a CH_2Cl_2-glass at 77°K. The presence of **101** was surmised from its 1867 cm^{-1} infrared absorption.

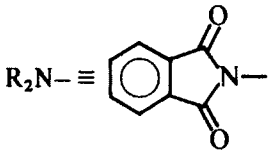


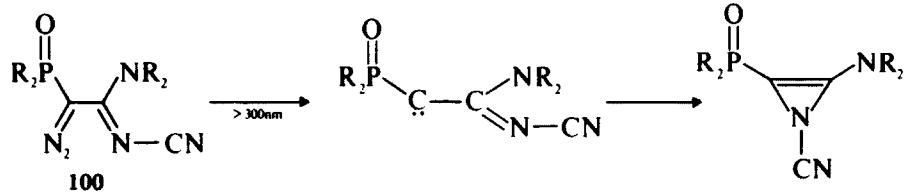
97 98



99

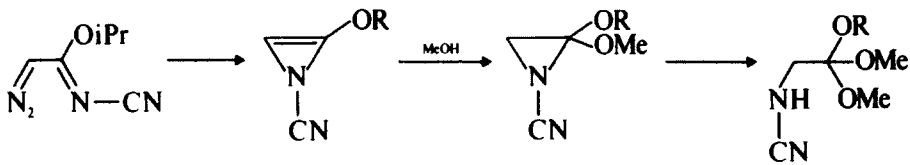
$R' = H; R'' = CH_3$
$R' = H; R'' = Pr$
$R' = H; R'' = n\text{-}Bu$
$R' = C_2H_5; R'' = C_2H_5$





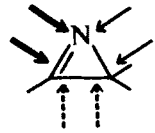
100 101

Similar C=C in frequencies (1880–1890 cm^{-1}) were observed on photolysis of an α-diazoiminoester in an argon matrix at 8°K. When the photolysis was carried out in methanol, one of the products was an ortho ester, a logical transformation product of a preliminarily formed 2-azirine.



VI. REACTIONS OF 1-AZIRINES

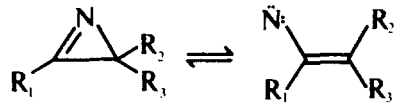
1-Azirines are reactive and versatile substrates because of certain inherent features within their structure. These include high ring strain, a reactive π bond, a lone pair of electrons on the nitrogen, and the ability to undergo ring cleavage on thermal or photochemical excitation to give such reactive fugitive species as vinyl nitrene, iminocarbene, and nitrile ylide. 1-Azirines are capable of acting in reactions as nucleophiles and electrophiles, as a 2π component in thermal cycloadditions, as precursors of vinyl nitrenes and iminocarbenes in thermal intramolecular reactions, as precursors of nitrile ylides, as a 4π component in photochemical cycloadditions, and as a substrate in metal-induced transformations.[42,50,53] These reactions can be regarded in general terms as involving the participation of the C=N, the C–C, or the C–N bond (see **1a**).



1a

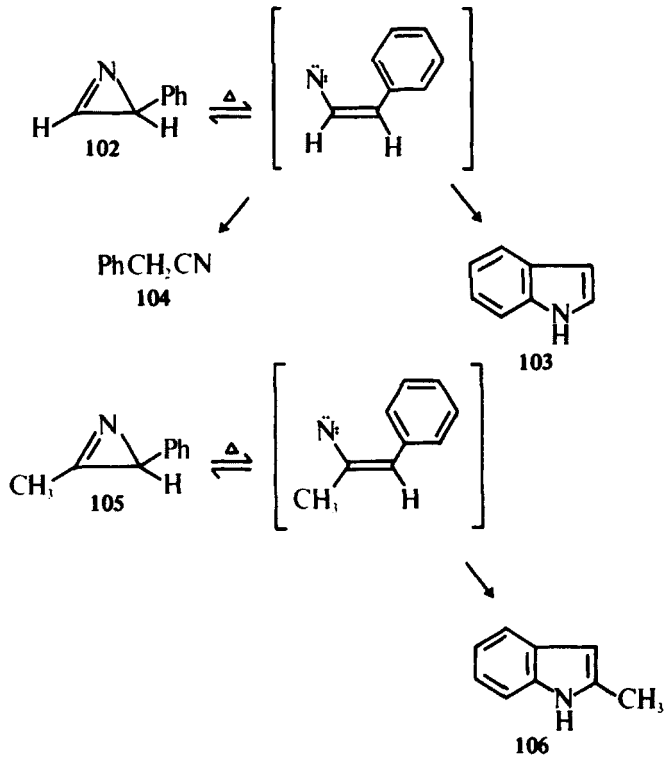
1. Thermal Decomposition and Rearrangement

Thermolysis of 1-azirines may involve C–N bond cleavage or C–C bond cleavage.[103] Ring opening involving the weaker C–N bond to give the vinyl nitrene is the reverse of the thermal electrocyclic closure (Scheme 2). The possibility that such an electrocyclic opening might be occurring during the pyrolysis of 1-azirines was implied in the work of Isomura, Kobayashi, and Taniguchi.[49] They reported that thermal decomposition of 3-phenyl-1-azirine (**102**) in refluxing hexadecane gave a 1:1 mixture of indole (**103**) and phenylacetonitrile (**104**) (Scheme 2a). When 2-methyl-3-phenyl-1-azirine (**105**) was similarly treated, only 2-methylindole (**106**) was isolated. A plausible mechanism for the formation of these products involves cleavage of the C–N bond to generate a vinyl nitrene. This intermediate can undergo insertion into the phenyl group to give indole, or it can rearrange to give phenylacetonitrile.



Scheme 2 Thermal equilibration between 1-azirine and vinyl nitrene.

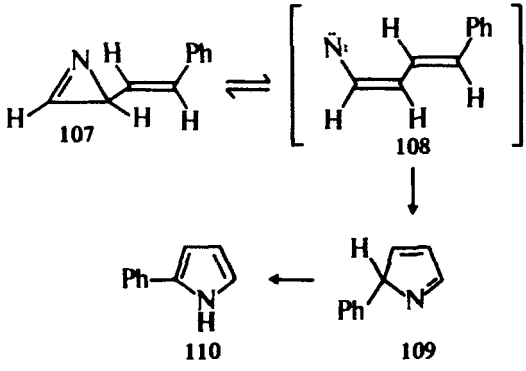
Thermal rearrangement of 2,3-diphenyl-1-azirine appears to be temperature dependent. When the azirine was heated at 250° for 3 hr in a sealed tube, 2-phenylindole, 2,3,4,5-tetraphenylpyrrole, 2,4,5-triphenylimidazole, and 1-benzyl-

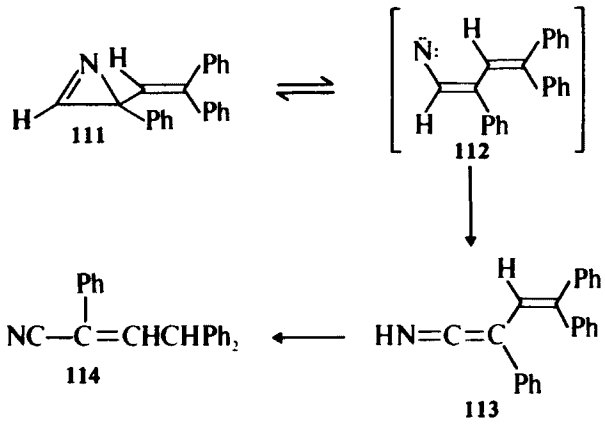


Scheme 2a Thermal rearrangement of 1-azirines to indoles.

2,4,5-triphenylimidazole were obtained as major products.[116] In contrast, thermolysis at 290° for 8 hr gave 2-phenylindole (54%) as the sole product.[117]

In a further study, Isomura, Okada, and Taniguchi examined the thermal rearrangement of 3-vinyl-azirines.[104] The results of this work also can be explained by C–N bond cleavage and formation of a transient vinyl nitrene. For example, the azirine **107** is converted thermally to 2-phenylpyrrole (**110**), presumably through the intermediacy of the vinyl nitrene **108**. The formation of nitrile **114** by thermolysis of the azirine **111** can be explained as proceeding through the nitrene **112**.





Padwa and his co-workers[73,109] examined the thermal rearrangement of ethyl-2-phenyl-1-azirine-3-(2-methylacrylate) (**115**). When this azirine was heated in xylene at 140° for 10 hr, the pyrrole **117** and the pyridine **118** were isolated. These transformations can best be rationalized in terms of an equilibration of the azirine with a transient vinyl nitrene **116**, which subsequently rearranges as shown in Scheme 3 to the products. The transient intermediacy of the vinyl nitrene was supported by trapping experiments. Thus, when the thermolysis of **115** was carried out in the presence of tris(dimethylamino)phosphine, the yields of **117** and **118** were significantly diminished and a 1:1 adduct of **116** and tris(dimethylamino)-phosphine (i.e., structure **119**) was isolated.

Ring expansion of a related system, 3-methyl-3-vinyl-2-dimethylamino-1-azirine has been reported by Ghosez et al.[77]

Thermolysis of iminoazirines results in the formation of pyrazoles (e.g., **120** → **121**).[72,105]

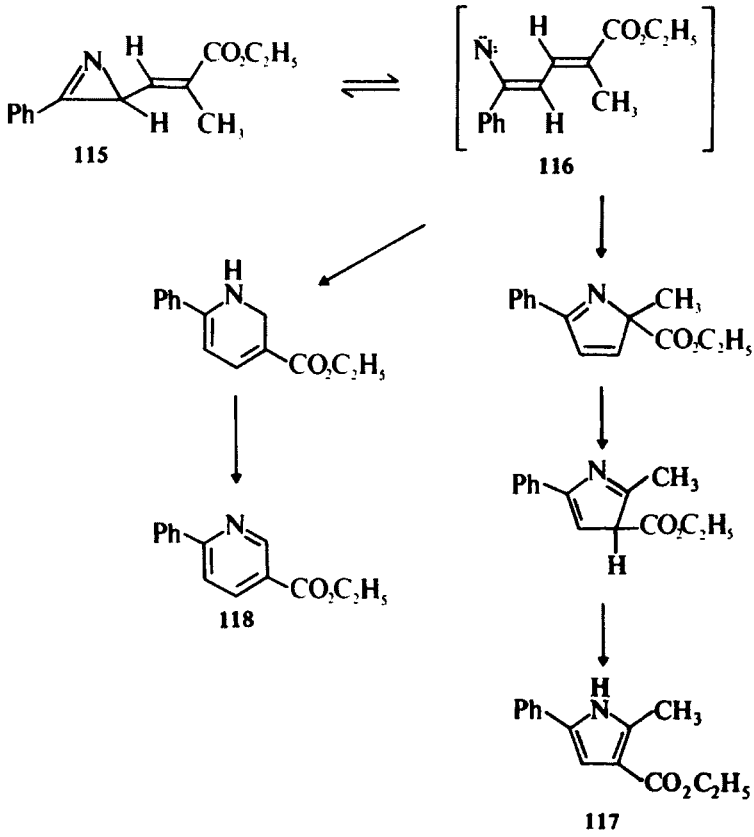
Rees and his co-workers[101,107] examined the thermal decomposition of 1-azirines **122** generated from the flash-vacuum pyrolysis of 1,2,3-triazoles at 400–500°. Their results (Scheme 4) also can be explained by initial carbon-nitrogen bond cleavage.

The pyrolysis of 2-phenyl-1-azirine-3-carboxamide (**123**) was studied by Nishiwaki and his co-workers.[108,109] The pyrazine-2,5-dicarboxamide **124** can be explained by invoking C–N or C–C bond cleavage (Scheme 5). Rupture of the C–N bond may lead to a diradical or a vinyl nitrene.

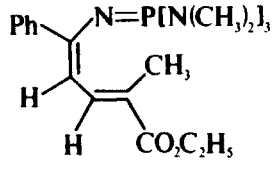
Although the azirinyl diene **125** was reported to produce an azepine (**127**) through intramolecular cyclization of the vinyl nitrene **126**,[105] the structure of this product has been subsequently shown to be the pyrrole **128**.[110]

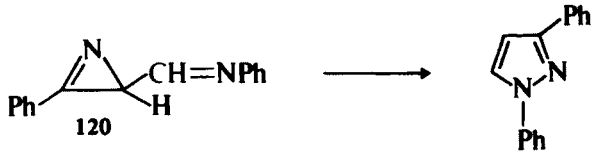
However, when the azirine **129** was subjected to thermolysis, the azepine **130** was isolated.[111]

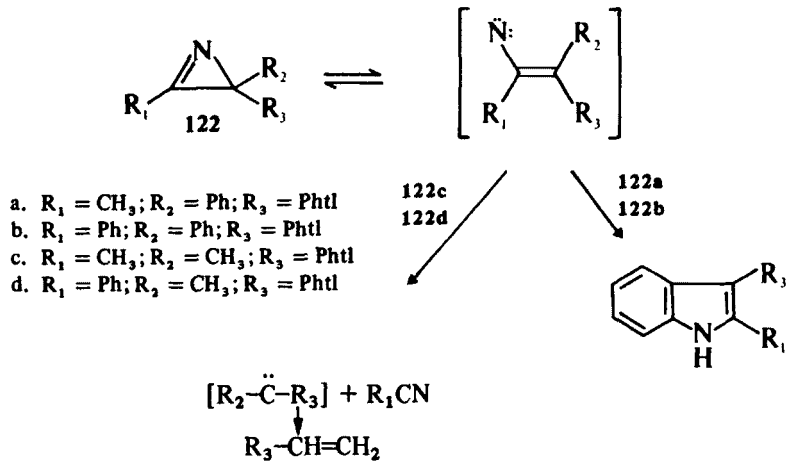
Padwa and Carlsen studied the interesting thermal rearrangements of 3-allyl-substituted azirines.[33,112,113] Thermolysis of 3-allyl-3-methyl-2-phenyl-1-azirine (**5**) in toluene at 195° for 180 hr gave 1-methyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**132**) in 90% yield. On prolonged heating, compound **132** is converted to 3-methyl-2-phenylpyridine (**133**). When the azirine **21c** was subjected to similar thermolysis



Scheme 3 Thermal rearrangements of a 3-vinyl-1-azirine. (Adapted from reference 105 with permission from the American Chemical Society.)



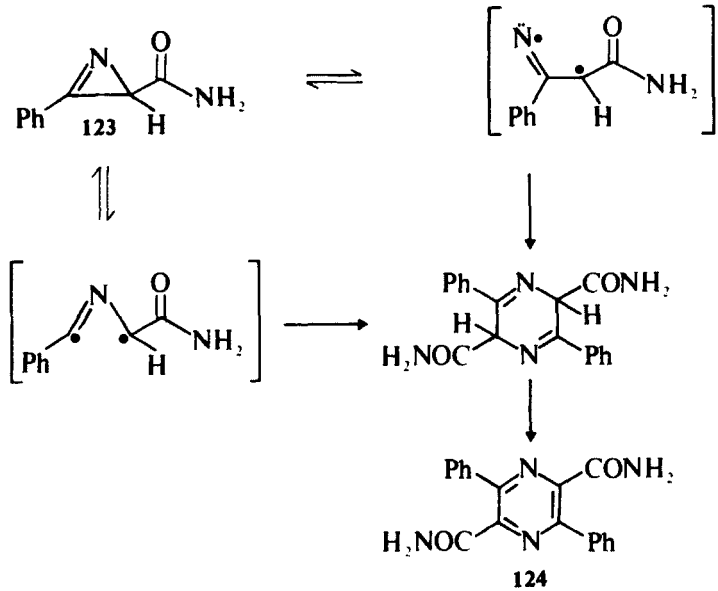




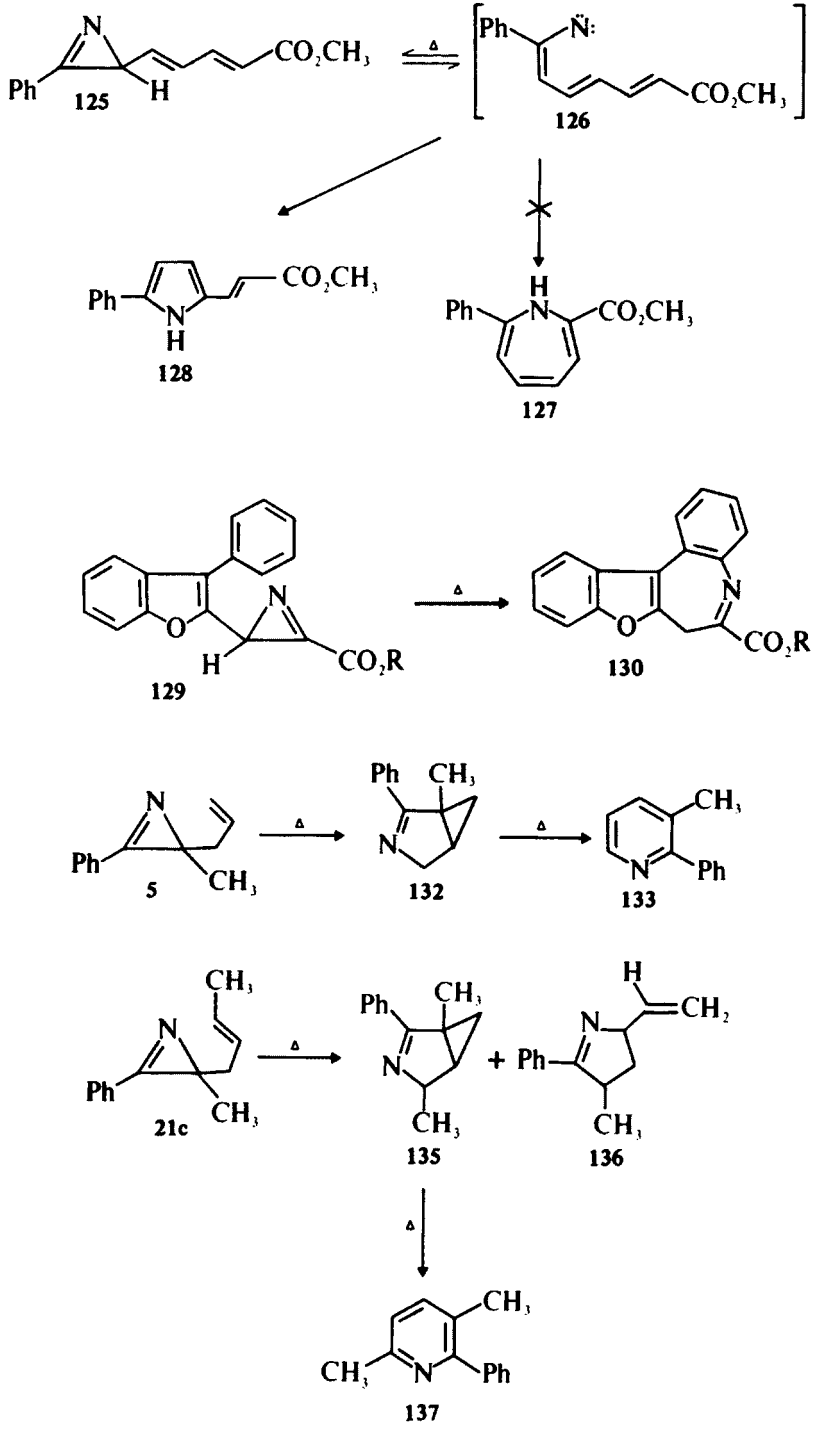
Scheme 4 Thermolysis of 1-azirines generated by flash-vacuum pyrolysis of triazoles (Phtl = phthalimido). (Adapted from reference 119 with permission from the American Chemical Society.)

conditions, the products **135** and **136** were isolated in 71 and 21% yields, respectively.

The formation of 3-azabicyclo[3.1.0]hex-2-enes probably involves initial C–N bond cleavage, and attack of the neighboring π system on the electrophilic singlet nitrene followed by bond reorganization (path 1, Scheme 6). An equally reasonable



Scheme 5 Pyrolysis of 2-phenyl-1-azirine-3-carboxamide.


Ph
N
H
CO2CH3
125
Δ
Ph
N:
CO2CH3
126
Ph
N
H
CO2CH3
128
Ph
N
H
CO2CH3
127
O
N
H
CO2R
129
Δ
O
N
CO2R
130
Ph
N
CH3
5
Δ
Ph
CH3
N
132
Δ
CH3
N
Ph
133
CH3
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N
CH3
21c
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Δ
CH3
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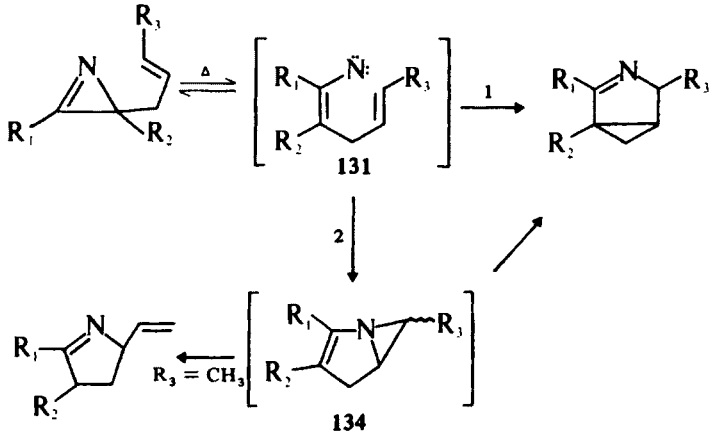
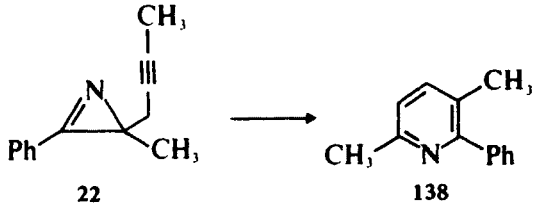
137



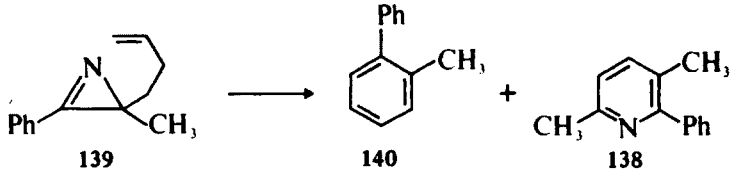
Scheme 6 Mechanism of formation of azabicyclohexenes from the thermolysis of 3-allyl-2-phenyl-1-azirines. (Adapted from reference 33 with permission from the American Chemical Society.)

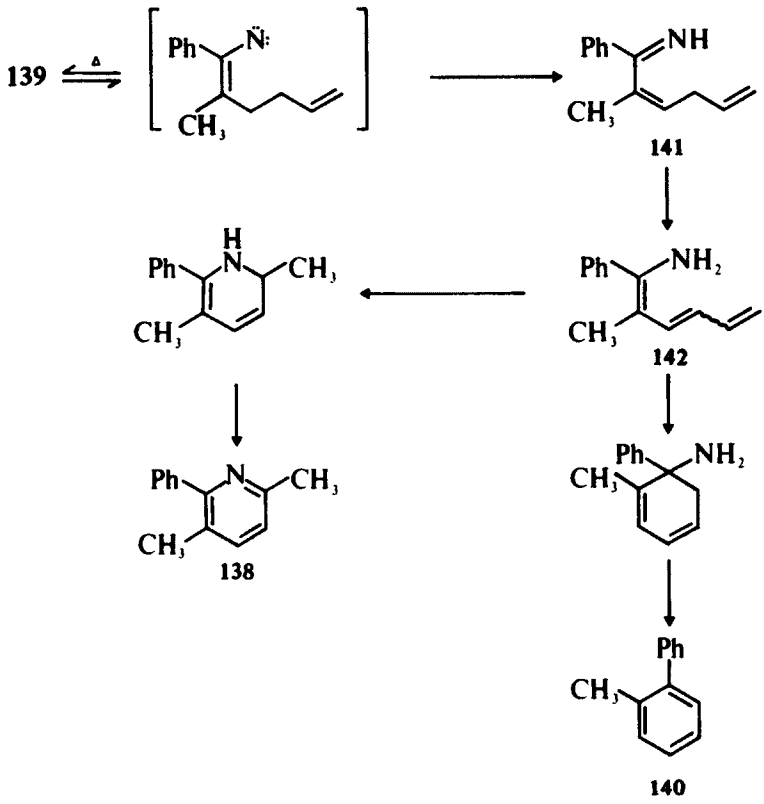
mechanism (path 2) involves intramolecular addition of the nitrene to the adjacent π bond followed by a 1,3-sigmatropic shift of the intermediate. Formation of the Δ^1-pyrroline ring system results from the latter intermediate probably by a homo[1,5]hydrogen migration.

Flash-vacuum pyrolysis (500° at 0.005 mm) of 3-(2-butynyl)-3-methyl-2-phenyl-1-azirine (**22**) gives 2,5-dimethyl-6-phenylpyridine (**138**), presumably through a vinyl nitrene intermediate.[33]



When but-3-enyl-substituted 1-azirines (e.g., **139**) are heated in toluene to 195°, 2-methylbiphenyl (**140**) and 2,5-dimethyl-6-phenylpyridine (**138**) are produced.[114,115] The mechanism of this thermolytic rearrangement (Scheme 7) can be explained by initial ring opening to the vinyl nitrene, followed by a 1,4-hydrogen transfer to produce an azatriene (**141**). This reactive system undergoes a 1,5-

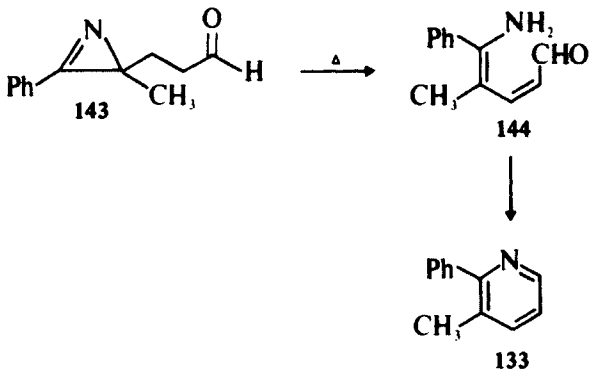




Scheme 7 Mechanism of thermal rearrangement of 3-(but-3-enyl)-2-phenyl-1-azirine. (Adapted from reference 115 with permission from the American Chemical Society.)

sigmatropic shift to give the thermodynamically more stable azatriene **142**, which can undergo cyclization and elimination to give the observed products. The proposed sequential 1,4- and 1,5-hydrogen transfers was supported by evidence from a related study (Scheme 8), where the azirine **143** is converted by ring cleavage and 1,4- and 1,5-hydrogen shifts to the dienaminal **144**. This intermediate cyclizes as expected to give the observed product, 2-phenyl-3-methylpyridine.

In almost all the aforementioned examples, thermolysis of the 1-azirine ring system examined led to products that could reasonably be explained as having arisen from initial C–N bond rupture. Excellent evidence for the occurrence of thermal C–C bond cleavage in the vapor phase pyrolysis of some 1-azirines was reported by Bergman and Wendling.[118,119] They studied the pyrolysis of 3-methyl-2-phenyl-1-azirine in the gas phase at 565° and 1 atm pressure of helium. The products were styrene (56%), benzonitrile (2%), and a reddish polymer. 3-Ethyl-2-phenyl-1-azirine gave similar results. The vapor phase pyrolysis of 3,3-dimethyl-2-phenyl-1-azirine at 472°, however, gave styrene (10%), benzonitrile (6%), ace-



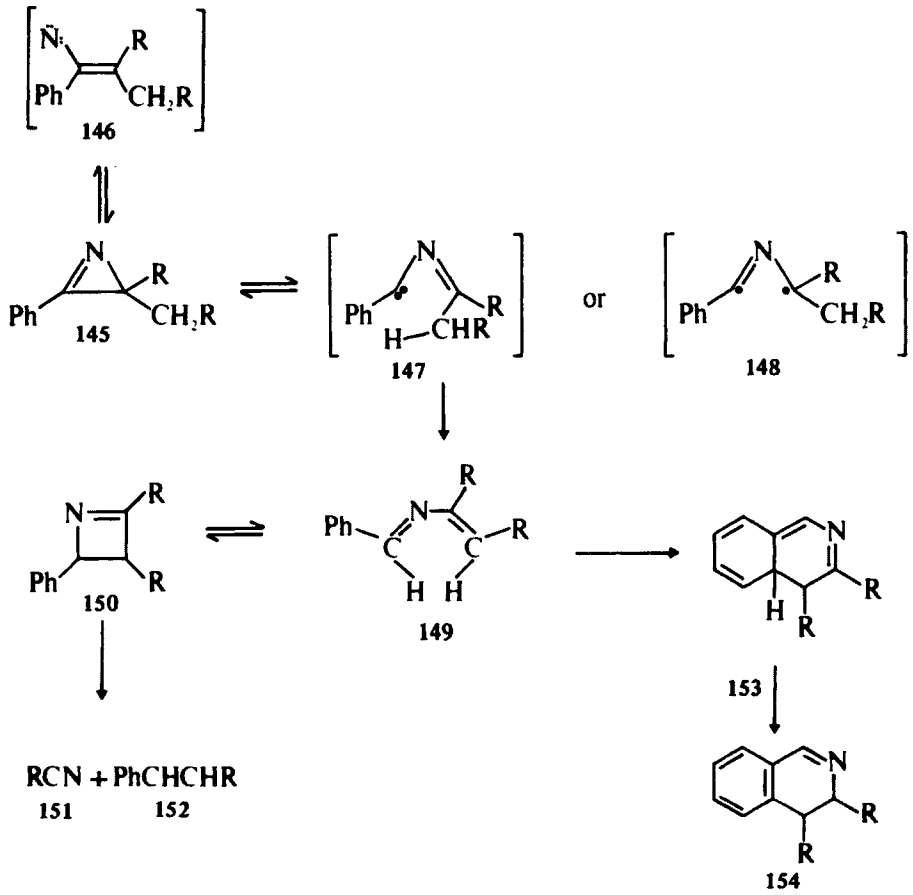
Scheme 8 Dienaminal formation in the thermolysis of the azirine **143**.

tonitrile (small and variable amounts), polymer (20%), and an azadiene (24%). When the pyrolysis temperature was raised to 545°, this azirine gave the following products: styrene (56%), benzonitrile (4%), 3-methyldihydroisoquinoline (5%), and polymer (32%).

From these and further supporting experiments, Bergman and Wendling proposed (Scheme 9) that the initial bond breaking involves the C–C bond and produces a vinyl carbene (**147**) or a 1,3-diradical species (**148**). Hydrogen abstraction by the carbene (or diradical) results in formation of the key intermediate in these reactions, that is, the azabutadiene **149**. An endothermic electrocyclization (4π electrons) may then generate a small steady state amount of azetine (**150**), which fragments to give the nitriles and styrenes observed. Electrocyclization involving 6π electrons produces **153**, which rearranges by a 1,5-sigmatropic hydrogen shift to give the dihydroisoquinoline **154**.

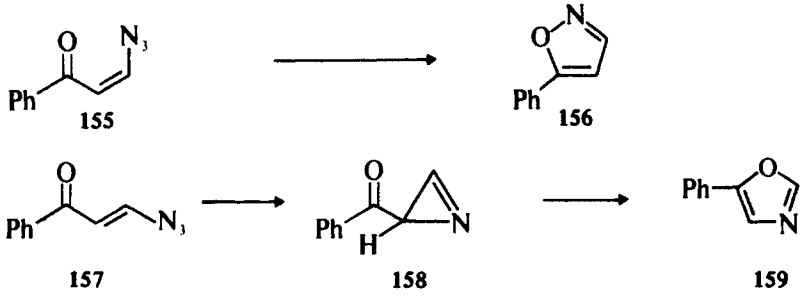
Further support for this mechanistic scheme was provided by Ghosez and his co-workers, who reported the isolation in high yield of an azabutadiene by the pyrolysis of 3,3-dimethyl-2-dimethylamino-1-azirine.[120] The absence of products arising from the vinyl nitrene **146** warrants discussion. It is reasonable to assume that C–N bond cleavage provides a lower energy pathway than C–C bond cleavage. However, the nitrenes formed in these cases apparently will not undergo 1,4-hydrogen abstractions (cf. Padwa and Kamigata[115]). Furthermore, 1,2-abstraction by the nitrene to form ketenimines occurs only when hydrogen is the group being transferred. Consequently, the only product path that seems to be available to the vinyl nitrene is regeneration of the azirine. Thus, reaction products with these azirines are observed only when pyrolysis temperatures are high enough to cause the rupture of the C–C bond.

Thermolytic products can be explained by invoking C–C bond cleavage of the 1-azirine ring system in other cases. For example, the *cis*-vinyl azide **155** is smoothly converted to the isoxazole **156** at room temperature, whereas the *trans* isomer **157** gives the oxazole **159**. In both cases, vinyl nitrenes are plausible intermediates. In the former case, the stereochemical arrangement of the intermediate vinyl nitrene

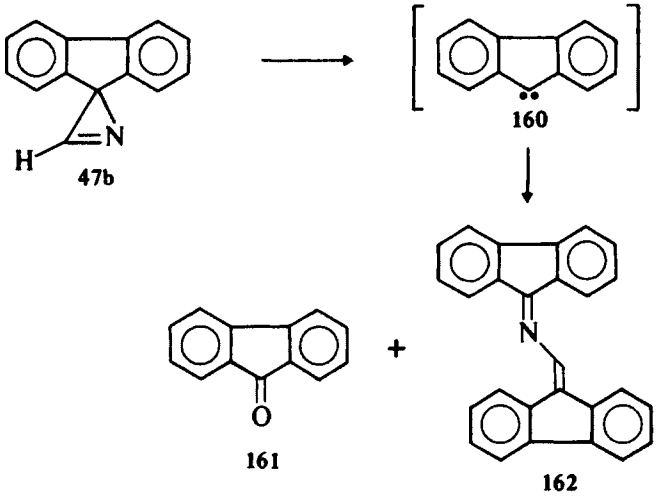


Scheme 9 Thermal C–C bond cleavage in the vapor phase pyrolysis of 1-azirines.

is favorable for a six-electron electrocyclization whereas in the latter case, a four-electron electrocyclization to the azirine **158** is probably the preferred pathway. Transformation of the azirine to the oxazole **159**, would require a C–C bond cleaveage.[121]



The azirine **47b** undergoes bond cleavage at both C–N and C–C to give products that can be explained as having arisen from the intermediate carbene **160**.[48]

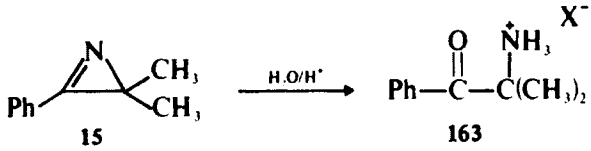


2. Reactions with Azirines as Nucleophiles

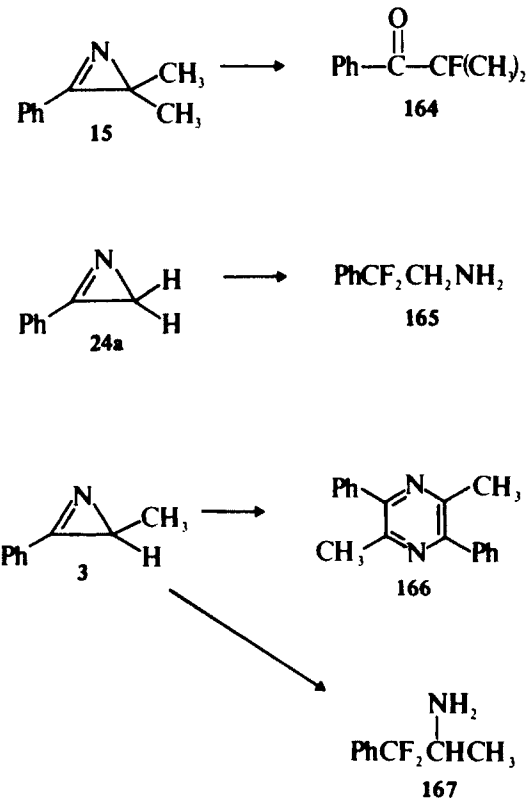
1-Azirines undergo a number of reactions in which the ring system plays the role of the nucleophile. The focal point of the initial nucleophilic step in these transformations is the heterocyclic nitrogen. The basicity of the nitrogen in azirines is much lower than in simple aliphatic amines. Calculations based on ^{13}C–H coupling constants[2,15,16] suggest a high degree of *s* character for the exocyclic bonds in this ring system. The basicity and nucleophilicity of 1-azirines appear to be comparable to that of simple aliphatic nitriles.[2]

A. *Reactions Involving Acids and Derivatives*

The acid-catalyzed hydrolysis of 1-azirines to α-aminoketones is well established. In fact, in many reactions of 1-azirines where acid catalysis is used, formation of α-aminoketones is difficult to avoid. Hydrolysis of 2-substituted 1-azirines (e.g., **15**) gives α-aminoisobutyrophenone (**163**).[122] With 2-unsubstituted 1-azirines, the hydrolysis products would be aminoaldehydes. The acid-catalyzed methanolysis of azirine **15** gives the dimethyl ketal of **163**, quantitatively.

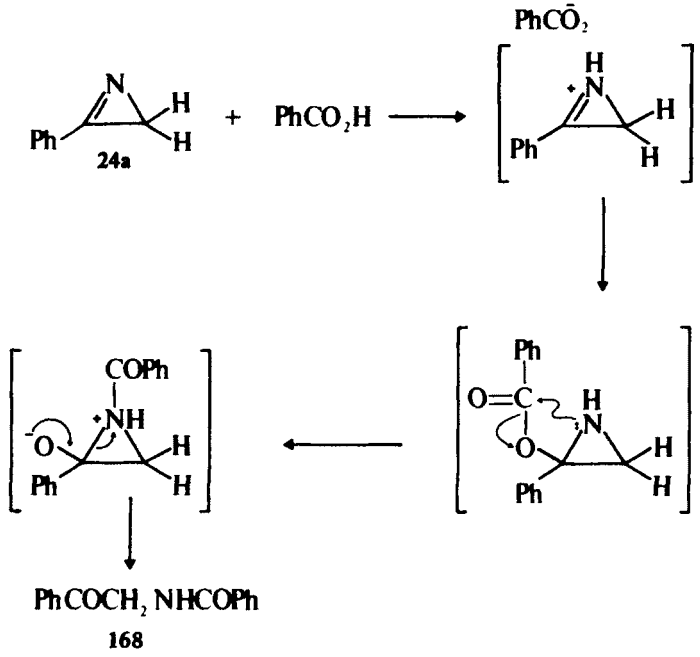


The reaction of HF in the presence of pyridine or triethylamine with 1-azirines gives products that depend on the structure of the 1-azirine as well as on the solvent used. For example, 3,3-dimethyl-2-phenyl-1-azirine (**15**) reacts with HF/pyridine in tetrahydrofuran to give the α-fluoroketone **164** almost quantitatively,[123] whereas 2-phenyl-1-azirine (**24a**) is converted by HF/pyridine in benzene to the difluoroamine **165** as the major product.[124] Variation of products results with the same azirine when different solvents are used. Thus, 3-methyl-2-phenyl-1-azirine **3** reacts with HF/pyridine in tetrahydrofuran to give the pyrazine **166** in 81% yield, whereas in benzene it is converted to the difluoroamine **167** in 75% yield.[125]



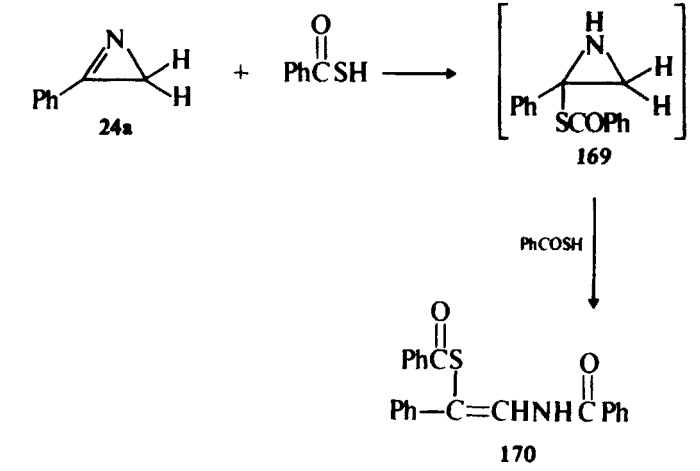
The reaction of 2-phenyl-1-azirine (**24a**) with benzoic acid gave *N*-benzoylphenacylamine (**168**).[126] The overall mechanism of the reaction in this case and in the two former examples involves initial protonation on nitrogen followed by addition of nucleophile to the azirinium ion, and finally ring opening. In the latter example (Scheme 10), a rearrangement following the nucleophilic attack must occur to account for the observed product **168**. α-Haloacids behave similarly.[131]

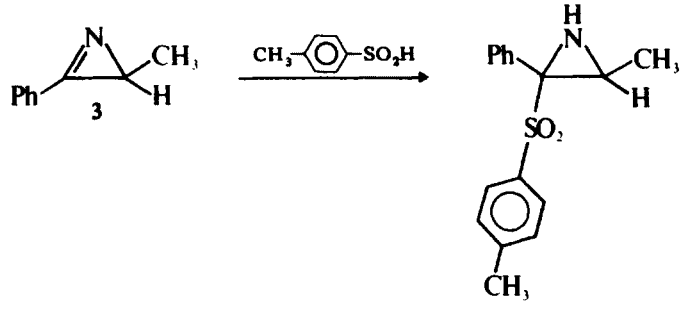
However, thiobenzoic acid reacted with azirine **24a** to give **170**, presumably through the intermediacy of the aziridine **169**.[126]



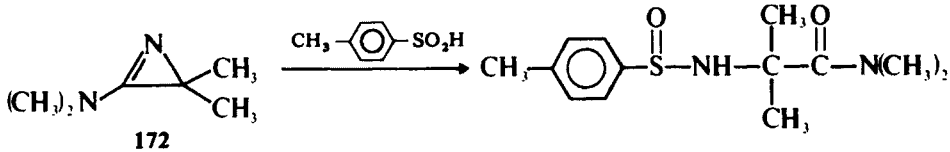
Scheme 10 Mechanism of reaction of 2-phenyl-1-azirine and benzoic acid.

Meek and Fowler[53] observed that the addition of *p*-toluenesulfinic acid to 3-methyl-2-phenyl-1-azirine (**3**) gave the sulfonylaziridine **171**. However, reaction of the 2-aminoazirine **172** with *p*-toluenesulfinic acid[127] gave the ring-opened product **173**. The reaction pathway followed in the latter case appears to be similar to that shown in Scheme 10 for the benzoic acid reaction with azirine (**24a**).





171



172 173

Sulfonic acids react with the aminoazirine **172** to give dimeric salts containing the piperazine ring.[127]

Activated phenols (e.g., **174**) react with the 2-aminoazirine **172** in boiling benzene to give the aniline derivatives **175**.[128] A plausible reaction mechanism is shown in Scheme 11: protonation of the azirine is followed by attack of the phenolate ion at the amidinium carbon atom. The resulting intermediate rearranges to a spiro-Meisenheimer complex, which undergoes ring opening to give the observed products **175**. Compound **175c** can also be produced by the reaction of **172** with 2,4-dinitrofluorobenzene.[128]

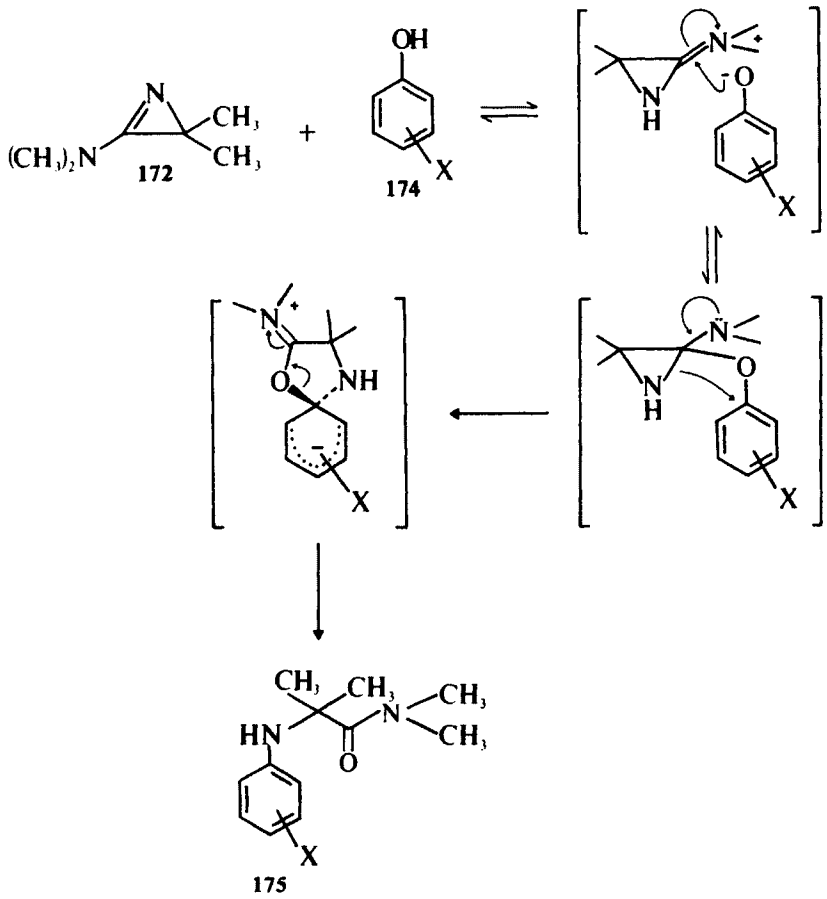
2-Formyl- and 2-acetylphenols (**176**) convert **172** to **177**.[128]

The 2-aminoazirine **172** reacts with formyl cycloalkanones **178** to give the 1 : 1 adducts **179** as shown in Scheme 12.[127]

The first example of the utilization of the protonated 1-azirine system for the synthesis of heterocyclic compounds was reported by Leonard and Zwanenburg.[122] They discovered that treatment of 3,3-dimethyl-2-phenyl-1-azirine (**15**) with anhydrous perchloric acid and acetone or acetonitrile gave the oxazolinium perchlorate **180** and the imidazolinium perchlorate **181**, respectively. Using elegant isotope labeling studies, they proposed that the mechanism of these conversions involved 1,3-bond cleavage of the protonated azirine and reaction with the carbonyl group (or nitrile) to produce a resonance-stabilized carbonium-oxonium ion (or carbonium-nitrilium ion), followed by attack of the nitrogen unshared pair of electrons to complete the cyclization (Scheme 13).

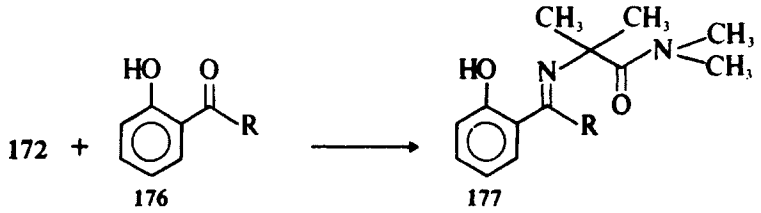
Similar results are also obtained when boron trifluoride etherate is substituted for perchloric acid or fluoroboric acid in these ring expansion reactions.[129]

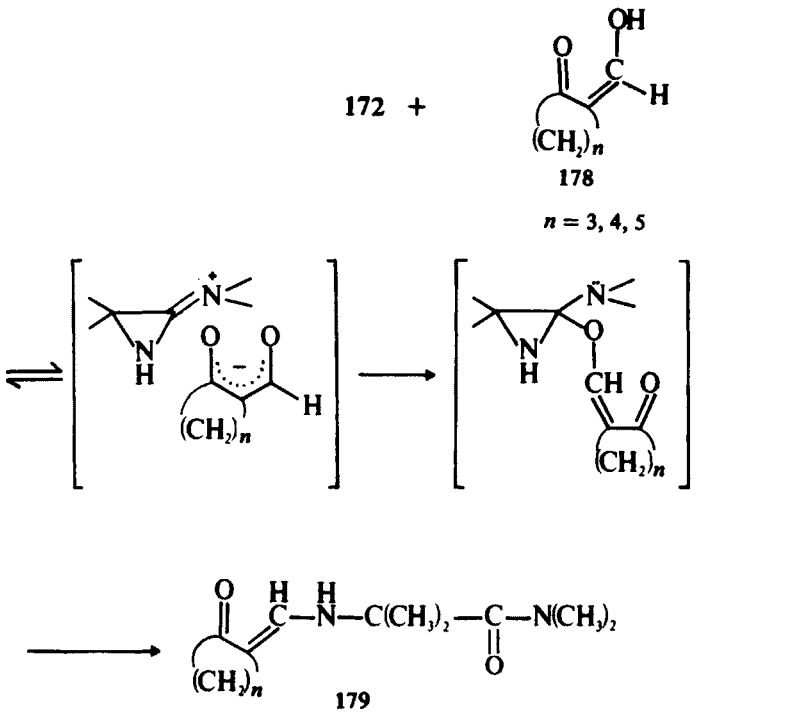
Leonard and Zwanenburg isolated the aziridine **182** from the reaction of azirine (**15**) and pyridinium perchlorate.[122] The structure of a similar product, prepared from Neber's azirine,[25] was proposed by Cram and Hatch.[27]



a. X = 2-nitro
b. X = 4-nitro
c. X = 2,4-dinitro
d. X = pentachloro

Scheme 11 Mechanism of reaction of 2-amino-1-azirines and activated phenols. (Adapted from reference 128 with permission from *Helvetica Chimica Acta*, Birkhauser Verlag.)



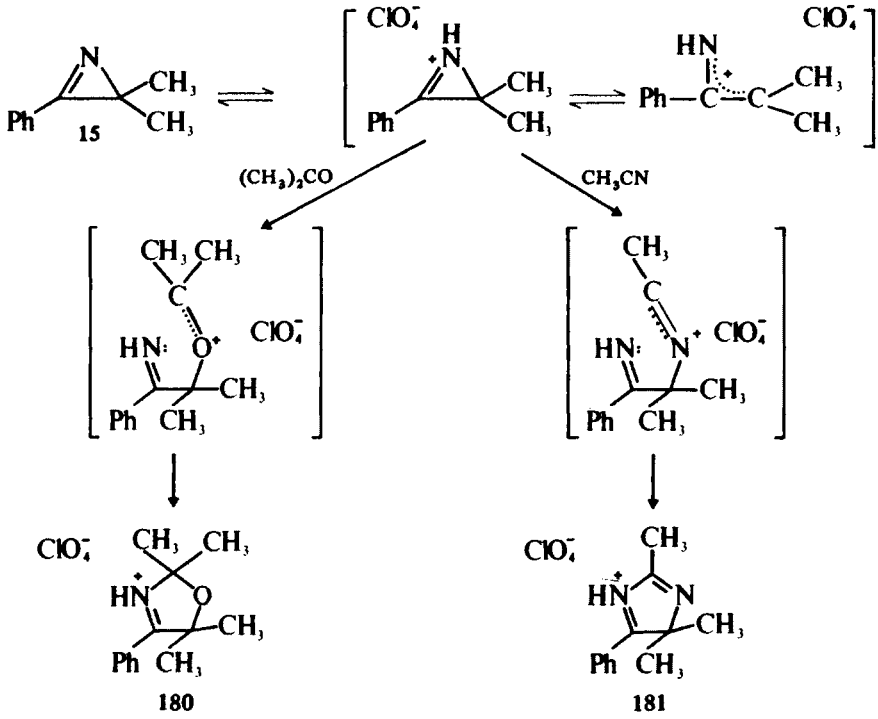


Scheme 12 Reaction of 2-amino-1-azirines with formyl cycloalkanones.

However, when Leonard, Muth, and Nair[130] treated the azirine **15** with anilinium perchlorate in acetonitrile at 0°, they found that it was quantitatively transformed into α-ammonium isobutyrophenone anil perchlorate (**186**). The probable first step in this conversion is the transfer of a proton to the azirine and attack by aniline on the iminium bond to give **184**. A second proton transfer from the anilinium to the more basic aziridine nitrogen would lead to intermediate **185**. Cleavage at the 1,2-bond of the strained ring to give a resonance-stabilized iminium ion would be followed by a final proton transfer to yield the product **186**. An intriguing feature of the mechanistic sequence is the effective transfer of all three protons from one nitrogen to the other (Scheme 14).

Reaction of azirine **63a** with hydrazine perchlorate gives the aminopyrazole **188**.[13] The mechanism is probably similar to that of the reaction of anilinium perchlorate and azirine (**15**). The intermediate **187** is therefore the precursor to the pyrazole **188**.

1-Azirines react with carboxylic acid chlorides in benzene to give aziridines, where RCOCl has been added to the C=N bond.[2,132,133] For example, Hassner and coworkers found that 3-methyl-2-phenyl-1-azirine (**3**) reacts with benzoyl chloride presumably through the azirinium ion **189** to give a stereoisomeric mixture of *N*-benzoyl-2-chloroaziridines (**190**). These unstable aziridines are converted in polar solvents or by heating into a mixture of oxazole (**191**) and dichloroamide (**192**)



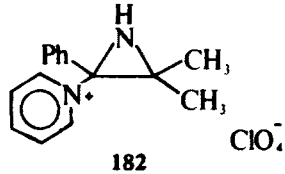
Scheme 13 Acid-catalyzed additions of acetone and acetonitrile to 1-azirines.

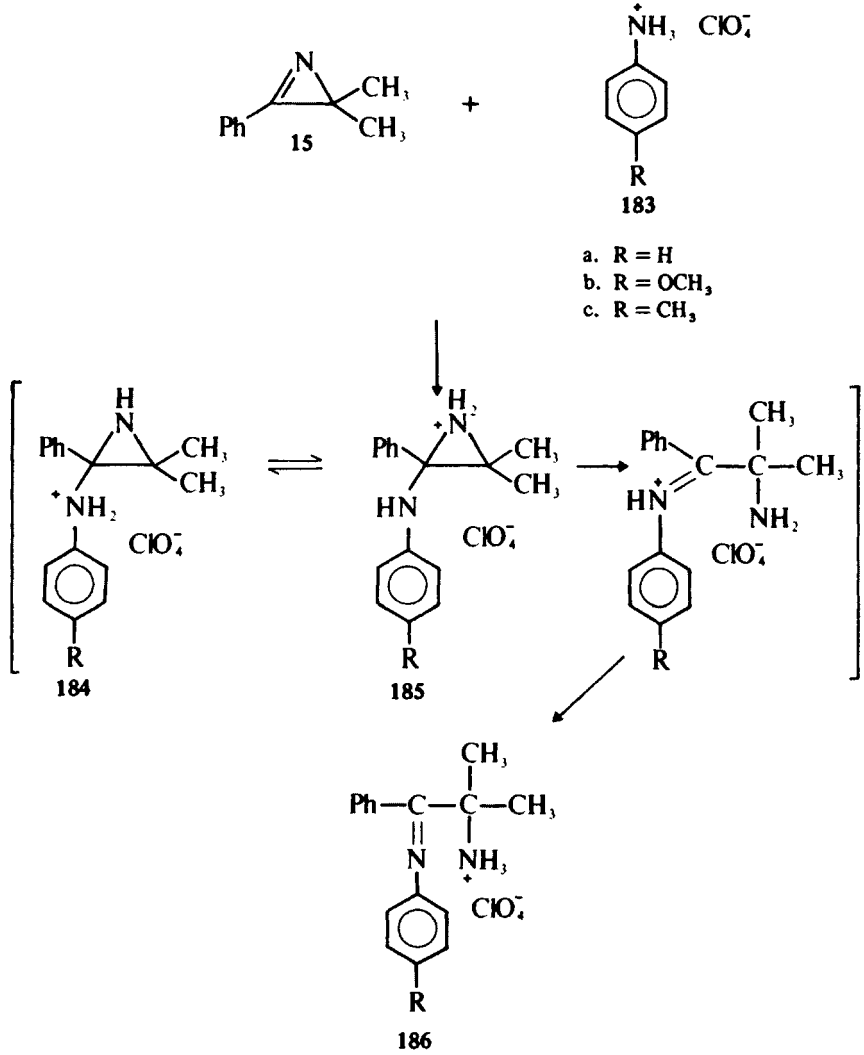
(Scheme 15). It should be noted that the rearrangement to the oxazole proceeds with opposite regiochemistry to that observed in the formally similar acid-catalyzed reaction of 1-azirines with ketones reported by Leonard and Zwanenburg.[122]

Sato and his co-workers[126] observed that the reaction of 2-phenyl-1-azirine (**24a**) with acid chlorides and anhydrides in the presence of triethylamine gave the oxazole directly. Thus **24a** was converted to the oxazole **193** when it was treated with acetic anhydride and triethylamine under reflux for 6 hr. Using a lower temperature and a shorter reaction time they were able to isolate the aziridine **194**.

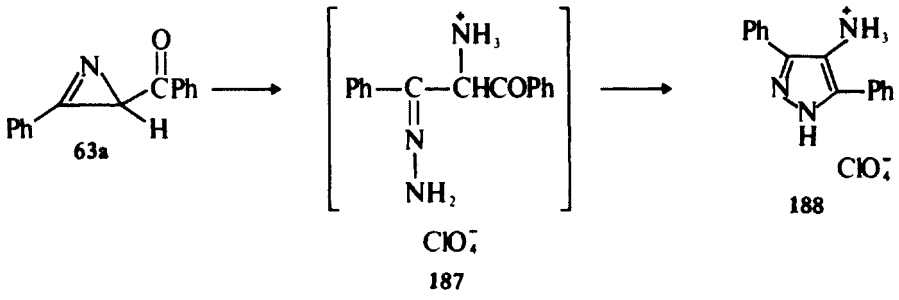
The reaction of phthalic anhydride with the azirine **24a** gives the ketoamide **196**. A likely intermediate in this conversion is **195**, which on hydrolysis gives the observed product.[126]

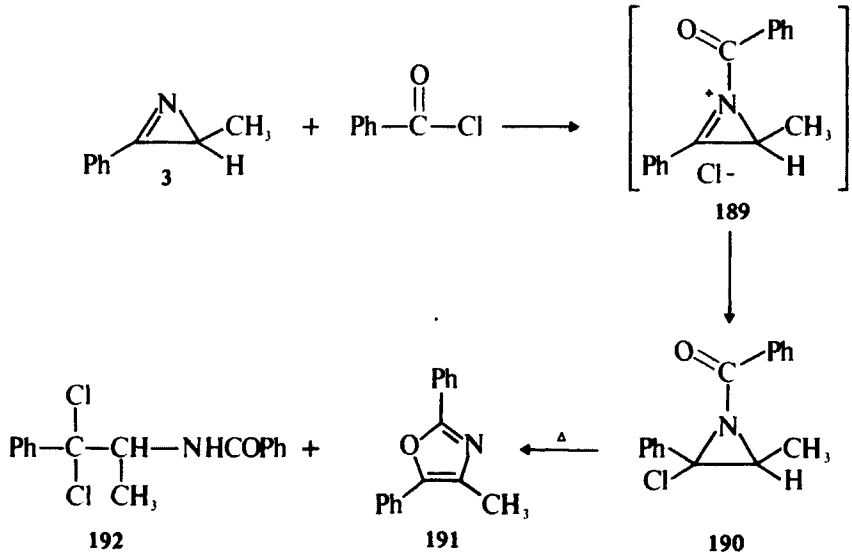
When azirine **3** was treated with an excess of benzenesulfonyl chloride in pyridine, a mixture of sulfonamides **198** and **199** was produced.[2] It is likely that





Scheme 14 Reaction of 1-azirines with anilinium perchlorates.



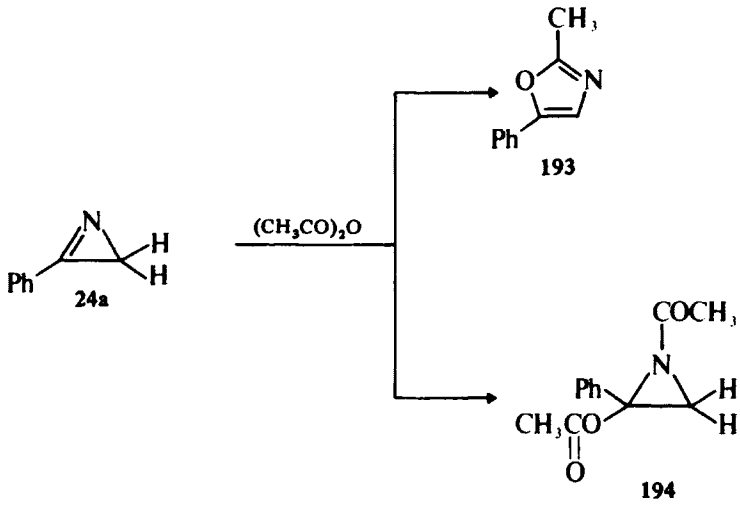


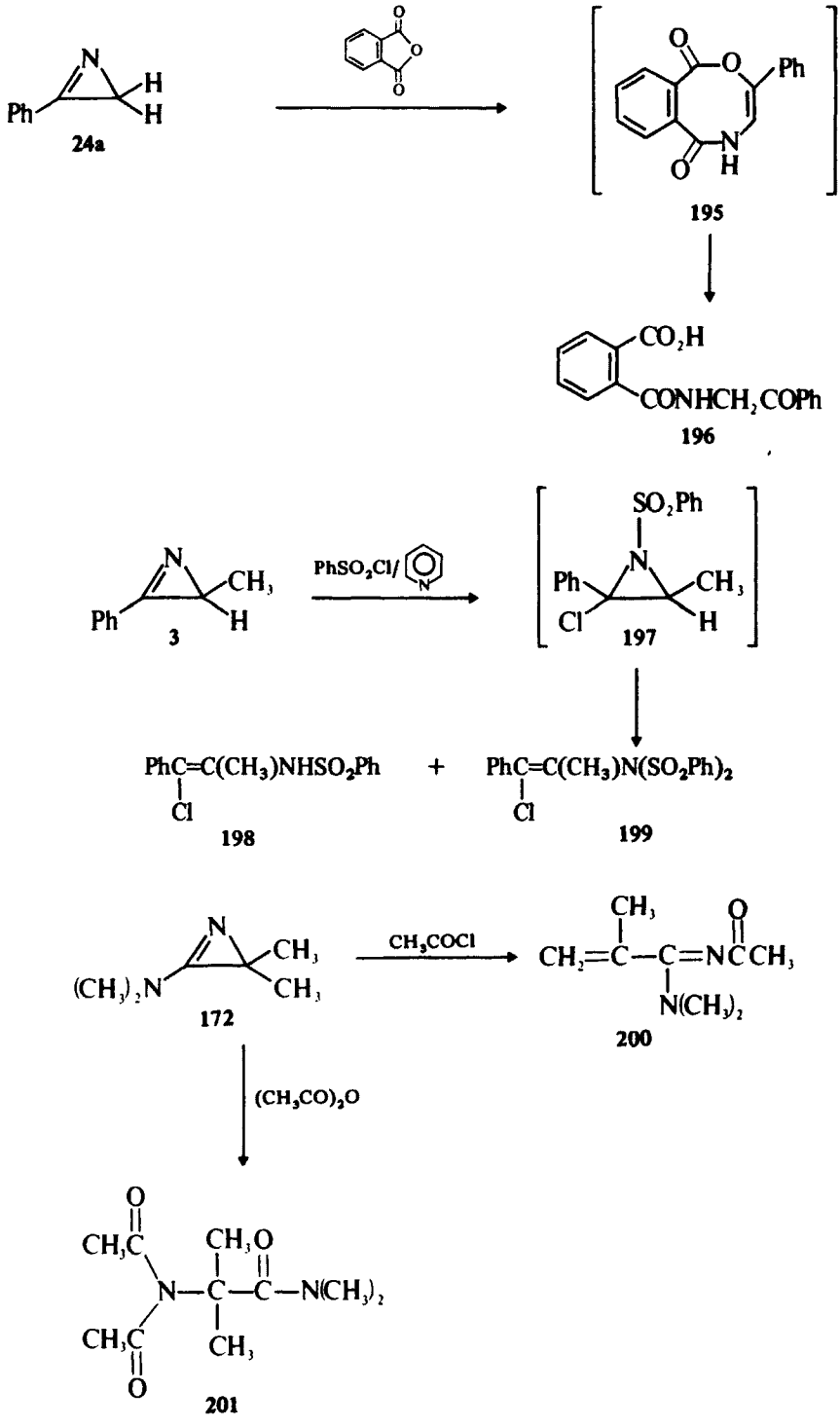
Scheme 15 Reaction of 1-azirines with carboxylic acid chlorides.

the chloroaziridine **197** is the precursor of **198**, since the rearrangement of *N*-sulfonylaziridines to vinyl sulfonamides is known.[134]

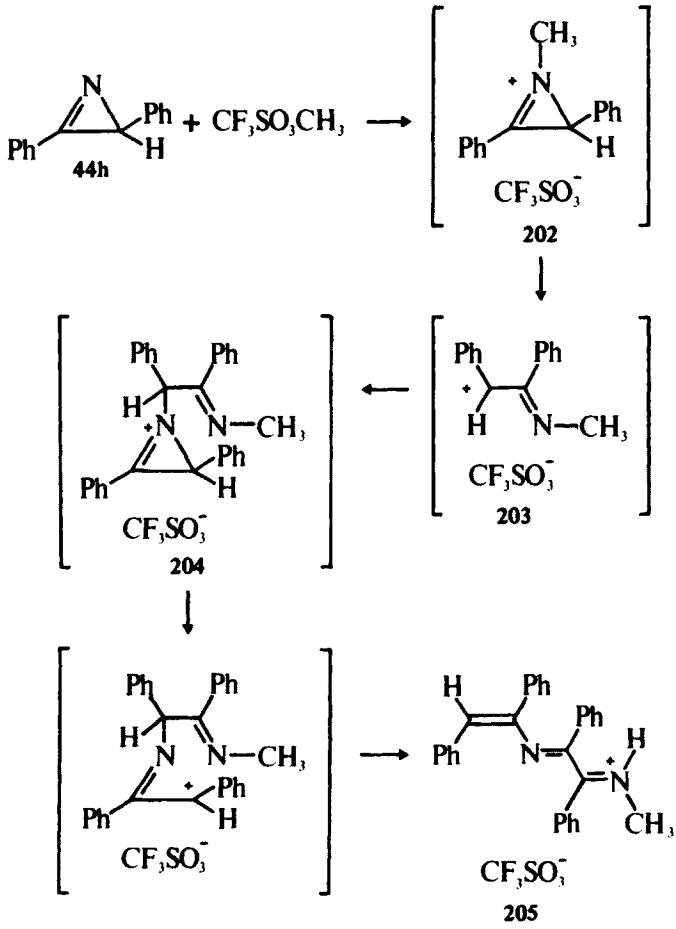
2-Dimethylamino-3,3-dimethyl-1-azirine (**172**) reacts with acid chlorides to give *N*-acylamidines (e.g., **200**) through 1,3-bond cleavage of the initially formed intermediate.[135] Carboxylic acid anhydrides, however, convert this azirine to diacylamino derivatives (e.g., **201**) in a reaction that involves 1,2-bond breaking.[135]

Deyrup and Szabo[136] have reported that alkylation of 1-azirines is possible with methyl triflate. Treatment of 2,3-diphenyl-1-azirine (**44h**) with methyl triflate




Ph
H
H
24a
195
Ph
CO2H
CONHCH2COPh
196
CH3
PhSO2Cl/
SO2Ph
Cl
197
3
PhC=C(CH3)NHSO2Ph
PhC=C(CH3)N(SO2Ph)2
198
199
(CH3)2N
172
CH3COCl
200
(CH3CO)2O
CH3C
CH3O
N(CH3)2
201

in dichloromethane gave **205**. The mechanism of formation of **205** is shown in Scheme 16. The initial step involves alkylation of the azirine to generate intermediate **202**. Ring cleavage produces cation **203**, which alkylates a second molecule of azirine to give via **204** the observed product **205**.

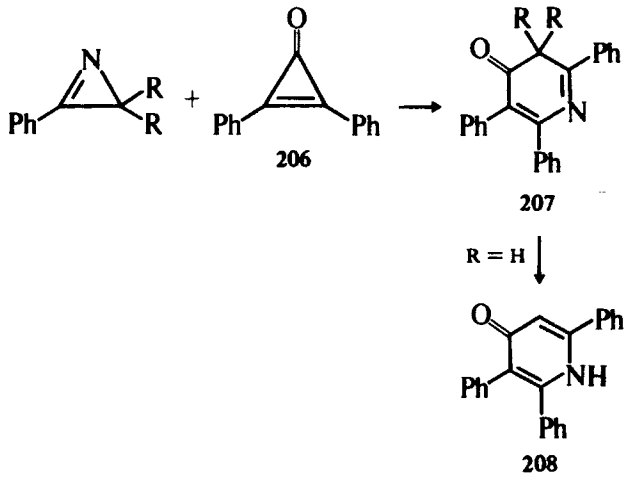


Scheme 16 Alkylation of 2,3-diphenyl-1-azirine with methyl triflate.

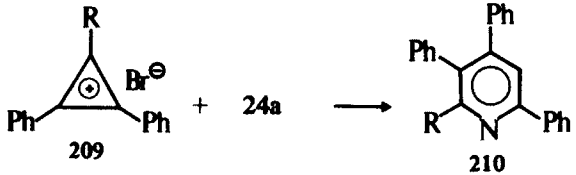
B. *Nucleophilic Reactions Involving Cyclopropenones and Cyclopropenyl Cations*

Hassner and Kascheres[137] found that diphenylcyclopropenone (**206**) reacts with 1-azirines to produce 4-pyridones (**208**). When R = CH_3, a prototropic shift is not possible and intermediate **207** can be isolated (Scheme 17).

Moerck and Battiste[138] reported that cyclopropenyl cations (**209**) convert 1-azirines (e.g., **24a**) to pyridines (**210**).



Scheme 17 Reaction of 1-azirines with diphenylcyclopropenone.

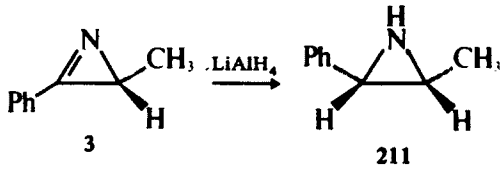


3. Reactions with Azirines as Electrophiles

1-Azirines also undergo reactions while participating as electrophiles. The electrophilicity of 1-azirines is associated with the polarized nature of the C=N bond.

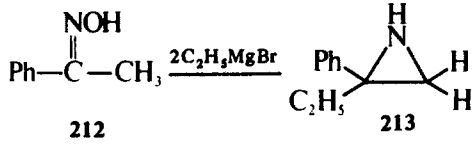
A. *Reactions Involving Organometallic Reagents*

Lithium aluminum hydride reduces 1-azirines in a highly stereospecific manner to give aziridines.[8,27] For example, 3-methyl-2-phenyl-1-azirine (**3**) is stereospecifically and quantitatively reduced to the *cis*-aziridine **211**. Approach of hydride occurs exclusively from the less hindered side of the azirine molecule. This reduction provides a useful preparation of *cis*-aziridines.



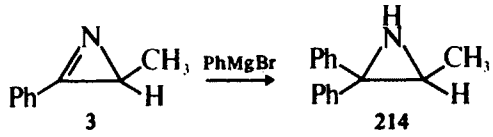
Sodium borohydride also has been reported to convert azirines to aziridines.[27]

Eguchi and Ishii[139] observed that the 1-azirine **24a** generated *in situ* from the oxime **212** reacts with a Grignard reagent to give aziridine **213**.



212 **213**

Hassner and Fowler[2] found that 3-methyl-2-phenyl-1-azirine (**3**) reacted readily with phenylmagnesium bromide to give 2,2-diphenyl-3-methylaziridine (**214**). The observed reactivity of 1-azirines toward Grignard reagents is an anomalous reaction of an imine. Generally, Grignard reagents react by α-hydrogen abstraction to give the enamine anion, which on work-up generates the starting imine. The failure of 1-azirines to follow this behavior can be explained in terms of the instability of the enamines that would be generated from α-hydrogen abstraction of 1-azirines. The reaction of 1-azirines with Grignard reagents exhibits similar stereospecificity as observed for hydride reductions.[146]



3 **214**

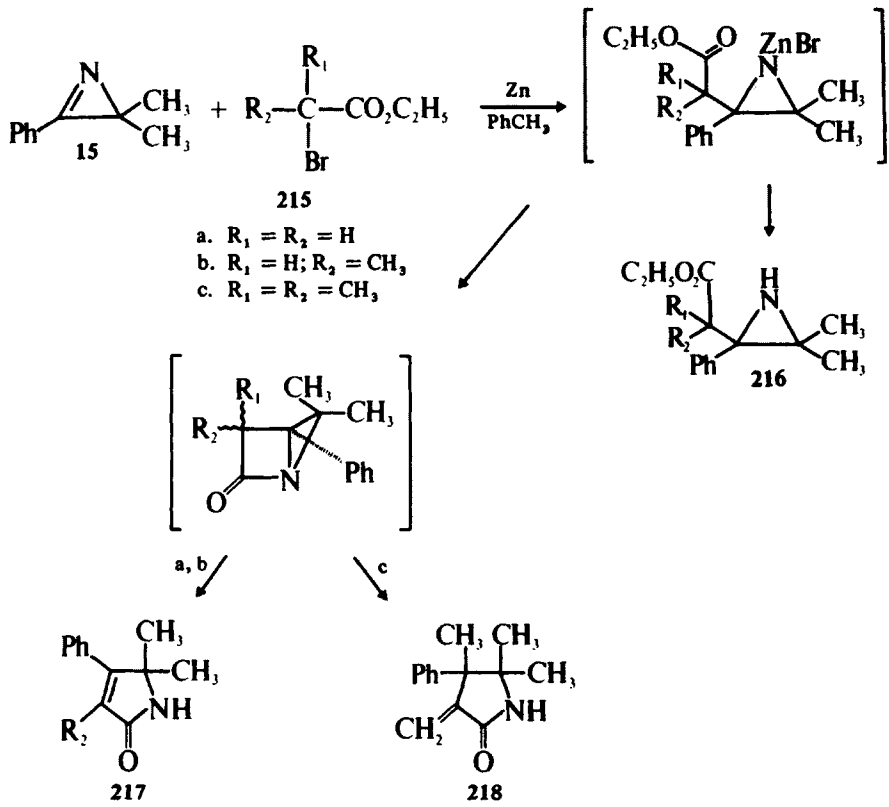
1-Azirines undergo the Reformatsky reaction.[140] For example, 3,3-dimethyl-2-phenyl-1-azirine (**15**) reacts with the α-bromoesters **215** to give **216** and **217** or **218** (Scheme 18).

B. *Reactions with Carbanions*

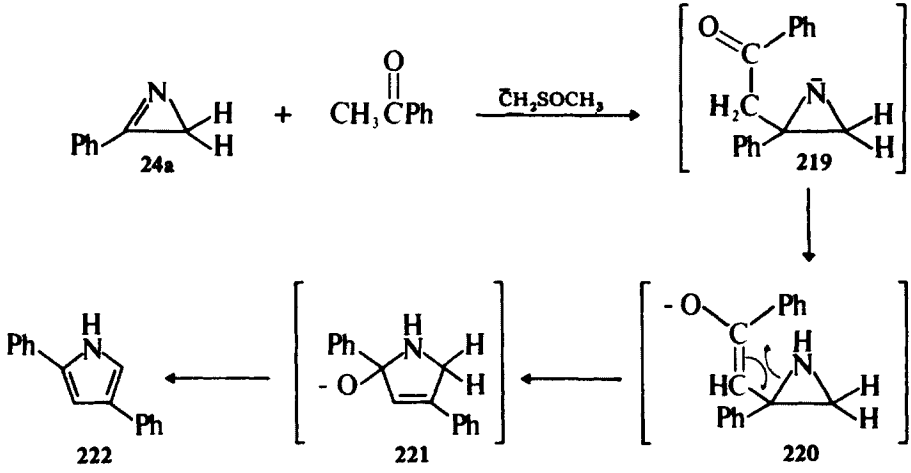
Sato, Kato, and Ohta[141,142] observed that 2-phenyl-1-azirine reacted with acetophenone in the presence of dimethylsulfinyl carbanion to give 2,4-diphenylpyrrole (**222**). A reasonable mechanism for this transformation involves initial nucleophilic attack by the enolate anion of acetophenone on the C=N bond to give **220** through **219**. Intermediate **220** undergoes 1,2-bond cleavage, cyclization, and hydroxyl group elimination to give **222** (Scheme 19).[53,141,142,158]

Benzyl cyanide reacts with azirine (**24a**) in the presence of dimethylsulfinyl carbanion to give 3,4-diphenyl-2-oxo-5-iminopyrroline (**224**), probably via intermediate **223**.

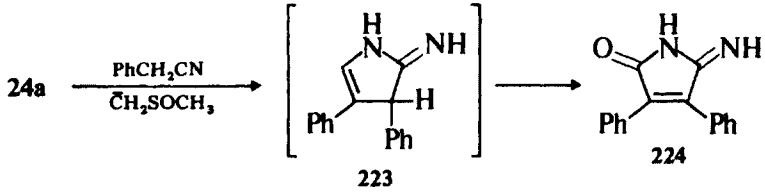
When no hydrogen is present at the 3-position of the azirine (i.e., with 3-disubstituted azirines), the reaction with carbanions produces different products.[143] For example, 3,3-dimethyl-2-phenyl-1-azirine (**15**) reacts with α-phenylethylacetate in dimethylsulfoxide and base to give **225**, **226**, and **227**.

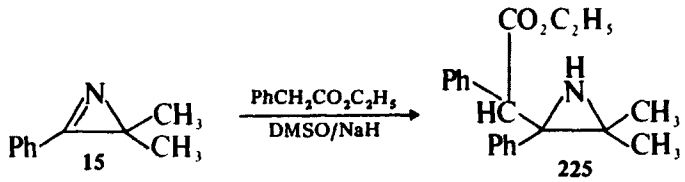


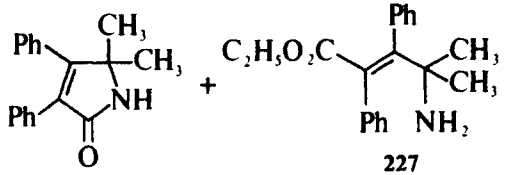
Scheme 18 Reformatsky reaction of 1-azirines. (Adapted from reference 140 with permission from Pergamon Press, Ltd.)



Scheme 19 Conversion of 1-azirines to pyrroles by reaction with carbanions. (Adapted from reference 53 with permission from Academic Press, Inc.)

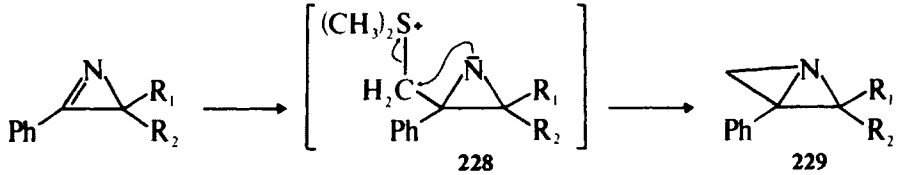






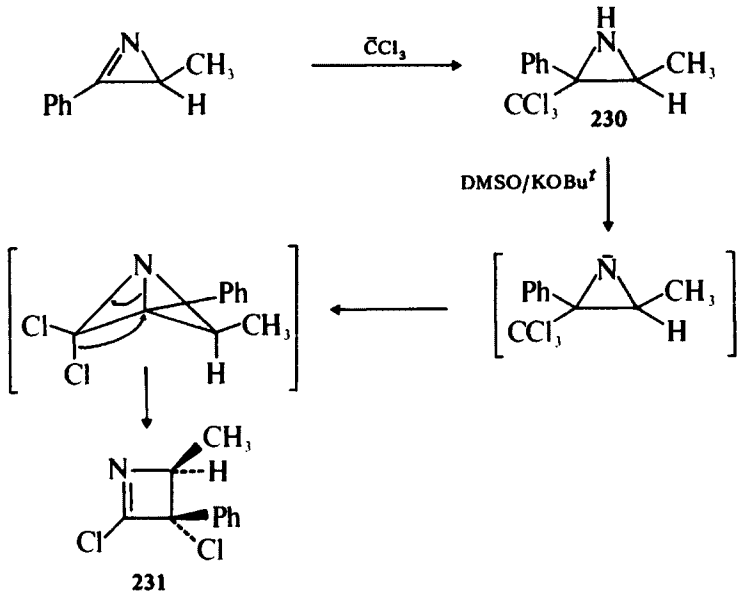
The reaction of activated methylene groups in β-dicarbonyl compounds with azirines can be conducted at room temperature and under nickel(II) catalysis to give high yields of pyrroles.[144]

Carbanions in the form of ylides also add to azirines. Hortmann and Robertson[145] reported the conversion of azirines (**3**, **15**, **24a**) with dimethylsulfonium methylide to 1-azabicyclobutanes (**229**) in good yields. The addition of the methylene group probably occurs by initial nucleophilic attack by the ylide to give the intermediate **228**, which cyclizes with expulsion of dimethyl sulfide.



3 $R_1 = H; R_2 = CH_3$
15 $R_1 = CH_3; R_2 = CH_3$
24a $R_1 = H; R_2 = H$

Addition of trichloromethide ion to azirine **3** was used by Hassner et al.[147] to generate, after work-up, the aziridine **230**. When this aziridine was treated with base, cyclization and rearrangement occurred and the azetine **231** was isolated (Scheme 20).[147]

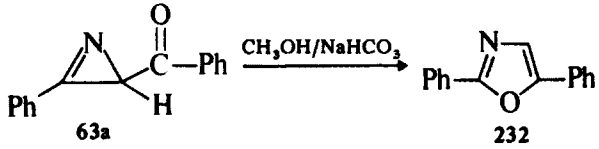


Scheme 20 Synthesis of 1-azetine from 1-azirine.

C. *Reactions with Alcohols*

1-Azirines react with alcohols in the presence of alkoxides to give alkoxyaziridines.[28,122] Further treatment with alcohol and alkoxide results in the formation of aminoketone acetals. Alkoxyaziridines are not isolated in general from the acid-catalyzed addition of methanol to azirines.[122]

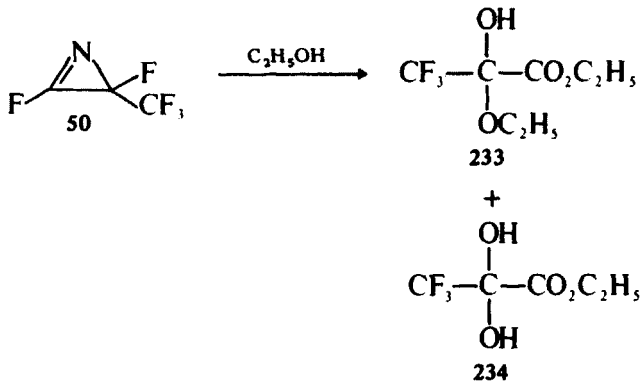
Oxazole **232** can be isolated in about 30% yield from the reaction of the azirine **63a** and weakly alkaline methanol.[13]



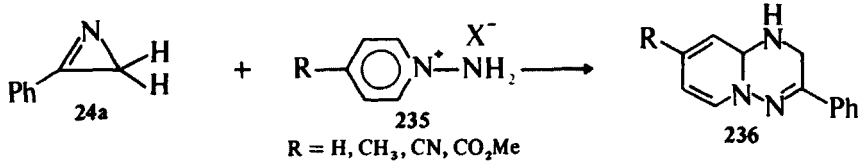
The perfluoroazirine **50** is converted by ethanolysis to ethyl-2-ethoxy-3,3,3-trifluoro-2-hydroxypropionate (**233**) and 3,3,3-trifluoro-2,2-dihydroxypropionate (**234**).[149]

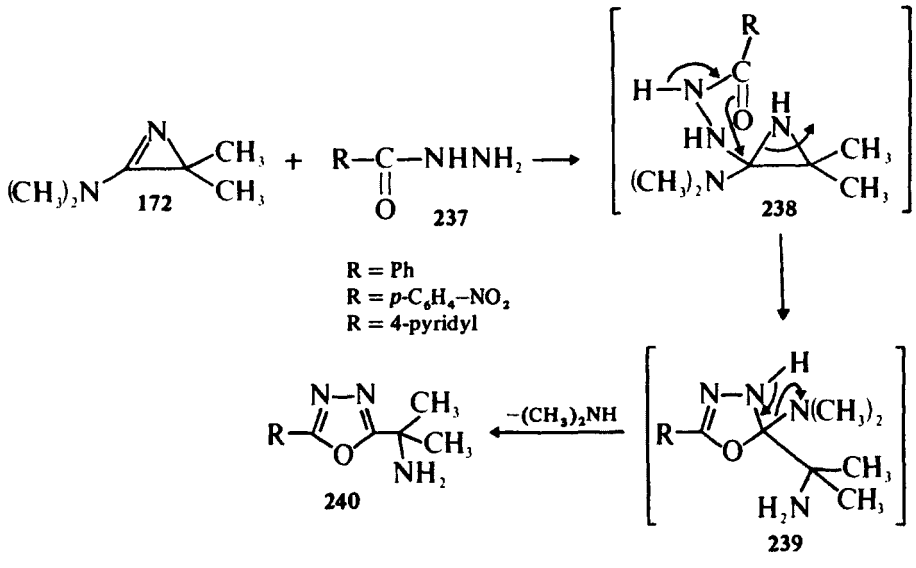
D. *Reactions with Amines and Derivatives*

The reaction of aniline with 2-phenyl-1-azirine (**24a**) was examined by Smolinsky and Feuer.[148] They isolated, after mild acid hydrolysis, benzanilide and smaller amounts of 2,5-diphenylpyrazine and 3,4-dianilino-1,2,5-triphenylpyrrole.

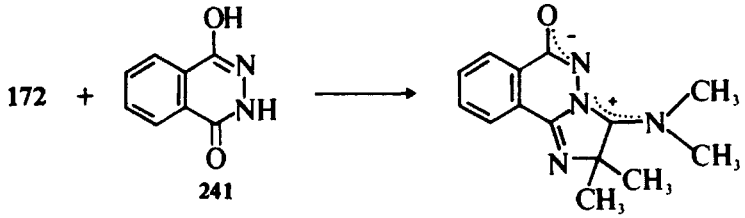


An interesting reaction of 1-azirines is with pyridine *N*-imines. It has been reported that the pyridine *N*-imine salts **235** react with 2-phenyl-1-azirine (**24a**) in the presence of base to give 1,9a-dihydro-2*H*-pyrido[1,2-b]as-triazines (**236**).[150–152] The mechanism of this transformation probably involves addition of the ylide from **235** to the C=N bond of the azirine followed by cyclization and rearrangement.



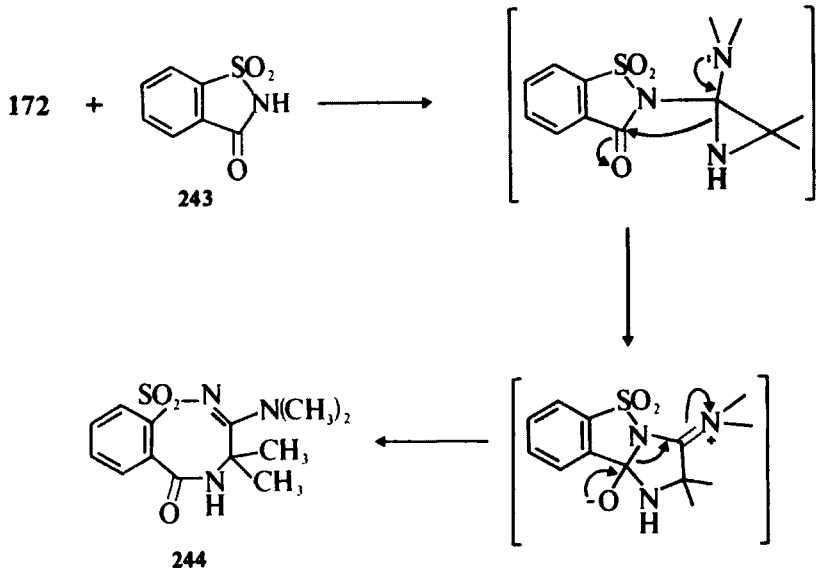


The amino azirine **172** also reacts with six-membered cyclic hydrazides (e.g., **241**) to give zwitterionic compounds (e.g., **242**).[154]



241 **242**

Another interesting reaction of the amino azirine **172** is with saccharin (**243**), where ring expansion to an eight-membered ring heterocycle **244** is observed.[155] The mechanism suggested for this transformation is shown in Scheme 21. Phthalimide undergoes a similar reaction with this amino azirine.[155]



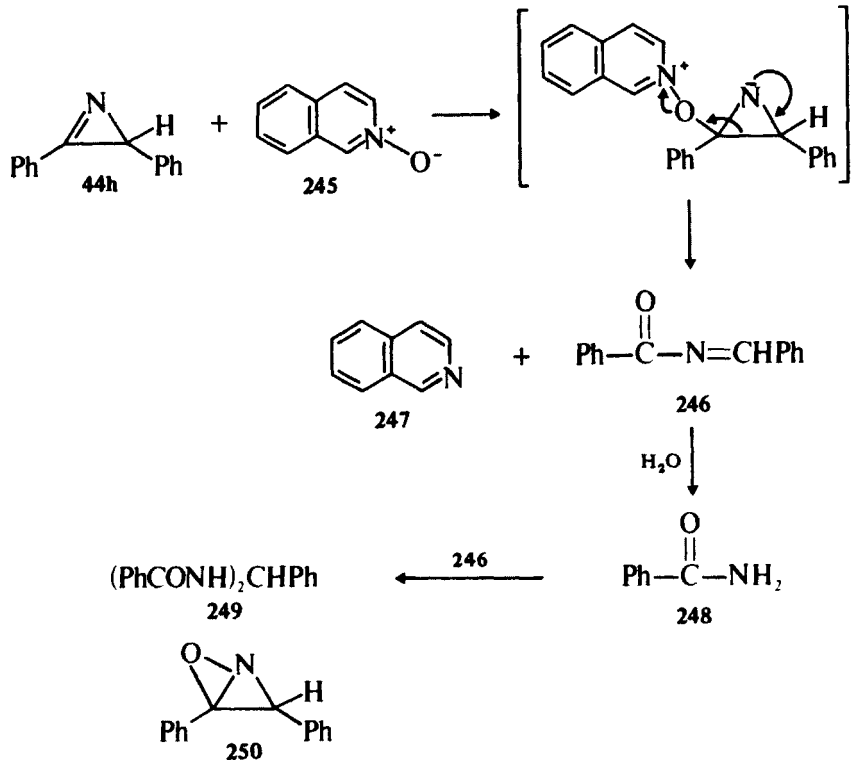
243 **244**

Scheme 21 Reaction of 2-amino-1-azirine with saccharin.

E. *Reactions with Nitrones*

Nitrones attack 1-azirines nucleophilically.[156] Thus, when 2,3-diphenyl-1-azirine (**44h**) was heated with isoquinoline *N*-oxide (**245**) in benzene at reflux temperatures, isoquinoline (**247**) and bis(benzamido)phenylmethane (**249**) were isolated in high yields. The reaction involves initial nucleophilic attack of the nitrone oxygen on the C=N bond of the azirine ring. This step bears some resemblance to the formation of alkoxyaziridines from the reaction of 1-azirines with alkoxide ion and

to the initial step of carbanion reaction with 1-azirines, both of which were mentioned previously. Bond reorganization results in formation of isoquinoline and a reactive imine intermediate (**246**). Partial hydrolysis of the imine **246** produces benzamide, which reacts further with **246** to produce **249** (Scheme 22). The bicyclic intermediate **250** may also be the precursor of **246** (cf. **228** → **229**).[4c] A similar reaction takes place when the 3-methyl analog of **44h** is treated with *m*-chloroperbenzoic acid to produce the methyl analog of **246**, presumably via an intermediate similar to **250**.[159]



Scheme 22 Reaction of 1-azirines with nitrone.

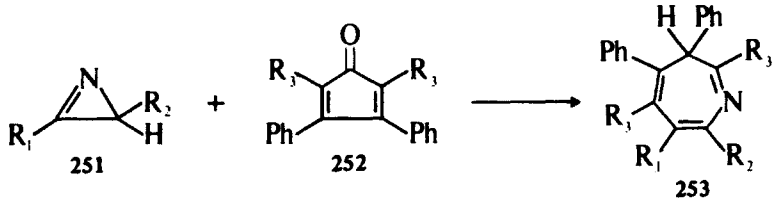
4. Thermal Cycloadditions

The 2π electrons of the carbon-nitrogen double bond of 1-azirines can participate in thermal symmetry-allowed [4 + 2] cycloadditions with cyclopentadienones, isobenzofurans, triazines, tetrazines, α-ketosulfenes, diazomethane, azomethine ylides, nitrile ylides, and nitrile oxides. Cycloadditions also occur with hetero-cumulenes such as ketenes, ketenimines, complex isocyanates, and carbon disulfide. 1-Azirines are reactive toward benzyne, and some 1-azirines form adducts with mesoionic compounds. It is possible also for the 2π electrons of 1-azirines to participate in "ene" reactions.

A. *Diels-Alder Reactions*

a. CYCLOPENTADIENONES

One of the first examples of cycloaddition of the 1-azirine ring system was reported independently by Nair[160] and by Hassner and Anderson.[161,162] They discovered that 3*H*-azepines (**253**) are formed directly when 1-azirines (**251**) and cyclopentadienones (**252**) are heated under reflux in benzene or toluene.



251 **252** **253**

a. R_1 = Ph; R_2 = H (**24a**)
b. R_1 = Ph; R_2 = CH_3 (**3**)
c. R_1 = Ph; R_2 = Ph (**44h**)
d. R_1 = Ph; R_2 = CH_2OH
e. R_1 = $PhCH_2$; R_2 = H (**44e**)

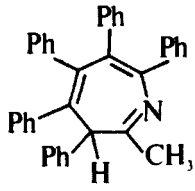
a. R_3 = Ph
b. R_3 = CH_3
c. R_3 = C_2H_5

a. R_1 = Ph; R_2 = H; R_3 = Ph
b. R_1 = Ph; R_2 = CH_3; R_3 = Ph
c. R_1 = Ph; R_2 = Ph; R_3 = Ph
d. R_1 = Ph; R_2 = CH_2OH; R_3 = Ph
e. R_1 = $PhCH_2$; R_2 = H; R_3 = Ph
f. R_1 = Ph; R_2 = H; R_3 = CH_3
g. R_1 = Ph; R_2 = CH_3; R_3 = CH_3
h. R_1 = Ph; R_2 = Ph; R_3 = CH_3
i. R_1 = $PhCH_2$; R_2 = H; R_3 = CH_3
j. R_1 = Ph; R_2 = H; R_3 = C_2H_5
k. R_1 = Ph; R_2 = CH_3; R_3 = C_2H_5

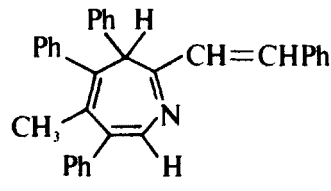
Hassner and Anderson showed that the cycloaddition occurs even with relatively unstable 1-azirines. These are generated *in situ* from the appropriate vinyl azide and reacted directly with the cyclopentadienones.[163]

Assignment of the 3*H*-azepine structure in the work of both Nair and Hassner and Anderson was facilitated by specific utilization of the cyclopentadienone, 2,5-dimethyl-3,4-diphenylcyclopentadienone (**252b**), and the azirine, 2-phenyl-1-azirine (**251a** = **24a**). The resulting azepine (**253f**) undergoes rapid deuterium exchange (D_2O) at the 2-methyl group, whereas deuterium exchange of methyl protons at other positions either were very slow or did not occur. Interestingly, a minor product identified as **254** and isolated in the reaction of azirine **251b** and cyclopentadienone **252a** showed as expected deuterium exchange at the methyl group. The azepine **253f** also underwent a smooth condensation with benzaldehyde in the presence of pyrrolidine to the styryl derivative **255**.[160] Further substantiation of structure came from nmr studies. In the azepine **253f**, the methyl resonance at δ 2.28 showed homoallylic coupling (J = 0.8 Hz) and in azepines **253e** and **253i** only singlets were observed for the benzylic protons.[164]

The mechanism of formation of the 3*H*-azepines merits discussion.[160,162,164] It is reasonable to assume that the first step of the cycloaddition is a symmetry-allowed [$\pi^4s + \pi^2s$] process to furnish an *endo*-adduct (**256**).[165] At least two pathways are possible from this adduct to the observed 3*H*-azepine product (Scheme 23). Mechanism **a** involves cheletropic fragmentation of the adduct **256** to furnish

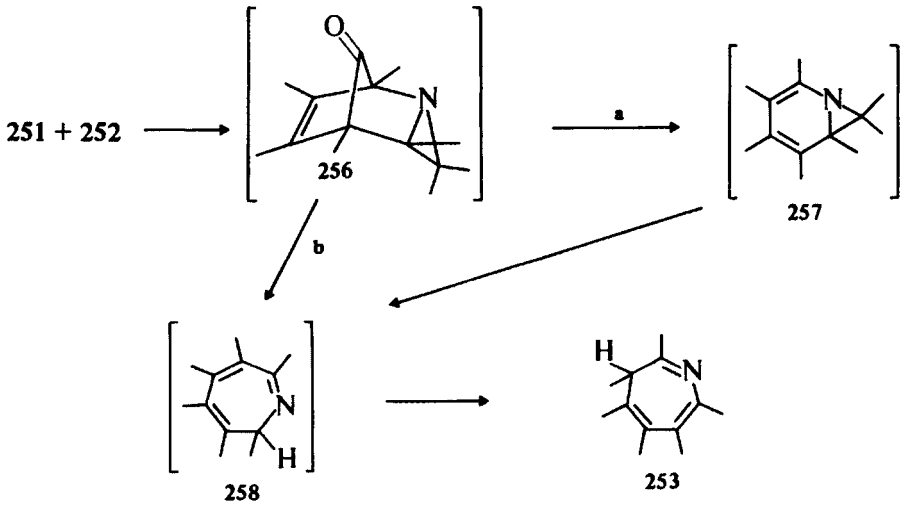


254



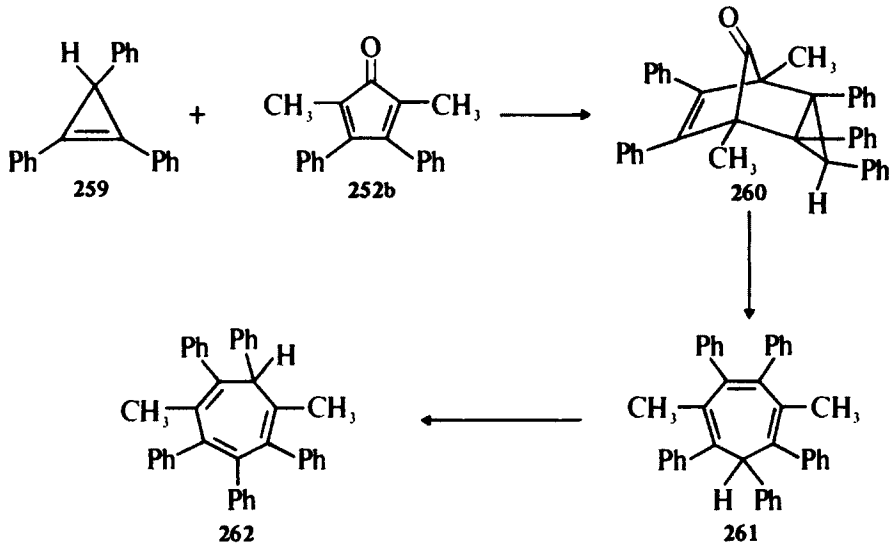
255

an azanorcaradiene (**257**). The symmetry-allowed disrotatory electrocyclic ring opening of the azanorcaradiene to its valence tautomer, the azacycloheptatriene (or 2*H*-azepine) **258**, is followed by a 1,5-suprafacial sigmatropic shift of the 2-hydrogen to give the thermodynamically more stable 3*H*-azepine **253**.[160] In mechanism **b**, loss of carbon monoxide from **256** occurs with participation of the aziridine carbon-nitrogen bond to afford **258**, which undergoes a 1,5-sigmatropic shift to give the 3*H*-azepine **253**.[162, 172]



Scheme 23 Mechanism of formation of 3*H*-azepines from 1-azirines and cyclopentadienones.

The main difference between these two mechanisms is that the elimination of carbon monoxide is concomitant with the disrotatory electrocyclic ring opening in mechanism **b**. Rate acceleration in the decarbonylation of *endo*-tricyclooctenones is known.[166, 167] Additional evidence for the concomitant participation of the three-membered ring in the decarbonylation of **256** came from two sets of experiments.[162] First, the cyclopropene adduct **260** from triphenylcyclopropene (**259** and **252b**) is converted on heating initially to the cycloheptatriene **261** and subsequently to the cycloheptatriene **262** (Scheme 24). Second, the cycloaddition of **259** and the 1,3-diphenylinden-2-one **263** gave the stable *exo*-adduct **264** and the cycloheptatriene **265** in a 1 : 4 ratio. It is likely that **265** was derived from the unstable *endo*-cycloadduct (Scheme 25).

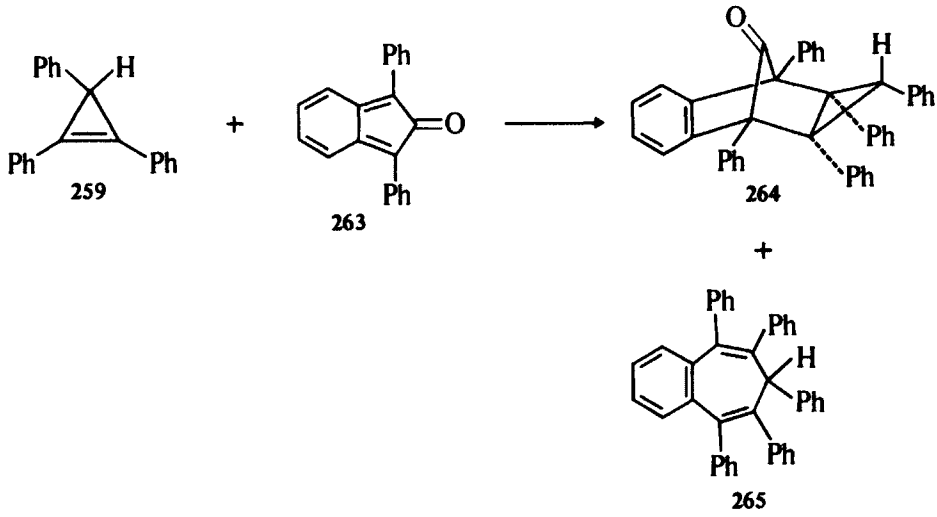


Scheme 24 Reaction of triphenylcyclopropene and 2,5-dimethyl-3,4-diphenylcyclopentadienone.

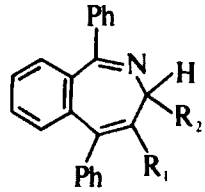
The 3*H*-azepine **254** isolated as a minor product in the reaction of azirine **251b** and cyclopentadienone **252a** must have arisen from the azepine **253b** by a further symmetry-allowed 1,5-sigmatropic shift. Hassner and Anderson[164] have provided evidence for this type of phenomenon.

The regiochemistry of these cycloadditions has been discussed.[164]

Hassner and Anderson[162] also reported apparently the first example of a stable 2*H*-azepine system **266** from the reaction of **263** and azirines **251a–251c**.



Scheme 25 Reaction of triphenylcyclopropene and 1,3-diphenylinden-2-one.

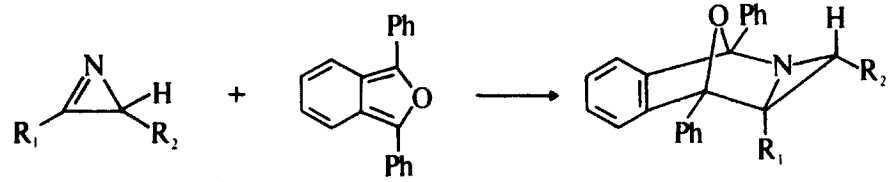


266

a. $R_1 = Ph; R_2 = H$
b. $R_1 = Ph; R_2 = CH_3$
c. $R_1 = Ph; R_2 = Ph$

b. ISOBENZOFURANS

1,3-Diphenylisobenzofuran (**268**) reacted readily with 3-methyl-2-phenyl-1-azirine (**3**) and with other azirines in refluxing toluene to give a cycloadduct (**269**), the primary product of a $[\pi^4 s + \pi^2 s]$ cycloaddition.[168,169] The adduct **269** was assigned the *exo* stereochemistry on the basis of its nmr data.



3 $R_1 = Ph; R_2 = CH_3$
267 $R_1 = H; R_2 = t\text{-Bu}$

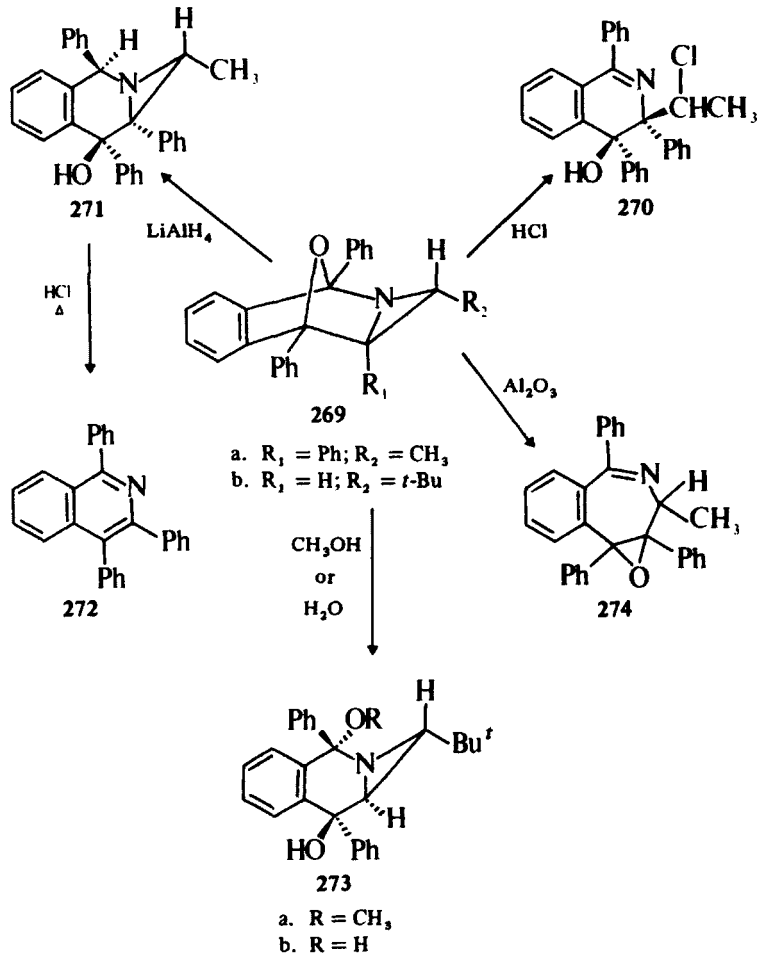
268

269
a. $R_1 = Ph; R_2 = CH_3$
b. $R_1 = H; R_2 = t\text{-Bu}$

The cycloadduct **269** undergoes a number of interesting reactions involving both the oxido bridge and the aziridine C–N bonds. Thus when **269a** was treated with anhydrous HCl in benzene, the hydrochloride salt of **270** was isolated. The reaction involves protonation of the aziridine nitrogen (easily monitored by ^{1}H nmr methods), followed by selective cleavage of one of the aziridine C–N bonds.[168] Reductive cleavage of adduct **269** with lithium aluminum hydride gave the benzoazanorcarane **271**. Attack of hydride is regiospecific and stereospecific.[169] Treatment of **271** with anhydrous HCl in refluxing benzene led to isolation of the triphenylisoquinoline **272**.[168] Other nucleophiles such as water and alcohols also cleave the oxido bridge at the benzylic position alpha to the aziridine nitrogen.[169] Thus, when **269b** was heated in methanol, compound **273a** was isolated. In the presence of silica gel and moist ether, **269b** was converted to **273b**.

An interesting isomerization reaction of the cycloadduct **269a** was reported by Hassner and Anderson.[169] When **269a** in benzene was stirred with Woelm neutral alumina, it was converted in good yields to the azepine **274**.

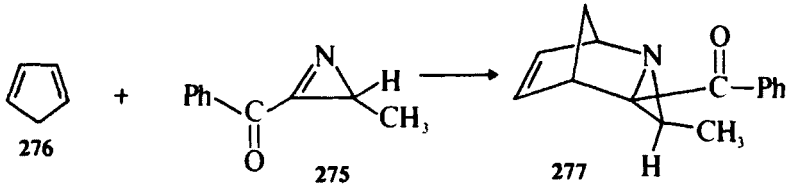
Although 1,3-diphenylisobenzofuran (**268**) reacts readily with 1-azirines monosubstituted at the 3-position, it is unreactive towards such 3-disubstituted azirines



as 3,3-dimethyl-2-phenyl-1-azirine (**15**).[169] Cyclopentadienones (**252**) are also unreactive toward this azirine.

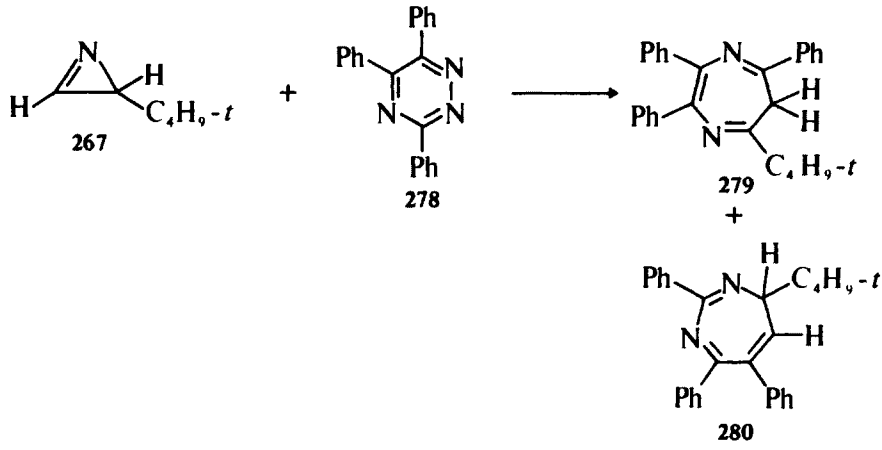
c. CYCLOPENTADIENE

3-Methyl-2-phenyl-1-azirine (**3**) and 2-phenyl-1-azirine (**24a**) are unreactive toward cyclopentadiene under a variety of conditions.[170] However, an electronically different azirine, 2-benzoyl-3-methyl-1-azirine (**275**), has been reported[171] to react with cyclopentadiene (**276**) to give the expected [4 + 2] cycloadduct **277**.



d. TRIAZINES

One example of the reaction of a triazine (**278**) with an azirine (**267**) has been reported.[172] The products, obtained only in low yields, are the diazepines **279** and **280**.

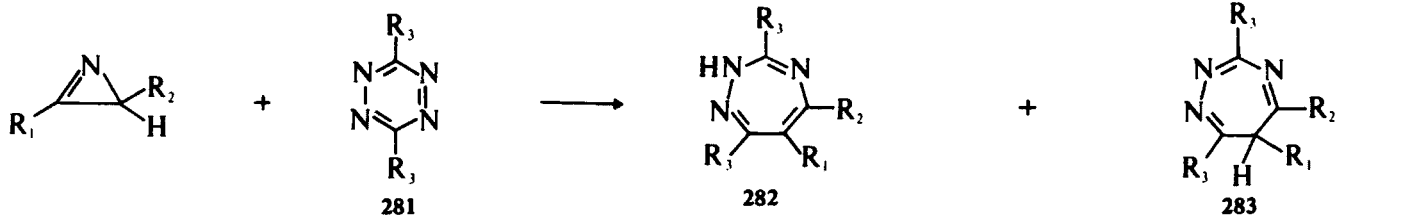


e. TETRAZINES

A more reactive system in which nitrogen is lost cheletropically after formation of the initial [4 + 2] cycloadduct is the tetrazine. Five research groups have reported on this cycloaddition.[173-177] A variety of heterocyclic products are produced depending on the structures of the azirine and tetrazine used and the reaction conditions. Azirines **24a**, **3**, and **267** react with the tetrazines **281a–281c** in toluene under reflux to give the triazepines **282** and **283**, the pyrimidines **284**, and the pyrazoles **285**. The tetrazine **281c** was the most reactive and gave the triazepine **282b** in 95% yield. Similarly, cycloaddition of **267** with **281c** gave the triazepine **282c** in 82% yield, whereas the reaction of **267** with **281a** afforded the pyrimidine **284c** in 92% yield.[174]

The triazepines **282** are the primary products of these reactions with tetrazines. Their formation occurs very likely from initial [4 + 2] cycloaddition followed by nitrogen elimination and electrocyclic ring opening, and then 1,5-sigmatropic shift of the intermediate 5*H*-1,2,4-triazepines. This pathway is analogous to that discussed for the cycloaddition with cyclopentadienones. A further symmetry-allowed 1,5-sigmatropic shift converts **282** to **283**. Both **282** and **283** may then undergo thermal fragmentations to give pyrimidines **284** (loss of :NH) or pyrazoles **285** (loss of R_2–C≡N).[172]

Anderson and Hassner had reported originally[174] the isolation of an unidentified product from these cycloadditions. This product appeared to be the major product from the azirine **3** and the tetrazines **281a** and **281b**. Elemental analysis showed 2 molecules of azirine and 1 molecule of tetrazine minus N_2 and CH_3CN. These products appear to result from the addition of the pyrazoles formed in the cyclo-



24a $R_1 = Ph; R_2 = H$
3 $R_1 = Ph; R_2 = CH_3$
267 $R_1 = H; R_2 = t\text{-Bu}$

281
a. $R_3 = Ph$
b. $R_3 = 4\text{-}CH_3\text{–}C_6H_4$
c. $R_3 =$ 

282
a. $R_1 = Ph; R_2 = H; R_3 = Ph$
b. $R_1 = Ph; R_2 = CH_3; R_3 =$ 
c. $R_1 = H; R_2 = t\text{-}C_4H_9; R_3 =$ 

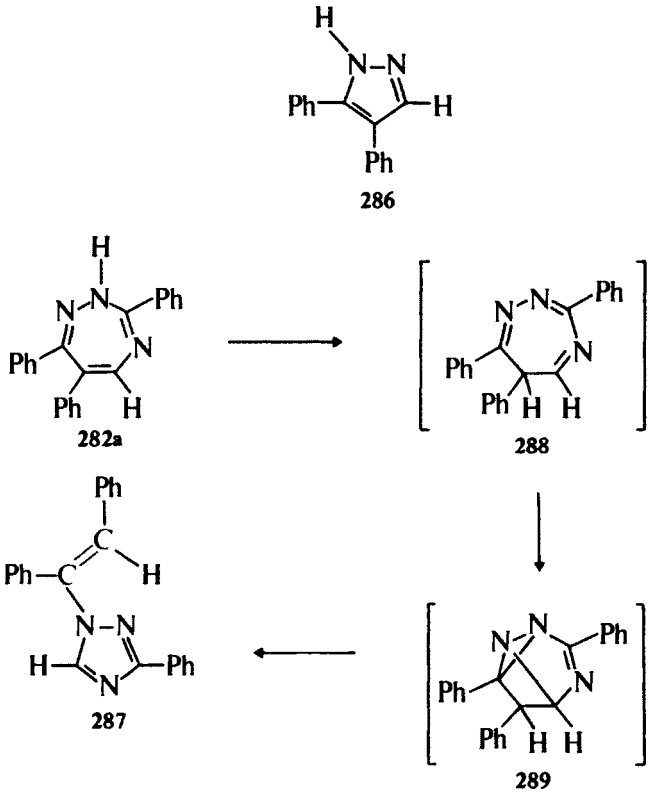
283
a. $R_1 = Ph; R_2 = CH_3; R_3 = Ph$
b. $R_1 = Ph; R_2 = CH_3; R_3 = 4\text{-}H_3C\text{–}C_6H_4$
c. $R_1 = H; R_2 = t\text{-}C_4H_9; R_3 =$ 

284
a. $R_1 = Ph; R_2 = H; R_3 = Ph$
b. $R_1 = Ph; R_2 = CH_3; R_3 = Ph$
c. $R_1 = H; R_2 = t\text{-}C_4H_9; R_3 = Ph$
d. $R_1 = Ph; R_2 = CH_3; R_3 = 4\text{-}H_3C\text{–}C_6H_4$

285
a. $R_1 = R_3 = Ph$
b. $R_1 = Ph; R_3 = 4\text{-}H_3C\text{–}C_6H_4$
c. $R_1 = Ph; R_3 =$ 

addition with the excess azirine present in the reaction mixture. This reaction is similar to the addition of amines to azirines, which has been mentioned already.

Nair reported on further details of the thermolysis of 2*H*-1,2,4-triazepines.[177] For example, when the triazepine **282a** was heated in refluxing mesitylene not only was **285a** formed (11%), but a second pyrazole **286** was also isolated in 29% yield. The pyrazoles are formed through elimination of HCN and PhCN from **282a** or an isomeric structure. In direct competition with nitrile extrusion in the thermolysis of **282a** is a remarkable skeletal rearrangement that gives a third product (**287**) in 28% yield. The formation of the triazolylstilbene **287** from **282a** requires an initial symmetry-allowed 1,5-sigmatropic shift of hydrogen to give **288**. Intermediate **288** can destroy itself by nitrile elimination to furnish **285a** and **286**, or it can undergo an intramolecular $[\pi^4a + \pi^2a]$ cycloaddition to give **289**, which subsequently rearranges in a reverse Diels-Alder fashion to **287**.

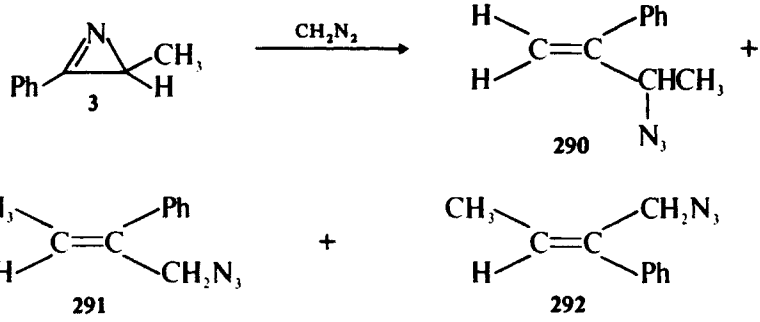


B. *1,3-Dipolar Cycloadditions*

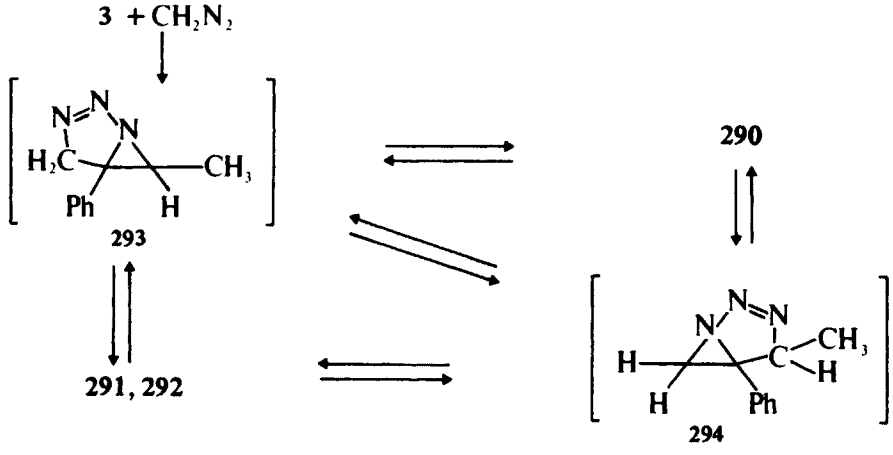
a. DIAZOMETHANE AND DERIVATIVES

The interaction of diazomethane with 1-azirines was the first example of 1,3-dipolar cycloaddition with this ring system. This reaction was reported by

Logothetis[178] and subsequently studied in more detail by Nair.[30,179] 3-Methyl-2-phenyl-1-azirine (**3**) reacts with diazomethane in ether at room temperature to give a 1.6:1:1 mixture of the allylic azides **290**, **291**, and **292**, respectively. Structural evidence for the allylic azides came from elemental analysis, ir spectra, and particularly the nmr data.[30]

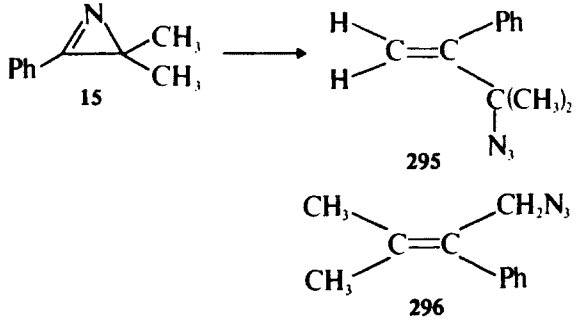


The mechanism of formation of the allylic azides (Scheme 26) is probably the result of at least a two-step process.[30,179] 1,3-Dipolar addition of diazomethane across the C=N bond of the azirine produces the triazoline adduct **293**. The adduct **293** can exist in equilibrium with its valence tautomer **294**, and the allylic azides can be produced from these triazolines by ring cleavage. Allylic azides are said to undergo isomerization very rapidly, and triazoline intermediates were proposed by Gagneux, Winstein, and Young[180] for the rapid equilibration of pentenyl and butenyl azides. Rapid equilibration of the allylic azides **290**, **291**, and **292** would explain both the appearance of the mixture as a single spot on thin layer chromatographic plates with several different solvent systems and our inability to separate these compounds.



Scheme 26 Mechanism of formation of allylic azides from 1-azirines and diazomethane.

3,3-Dimethyl-2-phenyl-1-azirine (**15**) also reacts with diazomethane to give the allylic azides **295** and **296**, respectively, in a ratio of 1 : 3.[30] This is in contrast to the lack of reactivity of this azirine toward cyclopentadienones and isobenzofurans.



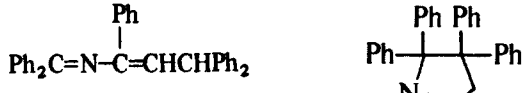
15 **295** **296**

Bowie, Nussey, and Ward[181] reported that treatment of 2,3-diphenyl-1-azirine (**44h**) with phenyldiazomethane gave as the major product (70%) the vinyl azide **298**. The precursor to the vinyl azide **298** may very likely be the allyl azide **297**, formed as suggested in Scheme 26. The rearrangement of **297** to **298** represents a 1,3-sigmatropic proton shift. Although this is a symmetry-forbidden shift, the prolonged heating and/or the copper powder used in this reaction may have been responsible for conversion of the allyl azide **297** to the thermodynamically more stable vinyl azide **298** and analogous rearrangements have been reported.[181b]

297 **298**

The behavior of diphenyldiazomethane toward 1-azirines follows a different pathway.[182] Diphenyldiazomethane acts as a source of diphenylcarbene in these reactions. Thus with 2-phenyl-1-azirine (**24a**), the primary product is 1,1,3-triphenyl-2-azabuta-1,3-diene (**299**). Electrophilic attack by diphenylcarbene on **299** followed by rearrangement produces three 1 : 2 adducts, **300**, **301**, and **302**.

299 **300**

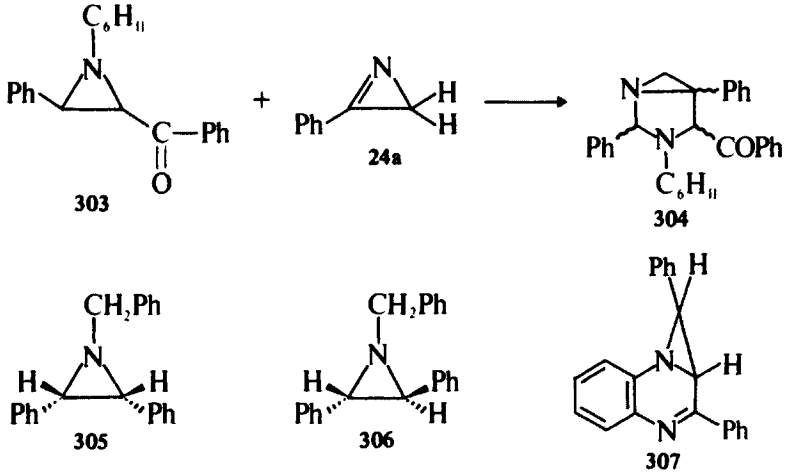


301

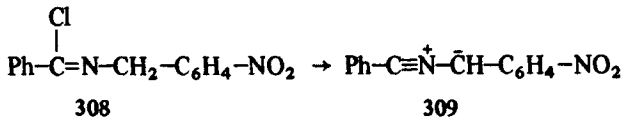
302

b. AZOMETHINE AND NITRILE YLIDES

Aziridines undergo thermal ring opening in a conrotatory manner to generate azomethine ylides.[183] These azomethine ylides are 4π components and can participate in [4 + 2] cycloadditions with 1-azirines as the 2π component. For example, the aziridine **303** reacts with 2-phenyl-1-azirine (**24a**) to give **304** as a stereochemical mixture. The *cis*-aziridine **305** also gives a mixture of two adducts. However, the *trans*-aziridine **306** and the fused aziridine **307** exhibit stereospecificity in their cycloadditions with **24a**.[184]

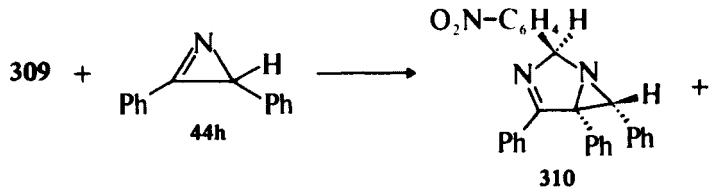


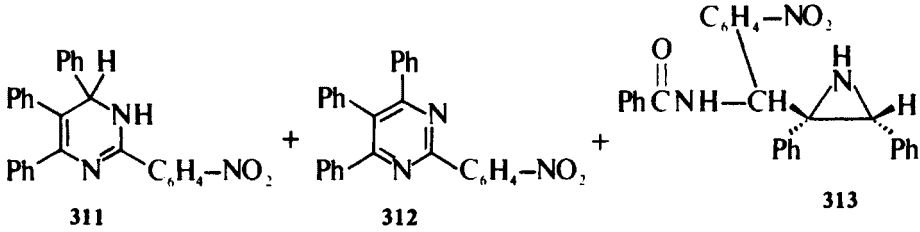
Benzonitrile ylide **309** is generated when **308** in benzene is treated with triethylamine. The nitrile ylide **309** reacts with 2,3-diphenyl-1-azirine (**44h**) to give 2-(*p*-nitrophenyl)-4,5,6-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**310**). Under the basic conditions of the reaction mixture **310** is converted to the dihydropyrimidine **311**, which is subsequently oxidized to the pyrimidine **312**. Another product **313** was also isolated. Yields were low.[185]



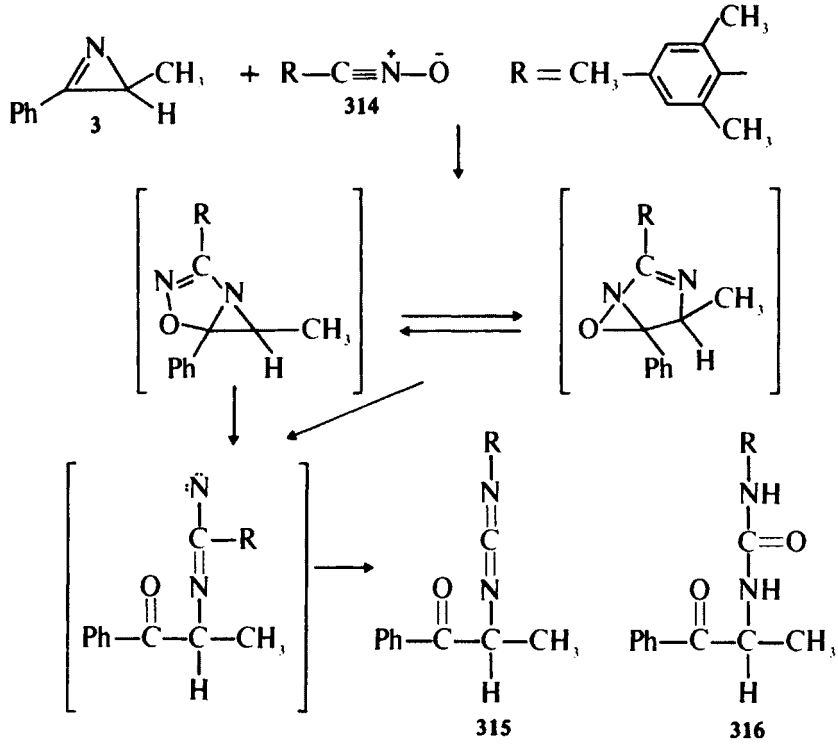
c. NITRILE OXIDES

The 4π-electron system of nitrile oxides can participate in 1,3-dipolar cycloaddition with 1-azirines. Nair[186] discovered that aromatic nitrile oxides react exothermically with 1-azirines to furnish carbodiimides in isolated yields exceeding 80%. Thus, when 3-methyl-2-phenyl-1-azirine (**3**) was treated with 2,4,6-trimethylbenzonitrile oxide (**314**) in anhydrous ether at 0° for 15 min, the carbodiimide **315** was isolated in almost quantitative yield. The carbodiimide was found to be highly hygroscopic, and hydrolysis to the urea **316** proceeded extremely rapidly and quantitatively.





A possible mechanism for the formation of the carbodiimide (Scheme 27) assumes the initial formation of a cycloadduct from a 1,3-dipolar addition between the nitrile oxide and the azirine. Ring cleavage of the bicyclic adduct or its valence tautomer is followed by a 1,2-migration of the R group of the nitrile oxide in a Beckmann-type rearrangement to give the carbodiimide.

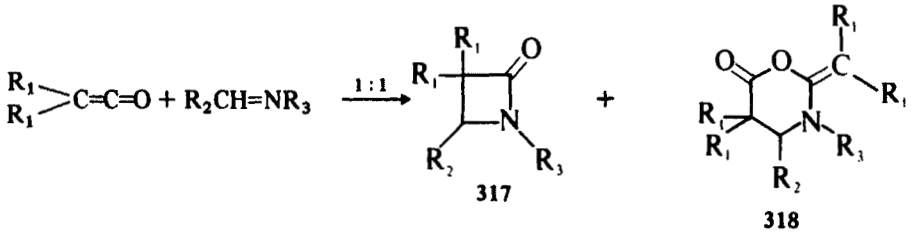


Scheme 27 Mechanism of formation of carbodiimides from 1-azirines and nitrile oxides.

C. *Cycloadditions with Heterocumulenes*

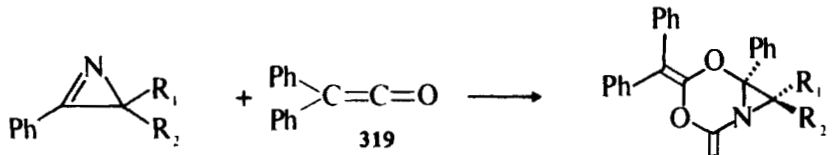
a. KETENES AND KETENIMINES

Ketenes generally react with a variety of imines to form as major products 1 : 1 adducts that are β-lactams (**317**), as well as 1 : 2 adducts possessing the dihydro-oxazinone structure **318**.[187]



317 **318**

Hassner and his co-workers reported that the 1-azirines (**3**, **15**, **24a**) react with diphenylketene (**319**) to give the 1 : 2 adducts **320**.[188-190] Analogous cycloadditions were observed with *t*-butylcyanoketene. However, 2,3-diphenyl-1-azirine (**44h**) reacted with diphenylketene to give a 1 : 1 adduct (**321**).

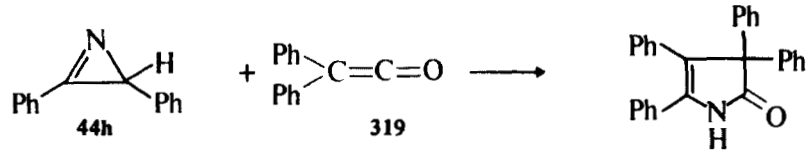


24a $R_1 = H; R_2 = H$
3 $R_1 = H; R_2 = CH_3$
15 $R_1 = CH_3; R_2 = CH_3$

319

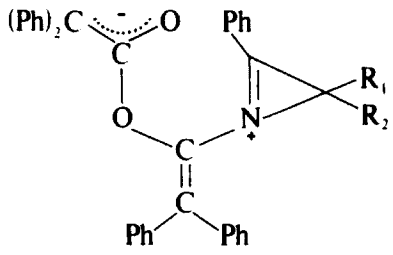
320

a. $R_1 = H; R_2 = H$
b. $R_1 = H; R_2 = CH_3$ *cis* and *trans*
c. $R_1 = CH_3; R_2 = CH_3$

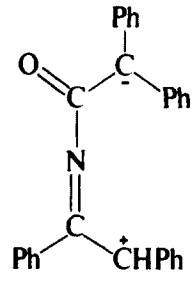


44h **319** **321**

The 1 : 2 adducts (bicyclic aziridines) **320** are different in structure from the 1 : 2 adducts **318** formed from simple imines and ketenes. It was suggested[188,190] that the formation of **320** proceeds via the intermediacy of a reactive azirinium ion **322**. The 1 : 1 adduct observed in the case of 2,3-diphenyl-1-azirine (**44h**) was interpreted as resulting from the intermediate **323**, where the presence of the 3-phenyl substituent in the azirine stabilizes the cationic site resulting from initial monoaddition to ketene.



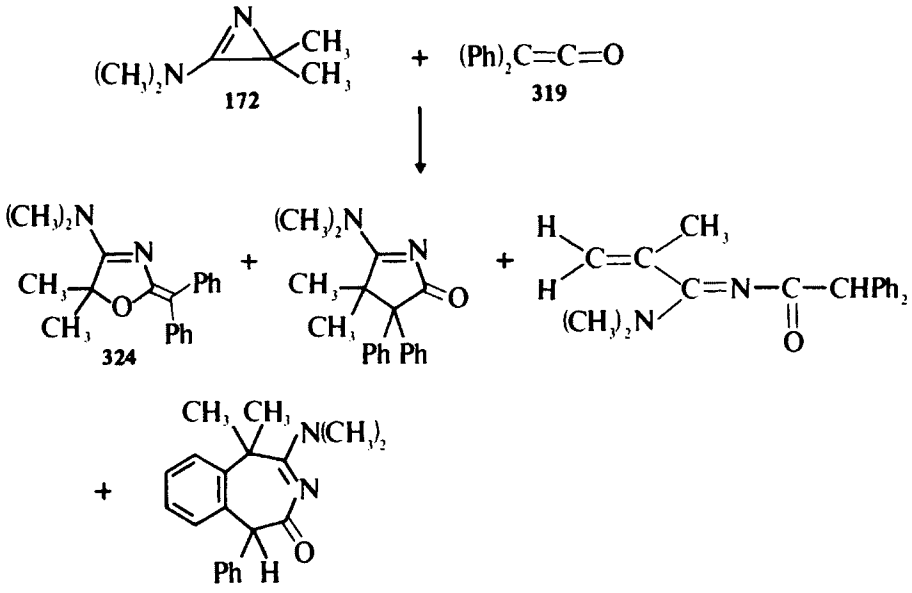
322



323

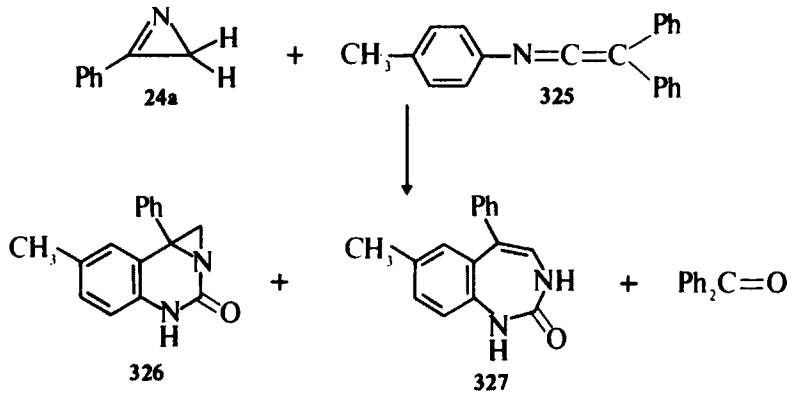
The reactions of these 1-azirines with ketenes represent nonconcerted additions and are formally different from the additions to 4π systems of dienes and 1,3-dipole compounds.

2-Amino-1-azirines behave somewhat differently from 2-aryl- and 2-alkyl-1-azirines, as mentioned previously. The aminoazirine **172** reacts with diphenylketene (**319**) in a nonconcerted manner to give the 3-oxazoline **324** as the major product.[191,196] Other products (generally minor) also have been reported from this and related reactions recently (Scheme 28).[196b]



Scheme 28 Reaction of aminoazirine and diphenylketene.

Ketenimine (**325**) reacts with 2-phenyl-1-azirine (**24a**) in refluxing benzene to give a mixture of the bicyclic aziridine **326** (15%), the benzodiazepinone **327** (15%), and benzophenone.[192] The benzodiazepinone **327** is a secondary product of this reaction and is produced from the thermal rearrangement of **326** (Scheme 29).



Scheme 29 Reaction of 1-azirine and ketenimine.

b. ISOCYANATES

Heterocumulenes containing a carbonyl or related unsaturation adjacent to the cumulative bonds usually possess high reactivity, and Nair and Kim[193,194] first reported on the interesting reactions of 1-azirines with such isocyanates.

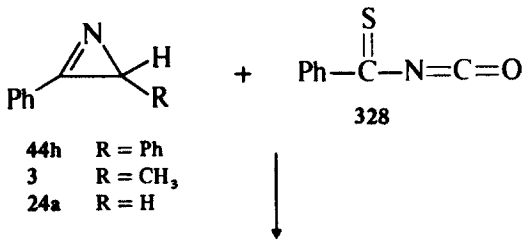
Thiobenzoyl isocyanate (**328**) can be generated from 2-phenylthiazoline-4,5-dione by thermal extrusion of carbon monoxide. Isocyanate **328**, prepared *in situ*, adds stereospecifically and regiospecifically at room temperature to give high yields of [4 + 2] cycloadducts, the bicyclic aziridines **329**.[172,193,194] The aziridines **329** undergo clean acid-catalyzed hydrolysis to the ureas **330**, providing excellent evidence for the regiospecificity of these cycloadditions.

The cycloadducts **329** exhibit other interesting behavior. For example, when **329a** was subjected to thermolysis in refluxing benzene, ring expansion to the novel thiadiazepinone **331** was observed. Prolonged thermolysis of **329a** at higher temperatures resulted in the removal of elemental sulfur and the formation of the pyrimidone **332**. The thiadiazepinone **331** was shown to be the intermediate in the thermal conversion of **329a** to **332**. A reasonable mechanism for the sulfur extrusion reaction is shown in Scheme 30. The initial formation of **331** is followed by a 1,5-sigmatropic shift and electrocyclization to a thiirane. Elimination of elemental sulfur is followed by tautomerization of the pyrimidine to the preferred pyrimidone structure **332**.[194]

The behavior of benzoyl isocyanate (**333**) toward 1-azirines paralleled those observed with thiobenzoyl isocyanate, and [4 + 2] cycloadducts **334** were isolated.[194] Hydrolysis to the ureas **335** occurred under acid-catalyzed conditions. Thermolysis to **336** was not observed. However, at 70°, a clean retro[4 + 2] pericyclic reaction occurred.

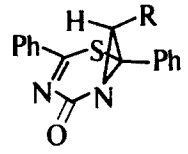
Benzoyl isothiocyanate (**337**) also reacts with 1-azirines. The cycloaddition apparently occurs in a [2 + 2] fashion across the C=S bond to give thiazoles **338** as final products.[194]

The marked difference in behavior between the exclusive [4 + 2] cycloaddition observed for benzoyl isocyanate (**333**) and thiobenzoyl isocyanate (**328**) and the



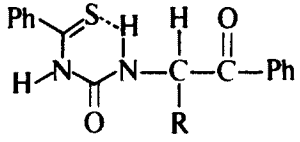
44h R = Ph
3 R = CH_3
24a R = H

328

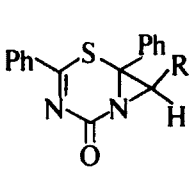


329

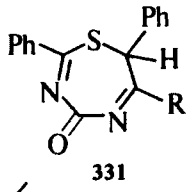
a. R = Ph
b. R = CH_3
c. R = H



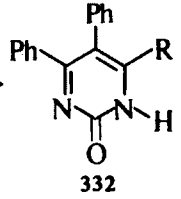
330



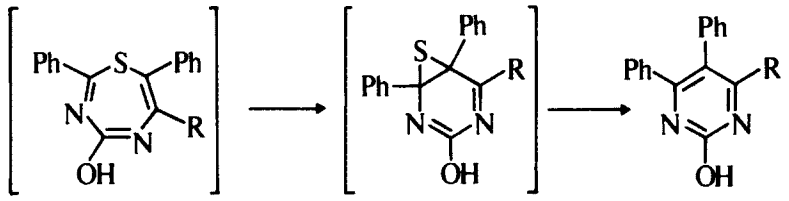
329a
R = Ph



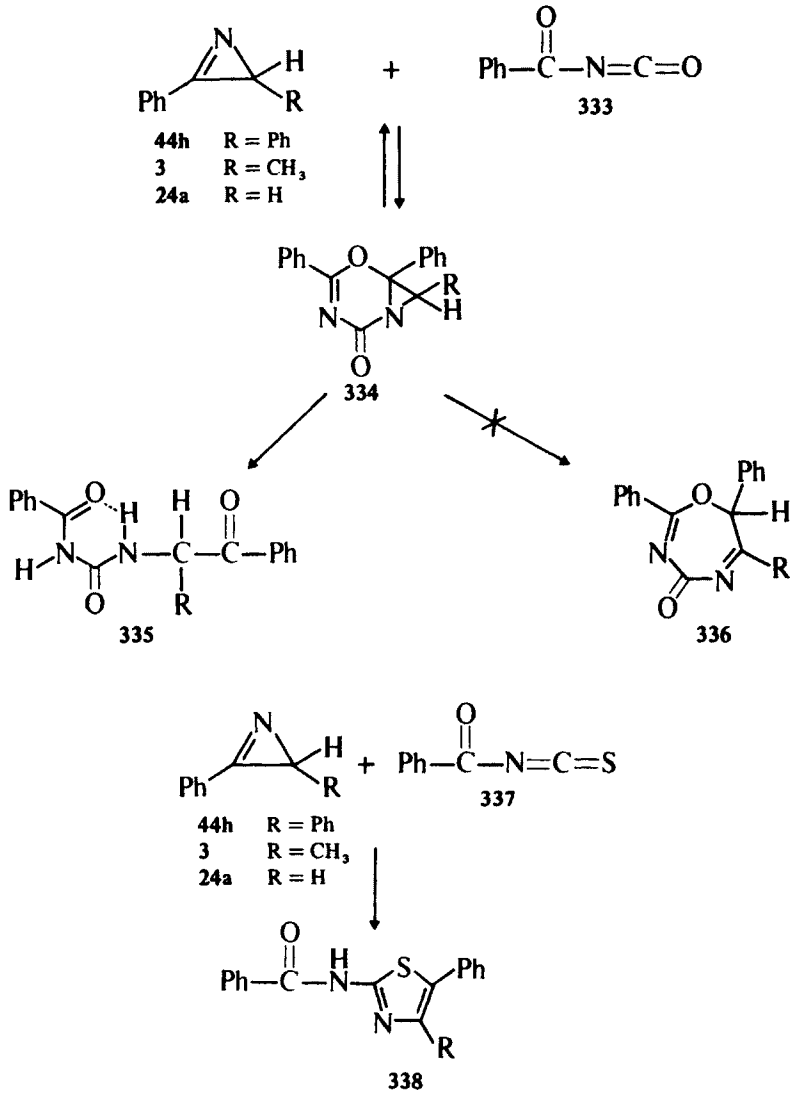
331



332



Scheme 30 Thermal rearrangements of bicyclic aziridines.

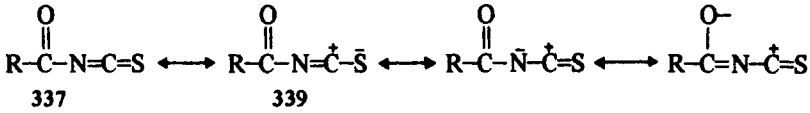


apparent [2 + 2] cycloaddition in a regiospecific manner to the C=S bond of **337** requires explanation. Orbital symmetry analysis[165] reveals a possible concerted $[\pi^2 s + \pi^2 a]$ pathway for addition involving the C=S bond. A striking clue to the nature of the transition state came from solvent polarity studies with **24a** at 75° (Table 5), which showed a dramatic increase in product yield with increase in the dielectric constant of the solvent.[194] This solvent dependency was interpreted as reflecting the presence of a polar transition state in the pathway to the formation of the initial cycloadduct. The polarization of **337** (Scheme 31) is similar to **333** except for the greater ability of sulfur to stabilize a negative charge[195] (see **339**). A dipolar transition state such as **340** could conceivably account not only for the

TABLE 5. REACTION OF 2-PHENYL-1-AZIRINE (24a) with BENZOYL ISOTHIOCYANATE (337) AT 75°

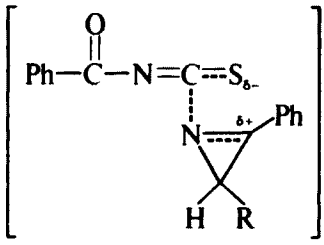
Solvent	Dielectric constant	Reaction time (hr)	Yield of 338 (R = H) (%)
Benzene	2.3	2	13.4 ± 1.5
Ethyl acetate	6.0	2	19.3 ± 1.5
Nitrobenzene	34.8	2	42.7 ± 1.5

solvent dependency but also for the marked difference in the behaviors of **328**, **333**, and **337**. Whether such a transition state would transform into a relatively stable dipolar intermediate to favor a two-step combination is not known.



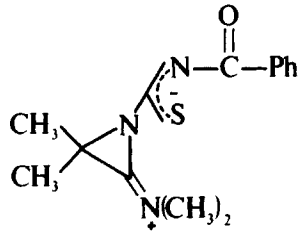
337 339

Scheme 31 Contributing resonance structures for benzoyl isothiocyanate. R = Ph.



340

Interestingly, 2-amino-1-azirine (**172**) reacts with benzoyl isothiocyanate to give the 1,4-dipolar compound **341**.[196]

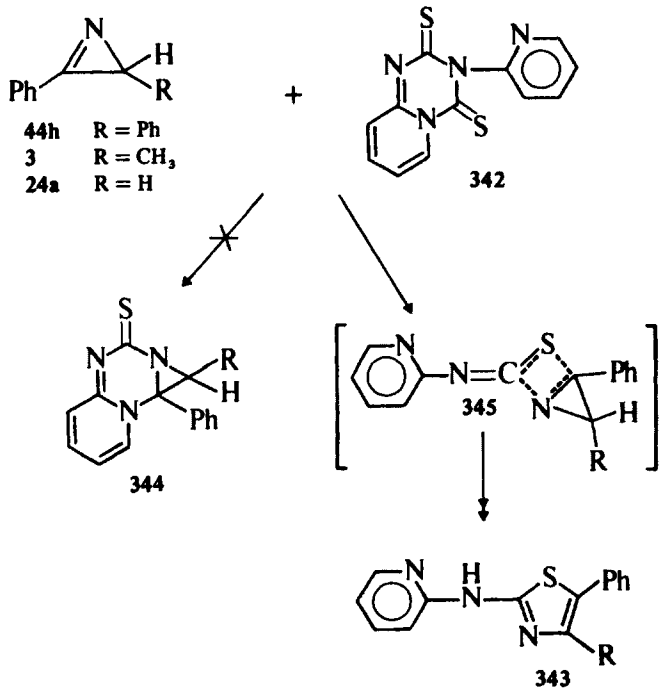


341

Although isothiocyanates such as methyl isothiocyanate, phenyl isothiocyanate, and *p*-nitrophenyl isothiocyanate react with 2-amino-1-azirines,[196,199] Kim and Nair[197] have found them to be normally unreactive toward 2-aryl-1-azirines.

Nair and Kim[198] also examined the reactivity of 2-pyridyl isothiocyanate toward 2-aryl-1-azirines. 2-Pyridyl isothiocyanate is produced by the reaction

of 2-aminopyridine and carbon disulfide in the presence of triethylamine. At room temperature, this compound exists as a dimer (**342**). When the azirines (**3**, **24a**, and **44h**) were heated in toluene under reflux with the **342**, thiazoles **343**, the result of regiospecific addition of the C=S bond of the monomer to the C=N bond of the azirines (see **345**), were isolated. Thiazoles arising from initial nucleophilic attack and 1,3-bond cleavage were not formed. Neither the product **344** nor its ring-expanded forms, the result of [4 + 2] cycloaddition, were isolated (Scheme 32).

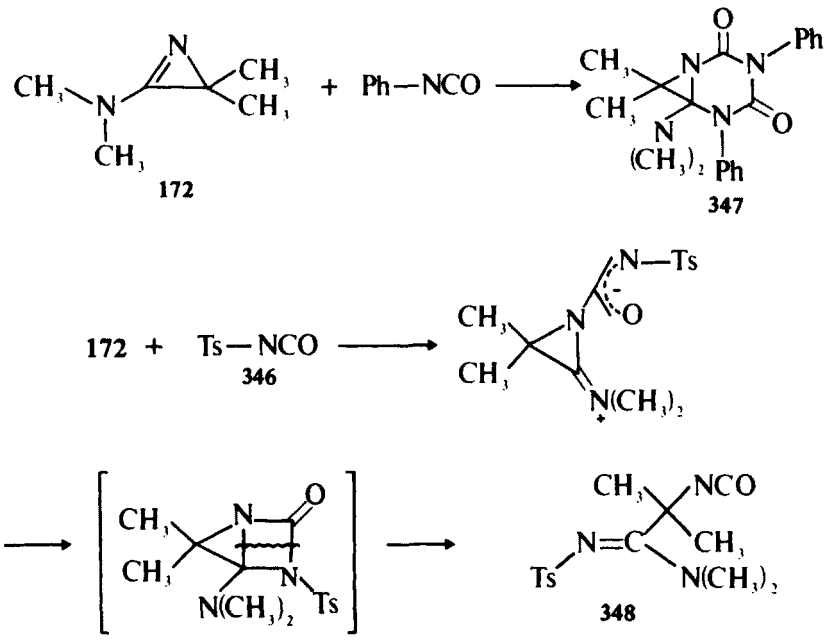


Scheme 32 Reaction of 2-pyridyl isothiocyanate with 1-azirines.

Simple aryl isocyanates such as phenyl isocyanate, *p*-methylphenyl isocyanate, *p*-chlorophenyl isocyanate, and *p*-nitrophenyl isocyanate are unreactive toward 2-aryl-1-azirines.[197] However, phenyl isocyanate has been reported to react at room temperature with the 2-amino-1-azirine **172** to give the 2:1 adduct **347**.[196] Adducts in a 3:1 ratio also have been reported.[191] Azirine **172** also reacts with *p*-toluenesulfonyl isocyanate (**346**) at room temperature to give the ring-opened 1:1 adduct **348** (Scheme 33).[196] The isocyanate **346** also has been found to react with 2-aryl-1-azirines.[172]

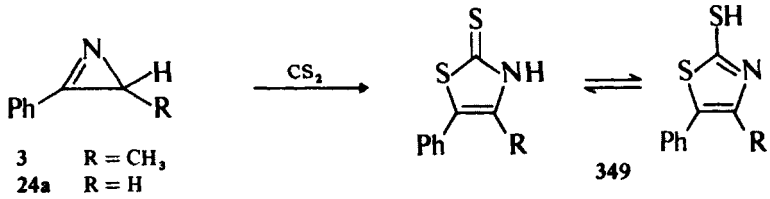
c. CARBON DISULFIDE

Carbon disulfide is a simple heterocumulene, and most of its reactions proceed from initial nucleophilic attack on the central carbon.[200] The few cycloadditions known are 1,3-dipolar in nature, with carbon disulfide as the dipolarophile.[201,202]



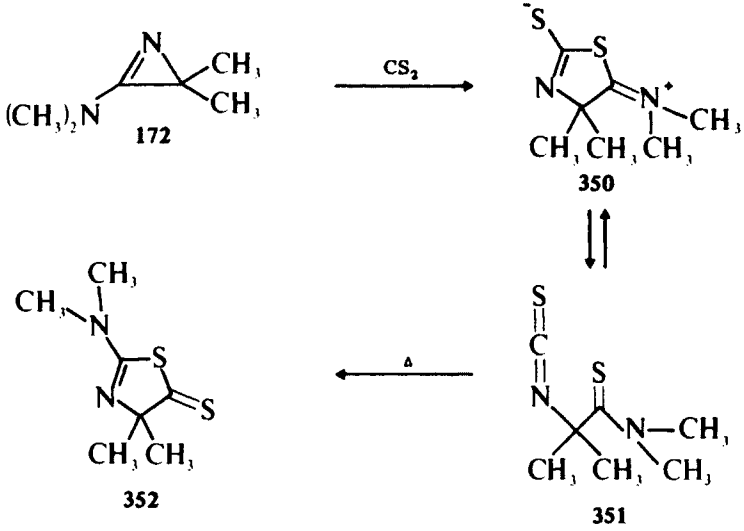
Scheme 33 Reactions of 2-amino-1-azirines with isocyanates.

Nair and Kim[203] discovered that 2-phenyl-1-azirine (**24a**) and 3-methyl-2-phenyl-1-azirine (**3**) react with carbon disulfide in a sealed tube at 100° to give the thiazoles **349**. These products are the result of regiospecific cycloadditions of carbon disulfide to the π bond of the 1-azirines.



In general, cycloaddition of 2-phenyl-1-azirine with heterocumulenes containing the C=S bond proceeds through a dipolar transition state where the ability of sulfur to stabilize the negative charge results in a lower energy electronic pathway to the cycloadducts.

2-Amino-1-azirines react differently with carbon disulfide. For example, 2-dimethylamino-3,3-dimethyl-1-azirine (**172**) reacts smoothly with carbon disulfide to give crystals that have the dipolar structure **350**.[204,205] In solution, the isomeric form **351** is the predominant structure. Thermolysis of the adduct leads to **352** in high yield.



172 350 351 352

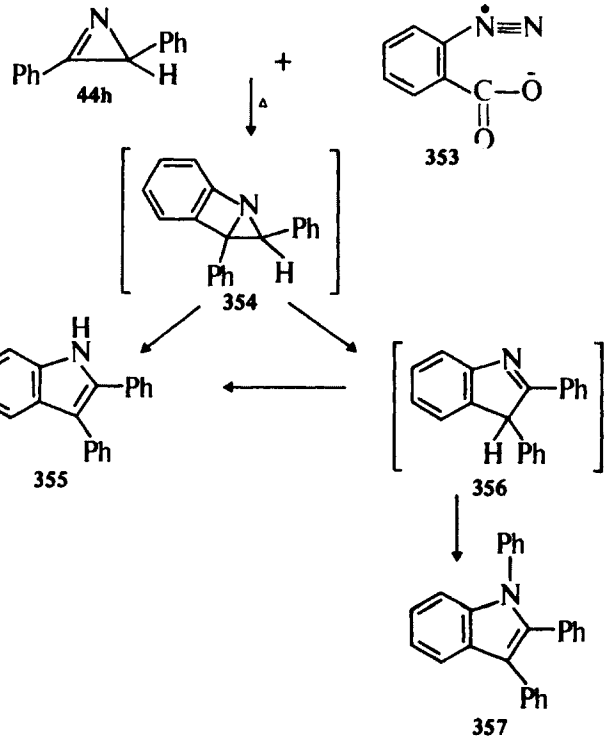
D. *Miscellaneous Cycloadditions*

a. BENZYNE

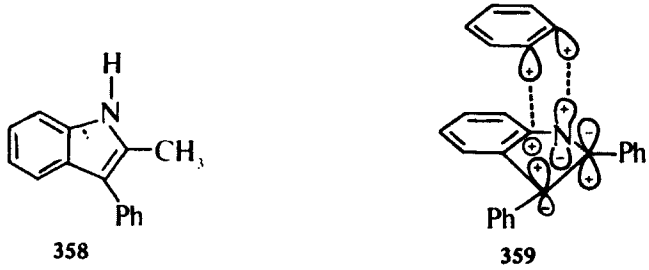
Nair and Kim[206] reported that 2,3-diphenyl-1-azirine (**44h**) reacts with *o*-benzyne, generated by the thermal decomposition of benzenediazonium 2-carboxylate (**353**), to give two products. The major product, a 1 : 1 adduct produced in 50% yield, was identified as 2,3-diphenylindole (**355**). A 1 : 2 adduct of azirine and benzyne, identified as 1,2,3-triphenylindole (**357**), was isolated in 14% yield. When the concentration of benzyne was increased, the yield of **357** also increased. 2,3-Diphenylindole (**355**) was found to be relatively inert to benzyne, and no triphenylindole **357** could be isolated from the reaction of **355** and benzyne even after extended reaction times. The mechanism of formation of 2,3-diphenylindole (**355**) (Scheme 34) may be interpreted as requiring the initial formation of **354**, the result of 1,2-addition on the azirine ring system. Moreover, as 2-methyl-3-phenylindole (**358**) is isolated from the reaction of 3-methyl-2-phenyl-1-azirine (**3**) and benzyne, initial 1,3-addition appears unlikely. Two reaction pathways are available for partitioning of intermediate **354**. Ring cleavage and a concomitant 1,2-hydrogen shift to the nitrogen would give the stable aromatic indole **355**. A similar 1,2-hydrogen shift to carbon would generate the 3*H*-indole system **356**, which can be trapped by benzyne to give the 1,2,3-triphenylindole **357**. The conversion of indolenine **356** to the indole **357** may proceed via a symmetry-allowed "ene" reaction (illustrated in **359**). An alternative explanation involves a competitive interaction of benzyne with the nitrogen of **354** leading via a zwitterion to **357**.[50]

b. ENE REACTION

When the azlactone **360** was heated under reflux in xylene with 2-phenyl-1-



Scheme 34 Reaction of 2,3-diphenyl-1-azirine with benzyne. (Adapted from reference 206 with permission from the American Chemical Society.)

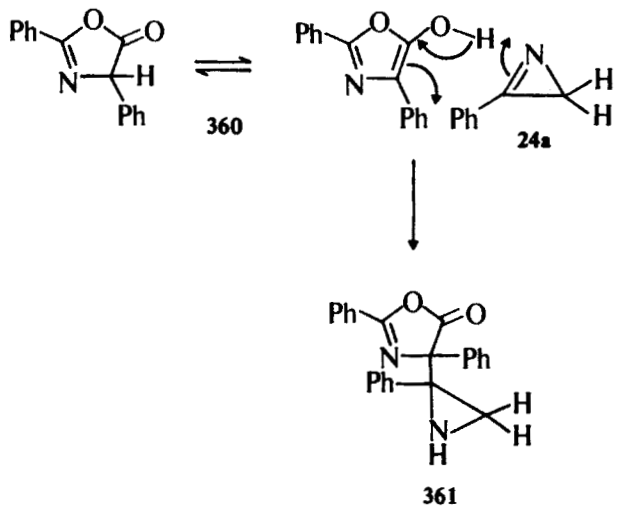


azirine (**24a**), the aziridine **361** was isolated in 92% yield.[185] Compound **361** is the product of an ene reaction as shown in Scheme 35.

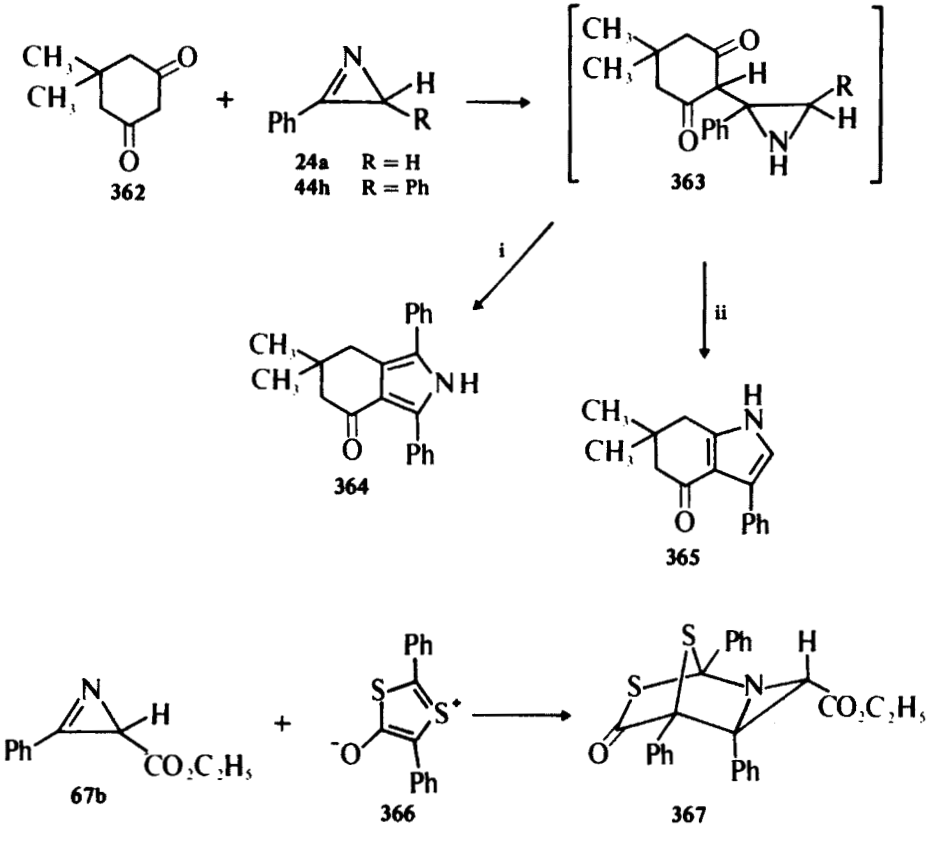
An ene reaction with dimedone also has been reported.[185] The ene product **363** is an intermediate in this case and undergoes C–C (i) or C–N (ii) bond cleavage to give, after H_2O elimination, the isolated products **364** or **365**, respectively.

c. MESOIONIC COMPOUNDS

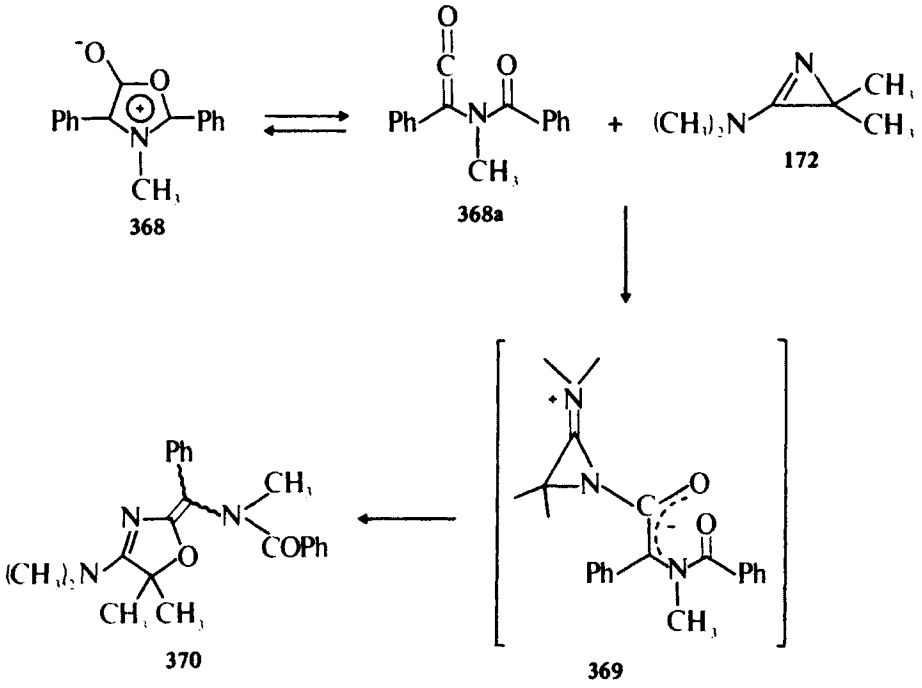
The mesoionic compound **366** adds to the azirine **67b** at 100° to give the adduct **367** in 92% yield.[207] The reaction is regiospecific and stereospecific.



Scheme 35 Ene reaction of 2-phenyl-1-azirine with an azlactone.

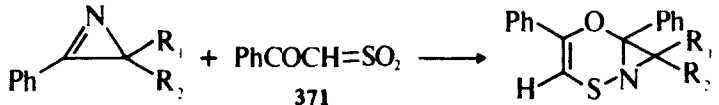


Lukac, Bieri, and Heimgartner[208,209] reported that the 2-dimethylamino-1-azirine (**172**) reacts with the mesoionic oxazole **368** at room temperature to give the adduct **370**, presumably through the intermediacy of **369**. The corresponding mesoionic dithiole shows similar behavior toward 2-amino-1-azirines.[209]



d. α-KETOSULFENES

The reaction of benzoylsulfene **371** and related cyclic α-ketosulfenes was studied by Tsuge and Noguchi.[210] The α-ketosulfene **371** reacts with the azirines **3**, **15**, **24a**, and **44h** to give the [4 + 2] cycloadducts **372**.

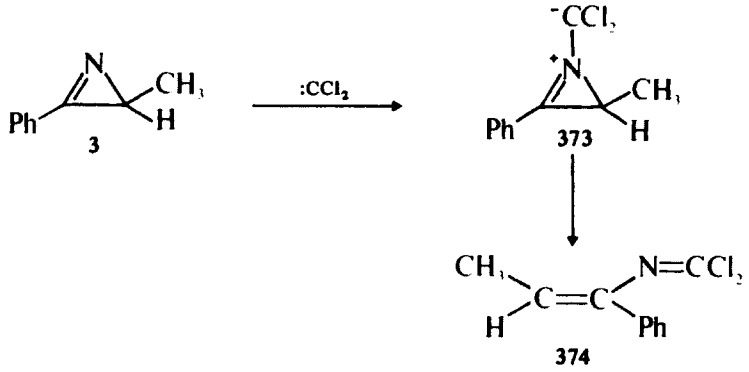


3 $R_1 = H; R_2 = CH_3$
15 $R_1 = CH_3; R_2 = CH_3$
24a $R_1 = H; R_2 = H$
44h $R_1 = H; R_2 = Ph$

e. CARBENES

Hassner et al.[147] showed that dichlorocarbene, generated from phenyl (trichloromethyl) mercury, reacts with 3-methyl-2-phenyl-azirine (**3**) to give the ring-opened product **374**. No azabicyclobutane was detected.[147] It was suggested that the

reaction involves initial nucleophilic attack by the azirine to generate the ylide **373**. This intermediate then undergoes ring opening with cleavage of the C–N bond to give **374**.



The conversion of 1-azirines with dimethylsulfonium methylide to give azabicyclobutanes[145] was mentioned previously.

The reaction of 1-azirines with diphenylcarbene[182] (generated by thermolysis of diphenyldiazomethane) was discussed in Section VI, 4, B on 1,3-dipolar cycloadditions.

5. Photochemical Reactions of 1-Azirines

Simple imines exhibit weak $n\pi^*$ absorption in the 235 nm region and generally are unreactive photochemically because of the deactivation of their excited state by (*E*)/(*Z*) isomerization. The C=N bond of 1-azirines, being part of a small heterocyclic system, cannot be deactivated in this manner after photochemical excitation. Considerable evidence has accrued to suggest that 1-azirines participate in photochemical reactions through initial ring cleavage. Many studies of the photoreactions of 1-azirines, both intermolecular and intramolecular, have been reported. Some photochemical reactions are described in two reviews.[211,212] This part of the chapter briefly discusses a wide variety of representative examples. The reader is referred to the original literature for more exhaustive coverage.

A. *Photochemical Excitation of 1-Azirines*

2-Aryl-1-azirines show a strong uv absorption at about 240 nm ($\epsilon > 10{,}000$) and a weak inflection on the long wavelength side of the principal band (*ca.* 285 nm, $\epsilon \sim 500$). The latter absorption is very likely associated with an $n\pi^*$ transition. It is likely that the first excited $n\pi^*$ singlet state of 2-aryl-1-azirines is responsible for its photochemistry. Padwa[211] and Schmid[212] and their co-workers have shown that 1-azirines undergo ring opening on $n\pi^*$ excitation to give nitrile ylides as reactive intermediates.

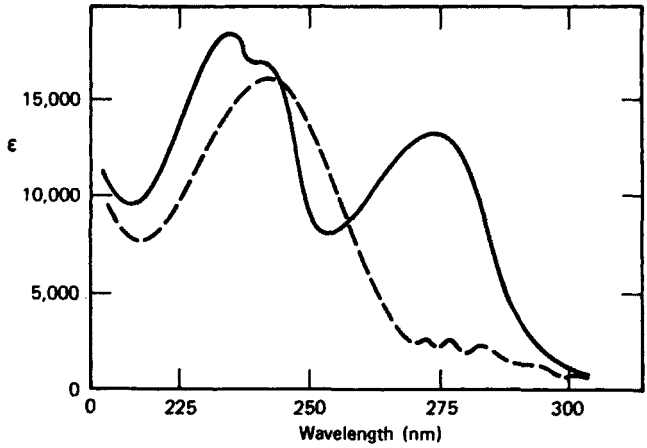
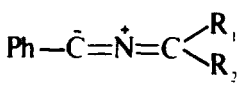


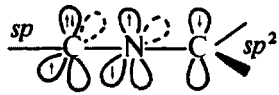
Figure 1. Irradiation (255 nm) of 3,3-dimethyl-2-phenyl-1-azirine in a rigid matrix at − 185°: solid curve, uv spectrum of azirine; dashed curve, uv spectrum of nitrile ylide. (Adapted from reference 213 with permission from *Helvetica Chimica Acta*, Birkhauser Verlag.)

Excellent direct experimental evidence for the generation of the nitrile ylides was provided by Schmid and his co-workers.[212-215] Irradiation of 3,3-dimethyl-2-phenyl-1-azirine (**15**) in a 2-methylpentane glass at − 185° with 255 nm light gave rise at 275 nm to a new absorption peak that was attributed to the nitrile ylide (Fig. 1). Similarly, irradiation of 2,3-diphenyl-1-azirine (**44h**) gave a nitrile ylide absorption at 350 nm. The dipolar species formed was shown to undergo photochemical but not thermal reversion to the starting azirine.[212,213] The absorption band due to the nitrile ylide disappeared slowly in the presence of a trapping agent such as a dipolarophile, suggesting that a thermally allowed 1,3-dipolar cycloaddition was occurring.

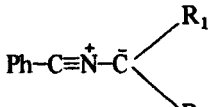
Structurally, nitrile ylides may be classified as nitrilium betaines, a class of 1,3-dipoles containing a central nitrogen atom and a π bond orthogonal to the 4π allyl system (**375a**).[211,216,217] However, a number of other forms (**375b–375e**) are possible for the ring-opened azirine. The structure may be partly diradical and partly zwitterionic.[218]



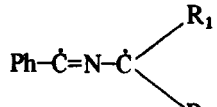
375a



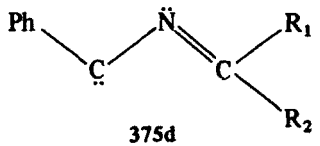
375a
Orbital representation.



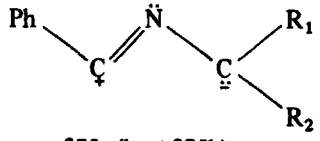
375b



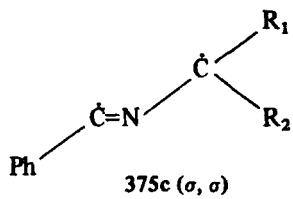
375c (σ, π)



375d



375e (bent 375b)

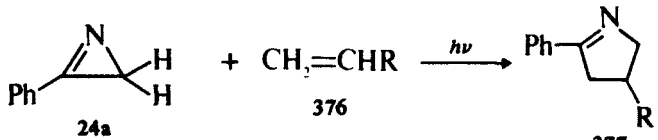


375c (σ, σ)

B. *Intermolecular Photochemical Reactions*

a. WITH ALKENES AND ALKYNES

Padwa and Smolanoff[219] reported that when a solution of 2-phenyl-1-azirine (**24a**) in excess methyl acrylate (**376a**) is photolyzed using a 450 W high pressure mercury lamp with a Vycor filter for 3 hr, 2-phenyl-4-carbomethoxy-Δ^1-pyrroline (**377a**) is produced in 80% yield. Similarly, when acrylonitrile (**376b**) was used as the olefin, Δ^1-pyrroline (**377b**) was isolated in 70% yield.



24a

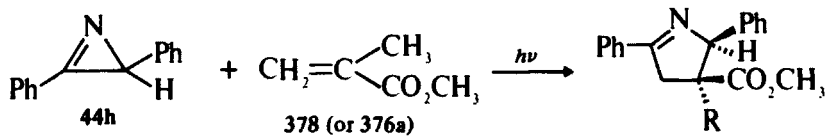
376

a. R = CO_2CH_3
b. R = CN

377

a. R = CO_2CH_3
b. R = CN

However, the photochemical addition of 2,3-diphenyl-1-azirine (**44h**) with methyl methacrylate (**378**) afforded a mixture of 2,5-diphenyl-4-methyl-4-carbomethoxy-Δ^1-pyrrolines **379** (40% yield) and **380** (60%).[220]

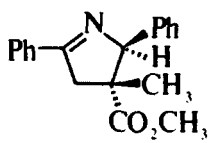


44h

378 (or 376a)

379, R = CH_3
(381, R = H)

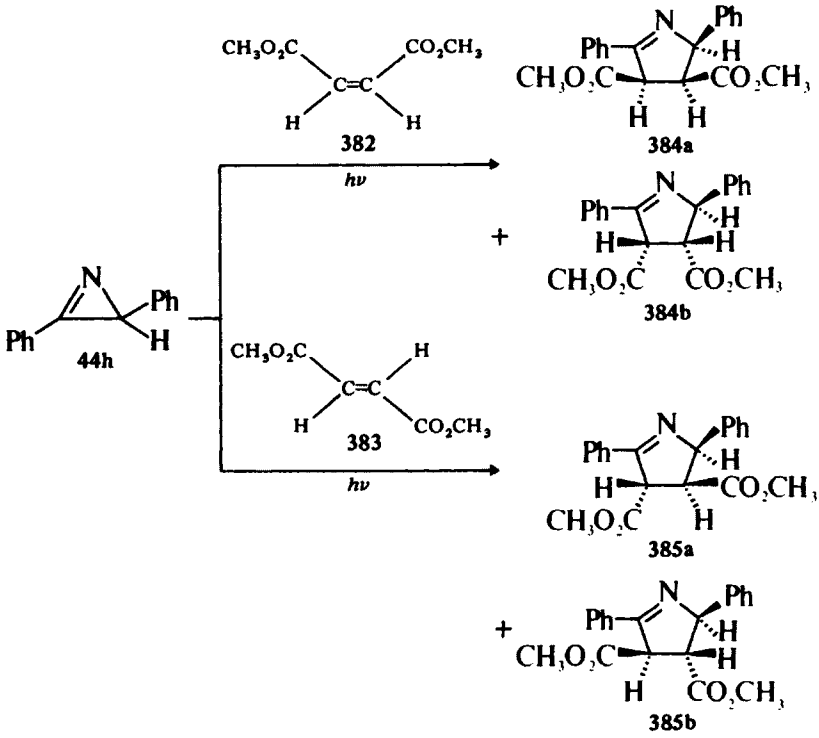
+



380

Irradiation of a mixture of **44h** and methyl acrylate (**376a**) led to a single photoproduct, 2,5-diphenyl-*cis*-4-carbomethoxy-Δ^1-pyrroline (**381**).

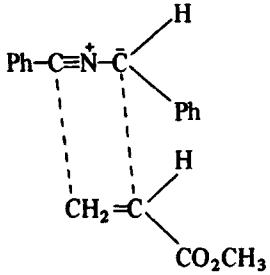
The photoadditions of 2,3-diphenyl-1-azirine (**44h**) also exhibit *syn* stereospecificity (Scheme 36). For example, irradiation of **44h** with maleic and fumaric acid esters **382** and **383** gave totally stereospecific addition, and the isomeric Δ^1-pyrrolines **384a**, **384b**, and **385a**, **385b** respectively, were isolated.



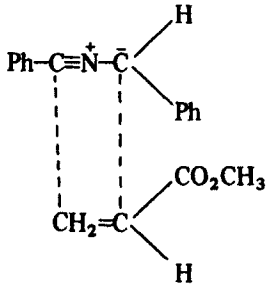
Scheme 36 Photochemical addition of 2,3-diphenyl-1-azirine with dimethyl maleate and dimethyl fumarate.

The photocycloaddition of 2-phenyl-1-azirines with electron-deficient olefins to produce Δ^1-pyrrolines generally shows characteristics of concerted reactions, including features of stereospecificity and regioselectivity. The reaction can be classified in simple terms as a thermal 1,3-dipolar cycloaddition of a nitrile ylide with a π bond.[221] If these dipolar additions proceed through a "two-plane" orientation complex, a number of possible arrangements can be drawn. For the reaction of diphenylazirine and methyl acrylate, two possible orientation complexes (**386** and **387**) exist. The interaction of the substituent groups in the *syn* complex **386** has both an attractive and a repulsive nature. These effects are relatively small in the *anti* complex **387**. However, the results of this photoaddition (*cis*-Δ^1-pyrroline, **381**, is the predominant product) suggest that the π overlap of the ester and phenyl groups in the *syn* complex more than compensates for the

adverse van der Waals repulsion of these substituents.[220,222] This, however, is not the case when the hydrogen in the position alpha to the carbomethoxyl is replaced by a methyl group. There is little discrimination between the *syn* and *anti* forms, and both products (**379** and **380**) are formed.

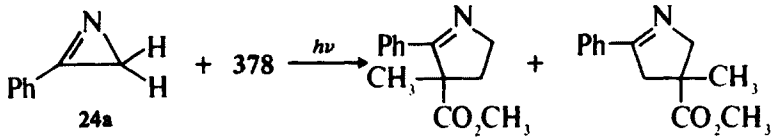


386



387

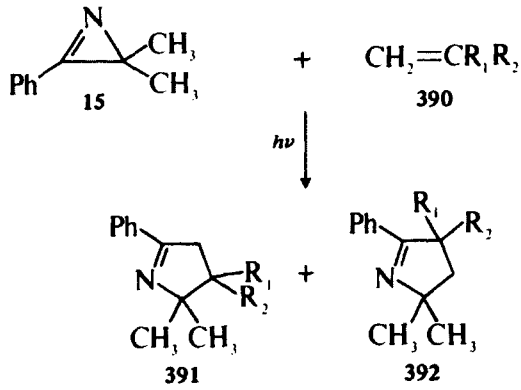
These photocycloadditions also exhibit regioselectivity. Frontier orbital theory has been used successfully to rationalize the observed regioselectivity of many 1,3-dipolar cycloadditions.[223] For example, with nitrile ylides the favored cycloadduct is that formed by the bonding of atoms with the largest coefficients in the dipole highest occupied molecular orbital (HOMO) and dipolarophile lowest unoccupied molecular orbital (LUMO). In the HOMO of the nitrile ylides under consideration, the electron density at the disubstituted carbon is somewhat greater than that at the trisubstituted carbon.[211] In electron-deficient olefins, the largest coefficient in the LUMO is on the unsubstituted carbon. This treatment adequately explains the photochemical reaction of diphenylazirine with methyl acrylate to produce only the 4-substituted regioisomer **381**. Padwa[211] explained the mixture of cycloadducts **388** and **389** in the reaction of 2-phenyl-1-azirine (**24a**) with methyl methacrylate by the lowering of the LUMO coefficient at the unsubstituted carbon atom of the dipolarophile by the presence of the methyl group. Apparently the terminal coefficients in the LUMO of methyl methacrylate are more nearly the same than they are for methyl acrylate, resulting in the observed loss of regioselectivity.



24a **388** **389**

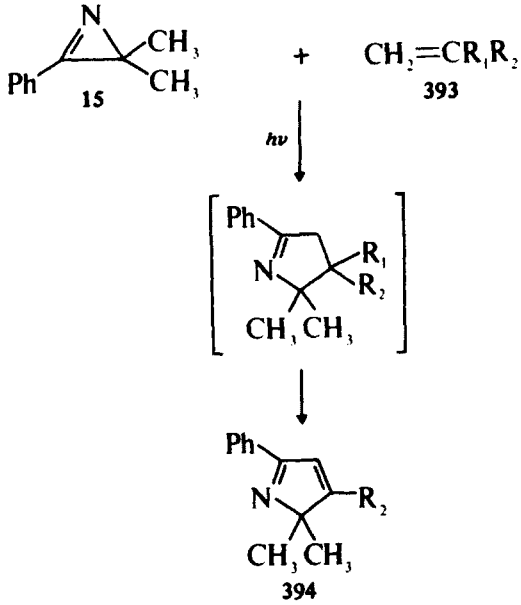
Regioselectivity is lost also in the photochemical cycloaddition of 3,3-dimethyl-2-phenyl-1-azirine (**15**) and diethylvinyl phosphonate or dimethylvinyl phosphine sulfide. The two Δ^1-pyrrolines **391** and **392** are formed in equal amounts.[212,224]

The photoaddition of azirine **15** to vinyl phosphonium salts (**393a** and **393b**) and to vinyl sulfones (**393c**) results in the isolation of the pyrroles **394a–394c** in the yields shown in Scheme 37. The initial photoadduct is presumably a Δ^1-



a. $R_1 = PO(OC_2H_5)_2$; $R_2 = H$
b. $R_1 = PS(CH_3)_2$; $R_2 = H$

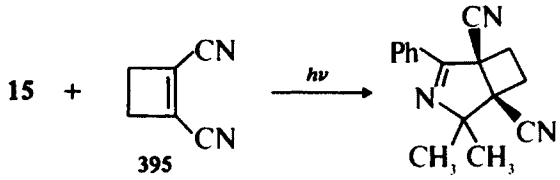
pyrroline from which the pyrroles are derived by elimination of $(Ph)_3P \cdot HBr$ or $PhSO_2H$.[225] α-Ethoxyacrylonitrile (**393d**) exhibits similar behavior,[226] eliminating acetic acid to produce the pyrrole **394d** (Scheme 37).

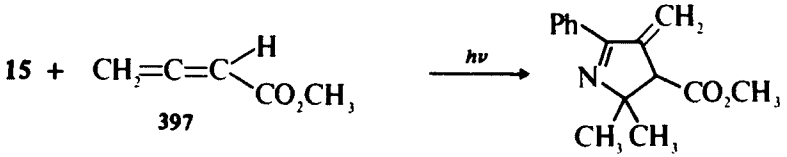


a. $R_1 = \overset{+}{P}(Ph)_3Br^-$; $R_2 = H$ (40%)
b. $R_1 = \overset{+}{P}(Ph)_3Br^-$; $R_2 = CH_3$ (26%)
c. $R_1 = SO_2Ph$; $R_2 = H$ (65%)
d. $R_1 = CN$; $R_2 = OCOCH_3$ (55%)

Scheme 37 2*H*-Pyrrole formation in the photocycloaddition of 3,3-dimethyl-2-phenyl-1-azirine and vinyl phosphonium salts, vinyl sulfones, and α-acetoxyacrylonitrile. (Adapted from reference 212 with permission from *Heterocycles*.)

1,2-Dicyanocyclobutene (**395**) reacts photochemically with azirine **15** to give in 68% conversion the bicyclic pyrroline **396**.[226] The allene **397** gives the pyrroline **398** in 90% yield.[212]





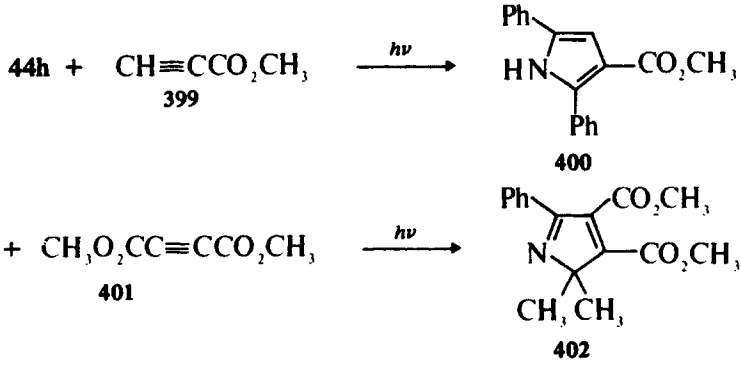
Other alkenes such as styrenes and vinylpyridines[212] are also reactive toward 1-azirines photochemically. Nonactivated alkenes such as cyclohexene are unreactive. The relative reactivities of a series of alkenes toward the nitrile ylide from 2,3-diphenyl-1-azirine (**44h**) are shown in Table 6.[233]

Alkynes also undergo cycloaddition to the nitrile ylides derived from 1-azirines. For example, the monosubstituted acetylene **399** adds to produce the pyrrole **400**, presumably via initial cycloaddition and subsequent 1,5-sigmatropic shift. When the 1,5-sigmatropic shift is prevented as in the reaction of the geminally disubstituted azirine **15** with dimethylacetylene dicarboxylate (**401**), the 2*H*-pyrrole **402** is the isolated product.[212,228,229]

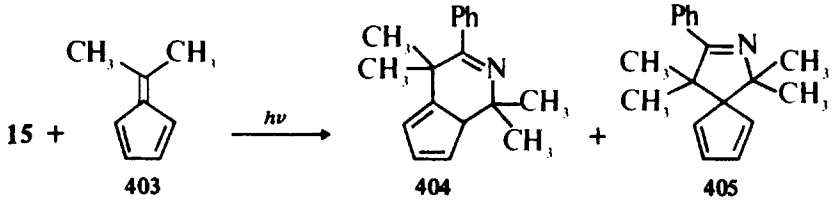
TABLE 6. RELATIVE REACTIVITY OF ALKENES TOWARD NITRILE YLIDE FROM AZIRINE 44h.[a]

Dipolarophile	Relative rate
Methyl crotonate	1
Methylacrylonitrile	3.6
Methyl methacrylate	9
Diethyl maleate	135
Methyl acrylate	160
Dimethyl maleate	166
Acrylonitrile	180
Dimethyl acetylenedicarboxylate	540
Maleonitrile	2,300
Diethyl fumarate	56,000
Dimethyl fumarate	84,000
Fumaronitrile	189,000

[a] Adapted from reference 233 with permission from the American Chemical Society.



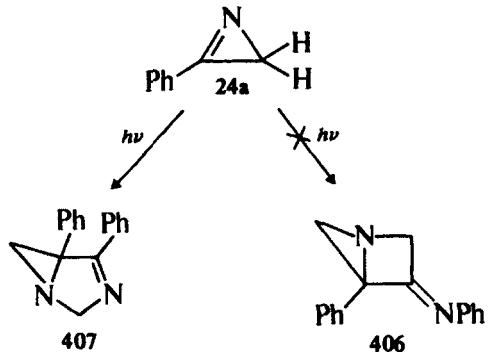
The reactions of the photochemically generated nitrile ylides with alkenes and alkynes represent thermally allowed [4 + 2] cycloadditions. Under appropriate conditions, these nitrile ylides can participate as 4π components in [6 + 4] cycloadditions. For example, irradiation of a 1:1 mixture of azirine **15** and 6,6-dimethylfulvene **403** in cyclohexane with Vycor filtered light gives two products (**404** and **405**) in a 3:1 ratio. Compound **405** is the result of a [4 + 2] cycloaddition similar to the reactions of alkenes already mentioned, and compound **404** represents a [6 + 4] adduct.[230]



b. WITH IMINES

Generally, imines such as benzylidene-methylamine do not react with 1-azirines under photochemical conditions. However, the nitrile ylides derived from 1-azirines are reactive toward the strained C=N bond of 1-azirines. The first report describing such a reaction was made by Woerner, Reimlinger, and Arnold.[231,232] However, the structure of the product from the photolysis of 2-phenyl-1-azirine (**24a**) was incorrectly assigned as an azabicyclopentane **406**. Padwa and his co-workers[233] subsequently showed that the photodimer isolated from this reaction was the diazabicyclohexane **407**.

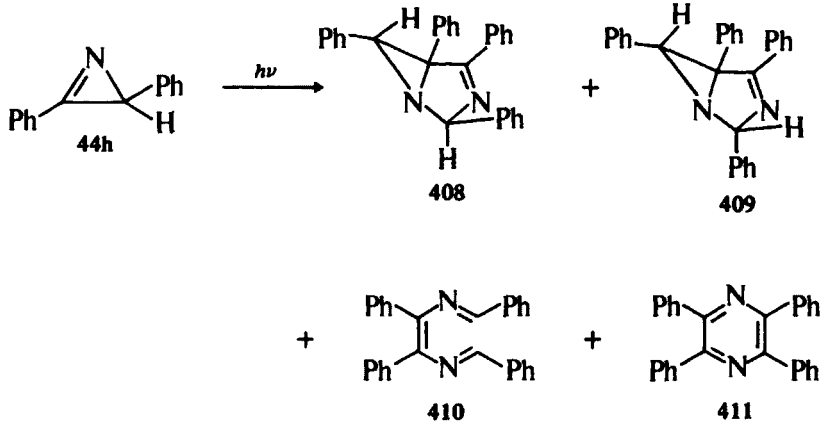
Further detailed analysis of this photodimerization was carried out with 2,3-diphenyl-1-azirine (**44h**).[233] Irradiation of azirine **44h** in cyclohexane for 17 hr with 300–340 nm light led to the complete disappearance of starting material and the formation of the photoadducts **408–411** (Scheme 38). The relative yields of these products varied as a function of time of irradiation. The formation of products **408** and **409** can be rationalized in terms of a 1,3-dipolar cycloaddition of the nitrile ylide $PhC^{-}=\overset{+}{N}=CHPh$ with the C=N bond of ground state azirine **44h**. This mechanism



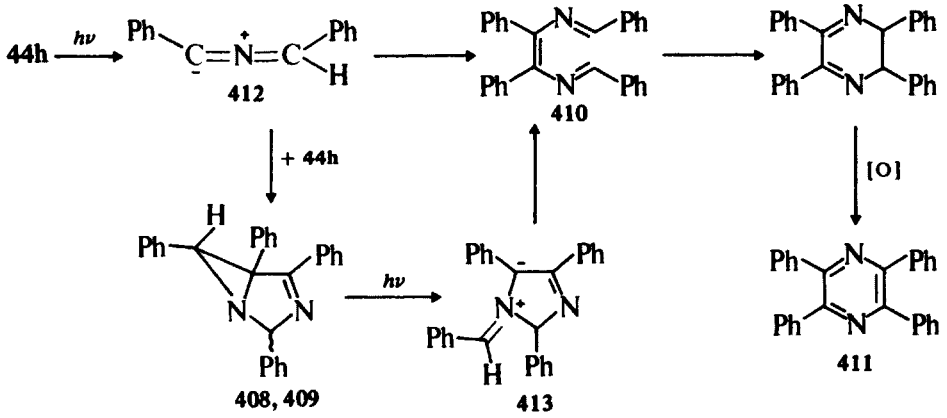
is consistent with Stern-Volmer plots obtained in these studies. On further irradiation, the stereoisomeric photodimers **408** and **409** are converted to the diazahexatriene **410**.[233,234] Schmid and his co-workers[215] have shown that the nitrile ylide **412** derived from **44h** can undergo quantitative dimerization to **410** at − 160°. Compound **410** can therefore be formed by both pathways. The intermediacy of the azomethine ylide **413** in the photochemical transformation of **408** and **409** to **410** was verified also by low temperature photolysis studies. It is very likely that formation of tetraphenylpyrazine (**411**) is due to the electrocyclization of **410** followed by oxidation (Scheme 39).

When a mixture of 2-phenyl-1-azirine (**24a**) and 2,3-diphenyl-1-azirine (**44h**) is photolyzed in such a way that only **44h** is excited (313 nm light), the sole products are 2-*exo*- and 2-*endo*-2,4,5-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**414**).[227] These are cross-dimerization products.

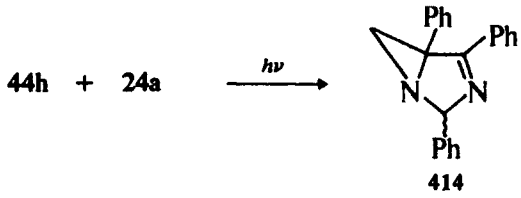
The photodimerization of these 1-azirines to 1,3-diazabicyclo[3.1.0] hex-3-enes appears to be a general reaction that exhibits some dependence on solvent, irradiation time, and substituents, mainly because of the inherent photochemical instability of the 1,3-diazabicyclohexenes.



Scheme 38 Products from the photodimerization of 2,3-diphenyl-1-azirine.



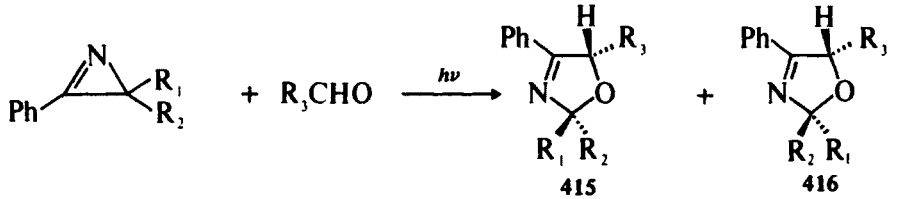
Scheme 39 Mechanism of photodimerization of 2,3-diphenyl-1-azirine. (Adapted from reference 211 with permission from the American Chemical Society.)



c. WITH ALDEHYDES, KETONES, AND α,β-UNSATURATED CARBONYL COMPOUNDS

Aldehydes, both aliphatic and aromatic, react regiospecifically with 2-phenylazirines under photolytic conditions to give 3-oxazoline derivatives exclusively and in isolated yields ranging approximately from 30 to 80%.[227,235,236] Where the possibility of stereochemistry exists, such as with 3-monosubstituted 1-azirines, both *cis*- and *trans*-isomeric 3-oxazolines are produced, with the *cis*- isomer being the major product (Scheme 40, Table 7).

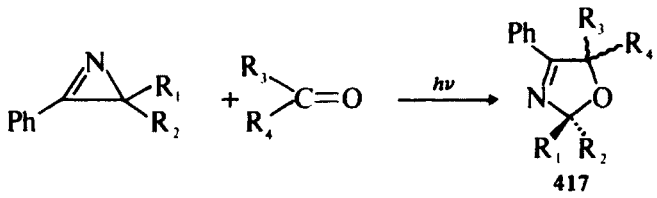
The reaction of ketones with these benzonitrile ylides is similar to the aldehyde reactions. Schmid and his co-workers reported[237,238] good yields of 3-oxazolines (417) generally from these reactions (Scheme 41, Table 8). Ketones with electron-withdrawing groups such as trifluoromethyl, ethoxycarbonyl, and nitrile in the



Scheme 40 General representation of the photoinduced reaction of 2-phenylazirines with aldehydes.

TABLE 7. ISOLATED YIELDS OF 3-OXAZOLINES IN THE PHOTOCYCLOADDITION OF 2-PHENYLAZIRINES WITH ALDEHYDES (SCHEME 40)[235,236]

Azirine	Aldehyde	3-Oxazoline	Yield (%)
$R_1 = R_2 = H$ (24a)	$R_3 = Ph$	$R_1 = R_2 = H; R_3 = Ph$	62
$R_1 = R_2 = H$ (24a)	$R_3 = p\text{-}CH_3\text{–}C_6H_4$	$R_1 = R_2 = H; R_3 = p\text{-}CH_3\text{–}C_6H_4$	54
$R_1 = R_2 = H$ (24a)	$R_3 = n\text{-}C_3H_7$	$R_1 = R_2 = H; R_3 = n\text{-}C_3H_7$	32
$R_1 = CH_3; R_2 = H$ (3)	$R_3 = Ph$	*cis*-416	18
		trans-415	9
		$R_1 = CH_3; R_2 = H; R_3 = Ph$	
$R_1 = Ph; R_2 = H$ (44h)	$R_3 = Ph$	*cis*-416	27
		trans-415	8
		$R_1 = Ph; R_2 = H; R_3 = Ph$	
$R_1 = Ph; R_2 = H$ (44h)	$R_3 = p\text{-}Cl\text{–}C_6H_4$	*cis*-416	19
		trans-415	7
		$R_1 = Ph; R_2 = H; R_3 = p\text{-}Cl\text{–}C_6H_4$	
$R_1 = Ph; R_2 = H$ (44h)	$R_3 = C_2H_5$	*cis*-416	32
		trans-415	13
		$R_1 = Ph; R_2 = H; R_3 = C_2H_5$	
$R_1 = Ph; R_2 = H$ (44h)	$R_3 = i\text{-}C_3H_7$	*cis*-416	35
		trans-415	9
		$R_1 = Ph; R_2 = H; R_3 = i\text{-}C_3H_7$	
$R_1 = R_2 = CH_3$ (15)	$R_3 = Ph$	$R_1 = R_2 = CH_3; R_3 = Ph$	60
$R_1 = R_2 = CH_3$ (15)	$R_3 = p\text{-}CH_3\text{–}C_6H_4$	$R_1 = R_2 = CH_3; R_3 = p\text{-}CH_3\text{–}C_6H_4$	70
$R_1 = R_2 = CH_3$ (15)	$R_3 = C_2H_5$	$R_1 = R_2 = CH_3; R_3 = C_2H_5$	74
$R_1 = R_2 = CH_3$ (15)	$R_3 = i\text{-}C_3H_7$	$R_1 = R_2 = CH_3; R_3 = i\text{-}C_3H_7$	80

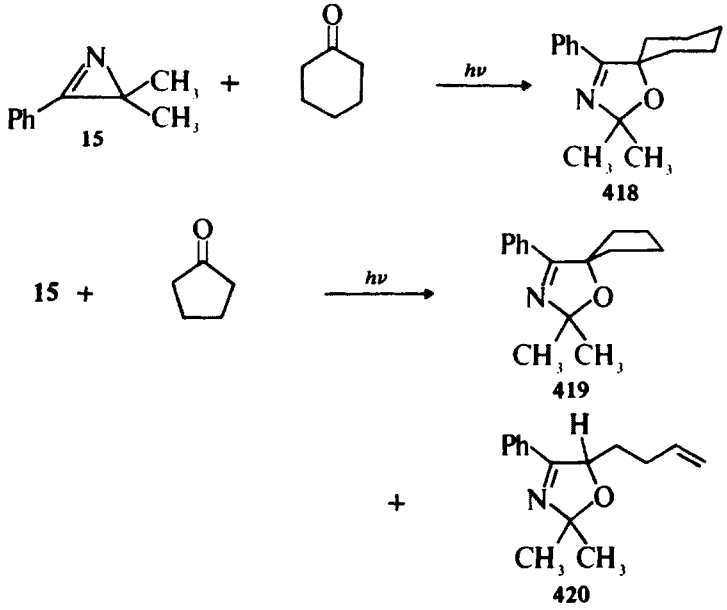


417

Scheme 41 General representation of the photoinduced reaction of 2-phenylazirines with ketones.

α-position react particularly smoothly. 3-Monosubstituted azirines such as **3** and **44h** react with unsymmetrical ketones to form mixtures of *cis*- and *trans*-3-oxazolines. It is of interest to compare these reactions with the acid-catalyzed addition of ketones to 1-azirines.

Cyclic ketones also react with 1-azirines under photochemical conditions (Scheme 42).[238] Irradiation of azirine **15** with cyclohexanone results in the formation of the spiro-3-oxazoline **418** in 86% yield. The photochemical behavior of **15** and cyclopentanone is dependent on the reaction conditions. When azirine **15** is irradiated and cyclopentanone slowly added, the spiro-3-oxazoline **419** is the major product. When cyclopentanone is irradiated first and the irradiation is continued with added azirine **15**, the only product isolated (80%) is the 3-oxazoline **420**. Product **420** must arise from the cycloaddition of the nitrile ylide with 4-pentenal. The latter is produced from cyclopentanone by Norrish type I cleavage and hydrogen transfer. Camphor and norcamphor also react after initial Norrish type I cleavage.



Scheme 42 Photochemical behavior 3,3-dimethyl-2-phenyl-1-azirine in the presence of cyclic ketones.

TABLE 8. ISOLATED YIELDS OF 3-OXAZOLINES (417) IN THE PHOTOCYCLOADDITION OF 2-PHENYLAZIRINES WITH KETONES.[237,238]

Azirine	Ketone	3-Oxazoline	Yield (%)
$R_1 = R_2 = CH_3$ (15)	$R_3 = R_4 = CH_3$	$R_1 = R_2 = R_3 = R_4 = CH_3$	98
$R_1 = CH_3; R_2 = H$ (3)	$R_3 = R_4 = CH_3$	$R_1 = R_3 = R_4 = CH_3; R_2 = H$	17
$R_1 = R_2 = CH_3$ (15)	$R_3 = CH_3; R_4 = Ph$	$R_1 = R_2 = R_3 = CH_3; R_4 = Ph$	84
$R_1 = R_2 = CH_3$ (15)	$R_3 = R_4 = Ph$	$R_1 = R_2 = CH_3; R_3 = R_4 = Ph$	88
$R_1 = R_2 = CH_3$ (15)	$R_3 = CF_3; R_4 = Ph$	$R_1 = R_2 = CH_3; R_3 = CF_3; R_4 = Ph$	80
$R_1 = Ph; R_2 = H$ (44h)	$R_3 = CF_3; R_4 = Ph$	$R_1 = R_4 = Ph; R_2 = H; R_3 = CF_3$	90
$R_1 = Ph; R_2 = H$ (44h)	$R_3 = CF_3; R_4 = CH_3$	$R_1 = Ph; R_2 = H; R_3 = CF_3; R_4 = CH_3$	65
$R_1 = R_2 = CH_3$ (15)	$R_3 = CH_3; R_4 = CO_2C_2H_5$	$R_1 = R_2 = R_3 = CH_3; R_4 = CO_2C_2H_5$	21
$R_1 = R_2 = CH_3$ (15)	$R_3 = R_4 = CO_2C_2H_5$	$R_1 = R_2 = CH_3; R_3 = R_4 = CO_2C_2H_5$	50
$R_1 = Ph; R_2 = H$ (44h)	$R_3 = R_4 = CO_2C_2H_5$	$R_1 = Ph; R_2 = H; R_3 = R_4 = CO_2C_2H_5$	59
$R_1 = R_2 = CH_3$ (15)	$R_3 = Ph; R_4 = CN$	$R_1 = R_2 = CH_3; R_3 = Ph; R_4 = CN$	65
$R_1 = Ph; R_2 = H$ (44h)	$R_3 = Ph; R_4 = CN$	$R_1 = R_3 = Ph; R_2 = H; R_4 = CN$	87
$R_1 = CH_3; R_2 = H$ (3)	$R_3 = Ph; R_4 = CN$	$R_1 = CH_3; R_2 = H; R_3 = Ph; R_4 = CN$	90

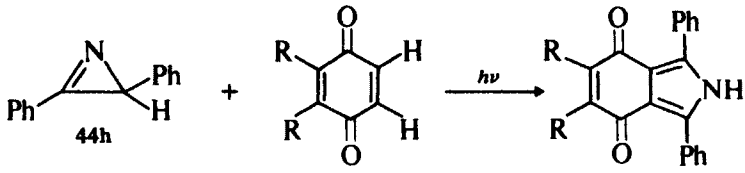
TABLE 9. PHOTOADDITION OF 3,3-DIMETHYL-2-PHENYL-1-AZIRINE WITH α,β-UNSATURATED CARBONYL COMPOUNDS.[a]

Compound	C=C Addition (%)	C=O Addition (%)
CH_2=CH–CHO	39	46
CH_3–CH=CH–CHO	–	84
C_2H_5O–CH=C(CH_3)–CHO	–	93
CH_2=CH–$COCH_3$	73	–
$(CH_3)_2C$=CH$COCH_3$	3	30
$(C_2H_5)_2OP$–CH=CH$COCH_3$	41	31
$Br^{\ominus}(Ph)_3\overset{\oplus}{P}$–CH=CH$COCH_3$	–	59
$(CH_3)_2C$=CH–$COPO(OCH_3)_2$	–	80

[a] Adapted from reference 212 with permission from *Heterocycles*.

α,β-Unsaturated carbonyl compounds may react with the benzonitrile ylides at the C=C component, at the C=O component, or at both, depending on the structural characteristics of the substrate. The reactions exhibit regiospecificity. In general, for relatively simple systems, the alkene and aldehyde groups appear to react at approximately equal rates, and both react faster than keto groups.[212] Steric hindrance and electronic factors may alter this order of reactivity. α,β-Unsaturated cyclic ketones such as cyclo-2-pentenone, cyclo-2-hexenone, and cyclo-2-heptenone react with azirine **15** exclusively at the C=C bond. Phosphorus-containing α,β-unsaturated compounds also react with 2-phenylazirines photolytically. Table 9 summarizes some data from representative α,β-unsaturated carbonyl systems.

1,4-Quinones (e.g., **421**) react at the C=C bond to give isoindolediones (**422**) in 30–40% yield.[239] Positions 5 and 6 in the quinone must be unsubstituted for the products **422** to form.

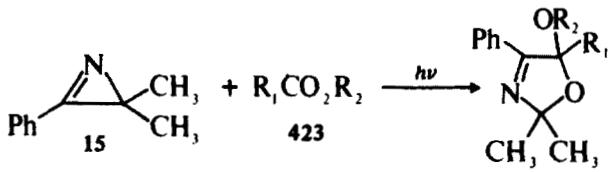


421 422

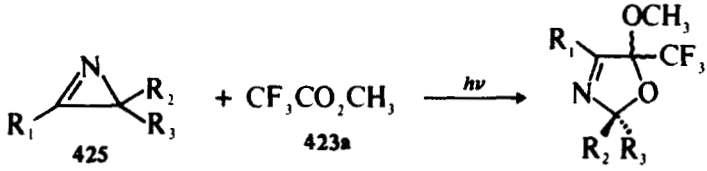
R = H, CH_3, OCH_3

d. WITH CARBOXYLIC ACID ESTERS, ANHYDRIDES, AND ACID CHLORIDES

Carboxylic acid esters (**423**), whose carbonyl groups are activated by electron-withdrawing groups in the alkyl or acyl moiety, react regiospecifically with benzonitrile ylides derived from 2-phenylazirines (e.g., **15**) to give 5-alkoxy-3-oxazolines (**424**).[240] Esters such as methyl acetate or methyl benzoate, which are not sufficiently activated, do not undergo these cycloadditions. Methyl trifluoroacetate was found to be the most reactive ester (Scheme 43). It underwent cycloaddition even to nitrile ylides derived from 2-alkylazirines.[241] Cycloadditions of 1-azirines that are monosubstituted at C-3 give rise to *trans-cis* mixtures of the 5-alkoxy-3-oxazolines.



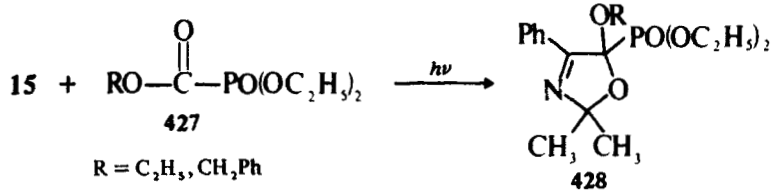
a. $R_1 = CF_3$; $R_2 = CH_3$
b. $R_1 = CH_2F$; $R_2 = CH_3$
c. $R_1 = CH_2Cl$; $R_2 = CH_3$
d. $R_1 = CH_2Br$; $R_2 = CH_3$
e. $R_1 = CO_2CH_3$; $R_2 = CH_3$
f. $R_1 = CN$; $R_2 = C_2H_5$
g. $R_1 = CH_3$; $R_2 = CH_2CF_3$
h. $R_1 = CH_3$; $R_2 = Ph$
i. $R_1 = CH_3$; $R_2 = CH{=}CH_2$
j. $R_1 = CH_3$; $R_2 = C{\equiv}CH$



a. $R_1 = Ph$; $R_2 = R_3 = H$ (24a)
b. $R_1 = Ph$; $R_2 = CH_3$; $R_3 = H$ (3)
c. $R_1 = Ph$; $R_2 = Ph$; $R_3 = H$ (44h)
d. $R_1 = R_2 = R_3 = Ph$
e. $R_1 = PhCH_2$; $R_2 = R_3 = H$ (44e)
f. $R_1 = R_2 = C_3H_7$; $R_3 = H$

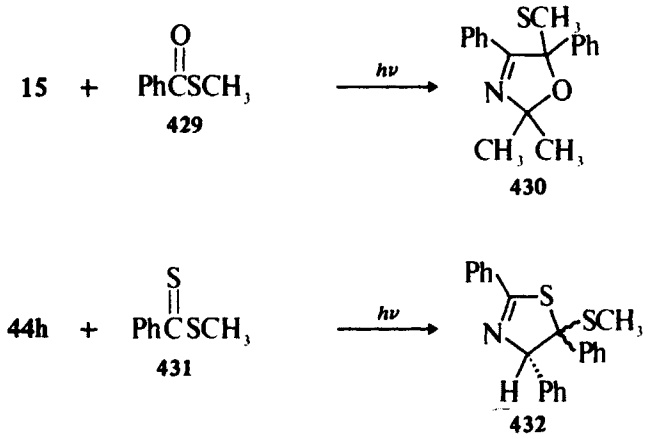
Scheme 43 Methyl trifluoroacetate as a dipolarophile for nitrile ylides derived photochemically from 1-azirines.

Ester carbonyl groups can be activated by the presence of other types of functionality. For example, ester carbonyls can be activated for photoaddition by the diethyl phosphonate residue. Thus, azirine **15** reacts photochemically with diethyl ethoxycarbonyl or benzyloxycarbonyl phosphonate (**427**) to give the corresponding 3-oxazolines (**428**) in almost quantitative yield.[212,224] The reaction is regiospecific, as expected.



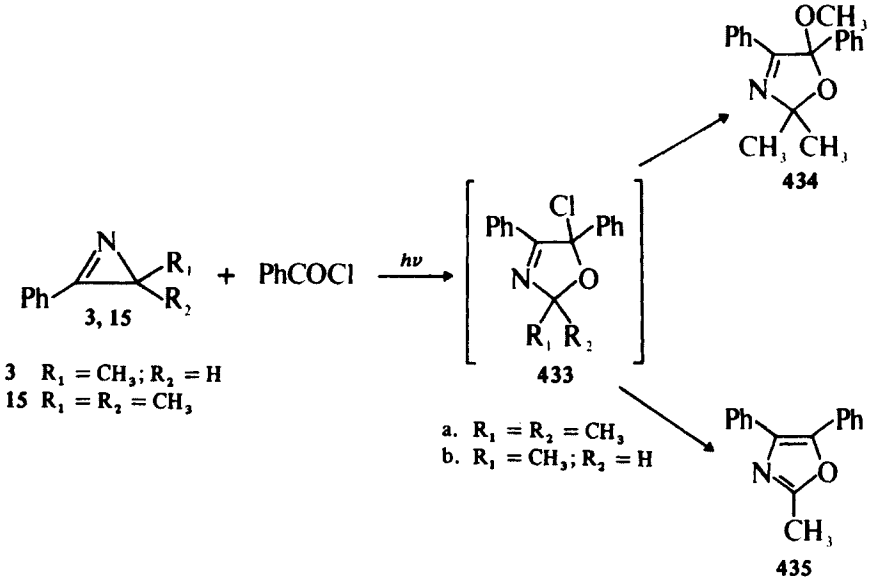
Thioesters are also reactive toward these nitrile ylides. *S*-Methyl thiobenzoate (**429**) reacts with azirine **15** to give the 3-oxazoline **430**.[240] However, in contrast

to the regiospecific addition with *S*-methyl thiobenzoate and other esters to produce Δ^3-oxazolines, the reaction of methyl dithiobenzoate **431** with 2,3-diphenyl-1-azirine (**44h**) proceeds with the inverse regiospecificity to give Δ^2-thiazolines (**432**). Since the azirine **44h** is monosubstituted at the 3-position, a mixture of *cis* and *trans* isomers is obtained (Scheme 44).[227,240]



Scheme 44 Photoinduced reaction of 2-phenylazirines with thioesters.

Cycloadditions have been observed also with acyl chlorides (Scheme 45).[242] Benzoyl chloride adds to the nitrile ylide from azirine **15** to give as the primary product the 5-chloro-4-phenyl-3-oxazoline **433a**. Because of its instability, this compound is best characterized as its 5-methoxy derivative **434**, obtained by



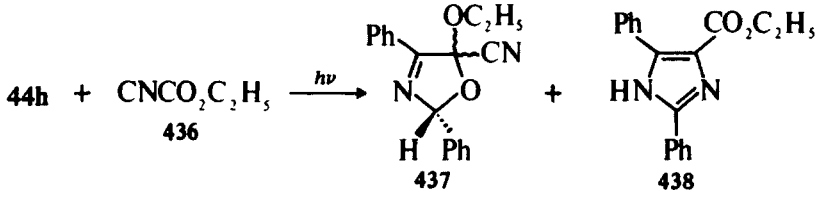
Scheme 45 Photochemical reaction of 2-phenylazirines with acid chlorides.

methanol treatment of **433a**. The primary adduct **433b**, which is monosubstituted at C-2, undergoes elimination of HCl on treatment with triethylamine to give the oxazole **435**. As discussed previously, the isomeric oxazole is produced in the thermal reaction of azirine **3** and benzoyl chloride.

A related photochemical reaction occurs with carboxylic acid anhydrides.[242]

e. WITH NITRILES

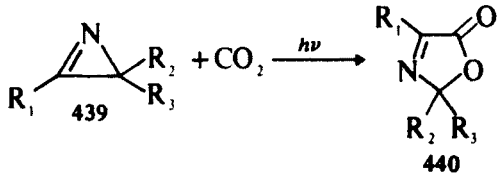
Under acid-catalyzed thermal conditions, 2-phenylazirines react readily with acetonitrile to furnish imidazolines. However, nitriles such as acetonitrile and benzonitrile are unreactive photochemically with 2-phenylazirines. "Activated" nitriles such as fluoroacetonitrile, trichloroacetonitrile, and 2- and 4-cyanopyridine react to give imidazoles.[212,226] Ethyl cyanoformate (**436**) interacts with azirine **44h** under photolytic conditions to give products of both carbonyl (**437**) and nitrile group (**438**) cycloadditions (Scheme 46).[237]



Scheme 46 Photocycloaddition of ethyl cyanoformate with 2,3-diphenyl-1-azirine.

f. WITH HETEROCUMULENES

The photoinduced combination of carbon dioxide with 2-phenyl- and 2-benzylazirines was first described by Schmid and his co-workers.[235] The reactions were carried out by passing carbon dioxide through benzene solutions of the 1-azirines under conditions of irradiation from a high pressure mercury lamp with a Vycor filter. Padwa and Wetmore[243] subsequently reported a similar photoaddition with carbon dioxide. The regiospecifically produced adducts in these reactions are 3-oxazolin-5-ones (Δ^3-oxazolin-5-ones), **440** (Scheme 47).



a. $R_1 = R_2 = Ph; R_3 = H$ (**44h**) — **440a** (65%)
b. $R_1 = Ph; R_2 = R_3 = CH_3$ (**15**) — **440b** (84%)
c. $R_1 = PhCH_2; R_2 = R_3 = H$ (**44e**) — **440c** (40%)
d. $R_1 = Ph; R_2 = CH_3; R_3 = H$ (**3**) — **440d** (88%)

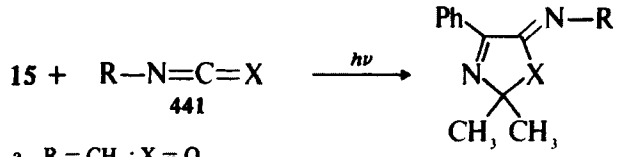
Scheme 47 Photoinduced combination of carbon dioxide with 2-arylazirines.

The photoaddition of carbon dioxide to these nitrile ylides is reversible, and irradiation of **440** results in generation of the starting nitrile ylides with quantum yields in the order of 0.3.[243]

When 3,3-dimethyl-2-phenyl-1-azirine (**15**) was photolyzed in the presence of carbon disulfide, only a 2:1 adduct, 5,5-spirobis(4,4-dimethyl-2-phenyl-2-thiazoline) could be isolated.[243]

Heterocumulenes such as isocyanates **441a** and **441b** and isothiocyanates **441c** and **441d** undergo photoreactions with 2-phenylazirines.[244,245] For isocyanates, reaction occurs at the C=O and isothiocyanates add at the C=S bond (Scheme 48). No photoreaction involving the C=N bond in these compounds was observed. A comparison of the thermal reaction with these heterocumulenes is of interest. Simple isocyanates and isothiocyanates such as **441a–441d** do not normally react under thermal conditions with 2-phenylazirines. However, the more reactive benzoyl isocyanate and benzoyl isothiocyanate are reactive under these conditions.

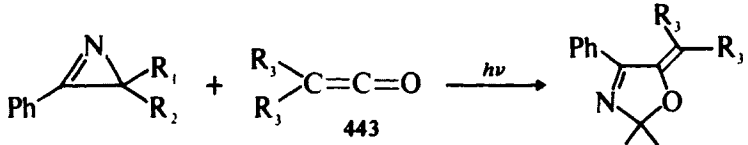
Carbodiimides (e.g., **441e**) undergo photoaddition to 2-phenylazirines (Scheme 48).[244,245]



a. $R = CH_3$; $X = O$
b. $R = Ph$; $X = O$
c. $R = CH_3$; $X = S$
d. $R = Ph$; $X = S$
e. $R = C_6H_4$–2-CH_3; $X = N$–C_6H_4–2-CH_3

Scheme 48 Reaction of isocyanates, isothiocyanates, and carbodiimides with 3,3-dimethyl-2-phenyl-1-azirine under photolytic conditions.

Ketenes react with 2-phenylazirines under thermal conditions (as previously discussed) to give, depending on the structure of the azirine, 1:2 adducts (bicyclic aziridine) or 1:1 adducts (pyrrolinones).[188–190] Photochemically, ketenes add to the nitrile ylides derived from 2-phenylazirines with participation of the C=O bond to give the 3-oxazolines **444**.[246]



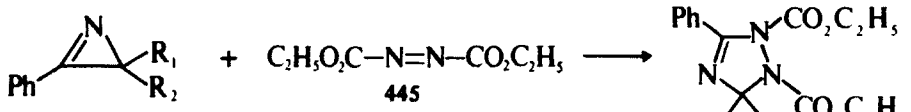
24a	$R_1 = R_2 = H$
3	$R_1 = CH_3$; $R_2 = H$
44h	$R_1 = Ph$; $R_2 = H$
15	$R_1 = R_2 = CH_3$

a. $R_3 = Ph$
b. $R_3 = H$

g. WITH AZO COMPOUNDS

2-Phenylazirines can interact photochemically with the N=N bond of azo compounds. Diethylazodicarboxylate (**445**) has been shown to react with 2-

phenylazirines (**3**, **15**, **24a**, **44h**) under irradiation to give Δ^3-1,2,4-triazolines (**446**) in good yields (*ca.* 50–70%).[247]



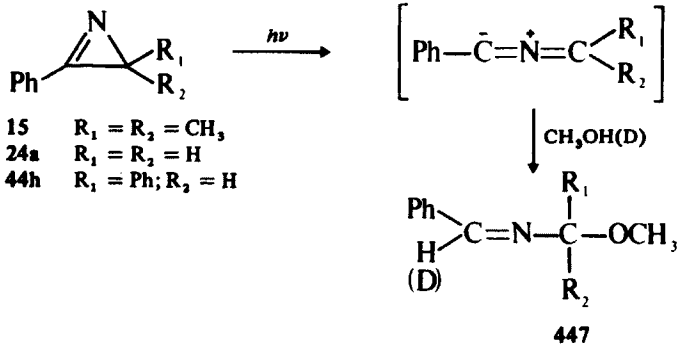
3 $R_1 = CH_3$; $R_2 = H$
15 $R_1 = R_2 = CH_3$
24a $R_1 = R_2 = H$
44h $R_1 = Ph$; $R_2 = H$

445

446

h. WITH ALCOHOLS

When 2-phenylazirines dissolved in methanol are photolyzed, almost quantitative yields of **447** are produced.[248,249] When deuterated methanol (CH_3OD) was used, the corresponding deuterated methoxyimines were produced (Scheme 49). Padwa and Smolanoff[248] suggested that these results provided good experimental evidence that in the HOMO of the nitrile ylide, the electron density at the disubstituted carbon is greater than at the trisubstituted carbon. The usefulness of these results in the explanation of the regiochemical data found in the photoaddition of 2-phenylazirines with dipolarophiles was discussed previously.



15 $R_1 = R_2 = CH_3$
24a $R_1 = R_2 = H$
44h $R_1 = Ph$; $R_2 = H$

447

Scheme 49 Photochemical addition of methanol to 2-phenylazirines.

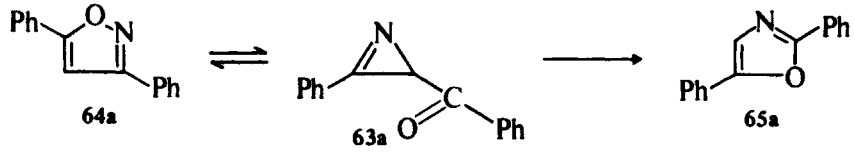
Products arising from initial protonation of the disubstituted carbon atom of these photochemically generated benzonitrile ylides have been observed in cycloadditions with ethyl cyanoacetate[240] and with ethyl acetoacetate.[238]

C. *Intramolecular Photorearrangements*

a. 3-AROYL-2-ARYL-1-AZIRINES

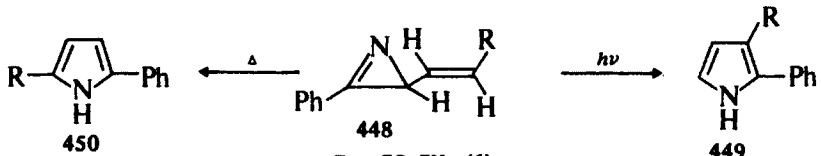
The first example of the intramolecular photochemical rearrangement of an azirine was reported by Ullman and Singh.[13,80,81] They discovered that the photo-

chemical behavior of 3-benzoyl-2-phenyl-1-azirine was markedly dependent on the wavelength of light used in the irradiation. With 3130 Å or shorter wavelength light (e.g., 2537 Å), **63a** rearranged almost quantitatively to the oxazole **65a**, whereas with 3340 Å light, quantitative conversion to the isoxazole **64a** was observed. Each reaction apparently proceeds with virtual exclusion of the other, since spectral monitoring produced nearly perfect isosbestic points. Using emission spectroscopy, sensitization experiments, quenching studies, and MO calculations, Singh and his co-workers[81] showed that a higher energy state associated with the nitrogen $n\pi^*$ transition results in azirine C–C bond cleavage and rearrangement to oxazole, whereas a lower energy excited state associated with the carbonyl $n\pi^*$ transition causes reorganization to the isoxazole.



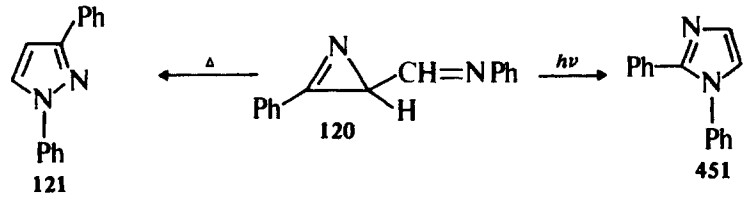
b. 3-VINYL-1-AZIRINES

Intramolecular rearrangement related to the conversion of **63a** to **65a** was reported by Padwa et al.[72,73,250] They found that irradiation of 3-vinyl-substituted azirines (**448**: *E* isomers) gave 2,3-disubstituted pyrroles (**449**). Thermolysis of **448**, however, results in the formation of 2,5-disubstituted pyrroles (**450**), as previously discussed. Photolysis of the 3-iminoazirine **120** gives the 1,2-diphenylimidazole exclusively, whereas its thermolysis affords 1,3-diphenylpyrazole (**121**).

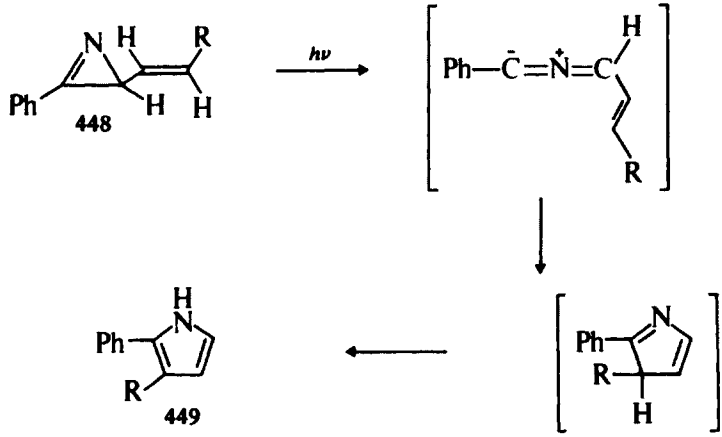


a. R = CO_2CH_3 (6)
b. R = CN
c. R = COPh
d. R = CHO

(**58a–58d**, *E* isomers)

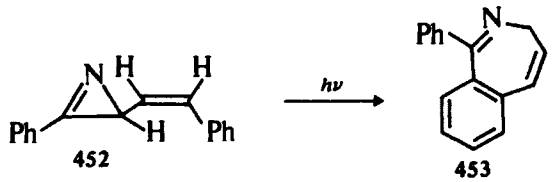


Evidence was provided[73] to support the suggestion that these photorearrangements proceed through the intermediacy of nitrile ylides (Scheme 50). Electrocyclization of the latter followed by a sigmatropic shift or shifts of the initially formed ring would give the observed products.



Scheme 50 Mechanism for the photorearrangement of 3-vinylazirines.

Photolysis of (*Z*)-2-phenyl-3-styryl-1-azirine **452** in contrast gave the benzazepine **453**. The isomeric *trans*-styrylazirine, however, produces 2,3-diphenylpyrrole as the major product. These results suggest that azirine ring cleavage and intramolecular cyclization proceed faster than isomerization of the styryl group. The formation of **453** from **452** also indicates that cyclization of the nitrile ylide from **452** to the seven-membered compound may be a faster process than the alternative cyclization to the five-membered pyrrole ring. Cyclization of the nitrile ylide from the *trans*-styrylazirine to a benzazepine is precluded on structural grounds. With naphthyl vinylazirines however, both (*Z*) and (*E*) isomers gave seven-membered rings, suggesting rapid C=C bond isomerization of the (*E*) isomers before azirine ring opening.[73]



c. 3-ALLYL-1-AZIRINES AND RELATED SYSTEMS

Padwa and Carlsen[29,251,252] examined the photochemistry of 3-allyl-1-azirines, particularly with respect to intramolecular cycloaddition. They reported that photolysis of 3-allyl-3-methyl-2-phenyl-1-azirine (**454a**) gave a 1:1 mixture of

azabicyclohexenes (**456a** and **457a**). On further irradiation, **457a** was quantitatively isomerized to **456a**. When the allylazirine **454b** (**21c**) was irradiated, the azabicyclohexene **456b** was produced as the primary photoproduct. Photolysis of the isomeric 3-allyl-2-methyl-3-phenyl-1-azirine **455a** gave **456a** and **457a**. The azirine **455b** gave the *endo* isomer **456b**, the thermodynamically less favored one, as the exclusive product on irradiation. From control experiments it was determined that azirines **454** and **455** were not being interconverted by a Cope rearrangement during the photolysis. The mechanism for the photoreactions has been proposed to proceed via C–C bond cleavage and generation of a bent nitrile ylide (carbene like) intermediate. Attack of the carbene carbon intramolecularly on the terminal position of the neighboring π bond generates a six-membered ring that may be regarded structurally as either a 1,3-dipole or a 1,3-diradical intermediate. Collapse of this intermediate results in the formation of the observed azabicyclohexenes. The photoconversion of **457** to **456** was explained in terms of the six-membered ring (Scheme 51). Formation of the thermodynamically less favored *endo* isomer **456b** from the irradiation of **454b** or **455b** was attributed to the greater torsional barrier in the transition state for cyclization to the *exo* isomer. Padwa and Carlsen classified these reactions in general terms as nonconcerted 1,1-cycloadditions.

A number of additional examples of these 1,1-cycloadditions, as well as spatial requirements and the role of substituents in controlling intramolecular cycloadditions, have been reported.[115,253-257] Several representative examples are discussed here.

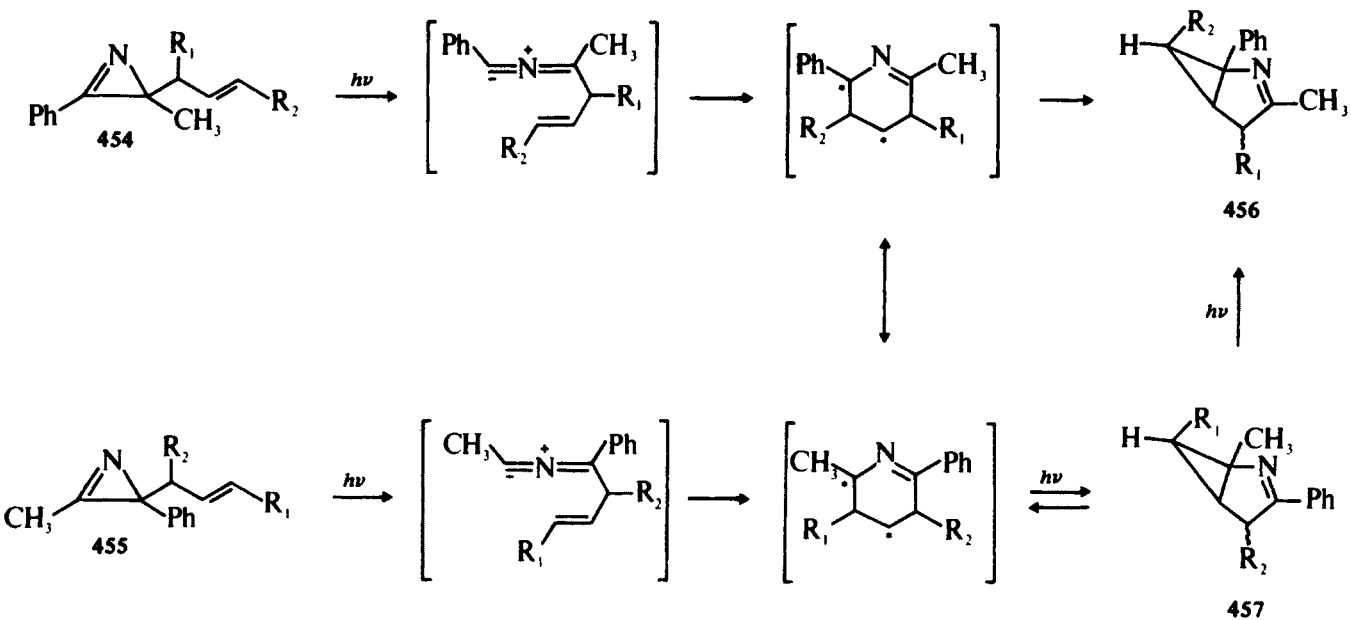
When the number of carbons between the azirine ring and the alkene moiety is increased from one (as in **454** and **455**) to three, 1,3-dipole cycloaddition is favored over the 1,1-cycloaddition. For example, the azirine **458** affords upon irradiation, a single photoproduct, the bicyclic pyrroline **459**.[115] Two interesting aspects of this conversion should be mentioned. First, the regiospecificity is opposite to that which would be expected on the basis of frontier orbital arguments. Padwa and Kamigata[115] attributed this change in regiospecificity to steric factors. Second, this intramolecular cyclization involves the cycloaddition of a nitrile ylide with an unactivated alkene, a substrate that is generally unreactive toward nitrile ylides in intermolecular cycloadditions.

The *o*-2-butenylphenyl-substituted 1-azirine **460**, however, gave a mixture of the *endo*- and *exo*-benzobicyclohexenes **462**, the product of 1,1-cycloaddition of the nitrile ylide **461**, in quantitative yield.[254,255]

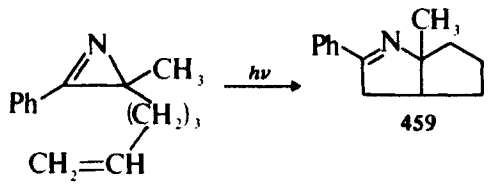
The mode of cyclization of the related *o*-allyloxyphenyl-substituted azirine **463** appears to be markedly controlled by the nature of the substituent groups attached to carbon-3 of the azirine.[256]

D. *Miscellaneous Photoreactions*

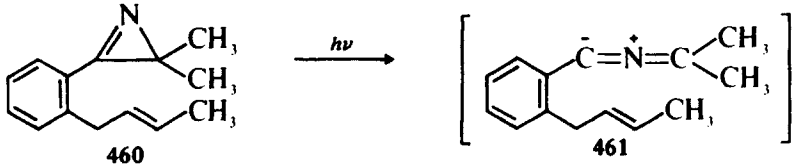
A number of other reactions of 2-phenylazirines induced by light have been investigated. For example, photolysis of a series of 3-hydroxymethyl-2-phenyl-1-azirine derivatives (**464**) was found to give 1-substituted 1-phenyl-2-azabutadienes



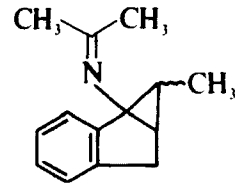
Scheme 51 Mechanism of formation of azabicyclohexenes from the photolysis of 3-allylazirines: asteriks indicates + or —. (Adapted from reference 29 with permission from the American Chemical Society.)



458 459



460 461



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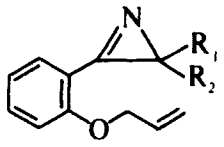
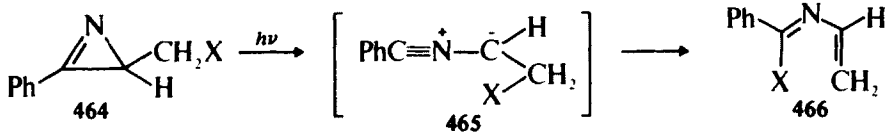


463

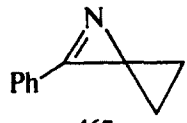
(**466**) in excellent yields. The conversion involves a 1,4-shift of the substituent X. The rate of the rearrangement was found to be directly related to the leaving group ability of X.[258]



464 465 466

X = Cl, Br, $OCOCH_3$, $OCOCF_3$, OCOAr

The photochemistry of the spiroazirine **467** has been reported.[249,259]



467

E. *Concluding General Remarks on the Photochemistry of 1-Azirines*

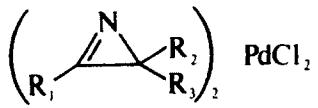
Spectroscopic data, sensitization and quenching experiments, MO calculations, and photoproduct analysis provide remarkably convincing evidence that 1-azirines, and particularly 2-phenyl-1-azirines, undergo photoreactions through initial 2–3 bond cleavage of the first excited $n\pi^*$ singlet state. This ring cleavage, which is photochemically reversible, produces a nitrile ylide that is the reactive participant in almost all the photochemical reactions, both intermolecular and intramolecular, discussed in this chapter. We have seen that the benzonitrile ylides derived from 2-phenylazirines can participate regiospecifically as 4π components in thermal 1,3-dipolar cycloadditions with species such as electron-deficient alkenes, as well as with carbonyl compounds, nitriles, imines, activated esters, azo compounds, and heterocumulenes. The benzonitrile ylides can also participate in thermal intramolecular reorganization processes such as 1,1-cycloadditions and 1,3-dipolar cyclizations. Ample precedent for some of these reactions can be found in the superb contributions of Huisgen and his co-workers on the chemistry of thermally generated nitrile ylides. The photochemical reactions of 1-azirines provide excellent routes to the synthesis of a wide variety of heterocyclic systems, particularly five-membered ring heterocycles.

6. Metal Complexes and Metal-Induced Reactions of 1-Azirines

The synthesis of metal-coordinated 1-azirines and the reactions of 1-azirines induced by metals have opened a new area in the chemistry of this small ring heterocycle. The mechanistic aspects of most of these reactions are not well understood. However, as this section of the chapter unfolds it will become apparent that many of the reactions mentioned here resemble previously discussed thermal and photochemical reactions of 1-azirines. Reactions of 1-azirines with some organometallic reagents (e.g., Grignard reagents, lithium aluminum hydride) and in the Reformatsky reaction were reviewed in an earlier part of this chapter.

A. *Synthesis of Stable Metal Complexes of 1-Azirines*

The synthesis of stable 2:1 complexes of 1-azirines with $AgSbF_6$, H_2PtCl_6, and $PdCl_2$ was achieved as early as 1971.[160b] The structure of the palladium and platinum complexes of azirines was elucidated by Hassner, Bunnell, and Haltiwanger[260] and confirmed by x-ray crystallography. These studies revealed coordination of the nitrogen of the azirine with palladium in a 2:1 azirine/$PdCl_2$ complex with a *trans* configuration about the planar palladium. It is of interest to compare these x-ray data with those reported recently for an uncomplexed 1-azirine.[275] Furthermore, the ir spectra of the series of 1-azirine–palladium chloride complexes **468** reported by Hassner et al.[260] showed strong C=N absorption bands in the 1760–1810 cm^{-1} region. This represents shifts of 30–40 cm^{-1} toward higher energy on complexation.



468

a. $R_1 = p\text{-}CH_3\text{–}C_6H_4$; $R_2 = R_3 = H$
b. $R_1 = p\text{-}OCH_3\text{–}C_6H_4$; $R_2 = R_3 = H$
c. $R_1 = Ph$; $R_2 = R_3 = CH_3$
d. $R_1 = Ph$; $R_2 = CH_3$; $R_3 = H$
e. $R_1 = Ph$; $R_2 = CO_2CH_3$; $R_3 = H$
f. $R_1 = Ph$; $R_2 = CH(OCH_3)_2$; $R_3 = H$
g. $R_1 = Ph$; $R_2 = CH_2OH$; $R_3 = H$
h. $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$

These palladium complexes were found to exhibit relatively high stability toward air, moisture, and uv light. Thermolysis gave a complex mixture of products.

Stable zinc complexes of 2-amino-1-azirines have been reported.[261]

B. *Metal-Induced Reactions*

a. INSERTION REACTIONS

Alper and Prickett[262,263] studied the reaction of a series of azirines with diiron enneacarbonyl in benzene. They found that azirines undergo coupling and insertion reactions under these conditions to give diimine complexes (**469**) and ureadiiron complexes (**470, 471**), as well as pyrroles and ketones. The yields of the diiron complexes **469–471** from three commonly encountered azirines are shown in Table 10. A mechanism for the formation of these products, which involves initial 1,3-bond cleavage and generation of a nitrene–iron carbonyl complex as intermediate, was proposed.

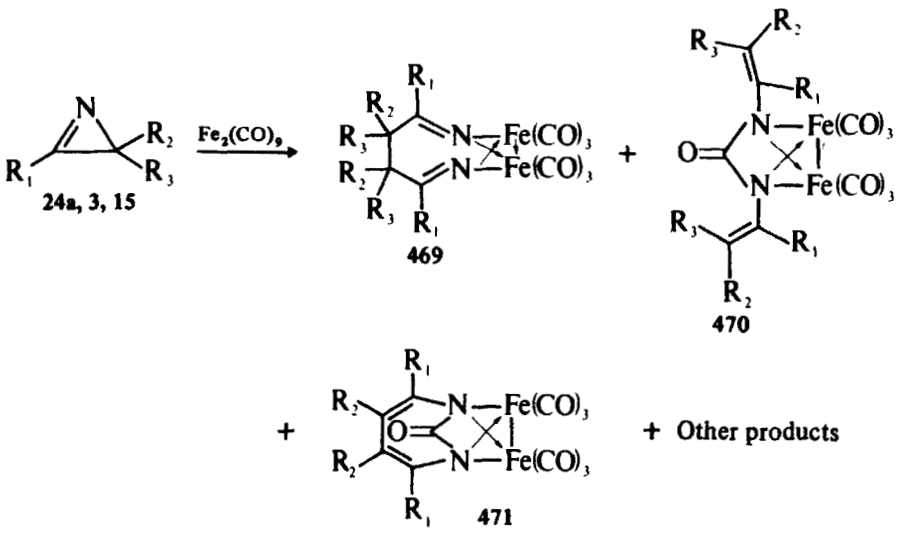
A related study was reported more recently by Schmid, Heimgartner, and their co-workers.[264]

b. DIMERIZATIONS

Reaction of 2-aryl-1-azirines with an equimolar amount of a group 6 metal carbonyl [$M(CO)_6$, M = Cr, Mo, W] gives 2,5-diarylpyrazines and isomeric dihydropyrazines in good yields (Scheme 52).[265,266] Conversion of 2-arylazirines

TABLE 10. YIELDS OF INSERTION AND COUPLING PRODUCTS 469–471 IN THE REACTION OF 1-AZIRINES WITH $Fe_2(CO)_9$

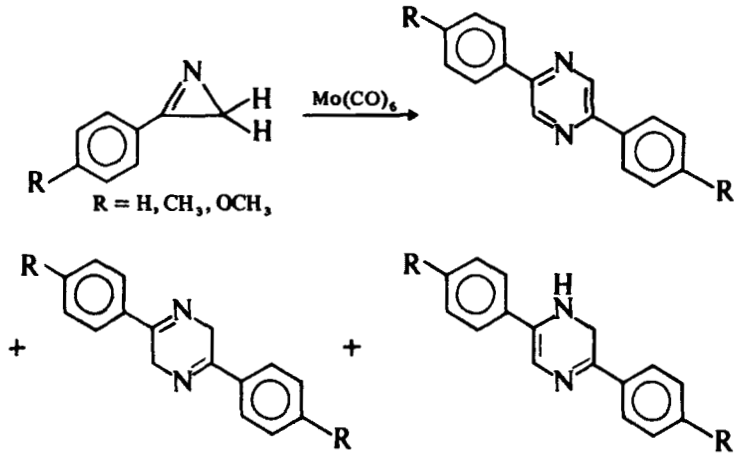
Azirine		Product	Yield (%)
24a	$R_1 = Ph$; $R_2 = H$; $R_3 = H$	**469**	7.8
		470	1.0
		471	3.0
3	$R_1 = Ph$; $R_2 = CH_3$; $R_3 = H$	**470**	9.1
15	$R_1 = Ph$; $R_2 = CH_3$; $R_3 = CH_3$	**470**	18.8



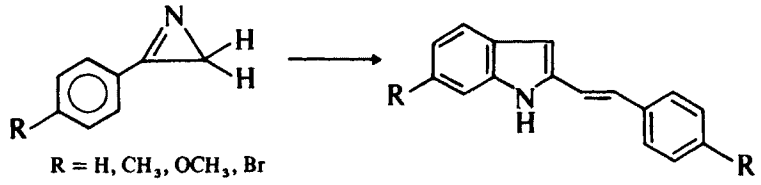
to 2,5-diarylpyrazines also has been reported.[267] The mechanisms of these reactions are poorly understood. It is interesting to compare these metal-induced dimerizations with the mechanistically well-established photochemical dimerizations of 1-azirines.

Dimerization reactions of 1-azirines with other transition metal compounds have been studied.[268]

Alper and Prickett[269,270] reported that 2-arylazirines can be converted to 2-styrylindoles with rhodium carbonyl compounds {e.g., $[Rh(CO)_2Cl]_2$ or $[(Ph_3P)_2Rh(CO)Cl]$} or with dicobalt octacarbonyl in benzene at room temperature (Scheme 53). The mechanism of this transformation is not understood. Although not formally a dimerization, the reaction is mentioned here mainly for convenience in presentation.



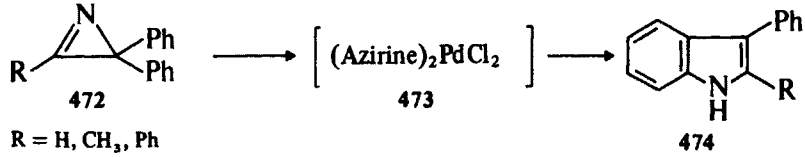
Scheme 52 Dimerization of 2-arylazirines induced by molybdenum hexacarbonyl.



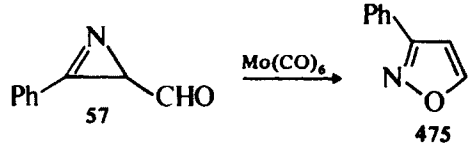
Scheme 53 Intramolecular cyclization of 2-arylazirines by $[Rh(CO)_2Cl]_2$ and $Co_2(CO)_8$.

c. INTRAMOLECULAR CYCLIZATIONS

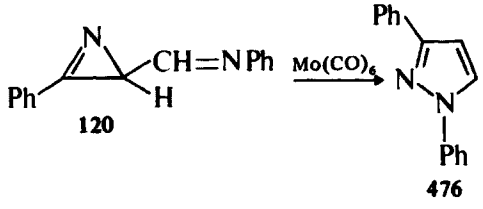
Taniguchi and his co-workers[271] showed that treatment of 1-azirines (**472**) with catalytic amounts of dichlorobis(benzonitrile)-palladium(II) at room temperature gave quantitative yields of the indoles **474**. These transformations presumably proceed through the intermediacy of the 2:1 azirine–palladium chloride complex **473**. Conversion of these azirines to indoles under uncatalyzed thermolytic conditions provides a mechanistically interesting comparison with the Pd(II)-catalyzed conversions. The C–N bond cleavage in the latter is apparently accelerated as a result of the coordination of the azirine to palladium. On the other hand, some platinum and palladium complexes of azirines were found to be extremely stable.[260]



When 3-formyl-2-phenyl-1-azirine (**57**) was treated with $Mo(CO)_6$ in tetrahydrofuran at room temperature for 5 hr, 3-phenylisoxazole (**475**) was isolated in 81% yield.[266] Photolysis converts **57** to **475** in 70% yield in 75 min. However, conversion of **57** to **475** by thermolysis requires 200° temperatures and reaction times of 3 days.[73]



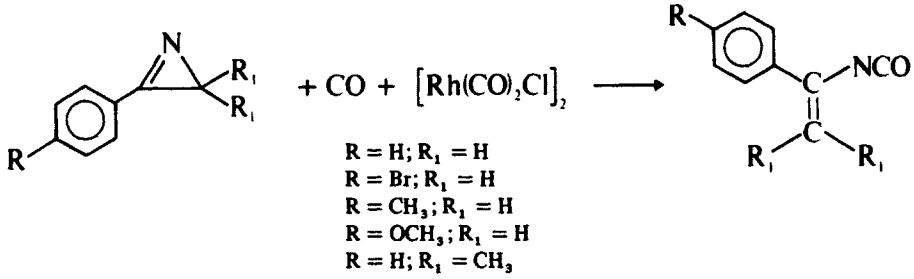
Similarly, 1-azirines with *N*-arylimines at the 3-position (e.g., **120**), were cleanly converted to 1-aryl-3-phenylpyrazoles (e.g., **476**) in high yield by treatment with $Mo(CO)_6$.[266]



d. INTERMOLECULAR ADDITION REACTIONS

The reaction of 1-azirines with activated ketones to give pyrrole derivatives can be catalyzed by nickel(II) compounds. Excellent yields of pyrroles are generally obtained.[144] This and related conversions were discussed previously.

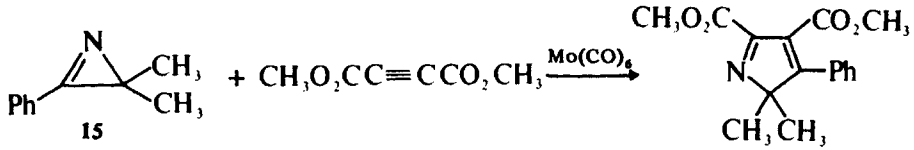
2-Aryl-1-azirines react with carbon monoxide at room temperature in the presence of chlorodicarbonyl rhodium(I) dimer to give isocyanates in yields of the order of 70–80% (Scheme 54). It was suggested that the isocyanates could arise either through carbonylation of a vinyl nitrene–rhodium complex or through carbonylation of a metallocyclic intermediate.[272]



Scheme 54 Carbonylation of 1-azirines catalyzed by rhodium(I).

An azirine-mediated formation of cyclopentadienone dimer from cyclopentadienyliron dicarbonyl dimer has been reported.[273]

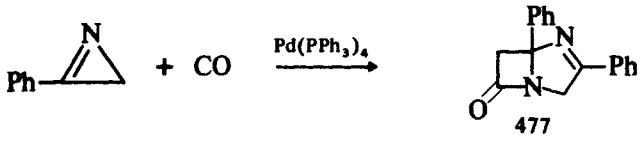
Heimgartner and his co-workers[274] studied the intermolecular cycloaddition of acetylenes with 2-phenylazirines induced by molybdenum hexacarbonyl. They isolated pyrrole derivatives that appear to arise from initial [2 + 2] cycloaddition followed by ring opening (Scheme 55).



Scheme 55 Addition of acetylene carboxylic esters to 2-phenylazirines induced by molybdenum hexacarbonyl.

7. Recent References

Recent work on 1-azirines is included in references 279–287. A noteworthy new development is the Pd catalyzed transformation of azirines to bicyclic β-lactams **477**,[279] as shown below:



VII. TABLES OF SYNTHETIC 1-AZIRINES

Tables 11–15 contain the structures, molecular formulas, melting points, boiling points, and literature references pertaining to preparation of most known 1-azirines. All boiling points given have the relevant pressures accompanying them in parentheses. For convenience in presentation, the compounds are classified according to the substitution at the 2-position of the azirine. These tables contain azirines with a wide range of interesting substituents at the 3-position. Ring-fused and spiroazirines also have been included.

TABLE 11. 2-ARYL-1-AZIRINES

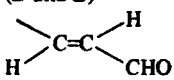
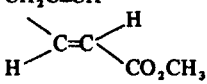
R_1	R_2	R_3	Molecular formula	m.p. or b.p. [°C (mm)]	Ref.
Ph	D	D	$C_8H_5D_2N$	–	82
4-F–C_6H_4	H	H	C_8H_6FN	63–66 (5.5)	43
4-Cl–C_6H_4	H	H	C_8H_6ClN	42.5–44.5	43
4-Br–C_6H_4	H	H	C_8H_6BrN	73–74.5	43
Ph	H	H	C_8H_7N	80 (10)	36
4-CF_3–C_6H_4	H	H	$C_9H_6F_3N$	42–44 (1.2)	43
Ph	CHO	H	C_9H_7NO	45–47	72–74
4-Cl–C_6H_4	CH_3	H	C_9H_8ClN	37–39 (0.05)	91
Ph	CH_3	H	C_9H_9N	96 (15)	8, 30
$PhCH_2$	H	H	C_9H_9N	74 (1.5)	8
4-CH_3–C_6H_4	H	H	C_9H_9N	75–76 (5)	43
4-OCH_3–C_6H_4	H	H	C_9H_9NO	101–102.5 (2.8) 29–31	43
Ph	CH_2OH	H	C_9H_9NO	58–59	249
4-Cl–C_6H_4	CO_2CH_3	H	$C_{10}H_8ClNO_2$	72–73	84
4-NO_2–C_6H_4	CO_2CH_3	H	$C_{10}H_8NO_4$	100	84
Ph	$COCH_3$	H	$C_{10}H_9NO$	–	81
Ph	CO_2CH_3	H	$C_{10}H_9NO_2$	98–102 (1) 45	8, 85
Ph	CH_3	CH_3	$C_{10}H_{11}N$	93.5–95 (15)	28, 122
Ph	CH=CHCN (*E* and *Z*)	H	$C_{11}H_8N_2$	–	73
Ph		H	$C_{11}H_9NO$	–	73
Ph	CH_2CHO	CH_3	$C_{11}H_{11}NO$	25 (0.05)	253
Ph	$CO_2C_2H_5$	H	$C_{11}H_{11}NO_2$	92–95 (0.5)	85
4-CH_3–C_6H_4	CO_2CH_3	H	$C_{11}H_{11}NO_2$	100–105 (0.6)	84
4-OCH_3–C_6H_4	CO_2CH_3	H	$C_{11}H_{11}NO_3$	108–112 (0.5)	84
Ph	CH_3	C_2H_5	$C_{11}H_{13}N$	37–40 (0.1)	91
Ph	$(CH_2)_3OH$	H	$C_{11}H_{13}NO$	–	249
Ph	$CH_2C{\equiv}CH$	CH_3	$C_{12}H_{11}N$	–	253
Ph		H	$C_{12}H_{11}NO_2$	–	73

TABLE 11. CONTINUED

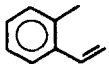
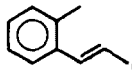
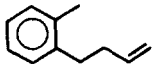
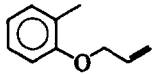
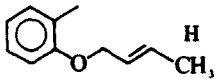
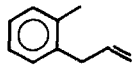
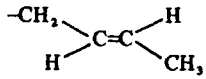
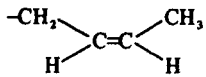
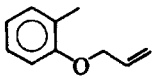
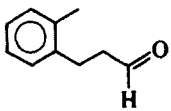
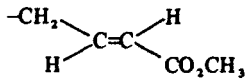
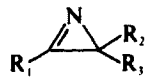
R_1	R_2	R_3	Molecular formula	m.p. or b.p. [°C (mm)]	Ref.
Ph	$-CH=NCH_2CH=CH_2$	H	$C_{12}H_{12}N_2$	–	105
Ph	$CH_2CH=CH_2$	CH_3	$C_{12}H_{13}N$	48–50 (0.04)	29
	CH_3	CH_3	$C_{12}H_{13}N$	43–45 (0.1)	255
	CH_3	H	$C_{12}H_{13}N$	57–60 (0.2)	255
	H	H	$C_{12}H_{13}N$	–	255
Ph	$-(CH_2)_2CHO$	CH_3	$C_{12}H_{13}NO$	–	115
	CH_3	H	$C_{12}H_{13}NO$	70–72 (0.01)	256
	H	H	$C_{12}H_{13}NO$	–	256
Ph	$-CH_2C\equiv CCH_3$	CH_3	$C_{13}H_{13}N$	80–81 (0.03)	33
Ph	$-(CH_2)_2CH=CH_2$	CH_3	$C_{13}H_{15}N$	69–71 (0.04)	115
	CH_3	CH_3	$C_{13}H_{15}N$	43–45 (0.3)	255
Ph	$-CH_2-\overset{CH_3}{\overset{\vert}{C}}=CH_2$	CH_3	$C_{13}H_{15}N$	49 (0.01)	29
Ph	$-\underset{CH_3}{\underset{\vert}{CH}}-CH=CH_2$	CH_3	$C_{13}H_{15}N$	96–97 (4.0)	29
Ph		CH_3	$C_{13}H_{15}N$	63–64 (0.04)	29
Ph		CH_3	$C_{13}H_{15}N$	61–62 (0.1)	29
Ph	$-(CH_2)_3CHO$	CH_3	$C_{13}H_{15}NO$	–	115
	CH_3	CH_3	$C_{13}H_{15}NO$	75–77 (0.2)	256
	CH_3	CH_3	$C_{13}H_{15}NO$	–	255
Ph	$-CO_2(CH_2)_3CH_3$	H	$C_{13}H_{15}NO_2$	100–103 (0.5)	85
Ph	Ph	H	$C_{14}H_{11}N$	59–61	39
Ph		CH_3	$C_{14}N_{15}NO_2$	–	253

TABLE 12. 2-ALKYL- AND 2-ARALKYL-1-AZIRINES



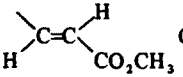
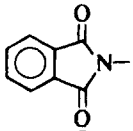
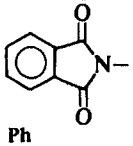
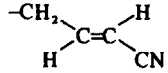
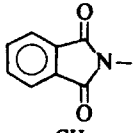
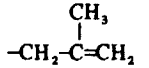
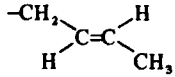
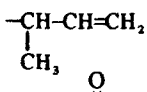
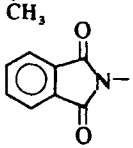
R_1	R_2	R_3	Molecular formula	m.p. or b.p. [°C (mm)]	Ref.
CH_3	H	H	C_3H_5N	42–43 (760)	82
F	CF_3	F	C_3F_5N	–	65, 66
CF_3	F	F	C_3F_5N	–	65, 66
C_2H_5	CH_3	Cl	C_5H_8ClN	–	71
CH_3	C_2H_5	Cl	C_5H_8ClN	–	71
CH_3	$CO_2C_2H_5$	H	$C_6H_9NO_2$	80–90 (70)	37
n-Bu	H	H	$C_6H_{11}N$	57 (54)	36
t-Bu	H	H	$C_6H_{11}N$	80 (760)	82
C_2H_5	C_2H_5	H	$C_6H_{11}N$	68 (130)	8
	CH_3	H	$C_7H_9NO_2$	–	75
CH_3	CH_3	$CO_2C_2H_5$	$C_7H_{11}NO_2$	95 (32)	37
CH_3		H	$C_{10}H_9NO$	40–41	81
$PhCH_2CH_2$	H	H	$C_{10}H_{11}N$	108–110 (10)	8
CH_3		H	$C_{11}H_8N_2O_2$	131	100
CH_3		CH_3	$C_{12}H_{10}N_2O_2$	78	100
CH_3	Ph	CH_2–CH=CH_2	$C_{12}H_{13}N$	52–53 (0.04)	29
CH_3		Ph	$C_{13}H_{12}N_2$	85 (0.02)	253
$CH_3CH_2CH_2$–		H	$C_{13}H_{12}N_2O_2$	46–47	100
CH_3		Ph	$C_{13}H_{15}N$	61–62 (0.05)	29
CH_3		Ph	$C_{13}H_{15}N$	66–67 (0.05)	29
CH_3		Ph	$C_{13}H_{15}N$	54–55 (0.05)	29
C_2H_5		C_2H_5	$C_{14}H_{14}N_2O_2$	–	100

TABLE 12. CONTINUED

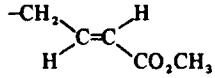
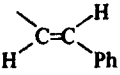
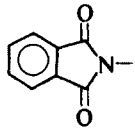
R_1	R_2	R_3	Molecular formula	m.p. or b.p. [°C (mm)]	Ref.
CH_3		Ph	$C_{14}H_{15}NO_2$	–	253
	Ph	H	$C_{16}H_{13}N$	67–68	75
CH_3		Ph	$C_{17}H_{12}N_2O_2$	119–120	102
C_8H_{17}	C_8H_{17}	H	$C_{18}H_{35}N$	121 (0.2)	70
$C_7H_{14}CO_2CH_3$	C_8H_{17}	H	$C_{19}H_{35}NO_2$	–	70
C_8H_{17}	$C_7H_{14}CO_2CH_3$	H	$C_{19}H_{35}NO_2$	–	70

TABLE 13. 2-AMINO-1-AZIRINES

R_1	R_2	R_3	Molecular formula	m.p. or b.p. [°C (mm)]	Ref.
	CH_3	CH_3	$C_6H_{12}N$	–	76, 196b
	$-CH=CH_2$	CH_3	$C_7H_{12}N_2$	–	196b
	CH_3	CH_3	$C_8H_{16}N_2$	42 (1)	76
	CH_3	CH_3	$C_9H_{16}N_2$	48–49 (0.3)	76
	CH_3	H	$C_{10}H_{12}N_2$	71–74 (0.2)	78
	$-(CH_2)_5-$		$C_{11}H_{20}N_2$	62–63 (0.2)	76
	C_2H_5	Ph	$C_{12}H_{16}N_2$	–	196b
	Ph	H	$C_{15}H_{14}N_2$	94–96	78

TABLE 14. 2-UNSUBSTITUTED 1-AZIRINES

R_1	R_2	R_3	Molecular formula	m.p. or b.p. [°C (mm)]	Ref.
H	H	H	C_2H_3N	–	63
H	C_3H_7	H	C_5H_9N	–	9
H	C_2H_5	C_2H_5	$C_6H_{11}N$	61–62 (110)	9
H	Ph	H	C_8H_7N	–	49
H	C_3H_7	C_3H_7	$C_8H_{15}N$	63–64 (24)	276
H	Ph	CH_3	C_9H_9N	73–74 (3)	16
H	PhCH=CH– (*E* isomer)	H	$C_{10}H_9N$	–	104
H	PhCO	CH_3	$C_{10}H_9NO$	–	278
H	$PhCH_2CH_2$	H	$C_{10}H_{11}N$	–	9
H	Ph	C_2H_5	$C_{10}H_{11}N$	52–53 (1)	9
H	Ph	C_3H_7	$C_{11}H_{13}N$	80–82 (0.1)	277
H	Ph	Ph	$C_{14}H_{11}N$	–	9

TABLE 15. RING-FUSED AND SPIRO-1-AZIRINES, BIS-1-AZIRINES

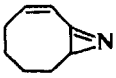
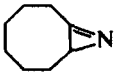
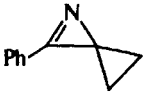
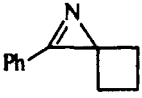
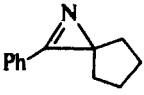
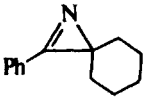
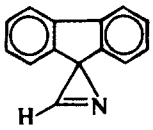
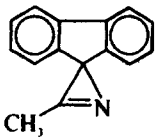
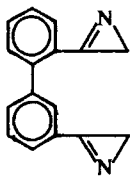
	Molecular formula	m.p. or b.p. [°C (mm)]	Ref.
	$C_8H_{11}N$	38 (0.2)	8
	$C_8H_{13}N$	76 (20)	8
	$C_{10}H_9N$	42–45 (0.1)	91
	$C_{11}H_{11}N$	–	249
	$C_{12}H_{13}N$	59–60 (0.1 mm)	249
	$C_{13}H_{15}N$	–	24

TABLE 15. CONTINUED

	Molecular formula	m.p. or b.p. [°C (mm)]	Ref.
	$C_{14}H_9N$	83–85 (decomp.)	48
	$C_{15}H_{11}N$	97–99	54
	$C_{16}H_{12}N_2$	84–85	96

VIII. REFERENCES

1. A. Streitwieser, Jr., *Molecular Orbital Theory for Organic Chemists*, Wiley, New York, 1961, pp. 117–135.
2. F. W. Fowler and A. Hassner, *J. Am. Chem. Soc.*, **90**, 2875 (1968).
3. (a) R. Breslow, J. Brown, and J. J. Gajewski, *J. Am. Chem. Soc.*, **89**, 4383 (1967); (b) R. Breslow, *Angew. Chem., Int. Ed. Engl.*, **7**, 565 (1968).
4. (a) A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, *Pure Appl. Chem.*, **33**, 339 1973; (b) P. Claus, T. Doppler, N. Gakis, M. Georgarakis, H. Giezendanner, P. Gilgen, H. Heimgartner, B. Jackson, M. Barky, N. S. Narashimhan, H. J. Rosenkranz, A. Wunderli, J. H. Hansen, and H. Smith, *ibid.*, **33**, 339 (1973); (c) A. Hassner, *Heterocycles*, **14**, 1517 (1980).
5. A. M. Patterson, "The Ring Index," American Chemical Society, Washington, D.C., 1960.
6. W. A. Lathan, L. Radom, P. C. Hariharan, W. J. Hehre, and J. A. Pople, in *Topics in Current Chemistry*, Vol. 40, Springer-Verlag, Berlin, 1973, pp. 1–45.
7. D. T. Clark, *Theor. Chim. Acta*, **15**, 225 (1969).
8. A. Hassner and F. W. Fowler, *J. Am. Chem. Soc.*, **90**, 2869 (1968).
9. K. Isomura, M. Okada, and H. Taniguchi, *Tetrahedron Lett.*, 4073 (1969).
10. L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Wiley, New York, 1975.
11. G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962).
12. P. Gilgen, H. Heimgartner, H. Schmid, and H. -J. Hansen, *Heterocycles*, **6**, 152 (1977).
13. B. Singh and E. F. Ullman, *J. Am. Chem. Soc.*, **89**, 6911 (1967).

14. J. B. Lambert, H. F. Shurvell, L. Verbit, R. G. Cooks, and G. H. Stout, *Organic Structural Analysis*, Macmillan, New York, 1976.
15. V. Nair, *Org. Magn. Reson.*, **6**, 483 (1974).
16. K. Isomura, H. Taniguchi, M. Mishima, M. Fujio, and Y. Tsuno, *Org. Magn. Reson.*, **9**, 559 (1977).
17. O. A. Subbotin, A. S. Kozumin, Y. K. Grishin, N. M. Sergeyev, and I. G. Bolesov, *Org. Magn. Reson.*, **4**, 53 (1972).
18. S. G. Davies and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 2*, 861 (1975).
19. R. Martino, P. Mison, F. W. Wehrli, and T. Wirthlin, *Org. Magn. Reson.*, 7, 175 (1975).
20. J. D. Roberts, *Angew. Chem., Int. Ed. Engl.*, **2**, 53 (1963).
21. N. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31**, 768 (1959).
22. J. N. Shoolery, *J. Chem. Phys.*, **31**, 1427 (1959).
23. D. Peters, *Tetrahedron*, **19**, 1539 (1963).
24. S. Sato, *Bull. Chem. Soc. Jpn.*, **41**, 1440 (1968).
25. P. W. Neber and A. Burgard, *Liebigs Ann. Chem.*, **493**, 281 (1932).
26. P. W. Neber and G. Huh, *Liebigs Ann. Chem.*, **515**, 283 (1935).
27. D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33, 38 (1953).
28. R. F. Parcell, *Chem. Ind. (London)*, 1396 (1963).
29. A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, **99**, 1514 (1977).
30. V. Nair, *J. Org. Chem.*, **33**, 2121 (1968).
31. D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 579 (1965).
32. D. F. Morrow and M. E. Butler, *J. Heterocycl. Chem.*, **1**, 53 (1964).
33. A. Padwa and P. H. J. Carlsen, *J. Org. Chem.*, **43**, 2029 (1978).
34. K. R. Henery-Logan and T. L. Fridinger, *J. Am. Chem. Soc.*, **89**, 5724 (1967).
35. G. Smolinsky, *J. Am. Chem. Soc.*, **83**, 4483 (1961).
36. G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962).
37. G. R. Harvey and K. W. Ratts, *J. Org. Chem.*, **31**, 3907 (1966).
38. A. Hassner and L. A. Levy, *J. Am. Chem. Soc.*, **87**, 4203 (1965).
39. F. W. Fowler, A. Hassner, and L. A. Levy, *J. Am. Chem. Soc.*, **89**, 2077 (1967).
40. A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968).
41. V. Nair, unpublished observations.
42. V. Nair and K. H. Kim, *Heterocycles*, **7**, 353 (1977).
43. A. G. Hortmann, D. A. Robertson, and B. A. Gillard, *J. Org. Chem.*, **37**, 322 (1972).
44. M. Rens and L. Ghosez, *Tetrahedron Lett.*, 3765 (1970).
45. M. Komatsu, S. Ichijima, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, **38**, 4341 (1973).
46. L. Horner, A. Christman, and A. Grass, *Chem. Ber.*, **96**, 399 (1963).
47. A. Hassner and F. W. Fowler, *Tetrahedron Lett.*, 1545 (1967).
48. W. Bauer and K. Hafner, *Angew. Chem., Int. Ed. Engl.*, **8**, 772 (1969).
49. K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 3499 (1968).
50. A. Hassner and V. Alexanian, in R. B. Mitra, N. R. Ayangar, V. N. Gogte, R. M. Acheson, and N. Cromwell, Eds., *New Trends in Heterocyclic Chemistry*, Elsevier, Amsterdam, 1979, pp. 178–201.
51. A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).
52. A. Hassner and F. P. Boerwinkle, *J. Am. Chem. Soc.*, **90**, 216 (1968).
53. F. W. Fowler, in A. R. Katritzky, Ed., *Advances in Heterocyclic Chemistry*, Vol. 13, Academic Press, New York, 1971, pp. 45–76.

54. G. Smolinsky and C. A. Pryde, *J. Org. Chem.*, **33**, 2411 (1968).
55. A. N. Nesmeyanov and M. I. Rybinskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 816 (1962).
56. S. Maiorana, *Ann. Chim.*, **56**, 1531 (1966).
57. V. G. Ostroverkhov and E. A. Shilov, *Ukr. Khim. Zh.*, **23**, 615 (1957); *Chem. Abstr.*, **52**, 7828d (1958).
58. D. Knittel, H. Hemetsberger, and H. Weidman, *Monatsh. Chem.*, **101**, 157 (1970).
59. H. Hemetsberger, D. Knittel, and H. Weidman, *Monatsh. Chem.*, **100**, 599 (1969).
60. H. Hemetsberger, D. Knittel, and H. Weidman, *Monatsh. Chem.*, **101**, 161 (1970).
61. W. Lwowski, *Nitrenes*, Wiley-Interscience, New York, 1970.
62. R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 797 (1969).
63. R. G. Ford, *J. Am. Chem. Soc.*, **99**, 2389 (1977).
64. I. L. Knunyants and E. G. Bykhovskaya, *Dokl. Akad. Nauk SSSR*, **131**, 1338 (1960).
65. C. S. Cleaver and C. G. Krespan, *J. Am. Chem. Soc.*, **87**, 3716 (1965).
66. R. E. Banks and G. J. Moore, *J. Chem. Soc., C*, 2304 (1966).
67. V. Nair and K. H. Kim, *J. Heterocycl. Chem.*, **13**, 873 (1976).
68. J. H. Boyer, W. E. Kruger, and R. Modler, *Tetrahedron Lett.*, 5979 (1968).
69. J. H. Boyer, W. E. Kruger, and G. J. Mikole, *J. Am. Chem. Soc.*, **89**, 5504 (1967).
70. T. A. Foglia, P. A. Barr, and G. Maerker, *J. Am. Oil Chem. Soc.*, **49**, 414 (1972).
71. J. Ciabattoni and M. Cabell, Jr., *J. Am. Chem. Soc.*, **93**, 1482 (1971).
72. A. Padwa, J. Smolanoff, and A. Tremper, *Tetrahedron Lett.*, 29 (1974).
73. A. Padwa, J. Smolanoff, and A. Tremper, *J. Am. Chem. Soc.*, **97**, 4682 (1975).
74. A. Padwa, T. Blacklock, and A. Tremper, in C. R. Johnson, Ed., *Organic Synthesis*, Vol. 57, Wiley, New York, 1977, pp. 83–87.
75. A. Hassner and J. Keogh, *Tetrahedron Lett.*, 1575 (1975).
76. M. Rens and L. Ghosez, *Tetrahedron Lett.*, 3765 (1970).
77. L. Ghosez, A. Demoulin, M. Henriet, E. Sonveaux, M. Van Meerssche, G. Germain, and J. P. Declercq, *Heterocycles*, **7**, 895 (1977).
78. M. Henriet, M. Houtekie, B. Techy, R. Touillaux, and L. Ghosez, *Tetrahedron Lett.*, **21**, 223 (1980).
79. M. Komatsu, S. Ichijima, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, **38**, 4341 (1973).
80. E. F. Ullman and B. Singh, *J. Am. Chem. Soc.*, **88**, 1844 (1966).
81. B. Singh, A. Zweig, and J. B. Gallivan, *J. Am. Chem. Soc.*, **94**, 1199 (1972).
82. A. Hassner and V. Alexanian, *J. Org. Chem.*, **44**, 3861 (1979).
83. D. W. Kurtz and H. Shechter, *J. Chem. Soc., Chem. Commun.*, 689 (1966).
84. T. Nishiwaki, T. Kitimura, and A. Nakano, *Tetrahedron*, **26**, 453 (1970).
85. T. Nishiwaki, *Tetrahedron Lett.*, **25**, 2049 (1969).
86. J. P. Ferris and R. W. Trimmer, *J. Org. Chem.*, **41**, 13 (1976).
87. K. H. Grellmann and E. Tauer, *J. Photochem.*, **6**, 365 (1977).
88. R. Huisgen and J. Wulff, *Tetrahedron Lett.*, 917 (1967).
89. R. Huisgen and J. Wulff, *Chem. Ber.*, **102**, 1833 (1969).
90. H. J. Bestmann and R. Kunstmann, *Angew. Chem., Int. Ed. Engl.*, **5**, 1039 (1966).
91. H. J. Bestmann and R. Kunstmann, *Chem. Ber.*, **102**, 1816 (1969).
92. G. J. DeVoghel, T. L. Eggerichs, B. Clamont, and H. G. Viehe, *Chimia*, **30**, 192 (1976).
93. H. Koenig, H. Metzger, and K. Seelert, *Chem. Abstr.*, **64**, 17409 (1966).
94. S. Yamada, T. Mizoguichi, and A. Ayata, *J. Pharm. Soc. Jpn.*, **77**, 452 (1957).

95. D. J. Anderson, T. L. Gilchrist, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 147 (1969).
96. A. Padwa, A. Ku, H. Ku, and A. Mazzu, *J. Org. Chem.*, **43**, 66 (1978).
97. R. Huisgen and H. Blaschke, *Chem. Ber.*, **98**, 2985 (1965).
98. J. Meinwald and D. H. Aue, *J. Am. Chem. Soc.*, **88**, 2849 (1966).
99. E. M. Burgess, R. Carithers, and L. McCullagh, *J. Am. Chem. Soc.*, **90**, 1923 (1968).
100. D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 550 (1973).
101. (a) T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1519 (1971); (b) T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 555 (1973).
102. A. C. Hopkinson, M. A. Lien, K. Yates and J. G. Csizmadia, *Intern. J. Quantum Chem.*, **12**, 355 (1977).
103. H. Taniguchi, K. Isomura, and T. Tanaka, *Heterocycles*, **6**, 1563 (1977).
104. K. Isomura, M. Okada, and H. Taniguchi, *Chem. Lett.*, 629 (1972).
105. A. Padwa, J. Smolanoff, and A. Tremper, *J. Org. Chem.*, **41**, 543 (1976).
106. M. Regitz, B. Arnold, D. Danion, H. Schubert, and G. Fusser, *Bull. Soc. Chim. Belg.*, **90**, 615 (1981).
107. D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1518 (1971).
108. T. Nishiwaki, *Tetrahedron Lett.*, 2049 (1969).
109. T. Nishiwaki, A. Nakano, and H. Matsuoka, *J. Chem. Soc., C*, 1825 (1970).
110. K. Isomura, T. Tanaka, and H. Taniguchi, *Chem. Lett.*, 397 (1977).
111. K. Isomura, H. Taguchi, T. Tanaka, and H. Taniguchi, *Chem. Lett.*, 401 (1977).
112. A. Padwa and P. H. J. Carlsen, *J. Org. Chem.*, **41**, 181 (1976).
113. A. Padwa and P. H. J. Carlsen, *Tetrahedron Lett.*, 433 (1978).
114. A. Padwa and N. Kamigata, *J. Chem. Soc., Chem. Commun.*, 789 (1975).
115. A. Padwa and N. Kamigata, *J. Am. Chem. Soc.*, **99**, 1871 (1977).
116. J. H. Bowie and B. Nussey, *J. Chem. Soc., Perkin Trans. 1*, 1693 (1973).
117. R. Selvarajan and J. H. Boyer, *J. Heterocycl. Chem.*, **9**, 87 (1972).
118. L. A. Wendling and R. G. Bergman, *J. Am. Chem. Soc.*, **96**, 308 (1974).
119. L. A. Wendling and R. G. Bergman, *J. Org. Chem.*, **41**, 831 (1976).
120. A. Demoulin, H. Gorrisen, A. -M. Hesbian-Frisque, and L. Ghosez, *J. Am. Chem. Soc.*, **97**, 4409 (1975).
121. M. I. Rybinskaya, A. N. Nesmeyanov, and N. K. Kochetkov, *Usp. Khim.*, **38**, 961 (1969); *Russ. Chem. Rev.*, **38**, 433 (1969).
122. N. J. Leonard and B. Zwanenburg, *J. Am. Chem. Soc.*, **89**, 4456 (1967).
123. G. Alvernhe, E. Kozlowska-Gramsz, S. Lacombe-Bar, and A. Laurent, *Tetrahedron Lett.*, 5203 (1978).
124. N. Wade and R. Guedj, *Tetrahedron Lett.*, 3247 (1978).
125. G. Alvernhe, S. Lacombe, and A. Laurent, *Tetrahedron Lett.*, **21**, 1437 (1980).
126. S. Sato, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 2938 (1967).
127. B. P. Chandrasekhar, U. Schmid, R. Schmid, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **58**, 1191 (1975).
128. B. P. Chandrasekhar, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **60**, 2270 (1977).
129. H. Bader and H. -J. Hansen, *Helv. Chim. Acta*, **61**, 286 (1978).
130. N. J. Leonard, E. F. Muth, and V. Nair, *J. Org. Chem.*, **32**, 827 (1967).

131. D. St. C. Black and J. E. Doyle, *Aust. J. Chem.*, **31**, 2313 (1978).
132. A. Hassner, S. S. Burke, and J. Cheng-fan I, *J. Am. Chem. Soc.*, **97**, 4692 (1975).
133. S. Sato, *Nippon Kagaku Zasshi*, **90**, 113 (1969); *Chem. Abstr.*, **70**, 96501 (1969).
134. O. C. Dermer and G. E. Ham, *Ethyleneimine and Other Aziridines*, Academic Press, New York, 1969.
135. E. Schaumann, E. Kausch, and W. Walter, *Chem. Ber.*, **108**, 2500 (1975).
136. J. A. Deyrup and W. A. Szabo, *Tetrahedron Lett.*, 1413 (1976).
137. A. Hassner and A. Kascheres, *J. Org. Chem.*, **37**, 2328 (1972).
138. R. E. Moerck and M. A. Battiste, *Tetrahedron Lett.*, 4421 (1973).
139. S. Eguchi and Y. Ishii, *Bull. Chem. Soc. Jpn.*, **36**, 1434 (1963).
140. P. B. Kryczka and A. Laurent, *Tetrahedron Lett.*, 31 (1977).
141. S. Sato, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 2936 (1967).
142. S. Sato, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 1014 (1967).
143. Z. Cebulska and A. Laurent, *Tetrahedron Lett.*, 3939 (1977).
144. P. F. dos Santos Filho and U. Schuchardt, *Angew. Chem., Int. Ed. Engl.*, **16**, 647 (1977).
145. A. G. Hortmann and D. A. Robertson, *J. Am. Chem. Soc.*, **94**, 2758 (1972).
146. R. M. Carlson and S. Y. Lee, *Tetrahedron Lett.*, 4001 (1969).
147. A. Hassner, J. O. Currie, Jr., A. S. Steinfeld, and R. F. Atkinson, *J. Am. Chem. Soc.*, **95**, 2982 (1973).
148. G. Smolinsky and B. Feuer, *J. Org. Chem.*, **31**, 1423 (1966).
149. R. E. Banks, D. Berry, and G. J. Moore, *J. Chem. Soc., C*, 2598 (1969).
150. A. Kakehi, S. Ito, and T. Manabe, *J. Org. Chem.*, **40**, 544 (1975).
151. A. Kakehi, S. Ito, T. Manabe, T. Maeda, and K. Imai, *J. Org. Chem.*, **42**, 2514 (1977).
152. A. Kakehi, S. Ito, T. Manabe, H. Amano, and Y. Shimaoka, *J. Org. Chem.*, **41**, 2739 (1976).
153. H. Link, *Helv. Chim. Acta*, **61**, 2419 (1978).
154. H. Link, K. Bernauer, S. Chaloupka, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **61**, 2116 (1978).
155. S. Chaloupka, P. Vittorelli, H. Heimgartner, H. Schmid, H. Link, K. Bernauer, and W. E. Oberhansli, *Helv. Chim. Acta*, **60**, 2476 (1977).
156. A. Padwa and K. Crosby, *J. Org. Chem.*, **39**, 2651 (1974).
157. T. Nishiwaki and F. Fujiyama, *J. Chem. Soc., Perkin Trans. 1*, 817 (1973).
158. A. Laurent, P. Mison, A. Nafti, and N. Pellissier, *Tetrahedron*, **35**, 2285 (1979).
159. A. Hassner, B. A. Belinka and A. S. Steinfeld, *Heterocycles*, **18**, 179 (1982).
160. (a) V. Nair, 15th Annual Report of the Petroleum Research Fund, administered by the American Chemical Society, Washington, D.C., 1971, p. 128; (b) V. Nair, *J. Org. Chem.*, **37**, 802 (1972).
161. D. J. Anderson and A. Hassner, *J. Am. Chem. Soc.*, **93**, 4339 (1971).
162. A. Hassner and D. J. Anderson, *J. Am. Chem. Soc.*, **94**, 8255 (1972).
163. D. J. Anderson and A. Hassner, *J. Org. Chem.*, **38**, 2565 (1973).
164. D. J. Anderson and A. Hassner, *J. Org. Chem.*, **39**, 3070 (1974).
165. R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 839 (1969).
166. B. Halton, M. A. Battiste, R. Rehberg, C. L. Deyrup, and M. E. Brennan, *J. Am. Chem. Soc.*, **89**, 5964 (1967).
167. S. C. Clarke and B. L. Johnson, *Tetrahedron*, **27**, 3557 (1971).
168. V. Nair, *J. Org. Chem.*, **37**, 2508 (1972).

169. D. J. Anderson and A. Hassner, *J. Org. Chem.*, **39**, 2031 (1974).
170. V. Nair, unpublished observations.
171. H. Hemetsberger and D. Knittel, *Monatsh. Chem.*, **103**, 205 (1972).
172. D. J. Anderson and A. Hassner, *Synthesis*, 483 (1975).
173. M. Takahashi, N. Suzuki, and Y. Igari, *Bull. Chem. Soc. Jpn.*, **48**, 2605 (1975).
174. D. J. Anderson and A. Hassner, *J. Chem. Soc., Chem. Commun.*, 45 (1974).
175. G. C. Johnson and R. H. Levin, *Tetrahedron Lett.*, 2303 (1974).
176. R. E. Moerck and M. A. Battiste, *J. Chem. Soc., Chem. Commun.*, 782 (1974).
177. V. Nair, *J. Heterocycl. Chem.*, **12**, 183 (1975).
178. A. L. Logothetis, *J. Org. Chem.*, **29**, 3049 (1964).
179. V. Nair, *J. Org. Chem.*, **33**, 4316 (1968).
180. A. Gagneux, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, **82**, 5956 (1960).
181. (a) J. H. Bowie, B. Nussey, and A. D. Ward, *Aust. J. Chem.*, **26**, 2547 (1973); (b) A. Hassner and J. S. Teeter, *J. Org. Chem.*, **36**, 2176 (1971).
182. M. Komatsu, N. Nishikaze, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, **41**, 3642 (1976).
183. R. Huisgen, W. Scheer, and H. Huber, *J. Am. Chem. Soc.*, **89**, 1753 (1967).
184. K. Matsumoto and K. Maruyama, *Chem. Lett.*, 759 (1973).
185. N. S. Narasimhan, H. Heimgartner, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 1351 (1973).
186. V. Nair, *Tetrahedron Lett.*, 4831 (1971).
187. J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, Jr., *J. Org. Chem.*, **36**, 2211 (1971), and earlier references mentioned therein.
188. A. Hassner, A. S. Miller, and M. J. Haddadin, *Tetrahedron Lett.*, 1353 (1972).
189. M. J. Haddadin and A. Hassner, *J. Org. Chem.*, **38**, 3466 (1973).
190. A. Hassner, M. J. Haddadin, and A. B. Levy, *Tetrahedron Lett.*, 1015 (1973).
191. G. Mukherjee-Muller, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **62**, 1429 (1979).
192. F. R. Woerner, H. Reimlinger, and R. Merenyi, *Chem. Ber.*, **104**, 2786 (1971).
193. V. Nair and K. H. Kim, *Tetrahedron Lett.*, 1487 (1974).
194. V. Nair and K. H. Kim, *J. Org. Chem.*, **39**, 3763 (1974).
195. H. Ulrich, *Cycloaddition Reactions of Heterocumulenes*, Academic Press, New York, 1967.
196. (a) E. Schaumann, E. Kausch, and W. Walter, *Chem. Ber.*, **107**, 3574 (1974); (b) E. Schaumann, S. Grabley, M. Henriet, L. Ghosez, T. Touillaux, J. P. Declercq, G. Germain, and M. Van Meerssche, *J. Org. Chem.*, **45**, 2951 (1980).
197. K. H. Kim, Ph.D. Thesis, University of Iowa, 1976.
198. V. Nair and K. H. Kim, *J. Heterocycl. Chem.*, **13**, 873 (1976).
199. U. Schmid, H. Heimgartner, H. Schmid, and W. E. Oberhansli, *Helv. Chim. Acta*, **59**, 2768 (1976).
200. E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, Vol. IV, Chemical Publishing Co., New York, 1963.
201. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
202. K. B. Sukumaran, C. S. Angadiyavar, and M. V. George, *Tetrahedron*, **28**, 3987 (1972).
203. V. Nair and K. H. Kim, *J. Org. Chem.*, **40**, 1348 (1975).
204. S. Chaloupka, H. Heimgartner, H. Schmid, H. Link, P. Schonholzer, and K. Bernauer, *Helv. Chim. Acta*, **59**, 2566 (1976).
205. E. Schaumann, S. Grabley, K. -D. Seidel, and E. Kausch, *Tetrahedron Lett.*, 1351 (1977).

206. V. Nair and K. H. Kim, *J. Org. Chem.*, **40**, 3784 (1975).
207. H. Gotthardt and C. M. Weisshuhn, *Chem. Ber.*, **111**, 3171 (1978).
208. J. Lukac, J. H. Bieri, and H. Heimgartner, *Helv. Chim. Acta*, **60**, 1657 (1977).
209. J. Lukac and H. Heimgartner, *Helv. Chim. Acta*, **62**, 1236 (1979).
210. O. Tsuge and M. Noguchi, *Heterocycles*, **9**, 423 (1978).
211. A. Padwa, *Acc. Chem. Res.*, **9**, 371 (1976), and references cited therein.
212. P. Gilgen, H. Heimgartner, H. Schmid, and H. -J. Hansen, *Heterocycles*, **6**, 143 (1977), and references cited therein.
213. U. Gerber, H. Heimgartner, H. Schmid, and W. Heinzelmann, *Helv. Chim. Acta*, **60**, 687 (1977).
214. W. Sieber, P. Gilgen, S. Chaloupka, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 1679 (1973).
215. A. Orahovats, H. Heimgartner, H. Schmid, and W. Heinzelmann, *Helv. Chim. Acta*, **58**, 2662 (1975).
216. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).
217. P. Caramella and K. N. Houk, *J. Am. Chem. Soc.*, **98**, 6397 (1976).
218. L. Salem, *J. Am. Chem. Soc.*, **96**, 3486 (1974).
219. A. Padwa and J. Smolanoff, *J. Am. Chem. Soc.*, **93**, 548 (1971).
220. A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **95**, 1945 (1973).
221. R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).
222. R. Huisgen and P. Eberhard, *Tetrahedron Lett.*, 4337, 4343 (1971).
223. K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975).
224. N. Gakis, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **58**, 748 (1975).
225. N. Gakis, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **57**, 1403 (1974).
226. W. Stegmann, P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **59**, 1018 (1976).
227. A. Padwa, J. Smolanoff, and S. I. Wetmore, Jr., *J. Org. Chem.*, **38**, 1333 (1973).
228. A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *Pure Appl. Chem.*, **33**, 269 (1973).
229. V. Nair, unpublished results.
230. A. Padwa and F. Nobs, *Tetrahedron Lett.*, 93 (1978).
231. F. P. Woerner, H. Reimlinger, and D. Arnold, *Angew. Chem., Int. Ed. Engl.*, **7**, 130 (1968).
232. F. P. Woerner and H. Reimlinger, *Chem. Ber.*, **103**, 1908 (1970).
233. A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **95**, 1954 (1973).
234. A. Padwa and E. Glazer, *J. Am. Chem. Soc.*, **94**, 7788 (1972).
235. H. Giezendanner, M. Marky, B. Jackson, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 745 (1972).
236. H. Giezendanner, H. Heimgartner, B. Jackson, T. Winkler, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 2611 (1973).
237. B. Jackson, M. Marky, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 919 (1972).
238. P. Claus, P. Gilgen, H. -J. Hansen, H. Heimgartner, B. Jackson, and H. Schmid, *Helv. Chim. Acta*, **57**, 2173 (1974).
239. P. Gilgen, B. Jackson, H. -J. Hansen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **57**, 2634 (1974).

240. P. Gilgen, H. -J. Hansen, H. Heimgartner, W. Sieber, P. Uebelhart, H. Schmid, P. Schonholzer, and W. E. Oberhansli, *Helv. Chim. Acta*, **58**, 1739 (1975).

241. A. Orahovats, H. Heimgartner, H. Schmid, and W. Heinzelmann, *Helv. Chim. Acta*, **57**, 2626 (1974).

242. U. Schmid, P. Gilgen, H. Heimgartner, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **57**, 1393 (1974).

243. A. Padwa and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **96**, 2414 (1974).

244. B. Jackson, N. Gakis, M. Marky, H. -J. Hansen, W. von Philipsborn, and H. Schmid, *Helv. Chim. Acta*, **55**, 916 (1972).

245. N. Gakis, M. Marky, H. -J. Hansen, H. Heimgartner, H. Schmid, and W. E. Oberhansli, *Helv. Chim. Acta*, **59**, 2149 (1976).

246. H. Heimgartner, P. Gilgen, U. Schmid, H. -J. Hansen, H. Schmid, K. Pfoertner, and K. Bernauer, *Chimia*, **26**, 424 (1972).

247. P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **57**, 1382 (1974).

248. A. Padwa and J. Smolanoff, *J. Chem. Soc., Chem. Commun.*, 342 (1973).

249. A. Padwa, J. K. Rasmussen, and A. Tremper, *J. Am. Chem. Soc.*, **98**, 2605 (1976).

250. A. Padwa and J. Smolanoff, *Tetrahedron Lett.*, 33 (1974).

251. A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, **97**, 3862 (1975).

252. A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, **98**, 2006 (1976).

253. A. Padwa and P. H. J. Carlsen, *J. Org. Chem.*, **43**, 3757 (1978).

254. A. Padwa, A. Ku, A. Mazzu, and S. I. Wetmore, *J. Am. Chem. Soc.*, **98**, 1048 (1976).

255. A. Padwa and A. Ku, *J. Am. Chem. Soc.*, **100**, 2181 (1978).

256. A. Padwa, P. H. J. Carlsen, and A. Ku, *J. Am. Chem. Soc.*, **100**, 3494 (1978).

257. A. Padwa, H. Ku, and A. Mazzu, *J. Org. Chem.*, **43**, 381 (1978).

258. A. Padwa, P. H. J. Carlsen, and A. Tremper, *J. Am. Chem. Soc.*, **100**, 4481 (1978).

259. A. Padwa and J. K. Rasmussen, *J. Am. Chem. Soc.*, **97**, 5912 (1975).

260. A. Hassner, C. A. Bunnell, and K. Haltwanger, *J. Org. Chem.*, **43**, 57 (1978).

261. K. Dietliker, U. Schmid, G. Mukherjee-Muller, H. Heimgartner, *Chimia*, **32**, 164 (1978).

262. H. Alper and J. E. Prickett, *Inorg. Chem.*, **16**, 67 (1977).

263. H. Alper and J. E. Prickett, *J. Chem. Soc., Chem. Commun.*, 191 (1976).

264. Y. Nakamura, K. Bachmann, H. Heimgartner, H. Schmid, and J. J. Daly, *Helv. Chim. Acta*, **61**, 589 (1978).

265. H. Alper and S. Wollowitz, *J. Am. Chem. Soc.*, **97**, 3541 (1975).

266. H. Alper, J. E. Prickett, and S. Wollowitz, *J. Am. Chem. Soc.*, **99**, 4330 (1977).

267. H. Alper and J. E. Prickett, *J. Chem. Soc., Chem. Commun.*, 983 (1976).

268. K. Hayashi, K. Isomura, and H. Taniguchi, *Chem. Lett.*, 1011 (1975).

269. H. Alper and J. E. Prickett, *J. Chem. Soc., Chem. Commun.*, 483 (1976).

270. H. Alper and J. E. Prickett, *Tetrahedron Lett.*, 2589 (1976).

271. K. Isomura, K. Uto, and H. Taniguchi, *J. Chem. Soc., Chem. Commun.*, 664 (1977).

272. T. Sakakibara and H. Alper, *J. Chem. Soc., Chem. Commun.*, 458 (1979).

273. H. Alper and T. Sakakibara, *Can. J. Chem.*, **57**, 1541 (1979).

274. A. Inada, H. Heimgartner, and H. Schmid, *Tetrahedron Lett.*, 2983 (1979).

275. N. Kanehisa, N. Yasuoka, N. Kasai, K. Isomura and H. Taniguchi, *J. Chem. Soc., Chem. Commun.*, 98 (1980).

276. K. Isomura, M. Shimizu, K. Hirakawa, and H. Taniguchi, *Kobunshi Ronbunshu*, **35**, 621 (1978).

277. H. Taniguchi and K. Isomura, personal communication.
278. K. Isomura, Y. Hirose, H. Shuyama, S. Abe, G. Ayabe, and H. Taniguchi, *Heterocycles*, 9, 1207 (1978).
279. H. Apler and C. P. Perera, *J. Am. Chem. Soc.* 103, 1289 (1981).
280. T. N. Wade and R. Kheribet, *J. Org. Chem.* 45, 5333 (1980).
281. J. A. Hyatt, *J. Org. Chem.* 46, 3953 (1981).
282. T. C. Gallagher and R. C. Storr, *Tetrahedron Lett.* 22, 2905 (1981).
283. T. C. Gallagher and R. C. Storr, *Tetrahedron Lett.* 22, 2909 (1981).
284. H. Alper, *Israel J. Chem.* 21, 203 (1981).
285. H. Heimgartner, *Israel J. Chem.* 21, 151 (1981).
286. S. Kato and K. Morokuma, *Chem. Lett.* 1021 (1981).
287. H. Tanaka, Y. Osamura, T. Matsushita, and K. Nishimoto, *Bull. Chem. Soc. Jpn.*, 54, 1293 (1981).

Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner

CHAPTER III

Three-Membered Rings Containing Sulfur

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I. INTRODUCTION

The history of three-membered rings containing sulfur begins more than 60 years ago with the synthesis of 2,2,3,3-tetraphenylthiirane (common name: tetraphenylethylene sulfide) by Staudinger and Pfenninger.[1,2] Following the preparation of the first pure aliphatic thiirane – ethylene sulfide – by Dele'pine[3] in 1920, the importance of this group of compounds as reactive substances suitable for a variety of chemical transformations was recognized. The chemistry of this class of compounds gained momentum when in 1934 Dachlauer and Jackel discovered a simple method for their synthesis from epoxides and alkali thiocyanates or thiourea.[4] The comprehensive studies conducted by Culvenor and Davies during the late 1940s and early 1950s[5–8] revealed significant and important aspects involved in the chemistry of thiiranes. Several summary or review articles on thiiranes and their chemical reactions were published since then.[9–14] In addition, a book in Russian on the chemistry of thiiranes is available.[14a]

Excluding a few isolated cases of earlier reported preparations of thiirane oxides, thiirane dioxides, and thiiranium salts, the chemistry of these classes of compounds was developed and established within the last two decades, beginning in the early 1960s. It is no wonder that the two comprehensive reviews on thiiranes from 1964[15] and 1966,[16] respectively, deal only with ethylene sulfides (substituted and unsubstituted), *not* with the other members of this class (i.e., thiiranium salts, thiirane oxides, thiirane dioxides, and closely related derivatives).

The principal sections in this chapter deal with thiiranes, thiiranium salts, thiirane oxides, thiirane dioxides, thiirenes, thiirenium ions, thiirene oxides, thiirene dioxides, and three-membered rings containing sulfur and additional heteroatoms. The first three sections not only update the chapter on ethylene sulfides written by Reynolds and Fields in this series in 1964, but also include a comprehensive and a reasonably complete presentation of thiiranes, their quaternary salts and oxides.

The relevant literature, which has been exhaustively covered through most of 1979, includes the literature pertaining to three-membered rings containing sulfur cited in *Chemical Abstracts* up to August 1979, and in *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Journal of the Chemical Society*, *Tetrahedron Letters*, and *Tetrahedron* up to the same date. In addition a "Highlights" section at the end of this chapter updates the chapter with important more recently published material.

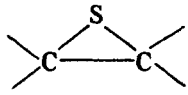
I thank my friends and colleagues for their encouragement. I am particularly grateful for the typing assistance provided by the Research Authority of Haifa University in Israel.

Most of all, I express my love for my family, my gratitude and appreciation for their being so helpful and encouraging, and my admiration for their patience while this work claimed most of my time and attention.

II. NOMENCLATURE

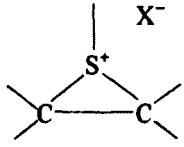
The International Union of Pure and Applied Chemistry (IUPAC) uses the name "thiirane" for a three-membered ring comprising one sulfur atom. However, many other designations had been used for this class of compounds and still are widely used in naming specific compounds. These include sulfides (e.g., the parent ethylene sulfide), alkene sulfides, episulfides, thiacyclopropanes, and thioalkylene oxides.

Thiirane has the general structure shown in **1**.

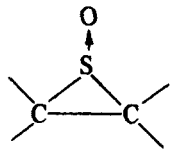


1

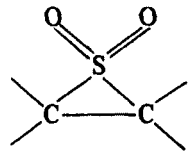
The oxidized thiiranes, cited in Section II, are represented as follows:



2
thiiranium salts



3
thiiranium oxides



4
thiiranium dioxides

Although the "thiirane"-based nomenclature has been slow to find a place in the literature – since some names are easy to construct from the name of the corresponding olefin – the term is now receiving more and more use as the "baseline" for constructing the names of both thiirane derivatives and closely related three-membered ring systems (i.e., thiirenes, thiaziridines, etc.).

Accordingly, the official names of the oxidized forms of thiiranes, namely, the commonly known episulfonium salts, episulfoxides, and episulfones, are thiiranium salts (i.e., **2**), thirane oxides (i.e., **3**), and thiirane dioxides (i.e., **4**), respectively.

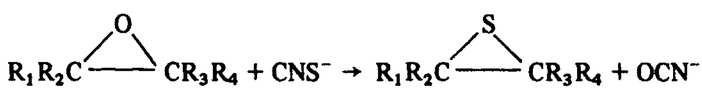
However, for certain more complex molecules (e.g., carbohydrates), the prefix "epithio-" attached to the name of the sulfur-free skeleton may be the more convenient nomenclature. Otherwise, the term "thiirane" is used for the atomic grouping **1** and its appropriate derivation for the corresponding systems **2–4**.

III. THIIRANES (ETHYLENE SULFIDES)

1. Methods of Preparation

A. *From Epoxides (Oxiranes)*

The conversion of epoxides with inorganic thiocyanate ion to yield the corresponding thiiranes appears to be the most important general method and is the method of choice for the synthesis of a broad spectrum of thiirane derivatives:



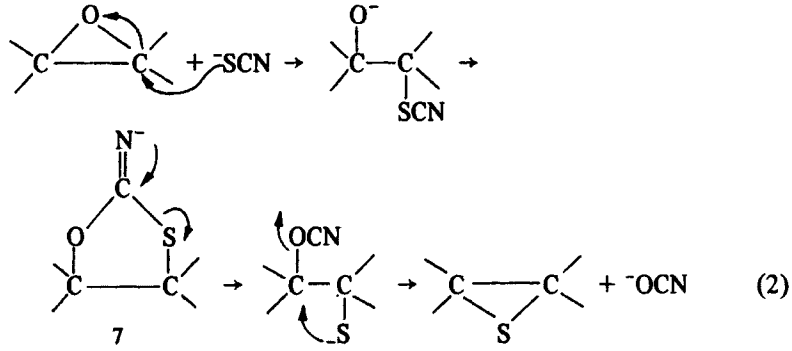
5 **6** (1)

This reaction, first described in the patent literature,[4] has been applied to the synthesis of the parent thiirane (ethylene sulfide,[4,17–23] methylthiirane (propylene sulfide),[24,25] *cis*- and *trans*-2,3-dimethylthiiranes (2-butene sulfides, optically active forms included),[26,27] isobutylene sulfide,[22] cyclopentene[28] and cyclohexene sulfide,[5,21,22,29] various 3-alkoxypropylene sulfides,[30,31] styrene sulfide,[32–34] and many other substituted thiiranes in yields varying normally between 40 and 58% (see Table 1 for details). A modification of this reaction has been used to obtain small yields of thiiranes from sugar epoxides.[35,36] Recently, stereoisomeric 2,2′-bithiiranes were prepared in high yield from the corresponding optically active 1,2,3,4-diepoxybutane using the same method.[37]

In general, the reaction is carried out by mixing an aqueous or alcoholic solution of the two reactants (i.e., the epoxide and potassium thiocyanate) at room temperature or below (0–20°). Keeping the reaction temperature within this range diminishes the risk of polymerization, which is rather substantial above 60°.[38] The use of water

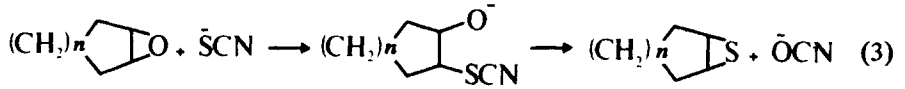
as the reaction medium is quite convenient for the isolation of the product in many cases, since all thiiranes are insoluble in water, whereas the low alkane oxides are water soluble. An excess of either the epoxides or the thio reagent facilitates high yields of the desired thiiranes.[4] At the conventional mole ratio of 1 : 1, the yields obtained are generally lower. The crude products usually contain a certain proportion of the original reactants and are commonly purified by fractional distillation.

The mechanism shown in Eq. 2 has been accepted for the reaction of epoxides with the thiocyanate ion.[27, 29, 39, 40]



(2)

This mechanism is corroborated by the observation that treatment of cyclopentene oxide (**8a**) with potassium thiocyanate under conditions equivalent to, or more vigorous than, those that brought about a 73% yield of thiirane (**10b**) from cyclohexane oxide (**8b**) gave only recovered **8a**. Furthermore, alkaline treatment of *trans*-2-hydroxycyclopentylthiocyanate (i.e., the alkoxy ion **9a**) did not yield thiirane, whereas by alkaline treatment the *trans*-2-hydroxycyclohexylthiocyanate was readily converted into the corresponding thiirane[29]:



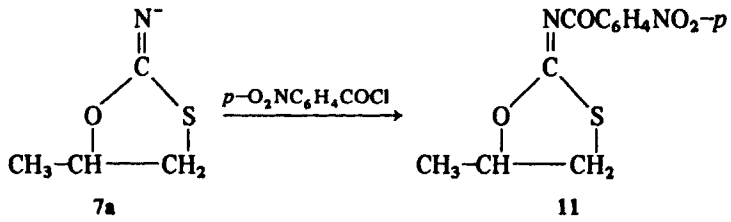
(3)

8a, b **9a, b** **10a, b**

a. $n = 1$;
b. $n = 2$

The involvement of a strained intermediate **7** (two five-membered rings fused *trans*) in the case of **8a**, is consistent with the reaction mechanism depicted in Eq. 2. Support for this mechanism has come from the isolation of the oxathiolane **11** when methyl epoxide and potassium thiocyanate were reacted in the presence of *p*-nitrobenzoyl chloride, which intercepted the intermediate of type **7**[27] (i.e., **7a**).

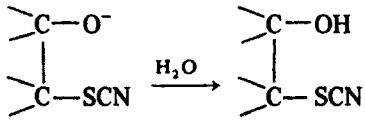
Apparently, the isolation of **11** was possible because the first two steps in the reaction sequence (from the epoxide to the intermediate **7** in Eq. 2) are very fast, whereas the last two steps (i.e., the opening of the oxathiolanimine ring **7** and the subsequent ring closure to form the final thiirane) take place at a very slow rate.



7a 11 (4)

It was shown that the entire reaction is accompanied by Walden inversion at both carbon atoms of the three-membered ring.[27] This can easily be understood in terms of the ring opening of the starting epoxide by the nucleophilic thiocyanate ion to give the "*trans*" intermediate and the closure of both the oxathiolane and the thiirane rings only in the *trans* position.

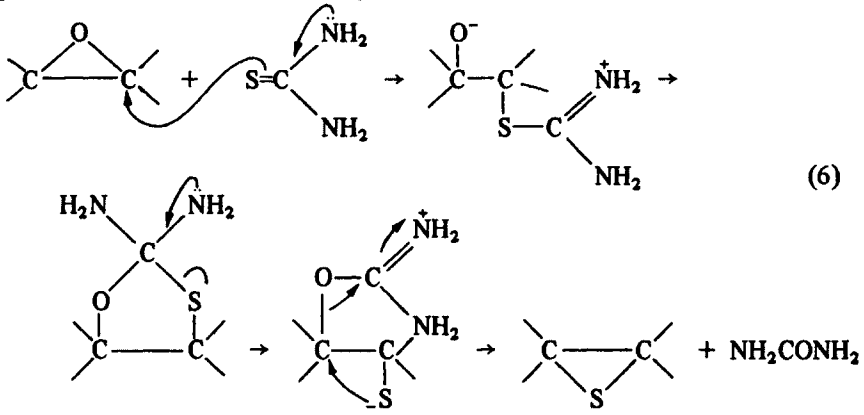
It has been shown[27] that the preparation of thiiranes from epoxides by the thiocyanate route is best carried out in weakly alkaline medium (addition of K_2CO_3), to reduce the amount of β-hydroxyisocyanates that otherwise might form through hydrolysis.



(5)

In acid solution and at room temperature several hydroxyisothiocyanates decompose to yield oxathiolane derivatives and thiiranes as well as other by-products.[27]

Another generally used method for preparing thiiranes from the corresponding epoxides[40–46] is the reaction of the latter with thiourea in a manner mechanistically analogous[7] to their reaction with thiocyanate ion:

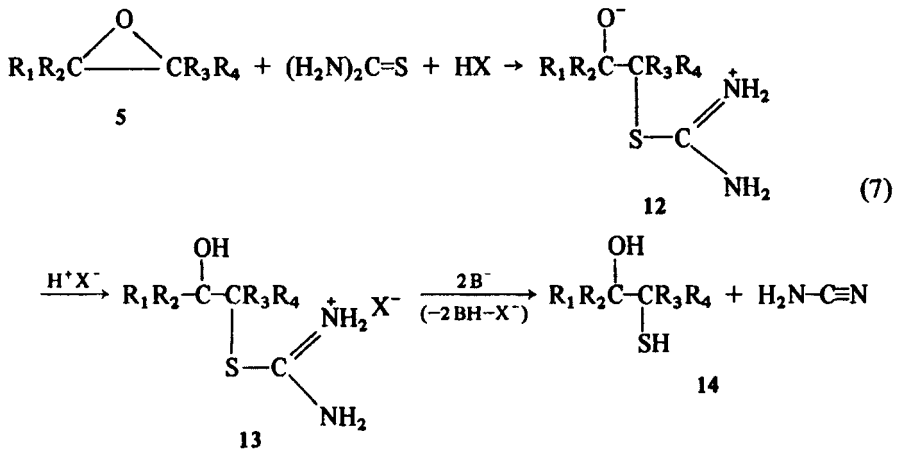


(6)

The following thiiranes have been prepared by the reaction of the corresponding epoxides with thiourea (see Table 1 for details): thiirane (ethylene sulfide),[4,43,47] methylthiirane,[5,8,21,40,48,49] chloromethylthiirane,[3,8,20,21] 2,3-dimethylthiirane,[50]

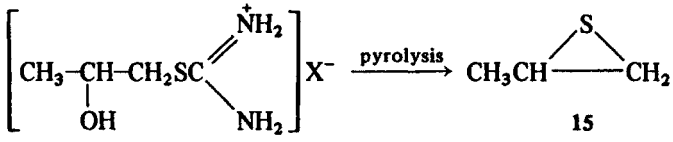
2,2-dimethylthiirane,[5] vinylthiirane (butadiene monosulfide),[6] 2-*n*-butylthiirane,[42] 2*n*-hexylthiirane,[45] cyclohexene sulfide,[5] 4-methylcyclohexene sulfide,[6] 2,3-diphenylthiiranes,[52] various 3-alkoxypropylene sulfides,[31, 52] thioglycidyl sulfides[52] and amines,[46] various ester[14, 54, 55] and bisester thiiranes,[53] and thiirane fatty acids,[14] fatty esters,[14, 54, 55] and fatty alcohols.[14]

There is some evidence, however, suggesting that at least in one case[51] the reaction may not have proceeded through the generally accepted double inversion path for conversion of epoxides to thiiranes.[29] When the reaction is conducted in the presence of at least an equimolar quantity of inorganic acid, the intermediate **12** (in Eq. 7) may be isolated as the isothiouronium salt **13** in high yields.[40, 51, 52]



(7)

Addition of alkali to the isothiouronium salts of type **13** or heating an aqueous solution of the salt with weak acids results in obtaining the corresponding thiiranes as the major products.[40] The best yields were obtained by neutralization with sodium carbonate.[40] The nature of the products obtained on alkaline hydrolysis of **13** depends on the procedure used. Thus, when an aqueous solution of **13** is added to an excess of aqueous alkali, the major product is the corresponding 2-hydroxyethanethiol (i.e., **14**).[40] Pyrolysis of some *dry* 2-hydroxy – 1-isothiouronium salts, also leads to the corresponding thiiranes as illustrated in Eq. 8.



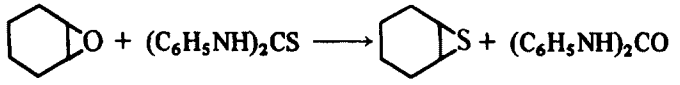
(8)

13a
X = acetate or benzoate

Interestingly, in the absence of acid or alkali, the strongly increasing pH values of the solution in the early stage of the reaction between epoxies and thiourea has an adverse effect on the yields of the thiiranes. This increase of the pH values may be attributed either to hydrolysis of the first intermediate (Eq. 6) or to hydrolysis to ammonia of the resulting urea.

Taking into consideration that the given mechanism (Eq. 6) applies to all thio reagents, one should not be surprised to find that the cleavage of the last intermediate accompanied by the ring closure to afford the thiirane is feasible only if the O–C bond is weakened by electron-withdrawing groups as in the case of *O*-uronium salts or cyanates. However, cyclization does not occur if a hydrogen atom or an alkyl group is attached to the oxygen atom.[7] This means that compounds of the type $HS–CH_2–CH_2–OR$ (R = H or alkyl) do not undergo cyclization analogous to **13** under comparable reaction conditions.

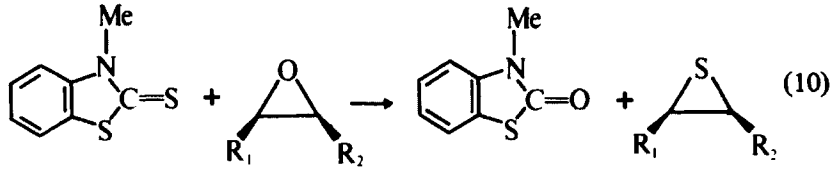
The reactions of thiocarbanilide,[5] thioacetamide, thiobenzamide, xanthamide, and thiobarbituric acid with certain epoxides are similar to the reaction of the latter with thiourea – namely, they form thiiranes and the oxygen analog of the thio reactant.[6] Nevertheless, polymerization prevents isolation of the thiiranes.



(9)

16 **17**

A recent communication[56] describes a simple method for converting oxiranes into thiiranes stereospecifically by using 3-methylbenzothiazole-2-thione in the presence of trifluroacetic acid:



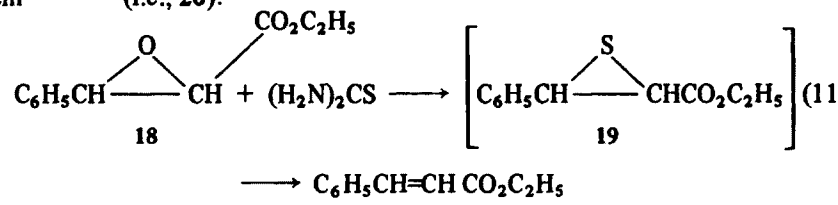
(10)

The reaction is run in dry CH_2Cl_2 at 0° and results in particularly high yields. Thus, cyclohexene oxide, styrene oxide, and *cis*-stilbene oxide are claimed to give quantitative yields of the corresponding thiiranes, whereas *trans*-stilbene afforded 80% of the thiirane.

The mechanism proposed is analogous to that of the reactions for thiocyanate (Eq. 2) and thiourea (Eq. 6).

The high yields and the simplicity of the above reaction make this method competitive with other available methods of thiirane synthesis.

Although thiourea (as well as the other thioamides) reacts with several substituted glycidates, no thiiranes could be prepared using this method when the loss of sulfur from the thiirane formed led to a highly stabilized conjugated system[5, 6, 54, 57] (i.e., **20**):

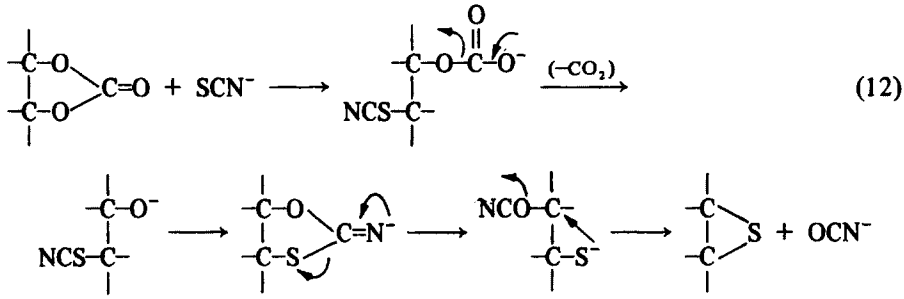


(11)

18 **19** **20**

B. *From Cyclic Carbonates*

The preparation of a long line of thiiranes can be accomplished by the reaction of alkali thiocyanates with cyclic carbonates of 1,2-diols (1,3-dioxolones) at 100–200°.[58,59] It has been suggested that the reaction proceeds by a four-step mechanism including two Walden inversions analogous to the reaction with epoxides[59]:



(12)

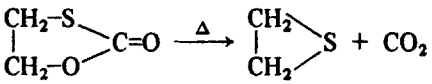
It seems reasonable that the decarboxylation occurs during or immediately after the attack of the thiocyanate ion on the α carbon atom. An alternative mechanism involving first decarboxylation of the cyclic carbonate to the epoxide, followed by its well-known reaction with thiocyanate (described above) can be excluded.[59] Such an alternative mechanism would require three Walden inversions, with a net inversion of configuration, since the epoxide formation from cyclic carbonates, proceeds with one Walden inversion.[59]

In general, the yields of thiiranes obtained from cyclic carbonates and cyanate salts are good, provided the reaction occurs below 150° and the resultant thiirane distills quickly. This holds for low molecular weight thiiranes and the corresponding starting cyclic carbonates. Thus, the yield of the parent thiirane obtained in this way is 80–85% and that of methylthiirane is 51%. Higher dioxolones react slowly and the yields are lower (e.g., 31% yield for the *cis*-dimethylthiirane).[59] Thiiranes and substituted thiiranes obtained from cyclic carbonates are tabulated in Table 1.[58–61]

The lack of reactivity of thiourea with the cyclic carbonates is probably due to its nucleophilicity being lower than that for thiocyanate ion. Nevertheless, a patent was issued protecting this reaction (only low yields are obtained).[60]

C. *By Pyrolysis of Thiolcarbonates and Mercaptoalkylcarbonates*

The synthesis of thiiranes by pyrolysis of certain cyclic monothiolcarbonates (e.g., **21**) is another important process for the preparation of this class of compounds[62]:

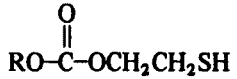


(13)

21 **22**

Starting compounds of type **21** are readily prepared by heating epoxides with H_2S followed by treating the resulting vicinal hydroxythiol with $COCl_2$-pyridine.[62] The inherent advantage of this method is that cyclic carbonates are stable and therefore storable for long periods of time. The desired thiirane can be prepared whenever desired by pyrolysis of the cyclic thiolcarbonates. Another advantage of this route is that the only by-product is carbon dioxide. Smooth decomposition requires alkaline catalysis (Na_2CO_3, $NaOCH_3$)[62] but is inhibited by acids.

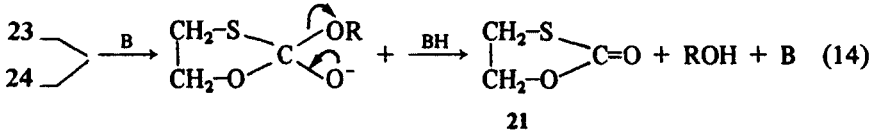
The cyclic thiolcarbonates may be replaced by the open-chain *O*- and *S*-carbonates (i.e., **23** and **24**, respectively,[64] likewise obtainable from 2-hydroxymercaptans).



23

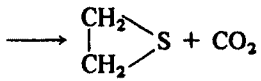
24

In the latter cases, however, the highest yield of the resulting thiiranes is obtained in the absence of a catalyst. The thiiranes produced are accompanied with an equimolar amount of alcohol. This is in accordance with the formation of a cyclic thiolcarbonate as an essential intermediate along the reaction coordinate:



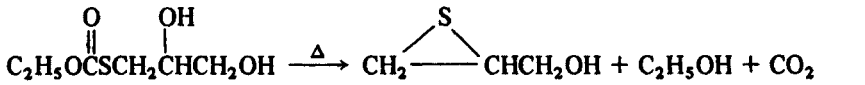
(14)

21



22

The generality of the pyrolysis is further demonstrated by the preparation of 2-hydroxymethylthiirane by pyrolysis of **25**[64] through the intermediacy of the corresponding thiolcarbonate:

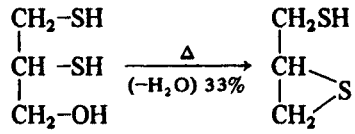


25 **26** (15)

Finally, a closely related synthesis – restricted to thiiranes that show a low tendency to polymerize – is the alkaline hydrolysis of cyclic trithiocarbonates (which are available from epoxides and alkali alkyl xanthates).[65]

D. *From Acylated Vicinal Hydroxythiols*

The only reference up to a decade ago to describe the direct synthesis of thiirane by dehyration of vicinal hydroxythiol deals with the dithioglycerol **27**[66a]:

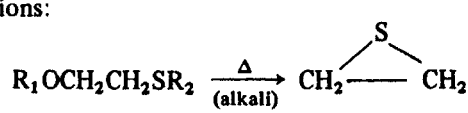


(16)

27 28

Other attempts to obtain thiiranes by a similar direct dehydration failed.[67] However, the acid-catalyzed intramolecular cyclodehydration of 2-mercaptoalkanols was shown to be not only a general reaction of these substances, but also a plausible route for obtaining thiiranes particularly for the more highly substituted homologs.[66b]

The use of potassium hydrogen sulfate as the acidic catalyst rather than a mineral acid, as well as a suitable choice of conditions that reduced the susceptibility of the products to acid-catalyzed polymerization, raised the yields of the thiiranes to the level of 34–70%.[66b] The method was applied to prepare the parent thiirane, 2-methylthiirane and 2-mercaptomethylthiirane (i.e., 28). The cyclization of vicinal hydroxythiols proved to be generally possible (and successful) via appropriate derivatives, that is, deacetylation of either their *S*-acetates,[67–69] *O*-acetates,[67–69] or *O*,*S*-diacetates.[67–71] Thus, deacetylation of the following three acetates, to yield thiirane, takes place when these derivatives are heated with aqueous alkali solutions:

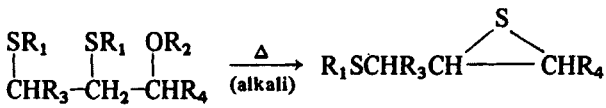


(17)

29 22

a. $R_1 = CH_3CO$; $R_2 = H$
b. $R_1 = H$; $R_2 = COCH_3$
c. $R_1 = CH_3CO$; $R_2 = COCH_3$

The thiiranes thus obtained should be continuously distilled during the reaction to reduce both possible ring opening and polymerization caused by the alkali. In general, the yields of this process are reported to be in the range of 25–80%. This method was used to prepare the following substituted thiiranes in addition to the parent: cyclopentene[69–71] and cyclohexene[67, 68] sulfides, 2-mercaptoalkylthiiranes (e.g., 31)[67, 68, 70, 72] and their homologs,[72] sugar thiiranes,[42] and steroidal thiiranes.[73, 74]



(18)

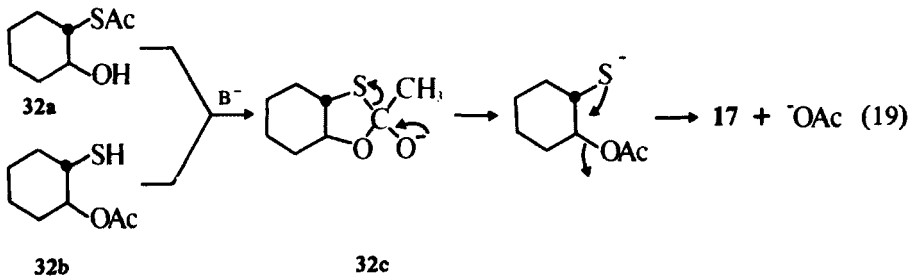
30 31

a. $R_1 = CH_3CO$; $R_2 = CH_3CO$; $R_3 = H$; $R_4 = H$
b. $R_1 = H$; $R_2 = CH_3CO$; $R_3 = H$; $R_4 = H$
c. $R_1 = CH_3CO$; $R_2 = CH_3CO$; $R_3 = CH_3$; $R_4 = H$
d. $R_1 = CH_3CO$; $R_2 = CH_3CO$; $R_3 = H$; $R_4 = CH_3$

a. $R_1 = CH_3CO$; $R_3 = H$; $R_4 = H$
b. $R_1 = H$; $R_3 = H$; $R_4 = H$
c. $R_1 = CH_3CO$; $R_3 = CH_3$; $R_4 = H$
d. $R_1 = CH_3CO$; $R_3 = H$; $R_4 = CH_3$

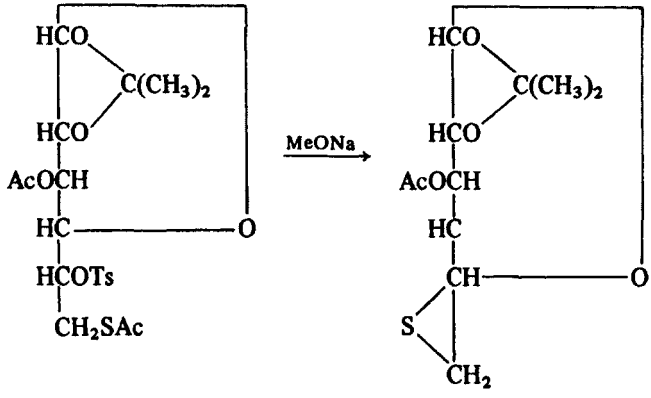
This method of synthesis has been studied in detail with respect to the preparation of the thiirane (17). The fact that 17 is formed from both the *S*- and the

O-monoacetates of *trans*-2-mercaptocyclohexanol (i.e., **32**) supports the generally accepted mechanism in which **32c** is the true precursor of the final thiirane and that this requires **32a** to undergo an isomerization (which is not required in the case of its isomer, **32b**.



E. *By Alkaline Hydrolysis of Vicinal Tosylates (or Mesylates); Thiolacetates*

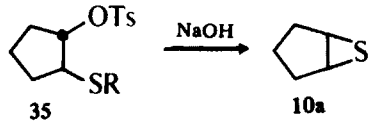
The synthesis of thiiranes by the alkaline hydrolysis of thiolacetates is closely related to the method described in the preceding section. Its most successful application has been in the synthesis of carbohydrate thiiranes[35, 42, 75] as illustrated below in the transformation of the 5-*O*-tosyl-6-acetylthio-α-D-glucose (**33**) to the corresponding thiirane (i.e., **34**).



33 34 (20)

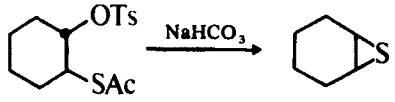
The direct conversion of the corresponding epoxides in these series, however, is difficult.[35, 36] Similarly, *trans*-2-acetylthiocyclopentyl *p*-toluenesulfonate, *trans*-2-benzoylcyclopentyl *p*-toluenesulfonate, and *trans*-2-acetylthiocyclohexyl *p*-toluenesulfonate were converted to the corresponding thiiranes with NaOH and $NaHCO_3$, respectively[69]:

Replacement of the tosyl group with a mesyl group in **35** likewise afforded the thiirane **10a**.



35 10a (21)

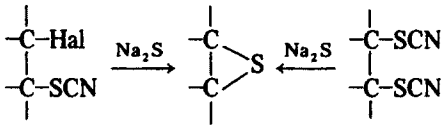
R = acetyl or benzoyl



36 17 (22)

F. *From Vicinal Halothiocyanates, Dithiocyanates, and Sodium Sulfide*

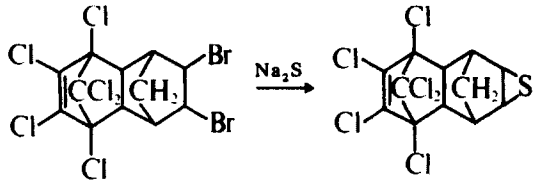
Thiiranes can readily be obtained by interaction of 2-halothiocyanates or of 1,2-bisthiocyanates with sodium sulfide[3,76,77]:



(23)

These preparations, as represented by Eq. 23, are of historical interest, since they were used by Dele'pine in the early syntheses of ethylene sulfide.

Usually, the starting compounds are obtainable by conversion of 1,2-dihalides with alkali thiocyanate or by addition of thiocyanogen or thiocyanogen chloride to olefins. The only example described in the literature for the direct synthesis of a thiirane from a dihalide and alkali sulfide — without the formation of polymeric thiiranes – is the following reaction:



37 38 (24)

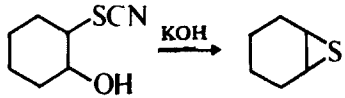
It is reasonable to assume that polymerization here is probably suppressed by overcrowding and for steric reasons.[16] However, a 20% yield of thiirane has been observed on reaction of 1,2-dibromoethane with hexamethylcyclotrisilthiane.[32]

The conversion of vicinal halothiocyanates or dithiocyanates to thiiranes is generally carried out with aqueous sodium sulfide in the presence of alcohol as

solubilizer at room temperature or with gentle heating. The reaction yields are reported to vary from poor to relatively high (see Table 1 for details) for the following compounds, which were prepared on the basis of 2-halothiocyanates: thiiranes,[3] methylthiirane,[76] ethylthiirane,[76] and cyclohexene sulfide.[78] Thiirane,[3] methyl- and ethylthiiranes,[76] 2,2-dimethyl-, 3-methyl-,[79] and 2,2,3,3-tetramethyl-[80] thiiranes, cyclohexene[81] and cyclooctene[82] sulfides, 2,2-pentamethylenethiirane,[81] and various thiirane carboxylic acids[65,83] have been prepared from the corresponding dithiocyanates. In a modified method alkali is used instead of sodium sulfide[65,83] with fair to good results.

G. *From Vicinal Hydroxythiocyanates (and O-Mesyl- or O-Tosylthiocyanates)*

Several vicinal hydroxythiocyanates – namely, thiocyanate alcohols and their sulfonic esters (i.e., *O*-mesylates or *O*-tosylates) – can be easily converted to the corresponding thiiranes by treatment with alkali. For example: slow addition of dilute potassium hydroxide to **39** yields **17**[29]:

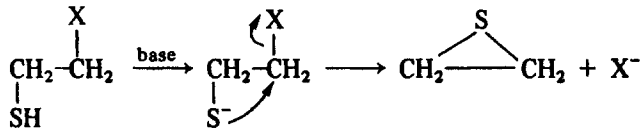


39 **17** (25)

Similarly, 2-thiocyanatocyclopentanol mesylate, in the presence of aqueous sodium hydroxide, furnished cyclopentene sulfide in a yield of 63%, whereas the corresponding tosylate furnished only small quantities of that thiirane.[28] The same method has been successfully applied in the preparation of sugar thiiranes from the sugar α-thiocyanomesylate precursors[75,76] and in the preparation of steroidal thiiranes.[74,84,85] The use of vicinal *O*-acetylthiocyanates (rather than *O*-mesyl or *O*-tosyl) as starting materials to prepare steroidal thiiranes on treatment with alkali[74,85] can be rightly classified under the same category.

H. *By Dehydrohalogenation of 2-Haloethanethiols*

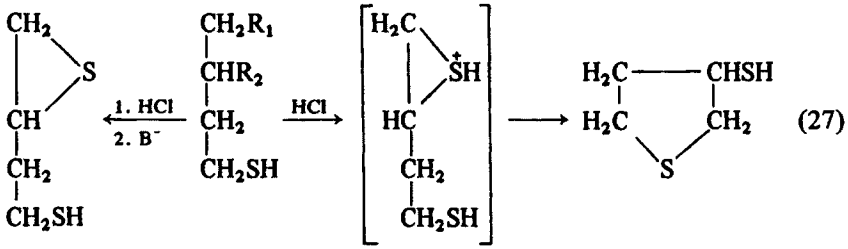
Just as epoxides are obtainable from 2-haloalcohols (chlorohydrins) and alkali, thiiranes are derived by treatment of 2-halomercaptans with alkali:



(26)

Optimum yields of the thiiranes are obtained by maintaining the pH between 7.5 and 9.5. Too high or too low pH values lead to polymerization of the thiirane

formed as intermediates. Therefore, weakly alkaline reagents such as $NaHCO_3$, CH_3CO_2Na, NaH_2PO_4, Na_2HPO_4, and NaHS (which in fact can maintain buffer conditions) are recommended to perform this transformation effectively.[86] The most common reagent is $NaHCO_3$. The fairly unstable 2-halomercaptans are ordinarily formed *in situ* by the treatment of 2-hydroxymercaptans with hydrochloric acid. The crude reaction mixture obtained (the interesting component of which is the 2-halothiol in case at hand) is treated, then, with aqueous $NaHCO_3$ solution after the excess acid has been removed. Yields between 35 and 90% are reported.[27, 72] Nevertheless, the action of cold concentrated hydrochloric acid on certain 2-hydroxythiols can lead to other products rather than to the desired thiiranes through the expected 2-chlorothiol, as illustrated in Eq. 27.[72]



(27)

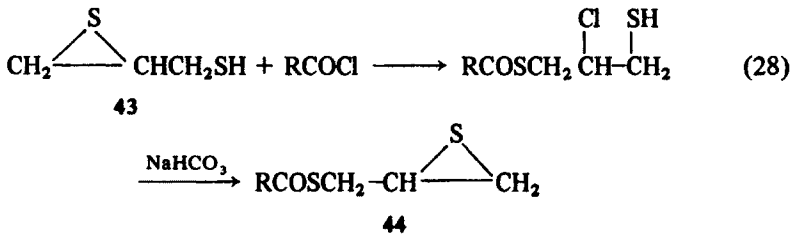
41 40 42

a. $R_1 = OH$; $R_2 = SH$
b. $R_1 = SH$; $R_2 = OH$

Cyclization of chloromercaptocarboxylic acid derivatives gave derivatives of thioglycidic acid.[86b]

Dehydrohalogenation of 2-haloethanethiols was the method through which the following compounds were prepared: the parent thiirane,[1, 86] 2,3-dimethylthiirane,[1, 27] 2-thiomethylthiirane,[72] 2-methyl, 2-thiomethylthiirane,[72] and cyclopentene sulfide.[29]

An interesting closely related variation of this method consists of the opening of an already existing thiirane ring in the course of modifying the substituent followed by the reclosure of the halothiol obtained with $NaHCO_3$:[52, 87]

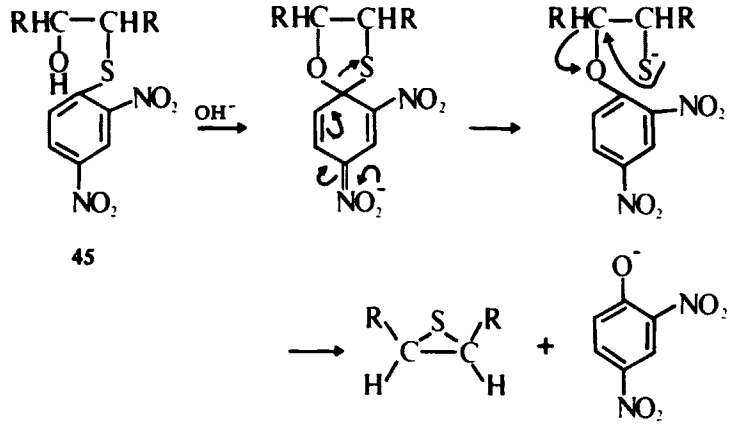


(28)

43 44

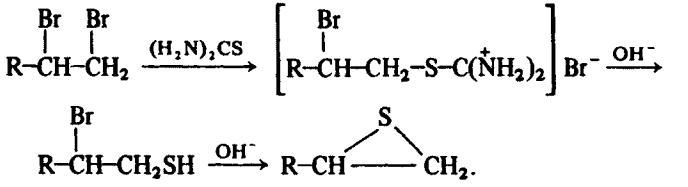
Yields between 35 and 99% are reported for this procedure.

The direct dehydration of 2-hydroxyethanethiols[66] has been mentioned previously (Section III, 1, D). Another interesting way to obtain thiiranes from vicinal hydroxymercaptans is to treat compounds of type **45** with dilute alkali.[7] Mechanistically, however, this reaction is probably related to the alkaline-catalyzed decomposition of cyclic thiolcarbonates (see Section III, 1, C):



45 (29)

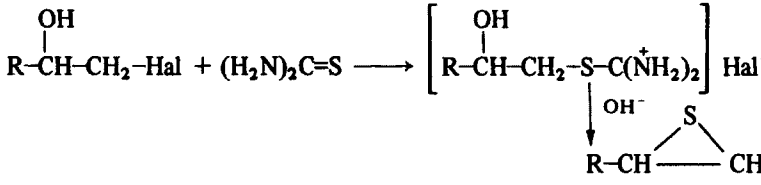
An indirect route for making thiiranes is the reaction of 1,2-dihalides with thiourea to give the monothiouronium salt and the decomposition of the latter by alkali. As Eq. 30 indicates, this method involves the *in situ* intermediate formation of 2-haloethanethiols, which finally generate the thiiranes by reaction with alkali.



(30)

This indirect method was successfully applied to the synthesis of hexene sulfide,[88] 2-phenylthiirane,[88] and quinoxaline-2,3-sulfide.[90]

Finally, interaction of 2-hydroxyalkyl halides with thiourea in a polar solvent results in the corresponding isothiouronium salts, which in turn yield the respective thiiranes upon treatment with alkali[91] (see Eq. 7). This is illustrated in Eq. 31.



(31)

Thiirane, 2-methylthiirane, 2,3-dimethylthiirane, and 2-ethylthiirane were prepared by using this method. The yields are reported to be "very high," although detailed figures are not available.[91]

I. *Directly from Olefins*

The most significant approaches for the synthesis of thiiranes can be classified in two groups. The first is the indirect route described earlier: that is, olefinic

compounds can be raised to the desired oxidation state and the resulting epoxides, dihalides, chlorohydrins (and closely related compounds) can be converted to the thiiranes by a variety of sulfur-containing reagents, such as KCNS and $(NH_2)_2C{=}S$.

The direct method, however, would be the oxidation of olefins with sulfur or active sulfur transfer reagents to the corresponding thiiranes.

The indirect route was almost exclusively used for laboratory synthesis till the end of the 1960s. The limitations involved in the use of this approach are particularly important with substrates containing easily oxidized functionality. The development of novel methods using the second approach (described in the subsections that follow) overcomes the difficulty just noted.

a. BY ADDITION OF SULFUR

The patent literature claims that unsaturated ketones, unsaturated carboxylic acids, or unsaturated carboxylic esters (and glycerides) are transformed into thiiranes by adding sulfur at the site of unsaturation.[92] However, definite compounds have not been isolated so far, nor is there any evidence establishing the presence of thiirane groups. As a matter of fact, it becomes apparent from reliable investigations[79,93] that the reaction of sulfur with unsaturated compounds leads primarily to the disulfides and polysulfides, in addition to a number of by-products not containing thiirane groups.

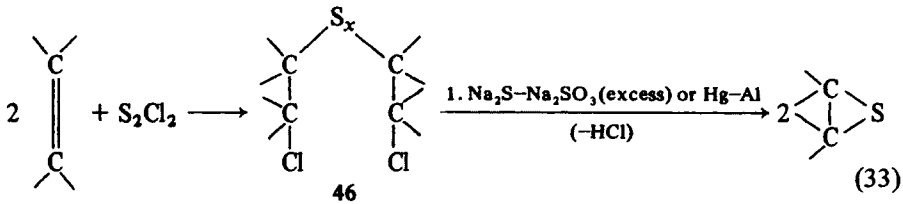
On the other hand, ethylene, propylene, and cyclohexene are converted in low yields into the corresponding thiiranes by reacting the olefin with ethyl tetrasulfide at approximately 150°. The latter serves as a source of monoatomic sulfur on heating:

$$CH_2{=}CH_2 + C_2H_5S_4C_2H_5 \xrightarrow{\Delta} \underset{\textbf{22}}{\overset{S}{\underset{CH_2}{\diagup\!\diagdown}}\!CH_2} \qquad (32)$$

Vapour phase photoreaction between carbonyl sulfide and olefins leads to the formation of thiiranes in high yields but at an extremely slow rate.[95a] This reaction shows that the problem in the "direct synthesis" of thiiranes from olefins and sulfur lies in the difficulty of obtaining monomeric sulfur. Furthermore, more recent investigations into the reaction of sulfur atom in its ^3P or ^1D state with olefins to yield thiirane[94b-94e] may find some practical synthetic application.

b. FROM OLEFINS AND SULFUR MONOCHLORIDE

A two-step synthesis of thiiranes from the corresponding olefins and sulfur monochloride is illustrated in Eq. 33.[95]



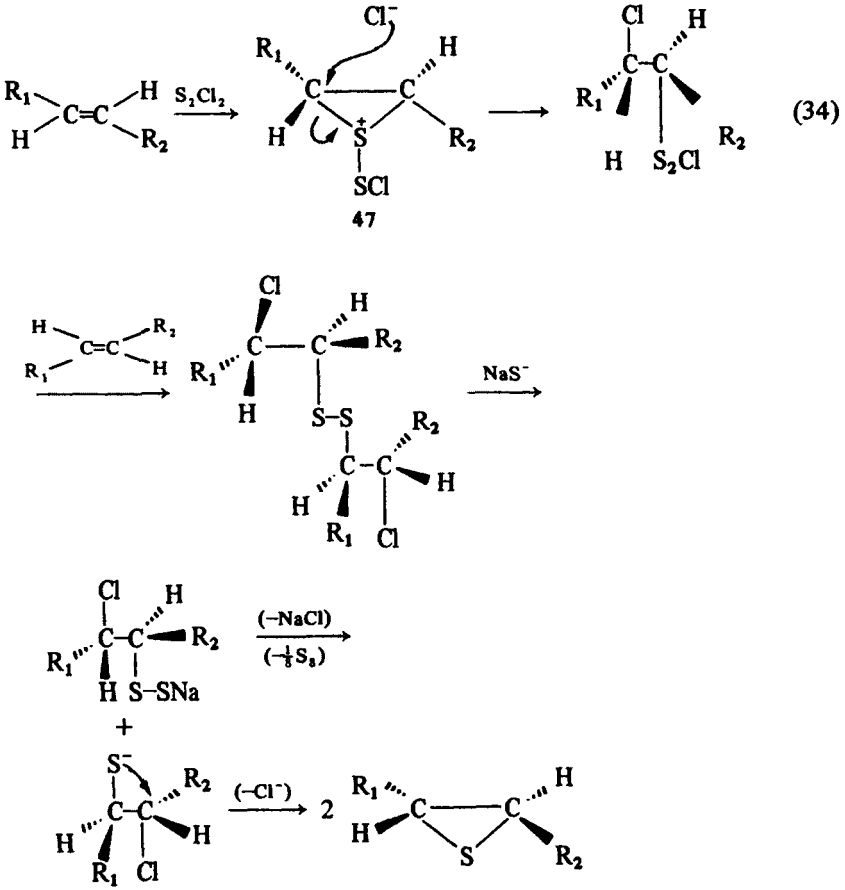
46

$x = 1\text{–}3$ (33)

Synthetic procedures that reduce the amount of **46** ($x = 1$) to a minimum were worked out,[95] since this adduct cannot be converted to the desired thiirane in the reduction-dehydrohalogenation step. In the case of simple unsymmetrical olefins the isomer distribution in mixture **46** is not important in determining the yield because they all can be converted to the same thiiranes. This distribution does affect, however, the product distribution obtainable from unsymmetrical substituted olefins – depending on the relative ease of displacement of the functional groups in the anti-Markovnikov adducts obtained in the first step.

The method has been applied successfully to the synthesis of the parent thiirane, several 2-alkylthiiranes (see Table 1), 2-phenylthiiranes, *cis*- and *trans*-2,3-dimethylthiiranes, 2,2-dimethylthiirane, cyclic thiiranes, monosubstituted alkenylthiiranes, and some α-substituted thiiranes obtained from the allylic-substituted olefins.[96] The yields vary within the range of 25–65%, being usually higher when the reduction is carried out with excess sodium sulfide rather than with aluminium amalgam.

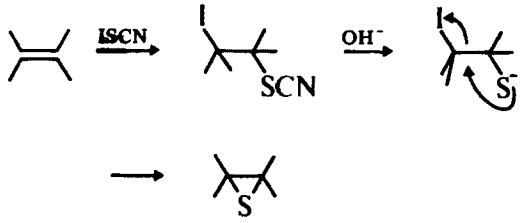
Since the synthesis of these thiiranes via their sulfur monochloride adducts is stereospecific, the mechanism involved in Eq. 34,[96] which is in accordance with the experimental results, is illustrative.



(34)

c. FROM OLEFINS AND IODINE THIOCYANATE

The method described in Section III, 1, I, b above, suffers from a major disadvantage in that a large excess of the alkene must be used. A convenient procedure that overcomes this problem is the addition of cyclic alkenes (i.e., cyclopentene, cyclohexene, 1,5-cyclooctadiene) to equimolar solutions of iodine and thiocyanogen followed by hydrolysis of the thiocyanate moiety in the intermediate with base and a final ring closure to the desired thiirane[97]:



(35)

Yields ranging from 26 to 57% were obtained[97] using ether as a solvent and methanolic potassium hydroxide as the base. The procedure appears suitable for some acyclic olefins as well.[97b] Strictly speaking, this method belongs to the indirect routes already discussed (see Section III, 1, F).

d. FROM OLEFINS AND ACTIVE SULFUR TRANSFER REAGENTS

Arenethiosulfenyl chlorides, readily prepared from the corresponding thiophenols and sulfur dichloride, were shown to be useful active sulfur transfer reagents in their reaction with olefins. The disulfide adducts initially formed are easily transformed stereospecifically into thiiranes in moderate yields by treatment with sodium amide or sulfide.[98] Basically, this procedure of thiirane preparation can be regarded as a modification of the synthesis of thiiranes from olefins and sulfur dichlorides[96] described above (Section III, 1, I, b). Also the mechanism is essentially the same, which explains the stereospecificity observed in the relevant cases.

Both *o*-nitrobenzenethiosulfenyl- and *p*-toluenethiosulfenyl chloride were applied in the preparation of cyclohexene episulfide,[98] cyclopentene episulfide,[98] and *cis*- and *trans*-2,3-dimethylthiiranes (from the *cis*- and *trans*-2-butenes, respectively).[98] This procedure was successfully applied to the synthesis of highly strained norbornene thiiranes.[99] The reported yields are in the range of 30–84%, with substantially better yields obtained when the reduction step was carried out with sodium sulfide rather than with sodium amide.[99] Norbornadienes yield *exo-endo* mixtures of the corresponding thiiranes in about 4:1 molar ratio. The structure of the isomers can be confirmed by their nmr spectra and they can be isolated by preparative column chromatography. In any case, the stable orientation of the episulfonium salt as an intermediate in the addition stage[96,97] exerts steric control on this reaction.

The experimental synthetic results[99] are included in Table 1.

J. *From Thioketones, Thioesters, Thiocarboxylic Chlorides, and Other Thiocarbonyl Compounds*

Aromatic thioketones react vigorously with Grignard reagents to yield substituted thiiranes[100]:

$$2Ar_2C{=}S + 2Ar_1MgX \longrightarrow Ar_2C\overset{S}{\diagup\!\diagdown}CAr_2 + Ar_1Ar_1 + MgX + MgS \qquad (36)$$

48 49

Significantly, the substitution pattern of the resulting thiirane (49) is dependent only on the starting thioketone (48), regardless of the Grignard reagent. The yield of the thiirane, however, depends both on the type of thioketone and on the Grignard reagent used. Aromatic thiiranes with Ar = *p*-CH_3O–C_6H_4 and Ar = *p*-CH_3CH_2O–C_6H_4 in 49 have been prepared using this method.[100] A modification of this method comprises the conversion of aromatic thioketones into the corresponding thiiranes by using a mixture of magnesium iodide and magnesium in ether[101]:

$$2Ar_2C{=}S + MgI_2 + Mg \longrightarrow Ar_2C\overset{S}{\diagup\!\diagdown}CAr_2 + MgI_2 + MgS \qquad (37)$$

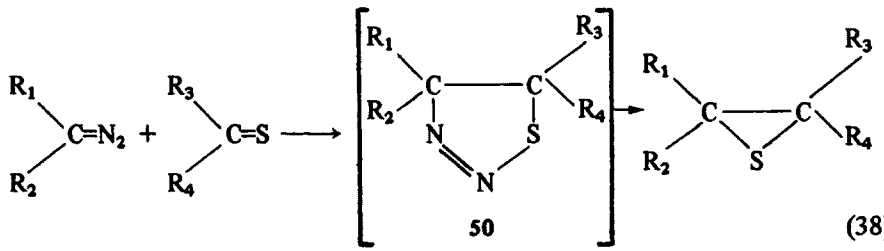
49

2,2,3,3-Tetraanisylthiirane has been prepared by this method. The yields of this procedure are inferior to those of the "classic" Grignard reaction (Eq. 36). To avoid loss of sulfur from the product (49), unnecessary heating must be avoided when the mixture is worked up.

Another possible route from thioketones to thiiranes is the treatment of the latter with sodium acetylide. However, the main products of this procedure are dimeric thioketones[102] and therefore the method is synthetically unimportant.

a. FROM DIAZO COMPOUNDS AND THIOCARBONYL COMPOUNDS

Various aromatic, heterocyclic, and unsymmetrical thiiranes have been prepared by the reaction of diazo compounds with thioketones according to the following scheme[2,103]:

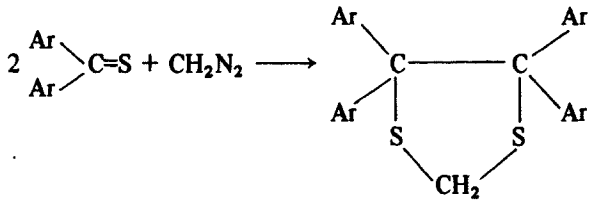


(38)

Although an unstable five-membered ring was postulated as an intermediate, which on loss of N_2 produces the thiirane, one cannot exclude a mechanism in which a

carbene or carbenoid species, generated by the diazo reagent, is inserted into the thiocarbonyl double bond to form the three-membered thiirane ring.

In contrast to the postulated mechanism, which involves the formation of the five-membered ring,[2] an alternative route in which a five-membered 1,3-dithiolane intermediate is formed in these reactions was suggested by Schonberg[104]:

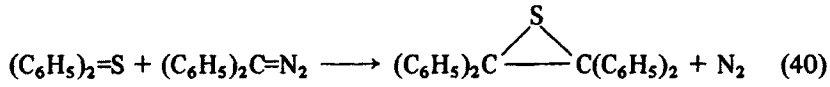


(39)

51

Indeed, the reaction of thiobenzophenone with diazomethane, diazoethane, and ethyldiazoacetate afforded only dithiolanes (**51**) instead of the aimed-for thiiranes.[2]

An illustrative example for the "diazo route" is the reaction of diphenyldiazomethane and thiobenzophenone:

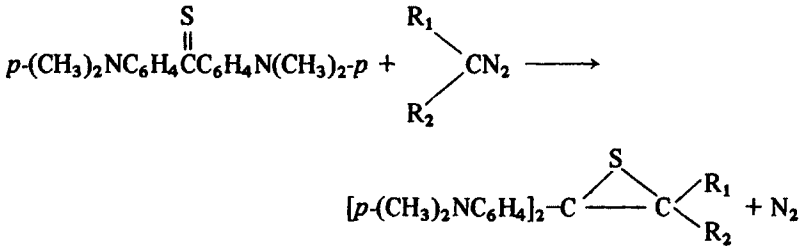


(40)

52 53

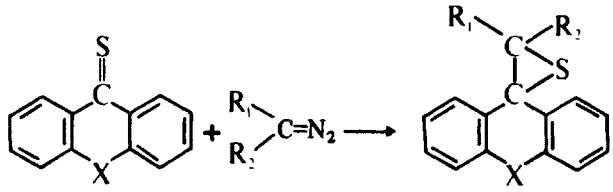
The noncarbonyl-substituted aliphatic diazo compounds (e.g., diphenyldiazomethane, phenyldiazomethane, biphenyldiazomethane) react very readily. Monocarbonyl-substituted compounds (e.g., diazoacetic esters and phenylbenzoyldiazomethane) react more slowly, and the dicarbonyl-substituted compounds (e.g., diazomalonic esters, ethylbenzoyldiazoacetate) do not react with thiobenzophenone.[2]

Several aryl-substituted thiiranes have been prepared by the reaction of various aromatic thioketones with different diazoalkanes[102, 103, 106, 107, 114] (see Table 1). Illustrative examples are the interaction of various aryldiazomethanes with bis(*p*-dimethylamino)thiobenzophenone, xanthione, and thiaxanthione, to furnish the corresponding thiiranes in high yield[105, 106]:



(41)

54



(42)

55

a. $x = O$
b. $x = S$

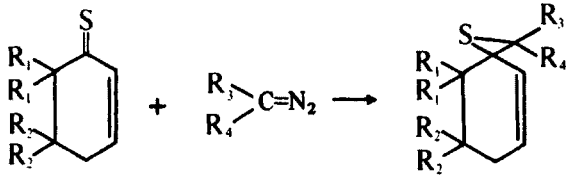
56

a. $x = O$
b. $x = S$

The only exceptions among aliphatic compounds are highly fluorinated thiocarbonyl compounds – for example, hexafluorothioacetone, which reacts with diphenyldiazomethane or with ethyldiazoacetate to give the corresponding thiiranes[108a] in the same manner.

It appears that the instability of some aliphatic or aromatic thioketones and/or the difficulty of their preparation in some other cases limit the general usefulness of the "diazo route" in the preparation of thiiranes. It has been shown, however, that aliphatic thioketones also react with diazomethane to give 2,2-dialkylthiiranes.[108b]

Some spirocyclic vinylthiiranes can be prepared by reacting appropriate α,β-cyclothioenones [cycloene-2-thiones (57)] with diazoalkanes[109]:



(43)

57

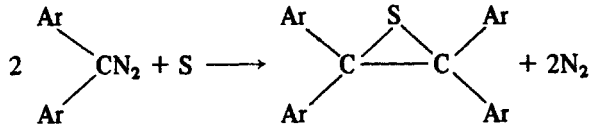
58

a. $R_1 = CH_3$; $R_2 = H$
b. $R_1 = H$; $R_2 = CH_3$

The yields of 58 are between 45 and 75% for diazomethane, diazoethane, and diphenyldiazomethane. However, the generality of this route is limited because olefins, dithiolanes, and unsaturated thioesters are generally the main products.[109]

b. FROM DIAZOALKANES AND SULFUR

Symmetric thiiranes of the general formula 59 can be directly produced by the reaction of diazoalkanes with elemental sulfur[106,110]:

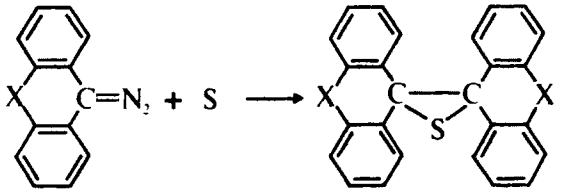


(44)

59

The reaction, which was discovered simultaneously by two different research groups,[106, 110] takes place readily at room temperature. It is accelerated by uv light, and the products are obtained in excellent yields.[106]

Besides tetraphenyl-[106, 110] and tetra-4-methoxyphenyl-[110] thiiranes, the condensed ring compounds 9-diazofluorenone, 9-diazoxanthene and 9-diazooxanthrene have been converted into the corresponding symmetrical thiiranes in this way. The synthesis of two such symmetric dispirothiiranes is exemplified in Eq. 45.



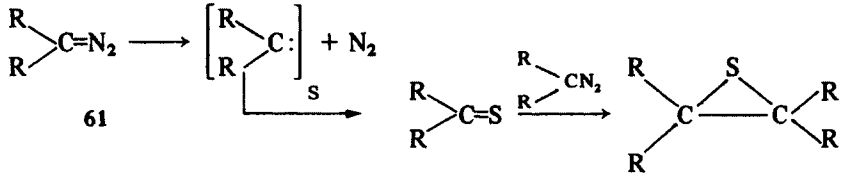
(45)

60

a. X = O
b. X = S

a. X = O
b. X = S

Concerning the mechanism of the reaction between diazoalkanes and elemental sulfur to produce directly the symmetrical thiiranes, it is assumed that this takes place by the initial decomposition of the diazoalkane to give a carbene or a carbene-type species. The latter then coordinates with sulfur giving the corresponding thioketone, which reacts directly with another molecule of the diazoalkane, producing the thiirane as in Eq. 46.[106]



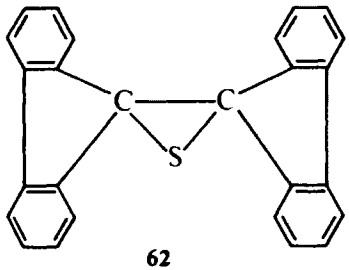
61

(46)

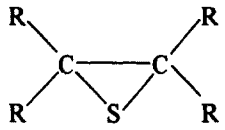
If, in fact, the mechanism above is correct, this method of thiirane preparation can be considered to be a variation of the general method in which thiiranes are produced from the treatment of thiocarbonyl compounds with diazo compounds.

A closely related method that circumvents the inaccessibility of some of the diazo compounds on the one hand and either the instability of some thioketones or the difficulty of their preparation on the other hand, is the direct production of symmetrical thiiranes from the readily available ketohydrazones.[111] It is believed that this direct production of thiiranes from ketohydrazones may proceed through the intermediate formation of the corresponding diazoalkane (i.e., **61**) which, in turn, gives the corresponding thioketone through its attack on sulfur and the simultaneous splitting off of nitrogen.[112] The thioketone formed reacts further with another molecule of the diazo compound to give the thiirane as in the cases of the reaction of diazoalkanes with elemental sulfur.

Thus, dispiro(xanthene-9,2′-thiirane-3′,9″-xanthene) (**60a**), dispiro(thioxanthene-9,2′-thiirane-3′,9″-thioxanthene) (**60b**), epithiobisdiphenyleneethane (**62**), and the tetrasubstituted thiiranes (**63a–63c**) are produced when the corresponding ketohydrazones are allowed to react with elemental sulfur and yellow mercuric oxide in boiling ether or benzene and in the presence of ethanolic potassium hydroxide. In the absence of mercuric oxide and/or alkali, the thiiranes are not obtained.



62



63

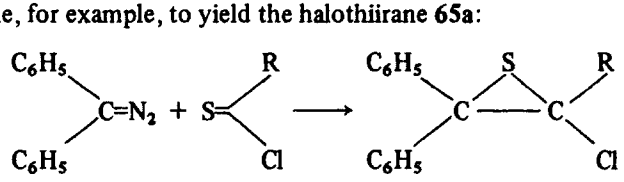
a. R = 

b. R = CH_3O 

c. R = CH_3 

c. FROM DIAZOMETHANES AND THIOACID CHLORIDES OR THIOESTERS

Chlorosubstituted aromatic thiiranes can be obtained by the reaction of aromatically substituted diazoalkanes with thiocarboxylic acid chlorides, thiophosgene, dithiocarbonic ester chlorides, and thiocarbonic ester chlorides. The reactions of thioesters ($RC(=S)-OR$)[103d] and dithioesters ($RC(=S)-SR$)[112] with diazoalkanes yield thiiranes and often the olefinic product formed by desulfurization of the thiirane, particularly if the thiocarbonyl group is capable of enolization. Thiophosgene reacts vigorously with certain diazo compounds – with diphenyldiazomethane, for example, to yield the halothiirane **65a**:



(47)

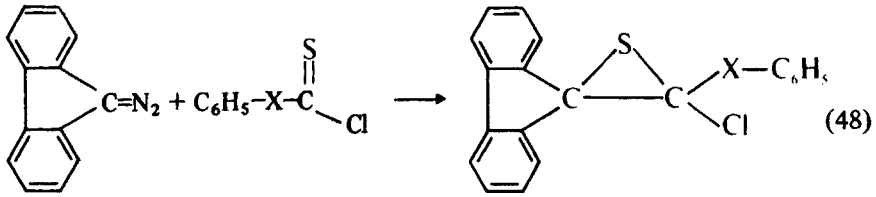
52 **64** **65**

a. R = Cl

a. R = Cl
b. R = C_6H_5
c. R = OC_6H_5
d. R = SC_6H_5
e. R = Br

The reaction of thiobenzoyl chloride with the aliphatic diazo compounds is quite analogous to that of the thiophosgene. It reacts rapidly with noncarbonyl-substituted diazo compounds, slowly with monocarbonyl derivatives, and not at all with dicarbonyl-substituted diazo compounds.

The following thiiranes were prepared using this method: **65a** and **65b** and **65c** and **65d**.[113] Biphenylenediazomethane reacts with the phenylchlorothiocarbonates as follows:



(48)

66 **67** **68**

a. X = S
b. X = O

a. X = S
b. X = O

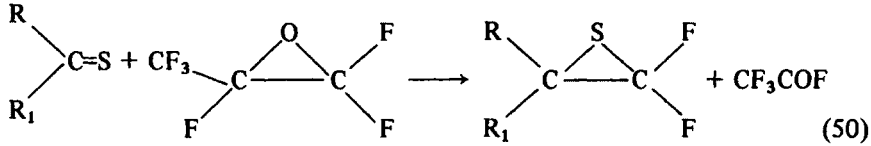
Very similar to the foregoing is the preparation of 2,2-diaryl-3,3-dithioaryl-thiiranes (**69**) from diaryldiazomethanes and arylthiocarbonates[114]:

(49)

69

a. Ar = C_6H_5
b. Ar = p-$CH_3C_6H_4$

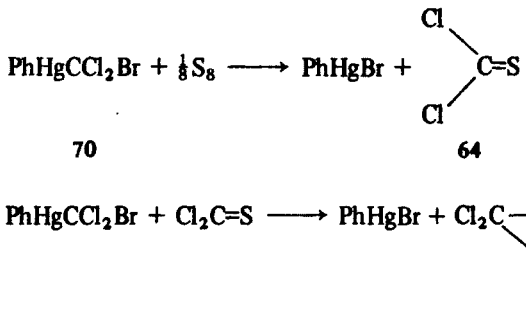
Reactions of diphenyldiazomethane with thiourea, thiobenzamide, carbon disulfide, phenylisothiocyanate, and other thiocarbonyl compounds did not afford thiiranes.[2] However, hexafluoropropene oxide reacts with perhalogenated thiocarbonyl compounds in a unique reaction carried out at high temperatures (175–400°) under pressure or in a vapor phase to afford perhalogenated thiiranes in about 50% yield[115]:



(50)

In this way, tetrafluorothiirane, chlorotrifluorthiirane, and 2,2-difluoro,3-hexafluoroethylthiirane have been prepared.[115]

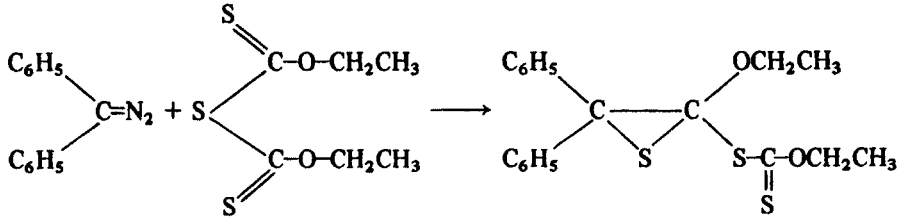
An interesting method to obtain the perchlorothiirane **71** is by the electrophilic attack by a dichlorocarbene – generated *in situ* from phenyl (bromodichloromethyl) mercury (**70**) – at a sulfur atom to form a thiophosgene (**64**). The thiophosgene thus obtained interacts with another mole of dichlorocarbene to give the final product in about 30% yield[116]:



(51)

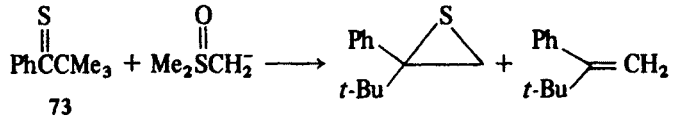
Although such CCl_2 addition to the C=S bond is probably a general reaction as indicated by the synthesis of **65a** and **65e** from **70** (or $PhHgCCl Br_2$) and thiobenzophenone,[116] it is quite possible that a free carbene mechanism is not operative. Mechanistic studies are required to answer this question.

Finally, one can obtain thiiranes (especially substituted; e.g., **72**) by the reaction of equimolar quantities of diaryldiazomethane and xanthogen acid anhydride at room temperature[117]:



72 (52)

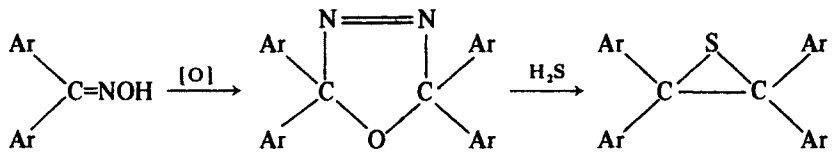
Substituted thiiranes and olefins are also obtained by treatment of nonenolizable thioketones (e.g., **73**) with dimethylsulfoxonium methylide[118]:



(52a)

K. *From Oxadiazolines and Thiadiazolines*

Oxadiazolines that are obtained by oxidation of aromatic ketoximes are converted to the corresponding thiiranes by the passing of dry hydrogen sulfide into their boiling ethanolic solution. Tetraaryl-substituted thiiranes (i.e., **76a–76c**) have been prepared in this way[119]:

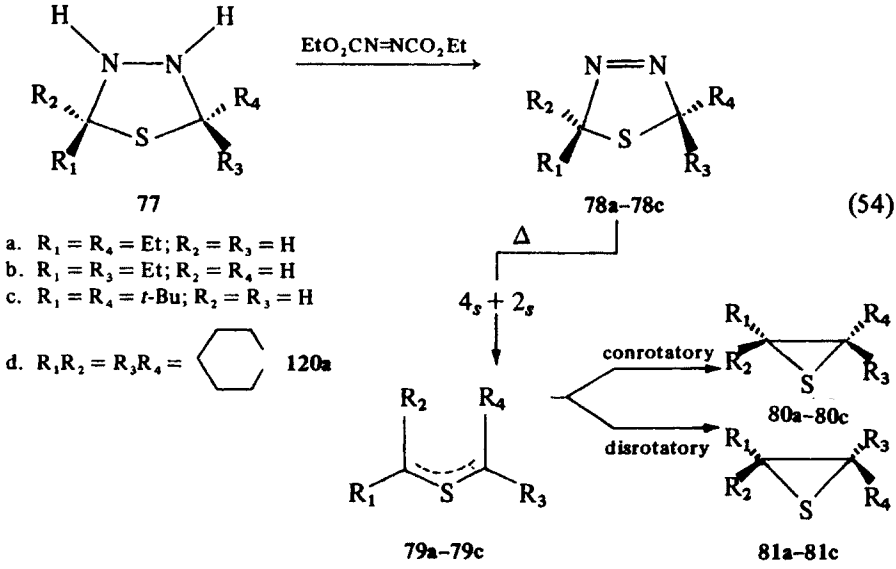


74 75 76 (53)

a. Ar = C_6H_5
b. Ar = p-$CH_3C_6H_4$
c. Ar = p-$CH_3OC_6H_4$

The chief reactions of thiocarbonyl ylides – the tetravalent sulfur compounds of type **79** – are ring closures to give thiiranes and formation of cycloadducts with suitable dipolarophiles.[120] The former reaction can be used for the preparation of thiiranes, although the difficulties often encountered in the synthesis of the precursor of the starting material, the sensitive thiadiazolidine **77**,[120b] constitute a severe drawback.

It turns out that on pyrolysis thiocarbonyl ylids are formed from thiadiazolines with retention of configuration, and they undergo conrotatory ring closure with nearly complete stereospecificity. This is illustrated in Eq. 54.[120]



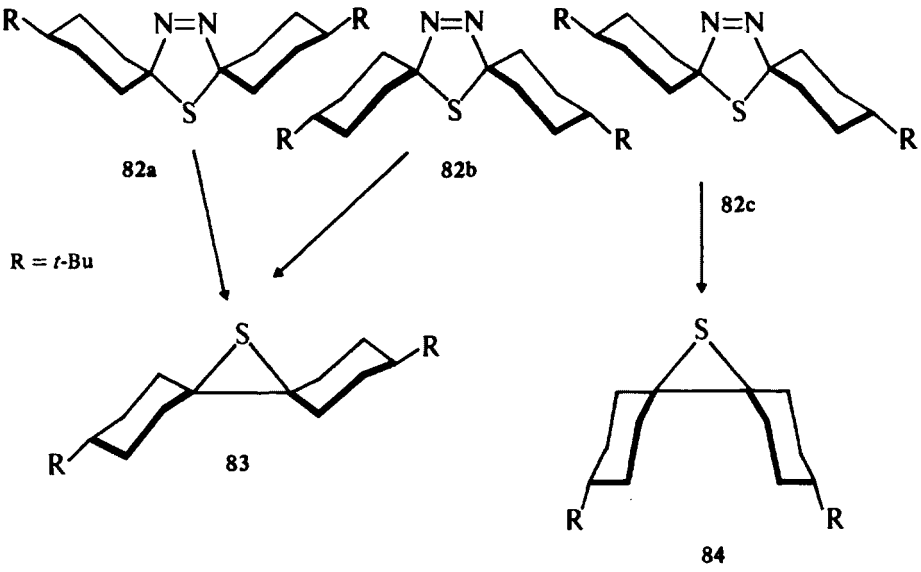
77 78a–78c (54)

a. $R_1 = R_4 = Et$; $R_2 = R_3 = H$
b. $R_1 = R_3 = Et$; $R_2 = R_4 = H$
c. $R_1 = R_4 = t$-Bu; $R_2 = R_3 = H$
d. $R_1R_2 = R_3R_4 =$ **120a**

79a–79c 80a–80c 81a–81c

Thus, the *trans* isomer **78a** gives a quantitative yield of the *cis* (conrotatory) product **80a**, the *cis* isomer **78b** yields the *trans*-thiirane **80b**, and **78c** decomposes smoothly, giving in 100% yield the *cis*-thiirane **80c**.[120] The overall conversion of the readily available *trans*- precursor **77c** to hindered *cis*-2,3-di-*t*-butylthiirane (**80c**) represents a particularly heartening victory of orbital symmetry over thermodynamics.

In a similar manner, both *trans,trans* and *cis,cis* isomers of thiazoline (**82a, 82b**) afforded on pyrolysis the *cis,trans*-thiirane **83** in essentially quantitative yield, whereas the *cis,trans* isomer (i.e., **82c**) afforded the *cis,cis*-thiirane (**84**)[121]:



In all cases the formation of the isomer observed is rationalized by conrotatory ring closure of the thiocarbonyl ylid intermediate. Also, tetrakis (trifluoromethyl)-thiadiazoline (i.e., **78**; $R_1 = R_2 = R_3 = R_4 = CF_3$) loses nitrogen on boiling to give tetrakis(trifluoromethyl)thiirane.[121a]

L. *From Chloromethyl Sulfides*

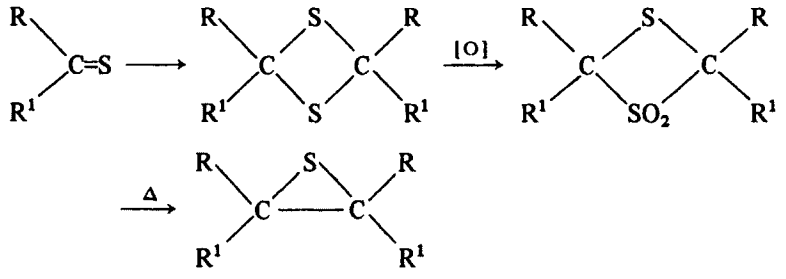
The formation of thiiranes by the reaction of hydrogen fluoride with alkane-chloromethyl sulfides is limited essentially to the following case[122]:

$$\underset{\textbf{85}}{C_2H_5SCH_2Cl} + HF \longrightarrow \underset{\textbf{86}}{C_2H_5SCH_2F} + HCl \qquad (55)$$

$$C_2H_5SCH_2F \longrightarrow CH_3CH\underset{\diagdown\,S\,\diagup}{\diagup\!\diagdown}CH_2 + HF$$

M. *From Dithietane Dioxides*

Highly fluorinated thioketones, which are readily dimerized to dithietanes, can be oxidized to their symmetric dioxides. Highly fluorinated thiiranes are obtained on pyrolysis of the dioxides following the loss of sulfur dioxide[107]:



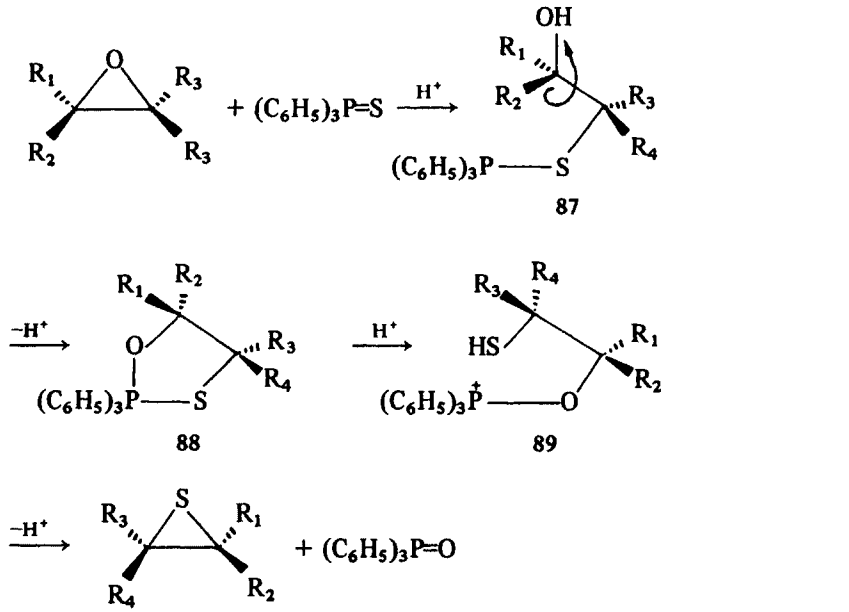
(56)

$R, R^1 = F, CF_3, CF_2Cl$

Apparently, this method is useful only for this particular type of fluorinated thiirane.

N. *By Conversion of Oxiranes with Phosphine Sulfides*

A principle that was demonstrated in an isolated example provided in the patent literature[123] was used to develop a practical method for the conversion of oxiranes to thiiranes. This method consists of the relatively rapid reaction of equimolar oxirane, phosphine sulfide, and trifluoroacetic acid in benzene at ambient temperatures followed by the neutralization of the reaction mixture and the isolation of the thiiranes obtained on column chromatography.[124] The reaction sequence including the proposed intermediates[125] (i.e., 87–89) is illustrated in Eq. 57.



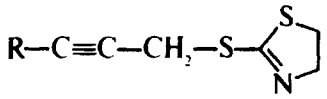
(57)

A stereochemical consequence of the implied mechanism is that the two Walden inversions must take place in the overall reaction.

This procedure is claimed to be competitive with or superior to existing methods of thiirane synthesis. It was successfully applied to the synthesis of 2-phenyl- and 2-*n*-hexylthiiranes as well as the thiiranes of cyclopentene, cyclohexene, and cyclooctene in yields of 35–64%[123] (see Table 1). Similarly, epithiochlorohydrin is obtained by treatment of epichlorohydrin with di(*O*-ethyl)dithiophosphoric acid and triethylamine.[125c]

O. *From Aldehydes and Ketones*

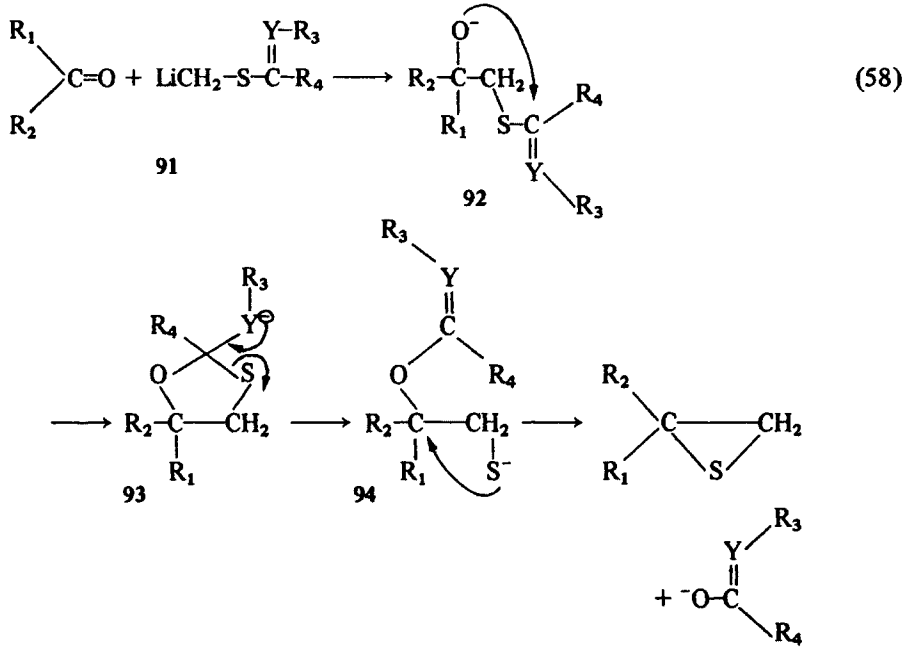
The direct conversions of aldehydes and ketones to homologous thiiranes have been concurrently, independently developed by two groups[126, 127] to become a very useful synthetic route. However, a Japanese group[128] should be credited for being the first to use benzaldehyde for thiirane synthesis. These investigators condensed the lithio salt of several 2-(propargylthio)-2-thiazolines **90** with benzaldehyde to provide the corresponding 2-ethyno-3-phenylthiiranes in low yields (*ca.* 20%). Apparently, the low yields discouraged further study.



R = H, Ph

90

All the methods leading from aldehydes and/or ketones to thiiranes involve variants of the reaction generalized in Eq. 58.[129]



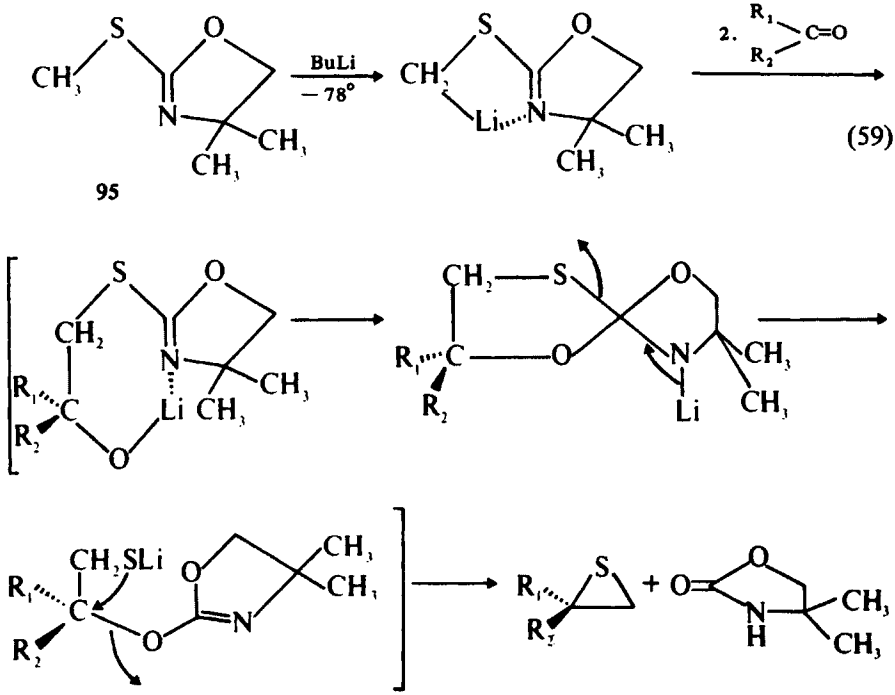
(58)

91 **92** **93** **94**

The group represented as $>C=Y-R_3$ acts as an alkoxide trap in intermediate **92** and as the oxy-leaving group in intermediate **94**.

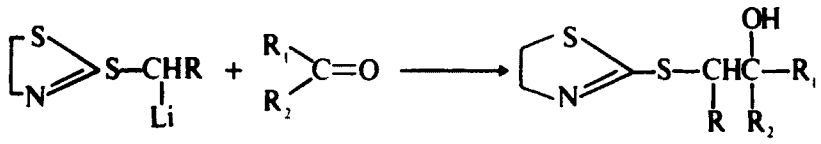
The 2-(thiomethyl)-2-oxazoline **95** – prepared by treating 4,4-dimethyloxazoline-2-thione[130] with sodium hydride and methyl iodide in THF – was found to readily metallate with *n*-butyl(lithium) and may be alkylated with various carbonyl compounds furnishing, in a single operation, the homologated thiiranes in 61–78% yields.

N-Hexylthiirane, cyclohexylthiirane, ferrocenylthiirane, 2-methyl,2-cyclohexylthiirane, cyclooctylthiirane, 2-methyl-2-benzylthiirane, and a mixture of isomers of α-decalinothiirane have been prepared[126] according to Eq. 59.[126]



Lithio salts of several 2-thioalkyl- (or aryl-) 2-thiazolines (e.g., **96**) were found to react with aldehydes and ketones to give alcohols. These alcohols when treated with base, acid, or heat gave thiiranes[127]:

A variety of other sulfur-stabilized carbanionic reagents were found to be capable of effecting such transformations when condensed with aldehydes or ketones, after lithiaton. Thus, a metallated 2-alkylthiopyridine (**98**) was transformed with benzaldehyde into a mixture of equimolar *cis-trans*-2,3-diphenylthiirane.[127] Similarly, reagents derived by lithiation of dithiacarbamate (e.g., **99**) and *O*-alkyl-, *S*-alkyldithiocarbonate (e.g., **100**) have also been effective for the synthesis of 2-ethyl-3-phenylthiirane (a *cis-trans* mixture) and *n*-hexylthiirane, respectively.[127] However, these reagents have a severe structural limitation; regardless of the base



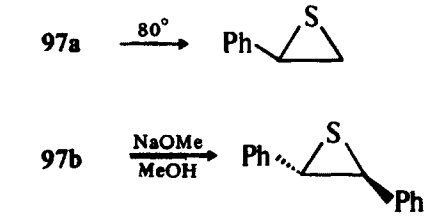
(60)

96

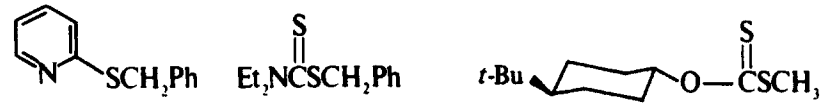
a. R = H
b. R = Ph

97

a. $R = R_1 = H; R_2 = Ph$
b. $R = R_1 = Ph; R_2 = H$
c. $R = Ph; R_1 = R_2 = CH_3$

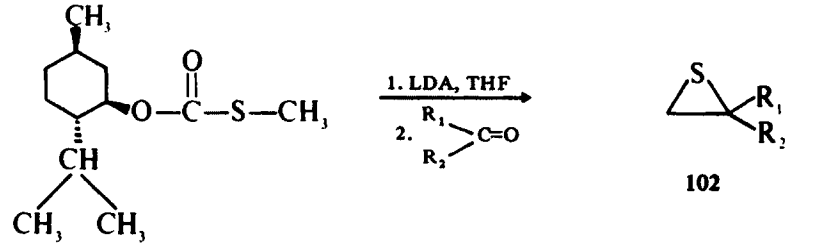


and solvent systems chosen, α-metallation was successful only when the *S*-alkyl group was methyl or benzyl. The *cis-trans* mixtures of the 2,3-disubstituted thiiranes obtained represent another drawback of these reagents.



98 99 100

In spite of the limitations mentioned, the readily accessible optically active reagents of type **100** (e.g., **101**), have been used successfully to induce an asymmetric synthesis of thiiranes.[129] This is illustrated in Eq. 61.



(61)

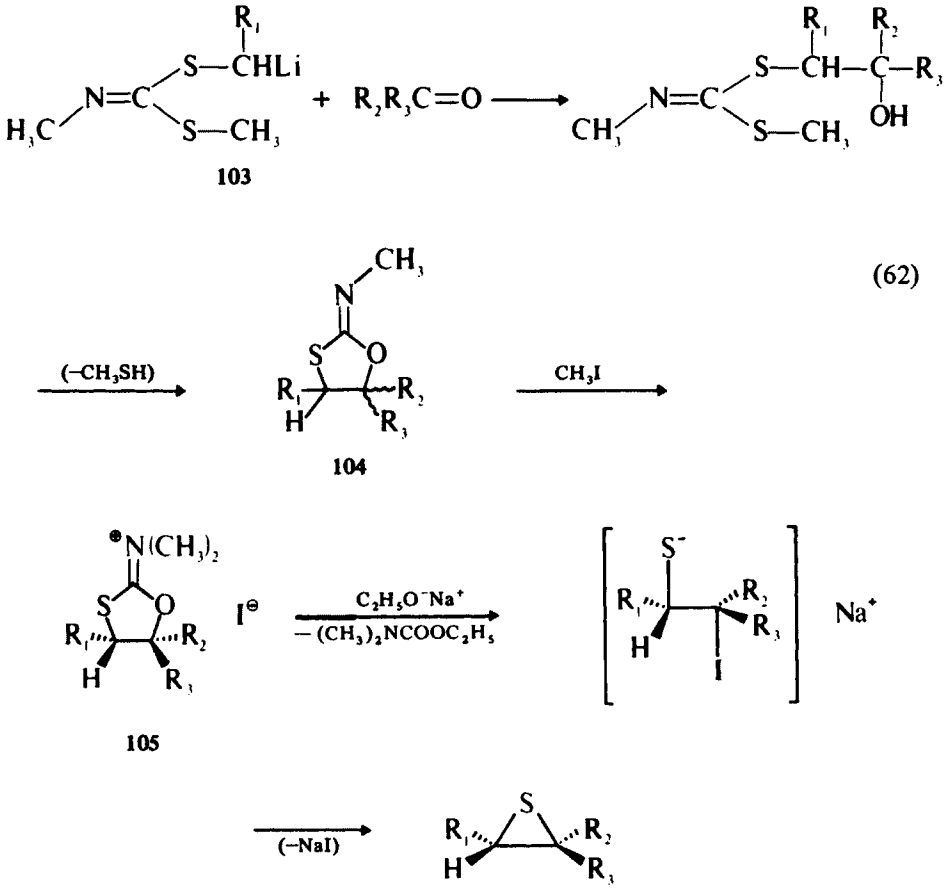
101

102

a. $R_1 = H; R_2 = Ph$
b. $R_1 = H; R_2 = n\text{-}C_6H_{13}$
c. $R_1 = CH_3; R_2 = Ph$
d. $R_1 = H; R_2 = n\text{-}C_5H_{11}$
e. $R_1 = H; R_2$ = cyclohexane
f. $R_1 = C_2H_5; R_2 = Ph$

The yields of **102a–102f** are in the range of 55–77%. Reagent **101** is recommended as the reagent of choice for transformations described in Eq. 58 even when asymmetric induction is of no consequence.[129]

A closely related method for the conversion of aldehydes and ketones to the homologous thiirane is the condensation of the carbonyl compounds with metallated dialkyl esters of the *N*-alkyl- (or *N*-aryl-) iminodithiacarbonic ester (**103**) followed by methylation of the 2-alkylimino-1,3-oxathiolane (**104**) and an action of a base on the immonium iodide (**105**).[131] This route is summarized in Eq. 62.[131]



(62)

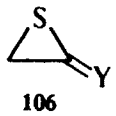
n-Hexyl-, cyclohex-3-enyl-, 2,6-dimethyl, 2-heptenyl, 2-methyl, 2-naphthyl-, 2-phenyl, 3-*t*-butyl-, 2-phenyl, 2-cyclohex-3-enyl, 2,3-diphenyl-, and 2,2-dimethyl, 3-phenylthiiranes were prepared through this method in good to high yields[131] (see Table 1). In this method too, one obtains mixtures of *cis-trans* isomers in the synthesis of 2,3-disubstituted thiiranes.

To conclude: all the variations of the method described in this section provide an efficient route to thiiranes from carbonyl compounds that may successfully be used as an alternative to the procedures involving oxiranes.

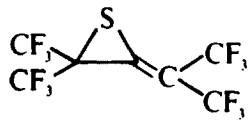
P. *The Preparation of Vinyl-, Vinylidene-, and Spirothiiranes*

a. ALLENIC THIIRANES (ALLENE EPISULFIDES)

In view of the fascinating chemistry associated with the cyclopropane–allene oxide tautomeric system[132] and for other reasons as well, several attempts to prepare the analogous thiirane system (i.e., **106a–106c**) were initiated recently.[133–136] The first example of an allenic thiirane (**106d**), however, had been prepared several years earlier.[121a]



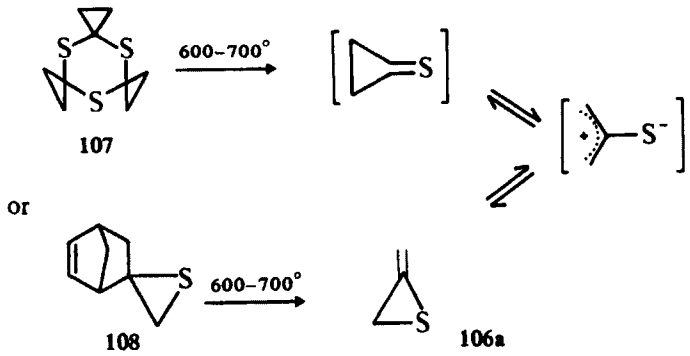
106



106d

a. Y = CH_2
b. Y = $C(CH_3)_2$
c. Y = N–Tos

The parent methylenethiirane (**106a**) was generated in an auxiliary study by E. Block and co-workers[133] by using flash-vacuum pyrolysis technique with either **107** or **108** as thermal precursor. These pyrolyses are consistent with the mechanistic picture presented in Eq. 63.[133]



107

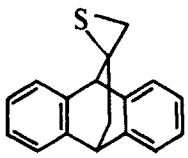
or

108

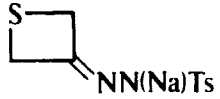
106a

(63)

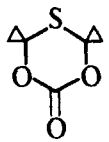
The thiirane **106a** is also formed on pyrolysis of either **109**, **110**,[133] or 8,9-dioxa-4-thiadispiro[2.1.2.3]decane-9-one (i.e., **111**).[134]



109

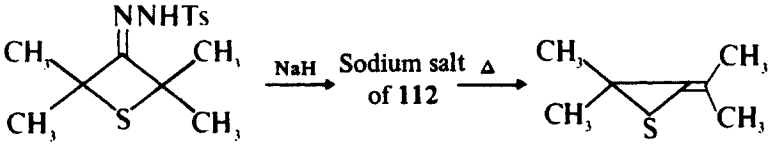


110



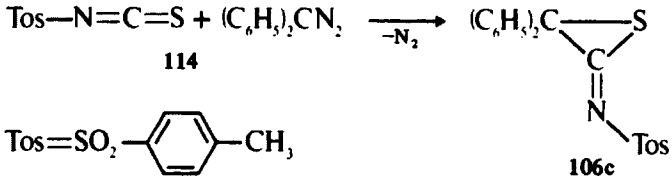
111

The half-life of **106a** was found to be of about 5 min at room temperature, whereas in dilute solution at $-30°$ **106a** was stable for several hours.[134] In contrast, slow heating of the dry sodium salt of **112** *in vacuo*, gave the stable tetramethylallene episulfide **113** as a colorless liquid in about 50% yield[135]:



112 **113** (64)

The thiiranimine **106c** was prepared by reacting tosylisothiocyanate with diphenyldiazomethane in anhydrous diethyl ether at 0°[136]:



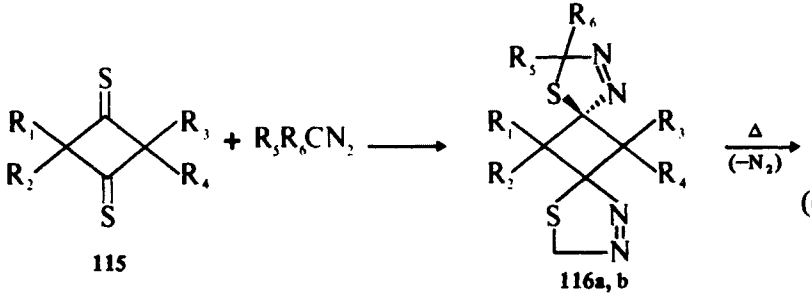
(65)

It is to be expected that further efforts in this area will result in new methods to synthesize thiiranes of type **106** with a variety of Y groups.

b. SPIROTHIIRANES

Several spirothiiranes have been mentioned (see, e.g., **108**,[133, 137] **109**,[133, 138] and reference 131) as being prepared in fair yields (52–54%) from the lithio salts of either the oxazoline reagents[126] or the dialkyl ester of the iminodithiacarbonic ester reagent[131] and the corresponding ketones. Others were mentioned in Sections III, 1, J, a (i.e., **56**) and III, 1, O.

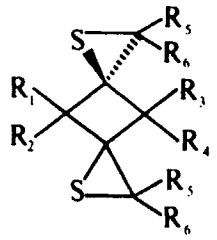
Several spirothiiranes have been synthesized by treating tetrasubstituted dithiones (i.e., **115a**) and dispirodithiones (i.e., **115b**) with etheral diazomethane followed by refluxing of the resulting bisthiadiazolines (i.e., **116a**, **116b**) in chloroform or carbon tetrachloride–hexane solutions. Nitrogen is readily lost, and one obtains a quantitative yield of the stereoisomeric mixtures of the corresponding spirothiiranes (e.g., **117a**, **117b**),[139] as illustrated in Eq. 66.



115 **116a, b** (66)

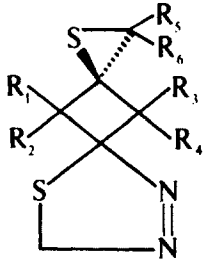
a. $R_1 = R_2 = R_3 = R_4 = CH_3$
b. $R_1R_2 = R_3R_4 = -(CH_2)_n-$; $n = 4$ or 5

$R_5 = R_6 = H$ or C_6H_5
Stereoisomeric mixture



117a, b

On repeated recrystallizations of the crude spirothiirane as a 70:30 *trans-cis* mixture of **117a** ($R_5 = R_6 = H$), the pure *trans*-dispirothiirane (**117a**) was isolated. Essentially the same *trans-cis* isomeric ratio is obtained in the other cases. When the mixture is allowed to stand at room temperature the monospirothiirane **118** can be obtained from **116**.

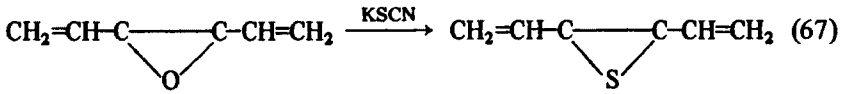


118

When diphenyldiazomethane is used rather than the parent diazomethane, a quantitative yield of **117** ($R = C_6H_5$; stereoisomeric dispirothiiranes) is immediately formed. Thus it appears that this route represents a suitable general method of spirothiirane synthesis.

c. DIVINYLTHIIRANE

The neat mixture of *cis*- and *trans*-2,3-divinyloxiranes (**119**) was treated with saturated aqueous solution of KSCN to give, after distillation on a high vacuum line, a 38:62 *cis-trans* mixture of 2,3-divinylthiirane (**120**) in 70% total yield[140]:



(67)

119; *cis-trans* **120**; *cis-trans*

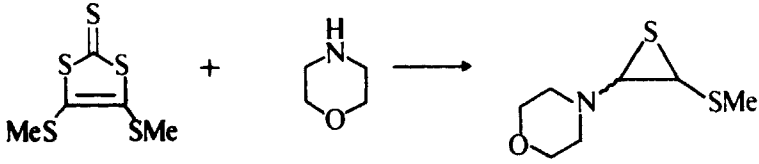
Both the pure *cis* and the pure *trans* forms of **120** are stable at room temperature if stored under nitrogen.

Although this is one of the classical methods of thiirane synthesis, its successful application in this particular case of the sensitive divinylthiirane is absolutely dependent on the particular procedure used.[140]

It may well be that reported unsuccessful attempts to prepare particular thiiranes reflect not the failure of the method used but rather its inappropriate application in the specific cases at hand.

Q. *Miscellaneous*

Treatment of 4,5-bis(methylthio)-1,3-dithiole-2-thione with morpholine gave a complex mixture of products, among which was a mixture of *cis*- and *trans*-thiiranes obtained in a moderate yield,[140a] see Eq. 68. A thiirane intermediate was suggested.



(68)

2. Structure and Physical Properties

Considerable effort has gone into the determination of the structure of three-membered heterocyclic ring systems, as well as selected key parameters (e.g., bond lengths, orders and energies, equilibrium geometries and angles, atomic charge distributions, total energies of the molecule, dipole moments) of these molecules through empirical, semiempirical, or nonempirical approaches. For the most part the nonempirical calculations have been performed on molecules of known structure so that direct comparison could be made between calculated and experimentally observable properties. Only relatively recently has much attention been given to using such calculations in a predictive role for molecules that are as yet unknown.

Thiiranes, as one of the first three-membered heterocyclic ring systems to be synthesized and characterized, became interesting (and useful) candidates for several tneoretical investigations, empirically based as well as nonempirical.

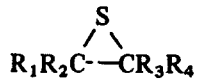
The first spectral studies of thiirane[144] were made in the region of 0.7–1.2 μm. The range was later extended to 1–17 μm[145] including the Raman spectrum.[146, 147]

The structure of thiirane was calculated on the basis of microwave measurements, and the following bond lengths and angles were reported[148a]:

Bond length (Å)			Angles		
C–S	C–C	C–H	< HCH	< CSC	< H_2CC
1.819	1.492 (1.484)[148b]	1.078	116°0′	65°48′	151°43′

These values suggest a partial double bond character of the thiirane C–C bond. This possibility applies to an even greater extent to the oxirane.[148a] The reported

TABLE 1. PREPARATION OF THIIRANES



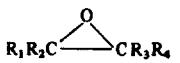
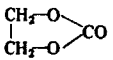
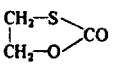
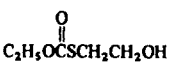
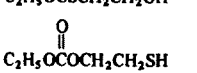
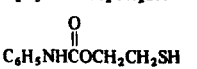
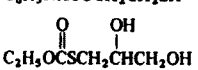
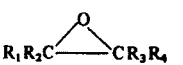
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
H	H	H	H		KSCN	27–97	4, 17–22, 30
					NH_4SCN	48	23
					$(NH_2)_2C=S$	48–60	4, 43, 47
					KSCN	65–85	58, 59, 61
					$(NH_2)_2C=S$	–	60
					Pyrolysis (+ alkaline catalysis)	70–88	62, 64
					Pyrolysis (+ alkaline catalysis)	77–high	64
							
							
							
				$AcSCH_2CH_2OH$ $HSCH_2CH_2OAc$	$NaOH$, KOH, or $NaHCO_3$	25–80	67, 68
				$ClCH_2CH_2SCN$ $NCSCH_2CH_2SCN$	Na_2S	–	3
				$ClCH_2CH_2SH$	$NaHCO_3$ or $NaOH$ or Na_2S	50–90	86
				$ClCH_2CH_2OH$	$(NH_2)_2C=S$	High	91
				$CH_2=CH_2$	$C_2H_5S_4C_2H_5$	15	94
					S_2Cl_2/Na_2S	75	96
					$(NH_2)_2C=S$	58–70	5, 8, 21, 48, 49

TABLE 1 CONTINUED

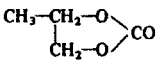
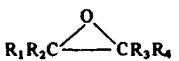
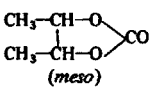
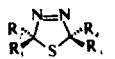
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
					KSCN	50-65	48, 59
				$ClCH(CH_3)CH_2SCN$ $NCSCH(CH_3)CH_2SCN$	Na_2S	–	77
				$HOCH_2CH_2SH$	$KHSO_4/\Delta$	35	66b
				$ClCH(CH_3)CH_2OH$	$(NH_2)_2C=S$	Good	91
CH_3	H	H	H	$CH_3CH=CH_2$	S_2Cl_2/Na_2S or Al-Hg	35-65	96
				$HOCH(CH_3)CH_2SH$	$KHSO_4$	34-40	66b
C_2H_5	H	H	H	$BrCH(C_2H_5CH_2SCN)_2$ $NCSCH(C_2H_5)CH_2SCN$	Na_2S	–	77
				$ClCH_2CH(OH)CH_2CH_3$	$(H_2N)_2CS-K_2CO_3$	Good	91
CH_3	H	CH_3	H		KSCN	76	26, 27
				(*cis*, *trans*)	$(NH_2)_2C=S$	73	50
				 (*meso*)	KSCN	31	59
				$ClCH(CH_3)CH(CH_3)SH$	$NaHCO_3$	80	86
				$ClCH(CH_3)CH(CH_3)OH$	$(H_2N)_2C=S/K_2CO_3$	Good	91
				$CH_3CH=CHCH_3$	S_2Cl_2/Na_2S	62-64	96
				(*cis*, *trans*)	$ArSSCl/Na_2S$ or $NaNH_2$ Ar = *p*-$CH_3C_6H_4$ or *o*-$NO_2C_6H_4$	40-60	98
C_2H_5	H	C_2H_5	H		Pyrolysis	100	120
t-Bu	H	*t*-Bu	H	$R_1 = R_4 = C_2H_5$ or *t*-Bu; $R_1 = R_3 = C_2H_5$			
t-Bu 	*cis*	*trans*  *t*-Bu		$R_1 = R_3$; $R_2 = R_4$ or			
				$R_2 = R_3 =$  R		100	121

TABLE 1 CONTINUED

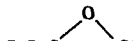
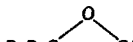
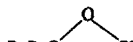
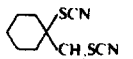
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
CH_3	CH_3	H	H		KSCN	73	22
					$(NH_2)_2C=S$	57	5
				$(CH_3)_2C=CH_2$	S_2Cl_2/Na_2S	58	95
CH_3	CH_3	CH_3	H or CH_3	$NCSC(CH_3)_2CR_4(CH_3)SCN$			
					Na_2S	90-95	80, 81
$ClCH_2$	H	H	H		$(NH_2)_2C=S$	50-67	5, 8, 20, 21
					NH_4SCN	38	
				$ClCH_2CH=CH_2$	S_2Cl_2/Na_2S or Al-Hg	29-41	96
$CH_2=CH$	H	H	H		$(NH_2)_2C=S$	50	6
$CH_2=CH(CH_2)_n$	H	H	H	$CH_2=CH(CH_2)_nCH=CH_2$ $n = 0$-4	S_2Cl_2/Na_2S	16-41	96
$-(CH_2)_5-$		H	H		Na_2S-H_2S		81
H	$-(CH_2)_3-$		H		KSCN	20	28
					$(C_6H_5)_3P=S/CF_3CO_2H$	35	124
					R = H $NaHCO_3$		
					R = Ac or: NaOH	20-82	69, 71
					$R = SO_2CH_3$ NaOH	66	71
					R = Ts NaOH (in diglyme)	35	71
					R = Ts; $(SCOC_6H_5)$ NaOH (in diglyme)	25	71
					R = H; K_2CO_3	Low	28
					SO_2CH_3 NaOH	63	29

TABLE 1 CONTINUED

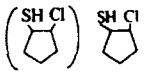
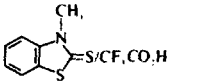
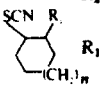
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
					$NaHCO_3$	75	29
					S_2Cl_2/Na_2S or Al-Hg	37-47	96
					$I_2 + (SCN)_2$	40	98
					$ArSSCl/NaNH_2$	54-55	98
H	$-(CH_2)_4-$		H		KSCN	43-73	5, 21, 22, 29
					NH_4SCN	43-61	5
				(and 4-methyl)	$(NH_2)_2C=S$	43-61	5, 6
						100	56
					$(C_6H_5)_3P=S/CF_3CO_2H$	50	124
H	$-(CH_2)_6-$		H		$n\text{-}Bu_3P=S/CF_3CO_2H$	64	124
					$I_2 + S(CNS)_2$	57	97
					$ArSSCl/NaNH_2$ or Na_2S	47-77	98
H	$-(CH_2)_4-$		H		(Ar = *p*-$CH_3C_6H_4$ or *o*-$NO_2C_6H_4$)		
					$C_2H_5S_4C_2H_5$	8	94
					S_2Cl_2/Na_2S or Al-Hg	29-46	96
				 R_1 = H or Ac R_2 = H or Ac	$NaHCO_3$ or KOH	55-70	67, 68
				$R_1 = [C(NH_2)_2]HSO_4$ R_2 = H	Na_2CO_3	69	40
				 R_1 = Cl or SCN	Na_2S or $Na_2S\text{-}H_2S$	50	79, 81, 82

TABLE 1 CONTINUED

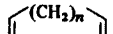
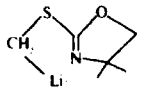
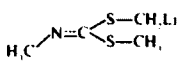
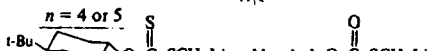
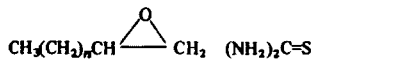
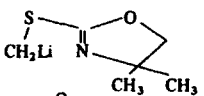
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
H	$-(CH_2)_n-CH=CH-(CH_2)_n-$		H	 $n = 1, 2$	S_2Cl_2/Al-Hg	15-16	96
					$I_2 + (SCN)_2$	26	97
$(CH_2)_nCH_3$	H	H	H	$CH_3(CH_2)_n-CHO$ $n = 5$		73	126
						54	131
				 $n = 4$ or 5		61-71	127, 129
				 $n = 3, 5$	$(NH_2)_2C=S$	52-78	41, 45
				$n = 3, 6, 7, 9$	S_2Cl_2/Hg-Al	25-41	96
				$n = 5$	$(C_6H_5)_3P=S/CF_3CO_2H$	58	124
	H	H	H		 or: Methyl-$OCSCH_2Li$	77, 78	126, 129
	H	H	H			68	126
	CH_3	H	H			66	126

TABLE 1 CONTINUED

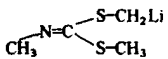
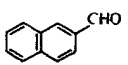
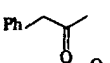
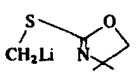
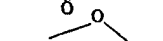
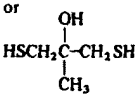
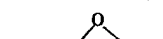
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
		H	H			61	126
		H	H			61	126
		H	H			54	131
$CH_2CH(CH_2)_2C(CH_3)_2$ CH_3	H	H	H	$OHC-CH_2CH(CH_2)_2CH=C(CH_3)_2$ CH_3		52	131
β-Naphthyl	H	H	H			25	31
$PhCH_2$	H	H	H	$PhCH_2CH=CH_2$	$S_2Cl_2/Hg\text{-}Al$	23	95
$PhCH_2$	CH_3	H	H			31	126
CH_2OR_5	H	H	H		$(NH_2)_2C=S$	81-90	31, 52, 53
CH_2SH	H or CH_3	H	H	$HOCH_2CH(OH)CH_2SH$ or 	$HCl\text{-}NaHCO_3$	54-57	72
				$HOCH_2CH(SH)CH_2SH$	$KHSO_4/\Delta$	70	66b
CH_2SR	H	H	H		$(NH_2)_2C=S$	19-60	52
					$RCOX + NaHCO_3$; RCOX	5-99	52, 87, 88

TABLE 1 CONTINUED

R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
				$RSCH_2CH(SR)CH_2OR_2$	$NaHCO_3$	27–80	67, 68, 72
CH_2SH	H	CH_2OH	H	$AcSCH_2CH(OAc)CHCH_2OAc$ (SAc)	HCl	–	70
R	H	R_1	$CHR_2(CH_2)_nSR$ $n = 0$–7	$CH_3COS-CH(R)C(O)C(R_1)CH(R_2)CH_2)_nSR$ ((S)$OCOCH_3$)	$NaHCO_3$	53–69	72
$CH_2N(C_2H_5)_5$	H	H	H	$(C_2H_5)_2NCH_2-CH(O)CH_2$		29–60	46, 52
$(CH_2)_nCO_2R$ $n = 1, 2$	H or CH_3	H	H or R	$RO_2C(CH_2)_n-C(O)(R)-CHR$	$(NH_2)_2CS$	17–58	14, 53–55
$(CH_2)_8CO_2CH_3$	H	H	H	$CH_3O_2C(CH_2)_8-CH(O)-CH_2$	$(NH_2)_2CS$	55	14
$(CH_2)_nCH_3$	H	$(CH_2)_nCO_2H$	H	$CH_3(CH_2)_nCH(O)CH-(CH_2)_nCO_2H$	$(NH_2)_2CS$	71–81	14[a]
$(CH_2)_nCH_3$ $n = 5, 7, 10$	H (*cis* and *trans*)	$(CH_2)_nCO_2H$ $n = 4, 7, 11$	H	$CH_3(CH_2)_nCH(R_1)-CH(CH_2)_nCO_2H$ (R_2)	KOH or Na_2S or NaOH	30–74	65, 83
				$R_1 = R_2 = SCN$ (*threo* and *erythro*) $R_1 = Cl$; $R_2 = SCN$			
				$CH_3(CH_2)_nCH(S-C(=S)-S)CH(CH_2)_nCO_2H$ $n = 5, 7, 10$ $n = 4, 7, 11$ (*erythro* and *threo*)	KOH	58–78	65

TABLE 1 CONTINUED

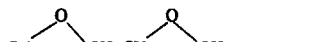
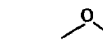
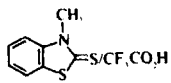
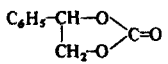
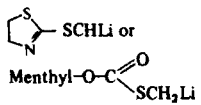
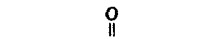
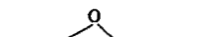
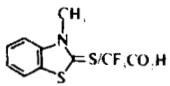
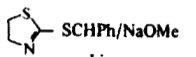
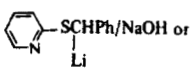
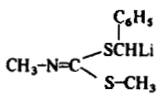
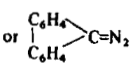
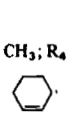
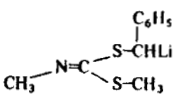
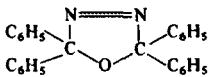
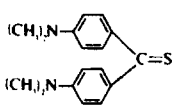
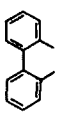
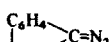
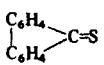
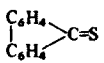
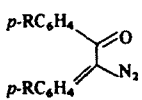
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
$(CH_2)_7CH_3$	H	$(CH_2)_nCH_2OH$ $n = 7, 9, 11$	H	$CH_3(CH_2)_7$–CH(O)CH–$(CH_2)_nCH_2OH$ *cis* and *trans*	$(NH_2)_2C{=}S$	60–65	14
	H	H	H	 (2R:3R; 25:35; *meso*)	KSCN	39	37
C_6H_5	H	H	H		KSCN	47–72	32–34
						100	56
					n-$Bu_3P{=}S/CF_3CO_2H$	62	124
					$(NH_2)_2C{=}S$	38	89
				C_6H_5CHO	KSCN	34	59
						55	127, 129
				$C_6H_5CH{=}CH_2$	S_2Cl_2/Na_2S	44	96
C_6H_5	H	CH_3CH_2	H	CH_3CH_2CHO		74 (*cis*, *trans*)	127
C_6H_5	CH_3 or C_2H_5	H	H	$C_6H_5COR_2$ $R = CH_3$ or C_2H_5		61–64	129

TABLE 1 CONTINUED

R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
C_6H_5	H	C_6H_5	H	 *cis* and *trans*	$(NH_2)_2C{=}S$	64, 86	51
						80–100	56
				PhCHO		80 (*trans*)	127
						44–76 (*cis-trans*)	127, 131
							
C_6H_5	C_6H_5	Cl	Cl	$(C_6H_5)_2C{=}S$	$C_6H_5HgCCl_2Br$	75	116
C_6H_5 or 	C_6H_5	Cl or $X{-}C_6H_5$ X = O or S	Cl	$(C_6H_5)_2C{=}N_2$ or 	$S{=}CCl_2$ or $C_6H_5\overset{S}{\overset{\|}{C}}Cl$ or $X{-}C_6H_5\overset{S}{\overset{\|}{C}}Cl$	30–70	112–114
C_6H_5	H	H or CH_3	R R = CH_3 or $C(CH_3)_3$ or 	$R_3R_4C{=}O$ R_3 = H or CH_3; R_4 = CH_3; $C(CH_3)_3$; 		31–75 (*cis-trans*)	131

R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
C_6H_5	C_6H_5	C_6H_5	C_6H_5	$(C_6H_5)_2C{=}S$	$(C_6H_5)_2C{=}N_2$	–	2
				$(C_6H_5)_2CN_2$	S	90–95	106, 110
				$(C_6H_5)_2C{=}NNH_2$	S/HgO	20–32	111
					H_2S	85	118
p-RC_6H_4	p-RC_6H_4	p-RC_6H_4	p-RC_6H_4	$(p\text{-}RC_6H_4)_2C{=}NNH_2$	S/HgO	20–32	111
				$(p\text{-}CH_3OC_6H_4)_2CN_2$	S	90–95	110
p-ROC_6H_4	p-ROC_6H_4 R = CH_3 or C_2H_5	p-ROC_6H_4	p-ROC_6H_4	$(p\text{-}ROC_6H_4)_2C{=}S$ R = CH_3 or C_2H_5	ArMgBr or Mg/MgI_2	40–70	100, 101
C_6H_5	C_6H_5	p-$CH_3OC_6H_5$	p-$CH_3OC_6H_5$	$(p\text{-}CH_3OC_6H_4)_2C{=}S$	$(C_6H_5)_2C{=}N_2$	–	2
C_6H_5	C_6H_5	SC_6H_5	SC_6H_5	$(C_6H_5S)_2C{=}S$	$(C_6H_5)_2C{=}N_2$	60	116
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	$(p\text{-}CH_3C_6H_4S)_2C{=}S$	$(p\text{-}CH_3C_6H_4)_2C{=}N_2$	–	116
$(CH_3)_2N$–C_6H_4	$(CH_3)_2N$–C_6H_4	C_6H_5	C_6H_5			Very good	2, 105
		p-$CH_3C_6H_4$	p-$CH_3C_6H_4$				
		p-ClC_6H_4	p-ClC_6H_4				
		CH_3	C_6H_5 or p-$CH_3C_6H_4$				
		C_6H_5					
		C_6H_5	C_6H_5	$(C_6H_5)_2C{=}S$		–	2
					$(C_6H_5)_2CN_2$	–	106
		C_6H_4p-R R = H, CH_3O, CH_3, Cl				8–81	141

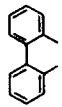
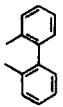
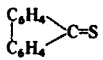
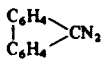
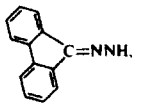
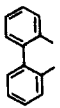
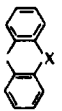
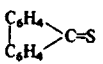
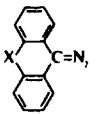
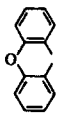
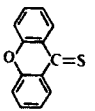
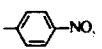
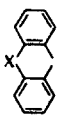
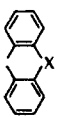
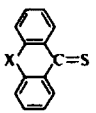
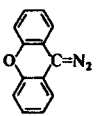
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
						68	106
					S/HgO	Very low	111
		 X = O or S				–	106
		C_6H_5 *p*-ClC_6H_4 *p*-$CH_3C_6H_4$	C_6H_5 *p*-ClC_6H_4 *p*-$CH_3C_6H_4$			Very good	105, 107
		C_6H_5	CH_3				
		C_6H_5					
		C_6H_5					
 X = O or S		 X = O or S		 X = O or S		80–85	106

TABLE 1 CONTINUED

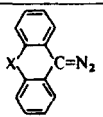
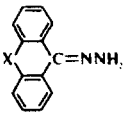
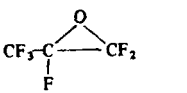
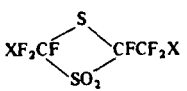
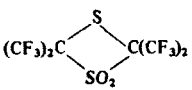
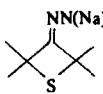
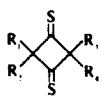
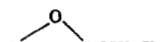
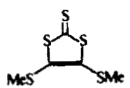
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
					S	60–93	106, 110
					S/NaOH, HgO	26–28	111
Cl	Cl	Cl	Cl	$PhHgCCl_2Br$	S	36	116
Ph	Ph	Cl	Cl	$Ph_2C{=}S$	$PhHgCCl_2Br$	75	116
Ph	Ph	Cl	Br		$PhHgCClBr_2$	74	116
C_6H_5	C_6H_5	CF_3	CF_3	$(CF_3)_2C{=}S$	$(C_6H_5)_2C{=}N_2$	–	108
C_6H_5	C_6H_5	=N–Tos		Tos–N=C=S	$(C_6H_5)_2C{=}N_2$	67	136
C_6H_5	C_6H_5	OC_2H_5	$SCOC_2H_5$	$(C_6H_5)_2C{=}N_2$	$(CH_3CH_2OC)_2S$	82	117
F	F or CF_3	F	F or Cl		$F_2C{=}S$ or $ClFC{=}S$ or $F(CF_3)C{=}S$	15–43	115
CF_3	CF_3	F	F		$(CF_3)_2C{=}S$	56	115
CF_2Cl	F	CF_2Cl	F	 X = F or Cl	Pyrolysis	–	107
CF_3	F	CF_3	F				
CF_3	CF_3	CF_3	CF_3		Pyrolysis	–	107
CH_3	CH_3				Pyrolysis	40–65	135

TABLE 1 CONTINUED

Miscellaneous

Compound	Starting material	Reagent	Yield (%)	Ref.
Sugar thiiranes	Sugar epoxides	NH_4SCN	20	35, 36
	Sugar *O*- and *S*-acetates Sugar-OTs; *S*-acetates	CH_3ONa	72–89	42
	Sugar-OMs-thiocyanates	KOH	62	74, 75
Steroidal thiiranes	Steroidal epoxides	KSCN	15	142
	Acetylated vicinal hydroxythiols and chlorothiocyanates	KOH	–	73, 74, 87
	Vicinal hydroxy-substituted thiols		–	142
	Vicinal hydroxy- (and *O*-mesyl- or *O*-acetoxy-) *O*-tosylthiocyanates	KOH (or Al_2O_3)	64–77	73, 74, 87
	2-Cholestene	$I_2 + (SCN)_2$	46	97
Dispirothiiranes		$R_5R_6CN_2$	Quantitative	139
Norbornenes and norbornadienes				
	R_1=R_2=H or CH_3 	$ArSSCl/Na_2S$ or $NaNH_2$ ($Ar = o\text{-}NO_2C_6H_4$ or $p\text{-}CH_3\text{-}C_6H_4$)	30–84 63–78 (*exo*:*endo* ≈ 4:1–1.5)	98 99

Miscellaneous

Compound					Starting material	Reagent	Yield (%)	Ref.
H		H	H	$(CH_2)_nCH_3$			55–87	143a
Me			H	H		$(MeO)_3P$	–	143b
			H	H		S_2Cl_2/Hg-Al	41	95
SMe			H	H			Moderate (*cis* and *trans*)	140a

[a] Doubly unsaturated fatty acids included.

values for the lengths of the corresponding C–C and C–H bonds in methylthiirane are 1.513 and 1.09 Å, respectively.[149]

A. *Molecular Orbital Calculations*

Nonempirical LCAO-MO-SCF (linear combination of atomic orbitals-molecular orbitals–self-consistent field) calculations with Gaussian type functions have been performed on the parent thiirane,[150] using the bond lengths derived from microwave spectroscopy and a medium-sized basis set [consisting of 5*s* and 6*p* (two each for *Px*, *Py*, and *Pz* orbitals) GTF for each C and S atom, and 2*s* for each hydrogen]. The *d* orbitals were not taken into consideration since *ab initio* work[151] indicated their inclusion to have a very small effect.

The values of total energy E_t, in atomic units (a.u.), ionization potential *Ip*, in electron volts (eV), and dipole moment μ, in debye units (D), of the parent thiirane, thus calculated[150] are given below together with the experimental values for comparison:

	Calculated	Experimental
E_t (a.u.)	−456.002	−477.916
Ip (eV)	4.18	8.87[152]
μ (D)	5.17	1.66[153]; 1.84[148]

Ab initio LCAO-MO-SCF calculations, which were carried out with uncontracted Gaussian basis sets containing 64 *spd* functions for thiirane, resulted in obtaining the values of −474.8717 a.u. and 0.97 eV for E_t and μ, respectively.[154]

The calculated values for E_t, *Ip*, and μ in the parent oxirane are −151.395 a.u., 11.19 eV, and 2.35 D, respectively,[150] whereas the corresponding experimental *Ip* and μ are 10.65 eV[152] and 1.88 D,[153] respectively.

The low ionization potential calculated and the considerably overestimated dipole moment for the thiirane (given above)[150] are in accord with the tendency of the Gaussian basis set to overestimate dipole movements and its limitation when employed for sulfur without the inclusion of *d* orbitals.

Group function calculations – which are known to improve the energy values significantly with respect to the SCF-MO method[155] – have been performed for the parent thiirane.[156] The ground state one-electron dipole moment was found[156] to be 0.5572 D and the molecular energy −474.619 a.u. compared with 0.8357 D and −474.5159 a.u. in the SCF-MO treatment with the same basis.[157]

Systematic *ab initio* and semiempirical molecular Hartree-Fock-type SCF-MO calculations have been performed on the sulfur atom–ethylene system and its reaction product thiirane, to elucidate the molecular structure of the latter.[158] The values obtained for the E_t and μ with 42 *sp* basis sets were −475.4206 a.u. and 1.74 D, respectively. Also the highest field and lowest vacant MO coefficients

in linear combination of the 48 *spd* AO for thiirane were computed[158] without finding any marked differences in the MO patterns of the two sets.

In a parallel nonempirical SCF-MO study of thiirane, it was found[159] that all its lower lying triplet and singlet states have a ring-distorted equilibrium conformation in which the terminal methylene plane is orthogonal to the CCS plane and there is a considerable energy barrier with respect to rotation of this methylene. The calculations evolved are consistent with the available uv spectra of thiirane, which display two overlapping long wavelength bands with maxima around 39,000 and 41,000 cm^{-1}. The first of these weak bands may be assigned to the nonvertical $S_0 \rightarrow S_1$ transition with a calculated excitation energy of 32,970 cm^{-1}.[159]

The nature of the bonding (e.g., the degree of "bond bending") in thiirane has been investigated through *ab initio* calculations using the floating spherical Gaussian orbital (FSGO) method.[160] In accord with chemical intuition, it was demonstrated[161] that the C–C ring bond becomes progressively more bent as the bond length is reduced. The C–C bonds were found to be more flexible than the C–S bond. Thus, the perpendicular distances from bond axis to orbital center measured by δ (in bohr) were calculated to be 0.1236 and 0.0755 for the C–C and C–S bonds, respectively, whereas the corresponding values for the C–C and C–O bonds in the oxirane were calculated to be 0.3429 and 0.0132, respectively.[161] The C–C bond lengths in thiirane and oxirane are 2.8195 and 2.7817 bohrs, respectively. Indeed, the key factor in determining δ is the internuclear distance. An excellent agreement between calculated and experimental bond distances of thiirane has been obtained in an *ab initio* MO-SCF-LCAO study using a medium-sized contracted Gaussian basis set.[162]

The calculated C–C and C–S distances were calculated to be 1.492 and 1.819 Å respectively,[162] identical to the experimental values (!). Furthermore, the calculated equilibrium geometry and orbital energies were shown[162] to be in good agreement with available microwave data and ionization energies of the outermost orbitals obtained from a photoelectron spectrum.[163]

B. *Strain Energy*

The strain energy of thiirane was estimated from the difference between the heat of formation and the individual bond energies.[164] It amounts to 9 kcal/mole, vs. 13 kcal/mole for the analogous oxirane and 25 kcal/mole for cyclopropane. More recent determination of the strain energy based on the difference between the measured and the calculated heats of formation show 18.6 for thiirane, about 28 for oxirane, about 23 for aziridine, and 27.5 kcal/mole for cyclopropane.[165] In any case, the thiiranes feature a lower strain energy than other saturated three-membered rings. The same pattern appears to hold with other classes of three-membered rings, for example, the unsaturated (i.e., thiirenes, oxirenes, cyclopropenes) and the oxidized series (i.e., thiirane oxides, cyclopropanone). Three-membered rings containing a sulfur atom in the ring are generally found to be energetically more stable than other analogous three-membered rings. This is

probably due to a lower strain energy for the former, apparently associated with the capacity of the sulfur atom to better accommodate the extra strain of the small ring compared with either the carbon atom or other heteroatoms (i.e., oxygen and nitrogen).

An energy profile for thiiranes (and oxiranes) as a function of the angle of twist around the C–C bond was proposed.[166] By interaction of the $^3(n, \sigma^*)$- and $^3(\sigma, \sigma^*)$-potential energy curves near the crossing points, interconversion of the two $^3(n, \sigma_1^*)$-state molecules becomes possible, with its probability being determined by the energy separation, E_A *cis* and E_A *trans*, between the twisted triplet and the *cis*-(n, σ_1^*)- and the *trans*-$(n\text{-}\sigma_1^*)$-states, respectively.

C. *Donor–Acceptor Properties*

The ability of different saturated hetero rings to donate electrons to phenol has been determined by ir measurements at different temperatures. Thiiranes have been found to be weaker donors than cyclic ethers and these are weaker than cyclic imines. Among the cyclic sulfides, the five-membered rings form the strongest hydrogen bridges, and thiiranes the weakest. A similar relationship between ring strain and donor ability is found with the cyclic ethers and imines showing increased *s* character of the free electrons at the heteroatom with increasing ring strain.[167] Analogous spectroscopic measurements on the iodine complexes of different cyclic sulfides indicate a decrease in electron donor ability in the following order: five- > six- > four- > three-membered rings.[168]

A recent qualitative study of the *acceptor* nature of the thiirane and oxirane rings used the phase transition in the systems methylthiirane and methyloxirane with a weak π donor mesitylene.[169] The thermograms of the mixtures recorded in the range from -160 to $-50°$ show the formation of eutectic mixtures of the $\pi\pi$ nature, confirming the idea of the sp^2-sp^2 nature of the C–C bond of the three-membered heterocyclic rings and the π-acceptor nature of the bonding orbital of its electrophilic center (i.e., the π^*-orbital).

D. *Ultraviolet Spectrocopic Data*

The uv spectra of the several thiiranes studied[21] both in solution and in the gas phase are characterized by a band in the region of 2600 Å (38,460 cm^{-1}). The solution spectra of the parent thiirane, methylthiirane, and cyclohexene sulfide have inflections in the region of 2450 Å. As expected the λ_{max} of phenyl-substituted thiiranes ("conjugated" thiiranes) is shifted toward a higher wavelength; thus, the absorption bands of *cis*- and *trans*-2,3-diphenylthiiranes are at 2680 and 2695 Å, respectively.[51] In analogy to the corresponding oxiranes,[21] such a red shift for the *trans* isomer relative to the *cis* is observed. In addition a strong band in the region of 2300 Å for phenyl-substituted thiiranes appear to be characteristic.

The uv spectra of phenylthiiranes substituted in the *para* position indicate a

conjugation effect of the thiirane ring, suggesting a pseudo-unsaturated character or electron-attracting properties of the thiirane ring.[170]

Following a study about a correlation of ring size and electron distribution in the ring,[171] comparative studies with the four-, five-, and six-membered homologs of thiirane[172] have shown that the absorption shifts to longer wavelengths as the electron density on the sulfur atom increases.

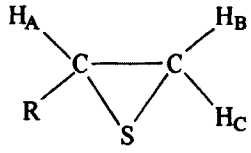
Semiempirical self-consistent field theory (CNDO/2 – complete neglect of differential overlap) studies have been applied to the understanding of the electronic spectra of rings containing either one or two bivalent sulfur atoms, including thiiranes.[173] It was shown that the uv spectra can be accounted for only if *d*-orbitals are included on the sulfur atoms; that is, the low energy excited states of thiirane must have large *d*-orbital character. The vacuum-uv spectrum of thiirane has also been interpreted.[173a]

E. *Nuclear Magnetic Resonance Spectroscopic Data*

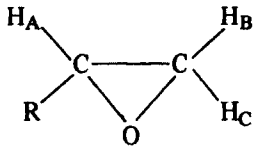
Several nmr studies (both ^1H and ^{13}C) have been performed on thiiranes in attempts to elucidate structural features, to determine configurational correlations, and to assess electronic (or charge) distribution in these molcules. In most cases, those studies include the analogous oxiranes and aziridines for comparison.

A well-documented measure for the electron density at the heteroatom is the chemical shift of the α- and β-CH_2 groups in the nmr spectrum. According to these measurements, the electron density at the heteroatom of saturated heterocycles decreases in the following order: N > O > S. With all three types, the three-membered compounds show the lowest electron density at the heteroatom.[174,175]

Difficult to explain is the strong difference of the proton coupling constants of methylthiirane and methyloxirane, whereas no difference is found between thiirane and oxirane.[176] However, large differences have been reported for the ^{13}C–H couplings of thiirane, oxirane, and aziridine.[177] Nmr parameters of six mono-substituted thiiranes (**121a–121g**) have been recorded.[178] They are summarized in Table 2 below and may be compared with the corresponding parameters of the related oxiranes **122**.



121



122

a. R = H
b. R = $MeOCH_2$
c. R = *n*-Bu
d. R = *t*-Bu
e. R = Me
f. R = CH_2Cl
g. R = Ph

TABLE 2. NMR PARAMETERS FOR THE RING PROTONS H_A, H_B, H_C IN THIIRANES (SOLVENT CCl_4)[178]: ARRANGED IN ORDER OF INCREASING δ_A

	Chemical shifts, δ (ppm)			Coupling constants (Hz)		
R	H_A	H_B	H_C	J_{AB}	J_{AC}	J_{BC}[a]
H[b]	2.27	2.27	2.27	6.9	5.7	0.8
$MeOCH_2$	2.58	2.05	1.75	6.0	5.3	1.1
n-Bu	2.75	2.38	2.03	6.2	5.4	0.8
t-Bu	2.78	2.23	2.10	6.0	6.0	1.0
Me	2.809	2.410	2.024	6.2	5.5	0.9
CH_2Cl	3.1 ± 0.05	2.58	2.24	7.5	4.5	1.2
Ph	3.67	2.65	2.43	6.8	5.7	1.4

[a] Sign reported negative for R = H,[179] Me,[179] and Ph.[180]
[b] Neat liquid.[179]

Although the same pattern is maintained in the chemical shifts (of the various protons) and the coupling constants of both thiiranes and oxiranes (Table 3), there are significant differences in the magnitude of the corresponding coupling constants. The vicinal coupling constants are larger and the geminal coupling constants much smaller for the thiiranes, which may be interpreted in terms of the lower electronegativity of sulfur relative to oxygen. In analogy to corresponding oxiranes, *J-cis* exceeds *J-trans* for the ring protons. This situation is opposite to that in alkenes, but is consistent with theoretical estimates.[183]

Nmr procedures based on diasteromeric interactions between enantiomeric solutes and optically active solvents[184] were applied in a study of configurational correlations for chiral thiiranes.[185] Thus, optically active 2,2,2-trifluorophenylethanol, when used as an nmr solvent, causes enantiomeric spectral dissimilarities for chiral thiiranes. The general point to emerge from this study[185] is that the relative field position of proton H_A (121) is correlated to the absolute configuration of the asymmetric C atoms (it is attached to) of the three-membered rings of the thiiranes (or thiirane oxides – also studied) in exactly the same manner as that observed for the chiral oxiranes having the same structure and the same absolute chirality.

An nmr study based on intramolecular hydrogen bonding was used to establish the absolute configuration of diastereomeric naturally occurring thiiranes.[186] The *threo* isomers of the compounds studied show a relatively strong *HCCH* coupling

TABLE 3. NMR PARAMETERS FOR THE RING PROTONS H_A, H_B, H_C IN OXIRANES (SOLVENT CCl_4)

	Chemical shifts, δ (ppm)			Coupling constants (Hz)			
R	H_A	H_B	H_C	J_{AB}	J_{AC}	J_{BC}	Ref.
H	2.54	2.54	2.54	4.4	3.1	–	177
n-Bu	2.72	2.55	2.27	4.0	3.0	5.5	178
Me	2.85	2.59	2.28	3.9	2.6	5.4	181
CH_2Cl	3.20	2.84	2.65	4.0	2.4	5.0	182
Ph	3.68	2.98	2.60	3.9	2.4	5.9	180

($J = 9.0$ Hz) vs. the *erythro* ($J = 2$–3 Hz). Also other nmr differences are apparent. The influence of molecular configuration on the chemical shift of the protons of steroidal thiiranes has been studied[187] as well.

Three bond coupling constants ($^3J_{CH}$) between carbon and hydrogen in oxiranes, thiiranes, and cyclopropanes, and to a limited extent aziridines, were determined.[188] These coupling constants appear to be sufficiently regular to aid in the assignment of stereochemistry, although substantial differences occur with change in heteroatom. The increase in $^3J_{CH}$ in the order O, N, S, CX_2 (**123**; X = O, N, S, CR_2) parallels the increase in the bond length of the ring C–C bond.

123

Interestingly, a similar pattern was established for the vicinal ^{1}H coupling constants: the increase is in the order X = O, N, S, CR_2, although thiiranes (**123**; X = S) rather poorly obey attempted correlations with electronegativity.[188]

F. *Infrared Spectroscopic Data*

As mentioned at the outset of this section, the ir absorption of thiirane was measured in the gaseous phase[146] and in the liquid phase.[145] The Raman spectrum is likewise known.[146, 147] The bands at 625 and 660 cm^{-1} were assigned to the C–S stretching vibration of thiirane.[145] The force constants of thiiranes, calculated from spectroscopic data, have been found to be very similar to the known constants of oxirane.[189] The potential functions for hindered internal rotation of the methyl group in methylthiirane has been determined from the far ir spectrum.[190]

The absolute configurations of the diasteromeric naturally occurring thiiranes have been established by ir studies of the effect of dilution on the inter- and intramolecular hydrogen bonds[186] and were confirmed by parallel nmr studies.

G. *Selected Physical Properties*

The molar ionization potential of thiirane has been determined to be 8.87 ± 0.15[191] and 8.9–9.1 eV,[192] based on mass spectroscopy (MS) studies.

The dipole moment of thiirane was found experimentally to be 1.66[193] and 1.84 D,[148] vs. 1.95 D for methylthiirane.[149]

The molar refraction of thiirane was found to be 17.33,[194] and the equation $R_D = 17.33 + 4.635Z$ (Z = number of C atoms of the alkyl group) applies to alkyl-substituted thiiranes. It was established that the refractive indices of the individual thiiranes are always larger than those of the analogous oxiranes.

The equation $\log p = 7.03725 - 1194.37(5 + 232.42)$ derived from vapor pressure measurements of thiirane was used to calculate its heat of vaporization (at 25°) to be 7240 ± 5 cal/mole.[145] The H_f of thiirane, derived from its heat of

combustion, was found to be 19.29 ± 0.16 kcal/mole under saturation pressure.[145] Microwave and ir spectra were used to determine the thermodynamic functions $(F_T^0 - H^0)T$, $H_T^0 - H_0^0$, as well as S^0 and C_p^0 of thiirane.[145]

Calorimetric determinations of heat of combustion (H_c) and heat of formation (H_f) at 25° for a number of thiiranes in the liquid phase furnished H_c values that ranged between −481.02 and −1098.24 kcal/mole and H_f values between + 12.38 and − 19.88 kcal/mole for a series of alkyl-substituted thiiranes beginning with the parent thiirane and ending with tetramethylthiirane.[145] The corresponding values for other thiiranes have been tabulated elsewhere.[195]

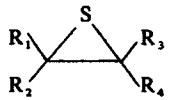
Studies of the polarizability anisotropy of thiirane[196] and measurements of the optical rotatory dispersion (ORD) and circular dichroism (CD) of optically active thiiranes[197, 198] have also been performed, as well as the X-ray analysis of the structures of certain thiiranes of steroids and thioglucosides.[199]

H. *Boiling Point and Refractive Indices*

The boiling points and densities of saturated three-membered ring heterocyclic compounds (thiiranes, oxiranes, aziridines, etc.) are usually considerably higher than those of substances of a cyclic structure with the same number of carbon atoms. This phenomenon can be explained in terms of both electron-donating and electron-accepting (withdrawing) centers in the ring giving rise to additional intramolecular interactions.

Tables 4 and 5 list characteristic physical properties (e.g., boiling points and refractive indices) of a few selected thiiranes.[15]

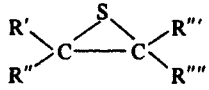
TABLE 4. BOILING POINTS AND REFRACTIVE INDICES OF SELECTED THIIRANES



R_1	R_2	R_3	R_4	B.p. [°C (mm)]	n_D^{20}	Ref.
H	H	H	H	55–56	1.4914	3, 21, 61, 76, 193
CH_3	H	H	H	75–77	1.4730	5, 21, 40, 76, 93, 118, 200
CH_3	H	CH_3	H	51–51.5 (130)	1.4765	26
$C_2H_5OCH_2$	H	H	H	79 (65)	1.4734	52
$C_6H_5OCH_2$	H	H	H	94 (4)	1.5742	24
CH_3SCH_2	H	H	H	98–99 (35)	1.5600	52
$(C_2H_5)_2NCH_2$	H	H	H	72 (14)	1.4857	52
$(C_2H_5O)_2CH$	H	H	H	84 (14)	1.4613	30
$CH_3COS(CH_2)_2$	H	H	H	66 (0.05)	1.5504[a]	71
$ClCH_2COSCH_2$	H	H	H	88 (0.2)	1.5836[a]	52

[a] n_D^{25}.

TABLE 5. AROMATIC-SUBSTITUTED THIIRANES[15]



R′	R″	R‴	R⁗	M.p. or b.p. [°C (mm)]	Ref.
C_6H_5	H	H	H	25–28 (0.01)	32
C_6H_5	C_6H_5	CH_3	H	64–67	20
C_6H_5	C_6H_5	C_6H_5	C_6H_5	178–179	2, 117
CH_3	C_6H_5	p-$(CH_3)_2NC_6H_4$	p-$(CH_3)_2NC_6H_4$	134	105
C_6H_5	C_6H_5	C_6H_5S	C_6H_5S	135	114
C_6H_5	C_6H_5	C_6H_5	Cl	70–71	112

3. Chemical Properties and Reactivity

Thiiranes are reactive species, capable of undergoing a wide spectrum of chemical reactions. These reactions – with very few exceptions – involve the opening of the three-membered ring in one mode or another, giving rise to relief of the inherent strain energy, followed either by the concomitant reorganization of the ring-opened intermediate or by its interception by another component present in the reaction mixture to afford the final product(s). Thus, thiiranes are capable of undergoing isomerizations, dimerizations, polymerizations, fragmentations, desulfurizations, and oxidative or reductive cleavages. Also, the dual nature of the ring, which is both a donor and an acceptor, allows thiiranes to easily undergo both nucleophilic and electrophilic ring cleavage with a variety of reagents. The latter quality makes thiiranes very useful synthetic intermediates, particularly for the synthesis of bifunctional compounds. The sulfur atom in the thiirane ring is usually the site of initial attack by electrophiles of all kinds, whereas one of the C-ring atoms is ordinarily the center of initial attack by nucleophiles. In fact, analogous with epoxide chemistry, the vast majority of the thiirane reactions that have been studied have involved the opening of the thiirane ring and the addition of a molecule of reagent either in neutral conditions or under both acidic and basic conditions. Thiirane chemistry that involves oxidation or substitutions leaving the three-membered ring intact is less common and typical for certain special cases (see, e.g., the chemistry of 2,3-di-*tert*-butylthiiranes; Section III, 3, J).

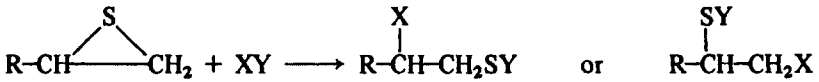
Considering the numerous reactions thiiranes are able to undergo, fundamental information is still scarce in the field.[16] Some results are published in the patent literature or in short communications. Furthermore, several statements reported in the earlier literature were found to be incorrect. The recent developments of more convenient methods of synthesis however, has made possible some basic studies on the structure and chemistry of thiiranes. Indeed, much activity in the area of thiirane chemistry is reflected in the chemical literature of the 1970s.

The chemistry of thiiranes is similar, in many respects, to that of oxiranes and the differences may be accounted for by the differences in the key structural

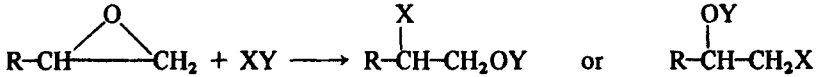
features and physical parameters of the two classes: the lower ring strain in thiiranes is obviously overruled by the lower bond energy of C–S vs. C–O bonds. Consequently, in reactions involving ring cleavage in the absence of either electrophiles or nucleophiles, thiiranes are more reactive than oxiranes. Such reactions include thermal desulfurization of thiiranes and closely related fragmentation reactions. As one would expect in reactions of this type, electron-attracting substituents enhance the reactivity of thiiranes drastically.

Since the polarity of the C–S bond is smaller than that of the C–O bond and the electron density at the sulfur atom in thiiranes is smaller than that at the oxygen atom in oxiranes, the former are expected to be less reactive toward electrophilic reagents than the latter. Indeed, this seems to be observed in several cases. Less clear is the situation concerning the relative reactivity of thiiranes and oxiranes toward nucleophilic reagents: the reactivity of thiiranes seems to be about the same or a little higher.[16]

Mercaptoethylation appears to be the most important reaction expected of thiiranes from the point of view of organic synthesis. However, owing to their relative ease of polymerization (i.e., they are catalyzed by either acids or bases), thiiranes have not been as broadly applied as mercaptoethylating agents (e.g., Eq. 69) as have the oxiranes as hydroxyethylating agents (e.g., Eq. 70).



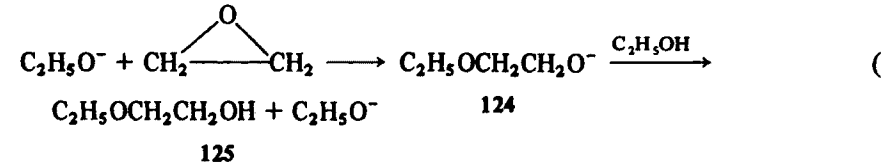
(69)



(70)

Base-catalyzed mercaptoethylations through a nucleophilic mechanism are usually preferred, polymerization being considered to be a special case of this reaction.

The reactions of ethoxide ion with oxirane and thiirane are given in Eqs. 71 and 72, respectively, to illustrate the points discussed above.

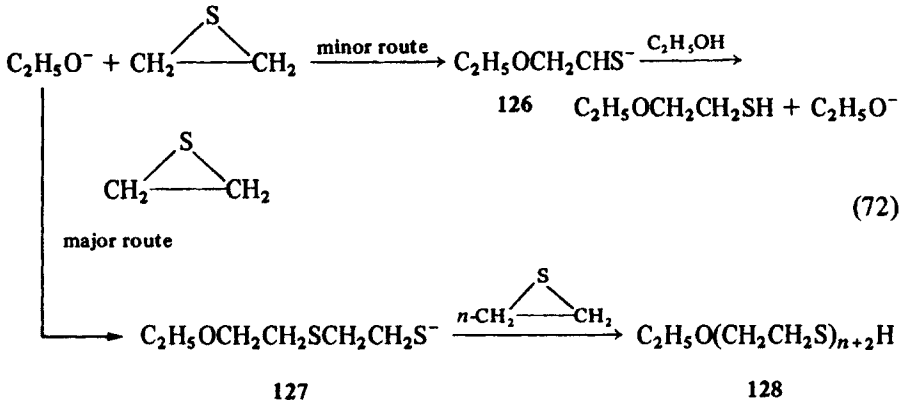


(71)

125 **124**

In both cases the ethoxide ion is acting as a nucleophile and attacks one of the carbon atoms of the ring, resulting in opening of the latter to form the intermediate nucleophiles **124** and **126**. In the oxirane sequence (Eq. 71) the reaction is completed by the solvent (EtOH) and the ethoxide ion is regenerated. The base-catalyzed hydroxyethylation is thus being accomplished.

However, in the case of the thiirane (i.e., Eq. 72), the intermediate **126** is not readily terminated by solvent. Rather, a polythiirane (**128**) is formed. This is



(72)

understood in terms of the mercaptide ion (i.e., **126** or **127**) being a weaker base than the ethoxide ion, but a much stronger nucleophile. The result is the continuous generation of mercaptide ions, which react with unreacted thiirane molecules to give polythiirane as the major (and most often the exclusive) reaction product under these conditions. Thus, the ethoxide-catalyzed reaction of oxirane in ethanol gives 95% yield of the glycol ether **125**, whereas the same reaction of thiirane ends up in 100% yield of the polymerization product **128**. As shown later (Section III, 3, F) similar results are typical for other nucleophiles.

Reactions of unsymmetric oxiranes entailing ring opening frequently yield a mixture of the two possible isomers, with the product of the ring-opening reaction at the primary C atom prevailing (referred to as "normal addition"; i.e., the second product in Eq. 69). For quite some time, however, the two possible isomers (i.e., the two products in Eq. 69) were difficult to isolate from reactions of unsymmetrical thiiranes and many reports in the literature indicated the formation of only one product,[16] in some cases that of normal, in others, that of "abnormal" addition.

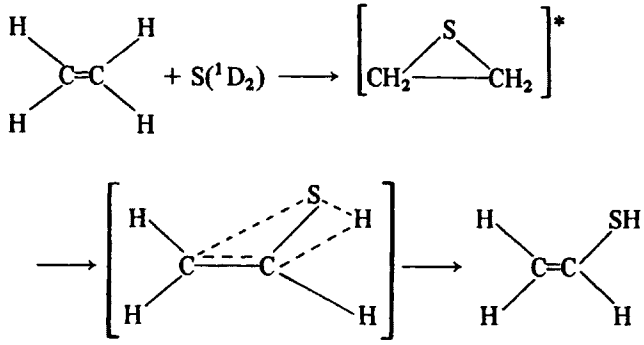
Following the development of new synthetic methods for the generation of thiiranes in nonionic media (see Section III, 2 for specifics), the emphasis on their synthetic use as potential mercaptoethylating agents has shifted; these compounds are now useful intermediates in the preparation of stereospecific olefins. Under such nonionic conditions, mechanistic and other systematic studies of thiirane reactions are more easily conducted.

A. *Isomerization*

cis-trans Stereoisomerization of substituted thiiranes can be accomplished by using the reaction of potassium thiocyanate in DMF or in water-ethanol.[201,202] The yields of the isomerized product have been reported to be 35–42% for *cis*- and *trans*-3-hydroxy and 3-acetoxyepithio-1,2-cyclohexanes[200] and 14–30% for a series of steroidal thiiranes.[201,202] The results can be compared with 20–65% yields in the case of epoxides of cyclopentene and cyclohexene and 20–48% in

the oxirane steroid series.[203] All stereoisomerizations were followed by nmr, and it is on the spectra that the configurational assignments of the starting thiiranes and of the final products were based.

From a recent detailed kinetic study of the reaction of excited $S(^1D_2)$ atoms with ethylene,[204] it was concluded that the chemically activated ground state thiirane undergoes a unimolecular isomerization to give vinylthiol through a bicyclic activated complex as depicted in Eq. 73.[204]

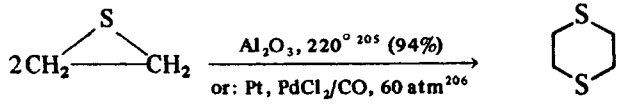


(73)

This novel rearrangement is the formal analog of the cyclopropane–propylene rearrangement with respect to both structural change and mechanism.

B. *Dimerization*

Dimerization of thiirane to give dithiirane in high yields requires catalysis, high pressure, and/or high temperature:



(74)

129

The importance of the reaction above is in the possibility of inducing thiiranes to undergo dimerization in view of their high tendency to polymerize. As far as the dithiane product is concerned, there exist alternatives for its formation – for instance, thermal decomposition of polythiirane.[207, 208]

C. *Polymerization of Thiiranes*

Numerous publications on polymerization of thiiranes and closely related aspects can be found in scientific journals, in publications and monographs issued by major industrial polymer producers, and as one would expect, in the patent

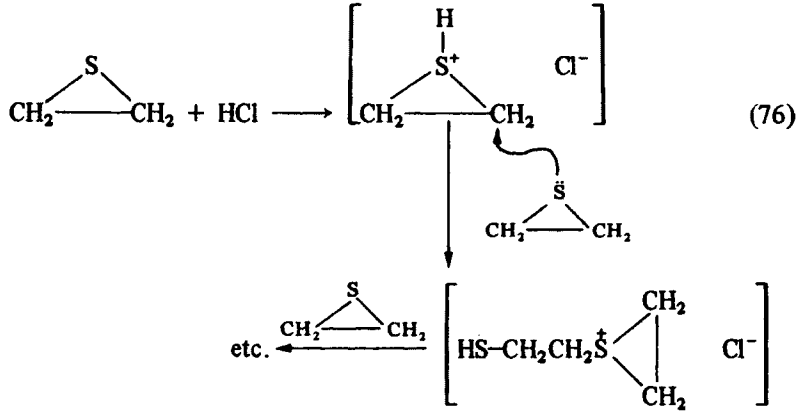
literature all over the world. Nonetheless, comprehensive coverage and thorough summary of this topic (including all the relevant aspects involved) are beyond the scope of this chapter. Instead, this section represents a "first approximation" introduction, dealing briefly with some "essentials" of the subject, based primarily on the review of Davis and Fettes on polythiiranes[209] and the corresponding section in reference 16. In addition to the references cited later in this section, the interested reader is referred to the following selected list of key references, some of which are reviews: episulfides for use in preparing polymers,[210] initiation mechanism for polymerization of episulfides by sodium naphthalene,[211] mechanism and kinetics of anionic polymerization of episulfides,[212] organozinc-nickel or cobalt catalysts for the polymerization of oxiranes and thiiranes,[213] anionic polymerization of thiiranes,[214] stereoregular and optically active polymers of episulfides,[215] stereoselective and asymmetric-selective polymerizations,[216] properties and methods of synthesis of several optically active polyoxiranes and polythiiranes,[217] selective and stereoselective polymerizations of oxiranes and thiiranes,[218] polymerization and block polymerization of cyclic sulfides,[219] ABA block copolymers of dienes and cyclic sulfides,[220] copolymerization of thiiranes with isothiocyanates,[221] and elastomeric block polymers from ethylene sulfide.[222]

Thiiranes undergo polymerization so readily even without initiator that polythiirane was known 80 years before the monomer was synthesized. Polythiirane, described as a white, amorphous, insoluble substance of the composition $(C_2H_4S)_n$, was obtained by the reaction of ethylene chloride or ethylene bromide with K_2S or Na_2S[207, 224, 225]:

$$\underset{X = Cl \text{ or } Br}{n(CH_2{=}CH{-}X)} \xrightarrow{K_2S \text{ or } Na_2S} \underset{130}{(C_2H_4S)_n} \qquad (75)$$

The earlier reports distinguish between two modifications of the polymer obtained: products had melting points of 145° and 113°, respectively. The polymer obtained from reaction with Na_2S is converted to dithiane on heating and was shown to contain organically combined halogen in substantial proportion.[207] Later papers reported that the polymers prepared either through the method shown in Eq. 75 or from 2,2′-dichlorodiethyl sulfide and potassium sulfide or disodium ethylenedithiolate and ethylene dibromide[226] did not melt below 180–190°.[227] The treatment of 2,2′-dichlorodiethyl sulfide with sodium metal resulted in evolution of gaseous ethylene and formation of polythiirane melting at 158–160°,[228] soluble in aniline or nitrobenzene, and oxidizable with H_2O_2 to the corresponding polythiirane dioxide. The white, amorphous, insoluble polymethylthiirane was prepared more than a century ago from 1,2-dibromopropane.[207, 226]

The polymerization of thiiranes under basic reaction conditions has been discussed. The polymerization tendencies of thiiranes are also encountered under acidic reaction conditions. Dilute hydrochloric acid, for example, instantly polymerizes thiiranes to an amorphous powder. The formation of the polythiirane thus obtained may be pictured as shown in Eq. 76.



(76)

Although one would expect from Eq. 76 that the chloride ion would compete successfully with unreacted thiirane in the nucleophilic opening of the thiirane ring, no better alternative mechanism has been advanced.

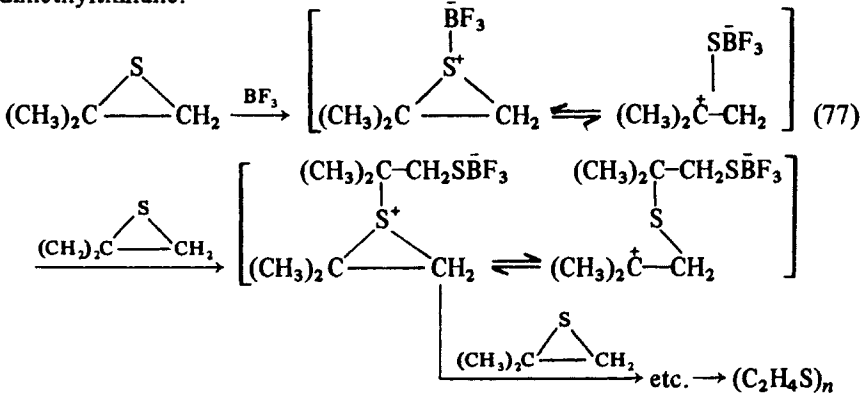
Polythiirane can be obtained by the interaction of 2-hydroxyethylmercaptan with 50% sulfuric acid at boiling temperature.[229] Two somewhat different modifications (A and B) of the polymer thus obtained were reported: fraction A with molecular weight ranging between 1400 and 1700 melted at 193–197°, and fraction B, which melted at 177–180°, showed a molecular weight of 1720 and gave substantial quantities of crystalline dithiane on heating. Similar polymers were prepared by the dehydration of 2-hydroxyethylmercaptan with phosphoric acid, zinc chloride, phosphorous pentoxide, or sodium hydroxide.[229] More recent repetition of this work furnished polythiirane, which melted at 158–165°.[228]

The pure monomer (e.g., the parent thiirane) was first prepared by Dele'pine,[77] who reported that it polymerized gradually on storage at room temperature, a process that was accelerated by the addition of either inorganic acids (HCl, H_2SO_4, etc.) or aqueous (or alcoholic) ammonia solutions and concentrated solution of caustic soda.[3,77] Some of these polymers were found to have a low degree of polymerization.

The polythiirane obtained in the absence of catalysis is a white powder (m.p. 140–150°), which is insoluble in conventional solvents.[229]

Since thiiranes are expected to undergo easy nucleophilic ring opening, most polymerizations are accomplished using base-type catalysts. The use of aqueous solution of sodium hydroxide in methanol furnished polythiirane that melted at 182–185°.[230] Initiation with ammonia, piperidine, pyridine, methylamine, hydrazine, and ethylenediamine afforded polymers whose molecular weights (calculated from their N content) ranged between 419 and 960.[230] Variations of the NH_3 concentration did not affect the molecular weight of the products. However, in the reaction of thiirane with molar quantities of primary or secondary amines, polymerization predominates when polar solvents and strongly basic amines (e.g., diethylamine) are used[231]; otherwise, the corresponding 2-mercaptoethylamines are obtained in appreciable yields. Polythiiranes having molecular weights below

1000 and apparently pronounced crystalline structure, were prepared by means of sodium hydroxide, sodium ethylate, and primary amines.[48] By using sodium naphthalenate as the catalyst, polymers that melted at 208–210° were obtained. The use of boron trifluoride etherate furnished a polymer melting at 192–195°.[232] Equation 77 gives the sequence of the latter polymerization for the case of 2,2-dimethylthiirane.[15]



(77)

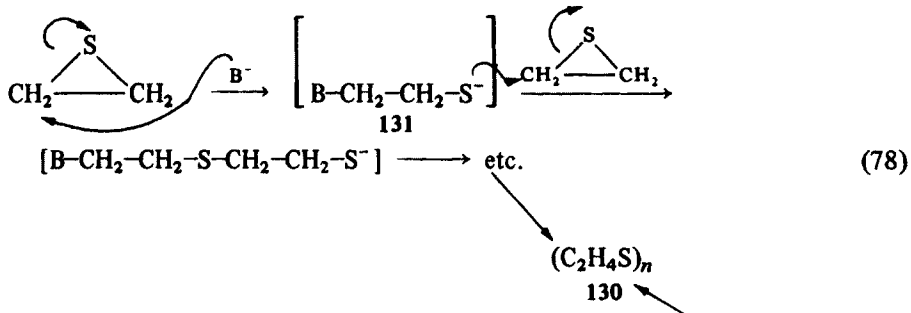
130

The rate of thiirane polymerization is higher in base-catalyzed reactions than in the presence of acids. This observation can be accounted for in terms of the higher nucleophilicity of the thiolate ion intermediate (i.e., 131) vs. that of the sulfur site incorporated in the thiirane three-membered ring. The nucleophilic rupture of the unreacted thiirane ring by the thiolate ion in the base-catalyzed polymerization is apparently easier (and therefore faster under comparable reaction conditions) than the cleavage of the C–S bond in the thiiranium intermediate (i.e., 132) by an unreacted molecule of thiirane in acid-catalyzed polymerizations.

Methyl- and ethylthiiranes have much lower tendency to polymerize than does the parent thiirane; the use of alkali or ammonia involves slow polymerization to viscous products, whereas no polymerization was observed with hydrochloric, nitric, or acetic acids.[76] Polymethylthiirane was prepared, however, by using catalytic amounts of sodium ethoxide,[233] $NaNH_2$, KOH, Na, $TiCl_4$, and $AlCl_3$.[48] The anionic catalysts (*ca.* 2% of catalyst at room temperature) yielded high molecular weight products, whereas the acidic chlorides gave low molecular weight polymers. All samples were soluble in chlorinated organic solvents (e.g., methylene chloride, chloroform, carbon tetrachloride), dioxane, benzene, and so on, and were insoluble in ether, acetone, alcohols, and water. By using naphthalene–sodium in THF and ultra high purity reagents, it was possible to obtain polymers of very low dispersity ($Mn/Mw \approx 1$) and molecular weights of 70,000–320,000[233] (determined by osmometry, light scattering, and end group analysis). High molecular weight crystalline products are obtained by using complex salts of cadmium as a catalyst.[234] These products are believed to be the isotactic modification, melting at 40–41°.[235]

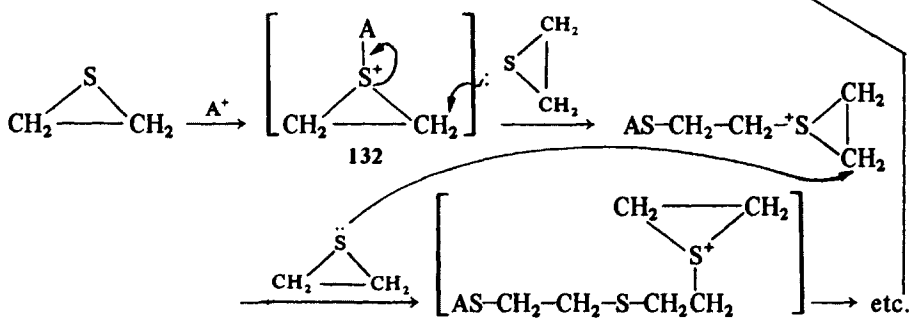
Polymerizations of different thiiranes using a variety of catalysts under various reaction conditions have been reported in the literature. The following are merely

1. *Base-catalyzed polymerization.*



(78)

2. *Acid-catalyzed polymerization.*



selected examples: chloromethylthiirane,[236] cyclohexene sulfide,[6,80,237] 1-octene sulfide (polymerizes readily on addition of $LiAlH_4$, a typical anionic catalyst),[45] and 2-phenylthiirane (styrene sulfide).[33] The polymerization of the latter is conducted by using aluminum trialkyls or heavy metal mercaptides as catalysts,[33] giving polymers of noncrystalline structure that melt at 50–120° and are soluble in organic solvents. In the presence of either basic or acidic catalysts, solid or viscous products with molecular weights of 1000–2000 are obtained.[238] The use of boron trifluoride as a catalyst effected the polymerization of sugar thiiranes.[239]

Highly fluorinated thiiranes undergo radical polymerizations initiated by either irradiation or organic peroxides.[115]

The preparation of different kinds of copolymer containing various percentages of thiiranes is claimed in the literature,[3,115,219–222,235,240] showing a broad spectrum of properties and technological qualities. These (and many other) copolymers and block copolymers are used as elastomers, lubricating oils or greases,[240] highly thermostable polymers, or vulcanizable, tough white gums.[235]

The current literature still contains many reports of investigations of the polymerization of thiiranes. However, there appears to be a distinct shift in the emphasis: many of the most recent publications describe stereoselective polymerizations of thiiranes and/or polythiiranes containing specific predesigned chiral centers. A selected list of topics extracted from these publications is given below.

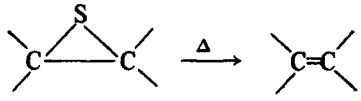
1. Polymerization of enantiomerically enriched monomer of *tert*-butylthiirane; mechanism of steroselective process; temperature effect on the stereoselective polymerization.[241]
2. Polythiirane containing a chiral center in the side chain; synthesis and optical purity of 1,2-epithio-3-methylpentane.[242]
3. Stereoselection in the polymerization of racemic methylthiirane.[243]
4. Polymerization of *trans*-2,3-dimethylthiirane with chiral initiators.[244]
5. Stereoselective polymerization of thiiranes.[244a]

D. *Desulfurization of Thiiranes*

The reaction of thiiranes with either nucleophiles or electrophiles results in the opening of the thiirane ring with concomitant formation of a mercaptide ion or a β-substituted mercaptan (or sulfide), respectively. In some instances, however, olefins are formed by the removal of sulfur from the thiirane. Several reagents have been found to be effective in realizing this desulfurization reaction in thiiranes: they include organometallics such as organolithium compounds and Grignard reagents, trivalent organophosphorous compounds (e.g., triphenylphosphine and trialkyl- or triarylphosphite), potassium *tert*-butoxide, and methyl iodide. Several thiiranes undergo thermal fragmentation to corresponding olefins and sulfur and/or photolytic decomposition to olefins and other products.

a. BY THERMAL DECOMPOSITION

Heating of thiiranes may cause fragmentation, leading to olefin and sulfur particularly in the aromatically substituted series[2, 105, 112, 114, 245]:



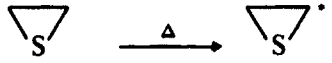
(79)

Similar decompositions have been observed with acylthiomethylthiirane,[52] cyclohexane sulfide,[80] and 2-heptylthiirane.[45] Substitution of thiiranes with more than one aromatic nucleus or with electron-attracting groups such as C=O, COOH, COOR, CN, and Cl promotes the abstraction of sulfur.[6] Phenyl, cyano, and ester groups are particularly effective in promoting extrusion of sulfur.[246] Consequently, thiiranes with two aryl groups can be isolated and purified only by crystallization, not through distillation.

Because of the facile decomposition of polyarylthiiranes to olefins, this reaction is regarded as one of the best methods to prepare certain arylolefins.[2, 112] The addition of copper bronze promotes these desulfurizations.[81, 113, 114]

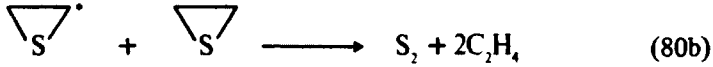
The gas phase thermolysis of thiirane below 250° have been investigated,[247] and the amount of ethylene produced was found to be equal to the amount of thiirane consumed. This behavior represents a significant departure from that of the analogous cyclopropane and oxirane, which upon low temperature thermolysis

undergo isomerizations to the acyclic structures by 1,2-hydrogen shifts. The low temperature thermolysis of *cis*- and *trans*-2,3-dimethylthiirane afforded more than 90% *cis*- and about 99% *trans*-but-2-enes, respectively, and is therefore stereospecific. It was concluded[247] that the reaction is pseudo-unimolecular where the rate-determining step is shown in Eq. 80a.



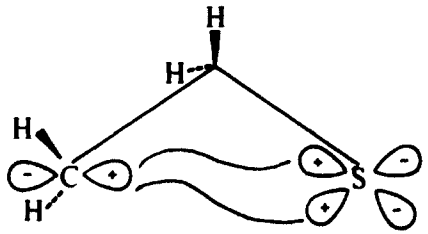
(80a)

133



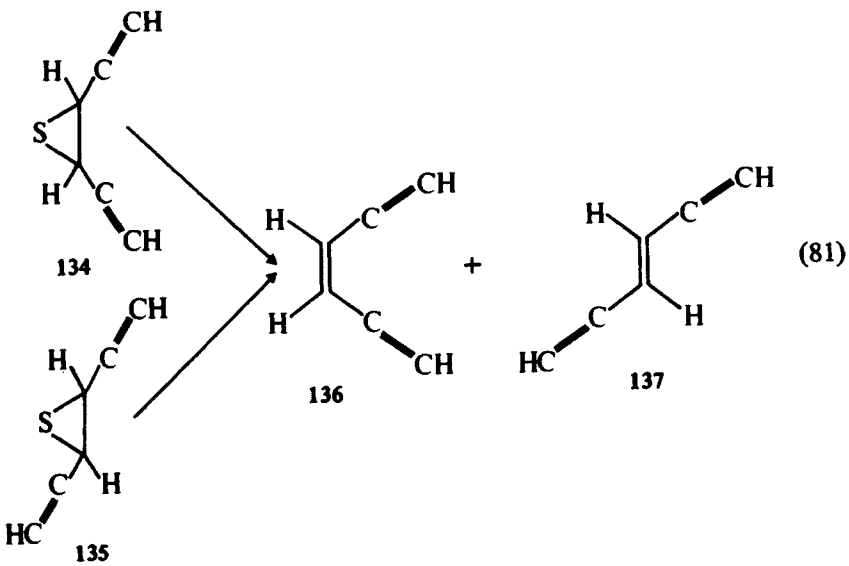
(80b)

The electronically excited species **133** is equivalent to a π-thiacyclopropane structure, analogous to the intermediate postulated in the thermolysis of cyclopropanes and pyrazolines.[248] This structure (i.e., **133**) accounts for all the observations.



133

Pyrolysis of either *cis*- or *trans*-1,2-diethynylthiiranes (i.e., **134** or **135**) yielded only the desulfurized olefins **136** and **137**.[249] In both cases the thermolysis occurs with greater than 90% retention of stereochemical configuration, in accord with

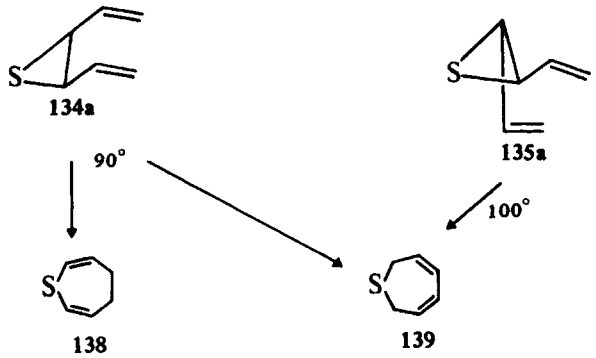


(81)

134 **135** **136** **137**

previous results.[247] However, at relatively high concentrations a bimolecular process was found to dominate.[249]

The analogous *cis*- and *trans*-divinylthiiranes behave differently on pyrolysis.[140] Decomposition takes place with loss of sulfur to yield nonstereospecifically a mixture of *cis*- and *trans*-1,3,5-hexatrienes (20:80); the total yield is between 20 and 25%. About 75% of the thermolysis, however, proceeds without loss of sulfur. The *cis* isomer rearranges smoothly at 90° with the formation of 52% 4,5-dihydrothiepin (**138**) and 48% 2,7-dihydrothiepin (**139**). The *trans* isomer gives at 100° the 2,7-dihydrothiepin (**139**) as the only rearrangement product.[140]



The formation of dihydrothiepin (**138**) is understood in terms of the Cope rearrangement, while that of dihydrothiepin (**139**) (from both isomers) is explained in terms of formation of isomeric interconvertible diradicals. The photochemical desulfurization of thiiranes is discussed in Section III, 3, H.

b. BY ORGANOPHOSPHOROUS COMPOUNDS

Practically quantitative stereospecific desulfurizations can be accomplished by reacting thiiranes with either trialkylphosphites (gentle heating is recommended) or trialkyl- and/or triarylphosphines (at room temperature).

Thus, triethylphosphite,[6, 26, 31, 46, 75, 250, 251] triethylphosphine,[6] tributylphosphine,[251] and triphenylphosphine[6, 117, 250, 252, 253] were employed to obtain olefins from thiiranes and the thionophosphates or the phosphine sulfides, respectively, as shown in the following equation:

$$R_3P + R'_2C\overset{S}{\diagup\!\diagdown}CR'_2 \longrightarrow R_3PS + R'_2C{=}CR'_2 \qquad (82)$$

R = alkyl, aryl, or alkoxy (or PCl_3)[116]

Pure *cis*- and pure *trans*-2-butenes have been obtained in essentially quantitative yields from their respective thiiranes with the trivalent organophosphorous compounds just named. This method of desulfurization has been also employed in the overall conversion of carbonyl compounds to olefins through the condensation of carbonyls with the lithio salt of 2-(thiomethyl)-2-oxazoline.[126]

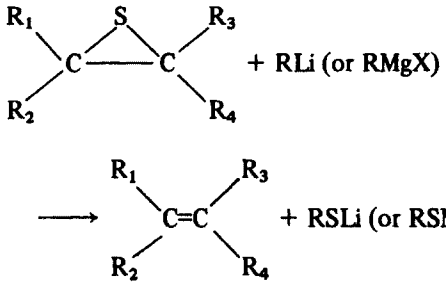
Kinetic studies[253] of the reaction of triphenylphosphine with *cis*- and *trans*-2,3-dimethylthiiranes and ethylthiirane, showed it to be first order with respect to the two reactants and relatively insensitive to the polarity of the reaction solvent. These results suggest a nucleophilic attack by the phosphorous on the sulfur to give the observed products (i.e., phosphine sulfide and olefin) in one step without the involvement of a charge-separated intermediate.

Desulfurizations of the following thiiranes were effected by using trivalent organophosphorous compounds: thiirane,[6,31] methylthiirane,[6,31,46] ethylthiirane,[252] 2,3-dimethylthiirane,[251,252] 2,2-dimethylthiirane,[6] chloromethylthiirane,[6,31,46] 2-phenylthiirane,[31] cyclohexene sulfide,[6,31,250] 2-methoxymethylthiirane,[31,46] 2-ethoxy, 2-propoxy-, 2-butoxy-, 2-phenoxy- and diethoxymethylthiiranes,[31] and 2-hexyl-, spirooctyl-, spironaphthyl-, 2-methyl-, 2-cyclohexenyl-, as well as other thiiranes.[117,126] Sugar thiiranes were also subjected to the reaction.[75]

Some investigators took advantage of this facile desulfurization method for alkylative coupling leading to the synthesis of secondary vinylogous amides and enolizable β-carbonyl compounds[252a] as well as for the synthesis of highly hindered olefins.[252b]

c. BY ORGANOMETALLICS

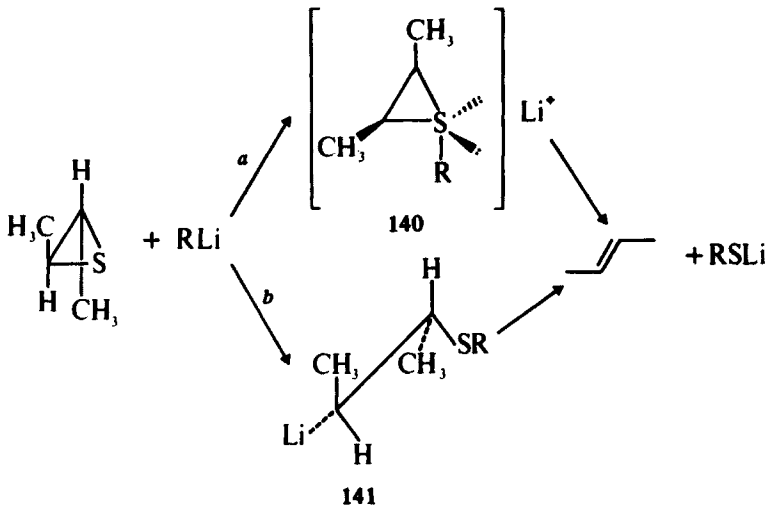
i. BY LITHIUM AND GRIGNARD REAGENTS. Alkyl- and aryllithium reagents desulfurize thiiranes essentially quantitatively to form the corresponding olefins[26,41] stereoselectively: the *cis*-thiirane yields the *cis*-olefin whereas the *trans*-thiirane yields the *trans*-olefin. The desulfurization with Grignard reagents appears to be less well defined. Yet, the formation of olefins seems to be the main course of the reaction.[41] In using these reagents one obtains in addition to the olefin, a metal thiolate:



(83)

The yields of olefins obtained through this route are usually lower than those obtained by using the trivalent organophosphorous compounds. However, the reaction is important for the synthesis of some thiophenols that are difficult to prepare by using alternative methods.[41]

A study of desulfurization of *cis*- and *trans*-2,3-dimethylthiiranes[254] revealed the complete stereospecificity of this reaction excluding the intermediacy of 2-lithio-3-alkyl sulfide (i.e., **141**) along the reaction coordinate. A mechanism involving a trigonal bipyramidal sulfurane (i.e., **140**) was advanced to explain the observed products as depicted in route *a* in Eq. 83a.[251,254]



(83a)

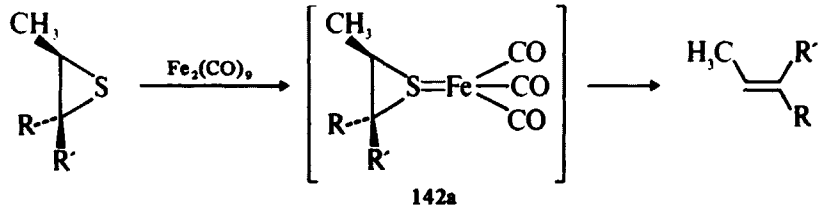
A concerted disrotatory fragmentation of the two weakest C–S bonds of the ring would also lead to the observed products of Eq. 83a. This explanation is unsatisfactory however, in terms of orbital symmetry, since this cheletropic sulfurane ring opening is forbidden by orbital symmetry for the least motion pathway.

The foregoing method of desulfurization was applied to the parent thiirane,[20,41] methylthiirane,[41] 2,3-dimethylthiirane,[251,254] cyclohexene sulfide,[41] and a number of 2-alkoxymethylthiiranes.[31]

ii. BY LITHIUM ALUMINUM HYDRIDE. Certain thiiranes were desulfurized quantitatively on treatment with lithium aluminum hydride[142,255] rather than undergoing the expected reductive nucleophilic ring cleavage to give thiols as their lithium salts.[41]

iii. BY DIIRON NONACARBONYL AND TRIIRON DODECACARBONYL. Like the organolithium-induced decompositions, the desulfurization of thiiranes with these iron-carbonyl reagents (in refluxing benzene) also proceed with a very high degree of stereospecificity.[254]

cis- and *trans*-2,3-Dimethylthiiranes yielded more than 93% of *cis*- and 97% of *trans*-butene-2, respectively, in about 80% total yield.[254] The reaction originally reported by King[256] may be envisioned as proceeding through metal π-sulfuranes (e.g., **142a**) as illustrated in Eq. 84.



(84)

The overall result is thus comparable to that of other methods of thiirane desulfurization.

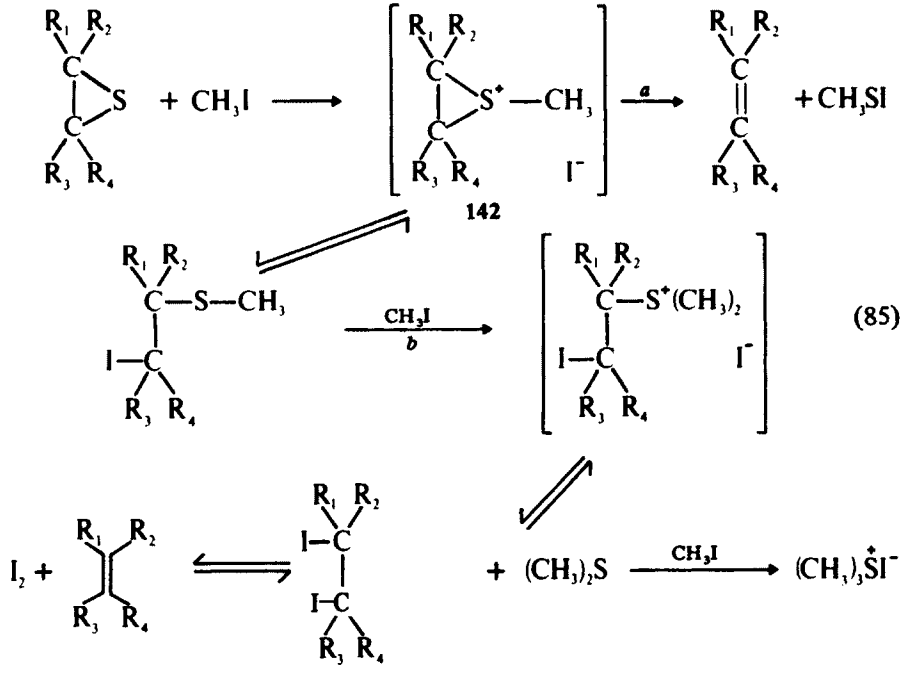
d. BY POTASSIUM *TERT*-BUTOXIDE

Potassium *tert*-butoxide was reported to be effective in the desulfurization of certain thiiranes to yield the corresponding olefins.[257] Acetylenic thiiranes, however, were reported to give low yields of thiophene derivatives on reaction with KO-*t*-C_4H_9.[258]

e. BY METHYL IODIDE

Stereospecific desulfurizations of 2,3-dimethylthiiranes and other 2,3-dialkylthiiranes can be effected by treatment with methyl iodide on heating[259, 261] or with catalytic amounts of iodine.[50] Several thiiranes (specifically, methyl-, chloromethyl-, and 2,3-cyclohexathiiranes) react with excess methyl iodide to give a 1,2-diodide and trimethylsulfonium iodide.[6]

In all the desulfurizations above the final results can be accounted for in terms of an unstable cyclic thiiranium intermediate, which is formed in the initial step[259] (Eq. 85). Indeed, open chain sulfonium salt intermediates have been isolated in the reaction of some thiiranes and methyl bromide.[260]



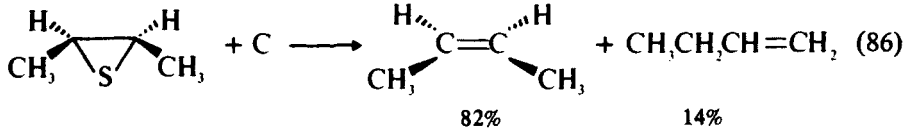
(85)

In analogy to the mechanisms proposed for other thiirane desulfurizations, the invoked intermediacy of **142** is in accord with the stereospecificity of the reaction (route *a* or *b* in Eq. 85). The formation of a crystalline salt of the approximate

composition $C_2H_4S \cdot CH_3I$ in the reaction of thiirane with methyl iodide and similar unstable salts with both methyl- and 2,3-dimethylthiiranes[3, 76] also corroborates the reaction sequence depicted in Eq. 85. The entire question of the intermediate formation of three-membered sulfonium (thiiranium) salts is discussed in detail later (see Section VI).

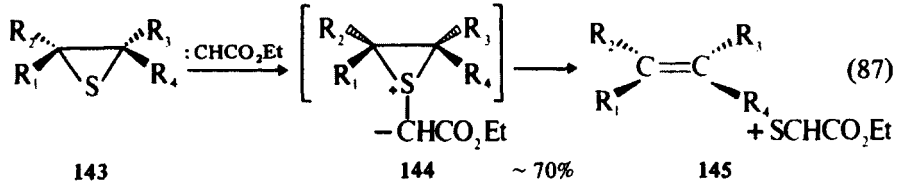
f. BY OTHER REAGENTS

Atomic carbon is a general desulfurizing agent; its reaction with 2,3-dimethylthiirane[262] is an example:



(86)

Another possible method for thiirane desulfurization is reaction with carbenes generated *in situ* from ethyl diazoacetate with the aid of $Cu(acac)_2$ as a catalyst.[263] The fragmentation of the assumed sulfide ylide intermediate (i.e., **144**) proceeds with complete retention of stereochemistry in overall good to high yields as illustrated in Eq. 87.[263]



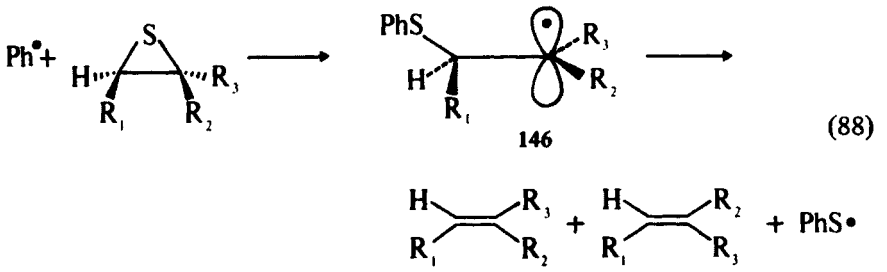
(87)

143 **144** ~ 70% **145**

a. $R_1 = CH_3$; $R_4 = i\text{-Pr}$; $R_2 = R_3 = H$
b. $R_1 = CH_3$; $R_3 = i\text{-Pr}$; $R_2 = R_4 = H$

The above reaction was successfully applied to cyclohexene sulfide and to *cis*-2,3-diphenylthiirane as well. The use of 4,4'-dimethoxybenzophenone hydrazone as the source of carbene was also realized.[263] The α-fragmentation of the *S*-ylide (**144**) is a property characteristic of three-membered rings and is not observed in either four-membered *S*- or *N*-ylides.[264]

Phenyl radicals generated by the thermolysis of phenylazotriphenylmethane (PAT) form β-phenylthio radicals (e.g., **146**) by homolysis of the carbon-sulfur bond in thiiranes.[265] The loss of the thiophenoxy radical from the intermediate **146** results in the formation of olefins nonstereospecifically[265]:



(88)

A rotation about the central carbon–carbon bond in **146** is possible, and thus explains the nonstereospecificity of this desulfurization reaction. Gas phase desulfurization of thiiranes can be induced by methyl radicals.[266]

Reactions of arylthiiranes with nascent hydrogen ($Zn–CH_3CO_2H$) also gives the corresponding olefins besides hydrogen sulfide.[117]

E. *Electrophilic Ring Opening of Thiiranes*

The thiirane ring (similar to the oxirane ring) constitutes a peculiar electron donor–electron acceptor dipole system of the $n\pi$ type, suggesting that its reactivity is determined by the features of the primary electron donor–electron acceptor interactions between the ring and the reactants.[267] It is not surprising, therefore, that electrophilic ring opening of thiiranes was thoroughly studied. However, the mechanism involved in such openings is still controversial, and both the formation of an intermediate thiiranium (episulfonium) ion and the "synchronous mechanism" – which involves, simultaneously, both the nucleophilic and electrophilic centers of the thiirane ring – have been advocated. The situation is complicated by reports that different proportions of regioselectively ring-opened products have sometimes been obtained with unsymmetrical thiiranes.

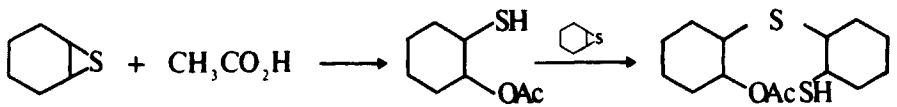
A recent study[267] summarizes the "state of the art" in this respect by claiming that " . . . the formation of monomeric products is associated with a synchronous reaction mechanism, and the formation of polymeric products is associated with an epi-ionic reaction mechanism. It is obvious that the extent of electron transfer in the complex, determines the direction of the polarization of the ring carbon–carbon bond, and therefore, the order of its opening."

A review of electrophilic thiirane ring opening with various reagents follows.

a. BY CARBOXYLIC ACIDS AND ANHYDRIDES

Acetic acid causes slow polymerization of thiirane, whereas methyl- and ethylthiiranes show no change.[3, 76]

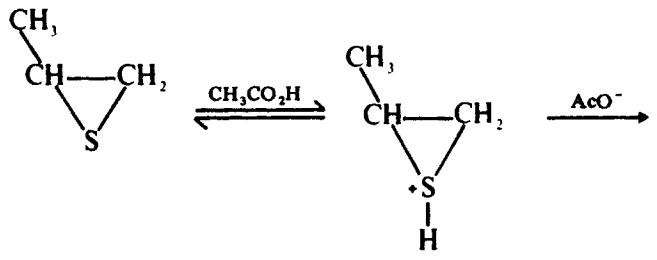
With excess of boiling glacial acetic acid, cyclohexene sulfide forms 26% monomeric and 48% dimeric acetoxymercaptan (i.e., **147**).[50] the dimeric **147** was found to be the major product in other similar studies as well.[6, 29]



147 (89)

The rates and products of solvolysis of methylthiirane in hot acetic acid have been determined.[268] The results show that terminal attack (concerning the orientation of ring opening) is preferred, although not exclusively.

In addition to **149** and **150**, the product contained a significant proportion of two higher molecular weight species, most probably the two possible isomeric dimers



(90)

148

CH_3CHCH_2OAc (SH) + CH_3CHCH_2SH (OAc)

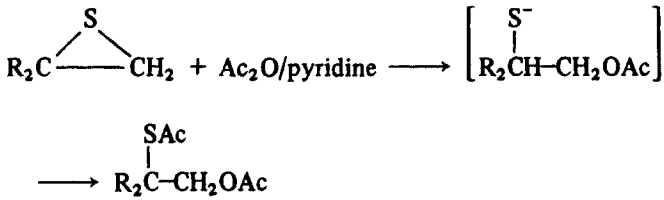
149 Normal product (55%) 150 Abnormal product (45%)

analogous to **147**. By comparison with rate constants and isotope effects observed in the case of methyloxirane, it was concluded[268] that the reaction in point proceeds via the protonated species **148** (i.e., thiiranium ion-type mechanism). Nevertheless, the ring opening of **148**, by virtue of its relative stability, would require a concomitant bond making while being ring-opened by the acetate ion. This means a more "S_N2" character of the ring rupture step. The ratio between the "normal" and the "abnormal" products (i.e., **149**:**150**) is governed both by the partial carbonium ion character assumed by the secondary compared with the primary carbon atom of the ring and by steric considerations. It is not apparent, however, why there is a marked difference in this respect between the results obtained with thiiranes and those obtained with oxiranes.

When 2-chloromethylthiirane is heated in glacial acetic acid in the presence of potassium acetate, one obtains the ring expansion product 2-acetoxytrimethylene sulfide,[52] presumably through the *S*-assisted solvolysis of the chloro atom on the side chain.

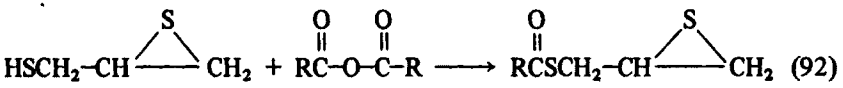
Trifluoroacetic acid (and its acid fluoride) is a strong initiator of polymerization of methylthiirane regardless of the ratios and mixing conditions of the reactants.[267]

The reaction of thiirane,[269] methylthiirane,[8,198] 2,2-dimethylthiirane,[270] and cyclohexene sulfide[29] with acetic anhydride in the presence of pyridine yields the corresponding diacetates of 2-mercaptoethanols with the ring fission occurring at the primary carbon (i.e., "normal" opening) in the relevant cases. Cyclohexene sulfide yields the *trans*-diacetate.



(91)

It is possible, however, to acylate a side chain thiol group of thiiranes with anhydrides or the more reactive mixed anhydrides, without apparent rupture of the ring[52,269]:



(92)

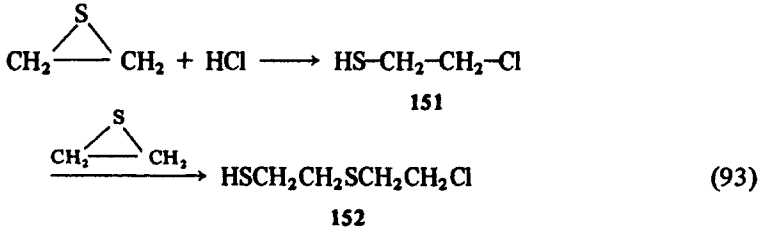
The use of dicarboxylic anhydrides results in polymeric esters.[269a]

The efficiency of the thiirane moiety as a neighboring group in acetolysis of a 2-chloromethylthiirane was studied, and was explained only in terms of the lone pair on sulfur.[269b]

Treatment of thiiranes with excess iodine in glacial acetic acid results in the quantitative formation of the acetoxydisulfide. This reaction can be used in the iodometric determination of thiiranes.[270] The reaction of fatty acids with thiirane in benzene at 100° yields the expected β-mercaptoethyl esters.[271]

b. BY HYDROGEN HALIDES AND ACYL HALIDES

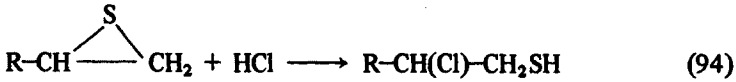
Hydrogen halides and acyl halides cause cleavage of the thiirane ring to yield the β-halothiols or β-halo-*S*-acylthiols. Thus, thiirane,[77] methylthiirane,[198] 2-chloromethylthiirane,[6] and cyclohexene sulfide[6] afforded 2-chlorothiols in fair yields (33–72%) in reaction with concentrated hydrochloric acid. Dilute hydrochloric acid, however, leads to polymers as exclusive products,[3,34,77] whereas addition of thiirane to an excess of concentrated hydrochloric acid enables one to isolate both the monomeric and the dimeric adducts[77]:



(93)

With gaseous HCl in etheral solution only **151** was obtained,[19] and HBr gave β-bromoethylmercaptan.[77]

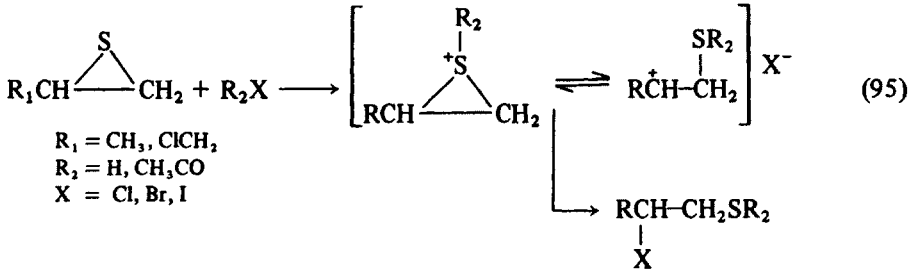
Surprisingly, the ring opening of asymmetric thiiranes by hydrogen halide occurred with halide opening mainly at the secondary carbon atom,[8,34] leading to the "abnormal" product:



(94)

No traces of the isomeric 1-chloro-2-thiols could be detected in the cases above, in contrast to the presence of the "normal" addition product in all the known cases of "abnormal" ring opening of oxiranes. All these results were explained in terms of an intermediate thiiranium ion[8] that underwent ring opening at the secondary carbon atom. The cleavage of the secondary carbon-sulfur bond[8,198,272] would be

predicted of a reaction following an S_N1 mechanism in which the carbon-sulfur bond breaking of the sulfonium ion intermediate is far more nearly complete in the transition state than the bond-making step with the attacking nucleophile:

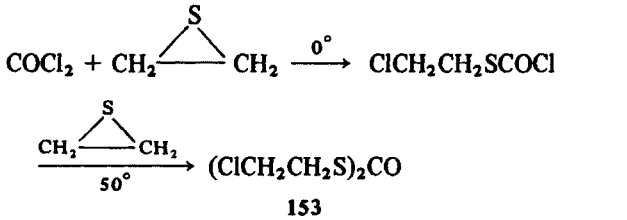


(95)

Reactions of acyl halides with thiirane and methylthiirane have been reported to give good yields of 2-haloalkyl thiolesters resulting from cleavage of the secondary carbon–sulfur bond,[8,34,272] yet, in other cases mixtures of regioisomers were found.[276] A survey of these reactions is summarized in Table 6.[15]

Acetyl bromide,[8,43,272] acetyl iodide,[272] chloroacetyl chloride,[19,118,272] chloroacetyl bromide,[19] propionyl and butyryl bromides,[43,272] benzoyl chloride,[6] and benzoyl bromide[43,272] react in the same manner as acetyl chloride. In contrast, benzoyl fluoride, picryl chloride, dinitrobenzoyl chloride, triphenylmethyl chloride and *p*-toluenesulfonyl chloride and fluoride react with methylthiirane according to a different mechanism, giving polymers as principal products.[6]

Phosgene and α-chloroalkyl ethers are also reactive toward thiiranes. The reaction of the former with thiirane, catalyzed by tertiary amines, proceeds in two steps[273]:



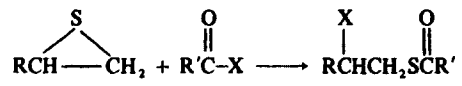
(96)

Chlorocarbonates react with thiiranes analogously to phosgene.[274]

Both phosgene and α-chloroalkyl ether follow the "abnormal" way in their addition to methylthiirane.[274,275] Catalyzed by $HgCl_2$, the reaction of α-chloroalkyl ethers takes place at room temperature.[275]

Interestingly, the reactions of methylthiirane, 2,2-dimethylthiirane, and chloromethylthiirane with hydrogen chloride, acetyl chlorides, and also with anhydrous chlorine, have been found, *contrary* to earlier reports already mentioned, to yield *mixtures* of isomeric products resulting from ring opening at *both* carbon-sulfur bonds (e.g., "normal" and "abnormal" products).[276] Mixtures of both possible isomeric products were also found when thiirane was treated with hydrogen bromide, acetyl bromide, and with acetic anhydride, benzoyl chloride, and bromine.[276]

TABLE 6. REACTIONS OF THIIRANES AND ACYL HALIDES

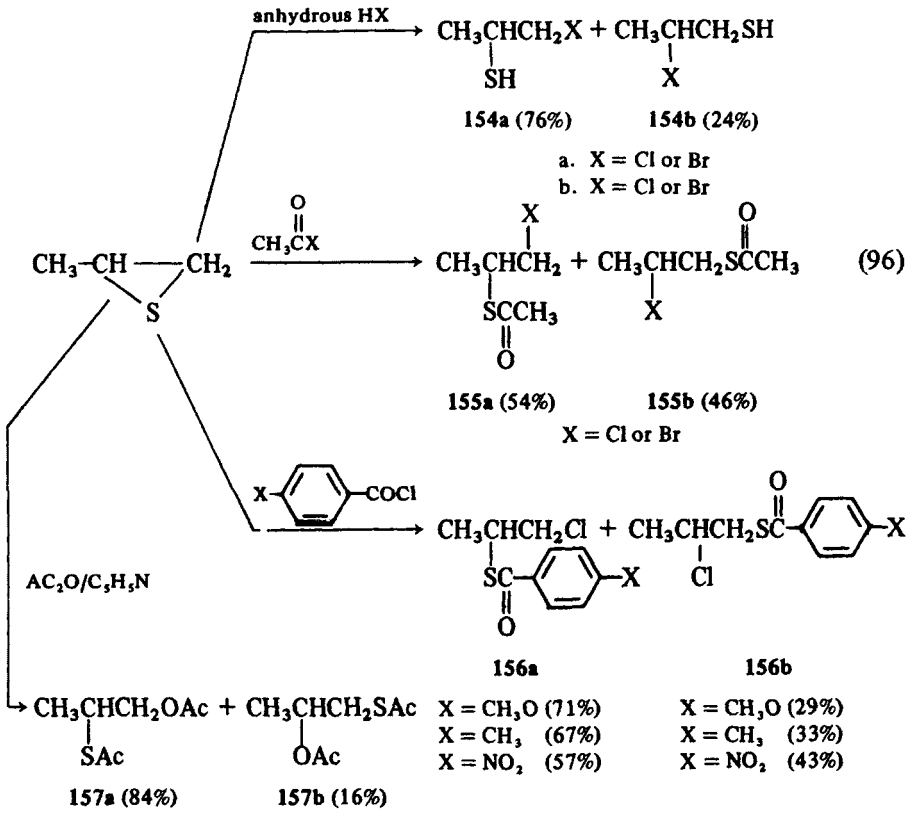


R	R'	X	Yield (%)	Ref.
H	CH_3	Cl	75	269
H	CH_3	Br	70	43, 272
H	CH_3	I	74	272
H	$ClCH_2$	Cl	–	19
H	$ClCH_2$	Br	–	19
H	$BrCH_2$	Br	65	272
H	Cl_3C	Cl	75	272
H	C_2H_5	Br	90	43, 272
H	*n*-C_3H_7	Br	76	43, 272
H	*n*-C_4H_9	Br	70	43
H	C_6H_5	Br	90	43, 272
CH_3	CH_3	Cl	–	6, 198, 269
CH_3	CH_3	Br	95	198, 272
CH_3	CH_3	I	71	272
CH_3	$ClCH_2$	Cl	67	118, 272
CH_3	$BrCH_2$	Br	49	272
CH_3	Cl_2CH	Cl	63	272
CH_3	Cl_3C	Cl	67	272
CH_3	C_2H_5	Br	73	272
CH_3	*n*-C_3H_7	Br	71	272
CH_3	C_6H_5	Cl	–	6
CH_3	C_6H_5	Br	43	43, 272
C_6H_5	CH_3	Cl	–	34
$ClCH_2$	CH_3	Cl	–	6, 8
$HSCH_2$	Alkyl	Cl	–	52
	CH_3	Cl	–	6, 29

Gas-liquid partition chromatography and nmr spectroscopy were used in structure assignment of *mixtures* of isomeric products in analogy to the mixtures obtained in the reactions of methyloxirane with hydrochloric or hydrobromic acids.[277] Selected results are given in Eq. 96[276].

In these cases, the dominance of the "normal" cleavage product (i.e., attack of the halide anion on the less hindered primary carbon atom of the ring) is persistently maintained. This is also true for the pyridine-catalyzed reaction of methylthiirane with acetic anhydride. In contrast, the addition of acetyl chloride to 2,2-dimethylthiirane proceeds predominantly by ring opening at the tertiary C–S bond.[276]

The results above are consistent with a thiiranium ion intermediate in which the site of attack by the nucleophile (the halide anion) is affected by *steric*[278] as well as by *polar* factors. The importance of the polar factors is particularly manifested when the electron-withdrawing ability of the group attached to the sulfur in the thiiranium ion is strong compared with hydrogen.



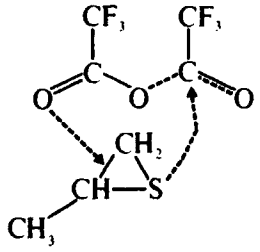
(96)

Interestingly, the addition of alkane-, arene-, and acetylthiosulfenyl chlorides to unsymmetrically substituted olefins yields mixtures of isomeric products.[278, 279]

A recent study[267] dealt with the solvolytic effects and the characteristics of the reaction of methylthiirane with hydrochloric acid, strong carboxylic acids (i.e., CF_3CO_2H), and their acid halides and anhydrides. The data obtained (particularly with respect to the isomer ratio) suggests that:

1. The yield of the monomeric products and their composition are greatly dependent on the order of mixing of reagents (the ratios in the reaction zone) and the nature of the solvent.
2. The formation of the monomeric products involves both the nucleophilic and electrophilic centers of the thiirane ring according to the synchronous mechanism.
3. The geometric parameters and the ability of the reactants to undergo hybridization determine the nature of the products. As the ability of the reactant to undergo hybridization decreases, its ability to initiate polymerization increases.

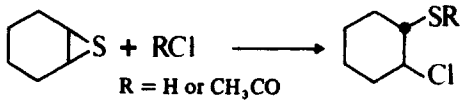
Thus, the geometry of trifluoroacetic anhydride is favorable for the synchronous conversions[267]:



$$\longrightarrow CF_3CSCHCH_2OCCF_3 + CF_3C{-}OCHCH_2SCCF_3 \quad (97)$$

Relevant findings, presented partially above, led to the conclusion[267] that the thiirane ring acts as a three-centred $n\pi$-dipolar system of mesomerically bonded atoms in the electrophilic opening of that ring to form monomeric substances. Furthermore, the limiting epi-ionic mechanism is operative only in the cases of oligomerization and polymerization reactions.

A stereochemical study[29] showed the *trans* products to be isolated from the reaction of cyclohexene sulfide with acetyl chloride and hydrochloric acid, respectively:



(98)

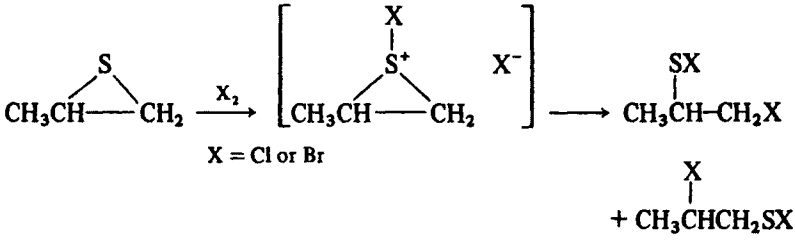
c. REACTION WITH HALOGENS

Addition of either chlorine or bromine to thiiranes in anhydrous solvents causes ring cleavage to give disulfides (i.e., **158**, **159**)[25,276,280] according to Eq. 99[251,276]:

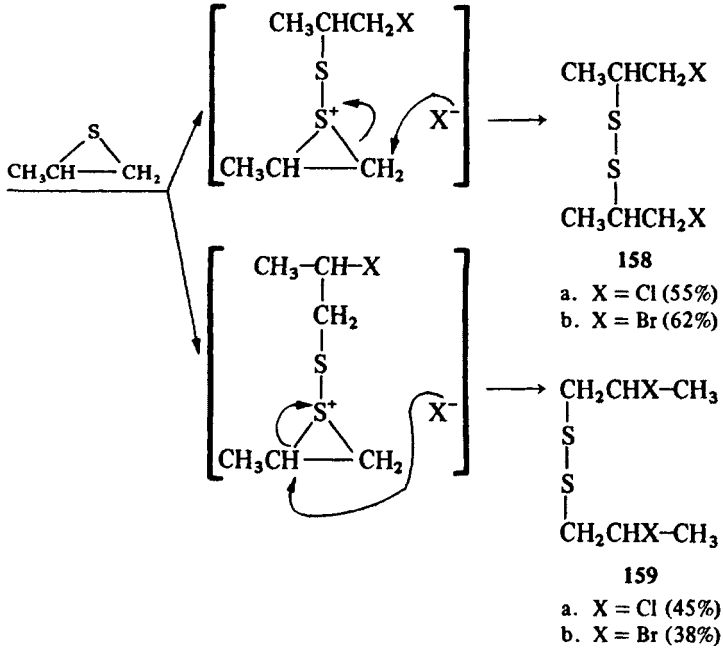
Aqueous chlorine reacts similarly to give the two possible isomers of the 2-chlorosulfonyl chlorides.[276] The corresponding two isomeric disulfides were isolated in the reactions of chlorine or bromine in organic solvents with 2,2-dimethylthiirane,[276] 2-chloromethylthiirane,[276,281] and 2-phenylthiirane[34] for which an "abnormal" ring opening was claimed.

The "abnormal" ring-opening products, β-alkyl-β-halosulfenyl halides, were claimed to be isolated when methylthiirane was added to a solution of chlorine or bromine in a mole ratio of 1 : 1.[280a] However, 2-methyl-2-methoxycarbonylthiirane reacted with chlorine in carbon tetrachloride to give both regioisomeric chlorosulfenyl chlorides.[280b]

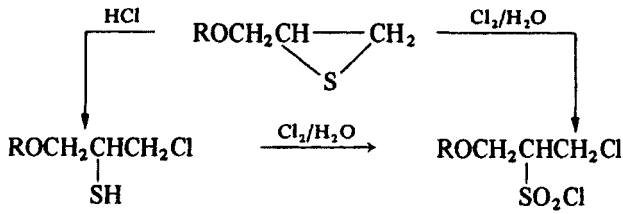
1,2-Dichlorocyclohexane has been isolated from the reaction of cyclohexene



(99)



sulfide with chlorine.[6] 2-Methoxy- and 2-ethoxythiiranes yield predominantly the "normal" ring-opening product in chlorooxidation or by the reaction with hydrogen chloride[282]:



(100)

However, the "abnormal" regioisomeric product is assumed for the analogous chlorooxidation of 2-phenylthiirane.[34]

The cleavage of thiirane on treatment with dichloro-3-iodopyridine[282a] and the cleavage of thiirane derivatives by α-chloroethers[282b] almost certainly involve nucleophilic attack by the chloride ion on an initially formed thiiranium ion (e.g., Eq. 99, first step).

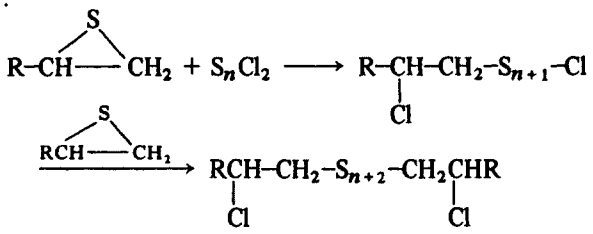
Treatment of 2,3-dimethylthiirane with iodine solution at room temperature gives the diiododisulfide, which on further treatment with warm iodine solution decomposes with desulfurization.[50]

Since the reaction of thiiranes with halogens is quantitative and fast, thiiranes can be titrated with bromine solution (chloroform or carbon tetrachloride as solvents) whenever a quantitative determination is required.

d. REACTION WITH SULFUR AND PHOSPHOROUS HALIDES

It appears that the additions of either sulfur or phosphorous halides to thiiranes obeys the same pattern seen when halogens are added to thiiranes.

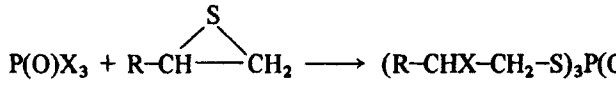
Thus, sulfur dichloride and disulfur dichloride yield the corresponding dimeric and monomeric products in reacting with thiiranes at molar ratios of 1:2 and 1:1, respectively[283]:



(101)

Ring opening is primarily abnormal, and yields of 40–85% have been reported. Sulfuryl chloride reacts with thiiranes in a similar manner with concomitant loss of sulfur dioxide.[280]

Phosphoric or phosphorous halides (i.e., PCl_3, PF_3, and POF_3) were reported to react with thiiranes to form β-halothiol esters[284]:



(102)

X = F or Cl — **160**

The correct regioisomeric structure of **160** is still an open question.

F. *Nucleophilic Ring Opening of Thiiranes*

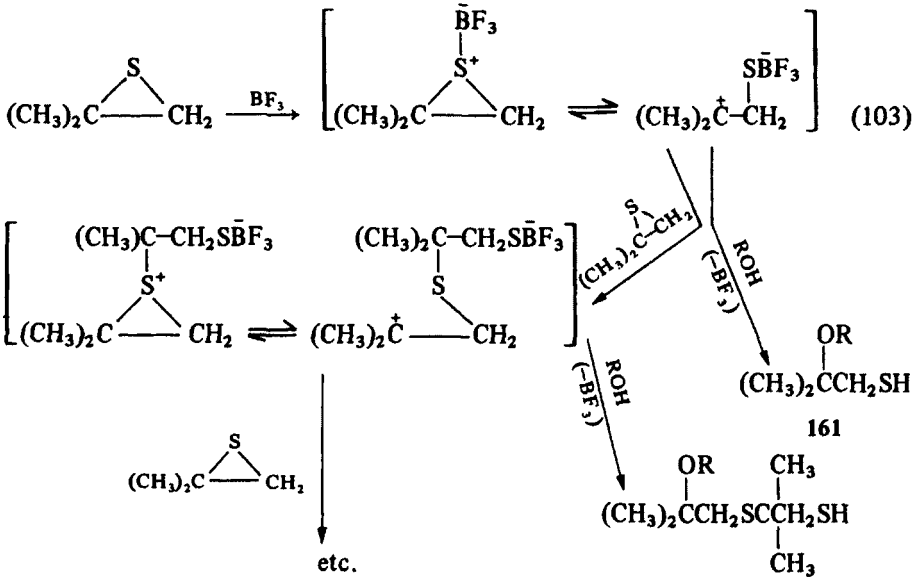
Nucleophilic ring opening of thiiranes, with one of the C-ring atoms being the site of initial attack by the approaching nucleophile, is probably the most-studied chemical reaction of this class. The results of these cleavages are quite similar to those found in oxiranes, indeed; thiiranes and oxiranes display about the same reactivity toward nucleophiles.

As mentioned in the outset of this chapter, facile polymerization almost without exception accompanies the reaction of thiiranes with nucleophiles. If polymerization of the reacting thiirane is to be avoided, special preventive measures must be undertaken. Ordinarily, mercaptoalkylation products are expected of the reaction of thiiranes with nucleophilic reagents.

a. REACTIONS WITH WATER, ALCOHOLS, AND PHENOLS

The reaction of thiiranes with primary alcohols in the presence of catalytic amounts of boron trifluoride yields the expected β-alkoxymercaptans[285] accompanied by higher boiling materials. The yield of the former drops drastically, whereas that of the higher molecular weight materials is further facilitated when secondary

alcohols such as 2-octanol or cyclohexanol are applied. The case of 2,2-dimethylthiirane is illustrated in Eq. 103.

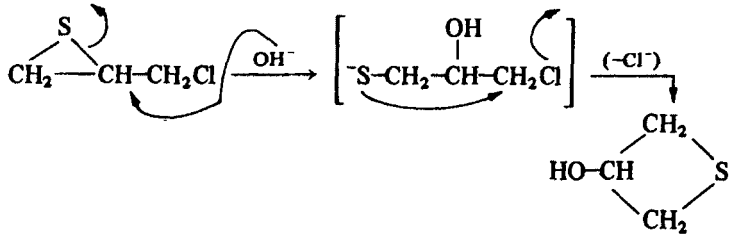


(103)

Methylthiirane and cyclohexene sulfide react similarly, the alkoxy group being added in the "abnormal" manner; the same is true in the addition of ethanol to phenylthiiranes.[257]

Interestingly, both alcohols and water react with thiiranes on heating to yield unidentified products.[6]

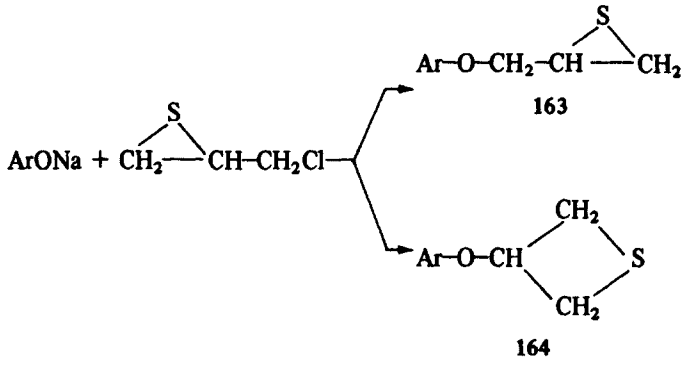
Alkaline hydrolysis of chloromethylthiirane yields 3-hydroxythietane, suggesting again a regiospecific "abnormal" ring opening:



(104)

The "abnormal" ring opening of thiiranes appears to be the favorable pattern in the reactions above, indicative of a regiochemical preference for fission of the secondary or tertiary carbon-sulfur bond. Apparently, the aliphatic alcohol (in Eq. 103) or the hydroxyl ion (in Eq. 104) is competitive with yet unreacted molecules of thiirane for the incipient carbonium (or thiiranium ion).[15] In a basic environment, the reaction of alcohols with thiiranes generally leads exclusively to polymeric materials,[230,233] as previously discussed.

Thiirane reacts with phenol to form β-phenoxyethylmercaptan,[20] whereas alkali phenoxides react with chloromethylthiirane to yield polymers, phenoxymethylthiirane (i.e., **163**) and thietane **164**, the formation of which is preferred in polar aprotic solvents.[271]

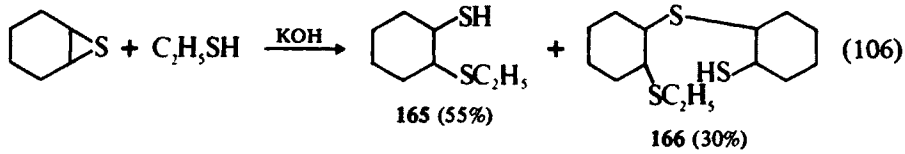


(105)

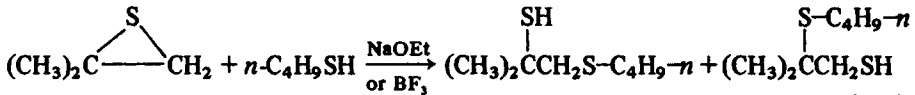
Again, as with alcohols, the "abnormal" ring scission of the thiirane ring is responsible for the formation of thietane (**164**). However, **163** can result either through initial "normal" ring opening or through a direct displacement of chloride.

b. BY THIOLS AND CLOSELY RELATED RS^- NUCLEOPHILES

As with alcohols, free thiols virtually do not cleave the thiirane ring.[6] Either base or acid catalysis is required to facilitate the formation of 2-mercaptoalkyl thiolethers and higher condensation products from alkyl- or aryl- thiols and thiiranes as depicted in Eqs. 106 and 107[6, 19, 285–288]:



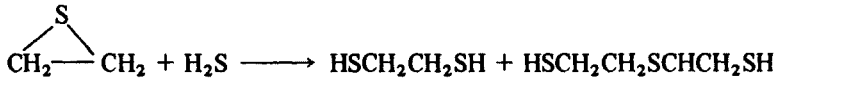
(106)



(107)

In both base and acid catalysis the nucleophilic ring opening of unsymmetrical thiiranes appears to be nonregioselective (e.g., Eq. 107).[285] The use of mercaptan in excess rather than in the theoretical amount results in a substantial increase of the *total* yield, which is generally low (20–50%). An attempt to add mercaptans to tetrasubstituted thiiranes was unsuccessful.[285] Nucleophilic opening of the thiirane ring by thiols proceeds with greater difficulty than in the case of the oxirane ring. Aliphatic and aromatic thiols in nonpolar solvents, using homogeneous catalysis by bases (with Et_3N, e.g.), can be unambiguously mercaptoethylated by selecting the necessary ratios of thiol compound and thiirane.[288c]

i. HYDROGEN SULFIDE AND ITS SALTS. Hydrogen sulfide reacts with thiirane at 45–60° to yield dithio- and trithioglycol[19]:



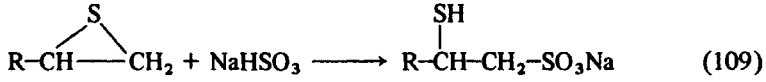
$$\underset{\text{S}}{\overset{\diagup\diagdown}{\text{CH}_2\text{—CH}_2}} + \text{H}_2\text{S} \longrightarrow \underset{\textbf{169 (50\%)}}{\text{HSCH}_2\text{CH}_2\text{SH}} + \underset{\textbf{170 (16\%)}}{\text{HSCH}_2\text{CH}_2\text{SCHCH}_2\text{SH}} \qquad (108)$$

The corresponding 1,2-dithiols are also formed upon interaction of potassium hydrogen sulfide with methylthiirane, cyclohexene sulfide,[6] and 1-octene sulfides.[45] Low yield of trithioglycerol is obtained from the reaction of KHS with chloromethylthiirane.[6] The formation of polymers is responsible for the poor yields of the 1,2-dithiols in these reactions.

ii. ALKOXYMERCAPTANS. Analogous to simple mercaptans, alkoxymercaptans react with thiiranes.[285, 288] Similarly, hydroxymercaptans and dithiols cleave the ring of methylthiirane in the presence of catalytic amounts of sodium ethoxide to furnish the corresponding 1:1 addition products (*ca.* 50% yield) besides 2:1 addition products. Addition of thiols to dithioglycidol results in obtaining only poor yields of the expected products.[286]

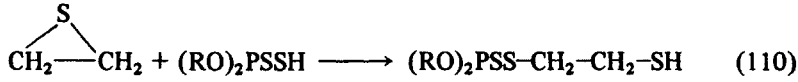
iii. MERCAPTIDES. The use of alkali mercaptides rather than mercaptans accompanied by catalytic amounts of alkali neither improves nor impairs the results as far as yields are concerned.[6, 19]

iv. BISULFITES. In analogy to oxiranes, reaction of thiiranes with aqueous solution of sodium hydrogen sulfite furnishes good yields of salts of β-mercaptosulfonic acid[289]:



$$\underset{\text{S}}{\overset{\diagup\diagdown}{\text{R—CH—CH}_2}} + \text{NaHSO}_3 \longrightarrow \overset{\text{SH}}{\underset{|}{\text{R—CH}}}\text{—CH}_2\text{—SO}_3\text{Na} \qquad (109)$$

v. THIOPHOSPHATES. Thiophosphates (specifically, dialkyldithiophosphates) react similarly[290]:

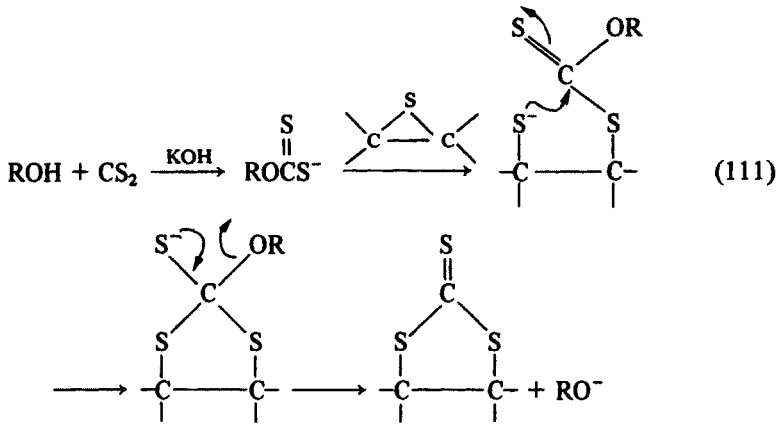


$$\underset{\text{S}}{\overset{\diagup\diagdown}{\text{CH}_2\text{—CH}_2}} + (\text{RO})_2\text{PSSH} \longrightarrow \underset{\textbf{50\%}}{(\text{RO})_2\text{PSS—CH}_2\text{—CH}_2\text{—SH}} \qquad (110)$$

$$\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, n\text{-C}_3\text{H}_7, i\text{-C}_3\text{H}_7, i\text{-C}_4\text{H}_9$$

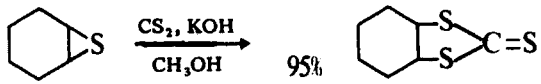
In the presence of NaOH, higher adducts are formed.

vi. XANTHATES. In analogy to the formation of trithiocarbonates from metallic xanthates and oxiranes,[5, 291] it is assumed that the formation of cyclic trithiocarbonate in the reaction of carbon disulfide with thiiranes in the presence of alkali hydroxide in methanolic solution, involves addition of the resultant xanthate ion, followed by the elimination of an alkoxide ion[6, 42, 257]:



(111)

Such an example is the conversion of cyclohexene sulfide to the corresponding trithiocarbonate[5]:



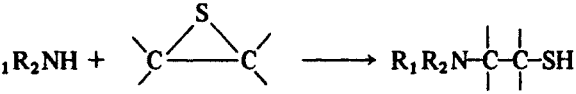
(112)

171

There are claims for the formation of similar trithiocarbonates from thiiranes and carbon disulfide under drastic conditions in the presence of a catalyst but without alkali.[292]

c. REACTIONS WITH AMINES

The reaction products of thiiranes with primary or secondary amines are the corresponding 2-aminoethanethiols **172**:



(113)

172

First described by Reppe and co-workers, this reaction has found wide use in synthesis since it has become the most general route to **172**. The two principal side reactions encountered are further alkylation of the thiol (Eq. 114) and bisalkylation of the primary amine (Eq. 115).

(114)

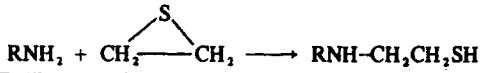
(115)

Aqueous ammonia solution causes polymerization of thiiranes.[3,76] It can therefore be understood why nonpolar reaction conditions should be employed with the strongly basic amines if extensive polymerization is to be avoided. In general, monomercaptoethylation is favored by the use of a two- to threefold excess of the

amine and elevated temperatures.[18] The conversion of a primary amine to the dimercaptan $RN(CH_2CH_2SH)_2$ is best performed in two steps, so that the primarily formed mercaptoamine acts as a basic catalyst.

Numerous aminothiols have been prepared from thiiranes and primary as well as secondary (aliphatic and aromatic) amines. Tables 7 and 8 summarize selected results.[15]

TABLE 7. BOILING AND MELTING POINTS AND REFRACTIVE INDICES FOR AMINOTHIOLS FROM THIIRANE AND ALIPHATIC OR AROMATIC PRIMARY AMINES

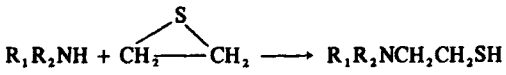


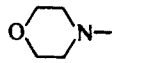
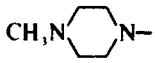
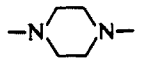
R	M.p. or b.p. [°C (mm)]	n_D^{25}	Ref.
C_2H_5	75 (63)	1.4751	294, 295
$HOCH_2CH_2$	–	–	294
$CH_3OCH_2CH_2$	57 (3)	1.4770[a]	296
$(C_2H_5)_2NCH_2CH_2$	92 (5)	1.4795[a]	18, 296
CH_2CHCH_2	68 (19)	1.4936	294
n-C_3H_7	82 (46)	1.4720	294, 295
iso-C_3H_7	81 (64) (34–35)[b]	–	294
n-C_4H_9	81 (18)	1.4694	294, 295, 297
iso-C_4H_9	76 (23)	1.4652	294
sec-C_4H_9	83 (33)	1.4676	294
tert-C_4H_9	71 (28) (41–43)[b]	–	294
C_6H_{11}	99 (7)	1.5040	47, 294
n-C_6H_{13}	97 (9)	1.4680	18, 294
n-C_7H_{15}	70 (2.5)	1.4703	22
n-C_8H_{17}	83 (0.3)	1.4691	294
n-$C_{10}H_{21}$	120 (0.6)	1.4674	294
$C_6H_5CH_2$	84 (0.1)	1.5585	18, 294
$C_6H_5CH_2CH_2$	108 (2)	1.5540[a]	47
$C_6H_5CH_2CH(CH_3)$	111 (2)	1.5462[a]	47
	139 (6)	1.5776[a]	47
C_6H_5	138 (12)	1.6057	18, 22, 47, 287, 293, 298
o-$CH_3C_6H_4$	132 (5)	1.5895	47, 298
m-$CH_3C_6H_4$	133 (5)	1.5874	47
p-$CH_3C_6H_4$	130 (5)	1.5862	47, 298
o-$CH_3OC_6H_4$	146 (5)	1.5918	47, 298
m-$CH_3OC_6H_4$	163 (5)	1.5930	47
p-$CH_3OC_6H_4$	151 (4)	1.5910	47, 298
o-$NH_2C_6H_4$	152 (1.5)	1.6320	47
m-$NH_2C_6H_4$	165 (1.5)	1.6483	47
o-$CH_3OCOC_6H_4$	151 (2)	1.6019	299
m-$CH_3OCOC_6H_4$	182 (3)	1.5936	299
p-$C_2H_5OCOC_6H_4$	185 (3) (58–58.5)[b]	–	299
p-ClC_6H_4	130 (1.5)	1.6132	299

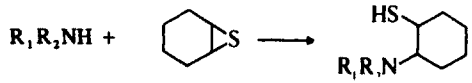
[a] Measured at 20°.

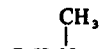
[b] Melting point.

TABLE 8. BOILING POINTS AND REFRACTIVE INDICES FOR AMINOTHIOLS FROM THIIRANES AND SECONDARY AMINES



R_1R_2N	B.p. [°C (mm)]	n_D^{25}	Ref.
$(CH_3)_2N$	58–59 (63)	1.4630	43, 47
$(C_2H_5)_2N$	85 (56)	1.4636	18, 47, 294, 295, 300
$(n\text{-}C_3H_7)_2N$	77 (10)	1.4614	47, 294
$(iso\text{-}C_3H_7)_2N$	73 (13)	1.4686	47, 294
$(n\text{-}C_4H_9)_2N$	66 (0.7)	1.4620	22, 47, 294, 295
$(iso\text{-}C_4H_9)_2N$	91 (10)	1.4572	47, 294
$(sec\text{-}C_4H_9)_2N$	93 (8)	1.4723	47
$(n\text{-}C_5H_{11})_2N$	91 (0.8)	1.4629	22, 47
$(iso\text{-}C_5H_{11})_2N$	85 (1)	1.4600	18, 47
$(n\text{-}C_7H_{15})_2N$	127 (2)	1.4660	22
$(n\text{-}C_8H_{17})_2N$	146 (2)	1.4658	22
$(CH_2{=}CHCH_2)_2N$	90 (17)	1.4895	18, 47
	79 (10)	1.4991	22, 294, 296
	92 (10)	1.5021	18, 294, 296
	95 (10)	1.5040	294
	96 (0.03)	–	294
	78 (0.9)	1.4977	294
$(C_6H_5CH_2)_2N$	[196–198 (2)][a]	1.5760[b]	47
	81 (22)	1.5004[b]	296, 298



Piperidino-	97–99 (1)	1.5190	22, 301
	175 (16)	–	6

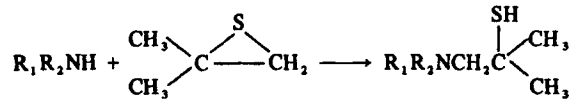
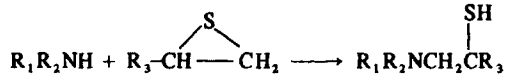


TABLE 8 CONTINUED

R_1	R_2			
n-C_7H_{15}	H	83–86 (2)	1.4630	22, 301
n-$C_{12}H_{25}$	H	138 (3)	–	22, 301
C_2H_5	C_2H_5	94 (52)	1.4597	22, 301
n-C_4H_9	n-C_4H_9	89 (2)	1.4748	22, 301
n-C_5H_{11}	n-C_5H_{11}	85–90 (2)	1.4653	22, 301
iso-C_5H_{11}	*iso*-C_5H_{11}	83–86 (2)	1.4677	22, 301
n-C_7H_{15}	n-C_7H_{15}	126 (2.5)	–	301
Morpholino		81 (6.5)	1.4886	22, 301
Piperidino		47 (2.5)	1.4840	22, 301
3-Methylpiperidino		51–53 (2)	1.4782	22, 301
4-Ethylpiperidino		74–76 (2.5)	1.4894	22, 301
Piperazino		127–131[b]	–	22, 301



$R_1R_2NH + R_3{-}CH(\overset{S}{\diagdown\diagup})CH_2 \longrightarrow R_1R_2NCH_2\underset{SH}{C}HR_3$

R_1	R_2	R_3			
n-C_5H_{11}	n-C_5H_{11}	CH_3	86–87 (2)	1.4634	22, 301
C_2H_5	C_2H_5	CHO	–	–	30

[a] Melting point.
[b] Measured at 20°.

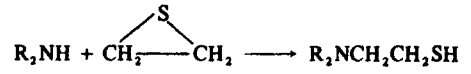
In the monomercaptoethylation of the weakly basic aromatic amines, the reaction is slow and is often facilitated by the use of ionizing solvents and by heating.[18,47] The presence of electron-donating substituents such as methyl or methoxy in the ortho or para positions of the primary arylamines does not affect the course of this reaction.[298] More drastic conditions (prolonged heating), however, are required for mercaptoalkylation of the more weakly basic substituted anilines such as esters of ortho-, meta-, and para-carboxyanilines.[299]

The rates of reaction of methylthiirane and methyloxirane with aniline showed the former to be less reactive than the latter and to have the higher activation energy (E_a = 14.64 kcal/mole, vs. 7.10 kcal/mole for the methyloxirane).[302]

The attack of the aniline was shown to take place primarily on the primary carbon atom of either the thiirane or the oxirane rings, as would be expected for steric reasons. The oxirane ring is more susceptible to cleavage than is the thiirane because of the greater polarization of the C–O bond than of the C–S bond.[302]

Several groups studied the reaction of equimolar quantities of secondary and primary amines with thiiranes at elevated temperature.[22,293] The reaction rate was found to drop not only with decreasing basicity, but also in the case of steric hindrance, provided the higher degree of branching (or the bulky group) is near the site of reaction, that is, on the carbon alpha to the amino nitrogen. Thus, for example, the strongly basic but sterically hindered dicyclohexylamine does not form an adduct with thiirane at 100°. The data given in Table 9 provide some insight into the steric effects encountered in mercaptoalkylation of aliphatic

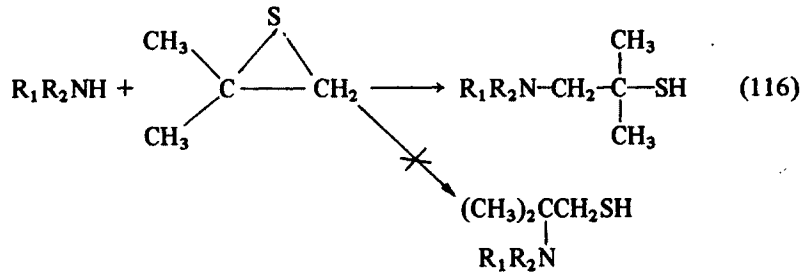
TABLE 9. STERIC EFFECTS OF USING THIIRANES IN THE MERCAPTOALKYLATION OF ALIPHATIC AMINES[15]



R_2NH	Yield (%)	R_2NH	Yield (%)
n-$C_3H_7NH_2$	75	$(n\text{-}C_3H_7)_2NH$	29.4
iso-$C_3H_7NH_2$	77	$(iso\text{-}C_3H_7)_2NH$	24.3
n-$C_4H_9NH_2$	66	$(n\text{-}C_4H_9)_2NH$	29.7
iso-$C_4H_9NH_2$	72	$(iso\text{-}C_4H_9)_2NH$	6.3
sec-$C_4H_9NH_2$	68	$(sec\text{-}C_4H_9)_2NH$	7
tert-$C_4H_9NH_2$	64		

amines with thiiranes. The lack of a definite trend in the recorded yields, even with the comparatively hindered *tert*-butylamine, indicates that indeed there is no pronounced steric effect unless the steric hindrance is close enough to the reacting site, as observed with both diisopropylamine and di-*sec*-butylamine.

Most of the studies on mercaptoalkylation of amines involved, primarily, the use of the parent thiirane. The reaction of amines with other thiiranes has received less attention, and any generalizations should be drawn with care until more data are available. Thus, contrary to previous studies,[293] the "normal" ring opening is claimed to be exclusively operative[285, 288] in the reaction of secondary amines with 2,2-dimethylthiirane: In this reaction the tertiary mercaptan is practically the only product obtained:

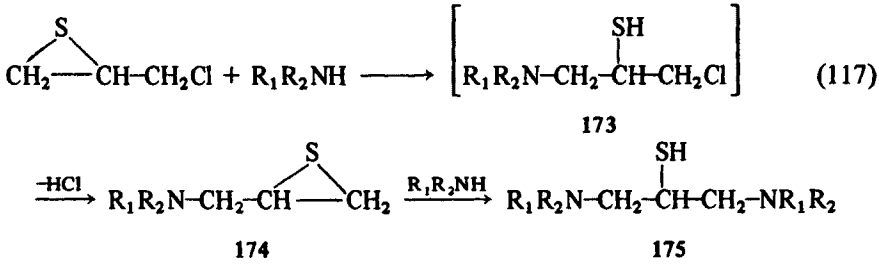


(116)

The reactions of secondary amines with substituted thiiranes (e.g., 2,2-dimethylthiirane) appear to occur less readily than with the parent thiirane. Neither base nor acid catalysis accelerates the reaction or improves the yields.[18, 300] In general, the yields of β-amino mercaptans from either primary or secondary amines range between 50 and 80%.[18, 22, 304] This includes the mercaptomethylation of hydroxyalkyl-, alkoxyalkyl-, and *t*-aminoalkylamines, and primary diamines.[305] Both high temperatures (e.g., 100°[18, 304] or 80°[305]) and room temperature[43, 49] were employed in these reactions. Most studies confirm the "normal" ring opening in the addition of amines to thiiranes.[22, 306] High yields of amino mercaptans (80–92%) have been obtained in the reaction of methoxy- and ethoxythiiranes with a

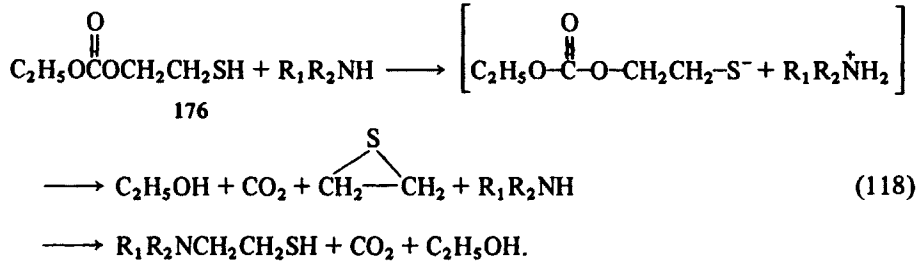
100% excess of piperidine or morpholine in boiling benzene.[307] However, only the starting materials were recovered upon interaction of alkoxythiiranes with diethylamine under the same reaction conditions. The authors attributed this result to a renewed cleavage of the resultant diethylamino mercaptans during distillation. Aqueous solutions of diethylamine exclusively involve polymerization of the thiirane. Similarly, secondary amines (i.e., dimethylamine, piperidine, and morpholine) react in solution with phenylthiirane under "normal" ring opening to yield the corresponding amino mercaptans (in about 60% yields),[34] whereas only sulfur-free products are obtained without the use of solvents.[32]

The reaction of chloromethylthiirane with secondary amines in aprotic solvents (e.g., ethyl ether or petroleum ether) in 1:1 or 1:2 molar ratios afforded mainly **174** and a mixture of **174** and **175**, respectively, meaning a "normal" ring opening. In no case has it been possible to isolate **173**. Only polymeric material could be obtained when primary amines were employed instead of secondary amines in the foregoing study.[281]



(117)

In lieu of preparing and handling large amounts of thiirane, ethyl-2-mercaptoethylcarbonate (**176**) has been successfully employed in the mercaptoethylation of primary and secondary amines[294]:



(118)

Ethylene monothiolcarbonate, 2-mercaptoethylcarbonate, and 2-hydroxyethylthiolcarbonates have also been studied for the same purpose.[308]

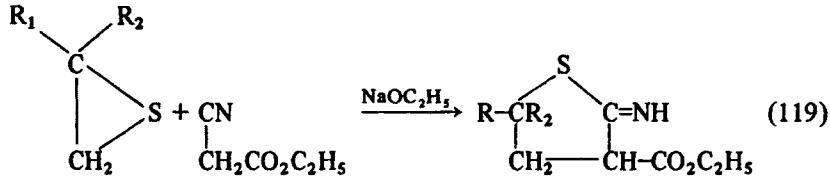
The β-mercaptoethylation of cyanamide, guanylurea, and biguanide is described in patent specifications.[303, 309]

In conclusion, the mercaptoalkylation reaction of amines by thiiranes obeys the regioselective "normal" ring-opening mechanism and needs no catalysis; moreover, each hydrogen atom at the nitrogen atom of the starting amine or at the sulfur in the resultant mercaptoalkylamine may undergo mercaptoalkylation. Side reactions,

primarily polymerizations, can be suppressed by using the amine in large molar excess and aprotic solvents of low polarity.

d. REACTIONS WITH ACTIVE METHYLENE COMPOUNDS

Ethyl cyanoacetate (but neither ethyl malonate nor ethyl acetoacetate) reacts with thiiranes in the presence of $NaOC_2H_5$ in the "normal" nucleophilic ring-opening fashion, to give ethyl 2-iminothiophane-3-carboxylate (**177**) in low to moderate yields[310]:



(119)

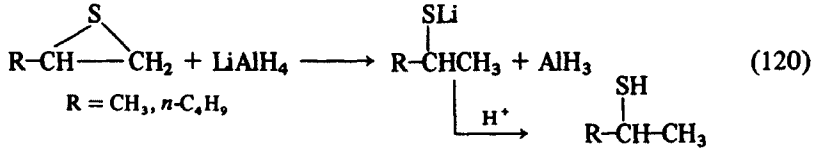
177

a. $R_1 = R_2 = H$ (23%)
b. $R_1 = CH_3$; $R_2 = H$ (30%)
c. $R_1 = R_2 = CH_3$ (60%)
d. $R_1 = Ph$; $R_2 = H$[32]

The yields reflect the extent of polymerization in each case.

e. REDUCTIVE NUCLEOPHILIC RING OPENING

The reaction of several thiiranes with lithium aluminum hydride proceeds with reductive ring cleavage to give thiols as their lithium mercaptides, which are isolated as thiols in about 75% yields. Asymmetrical thiiranes are reduced regioselectively to secondary thiols[41,276] with only about 0.5% of 1-propanethiol detectable by gas-liquid chromatography in the case of methylthiirane[276]:

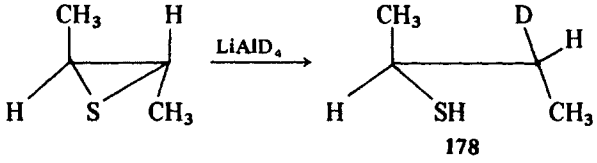


(120)

The reaction of the latter with sodium ethanethiolate also yielded exclusively the "normal" product.[276]

The yields of mercaptans amounted to 20% for hexylthiirane[45] and 75–85% for a number of alkoxymethylthiiranes.[307] The reduction of cyclohexene sulfide[41,311] and carbohydrate thiiranes[42] with $LiAlH_4$ was also reported. By-products obtained in the latter reactions are solid polymers and sulfur-containing compounds but not H_2S.[45]

The reductive cleavage of L-2,3-dimethylthiirane with lithium aluminum deuteride has been demonstrated to proceed with inversion of configuration[44,50]:



178 (121)

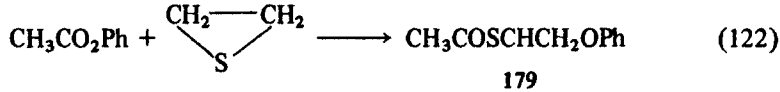
The resistance to reductive ring cleavage of some steroidal thiiranes at ambient temperatures makes it possible to reduce the carboxylic function to the corresponding alcohols without affecting ring cleavage.[83, 255]

Reductive desulfurizations of thiiranes with $LiAlH_4$ already have been discussed.[72, 142, 255] Reductive desulfurization may also be accomplished by Raney nickel in ethanol.[42, 83, 281]

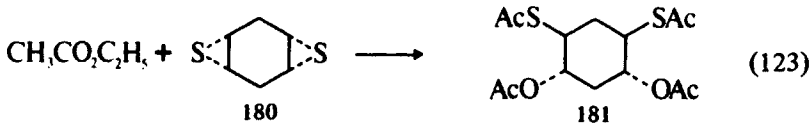
f. CATALYZED RING OPENING WITH ACETATES

Addition reactions of acetate esters to thiiranes with the concomitant catalyzed opening of the three-membered ring were recently reported.

Thus, a mixture of phenyl acetate and thiirane gave, in the presence of catalytic amounts of DBU, a very low yield of the addition product **179**.[312] Addition of ethyl acetate to a solution of the bisthiirane **180** in the presence of $Hg(OAc)_2$ afforded the tetraacetate **181**.[313]



179 (122)

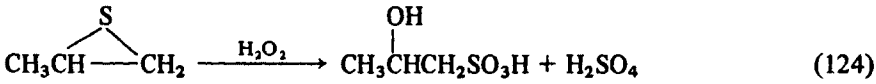


180 181 (123)

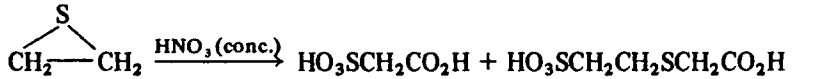
The scope and potential of this reaction are yet to be explored.

G. *Oxidation*

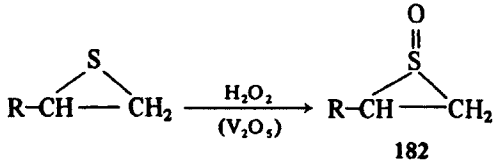
Although many attempts to oxidize thiiranes to the corresponding sulfoxides and/or sulfones failed because of ring opening[3, 6, 25, 77] (e.g., Eqs. 124[25] and 125[77]), it is possible to convert thiiranes to their sulfoxides by using H_2O_2 in the presence of catalytic amounts of V_2O_5.[314] By this means even sensitive thiirane oxides such as **182a** have been prepared.



(124)



(125)

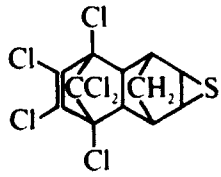


(126)

182

a. R = CH_2OH

Hydrogen peroxide reacts vigorously with thiirane,[6, 315] whereas sulfuric acid, dilute or concentrated, appears to have only polymerizing influence,[6] as is the case with either perbenzoic acid or dibenzoyl peroxide.[315] However, 2,3-diphenyl,2,3-dibenzoylthiirane (dibenzoylstilbene sulfide) has been oxidized to the corresponding sulfoxide or sulfone depending on the amount of hydrogen peroxide used.[316a] Oxidation of 1-vinylthiirane with the same reagent proceeds with rearrangement to the dihydrothiophene-1-oxide.[316b] The thiirane **183** has been oxidized to the corresponding sulfoxide with peracetic acid as described in a patent,[317a] and 2-methylthiirane has been oxidized with perbenzoic acid in the cold to the *trans*-2-methylthiirane-1-oxide sterospecifically.[317b]



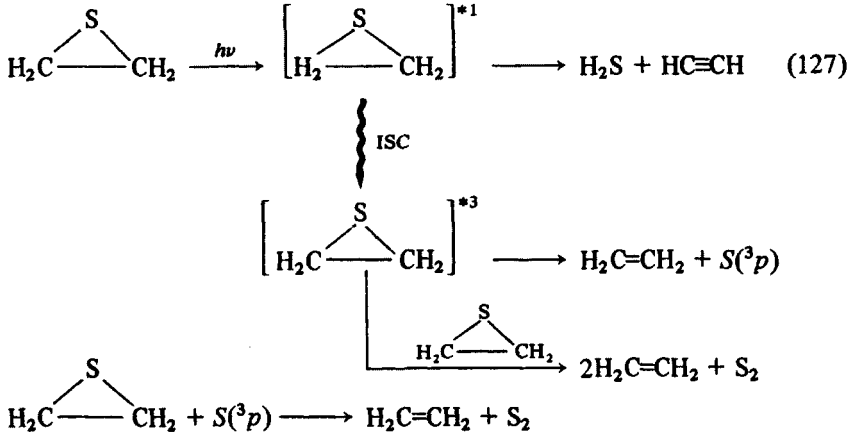
183

Both *cis*- and *trans*-2,3-di-*t*-butylthiiranes have been recently oxidized to the corresponding sulfoxides in 80–86% yield by using a single equivalent of *m*-chloroperbenzoic acid.[339] It appears, therefore, that either overcrowding at the two carbons of the thiirane ring or substitution of these carbons with bulky groups stabilizes the ring against cleavage by ordinary peroxy-oxidizing agents. More definite conclusions in this respect must await a systematic study on the oxidation of thiiranes with various peroxides.

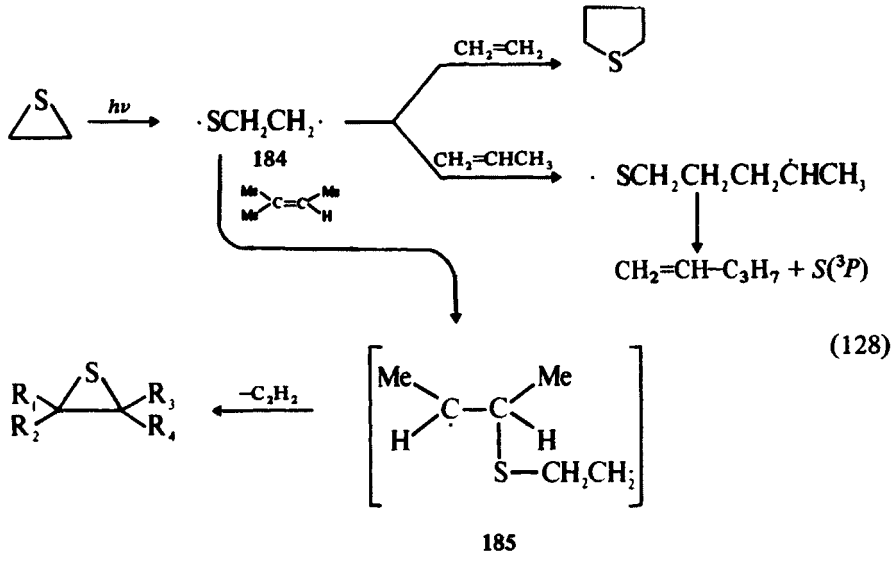
H. *The Photochemistry of Thiiranes*

An excellent essence-type review by A. Padwa[317] summarizes the state of the art in the photochemistry of thiiranes as of 1972. It turns out that the ease with which thiiranes undergo photochemical extrusion of sulfur[319–321] suggests that in certain cases this may be the method of choice for desulfurization to obtain the corresponding olefin from the three-membered ring.

The minor amounts (*ca.* 10%) of hydrogen sulfide and acetylene that are also formed are considered to arise by a molecular cleavage of the excited singlet state of the thiirane. A proposed mechanism for the formation of ethylene by derivation from the excited triplet state is shown in Eq. 127.[321]



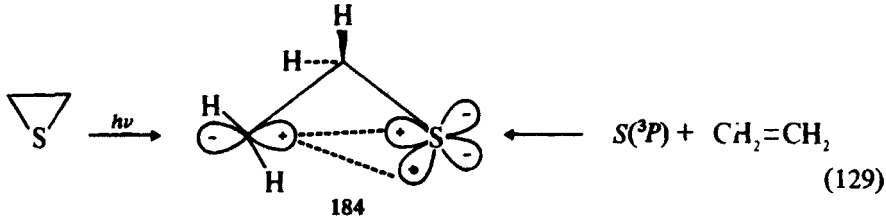
Photolysis of thiirane in the presence of ethylene or propylene results in a low yield of tetrahydrothiophene and a fairly good yield of 1-pentene, respectively. In the presence of *cis*-butene, direct or benzophenone-sensitized photolysis yielded the corresponding *cis*- and *trans*-2,3-dimethylthiiranes by losing ethylene apparently from intermediate **185**[322]:



185

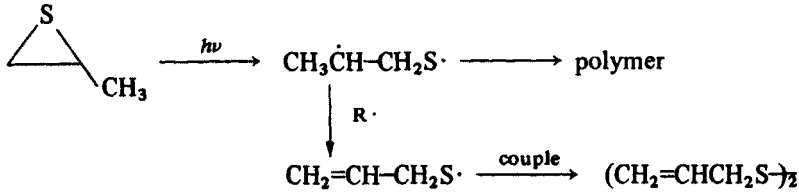
a. $R_1 = R_3 = Me$; $R_2 = R_4 = H$
b. $R_1 = R_4 = Me$; $R_2 = R_4 = H$

These results as well as the stereospecificity of the addition of triplet $S(^3P)$ atoms to olefins were explained[323] in terms of the unusual properties of thiadimethylene radical **184**, that is, its long lifetime and particularly slow rate of rotation about the C–C bond.



184 (129)

Ultraviolet irradiation of methylthiirane results in a major formation of polymeric resin and small quantities of alkyl disulfide[324]:



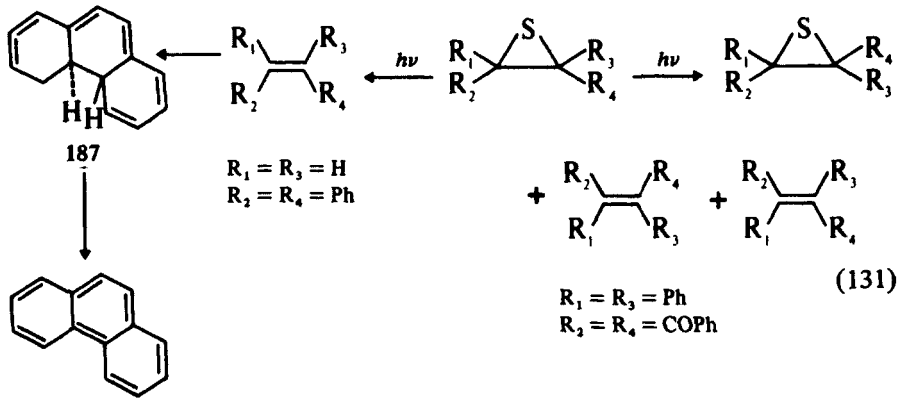
Similar results were obtained with tetrafluorothiirane in the presence of trace quantities of bis(trifluoromethyl)disulfide.[325]

In analogy to the vinylcyclopropane-cyclopentene isomerization,[326] the photolysis of vinylthiacyclopropane (**186**) has been shown to yield thiophene[322]:

186 (130)

Interestingly, photolysis of tetra(trifluoromethyl)thiophene gave a thiirane by 2*s* + 2*s* cycloaddition.[326a]

Photodesulfurization of 2,3-diphenylthiirane afforded phenanthrene[327] through the initially formed *cis*-stilbene, whereas *cis*-2,3-dibenzoylthiirane gave *cis*- and *trans*-dibenzoylstilbene accompanied by the corresponding *trans* isomer of the starting material (Eq. 131). It was shown[328] that the latter desulfurization is almost totally stereoselective, since the *trans*-dibenzoylstilbene is the *primary* reaction product.

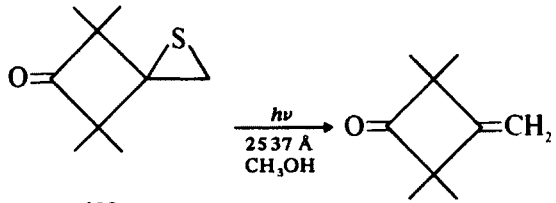


(131)

The desulfurization reaction is explained by assuming a cleavage of the C–S bond of the thiirane ring, followed by a loss of atomic sulfur. The driving force can be attributed to the tendency of the excited n–π^* state to eliminate α-substituents as odd-electron species. The activation energy for sulfur extrusion is estimated to be between 30 and 40 kcal/mole, and the energetics of sulfur extrusion from the thiodiradical intermediate to be less than the calculated upper limit of 67 kcal/mole because of the stabilized radical (by both the phenyl and benzoyl groups) obtained after the loss of sulfur.[319]

The high stereoselectivity observed demands that rotational isomerization be a relatively efficient process vs. sulfur extrusion. Furthermore, the diradical formed must possess a relatively long lifetime for efficient loss of sulfur to occur. It was concluded[328] that the van der Waals repulsive forces between the *cis*-oriented bulky groups is the decisive factor for the stereoselectivity observed in the desulfurization above.

A variation of product distribution as a function of wavelength in the photolysis of 4,4,6,6-tetramethyl-1-thiaspiro[2,3]hexane-5-one (**188**)[329] implies a reaction from two electronic states. The fact that the loss of sulfur is the major process at 2537 Å indicates that energy transfer from the n–σ^* state to the n–π^* state is inefficient and that scission of the C–S bond is a rapid process.



(132)

188 **189**

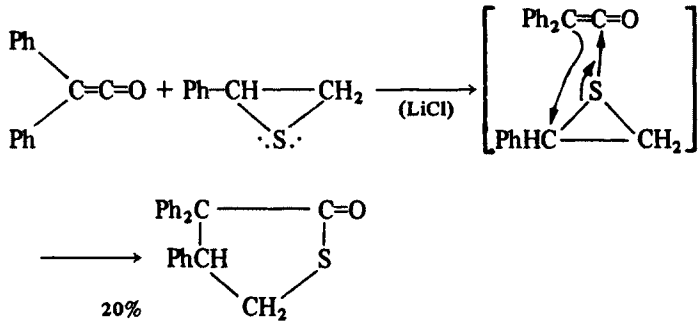
Finally, thiiranes have been suggested as photointermediates in several cases.[330] These intermediates may be desulfurized either by further irradiation or with the aid of an appropriate desulfurization agent.

I. *Miscellaneous Reactions*

The reaction of thiiranes with different reagents has been attempted with varying success. Some of these reactions are given below. Their scope and potential are still to be explored.

a. WITH DIPHENYLKETENE

The reaction of diphenylketene with phenylthiirane with (or without) the addition of LiCl as a catalyst results in the isolation of 2,3,3-triphenyl-γ-thiolactone (**190**) as the main product, accompanied by a small amount (2–3%) of 2,2,3-triphenylcyclobutanone-1.[331]



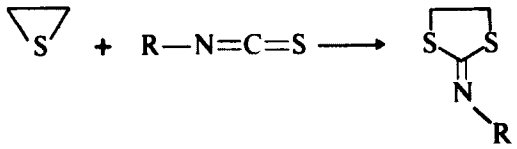
(133)

190

Interestingly, in the reactions of diphenylketene with chloromethylthiirane, ethoxymethylthiirane, or the parent thiirane, a γ-thiolactone was not isolated; rather, only polymeric materials were produced.

b. WITH ISOTHIOCYANATES AND ISOCYANIDES

The reaction of alkylisothiocyanates with thiiranes is another example of [2 + 3] cycloaddition of the latter with heterocumulenes.[332] However, here the three-membered ring of the thiirane cycloadds to the terminal carbon–sulfur double bond, whereas in the case of diphenylketene the addition to the central carbon-carbon double bond predominates. The yields of the iminodithiolanes **191** obtained are good.



(134)

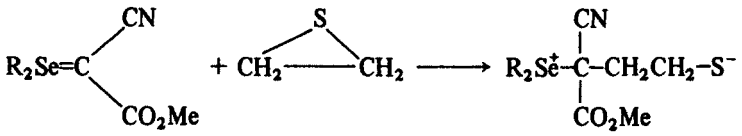
191

R = alkyl

5,6-Dihydro-4*H*-1,3-thiazines are obtained from α-metallated isocyanides and thiiranes.[332a]

c. WITH SELENIUM YLIDS

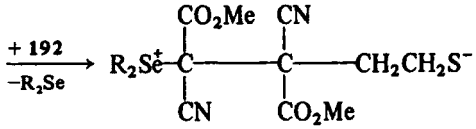
Dialkylselenonium cyano(methoxycarbonyl)methylides (e.g., **192**), react catalytically in chloroform at room temperature with aliphatic thiiranes to give mainly the reduced selenides and dicyanofumarate, accompanied by minor amounts of olefins and elemental sulfur, according to the mechanism depicted in Eq. 135.[333] Cyclohexene episulfide, phenylthiirane, and 2,3-dimethylthiirane gave results comparable to that obtained with the parent thiirane.[333] No reaction took place with 2,3-diphenylthiirane, probably because of steric hindrance.

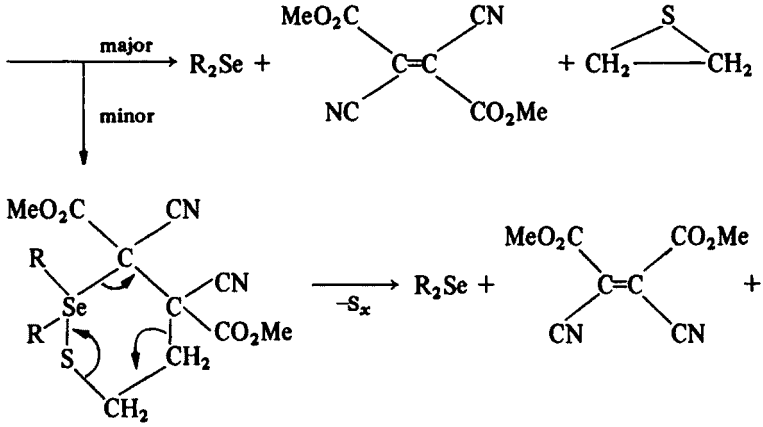


(135)

192

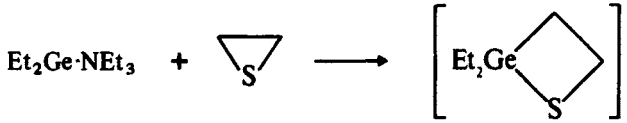
R = $PhCH_2$ or Me



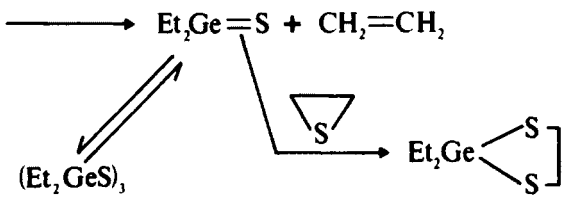


d. WITH COMPLEXED DIALKYLGERMYLENES

Complexed dialkylgermylenes R_2GeNR_3 or R_2GePy react with thiirane and lead to germathione via germathiacyclobutane. Germadithiolane (**193**), which is finally obtained, arises from condensation of germathione with another molecule of thiirane[334]:



(136)

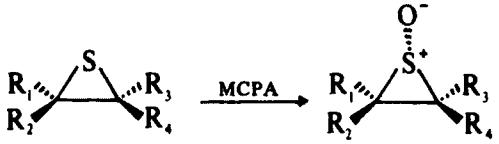


193

J. *Chemistry of cis- and trans-2,3-Di-tert-Butylthiiranes*

Interest in the chemistry of the two specially substituted thiiranes **194** and **195** has several sources: (*a*) the well-documented stabilizing effect imparted to sensitive three-membered rings by the bulky *tert*-butyl substituents,[335] (*b*) the steric hindrance associated with the *tert*-butyl group,[336] and (*c*) the strain introduced in many α,β-di-*tert*-butyl-substituted molecules because of the steric crowding that is involved.[337] Furthermore, the *cis* orientation of *tert*-butyl groups in **194**[338] appears to be unique among three-membered rings.

Oxidation of both *cis*- and *trans*-2,3-di-*tert*-butyl thiiranes (i.e., **194** and **195**) with one equivalent of *m*-chloroperbenzoic acid affords the coresponding thiirane oxides[339]:



(137)

194: $R_1 = R_3 = H$; $R_2 = R_4 = t$-Bu — *cis*-**196**
195: $R_1 = R_4 = t$-Bu; $R_2 = R_3 = H$ — *trans*-**197**

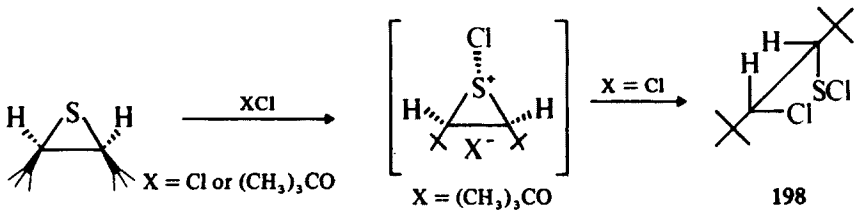
It is easier to obtain **196** from **194** than **197** from **195** primarily because of the thermal instability of the *trans* oxide **197**, from which the elements of sulfur monoxide are eliminated if heated above 50°. Under no circumstances using various oxidation reagents could the sulfoxides be oxidized further to the corresponding *S*-dioxides: The *cis* isomer remained essentially intact (steric hindrance?) while both **195** and **197** were consumed with excess oxidizing agent, but no stable products could be isolated.[399]

Reactions of **194** with chlorine and *t*-butyl hypochlorite gave the open products **198** and **199**, respectively, most probably through a chlorosulfonium intermediate[339].

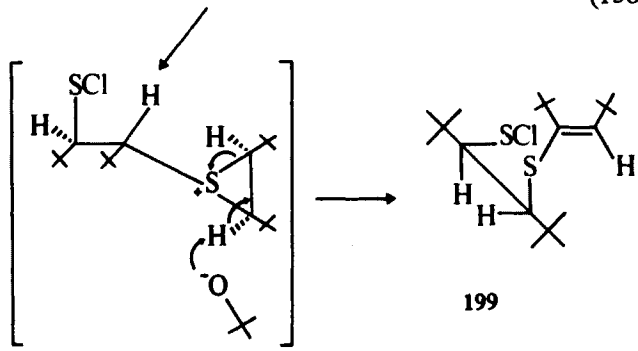
Again, the *trans* isomer (i.e., **195**) was not attacked appreciably by *t*-butyl hypochlorite even on prolonged standing.

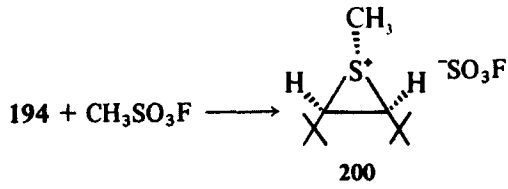
A crystallized moisture-sensitive sulfonium salt (e.g., **200**) can be isolated by the treatment of **194** with methylfluorosulfonate.

Higher temperatures were required to cause reaction between the *trans* isomer (i.e., **195**) and methylfluorosulfonate. However, no characterizable products were isolated,[339] apparently because the derived salt was not stable at the higher temperatures used. Finally, neither **194** nor **195** could be forced to react with either *p*-toluenesulfonyl azide or dry hydrogen chloride to give the corresponding *p*-toluenesulfonyl sulfinimides or the α-chlorothiols, respectively. Attempts to prepare a complex from **194** and iron pentacarbonyl or diiron nonacarbonyl also failed. However, protonation – which is a reaction with minimal steric requirements – did succeed quite well: both **194** and **195** could be completely protonated



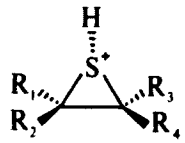
(138)





(139)

when added slowly to a solution of fluorosulfonic acid at $-60°$. All the evidence points to the closed-ring ions **201a** and **201b** as the most logical structures[339]:



201

a. $R_1 = R_3 = H$; $R_2 = R_4 = t$-Bu
b. $R_1 = R_4 = H$; $R_2 = R_3 = t$-Bu

Consideration of the results given above leads to the conclusion that in spite of the demonstrated protecting effect of the *tert*-butyl groups that prevent the three-membered thiirane from being attacked by external reagents, steric hindrance is a poor means for bringing about significant structural modifications. Nevertheless, in view of the relative inertness of *diphenyl*thiirane oxides to various reagents[340] vs. the reactivity of acyclic analogs (or closely related compounds) toward the same reagents, one tends to conclude that *stereoelectronic effects* should be considered

and tested through appropriate refined systems and measurements in both hindered and unhindered thiiranes as well as in their oxidized and/or unsaturated analogs.

4. Uses

The greatest use of thiiranes is as chemical intermediates in organic synthesis in the laboratory and in industry. It is their high reactivity that makes them valuable materials for the manufacture of other sulfur-containing materials or for the finishing of neutral synthetic polymers.

Potential applications of thiiranes have already been indicated in connection with the various chemical reactions they undergo. Mercapto compounds and olefins (via desulfurization) appear to be the required end products in most cases.

Following are a few selected cases in which reaction with thiiranes furnishes unidentified products of commercial interest: fabric and wool can be treated with thiirane to impart unshrinkability[17, 341]; the quality of various lubricant additives can be modified by treatment with thiirane[342]; the reaction products of cyanamide, guanylurea, and biguanide can be used as insecticides, vulcanization accelerators, plasticizers, or for the production of resins[303, 309]; copolymers of thiiranes are recommended as additives to lubricating oils, greases, or cutting oils[240]; copolymers from thiirane and methylthiirane are of potential interest as elastomers[235]; and polymers of fluorinated thiiranes serve as coatings and for water-repellent impregnation.[115]

A variety of thiiranes have antituberculosis activity.[52, 71, 286] Several thiiranes were reported to be useful as insecticides, fungicides, and nematocides.[91, 343]

Thiiranes derived from unsaturated fatty acids and esters are reported to be used in cosmetic preparations and as lubricants.[91] Several thiiranes have been used to modify the properties of synthetic polymeric materials.[24, 344] The grafting of cellulose was also investigated.[345] Fluorinated thiiranes may be used as refrigerants or as fire extinguishing agents.[115]

The patent literature contains many suggestions for the direct use of thiiranes and for the treatment of polymers with thiiranes to achieve various desired properties and/or modifications; however, it is beyond the scope of this chapter to mention or discuss all the applications and the practical potentials of those products.

5. References

1. H. Staudinger and F. Pfenninger, *Chem. Ber.*, **49**, 1941 (1916).
2. H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 833 (1920).
3. M. Dele'pine and P. Jaffeux, *Compt. Rend.*, **171**, 36 (1920); *Bull. Soc. Chim. Fr.*, (4) **27**, 740 (1920).
4. K. Dachlauer and L. Jackel, French Patent 797,621 (1936); German Patent 636,708 (1936); British Patent 465,662 (1937); U.S. Patents 2,094,837 and 2,094,914 (1937); *Chem. Abstr.*, **30**, 7122 (1936).

5. C. C. J. Culvenor, W. Davies, and K. H. Pausacker, *J. Chem. Soc.*, 1050 (1946).
6. C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 278 (1949); 282 (1949).
7. C. C. J. Culvenor, W. Davies, and W. E. Savige, *J. Chem. Soc.*, 4480 (1952).
8. W. Davies and W. E. Savige, *J. Chem. Soc.*, 317 (1950); 774 (1951).
9. D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951).
10. M. Ohta, *J. Jpn. Chem.*, 7, 756, 801 (1953); *Chem. Abstr.*, **48**, 13615 (1954).
11. A. Schönberg, in Houben-Weyl, *Methoden der organischen Chemie*, Vol. 9, Thieme, Stuttgart, 1955, p. 153.
12. D. V. Joffe and F. Yn. Rachinskii, *Usp. Khim.*, **26**, 678 (1957); *Chem. Abstr.*, **52**, 1133 (1958).
13. E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, Vol. III, Chemical Publishing Co., New York, 1960, pp. 11–19.
14. H. P. Kaufmann and R. Schickel, *Fette, Siefen, Anstrichm.*, **65**, 625 (1963); *Chem. Abstr.*, **60**, 5757 (1964).
14a. A. V. Fokin and A. F. Kolomiets, *Chemistry of Thiiranes* (in Russian), Nauka Moscow, USSR, 1979.
15. D. D. Reynolds and D. L. Fields, "Ethylene Oxides," in A. Weissberger, Ed., *Heterocyclic Compounds with Three- and Four-Membered Rings*, Part One, *The Chemistry of Heterocyclic Compounds*, Wiley-Interscience, New York, 1964, pp. 576–623.
16. M. Sander, *Chem. Rev.*, **66**, 297 (1966).
17. T. Barr and J. B. Speakman, *J. Soc. Dyers Colour.*, **60**, 238 (1944).
18. G. I. Braz, *J. Gen. Chem., USSR*, **21**, 757 (1951).
19. E. M. Meade and F. N. Woodward, *J. Chem. Soc.*, 1894 (1948).
20. K. Furukawa, M. Nomura, and R. Oda, *J. Chem. Soc., Jpn.*, **55**, 671 (1952); *Chem. Abstr.*, **49**, 1626 (1955).
21. R. E. Davis, *J. Org. Chem.*, **23**, 216, 1380 (1958).
22. H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Am. Chem. Soc.*, **69**, 2672 (1947).
23. P. F. Warner, U.S. Patent 3,071,593 (1963); *Chem. Abstr.*, **58**, 11329 (1963).
24. M. Kosmin, U.S. Patent 2,824,845 (1958); *Chem. Abstr.*, **52**, 9667 (1958).
25. J. M. Stewart and H. P. Cordts, *J. Am. Chem. Soc.*, **74**, 5880 (1952).
26. N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **81**, 578 (1959).
27. C. C. Price and P. F. Kirk, *J. Am. Chem. Soc.*, **75**, 2396 (1953).
28. L. Goodman and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 4924 (1959).
29. E. E. Van Tamelen, *J. Am. Chem. Soc.*, **73**, 3444 (1951); *Org. Synth.*, **32**, 39 (1952).
30. J. B. Wright, *J. Am. Chem. Soc.*, **79**, 1694 (1957).
31. R. D. Schuetz and R. L. Jacobs, *J. Org. Chem.*, **26**, 3467 (1961).
32. C. O. Guess and D. L. Chamberlain, Jr., *J. Am. Chem. Soc.*, **74**, 1342 (1952).
33. A. Noshay and C. C. Price, *J. Polym. Sci.*, **54**, 533 (1961).
34. J. M. Stewart, *J. Org. Chem.*, **28**, 596 (1963).
35. L. Goodman and J. Christensen, *J. Am. Chem. Soc.*, **82**, 4738 (1960).
36. R. D. Guthrie, *Chem. Ind. (London)*, 2121 (1962).
37. P. W. Feit, *J. Med. Chem.*, **12**, 556 (1969).
38. E. W. Abel, D. A. Armitage, and R. P. Bush, *J. Chem. Soc.*, 2455 (1964).
39. M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950).
40. F. G. Bordwell and H. M. Anderson, *J. Am. Chem. Soc.*, **75**, 4959 (1953).
41. F. G. Bordwell, H. M. Anderson, and B. M. Pitt, *J. Am. Chem. Soc.*, **76**, 1082 (1954).

42. A. M. Creighton and N. L. Owen, *J. Chem. Soc.*, 1024 (1960).
43. B. Hansen, *Acta Chem. Scand.*, **11**, 537 (1957).
44. G. K. Helmkamp and N. Schnautz, *Tetrahedron*, **2**, 304 (1958).
45. C. G. Moore and M. Porter, *J. Chem. Soc.*, 2062 (1958).
46. R. D. Schuetz and R. L. Jacobs, *J. Org. Chem.*, **23**, 1799 (1958).
47. F. I. Rachinskii, N. M. Slavachevskaia, and D. V. Ioffe, *J. Gen. Chem., USSR*, **28**, 3027 (1958).
48. S. Boileau and P. Sigwalt, *Compt. Rend.*, **252**, 882 (1961).
49. B. Hansen, *Acta. Chem. Scand.*, **13**, 151, 159 (1959).
50. G. K. Helmkamp and D. J. Pettit, *J. Org. Chem.*, **27**, 2942 (1962); G. K. Helmkamp and N. Schnautz, *Tetrahedron*, **2**, 304 (1958).
51. R. Ketcham and V. P. Shah, *J. Org. Chem.*, **28**, 229 (1963).
52. E. P. Adams, K. N. Ayad, F. P. Doyle, D. O. Holland, W. H. Hanter, J. H. C. Nayler, and A. Queen, *J. Chem. Soc.*, 2665 (1960).
53. H. W. Mackinney, U.S. Patent 2,962,457 (1960); *Chem. Abstr.*, **55**, 6009 (1961).
54. J. A. Durden, H. A. Stanbury, and W. H. Catlette, *J. Am. Chem. Soc.*, **81**, 1943 (1959).
55. T. C. Owen, C. L. Gladys, and L. Field, *J. Chem. Soc.*, 501 (1962).
56. V. Calo, L. Lopez, L. Marchese, and G. Pesce, *J. Chem. Soc., Chem. Commun.*, 621 (1975).
57. A. S. V. Choughuley and M. S. Chadha, *Indian J. Chem.*, **1**, 437 (1963); *Chem. Abstr.*, **60**, 4126 (1964).
58. S. Searles and E. F. Lutz, *J. Am. Chem. Soc.*, **80**, 3168 (1958).
59. S. Searles, H. R. Hays, and E. F. Lutz, *J. Org. Chem.*, **27**, 2832 (1962).
60. Société Nationale des Pétrols d'Aquitaine, French Patent 1,307,385 (1962); *Chem. Abstr.*, **58**, 9027 (1963).
61. S. Searles, E. F. Lutz, H. R. Hays, and H. E. Mortensen, *Org. Synth.*, **42**, 59 (1962).
62. D. D. Reynolds, *J. Am. Chem. Soc.*, **79**, 4951 (1957); U.S. Patent 2,828,318 (1958); *Chem. Abstr.*, **52**, 14651 (1958).
63. D. L. Johnson and D. L. Fields, U.S. Patent 3,072,676 (1963); *Chem. Abstr.*, **58**, 12426 (1963).
64. D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5130 (1961); D. L. Fields and D. D. Reynolds, Belgian Patent 616,671 (1962); *Chem. Abstr.*, **60**, 2890 (1964).
65. J. F. McGhie, W. A. Ross, F. J. Julietti, and B. E. Grimwood, *J. Chem. Soc.*, 4638 (1962).
66. (a) F. K. Signaigo, U.S. Patent 2,436,233 (1948); *Chem. Abstr.*, **42**, 3775 (1948); (b) A. D. B. Sloan, *J. Chem. Soc, C*, 1252 (1969).
67. L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 817 (1952).
68. J. S. Harding, L. W. C. Miles, and L. N. Owen, *Chem. Ind. (London)*, 887 (1951).
69. J. S. Harding and L. N. Owen, *J. Chem. Soc.*, 1528 (1954).
70. R. M. Evans, J. B. Fraser, and L. N. Owen, *J. Chem. Soc.*, 248 (1949).
71. L. Goodman, A. Benitez, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 1680 (1958).
72. E. P. Doyle, D. O. Holland, K. R. L. Mansford, J. H. C. Nayler, and A. Queen, *J. Chem. Soc.*, 2660 (1960).
73. K. Takeda and T. Komeno, *Chem. Ind. (London)*, 1793 (1962).
74. (a) K. Takeda, T. Komeno, J. Tawanami, S. Ishihara, H. Tokura, and H. Itani, *Tetrahedron*, **21**, 329 (1965); (b) T. Komeno, S. Ishihara, H. Itani, H. Iwakura, and T. Takeda, *Chem. Pharm. Bull. (Tokyo)*, **17**, 2110 (1969).

75. J. E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **83**, 3827 (1961).
76. M. Dele'pine and P. Jaffeux, *Compt. Rend.*, **172**, 158 (1921); *Bull. Soc. Chim. Fr.*, **29**, 136 (1921).
77. M. Dele'pine and S. Eschenbrenner, *Bull. Soc. Chim. Fr.*, **33**, 703 (1923).
78. E. H. Farmer and F. W. Shipley, *J. Chem. Soc.*, 1519 (1947).
79. (a) C. Calingaert, *Bull. Soc. Chim. Belg.*, **31**, 109 (1922); *Chem. Abstr.*, **16**, 3870 (1922); (b) A. Hassner and A. Terada, unpublished results; (c) J. C. Hinshaw, *Tetrahedron Lett.*, 3567 (1972).
80. M. A. Youtz and P. P. Perkins, *J. Am. Chem. Soc.*, **51**, 3508 (1929).
81. M. Mousseron, M. Bousquet, and O. Marret, *Bull. Soc. Chim. Fr.*, 84 (1948); M. Mousseron, *Compt. Rend.*, **215**, 201 (1942).
82. D. J. Pettitt and G. K. Helmkamp, *J. Org. Chem.*, **28**, 2932 (1963); **29**, 2702 (1964).
83. R. Salchow, *Kautschuk*, **14**, 12 (1938); *Chem. Abstr.*, **32**, 4007 (1938); *Kautschuk*, **13**, 119 (1937); *Chem. Abstr.*, **31**, 8991 (1937).
84. K. Takeda, T. Komeno, and J. Kawanami, *Chem. Pharm. Bull. (Tokyo)*, **8**, 621 (1960); *Chem. Abstr.*, **55**, 12451 (1960).
85. D. A. Lightner and C. Djerassi, *Tetrahedron*, **21**, 583 (1965).
86. (a) W. Coltoff, U.S. Patent 2,183,860 (1939); *Chem. Abstr.*, **34**, 2395 (1940); British Patent 508,932; *Chem. Abstr.*, **34**, 2863 (1940); Netherlands Patent 47,835 (1940); *Chem. Abstr.*, **34**, 6302 (1940); (b) N. M. Karimova, M. G. Linkova, O. V. Kildisheva, and I. L. Knunyats, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1788 (1973); *Chem. Abstr.*, **80**, 70619 (1974).
87. A. Queen, British Patent 810,389 (1959); *Chem. Abstr.*, **54**, 2360 (1960); U.S. Patent 2,918,476 (1959); *Chem. Abstr.*, **54**, 9956i (1960); German Patent 1,090,227 (1961); *Chem. Abstr.*, **54**, 1543d (1960).
88. F. P. Doyle and K. N. Ayad, British Patent 819,688 (1960); German Patent 1,131,695 (1962); Swiss Patent 358,794 (1962); *Chem. Abstr.*, **54**, 8849A (1960).
89. W. J. Wenisch, Dissertation, New York, 1955.
90. E. Traeger and Z. El Hewehi, *J. Prakt. Chem.*, **18**(4), 255 (1962).
91. R. N. Kienle, U.S. Patent 2,766,256 (1956); *Chem. Abstr.*, **51**, 3302 (1952).
92. (a) F. E. Dearborn, U.S. Patents 2,169,793 (1939), 2,237,096 (1941), 233,093 (1943), 2,427,717 (1947), 2,845,438 (1958); *Chem. Abstr.*, **34**, 214 (1940), **35**, 5305 (1941), **38**, 2170 (1944), **42**, 330 (1948), **53**, 4299 (1959); (b) F. P. Otto and F. E. Meyer, U.S. Patent 2,520,101 (1950); *Chem. Abstr.*, **44**, 10314 (1950).
93. (a) R. T. Armstrong, J. R. Little, and K. W. Doak, *Ind. Eng. Chem.*, **36**, 628, 2866 (1944); (b) L. Bateman, R. W. Glazebrook, C. G. Moore, M. Porter, G. W. Ross, and R. W. Saville, *J. Chem. Soc.*, 2838 (1958).
94. S. G. Jones and E. E. Reid, *J. Am. Chem. Soc.*, **60**, 2452 (1938).
95. (a) O. P. Strausz and H. E. Gunning, *J. Am. Chem. Soc.*, **84**, 4080 (1962); (b) D. D. Davis, R. B. Klemm, W. Braun, and M. Pilling, *Int. J. Chem. Kinet.*, **4**, 383 (1972); (c) D. D. Davis and R. B. Klemm, *ibid.*, **5**, 841 (1973); (d) J. D. Van Drumpt, *Rec. Trav. Chim. Pays-Bas*, **91**, 906 (1972); (e) H. E. Gunning and O. P. Strausz, *Adv. Photochem.*, **4**, 150 (1966).
96. F. Lautenschlager and N. V. Schwartz, *J. Org. Chem.*, **34**, 3391 (1969).
97. J. C. Hinshaw, *Tetrahedron Lett.*, **34**, 3567 (1972).
98. T. Fujisawa and T. Kobori, *Chem. Lett.*, 935 (1972).
99. T. Fujisawa and T. Kobori, *Chem. Lett.*, 1065 (1972).
100. (a) A. Schönberg, *Liebigs Ann. Chem.*, **454**, 37 (1927); (b) P. Beak and J. W. Worley, *J. Am. Chem. Soc.*, **94**, 597 (1972).

101. A. Schönberg and O. Schutz, *Ber.*, 2351 (1927).

102. W. Ried and H. Klug, *Chem. Ber.*, **94**, 368 (1961).

103. (a) B. Eisert, in *Newer Methods of Preparative Organic Chemistry*, Wiley-Interscience, New York, 1948, p. 513; (b) A. Schönberg, in Houben Weyl, *Methoden der organischen Chemie*, Vol. 9, Thieme, Stuttgart, 1955, p. 158; (c) A. Schönberg, E. Frees, W. Knofel, and K. Praefke, *Ber.*, **103**, 938 (1970); (d) J. M. Beiner, D. Lecadet, D. Paquer, A. Thullier, and J. Vialle, *Bull. Soc. Chim. Fr.*, 1979; 1983 (1973); (e) D. Paquer and R. Pou, *ibid.*, 3887 (1972); (f) A. Sammour, M. I. Selim, A. F. M. Fahmy, and K. Elewa, *Indian J. Chem.*, **11**, 437 (1973).

104. A. Schönberg, D. Cernik, and W. Urban, *Chem. Ber.*, **64**, 2579 (1931).

105. A. Schönberg, A. K. Fateeen, and A. M. A. Sammour, *J. Am. Chem. Soc.*, **79**, 6020 (1957).

106. N. Latif and I. Fathy, *J. Org. Chem.*, **27**, 1633 (1962).

107. A. Schönberg and S. Nickel, *Chem. Ber.*, **64**, 2323 (1931).

108. (a) W. J. Middleton, U.S. Patent 3,136,781 (1964); *Chem. Abstr.*, **61**, 5612 (1964); (b) D. Paquer and J. Vialle, *Bull. Soc. Chim. Fr.*, 3327 (1969).

109. P. Metzner, *Bull. Soc. Chim. Fr.*, 7–8, 2297 (1973).

110. A. Schönberg and E. Frese, *Chem. Ber.*, **95**, 2810 (1962).

111. N. Latif, I. Fathy, N. Mishriky, and B. Haggag, *J. Can. Chem.*, **44**, 629 (1966).

112. S. Holm and A. Senning, *Tetrahedron Lett.*, 2389 (1973).

113. (a) H. Skandinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 840 (1920); (b) A. Schönberg and L. V. Vargha, *Chem. Ber.*, **64**, 1390 (1931).

114. A. Schönberg and L. Vargha, *Liebigs Ann. Chem.*, **483**, 176 (1930).

115. F. C. McGrew, U.S. Patent 3,136,744 (1964); *Chem. Abstr.*, **61**, 4312 (1964).

116. (a) D. Seyferth and W. Tronich, *J. Am. Chem. Soc.*, **91**, 2138 (1969); (b) D. Seyferth, W. Tronich, R. S. Marmor, and W. S. Smith, *J. Org. Chem.*, 1537 (1972).

117. A. Schönberg, W. Knofel, E. Frese, and K. Praefcke, *Tetrahedron Lett.*, 2487 (1968); *Ber.*, **103**, 949 (1970).

118. D. Lecadet, D. Paquer, and A. Thullier, *Compt. Rend.*, **276C**, 875 (1973).

119. A. Schönberg and M. Z. Barakat, *J. Chem. Soc.*, 1074 (1939).

120. (a) R. M. Kellogg and S. Wassenaar, *Tetrahedron Lett.*, **54**, 1987 (1970); (b) R. M. Kellogg, S. Wassenaar, and J. Buter, *Tetrahedron Lett.*, **54**, 4689 (1970).

121. R. M. Kellogg, M. Noteboom, and J. K. Kaiser, *Tetrahedron*, **32**, 1641 (1976).

122a. W. J. Middleton, *J. Org. Chem.*, **34**, 3201 (1969).

122. K. A. Petrov and G. A. Sokolskii, *Zh. Obshch. Soc.*, 1074 (1939).

123. G. Schrader and W. Lorenz, German Patent 1,082,915 (1960); *Chem. Abstr.*, **55**, 25983 (1961).

124. T. H. Chan, J. R. Finkenbine, *J. Am. Chem. Soc.*, **94**, 2880 (1972).

125. (a) M. Grayson and C. E. Farley, *J. Chem. Soc., Chem. Commun.*, 831 (1967); (b) K. E. DeBruin, K. Naumann, G. Zon, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7031 (1969); (c) O. N. Nuretdinova and B. A. Arbuzov, *Mater. Nauch. Konf., Inst. Org. Fiz. Khim. Akad Nauk SSSR*, 17 (1969); *Chem. Abstr.*, **78**, 29513 (1973).

126. A. I. Meyers and M. E. Ford, *Tetrahedron Lett.*, **33**, 2861 (1975).

127. C. R. Johnson, A. Nakanishi, N. Nakanishi, and K. Tanaka, *Tetrahedron Lett.*, **33**, 2865 (1975).

128. K. Hiari, H. Matsuda, and Y. Kishida, *Chem. Pharm. Bull. (Tokyo)*, **20**, 2067 (1972).

129. C. R. Johnson and K. Tanaka, *Synthesis*, 413 (1976).

130. D. L. Germaise and A. F. McKay, *Can. J. Chem.*, **34**, 815 (1956).

131. D. Hoppe and R. Follmann, *Angew. Chem.*, **89**, 478 (1977).
132. (a) N. J. Turro, *Acc. Chem. Res.*, **2**, 25 (1969); (b) T. H. Chan and B. S. Ong, *J. Org. Chem.*, **43**, 2994 (1978).
133. E. Block, R. E. Penn, M. D. Ennis, T. A. Owens, and S. L. Yu, *J. Am. Chem. Soc.*, **100**, 7436 (1978).
134. E. Jongejan, T. S. V. Buys, H. Steinberg, and T. J. de Boer, *Rec. Trav. Chim. Pays-Bas*, **97**, 214 (1978).
135. A. G. Hortmann and A. Bhattacharjya, *J. Am. Chem. Soc.*, **98**, 7081 (1976).
136. V. G. l'Abbé, J. P. Dekerk, J. P. Declercq, G. Germain, and M. Van Meerssche, *Angew. Chem.*, **90**, 207 (1978).
137. A. I. Meyers and M. E. Ford, *J. Org. Chem.*, **41**, 1735 (1976).
138. P. F. Hudrlik, A. M. Hudrlik, and C. -N. Wan, *J. Org. Chem.*, **40**, 1116 (1975).
139. A. P. Krapcho, D. R. Rao, M. P. Silvon, and B. Abegaz, *J. Org. Chem.*, **36**, 3885 (1971).
140. M. P. Schneider and M. Schnaithmann, *J. Am. Chem. Soc.*, **101**, 254 (1979).
141a. S. Wawzonek and S. M. Heilmann, *J. Org. Chem.*, **39**, 511 (1974).
141. S. Mataka, S. Ishii, and M. Tashiro, *J. Org. Chem.*, **43**, 3730 (1978).
142. D. A. Lightner and C. Djerassi, *Chem. Ind. (London)*, 1236 (1962).
143. (a) G. Chrader and W. Lorenz, German Patent 1,082,915 (1960); *Chem. Abstr.*, **55**, 25983 (1961); (b) E. Gaydou, G. Peiffer, and A. Guillemonat, *Tetrahedron Lett.*, 239 (1971).
144. E. H. Eyster, *J. Chem. Phys.*, **6**, 576 (1938).
145. G. B. Guthrie, Jr., D. W. Scott, and G. Waddington, *J. Am. Chem. Soc.*, **74**, 2795 (1952).
146. H. W. Thompson and W. T. Cave, *Trans. Faraday Soc.*, **47**, 951 (1951).
147. H. W. Thompson and D. J. Dupré, *Trans. Faraday Soc.*, **36**, 805 (1940).
148. (a) G. L. Cunningham, Jr., A. W. Boyd, R. J. Meyers, and W. D. Gwinn, *J. Chem. Phys.*, **19**, 676 (1951); (b) K. Okiye, C. Hirose, D. G. Lister, and J. Sheridan, *Chem. Phys. Lett.*, **24**, 111 (1974).
149. S. S. Butcher, *J. Chem. Phys.*, **38**, 2310 (1963).
150. D. T. Clark, *Theor. Chim. Acta (Berlin)*, **15**, 225 (1969).
151. A. Rauk and I. G. Csizmadia, *Can. J. Chem.*, **46**, 1205 (1968).
152. V. I. Vedenelyer et al., *Bond Energies, Ionization Potentials and Electron Affinities*, Edward Arnold, London, 1966.
153. A. L. McClellan, *Tables of Experimental Dipole Moments*, Freeman, San Francisco, (1963).
154. I. Absar, L. J. Schaad, and J. R. Van Wazer, *Theor. Chim. Acta (Berlin)*, **29**, 173 (1973).
155. P. F. Franchini and C. Vergani, *Theor. Chim. Acta (Berlin)*, **13**, 46 (1969).
156. P. F. Franchini and M. Zandomeneghi, *Theor. Chim. Acta (Berlin)*, **21**, 90 (1971).
157. R. Bonaccorsi, E. Scrocco, and E. Tomasi, *J. Chem. Phys.*, **52**, 5270 (1970).
158. O. P. Strausz, R. K. Gosavi, A. S. Denes, and I. G. Csizmadia, *Theor. Chim. Acta (Berlin)*, **26**, 367 (1972).
159. O. P. Strausz, H. E. Gunning, A. S. Denes, and I. G. Csizmadia, *J. Am. Chem. Soc.*, **94**, 8317 (1972).
160. A. Frost, *J. Chem. Phys.*, **47**, 3707 (1967).
161. E. R. Talaty and G. Simons, *Theor. Chim. Acta (Berlin)*, **48**, 331 (1978).
162. M. M. Rohmer and B. Roos, *J. Am. Chem. Soc.*, **97**, 2025 (1975).
163. D. C. Frost, F. G. Herring, A. Katrib, and C. A. McDowell, *Chem. Phys. Lett.*, **20**, 401 (1973).

164. R. A. Nelson and R. S. Jessup, *J. Res. Nat. Bur. Stand.*, **48**, 206 (1952).
165. J. D. Cox, *Tetrahedron*, **19**, 1175 (1963).
166. E. Leppin and K. Gollnick, *Tetrahedron Lett.*, **43**, 3819 (1969).
167. E. Lippert and H. Prigge, *Liebigs Ann. Chem.*, **659**, 81 (1962).
168. M. Tamres and S. Searles, *J. Phys. Chem.*, **66**, 1099 (1962).
169. A. V. Fokin, A. F. Kolomiets, and V. I. Shevchenko, *Dokl. Akad. Nauk (SSSR)*, **226** (6), 1351 (1976).
170. L. A. Strait, R. Ketcham, D. Jambotkav, and V. P. Shah, *J. Am. Chem. Soc.*, **86**, 4628 (1964).
171. H. S. Gutowsky, R. L. Rutledge, M. Tamres, and S. Searles, *J. Am. Chem. Soc.*, **76**, 4242 (1954).
172. R. E. Davis, *J. Org. Chem. Soc.*, **23**, 1380 (1958).
173. D. R. Williams and L. T. Kontnik, *J. Chem. Soc. B*, 312 (1971).
174. H. S. Gutowsky, R. L. Ritedge, M. Tamres, and S. Searles, *J. Am. Chem. Soc.*, **76**, 4242 (1954).
175. E. Lippert and H. Prigge, *Ber. Bunsenges. Phys. Chem.*, **67**, 415 (1963).
176. J. J. Musher and R. G. Gordon, *J. Chem. Phys.*, **36**, 3097 (1962).
177. F. S. Mortimer, *J. Mol. Spectrosc.*, **5**, 199 (1960).
178. K. J. Ivin, E. D. Lillie, and I. H. Petersen, *Int. J. Sulfur Chem.*, **8**, 411 (1973).
179. M. Ohtsuru, K. Tori, and M. Fukuyama, *Tetrahedron Lett.*, 2877 (1970).
180. S. L. Smith and R. H. Cox, *J. Chem. Phys.*, **45**, 2848 (1966).
181. D. D. Elleman, S. L. Manatt, and C. D. Pearce, *J. Chem. Phys.*, **42**, 650 (1965).
182. C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **35**, 1522 (1961).
183. M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
184. W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **91**, 5150 (1969).
185. M. Bucciarelli, A. Forni, I. Moretti, and G. Torre, *Tetrahedron*, **33**, 999 (1977).
186. K. D. Karlson, D. Weisleder, and M. E. Daxenbichler, *J. Am. Chem. Soc.*, **92**, 6232 (1970).
187. K. Tork, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).
188. S. Manatt, D. Elleman, and S. Boris, *J. Am. Chem. Soc.*, **87**, 2220 (1965).
189. (a) K. Venkateswarin and G. Thyagarjan, *Proc. Indian Acad. Sci., Sect. A*, **52**, 101 (1960); *Chem. Abstr.*, **55**, 5123 (1961); (b) T. Hirokawa, M. Hayashi, and H. Murata, *J. Sci. Hiroshima Univ., Ser. A*, **37**, 283 (1973); *Chem. Abstr.*, **80**, 107784 (1974).
190. W. G. Fately and F. A. Miller, *Spectrochim. Acta*, **19**, 611 (1963).
191. E. J. Gallegos and R. W. Kiser, *J. Phys. Chem.*, **65**, 1177 (1961).
192. R. W. Kiser and E. J. Gallegos, *J. Phys. Chem.*, **66**, 947 (1962).
193. H. H. Günthard and T. Gaumann, *Helv. Chim. Acta*, **33**, 1958 (1950).
194. P. G. Maslov and A. A. Kolchikhin, *Zh. Obshch. Khim.*, **28**, 835 (1958); *Chem. Abstr.*, **52**, 17229 (1958).
195. H. Mackle and P. A. G. O'Hara, *Tetrahedron*, **19**, 961 (1963).
196. B. A. Arabuzov, L. K. Novkiova-Aleksandrova, S. G. Vul'fson, and A. N. Vereschagin, *Izv. Akad. Nauk SSSR*, **8**, 1932 (1978).
197. D. E. Bays, R. C. Cookson, R. R. Hill, J. F. McGhie, and G. E. Usher, *J. Chem. Soc.*, 1563 (1964).
198. (a) C. Djerassi, H. Wolf, D. A. Lightner, E. Bunnenberg, K. Takeda, T. Komeno, and K. Kuriyama, *Tetrahedron*, **19**, 1547 (1963); (b) G. L. Bendazzoli, P. Palmieri, G. Gottarelli, I. Morretti, and G. Torre, *J. Am. Chem. Soc.*, **98**, 2659 (1976); (c) G. L. Bendazzoli, G. Gottarelli, P. Palmieri, and G. Torre, *Mol. Phys.*, **25**, 473 (1973).

199. (a) K. Utsumi-Oda and H. Koyama, *J. Chem. Soc., Perkin Trans 2*, 1866 (1973); (b) R. B. Bates, R. A. Grady, and T. C. Sneath, *J. Org. Chem.*, **37**, 2145 (1972).

200. (a) W. Davies and W. E. Savige, *J. Chem. Soc.*, 317 (1950); (b) W. Davies and W. E. Savige, *ibid.*, 890 (1950).

201. K. Jankowski and R. Harvey, *Can. J. Chem.*, **50**, 3930 (1972).

202. K. Jankowski and R. Harvey, *Synthesis*, 627 (1972).

203. (a) K. Jankowski and J. Y. Daigle, *Synthesis*, 32 (1971); (b) K. Jankowski and J. Y. Daigle, *Can. J. Chem.*, **49**, 2594 (1971).

204. A. G. Sherwood, I. Safarik, B. Verkoczy, G. Almadi, H. A. Wiebe, and O. P. Strausz, *J. Am. Chem. Soc.*, **101**, 3000 (1979).

205. Y. K. Yuriev and L. S. German, *Zh. Obshch. Khim.*, **25**, 2527 (1955); *Chem. Abstr.*, **50**, 9428 (1956).

206. J. A. Scheben and I. L. Mador, U.S. Patent 3,480,632 (1970); *Chem. Abstr.*, **72**, 43694 (1970).

207. (a) J. M. Crafts, *Liebigs Ann. Chem.*, **124**, 110 (1862); **128**, 220 (1863); (b) A. Husemann, *ibid.*, **126**, 269 (1863).

208. A. Mailhe and M. Renaudie, *Compt. Rend.*, **195**, 391 (1932).

209. F. O. Davis and E. M. Fettes, in N. G. Gaylord, Ed., *Polyethers*, Part III, Wiley-Interscience, New York, 1962.

210. R. C. Vander Linden, J. M. Salva, and P. A. Smith, U.S. Patent 3,542,808 (1966); *Chem. Abstr.*, **74**, 53498 (1971).

211. S. Boileau, G. Champetier, and P. Sigwalt, *J. Polym. Sci., Part C*, **16**, 3021 (1968).

212. P. Sigwalt, *IUPAC Int. Symp. Macromol. Chem.*, Budapest, Hungary, 1969, pp. 251–280; *Chem. Abstr.*, **77**, 34,954 (1972).

213. K. Shikata, K. Konomi, and S. Nakao, German Patent 2,033,639, 1969; *Chem. Abstr.*, **74**, 142601 (1971).

214. A. Nicco and B. Boucheron, *Eur. Polym. J.*, **6**, 1477 (1970).

215. P. Sigwalt, *Int. J. Sulfur Chem., Part C*, **7**, 83 (1972).

216. T. Tsuruta, *J. Polym. Sci., Part D*, **6**, 179 (1972).

217. N. Spassky, P. Dumas, M. Sepulchre, and P. Sigwalt, *J. Polym. Sci., Polym. Symp.*, **52**, 327 (1975).

218. N. Spassky, *ACS Symp. Ser.*, **59**, 191 (1978).

219. N. Akron, *Br. Polym. J.*, **3**, 120 (1971).

220. M. Morton and S. L. Mikesell, *Polym. Prep., Am. Chem. Soc., Div. Polym. Chem.*, **13**, 61 (1972).

221. G. P. Belonovskaya, Z. D. Chernova, and B. A. Dolgoplosk, *Eur. Polym. J.*, **8**, 35 (1972).

222. W. Cooper, P. T. Hale, and J. S. Walker, *Polymer*, **15**, 175 (1974).

223. C. Loewig and S. Weidmann, *Poggendorffs Ann.*, **46**, 81 (1839); **49**, 128 (1839).

224. W. Mansfeld, *Chem. Ber.*, **19**, 693 (1886).

225. O. Masson, *J. Chem. Soc.*, **49**, 234 (1886).

226. V. Meyer, *Ber.*, **19**, 3259 (1886).

227. (a) R. C. Fuson, R. D. Lipscomb, B. C. McKusick, and L. J. Reed, *J. Org. Chem.*, **11**, 513 (1946); (b) J. Lal and G. S. Trick, *J. Polym. Sci.*, **50**, 13 (1961).

228. C. D. Hurd and K. Wilkinson, *J. Am. Chem. Soc.*, **71**, 3429 (1949).

229. K. Furukawa, M. Nomura, and R. Oda, *Bull. Inst. Chem. Res. Kyoto Univ.*, **28**, 74 (1952); *Chem. Abstr.*, **46**, 11,105 (1952).

230. M. Ohta, A. Kondo, and R. Ohi, *Nippon Kagaku Zasshi*, **75**, 985 (1954); *Chem. Abstr.*, **51**, 14668 (1957).

231. G. I. Braz, *Zh. Obshch. Khim.*, **21**, 688 (1951); *Chem. Abstr.*, **45**, 9473 (1951).
232. S. Boileau, J. Coste, J. Raynal, and P. Sigwalt, *Compt. Rend.*, **254**, 2774 (1962).
233. S. Boileau, G. Champetier, and P. Sigwalt, *Macromol. Chem.*, **69**, 180 (1963).
234. K. Endo and Kojima, Japanese Patent 21, 496 (1963); *Chem. Abstr.*, **60**, 3122 (1964).
235. S. Adamek, B. B. J. Wood, and R. T. Woodhams, *Rubber Age*, **96**, 581 (1965).
236. (a) K. Furukawa and R. Oda, *Bull. Inst. Res. Kyoto Univ.*, **30**, 50 (1952); *Chem. Abstr.*, **47**, 3611 (1953); (b) *J. Chem. Soc., Jpn.*, **56**, 189 (1953).
237. R. Bacskai, *J. Polym. Sci.*, **A1**, 2777 (1963).
238. H. Lüssi and H. Zahner, German Patent 1,122,710 (1962); *Chem. Abstr.*, **56**, 15,684 (1962); British Patent 898,314 (1962); *Chem. Abstr.*, **57**, 16889A (1962).
239. R. L. Whistler, *J. Polym. Sci.*, **A2**, 2595 (1964).
240. S. A. Ballard, R. C. Morris, and J. L. Van Winkle, U.S. Patent 2,484,370 (1949); *Chem. Abstr.*, **44**, 1255 (1950).
241. P. Dumas, N. Spassky, and P. Sigwalt, *J. Polym. Sci., Polym. Chem. Educ.*, **17**, 1595; 1605 (1979).
242. M. Goguelin and M. Sepulchre, *Macromol. Chem.*, **180**, 1215 (1979).
243. M. Marchetti, E. Chiellini, M. Sepulchre, and N. Spasski, *Macromol. Chem.*, **180**, 1305 (1979).
244. A. Momtaz, N. Spassky, and P. Sigwalt, *Polym. Bull. (Berlin)*, **1**, 267 (1979).
244a. N. Spassky, P. Dumas, and M. Sepulchre, *Charged React. Polym.*, **5**, 111 (1979).
245. (a) A. Schönberg, *Ber.*, **58**, 1793 (1925); (b) A. Schönberg and L. Vargha, *ibid.*, **64B**, 1390 (1931).
246. W. H. Mueller, *J. Org. Chem.*, **34**, 2955 (1969).
247. E. M. Lown, H. S. Sandhu, H. E. Gunning, and O. P. Strausz, *J. Am. Chem. Soc.*, **90**, 7164 (1968).
248. (a) R. Hoffmann, *J. Am. Chem. Soc.*, **90**, 1475 (1968); (b) R. J. Crawford, R. J. Dummel, and A. Mishra, *ibid.*, **87**, 3023 (1965); (c) R. J. Crawford and A. Mishra, *ibid.*, **87**, 3768 (1965), **88**, 3963 (1966).
249. K. Peter, C. Vollhardt, and R. G. Bergman, *J. Am. Chem. Soc.*, **95**, 7538 (1973).
250. R. E. Davis, *J. Org. Chem.*, **23**, 1767 (1958).
251. N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **81**, 578 (1959).
252. D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, **82**, 4736 (1960).
252. (a) M. Roth, P. Dubs, E. Gotchi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971); (b) D. H. R. Barton, E. H. Smith, and B. J. Willis, *J. Chem. Soc., Chem. Commun.*, 1226 (1970).
253. M. J. Boskin and D. B. Denney, *Chem. Ind. (London)*, 330 (1959).
254. (a) B. M. Trost and S. D. Ziman, *J. Org. Chem.*, **38**, 932 (1973); (b) *J. Chem. Soc., Chem. Commun.*, 181 (1969).
255. (a) J. F. McGhie, W. A. Ross, F. J. Julietti, B. E. Grimwood, G. Usher, and N. W. Waldron, *Chem. Ind. (London)*, 1980 (1962); (b) N. Latif and N. Mishriky, *Chem. Ind. (London)*, 491 (1969).
256. R. B. King, *Inorg. Chem.*, **2**, 326 (1963).
257. J. F. McGhie, W. A. Ross, F. J. Julietti, G. Swift, G. Usher, N. M. Waldron, and B. E. Grimwood, *Chem. Ind. (London)*, 460 (1964).
258. P. H. M. Schreurs, A. J. Jong, and L. Brandsma, *Rec. Trav. Chim. Pays-Bas*, **95**, 75 (1976).
259. G. K. Helmkamp and D. J. Pettitt, *Org. Chem.*, **25**, 1754 (1960).
260. G. K. Helmkamp and D. J. Pettitt, *J. Org. Chem.*, **29**, 3258 (1964).
261. D. Van Ende and A. Krief, *Tetrahedron Lett.*, **31**, 2709 (1975).

262. K. J. Klabunde and P. Skell, *J. Am. Chem. Soc.*, **93**, 3807 (1971).

263. Y. Hata and M. Watanabe, *J. Am. Chem. Soc.*, **97**, 2553 (1975).

264. (a) Y. Hata and M. Watanabe, *Tetrahedron Lett.*, 3827, 4659 (1972); (b) W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, and T. Migita, *J. Org. Chem.*, **37**, 1721 (1972).

265. J. K. Weseman, R. Williamson, J. L. Green, Jr., and P. B. Shelvin, *J. Chem. Soc., Chem. Commun.*, 901 (1973).

266. E. Jakubowski, M. G. Ahmed, E. M. Lown, H. S. Sandhu, R. K. Gosavi, and O. P. Strausz, *J. Am. Chem. Soc.*, **94**, 4094 (1972).

267. A. V. Fokin, A. F. Kolomets, T. I. Fedyushina, and V. I. Shevchenko, *Dokl. Akad. Nauk SSSR*, **237**, 364 (1977); transl. 0012-5008 by Plenum Publishing Corp., 1978.

268. N. S. Isaacs and K. Neelakantan, *Can. J. Chem.*, **46**, 1043 (1967).

269. (a) V. V. Alderman, M. M. Brubaker, and W. E. Hanford, U.S. Patent 2,212,141 (1940); *Chem. Abstr.*, **35**, 463 (1941); (b) H. Morita and S. Oae, *Tetrahedron Lett.*, 1347 (1969).

270. M. Sander, *Monatsh.*, **96**, 896 (1965).

271. Y. M. Slobodin, S. S. Altman, and K. D. Tammik, *Proizv. Smaz. Mater.*, **5**, 58 (1959); *Chem. Abstr.*, **54**, 12559 (1960).

272. (a) S. Z. Ivin, *J. Gen. Chem. USSR*, **26**, 177 (1956); (b) S. Z. Ivin, *ibid.*, **22**, 327 (1952).

273. H. Ringsdorf and C. G. Overberger, *Macromol. Chem.*, **44–46**, 418 (1961).

274. G. Y. Epshtein, I. A. Usov, and S. Z. Ivin, *Zh. Obshch. Khim.*, **34**, 1954 (1964); *Chem. Abstr.*, **61**, 8178 (1964).

275. B. A. Arbuzov and O. N. Nuretdinova, *Izv. Acad. Nauk SSSR, Otd. Khim. Nauk*, 927 (1963); *Chem. Abstr.*, **33**, 2895 (1968).

276. N. V. Schwartz, *J. Org. Chem.*, **33**, 2895 (1968).

277. C. A. Stewart, and C. A. Vander Werf, *J. Am. Chem. Soc.*, **76**, 1259 (1954).

278. M. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **88**, 2866 (1966).

279. W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **32**, 2925 (1967).

280. (a) G. Y. Epshtein, I. A. Usov, and S. Z. Ivin, *Zh. Obshch. Khim.*, **34**, 1948 (1964); *Chem. Abstr.*, **61**, 8178 (1964); (b) M. G. Lin'kova, A. M. Orlov, O. V. Kildesheva, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1148 (1969).

281. J. M. Stewart, *J. Org. Chem.*, **29**, 1655 (1964).

282. E. Kameyama, M. Nakajima, and T. Kuwamura, *Bull. Chem. Soc., Jpn.*, **45**, 3222 (1972).

282a. E. Vilsmaier and W. Sprugel, *Liebigs Ann. Chem.*, **749**, 62 (1971); (b) E. Vilsmaier and W. Schalk, *ibid.*, **750**, 104 (1971).

283. G. Y. Epshtein, I. A. Usov, and S. Z. Ivin, *Zh. Obshch. Khim.*, **34**, 1951 (1964); *Chem. Abstr.*, **61**, 8178 (1964).

284. A. J. Kolka, U.S. Patent 2,866,808 (1958); *Chem. Abstr.*, **53**, 12176 (1959).

285. (a) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Am. Chem. Soc.*, **69**, 2675 (1947); (b) H. R. Snyder and J. M. Stewart, U.S. Patent 2,497,422 (1950); *Chem. Abstr.*, **44**, 4025 (1950).

286. E. P. Adams, E. P. Doyle, D. L. Hatt, D. O. Holland, W. H. Hunter, K. R. L. Mansford, J. H. C. Nayler, and A. Queen, *J. Chem. Soc.*, 2649 (1960).

287. (a) W. Reppe et al., *Liebigs Ann. Chem.*, **601**, 127 (1956); W. Reppe and A. Freytag, German Patent 696,774 (1940); *Chem. Abstr.*, **35**, 5909 (1941).

288. (a) H. R. Snyder and J. M. Stewart, U.S. Patent 2,490,984 (1949); *Chem. Abstr.*, **44**, 2550 (1950); (b) U.S. Patent 2,497,100 (1950); *Chem. Abstr.*, **44**, 4025 (1950); (c) A. V. Fokin, A. F. Kolomiets, L. S. Rudnitskaya, and V. I. Shevchenko, *Izv. Acad. Nauk Khim., SSSR*, **3**, 660 (1974).

289. H. Ufer and A. Freitag, German Patent 696,773 (1940); *Chem. Abstr.*, **35**, 5909 (1941).

290. T. A. Mastryokova, V. N. Odnoralova, and M. I. Kabachnik, *Zh. Obshch. Khim.*, **28**, 1563 (1958); *Chem. Abstr.*, **53**, 1117 (1959).

291. S. M. Igbal and L. N. Owen, *J. Chem. Soc.*, 1030 (1960).

292. (a) A. F. Millikan, U.S. Patent 3,073,846 (1963); *Chem. Abstr.*, **58**, 13794 (1963); (b) G. A. Razuvaev, V. S. Etlis, and L. N. Grobov, *Zh. Obshch. Khim.*, **33**, 1366 (1963); *Chem. Abstr.*, **59**, 9827 (1963).

293. W. Reppe and F. Nicolai, German Patent 631,016 (1936); *Chem. Abstr.*, **30**, 6008 (1936); U.S. Patent 2,105,843 (1938).

294. D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5125 (1961).

295. H. M. Woodburn and B. C. Pautler, *J. Org. Chem.*, **19**, 863 (1954).

296. J. W. Haefele and R. W. Broge, *Am. Perfum. Aromat.*, **75**, 39 (1960).

297. I. R. Schmolka and P. E. Spoerri, *J. Am. Chem. Soc.*, **79**, 4716 (1957).

298. Y. K. Yurgev and L. S. German, *News Moscow State Univ., Phys. Chem. Ser.*, **1**, 197 (1956); *Chem. Abstr.*, **52**, 9069 (1958).

299. (a) Y. K. Yurgev and S. V. Dyatlovitskya, *J. Gen. Chem., USSR*, **27**, 1855 (1957); (b) Y. K. Yuryev, S. V. Dyatlovitskya, and L. S. Bulavin, *ibid.*, **27**, 3306 (1957).

300. H. Gilman and L. A. Woods, *J. Am. Chem. Soc.*, **67**, 1843 (1945).

301. H. R. Snyder and J. M. Stewart, U.S. Patent 2,505,870 (1950); *Chem. Abstr.*, **44**, 7352 (1950).

302. N. S. Isaacs, *Can. J. Chem.*, **44**, 395 (1965).

303. L. P. Moore and W. P. Ericks, U.S. Patent 2,453,333 (1948); *Chem. Abstr.*, **43**, 1799 (1949).

304. Y. K. Yuriev and S. V. Dyatlovitskaja, *Zh. Obshch. Khim.*, **27**, 1787 (1957); *Chem. Abstr.*, **52**, 4603 (1958); *Zh. Obshch. Khim.*, **29**, 3885 (1959); *Chem. Abstr.*, **54**, 21049 (1960).

305. R. J. Wineman, M. H. Gollis, J. C. James, and A. M. Pomponi, *J. Org. Chem.*, **27**, 4222 (1962).

306. S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **29**, 974 (1964).

307. R. L. Jacobs and R. D. Schuetz, *J. Org. Chem.*, **26**, 3472 (1961).

308. (a) D. D. Reinolds, M. K. Massad, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5109 (1961); (b) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *ibid.*, **26**, 5116 (1961); **26**, 5119 (1961).

309. L. P. Moore and W. P. Ericks, U.S. Patents 2,323,409 (1943), 2,442,957 (1948); *Chem. Abstr.*, **38**, 212 (1944); **42**, 7328 (1948).

310. H. R. Snyder and W. Alexander, *J. Am. Soc. Chem.*, **70**, 217 (1948).

311. M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1042 (1952).

312. F. Funahashi, *Chem. Lett. (Jpn.)*, 1043 (1978).

313. F. Haviv and B. Belleau, *Can. J. Chem.*, **56**, 2677 (1978).

314. F. E. Hardy, P. R. H. Speakman, and P. Robson, *J. Chem. Soc., C*, 2334 (1969).

315. G. Hesse, E. Reichold, and S. Majmudar, *Chem. Ber.*, **90**, 2106 (1957); **93**, 1129 (1960).

316. (a) D. C. Dittmer and G. C. Levy, *J. Org. Chem.*, **30**, 636 (1965); (b) F. Lautenschlager, *J. Org. Chem.*, **34**, 3998 (1969).

317. (a) S. B. Soloway, U.S. Patent 2,694,073 (1954); *Chem. Abstr.*, **49**, 3465 (1955); (b) K. Kondo, A. Negishi, and M. Fukuyama, *Tetrahedron Lett.*, 2461 (1969).

318. R. Raynolds, S. Zonnebelt, S. Bakker, and R. M. Kellogg, *J. Am. Chem. Soc.*, **96**, 3146 (1974).

319. A. Padwa, *Int. J. Sulfur Chem., B*, **7**, 331 (1972).

320. A. Padwa, in O. L. Chapman, Ed., *Organic Photochemistry*, Vol. I, Dekker, New York, 1967.

321. P. Fowles, M. de Sorgo, A. J. Yarwood, O. P. Strausz, and H. E. Gunning, *J. Am. Chem. Soc.*, **89**, 1056 (1967).

322. (a) R. S. Sidhu, E. M. Lown, O. P. Strausz, and H. E. Gunning, *J. Am. Chem. Soc.*, **88**, 254 (1966); (b) R. Kumar and K. S. Sidhu, *Indian J. Chem.*, **11**, 899 (1973).

323. E. M. Lown, H. S. Sandhu, H. E. Gunning, and O. P. Strausz, *J. Am. Chem. Soc.*, **90**, 7164 (1968).

324. R. J. Gritter and E. C. Savatino, *J. Org. Chem.*, **29**, 1965 (1964).

325. W. R. Brasen, H. N. Gripps, C. G. Bottomley, M. W. Farlow, and C. G. Krespan, *J. Org. Chem.*, **30**, 4188 (1965).

326. H. M. Frey, *Adv. Phys. Org. Chem.*, **4**, 147 (1966).

326a. H. A. Wiebe, S. Braslavsky, and J. Heicklen, *Can. J. Chem.*, **50**, 2721 (1972).

327. T. Sato, Y. Goto, T. Tohyama, S. Hayaski, and K. Hata, *Bull. Chem. Soc., Jpn.*, **40**, 2975 (1967).

328. (a) A. Padwa and D. Crumrine, *J. Chem. Soc., Chem. Commun.*, 506 (1965); (b) A. Padwa, D. Crumrine, and A. Shubber, *J. Am. Chem. Soc.*, **88**, 3064 (1966).

329. J. G. Pacifici and C. Diebert, *J. Am. Chem. Soc.*, **91**, 4595 (1969).

330. (a) A. Padwa and A. Battisti, *J. Am. Chem. Soc.*, **93**, 1304 (1971); (b) R. M. Kellogg, *ibid.*, **93**, 2344 (1971); (c) A. G. Anastassiu and B. Y. H. Chao, *J. Chem. Soc., Chem. Commun.*, 979 (1971).

331. Y. Ohshiro, T. Minami, K. Yasuda, and T. Agawa, *Tetrahedron Lett.*, **4**, 259 (1969).

332. Y. Veno, T. Nakai, and M. Okawara, *Bull. Chem. Soc., Jpn.*, **43**, 162 (1970).

332a. U. Schoelkopf, J. Reinhard, and M. Kusuma, *Justus Liebigs Ann. Chem.*, **4**, 451 (1979).

333. S. Tamagaki, K. Tamura, and S. Kozuka, *Chem. Lett.*, 375 (1977).

334. J. Barrau, M. Bouchaut, H. Lavayssiere, G. Dousse, and J. Satgé, *Helv. Chim. Acta*, **62**, 152 (1979).

335. (a) J. C. Sheehan and J. H. Beeson, *J. Am. Chem. Soc.*, **89**, 362 (1967); (b) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969).

336. H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, 1972.

337. E. M. Arnett, J. M. Bollinger, and M. Barber, *J. Am. Chem. Soc.*, **89**, 5889 (1967).

338. J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, **37**, 4045 (1972).

339. P. Raynolds, S. Zonnebelt, S. Baker, and R. M. Kellogg, *J. Am. Chem. Soc.*, **96**, 3146 (1974).

340. U. Zoller, unpublished results.

341. A. Gill, *J. Soc. Leather Trades Chem.*, **42**, 394 (1958); *Chem. Abstr.*, **43**, 11867 (1959).

342. (a) T. R. Hopkins, A. Rhodes, and A. N. Arakelian, German Patent 1,012,416 (1958); *Chem. Abstr.*, **54**, 15917 (1960); (b) A. Hrubesch, German Patents 964,772 and 1,002,329 (1957); *Chem. Abstr.*, **53**, 22893 (1959); (c) D. E. Adelson, G. L. Perry, and G. G. Pritzker, U.S. Patent 2,628,941 (1958).

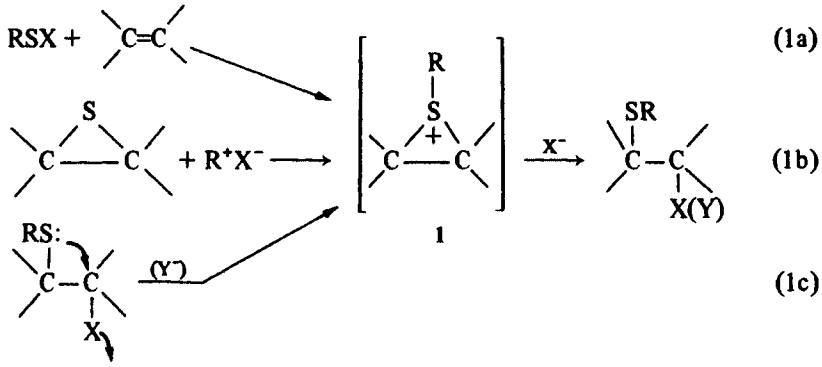
343. (a) D. E. Frear and E. J. Seiferle, *J. Econ. Entomol.*, **40**, 736 (1947); *Chem. Abstr.*, **42**, 2045 (1948); (b) C. Harukawa, M. Sakai, and K. Konishi, Japanese Patent 9997 (1962); *Chem. Abstr.*, **60**, 3440 (1964).

344. (a) Imperial Chemical Industries Ltd., British Patent 597,368 (1948); *Chem. Abstr.*, **42**, 7573 (1948); (b) W. A. Lazier and F. K. Signaigo, U.S. Patent 2,396,957 (1946); *Chem. Abstr.*, **40**, 3935 (1946); (c) T. Muroi, S. Morimoto, and A. Yamaouchi, Japanese Patent 9891/61; *Chem. Abstr.*, **56**, 3682 (1962); (d) A. Rakotomanga, P. Hemery, S. Boileau, and B. Lotz, *Eu. Polym. J.*, **14**, 581 (1978).

345. (a) G. Champetier and F. Hennequin-Lucas, *Compt. Rend.*, **252**, 2785 (1961). (b) D. K. Chaudhuri and J. J. Hermans, *J. Polym. Sci.*, **48**, 159 (1960).

IV. THIIRANIUM SALTS (EPISULFONIUM IONS)

Thiiranium salts comprise a class of charged, sulfur-containing, three-membered rings (**1**) that can be approached from two perspectives. The first, apparently the "historical" approach, envisions thiiranium ions as important, highly reactive chemical intermediate species along the reaction coordinate (*a*) in the addition of sulfenyl halides and closely related sulfur compounds to carbon-carbon double bonds;[1] (*b*) in the electrophilic ring opening in thiiranes initiated by the attack of the electrophile on the sulfur atom of the ring (i.e., sulfur protonation, alkylation, arylation, acetylation, etc.),[2] and (*c*) in the neighbor-assisted solvolysis of β-substituted leaving groups in sulfides.[3] All these processes are depicted in Eqs. 1.

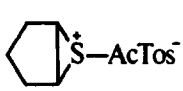


The alternative approach reflects an interest in thiiranium salts per se – that is as chemical entities in their own right. This approach envisions thiiranium salts as intriguing systems that constitute a real challenge to the chemist: synthetically, with respect to the preparation and isolation of stable examples, and chemically, by and large with respect to the thorough study of their unique properties.

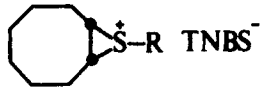
Understandably, there is no distinct difference between the two approaches. Rather, by emphasizing different aspects in the chemistry of the same system, they complement each other. Among the many factors that determine the state of the art in this area, two appear to dominate. The first, which has served to promote investigations in this field, is associated with the popularization of the cyclic "onium ion" advanced for electrophilic additions (Ad_E reactions) to carbon-carbon double bonds.[4] This mechanism continues to serve as a very convenient phenomenological basis for the understanding of the stereochemical course of many reactions. Indeed, thiiranium (episulfonium) salts have long been invoked as intermediates in organic reactions of various types (Eqs. 1), although until relatively recently there has been no evidence that they might be isolable.[5] Furthermore, even at present, as it was 30 years ago, the thiiranium ion mechanism is universally used for the discussion of the addition reaction of sulfenyl chlorides to olefins.[6,7] The second factor, on the other hand, which served as an inhibitor in the field and apparently had a deterring effect on synthetic attempts, was the (justified!)

concept of high susceptibility of this type of compound to interception by nucleophiles. However, extensive investigations on analogous heterocyclic systems (e.g., quaternary aziridinium salts[8]) contributed to the renewal of interest in small cationic sulfur-containing rings.[9]

The first physical evidence for the existence of a stable thiiranium salt was provided more than two decades ago by Goodman and co-workers,[10] who based their claim for the structure of cyclopentene-*S*-acetyl-thiiranium *p*-toluenesulfonate (2) on both starting materials and spectral data. Historically speaking, however, an earlier report[11] was the first to suggest the formation of the thiiranium salt by methylation of a terpene thiirane.



2



3

Later, the preparation and characterization of the stable *cis*-cyclooctene-*S*-alkylthiiranium 2,4,6-trinitrobenzenesulfonates (3) were achieved,[12] followed by other examples.[9]

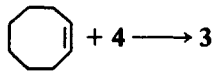
In many cases, product instability prevented isolation of materials other than dimeric or polymeric species under the given conditions.[9] However, several relatively stable thiiranium ions have been recently prepared.[13,14]

The classical mechanistic description of the Ad_E reaction of sulfenyl halides to alkenes suggests rare-determining formation of thiiranium ion 1, which undergoes a nucleophilic opening by halide anion at the second step (Eq. 1b). It follows, therefore, that if the halide is replaced in the sulfenyl compound by an anion with very low nucleophilicity, the thiiranium intermediate may be isolated. This was, in fact, the approach taken initially in the attempted preparations of thiiranium salts:[9]

$$Ag^+ArSO_3^- + RSBr \xrightarrow{CH_2Cl_2} RSOSO_2Ar + AgBr \qquad (2)$$

4

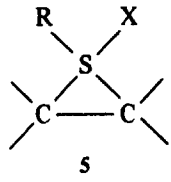
R = methyl, ethyl, propyl, butyl, *t*-butyl
Ar = 2,4,6-trinitrophenyl



Substitution with bulky groups on the alkene to stabilize the thiiranium salt was attempted later[15] (see below).

The uniformity and simplicity of the steric course of the addition of sulfenyl halides to alkenes are supposed to constitute convincing evidence in favor of the accepted "thiiranium ion" mechanism, whereas alternative suggestions about the involvement of bridged species such as covalent σ-sulfurane (5) have never attracted serious attention.[6]

A recent critical analysis[6] of existing experimental data delineates the "myth"



5

X = halogen

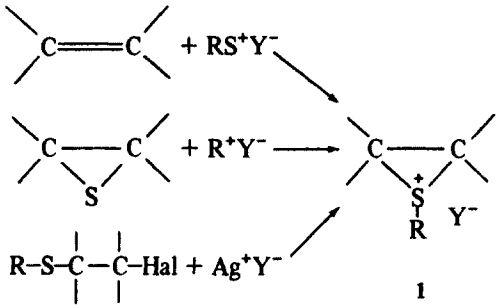
and the reality concerning thiiranium ions (Table 1) and points out serious discrepancies between the regularities of RSCl Ad_E reactions with olefins and generally held views about the reactivity patterns of cationoid intermediates. Regardless of the correct mechanism of the reaction above, the isolation and characterization of several distinct thiiranium salts as well as the study of their chemistry undoubtedly make the latter into a respectable challenging class of compounds within the broad "family" of three-membered rings containing sulfur.

1. Methods of Preparation

Several methods are available for the preparation of thiiranium salts: (*a*) synthesis by direct addition, (*b*) synthesis by alkylation, arylation, or protonation, and (*c*) synthesis by ring closure. All these three methods are illustrated in Eqs. 3. It appears, however, that only the first two are of general utility,[6,9,12-15] whereas the successful use of the method represented by Eq. 3c was reported only for the preparation of *S*-methylthiiranium salts from *cis*-di-*tert*-butylethylene[16] and for the series of *S*-alkylthiiranium salts from cyclooctene.[9,17]

TABLE 1. SUPPOSED AND ACTUAL CHARACTERISTICS OF THIIRANIUM IONS[6]

Myth	Reality
1. Are weak electrophiles having most of the positive charge on the sulfur	1. Are active electrophiles of the bridged carbenium ion type
2. Do not undergo skeletal rearrangements	2. Are able to undergo skeletal rearrangements
3. Should be regarded as "strongly bridged" species concerning stereochemical consequences of nucleophilic attack	3. Are bridged species capable of interconversion and nonstereospecific reactivity
4. Give *anti*-Markovnikov adducts as kinetically controlled products	4. Give preferentially Markovnikov adducts in reacting with nucleophiles
5. Are the intermediates in the addition reactions of RSCl to olefins under typical conditions	5. Are, most probably, not involved in the addition of RSCl to olefins under the usually accepted conditions[6]



Stable or quasi-stable thiiranium ions were alleged to be formed or have been invoked as reaction intermediates in numerous reactions.[18] However, in view of the difference in the interpretation of the available experimental data between the groups of Helmkamp[17] and Smit[6] – leading, eventually, to different conclusions concerning the real nature of thiiranium ions – a critical reexamination of all the claims about thiiranium intermediacy would be appropriate. Some of the most important relevant aspects are dealt with later (Section IV, 3: Chemical Properties and Reactivity).

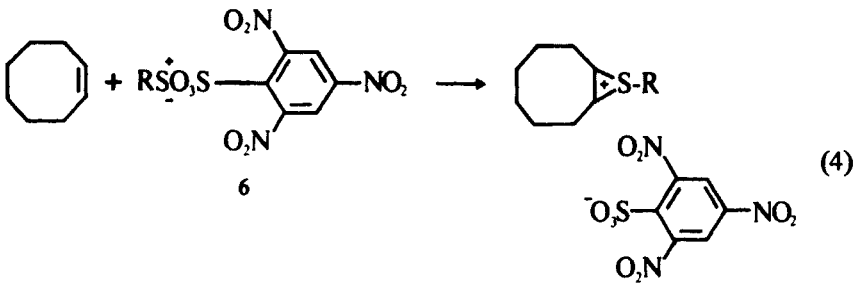
The essential feature of all the procedures that lead to the isolation of relatively stable thiiranium salts is the use of nonnucleophilic counterions such as BF_4^-, BF_6^-, SbF_6^-, $SbCl_6^-$, $TNBS^-$, and FSO_3^-. The formation of the desired salts proceeds quite smoothly in such ordinary organic solvents as CCl_4, CH_2Cl_2, $C_2H_4Cl_2$, CH_3CH, and CH_3NO_2. In general, the thiiranium salts prepared were found to be unstable at elevated temperatures, and only in rare cases were they isolated as pure substances.[13,14,16] The stability of the solutions of thiiranium salts (evaluated by nmr data and/or by the yields of quenching adducts) varies from several hours at $-70°$ up to several days at ambient temperatures[15,19] and even weeks at $-10°$ (and with the exclusion of moisture) in certain cases.[13]

A. *Synthesis by Direct Addition to Alkenes*

Stable thiiranium salts of the alkyl series can be prepared and isolated in moderate to high yield (60–70%) from the reaction of alkanesulfenyl 2,4,6-trinitrobenzenesulfonates with cyclooctene (see Table 1, Section III, 1, A). One crystallization from warm nitromethane-ether or acetone-ether gave pure products.[12]

The products above are solids, having a sharp melting point, and their structures are supported by physical and chemical properties as well as spectroscopic data (e.g., ir).[12] Reaction with **6** of other alkenes (e.g., cyclohexene) led to dimeric or polymeric species only, primarily because of the instability of the initial products.[13]

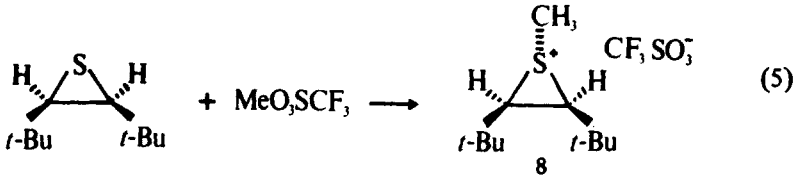
The preparation of stable thiiranium salts by direct addition to alkenes was successfully applied in the synthesis of the hindered 2,3-di-*tert*-butyl thiiranium salt **8**.[16]



(4)

6 7

a. R = CH_3
b. R = C_2H_5
c. R = n-C_3H_7
d. R = n-C_4H_9

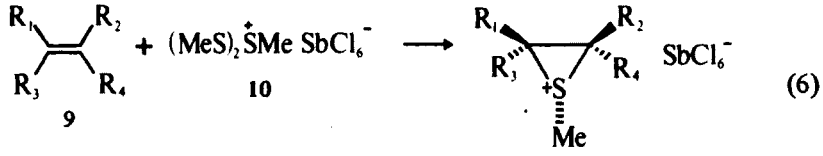


(5)

8

As previously (e.g., 7), the nonnucleophilicity of the anion $F_3CSO_3^-$ undoubtedly contributes to the relative stability of the three-membered ring product. The hindrance induced by the two bulky *tert*-butyl groups at the ring carbon atoms appears to be another decisive factor with respect to the stability of thiiranium (as well as thiirenium) salts. Indeed, this is a well-established effect that already has been mentioned (see Section V, 3, J) and is also applicable to the synthesis of stable thiiranium salts via ring closure (see Section III, 1, C).

A somewhat different approach to the synthesis of thiiranium ions is the use of the alkylthiolating properties of methyl(bismethylthio)sulfonium hexachloroantimonate (i.e., **10**). Thus, the thiiranium hexachloroantimonates **11a–11c** have been obtained in high yields (85–90%) by addition of the appropriate alkenes (**9a–9c**) to a solution of **10** in methylene chloride at 0° or in sulfur dioxide at −60°.[13]



(6)

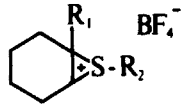
9 10 11a–11c

a. $R_1 = R_2 = R_3 = R_4 = Me$
b. $R_1 = R_4 = Et$; $R_2 = R_3 = H$
c. $R_1R^2 = -(CH_2)_6-$; $R_3 = R_4 = H$

Compounds **11a–11c** can be obtained in pure form using ordinary methods of work-up. They are stable for weeks at −10°. However, some decomposition does occur when they are left for hours at room temperature without exclusion of

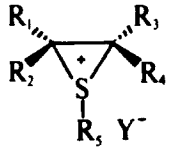
moisture.[13] An attempt to isolate other members of these sulfur-methylated thiiranium salts in a pure form was unsuccessful.[13]

Cationoid reagents of the type RS^+Y^- ($Y = BF_4$ or SbF_6) generated *in situ* by the reaction of RS-Hal with the corresponding silver salts proved to be generally useful in preparing stable solutions of thiiranium salts **12a–12c** and **13a–13d**.[6,15,20]



12

a. $R_1 = H; R_2 = CH_3$
b. $R_1 = H; R_2 = C_6H_5$
c. $R_1 = CH_3; R_2 = CH_3$



13

a. $R_1 = R_3 = R_4 = H; R_2 = C_6H_5; R_5 = CH_3; Y = BF_4$
b. $R_1 = R_2 = R_3 = H; R_2 = t\text{-Bu}; R_5 = C_6H_5; Y = BF_4$
c. $R_1 = R_3 = CH_3; R_2 = R_4 = H; R_5 = CH_3; Y = SbF_6$
d. $R_1 = R_4 = CH_3; R_2 = R_3 = H; R_5 = CH_3; Y = SbF_6$
e. $R_1 = R_3 = H; R_2 = R_4 = CH_3; R_5 = C_6H_4Cl\text{-}p; Y = SbF_6$
f. $R_1 = R_4 = H; R_2 = R_3 = CH_3; R_5 = C_6H_4Cl\text{-}p; Y = SbF_6$

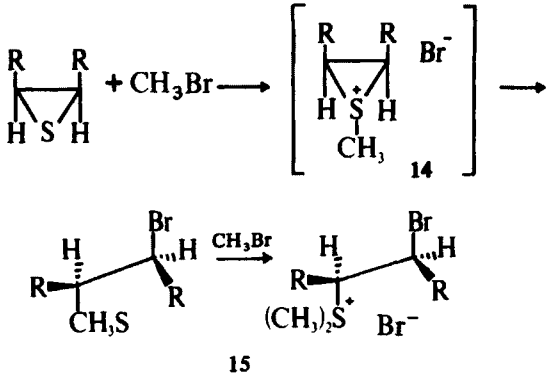
The ions above have been claimed to be stable for at least several hours at $-30°$ in the nonnucleophilic solvents CH_2Cl_2, $C_2H_4Cl_2$, SO_2, and CH_3NO_2. They were not isolated, however, and their structure and properties were deduced mainly on the basis of their mode of reaction with nucleophiles to afford the corresponding β-substituted thioethers as the major products[6,15] (see Section IV, 3).

B. *Synthesis by Sulfur Alkylation*

In principle, thiiranium salt preparation by way of sulfur alkylation includes the arylation, acetylation, and protonation of thiiranes as well.

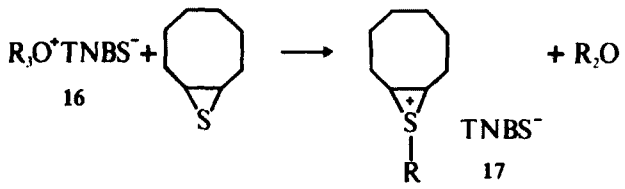
Nevertheless, the stability of the thiiranium ion thus obtained in a nonreacting solvent (i.e., of particularly low nucleophilicity) is intimately related to the nature of the incipient anion that is formed.

The effective desulfurization of thiiranes by methyl iodide has been known for many years and has been previously discussed (Section III, 3, D, e). The substitution of methyl bromide for methyl iodide produced **15**, which could have been formed via the intermediacy of thiiranium salt **14**.[9]



(8)

If (*a*) the alkylation of the thiirane is very rapid (to avoid dimerization-polymerization by the reaction of the remaining unreacted thiirane with the thiiranium intermediate), (*b*) both the solvent and the incipient anion from the alkylating agent are unreactive toward the thiiranium ion, and (*c*) the starting thiirane represents a poor substrate for nucleophilic attack on carbon, a relatively stable thiiranium salt can be prepared. This set of conditions was actually found for the following case:[12,21]



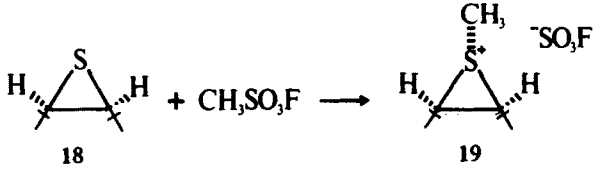
(9)

R = CH_3 or C_2H_5
TNBS = 2,4,6-trinitrobenzene sulfonate

a. R = CH_3
b. R = C_2H_5

The products **17a** and **17b** display high stability in the solid state and can easily be purified by crystallization under mild conditions (47–67% yield). The trialkyloxonium reagent (**16**) is prepared from the corresponding fluoborate and TNB-sulfonic acid, or, more conveniently, from the reaction of the latter with diazomethane in methyl ether solvent.[12,21]

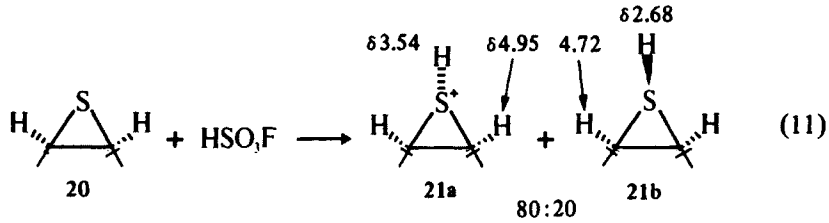
Methylation of the *cis*-2,3-di-*tert*-butylthiirane can be achieved on treatment with methylfluorosulfonate at about 0°.[16] The thiiranium salt **19** thus obtained can be isolated in crystalline form but this salt is very sensitive to moisture and decomposes on standing for a few hours at room temperature. Presumably, the methyl group in **19** is *trans* to the *t*-butyl substituents.



(10)

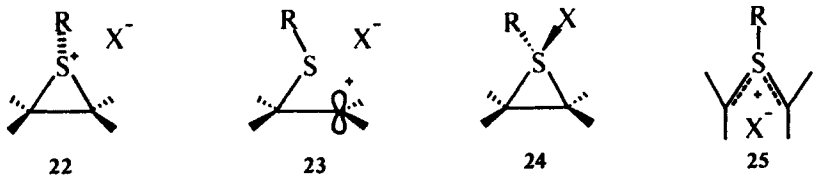
Ambient or higher temperatures were required to cause reaction between the *trans* isomer of **18** and the fluorosulfonate. However, no characterizable products were isolated, most probably because of the instability of the initially formed salt at these temperatures.[16]

Protonation of thiiranes to give the corresponding thiiranium ions was accomplished by using either FSO_3H–SbF_6 in the case of 2-methylthiirane[22] or just fluorosulfonic acid in the cases of the *cis*- and *trans*-di-*tert*-butylthiiranes and tetramethylthiirane.[16] Although the protonated products thus generated are stable at low temperatures (i.e., $-60°$ to $-70°$), no attempt has been made to isolate them as such. Wherever structurally possible, the protonated species exist as a *cis-trans* isomeric mixture according to the pertinent nmr data.[16,22] Equation 11 shows a representative case.[16]



(11)

Since proton exchange in protonated sulfide is slow relative to the nmr time scale, the observation of the geometrical isomerism is possible. Furthermore, the fairly close analogy in chemical shifts with that of *trans*-**20** as well as quenching and comparison with other reference data corroborate the commonly accepted structure **22** as being the correct one for thiiranium salts, not the other possible alternatives (i.e., **23–25**) given below (see Section IV, 2).

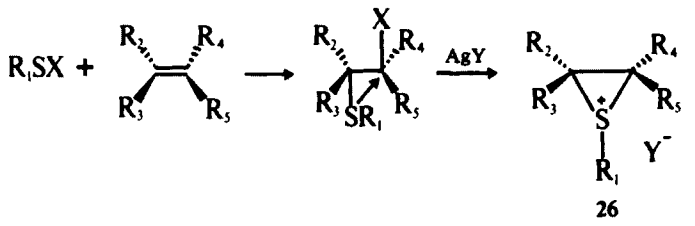


22 **23** **24** **25**

C. *Synthesis by Ring Closure*

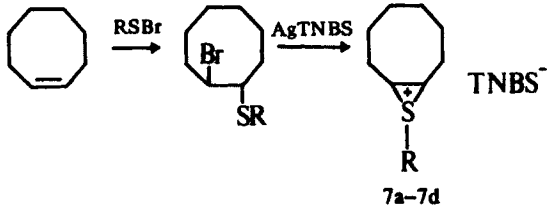
Preparation by ring closure is a method of general utility and probably is the one most commonly used. The starting materials, the β-halo-sulfides, are readily available (from olefins and sulfenyl halides), as are the silver complexes (i.e., $AgBF_4$, $AgPF_6$, $AgSbF_6$, $AgSbCl_6$) required to effect the ring formation. The general scheme of this route is given in Eq. 12.

This reaction sequence and the conditions are ideally suited for neighboring group participation (on the part of the sulfur), provided neither the anion Y nor the solvent will intercept the cyclic thiiranium salt formed. The use of aprotic and



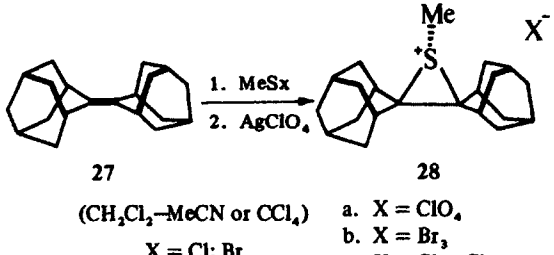
(12)

nonnucleophilic solvents (CH_2Cl_2, CH_3NO_2, etc.) is thus imperative. Compounds **7a–7d** can be prepared by the treatment of cyclooctene with alkanesulfenyl bromides followed by the addition of the crude 1-bromo-2-alkylthiocyclooctanes to a nitromethane solution of silver 2,4,6-trinitrobenzenesulfonate (AgTNBS);[12] addition of ether leads to salts in high yields (64–83%) and pure form.



(13)

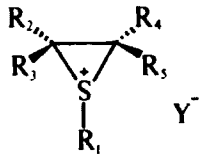
Several new stable thiiranium salts have been prepared recently through the ring closure method. Once again the extreme bulkiness of the substituents on the ring carbon atoms appears to be the main contributor to the stability of these adamantylideneadamantane-derived thiiranium salts:[14]



(14)

This method (e.g., Eq. 12) was extensively used for the preparation of stable solutions of thiiranium salts (**26a–26k**)[15,19,20] in SO_2, CH_3NO_2, or CH_2Cl_2–$C_2H_4Cl_2$ (at $-70°$ to $-30°$) that can react *in situ* with nucleophiles.

Although the chemistry of thiiranium ions (salts) has been quite thoroughly investigated, only a handful of this class of compounds were actually isolated, purified, and fully characterized. The starting materials and the reagents used for



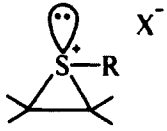
26

a. $R_1 = CH_3$; $R_2R_4 = -(CH_2)_4-$; $R_3 = R_5 = H$; $Y = BF_4$
b. $R_1 = C_6H_5$; $R_2R_4 = -(CH_2)_4$; $R_3 = R_5 = H$; $Y = BF_4$
c. $R_1 = CH_3$; $R_2 = C_6H_5$; $R_3 = R_4 = R_5 = H$; $Y = BF_4$
d. $R_1 = CH_3$; $R_2R_4 = -(CH_2)_4-$; $R_3 = CH_3$; $R_5 = H$; $Y = BF_4$
e. $R_1 = C_6H_5$; $R_2 = t$-Bu; $R_3 = R_4 = R_5 = H$; $Y = BF_4$
f. $R_1 = C_6H_5$; $R_2 = R_4 = CH_3$; $R_3 = R_5 = H$; $Y = SbF_6$
g. $R_1 = C_6H_5$; $R_2 = R_5 = CH_3$; $R_3 = R_4 = H$; $Y = SbF_6$
h. (i) $R_1 = 4\text{-}CH_3C_6H_4$; (ii) $2,4,6\text{-}(CH_3)_3C_6H_2$; (iii) $4\text{-}ClC_6H_4$; (iv) $4\text{-}CF_3C_6H_4$; (v) C_6F_5
$R_2 = CH_3$; $R_3 = R_4 = R_5 = H$; $Y = SbF_6$
i. $R_1 = 2,4,6\text{-}(CH_3)_3C_6H_2$; $R_2 = R_3 = CH_3$; $R_4 = R_5 = H$; $Y = SbF_6$
j. $R = 2,4\text{-}(NO_2)_2C_6H_3$; $R_2 = R_4 = CH_3$; $R_3 = R_5 = H$; $Y = SbF_6$
k. $R_1 = 2,4\text{-}(NO_2)_2C_6H_3$; $R_2 = R_5 = CH_3$; $R_3 = R_4 = H$; $Y = SbF_6$

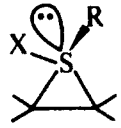
the preparation of these few, as well as the claimed yields obtained, are given in Table 2.

2. Structure and Physical Properties

The argument about the "real" structure of the thiiranium intermediates is as old as the chemistry of these species. Two main structures (**29** and **30**) have been advanced,[12] and considerable effort has been devoted to attempts to determine the structure based on experimental data.[6,12-20] In fact, only one of the proposed alternatives (i.e., **29**) is a true three-membered ring ion, whereas the second (i.e., **30**) is a three-membered ring sulfurane, containing a tetracovalent sulfur atom.



29

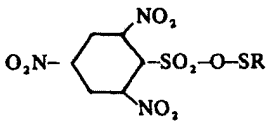
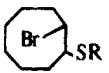
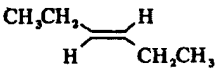
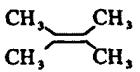
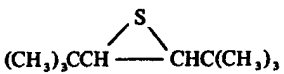
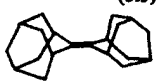


30

Difficulties in handling the very unstable thiiranium species have thus far prevented direct determination of bond distances, molecule geometries, atomic charge distribution, and so on. Rather, kinetic studies of the formation and interception of the presumed intermediate, as well as extensive studies of the product distribution derived from its nucleophilic ring opening, have been carried out in an attempt to elucidate the real nature of thiiranium ions (salts).[6,12-20] Relatively recently, ^{13}C and ^1H nmr studies have been used for this purpose.[9,14,16,19a] The experimental approach was accompanied by nonempirical calculations (to be discussed in Section IV, 2, A) on a number of model structures using LCAO-MO calculations,[17c] the CNDO/2 method,[23] and the *ab initio* SCF-MO approach.[24]

TABLE 2. PREPARATION OF THIIRANIUM SALTS 

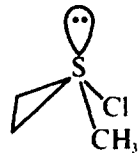
R = alkyl

R_1	R_2	R_3	R_4	Starting Material	Reagent	Yield (%)	Ref.
H	$-(CH_2)_6-$		H		$(MeS)_2SMe^+SbCl_6^-$	85–90	13
						60–70	12
					AgTNBS R = alkyl (i.e., CH_3, C_2H_5, n-C_3H_7, n-C_4H_9)	64–83	12
					$R_3O^+TNBS^-$ (R = CH_3 or C_2H_5)	47–67	12
H	CH_3CH_2 (*trans*)	CH_3CH_2	H		$(MeS)_2SMe^+SbCl_6^-$	85–90	13
CH_3	CH_3	CH_3	CH_3				
H	*t*-Bu	*t*-Bu	H	 (*cis*)	CH_3SO_3F	–	16
					$MeSX/AgClO_4$ (X = halogen)	–	14

The accumulated experimental data[6,9-20] as well as the results of theoretical calculations support the suggestion that both **29** and **30** represent "real" structures of the thiiranium ion (salt) and the balance between the two (or between them and another possible closely related structure) is rather delicate and should be subject to the effects of the medium (polar and nonpolar solvents), the nature of the substituents (electronic and steric effects), and the reagents used.[6,9,24] At present, there are no direct experimental data enabling one to specify unambiguously the structure of the thiiranium ion.[6] This gap in our knowledge has definite implications concerning the yet controversial mechanistic features of the addition reaction of RSX (X = halogen) to alkenes, which undoubtedly served as the main promoter of thiiranium chemistry.[6,9] Despite agreement that the reaction involves the formation of bridged intermediates (supported by their ability to form regioisomeric adducts on quenching with nucleophiles and their strong preference for rear-side nucleophilic attack), there is no agreement on their positive charge localization (i.e., mainly on sulfur or on carbon).[6] The latter-factor determines the site of initial attack by nucleophiles and therefore is of crucial importance to the understanding of thiiranium ion chemistry.

A. *Molecular Orbital Calculations*

Following the isolation and characterization of the first stable thiiranium salts,[12] LCAO-MO calculations were carried out on a number of models[17c] to provide a reasonable structure for the intermediate. The structure with the most stable arrangement about sulfur was found to be the sulfurane **31**, with a pseudo-square-pyramidal geometry.



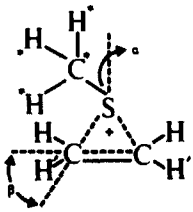
31

This result, in conjunction with the observation (by nmr) of a new intermediate in the reaction of **7a** with chloride ion, raises a question about the universal role of thiiranium salts in many reactions.[9] It might well be (as already mentioned) that a tetracovalent sulfur intermediate is the product of the first elementary process and that three-membered thiiranium ion may or may not be involved contingent on the particular reaction conditions and the reagents employed. The reactivity, regioselectivity and stereospecificity actually observed are a direct consequence of the intermediate structure.

Calculations were carried out for the thiiranium ions derived from ethylene, propylene, isobutylene, and butadiene by the CNDO/2 method to optimize the geometric parameters and investigate their electronic states.[23] The *p*-form intermediates but not sp^3 or sp^2, as so far supposed, were unexpectedly found to be

the most stable. Since it was found that the inclusion of the *S d*-orbitals in the calculations added a negligible contribution to the energy, the *S* orbitals only up to 3*p* were considered.

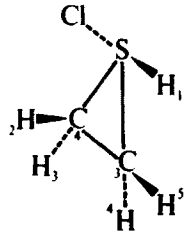
The cyclic form of the thiiranium ion was found to be much more stable than the open form by about 50 kcal/mole. The main results of the MO calculations made on **32** are summarized in Table 3.



32

Comparable results from the energetic point of view were obtained for the corresponding thiiranium ions of propylene and butadiene regardless of the change in β. Also, this kind of calculation showed that the difference in extension of the LUMOs on ethylenic carbon atoms in the intermediates has an important effect on the regiospecificity of the ring-opening of the thiiranium ion intermediates by nucleophiles.

Nonempirical or Hartree-Fock-type LCAO-SCF-MO calculations, using two different basis sets, were carried out on a cyclic sulfurane (i.e., **30**) and a thiiranium-chloride ion pair (i.e., **29**) to obtain theoretical insights into the relative stabilities of the two possible reaction intermediates (particularly with respect to the addition reaction of sulfenyl chloride to an alkene).[24] The optimum conformations of the cyclic parent sulfurane (e.g., **33**) have been calculated too.[24]



33

TABLE 3. CALCULATED NET CHARGE DENSITIES AND BOND ENERGIES IN METHYLTHIIRANIUM ION INTERMEDIATES[23]

		Total energy	Net charge density			Bond energy (a.u.)		
α	β	(a.u.)	*Qs*	*Qc*	*Qc**	*Es–c*	*Es–c**	*Ec–c*
0° (Sp^2)	0°	−36.5890	+0.021	+0.145	+0.042	−0.349	−0.575	−1.349
54° (Sp^3)	0°	−36.9221	+0.251	+0.086	+0.020	−0.294	−0.585	−1.430
90° (*p*)	0°	−36.9330	+0.292	+0.084	+0.006	−0.288	−0.579	−1.430
90°	15°	−36.9401	+0.298	+0.078	+0.006	−0.301	−0.579	−1.416

It has been found that the configuration about the sulfur atom is an approximate trigonal bipyramid. The S–C bond occupies two of the equatorial positions, with the HSC angle between them being 95'40°. The third equatorial position is considered to be taken by the lone pair of electrons. The apical positions are occupied by the electronegative chloride and the second S–C bond of the ring. The $\hat{CSCl}$ (axial) angle is 156'17°, with the distortion from linearity in the direction of the equatorial S–C and S–H bonds and away from the lone pair. The positional differences between the two carbon atoms are reflected in the different S–C bond lengths; the "apical" S–C bond length is 1.9397 Å, whereas the "equatorial" S–C bond length is 1.8447 Å. The rather significant deviation from the ideal trigonal bipyramid structure is due mainly to the presence of the three-membered ring.

The calculated energies[24] indicated that in the gas phase the covalent cyclic sulfurane is favored over the ionic species (> 90 kcal/mole more stable). This relative stability shows consistent improvement as the central sulfur becomes more heavily substituted.

These results support the suggestion that thiiranium ions prevail in polar solvents but tetracovalent sulfur intermediates are favored in solvents of low polarity. This is in accord with the suggestion of Helmkamp[17] and Zefirov et al.[6,25] that the thiiranium salt prevails in high polarity solvents that can solvate the halide ions well, but tight ion pairs or tetracovalent sulfur intermediates are favored in low polarity solvents.

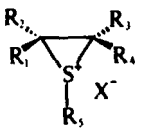
B. *Nuclear Magnetic Resonance Spectroscopic Data*

Only a few nmr studies (both ^1H and ^{13}C) have been performed on thiiranium ions[16,22] and salts[14,16,19] in an attempt to elucidate the identity and the structural features of these species. The ^1H nmr spectra of some selected thiiranium ions are collected in Table 4, which indicates that the available data are in accord with the assumed ring structure of the thiiranium ions (salts) containing pyramidal sulfur atoms.

^{13}C nmr chemical shifts are supposedly more sensitive to the charge density at a carbon atom than are the ^1H nmr chemical shifts. Having proved to be useful in understanding the structure of carbonium ions,[26] ^{13}C nmr was used to probe the structural features of thiiranium ions, particularly with respect to the formal positive charge on the sulfur atom. This should be reflected in a moderate to substantial deshielding of the ring carbon atoms, that is, a downfield shift in comparison to the respective ^{13}C nmr signals of covalent thiiranes. Indeed, this was established for both isolable thiiranium salts and stable ions in polar solvents. Some selected recorded spectra are listed in Table 5.

A $\Delta\delta_c$ of about 20–40 ppm is observed for the ring carbons compared with the ^{13}C nmr signals of the ring carbons in thiiranes. Another pattern is apparent: the bulkier the substituents on the ring carbon atoms, the greater is the chemical shift of these atoms. Whether this effect is primarily electronic or steric is still to be investigated. Correlation between the chemical shift of the ring carbons and the

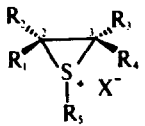
TABLE 4. PMR CHEMICAL SHIFTS AND COUPLING CONSTANTS OF SOME THIIRANIUM IONS AT −50° to −80°



No.	R_1	R_2	R_3	R_4	R_5	X	Chemical shifts, J_{H-H} (Hz)[a] 2,3-H	2,4-H	3,4-H	SH	SCH_3	Solvent	Ref.
1.	*t*-Bu	H	H	*t*-Bu	H[b]	SO_3F	4.95 (*d*, *J* = 8)	–	–	3.54 (*t*, *J* = 8)	–	FSO_3H	16
2.	*t*-Bu	H	*t*-Bu	H	H	SO_3F	–	4.96 (*d*, *J* = 6), 4.90 (*d*, *J* = 8)	–	3.01 (*dd*, *J* = ~ 6, 8)	–	FSO_3H	16
3.	*t*-Bu	H	H	*t*-Bu	H[c]	SO_3F	4.72 (*d*, *J* = 8)	–	–	2.68 (*t*, *J* = 8)	–	FSO_3H	16
4.	*t*-Bu	H	H	*t*-Bu	CH_3[c]	SO_3F	4.40 (*s*, !)	–	–	–	2.80	$CDCl_3$	16
5.	CH_3	CH_3	CH_3	CH_3	H	SO_3F	–	–	–	2.37 (*s*)	–	FSO_3H	16
6.	CH_3	CH_3	H	H	CH_3	$SbCl_6$	–	–	3.56 (*d*, *J* = 6), 3.85 (*d*, *J* = 6)	–	2.60	SO_2	13
7.	CH_3	H	H	CH_3	CH_3[d]	$SbCl_6$	4.32 (*m*)	–	–	–	2.64	SO_2	13
8.	CH_3	H	CH_3	H	CH_3	$SbCl_6$	4.0 (*m*)	–	–	–	2.55	SO_2	13

[a] All chemical shifts referred to TMS (1–3, 5: external; 4, 6–8: internal).
[b] *trans* to the *t*-Bu groups.
[c] *cis* to the *t*-Bu groups.
[d] *trans* to the other methyl groups.

TABLE 5. CHEMICAL SHIFTS AND $J_{^{13}C-H}$ COUPLINGS FOR SOME SELECTED THIIRANIUM IONS AND SALTS DETERMINED BY ^{13}C NMR



No.	R_1	R_2	R_3	R_4	R_5	X	Chemical shifts, $J_{^{13}C-H}$ (Hz)[a] C_2	C_3	$SC(R_5)$	Ref.
1.[b]	*t*-Bu	H	*t*-Bu	H	H	SO_3F	74.5 (*d*, $J = 167$)	75.1 (*d*, $J = 167$)	–	16
2.[b]	*t*-Bu	H	H	*t*-Bu	H[c]	SO_3F	78.3 (*d*, $J = 127$)	78.3 (*d*, $J = 127$)		
3.[d]	*t*-Bu	H	H	*t*-Bu	CH_3[c]	SO_3F	76.2 (*d*, $J = 165$)	76.2 (*d*, $J = 165$)	27.6 (*q*, $J = 128$)	16
4.[e]	CH_3	H	H	H	*p*-$CH_3C_6H_4$	SbF_6	62.3	50.6		19a
5.[e]	CH_3	H	H	H	*p*-ClC_6H_4	SbF_6	62.4	49.5		19a
6.[e]	CH_3	H	H	H	*p*-$CF_3C_6H_4$	SbF_6	66.4	50.9		19a
7.[e]	CH_3	H	H	H	C_6F_5	SbF_6	74.0	54.9		19a
8[f]	–Ada–		–Ada–		CH_3	ClO_4	92.3 (*s*)	92.3 (*s*)	11.1 (*q*, $J = 147$)	14

[a] Relative to TMS.
[b] In FSO_3H at $-50°C$.
[c] *trans* to the *t*-Bu groups.
[d] In $CDCl_3$.
[e] In liquid SO_2 at $-70°$; all the spectra reveal the presence of the corresponding signals of aromatic residue.
[f] In CH_2Cl_2.

relative electronegativity of the sulfur substituents, however, does not appear to exist. The existing nmr data do not contradict the suggestion of the comparatively low localization of positive charge on the ring carbon atoms, meaning a positively charged sulfur atom. The latter view is supported by kinetic studies on the relative rates of thiiranium ion formation.[27] The data obtained have been interpreted in terms of transition states in which the positive charge resides essentially on sulfur, and consequently alkyl substituents about the double bond (of the "mother" olefin used to generate the thiiranium ion) contribute relatively little toward delocalization of the positive charge. The observed reactivities reflect opposing steric and electronic factors.[27]

C. *Infrared Spectroscopic Data*

The relative stability of the thiiranium ion ring systems on the one hand, and the sparse information expected to be gained from the study of their ir spectra, are responsible for the lack of relevant ir data. Indeed, the retention of the three-membered ring of a thiiranium salt is claimed in only one case,[12] based on the presence of a weak ir band at 3010 cm^{-1}, characteristic of the C–H stretching frequency in that system. Any other available ir data refer to attached functional groups (in the substituents and counterions) but not to the ring system per se.

D. *Physical Properties*

Since only very few thiiranium salts are stable enough to be purified, isolated, and fully characterized, very few physical parameters of this system have been determined experimentally thus far. Thiiranium salts that have been isolated, are low melting solids, thermally unstable and very sensitive to moisture and nucleophiles. Table 6 gives characteristic melting points and nmr data.

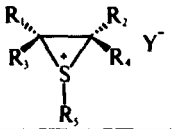
3. Chemical Properties and Reactivity

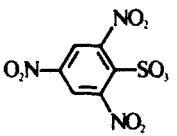
Depending on structure and conditions, thiiranium salts can undergo three principal reactions: (*a*) ring opening with a nucleophile by S_N2 substitution or E_2 elimination, provided the latter reaction is structurally possible and the nucleophile is sufficiently basic,[14] (*b*) attack at the positively charged sulfur[17,23] leading to either sulfenyl compounds[9] or to ultimate desulfurization with retention of configuration of the starting alkene,[14] and (*c*) dealkylation to afford thiirane and alkylated nucleophile.

A. *Nucleophilic Attack at the Carbon Atom*

Reaction *a* above (ring opening with a nucleophile) is operative in most cases, leading to the formation of β-substituted sulfides. It has been investigated by many

TABLE 6. MELTING POINTS AND SELECTED NMR DATA OF STABLE THIIRANIUM SALTS



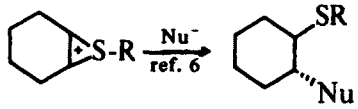
							Chemical shifts: nmr (ppm)			
R_1	R_2	R_3	R_4	R_5	Y	m.p. (C°)	$R_1 = H_A$	$R_2 = H_B$	$R_5 = CH_3$	Ref.
H	H	$-(CH_2)_6-$		CH_3		122–123				12, 20
				C_2H_5		123–124				12
				n-C_3H_7		116–117				12
				n-C_4H_9		104–105				12
				t-C_4H_9		110–111				12
H	H	$-(CH_2)_6-$				127–128		4.23[a]	2.65[a]	13
CH_3CH_2	H	H	CH_3CH_2	CH_3	$SbCl_6$	108–109		3.96[a]	2.56[a]	13
CH_3	CH_3	CH_3	CH_3			107–108			2.40[a]	13
H	H	t-Bu	t-Bu	CH_3	SO_3F	–		4.40[b]	2.80[b]	16
	Ada			CH_3	ClO_4	199–203 (decomp.)			2.51[b]	14
Ada					Br_3	173 (decomp.)			2.40[c]	

[a] Relative to internal TMS in SO_2 at $-60°$.

[b] $CDCl_3$.

[c] Pure Br_2.

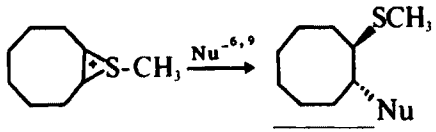
research groups[6,12,14-20] in their efforts to study the chemistry of thiiranium ions and salts. Indeed, being a charged three-membered ring system, thiiranium ions are highly susceptible to nucleophilic attack. Extensive experimental data show that, contrary to expectations, the most usual result of nonhindered thiiranium ion reactions with various nucleophiles is the formation of the corresponding 1,2-adducts arising from predominant C attack by the nucleophile.[6] This reactivity pattern was observed in thiiranium ions derived from alkenes of all kinds. Typical examples are given in Eqs. 15.[6,9,16,17]



(50–90%) (15a)

34

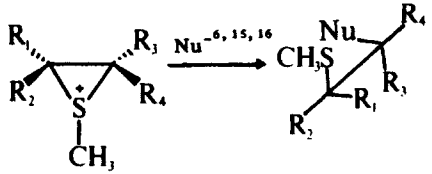
Nu = OH, OCH_3, OAc, F, Cl, SAr, $N(CH_3)_2$, NHCOR, $H(NaBH_4)$, $CH(CO_2CH_3)_2$
R = CH_3, C_6H_5



(70–95%) (15b)

35

Nu = OH, OCH_3, OA_C, $NHCOCH_3$, F, Cl, Br, $S(CH_3)_2$, $H(NaBH_4)$, Py



36 (50–75%) (15c)

37

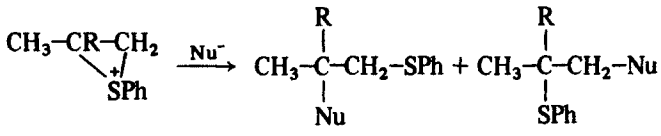
a.[6] $R_1 = R_2 = R_4 = H$; $R_3 = Ph$ (50–75%) Nu = OH, OCH_3, OAc, $NHCOCH_3$
b.[16] $R_1 = R_3 = H$; $R_2 = R_4 = t$-Bu (70–86%) Nu = OH, OCH_3, Cl, Br

Significantly, the stereochemistry of the products in the cyclic cases (e.g., Eqs. 15a and 15b) is *trans*, and that of adducts **37b** in Eq. 15c was assigned as *threo*.[16] Similarly, *trans*-2,3-dimethyl(*S*-aryl)thiiranium ions afforded exclusively *erythro* adducts, whereas the *cis* isomers afforded exclusively the *threo* adducts regardless of the nature of the *S*-aryl substituent or the variation of nucleophiles used in quenching.[15,20] It should be kept in mind, however, that thiiranium ions that are configurationally stable at low temperatures are capable of undergoing stereoconversion when moderately heated.[16]

The relative ease of the quenching reactions of thiiranium ions with various nucleophiles (many of the reactions of Eqs. 15 are usually complete within minutes even below 0°) demonstrates the typical cationoid electrophilicity and consequently

the chemical reactivity that is to be expected of such cyclic ions. It is noteworthy that the ring opening in the case of **36b** appears, at least on the basis of the evidence now available, to involve attack of a nucleophile at a (sterically badly hindered) neopentyl carbon rather than by the alternative "sulfurane mechanism" (first attack on the sulfur atom; discussed later). At any rate, σ-sulfurane analogous to **31** can presumably consume no more than one equivalent of oxidizing agent,[28] whereas oxidation to the respective sulfoxides and sulfones of **37** was carried out with the required amounts of *m*-chloroperbenzoic acid.[16]

Opening of the ring of thiiranium ions leads to the predominant or exclusive formation of regioisomer **38**[6,19]:



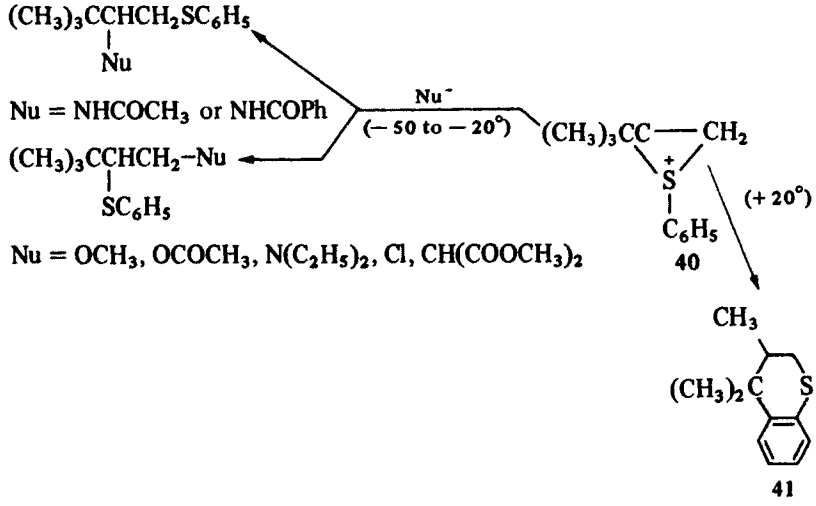
(16)

38 (M-adduct) **39** (aM-adduct)

a. R = H: **38**:**39** = 3:1 (Nu = OAc); **38**:**39** = 19:1 (Nu = F)
b. R = CH_3: **38**:**39** > 19:1 (Nu = OAc, OH, OCH_3)

Data concerning the influence of functional group substituents on the direction of the ring-opening attack by chloride ion[31] indicated that steric factors are quite important, preferential attack occurring at the least substituted carbon. However, the extent of thiiranium ion ring opening at the α-carbon decreases with decreasing ability of the functional group to accommodate a nucleophile (acid chloride > ester > amide > nitrile > sulfone).[31]

Finally, it was shown[20] that although the *t*-butyl-substituted thiiranium ion **40** is quite stable at -50 to $-20°$ and affords the usual 1,2-adducts on quenching,[15] it undergoes rearrangement by warming to $+20°$, resulting in the exclusive formation of **41**. This corresponds to a 1,2-methyl shift in the thiiranium ion, with the subsequent intramolecular aromatic alkylation of the *S*-aryl moiety[20]:



(17)

40

41

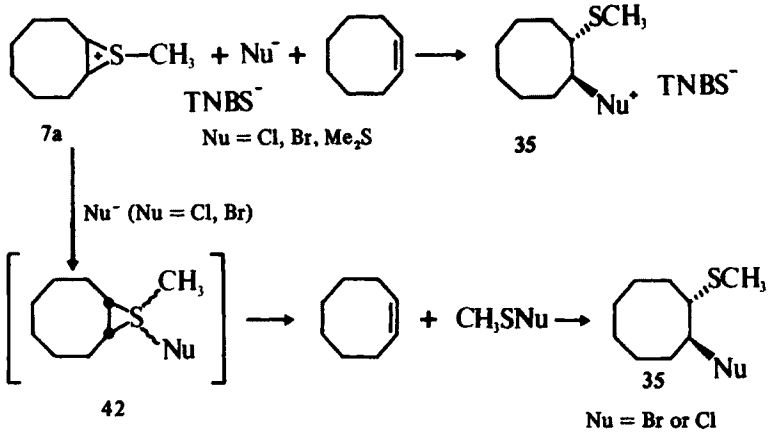
It thus appears that thiiranium ions (salts) should be regarded as "masked" carbenium ions capable of undergoing reactions that are typical for the latter, provided the appropriate conditions are applied. *S*-Chlorothiiranium ions are presumed to be intermediates in chlorinations of thiiranes. As expected, the final products of this reaction are the appropriate diasteromers (of β-substituted sulfenyl chlorides) obtained by the cleavage of the carbon-sulfur bond in the thiiranium intermediate by the nucleophilic counterion at the carbon ring.[16]

In a way, thiirane oxides may also be considered to be a special case of thiiranium ions. However, their reactions and chemistry are treated and discussed separately (see Section VII).

Taken together, the foregoing data leave no reasonable alternatives to the suggested (and widely accepted) structure of thiiranium ions.[15] The existence of bridging in these entities is strongly supported by their ability to form both Markovnikov and anti-Markovnikov adducts on quenching and the preference for rear-side nucleophilic attack leading to *trans* stereochemistry in the adducts. Their chemical behavior in several aspects patterns that of the open carbonium ion: attack at carbon atom for various nucleophiles, stereomutations, and skeletal rearrangements. Such behavior requires substantial positive charge localization on the carbon atoms of the ring or a comparatively low activation barrier for the thiiranium ring ion–open ion transition.[15] However, the alternative covalent sulfurane structure initiated by initial attack of the nucleophile at sulfur, should be equally considered to be an adequate representation of the thiiranium intermediates under appropriate reaction conditions (see Sections IV, 2 and IV, 3, B).

B. *Nucleophilic Attack at Sulfonium Sulfur*

The reaction path in which a nucleophile attacks at the positively charged sulfur in the thiiranium ion (path *b*, above), leads to either stable or unstable sulfenyl compounds, or reactive sulfenyl compounds that can be added to alkenes present in the reaction mixture.[9,12] An example is given in Eq. 18.[12]



(18)

It should be noted, that although **7a** ultimately provides **35** on treatment with chloride or bromide, it reacts initially at sulfur providing an unstable σ-sulfurane (**42**), which decomposes to methane sulfenyl halide and cyclooctene. Subsequent reaction between these two reagents provides ultimately **35**. Apparently, the rate of nucleophilic attack at sulfur in this and other similar cases is appreciably greater than S_N2 displacement at carbon.

Ultimate desulfurization (with retention of configuration of the alkene produced; e.g., **27** was observed in the reactions of the particularly hindered thiiranium salt **28a** with various nucleophiles in $CDCl_3$ at 35°.[14]

$$\mathbf{28a} + Nu^- \longrightarrow \mathbf{27} + MeSSMe \qquad (19)$$
$$Nu = Cl, Br, I, N_3, MeLi, MeS$$

Desulfurization leading to adamantilideneadamantane (**27**) was the exclusive reaction (*ca.* 100% yield) except for the reactions with chloride and bromide, which are capable of demethylating **28a** to give the corresponding thiirane (i.e., **43**) in addition to **27**.

Based on ^1H nmr monitoring of the reactions involved as well as trapping experiments (of the sulfenyl halide present in the reaction mixture), the following course of the reaction shown in Eq. 19 for the case of Br^- was proposed[14]:

$$\begin{array}{ccc} \mathbf{28a} + Br^- & \rightleftharpoons & \mathbf{27} + MeSBr \\ \downarrow\ Br^- \text{ (demethylation)} & & \uparrow\downarrow\ Br^- \\ \mathbf{43} + MeBr & & 0.5\ MeSSMe + Br_3 \end{array} \qquad (20)$$

A sulfurane analogous to **42** formed by initial attack at sulfur was proposed to be a reasonable intermediate in the reaction of Eq. 20, although its concentration is probably insufficient to be detectable. For the case of chloride and bromide as nucleophiles the desulfurization reaction is reversible.[14] Analogous processes have been proposed for nucleophilic displacement on silicon.[28]

The treatment of **7a** with iodide ion, tributyl amine, or fluoride ion yielded the cyclooctene as a result of desulfurization.[9,12] Similarly, small amounts of *cis*- and *trans*-di-*tert*-butylethylenes were noted in the reaction of **36b** with tetrabutylammonium iodide.[16] It was also observed[17] that more highly polarizable nucleophiles gave higher yields of cyclooctenes from **7a**, demonstrating the higher polarizability of the positively charged sulfur compared with that of the carbon atom in the same three-membered thiiranium ring.

All the above results do suggest the intermediacy of σ-sulfurane in several reactions of thiiranium salts with nucleophiles. It appears that in nonhindered thiiranium salts there is a competition between initial C-attack and S-attack and that steric factors (and apparently reaction conditions) affect markedly the rates of these competing processes. Excessive steric hindrance stops the nucleophilic attack on the carbon atom of the ring, whereas S-attack is suppressed in cases like **36b**[16] because the attack must be *syn* to the *t*-butyl groups.

The direct observation of the presumed sulfurane intermediate (**42**, Nu = Cl; the cyclooctane equivalent of **31**) was made by the rise and decay of a transient

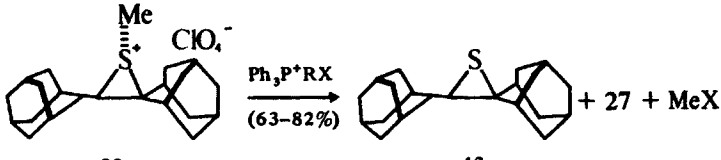
nmr signal at 2.03δ, which could be attributed to the *S*-methyl group, when mixing equal amounts of cyclooctane-*S*-methylthiiranium 2,4,6-trinitrobenzenesulfonate (**7a**) and tetraphenylarsonium chloride in perdeuteronitromethane.[17] The solutions of this intermediate were stable for at least 30 min at this temperature. By the addition of excess chloride ion at $-5°$ or by warming to room temperature, the intermediate sulfurane decomposed to (**35**, Nu = Cl).

Although these results are in accord with the "sulfurane mechanism" (i.e., initial attack on the sulfur atom) in the reactions of several thiiranium salts with certain nucleophiles, they raise a question about the universal role of these salts (ions) in ionic sulfenyl halide addition reactions.[29] It is reasonable to expect a sulfurane intermediate to be the product of the first elementary process. Subsequently, a thiiranium salt may or may not be involved, and the transition state for the entire process could be variable with structures of reactants and reaction conditions as well.[6,9,14]

The initial attack of thiiranium salts by soft nucleophiles[30] at sulfur might be explained in terms of the empty 3*d* orbitals of the latter. Possibly, the effect of both the positive charge on the polarizable sulfur atom and the ring strain may make the 3*d* orbitals of sulfur more energetically accessible for bonding interaction with a nucleophile.[17]

C. *Dealkylation*

Dealkylations of thiiranium salts to afford the corresponding thiiranes and the alkylated nucleophiles have been observed in the reaction of the highly hindered thiiranium salt **28a** with chlorides and bromides[14]:



28a RX = CH_2PhCl or CH_3Br **43** X = Cl or Br (21)

The course of the reaction shown in Eq. 21 is illustrated in Eq. 20. This kind of dealkylation is obviously a much higher energy pathway than the ordinary nucleophilic attack on either the sulfur atom or the carbon atom of the thiiranium ring (leading to desulfurization or ring-opening substituted adducts). It can be accomplished, however, with highly hindered thiiranium salts, where the steric factors involved assist markedly in keeping the ring from being cleaved by the nucleophile.

D. *Thiiranium Ions as Intermediates in Reactions*

The inception of thiiranium chemistry can be traced back to the work of Kharash

et al.,[1] who interpreted the mechanism of the addition of sulfenyl halides to alkenes in terms of the formation of a thiiranium intermediate that is intercepted by halide ion to form a β-halosulfide. It was claimed later[15] that it is implausible to suppose that thiiranium ions similar to 1 could be formed at the rate-determining step of Ad_E reaction of sulfenyl halides with alkenes. However, thiiranium ions were alleged to be formed and have been suggested as definite intermediates in many chemical reactions. Thus, the involvement of thiiranium ions has been invoked in several photochemical rearrangements,[32] as well as in numerous reactions where the initial addition of positive sulfur species, RS^+ (usually derived from sulfenyl halides) to olefins has been assumed.[33] Thiiranium ions are popular intermediates in reactions involving a good leaving group beta to a sulfide functional group. As already discussed, rearrangement and a *trans* stereochemistry with respect to the entering nucleophile (as well as the leaving group) and the sulfur-containing group often are observed when the above situation occurs.[34] Significantly, solvolysis of ω-halogenoalkyl sulfides reveals that the three-membered thiiranium ions are formed more rapidly than five-membered sulfonium ions.[35] Thiiranium ylids have been also postulated as intermediates.[36] All the foregoing points, as well as additional information concerning thiiranium ions as reaction intermediates, are briefly reviewed in References 18c and 18d, to which the interested reader is referred.

4. References

1. N. Kharasch and C. M. Buess, *J. Am. Chem. Soc.*, 71, 2724 (1949).
2. (a) N. S. Isaacs and K. Neelakantan, *Can. J. Chem.*, 46, 1043 (1967); (b) N. V. Schwartz, *J. Org. Chem.*, 33, 2895 (1968).
3. (a) R. Bird and C. J. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1221 (1973); (b) E. Block, *Reactions of Organosulfur Compounds*, Academic Press, New York, 1978, Chap. 4.
4. I. Roberts and G. E. Kimbal, *J. Am. Chem. Soc.*, 59, 947 (1937).
5. K. D. Gunderman, *Angew. Chem., Int. Ed. Engl.*, 2, 674 (1963).
6. W. A. Smit, N. S. Zefirov, I. V. Bodrikov and M. Z. Krimer, *Acc. Chem. Res.*, 12, 282 (1979).
7. G. H. Schmid and T. T. Tidwell, *J. Org. Chem.*, 43, 460 (1978).
8. (a) N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, 82, 6418 (1960); (b) N. J. Leonard, K. Jann, and I. V. Paukstelis, *J. Org. Chem.*, 28, 1499 (1963); (c) A. T. Bottini and R. L. Vanetten, *ibid.*, 30, 575 (1965); G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *ibid.*, 30, 666 (1965).
9. G. K. Helmkamp and D. C. Owsley, *Mech. React. Sulfur Compd.*, 4, 37 (1969).
10. L. Goodman, A. Benitez, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 1680 (1958).
11. P. P. Budnikov and E. A. Schilow, *Chem. Ber.*, 55B, 3848 (1922).
12. D. J. Pettitt and G. K. Helmkamp, *J. Org. Chem.*, 29, 2702 (1964).
13. G. Capozzi, O. DeLucchi, V. Lucchini, and G. Modena, *Tetrahedron Lett.*, 30, 2603 (1975).
14. J. Bolster and R. M. Kellogg, *J. Chem. Soc., Chem. Commun.*, 630 (1978).
15. W. A. Smit, M. Z. Krimer, and E. A. Vorobeva, *Tetrahedron Lett.*, 2451 (1975).
16. P. Raynolds, S. Zonnebelt, S. Bakker, and R. M. Kellogg, *J. Am. Chem. Soc.*, 96, 3146 (1974).

17. (a) G. H. Helmkamp, D. Owsley, W. M. Barness, and H. N. Cassey, *J. Am. Chem. Soc.*, 90, 1635 (1968); (b) D. Owsley, G. H. Helmkamp, and S. N. Spurlock, *ibid.*, 91, 3606 (1969); (c) D. Owsley, G. H. Helmkamp, and M. F. Rettig, *ibid.*, 91, 5238 (1969); (d) V. Calo, G. Scorrana, and G. Modena, *J. Org. Chem.*, 34, 2020 (1969).

18. (a) W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, 8, 482 (1969); (b) D. R. Christ and N. J. Leonard, *ibid.*, 8, 962 (1969); (c) D. H. Reid (Senior Reporter), *Organic Compounds of Sulfur, Selenium and Tellurium*, Vols. 1–3, The Chemical Society, London, 1970, 1973, 1975; (d) D. R. Hogg (Senior Reporter), *ibid.*, Vols. 4 and 5, 1977, 1979.

19. (a) W. A. Smit, A. S. Gybin, V. S. Bogdanov, M. Z. Krimer, and E. A. Vorob'eva, *Tetrahedron Lett.*, 1085 (1978); (b) A. S. Gybin, W. A. Smit, M. Z. Krimer, E. A. Vorob'eva, and V. S. Bogdanov, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, 510, 2156 (1978); (c) A. S. Gybin, M. Z. Krimer, W. A. Smit, N. S. Zefirov, L. U. Novgorodtseva, and N. K. Sadovaja, *Zh. Org. Khim.*, 15, 1361 (1979).

20. (a) E. A. Vorob'eva, M. Z. Krimer, and V. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 12, 2743 (1976); (b) *ibid.*, 12, 1318 (1976).

21. D. J. Pettit and G. K. Helmkamp, *J. Org. Chem.*, 28, 2932 (1963).

22. G. A. Olah and P. J. Szilagyi, *J. Org. Chem.*, 36, 1121 (1971).

23. Y. Kikuzono, T. Yamabe, S. Nagata, H. Kato, and K. Fukui, *Tetrahedron*, 30, 2197 (1974).

24. V. M. Csizmadia, G. H. Schmid, P. G. Mezey, and I. G. Csizmadia, *J. Chem. Soc., Perkin Trans. 2*, 1019 (1977).

25. I. V. Bodrikov, T. S. Ganghenko, and N. S. Zefirov, *Dokl. Akad. Nauk SSSR*, 226, 831 (1976).

26. (a) G. A. Olah, P. R. Cliford, Y. Halpern, and R. G. Johanson, *J. Am. Chem. Soc.*, 93, 4219 (1971); (b) H. C. Brown and E. N. Peters, *ibid.*, 95, 2400 (1973).

27. W. A. Thaler, *J. Org. Chem.*, 34, 871 (1969).

28. L. H. Sommer, *Stereochemistry, Mechanism and Silicon*, McGraw-Hill, New York, 1965.

29. W. L. Orr and N. Kharasch, *J. Am. Chem. Soc.*, 78, 1201 (1956).

30. (a) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, 84, 16 (1962); (b) R. G. Pearson and J. Songstadt, *ibid.*, 89, 1827 (1967).

31. (a) W. A. Thaler, W. H. Mueller, and P. E. Butler, *J. Am. Chem. Soc.*, 90, 2069 (1968); (b) H. Chartier and R. Vessier, *C.R. Acad. Sci. Paris, Ser. C*, 270, 646 (1970).

32. M. Maeda and M. Kojima, *Tetrahedron Lett.*, 3523 (1973).

33. (a) R. D. Rieke, S. E. Bales, and L. C. Roberts, *J. Chem. Soc., Chem. Commun.*, 974 (1972); (b) S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.*, 94, 7169 (1972); (c) K. Izawa, T. Okuyama, and T. Fueno, *J. Am. Chem. Soc.*, 95, 4090 (1973).

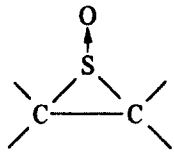
34. (a) G. A. Hull, F. A. Daniker, and T. F. Conway, *J. Org. Chem.*, 37, 1837 (1972); (b) G. S. Bethell and R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 2*, 1400 (1973); (c) N. Wigger and C. Ganter, *Helv. Chim. Acta*, 55, 2769 (1972); (d) D. I. Greichute, Y. Y. Kulis, and L. P. Rasteikene, *J. Org. Chem. (USSR)*, 9, 1860 (1974); (e) C. Leory, M. Martin, and L. Bassery, *Bull. Soc. Chim. Fr.*, 590 (1974).

35. R. Bird and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1221 (1973); *ibid.*, 1215 (1973).

36. (a) S. S. Hixon and S. H. Hixon, *J. Org. Chem.*, 37, 1279 (1972); (b) I. Ojima and K. Kondo, *Bull. Chem. Soc. Jpn.*, 46, 1539 (1973); (c) A. G. Schultz and R. H. Schlessinger, *Tetrahedron Lett.*, 4787, 4791 (1973); (d) P. S. Skell, K. J. Klabunde, J. H. Plonka, J. S. Roberts, and D. L. Williams-Smith, *J. Am. Chem. Soc.*, 95, 1547 (1973).

V. THIIRANE OXIDES

The three-membered ring system containing an oxidized sulfur atom (**1**) shows some structural and chemical features that make its members interesting candidates for both theoretical and experimental investigations.



1

Fortunately, thiirane oxides are thermodynamically more stable than their closely related thiiranium salts on the one hand and thiirane dioxides on the other hand. They are also more resistant to ring opening by nucleophiles or electrophiles than are the other two counterparts just mentioned. Until about 15 years ago they were rather rare;[1] indeed only one example had been reported, and its structure was not well characterized.[2] Since 1965 synthetic methods for the preparation of thiirane oxides have been explored consistently and systematically. At present, several well-established methods are available for their convenient preparation, the two major ones being the controlled oxidation of thiiranes[3] and the reaction of sulfines with diazoalkanes[4] (see Section V, 1).

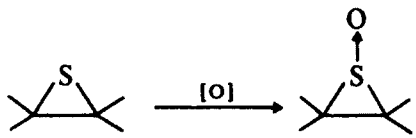
Generally speaking, thiirane oxides are rather stable compounds, provided they have *anti-* configuration with respect to the substituent(s) and sulfinyl oxygen. Those bearing one or more alkyl substituents and oxygen on the same side of the three-membered ring were quite unstable at room temperature: intramolecular hydrogen abstraction from the substituent followed by ring opening occurred, and allylic thiosulfinates were obtained as products.[3]

Both the physical and spectroscopic characteristics and the chemical properties of sulfoxides have been extensively studied, including their potential as synthetic intermediates. The chemistry of these compounds as well as methods for their synthesis have been reviewed.[5]

1. Methods of Preparation

A. *By Oxidation of Thiiranes*

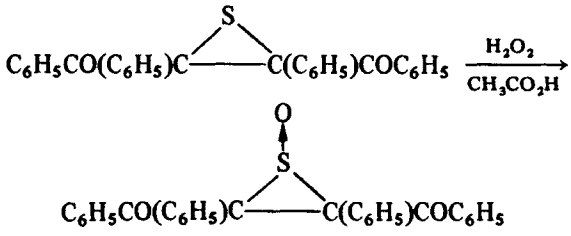
The straightforward oxidation of thiiranes to the corresponding thiirane oxides is the most logical method of obtaining the latter:



(1)

Surprisingly, however, nearly all attempts to oxidize thiiranes to the corresponding sulfoxides up to 1965 resulted in ring-opened products.[6] This result can be attributed either to the instability of the three-membered sulfoxides obtained or to the overoxidation to the corresponding thermally and/or chemically sensitive sulfones that could not survive the reaction conditions employed. Consequently, controlled oxidations under mild reaction conditions have had to be worked out to make this direct and simple route applicable for differently substituted thiiranes.

The first thiirane oxide to be prepared and structurally fully characterized appears to be the 2,3-diphenyl, 2,3-dibenzoylthiirane oxide (**2**)[1]:



(2)

2

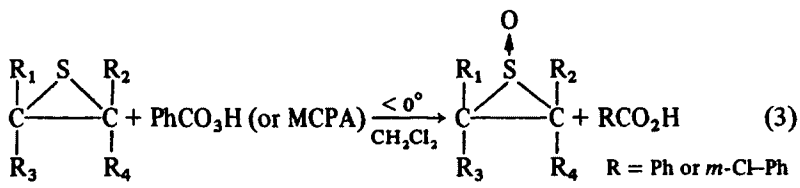
The oxidation was done using a limited amount of hydrogen peroxide with mild heating. Two isomeric thiirane sulfoxides (m.p. *ca.* 170° and *ca.* 145°, respectively) of the four possible isomers (DL-*trans* pair and two *meso-cis* forms) were isolated depending on the upper limit of heating during the oxidation. A later study,[6a] however, claims all the structural assignments of the above study to be erroneous.

The isolation of the pure parent thiirane oxide was achieved later by oxidizing thiirane either with sodium metaperiodate in methanol[7] or with the *t*-BuOH–H_2O–V_2O_5 system.[8]

The metaperiodate method is rather limited in scope and narrow in applicability: low yields of impure materials have been obtained, since it is difficult to extract the pure low molecular weight thiirane sulfoxides from the reaction mixture, and some of the latter are too unstable to handle under the reaction conditions.

A systematic study was undertaken[3,9] in an attempt to establish a reliable (and a general) oxidation method for the oxidation of thiiranes to the corresponding thiirane oxides, within the framework of which iodosobenzene, *t*-butyl hypochlorite, N_2O_4, H_2O_2, and organic peracids have been applied.

It turns out that either perbenzoic acid or *m*-chloroperbenzoic acid are the reagents of choice and the aprotic methylene chloride is the preferred solvent.[3,9]



(3)

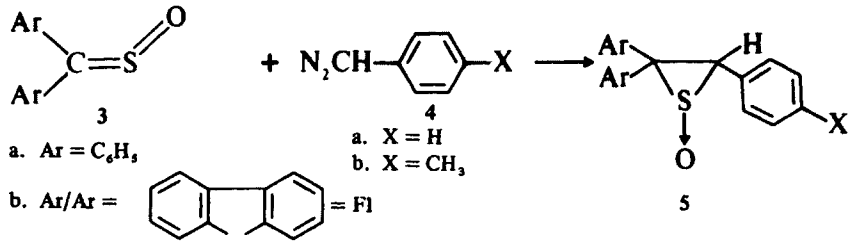
R = Ph or *m*-Cl–Ph

Equimolar amounts of the reactants are used, and the oxidation is completed within minutes. Dry NH_3 is flushed on the surface of the reaction to precipitate

ammonium benzoate, which is practically insoluble in CH_2Cl_2. Filtration affords a solution of essentially pure sulfoxide in almost quantitative yield.[3,9] Thiirane oxide, methyl-, 2,3-*cis*-dimethyl-, chloromethyl-, phenyl-, 2,3-*cis*-diphenyl-, 2,3-*trans*-diphenyl-, and 2,2,3,3-tetraphenylthiirane oxides, as well as the thiirane oxide of cyclohexene, have been prepared through this method[9] (see Table 1, Section III, 1, A). All the above compounds are stable when stored in the refrigerator but decompose gradually at room temperature and instantaneously at 100°. Pure products can be obtained by molecular distillation ($< 10^{-4}$ mm) at room temperature.[9] These thiirane oxides have the *anti* configuration with respect to the substituent(s) and sulfinyl oxygen as determined with the aid of nmr studies[9] (see later, Section V, 2: Structure and Physical Properties). Considering the steric hindrance of substituents in the peracid oxidation, the preferential formation of the *anti* isomer is to be expected. However, there is no significant deuterium isotope effect on the stereoselectivity on the sulfoxidation of *cis*-dideuteriothiirane, the two stereoisomers of the corresponding thiirane oxide being formed in equal amounts.[10]

B. *From the Reaction of Sulfines with Diazoalkanes*

This alternative appears to be the most important nonoxidative method for the preparation of thiirane oxides, particularly aryl-substituted ones. Thus, diarylsulfines (**3**) dissolved in aprotic solvents such as pentane or ether give the thiirane oxides (**5**) in good yields in a smooth reaction with aryldiazomethanes (**4**), as illustrated in Eq. 4.[4,11]

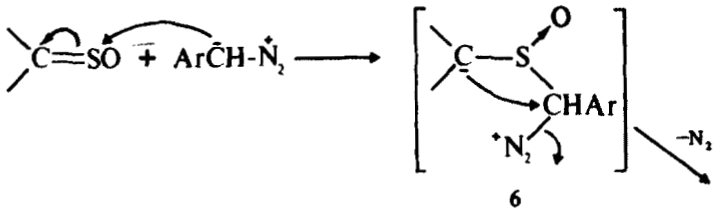


(4)

a. Ar = C_6H_5; X = H
b. Ar = C_6H_5; X = CH_3
c. Ar/Ar = Fl; X = H
d. Ar/Ar = Fl; X = CH_3

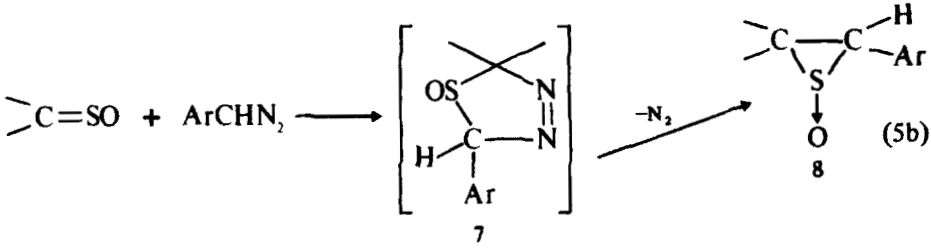
In view of the instability of the highly substituted thiirane oxides **5**, it is essential that the reaction conditions be chosen in such a way that the products crystallize from the cooled reaction mixture; otherwise product isolation is troublesome. Nevertheless, it is possible to obtain pure products even in the cases of sensitive sulfoxides by using ordinary separation methods.[4]

Two independent paths may account mechanistically for the formation of thiirane oxides from the reaction between sulfines and aryldiazomethanes.[4] These are depicted in Eqs. 5.



(5a)

6

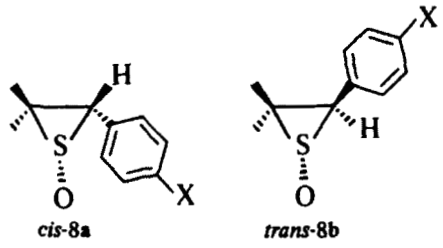


(5b)

7 8

In path Eq. 5a,[12] nucleophilic attack of the diazocarbon at the sulfine sulfur provides a zwitterionic diazonium compound (**6**). Subsequently, an internal 1,3-displacement of nitrogen produces the final thiirane oxide. It appears that steric crowding prevents the formation of the five-membered ring adduct and favors the less congested three-membered ring. In fact, this mechanistic path is analogous to the mechanism proposed to explain the formation of epoxides from ketones and diazo compounds.[13] Furthermore, although thermal extrusion of nitrogen from thiadiazolines to give thiiranes is a common process,[14] the same reaction does not occur in the corresponding *S*-oxides,[14] except in one case,[15] where a cyclic aliphatic *sulfine gave with diazomethane a thiirane oxide as the initially isolated product* instead of the expected five-membered ring system of the Δ^3-1,3,4-thiadiazoline-1-oxide.[16] These results suggest that the most probable mechanism for the non-stereospecific formation of thiirane oxides from sulfines and aryldiazoalkanes is indeed the one represented by Eq. 5a,[12] although Eq. 5b cannot be excluded.

All the thiirane oxides (**8**) having two asymmetric centers that have been obtained through this procedure are mixtures of the two possible *cis* and *trans* configurations (i.e., **8a** and **8b**, respectively):



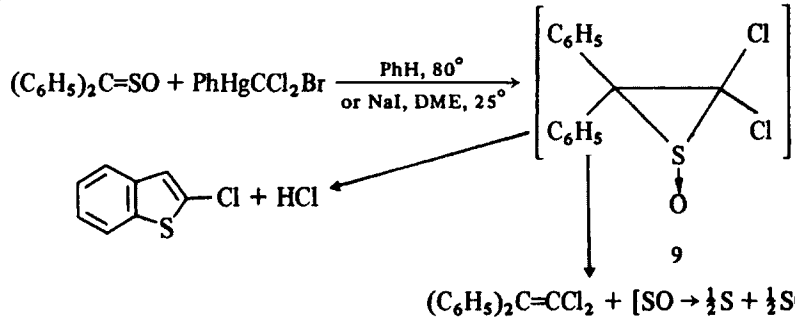
cis-**8a** *trans*-**8b**

Attempts to separate the two components by the usual chromatographic methods failed, owing to the instability of the thiirane oxides, which easily lose sulfur monoxide to give the corresponding olefinic derivatives.[11]

Although the isomer formed in higher quantity is always that thiirane oxide with the S=O bond and the aryl group in the 2-position having the *trans* configuration (*Z*/*E* ratio ranging from 1:4 to 2:3), the oxidation method of preparing thiirane oxides (Section V, 1, A) has the advantage in that pure isomers (having the *trans* configuration with respect to the substituents) can be obtained.

Total yields of the aryl-substituted thiirane oxides obtained by this method as well as the isomeric composition in each case are given in Table 1 (Section V, 1, C).

The reaction of sulfines with a variety of dichlorocarbene precursors has been examined in detail[4,17] in an attempt to synthesize (among others) the *gem*-2,2-dichlorothiirane oxide **9**. However, the intended sulfoxides could not be isolated, although the experimental results support the previously reported suggestion[17] that the intermediate in these reactions is indeed the thiirane oxide **9** as illustrated in Eq. 6.[4]



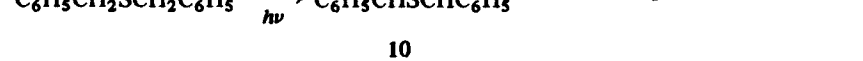
(6)

The decomposition of the highly unstable *gem*-dihalothiirane oxide **9** leads to the products that are finally observed. Several sulfines did not react at all with phenyl(bromodichloromethyl)mercury. It appears, therefore, that dihalocarbenes (and probably other carbenoids) are not appropriate candidates for the preparation of thiirane oxides through their reaction with sulfines.

C. *By Ring Closure of α,α'-Dibromobenzyl Sulfoxides*

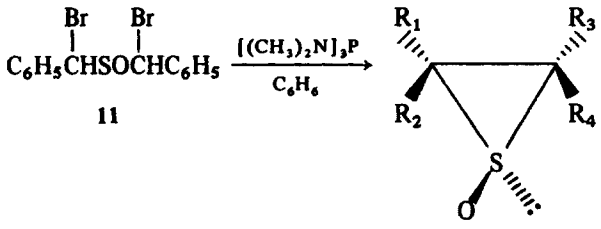
What appears to be a general and efficient nonoxidative route for the preparation of 2,3-diaryl-substituted thiirane oxides has been developed following the work of Carpino et al. on the synthesis of several thiirene oxides[18] and dioxides.[19]

This method involves the photolytic bromination of dibenzyl sulfide followed by the oxidation of the isolable intermediate dibromosulfide **10** to the corresponding mixture of benzylic α,α'-dibromosulfoxides (**11**). 1,3-Elimination of bromine from the dibromide by treatment with tris(dimethylamino)phosphine provides the three-membered sulfoxide stereospecifically[20] as shown in Eq. 7.



(7)

10



a. *meso*-dibromo a.[20] $R_1 = R_3 = C_6H_5$ (from **11a**)
b. (±)-α,α′-dibromo b.[20] $R_1 = R_4 = C_6H_5$ (from **11b**)

The fact that the *meso*-dibromide **11a** gave only *cis*-2,3-diphenylthiirane *trans*-1-oxide **12a**, whereas (±)-α,α′-dibromobenzyl sulfoxide (**11b**) gave only *trans*-2,3-diphenylthiirane 1-oxide (**12b**) reveals that the elimination occurred with inversion of configuration at each reacting center.[20] Such specificity in ring closure offers an advantage to users of this method of thiirane oxide preparation. The scope of the method, however, is practically limited to aryl-substituted members of this class of compounds. Table 1 gives preparation data for some thiirane oxides.

2. Structure and Physical Properties

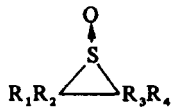
The following bond lengths and angles have been reported for the three-membered ring molecule of the parent thiirane oxide[21]:

Bond length (Å)				Angles			
C–S	C–C	C–H	S–O	< CSC	< HCH	< H_2CC	< OSC
1.822	1.504	1.078	1.483	48°46′	116°0′	151°43′	110°1′

These experimentally based parameters are normal for a three-membered ring containing sulfur. The corresponding geometries of thiirane (see Section III, 2)[22] are quite similar except for the CSC angle which is substantially smaller in the oxide (48°46′ vs. 65°48′ in the thiirane). In both cases, however, the data suggest a partial double bond character for the C–C bond. Since the C–C distance in the corresponding thiirane dioxide has been quoted to be the longest known (1.590 Å),[23] the character (and distance) of this bond appears to reciprocally correlate with the availability of the lone pair(s) of electrons on the sulfur atom of the ring (or equivalently, with its oxidation state).

Delineation of the physical parameters of thiirane oxide with those of the analogous open system (i.e., DMSO)[21,24] is illuminating in that only very minor differences, which probably are insignificant structurally and chemically, can be detected except for the obvious substantial difference in the < CSC of the two:

TABLE 1. PREPARATION OF THIIRANE OXIDES



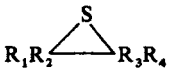
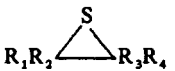
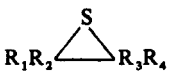
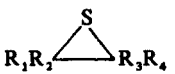
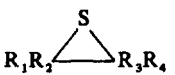
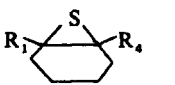
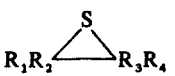
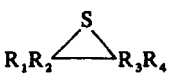
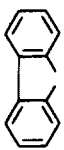
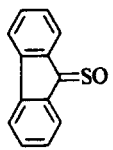
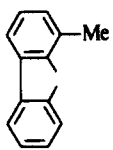
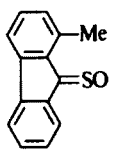
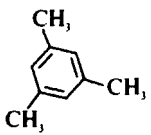
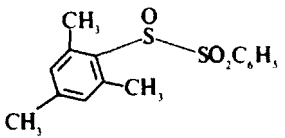
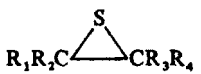
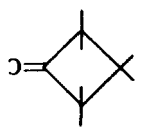
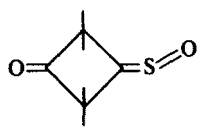
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
H	H	H	H		$NaIO_4$/MeOH	Low	7
					t-BuOH-H_2O/V_2O_5	–	8
					$PhCO_3H$ (or MCPA)	77	3, 9
H(D)	H(D)	H	D		MCPA	37[a] (*trans*:*cis* = 95:5)	10
CH_3	H	H	H		$PhCO_3H$ (or MCPA)	54	3, 9
CH_3	H	CH_3	H	 (*cis*)	$PhCO_3H$ (or MCPA)	41	3, 9
CH_2Cl	H	H	H		$PhCO_3H$ (or MCPA)	50	3, 9
H	$-(CH_2)_4-$		H		$PhCO_3H$ (or MCPA)	50	3, 9
C_6H_5	H	H	H		$PhCO_3H$ (or MCPA)	52	3, 9
C_6H_5	H	C_6H_5	H	 (*cis* and *trans*)	$PhCO_3H$ (or MCPA)	88–90	3, 9

TABLE 1. (CONTINUED)

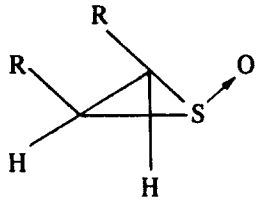
R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Ref.
				$C_6H_5CH(Br)-SO-CH(Br)C_6H_5$	$[(CH_3)_2N]_3P$	–	20
C_6H_5	C_6H_5	C_6H_5	H		Monoperphthalic acid	60	11
				$(C_6H_5)_2C=SO$	$C_6H_5CHN_2$	21 (*trans*:*cis* = 72:28)	4, 11
C_6H_5	C_6H_5	p-CH_3–C_6H_4	H		p-CH_3–$C_6H_4CHN_2$	22 (*trans*:*cis* = 83:17)	4, 11
		C_6H_5	H		$C_6H_5CHN_2$	65 (*trans*:*cis* = 63:37)	4, 11
		p-$CH_3C_6H_4$	H		p-CH_3–$C_6H_4CHN_2$	67.5 (*trans*:*cis* = 65:35)	4, 11
		C_6H_5	H		$C_6H_5CHN_2$	39 (*trans*:*cis* = 12:88)	4

	$SO_2C_6H_5$	CH_3	CH_3		$(CH_3)_2CN_2$	72.5 (*trans*:*cis* = 1:1)	12
C_6H_5	C_6H_5	C_6H_5	C_6H_5		$PhCO_3H$ (or MCPA)	70	3, 9
C_6H_5	COC_6H_5	C_6H_5	COC_6H_5		H_2O_2/CH_3CO_2H	–	1
		H	H		CH_2N_2	29	15

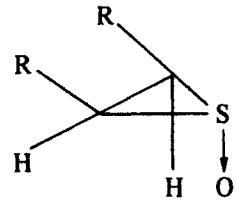
[a] Overall yield starting with (D)H, (H)D  H, D $\xrightarrow[2.\ KSCN]{1.\ MCPA}$ $\xrightarrow[3.\ MCPA]{}$ *trans*- and *cis*-thiirane oxide.

	Thiirane oxide	DMSO
Bond length γ (S–O)	1.483 Å	1.477 Å
Bond length γ (C–S)	1.822 Å	1.810 Å
Bond angle < OSC	110°1′	106°43′
Bond angle < CSC	48°46′	96°23′
Dipole moment	3.72 D	3.96 D

The geometrical position of the oxygen atom in thiirane oxide has been determined by the complete analysis of nmr[25] and microwave spectra.[21,26] It is situated out of plane of the three-membered-ring. Thus, mono- and *cis*-disubstituted thiirane oxides can exist in two conformations; that is, the *syn* isomer **13a** and the *anti* isomer **13b**:



13a



13b

The chemical shifts of the hydrogen on the carbon atom adjacent to the sulfoxide moiety are dependent on their relative configuration with respect to the sulfoxide oxygen (see Section V, 2, B). At any rate, thiirane oxide exhibits an A_2B_2 pattern in its nmr spectrum, indicating a stable pyramidal configuration at sulfur.[9]

Extended Hückel calculations have been performed on thiirane oxide[27] in an analysis of the irregularities in the structure of the series thiirane, thiirane oxide, thiirane dioxide. Contrary to the actual situation, the overlap populations obtained by these calculations[27] showed continuous changes along the series, the CS population increasing and the CC population decreasing.

The vertical ionization energy of thiirane oxide has been determined to be 9.78 eV.[28]

A. *Molecular Orbital Calculations*

A series of *ab initio* MO-SCF calculations using fairly extended Gaussian basis sets has been performed on thiirane oxide to obtain a detailed understanding of the electronic structure of this compound, including the influence of 3*d* orbitals in the strained three-membered ring system (compared with the situation in normal sulfur bond).

The calculated total energy with optimal geometry and the 3*d* orbitals of the sulfur atom (using medium-size contracted Gaussian basis set) was found to be − 549.994 a.u. This value is intermediate between − 475.319 a.u. and − 624.678 a.u. found for the corresponding thiirane and thiirane dioxide, respectively.[29]

TABLE 2. CALCULATED AND EXPERIMENTAL BOND LENGTHS (A) IN THIIRANE OXIDE[21]

	C–C	C–S	S–O
No 3*d* S orbitals	1.463	1.994	1.643
With 3*d* S orbitals	1.505	1.822	1.504
Experimental	1.504	1.822	1.483

Optimal C–C, C–S, and S–O distances have been determined, and the C–H bond distances, the HCH angles, and the CSO angle have been fixed at their experimental values in all the calculations. Calculated bond lengths are presented in Table 2. There is almost complete agreement between calculated (including 3*d S* functions) and observed bond lengths.

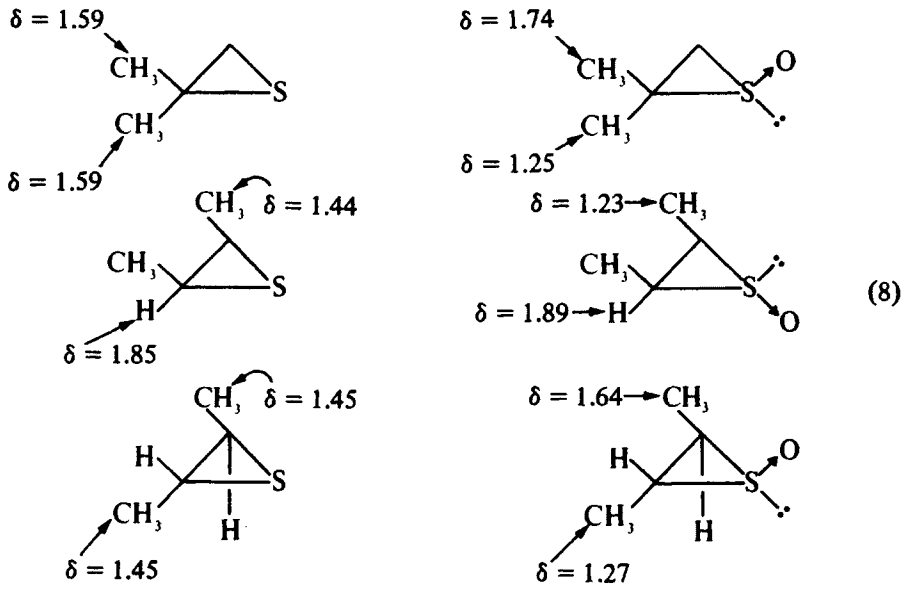
The largest deviation from experiment occurs for the SO bond, and this is strongly connected with the variation of the overlap populations. Calculated equilibrium geometries were found to be in good agreement with available microwave data. The binding mechanism was discussed in terms of a donor-acceptor complex between ethylene and the fragment SO. The variations of the calculated valence state orbital energies, together with the corresponding variations of the C–C overlap populations, can be used to understand the discontinuous variations of the C–C and the C–S bond lengths in the series thiiranes, thiirane oxides, thiirane dioxides. It turns out that the donor-acceptor strength of the fragment X (X = S, SO, and SO_2, respectively) and the 3*d S*-orbital participation are the important factors in understanding the features in these three-membered ring systems. There is no evidence, however, for an increased 3*d S* population in strained sulfur compounds like thiirane oxides.

B. *Nuclear Magnetic Resonance Spectroscopic Data*

Nmr techniques have been extensively used in determining both the configuration and the stereochemistry of thiirane oxides. This technique was particularly useful in choosing between the isomers in the mixtures obtained in the preparation of the oxides. Thus, configurational assignments were based on the accumulated data of the anisotropy effect of the S–O bond.[30]

An acetylenic-type anisotropy and a proximity effect of the S–O bond in cyclic systems have been well documented.[31] In certain six-,[32] five-,[33] and four-[34] membered ring sulfoxides, a β-hydrogen that is *syn* to the S–O bond experiences a profound deshielding effect, whereas a β-hydrogen that is *anti* to the S–O (i.e., *syn* to the lone pair of the sulfur atom) suffers from a shielding effect compared with the same protons of the parent sulfide.

Indeed, the validity of this approach was unequivocally demonstrated[3,9] by an examination of the nmr characteristics of 2,2-dimethylthiirane, *anti-cis*-2,3-dimethylthiirane, *trans*-2,3-dimethylthiirane, and their corresponding sulfoxides. This shielding and deshielding effect of the S–O bond in thiirane oxides on adjacent protons according to their stereo position (relative to this bond) is illustrated in Eq. 8.[3,9]



(8)

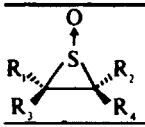
These observations may validate the applicability of the S–O anisotropy rule to the three-membered ring system.

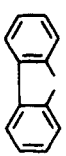
It is worth mentioning in this connection that although a remarkable upfield or downfield shift of β-protons in a rigid system, depending on the direction of the S–O bond, was noted in many cases, the same behavior could not be necessarily observed for the hydrogens directly attached to the three-membered thiirane oxide ring (see, e.g., 8). Occasionally, the shielding and deshielding effects of the S–O bond compensate each other at these hydrogens. The principle has been used successfully, however, to assign the configuration of a number of aryl(tri)-substituted thiirane oxides.[4]

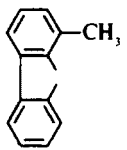
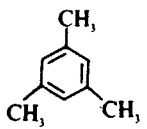
All the above chemical shift-based assignments were further confirmed by solvent-induced shift studies.[3,25b] The geminal coupling constants in thiirane oxide (− 6.4 Hz) and 2-methylthiirane oxide (− 6.0 Hz) were appreciably more negative than those in thiirane (− 0.7 Hz) and 2-methylthiirane (− 0.8 Hz), respectively[25b]; the trend to greater negative values of J_{gem} with increasing group electronegativity of the heteroatom is the converse of the usual nmr behavior of three-membered heterocycles. The vicinal coupling constants for the *syn* protons, namely 11.5 and 11.7 Hz in thiirane oxide, were also abnormal.[25] The fact that ^{1}H coupling constants were found to be of larger magnitude in thiirane oxides (and dioxides) than in thiiranes[35] was interpreted in terms of the Pople–Bothner–By model for spin coupling.[36] However, the larger ^3J values for thiirane oxide were ascribed to greater electronegativity of the SO vs. S in thiiranes. In general, the opposite effect is found in other three-membered heterocycles: an increase in ^3J is found as the electronegativity of the heteroatom decreases[37] and the magnitude of $^3J_{CH}$ roughly parallels $^3J_{HH}$ in this series of compounds.[38]

Chemical shifts for selected thiirane oxides are tabulated in Table 3.

TABLE 3. BOILING POINTS, IR ABSORPTIONS, AND NMR CHEMICAL SHIFTS OF SELECTED THIIRANE OXIDES



R_1	R_2	R_3	R_4	b.p. or m.p. [°C (mm)]	Ir absorption (cm^{-1})	Nmr (ppm; PhH) R_1	R_2	R_3	R_4	Ref.
H	H	H	H	53 (3)	1060	0.84	0.84	1.77	1.77	3
CH_3	H	H	H	Oil	1070, 1050	0.38	0.96	2.29	1.05	3
CH_3	CH_3	H	H	Oil	1080, 1065	0.49	0.49	2.56	2.56	3
CH_3	H	H	CH_3	–	–	0.68	1.38	1.92	1.35[a]	3
CH_2Cl	H	H	H	20–22 (m.p.)	1065	~ 2.3 ~ 2.7	1.24	~ 2.7	2.18	3
CH_3	H	CH_3	H	–	–	0.67	1.50	1.40	1.67[a]	3
$-(CH_2)_4-$		H	H	Oil	1065, 1050	0.46	1.50	2.74	2.74	3
C_6H_5	H	H	H	59–60 (m.p.)	1065	–	1.94	3.59	2.47	3
C_6H_5	C_6H_5	H	H	79 (m.p.)	1065	–	–	4.06	4.06	3
C_6H_5	H	H	C_6H_5	85 (m.p.)	1057	–	3.35	3.92	–	3
C_6H_5	C_6H_5	C_6H_5	C_6H_5	~ 40 (m.p.; decomp.)	1095	–	–	–	–	3
C_6H_5	COC_6H_5	COC_6H_5	C_6H_5[b]	169–173, 145–147 (m.p.)	1065, 1050	7.08	7.42	7.42	7.08[c]	1
C_6H_5	C_6H_5	C_6H_5	H[b]	91–92 (m.p.; decomp.)	1090–1050				4.83[c] 4.42	4, 11
C_6H_5	C_6H_5	p-CH_3–C_6H_4	H[b]	87 (m.p.; decomp.)	1090–1080				4.52[c] 4.18	4, 11
		C_6H_5	H	81–82 (m.p.; decomp.)	1075				5.20[c] 4.56	4, 11

		p-CH_3–C_6H_4	H	80–81 (m.p.; decomp.)	1085		5.16[c] 4.63	4, 11
		C_6H_5	H	84–85 (m.p.; decomp.)	1095–1085		5.25[c] 4.75	4
	$SO_2C_6H_5$	CH_3	CH_3	85–87 (m.p.)	1050	1.01 1.40	1.70 1.78	12

[a] In PhCl.
[b] *cis* and *trans* (mainly).
[c] In $CDCl_3$.

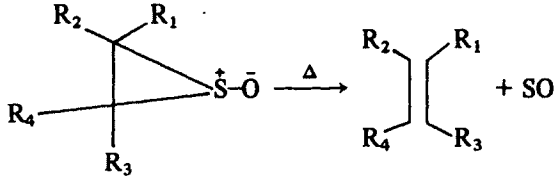
C. *Physical Properties*

The boiling or melting points, the ir absorption of the sulfoxide group, and the nmr chemical shifts of selected thiirane oxides are given in Table 3. Some typical characteristics are apparent: except for the few low molecular weight members, thiirane oxides are low melting solids that are unstable on heating. They can be easily characterized by both ir (strong band at *ca.* 1065 cm^{-1}) and nmr (anisotropy effect of the SO bond) spectra.

3. Chemical Properties and Reactivity

A. *Thermal Decomposition*

It has been generally assumed that thermal decomposition of thiirane oxides proceeds to the corresponding olefins by elimination of sulfur monoxide, possibly through a concerted nonlinear cheletropic reaction[39] with retention of configuration of the liberated olefin:



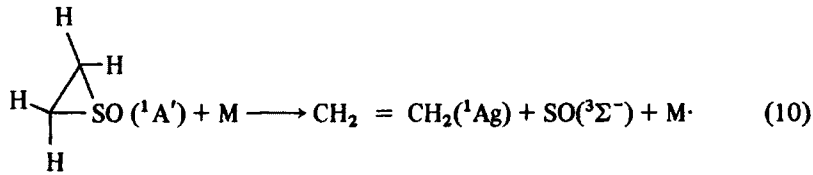
(9)

1a

This pattern was first observed through mass spectrometry and differential thermal analysis[7] and was used later as an effective source of sulfur monoxide[40] that reacted with dienes to yield cyclic sulfoxides.

Although the parent thiirane oxide is known to decompose at 100°, thiirane oxides bearing alkyl groups are unstable at ambient temperature. Their decomposition pathway, however, is different from that depicted in Eq. 9 (see Eq. 11, below).

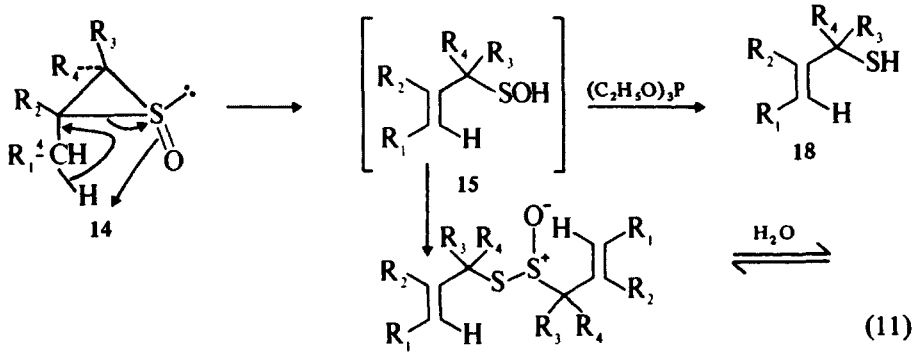
Pyrolysis of thiirane oxide followed by microwave spectroscopy to determine the electronic state in which the sulfur monoxide is generated in Eq. 9 led to the conclusion that the main reaction of the thermal decomposition is the following[41]:



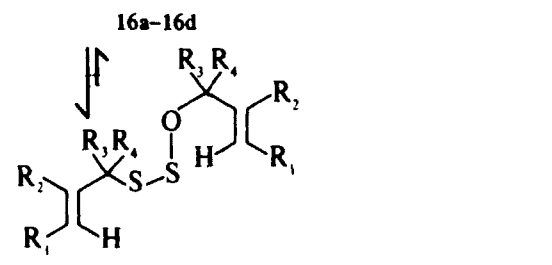
(10)

However, the possibility of the reaction that proceeds via the SO in the $^1\Delta$ state should not be excluded completely. A later study[41a] presented evidence based on the mechanism of the reaction of SO generated from thiirane oxide with dienes as well as thermochemical data that the ground state $^3\Sigma^-$ is formed exclusively.

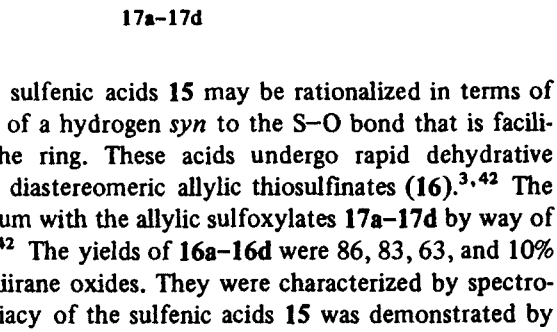
In the presence of α-alkyl substituents bearing suitably disposed hydrogen atoms, there occurs a more facile pathway for the thermal decomposition of thiirane oxides: namely, thermal rearrangement to the allylic sulfenic acids (**14** → **15**). This rearrangement has been found and described independently by two groups[3,42] and is shown in Eq. 11.



14 **15** **18**



16a–16d



17a–17d

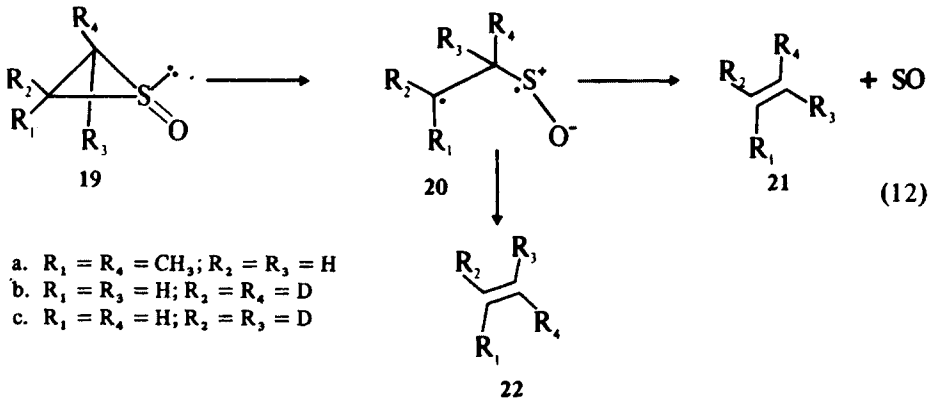
(11)

a. $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$
b. $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$
c. $R_1, R_2 = -(CH_2)_4-$; $R_3 = R_4 = H$
d. $R_1 = R_2 = R_3 = R_4 = H$

The formation of the allylic sulfenic acids **15** may be rationalized in terms of an intramolecular β-elimination of a hydrogen *syn* to the S–O bond that is facilitated by relief of strain in the ring. These acids undergo rapid dehydrative dimerization[43] to a mixture of diastereomeric allylic thiosulfinates (**16**).[3,42] The latter are themselves in equilibrium with the allylic sulfoxylates **17a–17d** by way of 2,3-sigmatropic rearrangements.[42] The yields of **16a–16d** were 86, 83, 63, and 10% respectively,[3] based on used thiirane oxides. They were characterized by spectroscopic analyses.[3] The intermediacy of the sulfenic acids **15** was demonstrated by their interception with triethylphosphite (a well-known trapping agent for sulfenic acid[44]) to give a 1:1 mixture of allylic mercaptan (**18**) and triethyl phosphate.[42]

Although there is no definitive evidence for the intramolecularity of the hydrogen abstraction, the presence of hydrogen on α-carbon of the ring substituent that is *syn* to the S–O bond is essential for the formation of the allylic thiosulfinates. Other thiirane oxides afford on thermolysis only olefins and sulfur monoxide.[3] However, rapid thermolysis of thiirane oxides of type **14** at high temperatures (200–340°), rather than at room temperature or lower, afforded mixtures of *cis*- and *trans*-olefins with the concomitant extrusion of sulfur monoxide.[42] The rationale proposed[42] for all these observations is that thiirane oxides may thermally

decompose by two routes: the first is a facile rearrangement to a sulfenic acid when the stereochemistry is favorable (Eq. 11, **14** → **15**), and the second is a pathway of higher activation energy (Eq. 12) that leads through a partially stereospecific route to the olefins and sulfur monoxide:



19 **20** **21** **22** (12)

a. $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
b. $R_1 = R_3 = H$; $R_2 = R_4 = D$
c. $R_1 = R_4 = H$; $R_2 = R_3 = D$

Diradical intermediates like **20** are readily formed in high temperature reactions of dipolar or ylid species.[45]

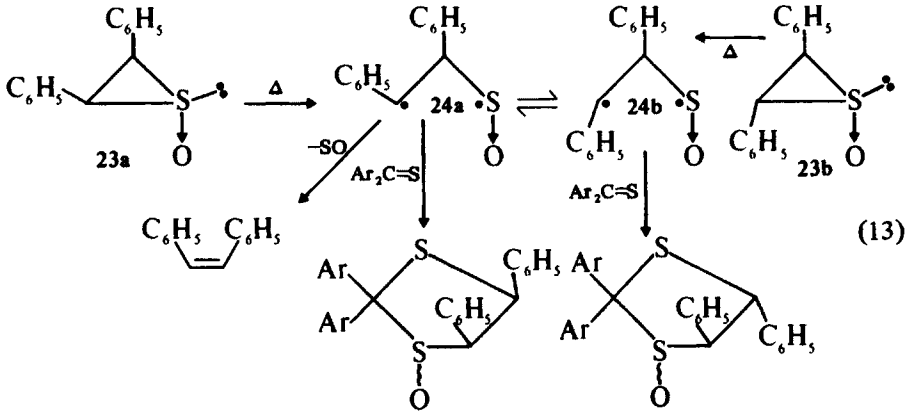
Pyrolysis of **19b** and **19c** in the gas or solution phase (150–350°) gave deuterated ethylenes (i.e., **21b** from **19b** and **21c** from **19c**) with about 95% retention of stereochemistry.[10] These results indicate that thiirane oxides are not unusual in their thermal behavior when compared with their higher or lower oxidized analogs, suggesting analogous modes of extrusion of the sulfur-containing species. Although a rather stereochemically rigid "biradical" (**20**) of the type proposed in thiirane decompositions[46] may account mechanistically for the results, a significant contribution from a concerted process cannot be ruled out.

Pyrolysis of the stereoisomeric 2,3-diphenylthiirane oxide proceeded smoothly in both liquid and gas phases to produce stilbenes in more than 70% yield and sulfur monoxide.[47] The extrusion of SO from the *trans* isomer proceeds almost stereospecifically, whereas that from the *cis* isomer occurs with complete loss of stereochemistry. This is indicative of a stepwise mechanism, not a symmetry-allowed nonlinear cheletropic reaction.[39] Based on the failure of all attempts to trap an intermediate with 1,3-dipolarophiles, whereas a 1 : 1 adduct was obtained in good yield (*ca.* 60%) with the carbon radical scavenger di-*p*-anisyl thioketone,[48] the following mechanistic scheme has been proposed for the unimolecular thermal fragmentation of **23**.[47]

This scheme is essentially in accord with Eq. 12. Although the radical intermediates are capable of internal rotation about the carbon-carbon bond; rotation for the 2,3-diphenyl case (Eq. 13) would be restricted owing to the steric repulsion of the two phenyl groups, conformer **24b** being thermodynamically more favorable.

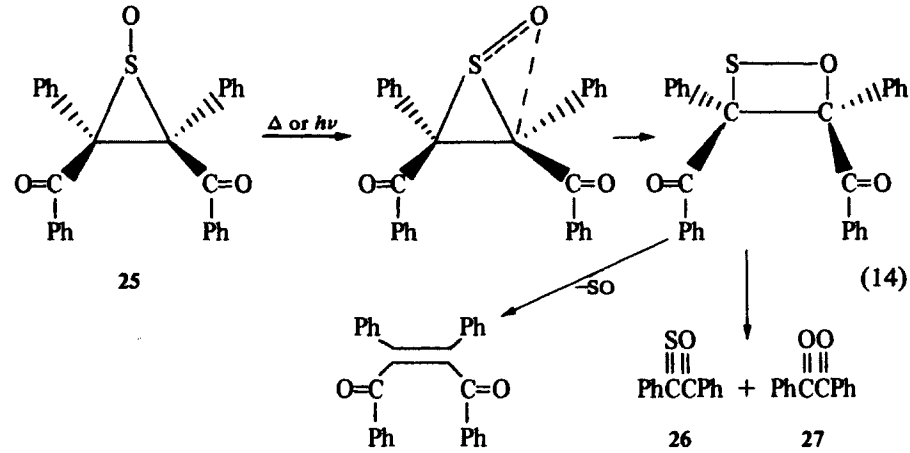
At any rate, the thermal fragmentation of thiirane oxides to afford olefins and sulfur monoxide is a general process typical for this class of compounds.

2,3-Dibenzoyl-2,3-diphenylthiirane oxide (**25**) behaves very differently from the



(13)

thiirane oxides previously discussed. Thus, pyrolysis or photolysis of **25** yields monothiobenzil **26** and benzil **27** with little *cis*- (**28**) and *trans*-dibenzoylstilbene.[48] The stereochemistry at sulfur has no effect on the mode of decomposition. A mechanism that involves ring expansion of the sulfoxide was suggested for the formation of the products in both the thermolysis and the photolysis[48] and is given in Eq. 14.



(14)

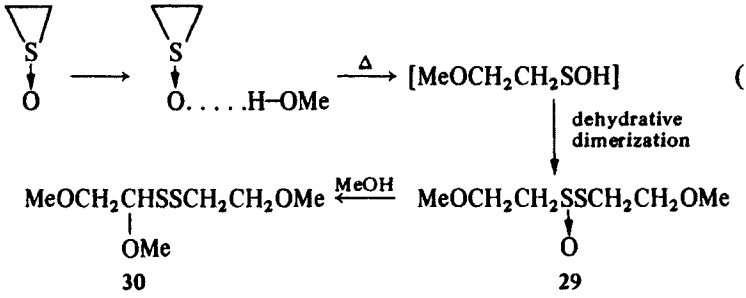
Expansions of cyclic sulfones to cyclic sulfinates are known,[49] and the oxathietane may decompose to four-membered peroxides (1,2-dioxetanes).[50] Strain in the three-membered ring **25** will dispose it to opening, but the influence of the electrophilic benzoyl and phenyl group can lead to the formation of the four-membered ring intermediate, which is less strained than its precursor.

A similar mechanistic pathway of three-membered ring expansion to a four-membered ring, has been suggested for the photolytic fragmentation of the analogous 2,3-diphenylthiirene oxide.[18]

Finally, the thermal reaction of thiirane oxide in methanol (90°) gave 2-

methoxyethyl,2-methoxyethanethiol sulfinate **29**, which was further transformed into 1,2,2′-trimethoxydiethyl disulfide (**30**) in 85% yield[53] by a Pummerer-type rearrangement.[52]

Based on further studies the following mechanism has been proposed to accommodate all the experimental results[51]:



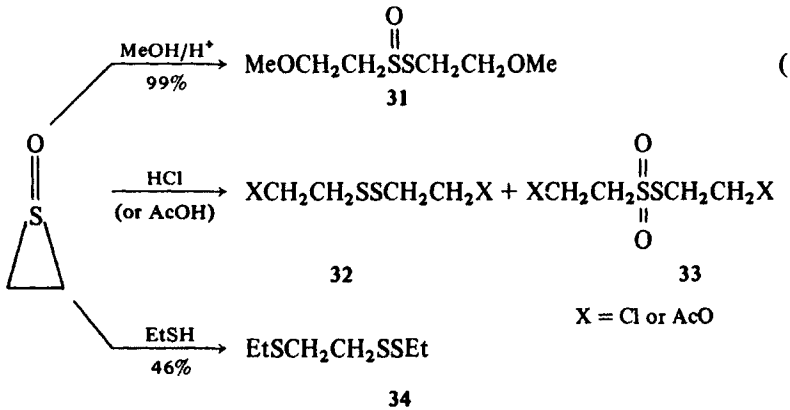
(15)

30 **29**

B. *Acid-Catalyzed Ring Opening*

The successful preparation and isolation of pure thiirane oxides bearing various substituents (see Section V, 1) made the systematic investigation of their acid-catalyzed ring openings possible. Such studies were needed to determine the scope of this reaction, which was first noted by Hartzell and Paige[7] and studied kinetically later.[53]

Thus, the acid-catalyzed ring-opening reaction of thiirane oxide in methanol (in the presence of sulfuric acid) yields thiosulfinate (**31**); with acetic acid or dry hydrogen chloride, a mixture of disulfide (**32**) and thiosulfonate (**33**) is obtained, and with ethane thiol a mercaptoethyl disulfide (**34**) is the product.[54] These results are illustrated in Eq. 16.



(16)

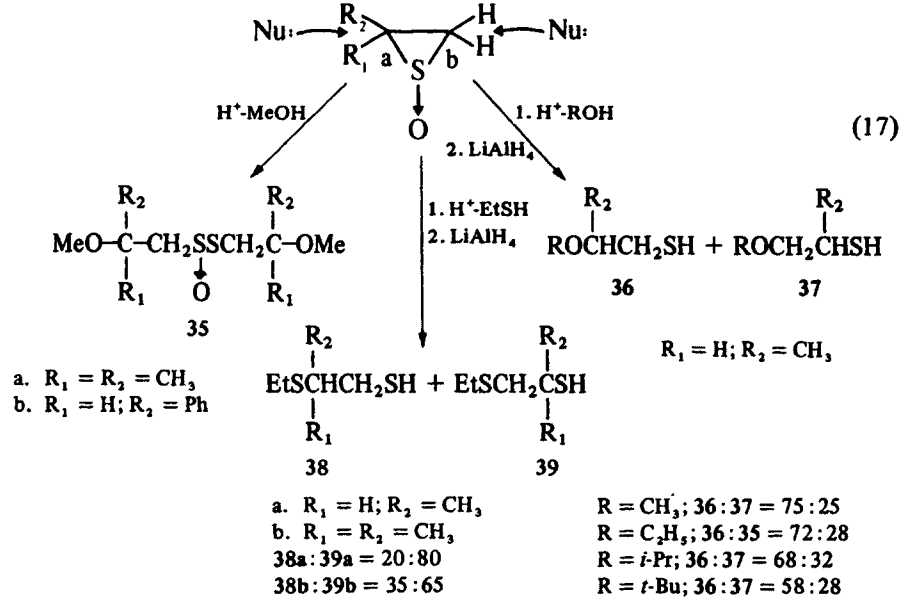
Reactions of other alcohols with thiirane oxide (in the presence of sulfuric acid) proceeded smoothly to give the ethyl-, isopropyl-, and *t*-butylthiosulfinates in yields of 77–95%. In the case of the reaction with hydrochloric or acetic acid it can be

assumed that the thermally unstable thiolsulfinates formed initially, disproportionate to the observed mixture of disulfide and thiosulfonate.[55]

The ring opening is generally stereospecific, inversion occurring at the ring carbon that is attacked by the nucleophile.[54]

The reaction of methylthiirane oxide with various alcohols afforded a mixture of thiolsulfinates (isolated as alkoxymercaptans after reduction with lithium aluminum hydride) with a preferential attack of the nucleophile at the most substituted carbon of the ring.

With 2,2-dimethyl- and 1-phenylthiirane oxides ring opening occurred exclusively at the substituted carbon. The foregoing results are summarized in Eq. 17.[54]



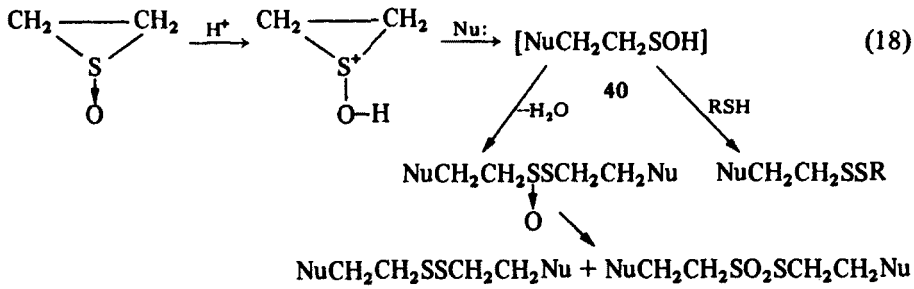
(17)

Clearly, the nucleophilic alkoxide is introduced to the carbon atom of the ring on which a developing positive charge might be better stabilized. The bulk of the nucleophile, undoubtedly, also constitutes an important factor.

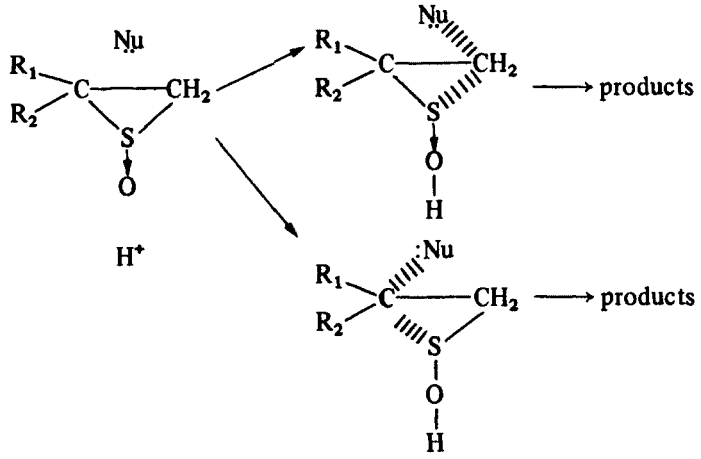
In sharp contrast to the reaction with alcohols, a preferential cleavage of bond b (Eq. 17) was observed with thiols as nucleophiles. Therefore, steric hindrance on the three-membered thiirane oxide appears to play a more important role in determining the orientation of attack by ethyl mercaptan.

Since sulfenic acids are too unstable to be isolated and either undergo dehydrative dimerization to thiolsulfinates or are effectively trapped by mercaptans to produce disulfides,[56] the sulfenic acid **40** can be assumed to be a common intermediate of the acid-catalyzed ring opening reaction. The overall reaction is formulated in Eq. 18.[54]

The experimental results of the acid-catalyzed ring-opening reaction of thiirane oxides have been interpreted in terms of a push-pull mechanism,[57] the transition state of which is shown in Eq. 19.[53]



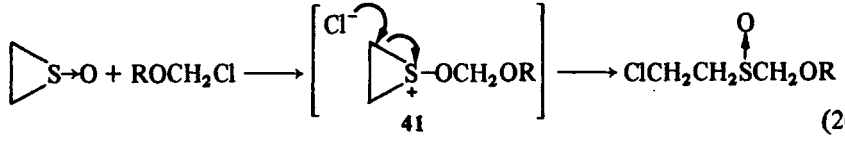
(18)



(19)

The foregoing explains the key role of (*a*) the nucleophilicity of the nucleophile, (*b*) the substituent effects, (*c*) the polarity of the reaction medium, and (*d*) the bulkiness of the nucleophile in determining the regio- and stereospecificity of the reaction. There is one catch, however, in this interpretation: nmr studies showed that thiirane oxide in FSO_3H-SbF_6 at $-78°$ was protonated at sulfur, *not* at oxygen.[58]

The reaction of alkylchloromethyl ethers with thiirane oxides to give sulfenic esters,[59] probably by way of the thiiranium salt intermediate **41**, appears to be analogous in many ways to the acid-catalyzed ring-opening reaction discussed here.



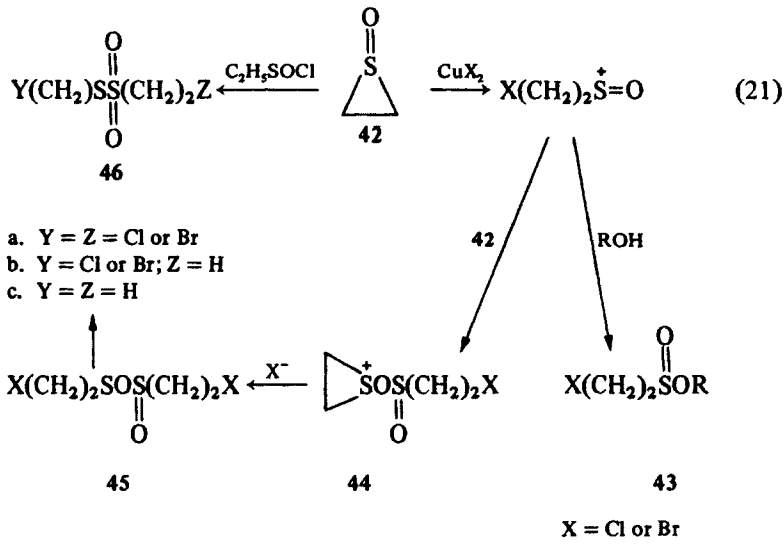
(20)

C. *Reactions with Metal Salts*

Whereas acyclic sulfoxides form complexes with various metal salts, thiirane oxides react with copper(II) chloride or bromide[60] in benzene at room temperature

to give the thiosulfonate **46a**. In alcoholic solution below 0° the major products are sulfinates (**43**).

An ionic rather than free-radical mechanism has been proposed to account for the results above, since the presence of various olefins had no effect. In accord with the proposed mechanism (Eq. 21),[60] thiirane oxide reacted with ethane sulfinyl chloride to give a mixture of thiolsulfinates **46b** and **46c**.



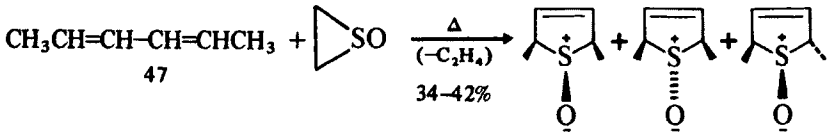
D. *Reactions with Dienes*

Practically speaking, the reaction of thiirane oxides with dienes refers primarily to the reaction of the parent thiirane, although in principle it can be applied to other members of the family that have no β-hydrogen available for abstraction (see Section V, 3, A).

It was first shown by Dobson and co-workers[40] that SO generated by thermolysis of thiirane oxide[7] could be trapped by dienes and trienes in the form of 2,5-dihydrothiophene (3-thiolene) and 2,7-dihydrothiepin sulfur oxides.

The reaction of the three geometrical isomers of 2,4-hexadiene with thiirane oxide afforded the three related 3-thiolene *S*-oxides **48** as depicted in Eq. 22.[61]

These results indicate that additions of SO to **47a** and **47b** are highly stereoselective at carbon (of the diene), as could have been predicted from the attack of its ground triplet state[41] on (mainly) *S-trans*-diene.[41a] Stereochemical control at sulfur is detectable only in 1,5-*cis*-dimethyl, *cis*-sulfoxides, but it is noteworthy that the *cis*-dimethyl sulfoxide from **47a** is exclusively the less stable isomer **48**-*trans, trans*.[61]



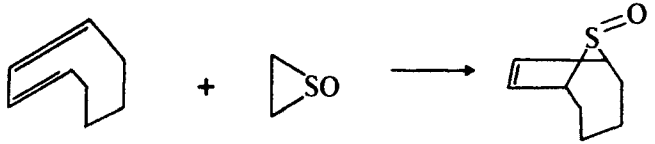
(22)

48

		Yield (%)*		
a. *trans-trans*	⟶	0	87	13
b. *cis-trans*	⟶	Trace	5	95
c. *cis-cis*	⟶	20	19	61

* Extrapolated to zero reaction time.

From equimolar quantities of isoprene and thiirane oxide in refluxing toluene, 3-methyl-3-thiolene oxide is obtained in 83% yield. The high stereoselectivity of the SO-diene reaction is demonstrated in the following reaction, where essentially only sulfoxide (**49**) was formed[61]:



(23)

49

It is likely that the SO-diene reaction will find a useful place in future organic syntheses.

4. References

1. C. D. Dittmer and G. C. Levy, *J. Org. Chem.*, 30, 636 (1965).
2. S. B. Soloway, U.S. Patent 2,694,073; *Chem. Abstr;* 49, 3465 (1955).
3. K. Kondo and A. Negishi, *Tetrahedron*, 27, 4821 (1971).
4. B. F. Bonini, A. Cappelli, G. Maccagnani, and G. Mazzanti, *Gazz. Chim. It.*, **105**, 827 (1975).
5. (a) K. Kondo, *Yuki Gosei Kagaku Kyokai Shi*, 29, 943 (1971); (b) A. Negishi, *ibid.*, 31, 331 (1973); *Chem. Abstr.*, 80, 59804 (1974).
6. M. Sander, *Chem. Rev.*, 66, 297 (1966).

6a. T. Kempe, Ph.D. Dissertation, Royal Institute of Technology, Denmark, 1974.

7. G. E. Hartzell and J. N. Paige, *J. Am. Chem. Soc.*, 88, 2616 (1966); *J. Org. Chem.*, 32, 459 (1967).
8. F. E. Hardy, P. R. Speckman, and P. Robson, *J. Chem. Soc., C*, 2334 (1969).
9. K. Kondo, A. Negishi, and M. Fukuyama, *Tetrahedron Lett.*, 29, 2461 (1969).
10. W. G. L. Albersberg, K. Peter, and C. Vollhardt, *J. Am. Chem. Soc.*, 99, 2792 (1977).
11. B. F. Bonini and G. Maccagnani, *Tetrahedron Lett.*, 37, 3585 (1973).
12. L. Thijs, A. Wagenaar, E. M. M. Van Rens, and B. Zwanenburg, *Tetrahedron Lett.*, 37, 3589 (1973).
13. (a) N. J. Turro and R. B. Gagosian, *J. Am. Chem. Soc.*, 92, 2036 (1970); (b) G. W. Corvell and A. Ledwith, *Q. Rev.*, 119 (1970).

14. (a) D. H. R. Barton and B. J. Willis, *J. Chem. Soc., Perkin Trans. 1*, 305 (1972); (b) R. M. Kellogg and S. Wassenaar, *Tetrahedron Lett.*, 1987 (1970); (c) J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, 37, 4045 (1972).

15. B. Zwanenburg, A. Wagenaar, L. Thijs, and J. Strating, *J. Chem. Soc., Perkin Trans. 1*, 73 (1973).

16. (a) B. F. Bonini, G. Maccagnani, A. Wagenaar, L. Thijs, and B. Zwanenburg, *J. Chem. Soc., Perkin Trans. 1*, 2490 (1972); (b) C. G. Venier and C. G. Gibbs, *Tetrahedron Lett.*, 2293 (1972).

17. C. G. Venier, C. G. Gibbs, and P. T. Crane, *J. Org. Chem.*, 39, 501, (1974).

18. L. A. Carpino and H. Wu Chen, *J. Am. Chem. Soc.*, 93, 785 (1971); 101, 390 (1979).

19. L. A. Carpino, L. V. McAdams III, R. H. Rynbrandt, and J. W. Spievak, *J. Am. Chem. Soc.*, 93, 476 (1971).

20. B. B. Jarvis, S. S. Duthey, and H. L. Ammon, *J. Am. Chem. Soc.*, 94, 2136 (1972).

21. S. Saito, *Bull. Chem. Soc. Jpn.*, 42, 663 (1969).

22. G. L. Cunningham, Jr., A. W. Boyd, R. J. Meyers, and W. D. Gwinn, *J. Chem. Phys.*, 19, 676 (1951).

23. Y. Nakano, S. Saito, and Y. Morino, *Bull. Chem. Soc. Jpn.*, 43, 368 (1970).

24. H. Dreizler and G. Dendl, *Z. Naturforsch. A*, 19, 512 (1964).

25. (a) R. W. Mitchell, F. A. Hartmann, and J. A. Merritt, *J. Mol. Spectrosc.*, 31, 388 (1969); (b) M. Ohtsuru, K. Tori, and M. Fukuyama, *Tetrahedron Lett.*, 2877 (1970).

26. W. F. White and J. E. Wollbrab, *Chem. Phys. Lett.*, 3, 25 (1969).

27. R. Hoffman, H. Fujimoto, J. R. Swenson, and C. -C. Wan., *J. Am. Chem. Soc.*, 95, 7644 (1973).

28. H. Bock and B. Solonki, *Angew. Chem.*, 84, 436 (1972).

29. M. M. Rohmer and B. Roos, *J. Am. Chem. Soc.*, 97, 2025 (1975).

30. A. B. Foster, T. D. Inch, M. H. Qudir, and J. M. Weber, *J. Chem. Soc., Chem. Commun.*, 1086 (1968).

31. P. B. Sollman, R. Nagarajan, and R. M. Dodson, *J. Chem. Soc., Chem. Commun.*, 552 (1967).

32. (a) B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *J. Am. Chem. Soc.*, 91, 3839 (1969); (b) J. C. Martin and J. J. Uebel, *ibid.*, 86, 2936 (1964).

33. J. J. Rigau, C. C. Bacon, and C. R. Johnson, *J. Org. Chem.*, 35, 3655 (1970).

34. C. R. Johnson and W. O. Siegl, *J. Am. Chem. Soc.*, 91, 2796 (1969); *J. Org. Chem.*, 35, 3657 (1970).

35. M. Ueyama and K. Tori, *Nippon Kagaku Zasshi*, 92, 741 (1971); *Chem. Abstr.*, 73, 34427i (1970).

36. J. Pople and A. Bothner-By, *J. Chem. Phys.*, 42, 1339 (1965).

37. C. A. Kingsbury, D. L. Durham, and R. Hutton, *J. Org. Chem.*, 43, 4696 (1978).

38. (a) V. Solkan and N. Sergeyev, *Org. Magn. Reson.*, 6, 200 (1974); (b) M. Cooper and S. Manatt, *J. Am. Chem. Soc.*, 91, 6325 (1969); (c) M. Bacon and G. Maciel, *Mol. Phys.*, 21, 257 (1971).

39. R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 8, 781 (1969).

40. (a) R. M. Dodson and R. F. Sauers, *J. Chem. Soc., Chem. Commun.*, 1189 (1967); (b) R. M. Dobson and J. P. Nelson, *ibid.*, 1159 (1969).

41. S. Saito, *Tetrahedron Lett.*, 48, 4961 (1968).

41a. D. M. Lemal and P. Chao, *J. Am. Chem. Soc.*, 95, 922 (1973).

42. J. A. Baldwin, G. Hofle, and Se Chun Choi, *J. Am. Chem. Soc.*, 93, 2810 (1971).

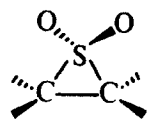
43. J. R. Shelton and K. E. Davis, *J. Am. Chem. Soc.*, 89, 718 (1967).

44. R. D. G. Cooper and F. J. Jose, *J. Am. Chem. Soc.*, 92, 2575 (1970).
45. J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, *J. Chem. Soc., Chem. Commun.*, 576 (1970).
46. E. M. Lown, H. S. Sandhu, H. E. Gunning, and O. P. Strausz, *J. Am. Chem. Soc.*, 90, 7164 (1968).
47. K. Kondo, M. Matsumoto, and A. Negishi, *Tetrahedron Lett.*, 21, 2131 (1972).
48. D. C. Dittmer, G. E. Kuhlmann, and G. C. Levy, *J. Org. Chem.*, 35, 3676 (1970).
49. D. C. Dittmer, R. S. Henion, and N. Takashina, *J. Org. Chem.*, 34, 1310 (1969).
50. (a) K. R. Kopecky and C. Mumford, *Can. J. Chem.*, 47, 709 (1969); (b) C. S. Foote and J. Lin, *Tetrahedron Lett.*, 3267 (1968).
51. K. Kondo and A. Negishi, *Chem. Lett.*, 1525 (1974).
52. G. A. Russel and G. J. Mikol, in *Mechanisms of Molecular Migrations*, Vol. 1, B.S. Thyagarijan, Ed., Wiley-Interscience, New York, 1968, p. 157.
53. G. E. Manser, A. D. Mesure, and J. G. Tillet, *Tetrahedron Lett.*, 3153 (1968).
54. (a) K. Kondo, A. Negishi, and I. Ojima, *J. Am. Chem. Soc.*, 94, 5786 (1972); (b) K. Kondo, A. Negishi, and G. Tsuchihashi, *Tetrahedron Lett.*, 37, 3173 (1969).
55. (a) L. D. Small, J. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, 71, 3565 (1949); (b) P. Allen and J. W. Brook, *J. Org. Chem.*, 27, 1019 (1962).
56. A. Schöberl and H. Gräfje, *Justus Liebigs Ann. Chem.*, 617, 71 (1958).
57. L. A. Paquette, *Principles of Modern Heterocyclic Chemistry*, Benjamin, New York, 1968, p. 26.
58. G. A. Olah and P. J. Szilagyi, *J. Org. Chem.*, 36, 1121 (1971).
59. E. Vilsmaier and B. Holch, *Synthesis*, 590 (1971).
60. K. Kondo, A. Negishi, and G. Tsuchihashi, *Tetrahedron Lett.*, 2743 (1969).
61. P. Chao and D. M. Lemal, *J. Am. Chem. Soc.*, 95, 920 (1973).

VI. THIIRANE DIOXIDES

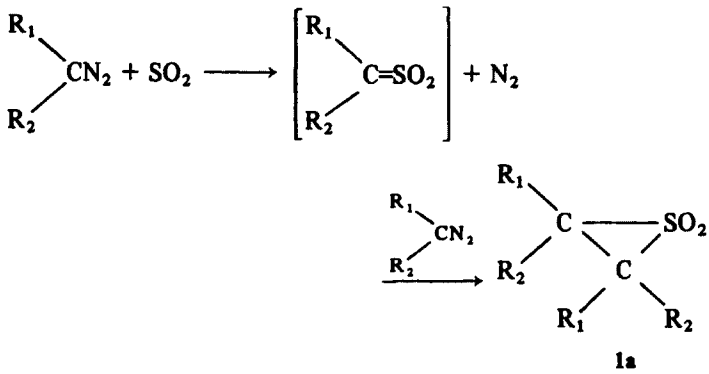
1. Introduction

The thiirane dioxides, which constitute a class of three-membered rings containing sulfur in its highest oxidation state (**1**), can be traced back to the work of Staudinger and Pfenninger,[1] who synthesized **1a** more than 60 years ago from diazoalkane and sulfur dioxide:



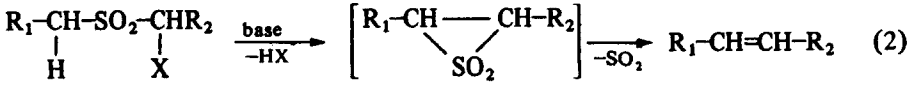
1

Furthermore, not only does the Ramberg-Bäcklund rearrangement, which was discovered about 40 years ago,[2] involve the intermediacy of thiirane dioxides,[3]



1a

but this base-induced rearrangement (a subject of extensive mechanistic studies in its own right[4]) has turned into an extremely useful synthetic tool[5,6] for the formation of carbon-carbon bonds from α-halosulfones:



(2)

$R_{1,2}$ = H, alkyl, aryl
X = Cl, Br, I

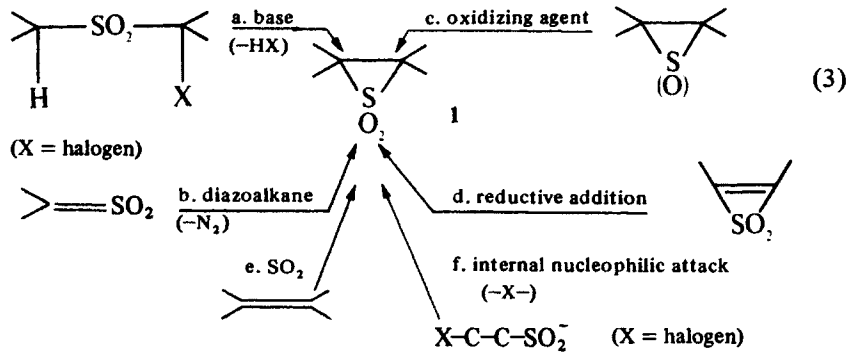
The mechanistically and synthetically oriented studies of the above reaction played a significant role not only in the chemistry of thiirane dioxides, but also in the present state of the art in the whole field of sulfur-containing three-membered rings.

Although known for a long time, the three-membered ring sulfones have received little attention, partly because of their low stability. However, during the 1960s, following the pioneering mechanistic studies conducted by Bordwell and Neureiter,[4] a number of thiirane dioxides have been synthesized (see Section VI, 2), their physical and chemical properties studied, and significant aspects in their chemistry established.[7-12]

2. Methods of Preparation

Practically speaking, only a few methods are available for the preparation and isolation of thiirane dioxides if they themselves are the ultimate target of the synthesis. This is because they are thermally unstable and very sensitive to nucleophilic reagents (bases included) that are usually present when the Ramberg-Bäcklund route is used.

The generation of thiiranes *in situ* represents the most popular approach for their use as chemical intermediates.[7,10,12] Some formal synthetic routes for the preparation of thiirane dioxides are shown and discussed below:



(3)

Route a, in which the carbon-carbon bond is formed, represents the classic Ramberg-Bäcklund approach[2,3,7] (see Sections VI, 2, A and VI, 4, A). However, the expected three-membered ring, which was unequivocally proved to be an intermediate in these based-induced reactions of α-halosulfones,[3,4,7] has not yet been isolated as such under the basic reaction conditions employed.[7,10–12] Therefore, this route for the actual synthesis of thiirane dioxides appears to have no practical value in spite of being, probably, the most thoroughly studied. This route, however, turned out to be very productive in the preparation of aryl-substituted thiirene oxides[13] and thiirene dioxides.[14]

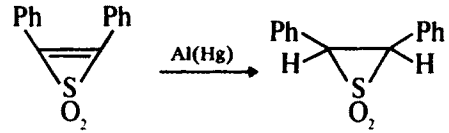
The relative stability of the unsaturated thiirene dioxides compared with that of the saturated thiirane dioxides under the Ramberg-Bäcklund reaction conditions employed can be attributed mainly to two factors: (*a*) the pseudo-aromatic nature of the Hückel-type unsaturated three-membered ring system,[14,15] and (*b*) the low nucleophilicity of the organic base used, which is sufficient for ring closure of the α,α′-dihalodibenzyl precursor.

Route b involves the formation of one carbon-carbon bond, and one carbon-sulfur bond. It belongs to the category of sulfene chemistry.[16] These intermediates react readily with diazoalkanes[5] to produce, after the loss of nitrogen, thiirane dioxides that are easily isolated and purified. So far, this appears to be the method of choice for the preparation of thiirane dioxides of all types (i.e., unsubstituted, alkyl and/or aryl, symmetrically and unsymmetrically substituted, thiirane dioxides).

Route c involves the oxidation of the divalent sulfur in thiiranes through the corresponding sulfoxides up to the dioxide stage. Several problems are associated with this route (to be discussed later); thus its scope is rather limited from a practical point of view.

Route d requires the application of available addition reactions to thiirene dioxides. Specifically, catalytic hydrogenation comes into mind. However, it appears that, except for unique purposes such as characterization of thiirene dioxides, this reductive addition method has little or no preparative value for the following reasons: (*a*) the preparation of thiirene dioxides is rather laborious (see Section X), and (*b*) many of the presently known thiirene dioxides are prepared through the intermediacy of the corresponding saturated thiirane oxides.[14] Indeed, the only example of this route reported in the literature is the catalytic reduction of 2,3-

diphenylthiirene dioxide with aluminum amalgam to *cis*-2,3-diphenylthiirane dioxide in very low yield (8%)[17] for characterization purposes:

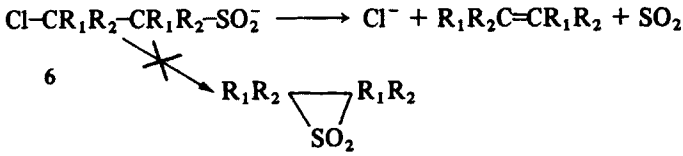


2 3 (4)

Routes e and f, although formally feasible, appear to be questionable on practical grounds. Thus, the formation of two C–S bonds by the addition of sulfur dioxide to ketene, which belongs to category *e*, has been reported to give 2-thiiranone dioxide (**4**).[18] However, the structural assignment of this adduct is in great doubt,[19] and it probably possesses the isomeric four-membered ring structure **5**.

4 **5**

Similarly, a carbon-sulfur bond can, in principle, be formed via an internal nucleophilic attack of the sulfinate group at the β-substituted position (route *f*). However, it has been shown[10] that this route does not yield thiirane dioxides. Rather, the corresponding β-chloroalkanesulfinates **6** decompose via a *trans*-coplanar elimination reaction to chloride ion, alkene, and sulfur dioxide:



(5)

a. *erythro* a. *cis*
b. *threo* b. *trans*

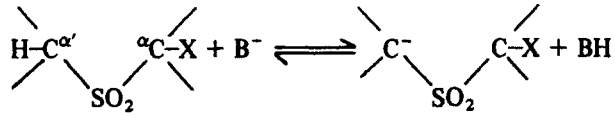
In fact, only routes *a–c* are of practical value for the preparation of thiirane dioxides; and they are discussed in detail below (see Sections VI; 2, A–VI, 2, C). However, in view of the severe limitations encountered with routes *a* and *c*, route *b* is ordinarily the method of choice for large-scale preparation and isolation of pure thiirane dioxides.

A. *Through the Base-Induced Reaction of α-Halosulfones*

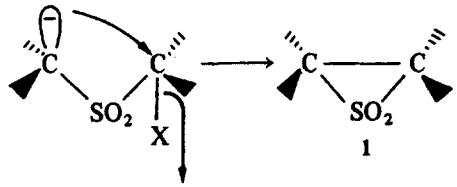
The formation of thiirane dioxides on treatment of α-halosulfones with an appropriate base (Ramberg-Bäcklund conditions) has been unequivocally proved.[3,4,6,7]

The reaction is generally viewed as occurring in three stages[9]: (a) pre-equilibrium α-proton abstraction leading to carbanion formation; (b) a rate-determining loss of

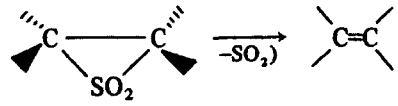
halide ion by backside intramolecular nucleophilic attack of the carbanion with formation of **1**; and (c) loss of sulfur dioxide from **1** leading to stereospecific formation of olefins (see Eqs. 6):



(6a)



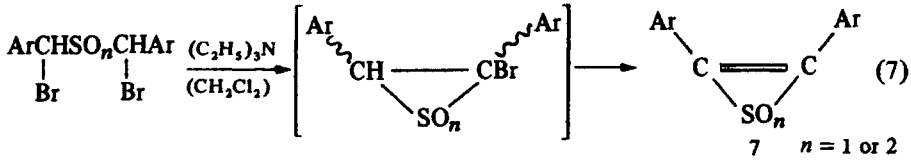
(6b)



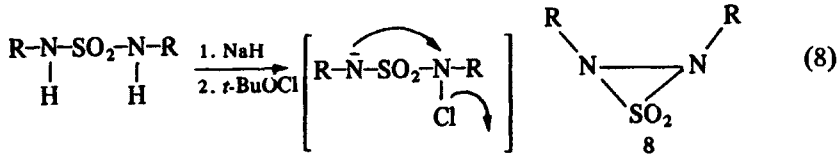
(6c)

Interestingly, thiirane dioxides (i.e., **1**), have not been isolated thus far in these base-initiated reactions. Rather, *cis*- and *trans*-olefins were the main products, and all attempts to obtain the three-membered ring system failed. Hence, this method is useful only for the *in situ* formation of **1** as intermediates in the synthesis of required olefins, acetylenes, polycyclic systems, and olefin sulfonates.[6,7,12] Alternatively, they may serve as *in situ* alkene precursors for potential trapping of the latter.

In a striking constrast to the inaccessibility of thiirane dioxides through the Ramberg-Bäcklund reaction, this method has been shown to be extremely useful and fruitful not only for the preparation of the unsaturated benzylic thiirene oxides[13] and dioxides[14,17] (see Sections IX, 2 and X, 2), but also for the preparation of thiadiaziridine 1,1-dioxides[20] as shown in Eqs. 7 and 8.



(7)



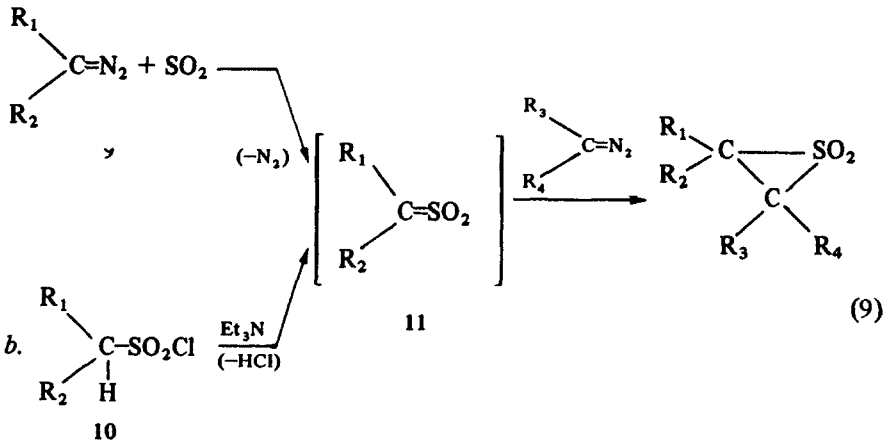
(8)

The particular set of reaction conditions, as well as the substitution patterns that are crucial for the successful isolation of the Ramberg-Bäcklund products (i.e., **7** and **8**) in these reactions are discussed in detail in the appropriate sections. Under ordinary reaction conditions (particularly in aqueous basic solutions), the thiirane

dioxides initially formed either decompose to alkene and sulfur dioxide or are cleaved by fission of the carbon-sulfur bond.

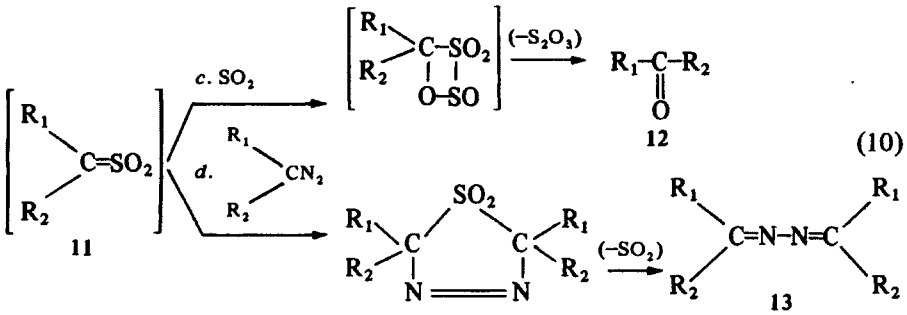
B. *Via Sulfenes and Diazoalkanes*

The only practical and general method for the synthesis of thiirane dioxides is the reaction of sulfenes generated *in situ* with diazoalkanes.[6] The sulfenes can be formed either by the reaction of diazoalkanes with sulfur dioxide or, more commonly, through the classical method of sulfene generation (e.g., dehydrohalogenation of sulfonyl chlorides containing α-hydrogens with a base, usually triethylamine). These two methods of synthesis of thiirane dioxides are depicted in Eq. 9.



(9)

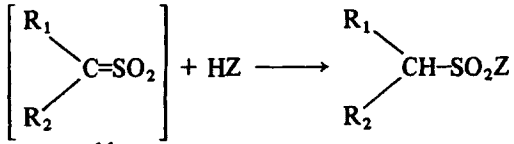
In route *a* the use of the diazoalkane in excess, necessarily leads to symmetrically substituted thiirane dioxides. When monoalkyl- or monoaryldiazoalkanes are used, mixtures of *cis* and *trans* isomers are formed.[4,11] The intermediate sulfene **11**, formed in the reaction between the diazoalkene **9** and sulfur dioxide sometimes gives other products – primarily ketones (**12**) and thiadiazolines, which in turn lose sulfur dioxide to produce ketazines (**13**). These alternative pathways are given in Eq. 10.[1,5,21,22]



(10)

Reaction *c* probably proceeds via a four-membered cyclic intermediate,[21] which upon subsequent loss of S_2O_3 yields the carbonyl compound **12**.

Reaction *d* (particularly with disubstituted diazoalkanes) leads to the Δ^3-1,3,4-thiadiazoline-1,1-dioxide, which decomposes to give **13**. In general, the preparation of thiirane dioxides by means of diazoalkanes and sulfur dioxide (route *a* Eq. 9) is carried out by adding gaseous or liquid sulfur dioxide to the solution of a diazoalkane preferably in anhydrous ether between 0° and −60°, depending on the stability of the resulting thiirane dioxide. Other dry, inert low boiling solvents (e.g., hexane, benzene, acetone, carbon disulfide) have also been employed. The presence in the reaction mixture of such "protic" impurities as water, alcohols, mercaptans, and amines lowers substantially the yield of the thiirane dioxides by either reacting directly with the sulfur dioxide or intercepting the sulfene intermediate[23]:



11 $Z = OH, OR, SR, NR_2$ (11)

A typical procedure for the preparation of thiirane dioxides[22,23] consists of bubbling sulfur dioxide through a chilled, (*ca.* −15°), distilled and *dried* solution of diazomethane.[24] Evaporation of the solvent leaves the crude thiirane dioxide, which can be further purified by distillation under reduced pressure or recrystallization from the appropriate solvent mixture.

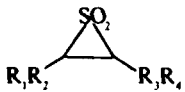
The following thiirane dioxides have been prepared through the Staudinger-Pfenninger method just described (see Eq. 9): the parent thiirane dioxide,[22,23] 2,3-dimethyl-,[4] 2,3-diphenyl-,[11,17,21,25] 2,3-diethyl,2,3-diphenyl-, 2,3-diethyl-, 2,3-di-parasubstituted phenyl-,[26] and 2,3-tetraphenylthiirane dioxides. The latter, though, is an unstable crystalline material.[1,11,27] Table 1 gives a summary.

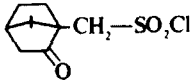
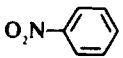
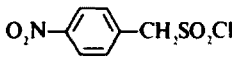
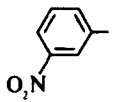
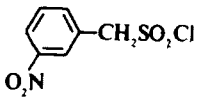
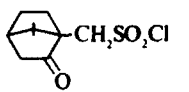
It turns out that the *cis-trans* ratio of the products varies significantly with the polarity of the medium in the reaction of diazoalkanes with sulfur dioxide: the higher the polarity of the solvent, the lower is the yield of the *cis* product. Thus, 23% of the *cis*-2,3-diphenylthiirane dioxide is formed in ether, whereas the yields of this product in benzene or *n*-hexane are 41 and 60%, respectively.

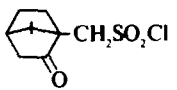
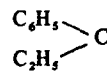
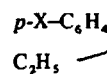
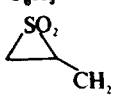
Under the reaction conditions of the Staudinger-Pfenninger procedure, the formation of the thiirane dioxides is usually accompanied by the formation of the corresponding olefins (through the loss of SO_2 from the thermally unstable thiirane dioxides) along with small amounts of ketazines (Eq. 10). Interestingly, ethyldiazoacetate does not react with sulfur dioxide,[28] at least under the ordinary reaction conditions applied in the cases of diazoalkanes and sulfur dioxide.

The method of choice for the preparation of either symmetrically or unsymmetrically substituted thiirane dioxides is the generation of sulfenes by the reaction of sulfonyl halides with tertiary amines (usually triethylamine) in an inert solvent, and the interaction of the former with an appropriate diazoalkane, route *b* Eq. 9.[16,29-32]

TABLE 1. PREPARATION OF THIIRANE DIOXIDES FROM DIAZOALKANES AND SULFUR DIOXIDE (ROUTE *b*, METHOD A) OR SULFONYL CHLORIDES (ROUTE *b*, METHOD B)

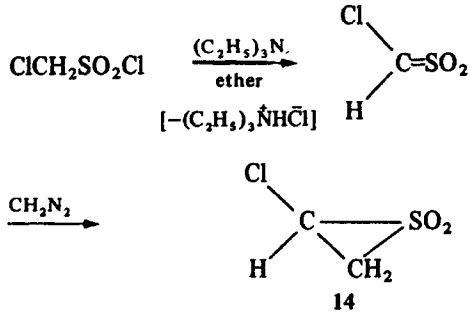


R_1	R_2	R_3	R_4	Starting material	Reagent	Yield (%)	Method	Ref.
H	H	H	H	CH_2N_2	SO_2	70	A	22, 23
					CH_3SO_2Cl	64	B	5, 30
C_2H_5	H	H	H		$C_2H_5SO_2Cl$	95	B	5, 30
C_6H_5	H	H	H	CH_2N_2	$C_6H_5CH_2SO_2Cl$	35–90[a]	B	5, 11, 25, 30
C_6H_5–CH_2	H	H	H	CH_2N_2	$C_6H_5CH_2CH_2SO_2Cl$	99	B	5, 30
	H	H	H	CH_2N_2		92 (two epimers)	B	5, 30, 31, 33
Cl	H	H	H	CH_2N_2	$ClCHSO_2Cl$	83	B	5, 29, 30, 32, 34
	H	H	H	CH_2N_2		–	B	35
	H	H	H	CH_2N_2		–	B	35
CH_3	H	CH_3	H	CH_3CHN_2	SO_2	56 (1:1, *cis-trans*)	A	4
CH_3	H		H	CH_3CHN_2		71 (1:9, *cis-trans*)	B	5, 30
CH_3	Br	H	H	CH_2N_2	$CH_3CH(Br)SO_2Cl$	64	B	36

	H	*i*-C_3H_7	H	$(CH_3)_2CHCHN_2$		64	B	5, 30
CH_3	H	C_6H_5	H	CH_3CHN_2	$C_6H_5CH_2SO_2Cl$	70 (~ 2:1, *cis-trans*)	B	5
C_6H_5	H	C_6H_5	H	$C_6H_5CHN_2$	SO_2	23–60 (*cis*; molar %)	A	17, 21, 25
					$C_6H_5CH_2SO_2Cl$	(~ 1:1, *cis-trans*)	B	5
C_6H_5–CH_2–	H	*i*-C_3H_7	H	$(CH_3)_2CH_2CHN_2$	$C_6H_5(CH_2)_2SO_2Cl$	(~ 2:1, *cis-trans*)	B	5, 30
C_2H_5	C_6H_5	C_2H_5	C_2H_5		SO_2	33 (mainly *trans*)	A	26
C_2H_5	*p*-X–C_6H_4	C_2H_5	*p*-X–C_6H_4	 (X = Br or OCH_3)	SO_2	25–80 (mainly *trans*)	A	26
C_6H_5	C_6H_5	C_6H_5	C_6H_5	$(C_6H_5)_2CN_2$	SO_2	48	A	1, 11, 27
	H	H	H	CH_2N_2	$ClO_2SCH_2CH_2CH_2SO_2Cl$	68	B	5

[a] Temperature dependent.

The diazoalkanes **9** that have been successfully applied are those in which R_1 is hydrogen, alkyl, cycloalkyl or aryl, whereas R_2 is hydrogen, chlorine, or bromine. Equation 12 illustrates this method for the bench-scale preparation (80–84%) of 2-chlorothiirane dioxide (**14**).[32]

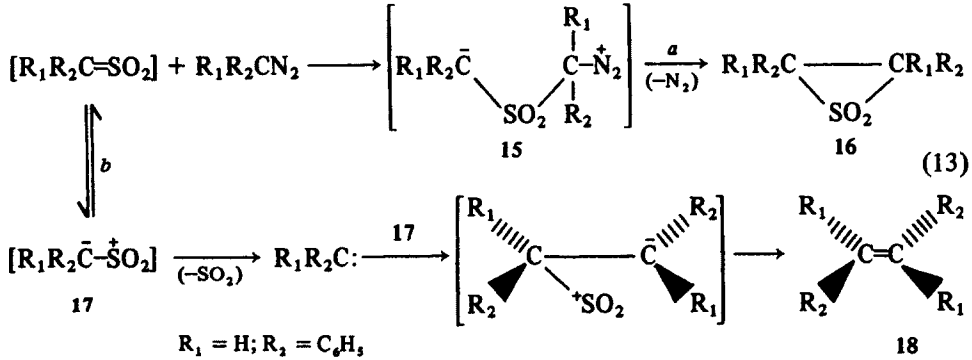


(12)

14

In a typical procedure,[29–32] a dry solution of the sulfonyl chloride in ether is added to a cold (< 0°) etheral solution of the diazoalkane (taken in about 10% molar excess) and triethylamine (5–10% molar excess). Filtration to remove the triethylamine hydrochloride formed is followed by evaporation of the filtrate under reduced pressure to give the relatively pure thiirane dioxide. Further purification can be easily achieved by successive recrystallizations, preferably *below* room temperature,[11] to avoid spontaneous fragmentation of the product into sulfur dioxide and the related olefin. In general, when the temperature of the reaction above is lowered, the yields are improved without a drastic decrease in reactivity.[31] Clearly, the lowering of reaction temperature is of particular importance in cases in which the thiirane dioxide is known to decompose at 0° or within this range. Thiirane dioxides that have been synthesized through this dehydrohalogenative method of sulfene formation are summarized in Table 1.

Strictly speaking, the mechanism for the formation of thiirane dioxides from sulfenes (regardless of their origin) and diazolkanes is not known. However, supporting evidence[4,16,21] suggests the zwitterion **15**, which could arise by nucleophilic attack of the diazoalkane molecule at the sulfur atom of the sulfene, as a highly likely intermediate.



(13)

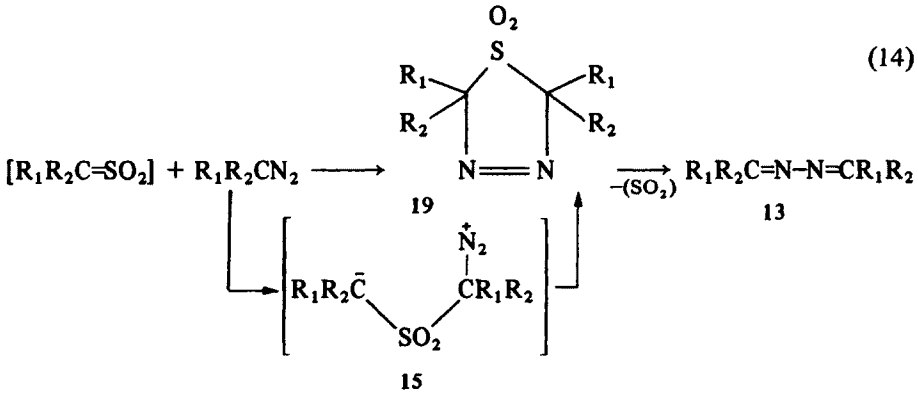
15 **16** **17** **18**

$R_1 = H; R_2 = C_6H_5$

The mechanism depicted in route *a* of Eq. 13 is in accord with the known favored attack of nucleophiles at the sulfur atom of sulfenes.[16] The stereochemistry of the thiirane dioxide product (i.e., **16**) is more difficult to account for. Thus, for example, the *cis*-2,3-diphenylthiirane dioxide was formed exclusively when sulfur dioxide was added to phenyldiazomethane in excess, and no *trans*-thiirane dioxide was found in the reaction mixture.[21a] It was argued[21] that the C–C distance in **15** is elongated so that the London force attraction between the two phenyl rings would be stronger than the repulsive force between them,[37] and thus the *cis* isomer might be formed. However, it is possible that the *trans* isomer is also formed and decomposes into *trans*-stilbene owing to the lower stability of the *trans*-2,3,-diphenylthiirane dioxide. In fact, the yields of *trans*-stilbene isolated in all the runs of the study above[21a] approximately complement the yield of the *cis*-thiirane dioxide essentially up to the theoretical yield.

Another possible explanation for the formation of the *trans*-olefin is illustrated in Eq. 13, route *b*, and involves a carbene arising from α-elimination of SO_2 from sulfene. In this case the *trans* isomer **18** is formed owing to steric repulsion of the substituent groups (phenyl groups in this particular case).

The sulfene intermediate **15** may give rise also to Δ^3-1,3,4-thiadiazoline-1,1-dioxide (**19**), which would explain the formation of ketazines that often accompanies the synthesis of thiirane dioxides.

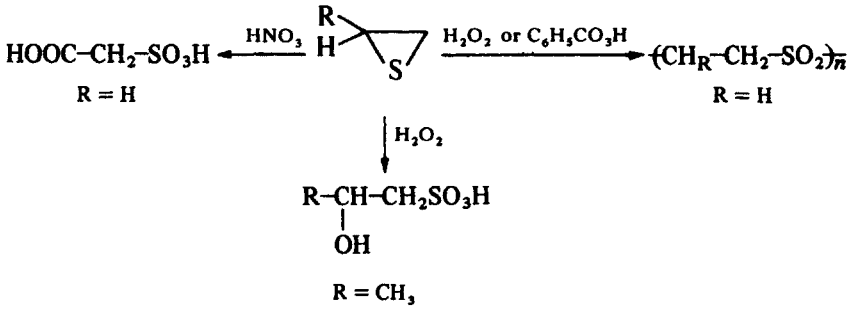


(14)

Given the ease of elimination of sulfur dioxide from **19** to form **13**,[38] it is unlikely that **19** functions as an intermediate in the formation of thiirane dioxides. Alkenes, however, together with ketazines, have been isolated on pyrolysis of **19**.[38,39] On the other hand, alkenes (**18**: Eq. 13) may be formed from intermediate **15** or **19** via the elimination of both nitrogen and sulfur dioxide.

C. *By Oxidation of Thiiranes or Thiirane Oxides*

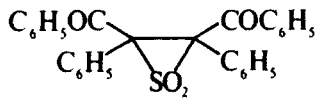
All attempts to prepare thiirane dioxides by the oxidation of thiiranes have failed thus far,[10,22,40] and usually ring opening of thiirane occurs under the reaction conditions employed. This is illustrated schematically in Eq. 15.



(15)

Although no successful oxidation of thiiranes to the corresponding thiirane dioxides is known to date, the successfully controlled oxidations of the former to the corresponding thiirane oxides are well-established processes[41,42] (see Section V, 1, A).

Indeed, the only supposedly successful preparation of a thiirane dioxide by oxidation of the corresponding thiirane[43] was later shown[10] *not* to be the claimed 2,3-dibenzoyl-2,3-diphenylthiirane **20**, but rather the 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide **21**.



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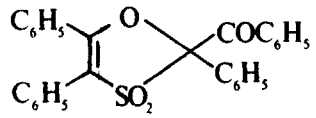

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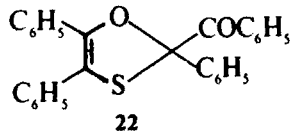
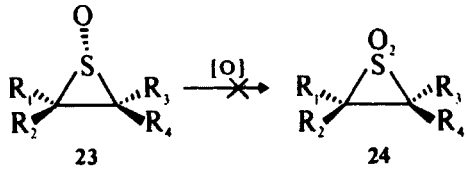


22

Furthermore, it turned out that the starting material was not the thiirane that had been sought but undoubtedly the oxathiole **22**.[10] The sterically hindered 2,3-di-*tert*-butylthiirane oxides **23a** and **23b** also failed[44] to be oxidized to **24**.



23 **24**

(16)

a. $R_1 = R_3 = H$; $R_2 = R_4 = t$-Bu
b. $R_1 = R_4 = H$; $R_2 = R_3 = t$-Bu

Reagents investigated included *m*-chloroperbenzoic acid, sodium peroxide, hydrogen peroxide, ozone, and aqueous potassium permanganate. The *cis* oxide (**23a**) was resistant to further reaction (steric hindrance, probably). The *trans* isomer (**23b**)

and also the corresponding thiirane were consumed with excess oxidizing agent, but no identifiable products could be isolated.[14]

Thus, the oxidation route for the preparation of thiirane dioxides from thiiranes, though probably the most logical, is practically inapplicable.

3. Structure and Physical Properties

A. *Experimental Physical and Spectroscopic Data*

Most isolated thiirane dioxides are low melting substances (m.p. usually 35–85°) that slowly decompose at room temperature and rapidly at about 80° or above their melting points to give sulfur dioxide and the related alkenes. This thermal fragmentation of thiirane dioxides is so facile that only under an inert atmosphere in the freezing compartment can the rate of decomposition be reduced substantially enough to make the systematic study of these molecules possible.

Investigations of the molecular structure of selected thiirane dioxides by x-ray diffraction techniques[45] and by gas phase microwave spectroscopy[46,47] showed the compounds to possess a carbon-carbon bond distance of 1.6 Å, which has been cited as the longest known.[47] The angles OSO, CSC, HCH, and H_2CC of the parent thiirane dioxide are 121°26′, 54°40′, 116°0′, and 151°43′, respectively.[46]

The uv spectra of thiirane dioxides have not been studied because they do not appear to exhibit any characteristic uv absorption above 220 nm. The ir spectrum, however, exhibits C–H stretching vibrations at 3000–3100 cm^{-1}, as expected for a three-membered ring compound, and the typical stretching frequency of the sulfone group is at about 1320 and 1160 cm^{-1}.[32,48] The scissoring vibrations of the sulfone group in the Raman spectrum were found to be at 1375 and 1388 cm^{-1}, vs. 1400 and 1418 cm^{-1} for the sulfoxide.[48] The three-membered ring has little effect on the frequency of the sulfone group.

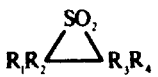
The positions of the three-membered ring proton signals in the nmr spectra of thiirane dioxides depend on the environment of these protons[5] and the solvents used[49] and are not uniquely indicative of this class of compound. The highfield shift of the three-membered ring protons of thiirane dioxides vs. the α-protons in the four-membered sulfone ring may partly be due to the diamagnetic anisotropy of the three-membered ring.[10]

The physical parameters of some selected thiirane dioxides are summarized in Table 2 for the sake of illustration.

B. *Molecular Orbital Calculations*

Ab initio MO-SCF calculations have been performed recently on the three-membered ring structure of the parent thiirane dioxide[50] following an earlier study based on extended Hückel calculations.[51] Hoffman et al.[51] concluded that the long C–C bond of thiirane dioxide is due to (*a*) the effective population of the π^*

TABLE 2. PHYSICAL PARAMETERS AND CHARACTERISTIC SPECTROSCOPIC DATA FOR SOME SELECTED THIIRANE DIOXIDES



R_1	R_2	R_3	R_4	Bond length (A) C–C	Bond length (A) C–S	m.p. (°C)	Ir stretching frequency (cm^{-1}) C–H	Ir stretching frequency (cm^{-1}) SO_2	Nmr chemical shift (ppm)	Ref.
H	H	H	H	1.590	1.731	19	3100; 3000	1310; 1160	3.15[a]	30, 46–49
				1.586	1.76					
Cl	H	H	H			53–54	3086	1328; 1168	3.17; 3.75; 4.85	32
cis-CH_3	H	*cis*-CH_3	H	1.60	1.730	57 (decomp.)			3.36	4, 45
C_6H_5	H	H	H			39–40 (decomp.)				5, 30
cis-C_6H_5	H	*cis*-C_6H_5	H			86–88 (decomp.)			5.21	17, 21, 25

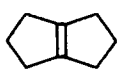
[a] Depending on the solvents used.

level of the ethylene fragment through a low-lying orbital ($3b_2$ of π symmetry) in SO_2, and (*b*) the action of the 3*d* orbitals in SO_2 as effective acceptors, thus depopulating the orbital of C_2H_4. The combination of these two effects leads to a weakening of the carbon-carbon bond. Consequently, the cleavage of this bond should be disrotatory, but conrotatory in thiirane itself. However, the extended Hückel data were not able to explain the observed discontinuity in the structural changes in the series thiirane, thiirane oxide, thiirane dioxide. Using a medium-sized contracted Gaussian basis set, optimal CC, CS, and SO distances have been determined,[50] and the calculated equilibrium geometries have been found to be in good agreement with available microwave data. Thus, the calculated total energy was found[50] to be -624.678 a.u. and the carbon-carbon, carbon-sulfur, and sulfur-oxygen bond distances (with the use of the 3*d* S orbitals) to be 1.590, 1.755, and 1.452 Å, respectively (vs. experimental values[46] 1.590, 1.731, and 1.439 Å). It turns out[50,51] that two factors are important in explaining the structural features in thiirane dioxides: the donor-acceptor strength of the fragment SO_2 and the 3*d* sulfur orbital participation. The latter factor provides the explanation for the extraordinarily long carbon-carbon distance in thiirane dioxides.

4. Chemical Properties and Reactivity

A. *The Ramberg-Bäcklund Rearrangement*

The intriguing transformation of α-halosulfones into alkenes on treatment with either inorganic or organic bases has been of both synthetic and mechanistic interest. This rearrangement has been named after Ramberg and Bäcklund, who were the first to report[2] the final result of the reaction without going into the mechanistic details. Since then, this rearrangement has been extensively studied[3,4,6-9] and has found wide synthetic work.[7,9,12,14] Following some practical synthetic schemes that were first reported in the 1960s,[52,53] the Ramberg-Bäcklund rearrangement began to show new promise as a synthetic tool in its application for (*a*) introduction of bridgehead double bonds in otherwise remotely accessible ring systems (e.g., **25**),[54] (*b*) preparation of thiapropellanes (e.g., **26**),[6] (*c*) preparation of dihaloalkyl-sulfones,[55] and (*d*) synthesis of acetylenes and olefin sulfonates (e.g., **27**).[6,7,12]



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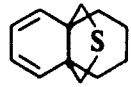

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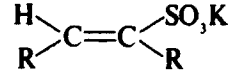


27

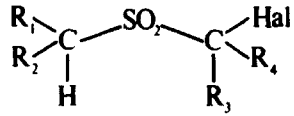
R = Me, Et, *n*-Pr, *n*-Bu, etc.[12]

The synthesis of alkenes through the intermediacy of thiirane dioxides that stereospecifically lose sulfur dioxide on heating undoubtedly constitutes an integral part of the Ramberg-Bäcklund rearrangement complex.

It became clear from the pioneering work of Bordwell et al.[3,4] on the mechanism

of the Ramberg-Bäcklund rearrangement that the three-membered ring of the thiirane dioxide is definitely involved in this transformation. The chemistry of thiirane dioxides is thus tied strongly to the chemistry of the Ramberg-Bäcklund reaction, and the two have usually been developed and studied concurrently and/or simultaneously.

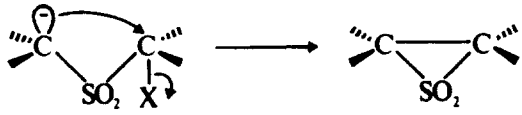
With very few exceptions, the rearrangement is general for molecules containing the structural elements of a sulfonyl group, an α-halogen, and at least one α′-hydrogen atom, that is, 28.



28

Mechanistic studies of the Ramberg-Bäcklund reaction by Bordwell and Cooper[4] led to the present accepted mechanistic pattern depicted previously in Eq. 6.

The reaction was found to be first order in both hydroxide ion and sulfone.[4] The pre-equilibrium reversible step has been substantiated by deuterium labeling,[4,7,56] kinetic relationships,[3,4,56] and leaving group effects.[3,56b,56c] The presence of at least a steady state of carbanion intermediate (Eqs. 6) also has been substantiated in these studies.[3,7,57] In a rate-determining step involving an intramolecular S_N2 process,[3,4,7] the thiirane dioxide intermediate is formed with double inversion,[8] which requires the carbanion and displacement centers to be coplanar[7,56]:



(17)

Additional support for the mechanistic pattern above is supplied by the requirement for the existence of an α-sulfonyl proton that bisects the angle of the oxygen atoms of the sulfonyl group[7,58] if the rearrangement is to take place in rigid ring systems.

The involvement of thiirane dioxides in the rearrangement has been indirectly supported by subjecting authentic thiirane dioxides obtained from using alternative methods, primarily through sulfenes, to Ramberg-Bäcklund conditions and isolating stereospecific alkenes and other products that one obtains in the "classical" Ramberg-Bäcklund reaction.[4,7] It has been concluded[3,7] that the stereochemistry of the final alkene products is determined in the ring closure step (e.g., Eq. 17) which, in turn, determines the stereochemistry of the alkene precursor, namely, that of the thiirane dioxide intermediate. The thermal decomposition of thiirane dioxides to olefins and sulfur dioxide is known to be stereospecific.[4]

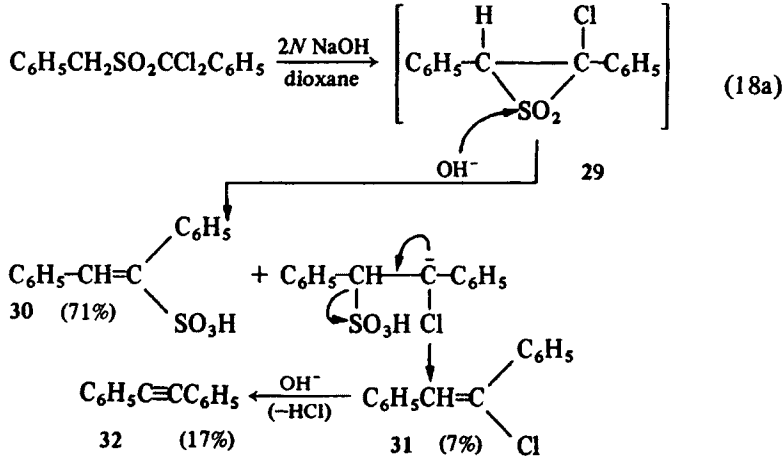
It was found[4c] that the stereochemistry of the Ramberg-Bäcklund reaction is remarkably insensitive to changes in the nature of the solvent and, over a wide range, in the nature of the base. However, with a strong hindered base (e.g., potassium *t*-butoxide), a profound change in stereochemistry of the olefinic

products does occur.[4c] Thus, *cis*-alkene predominates in acyclic α-halosulfones except with *t*-butoxide, when the *trans*-alkenes are the major products.[2,4,59] Under these conditions cyclic α-halosulfones undergo little or no reaction to form cyclic alkenes.[5-9] The reason for the preference of formation of *cis*-thiirane dioxides is not clear.[40] Mechanistic and stereochemical studies of the Ramberg-Bäcklund reaction suggest[60] that the stereochemistry (i.e., *cis-trans* ratio) of the thiirane dioxide intermediates formed in many cases is dictated to an appreciable extent by the formation of one of two possible diasteromeric carbanions (Eq. 6a) in a higher equilibrium concentration. The isomeric ratio in the three-membered ring intermediate determines, in the final analysis, the *cis-trans* ratio of the resulting alkenes.

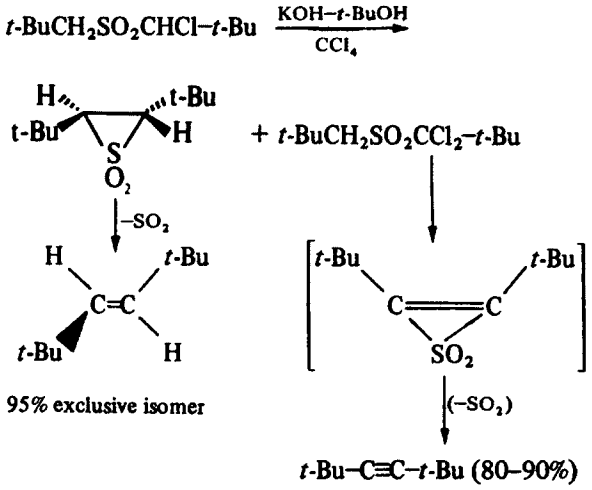
Several mechanistic explanations have been advanced for the decomposition of thiirane dioxides to the olefinic final products. Since concerted thermal decomposition was believed to be symmetry forbidden according to the Woodward-Hoffmann rules for cyclo- and retrocycloadditions,[61] a nonconcerted, yet stereospecific pathway was initially suggested.[7] Thus, a tight ion pair or a rearranged species incorporating the $-SO_2-$ moiety into a five-membered ring was believed to be responsible for the stereospecificity of the reaction.

Bordwell and co-workers[11] presented data in favor of a nonconcerted diradical or base-promoted radical anion mechanism as the route for the transformation of thiirane dioxide into alkene and sulfur dioxide in the Ramberg-Bäcklund reaction. However, the *concerted* symmetry-allowed nonlinear cheletropic path can also account for the available experimental data on this rearrangement.[62] At present, there is no conclusive support for any of the paths suggested for the fragmentation of thiirane dioxides to alkenes and sulfur dioxide, and additional studies will be required.[9]

Acyclic α,α- and α,α′-dihalosulfones afford acetylenes and vinylsulfonic acids as the main reaction products[7,12,59,63] on treatment with base under the Ramberg-Bäcklund reaction conditions. Smaller amounts of vinyl halides are also obtained. Illustrative examples are given in Eqs. 18.[12a,57]



(18a)

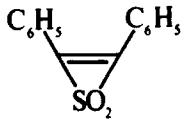


(18b)

Interestingly, the isolation of *trans*-di-*tert*-butylethyelene is in fact unusual because the Ramberg-Bäcklund method, generally leads to *cis*-olefins predominantly.[64]

Using somewhat milder reaction conditions, stable thiirene oxides and dioxides (Eq. 7) can be prepared from α,α'-dihalobenzyloxides and dioxides.[13,14,17] The route by which α,α- or α,α'-dihalosulfones are converted to vinylic sulfonates, acetylenes, and vinyl halides can be rationalized in terms of a common thiirane dioxide intermediate like **29**. The sulfonic acid **30** arises by the concerted attack of hydroxide ion at tetravalent sulfur and concomitant ejection of chloride ion. The vinylic halide (i.e., **31**) most probably results from stepwise cleavage of the three-membered ring to give an anion, which in suitable cases (benzylic position) may enjoy an appreciable lifetime. This anion then inverts and subsequently displaces bisulfite ion from the normal rearward position.[57] Based-induced dehydrohalogenation of **31** yields acetylene (**32**).

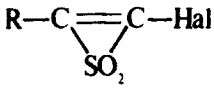
Alternatively, the results may be accounted for by assuming the formation of thiirene (**33**) from intermediate **29** via loss of a second molecule of hydrogen halide. Loss of SO_2 from **33** will lead to **32**, whereas ring opening through nucleophilic attack of the base on the sulfone sulfur in **33** will afford the vinylic sulfonate **30**.[7] In fact, the existence of **33** has been demonstrated by its direct preparation and isolation,[14,65] and the conversion of thiirene dioxides to the Ramberg-Bäcklund



33

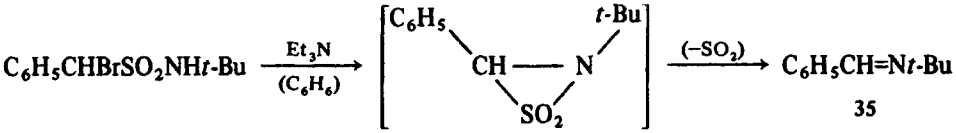
final products (e.g., diphenylacetylene) has been also demonstrated.[7,14] α,α,α-Trihalosulfones are convertible to dihalothiirane dioxides or monohalothiirene dioxides (e.g., **34**), which yield α,β-unsaturated sulfonic acids, acetylenes, and

β-ketosulfonic acids. Saturated dichlorosulfonic acids are also formed in certain cases.[9,59]



34

Base-induced rearrangements of α-halo- or α,α-dihalosulfonamides to Schiff bases (i.e., **35**) or nitriles **36**, respectively, can be easily explained in an analogous manner, invoking a three-membered ring α-sultam as an intermediate.[4,7,66] A case in point is depicted in Eqs. 19.[67]



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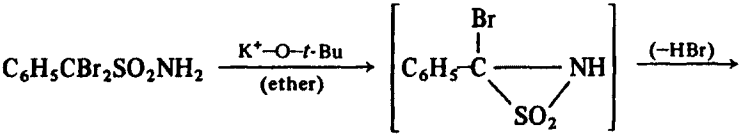
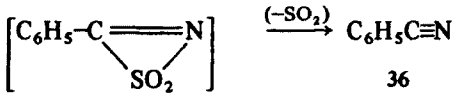
(19a)



(19b)



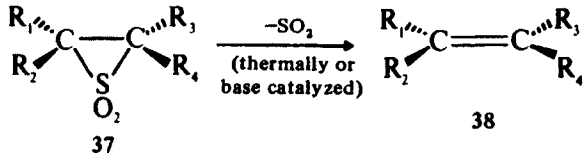
36

Indeed, the Schiff base **35** and the benzonitrile **36** have been isolated in 79 and 62% yields, respectively, on based-induced cyclization attempts[67] of the corresponding α-halo- and α,α-dihalosulfonamides under the Ramberg-Bäcklund conditions.

Finally, a fragmentation process analogous to the Ramberg-Bäcklund rearrangement is responsible for the formation of some major ions in the mass spectra of benzylic β-disulfones.[68] This appears to be a general pattern in the mass spectra of this class of compounds under electron impact conditions with a thiirane dioxide as an intermediate along the fragmentation coordinate.

B. *Sulfur Dioxide Elimination and Formation of Alkenes*

Most thiirane dioxides decompose near room temperature to give sulfur dioxide[1,4,5,17,21,22,26,30] and alkenes with retention of configuration:



37 38

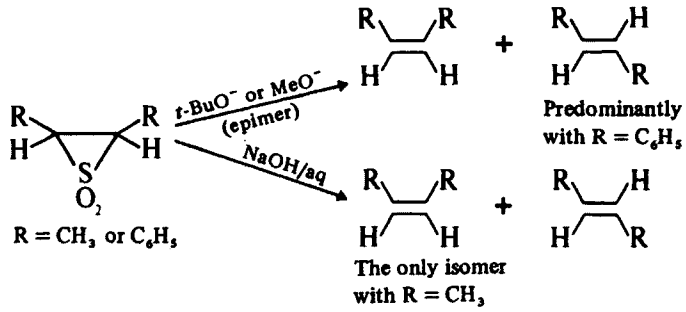
a. $R_1 = R_3 = H$
$R_2 = R_4$ = alkyl or aryl

b. $R_1 = R_4 = H$
$R_2 = R_3$ = alkyl or aryl

Although the mechanism of this fragmentation is not agreed on[7,10,11,62] (see Section VI, 4, A), the final result is very useful in the synthesis of alkenes with well defined configurations. In most established procedures the desired thiirane dioxides are generated *in situ* through either the reaction of diazoalkanes with sulfenes (see Section VI, 2, B) or the base-induced cyclization of α-halosulfones (see Section VI, 4, A). The crude thiirane dioxides thus obtained are converted without prior purification into the corresponding alkenes by thermal- or base-catalyzed elimination of sulfur dioxide. In most cases, this elimination takes place under the already employed reaction conditions.

Thermal decompositions follow first-order rates and were found to correlate surprisingly well with the ionizing power of the medium.[11] The rates are also base accelerated,[11] although the effect is rather small.[8]

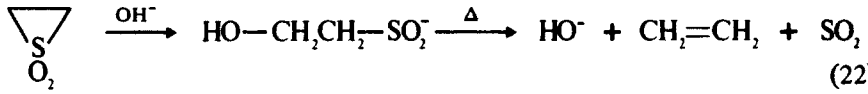
However, the stereochemistry of alkenes is not assured in the presence of a sufficiently strong base and sufficiently acidic protons in the three-membered ring. Under such conditions (essentially those typical for the Ramberg-Bäcklund reaction), epimerization via a carbanion intermediate produces an equilibrium mixture of thiirane dioxides.[4c,11] For example, *cis*-2,3-dimethylthiirane dioxide gives a mixture of *cis*- and *trans*-butene in the presence of potassium *tert*-butoxide. *cis*-2,3-Diphenylthiirane dioxide epimerizes in the presence of alkoxide ions predominantly to *trans*-2,3-diphenylthiirane dioxide, and consequently the *trans*-stilbene is obtained almost quantitatively as the final product.[11] In contrast, *cis*-2,3-dimethylthiirane dioxide eliminates sulfur dioxide without epimerization[4c] to give *cis*-2-butene in the presence of sodium hydroxyde, whereas *cis*-2,3-diphenylthiirane dioxide gives a mixture of *cis*- and *trans*-stilbenes[21a] under such conditions. These results are summarized in Eq. 21.



(21)

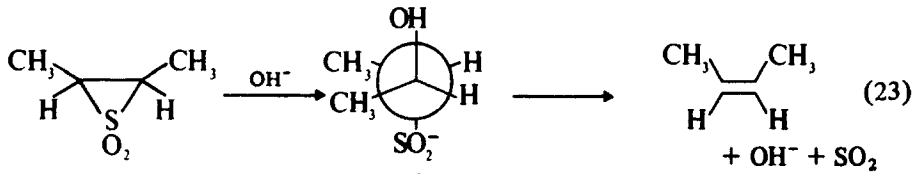
It appears that the diazoalkane-sulfene route should be preferred to that of the Ramberg-Bäcklund route for *in situ* dioxides generation in instances requiring a "clean" isomer of the alkene. This pragmatic conclusion may be altered in extreme cases with bulky substitutents (see Eq. 18b).

Although no definite conclusions can be drawn concerning the actual participation of bases in the conversion of aliphatic thiirane dioxides into alkenes, the known reaction of sulfones with alkali (Eq. 10),[22] suggests a nucleophilic attack of hydroxide ion on such thiirane oxides[10] (Eq. 22).



(22)

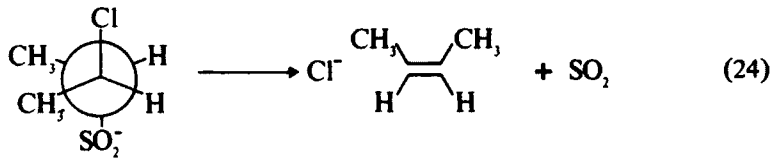
Similarly, the stereospecific formation of *cis*-2-butene from *cis*-2,3-dimethylthiirane dioxide[4c] may be rationalized in terms of a stereospecific ring opening of the thiirane dioxide to give the *threo*-sulfinate **39**, which in turn decomposes stereospecifically to yield the *cis*-alkene, hydroxide ion, and sulfur dioxide[10]:



(23)

39

Indeed, a similar case has been demonstrated experimentally in the thermal decomposition of the corresponding *threo*-3-chloro-2-butane sulfonate as shown in Eq. 24.[10]



(24)

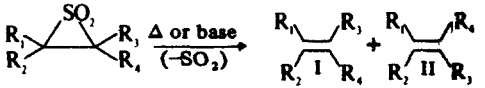
With few exceptions, good yields of alkenes are obtained through the intermediacy of thiirane dioxides obtained *in situ* either under the Ramberg-Bäcklund reaction conditions or via the sulfene route. Examples of the synthesis of alkenes via thiirane dioxides are summarized in Table 3.

The Ramberg-Bäcklund rearrangement of appropriate α-chlorosulfones to yield polyunsaturated propellanes[6] is a closely related extension of this route of alkene synthesis both mechanistically and synthetically.

C. *Decomposition of Thiirane Dioxides in the Presence of Bases*

The base-promoted elimination of sulfur dioxide from thiirane dioxide has been mainly conducted in connection with the mechanistic studies of the Ramberg-

TABLE 3. SYNTHESIS OF ALKENES VIA THIIRANE DIOXIDES:



R_1	R_2	R_3	R_4	Yield (%)	Procedure[a]	Ratio of I to II	Ref.
	H	H	H	71	B		5
C_6H_5	H	H	H	93; 80[b]	B; C		5, 11, 11b, 25, 30
$C_6H_5CH_2$	H	H	H	97	B		5
CH_3	Br	H	H	64[c]	B		36
CH_3	H	CH_3	H	55; 11; 100[b]	A; B; C	–; ~ 1:1; 99.5:0.5	4, 4c, 5
C_2H_5	H	CH_3	H	20	B	~ 2:3	5
$C_6H_5CH_2$	H	CH_3	H	70	B	~ 2:1	5
	H	CH_3	H	65	B	~ 1:9	5
	H	H	*i*-C_3H_7	54	B	I (exclusively)	12
t-Bu	H	H	*t*-Bu	95	D		5
C_6H_5	H	C_6H_5	H	49[c]; –[b]; 70[d]	A; B	~ 4.5:5.5; ~ 1:13; ~ 13:1	5, 11, 11b, 17, 21, 25
C_6H_5	C_6H_5	CH_3	H	> 96	D		70
p-BrC_6H_4–	C_2H_5	*p*-BrC_6H_4	C_2H_5	80[e]	A	~ 1:4	26
C_6H_5	C_6H_5	C_6H_5	C_6H_5	48[c]; 92[b]; > 96	A; D		1, 11b, 27, 70
C_6H_5	C_6H_5	CH_3	CH_3	> 96	D		70
C_6H_5	CH_3	C_6H_5	CH_3	~ 100	D	~ 9:1	12a
H	C_6H_4	H	C_6H_4	50	D		12, 69a

[a] Procedure A: diazoalkane + SO_2[1,5]; procedure B: diazoalkane + sulfonyl chloride + triethylamine[5,30,31]; procedure C: base-catalyzed elimination of SO_2; procedure D: sulfones + CCl_4–KOH–*t*-BuOH.[12,69-70]

[b] 2*N* NaOH.

[c] Yield refers to the thiirane dioxide.

[d] *n*-C_4H_9Li/THF.

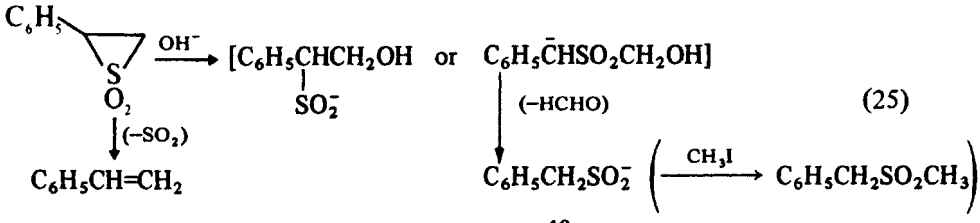
[e] Yield based on the hydrazone from which the diazoalkane was derived.

Bäcklund reaction (see Section VI, 4, A). In general, the thiirane dioxide (previously isolated or formed *in situ*) is treated with a large excess of the base in an appropriate solvent system for several hours at room temperature or below.[3-7,11,12] Bases commonly used are 2*N* NaOH (in water), $NaOCH_3$ (in methanol), KO-*t*-Bu (in *t*-BuOH), and *n*-BuLi (in tetrahydrofuran) or KOH-CCl_4 (in *t*-BuOH). In some cases (alkyl-substituted thiirane dioxides) temperatures above 20° are used.[12] It is often advantageous to use mixed solvents to ensure a homogeneous reaction mixture.

The elimination of sulfur dioxide from thiirane dioxides leading to the corresponding alkenes is not the only result of their base-induced reactions; other products are also formed. This fact raises the question of the mechanistic pathway of this reaction, which is briefly discussed next.

a. NUCLEOPHILIC ATTACK ON CARBON

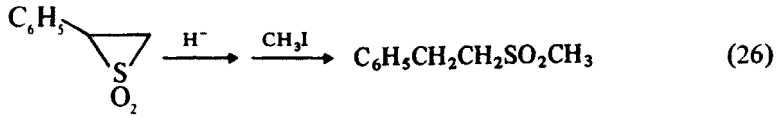
In the presence of aqueous sodium hydroxide, 2-phenylthiirane dioxide gives styrene and benzylsulfinate (**40**). These results have been interpreted[11b] in terms of initial *nucleophilic* attack of the hydroxide ion at the *carbon atom* of the three-membered ring or sulfur dioxide elimination as depicted in Eq. 25, which is comparable to Eq. 22.



(25)

40

Although the hydride ion ($LiAlH_4$ or $LiBH_5$)[25] selectively attacks thiiranes

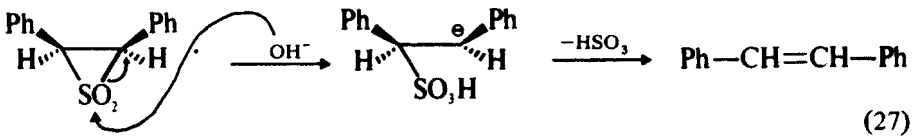


(26)

at C-2, the sterically larger OH^- species may attack at the less hindered C-3 site.

b. NUCLEOPHILIC ATTACK ON THE SULFONE GROUPS

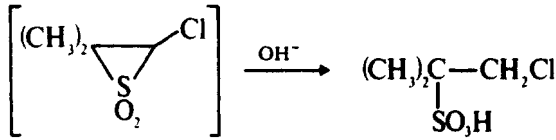
A nucleophilic attack of the hydroxide (or the alkoxide) ions on the *sulfur* atom of the thiirane dioxide ring to give sulfonic acids or similar intermediates, which then decompose to alkenes and bisulfite ion, has been suggested[11]:



(27)

41

Sulfonic acids (e.g., protonated form of **41**) should be sufficiently stable to be isolated and identified. Indeed, analogous sulfonic acids (e.g., **42**) have been isolated and identified in the Ramberg-Bäcklund rearrangement of 2-halothiirane dioxides[7,34]:

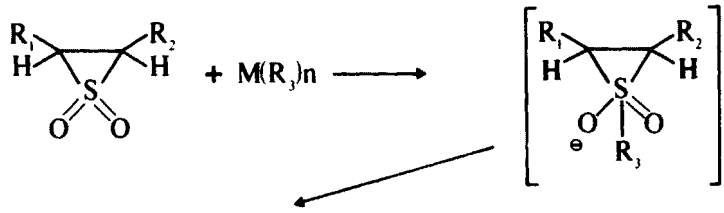


(28)

42

Thus, the sulfonic acid **42** is probably formed via a nucleophilic attack of the base on the *sulfur* atom of the sulfone group in the three-membered ring intermediate.[34]

The reaction of the parent thiirane dioxide, the 2-chloro- and 2,3-*cis*-dimethylthiirane dioxides with either Grignard reagents or alkyllithium reagent has been studied extensively.[71] The fair to good yields of the sulfinates **43** obtained (48–82%), accompanied by the corresponding alkene (**44**) have been interpreted[71] in terms of initial nucleophilic attack of the basic reagent on the *sulfur* atom of the thiirane dioxide ring as depicted in Eq. 29.



(29)

$(R_3SO_2)_nM$ + $R_1CH{=}CHR_2$

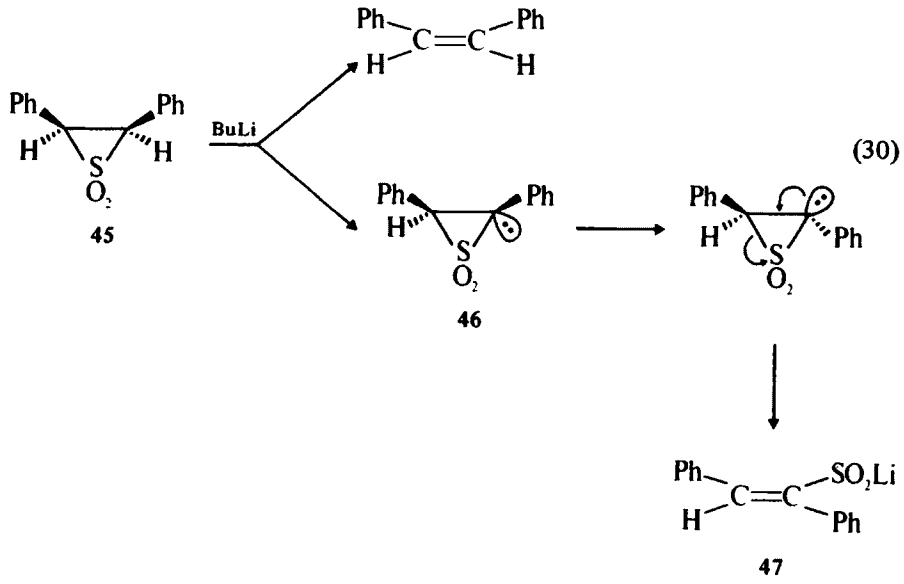
43 **44**

a. $R_1 = R_2 = H$; M = Li; $n = 1$; $R_3 = CH_3$ or n-C_4H_9
b. $R_1 = H$; $R_2 = Cl$; M = Li; $n = 1$; $R_3 = CH_3$ or n-C_4H_9
c. $R_1 = R_2 = CH_3$; M = Li; $n = 1$; $R_3 = n$-C_4H_9
d. $R_1 = R_2 = H$; M = Mg; $n = 2$; $R_3 = CH_3$ or C_2H_5 or $(CH_3)_2CHCH_2$ or $C_6H_5CH_2$

c. DECOMPOSITION THROUGH CARBANION FORMATION

A different pathway of ring opening is manifested in the reaction of thiirane dioxides with reagents that are weak nucleophiles but strong bases (e.g., butyllithium). Thus, *trans*-2,3-diphenylthiirane sulfinate (i.e., **47**) is formed in low yield when *cis*-2,3-diphenylthiirane dioxide (**45**) is treated with butyllithium.[11b]

The reaction apparently proceeds via the carbanion intermediate, which rearranges with inversion of configuration. The reactions involved are outlined in Eq. 30.[11]

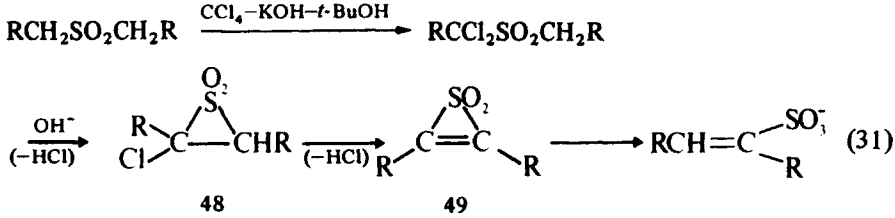


(30)

The formation of both *cis*- and *trans*-stilbene can thus be accounted for in accepting the interpretation above. A similar rearrangement has been observed for thietane 1,1-dioxide.[72] The difference between *n*-BuLi and OH^- may exist because the former is too sterically hindered to attack the *sulfur* atom. The α-sulfonyl carbanion intermediate **46** possesses considerable stability.

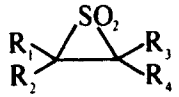
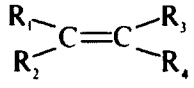
d. SUBSTITUENT EFFECTS ON THE DISPOSITION OF THIIRANE DIOXIDES

Substitution effects in the base-induced reactions of thiirane dioxides have been studied systematically by treatment of sulfones with KOH-CCl_4-*t*-BuOH.[12,69,70] It was shown that the 2-halothiirane dioxide initially formed (e.g., **48**) undergoes dehydrohalogenation to afford the thiirene dioxide intermediate (e.g., **49**), which is opened under the reaction conditions to give the sulfone product. This is illustrated in Eq. 31.[74]

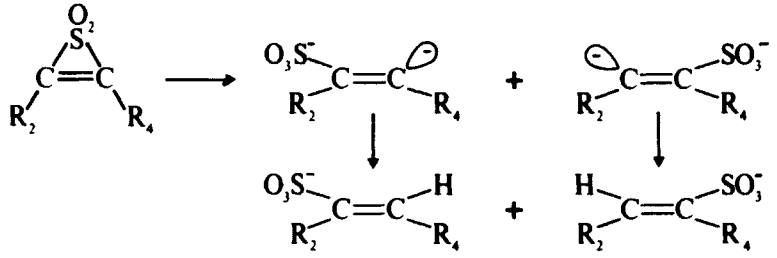


(31)

Some examples that illustrate the dependence of the final product (alkene or vinyl sulfonic acid) on the substitution pattern of the thiirane dioxide are given below[73]:

Thiirane dioxide formed *in situ*	Product
	
50	51
a. $R_1 = R_4 = Ph$; $R_2 = R_3 = H$	a. $R_1 = R_4 = Ph$; $R_2 = R_3 = H$
b. $R_1 = R_3 = H$; $R_2 = R_4 = Ph$	b. $R_1 = H$; $R_2 = Ph$; $R_3 = SO_3H$; $R_4 = Ph$
c. $R_1 = R_2 = Ph$; $R_3 = H$; $R_4 = CH_3$	c. $R_1 = R_2 = Ph$; $R_3 = H$; $R_4 = CH_3$
d. $R_1 = R_2 = R_4 = Ph$; $R_3 = H$	d. $R_1 = R_2 = R_4 = Ph$; $R_3 = SO_3H$
e. $R_1 = R_4 = t$-Bu; $R_2 = R_3 = H$	e. $R_1 = R_4 = t$-Bu; $R_2 = R_3 = H$

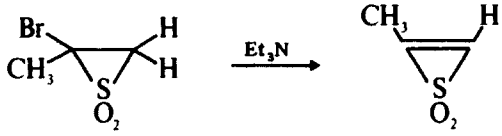
In accordance with previous studies, the formation of **51** ($R_2 = CH_3$; $R_3 = SO_3H$) from **49** is envisioned as follows[73]:



(32)

e. DEHYDROHALOGENATION OF HALOSUBSTITUTED THIIRANE DIOXIDES

Treatment of 2-halothiirane dioxides with organic bases such as triethylamine in organic solvents (e.g., methylene chloride) under mild conditions yield thiirene dioxides (e.g., **52**) via a dehydrohalogenation reaction[14]:

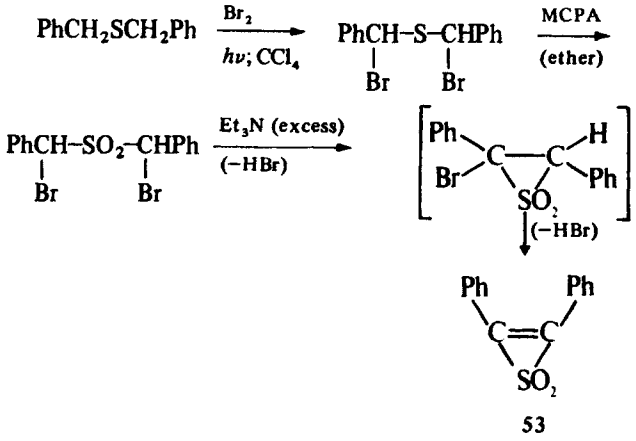


(33)

52

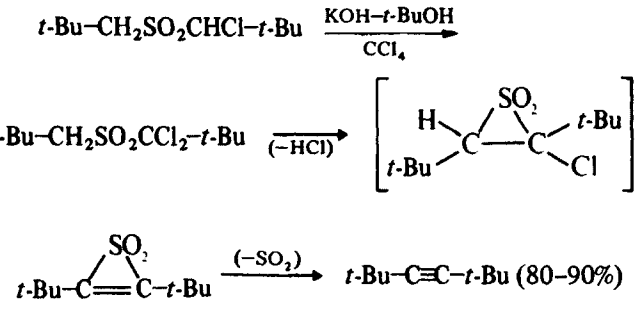
This dehydrohalogenation proved to be exceptionally useful in the benzilic series, where the 2-3-diphenylthiirene dioxide **53** could be prepared and isolated in bench-scale yields as follows.[14]

Moreoever, in certain cases, the thermodynamically unstable and nucleophilically sensitive thiirene dioxides formed via the dehydrohalogenation of the 2-halothiirane dioxides facilitate the synthesis of unique compounds otherwise difficult to obtain. An example is given in Eq. 35.[12]



(34)

53

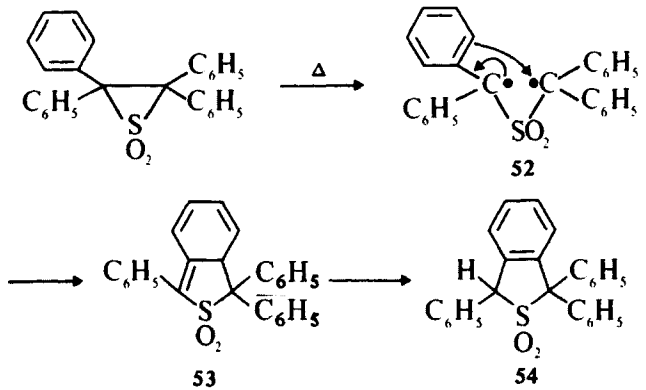


(35)

D. *Carbon-Carbon Bond Cleavage*

a. THERMAL C–C BOND CLEAVAGE

The thermal rearrangement of tetraphenylthiirane dioxide to give cyclic sulfones (i.e., **54**)[27] probably proceeds via a homolytic cleavage of the carbon-carbon bond to give a diradical intermediate (i.e., **52**). The latter cyclyzes to the sulfone **53**, which isomerizes to **54**[10,27]:



(36)

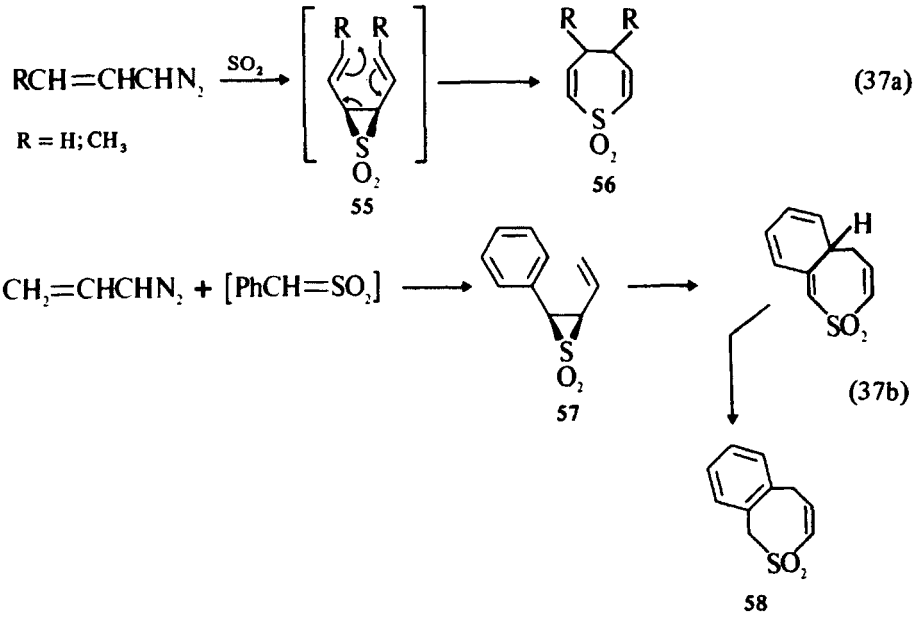
52

53

54

Since the above reaction is accompanied by sulfur dioxide elimination (to yield the corresponding tetraphenylethene), the activation energies for the C–C and the C–S bond cleavages appear to be comparable.

Regardless of the correct mechanism in Eq. 36, the thermal carbon-carbon cleavage of thiirane dioxides appropriately substituted can effectively be used for synthetic purposes. Indeed, this has been elegantly demonstrated by Paquette et al. in their convenient new synthesis of thiepine dioxides through a Cope-type rearrangement[76] of divinylthiirane dioxides, as illustrated in Eqs. 37.[75]



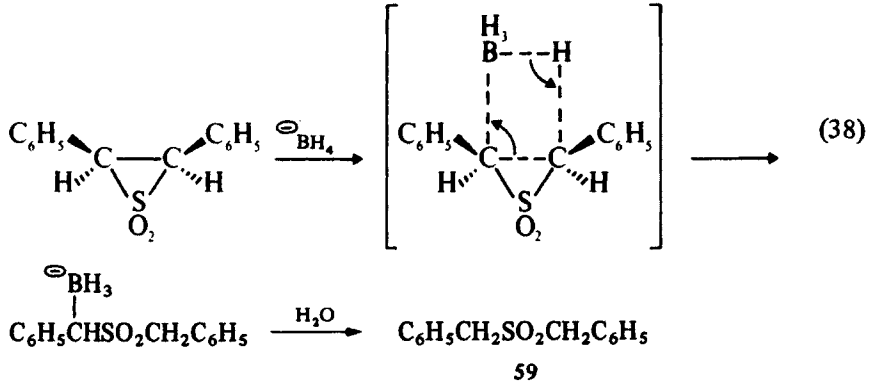
In **55**, carbon-carbon cleavage in the Cope rearrangement (the activation energy for related transformations[77] is *ca.* 12 kcal/mole) can compete effectively with the customarily observed fragmentation pathway (C–S bond rupture). Interestingly, in the case of **57** the competition between Cope rearrangement (estimated[78] E_{act} *ca.* 19–20 kcal/mole) and its thermal fragmentation (estimated[11] E_{act} *ca.* 19–21 kcal/mole) is nearly evenly balanced.[75]

The synthetic potential of such transformations in the thiirane dioxide series appears to be rather promising.

b. WITH METAL HYDRIDES

A reductive cleavage of the carbon-carbon bond in the three-membered ring of the thiirane dioxides can be accomplished[25,79] by the typical nucleophilic reducing agents lithium and sodium borohydride and lithium aluminum hydride. Thus, 2,3-*cis*-diphenylthiirane dioxide afforded 45% yield of dibenzyl sulfone (**59**) on reaction at room temperature with either $LiBH_4$ or $NaBH_4$, but only 0–10% yield of the sulfone on reaction with $LiAlH_4$. The reduction of 2,2,3,3-

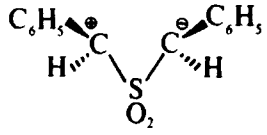
tetraphenylthiirane dioxide gave the corresponding sulfone in 68% yield, whereas the reduction of 2-phenylthiirane dioxide with the same reagents gave no carbon-carbon cleavage product, but rather a carbon-sulfur fission product (e.g., sulfinic acid salt). Based on these results and solvent effects that were found to be operative in these reactions, the following four-centered reaction mechanism has been proposed[25,79]:



(38)

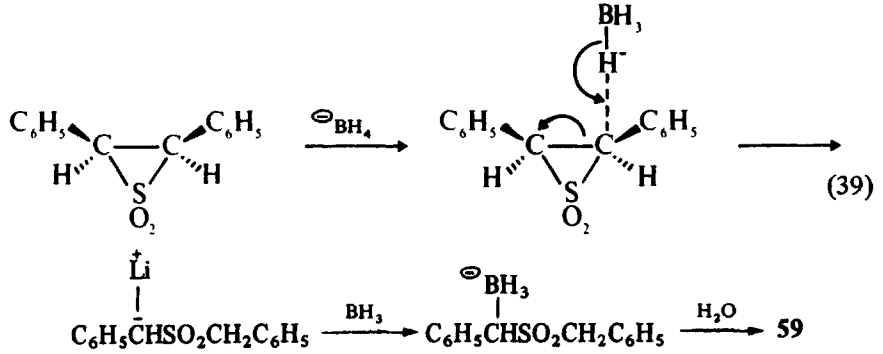
59

Two other alternative mechanisms for the C–C bond fission cannot be excluded[25] based on the available data. One involves an activated species like **60**, which then reacts with complex metal hydrides by a 1,3-dipolar-type reaction.



60

The other involves an S_N2-type mechanistic route as in epoxide reduction[25]:



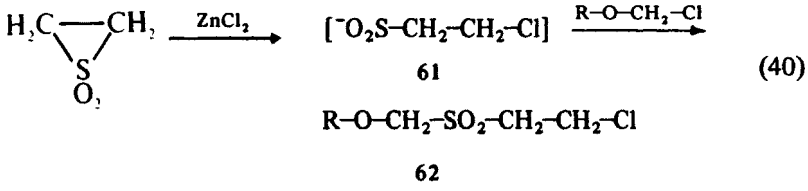
(39)

There is no clear reason to prefer either of these mechanisms, since stereochemical and kinetic data are lacking. Solvent effects also give no clues to the problem. At any rate, it is possible that the carbon-carbon bond strength is weakened

by an increasing number of phenyl substituents resulting in more C–C bond cleavage products, as indeed is found experimentally. All these reductive reactions of thiirane dioxides with metal hydrides are accompanied by the formation of the corresponding alkenes via the "usual" elimination of sulfur dioxide.

c. WITH METAL HALIDES

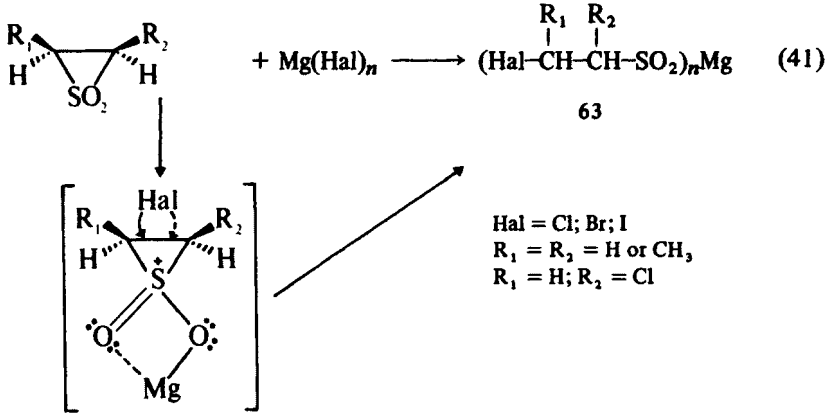
Reaction of the parent thiirane dioxide with chloromethyl ethers in the presence of zinc chloride gave alkoxymethyl-2-chloroethyl sulfones (**62**), presumably through the intermediacy of the chlorosulfinate **61**.[80] This transformation is depicted in Eq. 40.



(40)

The zinc chloride is thus acting here as a Lewis acid.

The reaction of thiirane dioxides with metal halides such as lithium and magnesium chlorides, bromides, and iodides in ether or THF solution afforded the halometal sulfinates **63** in yields ranging between 50 and 65%.[81] The suggested mechanism (for magnesium halides) is given in Eq. 41.[81]



(41)

The analogy of these reactions with that of thiirane dioxides with $ZnCl_2$ (Eq. 40) is apparent.

E. *Reactions via Intermediate Thiirane Dioxides*

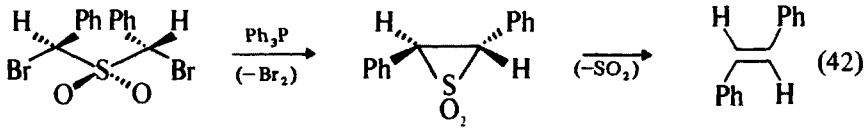
As has been shown in this section, most of the chemistry of thiirane dioxides involves their *in situ* generation followed (ordinarily) by decomposition to alkenes

and sulfur dioxides under reaction conditions. In some cases, however (see Section VI, 4, D), carbon-carbon bond cleavage occurs.

Many reactions in which the intermediacy of thiirane dioxides has been either proposed or unequivocally proved are known. A brief review of selected reactions (which have not been previously discussed in this section) follows.

a. REDUCTION

Treatment of *d,l-* and *meso*-bis-α-bromobenzyl sulfone with triphenylphosphine gave *trans-* and *cis*-stilbene, respectively, via α-sulfonyl carbanions that undergo cyclization at the remaining chiral center to yield *trans-* and *cis*-2,3-diphenylthiirane dioxides as intermediates. The reaction was assumed to proceed via a double inversion mechanism – one at each chiral center as shown by Eq. 42 for the *dl*-isomer[82]:

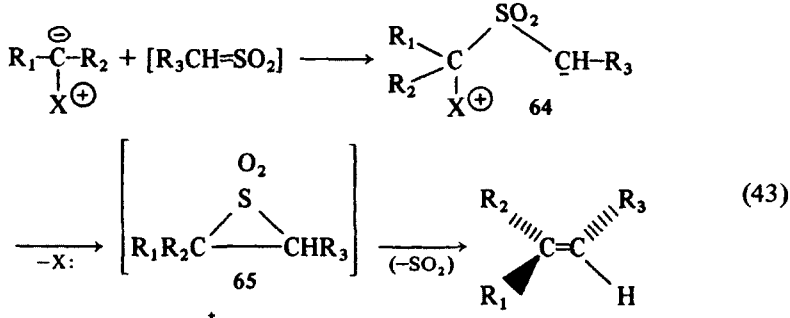


(42)

The same mechanism apparently operates in the reduction of the *meso*-α,α′-dibromodibenzyl sulfoxide with the phosphine reagent $[(CH_3)_2N]_3P$.[83]

b. REACTION OF YLIDES WITH SULFENES

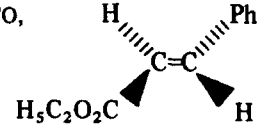
The reaction of stable phosphonium,[84] sulfonium,[85] and sulfoxonium ylides[86] with *in situ* generated sulfenes (dehydrohalogenation of sulfonyl chlorides in the presence of triethylamine) to give alkenes stereospecifically can be formulated as follows:



(43)

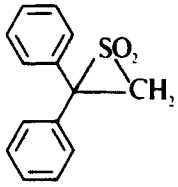
X = Ph_3P^+; R_2S^+; $R_2\overset{+}{S}O$

R_1 = COOR, PhCO,



R_2 = H, CH_3, Ph; R_3 = H, CH_3, Ph

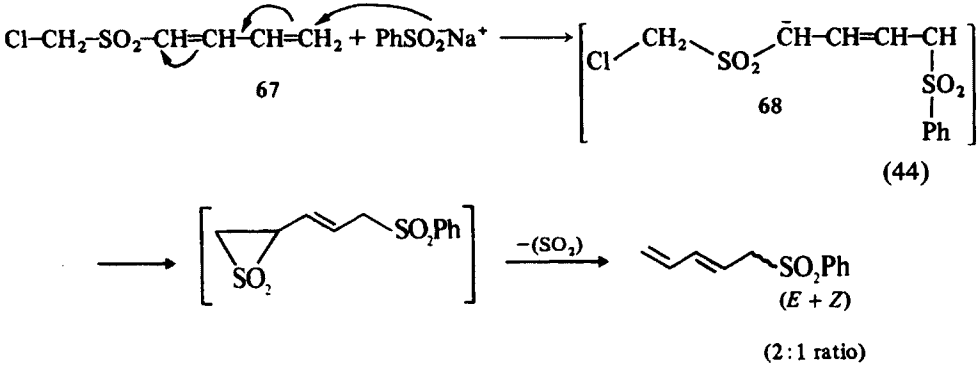
The yield of alkenes in these reactions is variable; the best is in the 63–78% range. Nevertheless, the *trans*-alkene always dominates, which provides a hint about the stereochemistry of the thiirane dioxide intermediates involved. The suggested precursors of the thiirane dioxides (i.e., **64**) are similar to those postulated in the Ramberg-Bäcklund reaction.[3,7] In at least one case, the reaction of ylides with sulfenes, the thiirane dioxide intermediate (e.g., **66**) was claimed to have been isolated in modest yield.[84] However, the structure assigned to **66** was shown later[10] to be incorrect.



66

c. MICHAEL-INDUCED RAMBERG-BÄCKLUND REARRANGEMENTS

The sulfonyl carbanion intermediate **68** may be produced upon Michael addition of a suitable anion to α-halosulfones carrying a Michael acceptor system (**67**). The formation of **68** then leads to a thiirane dioxide intermediate, which in turn gives (after sulfur dioxide elimination) the corresponding alkene. This scheme was successfully realized in the following case[87]:

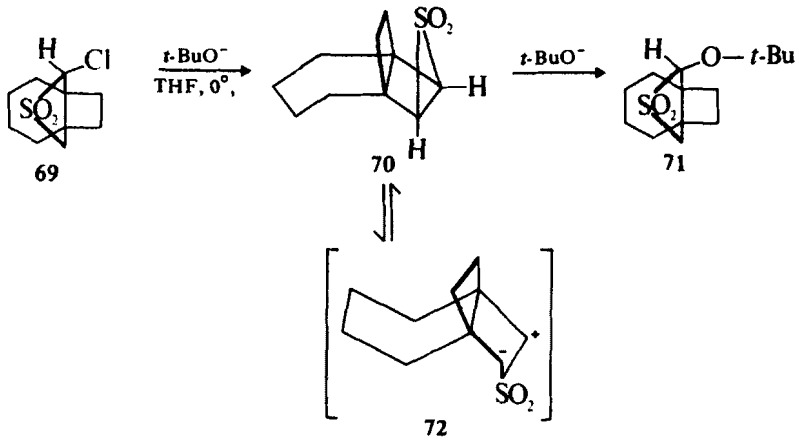


(44)

This approach appears to have potential in step-by-step polyene building.

d. NUCLEOPHILIC SUBSTITUTION OF STRAINED THIIRANE DIOXIDES

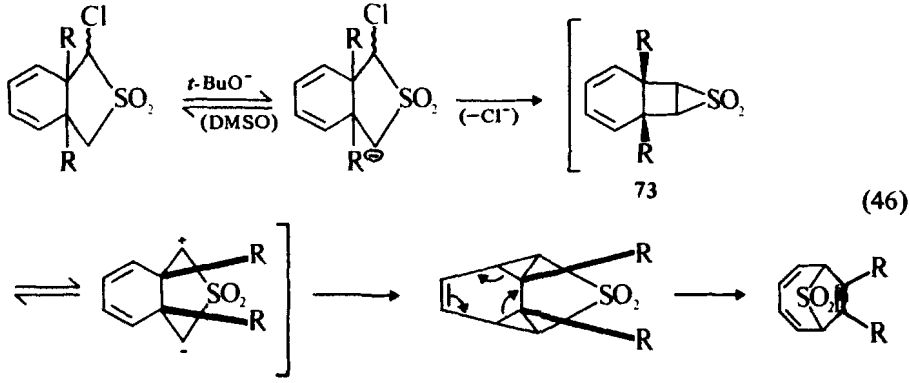
Treatment of the five-membered α-chlorosulfone propelane (**69**) with potassium *tert*-butoxide gave in 40% yield the *tert*-butoxypropelane **71**.[88] No sulfur dioxide is eliminated from the strained three-membered ring intermediate **70**. Rather, **70** affords **71** either directly or through a dipolar intermediate **72**, as depicted in Eq. 45.[88]



(45)

The carbon-carbon bond cleavage in the thiirane dioxide intermediate (i.e., **70**) is promoted by the built-in strain on the one hand and the interactions between one of the sulfone oxygens and the cyclobutane ring in **70** on the other. Equilibration of **69** with potassium *tert*-butoxide at room temperature in THF results in the formation of both **71** and its *anti* isomer (with respect to the four-membered ring) in a 1 : 4 ratio.

Carbon-carbon cleavage presumably promoted by steric compression occurs in other strained thiirane dioxides and leads to various rearrangements in the skeleton of the intermediate. A case in point is the following[89,90]:



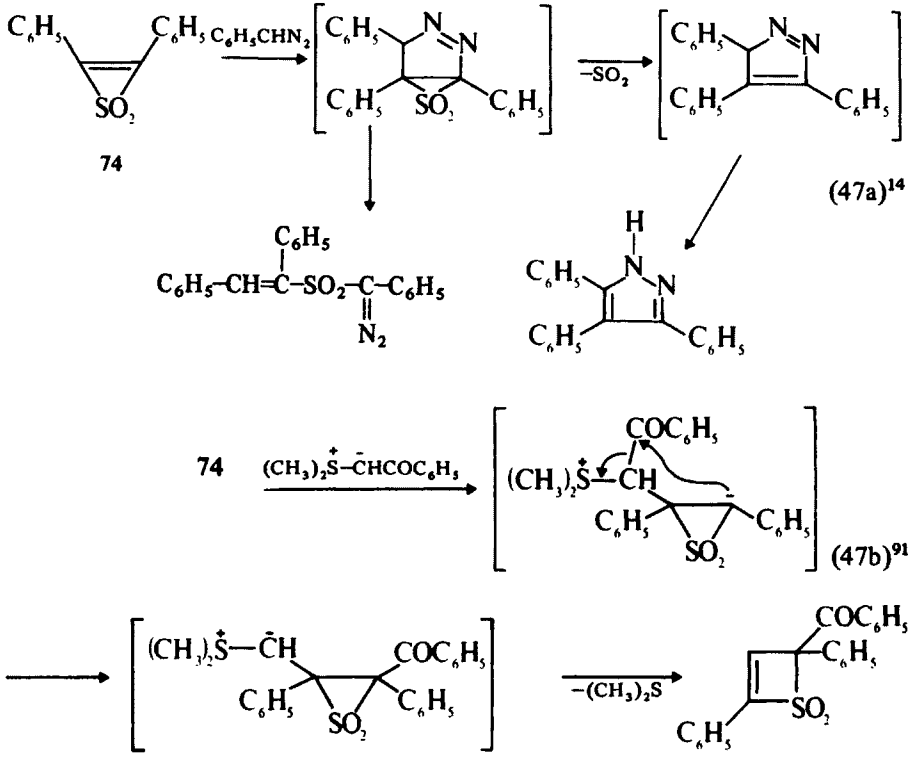
(46)

Other similar cases[89,90] involving strained thiirane dioxides are known.

The C–C bond cleavage and the accompanying sulfur dioxide elimination from the postulated **73** appear to be solvent dependent.[6]

e. REACTIONS OF THIIRENE DIOXIDES

Some reactions of the pseudo-aromatic 2,3-diphenylthiirene dioxide system are assumed to proceed through the intermediacy of an initially formed thiirane dioxide intermediate.[14] Two examples are given in Eqs. 47.

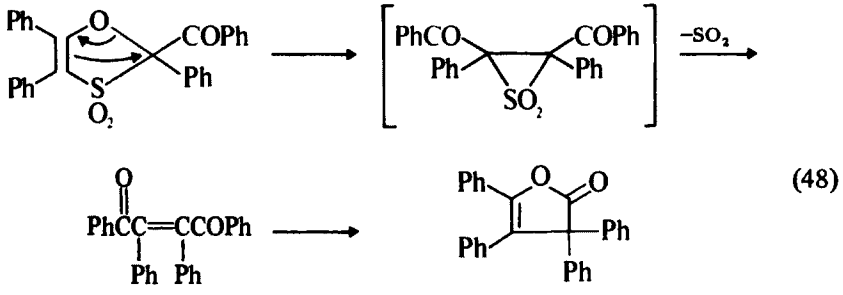


(47a)[14]

(47b)[91]

f. THERMAL DECOMPOSITION OF OXATHIOLS DIOXIDES

One of the products obtained in the pyrolysis of this class of compounds is rationalized in terms of thiirane dioxide intermediates as illustrated by the following example[10]:



(48)

g. CONCLUSION

Although the thiirane dioxide itself is not easy to isolate under the reaction conditions ordinarily employed, evidence based on the product pattern, the stereochemistry, and the kinetics involved provides convincing support for the concept of its actual involvement in a number of reactions.

5. References

1. H. Staudinger and F. Pfenninger, *Chem. Ber.*, 49, 1941 (1916).
2. L. Ramberg and B. Bäcklund, *Ark. Kemi. Mineral. Geol.*, **13A**: 27 (1940); *Chem. Abstr.*, 34, 4725 (1940).
3. F. G. Bordwell, in *Organosulfur Compounds*, M. J. Janssen, Ed., Wiley, New York, 1967, pp. 271–284.
4. (a) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, 73, 5187 (1951); (b) P. Neureiter and F. G. Bordwell, *ibid.*, 85, 1209 (1963); (c) N. P. Neureiter, *ibid.*, 88, 558 (1966).
5. N. H. Fischer, *Synthesis*, 393 (1970).
6. (a) L. A. Paquette, R. E. Wingard, Jr., J. C. Philips, G. L. Thompson, L. K. Read, and J. Clardy, *J. Am. Chem. Soc.*, 93, 4508 (1971); (b) L. A. Paquette, J. C. Philips, and R. E. Wingard, Jr., *ibid.*, 93, 4516 (1971).
7. (a) L. A. Paquette, in *Mechanisms of Molecular Migrations*, Vol. 1, B. S. Thyagarajan, Ed., Wiley, Interscience, New York, 1968, pp. 121–156; (b) L. Paquette, *Acc. Chem. Res.* 1, 209 (1968).
8. F. G. Bordwell, E. Doomes, and P. W. R. Corfield, *J. Am. Chem. Soc.*, 92, 2581 (1970).
9. S. W. Schneller, *Int. J. Sulfur Chem.*, 8, 583 (1976).
10. T. Kempe, Ph.D. Dissertation, Royal Institute of Technology, Denmark, 1974.
11. F. G. Bordwell, J. M. Williams, E. B. Hoyt, Jr., and B. B. Jarvis, *J. Am. Chem. Soc.*, 90, 429 (1968); (b) S. Matsumura, T. Nagai, and N. Tokura, *Bull. Chem. Soc., Jpn.*, 41, 2672 (1968).
12. (a) C. Y. Meyers, *Topics in Organic Sulfur Chemistry*, M. Tišler, Ed., University Press, Ljubljana, Yugoslavia, 1978, pp. 207–260; (b) C. Y. Meyers, in *Catalysis in Organic Synthesis*, Academic Press, New York, 1977, pp. 218–251.
13. L. A. Carpino and H. -W. Chen, *J. Am. Chem. Soc.*, **101**, 390 (1979).
14. L. A. Carpino, L. V. McAdams III, R. H. Rynbrandt, and J. W. Spiewak, *J. Am. Chem. Soc.*, 93, 476 (1971).
15. U. Zoller, *Eighth International Symposium on Organic Sulfur Chemistry, Portoroz, Yugoslavia, June 1978*, pp. 256–257.
16. G. Opitz, *Angew. Chem., Int. Ed. Engl.*, 6, 107 (1967).
17. L. A. Carpino and L. V. McAdams III, *J. Am. Chem. Soc.*, 87, 5804 (1965).
18. (a) A. de S. Gomes and M. M. Joullie, *J. Heterocycl. Chem.*, 6, 729 (1969); (b) J. M. Bohen and M. M. Joullie, *J. Org. Chem.*, 38, 2652 (1973).
19. E. Tempesti, L. Giuffre, M. Fornaroli, and G. Airoldi, *Chem. Ind. (London)*, 183 (1973).
20. (a) J. W. Timberlake and M. L. Hodges, *J. Am. Chem. Soc.*, 95, 634 (1973); (b) H. Quast and F. Kees, *Tetrahedron Lett.*, 19, 1655 (1973).
21. (a) N. Tokura, T. Nagai, and S. Matsumura, *J. Org. Chem.*, 31, 349 (1966); (b) T. Nagai, H. Namikoshi, and N. Tokura, *Tetrahedron*, 24, 3267 (1968).
22. G. Hesse, E. Reichold, and S. Majmudar, *Chem. Ber.*, 90, 2106 (1957).
23. G. Hesse and S. Majmudar, *Chem. Ber.*, 93, 1129 (1960).
24. F. Arndt, *Org. Synth.*, Collect. Vol. II, 165 (1950).
25. S. Matsumura, T. Nagai, and N. Tokura, *Bull. Chem. Soc. Jpn.*, 41, 635 (1968).
26. L. V. Vargha and E. Kovacś, *Chem. Ber.*, 75, 794 (1942).
27. H. Kloosterziel and H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, 71, 1235 (1952).
28. E. Reichhold, Dissertation, University of Erlangen, 1955.
29. G. Opitz and K. Fischer, *Z. Naturforsch. b*, 18, 775 (1963).

30. G. Opitz and K. Fischer, *Angew. Chem.*, 77, 41 (1965); *Angew. Chem., Int. Ed. Engl.*, 4, 70 (1965).
31. N. Fischer and G. Opitz, *Org. Synth.*, 48, 106 (1968).
32. L. A. Paquette and L. S. Wittenbrook, *Org. Synth.*, 49, 18 (1969).
33. T. Kempe and T. Norin, *Acta Chem. Scand.*, 4, 27 (1973).
34. (a) L. A. Paquette and L. S. Wittenbrook, *J. Chem. Soc., Chem. Commun.*, 471 (1966); (b) L. A. Paquette, L. S. Wittenbrook, and V. V. Kane, *J. Am. Chem. Soc.*, 89, 4487 (1967).
35. S. Rossi and S. Maiorana, *Tetrahedron Lett.*, 263 (1966).
36. L. A. Carpino and R. H. Rynbrandt, *J. Am. Chem. Soc.*, 88, 5682 (1966).
37. K. S. Pitzer and E. Catalano, *J. Am. Chem. Soc.*, 78, 4844 (1956).
38. G. Hesse and E. Reichold, *Chem. Ber.*, 90, 2101 (1957).
39. H. H. Inhoffen, R. Jonas, H. Krosche, and U. Eder, *Justus Liebigs Ann. Chem.*, 694, 19 (1966).
40. (a) C. C. J. Culvenor, W. Davies, and N. S. Neath, *J. Chem. Soc.*, 282 (1949); (b) J. M. Stewart and H. P. Cordts, *J. Am. Chem. Soc.*, 74, 5880 (1952); (c) M. Dele'pine and S. Eschenbrenner, *Bull. Soc. Chim. Fr.*, 33, 703 (1923).
41. (a) G. E. Hartzell and J. N. Paige, *J. Am. Chem. Soc.*, 88, 2616 (1966); (b) F. E. Hardy, P. R. Speckman, and P. Robson, *J. Chem. Soc., C*, 2334 (1969).
42. (a) K. Kondo, A. Negishi, and M. Fukuyama, *Tetrahedron Lett.*, 29, 2461 (1969); (b) K. Kondo and A. Negishi, *Tetrahedron*, 27, 4821 (1971).
43. D. C. Dittmer and G. C. Levy, *J. Org. Chem.*, 30, 636 (1965).
44. P. Raynolds, S. Sonnebelt, S. Bakker, and R. M. Kellogg, *J. Am. Chem. Soc.*, 96, 3146 (1974).
45. R. Desiderato and R. L. Sass. *Acta Crystallogr.*, 23, 430 (1967).
46. Y. Nakano, S. Saito, and Y. Morino, *Bull. Chem. Soc. Jpn.*, 43, 368 (1970).
47. H. Kim, *J. Chem. Phys.*, 57, 1075 (1972).
48. G. M. Kuźyants and V. T. Aleksanyan, *Zh. Strukt. Khim.*, 13, 617 (1972); *J. Struct. Chem., USSR*, 13, 576 (1972).
49. (a) P. Biscarini, F. Taddei, and C. Zauli, *Boll. Sci. Fac. Chim. Ind. Bologna*, 21, 169 (1963); (b) M. Ueyama, K. Tori, and M. Fukuyama, *Org. Magn. Reson.*, 4, 441 (1972).
50. M. M. Rohmer and B. Roos, *J. Am. Chem. Soc.*, 97, 2025 (1975).
51. R. Hoffman, H. Fujimoto, J. R. Swenson, and C.-C. Wan, *J. Am. Chem. Soc.*, 95, 7644 (1973).
52. N. P. Neureiter, *J. Org. Chem.*, 30, 1313 (1965).
53. L. A. Paquette, *J. Am. Chem. Soc.*, 86, 4383 (1964).
54. (a) E. J. Corey and E. Block, *J. Org. Chem.*, 34, 1233 (1969); (b) L. A. Paquette and R. W. Houser, *J. Am. Chem. Soc.*, 91, 3870 (1970).
55. W. Middlebos, J. Strating, and B. Zwanenberg, *Tetrahedron Lett.*, 351 (1971).
56. (a) L. A. Paquette, *J. Am. Chem. Soc.*, 86, 4085 (1964); (b) F. G. Bordwell and J. M. Williams, Jr., *ibid.*, 90, 435 (1968); (c) F. G. Bordwell and M. D. Wolfinger, *J. Org. Chem.*, 39, 2521 (1974).
57. L. A. Paquette, *J. Am. Chem. Soc.*, 86, 4089 (1964).
58. L. A. Paquette and L. S. Wittenbrook, *J. Am. Chem. Soc.*, 90, 6783 (1968).
59. (a) H. Krauch and W. Kunz, *Organic Name Reactions*, Wiley, New York, 1964, p. 220; (b) K. J. Farrington and W. K. Warburton, *J. Org. Chem.*, 30, 2763 (1965).
60. F. G. Bordwell and E. Doomes, *J. Org. Chem.*, 39, 2526 (1974).

61. R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, 87, 395, 2046 (1965).
62. R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, 8, 781 (1969).
63. P. Kirby, S. B. Soloway, J. H. Davies, and S. B. Webb, *J. Chem. Soc., C*, 2250 (1970).
64. L. A. Paquette, *Org. React.*, 25, Chap. 1 (1977).
65. J. C. Phillips, J. V. Swisher, D. Haidukewych, and O. Morales, *J. Chem. Soc., Chem. Commun.*, 22 (1971).
66. W. F. Farrar, *J. Chem. Soc.*, 3058 (1960).
67. J. C. Sheehan, U. Zoller, and D. Ben Ishai, *J. Org. Chem.*, 39, 1817 (1974).
68. (a) W. R. Hardstaff and R. F. Langler, *Org. Mass Spectrom.*, 10, 215 (1975); (b) R. F. Langler, W. S. Mantle, and M. Newman, *ibid.*, 10, 1135 (1975).
69. (a) C. Y. Meyers, A. M. Malte, and W. S. Matthews, *J. Am. Chem. Soc.*, 91, 7510 (1969); (b) C. Y. Meyers and A. M. Malte, *ibid.*, 91, 2123 (1969); (c) C. Y. Mayers and L. L. Ho, *Tetrahedron Lett.*, 4319 (1972).
70. C. Y. Meyers, W. S. Matthews, G. J. McCollum, and J. C. Branca, *Tetrahedron Lett.*, 13, 1105 (1974).
71. E. Vilsmaier, R. Tropitzsch, and O. Vostrowsky, *Tetrahedron Lett.*, 46, 3987 (1974).
72. (a) R. M. Dodson, P. D. Hammen, E. H. Jancis, and G. Klose, *J. Org. Chem.*, 36, 2698 (1971); (b) R. M. Dodson, P. D. Hammen, and J. Y. Fan, *ibid.*, 36, 2703 (1971).
73. C. Y. Meyers, W. S. Matthews, and J. McCollum, *Heterocycles*, 9, 1486 (1978).
74. C. Y. Meyers, L. L. Ho, G. J. McCollum, and J. Branca, *Tetrahedron Lett.*, 2, 1843 (1973).
75. L. A. Paquette and S. Maiorana, *J. Chem. Soc., Chem. Commun.*, 313 (1971).
76. (a) E. Vogel, *Angew. Chem., Int. Ed. Engl.*, 1, 53 (1963); (b) E. L. Stogryn, M. H. Gianni, and A. J. Passanate, *J. Org. Chem.*, 29, 1275 (1964); (c) R. A. Braun, *ibid.*, 28, 1383 (1963).
77. G. Schröder, J. F. M. Oth, and M. Merenyi, *Angew. Chem.*, 77, 774 (1965); *Angew. Chem., Int. Ed. Engl.*, 4, 752 (1965).
78. E. Vogel, D. Wendisch, and W. R. Roth, *Angew. Chem.*, 76, 432 (1964); *Angew. Chem., Int. Ed. Engl.*, 3, 443 (1964).
79. S. Matsumura, T. Nagai, and N. Tokura, *Tetrahedron Lett.*, 3929 (1966).
80. E. Vilsmaier and B. Hloch, *Synthesis*, 428 (1971).
81. E. Vilsmaier, R. Tropitzsch, and O. Vostrowsky, *Tetrahedron Lett.*, 37, 3275 (1974).
82. F. G. Bordwell and B. B. Jarvis, *J. Am. Chem. Soc.*, 95, 3585 (1973).
83. B. B. Jarvis, S. D. Dutkey, and H. L. Ammon, *J. Am. Chem. Soc.*, 94, 2136 (1972).
84. Y. Ito, M. Okano, and R. Oda, *Tetrahedron*, 23, 2137 (1967).
85. (a) H. Nozaki, M. Takaku, and Y. Hayashi, *Tetrahedron Lett.*, 2303 (1967); (b) H. Nozaki, M. Takaku, Y. Hayashi, and K. Kondo, *Tetrahedron*, 24, 6563 (1968).
86. J. Ide and Y. Yura, *Tetrahedron Lett.*, 3491 (1968).
87. T. B. R. A. Chen, J. J. Burger, and E. R. de Waard, *Tetrahedron Lett.*, 51, 4527 (1977).
88. L. A. Paquette and R. W. Houser, *J. Am. Chem. Soc.*, 93, 4522 (1971).
89. L. A. Paquette, R. H. Meisinger, and R. E. Wingard, Jr., *J. Am. Chem. Soc.*, 95, 2230 (1973).
90. L. A. Paquette, R. E. Wingard, Jr., and R. H. Meisinger, *J. Am. Chem. Soc.*, 93, 1047 (1971).
91. Y. Hayashi, H. Nakamura, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 46, 667 (1973).

VII. THIIRENES

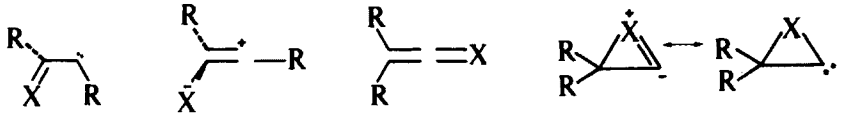
1. Introduction

Unsaturated three-membered rings are of particular interest both theoretically and synthetically. Unsaturated three-membered heterocycles possessing a cycle of 4π electrons (i.e., **1**) are even more intriguing.

1

X = N, O, S, Se, etc.

This class of compounds, which may be considered to be the heterocyclic analogs of cyclobutadiene, were thought for quite some time to be an elusive breed. Not only do they belong to the [$4n$] π-electron ring systems, which defy Hückel's aromaticity rule, but according to Breslow's postulate[1] these systems possess an antiaromatic character. As such they offer a considerable challenge to synthesis. Because of their strain and putative electronic destabilization,[2] these molecules are expected to manifest low thermodynamic stability and to be both unimolecularly and bimolecularly reactive, if they exist at all as energy minima.[2,3] However, in view of the interest in antiaromatic thiirenes (**1**; X = S)[4] as reaction intermediates as well as in their energy relative to the isomeric carbene **2**, the zwitterion **3**, the heterocumulene **4**, and the cyclic carbene **5**, calculations using Modified Intermediate Neglect Differential Overlap (MINDO/3) and a newly parameterized version of No Neglect Differential Overlap (NNDO) have been performed[5] on these species. These calculations indicated that thiirene **1** (X = S) does lie in a local energy minimum, implying that if it is generated in chemical reactions under appropriate conditions, it should be isolable as a stable intermediate. The same conclusion has been reached with respect to the other antiaromatic members of series **1**.

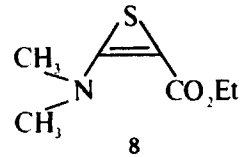


2 **3** **4** **5**

In spite of numerous attempts, neither the parent nor a single derivative of heterocyclic molecules of type **1** (namely, thiirene and its kindred systems, azirene, oxirene, and selenirene) had been prepared until 1976, excluding several derivatives of both thiirene oxide (**6**)[5] and thiirene dioxide (**7**)[7] that have been prepared by Carpino and co-workers.

6 7

Nevertheless, **7** should probably be related to the corresponding cyclopropenones and the cyclopropylium cations, respectively, rather than to the antiaromatic species of series **1**. Indeed, both thiirene oxides and thiirene dioxides (i.e., **6** and **7**) proved to be rather stable compounds[6,7] (particularly **6**; R = phenyl),[8] whereas several thiirene molecules have been only very recently prepared and characterized under low temperature matrix conditions.[9,10] Evidence for the transient existence of thiirenes as short-lived reaction intermediates accumulated (see Section IX, 4) beginning about 10 years before the first matrix-prepared thiirene. However, since (*a*) several thiirenes can be prepared and characterized (though in matrix and under exceptionally mild conditions),[9,10] (*b*) MINDO/3 predicts the parent thiirene (**1**; X = S) to be much more stable than **5** (the difference being 78 kJ/mole),[5] and (*c*) the heat of hydrogenation (which provides a measure of antiaromaticity) of **1** (X = S) is about the same as that of cyclopropene, the preparation of a relatively stable thiirene possibly of the push-pull type (i.e., **8**), may turn out to be successful. Interestingly, electron-withdrawing substituents were found to exert a marked stabilizing effect on the 4π-electron ring system.[10]



8

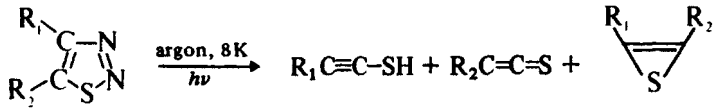
However, attempts to prepare the thiirenes **9**[11] and **10**[8] using various techniques and methodologies (excluding that of low temperature matrix) have failed thus far.

9 10

2. Methods of Preparation and Characterization

The preparation and characterization of thiirenes have been realized so far only through the use of low-temperature matrix isolation (and characterization) technique. Almost in all successful known cases, the "synthesis" has been realized by irradiation in an argon matrix of 1,2,3-thiadiazoles (e.g., **11**) with light of λ = 2350–2800 Å at 8 K.

Thus, the 268 m photolysis of the parent thiadiazole (**11**; $R_1 = R_2 = H$) at about 8 K afforded ethynyl mercaptan (**12**) and thioketene (**13**), along with the sought-for thiirene (**14a**)[9]:



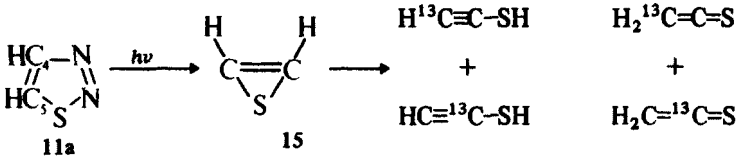
(1)

11 12 13 14

a. $R_1 = R_2 = H$
b. $R_1 = H; R_2 = CH_3$
c. $R_1 = R_2 = CH_3$

Evidence for the formation of thiirenes **14** in the irradiation of thiadiazoles is based primarily on (*a*) their ir spectra (see Section VII, 3), which are reminiscent of those of the analogous cyclopropenes,[12] (*b*) their transformation with light of $\lambda = 3300–3700$ Å to ethynyl mercaptans and thioketenes,[9] and (*c*) the expected label scrambling in the products of both C^{13} labeled and deuterated thiadiazoles that are photolyzed in the matrix under the same conditions.[9]

The latter result is illustrated in Eq. 2.

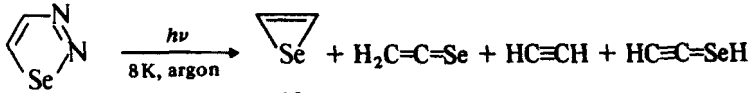


(2)

11a 15

a. $C_4 = {}^{13}C$
b. $C_5 = {}^{13}C$

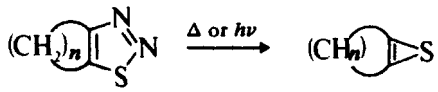
The following thiirenes were prepared and characterized by using the same methodology: 2-methyl,[9] 2,3-dimethyl,[9] 2-trifluoromethyl,[10] 2-methyl,3-carboethoxy,[10] and benzo[10] (see Table 1). Furthermore, what appears to be the first selenium-containing three-membered ring (i.e., selenirene **16**) has been prepared and characterized in an analogous manner[9]:



(3)

16

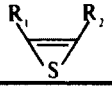
Although the production of thiirenes during the photodecomposition of 1,2,3-thiadiazoles (**11**) is quite probably a general process, a word of reservation with respect to bicyclothiazoles (i.e., **17**) is appropriate.

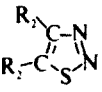
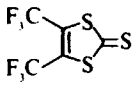
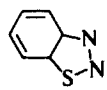
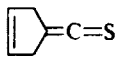


(4)

17 18

TABLE 1. PREPARATION OF THIIRENES

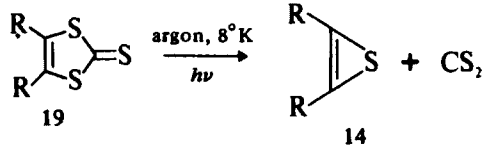


R_1	R_2	Starting material	Accompanying products	Ref.
H	H	 or 	$HC{\equiv}C{-}SC$; $H_2C{=}C{=}S$	9, 10
		$R_1 = R_2 = H$		
CH_3	H	$R_1 = CH_3$; $R_2 = H$	$CH_3CH{=}C{=}S$	9
CH_3	CH_3	$R_1 = R_2 = CH_3$	$(CH_3)_2C{=}C{=}S$	9
CF_3	H	$R_1 = CF_3$; $R_2 = H$	$CF_3C{\equiv}SH$; $CF_3CH{=}C{=}S$; $CF_3C{\equiv}CH$	10
CH_3	CO_2Et	$R_1 = CH_3$; $R_2 = CO_2Et$ $R_1 = CO_2Et$; $R_2 = CH_3$		10
CF_3	CF_3			14
				10

It was recently shown[13] that the products obtained by either pyrolysis or photolysis of **17** ($n = 4$) could *not* result from the thiirene intermediate **18**.

An alternative source for the generation of thiirenes, but nevertheless, using the same low temperature matrix photolysis techniques, consists of the vinylene trithiocarbonate **19** and its derivatives.

Thus, the $\lambda = 230$ nm photolysis of argon matrix isolated vinylene trithiocarbonate (**19a**) produces the parent thiirene **14a**, CS_2, and small amounts of thioketene.[14] Photolysis of the bis(trifluoromethyl) derivatives[15] leads to the formation of CS_2 and high yields of the corresponding thiirenes as illustrated in Eq. 5.[14]



(5)

19

a. R = H
b. R = CF_3

14

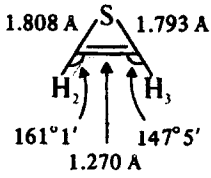
a. R = H
b. R = CF_3

Since electron-withdrawing disubstituted vinylene trithiocarbonates are readily available, they can be used as starting materials for the preparation of disubstituted and relatively stable thiirenes.

3. Structural and Spectroscopic Data

A. *Theoretical Calculations*

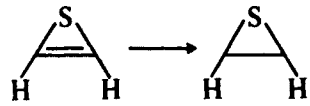
As already mentioned, calculations using MINDO/3 and a newly parameterized version of NDDO indicated the parent thiirene (**1**; R = H) to be potentially stable intermediates in reactions.[5] These calculations also predicted the acyclic carbene H–C(=S)–CH: to rearrange to the corresponding antiaromatic heterocycle **1**; R = H without activation. The heat of formation and the heat of hydrogenation of thiirene were calculated[5] to be 205.4 and 207.5 kJ/mole, respectively, vs. 138.9 and 249.8 kJ/mole for the oxirene and 248.5 (observed 278.7[16]) and 212.6 (observed 225.5[16]) kJ/mole for the cyclopropene. The calculated structure of the thiirene[5] is shown below:



20

The C–H_2 and C–H_3 distances were calculated to be 1.086 and 1.080 Å, respectively. The small deviations from C_{2v} symmetry are probably due to incomplete convergence of the iterative (SIMPLEX) procedure used. It is interesting to note that while the R(C=C) was calculated by another group[17] to be the same as given above (i.e., 1.270 Å), the calculated values for the R(CH, vinyl), α(C=CH), and R(CS) were given[17] as 1.074 Å, 149°55′, and 1.810 Å, respectively. The corresponding values for the cyclopropene are: R(C=C) = 1.300 Å; R(CH, vinyl) = 1.070 Å, and α(C=H) 149°18′.[18]

The comparison with the structural parameters of cyclopropene is appropriate because the available data of the latter are very useful in the estimation of thiirene antiaromaticity and in the assignment of its ir bands (see Section VII, 3, B). Thus, a measure of the antiaromatic destabilization of the thiirene could be obtained from the calculated heat of hydrogenation given by Eq. 6.



14a (6)

The change in ring strain for the above reaction should be about the same as for the hydrogenation of cyclopropene into cyclopropane. Consequently, the heat of hydrogenation of **14a** relative to that of cyclopropane should provide a measure of its antiaromaticity. The corresponding numbers are 207.5[5] and 212.6,[16] respective-

ly, which is remarkably surprising and unexpected. The result clearly suggests that antiaromatic thiirenes should possess some stability, and this indeed was demonstrated experimentally (Section VII, 2).

Previous nonempirical LCAO-MO-SCF calculations with Gaussian-type functions on thiirene[19] gave values of −454.8095 a.u., 2.78 eV, and 3.81 D for the total energy, ionization potential, and dipole moment, respectively, compared with −114.7725 a.u., 9.73 eV, and 0.48 D for the corresponding parameters of the cyclopropene. Since the same study came up with considerably overestimated values for the thiirane compared with those of the cyclopropane, the result, most probably, reflects the limitation of the basis set employed for sulfur, which did not include the important *d* orbitals.

B. *Infrared Spectroscopic Data*

In low temperature matrix isolation synthesis, the principal tool for the detection, characterization, and structural identification of thiirenes is ir spectroscopy.[9,10] The seven ir bands assigned[10] to the parent thiirene molecule are: 3208 (w), 3170 (m), 1660 (w), 912 (s), 660 (m), 563 (m) and 425 (m) cm^{-1}. These bands are expected for thiirene. The assignment of these bands to C–H and C=C stretch, C–H in-plane and out-of-plane bend, and ring deformation was based[10] on the similarity between the fully optimized *ab initio* MO geometry of thiirene[17] and that of cyclopropene[18] and thiirane.[20] The bands at 3166 and 3175 cm^{-1} reported for thiirene and monodeuterated thiirene[9] were considered to be inconsistent with their structure.[10]

The ir spectra of several thiirenes are summarized in Table 2. The relevant data of the reference compounds cyclopropene and thiirane are also given.

Not only is the similarity between the ir spectrum of cyclopropene and that of thiirene apparent, but also the shifts of the C=C stretching due to electron-withdrawing substituents on both compounds[10,14,23] are in the same direction and of the same order of magnitude.

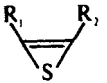
4. Chemical Properties and Reactivity

A. *Stability*

The main feature of thiirenes is their thermal instability. The parallel behavior of thiirene and cyclopropene extends to their ring-opening reaction (under the photolytic reaction conditions of their generation), leading to methylacetylene[24] and ethynylthiol, respectively. Alkyl substituents appear to hinder the rearrangement of thiirenes.

Finally, electron-withdrawing substituents impart increased stability to the thiirene ring, which is manifested in its stability to higher temperatures on the warming of the frozen matrix.[10]

TABLE 2. IR BANDS OF THIIRENES



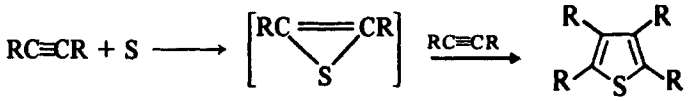
Thiirene	Assigned bands (cm^{-1})	Ref.
$R_1 = R_2 = H$	3208, 3170 1660 912 660 563 425	10
	3207, 3169, 3166 1633 912	9
$R_1 = H; R_2 = D$	3219, 3181, 3175; 2423, 2420, 2415 1611 892 467	9
$R_1 = R_2 = D$	2485 1567 873 423	9
$R_1 = CH_3; R_2 = H$	3203 2930 1440, 1429, 1036 897 650	9
$R_1 = R_2 = CH_3$	2970, 2921, 2865, 1923, 1440, 1427 1041 586 471	9
$R_1 = H; R_2 = CF_3$	3210 1240, 1190, 1180 720	10
$R_1 = CH_3; R_2 = CO_2Et$	3205, 3000, 1875, 1715, 1440, 1400, 1370, 1270, 1070, 1040, 1020, 760, 730 490	10
$R_1 = CF_3; R_2 = CF_3$	1800, 1255, 1030, 975 860, 760	14
$R_1 + R_2 =$	1670, 1440, 970, 950, 720 680, 670	10
Cyclopropene	3158, 3124 1656, 1010, 905 570	21
Thiirane	646, 633	22

B. *Thiirenes as Intermediates in Reactions*

Thiirenes were first postulated as short-lived transients in the addition of $^1D_2$ sulfur atoms to alkynes.[25]

Several reports in the literature provide indirect but compelling evidence for the transient existence of thiirenes as short-lived intermediates.[26]

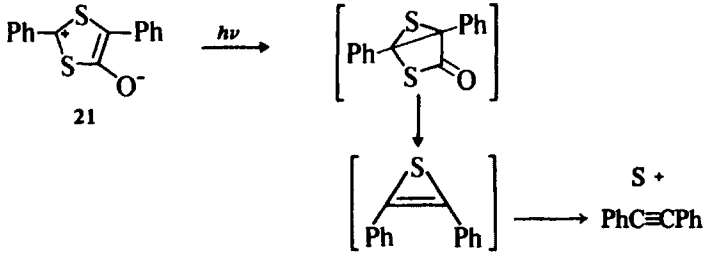
For example, the reaction of sulfur atoms (originated in COS) with acetylenes under flash photolysis conditions[4c] pointed to either the corresponding thioketene or the thiirene structure as the reasonable species, having the decay half-lives in the order of a few seconds. Because thiophenes were also found in these photolyses and given the general behavior of the sulfur atom–olefin system,[4c,27] the intermediacy of thiirenes was concluded. The overall mechanism suggested[4c] is given in Eq. 7.



(7)

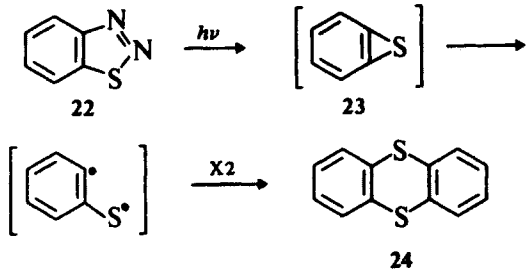
R = H; CH_3CH_2; CF_3CH_2

Irradiation of mesoionic 2,5-diphenyl-1,3-dithiol-4-one (**21**) yielded a mixture containing diphenylacetylene and sulfur in equivalent amounts, in addition to starting material. Transannular cyclization of **21** followed by a loss of COS were suggested to account for the results[28]:



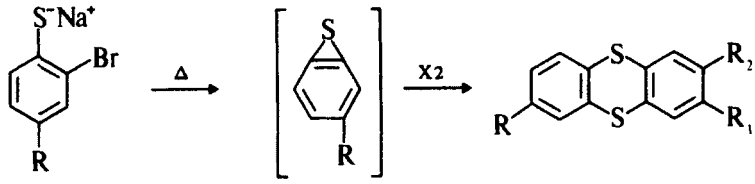
(8)

Photolysis of benzothiadiazole (**22**) has been reported[29] to yield thianthrene (**24**) as the sole product, which suggests the intermediacy of benzothiirene (i.e., **23**):



(9)

Thermolysis of sodium *o*-bromobenzenethiolate (**25a**) yielded thianthrene (**24a**), whereas the 4-methyl derivative **25b** afforded a 1:1 mixture of thianthrenes **24b** and **24c**, which can arise from a benzothiirene intermediate (**26**)[30]:



(10)

25 **26** **24**

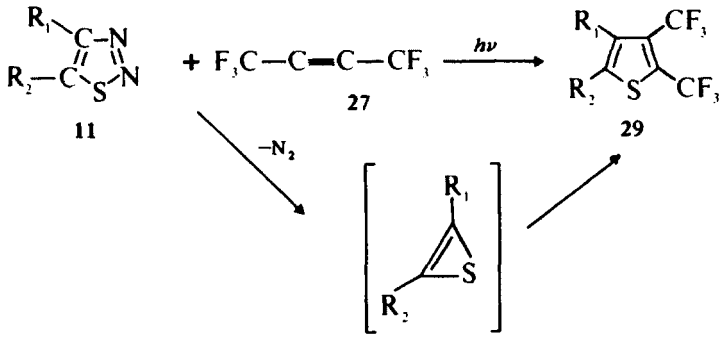
a. R = H
b. R = CH_3

a. $R = R_1 = R_2 = H$
b. $R = R_1 = CH_3$; $R_2 = H$
c. $R = R_2 = CH_3$; $R_1 = H$

Thermolysis of 6-carbomethoxybenzothiadiazole gave a similar mixture of thiianthrenes[31] (**24**, R = CO_2Me; R_1 = H or CO_2M; R_2 = H or CO_2Me). This result corroborates the suggestion that benzothiirene is indeed the intermediate in the thermolyses above.

The involvement of thiirenes in the matrix photolysis of 1,2,3-thiadiazole was suggested[32] before its actual identification and characterization based on the study of the photoproducts thioketene (**13**) and ethynylmercaptan (**12**) (Eq. 1).

Finally, the chemical trapping of thiirenes from the gas phase photolysis of 1,2,3-thiadiazoles and 4- or 5-methyl-1,2,3-thiadiazoles with hexafluoro-2-butyne to yield 2,3-bis(triflurormethyl)thiophene has also been demonstrated recently[33]:



(11)

11 **27** **29** **28**

a. $R_1 = R_2 = H$
b. $R_1 = CH_3$; $R_2 = H$
c. $R_1 = H$; $R_2 = CH_3$

a. $R_1 = R_2 = H$
b. $R_1 = CH_3$; $R_2 = H$
c. $R_1 = H$; $R_2 = CH_3$

a. $R_1 = R_2 = H$
b. $R_1 = CH_3$; $R_2 = H$
c. $R_1 = H$; $R_2 = CH_3$

Since both isomers **11b** and **11c** yield only one and the same product (**29c**), a common precursor, namely methylthiirene (**28b** or **28c**), is mandatory.

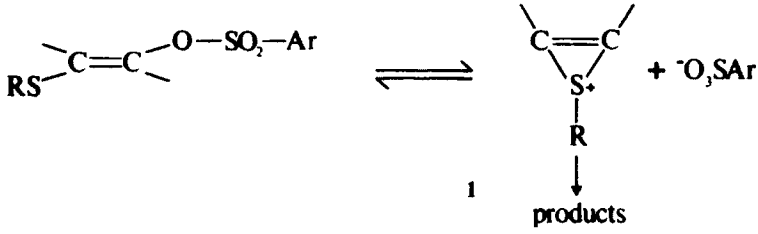
5. References

1. R. Breslow, *Acc. Chem. Res.*, 6, 393 (1973).
2. W. A. Lathan, L. Radom, P. C. Hariharan, W. J. Hehre, and J. A. Pople, *Fortschr. Chem. Forsch.*, 40, 1 (1973).
3. (a) R. Zahradnic, *Adv. Heterocycl. Chem.*, 5, 14 (1965); (b) B. A. Hess, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, 95, 3907 (1973); (c) I. G. Csizmadia, H. E. Gunning, R. K. Gosavi, and O. P. Strausz, *ibid.*, 95, 113 (1973).
4. (a) P. G. Mente and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 418, 1972; (b) G. N. Schrauzer and H. Kisch, *J. Am. Chem. Soc.*, 95, 2501 (1973); (c) O. P. Strausz, J. Font, E. L. Dedio, P. Kebarle, and H. E. Gunning, *ibid.*, 89, 4805 (1967).
5. M. J. S. Dewar and C. A. Ramsden, *J. Chem. Soc., Chem. Commun.*, 688 (1973).
6. L. A. Carpino and W. Wu Chen, *J. Am. Chem. Soc.*, 93, 785 (1971); 101, 390 (1979).
7. L. A. Carpino, L. V. McAdams III, R. H. Rynbrandt, and J. W. Spievak, *J. Am. Chem. Soc.*, 93, 476 (1971).
8. U. Zoller, unpublished results.
9. A. Krantz and J. Laureni, *J. Am. Chem. Soc.*, 99, 4842 (1977); *Ber. Bunsenges. Phys. Chem.*, 82, 13 (1978).
10. M. Torres, A. Clement, J. E. Bertie, H. E. Gunning, and O. P. Strausz, *J. Org. Chem.*, 43, 2490 (1978).
11. P. Raynolds, S. Zonnebelt, S. Bakker, and R. M. Kellogg, *J. Am. Chem. Soc.*, 96, 3146 (1974).
12. (a) K. B. Wiberg and B. Nist, *J. Am. Chem. Soc.*, 83, 1226 (1961); (b) D. F. Eggers, J. W. Schultz, K. B. Wiberg, E. L. Wagner, L. M. Jackman, and R. L. Erskine, *J. Chem. Phys.*, 47, 946 (1967); (c) G. L. Closs, *Adv. Alicycl. Chem.*, 1, 53 (1966).
13. U. Timm, H. Bühl, and H. Meier, *J. Heterocycl. Chem.*, 15, 697 (1978).
14. M. Torres, A. Clement, H. E. Gunning, and O. P. Strausz, *Nouv. J. Chim.* 3, 149 (1979).
15. B. R. O'Connor and F. N. Jones, *J. Org. Chem.*, 35, 2002 (1970).
16. K. B. Wiberg, W. J. Bartley, and F. P. Lossing, *J. Am. Chem. Soc.*, 84, 3980 (1962).
17. O. P. Strausz, R. K. Kosavi, F. Bernardi, P. G. Mezey, J. D. Goddard, and I. G. Csizmadia, *Chem. Phys. Lett.*, 53, 211 (1978).
18. P. H. Kasai, R. J. Myers, D. F. Eggers, Jr., and K. B. Wiberg, *J. Chem. Phys.*, 30, 512 (1959).
19. D. T. Clark, *Theor. Chim. Acta*, 15, 225 (1969).
20. G. L. Cunningham, Jr., A. W. Boyd, R. J. Myers, W. D. Gwinn, and W. J. LeVan, *J. Chem. Phys.*, 19, 676 (1951).
21. R. W. Mitchell, E. A. Dorko, and J. A. Merritt, *J. Mol. Spectrosc.* 26, 197 (1968).
22. M. Falk, Ph.D. Thesis, the University of Alberta, 1974.
23. G. L. Closs in *Advances in Alicyclic Chemistry*, Vol. 1, H. Hart and G. J. Karabastos, Eds., Academic Press, New York, 1966, p. 75.
24. K. B. Wiberg and W. J. Bartley, *J. Am. Chem. Soc.*, 82, 6375 (1960).
25. E. L. Dedio, Ph.D. Thesis, the University of Alberta, 1967.
26. (a) J. Fenwick, G. Frater, K. Ogi, and O. P. Strausz, *J. Am. Chem. Soc.*, 95, 124 (1973) and references cited therein; (b) T. L. Gilchrist, G. E. Cymet, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1 (1975); (c) C. Thetaz and C. Wentrup, *J. Am. Chem. Soc.*, 98, 1258 (1976); (d) T. L. Gilchrist, R. G. Mente, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2165 (1972); (e) F. Boberg, J. Schröder, and R. Schardt, *Ann. Chem.*, 2267 (1976).

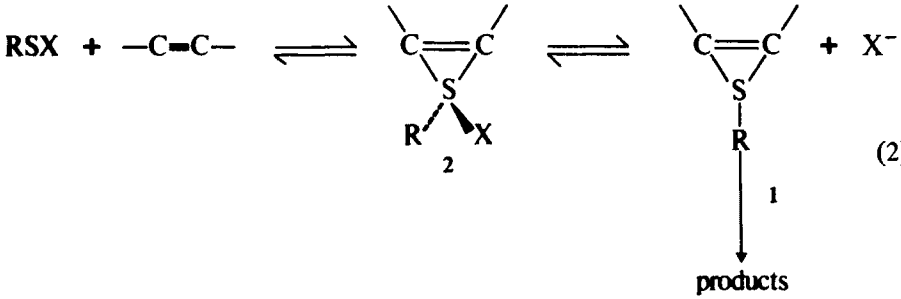
27. H. E. Gunning and O. P. Strausz, *Adv. Photochem.*, 4, 143 (1966).
28. H. Kato, M. Kowamura, T. Shiba, and M. Ohta, *J. Chem. Soc., Chem. Commun.*, 959 (1970).
29. K. P. Zeller, H. Meier, and E. Müller, *Tetrahedron Lett.*, 537 (1971).
30. J. I. Cadogan, J. T. Sharp, and M. J. Trottles, *J. Chem. Soc., Chem. Commun.*, 900 (1974).
31. T. Wooldridge and T. D. Roberts, *Tetrahedron Lett.*, 2643 (1977).
32. A. Krantz and J. Laureni, *J. Am. Chem., Soc.*, 96, 6768 (1974).
33. J. Font, M. Torres, H. E. Gunning, and O. P. Strausz, *J. Org. Chem.*, 43, 2487 (1978).

VIII. THIIRENIUM IONS (THIIRENIUM SALTS)

The history of thiirenium ions is barely more than 10 years old: several papers by the group of Modena and co-workers[1-5] presented evidence that species of this class are involved as intermediates both in the addition of arylsulfenyl halides to disubstituted acetylenes[5] and in unimolecular substitution reactions of β-arylthiovinyl sulfonates. Nevertheless, these reactive species undergo either nucleophilic attack by the counterion under the reaction conditions or further chemical transformation to give noncyclic products. These two routes for the generation of thiirenium ions are exemplified in Eqs. 1 and 2.



(1)



(2)

The thiirenium ions **1** have been postulated as intermediates for quite some time.[4,7] Their existence, however, was demonstrated by chemical, stereochemical, and kinetic studies only in the late 1960s[1,5] and early 1970s.[6] Although the cyclic cationic structure depicted in **1** did explain all the available experimental

data, and some thiirenium ions have been detected by nmr spectroscopy[8] as stable species in liquid SO_2 at low temperature, their actual isolation as hexachloroantimonate or tetrafluoroborate has been achieved only very recently.[9] The intervention of a sulfurane species of type 2 in addition reactions of sulfenyl halides to acetylenic compounds in low polarity solvents has also been recently invoked.[10]

It is worth mentioning not only the analogy and similarity between the chemistry of the thiirenium ions and that of the thiiranium ions, their saturated counterparts (see Section IV), but also the correlation in the development of the chemistry of both "families" as summarized below:

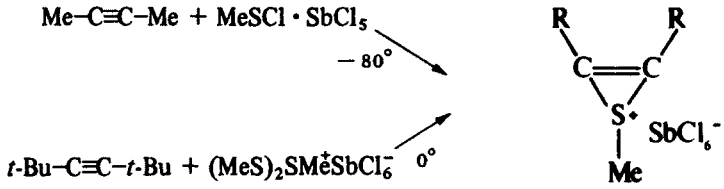
1. Intermediacy postulated.
2. Intermediacy demonstrated experimentally by means of chemical, stereochemical, and kinetical studies.
3. Existence detected by low temperature spectroscopy.
4. Preparation, isolation, and characterization.

This history is probably typical for chemically and thermodynamically unstable three-membered rings containing sulfur and/or other heteroatoms as well.

1. Methods of Preparation

The observation that several alkyl-substituted thiirenium hexachloroantimonates are stable for long periods at low temperature in liquid sulfur dioxide[8] led eventually to the first synthesis and isolation of relatively stable thiirenium salts. As with other three-membered rings,[11-15] bulky alkyl substituents impart special stability to this ring system. The only isolated member of the series that is stable at room temperature is the 1-methyl-2,3-di-*t*-butylthiirenium hexachloroantimonate (**3**).

The preparation of relatively stable and isolable thiirenium salts can be realized by the addition of sulfonium hexachloroantimonates to disubstituted acetylenes in dichloromethane[9] as depicted in Eq. 3.

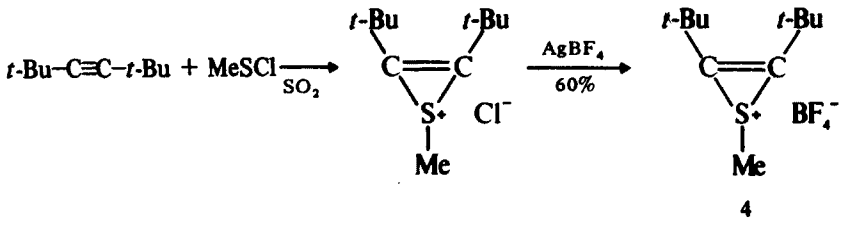


(3)

3

a. R = CH_3
b. R = *t*-Bu

While **3a** decomposes in the solid state above $-40°$ and is very sensitive to moisture, **3b** can be recrystallized and is stable at room temperature. The chloride of **3b** can also be prepared and transformed into a relatively stable tetrafluoroborate salt (**4**)[9]:



(4)

4

Since alkyl-substituted thiirenium chlorides (e.g., trimethylthiirenium ion) easily react with chloride ion to give methylthiovinyl chlorides, the low nucleophilicity of the antimonate and borate counterions clearly contributes to the stability of **3** and **4**. The similarity of the problems and chemistry involved in the preparation of thiiranium and thiirenium salts is apparent.

2. Structure and Physical Properties

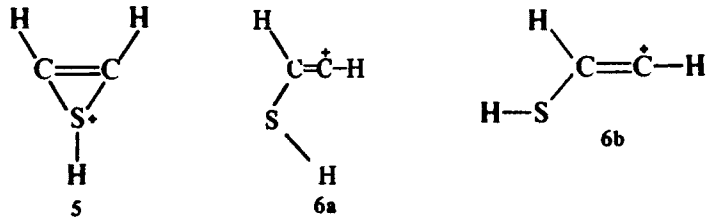
Table 1 summarizes the available physical and spectral data of the isolable or the *in situ* formed thiirenium salts. A recent low temperature x-ray study[16] of 1-methyl-2-2-di-*t*-butylthiirenium tetrafluoroborate (**4**) allowed the full characterization of the molecular structure of this heterocyclic system, and selected relevant parameters are also included in Table 1.

The general molecular structure of thiirenium salts as reflected in the parameters determined for **4** agrees with predictions based on theoretical calculations (see Section VIII, 2, A). Clearly, the sulfonium sulfur atom assumes a pyramidal conformation so that the alkyl substituent (methyl in this particular case) is out of the plane of the three-membered ring.

The length of the S–C_4 bond compares favorably with that for a C(sp^3)–S bond.[17] C_2–S and C_3–S bond lengths are consistent with the expected absence of any double bond character,[16] and the C_2=C_3 double bond can be compared with the analogous double bond in cyclopropene (1.294 Å).[18]

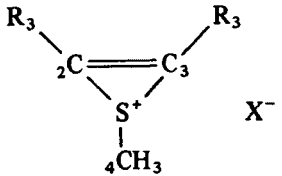
A. *Theoretical Calculations on Thiirenium Ions*

Nonempirical SCF-MO investigations with split-valence basis sets were performed[19,20] on the $C_2H_2SH^+$ cation with optimization of four limiting structures corresponding to the pyramidal and planar thiirenium ions **5** and to the *S-cis* and *S-trans* vinyl cations **6**[19]:



5 6a 6b

TABLE 1. PHYSICAL, SPECTRAL, AND STRUCTURAL DATA FOR STABLE THIIRENIUM SALTS



			Nmr chemical shift, δ (ppm)[a]			Bond lengths (A)			Bond angles (°)[b]			
R_2, R_3	X	m.p. (°C)	δCH_3	$\delta R_2, R_3$	^{13}C nmr (ppm) C_2, C_3	C_2–C_3	C_2–S	C_3–S	C_2SC_3	SC_2C_3	C_2C_3S	Ref.
CH_3	$SbCl_6$	−40 (dec.)	2.51	2.77								9
t-Bu	$SbCl_6$	151–152 (decomp.)	2.62	1.54	113.4							9
t-Bu	BF_4	137–138 (decomp.)	2.62	1.54		1.277	1.819	1.820	41.1	69.5	69.4	9, 16

[a] In SO_2.
[b] Angles C_2S,C_4 and C_3S,C_4 are 106°3′ and 106°, respectively.

TABLE 2. OPTIMIZED GEOMETRIES AND CORRESPONDING ENERGIES FOR 5: CYCLIC $C_2H_2SH^+$

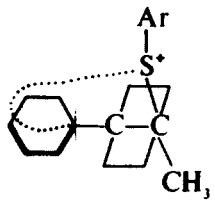
	Pyramidal thiirenium ion	Planar thiirenium ion
Bonds		
C=S	1.2544 Å	1.2897 Å
C–S	2.0515 Å	1.9124 Å
C–H	1.0714 Å	1.0666 Å
S–H	1.3682 Å	1.3558 Å
Angles		
SSC	72.20°	70.30°
HCC	161.54°	154.61°
HSC	97.58°	160.30°
E_{total}	−474.0298 kcal/mole	−473.9118 kcal/mole

It was found[19] that the pyramidal bridged structure (i.e., **5** with pyramidal conformation at the sulfur atom) was somewhat more stable than both open structures. The planar bridged structure was found to be on an energy maximum. In all these computations[19,20] one geometrical parameter was varied at a time and the remaining parameters were kept constant. The cyclic structures (e.g., **5** pyramidal and **5** planar) have been optimized with the symmetry constraints characteristic to them. Table 2 summarizes the optimized geometries and the relative energies that were calculated.[19]

B. *Conclusions*

The comparison of the calculated values with those found experimentally for **4**[16] (see Table 1) is rather instructive. The planar bridged structure may be considered as the transition state for the formal process of pyramidal inversion. However, the pyramidal inversion energy is rather large (74.03 kcal/mole).[19] At any rate, there are very easy paths (energetically) for the interconversion of the two enantiomeric pyramidal thiirenium ions via the β-thiovinyl open structures (i.e., *s-cis* and *s-trans* **6**), whereas the pure pyramidal inversions seem to be energetically forbidden. Indeed, overall, the calculated results are in fair agreement with the available experimental results; namely the x-ray determined molecular structure of the thiirenium salt **4** and the easy collapse of thiirenium halides to the corresponding thiovinyl halides.

Furthermore, the favored pyramidal conformation at the sulfur atom in the three-membered thiirenium molecule rules out any degree of aromaticity from being assigned to this $[4n + 2]$ $(n = 0)$ array of π electrons. It is not surprising, therefore, that in a recent study[21] of the structure of the intermediate phenylthiirenium ion formed by the addition of arenesulfenyl chloride to phenyl-substituted acetylene, the *charge* was depicted as delocalized into the phenyl ring, as best represented by structure **7** rather than by structure **8**:



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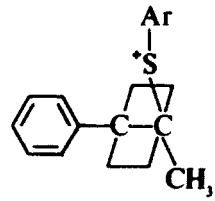
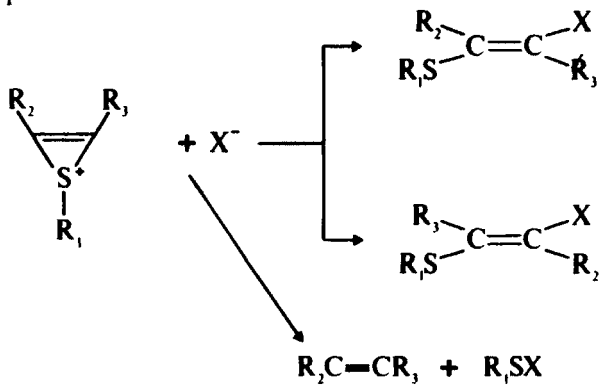


8

3. Chemical Properties

In view of the exceptional instability of the "ordinary" thiirenium three-membered ring system, it is not surprising that its chemical properties have not yet been extensively explored. From the available data, two distinct properties are apparent: first, thiirenium ions or salts are reasonably stable only at low temperatures (excluding those substituted with very bulky groups like 2,3-di-*tert*-butyl-); second, the three-membered ring is easily opened by nucleophiles to give the corresponding thiovinyls[1-5,8-10] via an attack on the ring carbon, or to give acetylenes and sulfenyl compounds via attack of the nucleophile at the sulfur atom,[5] as illustrated in Eq. 5.



(5)

As expected, there is a great deal of a similarity between the chemistry of thiirenium ions and that of thiiranium ions. Yet, many aspects of thiirenium ion chemistry remain to be explored and clarified.

4. References

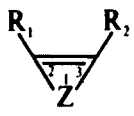
1. G. Capozzi, G. Melloni, G. Modena, and U. Tonellato, *J. Chem. Soc., Chem. Commun.*, 1520 (1969).
2. (a) G. Capozzi, G. Melloni, and G. Modena, *J. Chem. Soc., C*, 2621 (1970); (b) G. Capozzi, G. Melloni, and G. Modena, *ibid.*, 2625; (c) G. Capozzi, G. Melloni, and G. Modena, *ibid.*, 3018.
3. (a) G. Modena and U. Tonellato, *J. Chem. Soc. B*, 381 (1971); (b) G. Modena and U. Tonellato, *ibid.*, 374.

4. (a). G. Modena and G. Scorrano, in *Mechanisms of Reaction of Sulfur Compounds*, Vol. III, N. Kharasch, B. S. Thyagarajan, and A. I. Khodair, Eds., Intrascience Research Foundation, Santa Monica, 1968, p. 115; (b) G. H. Schmid and M. Heinola, *J. Am. Chem. Soc.*, 90, 3466 (1968).
5. G. Modena, G. Scorrano, and U. Tonellato, *J. Chem. Soc., Perkin Trans. 2*, 493 (1973).
6. A. Burighel, G. Modena, and U. Tonellato, *J. Chem. Soc., Chem. Commun.*, 1325 (1971).
7. M. E. Volpin, Y. D. Koreshkov, V. G. Dulova, and D. N. Kursanov, *Tetrahedron*, 18, 107 (1962).
8. G. Capozzi, O. De Lucchi, V. Lucchini, and G. Modena, *J. Chem. Soc., Chem. Commun.*, 248 (1975).
9. G. Capozzi, V. Lucchini, G. Modena, and P. Scrimin, *Tetrahedron Lett.*, 11, 911 (1977).
10. G. Cappozzi, V. Lucchini, and G. Modena, paper presented at the Eighth International Symposium on Organic Sulfur Chemistry, Portoroz, Yugoslavia, June 1978.
11. (a) J. C. Sheehan and J. H. Beeson, *J. Am. Chem. Soc.*, 89, 362 (1967); (b) F. D. Green, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, 34, 2254 (1969); (c) H. Quast and F. Kees, *Angew. Chem.*, 86, 816 (1974).
12. H. Quast and F. Kees, *Angew Chem., Int. Ed. Engl.*, 13, 742 (1974).
13. J. W. Timberlake and M. L. Hodges, *J. Am. Chem. Soc.*, 95, 634 (1973).
14. P. Raynolds, S. Zonnebelt, S. Bakker, and R. M. Kellogg, *J. Am. Chem. Soc.*, 96, 3146 (1974).
15. J. Ciabattoni and E. C. Nathan, *Tetrahedron Lett.*, 4997 (1969), and references cited therein.
16. R. Destro, T. Pilati, and M. Simonetta, *J. Chem. Soc., Chem. Commun.*, 576 (1977).
17. W. Maier, *Angew. Chem.*, 73, 120 (1961).
18. J. D. Dunitz, H. G. Feldman, and V. Schomaker, *J. Chem. Phys.*, 20, 1708 (1952).
19. (a) I. C. Csizmadia, F. Bernardi, V. Lucchini, and G. Modena, *J. Chem. Soc., Perkin Trans. 2*, 542 (1977); (b) I. G. Csizmardia, A. J. Duke, V. Lucchini, and J. Modena, *ibid.*, 1808 (1974).
20. A. S. Denes and I. G. Csizmadia, *J. Chem. Soc., Chem. Commun.*, 8 (1972).
21. G. H. Schmid, A. Modro, D. G. Garrat, and K. Yates, *Can. J. Chem.*, 54, 3045 (1976).

IX. THIIRENE OXIDES

1. Introduction

It is quite surprising that until 1965 not a single stable compound with a heteroatom substituted at position 1 as in 1 had been synthesized or isolated.



1

Z = O, NR_3, PR_3, S, Se, etc.

Previously, the only stable isolable compounds incorporating a heteroatom in a cyclopropene ring system were derivatives of the 1-azirine[1] and 1-diazirine[2] systems (i.e., 2 and 3, respectively). In these systems the double bond is adjacent to the heteroatom(s), not "conjugated" to it as in 1.

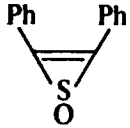
2

3

There is a uniqueness in systems of type 1. In cases of Z = O, NR, or PR_3 they may be considered to be "classical" antiaromatic[3–5] systems featuring a cyclic array of 4π electrons and predicted by theory to be highly unstable.[6]

On the other hand, on the basis of a naive analogy with the now well-known cyclopropenones, some kind of "aromaticity" can, in principle, be assigned in the case of the third-row elements by assuming *d*-orbital conjugation effects.[7] This is particularly valid when position 1 is occupied by oxidized forms of the heteroatom (i.e., 1; Z = SO, SO_2; S = NR, etc.). However, there is considerable controversy over whether conjugative effects can be transmitted through a center second-row atom using *d* orbitals.[8]

The first members of this class of thiirene sulfoxide (e.g., 4)[9] and thiirene sulfones (e.g., 5–7)[7] were synthesized, isolated, and characterized by L. Carpino and co-workers.[7,9]



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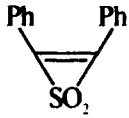

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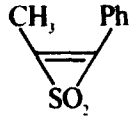

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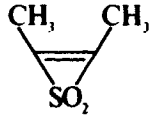


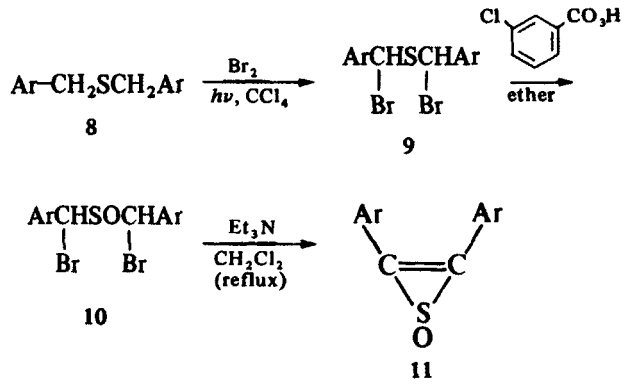
7

Thiirene sulfoxides appear to be the only unsaturated "antiaromatic" three-membered ring system that can be handled on a "bench scale" under ordinary laboratory conditions.

2. Methods of Preparation

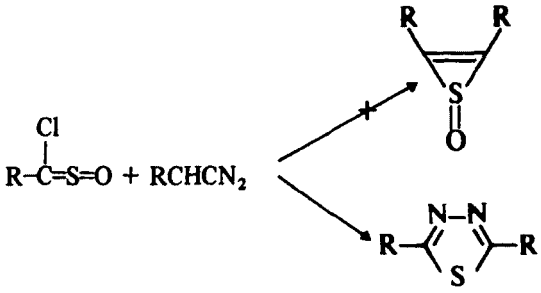
Three-membered rings have been prepared by a variety of cyclization methods.[10] One of the most useful cyclization methods for the preparation of sulfur-containing three-membered rings[11] is the Ramberg–Bäcklund reaction.[12] This approach also was developed into a general route to the corresponding thiirene oxides via reaction of benzylic α,α'-dibromosulfoxides with triethylamine. In fact, all thiirene oxides known to date have been synthesized by this procedure,[7,9,13] which is shown in Eq. 1.[13]

Although the route is laborious and lengthy, and the overall yield is rather low, it is the only method available thus far for the preparation of thiirene oxides and



(1)

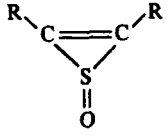
has been applied only to symmetrically aryl-substituted members (**11**)[9,13] (see Table 1). The alkyl-substituted analogs are unknown, and their preparation apparently must await the development of an appropriate alternative synthetic method. As a matter of fact, several methods that were examined[14] for the preparation of such unsaturated sulfoxides failed. The following is an example:

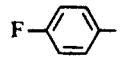


(2)

for R = C_6H_5; no reaction for R = CH_3

TABLE 1. THIIRANE OXIDES PREPARED THROUGH THE MODIFIED RAMBERG-BÄCKLUND ROUTE[9,13]



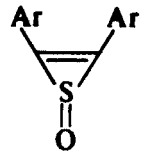
R	m.p. (C°)	Overall yield (%)[a]	Recrystallization solvent	Ref.
C_6H_5	92.5–93.1	14–22	Ligroin	9, 13
	157–160 (decomp.)	16.5	Benzene-ligroin	13, 14
	120–121	19	Benzene-ligroin	13, 14

[a] Starting with the corresponding dibenzyl sulfide **8** (Eq. 1).

It should be emphasized that the overall yields cited in Table 1 refer to a very careful work-up in each step of the sequence depicted in Eq. 1. Pure recrystallized α,α′-dibromobenzyl sulfides (**9**) as well as α,α′-dibromobenzyl sulfoxides (**10**) should be obtained and isolated in the appropriate steps *before* being applied in the next step; otherwise, the overall yield will be even poorer. However the key cyclization step (i.e., the transformation of the **10** to **11**), using excess of triethylamine in refluxing methylene chloride for 24–48 hr, gives the desired thiirene oxides in about 50% yield.[9, 13, 14] The cyclization of **10** (Ar=C_6H_5) to the thiirene oxide **4** can also be effected by using aqueous NaOH, although the yield is low (9%).[13]

3. Structure and Physical Properties

The known thiirene oxides (**11a–11c**) are colorless solids having relatively high melting points (see Table 1); they are readily soluble in common organic solvents. Their uv spectra closely resemble those of the analogous cyclopropenones,[9] and a certain similarity can be found in the nmr spectra of the two analogously substituted systems.[9]

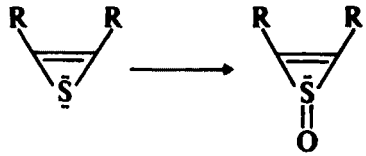


11

a. Ar = C_6H_5
b. Ar = *p*-F–C_6H_5
c. Ar = *m*-F–C_6H_5

A. *Conjugative Effects*

Oxidation of thiirenes into their corresponding oxides (Eq. 3) should have two major effects with respect to the $4n$ ($n = 1$) cyclic π-electron array:

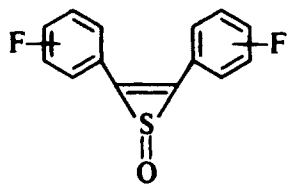


(3)

First, the antiaromatic properties of the thiirene system should be diminished by a reduction in the unshared electron density on sulfur; and second, the interaction of the sulfur $3d$ orbitals with the $2p$ orbitals of both the adjacent carbon and oxygen atoms should increase significantly. Both effects should facilitate some kind of conjugation of the carbon–carbon double bond π electrons with the formally

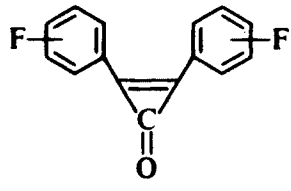
unoccupied 3*d* orbitals, giving rise to Hückel-type stabilization associated with an array of $4n + 2$ ($n = 0$) π electrons. So far the experimental evidence regarding conjugative stabilization is not decisive.

Based on the work of Taft and co-workers[16] on fluorobenzenes, which permitted the isolation of the inductive (σ_I) and conjugative (σ_R) effects, the σ values of the 2,3-di-meta- and 2,3-di-parafluorophenylthiirene oxides (**12a, 12b**) were calculated (based on the measured shielding parameters of these compounds)[13] and compared with the σ values of corresponding bis(meta- and parafluorophenyl) cyclopropenones (**13a, 13b**).



12

a. para-F
b. meta-F



13

a. para-F
b. meta-F

These comparisons of σ_R (0.16 and 0.25 for **12** and **13** respectively), showed that the electron-withdrawing conjugative effect increases in the order thiirene oxide < thiirene dioxide < cyclopropene. Although this result agrees with earlier studies on the relative order of conjugative interaction in simple sulfoxides and sulfones vs. enones, it does not prove whether these are simple conjugative interactions or involve *cyclic* conjugative effects with transmission through the sulfur atom.[8]

It is relevant to point out in this respect that the chemical shifts of the ring carbon atoms in ^{13}C studies were found to be 137.3,[17] 158.9,[17] and 148.5 ppm for 2,3-diphenylthiirene oxide (**4**), 2,3-diphenylthiirene dioxide (**5**), and 2,3-diphenylcyclopropenone, respectively. These values probably reflect the relative magnitudes of conjugative effects in these systems.

B. *Molecular Structure*

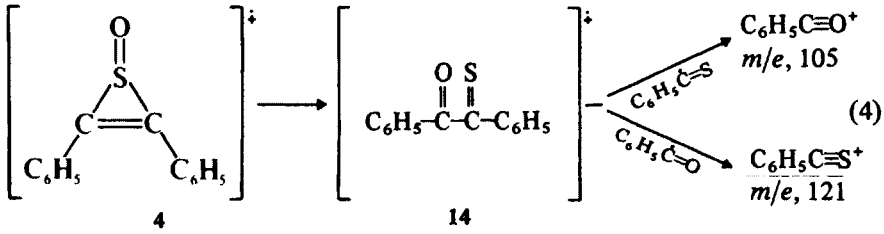
The structure of 2,3-diphenylthiirene oxide (**4**) has been determined[18] with molybdenum K_α diffractometer data (x-ray crystallography). The following bond lengths and angles for the ring of **4** were determined:

Bond lengths (Å)			Angles		
C–C	C–S	S–O	<CSC	<SCC	<CSO
1.305	1.784	1.467	42°9′	68°5′, 68°6′	114°9′, 115°0′

The molecule, thus, has the expected C_s symmetry. The structure also facilitates the maximum degree of phenyl to three-membered-ring conjugation, while minimizing the intramolecular phenyl-phenyl nonbonded interactions as was found for other similar phenyl-substituted three-membered systems.[19] Although an increase in cyclic π delocalization from thiirene to thiirene oxide to thiirene dioxide would result – as was indeed found[18] – in a corresponding increase in the C=C distance and decrease in the C–S distance the interpretation of these differences as evidence for π delocalization is *not* necessarily correct.[18] The S–O distance is similar to bond lengths found in other sulfoxide compounds. Consequently, the S–O bond distance provides an unsatisfactory measure of S–π electron interactions.

C. *Mass Spectrometry*

The electron impact and chemical ionization mass spectra of thiirene oxide (**4**) have been studied.[20] A common feature in the mass spectrum is the high abundance of the substituted acetylene ion (e.g., $[PhC{\equiv}CPh]^{+\cdot}$) formed by elimination of sulfur monoxide. In fact, this ion constitutes the base peak in the spectrum of **4**. The molecular ion, however, has a rather insignificant intensity (0.25% Σ of M^+).[20] Excluding minor peaks that correspond to losses of O and H_2O, the majority of the other ions are products of further decomposition of the diphenylacetylene ion (*m/e* 178). The formation of the other ions can be rationalized in terms of fragmentation products of the monothiobenzyl[21] ion **14**, as depicted in Eq. 4.[26]



(4)

4 **14**

Fragmentation studies by means of chemical ionization (CI) mass spectrometry[22] were also applied to thiirene oxides.[20a] The methane CI spectrum of **4** was found to be dominated by the $(C_6H_5C{\equiv}CC_6H_5 + H)^+$ ion. A distinct molecular ion species at an *m/e* value corresponding to $(M + H)^+$ was observed in this mass spectrum of thiirene oxide **4** (26% Σ 40). Furthermore, the relative intensity of the $(M + H)^+$ peak of **4** was shown to increase substantially in the isobutane and dimethylamine CI mass spectra.

D. *Theoretical Calculations*

Standard CNDO/2 calculations on models of thiirenes have been performed[18] in an attempt to obtain a picture of the bonding in these compounds. Both the

atomic charge densities and bond indices[23] of the parent thiirene, thiirene oxide, and thiirene dioxide have been calculated using model parameters. Although the trends in the carbon-carbon and carbon-sulfur bond indices qualitatively agree with the trends observed in the experimental bond lengths,[18] the sulfur-oxygen indices predicted that the sulfoxide distance should be smaller than the sulfone distance – in contrast to the experimental results. Thus, it was concluded[18] that oxygen charge densities and sulfur-oxygen bond orders provide an insensitive measure of S . . . π-electron interactions, and that the in-plane (C_{Pz}) orbitals are primarily responsible for the bond length variations. The contributions of the out-of-plane $C_{(Py)}$–S interactions to the C–S bond orders in the thiirene series suggest that π delocalization may be of a magnitude comparable to that in cyclopropenones.

The photoelectron spectra of thiirene oxide (4) was interpreted and analyzed in terms of inductive and conjugative interactions between the subunit SO and PhC=CPh.[24] The inductive and conjugative abilities of the sulfoxide group were compared with theoretical data obtained by using the "cutoff" procedure[25] also used to calculate aromaticities and π charge transfer. From these results and corresponding data derived from the parent (unsubstituted) thiirene oxide, it was concluded that 4 is as much an aromatic compound as its parent system is. The conjugative interactions of 4 (i.e., the sum of the energetically unfavorable interaction between the occupied $\pi_{C=C}$ orbital with occupied orbitals of SO and the energetically favorable interaction between the filled $\pi_{C=C}$ orbital and vacant orbital of SO) have been estimated to be 0.25 eV for π_1,[24] vs. the calculated value of 0.1 eV using the CNDO/2 method. The corresponding values for the 2,3-diphenylcyclopropenone are 0.1–0.35 and 0.04 eV, respectively.

E. *AB Initio and Valence Electron Study*

The method of conjugative interruption in conjunction with the CNDO/2[26] and an *ab initio* method have been applied to the intriguing series of molecules shown below:

X = CH_2, C=O, C=S, S=O, and SO_2

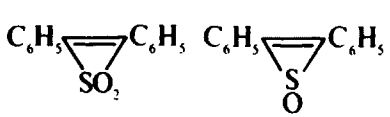
Thus the orbital interactions between the π orbitals of the carbon-carbon double bond and X subunits were quantitatively analyzed with respect to the conjugative and inductive ability of X, the aromaticities and the geometries of the above molecules. Both CNDO/2 and *ab initio* calculations (both in *sp* and *spd* bases) predict the same sequence of orbitals. It was concluded that contributions from hyperconjugation (responsible for π charge transfer from C=C to S=O) and spiroconjugation[28] stabilize the thiirene oxide molecule and that the *d* orbitals play an appreciable role in chemical bonding of this class of compounds. The calculated aromaticity and geometry of the thiirene oxide were found to be in full accord[27]

with the hypothesis that charge is transferred from the bonding $\pi_{C=C}$ orbital into the antibonding $\pi^*_{S=O}$ orbital.

4. Chemical Properties and Reactivity

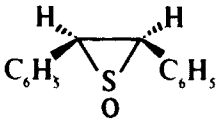
A. *Thermal Stability*

The 2,3-diarylthiirene oxides **11** have been found to have much more thermal stability than both the saturated analogs (e.g., thiiranes) and the corresponding thiirene dioxides. Thus, the 2,3-diphenylthiirene oxide **4** is far more stable than either of the two saturated sulfoxides **15** in spite of the significantly smaller angular strain in *cis*- and *trans*-**15**.

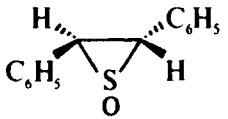


5

4

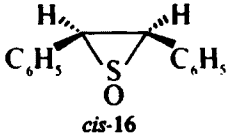


cis-**15**

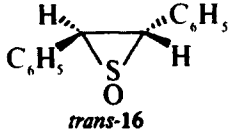


trans-**15**

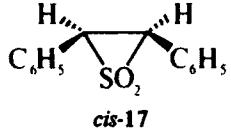
Both *cis*- and *trans*-thiiranes (**15**) lost sulfur monoxide readily on warming.[29] Sulfoxide **4** is markedly more stable than the analogous sulfone **5**: thus, a solution of **4** in refluxing benzene showed only slight decomposition after 24 hr, whereas similar treatment of **5** results in complete decomposition after less than 6 hr.[9] Clearly, there can be no significant antiaromatic destabilizing effects ascribable to the presence of an unshared pair of electrons on the sulfur atom of the thiirene oxide. Furthermore, any stabilizing conjugative effects, if operating, are expected to be greater in sulfoxide rather than in sulfones.[30] Nonetheless, it is highly probable that the lesser stability of thiirene dioxides compared with that of the thiirene oxides simply reflects the more facile extrusion of sulfur dioxide relative to that of sulfur monoxide. In fact, the same effect is probably operative in the case of the *cis*- and *trans*-thiirane oxides **16**[9] vs. the *cis*- and *trans*-thiirane dioxides **17**[31]: the former were found to be more stable toward thermal decomposition than the latter.



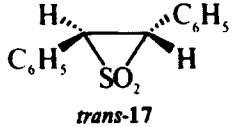
cis-**16**



trans-**16**

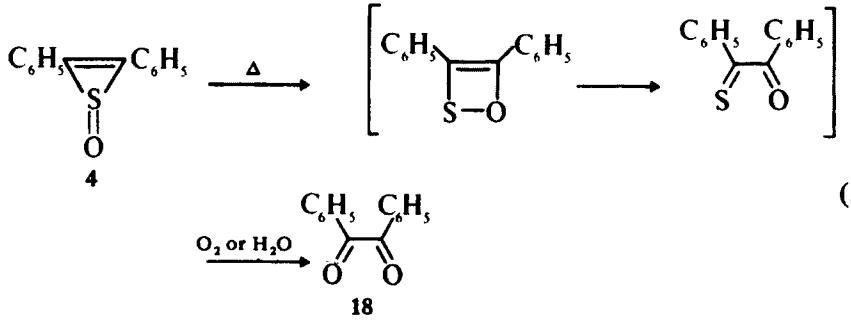


cis-**17**



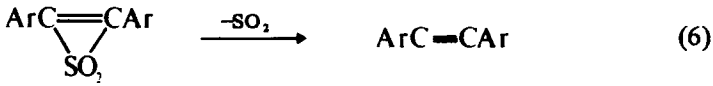
trans-**17**

Thermolysis of **4** at 130° gave benzil (**18**) as the only isolable product,[13] probably according to the scheme outlined in Eq. 5.[13]



(5)

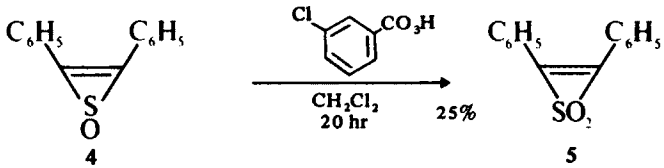
In contrast, uv irradiation of thiirene oxide **4** at 30° in a quartz vessel gave diphenylacetylene[13] (86.5%). Interestingly, all aryl-substituted thiirene dioxides undergo a facile *thermal* decomposition to give the corresponding diarylacetylenes following the loss of sulfur dioxide[7, 13]:



(6)

B. *Oxidation*

In contrast to the unsuccessful attempts to oxidize thiirane oxides to thiirane dioxides,[32] thiirene oxides are oxidizable to the corresponding thiirene dioxides[9, 13] as illustrated in Eq. 7. Metachloroperbenzoic acid appears to be the reagent of choice for this purpose.



(7)

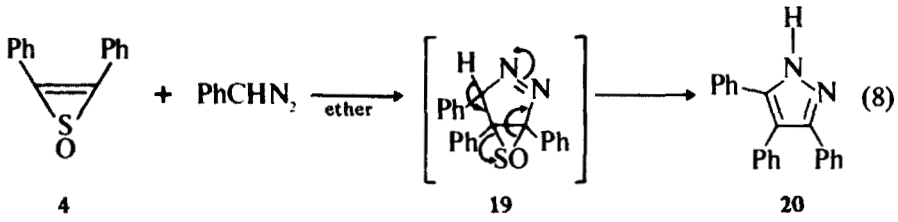
C. *Reduction*

All attempts to reduce the carbon-carbon double bond of the 2,3-diphenylthiirene oxide **4** using different reagents (e.g., Pd/C, Pt sulfide/C, Al(Hg) x H_2O) under a variety of reaction conditions failed.[13] Raney nickel afforded only dibenzyl.[13]

D. *Reactivity of the Carbon-Carbon Double Bond*

a. WITH DIAZO REAGENTS

Treatment of 2,3-diphenylthiirene oxide (**4**) with phenyldiazomethane in ether gave the pyrazole **20** in very low yield, presumably via the labile intermediate **19** as shown in Eq. 8.[13]

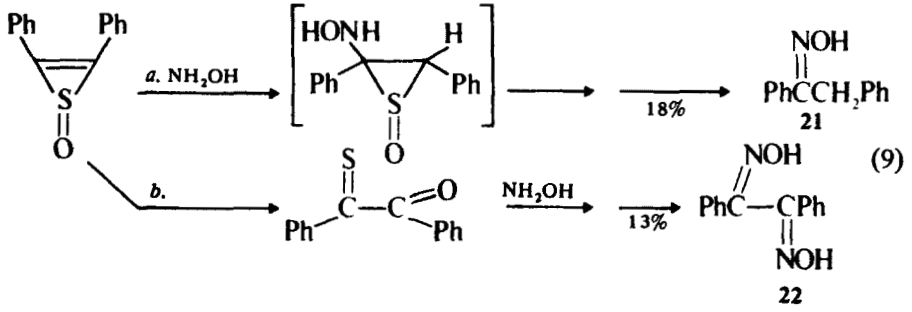


4 19 20

A substantial portion of the thiirene oxide was recovered unchanged.

b. WITH HYDROXYLAMINE

A reaction of thiirene oxide (**4**) with hydroxylamine results in a mixture of the monoxime **21** and the dioxime **22**, presumably as outlined in Eq. 9.



The proposed route *b*[13] is questionable, however, since the monothiobenzyl suggested to be the precursor in this case is *not expected* to form at room temperature.

c. WITH GRIGNARD REAGENTS

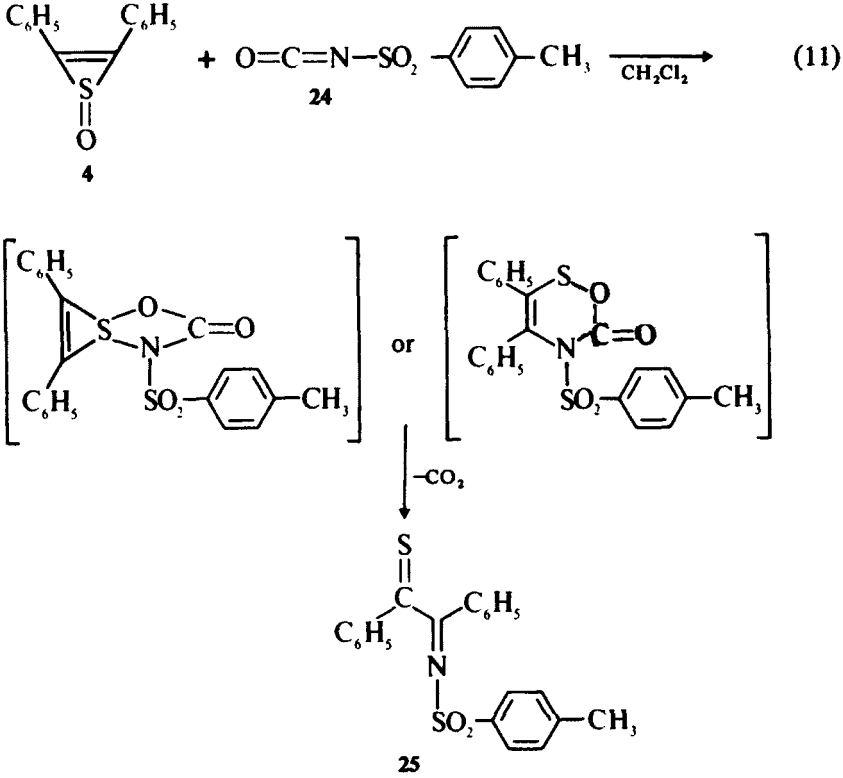
Treatment of 2,3-diphenylthiirene oxide (**4**) with 2 equivalents of phenylmagnesium bromide converts it to phenyltriphenylvinyl sulfide (**23**) in fair yield[13]:

The formation of olefin **23** can be rationalized by attack of the Grignard reagent either at the carbon-carbon double bond or at the sulfoxide function. The former alternative, however, is more likely.

E. *Reactivity of the Sulfoxide Function*

The only reaction of thiirene oxides in which the sulfoxide function is definitely involved in the initial step is that with isocyanates. Thus, treatment of thiirene

oxide (4) with tosylisocyanate (24) gave the blue imine of monothiobenzyl (25) as shown below:[17]



This reaction appears to be general for "active" isocyanates and thiirene oxides, and its full scope is currently under investigation.[17] This reaction is important because the sulfoxide function of **4** does not behave chemically as ordinary sulfoxides do. Indeed, many oxidative reagents that proved to react smoothly with acyclic sulfoxides (i.e., dialkyl sulfoxides and alkylaryl sulfoxides) left the thiirene oxides intact under comparable reaction conditions.[17]

5. References

1. A. Hassner and F. W. Fowler, *J. Am. Chem. Soc.*, **90**, 2869 (1968).
2. E. Schmitz, *Dreiringe mit Zwei Heteroatomen*, Springer-Verlag, Berlin, 1967.
3. (a) R. Breslow, *Acc. Chem. Res.*, **6**, 393 (1973); (b) R. Breslow, J. Brown, and J. J. Gajewski, *J. Am. Chem. Soc.*, **89**, 4383 (1967); (c) R. Breslow, *Angew. Chem., Int. Ed. Engl.*, 565 (1968).
4. M. J. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, New York, 1969, pp. 180, 212.
5. D. T. Clark, *Theor. Chim. Acta*, **15**, 225 (1969).

6. (a) R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.*, **86**, 4866 (1964); (b) J. K. Stille and D. D. Whitehurst, *ibid.*, **86**, 4871 (1964); (c) D. J. Anderson, T. L. Gilchrist, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 147 (1969).
7. L. A. Carpino, L. V. McAdams, III, R. H. Rynbrandt, and J. W. Spiewak, *J. Am. Chem. Soc.*, **93**, 476 (1971).
8. (a) S. Bradamante, S. Moiorana, A. Mangia, and G. Pagani, *J. Chem. Soc., B*, 74 (1971); (b) A. G. Hortman and R. L. Harris, *J. Am. Chem. Soc.*, **93**, 2471 (1971); (c) M. P. Cava and J. McGrady, *J. Org. Chem.*, **40**, 72 (1975); (d) J. -M. Lehn and G. Wipff, *J. Am. Chem. Soc.*, **98**, 7498 (1976); (e) N. D. Epiotis, R. L. Yates, F. Bernardi, and S. Wolfe, *ibid.*, **98**, 5435 (1976); (f) R. S. Glass and J. R. Duchek, *ibid.*, **98**, 965 (1976); (g) F. Bernardi, I. G. Csizmadia, A. Mangini, H. B. Schiegel, M. -H. Whangbo, and S. Wolfe, *ibid.*, **97**, 2209 (1975); (h) A. Streitwieser, Jr., and J. E. Williams, Jr., *ibid.*, **97**, 191 (1975); (j) G. A. Pagani, *J. Chem. Soc., Perkin Trans. 2*, 1389, 1399 (1974); (i) G. D. Andretti, G. Bocelli, and P. Sgarbotto, *J. Chem. Soc., Chem. Commun.*, 586 (1974); (k) C. Müller, A. Schweig, and H. Vermeer, *J. Am. Chem. Soc.*, **97**, 982 (1975); (n) F. de Jong, A. J. Noorduin, T. Bouwman, and M. J. Janssen, *Tetrahedron Lett.*, 1209 (1974); (o) W. Schafer, A. Schweig, K. Dimroth, and H. Kantor, *J. Am. Chem. Soc.*, **98**, 4410 (1976).
9. L. A. Carpino and H. Wu Chen, *J. Am. Chem. Soc.*, **93**, 785 (1971).
10. L. A. Paquette, *Principles of Modern Heterocyclic Chemistry*, Benjamin, New York, 1968.
11. J. C. Sheehan, U. Zoller, and D. Ben-Ishai, *J. Org. Chem.*, **39**, 1817 (1974).
12. L. Ramberg and B. Backlünd, *Ark. Kem. Min. Geol.*, **13A**, 1 (1940); *Chem. Abstr.*, **34**, 4725 (1940).
13. L. A. Carpino, and H. Wu Chen, *J. Am. Chem. Soc.*, **101**, 390 (1979).
14. L. A. Carpino, H. Wu Chen, and J. R. Williams, private communication of unpublished results.
15. H. H. Jaffe and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy*, Wiley, New York, pp. 466–474, 1962.
16. (a) R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960); (b) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709, 3146 (1963); (c) J. W. Rakshys, R. W. Taft, and W. A. Sheppard, *ibid.*, **90**, 5236 (1968).
17. (a) U. Zoller, unpublished results; (b) U. Zoller and E. M. Burgess, to be published.
18. H. L. Ammon, L. Fallon, and L. A. Plastas, *Acta Crystallogr., Sect. B*, **32**, 2171 (1976).
19. (a) H. L. Ammon, *J. Am. Chem. Soc.*, **95**, 7093 (1973); (b) R. L. Sime and R. J. Sime, *ibid.*, **96**, 892 (1974).
20. (a) P. Vouros and L. A. Carpino, *J. Org. Chem.*, **39**, 3777 (1974); (b) P. Vouros, *J. Heterocycl. Chem.*, **12**, 21 (1975).
21. D. C. Dittmer and G. E. Kuhlmann, *J. Org. Chem.*, **35**, 4224 (1970).
22. F. H. Field, *Acc. Chem. Res.*, **1**, 42 (1968).
23. H. K. Wiberg, *Tetrahedron*, **24**, 1083 (1968).
24. C. Müller, A. Schweig, and H. Vermeer, *J. Am. Chem. Soc.*, **100**, 8056 (1978).
25. (a) N. C. Baird, *Theor. Chim. Acta*, **16**, 239 (1970); (b) C. Müller, A. Schweig, and H. Vermeer, *Angew. Chem.*, **87**, 275 (1974); *Angew. Chem., Int. Ed. Engl.*, **13**, 273 (1976).
26. H. H. Jaffé, *Acc. Chem. Res.*, **2**, 136 (1969).
27. H. -L. Hase, C. Müller, and A. Schweig, *Tetrahedron*, **34**, 2983 (1978).
28. H. E. Simmons and T. Fukunaga, *J. Am. Chem. Soc.*, **89**, 5208 (1967).
29. (a) K. Kondo and A. Negishi, *Tetrahedron*, **27**, 4821 (1971); (b) K. Kondo, M. Matsumoto, and A. Negishi, *Tetrahedron Lett.*, 2131 (1972); (c) B. F. Bonini, G. Maccagnani, and G. Mazzanti, *J. Chem. Soc., Chem. Commun.*, 431 (1976).

30. (a) C. G. Swain and C. Lupton, Jr., *J. Am. Chem. Soc.*, **90**, 4328 (1968); (b) C. C. Price and S. Oae, *Sulfur Bonding*, Ronald Press, New York, 1962, pp. 138–139.

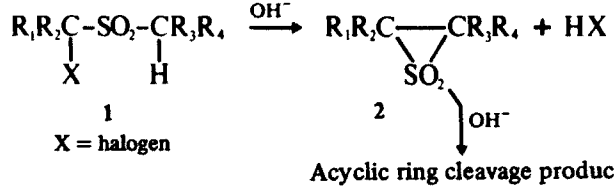
31. F. B. Bordwell, J. M. Williams, Jr., E. B. Hoyt, Jr., and B. B. Jarvis, *J. Am. Chem. Soc.*, **90**, 429 (1968).

32. (a) T. Kempe, Ph.D. Dissertation, Royal Institute of Technology, Denmark, 1974; (b) P. Raynolds, S. Sonnebelt, S. Bakker, and R. M. Kellogg, *J. Am. Chem. Soc.*, **96**, 3614 (1974).

X. THIIRENE DIOXIDES

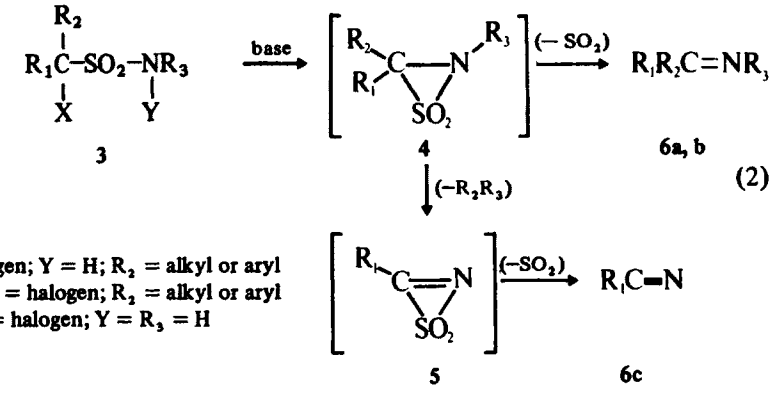
1. Introduction

The Ramberg-Bäcklund rearrangement[1] (see Section VI, 4, A), in which α-halosulfones containing an α′-carbon atom with at least one hydrogen are first transformed into three-membered ring intermediates by base-induced dehydrohalogenation followed by further attack by base on the ring, has been known since 1940 (see below):



(1)

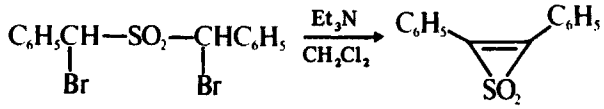
The mechanistic details of this rearrangement,[2,3] the effects of different bases,[4] and the disposition of the intermediate thiirane and thiirene dioxides[5,6] have been studied extensively. Moreover, the intermediacy of thiirane dioxides and their vinyl analogs (e.g., thiirene dioxides) in these studies has been established,[2–5] and the intermediacy of a three-membered ring containing nitrogen has been suggested in complementary studies,[2b,7,8] as depicted in Eq. 2.[8]



(2)

a. X = halogen; Y = H; R_2 = alkyl or aryl
b. X = H; Y = halogen; R_2 = alkyl or aryl
c. X = R_2 = halogen; Y = R_3 = H

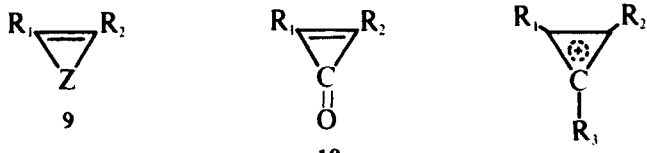
However, it was not until a quarter-century after the original report of Ramberg and Bäcklund[1] that the first compound of type **8** was synthesized and characterized.[9]



(3)

7 **8**

Since special instability had been suggested for all species in class **9** that bear an unshared electron pair on the heteroatom,[12] the successful preparation of thiirene dioxides (e.g., **9**; $Z = SO_2$), accompanied by the successful synthesis of thiirene oxides[13] (see Section IX, 2) opened the door for extensive research involving the theoretical, mechanistic, and experimental aspects of this class of intriguing compounds having (at least formally) a "Hückel aromatic" nature.[9] On the basis of analogy with cyclopropenones (e.g., **10**), the thiirene dioxides may be considered to be a possible nonbenzenoid aromatic system in which aromaticity effects, if any, would require transmission through the *d* orbitals of the sulfur atom.[14] Thus, both the fascinating question of π-*d* bonding in conjugated unsaturated sulfones and the aromatic nature of sulfur-containing heterocycles can be studied using thiirene dioxides as a model. The most remarkable property of the thiirene oxides prepared thus far is their great stability relative to their saturated analogs in spite of the additional angle strain[9] compared with the latter. This relative stability suggests that special conjugative effects may be operable in this case, although a clear answer must await additional data.



9 **10** **11**

Z = O, NR, S, SO, Se, etc.

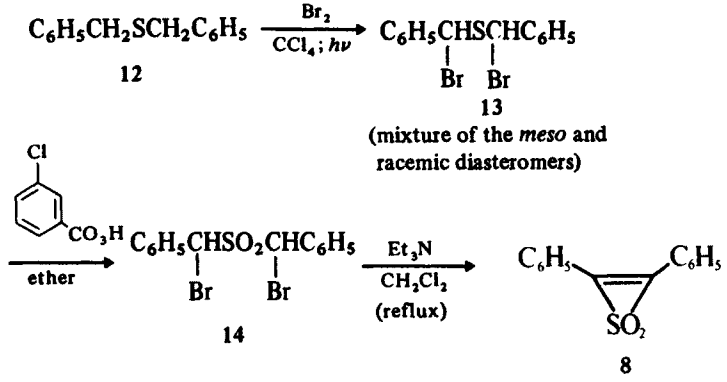
2. Methods of Preparation

A. *By a Modified Ramberg-Bäcklund Reaction*

Most of the thiirene dioxides that have been synthesized thus far have been prepared through a modified Ramberg-Bäcklund reaction in the last crucial cyclization step.

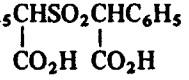
Three-membered heterocycles have been prepared by a variety of cyclization reactions.[15] However, in the case of thiirene dioxides, the application of strong inorganic bases in aqueous solutions always resulted in the isolation of cleavage products, which sometimes were usable to great synthetic advantage.[16]

The successful application of the Ramberg-Bäcklund reaction to the synthesis of thiirene dioxides required two major modifications of the original reaction[1]: first, the inorganic base was replaced by the less basic and less nucleophilic organic base triethylamine,[17] and second, the aqueous medium was substituted by an aprotic organic solvent (i.e., methylene chloride). The entire route toward the synthesis of 2,3-diphenylthiirene dioxide 8 – the first member of this series to be prepared – is given below,[9,18] to illustrate the most convenient (albeit rather lengthy and laborious) way for the preparation of diarylthiirene dioxides that is available to date.



(4)

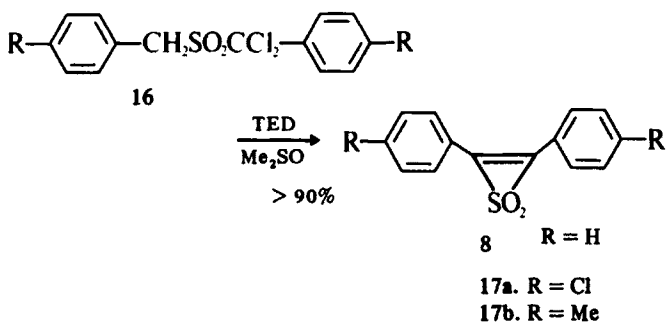
α,α′-Dibromodibenzyl sulfone (**14**) can also be prepared by the brominative decarboxylation of the corresponding sulfone dicarboxylic acid (**15**).[9]



15

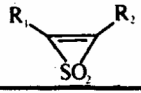
By essentially the same scheme both 2,3-bis-(*m*-fluorophenyl)thiirene[19]- and 2,3-bis(*p*-fluorophenyl)thiirene dioxides have been prepared (see Table 1).

In a similar way, 2,3-diarylthiirene dioxides (**8**; **17a**, **17b**) were prepared by the rearrangement of α,α-dichlorobenzyl sulfones in dimethyl sulfoxide that was treated by triethylenediamine [TED (or DABCO)] at ambient temperature[20]:



(5)

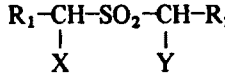
TABLE 1. PREPARATION OF THIIRENE DIOXIDES



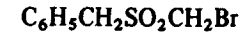
R_1	R_2	Starting material	Reagents	Procedure	Yield (%)	Ref.
H	CH_3	$CH_3-\underset{\displaystyle Br}{\underset{\vert}{CH}}-SO_2-Cl$	CH_2N_2; Et_3N	Via sulfene	22–51[a]	9, 23
CH_3	CH_3	$CH_3-\underset{\displaystyle Br}{\underset{\vert}{CH}}-SO_2-Cl$	CH_3-CHN_2; Et_3N; DBN	Via sulfene	25[b]	9
CH_3 or C_2H_5	CH_3 or C_2H_5	$R-CBr_2-SO_2-CBr_2-R$	$(C_6H_5)_3P$ or $[(CH_3)_2N]_3P$		50–89	26
CH_3	C_6H_5	$CH_3-\underset{\displaystyle Br}{\underset{\vert}{CH}}-SO_2-Cl$	$C_6H_5-CHN_2$; Et_3N		13–14[b]	9
C_6H_5	C_6H_5	$C_6H_5-\underset{\displaystyle Br}{\underset{\vert}{CH}}-SO_2-\underset{\displaystyle Br}{\underset{\vert}{CH}}-C_6H_5$	Et_3N	Ramberg-Bäcklund	70	9
		$C_6H_5-CH_2-SO_2-CCl_2-C_6H_5$	TED[c]	Ramberg-Bäcklund	> 90	20
m-FC_6H_4	*m*-FC_6H_4	*m*-$FC_6H_4CH(Br)-SO_2-CH(Br)-C_6H_4F$-*m*		Ramberg-Bäcklund	83.5	19
p-FC_6H_4	*p*-FC_6H_4	*p*-$FC_6H_4-CH(Br)-SO_2-CH(Br)-C_6H_4F$-*p*		Ramberg-Bäcklund	29.7	9
p-Cl C_6H_4	*p*-Cl C_6H_4	*p*-R-$C_6H_4-CH_2-SO_2-CCl_2-C_6H_4$-R-*p* R = Cl or CH_3	TED	Ramberg-Bäcklund	> 90	20
p-CH_3 C_6H_4	*p*-CH_3 C_6H_4					
C_6H_5 *p*-RC_6H_4	*p*-*t*-Bu C_6H_4 *p*-RC_6H_4	*p*-$RC_6H_4-CH_2-SO_2-CCl_2-C_6H_4R$-*p* R = H or Br or *t*-Bu	TED	Ramberg-Bäcklund		47

[a] Based on the 2-bromo-2-methylthiirane dioxide 23.
[b] Based on α-bromoethanesulfonyl chloride.
[c] Triethylenediamine (DABCO).

Neither of these two modified Ramberg-Bäcklund approaches proved to work with α,α- or α,α′-dihaloalkyl sulfones (**18a–18e**). Thus, dibromosulfones **18a**, **18b**, and **18d** were unaffected by treatment with triethylamine in refluxing methylene chloride.[9] Even the monophenylated derivatives **18c** and **18e** either were unaffected by triethylamine or depending on the conditions, were reduced to **19**.[4a,9,21]



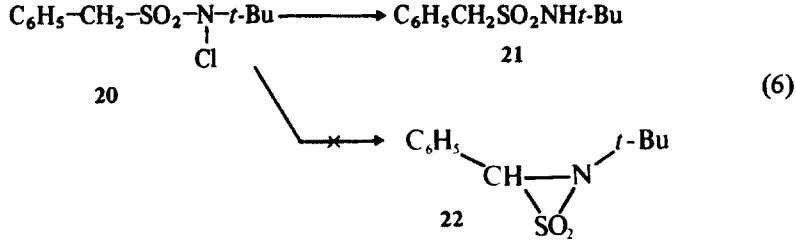
18



19

a. $R_1 = R_2 = H$; X = Y = Br
b. $R_1 = R_2 = CH_3$; X = Y = Br
c. $R_1 = C_6H_5$; $R_2 = H$; X = Y = Br
d. $R_1 = CH_3$; R_2 = Y = Br; X = H
e. $R_1 = C_6H_5$; R_2 = Y = Br; X = H

Interestingly, treatment of the *N*-chloro compound **20** with triethylamine in methylene chloride or with potassium *tert*-butoxide in ether gave also the reduction product **21**, not the expected α-sultam **22**.[8]



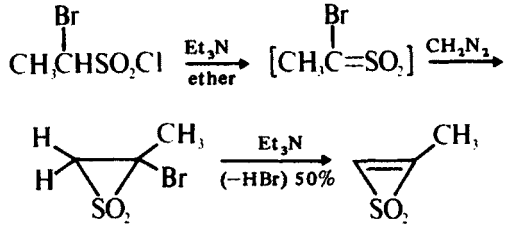
20 **21** **22** (6)

In refluxing methylene chloride α,α-dichlorosulfone (**16**; R = H) also reacts with TED to yield the corresponding thiirene dioxide **8**, but the transformation is further complicated by the slow cyclization under these conditions and by a competing reaction of the solvent with TED.[20]

B. *Via Sulfenes and Diazomethane*

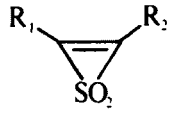
The preparation of alkylsubstituted thiirene dioxides via sulfenes and diazomethane is based on the reactions of diazoalkanes[22] with appropriate α-halosulfenes generated *in situ* by the reaction of sulfonyl halides with tertiary amines [e.g., triethylamine in an inert solvent (see Section VI, 2, B)]. The 2-halosubstituted three-membered thiirane dioxide ring thus formed is treated with a base to yield the required thiirene dioxide through dehydrohalogenation, as depicted in Eq. 7 in the case of the synthesis of 2-methylthiirene dioxide (**24**)[9,23]:

In a similar manner, both the 2,3-dimethyl- and the 2-methyl-3-phenylthiirene dioxides (i.e., **25a**, **25b**) have been prepared in rather low yields.[9]



(7)

23 24



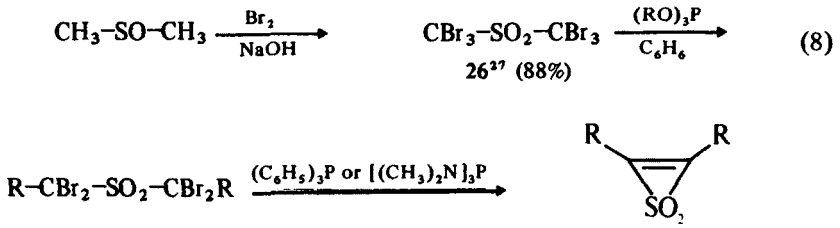
25

a. $R_1 = R_2 = CH_3$
b. $R_1 = CH_3$; $R_2 = C_6H_5$

However, in both cases, alcohol-free solutions of diazomethane[24] must be used to avoid destruction of the intermediate sulfene,[22] and a stronger base such as 1.5-diazabicyclo[4.3.0]non-5-ene[25] is required for the final dehydrohalogenation step.

C. *By Debromination of Tetrabromosulfones*

Since thiirene derivatives bearing alkyl substituents are not accessible via sulfenes and diazoalkanes (see above) on a large scale, the route to dialkylthiirene dioxides by debromination of tetrabromosulfones summarized in Eq. 8[26-28] is of particular significance.



(8)

27[28] 28

a. $R = CH_3$
b. $R = CH_3CH_2$

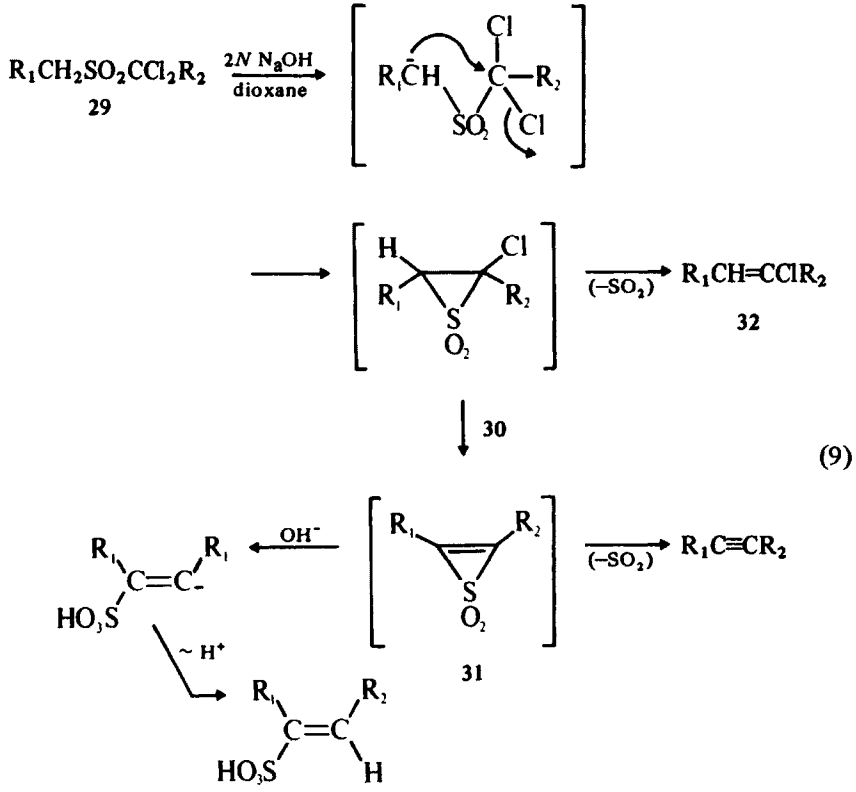
a. $R = CH_3$
b. $R = CH_3CH_2$

This relatively new approach makes the dialkylthiirene dioxides as easily obtainable as the diaryl analogs. Both the 2,2-dimethyl- and 2,2-diethylthiirene dioxides (**28a, 28b**) have been prepared by this method[26] in 89 and 50% yields, respectively, in the last debromination-cyclization step.

D. *In Situ Generation of Thiirene Dioxides*

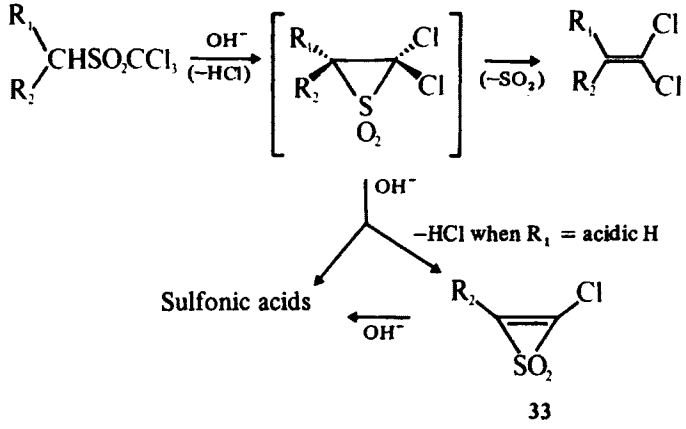
Since 2,3-diphenylthiirene dioxide[9] enjoys greater thermal stability than *cis*- and *trans*-2,3-diphenylthiirane dioxides,[29] it can be generated *in situ* and then attacked by the base that is present in the reaction mixture to form a variety of vinylic products.

In a series of papers, Paquette et al.,[4,5] proved unequivocally that thiirene dioxides are generated *in situ* on treatment of α,α- and α,α'-dihalosulfones with strong bases (e.g., NaOH or K *t*-butoxide) in aqueous dioxane and are further transformed into ethenesulfonates,[4,5] and alkynes[4,5,30] under the reaction conditions employed. This is illustrated in Eq. 9.[5]



(9)

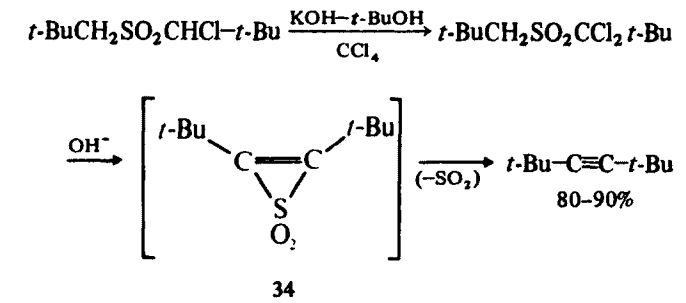
The vinyl halide **32** results from intermediate **30**, not from the thiirene dioxide **31**. Similarly, several trichloromethyl sulfones were found[31] under the Ramberg-Bäcklund reaction conditions (refluxing 2*N* NaOH-THF solution) to yield the chlorothiirene dioxide **33** at a competitive rate only when the dichlorothiirane proton to be extracted in the final step was appreciably acidic. Otherwise, a hydroxide ion attacks at tetravalent sulfur, with ring opening of the strained three-membered ring as depicted in Eq. 10.[30]



33

It turns out that α-halosulfones in general display a marked tendency for cyclization via alkali-induced dehydrohalogenation to form halogen-substituted thiirane dioxides followed by additional dehydrohalogenation, which results in the *in situ* generation of thiirene dioxides, irrespective of the degree or the regiochemistry of the polysubstitution (e.g., α,α-dihalo-,[4,5] α,α′-dihalo-,[4c] and α,α,α-trihalosulfones[30]).

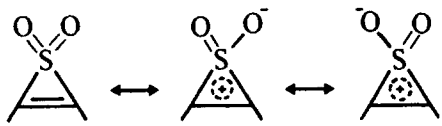
It is not surprising, therefore, that the *in situ* generation of thiirene dioxides could be affected by using a somewhat related approach[32] as illustrated in Eq. 11.[6]



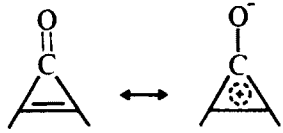
34

3. Structure and Physical Properties

The structural features, the physical properties, and the spectroscopic characteristics of the thiirene dioxide system (**35**) are of special theoretical interest, since on the basis of analogy with cyclopropenone (**36**), the former is a possible nonbenzoid aromatic system with all the associated physical and chemical implications.



35

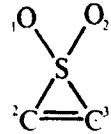


36

Conjugation of the π electrons of the carbon-carbon double bond with the LUMO sulfur 3*d* orbitals would be expected to stabilize the Hückel $4n + 2$ ($n = 0$) array of π electrons in the thiirene dioxide system. This has stimulated several studies[33,35-37,39,41] to determine whether thiirene dioxides should be considered to be aromatic (or "pseudo-aromatic") and to what extent conjugation effects are operative in these systems.

A. *x-Ray Data*

The structure of 2,3-diphenylthiirene dioxide (8) has been determined[33] with Mo K_α diffractometer data using direct methods. The selected bond lengths and angles of the ring system of compound 8 are summarized below.[33]

C_2–S	1.703 Å		$< C_2SC_3$	46.7°
C_3–S	1.716 Å		$< SC_2C_3$	67.2°
C_2–C_3	1.354 Å		$< SC_3C_2$	66.2°
S–O_1	1.444 Å		$< O_1SO_2$	116.1°
S–O_2	1.453 Å			

The expected C_{2v} symmetry for this molecule has thus been established. The corresponding parameters for the 2,3-dimethylthiirene dioxide were found[33] to be somewhat shorter for the bond lengths (1.692, 1.333, and 1.449 Å for the C_2–S, C_2–C_3, and S–O_2, respectively) and somewhat smaller for the ring angles (46°4′ and 144°8′ for $< C_2SC_3$ and $< O_1SO_2$, respectively). More significant, however, the changes from 1.305[33] to 1.354 Å for the C_2–C_3 bond lengths, and from 1.784 to 1.709 Å for the C–S bond length in thiirene oxide and thiirene dioxide, respectively, are quite remarkable and were interpreted[33] in terms of substantial π delocalization. However, cyclic sulfones have also been found to have shorter carbon-sulfur bond lengths than cyclic sulfoxides.[34] The sulfur-oxygen bond lengths found in the thiirene dioxides are similar to lengths found in other -SO_2-containing compounds, which *does not* corroborate the Hückel-type π delocalization illustrated by structure 37.

37

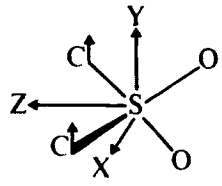
Indeed, CNDO/S[35] and CNDO/2[36] calculations of total charge densities also show that oxygen charges are about the same in both thiirene dioxides and thiirane

dioxides. On the other hand, the apparent insensitivity of the SO_2 bond lengths (and oxygen charge densities) to structural variations in the carbon skeleton portion of the molecule might well be due to an "insulating effect" of the LUMO sulfur *d* orbitals; that is, electronic interactions between the carbon framework and sulfur can occur without appreciable change in the oxygen-sulfur interactions. Based on the experimental results and complementary calculations, an out-of-plane π delocalization is suggested[33] for thiirene dioxides.

B. *Theoretical Calculations and Electronic Structure*

The trends in the C–C and C–S bond indices obtained by CNDO/2 calculations on a model of thiirene dioxide[33] were found to agree qualitatively with the trends observed in the experimental bond lengths. The calculations above indicated that in both thiiranes and thiirenes the in-plane $C(p_z)$ orbitals are primarily responsible for the bond length variations, and also that the contribution of the out-of-plane $C(p_y)$–S interactions to the C–S bond order suggests π delocalization of a magnitude comparable to that of the cyclopropenone system.

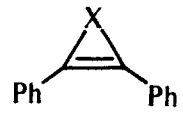
To justify the validity of ketone-sulfone analogies, a series of CNDO/2 calculations on a number of model cyclic unsaturated sulfones and ketones was undertaken.[36] It was found that (*a*) only little charge separation occurs in thiirene dioxides, (*b*) the differences in charge density on oxygen in the series of ketones are not reproduced by the sulfones, and (*c*) in contrast to cyclopropenone, thiirene dioxide is a weak acceptor in hydrogen bonding. It was concluded[36] that a comparison of cyclic unsaturated sulfones and ketones is of little value, and that although the d_{yz} orbital of the sulfur atom (see **38**) can and does promote resonance structures (e.g., **35**) analogous to the predominant polar resonance structures in ketones (e.g., **36**), the d_{xy} orbital has a contrary effect of comparable magnitude.



38

The thiirene dioxide system was investigated by analysis of the inductive and conjugative interactions between the carbon-carbon (C=C) and the sulfonyl (SO_2) subunits and consideration of the possible "aromaticity" of this species.[35] By using a method[37] that makes it possible to distinguish inductive from conjugative effects, the C=C–SO_2 interactions could be evaluated and compared to the results obtained by the analysis of uv photoelectron spectra of thiirene dioxides.[35] Both approaches revealed a strong hyperconjugative interaction between the occupied C=C π MO and an occupied SO_2 σ MO_1 and a modest mixing between the former and a vacant $SO_2\sigma^*$ which is a nearly pure sulfur *d* atomic orbital. The $\pi\sigma^*$ inter-

action is responsible for a small π charge transfer from the carbon-carbon double bond to the sulfonyl unit. In spite of this charge transfer being much smaller in magnitude than in the corresponding cyclopropenone, it was concluded[35] that thiirene dioxides do tend to exhibit properties expected of an "aromatic" model. However, the degree (but not the nature) of this tendency is much smaller for the thiirene dioxides than for the corresponding ketones. In a complementary study,[39] the photoelectron spectra of 2,3-diphenyl-substituted compounds (**39**) were interpreted and analyzed in terms of inductive and conjugative interactions between the subunits C=C and X. The values obtained were compared with theoretical data obtained by using the "cutoff" procedure.[37,38]



39

$X = CH_2, CO; C = S, SO, SO_2$

The calculated and experimental conjugative and inductive effects in selected relevant systems (**39**) are gathered in Table 2 and appear – in view of the various approximations involved – to be in satisfactory agreement. The calculated aromaticities (conjugation energies: −52.84; −22.05, and −21.84 kcal/mole, respectively) and the π charge transfer from PhC=CPh to X (245.4×10^{-3} or 82.2×10^{-3} and 81.4×10^{-3}, respectively) in the compounds listed in Table 2[39] suggested that diphenyl-substituted molecules are as likely aromatic compounds as their parent systems are.

A detailed comparison of the *ab initio* and CNDO/S[40] valence electron methods established the surprising concurring results for the two methods with respect to unsaturated systems represented by **39**.[41] Furthermore, spiroconjugation for thiirene dioxide was found to be negligible relative to hyperconjugation, and the influence of *d* orbitals of sulfur on the electronic structure of this system was shown to be rather pronounced. Both aromaticity orders derived from the *ab initio* and CNDO/S charge transfer values concur and agree with the CNDO/S conjugation energy order, and both suggested that thiirene dioxides are at least to some extent aromatic.

TABLE 2. CALCULATED[39] CNDO/2 INDUCTIVE AND CNDO/S CONJUGATIVE EFFECTS OF X = CO, SO, AND SO_2 ON THE π_1 ORBITAL OF THE PhC=CPh SUBUNIT OF 39

 **39**	Inductive		Conjugative	
	Calculated	Experimental	Calculated	Experimental
i. X = CO	−0.35	−0.75	0.04	0.1–0.35
ii. X = SO	−0.45	−0.65	0.1	0.25
iii. $X = SO_2$	−0.95	–	0.06	–

C. *Ultraviolet, Infrared, and Nuclear Magnetic Resonance Spectroscopic Data*

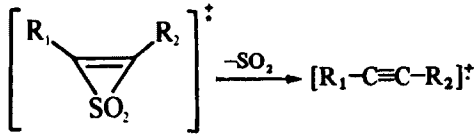
Being a unique class of compounds, thiirene dioxide are easily characterized spectroscopically. A selection of spectroscopic data of some well-known members of this class is given in Table 3.

The most striking feature of Table 3 is undoubtedly the anomalous asymmetric stretching[42] frequency of the SO_2 group in thiirene dioxides. Usually, an internal correlation is observed between the asymmetric and symmetric stretching frequencies of the SO_2 group in sulfones as well as in other compounds containing the sulfonyl ($-SO_2-$) group. In contrast, thiirene dioxides show a marked shift of the asymmetric absorption to lower frequencies (vs. other sulfones), accompanied by a lesser shift of the symmetric band to higher frequencies. The net result is that the Bellamy-Williams correlation[42b] no longer holds for these compounds. Although the reason for that phenomonon is not yet clear, it appears that the ring strain alone cannot be responsible for this effect.[9]

The positions of the methyl and H absorption in the nmr spectrum of 2-methylthiirene dioxide are of particular interest, since they are comparable to those observed for methyl cyclopropene (δ 2.40 and 8.70 ppm, respectively).[43] The chemical shift of the methyl protons in other methyl-substituted thiirene dioxides is similar to that of the 2-methylthiirene dioxide.

D. *Mass Spectra*

Verification of the molecular weight of thiirene dioxides by mass spectrometry, employing the conventional electron impact (EI) ionization method, has been unsuccessful because of the absence or insignificant intensity of molecular ion peaks in their mass spectra.[45] The base peak is rather characteristic, however, and corresponds to the formation of the disubstituted acetylene ion by loss of sulfur dioxide.[45]

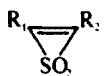


(12)

In fact, considerable thermal decomposition may precede ionization, as suggested by the fact that only the relatively volatile 2,2-dimethylthiirene dioxide gave any evidence for the molecular ion. Retention of the positive charge with the sulfone function is responsible for the ion at *m/e* 64 ($SO_2^+ \cdot$) and its decomposition product in the mass spectra of thiirene dioxides.[45b]

The CI mass spectrometry techniques[46] proved to be very useful in the case of thiirene dioxides because by using different reagent gases (i.e., methane, isobutane, ammonia, and dimethylamine), the relative abundance of molecular adduct ions

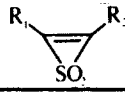
TABLE 3. SELECTED UV, IR, AND NMR DATA FOR THIIRENE DIOXIDES



		Spectroscopic data				
			Ir in $CHCl_3$ (microns)			
R_1	R_2	Uv wavelength λ_{max} (nm)[a]	Asymmetric SO_2	Symmetric SO_2	Nmr chemical shifts, δ (ppm)[b]	Ref.
H	CH_3		7.82	8.42[a]	2.50 (3H, *d*), 2.44 9.04(1H, *q*) 8.99	23, 44
CH_3	CH_3		7.96	8.58	2.28(*s*)	9
CH_3	C_6H_5	255	7.95	8.56	2.55(3H, *s*), 2.61 7.51(*s*, 5H)	9, 44
C_6H_5	C_6H_5	222.5, 296, 307, 322	7.82	8.57[c]	7.55(*m*)	9
p-FC_6H_4	*p*-FC_6H_4		8.00	8.70[d]	7.1–7.9(*m*)	13b
m-FC_6H_4	*m*-FC_6H_4		7.90	8.65[d]	7.2–7.7(*m*)	19

[a] In 95% C_2H_5OH.
[b] In $CDCl_3$.
[c] In CCl_4.
[d] Nujol.

TABLE 4. MELTING POINTS OF THIIRENE DIOXIDES



R_1	R_2	m.p. (°c)	Ref.
H	CH_3	59–60	23
CH_3	CH_3	101–101.5	9
CH_3	C_6H_5	117–118 (decomp.)	9
C_6H_5	C_6H_5	116–126 (decomp.)	9
p-FC_6H_4	*p*-FC_6H_4	141–148 (decomp.)	13b
m-FC_6H_4	*m*-FC_6H_4	129–131 (decomp.)	19

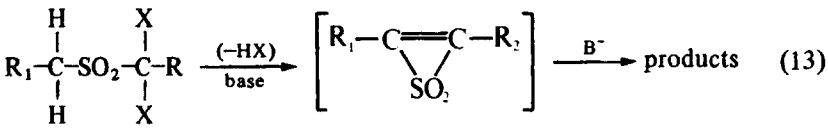
was enhanced, permitting the establishment of the molecular weight of the thiirene dioxides being investigated.[45a] Thus the formation of $(R_1C{\equiv}CR_2 + H)^+$ and $(SO_2 + H)^+$ in the methane CI spectra occurred via the elimination of SO_2 from $(M + H)^+$. Here too, the acetylenic ion dominated the spectra. Similar results were obtained with the other reagent gases. The advantage of the CI technique over ordinary EI for the determination of the molecular weight of thiirene dioxides is thus apparent.

E. *Melting Points*

The available data are summarized in Table 4. Since thiirene dioxides easily lose sulfur dioxide, however, their melting points (above which they rapidly decompose) vary with the rate of heating.

4. Chemical Properties and Reactivity

An extensive and thorough study of the thiirene dioxide system was possible "de facto" even before the successful synthesis and isolation of the first member of this class by Carpino et al.[9] because under the Ramberg-Bäcklund reaction conditions the *in situ* generation of thiirene dioxide – as a reaction intermediate – is straightforward and facile. It is not surprising, therefore, that the early investigations of this system concentrated around the fate of the thiirene dioxides[1-7] that were formed *in situ* under the basic conditions employed. These studies involved, in essence, nucleophilic ring opening of the thiirene dioxide by a variety of bases – usually in aqueous solutions – accompanied by mechanistic and kinetic studies of these ring openings using changing base concentrations at different temperatures as depicted in Eq. 13.

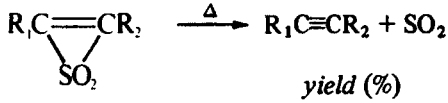


(13)

Even after this ring system has become easily accessible, the chemistry most explored has been reaction with a wide spectrum of nucleophiles (see below). Nevertheless, the door is still open for further studies of their chemical properties and reactivity of these three-membered rings.

A. *Sulfur Dioxide Extrusion*

Thermal decomposition of thiirene dioxides results in the extrusion of sulfur dioxide and the formation of the corresponding diphenylacetylenes in high yields[9,20,47]:



(14)

yield (%)

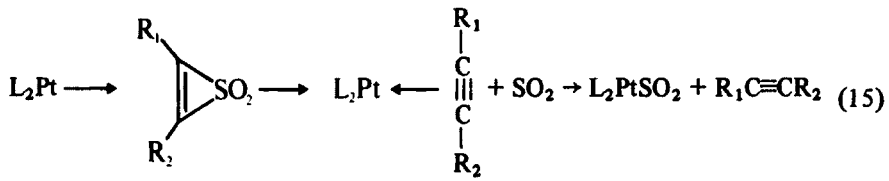
a. $R_1 = R_2 = CH_3$ (not specified)[9]
b. $R_1 = R_2 = C_6H_5$ (97%)[9]
c. $R_1 = R_2 = p\text{-Cl}-C_6H_4$ (> 90%)[20]
d. $R_1 = R_2 = p\text{-CH}_3-C_6H_4$ (> 90%)[20]

Kinetic studies[47] showed that this thermally induced extrusion is facilitated by electron-donating substituents (e.g., alkyl groups). In addition, the data that correlate best with the sum of σ_p^+ substituent constants[48] suggest that a free-radical, stepwise (rather than a nonlinear, symmetry-allowed) concerted extrusion mechanism[49] is operable. It is worth mentioning in this regard that the stereospecific extrusion of sulfur dioxide from thiirane dioxides to give alkenes was also suggested to be a nonconcerted process[50] (see Section VI, 4, A).

At present, however, there is no conclusive support for any of the paths suggested for the fragmentation of thiirane dioxides to the corresponding alkenes and sulfur dioxide.[51]

Interestingly, the decomposition of thiirene dioxide (8) to diphenylacetylene was found to be 10^4 times slower than that of its saturated analog (to *trans*-stilbene).[4c]

The transition metal catalyzed decomposition of thiirene dioxides has been investigated primarily via kinetic studies.[44] Zero-valent platinum and palladium complexes and monovalent iridium and rhodium complexes were found to affect this process, whereas divalent platinum and palladium had no effect. The kinetic data suggested the following mechanism for the decomposition of the complexes:



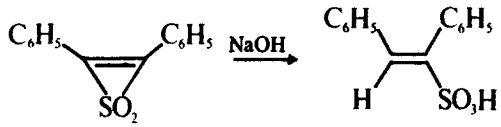
(15)

Since the rates of decomposition of thiirene dioxide complexes and those of thiirane dioxides were similar, it was suggested[44] that upon coordination, the carbon-carbon bond order of thiirene dioxides decreases and the ligand becomes thiirane dioxide-like. The role of the metal is thus to "saturate" the carbon-carbon double bond so that the reactivity of the coordinated thiirene dioxide approaches that of the thermally less stable thiirane dioxide.

B. *Reactions of Thiirene Dioxides with Nucleophiles*

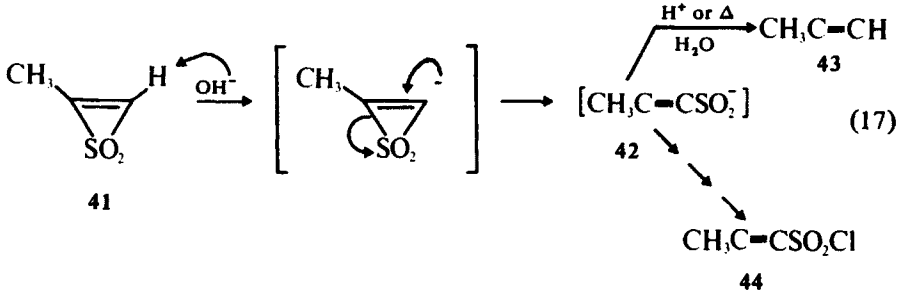
a. WITH STRONG BASES

As expected from the studies of the Ramberg-Bäcklund reaction,[1-5] treatment of thiirene dioxides with sodium hydroxide in aqueous solution results in ring opening to give in the case of **8** the unsaturated sulfonic acid **40**[9] characterized as its *p*-toluidine salt.



8 **40** (16)

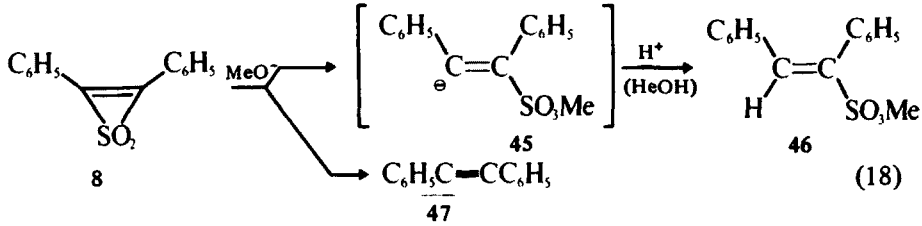
The same sulfonic acid (**40**) was obtained by direct treatment of α,α'-dibromodibenzyl sulfone with sodium hydroxide. On the other hand, no sulfonic acid was isolated on treatment of 2-methylthiirene dioxide with aqueous sodium hydroxide. Further studies with this compound[23] revealed that the hydroxide ion is diverted from attack at the sulfonyl group because of the pronounced acidity of the vinyl proton in this compound.[23]



41 (17)

Although sulfinate **42** was not isolated but rather converted to the isolable 1-propynsulfonyl chloride **44**, its presence in the reaction mixture was apparent by conversion to methylacetylene. The results above, combined with those of other studies,[4] clearly show that acetylenic products formed from either the treatment of thiirene dioxides with alkali or upon Ramberg-Bäcklund treatment of dihalosulfones do not need to arise by thermal elimination of sulfur dioxide from the three-membered ring.

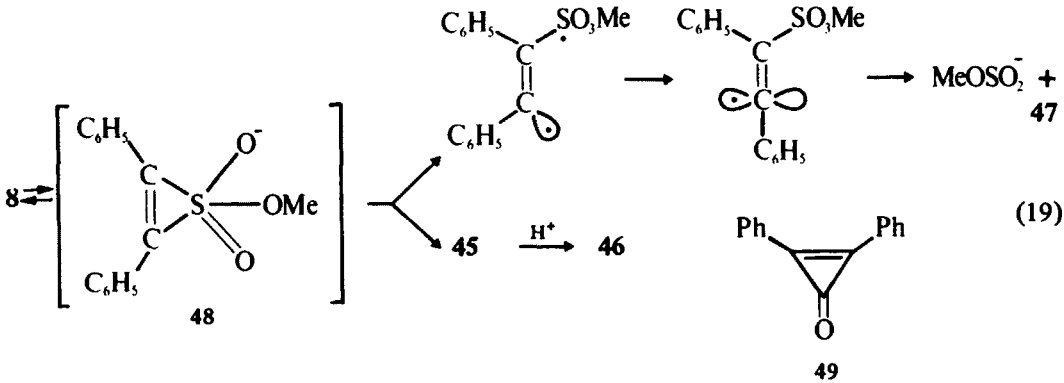
By analogy to the reaction with sodium hydroxide, thiirene dioxide **8** underwent competitive first-order reactions with methoxide ions to give, in addition to diphenylacetylene, the *cis*-1,2-diphenylethene sulfonate **46**[4c]:



(18)

The ratio of **46** to **47** was found (as expected) to be temperature dependent. Similar results were obtained with potassium *t*-butoxide (in *t*-butyl alcohol) and with hydroxide ion in 40% dioxane-water solution.[4c]

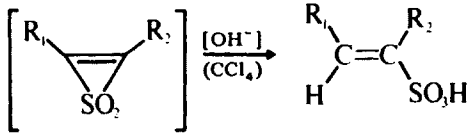
Mechanistically, the reaction appears to involve attack of methoxide ion on sulfur, leading to carbanion **45**, which rapidly abstracts a proton from methanol so that its stereochemistry is maintained. Based on all the available data, the common sulfurane intermediate **48** has been advanced[4c] to account for the formation of **46** and **47**:



(19)

In a complementary kinetic study the relative rates of cleavage by alkoxide ions of diphenylcyclopropenone (**49**) and diphenylthiirene dioxide (**8**) have been determined at several temperatures.[52] The relative rates of **8** to **49** were about 5000:1. This surprising result was attributed to a marked conjugative stabilization of **49** as compared with that of **8**. At any rate, the relative ratio appears to reflect the aromaticity inherent in **8** vs. that of **49**.

Finally, using the KOH-CCl_4-BuOH system,[53] it is possible to generate *in situ* a variety of substituted thiirene dioxides[6,53] as intermediates. Under these reaction conditions the intermediates decompose rapidly and specifically into products whose nature is dependent on the substitution pattern. Thus, whereas both the 2,3-di-*n*-butyl- and 2-chloro-3-*n*-butylthiirene dioxides formed *in situ* give the expected *cis*-unsaturated sulfonic acids analogous to **40**,[9] 2,3-di-*tert*-butylthiirene dioxide yields di-*tert*-butylacetylene as shown in Eq. 20.

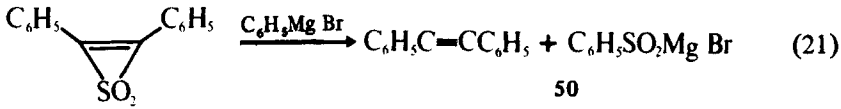


when $R_1 = n$-Bu; $R_2 = n$-Bu or Cl

or $R_1C{\equiv}CR_2$ when $R_1 = R_2 = t$-Bu (20)

b. WITH GRIGNARD AND LITHIUM REAGENTS

Treatment of 2,3-diphenylthiirene dioxide (**8**) with phenylmagnesium bromide gives diphenylacetylene and the salt of benzene sulfinic acid **50**, as shown in Eq. 21.[9]

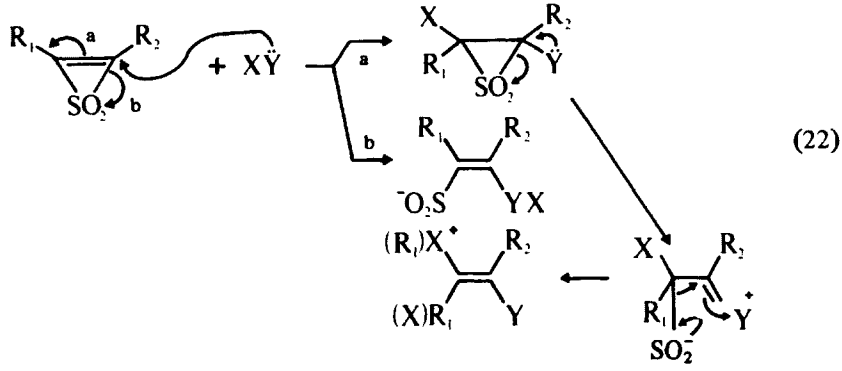


8 **50** (21)

Lithium aluminum hydride reacts similarly. These ring-opening reactions are thus comparable to those with aqueous sodium hydroxide discussed in Section X, 4, B, a.

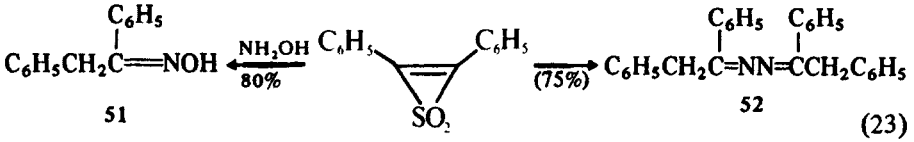
c. WITH SOFT NUCLEOPHILES

α,β-Unsaturated sulfones,[54] like other alkenes substituted with electron-withdrawing groups,[55] are susceptible to nucleophilic additions, and thiirene dioxides are no exception. However, these additions are always accompanied by ring cleavage (of one of the carbon-sulfur bonds) followed *some times* by a loss of the sulfur dioxide unit. A tentative pathway is described in Eq. 22.



(22)

i. WITH HYDROXYLAMINE AND HYDRAZINE. The reaction of the model thiirene dioxide (**8**) with either hydroxylamine or hydrazine gives desoxybenzoin oxime (**51**) and desoxybenzoin azine (**52**) in good yields[9]:



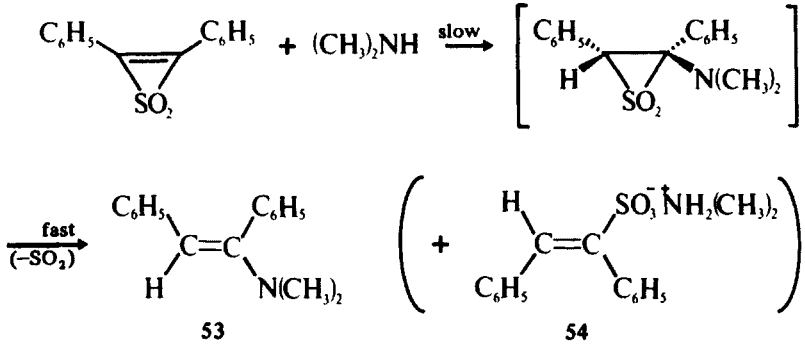
(23)

These results were rationalized[9] in terms of an initial nucleophilic addition to the α,β-unsaturated sulfone system of **8**, followed by loss of sulfur dioxide and tautomerization. Interestingly, treatment of the corresponding thiirene oxide with hydroxylamine also afforded **51**,[13b] albeit in a lower yield (i.e., 36%). Apparently, the same conjugative addition mechanism is operative in both cases.

As one can see, in contrast to the previously discussed hard nucleophiles, which react with sulfur dioxides via attack at the sulfur center, the softer nucleophiles hydroxylamine and hydrazine attack initially at the vinyl carbon center. This was shown to be the case with other "soft" nucleophiles[56,57] as is discussed below.

ii. WITH AMINES AND AMIDINES. Thiirene dioxides do not react with typical tertiary amines like triethylamine and 1,4-diazabicyclo[2.2.2]octane (DABCO), and therefore can be prepared from α,α'-dihalosulfones by using these bases for the dehydrohalogenation-cyclization. However, they do react with the secondary dimethylamine and the highly reactive tertiary amine (amidine), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).[55]

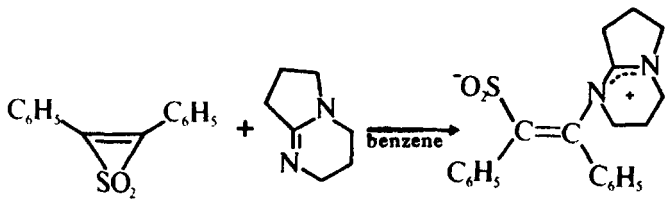
Thus, the reaction of 2,3-diphenylthiirene dioxide (**8**) with diethylamine in benzene gives vinylamine (**53**) in high yield[57]:



(24)

This is accompanied by a small amount of salt (**54**), presumably because of a small amount of water present in the reagents. The reaction was found to be second order in amine[56] – typical for the addition of amines to olefins in aprotic solvents[54,55] – and to have *syn* stereochemistry. Hence, a concerted addition across the carbon-carbon double bond or a stepwise addition, involving two molecules of the amine per molecule of the thiirene dioxide, has been proposed.[56]

DBN reacts smoothly with **8** to give a 1:1 adduct, the yellow betaine **55**, in essentially quantitative yields[56,57]:

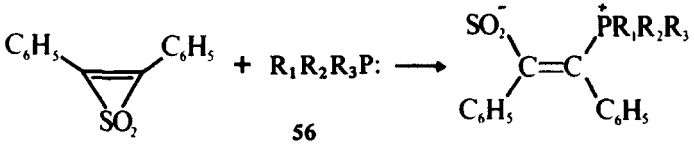


(25)

55

Preliminary results show that thiirene oxides also react with amidines (e.g., DBU) in a similar way.[58]

iii. WITH TERTIARY PHOSPHINES. Reactive phosphines react rapidly with 2,3-diphenylthiirene dioxide to give the betaines **57** in essentially quantitative yield[56,57]:



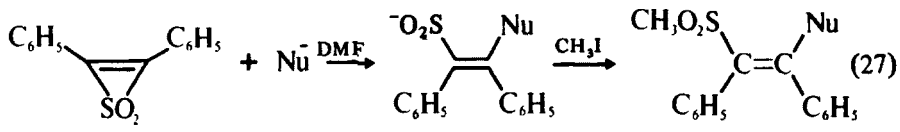
(26)

8 56 57

a. $R_1 = R_2 = R_3 = N(CH_3)_2$
b. $R_1 = R_2 = R_3 = n\text{-Bu}$
c. $R_1 = R_2 = Et; R_3 = C_6H_5$
d. $R_1 = R_2 = C_6H_5; R_3 = CH_3$

Triphenylphosphine is not reactive toward **8** below temperatures at which the latter begins to undergo thermal decomposition. Betains (**57**) are insoluble in nonpolar solvents but show appreciable solubility in polar organic solvents. Their structure was established by x-ray crystallographic analysis.[56] Attack of the nucleophile on the vinylic carbon of the thiirene dioxide is likely.

iv. WITH CYANIDE, BENZENESULFINATE, AND AZIDE IONS. Cyanide and benzenesulfinate ions react readily with thiirene dioxide (**8**) to give the vinylsulfinates **58**. The latter could be trapped with CH_3I to isolate the respective methyl sulfones **59a** and **59b**, as depicted in Eq. 27.[57]



(27)

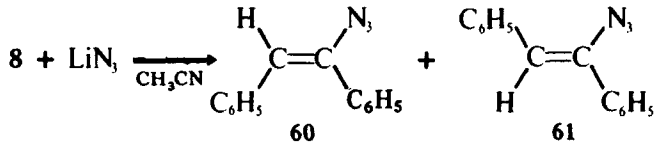
8 58 59

a. Nu = CN^-
b. Nu = $C_6H_5SO_2^-$

a. Nu = CN
b. Nu = $C_6H_5SO_2$

The stereochemistry of the electrocyclic ring opening following the attack of the nucleophile on the vinylic carbon appears to be governed by the principle of least motion.[59]

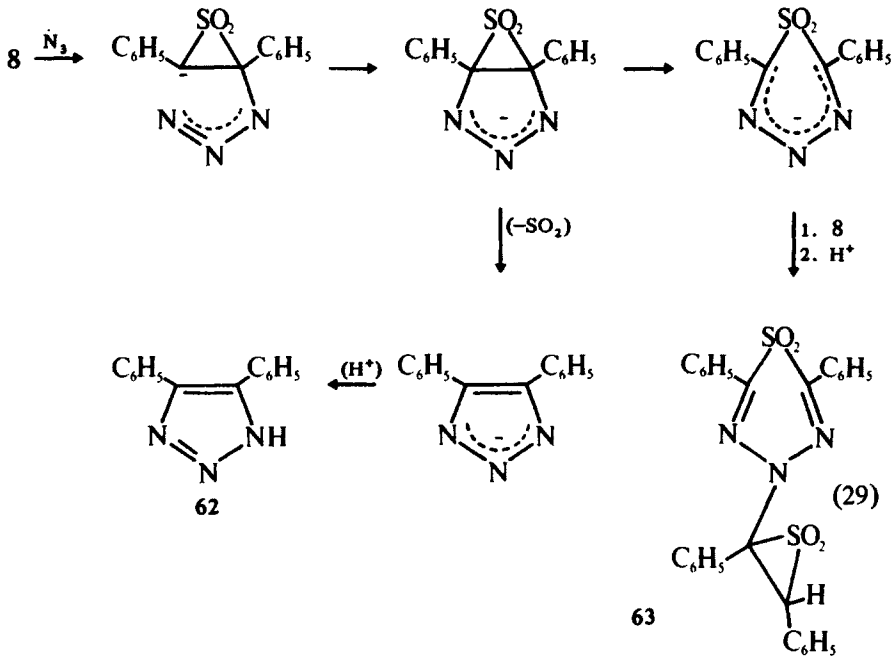
Treatment of **8** with lithium azide afforded, among others, the vinyl azides **60** and **61** as the major products.[60]



(28)

+ **62** + **63**

The formation of the other products in this reaction [i.e., triazole (**62**) and thiatriazine dioxide (**63**)] was rationalized[60] by assuming an initial stepwise cycloaddition of the azide ion with the double bond of the thiirene dioxide, as illustrated in Eq. 29.

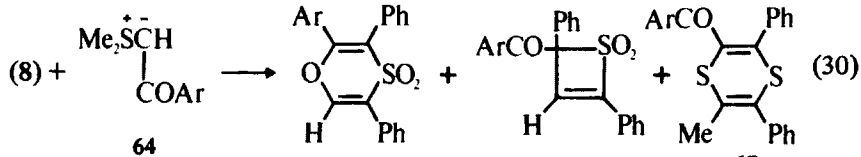


(29)

Although triazole (**62**) was known before,[61] the thiatriazine dioxide **63** is the first reported member of a new class of compounds.

d. WITH SULFONIUM AND PYRIDINIUM YLIDS

The reaction of 2,3-diphenylthiirane dioxide with equimolar acylsubstituted sulfonium ylids (e.g., **64**) afforded besides the major product tolane (67%), oxathiin dioxide (**65**), thiete dioxide (**66**), and dithiin (**67**) in very low yields.[62]



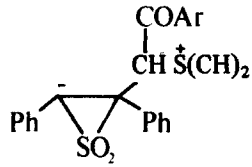
(30)

64

a. Ar = Ph
b. Ar = P-MeC$_6$H$_4$

65 66 67

The formation of compounds **65–67** was rationalized[62] in terms of an initial attack of the nucleophilic carbon of ylid **64** on the vinylic carbon of thiirene dioxide (**8**). Further transformations of the intermediate (**68**) will lead to the observed products.



68

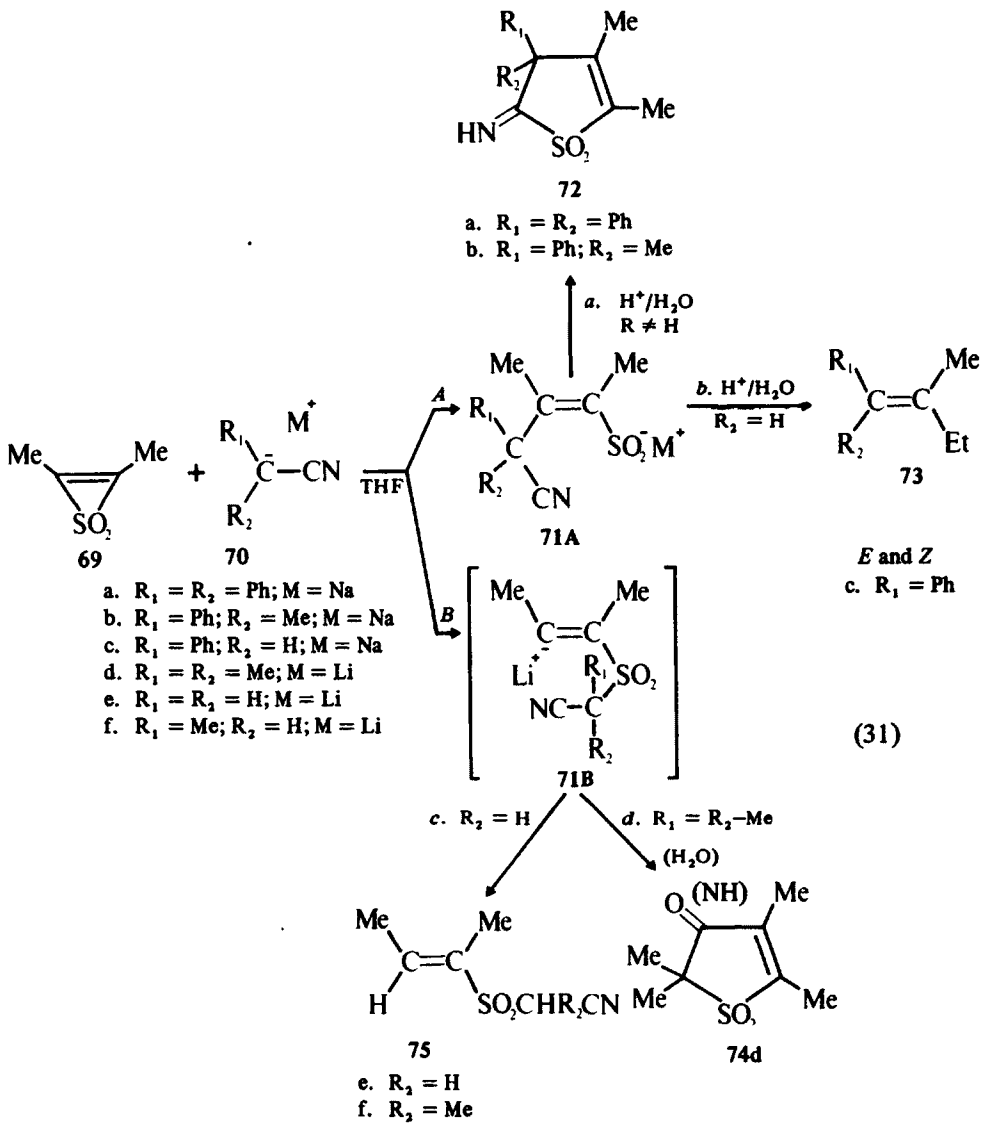
e. WITH α-METALLATED NITRILES

2,3-Dimethylthiirene dioxide was found to act as an ambident electrophile in its reaction with α-metallated nitriles. Thus, two types of sulfur-containing cyclic products (i.e., **72** and **74**) are formed in moderate yield (after appropriate work-up) when the metallated nitriles have no α-hydrogen atom. When α-hydrogen is present in the metallated nitriles, the reaction takes a different course. The results of the foregoing study[62] are summarized in Eq. 31.

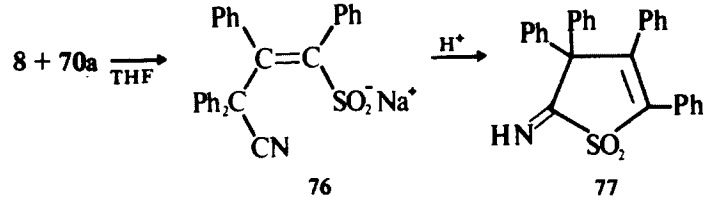
It turns out that sulfolene (**72**) is a result of an initial nucleophilic attack of the aryl-substituted carbanions (i.e., **70a–70c**) on the vinylic carbon of thiirene (**69**) to form the sulfinate intermediate **71A**, which upon acidification cyclizes to give the heterocycle **72**. On the other hand, attack of the alkyl-substituted carbanions (i.e., **70d–70f**) on the sulfur atom of the starting thiirene dioxide will lead through intermediate **71B** to heterocycle **74d** (after hydrolysis). Acyclic products (e.g., **73** and **75**) are obtained when the nitriles employed bear an α-hydrogen atom. In such cases, either a 1,3-hydrogen shift in intermediate **71A** is responsible – after sulfur dioxide elimination – for the formation of the vinyl nitrile **73**, or an intramolecular anion exchange in **71B** results in the formation of **75**.

In contrast to **69**, 2,3-diphenylthiirene dioxide (**8**) suffers of nucleophilic attack only at the ring carbon,[62a] the sulfinate **76** being formed in 64% yield. Acidification with an equimolar amount of hydrochloric acid affords sulfolene (**77**) similar to **72**.

Similar to α,β-unsaturated ketones,[55] thiirene dioxides are in general preferentially attacked by the less basic nucleophiles on the vinylic carbon atom of the ring, and by the strongly basic nucleophiles on the sulfonyl sulfur (see Sections IX, 4, B–IX, 4, B, e). Ordinary α,β-unsaturated sulfones normally react with nucleophiles to give addition only across the carbon-carbon double bond, the sulfonyl group



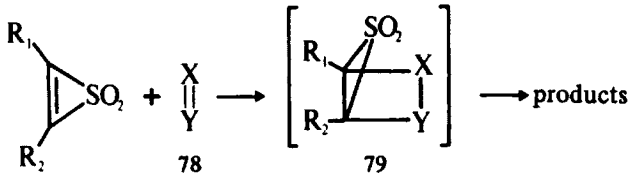
being attacked by nucleophiles only with difficulty.[63] The reason for this difference in behavior is not yet clear, but it most probably involves the particular electronic structure and geometry of this class of compounds.



(32)

C. *Cycloaddition Reactions*

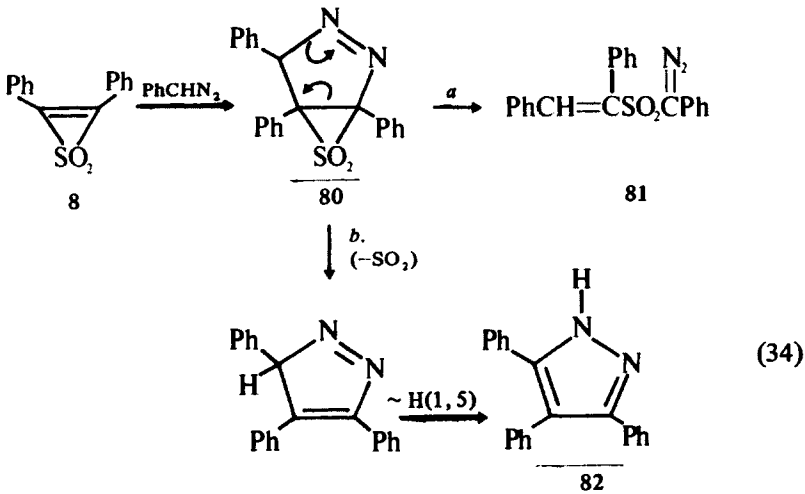
The cycloaddition capability of thiirene dioxides via the carbon-carbon double bond in the three-membered ring system has been quite extensively explored.[9,61,64,65] Based on the known cycloaddition capacity of α,β-unsaturated sulfones with electron-rich olefins,[66] it could be anticipated that thiirene dioxides might also undergo similar cycloadditions with these "nucleophilic-type" reagents to initially provide cycloadducts that would eventually lead to novel medium-sized sulfur-containing heterocycles and acyclic systems as well. This idea is schematically represented in Eq. 33.



(33)

Since only nucleophilic-type reagents (**78**) have been used in these cycloadditions, the transformation **78** → **79** indicates the extent of conjugation ("aromaticity") in thiirene dioxides vs. ordinary α,β-unsaturated sulfones.

The first reported cycloaddition reaction of thiirene dioxide was that in which the latter was treated with phenyldiazomethane to give 3,4,5-triphenylpyrazole (**82**) (albeit in low yield) and the acyclic α-diazobenzyl-1,2-diphenylvinyl sulfone **81**, both presumably originating from the 1,3-dipolar cycloaddition product **80**.[9]

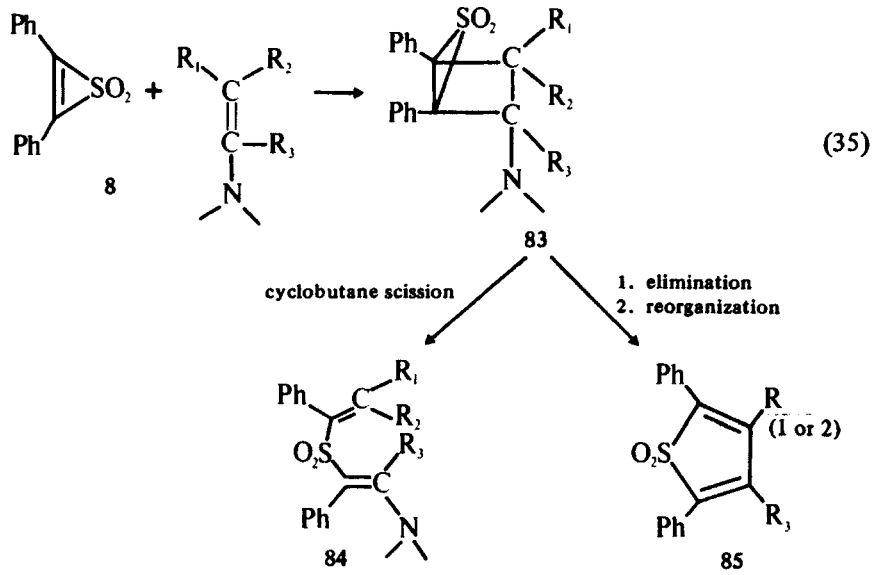


(34)

The ring-opening process leading to **81** (route *a*) is analogous to that which has been demonstrated to follow the cycloadditions of tosyl azide to certain enamines.[67] Similar results have been reported for the reaction of 2,3-diphenyl-

cyclopropenone with 2-diazopropane.[68] Other 1,3-dipolar cycloadditions with thiirene dioxides were also accomplished (see later in this section).

Thiirene dioxide (**8**) readily reacts with an entire spectrum of enamines to provide novel acyclic and cyclic systems.[64] These products are represented in Eq. 35, in which **83** accounts, directly, or indirectly, for all the observed products.[64]

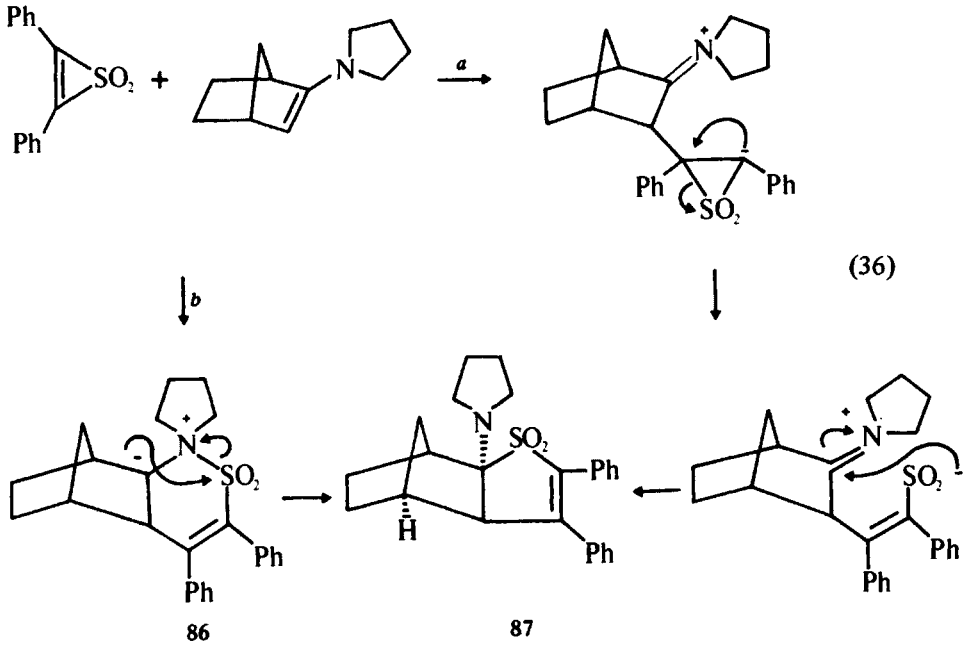


(35)

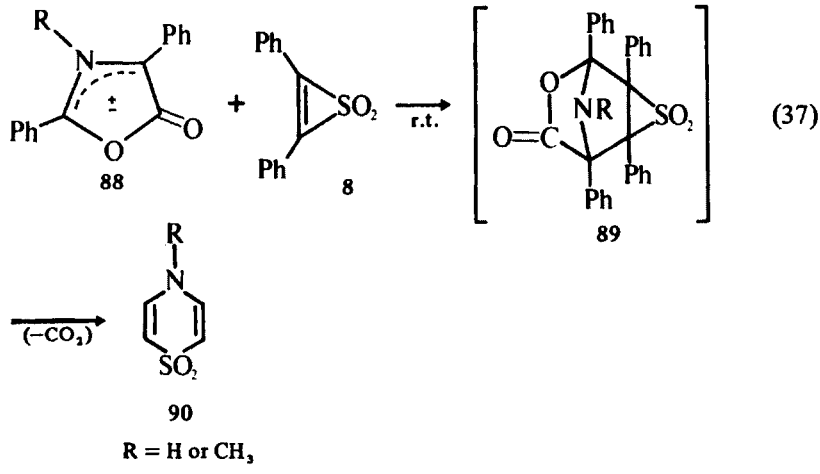
The synthetic value of the transformation above may be appreciated by examining Table 5, which summarizes selected results of the relevant study.[64]

It is generally accepted that the reaction of enamines with thiirene dioxides is a nonconcerted thermal [2 + 2] cycloaddition.[49] However, these transformations can be interpreted in terms of a concerted [4*n* + 2] cycloaddition in which the lone pair of electrons of the enamine nitrogen participates. Bond reorganization of the resultant zwitterion (i.e., **86**) could then afford all the described products. Although a similar intermediate has been invoked for the corresponding reaction with diphenylcyclopropenone,[69] such an interpretation (e.g., route *b*, Eq. 36) seems unnecessary, even though it accounts for the formation of **87** (incidentally, shown to have antifertility activity[64b]), since this compound could arise from an initial Michael addition with subsequent bond reorganization (e.g., route *a*, Eq. 36). In general, the cycloadditions just discussed are exothermic and much faster than those of diphenylcyclopropenone. Perhaps this is further evidence for the lack of substantial aromaticity of thiirene dioxides.

1,3-Dipolar cycloadditions with thiirene dioxides as the dipolarophiles have been used in cycloaddition-extrusion reactions leading to the formation of a variety of heterocycles. Thus, in analogy to the cycloaddition-extrusion reactions of five-membered mesoionic compounds with diphenylcyclopropenone and related compounds,[71] the reaction of the five membered oxazolone **88** with 2,3-diphenylthiirene dioxide (**8**) afforded thiazine (**90**) in good yield.[65]



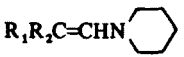
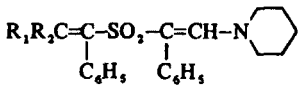
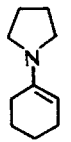
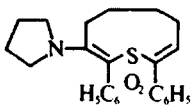
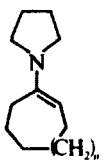
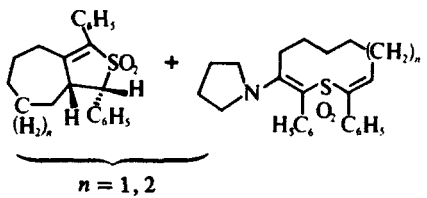
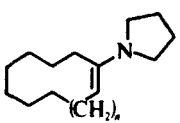
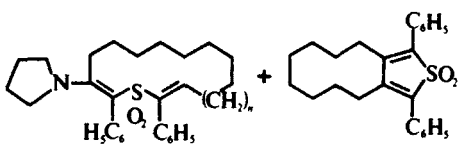
(36)

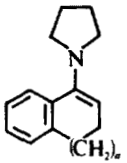


(37)

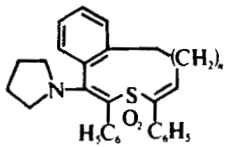
These results suggest that the cycloaddition of **88** takes place across the 2,3-double bond of the thiirene dioxide to give the intermediate **89**, which is followed by both carbon dioxide extrusion (preferentially to sulfur dioxide extrusion) and a cleavage of the three-membered ring. In contrast, the reaction of thiirene dioxide (**8**) with a six-membered mesoionic compound[70] or with pyridinium ylids[61] is known to give adducts resulting from extrusion of sulfur dioxide (see e.g., Eq. 38).[61]

TABLE 5. PRODUCTS OF THE CYCLOADDITION BETWEEN 2,3-DIARYLTHIIRENE DIOXIDES AND ENAMINES[64]

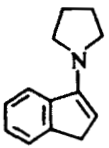
Enamine	Aryl	Products[a]
 a. $R_1 = CH_3$, $R_2 = H$ b. $R_1 = R_2 = CH_3$ c. $R_1 = C_6H_3$, $R_2 = H$	C_6H_5 or p-ClC_6C_4	
		
 $n = 1, 2$	C_6H_5	 $n = 1, 2$
 $n = 1$–3	C_6H_5	 $n = 1$–3



C_6H_5 or p-ClC_6H_4

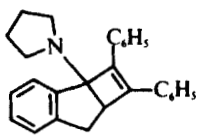


$n = 1–3$

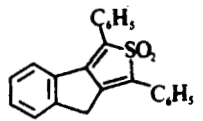


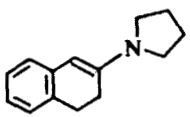
$n = 1, 2$

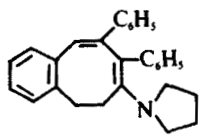
C_6H_5



+







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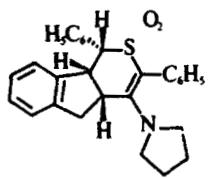
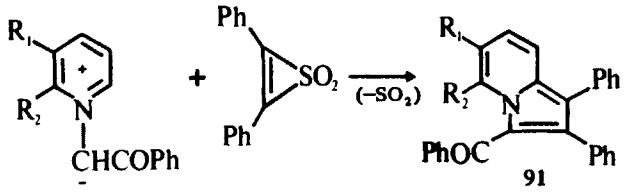


[a] In all cases of medium-sized heterocycles, only one of the possible structural assignments is shown.



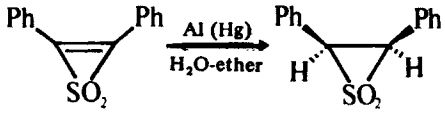
(38)

a. $R_1 = R_2 = H$

b. $R_1; R_2 =$ 

D. *Reduction*

Only one successful selective reduction of the carbon-carbon double bond in thiirene dioxides (i.e., without effecting any other changes in the molecule) is mentioned in the literature; it is observed when aluminum amalgam at $-45°$ in wet ether was used to afford the *cis*-2,3-diphenylthiirane dioxide **92** in low yield.

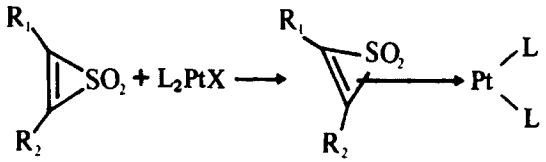


8 92 (16%)

(39)

E. *With Transition Metal Complexes*

Zero-valent platinum and palladium complexes of the thiirenes 1,1-dioxides can be easily prepared by ligand exchange with platinum complexes of the type L_2PtX at ambient temperature[44]:



93 94

(40)

a. $R_1 = H; R_2 = CH_3$
b. $R_1 = R_2 = CH_3$
c. $R_1 = CH_3; R_2 = C_6H_5$
d. $R_1 = R_2 = C_6H_5$

$L = (C_6H_5)_3P$
$X = (C_6H_5)_3P; CH_2{=}CH_2; CS_2$

Of all attempted thiirene dioxides, only **93a** coordinated to Vaska's complex [*trans*-$IrL_2(CO)Cl$]. The structural assignments were based on both ir and nmr spectroscopy (i.e., coupling constants), according to which both the platinum and the palladium complexes of thiirene dioxides **93a** and **93b** were isolated at subzero temperatures. Attempts to isolate the complexes with **93c** and **93d** failed.

Furthermore, the zero-valent palladium and platinum complexes as well as monovalent rhodium and iridium complexes were found[44] to catalyze the decomposition of thiirene dioxide, whereas divalent platinum and palladium complexes had no effect (see Section IX, 4, A).

5. References

1. L. Ramberg and B. Bäcklund, *Ark. Kem. Miner. Geol.*, 13A (27), 1 (1940); *Chem. Abstr.*, 34, 4725 (1940).
2. (a) F. G. Bordwell, in *Organosulfur Compounds*, M. J. Janssen, Ed., Wiley, New York, 1967, pp. 271–284; (b) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, 73, 5187 (1951); (c) N. P. Neureiter and G. F. Bordwell, *ibid.*, 85, 1209 (1963); (d) N. P. Neureiter, *ibid.*, 88, 558 (1966).
3. (a) L. A. Paquette, in *Mechanisms of Molecular Migrations*, Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, 1971, pp. 121–156; (b) L. Paquette, *Acc. Chem. Res.*, 1, 209 (1968); (c) S. W. Schneller, *Int. J. Sulfur Chem.*, 7, 583 (1976).
4. (a) L. A. Paquette and L. S. Wittenbrook, *J. Am. Chem. Soc.*, 89, 4483 (1967); (b) L. A. Paquette, L. S. Wittenbrook, and V. V. Kane, *ibid.*, 89, 4487 (1967); (c) F. G. Bordwell, J. M. Williams, Jr., and B. B. Jarvis, *J. Org. Chem.*, 33, 2026 (1968).
5. (a) L. A. Paquette and L. S. Wittenbrook, *J. Chem. Soc., Chem. Commun.*, 471 (1966); (b) F. G. Bordwell, E. B. Hoyt, Jr., B. B. Jarvis, and J. M. Williams, Jr., *J. Org. Chem.*, 33, 2030 (1968).
6. C. Y. Meyers, W. S. Mathews, G. J. McCollum, L. L. Ho, and H. H, Duy, *Hetereocycles*, 9, 1486 (1978).
7. (a) T. B. Johnson and I. B. Douglas, *J. Am. Chem. Soc.*, 63, 1571 (1941); (b) L. A. Paquette, *ibid.*, 86, 486, 4085 (1964).
8. J. C. Sheehan, U. Zoller, and D. Ben Ishai, *J. Org. Chem.*, 39, 1817 (1974).
9. (a) L. A. Carpino and L. V. McAdams III, *J. Am. Chem. Soc.*, 87, 5804 (1965); (b) L. A. Carpino, L. V. McAdams III, R. H. Rynbrandt, and J. W. Spiewak, *ibid.*, 93, 476 (1971).
10. A. Hassner and F. W. Fowler, *J. Am. Chem. Soc.*, 90, 2869 (1968).
11. E. Schmitz, *Dreiringe mit Zwei Heteroatomen*, Springer-Verlag, Berlin, 1967.
12. (a) R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.*, 86, 4866 (1964); (b) J. K. Stille and D. D. Whitehurst, *ibid.*, 86, 4871 (1964); (c) D. J. Anderson, T. L. Gilchrist, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 147 (1969); (d) D. T. Clark, *Theor. Chim. Acta*, 15, 225 (1969); (e) R. Breslow, *Acc. Chem. Res.*, 6, 393 (1973); (f) W. A. Lathan, L. Radom, P. C. Hariharan, W. J. Hehre, and J. A. Pople, *Fortschr. Chem. Forsch.*, 40, 1 (1973).
13. (a) L. Carpino and H. -W. Chen, *J. Am. Chem. Soc.*, 93, 785 (1971); (b) L. Carpino and H. -W. Chen, *ibid.*, 101, 390 (1979).
14. (a) M. J. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, New York, 1969, pp. 430–440; (b) K. A. R. Mitchell, *Chem. Rev.*, 69, 157 (1969).

15. L. A. Paquette, *Principles of Modern Heterocyclic Chemistry*, Benjamin, New York, 1968.

16. (a) E. J. Corey and E. Block, *J. Org. Chem.*, 34, 1233 (1969); (b) L. A. Paquette and R. W. Houser, *J. Am. Chem. Soc.*, 91, 3870 (1970); (c) L. A. Paquette, J. C. Philips, and R. E. Wingard, Jr., *ibid.*, 93, 4516 (1971); (d) W. Middlebos, J. Strating, and B. Zwanenberg, *Tetrahedron Lett.*, 351 (1971); (e) L. Paquette, *Acc. Chem. Res.*, 1, 209 (1968); (f) C. Meyers, in *Topics in Organic Sulfur Chemistry*, M. Tišler, Ed., University Press, Ljubljana, Yugoslavia, 1978, pp. 207–260.

17. Cf. (a) L. A. Carpino, P. H. Terry, and S. D. Thatte, *Tetrahedron Lett.*, 3329 (1964); (b) R. Breslow, J. Posner, and A. Krebs, *J. Am. Chem. Soc.*, 85, 234 (1963).

18. L. A. Carpino and L. V. McAdams III, *Org. Synth.*, 50, 65 (1970).

19. L. A. Carpino and H. -W. Chen, private communication.

20. J. Philips, J. V. Swisher, D. Haydukewych, and O. Morales, *J. Chem. Soc., Chem. Commun.*, 22 (1971).

21. J. M. Williams, Jr., Ph.D. Thesis, Northwestern University, Evanston, Il, 1966.

22. (a) G. Opitz, *Angew. Chem., Int. Ed. Engl.*, 6, 107 (1967); (b) G. Opitz and K. Fischer, *Z. Naturforsch. B*, 18, 775 (1963); (c) N. Fischer and G. Opitz, *Org. Synth.*, 48, 106 (1968).

23. L. A. Carpino and R. H. Rynbrandt, *J. Am. Chem. Soc.*, 88, 5682 (1966).

24. (a) F. Arndt, in *Organic Synthesis*, Collected Vol. II, Wiley, New York, 1943, pp. 165, 461; (b) D. Kubik and V. I. Sternberg, *Chem. Ind. (London)*, 248 (1966).

25. H. Oediger, H. -J. Kabbe, F. Möller, and K. Eiter, *Chem. Ber.*, 99, 2012 (1966).

26. L. A. Carpino and J. R. Williams, *J. Org. Chem.*, 39, 2320 (1974).

27. (a) W. V. Farrar, *J. Chem. Soc.*, 508 (1956); (b) H. Liebig, German Patent 1,256,216; *Chem. Abstr.*, 69, 18609 (1969).

28. K. Szabo, U.S. Patent 3,106,585; *Chem. Abstr.*, 60, 2841 b (1964); U. S. Patent 3,294,845; *Chem. Abstr.*, 67, 11210 c (1967).

29. F. G. Bordwell, J. M. Williams, Jr., E. B. Hoyt, and B. B. Jarvis, *J. Am. Chem. Soc.*, 90, 429 (1968).

30. L. Paquette and S. Wittenbrook, *J. Am. Chem. Soc.*, 90, 6790 (1968).

31. L. A. Paquette, *J. Am. Chem. Soc.*, 86, 4089 (1964).

32. C. Y. Meyers, in *Topics in Organic Sulfur Chemistry*, M. Tišler, Ed., University Press, Ljubljana, Yugoslavia, 1978.

33. H. L. Ammon, L. Fallon, and L. A. Plastas, *Acta Crystallogr., Sect. B*, 32, 2171 (1976).

34. (a) M. L. Ziegler, J. Weiss, H. Schildknecht, N. Grund, and H. -E. Sasse, *Liebigs Ann. Chem.*, 1702 (1973); (b) G. L. Hardgrove, J. S. Bratholdt, and M. M. Lein, *J. Org. Chem.*, 39, 246 (1974); (c) S. S. C. Chu, *Acta Crystallogr., Sect. B*, 31, 1082 (1975).

35. C. Müller, A. Schweig, and H. Vermeer, *J. Am. Chem. Soc.*, 97, 982 (1975).

36. F. de Jong, A. J. Noorduin, T. Bouwman, and M. J. Janssen, *Tetrahedron Lett.*, 13, 1209 (1974).

37. (a) C. Müller, A. Schweig, and H. Vermeer, *Angew. Chem., Int. Ed. Engl.*, 13, 273 (1974); (b) W. Schäfer, A. Schweig, G. Maier, T. Sayrac, and K. J. Crandall, *Tetrahedron Lett.*, 1213 (1976).

38. (a) N. C. Baird, *Theor. Chim. Acta*, 16, 239 (1970); (b) H. -L. Hase and A. Schweig, *Tetrahedron*, 29, 1759 (1973); (c) C. Müller, A. Schweig, M. P. Cava, and M. V. Lashmikantharmi, *J. Am. Chem. Soc.*, 98, 7187 (1976).

39. C. Müller, A. Schweig, and H. Vermeer, *J. Am. Chem. Soc.*, 100, 8056 (1978).

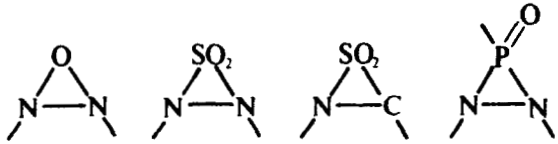
40. (a) H. H. Jaffe, *Acc. Chem. Res.*, 2, 136 (1969); (b) K. -W. Schulte and A. Schweig, *Theor. Chim. Acta*, 33, 19 (1974).

41. H. L. Hase, C. Müller, and A. Schweig, *Tetrahedron*, 34, 2983 (1978).
42. (a) D. Barnard, J. M. Fabian, and H. P. Koch, *J. Chem. Soc.*, 2442 (1949); (b) L. J. Bellamy and R. L. Williams, *J. Chem. Soc.*, 863 (1957); (c) E. A. Robinson, *Can. J. Chem.*, 39, 247 (1961); (d) P. M. Bavin, G. W. Gray, and A. Stephenson, *Spectrochim. Acta*, 16, 1312 (1960).
43. R. Breslow and L. J. Altman, *J. Am. Chem. Soc.*, 88, 504 (1966).
44. D. N. Reinhoudt, C. G. Kouwenhoven, and J. P. Visser, *J. Organomet. Chem.*, 57, 403 (1973).
45. (a) P. Vouros and L. A. Carpino, *J. Org. Chem.*, 39, 3777 (1974); (b) P. Vouros, *J. Heterocycl. Chem.*, 12, 21 (1975).
46. (a) F. H. Field, *Acc. Chem., Res.*, 1, 42 (1968); (b) B. Munson, *Anal. Chem. Rev.*, 43, 28 (1971).
47. J. C. Philips and O. Morales, *J. Chem. Soc., Chem. Commun.*, 713 (1977).
48. H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, 80, 4979 (1958).
49. (a) R. B. Woodward and R. Hoffman, *Angew. Chem., In. Ed. Engl.*, 8, 181 (1969); (b) R. Hoffmann and R. B. Woodward, *Science*, 167, 825 (1970).
50. (a) L. Paquette, *Acc. Chem. Res.*, 1, 209 (1968); (b) F. G. Bordwell, J. M. Williams, E. B. Hoyt, Jr., and B. B. Jarvis, *J. Am. Chem. Soc.*, 90, 429 (1968).
51. S. W. Schneller, *Int. J. Sulfur Chem.*, 8, 583 (1976).
52. F. G. Bordwell and S. C. Crooks, *J. Am. Chem. Soc.*, 91, 2084 (1969).
53. C. Y. Meyers, *Catalysis in Organic Synthesis*, Academic Press, New York, 1977, pp. 218–251.
54. S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc., B*, 343 (1967).
55. (a) S. Patai and Z. Rappoport, in *The Chemistry of Alkenes*, S. Patai (Ed.), Wiley-Interscience, New York, 1964, Ch. 8; (b) H. Shenhav, Z. Rappoport, and S. Patai, *J. Chem. Soc., B*, 469 (1970).
56. B. B. Jarvis, W. P. Tong, and H. L. Ammon, *J. Org. Chem.*, 40, 3189 (1975).
57. B. B. Jarvis and W. P. Tong, *Synthesis*, 102 (1975).
58. U. Zoller and E. M. Burgess, unpublished results.
59. O. S. Tee, J. A. Altmann, and K. Yates, *J. Am. Chem. Soc.*, 96, 3141 (1974).
60. B. B. Jarvis, G. P. Stahy, and H. L. Ammon, *Tetrahedron Lett.*, 3781 (1978).
61. Y. Hayasi, H. Nakamura, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 46, 667 (1973).
62. (a) Y. Yoshida, M. Komatsu, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, 44, 830 (1979); (b) T. Agawa, Y. Yoshida, M. Komatsu, and J. Ohshiro, *J. Chem. Soc., Chem. Commun.*, 931 (1977).
63. R. V. Vizgert, *Russ. Chem. Rev.*, 32, 1 (1963).
64. (a) M. H. Rosen and G. Bonet, *J. Org. Chem.*, 39, 3805 (1974); (b) M. H. Rossen, I. Fingler, and G. Bonet, *J. Med. Chem.*, 19, 414 (1976).
65. H. Matsujubo, M. Kojima, and H. Kato, *Chem. Lett.* 1153 (1975).
66. (a) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, 29, 801 (1964); (b) A. Risaliti, S. Fatutta, and M. Forchiassin, *Tetrahedron*, 23, 1451 (1967).
67. R. Fusco, G. Bianchetti, R. Pocar, and R. Ugo, *Chem. Ber.*, 96, 802 (1963).
68. M. Franck-Neumann and C. Buchecker, *Tetrahedron Lett.*, 2659 (1969).
69. (a) M. H. Rosen, I. Fengler, and G. Bonet, *Tetrahedron Lett.*, 949 (1973); (b) V. Bilinski and A. S. Dreiding, *Helv. Chim. Acta*, 55, 1271 (1972); (c) T. Eicher and S. Böhm, *Tetrahedron Lett.*, 2603, 3965 (1973).
70. K. T. Potts, A. J. Elliott, and M. Sorm, *J. Org. Chem.*, 37, 3838 (1972).

XI. THREE-MEMBERED RINGS CONTAINING SULFUR AND ONE OR MORE ADDITIONAL HETEROATOMS

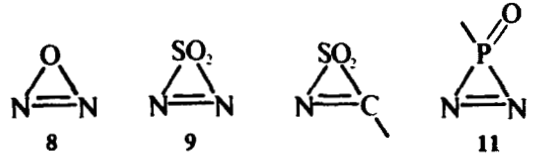
Although no three-membered ring with two heteroatoms had been prepared before 1950, several isolable compounds incorporating at least two heteroatoms are known to date. In this category investigation of three-membered rings containing two nitrogen atoms (i.e., diaziridines and diazirines; **1** and **2**, respectively)[1] or one nitrogen and one oxygen (i.e., oxaziranes, **3**)[1,2] preceded the preparation and actual isolation of three-membered rings containing sulfur as one of the heteroatoms. In fact, the latter are products of the 1970s. Following the synthesis of the first three-membered ring comprised solely of heteroatoms (i.e., oxadiaziridine, **4**),[3] the synthesis of the thiadiaziridine dioxide **5** was reported,[4] followed by the successful isolation and characterization of the thiaziridine dioxide system **6**[5] and of the P-analog **7**.[6]

1 **2** **3**



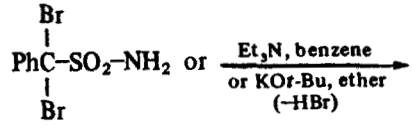
4 **5** **6** **7**

Essentially nothing is known about the analogous unsaturated systems, that is, **8–11**.



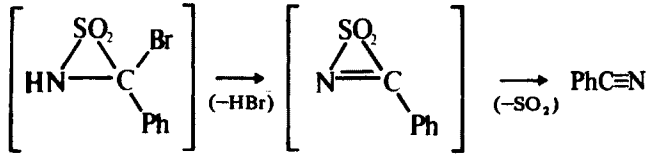
8 **9** **10** **11**

However, the intermediacy of system **10** – the aza analog of the thiirene dioxide (e.g., **13**) has been established in the base-induced successive dehydrohalogenations of the α,α-dibromobenzylsulfonamide **12**[7]:



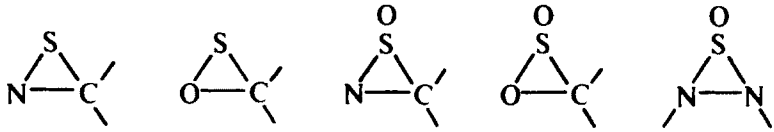
(1)

12



13

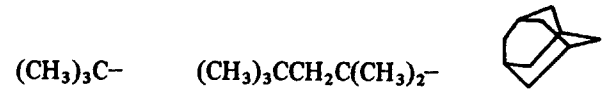
Evidence for the intermediacy of other "vinyloges" of thiirenes and thiirene oxides and dioxides has also been reported.[8,9] Interestingly, except as proposed reaction intermediates (discussed later), the saturated three-membered ring systems **14–18** have not been synthesized thus far.



14 **15** **16** **17** **18**

The high energy inherent in the sulfur-containing three-membered ring systems such as **5–6**, **9–10**, and **14–18**, turned them by and large into very reactive species, which are sensitive both chemically and thermodynamically, particularly to nucleophiles.

It is not surprising that in view of the well-documented stabilizing effect imparted to sensitive three-membered rings by bulky substituents,[10] all the successful syntheses and isolations of stable three-membered rings containing sulfur and additional heteroatoms (e.g., **5** and **6**) as well as other isolable heteroatomic three-membered rings (e.g., **7**) are those in which the ring carbon or nitrogen atom (or both) are substituted with very bulky groups: the *tert*-butyl, the 1,1,3,3-tetramethylbutyl, and adamantyl, **19–21**, respectively.



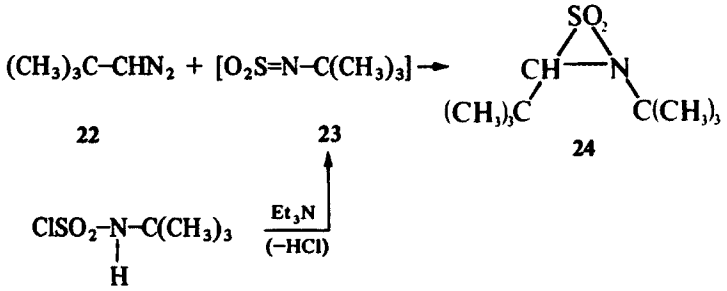
$(CH_3)_3C-$ $(CH_3)_3CCH_2C(CH_3)_2-$

19 **20** **21**

It is to be expected that the same strategy with respect to substitution will be adopted in future attempts to synthesize the as yet elusive sulfur-containing three-membered ring systems **10**, **14–18**, and others as well.

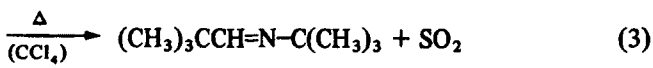
1. Thiaziridine Dioxides

The only known thiaziridine dioxide has been recently synthesized[5] by the application of the reaction of diazo compounds with sulfenes[11,12] (see Section VI, 2, B) to the *N*-sulfonylamine **23**. The synthetic scheme is shown below in Eq. 2.



(2)

Thiaziridine dioxide (24), which crystallizes as colorless needles from pentane at $-78°$, is thermally unstable and easily decomposes quantitatively to sulfur dioxide and azomethine (24a). This first-order decomposition has been shown[5] to occur over more than three half-lives with K (25°) = (9.05 ± 0.05) x 10^{-5} sec^{-1}.

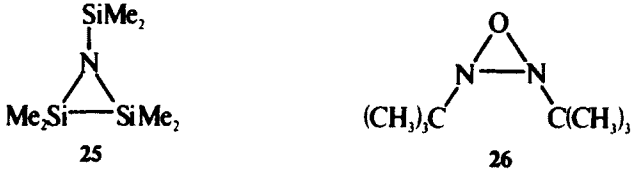


(3)

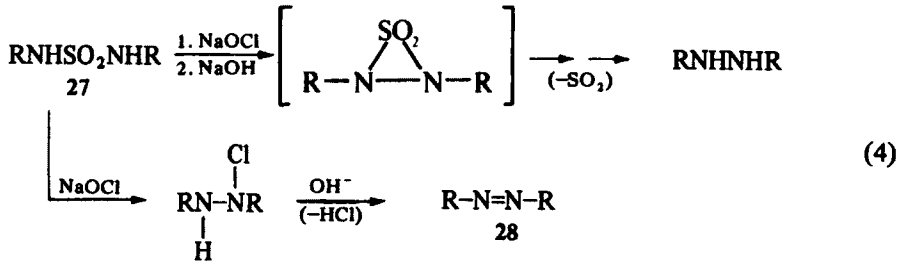
The ir and nmr spectra of 24 are in accord with the assigned structures: ir (CCl_4): 1325, 1177 cm^{-1} (SO_2); and nmr (CCl_4): δ = 1.03 (*s*, *t*-Bu), 1.33 (*s*, *t*-Bu), and 3.72 ppm (*s*, CH).

2. Thiadiaziridine Dioxides

Before the successful synthesis of the first member of the thiadiaziridine dioxides in 1972,[4] only two ring systems comprised entirely of heteroatoms had been isolated and fully characterized, the disilaziridine 25[12] and the oxadiazirine 26.



Before 1972 thiadiaziridine dioxides were postulated as intermediates in the classic synthesis of azoalkanes (28)[14]:



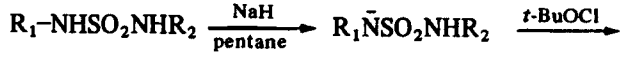
(4)

However, under the reaction conditions employed, the actual isolation of these postulated intermediates has not been achieved.

A. *Method of Preparation*

All known thiadiaziridine dioxides have been prepared by essentially the same method starting with substituted sulfamides (27): the latter are treated with a non-nucleophilic base to form the monoanion of the sulfamide 27 (i.e., 29), which on treatment with *t*-butyl hypochlorite give the *N*-chloroanion 30.

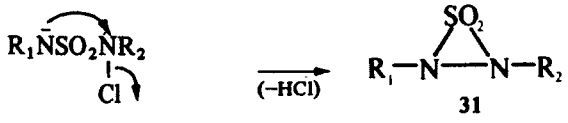
Dehydrohalogenation in the final crucial step affords the desired cyclized thiadiaziridine dioxide system (e.g., 31) as depicted in Eq. 5.[4,5]



27 29[15,16]

a. $R_1 = R_2 = t$-Bu
b. $R_1 = R_2 = (CH_3)_3CCH_2C(CH_3)_2$
c. $R_1 = R_2$ = adamantyl
d. $R_1 = t$-Bu; $R_2 = (CH_3)_3CCH_2C(CH_3)_2$

(5)



30 31

a. $R_1 = R_2 = t$-Bu[4,15,16] (46%,[4] 61%[16])
b. $R_1 = R_2 = (CH_3)_3CCH_2C(CH_3)_2$[4,15] (90%)
c. $R_1 = R_2$ = adamantyl[17] (95%)
d. $R_1 = t$-Bu; $R_2 = (CH_3)_3CCH_2C(CH_3)_2$[15] (–)

The symmetrical 2,3-di-*tert*-butyl,[4,15,16] 2,3-di-(1,1,3,3)-tetramethylbutyl,[4,15] and 2,3-diadamantyl,[4,17] as well as the unsymmetrical 2-*tert*-butyl, 3-(1,1,3,3)-tetramethylbutyl[15] thiaziridine dioxides (i.e., **31a–31d**), have thus been prepared. Thiaziridine (**31c**) was also prepared by the treatment of the corresponding sulfamide (i.e., **27c**) with 2 mole equivalents of both potassium *t*-butoxide and *t*-butyl hypochlorite in *t*-butyl alcohol–carbon tetrachloride.[17] It turns out that the order of introducing the sodium hydride and *t*-butyl hypochlorite into the sulfamide solution is crucial, since if the *N*-chlorination precedes the formation of the anion **29**, the α-halosulfamide formed is reduced back to the starting sulfamide **27** upon treatment with sodium hydride and therefore the thiaziridines (**31**) are not formed.[15,16]

The synthesis of thiaziridine dioxide (**31d**) through the unsymmetrical sulfamide **30d**[18] opens the way for the preparation of unsymmetrical thiaziridine dioxides other than **31d**.

B. *Structure and Physical Properties*

Thiaziridine dioxides are colorless solids [m.p. 35–36, 49.5–50, 169–170° and 160 (1.5 mm) for **31a–31d**, respectively][15–17] having the *trans* configuration (concerning the nitrogen substituents). This has been unambiguously established by X-ray analysis for **31b**[19] and deduced from the smooth rearrangement of thiaziridine dioxide (**31a**) to afford *trans*-azoalkane (**28**; R = *t*-Bu).[16] The spectral data (see below) further substantiate the *trans* configuration.

The S–N average bond length and the N–N bond length in **31b** were found to be 1.62 and 1.67 Å respectively,[19] the latter being significantly longer than any analogous distance for the C–N bond in aziridine.[20] Such lengthening facilitates the angle NSN to maintain a value of 62° (which is near the "normal" expected value of 60° for a three-membered ring). The relative weakening of the N–N bond in this ring system is a logical consequence.

The ir and nmr data of the known systems are given in Table 1.

The magnetic nonequivalence of the two methyl groups closest to the ring nitrogens in **31b** in benzene (although they are equivalent in CCl_4 and $CHCl_3$) suggest a slow inversion about both nitrogen bonds, as suggested for the di-*tert*-octyldiaziridinone.[21]

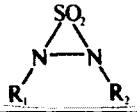
A competing mechanism (e.g., bond breaking, inversion, bond reformation) cannot be ruled out, however.[3]

C. *Chemical Properties and Reactivity*

a. HYDROLYSIS

The thiadiaziridine dioxides synthesized thus far are rather stable toward dilute acids or bases,[15–17] most probably because of the hindrance effect of their bulky substituents. In fact, both thiaziridine dioxides **31a** and **31b** can be recovered

TABLE 1. IR AND NMR DATA FOR THIADIAZIRIDINE DIOXIDES

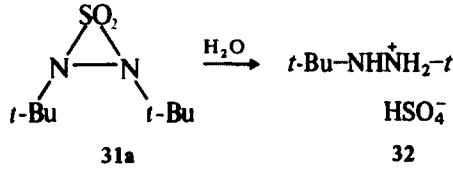


R_1	R_2	Ir bands; SO_2 (cm^{-1})	Nmr chemical shift δ (ppm)	Ref.
t-Bu	*t*-Bu	1395 1372[a]	1.32(*s*)[b] 133(*s*)[c]	15, 16
$(CH_3)_3CCH_2C(CH_3)_2$	$(CH_3)_3CCH_2C(CH_3)_2$		0.96(*s*, 18H), 1.12(*s*, 12H), 1.78(*s*, 4H)	15
Adamantyl	Adamantyl	1335 1202[d]	1.67, 1.93, 2.15 (broad)[b]	17

[a] KBr. [b] CCl_4. [c] $CDCl_3$. [d] Nujol.

unchanged from 2*N* aqueous hydrochloric acid, 2*N* aqueous sodium hydroxide, aqueous potassium permanganate, and 30% aqueous hydrogen peroxide.[4,15] The reaction of **31b** with 2*N* sodium methoxide is slow.[15]

Hydrolysis of **31a** occurs slowly in an open container at room temperature and more rapidly in refluxing *wet* benzene to 1,2-di-*tert*-butylhydrazine hydrogen sulfate as shown in Eq. 6.



31a **32** (6)

The hydrolysis of **31b** in wet benzene is much slower, and both **31b** and **31c** are essentially stable at room temperature.

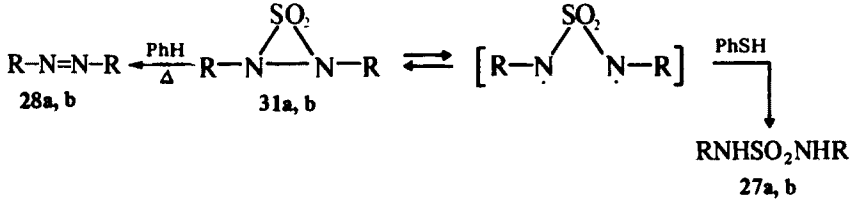
The transformation above is consistent with the proposed mechanism for the azoalkane synthesis from sulfamides.[14]

b. THERMOLYSIS

On prolonged reflux in pentane or benzene, the thiaziridine dioxide **31a** smoothly decomposes to afford the *trans*-diazoalkane **28** (R = *t*-Bu) in nearly quantitative yield. This thermal sulfur dioxide extrusion is very similar to that observed in the pyrolysis of *cis*- and *trans*-2,3-diphenylthiirane dioxides.[21] It is not known, however, whether this sulfur dioxide elimination is a stepwise or a concerted process.[22]

The difference in thermal stability between some thiaziridine oxides is striking. In contrast to the smooth thermolysis of **31a**, **31b** can be recovered after 1 hr of refluxing in toluene.[3] It does decompose, however, above 130° but product analysis is complicated.[3] Heating of **31c** in mesitylene afforded only 15% sulfur dioxide and 43% sulfamide (**27c**).[17] Although the difference in thermal stability can be interpreted in terms of added hindrance to concerted ring opening by the bulkier groups, the role of the adamantyl substituent compared with that of the 1,1,3,3-tetramethylbutyl group must wait further study.

Interestingly, both **31a** and **31b** give quantitative yields of alkyl sulfamides (i.e., **27a**, **27b**) when heated in aromatic solvents with added thiophenol as represented in Eq. 7.[15]

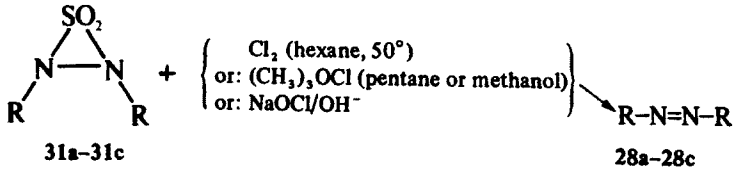


28a, b **31a, b** **27a, b** (7)

c. WITH OXIDIZING AGENTS

Although dilute aqueous solution of hydrogen peroxide or potassium per-

manganate has no effect on thiaziridine dioxides, their treatment with chlorine, *t*-butyl hypochlorite, and alkaline sodium hypochlorite resulted in the isolation of the azoalkanes **28a–28c** in good yields[15–17]:



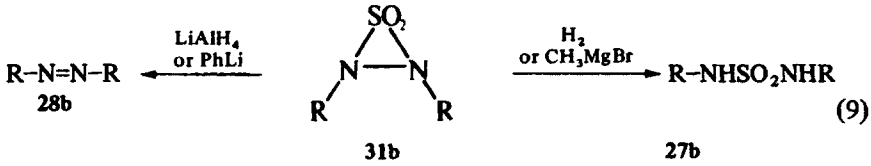
31a–31c **28a–28c** (8)

d. WITH REDUCING AGENTS

Reduction of thiaziridine dioxide (**31b**) with hydrogen afforded the sulfamide **27a**, whereas the azoalkane **28b** was obtained with $LiAlH_4$ (see Eq. 9, below), accompanied by small amounts of sulfamide **27**.[15]

e. WITH GRIGNARD AND LITHIUM REAGENTS

Treatment of **31b** with methylmagnesium bromide gave **27b**, whereas the lithium reagent afforded the azo compound[15]:



28b **31b** **27b** (9)

f. MISCELLANEOUS

The azo compound **28b** is obtained when thiaziridine dioxide (**31b**) is treated with either acids (e.g., HCl gas) or bases (e.g., $NaOCH_3$) in nonaqueous media.[15]

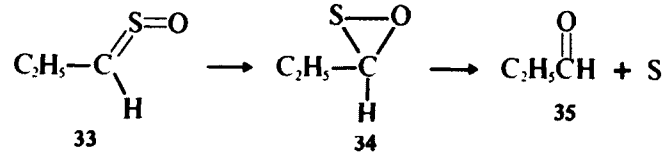
A Diels-Alder adduct is formed in the reaction of the 2,3-diphenylthiaziridine dioxide **31a** with 1,3-diphenylisobenzofuran.[16]

Further exploration of the chemistry of the thiaziridine dioxides is required before the full scope of their chemical behavior and potential synthetic usefulness can be established.

3. Oxathiiranes

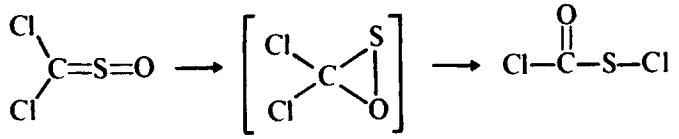
Oxathiiranes, having the ring structure represented by **15**, are not known to date. However, their existence as intermediates in several reactions involving sulfines has been proposed.

Thus, an oxathiirane (34) has been proposed[23] as the thermal intermediate in the decomposition of thiopropenal *S*-oxide (33) (identified as the lachrymatory factor in onions) at room temperature to give largely propionaldehyde and sulfur[24] as shown in Eq. 10.



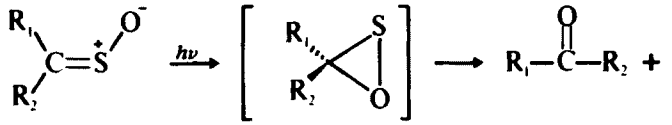
33 34 35 (10)

The complicated decomposition of thiophosgene *S*-oxide (37) has been pictured similarly[25]:



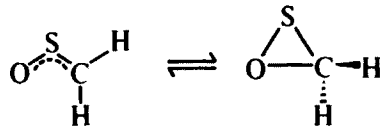
37 38 39 (11)

Likewise, it has been suggested that oxathiiranes (40) intervene in the photochemical conversions of various thiocarbonyl *S*-oxides (sulfines) to carbonyl compounds[26] as illustrated in Eq. 12.



40 (12)

Both the open structure 41 and the oxathiirane ring structure 42 were energy-geometry optimized[27] by means of Boyd's MO-SCF-CNDO procedure.[28] Oxathiirane creation (i.e., 41 → 42) was predicted[29] to be an allowed thermal reaction,[30] although stereochemically uninteresting.

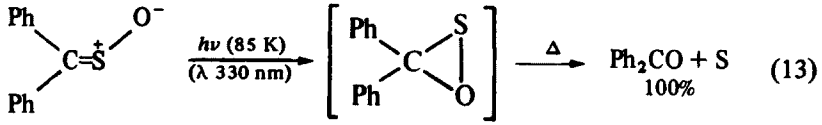


41 42

The electron density on the oxygen atom is a crucial factor in the energy level stabilization: the π_{HOMO} of 41 and the σ_l lone-pair orbital of 42 drop significantly in energy and as a consequence the ring closure is favored by taking advantage of a π_{HOMO}–π_{HOMO} correlation, while the π_{HOMO}–σ_l interaction is avoided (presum-

ably on energy grounds).[29] Hence the reordering of the energy levels in the system can be attributed to the strong asymmetric perturbations introduced by the heteroatom.

Indeed, oxathiirane (44) has been observed spectroscopically by the irradiation of thiobenzophenone *S*-oxide (43) at 85 K within the region of 330 nm in EPA glass[31]:

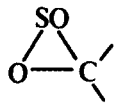


43 44 (13)

The intermediacy of 44 was further confirmed by a series of accompanied photochemical experiments and transformations[31] as well as by comparisons with closely related systems. Significantly, CNDO/S calculations[12] predict a weak maximum at $\lambda = 396$ nm for the electronic absorption spectrum of unsubstituted oxathiirane 42.

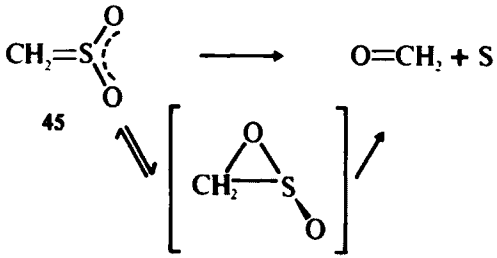
4. Oxathiirane Oxides (α-Sultines)

Oxathiirane oxides represented by structure 17, have been proposed as intermediates in several reactions to account for the observed products.



17

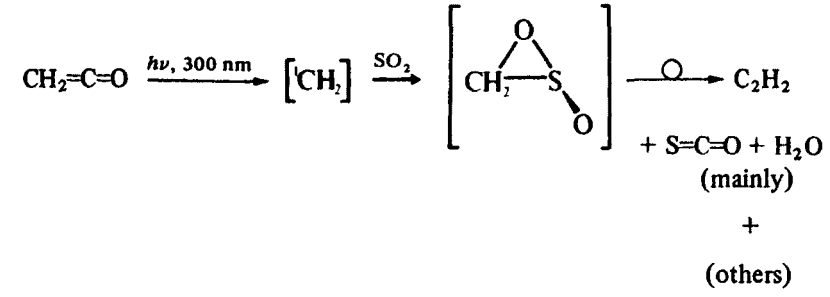
Thus, when sulfene[33] (45) is generated in the gas phase at high temperatures, formaldehyde and sulfur monoxide are formed.[34]



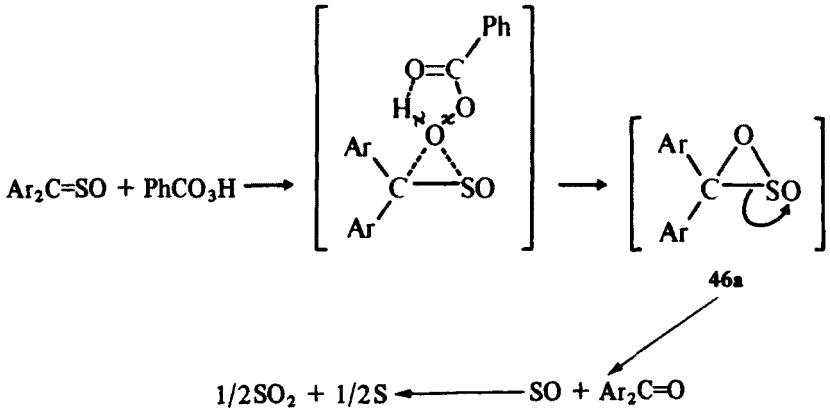
45 46

It has been suggested[34, 35] that the cyclization of the sulfene 45 into the α-sultine 46 precedes the final fragmentation to the observed products.

More recently, the preparation of transitory 46 at room temperature has been reported both in the addition of singlet methylene to sulfur dioxide[36] and in the oxidation of thiocarbonyl *S*-oxide with perbenzoic acid.[37] Equations 14 and 15 give the overall schemes of the two claimed transformations.



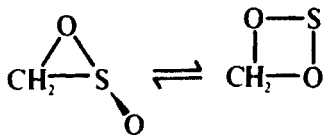
(14)



(15)

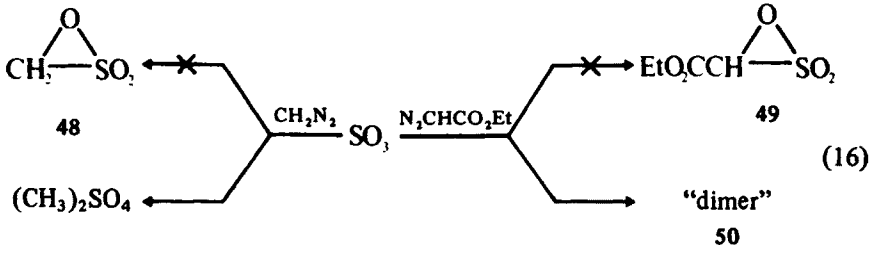
The intermediacy of oxathiirane oxide (**46a**) is corroborated not only by kinetic studies[37] of the given oxidation with several different diarylthione *S*-oxides but also by the observed substituent and solvent effects, which were similar to those reported for the oxidation of thiones, alkenes, acetylenes, and diazoalkanes with the same peroxyacid. Furthermore, the transient formation of an α-lactone formally similar to **46** has been assumed[38] in the reaction of ketenes with peracids.

Although only the direct observation (spectroscopically) or isolation of a stable member of the so far elusive oxathiirane oxide system would serve as an "ultimate proof" for its existence a CNDO/B semiempirical calculation predicts that the electrocyclic ring closure of sulfene (**45**) to α-sultine (**46**) follows an "allowed" pathway. Because of the evident *n*-π correlation and the high lying nonbonding oxygen levels introduced by *S*-oxidation, it has been argued[39] that a four-membered ring cyclic sulfoxylate ester of type **47** should be involved in the chemistry of the previously postulated oxathiirane oxide (α-sultine, **46**).



46 **47**

Attempts to prepare *S*-dioxides analogous to the α-sultines, namely the oxathiirane dioxides (α-sultones, **48** and **49**) were unfruitful. The reaction of sulfur trioxide with either diazomethane or diazoethyl acetate resulted, after work-up, in the isolation of dimethyl sulfate and a "dimer" (**50**, not fully characterized), respectively[40]:

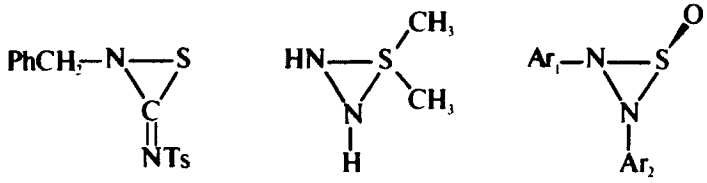


(16)

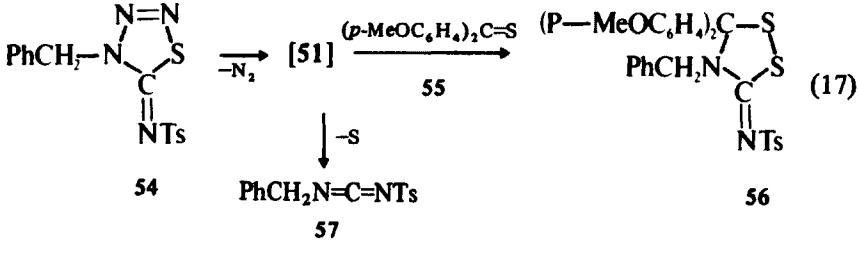
Nevertheless, the isolation of "properly" substituted oxathiirane oxides (or dioxides) still may prove to be possible under carefully selected reaction conditions.

5. Thiaziridinimines, Thiadiaziridines, and Thiadiaziridine Oxides

The thiaziridinimines, thiadiaziridines, and thiadiaziridine oxides are sulfur-containing, three-membered ring systems; they are represented in **51–53** by the particular members of each class that have been proposed as intermediates in certain chemical reactions studied.



Thus, thermolysis of 3-benzyl-5-tosylimino-1,2,3,4-thiatriazoline (**54**) in the presence of thione (**55**) furnished 1,2,4-dithiazolidine-5-imine (**56**) in moderate yield.[41] These results have been interpreted in terms of an unstable thiaziridinimine intermediate (**51**), which is trapped by the C=S compound in a regiospecific manner as depicted in Eq. 17.[41]



(17)

Thermolysis without the presence of **55** leads to the isolation of sulfonylcarbodiimide.

The intermediacy of dialkyl sulfurane of type **52** in the reaction of dialkyl sulfides with chloramine was considered.[42] The experimental evidence, however, does not substantiate this structure.

The thermal photochemical reaction between arylazides and *N*-sulfinylanilines has been shown to yield several products; the major one is the azo aromatic **58**[43]:

$$Ar_1N_3 + Ar_2N{=}S{=}O \xrightarrow{-N_2} [53] \longrightarrow Ar_1{-}N{=}N{-}Ar_2 + \text{other products} \quad (18)$$

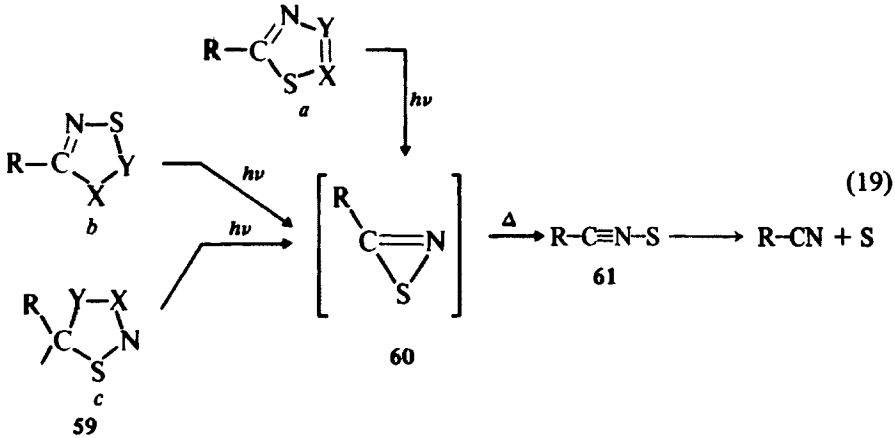
a. $Ar_1 = Ph$; $Ar_2 = p\text{-}MeC_6H_4$
b. $Ar_1 = p\text{-}MeC_6H_4$; $Ar_2 = Ph$
c. $Ar_1 = Ph$; $Ar_2 = p\text{-}ClC_6H_4$
d. $Ar_1 = p\text{-}ClC_6H_4$; $Ar_2 = Ph$
e. $Ar_1 = Ph$; $Ar_2 = p\text{-}OMeC_6H_4$

58 (major)

The experimental results (including the formation of sulfur and sulfur dioxide from the presumably formed sulfur monoxide) were interpreted in terms of the intermediacy of thiadiaziridine oxide (**53**). However, a distinction between direct nitrene addition to the N=SO bond and the concerted cycloaddition of the azide on the same bond before the formation of the three-membered ring could not be made based on the available experimental results.

6. Thiazirines: Three-Membered Sulfoximides

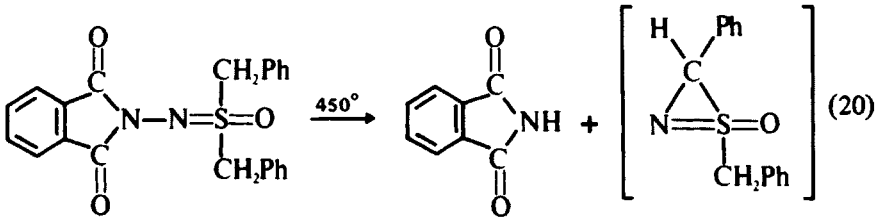
Thiazirines, the aza analogs of thiirenes, belong to the group of antiaromatic compounds[44]; hence their preparation should be possible only at very low temperatures. In analogy with the matrix isolation and characterization of thiirene and selenirene[45] (see Section V, 2), a number of five-membered heterocyclic compounds of type **59a–59c** were irradiated to produce the thermally labile nitrile sulfides **61**,[46] apparently through the intermediacy of the three-membered ring thiazirines **60**[9]:



(19)

Unfortunately, although the intermediacy of thiazirine (**60**) does account for all the experimental results in the investigation cited,[8] no separate spectral peak could be assigned unambiguously to this compound because the complicated spectra were obscured by the presence of other products and starting materials.

The oxidation of *N*-amino-lactams with lead tetraacetate in the presence of sulfoxides gave sulfoximides.[9] Thermolysis of the dibenzylsulfoximide **62** thus formed resulted in an N–N bond cleavage and formation of phthalimide (**63**) as the only reaction observed. It has been proposed[9] that the sulfur-containing products generated in this hydrogen transfer process have the three-membered ring sulfoximide structure **64**:



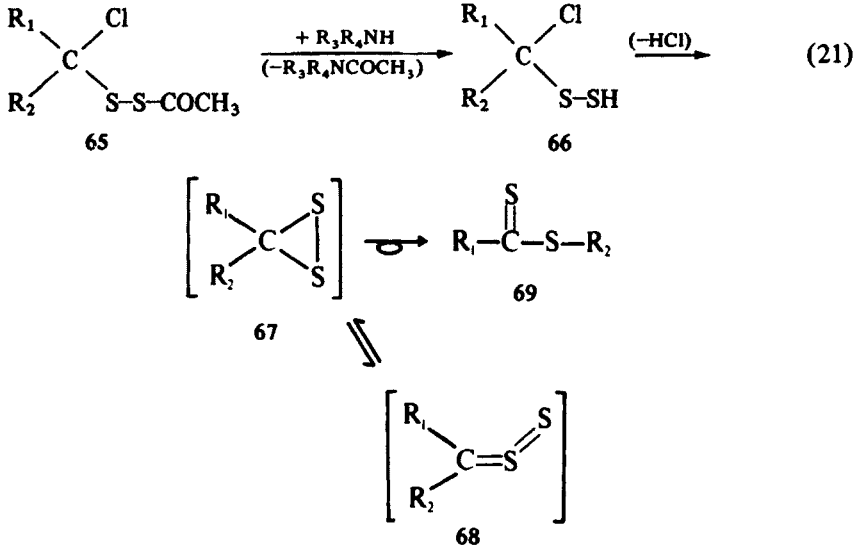
(20)

62 **63** **64**

Several attempts to isolate a product other than phthalimide from the reaction were unsuccessful.

7. Dithiiranes

Preparative reactions involving the proposed intermediacy of dithiiranes (**67**) have been recently reported.[47] The approach to the generation of this system is illustrated in Eq. 21.[47]



(21)

65 **66** **67** **69** **68**

Depending on the nature of R_1 and R_2, either the rearrangement of the presumed **67** to **69** or 1,3-addition to **68** is observed.

CNDO calculations of the parent dithiirane (**67**; $R_1 = R_2 = H$) have been performed, and the geometries of the as yet elusive molecule have been optimized.[48] Interestingly, an exception to the inverse relationship between $\Delta E_{HOMO-LUMO}$ and the long wavelength λ_{max} was found for both the dithiirane and the analogous oxythiirane.

8. References

1. E. Schmitz, *Dreiringe mit Zwei Heteroatomen*, Springer-Verlag, Berlin, 1967.
2. W. D. Emons, in *Heterocyclic Compounds with Three- and Four-Membered Rings*, A. Weissberger, Ed., Wiley-Interscience, New York, 1964.
3. F. D. Greene and S. S. Hecht, *J. Org. Chem.*, **35**, 2482 (1970).
4. (a) J. W. Timberlake and M. L. Hodges, *J. Am. Chem. Soc.*, **95**, 634 (1973); (b) J. W. Timberlake, M. L. Hodges, and K. Betterton, *Synthesis*, 632 (1972).
5. H. Quast and F. Kees, *Angew. Chem., Int. Ed. Engl.*, **13**, 742 (1974); *Angew. Chem.*, **86**, 816 (1974).
6. H. Quast, M. Heuschmann, and M. O. Abdel-Rahman, *Angew. Chem.*, **87**, 487 (1975).
7. J. C. Sheehan, U. Zoller, and D. Ben Ishai, *J. Org. Chem.*, **13**, 1817 (1974).
8. A. Holm, N. Harrit, and I. Trabjerg, *J. Chem. Soc., Perkin Trans 1*, 746 (1978).
9. D. J. Anderson, D. C. Horwell, and E. Stanton, *J. Chem. Soc., Perkin Trans. 1*, 1317 (1972).
10. (a) J. C. Sheehan and J. H. Beeson, *J. Am. Chem. Soc.*, **89**, 362 (1967); (b) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969); (c) H. Quast and E. Schmitt, *Angew. Chem., Int. Ed. Engl.*, **8**, 449 (1969); (d) J. F. Pajos and F. D. Greene, *J. Am. Chem. Soc.*, **89**, 1030 (1967); (e) R. Wealand and P. D. Bartlett, *ibid.*, **92**, 6057 (1970).
11. N. H. Fischer, *Synthesis*, 393 (1970).
12. (a) W. Fink, *Helv. Chim. Acta*, **46**, 720 (1963); *Angew. Chem.*, **78**, 803 (1966); (b) I. Haiduc, *The Chemistry of Inorganic Ring Systems*, Wiley-Interscience, New York, 1970.
13. (a) S. S. Hecht and F. D. Greene, *J. Am. Chem. Soc.*, **89**, 6761 (1967); (b) J. Swigert and K. G. Taylor, *ibid.*, **93**, 7337 (1971); (c) K. G. Taylor and R. Riehl, *ibid.*, **94**, 250 (1972).
14. (a) R. Ohme and E. Schmitz, *Angew. Chem., Int. Ed. Engl.*, **4**, 433 (1965); (b) R. Ohme and H. Preuschhof, *Justus Liebigs Ann. Chem.*, **713**, 74 (1968).
15. J. W. Timberlake, M. L. Hodges, and A. W. Garner, *Tetrahedron Lett.*, **39**, 3843 (1973).
16. H. H. Chang and B. Weinstein, *J. Chem. Soc., Chem. Commun.*, 397 (1973).
17. H. Quast and F. Kees, *Tetrahedron Lett.*, 1655 (1973).
18. J. B. Hendrickson and I. Joffe, *J. Am. Chem. Soc.*, **95**, 4083 (1973).
19. L. M. Trefonas and L. D. Cheung, *J. Am. Chem. Soc.*, **95**, 636 (1973).
20. T. C. Turner, V. C. Fiora, and W. M. Kendrick, *J. Chem. Phys.*, **23**, 1966 (1955).
21. F. G. Bordwell, J. M. Williams, E. B. Hoyt, and B. B. Jarvis, *J. Am. Chem. Soc.*, **90**, 429 (1968).

22. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970, p. 152.
23. W. F. Wilkens, Cornell Agricultural Experiment Station, Memoir 385, Ithaca, NY, January 1964.
24. (a) C. G. Spare and A. I. Virtanen, *Acta Chem. Scand.*, 17, 641 (1963); (b) W. F. Wilkens, Ph.D. Thesis, Cornell University, Ithaca, NY, 1961; (c) M. H. Brodnitz and J. V. Pascale, *J. Agric. Food Chem.*, 19, 269 (1971); (d) J. B. Bredenberg, E. Honkanen, and A. I. Virtanen, *Acta Chem. Scand.*, 16, 513 (1962).
25. J. Silhanek and M. Zbirovsky, *J. Chem. Soc., Chem. Commun.*, 878 (1969).
26. (a) B. Zwanenberg, L. Thijs, and J. Strating, *Tetrahedron Lett.*, 3453 (1967); (b) A. M. Hamid and S. Trippett, *J. Chem. Soc., C*, 1612 (1968); (c) A. G. Schultz, C. D. de Boer, and R. Schlessinger, *J. Am. Chem. Soc.*, 90, 5314 (1968); (d) R. H. Schlessinger and A. G. Schultz, *Tetrahedron Lett.*, 4513 (1969); (e) A. Padwa, *Int. J. Sulfur Chem.*, Part B, 7, 331 (1972); (f) A. G. Schultz and R. H. Schlessinger, *J. Chem. Soc., Chem. Commun.*, 1051 (1970); (g) B. Zwanenburg and J. Strating, *Q. Rep. Sulfur Chem.*, 5, 79 (1970).
27. J. P. Snyder and D. N. Harpp, *J. Chem. Soc., Chem. Commun.*, 1305 (1972).
28. R. J. Boyd and M. A. Whitehead, *J. Chem. Soc., Dalton Trans.*, 73, 78, 82 (1972).
29. J. P. Snider, *J. Am. Chem. Soc.*, 96, 5006 (1974).
30. R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 8, 781 (1969).
31. L. Carlsen, N. Harrit, and A. Holm, *J. Chem. Soc., Perkin Trans 1*, 1404 (1976).
32. J. P. Snider, unpublished results.
33. G. Opitz, *Angew. Chem., Int. Ed. Engl.*, 6, 107 (1967).
34. (a) J. F. King, P. de Mayo, and D. L. Verdun, *Can. J. Chem.*, 47, 4509 (1969); (b) C. L. Mcintosh and P. de Mayo, *J. Chem. Soc., Chem. Commun.*, 32 (1969); J. F. King, P. de Mayo, C. L. Mcintosh, K. Pien, and D. J. H. Smith, *Can. J. Chem.*, 48, 3704 (1970).
35. R. F. J. Langendries and F. C. De Schryver, *Tetrahedron Lett.*, 4781 (1970).
36. H. Hiraoka, *J. Chem. Soc., Chem. Commun.*, 1014 (1974).
37. (a) A. Battaglia, A. Dondoni, G. Maccagnani, and G. Mazzanti, *J. Chem. Soc., Perkin Trans 2*, 610 (1974); (b) W. Walter and O. H. Bauer, *Justus Liebigs Ann. Chem.*, 305 (1975); 1584 (1976).
38. J. K. Crandall and S. A. Sojka, *Tetrahedron Lett.*, 1641 (1972).
39. L. Carlsen and J. P. Snider, *J. Org. Chem.*, 43, 2216 (1978).
40. U. Zoller, unpublished results.
41. G. l'Abbé and C. C. Yu, *J. Heterocycl. Chem.*, 13, 883 (1976).
42. R. Appel, H. W. Fehlhaber, D. Hänssgen, and R. Schöllhorn, *Chem. Ber.*, 99, 3108 (1966).
43. L. Benati, G. DeLuca, G. Maccagnani, and A. Tundo, *J. Chem. Soc., Chem. Commun.*, 702 (1972).
44. R. Breslow, *Acc. Chem. Res.*, 6, 393 (1973).
45. (a) A. Krantz and J. Laureni, *J. Am. Chem. Soc.*, 99, 4842 (1977); (b) M. Torres, A. Clement, J. E. Bertie, H. E. Gunning, and O. P. Strausz, *J. Org. Chem.*, 43, 2490 (1978).
46. A. Holm, N. Harrit, and N. H. Toubro, *J. Am. Chem. Soc.*, 97, 6197 (1975).
47. A. Senning, ACS/CSY Congress, Honolulu, April 1979, ORGN, 347.
48. J. P. Snyder and L. Carlsen, *J. Am. Chem. Soc.*, 99, 2931 (1977).

XII. EPILOGUE

This chapter constitutes a walk on the trail of the fascinating and stimulating sulfur containing, three-membered ring systems which, excluding the thiiranes, are the result of no more than two decades of effort by the chemical community. Therefore, although much has been accomplished thus far and several of these classes of compounds have been prepared, isolated, characterized, and studied, a tremendous amount of work remains to be done in this area. The challenge is there, since many of these systems have been elusive thus far and their existence has been inferred only indirectly or circumstantially.

In view of the recent success in synthesizing thermally and chemically sensitive compounds and based on the accumulated data and experience gained, it is to be expected that many hitherto unknown three-membered rings containing sulfur (some of which have been mentioned in this chapter), will be successfully synthesized, characterized, and thoroughly studied in the very near future.

XIII. THREE-MEMBERED RINGS CONTAINING SULFUR: 1980 HIGHLIGHTS

The interest and research activity in the exciting field of three-membered rings containing sulfur is still growing and, in fact, expanding. Not only have the chemistry, properties, and mechanisms associated with the known systems been further investigated and explored during the past year, but recently developed approaches and more sophisticated techniques and methodologies have been used in attempts to prepare and/or to characterize unequivocally some of the so far elusive sulfur-containing three-membered systems.

This section serves to bring the interested reader up to date through a brief review of the 1980 literature.

Only selected highlights of the papers published during 1980 are presented and occasionally discussed. In a few cases some papers of the 1979 literature are also briefly reviewed to complement the corresponding topics already covered.

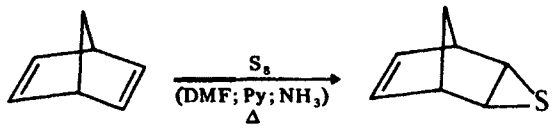
1. Preparation of Thiiranes Directly from Olefins

A. *By the Addition of Sulfur* [III, 1, I, a]*

While polycyclic 1,2,3-trithiolanes are produced by the reaction with elemental sulfur of the cyclopentadiene dimer, cyclopentadiene trimer, and norbornene, the

* Bracketed section numbers reference the subsection being updated.

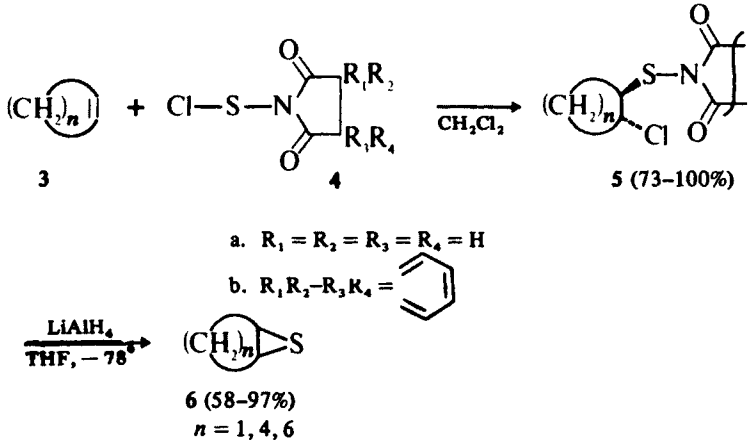
reaction of norbornadiene 1 with elemental sulfur produced the thiirane 2, although in small yield[1]:



1 2 (1)

B. *Via Succinimide- or Phthalimide-N-Sulfenyl Chlorides* [III, 1, I, b]

Since many of the procedures for preparing thiiranes suffer from synthetic limitations, a new method of preparation has been advanced.[2] In this procedure, either succinimide-*N*-sulfenyl chloride or phthalimide-*N*-sulfenyl chloride, conveniently prepared from the corresponding disulfides by chlorinolysis, reacts in methylene chloride with selected olefins to form the *trans* addition[3] products 5. The latter can be reduced with lithium aluminum hydride at $-78°$ to form thiiranes in yields in the range of 49–79% as illustrated in Eq. 2.



(2)

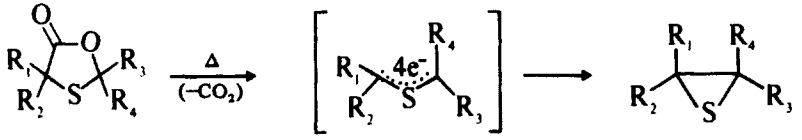
The cyclic thiiranes 6, derived of cyclopropene, cyclohexene, and cyclooctene, were thus prepared. Similarly, the thiiranes of styrene and norbornene were also prepared in good yields.

The mechanism proposed[2] for the formation of the thiiranes involves a reduction of the S–N bond of the adduct 5 to form a thiol intermediate, which rapidly forms the thiolate anion with the excess of the hydride reagent. On warming, this anion readily cyclizes by nucleophilic displacement of a chloride ion.[4]

The route described above for the preparation of thiiranes appears to compare very favorably with other available routes.

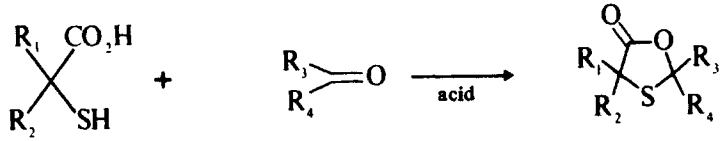
2. Preparation of Thiiranes from Pyrolysis of 1,3-Oxathiolan-5-ones [III, 1, K]

In analogy to the pyrolysis of thiadiazolines[5] to yield ylides that undergo conrotatory ring closure to afford thiiranes, the 1,3-oxathiolan-5-ones (7) can also be converted to the corresponding thiiranes. Thus, flash-vacuum pyrolysis[6] of 1,3-oxathiolan-5-ones gives the corresponding thiiranes in excellent yields through the intermediacy of thiocarbonyl ylids 8, as depicted in Eq. 3.[7]



7 8 (3)

The reaction is stereospecific, suggesting a concerted loss of carbon dioxide, and proceeds with inversion of configuration. Because of the ease of preparation of the starting 1,3-oxathiolan-5-ones (Eq. 4),[8] this method represents a preparative approach of considerable synthetic utility.



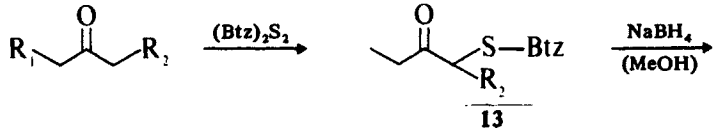
7 (4)

By using the method above, pure 2,3-diphenyl-, 2-methyl-, 3-phenyl-, 2-phenylspirocyclohexyl-, 2-methylspirocyclohexyl-, and 2-methyl, 3-propylthiiranes were obtained in 89–95% yield.[7]

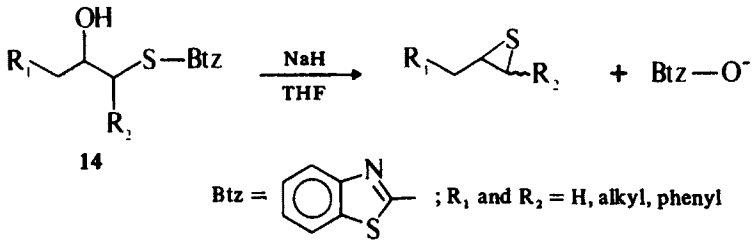
3. Preparation of Thiiranes from α-Ketosulfides of Benzothiazole-2-Thiol [III, 1, O]

β-Hydroxysulfides are readily converted into thiiranes by a simple treatment with sodium hydride in tetrahydrofuran.[11] In fact, all the methods leading from aldehydes and/or ketones to thiiranes are in one way or another a variation of this route.

A modified procedure to prepare thiiranes is based on the reduction of the α-ketosulfides **13** to the corresponding hydroxy compounds **14**, and the treatment of the latter with sodium hydride as illustrated in Eq. 5.



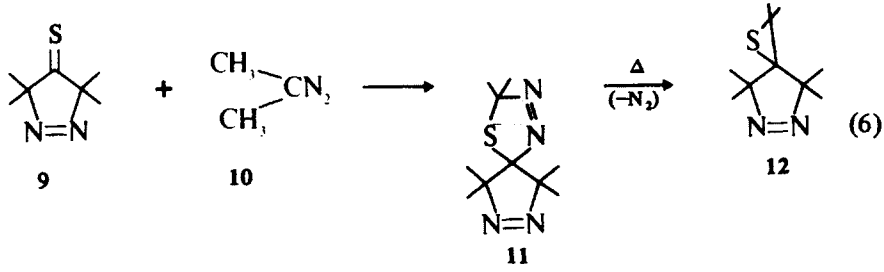
13 (5)



Yields in the range of 60–95% have been claimed[12] for a variety of thiiranes prepared by using this methodology (e.g., methyl-, phenyl-, cyclohexene, methylcyclohexene-, 2-methyl, 3-spirocyclohexyl-, and 2-methyl-3-benzylthiiranes).

4. Preparation of Spirothiiranes: Update [III, 1, P]

The reaction of the thioketone (**9**) with the 2-diazopropane (**10**) results in the formation of the thiadiazoline (**11**). In analogy to the synthesis of spirothiiranes from tetrasubstituted dithiones[9] (see Section III, 1, P, b), gentle warming of the solution of **11** affords the spirothiirane **12** in essentially quantitative yield[10]:

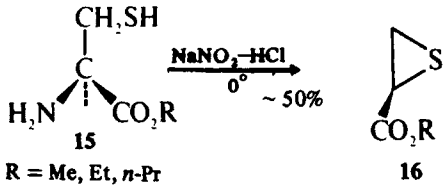


(6)

In a similar manner, differently substituted spirothiiranes can be prepared by replacing the 2-diazopropane **10** with diazomethane, diazoethane, di-*tert*-butyldiazomethane, phenyldiazomethane, diphenyldiazomethane, diazoethylacetate, diazoethylmalonate, and diazomalononitrile.[10]

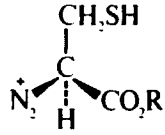
5. Preparation of Chiral Thiirane Carboxylates

The first examples of optically active thiirane carboxylic acid derivatives have been prepared recently[13] by the reaction of methyl-, ethyl-, or propyl-(*R*)-cysteinate with sodium nitrite–hydrochloric acid. Optically pure methyl-, ethyl-, or propyl-(*S*)-thiirane carboxylates (**16**) were thus prepared as depicted in Eq. 7.



(7)

The method represents a deaminative cyclization that most probably proceeds via the diazonium compound **17** and an S_N2-like displacement of nitrogen by the thiol group.

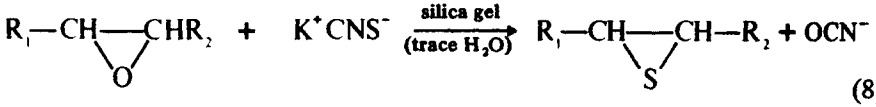


17

Although the overall yield of this method is modest (25–50%), it provides the hitherto unavailable optically active alkylthiirane carboxylates as well as their free carboxylic acid (i.e., **16**; R = H).

6. Preparation of Thiiranes Using Silica Gel

Silica gel can be used either as a support for potassium thiocyanate or as a catalyst. Thus the inorganic reagent, first being crushed with or coated onto silica gel, is treated with long-chain, alkyl-substituted epoxides or cycloalkene epoxides in toluene to yield, after prolonged stirring at 90°, the corresponding thiiranes in good to high yields[14]:



(8)

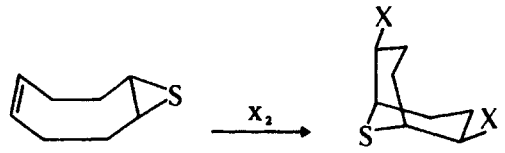
Obviously, this is the classical method of thiirane synthesis. Nevertheless, the present modified method proceeds with high stereospecificity and requires only filtration and solvent evaporation for product isolation. Moreover, in certain cases the "classical method" (i.e., treatment of the epoxide with potassium thiocyanate without silica gel) yields no detectable product after many hours.

In general, high yields of monosubstituted episulfides are produced in reasonably short periods, whereas disubstituted epoxides react much more slowly. In some extreme cases, the reaction rates are very slow and the yields are low.

7. Chemical Properties and Reactivity of Thiiranes

A. *Electrophilic Cleavage of Unsaturated Thiiranes* [III, 3, E, c–d]

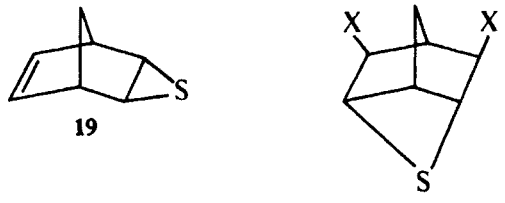
Chlorinolysis of the unsaturated thiiranes **18** and **19** afforded the halogenosulfides **20a** and **21a**, respectively, and the same kinds of product are formed when **18** and **19** are treated at room temperature with either bromine or iodine[15]:



18 20

a. X = Cl
b. X = Br
c. X = I

(8a)



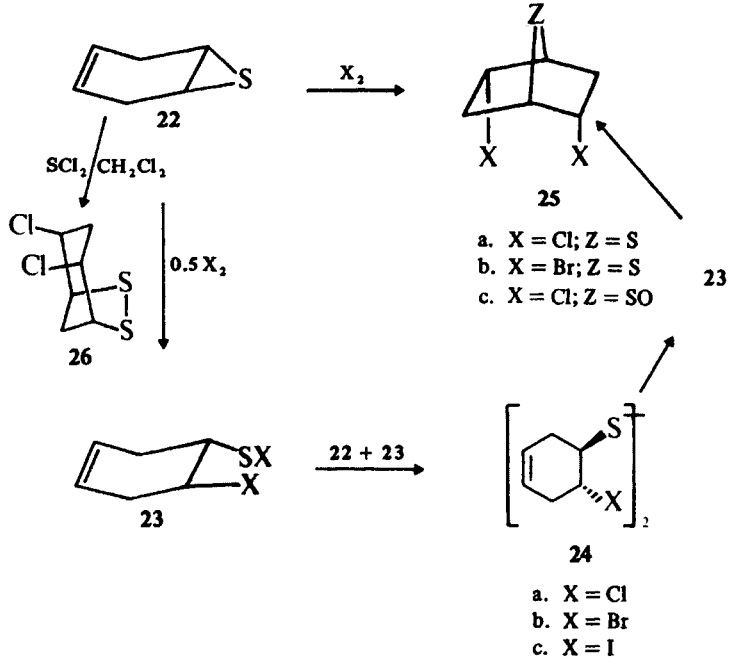
19 21

a. X = Cl
b. X = Br

(8b)

No intermediates could be detected in these transformations.[15]

In contrast, reaction of the thiirane 22 with halogens did afford isolable intermediates (the disulfides **24a–24c**) in addition to the final halogenosulfides **25a** and **25b** and the sulfoxide **25c**, depending on the stoichiometry of the reactants and on the reaction conditions. These results are summarized in Eq. 9.[15]

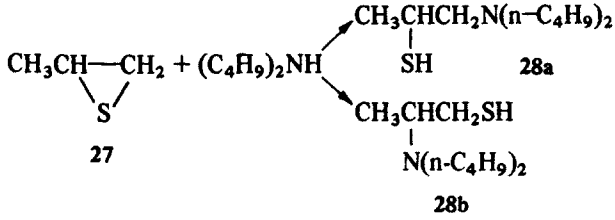


(9)

The reaction of the thiirane **22** with sulfur dichloride gave the intramolecular disulfide **26** in 42% yield. This reaction represents a new method of preparing a cyclic disulfide. In all the reactions above of unsaturated thiiranes with electrophiles, the thiirane ring opening is the initial step.

B. *Nucleophilic Ring Opening of Thiiranes with Dibutylamine* [III, 3, F, c]

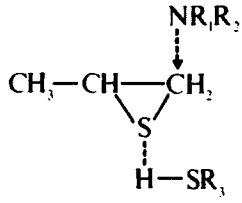
The rate of ring opening of methylthiirane with dibutylamine to yield both the regioisomeric 2-aminopropane thiols have been studied recently.[16]



(10)

The reaction in DMSO-toluene mixtures was found to be either second order (first order both in methylthiirane and dibutylamine) or third order by the participation of the reaction products.[16] The increased reactivity of methylthiirane compared with that of methyloxirane was based on the selective solvation of thiolate anion by DMSO in the transition state. The normal product **28a** appeared in larger amounts under more basic conditions.

It was established[15] that the "pull" process is an important factor in the base-catalyzed ring opening, as schematically depicted in **29**.



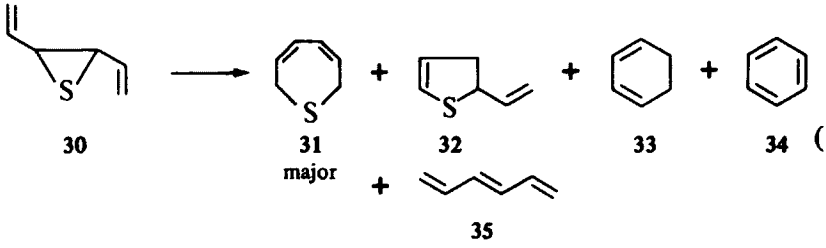
29

C. *Oxidation: Gas Phase Reaction with Ozone* [III, 3, G]

The autocatalytic reaction of ozone with thiirane has been studied at room temperature and 8 torr.[17] The major products that resulted as a consequence of free-radical chain reactions[17] were C_2H_4, SO_2, H_2CO, and CO_2. The specific rate of the primary attack of ozone on thiirane was found to be immeasurably slow [$K < 10^4$ cm^3/(mole)(sec)].

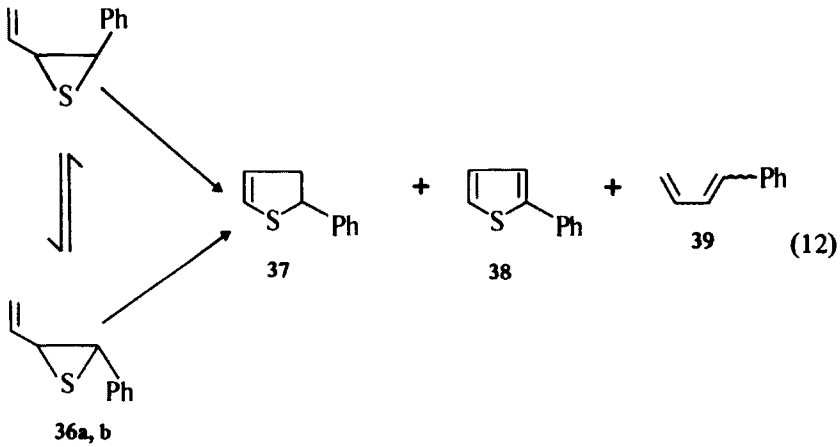
D. *Thermolysis of Vinyl- and Divinylthiiranes*

Pyrolysis of *trans*-2,3-divinylthiirane (**30**) under flow conditions between 360–460° gave rise to compounds **31–35** (**31** and **34** being the major products)[18]:



(11)

This *cis*- and *trans*-2-phenyl-3-vinylthiiranes gave rise to the substituted dihydrothiophen and thiophens **37** and **38**, respectively, and the diene **39**:



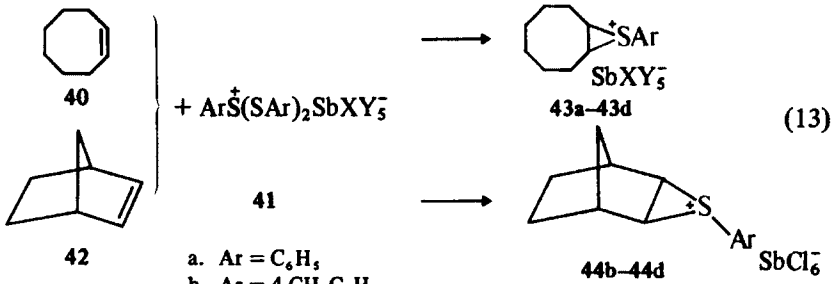
(12)

All these results can be rationalized in terms of a competition between the carbon-carbon and carbon-sulfur bond cleavage during the pyrolysis. Concerted opening of the thiirane ring (C–C bond cleavage) may explain the formation of some of the observed products, whereas a diradical formed as a result of C–S bond cleavage may lead to the conjugated polyenes.[18] The aromatic products may result from the catalysis of sulfur formed during the pyrolysis.

8. Preparation of Thiiranium Salts (Episulfonium Ions) by Addition of Arylbis(thioaryl)sulfonium Salts to Alkenes [IV, 1, A]

The ability of arylbis(thioaryl)sulfonium salts (**41a–41d**) to serve as *S*-aryl transfer agents, has been successfully used[19] for the synthesis of stable thiiranium salts of types **43** and **44**.

Thus, the introduction of alkenes **40** and **42** into a solution of **41a–41d** in methylene chloride in a 1:1 molar ratio at $-60°$ gave almost quantitative yields of the sulfonium salts **43a–43d** and **44b–44d**, respectively, after work-up,[19] as summarized in Eq. 13.



(13)

a. Ar = C_6H_5
b. Ar = 4-$CH_3C_6H_4$
c. Ar = 4-ClC_6H_4
d. Ar = 2,4,6-$(CH_3)_3C_6H_2$

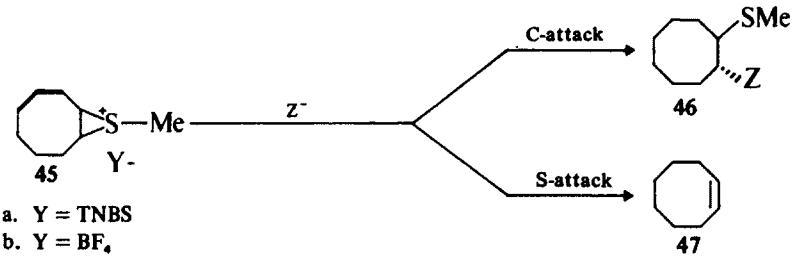
X = Y = Cl
or X = Cl; Y = F

Interestingly, all the isolated thiiranium salts thus obtained are finely crystalline powders with sharp melting points; they can be stored unchanged at least for several days at 0–20°.

The quenching of salts **43** and **44** with a $(CH_3)_4NOAc$-AcOH mixture proceeds in a manner usual with other thiiranium salts to produce the 1-acetoxy-2-arylthio adducts as the major products (see Section IV, 3).

9. Chemical Properties and Reactivities of Thiiranium Salts: Nucleophilic Attack at the Carbon Atom – Update [IV, 3, A]

In view of the contradictory conclusions in the literature[20] regarding the site of nucleophilic attack on the three-membered thiiranium rings, a study of the reaction of thiiranium salts **45a–45c** with various nucleophiles has been undertaken.[21] The results of this study are summarized in Eq. 14.



(14)

a. Y = TNBS
b. Y = BF_4
c. Y = SbF_6

C-attack → Z = $OCOCH_3$, $NHCOCH_3$, H, OCH_3, OH, F, Cl, Br, Me_2S

S-attack → Nucleophiles, Bu_3P, $(CH_3)_4NI$, Et_3N, NH_2CSNH_2, $NaCH(CO_2CH_3)_2$

As one can see, reaction with many nucleophiles proceeds mainly (or preferentially) on the *carbon* atom of the episulfonium ring. Nevertheless, it appears that the site of the attack as well as the product distribution of this nucleophilic ring opening is dependent on the type of nucleophile on the one hand and on the particular set of reaction conditions on the other.

10. Chemical Properties and Reactivities of Thiirane Oxides: Reactions with Organolithium Compounds

The reactions of organolithium compounds with 2,3-diphenylthiirane oxides lead to stereospecific desulfurization and to ring opening, the stereochemistry of which depends on the structural features[22] (i.e., stereospecific only for **48**). Thus, on treatment with BuLi (2 equiv; 0°; ether) *cis*- and *trans*-2,3-diphenylthiirane oxides gave a number of products the formation of which was rationalized as depicted in Eq. 15.

Comparable results were obtained with phenyllithium.[22]

11. Structural and Spectroscopic Data on Thiirenes

A. *Theoretical Calculations: Update* [VII, 3, A]

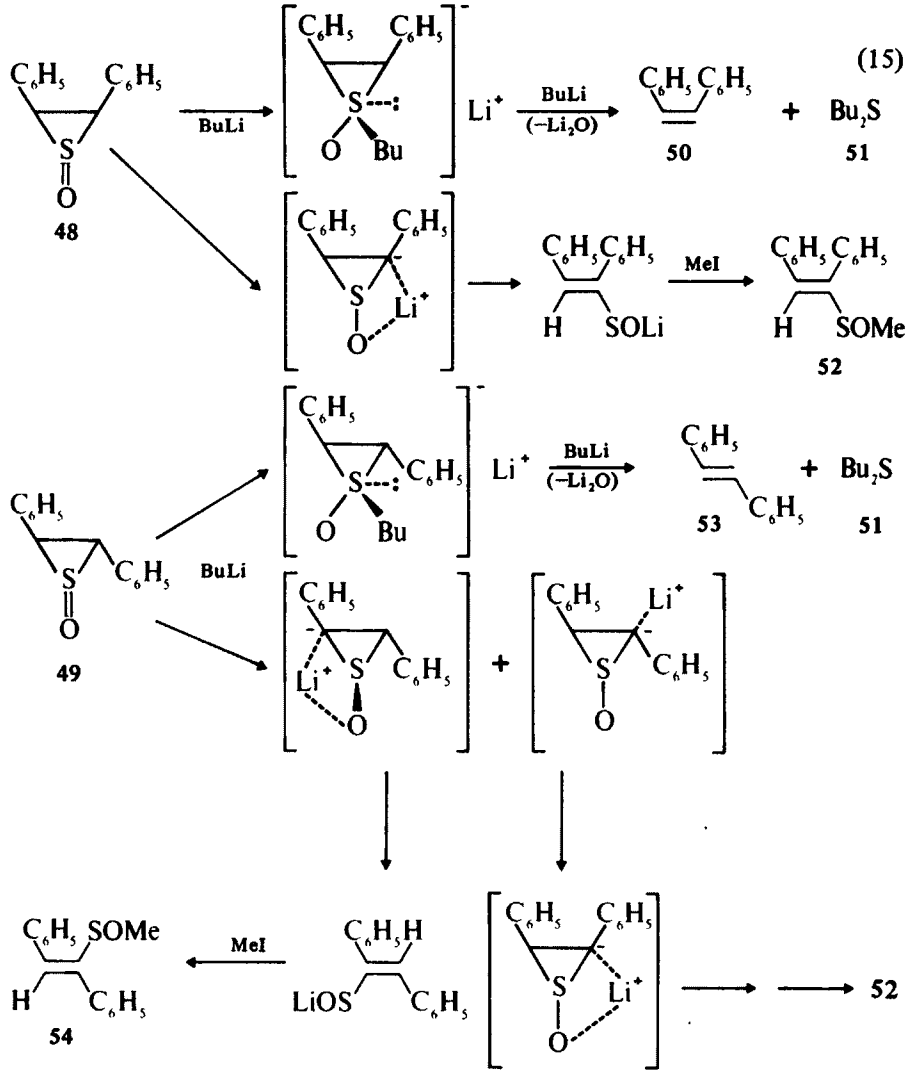
The equilibrium structure and ir spectrum of thiirene using an *ab initio* single configuration method and the 4–31 G basis of Pople and Hehre[23] have been calculated.[24] Geometry optimization (assuming C_{2v} structure) gave the following bond distances and angles:

$$C\text{–}S = 1.9782\,\text{Å}, \qquad C\text{=}C = 1.2509\,\text{Å}, \qquad C\text{–}H = 1.0556\,\text{Å}$$

$$< HCC = 154°94'$$

The energy was found to be -473.725975 hartees, which is 2 hartees lower than the best previous *ab initio* calculation on thiirene.[25] All in all, these results reflect the expected antiaromaticity of thiirene, which is particularly reflected in the tendency of the molecule to minimize conjugation between the sulfur atom and the carbon-carbon double bond. The force constant matrix for each vibrational symmetry was also calculated, followed by the computation of the ir intensities.[24] The latter were found to lie too high as compared with the experimental results,[26] although all the C–C and the C–H stretches are of the correct symmetry.

The overall agreement in frequency and intensity between the calculated[24] and experimental patterns[25] is very good.



(15)

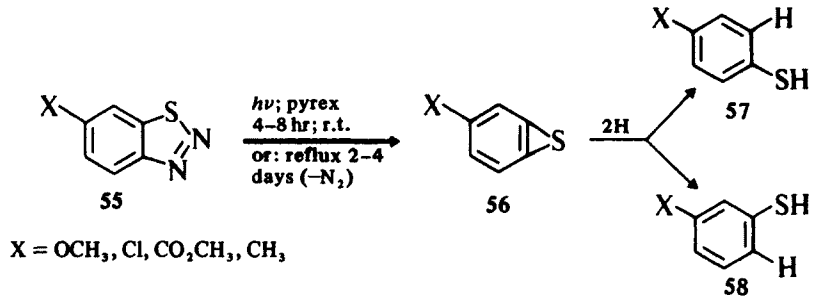
B. *Normal Coordinate Analysis for the Infrared Spectra*

Based on detailed study of the ir spectrum of propene along with all its deuterated derivatives[27] and a recently reported analysis of the cyclopropene molecule,[28] the recalculated normal ir frequencies of thiirene, the deuterated thiirenes, and the experimental values were recently compared.[29]

It has been calculated[29] that the present results do not affect the earlier conclusions[26] with regard to the spectral assignment in the thiirene molecule. The assignment of the in-plane bending modes, however, requires further experimental study.

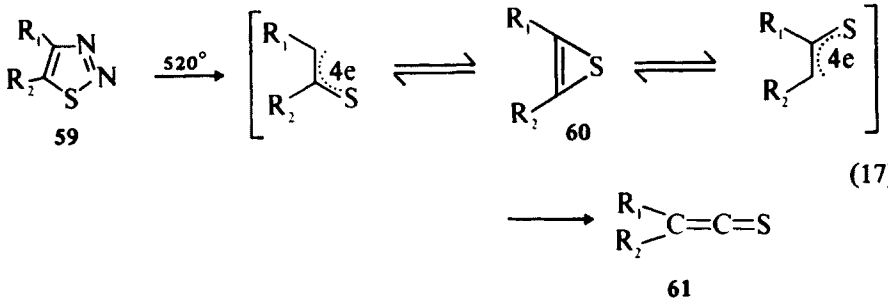
12. Chemical Properties and Reactivities of Thiirenes as Intermediates in Reactions: Update [VII, 4, B]

Thermal and photochemical extrusion of nitrogen from benzothiazoles (**55**) in tetrahydronaphthalene (an H-donor solvent) were shown to afford the anticipated thiophenols **57** and **58**, followed by the conversion of the latter to the corresponding thiol acetates (by acetyl chloride, pyridine). The results have been interpreted in terms of a benzothiirene intermediate (**56**) as depicted in Eq. 16.[30]



(16)

The intermediacy of 2,3-dialkyl-; 2-alkyl, 3-aryl-; and 2-alkyl, 3-chloro (or cyano-) thiirenes (i.e., **60**) has been claimed[31] in the flash thermolysis of thiadiazoles (**59**) to the corresponding thioketenes (**61**):

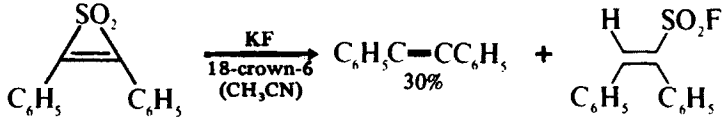


(17)

13. Chemical Properties and Reactivities of Thiirene Dioxides: Reactions with Soft Nucleophiles [X, 4, B, c]

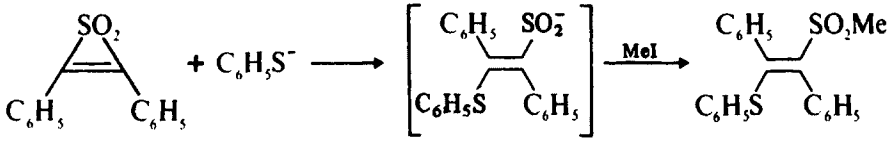
A. *With Fluoride Ion, Thiophenoxide, and Azide Ion*

Treatment of 2,3-diphenylthiirene dioxide with potassium fluoride and 18-crown-6, (crown ether mediated solid-liquid transfer[32] agent) in acetonitrile at room temperature afforded diphenylacetylene and the sulfonyl fluoride **64**[34]:



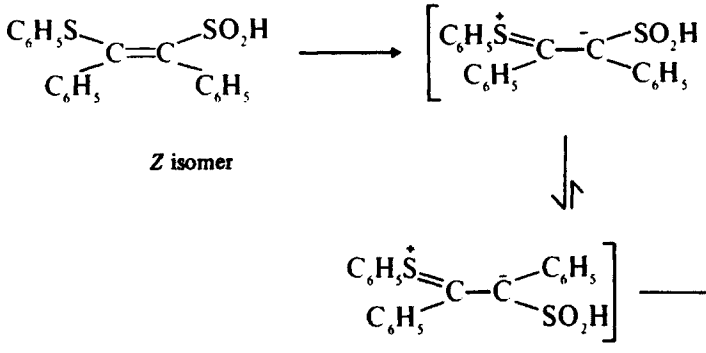
62 63 64 (18)

The softer, less basic halides bromide and iodide did not react with the thiirene dioxide **62**. The latter was also inert toward potassium thiocyanate, selenocyanate, and potassium nitrite.[34] It did react, however, with potassium thiophenoxide in DMF at room temperature to yield, most probably, the vinylsulfinate **65**, isolated as the corresponding sulfone[34] (Eq. 19).



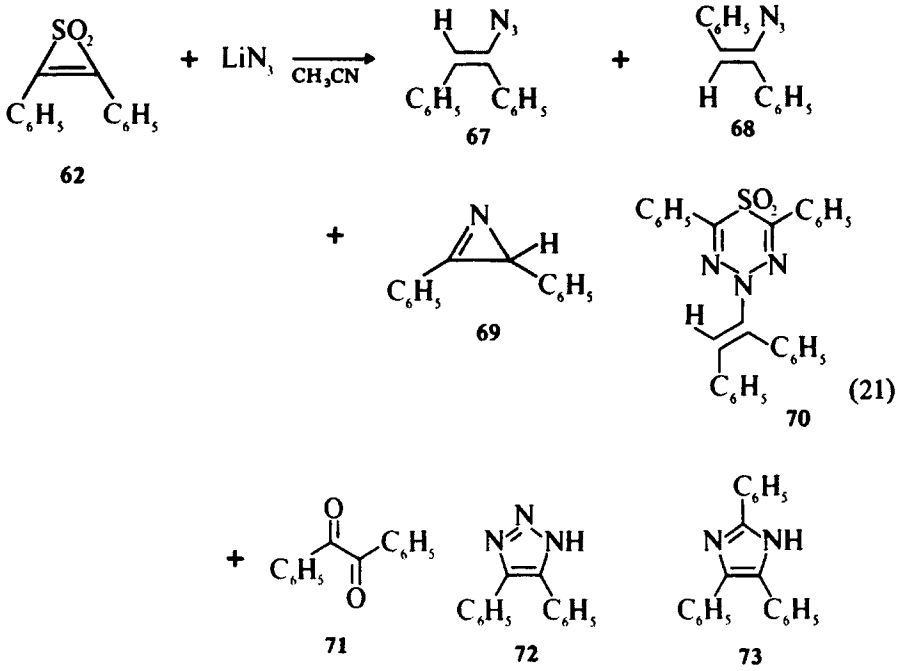
62 65 66 (19)

The isolation of the *E* isomer **66** was in fact unexpected, since all tetrasubstituted olefins previously obtained from thiirene dioxide (**62**) have been assigned the *cis* configuration with respect to the two phenyl substituents (see Section X, 4) based on application of the principle of least motion to the ring opening to give the olefins.[34] It might well be, therefore, that the *E* isomer of **65** is obtained through the isomerization of the initially formed *Z* isomer, that is,



(20)

The reaction of LiN_3 with 2,3-diphenylthiirene dioxide is given in Eq. 21.[34]



The azirine **69** presumably arises by cyclization of azides **67**.[33] The distribution of the products **67–73** is dependent on the reactant mole ratio and the scale of the reaction.[34] The yields of benzyl **71** and imidazole **73** are very small. The mechanism of formation of the various products in this reaction has already been discussed (Section X, 4, B, c, iv).

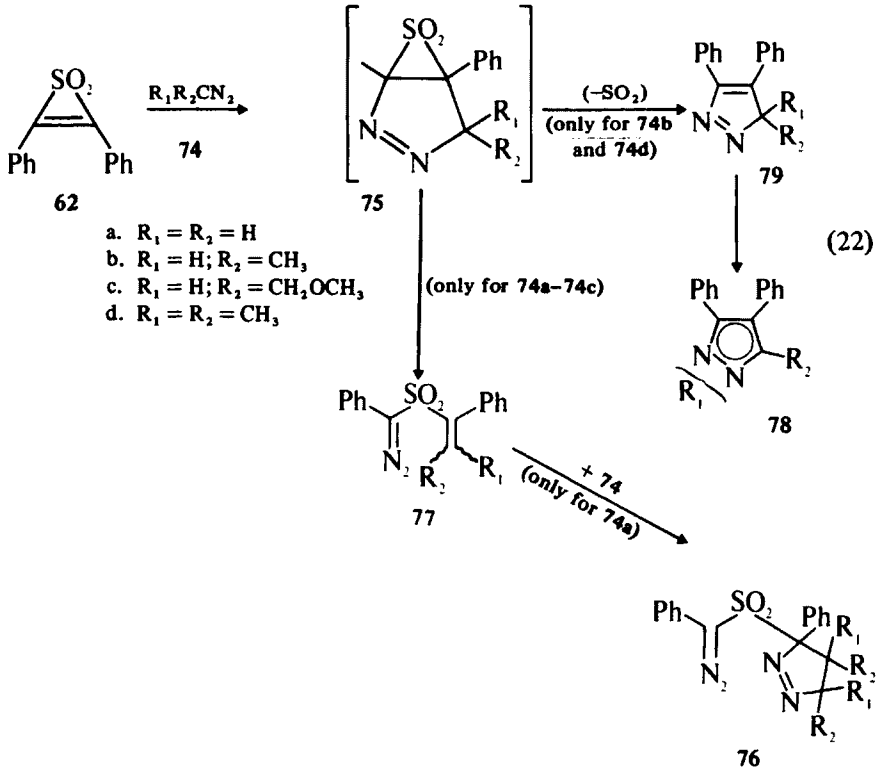
B. *Summary*

The reactions above follow courses similar to those found for the reactions of thiirene dioxides with soft and hard nucleophiles as well as for the reaction of other alkyl, aryl, and vinyl sulfonyl compounds.[35] The soft, less basic nucleophiles (phenoxides, azides, etc.) attack the ring carbon, whereas the harder hydroxide ion, methoxide ion, and the like, are known to attack the sulfonyl sulfur.

C. *Cycloaddition Reactions with Diazoalkanes* [X, 4, C]

2,3-Diphenylthiirene dioxide reacts with azoalkanes **74a–74d** not only under diazo group transfer to give **76a** or **77b** and **77c** but also under loss of sulfur dioxide to form pyrazoles **78b**, **78c**, and **79d** through a common intermediate (**75**) as depicted in Eq. 22[36]:

The yields of these products are in the range of 17–51%.

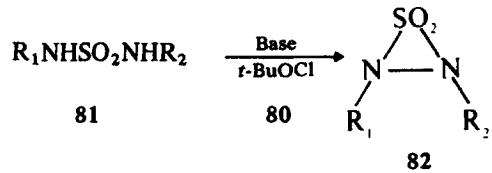


a. $R_1 = R_2 = H$
b. $R_1 = H; R_2 = CH_3$
c. $R_1 = H; R_2 = CH_2OCH_3$
d. $R_1 = R_2 = CH_3$

(22)

14. Preparation of Thiadiaziridine Dioxides: Update [XI, 2, A]

By using essentially the "classical" method of thiadiaziridine dioxide synthesis[37] (see Section XI, 1) starting with the appropriately substituted sulfamides (81), several branched alkyl-substituted thiadiaziridine dioxides have been prepared[38]:



(23)

a. $R_1 = R_2$ = 1,1,2,2-tetramethylpropyl
b. $R_1 = R_2$ = 1,1-*n*-methylpentyl
c. $R_1 = R_2$ = 1,1-diethylpentyl
d. $R_1 = R_2$ = cumyl
e. $R_1 = R_2$ = dimethyl-2-phenylethyl
f. $R_1 = R_2$ = 1,1,3-trimethyl-3-phenylbutyl
g. R_1 = adamant-1-yl; R_2 = *tert*-butyl

In view of other unsuccessful syntheses of thiadiaziridine dioxides, it has been concluded[38] that increasing size of the substituent at the γ-carbon is responsible for the stability of the system.

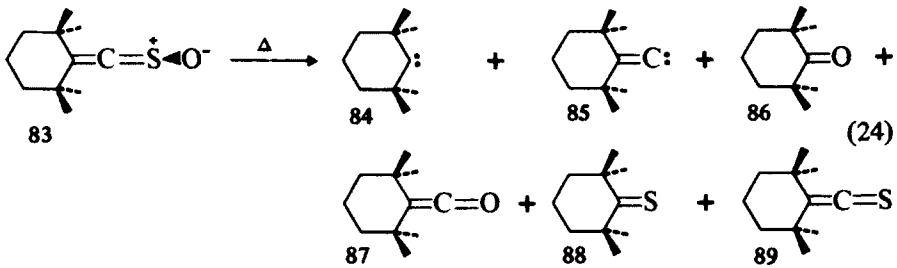
15. Mechanism of Thermal Decomposition of Thiadiaziridine Dioxides [XI, 2, C, b]

Based on trapping experiments and isolation of rearrangement products, the formation of a diradical that decomposes to a nitrene intermediate has been postulated[38] for the thermal decomposition of thiadiaziridine dioxides.

16. Oxathiiranes: Update [XI, 3]

In contrast to the thermally labile oxiranes postulated to be formed (as intermediates) either thermally or photolytically from thiobenzophenone *S*-oxides (see Section XI, Eq. 13),[39] it was found that the possible formation of a methylene oxathiirane *does not* play any major role in the photolysis of thioketene *S*-oxides.[40]

Gas phase thermolytic decomposition (using a flash-vacuum thermolysis technique) of 1,1,3,3-tetramethyl-2-thiocarbonylcyclohexane-*S*-oxide (83) gave carbenes **84** and **85**, the ketone **86**, the ketene **87**, the thioketone **88**, and the thioketene **89** as shown in Eq. 24[40, 41]:

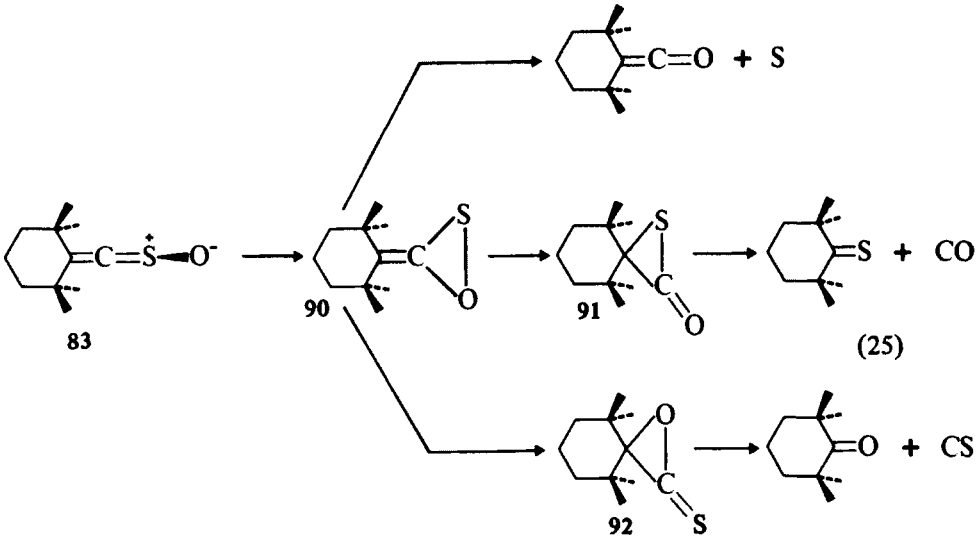


(24)

The results were mechanistically rationalized[40, 41] by assuming two primary processes: the extrusion of atomic oxygen leading to the thioketene **89**, and the electrocyclic ring closure into the corresponding three-membered ring oxathiirane **90**. The latter route as well as the fate of the short-lived oxathiirane intermediate are summarized in Eq. 25[40]:

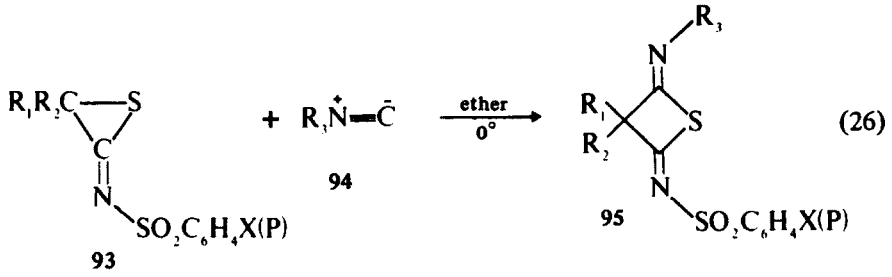
The formation of the oxathiirane intermediate **90** is kinetically controlled. Its decomposition, however, may be expressed in terms of kinetically vs. thermodynamically controlled processes to account for the observed products.

Interestingly, the reaction between thioformaldehyde and singlet oxygen has been studied theoretically[42] within the CNDO/B framework, and it was found that a three-membered oxathiirane-*O*-oxide is stabilized relative to the two starting materials.



17. Thiaziridinimines vs. Iminothiiranes [XI, 5]

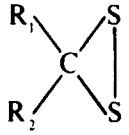
Thiaziridinimine has been suggested as an unstable intermediate in the thermolysis of some thiatriazolines[43] but was never isolated (see Section XI, 3). In contrast, the analogous sulfonyliminothiirane **93** not only is a stable isolable compound, but it cycloadds to isothiocyanates (**94**) to form bis(imino)thietanes (**95**)[44] as depicted in Eq. 26:



a. $R_1 = R_2 = C_6H_5$; $X = CH_3$
$R_3 = p\text{-}CH_3OC_6H_4$
b. $R_1 = R_2 = C_6H_5$; $R_3 = (CH_3)_3C$; $X = Cl$

18. Dithiiranes: Update [XI, 7]

A recent paper by Senning[46] gives more details, experimental data included, about the previously reported[47] attempted synthesis of the elusive dithiiranes **96a–96d**.

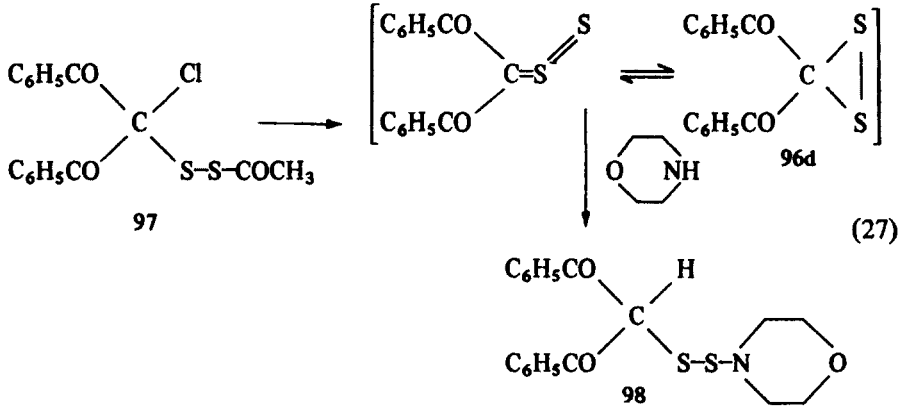


96

a. $R_1 = R_2 = H$
b. $R_1 = R_2 = Cl$
c. $R_1 = C_6H_5S$; $R = 4\text{-}CH_3C_6H_4SO_2$
d. $R_1 = R_2 = C_6H_5CO$

The intermediacy of **96** is postulated[46] by analogy with the hypothetical dioxiranes in the ester analogs.[48]

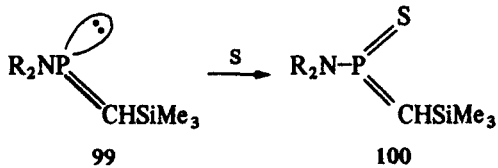
Equation 27 illustrates the transformation that is postulated to occur through the intermediacy of dithiirane (**96d**):



97 96d 98 (27)

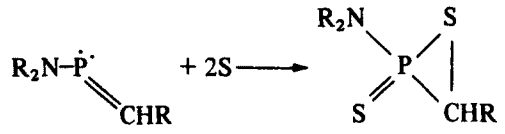
19. Thiaphosphiranes

The unknown three-membered ring system containing both sulfur and phosphorus in the ring array (i.e., 1,2-λ^5-thiaphosphirane, **101**) has been recently synthesized[49] and isolated as a by-product of the following reaction:



99 100 (28)

The thiaphosphirane **101** formed by the [1 + 2] cycloaddition of sulfur to compound **100** can be prepared quantitatively by the reaction of species **99** with 2 equiv of sulfur[49]:



(29)

101

^{31}P, ^{1}H, ^{13}C, and ^{29}Si nmr data are given for compound **101** that substantiate the assigned structure.

20. References

1. J. Emsley and D. W. Griffiths, *J. Chem. Soc., Perkin Trans. 1*, 228 (1979).
2. M. U. Bombala and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 3013 (1979).
3. T. G. Katz and K. C. Nicolaou, *J. Am. Chem. Soc.*, **46**, 1948 (1975).
4. E. E. Van Tamelen, *J. Am. Chem. Soc.*, **73**, 3444 (1951).
5. (a) J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, **37**, 4045 (1972); (b) G. M. Kaufmann, J. A. Smith, G. G. Vander Stouw, and H. J. Shechter, *J. Am. Chem. Soc.*, **87**, 935 (1965).
6. G. Seybold, *Angew. Chem., Int. Ed. Engl.*, **2**, 365 (1963).
7. (a) T. B. Cameron and H. W. Pinnik, *J. Am. Chem. Soc.*, **101**, 4755 (1979); (b) T. B. Cameron and H. W. Pinnik, *ibid.*, **102**, 744 (1980).
8. E. H. Miller, I. Hechenbleikner, and O. A. Homberg, French Patent 1,386,914; *Chem. Abstr.*, **63**, 605c (1965).
9. A. P. Krapcho, D. R. Rao, M. P. Silvon, and B. Abegaz, *J. Org. Chem.*, **36**, 3885 (1971).
10. R. J. Bushby and M. D. Pollard, *J. Chem. Soc., Perkin Trans. 1*, 2401 (1979).
11. C. R. Johnson, A. Nakanishi, N. Nakanishi, and K. Tanaka, *Tetrahedron Lett.*, **33**, 2865 (1975).
12. V. Calo, L. Lopez, and G. Pesce, *Gazz. Chim. Ital.*, **109**, 703 (1979).
13. C. D. Maycock and R. J. Stoodly, *J. Chem. Soc., Perkin Trans. 1*, 1852 (1979).
14. M. O. Birmeyer, A. Mehrota, S. Quici, A. Nigam, and S. L. Regen, *J. Org. Chem.*, **45**, 4254 (1980).
15. P. McCabe and A. Stewart, *J. Chem. Soc., Chem. Commun.*, 100 (1980).
16. H. Kakiuchi, T. Iijima, and H. Horie, *Tetrahedron*, **35**, 303 (1979).
17. R. I. Martinez and J. P. Herron, *Chem. Phys. Lett.*, **72**, 74 (1980).
18. J. -C. Pommelet and J. Chuche, *J. Chem. Res.*, 56 (1979).
19. A. S. Gybin, W. A. Smit, and V. S. Bogdanov, *Tetrahedron Lett.*, 383 (1980).
20. (a) D. C. Owsley, G. K. Helmkamp, and S. N. Spurlock, *J. Am. Chem. Soc.*, **91**, 3606 (1969); (b) W. A. Smit, M. Z. Krimer, and E. A. Vorobieva, *Tetrahedron Lett.*, 2451 (1975).
21. A. S. Gybin, A. Smith, M. Z. Krimer, N. S. Zefirov, L. A. Novgorodtseva, and N. K. Sadovaya, *Tetrahedron*, **36**, 1361 (1980).
22. B. F. Bonini, G. Maccagnani, G. Mazzanti, and P. Piccinelli, *Tetrahedron Lett.*, **41**, 3987 (1979).
23. (a) R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1970); (b) W. J. Hehre and W. A. Lathan, *ibid.*, **56**, 5255 (1972).

24. B. A. Hess, Jr., L. J. Schaad, and C. S. Ewig, *J. Am. Chem. Soc.*, **102**, 2507 (1980).
25. O. P. Strausz, R. K. Gosavi, F. Bernardi, P. G. Mezey, J. K. Goddard, and I. G. Csizmadia, *Chem. Phys. Lett.*, **53**, 211 (1978).
26. M. Torres, I. Safarik, A. Clement, J. E. Bertie, and O. P. Strausz, *Nouv. J. Chim.*, **3**, 365 (1979).
27. Y. T. Yum and D. F. Eggers, Jr., *J. Phys. Chem.*, **83**, 501 (1979).
28. K. B. Wiberg and J. J. Wendoloski, *J. Phys. Chem.*, **83**, 497 (1979).
29. I. Safarik, M. Torres, and O. P. Strausz, *Chem. Phys. Lett.*, **72**, 388 (1980).
30. R. C. White, J. Scoby, and T. D. Roberts, *Tetrahedron Lett.*, 2785 (1979).
31. E. Schaumann, J. Ehlers, and H. Mrotzek, *Justus Liebigs Ann. Chem.*, 1734 (1979).
32. (a) W. P. Weber and G. W. Gokel, *Phase Transfer Catalysis in Organic Synthesis*, Springer-Verlag, New York, 1977; (b) C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, **96**, 2250 (1974).
33. A. Hassner and L. A. Levy, *J. Am. Chem. Soc.*, **87**, 4203 (1965).
34. (a) B. B. Jarvis and G. P. Stahly, *J. Org. Chem.*, **45**, 2604 (1980); (b) B. B. Jarvis, W. P. Tong, and H. L. Ammon, *J. Org. Chem.*, **40**, 3189 (1975).
35. (a) J. Ferns and A. Lapworth, *J. Chem. Soc.*, **101**, 273 (1912); (b) F. G. Bordwell, B. M. Pitts, and M. Knell, *J. Am. Chem. Soc.*, **73**, 5004 (1951); (c) J. F. Bunnet and J. Y. Basset, Jr., *ibid.*, **81**, 2104 (1959).
36. M. Regitz and B. Mathieu, *Chem. Ber.*, **113**, 1632 (1980).
37. (a) F. D. Greene and S. S. Hecht, *J. Org. Chem.*, **35**, 2482 (1970); (b) J. W. Timberlake, M. L. Hodges, and K. Betterton, *Synthesis*, 632 (1972).
38. C. A. Ozmeral, Ph.D. Dissertation, University of New Orleans, 1979; *Diss. Abstr. Int. B.*, **40**, 3749 (1980).
39. (a) L. Carlsen, N. Harrit, and A. Holm, *J. Chem. Soc., Perkin Trans. 1*, 1404 (1976); (b) L. Carlsen, A. Holm, E. Koch, and B. Stilkerieg, *Acta Chem. Scand.*, **B31**, 679 (1977).
40. L. Carlsen, H. Egsgaard, and E. Schaumann, *J. Chem. Soc., Perkin Trans. 2*, 1206 (1980).
41. L. Carlsen, H. Egsgaard, E. Schaumann, and J. Ehlers, *Chem. Ind.*, 851 (1979).
42. L. Carlsen, *J. Chem. Soc., Perkin Trans. 2*, 188 (1980).
43. C. l'Abbé and C. C. Yu, *J. Heterocycl. Chem.*, **13**, 883 (1976).
44. G. l'Abbé, J. -P. Dekerk, J-. P. Declercq, G. Germain, and M. Van Meerssche, *Angew. Chem.*, **90**, 207 (1978); *Angew. Chem., Int. Ed. Engl.*, **17**, 195 (1978).
45. G. l'Abbé and J. -P. Dekerk, *Tetrahedron Lett.*, 3213 (1979).
46. A. Senning, *Angew. Chem.*, **91**, 1006 (1979).
47. A. Senning, ACS/CSY Congress, Honolulu, April 1980. Ref. ORGN 347.
48. W. V. E. Doering and E. Dorfman, *J. Am. Chem. Soc.*, **75**, 5595 (1953).
49. E. Niecke and D. -A. Wildbredt, *J. Chem. Soc., Chem. Commun.*, 72 (1981).

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