HETEROCYCLES, Vol. 7, No. 1, 1977

1-AZIRINE RING CHEMISTRY

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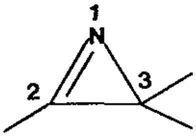
Dedicated to Professor R. B. Woodward
on the occasion of his sixtieth birthday.

The chemistry of the highly-strained small-ring heterocycle, 1-azirine, has been vigorously pursued in the last decade. This article attempts to highlight the major contributions in this area from the viewpoint of both synthetic and mechanistic organic chemistry.

The azirine ring system is a three-membered heterocycle containing one nitrogen atom and one double bond. There are two isomeric azirines (1 and 2) which have been named as 2H- and 1H-azirine, respectively, by Chemical Abstracts.[1] A system of nomenclature that designates the position of the double bond has been used more frequently. Compounds (1) and (2) under this system are named as 1-azirine and 2-azirine, respectively.



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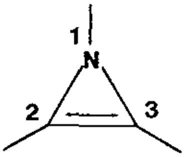

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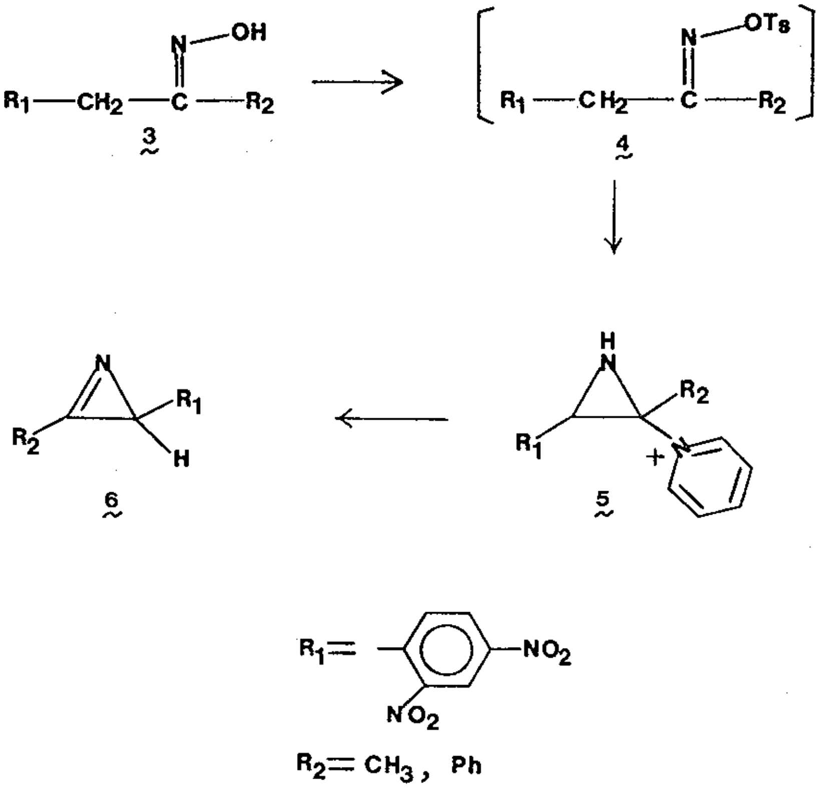
The recent developments in the chemistry of these nitrogen containing small ring molecules is the cumulative outcome of theoretical, mechanistic, and synthetic ramifications. The theoretical and mechanistic interests are associated with their stability, inherent strain energy, and the ability of the carbon-nitrogen bond to participate in and direct the course of many mechanistically significant reactions. The synthetic potentialities for transformations into other heterocyclic systems and for incorporation into compounds containing certain desirable functions are large. A number of 1-azirines have been synthesized and examined for their reactivity towards various reagents. The isomeric 2-azirines have not been isolated as yet despite several synthetic attempts. This failure may be a result of the inherent instability arising from the antiaromatic character of the 2-azirine ring system.

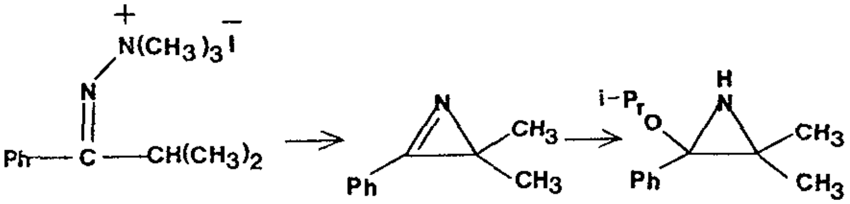
I. Synthesis of 1-Azirines

A. Neber and Related Reactions

Neber and his co-workers first suggested the intermediacy of a 1-azirine in 1932[2,3] while studying the conversion of oxime *p*-toluenesulfonates (**4**) to aminoketones with base. The structure of the 1-azirine was confirmed subsequently by Cram and Hatch.[4] In the presence of tosyl chloride and pyridine, **3** is converted *via* **4** into aziridines **5**, and 1-azirines **6** could then be prepared by treating **5** with sodium carbonate.

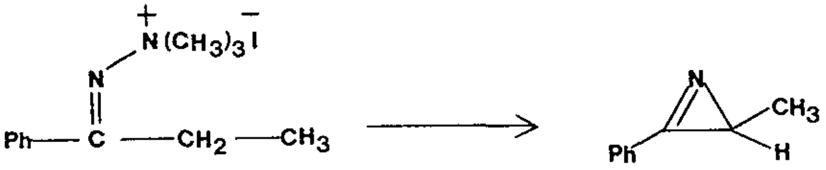


However, the Neber reaction lacked generality, and several modified Neber reactions have been developed during the last decade. For example, the synthesis of 3,3-dimethyl-2-phenyl-1-azirine (**8**) was carried out by the reaction of the dimethylhydrazone methiodide **7** with sodium isopropoxide in isopropanol.[5] This method was applied successfully to the preparation of certain spiro *1-azirines.*[6] *Because of the formation of* alkoxyaziridine during the reaction with sodium isoproxide, only poor yields of the azirine **11** were obtained. A more practical synthesis was developed[7] using dimethylsulfinyl carbanion as



7 **8** **9**

the base and dimethyl sulfoxide as solvent, and 3-methyl-2-phenyl-1-azirine (**11**) could be obtained from propiophenone dimethylhydrazone methiodide (**10**) in 63% *yield. The synthesis of a certain steroidal spiroazirine* using this method had been previously reported.[8,9]



10 **11**

Unfortunately, these modified Neber reactions also do not always ensure the preparation of 1-azirines,[6,10] as this method is apparently dependent upon the type of hydrogen that is available on the α-carbon of the hydrazone.

B. Pyrolysis and Photolysis of Vinyl Azides

Smolinsky developed the first general synthesis of 1-azirines by the vapor phase pyrolysis of vinyl azides 12 .[11,12] In addition to moderate yields of 1-azirines, small amounts of the ketenimines 14 were also isolated.

12

a, R= Ph

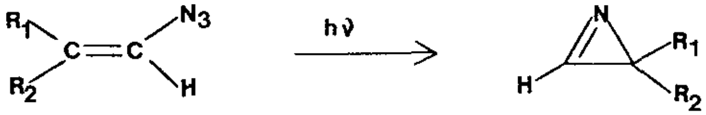
b, R= o-$CH_3C_6H_4$

c, R= n-C_4H_9

13

14

Recent developments in the preparation of vinyl azides have made the pyrolysis or photolysis of vinyl azides as the preferred general method for the synthesis of 1-azirines.[13-20] For example, 2,3-diphenyl-1-azirine could be synthesized from the readily available starting material, trans-stilbene, after addition of iodine azide, elimination of hydrogen iodide by base, and thermolysis of the resultant vinyl azide.[15,16] Irradiation of vinyl azides also produces 1-azirines.[21-23] In some instances it is the method of choice since the reaction can be carried out at relatively low temperatures which retard side reactions such as polymerizations. For example, it is known that 2-unsubstituted 1-azirines 16 are very unstable compared with those substituted at the 2-position, polymerizing rapidly even at the room temperature in air. The photolytic approach is therefore preferred for these 1-azirines.



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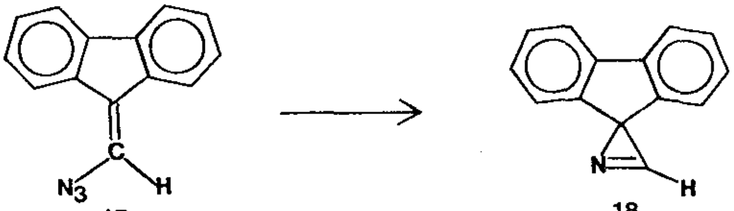
a, R_1= H, R_2= Ph

b, R_1= CH_3, R_2= Ph

16

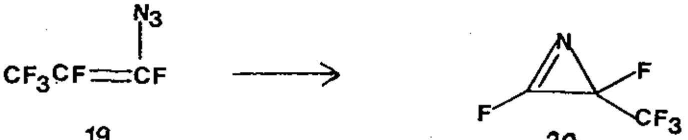
For example, the synthesis of 1-azirine **18** by irradiation of the vinyl azide **17** at -15°, could not be achieved by the thermolysis approach.[24]



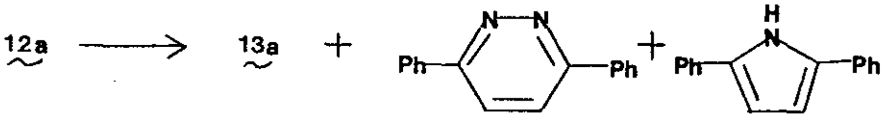
17 **18**

It has also been shown that in some cases both photolysis and pyrolysis of vinyl azides can lead to good yields of 1-azirines.[25,26] The vinyl azide approach has also been used for the synthesis of perfluoro azirine (**20**).[27,28]

In addition to 2-phenyl-1-azirine (**13a**), 3,6-diphenylpyridazine (**21**) and 2,5-diphenylpyrrole (**22**) were observed on storage of α-azido styrene (**12a**) at room temperature for one month.[29] This is quite unusual since the pyrolysis



19 **20**



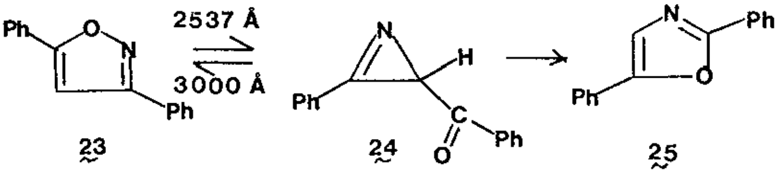
21 **22**

of **12a** only produces 2-phenyl-1-azirine (**13a**) and the ketenimine **14a**. However, we have recently observed that thermal decomposition of the corresponding vinyl azide from 2-vinylpyridine gave the pyrrole and pyridazine instead of 2-(2-pyridyl)-1-azirine.[30]

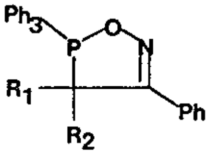
The decomposition of vinyl azides therefore offers an excellent method for the preparation of 1-azirines. However, the main limitation of this method is the availability and stability in some cases of the prerequisite vinyl azide.

C. Miscellaneous Reactions

Even though their synthetic utility is not large, several other approaches for the preparation of 1-azirines have been reported. Photolysis and pyrolysis of isoxazoles have been studied. For example, in the photochemical rearrangement of 3,5-diphenylisoxazole (23) to 2,5-diphenyloxazole (25), 3-benzoyl-2-phenyl-1-azirine (24) was observed as an intermediate.[31] This reaction exhibited wavelength dependence. The azirine 24 can be isolated during the reaction. A related photolysis reaction of isoxazoles has been reported to give ketenimines as well as oxazoles and 1-azirines.[32] The pyrolysis of 5-alkoxy-substituted isoxazoles also gave the 1-azirines in modest yields.[33]



The pyrolysis of 4,5-dihydro-1,2,5-oxazaphospholes (26) was found to be a useful method for the synthesis of 1-azirines in some cases.[34-37] For example, following this approach a relatively stable spiroazirine 27 could be produced.



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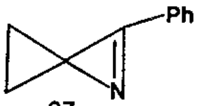

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There is a brief mention in the literature[38] on the isolation of 2-phenyl-1-azirine (13a) by the reaction of dimethyloxosulfonium methylide with benzonitrile, but details of the reaction were not reported.

Although several attempts to isolate the 2-azirine ring system 2 have been made, none has been successful so far.[16,39-45] Intermediacy of the antiaromatic 2-azirine system and its immediate rearrangement to the thermodynamically more stable 1-azirine has been noted by Rees and his co-workers.[42-47]

II. Reactions of 1-Azirines

In studies of the synthetically and mechanistically useful transformations of 1-azirines, advantage can be taken of certain inherent features within their structure such as:

(i) high ring strain;

(ii) reactivity of the π bond - availability for cycloaddition reactions;

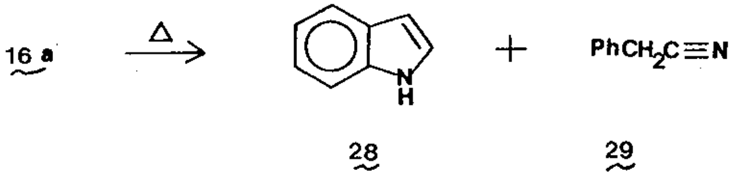
(iii) rigidity of the C=N bond - in the electronically excited state, energy dissipation by rotation of the C=N bond is not possible (as is postulated to occur in imines), and reaction from this state is possible;

(iv) basicity of nitrogen - availability of the lone pair of electrons for protonation and complexation with metals;

(v) possible thermal conversion to a vinyl nitrene or iminocarbene - rearrangement and reactions of these fugitive species.

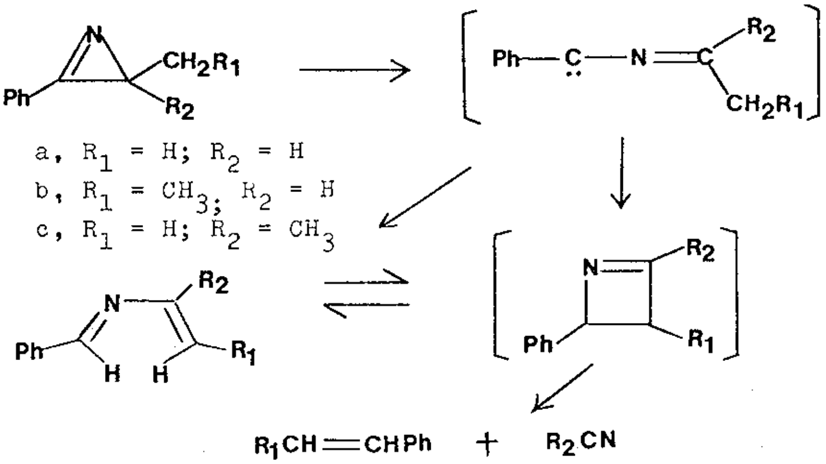
A. Decomposition and Rearrangement

Many 2-unsubstituted 1-azirines decompose to polymeric materials even *at room temperature. The relatively stable 3-phenyl-1-azirine* (16a) undergoes rearrangement in boiling n-hexadecane to give an equimolar mixture of indole (28) and phenylacetonitrile (29).[25] This result suggests the possibility that the azirine 16a may be in thermal equilibrium with the corresponding vinyl nitrene, because formation of 28 and 29 can be explained by intramolecular reactions of the fugitive vinyl nitrene.



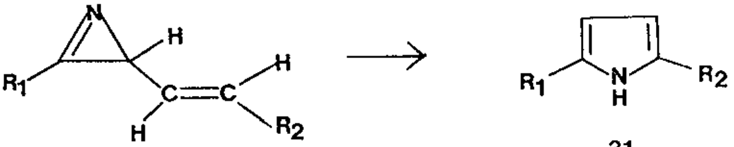
Thermal rearrangement of 2,3-diphenyl-1-azirine appears to be temperature dependent. When the azirine was heated at 250° for 3 hr in a sealed tube, 2-phenylindole, 2,3,4,5-tetraphenylpyrrole, 2,4,5-triphenylimidazole, and 1-benzyl-2,4,5-triphenylimidazole were obtained as major products.[48] In contrast, thermolysis at 290° for 8 hr, gave 2-phenylindole (54%) as the sole product.[49] The formation of 2-phenylindole suggests the vinyl nitrene as a probable intermediate during the course of rearrangement. Interestingly, when the thermolysis temperature is increased to 565°, different decomposition products are obtained.[50] For example, in the case of 3-methyl-2-phenyl-1-azirine (11), the major products were styrene, a reddish polymer, and hydrogen cyanide. From the results of several 1-azirine decompositions, it was proposed that initial carbon-carbon (2-3) bond cleavage rather than carbon-nitrogen (1-3) bond cleavage had occurred as can be seen in Scheme 1. This was the first observation of a thermal carbon-carbon (2-3) bond cleavage of 1-azirines. Interestingly, the spiroazirine 18 decomposed readily at above ambient temperatures to produce hydrogen cyanide and an unstable carbene which is quenched by the vinyl nitrene derived from 18.[24] This type of carbene involvement has also been proposed in other studies of azirine thermolysis.[43,45]

Scheme 1. Mechanism for the Thermal Decomposition of 1-Azirines Involving C-C Bond Cleavage



a, R_1 = H; R_2 = H
b, R_1 = CH_3; R_2 = H
c, R_1 = H; R_2 = CH_3

Another area of thermal rearrangement of 1-azirines is intramolecular cyclization. The pyrroles 31 were formed from the azirines 30 .[51,52]



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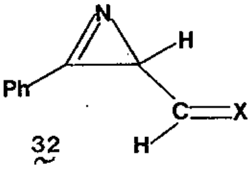
31

R_1= H, CH_3, or Ph

R_2= CN, CHO, $COOCH_3$, CH_3, or Ph

Similarly, thermolysis of the 3-iminomethyl-1-azirine 32a produces the pyrazole 33 .[52] This type of thermal ring expansion[51-53] is believed to



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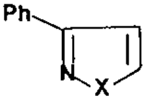
a, X= N-Ph
b, X= O



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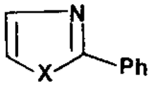

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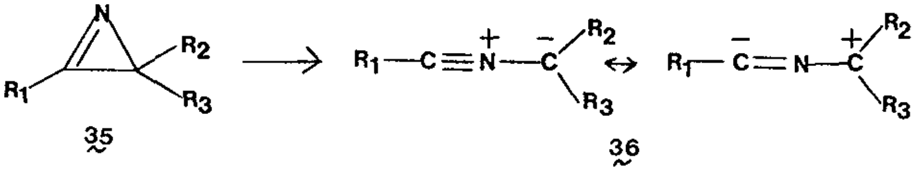
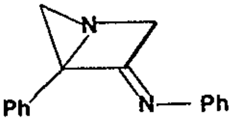
involve participation of a vinyl nitrene resulting from 1-3 bond cleavage of 1-azirine.

The photochemical decomposition and rearrangement of 1-azirines has also received some attention. It is now established that the photolysis of 1-azirines leads to irreversible ring opening via 2-3 bond cleavage and the formation of nitrile ylids 36 as intermediates. Thus the reported photoinduced formation of the azabicyclopentane 37[54,55] from 2-phenyl-1-azirine (13a) has been found to be incorrect and the actual photodimer is 38, the result of addition of the photochemically derived nitrile ylide to 1-azirine.[99]



R_1, R_2, R_3 = alkyl or aryl



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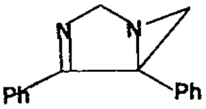

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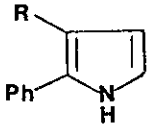
The intramolecular photocyclization of 24 to 25 which was mentioned earlier[30,31] reveals the sensitivity of the photochemical dissociation of 1-azirines. The azirine 24 rearranged to 2,5-diphenyloxazole (25) at 2537 Å by a nitrile ylide intermediate, but at higher wavelengths than 3000 Å, it rearranged to 3,5-diphenylisoxazole (23) presumably via the vinyl nitrene. The irradiation of 3-vinyl-1-azirines (30 when R_1 = Ph and R_2 = CN, CHO, or $COOCH_3$) gives the pyrroles 39 as expected, except in the cases of 3-cis or 3-trans-styryl side chain and 2-phenyl substitution, when ring expansion to the benzazepine 40 occurred.[56] A related photochemical study



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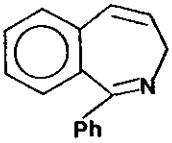

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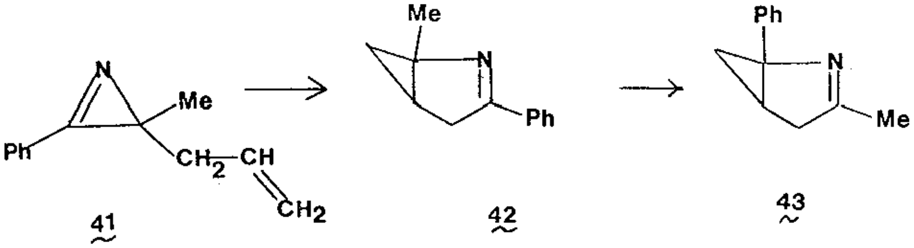
involved compounds 32 which give imidazole 34a or oxazole 34b via nitrile ylides.[52,56]

Recently the photochemistry of 2-phenyl-3-methyl-3-allyl-1-azirine (41) was reported.[57,99] When the azirine 41 was irradiated, intramolecular cycloaddition resulted in a 1:1 mixture of 42 and 43. On further irradiation, 42 was quantitatively isomerized to 43.



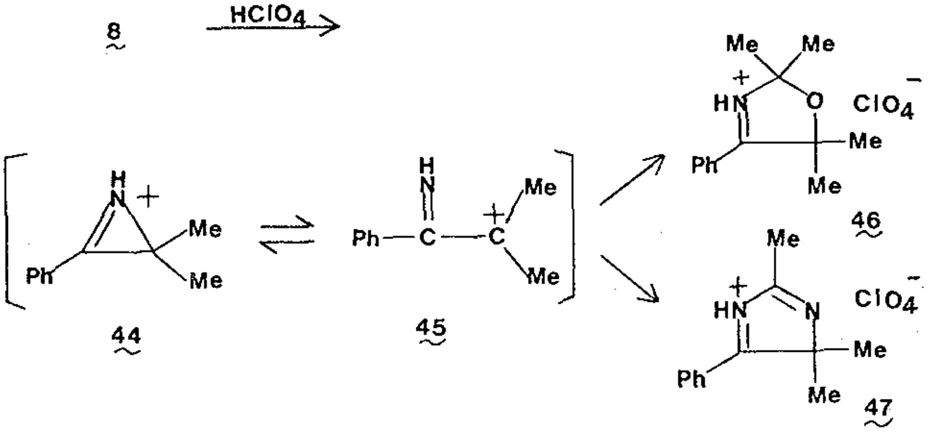
Irradiation of hydroxymethyl-2H-azirine derivatives which contain good leaving groups gave N-vinylamines via a novel 1,4-substituent shift.[99]

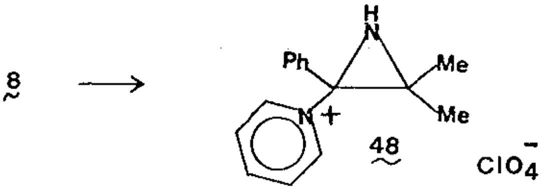
It has been observed that some 1-azirines dimerize slowly to pyrazines by themselves or by catalytic amounts of water.

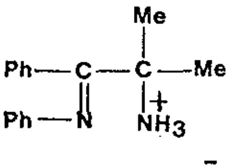
B. Acid-catalyzed Reactions

The basicity of 1-azirines is due to the lone pair of electrons on the nitrogen atom. Studies[16] indicate that 1-azirines are weak bases, their basicity being comparable to that of acetonitrile.

Leonard and his coworkers studied[59,60] the acid-catalyzed reactions of 3,3-dimethyl-2-phenyl-1-azirine (**8**) with acetone, acetonitrile, pyridine, and aniline. The treatment of azirine **8** with anhydrous perchloric acid along with acetone or acetonitrile gave the products **46** and **47** respectively. The mechanism of the reaction was explained as proceeding via the protonated azirine **44** which cleaves to form the resonance-stabilized cation **45** which then adds to the carbon-oxygen double bond or carbon-nitrogen triple bond to give **46** and **47**, respectively. The aziridine derivative **48** was obtained when 1-azirine **8** was treated with pyridinium perchlorate.[59] Treatment of **8** with anilinium perchlorate in acetonitrile at 0° gave α-ammoniumisobutyrophenone anil perchlorate (**49**).[60] The mechanism of the latter transformation probably involves initial addition to form an aziridine, followed by proton transfers and ring cleavage.[60]



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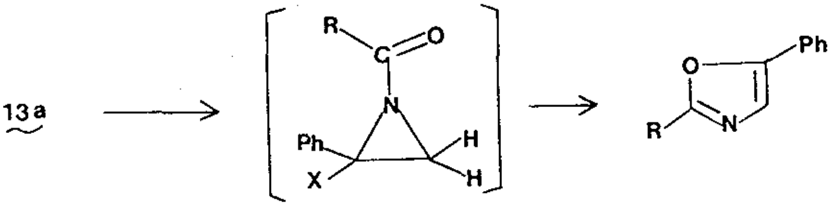
The addition of p-toluenesulfinic acid to 3-methyl-2-phenyl-1-azirine and 2,3-diphenyl-1-azirine gave the corresponding sulfonyl aziridines.[61] However, the reaction of 2-amino-1-azirine (52) with sulfinic acid results in ring destruction,[62] so that the ring-opened product is obtained rather than the aziridine derivative. The reaction of 2-phenyl-1-azirine (13a) with benzoic acid and with thiobenzoic acid also gives ring-opened products,[63] but the aziridines appear to be the probable intermediates. The acid-catalyzed hydrolysis of 1-azirines to aminoketones is commonly observed.[64]

When 2-phenyl-1-azirine (13a) reacts with cationoid reagents, such as acid chlorides or acid anhydrides, 2,5-disubstituted oxazoles 51 are formed.[15,16,63] The aziridine 50 is believed to be the primary product of the reaction. Similarly, 1,2,5-triphenylimidazole is produced when N-phenylbenzimidoyl chloride is treated with 2-phenyl-1-azirine. With phthalic anhydride, however, the ketoamide is formed rather than the oxazole, presumably through hydrolysis of an initially formed cyclic intermediate.



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C. Reactions with Nucleophilic Reagents

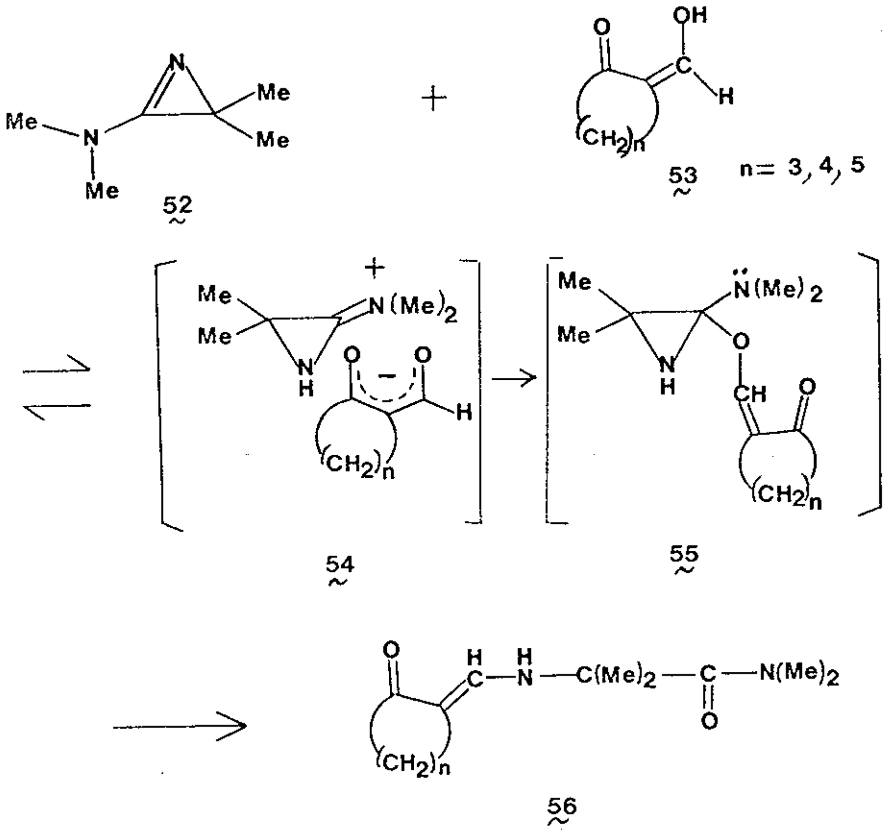
Some alkoxyaziridines can be obtained by treating 1-azirines with methanol containing catalytic amounts of sodium methoxide.[16,59] For example, treatment of 3-methyl-2-phenyl-1-azirine (11) with methanol gives 2-methoxyaziridine.[16]

Amines also react with 1-azirines. The treatment of 2-phenyl-1-azirine with aniline followed by mild acid hydrolysis gives benzanilide and small amounts of 2,5-diphenylpyrazine and 3,4-dianilino-1,2,5-triphenylpyrrole.[64] These products have been rationalized as proceeding by initial nucleophilic attack of the amine at C-2 of the azirine ring.

Several 1-azirines have been reduced to the aziridines with lithium aluminum hydride. The reaction usually proceeds in high yield and is stereospecific.[11,12] In some cases this can be the method of choice for the preparation of cis-aziridines. The reaction of 1-azirines with sodium borohydride also gives aziridines. We have been successful in isolating some aziridines by this reduction method. Interestingly enough, catalytic hydrogenation by palladium or Raney nickel results in reduction of the carbon-nitrogen single bond rather than the double bond.[4,22,42] However, there is a report that when platinum oxide is used as catalyst, a steroidal 1-azirine is reduced smoothly to the corresponding aziridine.[8,9]

Grignard reagents have been shown to react with 1-azirines to give aziridines.[66,16,58] Furthermore, attack of the Grignard reagent has been proven to occur stereospecifically from the less sterically hindered side of the azirine.[67] This is analogous to the stereospecific reduction of azirines to aziridines by lithium aluminum hydride.

An unusual ring transformation of 2-phenyl-1-azirine (**13a**) in the presence of dimethyl sulfinyl carbanion has been reported.[68] Azirine **13a** gives 2,4-diphenylpyrrole when it is treated with acetophenone and dimethyl sulfinyl carbanion. The reaction was explained as involving initial attack of the enolate anion from acetophenone on the carbon-nitrogen double bond of 1-azirine, followed by rearrangement to the 5-membered ring, and loss of hydroxide ion. A similar reaction of ethyl benzoylacetate yields 3-benzoyl-4-phenyl-2-oxopyrroline. Benzyl cyanide under the same conditions gives 3,4-diphenyl-2-oxo-5-iminopyridine. A recent report[62] on the reaction of 2-dimethylamino-3,3-dimethyl-1-azirine (52) with the formylcycloalkanones 53 in boiling benzene is noteworthy. The unusual ring-opening product 56 has been explained as arising through the intermediacy of 55.

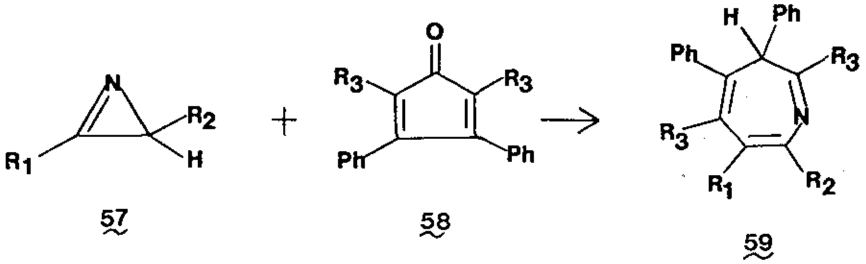


D. Cycloadditions of 1-Azirines

(i) Thermal Diels-Alder Reactions

Under appropriate reaction conditions advantage can be taken of the inherent reactivity of the rigid carbon-nitrogen double bond of 1-azirines to effect cycloadditions. The 2-π electrons of this system can participate in thermal symmetry-allowed [4 + 2] cycloaddition reactions[20] as dienophiles. During the past several years, the formation of various heterocyclic compounds using 1-azirines as dienophiles has been reported.

The 3H-azepines 59 are obtained directly upon refluxing the 1-azirines 57 with cyclopentadienones 58 in benzene or toluene.[69-73] Initially, it had been proposed[69,70] that a possible mechanism (route a) for the formation of the 3H-azepines 59 involved a Diels-Alder cycloaddition to furnish a strained adduct which undergoes a cheletropic fragmentation to give an azanorcaradiene. The symmetry-allowed electrocyclic rearrangement of this azanorcaradiene to its valence tautomer, the 2H-azepine, is followed by a 1,5-suprafacial sigmatropic shift of the 2-hydrogen to give the thermodynamically more stable 3H-azepine.[78] When this cycloaddition reaction was extended to 1,3-diphenylbenzocyclopentadienone and to 1,3-diphenylphencyclone,

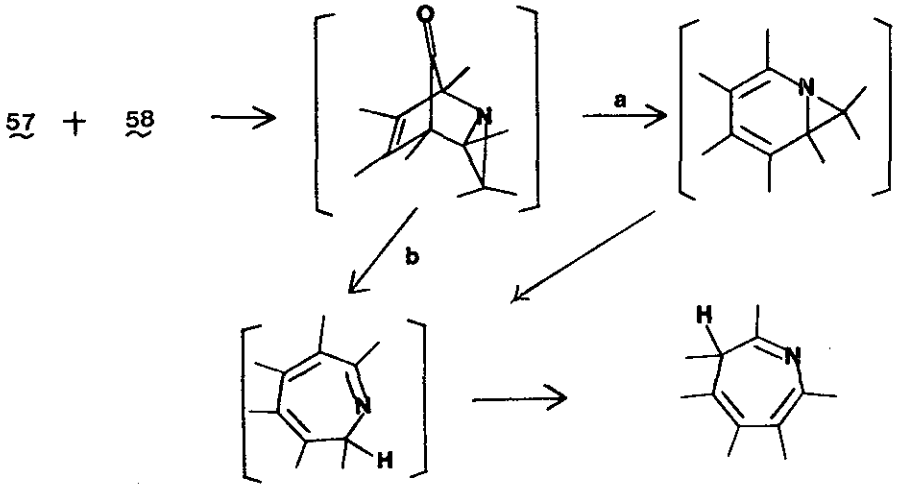


$R_1 = C_6H_5$ or $C_6H_5CH_2$

$R_2 = H, CH_3, C_6H_5,$ or CH_2OH

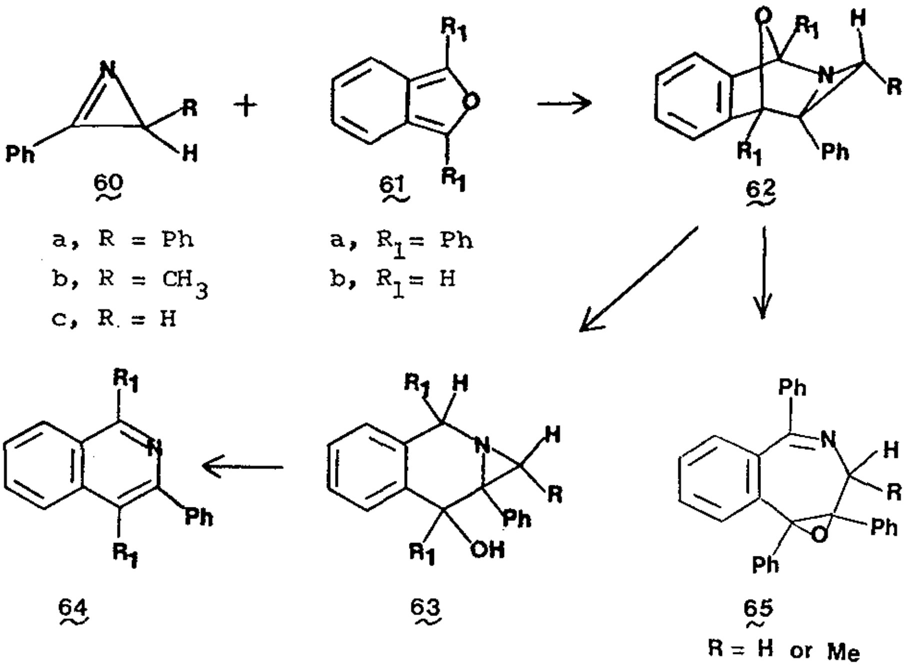
$R_3 = C_6H_5, CH_3,$ or C_2H_5

Scheme 2. Mechanism for the Cycloaddition of 1-Azirines with Cyclopentadienones



2H-benzoazepine and 2H-phenanthroazepine respectively, were obtained.[71,72] These results were interpreted as favoring mechanism (b) (Scheme 2) in which loss of carbon monoxide through participation of the aziridine carbon-nitrogen bond is concomitant with ring expansion to give 2H-azepine.[72]

Interest in isolation and examination of the initially formed cycloadduct prompted examination of the cycloaddition of 1,3-diphenylisobenzofuran (61a) with 1-azirines 60.[74] On the basis of spectral evidence and chemical transformations, the adducts were assigned the exo cycloadduct structures 62. Reductive ring opening of 62 with lithium aluminum hydride gave the benzoazanorcarane 63 which could be converted to the isoquinoline 64 . The reaction of isobenzofuran 61b with 1-azirines gave parallel results.[76] In a similar study, Hassner and Anderson[75] reported rearrangement of two of the adducts 62 in the presence of neutral alumina to give the epoxybenzo-2H-azepines 65 .



60
a, $R = Ph$
b, $R = CH_3$
c, $R = H$

61
a, $R_1 = Ph$
b, $R_1 = H$

62

63

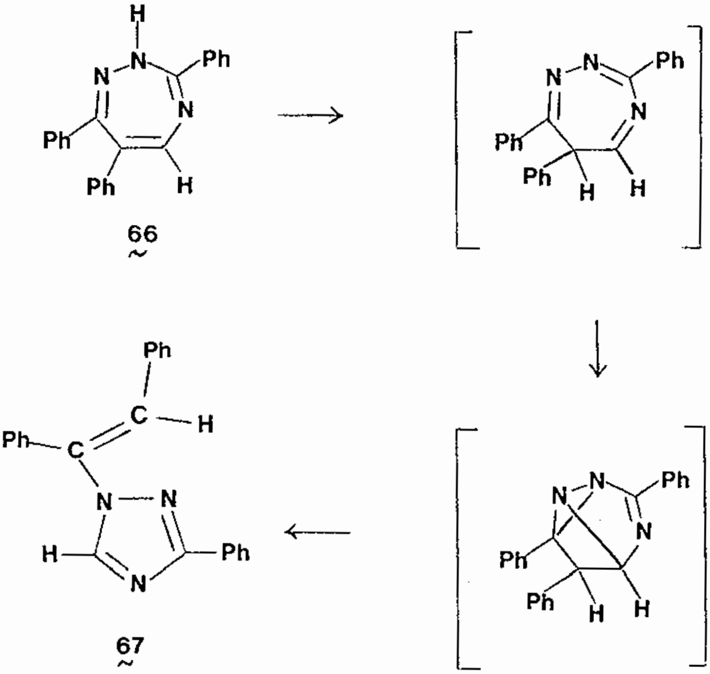
64

65
R = H or Me

Although 2-aryl-1-azirines do not react with cyclopentadiene under various conditions, the reaction of 2-benzoyl-3-methyl-1-azirine with cyclopentadiene furnished the expected [4 + 2] cycloadduct.[77] The success of the above reaction may be attributed to the increased reactivity of this azirine.

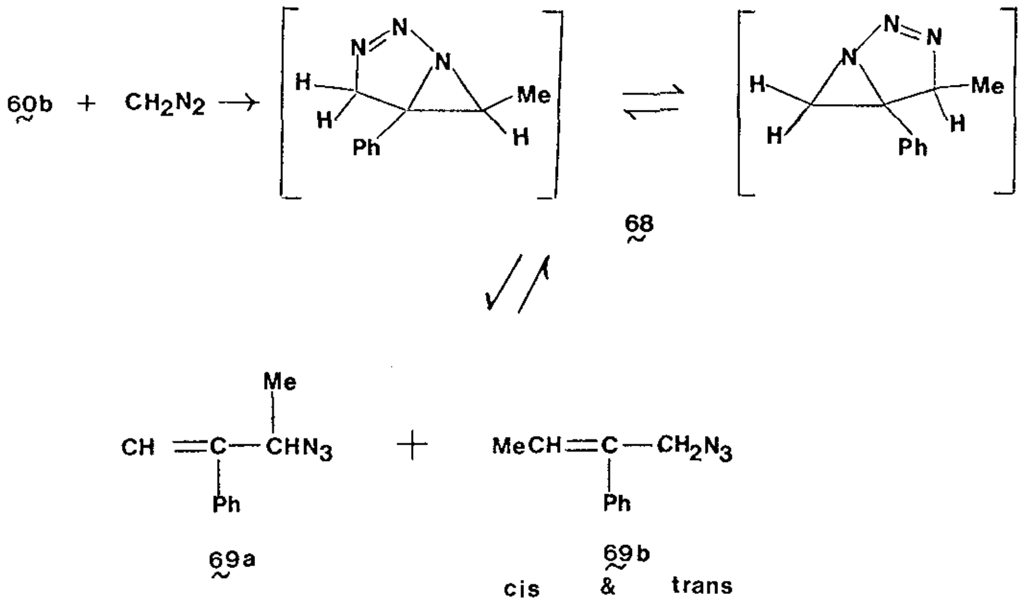
Cycloaddition of azirines can occur with diene components where subsequent loss of nitrogen occurs following [4 + 2] cycloaddition. Although triazines react sluggishly to give diazepines in very low yields,[73] the reaction with s-tetrazines is relatively rapid, and depending upon both the azirine and the tetrazine chosen and the reaction conditions, 1,2,4-triazepines can be synthesized along with pyrimidines or pyrazoles.[78-82]

In addition, the triazepine 66 undergoes a fascinating skeletal rearrangement to give the triazole 67 .[82]



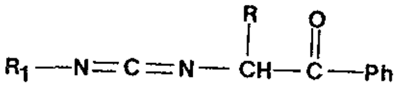
(ii) 1,3-Dipolar Reactions

The first example of this type of reaction that was studied was the addition of diazomethane to 1-azirines.[7,83] The products, allyl azides 69 , could be explained[7] as arising from the triazoline cycloadduct 68 . The reaction of 2,3-diphenyl-1-azirine with phenyldiazomethane was reported[84] to give the vinyl azide, 1-azido-1,2,3-triphenyl-1-propene.



Exclusive carbodiimide formation[85] was observed from the reaction of mesityl nitrile oxide with 1-azirines 60 in ether solution at 0°. The reaction is exothermic and is interpreted as involving initial 1,3-dipolar cycloaddition followed by ring opening and R group migration to give the carbodiimides 70 .

The addition of aziridines to 1-azirines[86] can also be explained as 1,3-dipolar reactions, if we assume that azomethine ylids are generated from the conrotatory thermal opening of aziridines. High yields of bicyclic aziridines are obtained from these additions. Benzonitrilium-p-nitrobenzylide, generated from the corresponding vinyl chloride with triethylamine at 0° in benzene, reacts with 2-phenyl-1-azirine to give a bicyclic aziridine in 28% yield.[87] An attempted 1,3-dipolar addition with an azlactone, resulted only in an ene product.[87] Another 1,3-dipolar



$$R_1-N=C=N-\underset{}{\overset{R}{\overset{|}{C}}}H-\overset{O}{\overset{\|}{C}}-Ph$$

70

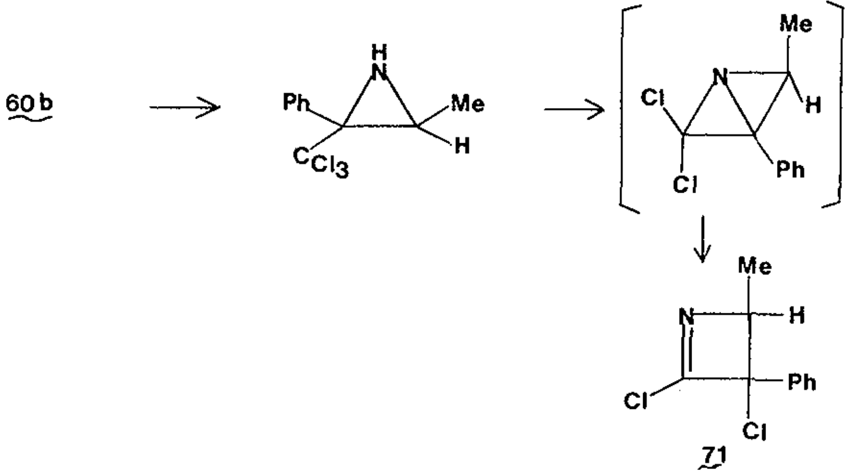
R_1 = Mesityl

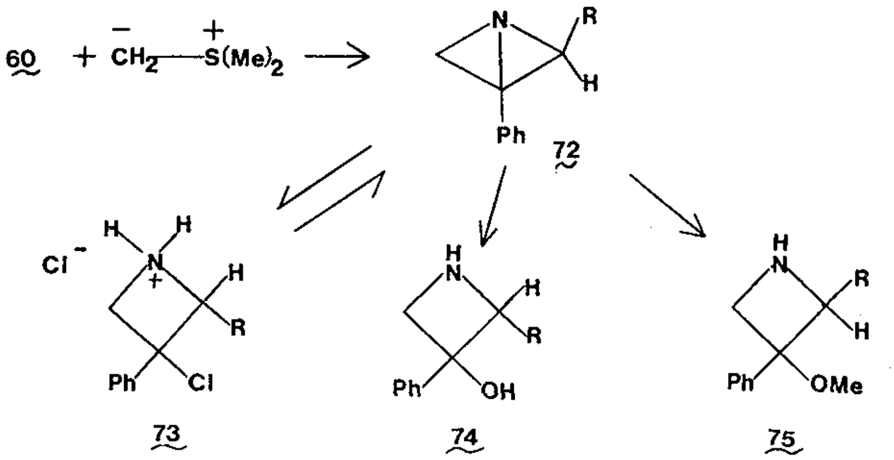
substrate for 1-azirines is a nitrone, and it has been shown that 2,3-diphenyl-1-azirine reacts with N,C-diphenylnitrone to give N-benzilidene aniline and *bis*(benzamino)phenylmethane as major products rather than the expected 1,3-dipolar 1:1 adducts, and similar results were obtained with isoquinoline N-oxide.[88]

(iii) Carbene and Carbenoid Additions

The reaction of dichlorocarbene generated from phenyl(trichloromethyl)-mercury with 1-azirine was reported to give N-vinyl imine rather than the expected bicyclic compound, azabicyclobutane.[89,90] However, stepwise nucleophilic addition of trichloromethyllithium to 3-methyl-2-phenyl-1-azirine (60b) followed by treatment with base gave 2,3-dichloro-*cis*-4-methyl-3-phenyl-1-azetine (71) presumably *via* the azabicyclobutane.

The successful synthesis of azabicyclobutanes 72 was accomplished by the treatment of 1-azirines with dimethylsulfonium methylide in tetrahydrofuran at low temperatures.[91,92] The azabicyclobutanes 72 can be transformed under suitable conditions to azetidine hydrochlorides 73, azetidinols 74, and the methoxyazetidine 75.[92] The hydrochlorides 73 recyclize quantitatively to azabicyclobutanes 72 on treatment with dilute sodium carbonate at 0°.





The reaction of 1-azirines with diphenylcarbene (generated by thermolysis of diphenyldiazomethane) gave as initial 1:1 adducts, 2-azabutadienes. These were converted by further reaction to 1:2 adducts.[92]

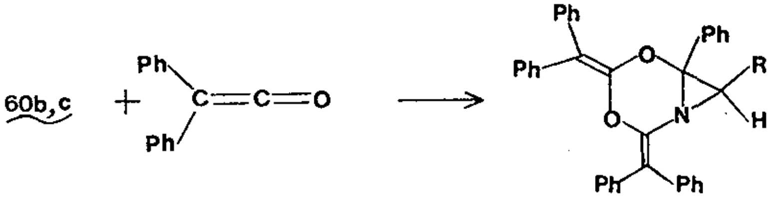
(iv) Cycloaddition with Heterocumulenes

It has been demonstrated so far that 1-azirines can be extremely useful precursors for the synthesis of heterocyclic compounds and can be incorporated into compounds containing desirable functions. Heterocumulenes[114] are a class of reactive reagents that can provide entry into complex heterocyclic systems through cycloadditions with 1-azirines.

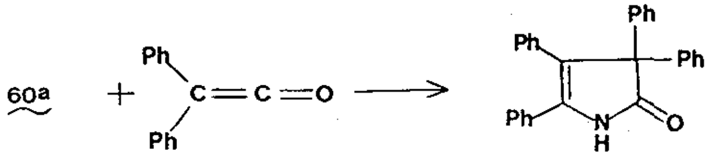
The reaction of 1-azirines with dephenylketene give, in general, only 1:2 adducts 76 which is in contrast to the behavior of simple imines which react to give 1:1 adducts (β-lactams) as major products and 1:2 adducts (possessing lactone structures) as minor products.[93-96] 2,3-Diphenyl-1-azirine behaves differently and gives a 1:1 adduct 77 in low yield.[94]

The adducts 76 were found to be very susceptible to acid, base, thermal, and photochemical rearrangements to yield a variety of heterocyclic systems.[95]

Ketenimines react with 1-azirines to give as the final products, benzodiazepinones.[93]



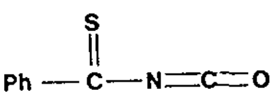
76



77

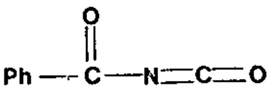
Although it is well known that simple isocyanates react with carbon-nitrogen double bonds,[114] we found phenyl isocyanate, p-methylphenyl isocyanate, p-chlorophenyl isocyanate, and p-nitrophenyl isocyanate to be inert towards 1-azirines. However, 2-amino-1-azirines have been reported recently to be reactive towards phenyl isocyanate and tosyl isocyanate.[117]

Heterocumulenes containing a carbonyl or related unsaturation adjacent to the cumulative bonds are usually very reactive, and thiobenzoyl isocyanate (78) and benzoyl isocyanate (79) would then be excellent compounds for cycloaddition with *1-azirines* 60 .



$Ph-C(=S)-N=C=O$

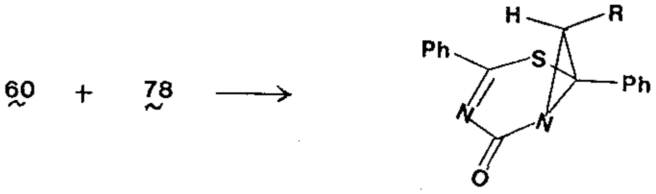
78



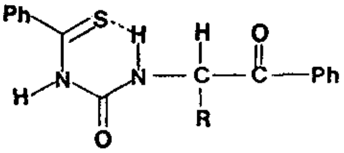
$Ph-C(=O)-N=C=O$

79

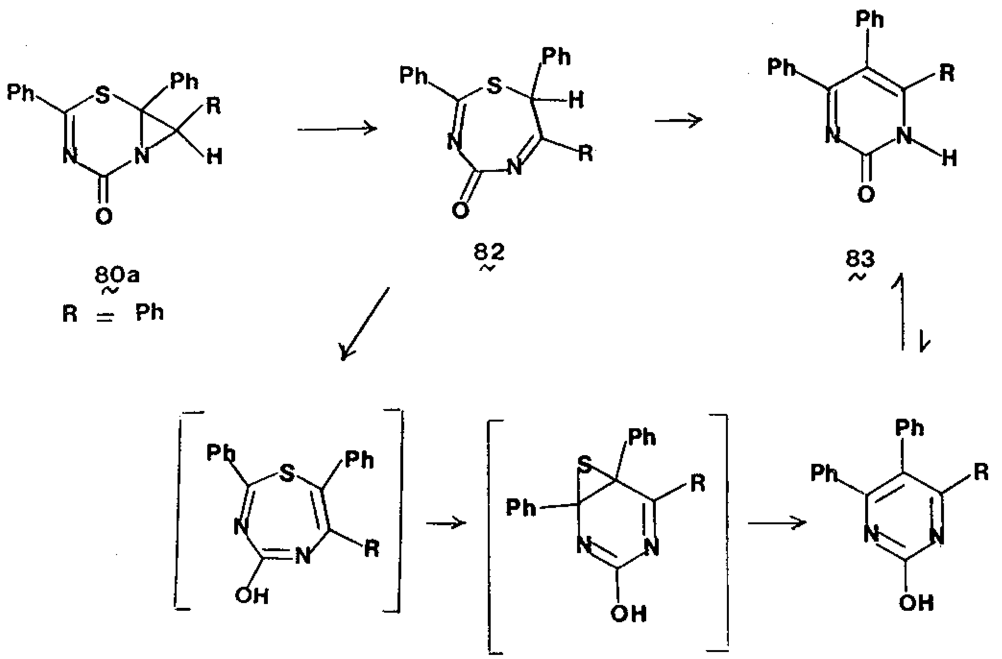
Thiobenzoyl isocyanate adds stereospecifically and regiospecifically at room temperature to 1-azirines to give exclusively [4 + 2] cycloadducts, the *cis* bicyclic aziridines 80 .[115,116] The latter undergoes acid-catalyzed hydrolysis to the ureas 81. When the cycloadduct 80a was subjected to thermolysis, a smooth rearrangement to the thiadiazepinone 82 occurred. On prolonged thermolysis, 82 undergoes extrusion of elemental sulfur presumably *via* an episulfide to give eventually a pyrimidone 83. The behavior of benzoyl isocyanate paralleled those of thiobenzoyl isocyanate and [4 + 2] cycloadducts were isolated.[116] However, benzoyl isothiocyanate (84)



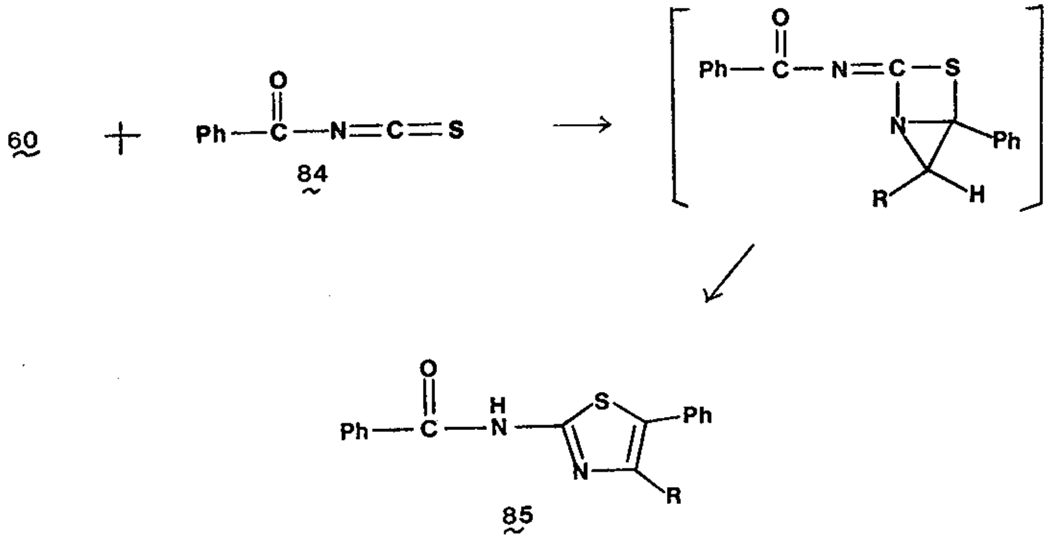
80



81

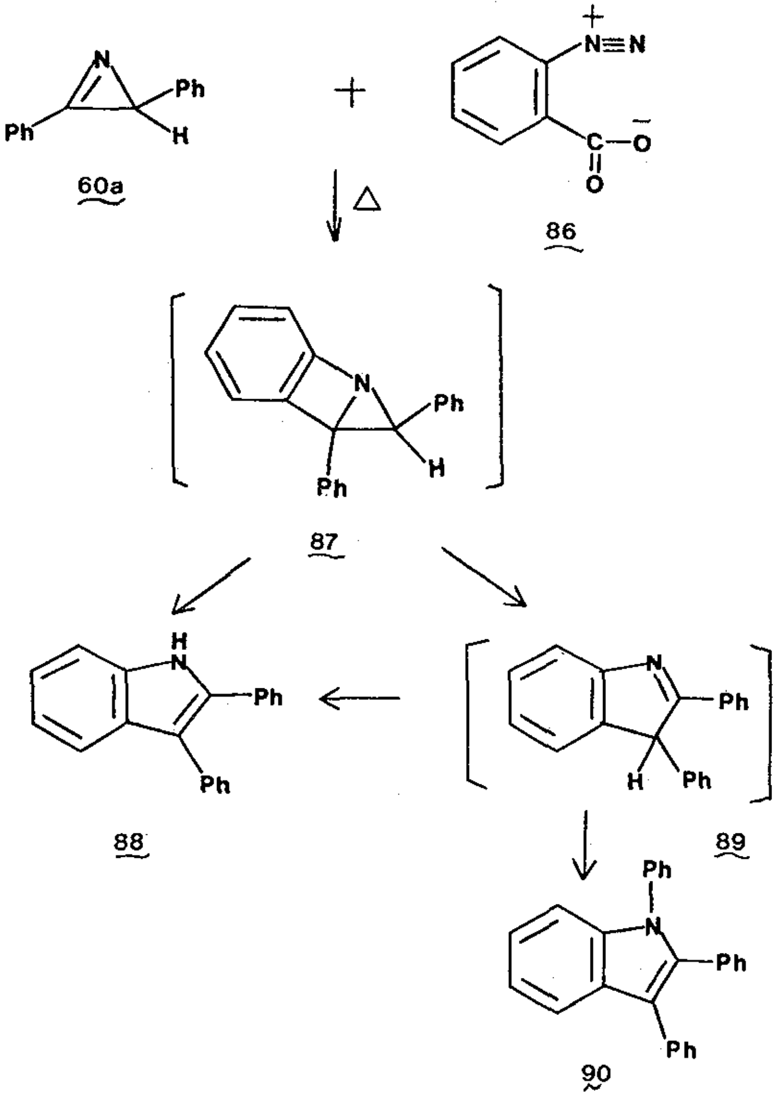


undergoes an apparent [2 + 2] cycloaddition utilizing its C=S bond to give thiazoles 85 as final products.[116] Another heterocumulene, carbon disulfide, also adds in a [2 + 2] fashion across its C=S bond to give thiazoles.[118]



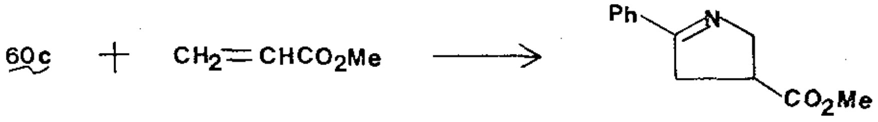
(v) Reaction with Benzyne

Benzyne, generated thermally from benzenediazonium-2-carboxylate (86) adds to 2,3-diphenyl-1-azirine (60a) to give 2,3-diphenylindole (88) and 1,2,3-triphenylindole (90).[119] The mechanism of formation of 88 and 90 was interpreted as involving initial formation of 87 and partitioning of this to 88 or the transient indolenine 89. The conversion of 89 to 90 then occurs through a symmetry-allowed[20] "ene" reaction.

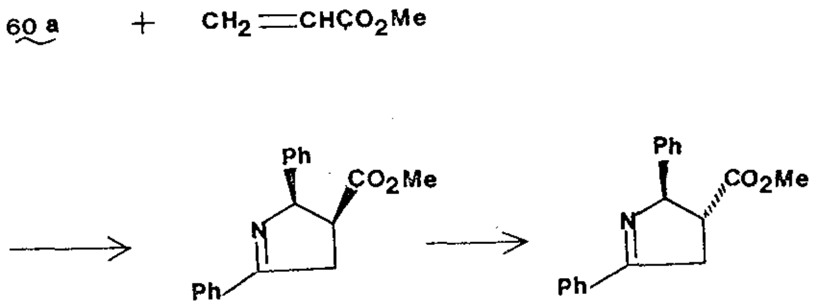


(vi) Photochemical Cycloadditions

Recently Padwa, Schmid and their co-workers have carried out extensive studies on photochemical reactions of 1-azirines and have reviewed their findings.[99] As mentioned earlier, the photolysis of 1-azirines leads to irreversible 2-3 bond cleavage of the ring and generation of nitrile ylids **36**.[99] These may be intercepted as 1,3-dipoles with a variety of dipolarophiles to form 5-membered ring heterocyclic compounds. Several electron deficient olefins have been treated with 1-azirines photolytically to produce Δ^1-pyrrolines regiospecifically.[97,98] For example, irradiation of a solution of 2-phenyl-1-azirine (**60c**) in excess methyl acrylate using a 450-W high pressure mercury lamp with a Vycor filter for 3 hr yields 80% 2-phenyl-4-carbomethoxy-Δ^1-pyrroline (**91**). Photolysis of 2,3-diphenyl-1-azirine (**60a**) with methyl acrylate for 3 hr gives 2,5-diphenyl-<u>cis</u>-4-methoxycarbonyl-Δ^1-pyrroline (**92**) as a single photoadduct. Treatment

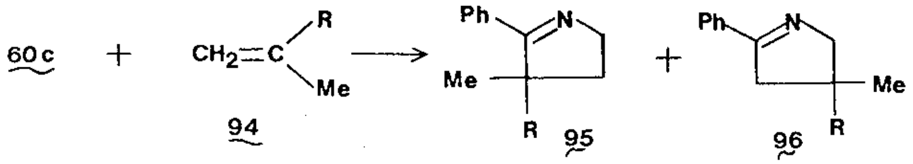


91



92 **93**

of the *cis*-adduct 92 with a suitable base converts it to the less crowded *trans* isomer 93. Interestingly, the photoaddition of 2-phenyl-1-azirine (60c) to methyl methacrylate produced two major products 95 and 96. Similar results were obtained using methyl acrylonitrile as substrate. Dimethyl acetylenedicarboxylate

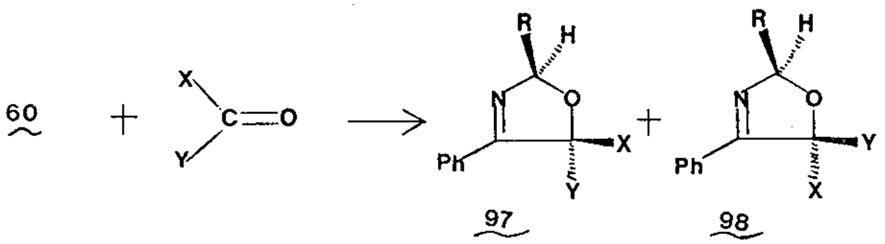


a, R = CO_2CH_3

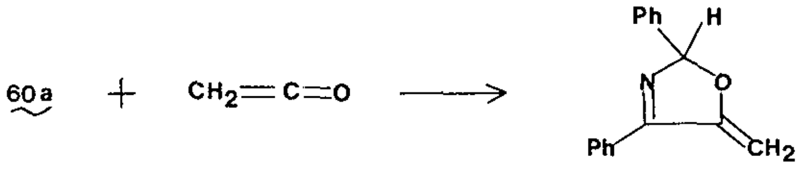
b, R = CN

reacts with 2,3-diphenyl-1-azirine (60a) under photochemical conditions to give 2,5-diphenyl-3,4-dicarbomethoxypyrrole. The addition of 1,4-quinones to 1-azirines has also been reported.[100]

The photochemical reaction of 1-azirines with carbon-oxygen double bonds and with carbon-sulfur double bonds has been extensively studied. The photochemical additions of 1-azirines to the carbonyl of aldehydes,[101,102,105] ketones[103,105,106] and esters[103,104,107] show complete regiospecificity to give the stereoisomeric oxazolines 97 and 98 exclusively. The addition of



some heterocumulenes has been also studied.[108,109] The irradiation of 2,3-diphenyl-1-azirine (60a) in benzene in the presence of ketene yields oxazoline 99, and similar results were obtained when 1-azirines were irradiated with diphenylketene. Isocyanates and isothiocyanates also give 5-membered ring heterocycles with 1-azirines photochemically by the addition to the C=O and C=S bonds, respectively. Carbon dioxide addition gives a single lactone 100. A recent report on the photochemical cycloaddition of 2-phenyl-1-azirine (60c) with benzoyl-, ethoxycarbonyl-, and vinyl-phosphonate gave similar results.[110]



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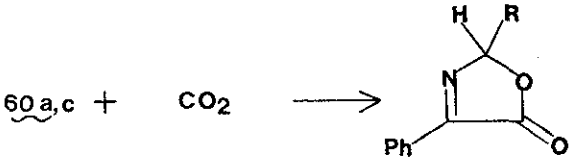
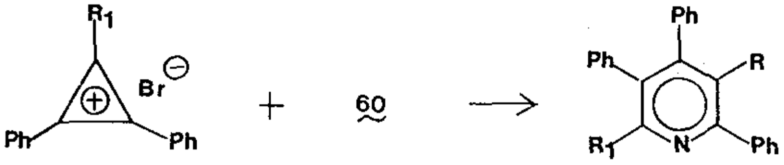


100

E. Miscellaneous Reactions

The reaction of diphenylcyclopropenone with 1-azirines in refluxing toluene produces 4-pyridones.[111] The addition of cyclopropenyl cations **101** to 1-azirines has been reported[112] to give pyridine derivatives **102** .

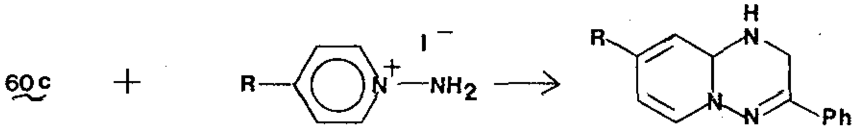


101

102

R_1 = H or Ph

An interesting reaction of 2-phenyl-1-azirine (**60c**) is the addition of pyridinium N-imines.[113,120] Pyridinium N-imine hydroiodides **103** react with **60c** in the presence of base to give the bicyclic triazine derivatives **104** in good yields.

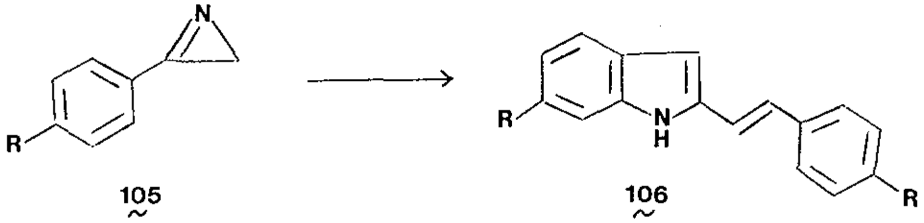


103

104

R = H, CH_3

Several recent reports on metal interactions with 1-azirines are noteworthy. The group 6 metal hexacarbonyls, $M(CO)_6$ (M = Cr, Mo, W), cause dimerization of 2-phenyl-1-azirine (**60c**) to two isomeric dihydropyrazines and 2,5-diphenylpyrazine.[121] With $Fe_2(CO)_9$ however, 2,5-diarylpyrrole and several binuclear iron carbonyl complexes were isolated.[122] 2-Aryl-1-azirines **105** undergo an unusual transformation in benzene in the presence of $[Rh(CO)_2Cl]_2$ or $[Co_2(CO)_8]$ to give 2-styrylindoles **106** .[123,124]



105 **106**

R = H, CH_3, OCH_3, Br

Alkylation of 2,3-diphenyl-1-azirine (**60a**) with methyl triflate has been reported.[125]

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Received, 23rd March, 1977