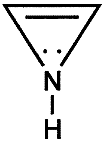
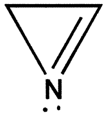
1.1.2 Azirines (Azacyclopropenes)

Introduction of unsaturation in the small rings satisfying the requirement of 120° bond angle for sp^2-hybridized atoms inevitably increases the ring strain. Unsaturated small ring heterocycles are, therefore, less stable as compared to their saturated counterparts and are difficult to prepare. Azirines[34] can exist in two isomeric forms; 1*H*-azirines (enamines or 2-azirines) **59** and 2*H*-azirines (imines or 1-azirines) **60**.

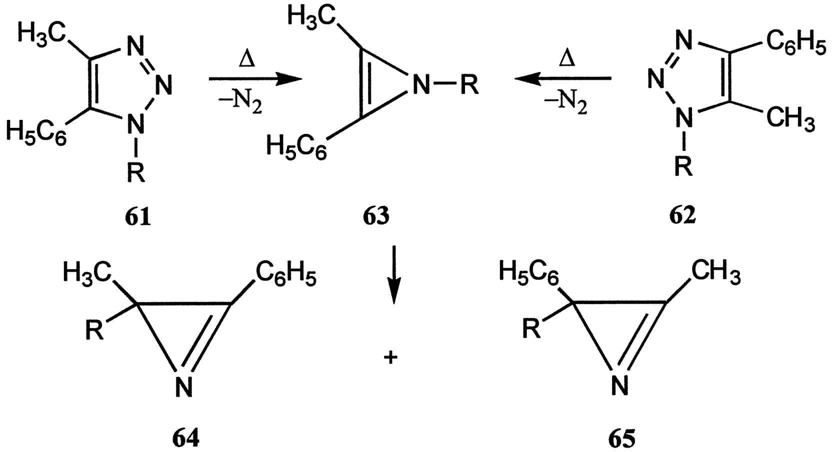


59



60

1*H*-Azirine is isoelectronic with cyclobutadiene having four π-electrons in planar cyclic conjugation. It is an antiaromatic and reasonance destabilized as defying the Hückel's aromaticity rule. The instability of 1*H*-azirines **59** is not only due to the large angle strain in the unsaturated three-membered ring, but also due to the potential overlap of the lone pair of electrons at nitrogen with the olefinic π-electrons. The instability, coupled with considerable ring strain, makes the synthesis of 1*H*-azirines very unlikely. However, 1*H*-azirine (2-azirine) **63** is formed as an intermediate in the pyrolysis of triazolines **61** and **62** where both the compounds yield an indentical mixture of 2*H*-azirines **64** and **65** (scheme-28).



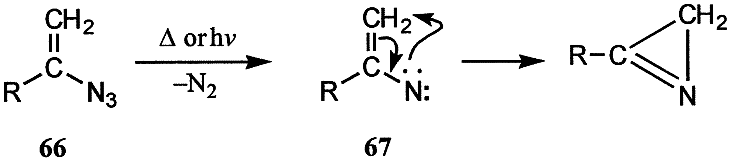
Scheme-28

2*H*-Azirine is more stable than isomeric 1*H*-azirine by 168.62 kJ/mol. 2*H*-Azirines are non-basic because of considerably increased s-character of the C–H bond and of the lone pair on nitrogen atom. The strained nature of 2*H*-azirines is reflected from the abnormal C=N stretching frequency (1800 cm^{-1}) as compared to the normal value (1650 cm^{-1}) of unstrained imines in infrared spectra and the considerably higher coupling constant (^{13}C–H=176 ppm) than in open chain analogs (^{13}C–H=132 ppm) in NMR spectra. 2*H*-Azirines are very strained, but are not antiaromatic.

1.1.2.1 Synthesis

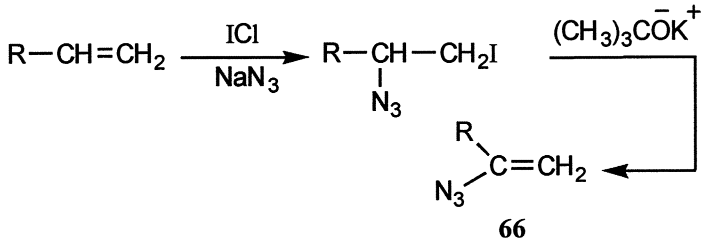
1.1.2.1.1 Thermal and Photochemical Decompositions of Vinylazides

Thermal and photochemical decompositions of vinylazides **66** provide 2*H*-azirines via the formation of vinyl nitrene intermediate **67** (scheme-29)[38-40].



Scheme-29

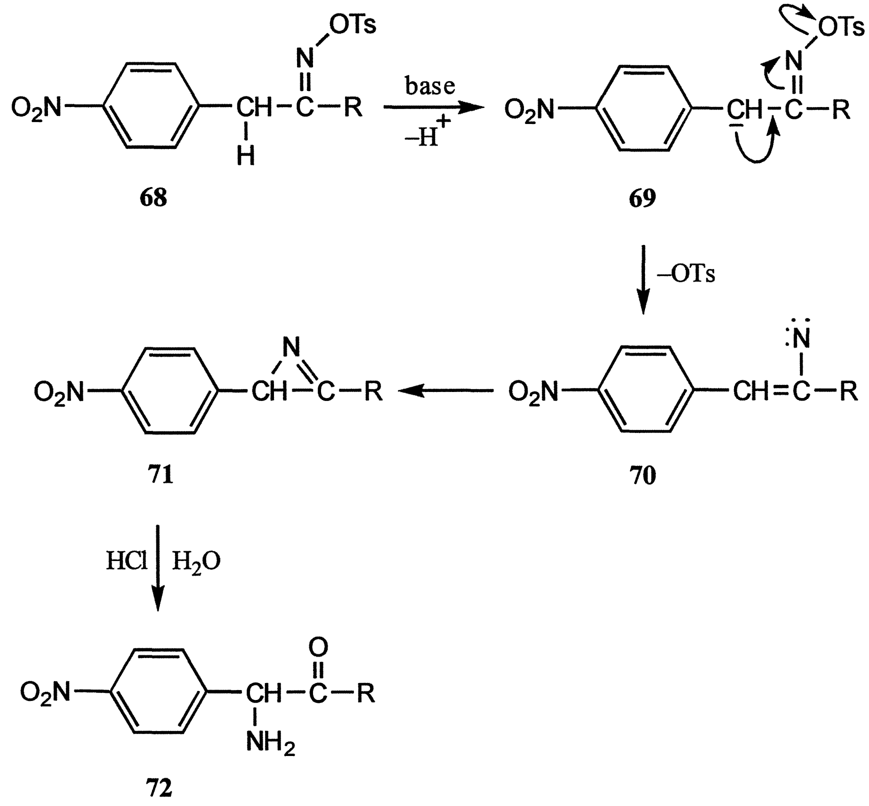
Vinylazides **66** are prepared by the following sequence of the reactions (scheme-30).



Scheme-30

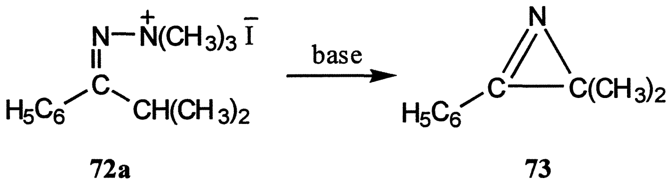
1.1.2.1.2 Modified Neber Rearrangement

The base catalyzed rearrangement of oxime-p-toluene sulfonates **68** to α-amino ketones **72** via an azirine intermediate **71** is known as Neber rearrangement (scheme-31)[41].



Scheme-31

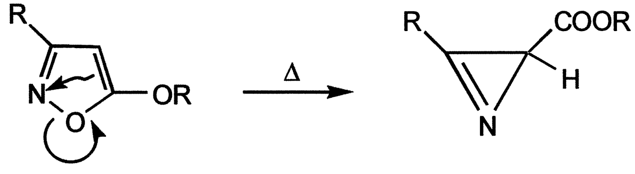
The rearrangement involves α-proton abstraction by a base and loss of tosylate ion to form α,β-unsaturated nitrene **70** which cyclizes to azirine **71**. The isolation of 2*H*-azirines is difficult and, therefore, a modification has been introduced in which dimethylhydrazone methiodide **72a** with a strong base provides isolable 2*H*-azirines **73** (scheme-32)[42].



Scheme-32

1.1.2.1.3 Thermal and Photolytic Ring Contractions of Isoxazoles

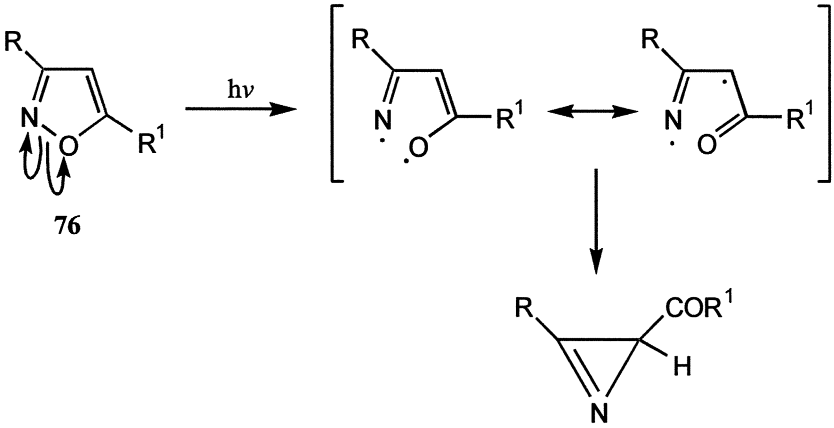
Pyrolysis of 5-alkoxyisoxazoles **74** involves ring contraction providing isolable 2*H*-azirines **75** (scheme-33)[43].



74 **75**

Scheme-33

Photolysis of 3,5-disubstituted isoxazoles **76** also produces 2*H*-azirines 77 (scheme-34)[44].



76

77

Scheme-34

1.1.2.2 Reactions

The inherent structural features within the ring system, high ring strain, reactive π-bond and a lone pair on nitrogen, are important in determining the chemistry of 2*H*-azirines. The reactions can be categorized into three classes :

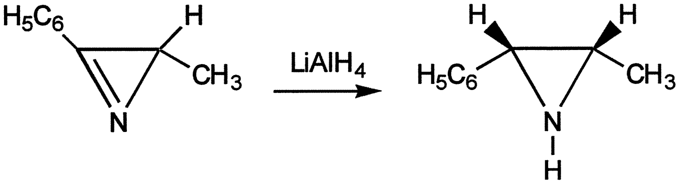
(i) Reactions at C=N bond
(ii) Thermal cleavage of N–C_2 bond
(iii) Cleavage of C_2–C_3 bond.

1.1.2.2.1 Reactions at C=N Bond

The addition of nucleophiles to C=N bond takes place stereospecifically on the least hindered side of the molecule.

1.1.2.2.1.1 Reaction with Lithium Aluminium Hydride

Lithium aluminium hydride reduces C=N bond providing aziridines (scheme-35)[45].

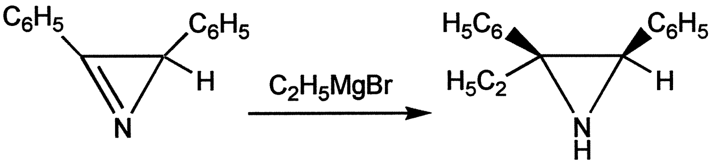


78 **79**

Scheme-35

1.1.2.2.1.2 Reaction with Grignard Reagents

Azirines undergo *cis*-addition with Grignard reagents (scheme-36).

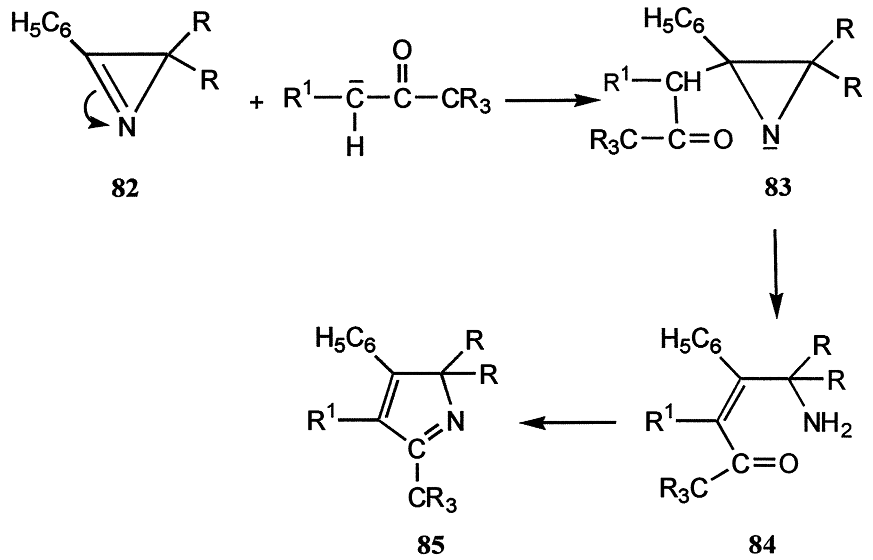


80 **81**(cis)

Scheme-36

1.1.2.2.1.3 Reaction with Carbanions

The carbanion attacks an imine carbon of 2*H*-azirine and results in an intermediate **83** which undergoes ring cleavage followed by cyclization to yield a five-membered heterocycle **85** (scheme-37)[45,46].



Scheme-37

1.1.2.2.1.4 Reaction with Trichloromethide Anion

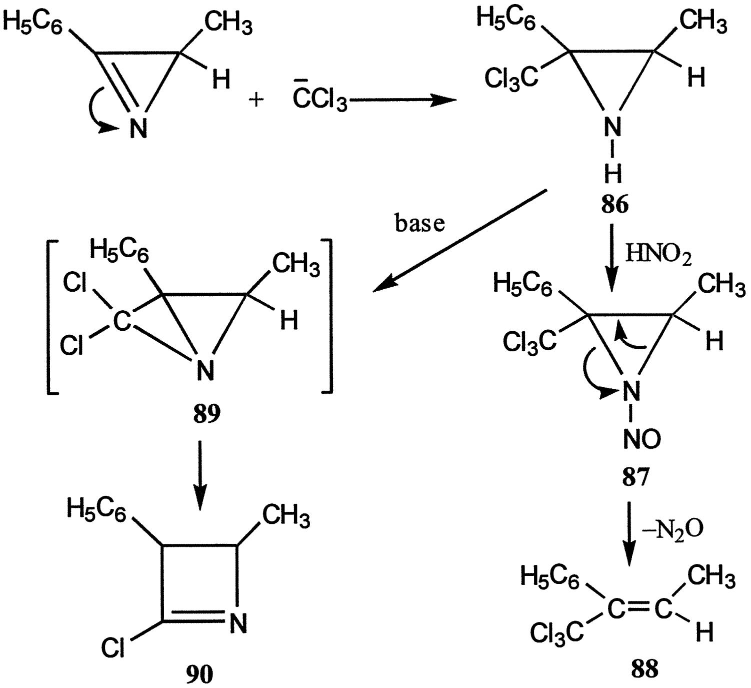
Trichloromethide anion adds stereoselectively to 2*H*-azirines to form aziridines **86** which with nitrous acid yield alkenes **88** via the formation of nitroso derivatives **87**; and with a base undergo rearrangement yielding azetidines **90** via the formation of bicyclobutane derivatives **89** (scheme-38)[45,47].

1.1.2.2.1.5 Cycloaddition

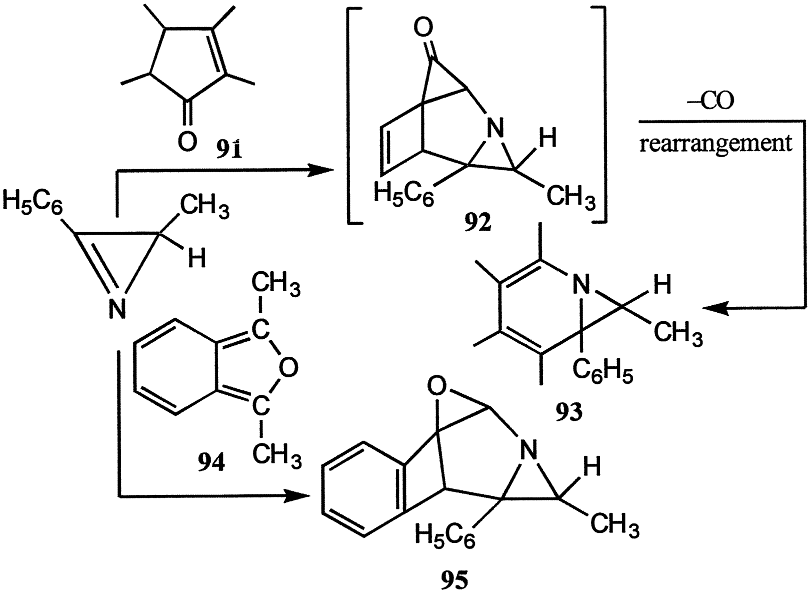
2*H*-Azirines undergo cycloaddition with dienes **91** and heterodienes **94** providing cycloaddition products **92** and **95**, respectively[48]. The C=N bond of strained 2*H*-azirines shows increased reactivity than the corresponding bond in unstrained imines (scheme-39).

1.1.2.2.2 Thermal Cleavage of N–C_2 Bond

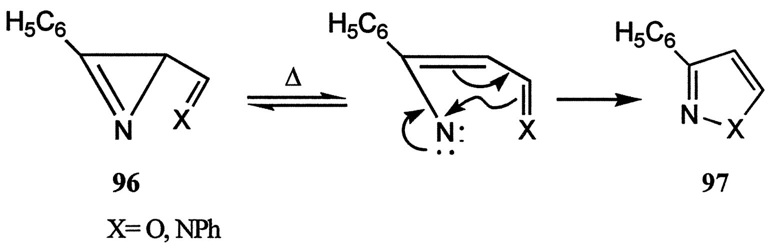
Thermolysis of azirines containing conjugative substituent at C-2 results in the formation of five-membered rearranged product **97** as a major product with the cleavage of N–C_2 bond (scheme-40)[49].



Scheme-38



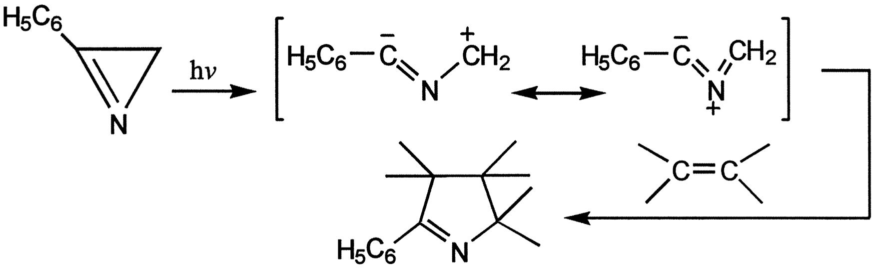
Scheme-39



Scheme-40

1.1.2.2.3 Photolytic Cleavage of C_2–C_3 Bond

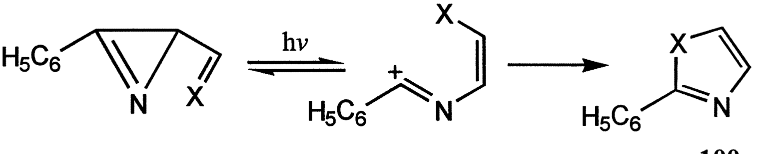
Photolysis of azirines, in contrast to thermolysis, usually results in the cleavage of C_2–C_3 bond forming nitrile ylides which can be trapped by a number of dipolarophiles (scheme-41)[49].



99

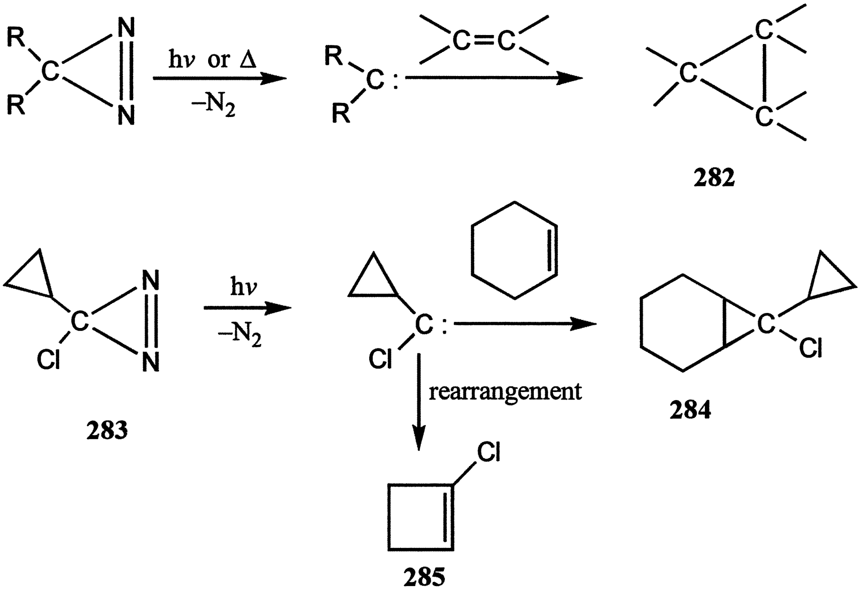
Scheme-41

In the absence of dipolarophile, the intermediate nitrile ylide, formed by azirine containing stabilizing group at C-3, undergoes intramolecular cyclization yielding an isolable product **100** (scheme-42).

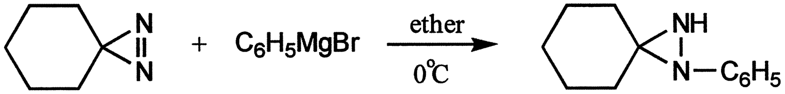


100

Scheme-42



Scheme-116

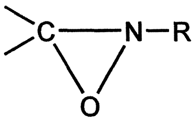


Scheme-117

2.3 Oxaziridines (Oxaziranes)

2.3.1 General

Three-membered saturated heterocycles with carbon, nitrogen and oxygen atoms are known as oxaziridines or oxaziranes **286**[134]. Oxaziridines are non-basic and do not form salts with acids. Oxaziridine shows remarkable conformational stability about nitrogen because of with considerably higher nitrogen inversion barrier. Thus, the isomers which differ only in their configuration about nitrogen are resolvable and configurationally stable[135].

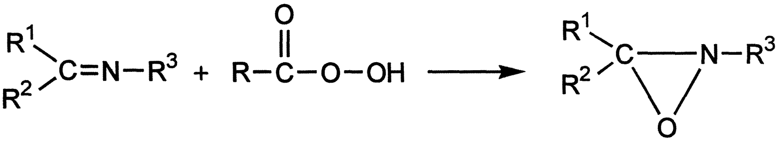


286

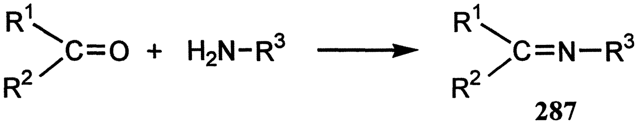
2.3.2 Synthesis

2.3.2.1 Peracid Oxidation of Imines or Schiff Bases (Insertion of Oxygen Atom into C=N Bond)

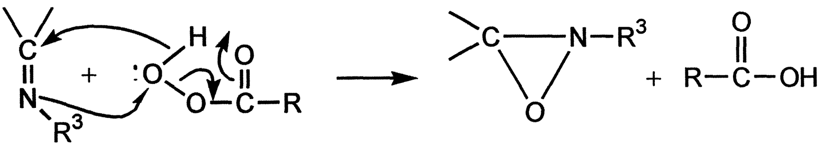
It involves direct insertion of oxygen atom into C=N bond and can be easily accomplished by the oxidation of imines (schiff bases) with peracids (scheme-118)[136]. The reaction is of wide applicability as the required imines can be easily prepared by the reaction of primary amines with ketones and aldehydes (scheme-119). The mechanism of peracid-imine reaction is similar to that of the epoxidation of alkenes (scheme-120).



Scheme-118



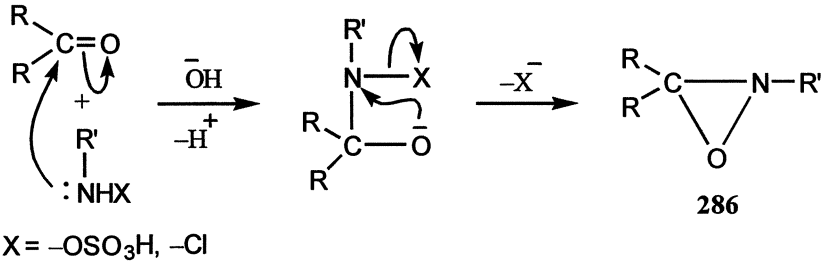
Scheme-119



Scheme-120

2.3.2.2 Reaction of Aldehydes and Ketones with Hydroxylamine-O-sulfonic Acids and Chloramines (Insertion of Nitrogen Atom into C=O Bond)

The reaction of aldehydes and ketones with hydroxylamine-O-sulfonic acids or chloramines involves the insertion of nitrogen atom into C=O bond yielding oxaziridines (scheme-121)[137-139].



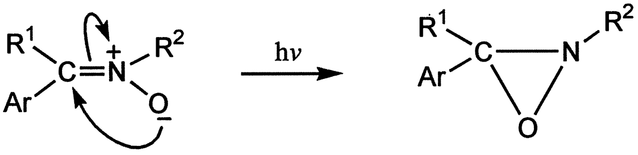
286

Scheme-121

The reaction proceeds by 1,2-addition of nitrogen-containing component to the carbonyl group, followed by the intramolecular cyclization.

2.3.2.3 Photoisomerization of Nitrones

Photoisomerization of nitrones **288** to oxaziridines **289** provides another route for the synthesis of oxaziridines (scheme-122)[140,141]



288 **289**

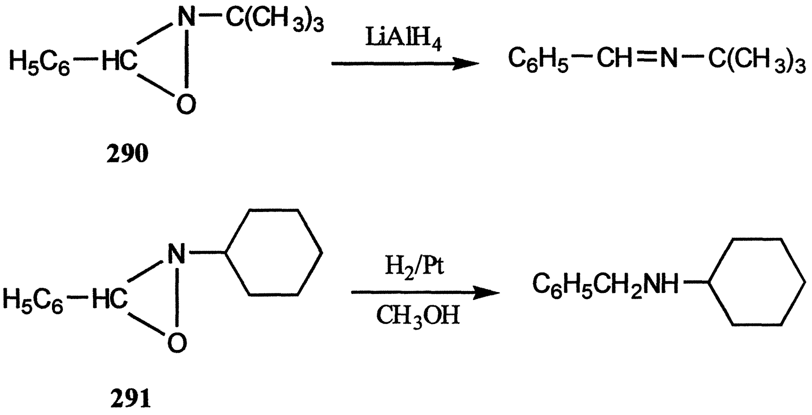
Scheme-122

2.3.3 Reactions

Oxaziridines have high strain energy and as such undergo ring opening reactions involving the cleavage of C–O, C–N and N–O bonds. However, their stability varies with the nature and the number of substituents.

2.3.3.1 Reaction with Reducing Agents

Oxaziridines undergo reductive cleavage with lithium aluminium hydride and with catalytic hydrogen providing the corresponding imines and secondary amines respectively (scheme-123)[142,143].

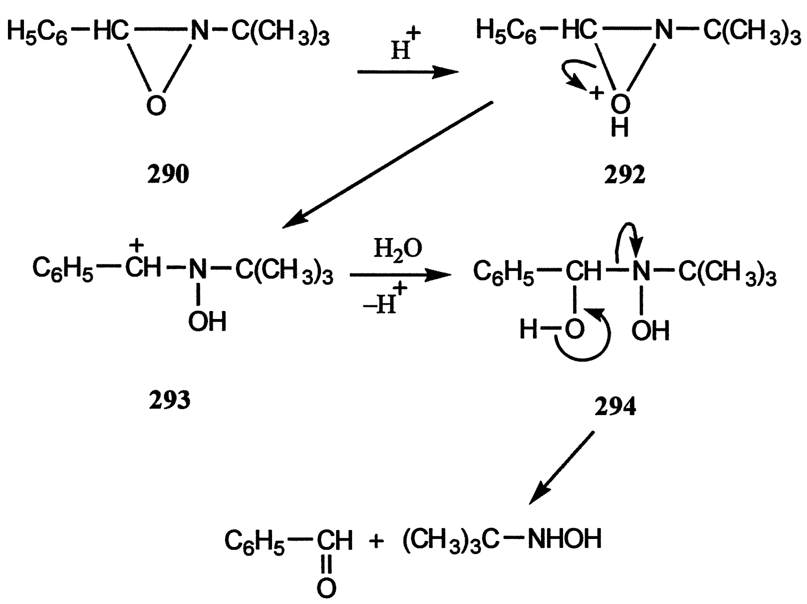


Scheme-123

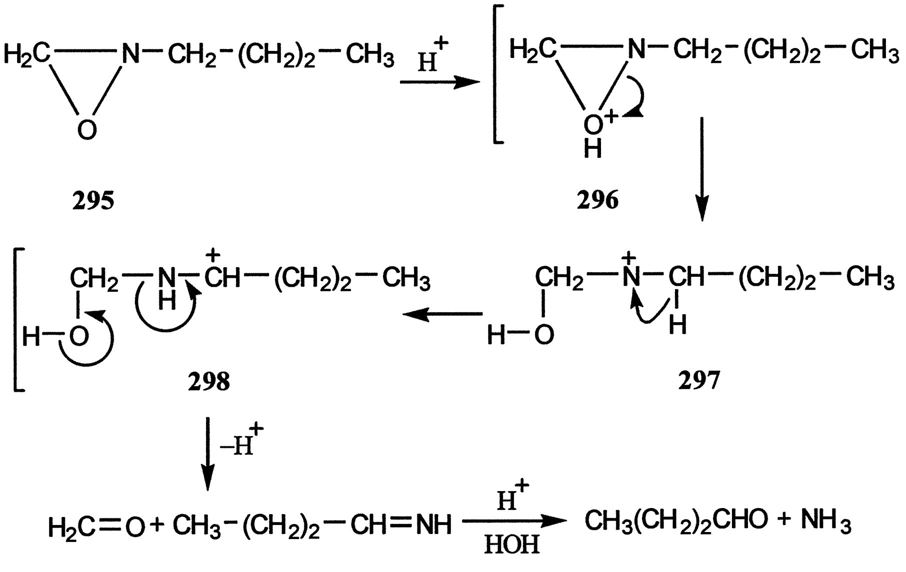
2.3.3.2 Acid Hydrolysis

Acid hydrolysis of oxaziridines proceeds with the cleavage of C–N or N–O bond depending on the nature of substituents. 3-Aryloxaziridines **290** undergo acid hydrolysis involving cleavage of the C–N bond with the formation of aromatic aldehydes and alkyl hydroxylamine (scheme-124)[142,143].

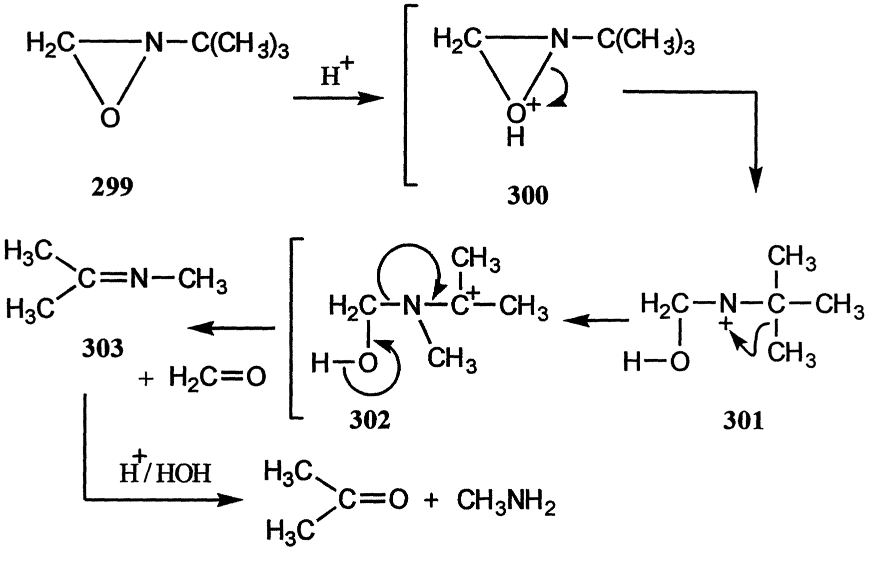
The reaction involves protonation of oxygen to form stabilized benzylic carbonium ion **293** with the cleavage of C–O bond. The carbonium ion **293** is then attacked by the hydroxyl ion, followed by the C–N bond fission forming aromatic aldehyde and hydroxylamine. In case of alkyloxaziridines **295**, the reaction proceeds via the formation of electron-deficient nitrogen species with the cleavage of N–O bond. The migration of hydride ion occurs from the neighbouring carbon atom providing aldehydes and ammonia (scheme-125). However, if hydrogen is not available on the neighbouring carbon atom, the migration of alkyl group to the nitrogen atom occurs with the formation of an amine (scheme-126)[144,145].



Scheme-124



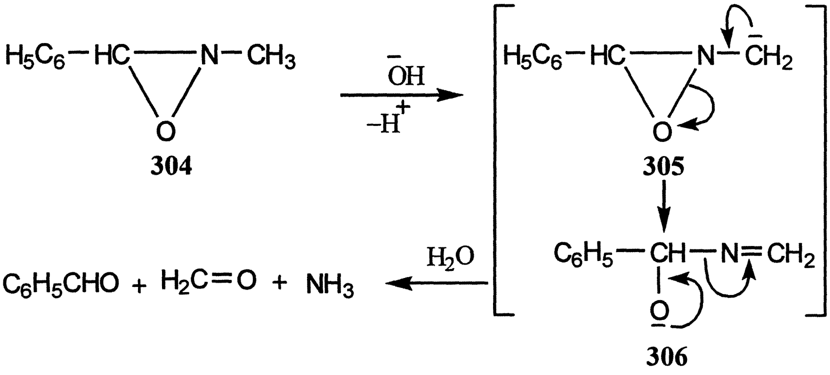
Scheme-125



Scheme-126

2.3.3.3 Reaction with Basic Reagents

The oxaziridine ring itself is unreactive towards basic reagents, but suitably substituted oxaziridines are decomposed with the N-O bond fission (scheme-127)[146-148].



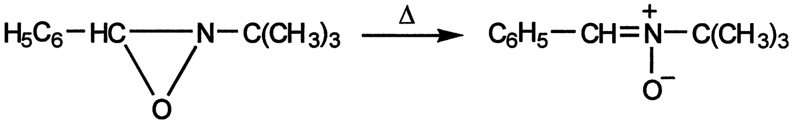
Scheme-127

The reaction proceeds with the formation of carbanion **305** which undergoes degradation to form carbonyl compound.

2.3.3.4 Thermal Rearrangements

Thermal rearrangements of oxaziridines depend upon the substituents at the position-3.

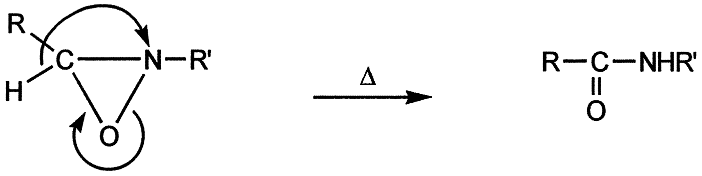
2.3.3.4.1 Oxaziridines **290**, substituted with an aryl group at the position-3, isomerize to nitrones **288** involving C–O bond fission (scheme-128)[142].



290 **288**

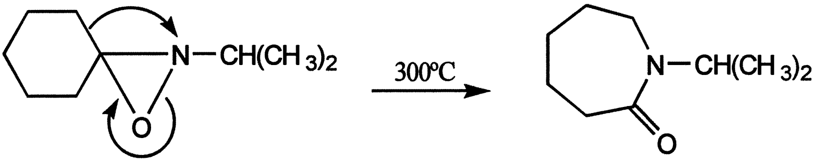
Scheme-128

2.3.3.4.2 The oxaziridines with an alkyl group at the ring carbon rearrange to amides with the cleavage of N–O bond (scheme-129).



Scheme-129

2.3.3.4.3 The oxaziridines derived from the cyclic ketones undergo ring expansion during thermal rearrangement (scheme-130).

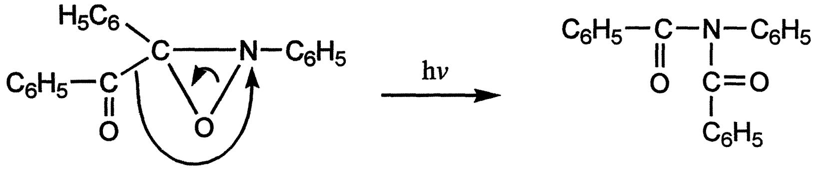


308 **309**

Scheme-130

2.3.3.5 Photochemical Rearrangements

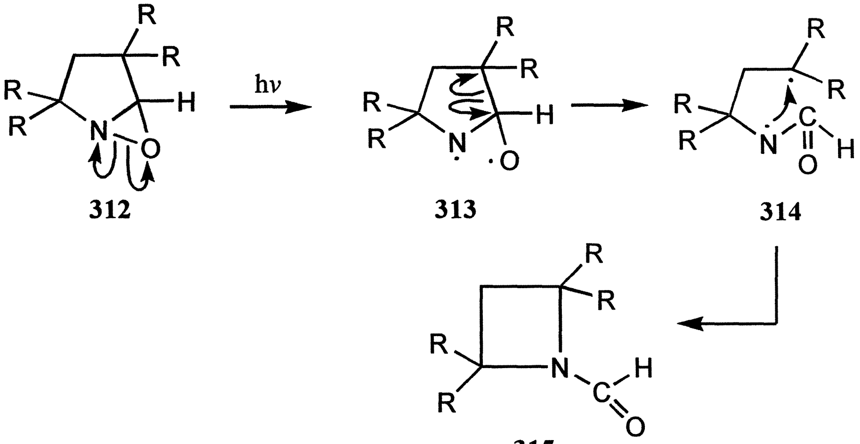
Photochemical rearrangement proceeds with the migration of a group from carbon to nitrogen involving cleavage of N–O bond to form amides (scheme-131)[149].



310 **311**

Scheme-131

Bicyclic oxaziridines **312** on photolysis undergo ring expansion. The reaction has been considered to proceed via free radical mechanism with the cleavage of N–O bond (scheme-132)[150-153].



312 **313** **314** **315**

Scheme-132

REFERENCES

1. J. A. Deyrup in A. Hassner (Ed.), *Small Ring Heterocycles*, Part I, Wiley-Interscience, New York, 1983, pp. 1.
2. O. C. Dermer and G. E. Ham, *Ethyleneimine and Other Aziridines*, Academic Press, New York, 1969; D. Tanner and C. Birgersson, *Tetrahedron Lett.* 2533 (1991)

direct intramolecular cyclization than the three-membered heterocycles because ring forming ability falls off with the chain length. The molecules of oxetane **2** and thietane **3** are planar, but not square because of relatively larger size of the oxygen and sulfur atoms than the carbon atom. The planarity of these heterocycles **2** and **3**, as compared to cyclobutane which is puckered, has been attributed to the reduction in the number of non-bonded interactions between methylene groups.

1 FOUR-MEMBERED AZAHETEROCYCLES

1.1 Azetidines

1.1.1 General

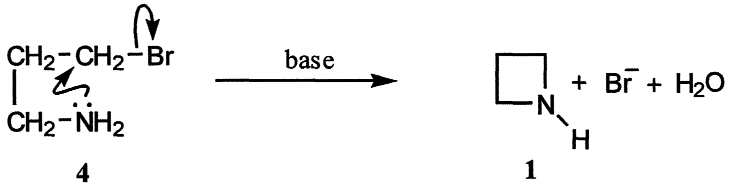
The azetidine ring is much less strained than that of aziridine and, therefore, azetidine and its N-substituted derivatives[1,2] behave in many respects as secondary and tertiary amines. Azetidine is considerably stronger base (pK_a= 11.29) than aziridine (pK_a = 8.04). In IR-spectra, the asymmetric C–H strectching frequency decreases (3047 cm^{-1} to 2966 cm^{-1}) with increasing the ring size. The effect of angle strain on the barrier to nitrogen inversion in azetidines is much smaller than in aziridines. However, the effects of substituents on the nitrogen inversion are the same as in aziridines. N-Alkyl-, N-acyl- and A-arylazetidines undergo nitrogen inversion faster as compared in the azetidines containing electron-withdrawing substituents with an adjacent lone pair (N-halo, N-amino, N-alkoxy and N-nitroso). The halo substituents on the nitrogen atom drastically slow the inversion rate so that N-chloro-2-methylazetidine can be resolved into two diastereomers.

1.1.2 Synthesis

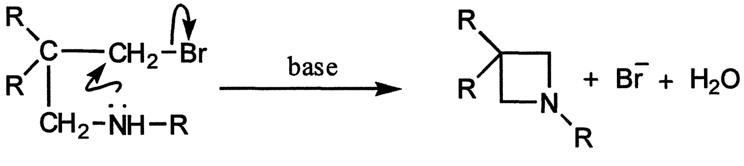
1.1.2.1 Intramolecular Cyclization

Azetidines are frequently synthesized by intramolecular cyclization of γ-haloalkylamines **4** in the presence of a base (scheme-1). The rate of cyclization is very low in the case of unsubstituted γ-haloalkylamines **4**, but the chain substitution facilitates cyclization (scheme-2)[3].

The intramolecular cyclization proceeds by nucleophilic displacement of a suitable leaving group in the γ-position of a three carbon chain by an amino group.



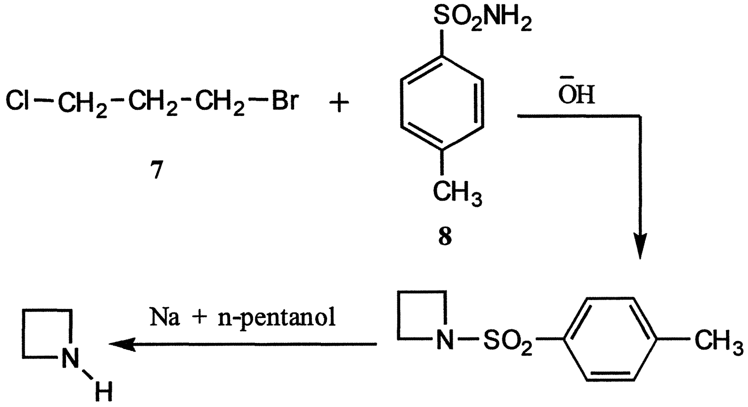
Scheme-1



Scheme-2

1.1.2.2 Cycloaddition

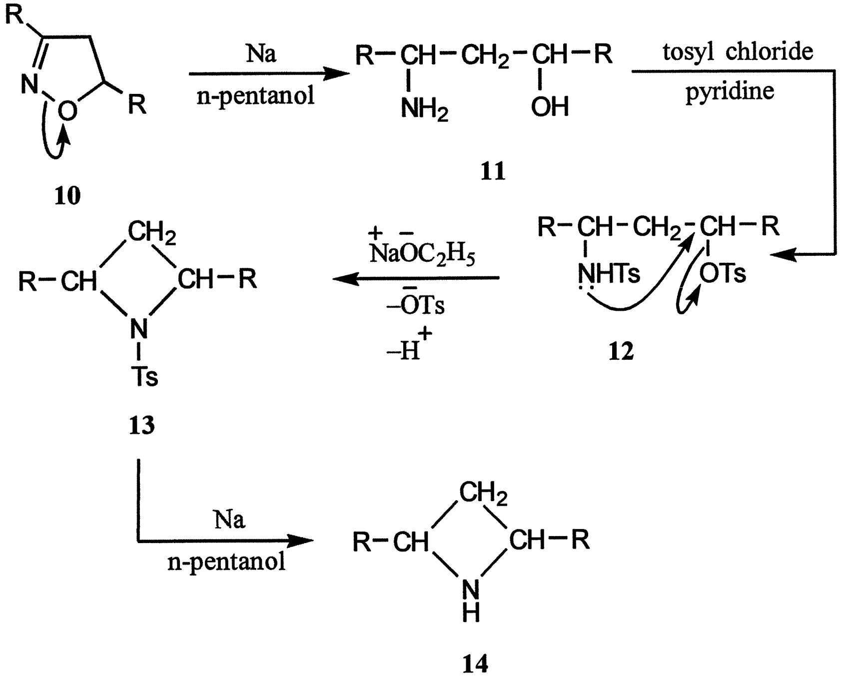
Azetidine **1** is best prepared by the cycloaddition of trimethylene chlorobromide **7** with *p*-toluenesulfonamide, followed by the reduction with sodium and n-pentanol (scheme-3)[4,5].



Scheme-3

1.1.2.3 From Isoxazolines

Isoxazolines **10** undergo ring opening reaction with the cleavage of N–O bond on treatment with sodium in *n*-pentanol and subsequently with tosyl chloride and pyridine providing tosylates **12** which on cyclization and reduction yield azetidines (scheme-4)[6].



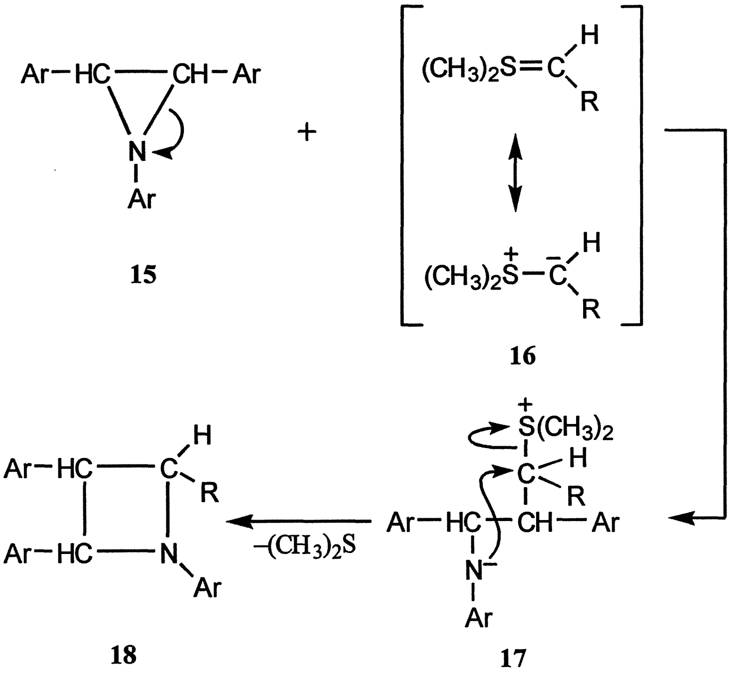
Scheme-4

1.1.2.4 From Aziridines

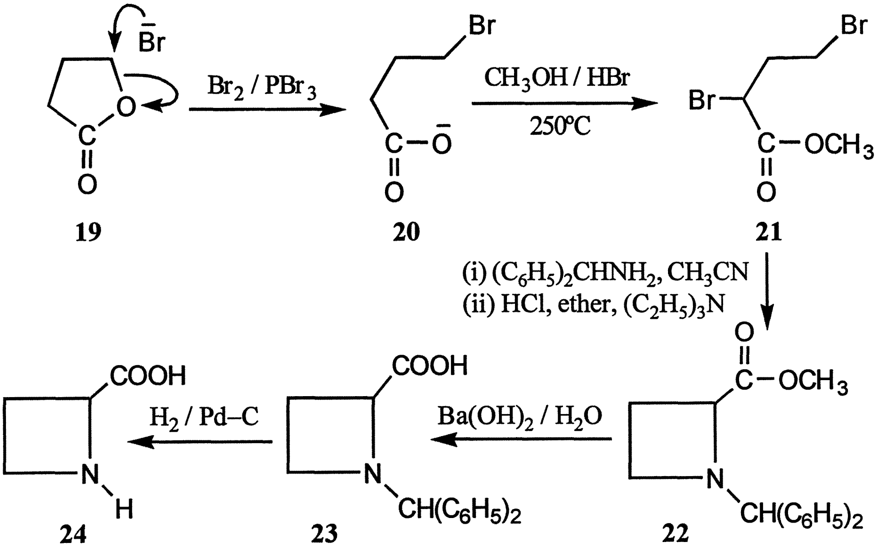
The reaction of aziridines **15** with sulfur ylides **16** proceeds with the transfer of a methylene group (> CHR or > CR_2) from the sulfur ylide and results in the formation of azetidines (scheme-5)[7].

1.1.2.5 From γ-Lactones

Following sequence of the reactions involving ring opening and ring closure in γ-lactones provides azetidines **24** (scheme-6)[8,9].



Scheme-5

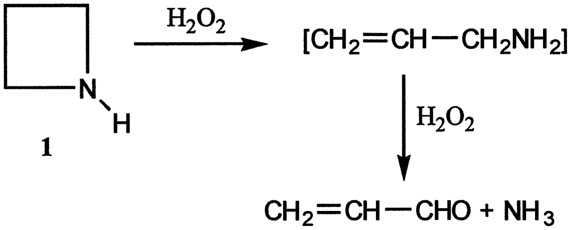


Scheme-6

1.1.3 Reactions

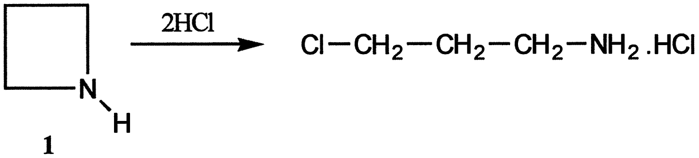
1.1.3.1 Ring Opening Reactions

Azetidines, being less strained than the three-membered aziridines, show lesser degree of reactivity and the cleavage of azetidine ring is relatively sluggish. Nucleophiles react with azetidines at very reduced rate as compared to aziridines. Azetidines are quite resistant to the action of bases and nucleophiles. However, hydrogen peroxide cleaves the ring with the formation of acrolein and ammonia (scheme-7).



Scheme-7

Azetidines are susceptible to attack by electrophiles and the ring cleavage is considerably accelerated in the acid catalyzed reactions. The reaction with hydrochloric acid provides 3-chloropropylamine hydrochloride[10] (scheme-8).

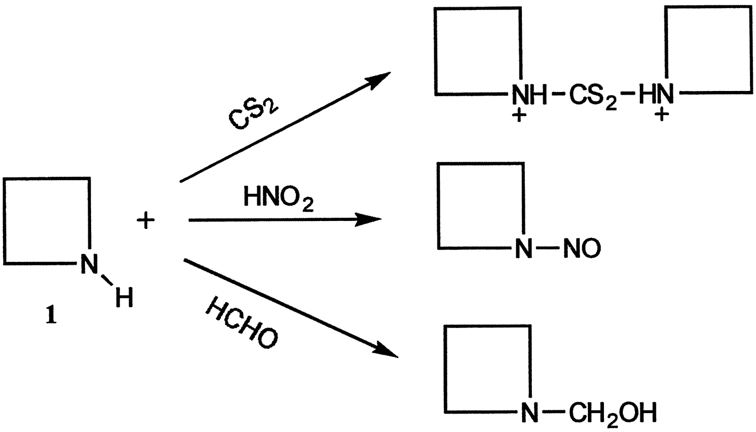


Scheme-8

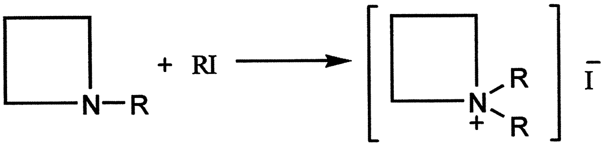
1.1.3.2 Functionalization at Nitrogen

Azetidine behaves like secondary aliphatic amines and undergoes similar reactions. The reaction with carbon disulfide forms a salt and with nitrous acid gives N-nitrosoazetidine. The reaction with formaldehyde provides N-hydroxymethyl-azetidine (scheme-9).

N-Alkylazetidine reacts similarly as tertiary amine and forms quaternary salt (scheme-10).



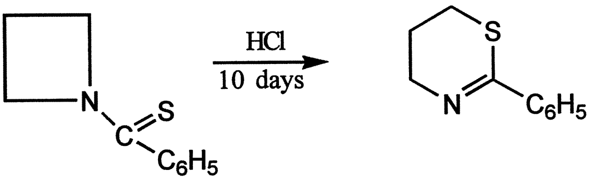
Scheme-9



Scheme-10

1.1.3.3 Rearrangements

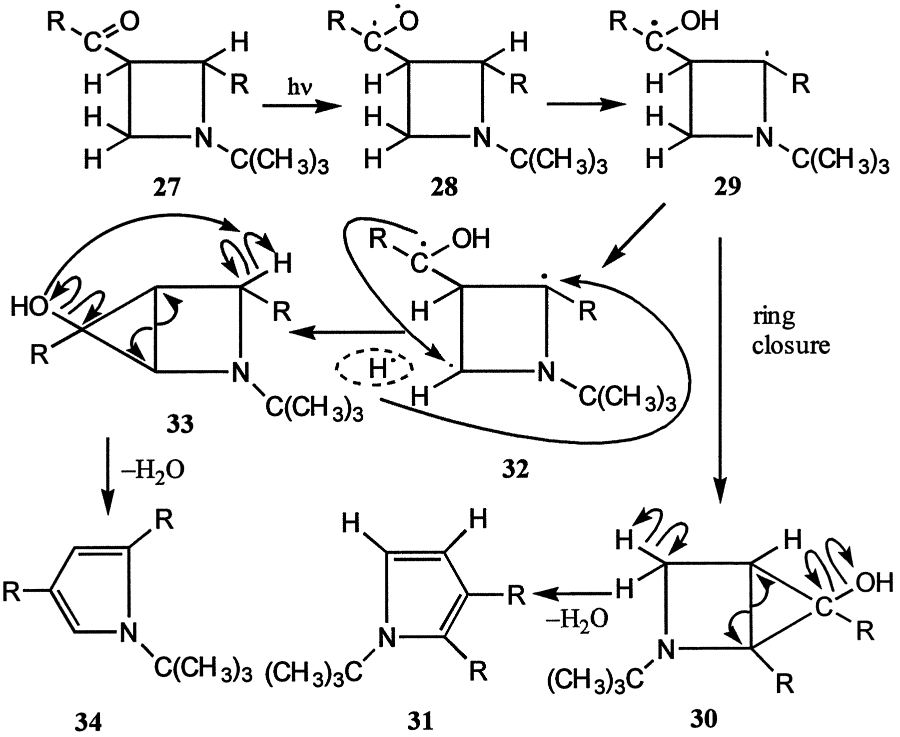
Azetidines undergo rearrangement reactions similar to three-membered aziridines. Since less relief of strain is involved in the ring opening reaction of azetidine, more severe reaction conditions are required (scheme-11).



25 **26**

Scheme-11

Azetidine ketones **27** undergo photochemical rearrangement resulting in ring expansion to pyrroles **31** and **34** (scheme-12)[11]. The reaction proceeds to involve intramolecular hydrogen shift with the generation of 1,3-biradical intermediate **29** which undergoes ring closure to form bicyclic unstable compounds **30** and **33** which, in turn, finally lead to the formation of pyrroles **31** and **34**, respectively with the loss of water molecules.



Scheme-12

1.2 Azetidinones (β-Lactams)

1.2.1 General

Azetidinones[13,14] are the carbonyl derivatives of azetidines containing carbonyl group at the position-2. These are also known as 2-azetidinones or more commonly β-lactams **35**. Azetidinone or β-lactam chemistry is of great importance because of the use of β-lactam derivatives as antibacterial agents[15,16].

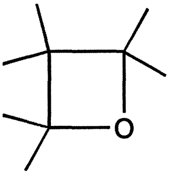
2 FOUR-MEMBERED OXAHETEROCYCLES

2.1 Oxetanes

2.1.1 General

Four-membered saturated heterocycles containing oxygen as heteroatom are known as oxetanes **2**[56]. These are also named as oxacyclobutanes assigning position-1 to the oxygen atom.

Oxetane ring is planar, contrary to the puckered cyclobutane ring, because the replacement of the methylene group by a divalent oxygen atom causes the reduction in the number of non-bonding interactions between the neighbouring hydrogen atoms.



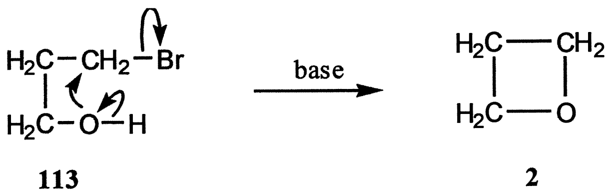
2

The C–C bond length (1.54Å) is greater than the C–O bond length (1.46Å), thus indicating the molecule not to be perfect square. The higher calculated value of the dipole moment of oxetane (2.01D) than that of ether (1.22D) or dimethyl ether (1.31D) indicates more electron density at the oxygen atom in oxetane than in acyclic aliphatic ethers. Oxygen atom in oxetane can donate electrons much more easily than in three-membered oxirane.

2.1.2 Synthesis

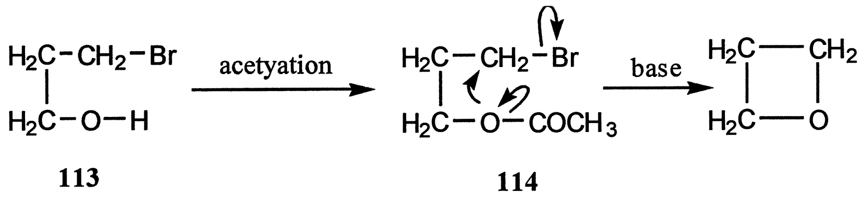
2.1.2.1 Intramolecular Cyclization

Oxetanes are prepared by the intramolecular cyclization of 1,3-halohydrins **113** in the presence of a base (scheme-39)[57,58].

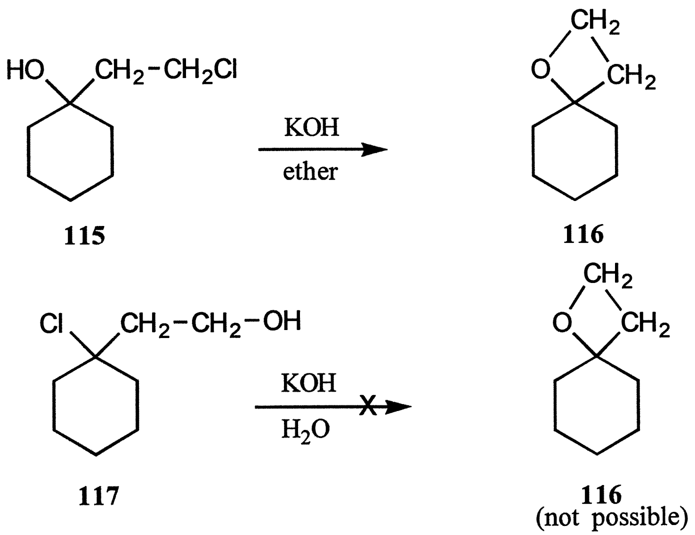


Scheme-39

The rate of cyclization is very low, but prior acetylation of 1,3-halohydrin accelerates intramolecular cyclization. The acetyl group is supposed to limit the concentration of alkoxide ions and favours cyclization rather than intramolecular polymerization (scheme-40).

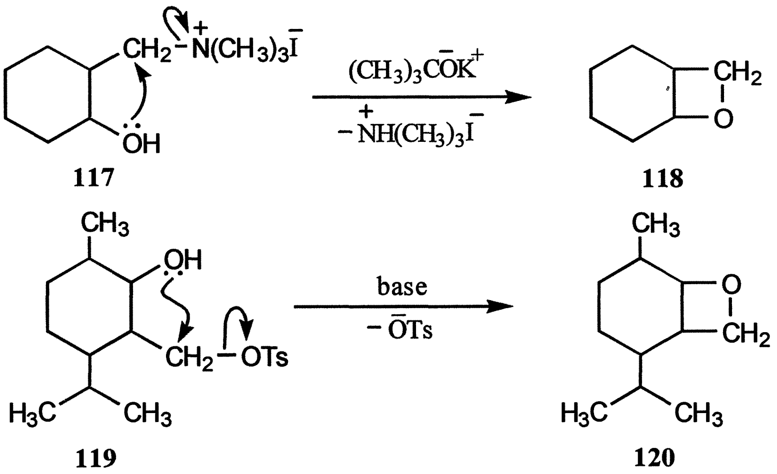


Scheme-40



Scheme-41

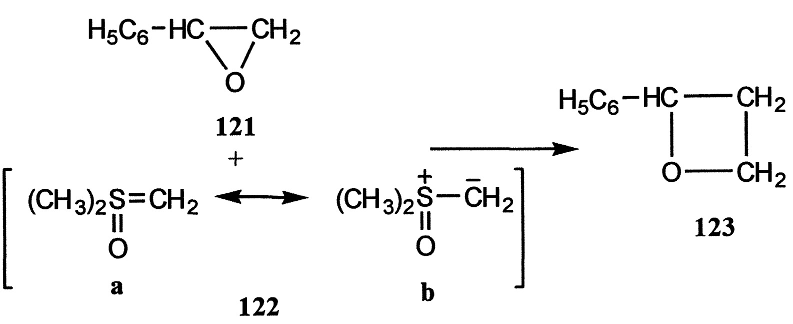
The rate of cyclization is markedly influenced by the presence of substituents and their positions of the attachment. The presence of an alkyl group at the carbon atom bearing –OH group enhances the rate of cyclization, while an alkyl substituent at carbon atom bearing halogen atom retards the rate of cyclization and causes difficulty in the formation of oxetane (scheme-41) as the elimination predominates over cyclization[59,60]. Trimethylamino- or tosylate group can also be used as leaving group in place of halogen in the intramolecular cyclization reactions (scheme-42).



Scheme-42

2.1.2.2 Methylene Insertion Reaction

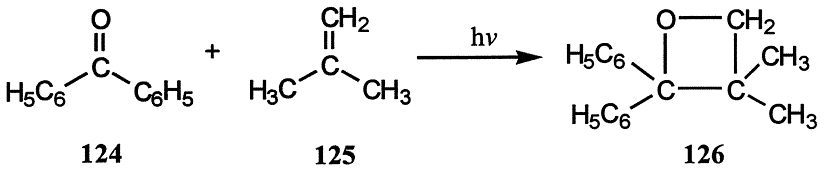
The reaction of oxiranes **121** with sulfur ylides **122** provides oxetanes **123** involving methylene insertion from the less hindered side (scheme-43)[61].



Scheme-43

2.1.2.3 Photochemical Cycloaddition

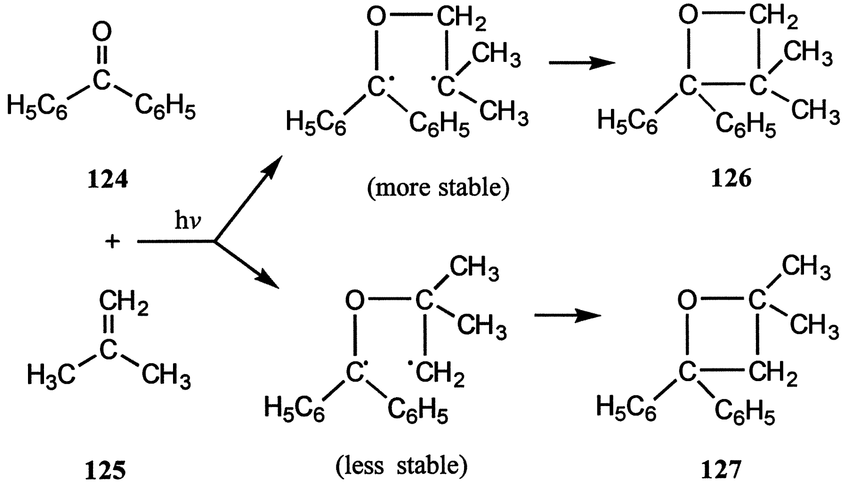
Photochemical [2 + 2] cycloaddition of carbonyl compounds to olefins gives oxetanes. This reaction is known as Paterno–Büchi reaction (scheme-44)[62-66].



Scheme-44

The mechanism of this reaction involves the addition of an excited state of the carbonyl compound (the singlet or triplet state formed by *n*→π* transition) to olefins[67].

The stereochemistry of this photocycloaddition has been proposed to involve the formation of a diradical intermediate by the interaction of electron-deficient carbonyl lone pair orbital with the π-orbitals of electron-rich olefin. The product **126** formed by subsequent cyclization of more stable biradical predominates (scheme-45).



Scheme-45

2.1.3 Reactions

The oxetane ring is less strained than the three-membered oxirane ring. However, its chemical properties are similar to those of oxirane in many respects.

2.1.3.1 Ring Opening Reactions

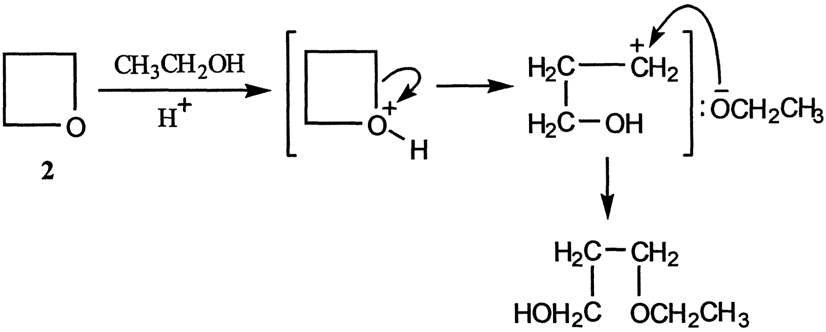
2.1.3.1.1 Electrophilic Ring Opening Reactions

Oxetanes are susceptible to the attack by electrophiles. Although the structure and hybridizations of the oxetane and oxirane rings are fundamentally different, the reactivity of two ring systems is identical under acidic conditions. The lesser degree of strain in oxetane as compared in oxirane can be compensated for the greater electron donor capability of the oxygen atom in oxetane.

Oxetane readily undergoes ring opening reaction under acidic conditions (scheme-46). But in unsymmetrically substituted oxetane, the direction of ring cleavage depends on the 'push-pull' mechanism and generally two products are formed (scheme-47).

The formation of two products can be explained by the formation of oxonium ion as an intermediate which is attacked both at C-2 and C-4, preferably at the least hindered α-carbon atom (scheme-48)[68-71].

The oxonium ion intermediate does not undergo ring opening to form a stable carbonium ion but directs the attack preferably at the least hindered carbon atom. The presence of carbonium ion stabilizing groups can override this effect and the reaction proceeds to form a single product involving pull-mechanism (scheme-49).



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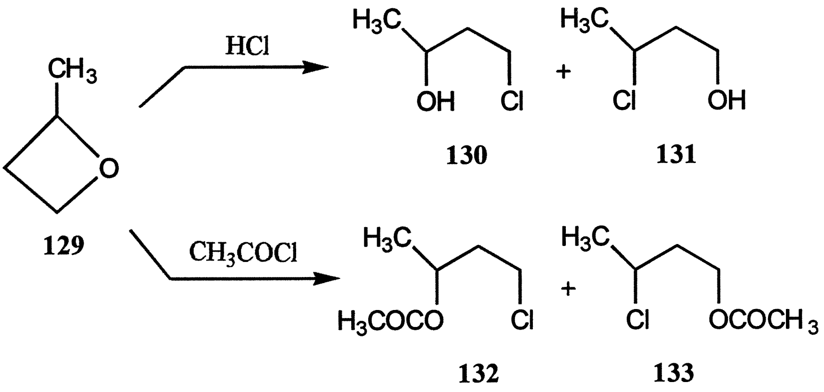
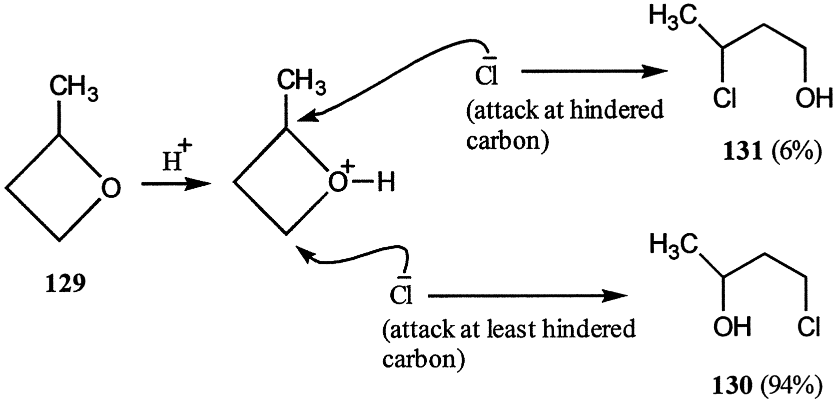
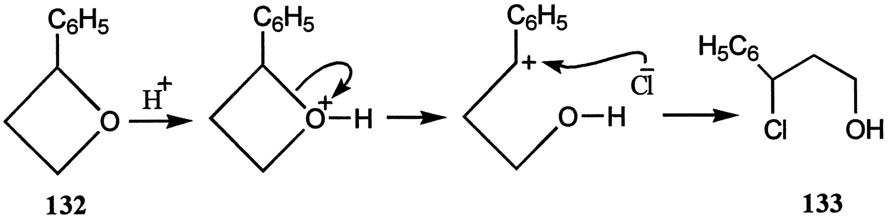
Scheme-46



Scheme-47

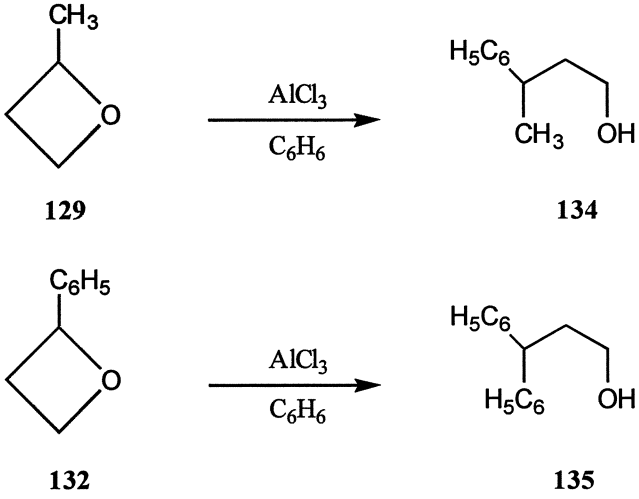


Scheme-48



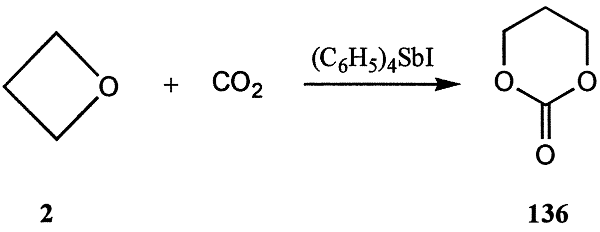
Scheme-49

The formation of single products in Friedel–Crafts reaction of 2-methyloxetane and 2-phenyloxetane is due to the generation of stabilized carbonium ions (scheme-50).



Scheme-50

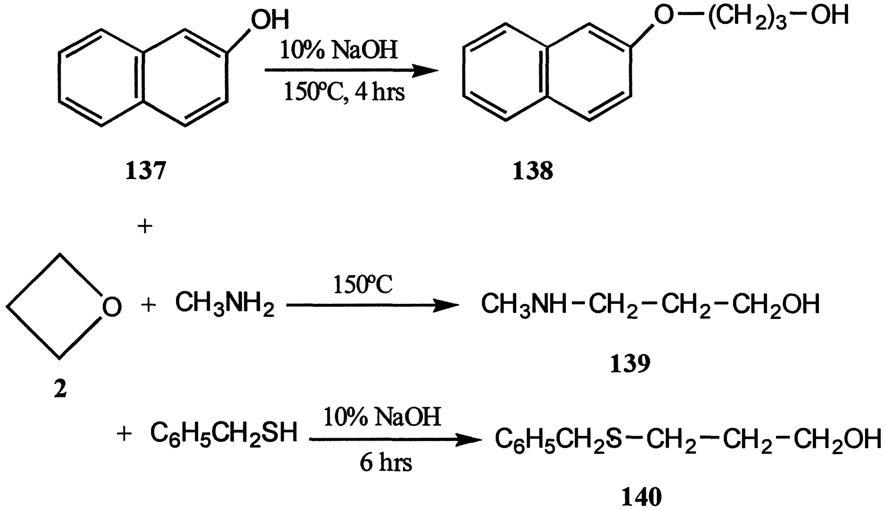
Oxetane also reacts with carbon dioxide in the presence of tetraphenylantimony iodide providing trimethylene carbonate (scheme-51).



Scheme-51

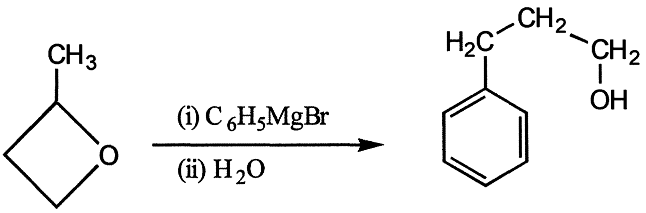
2.1.3.1.2 Nucleophilic Ring Opening Reactions

Four-membered heterocycles react with nucleophiles at considerably reduced rates as compared to three-membered analogs and, therefore, the cleavage of oxetane ring requires generally more vigorous conditions than those for the ring opening of oxirane. There is less contribution of the leaving group in the ring cleavage reactions which require strong nucleophilic reagents and the reaction occurs by SN^2 or push mechanism (scheme-52).



Scheme-52

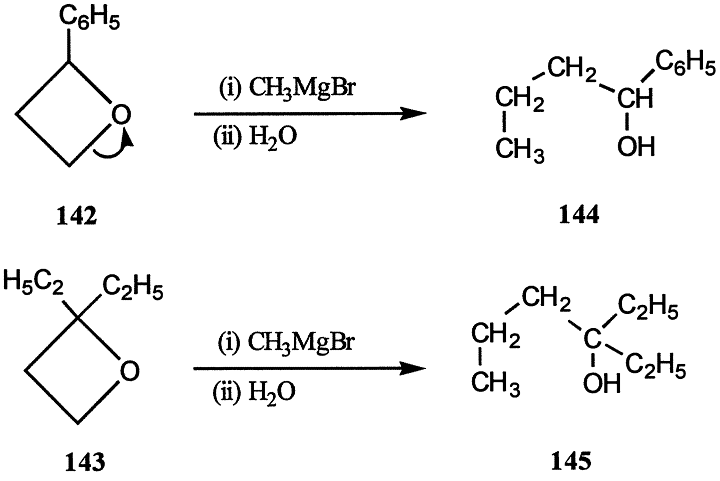
Oxetane reacts with Grignard reagents at higher temperature with the lengthening of carbon chain (scheme-53). If unsymmetrical oxetane is involved, the less



2 **141**

Scheme-53

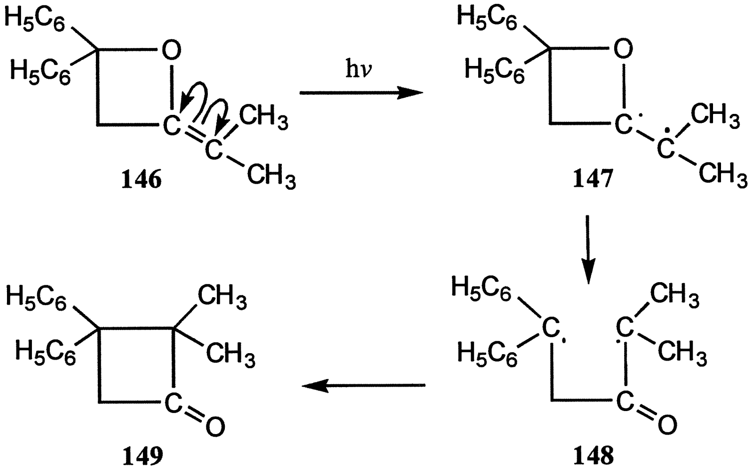
substituted carbon atom attached to the oxygen atom is attacked by nucleophile and the formation of single product predominates (scheme-54).



Scheme-54

2.1.3.2 Photochemical Reactions

Oxetanes **146** substituted with chromophoric substituents undergo photochemical transformations providing rearranged products **149** (scheme-55)[64,65].



Scheme-55