

The Chemistry of Heterocycles

Structure, Reactions, Syntheses, and Applications

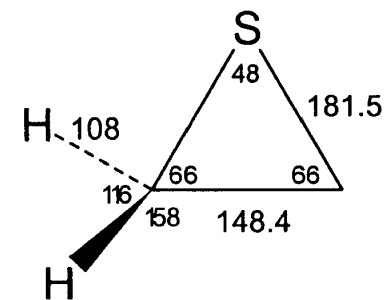
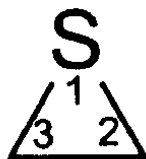
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The Chemistry of Heterocycles, (Second Edition).

By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Verlag GmbH, 2003

3.2 Thiirane

[A] Thiiranes are also known as episulfides. As a result of the greater atomic radius of the S-atom, the three atoms form an acute-angled triangle.



Structure of thiirane
(bond lengths in pm, bond angles in degrees)

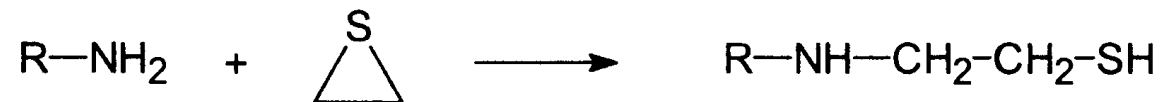
The thermochemically determined strain enthalpy of thiirane of 83 kJ mol⁻¹ is less than that of oxirane. The ionization potential amounts to 9.05 eV, the dipole moment to 1.66 D. Both values are below those of oxirane. The chemical shifts in the NMR spectra are $\delta_{\text{H}} = 2.27$, $\delta_{\text{C}} = 18.1$.

[B] The properties of the thiiranes are primarily due to ring strain. In spite of the smaller strain enthalpy, thiirane is thermally less stable than oxirane. Even at room temperature, linear macromolecules are formed because of polymerization of ring-opened products.

Substituted thiiranes are thermally more stable. The following reactions are typical for thiiranes:

Ring-opening by nucleophiles

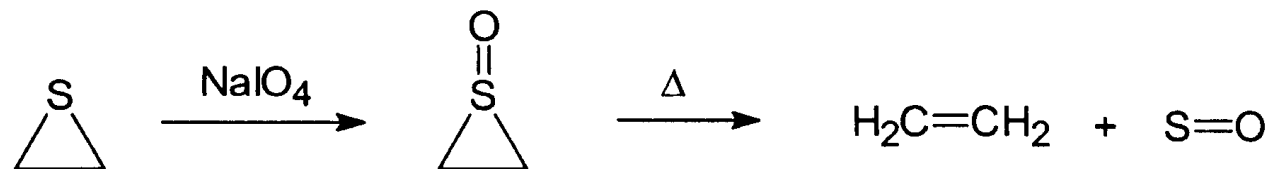
Ammonia, or primary or secondary amines, react with thiiranes to give β -amino thioles:



The mechanism is the same as described for oxiranes. However, the yields are lower, due to competing polymerization. Concentrated hydrochloric acid reacts with thiiranes to give β -chlorothioles (protonation on the S-atom and ring-opening by the nucleophilic chloride ion).

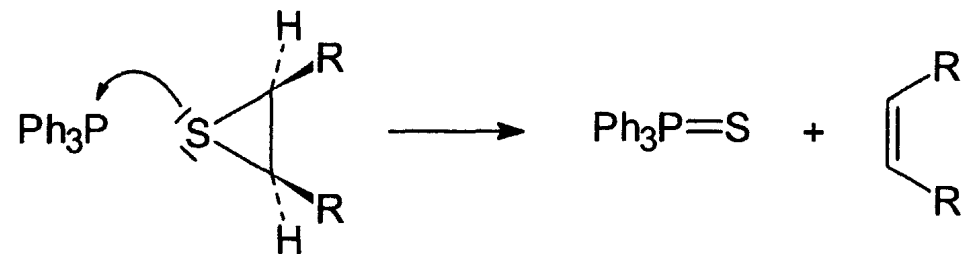
Oxidation

Thiiranes are oxidized by sodium periodate or peroxy acids to give thiirane oxides. They decompose at higher temperature into alkenes and sulfur monoxide:



Desulfurization to alkenes

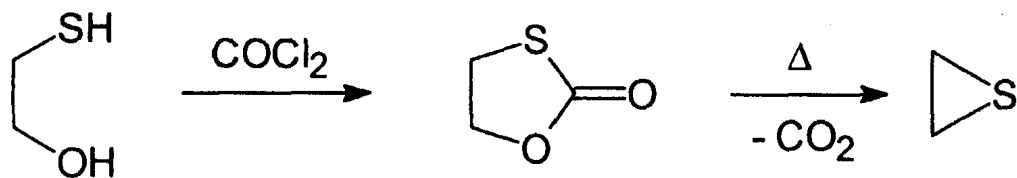
Triphenylphosphane, as well as trialkyl phosphites, have proved to be reliable reagents for this purpose. The reaction is **stereospecific**. *Cis*-thiiranes yield (*Z*)-olefins and *trans*-thiiranes yield (*E*)-olefins. The electrophilic attack of the trivalent phosphorus on the heteroatom is different from that described previously. Metallic reagents, e.g. *n*-butyllithium, also bring about a stereospecific desulfurization of thiiranes.



[C] The synthesis of thiiranes starting from β -substituted thioles and oxiranes can be achieved as follows.

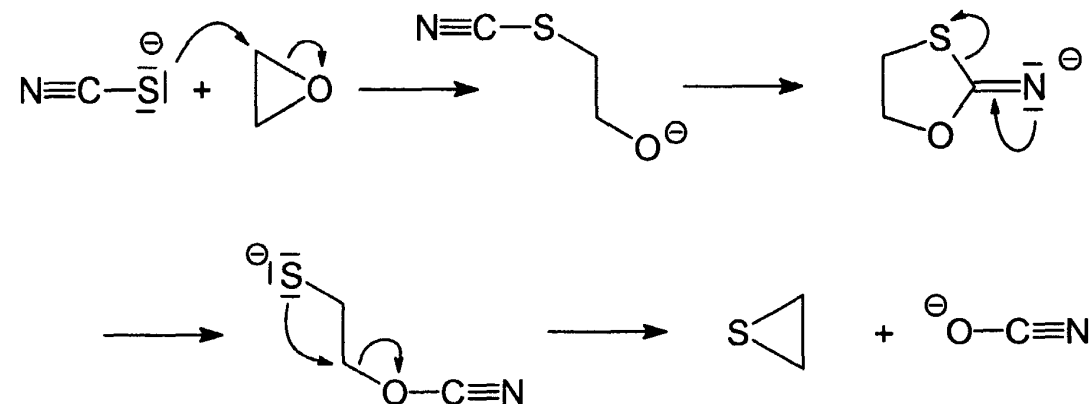
(1) Cyclization of β -substituted thioles

By analogy with the oxirane synthesis, halothiols react with bases to give thiiranes. β -Acetoxythiols also yield thiiranes under similar conditions. 2-Sulfanylethanol reacts with phosgene in the presence of pyridine to give 1,3-oxathiolan-2-one, which on heating to 200 °C decarboxylates to give thiirane.



(2) Ring transformation of oxiranes

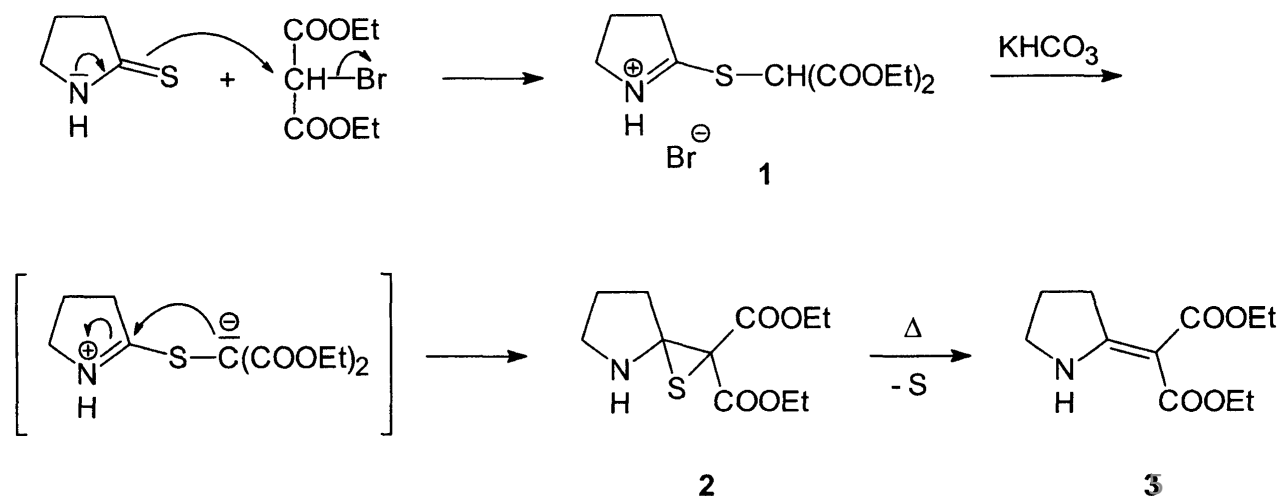
Conversion of one heterocyclic system into another is known as ring transformation. Oxiranes react with aqueous ethanolic potassium rhodate to give thiiranes, probably according to the following mechanism:



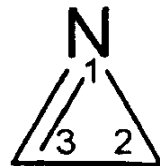
[D] Thiirane (ethylene sulfide) is a colorless liquid, sparingly soluble in water and of bp 55°C .

[E] A method for C-C coupling, which is based on closing a thiirane ring and opening it by desulfurization, is known as sulfide contraction after ESCHENMOSER.

Pyrrolidine-2-thione is S-alkylated with bromomalononic diethyl ester. On treatment with a solution of KHCO_3 , the resulting iminium salt **1** yields a thiirane **2** which desulfurizes at 60°C to give **3**.



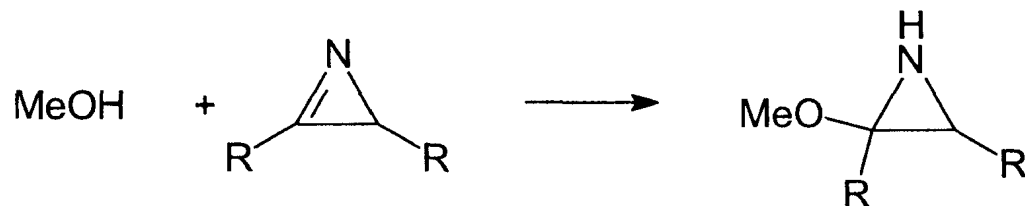
3.3 2*H*-Azirine



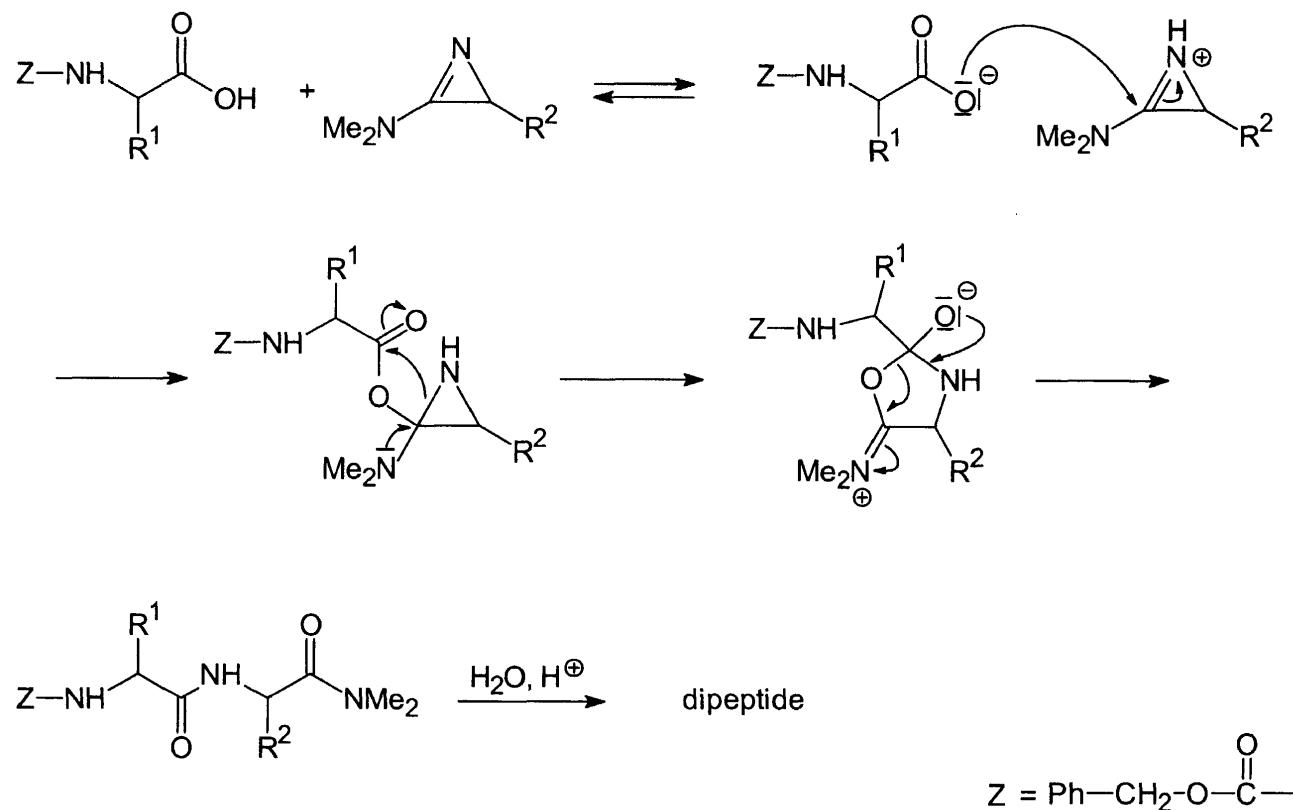
[A] Unlike 1*H*-azirine, 2*H*-azirines can be used preparatively, although the ring strain is substantially greater than that of the saturated three-membered heterocycles. The ring strain enthalpy amounts to approximately 170 kJ mol⁻¹.

[B] 2*H*-Azirine is thermally unstable and has to be stored at very low temperatures. Substituted 2*H*-azirines are more stable. They are liquids or low melting solids. Their basicity is substantially lower than that of comparable aliphatic compounds. For instance, 2-methyl-3-phenyl-2*H*-azirine is not soluble in hydrochloric acid.

The ring strain endows the C=N double bond with an exceptionally high reactivity. Electrophilic reagents attack the N-atom, nucleophilic reagents the C-atom. For example, methanol added in the presence of a catalytic amount of sodium methoxide produces 2-methoxyaziridines:



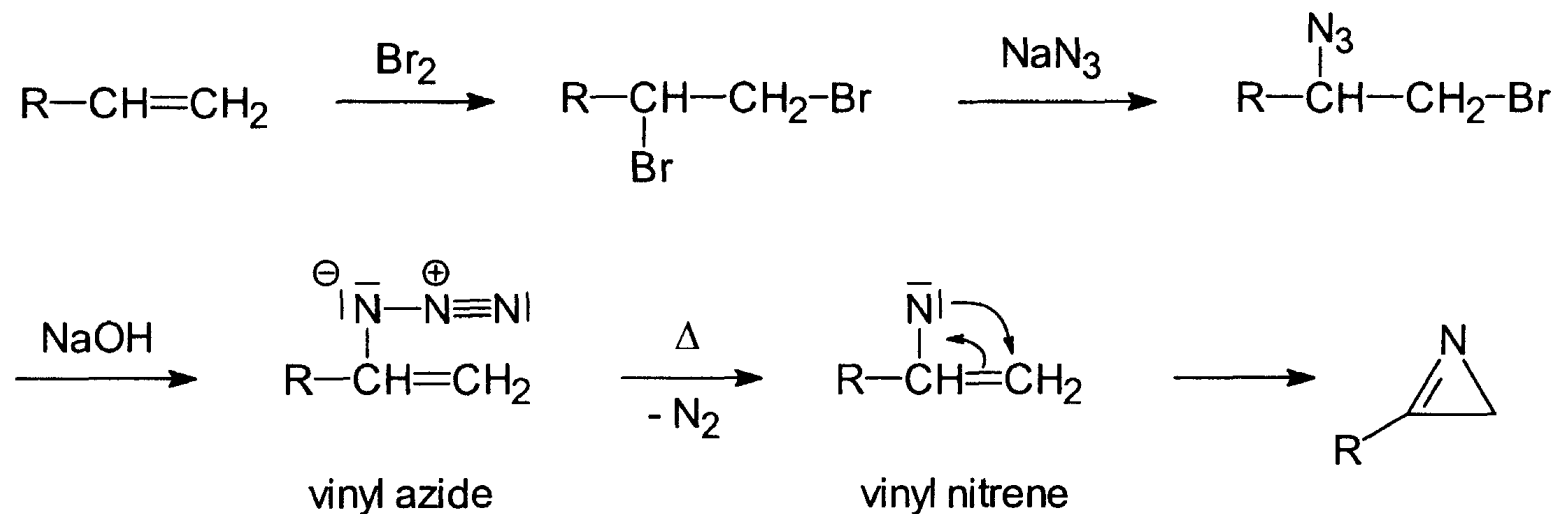
Carboxylic acids also add to the C=N double bond and the products rearrange to more stable compounds with opening of the aziridine ring. A method for peptide synthesis is based on these reactions:



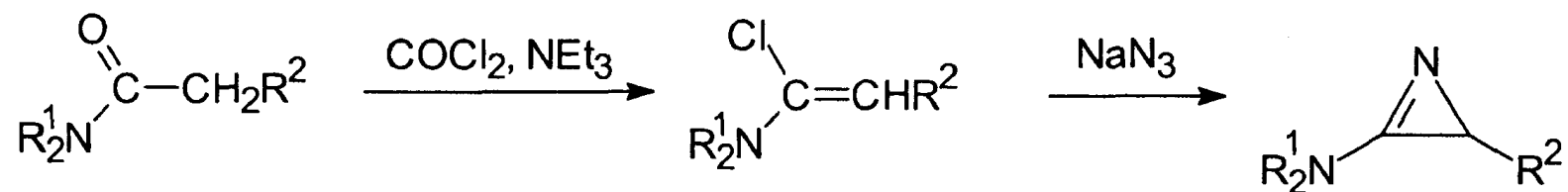
For instance, when the carboxyl group of an *N*-(benzyloxycarbonyl)amino acid reacts with a 2-substituted or a 2,2-disubstituted 3-(dimethylamino)-2*H*-azirine in diethyl ether at room temperature, the *N,N*-dimethylamide of the dipeptide is obtained quantitatively. Its hydrolysis with 3N hydrochloric acid yields the *N*-(benzyloxycarbonyl)dipeptide.

2*H*-Azirines undergo cycloadditions. They react, for instance, as dienophiles in [4+2] cycloadditions.

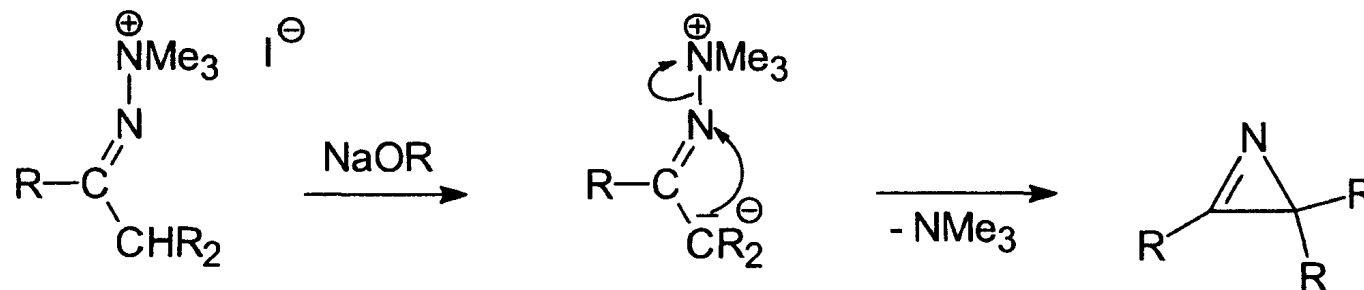
[C] 2*H*-Azirines are prepared by thermolysis or photolysis of vinyl azides, which are obtainable from alkenes. The dediazoniation of the vinyl azide proceeds via vinyl nitrene.



A variant of this synthesis enables the preparation of 3-(dialkylamino)-2*H*-azirines starting from *N,N*-disubstituted acid amides:

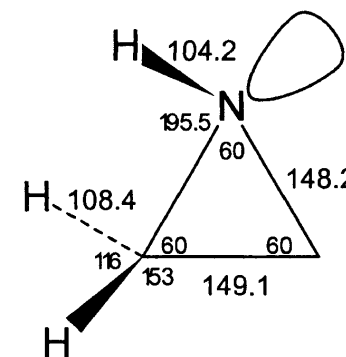
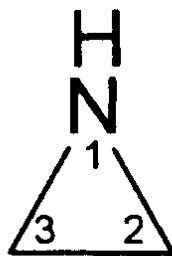


The methyl iodides of dimethyl hydrazones furnish *2H*-azirines when treated with bases such as sodium propoxide:



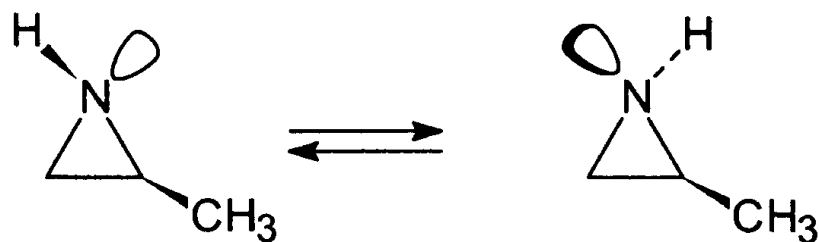
3.4 Aziridine

[A] Aziridine was once known as ethylene imine. Bond lengths and bond angles are essentially the same as those in oxirane. The plane in which the N-atom, its nonbonding electron pair and the N-H bond are situated is perpendicular to the plane of the aziridine ring.



Structure of aziridine
(Bond lengths in pm, bond angles in degrees)

2-Methylaziridine would be expected, therefore, to display diastereoisomerism. Trivalent N-atoms are, however, liable to pyramidal inversion.



Although the activation enthalpy of this process $\Delta G^* = 70 \text{ kJ mol}^{-1}$, i.e. substantially greater than with a secondary aliphatic amine, inversion occurs so rapidly at room temperature that the diastereoisomers are not separable. However, in the case of 1-chloro-2-methylaziridine, where $\Delta G^* = 112 \text{ kJ mol}^{-1}$, the mixture of stereoisomers can be separated.

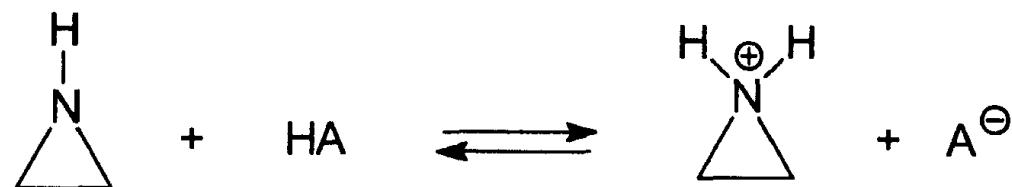
The strain enthalpy of aziridine determined thermochemically amounts to 113 kJ mol^{-1} and is, therefore, almost identical to that of oxirane. The ionization potential was found to be 9.8 eV and the excited electron derives from the nonbonding electron pair of the N-atom.

The dipole moment of 1.89 D is almost the same as that of oxirane. The chemical shifts in the NMR spectra are $\delta_{\text{H}} = 1.5 \text{ (CH)}$, 1.0 (NH) and $\delta_{\text{C}} = 18.2$.

[B] Care is advisable when handling aziridines, because many show considerable toxicity. The following reactions are of importance:

Acid base reactions

Aziridines unsubstituted on the N-atom behave like secondary amines; *N*-substituted aziridines behave like tertiary amines. They react with acids to give aziridinium salts:

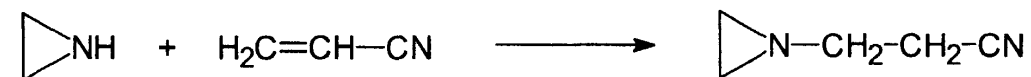
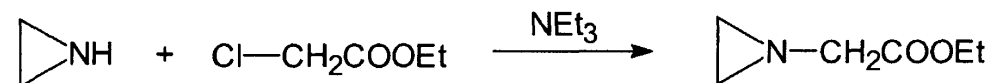


The pK_a value of the aziridinium ion is 7.98. Aziridine is thus a weaker base than dimethylamine ($pK_a = 10.87$), but stronger than aniline ($pK_a = 4.62$).

The aziridine ring is destabilized by salt formation, and ring-opening by nucleophiles is favored. Aziridine itself reacts with acids explosively to give polymeric products.

Reactions with electrophilic reagents

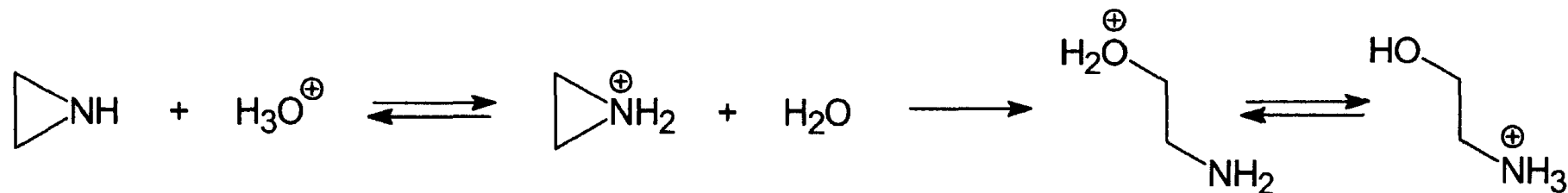
Aziridines, like amines, are nucleophiles and react with electrophiles. A nucleophilic substitution on a saturated C-atom and a nucleophilic addition to an alkene bearing an acceptor group serve as examples:



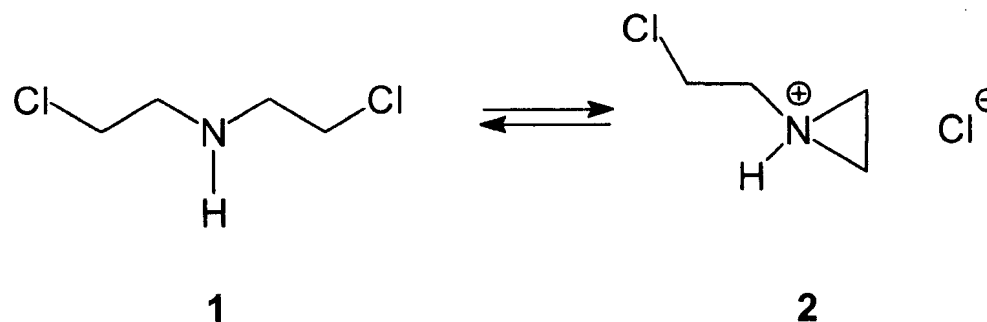
Ring-opening by nucleophiles

Ammonia and primary amines react with aziridines to give 1,2-diamines. The mechanism and the stereochemistry of this reaction are similar to the corresponding reactions of the oxiranes.

The ring-opening of the aziridines is catalyzed especially effectively by acids (A2 mechanism). The acid-catalyzed hydrolysis to give amino alcohols serves as an example:



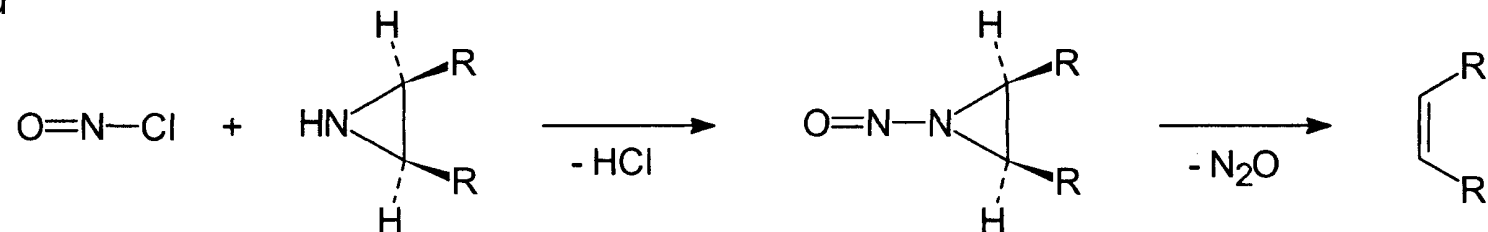
Such reactions can also be interpreted as alkylation of the nucleophile. This explains the cytostatic and anti-tumor action of aziridines and of bis(2-chloroethyl)amine **1**. An equilibrium exists between **1** and 1-(2-chloroethyl)aziridinium chloride **2**.



Nucleophilic cell components, e.g. the amino groups of the guanine bases in DNA, are alkylated by the aziridinium ion as a result of a nucleophilic ring-opening. In the case of bis(2-chloroethyl)amine, the reaction can be repeated on a guanine base of the other DNA strand of the double helix. This results in cross-linking of the two DNA strands and consequently blocks replication.

Deamination to alkenes

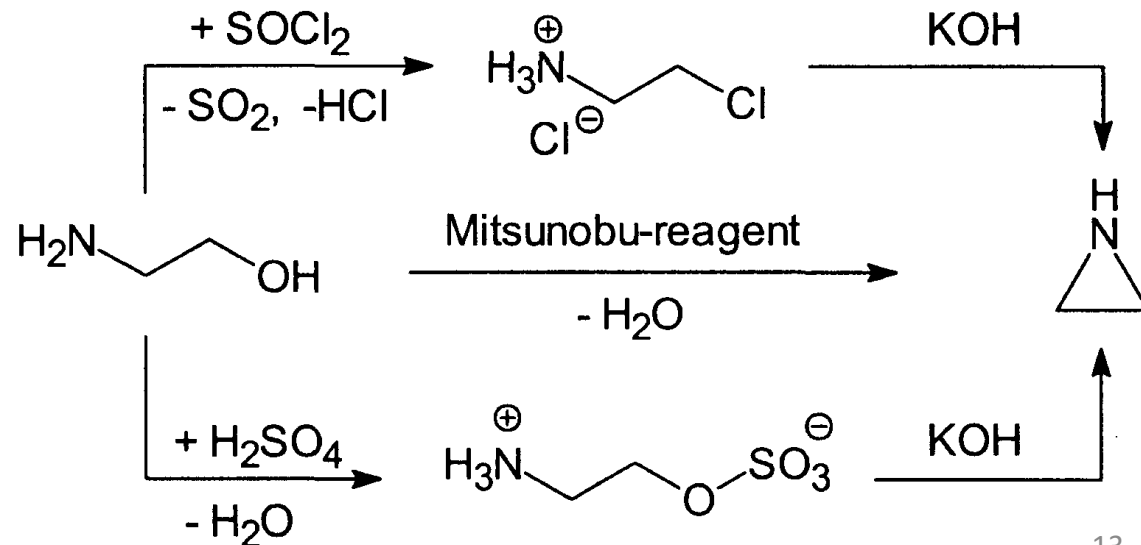
Aziridines with an unsubstituted N-atom are stereospecifically deaminated by nitrosyl chloride via the corresponding *N*-nitroso compound:



[C] The synthesis of aziridines can be achieved from substituted amines or alkenes.

(1) Cyclization of β -substituted amines

β -Amino alcohols, which are conveniently made from oxiranes with ammonia or amines, react with thionyl chloride to give chloroamines, which can be cyclized to aziridines by alkali hydroxide (GABRIEL 1888).



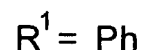
Sulfate esters, obtained from amino alcohols and sulfuric acid, when treated with alkali also form aziridines (WENKER 1935).

In both cases, the amine is liberated from the ammonium salts by the base. The leaving group Cl or OSO_3^- is substituted intramolecularly by the amino group on the β -C-atom.

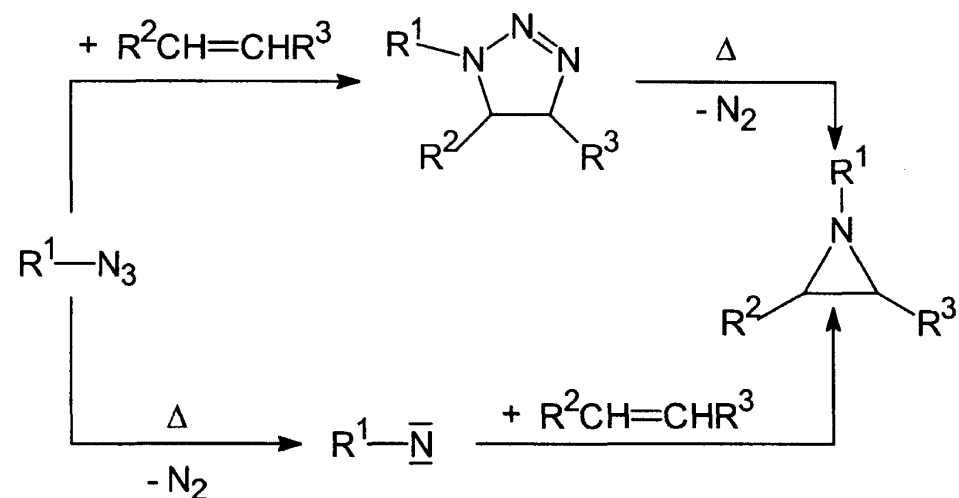
The direct cyclodehydration of β -amino alcohols can be effected with the MITSUNOBU reagent (triphenylphosphane/diethyl azodicarboxylate).

(2) Thermal or photochemical reaction of azides with alkenes

Phenyl azide reacts with alkenes to give 4,5-dihydro-1,2,3-triazoles (1,3-dipolar cycloaddition), which are thermally or photochemically converted into aziridines through loss of nitrogen:

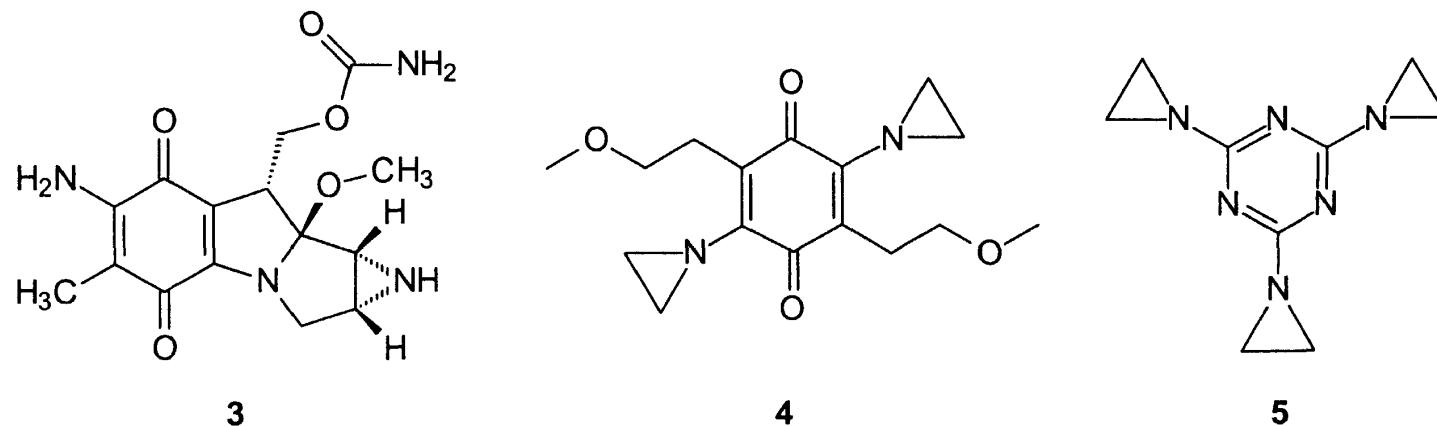


Thermolysis of ethyl azidoformate, however, produces ethoxycarbonylnitrene, which by a [2+1] cycloaddition reacts with alkenes to form aziridines. The mechanism is thus influenced by the azide substituent R^1 .



[D] Aziridine, a colorless, water-soluble, poisonous liquid (bp 57 °C) of ammoniacal odor is relatively stable, thermally, but is best stored in a refrigerator over sodium hydroxide.

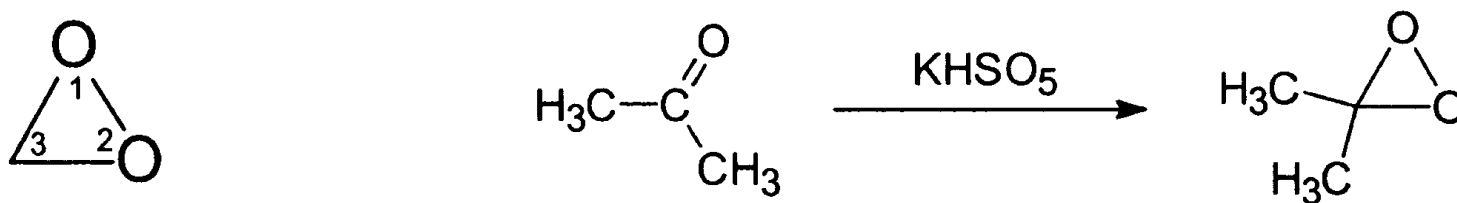
Some natural products contain an aziridine ring, e.g. mitomycins (**3**: mitomycin C). This is responsible for the cytostatic and anti-tumor activity of these antibiotics. Many synthetic aziridines have been screened for their anti-tumor activity. Some have reached the clinic, especially as anti-leukaemic agents, e.g. **4** and **5**.



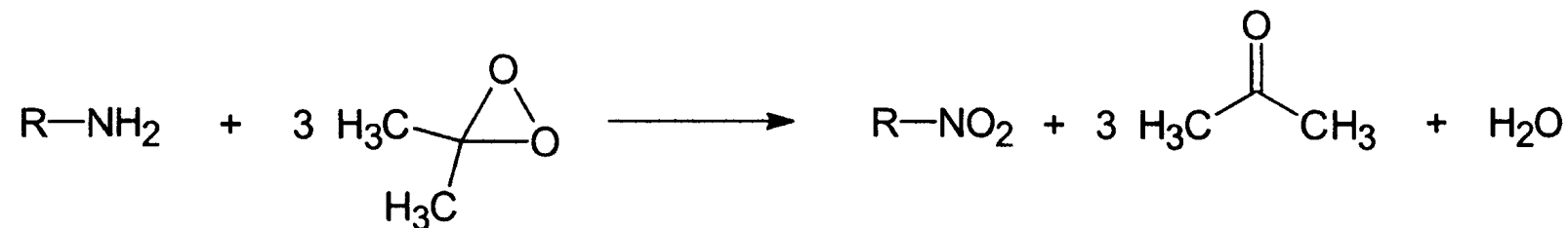
[E] Aziridines with C2 symmetry have been used successfully as chiral auxiliaries for alkylations and aldol reactions.

3.5 Dioxirane

[A-C] Dioxiranes have been available only since the mid-eighties. They are synthesized by oxidation of ketones with potassium hydrogen peroxysulfate (oxone®), e.g.:

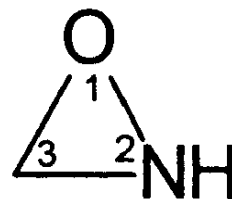


Dimethyldioxirane, together with acetone, is removed from the reaction vessel by distillation. The yellow 0.1-0.2 M solution can be used as an oxidizing agent, e.g. for the epoxidation of olefins, for the oxidation of enolates to α -hydroxycarbonyl compounds and for the oxidation of primary amines into nitro compounds:



Boron trifluoride catalyzes the isomerization of dimethyldioxiranes to methyl acetate. Difluorooxirane is formed as a pale-yellow, normally stable gas when an equimolar mixture of FCO_2F and ClF is passed over a CsF catalyst.

3.6 Oxaziridine



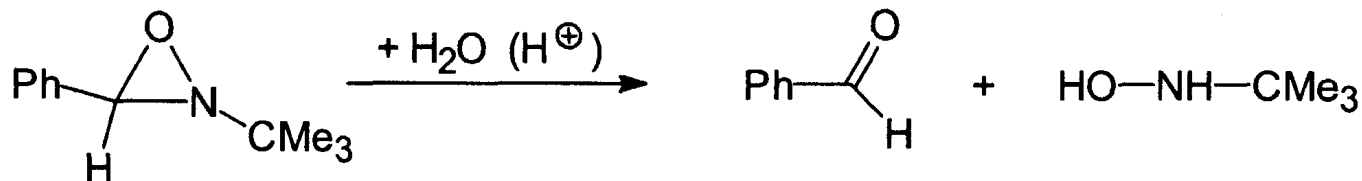
[A,B] Oxaziridines are structural isomers of oximes and nitrones. Trialkyl oxaziridines are colorless liquids, sparingly soluble in water. The following reactions are typical for oxaziridine.

Isomerization to nitrones

As a reversal to the photoisomerization of nitrones, oxaziridines can be converted into nitrones by thermolysis. The required temperature depends on the type of oxaziridine substituents.

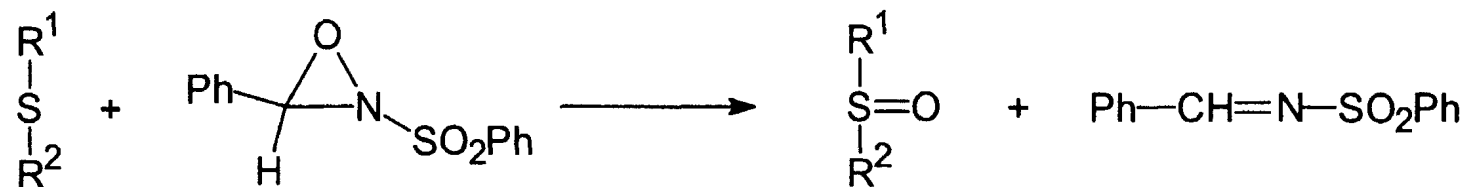
Ring-opening by nucleophiles

On acid-catalyzed hydrolysis, 2-alkyl-3-phenyloxaziridines yield benzaldehyde and *N*-alkylhydroxylamines, e.g.:



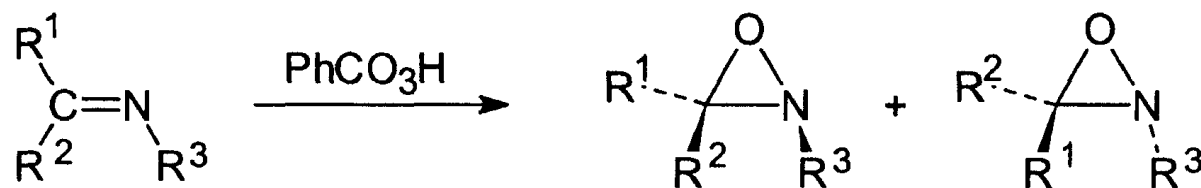
Reduction to imines

Oxaziridines, particularly 2-(phenylsulfonyl)oxaziridines, are used as reagents in a number of oxidation procedures. The oxidation of sulfides to sulfoxides may serve as an example:



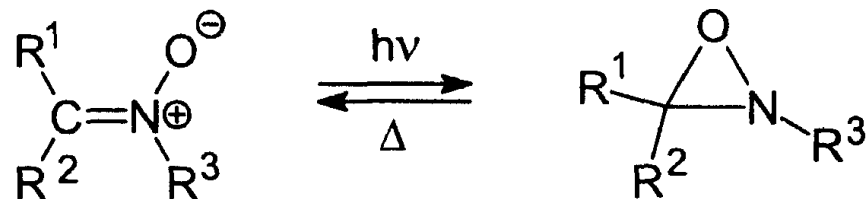
[C] The synthesis of oxaziridines can be accomplished from imines, nitrones or carbonyl compounds:

(1) Oxidation of imines with peroxy acids:



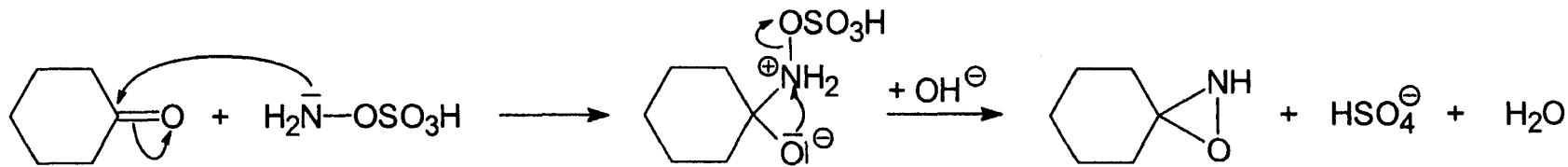
As in the epoxidation of alkenes, a stereospecific *cis*-addition is involved. In the case of 2-substituted oxaziridines ($\Delta G^\ddagger = 100\text{--}130 \text{ kJ mol}^{-1}$), the activation enthalpy of the pyramidal inversion of the N-atom is so high that the configuration of the N-atom is fixed at room temperature. Thus, the configuration of the starting material is preserved and the racemate of one of the diastereoisomeric oxaziridines is formed. In the case of chiral imines or chiral peroxy acids, the reaction proceeds enantioselectively.

(2) Photoisomerization of nitrones:

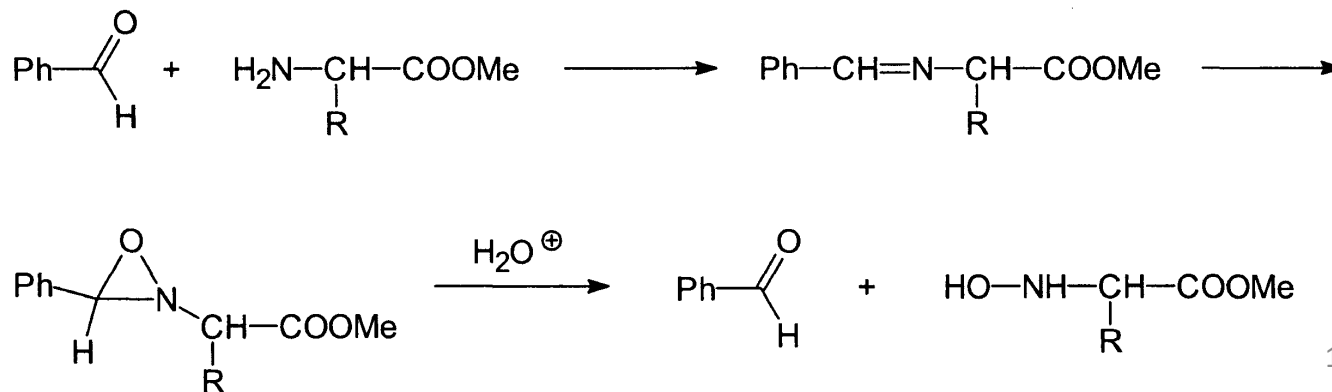


(3) Amination of carbonyl compounds:

In the presence of a base, hydroxylamine-O-sulfonic acid or chloramine amine carbonyl compounds nucleophilically (SCHMITZ 1961). In this reaction, the intramolecular nucleophilic substitution occurs on an N-atom.



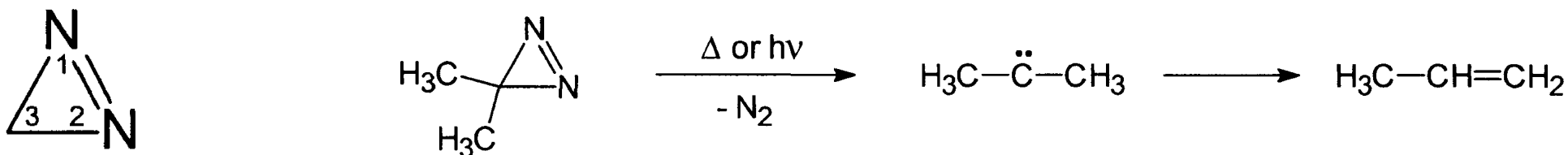
[E] Oxaziridines are oxidizing agents as well as important synthetic intermediates. For instance, *N*-hydroxyaminocarboxylic esters **2** can be prepared from α -aminocarboxylic acid esters with oxaziridines **1** as intermediates as follows:



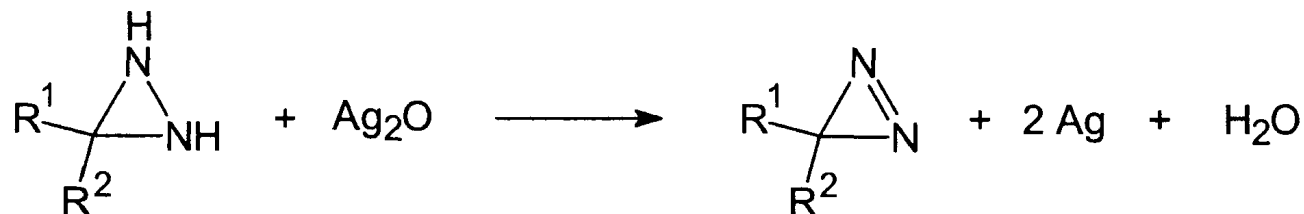
3.7 3*H*-Diazirine

[A-D] 3*H*-Diazirines are structural isomers of diazoalkanes. They are gases or colorless liquids, e.g. 3,3-dimethyldiazirine, bp 21 °C. Liquid 3*H*-diazirines can decompose explosively. Their basicity is very low. Unlike diazoalkanes, they react with acids only slowly, with the liberation of nitrogen.

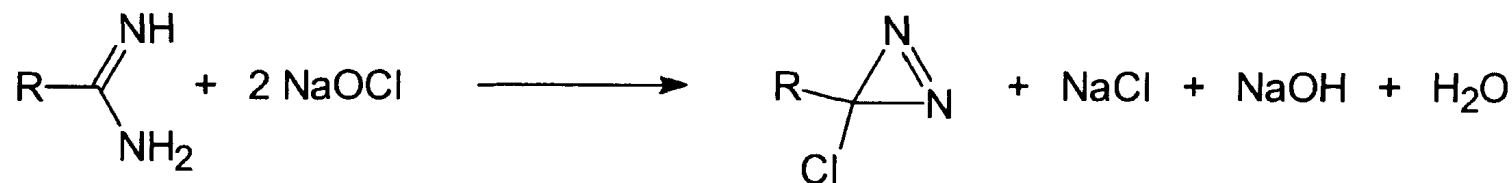
The dediazonation of 3*H*-diazirines can be effected thermally or photochemically. In the absence of carbene acceptors, the initially formed carbenes isomerize to give olefins, e.g.:



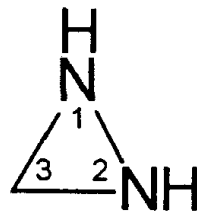
3*H*-Diazirines are prepared by oxidation of *N*-unsubstituted diaziridines with silver oxide or mercury oxide (PAULSEN 1960, SCHMITZ 1961)



3-Chloro-3*H*-diazirines are formed by oxidation of amidines with sodium hypochlorite:

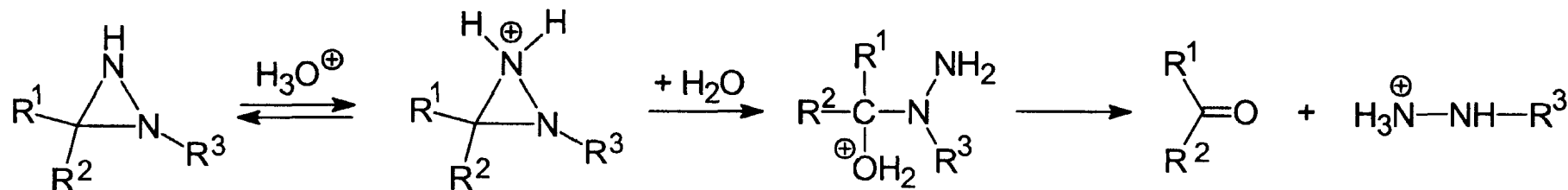


3.8 Diaziridine



[A-C] Diaziridines are crystalline, weakly basic compounds. As already explained in connection with oxaziridines, the N-atoms are configurationally stable so that stereoisomerism is possible.

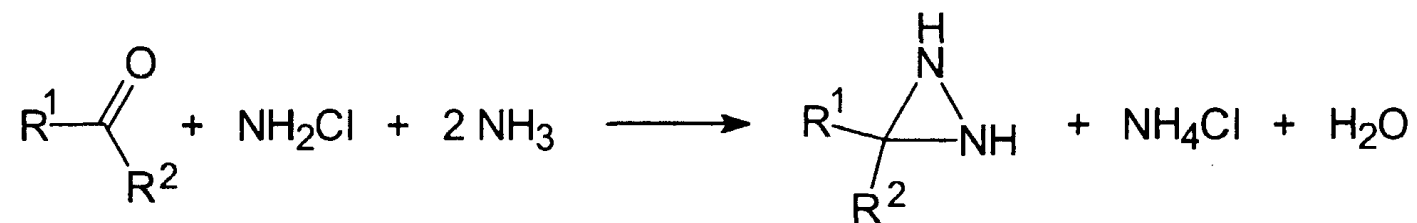
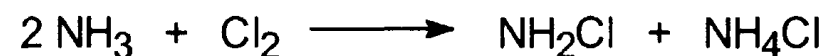
The acid-catalyzed hydrolysis of diaziridines yields ketones and hydrazines:



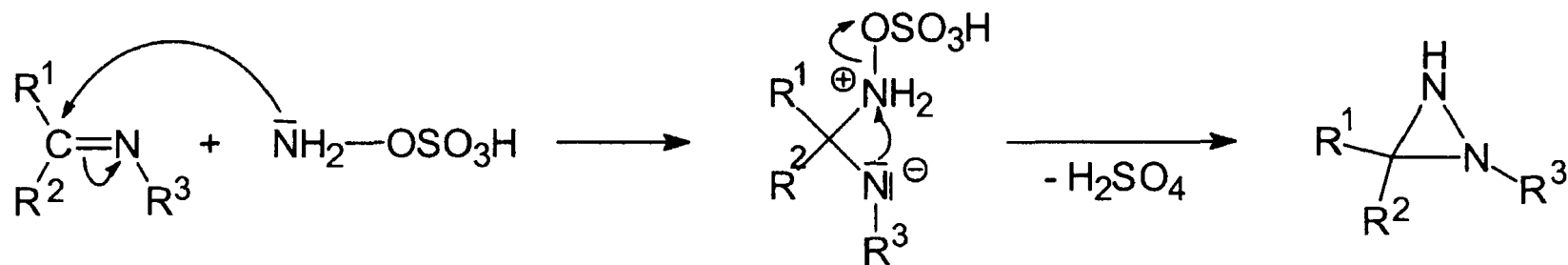
Thus, a synthesis of hydrazines is available starting from imines and hydroxylamine-*O*-sulfonic acid, or from *N*-substituted hydroxylamine-*O*-sulfonic acids.

Diaziridines unsubstituted on the N-atoms can be oxidized to give 3*H*-diazirines.

Diaziridines are prepared by the action of ammonia and chlorine on ketones (PAULSEN, SCHMITZ 1959). Initially, chloramine is formed:



The action of ammonia or primary amines and hydroxylamine-O-sulfonic acid upon ketones also yields diaziridines. Likewise, the amination of imines (azomethines) with hydroxylamine-O-sulfonic acid yields diaziridines:



Summary of the general chemistry of three-membered heterocycles

- The reactivity of the compounds is determined mainly by the ring strain, but also by the nature of the heteroatom or heteroatoms.
- A typical reaction of three-membered heterocycles is nucleophilic ring-opening resulting in the formation of 1,2-disubstituted aliphatic compounds.
- A consequence of three-membered heterocycles possessing nonbonding electron pairs is that they behave as BRÖNSTED bases as well as LEWIS bases. Accordingly, they react with BRÖNSTED acids and with electrophiles.
- Some systems isomerize to give aliphatic compounds, namely
 - oxiranes give carbonyl compounds
 - dioxiranes give esters of carboxylic acids
 - oxaziridines give nitrones
- Appropriate reagents remove the heteroatoms to form alkenes (deoxygenation, desulfonation, deamination, dediazonation).

- The most important synthetic principle is the intramolecular nucleophilic substitution of a β -positioned leaving group
 - by an O-atom (oxiranes)
 - by an S-atom (thiiranes)
 - by an N-atom (aziridines)
 - by an anionic C-atom (*2H*-azirines)
- Oxygen-containing heterocycles can be synthesized by the action of peroxy compounds on alkenes, ketones or imines.
- Amination of carbonyl compounds or imines yield oxaziridines and diaziridines.
- Azides and alkenes furnish *N*-heterocycles (aziridines, *2H*-azirines)
- Only oxiranes are important in preparative chemistry. In some cases, however, other three-membered heterocycles are useful synthetic intermediates or reagents (*2H*-azirines, dioxiranes, oxaziridines, diaziridines).