# The Chemistry of Heterocycles

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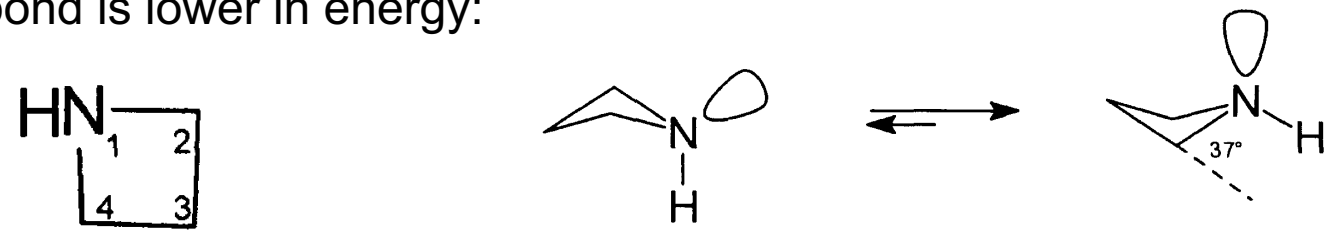
# 4.4 Azetidine

**[A]** Azetidine was previously called trimethyleneimine. The activation energy of the ring inversion is 5.5 kJ $mol^{-1}$ and is therefore only slightly below the value for cyclobutane (6.2 kJ $mol^{-1}$). The conformer with an equatorial N-H bond is lower in energy:



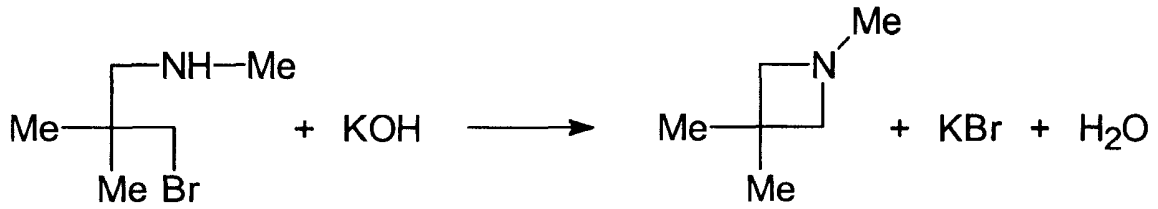

**[B]** Azetidines are thermally stable and less reactive than aziridines. They behave in their reactions almost like secondary alkylamines. The p$K_a$ value of azetidine is 11.29 and so it is more basic than aziridine (p$K_a$ = 7.98) and even dimethylamine (p$K_a$ = 10.73). Azetidines unsubstituted on the N-atom react with alkyl halides to give 1-alkylazetidines which can react further to give quaternary azetidinium salts. With acyl halides, they produce acylazetidines and with nitrous acid, they give 1-nitrosoazetidines.

A positive charge on the N-atom destabilizes the ring, as is the case with the aziridines. Ring-opening by nucleophiles proceeds with acid catalysis. Hydrogen chloride yields $\gamma$-chloroamines. 1,1-Dialkylazetidinium chlorides isomerize on heating to give tertiary $\gamma$-chloroamines. By contrast, neither bases nor reducing agents open the aziridine ring.

**[C]** The synthesis of azetidines can be accomplished starting with $\gamma$-substituted amines or 1,3-dihaloalkanes:

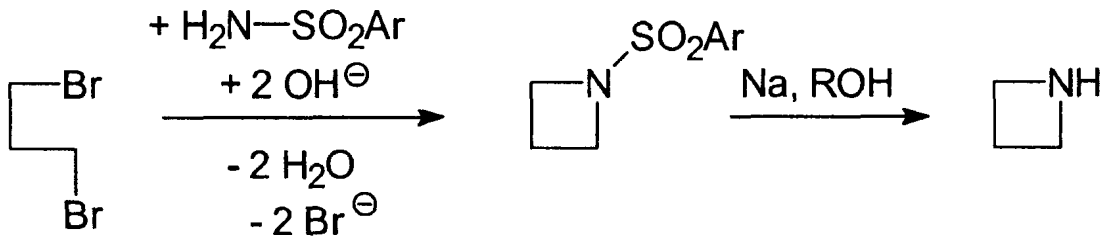
***(1) Cyclization of $\gamma$-substituted amines***

$\gamma$-Halogen substituted amines are dehydrohalogenated by bases, e.g.:




The yields are lower than in the analogous aziridine synthesis. The MITSUNOBU reagent is suitable for the cyclodehydration of $\gamma$-amino alcohols.

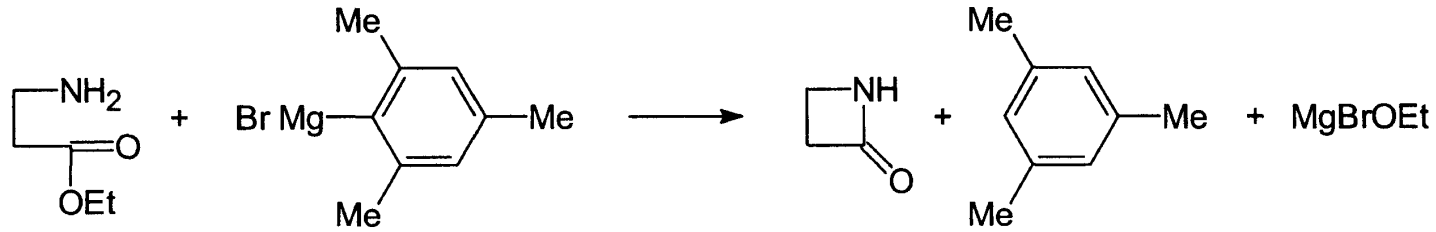
***(2) Action of p-toluenesulfonamide and bases on 1,3-dihaloalkanes:***




The tosyl group can be reductively removed from the 1-tosylazetidine.

**[D] Azetidine** is a water-miscible, colorless liquid of bp 61.5 °C. It smells like ammonia and fumes in air.

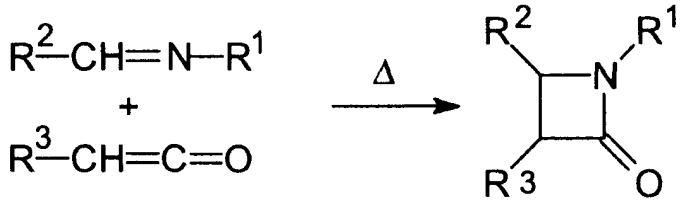
**Azetidin-2-ones** are also $\beta$-lactams. The cyclodehydration of $\beta$-amino carboxylic acids to give azetidin-2-ones is best carried out with $CH_3SO_2Cl$ and $NaHCO_3$ in acetonitrile. The cyclization of ethyl $\beta$-aminopropionate can be carried out with 2,4,6-trimethylphenylmagnesium bromide:




[2+2] Cycloadditions are of great importance for the synthesis of azetidin-2-ones. Three approaches have proved successful.

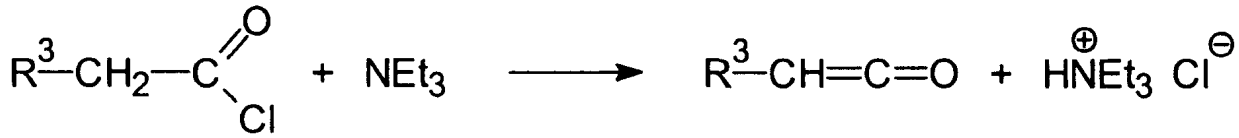
• ***Imines + ketenes***

This [2+2] cycloaddition was found by STAUDINGER already in 1907.



• ***Imines + activated carboxylic acids***

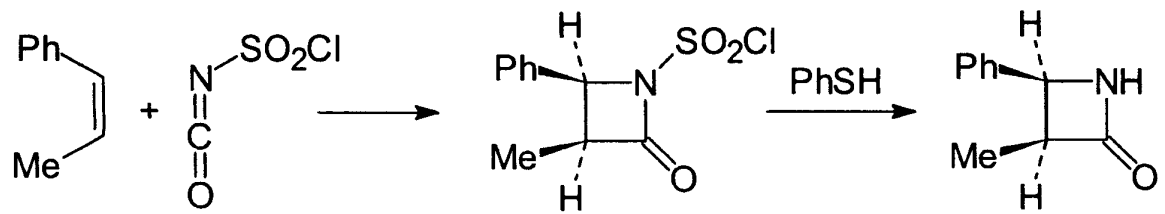
Imines react with acyl halides in the presence of triethylamine to give azetidin-2-ones. An intermediate ketene is formed from the acyl chloride and the amine:



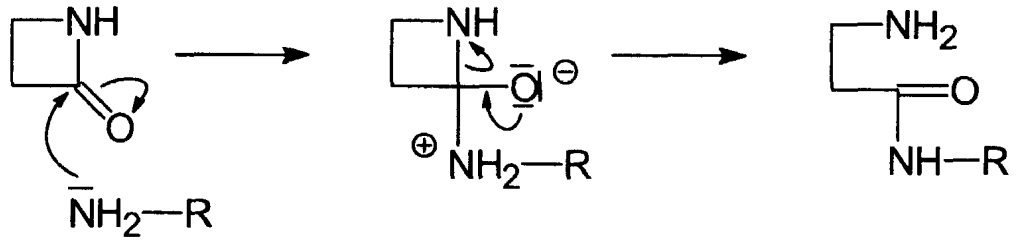

The activation of the carboxylic acids can be achieved also with the MUKAIYAMA reagent (2-chloro-1-methylpyridinium iodide). Carboxylic acids react with this reagent, tri-*n*-propylamine and imines in dichloromethane to give azetidin-2-ones.

• ***Chlorosulfonyl isocyanate + alkenes***

Chlorosulfonyl isocyanate is prepared from chlorocyanogen and sulfur trioxide. It reacts with alkenes to form 1-Chlorosulfonyl azetidin-2-ones, from which the corresponding compounds, unsubstituted in the 1-position, can be obtained by the action of thiophenol. The cycloaddition occurs stereospecifically; *cis*-azetidin-2-one is formed from a *Z*-alkene:

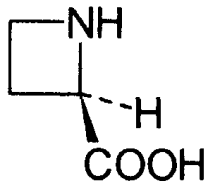


Azetidin-2-ones are more reactive than $\gamma$- and $\delta$-lactams because of ring strain. This is true for the alkaline fission to give salts of $\beta$-amino carboxylic acids, as well as for the acid-catalyzed hydrolysis to $\beta$-carboxyethylammonium salts. Starting from alkenes and chlorosulfonyl isocyanate, a stereocontrolled synthesis of $\beta$-amino carboxylic acids can be realized. Ammonia and amines react with azetidin-2-ones, also with ring-opening, to produce $\beta$-amino carboxylic amides. Hence they are acylated by azetidin-2-ones:

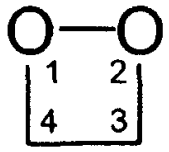



Azetidin-2-ones are reduced chemoselectively by diisobutylaluminium hydride or by chloroaluminium and dichloroaluminium hydrides in THF to form azetidines.

The azetidin-2-one system is present in penicillins and cephalosporines. These natural products are known as $\beta$-lactam antibiotics. They block the biosynthesis of compounds which form the bacterial cell walls. The $\beta$-lactam antibiotics are the most prescribed antibiotics today.
*(S)*-Azetidine-2-carboxylic acid is a cyclic amino acid, not present in proteins, found in agaves and liliaceous plants. It was first isolated from lilies of the valley:

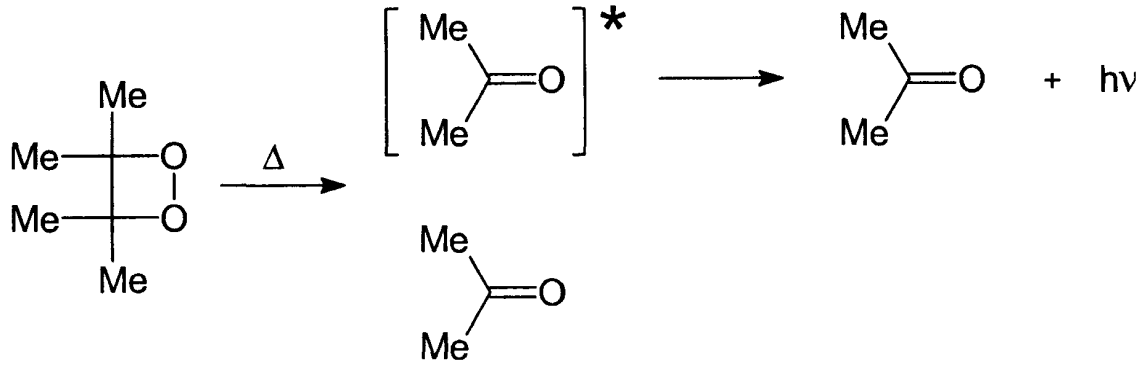


# 4.5 1,2-Dioxetane




**[A,B]** 1,2-Dioxetanes are highly endothermic compounds. This is partly due to ring strain, but above all to the low bond energy of the peroxide bond.

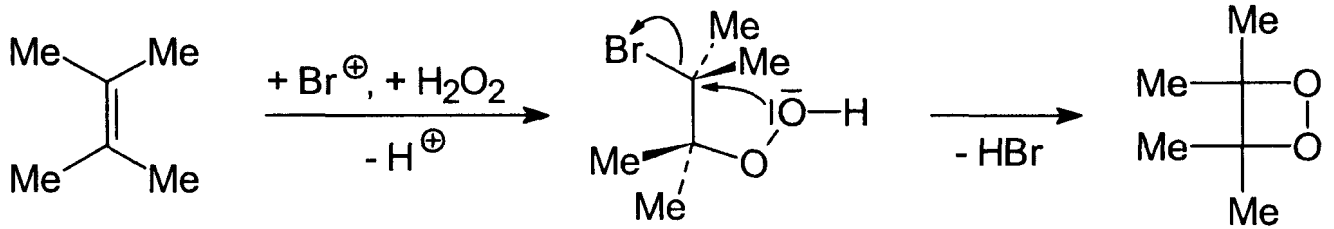
The typical reaction of 1,2-dioxetanes is thermal decomposition. On warming tetramethyl-1,2-dioxetane in benzene or other solvents, blue light is emitted. Such a phenomenon is known as **chemiluminescence**. It has been demonstrated that, according to the principle of conservation of orbital symmetry, one mole of acetone in an electronically excited state is formed. In this way, an electronically excited molecule (symbolized by *) is created by a thermal process. With emission of light, the ground state is restored:




**[C]** Two syntheses are available for the preparation of 1,2-dioxetanes starting from $\beta$-halohydroperoxides or alkenes.

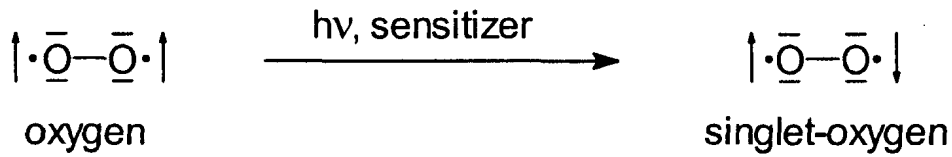
***(1) Dehydrohalogenation of ß-halo hydroperoxides***

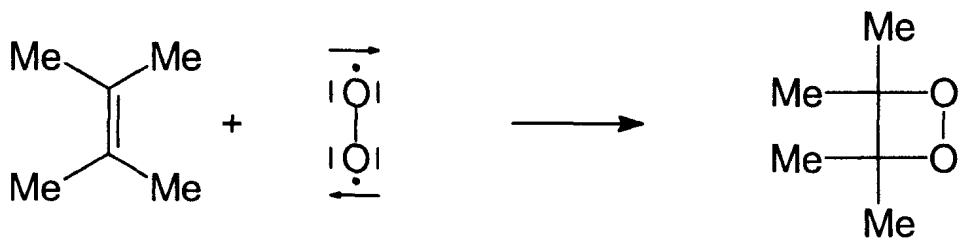
The electrophilic bromination of alkenes, e.g. with 1,3-dibromo-5,5-dimethylhydantoin, in the presence of coned hydrogen peroxide, leads to $\beta$-bromo hydroperoxides. They are cyclized with bases or with silver acetate to give 1,2-dioxetanes (KoPECKi 1973):




***(2) Photooxygenation of alkenes***

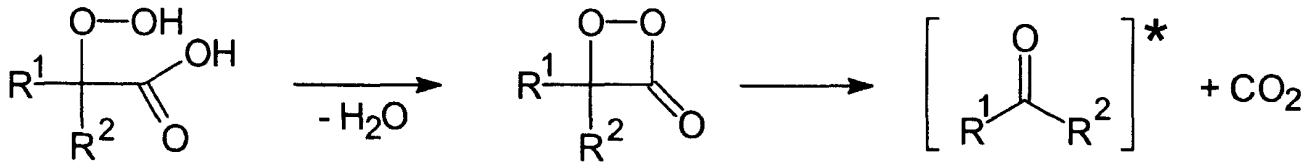
Donor-substituted alkenes in particular react with singlet oxygen to yield 1,2-dioxetanes by a [2+2] cycloaddition. The singlet oxygen is generated in the presence of the alkene by passing oxygen through a solution of the alkene in the presence of a sensitizing dye, e.g. methylene blue under irradiation:



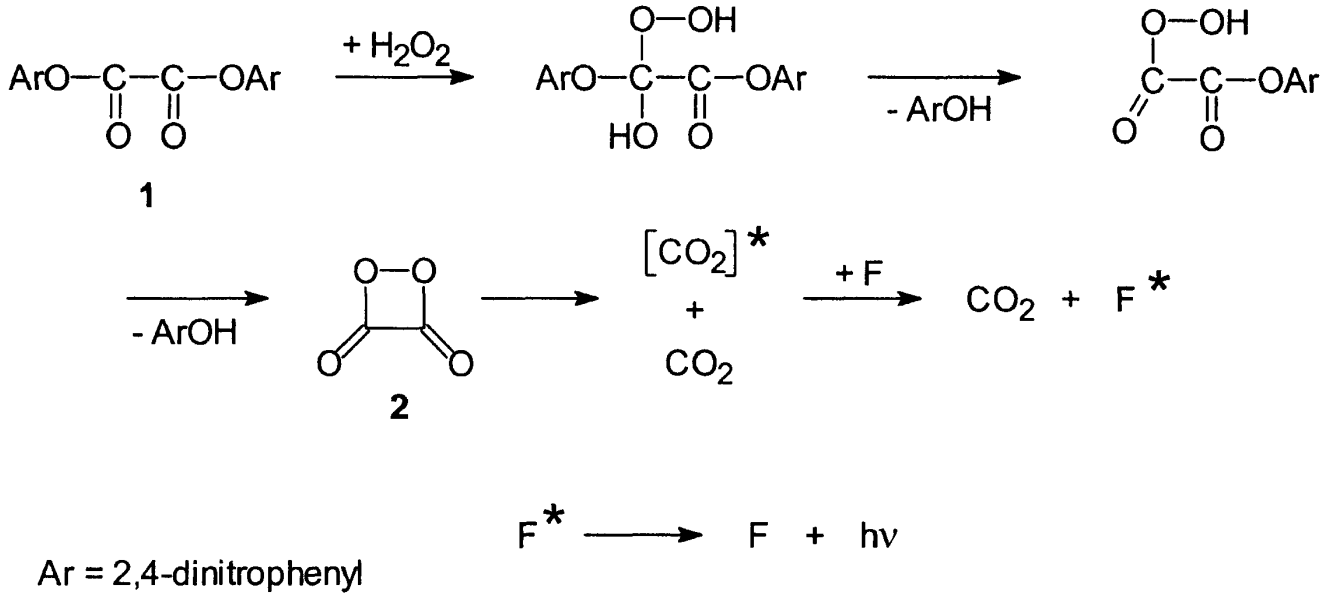
**[D] Tetramethyl-1,2-dioxetane**, yellow crystals, mp 76-77°C, emits light a few degrees above its melting point.

**1,2-Dioxetan-3-ones** are also $\alpha$-peroxy lactones. They can be prepared in solution at low temperature by cyclodehydration of $\alpha$-hydroperoxycarboxylic acids with dicyclohexylcarbodiimide. They decompose at room temperature with chemiluminescence:

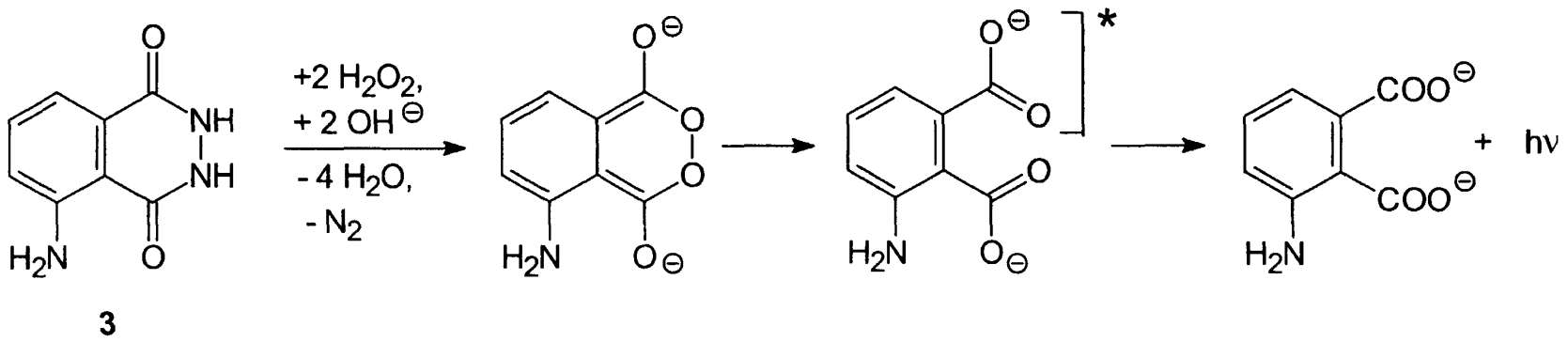



The bioluminescence observed in glowworms and fireflies is due to the decomposition of 1,2-dioxetan-3-ones.

The 2,4-dinitrophenyl ester of oxalic acid **1**, which reacts with 30% hydrogen peroxide solution to give 1,2-dioxetane-3,4-dione **2**, is an excellent example for the demonstration of chemiluminescence. It decomposes producing two moles of carbon dioxide, with one mole being generated in an electronically excited state. The light that is emitted on degradation to the ground state lies in the UV region and is made visible by addition of a fluorophore (F), e.g. 9,10-diphenylanthracene:

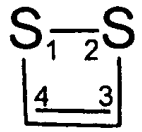



By a similar mechanism, 5-amino-2,3-dihydrophthalazine-1,4-dione **3** (luminol) displays an intensely blue chemiluminescence on oxidation with hydrogen peroxide in the presence of complex iron salts, e.g. haemin.



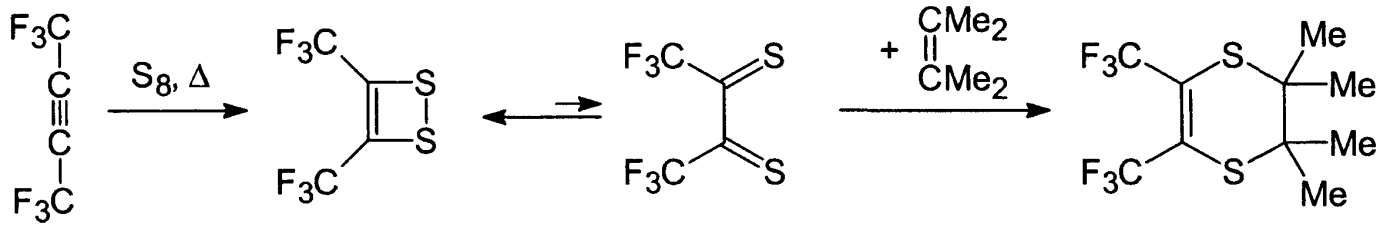

The chemiluminescence of dioxetanes, luminol and other heterocyclic compounds plays an important role in the solution of analytical problems in biochemistry and immunology.

# 4.6 1,2-Dithiete



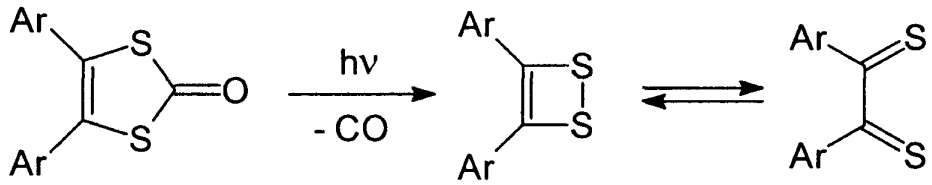

**[A-D]** This system is iso-$\pi$-electronic with benzene. MO calculations predicted a delocalization energy of 92 kJ mol$^{-1}$, which overcompensates for the strain enthalpy of 43 kJ mol$^{-1}$ and results in stabilization of the molecule. However, the parent compound has not yet been prepared.

**3,4-Bis(trifluoromethyl)-1,2-dithiete**, a yellow liquid, bp 95 °C, is formed in 80% yield on heating hexafluorobut-2-yne with sulfur.




Typical for disubstituted 1,2-dithietes is their valence isomerization, which results in the formation of 1,2-dithiones. The equilibrium favors the 1,2-dithiete with electron-withdrawing substituents such as $CF_3$. The reaction with 2,3-dimethylbut-2-ene to give a hexasubstituted 2,3-dihydro-1,4-dithiine proceeds, however, as a [4+2] cycloaddition via the 1,2-dithione.

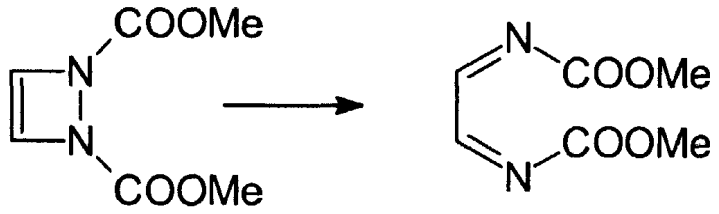
**3,4-Bis(4-dimethylaminophenyl)-1,2-dithiete** exists in solution in equilibrium with the corresponding 1,2-dithione:



**3,4-Di-*tert*-butyl-1,2-dithiete** was obtained by heating 2,2,5,5-tetramethylhex-3-yne (di-*tert*-butyl acetylene) with sulfur in benzene in an autoclave at 190 °C. It is thermally stable and exists in the dithiete form. Valence isomerization into the dithione form would enhance the steric strain in the molecule.

## 4.7 1,2-Dihydro-1,2-diazete

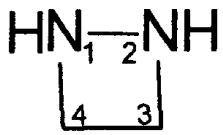

Although this system is iso-$\pi$-electronic with benzene, only one analogue has been prepared to date, namely 1,2-bis(methoxycarbonyl)-1,2-dihydro-1,2-diazete. Even at room temperature, it undergoes a slow valence isomerism to the corresponding 1,2-diimine:

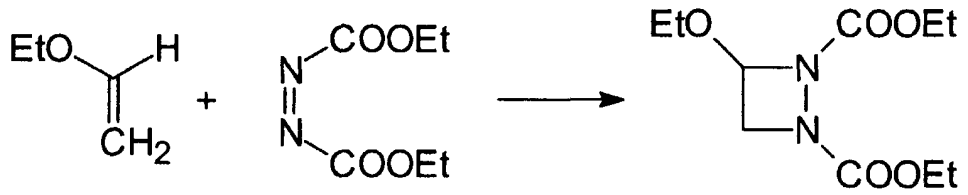


# 4.8 1,2-Diazetidine

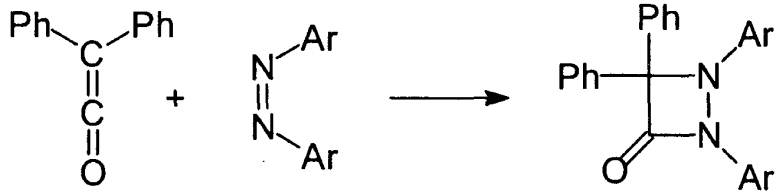
**[A-C]** Again, the preparation of the parent compound has, as yet, not been achieved. However, numerous 1,2-diazetidines are known.

The standard synthesis is a [2+2] cycloaddition of electron-rich alkenes such as enol ethers or enamines to azo compounds, e.g.:



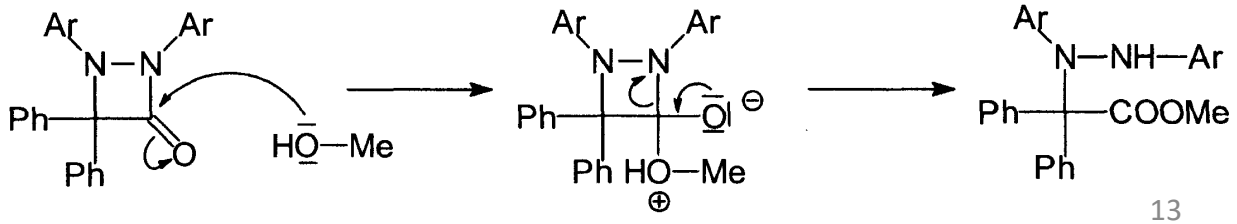

The [2+2] cycloaddition of ketenes to azo compounds yields 1,2-diazetidin-3-ones, e.g.:




1,2-Diazetidines and 1,2-diazetidin-3-ones are thermally very stable. On strong heating, they decompose either into an azo compound and an alkene or ketene, or into two molecules of imine or an imine and isocyanate.

By analogy with $\beta$-lactams, 1,2-diazetidin-3-ones react with nucleophiles with ring-opening, e.g.:

A few 1,2-diazetidin-3-ones are so reactive that ring-opening occurs in moist air.



**Summary of the general chemistry of four-membered heterocycles:**

• The stability and reactivity of the compounds are determined by the ring strain and the nature of the heteroatom or heteroatoms. While azete, as an antiaromatic system, is extremely reactive, the aromatic systems 1,2-dithiete and 1,2-dihydro-1,2-diazete are hardly any more stable and are very reactive.

• Ring-opening by nucleophiles proceeds more slowly than with three-membered heterocycles and is catalyzed by acids.

• Special ring-openings are [2+2] cyclo-reversions (oxetan-2-ones, 1,2-dioxetanes, 1,2-dioxetan-3-ones, 1,2-diazetidines, 1,2-diazetidin-3-ones) and valence isomerizations (1,2-dithiete, 1,2-dihydro-1,2-diazete).

• Oxetan-2-ones, azetidin-2-ones and 1,2-diazetidin-3-ones are more reactive than five- and six-membered homologues. They are attacked by nucleophiles on the C-atom of the carbonyl group. Ring-opening occurs to give $\gamma$-substituted carboxylic acids or carboxylic acid derivatives.

• An important synthetic principle is the intramolecular nucleophilic substitution of a $\gamma$-substituted leaving group
— by an O-atom (oxetanes, oxetan-2-ones, 1,2-dioxetanes, 1,2-dioxetan-2-ones)
— by an S-atom (thietanes)
— by an N-atom (azetidines, azetidin-2-ones)

The rate of reaction is greater than that of the three-membered heterocycles because of the smaller ring strain of the products. At the same time, however, the entropy gain is smaller, because two degrees of freedom of inner rotation are lost en route to the activated complex.

• [2+2] Cycloadditions are of great importance for synthetic purposes

— carbonyl compounds + alkenes → oxetanes
— aldehyde + ketenes → oxetan-2-ones
— imine + ketenes → azetidin-2-ones
— isocyanates + alkenes → azetidin-2-ones
— singlet oxygen + alkenes → 1,2-dioxetanes
— alkenes + azo compounds → 1,2-diazetidines
— ketene + azo compounds → 1,2-diazetidin-3-ones

• The importance of four-membered heterocycles for organic synthesis is limited. Examples are the alkene synthesis involving oxetan-2-ones and the $\beta$-aminocarboxylic acid synthesis involving azetidin-2-ones.