The Chemistry of Heterocycles

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The Chemistry of Heterocycles, (Second Edition).

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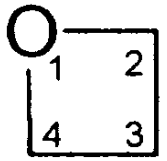
4 Four-Membered Heterocyles

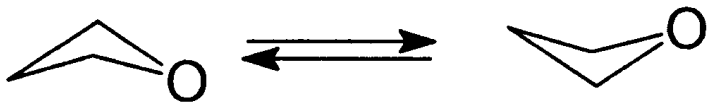
In four-membered heterocycles, the ring strain is less than in the corresponding three-membered compounds and is approximately equal to that found in cyclobutane. Nevertheless, ring-opening reactions forming acyclic products predominate. At the same time, analogy with the reactivity of the corresponding aliphatic compounds (ethers, thioethers, secondary and tertiary amines, imines) becomes more evident.

4.1 Oxetane

[A] The oxetane ring represents a slightly distorted square because the bond angle at the O-atom is 92°. The strain enthalpy has been determined thermochemically to be 106.3 kJ mol^{-1} and so only 7.7 kJ mol^{-1} less than that of oxirane, although the bond angles are 30° larger.

The reason for this is that the planarity of the oxetane ring causes a considerable PITZER strain due to the eclipsing interactions of the C-H bonds. This strain is reduced by ring-puckering between two nonplanar structures, which simultaneously leads to a reduction in the bond angles.





This results in a compromise between bond angle strain and PITZER strain, which minimizes the total strain energy. The activation energy of the ring inversion amounts to 0.181 kJ mol^{-1}, which is less than the energy of the molecular vibration. Consequently, the process occurs so fast that the molecule should be regarded as planar.

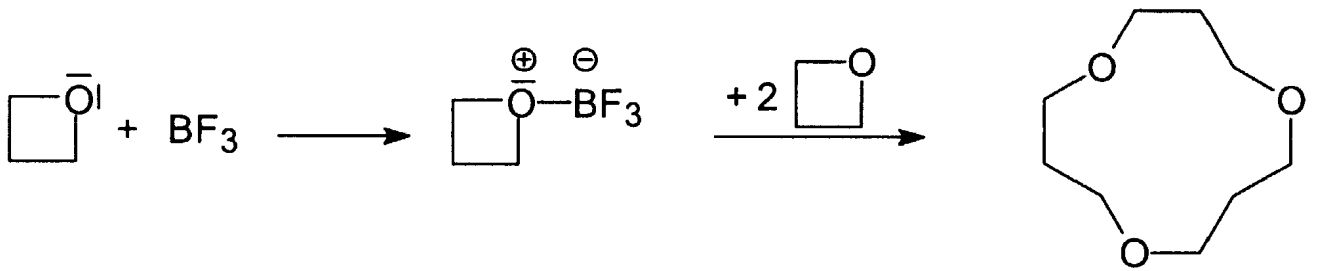
[B] Oxetanes react like oxiranes with ring-opening at a slower rate and under forcing conditions. Two reactions are of general importance:

Acid-catalyzed ring-opening by nucleophiles

Hydrogen halides react with oxetanes to give 3-halo alcohols. The acid-catalyzed hydrolysis yields 1,3-diols.

Cyclooligomerization and polymerization

LEWIS acids, e.g. boron trifluoride, can add to a nonbonding electron pair of the O-atom. Thus, in dichloromethane as solvent, a Cyclooligomerization is induced. The main product is the cyclotrimer 1,5,9-trioxacyclododecane:

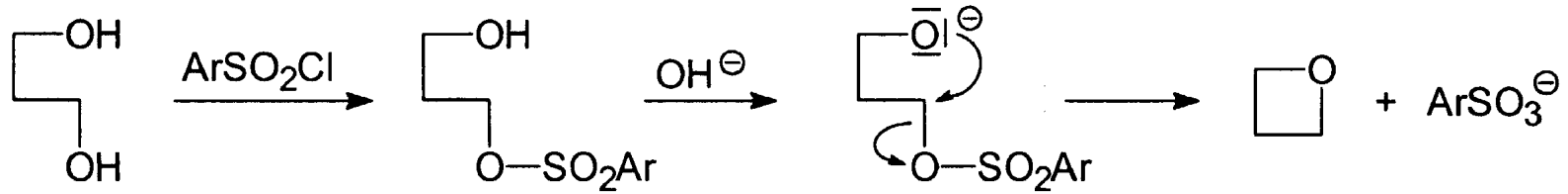


Under different conditions, especially in the presence of water, linear polymers are formed.

[C] For the synthesis of oxetanes, two methods are useful, namely the cyclization of γ-substituted alcohols and the PATERNO-BÜCHI reaction.

(1) Cyclization of γ-substituted alcohols

Alcohols with a nucleofuge leaving group in the γ-position can be cyclized to give oxetanes. Thus the cyclodehydrohalogenation of γ-halo alcohols occurs in an analogous way to the oxirane synthesis from β-halogenated alcohols. Oxetanes can be prepared from 1,3-diols via monoarene sulfonates:

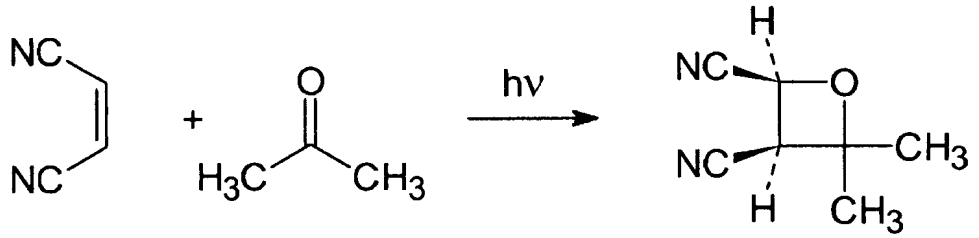


In an alternative synthesis, the 1,3-diol in THF is converted to the lithium alkoxide with *n*-butyllithium. This is followed by addition of tosyl chloride; cyclization is finally effected with *n*- butyllithium.

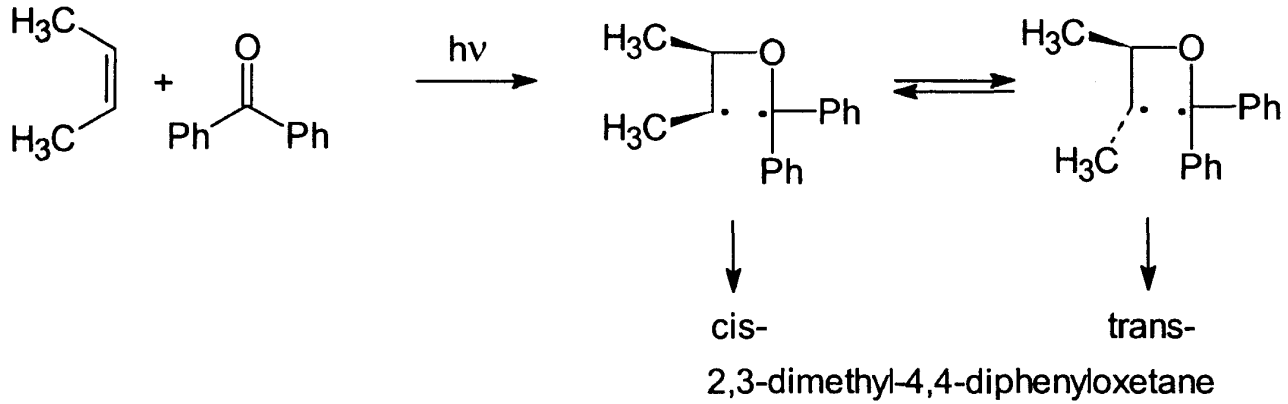
(2) Paterno-Büchi reaction

The photochemical [2+2] cycloaddition of carbonyl compounds to alkenes yielding oxetanes is known as the PATERNO-BÜCHI reaction. The carbonyl compound is converted by absorption of a quantum of light into an electronically excited state (n$\rightarrow\pi^*$ transition), which at first is in the singlet state (in which the spin moments of the electron in the n-MO and the electron in the π^*-MO are antiparallel). This is followed by conversion into the lower energy triplet state (in which the spin moments of the two electrons are parallel).

The ensuing addition of the alkene should, according to the WOODWARD-HOFFMANN rules, occur in a concerted and, therefore, stereospecific manner. This is in- deed observed with alkenes possessing electron-withdrawing groups, e.g.:



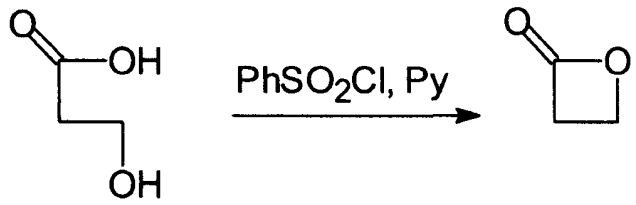
In contrast, alkenes with donor substituents react via radical intermediates, e.g.:



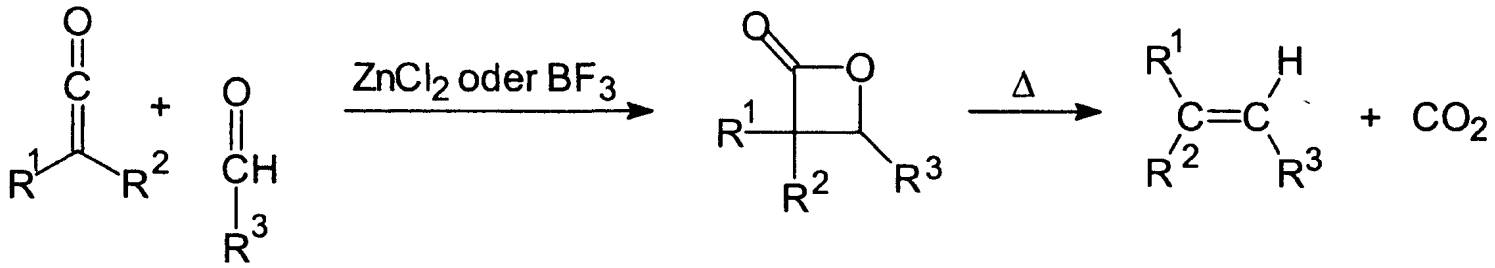
Even the C-O double bonds of quinones and carboxylic esters can undergo the PATERNO-BÜCHI reaction.

[D] Oxetane, a colorless, water-miscible liquid of bp 48°C, is obtained in 40% yield by heating (3-chloropropyl)acetate with coned KOH solution.

Oxetane-2-ones are also β-lactones. They are prepared by cyclodehydration of β-hydroxycarboxylic acids with phenylsulfonyl chloride in pyridine:



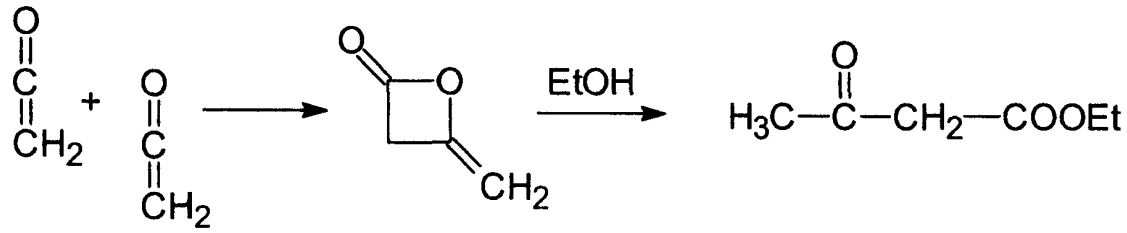
A further method is the [2+2] cycloaddition of aldehydes to ketenes catalyzed by LEWIS acids:



Oxetan-2-ones decarboxylate on heating to give olefins. The synthesis of olefins starting from β-hydroxycarboxylic acids or from ketenes and aldehydes can thus be carried out as an alternative to the WITTIG reaction.

Oxetan-2-ones are more reactive than γ- and δ-lactones because of ring strain. On treatment with sodium hydroxide, salts of β-hydroxycarboxylic acids are formed owing to attack of hydroxide ions on the C-atom of the carbonyl group.

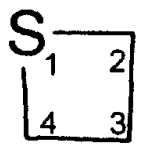
Diketene (4-methyleneoxetane-2-one) is formed by dimerization of ketene which in turn is prepared by pyrolysis of acetone or acetic acid. The compound is an industrial intermediate. It ring-opens with ethanol to give ethyl acetoacetate; the nucleophile attacks the C-atom of the carbonyl group.



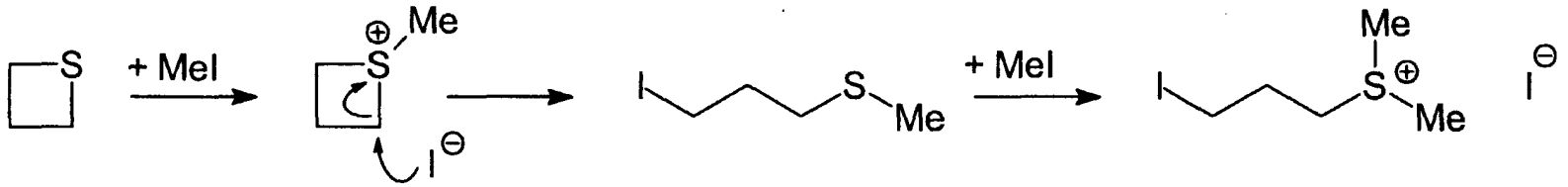
Oxetanes rarely occur in nature. The diterpene alcohol taxol (paclitaxel®) was isolated in 1971 from the bark of the pacific yew tree (*Taxus brevifolia*) native to the northwest USA, and its structure elucidated. The compound, which is now marketed, contains an oxetane ring and displays a strong anti-tumor and anti-leukemia activity. Its total synthesis has been achieved.

4.2 Thietane

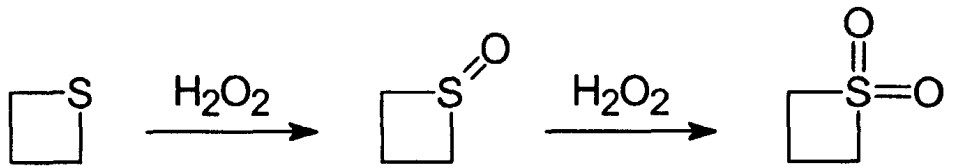
[A] The thermochemically determined strain enthalpy of thietane is only 80 kJ mol^{-1}. The activation energy for the ring inversion was found spectroscopically to be 3.28 kJ mol^{-1} and lies above the four lowest vibration levels. The ring is thus **not** planar:



[B] The reactivity of thietanes towards nucleophiles is much less than that of thiiranes. For instance, thietane does not react with ammonia or amines at room temperature. **Electrophiles** attack the S-atom and can thereby cause ring-opening. Thus, addition of acids leads to polymerization. A further example is their ring-opening by haloalkanes:

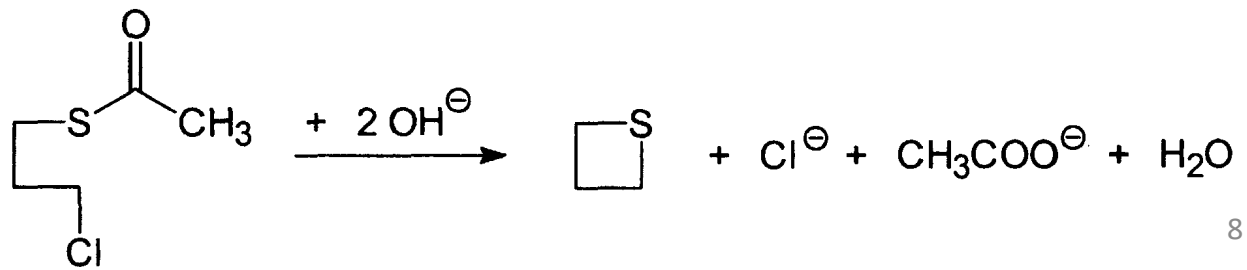


This demonstrates again that a positive charge on the heteroatom destabilizes the ring.
Hydrogen peroxide or peroxy acids oxidize thietanes to 1,1-dioxides (cyclic sulfones) via 1-oxides:

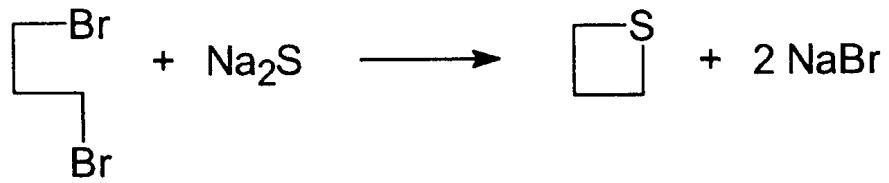


[C] Thietanes can be prepared from γ-halo thiols or 1,3-dihaloalkanes as follows:

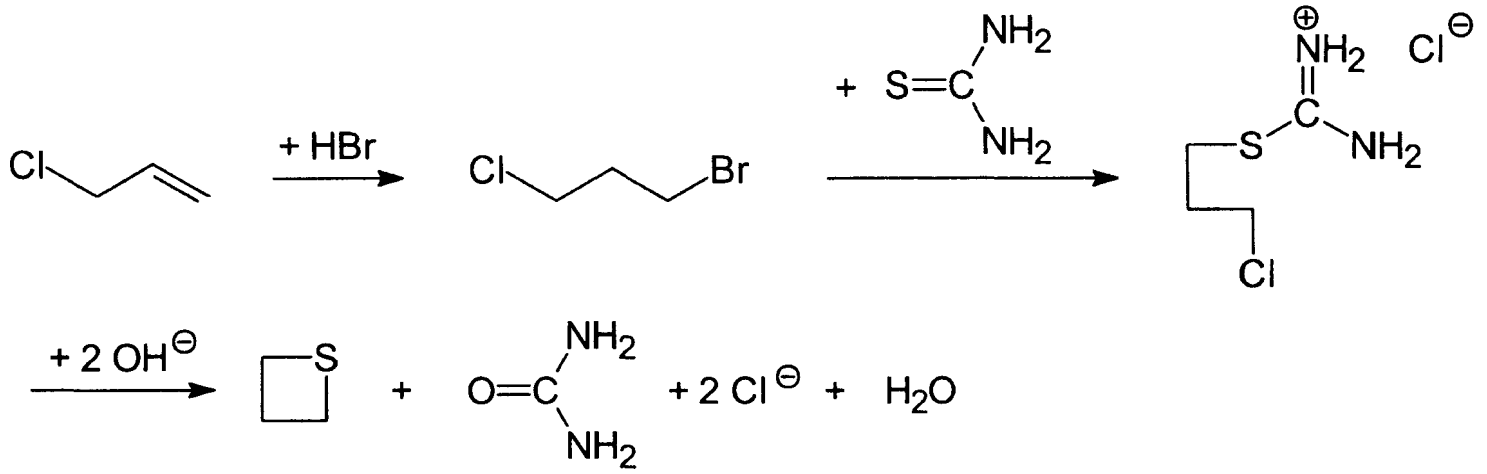
(1) Cyclization of γ-halo thiols or their acetyl derivatives by bases:



(2) Action of sodium or potassium sulflde on 1,3-dihaloalkanes:



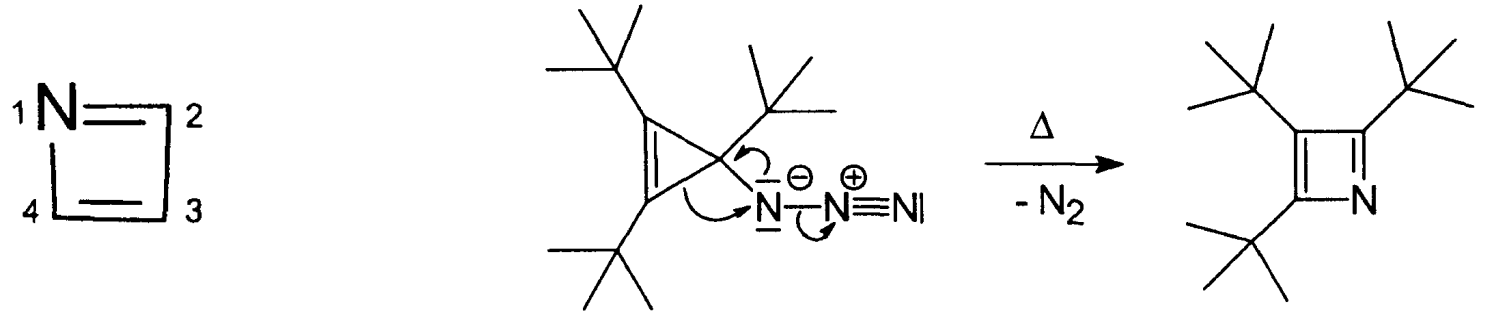
Better yields are obtained from (3-chloropropyl)isothiouronium bromide starting with 1-bromo-3-chloropropane. The latter is available by addition of hydrogen bromide to allyl chloride:



[D] Thietane is a colorless, water-insoluble liquid, bp 94°C, polymerizing slowly at room temperature, faster on exposure to light.

4.3 Azete

[A-D] Azete is iso-π-electronic with cyclobutadiene and is therefore the simplest antiaromatic heteroannulene. It would be expected to be thermally unstable and extremely reactive, and as yet the parent compound has not been synthesized. In 1973, tris(dimethylamino)azete was described. In 1986, REGITZ succeeded in synthesizing tri-*tert*-butylazete by thermolysis of 3-azido-1,2,3-tri-*tert*-butylcyclopropene:



Tri-*tert*-butylazete crystallizes as reddish needles, mp 37°C. The space-filling *tert*-butyl groups protect the ring so strongly that polymerization proceeds extremely slowly; ΔG^* is high even at elevated temperatures. ΔG^* is also very high for the decomposition of the compound into an alkyne and a nitrile as a consequence of a conceited [2+2] cyclo-reversion, because the reaction is not allowed according to the WOODWARD-HOFFMANN rules. Tri-*tert*-butyl azete is, therefore, in two ways kinetically stabilized.