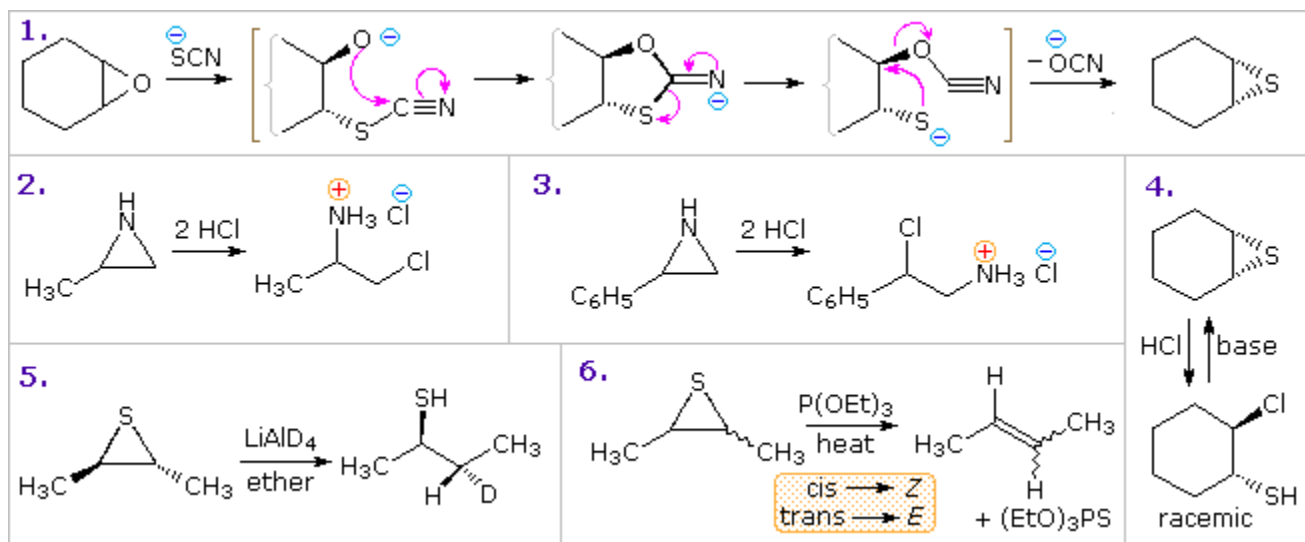


# Preparation and Reactions of Heterocyclic Compounds I

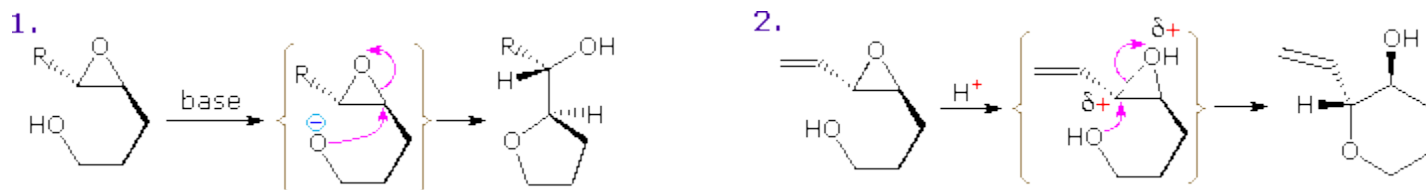
## Three-Membered Rings

Oxiranes (epoxides) are the most commonly encountered three-membered heterocycles. Epoxides are easily prepared by reaction of alkenes with peracids, usually with good stereospecificity. Because of the high angle strain of the three-membered ring, epoxides are more reactive than unstrained ethers. Addition reactions proceeding by electrophilic or nucleophilic opening of the ring constitute the most general reaction class. Example 1 in the following diagram shows one such transformation, which is interesting due to subsequent conversion of the addition intermediate into the corresponding thiirane. The initial ring opening is stereoelectronically directed in a trans-diaxial fashion, the intermediate relaxing to the diequatorial conformer before cyclizing to a 1,3-oxathiolane intermediate. Other examples show similar addition reactions to thiiranes and aziridines. The acid-catalyzed additions in examples 2 and 3, illustrate the influence of substituents on the regioselectivity of addition. Example 2 reflects the  $S_N2$  character of nucleophile (chloride anion) attack on the protonated aziridine (the less substituted carbon is the site of addition). The phenyl substituent in example 3 serves to stabilize the developing carbocation to such a degree that  $S_N1$  selectivity is realized. The reduction of thiiranes to alkenes by reaction with phosphite esters (example 6) is highly stereospecific, and is believed to take place by an initial bonding of phosphorous to sulfur.



By clicking on the above diagram, four additional examples of three-membered heterocycle reactivity or intermediacy will be displayed. Examples 7 and 8 are thermal reactions in which both the heteroatom and the strained ring are important factors. The  $\alpha$ -lactone intermediate shown in the solvolysis of optically active 2-bromopropanoic acid (example 9) accounts both for the 1st-order kinetics of this reaction and the retention of configuration in the product. Note that two inversions of configuration at C-2 result in overall retention. Many

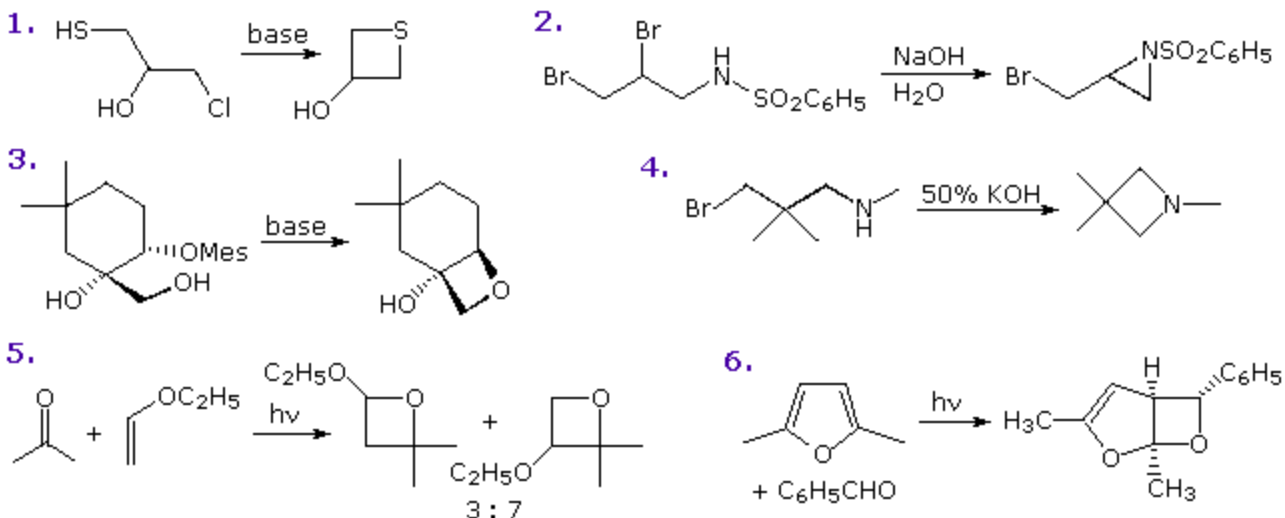
examples of intramolecular interactions, such as example 10, have been documented. An interesting regioselectivity in the intramolecular ring-opening reactions of disubstituted epoxides having a pendant  $\gamma$ -hydroxy substituent has been noted. As illustrated below, acid and base-catalyzed reactions normally proceed by 5-exo-substitution (reaction 1), yielding a tetrahydrofuran product. However, if the oxirane has an unsaturated substituent (vinyl or phenyl), the acid-catalyzed opening occurs at the allylic (or benzylic) carbon (reaction 2) in a 6-endo fashion. The  $\pi$ -electron system of the substituent assists development of positive charge at the adjacent oxirane carbon, directing nucleophilic attack to that site.



## Four-Membered Rings

### Preparation

Several methods of preparing four-membered heterocyclic compounds are shown in the following diagram. The simple procedure of treating a 3-halo alcohol, thiol or amine with base is generally effective, but the yields are often mediocre. Dimerization and elimination are common side reactions, and other functions may compete in the reaction. In the case of example 1, cyclization to an oxirane competes with thietane formation, but the greater nucleophilicity of sulfur dominates, especially if a weak base is used. In example 2 both aziridine and azetidine formation are possible, but only the former is observed. This is a good example of the kinetic advantage of three-membered ring formation. Example 4 demonstrates that this approach to azetidine formation works well in the absence of competition. Indeed, the exceptional yield of this product is attributed to the **Thorpe-Ingold effect**, which is believed to favor coiled chain conformations. The relatively rigid configuration of the substrate in example 3, favors oxetane formation and prevents an oxirane cyclization from occurring. Finally, the Paterno-Buchi photocyclizations in examples 5 and 6 are particularly suited to oxetane formation.



## Reactions

Reactions of four-membered heterocycles also show the influence of ring strain. Some examples are given in the following diagram. Acid-catalysis is a common feature of many ring-opening reactions, as shown by examples 1, 2 & 3a. In the thietane reaction (2), the sulfur undergoes electrophilic chlorination to form a chlorosulfonium intermediate followed by a ring-opening chloride ion substitution. Strong nucleophiles will also open the strained ether, as shown by reaction 3b. Cleavage reactions of  $\beta$ -lactones may take place either by acid-catalyzed acyl exchange, as in 4a, or by alkyl-O rupture by nucleophiles, as in 4b. Example 5 is an interesting case of intramolecular rearrangement to an ortho-ester. Finally, the  $\beta$ -lactam cleavage of penicillin G (reaction 6) testifies to the enhanced acylating reactivity of this fused ring system. Most amides are extremely unreactive acylation reagents, thanks to stabilization by p- $\pi$  resonance. Such electron pair delocalization is diminished in the penicillins, leaving the nitrogen with a pyramidal configuration and the carbonyl function more reactive toward nucleophiles.

