SYNTHESIS OF THREE MEMBERED HETEROCYCLES
Three-Membered Heterocycles

Structure

• The bond angles in all these systems fall far below the ideal 109.5° tetrahedral bond angle and therefore highly strained.

• Due to the strained bond angle, these three-membered heterocycles have bent bonds (banana bonds).

• Among these three-membered heterocycles, the oxiranes are the most common and easier to synthesize.
Synthesis of Oxiranes
Epoxidation of Alkenes to Oxiranes

• Oxiranes (epoxides), three-membered ring cyclic ethers, are commonly formed by epoxidation of alkenes.
• The most common epoxidation involves the reaction of alkenes with peroxy acids.

\[
\begin{align*}
\text{H}_2\text{C} & \text{= CH}_2 + \text{R}_2\text{C} & \text{O} & \text{OH} \rightarrow \text{H}\text{C} & \text{= C(H)} & \text{O} & \text{C(H)} & \text{H} \\
\text{Peroxy acid} & & & & & & & \\
\end{align*}
\]

• The most commonly used peroxy acid is \(m\)-chloroperoxybenzoic acid (MCPBA).

\[\text{Cl} \quad \text{O} \quad \text{OH} \quad m\text{-Chloroperoxybenzoic acid (MCPBA)}\]
Synthesis of Oxiranes

Reaction of Alkenes with MCPBA to Oxiranes

• The epoxidation with MCPBA involves a concerted reaction that is stereospecific.
Synthesis of Oxiranes

Epoxidation of Alkenes to Oxiranes

- One of the mildest epoxidizing agent in current use is dimethyldioxirane (DMDO).

![Chemical reaction diagram]

- The epoxidation with DMDO is a concerted reaction and DMDO behaves like an electrophilic reagent.

- The epoxidations with dimethyldioxirane can lend access to strained spiroheterocycles as illustrated below:

![Chemical reaction diagram]
Synthesis of Oxiranes

Reaction of Sulphur Ylides with Aldehydes and Ketones to Oxiranes

- Sulphur ylides (e.g. dimethylsulphonium methylide) react with aldehydes and ketones to provide oxiranes.

- The reaction is presumed to occur as illustrated below:
Synthesis of Oxiranes

Reaction of Sulphur Ylides with Ketones to Oxiranes

- The use of sulphur ylides is convenient since aldehydes and ketones can be readily obtained by oxidation of alcohols.

- The advantage of this strategy is that other functional groups (e.g. alkenes) can be readily tolerated during the reaction.
Synthesis of Aziridines

β-Aminoalcohols to Aziridines

- β-Amino alcohols, conveniently made from the reaction of oxiranes with ammonia or amines, react with bromine in the presence of triphenylphosphine to provide aziridines.

- To aid the formation of a strong P-O bond, the triphenylphosphine serves to convert the OH group into a good leaving group that is displaced intramolecularly by the amino group.

- Reduction of α-amino acids also provides β-amino alcohols and therefore could lend access to aziridines.
Synthesis of Aziridines

\( \beta \)-Aminoalcohols to Aziridines

- \( \alpha \)-Amino acids are prevalent in natural proteins. Hydrolysis of the peptide bonds of these natural proteins followed by separation using electrophoresis provides amino acids.

\[
\begin{align*}
\text{(S)-Valine} & \xrightarrow{\text{BH}_3} \text{Amino alcohol} & \xrightarrow{\text{Br}_2, \text{PPh}_3} \text{Aziridine}
\end{align*}
\]

- With the diversity of \( \alpha \)-amino acids available in nature, diverse aziridines can be accessed.
Synthesis of Aziridines
Alkenes to Aziridines

- Alkenes react with iodonium azide with the addition of IN$_3$ proceeding via a three-membered ring iodonium species, resulting from attack of I$^+$ on the double bond.
- The amino group resulting from reduction of the azide is sufficiently nucleophilic to displace the halide.
- Thus, airidine can be prepared as illustrated below:
Synthesis of Aziridines

Reaction of Sulphur Ylides with Imines to Aziridines

- Sulphur ylides (e.g. dimethylsulfonium methylide) react with imines to provide aziridines.

\[
\text{R-C=H} + \text{CH}_3\text{S-CH}_2\text{CH}_3 \rightarrow \text{R-C-CH}_2\text{H} + \text{CH}_3\text{S-S-CH}_3
\]

- The reaction can be rationalized stepwise as proceeding as illustrated below:
Synthesis of Aziridines
Reaction of Sulphur Ylides with Imines

• The use of sulphur ylides with imines is convenient route to aziridines.

• Due to the strain and reactivity associated with these aziridines intramolecular ring opening reactions of these systems provide rings of synthetic interest.
Synthesis of Thiiranes
Reaction of Sulphur Ylides with Thiocarbonyls to Thiiranes

• Sulphur ylides (e.g. dimethylsulphonium methylide) react with thiocarbonyl compounds to provide thiiranes.

\[
\begin{align*}
\text{S} & \quad \text{CH}_3 \quad \text{S} \quad \text{CH}_2 \\
\text{R} \quad \text{C} \quad \text{H} & + \quad \text{CH}_3 \quad \text{S} \quad \text{CH}_2 \quad \text{CH}_3 & \rightarrow & \text{R} \quad \text{C} \quad \text{H} & + \quad \text{CH}_3 \quad \text{S} \quad \text{CH}_2 \quad \text{CH}_3
\end{align*}
\]

• The reaction can be rationalized stepwise as proceeding as illustrated below:

\[
\begin{align*}
\text{CH}_3 & \quad \text{S} \quad \text{CH}_2 \quad \text{CH}_3 \\
\text{CH}_3 \quad \text{S} \quad \text{CH}_2 \quad \text{CH}_3 & + \quad \text{R} \quad \text{C} \quad \text{H} & \rightarrow & \text{R} \quad \text{C} \quad \text{H} & + \quad \text{CH}_3 \quad \text{S} \quad \text{CH}_2 \quad \text{CH}_3
\end{align*}
\]

Good leaving group
Synthesis of Thiiranes

Reaction of Sulphur Ylides Providing Thiiranes

• The use of sulphur ylides is convenient in converting thiocarbonyl compounds, prepared by thionation of ketones and aldehydes with phosphorus pentasulphide, to thiiranes.

• The Lawesson’s reagent is also commonly used in the thionation of carbonyl compounds.
Synthesis of Thiiranes

**Oxiranes to Thiiranes**

- Oxiranes can be converted directly to thiiranes using aqueous potassium thiocyanate.

![Chemical Reaction Diagram]

- This transformation occurs as rationalized below:

\[
\text{Oxirane} \xrightarrow{\text{aq. KSCN, -5 °C}} \text{Thiirane} + \text{OCN}
\]
Synthesis of Thiiranes

Oxiranes to Thiiranes

• The conversion of oxiranes to thiiranes is stereospecific.

• The stereospecificity of the transformation is rationalized based on $S_N$2 steps below:
**Synthesis of Thiiranes**

**β-Mercaptoalcohols to Thiiranes**

- Reacting β-thioalcohols, obtained from ring opening of oxiranes, with phosgene and subsequent heating also generates thiiranes.

\[ \text{2-Mercaptoethanol} \xrightarrow{\text{Cl}_2} \text{1,3-Oxathiolan-2-one} \xrightarrow{\text{HEAT}} \text{Thiirane} \]

- Different oxiranes can therefore provide access to diverse thiiranes.
Synthesis of Thiiranes 
β-Mercaptoalcohols to Thiiranes

• For instance, cyclohexanone can be converted to 1-thiaspiro[2,5]octane based on the sequence below.

• The reactions of these strained three-membered heterocycles have a potential of lending access to diverse structures.
Complete the following reactions by giving the principal organic product.

\[
\text{O} \quad \text{O} \quad + \quad \text{O} \quad \text{O} \quad \text{P}_2\text{S}_5 \quad \text{A} \quad \text{B}
\]

Propose a reasonable and stepwise reaction mechanism for the transformation below:

\[
\text{O} \quad \text{O} \quad + \quad \text{O} \quad \text{O} \quad \text{1,4-Dioxaspiro[2.3]hexane}
\]