SYNTHESIS OF FOUR MEMBERED HETEROCYCLES
Four-Membered Heterocycles

Structure

- In four-membered heterocycles, the ring strain is less than in the corresponding three-membered compounds.
- For example, the oxetane ring represents a slightly distorted square approximately equal to that of cyclobutane with a bond angle at the O-atom of 92°.
- The strain in oxetanes is reduced by ring-puckering between two nonplanar structures, which simultaneously leads to a reduction in the bond angles.
Strategies for Synthesis of Four-Membered Heterocycles

• The three common strategies for accessing four membered heterocycles are:
  • Intramolecular cyclization
    
  • Cycloaddition
    
  • Ring expansion
Synthesis of Oxetanes
Intramolecular SN$_2$ Cyclization

• Although the intramolecular Williamson ether synthesis is a common approach to oxetanes, the esterification of 1,3-haloxydrins enhances the efficiency.

\[
\text{Cl-CH}_2-\text{CH(OH)}-\text{CHCl} + \text{KOH} \rightarrow \circ + \text{CH}_3\text{COOH} + \text{KCl}
\]

• The reaction mechanism is illustrated below:

(i) \[
\text{Cl-CH}_2-\text{CH(OH)}-\text{CHCl} + \text{OH}^{-} \rightarrow \text{Cl-CH}_2-\text{CH}_2-\text{OH} + \text{CHCl}_3
\]

(ii) \[
\text{Cl-CH}_2-\text{CH}_2-\text{OH} \rightarrow \circ + \text{CH}_3\text{COOH} + \text{Cl}^{-}
\]
Synthesis of Thietanes
Intramolecular Cyclization with Sodium or Potassium Sulphide

• Intramolecular cyclization of 1,3-dihaloalkanes using sodium or potassium sulphide provides thietanes.

\[
\text{Br-} + \text{Br} + \text{Na}_2\text{S} \rightarrow \square + 2\text{NaBr}
\]

• The reaction mechanism is illustrated below:

• The reaction proceeds through two sequential nucleophilic substitutions.
Synthesis of Four-Membered Heterocycles

Cycloaddition

• Cycloaddition is the union of two $\pi$-systems to form a ring through a cyclic movement of electrons.
• A cycloaddition reaction is categorized as a $[m + n]$-cycloaddition when a system of $m$ conjugated atoms combines with another system of $n$ conjugated atoms.
• Photochemical $[2+2]$ cycloaddition of carbonyls, imines and thiocarbonyls with alkenes lends access to four-membered heterocycles.
Synthesis of Oxetanes

Photochemical [2+2] Cycloaddition

• Photochemical [2+2] cycloaddition of aldehydes or ketones with alkenes provides oxetanes. Through this approach, a diversity of oxetanes can be accessed.

\[
\text{Aldehyde or ketone} + \text{Alkene} \xrightarrow{hv} \text{Oxetane}
\]

• The carbonyl is usually the light absorbing species.

• One of the challenges of this approach for unsymmetrical alkenes is the potential to produce a mixture of regioisomers.

\[
\text{Ph\text{-}H} + \text{Alkene} \xrightarrow{hv} \text{Oxetane} + \text{Oxetane}
\]
Synthesis of Azetidines

Photochemical [2+2] Cycloaddition

• Photochemical [2+2] cycloaddition of imines with alkenes lends access to azetidines.

• Through this approach, a diversity of azetidines can be accessed.
**Synthesis of Oxetanes**

**Reaction of Ketones with Sulphur Ylides**

- Although the more common reaction of sulfonium ylides with aldehydes and ketones provides oxiranes, the use of excess sulfonium ylide leads to the ring expansion of epoxides to oxetanes.

- This allows for a one-pot conversion of aldehydes/ketones to 2-substituted oxetanes.

\[
\begin{align*}
\text{RCHO} \quad \text{CH}_3\text{S} \equiv \text{CH}_3 \quad \rightarrow \quad \text{RCH(O)CH}_2\text{O} \quad + \quad \text{CH}_3\text{SSCH}_3 \\
\text{(Atleast 2 equivalents)}
\end{align*}
\]

- 1-Oxaspiro[3.5]nonane can be obtained based on the reaction shown below:

\[
\begin{align*}
\text{Cyclohexanone} \quad + \quad \text{CH}_3\text{S} \equiv \text{CH}_3 \quad \rightarrow \quad \text{1-Oxaspiro[3.5]nonane} \quad + \quad \text{CH}_3\text{SSCH}_3 \\
\text{(2 Equivalents)}
\end{align*}
\]
Synthesis of Oxetanes

Reaction of Ketones with Sulphur Ylides

• The mechanism of the reaction is illustrated below:
Synthesis of Oxetanes

Ring Expansion of Oxiranes

• A more efficient approach to oxetanes based on sulfonium ylides is through the ring opening of oxiranes with dimethylsulfonium methylide.

• Subsequent cyclization in the same step with release of dimethyl sulfide affords 2-substituted oxetanes.

• 1-Oxaspiro[3.5]nonane can be obtained based on the reaction shown below:
Synthesis of Oxetanes
Ring Expansion of Oxiranones

• The mechanism of the reaction is illustrated below:
Synthesis of Azetidines
Ring Expansion of Aziridines

- Azetidines can be accessed through ring expansion of aziridines with dimethylsulfonium methylide.
- The reaction starts with ring opening of the aziridine. Subsequent cyclization affords 2-substituted azetidines.

\[
\begin{align*}
\text{O} &\quad \text{Ph} \\
\text{S} &\quad \text{S} \\
\text{O} &\quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{O} &\quad \text{Ph} \\
\text{S} &\quad \text{S} \\
\text{O} &\quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} &\quad \text{S} \\
\text{N} &\quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{O} &\quad \text{Ph} \\
\text{S} &\quad \text{S} \\
\text{O} &\quad \text{N}
\end{align*}
\]

- 1-Benzenesulphonyl-azetidine can be obtained based on the reaction shown below:
Synthesis of Azetidines

Ring Expansion of Aziridines

• The mechanism of the ring expansion is illustrated below:

(i)  

(ii)  

(iii)
Complete the following reactions by giving the principal organic product.

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