4-Membered ring

1. Cyclobutanes and Cyclobutenes
2. Oxetanes
3. Lactones and Lactams

Methods for 4-membered ring formation

1. Photochemical cycloadditions
2. Staudinger reaction
3. Acyloan reaction
4. Sulfur ylide
5. Electrocyclic
Problem of incompatible symmetry is avoided by converting one of them into excited state photochemically.

\[ \text{ground state of alkene} \quad \rightarrow \quad \text{excited state of alkene} \]

\[ \pi^* \quad \rightarrow \quad \pi \quad \quad \Updownarrow \]

\[ \text{UV light (hv)} \quad \rightarrow \quad \pi^* \quad \rightarrow \quad \pi \quad \quad \Updownarrow \]
Now combining excited state of alkene with ground state of another one solves the symmetry problem.

Alkene can be dimerized photochemically in this way.
[2+2] Cycloadditions

If one alkene is bonded to Conjugate group it alone absorbs UV light

Reaction is stereospecific

Least hindered transition state is observed
[2+2] Cycloadditions

Regioselectivity

\[ \text{alkene LUMO} \quad \text{alkene HOMO} \quad \text{enone LUMO} \]
[2+2] Cycloadditions

Enones with Olefins

CH\textsubscript{2}CH\textsubscript{2} + CH\textsubscript{2}CH\textsubscript{2} \rightarrow \text{products} (90%)

CH\textsubscript{2} = \text{products} \rightarrow \text{products}

Caryophellene

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[2+2] Cycloadditions

Hot Ground State?

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[2+2] Cycloadditions

Synthesis of lycorine

\[
\text{Base} \quad \text{hv} \quad \text{lycorine}
\]
[2+2] Cycloadditions

Cycloaddition of 1,3-butadiene with Me_2CO under irradiation.

Cycloaddition of diene with dienophile to form adducts.

Cycloaddition of diene with dienophile to form adducts.
[2+2] Cycloadditions

Enone with Allenes

\[
\text{H}_2\text{C}≡\text{C}=\text{CH}_2 \xrightarrow{h\nu} \text{product} + \text{product} \quad 2:1
\]

Enones with Acetylene

DeMayo Reaction (Enol with Alkene)

\[
\text{CO}_2\text{Me} \xrightarrow{p\text{-TSA, MeOH reflux}} \text{product}
\]
[2+2] Cycloadditions

\[ \text{h}_\nu \]

\[ \text{favored} \]

70-80% de

\[ \text{disfavored} \]
Photochemistry of ketones

Norrish type I and type II reactions

\[ \text{ketone} \xrightarrow{\text{hv, 254, 307 nm}} \text{allyl radical} \xrightarrow{\text{Norrish I cleavage}} \text{alkene radical} \]

\[ \text{allyl radical} \xrightarrow{\text{Norrish II cleavage}} \text{radical} \]

\[ \text{radical} \xrightarrow{\text{Yang reaction}} \text{alcohol} + \text{vinyl radical} \]
Photochemistry of ketones

Yang reaction

\[
\text{MOMO} \quad \text{h} \nu (254 \text{ nm}) \quad \text{C}_6\text{H}_6 \\
\text{SEMO} \quad \text{CH}_3 \\
\]

Filtering photochemical reaction to prevent Norrish reactions

Quartz 180 nm
Vycor 200nm
Pyrex 280nm
Uranium glass 320nm
Thermal [2+2] cycloadditions

It must have two double bonds at same carbon atom

\[
\begin{align*}
\text{ketene} & : \quad \text{R} & \quad \text{R} & \quad \text{C} & \quad \text{=O} \\
\text{isocyanate} & : \quad \text{R} & \quad \text{N} & \quad \text{C} & \quad \text{=O}
\end{align*}
\]

\[
\text{heat} \quad \begin{array}{c}
\text{O} \\
\text{C} \\
\text{O} \\
\text{C}
\end{array}
\]

\[
\text{heat} \quad \begin{array}{c}
\text{O} \\
\text{C} \\
\text{N} \\
\text{SO} \text{Cl}
\end{array}
\]
Thermal [2+2] cycloadditions

HOMO/LUMO combination is antibonding at one end

- rotate 90°
- add LUMO of other alkene
- bonding
- antibonding
Ketenes

central sp carbon atom with extra $\pi$ bond

electrophilic, low-energy LUMO

preparation of ketenes

\[
\begin{align*}
\text{(1) } & \quad \text{O} & \quad \Delta \quad \text{O} & \quad \text{H} & \quad \text{C}=\text{O} \\
\text{(2) } & \quad \text{O} & \quad \text{Et}_3\text{N} \quad \text{O} & \quad \text{H} & \quad \text{C}=\text{O} \\
\text{(3) } & \quad \text{O} & \quad \text{Zn} \quad \text{O} & \quad \text{H} & \quad \text{C}=\text{O} \\
\text{(4) } & \quad \text{R} & \quad \text{hv} \quad \text{R} & \quad \text{H} & \quad \text{C}=\text{O}
\end{align*}
\]
Ketene [2+2] cycloadditions

More nucleophilic carbon will attack

\[ \text{AcOH} \quad \text{Zn/AcOH} \]

Stereochemistry can be controlled
Ketene [2+2] cycloadditions

\[ \text{Ph} \quad \text{Cl}_3C\text{O} \quad \text{Cl} \quad \text{Zn-Cu, Et}_2O \quad \text{CH}_2\text{N}_2 \quad \text{Ar} \]

1) [Chemical Structure]
2) [Chemical Structure]
3) [Chemical Structure]
4) [Chemical Structure]
5) [Chemical Structure]
Reaction of ketene with enamines

\[
\begin{align*}
\text{Enamine} & \quad \text{Ketene} \quad \rightarrow \quad \text{Product} \\
\text{With olefins} & \quad \text{With acetylene-biradical mechanism}
\end{align*}
\]

Difluorodihaloethylene

\[
\begin{align*}
\text{R} & \quad \text{F}_2\text{C} = \text{CX}_2 \\
\text{R} & \quad \text{F}_2\text{C} = \text{CX}_2 \\
\text{R} & \quad \text{F}_2\text{C} = \text{CX}_2 \\
\end{align*}
\]
β-lactams by [2+2] cycloadditions

Staudinger reaction
$S_N2$ Reactions

$$\text{KH, DMSO}$$

$$\text{Grandisol}$$

$$\text{NBS}$$

$$\text{Tf}_2\text{O, CH}_2\text{Cl}_2$$

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Acyloin reaction

\[(\text{CH}_2)_n\text{CO}_2\text{Me} \xrightarrow{\text{Na, TMS-Cl}} (\text{CH}_2)_n\text{OTMS} \xrightarrow{\text{F}^-} (\text{CH}_2)_n\text{CO}_2\text{Me} \]

Benzocyclobutanes

benzocyclobutanes

o-quinodimethane

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Cyclotrimerization

\[
\begin{align*}
\text{CpCo(CO)\textsubscript{2}} & \quad \text{Me\textsubscript{3}Si=\textsubscript{SiMe\textsubscript{3}}} \\
\end{align*}
\]

Sulfur ylides

\[
\begin{align*}
\text{BF\textsubscript{3}} & \quad \text{O} \\
\end{align*}
\]
Oxetanes

Paterno-Buchi reaction

\[
\begin{align*}
\text{R} & \quad \text{R'} \quad \xrightleftharpoons[\text{H}_2\text{C}≡\text{CH}_2\quad \text{hv}]{\text{hv}} \quad \text{R} \quad \text{R'} \\
\text{R} & \quad \text{R'} \quad \xrightleftharpoons[\text{H}_2\text{C}=\text{C}≡\text{CH}_2\quad \text{hv}(254\text{nm})]{\text{hv}} \quad \text{R} \quad \text{R'} \\
\text{O} & \quad \text{O} \quad \xrightleftharpoons[\text{Me}_2\text{C}=\text{CMe}_2\quad \text{hv}]{\text{hv}} \quad \text{O} \quad \text{O}
\end{align*}
\]
Paterno-Buchi reaction

Regioselectivity depends on more stable of the two possible diradical intermediates

\[
\text{PhCHO} + \text{H}_2\text{C}≡\text{X} \rightarrow \begin{aligned}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O}
\end{aligned}
\]

or

\[
\text{Ph} \quad \text{Ph} \\
\text{X} & \quad \text{X}
\]

major

diradicals intermediates

\[
\begin{aligned}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O}
\end{aligned}
\]

> 

more stable
β-lactams

\[
\text{LDA, THF} \quad \xrightarrow{\text{R}_1 \text{R}_2 \text{R}_3 \text{R}_4} \quad \text{O\text{SPh}} \\
\text{O\text{SPh}} \quad \xrightarrow{\text{R}_1 \text{R}_2 \text{R}_3 \text{R}_4} \quad \text{O\text{SPh}} \\
\text{DEAD, Ph}_3\text{P} \quad \xrightarrow{\text{R}_2\text{CuLi}} \quad \text{NH\text{CO}_2\text{H}}
\]

1) MgBr\text{OEt}_2 \\
2) KF, H_2O, CH_3CN

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4-Membered ring

Cubane

Challenges

1. Six - 4 membered rings fused together
2. No functional groups
3. Highly strained
4. Low molecular weight $C_8H_8=104$
Retrosynthesis

1. 4-membered rings could be formed by photochemical reaction

2. How many 4-membered rings could be formed by photochemical reaction?

How about this?

Many Problems:

1. Reversibility
2. Stability of the starting material
3. Intermolecular reaction
Cubane

Solutions

1. Introduce a functional group

2. Which functional group?
   a. The functional group should be removed easily
   b. It also should be formed easily from another precursor
   c. This should be introduced along with either ring contraction or ring expansion

Ring Expansion or Ring Contraction?

\[
\begin{align*}
\Delta & \rightarrow \square & \text{Ring Expansion} \\
\pentagon & \rightarrow \square & \text{Ring Contraction}
\end{align*}
\]

Which functional group could be formed along with this reaction?
Cubane

Ring Expansion or Ring Contraction?

Therefore, need to go for ring contraction
- Favorskii reaction will be better
Cubane

One Carboxylic Acid or Two Carboxylic Acids?

1. One carboxylic acid- precursor will have only one 5-membered ring and remaining will be 4-membered ring

2. Two carboxylic acid- precursor will have only two 5-membered ring and remaining will be 4-membered ring
Cubane

Two Carboxylic Acids

Where and what is the relationship?

Molecule could be symmetrical or non-symmetrical

Which will be easier from synthetic point of view?
Cubane

Quasi-Favorskii Rearrangement

\[
\begin{align*}
\text{Cubane} & \quad \xrightarrow{\text{1,2}} \quad \text{carboxylic acid} \\
\text{Cubane} & \quad \xrightarrow{\text{1,3}} \quad \text{carboxylic acid} \\
\text{Cubane} & \quad \xrightarrow{\text{1,4}} \quad \text{carboxylic acid}
\end{align*}
\]
Cubane

Two disconnections for photochemical reaction
Cubane

Problems in Starting Material

1. Cyclopentadienone is highly unstable
2. Difficult to prepare

Synthesis

\[
\text{Cyclopentadienone} \xrightarrow{\text{NBS, } \text{hv}} \text{Bromoepoxide} \xrightarrow{\text{Br}_2} \text{Bromo-epoxide} \xrightarrow{\text{Et}_3\text{N}} \text{Cubane}
\]

\[
\begin{align*}
\text{Cyclopentadienone} & \quad \xrightarrow{\text{NBS, } \text{hv}} \quad \text{Bromoepoxide} \\
\text{Bromoepoxide} & \quad \xrightarrow{\text{Br}_2} \quad \text{Bromo-epoxide} \\
\text{Bromo-epoxide} & \quad \xrightarrow{\text{Et}_3\text{N}} \quad \text{Cubane}
\end{align*}
\]
Cubane synthesis

1) SOCl₂
2) Pyridine

10% KOH

75% H₂SO₄

Philip Eaton, University of Chicago
Cubane synthesis

Modified Synthesis

1) \( \text{H}^+ \)
2) \( \text{H}_2\text{SO}_4 \)

1) \( \text{NaOH} \)
2) \( \text{H}^+ \)

1) \( \text{hv} \)
2) \( \text{H}_2\text{SO}_4 \)