Alpha sub of Carbonyl Compounds
Enols and Enolate

1.

Base used is LDA lithium diisopropyl amine- good base but poor nucleophile

Condensation with ketones and aldehydes
ketones in the presence of acid.

2. alpha halogenation

Rxn of methyl ketones

1. Basic conditions-

Use I$_2$ to identify methyl ketones.
2. Acidic conditions -

Mono halogenation

3. alpha bromination of acids - HVZ rxn.
Alkylation of enolate ions-

\[
\begin{array}{c}
\text{two possible places of attack} \\
\text{small yield}
\end{array}
\]

1. Use LDA as the base.
2. Need to have only one type of alpha proton or get complex mixture.

Ex.

Milder way to complete the same rxn. Enamine Rxn.
Stork Rxn- use active alkyl halides

Ph-CH₂-X  CH₃-X  C=C=C-X
RCl

Ex.

Problem
Aldol Condensation

1. Self condensation.

Two mechanisms –
1. Base catalyzed-

Two mechanisms –
1. Base catalyzed-
2. Acid catalyzed-

Show dehydration steps. Always get alpha beta unsaturated ketone more stable thermodynamically.

2. Crossed Aldol condensation (show overviewed)

Cross aldol condensation. Need to fix one reactant with no alpha protons.

Ex.

A) Crossed Aldol
B) Aldol Cyclizations

Will prefer to form 5 and 6 membered rings only.

Ex.

3. Claisen Ester Condensation

H₃C- CO- H₃C-CH₃
pKa 24  pKa 20  because  [H₃C-O-]
ester less acidic  partially resonance puts minus on O
Ex. Make

Can not do. No beta

Ex.

Crossed Ester Condensation- one component can not have an alpha proton.
Ex.

\[
\text{H}_3\text{CO}-\text{CO}-\text{OCH}_3 + \text{H}_3\text{CO}-\text{COC}_2\text{H}_5 \rightarrow \begin{array}{c}
\text{H}_3\text{C} \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{O}
\end{array} + \begin{array}{c}
\text{H}_3\text{CO} \\
\text{CH}
\end{array}
\]

no alpha protons

Ex.

\[
\text{Ph} \text{CO} - \text{OCH}_3 + \text{Ph} \text{CO} - \text{OCH}_3 \rightarrow \begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{C} \\
\text{Ph}
\end{array} + \text{HOCH}_3
\]

Can use an ester and ketone
1) NaOCH₃
2) H₃O⁺

*More acidic

Ex. Make the following.

a)

b)

Ketone more acidic.

Claisen Cyclization with Esters.
1) Ex. Make

\[
\begin{align*}
\text{Et} & \quad \text{Et} \\
\text{Et} & \quad \text{Et}
\end{align*}
\]

a) Can not do. Must be alpha beta position.

2) Make

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

a)
Crossed ester condensation- one component must not have any alpha protons.

Possibilities-

Ex.

Can use an ester or ketone, ketone more acidic.
6. Beta-dicarbonyl compounds, more acidic.

Ex.

Malonic Ester synthesis.

A) General Rxn, single alkylation
Mechanism of decarboxylation.

B) Dialkylation

Dialkylation can also be used to form 4-member rings. Use 1,3-dibromopropane.
Overall Ex.

Make

Michael Rxn- 1,4 addition to $\alpha,\beta$ unsaturated ketones.

By resonance generate positive charges at position 1 and 4. Can get addition of a nucleophile at 1,4 and 1,2. Addition of Nu and H.
Nuc: Michael donor, ketone Michael acceptor

Ex. Make.

\[
\text{1,2} \quad \text{Nuc:} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OEt}
\end{array} \quad 1) \text{NaOEt} \\
\quad \begin{array}{c}
\text{CN} \\
\text{O} \\
\text{OEt}
\end{array} \quad 2) \text{H}_3\text{O}^+ \\
\text{H} \\
\text{H} \\
\text{O}
\]

Ex. Make

\[
\text{Can do it two ways:}
\]

a) \[
\text{1,4} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OEt}
\end{array} \quad 1) \text{NaOEt} \\
\quad \begin{array}{c}
\text{CN} \\
\text{O} \\
\text{OEt}
\end{array} \quad 2) \text{H}_3\text{O}^+ \\
\text{H} \\
\text{H} \\
\text{O}
\]
b) Can use another way but need to be careful. Need only one nucleophile.

\[
\text{K} + \text{NaOEt} \quad 1) \quad \text{Bad, competing aldols} \\
\text{H}_2\text{O}^+ \quad 2)
\]

Fix with amine

\[
\text{Intermediates in Mechanism:}
\]

Michael plus Claisen. Robinson annulation.

\[
\text{Intermediates in Mechanism:}
\]
Michael Product

EX.

Make:

Answer: