

CH 318 N

LECTURE 17

**Textbook Assignment: Chapter 19**

**Homework (for credit): POW 8 posted**

**Today's Topics: Enolates**

*Notice & Announcements:*

**Exam II: Grading in Progress**

ORGANIC LECTURE SERIES

# **Enolate Anions and Enamines**

## Acidity of $\alpha$ -Hydrogens

Hydrogens alpha to a carbonyl group are more acidic than hydrogens of alkanes, alkenes, and alkynes but less acidic than the hydroxyl hydrogen of alcohols

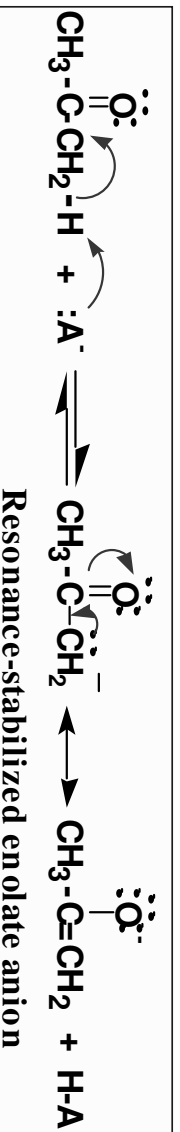
Type of Bond	pK <sub>a</sub>
$\text{CH}_3\text{CH}_2\text{O-H}$	16
$\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\text{-H}$	20
$\text{CH}_3\text{C}\equiv\text{C-H}$	25
$\text{CH}_2=\text{CH-H}$	44
$\text{CH}_3\text{CH}_2\text{-H}$	51

$$\text{pK}_a = -\log K_a$$

$$\text{Sec 16.12} \quad 3$$

$\alpha$ -Hydrogens are more acidic because the enolate anion is stabilized by:

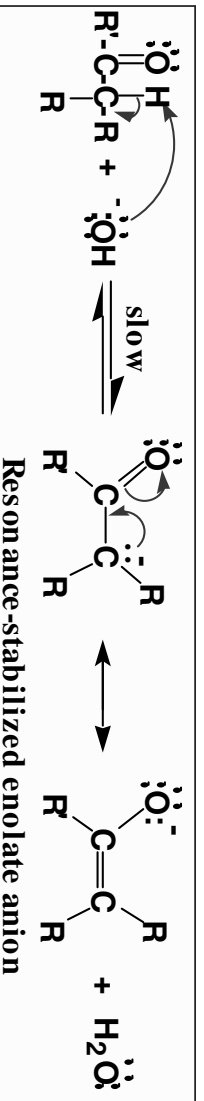
1. delocalization of its negative charge
2. the electron-withdrawing inductive effect of the adjacent electronegative oxygen



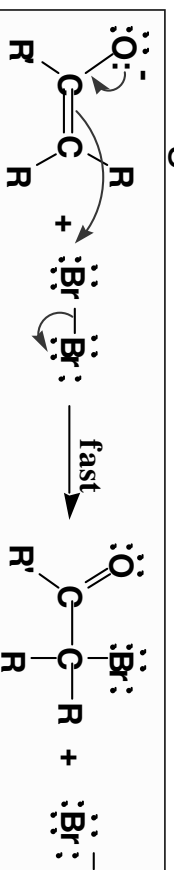
## Enolates in Use

- Base-promoted  $\alpha$ -halogenation

Step 1: formation of an **enolate anion**



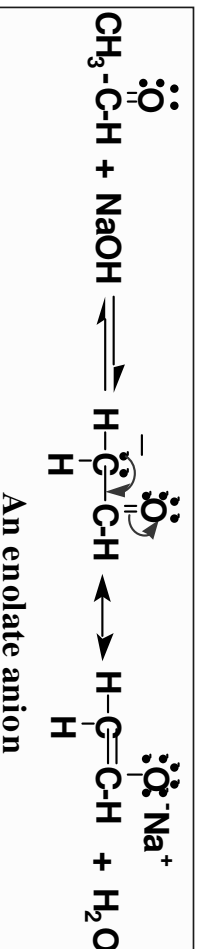
Step 2: nucleophilic attack of the enolate anion on halogen



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## Formation of an Enolate Anion

- Enolate anions are formed by treating an aldehyde or ketone with base

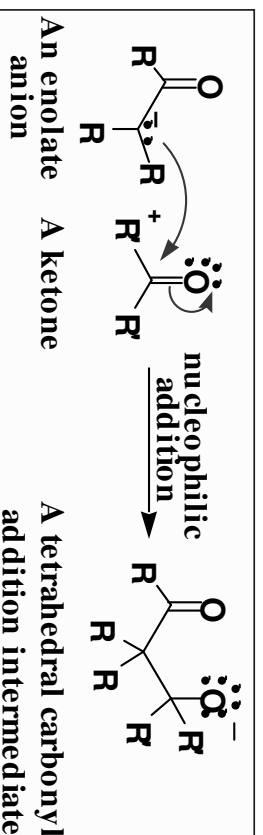
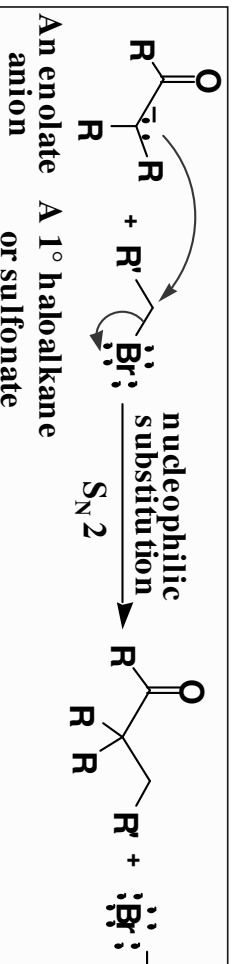


- most of the negative charge in an enolate anion is on oxygen

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## Enolate Anions

- Enolate anions are nucleophiles in  $S_N2$  reactions and carbonyl addition reactions



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## The Aldol Reaction

- The most important reaction of enolate anions is nucleophilic addition to the carbonyl group of another molecule of the same or different compound
  - although these reactions may be catalyzed by either acid or base, **base catalysis is more common**
  - The reaction results in a new C—C bond**

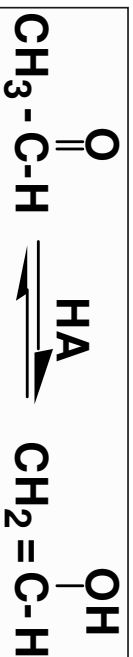
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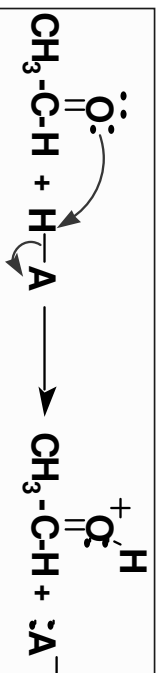
## The Aldol Reaction-Acidic

- Acid-catalyzed aldol reaction

– Step 1: acid-catalyzed equilibration of keto and enol forms



– Step 2: proton transfer from HA to the carbonyl group of a second molecule of aldehyde or ketone

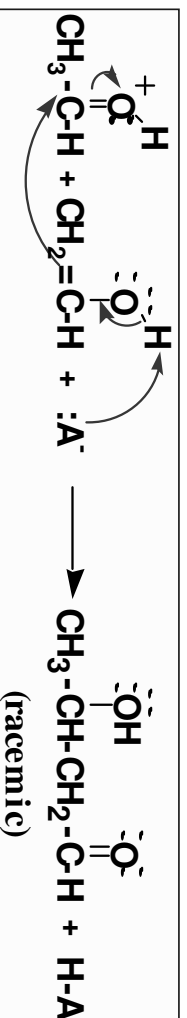


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## The Aldol Reaction-acidic

– Step 3: attack of the enol of one molecule on the protonated carbonyl group of another molecule

– Step 4: proton transfer to A<sup>-</sup> completes the reaction

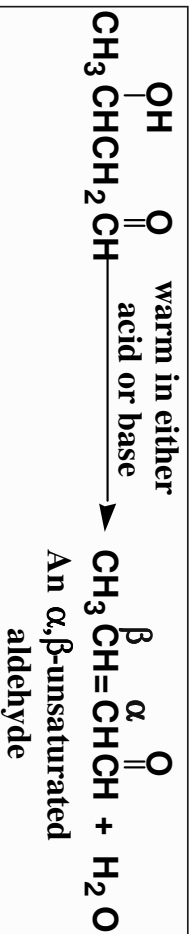


(Steps 3 & 4 are combined here)

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## The Aldol Products-H<sub>2</sub>O

– aldol products are very easily dehydrated to  $\alpha,\beta$ -unsaturated aldehydes or ketones

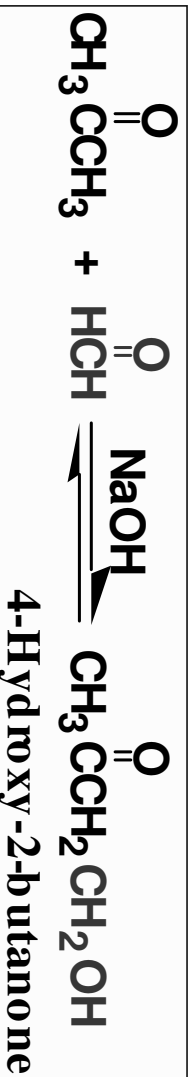


- aldol reactions are reversible and often little aldol present at equilibrium
- $K_{\text{eq}}$  for dehydration is generally large
- if reaction conditions bring about dehydration, good yields of product can be obtained

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## Crossed Aldol Reaction

In a crossed aldol reaction, one kind of molecule provides the enolate anion and another kind provides the carbonyl group

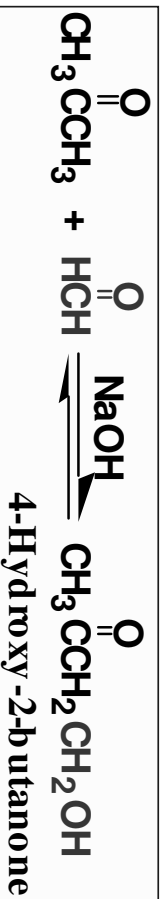
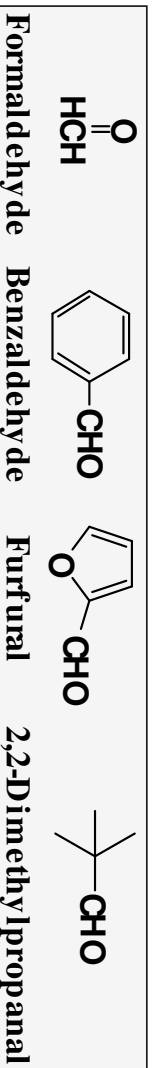


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## Crossed Aldol Reaction

Crossed aldol reactions are successful if:

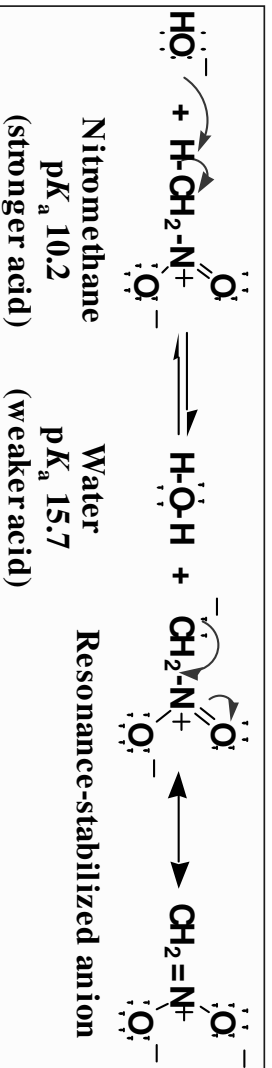
1. one of the reactants has no  $\alpha$ -hydrogen and, therefore, cannot form an enolate anion and
2. the other reactant has a more reactive carbonyl group, namely an aldehyde



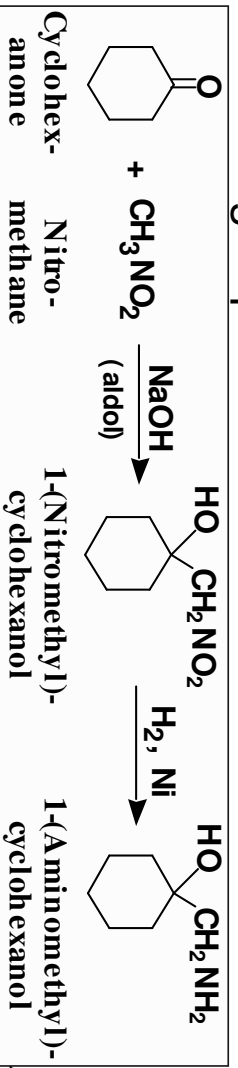
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## Crossed Aldol Reaction

- Nitro groups can be introduced by way of an aldol reaction using a nitroalkane



– nitro groups can be reduced to 1° amines

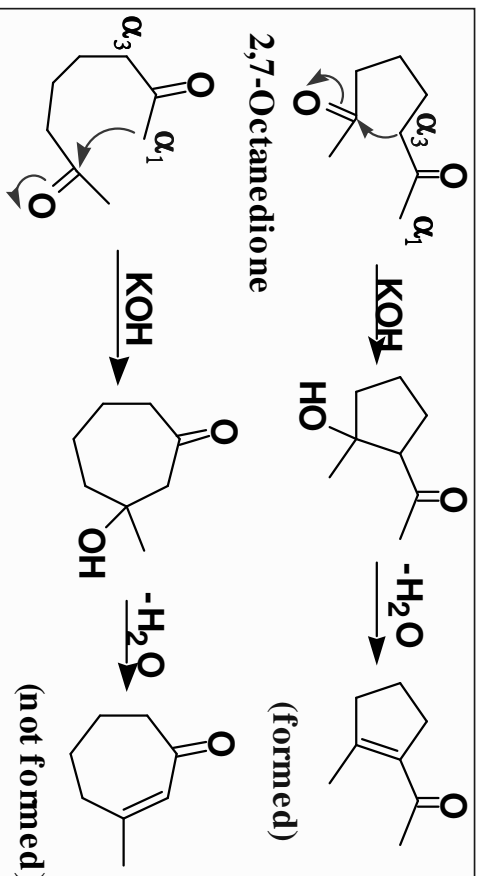


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## Intramolecular Aldol Reactions

intramolecular aldol reactions are most successful for formation of five- and six-membered rings

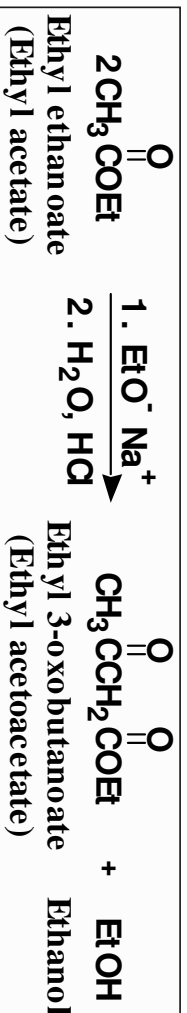
consider 2,7-octadione, which has two  $\alpha$ -carbons



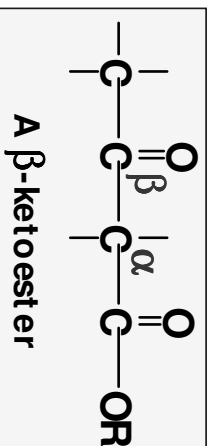
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## Claisen Condensation

- Esters also form enolate anions which participate in nucleophilic acyl substitution



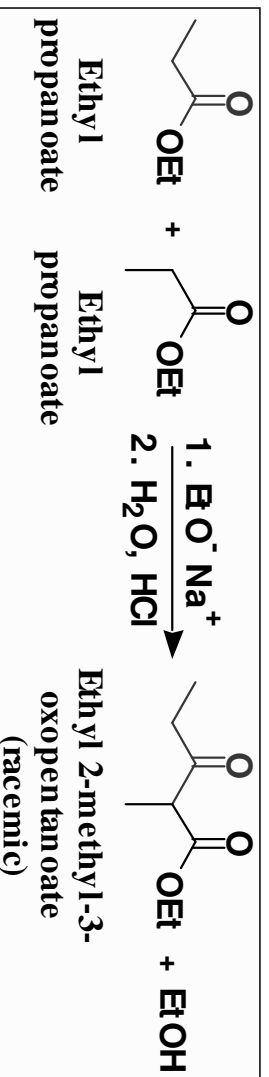
the product of a Claisen condensation is a  $\beta$ -ketoester



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## Claisen Condensation

– Claisen condensation of ethyl propanoate gives this  $\beta$ -ketoester

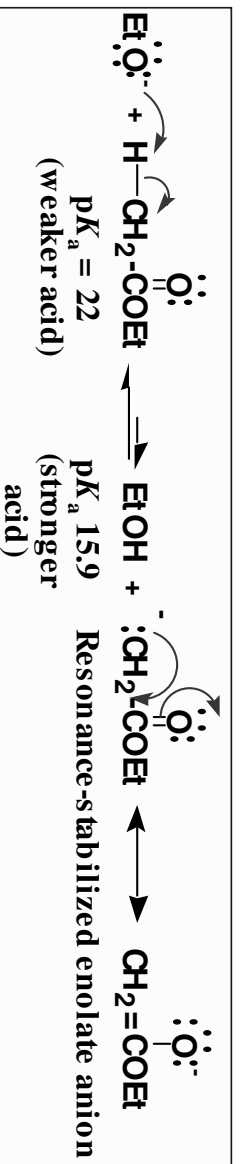


*Nota bene:* the base should be the alkoxide of the ester group  
(This will overcome trans-esterification.)

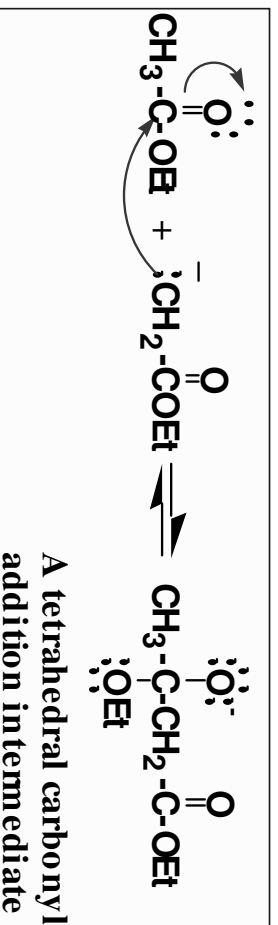
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## Claisen Condensation

Step 1: formation of an enolate anion



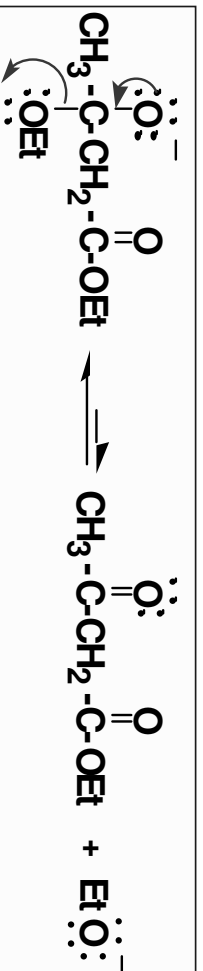
Step 2: attack of the enolate anion on a carbonyl carbon gives a TCAI



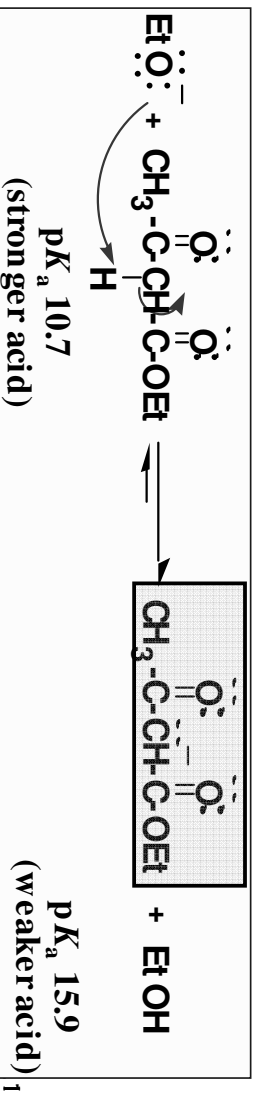
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## Claisen Condensation

Step 3: collapse of the TCAI gives a  $\beta$ -ketoester and an alkoxide ion:

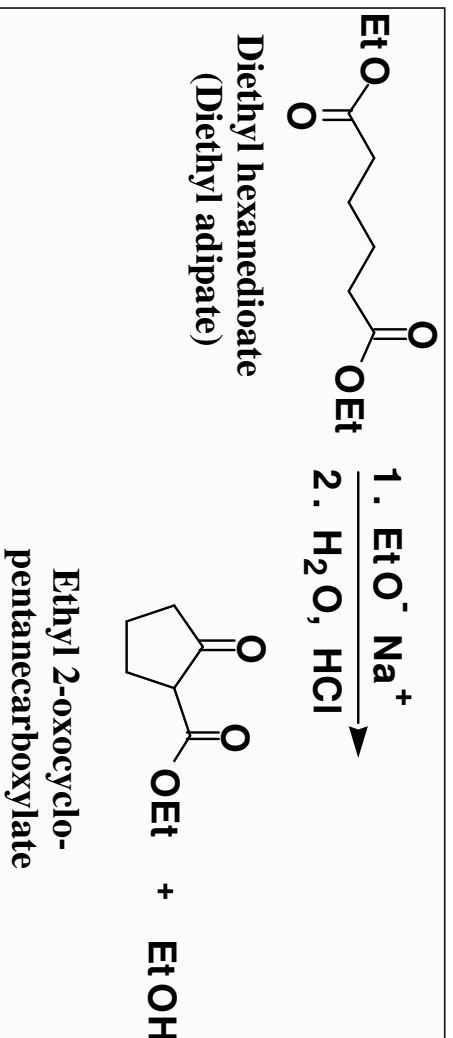


Step 4: an acid-base reaction drives the reaction to completion:



## Dieckman Condensation

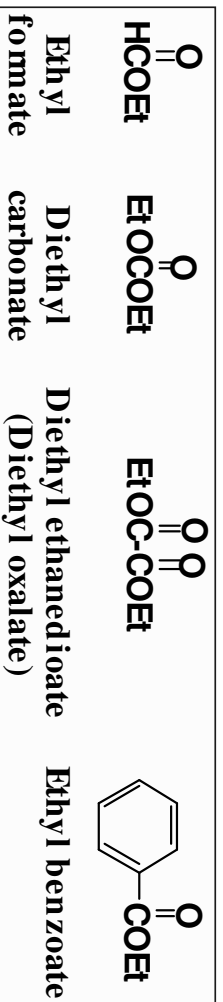
- An intramolecular Claisen condensation



## Crossed Claisen Condensations

Crossed Claisen condensations between two different esters, each with  $\alpha$ -hydrogens, give mixtures of products and are not useful

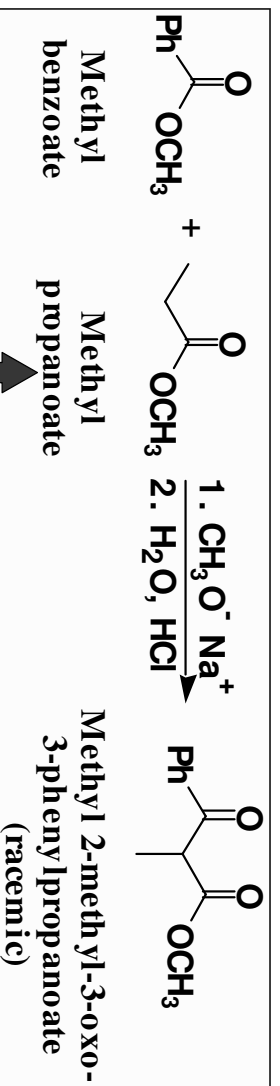
- crossed Claisen condensations are useful, if there is an appreciable difference in reactivity between the two esters; when one of them has no  $\alpha$ -hydrogens



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## Crossed Claisen Condensations

- the ester with no  $\alpha$ -hydrogens is generally used in excess

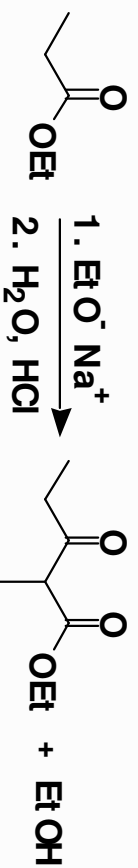


Only this enolate can be formed

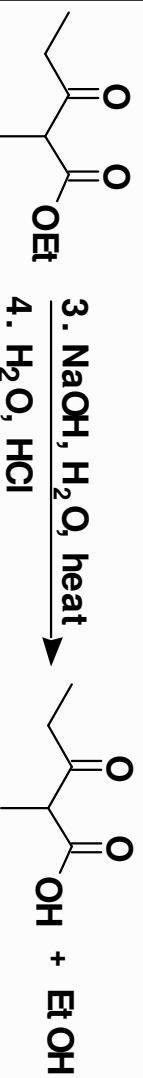
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# Claisen condensations as routes to ketones

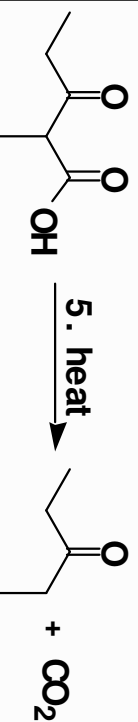
Reactions 1 & 2: Claisen condensation followed by acidification



Reactions 3 & 4: Saponification and acidification



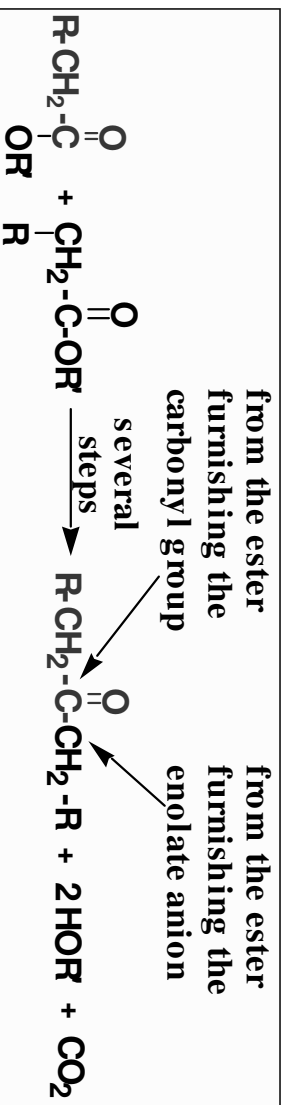
Reaction 5: thermal decarboxylation



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## Claisen Condensations

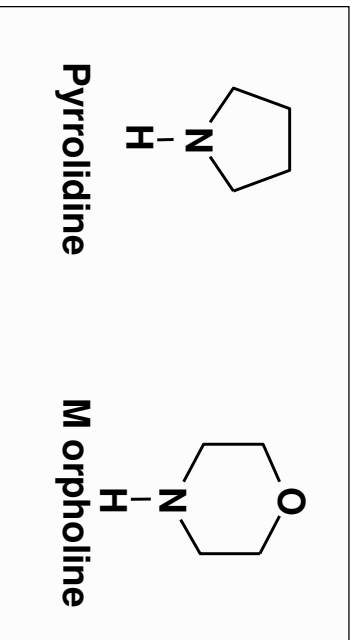
The result of Claisen condensation, saponification, acidification, and decarboxylation is a ketone:



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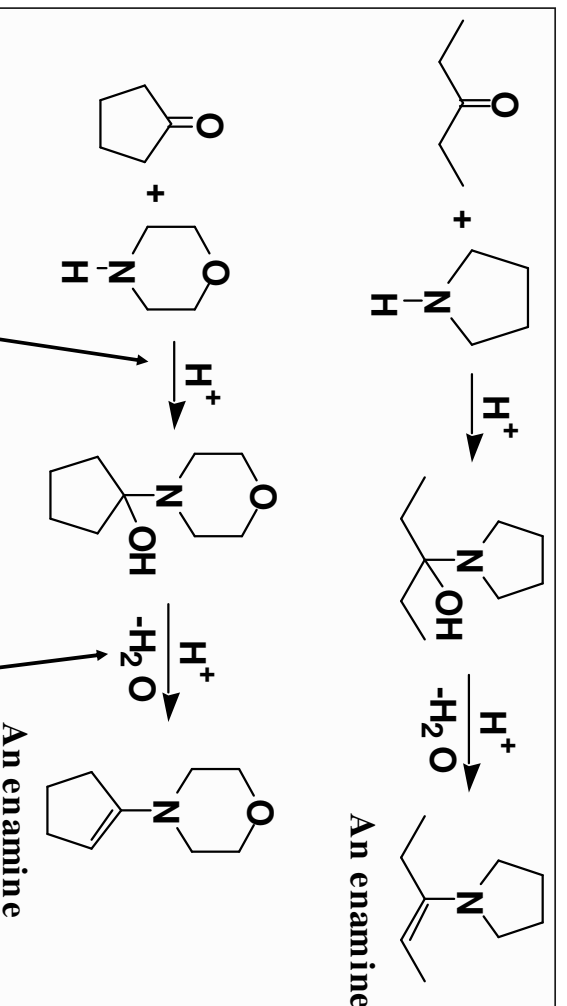
## Enamines

Enamines are formed by the reaction of a **2° amine with the carbonyl group of an aldehyde or ketone**  
 the 2° amines most commonly used to prepare enamines are pyrrolidine and morpholine:



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## Preparation of Enamines



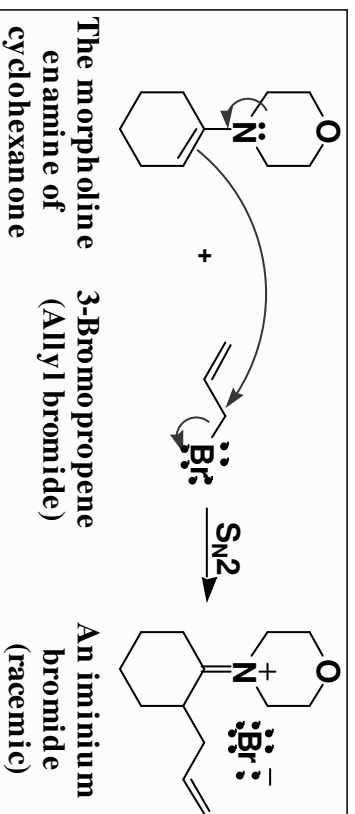
Acid catalyst is usually TsOH; azeotropic removal of  $\text{H}_2\text{O}$ .

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## Enamines-Alkylation

The value of enamines is that the  $\beta$ -carbon is nucleophilic (**same C that was  $\alpha$  to carbonyl**)

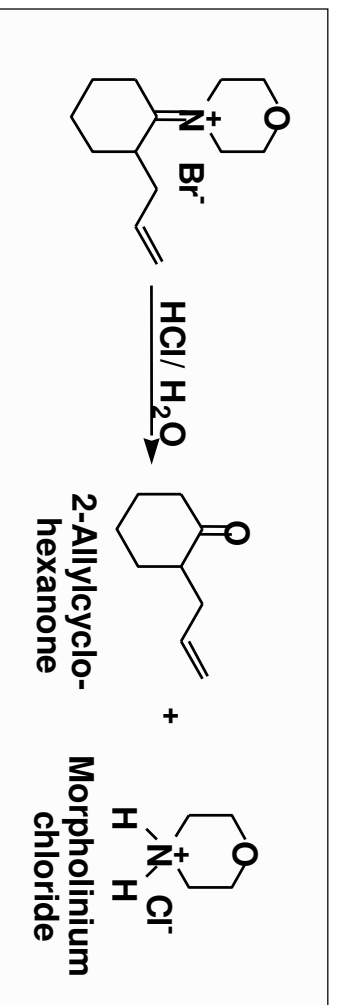
- enamines undergo  $S_N2$  reactions with methyl and 1 $^\circ$  haloalkanes,  $\alpha$ -haloketones, and  $\alpha$ -haloesters
- treatment of the enamine with one equivalent of an alkylating agent gives an iminium halide



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## Enamines-Alkylation

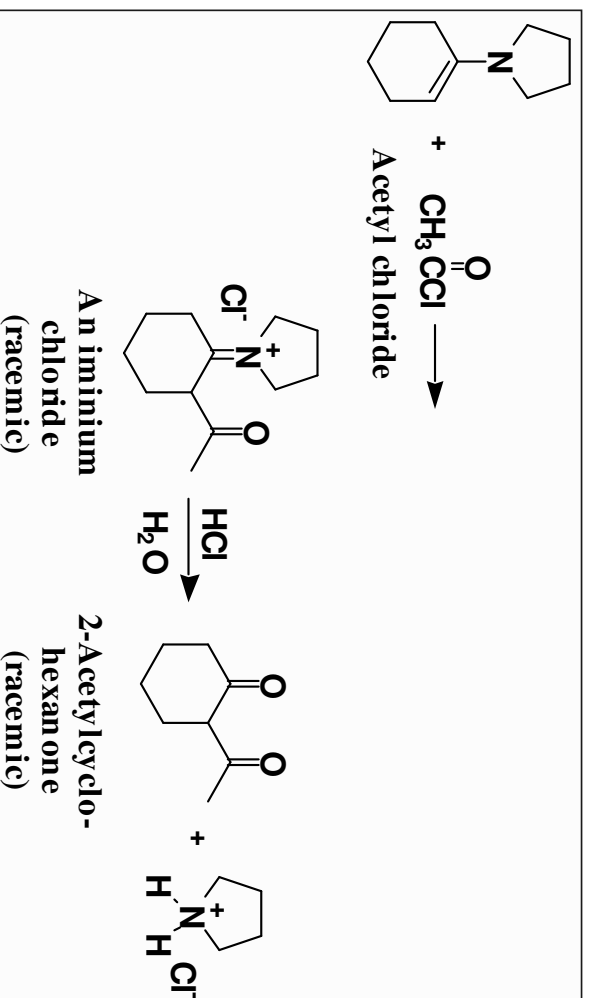
hydrolysis of the iminium halide (salt) gives the alkylated aldehyde or ketone:



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## Enamines-Acylation

**enamines undergo acylation** when treated with acid chlorides and acid anhydrides



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## Synthetic Advantages of Enamines vs Enolates

- 1) Avoids proton transfer.
- 2) Regiochemistry of alkylation can be controlled. (For un-symmetric ketones)
- 3) Avoids polyalkylation.
- 4) Avoids O-alkylation.

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