

CH 310 N

TH 2-3:30

LECTURE 16

Textbook Assignment: Chapter 19

Homework (for credit): POW 8 posted

Today's Topics: Enolates & Enamines

Notice & Announcements:

Exam II: Grading in Progress

ORGANIC LECTURE SERIES

Enolate Anions and Enamines

Acidity of α -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

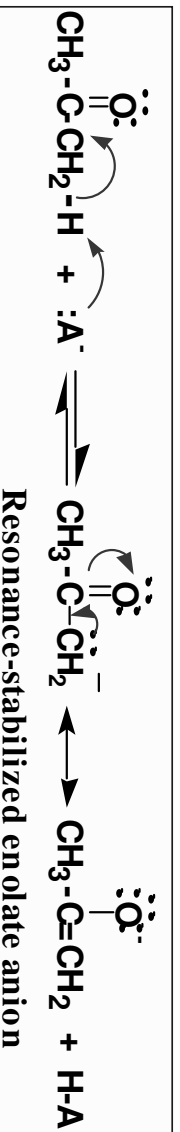
Type of Bond	pK _a
$\text{CH}_3\text{CH}_2\text{O-H}$	16
$\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\text{-H}$	20
$\text{CH}_3\text{C}\equiv\text{C-H}$	25
$\text{CH}_2=\text{CH-H}$	44
$\text{CH}_3\text{CH}_2\text{-H}$	51

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

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

α -Hydrogens are more acidic because the enolate anion is stabilized by:

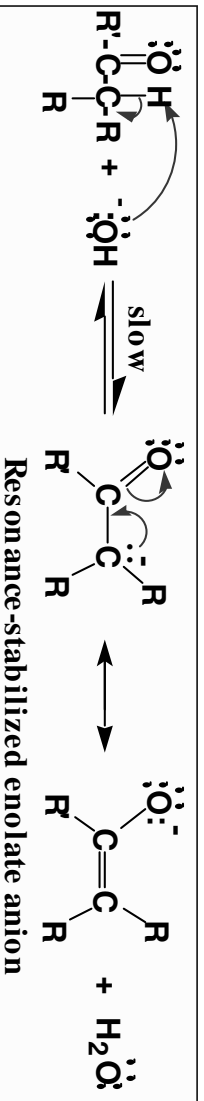
1. delocalization of its negative charge
2. the electron-withdrawing inductive effect of the adjacent electronegative oxygen



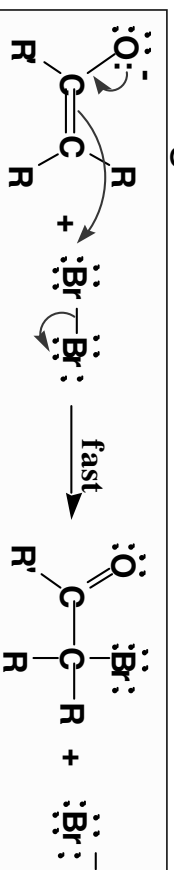
Enolates in Use

- Base-promoted α -halogenation

Step 1: formation of an enolate anion



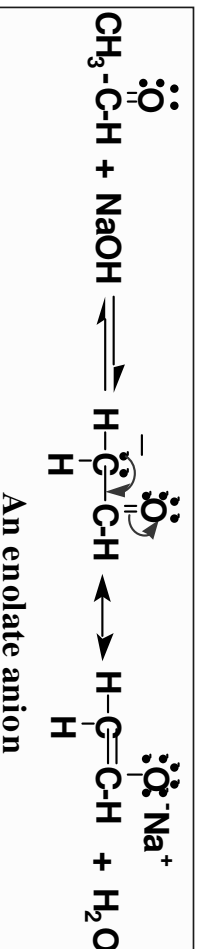
Step 2: nucleophilic attack of the enolate anion on halogen



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Formation of an Enolate Anion

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

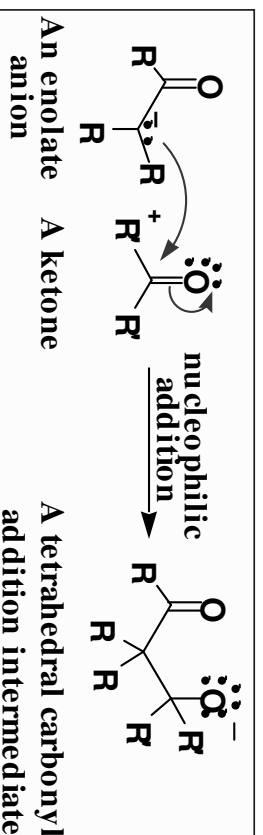
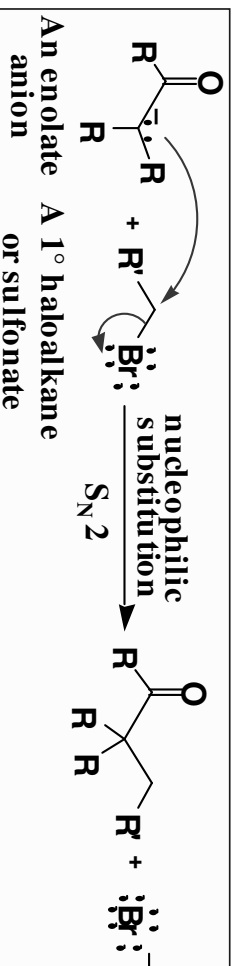


- most of the negative charge in an enolate anion is on oxygen

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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

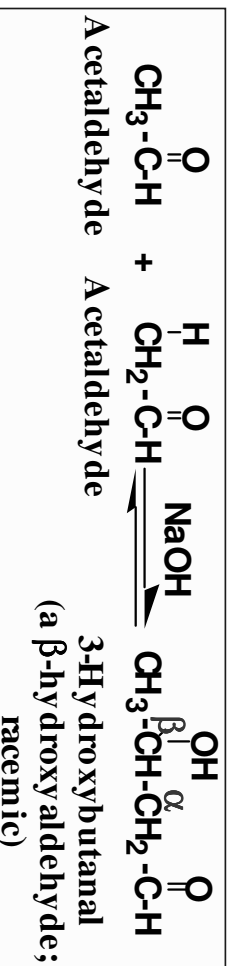
- The most important reaction of enolate anions is nucleophilic addition to the carbonyl group of another molecule (of the same or different compound)
 - although these reactions may be catalyzed by either acid or base, **base catalysis is more common**
 - The reaction results in a new C—C bond**

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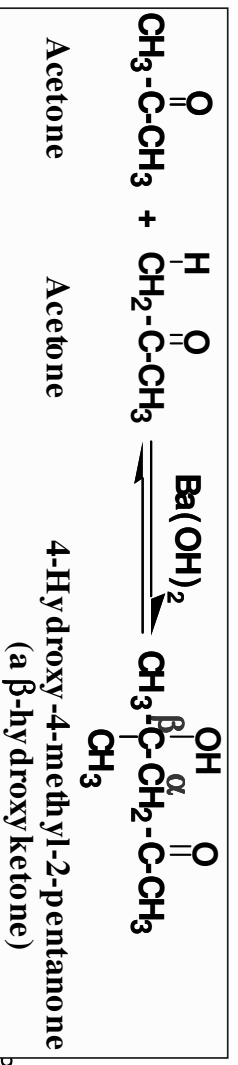
The Aldol Reaction

- The **product of an aldol reaction** is

– a β -hydroxyaldehyde



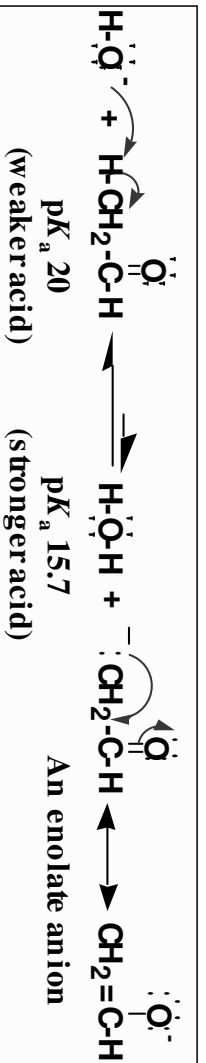
– or a β -hydroxyketone



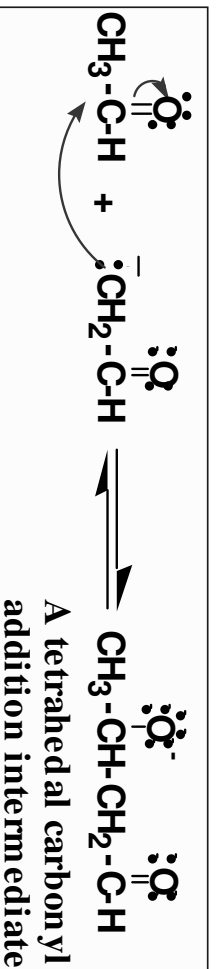
The Aldol Reaction

- Base-catalyzed aldol reaction**

Step 1: formation of a resonance-stabilized enolate anion



Step 2: carbonyl addition gives a TCAI

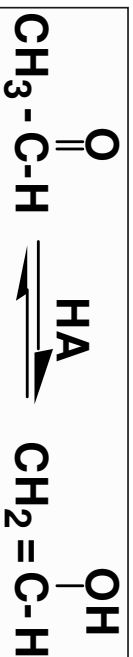


Step 3: proton transfer to O⁻ completes the aldol reaction

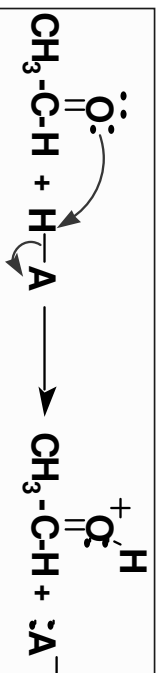
The Aldol Reaction-Acidic

- 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

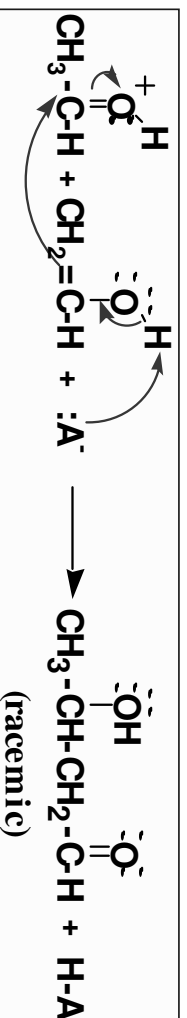


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The Aldol Reaction-acidic

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

– Step 4: proton transfer to A⁻ completes the reaction

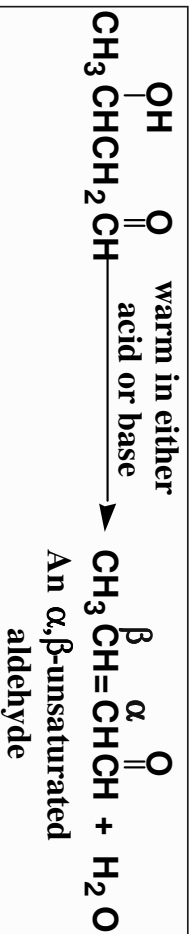


(Steps 3 & 4 are combined here)

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The Aldol Products-H₂O

– aldol products are very easily dehydrated to α,β -unsaturated aldehydes or ketones

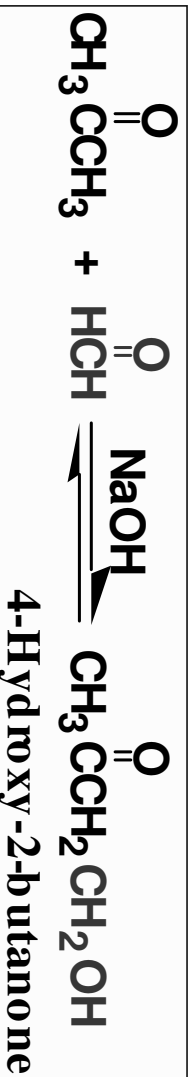


- aldol reactions are reversible and often little aldol present at equilibrium
- K_{eq} for dehydration is generally large
- if reaction conditions bring about dehydration, good yields of product can be obtained

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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

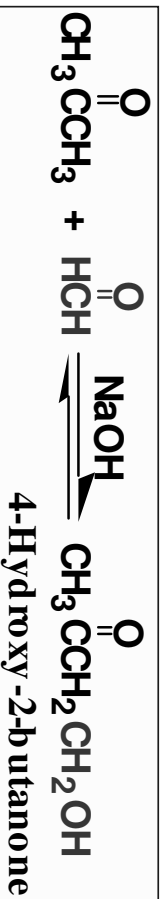
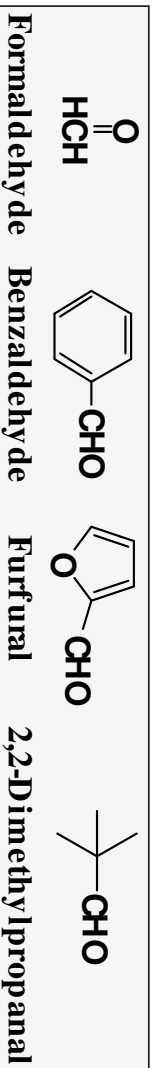


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Crossed Aldol Reaction

Crossed aldol reactions are successful if:

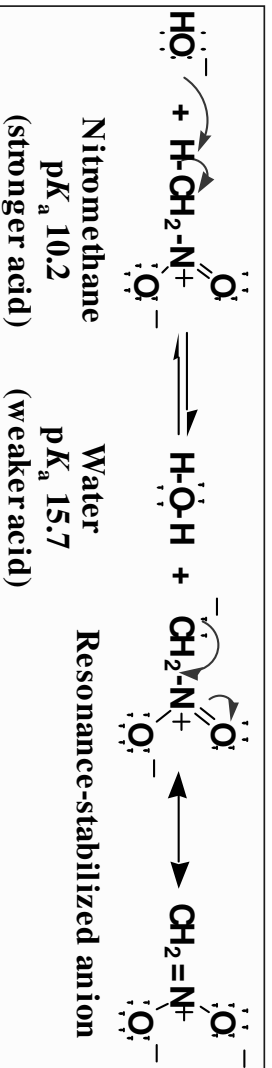
1. one of the reactants has no α -hydrogen and, therefore, cannot form an enolate anion and
2. the other reactant has a more reactive carbonyl group, namely an aldehyde



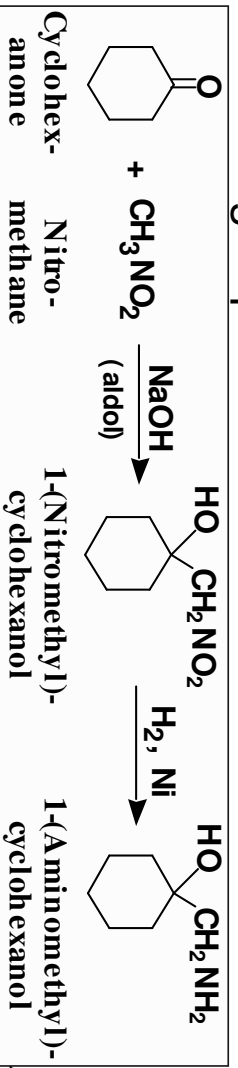
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Crossed Aldol Reaction

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



– nitro groups can be reduced to 1° amines

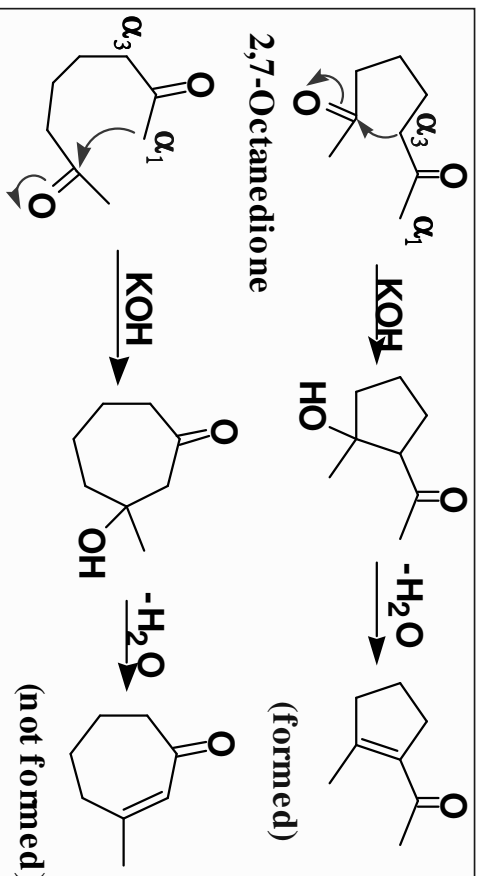


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Intramolecular Aldol Reactions

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

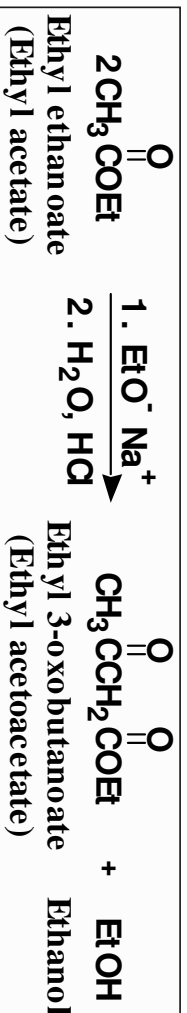
consider 2,7-octadione, which has two α -carbons



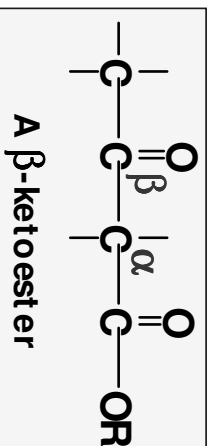
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Claisen Condensation

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



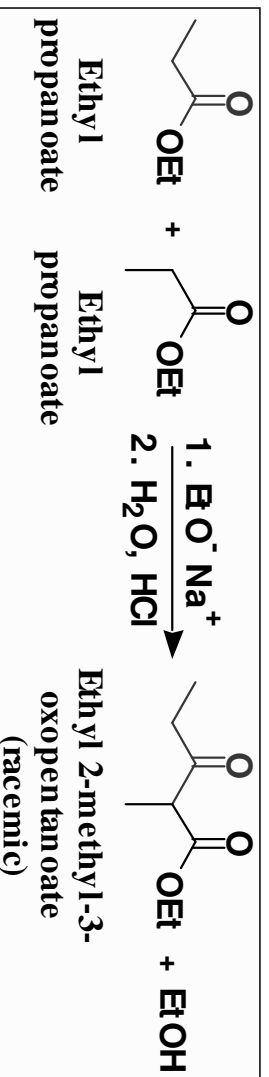
the product of a Claisen condensation is a β -ketoester



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Claisen Condensation

– Claisen condensation of ethyl propanoate gives this β -ketoester

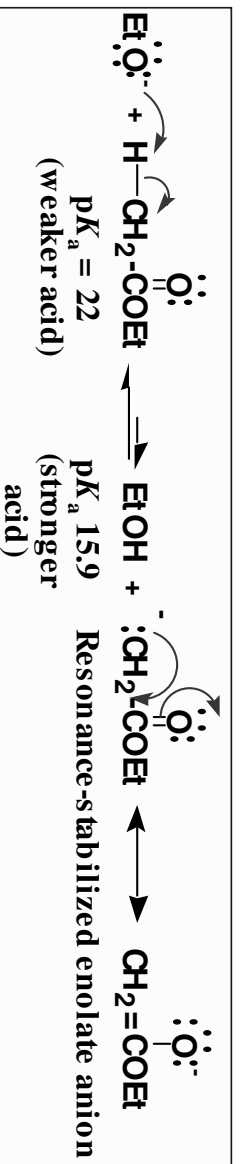


Nota bene: the base should be the alkoxide of the ester group
(This will overcome trans-esterification.)

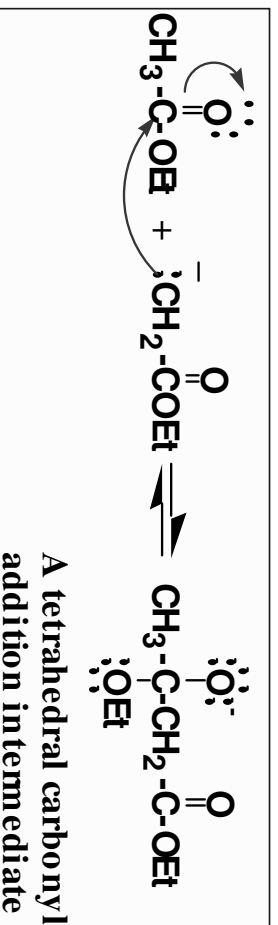
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Claisen Condensation

Step 1: formation of an enolate anion



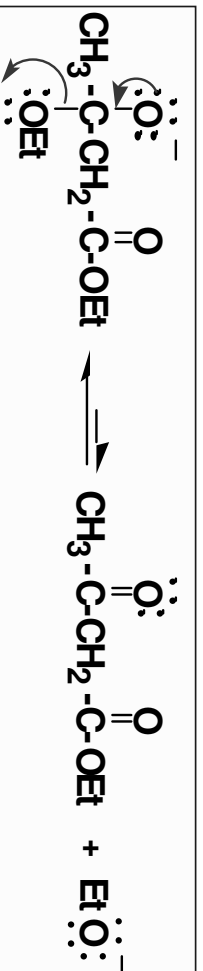
Step 2: attack of the enolate anion on a carbonyl carbon gives a TCAI



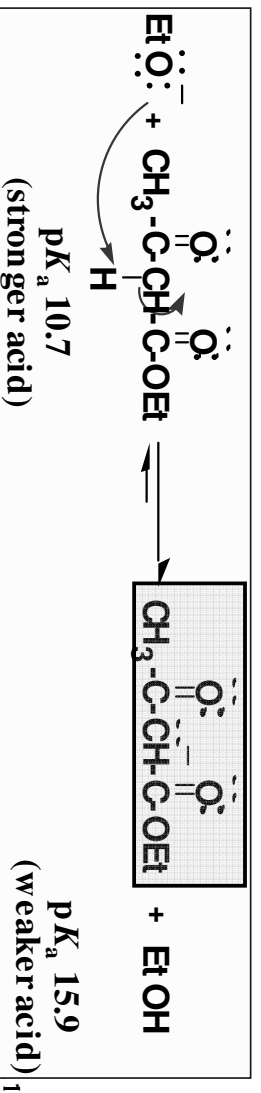
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Claisen Condensation

Step 3: collapse of the TCAI gives a β -ketoester and an alkoxide ion:

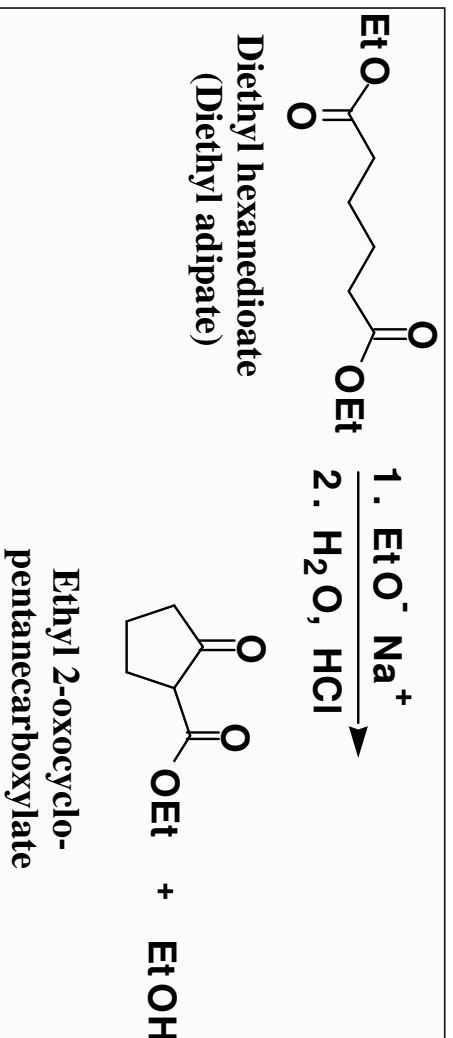


Step 4: an acid-base reaction drives the reaction to completion:



Dieckman Condensation

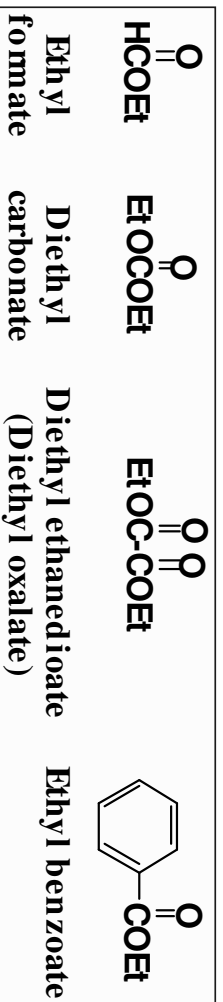
- An intramolecular Claisen condensation



Crossed Claisen Condensations

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

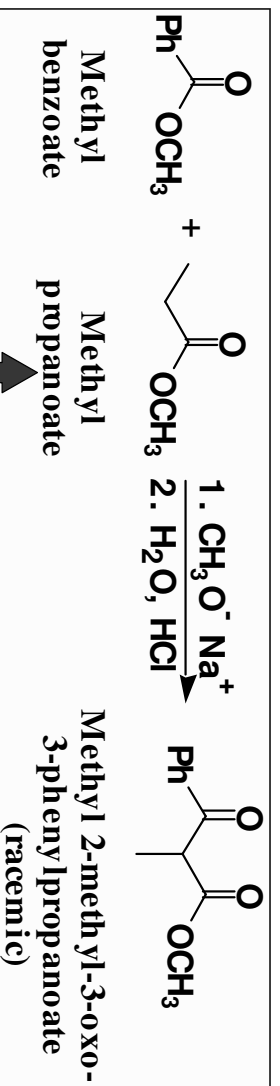
- crossed Claisen condensations are useful, if there is an appreciable difference in reactivity between the two esters; when one of them has no α -hydrogens



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Crossed Claisen Condensations

- the ester with no α -hydrogens is generally used in excess

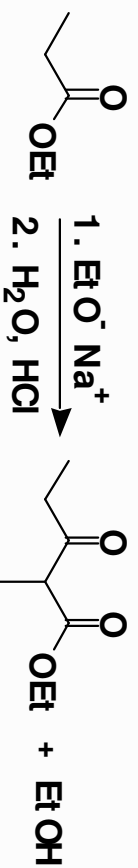


Only this enolate can be formed

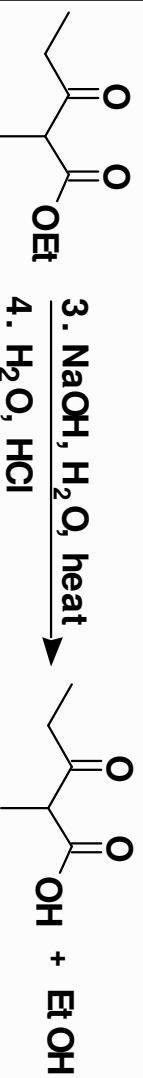
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Claisen condensations as routes to ketones

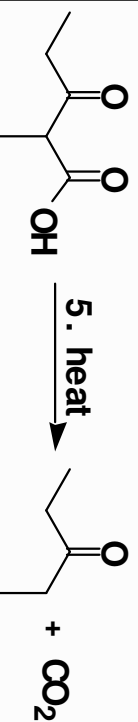
Reactions 1 & 2: Claisen condensation followed by acidification



Reactions 3 & 4: Saponification and acidification



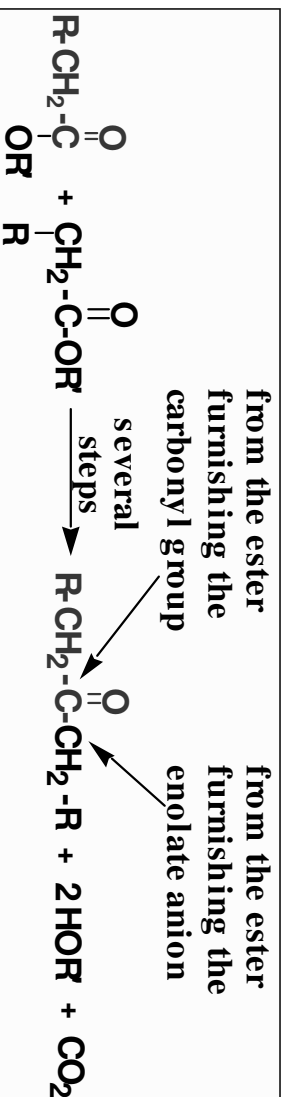
Reaction 5: thermal decarboxylation



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Claisen Condensations

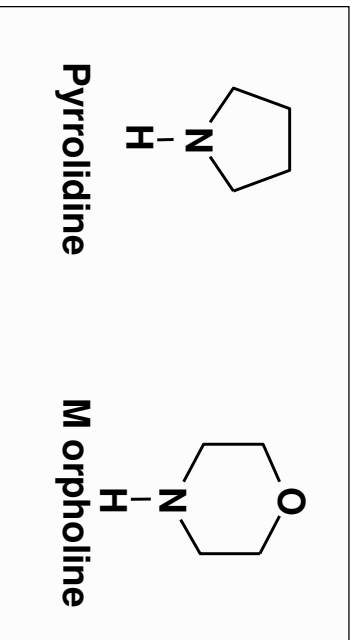
The result of Claisen condensation, saponification, acidification, and decarboxylation is a ketone:



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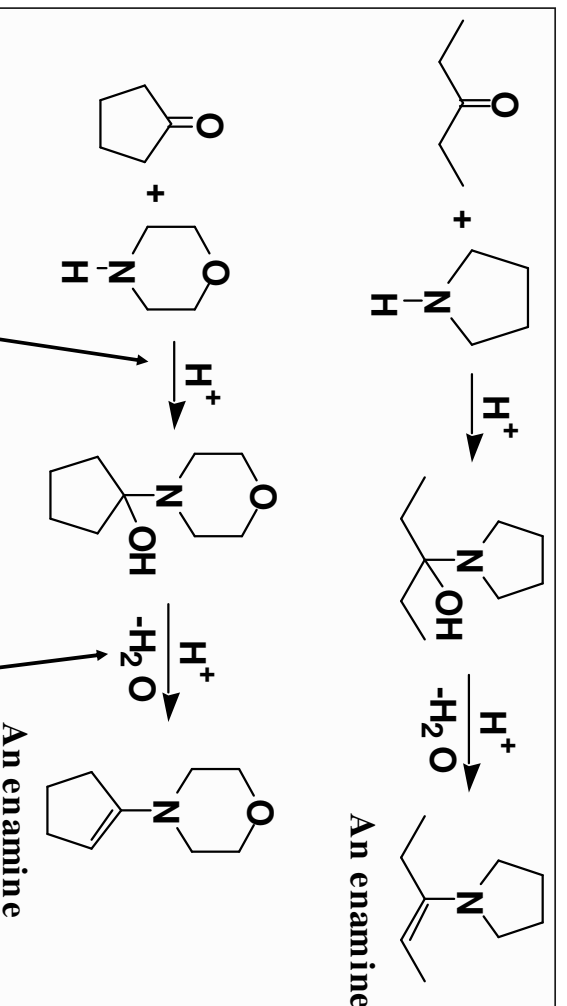
Enamines

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



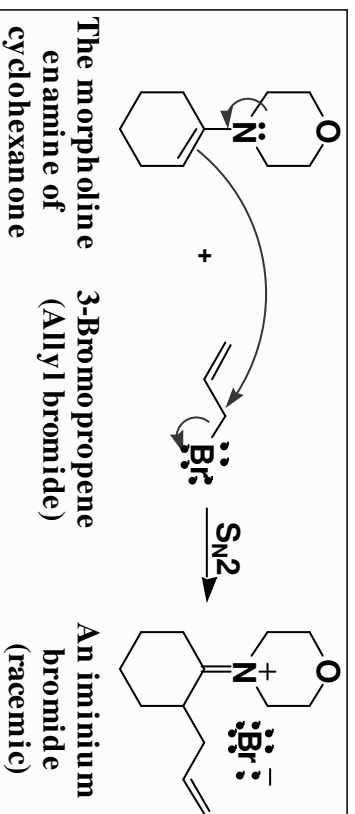
Acid catalyst is usually TsOH; azeotropic removal of H₂O.

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Enamines-Alkylation

The value of enamines is that the β -carbon is nucleophilic (**same C that was α to carbonyl**)

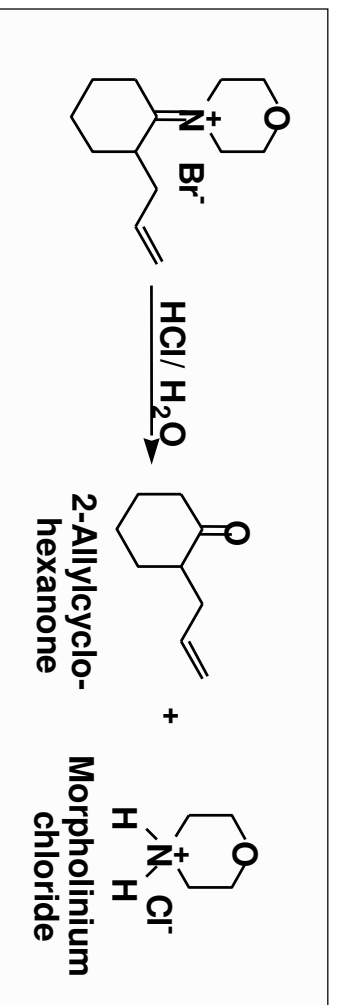
- enamines undergo S_N2 reactions with methyl and 1 $^\circ$ haloalkanes, α -haloketones, and α -haloesters
- treatment of the enamine with one equivalent of an alkylating agent gives an iminium halide



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Enamines-Alkylation

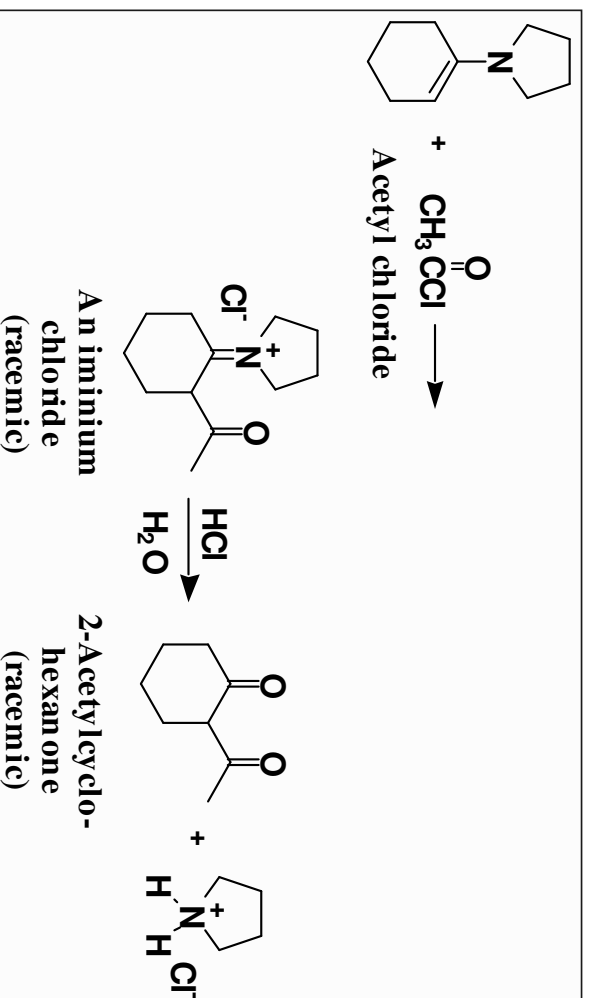
hydrolysis of the iminium halide (salt) gives the alkylated aldehyde or ketone:



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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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