

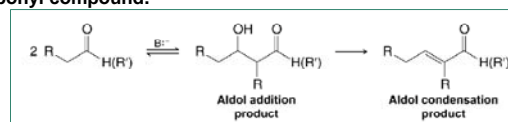
Chapter 19

More Chemistry of Enolate Anions (Aldol Reactions) and Conjugate Additions

Carbonyl Condensation Reactions

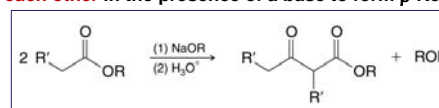
The Aldol Reaction

- In the aldol reaction, **two molecules of an aldehyde or ketone react with each other** in the presence of a base to form a β -hydroxy carbonyl compound.



The Claisen Condensation

- In the Claisen condensation **two molecules of an ester react with each other** in the presence of a base to form β -keto ester

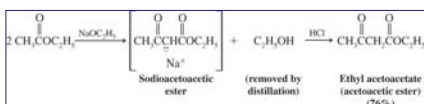


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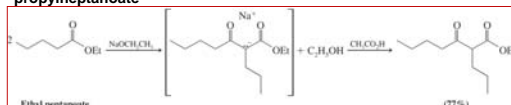
◆ The Claisen Condensation: Synthesis of β -Keto Esters

→ Ethyl acetate undergoes a Claisen condensation when treated with sodium ethoxide

• The product is commonly called an **acetoacetic ester**, whose chemistry we studied in previous chapter (18)



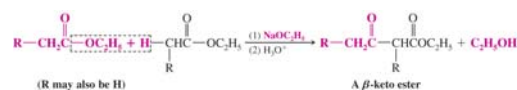
→ Ethyl pentanoate undergoes an analogous reaction to form 3-oxo-2-propylheptanoate



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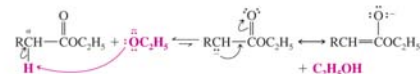
The Claisen Condensation - Mechanism

→ Please note that the overall reaction involves loss of an α hydrogen from one ester and loss of ethoxide from another

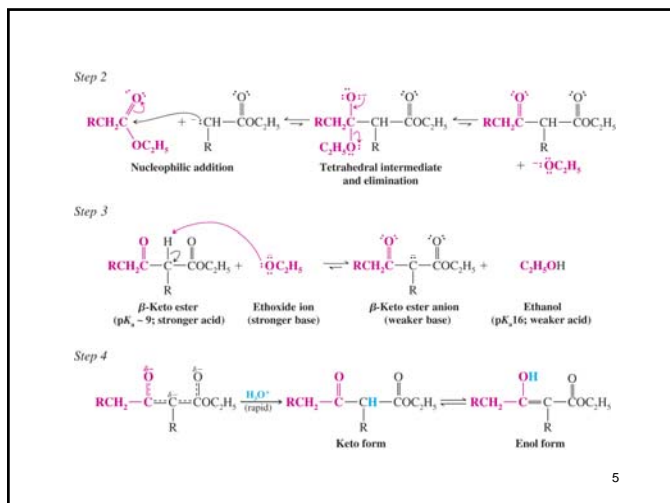


→ The mechanism is very straightforward and follow the general process of **nucleophilic addition-elimination** at an ester carbonyl

Step 1



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The Claisen Condensation – A few notes

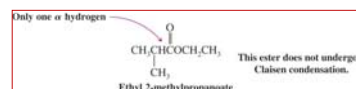
→ The alkoxide base must have the same alkyl group as the alkoxy group of the ester

↳ The use of a different alkoxide would result in formation of some transesterification products

→ Esters with only one α hydrogen do not undergo Claisen condensation

↳ A second hydrogen on the α carbon is necessary so that it can be deprotonated in Step 3

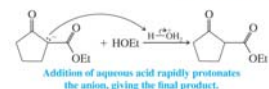
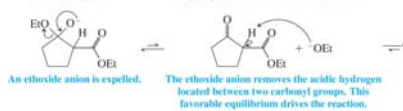
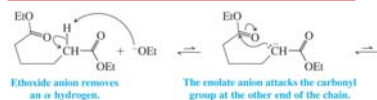
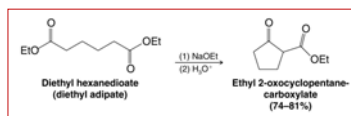
↳ This deprotonation and formation of the resonance stabilized β -keto ester ion drives the reaction to completion



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The Dieckmann condensation is an intramolecular Claisen condensation

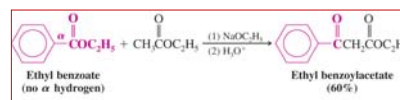
Only 5- and 6-membered rings may be prepared in this way



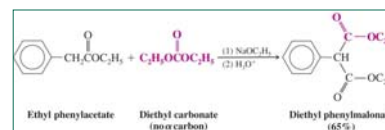
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• Crossed Claisen Condensations

→ Crossed Claisen condensations between two esters can lead to one major product when one of the two esters has no α hydrogen

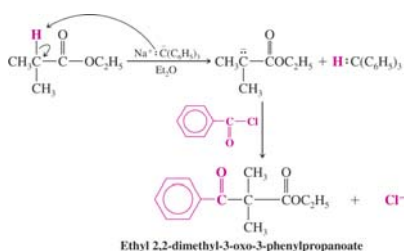


Detailed mechanism for this Claisen condensation is given on page 874 (Solved problem 19.1)



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→ Esters with one α hydrogen can, however, react in Claisen condensations if they are deprotonated with a strong base and acylated with an acyl chloride to give β -keto ester

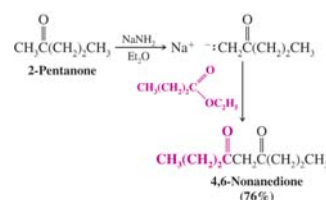


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• Acylation of Other Carbanions

→ Ketone enolates formed with strong bases can also be acylated to form β -dicarbonyl compounds

→ Addition of strong base to 2-pentanone results in formation of the kinetic enolate (Why?) which can be acylated with an ester

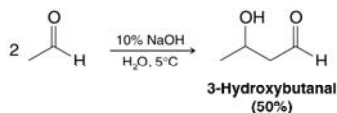


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Carbonyl Condensation Reactions- The Aldol Reaction

- In the aldol reaction, two molecules of an aldehyde or ketone react with each other in the presence of a base to form a β -hydroxy carbonyl compound.

Aldol additions represent an important class of carbon-carbon bond-forming reaction.



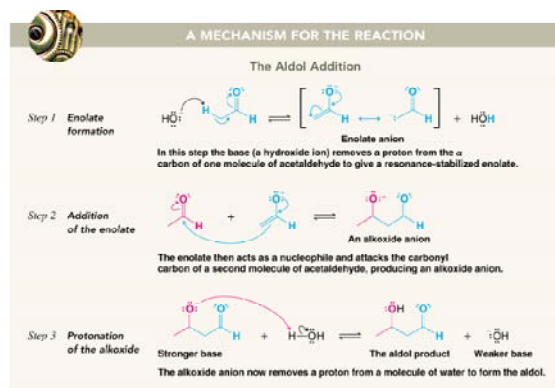
Because the product contains both an aldehyde and an alcohol functional group, reaction of this type is known as aldol addition.

OH^- is the base typically used in an aldol reaction. Although with OH^- only a small amount of enolate is formed, this is appropriate because the starting aldehyde is needed to react with the enolate in the second step of the reaction.

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The Aldol Reaction

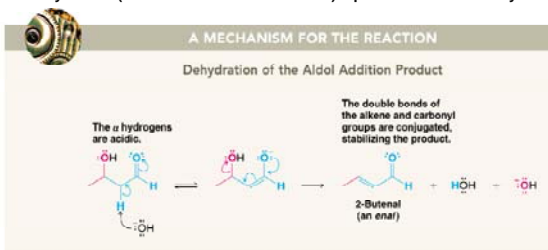
The mechanism of the aldol reaction occurs in three steps.



The Aldol Reaction

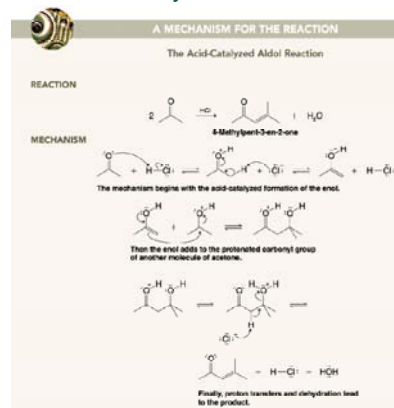
Dehydration of the aldol addition product: Conversion of the β -hydroxy carbonyl adduct to a conjugated α,β -unsaturated carbonyl system

- Under the basic reaction conditions, the initial aldol product is often not isolated. Instead, it loses the elements of H_2O from the α and β carbons to form an α,β -unsaturated carbonyl compound
- Regular alcohols dehydrate only in the presence of acid, not base, because hydroxide is a poor leaving group. However, when the hydroxy group is β to a carbonyl, loss of H and OH from the α and β carbons forms a conjugated double bond, and the stability of the conjugated system makes up for having such a poor leaving group
- The dehydration (elimination of water molecule) equilibrium is essentially irreversible



The Aldol Reaction

Acid-catalyzed aldol condensation- mechanism



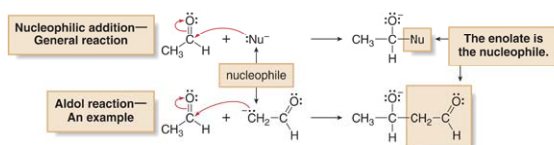
Please note that reaction starts with the protonation of the oxygen from the carbonyl group.

Acid also protonates hydroxyl group in the intermediary adduct changing as a result a poor leaving group into a good one.

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Carbonyl Condensation Reactions: The Aldol Reaction

- Recall that the characteristic reaction of aldehydes and ketones, which we studied in Chapter 16, is a nucleophilic addition.
- An aldol reaction is a nucleophilic addition in which an enolate is the nucleophile.



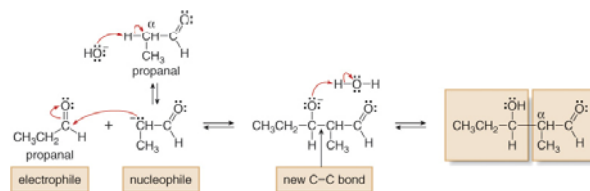
- Aldehydes and ketones react by nucleophilic addition. In an aldol reaction, an enolate is the nucleophile that adds to the carbonyl group.

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The Aldol Reaction: Synthetic Applications

- Aldol reaction of the propanal as the starting material:
- The two molecules of the aldehyde that participate in the aldol reaction react in opposite ways.

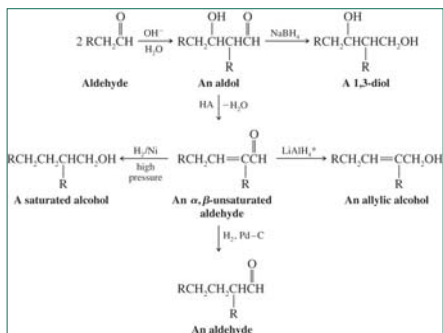
- One molecule of propanal becomes an enolate—an electron-rich *nucleophile*.
- One molecule of propanal serves as the *electrophile* because its carbonyl carbon is electron deficient.



Please note that in aldol reactions the α carbon of one carbonyl component becomes bonded to the carbonyl carbon of the other component.

Synthetic Applications

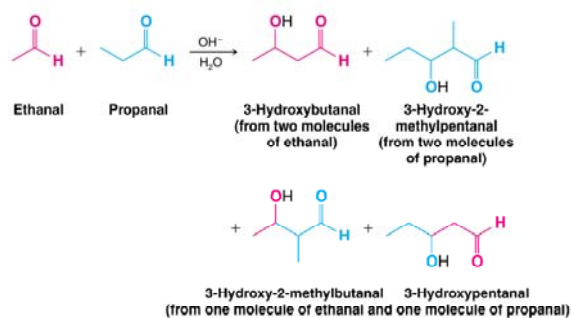
- The aldol reaction links two smaller molecules and creates a new carbon-carbon bond.
- The aldol adducts are useful for further synthetic transformations



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Crossed Aldol Condensation

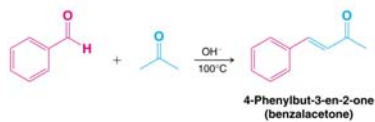
- Aldol reaction which starts with two different carbonyl compounds (aldehydes) is called **Cross Aldol**
- It can lead to a mixture of four products.



Crossed Aldol Condensation with weak bases (NaOH)

- To avoid self-condensation:

- one carbonyl reactant **without α -hydrogen** (e.g., benzaldehyde) used.
- The other carbonyl reagent is added slowly to a solution of the first reactant and the base. Under such conditions the concentration of the reactant with an α -hydrogen is always low

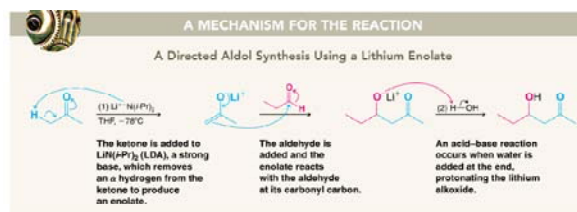


This Reactant with No α Hydrogen is Placed in Base	This Reactant with an α Hydrogen is Added Slowly	Product
Benzaldehyde	Propanal	3-Methyl-3-phenyl-2-propanal (2-methyl-3-oxobenzaldehyde) (68%)
Benzaldehyde	Phenylacetaldhyde	2,3-Diphenyl-2-propanal

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Crossed Aldol Condensation with strong bases (LDA) Lithium Enolates and Directed Aldol Reactions

- Reactions of lithium enolates obtained from a **ketone as one component** and an **aldehyde or ketone as the other** are called **Directed Aldol Reactions**

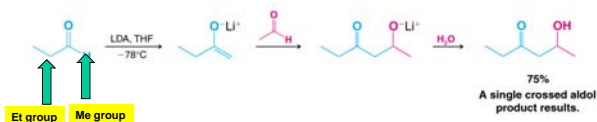


So, the crossed aldol reactions proceed effectively when a ketone is first deprotonated with a strong base such as LDA and the aldehyde is added slowly to the enolate

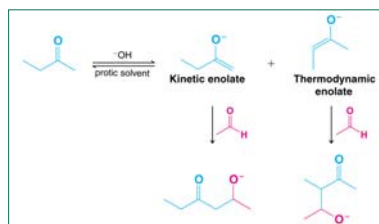
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The regioselectivity of the cross-aldol reactions with unsymmetrical ketones

An unsymmetrical ketone can be selectively deprotonated with LDA in aprotic solvent (THF) to form the **kinetic enolate** and this will react with an aldehyde to give primarily one product



Please note that the proton has been removed from the less substituted α -carbon



Using weaker base (NaOH) under protic conditions would produce mixture of two products via both kinetic and thermodynamic enolates

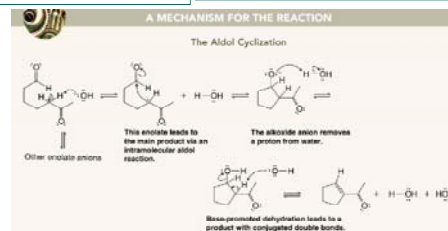
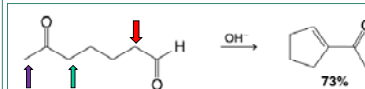
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Cyclization via Aldol Reactions: Intramolecular Condensation

- Aldol reactions with dicarbonyl compounds can be used to make five- and six-membered rings
- The enolate formed from one carbonyl group is the nucleophile, and the carbonyl carbon of the other is the electrophile.

In the following example we can generate **three different enolates**. However it is enolates from ketone side of the molecule that adds to aldehyde:

Recall that aldehyde are more reactive than ketones towards nucleophilic additions.
Consider also possible ring sizes



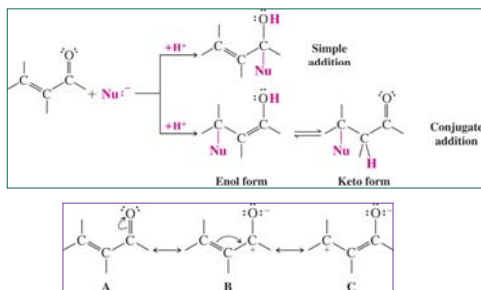
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Michael Additions: Additions to α,β -Unsaturated Aldehydes and Ketones

→ A Michael addition involves conjugate addition of the nucleophile or an anion derived from an active hydrogen compound (e.g., an enolate) to an α,β -unsaturated carbonyl compound

→ α,β -Unsaturated aldehydes and ketones can react by simple (1,2) or conjugate (1,4) addition

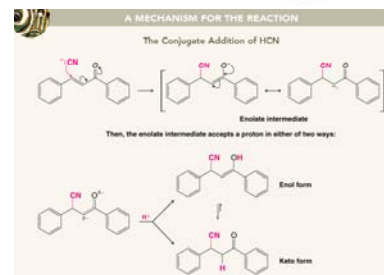
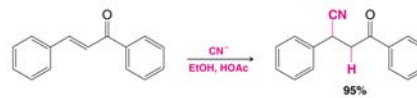
Both the carbonyl carbon and the β carbon are electrophilic and can react with nucleophiles



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Michael Additions: The conjugate addition of nucleophiles

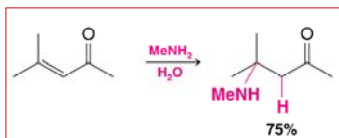
Most nucleophiles will add to β carbon of the α,β -unsaturated carbonyl system



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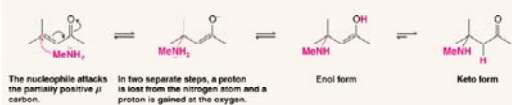
◆ Michael Additions: The conjugate addition of nucleophiles

Amines add to β carbon of the α,β -unsaturated carbonyl system in high yield



A MECHANISM FOR THE REACTION

The Conjugate Addition of an Amine



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● Conjugate Michael Additions

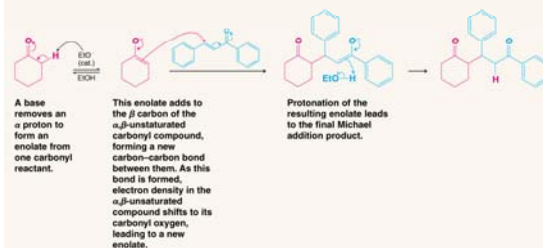
→ Addition of an enolates (C-nucleophiles) to an α,β -unsaturated carbonyl compound usually occurs by conjugate addition

→ This reaction is called a Michael addition and its pathway involves three steps



A MECHANISM FOR THE REACTION

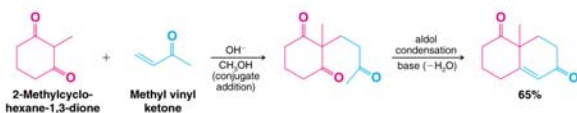
The Michael Addition



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Carbonyl Condensation Reactions: The Robinson Annulation

- The Robinson annulation is a ring-forming reaction that combines a Michael reaction with an intramolecular aldol reaction.
- The starting materials for a Robinson annulation are an α,β -unsaturated carbonyl compound and an enolate.
- In overall, the Robinson annulation forms a six-membered ring and three new C—C bonds—two σ bonds and one π bond.
- It is frequently used to build one ring into another

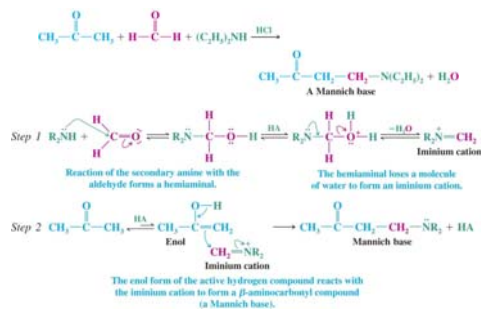


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◆ The Mannich Reaction

→ Compounds which can form enols react with imines or iminium ions derived from formaldehyde

- Primary or secondary amines can be used to form the corresponding formaldehyde imines or iminium ions



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