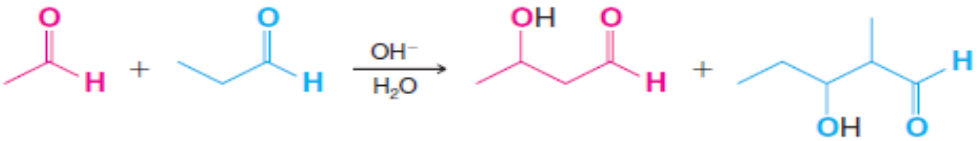
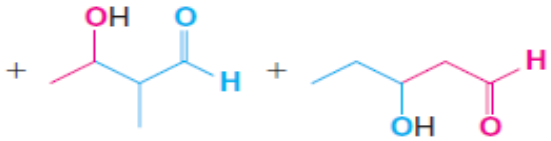
Crossed Aldol Condensations:

An aldol reaction that starts with two different carbonyl compounds is called a **crossed aldol reaction**.

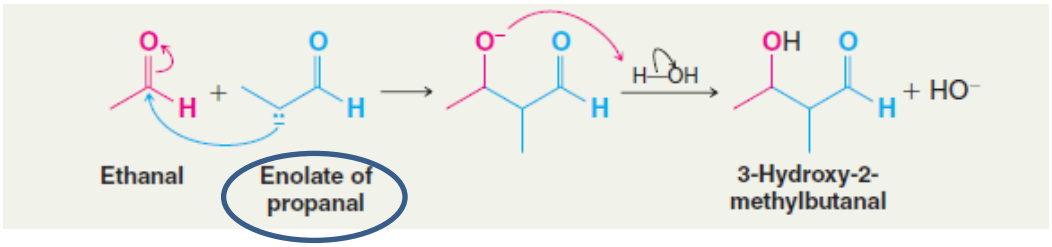
Unless specific conditions are involved, a crossed aldol reaction can lead to a mixture of products from various pairings of the carbonyl reactants, as the following example illustrates with ethanal and propanal.

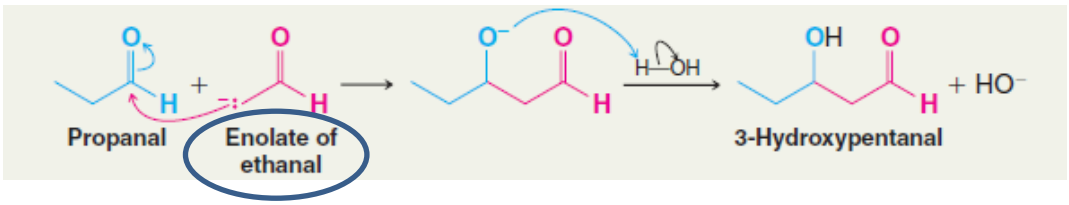


Ethanal Propanal 3-Hydroxybutanal (from two molecules of ethanal) 3-Hydroxy-2-methylpentanal (from two molecules of propanal)



3-Hydroxy-2-methylbutanal 3-Hydroxypentanal
(from one molecule of ethanal and one molecule of propanal)



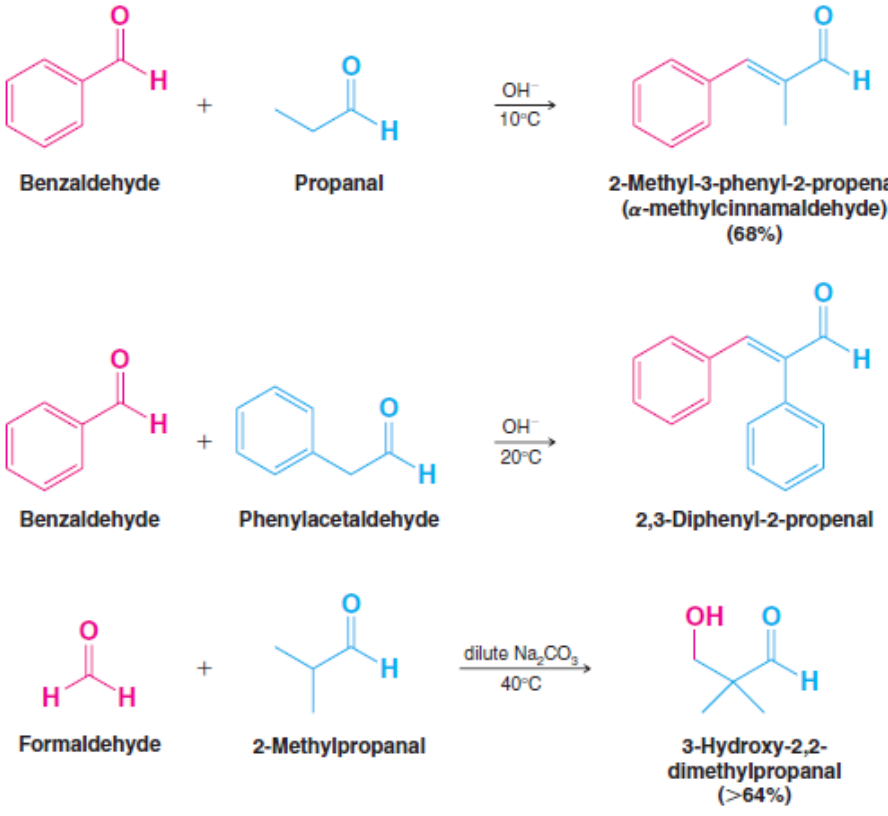


Crossed Aldol Condensations Using Weak Bases:

Crossed aldol reactions are possible with weak bases such as hydroxide or an alkoxide **when one carbonyl reactant does not have an a hydrogen**.

A reactant without a hydrogens cannot self-condense because it cannot form an enolate.

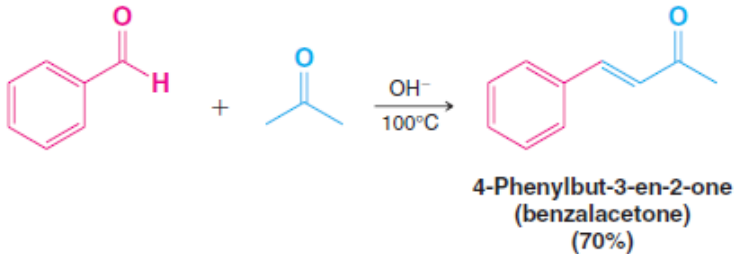
We avoid self-condensation of the other reactant, that which has an a hydrogen, by **adding it slowly** to a solution of the first reactant and the base. Under these conditions the concentration of the reactant with an a hydrogen is always low, and it is present mostly in its enolate form. The main reaction that takes place is between this enolate and the carbonyl compound that has no a hydrogens.



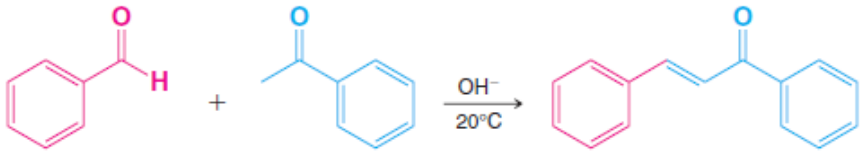
A **ketone** can be used as one reactant, however, because ketones do not self-condense appreciably due to steric hindrance in the aldol addition stage.

Reactions such as these are sometimes called **Claisen–Schmidt condensations**.

In these reactions, dehydration occurs readily because the double bond that forms is conjugated both with the carbonyl group and with the benzene ring. In general, dehydration of the aldol is especially favorable when it leads to extended conjugation.

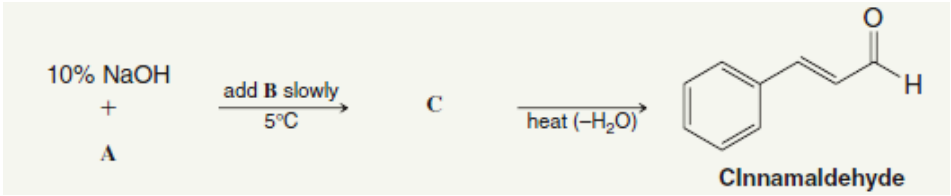


4-Phenylbut-3-en-2-one
(benzalacetone)
(70%)



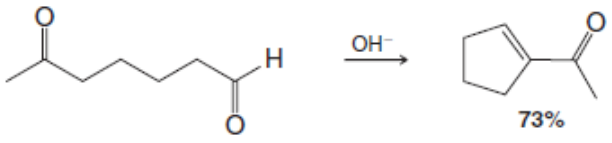
1,3-Diphenylprop-2-en-1-one
(benzalacetophenone)
(85%)

Homework:
Outlined below is a practical crossed aldol reaction that can be used for the synthesis of cinnamaldehyde (the essence of cinnamon, used in cooking). Provide the missing ingredients for this recipe.

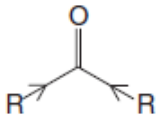


Cinnamaldehyde

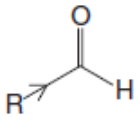
Cyclizations via Aldol Condensations (intramolecular aldol condensation)



This reaction almost certainly involves the formation of at least three different enolates.
However, it is the enolate from the ketone side of the molecule that adds to the aldehyde group leading to the product. Why?!



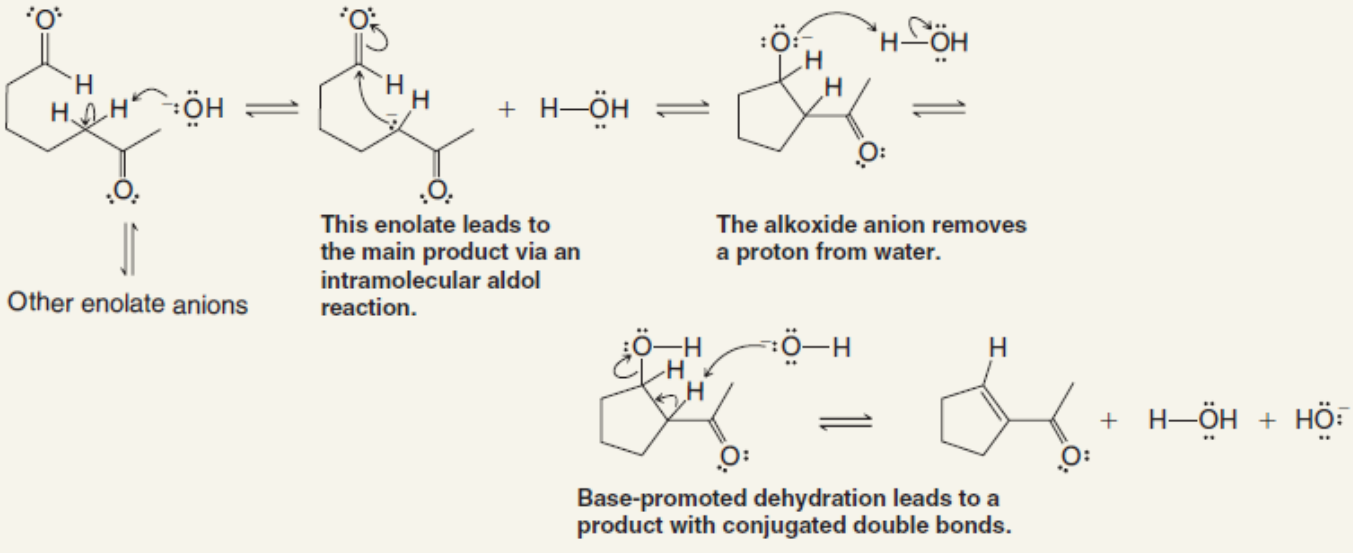
Ketones are less reactive toward nucleophiles.



Aldehydes are more reactive toward nucleophiles.

In reactions of this type, five-membered rings form far more readily than sevenmembered rings, and six-membered rings are more favorable than four- or eight-membered rings, when possible.

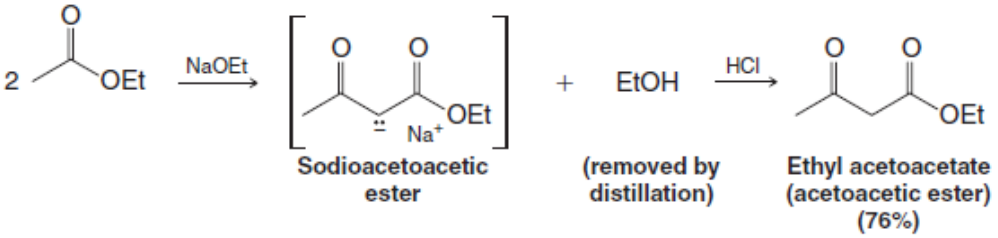
The Mechanism:



The Claisen Condensation: A Synthesis of β-Keto Esters:

In a Claisen condensation, the enolate of one ester molecule adds to the carbonyl group of another, resulting in an acyl substitution reaction that forms a b-keto ester and an alcohol molecule. The alcohol molecule that is formed derives from the alkoxyl group of the ester.

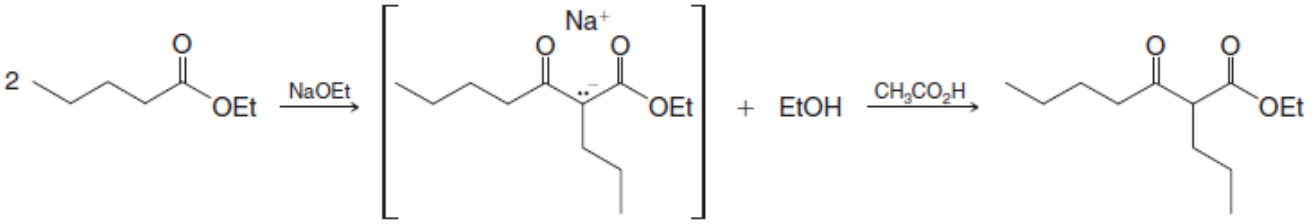
Examples:



Sodioacetoacetic ester

(removed by distillation)

Ethyl acetoacetate (acetoacetic ester) (76%)

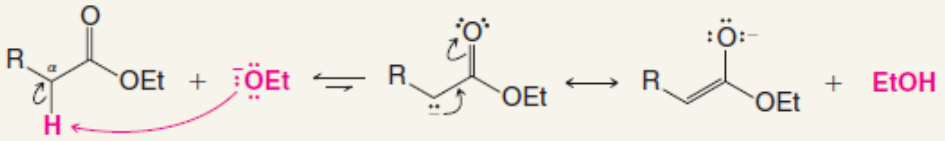


Ethyl pentanoate

Ethyl 3-oxo-2-propylheptanoate (77%)

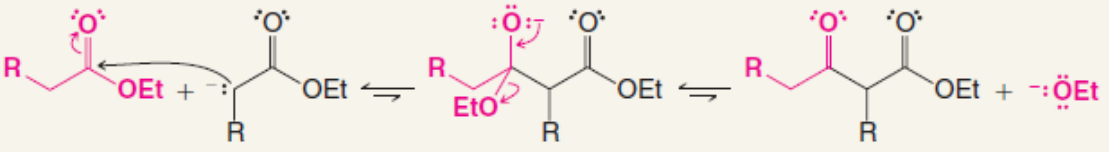
The Mechanism:

Step 1



An alkoxide base removes an α proton from the ester, generating a nucleophilic enolate ion. (The alkoxide base used to form the enolate should have the same alkyl group as the ester, e.g., ethoxide for an ethyl ester; otherwise transesterification may occur.) Although the α protons of an ester are not as acidic as those of aldehydes and ketones, the resulting enolate is stabilized by resonance in a similar way.

Step 2

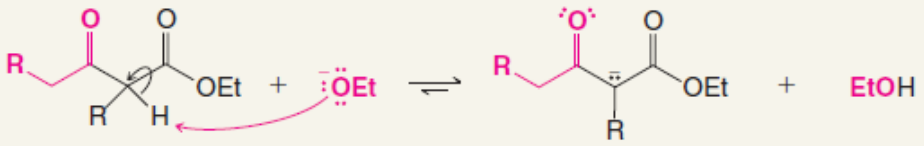


Nucleophilic addition

Tetrahedral intermediate and elimination

The enolate attacks the carbonyl carbon of another ester molecule, forming a tetrahedral intermediate. The tetrahedral intermediate expels an alkoxide ion, resulting in substitution of the alkoxide by the group derived from the enolate. The net result is nucleophilic addition–elimination at the ester carbonyl group. *The overall equilibrium for the process is unfavorable thus far, however*, but it is drawn toward the final product by removal of the acidic α hydrogen from the new β-dicarbonyl system.

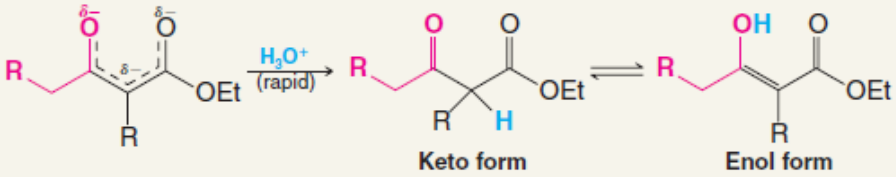
Step 3



β-Keto ester (pK_a ~9; stronger acid) | Ethoxide ion (stronger base) | β-Keto ester anion (weaker base) | Ethanol (pK_a 16; weaker acid)

An alkoxide ion removes an α proton from the newly formed condensation product, resulting in a resonance stabilized β-keto ester ion. This step is highly favorable and draws the overall equilibrium toward product formation. The alcohol by-product (ethanol in this case) can be distilled from the reaction mixture as it forms, thereby further drawing the equilibrium toward the desired product.

Step 4



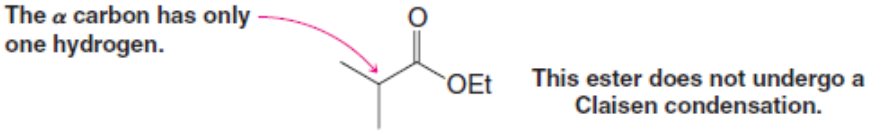
Keto form | Enol form

Addition of acid quenches the reaction by neutralizing the base and protonating the Claisen condensation product. The β-keto ester product exists as an equilibrium mixture of its keto and enol tautomers.

Notes:

When planning a reaction with an ester and an alkoxide ion it is important to use an alkoxide that has the same alkyl group as the alkoxyl group of the ester to avoid the transesterification.

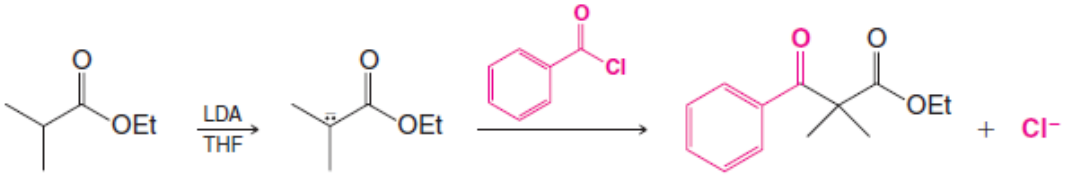
Esters that have only one a hydrogen do not undergo the usual Claisen condensation.



Ethyl 2-methylpropanoate

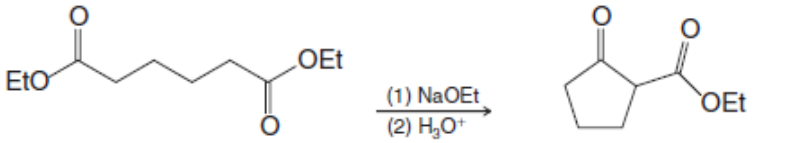
an ester with only one a hydrogen will not have an acidic hydrogen when step 3 is reached, and step 3 provides the favorable equilibrium that ensures the success of the reaction.

However, they can be converted to β-keto esters by reactions that use very strong bases such as lithium diisopropylamide (LDA), The strong base converts the ester to its enolate ion in nearly quantitative yield. This allows us to *acylate* the enolate ion by treating it with an acyl chloride or an ester.



Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate

Intramolecular Claisen Condensations: The Dieckmann Condensation

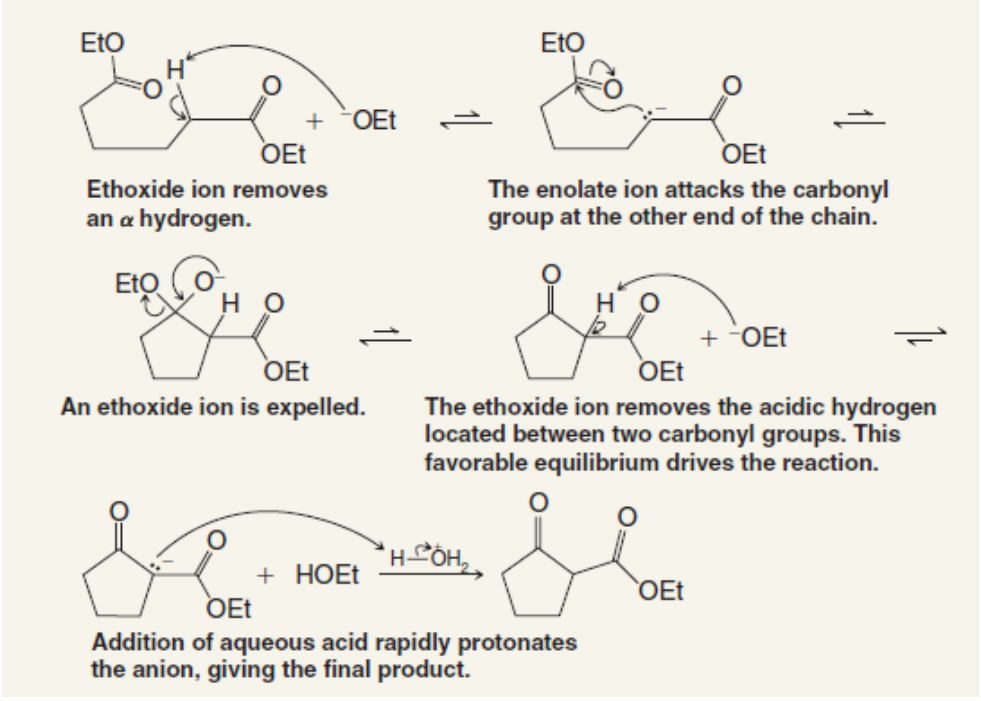


Diethyl hexanedioate (diethyl adipate)

Ethyl 2-oxocyclopentane-carboxylate (74–81%)

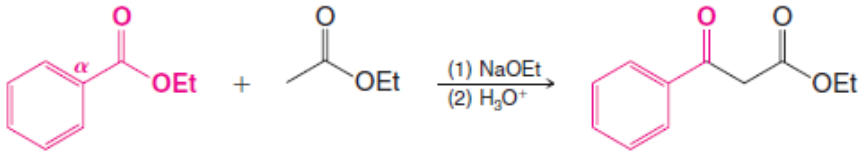
In general, the Dieckmann condensation is useful only for the preparation of fiveand six-membered rings.

The Mechanism:



Crossed Claisen Condensations:

Crossed Claisen condensations are possible **when one ester component has no α hydrogens** and, therefore, is unable to form an enolate ion and undergo selfcondensation.

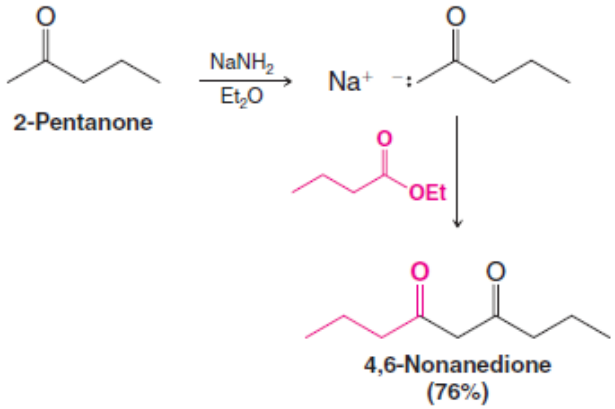


Ethyl benzoate (no α hydrogen)

Ethyl benzoylacetate (60%)

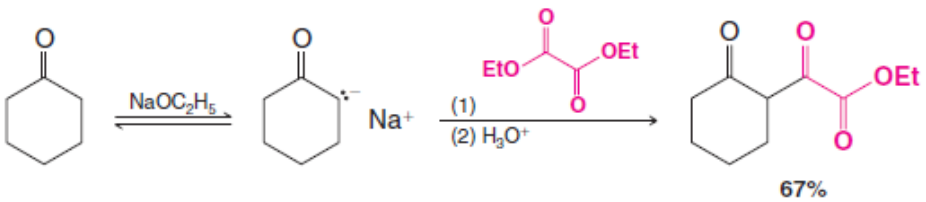
Homework:
Write a mechanism for all of the steps in the Claisen condensation above between ethyl benzoate and ethyl acetate.

β-Dicarbonyl Compounds by Acylation of Ketone Enolates:



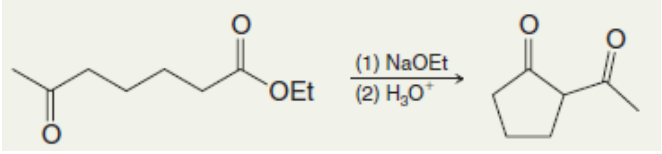
2-Pentanone

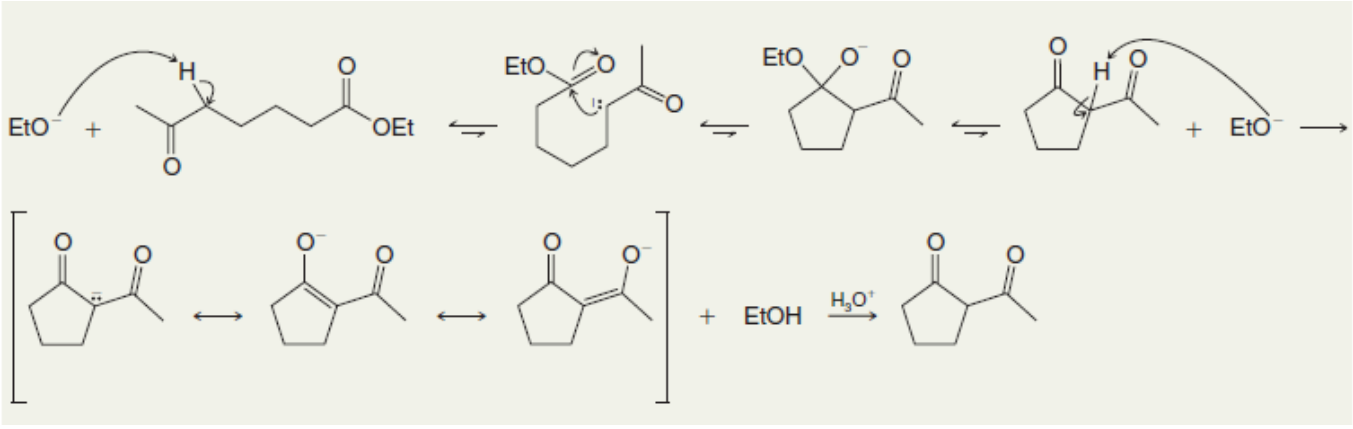
4,6-Nonanedione (76%)



67%

Keto esters are capable of undergoing cyclization reactions similar to the Dieckmann condensation.

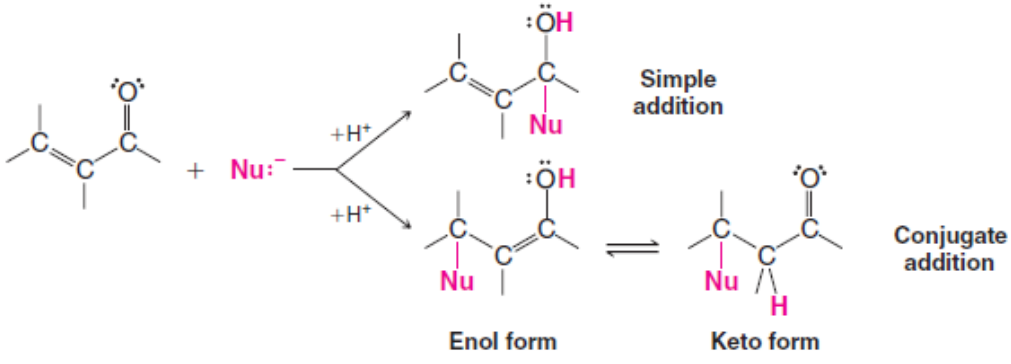




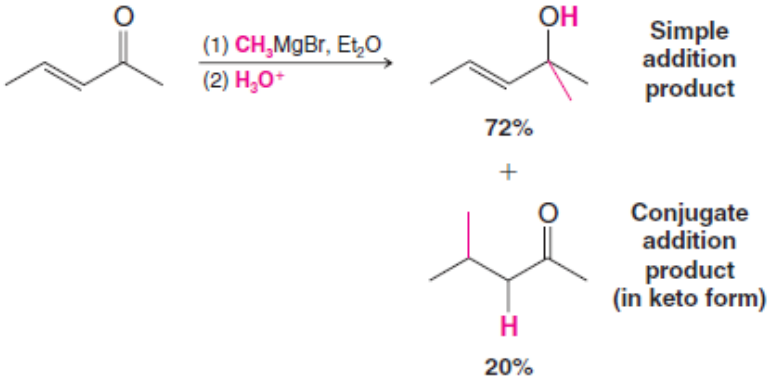
Additions to α,β-Unsaturated Aldehydes and Ketones:

When α,β -unsaturated aldehydes and ketones react with nucleophilic reagents, they may do so in two ways.

They may react by a **simple addition,** that is, one in which the nucleophile adds across the double bond of the carbonyl group; or they may react by a **conjugate addition.**

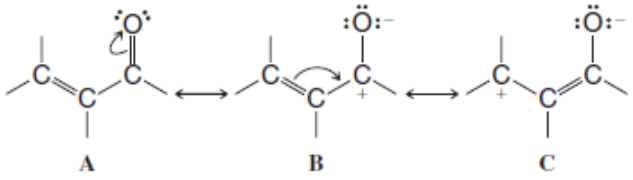


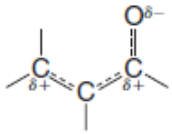
In many instances both modes of addition occur in the same mixture. As an example, let us consider the Grignard reaction shown here:



In this example we see that simple addition is favored, and this is generally the case with strong nucleophiles. Conjugate addition is favored when weaker nucleophiles are employed.

The resonance structures that contribute to the overall hybrid for an α,β-unsaturated aldehyde or ketone:

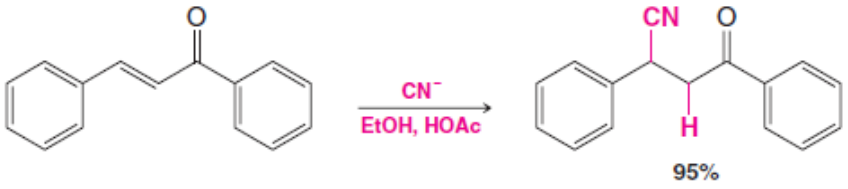


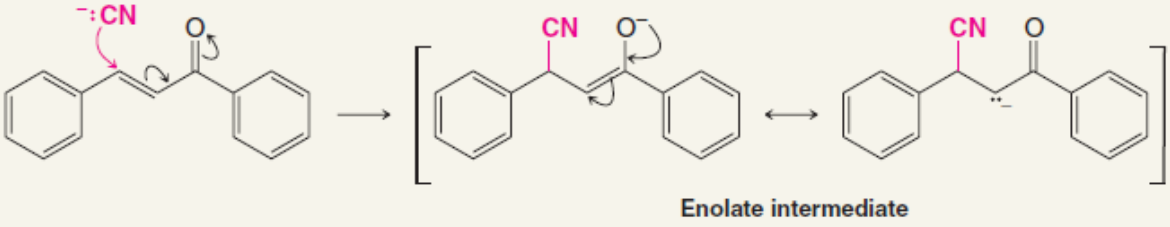


This structure tells us that we should expect a nucleophilic reagent to attack either the carbonyl carbon or the β-carbon.

Almost every nucleophilic reagent that adds at the carbonyl carbon of a simple aldehyde or ketone is capable of adding at the b carbon of an α,β-unsaturated carbonyl compound.

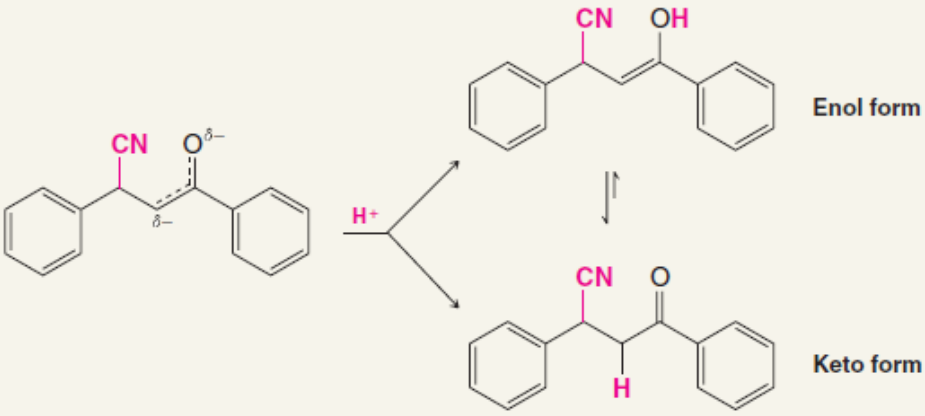
In many instances when weaker nucleophiles are used, conjugate addition is the major reaction path. Consider the following addition of hydrogen cyanide:





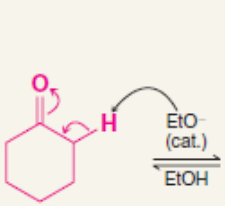
Enolate intermediate

Then, the enolate intermediate accepts a proton in either of two ways:

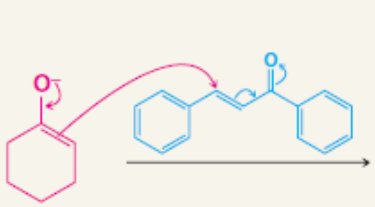


Conjugate Additions of Enolates: Michael Additions

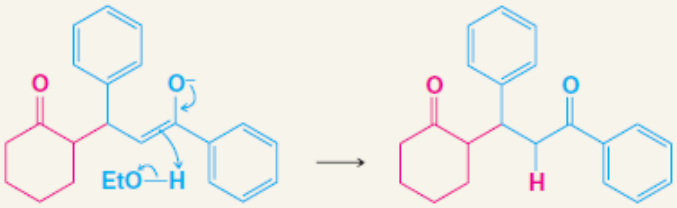
Conjugate additions of enolates to α,β-unsaturated carbonyl compounds are known generally as Michael additions



A base removes an α proton to form an enolate from one carbonyl reactant.



This enolate adds to the β carbon of the α,β-unstaturated carbonyl compound, forming a new carbon–carbon bond between them. As this bond is formed, electron density in the α,β-unsaturated compound shifts to its carbonyl oxygen, leading to a new enolate.



Protonation of the resulting enolate leads to the final Michael addition product.