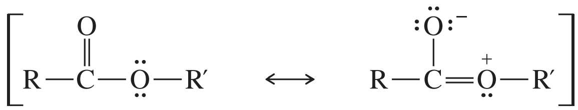
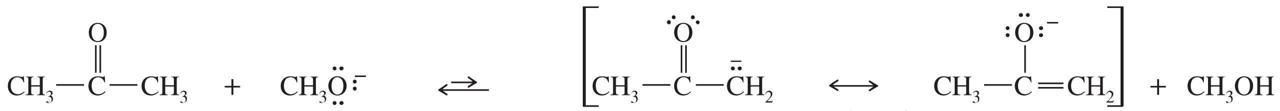
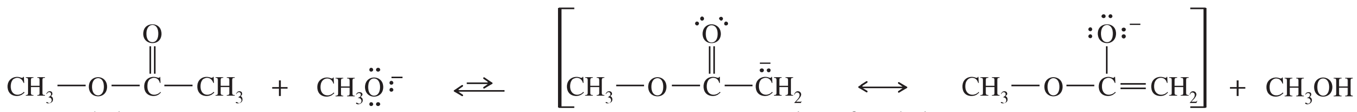
22-12 The Claisen Ester Condensation

The α hydrogens of esters are weakly acidic, and they can be deprotonated to give enolate ions. Esters are less acidic than ketones and aldehydes because the ester carbonyl group is stabilized by resonance with the other oxygen atom. This resonance makes the carbonyl group less capable of stabilizing the negative charge of an enolate ion.



A typical pK_a for an α proton of an ester is about 24, compared with a pK_a of about 20 for a ketone or aldehyde. Even so, strong bases do deprotonate esters.





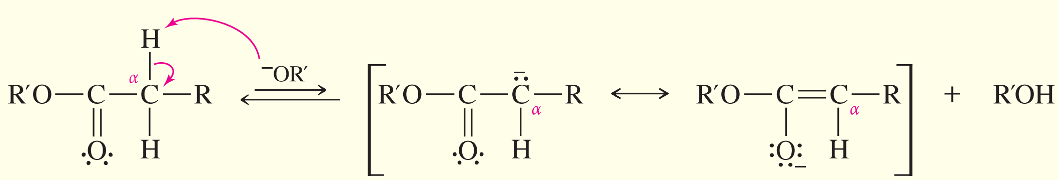
Ester enolates are strong nucleophiles, and they undergo a wide range of interesting and useful reactions. Most of these reactions are related to the Claisen condensation, the most important of all ester condensations.

The **Claisen condensation** results when an ester molecule undergoes nucleophilic acyl substitution with an enolate ion serving as the nucleophile. First, the enolate attacks the carbonyl group, forming a tetrahedral intermediate. The intermediate has an alkoxy (—OR) group that acts as a leaving group, leaving a β-keto ester. The overall reaction combines two ester molecules to give a β-keto ester.

KEY MECHANISM 22-12 The Claisen Ester Condensation

The Claisen condensation is a nucleophilic acyl substitution on an ester, in which the attacking nucleophile is an enolate ion.

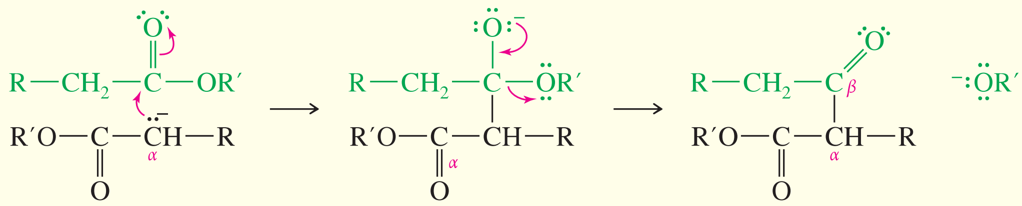
Step 1: Formation of the enolate ion.



ester enolate ion

(CONTINUED)

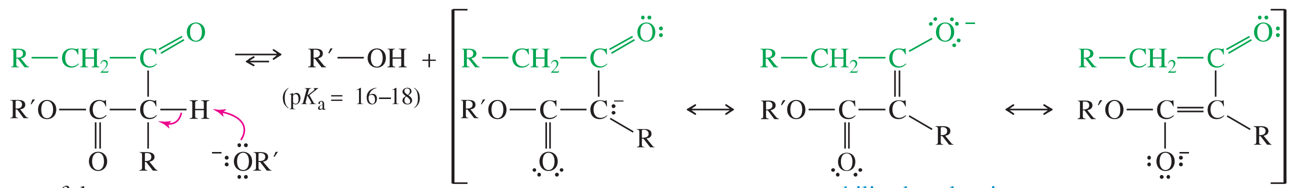
Step 2: Addition of the enolate to give a tetrahedral intermediate. ***Step 3:*** Elimination of the alkoxide leaving group.



ester enolate — tetrahedral intermediate — a β-keto ester

Notice that one molecule of the ester (deprotonated, reacting as the enolate) serves as the nucleophile to attack another molecule of the ester, which serves as the acylating reagent in this nucleophilic acyl substitution.

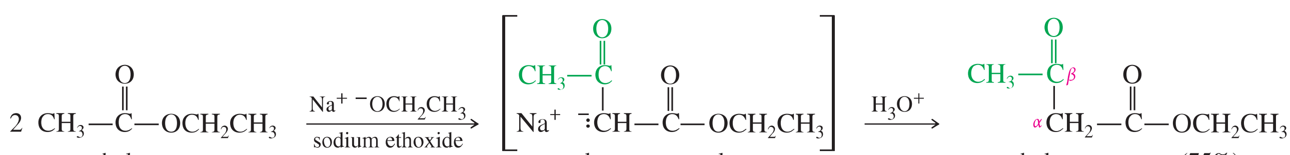
The β-keto ester products of Claisen condensations are more acidic than simple ketones, aldehydes, and esters because deprotonation gives an enolate whose negative charge is delocalized over both carbonyl groups. β-Keto esters have pK_a values around 11, showing they are stronger acids than water. In strong base such as ethoxide ion or hydroxide ion, the β-keto ester is rapidly and completely deprotonated.



a β-keto ester (pK_a = 11) — (pK_a = 16–18) — resonance-stabilized enolate ion

Deprotonation of the β-keto ester provides a driving force for the Claisen condensation. The deprotonation is strongly exothermic, making the overall reaction exothermic and driving the reaction to completion. Because the base is consumed in the deprotonation step, a full equivalent of base must be used, and the Claisen condensation is said to be *base-promoted* rather than *base-catalyzed*. After the reaction is complete, addition of dilute acid converts the enolate back to the β-keto ester.

The following example shows the self-condensation of ethyl acetate to give ethyl acetoacetate (ethyl 3-oxobutanoate). Ethoxide is used as the base to avoid transesterification or hydrolysis of the ethyl ester (see Problem 22-34). The initial product is the enolate of ethyl acetoacetate, which is reprotonated in the final step.



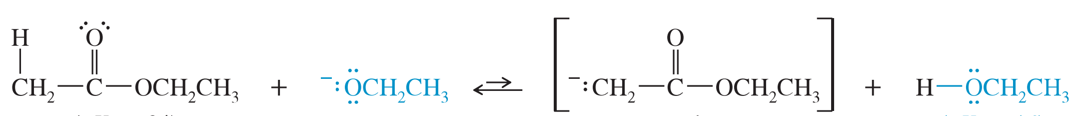
ethyl acetate — sodium ethoxide — keto ester enolate — ethyl acetoacetate (75%)

SOLVED PROBLEM 22-4

Propose a mechanism for the self-condensation of ethyl acetate to give ethyl acetoacetate.

SOLUTION

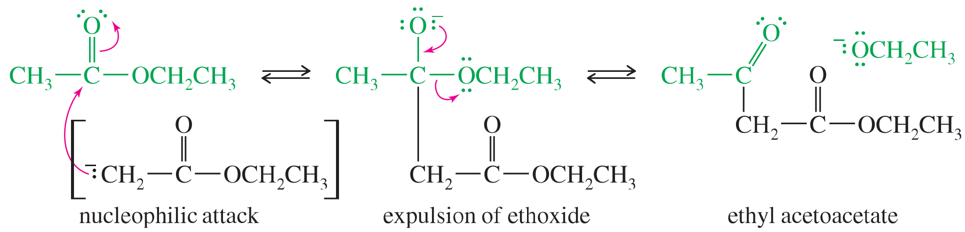
The first step is formation of the ester enolate. The equilibrium for this step lies far to the left; ethoxide deprotonates only a small fraction of the ester.



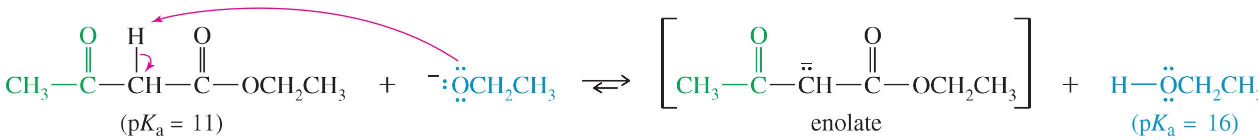
(pK_a = 24) — enolate — (pK_a = 16)

(continued)

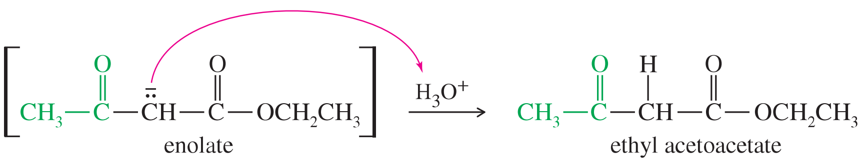
The enolate ion attacks another molecule of the ester; expulsion of ethoxide ion gives ethyl acetoacetate.



In the presence of ethoxide ion, ethyl acetoacetate is deprotonated to give its enolate. This exothermic deprotonation helps to drive the reaction to completion.



When the reaction is complete, the enolate ion is reprotonated to give ethyl acetoacetate.



PROBLEM 22-34

Ethoxide is used as the base in the condensation of ethyl acetate to avoid some unwanted side reactions. Show what side reactions would occur if the following bases were used.
(a) sodium methoxide **(b)** sodium hydroxide

Application: Biochemistry

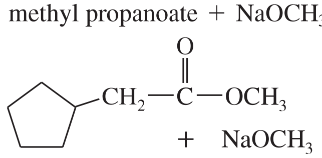
Enzymes called polyketide synthases catalyze a series of Claisen-type reactions to generate many useful natural products, such as the antibiotic erythromycin (page 1089). These enzymes use thioesters instead of the oxygen esters.

PROBLEM 22-35

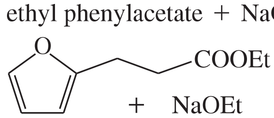
Esters with only one α hydrogen generally give poor yields in the Claisen condensation. Propose a mechanism for the Claisen condensation of ethyl isobutyrate, and explain why a poor yield is obtained.

PROBLEM 22-36

Predict the products of self-condensation of the following esters.
(a) methyl propanoate + $NaOCH_3$ **(b)** ethyl phenylacetate + $NaOCH_2CH_3$
(c)

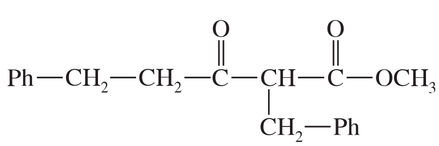


(d)



SOLVED PROBLEM 22-5

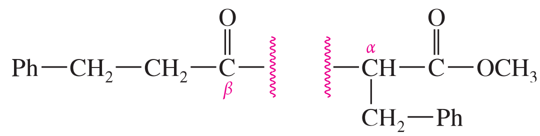
Show what ester would undergo Claisen condensation to give the following β-keto ester.



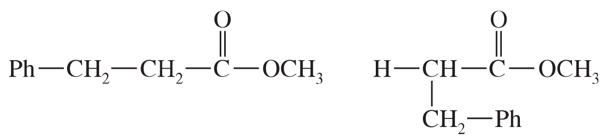
(continued)

SOLUTION

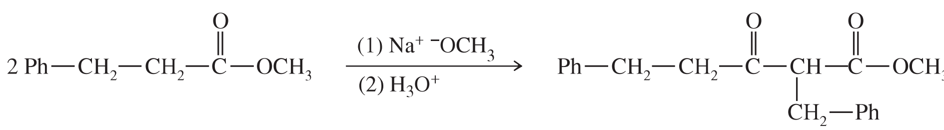
First, break the structure apart at the α,β bond (α,β to the ester carbonyl). This is the bond formed in the Claisen condensation.



Next, replace the α proton that was lost, and replace the alkoxy group that was lost from the carbonyl. Two molecules of methyl 3-phenylpropionate result.



Now draw out the reaction. Sodium methoxide is used as the base because the reactants are methyl esters.



PROBLEM-SOLVING HINT

The Claisen condensation occurs by a nucleophilic acyl substitution, with different forms of the ester acting as both the nucleophile (the enolate) and the electrophile (the ester carbonyl).

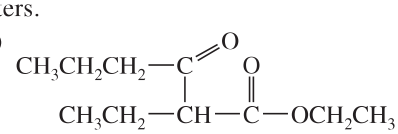
PROBLEM 22-37

Propose a mechanism for the self-condensation of methyl 3-phenylpropionate promoted by sodium methoxide.

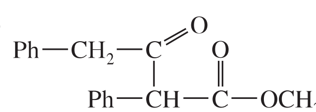
PROBLEM 22-38

Show what esters would undergo Claisen condensation to give the following β-keto esters.

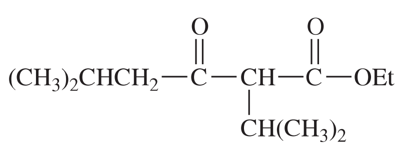
(a)



(b)



(c)



22-13 The Dieckmann Condensation: A Claisen Cyclization

An internal Claisen condensation of a diester forms a ring. Such an internal Claisen cyclization is called a **Dieckmann condensation** or a **Dieckmann cyclization.** Five- and six-membered rings are easily formed by Dieckmann condensations. Rings smaller than five carbons or larger than six carbons are rarely formed by this method.

The following examples of the Dieckmann condensation show that a 1,6-diester gives a five-membered ring, and a 1,7-diester gives a six-membered ring.