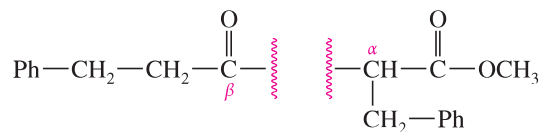
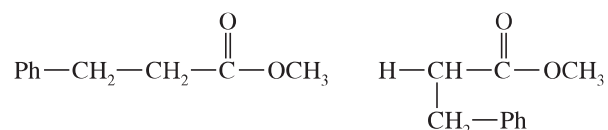


**SOLUTION**

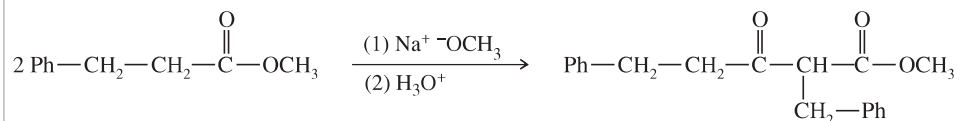
First, break the structure apart at the  $\alpha,\beta$  bond ( $\alpha,\beta$  to the ester carbonyl). This is the bond formed in the Claisen condensation.



Next, replace the  $\alpha$  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**

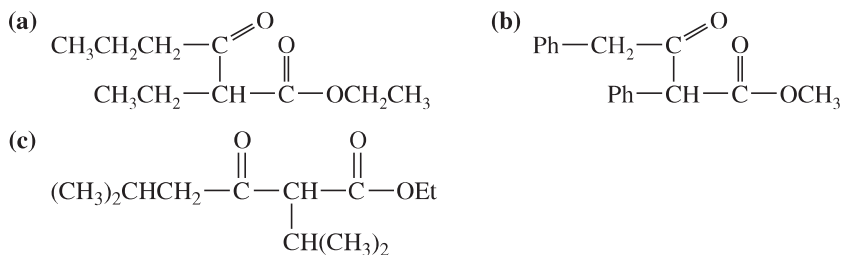
The Claisen condensation occurs by a nucleophilic acyl substitution, with different forms of the ester acting as both the nucleophile (the enolate) and the electrophile (the ester carbonyl).

**PROBLEM 22-37**

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

**PROBLEM 22-38**

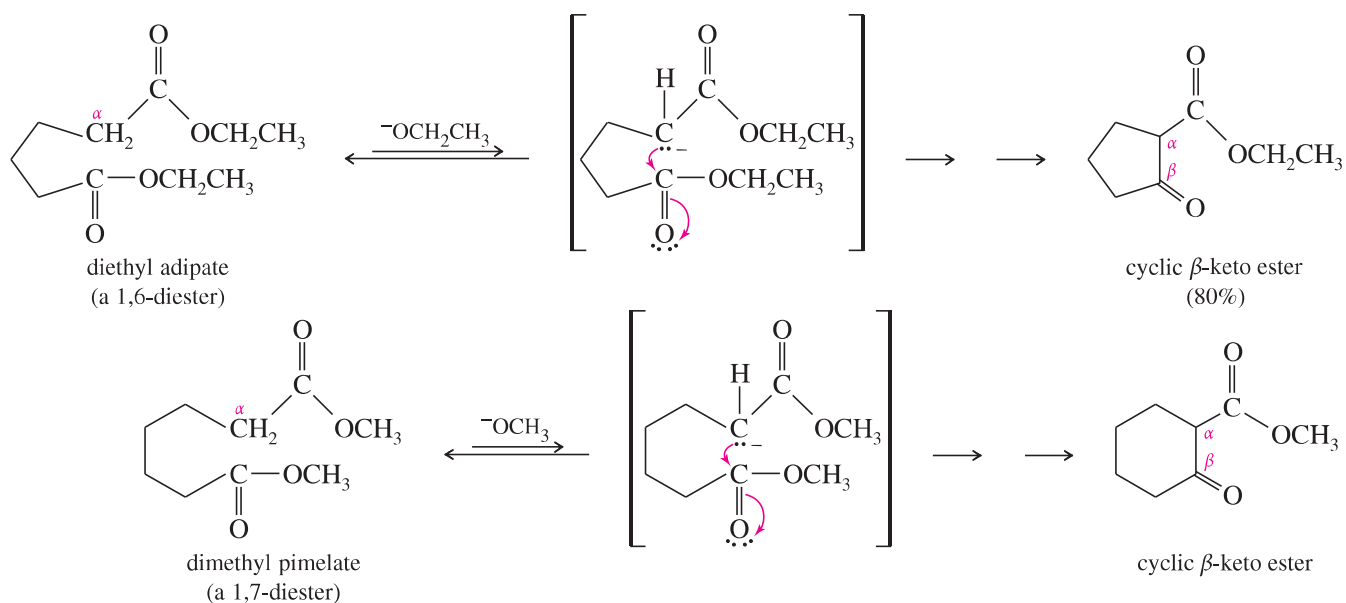
Show what esters would undergo Claisen condensation to give the following  $\beta$ -keto esters.



## 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.

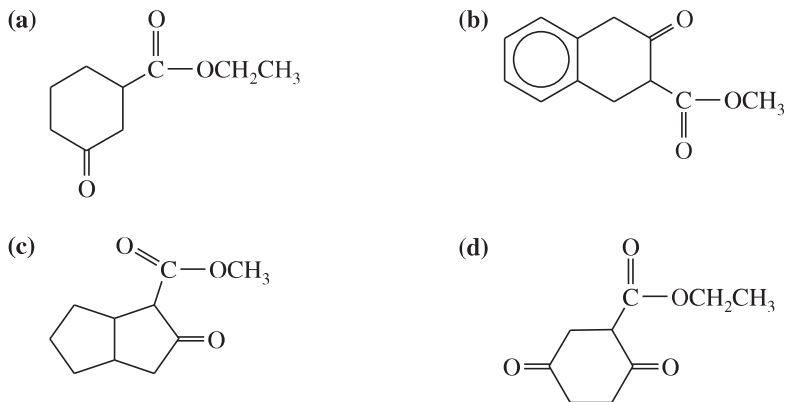
The following examples of the Dieckmann condensation show that a 1,6-diester gives a five-membered ring, and a 1,7-diester gives a six-membered ring.

**PROBLEM 22-39**

Propose mechanisms for the two Dieckmann condensations just shown.

**PROBLEM 22-40**

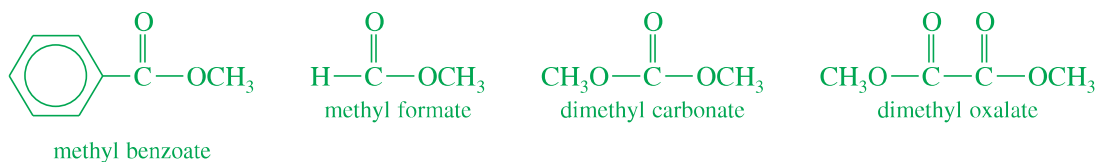
Some (but not all) of the following keto esters can be formed by Dieckmann condensations. Determine which ones are possible, and draw the starting diesters.



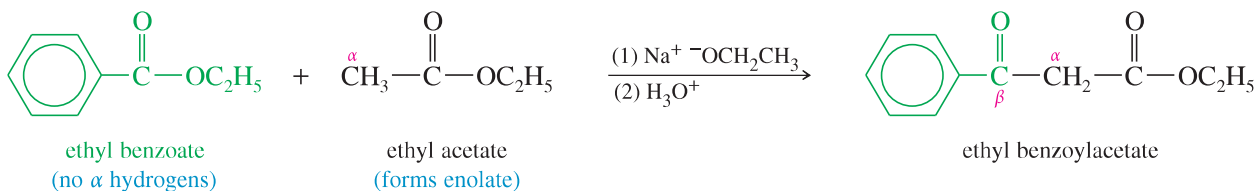
(Hint: Consider using a protecting group.)

**22-14 Crossed Claisen Condensations**

Claisen condensations can take place between different esters, particularly when only one of the esters has the  $\alpha$  hydrogens needed to form an enolate. In a **crossed Claisen condensation**, an ester without  $\alpha$  hydrogens serves as the electrophilic component. Some useful esters without  $\alpha$  hydrogens are benzoate, formate, carbonate, and oxalate esters.



A crossed Claisen condensation is carried out by first adding the ester without  $\alpha$  hydrogens to a solution of the alkoxide base. The ester with  $\alpha$  hydrogens is slowly added to this solution, where it forms an enolate and condenses. The condensation of ethyl acetate with ethyl benzoate is an example of a crossed Claisen condensation.

**PROBLEM 22-41**

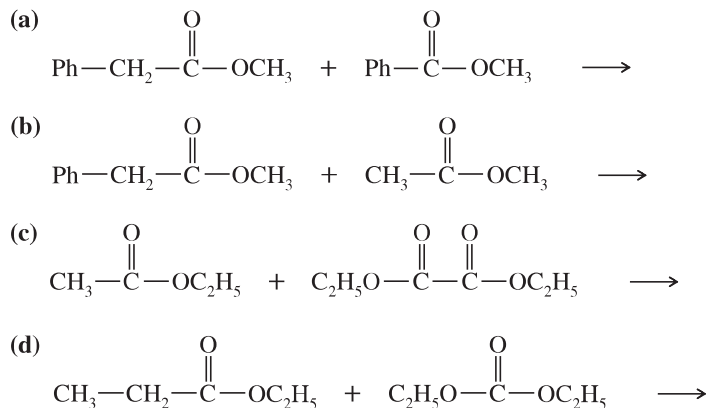
Propose a mechanism for the crossed Claisen condensation between ethyl acetate and ethyl benzoate.

**Application: Biochemistry**

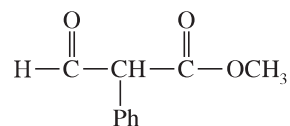
Fatty acids are made in the body by a series of Claisen-type reactions catalyzed by a class of enzymes called fatty acid synthases. The enzymes use the thioesters of malonate and acetate as building blocks (see Figure 22-3 on page 1150).

**PROBLEM 22-42**

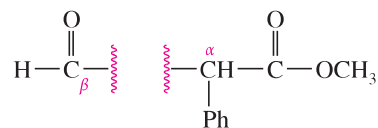
Predict the products from crossed Claisen condensation of the following pairs of esters. Indicate which combinations are poor choices for crossed Claisen condensations.

**SOLVED PROBLEM 22-6**

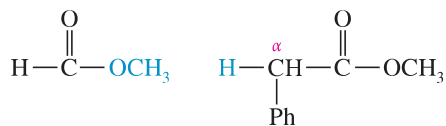
Show how a crossed Claisen condensation might be used to prepare

**SOLUTION**

Break the  $\alpha,\beta$  bond of this  $\beta$ -keto ester, since that is the bond formed in the Claisen condensation.

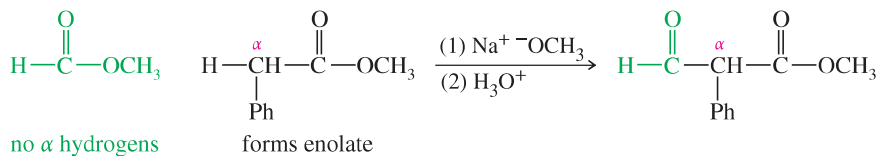


Now add the alkoxy group to the carbonyl and replace the proton on the  $\alpha$  carbon.



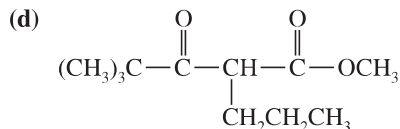
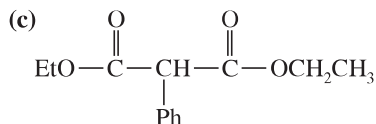
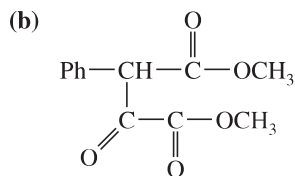
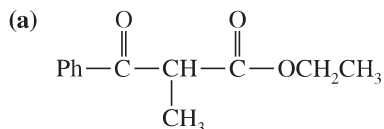
(continued)

Write out the reaction, making sure that one of the components has  $\alpha$  hydrogens and the other does not.

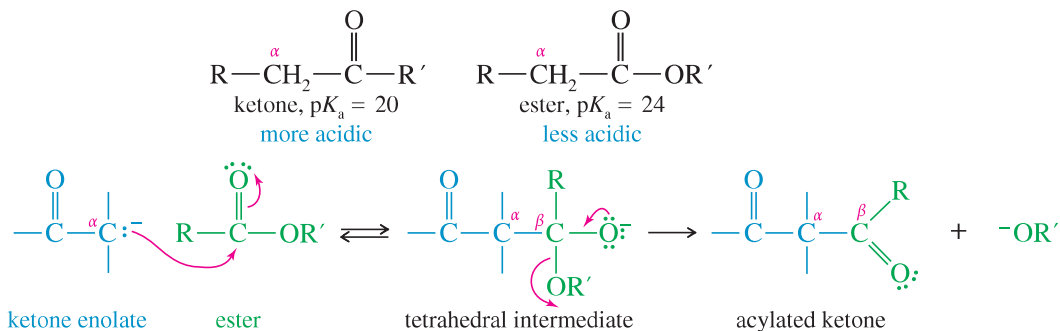


### PROBLEM 22-43

Show how crossed Claisen condensations could be used to prepare the following esters.



Crossed Claisen condensations between ketones and esters are also possible. Ketones are more acidic than esters, and the ketone component is more likely to deprotonate and serve as the enolate component in the condensation. The ketone enolate attacks the ester, which undergoes nucleophilic acyl substitution and thereby acylates the ketone.



This condensation works best if the ester has no  $\alpha$  hydrogens, so that it cannot form an enolate. Because of the difference in acidities, however, the reaction is sometimes successful between ketones and esters even when both have  $\alpha$  hydrogens. The following examples show some crossed Claisen condensations between ketones and esters. Notice the variety of difunctional and trifunctional compounds that can be produced by appropriate choices of esters.

