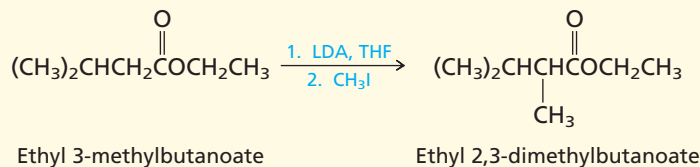


isopropyl halides in  $S_N2$  reactions and cannot undergo elimination as a competing process; therefore, choose the synthesis in which bond ⑥ is formed by alkylation.

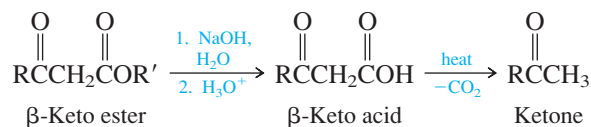


(This synthesis has been reported in the chemical literature and gives the desired product in 95% yield.)

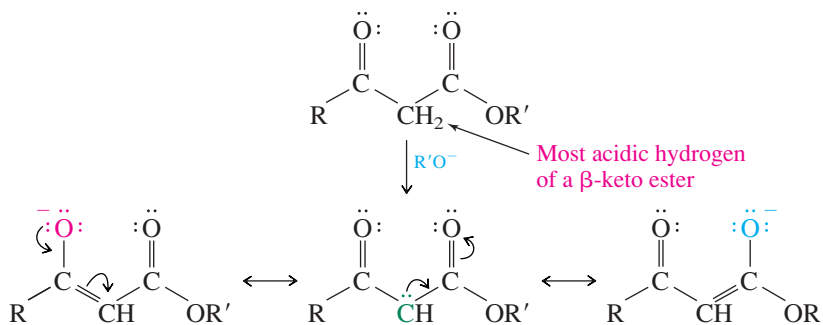
## 21.11 SUMMARY

Sections 21.1–21.4  $\beta$ -Keto esters, which are useful reagents for a number of carbon–carbon bond-forming reactions, are prepared by the methods shown in Table 21.1.

Section 21.5 Hydrolysis of  $\beta$ -keto esters, such as those shown in Table 21.1, gives  $\beta$ -keto acids which undergo rapid decarboxylation, forming ketones.

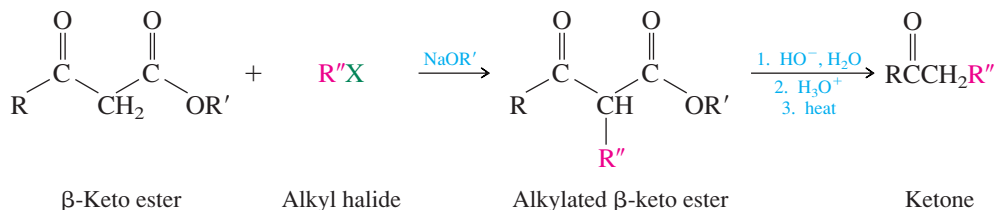


$\beta$ -Keto esters are characterized by  $pK_a$ 's of about 11 and are quantitatively converted to their enolates on treatment with alkoxide bases.



Resonance forms illustrating charge delocalization in enolate of a  $\beta$ -keto ester

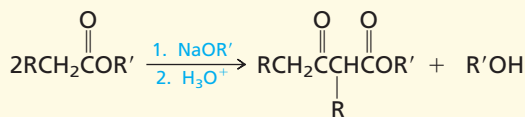
The anion of a  $\beta$ -keto ester may be alkylated at carbon with an alkyl halide and the product of this reaction subjected to ester hydrolysis and decarboxylation to give a ketone.



**TABLE 21.1** Preparation of  $\beta$ -Keto Esters

**Reaction (section) and comments**
**General equation and specific example**
**Claisen condensation (Section 21.1)** Esters of the

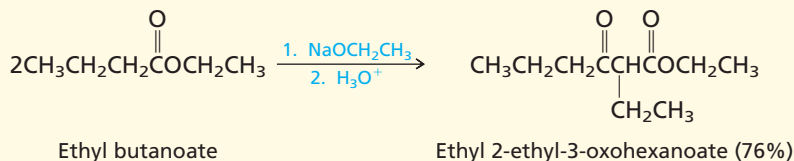
$\text{RCH}_2\text{COR}'$  type are converted to  $\beta$ -keto esters on treatment with alkoxide bases. One molecule of an ester is converted to its enolate; a second molecule of ester acts as an acylating agent toward the enolate.



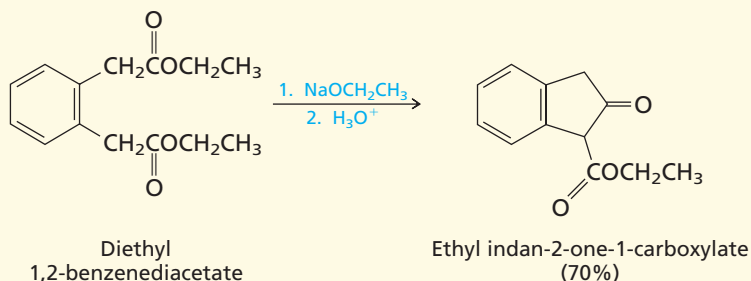
Ester

 $\beta$ -Keto ester

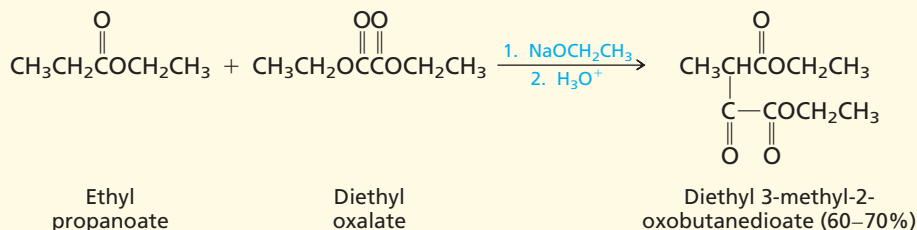
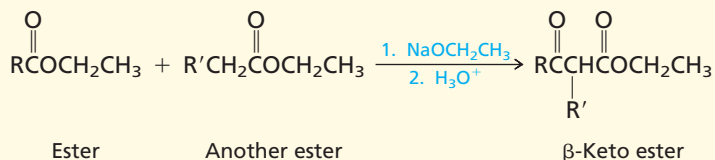
Alcohol



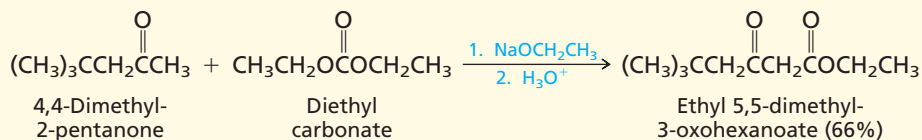
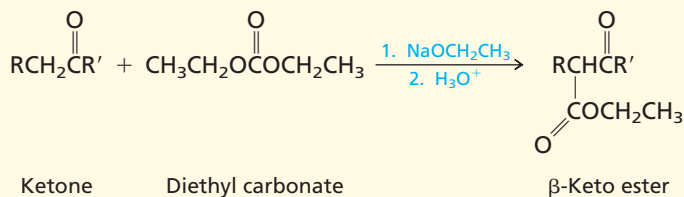
**Dieckmann cyclization (Section 21.2)** An intramolecular analog of the Claisen condensation. Cyclic  $\beta$ -keto esters in which the ring is five- to seven-membered may be formed by using this reaction.



**Mixed Claisen condensations (Section 21.3)** Diethyl carbonate, diethyl oxalate, ethyl formate, and benzoate esters cannot form ester enolates but can act as acylating agents toward other ester enolates.

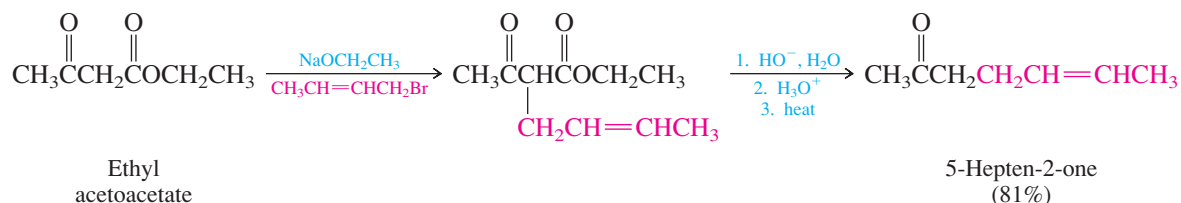


**Acylation of ketones (Section 21.4)** Diethyl carbonate and diethyl oxalate can be used to acylate ketone enolates to give  $\beta$ -keto esters.

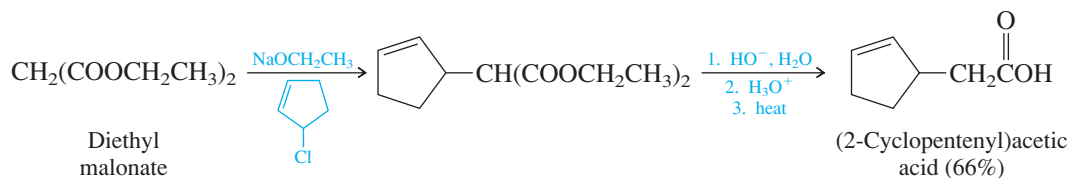


Section 21.6 The **acetoacetic ester synthesis** is a procedure in which ethyl acetoacetate is alkylated with an alkyl halide as the first step in the preparation

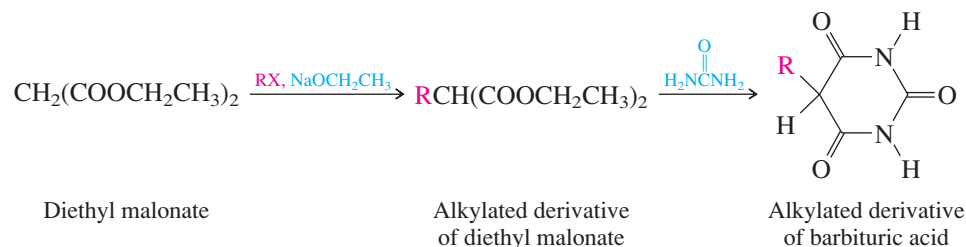
of ketones of the type  $\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\text{R}$ .



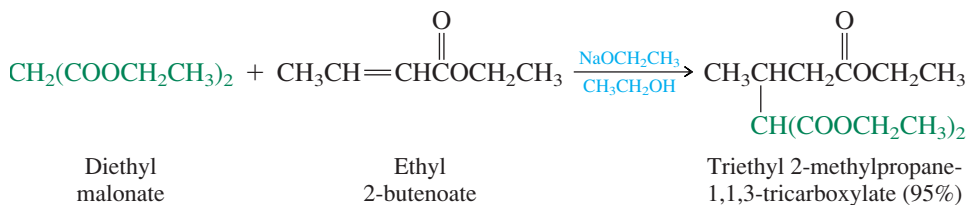
Section 21.7 The **malonic ester synthesis** is related to the acetoacetic ester synthesis. Alkyl halides (RX) are converted to carboxylic acids of the type  $\text{RCH}_2\text{COOH}$  by reaction with the enolate ion derived from diethyl malonate, followed by saponification and decarboxylation.



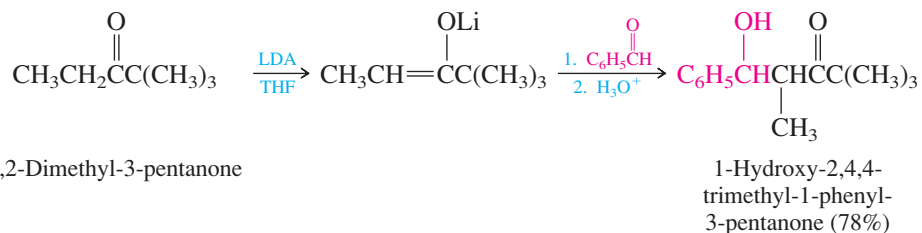
Section 21.8 Alkylation of diethyl malonate, followed by reaction with urea, gives derivatives of barbituric acid, called **barbiturates**, which are useful sleep-promoting drugs.



Section 21.9 **Michael addition** of the enolate ions derived from ethyl acetoacetate and diethyl malonate provides an alternative method for preparing their  $\alpha$ -alkyl derivatives.

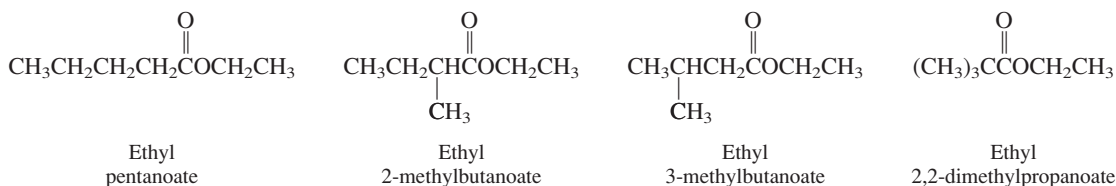


Section 21.10 It is possible to generate ester enolates by deprotonation provided that the base used is very strong. Lithium diisopropylamide (LDA) is often used for this purpose. It also converts ketones quantitatively to their enolates.

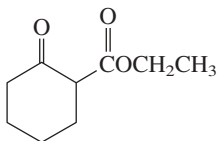


## PROBLEMS

**21.15** The following questions pertain to the esters shown and their behavior under conditions of the Claisen condensation.



- (a) Two of these esters are converted to  $\beta$ -keto esters in good yield on treatment with sodium ethoxide and subsequent acidification of the reaction mixture. Which two are these? Write the structure of the Claisen condensation product of each one.
- (b) One ester is capable of being converted to a  $\beta$ -keto ester on treatment with sodium ethoxide, but the amount of  $\beta$ -keto ester that can be isolated after acidification of the reaction mixture is quite small. Which ester is this?
- (c) One ester is incapable of reaction under conditions of the Claisen condensation. Which one? Why?
- 21.16**
- (a) Give the structure of the Claisen condensation product of ethyl phenylacetate ( $\text{C}_6\text{H}_5\text{CH}_2\text{COOCH}_2\text{CH}_3$ ).
- (b) What ketone would you isolate after saponification and decarboxylation of this Claisen condensation product?
- (c) What ketone would you isolate after treatment of the Claisen condensation product of ethyl phenylacetate with sodium ethoxide and allyl bromide, followed by saponification and decarboxylation?
- (d) Give the structure of the mixed Claisen condensation product of ethyl phenylacetate and ethyl benzoate.
- (e) What ketone would you isolate after saponification and decarboxylation of the product in part (d)?
- (f) What ketone would you isolate after treatment of the product in part (d) with sodium ethoxide and allyl bromide, followed by saponification and decarboxylation?
- 21.17** All the following questions concern ethyl (2-oxocyclohexane)carboxylate.



Ethyl (2-oxocyclohexane)carboxylate