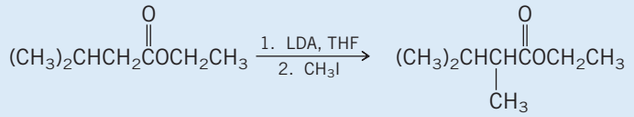
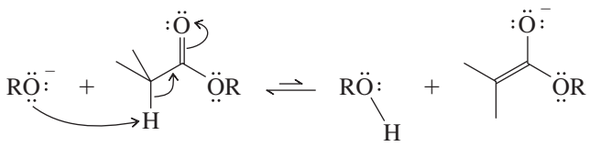


Ethyl 3-methylbutanoate — Ethyl 2,3-dimethylbutanoate

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

21.11 SUMMARY

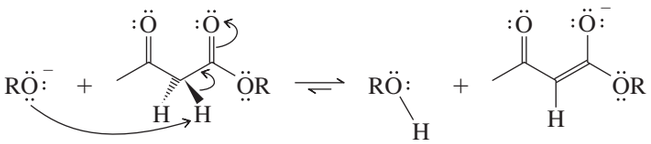
Section 21.1 The most acidic proton of an ester is on the α carbon and has a pK_a value of about 24. When treated with alkoxide bases an ester enolate is formed that is in equilibrium with the starting ester. The ester is the major component of the equilibrium.



Ester — Ester enolate

Very strong bases such as lithium diisopropylamide (LDA) convert an ester entirely to its enolate.

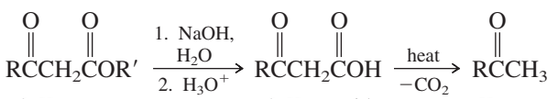
β-Keto esters have pK_a values of approximately 11 and are converted completely to their enolates by alkoxide bases.



β-Keto ester — β-Keto ester enolate

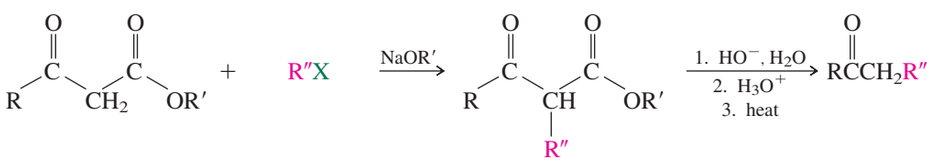
Sections 21.2–21.5 β-Keto esters are prepared by the methods shown in Table 21.1.

Section 21.6 Hydrolysis of β-Keto esters, such as those shown in Table 21.1, gives β-keto acids which undergo rapid decarboxylation, forming ketones.



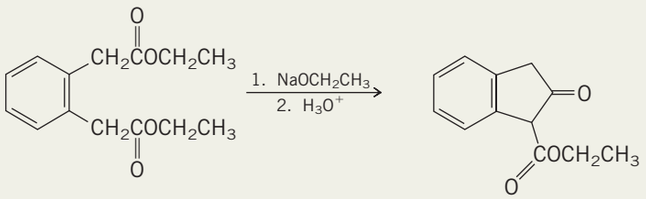
β-Keto ester — β-Keto acid — Ketone

The enolate of a β-keto ester may be alkylated with an alkyl halide and the product of this reaction subjected to ester hydrolysis and decarboxylation to give a ketone.

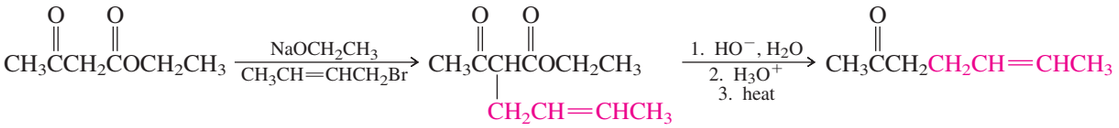


β-Keto ester — Alkyl halide — Alkylated β-keto ester — Ketone

TABLE 21.1 Preparation of β-Keto Esters

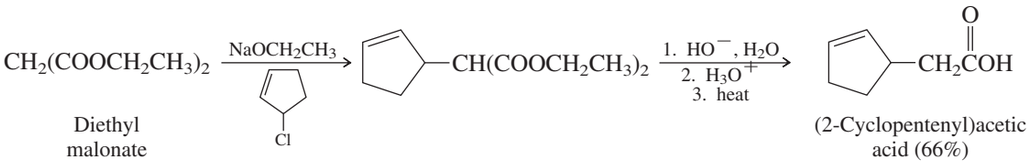
Reaction (section) and comments	General equation and specific example
Claisen condensation (Section 21.2) Esters of the type RCH_2COR' are converted to β-keto esters on treatment with alkoxide bases. One molecule of an ester is converted to its enolate; a second molecule of ester acts as an acylating agent toward the enolate.	$2RCH_2COR' \xrightarrow[2.\ H_3O^+]{1.\ NaOR'} RCH_2CCHCOR' + R'OH$ (R at the α-carbon) Ester → β-Keto ester + Alcohol $2CH_3CH_2CH_2COCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3CH_2CH_2CCHCOCH_2CH_3$ (CH_2CH_3 at the α-carbon) Ethyl butanoate → Ethyl 2-ethyl-3-oxohexanoate (76%)
Dieckmann cyclization (Section 21.3) An intramolecular analog of the Claisen condensation. Cyclic β-keto esters in which the ring is five- to seven-membered may be formed by using this reaction.	 Diethyl 1,2-benzenediacetate → Ethyl indan-2-one-1-carboxylate (70%)
Mixed Claisen condensations (Section 21.4) Diethyl carbonate, diethyl oxalate, ethyl formate, and benzoate esters cannot form ester enolates but can act as acylating agents toward other ester enolates.	$RCOCH_2CH_3 + R'CH_2COCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} RCCHCOCH_2CH_3$ (R′ at the α-carbon) Ester + Another ester → β-Keto ester $CH_3CH_2COCH_2CH_3 + CH_3CH_2OCCOCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3CHCOCH_2CH_3$ (C—$COCH_2CH_3$ at the α-carbon) Ethyl propanoate + Diethyl oxalate → Diethyl 3-methyl-2-oxobutanedioate (60–70%)
Acylation of ketones (Section 21.5) Diethyl carbonate and diethyl oxalate can be used to acylate ketone enolates to give β-keto esters.	$RCH_2CR' + CH_3CH_2OCOCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} RCHCR'$ ($COCH_2CH_3$ at the α-carbon) Ketone + Diethyl carbonate → β-Keto ester $(CH_3)_3CCH_2CCH_3 + CH_3CH_2OCOCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} (CH_3)_3CCH_2CCH_2COCH_2CH_3$ 4,4-Dimethyl-2-pentanone + Diethyl carbonate → Ethyl 5,5-dimethyl-3-oxohexanoate (66%)

Section 21.7 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 CH_3CCH_2R.



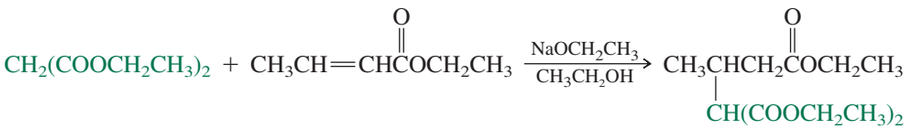
Ethyl acetoacetate — 5-Hepten-2-one (81%)

Section 21.8 The **malonic ester synthesis** is related to the acetoacetic ester synthesis. Alkyl halides (RX) are converted to carboxylic acids of the type RCH_2COOH by reaction with the enolate ion derived from diethyl malonate, followed by saponification and decarboxylation.



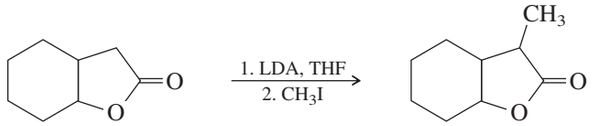
Diethyl malonate — (2-Cyclopentenyl)acetic acid (66%)

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



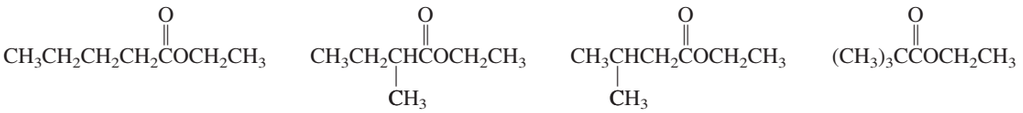
Diethyl malonate — Ethyl 2-butenoate — Triethyl 2-methylpropane-1,1,3-tricarboxylate (95%)

Section 21.10 Deprotonation of esters with lithium diisopropylamide gives the corresponding enolate quantitatively. Ester enolates generated under these conditions act as nucleophiles toward alkyl halides, aldehydes and ketones, and esters. The example shows the generation and alkylation of an enolate derived from a lactone.



PROBLEMS

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



Ethyl pentanoate — Ethyl 2-methylbutanoate — Ethyl 3-methylbutanoate — Ethyl 2,2-dimethylpropanoate