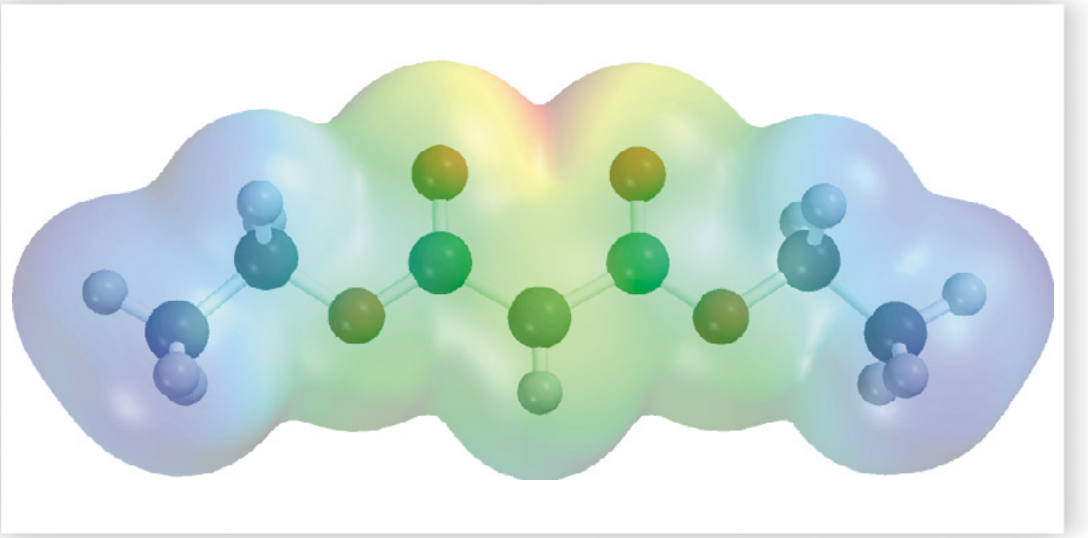
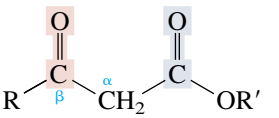


CHAPTER 21

ESTER ENOLATES

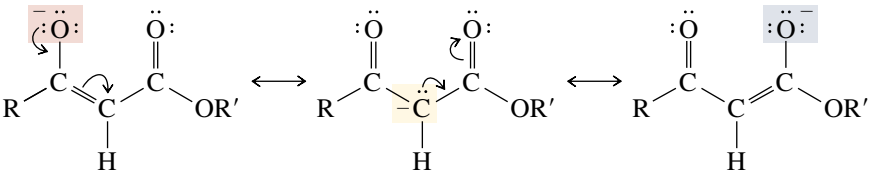
You have already had considerable experience with carbanionic compounds and their applications in synthetic organic chemistry. The first was acetylide ion in Chapter 9, followed in Chapter 14 by organometallic compounds—Grignard reagents, for example—that act as sources of negatively polarized carbon. In Chapter 18 you learned that enolate ions—reactive intermediates generated from aldehydes and ketones—are nucleophilic, and that this property can be used to advantage as a method for carbon–carbon bond formation.

The present chapter extends our study of carbanions to the enolate ions derived from esters. **Ester enolates** are important reagents in synthetic organic chemistry. The stabilized enolates derived from **β-keto esters** are particularly useful.



β-Keto ester: a ketone carbonyl is β to the carbonyl group of the ester.

A proton attached to the α-carbon atom of a β-keto ester is relatively acidic. Typical acid dissociation constants K_a for β-keto esters are $\approx 10^{-11}$ (pK_a 11). Because the α-carbon atom is flanked by two electron-withdrawing carbonyl groups, a carbanion formed at this site is highly stabilized. The electron delocalization in the anion of a β-keto ester is represented by the resonance structures



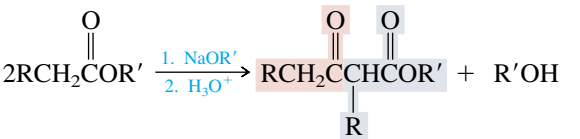
Principal resonance structures of the anion of a β-keto ester

We'll begin by describing the preparation and properties of β-keto esters, proceed to a discussion of their synthetic applications, continue to an examination of related species, and conclude by exploring some recent developments in the active field of synthetic carbanion chemistry.

21.1 THE CLAISEN CONDENSATION

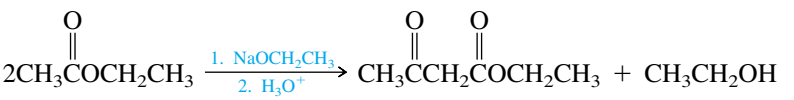
Before describing how β-keto esters are used as reagents for organic synthesis, we need to see how these compounds themselves are prepared. The main method for the preparation of β-keto esters is a reaction known as the **Claisen condensation:**

Ludwig Claisen was a German chemist who worked during the last two decades of the nineteenth century and the first two decades of the twentieth. His name is associated with three reactions. The *Claisen–Schmidt reaction* was presented in Section 18.10, the *Claisen condensation* is discussed in this section, and the *Claisen rearrangement* will be introduced in Section 24.13.



Ester β-Keto ester Alcohol

On treatment with alkoxide bases, esters undergo self-condensation to give a β-keto ester and an alcohol. Ethyl acetate, for example, undergoes a Claisen condensation on treatment with sodium ethoxide to give a β-keto ester known by its common name *ethyl acetoacetate* (also called *acetoacetic ester*):



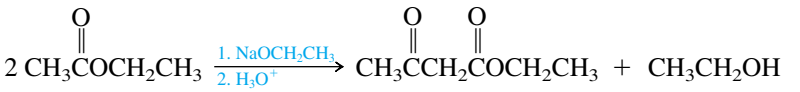
Ethyl acetate Ethyl acetoacetate (75%) (acetoacetic ester) Ethanol

The systematic IUPAC name of ethyl acetoacetate is *ethyl 3-oxobutanoate.* The presence of a ketone carbonyl group is indicated by the designation "*oxo*" along with the appropriate locant. Thus, there are four carbon atoms in the acyl group of ethyl 3-oxobutanoate, C-3 being the carbonyl carbon of the ketone function.

The mechanism of the Claisen condensation of ethyl acetate is presented in Figure 21.1. The first two steps of the mechanism are analogous to those of aldol addition (Section 18.9). An enolate ion is generated in step 1, which undergoes nucleophilic addition to the carbonyl group of a second ester molecule in step 2. The species formed in this step is a tetrahedral intermediate of the same type that we encountered in our discussion of nucleophilic acyl substitution of esters. It dissociates by expelling an ethoxide ion, as shown in step 3, which restores the carbonyl group to give the β-keto ester. Steps 1 to 3 show two different types of ester reactivity: one molecule of the ester gives rise to an enolate; the second molecule acts as an acylating agent.

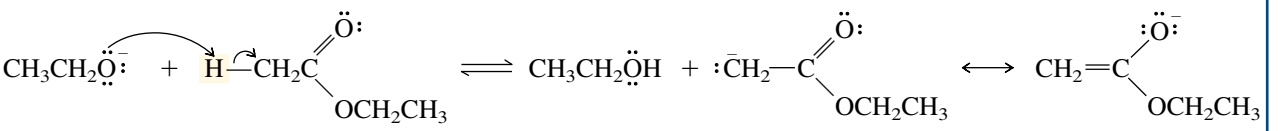
Claisen condensations involve two distinct experimental operations. The first stage concludes in step 4 of Figure 21.1, where the base removes a proton from C-2 of the β-keto ester. Because this proton is relatively acidic, the position of equilibrium for step 4 lies far to the right.

Overall reaction:



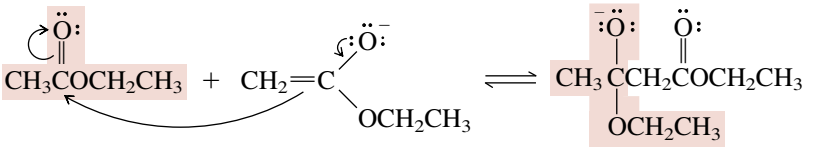
Ethyl acetate — Ethyl 3-oxobutanoate (ethyl acetoacetate) — Ethanol

Step 1: Proton abstraction from the α carbon atom of ethyl acetate to give the corresponding enolate.



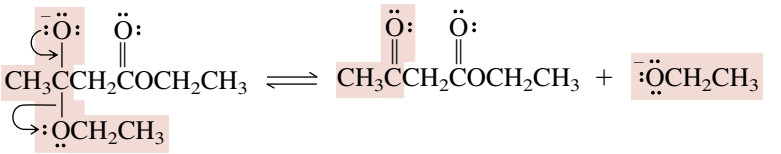
Ethoxide — Ethyl acetate — Ethanol — Enolate of ethyl acetate

Step 2: Nucleophilic addition of the ester enolate to the carbonyl group of the neutral ester. The product is the anionic form of the tetrahedral intermediate.



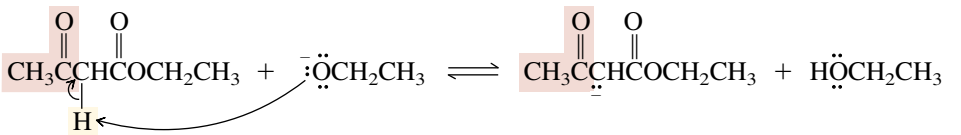
Ethyl acetate — Enolate of ethyl acetate — Anionic form of tetrahedral intermediate

Step 3: Dissociation of the tetrahedral intermediate.



Anionic form of tetrahedral intermediate — Ethyl 3-oxobutanoate — Ethoxide ion

Step 4: Deprotonation of the β-keto ester product.

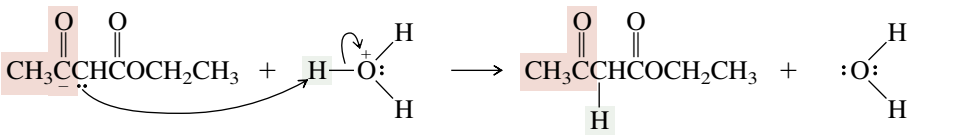


Ethyl 3-oxobutanoate (stronger acid) — Ethoxide ion (stronger base) — Conjugate base of ethyl 3-oxobutanoate (weaker base) — Ethanol (weaker acid)

—Cont.

FIGURE 21.1 The mechanism of the Claisen condensation of ethyl acetate.

Step 5: Acidification of the reaction mixture. This is performed in a separate synthetic operation to give the product in its neutral form for eventual isolation.

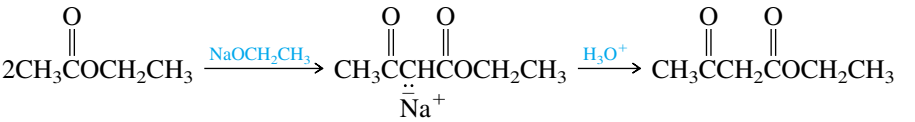


Conjugate base of ethyl 3-oxobutanoate (stronger base) | Hydronium ion (stronger acid) | Ethyl 3-oxobutanoate (weaker acid) | Water (weaker base)

FIGURE 21.1 (*Continued*)

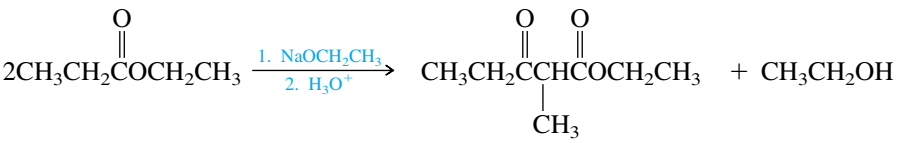
In general, the equilibrium represented by the sum of steps 1 to 3 is not favorable for condensation of two ester molecules to a β-keto ester. (Two ester carbonyl groups are more stable than one ester plus one ketone carbonyl.) However, because the β-keto ester is deprotonated under the reaction conditions, the equilibrium represented by the sum of steps 1 to 4 does lie to the side of products. On subsequent acidification (step 5), the anion of the β-keto ester is converted to its neutral form and isolated.

Organic chemists sometimes write equations for the Claisen condensation in a form that shows both stages explicitly:



Ethyl acetate | Sodium salt of ethyl acetoacetate | Ethyl acetoacetate

Like aldol condensations, Claisen condensations always involve bond formation between the α-carbon atom of one molecule and the carbonyl carbon of another:

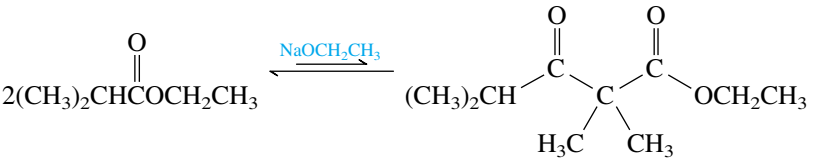


Ethyl propanoate | Ethyl 2-methyl-3-oxopentanoate (81%) | Ethanol

PROBLEM 21.1 One of the following esters cannot undergo the Claisen condensation. Which one? Write structural formulas for the Claisen condensation products of the other two.

$CH_3CH_2CH_2CH_2CO_2CH_2CH_3$	$C_6H_5CO_2CH_2CH_3$	$C_6H_5CH_2CO_2CH_2CH_3$
Ethyl pentanoate	Ethyl benzoate	Ethyl phenylacetate

Unless the β-keto ester can form a stable anion by deprotonation as in step 4 of Figure 21.1, the Claisen condensation product is present in only trace amounts at equilibrium. Ethyl 2-methylpropanoate, for example, does not give any of its condensation product under the customary conditions of the Claisen condensation.



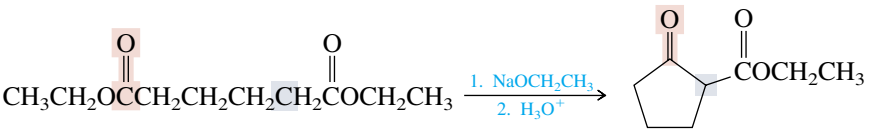
Ethyl 2-methylpropanoate

Ethyl 2,2,4-trimethyl-3-oxopentanoate
(cannot form a stable anion; formed in no more than trace amounts)

At least two protons must be present at the α carbon for the equilibrium to favor product formation. Claisen condensation is possible for esters of the type RCH_2CO_2R', but not for R_2CHCO_2R'.

21.2 INTRAMOLECULAR CLAISEN CONDENSATION: THE DIECKMANN REACTION

Esters of *dicarboxylic acids* undergo an intramolecular version of the Claisen condensation when a five- or six-membered ring can be formed.

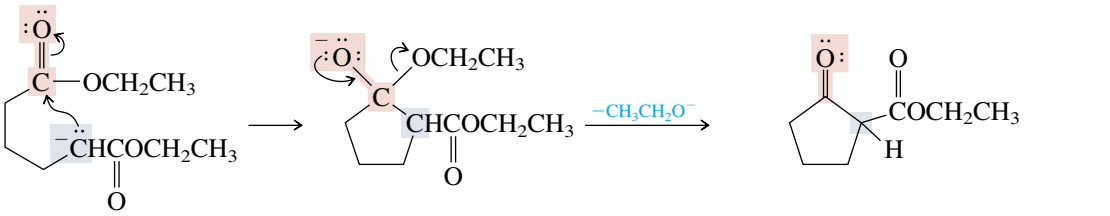


Diethyl hexanedioate

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

This reaction is an example of a **Dieckmann cyclization.** The anion formed by proton abstraction at the carbon α to one carbonyl group attacks the other carbonyl to form a five-membered ring.

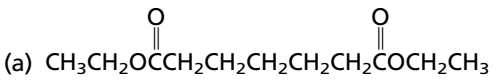
Walter Dieckmann was a German chemist and a contemporary of Claisen.

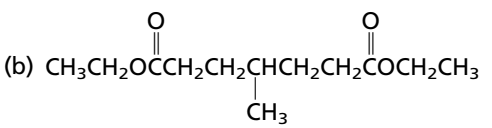


Enolate of diethyl hexanedioate

Ethyl (2-oxocyclopentane)carboxylate

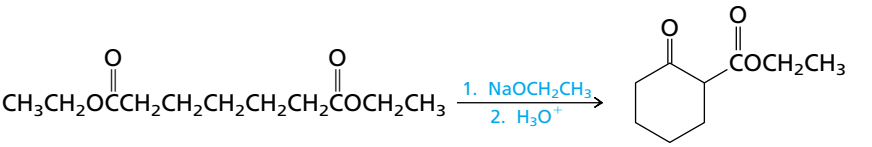
PROBLEM 21.2 Write the structure of the Dieckmann cyclization product formed on treatment of each of the following diesters with sodium ethoxide, followed by acidification.





(c) $CH_3CH_2OCCHCH_2CH_2CH_2COCH_2CH_3$ (with CH_3 on the α-carbon)

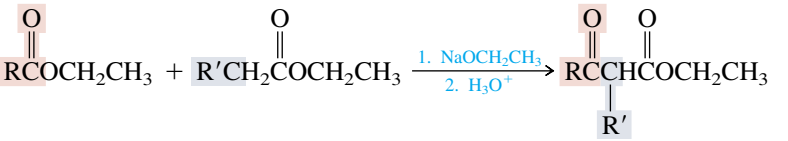
SAMPLE SOLUTION (a) Diethyl heptanedioate has one more methylene group in its chain than the diester cited in the example (diethyl hexanedioate). Its Dieckmann cyclization product contains a six-membered ring instead of the five-membered ring formed from diethyl hexanedioate.



Diethyl heptanedioate — Ethyl (2-oxocyclohexane)-carboxylate

21.3 MIXED CLAISEN CONDENSATIONS

Analogous to mixed aldol condensations, mixed Claisen condensations involve carbon–carbon bond formation between the α-carbon atom of one ester and the carbonyl carbon of another.

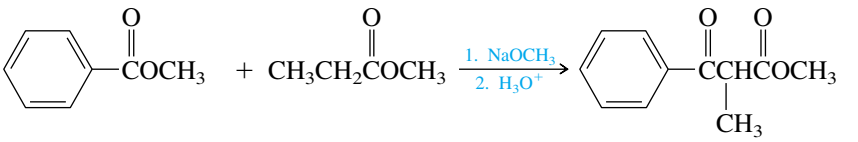


Ester — Another ester — β-Keto ester

The best results are obtained when one of the ester components is incapable of forming an enolate. Esters of this type include the following:

Formate esters — Carbonate esters — Oxalate esters — Benzoate esters

The following equation shows an example of a mixed Claisen condensation in which a benzoate ester is used as the nonenolizable component:

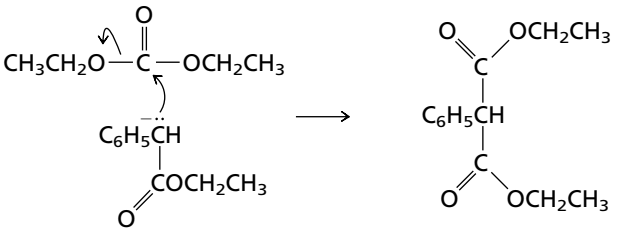


Methyl benzoate (cannot form an enolate) — Methyl propanoate — Methyl 2-methyl-3-oxo-3-phenylpropanoate (60%)

PROBLEM 21.3 Give the structure of the product obtained when ethyl phenylacetate ($C_6H_5CH_2CO_2CH_2CH_3$) is treated with each of the following esters under conditions of the mixed Claisen condensation:

(a) Diethyl carbonate
(b) Diethyl oxalate
(c) Ethyl formate

SAMPLE SOLUTION (a) Diethyl carbonate cannot form an enolate, but ethyl phenylacetate can. Nucleophilic acyl substitution on diethyl carbonate by the enolate of ethyl phenylacetate yields a *diester.*

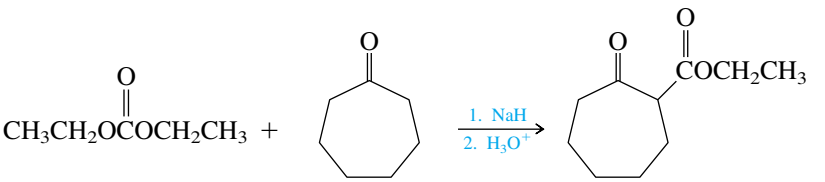


Diethyl 2-phenylpropanedioate
(diethyl phenylmalonate)

The reaction proceeds in good yield (86%), and the product is a useful one in further synthetic transformations of the type to be described in Section 21.7.

21.4 ACYLATION OF KETONES WITH ESTERS

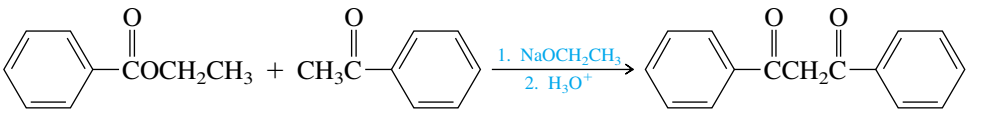
In a reaction related to the mixed Claisen condensation, nonenolizable esters are used as acylating agents for ketone enolates. Ketones (via their enolates) are converted to β-keto esters by reaction with diethyl carbonate.



Diethyl carbonate — Cycloheptanone — Ethyl (2-oxocycloheptane)-carboxylate (91–94%)

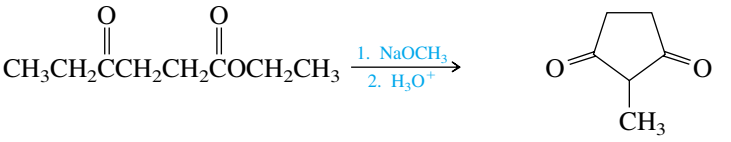
Sodium hydride was used as the base in this example. It is often used instead of sodium ethoxide in these reactions.

Esters of nonenolizable monocarboxylic acids such as ethyl benzoate give β-diketones on reaction with ketone enolates:



Ethyl benzoate — Acetophenone — 1,3-Diphenyl-1,3-propanedione (62–71%)

Intramolecular acylation of ketones yields cyclic β-diketones when the ring that is formed is five- or six-membered.



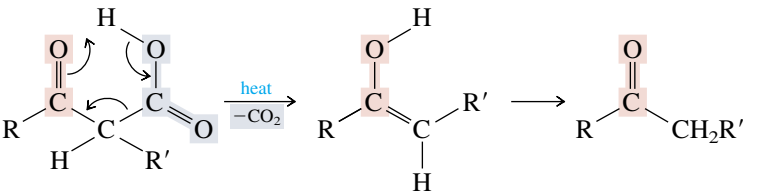
Ethyl 4-oxohexanoate — 2-Methyl-1,3-cyclopentanedione (70–71%)

PROBLEM 21.4 Write an equation for the carbon–carbon bond-forming step in the cyclization reaction just cited. Show clearly the structure of the enolate ion, and use curved arrows to represent its nucleophilic addition to the appropriate carbonyl group. Write a second equation showing dissociation of the tetrahedral intermediate formed in the carbon–carbon bond-forming step.

Even though ketones have the potential to react with themselves by aldol addition, recall that the position of equilibrium for such reactions lies to the side of the starting materials (Section 18.9). On the other hand, acylation of ketone enolates gives products (β-keto esters or β-diketones) that are converted to stabilized anions under the reaction conditions. Consequently, ketone acylation is observed to the exclusion of aldol addition when ketones are treated with base in the presence of esters.

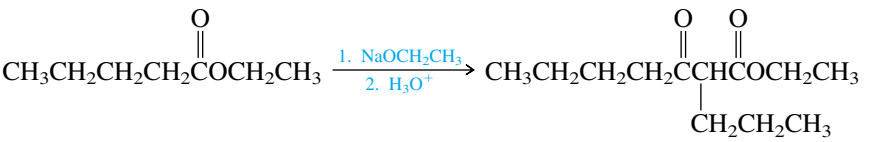
21.5 KETONE SYNTHESIS VIA β-KETO ESTERS

The carbon–carbon bond-forming potential inherent in the Claisen and Dieckmann reactions has been extensively exploited in organic synthesis. Subsequent transformations of the β-keto ester products permit the synthesis of other functional groups. One of these transformations converts β-keto esters to ketones; it is based on the fact that β-keto *acids* (not esters!) undergo decarboxylation readily (Section 19.17). Indeed, β-keto acids, and their corresponding carboxylate anions as well, lose carbon dioxide so easily that they tend to decarboxylate under the conditions of their formation.

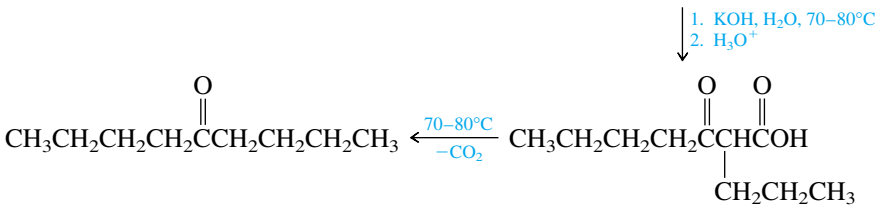


β-Keto acid | Enol form of ketone | Ketone

Thus, 5-nonanone has been prepared from ethyl pentanoate by the sequence



Ethyl pentanoate | Ethyl 3-oxo-2-propylheptanoate (80%)



5-Nonanone (81%) | 3-Oxo-2-propylheptanoic acid (not isolated; decarboxylates under conditions of its formation)

The sequence begins with a Claisen condensation of ethyl pentanoate to give a β-keto ester. The ester is hydrolyzed, and the resulting β-keto acid decarboxylates to yield the desired ketone.

PROBLEM 21.5 Write appropriate chemical equations showing how you could prepare cyclopentanone from diethyl hexanedioate.

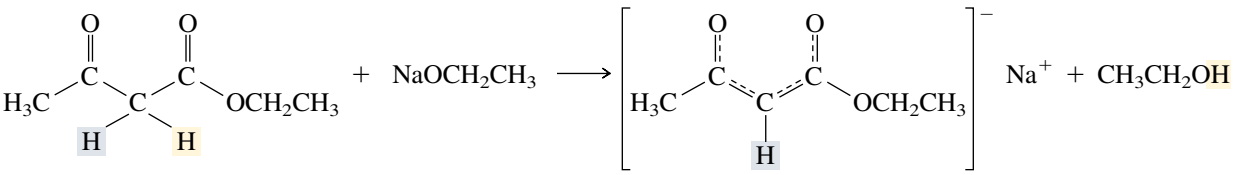
The major application of β-keto esters to organic synthesis employs a similar pattern of ester saponification and decarboxylation as its final stage, as described in the following section.

21.6 THE ACETOACETIC ESTER SYNTHESIS

Ethyl acetoacetate (acetoacetic ester), available by the Claisen condensation of ethyl acetate, has properties that make it a useful starting material for the preparation of ketones. These properties are

1. The acidity of the α proton
2. The ease with which acetoacetic acid undergoes thermal decarboxylation

Ethyl acetoacetate is a stronger acid than ethanol and is quantitatively converted to its anion on treatment with sodium ethoxide in ethanol.



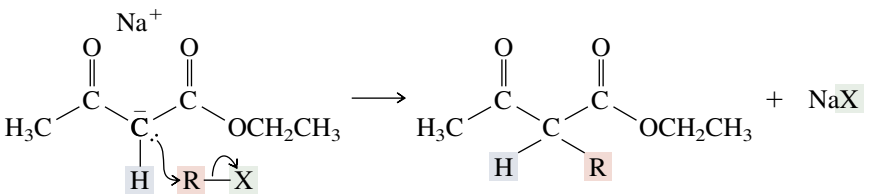
Ethyl acetoacetate (stronger acid) K_a 10^{-11} (pK_a 11)

Sodium ethoxide (stronger base)

Sodium salt of ethyl acetoacetate (weaker base)

Ethanol (weaker acid) K_a 10^{-16} (pK_a 16)

The anion produced by proton abstraction from ethyl acetoacetate is nucleophilic. Adding an alkyl halide to a solution of the sodium salt of ethyl acetoacetate leads to alkylation of the α carbon.



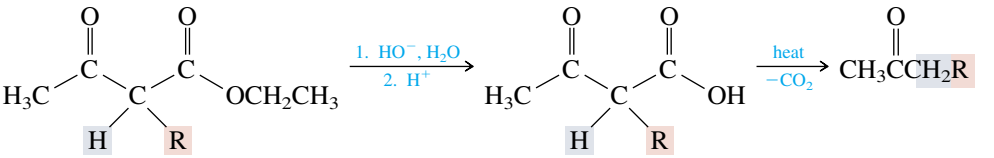
Sodium salt of ethyl acetoacetate; alkyl halide

2-Alkyl derivative of ethyl acetoacetate

Sodium halide

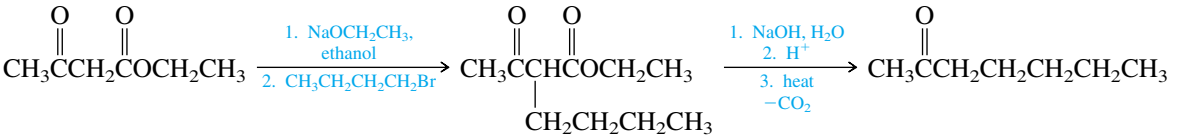
The new carbon–carbon bond is formed by an S_N2-type reaction. The alkyl halide must therefore be one that is not sterically hindered. Methyl and primary alkyl halides work best; secondary alkyl halides give lower yields. Tertiary alkyl halides react only by elimination, not substitution.

Saponification and decarboxylation of the alkylated derivative of ethyl acetoacetate yields a ketone.



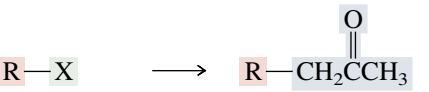
2-Alkyl derivative of ethyl acetoacetate | 2-Alkyl derivative of acetoacetic acid | Ketone

This reaction sequence is called the **acetoacetic ester synthesis.** It is a standard procedure for the preparation of ketones from alkyl halides, as the conversion of 1-bromobutane to 2-heptanone illustrates.



Ethyl acetoacetate | Ethyl 2-butyl-3-oxobutanoate (70%) | 2-Heptanone (60%)

The acetoacetic ester synthesis brings about the overall transformation of an alkyl halide to an alkyl derivative of acetone.



Primary or secondary alkyl halide | α-Alkylated derivative of acetone

We call a structural unit in a molecule that is related to a synthetic operation a **synthon.** The three-carbon unit $-CH_2\overset{O}{\overset{\|}{C}}CH_3$ is a synthon that alerts us to the possibility that a particular molecule may be accessible by the acetoacetic ester synthesis.

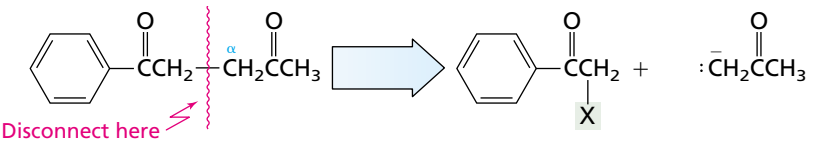
E. J. Corey (page 557) invented the word "synthon" in connection with his efforts to formalize synthetic planning.

PROBLEM 21.6 Show how you could prepare each of the following ketones from ethyl acetoacetate and any necessary organic or inorganic reagents:

(a) 1-Phenyl-1,4-pentanedione (c) 5-Hexen-2-one

(b) 4-Phenyl-2-butanone

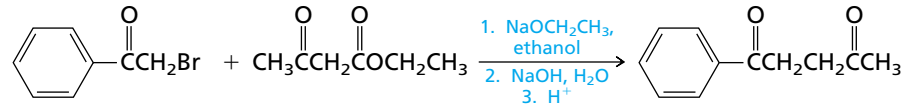
SAMPLE SOLUTION (a) Approach these syntheses in a retrosynthetic way. Identify the synthon $-CH_2\overset{O}{\overset{\|}{C}}CH_3$ and mentally disconnect the bond to the α-carbon atom. The $-CH_2\overset{O}{\overset{\|}{C}}CH_3$ synthon is derived from ethyl acetoacetate; the remainder of the molecule originates in the alkyl halide.



1-Phenyl-1,4-pentanedione | Required alkyl halide | Derived from ethyl acetoacetate

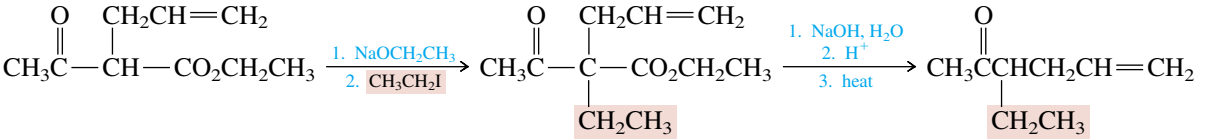
Analyzing the target molecule in this way reveals that the required alkyl halide is an α-halo ketone. Thus, a suitable starting material would be bromomethyl phenyl ketone.

Can you think of how bromomethyl phenyl ketone might be prepared?



Bromomethyl phenyl ketone | Ethyl acetoacetate | 1-Phenyl-1,4-pentanedione

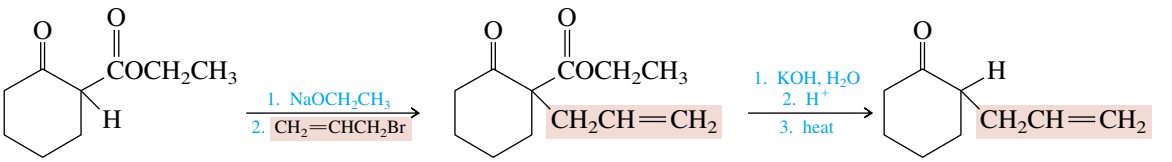
Dialkylation of ethyl acetoacetate can also be accomplished, opening the way to ketones with two alkyl substituents at the α carbon:



Ethyl 2-allylacetoacetate | Ethyl 2-allyl-2-ethyl-acetoacetate (75%) | 3-Ethyl-5-hexen-2-one (48%)

Recognize, too, that the reaction sequence is one that is characteristic of β-keto esters in general and not limited to just ethyl acetoacetate and its derivatives. Thus,

The starting material in the example is obtained by alkylation of ethyl acetoacetate with allyl bromide.



Ethyl 2-oxocyclohexanecarboxylate | Ethyl 1-allyl-2-oxocyclohexanecarboxylate (89%) | 2-Allylcyclohexanone (66%)

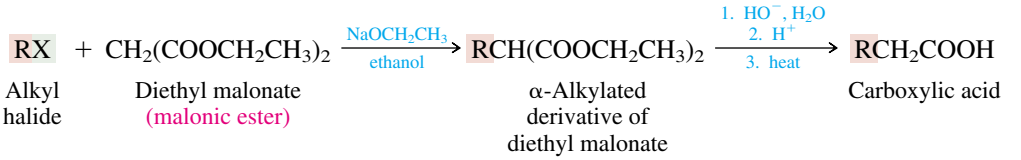
It's reasonable to ask why one would prepare a ketone by way of a keto ester (ethyl acetoacetate, for example) rather than by direct alkylation of the enolate of a ketone. One reason is that the monoalkylation of ketones via their enolates is a difficult reaction to carry out in good yield. (Remember, however, that *acylation* of ketone enolates as described in Section 21.4 is achieved readily.) A second reason is that the delocalized enolates of β-keto esters, being far less basic than ketone enolates, give a higher substitution–elimination ratio when they react with alkyl halides. This can be quite important in those syntheses in which the alkyl halide is expensive or difficult to obtain.

The starting material in this example is the Dieckmann cyclization product of diethyl heptanedioate (see Problem 21.2a).

Anions of β-keto esters are said to be *synthetically equivalent* to the enolates of ketones. The anion of ethyl acetoacetate is synthetically equivalent to the enolate of acetone, for example. The use of synthetically equivalent groups is a common tactic in synthetic organic chemistry. One of the skills that characterize the most creative practitioners of organic synthesis is an ability to recognize situations in which otherwise difficult transformations can be achieved through the use of synthetically equivalent reagents.

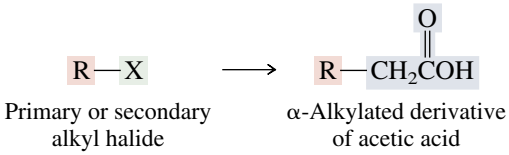
21.7 THE MALONIC ESTER SYNTHESIS

The **malonic ester synthesis** is a method for the preparation of carboxylic acids and is represented by the general equation



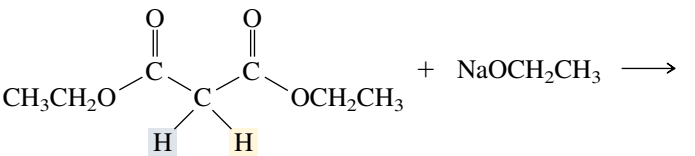
Among the methods for preparing carboxylic acids, carboxylation of a Grignard reagent and preparation and hydrolysis of a nitrile convert RBr to RCO_2H. The malonic ester synthesis converts RBr to RCH_2CO_2H.

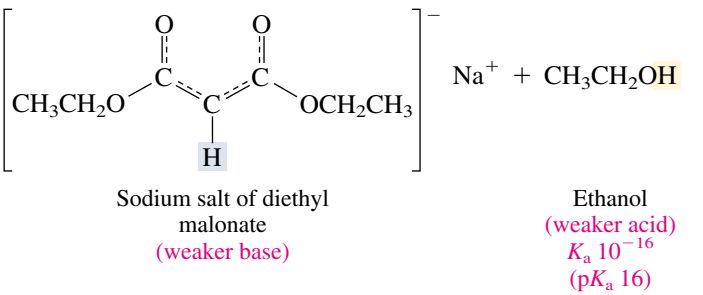
The malonic ester synthesis is conceptually analogous to the acetoacetic ester synthesis. The overall transformation is



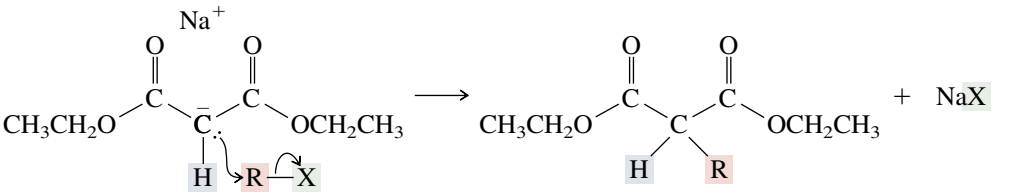
Diethyl malonate (also known as malonic ester) serves as a source of the synthon $-CH_2\overset{\overset{O}{\|}}{C}OH$ in the same way that the ethyl acetoacetate serves as a source of the synthon $-CH_2\overset{\overset{O}{\|}}{C}CH_3$.

The properties of diethyl malonate that make the malonic ester synthesis a useful procedure are the same as those responsible for the synthetic value of ethyl acetoacetate. The protons at C-2 of diethyl malonate are relatively acidic, and one is readily removed on treatment with sodium ethoxide.



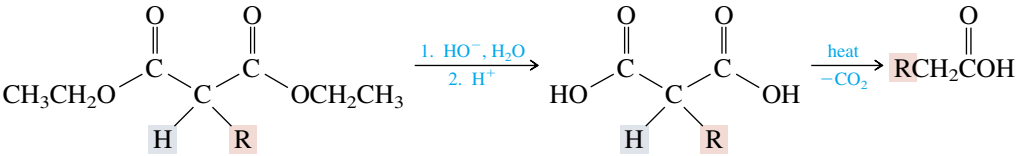


Treatment of the anion of diethyl malonate with alkyl halides leads to alkylation at C-2.



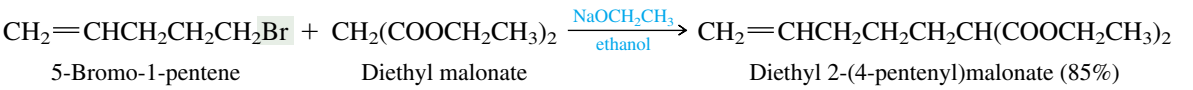
Sodium salt of diethyl malonate; alkyl halide — 2-Alkyl derivative of diethyl malonate — Sodium halide

Converting the C-2 alkylated derivative to the corresponding malonic acid derivative by ester hydrolysis gives a compound susceptible to thermal decarboxylation. Temperatures of approximately 180°C are normally required.

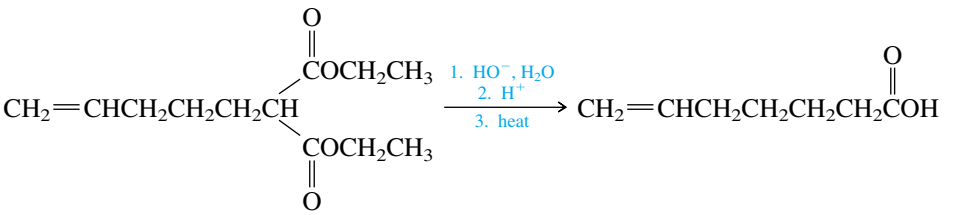


2-Alkyl derivative of diethyl malonate — 2-Alkyl derivative of malonic acid — Carboxylic acid

In a typical example of the malonic ester synthesis, 6-heptenoic acid has been prepared from 5-bromo-1-pentene:



5-Bromo-1-pentene — Diethyl malonate — Diethyl 2-(4-pentenyl)malonate (85%)

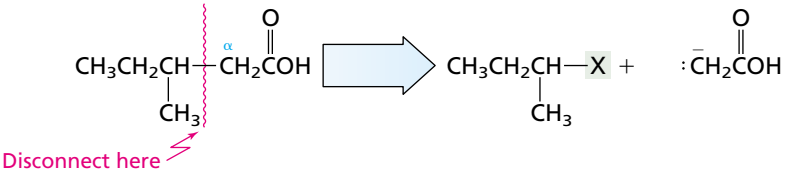


Diethyl 2-(4-pentenyl)malonate — 6-Heptenoic acid (75%)

PROBLEM 21.7 Show how you could prepare each of the following carboxylic acids from diethyl malonate and any necessary organic or inorganic reagents:

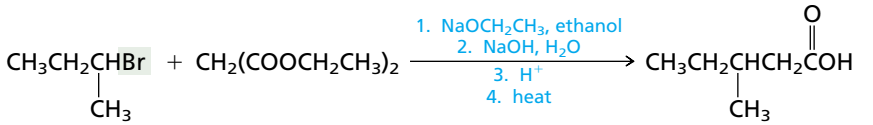
(a) 3-Methylpentanoic acid
(b) Nonanoic acid
(c) 4-Methylhexanoic acid
(d) 3-Phenylpropanoic acid

SAMPLE SOLUTION (a) Analyze the target molecule retrosynthetically by mentally disconnecting a bond to the α-carbon atom.



3-Methylpentanoic acid — Required alkyl halide — Derived from diethyl malonate

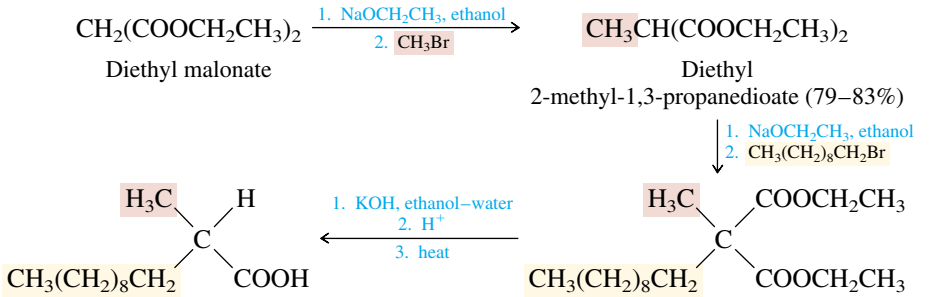
We see that a secondary alkyl halide is needed as the alkylating agent. The anion of diethyl malonate is a weaker base than ethoxide ion and reacts with secondary alkyl halides by substitution rather than elimination. Thus, the synthesis of 3-methylpentanoic acid begins with the alkylation of the anion of diethyl malonate by 2-bromobutane.



2-Bromobutane Diethyl malonate 3-Methylpentanoic acid

As actually carried out and reported in the chemical literature, diethyl malonate has been alkylated with 2-bromobutane in 83–84% yield and the product of that reaction converted to 3-methylpentanoic acid by saponification, acidification, and decarboxylation in 62–65% yield.

By performing two successive alkylation steps, the malonic ester synthesis can be applied to the synthesis of α,α-disubstituted derivatives of acetic acid:



Diethyl malonate

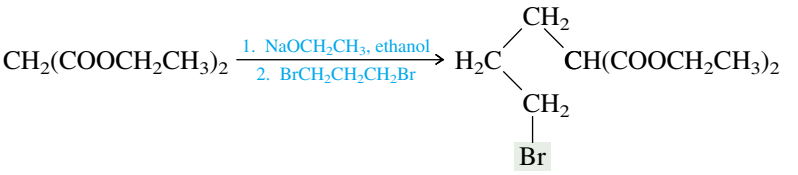
Diethyl 2-methyl-1,3-propanedioate (79–83%)

2-Methyldodecanoic acid (61–74%)

Diethyl 2-decyl-2-methyl-1,3-propanedioate

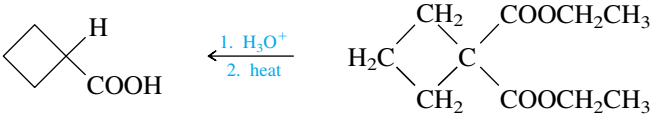
PROBLEM 21.8 Ethyl acetoacetate may also be subjected to double alkylation. Show how you could prepare 3-methyl-2-butanone by double alkylation of ethyl acetoacetate.

The malonic ester synthesis has been adapted to the preparation of cycloalkanecarboxylic acids from dihaloalkanes:



Diethyl malonate

(Not isolated; cyclizes in the presence of sodium ethoxide)



Cyclobutanecarboxylic acid (80% from diester)

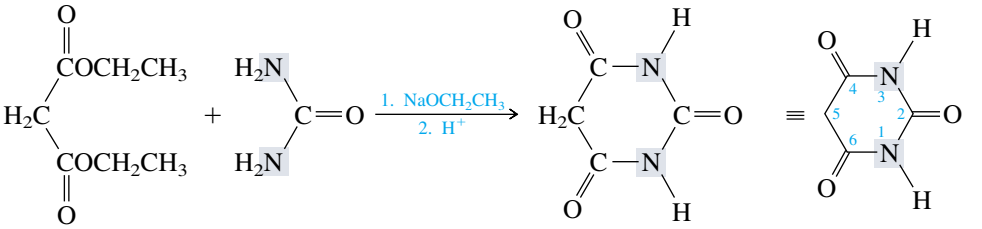
Diethyl 1,1-cyclobutanedicarboxylate (60–65%)

The cyclization step is limited to the formation of rings of seven carbons or fewer.

PROBLEM 21.9 Cyclopentyl methyl ketone has been prepared from 1,4-dibromobutane and ethyl acetoacetate. Outline the steps in this synthesis by writing a series of equations showing starting materials, reagents, and isolated intermediates.

21.8 BARBITURATES

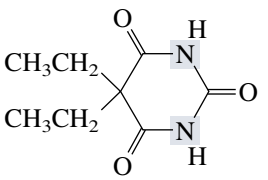
Diethyl malonate has uses other than in the synthesis of carboxylic acids. One particularly valuable application lies in the preparation of *barbituric acid* by nucleophilic acyl substitution with urea:



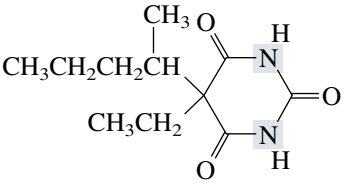
Diethyl malonate Urea Barbituric acid (72–78%)

Barbituric acid was first prepared in 1864 by Adolf von Baeyer (page 98). A historical account of his work and the later development of barbiturates as sedative–hypnotics appeared in the October 1951 issue of the *Journal of Chemical Education* (pp. 524–526).

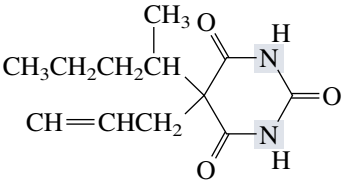
Barbituric acid is the parent of a group of compounds known as **barbiturates.** The barbiturates are classified as *sedative–hypnotic agents,* meaning that they decrease the responsiveness of the central nervous system and promote sleep. Thousands of derivatives of the parent ring system of barbituric acid have been tested for sedative–hypnotic activity; the most useful are the 5,5-disubstituted derivatives.



5,5-Diethylbarbituric acid (barbital; Veronal)

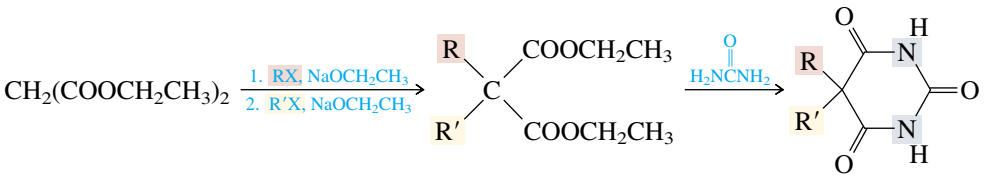


5-Ethyl-5-(1-methylbutyl)-barbituric acid (pentobarbital; Nembutal)



5-Allyl-5-(1-methylbutyl)-barbituric acid (secobarbital; Seconal)

These compounds are prepared in a manner analogous to that of barbituric acid itself. Diethyl malonate is alkylated twice, then treated with urea.



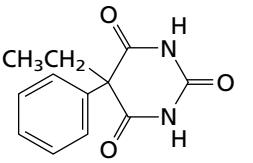
Diethyl malonate Dialkylated derivative of diethyl malonate 5,5-Disubstituted derivative of barbituric acid

PROBLEM 21.10 Show, by writing a suitable sequence of reactions, how you could prepare pentobarbital from diethyl malonate. (The structure of pentobarbital was shown in this section.)

Barbituric acids, as their name implies, are weakly acidic and are converted to their sodium salts (sodium barbiturates) in aqueous sodium hydroxide. Sometimes the drug is dispensed in its neutral form; sometimes the sodium salt is used. The salt is designated by appending the word "sodium" to the name of the barbituric acid—*pentobarbital sodium,* for example.

PROBLEM 21.11 Thiourea (H_2NCNH_2, with S double-bonded to C) reacts with diethyl malonate and its alkyl derivatives in the same way that urea does. Give the structure of the product obtained when thiourea is used instead of urea in the synthesis of pentobarbital. The anesthetic *thiopental* (*Pentothal*) *sodium* is the sodium salt of this product. What is the structure of this compound?

PROBLEM 21.12 Aryl halides react too slowly to undergo substitution by the S_N2 mechanism with the sodium salt of diethyl malonate, and so the phenyl substituent of *phenobarbital* cannot be introduced in the way that alkyl substituents can.



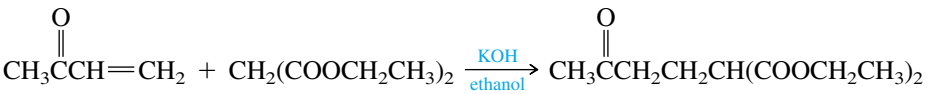
5-Ethyl-5-phenylbarbituric acid
(phenobarbital)

One synthesis of phenobarbital begins with ethyl phenylacetate and diethyl carbonate. Using these starting materials and any necessary organic or inorganic reagents, devise a synthesis of phenobarbital. (*Hint:* See the sample solution to Problem 21.3a.)

The various barbiturates differ in the time required for the onset of sleep and in the duration of their effects. All the barbiturates must be used only in strict accordance with instructions to avoid potentially lethal overdoses. Drug dependence in some individuals is also a problem.

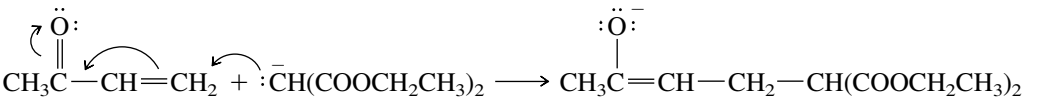
21.9 MICHAEL ADDITIONS OF STABILIZED ANIONS

Stabilized anions exhibit a pronounced tendency to undergo conjugate addition to α,β-unsaturated carbonyl compounds. This reaction, called the *Michael reaction,* has been described for anions derived from β-diketones in Section 18.13. The enolates of ethyl acetoacetate and diethyl malonate also undergo Michael addition to the β-carbon atom of α,β-unsaturated aldehydes, ketones, and esters. For example,

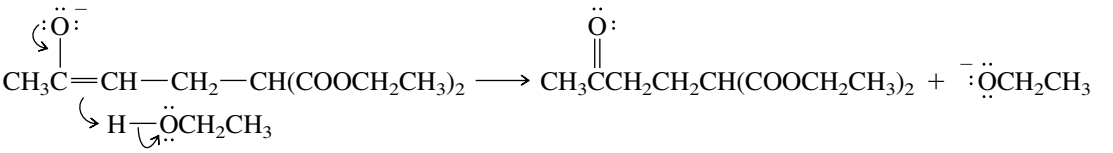


Methyl vinyl ketone + Diethyl malonate → (KOH, ethanol) Ethyl 2-carboethoxy-5-oxohexanoate (83%)

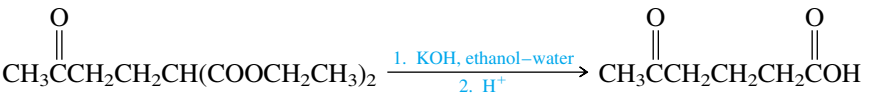
In this reaction the enolate of diethyl malonate adds to the β carbon of methyl vinyl ketone.



The intermediate formed in the nucleophilic addition step abstracts a proton from the solvent to give the observed product.



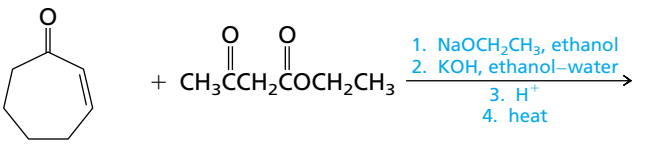
After isolation, the Michael adduct may be subjected to ester hydrolysis and decarboxylation. When α,β-unsaturated ketones are carried through this sequence, the final products are 5-keto acids (δ-keto acids).



Ethyl 2-carboethoxy-5-oxohexanoate (from diethyl malonate and methyl vinyl ketone)

5-Oxohexanoic acid (42%)

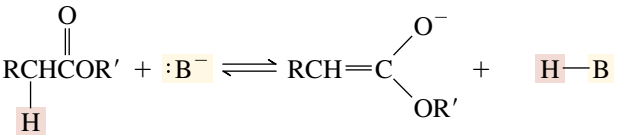
PROBLEM 21.13 Ethyl acetoacetate behaves similarly to diethyl malonate in its reactivity toward α,β-unsaturated carbonyl compounds. Give the structure of the product of the following reaction sequence:



2-Cycloheptenone Ethyl acetoacetate

21.10 α DEPROTONATION OF CARBONYL COMPOUNDS BY LITHIUM DIALKYLAMIDES

Most of the reactions of ester enolates described so far have centered on stabilized enolates derived from 1,3-dicarbonyl compounds such as diethyl malonate and ethyl acetoacetate. Although the synthetic value of these and related stabilized enolates is clear, chemists have long been interested in extending the usefulness of nonstabilized enolates derived from simple esters. Consider the deprotonation of an ester as represented by the acid–base reaction

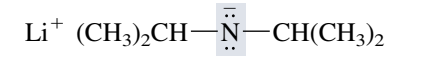


Ester Base Ester enolate Conjugate acid of base

We already know what happens when simple esters are treated with alkoxide bases—they undergo the Claisen condensation (Section 21.1). Simple esters have acid dissociation constants K_a of approximately 10^{-22} (pK_a 22) and are incompletely converted to their enolates with alkoxide bases. The small amount of enolate that is formed reacts by nucleophilic addition to the carbonyl group of the ester.

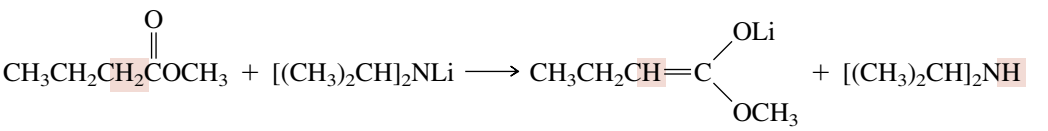
What happens if the base is much stronger than an alkoxide ion? *If the base is strong enough, it will convert the ester completely to its enolate.* Under these conditions the Claisen condensation is suppressed because there is no neutral ester present for the enolate to add to. A very strong base is one that is derived from a very weak acid. Referring to the table of acidities (Table 4.2, page 135), we see that ammonia is quite a weak acid; its K_a is 10^{-36} (pK_a 36). Therefore, amide ion ($H_2\ddot{N}:^-$) is a very strong base—more than strong enough to deprotonate an ester quantitatively. Amide ion, however, also tends to add to the carbonyl group of esters; to avoid this complication, highly hindered analogs of $H_2\ddot{N}:^-$ are used instead. The most frequently used base for ester enolate formation is *lithium diisopropylamide* (LDA):

Lithium diisopropylamide is commercially available. Alternatively, it may be prepared by the reaction of butyllithium with $[(CH_3)_2CH]_2NH$ (see Problem 14.4a for a related reaction).



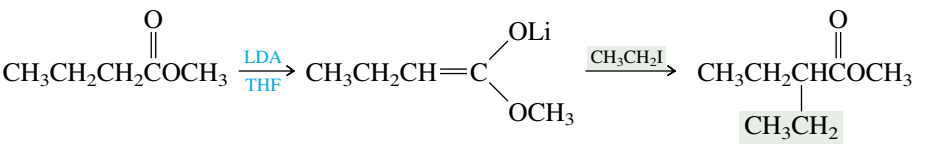
Lithium diisopropylamide

Lithium diisopropylamide is a strong enough base to abstract a proton from the α-carbon atom of an ester, but because it is so sterically hindered, it does not add readily to the carbonyl group. To illustrate,



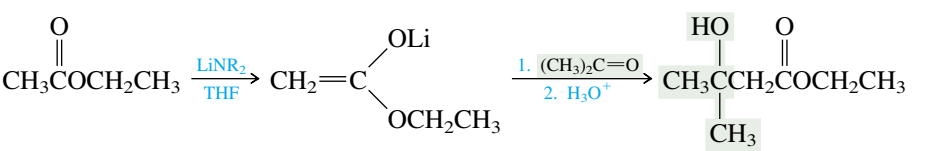
Methyl butanoate (stronger acid) K_a 10^{-22} (pK_a 22)	Lithium diisopropylamide (stronger base)	Lithium enolate of methyl butanoate (weaker base)	Diisopropylamine (weaker acid) K_a 10^{-36} (pK_a 36)

Direct alkylation of esters can be carried out by forming the enolate with LDA followed by addition of an alkyl halide. Tetrahydrofuran (THF) is the solvent most often used in these reactions.



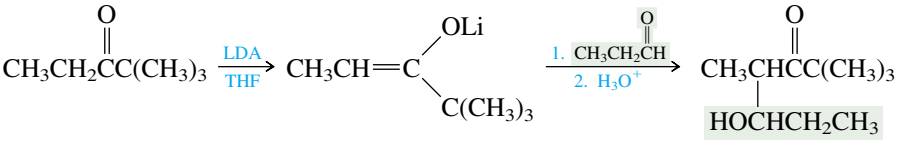
Methyl butanoate	Lithium enolate of methyl butanoate	Methyl 2-ethylbutanoate (92%)

Ester enolates generated by proton abstraction with dialkylamide bases add to aldehydes and ketones to give β-hydroxy esters.



Ethyl acetate	Lithium enolate of ethyl acetate	Ethyl 3-hydroxy-3-methylbutanoate (90%)

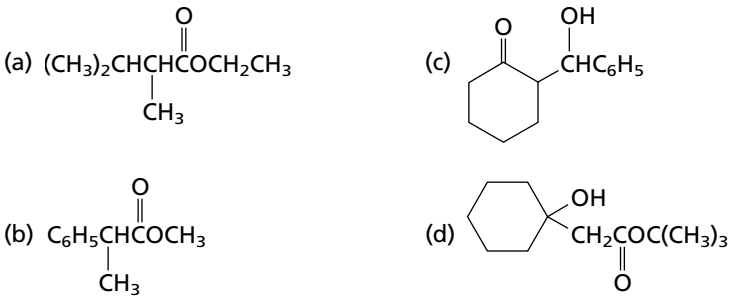
Lithium dialkylamides are excellent bases for making ketone enolates as well. Ketone enolates generated in this way can be alkylated with alkyl halides or, as illustrated in the following equation, treated with an aldehyde or a ketone.



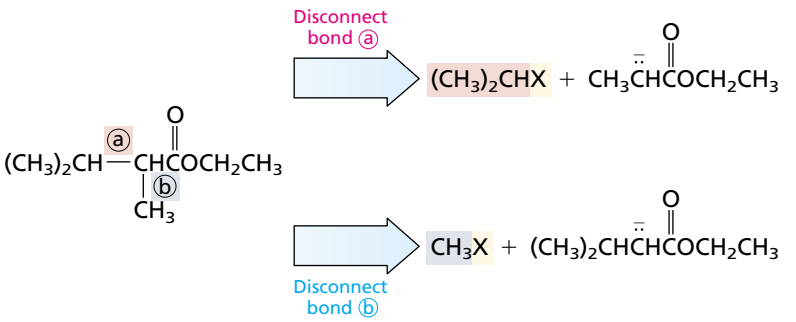
2,2-Dimethyl-3-pentanone | Lithium enolate of 2,2-dimethyl-3-pentanone | 5-Hydroxy-2,2,4-trimethyl-3-heptanone (81%)

Thus, mixed aldol additions can be achieved by the tactic of quantitative enolate formation using LDA followed by addition of a different aldehyde or ketone.

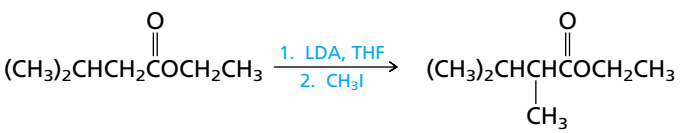
PROBLEM 21.14 Outline efficient syntheses of each of the following compounds from readily available aldehydes, ketones, esters, and alkyl halides according to the methods described in this section:



SAMPLE SOLUTION (a) The α-carbon atom of the ester has two different alkyl groups attached to it.



The critical carbon–carbon bond-forming step requires nucleophilic substitution on an alkyl halide by an ester enolate. Methyl halides are more reactive than isopropyl halides in S_N2 reactions and cannot undergo elimination as a competing process; therefore, choose the synthesis in which bond ⓑ is formed by alkylation.



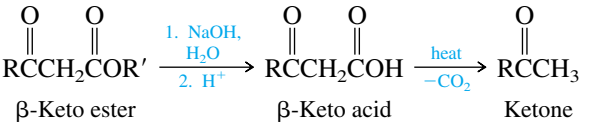
Ethyl 3-methylbutanoate | Ethyl 2,3-dimethylbutanoate

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

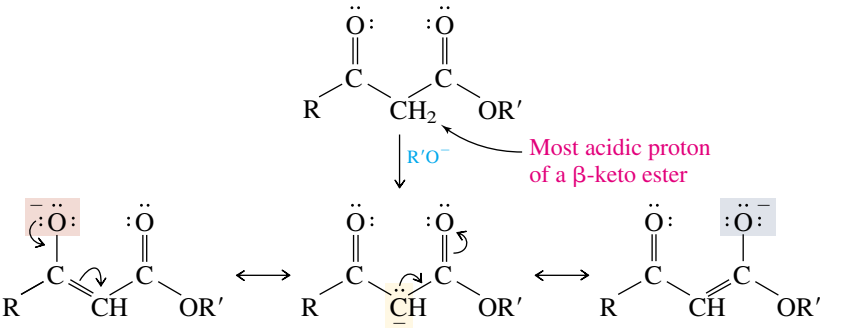
21.11 SUMMARY

Sections 21.1–21.4 β-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 β-keto esters, such as those shown in Table 21.1, gives β-keto acids which undergo rapid decarboxylation, forming ketones.

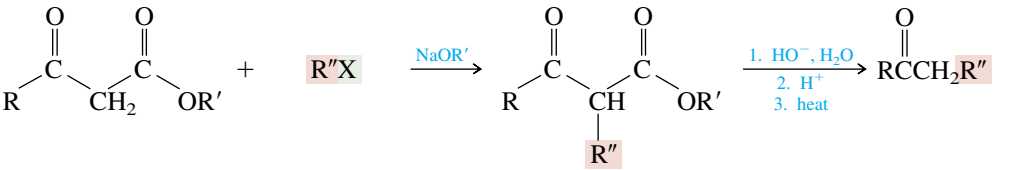


β-Keto esters are characterized by K_a's of about 10^{-11} (pK_a 11) and are quantitatively converted to their enolates on treatment with alkoxide bases.



Resonance forms illustrating charge delocalization in enolate of a β-keto ester

The anion of a β-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.



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 CH_3CCH_2R.

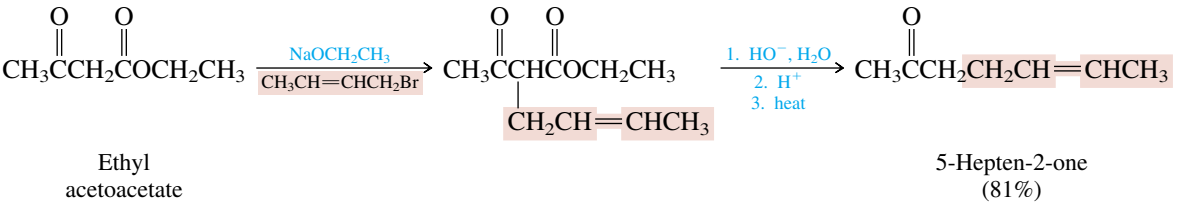
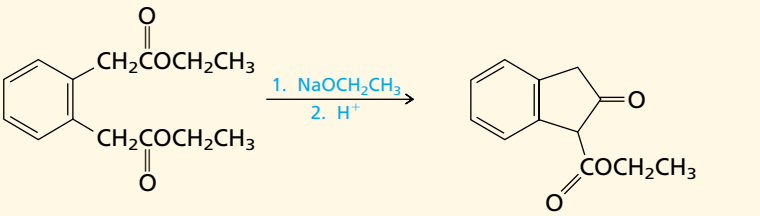


TABLE 21.1 Preparation of β-Keto Esters

Reaction (section) and comments	General equation and specific example
Claisen condensation (Section 21.1) 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.	$2RCH_2COR' \xrightarrow[2.\ H^+]{1.\ NaOR'} RCH_2CCHCOR' + R'OH$ (R at the α-carbon) Ester → β-Keto ester + Alcohol $2CH_3CH_2CH_2COCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} CH_3CH_2CH_2CCHCOCH_2CH_3$ (CH_2CH_3 at the α-carbon) Ethyl butanoate → Ethyl 2-ethyl-3-oxohexanoate (76%)
Dieckmann cyclization (Section 21.2) 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 21.3) Diethyl carbonate, diethyl oxalate, ethyl formate, and benzoate esters cannot form ester enolates but can act as acylating agents toward other ester enolates.	$RCOCH_2CH_3 + R'CH_2COCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} RCCHCOCH_2CH_3$ (R′ at the α-carbon) Ester + Another ester → β-Keto ester $CH_3CH_2COCH_2CH_3 + CH_3CH_2OCCOCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} CH_3CHCOCH_2CH_3$ ($C(=O)COCH_2CH_3$ at the α-carbon) Ethyl propanoate + Diethyl oxalate → Diethyl 3-methyl-2-oxobutanedioate (60–70%)
Acylation of ketones (Section 21.4) Diethyl carbonate and diethyl oxalate can be used to acylate ketone enolates to give β-keto esters.	$RCH_2CR' + CH_3CH_2OCOCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} RCHCR'$ ($COCH_2CH_3$ at the α-carbon) Ketone + Diethyl carbonate → β-Keto ester $(CH_3)_3CCH_2CCH_3 + CH_3CH_2OCOCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} (CH_3)_3CCH_2CCH_2COCH_2CH_3$ 4,4-Dimethyl-2-pentanone + Diethyl carbonate → Ethyl 5,5-dimethyl-3-oxohexanoate (66%)

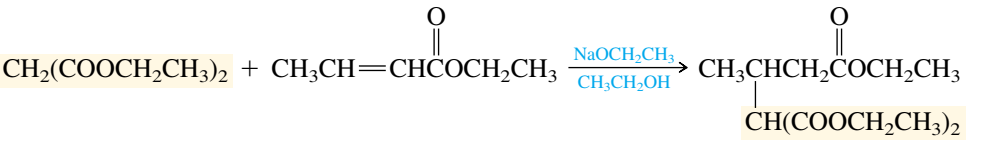
Section 21.7 The **malonic ester synthesis** is related to the acetoacetic ester synthesis. Alkyl halides (RX) are converted to carboxylic acids of the type RCH_2COOH by reaction with the enolate ion derived from diethyl malonate, followed by saponification and decarboxylation.

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

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

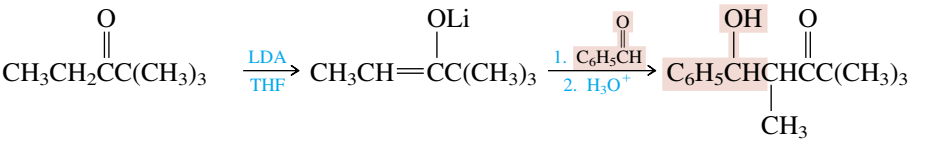
Diethyl malonate — Alkylated derivative of diethyl malonate — Alkylated derivative of barbituric acid

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%)

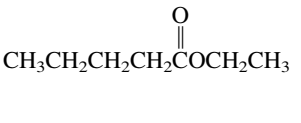
Section 21.10 It is possible to generate ester enolates by deprotonation provided that the base used is very strong. Lithium diisopropylamide (LDA) is often used for this purpose. It also converts ketones quantitatively to their enolates.



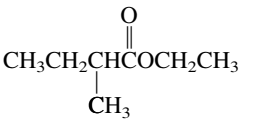
2,2-Dimethyl-3-pentanone — 1-Hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone (78%)

PROBLEMS

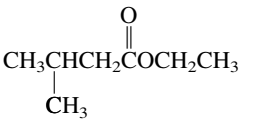
21.15 The following questions pertain to the esters shown and their behavior under conditions of the Claisen condensation.



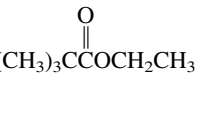
Ethyl pentanoate



Ethyl 2-methylbutanoate



Ethyl 3-methylbutanoate



Ethyl 2,2-dimethylpropanoate

(a) Two of these esters are converted to β-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 β-keto ester on treatment with sodium ethoxide, but the amount of β-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 ($C_6H_5CH_2COOCH_2CH_3$).

(b) What ketone would you isolate after saponification and decarboxylation of this Claisen condensation product?

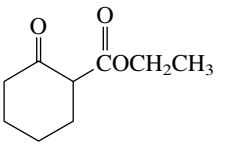
(c) What ketone would you isolate after treatment of the Claisen condensation product of ethyl phenylacetate with sodium ethoxide and allyl bromide, followed by saponification and decarboxylation?

(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

(a) Write a chemical equation showing how you could prepare ethyl (2-oxocyclohexane)carboxylate by a Dieckmann reaction.

(b) Write a chemical equation showing how you could prepare ethyl (2-oxocyclohexane)-carboxylate by acylation of a ketone.

(c) Write structural formulas for the two most stable enol forms of ethyl (2-oxocyclohexane)carboxylate.

(d) Write the three most stable resonance forms for the most stable enolate derived from ethyl (2-oxocyclohexane)carboxylate.

(e) Show how you could use ethyl (2-oxocyclohexane)carboxylate to prepare 2-methylcyclohexanone.

(f) Give the structure of the product formed on treatment of ethyl (2-oxocyclohexane)carboxylate with acrolein ($CH_2{=}CHC(=O)H$) in ethanol in the presence of sodium ethoxide.

21.18 Give the structure of the product formed on reaction of ethyl acetoacetate with each of the following:

(a) 1-Bromopentane and sodium ethoxide

(b) Saponification and decarboxylation of the product in part (a)

(c) Methyl iodide and the product in part (a) treated with sodium ethoxide

(d) Saponification and decarboxylation of the product in part (c)

(e) 1-Bromo-3-chloropropane and one equivalent of sodium ethoxide

(f) Product in part (e) treated with a second equivalent of sodium ethoxide

(g) Saponification and decarboxylation of the product in part (f)

(h) Phenyl vinyl ketone and sodium ethoxide

(i) Saponification and decarboxylation of the product in part (h)

21.19 Repeat the preceding problem for diethyl malonate.

21.20 (a) Only a small amount (less than 0.01%) of the enol form of diethyl malonate is present at equilibrium. Write a structural formula for this enol.

(b) Enol forms are present to the extent of about 8% in ethyl acetoacetate. There are three constitutionally isomeric enols possible. Write structural formulas for these three enols. Which one do you think is the most stable? The least stable? Why?

(c) Bromine reacts rapidly with both diethyl malonate and ethyl acetoacetate. The reaction is acid-catalyzed and liberates hydrogen bromide. What is the product formed in each reaction?

21.21 (a) On addition of one equivalent of methylmagnesium iodide to ethyl acetoacetate, the Grignard reagent is consumed, but the only organic product obtained after working up the reaction mixture is ethyl acetoacetate. Why? What happens to the Grignard reagent?

(b) On repeating the reaction but using D_2O and DCl to work up the reaction mixture, it is found that the recovered ethyl acetoacetate contains deuterium. Where is this deuterium located?

21.22 Give the structure of the principal organic product of each of the following reactions:

(a) Ethyl octanoate $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$

(b) Product of part (a) $\xrightarrow[3.\ \text{heat}]{1.\ NaOH,\ H_2O \quad 2.\ H^+}$

(c) Ethyl acetoacetate + 1-bromobutane $\xrightarrow{NaOCH_2CH_3,\ \text{ethanol}}$

(d) Product of part (c) $\xrightarrow[3.\ \text{heat}]{1.\ NaOH,\ H_2O \quad 2.\ H^+}$

(e) Product of part (c) + 1-iodobutane $\xrightarrow{NaOCH_2CH_3,\ \text{ethanol}}$

(f) Product of part (e) $\xrightarrow[3.\ \text{heat}]{1.\ NaOH,\ H_2O \quad 2.\ H^+}$

(g) Acetophenone + diethyl carbonate $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$

(h) Acetone + diethyl oxalate $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$

(i) Diethyl malonate + 1-bromo-2-methylbutane $\xrightarrow{NaOCH_2CH_3,\ ethanol}$

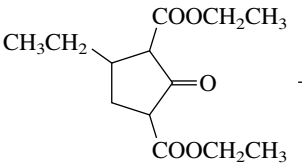
(j) Product of part (i) $\xrightarrow[3.\ heat]{1.\ NaOH,\ H_2O \\ 2.\ H^+}$

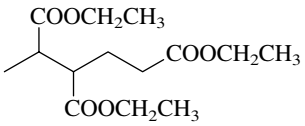
(k) Diethyl malonate + 6-methyl-2-cyclohexenone $\xrightarrow{NaOCH_2CH_3,\ ethanol}$

(l) Product of part (k) $\xrightarrow{H_2O,\ HCl,\ heat}$

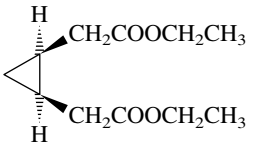
(m) *tert*-Butyl acetate $\xrightarrow[3.\ H^+]{1.\ [(CH_3)_2CH]_2NLi,\ THF \\ 2.\ benzaldehyde}$

21.23 Give the structure of the principal organic product of each of the following reactions:

(a)  $\xrightarrow[heat]{H_2O,\ H_2SO_4}$ $C_7H_{12}O$

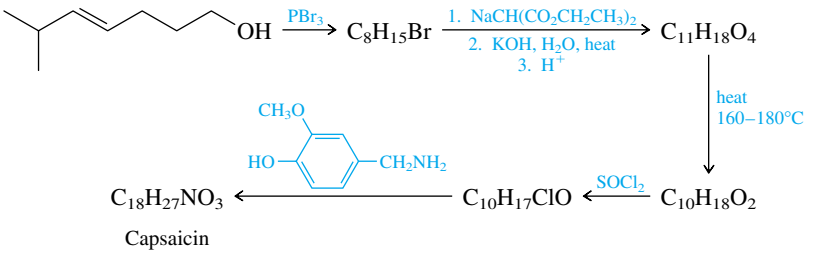
(b)  $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$ $C_{12}H_{18}O_5$

(c) Product of part (b) $\xrightarrow[heat]{H_2O,\ H^+}$ $C_7H_{10}O_3$

(d)  $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$ $C_9H_{12}O_3$

(e) Product of part (d) $\xrightarrow[3.\ heat]{1.\ HO^-,\ H_2O \\ 2.\ H^+}$ C_6H_8O

21.24 The spicy flavor of cayenne pepper is due mainly to a substance called *capsaicin.* The following sequence of steps was used in a 1955 synthesis of capsaicin. See if you can deduce the structure of capsaicin on the basis of this synthesis.



Capsaicin

21.25 Show how you could prepare each of the following compounds. Use the starting material indicated along with ethyl acetoacetate or diethyl malonate and any necessary inorganic reagents. Assume also that the customary organic solvents are freely available.

(a) 4-Phenyl-2-butanone from benzyl alcohol

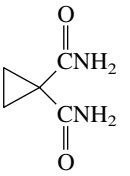
(b) 3-Phenylpropanoic acid from benzyl alcohol

(c) 2-Allyl-1,3-propanediol from propene

(d) 4-Penten-1-ol from propene

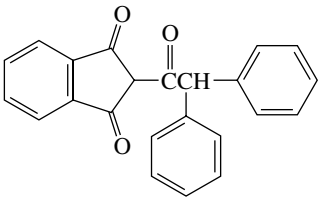
(e) 5-Hexen-2-ol from propene

(f) Cyclopropanecarboxylic acid from 1,2-dibromoethane

(g)  from 1,2-dibromoethane

(h) $HO_2C(CH_2)_{10}CO_2H$ from $HO_2C(CH_2)_6CO_2H$

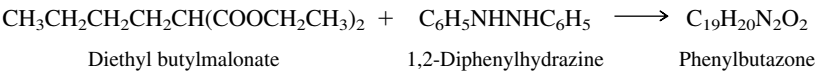
21.26 *Diphenadione* inhibits the clotting of blood; that is, it is an *anticoagulant.* It is used to control vampire bat populations in South America by a "Trojan horse" strategy. A few bats are trapped, smeared with diphenadione, and then released back into their normal environment. Other bats, in the course of grooming these diphenadione-coated bats, ingest the anticoagulant and bleed to death, either internally or through accidental bites and scratches.



Diphenadione

Suggest a synthesis of diphenadione from 1,1-diphenylacetone and dimethyl 1,2-benzenedicarboxylate.

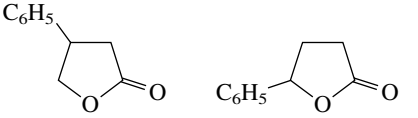
21.27 *Phenylbutazone* is a frequently prescribed antiinflammatory drug. It is prepared by the reaction shown.



$CH_3CH_2CH_2CH_2CH(COOCH_2CH_3)_2$	+	$C_6H_5NHNHC_6H_5$	⟶	$C_{19}H_{20}N_2O_2$
Diethyl butylmalonate		1,2-Diphenylhydrazine		Phenylbutazone

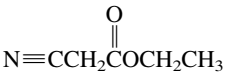
What is the structure of phenylbutazone?

21.28 The use of epoxides as alkylating agents for diethyl malonate provides a useful route to γ-lactones. Write equations illustrating such a sequence for styrene oxide as the starting epoxide. Is the lactone formed by this reaction 3-phenylbutanolide, or is it 4-phenylbutanolide?



3-Phenylbutanolide 4-Phenylbutanolide

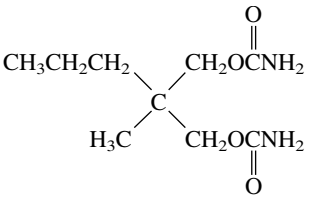
21.29 Diethyl malonate is prepared commercially by hydrolysis and esterification of ethyl cyanoacetate.



Ethyl cyanoacetate

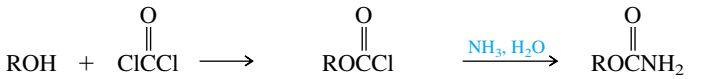
The preparation of ethyl cyanoacetate proceeds via ethyl chloroacetate and begins with acetic acid. Write a sequence of reactions describing this synthesis.

21.30 The tranquilizing drug *meprobamate* has the structure shown.



Meprobamate

Devise a synthesis of meprobamate from diethyl malonate and any necessary organic or inorganic reagents. *Hint: Carbamate esters,* that is, compounds of the type $ROCNH_2$, are prepared from alcohols by the sequence of reactions



Alcohol Phosgene Chlorocarbonate ester Carbamate ester

21.31 When the compound shown was heated in refluxing hydrochloric acid for 60 hours, a product with the molecular formula $C_5H_6O_3$ was isolated in 97% yield. Identify this product. Along with this product, three other carbon-containing substances are formed. What are they?