23 Carbonyl Condensation Reactions

Organic KNOWLEDGE TOOLS

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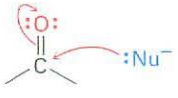
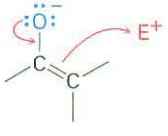
We've now studied three of the four general kinds of carbonyl-group reactions and have seen two general kinds of behavior. In nucleophilic addition and nucleophilic acyl substitution reactions, a carbonyl compound behaves as an electrophile. In α-substitution reactions, however, a carbonyl compound behaves as a nucleophile when it is converted into its enol or enolate ion. In the carbonyl condensation reaction that we'll study in this chapter, the carbonyl compound behaves *both* as an electrophile and as a nucleophile.



Electrophilic carbonyl group reacts with nucleophiles.



Nucleophilic enolate ion reacts with electrophiles.

WHY THIS CHAPTER?

We'll see later in this chapter and again in Chapter 29 that carbonyl condensation reactions occur frequently in metabolic pathways. In fact, almost all classes of biomolecules—carbohydrates, lipids, proteins, nucleic acids, and many others—are biosynthesized through pathways that involve carbonyl condensation reactions. As with the α-substitution reaction discussed in the previous chapter, the great value of carbonyl condensations is that they are one of the few general methods for forming carbon–carbon bonds, thereby making it possible to build larger molecules from smaller precursors. We'll see how and why these reactions occur in this chapter.

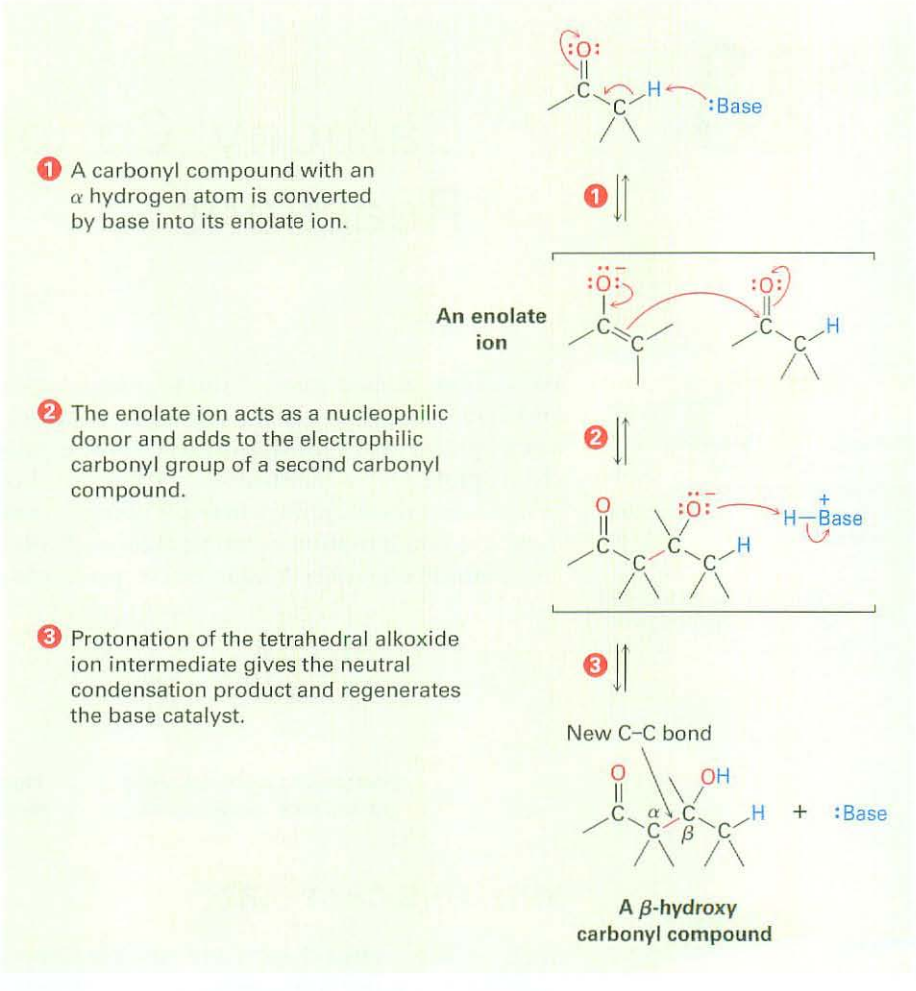
23.1 Carbonyl Condensations: The Aldol Reaction

Carbonyl condensation reactions take place between two carbonyl partners and involve a *combination* of nucleophilic addition and α-substitution steps. One partner is converted into an enolate-ion nucleophile and adds to the

Sean Duggan

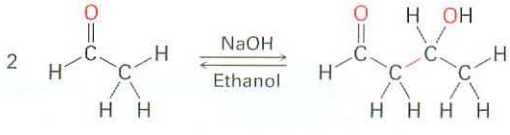
electrophilic carbonyl group of the second partner. In so doing, the nucleophilic partner undergoes an α-substitution reaction and the electrophilic partner undergoes a nucleophilic addition. The general mechanism of the process is shown in Figure 23.1.

Active Figure 23.1
MECHANISM: The general mechanism of a carbonyl condensation reaction. One partner becomes a nucleophilic donor and adds to the second partner as an electrophilic acceptor. The product is a β-hydroxy carbonyl compound. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*



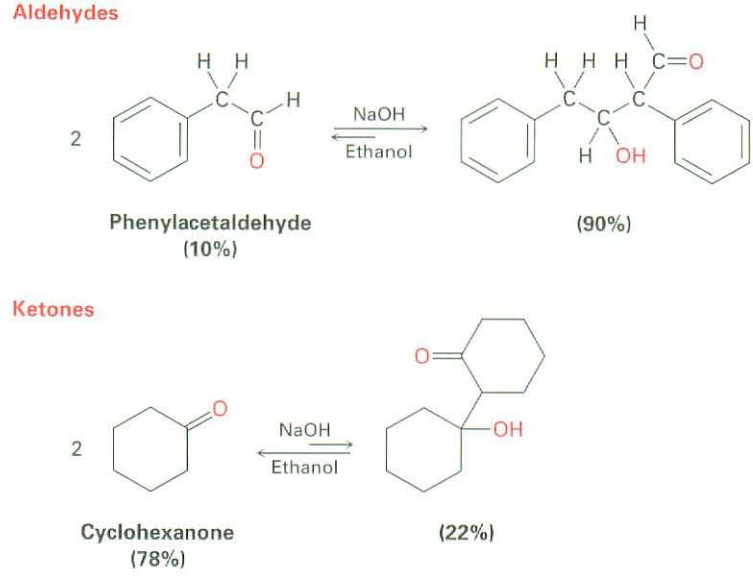
ThomsonNOW Click *Organic Interactive* to **learn to draw the structures of products from aldol-type condensation reactions.**

Aldehydes and ketones with an α hydrogen atom undergo a base-catalyzed carbonyl condensation reaction called the **aldol reaction**. For example, treatment of acetaldehyde with a base such as sodium ethoxide or sodium hydroxide in a protic solvent leads to rapid and reversible formation of 3-hydroxybutanal, known commonly as *aldol* (*ald*ehyde + alcoh*ol*), hence the general name of the reaction.



Acetaldehyde **3-Hydroxybutanal (aldol)**

The exact position of the aldol equilibrium depends both on reaction conditions and on substrate structure. The equilibrium generally favors condensation product in the case of aldehydes with no α substituent (RCH_2CHO) but favors reactant for disubstituted aldehydes (R_2CHCHO) and for most ketones. Steric factors are probably responsible for these trends, since increased substitution near the reaction site increases steric congestion in the aldol product.



Aldol reactions, like all carbonyl condensations, occur by nucleophilic addition of the enolate ion of the donor molecule to the carbonyl group of the acceptor molecule. The resultant tetrahedral intermediate is then protonated to give an alcohol product (Figure 23.2). The reverse process occurs in exactly the opposite manner: base abstracts the $-OH$ hydrogen from the aldol to yield a β-keto alkoxide ion, which cleaves to give one molecule of enolate ion and one molecule of neutral carbonyl compound.

WORKED EXAMPLE 23.1 *Predicting the Product of an Aldol Reaction*

What is the structure of the aldol product from propanal?

Strategy An aldol reaction combines two molecules of reactant by forming a bond between the α carbon of one partner and the carbonyl carbon of the second partner. The product is a β-hydroxy aldehyde or ketone, meaning that the two oxygen atoms in the product have a 1,3 relationship.

Solution

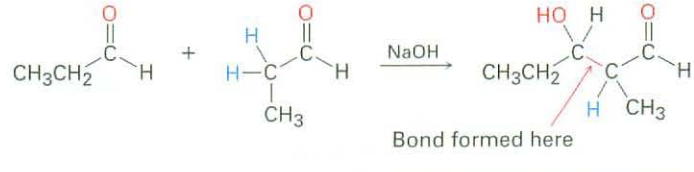
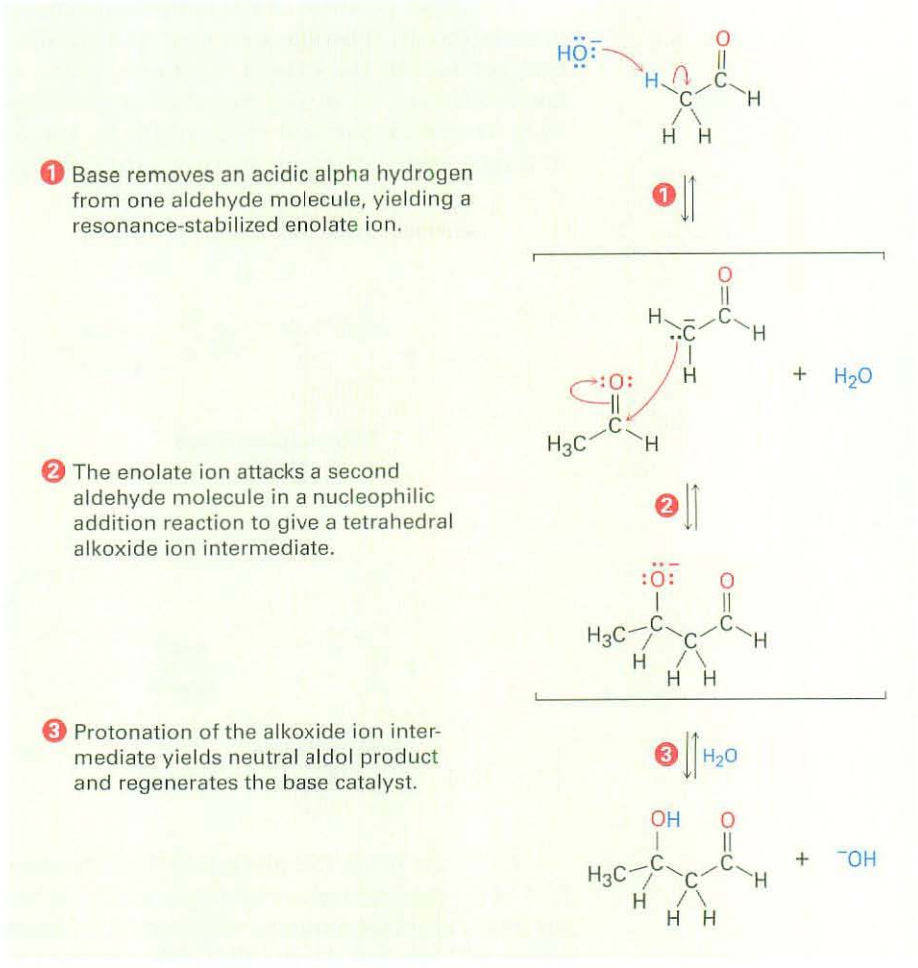
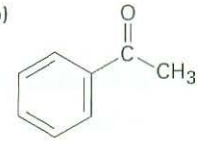
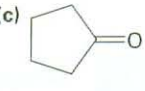


Figure 23.2 MECHANISM:
Mechanism of the aldol reaction, a typical carbonyl condensation.



Problem 23.1 Predict the aldol reaction product of the following compounds:

(a) $CH_3CH_2CH_2CH{=}O$ (b)  (c) 

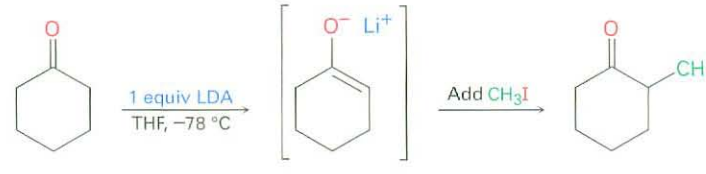
Problem 23.2 Using curved arrows to indicate the electron flow in each step, show how the base-catalyzed reverse aldol reaction of 4-hydroxy-4-methyl-2-pentanone takes place to yield 2 equivalents of acetone.

23.2 Carbonyl Condensations versus Alpha Substitutions

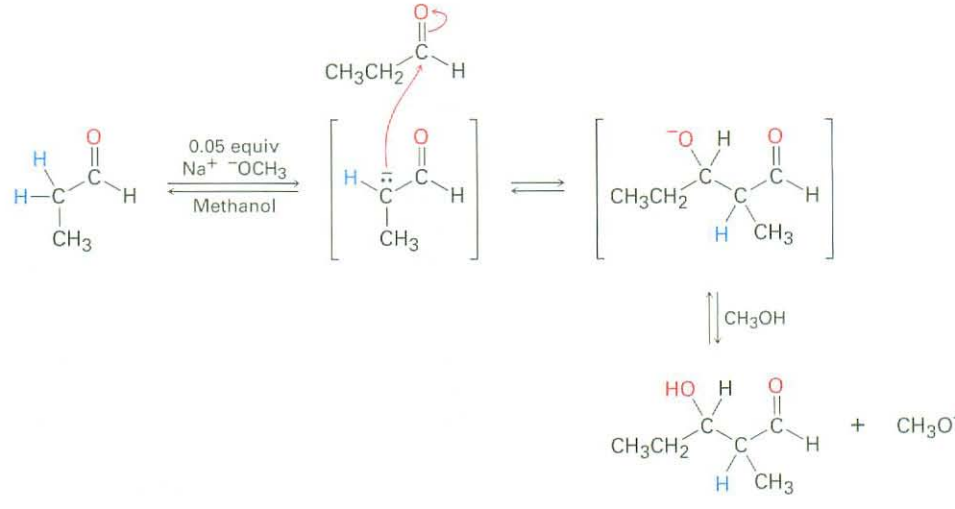
Two of the four general carbonyl-group reactions—carbonyl condensations and α substitutions—take place under basic conditions and involve enolate-ion intermediates. Because the experimental conditions for the two reactions

are similar, how can we predict which will occur in a given case? When we generate an enolate ion with the intention of carrying out an α alkylation, how can we be sure that a carbonyl condensation reaction won't occur instead?

There is no simple answer to this question, but the exact experimental conditions usually have much to do with the result. Alpha-substitution reactions require a full equivalent of strong base and are normally carried out so that the carbonyl compound is rapidly and completely converted into its enolate ion at a low temperature. An electrophile is then added rapidly to ensure that the reactive enolate ion is quenched quickly. In a ketone alkylation reaction, for instance, we might use 1 equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran solution at −78 °C. Rapid and complete generation of the ketone enolate ion would occur, and no unreacted ketone would be left so that no condensation reaction could take place. We would then immediately add an alkyl halide to complete the alkylation reaction.



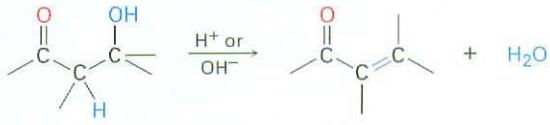
On the other hand, carbonyl condensation reactions require only a *catalytic* amount of a relatively weak base rather than a full equivalent so that a small amount of enolate ion is generated in the presence of unreacted carbonyl compound. Once a condensation has occurred, the basic catalyst is regenerated. To carry out an aldol reaction on propanal, for instance, we might dissolve the aldehyde in methanol, add 0.05 equivalent of sodium methoxide, and then warm the mixture to give the aldol product.



23.3 Dehydration of Aldol Products: Synthesis of Enones

ThomsonNOW Click *Organic Process* to **view an animation showing the aldol condensation reaction.**

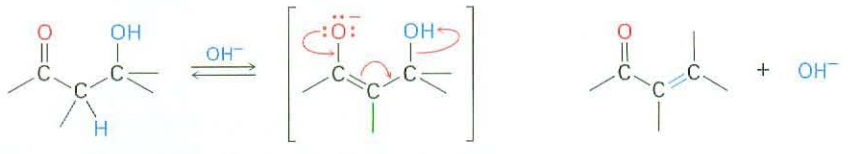
The β-hydroxy aldehydes or ketones formed in aldol reactions can be easily dehydrated to yield α,β-unsaturated products, or conjugated enones. In fact, it's this loss of water that gives the *condensation* reaction its name, because water condenses out of the reaction when the enone product forms.



A β-hydroxy ketone or aldehyde **A conjugated enone**

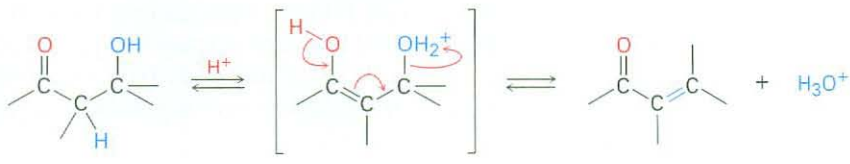
Most alcohols are resistant to dehydration by base (Section 17.6) because hydroxide ion is a poor leaving group, but aldol products dehydrate easily because of the carbonyl group. Under *basic* conditions, an acidic α hydrogen is removed, yielding an enolate ion that expels the $^-$OH leaving group in an E1cB reaction (Section 11.10). Under *acidic* conditions, an enol is formed, the −OH group is protonated, and water is expelled in an E1 or E2 reaction.

Base-catalyzed



Enolate ion

Acid-catalyzed



Enol

The reaction conditions needed for aldol dehydration are often only a bit more vigorous (slightly higher temperature, for instance) than the conditions needed for the aldol formation itself. As a result, conjugated enones are usually obtained directly from aldol reactions without isolating the intermediate β-hydroxy carbonyl compounds.

Conjugated enones are more stable than nonconjugated enones for the same reason that conjugated dienes are more stable than nonconjugated dienes (Section 14.1). Interaction between the π electrons of the C=C bond and the π electrons of the C=O group leads to a molecular orbital description for a conjugated enone that shows an interaction of the π electrons over all four atomic centers (Figure 23.3).

The real value of aldol dehydration is that removal of water from the reaction mixture can be used to drive the aldol equilibrium toward product. Even though the initial aldol step itself may be unfavorable, as it usually is for ketones, the subsequent dehydration step nevertheless allows many aldol condensations to be

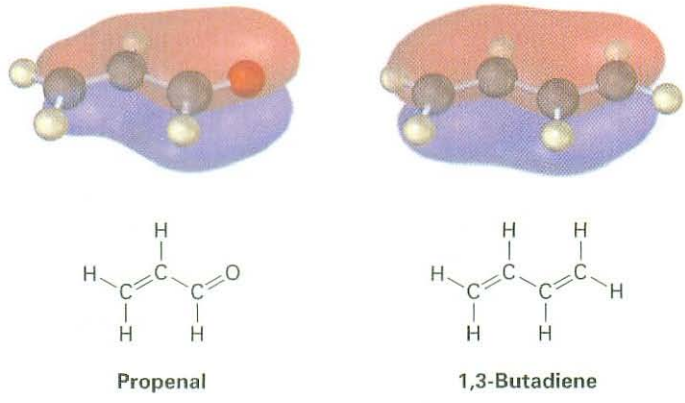
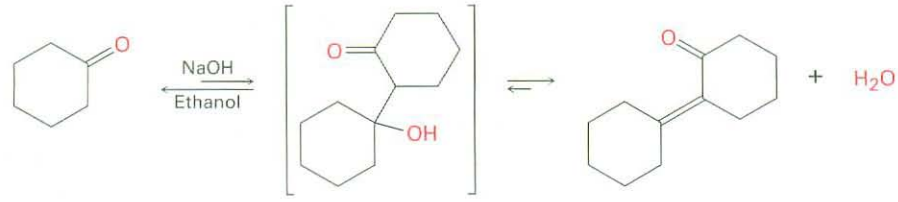


Figure 23.3 The π bonding molecular orbitals of a conjugated enone (propenal) and a conjugated diene (1,3-butadiene) are similar in shape and are spread over the entire π system.

Propenal **1,3-Butadiene**

carried out in good yield. Cyclohexanone, for example, gives cyclohexylidenecyclohexanone in 92% yield even though the initial equilibrium is unfavorable.



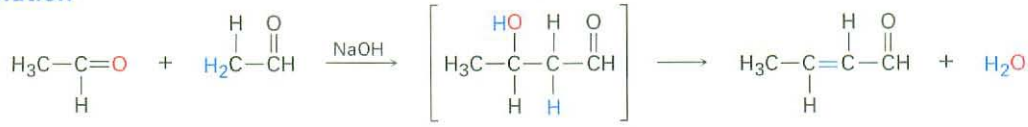
Cyclohexanone **Cyclohexylidenecyclohexanone (92%)**

WORKED EXAMPLE 23.2 *Predicting the Product of an Aldol Reaction*

What is the structure of the enone obtained from aldol condensation of acetaldehyde?

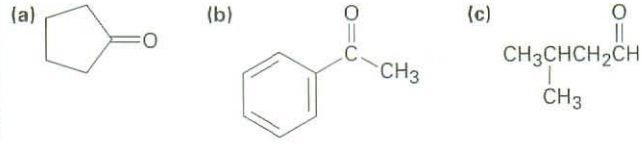
Strategy In the aldol reaction, H_2O is eliminated and a double bond is formed by removing two hydrogens from the acidic α position of one partner and the carbonyl oxygen from the second partner. The product is thus an α,β-unsaturated aldehyde or ketone.

Solution



2-Butenal

Problem 23.3 What enone product would you expect from aldol condensation of each of the following compounds?

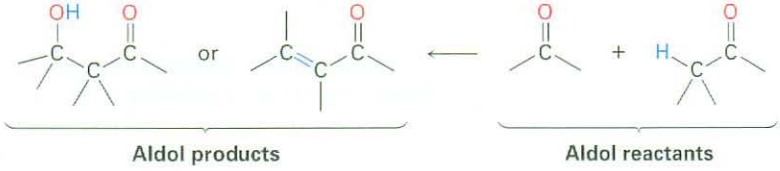


Problem 23.4 Aldol condensation of 3-methylcyclohexanone leads to a mixture of two enone products, not counting double-bond isomers. Draw them.

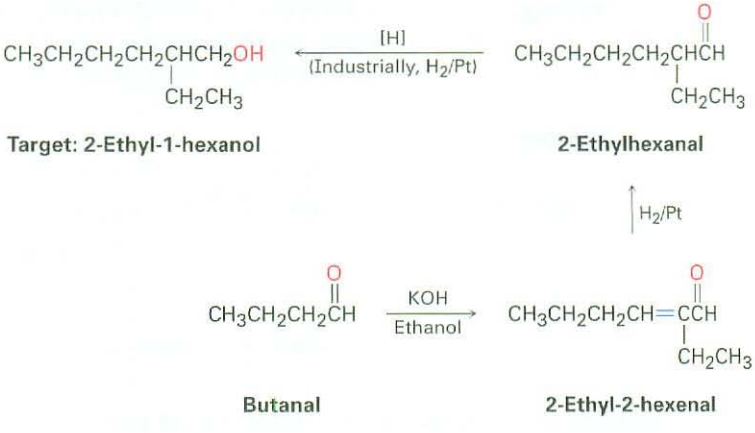
23.4 Using Aldol Reactions in Synthesis

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to design syntheses utilizing aldol-type reactions.**

The aldol reaction yields either a β-hydroxy aldehyde/ketone or an α,β-unsaturated aldehyde/ketone, depending on the experimental conditions. By learning how to think *backward,* it's possible to predict when the aldol reaction might be useful in synthesis. Whenever the target molecule contains either a β-hydroxy aldehyde/ketone or a conjugated enone functional group, it might come from an aldol reaction.



We can extend this kind of reasoning even further by imagining that subsequent transformations might be carried out on the aldol products. For example, a saturated ketone might be prepared by catalytic hydrogenation of the enone product. A good example can be found in the industrial preparation of 2-ethyl-1-hexanol, an alcohol used in the synthesis of plasticizers for polymers. Although 2-ethyl-1-hexanol bears little resemblance to an aldol product at first glance, it is in fact prepared commercially from butanal by an aldol reaction. Working backward, we can reason that 2-ethyl-1-hexanol might come from 2-ethylhexanal by a reduction. 2-Ethylhexanal, in turn, might be prepared by catalytic reduction of 2-ethyl-2-hexenal, which is the aldol condensation product of butanal. The reactions that follow show the sequence in reverse order.

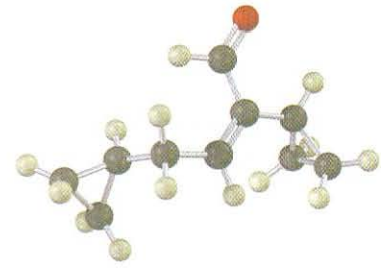


Problem 23.5 Which of the following compounds are aldol condensation products? What is the aldehyde or ketone precursor of each?

(a) 2-Hydroxy-2-methylpentanal (b) 5-Ethyl-4-methyl-4-hepten-3-one

Problem 23.6 1-Butanol is prepared commercially by a route that begins with an aldol reaction. Show the steps that are likely to be involved.

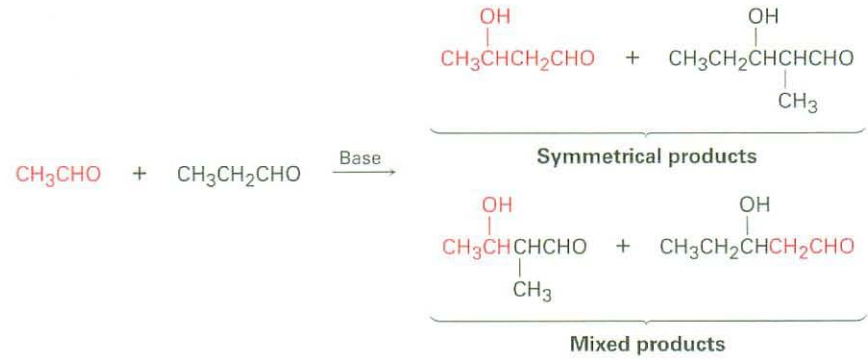
Problem 23.7 Show how you would synthesize the following compound using an aldol reaction:



23.5 Mixed Aldol Reactions

Until now, we've considered only *symmetrical* aldol reactions, in which the two carbonyl components have been the same. What would happen, though, if a *mixed* aldol reaction were carried out between two different carbonyl partners?

In general, a mixed aldol reaction between two similar aldehyde or ketone partners leads to a mixture of four possible products. For example, base treatment of a mixture of acetaldehyde and propanal gives a complex product mixture containing two "symmetrical" aldol products and two "mixed" aldol products. Clearly, such a reaction is of no practical value.

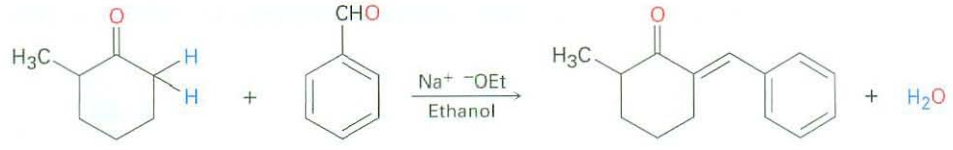


On the other hand, mixed aldol reactions *can* lead cleanly to a single product if either of two conditions is met:

- If one of the carbonyl partners contains no α hydrogens, and thus can't form an enolate ion to become a donor, but does contain an unhindered carbonyl group and so is a good acceptor of nucleophiles, then a mixed aldol reaction is likely to be successful. This is the case, for instance, when either benzaldehyde or formaldehyde is used as one of the carbonyl partners.

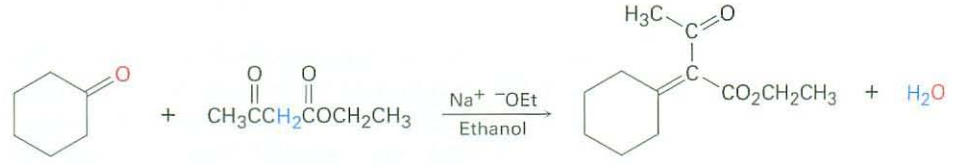
  Neither benzaldehyde nor formaldehyde can form an enolate ion to add to another partner, yet both compounds have an unhindered carbonyl group.

The ketone 2-methylcyclohexanone, for instance, gives the mixed aldol product on reaction with benzaldehyde.



2-Methylcyclohexanone (donor) **Benzaldehyde (acceptor)** **78%**

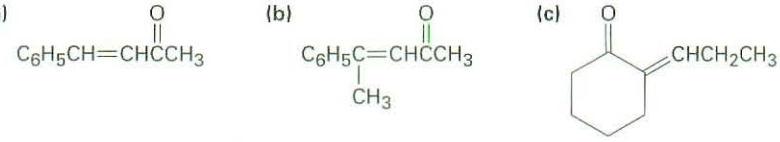
If one of the carbonyl partners is much more acidic than the other and so is transformed into its enolate ion in preference to the other, then a mixed aldol reaction is likely to be successful. Ethyl acetoacetate, for instance, is completely converted into its enolate ion in preference to enolate ion formation from monocarbonyl partners. Thus, aldol condensations of monoketones with ethyl acetoacetate occur preferentially to give the mixed product.



Cyclohexanone (acceptor) **Ethyl acetoacetate (donor)** **80%**

The situation can be summarized by saying that a mixed aldol reaction leads to a mixture of products unless one of the partners either has no α hydrogens but is a good electrophilic acceptor (such as benzaldehyde) or is an unusually acidic nucleophilic donor (such as ethyl acetoacetate).

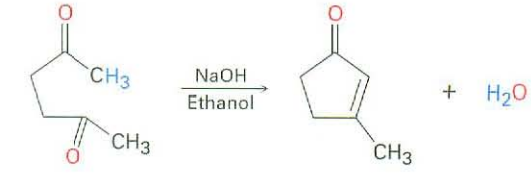
Problem 23.8 Which of the following compounds can probably be prepared by a mixed aldol reaction? Show the reactants you would use in each case.



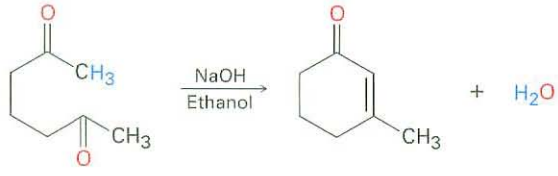
23.6 Intramolecular Aldol Reactions

The aldol reactions we've seen thus far have all been intermolecular, meaning that they have taken place between two different molecules. When certain *di*carbonyl compounds are treated with base, however, an *intra*molecular aldol reaction can occur, leading to the formation of a cyclic product. For example, base treatment of a 1,4-diketone such as 2,5-hexanedione yields a cyclopentenone

product, and base treatment of a 1,5-diketone such as 2,6-heptanedione yields a cyclohexenone.



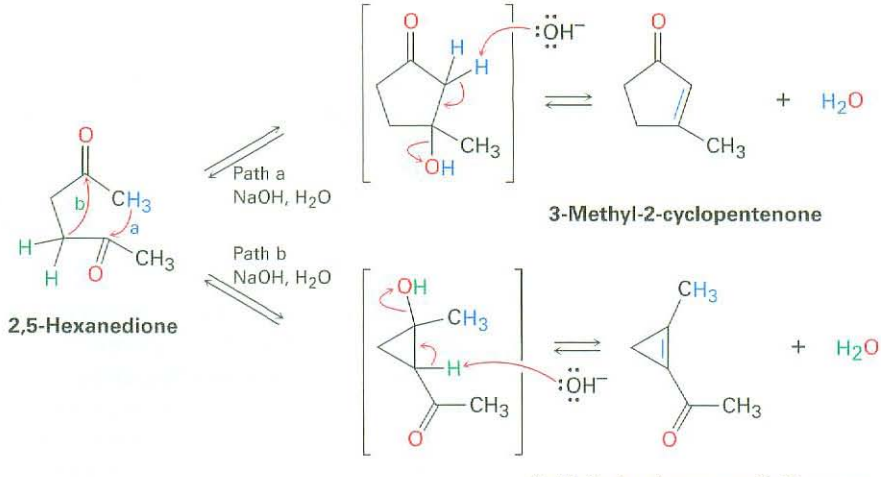
2,5-Hexanedione (a 1,4-diketone) **3-Methyl-2-cyclopentenone**



2,6-Heptanedione (a 1,5-diketone) **3-Methyl-2-cyclohexenone**

The mechanism of intramolecular aldol reactions is similar to that of intermolecular reactions. The only difference is that both the nucleophilic carbonyl anion donor and the electrophilic carbonyl acceptor are now in the same molecule. One complication, however, is that intramolecular aldol reactions might lead to a mixture of products, depending on which enolate ion is formed. For example, 2,5-hexanedione might yield either the five-membered-ring product 3-methyl-2-cyclopentenone or the three-membered-ring product (2-methylcyclopropenyl)ethanone (Figure 23.4). In practice, though, only the cyclopentenone is formed.

Figure 23.4 Intramolecular aldol reaction of 2,5-hexanedione yields 3-methyl-2-cyclopentenone rather than the alternative cyclopropene.



2,5-Hexanedione

3-Methyl-2-cyclopentenone

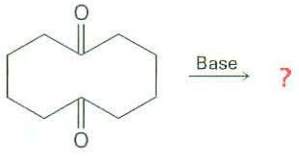
(2-Methylcyclopropenyl)ethanone
(NOT formed)

The selectivity observed in the intramolecular aldol reaction of 2,5-hexanedione is due to the fact that all steps in the mechanism are reversible, so an

equilibrium is reached. Thus, the relatively strain-free cyclopentenone product is considerably more stable than the highly strained cyclopropene alternative. For similar reasons, intramolecular aldol reactions of 1,5-diketones lead only to cyclohexenone products rather than to acylcyclobutenes.

Problem 23.9 Treatment of a 1,3-diketone such as 2,4-pentanedione with base does not give an aldol condensation product. Explain.

Problem 23.10 What product would you expect to obtain from base treatment of 1,6-cyclodecanedione?

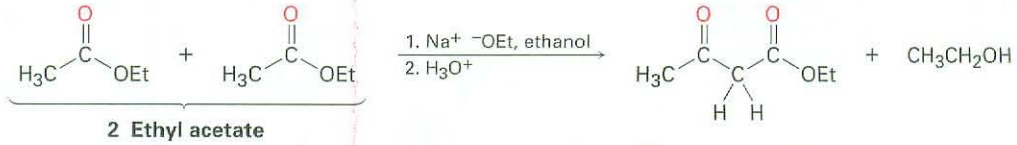


1,6-Cyclodecanedione

23.7 The Claisen Condensation Reaction

ThomsonNOW Click *Organic Process* to view an animation showing the mechanism of the Claisen condensation reaction.

Esters, like aldehydes and ketones, are weakly acidic. When an ester with an α hydrogen is treated with 1 equivalent of a base such as sodium ethoxide, a reversible carbonyl condensation reaction occurs to yield a β-keto ester. For example, ethyl acetate yields ethyl acetoacetate on base treatment. This reaction between two ester molecules is known as the **Claisen condensation reaction**. (We'll use ethyl esters, abbreviated "Et," for consistency, but other esters will also work.)

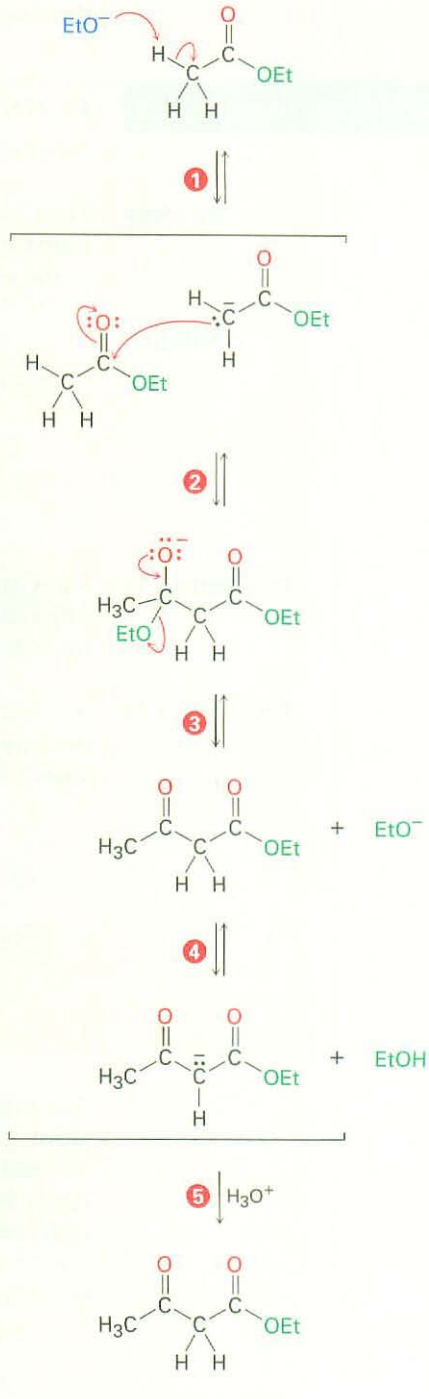


2 Ethyl acetate

Ethyl acetoacetate, a β-keto ester (75%)

The mechanism of the Claisen condensation is similar to that of the aldol condensation and involves the nucleophilic addition of an ester enolate ion to the carbonyl group of a second ester molecule. The only difference between the aldol condensation of an aldehyde or ketone and the Claisen condensation of an ester involves the fate of the initially formed tetrahedral intermediate. The tetrahedral intermediate in the aldol reaction is protonated to give an alcohol product—exactly the behavior previously seen for aldehydes and ketones (Section 19.4). The tetrahedral intermediate in the Claisen reaction, however, expels an alkoxide leaving group to yield an acyl substitution product—exactly the behavior previously seen for esters (Section 21.6). The mechanism of the Claisen condensation reaction is shown in Figure 23.5.

Active Figure 23.5
MECHANISM: Mechanism of the Claisen condensation reaction. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*



If the starting ester has more than one acidic α hydrogen, the product β-keto ester has a highly acidic, doubly activated hydrogen atom that can be abstracted by base. This deprotonation of the product requires that a full equivalent of base rather than a catalytic amount be used in the reaction. Furthermore, the

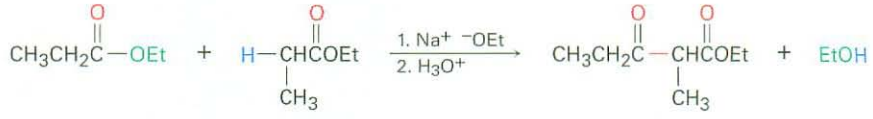
deprotonation serves to drive the equilibrium completely to the product side so that high yields are usually obtained in Claisen condensations.

WORKED EXAMPLE 23.3 ***Predicting the Product of a Claisen Condensation Reaction***

What product would you obtain from Claisen condensation of ethyl propanoate?

Strategy The Claisen condensation of an ester results in loss of one molecule of alcohol and formation of a product in which an acyl group of one reactant bonds to the α carbon of the second reactant. The product is a β-keto ester.

Solution

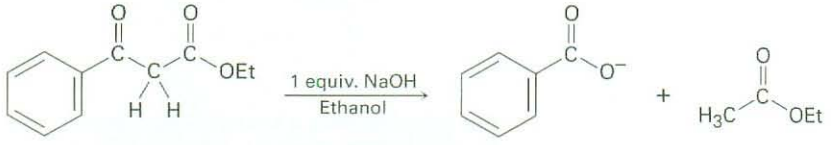


2 Ethyl propanoate — Ethyl 2-methyl-3-oxopentanoate

Problem 23.11 Show the products you would expect to obtain by Claisen condensation of the following esters:

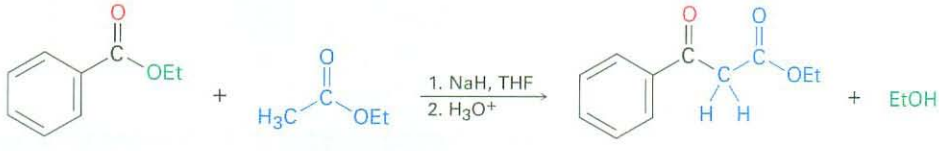
(a) $(CH_3)_2CHCH_2CO_2Et$ (b) Ethyl phenylacetate (c) Ethyl cyclohexylacetate

Problem 23.12 As shown in Figure 23.5, the Claisen reaction is reversible. That is, a β-keto ester can be cleaved by base into two fragments. Using curved arrows to indicate electron flow, show the mechanism by which this cleavage occurs.



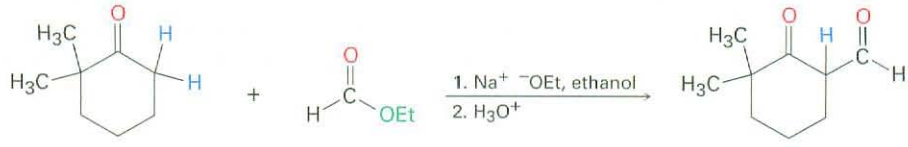
23.8 Mixed Claisen Condensations

The mixed Claisen condensation of two different esters is similar to the mixed aldol condensation of two different aldehydes or ketones (Section 23.5). Mixed Claisen reactions are successful only when one of the two ester components has no α hydrogens and thus can't form an enolate ion. For example, ethyl benzoate and ethyl formate can't form enolate ions and thus can't serve as donors. They can, however, act as the electrophilic acceptor components in reactions with other ester anions to give mixed β-keto ester products.



Ethyl benzoate (acceptor) — Ethyl acetate (donor) — Ethyl benzoylacetate

Mixed Claisen-like reactions can also be carried out between an ester and a ketone, resulting in the synthesis of a β-diketone. The reaction works best when the ester component has no α hydrogens and thus can't act as the nucleophilic donor. For example, ethyl formate gives high yields in mixed Claisen condensations with ketones.



2,2-Dimethylcyclohexanone (donor) + **Ethyl formate (acceptor)** → **A β-keto aldehyde (91%)**

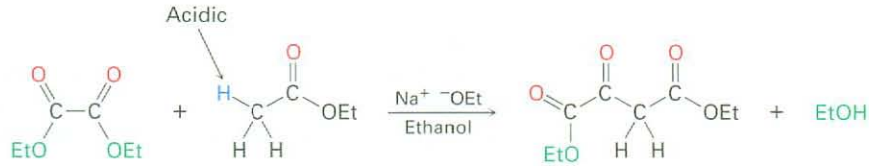
WORKED EXAMPLE 23.4

Predicting the Product of a Mixed Claisen Condensation Reaction

Diethyl oxalate, $(CO_2Et)_2$, often gives high yields in mixed Claisen reactions. What product would you expect to obtain from a mixed Claisen reaction of ethyl acetate with diethyl oxalate?

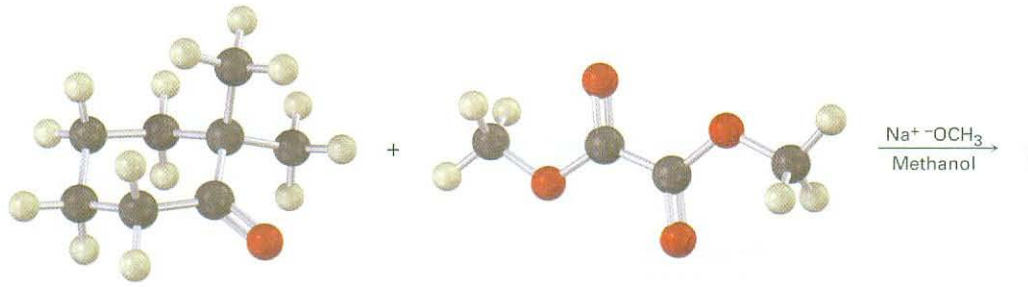
Strategy A mixed Claisen reaction is effective when only one of the two partners has an acidic α hydrogen atom. In the present case, ethyl acetate can be converted into its enolate ion, but diethyl oxalate cannot. Thus, ethyl acetate acts as the donor and diethyl oxalate as the acceptor.

Solution



Diethyl oxalate + **Ethyl acetate**

Problem 23.13 | What product would you expect from the following mixed Claisen-like reaction?

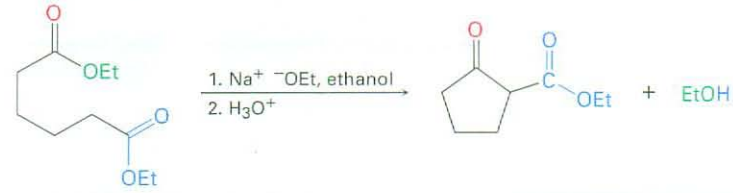


23.9 Intramolecular Claisen Condensations: The Dieckmann Cyclization

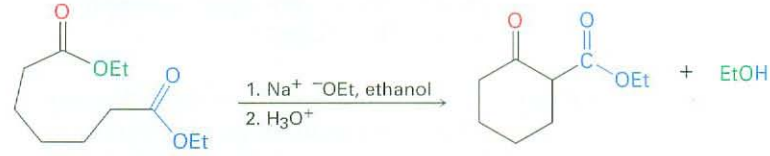
Walter Dieckmann

Walter Dieckmann (1869–1925) was born in Hamburg, Germany, and received his Ph.D. at the University of Munich. He then stayed on at Munich as professor of chemistry.

Intramolecular Claisen condensations can be carried out with diesters, just as intramolecular aldol condensations can be carried out with diketones (Section 23.6). Called the **Dieckmann cyclization**, the reaction works best on 1,6-diesters and 1,7-diesters. Intramolecular Claisen cyclization of a 1,6-diester gives a five-membered cyclic β-keto ester, and cyclization of a 1,7-diester gives a six-membered cyclic β-keto ester.



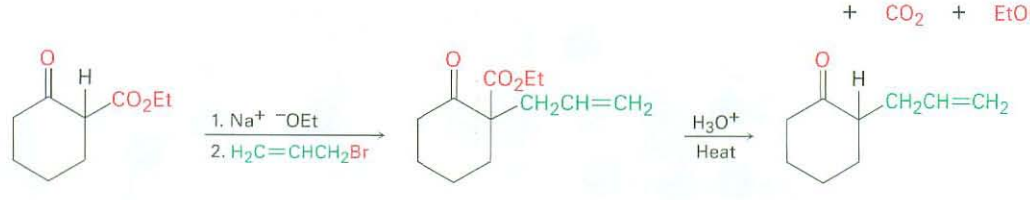
Diethyl hexanedioate (a 1,6-diester) — **Ethyl 2-oxocyclopentanecarboxylate (82%)**



Diethyl heptanedioate (a 1,7-diester) — **Ethyl 2-oxocyclohexanecarboxylate**

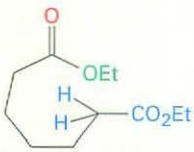
The mechanism of the Dieckmann cyclization, shown in Figure 23.6, is the same as that of the Claisen condensation. One of the two ester groups is converted into an enolate ion, which then carries out a nucleophilic acyl substitution on the second ester group at the other end of the molecule. A cyclic β-keto ester product results.

The cyclic β-keto ester produced in a Dieckmann cyclization can be further alkylated and decarboxylated by a series of reactions analogous to those used in the acetoacetic ester synthesis (Section 22.7). For example, alkylation and subsequent decarboxylation of ethyl 2-oxocyclohexanecarboxylate yields a 2-alkylcyclohexanone. The overall sequence of (1) Dieckmann cyclization, (2) β-keto ester alkylation, and (3) decarboxylation is a powerful method for preparing 2-substituted cyclohexanones and cyclopentanones.

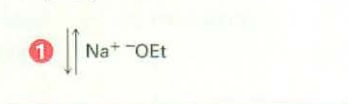


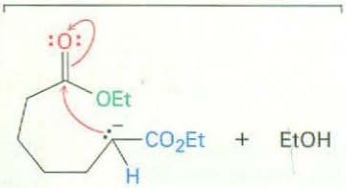
Ethyl 2-oxocyclohexanecarboxylate — **2-Allylcyclohexanone (83%)**

Figure 23.6 MECHANISM: Mechanism of the Dieckmann cyclization of a 1,7-diester to yield a cyclic β-keto ester product.

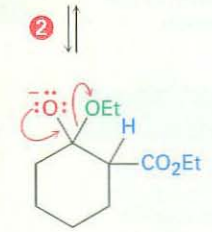


1. Base abstracts an acidic α proton from the carbon atom next to one of the ester groups, yielding an enolate ion.

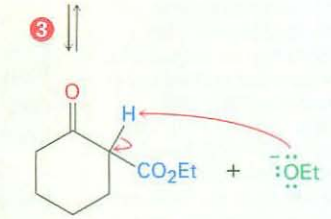




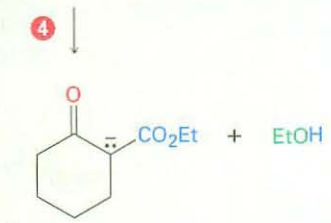
2. Intramolecular nucleophilic addition of the ester enolate ion to the carbonyl group of the second ester at the other end of the chain then gives a cyclic tetrahedral intermediate.



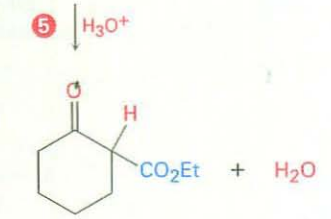
3. Loss of alkoxide ion from the tetrahedral intermediate forms a cyclic β-keto ester.



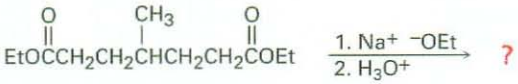
4. Deprotonation of the acidic β-keto ester gives an enolate ion . . .



5. . . . which is protonated by addition of aqueous acid at the end of the reaction to generate the neutral β-keto ester product.



Problem 23.14 What product would you expect from the following reaction?

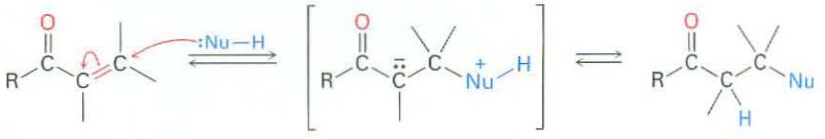


Problem 23.15 Dieckmann cyclization of diethyl 3-methylheptanedioate gives a mixture of two β-keto ester products. What are their structures, and why is a mixture formed?

23.10 Conjugate Carbonyl Additions: The Michael Reaction

ThomsonNOW Click *Organic Process* to **view an animation showing the mechanism of the Michael addition reaction.**

We saw in Section 19.13 that certain nucleophiles, such as amines, react with α,β-unsaturated aldehydes and ketones to give the conjugate addition product, rather than the direct addition product.



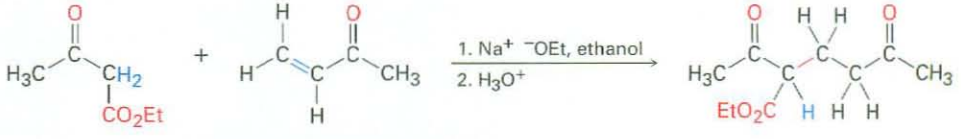
Conjugate addition product

Arthur Michael

Arthur Michael (1853–1942) was born to a wealthy family in Buffalo, New York. Although he received no formal university degrees, he studied in Heidelberg, Berlin, and the École de Médecine, Paris. Returning to the United States, he became professor of chemistry at Tufts University (1882–1889, 1894–1907), and then at Harvard University (1912–1936). Perhaps his most important contribution to science was his instrumental role in bringing the European research model of graduate education to the United States.

Exactly the same kind of conjugate addition can occur when a nucleophilic enolate ion reacts with an α,β-unsaturated carbonyl compound—a process known as the **Michael reaction**.

The best Michael reactions are those that take place when a particularly stable enolate ion such as that derived from a β-keto ester or other 1,3-dicarbonyl compound adds to an unhindered α,β-unsaturated ketone. For example, ethyl acetoacetate reacts with 3-buten-2-one in the presence of sodium ethoxide to yield the conjugate addition product.

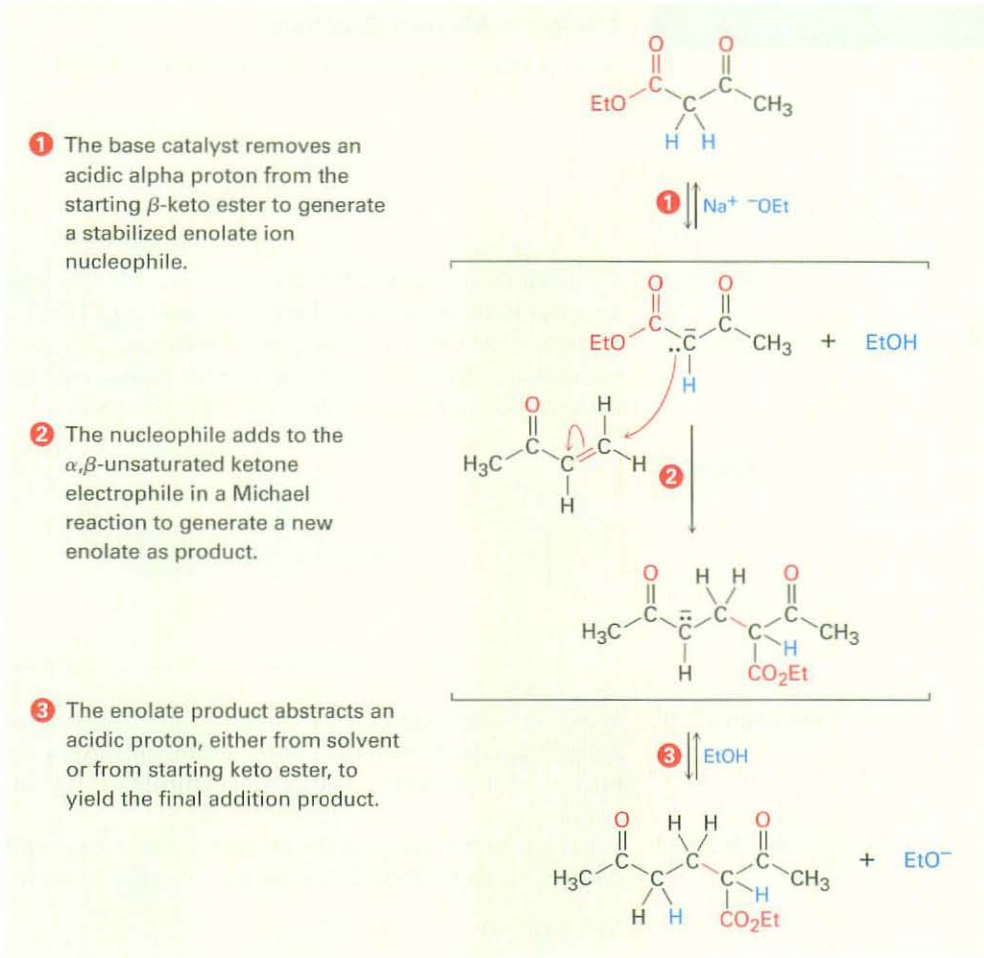


Ethyl acetoacetate **3-Buten-2-one**

Michael reactions take place by addition of a nucleophilic enolate ion donor to the β carbon of an α,β-unsaturated carbonyl acceptor, according to the mechanism shown in Figure 23.7.

The Michael reaction occurs with a variety of α,β-unsaturated carbonyl compounds, not just conjugated ketones. Unsaturated aldehydes, esters, thioesters, nitriles, amides, and nitro compounds can all act as the electrophilic acceptor component in Michael reactions (Table 23.1). Similarly, a variety of different donors can be used, including β-diketones, β-keto esters, malonic esters, β-keto nitriles, and nitro compounds.

Active Figure 23.7
MECHANISM: Mechanism of the Michael reaction between a β-keto ester and an α,β-unsaturated ketone. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*



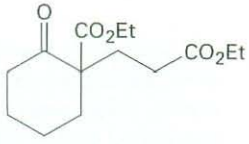
ThomsonNOW Click *Organic Interactive* to **learn to predict products in Michael-style addition reactions.**

Table 23.1 Some Michael Acceptors and Michael Donors

Michael acceptors		Michael donors	
$H_2C{=}CHCH{=}O$	Propenal	$RCCH_2CR'$ (O, O)	β-Diketone
$H_2C{=}CHCCH_3$ (O)	3-Buten-2-one	$RCCH_2COEt$ (O, O)	β-Keto ester
$H_2C{=}CHCOEt$ (O)	Ethyl propenoate	$EtOCCH_2COEt$ (O, O)	Diethyl malonate
$H_2C{=}CHCNH_2$ (O)	Propenamide	$RCCH_2C{\equiv}N$ (O)	β-Keto nitrile
$H_2C{=}CHC{\equiv}N$	Propenenitrile	RCH_2NO_2	Nitro compound
$H_2C{=}CH(NO_2)$	Nitroethylene		

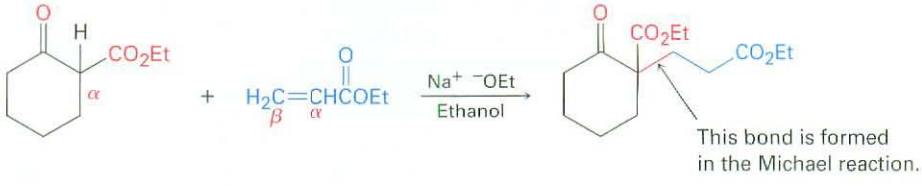
WORKED EXAMPLE 23.5 ***Using the Michael Reaction***

How might you obtain the following compound using a Michael reaction?



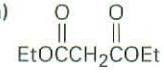
Strategy A Michael reaction involves the conjugate addition of a stable enolate ion donor to an α,β-unsaturated carbonyl acceptor, yielding a 1,5-dicarbonyl product. Usually, the stable enolate ion is derived from a β-diketone, β-keto ester, malonic ester, or similar compound. The C–C bond made in the conjugate addition step is the one between the α carbon of the acidic donor and the β carbon of the unsaturated acceptor.

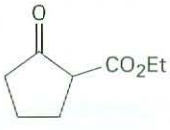
Solution



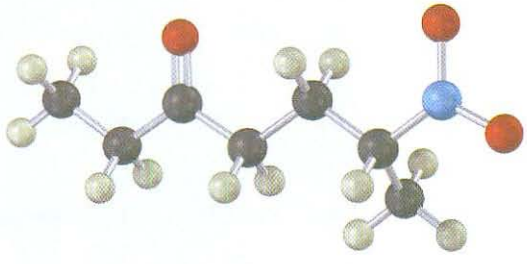
Problem 23.16 What product would you obtain from a base-catalyzed Michael reaction of 2,4-pentanedione with each of the following α,β-unsaturated acceptors?
(a) 2-Cyclohexenone (b) Propenenitrile (c) Ethyl 2-butenoate

Problem 23.17 What product would you obtain from a base-catalyzed Michael reaction of 3-buten-2-one with each of the following nucleophilic donors?

(a) 

(b) 

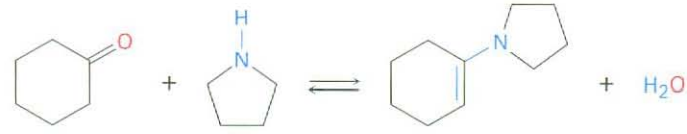
Problem 23.18 How would you prepare the following compound using a Michael reaction?



23.11 Carbonyl Condensations with Enamines: The Stork Reaction

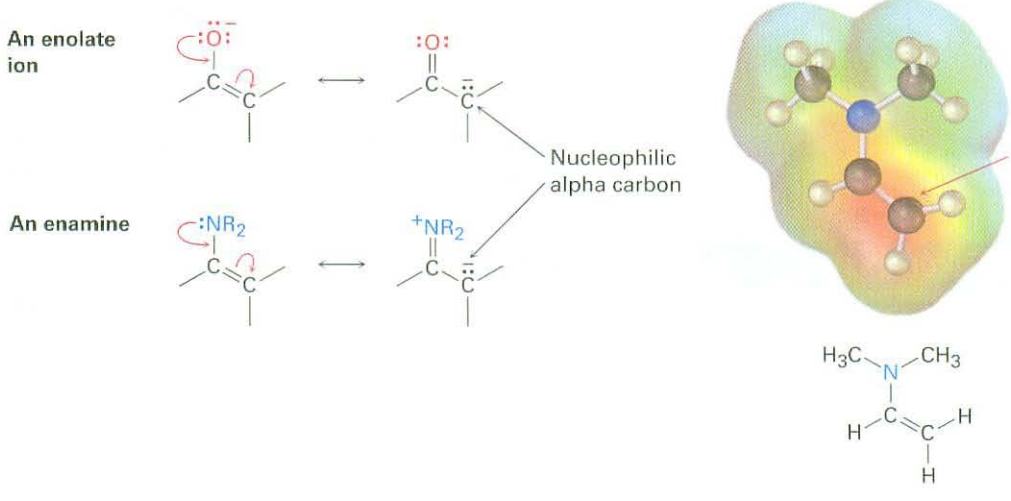
In addition to enolate ions, other kinds of carbon nucleophiles also add to α,β-unsaturated acceptors in Michael-like reactions. Among the most important such nucleophiles, particularly in biological chemistry, are *enamines*, which are

readily prepared by reaction between a ketone and a secondary amine, as we saw in Section 19.8. For example:



Cyclohexanone **Pyrrolidine** **1-Pyrrolidino-cyclohexene (87%)**

As the following resonance structures indicate, enamines are electronically similar to enolate ions. Overlap of the nitrogen lone-pair orbital with the double-bond p orbitals leads to an increase in electron density on the α carbon atom, making that carbon nucleophilic. An electrostatic potential map of *N*,*N*-dimethylaminoethylene shows this shift of electron density (red) toward the α position.



Gilbert Stork

Gilbert Stork (1921–) was born on New Year's eve in Brussels, Belgium. He received his secondary education in France, his undergraduate degree at the University of Florida, and his Ph.D. with Samuel McElvain at the University of Wisconsin in 1945. Following a period on the faculty at Harvard University, he has been professor of chemistry at Columbia University since 1953. A world leader in the development of organic synthesis, Stork has devised many useful new synthetic procedures and has accomplished the laboratory synthesis of many complex molecules.

Enamines behave in much the same way as enolate ions and enter into many of the same kinds of reactions. In the **Stork reaction**, for example, an enamine adds to an α,β-unsaturated carbonyl acceptor in a Michael-like process. The initial product is then hydrolyzed by aqueous acid (Section 19.8) to yield a 1,5-dicarbonyl compound. The overall reaction is thus a three-step sequence of (1) enamine formation from a ketone, (2) Michael addition to an α,β-unsaturated carbonyl compound, and (3) enamine hydrolysis back to a ketone.

The net effect of the Stork reaction is the Michael addition of a ketone to an α,β-unsaturated carbonyl compound. For example, cyclohexanone reacts with the cyclic amine pyrrolidine to yield an enamine; further reaction with an enone such as 3-buten-2-one yields a Michael adduct; and aqueous hydrolysis completes the sequence to provide a 1,5-diketone (Figure 23.8).

There are two advantages to the enamine–Michael reaction versus the enolate-ion–Michael that make enamines so useful in biological pathways. First, an enamine is neutral, easily prepared, and easily handled, while an enolate ion is charged, sometimes difficult to prepare, and must be handled with care.

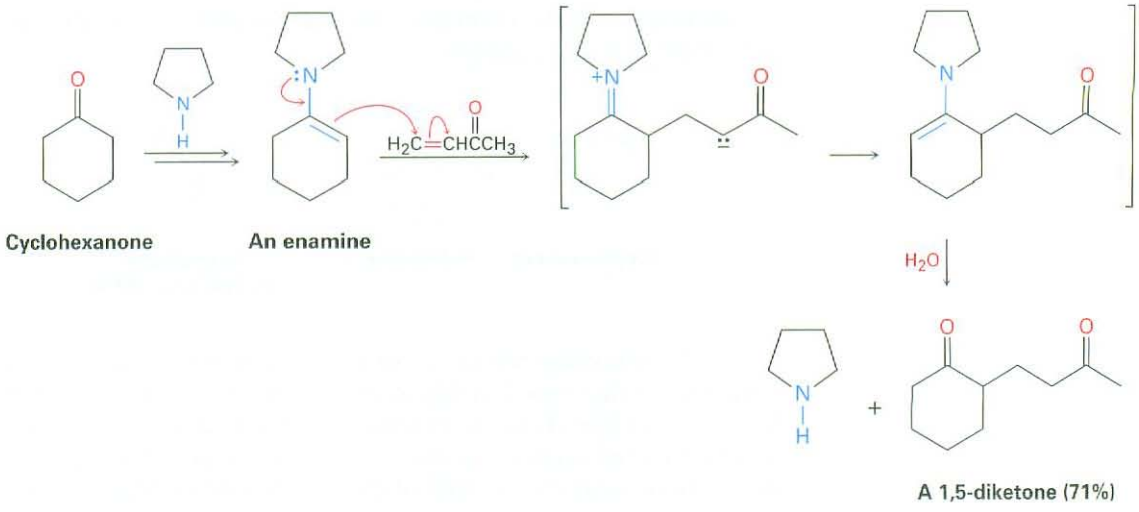
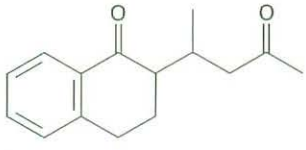


Figure 23.8 The Stork reaction between cyclohexanone and 3-buten-2-one. Cyclohexanone is first converted into an enamine, the enamine adds to the α,β-unsaturated ketone in a Michael reaction, and the conjugate addition product is hydrolyzed to yield a 1,5-diketone.

Second, an enamine from a *mono*ketone can be used in the Michael addition, whereas enolate ions only from β-*di*carbonyl compounds can be used.

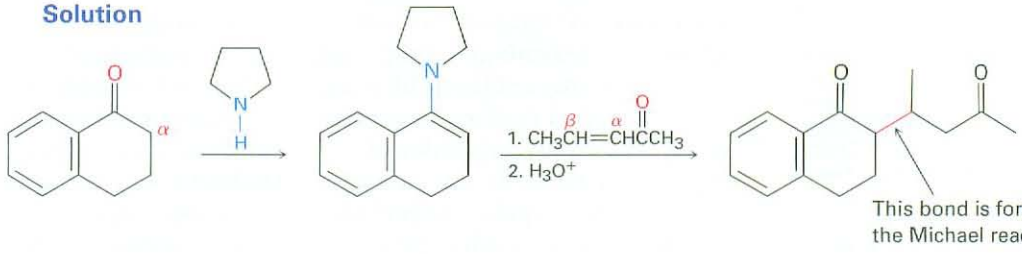
WORKED EXAMPLE 23.6 ***Using the Stork Enamine Reaction***

How might you use an enamine reaction to prepare the following compound?



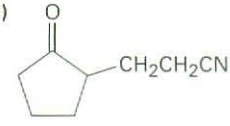
Strategy The overall result of an enamine reaction is the Michael addition of a ketone as donor to an α,β-unsaturated carbonyl compound as acceptor, yielding a 1,5-dicarbonyl product. The C–C bond made in the Michael addition step is the one between the α carbon of the ketone donor and the β carbon of the unsaturated acceptor.

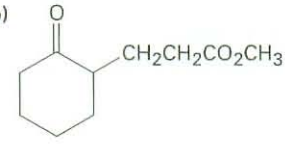
Solution



Problem 23.19 What products would result after hydrolysis from reaction of the enamine prepared from cyclopentanone and pyrrolidine with the following α,β-unsaturated acceptors?
(a) $CH_2{=}CHCO_2Et$ (b) $H_2C{=}CHCHO$ (c) $CH_3CH{=}CHCOCH_3$

Problem 23.20 Show how you might use an enamine reaction to prepare each of the following compounds:

(a) 

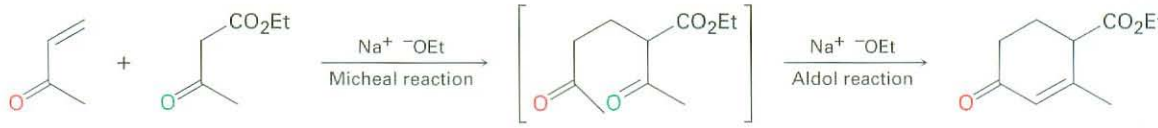
(b) 

23.12 The Robinson Annulation Reaction

Carbonyl condensation reactions are perhaps the most versatile methods available for synthesizing complex molecules. By putting a few fundamental reactions together in the proper sequence, some remarkably useful transformations can be carried out. One such example is the **Robinson annulation reaction** for the synthesis of polycyclic molecules. The word *annulation* comes from the Latin *annulus*, meaning "ring," so an annulation reaction builds a new ring onto a molecule.

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to design syntheses utilizing carbonyl condensation and addition reactions.**

The Robinson annulation is a two-step process that combines a Michael reaction with an intramolecular aldol reaction. It takes place between a nucleophilic donor, such as a β-keto ester, an enamine, or a β-diketone, and an α,β-unsaturated ketone acceptor, such as 3-buten-2-one. The product is a substituted 2-cyclohexenone.



3-Buten-2-one + **Ethyl acetoacetate** → **Michael product** → **Annulation product**

Sir Robert Robinson

Sir Robert Robinson (1886–1975) was born in Chesterfield, England, and received his D.Sc. from the University of Manchester with William Henry Perkin, Jr. After various academic appointments, he moved in 1930 to Oxford University, where he remained until his retirement in 1955. An accomplished mountain climber, Robinson was instrumental in developing the mechanistic descriptions of reactions that we use today. He received the 1947 Nobel Prize in chemistry.

The first step of the Robinson annulation is simply a Michael reaction. An enamine or an enolate ion from a β-keto ester or β-diketone effects a conjugate addition to an α,β-unsaturated ketone, yielding a 1,5-diketone. But as we saw in Section 23.6, 1,5-diketones undergo intramolecular aldol condensation to yield cyclohexenones when treated with base. Thus, the final product contains a six-membered ring, and an annulation has been accomplished. An example occurs during the commercial synthesis of the steroid hormone estrone (Figure 23.9).

In this example, the β-diketone 2-methyl-1,3-cyclopentanedione is used to generate the enolate ion required for Michael reaction and an aryl-substituted α,β-unsaturated ketone is used as the acceptor. Base-catalyzed Michael reaction between the two partners yields an intermediate triketone, which then cyclizes in an intramolecular aldol condensation to give a Robinson annulation product. Several further transformations are required to complete the synthesis of estrone.

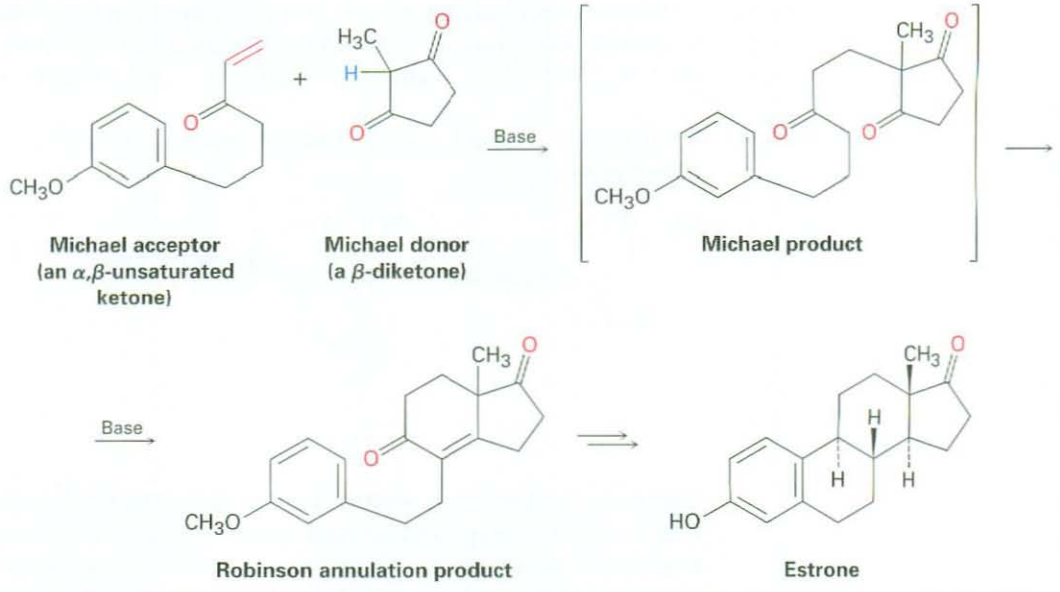
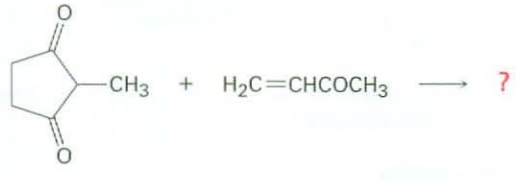
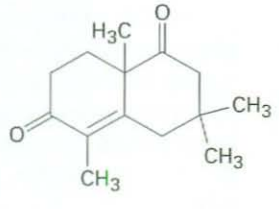


Figure 23.9 This Robinson annulation reaction is used in the commercial synthesis of the steroid hormone estrone. The nucleophilic donor is a β-diketone.

Problem 23.21 What product would you expect from a Robinson annulation reaction of 2-methyl-1,3-cyclopentanedione with 3-buten-2-one?



Problem 23.22 How would you prepare the following compound using a Robinson annulation reaction between a β-diketone and an α,β-unsaturated ketone? Draw the structures of both reactants and the intermediate Michael addition product.



23.13 Some Biological Carbonyl Condensation Reactions

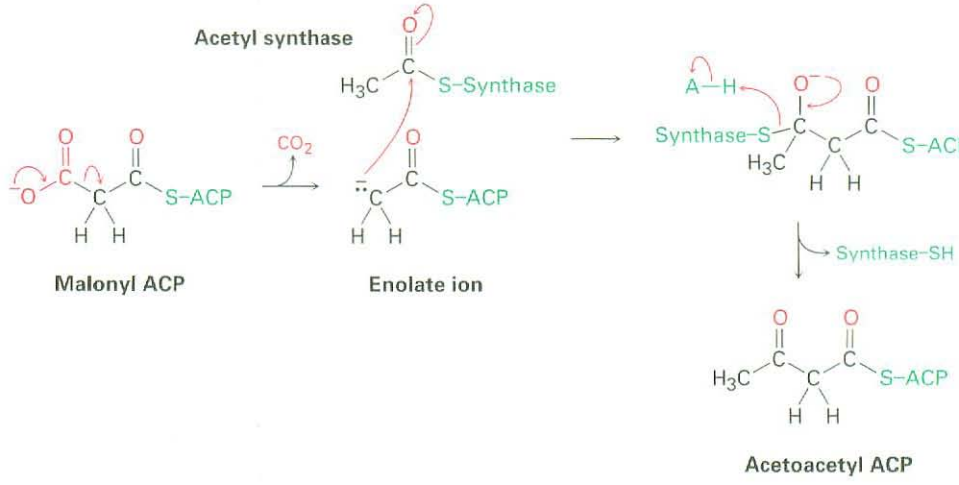
Biological Aldol Reactions

Aldol reactions occur in many biological pathways, but are particularly important in carbohydrate metabolism, where enzymes called *aldolases* catalyze the addition of a ketone enolate ion to an aldehyde. Aldolases occur in all organisms and are of two types. Type I aldolases occur primarily in animals and higher plants; type II aldolases occur primarily in fungi and bacteria. Both types catalyze the same kind of reaction, but type I aldolases operate place through an enamine, while type II aldolases require a metal ion (usually Zn^{2+}) as Lewis acid and operate through an enolate ion.

An example of an aldolase-catalyzed reaction occurs in glucose biosynthesis when dihydroxyacetone phosphate reacts with glyceraldehyde 3-phosphate to give fructose 1,6-bisphosphate. In animals and higher plants, dihydroxyacetone phosphate is first converted into an enamine by reaction with the $-NH_2$ group on a lysine amino acid in the enzyme. The enamine then adds to glyceraldehyde 3-phosphate, and the iminium ion that results is hydrolyzed. In bacteria and fungi, the aldol reaction occurs directly, with the ketone carbonyl group of glyceraldehyde 3-phosphate complexed to a Zn^{2+} ion to make it a better acceptor (Figure 23.10, page 902).

Biological Claisen Condensations

Claisen condensations, like aldol reactions, also occur in a large number of biological pathways. In fatty-acid biosynthesis, for instance, an enolate ion generated by decarboxylation (Section 22.7) of malonyl ACP adds to the carbonyl group of another acyl group bonded through a thioester linkage to a synthase enzyme. The tetrahedral intermediate that results then expels the synthase, giving acetoacetyl ACP.



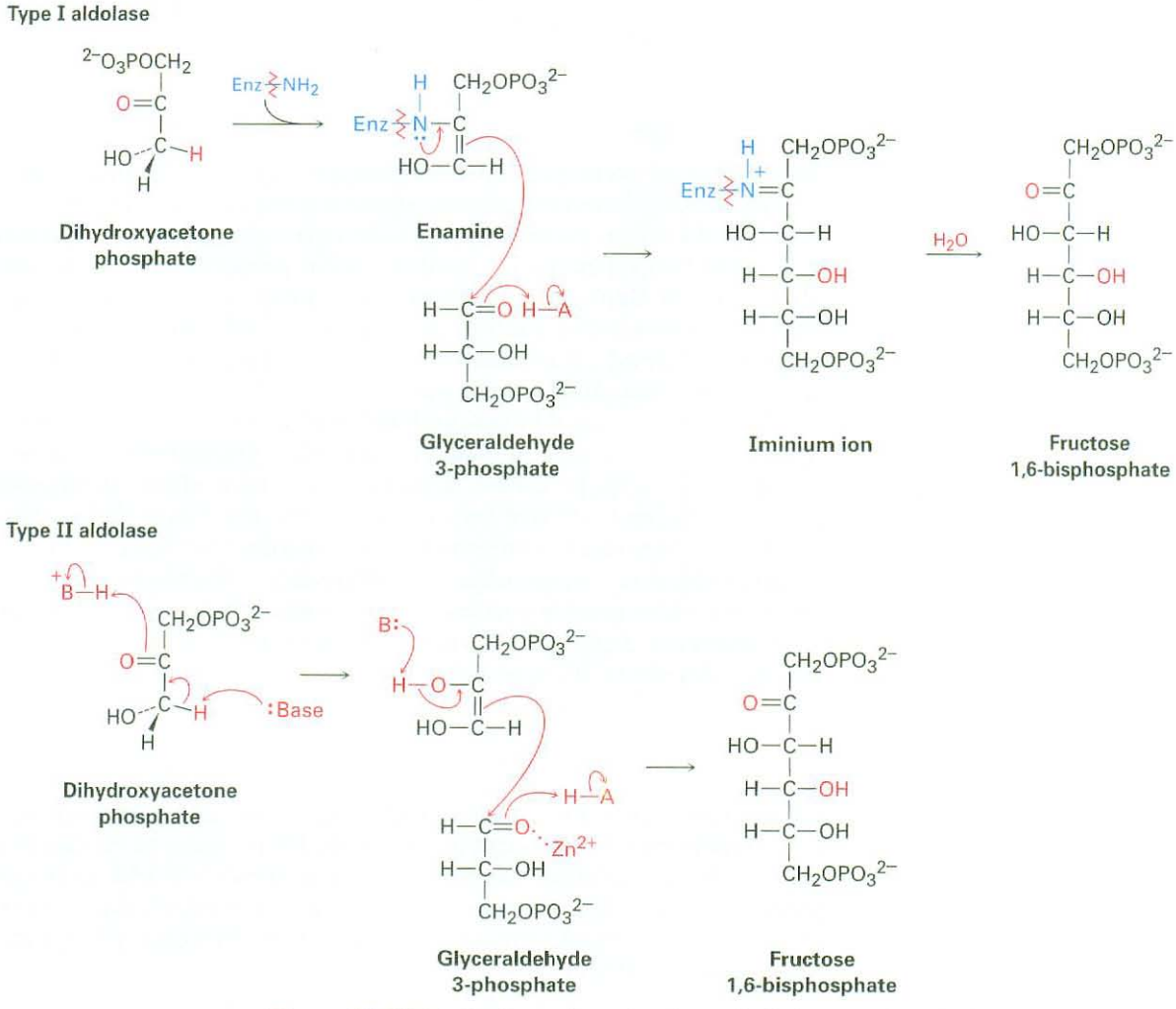
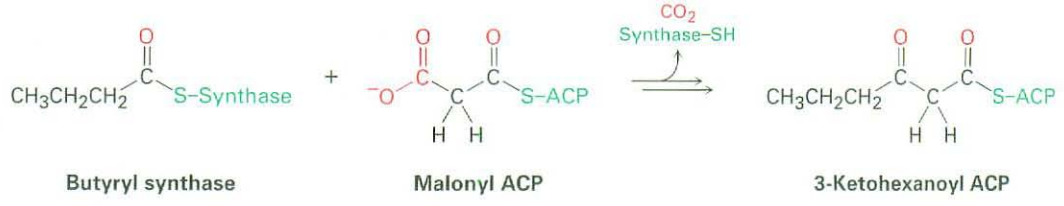


Figure 23.10 Mechanisms of type I and type II aldolase reactions in glucose biosynthesis.

Mixed Claisen condensations (Section 23.8) also occur frequently in living organisms, particularly in the pathway for fatty-acid biosynthesis that we'll discuss in Section 29.4. Butyryl synthase, for instance, reacts with malonyl ACP in a mixed Claisen condensation to give 3-ketohexanoyl ACP.



Focus On . . .

A Prologue to Metabolism

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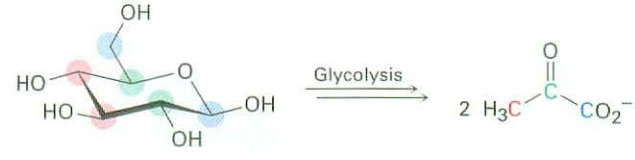
You are what you eat. Food molecules are metabolized by pathways that involve the four major carbonyl-group reactions.

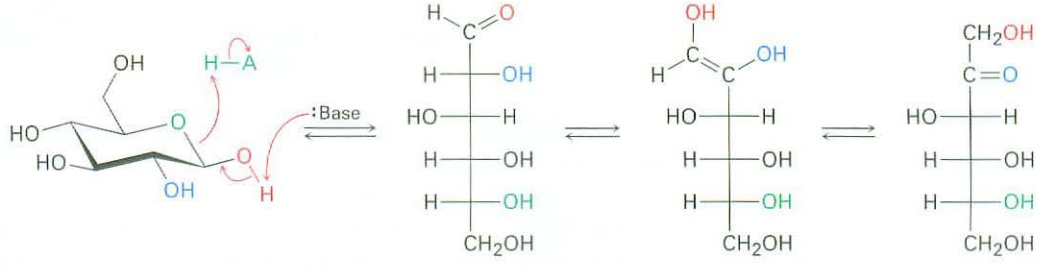
Biochemistry *is* carbonyl chemistry. Almost all metabolic pathways used by living organisms involve one or more of the four fundamental carbonyl-group reactions we've seen in Chapters 19 through 23. The digestion and metabolic breakdown of all the major classes of food molecules—fats, carbohydrates, and proteins—take place by nucleophilic addition reactions, nucleophilic acyl substitutions, α substitutions, and carbonyl condensations. Similarly, hormones and other crucial biological molecules are built up from smaller precursors by these same carbonyl-group reactions.

Take *glycolysis*, for example, the metabolic pathway by which organisms convert glucose to pyruvate as the first step in extracting energy from carbohydrates.



Glucose **Pyruvate**

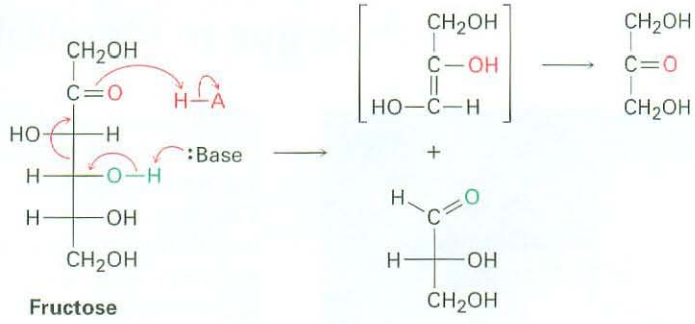
Glycolysis is a ten-step process that begins with isomerization of glucose from its cyclic hemiacetal form to its open-chain aldehyde form—a reverse nucleophilic addition reaction. The aldehyde then undergoes tautomerization to yield an enol, which undergoes yet another tautomerization to give the ketone fructose.



Glucose (hemiacetal) **Glucose (aldehyde)** **Glucose (enol)** **Fructose**

(continued)

Fructose, a β-hydroxy ketone, is then cleaved into two three-carbon molecules—one ketone and one aldehyde—by a reverse aldol reaction. Still further carbonyl-group reactions then occur until pyruvate results.

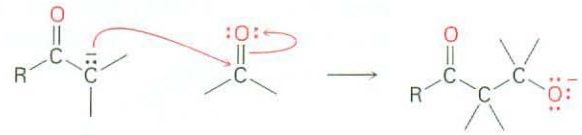


These few examples are only an introduction; we'll look at several of the major metabolic pathways in much more detail in Chapter 29. The bottom line is that you haven't seen the end of carbonyl-group chemistry. A solid grasp of carbonyl-group reactions is crucial to an understanding of biochemistry.

SUMMARY AND KEY WORDS

aldol reaction, 878
carbonyl condensation reaction, 877
Claisen condensation reaction, 888
Dieckmann cyclization, 892
Michael reaction, 894
Robinson annulation reaction, 899
Stork reaction, 897

A **carbonyl condensation reaction** takes place between two carbonyl partners and involves both nucleophilic addition and α-substitution steps. One carbonyl partner (the donor) is converted by base into a nucleophilic enolate ion, which adds to the electrophilic carbonyl group of the second partner (the acceptor). The donor molecule undergoes an α substitution, while the acceptor molecule undergoes a nucleophilic addition.



The **aldol reaction** is a carbonyl condensation that occurs between two aldehyde or ketone molecules. Aldol reactions are reversible, leading first to a β-hydroxy aldehyde or ketone and then to an α,β-unsaturated product. Mixed aldol condensations between two different aldehydes or ketones generally give a mixture of all four possible products. A mixed reaction can be successful, however, if one of the two partners is an unusually good donor (ethyl acetoacetate, for instance) or if it can act only as an acceptor (formaldehyde and benzaldehyde, for instance). Intramolecular aldol condensations of 1,4- and 1,5-diketones are also successful and provide a good way to make five- and six-membered rings.

The **Claisen reaction** is a carbonyl condensation that occurs between two ester molecules and gives a β-keto ester product. Mixed Claisen condensations

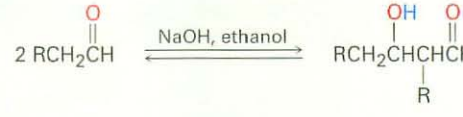
between two different esters are successful only when one of the two partners has no acidic α hydrogens (ethyl benzoate and ethyl formate, for instance) and thus can function only as the acceptor partner. Intramolecular Claisen condensations, called **Dieckmann cyclization reactions**, provide excellent syntheses of five- and six-membered cyclic β-keto esters starting from 1,6- and 1,7-diesters.

The conjugate addition of a carbon nucleophile to an α,β-unsaturated acceptor is known as the **Michael reaction**. The best Michael reactions take place between unusually acidic donors (β-keto esters or β-diketones) and unhindered α,β-unsaturated acceptors. Enamines, prepared by reaction of a ketone with a disubstituted amine, are also good Michael donors.

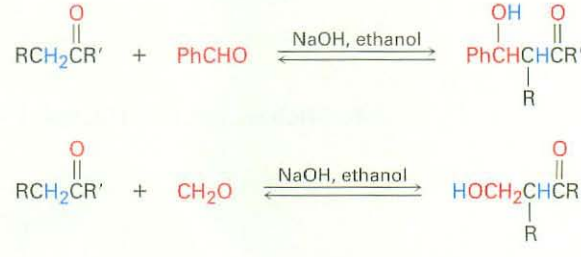
Carbonyl condensation reactions are widely used in synthesis. One example of their versatility is the **Robinson annulation reaction**, which leads to the formation of an substituted cyclohexenone. Treatment of a β-diketone or β-keto ester with an α,β-unsaturated ketone leads first to a Michael addition, which is followed by intramolecular aldol cyclization. Condensation reactions are also used widely in nature for the biosynthesis of such molecules as fats and steroids.

SUMMARY OF REACTIONS

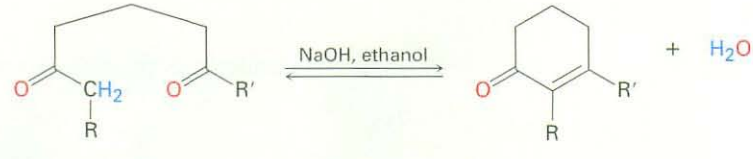
1. Aldol reaction (Section 23.1)



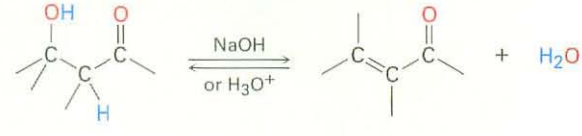
2. Mixed aldol reaction (Section 23.5)



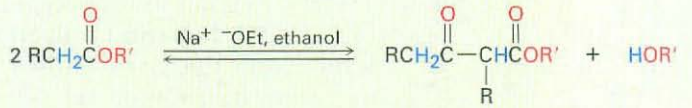
3. Intramolecular aldol reaction (Section 23.6)



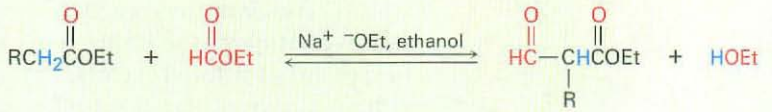
4. Dehydration of aldol products (Section 23.3)



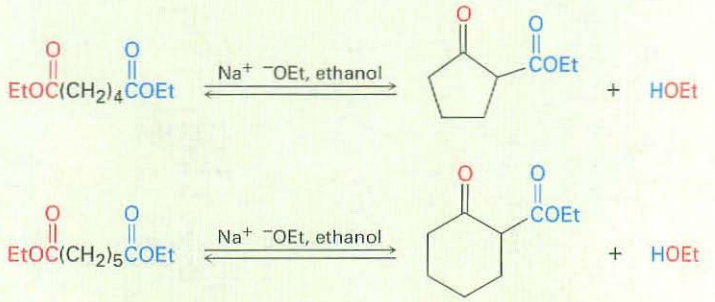
5. Claisen condensation reaction (Section 23.7)



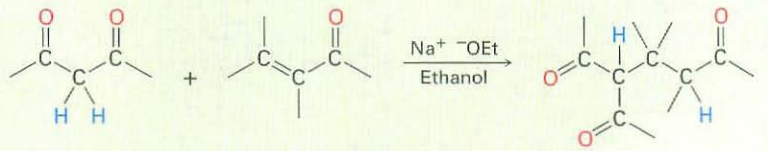
6. Mixed Claisen condensation reaction (Section 23.8)



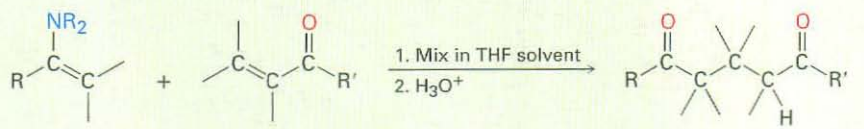
7. Intramolecular Claisen condensation (Dieckmann cyclization; Section 23.9)



8. Michael reaction (Section 23.10)



9. Carbonyl condensations with enamines (Stork reaction; Section 23.11)



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

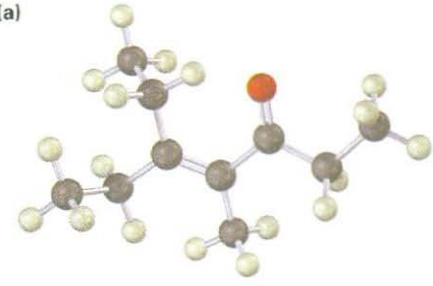
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

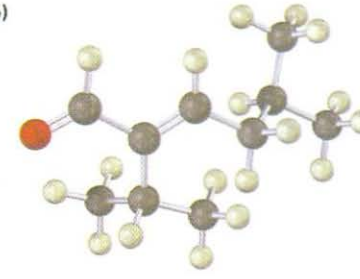
(Problems 23.1–23.22 appear within the chapter.)

23.23 ■ What ketones or aldehydes might the following enones have been prepared from by aldol reaction?

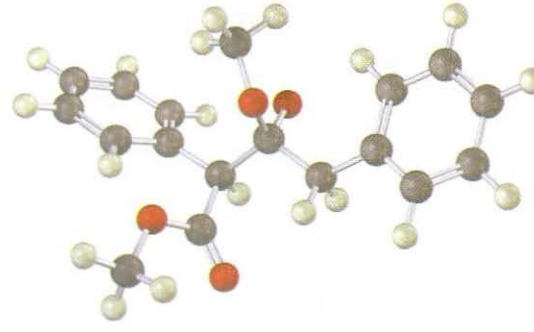
(a)



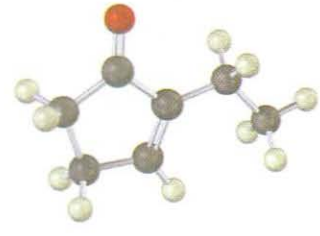
(b)



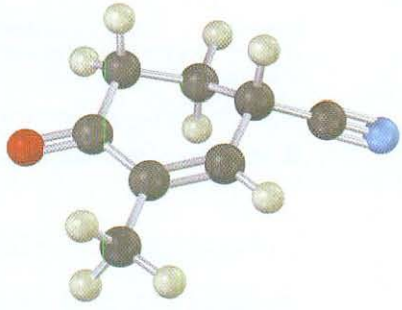
23.24 ■ The following structure represents an intermediate formed by addition of an ester enolate ion to a second ester molecule. Identify the reactant, the leaving group, and the product.



23.25 ■ The following molecule was formed by an intramolecular aldol reaction. What dicarbonyl precursor was used for its preparation?



23.26 The following molecule was formed by a Robinson annulation reaction. What reactants were used?



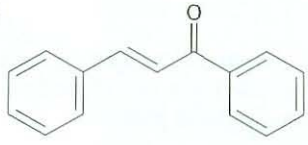
ADDITIONAL PROBLEMS

23.27 ■ Which of the following compounds would you expect to undergo aldol self-condensation? Show the product of each successful reaction.

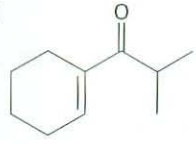
(a) Trimethylacetaldehyde
(b) Cyclobutanone
(c) Benzophenone (diphenyl ketone)
(d) 3-Pentanone
(e) Decanal
(f) 3-Phenyl-2-propenal

23.28 ■ How might you synthesize each of the following compounds using an aldol reaction? Show the structure of the starting aldehyde(s) or ketone(s) you would use in each case.

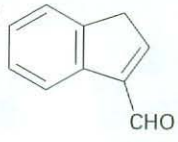
(a)



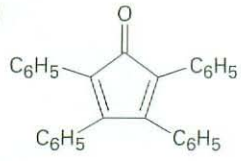
(b)



(c)



(d)



23.29 What product would you expect to obtain from aldol cyclization of hexanedial, $OHCCH_2CH_2CH_2CH_2CHO$?

23.30 Intramolecular aldol cyclization of 2,5-heptanedione with aqueous NaOH yields a mixture of two enone products in the approximate ratio 9:1. Write their structures, and show how each is formed.

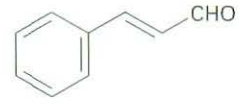
23.31 The major product formed by intramolecular aldol cyclization of 2,5-heptanedione (Problem 23.30) has two singlet absorptions in the ^1H NMR spectrum at 1.65 δ and 1.90 δ, and has no absorptions in the range 3 to 10 δ. What is its structure?

23.32 Treatment of the minor product formed in the intramolecular aldol cyclization of 2,5-heptanedione (Problems 23.30 and 23.31) with aqueous NaOH converts it into the major product. Propose a mechanism to account for this base-catalyzed isomerization.

23.33 ■ The aldol reaction is catalyzed by acid as well as by base. What is the reactive nucleophile in the acid-catalyzed aldol reaction? Propose a mechanism.

23.34 How can you account for the fact that 2,2,6-trimethylcyclohexanone yields no detectable aldol product even though it has an acidic α hydrogen?

23.35 Cinnamaldehyde, the aromatic constituent of cinnamon oil, can be synthesized by a mixed aldol condensation. Show the starting materials you would use, and write the reaction.



Cinnamaldehyde

23.36 The bicyclic ketone shown below does not undergo aldol self-condensation even though it has two α hydrogen atoms. Explain.

23.37 ■ What condensation products would you expect to obtain by treatment of the following substances with sodium ethoxide in ethanol?

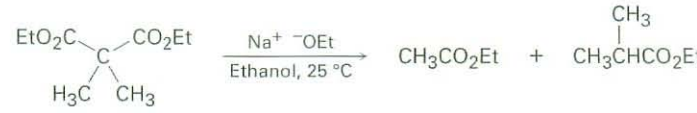
(a) Ethyl butanoate
(b) Cycloheptanone
(c) 3,7-Nonanedione
(d) 3-Phenylpropanal

23.38 In the mixed Claisen reaction of cyclopentanone with ethyl formate, a much higher yield of the desired product is obtained by first mixing the two carbonyl components and then adding base, rather than by first mixing base with cyclopentanone and then adding ethyl formate. Explain.

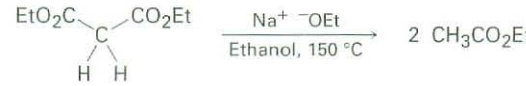
23.39 Give the structures of the possible Claisen condensation products from the following reactions. Tell which, if any, you would expect to predominate in each case.

(a) $CH_3CO_2Et + CH_3CH_2CO_2Et$
(b) $C_6H_5CO_2Et + C_6H_5CH_2CO_2Et$
(c) $EtOCO_2Et$ + Cyclohexanone
(d) $C_6H_5CHO + CH_3CO_2Et$

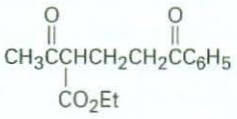
23.40 Ethyl dimethylacetoacetate reacts instantly at room temperature when treated with ethoxide ion to yield two products, ethyl acetate and ethyl 2-methylpropanoate. Propose a mechanism for this cleavage reaction.

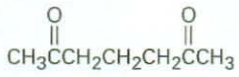


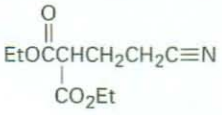
23.41 In contrast to the rapid reaction shown in Problem 23.40, ethyl acetoacetate requires a temperature over 150 °C to undergo the same kind of cleavage reaction. How can you explain the difference in reactivity?

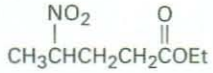


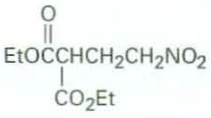
23.42 ■ How might the following compounds be prepared using Michael reactions? Show the nucleophilic donor and the electrophilic acceptor in each case.

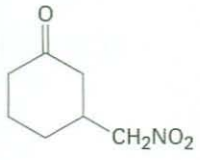
(a) 

(b) 

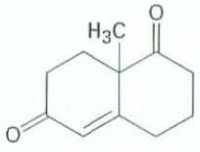
(c) 

(d) 

(e) 

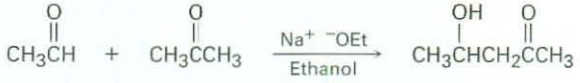
(f) 

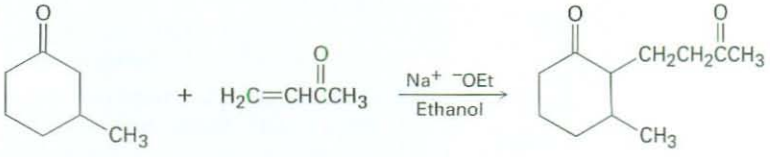
23.43 The so-called Wieland–Miescher ketone is a valuable starting material used in the synthesis of steroid hormones. How might you prepare it from 1,3-cyclohexanedione?

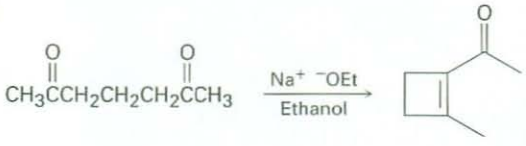


Wieland–Miescher ketone

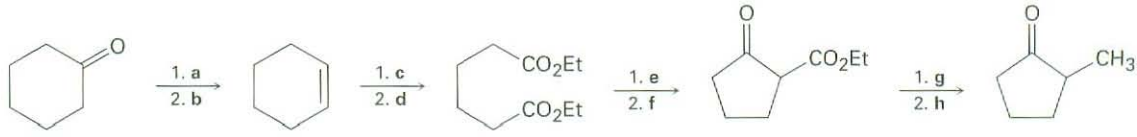
23.44 The following reactions are unlikely to provide the indicated product in high yield. What is wrong with each?

(a) 

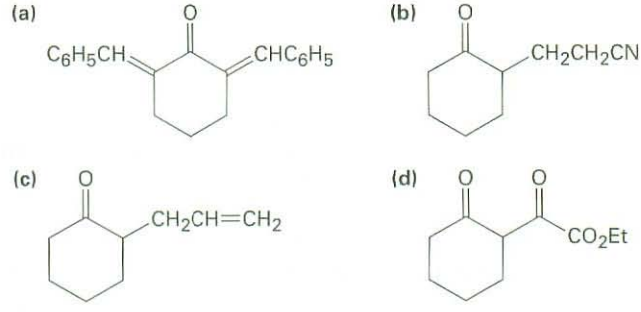
(b) 

(c) 

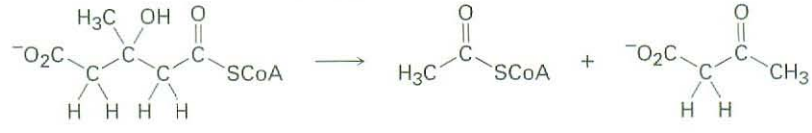
23.45 ■ Fill in the missing reagents **a–h** in the following scheme:



23.46 How would you prepare the following compounds from cyclohexanone?

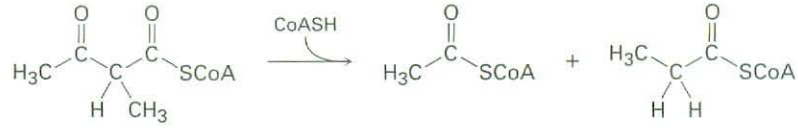


23.47 Leucine, one of the twenty amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



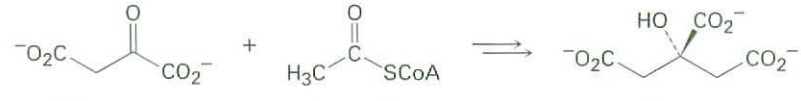
3-Hydroxy-3-methyl-glutaryl CoA **Acetyl CoA** **Acetoacetate**

23.48 Isoleucine, another of the twenty amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



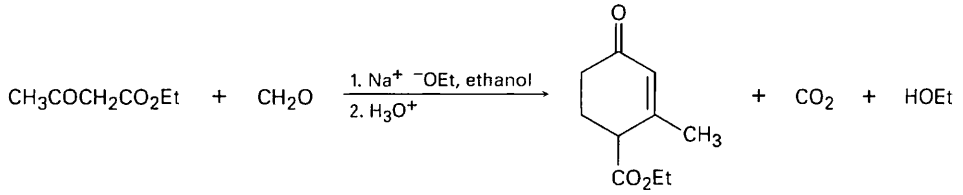
2-Methyl-3-keto-butyryl CoA **Acetyl CoA** **Propionyl CoA (propanoyl CoA)**

23.49 The first step in the citric acid cycle is reaction of oxaloacetate with acetyl CoA to give citrate. Propose a mechanism, using acid or base catalysis as needed.



Oxaloacetate **Acetyl CoA** **Citrate**

23.50 The compound known as *Hagemann's ester* is prepared by treatment of a mixture of formaldehyde and ethyl acetoacetate with base, followed by acid-catalyzed decarboxylation.



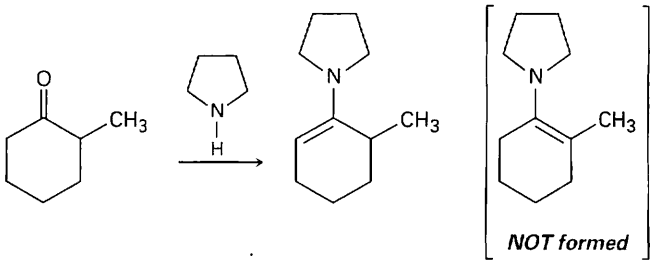
Hagemann's ester

(a) The first step is an aldol-like condensation between ethyl acetoacetate and formaldehyde to yield an α,β-unsaturated product. Write the reaction, and show the structure of the product.

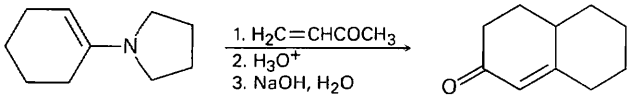
(b) The second step is a Michael reaction between ethyl acetoacetate and the unsaturated product of the first step. Show the structure of the product.

23.51 The third and fourth steps in the synthesis of Hagemann's ester from ethyl acetoacetate and formaldehyde (Problem 23.50) are an intramolecular aldol cyclization to yield a substituted cyclohexenone, and a decarboxylation reaction. Write both reactions, and show the products of each step.

23.52 When 2-methylcyclohexanone is converted into an enamine, only one product is formed despite the fact that the starting ketone is unsymmetrical. Build molecular models of the two possible products, and explain the fact that the sole product is the one with the double bond away from the methyl-substituted carbon.

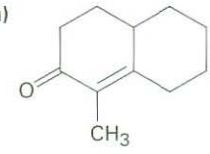


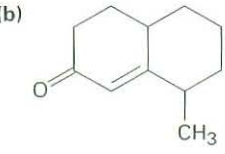
23.53 The Stork enamine reaction and the intramolecular aldol reaction can be carried out in sequence to allow the synthesis of cyclohexenones. For example, reaction of the pyrrolidine enamine of cyclohexanone with 3-buten-2-one, followed by enamine hydrolysis and base treatment, yields the product indicated. Write each step, and show the mechanism of each.

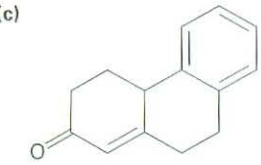


■ Assignable in OWL

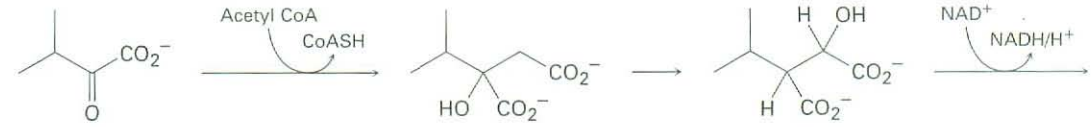
23.54 ■ How could you prepare the following cyclohexenones by combining a Stork enamine reaction with an intramolecular aldol condensation? (See Problem 23.53.)

(a) 

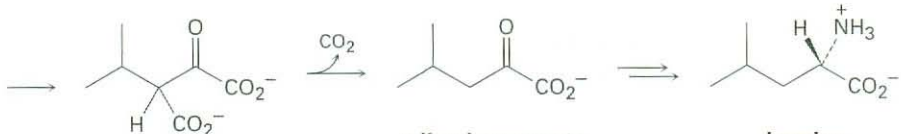
(b) 

(c) 

23.55 ■ The amino acid leucine is biosynthesized from α-ketoisovalerate by the following sequence of steps. Show the mechanism of each.

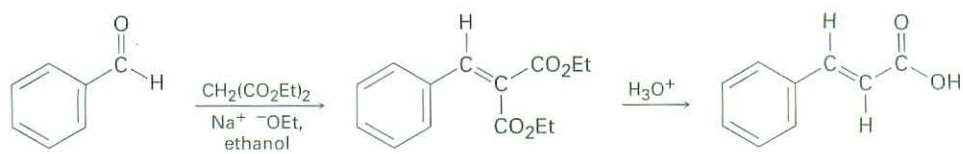


α-Ketoisovalerate — 1-Isopropylmalate — 2-Isopropylmalate



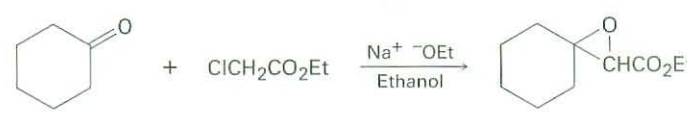
α-Ketoisocaproate — Leucine

23.56 The *Knoevenagel reaction* is a carbonyl condensation reaction of an ester with an aldehyde or ketone to yield an α,β-unsaturated product. Show the mechanism of the Knoevenagel reaction of diethyl malonate with benzaldehyde.

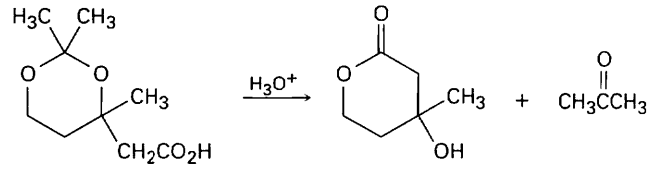


Benzaldehyde — Cinnamic acid (91%)

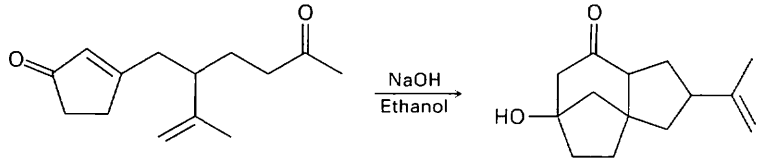
23.57 The *Darzens reaction* involves a two-step, base-catalyzed condensation of ethyl chloroacetate with a ketone to yield an epoxy ester. The first step is a carbonyl condensation reaction, and the second step is an S_N2 reaction. Write both steps, and show their mechanisms.



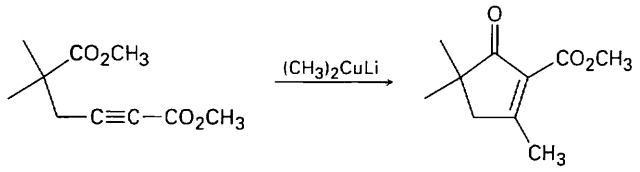
23.58 The following reaction involves a hydrolysis followed by an intramolecular nucleophilic acyl substitution reaction. Write both steps, and show their mechanisms.



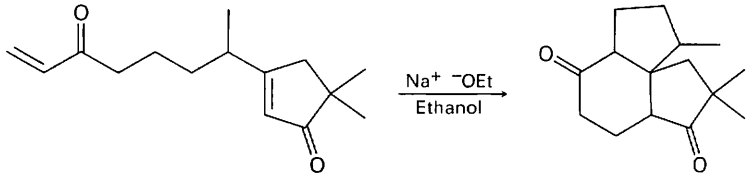
23.59 The following reaction involves an intramolecular Michael reaction followed by an intramolecular aldol reaction. Write both steps, and show their mechanisms.



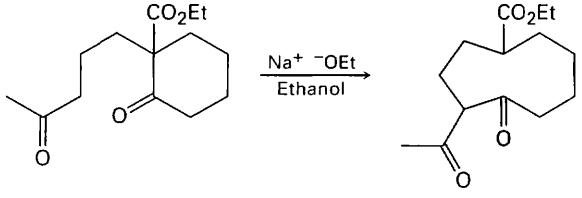
23.60 The following reaction involves a conjugate addition reaction followed by an intramolecular Claisen condensation. Write both steps, and show their mechanisms.



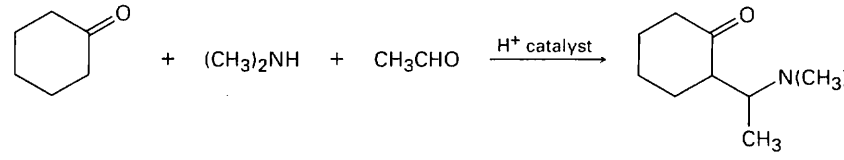
23.61 The following reaction involves two successive intramolecular Michael reactions. Write both steps, and show their mechanisms.



23.62 The following reaction involves an intramolecular aldol reaction followed by a *retro* aldol-like reaction. Write both steps, and show their mechanisms.



23.63 The *Mannich reaction* of a ketone, an amine, and an aldehyde is one of the few three-component reactions in organic chemistry. Cyclohexanone, for example, reacts with dimethylamine and acetaldehyde to yield an amino ketone. The reaction takes place in two steps, both of which are typical carbonyl-group reactions.



(a) The first step is reaction between the aldehyde and the amine to yield an intermediate iminium ion ($R_2C{=}NR_2^+$) plus water. Propose a mechanism, and show the structure of the intermediate iminium ion.

(b) The second step is reaction between the iminium ion intermediate and the ketone to yield the final product. Propose a mechanism.

23.64 Cocaine has been prepared by a sequence beginning with a Mannich reaction (Problem 23.63) between dimethyl acetonedicarboxylate, an amine, and a dialdehyde. Show the structures of the amine and dialdehyde.