22 Carbonyl Alpha-Substitution Reactions

Organic KNOWLEDGE TOOLS

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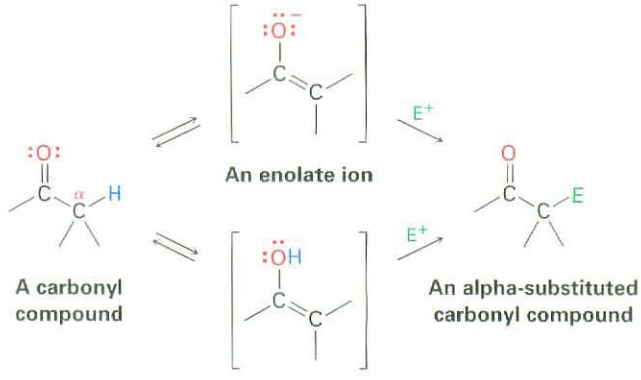
We said in *A Preview of Carbonyl Compounds* that much of the chemistry of carbonyl compounds can be explained by just four fundamental reaction types: nucleophilic additions, nucleophilic acyl substitutions, α substitutions, and carbonyl condensations. Having studied the first two of these reactions in the past three chapters, let's now look in more detail at the third major carbonyl-group process—the **α-substitution reaction**.

Alpha-substitution reactions occur at the position *next to* the carbonyl group—the *α position*—and involve the substitution of an α hydrogen atom by an electrophile, E, through either an *enol* or *enolate ion* intermediate. Let's begin by learning more about these two species.



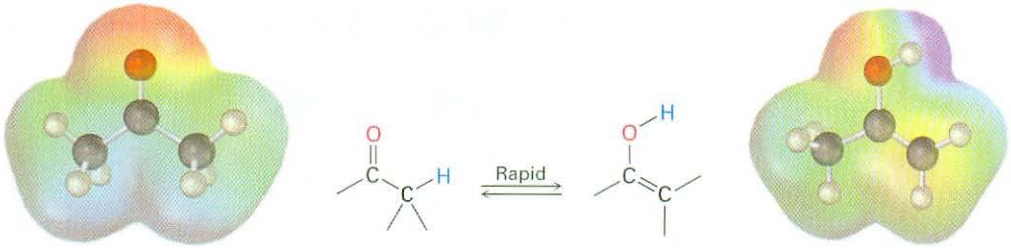
WHY THIS CHAPTER?

As with nucleophilic additions and nucleophilic acyl substitutions, many laboratory schemes, pharmaceutical syntheses, and biochemical pathways make frequent use of carbonyl α-substitution reactions. Their great value is that they constitute 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.

Sean Duggan

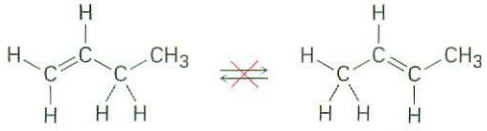
22.1 Keto–Enol Tautomerism

A carbonyl compound with a hydrogen atom on its α carbon rapidly equilibrates with its corresponding **enol** (Section 8.4). This rapid interconversion between two substances is a special kind of isomerism known as *keto–enol tautomerism*, from the Greek *tauto*, meaning "the same," and *meros*, meaning "part." The individual isomers are called **tautomers**.



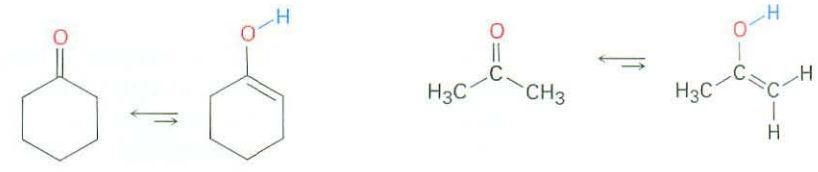
Keto tautomer **Enol tautomer**

Note the difference between tautomers and resonance forms. Tautomers are constitutional isomers—different compounds with different structures—while resonance forms are different representations of a single structure. Tautomers have their *atoms* arranged differently, while resonance forms differ only in the position of their *electrons*. Note also that tautomers are *rapidly* interconvertible. Thus, keto and enol isomers are tautomers, but alkene isomers such as 1-butene and 2-butene are not, because they don't interconvert rapidly under normal circumstances.



1-Butene **2-Butene**

Most carbonyl compounds exist almost exclusively in the keto form at equilibrium, and it's usually difficult to isolate the pure enol. For example, cyclohexanone contains only about 0.0001% of its enol tautomer at room temperature, and acetone contains only about 0.000 000 1% enol. The percentage of enol tautomer is even less for carboxylic acids, esters, and amides. Even though enols are difficult to isolate and are present only to a small extent at equilibrium, they are nevertheless responsible for much of the chemistry of carbonyl compounds because they are so reactive.



99.999 9% 0.000 1% 99.999 999 9% 0.000 000 1%

Cyclohexanone **Acetone**

Keto–enol tautomerism of carbonyl compounds is catalyzed by both acids and bases. Acid catalysis occurs by protonation of the carbonyl oxygen atom to give an intermediate cation that loses H^+ from its α carbon to yield a neutral enol (Figure 22.1). This proton loss from the cation intermediate is similar to what occurs during an E1 reaction when a carbocation loses H^+ to form an alkene (Section 11.10).

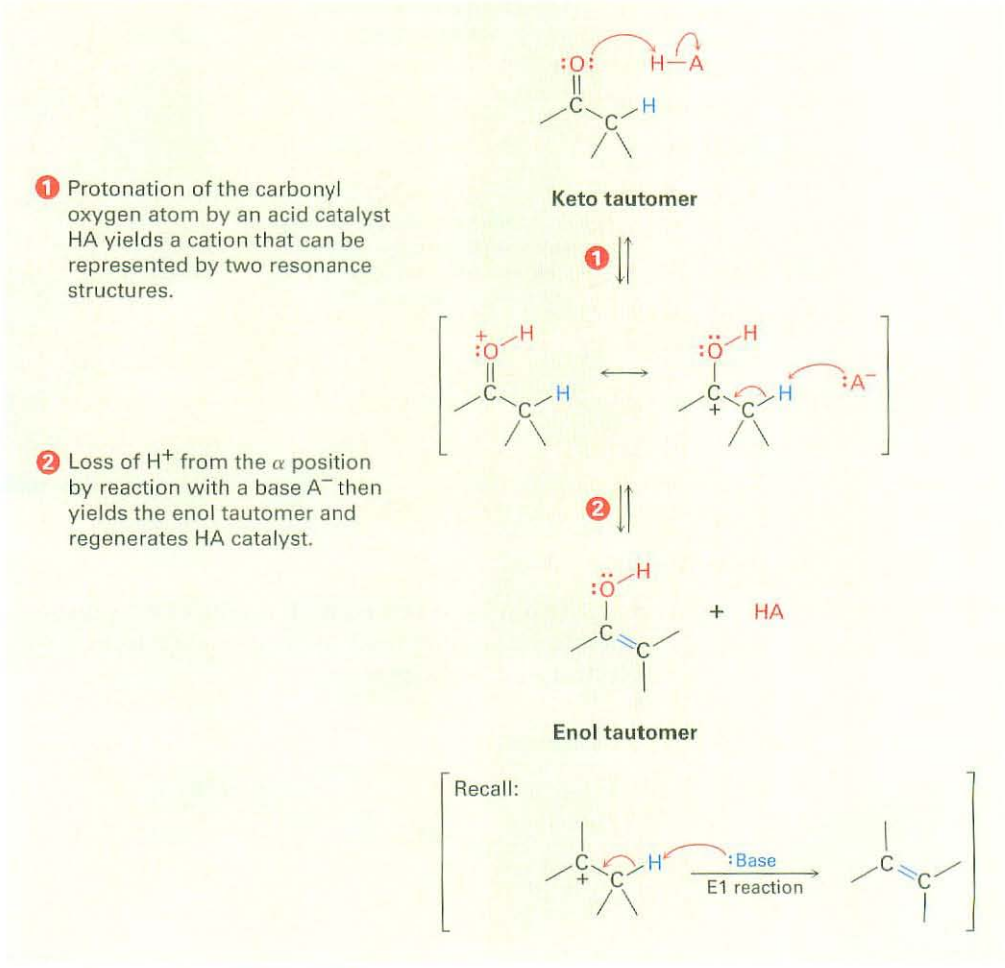


Figure 22.1 MECHANISM: Mechanism of acid-catalyzed enol formation. The protonated intermediate can lose H^+, either from the oxygen atom to regenerate the keto tautomer or from the α carbon atom to yield an enol.

Base-catalyzed enol formation occurs because the carbonyl group makes the hydrogens on the α carbon weakly acidic. Thus, a carbonyl compound can donate one of its α hydrogens to the base, giving an **enolate ion** that is then protonated. Because the enolate ion is a resonance hybrid of two forms, it can be protonated either on the α carbon to regenerate the keto tautomer or on oxygen to give the enol tautomer (Figure 22.2).

Note that only the hydrogens on the α position of a carbonyl compound are acidic. Hydrogens at β, γ, δ, and so on, are not acidic and can't be removed by

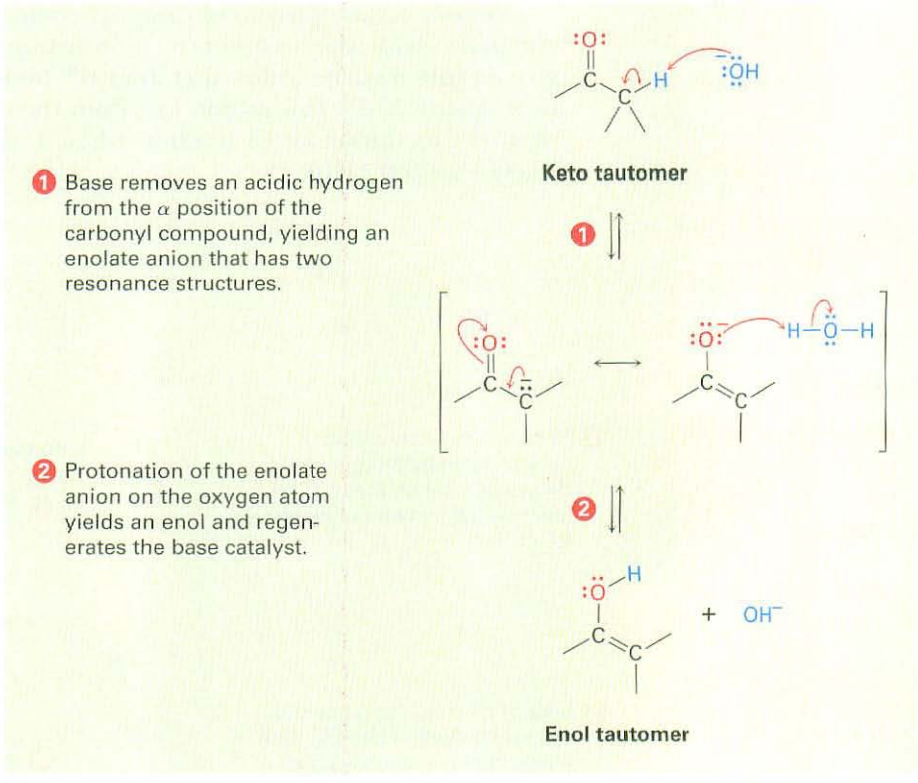
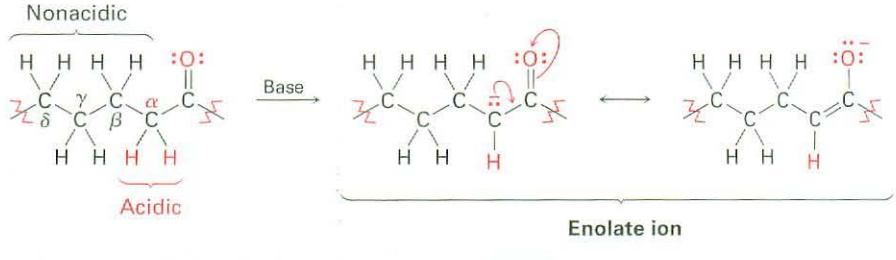


Figure 22.2 MECHANISM: Mechanism of base-catalyzed enol formation. The intermediate enolate ion, a resonance hybrid of two forms, can be protonated either on carbon to regenerate the starting keto tautomer or on oxygen to give an enol.

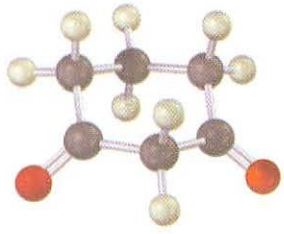
base. This unique behavior of α hydrogens is due to the fact that the resultant enolate ion is stabilized by a resonance form that places the charge on the electronegative oxygen.



Problem 22.1 Draw structures for the enol tautomers of the following compounds:
(a) Cyclopentanone (b) Methyl thioacetate (c) Ethyl acetate
(d) Propanal (e) Acetic acid (f) Phenylacetone

Problem 22.2 How many acidic hydrogens does each of the molecules listed in Problem 22.1 have? Identify them.

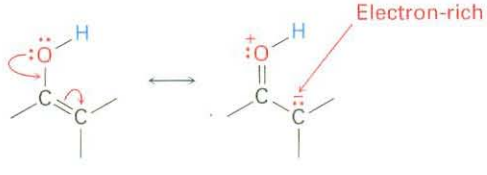
Problem 22.3 Draw structures for all monoenol forms of the following molecule. Which would you expect to be most stable? Explain.



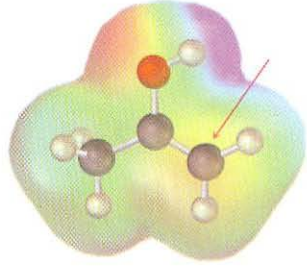
22.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

ThomsonNOW Click *Organic Process* to **view an animation showing substitution occurring alpha to a carbonyl.**

What kind of chemistry do enols have? Because their double bonds are electron-rich, enols behave as nucleophiles and react with electrophiles in much the same way that alkenes do. But because of resonance electron donation of a lone-pair of electrons on the neighboring oxygen, enols are more electron-rich and correspondingly more reactive than alkenes. Notice in the following electrostatic potential map of ethenol ($H_2C{=}CHOH$) how there is a substantial amount of electron density (yellow–red) on the α carbon.

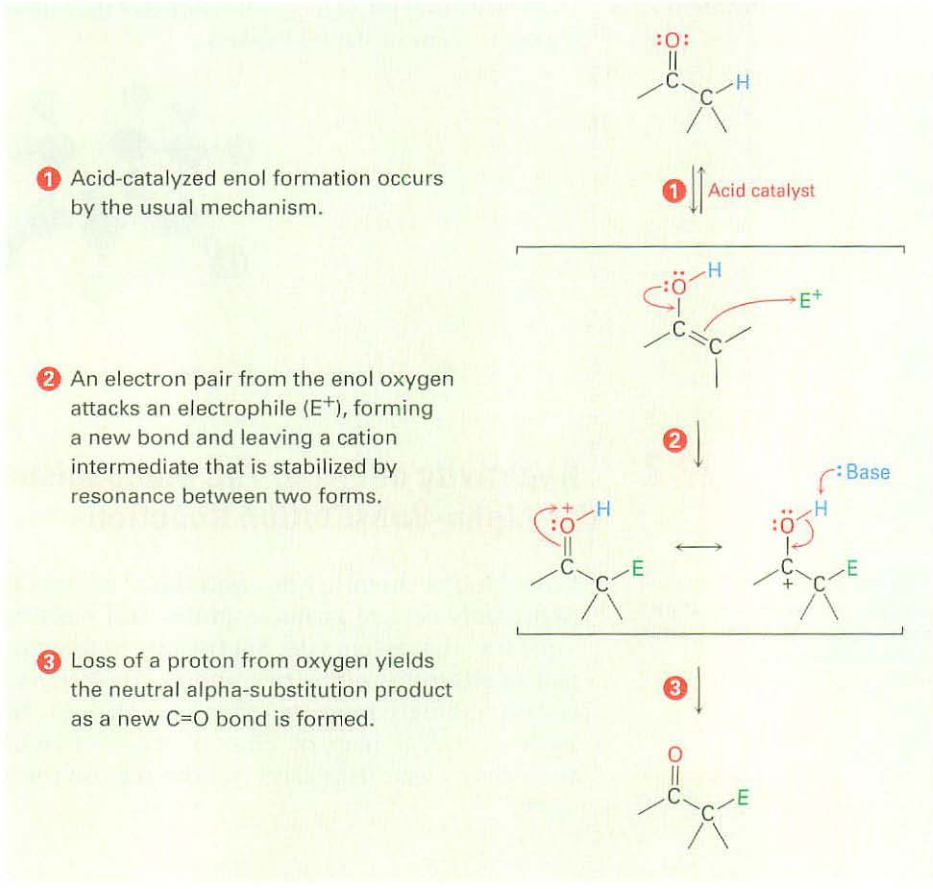


Enol tautomer



When an *alkene* reacts with an electrophile, such as HCl, initial addition of H^+ gives an intermediate cation and subsequent reaction with Cl^- yields an addition product (Section 6.7). When an *enol* reacts with an electrophile, however, only the initial addition step is the same. Instead of reacting with Cl^- to give an addition product, the intermediate cation loses the $-OH$ proton to give an α-substituted carbonyl compound. The general mechanism is shown in Figure 22.3.

Active Figure 22.3
MECHANISM: General mechanism of a carbonyl α-substitution reaction. The initially formed cation loses H^+ to regenerate a carbonyl compound. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

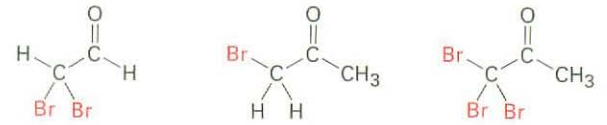


22.3 Alpha Halogenation of Aldehydes and Ketones

A particularly common α-substitution reaction in the laboratory is the halogenation of aldehydes and ketones at their α positions by reaction with Cl_2, Br_2, or I_2 in acidic solution. Bromine in acetic acid solvent is often used.

Acetophenone **α-Bromoacetophenone (72%)**

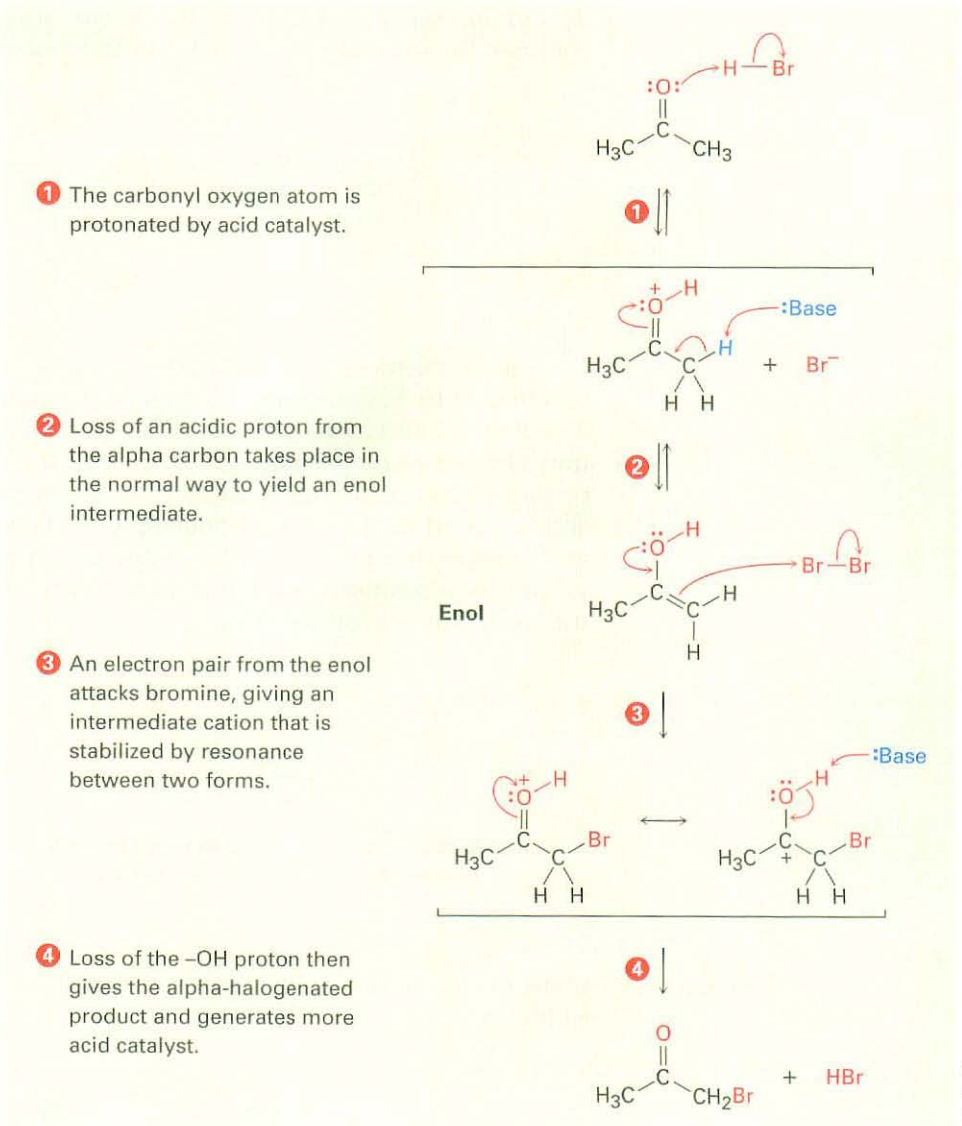
Remarkably, ketone halogenation also occurs in biological systems, particularly in marine alga, where dibromoacetaldehyde, bromoacetone, 1,1,1-tribromoacetone, and other related compounds have been found.



From the Hawaiian alga *Asparagopsis taxiformis*

The halogenation is a typical α-substitution reaction that proceeds by acid-catalyzed formation of an enol intermediate, as shown in Figure 22.4.

Figure 22.4 MECHANISM: Mechanism of the acid-catalyzed bromination of acetone.

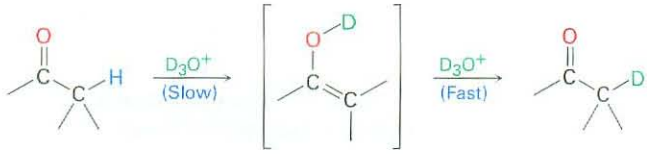


Evidence for the mechanism shown in Figure 22.4 includes the observation that acid-catalyzed halogenations show second-order kinetics and follow the rate law

$$\text{Reaction rate} = k\,[\text{Ketone}]\,[H^+]$$

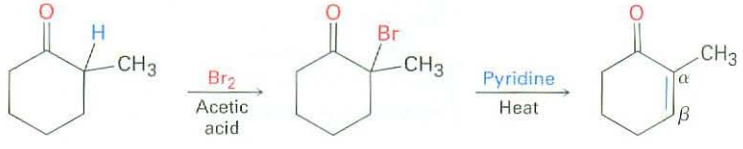
In other words, the rate of halogenation depends only on the concentrations of ketone and acid and is independent of halogen concentration. Halogen is not involved in the rate-limiting step, so chlorination, bromination, and iodination of a given substrate all occur at the same rate.

Furthermore, if an aldehyde or ketone is treated with D_3O^+, the acidic α hydrogens are replaced by deuterium. For a given ketone, the rate of deuterium exchange is identical to the rate of halogenation, implying that a common intermediate is involved in both processes.



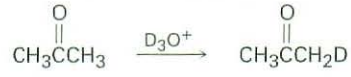
Enol

α-Bromo ketones are useful in the laboratory because they can be dehydrobrominated by base treatment to yield α,β-unsaturated ketones. For example, 2-methylcyclohexanone gives 2-bromo-2-methylcyclohexanone on halogenation, and the α-bromo ketone gives 2-methyl-2-cyclohexenone when heated in pyridine. The reaction takes place by an E2 elimination pathway (Section 11.8) and is a good method for introducing C=C bonds into molecules. Note that bromination of 2-methylcyclohexanone occurs primarily on the more highly substituted α position because the more highly substituted enol is favored over the less highly substituted one (Section 6.6).



2-Methylcyclohexanone → **2-Bromo-2-methylcyclohexanone** → **2-Methyl-2-cyclohexenone (63%)**

Problem 22.4 Write the complete mechanism of the deuteration of acetone on treatment with D_3O^+.



Problem 22.5 Show how you might prepare 1-penten-3-one from 3-pentanone.

22.4 Alpha Bromination of Carboxylic Acids: The Hell–Volhard–Zelinskii Reaction

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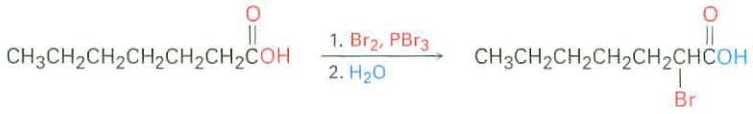
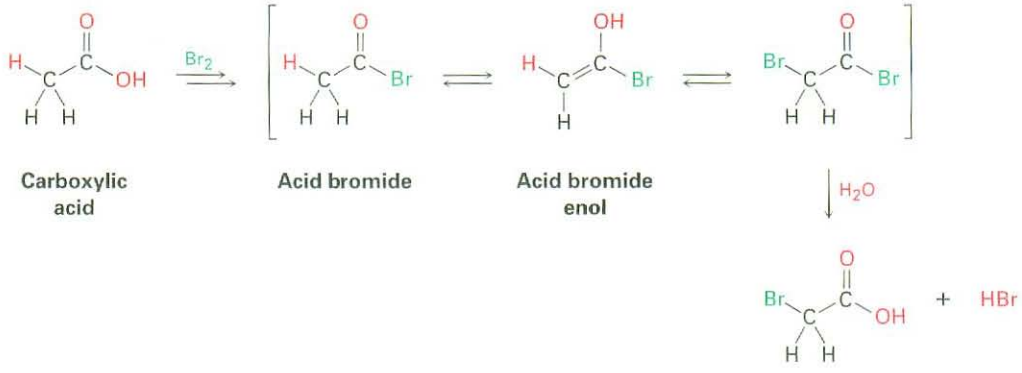
The α bromination of carbonyl compounds by Br_2 in acetic acid is limited to aldehydes and ketones because acids, esters, and amides don't enolize to a sufficient extent. Carboxylic acids, however, can be α brominated by a mixture of Br_2 and PBr_3 in the **Hell–Volhard–Zelinskii (HVZ) reaction**.



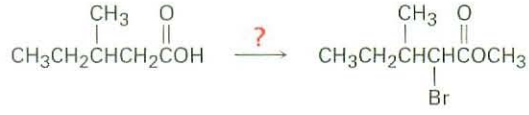
Heptanoic acid **2-Bromoheptanoic acid (90%)**

The Hell–Volhard–Zelinskii reaction is a bit more complex than it looks and actually involves α substitution of an *acid bromide enol* rather than a carboxylic acid enol. The process begins with reaction of the carboxylic acid with PBr_3 to form an acid bromide plus HBr (Section 21.4). The HBr then catalyzes enolization of the acid bromide, and the resultant enol reacts with Br_2 in an α-substitution reaction to give an α-bromo acid bromide. Addition of water hydrolyzes the acid bromide in a nucleophilic acyl substitution reaction and yields the α-bromo carboxylic acid product.



Carboxylic acid **Acid bromide** **Acid bromide enol**

Problem 22.6 If methanol rather than water is added at the end of a Hell–Volhard–Zelinskii reaction, an ester rather than an acid is produced. Show how you could carry out the following transformation, and propose a mechanism for the ester-forming step.



22.5 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

As noted in Section 22.1, a hydrogen on the α position of a carbonyl compound is weakly acidic and can be removed by a strong base to yield an enolate ion. In comparing acetone ($pK_a = 19.3$) with ethane ($pK_a \approx 60$), for instance, the

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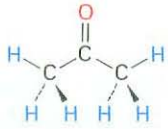
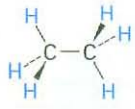
presence of a neighboring carbonyl group increases the acidity of the ketone over the alkane by a factor of 10^{40}.



Acetone
($pK_a = 19.3$)



Ethane
($pK_a \approx 60$)

Abstraction of a proton from a carbonyl compound occurs when the α C–H bond is oriented roughly parallel to the p orbitals of the carbonyl group. The α carbon atom of the enolate ion is sp^2-hybridized and has a p orbital that overlaps the neighboring carbonyl p orbitals. Thus, the negative charge is shared by the electronegative oxygen atom, and the enolate ion is stabilized by resonance (Figure 22.5).

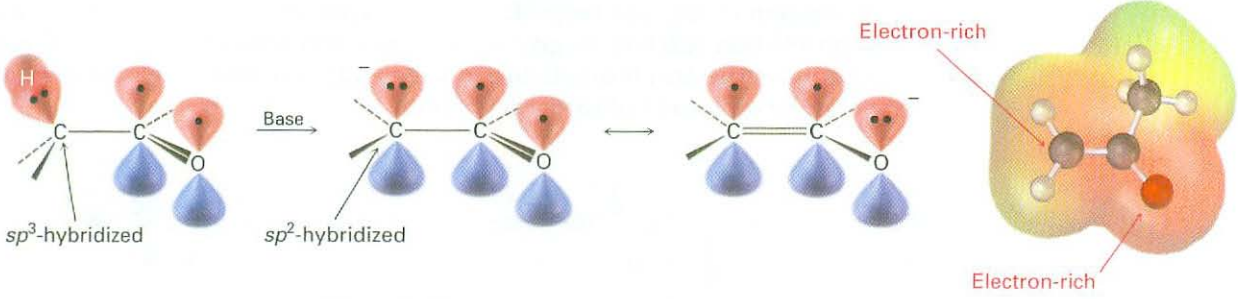
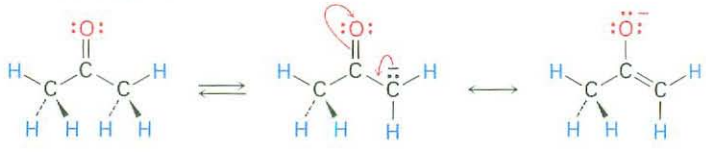


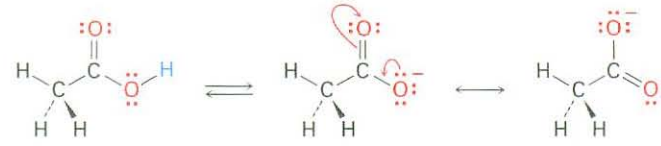
Figure 22.5 Mechanism of enolate ion formation by abstraction of an α proton from a carbonyl compound. The enolate ion is stabilized by resonance, and the negative charge (red) is shared by the oxygen and the α carbon atom, as indicated by the electrostatic potential map.

Carbonyl compounds are more acidic than alkanes for the same reason that carboxylic acids are more acidic than alcohols (Section 20.2). In both cases, the anions are stabilized by resonance. Enolate ions differ from carboxylate ions, however, in that their two resonance forms are not equivalent—the form with the negative charge on oxygen is lower in energy than the form with the charge on carbon. Nevertheless, the principle behind resonance stabilization is the same in both cases.



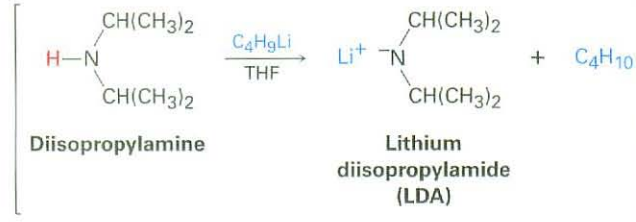
Acetone
($pK_a = 19.3$)

Nonequivalent resonance forms

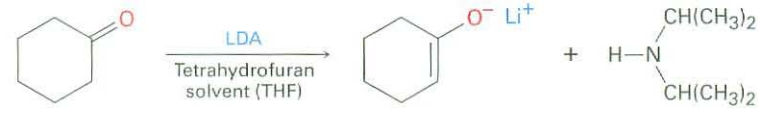


Acetic acid ($pK_a = 4.76$) **Equivalent resonance forms**

Because carbonyl compounds are only weakly acidic, a strong base is needed for enolate ion formation. If an alkoxide such as sodium ethoxide is used as base, deprotonation takes place only to the extent of about 0.1% because acetone is a weaker acid than ethanol ($pK_a = 16$). If, however, a more powerful base such as sodium hydride (NaH) or lithium diisopropylamide [$LiN(i\text{-}C_3H_7)_2$] is used, a carbonyl compound can be completely converted into its enolate ion. Lithium diisopropylamide (LDA), which is easily prepared by reaction of the strong base butyllithium with diisopropylamine, is widely used in the laboratory as a base for preparing enolate ions from carbonyl compounds.



Diisopropylamine **Lithium diisopropylamide (LDA)**

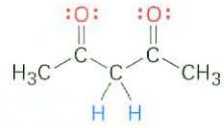


Cyclohexanone **Cyclohexanone enolate ion** **Diisopropylamine**

Many types of carbonyl compounds, including aldehydes, ketones, esters, thioesters, acids, and amides, can be converted into enolate ions by reaction with LDA. Table 22.1 lists the approximate pK_a values of different types of carbonyl compounds and shows how these values compare to other acidic substances we've seen. Note that nitriles, too, are acidic and can be converted into enolate-like anions.

When a hydrogen atom is flanked by two carbonyl groups, its acidity is enhanced even more. Table 22.1 thus shows that compounds such as 1,3-diketones (β-diketones), 3-oxo esters (β-keto esters), and 1,3-diesters are more acidic than water. This enhanced acidity of β-dicarbonyl compounds is due to the stabilization of the resultant enolate ions by delocalization of the negative charge over both carbonyl groups. The enolate ion of 2,4-pentanedione, for instance,

has three resonance forms. Similar resonance forms can be drawn for other doubly stabilized enolate ions.



2,4-Pentanedione ($pK_a = 9$)

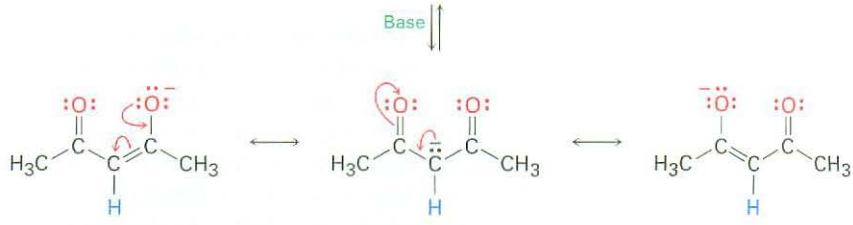
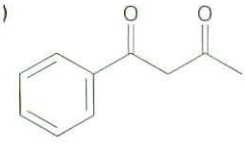


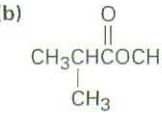
Table 22.1 Acidity Constants for Some Organic Compounds

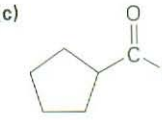
Functional group	Example	pK_a
Carboxylic acid	CH_3COH	5
1,3-Diketone	$CH_3CCH_2CCH_3$	9
3-Keto ester	$CH_3CCH_2COCH_3$	11
1,3-Diester	$CH_3OCCH_2COCH_3$	13
Alcohol	CH_3OH	16
Acid chloride	CH_3CCl	16
Aldehyde	CH_3CH	17
Ketone	CH_3CCH_3	19
Thioester	CH_3CSCH_3	21
Ester	CH_3COCH_3	25
Nitrile	$CH_3C{\equiv}N$	25
N,N-Dialkylamide	$CH_3CN(CH_3)_2$	30
Dialkylamine	$HN(i\text{-}C_3H_7)_2$	40

WORKED EXAMPLE 22.1 ***Identifying the Acidic Hydrogens in a Compound***

Identify the most acidic hydrogens in each of the following compounds, and rank the compounds in order of increasing acidity:

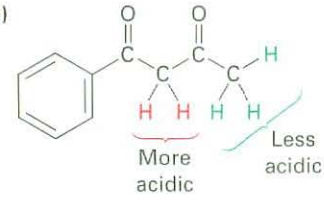
(a) 

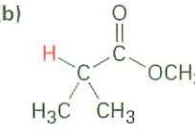
(b) 

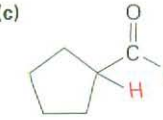
(c) 

Strategy Hydrogens on carbon next to a carbonyl group are acidic. In general, a β-dicarbonyl compound is most acidic, a ketone or aldehyde is next most acidic, and a carboxylic acid derivative is least acidic. Remember that alcohols, phenols, and carboxylic acids are also acidic because of their –OH hydrogens.

Solution The acidity order is (a) > (c) > (b). Acidic hydrogens are shown in red.

(a) 

(b) 

(c) 

Problem 22.7 Identify the most acidic hydrogens in each of the following molecules:

(a) CH_3CH_2CHO (b) $(CH_3)_3CCOCH_3$ (c) CH_3CO_2H

(d) Benzamide (e) $CH_3CH_2CH_2CN$ (f) $CH_3CON(CH_3)_2$

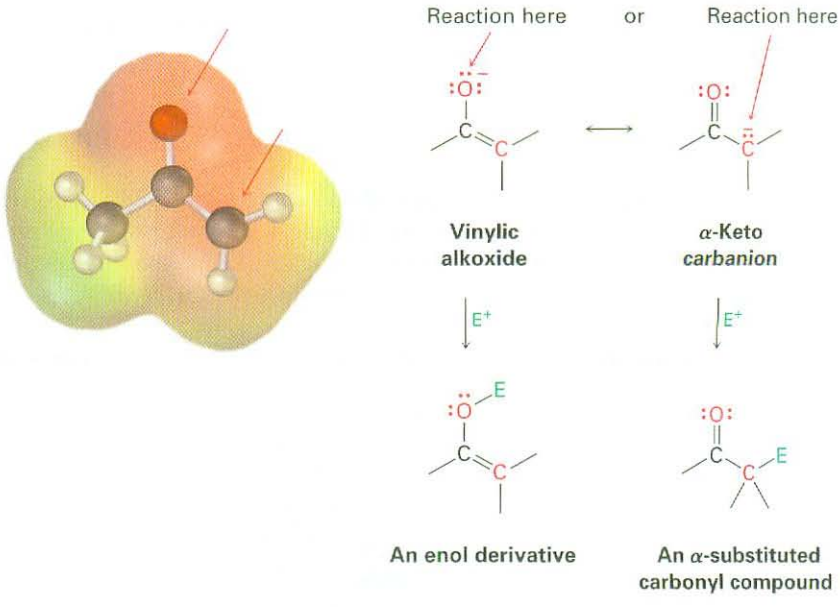
Problem 22.8 Draw a resonance structure of the acetonitrile anion, $^-:CH_2C{\equiv}N$, and account for the acidity of nitriles.

22.6 Reactivity of Enolate Ions

Enolate ions are more useful than enols for two reasons. First, pure enols can't normally be isolated but are instead generated only as short-lived intermediates in low concentration. By contrast, stable solutions of pure enolate ions are easily prepared from most carbonyl compounds by reaction with a strong base. Second, enolate ions are more reactive than enols and undergo many reactions that enols don't. Whereas enols are neutral, enolate ions are negatively charged, making them much better nucleophiles. As a result, enolate ions are more common than enols in both laboratory and biological chemistry.

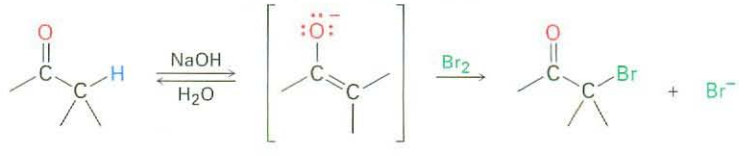
Because they are resonance hybrids of two nonequivalent forms, enolate ions can be looked at either as vinylic alkoxides (C=C–O$^-$) or as α-keto

carbanions ($^-C-C=O$). Thus, enolate ions can react with electrophiles either on oxygen or on carbon. Reaction on oxygen yields an enol derivative, while reaction on carbon yields an α-substituted carbonyl compound (Figure 22.6). Both kinds of reactivity are known, but reaction on carbon is more common.



Active Figure 22.6 The electrostatic potential map of acetone enolate ion shows how the negative charge is delocalized over both the oxygen and the α carbon. As a result, two modes of reaction of an enolate ion with an electrophile E^+ are possible. Reaction on carbon to yield an α-substituted carbonyl product is more common. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

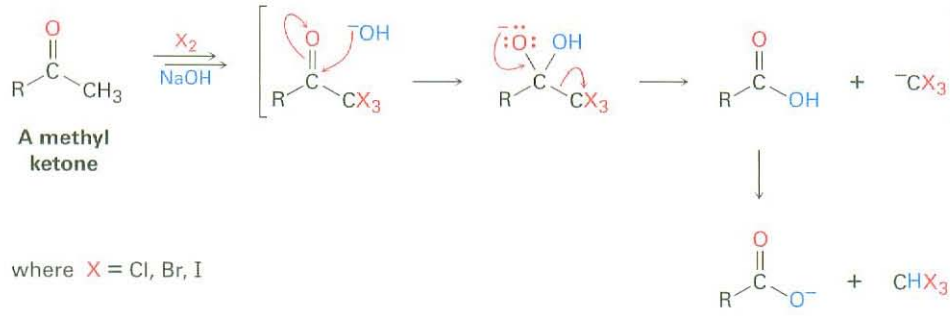
As an example of enolate-ion reactivity, aldehydes and ketones undergo base-promoted α halogenation. Even relatively weak bases such as hydroxide ion are effective for halogenation because it's not necessary to convert the ketone completely into its enolate ion. As soon as a small amount of enolate is generated, it reacts immediately with the halogen, removing it from the reaction and driving the equilibrium for further enolate ion formation.



Base-promoted halogenation of aldehydes and ketones is little used in practice because it's difficult to stop the reaction at the monosubstituted product. An α-halogenated ketone is generally more acidic than the starting, unsubstituted ketone because of the electron-withdrawing inductive effect of the halogen atom. Thus, the monohalogenated products are themselves rapidly turned into enolate ions and further halogenated.

If excess base and halogen are used, a methyl ketone is triply halogenated and then cleaved by base in the *haloform reaction*. The products are a carboxylic acid plus a so-called haloform (chloroform, $CHCl_3$; bromoform,

$CHBr_3$; or iodoform, CHI_3). Note that the second step of the reaction is a nucleophilic acyl substitution of $^-CX_3$ by ^-OH. That is, a halogen-stabilized *carbanion* acts as a leaving group.

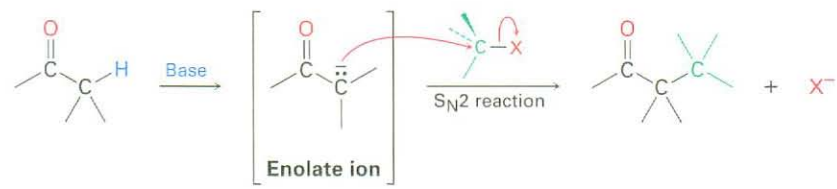


Problem 22.9 Why do you suppose ketone halogenations in acidic media referred to as being acid-*catalyzed*, whereas halogenations in basic media are base-*promoted*? In other words, why is a full equivalent of base required for halogenation?

22.7 Alkylation of Enolate Ions

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products in halogenation and alkylation reactions of carbonyl enolates.**

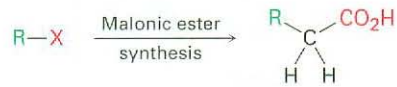
Perhaps the single most important reaction of enolate ions is their *alkylation* by treatment with an alkyl halide or tosylate, thereby forming a new C–C bond and joining two smaller pieces into one larger molecule. Alkylation occurs when the nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction and displaces the leaving group by backside attack.



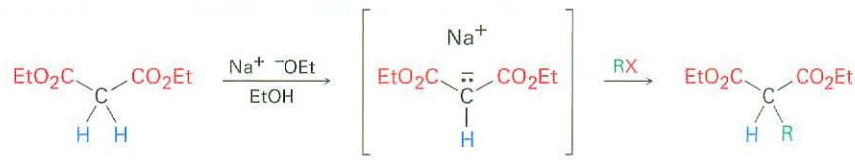
Alkylation reactions are subject to the same constraints that affect all S_N2 reactions (Section 11.3). Thus, the leaving group X in the alkylating agent R–X can be chloride, bromide, iodide, or tosylate. The alkyl group R should be primary or methyl, and preferably should be allylic or benzylic. Secondary halides react poorly, and tertiary halides don't react at all because a competing E2 elimination of HX occurs instead. Vinylic and aryl halides are also unreactive because backside approach is sterically prevented.

The Malonic Ester Synthesis

One of the oldest and best known carbonyl alkylation reactions is the **malonic ester synthesis**, a method for preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms.

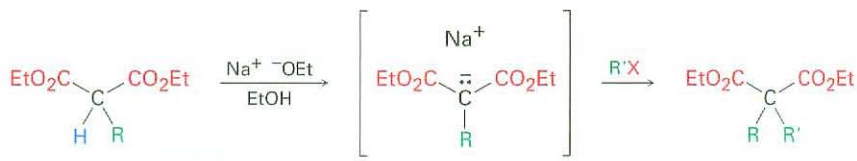


Diethyl propanedioate, commonly called diethyl malonate or *malonic ester*, is more acidic than monocarbonyl compounds ($pK_a = 13$) because its α hydrogens are flanked by two carbonyl groups. Thus, malonic ester is easily converted into its enolate ion by reaction with sodium ethoxide in ethanol. The enolate ion, in turn, is a good nucleophile that reacts rapidly with an alkyl halide to give an α-substituted malonic ester. Note in the following examples that the abbreviation "Et" is used for an ethyl group, $-CH_2CH_3$.



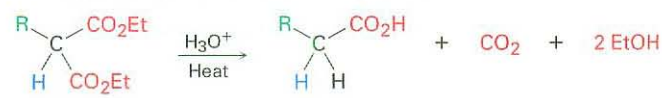
Diethyl propanedioate (malonic ester) **Sodio malonic ester** **An alkylated malonic ester**

The product of malonic ester alkylation has one acidic α hydrogen atom left, so the alkylation process can be repeated a second time to yield a dialkylated malonic ester.



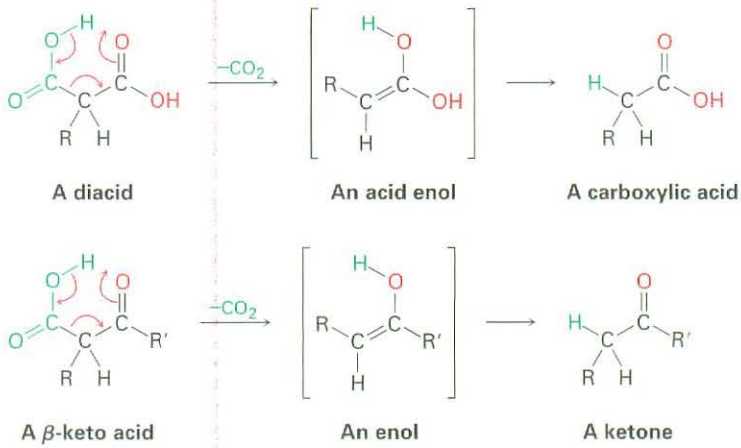
An alkylated malonic ester **A dialkylated malonic ester**

On heating with aqueous hydrochloric acid, the alkylated (or dialkylated) malonic ester undergoes hydrolysis of its two ester groups followed by *decarboxylation* (loss of CO_2) to yield a substituted monoacid.

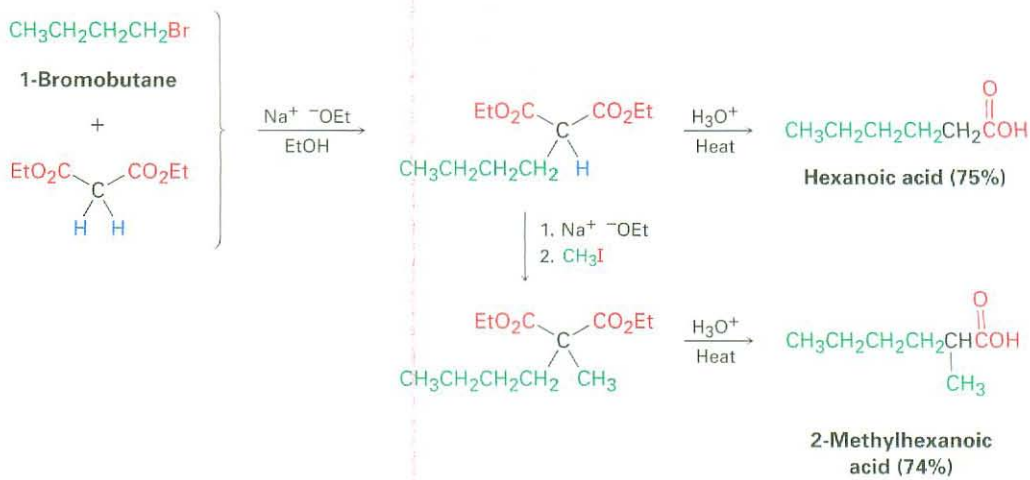


An alkylated malonic ester **A carboxylic acid**

Decarboxylation is not a general reaction of carboxylic acids. Rather, it is unique to compounds that have a *second* carbonyl group two atoms away from the $-CO_2H$. That is, only substituted malonic acids and β-keto acids undergo loss of CO_2 on heating. The decarboxylation reaction occurs by a cyclic mechanism and involves initial formation of an enol, thereby accounting for the need to have a second carbonyl group appropriately positioned.

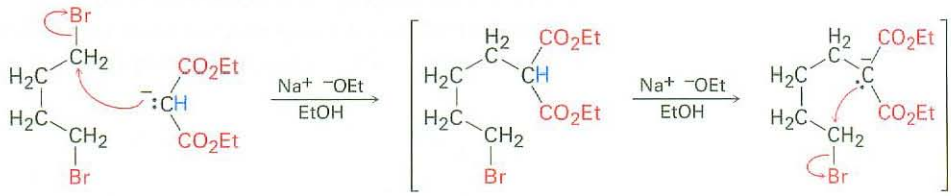


As noted previously, the overall effect of the malonic ester synthesis is to convert an alkyl halide into a carboxylic acid while lengthening the carbon chain by two atoms.

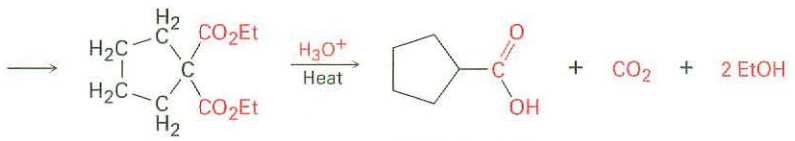


The malonic ester synthesis can also be used to prepare *cyclo*alkanecarboxylic acids. For example, when 1,4-dibromobutane is treated with diethyl malonate in the presence of 2 equivalents of sodium ethoxide base, the second alkylation step occurs *intramolecularly* to yield a cyclic product. Hydrolysis and decarboxylation then give cyclopentanecarboxylic acid. Three-, four-, five-,

and six-membered rings can be prepared in this way, but yields decrease for larger ring sizes.



1,4-Dibromobutane



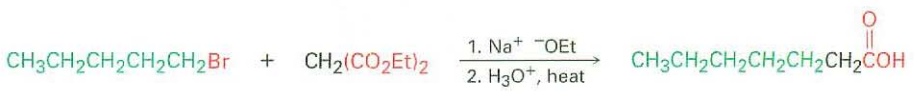
Cyclopentane-carboxylic acid

WORKED EXAMPLE 22.2 *Using the Malonic Ester Synthesis to Prepare a Carboxylic Acid*

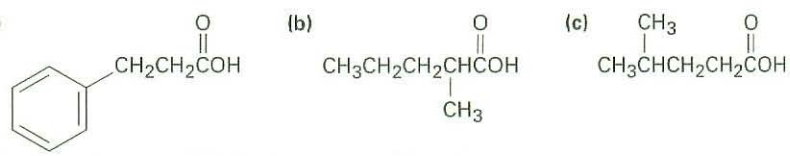
How would you prepare heptanoic acid using a malonic ester synthesis?

Strategy The malonic ester synthesis converts an alkyl halide into a carboxylic acid having two more carbons. Thus, a *seven*-carbon acid chain must be derived from the *five*-carbon alkyl halide 1-bromopentane.

Solution

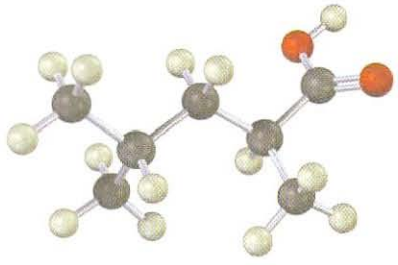


Problem 22.10 How could you use a malonic ester synthesis to prepare the following compounds? Show all steps.



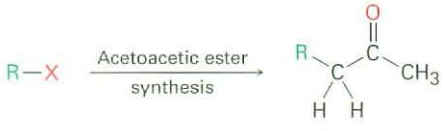
Problem 22.11 Monoalkylated and dialkylated acetic acids can be prepared by the malonic ester synthesis, but trialkylated acetic acids (R_3CCO_2H) can't be prepared. Explain.

Problem 22.12 How could you use a malonic ester synthesis to prepare the following compound?

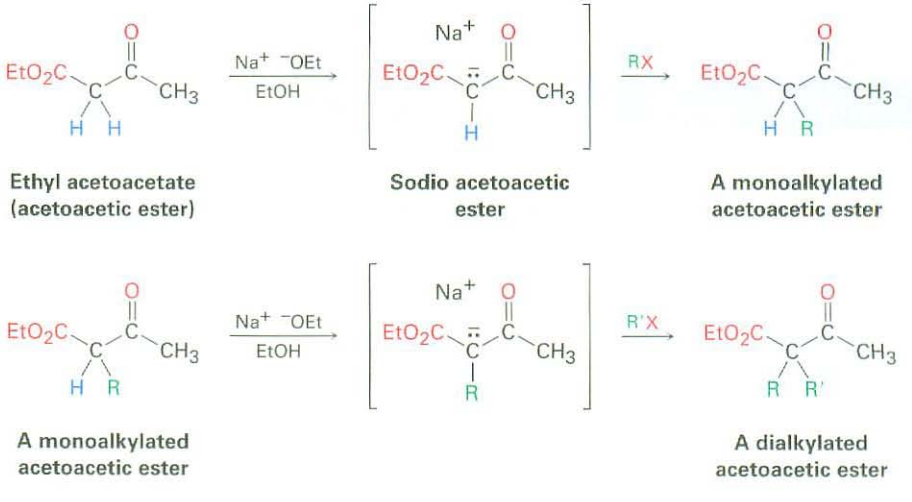


The Acetoacetic Ester Synthesis

Just as the malonic ester synthesis converts an alkyl halide into a carboxylic acid, the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone having three more carbons.

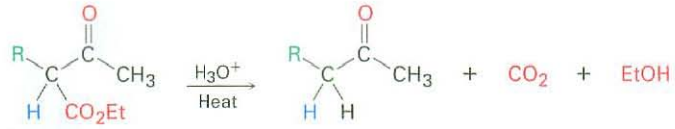


Ethyl 3-oxobutanoate, commonly called ethyl acetoacetate or *acetoacetic ester,* is much like malonic ester in that its α hydrogens are flanked by two carbonyl groups. It is therefore readily converted into its enolate ion, which can be alkylated by reaction with an alkyl halide. A second alkylation can also be carried out if desired, since acetoacetic ester has two acidic α hydrogens.



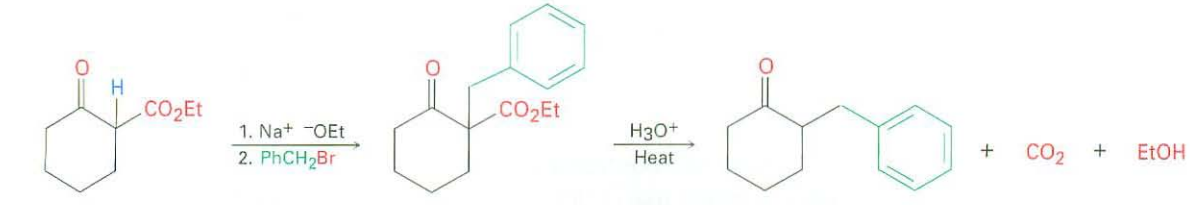
On heating with aqueous HCl, the alkylated (or dialkylated) acetoacetic ester is hydrolyzed to a β-keto acid, which then undergoes decarboxylation to

yield a ketone product. The decarboxylation occurs in the same way as in the malonic ester synthesis and involves a ketone enol as the initial product.



An alkylated acetoacetic ester **A methyl ketone**

The three-step sequence of (1) enolate ion formation, (2) alkylation, and (3) hydrolysis/decarboxylation is applicable to all β-keto esters with acidic α hydrogens, not just to acetoacetic ester itself. For example, *cyclic* β-keto esters such as ethyl 2-oxocyclohexanecarboxylate can be alkylated and decarboxylated to give 2-substituted cyclohexanones.



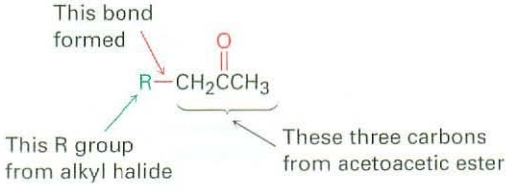
Ethyl 2-oxocyclohexane-carboxylate (a cyclic β-keto ester)

2-Benzylcyclohexanone (77%)

WORKED EXAMPLE 22.3 *Using the Acetoacetic Ester Synthesis to Prepare a Ketone*

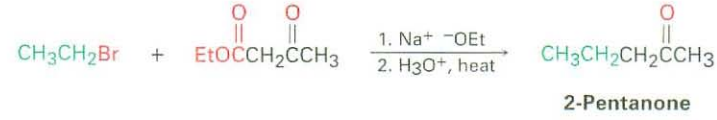
How would you prepare 2-pentanone by an acetoacetic ester synthesis?

Strategy The acetoacetic ester synthesis yields a methyl ketone by adding three carbons to an alkyl halide.

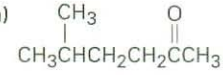


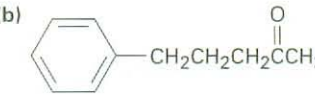
Thus, the acetoacetic ester synthesis of 2-pentanone must involve reaction of bromoethane.

Solution



Problem 22.13 What alkyl halides would you use to prepare the following ketones by an acetoacetic ester synthesis?

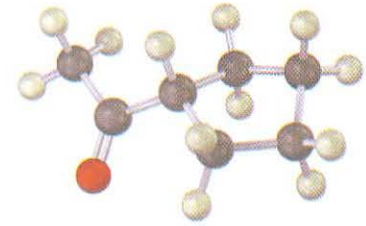
(a) 

(b) 

Problem 22.14 Which of the following compounds *cannot* be prepared by an acetoacetic ester synthesis? Explain.

(a) Phenylacetone (b) Acetophenone (c) 3,3-Dimethyl-2-butanone

Problem 22.15 How would you prepare the following compound using an acetoacetic ester synthesis?

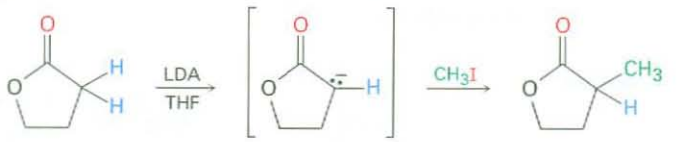


Direct Alkylation of Ketones, Esters, and Nitriles

Both the malonic ester synthesis and the acetoacetic ester synthesis are easy to carry out because they involve unusually acidic dicarbonyl compounds. As a result, relatively mild bases such as sodium ethoxide in ethanol as solvent can be used to prepare the necessary enolate ions. Alternatively, however, it's also possible in many cases to directly alkylate the α position of *mono*carbonyl compounds. A strong, sterically hindered base such as LDA is needed so that complete conversion to the enolate ion takes place rather than a nucleophilic addition, and a nonprotic solvent must be used.

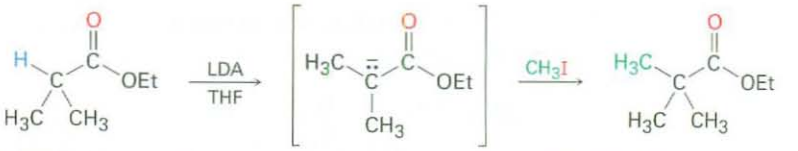
Ketones, esters, and nitriles can all be alkylated using LDA or related dialkylamide bases in THF. Aldehydes, however, rarely give high yields of pure products because their enolate ions undergo carbonyl condensation reactions instead of alkylation. (We'll study this condensation reaction in the next chapter.) Some specific examples of alkylation reactions are shown.

Lactone



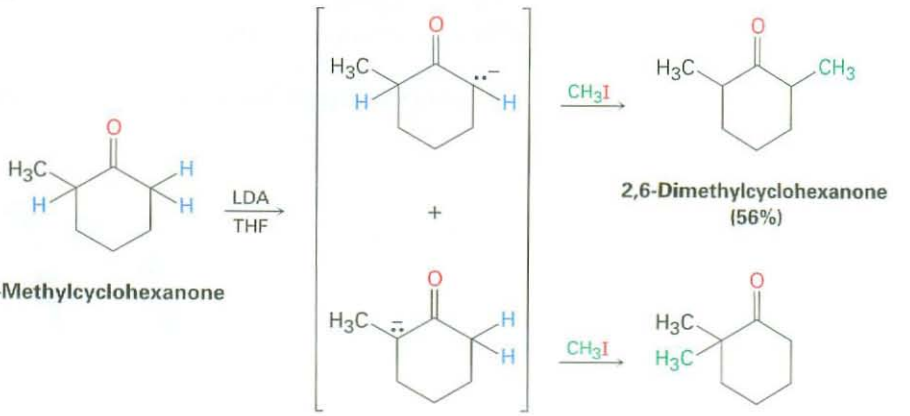
Butyrolactone — 2-Methylbutyrolactone (88%)

Ester



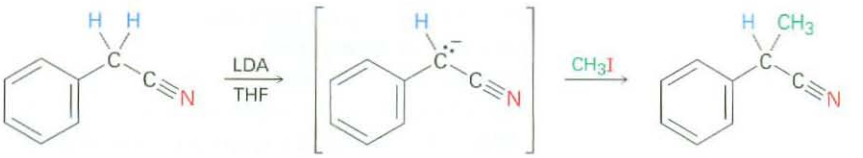
Ethyl 2-methylpropanoate — Ethyl 2,2-dimethylpropanoate (87%)

Ketone



2-Methylcyclohexanone — 2,6-Dimethylcyclohexanone (56%) — 2,2-Dimethylcyclohexanone (6%)

Nitrile

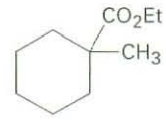


Phenylacetonitrile — 2-Phenylpropane-nitrile (71%)

Note in the ketone example that alkylation of 2-methylcyclohexanone leads to a mixture of products because both possible enolate ions are formed. In general, the major product in such cases occurs by alkylation at the less hindered, more accessible position. Thus, alkylation of 2-methylcyclohexanone occurs primarily at C6 (secondary) rather than C2 (tertiary).

WORKED EXAMPLE 22.4 ***Using an Alkylation Reaction to Prepare a Substituted Ester***

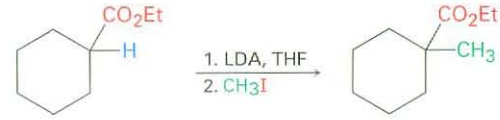
How might you use an alkylation reaction to prepare ethyl 1-methylcyclohexanecarboxylate?



Ethyl 1-methylcyclohexanecarboxylate

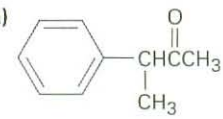
Strategy An alkylation reaction is used to introduce a methyl or primary alkyl group onto the α position of a ketone, ester, or nitrile by S_N2 reaction of an enolate ion with an alkyl halide. Thus, we need to look at the target molecule and identify any methyl or primary alkyl groups attached to an α carbon. In the present instance, the target has an α methyl group, which might be introduced by alkylation of an ester enolate ion with iodomethane.

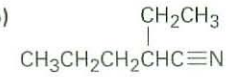
Solution

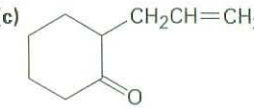


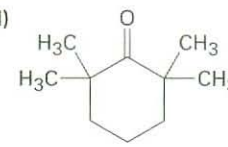
Ethyl cyclohexanecarboxylate **Ethyl 1-methylcyclohexanecarboxylate**

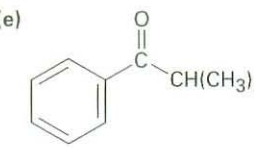
Problem 22.16 How might you prepare the following compounds using an alkylation reaction as the key step?

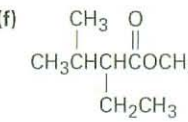
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Biological Alkylations

Alkylations are rare but not unknown in biological chemistry. One example occurs during biosynthesis of the antibiotic indolmycin from indolylpyruvate when a base abstracts an acidic hydrogen from an α position and the resultant enolate ion carries out an S_N2 alkylation reaction on the methyl group of *S*-adenosylmethionine (SAM; Section 11.6). Although it's convenient to speak of "enolate ion" intermediates in biological pathways, it's unlikely that they exist for long in an aqueous cellular environment. Rather, proton removal and alkylation probably occur at essentially the same time (Figure 22.7).

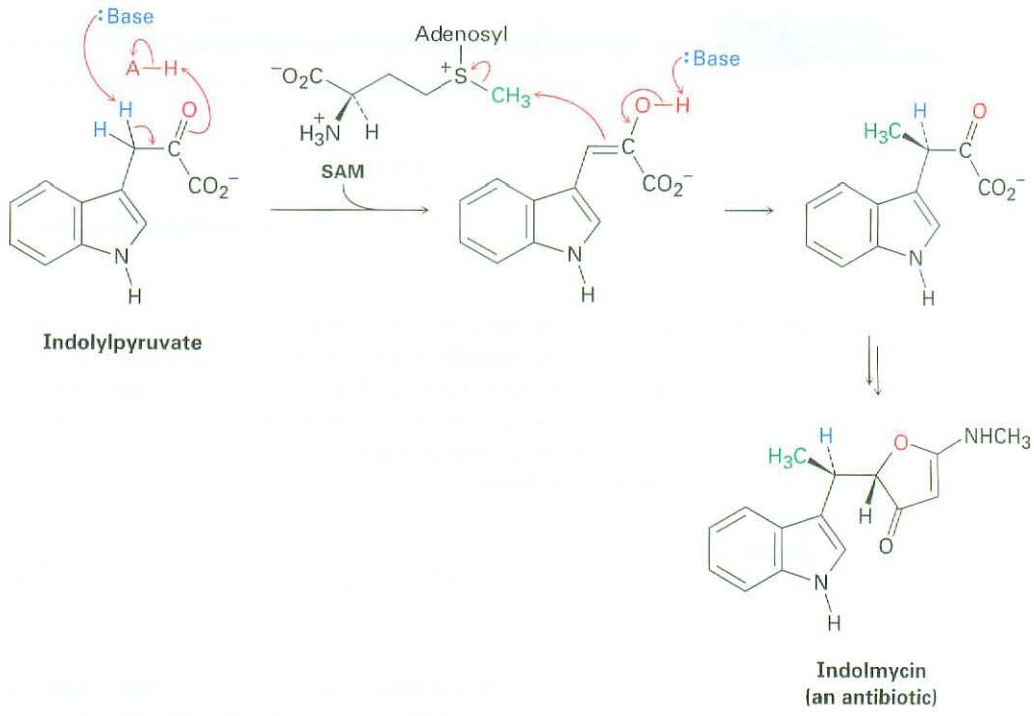


Figure 22.7 The biosynthesis of indolmycin from indolylpyruvate occurs through a pathway that includes an alkylation reaction of a short-lived enolate ion intermediate.

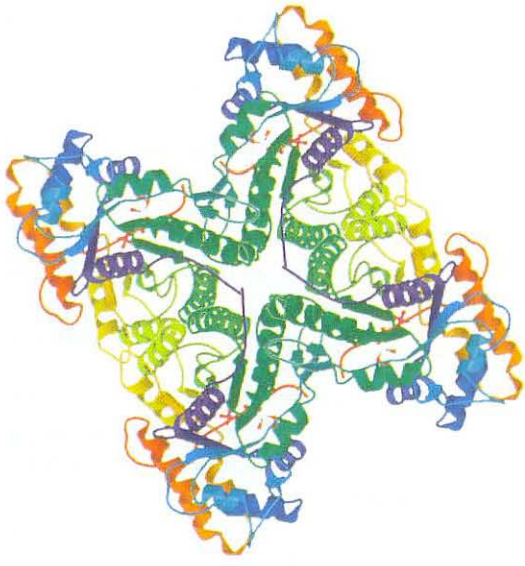
Focus On . . .

X-Ray Crystallography

Determining the three-dimensional shape of an object around you is easy—you just look at it, let your eyes focus the light rays reflected from the object, and let your brain assemble the data into a recognizable image. If the object is small, you use a microscope and let the microscope lens focus the visible light. Unfortunately, there is a limit to what you can see, even with the best optical microscope. Called the "diffraction limit," you can't see anything smaller than the wavelength of light you are using for the observation. Visible light has wavelengths of several hundred nanometers, but atoms in molecules have dimension on the order of 0.1 nm. Thus, to "see" a molecule—whether a small one in the laboratory or a large, complex enzyme with a molecular weight in the tens of thousands—you need wavelengths in the 0.1 nm range, which corresponds to X rays.

Let's say that we want to determine the structure and shape of an enzyme or other biological molecule. The technique used is called *X-ray crystallography*.

(continued)



The structure of human muscle fructose-1,6-bisphosphate aldolase, as determined by X-ray crystallography and downloaded from the Protein Data Bank. (PDB ID: 1ALD; Gamblin, S. J., Davies, G. J., Grimes, J. M., Jackson, R. M., Littlechild, J. A., Watson, H. C. Activity and specificity of human aldolases. *J. Mol. Biol.* v219, pp. 573–576, 1991.)

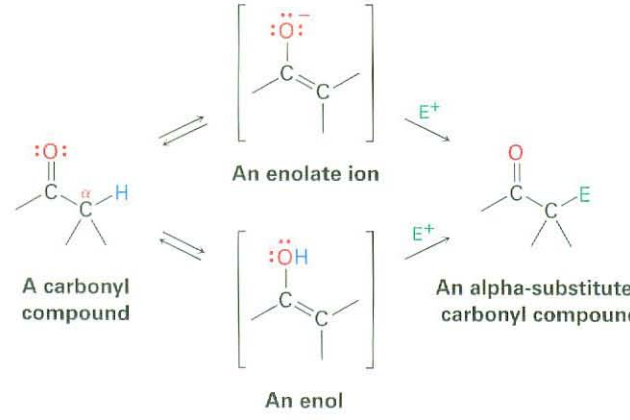
First, the molecule is crystallized (which often turns out to be the most difficult and time-consuming part of the entire process) and a small crystal with a dimension of 0.4 to 0.5 mm on its longest axis is glued to the end of a glass fiber. The fiber and attached crystal are then mounted in an instrument called an *X-ray diffractometer,* consisting of a radiation source, a sample positioning and orienting device that can rotate the crystal in any direction, a detector, and a controlling computer.

Once mounted in the diffractometer, the crystal is irradiated with X rays, usually so-called Cu$K\alpha$ radiation with a wavelength of 0.154 nm. When the X rays strike the enzyme crystal, they interact with electrons in the molecule and are scattered into a diffraction pattern, which, when detected and visualized, appears as a series of intense spots against a null background.

Manipulation of the diffraction pattern to extract three-dimensional molecular data is a complex process, but the final result is that an electron-density map of the molecule is produced. Because electrons are largely localized around atoms, any two centers of electron density located within bonding distance of each other are assumed to represent bonded atoms, leading to a recognizable chemical structure. So important is this structural information for biochemistry that an online database of more than 40,000 biological substances has been created. Operated by Rutgers University and funded by the U.S. National Science Foundation, the Protein Data Bank (PDB) is a worldwide repository for processing and distributing three-dimensional structural data for biological macromolecules. We'll see how to access the PDB in the Chapter 26 *Focus On.*

SUMMARY AND KEY WORDS

The **α-substitution reaction** of a carbonyl compound through either an **enol** or **enolate ion** intermediate is one of the four fundamental reaction types in carbonyl-group chemistry.

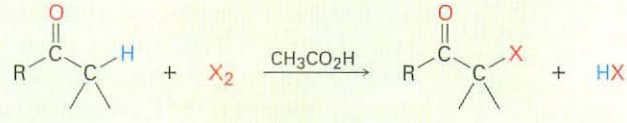


Carbonyl compounds are in a rapid equilibrium with their enols, a process called keto–enol tautomerism. Although enol **tautomers** are normally present to only a small extent at equilibrium and can't usually be isolated in pure form, they nevertheless contain a highly nucleophilic double bond and react with electrophiles. For example, aldehydes and ketones are rapidly halogenated at the α position by reaction with Cl_2, Br_2, or I_2 in acetic acid solution. Alpha bromination of carboxylic acids can be similarly accomplished by the **Hell–Volhard–Zelinskii (HVZ) reaction**, in which an acid is treated with Br_2 and PBr_3. The α-halogenated products can then undergo base-induced E2 elimination to yield α,β-unsaturated carbonyl compounds.

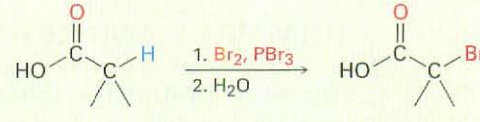
Alpha hydrogen atoms of carbonyl compounds are weakly acidic and can be removed by strong bases, such as lithium diisopropylamide (LDA), to yield nucleophilic enolate ions. The most important reaction of enolate ions is their S_N2 alkylation with alkyl halides. The **malonic ester synthesis** converts an alkyl halide into a carboxylic acid with the addition of two carbon atoms. Similarly, the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone. In addition, many carbonyl compounds, including ketones, esters, and nitriles, can be directly alkylated by treatment with LDA and an alkyl halide.

SUMMARY OF REACTIONS

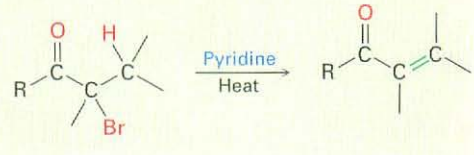
1. Aldehyde/ketone halogenation (Section 22.3)



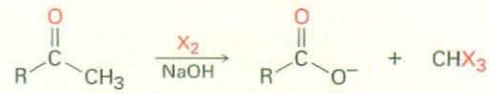
2. Hell–Volhard–Zelinskii bromination of acids (Section 22.4)



3. Dehydrobromination of α-bromo ketones (Section 22.3)

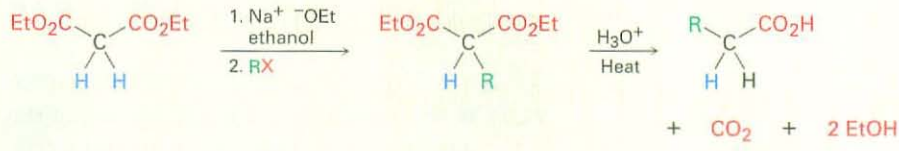


4. Haloform reaction (Section 22.6)

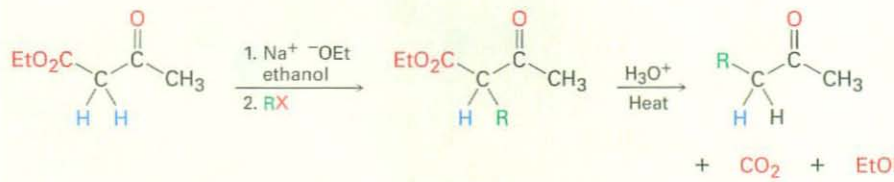


5. Alkylation of enolate ions (Section 22.7)

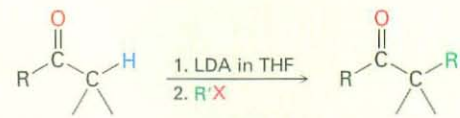
(a) Malonic ester synthesis



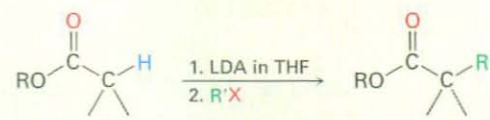
(b) Acetoacetic ester synthesis



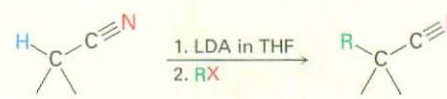
(c) Direct alkylation of ketones



(d) Direct alkylation of esters



(e) Direct alkylation of nitriles



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.

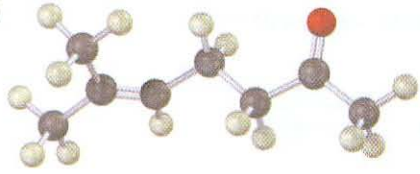
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

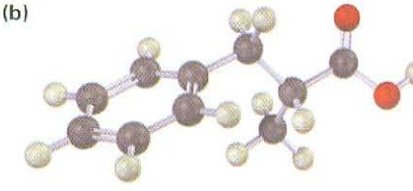
(Problems 22.1–22.16 appear within the chapter.)

22.17 ■ Show the steps in preparing each of the following substances, using either a malonic ester synthesis or an acetoacetic ester synthesis:

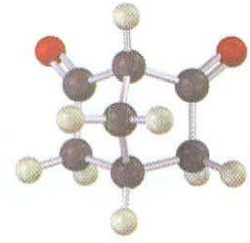
(a)



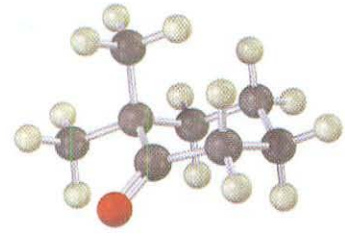
(b)



22.18 Unlike most β-diketones, the following β-diketone has no detectable enol content and is about as acidic as acetone. Explain.

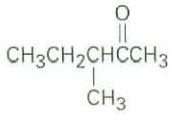


22.19 ■ For a given α hydrogen atom to be acidic, the C–H bond must be parallel to the *p* orbitals of the C=O bond (that is, perpendicular to the plane of the adjacent carbonyl group). Identify the most acidic hydrogen atom in the conformation shown for the following structure. Is it axial or equatorial?

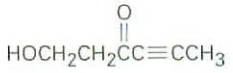


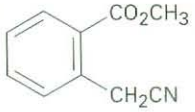
ADDITIONAL PROBLEMS

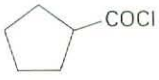
22.20 ■ Identify all the acidic hydrogens ($pK_a < 25$) in the following molecules:

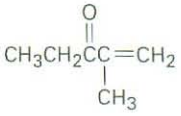
(a) 

(b) 

(c) 

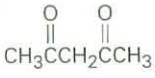
(d) 

(e) 

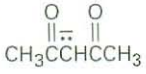
(f) 

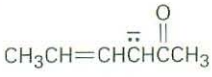
22.21 ■ Rank the following compounds in order of increasing acidity:

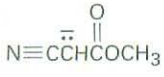
(a) $CH_3CH_2CO_2H$ (b) CH_3CH_2OH (c) $(CH_3CH_2)_2NH$

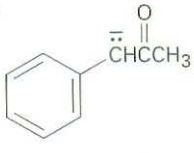
(d) CH_3COCH_3 (e)  (f) CCl_3CO_2H

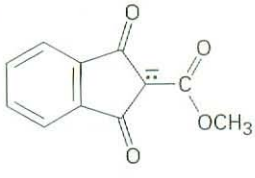
22.22 ■ Write resonance structures for the following anions:

(a) 

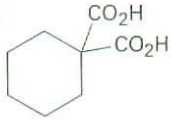
(b) 

(c) 

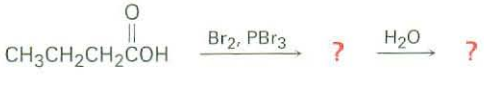
(d) 

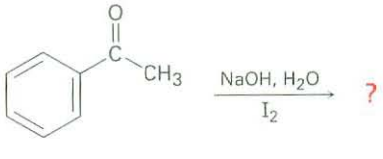
(e) 

22.23 ■ Predict the product(s) of the following reactions:

(a) 

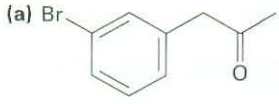
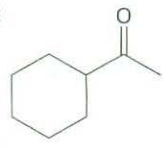
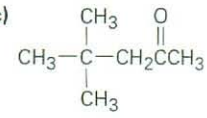
(b) 

(c) 

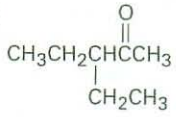
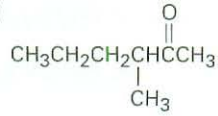
(d) 

22.24 ■ Which, if any, of the following compounds can be prepared by a malonic ester synthesis? Show the alkyl halide you would use in each case.
(a) Ethyl pentanoate (b) Ethyl 3-methylbutanoate
(c) Ethyl 2-methylbutanoate (d) Ethyl 2,2-dimethylpropanoate

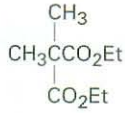
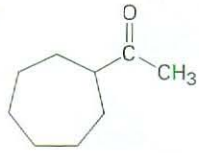
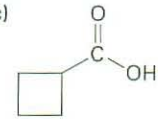
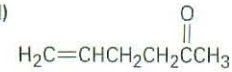
22.25 ■ Which, if any, of the following compounds can be prepared by an acetoacetic ester synthesis? Explain.

(a) 
(b) 
(c) 

22.26 ■ How would you prepare the following ketones using an acetoacetic ester synthesis?

(a) 
(b) 

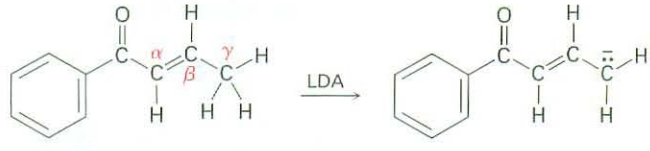
22.27 ■ How would you prepare the following compounds using either an acetoacetic ester synthesis or a malonic ester synthesis?

(a) 
(b) 
(c) 
(d) 

22.28 ■ Which of the following substances would undergo the haloform reaction?
(a) CH_3COCH_3 (b) Acetophenone (c) CH_3CH_2CHO
(d) CH_3CO_2H (e) $CH_3C{\equiv}N$

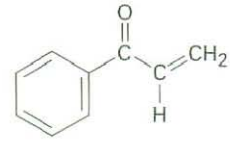
22.29 ■ One way to determine the number of acidic hydrogens in a molecule is to treat the compound with NaOD in D_2O, isolate the product, and determine its molecular weight by mass spectrometry. For example, if cyclohexanone is treated with NaOD in D_2O, the product has MW = 102. Explain how this method works.

22.30 Base treatment of the following α,β-unsaturated carbonyl compound yields an anion by removal of H^+ from the γ carbon. Why are hydrogens on the γ carbon atom acidic?



■ Assignable in OWL

22.31 Treatment of 1-phenyl-2-propenone with a strong base such as LDA does not yield an anion, even though it contains a hydrogen on the carbon atom next to the carbonyl group. Explain.



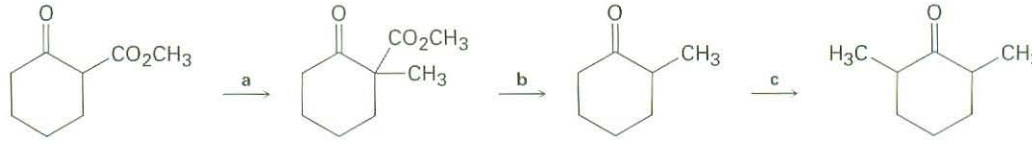
1-Phenyl-2-propenone

22.32 ■ When optically active (*R*)-2-methylcyclohexanone is treated with either aqueous base or acid, racemization occurs. Explain.

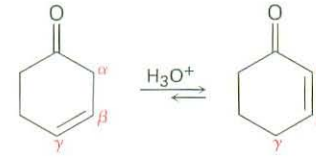
22.33 Would you expect optically active (*S*)-3-methylcyclohexanone to be racemized on acid or base treatment in the same way as 2-methylcyclohexanone (Problem 22.32)? Explain.

22.34 When an optically active carboxylic acid such as (*R*)-2-phenylpropanoic acid is brominated under Hell–Volhard–Zelinskii conditions, is the product optically active or racemic? Explain.

22.35 Fill in the reagents **a**–**c** that are missing from the following scheme:

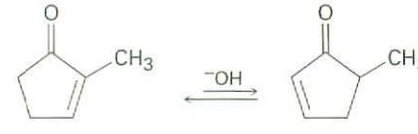


22.36 ■ Nonconjugated β,γ-unsaturated ketones, such as 3-cyclohexenone, are in an acid-catalyzed equilibrium with their conjugated α,β-unsaturated isomers. Propose a mechanism for this isomerization.

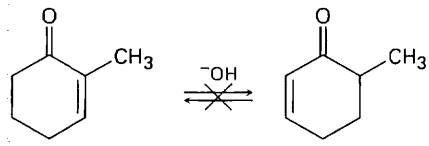


22.37 The interconversion of unsaturated ketones described in Problem 22.36 is also catalyzed by base. Explain.

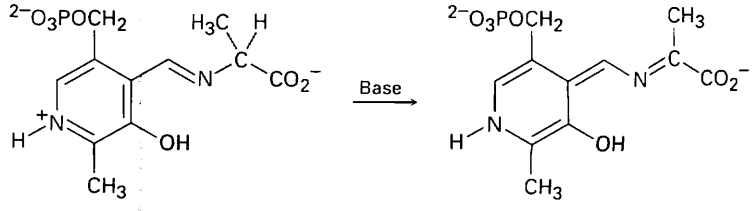
22.38 An interesting consequence of the base-catalyzed isomerization of unsaturated ketones described in Problem 22.37 is that 2-substituted 2-cyclopentenones can be interconverted with 5-substituted 2-cyclopentenones. Propose a mechanism for this isomerization.



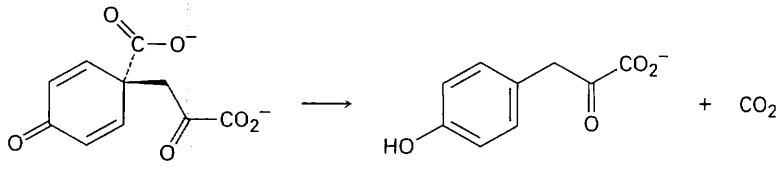
22.39 Although 2-substituted 2-cyclopentenones are in a base-catalyzed equilibrium with their 5-substituted 2-cyclopentenone isomers (Problem 22.38), the analogous isomerization is not observed for 2-substituted 2-cyclohexenones. Explain.



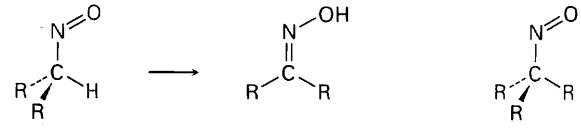
22.40 Using curved arrows, propose a mechanism for the following reaction, one of the steps in the metabolism of the amino acid alanine.



22.41 Using curved arrows, propose a mechanism for the following reaction, one of the steps in the biosynthesis of the amino acid tyrosine.

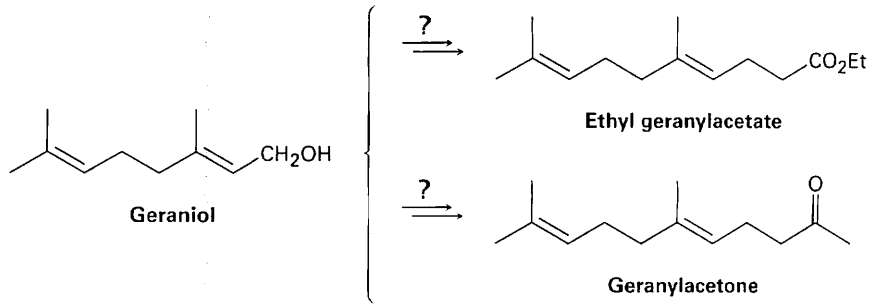


22.42 All attempts to isolate primary and secondary nitroso compounds result only in the formation of oximes. Tertiary nitroso compounds, however, are stable. Explain.



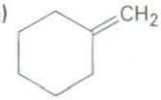
A 1° or 2° nitroso compound (unstable) **An oxime** **A 3° nitroso compound (stable)**

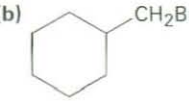
22.43 How might you convert geraniol into either ethyl geranylacetate or geranylacetone?

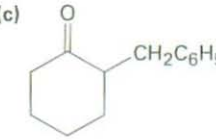


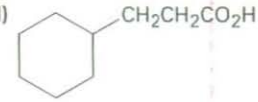
Geraniol **Ethyl geranylacetate** **Geranylacetone**

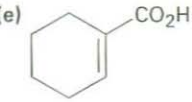
22.44 ■ How would you synthesize the following compounds from cyclohexanone? More than one step may be required.

(a) 

(b) 

(c) 

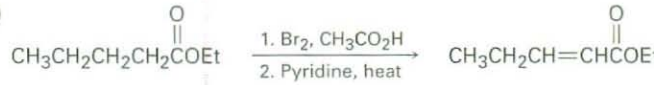
(d) 

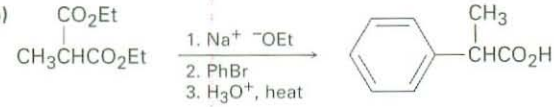
(e) 

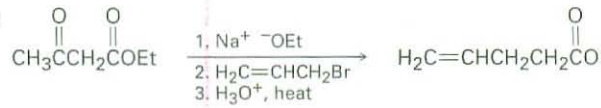
(f) 

22.45 The two isomers *cis*- and *trans*-4-*tert*-butyl-2-methylcyclohexanone are interconverted by base treatment. Which isomer do you think is more stable, and why?

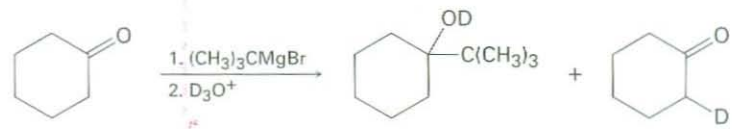
22.46 The following synthetic routes are incorrect. What is wrong with each?

(a) 

(b) 

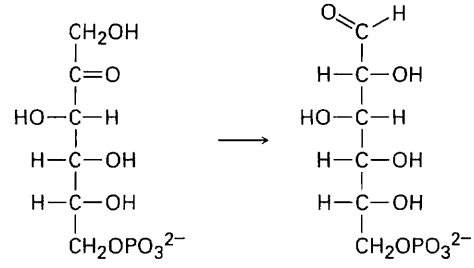
(c) 

22.47 Attempted Grignard reaction of cyclohexanone with *tert*-butylmagnesium bromide gives only about 1% yield of the expected addition product along with 99% unreacted cyclohexanone. If D_3O^+ is added to the reaction mixture after a suitable period, however, the "unreacted" cyclohexanone is found to have one deuterium atom incorporated into it. Explain.



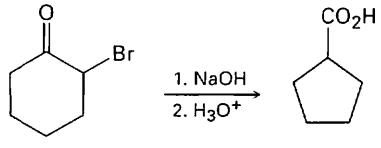
1% **99%**

22.48 One of the later steps in glucose biosynthesis is the isomerization of fructose 6-phosphate to glucose 6-phosphate. Propose a mechanism, using acid or base catalysis as needed.

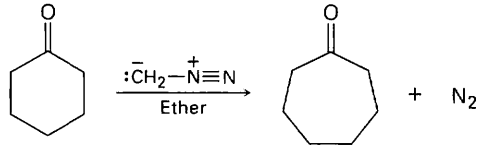


Fructose 6-phosphate **Glucose 6-phosphate**

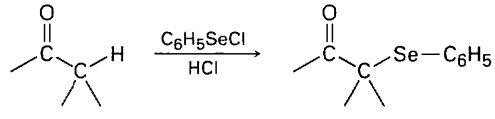
22.49 The *Favorskii reaction* involves treatment of an α-bromo ketone with base to yield a ring-contracted product. For example, reaction of 2-bromocyclohexanone with aqueous NaOH yields cyclopentanecarboxylic acid. Propose a mechanism.



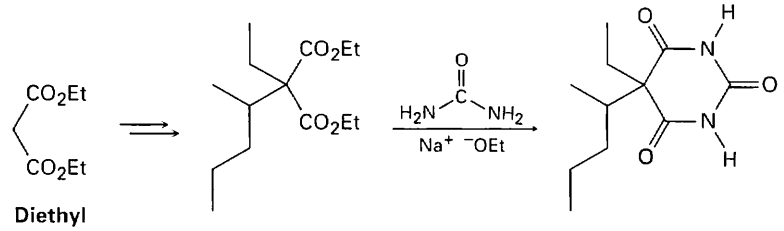
22.50 Treatment of a cyclic ketone with diazomethane is a method for accomplishing a *ring-expansion reaction*. For example, treatment of cyclohexanone with diazomethane yields cycloheptanone. Propose a mechanism.



22.51 Ketones react slowly with benzeneselenenyl chloride in the presence of HCl to yield α-phenylseleno ketones. Propose a mechanism for this acid-catalyzed α-substitution reaction.



22.52 Pentobarbital, marketed under the name Nembutal, is a barbiturate used i treating insomnia. It is synthesized in three steps from diethyl malonate Show how you would synthesize the dialkylated intermediate, and then pro pose a mechanism for the reaction of that intermediate with urea to giv pentobarbital.

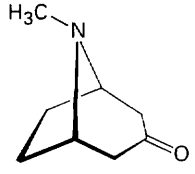


Diethyl malonate

Dialkylated diethyl malonate

Pentobarbital (Nembutal)

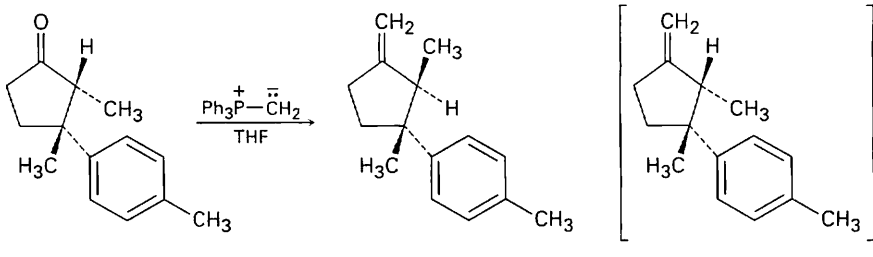
22.53 As far back as the 16th century, South American Incas chewed the leaves o the coca bush, *Erythroxylon coca*, to combat fatigue. Chemical studies of *Ery throxylon coca* by Friedrich Wöhler in 1862 resulted in the discovery of *cocaine*, $C_{17}H_{21}NO_4$, as the active component. Basic hydrolysis of cocaine leads to methanol, benzoic acid, and another compound called *ecgonine*, $C_9H_{15}NO_3$. Oxidation of ecgonine with CrO_3 yields a keto acid that readily loses CO_2 on heating, giving tropinone.



Tropinone

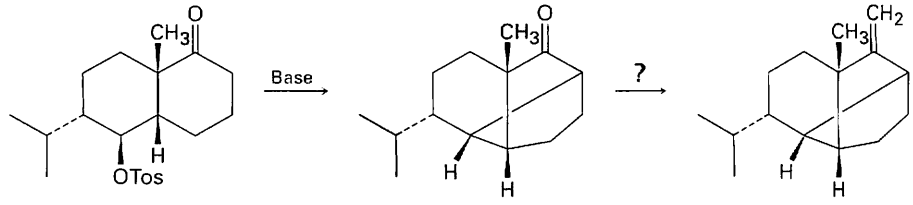
(a) What is a likely structure for the keto acid?
(b) What is a likely structure for ecgonine, neglecting stereochemistry?
(c) What is a likely structure for cocaine, neglecting stereochemistry?

22.54 The final step in an attempted synthesis of laurene, a hydrocarbon isolated from the marine alga *Laurencia glandulifera*, involved the Wittig reaction shown. The product obtained, however, was not laurene but an isomer. Pro pose a mechanism to account for these unexpected results.



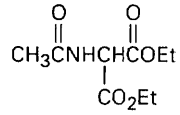
Laurene
(NOT formed)

22.55 The key step in a reported laboratory synthesis of sativene, a hydrocarbon isolated from the mold *Helminthosporium sativum*, involves the following base treatment of a keto tosylate. What kind of reaction is occurring? How would you complete the synthesis?



A keto tosylate **Sativene**

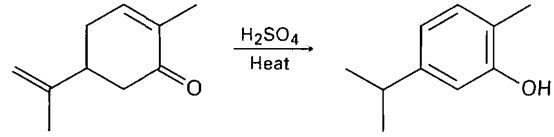
22.56 Amino acids can be prepared by reaction of alkyl halides with diethyl acetamidomalonate, followed by heating the initial alkylation product with aqueous HCl. Show how you would prepare alanine, $CH_3CH(NH_2)CO_2H$, one of the twenty amino acids found in proteins, and propose a mechanism for acid-catalyzed conversion of the initial alkylation product to the amino acid.



Diethyl acetamidomalonate

22.57 Amino acids can also be prepared by a two-step sequence that involves Hell–Volhard–Zelinskii reaction of a carboxylic acid followed by treatment with ammonia. Show how you would prepare leucine, $(CH_3)_2CHCH_2CH(NH_2)CO_2H$, and identify the mechanism of the second step.

22.58 Heating carvone with aqueous sulfuric acid converts *it into* carvacrol. Propose a mechanism for the isomerization.



Carvone **Carvacrol**