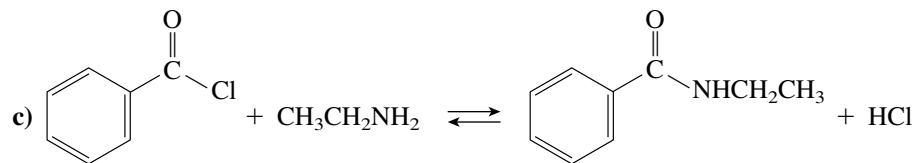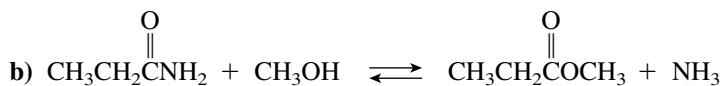**PROBLEM 19.2**

Explain whether these equilibria favor the reactants or the products:

a) $CH_3\overset{\text{O}}{\underset{\|}{C}}O\overset{\text{O}}{\underset{\|}{C}}CH_3$ + (cyclopentanol, OH) $\rightleftharpoons$ (cyclopentyl acetate, $O\overset{\text{O}}{\underset{\|}{C}}CH_3$) + $CH_3\overset{\text{O}}{\underset{\|}{C}}OH$

b) $CH_3CH_2\overset{\text{O}}{\underset{\|}{C}}NH_2$ + CH_3OH $\rightleftharpoons$ $CH_3CH_2\overset{\text{O}}{\underset{\|}{C}}OCH_3$ + NH_3

c) (phenyl) $\overset{\text{O}}{\underset{\|}{C}}$–Cl + $CH_3CH_2NH_2$ $\rightleftharpoons$ (phenyl) $\overset{\text{O}}{\underset{\|}{C}}$–$NHCH_2CH_3$ + HCl
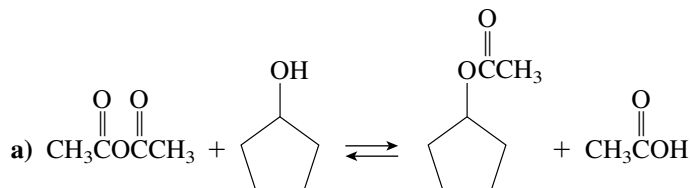
PROBLEM 19.3

Explain which of these reactions is faster:

$$CH_3\overset{\text{O}}{\underset{\|}{C}}OCH_3 + \,^-OH \longrightarrow CH_3\overset{\text{O}}{\underset{\|}{C}}O^- + CH_3OH$$

or

$$CH_3\overset{\text{O}}{\underset{\|}{C}}NHCH_3 + \,^-OH \longrightarrow CH_3\overset{\text{O}}{\underset{\|}{C}}O^- + CH_3NH_2$$
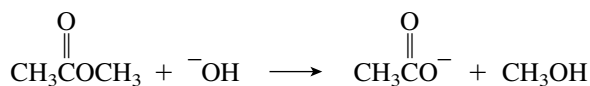
PROBLEM 19.4

Suggest a reaction that could be used to prepare this amide:

$$CH_3CH_2CH_2\overset{\text{O}}{\underset{\|}{C}}NHCH_2CH_2CH_3$$
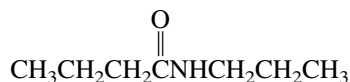
19.2 PREPARATION OF ACYL CHLORIDES

Because they are readily available from a number of synthetic reactions, carboxylic acids are the most common starting materials for the preparation of the other members of this family. Conversion of a carboxylic acid to an acyl chloride provides access to any of the other derivatives because the acyl chloride is at the top of the reactivity scale. But how can the acyl chloride be prepared from the acid when the acid is lower on the reactivity scale? This can be accomplished by using an even more reactive compound to drive the equilibrium in the desired direction. The reagent that is employed in the vast majority of cases is thionyl chloride, $SOCl_2$. Phosphorus trichloride, PCl_3, and phosphorus pentachloride, PCl_5, are also used occasionally. Examples are provided in the following equations:

$$CH_3CH\underset{CH_3}{-}C\overset{O}{-}OH + Cl-\overset{O}{S}-Cl \longrightarrow CH_3CH\underset{CH_3}{-}C\overset{O}{-}Cl + SO_2\,(g) + HCl\,(g) \quad (90\%)$$

2-Methylpropanoic acid   Thionyl chloride   2-Methylpropanoyl chloride

$$\text{(structure)} + 2\ PCl_5 \longrightarrow \text{(structure)} + 2\ POCl_3 + 2\ HCl \quad (66\%)$$

Phosphorus pentachloride
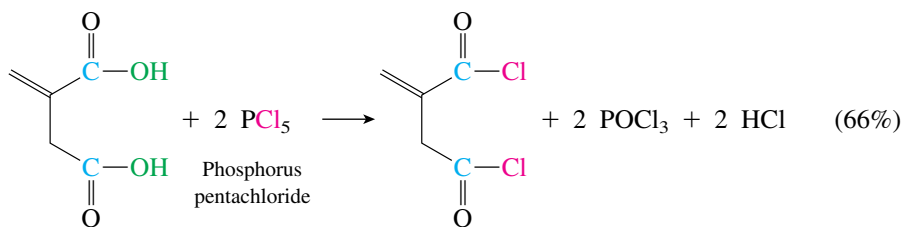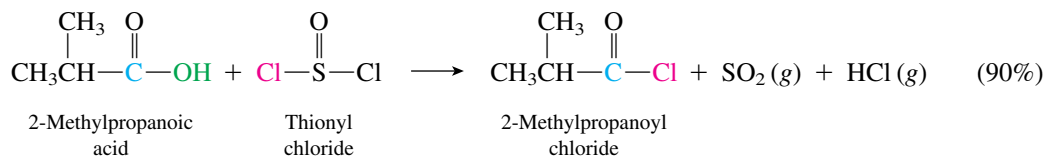
Thionyl chloride can be viewed as the di(acid chloride) of sulfurous acid. It is even more reactive than the acyl halide. Its reactivity, along with the formation of gaseous products (SO_2 and HCl), serves to drive the equilibrium to the acyl chloride. The mechanism for this reaction is shown in Figure 19.2. It is interesting to note that thionyl chlo-

❶ Thionyl chloride reacts like an acyl chloride. In this step, its sulfur–oxygen double bond plays the role of the carbonyl group of an acyl chloride. The nucleophile, the oxygen of the carboxylic acid, attacks the sulfur and displaces the pi electrons onto the oxygen.

❷ The reaction continues like the mechanism in Figure 19.1, but at sulfur rather than carbon. The electrons on the oxygen help displace the chloride.

This compound is a mixed anhydride of the carboxylic acid and sulfurous acid and is more reactive than the acyl chloride.

❸ The nucleophilic chloride anion bonds to the carbon, displacing the pi electrons onto the oxygen.

Thionyl chloride

A carboxylic acid

A mixed anhydride
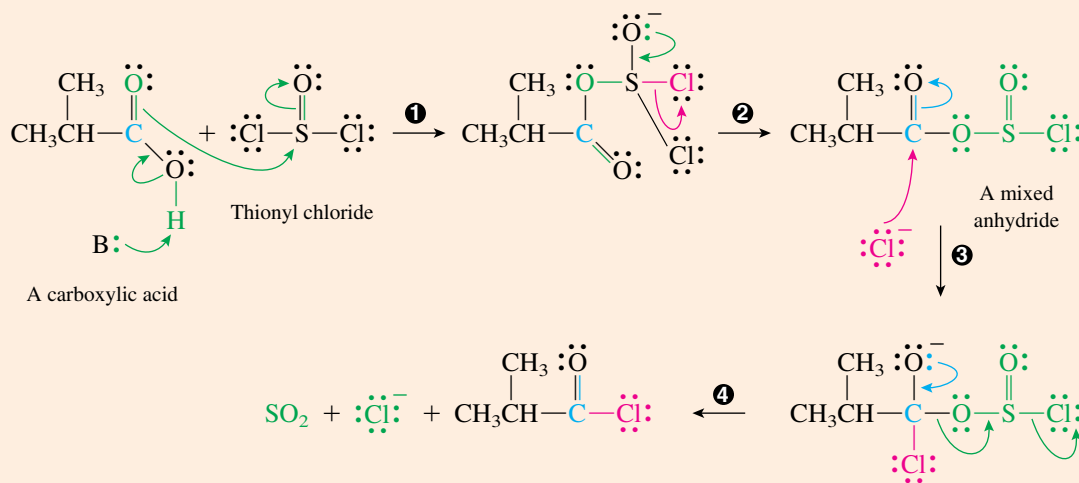
❹ The electrons on the oxygen help displace the leaving group, which fragments to SO_2 and Cl^-.

Figure 19.2

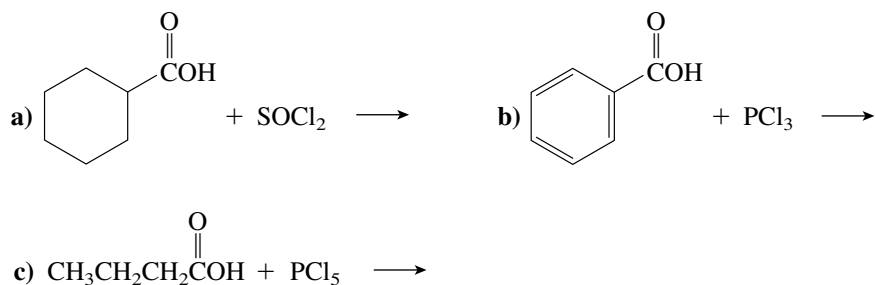MECHANISM OF THE REACTION OF A CARBOXYLIC ACID WITH THIONYL CHLORIDE.

ride reacts just like an acyl chloride; that is, the nucleophile attacks at the sulfur, displacing the electrons onto the oxygen. In the next step these electrons help to displace the leaving group.

Sulfurous acid   Thionyl chloride

The major use for acyl chlorides is as starting materials for the preparation of the other carboxylic acid derivatives. Acyl fluorides, bromides, and iodides could potentially be employed to prepare the other derivatives also. However, because they offer no advantages over the acyl chlorides, they are seldom used.
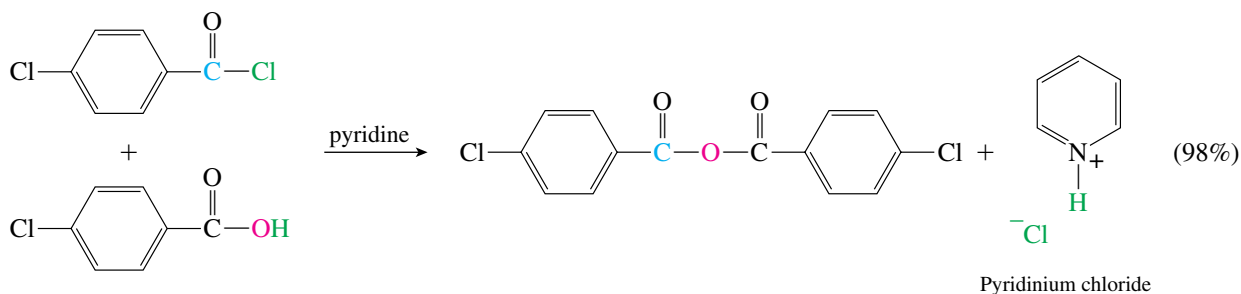
PROBLEM 19.5
Show the products of these reactions:

a) + SOCl$_2$ →   b) + PCl$_3$ →
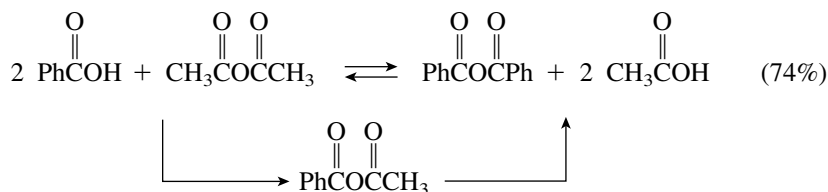
c) $CH_3CH_2CH_2COH$ + PCl_5 →

19.3 PREPARATION OF ANHYDRIDES

An anhydride can be prepared by the reaction of a carboxylic acid, or its conjugate base, with an acyl chloride as illustrated in the following equation:


Pyridinium chloride

Pyridine is often added to these reactions, or used as a solvent, to react with the HCl that is produced and prevent the reaction mixture from becoming strongly acidic, which may cause decomposition and lower yields.

Anhydrides can also be prepared by the reaction of a carboxylic acid with another anhydride, usually acetic anhydride. A mixed anhydride is an intermediate in this reaction:

$$2 \text{ PhCOH} + \text{CH}_3\text{COCCH}_3 \rightleftharpoons \text{PhCOCPh} + 2 \text{ CH}_3\text{COH} \quad (74\%)$$
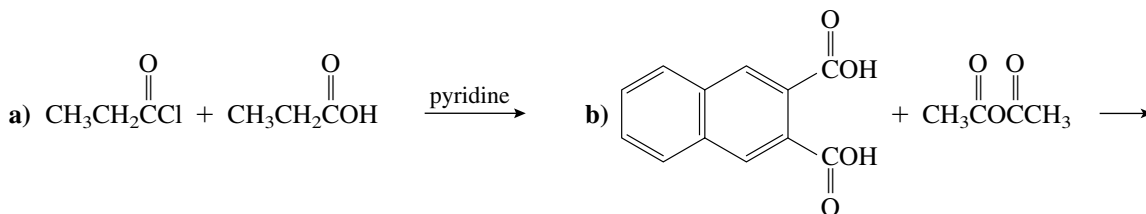
$$\text{PhCOCCH}_3$$

To make this preparation useful, the equilibrium is driven to the right by removal of the acetic acid by careful distillation. This is often the method of choice for the preparation of cyclic anhydrides, in which the equilibrium is favored by entropy:


$$+ \text{ CH}_3\text{COCCH}_3 \longrightarrow \quad + 2 \text{ CH}_3\text{COH} \quad (88\%)$$
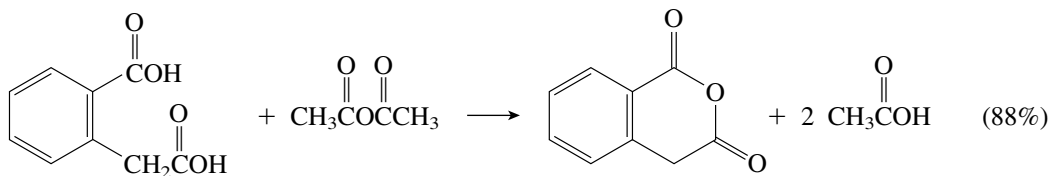
PROBLEM 19.6

Show the products of these reactions:

a) $\text{CH}_3\text{CH}_2\text{CCl} + \text{CH}_3\text{CH}_2\text{COH} \xrightarrow{\text{pyridine}}$ **b)**

19.4 PREPARATION OF ESTERS

Esters are readily prepared by reaction of an alcohol with either an acyl chloride or an anhydride. Because it is more easily prepared from the acid, the acyl chloride is commonly employed. Again, a base, such as pyridine, is often added to react with the HCl that is produced. Acetic anhydride, which is commercially available, is often used for the preparation of acetate esters. Following are several examples.

(75%)

Salicylic acid

Acetylsalicylic acid
(aspirin)

(88%)
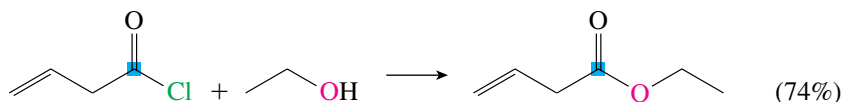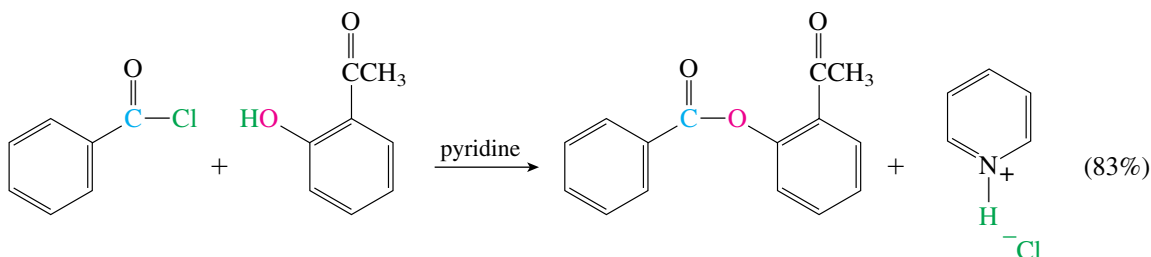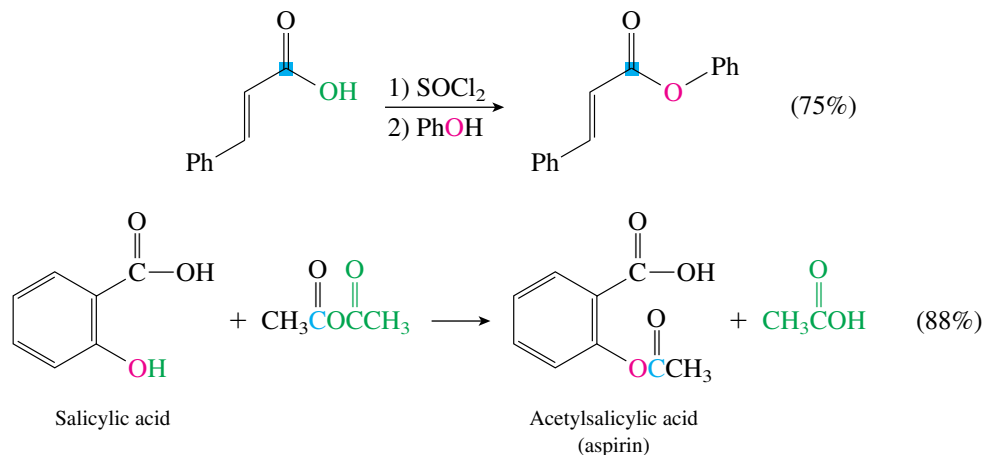
It is also common to prepare esters directly from the carboxylic acid without passing through the acyl chloride or the anhydride, as follows:


(93%)
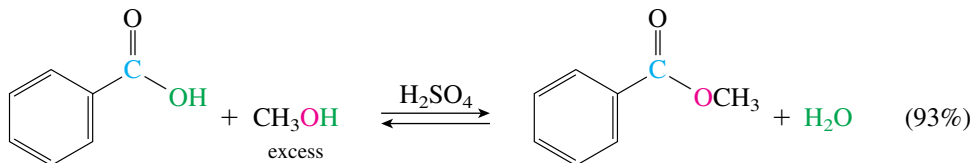
This reaction, known as **Fischer esterification,** requires the presence of an acid catalyst. Because the carboxylic acid and the ester have similar reactivities, the reaction is useful only if a method can be found to drive the equilibrium in the direction of the desired product—the ester. In accord with Le Chatelier's principle, this is accomplished by using an excess of one of the reactants or by removing one of the products. An excess of the alcohol is used if it is readily available, as is the case for methanol or ethanol. Or water can be removed by azeotropic distillation with a solvent such as toluene.

The mechanism for the Fischer esterification is shown in Figure 19.3. Sulfuric acid, hydrochloric acid, or p-toluenesulfonic acid is most often used as a catalyst. The mechanism will be easier to remember if you note the similarities to other acid-catalyzed mechanisms, such as the one for the formation of acetals in Figure 18.5. Also note that the steps leading from the tetrahedral intermediate to the carboxylic acid and alcohol starting materials and to the ester and water products are very similar.

Other examples of the Fischer esterification are provided by the following equations:

(78%)

(97%)
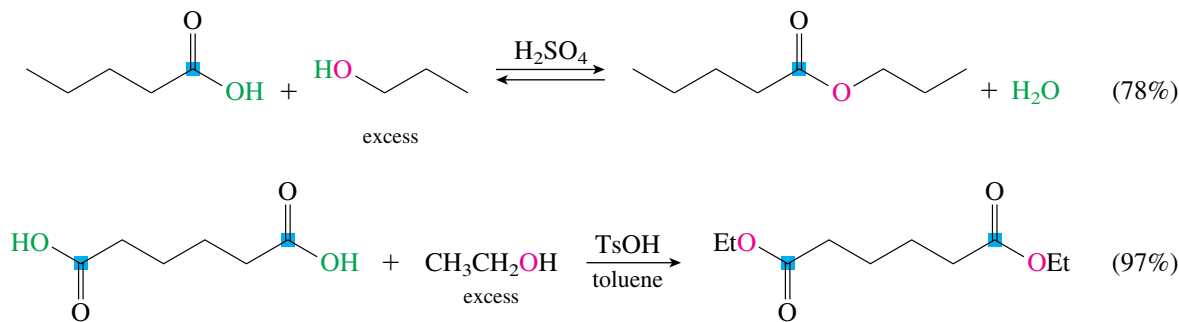
Lactones are cyclic esters. Their formation is very favorable when a hydroxy group and a carboxylic acid in the same molecule can react to form a five- or six-membered ring:
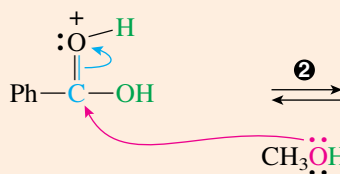

A lactone
(a cyclic ester)
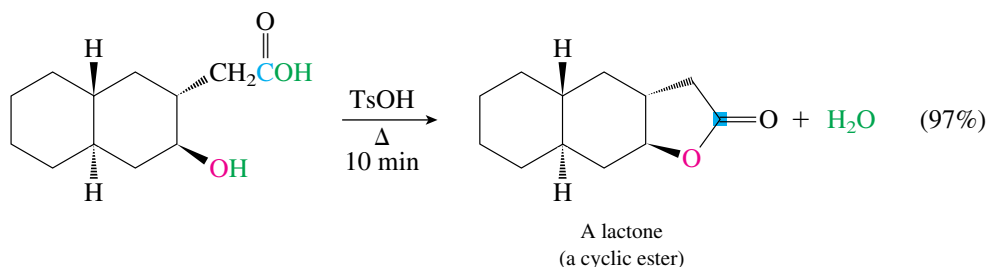
ORGANIC
Chemistry Now™
Click *Mechanisms in Motion* to view the **Mechanism of Fischer Esterification.**
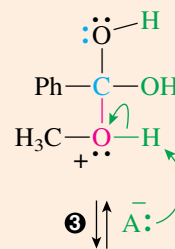
❶ Acid-catalyzed reactions begin by protonation of the oxygen of the carbonyl group to make the carbon more electrophilic.

❷ Then the nucleophile, the oxygen of the alcohol, bonds to the carbonyl carbon.

❸ Next, a proton is transferred to some base in the solution.

This is the tetrahedral intermediate in the mechanism for acidic conditions. It differs from the one in Figure 19.1 only in that the oxygen is protonated. Note the similarity of the steps leading away from this intermediate in both directions.

Tetrahedral intermediate
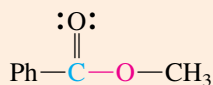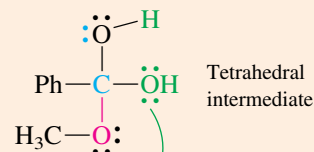
❻ Only a proton transfer is needed to complete the reaction. This step resembles the reverse of step 1. The acid, HA, is regenerated here, so the reaction is acid catalyzed.

❺ Then water leaves in a step that resembles the reverse of step 2.
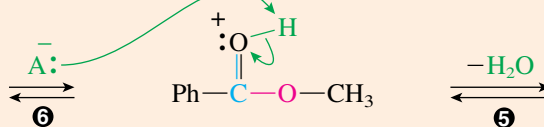
❹ Before the oxygen leaves, it is protonated to make it a better leaving group, water. This resembles the reverse of step 3.
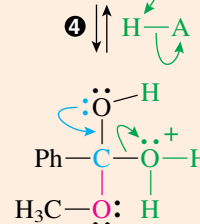
Figure 19.3

MECHANISM OF FISCHER ESTERIFICATION.

PROBLEM 19.7
Show all of the steps in the mechanism for this reaction:

$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}Cl + CH_3OH \longrightarrow CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH_3 + HCl$$

PROBLEM 19.8
Salicylic acid has two nucleophilic sites: the oxygen of the phenol and the oxygen of the carboxylic acid. Explain why its reaction with acetic anhydride produces aspirin rather than this compound:
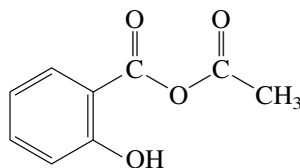
PROBLEM 19.9
Show the products of these reactions:

a) $CH_3\overset{\overset{\displaystyle O}{\|}}{C}Cl$ +

b)

 + $CH_3CH_2CH_2OH$ $\xrightarrow{H_2SO_4}$

c) $CH_3\overset{\overset{\displaystyle O}{\|}}{C}O\overset{\overset{\displaystyle O}{\|}}{C}CH_3$ + $CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2OH$ $\longrightarrow$

d)

 $\xrightarrow{H_2SO_4}$

e)

 $\xrightarrow{SOCl_2}$ $\xrightarrow{CH_3OH}$

f)

 + CH_3OH $\xrightarrow{TsOH}$
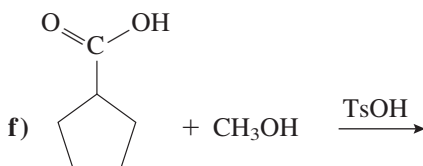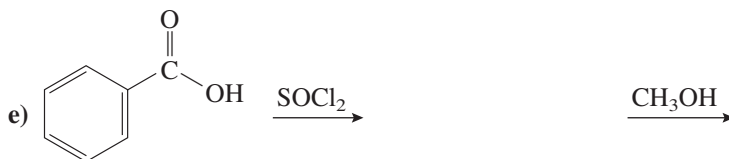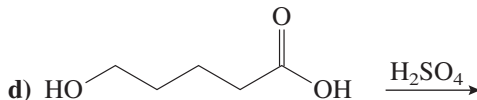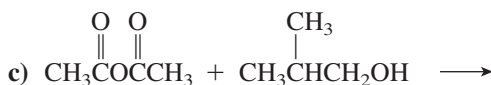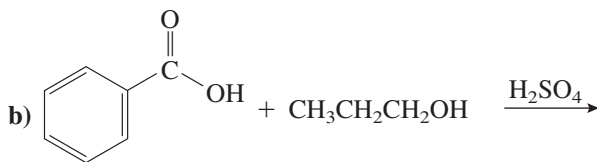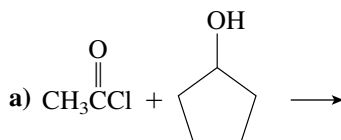
19.5   PREPARATION OF CARBOXYLIC ACIDS

Carboxylic acids commonly are used as the starting materials for the preparation of the other acid derivatives. However, any of the acid derivatives can be hydrolyzed to the carboxylic acid by reaction with water under the appropriate conditions. Acid or base catalysis is necessary for the less reactive derivatives.

Acyl Chloride and Anhydride Hydrolysis

Acyl chlorides and anhydrides must be protected from water because they react readily, often vigorously, with water to produce carboxylic acids. This reaction is not of much synthetic usefulness because the acyl chloride or anhydride is usually prepared from the acid. However, the hydrolysis reaction is occasionally used for the preparation of a carboxylic acid if the acyl chloride or anhydride is available from some other source. The following equation provides an example:
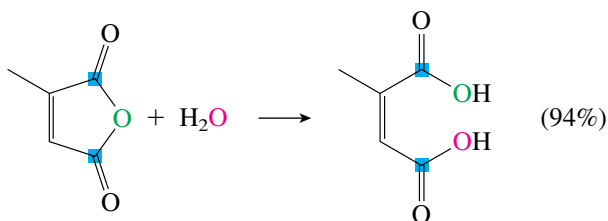
Ester Hydrolysis

Esters can be hydrolyzed to carboxylic acids under either acidic or basic conditions. Under acidic conditions the mechanism is the exact reverse of the Fischer esterification mechanism shown in Figure 19.3. Again, because the acid and the ester have comparable reactivities, some method must be used to drive the equilibrium toward the desired product—the acid in this case. This can be accomplished by using water as the solvent, providing a large excess of this reagent that, by Le Chatelier's principle, shifts the equilibrium toward the carboxylic acid.

PROBLEM 19.10

Show all of the steps in the mechanism for this reaction:

$$CH_3\overset{\text{O}}{\overset{\|}{C}}OCH_2CH_3 \ + \ H_2O \ \underset{}{\overset{H_2SO_4}{\rightleftharpoons}} \ CH_3\overset{\text{O}}{\overset{\|}{C}}OH \ + \ CH_3CH_2OH$$
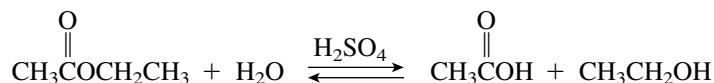
It is more common to hydrolyze esters under basic conditions because the equilibrium is favorable. The mechanism for this process, called **saponification,** is presented in Figure 19.4. The production of the conjugate base of the carboxylic acid, the carboxylate anion, which is at the bottom of the reactivity scale, drives the equilibrium in the desired direction. To isolate the carboxylic acid, the solution must be acidified after the hydrolysis is complete. Some examples are provided in the following equations. We saw another example of this hydrolysis reaction in Chapter 10, where it was

❶ This step is the same as the first step of Figure 19.1. The nucleophile, hydroxide ion in this case, bonds to the carbonyl carbon, displacing the pi electrons onto the oxygen.

❷ Next, the leaving group, ethoxide ion, departs as an electron pair from the negative oxygen reforms the double bond of the carbonyl group.

❸ Ethoxide ion, a strong base, removes a proton from acetic acid. The formation of the weak base, acetate ion, in this step drives the equilibrium to the final products, the alcohol and the carboxylate anion.

Figure 19.4

MECHANISM OF THE BASE-CATALYZED HYDROLYSIS (SAPONIFICATION) OF AN ESTER.

used in the preparation of alcohols by the acetate method (see Section 10.2 and Figure 10.1 on page 351).
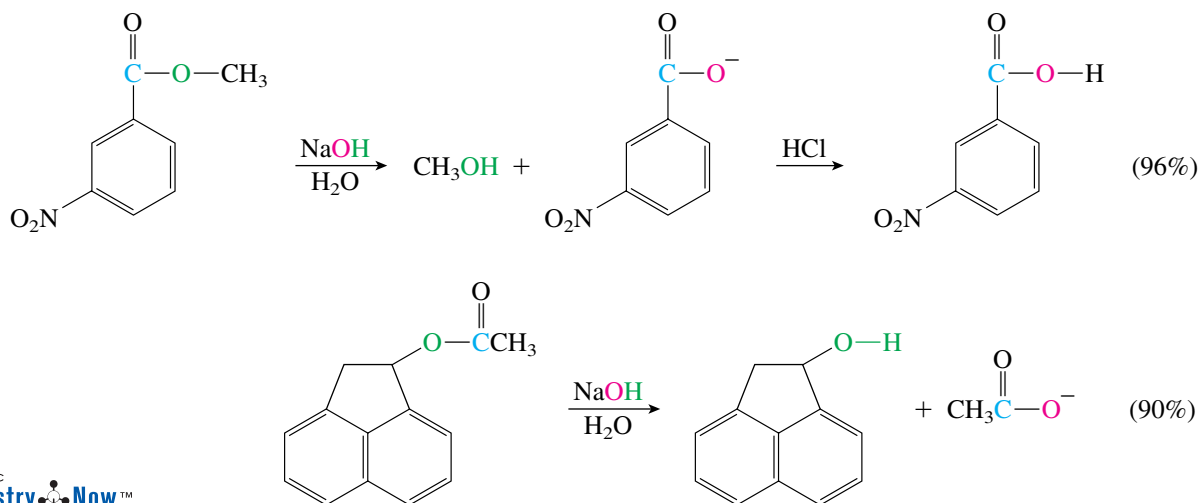
As we have seen before, a variety of experiments are used to support or disprove a mechanism that has been postulated for a par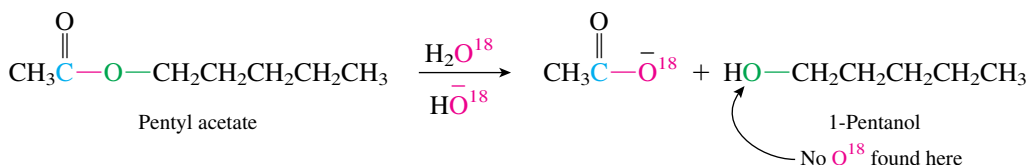ticular reaction. The mechanism for the basic hydrolysis of esters, shown in Figure 19.4, involves cleavage of the bond between

the ether oxygen of the ester and the carbonyl carbon rather than the cleavage of the bond between this oxygen and the carbon of the alcohol part of the ester.
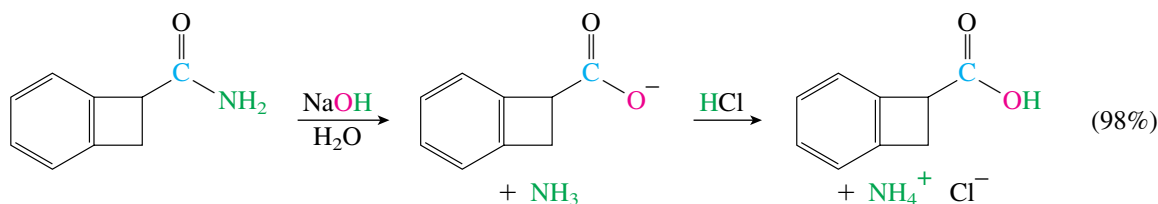
$$CH_3C \overset{\overset{\displaystyle O}{\|}}{\underset{}{}} -O-CH_2CH_2CH_2CH_2CH_3$$

The acyl C—O
bond is cleaved.

The alkyl C—O bond
remains intact.
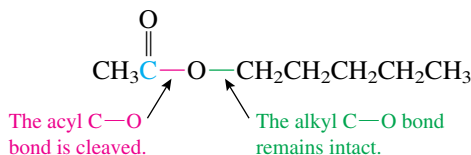
Proof that it is indeed this bond that is cleaved was provided by conducting the hydrolysis in water with an enriched content of ^{18}O. Pentyl acetate was hydrolyzed in this isotopically enriched water. The 1-pentanol product was shown by mass spectrometry to contain only the normal amount of ^{18}O, demonstrating that the alkyl C—O bond was not broken during the reaction.

$$CH_3C \overset{\overset{\displaystyle O}{\|}}{\underset{}{}} -O-CH_2CH_2CH_2CH_2CH_3 \xrightarrow[\overset{-}{HO}{}^{18}]{H_2O^{18}} CH_3C \overset{\overset{\displaystyle O}{\|}}{\underset{}{}} -\overset{-}{O}{}^{18} + HO-CH_2CH_2CH_2CH_2CH_3$$

Pentyl acetate   1-Pentanol

No O^{18} found here

Amide Hydrolysis

Amides are less reactive than esters, and their hydrolysis often requires vigorous heating in either aqueous acid or base. The mechanism for acidic conditions is quite similar to the reverse of the Fischer esterification mechanism shown in Figure 19.3. The mechanism for basic conditions is related to that depicted in Figure 19.4 for ester saponification and a similar tetrahedral intermediate is formed in the first step. However, NH_2^- is a strong base and a poor leaving group, so the nitrogen must usually be protonated before it can leave. The exact timing of the various proton transfers that occur in this mechanism (and many others) is difficult to establish and depends on both the structure of the amide and the reaction conditions. One possible mechanism is shown in Figure 19.5.

Under acidic conditions the equilibrium for the hydrolysis of an amide is driven toward the products by the protonation of the ammonia or amine that is formed. Under basic conditions the equilibrium is driven toward the products by the formation of the carboxylate anion, which is at the bottom of the reactivity scale. The pH of the final solution may need to be adjusted, depending on which product is to be isolated. If the carboxylic acid is desired, the final solution must be acidic, whereas isolation of the amine requires that the solution be basic. Several examples are shown in the following equations. Also, note that the last step of the Gabriel amine synthesis, the hydrolysis of the phthalimide (see Section 10.6 and Figure 10.5 on page 365), is an amide hydrolysis.

$$\text{(aryl)NH}-\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \quad \xrightarrow[\substack{H_2O \\ CH_3OH}]{KOH} \quad \text{(aryl)}NH_2 \; + \; CH_3\overset{\overset{\displaystyle O}{\|}}{C}-O^- \quad (97\%)$$

$$CH_3CH_2-\overset{\displaystyle |}{N}(aryl)-\overset{\overset{\displaystyle O}{\|}}{C}H \quad \xrightarrow[\,H_2O\,]{HCl} \quad CH_3CH_2-\overset{+}{N}H_2(aryl) \; + \; HO\overset{\overset{\displaystyle O}{\|}}{C}H \quad \xrightarrow{KOH} \quad CH_3CH_2-\overset{\displaystyle |}{N}H(aryl) \; + \; {}^-O\overset{\overset{\displaystyle O}{\|}}{C}H \quad (92\%)$$
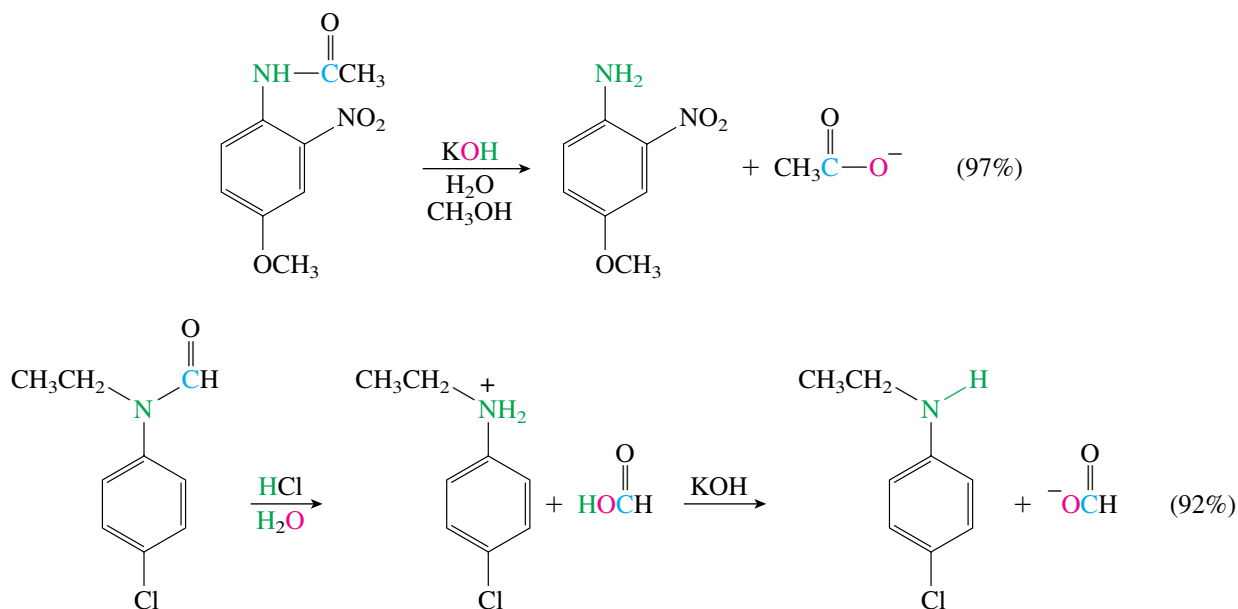
❶ A hydroxide ion nucleophile bonds to the carbon of the carbonyl group, exactly as the mechanism for the saponification of an ester begins.

❷ At this point, this mechanism deviates slightly from the ester saponification mechanism. Because amide ion (NH₂⁻) is a poor leaving group, the nitrogen is first protonated by the solvent to convert it to a better leaving group.

❸ Ammonia leaves while an electron pair from the negative oxygen reforms the double bond of the carbonyl group.

$$CH_3\overset{\overset{\displaystyle :\!O:}{\|}}{C}-NH_2 \;\; + \;\; {}^-\!\!:OH \;\; \overset{❶}{\rightleftharpoons} \;\; CH_3\overset{\overset{\displaystyle :O:^-}{|}}{\underset{\underset{\displaystyle :OH}{|}}{C}}-NH_2 \;\; \overset{❷}{\rightleftharpoons} \;\; CH_3\overset{\overset{\displaystyle :O:^-}{|}}{\underset{\underset{\displaystyle :OH}{|}}{C}}-\overset{+}{N}H_3 \; + \; {}^-\!\!:OH$$

$$CH_3\overset{\overset{\displaystyle :O}{\|}}{C}-O:^- \; + \; H_2O: \quad \overset{❹}{\longleftarrow} \quad CH_3\overset{\overset{\displaystyle :O}{\|}}{C}-O-H \; + \; :NH_3$$
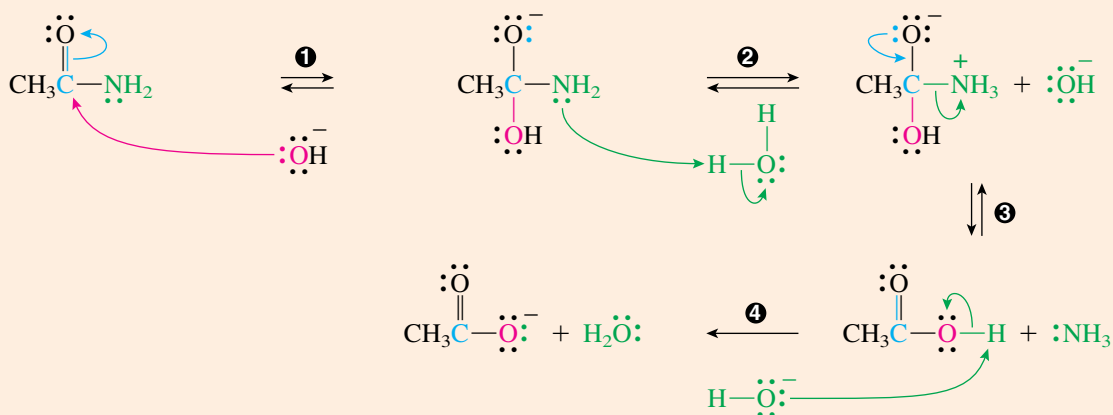
❹ A proton transfer from the carboxylic acid to a hydroxide ion completes the process.

Figure 19.5

POSSIBLE MECHANISM OF THE HYDROLYSIS OF AN AMIDE UNDER BASIC CONDITIONS.

Focus On

The Preparation of Soap

The preparation of a solution of soap by the reaction of fat with water in the presence of base was probably one of the e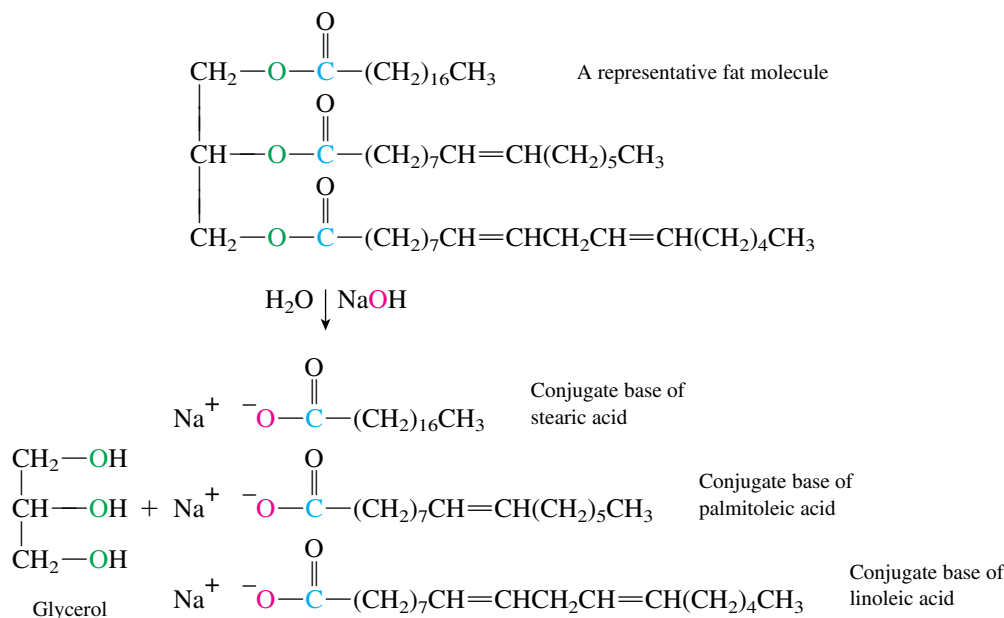arliest chemical processes discovered by humans. Although the details of this discovery are lost in antiquity, we can imagine early humans finding that water that had been in contact with wood ashes from the campfire could be used to remove grease from hands and other objects and that this water became a more effective cleaning agent as it was used. The water leaches some alkaline compounds from the ashes, and this basic water hydrolyzes the esters of the fat or grease to alcohols and soap. This is why the hydrolysis of esters under basic conditions is called saponification (the Latin word for soap is *sapo*).

Fats are triesters formed from a triol (glycerol) and fatty acids, which are carboxylic acids with long, unbranched alkyl chains. These alkyl chains may be saturated, or they may have one or more double bonds. Usually, the three carboxylic acids of a fat molecule are not the same. The following equation illustrates the hydrolysis of a representative fat molecule to glycerol and the conjugate bases of stearic acid, palmitoleic acid, and linoleic acid. Addition of NaCl causes the fatty acid salts to precipitate. The resulting solid is formed into bars of soap.

$$CH_2-O-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_{16}CH_3 \quad \text{A representative fat molecule}$$

$$CH-O-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_7CH=CH(CH_2)_5CH_3$$

$$CH_2-O-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_7CH=CHCH_2CH=CH(CH_2)_4CH_3$$

$$H_2O \downarrow NaOH$$

$$Na^+ \quad {}^-O-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_{16}CH_3 \quad \text{Conjugate base of stearic acid}$$

$$\begin{aligned}&CH_2-OH\\&CH-OH \;+\; Na^+ \quad {}^-O-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_7CH=CH(CH_2)_5CH_3 \quad \text{Conjugate base of palmitoleic acid}\\&CH_2-OH\end{aligned}$$

Glycerol

$$Na^+ \quad {}^-O-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_7CH=CHCH_2CH=CH(CH_2)_4CH_3 \quad \text{Conjugate base of linoleic acid}$$

The cleaning action of soap is due to the dual nature of the conjugate base of the fatty acid molecule. On one end is the ionic carboxylate anion group; the rest of the molecule consists of a nonpolar hydrocarbon chain. The ionic part, called the head, is attracted to a polar solvent such as water and is hydrophilic, whereas the long hydrocarbon tail is hydrophobic. In water, soap molecules tend to group together in clusters called micelles, with their ionic heads oriented toward the water molecules and their hydrocarbon tails in the interior of the cluster so that unfavorable interactions with water are avoided. Non-

Continued

polar grease and fat molecules dissolve in the interior of the micelle. The ionic heads keep the micelle in solution and allow water to wash it away, along with the grease.

A fatty acid anion

Cross section of a soap micelle in water

Na⁺ ions

Ionic head

Hydrocarbon tail
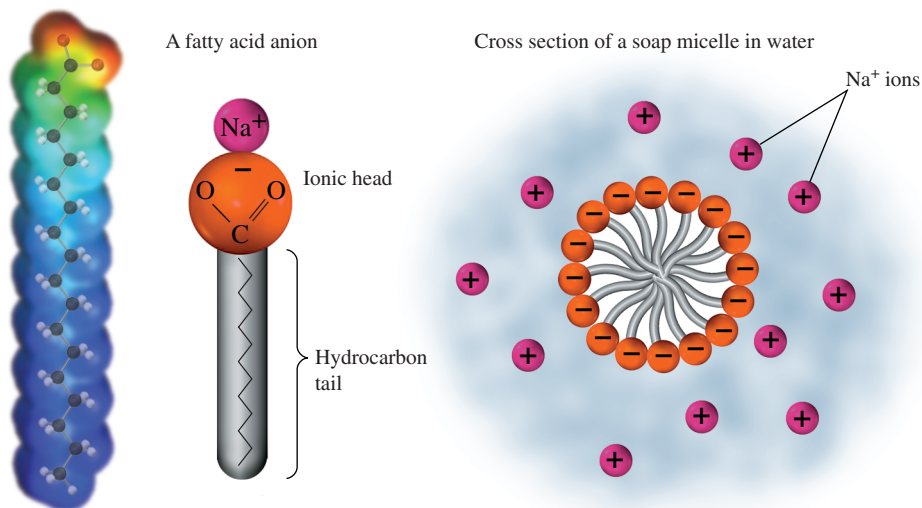
PROBLEM 19.11

Show the products that are formed when this fat is saponified:

$$CH_2-OC(CH_2)_7CH=CH(CH_2)_7CH_3$$
$$CH-OC(CH_2)_{14}CH_3$$
$$CH_2-OC(CH_2)_{12}CH_3$$
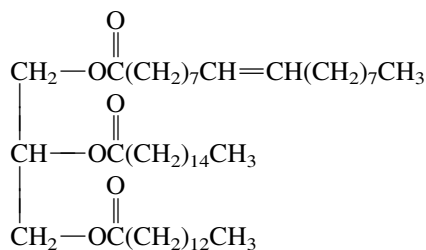
As mentioned previously, acyl chlorides and anhydrides are hydrolyzed to carboxylic acids by water without the need for acid or base catalysis. If an acyl chloride or anhydride is stored for an extended period, it is often found to be contaminated with the corresponding carboxylic acid because of contact with water from the air or some other source.

Esters and amides, on the other hand, require the presence of an acid or base catalysis to react with water. These reactions are not instantaneous but require rather strongly acidic or basic conditions and heat to proceed at a reasonable rate. For example, a typical ester saponification is usually conducted with 10% NaOH in water, and the solution is refluxed until the ester layer disappears. (Most esters are not soluble in water.) This may require from 15 minutes up to several hours of reflux. Similarly, a typical amide hydrolysis is often conducted by refluxing the amide in concentrated hydrochloric acid for a period ranging from 15 minutes up to several hours. Esters and amides are relatively stable to the near-neutral conditions found in living organisms, which is one reason why they are important functional groups in biochemistry.
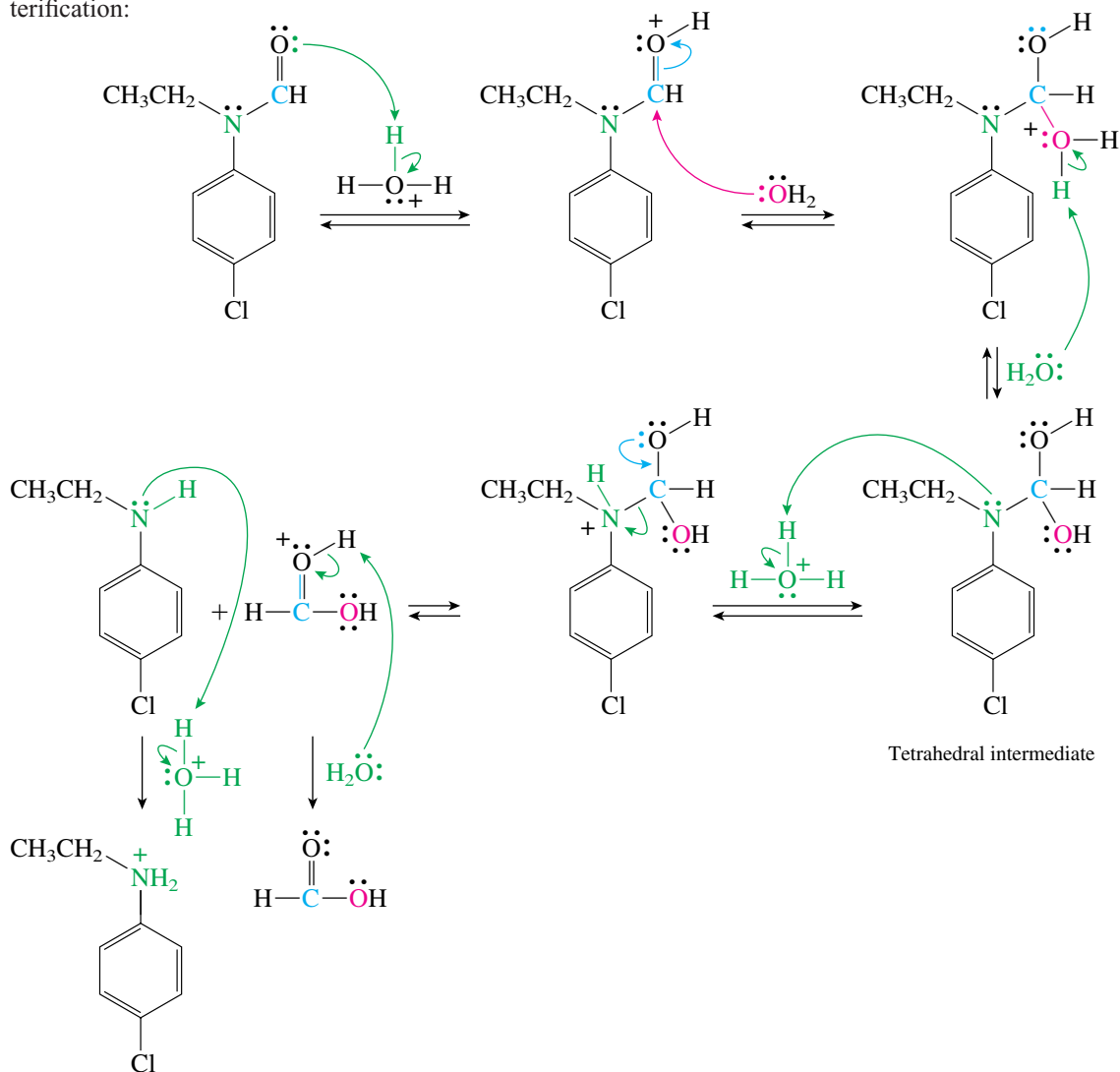
PRACTICE PROBLEM 19.2

Show all of the steps in the mechanism for this reaction:
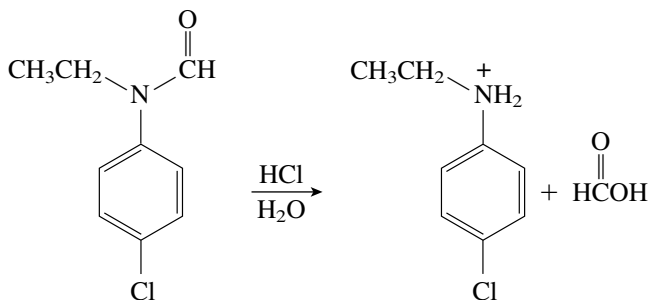
Solution

This acid-catalyzed mechanism resembles the reverse of the mechanism for Fischer esterification:


Tetrahedral intermediate

Nitrile Hydrolysis

Nitriles are often considered as derivatives of carboxylic acids because they can be hydrolyzed to the carboxylic acid under acidic or basic conditions, as illustrated in the following equation:
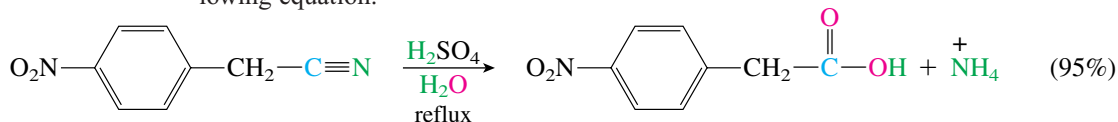
The amide is an intermediate in the hydrolysis, and because it is less reactive than the nitrile, the reaction can often be stopped at the amide stage, if so desired, by using milder reaction conditions, such as shorter reaction times, lower temperatures, or weaker base:
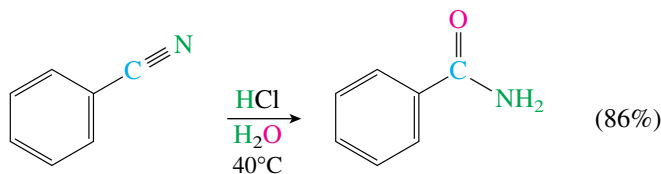

Many of the reactions of a CN triple bond resemble those of a CO double bond, and the mechanisms have many similarities also. The mechanism for the hydrolysis of a nitrile to an amide under basic conditions is shown in Figure 19.6.

❶ The cyano group resembles a carbonyl group in many of its reactions. This mechanism begins with the nucleophile, hydroxide ion, bonding to the electrophilic carbon of the nitrile. One pair of pi electrons is displaced onto the nitrogen.

❷ Next, the negative nitrogen is protonated by a water molecule.

This compound is a tautomer of an amide. Tautomerization occurs in the same manner as was the case for the conversion of an enol to its carbonyl tautomer.

**❸** A proton on the oxygen is removed by a base in the solution.
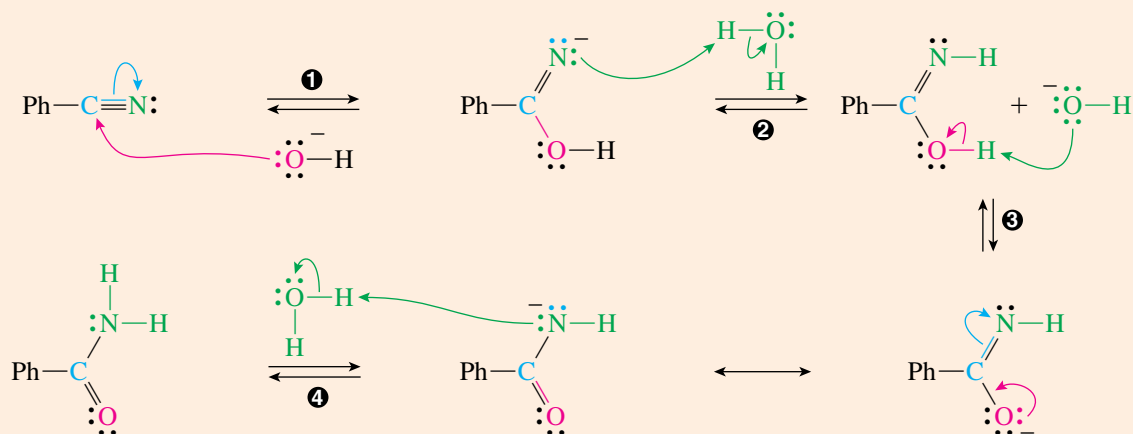
❹ Reprotonation occurs on the nitrogen to produce the amide. As was the case with the carbonyl–enol tautomerization, the stability of the carbon–oxygen double bond causes the amide tautomer to be favored at equilibrium.
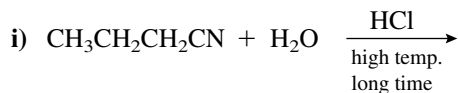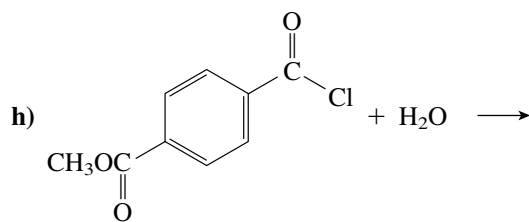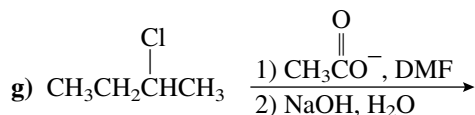
Figure 19.6

MECHANISM OF THE HYDROLYSIS OF A NITRILE TO AN AMIDE UNDER BASIC CONDITIONS.

The use of cyanide ion as a nucleophile in an S_N2 reaction (see Section 10.8), followed by hydrolysis of the product nitrile, provides a useful preparation of carboxylic acids that contain one more carbon than the starting compound:

(93%)   (87%)
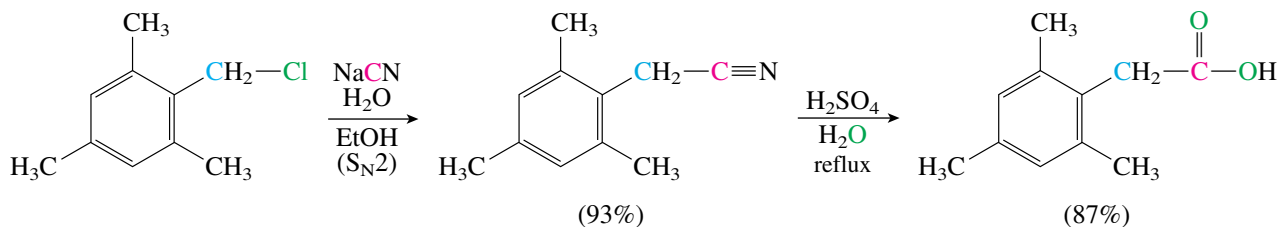
PROBLEM 19.12

Show the products of these reactions:

a) $CH_3\overset{O}{\overset{||}{C}}\overset{O}{\overset{||}{C}}CH_3 + H_2O \longrightarrow$

b) $PhC\overset{O}{\overset{||}{}}-OCH_2CH_3 + H_2O \xrightarrow{\text{NaOH}}$

c) $CH_3\overset{O}{\overset{||}{C}}NHPh + H_2O \xrightarrow{HCl}$

d) $O_2N-\!\!\!\bigcirc\!\!\!-\overset{O}{\overset{||}{C}}Cl + H_2O \longrightarrow$

e) $CH_3CH_2\overset{O}{\overset{||}{C}}OCH_2CH_3 + H_2O \xrightarrow{H_2SO_4}$

f) (phenyl)$\overset{O}{\overset{||}{C}}CH_2CN + H_2O \xrightarrow[\text{short time}]{\substack{\text{NaOH} \\ \text{low temp.}}}$

g) $CH_3CH_2\overset{Cl}{\underset{}{C}}HCH_3 \xrightarrow[\text{2) NaOH, H}_2\text{O}]{\text{1) CH}_3\overset{O}{\overset{||}{C}}O^-, \text{DMF}}$

h) $CH_3O\overset{O}{\overset{||}{C}}-\!\!\!\bigcirc\!\!\!-\overset{O}{\overset{||}{C}}Cl + H_2O \longrightarrow$

i) $CH_3CH_2CH_2CN + H_2O \xrightarrow[\substack{\text{high temp.} \\ \text{long time}}]{HCl}$
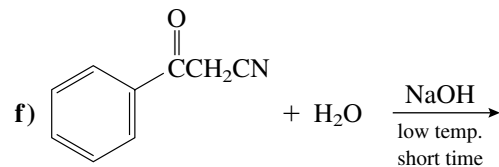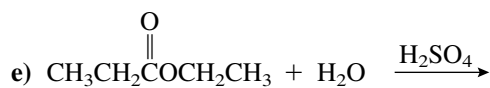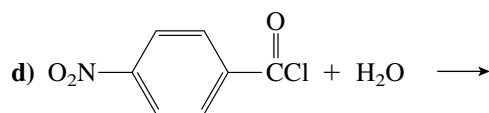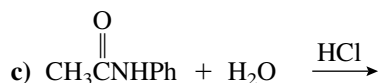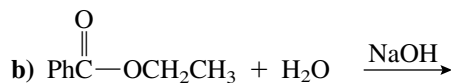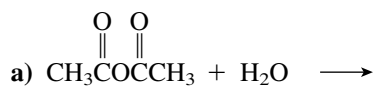
PROBLEM 19.13

Suggest a synthesis of 2-phenylacetic acid from benzyl bromide:
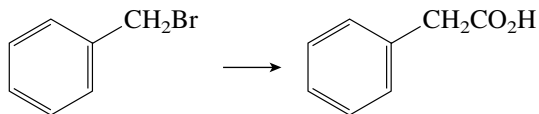
19.6   PREPARATION OF AMIDES

Amides are most commonly prepared by reaction of an acyl chloride or an anhydride with ammonia or an amine. Because the by-products of these reactions are acidic, base must also be added to the reaction. An excess of the amine can be employed as the base if it is inexpensive, or the reaction may be done in the presence of sodium hydroxide or some other base. Following are several examples.
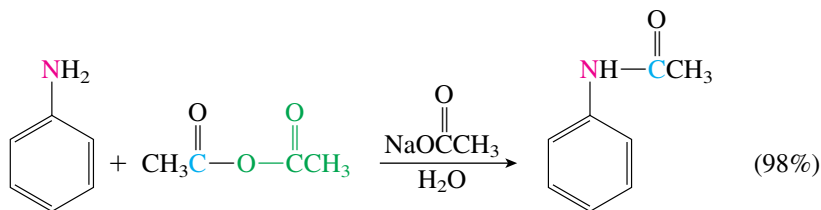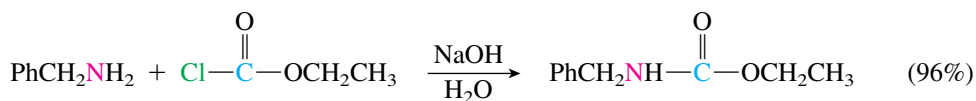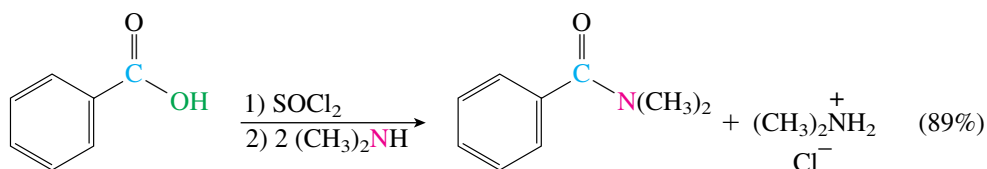
Although a carboxylic acid is higher on the reactivity scale than an amide, the reaction of an acid with an amine does not directly produce the amide because of the fast acid–base reaction that occurs with these compounds to form the carboxylate anion and the ammonium cation derived from the amine. Vigorous heating of this salt does drive off water to produce the amide, but this procedure is seldom of preparative value except for the formation of **cyclic amides** (called **lactams**) containing five or six atoms in the ring. The following equation shows such a reaction of a dicarboxylic acid to form two amide bonds, producing a cyclic **imide:**

An imide
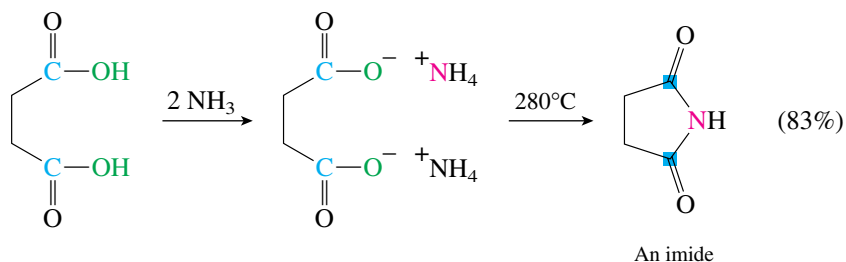
By using the reactions described in Sections 19.2 through 19.6, it is possible to convert one carboxylic acid derivative to any other carboxylic acid derivative. Now let's examine the reactions of these compounds with hydride and organometallic nucleophiles. In these cases the products are no longer carboxylic acid derivatives.

PROBLEM 19.14

Show the products of these reactions:

a) [structure: 3-methoxyaniline with NH$_2$ and CH$_3$O substituents] + CH$_3$COCCH$_3$ (acid anhydride) ⟶

b) CH$_3$CH$_2$CH$_2$COH $\xrightarrow{\text{1) SOCl}_2 \\ \text{2) (CH}_3\text{CH}_2)_2\text{NH} \\ \text{excess}}$

c) [cyclopentyl–C(=O)–Cl] + NH$_2$Ph $\xrightarrow{\text{NaOH}}$

d) [phenyl with COCH$_3$ group] + NH$_2$CH$_3$ ⟶
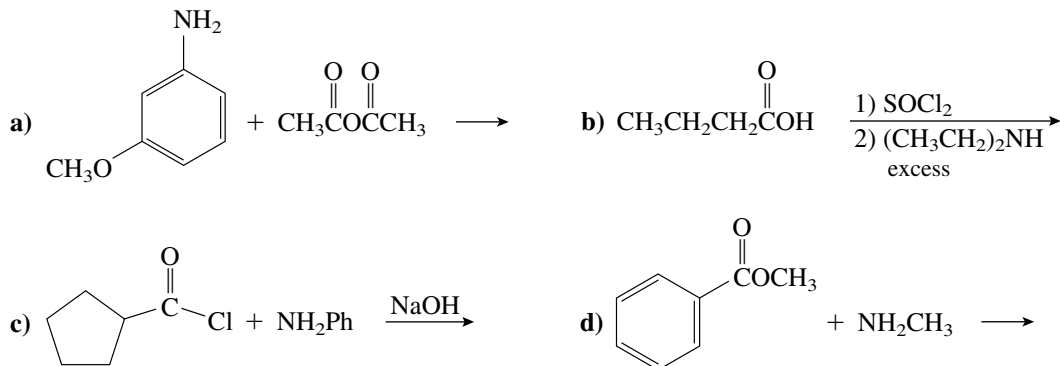
PROBLEM 19.15

Show all of the steps in the mechanism for this reaction and explain why the indicated product is formed and the other is not:

PhCH$_2$NH$_2$ + ClCOCH$_2$CH$_3$ ⟶ PhCH$_2$NHCOCH$_2$CH$_3$ PhCH$_2$NHCCl

                                    Formed   Not formed
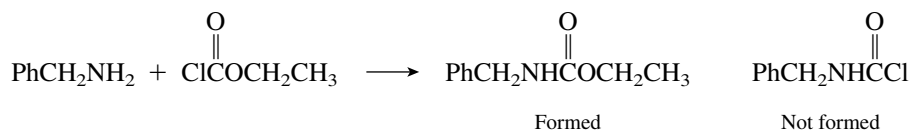
PRACTICE PROBLEM 19.3

Suggest reactions that could be used to convert this amide to the methyl ester:

[cyclopentyl–CH$_2$CNH$_2$ (amide)] ⟶ [cyclopentyl–CH$_2$COCH$_3$ (ester)]
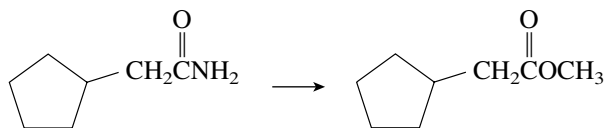
Strategy

Any carboxylic acid derivative can be converted to any other using one or more of the reactions discussed in the previous sections. If the conversion requires going from a less reactive derivative to a more reactive one, then an indirect route may be necessary. Remember that any derivative can be hydrolyzed to a carboxylic acid using water and acid or base. Also remember that the carboxylic acid can be converted to the acyl chloride with thionyl chloride, providing access to the other derivatives.

Solution

There is no reaction that directly converts an amide to an ester because the amide is less reactive. Therefore, the amide is first hydrolyzed to the acid and then the acid is esterified:

[cyclopentyl–CH$_2$CNH$_2$] $\xrightarrow{\text{HCl} \\ \text{H}_2\text{O}}$ [cyclopentyl–CH$_2$COH] $\xrightarrow{\text{CH}_3\text{OH} \\ \text{H}_2\text{SO}_4}$ [cyclopentyl–CH$_2$COCH$_3$]
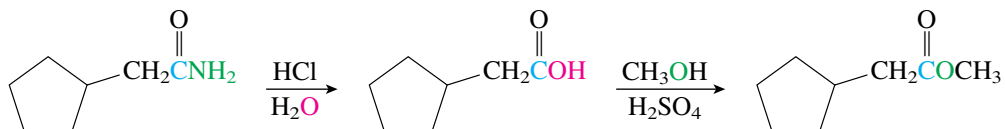
PROBLEM 19.16

Suggest reactions that would accomplish these transformations. More than one step may be necessary in some cases.

a)

b)

c)
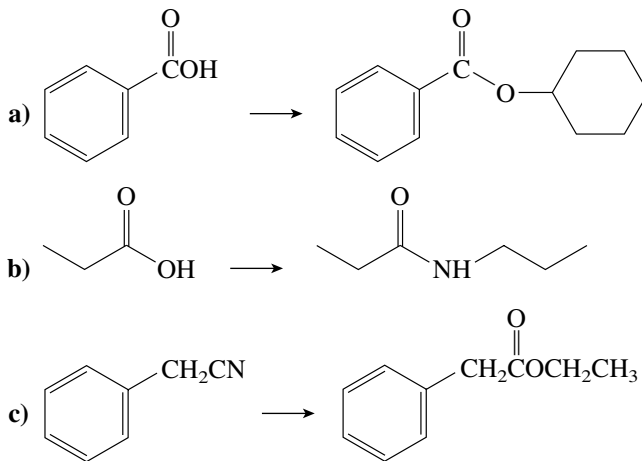
19.7 REACTION WITH HYDRIDE NUCLEOPHILES

On the basis of what we have already learned about the reactions of lithium aluminum hydride with aldehydes and ketones (Chapter 18) and the mechanisms presented so far in this chapter, we can readily predict the product that results when hydride reacts with a carboxylic acid derivative. Consider, for example, the reaction of ethyl benzoate with lithium aluminum hydride. As with all of the reactions in this chapter, this reaction begins with attack of the nucleophile, hydride ion, at the carbon of the carbonyl group, displacing the pi electrons onto the oxygen (see Figure 19.7). Next, these electrons help displace ethoxide from the tetrahedral intermediate. The product of this step is an aldehyde. But recall from Chapter 18 that aldehydes also react with lithium aluminum hydride. Therefore, the product, after workup with acid, is a primary alcohol.

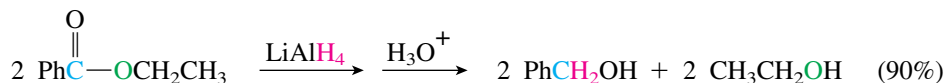From the mechanism it can be seen that it takes two hydride nucleophiles to accomplish this reduction. Therefore, 1 mole of lithium aluminum hydride will reduce 2 moles of the ester.

$$2 \ PhC{-}OCH_2CH_3 \quad \xrightarrow{\text{LiAlH}_4 \quad H_3O^+} \quad 2 \ PhCH_2OH \ + \ 2 \ CH_3CH_2OH \quad (90\%)$$

What happens if less hydride reagent is used? Even though the aldehyde is produced first in the mechanism, the reaction cannot be stopped at the aldehyde stage because the aldehyde is higher on the reactivity scale than the ester. The aldehyde reacts with the hydride nearly as fast as it is formed. If less than 1 mole of hydride per 2 moles of ester is used, a mixture of the ester and the alcohol is produced, along with some of the aldehyde. A reaction that produces a mixture of products like this is not synthetically useful.

On the basis of this mechanistic reasoning, it is apparent that acyl chlorides and anhydrides should also be reduced to primary alcohols by lithium aluminum hydride. Indeed, this is the case. However, because these compounds are less convenient to work with than esters and offer no advantages in synthesis, they are seldom used as substrates for such reductions.

Carboxylic acids are also reduced to primary alcohols by lithium aluminum hydride. The first step in the mechanism for this reaction is an acid–base reaction between the

❶ As usual, the hydride nucleophile attacks the carbonyl carbon and displaces the pi electrons onto the oxygen.

❷ The electrons on the negative oxygen reform the pi bond as ethoxide ion leaves.

❸ The product aldehyde is more reactive toward nucleophiles than is the ester and is attacked by hydride ion, as discussed in Chapter 18.
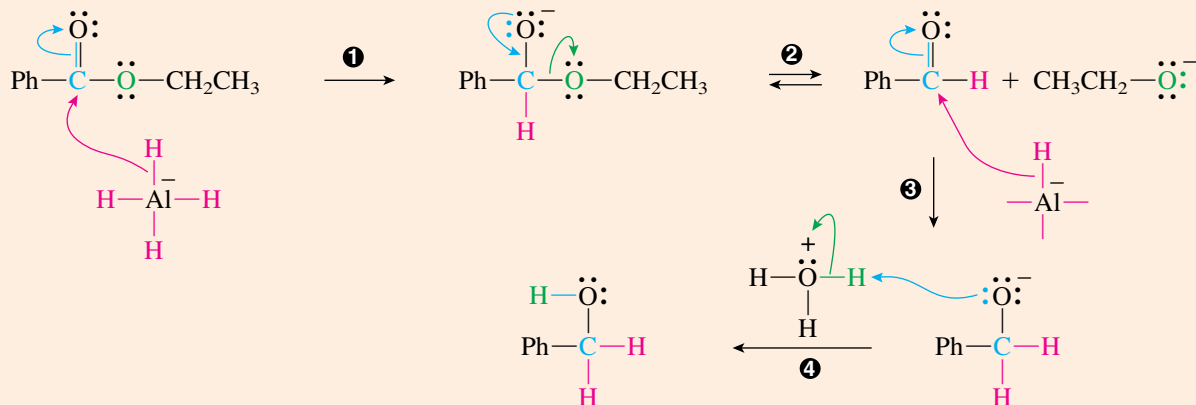
❹ When the acid is added in the second step of the reaction, the oxygen is protonated to produce the final product, a primary alcohol.

The reaction stops at the stage of the alkoxide ion, the conjugate base of an alcohol, until acid is added during the workup phase.

Figure 19.7

MECHANISM OF THE REDUCTION OF AN ESTER WITH LITHIUM ALUMINUM HYDRIDE.

hydride and the acid, as shown in Figure 19.8. Lithium aluminum hydride is reactive enough to attack the relatively unreactive carbonyl group of the carboxylate anion. For the reaction to proceed further, one of the negatively charged oxygens must act as a leaving group. The oxygen is assisted in this process by Lewis acid–base coordination with aluminum. This makes the oxygen less basic and better able to leave. (Similar Lewis acid–base coordination occurs in many other reactions. This is usually ignored in this text unless it makes a particularly important contribution to the reaction.)

In summary, reductions of carboxylic acid derivatives to primary alcohols are usually accomplished by reaction of esters or acids with lithium aluminum hydride. The following equations provide several examples:

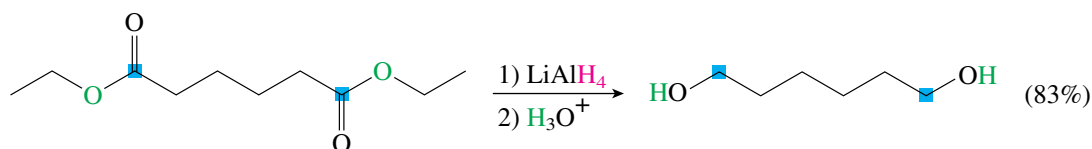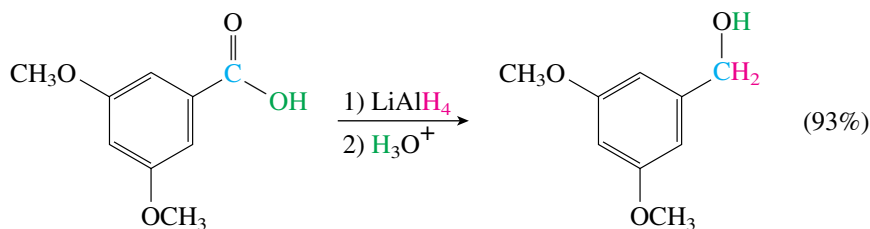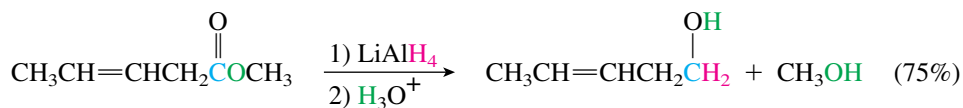$CH_3CH{=}CHCH_2COCH_3$ $\xrightarrow[\text{2) } H_3O^+]{\text{1) LiAlH}_4}$ $CH_3CH{=}CHCH_2CH_2 + CH_3OH$ (75%)

❶ The strongly basic hydride ion removes the acidic proton from the carboxylic acid.

❷ Even though the carboxylate anion is at the bottom of the reactivity scale, lithium aluminum hydride is still powerful enough to react with it.

$$Ph-\overset{\overset{\displaystyle \ddot{O}:}{\|}}{C}-\ddot{\underset{\displaystyle \ddot{}}{O}}-H \quad + \quad H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{-}{Al}}}-H \xrightarrow[\text{(fast)}]{} Ph-\overset{\overset{\displaystyle \ddot{O}:}{\|}}{C}-\ddot{\underset{\displaystyle \ddot{}}{O}}:^{-} \;+\; H_2$$

❶

❷ (slow)

$$\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{-\overset{-}{Al}-}}$$

❹ (fast)

$$Ph-\overset{\overset{\displaystyle \ddot{O}:}{}}{\underset{\underset{\displaystyle -\overset{|}{Al}-}{|}}{C}}-H$$

❸ (fast)

$$Ph-\overset{\overset{\displaystyle :\ddot{O}:^{-}}{}}{\underset{\underset{\displaystyle H}{|}}{C}}-\ddot{O}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{Al}}-H$$

❹ The reduction of the aldehyde proceeds as shown in Figure 19.7.

❸ Although a negative oxygen is a very poor leaving group, coordination with an aluminum compound, such as the one shown or a related one, enables it to leave in this step.
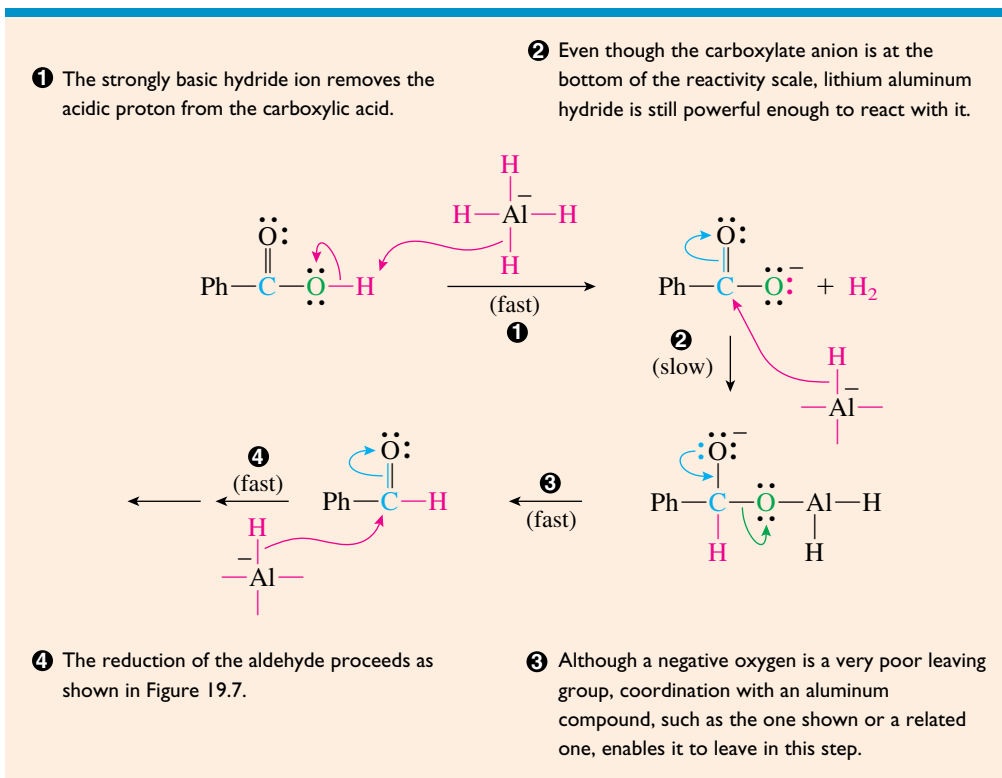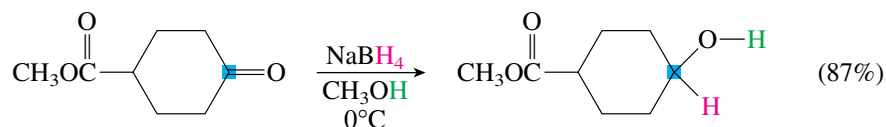
Figure 19.8

MECHANISM OF THE REDUCTION OF A CARBOXYLIC ACID WITH LITHIUM ALUMINUM HYDRIDE—THE FIRST STEPS.

Sodium borohydride is much less reactive than lithium aluminum hydride and reacts only slowly with esters, so it is seldom used for their reduction. However, this property can be used to advantage when we want to reduce an aldehyde or ketone group without reducing an ester group in the same compound.

$$CH_3O\overset{\overset{\displaystyle O}{\|}}{C}-\!\!\!\left\langle \ \right\rangle\!\!=\!O \xrightarrow[\substack{CH_3OH \\ 0°C}]{NaBH_4} CH_3O\overset{\overset{\displaystyle O}{\|}}{C}-\!\!\!\left\langle \ \right\rangle\!\!\!\overset{\displaystyle O-H}{\underset{\displaystyle H}{\times}} \quad (87\%)$$

The reduction of amides with lithium aluminum hydride takes a somewhat different course. The carbonyl group is reduced to a CH_2 group to produce an amine as shown in the following example:

$$CH_3(CH_2)_{10}\overset{\overset{\displaystyle O}{\|}}{C}NHCH_3 \xrightarrow[\text{2) } H_2O]{\text{1) LiAlH}_4} CH_3(CH_2)_{10}CH_2NHCH_3 \quad (95\%)$$
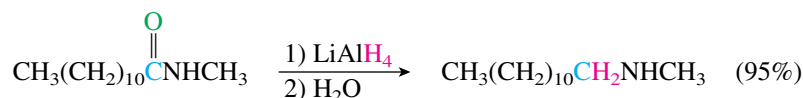
Although this reaction may look strange at first, it follows essentially the same mechanism as the reduction of a carboxylic acid. But the oxygen leaves rather than the nitrogen because the oxygen group is less basic. The mechanism is outlined in Figure 19.9. Note the similarity of this mechanism to that of Figure 19.8. The reduction

❶ Like the reaction shown in Figure 19.8, the mechanism begins with the basic hydride ion removing an acidic proton. Here, it is the proton on the nitrogen.

❷ Next, another hydride ion acts as a nucleophile, attacking the carbon of the carbonyl group.

❸ The oxygen, coordinated with aluminum, leaves in this step rather than the nitrogen because the oxygen is a weaker base and therefore a better leaving group.

❺ The final step in the mechanism is protonation of the negative nitrogen by water that is added during the workup.

❹ The carbon–nitrogen double bond of the imine is attacked by the hydride nucleophile just like a carbon–oxygen double bond.

Figure 19.9

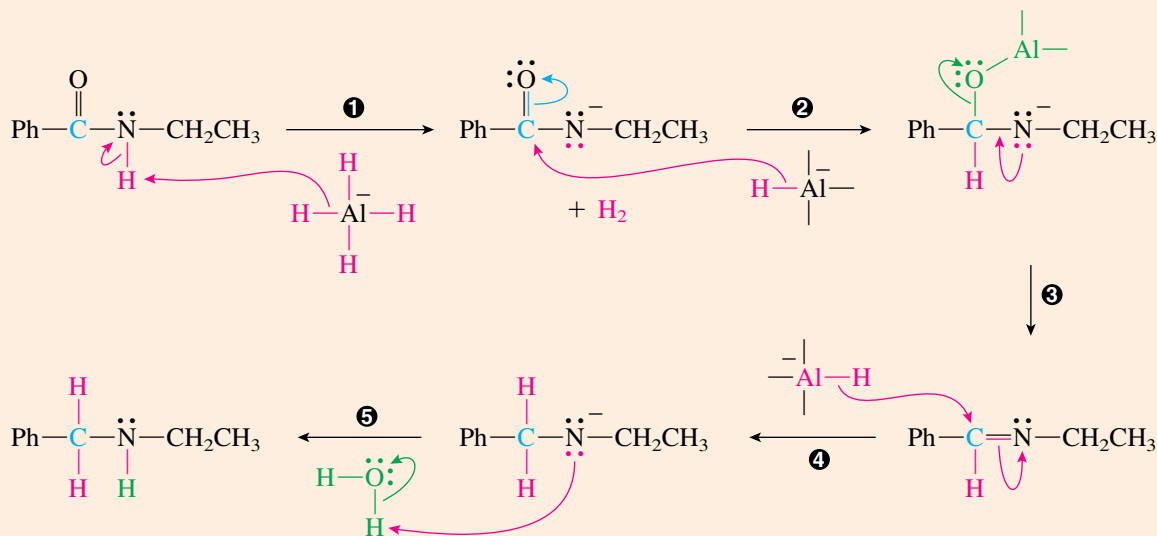**MECHANISM OF THE REDUCTION OF AN AMIDE TO AN AMINE BY LITHIUM ALUMINUM HYDRIDE.**

of amides with lithium aluminum hydride provides an important method for the preparation of amines. Primary, secondary, or tertiary amines can be prepared in this manner.

Another method that can be used to prepare primary amines is the reduction of nitriles with lithium aluminum hydride. The mechanism for this reaction involves sequential addition of two hydride nucleophiles to the electrophilic carbon of the cyano group. The addition of water in the workup step supplies the two protons on the nitrogen in the product. An example follows:

$$ \text{(o-tolyl)C} \equiv \text{N} \quad \xrightarrow[\text{2) H}_2\text{O}]{\text{1) LiAlH}_4\text{, ether, reflux}} \quad \text{(o-tolyl)CH}_2\text{NH}_2 \quad (88\%) $$
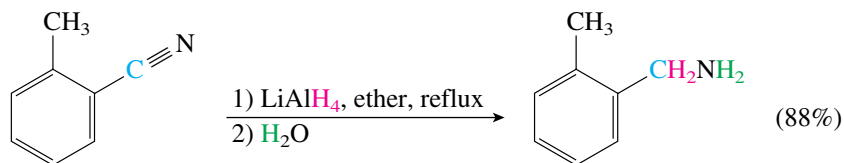
PROBLEM 19.17

Show the products of these reactions:

a) $CH_3CH_2CH_2COCH_3$ $\xrightarrow[\text{2) H}_3\text{O}^+]{\text{1) LiAlH}_4}$

b) (m-methylbenzamide, $CNHCH_3$) $\xrightarrow[\text{2) H}_2\text{O}]{\text{1) LiAlH}_4}$

c) [structure: cyclohex-3-enyl acetate, $OCCH_3$ ester with O] $\xrightarrow[\text{2) H}_3\text{O}^+]{\text{1) LiAlH}_4}$

d) [structure: benzene ring with two $COCH_2CH_3$ / CCH_3 ketone groups, each with O] $\xrightarrow[\text{CH}_3\text{OH}]{\text{NaBH}_4}$

e) [structure: pentanenitrile chain ending in N] $\xrightarrow[\text{2) H}_2\text{O}]{\text{1) LiAlH}_4}$
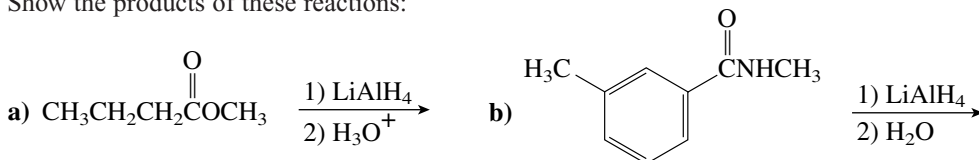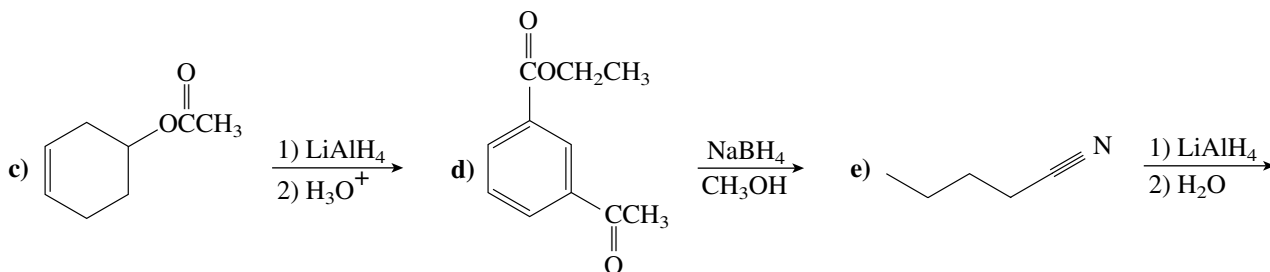
PROBLEM 19.18

Explain why water, rather than H_3O^+, is added to protonate the products of the reduction of amides and nitriles with lithium aluminum hydride.

19.8 REDUCTION OF ACID DERIVATIVES TO ALDEHYDES

As illustrated in Figure 19.7, the reduction of an acid derivative, such as an ester, with lithium aluminum hydride produces an aldehyde as an intermediate. Reduction of the aldehyde gives a primary alcohol as the ultimate product. It would be useful to be able to stop such a reduction at the aldehyde stage so that an aldehyde could be prepared directly from a carboxylic acid derivative.

Let's analyze how such a conversion might be accomplished. What carboxylic acid derivative might be a suitable starting material for reduction to an aldehyde? An ester does not appear to be a good choice because it is less reactive than an aldehyde. Any reagent that is reactive enough to reduce the ester will also be reactive enough to reduce the aldehyde product. However, a more reactive carboxylic acid derivative, such as an acyl chloride, might prove suitable. An acyl chloride is more reactive than an aldehyde, so it is possible, at least in theory, to find a reducing agent that is reactive enough to reduce the acyl chloride but not reactive enough to reduce the aldehyde product. In fact, lithium tri-*t*-butoxyaluminum hydride, LiAlH(O*t*-Bu)$_3$, has been found to have just such reactivity:
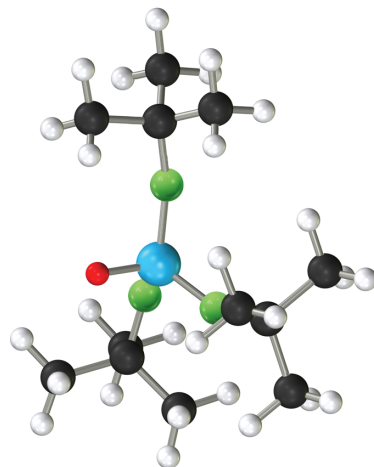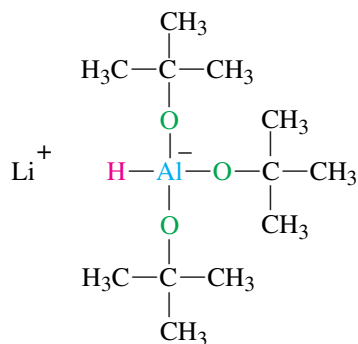

Lithium tri-*t*-butoxyaluminum hydride [LiAlH(O*t*-Bu)$_3$]
(reduces an acyl chloride but not an aldehyde)

The steric hindrance caused by the bulky tertiary butoxy groups makes this reagent much less reactive than lithium aluminum hydride. At low temperature ($-78°C$) it is reactive enough to attack the carbonyl carbon of an acyl chloride, but it reacts only slowly with the aldehyde product. Examples of the use of this reagent to prepare aldehydes are provided in the following equations:
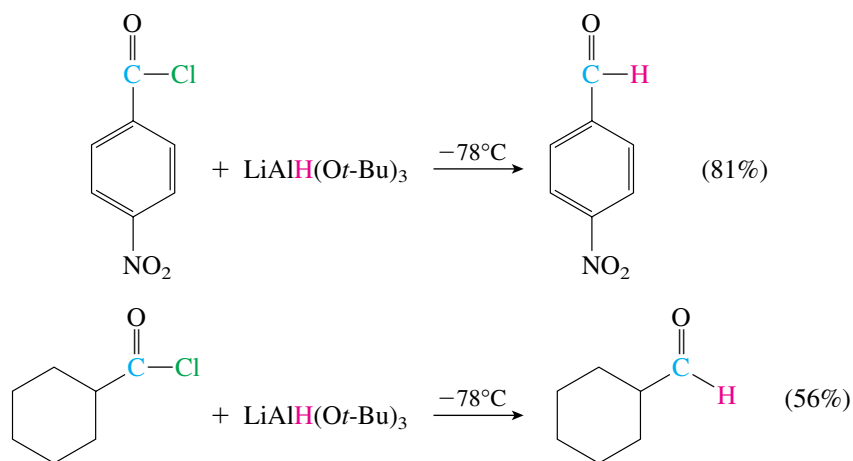
Numerous other metal hydride reagents have been developed to accomplish a variety of specialized reductions. The only other one that will be discussed here is diisobutylaluminum hydride, i-Bu_2AlH or DIBALH:
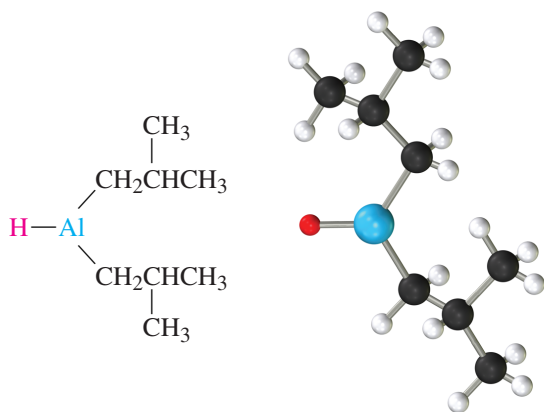
Diisobutylaluminum hydride
(DIBALH or i-Bu_2AlH)

This reagent reduces esters to aldehydes at low temperatures. On the basis of the preceding discussion, we might wonder why the aldehyde is not also reduced by this reagent, because it is reactive enough to attack the ester. The reason is that the aldehyde is not produced until acid is added to the reaction mixture during the workup. The initial intermediate, with a diisobutylaluminum group bonded to the oxygen, is stable at low temperature and does not expel ethoxide ion to produce the aldehyde. Therefore, the aldehyde is never in the presence of the reducing agent. The following equation provides an example:

CH₃ O
| ‖
CH₃CH—C—O—CH₂CH₃   → 1) i-Bu₂AlH −78°C 2) H₃O⁺ →   CH₃CH—C—H   (80%)

CH₃ O
| ‖
CH₃CH—C—H

[Al(i-Bu)₂
       CH₃ O
       | |
  CH₃CH—C—H
           |
           O
            `CH₂CH₃   ]

H₃O⁺

This intermediate is stable
at −78°C until acid is added.
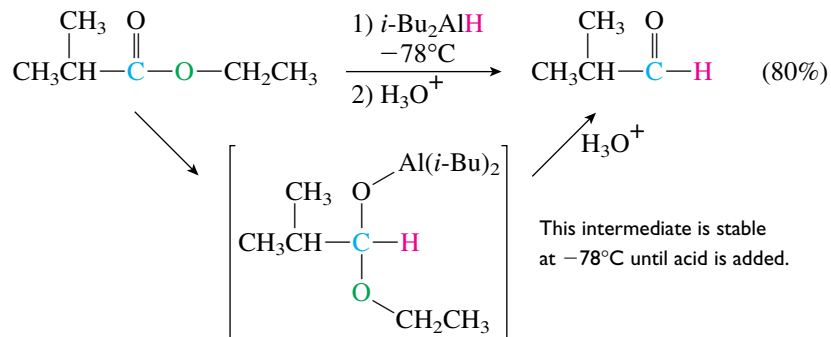
PROBLEM 19.19
Show the products of these reactions:

a)   CH₃ O
         | ‖
    CH₃CH—CCl   → LiAlH(Ot-Bu)₃ −78°C

b)   [aromatic ring with COCH₂CH₃ and OCH₃ substituents]   → 1) i-Bu₂AlH 2) H₃O⁺

c)   [benzene ring with CH₂COH group]   → 1) SOCl₂ 2) LiAlH(Ot-Bu)₃, −78°C
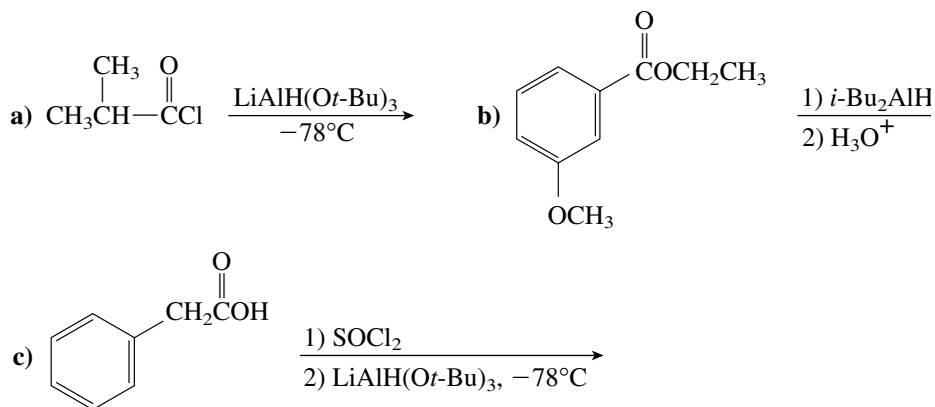
PROBLEM 19.20
Suggest methods to accomplish the following transformations. More than one step may be necessary in some cases.

a) PhCOH ⟶ PhCH

b) PhCOH ⟶ PhCH₂NHPh

c) [pentanenitrile structure with N] ⟶ [pentanal structure with O and H]

d) PhCN ⟶ Ph⌃NH⌃
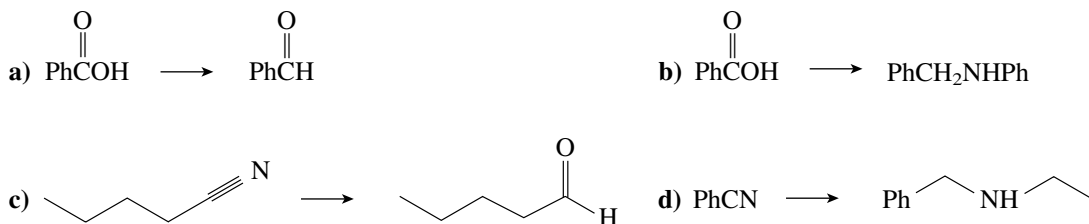
19.9 REACTIONS WITH ORGANOMETALLIC NUCLEOPHILES

Similar to the case for its reaction with lithium aluminum hydride, an ester reacts with a Grignard or organolithium reagent to produce a ketone as the initial product. But because the ketone also reacts with the organometallic reagent, an alcohol is the final product. The mechanism for this reaction is shown in Figure 19.10. Note the similarities between this mechanism and that shown in Figure 19.7 for the reduction of an ester with lithium aluminum hydride.

❶ The organometallic nucleophile attacks the carbonyl carbon and displaces the pi electrons onto the oxygen.

❷ The electrons on the negative oxygen reform the pi bond as the ethoxide anion leaves.

❸ The ketone also reacts with the Grignard reagent as discussed in Chapter 18.
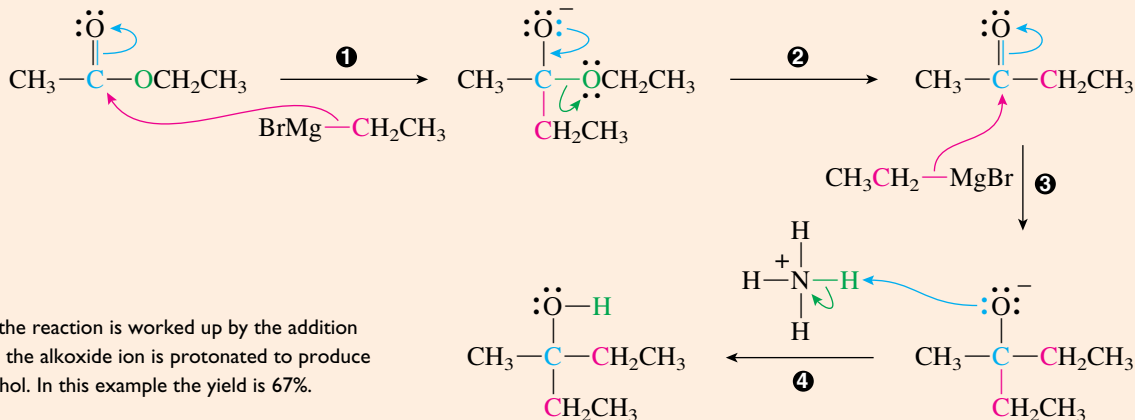
❹ When the reaction is worked up by the addition of acid, the alkoxide ion is protonated to produce an alcohol. In this example the yield is 67%.

Figure 19.10

MECHANISM OF THE REACTION OF A GRIGNARD REAGENT WITH AN ESTER.

This reaction is a useful method to prepare alcohols with two identical groups on the carbon bonded to the hydroxy group. Formate esters produce secondary alcohols; other esters produce tert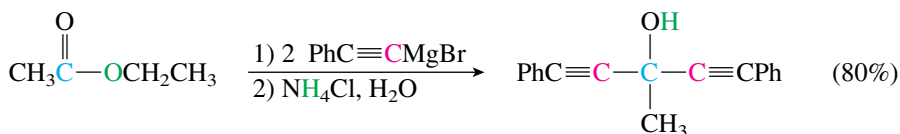iary alcohols. Examples are provided in the following equations. Again, acyl chlorides and anhydrides also give this reaction, but they are seldom used because they offer no advantages over esters.

$$H-\overset{\overset{O}{\|}}{C}-OCH_2CH_3 \quad \xrightarrow[\text{2) } H_3O^+]{\text{1) 2 } CH_3CH_2CH_2CH_2MgBr} \quad CH_3CH_2CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_2CH_2CH_2CH_3 \quad (85\%)$$

$$CH_3\overset{\overset{O}{\|}}{C}-OCH_2CH_3 \quad \xrightarrow[\text{2) } NH_4Cl, H_2O]{\text{1) 2 } PhC\equiv CMgBr} \quad PhC\equiv C-\overset{\overset{OH}{|}}{\underset{\underset{CH_3}{|}}{C}}-C\equiv CPh \quad (80\%)$$
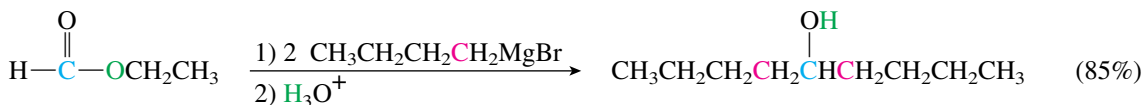
PROBLEM 19.21

Show the products of these reactions:

a) [structure: cyclohexyl–CH(COCH₃)] $\xrightarrow[\text{2) } NH_4Cl, H_2O]{\text{1) 2 PhMgBr}}$

b) $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_3$ $\xrightarrow[\text{2) } NH_4Cl, H_2O]{\text{1) 2 } CH_3Li}$

c) $H\overset{\overset{O}{\|}}{C}OCH_3$ $\xrightarrow[\text{2) } H_3O^+]{\text{1) 2 [cyclopentyl–MgBr]}}$
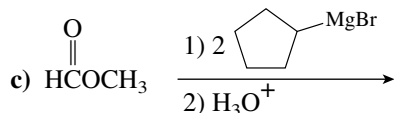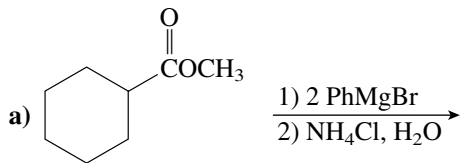
PROBLEM 19.22

Show all of the steps in the mechanism for this reaction:

$$\text{PhCOCH}_2\text{CH}_3 \xrightarrow[\text{2) NH}_4\text{Cl, H}_2\text{O}]{\text{1) 2 CH}_3\text{Li}} \text{PhCCH}_3 \text{ (OH, CH}_3)$$
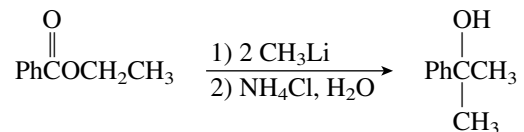
19.10 PREPARATION OF KETONES

The reaction of a Grignard reagent with an ester produces a ketone as an intermediate on the pathway to the alcohol product. It would be useful to be able to stop such a reaction at the intermediate stage so that it could be used as a method for the preparation of ketones. Of course, this is not possible when a Grignard reagent is used because the reaction between the Grignard reagent and the ketone is quite rapid. However, this transformation can be accomplished by using the same strategy described in Section 19.8 for the reduction of carboxylic acid derivatives to aldehydes. A carboxylic acid derivative that is more reactive than a ketone, such as an acyl chloride, and an organometallic nucleophile that will react with the acyl chloride but not the ketone are required.

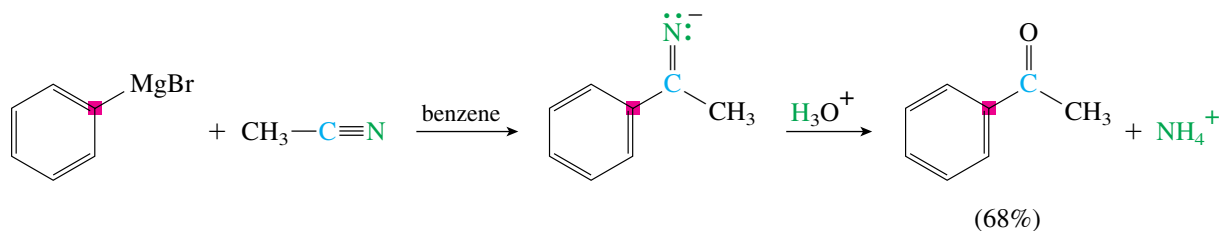This transformation can be accomplished by the reaction of a lithium diorganocuprate reagent with an acyl chloride. Recall that this reagent is prepared from the organolithium reagent by reaction with cuprous iodide, CuI (see Section 18.10). Those containing methyl, primary alkyl, aryl, or vinyl groups add to acyl chlorides to give ketones as illustrated in the following examples:

$$\text{CH}_3\text{CH}-\overset{\text{CH}_3}{\underset{}{\text{C}}}-\text{Cl} + \text{Ph}_2\text{CuLi} \longrightarrow \text{CH}_3\text{CH}-\overset{\text{CH}_3}{\underset{}{\text{C}}}-\text{Ph} \quad (67\%)$$

$$+ \left(\diagup\!\!\!\!\diagdown\right)_2\text{CuLi} \longrightarrow \qquad (70\%)$$
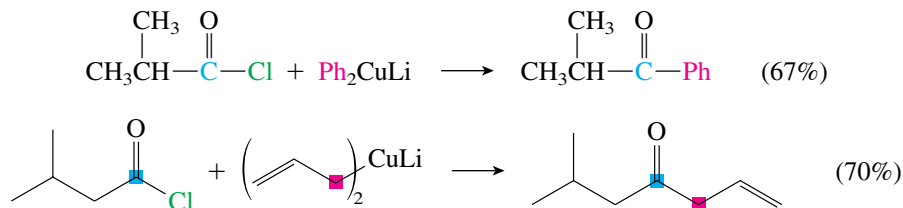
Another method that can be used to prepare ketones is the reaction of a nitrile with a Grignard reagent. In this case the CN double bond of the initial adduct (see Figure 19.11) does not react with the Grignard reagent because the negative charge on the nitrogen makes the carbon too weak as an electrophile. Addition of acid during the workup produces an imine, which is hydrolyzed to a ketone by the reverse of the mechanism shown in Figure 18.3 on page 766. An example is shown in the following equation:
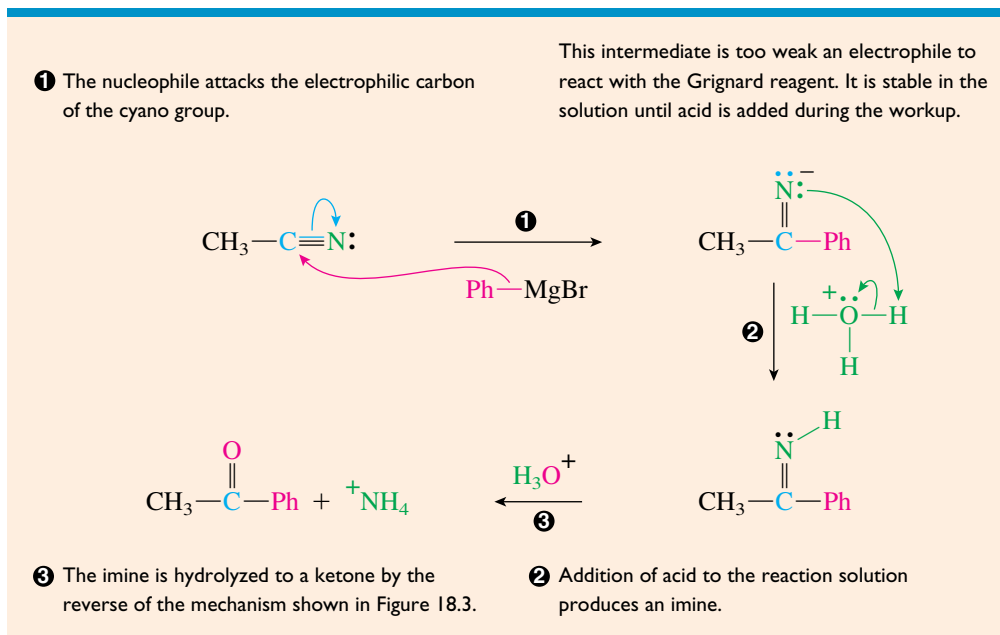

$$+ \text{ CH}_3-\text{C}\equiv\text{N} \xrightarrow{\text{benzene}} \qquad \xrightarrow{\text{H}_3\text{O}^+} \qquad + \text{ NH}_4^+$$

(68%)

① The nucleophile attacks the electrophilic carbon of the cyano group.

This intermediate is too weak an electrophile to react with the Grignard reagent. It is stable in the solution until acid is added during the workup.

$$CH_3-C\equiv N: \quad \xrightarrow{\text{①}} \quad CH_3-\overset{\overset{\displaystyle \ddot{N}:^-}{\|}}{C}-Ph$$

Ph—MgBr

②
$$H-\overset{+}{\overset{\displaystyle \ddot{O}}{|}}-H$$
H

$$CH_3-\overset{O}{\overset{\|}{C}}-Ph + {}^+NH_4 \quad \xleftarrow{\;\; H_3O^+ \;\;}{\text{③}} \quad CH_3-\overset{\overset{\displaystyle \overset{H}{N}}{\|}}{C}-Ph$$

③ The imine is hydrolyzed to a ketone by the reverse of the mechanism shown in Figure 18.3.

② Addition of acid to the reaction solution produces an imine.

Figure 19.11

MECHANISM OF THE REACTION OF A GRIGNARD REAGENT WITH A NITRILE TO PRODUCE A KETONE.

PROBLEM 19.23

Show the products of these reactions:

a) PhCN $\xrightarrow[\text{2) H}_3\text{O}^+]{\text{1)} \; \diagup\diagdown\text{MgBr}}$

b)
$+ \left(\diagup\diagdown \right)_2 \text{CuLi} \longrightarrow$
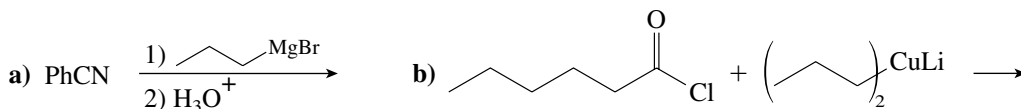
PROBLEM 19.24

Suggest methods to accomplish the following transformations. More than one step may be necessary in some cases.

a) $CH_3CH_2\overset{O}{\overset{\|}{C}}OH \longrightarrow CH_3CH_2\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}-Ph$

b) $CH_3CH_2\overset{O}{\overset{\|}{C}}OH \longrightarrow CH_3CH_2\overset{O}{\overset{\|}{C}}-\!\!\!\diagdown\!\!\!\diagup\!\!-CH_3$

c)

d)