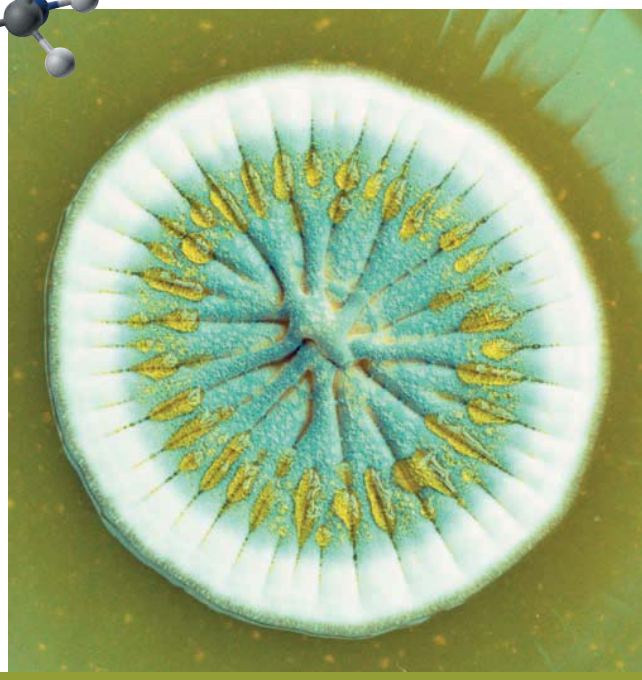
14

Functional Derivatives of Carboxylic Acids



Macrophotograph of the fungus *Penicillium notatum* growing on a petri dish culture of Whickerman's agar. This fungus was used as an early source of the first penicillin antibiotic. Inset: A model of amoxicillin, a compound that contains two amide functional groups. Amides are functional derivatives of carboxylic acids. (Andrew McClenaghan/Photo Researchers, Inc.)

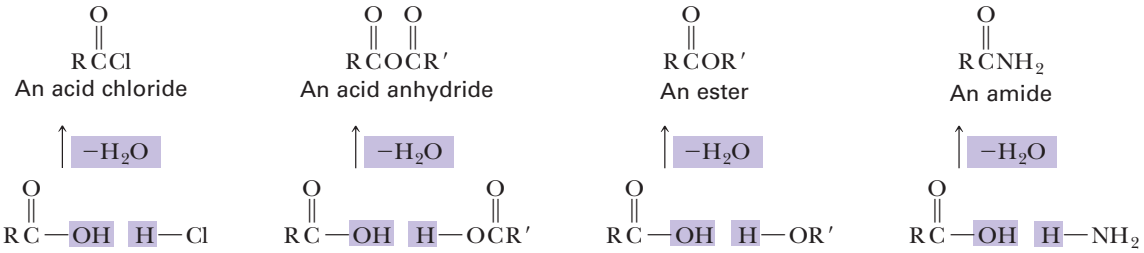
KEY QUESTIONS

HOW TO

CHEMICAL CONNECTIONS

IN THIS CHAPTER, we study four classes of organic compounds, all derived from the carboxyl group: acid halides, acid anhydrides, esters, and amides. Under the general formula of each functional group is a drawing to help you see how the group is formally related to a carboxyl group. The loss of —OH from a carboxyl group and H— from H—Cl, for example,

gives an acid chloride, and similarly, the loss of —OH from a carboxyl group and H— from ammonia gives an amide:

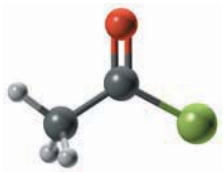


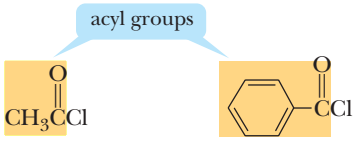
14.1 What Are Some Derivatives of Carboxylic Acids, and How Are They Named?

A. Acid Halides

The functional group of an **acid halide** (acyl halide) is an **acyl group (RCO—)** bonded to a halogen atom (Section 13.7). The most common acid halides are acid chlorides:

Acid halide A derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen—most commonly, chlorine.





Ethanoyl chloride (Acetyl chloride) Benzoyl chloride

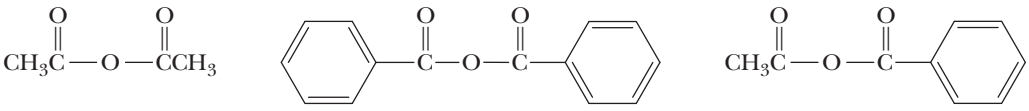
Acid halides are named by changing the suffix *-ic acid* in the name of the parent carboxylic acid to *-yl halide*.

B. Acid Anhydrides

Carboxylic Anhydrides

The functional group of a **carboxylic anhydride** (commonly referred to simply as an anhydride) is two acyl groups bonded to an oxygen atom. The anhydride may be symmetrical (having two identical acyl groups), or it may be mixed (having two different acyl groups). Symmetrical anhydrides are named by changing the suffix *acid* in the name of the parent carboxylic acid to *anhydride*.

Carboxylic anhydride A compound in which two acyl groups are bonded to an oxygen.



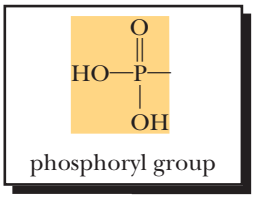
Acetic anhydride Benzoic anhydride Acetic benzoic anhydride (a mixed anhydride)

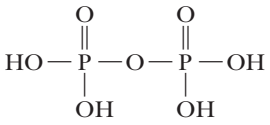
Mixed anhydrides are named by identifying the two parent carboxylic acids from both acyl groups and placing those names in succession, in alphabetical order, without the "acid" part of the name followed by the word *anhydride*.

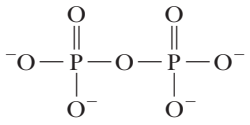
Phosphoric Anhydrides

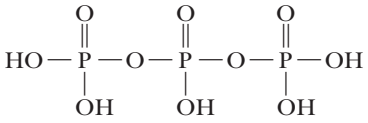
Because of the special importance of anhydrides of phosphoric acid in biochemical systems (Chapter 21), we include them here to show the similarity between them and the anhydrides of carboxylic acids. The functional group of a **phosphoric anhydride** is two

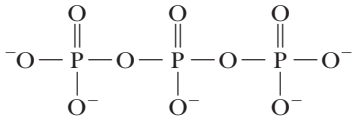
phosphoryl groups bonded to an oxygen atom. Shown here are structural formulas for two anhydrides of phosphoric acid, H_3PO_4, and the ions derived by ionization of the acidic hydrogens of each:




Diphosphoric acid
(Pyrophosphoric acid)


Diphosphate ion
(Pyrophosphate ion)


Triphosphoric acid

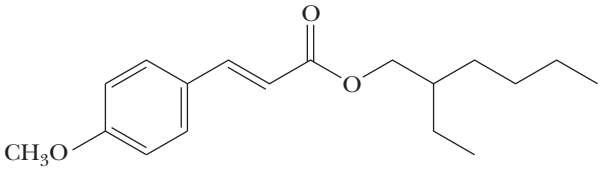

Triphosphate ion

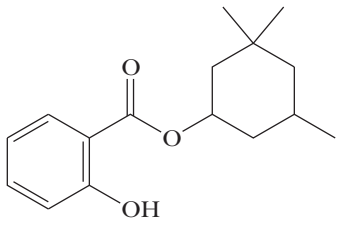
Chemical Connections 14A

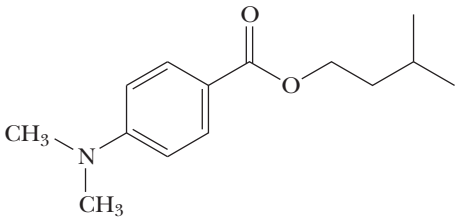
ULTRAVIOLET SUNSCREENS AND SUNBLOCKS

Ultraviolet (UV) radiation (Section 11.1, Table 11.1) penetrating the earth's ozone layer is arbitrarily divided into two regions: UVB (290–320 nm) and UVA (320–400 nm). UVB, a more energetic form of radiation than UVA, interacts directly with molecules of the skin and eyes, causing skin cancer, aging of the skin, eye damage leading to cataracts, and delayed sunburn that appears 12 to 24 hours after exposure. UVA radiation, by contrast, causes tanning. It also damages skin, albeit much less efficiently than UVB. The role of UVA in promoting skin cancer is less well understood.

Commercial sunscreen products are rated according to their sun protection factor (SPF), which is defined as the minimum effective dose of UV radiation that produces a delayed sunburn on protected skin compared with unprotected skin. Two types of active ingredients are found in commercial sunblocks and sunscreens. The most common sunblock agent is zinc oxide, ZnO, a white crystalline substance that reflects and scatters UV radiation. Sunscreens, the second type of active ingredient, absorb UV radiation and then reradiate it as heat. Sunscreens are most effective in screening out UVB radiation, but they do not screen out UVA radiation. Thus, they allow tanning, but prevent the UVB-associated damage. Given here are structural formulas for three common esters used as UVB-screening agents, along with the name by which each is most commonly listed in the "Active Ingredients" label on commercial products:


Octyl *p*-methoxycinnamate


Homosalate


Padimate A

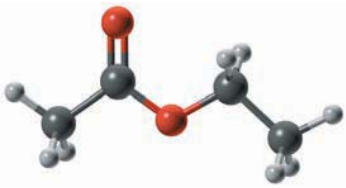
Question

Show how each sunscreen can be synthesized from a carboxylic acid and alcohol using the Fischer esterification reaction (Section 13.6).

C. Esters and Lactones

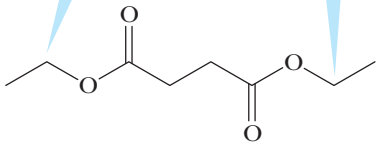
Esters of Carboxylic Acids

The functional group of a **carboxylic ester** (commonly referred to simply as an ester) is an acyl group bonded to —OR or —OAr. Both IUPAC and common names of esters are derived from the names of the parent carboxylic acids. The alkyl or aryl group bonded to oxygen is named first, followed by the name of the acid, in which the suffix *-ic acid* is replaced by the suffix *-ate*:



the name of the group bonded to the —O— comes first

Ethyl ethanoate
(Ethyl acetate)

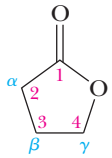


Diethyl butanedioate
(Diethyl succinate)

A cyclic ester is called a **lactone**. The IUPAC name of a lactone is formed by dropping the suffix *-oic acid* from the name of the parent carboxylic acid and adding the suffix *-olactone*. The common name is similarly derived. The location of the oxygen atom in the ring is indicated by a number if the IUPAC name of the acid is used and by a Greek letter α, β, γ, δ, ε, and so forth if the common name of the acid is used.

Lactone A cyclic ester.

4-Butanolactone
(A γ-lactone)

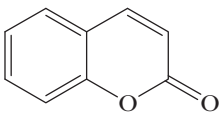


Chemical Connections 14B

FROM MOLDY CLOVER TO A BLOOD THINNER

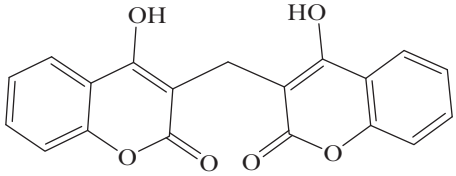
In 1933, a disgruntled farmer delivered a pail of unclotted blood to the laboratory of Dr. Karl Link at the University of Wisconsin and told tales of cows bleeding to death from minor cuts. Over the next couple of years, Link and his collaborators discovered that when cows are fed moldy clover, their blood clotting is inhibited, and they bleed to death from minor cuts and scratches. From the moldy clover, Link isolated the anticoagulant dicoumarol, a substance that delays or prevents blood from clotting. Dicoumarol exerts its anticoagulation effect by interfering with vitamin K activity (Section 20.6D). Within a few years after its discovery, dicoumarol became widely used to treat victims of heart attack and others at risk for developing blood clots.

Dicoumarol is a derivative of coumarin, a cyclic ester that gives sweet clover its pleasant smell. Coumarin, which does not interfere with blood clotting and has been used as a flavoring agent, is converted to dicoumarol as sweet clover becomes moldy. Notice that coumarin is a lactone (cyclic ester), whereas dicoumarol is a dilactone:



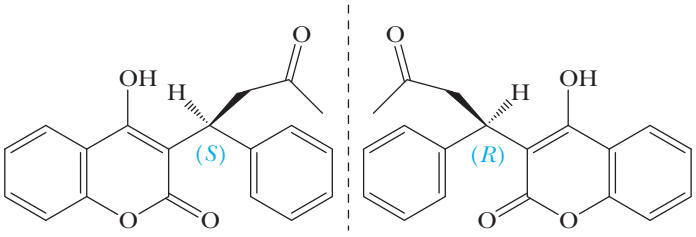
as sweet clover becomes moldy

Coumarin
(from sweet clover)



Dicoumarol
(an anticoagulant)

In a search for even more potent anticoagulants, Link developed warfarin (named after the Wisconsin Alumni Research Foundation), now used primarily as



Warfarin
(a synthetic anticoagulant)

a rat poison: When rats consume warfarin, their blood fails to clot, and they bleed to death. Sold under the brand name Coumadin®, warfarin is also used as a blood thinner in humans. The *S* enantiomer is more active than the *R* enantiomer. The commercial product is a racemic mixture.

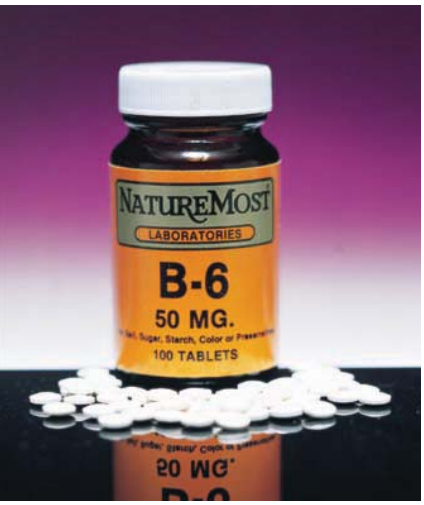
© Daniel MAR/iStockphoto

The powerful anticoagulant dicoumarol was first isolated from moldy clover.

Question

Identify warfarin as an α, β, γ, etc., lactone. Identify each part of warfarin that can undergo keto–enol tautomerization and show the tautomer at that position.

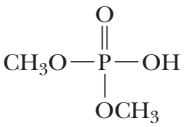
Charles D. Winters



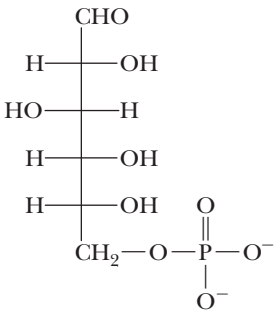
Vitamin B_6, pyridoxal.

Esters of Phosphoric Acid

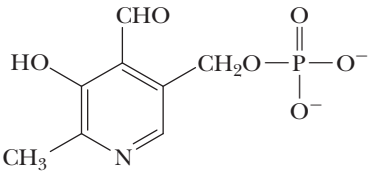
Phosphoric acid has three —OH groups and forms mono-, di-, and triphosphoric esters, which are named by giving the name(s) of the alkyl or aryl group(s) bonded to oxygen, followed by the word *phosphate*—for example, dimethyl phosphate. In more complex phosphoric esters, it is common to name the organic molecule and then show the presence of the phosphoric ester by using either the word *phosphate* or the prefix *phospho-*. On the right are two phosphoric esters, each of special importance in the biological world. The first reaction in the metabolism of glucose is the formation of a phosphoric ester of D-glucose (Section 21.3), to give D-glucose 6-phosphate. Pyridoxal phosphate is one of the metabolically active forms of vitamin B_6. Each of these esters is shown as it is ionized at pH 7.4, the pH of blood plasma; the two hydrogens of each phosphate group are ionized, giving the phosphate group a charge of −2:



Dimethyl phosphate



D-Glucose 6-phosphate



Pyridoxal phosphate

Chemical Connections 14C

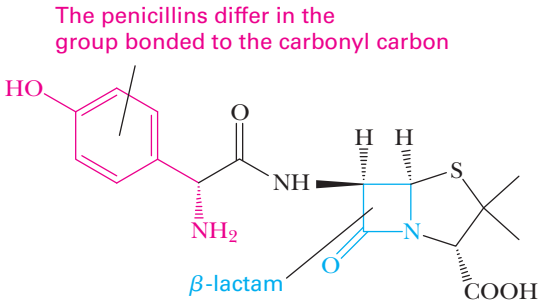
THE PENICILLINS AND CEPHALOSPORINS: β-LACTAM ANTIBIOTICS

The **penicillins** were discovered in 1928 by the Scottish bacteriologist Sir Alexander Fleming. As a result of the brilliant experimental work of Sir Howard Florey, an Australian pathologist, and Ernst Chain, a German chemist who fled Nazi Germany, penicillin G was introduced into the practice of medicine in 1943. For their

pioneering work in developing one of the most effective antibiotics of all time, Fleming, Florey, and Chain were awarded the Nobel Prize in Medicine or Physiology in 1945.

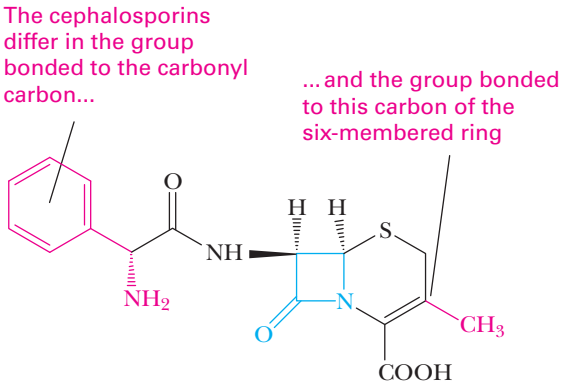
The mold from which Fleming discovered penicillin was *Penicillium notatum*, a strain that gives a relatively low yield of penicillin. Commercial production of the antibiotic uses *P. chrysogenum*, a strain cultured from a mold found growing on a grapefruit in a market in Peoria, Illinois. The penicillins owe their antibacterial activity to a common mechanism that inhibits the biosynthesis of a vital part of bacterial cell walls.

The structural feature common to all penicillins is a **β-lactam** ring fused to a five-membered ring containing one S atom and one N atom:



Amoxicillin
(a β-lactam antibiotic)

Soon after the penicillins were introduced into medical practice, penicillin-resistant strains of bacteria began to appear and have since proliferated. One approach to combating resistant strains is to synthesize newer, more effective penicillins. Among those that have been developed are ampicillin, methicillin, and amoxicillin. Another approach is to search for newer, more effective β-lactam antibiotics. The most effective of these discovered so far are the **cephalosporins**, the first of which was isolated from the fungus *Cephalosporium acremonium*. This class of β-lactam antibiotics has an even broader spectrum of antibacterial activity than the penicillins and is effective against many penicillin-resistant bacterial strains.



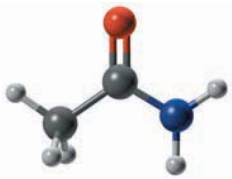
Keflex
(a β-lactam antibiotic)

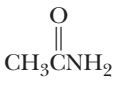
Question

What would you except to be the major form of amoxicillin present in aqueous solution at (a) pH 2.0, (b) at pH 5–6, and (c) at pH 11.0? Explain.

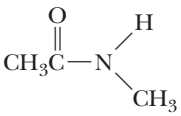
D. Amides and Lactams

The functional group of an **amide** is an acyl group bonded to a trivalent nitrogen atom. Amides are named by dropping the suffix *-oic acid* from the IUPAC name of the parent acid, or *-ic acid* from its common name, and adding *-amide*. If the nitrogen atom of an amide is bonded to an alkyl or aryl group, the group is named and its location on nitrogen is indicated by *N-*. Two alkyl or aryl groups on nitrogen are indicated by *N,N*-di- if the groups are identical or by *N*-alkyl-*N*-alkyl if they are different:

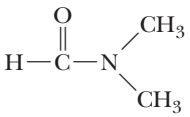




Acetamide
(a 1° amide)



N-Methylacetamide
(a 2° amide)

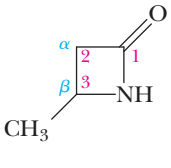


N,N-Dimethylformamide (DMF)
(a 3° amide)

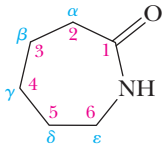
Amide bonds are the key structural feature that joins amino acids together to form polypeptides and proteins (Chapter 18).

Lactam A cyclic amide.

Cyclic amides are given the special name **lactam**. Their common names are derived in a manner similar to those of lactones, with the difference that the suffix *-olactone* is replaced by *-olactam*:



3-Butanolactam
(A β-lactam)

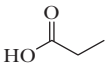
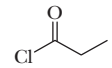
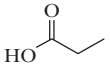
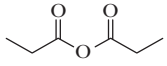
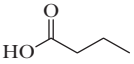
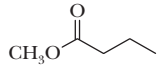
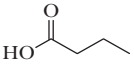
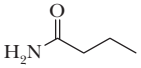


6-Hexanolactam
(An ε-lactam)

6-Hexanolactam is a key intermediate in the synthesis of nylon-6 (Section 16.4A).

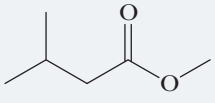
HOW TO 14.1 Name Functional Derivatives of Carboxylic Acids

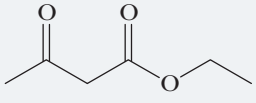
The key to naming one of the four main functional derivatives of carboxylic acids is to realize how its name differs from that of the corresponding carboxylic acid. The following table highlights the difference for each derivative in italics.

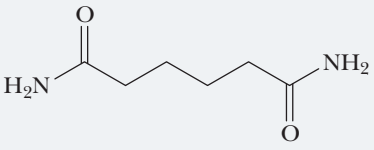
Functional Derivative	Carboxylic Acid Name	Derivative Name	Example
acid halide	alkanoic *acid*	alkanoyl *halide*	 propanoic acid  propanoyl chloride
acid anhydride	alkanoic *acid*	alkanoic *anhydride*	 propanoic acid  propanoic anhydride
ester	alkanoic *acid*	*alkyl* alkano*ate*	 butanoic acid  methyl butanoate
amide	alkanoic *acid*	alkan*amide*	 butanoic acid  butanamide

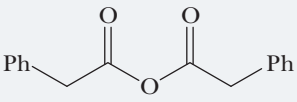
EXAMPLE 14.1

Write the IUPAC name for each compound:

(a) 

(b) 

(c) 

(d) 

STRATEGY

Identify the longest chain containing the functional derivative to establish the root name. Treat the molecule as if each functional derivative group were a carboxyl group and name it as a carboxylic acid. Then change the suffix of the name to reflect the derivative. See HowTo 14.1 for examples.

SOLUTION

Given first are IUPAC names and then, in parentheses, common names:

(a) Methyl 3-methylbutanoate (methyl isovalerate, from isovaleric acid)
(b) Ethyl 3-oxobutanoate (ethyl β-ketobutyrate, from β-ketobutyric acid)
(c) Hexanediamide (adipamide, from adipic acid)
(d) Phenylethanoic anhydride (phenylacetic anhydride, from phenylacetic acid)

See problems 14.9–14.11

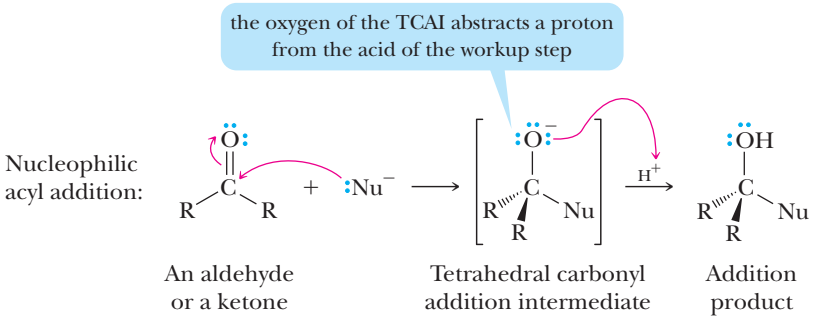
PROBLEM 14.1

Draw a structural formula for each compound:

(a) *N*-Cyclohexylacetamide
(b) *sec*-Butyl acetate
(c) Cyclobutyl butanoate
(d) *N*-(2-Octyl)benzamide
(e) Diethyl adipate
(f) Propanoic anhydride

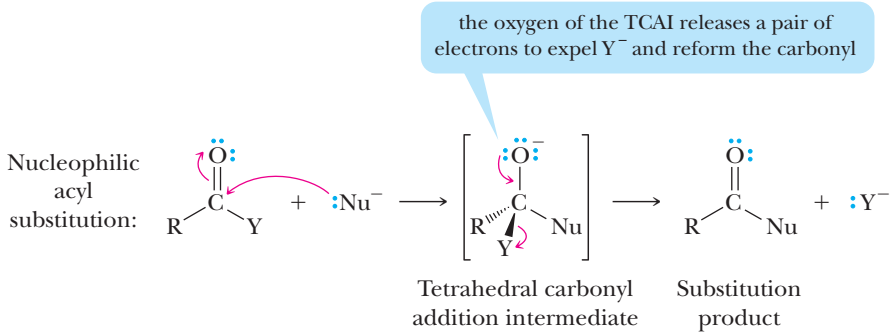
14.2 What Are the Characteristic Reactions of Carboxylic Acid Derivatives?

The most common reaction theme of acid halides, anhydrides, esters, and amides is the addition of a nucleophile to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate. To this extent, the reactions of these functional groups are similar to nucleophilic addition to the carbonyl groups in aldehydes and ketones (Section 12.4). The **tetrahedral carbonyl addition intermediate** (TCAI) formed from an aldehyde or a ketone then adds H^+. The result of this reaction is nucleophilic addition to a carbonyl group of an aldehyde or a ketone:



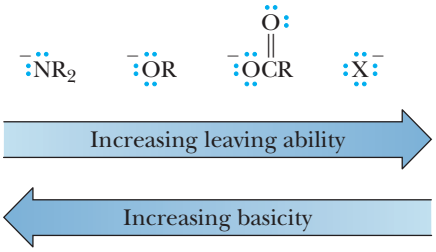
For functional derivatives of carboxylic acids, the fate of the tetrahedral carbonyl addition intermediate is quite different from that of aldehydes and ketones. This intermediate collapses to expel the leaving group and regenerate the carbonyl group. The result of this addition–elimination sequence is **nucleophilic acyl substitution**:

Nucleophilic acyl substitution A reaction in which a nucleophile bonded to a carbonyl carbon is replaced by another nucleophile.

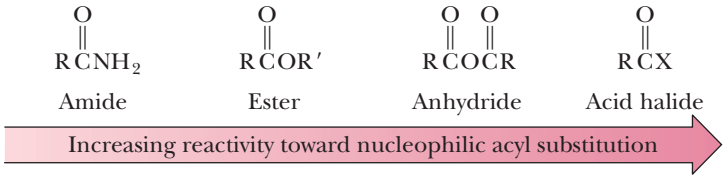


The major difference between these two types of carbonyl addition reactions is that aldehydes and ketones do not have a group, Y, that can leave as a stable anion. They undergo only nucleophilic acyl addition. The four carboxylic acid derivatives we study in this chapter do have a group, Y, that can leave as a stable anion; accordingly, they undergo nucleophilic acyl substitution.

In this general reaction, we show the nucleophile and the leaving group as anions. That need not be the case, however: Neutral molecules, such as water, alcohols, ammonia, and amines, may also serve as nucleophiles in the acid-catalyzed version of the reaction. We show the leaving groups here as anions to illustrate an important point about leaving groups, namely, that the weaker the base, the better is the leaving group (Section 7.5C):



The weakest base in this series, and thus the best leaving group, is halide ion; acid halides are the most reactive toward nucleophilic acyl substitution. The strongest base, and hence the poorest leaving group, is amide ion; amides are the least reactive toward nucleophilic acyl substitution. Acid halides and acid anhydrides are so reactive that they are not found in nature. Esters and amides, however, are universally present.

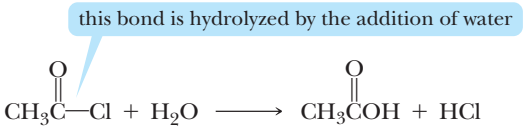


14.3 What Is Hydrolysis?

Hydrolysis (Greek: *hudor*, water; *lyein*, separate) is a chemical process whereby a bond (or bonds) in a molecule is broken by its reaction with water. In hydrolysis, the water molecule is also typically split into H^+ and OH^-.

A. Acid Chlorides

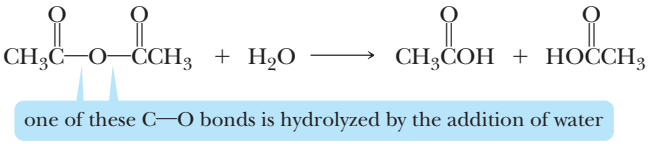
Low-molecular-weight acid chlorides react very rapidly with water to form carboxylic acids and HCl:



Higher-molecular-weight acid chlorides are less soluble and consequently react less rapidly with water.

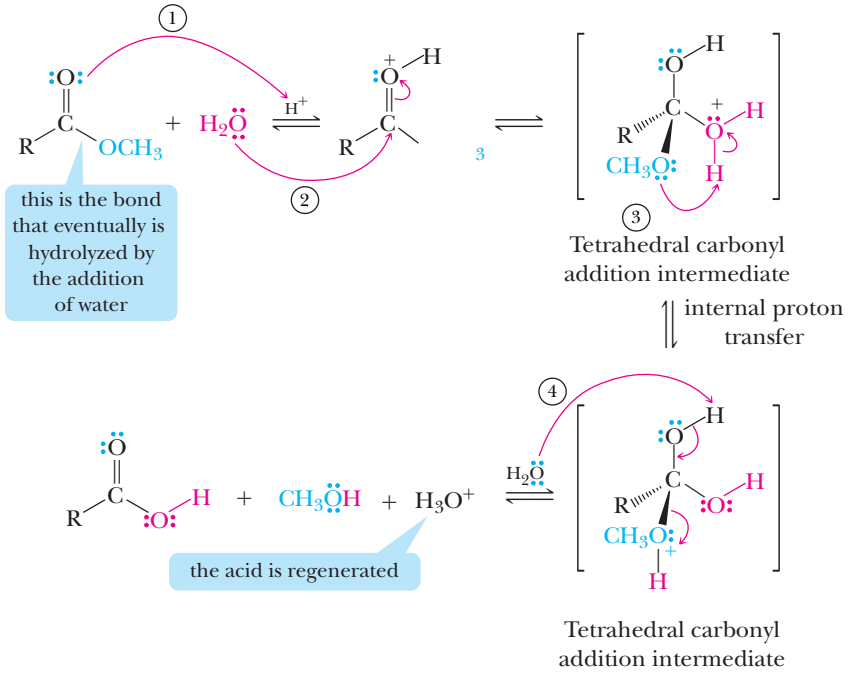
B. Acid Anhydrides

Acid anhydrides are generally less reactive than acid chlorides. The lower-molecular-weight anhydrides, however, react readily with water to form two molecules of carboxylic acid:



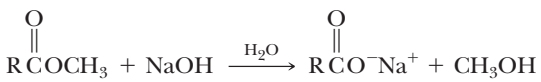
C. Esters

Esters are hydrolyzed only very slowly, even in boiling water. Hydrolysis becomes considerably more rapid, however, when esters are refluxed in aqueous acid or base. When we discussed acid-catalyzed (Fischer) esterification in Section 13.6, we pointed out that esterification is an equilibrium reaction. Hydrolysis of esters in aqueous acid is also an equilibrium reaction and proceeds by the same mechanism as esterification, except in reverse. The role of the acid catalyst is to protonate the carbonyl oxygen **(Step 1: Add a proton)**, thereby increasing the electrophilic character of the carbonyl carbon toward attack by water **(Step 2: Reaction of a nucleophile and an electrophile to form a new covalent bond)** to form a tetrahedral carbonyl addition intermediate. An internal proton transfer to the alkoxy group **(Step 3: Internal proton transfer)** makes that group a good leaving group and allows the collapse of this intermediate **(Step 4: Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group)** to give a carboxylic acid and an alcohol. In this reaction, acid is a catalyst; it is consumed in the first step, but another is generated at the end of the reaction:



Hydrolysis of esters may also be carried out with hot aqueous base, such as aqueous NaOH. Hydrolysis of esters in aqueous base is often called **saponification**, a reference to the use of this reaction in the manufacture of soaps (Section 19.2A). Each mole of ester hydrolyzed requires 1 mole of base, as shown in the following balanced equation:

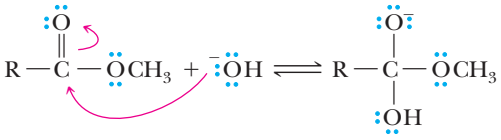
Saponification Hydrolysis of an ester in aqueous NaOH or KOH to an alcohol and the sodium or potassium salt of a carboxylic acid.



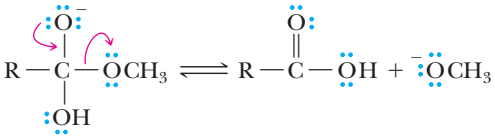
Mechanism

Hydrolysis of an Ester in Aqueous Base

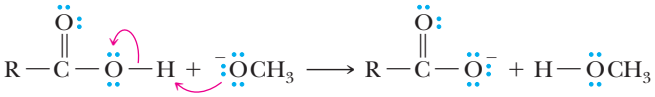
STEP 1: Reaction of a nucleophile and an electrophile to form a new covalent bond. Addition of hydroxide ion to the carbonyl carbon of the ester gives a tetrahedral carbonyl addition intermediate:



STEP 2: Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group. Collapse of this intermediate gives a carboxylic acid and an alkoxide ion:



STEP 3: Take a proton away. Proton transfer from the carboxyl group (an acid) to the alkoxide ion (a base) gives the carboxylate anion. This step is irreversible because the alcohol is not a strong enough nucleophile to attack a carboxylate anion:

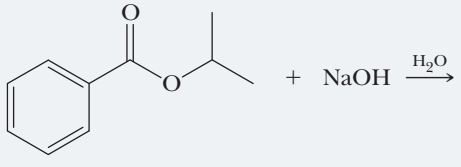


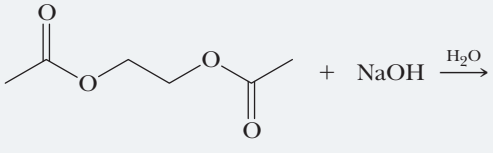
There are two major differences between the hydrolysis of esters in aqueous acid and that in aqueous base:

1. For hydrolysis in aqueous acid, acid is required in only catalytic amounts. For hydrolysis in aqueous base, base is required in equimolar amounts, because it is a reactant, not just a catalyst.
2. Hydrolysis of an ester in aqueous acid is reversible. Hydrolysis in aqueous base is irreversible because a carboxylic acid anion is not attacked by ROH.

EXAMPLE 14.2

Complete and balance equations for the hydrolysis of each ester in aqueous sodium hydroxide, showing all products as they are ionized in aqueous NaOH:

(a) 

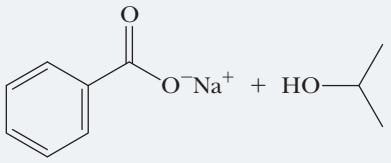
(b) 

STRATEGY

The hydrolysis of an ester results in a carboxyl group and an alcohol for every ester group in the molecule. In aqueous base, one mole of NaOH is consumed for every ester group in the molecule.

SOLUTION

The products of hydrolysis of (a) are benzoic acid and 2-propanol. In aqueous NaOH, benzoic acid is converted to its sodium salt. Therefore, 1 mole of NaOH is required for the hydrolysis of 1 mole of this ester. Compound (b) is a diester of ethylene glycol. Two moles of NaOH are required for its hydrolysis:

(a) 

Sodium benzoate — 2-Propanol (Isopropyl alcohol)

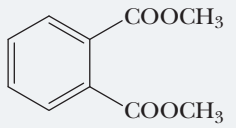
(b) $2\ CH_3CO^-Na^+ + HOCH_2CH_2OH$

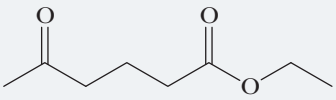
Sodium acetate — 1,2-Ethanediol (Ethylene glycol)

See problems 14.19, 14.20, 14.31

PROBLEM 14.2

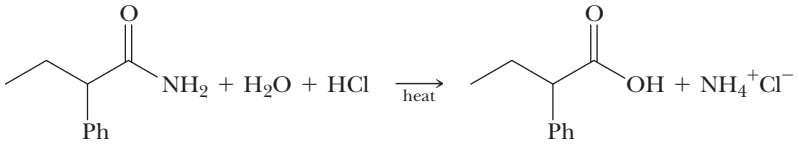
Complete and balance equations for the hydrolysis of each ester in aqueous solution, showing each product as it is ionized under the given experimental conditions:

(a)  $+ NaOH \xrightarrow{H_2O}$ (excess)

(b)  $+ H_2O \xrightarrow{HCl}$

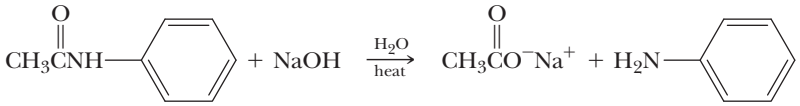
D. Amides

Amides require considerably more vigorous conditions for hydrolysis in both acid and base than do esters. Amides undergo hydrolysis in hot aqueous acid to give a carboxylic acid and ammonia. Hydrolysis is driven to completion by the acid–base reaction between ammonia or the amine and acid to form an ammonium salt. One mole of acid is required per mole of amide:



2-Phenylbutanamide — 2-Phenylbutanoic acid

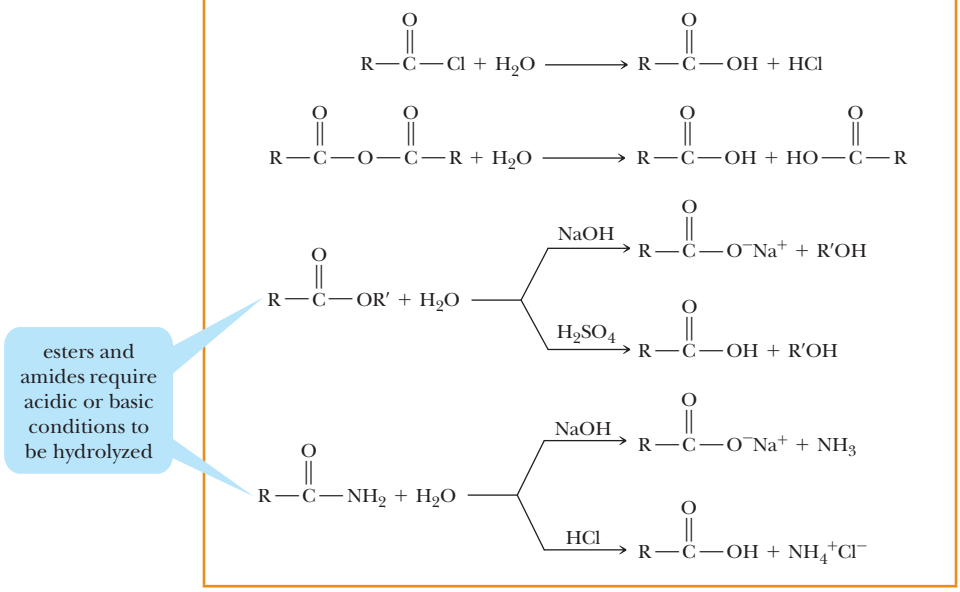
In aqueous base, the products of amide hydrolysis are a carboxylic acid and ammonia or an amine. Base-catalyzed hydrolysis is driven to completion by the acid–base reaction between the carboxylic acid and base to form a salt. One mole of base is required per mole of amide:



N-Phenylethanamide (*N*-Phenylacetamide, Acetanilide) — Sodium acetate — Aniline

The reactions of these functional groups with water are summarized in Table 14.1. Remember that, although all four functional groups react with water, there are large differences in the rates and experimental conditions under which they undergo hydrolysis.

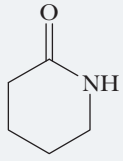
TABLE 14.1 Summary of Reaction of Acid Chlorides, Anhydrides, Esters, and Amides with Water



EXAMPLE 14.3

Write equations for the hydrolysis of these amides in concentrated aqueous HCl, showing all products as they exist in aqueous HCl and showing the number of moles of HCl required for the hydrolysis of each amide:

(a) $CH_3CN(CH_3)_2$ **(b)**



STRATEGY

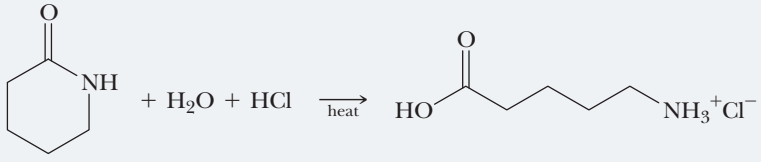
The hydrolysis of an amide results in a carboxyl group and an ammonium chloride ion for every amide group in the molecule. Either 1 mole of NaOH (basic conditions) or 1 mole of HCl (acidic conditions) is consumed for every amide group in the molecule.

SOLUTION

(a) Hydrolysis of *N,N*-dimethylacetamide gives acetic acid and dimethylamine. Dimethylamine, a base, is protonated by HCl to form dimethylammonium ion and is shown in the balanced equation as dimethylammonium chloride. Complete hydrolysis of this amide requires 1 mole of HCl for each mole of the amide:

$$CH_3CN(CH_3)_2 + H_2O + HCl \xrightarrow[\text{heat}]{} CH_3COH + (CH_3)_2NH_2^+Cl^-$$

(b) Hydrolysis of this δ-lactam gives the protonated form of 5-aminopentanoic acid. One mole of acid is required per mole of lactam:



See problems 14.29, 14.32

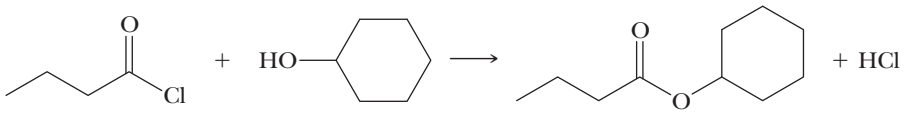
PROBLEM 14.3

Complete equations for the hydrolysis of the amides in Example 14.3 in concentrated aqueous NaOH. Show all products as they exist in aqueous NaOH, and show the number of moles of NaOH required for the hydrolysis of each amide.

14.4 How Do Carboxylic Acid Derivatives React with Alcohols?

A. Acid Chlorides

Acid chlorides react with alcohols to give an ester and HCl:

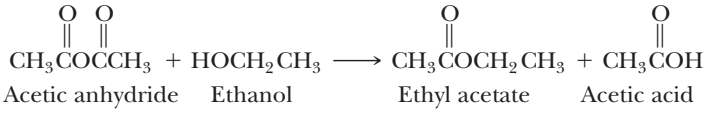


Butanoyl chloride Cyclohexanol Cyclohexyl butanoate

Because acid chlorides are so reactive toward even weak nucleophiles such as alcohols, no catalyst is necessary for these reactions. Phenol and substituted phenols also react with acid chlorides to give esters.

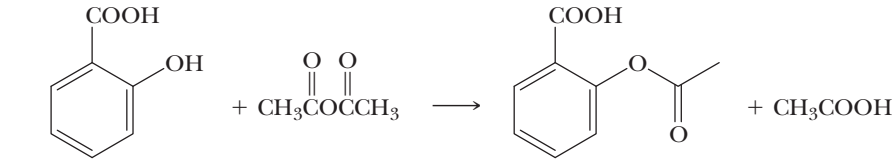
B. Acid Anhydrides

Acid anhydrides react with alcohols to give 1 mole of ester and 1 mole of a carboxylic acid.



Acetic anhydride Ethanol Ethyl acetate Acetic acid

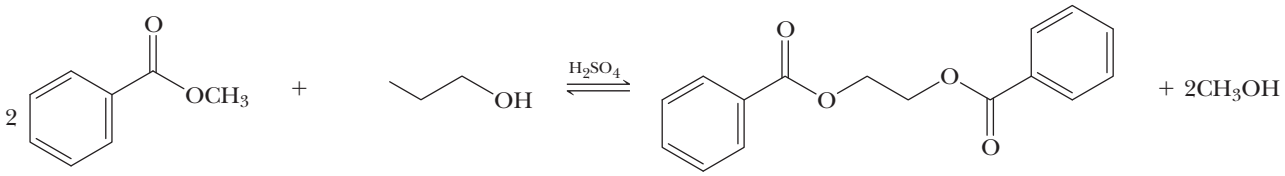
Thus, the reaction of an alcohol with an anhydride is a useful method for synthesizing esters. Aspirin is synthesized on an industrial scale by reacting acetic anhydride with salicylic acid:



2-Hydroxybenzoic acid (Salicylic acid) Acetic anhydride Acetylsalicylic acid (Aspirin) Acetic acid

C. Esters

When treated with an alcohol in the presence of an acid catalyst, esters undergo an exchange reaction called **transesterification**. In this reaction, the original —OR group of the ester is exchanged for a new —OR group. In the following example, the transesterification can be driven to completion by heating the reaction at a temperature above the boiling point of methanol (65 °C) so that methanol distills from the reaction mixture:



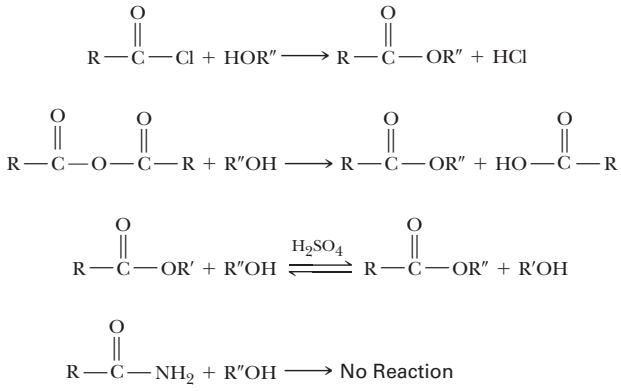
Methyl benzoate 1,2-Ethanediol (Ethylene glycol) (A diester of ethylene glycol)

D. Amides

Amides do not react with alcohols under any experimental conditions. Alcohols are not strong enough nucleophiles to attack the carbonyl group of an amide.

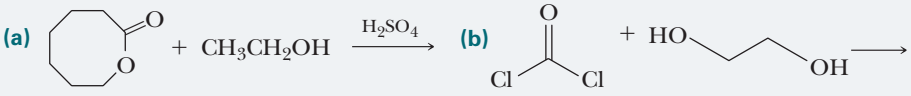
The reactions of the foregoing functional groups with alcohols are summarized in Table 14.2. As with reactions of these same functional groups with water (Section 14.3), there are large differences in the rates and experimental conditions under which they undergo reactions with alcohols. At one extreme are acid chlorides and anhydrides, which react rapidly; at the other extreme are amides, which do not react at all.

TABLE 14.2 Summary of Reaction of Acid Chlorides, Anhydrides, Esters, and Amides with Alcohols



EXAMPLE 14.4

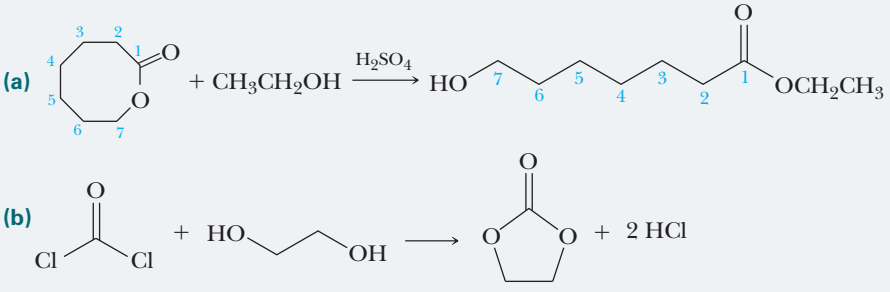
Complete these equations:



STRATEGY

Acid halides, anhydrides, and esters undergo nucleophilic acyl substitution with alcohols (HOR′), the net result being the replacement of each —X, —OC(O)R, or —OR group with the —OR′ group of the alcohol.

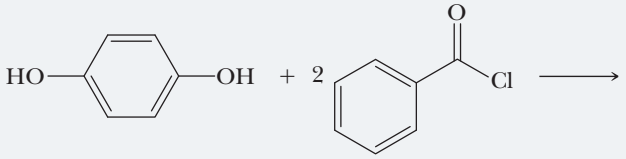
SOLUTION

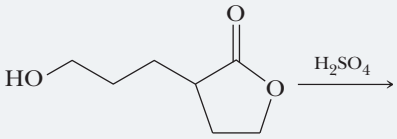


See problems 14.16, 14.17, 14.19–14.22, 14.28

PROBLEM 14.4

Complete these equations (the stoichiometry of each is given in the equation):

(a) 

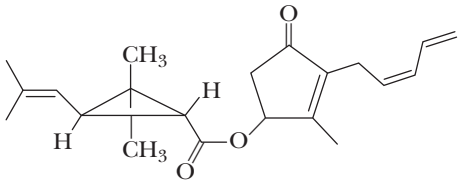
(b) 

Chemical Connections 14D

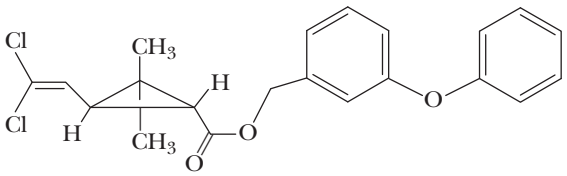
THE PYRETHRINS: NATURAL INSECTICIDES OF PLANT ORIGIN

Pyrethrum is a natural insecticide obtained from the powdered flower heads of several species of *Chrysanthemum*, particularly *C. cinerariaefolium*. The active substances in pyrethrum, principally pyrethrins I and II, are contact poisons for insects and cold-blooded vertebrates. Because their concentrations in the pyrethrum powder used in chrysanthemum-based insecticides are nontoxic to plants and higher animals, pyrethrum powder is used in household and livestock sprays, as well as in dusts for edible plants. Natural pyrethrins are esters of chrysanthemic acid.

While pyrethrum powders are effective insecticides, the active substances in them are destroyed rapidly in the environment. In an effort to develop synthetic compounds as effective as these natural insecticides but with greater biostability, chemists have prepared a series of esters related in structure to chrysanthemic acid. Permethrin is one of the most commonly used synthetic pyrethrinlike compounds in household and agricultural products.



Pyrethrin I



Permethrin

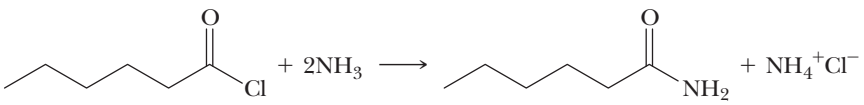
Question

Show the compounds that would result if pyrethrin I and permethrin were to undergo hydrolysis.

14.5 How Do Carboxylic Acid Derivatives React with Ammonia and Amines?

A. Acid Chlorides

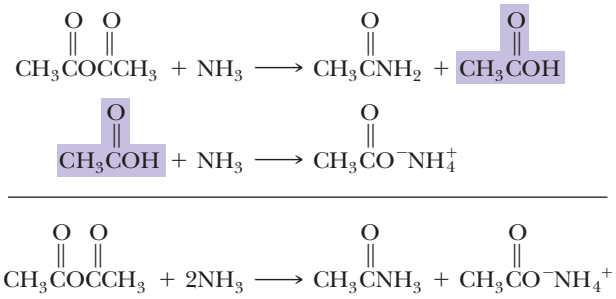
Acid chlorides react readily with ammonia and with 1° and 2° amines to form amides. Complete conversion of an acid chloride to an amide requires 2 moles of ammonia or amine: one to form the amide and one to neutralize the hydrogen chloride formed:



Hexanoyl chloride Ammonia Hexanamide Ammonium chloride

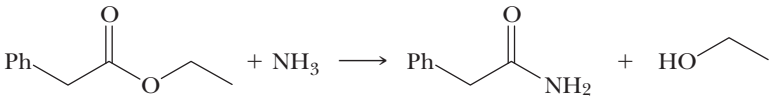
B. Acid Anhydrides

Acid anhydrides react with ammonia and with 1° and 2° amines to form amides. As with acid chlorides, 2 moles of ammonia or amine are required—one to form the amide and one to neutralize the carboxylic acid by-product. To help you see what happens, this reaction is broken into two steps, which, when added together, give the net reaction for the reaction of an anhydride with ammonia:



C. Esters

Esters react with ammonia and with 1° and 2° amines to form amides:



Ethyl phenylacetate | Phenylacetamide | Ethanol

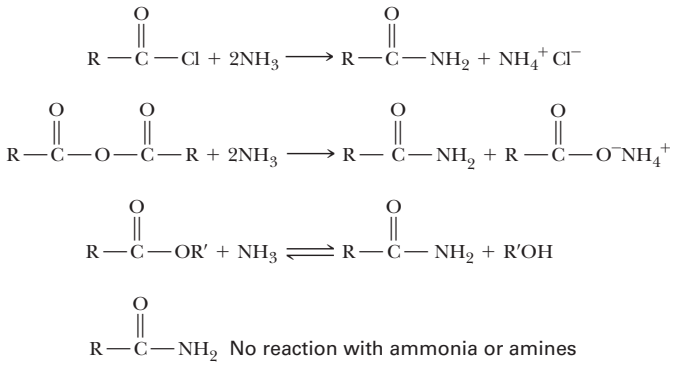
Because an alkoxide anion is a poor leaving group compared with a halide or carboxylate ion, esters are less reactive toward ammonia, 1° amines, and 2° amines than are acid chlorides or acid anhydrides.

D. Amides

Amides do not react with ammonia or amines.

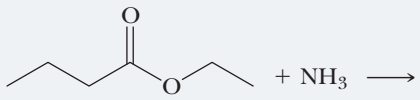
The reactions of the preceding four functional groups with ammonia and amines are summarized in Table 14.3.

TABLE 14.3 Summary of Reaction of Acid Chlorides, Anhydrides, Esters, and Amides with Ammonia and Amines

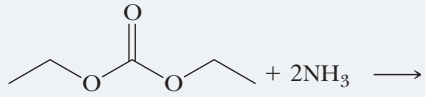


EXAMPLE 14.5

Complete these equations (the stoichiometry of each is given in the equation):

(a) 

Ethyl butanoate

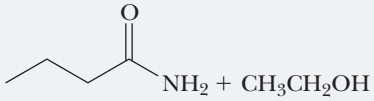
(b) 

Diethyl carbonate

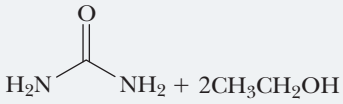
STRATEGY

Acid halides, anhydrides, and esters undergo nucleophilic acyl substitution with ammonia or amines, the net result being the replacement of each —X, —OC(O)R, or —OR group with the $—NH_2$ group of ammonia or the —NHR or $—NR_2$ group of the amine.

SOLUTION

(a) 

Butanamide

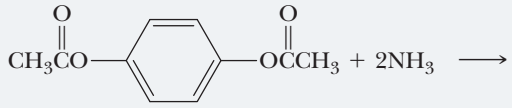
(b) 

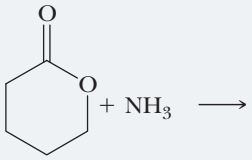
Urea

See problems 14.18–14.22, 14.24–14.26, 14.31, 14.35

PROBLEM 14.5

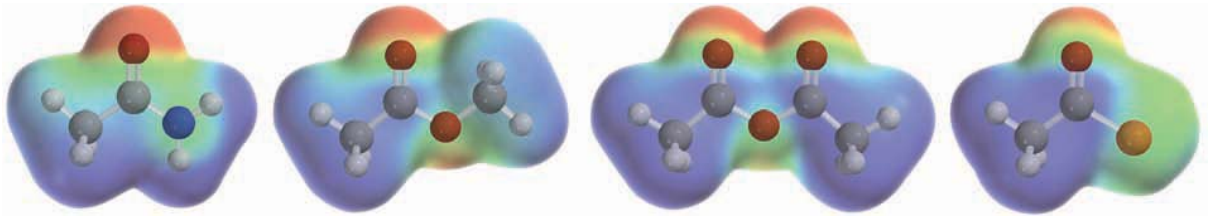
Complete these equations (the stoichiometry of each is given in the equation):

(a) 

(b) 

14.6 How Can Functional Derivatives of Carboxylic Acids Be Interconverted?

In the last few sections, we have seen that acid chlorides are the most reactive carboxyl derivatives toward nucleophilic acyl substitution and that amides are the least reactive:



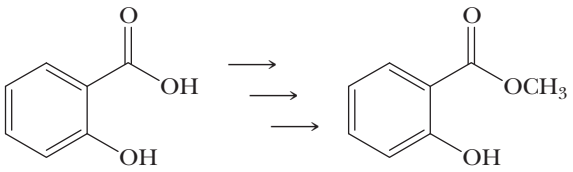
Amide < Ester < Acid anhydride < Acid halide

Increasing reactivity toward nucleophilic acyl substitution

Chemical Connections 14E

SYSTEMATIC ACQUIRED RESISTANCE IN PLANTS

The use of germicides to protect plants from harmful pathogens is common in farming. Recently, plant physiologists discovered that some plant species are able to generate their own defenses against pathogens. The tobacco mosaic virus (TMV), for example, is a particularly devastating pathogen for plants such as tobacco, cucumber, and tomato. Scientists have found that certain strains of these plants produce large amounts of salicylic acid upon being infected with TMV. Accompanying the infection is the appearance of lesions on the leaves of the plants, which help to contain the infection to those localized areas. Furthermore, scientists have discovered that neighboring plants tend to acquire some resistance to TMV. It appears that the infected plant somehow signals neighboring plants of the impending danger by converting salicylic acid to its ester, methyl salicylate:



Salicylic acid — Methyl salicylate

© punyafamily/iStockphoto

The tobacco plant, *Nicotiana tobacum*.

With a lower boiling point and higher vapor pressure than salicylic acid has, the methyl salicylate diffuses into the air from the infected plant, and the surrounding plants use it as a signal to enhance their defenses against TMV.

Question

An early proposal in this research was that the tobacco plant could utilize two molecules of salicylic acid (molar mass 138.12 g/mol) in a nucleophilic acyl substitution reaction to yield a compound with a molar mass of 240.21 g/mol that would be less polar than salicylic acid. Propose a structure for this reaction product.

Another useful way to think about the relative reactivities of these four functional derivatives of carboxylic acids is summarized in Figure 14.1. Any functional group in this figure can be prepared from any functional group above it by treatment with an appropriate oxygen or nitrogen nucleophile. An acid chloride, for example, can be converted to an

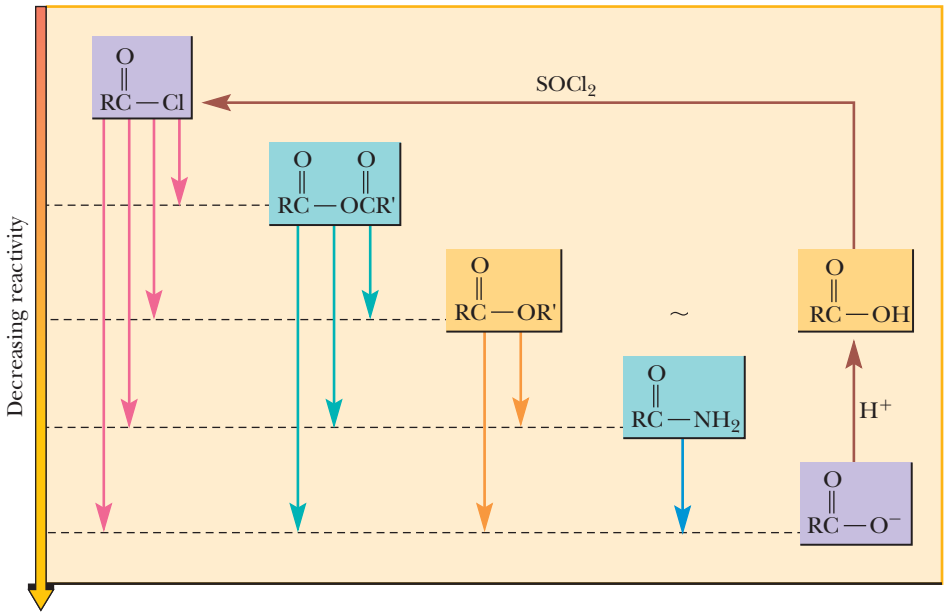


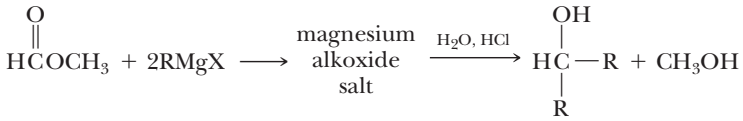
FIGURE 14.1
Relative reactivities of carboxylic acid derivatives toward nucleophilic acyl substitution. A more reactive derivative may be converted to a less reactive derivative by treatment with an appropriate reagent. Treatment of a carboxylic acid with thionyl chloride converts the carboxylic acid to the more reactive acid chloride. Carboxylic acids are about as reactive as esters under acidic conditions, but are converted to the unreactive carboxylate anions under basic conditions.

acid anhydride, an ester, an amide, or a carboxylic acid. An acid anhydride, ester, or amide, however, does not react with chloride ion to give an acid chloride.

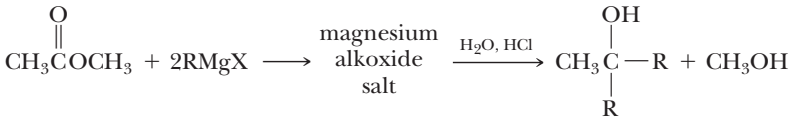
Notice that all carboxylic acid derivatives can be converted to carboxylic acids, which in turn can be converted to acid chlorides. Thus, any acid derivative can be used to synthesize another, either directly or via a carboxylic acid.

14.7 How Do Esters React with Grignard Reagents?

Treating a formic ester with 2 moles of a Grignard reagent, followed by hydrolysis of the magnesium alkoxide salt in aqueous acid, gives a 2° alcohol, whereas treating an ester other than a formate with a Grignard reagent gives a 3° alcohol in which two of the groups bonded to the carbon bearing the —OH group are the same:



An ester of formic acid — A 2° alcohol



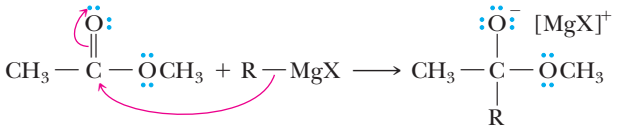
An ester other than formic acid — A 3° alcohol

Reaction of an ester with a Grignard reagent involves the formation of two successive tetrahedral carbonyl addition compounds. The first collapses to give a new carbonyl compound—an aldehyde from a formic ester, a ketone from all other esters. The second intermediate is stable and, when protonated, gives the final alcohol. It is important to realize that it is not possible to use RMgX and an ester to prepare an aldehyde or a ketone: The intermediate aldehyde or ketone is more reactive than the ester and reacts immediately with the Grignard reagent to give a tertiary alcohol.

Mechanism

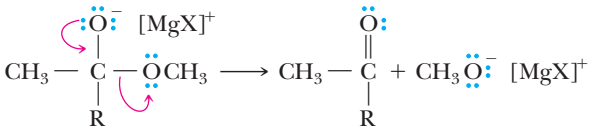
Reaction of an Ester with a Grignard Reagent

STEP 1: Reaction of a nucleophile and an electrophile to form a new covalent bond. Reaction begins with the addition of 1 mole of Grignard reagent to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate:



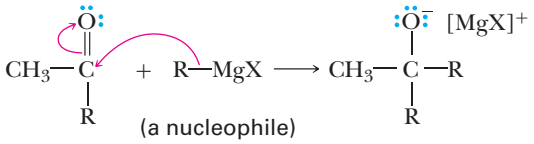
(an electrophile) (a nucleophile) — A magnesium salt (a tetrahedral carbonyl addition intermediate)

STEP 2: Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group. This intermediate then collapses to give a new carbonyl-containing compound and a magnesium alkoxide salt:



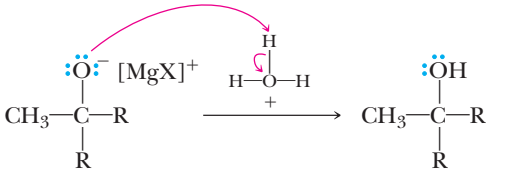
A ketone

STEP 3: Reaction of a nucleophile and an electrophile to form a new covalent bond. The new carbonyl-containing compound reacts with a second mole of Grignard reagent to form a second tetrahedral carbonyl addition compound:



A ketone (an electrophile) (a nucleophile) Magnesium salt

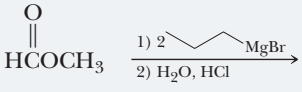
STEP 4: Add a proton. Workup in aqueous acid gives a 3° alcohol (or a 2° alcohol if the starting ester was a formate):

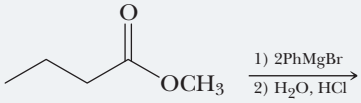


Magnesium salt A 3° alcohol

EXAMPLE 14.6

Complete each Grignard reaction:

(a) 

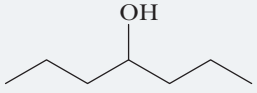
(b) 

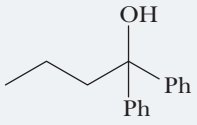
STRATEGY

Reaction of a Grignard reagent with an ester results in an alcohol containing two identical R groups (the R groups from the Grignard reagent) bonded to the former carbonyl carbon.

SOLUTION

Sequence (a) gives a 2° alcohol, and sequence (b) gives a 3° alcohol:

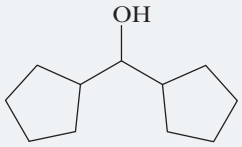
(a) 

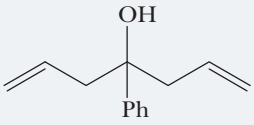
(b) 

See problems 14.30, 14.33, 14.34

PROBLEM 14.6

Show how to prepare each alcohol by treating an ester with a Grignard reagent:

(a) 

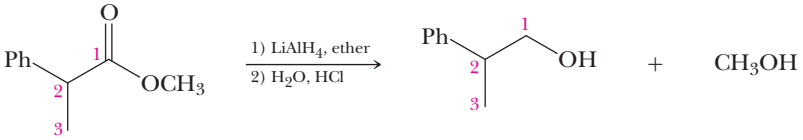
(b) 

14.8 How Are Derivatives of Carboxylic Acids Reduced?

Most reductions of carbonyl compounds, including aldehydes and ketones, are now accomplished by transferring hydride ions from boron or aluminum hydrides. We have already seen the use of sodium borohydride to reduce the carbonyl groups of aldehydes and ketones to hydroxyl groups (Section 12.10B). We have also seen the use of lithium aluminum hydride to reduce not only the carbonyl groups of aldehydes and ketones, but also carboxyl groups (Section 13.5A), to hydroxyl groups.

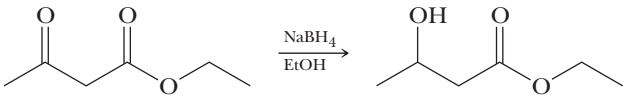
A. Esters

An ester is reduced by lithium aluminum hydride to two alcohols. The alcohol derived from the acyl group is primary:



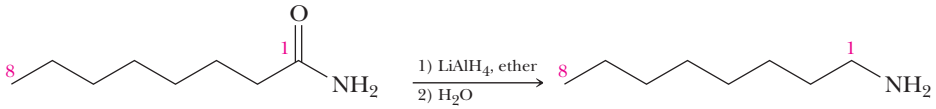
Methyl 2-phenylpropanoate — 2-Phenyl-1-propanol (a 1° alcohol) — Methanol

Sodium borohydride is not normally used to reduce esters because the reaction is very slow. Because of this lower reactivity of sodium borohydride toward esters, it is possible to reduce the carbonyl group of an aldehyde or a ketone to a hydroxyl group with this reagent without reducing an ester or a carboxyl group in the same molecule:

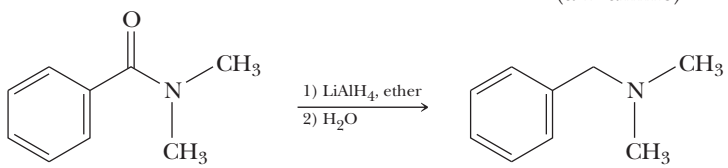


B. Amides

Reduction of amides by lithium aluminum hydride can be used to prepare 1°, 2°, or 3° amines, depending on the degree of substitution of the amide:



Octanamide — 1-Octanamine (a 1° amine)

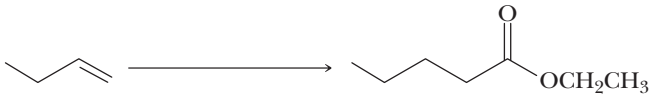


N,N-Dimethylbenzamide — *N,N*-Dimethylbenzylamine (a 3° amine)

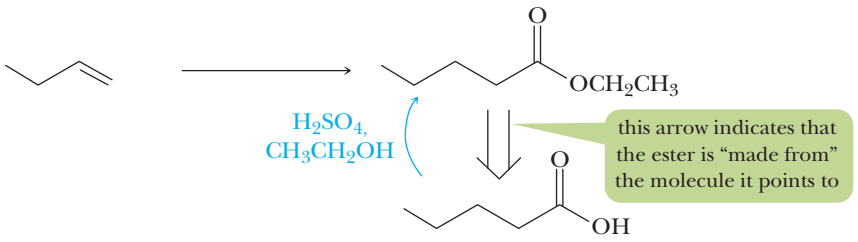
HOW TO 14.2

Approach Multistep Synthesis Problems

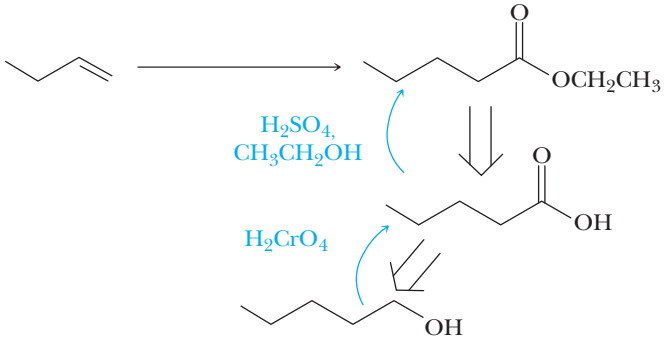
(a) When a given chemical transformation cannot be achieved with a known chemical reaction, it is necessary to use multiple steps to complete the synthesis. One of the most effective ways to accomplish this is through retrosynthetic analysis. The technique, formalized by Harvard Professor and Nobel Laureate E. J. Corey, involves working backwards from a target molecule until the synthesis is achieved. The technique is illustrated using the following transformation:



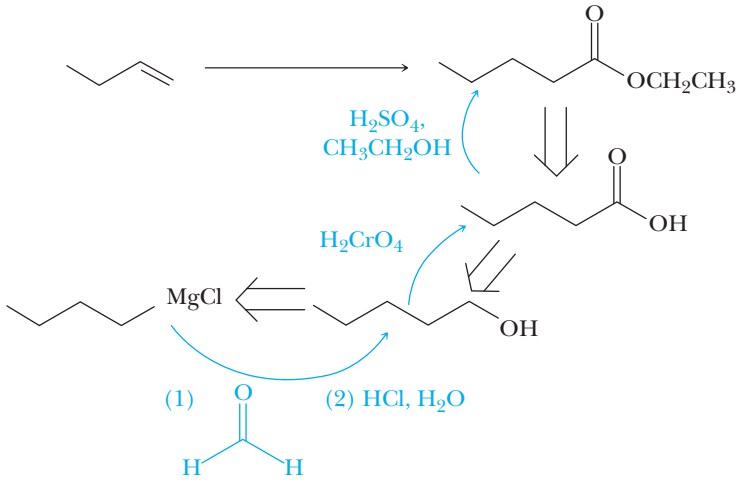
(b) Because there is no reaction that converts an alkene into an ester while also forming a new C—C bond, we work backwards from the ester. The goal is to identify a reaction (or reactions) that can synthesize esters. One such reaction is the Fischer esterification:



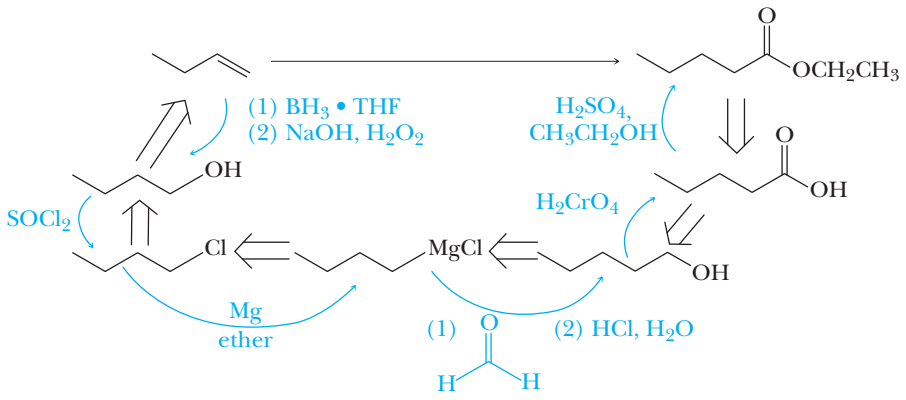
(c) Now that we've proposed that the ester can be made from pentanoic acid via Fischer esterification, the next step is to identify a reaction that can produce pentanoic acid. Here we propose oxidation of a 1° alcohol:



(d) The 1° alcohol, in turn, can be made from a Grignard reagent and formaldehyde:



(e) In this manner, the alkene can be arrived at retrosynthetically:



EXAMPLE 14.7

Show how to bring about each conversion:

(a) $C_6H_5COH \longrightarrow C_6H_5CH_2{-}N$ **(b)** $\bigcirc\!\!-COH \longrightarrow \bigcirc\!\!-CH_2NHCH_3$

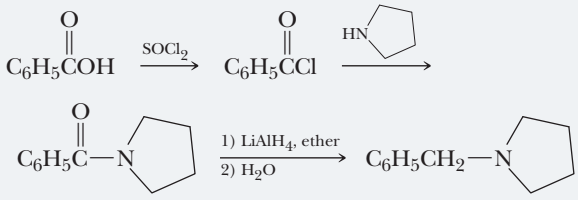
STRATEGY

The key in each part is to convert the carboxylic acid to an amide (Section 14.5D) and then reduce the amide with $LiAlH_4$ (Section 14.8B).

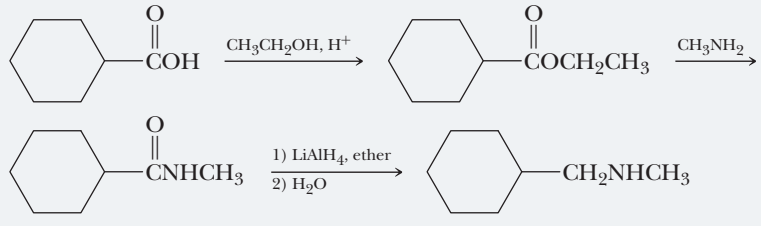
SOLUTION

Each amide can be prepared by treating the carboxylic acid with $SOCl_2$ to form the acid chloride (Section 13.7) and then treating the acid chloride with an amine (Section 14.5A). Alternatively, the carboxylic acid can be converted to an ester by Fischer esterification (Section 13.6) and the ester treated with an amine to give the amide. Solution (a) uses the acid chloride route, solution (b) the ester route:

(a)



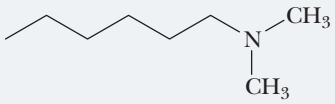
(b)

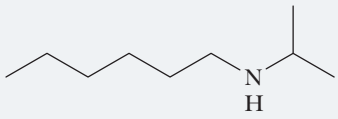


See problems 14.27, 14.29, 14.31, 14.32, 14.39, 14.46

PROBLEM 14.7

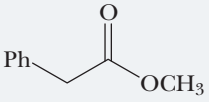
Show how to convert hexanoic acid to each amine in good yield:

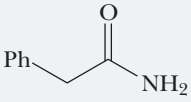
(a) 

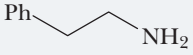
(b) 

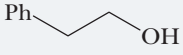
EXAMPLE 14.8

Show how to convert phenylacetic acid to these compounds:

(a) 

(b) 

(c) 

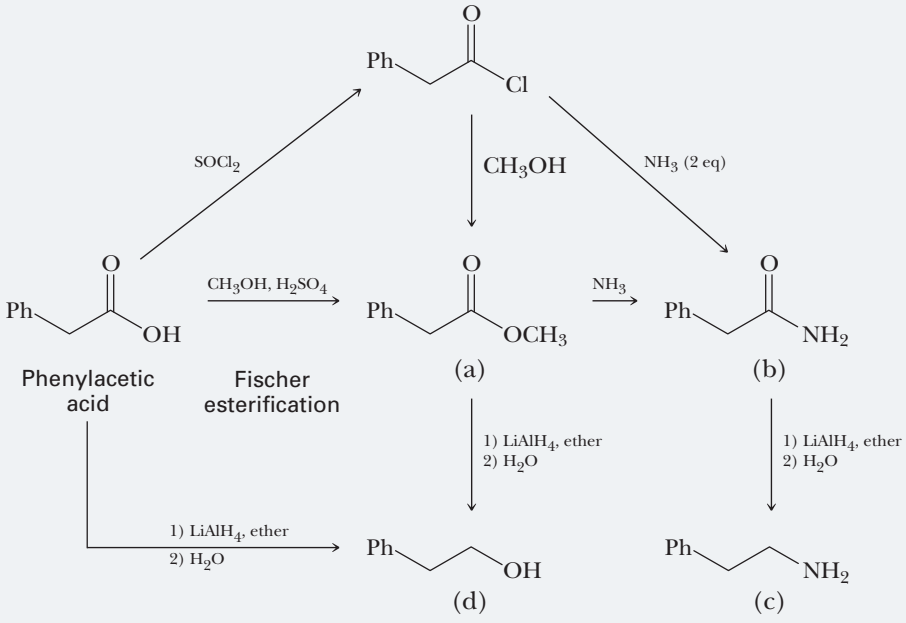
(d) 

STRATEGY

Decide whether the functional group interconversion can be done in one step. If not, try to determine what functional group can be converted to the targeted group. For example, a carboxyl group cannot be converted directly to an amine. However, an amide can be converted to an amine. Therefore, one only needs to convert the carboxyl group into an amide to eventually be able to produce the amine.

SOLUTION

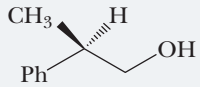
Prepare methyl ester (a) by Fischer esterification (Section 13.6) of phenylacetic acid with methanol. Then treat this ester with ammonia to prepare amide (b). Alternatively, treat phenylacetic acid with thionyl chloride (Section 13.7) to give an acid chloride, and then treat the acid chloride with two equivalents of ammonia to give amide (b). Reduction of amide (b) by $LiAlH_4$ gives the 1° amine (c). Similar reduction of either phenylacetic acid or ester (a) gives 1° alcohol (d):



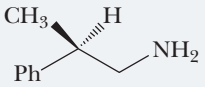
See problem 14.46

PROBLEM 14.8

Show how to convert (*R*)-2-phenylpropanoic acid to these compounds:

(a) 

(*R*)-2-Phenyl-1-propanol

(b) 

(*R*)-2-Phenyl-1-propanamine

SUMMARY OF KEY QUESTIONS

14.1 What Are Some Derivatives of Carboxylic Acids, and How Are They Named?

- The functional group of an **acid halide** is an acyl group bonded to a halogen.
- Acid halides are named by changing the suffix *-ic acid* in the name of the parent carboxylic acid to *-yl halide*.
- The functional group of a **carboxylic anhydride** is two acyl groups bonded to an oxygen.
- Symmetrical anhydrides are named by changing the suffix *acid* in the name of the parent carboxylic acid to *anhydride*.
- The functional group of a **carboxylic ester** is an acyl group bonded to —OR or —OAr.
- An ester is named by giving the name of the alkyl or aryl group bonded to oxygen first, followed by the name of the acid, in which the suffix *-ic acid* is replaced by the suffix *-ate*.
- A cyclic ester is given the name **lactone**.
- The functional group of an **amide** is an acyl group bonded to a trivalent nitrogen.
- Amides are named by dropping the suffix *-oic acid* from the IUPAC name of the parent acid, or *-ic acid* from its common name, and adding *-amide*.
- A cyclic amide is given the name **lactam**.

14.2 What Are the Characteristic Reactions of Carboxylic Acid Derivatives?

- A common reaction theme of functional derivatives of carboxylic acids is **nucleophilic acyl addition** to the carbonyl carbon to form a **tetrahedral carbonyl addition intermediate**, which then collapses to regenerate the carbonyl group. The result is **nucleophilic acyl substitution**.

14.3 What Is Hydrolysis?

- **Hydrolysis** is a chemical process whereby a bond (or bonds) in a molecule is broken by its reaction with water.
- Hydrolysis of a carboxylic acid derivative results in a carboxylic acid.

14.4 How Do Carboxylic Acid Derivatives React with Alcohols?

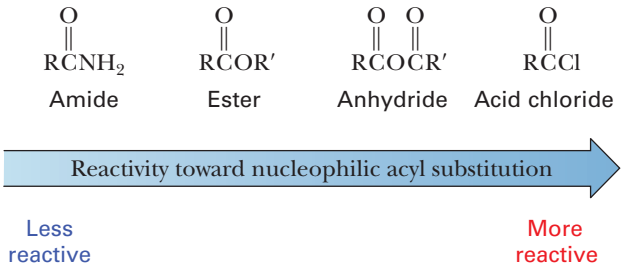
- Carboxylic acid derivatives (except for amides) react with alcohols to give esters.
- The reaction conditions required (i.e., neutral, acidic, or basic) depend on the type of derivative.

14.5 How Do Carboxylic Acid Derivatives React with Ammonia and Amines?

- Carboxylic acid derivatives (except for amides) react with ammonia and amines to give amides.

14.6 How Can Functional Derivatives of Carboxylic Acids Be Interconverted?

- Listed in order of increasing reactivity toward nucleophilic acyl substitution, these functional derivatives are:



- Any more reactive functional derivative can be directly converted to any less reactive functional derivative by reaction with an appropriate oxygen or nitrogen nucleophile.

14.7 How Do Esters React with Grignard Reagents?

- Reaction of an ester with a Grignard reagent involves the formation of two successive tetrahedral carbonyl addition compounds. The result of the overall reaction is an alcohol containing the two identical alkyl groups from the Grignard reagent.

14.8 How Are Derivatives of Carboxylic Acids Reduced?

- Derivatives of carboxylic acids are resistant to reduction by $NaBH_4$. Therefore, ketones and aldehydes can be selectively reduced in the presence of a carboxylic acid derivative.
- Derivatives of carboxylic acids are resistant to catalytic hydrogenation by H_2/M. Therefore, C—C double and triple bonds can be selectively reduced in the presence of a carboxylic acid derivative.
- $LiAlH_4$ reduces the carboxyl group of acid halides, acid anhydrides, and esters to a 1° alcohol group.
- $LiAlH_4$ reduces amides to amines.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. The stronger the base, the better the leaving group. (14.2)
2. Anhydrides can contain C—O double bonds or P—O double bonds. (14.1)
3. Acid anhydrides react with ammonia and amines without the need for acid or base. (14.5)
4. Derivatives of carboxylic acids are reduced by H_2/M. (14.8)
5. Aldehydes and ketones undergo nucleophilic acyl substitution reactions, while derivatives of carboxylic acids undergo nucleophilic addition reactions. (14.2)
6. Esters react with ammonia and amines without the need for acid or base. (14.5)
7. An acyl group is a carbonyl bonded to an alkyl (R) group. (14.1)
8. Hydrolysis is the loss of water from a molecule. (14.3)
9. Esters react with water without the need for acid or base. (14.4)
10. Acid anhydrides react with water without the need for acid or base. (14.3)
11. An acid halide can be converted to an amide in one step. (14.6)
12. An ester can be converted to an acid halide in one step. (14.6)
13. In the hydrolysis of an ester with base, hydroxide ion is a catalyst. (14.3)
14. Derivatives of carboxylic acids are reduced by $NaBH_4$. (14.8)
15. Acid anhydrides react with alcohols without the need for acid or base. (14.4)
16. Acid halides react with water without the need for acid or base. (14.3)
17. An ester of formic acid reacts with Grignard reagents to form a 3° alcohol. (14.7)
18. Acid halides react with ammonia and amines without the need for acid or base. (14.5)
19. A cyclic amide is called a lactone. (14.1)
20. The reactivity of a carboxylic acid derivative is dependent on the stability of its leaving group. (14.2)
21. Amides react with ammonia and amines without the need for acid or base. (14.5)
22. An amide can be converted to an ester in one step. (14.6)

23. Amides react with water without the need for acid or base. (14.3)
24. Esters react with alcohols without the need for acid or base. (14.3)
25. Amides react with alcohols under acidic or basic conditions. (14.4)
26. Esters other than formic acid esters react with Grignards to form ketones. (14.7)
27. Acid halides react with alcohols without the need for acid or base. (14.4)
28. An —OR group attached to a P—O double bond is known as an ester. (14.1)

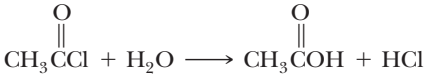
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) F (2) T (3) T (4) F (5) F (6) T (7) T (8) F (9) F (10) T (11) T (12) F (13) F (14) F (15) T (16) T (17) F (18) T (19) F (20) T (21) F (22) F (23) F (24) F (25) F (26) F (27) T (28) T

KEY REACTIONS

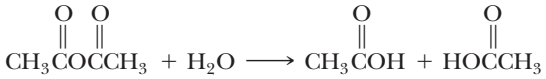
1. **Hydrolysis of an Acid Chloride (Section 14.3A)**

   Low-molecular-weight acid chlorides react vigorously with water; higher-molecular-weight acid chlorides react less rapidly:



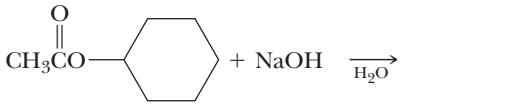
2. **Hydrolysis of an Acid Anhydride (Section 14.3B)**

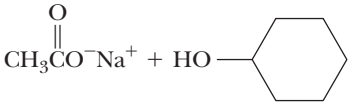
   Low-molecular-weight acid anhydrides react readily with water; higher-molecular-weight acid anhydrides react less rapidly:

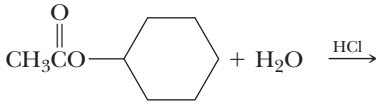


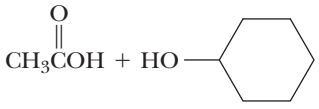
3. **Hydrolysis of an Ester (Section 14.3C)**

   Esters are hydrolyzed only in the presence of base or acid; base is required in an equimolar amount, acid is a catalyst:



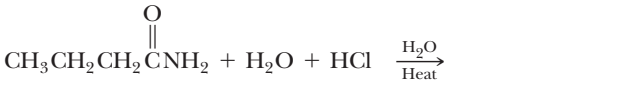


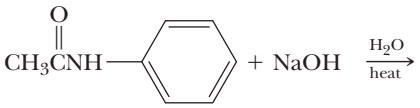


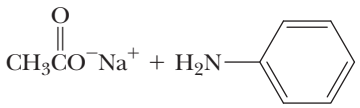


4. **Hydrolysis of an Amide (Section 14.3D)**

   Either acid or base is required in an amount equivalent to that of the amide:

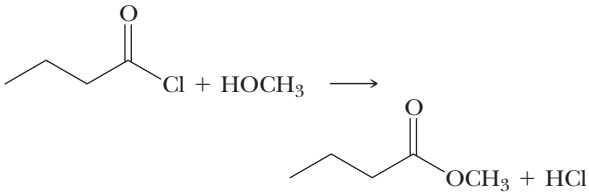






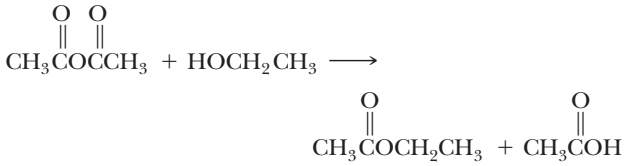
5. **Reaction of an Acid Chloride with an Alcohol (Section 14.4A)**

   Treatment of an acid chloride with an alcohol gives an ester and HCl:



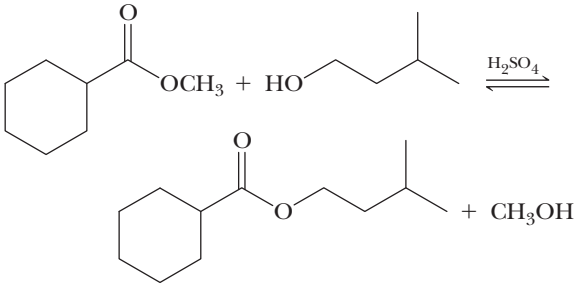
6. **Reaction of an Acid Anhydride with an Alcohol (Section 14.4B)**

   Treatment of an acid anhydride with an alcohol gives an ester and a carboxylic acid:



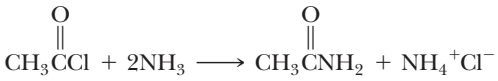
7. **Reaction of an Ester with an Alcohol (Section 14.4C)**

   Treatment of an ester with an alcohol in the presence of an acid catalyst results in transesterification—that is, the replacement of one —OR group by a different —OR group:



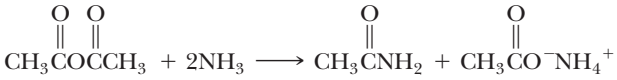
8. Reaction of an Acid Chloride with Ammonia or an Amine (Section 14.5A)

Reaction requires 2 moles of ammonia or amine—1 mole to form the amide and 1 mole to neutralize the HCl by-product:



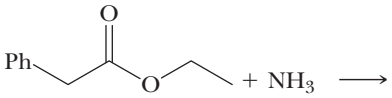
9. Reaction of an Acid Anhydride with Ammonia or an Amine (Section 14.5B)

Reaction requires 2 moles of ammonia or amine—1 mole to form the amide and 1 mole to neutralize the carboxylic acid by-product:

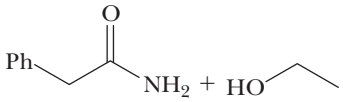


10. Reaction of an Ester with Ammonia or an Amine (Section 14.5C)

Treatment of an ester with ammonia, a 1° amine, or a 2° amine gives an amide:



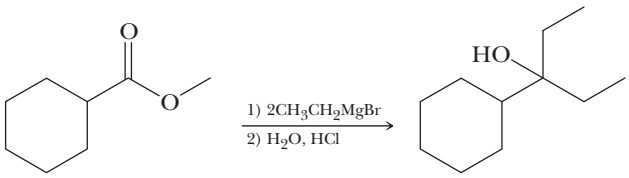
Ethyl phenylacetate



Phenylacetamide Ethanol

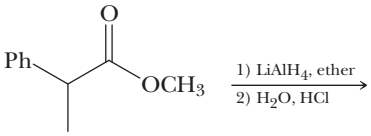
11. Reaction of an Ester with a Grignard Reagent (Section 14.7)

Treating a formic ester with a Grignard reagent, followed by hydrolysis, gives a 2° alcohol, whereas treating any other ester with a Grignard reagent gives a 3° alcohol:

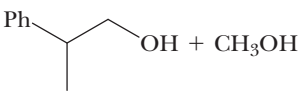


12. Reduction of an Ester (Section 14.8A)

Reduction by lithium aluminum hydride gives two alcohols:



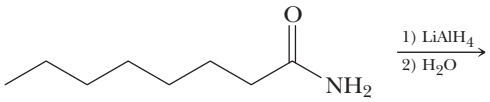
Methyl 2-phenylpropanoate



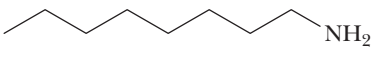
2-Phenyl-1-propanol Methanol

13. Reduction of an Amide (Section 14.8B)

Reduction by lithium aluminum hydride gives an amine:



Octanamide



1-Octanamine

PROBLEMS

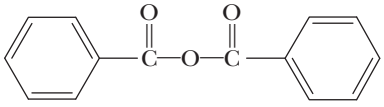
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

Section 14.1 Structure and Nomenclature

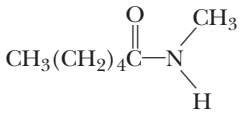
14.9 Draw a structural formula for each compound: **(See Example 14.1)**

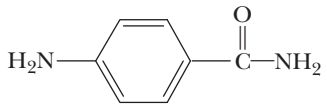
(a) Dimethyl carbonate
(b) *p*-Nitrobenzamide
(c) Octanoyl chloride
(d) Diethyl oxalate
(e) Ethyl *cis*-2-pentenoate
(f) Butanoic anhydride
(g) Dodecanamide
(h) Ethyl 3-hydroxybutanoate
(i) Ethyl benzoate
(j) Benzoyl chloride
(k) *N*-Ethylpentanamide
(l) 5-Methylhexanoyl chloride

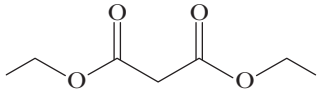
14.10 Write the IUPAC name for each compound: **(See Example 14.1)**

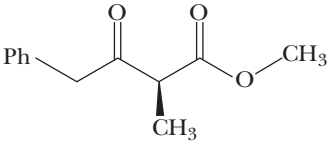
(a) 

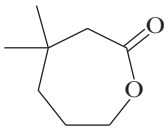
(b) $CH_3(CH_2)_{14}COCH_3$

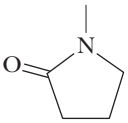
(c) 

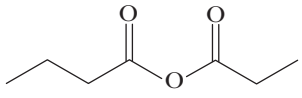
(d) 

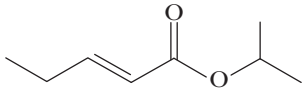
(e) 

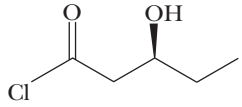
(f) 

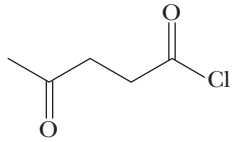
(g) 

(h) 

(i) 

(j) 

(k) 

(l) 

***14.11** When oil from the head of a sperm whale is cooled, spermaceti, a translucent wax with a white, pearly luster, crystallizes from the mixture. Spermaceti, which makes up 11% of whale oil, is composed mainly of hexadecyl hexadecanoate (cetyl palmitate). At one time, spermaceti was widely used in the making of cosmetics, fragrant soaps, and candles. Draw a structural formula of cetyl palmitate. **(See Example 14.1)**

Wolfgang Poelzer/Waterframe RM/ Getty Images, Inc.

Sperm whale, *Physterer macrocephalus*, diving, Kaikoura, NZ.

Physical Properties

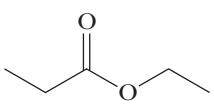
14.12 Acetic acid and methyl formate are constitutional isomers. Both are liquids at room temperature, one with a boiling point of 32 °C, the other with a boiling point of 118 °C. Which of the two has the higher boiling point?

14.13 Butanoic acid (M. W. 88.11 g/mol) has a boiling point of 162 °C, whereas its propyl ester (M.W. 130.18 g/mol) has a boiling point of 142 °C. Account for the fact that the boiling point of butanoic acid is higher than that of its propyl ester, even though butanoic acid has a lower molecular weight.

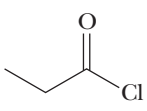
14.14 The constitutional isomers pentanoic acid and methyl butanoate are both slightly soluble in water. One of these compounds has a solubility of 1.5 g/100 ml (25 °C), while the other has a solubility of 4.97 g/100 ml (25 °C). Assign the solubilities to each compound and account for the differences.

Sections 14.2–14.8 Reactions

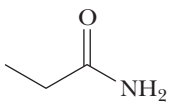
14.15 Arrange these compounds in order of increasing reactivity toward nucleophilic acyl substitution:



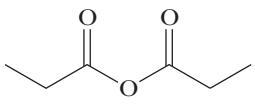
(1)



(2)



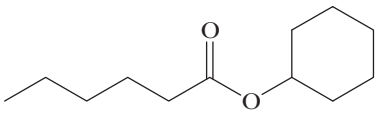
(3)

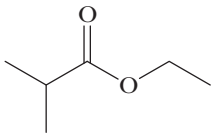


(4)

14.16 A carboxylic acid can be converted to an ester by Fischer esterification. Show how to synthesize each

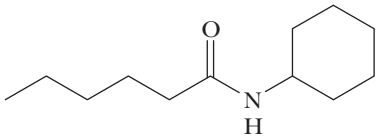
ester from a carboxylic acid and an alcohol by Fischer esterification: **(See Example 14.4)**

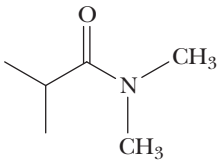
(a) 

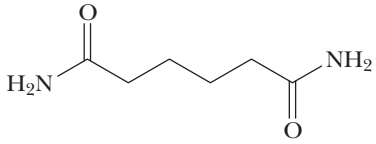
(b) 

14.17 A carboxylic acid can also be converted to an ester in two reactions by first converting the carboxylic acid to its acid chloride and then treating the acid chloride with an alcohol. Show how to prepare each ester in Problem 14.16 from a carboxylic acid and an alcohol by this two-step scheme. **(See Example 14.4)**

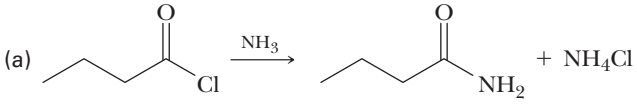
14.18 Show how to prepare these amides by reaction of an acid chloride with ammonia or an amine: **(See Example 14.5)**

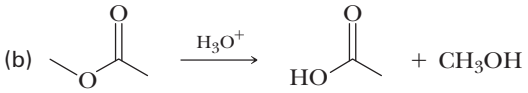
(a) 

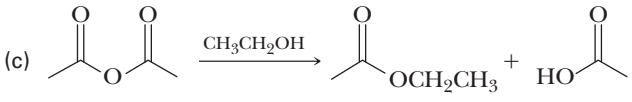
(b) 

(c) 

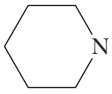
14.19 Balance and write a mechanism for each of the following reactions. **(See Examples 14.2, 14.4, 14.5)**

(a) 

(b) 

(c) 

14.20 What product is formed when benzoyl chloride is treated with these reagents? **(See Examples 14.2, 14.4, 14.5)**

(a) C_6H_6, $AlCl_3$
(b) $CH_3CH_2CH_2CH_2OH$
(c) $CH_3CH_2CH_2CH_2SH$
(d) $CH_3CH_2CH_2CH_2NH_2$ (2 equivalents)
(e) H_2O
(f)  (2 equivalents)

14.21 Write the product(s) of the treatment of propanoic anhydride with each reagent: **(See Examples 14.4, 14.5)**

(a) Ethanol (1 equivalent)
(b) Ammonia (2 equivalents)

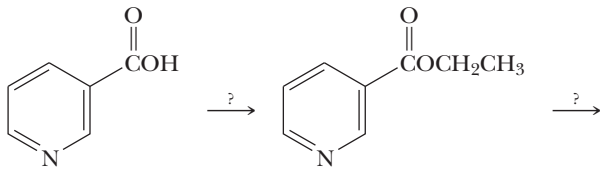
14.22 Write the product of the treatment of benzoic anhydride with each reagent: **(See Examples 14.4, 14.5)**

(a) Ethanol (1 equivalent)
(b) Ammonia (2 equivalents)

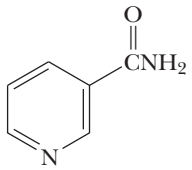
***14.23** The analgesic phenacetin is synthesized by treating 4-ethoxyaniline with acetic anhydride. Write an equation for the formation of phenacetin.

***14.24** The analgesic acetaminophen is synthesized by treating 4-aminophenol with one equivalent of acetic anhydride. Write an equation for the formation of acetaminophen. (*Hint*: Remember from Section 7.5A that an $-NH_2$ group is a better nucleophile than an $-OH$ group.) **(See Example 14.5)**

***14.25** Nicotinic acid, more commonly named niacin, is one of the B vitamins. Show how nicotinic acid can be converted to ethyl nicotinate and then to nicotinamide: **(See Example 14.5)**

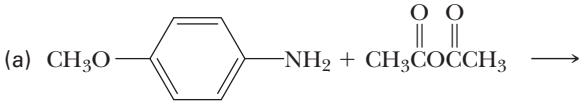


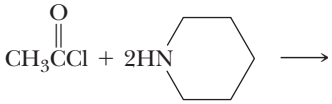
Nicotinic acid (Niacin) — Ethyl nicotinate

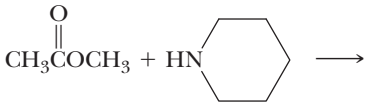


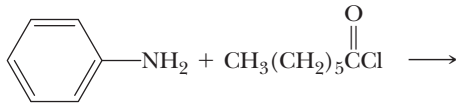
Nicotinamide

14.26 Complete these reactions: **(See Example 14.5)**

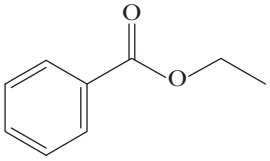
(a) 

(b) 

(c) 

(d) 

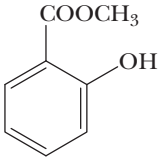
14.27 What product is formed when ethyl benzoate is treated with these reagents? **(See Example 14.7)**



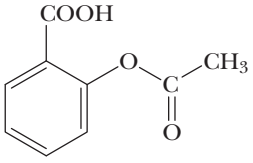
Ethyl benzoate

(a) H_2O, NaOH, heat
(b) $LiAlH_4$, then H_2O
(c) H_2O, H_2SO_4, heat
(d) $CH_3CH_2CH_2CH_2NH_2$
(e) C_6H_5MgBr (2 moles) and then H_2O/HCl

***14.28** Show how to convert 2-hydroxybenzoic acid (salicylic acid) to these compounds: **(See Example 14.4)**

(a) 

Methyl salicylate
(Oil of wintergreen)

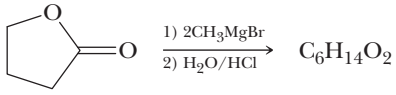
(b) 

Acetyl salicylic acid
(Aspirin)

14.29 What product is formed when benzamide is treated with these reagents? **(See Examples 14.3, 14.7)**

(a) H_2O, HCl, heat
(b) NaOH, H_2O, heat
(c) $LiAlH_4$/ether, then H_2O

14.30 Treating γ-butyrolactone with two equivalents of methylmagnesium bromide, followed by hydrolysis in aqueous acid, gives a compound with the molecular formula $C_6H_{14}O_2$: **(See Example 14.6)**



Propose a structural formula for this compound.

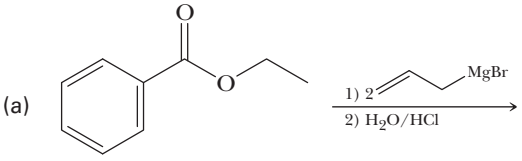
14.31 Show the product of treating γ-butyrolactone with each reagent: **(See Examples 14.2, 14.5, 14.7)**

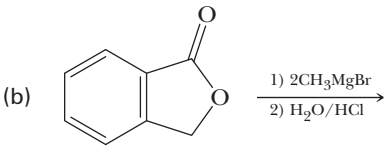
(a) NH_3
(b) $LiAlH_4$/ether, then H_2O
(c) NaOH, H_2O, heat

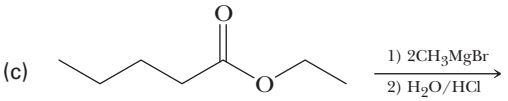
14.32 Show the product of treating *N*-methyl-γ-butyrolactam with each reagent: **(See Examples 14.3, 14.7)**

(a) H_2O, HCl, heat
(b) NaOH, H_2O, heat
(c) $LiAlH_4$/ether, then H_2O

14.33 Complete these reactions: **(See Example 14.6)**

(a) 

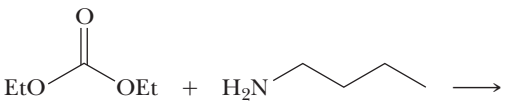
(b) 

(c) 

14.34 What combination of ester and Grignard reagent can be used to prepare each alcohol? **(See Example 14.6)**

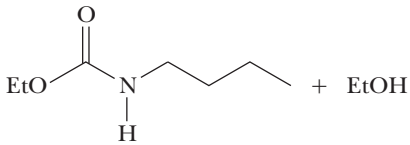
(a) 2-Methyl-2-butanol
(b) 3-Phenyl-3-pentanol
(c) 1,1-Diphenylethanol

14.35 Reaction of a 1° or 2° amine with diethyl carbonate under controlled conditions gives a carbamic ester: **(See Example 14.5)**



Diethyl carbonate

1-Butanamine (Butylamine)

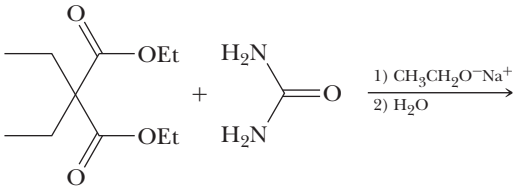


A carbamic ester

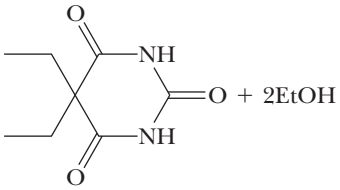
Propose a mechanism for this reaction.

14.36 Barbiturates are prepared by treating diethyl malonate or a derivative of diethyl malonate with urea in the presence of sodium ethoxide as a catalyst.

Following is an equation for the preparation of barbital from diethyl 2,2-diethylmalonate and urea (barbital, a long-duration hypnotic and sedative, is prescribed under a dozen or more trade names):



Diethyl 2,2-diethylmalonate — Urea

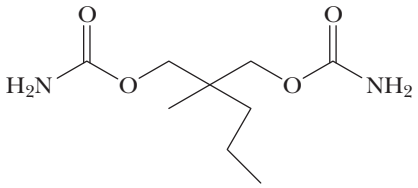


5,5-Diethylbarbituric acid (Barbital)

(a) Propose a mechanism for this reaction.
(b) The pK_a of barbital is 7.4. Which is the most acidic hydrogen in this molecule, and how do you account for its acidity?

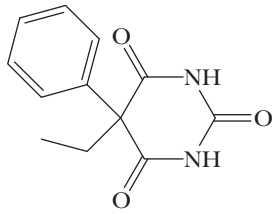
***14.37** Name and draw structural formulas for the products of the complete hydrolysis of meprobamate and phenobarbital in hot aqueous acid. Meprobamate is a tranquilizer prescribed under 58 different trade names. Phenobarbital is a long-acting sedative, hypnotic, and anticonvulsant. [*Hint*: Remember that, when heated, β-dicarboxylic acids and β-ketoacids undergo decarboxylation (Section 13.8B).]

(a)



Meprobamate

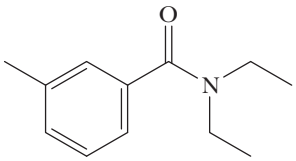
(b)



Phenobarbital

Synthesis

***14.38** The active ingredient in several common insect repellents *N,N*-Diethyl-*m*-toluamide (Deet) is synthesized from 3-methylbenzoic acid (*m*-toluic acid) and diethylamine:

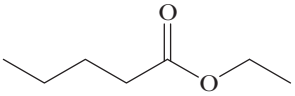


N,N-Diethyl-*m*-toluamide (Deet)

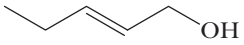
Show how this synthesis can be accomplished.

14.39 Show how to convert ethyl 2-pentenoate into these compounds: **(See Example 14.7)**

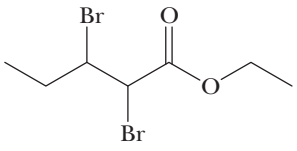
(a)



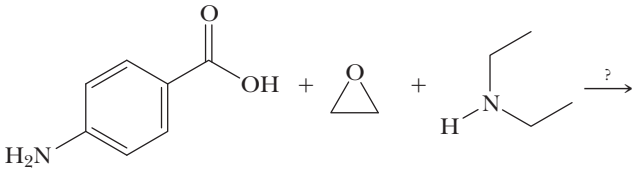
(b)



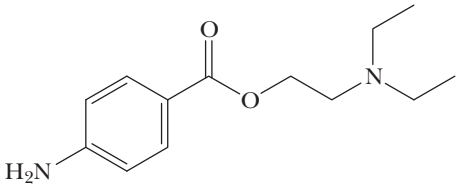
(c)



***14.40** Procaine (whose hydrochloride is marketed as Novocaine®) was one of the first local anesthetics for infiltration and regional anesthesia. Show how to synthesize procaine, using the three reagents shown as the sources of carbon atoms:



4-Aminobenzoic acid — Ethylene oxide — Diethylamine

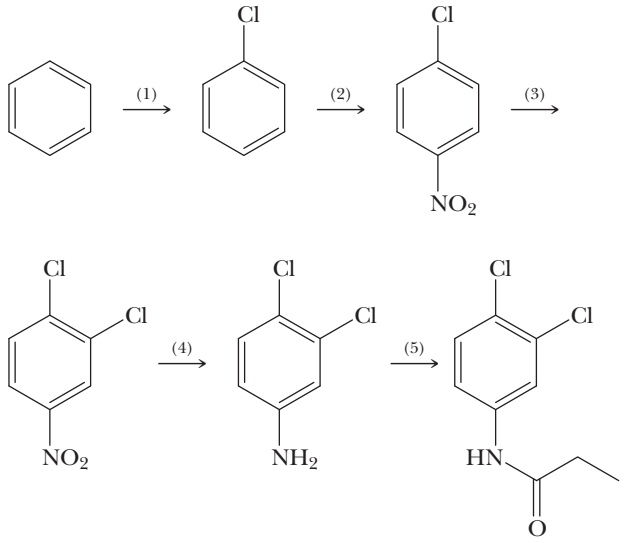


Procaine

***14.41** There are two nitrogen atoms in procaine. Which of the two is the stronger base? Draw the structural formula for the salt that is formed when procaine is treated with 1 mole of aqueous HCl.

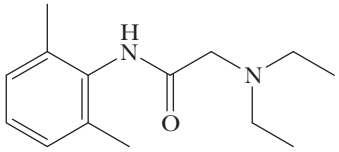
***14.42** Starting materials for the synthesis of the herbicide propanil, a weed killer used in rice paddies, are

benzene and propanoic acid. Show reagents to bring about this synthesis:

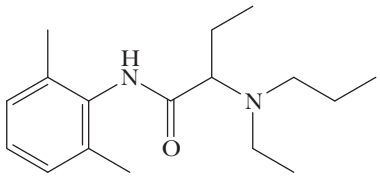


Propanil

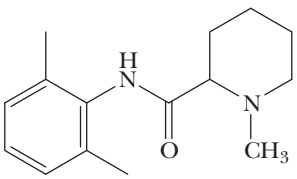
***14.43** Following are structural formulas for three local anesthetics: Lidocaine was introduced in 1948 and is now the most widely used local anesthetic for infiltration and regional anesthesia. Its hydrochloride is marketed under the name Xylocaine®. Etidocaine (its hydrochloride is marketed as Duranest®) is comparable to lidocaine in onset, but its analgesic action lasts two to three times longer. Mepivacaine (its hydrochloride is marketed as Carbocaine®) is faster and somewhat longer in duration than lidocaine.



Lidocaine
(Xylocaine®)



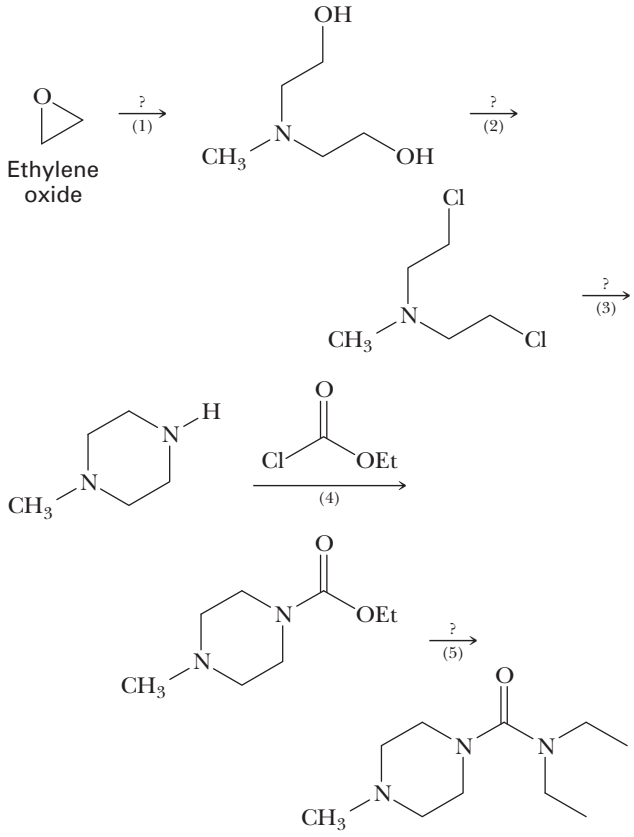
Etidocaine
(Duranest®)



Mepivacaine
(Carbocaine®)

(a) Propose a synthesis of lidocaine from 2,6-dimethylaniline, chloroacetyl chloride ($ClCH_2COCl$), and diethylamine.
(b) Propose a synthesis of etidocaine from 2,6-dimethylaniline, 2-chlorobutanoyl chloride, and ethylpropylamine.
(c) What amine and acid chloride can be reacted to give mepivacaine?

***14.44** Following is the outline of a five-step synthesis for the anthelmintic (against worms) diethylcarbamazine:

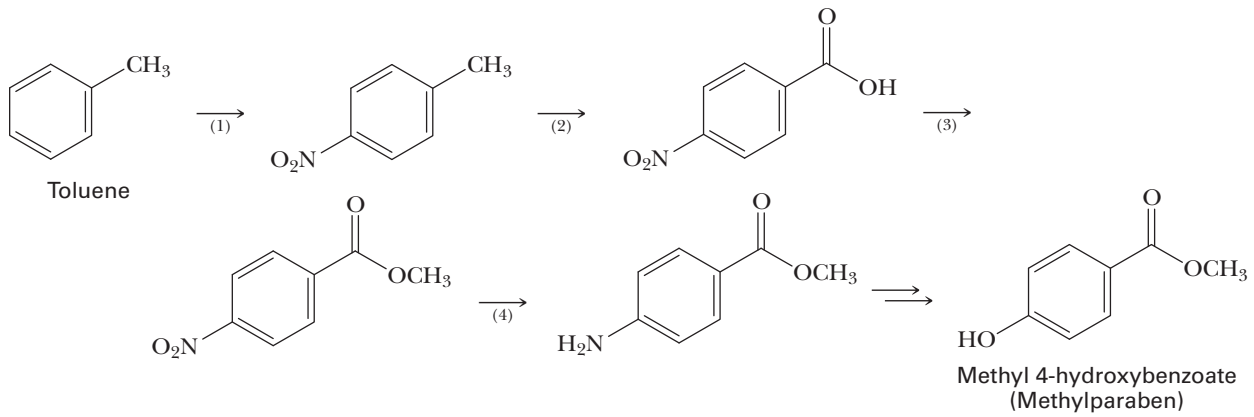


Diethylcarbamazine

Diethylcarbamazine is used chiefly against nematodes, small cylindrical or slender threadlike worms such as the common roundworm, which are parasitic in animals and plants.

(a) Propose a reagent for Step 1. Which mechanism is more likely for this step, S_N1 or S_N2? Explain.
(b) Propose a reagent for Step 2.
(c) Propose a reagent for Step 3.
(d) Ethyl chloroformate, the reagent for Step 4, is both an acid chloride and an ester. Account for the fact that Cl, rather than OCH_2CH_3, is displaced from this reagent.

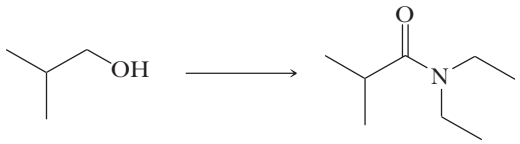
***14.45** Following is an outline of a multi-step synthesis for methylparaben, a compound widely used as a preservative in foods:

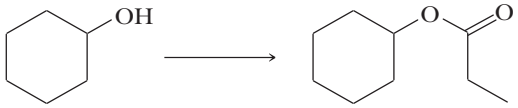


Propose reagents for Steps 1–4.

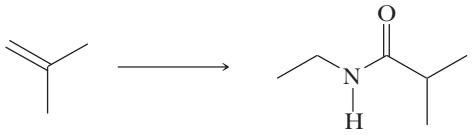
CHEMICAL TRANSFORMATIONS

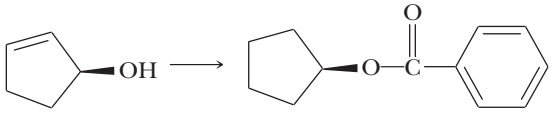
14.46 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note*: Some will require more than one step. **(See Examples 14.7, 14.8)**

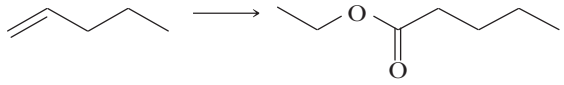
(a) 

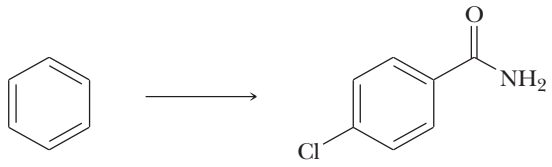
(b) 

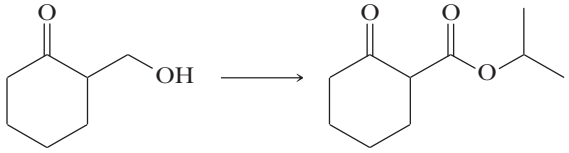
(c) 

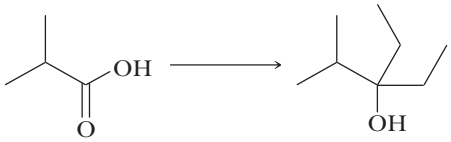
(d) 

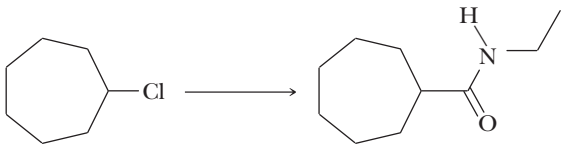
(e) 

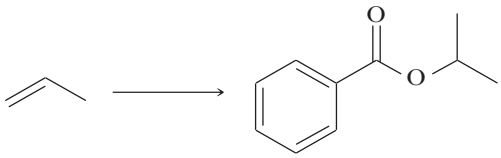
(f) 

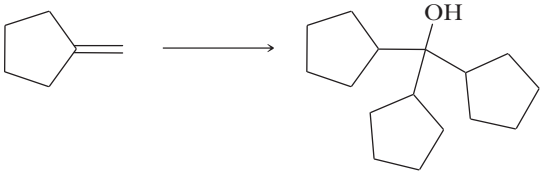
(g) 

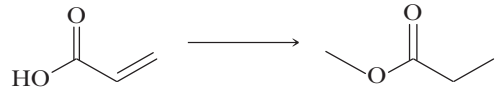
(h) 

(i) 

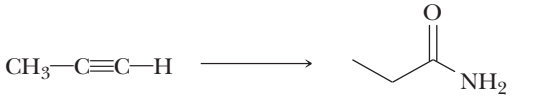
(j) 

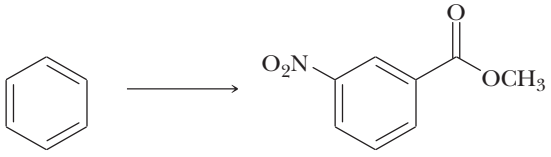
(k) 

(l) 

(m) 

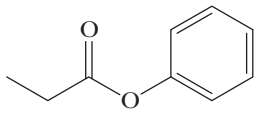
(n) 

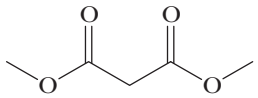
(o) 

(p) 

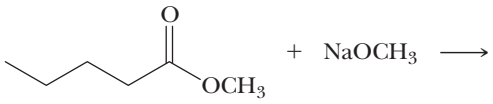
LOOKING AHEAD

14.47 Identify the most acidic proton in each of the following esters:

(a) 

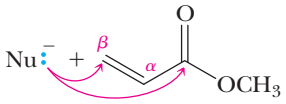
(b) 

14.48 Does a nucleophilic acyl substitution occur between the ester and the nucleophile shown?

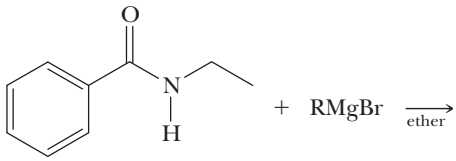


Propose an experiment that would verify your answer.

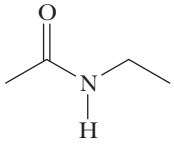
14.49 Explain why a nucleophile, Nu, attacks not only the carbonyl carbon, but also the β-carbon, as indicated in the following α,β-unsaturated ester:



14.50 Explain why a Grignard reagent will not undergo nucleophilic acyl substitution with the following amide:



14.51 At low temperatures, the following amide exhibits *cis–trans* isomerism, while at higher temperatures it does not:

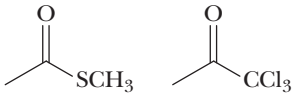


Explain how this is possible.

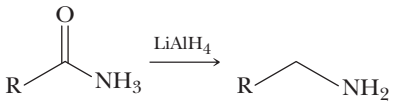
GROUP LEARNING ACTIVITIES

14.52 Following are two compounds that can also undergo nucleophilic acyl substitution. As a group:

(a) Predict the product if each was treated with NaOH.
(b) Provide a mechanism for each reaction.
(c) Compare the leaving group ability of $^-SCH_3$ with that of $^-OCH_3$ and of $^-CCl_3$ with that of $^-CH_3$.



14.53 The mechanism of the reduction of amides to amines by $LiAlH_4$ contains many steps. Work as a group to figure out this mechanism. *Hint*: The carbonyl oxygen is removed as $^-OAlH_2$.

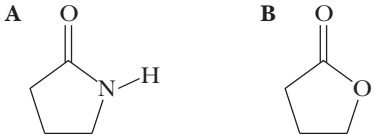


PUTTING IT TOGETHER

The following problems bring together concepts and material from Chapters 12–14. Although the focus may be on these chapters, the problems will also build upon concepts discussed throughout the text thus far.

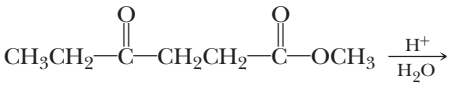
Choose the best answer for each of the following questions.

1. Which of the following statements is true concerning the following two carboxylic acid derivatives?



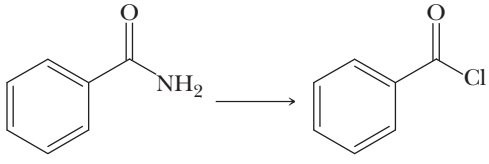
(a) Only molecule **A** can be hydrolyzed.
(b) Only molecule **B** can be hydrolyzed.
(c) Both molecules are hydrolyzable, but **A** will react more quickly than **B**.
(d) Both molecules are hydrolyzable, but **B** will react more quickly than **A**.
(e) **A** and **B** are hydrolyzed at roughly the same rate.

2. How many unique reaction products are formed from the following reaction?



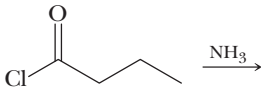
(a) one (b) two (c) three (d) four (e) five

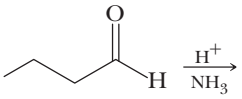
3. What sequence of reagents will accomplish the following transformation?

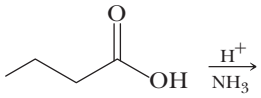


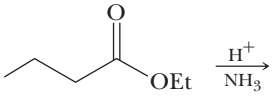
(a) 1) $SOCl_2$ (b) 1) H_2O_2, $SOCl_2$
(c) 1) H_2O_2, HCl (d) 1) H^+/H_2O_2 2) $SOCl_2$
(e) All of the above

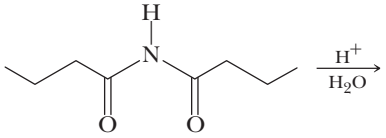
4. Which of the following reactions will not yield butanamide?

(a) 

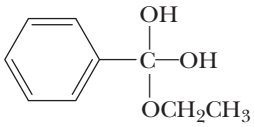
(b) 

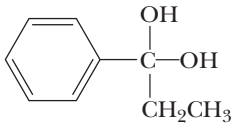
(c) 

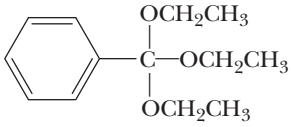
(d) 

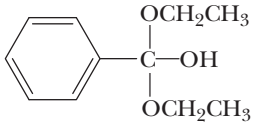
(e) 

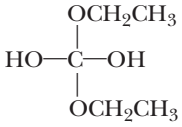
5. Which of the following is the tetrahedral carbonyl addition intermediate (TCAI) for the Fischer esterification of ethanol and benzoic acid?

(a) 

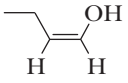
(b) 

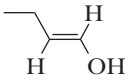
(c) 

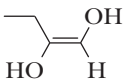
(d) 

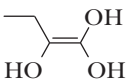
(e) 

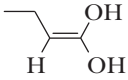
6. Which of the following is the enol intermediate in the decarboxylation of ethylpropanedioic acid?

(a) 

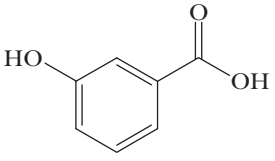
(b) 

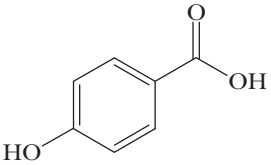
(c) 

(d) 

(e) 

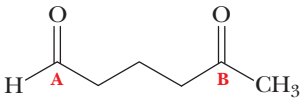
7. Which of the following statements is true concerning the two carboxylic acids shown?

A 

B 

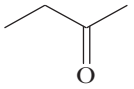
(a) **A** is more acidic than **B** because of an additional resonance effect.
(b) **B** is more acidic than **A** because of an additional resonance effect.
(c) Only the conjugate base of **A** experiences an inductive effect.
(d) Only the conjugate base of **B** experiences an inductive effect.
(e) None of the above.

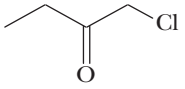
8. What would be the expected outcome if one equivalent of a Grignard reagent were reacted with the molecule below?

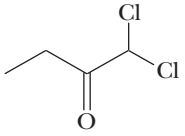


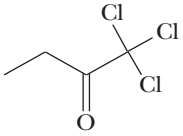
(a) 100% addition at carbonyl **A**.
(b) 100% addition at carbonyl **B**.
(c) Equal addition at both carbonyls.
(d) Greater distribution of addition at **A**.
(e) Greater distribution of addition at **B**.

9. Which of the following carbonyl carbons would be considered the most electrophilic?

(a) 

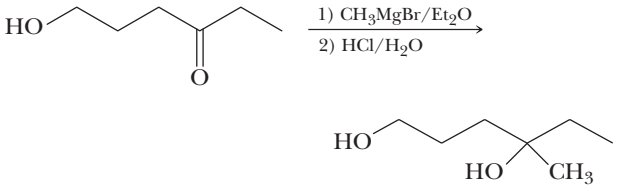
(b) 

(c) 

(d) 

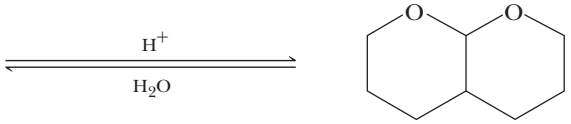
(e) All are equally electrophilic.

10. The following reaction will occur as shown:

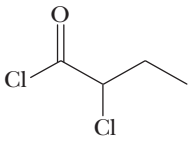


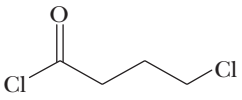
(a) True (b) False

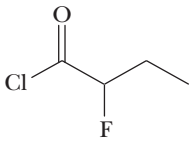
11. Provide a structure for the starting compound needed to produce the product shown. Then show the mechanism of its formation. Show all charges and lone pairs of electrons in your structures.

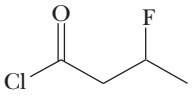


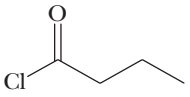
12. Rank the following from most to least reactive with EtOH. Provide a rationale for your ranking.

(a) 

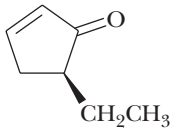
(b) 

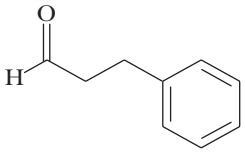
(c) 

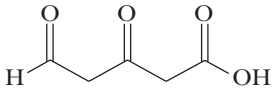
(d) 

(e) 

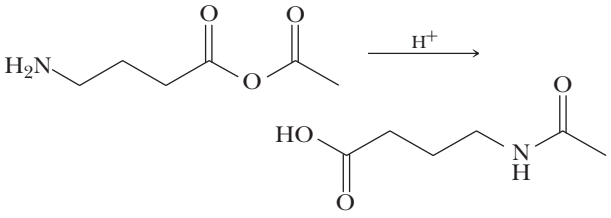
13. Provide IUPAC names for the following compounds.

(a) 

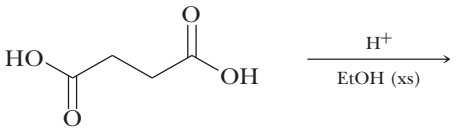
(b) 

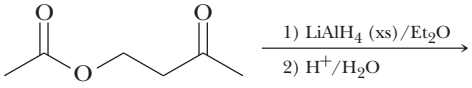
(c) 

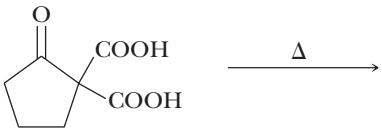
14. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures, as well as the structures of all intermediates.

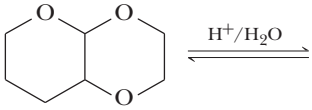


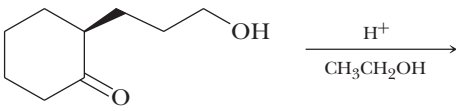
15. Predict the major product of each of the following reactions.

(a) 

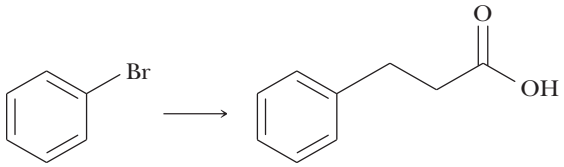
(b) 

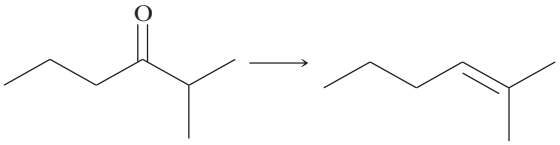
(c) 

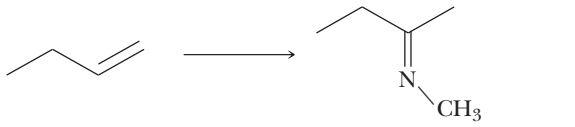
(d) 

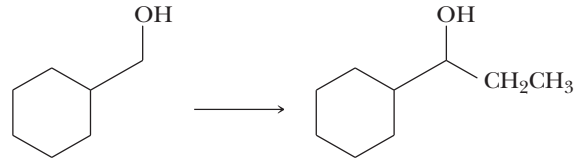
(e) 

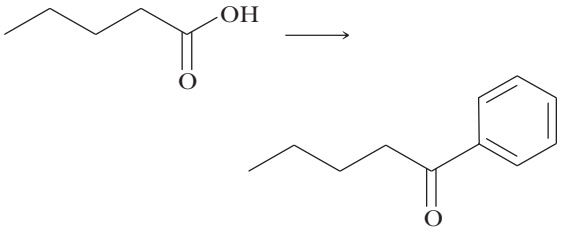
16. Complete the following chemical transformations.

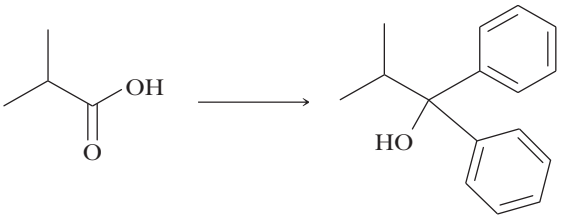
(a) 

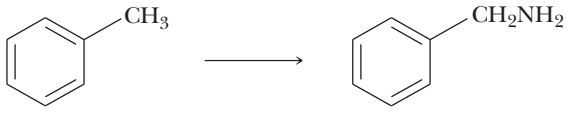
(b) 

(c) 

(d) 

(e) 

(f) 

(g) 

(h)