Chapter 12 Carboxylic Acids and Derivatives

Contents

Oxidations of most of organic compounds under moderate conditions provide carboxylic acids as final products. Chemical reactions that take place in nature filled with air containing oxygen are in principle oxidation. For this reason, there exist a variety of carboxylic acids and their derivatives.

Carboxylic acids and their derivatives, together with carbonyl compounds, are principal group of the organic compounds. Carboxylic acids and their derivatives are extremely important as such and as the staring materials of a variety of compounds. There are some carboxylic acids possessing two or more than two carboxy groups, and possessing functional groups other than the carboxy group. Though the latter type of compounds will not be discussed in this book, it is evident that these compounds will make the region of carboxylic acids richer and richer. The representative one should be amino acids possessing the amino group.

Because of the carboxy group, carboxylic acids exhibit weak acidity, the strength of which depends largely on the molecular structure. The remarkable advance of theoretical organic chemistry has been achieved by the study of structure-acidity relation.

12.1 Types and nomenclature of carboxylic acids

(a) Types of carboxylic acids
Compounds which are made by substituting hydrogen atoms of hydrocarbons by a carboxy group –COOH-- are the **carboxylic acids.** Compounds which are made by substituting the –OH of the carboxy group with hydrocarbon groups, other atoms, or the group of atoms, are generally named as **carboxylic acid derivatives.** In addition to carboxylic acids with one carboxy group (monocarboxylic acids), there are **polycarboxylic acids** with two or more than two carboxy groups. **Dicarboxylic acid**s have two carboxy groups and **tricarboxylic acids** three carboxy groups.

Aliphatic carboxylic acids are named **fatty acids** (Table 12.1). Among fatty acids, those with many carbon atoms, *i.e.*, palmitic acid $CH_3(CH_2)_{14}COOH$, are the component of fats. This is the reason why such carboxylic acids are named fatty acids.

In addition to aliphatic carboxylic acids, aromatic carboxylic acids, in which the carboxy group is bonded to a benzene ring, are an important class of compounds. Representative examples are given in Table 12.2.

(b) Nomenclature of carboxylic acids
Many of popular carboxylic acids have common names, and these are usually used. There are two ways in substitutive nomenclature.
(i) The carboxy group is treated as a characteristic group and the suffix "carboxylic acid" is used.
(ii) The carbon atom of the carboxy group is included in the name of parent compound, and the carboxy group is represented by suffix"-oic acid".

Care should be taken for the difference whether the carbon atom of the carboxy group is included in the number of carbon atoms of the parent hydrocarbon.
[Example] $CH_3CH_2CH_2COOH$

$CH_3CH_2CH_2COOH$	butyric acid (common name)
$CH_3CH_2CH_2COOH$	propanecarboxylic acid (substitutive name)
$CH_3CH_2CH_2COOH$	butanoic acid (substitutive name)

Table 12.1 Representative aliphatic carboxylic acids

common name	systematic name	rational formulas	m.p. (℃)	b.p. (℃)
formic acid*	methanoic acid	HCOOH	8.4	100.8
acetic acid*	ethanoic acid	CH_3COOH	16.635	117.8
propionic acid*	propanoic acid	CH_3CH_2COOH	-20.83	140.80
butyric acid*	butanoic acid	$CH_3CH_2CH_2COOH$	-5.26	164.05
valeric acid*	pentanoic acid	$CH_3CH_2CH_2CH_2COOH$	-34.5	184
phenylacetic acid	phenylethnaoic acid	$C_6H_5CH_2COOH$	78	227
acrylic acid*	propenoic acid	$CH_2=CHCOOH$	14	141[1]
methacrylic acid*	2-methylpropenoic acid	$CH_2=C(CH_3)COOH$	16	159
oxalic acid*	ethanedioic acid	HOOCCOOH	187(α) 182(β)	-
malonic acid*	propanedioic acid	$HOOCCH_2COOH$	135(decom.)	-
succinic acid*	butanedioic acid	$HOOCCH_2CH_2COOH$	188	235[2]
fumalic acid*	*trans*-2-butenedioic acid	*trans*-HOOCHC=CHCOOH	300~302[3]	sublimation
maleic acid*	*cis*-2-butenedioic acid	*cis*-HOOCHC=CHCOOH	133~134[4]	-

* Common names are recommended. For substituted species, however, systematic names may be used.
[1] 755 mmHg, [2] converted to succinic anhydride, [3] converted to maleic anhydride, [4] converted to fumaric acid

Even if substituents (including unsaturated bonds) other than carboxy groups are included, such compounds are also named as carboxylic acids because the priority of carboxy group is higher.

[Example] $CH_2(OH)CH_2CH_2COOH$

4-hydroxybutanoic acid (substitutive name (ii))

(3-carboxypropanol is not correct)

Table 12.2 Representative aromatic carboxylic acid

common name	systematic name	rational formula	m.p. (℃)	b.p. (℃)
benzoic acid	benzenecarboxylic acid	C_6H_5COOH	122.5	250.03
phthalic acid	benzene-1,2-dicarboxylic acid	$o\text{-}HOOCC_6H_4COOH$	234	decomposition
isophthalic acid	benzene-1,3-dicarboxylic acid	$m\text{-}HOOCC_6H_4COOH$	348.5	sublimation
terephthalic acid	benzene-1,4-dicarboxylic acid	$p\text{-}HOOCC_6H_4COOH$		300(sublimation)

In systematic names of dicarboxylic acids, suffix "–dioic acid" may be used

[Example] $HOOCCH(CH_2CH_2CH_3)CH=CHCOOH$

4-propyl-2-pentene-1,4-dioic acid

Exercise12.1

(1) Name the following carboxylic acids.

   (a) $CH_3CH_2CH_2CH_2COOH$

   (b) $CH_3CH=CHCH_2CH_2COOH$

(2) Draw the rational formulas of the following carboxylic acids.

   (c) 2-chlorobutanoic acid

   (d) 3-phenylpropanoic acid

Answer

(a)   valeric acid (common name)   pentanoic acid (substitutive name)

        butanecarboxylic acid (substitutive name)

(b)   4-hexenoic acid

(c) $CH_3CH_2CHClCOOH$ (d) $-CH_2CH_2COOH$

12.2 Types and nomenclature of carboxylic acid derivatives
(a) Types of carboxylic acid derivatives

Carboxylic acid derivatives are classified according to the atom or group of atoms replacing the OH in the carboxy group as is shown in Table 12.3. Examples are given as derivatives of acetic acid.

Acid halides

These are obtained by replacing –OH in the carboxy group by halogens (in most cases Cl, Br, and I). Chlorides, for instance, can be prepared by the reaction between carboxylic acids and strong halogenating reagent such as thionyl chloride.
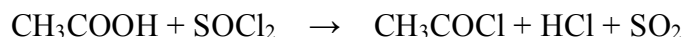
$$CH_3COOH + SOCl_2 \quad \rightarrow \quad CH_3COCl + HCl + SO_2$$

Table 12.3 Examples of carboxylic acid derivatives (RCOX)

X	common name	example (acetic acid derivatives)
-OH	carboxylic acid	acetic acid
-Cl, -Br,- I	(acid) halide	acetyl halide
RCO-	(acid) anhydride	acetic anhydride
R-	ester	ethyl acetate
$-NH_2$	primary amide	acetamide
-NHR	secondary amide	N-methylacetamide
-NRR"	tertiary amide	N,N –dimethylacetamide
-CN	nitrile	acetonitrile

acetic acid   acetyl chloride   acetic anhydride   ethyl acetate

acetamide   N-methylacetamide   N ,N-dimethylacetamide   acetonitrile
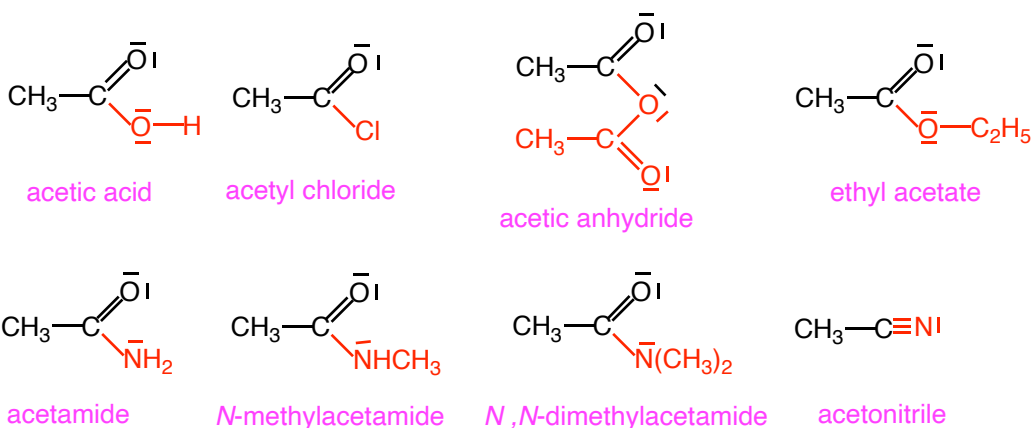
Acid halides are the most reactive among carboxylic acid derivatives, and these are very useful as the starting materials of other carboxylic acid derivatives.

Acid anhydrides

The structure of acid anhydride is a compound made from dehydration condensation of two molecules of carboxylic acids. Some anhydrides are, like acetic anhydride, composed of two identical carboxylic acids. There are other anhydrides, like maleic anhydride, composed of a dicarboxylic acid.

maleic anhydrie   futalic anhydrie
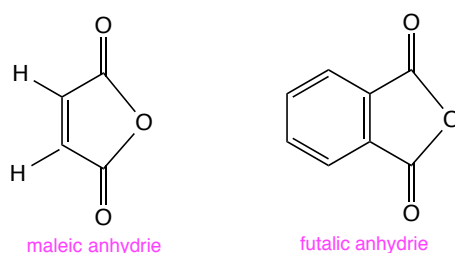
Ester (carboxylic ester)

Carboxylic ester, or simply ester, are composed by dehydration condensation of one molecule of carboxylic acid and one molecule of alcohol. The –COO- bond contained in esters is named the ester bond, and is regarded as a kind of a functional group. Esters composed of aliphatic acid of relatively small molecular weight and alcohols have fragrance of fruits. In fact, the fragrance of fruits come from varieties of esters the fruits contain. Esters are used as organic solvents since these can dissolve many organic compounds. By hydrolysis, esters return to carboxylic acids and alcohols.

Nitrile

Carboxylic acid derivatives other than nitriles have a common feature that –OH of carboxy group is replaced by other atom or a group of atoms. In the case of nitriles, the carboxy group itself is replaced by the cyano group –CN. In this regard, nitriles are structurally different from other carboxylic acid derivatives. Since a nitrile group is hydrolyzed to a carboxy group, nitriles are accepted as a member of carboxylic acid derivatives.

(b) Nomenclature of carboxylic acid derivatives

(1) Names of acyl groups

The group obtained by removing   -OH from carboxy group is named an acyl group (RCO-). Representative acyl groups have common names.

[Example]   HCO-
  formyl (common name)

[Example] CH_3CO-
  acetyl (common name)

Generally, the suffix of common names of carboxylic acid "-oic acid" is changed to "-oyl"

[Example] C_6H_5CO-
  benzoyl   (←) benzoic acid

Substitutive names are made by changing suffix "carboxylic acid" into "carbonyl"

[Example] $CH_3CH_2CH_2CH_2CO$-
  butanecarbonyl   (←) butanecarboxylic acid

(2) Names of acyl halides

Simple halides are named like "acyl halides"

[Example] CH_3COCl
  acetyl chloride

More complex ones are named as shown below.

[Example] $CH_3CH_2CH_2CH_2COCl$
  butanecarbonyl chloride; valeroyl chloride (common name)

(3) Names of acyl anhydrides

To name acid anhydride derived from the same two carboxylic acids, or intramolecular acid anhydride of polycarboxylic acids, "anhydride" is added to the name of carboxylic acid.

[Example] $(C_6H_5CO)_2O$
  benzoic anhydride

(4) Name of salts of carboxylic acids

The name of cation is followed by the name of the anion of carboxylic acid.

[Example] $CH_3CH_2CH_2CH_2COONa$
  sodium pentanoate, sodium butanecarboxylate, sodium valerate

(5) Name of esters

The name of hydrocarbon group is followed by the name of the anion of carboxylic acid.

[Example] $CH_3CH_2CH_2CH_2COOCH_3$
  methyl pentanoate, methyl butanecarboxylate, methyl valerate

(6) Name of amides

The name of primary amide is the basis of names of secondary and tertiary amides. The amide carbon is to be included in the parent compound, and to suffix "amide" is to be added.

[Example] $CH_3CH_2CH_2CH_2CONH_2$
  pentanamide

Secondary and tertiary amides are named as *N*- or *N, N*-derivatives of primary amide.

[Example] $HCON(CH_3)_2$
   N, N-dimethylformamide

Exercise 12.2 Names of carboxylic acid derivatives
(1) Name the following compounds
(a) CH_3CH_2COCl (b) $(CH_3CH_2CO)_2O$ (c) $CH_3CH_2COOCH(CH_3)_2$
(d) $CH_3CONCH_2CH_3$
(2) Draw the rational formulas
(e) p-chlorobenzoyl chloride   (f) benzoic anhydride   (g) isopropyl pentanoate
(h) N-ethyl-N-methylhexanamide

Answer
(1)
(a) propionyl chloride   (b) propionic anhydride   (c) isopropyl propionate
(d) N-ethylacetamide
(2)
(e) p-ClC_6H_4COCl (f) $(C_6H_5CO)_2O$ (g) $CH_3CH_2CH_2CH_2COOCH(CH_3)_2$
(h) $CH_3CH_2CH_2CH_2 CH_2CON(CH_3)CH_2CH_3$

12.3 Structure of carboxylic acid and their derivatives

(a) Structure of carboxylic acids and their dimerization

Carboxylic acids form considerably stable dimers by hydrogen bonds. Dimerization takes place not only in solid and liquid states, but also in gas state. The proportion of the dimer increases as the temperature will be higher.

The dimer has a planar structure. The C=O bond length is prolonged from 0.1221 nm to 0.1231 nm by dimerization. On the other hand, the C=C bond length is shortened from 0.1364 nm to 0.1334 nm.
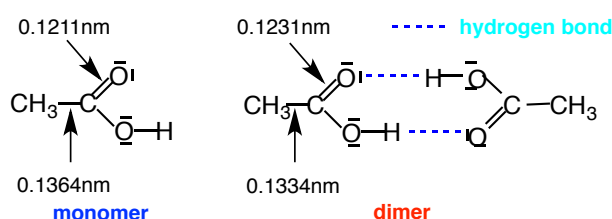
In esters, the carbonyl oxygen and the hydrocarbon residue bonded to another oxygen atom are in *cis* conformation.
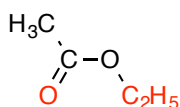
(b) Comparison between the reaction of carboxylic acids and that of carbonyl compounds

Since carboxylic acids and their derivatives (except nitriles) contain carbonyl groups, it is expected that the former has the reactivity similar to the carbonyl compounds. The representative

reaction of carbonyl compounds is nucleophilic addition. The carbonyl carbon atom in the carboxy group also has a partial positive charge, and it will suffer from the attack of the nucleophilic part (Nu⁻) of nucleophile NuE.

The result of the reaction is not necessarily identical. In the case of carboxylic acids and their derivatives, hydroxy group (in the case of carboxylic acids), or alkoxy group (in the case of esters), or halogens (in the case of halides) are bonded to the carboxy carbon atom. These are all good leaving groups in the nucleophilic substitution.

Hence, reactions similar to nucleophilic substitution at sp^3 carbon atom, nucleophilic substitution at sp^2 carbon atoms, so called **acyl substitution**, may take place. Initially, however, the addition reaction takes place to form a tetracoordinate intermediate, and elimination follows. Thus, the reaction is two-step one (Figure 12.1).

The reaction mechanism of nucleophilic substitution at sp^2 is different from that at sp^3 (S$_N$ type reaction) though there is some formal resemblance between them.
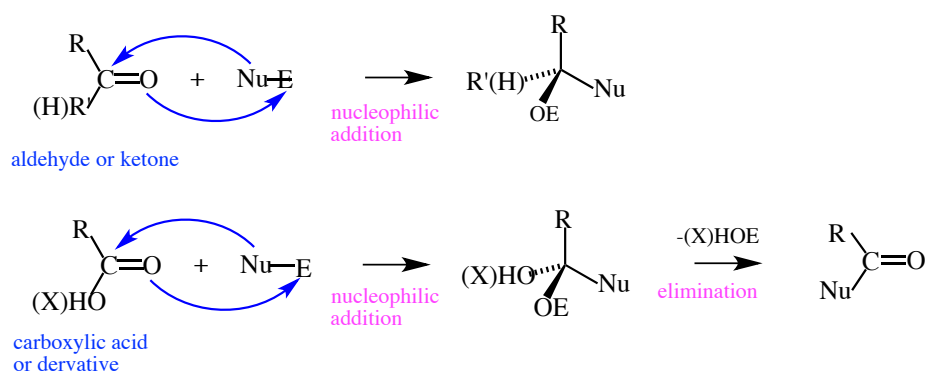
Figure 12.1 Difference between acyl addition and acyl substitution

(c) Comparison among the reactivity of carboxylic acid derivatives

For carboxylic acid derivatives, when the functional group X bonded to carbonyl carbon atom is electron-withdrawing, the carbonyl group will further be activated, while if X is electron-donating, the carbonyl group will not be activated. The order of reactivity among carboxylic acid derivatives in nucleophilic substation is given in Figure 12.2. The reactivity of carboxylic acids is much the same with that of esters. The order of reactivity is useful when syntheses of carboxylic acid derivatives are planned
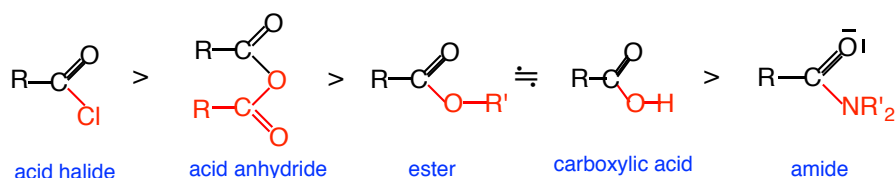
Figure 12.2 Nucleophilic reactivity of carboxylic acid derivatives

12. 4 Reaction of carboxylic acids and their derivatives
(a) Acidity of carboxylic acids

The relation between the structure (type of groups) and the strength of acidity has already been discussed in Ch. 3.3. Carboxylic acids are neutralized by such strong bases as sodium hydroxide to yield salts.

$$C_6H_5COOH + NaOH \rightarrow C_6H_5COONa + HOH$$
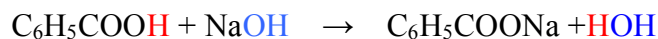
Since carboxylate salts are generally easily soluble in water, this property is conveniently employed to extract carboxylic acids from a mixture of organic compounds hardly soluble in water. The method is as follows; aqueous sodium hydroxide is added to an ether solution of a mixture of organic compounds, and the mixture is shaken with the aid of separatory funnel. Carboxylic acids which are hardly soluble in water (*e.g.* benzoic acid) is changed into their salts and move to the aqueous layer. The ether layer and the aqueous layer are separated to complete separation of benzoic acid from other organic species.

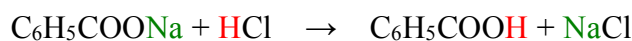Almost all carboxylic acids are weak acids, and their salts are hydrolyzed by strong bases such as hydrochloric acid to isolate carboxylic acids. When hydrochloric acid is added to sodium benzoate, benzoic acid can be isolated by extraction with ether.

$$C_6H_5COONa + HCl \rightarrow C_6H_5COOH + NaCl$$

(b) Oxidation and reduction
(1) Oxidation

When alcohols and aldehydes are oxidized by standard oxidizing reagents, the products are carboxylic acids. When carboxylic acids and their derivatives are oxidized by hydrogen peroxide, the products are **peracids** in which one additional oxygen atom is attached. Peracids are in the highest oxidation state among oxygen-containing organic compounds, and readily release an oxygen atom.

Benzoyl peroxide, which is widely used as the initiator of radical reactions, is a derivative of benzoyl chloride to which an oxygen atom is added.

benzoyl peroxide
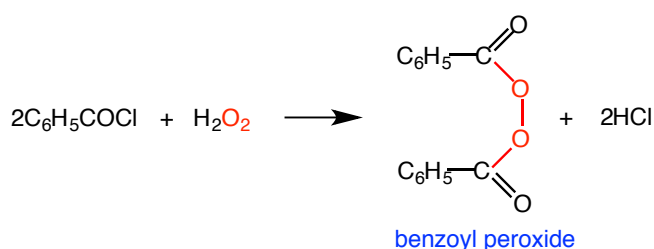
(2) Reduction

By oxidation of primary alcohols, carboxylic acids are formed. The reverse process of this reaction, reduction of carboxylic acids and derivatives, is very important as the method to prepare alcohols. The useful reagents for these reactions are lithium aluminum hydride (LAH) which is used to reduce carbonyl compounds.

The reaction proceeds under a very mild condition to give the corresponding primary alcohols.

$$4C_6H_5COOH + 3LiAlH_4 \longrightarrow 4H_2 + 4C_6H_5CH_2O \tfrac{1}{4}(LiAl) + \text{metal oxide}$$

$$4C_6H_5CH_2O \tfrac{1}{4}(LiAl) \xrightarrow{+H_2O} 4C_6H_5CH_2OH$$
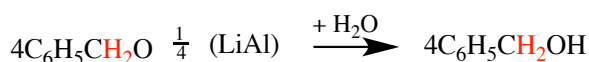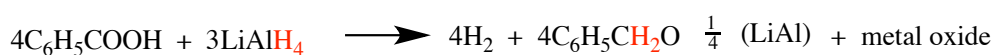
Sodium borohydride is a much weaker reducing agent, and hence it cannot reduce carboxylic acids and derivatives.

Exercise 12.3 Reduction of amides

Amides can be reduced by LAH. Predict the product obtaining reduction of benzamide by LAH.

Answer

It is expected that the carbonyl group is reduced to methylene group as is the case with carboxylic acids. The product is benzylamine $C_6H_5CH_2NH_2$.

(c) Grignard reaction

The carbonyl group of carboxylic acids and their derivatives also reacts with Grignard reagents. As an example, the reaction between ethyl benzoate and ethylmagnesium bromide is shown in Figure 12.3. The reaction proceeds in the following order.

(1) Addition of Grignard reagent to carbonyl group: The situation is the same with that of carbonyl compounds. A tetra coordinated and tetrahedral intermediate is formed.

(2) The following is different from the case of carbonyl compounds because in the case of carboxylic acids, the intermediate has an alkoxy group which readily leaves from the intermediate. $C_2H_5O^-$ and $MgBr^+$ will leave to regenerate the double bond, and hence propiophenone is formed.

(3) Propiophenone does react with excess Grignard reagent to form an adduct. This stage of the reaction follows that of carbonyl compounds.

(4) Hydrolysis of the adduct will give 3-phenyl-3-pentanol.

This means that to complete this reaction, two moles of Grignard reagent are necessary for one mole of ester.
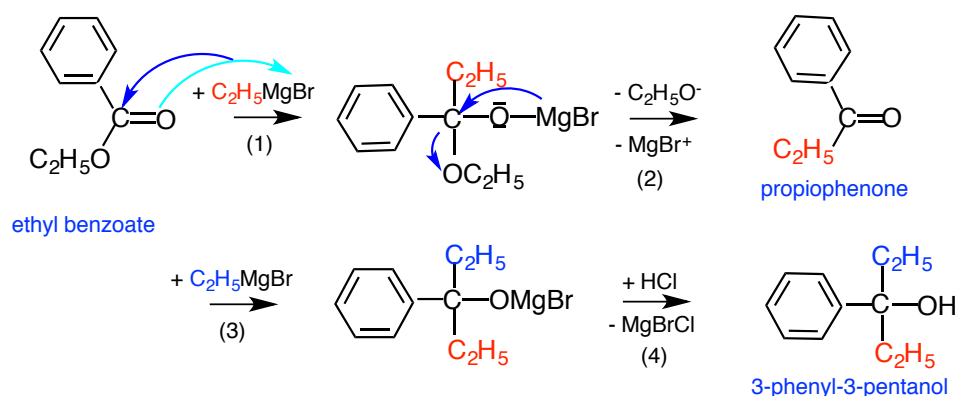
Figure 12.3 Grignard reaction of a carboxylic acid derivative

---

Exercise 12.4 Grignard reaction of an ester

Draw the structure of the product of the reaction between ethyl acetate and phenylmagnesium bromide.

Answer

The product is 1,1-diphenylethanol.
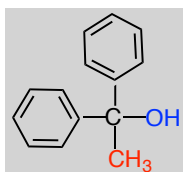
It is impossible to stop this reaction at the stage of ketone by using only one mole of Grignard reagent.   As for the reactivity toward Grignard reagent, there is little difference between esters and ketones,   When only 1 mole of Grignard reagent is used, ketones once formed do react with Grignard reagents. Thus, the final product is a mixture of ester, unreacted, ketone, and alcohol.

In some cases, however, it is possible to stop the reaction at the stage of carbonyl compounds. Since the acid halides are particularly reactive, in the reaction between 1 mole of acid halides and 1 mole of Grignard reagent, only the former selectively reacts with Grignard reagent to yield solely the carbonyl compound.

$$C_6H_5COCl \ + \ CH_3MgI \ \rightarrow \ C_6H_5COCH_3 \ + \ MgClI$$
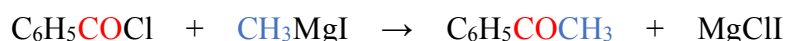
When carbon dioxide CO_2 is reacted with Grignard reagent, CO_2 molecule is inserted between carbon atom and bromine atom. By hydrolyzing the resultant carboxylate salt, a carboxylic acid is obtained.
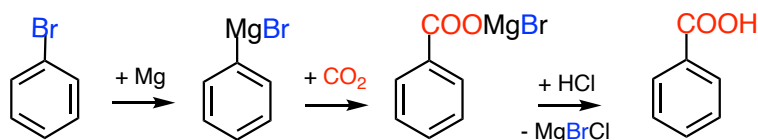
(d) Interconversion among carboxylic acids and their derivatives

Since carboxylic acids are readily obtainable by oxidizing alcohols, the interconversion among carboxylic acids and their derivative is extremely important in the field of organic synthesis. The conversion from the one with higher reactivity to the one with lower reactivity is easy. The reverse conversion is, however, much more difficult and to achieve this conversion, some special ingenuity is required.

(1) Conversion from acid halides

Acid halides, which is the highest in reactivity, readily react with carboxylic acids, alcohols, water, and amines to give acid anhydride, ester, carboxylic acids, amides, respectively (Figure 12.4).   To prepare acid anhydrides, it is more effective to use carboxylate ions rather than to use carboxylic acids. The reaction with ammonia, a product in which two hydrogen atoms are substituted is simultaneously formed.

$$C_6H_5-\overset{O}{\underset{Cl}{C}} + CH_3COONa \longrightarrow \overset{O}{\underset{}{CH_3-C}} \overset{}{\underset{O}{C_6H_5-C}} \overset{O}{\underset{O}{}} + NaOH$$

benzoyl chloride

acetic benzoic anhydride

$$CH_3COCl + C_2H_5OH \longrightarrow CH_3COOC_2H_5 + H_2O$$
acetyl chloride

ethyl acetate

$$CH_3CH_2COCl + H_2O \longrightarrow CH_3CH_2COOH + H_2O$$
propionyl chloride

propionic acid

$$(C_2H_5)_2CHCOCl + NH_3 \longrightarrow (C_2H_5)_2CHCONH_2 + [(C_2H_5)_2CHCO]_2NH$$
2-ethylbutanoyl chloride

2-ethylbutanamide (91%)

bis(2-ethylbutan)amide (9%)
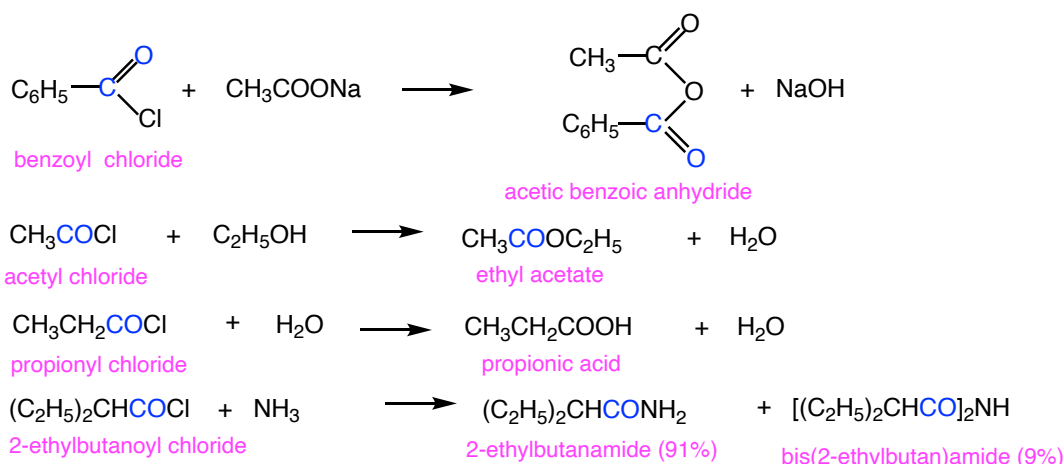
Figure 12.4 Conversion from acid halides to other carboxylic acid derivatives

(2) Conversion from acid anhydrides

Acid anhydrides react with alcohols, water, and amines to give esters, carboxylic acids, and amides together with 1 molecule of carboxylic acid (Figure. 12.5).

$$\overset{O}{\underset{}{C_6H_5-C}} \overset{}{\underset{O}{C_6H_5-C}} \overset{O}{\underset{O}{}} + C_2H_5OH \longrightarrow C_6H_5COOC_2H_5 + C_6H_5COOH$$

benzoic anhydride

ethyl benzoate

$$(CH_3CO)_2O + H_2O \longrightarrow 2CH_3COOH$$
acetic anhydride

$$(CH_3CO)_2O + (CH_3)_2NH \longrightarrow CH_3CON(CH_3)_2 + CH_3COOH$$

dimethylamine

N,N-dimethylacetamide
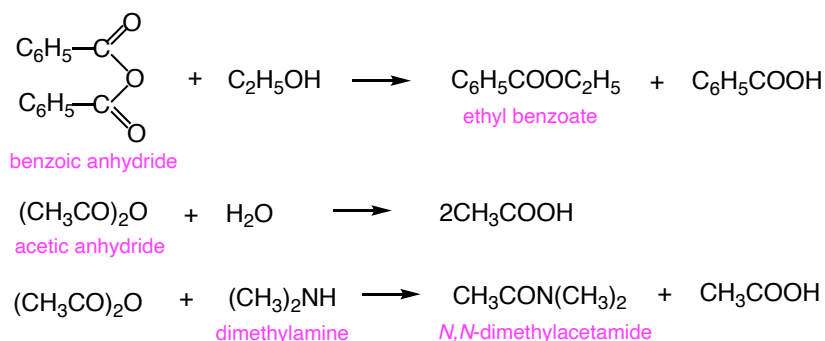
Figure 12.5 Conversion from acid anhydrides

(3) Conversion from carboxylic acids and esters

In order to convert carboxylic acids to derivatives of higher rank, *e.g.*, acid halides, use of stronger halogenated reagents such as thionyl chloride or diphosphorous decachloride are required.

The reactivities of carboxylic acids and esters are much the same, the interconversion between them is possible but the reaction is necessarily an equilibrium.

It is difficult to convert carboxylic acids directly to amides. The reaction between a carboxylic acid and ammonia gives only the ammonium salt of the carboxylic acid. In some cases, an ammonium salt decomposes to give an amide (Figure 12.6).

Esters react with amines to give amides.

$$C_6H_5COOH + SOCl_2 \longrightarrow C_6H_5COCl + SO_2 + HCl$$

benzoyl chloride

$$CH_3COOH + NH_3 \longrightarrow CH_3COONH_4$$
acetic acid

ammonium acetate

$$CH_3COONH_4 \xrightarrow{heat} CH_3CONH_2 + H_2O$$

acetamide

$$C_6H_5COOC_2H_5 + C_6H_5CH_2NH_2 \longrightarrow C_6H_5CONHCH_2C_6H_5 + C_2H_5OH$$
benzylamine

N-benzylbenzamide

Figure 12.6 Conversion from carboxylic acids

(4) Conversion from amides

Amides are stable compounds, and direct conversion of them to higher carboxylic acid derivatives is difficult. If, however, these are heated with aqueous strong base, salts of carboxylic acids are obtained.

$$CH_3CONH_2 \; + \; NaOH \; \rightarrow \; CH_3COONa \; + \; NH_3$$
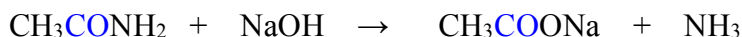
Exercise 12.5 Interconversion among carboxylic acid derivatives
(1) Show the reaction formulas of the reactions of acetyl chloride with the following reagents.
   (a) water
   (b) 2-propanol (isopropyl alcohol)
   (c) dimethylamine
(2) Show the reaction formulas of the reactions of acetic anhydride with the following reagents.
   (d) water
   (e) ethanol
   (f) diethylamine
(3) Show the reaction formulas of the reactions of methyl acetate with the following reagents.
   (g) aqueous potassium hydroxide
   (h) LAH
   (i) ammonia

Answer

(a) $CH_3COCl \; + \; HOH \longrightarrow CH_3COOH \; + \; HCl$
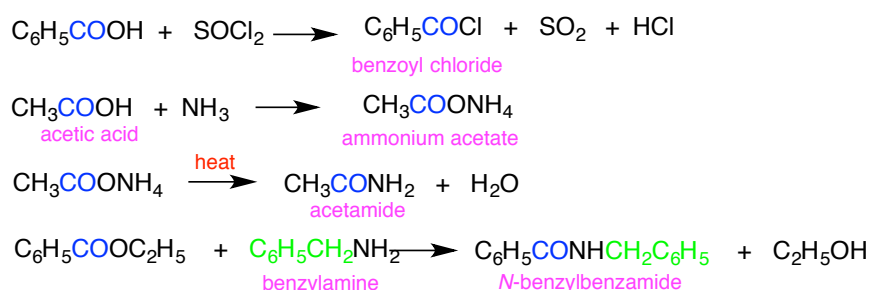
(b) $CH_3COCl \; + \; (CH_3)_2CHOH \longrightarrow CH_3COOCH(CH_3)_2 \; + \; HCl$

(c) $CH_3COCl \; + \; (CH_3)_2NH \longrightarrow CH_3CON(CH_3)_2 \; + \; HCl$

(d) $(CH_3CO)_2O \; + \; HOH \longrightarrow 2CH_3COOH$

(e) $(CH_3CO)_2O \; + \; C_2H_5OH \longrightarrow CH_3COOC_2H_5 \; + \; CH_3COOH$

(f) $(CH_3CO)_2O + (CH_3)_2NH \longrightarrow CH_3CON(CH_3)_2 \; + \; CH_3COOH$

(g) $CH_3COOCH_3 \; + \; KOH \longrightarrow CH_3COOK \; + \; CH_3OH$

(h) $2CH_3COOCH_3 \; + \; LiAlH_4 \; + \; 4HCl$
$\longrightarrow 2CH_3CH_2OH \; + \; 2CH_3OH \; + \; LiCl \; + \; AlCl_3$

(i) $CH_3COOCH_3 \; + \; NH_3 \longrightarrow CH_3CONH_2 \; + \; CH_3OH$
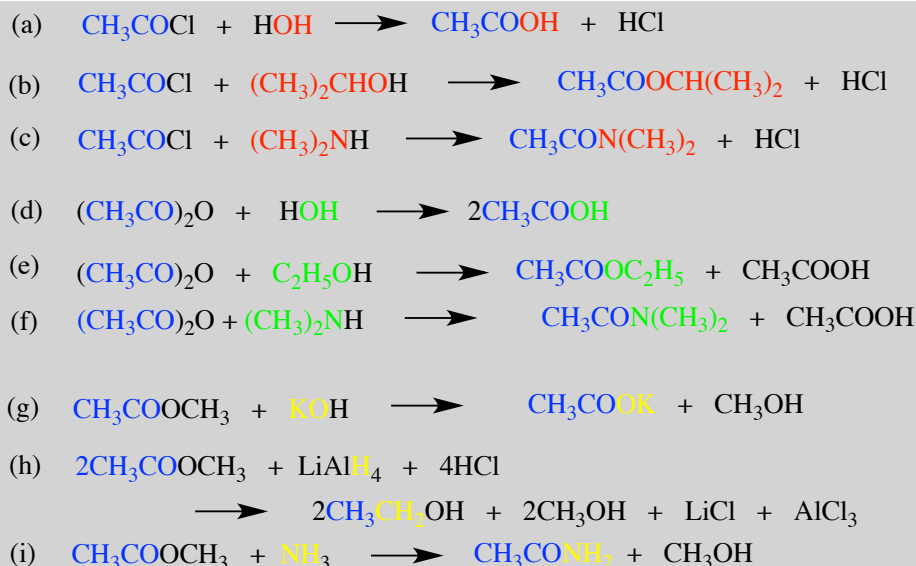
(e) Esterification and hydrolysis of esters
(1) Acid-catalyzed condition

Among the reactions of carboxylic acids and their derivatives, esterification and hydrolysis of esters are particularly important for both synthetic purposes and reaction mechanism. Esterification of carboxylic acid under an acidic condition is well-known Fisher's ester synthesis. The reaction between acetic acid and ethanol under an acidic condition is described as an example. The reaction proceeds as indicated in Figure 12.7.

(1) Proton, the catalyst, adds to the carbonyl group to give an oxonium-type intermediate. By this protonation, the carbonyl group is activated.

(2) Nucleophilic attack takes place to the activated carbon atom. Under an acidic condition, ethoxide ion cannot exist; hence the nucleophilic reagent is necessarily ethanol itself. As a nucleophilic reagent, ethanol is not strong, but it can attack the carbonyl carbon which is activated by protonation. The intermediate formed has a tetrahedral structure.
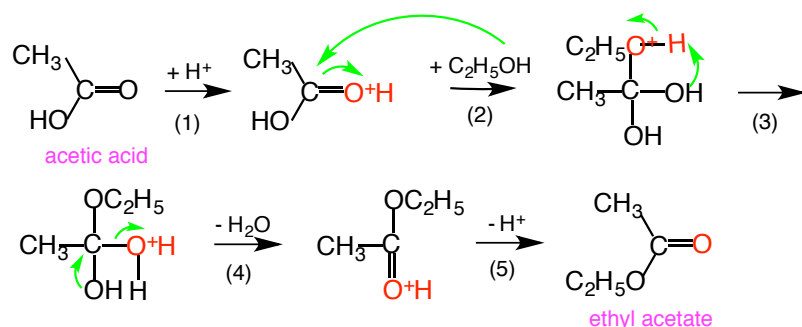
Figure 12.7 Esterification of acetic acid

(3) A proton transfer takes place from alkoxy oxygen to hydroxy oxygen. (The lone pair of hydroxy oxygen is coordinated to proton.)

(4) Water is eliminated and the lone pair is migrated to form oxonium-type intermediate.

(5) Proton is eliminated, and ethyl acetate is formed.

The second step, the nucleophilic attack by ethanol is the key reaction. As a result, the reaction is nucleophilic substitution in which a hydroxy group is substituted by ethoxy group.

Each step of the reaction proceeds as a reverse step. Hence the acid-catalyzed hydrolysis of esters proceeds as indicated in Figure. 12.8. The reaction also proceeds *via* tetracoordinated intermediate.
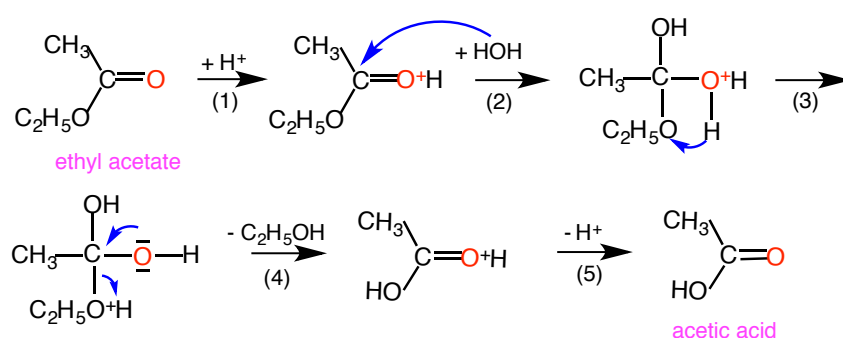
Figure 12.8 Acid-catalyzed hydrolysis of esters

Exercise 12.6 Equilibrium between esterification and hydrolysis

Using the fact that esterification and hydrolysis of esters are in equilibrium, draw a figure by combining Figure 12. 7 and Figure 12.8. (Hint: Draw a double arrow between compounds.)

Answer
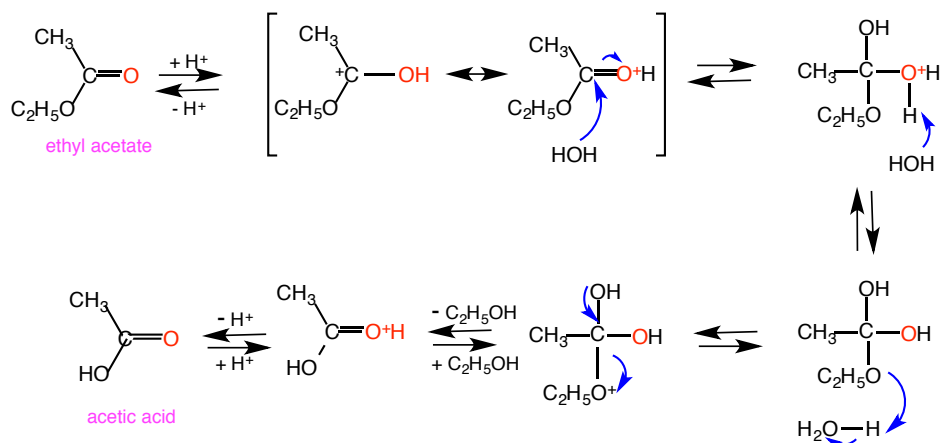
(2) Base-catalyzed condition

Under a basic condition, carboxylic acids turn into salts of carboxylic acids, which cannot react with alcohols. To convert carboxylic acids to esters under a basic condition, nucleophilic substitution between salts of carboxylic acids and alkyl halides (S_N2) is employed.

$$CH_3COONa + C_2H_5Br \rightarrow CH_3COOC_2H_5 + NaBr$$
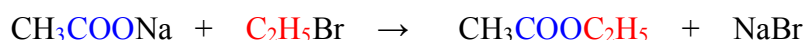
Hydrolysis of esters under a basic condition is called **saponification**. This reaction is very important and is the same to produce soap from fat (Figure 12.9).

(1) The 1st stage of the reaction is the attack of hydroxide ion, which is the catalyst and at the same time the nucleophilic reagent, to the carbonyl carbon. An intermediate with tetrahedral structure is formed.

(2) An alkoxide ion is deleted from the intermediate, and if the immigration of proton takes place, carboxylic acids are formed.

(3) Under the basic condition, carboxylic acids turn to salts to form alcohols.

Figure 12.9 Saponification of esters

Exercise 12.7 Saponification of fats

Draw the reaction formula of saponification of tristearin

$$CH_2OCO(CH_2)_{16}CH_3$$
$$CHOCO(CH_2)_{16}CH_3$$
$$CH_2OCO(CH_2)_{16}CH_3$$

Answer

Three moles of sodium hydroxide are necessary for 1 mole of fat.

$CH_2OCO(CH_2)_{16}CH_3$
$CHOCO(CH_2)_{16}CH_3$ + 3NaOH $\longrightarrow$ $3CH_3(CH_2)_{16}COONa$ + $CHOH$
$CH_2OCO(CH_2)_{16}CH_3$

CH_2OH
sodium tristearate
$CHOH$
CH_2OH

tristearin
(glycerol tristearate)

glycerin

(f) Reactions of α-carbon
(1) Claisen condensation
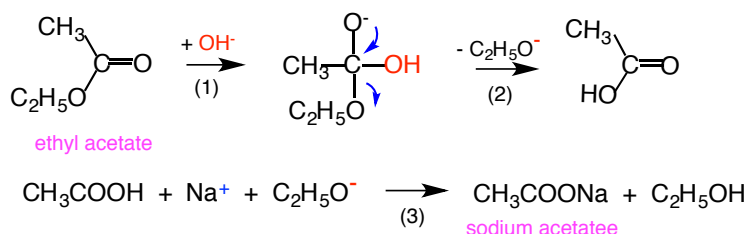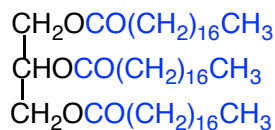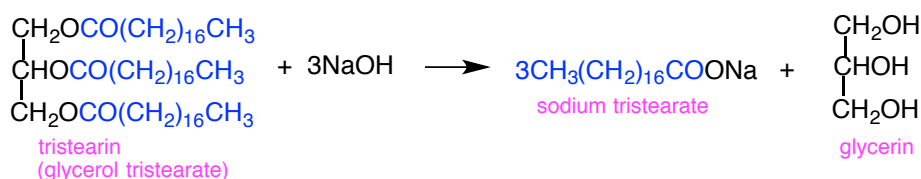
For carboxylic acids and their derivatives, α-carbon atom of the carboxy group is very reactive, the situation of which is similar to aldehydes and ketones. When it has Hα, reactions similar to aldol condensation take place. Reactions of two ester molecules similar to these are named **Claisen condensation** reported by Rainer Ludwig Claisen (1851-1930). This is much the same with carbonyl compounds and carboxylic acids (and derivatives) for both of which Grignard reactions take place. As an example, Claisen condensation of ethyl acetate under the presence of sodium ethoxide to form ethyl 2-oxobutanoate (ethyl acetoacetate) is shown. The progress of the reaction is shown with the aid of Figure 12.10.

(1) Formation of carbanion: Initially ethoxide ion withdraws Hα of the ester to give a carbanion.
(2) The carbanion formed attacks the carbonyl carbon atom of the ester. In the case of aldol condensation, proton will add to the anion intermediate formed from the reaction between carbonyl compounds and carbanion to give aldol. In the case of the reaction between esters and carbanions, the anion intermediate formed has an ethoxy group OC_2H_5, which is a good leaving group. Elimination of this leaving group and regeneration of C=O bond follows to give ethyl 2-oxobutanoate

The difference between aldol condensation and Claisen condensation is whether the carbon atom, the center of reaction possesses a leaving group or not. Remember that, in Grignard reaction, the difference in the reactions between carbonyl compounds and carboxylic acids (and derivatives) depends on whether the carbon atom, *i.e.*, the center of the reaction, has a leaving group or not.

$$CH_3COOC_2H_5 + C_2H_5ONa \longrightarrow C^-H_2COOC_2H_5 + C_2H_5OH + Na^+ \quad (1)$$

Figure with reaction (2):

$$CH_3C(=O)OC_2H_5 + C^-H_2COOC_2H_5 \longrightarrow \left[\begin{array}{c} CH_3 \\ C_2H_5O-\overset{|}{C}-CH_2COOC_2H_5 \\ O^- \end{array} \right] \quad (2)$$

$$\xrightarrow{-\ OC_2H_5^-} CH_3-\overset{\overset{\displaystyle}{||}}{\underset{O}{C}}-CH_2COOC_2H_5$$

ethyl 2-oxobutanote
(ethyl acetoacetate)
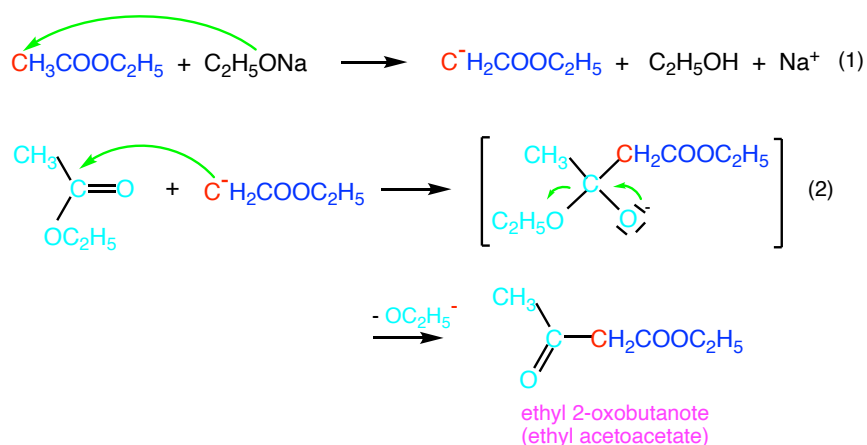
Figure 12.10 Claisen condensation

Exercise 12. 8 Claisen condensation
Complete the following reaction formula.

$$CH_3CH_2COOC_2H_5 \xrightarrow{C_2H_5ONa} \quad ?$$

Answer

$$CH_3CH_2COOC_2H_5 \xrightarrow{C_2H_5ONa} CH_3C^-HCOOC_2H_5$$

$$CH_3CH_2COOC_2H_5 + CH_3C^-HCOOC_2H_5 \longrightarrow \left[\begin{array}{c} CH_3CH_2 \quad CH_3CHCOOC_2H_5 \\ C \\ C_2H_5O \quad O^- \end{array} \right]$$

$$\longrightarrow \begin{array}{c} CH_3CHCOOC_2H_5 \\ | \\ CH_3CH_2C=O \end{array}$$
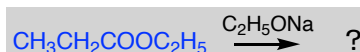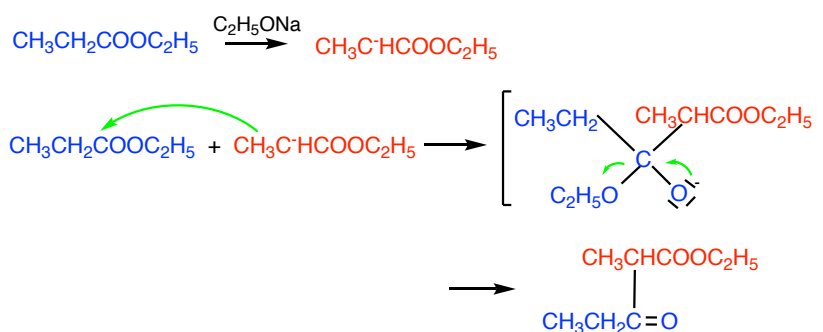
(2) Mixed Claisen condensation

Similar to aldol condensation, mixed Claisen condensation gives in principle four kinds of products. In this regard, this reaction is not suitable for preparing a particular compound. Carboxylic acids and their derivatives which do not have Hα will not become carbanions, and hence act only as substrates. For this reason, the reaction is generally rather simple.

Ethyl formate $HCOOC_2H_5$ and ethyl benzoate $C_6H_5COOC_2H_5$ are examples of compounds without Hα. The mixed Claisen condensation between ethyl acetate and ethyl formate will give ethyl 2-oxobutanoate and ethyl formylacetate $OHCCH_2COOC_2H_5$.

Exercise 12.9 Mixed Claisen condensation

Predict the products of the reaction between ethyl benzoate and ethyl acetate under the reaction condition of Claisen condensation.

Answer

In addition to ethyl 2-oxobutanoate, ethyl benzoylacetate $C_6H_5COCH_2COOC_2H_5$, which is formed by the attack of $C^-H_2COOC_2H_5$ to ethyl benzoate, will be obtained.

(3) Active methylene compounds

The methylene group $-CH_2-$ in ethyl acetoacetate is sandwiched by two carbonyl groups C=O. Such a methylene group is named as **active methylen**e, and compounds having such a group is named **active methylene compounds**. Active methylene compounds are classified, as shown in Table 12.4, depending on the type of C=O groups sandwiching the methylene group. Many active methylene compounds have common names.

Table 12.4 Representative active methylene compounds

structural formula	common name (systematic name)
$OHCCH_2CHO$	malondialdehyde (propanedial)
$CH_3COCH_2COCH_3$	acetylacetone (pentane-2,4-dione)
$CH_3COCH_2COOC_2H_5$	ethyl acetoacetate (ethyl 2-oxo-butanoate)
$C_2H_5COO\ CH_2COOC_2H_5$	diethyl malonate (diethyl propanedioate)

The pK_a of the representative active methylene compound, acetyl acetone, is 10.2, which is close to the pK_a of phenol, and it may be regarded as a weak acid. This is because the enolate ion can resonate with two C=O groups (Figure 12 11).
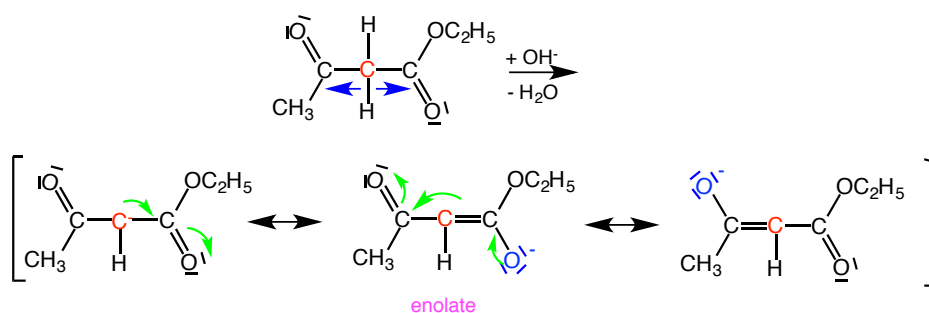
Figure 12.11 The enolate ion of an active methylene compound

(4) Malonic ester synthesis

Carbanions generated from active methylene compounds have strong nucleophilic power similar to those generated from carboxylic acids and their derivatives. The pattern of the reaction is somewhat different from those of carbonyl compounds. One example is a type of reaction called **malonic ester synthesis** in which carbanions attack the substrates such as alkyl halides to induce nucleophilic substitution. When carbanions react with methyl iodide under the presence of strong bases (such as alkoxides), diethyl malonate, in which hydrogens of active methylene group are substituted by methyl groups.

Interestingly, this reaction does not stop at this stage. The remaining hydrogens are also active, and carbanions are formed if strong bases are present. If this carbanion is reacted with an alkyl halide different from the first one, a diethyl malonate derivative substituted by two different alkyl groups are obtained.
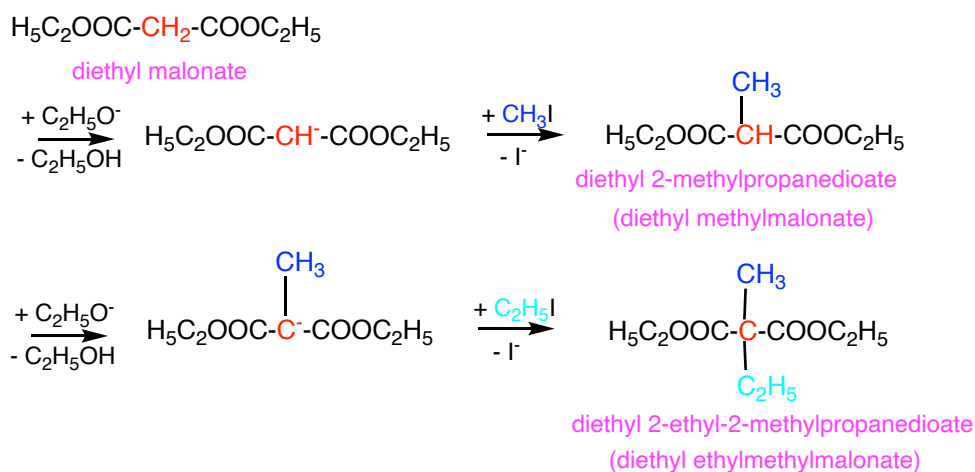
Figure 12.12 Malonic ester synthesis

Hydrolysis of dialkylmalonate esters under a standard condition will give a dialkymalonic acid. Dicarboxylic acids with two carboxylic acid moieties on one carbon atom relatively easily release carbon dioxide (decarboxylation). This series of reactions is generally used to synthesize carboxylic acids.
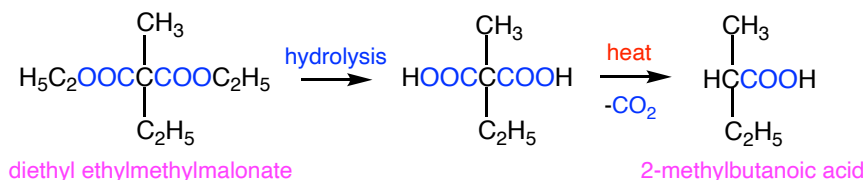
Exercise 12.10 Malonic ester synthesis

A carboxylic acid $CH_3CH_2CH_2CH(CH_3)COOH$ is to be synthesized from diethyl malonate and other reagents.   Show the other reagents required.

Answer

Since the CHCOOH part of product comes from malonic acid, CH_3I and $CH_3CH_2CH_2I$ are sequentially reacted with diethyl malonate and the product is finally hydrolyzed.

---

(5) Acetoacetic ester synthesis

Like malonic esters, acetoacetic esters are also used to synthetic purpose with the aid of their active methylene groups. Enolate ions obtained by treating acetoacetic esters with strong bases react with alkyl halides to alkylate acetoacetic esters.

$$CH_3COCH_2COOC_2H_5 \xrightarrow[- C_2H_5OH]{+ C_2H_5O^-} CH_3COC^-HCOOC_2H_5 \xrightarrow{CH_3(CH_2)_2CH_2Br} \begin{array}{c} CH_2(CH_2)_2CH_3 \\ | \\ CH_3COCHCOOC_2H_5 \end{array}$$

ethyl acetoacetate
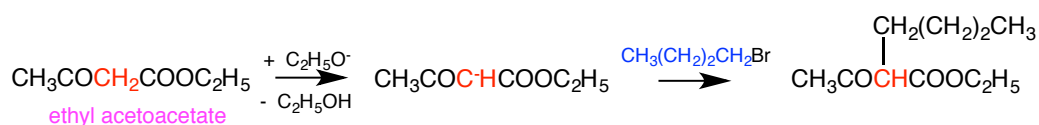
The difference between malonic ester synthesis and acetoacetic ester synthesis is that in the latter the methylene group is activated by a ketone group and a carboxy group; After the product is hydrolyzed in an acidic condition and heated, decarboxylation takes place to give ketones. This is a general method to obtain ketones from alkyl halides and ethyl acetoacetate.

$$\begin{array}{c} CH_2(CH_2)_2CH_3 \\ | \\ CH_3COCHCOOC_2H_5 \end{array} \xrightarrow[\text{acidic condition}]{\text{hydrolysis}} \begin{array}{c} CH_2(CH_2)_2CH_3 \\ | \\ CH_3COCHCOOH \end{array} \longrightarrow \begin{array}{c} CH_2(CH_2)_2CH_3 \\ | \\ CH_3COCH_2 \end{array}$$

2-heptanone
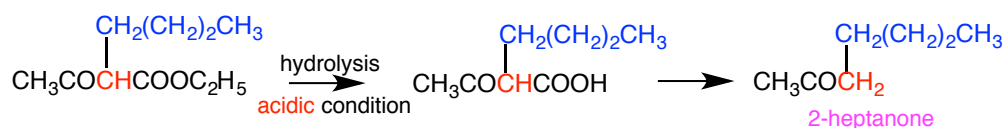
If the product is hydrolyzed in a basic condition, the molecule cleaves in two parts, and give two kinds of carboxylic acids at the active methylene site.

$$\begin{array}{c} CH_2(CH_2)_2CH_3 \\ | \\ CH_3COCHCOOC_2H_5 \end{array} \xrightarrow[\text{basic condition}]{\text{hydrolysis}} \begin{array}{c} CH_2(CH_2)_2CH_3 \\ | \\ CH_3COCHCOOH \end{array}$$

$$\longrightarrow CH_3COOH + CH_3(CH_2)_2CH_2CH_2COOH$$
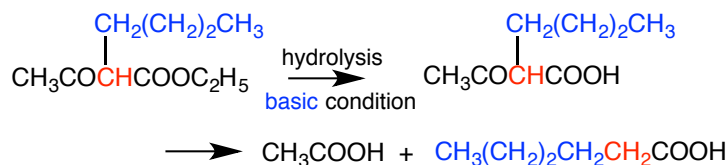
The general method to synthesize ketones and carboxylic acids with the aid of ethyl acetoacetate is called **acetoacetic ester synthesi**s.

So far, we have seen that the great world of organic synthesis is developed based on carbonyl compounds and carboxylic acids and their derivatives. In this book we could survey only the surface of this world of organic chemistry. If you are interested, you are advised to continue your study with the aid of more advanced textbooks.

Problems

12.1

Name the following compounds.

a) CH₃CHCH₂COOH (with Br on the CH)

b) CH₃CHCH₂CHCH₂COOH (with CH₃ groups)

c) cyclohexane with H, COOH and two CH₃ groups

d) benzene ring with COOH and C₂H₅

e) naphthalene with two COOH groups

12.2

Name the following compounds.

a) CH₃COBr

b) (CH₃CH₂CH₂CO)(CH₃CH₂CO)O anhydride

c) benzene ring with COOCH(CH₃)₂ and Br

d) CH₃CH₂CON(CH₂CH₃)₂
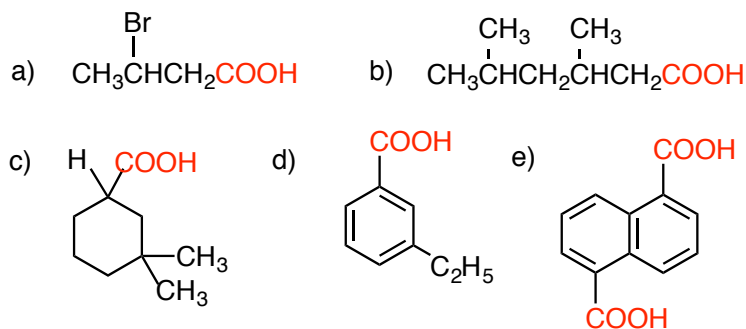
e) cyclohexane with H, CN and two CH₃ groups
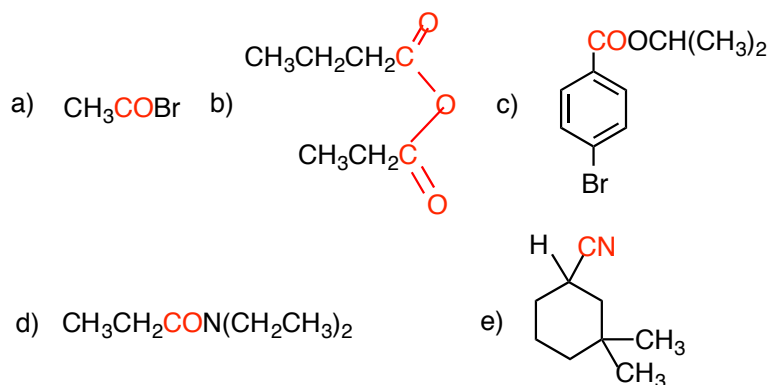
12.3

Draw the structures of the following compounds.

a) 3-chlorobutanoic acid   b) acetic benzoic anhydride

c) *N*-ethyl-*N*-methylacetamide   d) 2-butyl pentanoate

e) cyanoacetic acid   f) 4-methylpentanenitrile

12.4

Draw the reaction formulas of the reactions between benzoic acid and the following reagents, respectively.

a) aqueous NaOH   b) $CH_3OH + H_2SO_4$ (heat)

c) lithium aluminum hydride (LAH)   d) thionyl chloride $SOCl_2$

12.5

Draw the structures and names of the products of the following reactions.

a) C_6H_5COCl + $(CH_3)_2NH$ $\xrightarrow{\text{NaOH}}$?

b) $C_2H_5COOC_2H_5$ + P_2Cl_{10} $\longrightarrow$?

c) $HCOOC_2H_5$ + CH_3COONa $\xrightarrow{\text{NaOC}_2\text{H}_5}$?

d) C_6H_5COOH + C_2H_5MgBr $\xrightarrow{\text{H}^+,\ \text{H}_2\text{O}}$?

e) $CH_3COOC_2H_5$ + $LiAlH_4$ $\longrightarrow$?
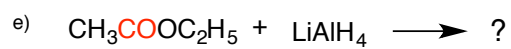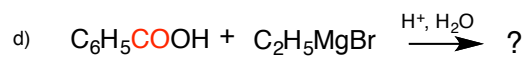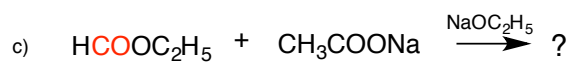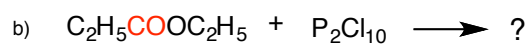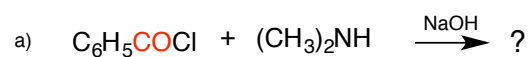
12.6

(1) Draw the reaction formula to prepare 2-ethylhexanoic acid with the aid of malonic ester synthesis.

(2) Draw the reaction formula to prepare 2-heptanone with the aid of acetoacetic ester synthesis.

Answers

12.1

a) 3-bromobutanoic acid

b) 3,5-dimethylhaxanoic acid

c) 3,3-dimethylcyclohexanecarboxlylic acid

d) 3-ethylbenzoic acid

e) naphthalene-1,5-dicarboxylic acid

12.2

a) acetyl bromide

b) lactic propionic anhydride

c) isopropyl *p*-bromobenzoate

d) *N,N*-diethylpropionamide

e) 3,3-dimethylcyclohexanecarbonitrile

12.3

a) CH_3CCH_2COOH

   $|$
   Cl

b) $CH_3CH_2CH_2C$ (with $=O$ and O) benzene ring, C with two O

c) CH_3CON CH_2CH_3 / CH_3

d) $CH_3CH_2CH_2CH_2COOCH$

   CH_2CH_3
   CH_3

e) $NCCH_2COOH$

f) $CH_3CHCH_2CH_2CN$

   $|$
   CH_3

12.4

a) $C_6H_5COOH + NaOH \longrightarrow C_6H_5COONa + H_2O$

b) $C_6H_5COOH + CH_3OH \xrightarrow{\Delta} C_6H_5COOCH_3 + H_2O$

c) $C_6H_5COOH + LiAlH_4 \longrightarrow \longrightarrow C_6H_5CH_2OH$

   (Details will be found in the text)

d) $C_6H_5COOH + SOCl_2 \longrightarrow C_6H_5COCl + SO_2 + HCl$

12.5

a) $C_6H_5CONH(CH_3)_2$

   N,N-dimethylbenzamide

b) C_2H_5COCl

   propionyl chloride

c) $HCOCH_2COOC_2H_5$

   ethyl formylacetate

d) $C_6H_5(C_2H_5)_2COH$

   3-phenyl-3-pentanol

e) CH_3CH_2OH

   ethanol

12.6

(1) $H_5C_2OOCCH_2COOC_2H_5$ $\xrightarrow[-\ C_2H_5OH]{+\ C_2H_5O^-}$ $H_5C_2OOCCH^-COOC_2H_5$ $\xrightarrow{+\ CH_3CH_2CH_2CH_2Br}$

diethyl malonate

$$H_5C_2OOCCHCOOC_2H_5 \quad \xrightarrow{+\ C_2H_5Br} \quad H_5C_2OOCCCOOC_2H_5 \quad \xrightarrow{hydrolysis} \quad CH_3CH_2CH_2CH_2CHCOOH$$

with $CH_2CH_2CH_2CH_3$ branch (diethyl butylmalonate); product with $CH_2CH_2CH_2CH_3$ and CH_2CH_3 branches (diethyl butylethylmalonate); acid with CH_2CH_3 branch: 2-ethylhexanoic acid

(2) $CH_3COCH_2COOC_2H_5$ $\xrightarrow[-\ C_2H_5OH]{+\ C_2H_5O^-}$ $CH_3COC^-HCOOC_2H_5$ $\xrightarrow{CH_3CHCH_2CH_2Br}$ $CH_3COCHCOOC_2H_5$

ethyl acetoacetate; product with $CH_2CH_2CH_2CH_3$ branch: ethyl 2-butyl-3-oxobutanoate (ethyl 2-butylacetoacetate)

$\xrightarrow[acidic\ condition]{hydrolysis}$ $CH_3COCHCOOH$ $\longrightarrow$ CH_3COCH_2

product with $CH_2CH_2CH_2CH_3$ branch; 2-heptanone with $CH_2CH_2CH_2CH_3$ branch