17

Organic Chemistry

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Carboxyl Derivatives

Chapter 17
In this chapter, we study five classes of organic compounds. Under the structural formula of each is a drawing to help you see its relationship to the carboxyl group.

- An acid chloride: $\text{RC-Cl}$
- An acid anhydride: $\text{RCOOCR'}$
- An ester: $\text{RCOOR'}$

- $\text{RCCl}$
- $\text{RCOCl}$
- $\text{RCOOR}$

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An amide is formally related to a carboxyl group by loss of -OH from the carboxyl and -H from ammonia.

Loss of -OH and -H from an amide gives a nitrile.

The enol of an amide.
The most important reaction of the first four classes of compounds (acid halides, acid anhydrides, esters, and amides) is nucleophilic acyl substitution.

\[
R-C-Y + \text{Nu}^- \rightarrow \text{Tetrahedral carbonyl addition intermediate}
\]

\[
\begin{array}{c}
\text{Nu} \\
\end{array}
\]

\[
\text{R-C-Nu} + \text{Y}^- \rightarrow \text{R-C-Nu}
\]
The functional group of an acid halide is an acyl group bonded to a halogen.

To name, change the suffix -ic acid to -yl halide.

- Ethanooyl chloride (Acetyl chloride)
- Benzoyl chloride
- Hexanedioyl chloride (Adipoyl chloride)
Replacement of -OH in a sulfonic acid by -Cl gives a sulfonyl chloride.

- Methanesulfonic acid
- Methanesulfonyl chloride (Mesyl chloride, MsCl)
- p-Toluenesulfonic acid
- p-Toluenesulfonyl chloride (Tosyl chloride, TsCl)
The functional group of a acid anhydride is two acyl groups bonded to an oxygen atom.

- The anhydride may be symmetrical (two identical acyl groups) or mixed (two different acyl groups).

To name, replace acid of the parent acid by anhydride.

- Acetic anhydride: CH₃COCCH₃
- Benzoic anhydride: C₆H₅-CO-CO-C₆H₅
- Acetic benzoic anhydride: CH₃COC-C₆H₅
Cyclic anhydrides are named from the dicarboxylic acids from which they are derived.

- Succinic anhydride
- Maleic anhydride
- Phthalic anhydride
Acid Anhydrides

A phosphoric acid anhydride contains two phosphoryl groups bonded to an oxygen atom.

\[
\begin{align*}
\text{HO-P-O-P-OH} & \quad \text{HO-P-O-P-O-P-OH} \\
\text{OH OH} & \quad \text{OH OH OH}
\end{align*}
\]

- Diphosphoric acid (Pyrophosphoric acid)
- Triphosphoric acid

\[
\begin{align*}
-\text{O-P-O-P-O} & \quad -\text{O-P-O-P-O-P-O} \\
\text{O} & \quad \text{O} \quad \text{O} \\
\text{OH} & \quad \text{OH} \quad \text{OH}
\end{align*}
\]

- Diphosphate ion (Pyrophosphate ion)
- Triphosphate ion
17 Esters

- The functional group of an ester is an acyl group bonded to -OR or -OAr.
- Name the alkyl or aryl group bonded to oxygen; follow by the name of the acid but with the suffix -ic acid changed to -ate.

Ethyl ethanoate  
(Ethyl acetate)

Isopropyl benzoate
17 Esters

- Cyclic esters are called lactones
- Name the parent carboxylic acid, drop the suffix -ic acid, and add -olactone

3-Butanolactone (β-Butyrolactone)  4-Butanolactone (γ-Butyrolactone)  5-Hexanolactone (δ-Caprolactone)
The functional group of an amide is an acyl group bonded to a nitrogen atom.

IUPAC: drop -oic acid from the name of the parent acid and add -amide.

If the amide nitrogen is bonded to an alkyl or aryl group, name the group and show its location on nitrogen by N-

- Acetamide: CH$_3$C$_2$H$_4$N\(\text{H}_2\) (a 1° amide)
- Benzamide: \(\text{C}_6\text{H}_5\text{C}_2\text{H}_4\text{N}\text{H}_2\) (a 1° amide)
- N-Methylacetamide: CH$_3$C$_2$H$_4$N\(\text{CH}_3\) (a 2° amide)
Cyclic amides are called lactams.

Name the parent carboxylic acid, drop the suffix -ic acid, and add -lactam.
The penicillins are a family of $\beta$-lactam antibiotics. The penicillins differ in the group bonded to the acyl carbon.

Penicillin G
17 Penicillin G

\[
\text{Chemical Structure of Penicillin G}
\]

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The cephalosporins are also $\beta$-lactam antibiotics. The cephalosporins differ in the group bonded to the acyl carbon and the side chain bonded to the thiazine ring.
Cefetamet

\[
\begin{align*}
H_2N & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{C} \\
\text{N} & \quad \text{N} \\
\text{OCH}_3 & \quad \text{CO}_2H \\
\text{CH}_3 &
\end{align*}
\]
17 Cephalosporins

- Cefetamet
17 Nitriles

- The functional group of a nitrile is a cyano group
- IUPAC: name as an alkanenitrile
- Common: drop the suffix -ic acid and add -onitrile

CH$_3$C≡N  \[ \text{Ethanenitrile (Acetonitrile)} \]

\[ \text{C≡N} \]  \[ \text{Benzonitrile} \]

[\text{CH$_2$C≡N}]  \[ \text{Phenylethanenitrile (Phenylacetonitrile)} \]
17 Acidity of N-H bonds

- Amides are comparable in acidity to alcohols
- Water-insoluble amides do not react with NaOH or other alkali metal hydroxides to form water soluble salts

\[
\begin{align*}
\text{Acetamide} & \quad \text{pK}_a \ 15-17 \\
\text{Succinimide} & \quad \text{pK}_a \ 9.7 \\
\text{Phthalimide} & \quad \text{pK}_a \ 8.3
\end{align*}
\]
Imides are more acidic than amides because
1. the electron-withdrawing inductive of the two adjacent C=O groups weakens the N-H bond, and
2. the imide anion is stabilized by resonance delocalization of the negative charge.

\[
\text{Succinimide} \quad \overset{\text{N-H} + \text{H}_2\text{O}}{\xrightarrow{\text{H}_3\text{O}^+}} \quad \text{A resonance-stabilized anion}
\]
Imides such as phthalimide readily dissolve in aqueous NaOH as water-soluble salts.

\[ \text{Imide} + \text{NaOH} \rightarrow \text{Salt} \]

- Imide: (stronger base) \[ pK_a = 8.3 \]
- Salt: (weaker base) \[ pK_a = 15.7 \]

Equilibrium:

\[ \text{Salt} + \text{H}_2\text{O} \rightarrow \text{Imide} + \text{Na}^- + \text{H}^+ \]

- \[ pK_{eq} = -7.4 \]
- \[ K_{eq} = 2.5 \times 10^7 \]
The most characteristic fragmentation patterns of esters and amides are $\alpha$-cleavage and McLafferty rearrangement.

- $\alpha$-cleavage

$$\text{CH}_3\text{CH}_2\text{CH}_2-\text{C-OCH}_3$$

$$\text{CH}_3\text{CH}_2\text{CH}_2\cdot + \text{OCH}_3$$

$$\text{CH}_3\text{CH}_2\text{CH}_2\cdot + \text{C-OCH}_3$$

$m/z$ 71

$m/z$ 59
17 Mass Spectrometry

- McLafferty rearrangement: a redistribution of electrons in a six-membered cyclic transition state

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H} \\
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{H}_2\text{C} & \quad \text{C} \\
\text{C} & \quad \text{OCH}_3
\end{align*}
\]

\[\rightarrow\]

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H}_2\text{C} \\
\text{CH}_2 & \quad \text{C} \\
\text{C} & \quad \text{OCH}_3
\end{align*}
\]

\[m/z\ 74\]
17 NMR Spectroscopy

\( ^{1} \text{H-NMR} \)

- H on the \( \alpha \)-carbon to a C=O group are slightly deshielded and come into resonance at \( \delta \) 2.0-2.6
- H on carbon of the ester oxygen are more strongly deshielded and come into resonance at \( \delta \) 3.6-4.1

\[ \delta 2.33(q) \quad \delta 3.68(s) \]

\( \text{CH}_3-\text{CH}_2-\text{C}-\text{O-CH}_3 \)

Methyl propanoate

\( ^{13} \text{C-NMR} \)

- the carbonyl carbons of esters show characteristic resonance at \( \delta \) 160-180
## IR Spectroscopy

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>C=O Stretch (cm(^{-1}))</th>
<th>Additional Stretchings (cm(^{-1}))</th>
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</thead>
<tbody>
<tr>
<td>O</td>
<td>1740-1760 and 1800-1850</td>
<td>C-O at 900-1300</td>
</tr>
<tr>
<td>RCO(_2)CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>1735-1800</td>
<td>C-O at 1000-1100 and 1200-1250</td>
</tr>
<tr>
<td>RCO(_2)R</td>
<td>1700-1725</td>
<td>O-H at 2400-3400</td>
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<td>RCOH</td>
<td>1630-1680</td>
<td>N-H at 3200 and 3400</td>
</tr>
<tr>
<td>RCONH(_2)</td>
<td>(1° have two N-H peaks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2° have one N-H peak)</td>
<td></td>
</tr>
</tbody>
</table>
Nucleophilic acyl substitution: an addition-elimination sequence resulting in substitution of one nucleophile for another

\[
\begin{align*}
\text{R} & \quad \text{Nu}^- \quad \text{Y} \\
\rightarrow & \\
\text{R} & \quad \text{C} & \quad \text{Nu}^- \quad \text{Y} \\
\rightarrow & \\
\text{R} & \quad \text{C} & \quad \text{Nu} \\
\end{align*}
\]

Tetrahedral carbonyl addition intermediate

Substitution product
In this general reaction, we have shown the leaving group as an anion to illustrate an important point about them: the weaker the base, the better the leaving group.

Increasing basicity

Increasing leaving ability
17 Characteristic Reactions

- Halide ion is the weakest base and the best leaving group; acid halides are the most reactive toward nucleophilic acyl substitution.
- Amide ion is the strongest base and the poorest leaving group; amides are the least reactive toward nucleophilic acyl substitution.

\[
\begin{align*}
\text{Amide} & : \text{RCNH}_2 \\
\text{Ester} & : \text{RCOR'} \\
\text{Anhydride} & : \text{RCOCR} \\
\text{Acid halide} & : \text{RCX}
\end{align*}
\]

Reactivity toward nucleophilic acyl substitution
Low-molecular-weight acid chlorides react rapidly with water. Higher-molecular weight acid chlorides are less soluble in water and react less readily.

\[
\text{CH}_3\text{CCl} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COH} + \text{HCl}
\]
Low-molecular-weight acid anhydrides react readily with water to give two molecules of carboxylic acid.

Higher-molecular-weight acid anhydrides also react with water, but less readily.

\[ \text{CH}_3\text{COCCCH}_3 + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COH} + \text{HOCCCH}_3 \]
Esters are hydrolyzed only slowly, even in boiling water.

Hydrolysis becomes more rapid if they are heated with either aqueous acid or base.

Hydrolysis in aqueous acid is the reverse of Fischer esterification:

- The role of the acid catalyst is to protonate the carbonyl oxygen and increase its electrophilic character toward attack by water to form a tetrahedral carbonyl addition intermediate.
- Collapse of this intermediate gives the carboxylic acid and alcohol.
Acid-catalyzed ester hydrolysis

\[
\begin{align*}
\text{RCOCH}_3 \quad + \quad \text{H}_2\text{O} \quad &\xrightarrow{H^+} \quad \text{RCOOH} \quad + \quad \text{CH}_3\text{OH} \\
\text{Tetrahedral carbonyl addition intermediate}
\end{align*}
\]
Hydrolysis of an ester in aqueous base involves formation of a tetrahedral carbonyl addition intermediate followed by its collapse and proton transfer.
Base-promoted ester hydrolysis

$$\text{R-C-O-CH}_3 + \text{OH} \rightleftharpoons \text{R-C-O-CH}_3$$

$$\text{R-C} + \text{O-CH}_3 \rightarrow \text{R-C} + \text{O-CH}_3$$
Hydrolysis of an amide in aqueous acid requires 1 mol of acid per mol of amide

\[
\text{2-Phenylbutanamide} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{2-Phenylbutanoic acid}
\]
Acid-catalyzed hydrolysis of an amide is divided into three steps

**Step 1:** protonation of the carbonyl oxygen

\[
\begin{align*}
\text{R-C-NH}_2^+ + \text{H}_2\text{O} & \rightarrow \\
\text{R-C-NH}_2^+ + \text{H}_2\text{O} & \rightarrow \\
\text{R-C=N}^+\text{NH}_2 & + \text{H}_2\text{O}^-
\end{align*}
\]

Resonance-stabilized cation
Step 2: addition of H$_2$O to the carbonyl carbon followed by proton transfer

\[
\begin{align*}
\text{R-C=NH}_2 + \cdot\text{OH} & \rightarrow \text{Tetrahedral carbonyl addition intermediate} \\
\end{align*}
\]
Step 3: collapse of the intermediate coupled with proton transfer to give the carboxylic acid and ammonium ion.

\[
\text{R-C-NH}_3^+ + \text{OH}^- \rightarrow \text{R-C-OH} + \text{NH}_4^+ + \text{H}_2\text{O}
\]
Hydrolysis of an amide in aqueous base requires 1 mol of base per mol of amide

\[
\text{CH}_3\text{C} = \text{HN} \quad + \quad \text{NaOH} \quad \xrightarrow{\text{H}_2\text{O} \text{ heat}} \quad \text{CH}_3\text{CO}^- \quad \text{Na}^+ \quad + \quad \text{H}_2\text{N} \quad \text{Aniline}
\]

N-Phenylethanamide (N-Phenylacetamide, Acetanilide)
Hydrolysis of an amide in aqueous base is divided into three steps:

**Step 1:** addition of hydroxide ion to the carbonyl carbon

\[
\begin{align*}
R-\overset{\cdot}{C}-\overset{\cdot}{\text{NH}}_2 + \overset{\cdot}{\text{OH}} & \rightarrow R-\overset{\cdot}{C}-\overset{\cdot}{\text{NH}}_2 \\
& \text{Tetrahedral carbonyl addition intermediate}
\end{align*}
\]
Step 2: collapse of the intermediate to form a carboxylic acid and ammonia

\[
\begin{align*}
R-\overset{\text{tetrahedral carbonyl}}{\overset{\text{addition intermediate}}{\text{C}}}-\overset{\text{NH}_2}{\text{H}} + \overset{\text{OH}}{\text{H}} & \rightarrow R-\overset{\text{C}}{\text{C}} + \overset{\text{NH}_3}{\text{NH}_3} + \overset{\text{HO}}{-\text{OH}}
\end{align*}
\]
Step 3: proton transfer to form the carboxylate anion and water. Hydrolysis is driven to completion by this acid-base reaction

\[
\text{R-C-O-H} + \text{H-O-H} \rightarrow \text{R-C-O}^- + \text{H-O-H}
\]
The cyano group of a nitrile is hydrolyzed in aqueous acid to a carboxyl group and ammonium ion.

\[
\text{Phenylacetonitrile} + 2 \text{H}_2\text{O} + \text{H}_2\text{SO}_4 \xrightarrow{\text{H}_2\text{O}} \text{Phenylacetic acid} + \text{NH}_4^+\text{HSO}_4^- 
\]
Protonation of the cyano nitrogen gives a cation that reacts with water to give an imidic acid.

Keto-enol tautomerism of the imidic acid gives the amide:

\[
R-C≡N + H_2O \xrightarrow{H^+} R-C≡NH \xrightleftharpoons{} R-C-NH_2
\]

An imidic acid (enol of an amide)
Hydrolysis of a cyano group in aqueous base gives a carboxylic anion and ammonia; acidification converts the carboxylic anion to the carboxylic acid.

\[
\text{CH}_3(\text{CH}_2)_9\text{C}≡\text{N} + \text{H}_2\text{O} + \text{NaOH} \xrightarrow{\text{heat}} \text{CH}_3(\text{CH}_2)_9\text{CO}^-\text{Na}^+ + \text{NH}_3
\]

Sodium undecanoate

\[
\text{CH}_3(\text{CH}_2)_9\text{CO}^-\text{Na}^+ + \text{HCl} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3(\text{CH}_2)_9\text{COH} + \text{NaCl}
\]

Sodium undecanoate

Undecanoic acid
Hydrolysis of a cyano group in aqueous base involves initial formation of an imidic acid which undergoes keto-enol tautomerism to give an amide.

\[
\text{HO}^- + \text{R-C} \equiv \text{N}^+ \rightarrow \text{R-C} = \text{N}^+ \quad \xrightarrow{\text{H}^+} \quad \text{OH}^- \quad \text{R-C} = \text{N-H}^+ + \text{OH}^- \\
\text{An imidic acid}
\]

\[
\text{R-C} = \text{N-H} \rightarrow \text{R-C} - \text{NH}_2 \\
\text{An imidic acid} \quad \text{An amide}
\]
Hydrolysis of nitriles is a valuable route to carboxylic acids.

Benzaldehyde cyanohydrin (Mandelonitrile) can be converted to 2-Hydroxyphenylacetic acid (Mandelic acid) through the following reaction:

\[ \text{Benzaldehyde cyanohydrin} \xrightarrow{\text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{2-Hydroxyphenylacetic acid} \]
Acid halides react with alcohols to give esters

- because acid halides are so reactive toward even weak nucleophiles such as alcohols, no catalyst is necessary
- where the alcohol or resulting ester is sensitive to HCl, reaction is carried out in the presence of a 3° amine to neutralize the acid

\[ \text{Butanoyl chloride} + \text{Cyclohexanol} \rightarrow \text{Cyclohexyl butanoate} + \text{HCl} \]
Acid anhydrides react with alcohols to give one mol of ester and one of carboxylic acid.

\[
\text{Phthalic anhydride} + \text{2-Butanol (sec-Butyl alcohol)} \rightarrow \text{sec-Butyl hydrogen phthalate}
\]
Aspirin is synthesized by treatment of salicylic acid with acetic anhydride

\[
\text{2-Hydroxybenzoic acid (Salicylic acid)} + \text{Acetic anhydride} \rightarrow \text{Acetylsalicylic acid (Aspirin)} + \text{Acetic acid}
\]
Esters react with alcohols in the presence of an acid catalyst in a reaction called transesterification, an equilibrium reaction.

\[
\begin{align*}
\text{CH}_2=\text{CHCOCH}_3 \quad &+ \quad \text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \quad \xrightarrow{\text{HCl}} \\
\text{Methyl propenoate} \quad &+ \quad \text{1-Butanol} \quad \text{(bp 81°C)} \\
\text{(Methyl acrylate)} \quad &\quad \text{(bp 117°C)} \\
\text{CH}_2=\text{CHCOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \quad &+ \quad \text{CH}_3\text{OH} \\
\text{Butyl propenoate} \quad &+ \quad \text{Methanol} \quad \text{(bp 147°C)} \\
\text{(Butyl acrylate)} \quad &\quad \text{(bp 65°C)}
\end{align*}
\]
Acid halides react with ammonia, and 1° and 2° amines to form amides

- 2 mol of the amine are required per mol of acid chloride

\[
\text{Hexanoyl chloride} + 2 \text{NH}_3 \rightarrow \text{Hexanamide} + \text{NH}_4^+ \text{Cl}^-
\]

\[
\text{CH}_3(\text{CH}_2)_4\text{CCl} + 2\text{NH}_3 \rightarrow \text{CH}_3(\text{CH}_2)_4\text{CNH}_2 + \text{NH}_4^+ \text{Cl}^-
\]
Reaction occurs in three steps:
1. nucleophilic addition to the carbonyl carbon
2. collapse of the TCAI
3. proton transfer to ammonia

\[
\begin{align*}
\text{R-C-Cl} & \quad + \quad \text{NH}_3 & \text{(1)} \\
\text{R-C} & \quad \text{Cl} & \quad -\text{Cl} & \quad \text{NH}_3 & \quad \text{R-C-NH}_2 & + & \text{NH}_4^+ \\
\text{H-N} & \quad \text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H}
\end{align*}
\]
Acid anhydrides react with ammonia, and 1° and 2° amines to form amides.

- 2 mol of ammonia or amine are required

\[
\text{Acetic anhydride} + 2 \text{NH}_3 \rightarrow \text{Ethanamide (Acetamide)} + \text{Ammonium acetate}
\]
Esters react with ammonia, and 1° and 2° amines to form amides

- esters are less reactive than either acid halides or acid anhydrides

\[
\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_2\text{CH}_3 + \text{NH}_3 \rightarrow \text{C}_6\text{H}_5\text{CH}_2\text{CNH}_2 + \text{CH}_3\text{CH}_2\text{OH}
\]

Amides do not react with ammonia, or 1° or 2° amines
Treatment of a formic ester with 2 mol of Grignard reagent followed by hydrolysis with aqueous acid gives a $2^\circ$ alcohol.

An ester of formic acid:

$$\text{HCOCH}_3 + 2 \text{RMgX} \rightarrow \text{HC-R}$$

A $2^\circ$ alcohol:

$$\text{HC-R}$$
Treatment of an ester other than formic followed by hydrolysis in aqueous acid gives a 3° alcohol

\[
\text{O} \\
\text{CH}_3\text{COCH}_3 + 2 \text{RMgX} \rightarrow
\]

An ester of any acid other than formic acid

\[
\text{O}^- [\text{MgX}]^+ \\
\text{CH}_3\text{C-R} \quad \text{HCl} \quad \text{H}_2\text{O} \quad \text{CH}_3\text{C-R} \\
\text{R} \quad \text{OH} \quad \text{R} \\
\text{A 3° alcohol}
\]
17 Rexns with Grignards

1. addition of 1 mol of RMgX to the carbonyl carbon to form a TCAI
2. collapse of the TCAI gives a ketone (an aldehyde from a formic ester)
3. reaction of the ketone with a 2nd mol of RMgX

A ketone $+ \text{CH}_3\text{O}^-[\text{MgX}]^+$
Organolithium compounds are even more powerful nucleophiles than Grignard reagents

- they react with esters to give the same types of $2^\circ$ and $3^\circ$ alcohols as do Grignard reagents
- and often in higher yields

\[
\begin{align*}
\text{RCOCH}_3 & \xrightarrow{1. \ 2 \ R'Li} \text{R-C-R'} \\
\text{R-C-R'} & \xrightarrow{2. \ H_2O, HCl} \text{OH}
\end{align*}
\]
17 Gilman Reagents

Acid chlorides react with Gilman reagents at -78°C to give ketones.

- under these conditions, the TCAI is stable, and it is not until acid hydrolysis that the ketone is liberated

\[
\text{CH}_3(CH_2)_3CCl + (CH_3)_2CuLi, \text{ ether, } -78^\circ C \rightarrow \text{CH}_3(CH_2)_3CCH_3
\]

Pentanoyl chloride

2-Hexanone
Gilman reagents react only with acid chlorides.

They do not react with acid anhydrides, esters, amides, or nitriles under the conditions described.

\[
\begin{align*}
\text{CH}_3\text{OCCH}_2\text{CH}_2\text{CCl} & \quad \overset{1. \quad (\text{CH}_3)_2\text{CuLi, ether, } -78^\circ C}{\rightarrow} \\
& \quad \overset{2. \quad \text{H}_2\text{O}}{\rightarrow} \\
\text{CH}_3\text{OCCH}_2\text{CH}_2\text{CCCH}_3
\end{align*}
\]
Interconversion

Relative reactivities of carboxyl derivatives

- Decreasing reactivity:
  - RC-Cl
  - RC-OOCR'
  - RC-OR'
  - RC-NH₂
  - RC-O⁻
Most reductions of carbonyl compounds are now accomplished by hydride reducing agents.

Esters are reduced by LiAlH$_4$ to two alcohols:
- The alcohol derived from the carbonyl group is primary.

\[
\text{Methyl 2-phenyl-propanoate} \quad \xrightarrow{1. \text{LiAlH}_4, \text{ether}} \quad \xrightarrow{2. \text{H}_2\text{O, HCl}} \quad \text{2-Phenyl-1-propanol} + \text{Methanol}
\]
Reduction occurs in three-steps

1. Transfer of hydride ion to the carbonyl carbon forms a TCAI. Hydride ion is not free, but is donated by the AlH$_4^-$ ion

2. Collapse of the TCAI gives a new carbonyl-containing compound (an aldehyde or ketone),

3. Which is then reduced by a 2nd mol of H$^-$:

$$\text{R-C-O-R'} + \text{H}^- \rightarrow \text{R-C-O-R'} \rightarrow \text{R-C} + \text{H}_2O$$
NaBH₄ does not normally reduce esters, but it does reduce aldehydes and ketones.

Selective reduction is often possible by the proper choice of reducing agents and experimental conditions.

\[
\text{CH}_3\text{CCH}_2\text{COCH}_2\text{CH}_3 + \text{NaBH}_4 \rightarrow \text{CH}_3\text{CHCH}_2\text{COCH}_2\text{CH}_3 + \text{OH}
\]
Diisobutylaluminum hydride (DIBAIH) at -78°C selectively reduces esters to aldehydes.

- at -78°C, the TCAI does not collapse and it is not until hydrolysis in aqueous acid that the carbonyl group of the aldehyde is liberated.

\[ \text{Methyl dodecanoate} \rightarrow \text{Dodecanal} \]

1. DIBALH, toluene, -78°C
2. H\textsubscript{2}O, HCl

\[ \text{CH}_3(\text{CH}_2)_{10}\text{COCH}_3 + \text{H}_2\text{O, HCl} \rightarrow \text{CH}_3(\text{CH}_2)_{10}\text{CH} + \text{CH}_3\text{OH} \]
LiAlH₄ reduction of an amide gives a 1°, 2°, or 3° amine, depending on the degree of substitution of the amide:

Octanamide

\[
\text{CH}_3(\text{CH}_2)_6\text{CNH}_2 \rightarrow \begin{array}{c}
\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{NH}_2 \\
\text{1-Octanamine}
\end{array} \]

N,N-Dimethylbenzamide

\[
\text{C} = \text{N}(\text{CH}_3)_2 \rightarrow \begin{array}{c}
\text{CH}_2\text{N}(\text{CH}_3)_2 \\
\text{N,N-Dimethylbenzylamine}
\end{array} \]

1. LiAlH₄
2. H₂O
The mechanism of amide reduction is shown divided into 4 steps.

1. An iminium ion is formed.
2. An iminium ion is reduced to an amine.
3. An amine is reduced to an amino group.
4. An amino group is further reduced to a primary amine.
The cyano group of a nitrile is reduced by LiAlH₄ to a 1° amine.

\[
\text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}≡\text{N} \xrightarrow{1. \text{LiAlH}_4} \text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2
\]

6-Octenenitrile

6-Octen-1-amine
Problem: show reagents and experimental conditions to bring about each reaction

1. PhCH₂COH
2. PhCH₂COCH₃
3. PhCH₂CH₂OH
4. PhCH₂CCl
5. PhCH₂CNH₂
6. PhCH₂COCH₃
7. PhCH₂CH₂NH₂
8. PhCH₂CH CH
9. PhCH₂COH
10. PhCH₂CH CH
When a 1° amide is treated with bromine or chlorine in aqueous NaOH or KOH,
• the carbonyl carbon is lost as carbonate ion, and
• the amide is converted to an amine of one fewer carbon atoms

\[
\text{(R)-2-Phenylpropanamide} \xrightarrow{\text{Br}_2, \text{NaOH}} \text{H}_2\text{O} \rightarrow \text{(R)-1-Phenylethanamine} + \text{Na}_2\text{CO}_3
\]
Stage 1: acid-base reaction between the amide and hydroxide ion gives an amide anion, which reacts as a nucleophile with Br\(_2\).

\[
\begin{align*}
\text{R–C–N–H} & \quad \text{HO}^- \quad \longrightarrow \quad \text{R–C–N}^– \quad \text{Br} – \text{Br}
\end{align*}
\]

An amide anion

\[
\begin{align*}
\text{R–C–N–Br} & \quad + \quad \text{Br}^- \\
\text{An N-bromoamide}
\end{align*}
\]
Stage 2: a 2nd acid-base reaction followed by elimination of Br\(^{-}\) gives a nitrene, an electron-deficient species. Rearrangement of the nitrene gives an isocyanate.

An acyl nitrene

An isocyanate
Stage 3: Addition of $\text{H}_2\text{O}$ to the isocyanate to give a carbamic acid

$$\text{R} = \tilde{\text{N}} = \text{C} = \tilde{\text{O}} : + \text{H}_2\text{O} \rightarrow \text{R} = \tilde{\text{N}} = \text{C} \cdot \tilde{\text{O}} \cdot \text{H}$$

A carbamic acid

Stage 4: Carbamic acids are unstable and undergo decarboxylation to give the 1° amine and $\text{CO}_2$

$$\text{R} = \tilde{\text{N}} = \text{C} \cdot \tilde{\text{O}} \cdot \text{H} \rightarrow \text{R} = \tilde{\text{N}} = \text{H} + \text{CO}_2$$

A primary amine
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Derivatives of Carboxylic Acids

End Chapter 17