Chapter 21. Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions

Based on McMurry’s *Organic Chemistry, 7th edition*
Carboxylic acid and derivatives

Compounds

- Acyl group bonded to $X$, an electronegative atom or leaving group
- Includes: $X = \text{halide (acid halides), acyloxy (anhydrides), alkoxy (esters), amine (amides), thiolate (thioesters), phosphate (acyl phosphates)}$

\[
\begin{align*}
\text{Carboxylic acid:} & \quad RCOOH \\
\text{Acid halide:} & \quad RX \\
\text{Acid anhydride:} & \quad RCOOR' \\
\text{Ester:} & \quad RCOOR' \\
\text{Amide:} & \quad RCONH_2 \\
\text{Thioester:} & \quad RCOSSR' \\
\text{Acyl phosphate:} & \quad RCOPO_2^{-} (or OR')
\end{align*}
\]
General Reaction Pattern

- Nucleophilic acyl substitution

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

Why this Chapter?

- Carboxylic acids are among the most widespread of molecules.
- A study of them and their primary reaction “nucleophilic acyl substitution” is fundamental to understanding organic chemistry.
21.1 Naming Carboxylic Acid Derivatives

- Acid Halides, RCOX
  - Derived from the carboxylic acid name by replacing the 
    - *ic acid* ending with *-yl* or the *-carboxylic acid* ending 
    with *-carbonyl* and specifying the halide

**Examples:**
- Acetyl chloride
- Benzoyl bromide
- Cyclohexanecarbonyl chloride
Naming Acid Anhydrides, $\text{RCO}_2\text{COR'}$

- If symmetrical replace “acid” with “anhydride” based on the related carboxylic acid.

- Unsymmetrical anhydrides—cite the two acids alphabetically.

![Acetic anhydride](image1.png) ![Benzoic anhydride](image2.png) ![Succinic anhydride](image3.png)

![Acetic benzoic anhydride](image4.png)
Naming Amides, RCONH₂

- With unsubstituted —NH₂ group. replace -oic acid or -ic acid with -amide, or by replacing the -carboxylic acid ending with –carboxamide.

- If the N is further substituted, identify the substituent groups (preceded by “N”) and then the parent amide.
Naming Esters, $RCO_2R'$

- Name $R'$ and then, after a space, the carboxylic acid ($RCOOH$), with the “-ic acid” ending replaced by “-ate”
Thioesters, RCOSR

- Thio-oate or -carboxylate ending is replaced by -thioate or -carbothioate.
- Butanoate becomes butanethioate and cyclohexanecarboxylate becomes cyclohexanecarbothioate.
Acyl phosphates, $RCO_2PO_3^-\text{ and } RCO_2PO_3R^-$
21.2 Nucleophilic Acyl Substitution

- Carboxylic acid derivatives have an acyl carbon bonded to a group —Y that can leave.
- A tetrahedral intermediate is formed and the leaving group is expelled to generate a new carbonyl compound, leading to substitution.

1. Addition of a nucleophile to the carbonyl group occurs, yielding a tetrahedral intermediate.

2. An electron pair from oxygen displaces the leaving Y group, generating a new carbonyl compound as product.

Y is a leaving group: −OR, −NR₂, −Cl
Relative Reactivity of Carboxylic Acid Derivatives

- Nucleophiles react more readily with unhindered carbonyl groups
- More electrophilic carbonyl groups are more reactive to addition (acyl halides are most reactive, amides are least)
- The intermediate with the best leaving group decomposes fastest
Substitution in Synthesis

- We can readily convert a more reactive acid derivative into a less reactive one.
- Reactions in the opposite sense are possible but require more complex approaches.
General Reactions of Carboxylic Acid Derivatives

- water
- carboxylic acid
- alcohols
- esters
- ammonia or an amine
- an amide
- hydride source
- an aldehyde or an alcohol
- Grignard reagent
- a ketone or an alcohol
21.3 Nucleophilic Acyl Substitution
Reactions of Carboxylic Acids

- Must enhance reactivity
- Convert \(-\text{OH}\) into a better leaving group
- Specific reagents can produce acid chlorides, anhydrides, esters, amides
Conversion of Carboxylic Acids into Acid Chlorides

- Reaction with thionyl chloride, $\text{SOCl}_2$

\[
\text{2,4,6-Trimethylbenzoic acid} \xrightarrow{\text{SOCl}_2/\text{CHCl}_3} \text{2,4,6-Trimethylbenzoyl chloride (90%)} + \text{HCl} + \text{SO}_2
\]
Mechanism of Thionyl Chloride Reaction

- Nucleophilic acyl substitution pathway
- Carboxylic acid is converted into a chlorosulfite which then reacts with chloride
Conversion of Carboxylic Acids into Acid Anhydrides

Acid anhydrides can be derived from two molecules of carboxylic acid by strong heating to remove water.

\[
\begin{align*}
\text{Acetic acid} & \quad 800 \degree C \quad \text{Acetic anhydride} \\
\mathrm{H_3C-C-OH} & \quad \rightarrow \\
\mathrm{H_3C-C-O-C-CH_3} & \quad + \quad \mathrm{H_2O}
\end{align*}
\]
Conversion of Carboxylic Acids into Esters

- Methods include reaction of a carboxylate anion with a primary alkyl halide

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{C} & \quad \text{O}^- \quad \text{Na}^+ & + & \quad \text{CH}_3\text{I} & \quad \xrightarrow{\text{SN}_2 \text{ reaction}} & \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{C} & \quad \text{O} \quad \text{CH}_3 \quad + & \quad \text{NaI}
\end{align*}
\]

**Sodium butanoate**

**Methyl butanoate (97%)**

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Fischer Esterification

Heating a carboxylic acid in an alcohol solvent containing a small amount of strong acid produces an ester from the alcohol and acid.

\[
\text{Mandelic acid} \quad \xrightarrow{\text{CH}_3\text{CH}_2\text{OH} \quad \text{HCl}} \quad \text{Ethyl mandelate (86%)} + \text{H}_2\text{O}
\]
The reaction is an acid-catalyzed, nucleophilic acyl substitution of a carboxylic acid.

When $^{18}$O-labeled methanol reacts with benzoic acid, the methyl benzoate produced is $^{18}$O-labeled but the water produced is unlabeled.
21.4 Chemistry of Acid Halides

- Acid chlorides are prepared from carboxylic acids by reaction with $\text{SOCl}_2$
- Reaction of a carboxylic acid with $\text{PBr}_3$ yields the acid bromide
Reactions of Acid Halides

- Nucleophilic acyl substitution
- Halogen replaced by —OH, by —OR, or by —NH₂
- Reduction yields a primary alcohol
Hydrolysis: Conversion of Acid Halides into Acids

- Acid chlorides react with water to yield carboxylic acids
- HCl is generated during the hydrolysis: a base is added to remove the HCl
Conversion of Acid Halides to Esters

- Esters are produced in the reaction of acid chlorides with alcohols in the presence of pyridine or NaOH. This is called **Alcoholysis**.
- The reaction is better with less steric bulk.

```
\[
\text{Benzoyl chloride} + \text{Cyclohexanol} \xrightarrow{\text{Pyridine}} \text{Cyclohexyl benzoate (97%)}
\]
```

Primary alcohol (less hindered and more reactive)
Secondary alcohol (more hindered and less reactive)
Aminolysis: Conversion of Acid Halides into Amides

- Amides result from the reaction of acid chlorides with NH₃, primary (RNH₂) and secondary amines (R₂NH).
- The reaction with tertiary amines (R₃N) gives an unstable species that cannot be isolated.
- HCl is neutralized by the amine or an added base.

\[
\text{CH}_3\text{CHCHCCl} + 2\text{NH}_3 \rightarrow \text{CH}_3\text{CHCHCNH}_2 + \text{NH}_4\text{Cl}^- \\
\text{2-Methylpropanoyl chloride} \quad \quad \text{2-Methylpropanamide} \quad (83\%)
\]

\[
\text{C} + 2\text{NH(CH}_3\text{)}_2 \rightarrow \text{C}_6\text{H}_5\text{C}^\text{N}\text{CH}_3 + (\text{CH}_3\text{)}_2\text{NH}_2\text{Cl}^- \\
\text{Benzoyl chloride} \quad \quad N,N\text{-Dimethylbenzamide} \quad (92\%)
\]
Reduction: Conversion of Acid Chlorides into Alcohols

- LiAlH₄ reduces acid chlorides to yield aldehydes and then primary alcohols

```
C   Cl
O   C
```

1. LiAlH₄, ether
2. H₃O⁺

Benzoyl chloride

```
H   H
O   C   OH
```

Benzyl alcohol (96%)
Reaction of Acid Chlorides with Organometallic Reagents

- Grignard reagents react with acid chlorides to yield tertiary alcohols in which two of the substituents are the same.

\[
\text{Acid chloride} + 2 \text{R'MgX} \rightarrow \text{R' \_ \_ \_ \_ R'}
\]

1. Mix in ether
2. \( \text{H}_3\text{O}^+ \)

\( \text{3° Alcohol} \)

Benzoyl chloride

\[
\text{CH}_3\text{MgBr} \quad \text{Ethere}
\]

Acetophenone (NOT isolated)

1. \( \text{CH}_3\text{MgBr} \)
2. \( \text{H}_3\text{O}^+ \)

2-Phenyl-2-propanol (92%)
Formation of Ketones from Acid Chlorides

- Reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, \( \text{Li}^+ \text{R}_2\text{Cu}^- \)
- Addition produces an acyl diorganocopper intermediate, followed by loss of \( \text{R’Cu} \) and formation of the ketone
21.5 Chemistry of Acid Anhydrides

Prepared by nucleophilic acyl substitution of a carboxylate with an acid chloride

\[
\text{Benzoyl chloride} + \text{Sodium acetate} \rightarrow \text{Acetic benzoic anhydride}
\]
Reactions of Acid Anhydrides

- Similar to acid chlorides in reactivity
Acetylation

- Acetic anhydride forms acetate esters from alcohols and $N$-substituted acetamides from amines
21.6 Chemistry of Esters

- Many esters are pleasant-smelling liquids: fragrant odors of fruits and flowers
- Also present in fats and vegetable oils

![Chemical structures of esters](image)

- **Methyl butanoate** (from pineapples)
- **Isopentyl acetate** (from bananas)
- **A fat** (R = C_{11-17} chains)
Preparation of Esters

- Esters are usually prepared from carboxylic acids

\[
\begin{align*}
\text{R-COOH} & \xrightarrow{\text{SOCl}_2} \text{R-COCI} \\
\text{1. NaOH} & \quad \text{R’OH} \quad \text{HCl} \quad \text{R’OH} \\
\text{2. R’X} & \\
\text{R-COR’} & \text{Method limited to primary alkyl halides} \\
\text{R-COR’} & \text{Method limited to simple alcohols} \\
\text{R-COR’} & \text{Method is very general}
\end{align*}
\]
Reactions of Esters

- Less reactive toward nucleophiles than are acid chlorides or anhydrides

- Cyclic esters are called lactones and react similarly to acyclic esters
Hydrolysis: Conversion of Esters into Carboxylic Acids

An ester is hydrolyzed by aqueous base or aqueous acid to yield a carboxylic acid plus an alcohol.

\[
\begin{align*}
\text{Ester} & \quad \xrightarrow{\text{H}_2\text{O}, \text{NaOH} \quad \text{or} \quad \text{H}_3\text{O}^+} \quad \text{Acid} + \text{Alcohol} \\
R\text{C}=&\text{OR}' & \quad \xrightarrow{\quad \quad \quad \quad \quad \quad \quad \quad} \quad R\text{C}=&\text{OH} + \text{R'O}H
\end{align*}
\]
Mechanism of Ester Hydrolysis

- Hydroxide catalysis via an addition intermediate

1. Nucleophilic addition of hydroxide ion to the ester carbonyl group gives the usual tetrahedral alkoxide intermediate.

2. Elimination of alkoxide ion then generates the carboxylic acid.

3. Alkoxide ion abstracts the acidic proton from the carboxylic acid and yields a carboxylate ion.

4. Protonation of the carboxylate ion by addition of aqueous mineral acid in a separate step then gives the free carboxylic acid.
Aminolysis of Esters

- Ammonia reacts with esters to form amides

\[
\text{Methyl benzoate} \xrightarrow{\text{NH}_3, \text{Ether}} \text{Benzamide} + \text{CH}_3\text{OH}
\]
Reduction: Conversion of Esters into Alcohols

- Reaction with LiAlH$_4$ yields primary alcohols

$$\text{CH}_3\text{CH}_2\text{CH}═\text{CHCOCH}_2\text{CH}_3$$

1. LiAlH$_4$, ether  
2. H$_3$O$^+$

$$\text{CH}_3\text{CH}_2\text{CH}═\text{CHCH}_2\text{OH} + \text{CH}_3\text{CH}_2\text{OH}$$

2-Penten-1-ol (91%)

$$\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CHCH}_3$$

1. LiAlH$_4$, ether  
2. H$_3$O$^+$

1,4-Pentanediol (86%)
Mechanism of Reduction of Esters

- Hydride ion adds to the carbonyl group, followed by elimination of alkoxide ion to yield an aldehyde
- Reduction of the aldehyde gives the primary alcohol
Reaction of Esters with Grignard Reagents

- React with 2 equivalents of a Grignard reagent to yield a tertiary alcohol

Methyl benzoate

Triphenylmethanol (96%)
21.7 Chemistry of Amides

Amides are abundant in all living organisms...proteins, nucleic acids, and other pharmaceuticals have amid functional groups.
Preparation of Amides

- Prepared by reaction of an acid chloride with ammonia, monosubstituted amines, or disubstituted amines

\[
\begin{align*}
\text{NH}_3 & \quad \text{R'NH}_2 \\
\text{RCl} & \quad \text{R'}\text{NH}_2 \\
\text{R'NH}_2 & \quad \text{R}\text{NR'}_2
\end{align*}
\]
Reactions of Amides

- Heating in either aqueous acid or aqueous base produces a carboxylic acid and amine
- Acidic hydrolysis by nucleophilic addition of water to the protonated amide, followed by loss of ammonia

\[
\begin{align*}
\text{An amide} & \quad \overset{\text{H}_3\text{O}^+}{\leftrightarrow} \quad \text{A carboxylic acid} \\
\overset{\text{NH}_4^+ + \text{H}_2\text{O}}{\leftrightarrow} \quad \text{ammonium ion} + \text{water}
\end{align*}
\]
Basic Hydrolysis of Amides

- Addition of hydroxide and loss of amide ion

An amide

\[ R\text{-C} = \text{NH}_2 \]

A carboxylate ion

\[ R\text{-C}O^- + \text{NH}_3 \]

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Reduction: Conversion of Amides into Amines

- Reduced by LiAlH₄ to an amine rather than an alcohol
- Converts C=O → CH₂
Mechanism of Reduction

- Addition of hydride to carbonyl group
- Loss of the oxygen as an aluminate anion to give an iminium ion intermediate which is reduced to the amine
Uses of Reduction of Amides

- Works with cyclic and acyclic
- Good route to cyclic amines

A lactam \[ \xrightarrow{1. \text{LiAlH}_4, \text{ether}} \xrightarrow{2. \text{H}_2\text{O}} \text{A cyclic amine (80%)} \]