Carboxylic acid derivatives

Nucleophilic acyl substitution reaction

Among the most important reactions of carboxylic acids are those that convert the carboxyl group into other acid derivatives by a nucleophilic acyl substitution reaction.

\[
\begin{align*}
\text{R} & \quad \text{O} \quad \text{Cl} \\
\text{R} & \quad \text{O} \quad \text{H} \\
\text{R} & \quad \text{O} \quad \text{Cl} \\
\text{R} & \quad \text{N} \quad \text{R}_1 \\
\text{R} & \quad \text{O} \quad \text{R}_1 \\
\end{align*}
\]
Acyl chloride

Preparation of acyl chlorides

Acid chlorides can not be prepared by reaction between carboxylic acid and HCl. This is because the carbonyl carbon is not electrophilic enough to be attacked by chloride and also the fact that the hydroxyl group is a bad leaving group.

We use PCl$_5$ (an acid chloride of phosphoric acid), PCl$_3$ (an acid chloride of phosphorous acid), SOCl$_2$ (Thionyl chloride), an acid chloride of sulfurous acid, or oxalyl chloride, an acid chloride of oxalic acid.
Very reactive

Leaving Group

Good electrophile

\[ \text{O=S=O} + \text{HCl} \]

\[ \text{R-Cl} + \text{O=S=O} + \text{HCl} \]
Reaction of acyl chlorides

Acyl chlorides are the most reactive of acyl compounds towards nucleophiles. Lower molecular weight saturated acyl chlorides react explosively with water, and even more rapidly with stronger nucleophiles.

\[
\begin{align*}
\text{O} & \quad \text{H}_2\text{O} & \quad \text{O} \\
\text{R} & \quad \text{Cl} & \quad \text{R} \quad \text{OH} + \text{HCl}
\end{align*}
\]

Because of their reactivity and the ease with which they can be prepared from carboxylic acids, acyl chlorides are the most commonly used starting materials for the synthesis of carboxylic acid derivatives in general.
Most nucleophilic acyl substitution reactions of acyl chlorides are irreversible.
Hydrolysis: Conversion into acids

Acyl chlorides are hydrolyzed by water to give the corresponding carboxylic acid.

\[
\text{Acyl chloride} + \text{H}_2\text{O} \rightarrow \text{Acid chloride} + \text{HCl}
\]

Pyridine scavenges the HCl
Alcoholysis: Ester formation

In most cases this reaction is carried out in the presence of a base such as triethylamine, pyridine which will scavenge the acid (HCl).
Ammonolysis: Conversion into amides

\[
\text{RCl} \quad \text{H} \quad \text{R''} \quad \rightarrow \quad \text{R} \quad \text{N} \quad \text{R''} \quad \text{R} + \quad \text{H} \quad \text{N} \quad \text{R''} \quad \Theta_{::\text{Cl}}:
\]

The reaction is carried out using an excess of the amine, which serves to remove the acid (HCl) as a salt.

Example

3-Methylbenzoyl chloride + Diethylamine (Excess) → N,N-Diethyl-m-toluamide (DEET)

DEET, the active ingredient in the most widely used insect repellents, is effective against mosquitoes, fleas, and ticks.
Ammonolysis reactions carried with NaOH are sometimes referred to as Schotten – Baumann reaction.

![Chemical Reaction]

Trimetozine (Opalene, Trimolide, Trioxazine) is a sedative that has been marketed in Europe since 1959. It also has mild tranquilizing effects and has been used in the treatment of anxiety.
The search for a synthetic fiber with properties similar to silk led to the discovery of nylon, a polyamide. There are several different kinds of nylon, but the most well-known is called nylon 6,6. It can be synthesized from two six-carbon monomers (hence its name)—adipoyl chloride (ClOC-(CH₂)₄-COCl) and hexamethylenediamine (H₂N(CH₂)₆NH₂).
Reduction: Conversion into alcohols

\[
\begin{align*}
\text{R-Cl} & \xrightarrow{\text{LiAlH}_4} \text{R-C} & \xrightarrow{\text{LiAlH}_4} \text{R-CH} & \xrightarrow{\text{LiAlH}_4} \text{R-OH}
\end{align*}
\]

Not isolated

1° alcohol

Example

\[
\begin{align*}
\text{Ph-Cl} & \xrightarrow{\text{LiAlH}_4, \text{THF}} \text{Ph-CH} & \xrightarrow{\text{H}_2\text{O}} \text{Ph-CH}_2\text{OH}
\end{align*}
\]

The aldehyde intermediate can be isolated if the less powerful reducing agent, LiAlH (Ot-Bu)\textsubscript{3}.

Example

\[
\begin{align*}
\text{Ph-Cl} & \xrightarrow{\text{LiAlH(Ot-Bu)}_3} \text{Ph-CH}_2\text{H}
\end{align*}
\]
Reaction with aromatic compounds

The Friedel Crafts acylation

\[
\begin{align*}
R' &\text{Cl} \\
\text{AlCl}_3 &\rightarrow \\
\text{R} &\text{C}l
\end{align*}
\]

Acyl benzene

Reaction with Organometallic reagents

Grignard reagent

Organolithiums react similarly to give tertiary alcohols.
Organocopper \((R_2CuLi)\) (Gilman) reagents

Less reactive than Grignard/organolithium reagent and yield ketones rather than tertiary alcohols.

Example

The ester functional group is not affected.
Summary of the reactions of acid chlorides

1. \( \text{R'}\text{Cl} \rightarrow \text{R'OH} \)  
   - Pyridine

2. \( \text{NHR}_1\text{R}_2 \rightarrow \text{R'OH} \)  
   - Pyridine

3. \( \text{R'}\text{MgBr} \) or \( \text{R'Li} \)  
   - \( \text{H}_2\text{O} \)

4. \( \text{R'}\text{CuLi} \)  
   - \( \text{R'}\text{R''} \)

5. \( \text{LiAlH}_4 \)  
   - \( \text{R'}\text{R''} \)  
   - \( \text{2. H}_2\text{O} \)

6. \( \text{LiAlH(OtBu)}_3 \)  
   - \( \text{OH} \)

7. \( \text{AlCl}_3 \)  
   - \( \text{ArCOH} \)

8. \( \text{H}_2\text{O} \)  
   - \( \text{ArCHO} \)

9. \( \text{AlCl}_3 \)  
   - \( \text{ArCO} \)
Assignment 21

I. How do you achieve the following transformation?

a) Cl

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl} & \rightarrow \text{CH}_2\text{CH}_2\text{N}_n\text{CH}_2\text{CH}_2\text{CH}_2\text{N}_n\text{CH}_2\text{CH}_2\text{CH}_2\text{N}_n\text{CH}_2\text{CH}_2\text{CH}_2\text{N}_n
\end{align*}
\]

b) Br

\[
\begin{align*}
\text{C}_6\text{H}_12\text{Br} & \rightarrow \text{C}_6\text{H}_12\text{N}_n\text{C}_6\text{H}_12\text{N}_n
\end{align*}
\]

II. Qiana, a polyamide fiber with a silky texture, has the following structure. What are the monomer units used in the synthesis of Qiana?

\[
\begin{align*}
\left(\text{C}_6\text{H}_12\text{N}_n\text{C}_6\text{H}_12\text{N}_n\right)_n
\end{align*}
\]
**Acid anhydrides**

![Chemical structure of anhydride](image)

The 2\textsuperscript{nd} most reactive carboxylic acid derivatives.

**Preparation of acetic anhydrides**

From acid chlorides

\[ R\text{Cl} + R_1\text{OH} \xrightarrow{\text{Base}} R\text{O}_2\text{CR}_1 + \text{HCl} \]

Most commonly used bases are pyridine and triethylamine.
Example

\[
\text{PhCH(OH)} + \text{CHCl} \rightarrow \text{PhCOOCH} + \text{Cl}^-
\]

Mechanism

O
C
O
O
H
\text{NEt}_3
O
\text{Cl}

\[
\text{PhCH(OH)} \rightarrow \text{PhCOOCH} + \text{Cl}^-
\]
Reactions of acid anhydrides

The chemistry of anhydrides is similar to that of acid chlorides except that anhydrides react more slowly, but the kind of reactions the two groups undergo are the same.
Examples

\[ \text{p-Hydroxyaniline} + \text{Acetone} \xrightarrow{\text{NaOH}, \text{H}_2\text{O}} \text{Acetaminophen} + \text{Formaldehyde} \]

\[ \text{Salicylic acid} + \text{Acetone} \xrightarrow{\text{NaOH}, \text{H}_2\text{O}} \text{Acetylsalicylic acid} + \text{Formaldehyde} \]
Many simple low molecular weight esters are pleasant smelling liquids that are responsible for the fragrant odors of fruits and flowers.
Commercial applications of esters

The characteristics fruity smell of esters lead to their use in artificial fruit essences.

- Methyl 3-methylbutanoate
- Propyl propionate
- Butyl acetate
- 3-Methylbutyl acetate
- Methyl octanoate
- Benzyl butanoate
Preparation of esters

Fisher esterification

General reaction

\[ \text{Carboxylic acid} + \text{Alcohol} \xrightleftharpoons{\text{HEAT}} \text{Ester} + \text{H}_2\text{O} \]

Catalyzed by conc. \( \text{H}_2\text{SO}_4 \) or \( \text{HCl} \).

Equilibrium reaction and yield can be increased by:

a) Use of excess of acid or alcohol
b) Removing water from the reaction mixtures as it is formed.
Mechanism
Carboxylic acids whose molecules have a hydroxyl group on a γ- or δ- carbon undergo intramolecular esterification to give cyclic esters (Lactones) known as γ- or δ- lactones.

Example

\[
\begin{align*}
\text{γ-Hydroxy acid} & \quad \text{γ-Lactone} \\
R & \quad \beta & \quad \alpha & \quad \text{H}_3\text{O}^+ \\
\text{δ-Hydroxy acid} & \quad \text{δ-Lactone} \\
R & \quad \beta & \quad \alpha & \quad \text{H}_3\text{O}^+
\end{align*}
\]
From acid chlorides/acid anhydride/carboxylic acid salts

**General reaction**

\[
\begin{align*}
\text{RCOCl} & \quad \text{Pyridine} & \quad \text{R'}-\text{OH} & \quad \text{RCOOR'} + \text{HCl} \\
\text{RCOOOR} & \quad \text{R'}-\text{OH} & \quad \text{RCOOR'} + \text{RCOOH} \\
\text{ROO}^- \text{Na}^+ & \quad \text{R'}-\text{X} & \quad \text{SN}_2 & \quad \text{RCOOR'} + \text{NaX}
\end{align*}
\]

**Williamson ester synthesis**
Diazomethane esterification

Diazomethane, $\text{CH}_2\text{N}_2$, which is best drawn as a hybrid of two contributing structures, can be used to synthesize esters from carboxylic acid.

Example

Diazomethane, $\text{CH}_2\text{N}_2$, which is best drawn as a hybrid of two contributing structures, can be used to synthesize esters from carboxylic acid.
Reactions of Esters

\[ R\text{CH}_2\text{OH} + R'\text{OH} \xrightarrow{\underset{\text{[H]}}{\text{H}^+ / \text{OH}^-}} R\text{CH}_2\text{O}H + R'\text{OH} \]

\[ R\text{CH}_2\text{O}H + R''\text{MgX} \xrightarrow{\text{R}_2\text{NH}} R\text{CH}_2\text{O}H + R'\text{OH} \]

\[ R\text{CH}_2\text{O}H + R'\text{OH} \xrightarrow{\underset{\text{[H]}}{\text{H}^+ / \text{OH}^-}} R\text{CH}_2\text{O}H + R'\text{OH} \]
Hydrolysis of Esters

\[
\begin{align*}
R\text{O} & \quad + \quad R'\text{OH} \\
\text{H}_2\text{O} & \quad \text{H}_3\text{O}^+ \quad \text{HO}^- \\
\end{align*}
\]

Examples

\[
\text{[Chemical Structure]} + \text{H}_2\text{O} \quad \xrightarrow{\text{H}_3\text{O}^+} \quad \text{[Chemical Structure]} + \text{Ethanol}
\]

Reversible, Why?

\[
\text{[Chemical Structure]} + \text{H}_2\text{O} \quad \xrightarrow{\text{NaOH}} \quad \text{[Chemical Structure]}^- \quad + \quad \text{[Chemical Structure]}^\text{alcohol}
\]

Irreversible, Why?
All soaps are salts of fatty acids. The main difference between soaps is the addition of other ingredients that do not alter their cleaning properties: dyes for color, scents for a pleasing odor, and oils for lubrication. Soaps that float are aerated so that they are less dense than water.
Transesterification is the conversion of an ester into another ester by heating it with an excess of either an alcohol or a carboxylic acid in the presence of an acid or a base catalyst.

In an equilibrium reaction, either the alcohol or the acid portion of the original ester is removed.
Example

The equilibrium is shifted to the right by allowing the low boiling alcohol to distil from the reaction mixture.
Biodiesel is produced from renewable sources such as vegetable oils and animal fats and is a cleaner replacement for petroleum. It is nontoxic and biodegradable. It has physical properties similar to those of petroleum diesel.
Assignment 22

Draw a stepwise mechanism for each reaction.

a) [Chemical structure image]

1. CH₃MgBr
2. H₂O

b) [Chemical structure image]

BrMg → MgBr

H₃O⁺
I. The following reactivity order has been found for the saponification of \( p \)-substituted methyl benzoates:

\[
Y = \text{NO}_2 > \text{Br} > \text{H} > \text{CH}_3 > \text{OCH}_3
\]

How can you explain this reactivity order? Where would you expect \( Y = \text{CHO} \) and \( Y = \text{NH}_2 \) to be in the reactivity list?

II. When ethyl benzoate is heated in methanol containing a small amount of HCl, methyl benzoate is formed. Propose a mechanism for the reaction.
Reduction of Esters

The aldehyde intermediate can be isolated if 1 equivalent of the less reactive reducing agent diisobutylaluminum hydride (DIBAH) is used instead of LiAlH₄. The reaction is carried out at -78°C to avoid further reduction to the alcohol.

Diisobutylaluminum hydride (DIBAH)
**Ethyl dodecanoate**

1. DIBAH, $-78^\circ$C  
2. $\text{H}_3\text{O}^+$

**Dodecanal**
Assignment 24

I. Predict the major product(s) for each of the following reactions:

a) \( \text{CH}_3\text{CH}_2\text{COOMe} \xrightarrow{1. \text{LiAlH}_4} \text{CH}_3\text{CH}_2\text{COOH} \xrightarrow{2. \text{H}_2\text{O}} \)

b) \( \text{CH}_3\text{CH}_2\text{COOMe} \xrightarrow{1. \text{EtMgBr}} \text{CH}_3\text{CH}_2\text{COEt} \xrightarrow{2. \text{H}_2\text{O}} \)

c) \( \text{C}_6\text{H}_4\text{CH}=\text{CH}_2 \xrightarrow{1. \text{LiAlH}_4} \text{C}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OH} \xrightarrow{2. \text{H}_2\text{O}} \)

d) \( \text{C}_6\text{H}_4\text{COOH} \xrightarrow{1. \text{NaOH}} \text{C}_6\text{H}_4\text{COONa} \xrightarrow{2. \text{EtI}} \)

II. Explain why ester A is more reactive than ester B in nucleophilic substitution.
Amides

No free rotation across the C-N bond

Preparation of amides

From acid chlorides

Excess

Dr. Solomon Derese
From acid anhydrides

\[ R_2 \cdot \cdot \cdot H + R_2\cdot N\cdot R_1 \rightarrow R_2\cdot N\cdot R_1 + R_1\cdot O\cdot H \]

From esters

\[ R_2 \cdot \cdot \cdot H + R_2\cdot N\cdot R_1 \rightarrow R_2\cdot N\cdot R_1 + R_1\cdot O\cdot H \]
Carboxylic acids react with aqueous ammonia to form ammonium salts:

An ammonium carboxylate

Because of the low reactivity of the carboxylate ion toward nucleophilic substitution reaction, further reaction does not usually take place in aqueous solution.
Amides are of great importance in life. The linkages that join individual amino acids together to form proteins are primarily amide linkages. Proteins/peptides are formed by reacting the carboxyl group of one amino acid with the amino group another amino acid.

As a consequence, much research has been done to find convenient and mild ways for amide synthesis. Dialkylcarbodiimides \((R-N=C=N=R)\), for example dicyclohexylcarbodiimide (DCC), are especially useful reagents for amide synthesis.
The carbonyl carbon is now more electrophilic than the carboxyl and the bad leaving group –OH is replaced by a good leaving group.
Assignment 25

The following reaction will not happen as shown.

a. Show what would happen instead.

b. How could you obtain the desired product? Show the reagents to be used and the structures of any intermediates.
Reactions of amides

**Hydrolysis**

Amides are hydrolyzed in either acidic or alkaline solution. In either case, the acid or base is a reactant, not a catalyst, and must be used in a 1.1 molar ratio or in excess.

\[
\text{R} - \text{N} - \text{H} \xrightarrow{\text{H}_3\text{O}^+ \text{ or } \text{H-O}^-} \text{R} \text{C} = \text{O} + \text{R}_2 \text{N} - \text{H}
\]

This property is at most important in biological systems for the stability of proteins. If the amide could hydrolyze easily we wont even be able to touch water.
Reduction

Mechanism

\[
\text{R}^\text{N} - \text{R}'' \xrightarrow{\text{LiAlH}_4} \text{R}^\text{N} - \text{R}'
\]

\[
\text{R}^\text{N} - \text{R}'' \xrightarrow{\text{AlH}_3} \text{R}^\text{N} - \text{R}'
\]

\[
\text{R}^\text{N} - \text{R}'' \xrightarrow{\text{LiAlH}_4} \text{R}^\text{N} - \text{R}'
\]

\[
\text{R}^\text{N} - \text{R}'' \xrightarrow{\text{AlH}_3} \text{R}^\text{N} - \text{R}'
\]
Assignment 26

I. Predict the major product(s) for each of the following reactions:

a) \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \xrightarrow{\text{LiAlH}_4} \)  
\( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \)

b) \( \text{PhCOCl} \xrightarrow{\text{NH}_3} \)  
\( \text{PhCOH} \)

II. Propose a mechanism for each of the following transformations:

a) \( \text{H}_3\text{O}^+ \)  
\( \text{CH}_2=\text{NH} \)  
\( \xrightarrow{\text{H}_2\text{N}} \)  
\( \text{H}_2\text{NCH}_2\text{CH}_2\text{COOH} \)

b) \( \text{1. NaOH} \)  
\( \text{H}_3\text{O}^+ \)  
\( \xrightarrow{\text{H}_2\text{N}} \)  
\( \text{H}_2\text{NCH}_2\text{CH}_2\text{COOH} \)

\( \text{2. H}_3\text{O} \)

c) \( \text{HCl} \)  
\( \text{H}_3\text{O}^+ \)  
\( \xrightarrow{\text{H}_2\text{N}} \)  
\( \text{H}_2\text{NCH}_2\text{CH}_2\text{COOH} \)
Nitriles

R—C≡N

Preparation of nitriles

I. From dehydration of amides

\[
\text{R—O—O—H} \xrightarrow{\text{SOCl}_2} \text{R—O—Cl} \xrightarrow{\text{NH}_3} \text{R—C—N—H} \xrightarrow{\text{SOCl}_2, \text{Base}} \text{R—C≡N} + \text{SO}_2 + \text{HCl}
\]
**Mechanism**

\[
\text{R} - \text{C}=\text{N} + \text{SO}_2 + \text{HCl} \rightarrow \text{R} - \text{C}=\text{N} + \text{SO}_2 + \text{HCl}
\]

**Example**

\[
\text{R} - \text{C}=\text{N} + \text{SO}_2 + \text{HCl} \rightarrow \text{R} - \text{C}=\text{N} + \text{SO}_2 + \text{HCl}
\]
$S_N^2$ reaction of cyanide ion with primary alkyl halides

$$R-\text{CH}_2-X + \text{NaCN} \xrightleftharpoons{S_N^2} R-\text{CH}_2-\text{CN} + \text{NaX}$$

Example

![Chemical structures](image_url)
Reactions of nitriles

Hydrolysis of nitrites

1. LiAlH₄
2. H₂O

Reduction of nitriles

1. DIBAH, -78°C
2. H₃O⁺
Mechanism

Example

1. DIBAH
2. H₂O

1. LiAlH₄
2. H₂O
Reaction with organometallic reagents

1. R'MgBr
2. H₂O

1. PhMgBr
2. H₂O

An alternative to Friedel-Crafts acylation
\[
\begin{align*}
R - \text{C} &= N \quad \overset{\text{R'} \text{MgBr}}{\longrightarrow} \\
R - \text{C} &= N: \quad \overset{\text{H}}{\longrightarrow} \\
R - \text{C} &= N: \quad \overset{\text{H}}{\longrightarrow} \\
\text{H}_2\text{O}^+ &\quad \overset{\text{H}}{\longrightarrow} \\
\text{O}^+ &\quad \overset{\text{H}}{\longrightarrow} \\
\text{NH}_3 &\quad \overset{\text{H}}{\longrightarrow} \\
\text{N}^+ &\quad \overset{\text{H}}{\longrightarrow} \\
\text{H}_2\text{O}^+ &\quad \overset{\text{H}}{\longrightarrow} \\
\text{N}^+ &\quad \overset{\text{H}}{\longrightarrow} \\
\text{H}_2\text{O}^+ &\quad \overset{\text{H}}{\longrightarrow} \\
\end{align*}
\]
Assignment 27

I. Predict the major product(s) for each of the following reactions:

a) \[ \text{CH}_3\text{CN} \rightarrow 1. \text{LiAlH}_4 \rightarrow 2. \text{H}_2\text{O} \]

b) \[ \text{Br} \rightarrow 1. \text{NaCN} \rightarrow 2. \text{MeMgBr} \rightarrow 3. \text{H}_3\text{O}^+ \]

c) \[ \text{CN} \rightarrow 1. \text{EtMgBr} \rightarrow 2. \text{H}_2\text{O} \rightarrow 3. \text{LiAlH}_4 \rightarrow 4. \text{H}_3\text{O}^+ \]
II. Propose a mechanism for the following transformation:

III. Propose an efficient synthesis for each of the following transformations:
IV. Identify compounds A–M in the following reaction sequence.
Reduction of carboxylic acid

General reaction

\[
\text{R-COOH} \xrightarrow{1. \text{LiAlH}_4} \text{R-CHOH} \xrightarrow{2. \text{H}_3\text{O}^+} \text{R-CH(OH)CH}_3
\]

Reduced by LiAlH₄

\[
\text{R-COOH} < \text{R-COOR'} < \text{R-COR} < \text{R-CH}_2\text{CH}_3
\]

Reduced by NaBH₄

EASE OF REDUCTION
Example

Selectively reduces carboxylic acids in the presence of aldehydes/ketones and esters
Decarboxylation of β-keto acids and β-diacids

Acids whose molecules have a carbonyl group one carbon removed from the carboxyl group, called β-keto acids, decarboxylate readily when they are heated to 100-150°C.

\[ \text{β-Ketoacid} \rightarrow \text{α-Ketoacid} + \text{CO}_2 \]
There are two reasons for this ease of decarboxylation.  

1) When the carboxylate ion decarboxylate, it forms a resonance stabilized enolate anion:

\[
\begin{align*}
\text{β-Ketoacid} & \\
\text{Resonance stabilized anion} & 
\end{align*}
\]
II. The decarboxylation takes place though a stable six-membered cyclic transition state.

\[ \beta\text{-Keto carboxylic acid} \]

**Example**

\[ \begin{align*}
\text{HEAT} & \quad \text{HEAT} \\
\begin{array}{c}
\text{H}_3\text{C} \quad \text{H}_3\text{C} \\
\text{O} \quad \text{CH}_3 \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{H} \\
\hline
\text{H}_3\text{C} \quad \text{H}_3\text{C} \\
\text{O} \quad \text{CH}_3 \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{H} \\
\end{array}
\end{align*} \]
Assignment 28

Write the organic product(s) and reaction mechanism of the following reaction: