Please Note: The terms "acid halide" and "acyl halide" are synonymous and are both used in this text. In biochemistry, the term "acyl" is used more frequently.

**Acid Halide Synthesis**

Carboxylic acids react with thionyl chloride (SOCl₂) or oxalyl chloride (C₂O₂Cl₂) to form acid chlorides. Typically the reactions occur in the presence of a proton scavanger like pyridine to minimize unwanted side reactions. During the reaction the hydroxyl group of the carboxylic acid is converted to a chlorosulfite intermediate making it a better leaving group. The chloride anion produced during the reaction acts a nucleophile.

\[
\begin{align*}
\text{R-COOH} & \xrightarrow{\text{SOCl}_2} \text{R-COCl} + \text{HCl} + \text{SO}_2 \\
\end{align*}
\]

Analogous to the reactions of primary and secondary alcohols with PBr₃ to produce the corresponding alkyl bromide, acid bromides can be formed from the reaction of phosphorous tribromide with carboxylic acids.

\[
\begin{align*}
\text{R-COOH} & \xrightarrow{\text{PBr}_3, \text{ether}} \text{R-CBr} \\
\end{align*}
\]

**Acyl Halide Reactivity**

Acyl halides can be hydrolyzed to carboxylic acids and converted to carboxylic acid derivatives. Acid halides can also undergo reduction reactions and reactions with Grignard reagents and organolithium cuprates along with Fridel-Crafts acylation of benzene. The reaction map below summarizes the reactivity of acyl halides.
Acid Halide Hydrolysis

The hydrolysis reaction of acid chlorides is shown below.

\[ \text{Acid Chloride} + \text{H}_2\text{O} \rightarrow \text{Carboxylic Acid} + \text{HCl} \]

The hydrolysis of butyronyl chloride is shown below as an example.
Example: Acyl Chloride Hydrolysis

\[ \overset{\text{Cl}}{\text{C}} - \overset{\text{O}}{\text{R}} \ + \overset{\text{OH}}{\text{H}_2\text{O}} \rightarrow \overset{\text{OH}}{\text{R}} - \overset{\text{C}}{\text{C}} \ + \overset{\text{Cl}}{\text{H}} \]

Carboxylic Acid Derivative Synthesis from Acyl Chlorides

Carboxylic acid derivatives can be synthesized from acyl chlorides via the nucleophilic acyl substitution mechanism previously discussed.

Anhydride Synthesis

Acid chlorides react with carboxylic acids to form acid anhydrides as shown in the reaction below.

\[ \text{Acid Chloride} + \text{Carboxylic Acid} \rightarrow \text{Acid Anhydride} + \text{HCl} \]

The synthesis of benzoic anhydride from benzoyl chloride and benzoic acid is shown as an example.
Example: Anhydride Synthesis from Acyl Chlorides

\[ \overset{\text{Cl}}{\text{C}} - \overset{\text{O}}{\text{R}} + \overset{\text{O}}{\text{H}} - \overset{\text{A}}{\text{B}} \rightarrow \overset{\text{O}}{\text{R}} - \overset{\text{R}}{\text{R}} - \overset{\text{O}}{\text{O}} \]

Ester Synthesis

Acid chlorides react with alcohols to form esters as shown in the reaction below.

\[ \text{Acid Chloride} + \text{Alcohol} \rightarrow \text{Ester} + \text{HCl} \]

The synthesis of ethyl benzoate from benzoyl chloride and ethanol is shown as an example.
Example: Ester Synthesis from Acid Chlorides

\[ \overset{\text{Cl}}{\text{C}} - \overset{\text{O}}{\text{R}} + \overset{\text{O}}{\text{HO}} - \overset{\text{R'}}{\text{R}} \rightarrow \overset{\text{O}}{\text{R}} - \overset{\text{R'}}{\text{R}} + \overset{\text{Cl}}{\text{H}} \]
Amide Synthesis

Acid chlorides react with "ammonia, 1\textsuperscript{\textdegree} amines and 2\textsuperscript{\textdegree} amines" to form amides as shown in the reaction below.

The reaction requires 1 equivalent of the "ammonia/1\textsuperscript{\textdegree} or 2\textsuperscript{\textdegree} amine" with a proton scavenger (aka base) like pyridine OR two equivalents of "ammonia/1\textsuperscript{\textdegree} or 2\textsuperscript{\textdegree} amine". The additional equivalent the nucleophile or base is needed to maintain the nucleophilic character of "ammonia/1\textsuperscript{\textdegree} or 2\textsuperscript{\textdegree} amine". As shown in the mechanism below, the amide is briefly protonated after the carbonyl reforms from the tetrahedral complex. Since amides are considered neutral with no significant basicity, the "ammonia/1\textsuperscript{\textdegree} or 2\textsuperscript{\textdegree} amine" quickly accepts their proton and is no longer a nucleophile. The second equivalent of "ammonia/1\textsuperscript{\textdegree} or 2\textsuperscript{\textdegree} amine" restores the concentration of the nucleophile. For clarity, the mechanism below is shown with ammonia as the nucleophile.

Mechanism

The syntheses of acetamide and N-ethylacetamide from acetyl chloride are shown as examples.

Example: Amide Synthesis from Acyl Chlorides

Acid Chloride Reduction

Acid chlorides can be fully reduced to primary alcohols using either sodium borohydride or lithium aluminum hydride. Acid chlorides can be partially reduced to aldehydes using the lithium tri-tert-butoxyaluminum hydride (LiAlH(O-t-Bu)\textsubscript{3}).
Acid Chloride Reactions with Organometallic Compounds

Grignard reagents

Acid chlorides react with Grignard reagents to produce tertiary alcohols. Two equivalents of the Grignard reagent are needed because the first equivalent reacts to form a ketone which then reacts with the second equivalent. Because of the high reactivity of the Grignard reagent, the reaction can NOT be stopped at the ketone.

The syntheses of 3-phenylpentan-3-ol from benzoyl chloride is shown as an example.

Example: Acyl Chloride Reactions with Grignard Reagents
Organolithium Cuprates

Organolithium cuprate reagents are less reactive than Grignard reagents and can convert acid chlorides to ketones as shown below.

The synthesis of 1-phenylpropan-1-one from benzoyl chloride is shown as an example.
Example: Acyl Chloride Reactions with Organolithium Cuprates

Friedel-Crafts Acylation of Benzene

Benzene rings can be acylated via the Friedel-Crafts acylation reaction with acid chlorides in the presence of aluminum chloride followed by an aqueous work-up as shown below.

For F-C Acylation, the benzene ring can have electron-donating groups or a halogen, but cannot contain electron-withdrawing groups, such as the nitro (NO₂) or sulfonyl (SO₃H) groups.

The synthesis of 1-(4-tert-butylphenyl)butan-1-one from t-butylbenzene and butonyl chloride is shown as an example.
Example: Friedel-Crafts Acylation

Exercise

4. Draw the mechanism for the following reaction
5. Propose a synthesis of the following molecules from an acid chloride and an amide.

(a)

(b)

(c)

Answer
5.

a) Acetyl chloride and dimethylamine

b) Benzoyl chloride and ethylamine

c) Acetyl chloride and ammonia

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