Chapter 21 - Carboxylic Acid Derivatives and Nucleophilic Acyl Substitution

Reactions of Carboxylic Acids - Preparation of Acid Chlorides and Anhydrides

Acid chlorides can be directly converted into more reactive acid chlorides using thionyl chloride. This is very convenient and the byproducts are all gasses. This helps drive the reaction forward. Anhydrides can be made from readily available inexpensive acids by heating to drive off the water. This is pretty much limited to simple acids like acetic acid and diacids.

**Acid Chlorides**

\[
\begin{align*}
\text{Acid} &\quad + \quad \text{SOCl}_2 \\
\rightarrow &\quad \text{Acid Chloride} \\
\end{align*}
\]

base (solvent or Cl⁻) (This step may happen later after kicking off HOSOCl)

**Acid Anhydrides**

\[
\begin{align*}
\text{Acid} &\quad + \quad \text{Acid} \quad \xrightarrow{\text{Heat}} \quad \text{Anhydride} \\
\rightarrow &\quad \text{Anhydride} \quad + \quad \text{Water} \\
\end{align*}
\]

Reactions of Carboxylic Acids - Preparation of Esters

The preparation of esters from acids is limited. The deprotonated acid will react with methyl or primary alkyl halides via an S_N2 reaction. With a large excess of alcohol and an acid catalyst, a Fischer Ester Synthesis can be undertaken. This is limited to cheap readily available alcohols like methanol and ethanol. Other esters are more easily prepared from the acid chloride.
Reactions of Carboxylic Acids - Preparation of Amides

It is very difficult to prepare amides directly from carboxylic acids. This is because the acid and amine will simply do an acid-base reaction to make an ammonium cation and carboxylate anion. This salt is generally unreactive. However, industrially, nylon-6,6 is prepared by heating adipic acid and hexamethylenediamine together under high heat and pressure to make the polyamide. In laboratory preparation of amides, it is most convenient to use the acid chloride.
Hydrolysis of Esters - Acid and Base Catalysis

The hydrolysis of esters can be either acid or base catalyzed. The acid catalyzed process is similar to any of the acid catalyzed mechanisms we have already studied. Acid catalyzed hydrolysis of esters is not the best way because the reaction is readily reversible (reverse is Fischer Esterification). Base catalysis is best because the final acid is deprotonated by the alkoxide and this drives the reaction completely to the products.

**NEED TO KNOW MECHANISMS**

**Acid Catalyzed Hydrolysis**

![Acid Catalyzed Hydrolysis](image)

**Base Catalyzed Hydrolysis (Saponification)**

![Base Catalyzed Hydrolysis](image)

Rapid acid-base reaction takes place

Carboxylate is a thermodynamic sink and makes the reaction essentially non-reversible. To get the carboxylic acid, add acid to protonate.