Chapter 21 - Carboxylic Acid Derivatives and Nucleophilic Acyl Substitution

**Acid Chlorides**

Recall from last lecture that we can make acid chlorides from acids with thionyl chloride.

**Preparation of Acid Chlorides**

\[ \text{ROH} + \text{SOCl}_2 \rightarrow \text{RCl} + \text{SO}_2 + \text{HCl} \]

The most reactive and versatile derivative, acid chlorides can be used to make many acid derivatives.

**Reactions of Acid Chlorides**

- **Hydrolysis**
  \[ \text{RCl} + \text{H}_2\text{O} \rightarrow \text{ROH} + \text{HCl} \]

- **Alcoholysis**
  \[ \text{RCl} + \text{R'O} \rightarrow \text{RO} + \text{Pyridine-HCl} \]

- **Aminolysis**
  \[ \text{RCl} + 2\text{NH}_3 \rightarrow \text{RNH}_2 + \text{NH}_4\text{Cl} \]

Use 2 equiv. of amine or 1 equiv. amine and 1 equiv. of pyridine as base.

**Acid Anhydrides**

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. If an unsymmetric anhydride is desired, a more controlled reaction is required to avoid statistical mixtures of products. Acid halides can be reacted with carboxylate salts to form unsymmetric anhydrides with complete control.

**Acid Anhydrides**

- **Symmetric**
  \[ \text{RO} + \text{HOCOR} \rightarrow \text{ROCOR} + \text{HOH} \]

- **Limited to symmetric anhydrides**

- **Unsymmetric**
  \[ \text{RCl} + \text{NaOOCR'} \rightarrow \text{ROOCR'} + \text{NaCl} \]

  Can make unsymmetric anhydrides
Anhydrides will react very similar to acid chlorides. They are less reactive than acid chlorides which makes handling them easier. Usually we use anhydrides when we need to introduce simple, readily available acyl groups like acetyl.

![Chem 342 page 2 Spring 2009](image-url)

**Preparation of Esters**

As we have seen, esters can be prepared by alcoholysis of acid chlorides and anhydrides. But some of the more common simple esters can be made directly from the carboxylic acid. The preparation of esters from acids is limited, however. A deprotonated acid (carboxylate) will react with methyl or primary alkyl halides via a S\textsubscript{N}2 reaction.
Daily Quiz

Q: What is the product of the reaction of p-aminophenol with acetic anhydride?

\[ \text{H}_2\text{N} - \text{C}_6\text{H}_4\text{OH} + \text{O} = \text{O} \rightarrow \text{H}_2\text{N} - \text{C}_6\text{H}_4\text{OH} \]

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