Chapter 21 - Carboxylic Acid Derivatives and Nucleophilic Acyl Substitution

Preparation of Esters

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.

\[
\text{R} \quad \text{O} \quad \text{H} \quad \xrightarrow{\text{HA (cat)}} \quad \text{O} \quad \text{R} \quad \text{OCH}_3
\]

Fischer Esterification

NEED TO KNOW MECHANISM

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. This process is called saponification.
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 Amides

Because the C-N bond of amides is very strong (amine anions are terrible leaving groups) the best way to hydrolyze an amide is under acid catalyzed conditions. The mechanism is very similar to other acid-catalyzed reactions such as Fischer esterification or ester hydrolysis.

Reactions of Amides

Amides are the most stable of the carboxylic acid derivatives. Thus, there are not a lot of reactions that they undergo. Hydrolysis can be done as described above. Another important reaction is the reduction with lithium aluminum hydride. This results in loss of the oxygen not the nitrogen giving an amine as the product.
What is the product of the following sequence of reactions?

1) KMnO₄
2) SOCl₂
3) CH₃NH₂, pyridine