

I. Nitriles

Nitriles consist of the CN functional group, and are linear with sp hybridization on C and N. *Nitriles are non-basic at nitrogen*, since the lone pair exists in an sp orbital (50% s character places electron density close to nucleus, making the lone pair relatively unreactive).

Synthesis of Nitriles

- a. dehydration of 1° amides using POCl₃;

- b. SN2 reaction of cyanide ion on halides:

- c. Cyanohydrin formation from aldehydes and ketones

Reactions of Nitriles

1. Hydrolysis of nitriles to carboxylic acids occurs under acidic or basic conditions; the reaction can be stopped at the 1° amide stage, since hydrolysis of the amide to the acid requires heating in concentrated aqueous acid.

Under basic conditions, hydroxide ion is the nucleophile; under acidic conditions, protonation of the nitrile nitrogen generates a nitrilium ion that undergoes nucleophilic attack by water

Reduction of Nitriles

Nitriles are reduced to amines by hydrogenation over a palladium/platinum catalyst or by hydride reduction with LiAlH_4 :

Reaction of Nitriles with Grignard Reagents

Nitriles react with Grignard reagents to form ketones; the intermediate imine anion-magnesium salt is stable and does not undergo a second addition of reagent.

II. Acid Anhydrides

Anhydrides result from the dehydration of carboxylic acids. Like acid chlorides, anhydrides are highly reactive substrates for nucleophilic acyl substitution, with the leaving group being the carboxylate anion, a stabilized negative charge because of resonance delocalization. *Note that in nucleophilic acyl substitution, half of the anhydride*

unit is lost, being converted to the corresponding carboxylic acid. As a result nucleophilic acyl substitution of anhydrides is not an efficient process unless the parent carboxylic acid is plentiful and inexpensive; conversion of an acid to the acid chloride and reaction with a nucleophile is a more practical and efficient process.

Common anhydrides:

Resonance stabilization of an anhydride is like that of an ester, but the stabilization is shared between the two carbonyl groups:

Synthesis of anhydrides

- from acid chlorides: two direct methods exist. From acid chlorides:

•by direct dehydration of acids, which is employed in the industrial synthesis of acetic anhydride:

Reactions of Acid Anhydrides

General Form: Nucleophilic Acyl Substitution

The nucleophile can be water, an alcohol or an amine, leading to carboxylic acids, esters, or amides:

Anhydrides can also participate in Friedel-Crafts reactions just like acid chlorides:
Propose a mechanism for the following transformations

Acetic anhydride is a common reagent used to introduce acetate esters into molecules; acetic formic anhydride is a common formylating agent. Both types of reactions are done in the presence of the weak base pyridine.

Nucleophiles react with cyclic anhydrides at only one carbonyl carbon:

III. Acid Chlorides

Acid chlorides are precursors to almost every oxygen-containing functional group. They can be used to prepare anhydrides, esters, amides, acids, aldehydes, ketones, and alcohols. Again, nucleophilic acyl substitution is the primary mechanism operating for all reactions of acid chlorides. Acid chlorides are reactive for two reasons: excellent leaving group (low basicity of Cl⁻, large atom which can spread negative charge over a large volume of space) and poor resonance stabilization of the acid chloride due to weak π overlap of chlorine lone pair with carbonyl carbon.

Friedel-Crafts acylation is one of the most useful methods of introducing acyl/alkyl groups onto an aromatic ring:

IV. Thioesters, carbonates, carbamates, and ureas

Thioesters have the general form $RC(=O)SR'$, and are less reactive than acid chlorides or anhydrides toward nucleophilic acyl substitution. However, they are more reactive than esters toward nucleophilic acyl substitution:

Thioesters have less resonance stabilization than esters due to weak π overlap between p orbital on sulfur and p orbital on carbon. Furthermore, RS^- is a better leaving group than RO^- , since S is a larger and more polarizable atom. As a result, charge is spread out over a larger volume of space and there is more bonding in the transition state as S is leaving.

Note: even weaker overlap is observed for acid chlorides, which leads to their high reactivity.

Thioesters are selective acylating agents since they are hydrolytically stable (do not react with water) yet react readily with strong nucleophiles. As a result, nature uses a thioester (present in acyl coenzyme A) to transfer an acetyl group to nucleophiles in biological molecules.

Carbonates, urethanes (carbamates), and ureas

A carbonate ester (a diester of carbonic acid) results from the reaction of two molecules of alcohol with the molecule phosgene. Carbonates are even less reactive than esters due to resonance donation from two oxygens attached to the carbonyl carbon.

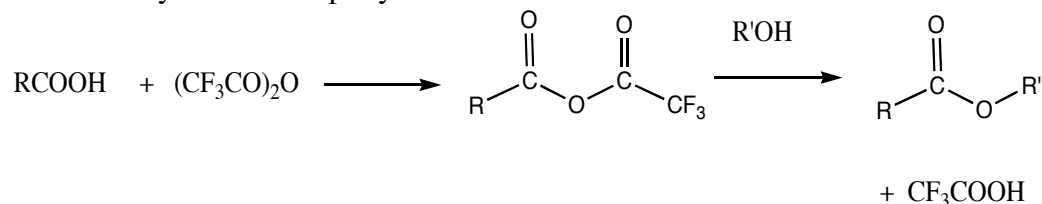
Carbamates or urethanes are stable esters of carbamic acid (NH_2COOH) and are formed from addition to phosgene of one equivalent each of an alcohol and an amine. They are even less reactive than carbonates due to the strong resonance overlap of the nitrogen lone pair as in amides.

An alternative preparation of carbamates involves treatment of an alcohol with an isocyanate, the anhydride of carbamic acid

Ureas are the least reactive of the series and result from treatment of phosgene with two equivalents of an amine

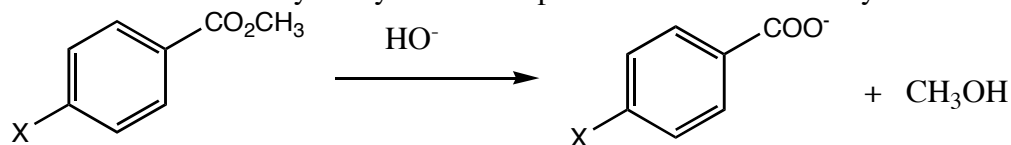
Problems for additional practice:

1. A particularly mild method of esterification involves the use of trifluoroacetic anhydride. Treatment of a carboxylic acid with trifluoroacetic anhydride leads to a mixed anhydride that rapidly reacts with alcohol:



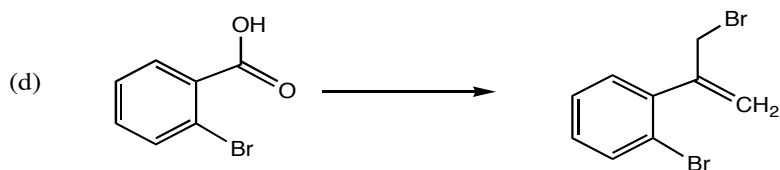
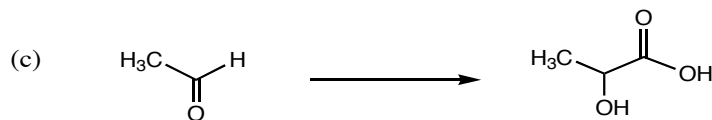
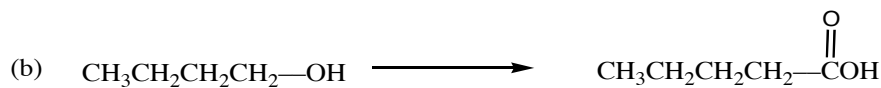
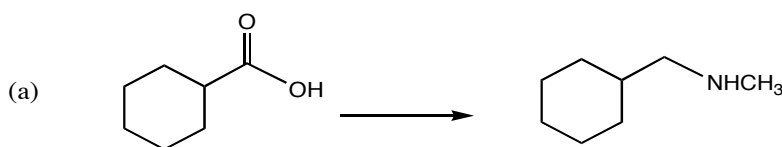
- (a) propose a mechanism for formation of the mixed anhydride
- (b) Why does the mixed anhydride react as indicated, rather than giving trifluoroacetate ester plus carboxylic acid?

2. In the basic hydrolysis of para-substituted methyl benzoates,

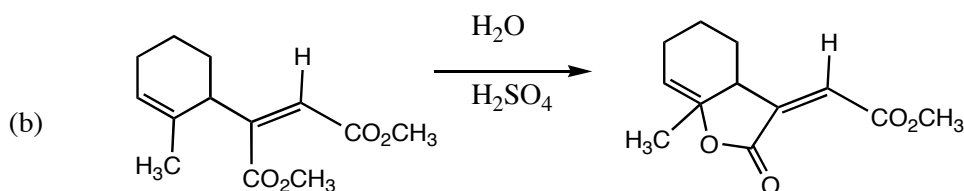
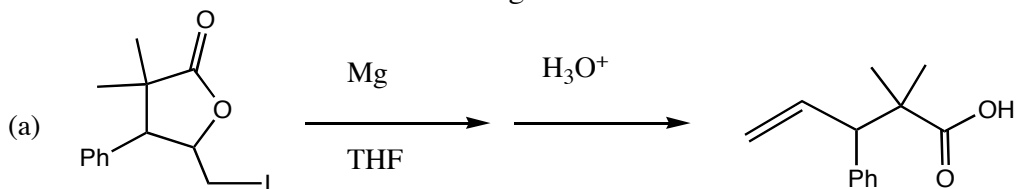


the following reactivity order has been found for X: $\text{NO}_2 > \text{Br} > \text{H} > \text{CH}_3 > \text{OCH}_3$. How can you explain this reactivity order? Where would you expect X=CN, X=CHO and X=NH₂ to be in this list?

3. Show a synthetic sequence to accomplish the following transformations:



4. Show a mechanism for the following transformations:



5. Outline a synthesis of each of the following compounds from the indicated starting material:

