

I. Reactions of Carboxylic Acids & Derivatives

A. Nucleophilic Acyl Substitution

A nucleophile replaces a leaving group on the acyl carbon. *Note:* this mechanism is not operative for ketones and aldehydes because H and C are poor leaving groups.

Examples of carboxylic acid derivatives that undergo nucleophilic acyl substitution

Mechanism of Nucleophilic Acyl Substitution:

- X must be a good leaving group: an atom sufficiently able to bear a negative charge. Note the reactivity order toward nucleophilic acyl substitution parallels leaving group ability:

- Aldehydes and ketones undergo addition, not substitution:

B. Fisher Esterification

The conversion of carboxylic acids to esters is an acid catalyzed equilibrium process:

Examples:

Mechanism of Fisher esterification:

The Fisher esterification is an equilibrium process; the product ester is favored only for 1° alcohols.

- To drive equilibrium to the right, one can use an excess of one of the reactants, either the acid or the alcohol as solvent.
- Alternatively, the by-product water can be removed by distillation or a dehydrating agent.

Esters can be converted back to acids by aqueous acidic hydrolysis:

II. Synthesis and use of Acid Chlorides

Halide ions are excellent leaving groups, and thus the addition/elimination mechanism in nucleophilic acyl substitution is very favored in reactions of acid chlorides

Preparation of Acid Chlorides:

Reaction of an acid with SOCl_2 or oxalyl chloride gives an acid chloride:

Mechanism of acid chloride formation:

Acid chlorides react with alcohols to give esters. This provides an efficient two-step protocol for ester synthesis from acids:

Amides can also be prepared by subjecting acid chlorides to amines in the presence of a base such as pyridine to react with the acid generated. Excess acid buildup inhibits the reaction by protonating the amine, generating the non-nucleophilic ammonium ion. Similarly, anhydrides are obtained from the condensation of acid chlorides with carboxylic acids in the presence of pyridine

III. Esterification of acids with diazomethane

Methyl esters can easily be prepared by reaction of acids with diazomethane, a toxic, explosive yellow gas which is stable in ethereal solutions. The only by-product of the reaction is N₂ gas:

IV. Direct Synthesis of Amides

Reaction of acids and amines forms carboxylate salts; heating of these salts above 100°C effects dehydration to form amides:

V. Reduction of acids to alcohols:

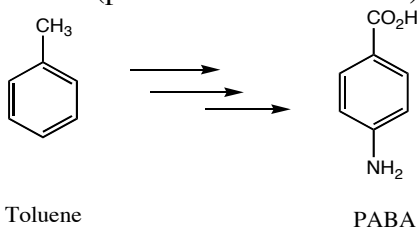
Two methods exist to reduce acids to alcohols: LiAlH_4 and BH_3 . The BH_3 is very selective for the reduction of acids in the presence of other carbonyl functionality. Ketones, aldehydes, esters, and amides are unaffected by borane:

Reduction of acids to aldehydes.

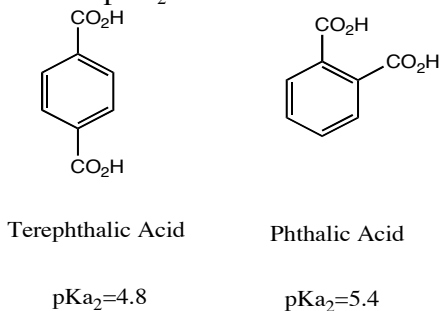
Partial reduction of acids to aldehydes can only be accomplished via the acid chloride, which is more highly reactive toward reduction than aldehydes. A mild reducing agent like $\text{LiAlH}(\text{OtBu})_3$ is often employed so optimal production of the aldehyde is obtained:

Additional Problems for practice:

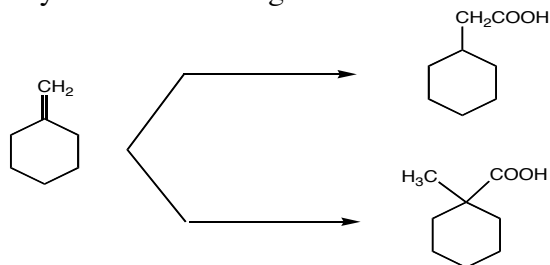
1. Propose a synthesis of PABA (para aminobenzoic acid) from toluene:



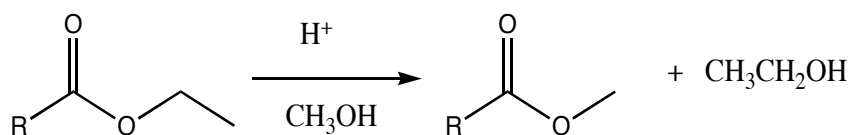
2. Account for the fact that phthalic acid has a *second* pK_a (pK_{a_2}) that is 5.4, whereas terephthalic acid has $\text{pK}_{a_2}=4.8$:



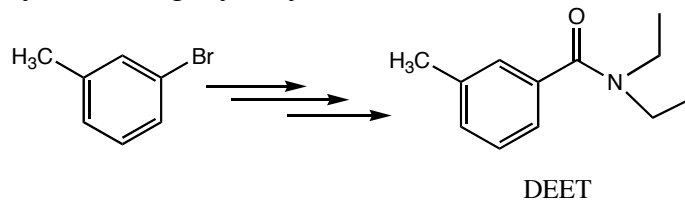
3. How would you carry out the following transformations?



4. Account for the fact that treatment of an ethyl ester with an acid catalyst in methanol solution yields the methyl ester product:



5. DEET (N,N-Diethyl-m-toluamide) is the active ingredient in many insect-repellent sprays. How might you synthesize this substance from m-bromotoluene.



6. Indicate appropriate methods for the following acid syntheses:

