

PHARMACEUTICAL ORGANIC CHEMISTRY-II
SECOND YEAR B. PHARMACY
(SEMESTER-III)
AROMATIC ACIDS



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INTRODUCTION

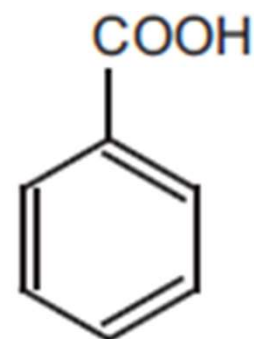
- The organic compounds having carboxyl functional group are called carboxylic acids.
- The carboxyl group carries a carbonyl group CO attached to hydroxyl OH group, therefore, the name carboxyl.
- The simplest series of carboxylic acids are the alkanonic or aranoic acids, R-COOH, where, R is a hydrogen or an alkyl or an aryl group. Compounds may also have two or more carboxylic acid groups per molecule and are called dicarboxylic acids.



Formic acid



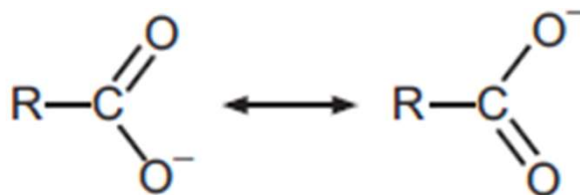
Acetic acid



Benzoic acid

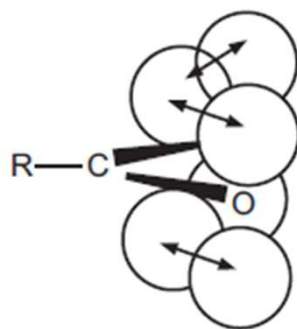
Structure of Carboxylate Ion:

The carboxylate ion has two canonical structures, both equally stable. The carbon atom is joined to two oxygen atoms, one by a single bond and the other by a double bond. But due to resonance the bonds continuously shift from one oxygen atom to the other. So neither of the bonds can be called as a single or a double bond. Hence, the bond between carbon atom and each oxygen atom is said to be “one-and-a half” bond.



The carbon atom of the carboxyl group is sp^2 hybridized and the three orbitals form the sigma bonds. The remaining p-orbitals of the carbon overlap very well with the p-orbitals of the oxygen atom. Hence, the electrons are bound to three nuclei and thus held very strongly.

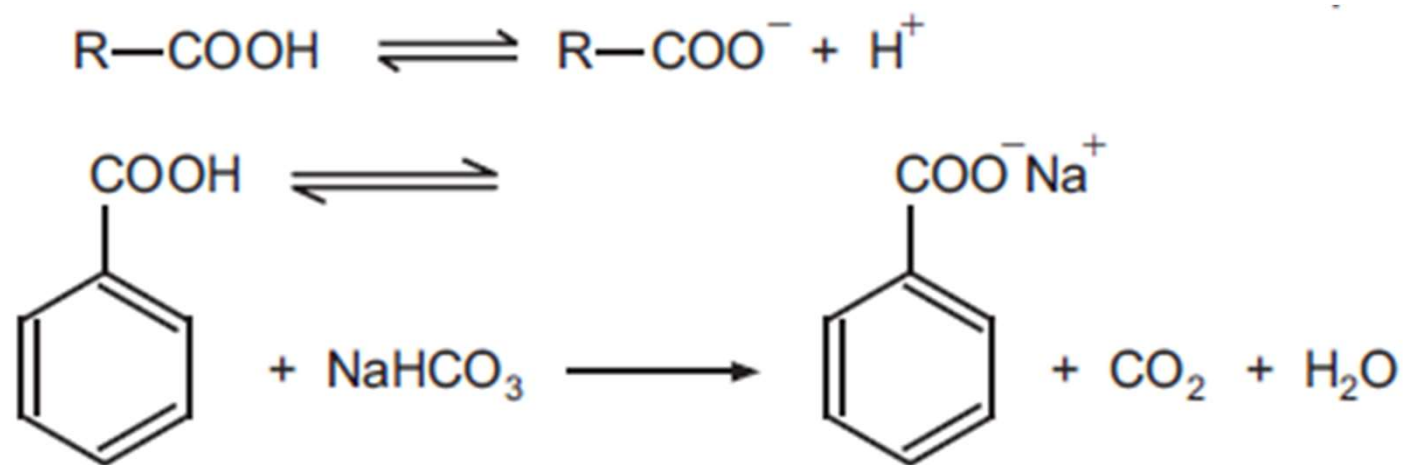
Thus, the carboxylate anion is more stable. All the bond angles around the carboxyl carbon are 120° .



Overlap of p-orbitals

ACIDITY : SALT FORMATION

- Carboxylic acids are weaker than the strong mineral acids. However, in comparison with other organic acids like alcohols and acetylene; carboxylic acids are very strong. Also they are stronger than water. They readily react with aqueous hydroxides and weak bases like sodium bicarbonate to form salts. The salts are crystalline, non-volatile and have very high melting points. The alkali metal salts are soluble in water but, insoluble in non-polar solvents.



Substituted carboxylic acids can be either stronger or weaker acids, as compared to the parent acid. This depends on the nature of substituents. If the substituent stabilizes the carboxylate anion then it increases the acidity of the acid. Similarly, if the substituent decreases the stability of the carboxylate anion, then it decreases the acidity of the acid.

Electron-withdrawing substituents have tendency to disperse the negative charge thus, stabilizing the carboxylate ion and hence increase the acidity whereas electron-releasing substituents destabilize the carboxylate ion and hence decrease the acidity. Higher the value of K_a , stronger the acid. As a matter of fact compared to a simple alkyl carboxylic acid

(e.g., methanoic acid), an aryl carboxylic acid (e.g., benzoic acid) is a stronger acid. This is because of two reasons:

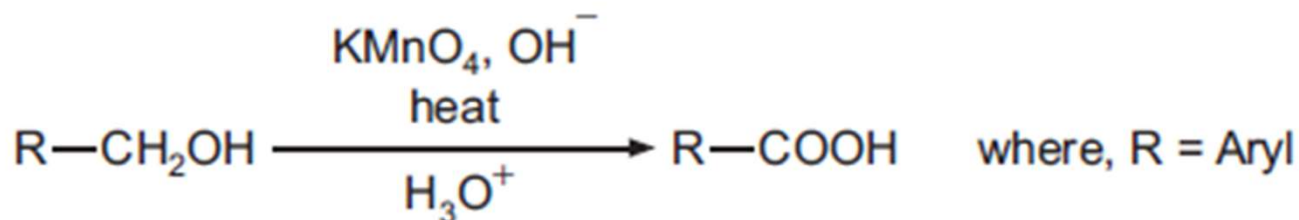
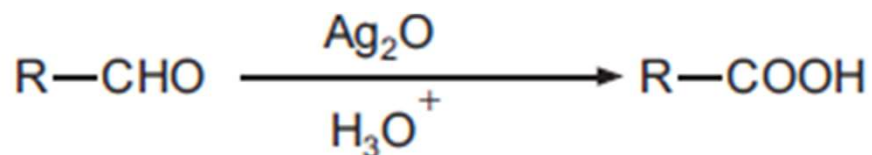
1. The alkyl carboxylate anion is less stable than the aryl carboxylate anion, the later being stabilized by resonance.
2. The alkyl group R of alkyl carboxylic acid is having an electron donating (+I) effect on the carboxyl carbon, thus, making it weaker acid. On the other hand, the aryl carboxylic acid is having an electron withdrawing (- I) effect on the carboxyl carbon, thus, making it relatively stronger acid.

METHODS OF PREPARATION OF ARYL CARBOXYLIC ACIDS

1. Oxidation of primary alcohols and aldehydes:

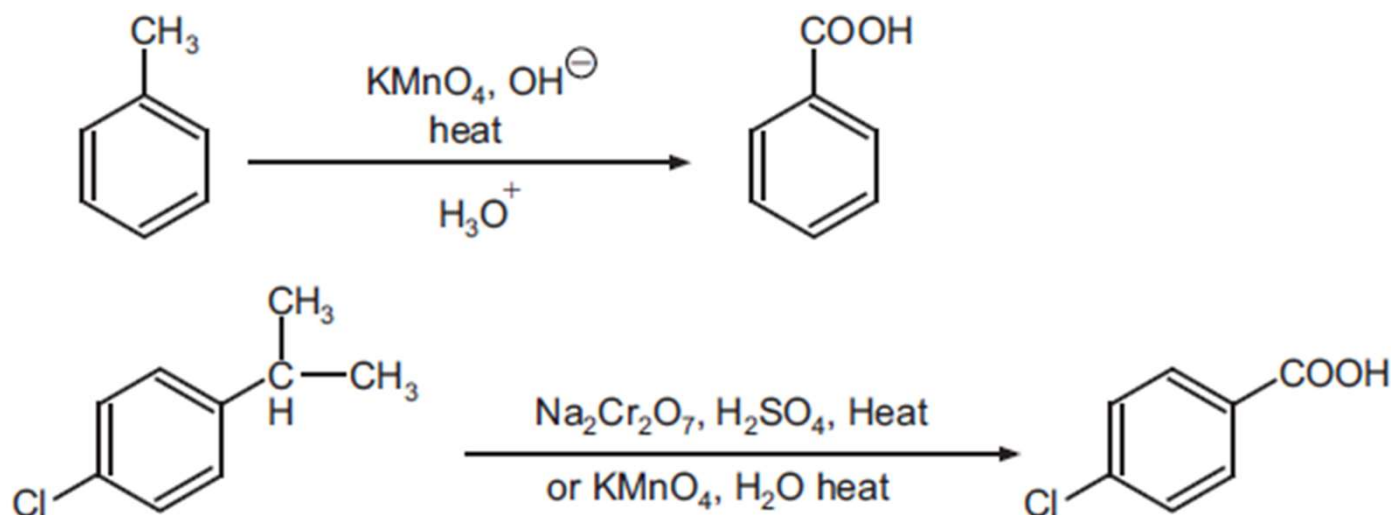
Primary alcohols can be oxidized with KMnO_4 to give carboxylic acids. Aldehydes can also be oxidized to carboxylic acids using mild oxidizing agents such as $\text{Ag}(\text{NH}_4)^+ \text{OH}^-$.

Aromatic aldehydes and primary alcohols are oxidized to carboxylic acids with chromic acid (H_2CrO_4) in aqueous acetone (Jones oxidation). Other reagents like potassium dichromate, potassium permanganate or sodium chlorite also can be used.



2. Oxidation of alkyl benzenes:

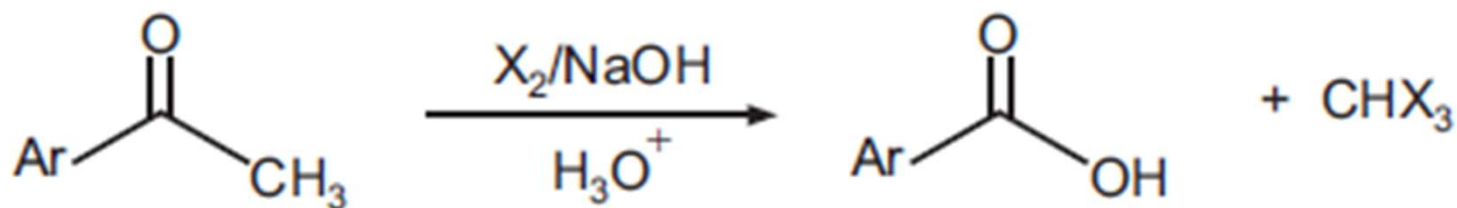
Primary and secondary alkyl groups directly attached to the benzene ring can be oxidized to carboxylic acid. Tertiary groups do not undergo this reaction. The oxidizing agents used are strong ones and ensure complete oxidation to the carboxylic acids.



3. Oxidation of methyl ketones:

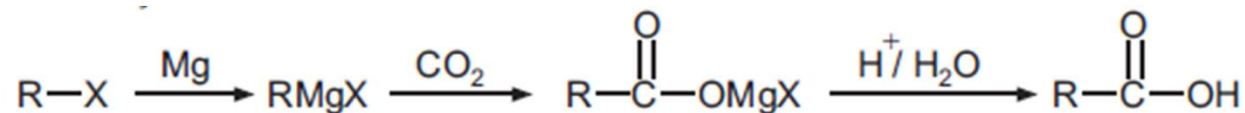
Methyl ketones can be converted to carboxylic acids *via haloform reaction*.

Iodoform, therefore is preferred haloform and the reaction is therefore called as Haloform reaction.

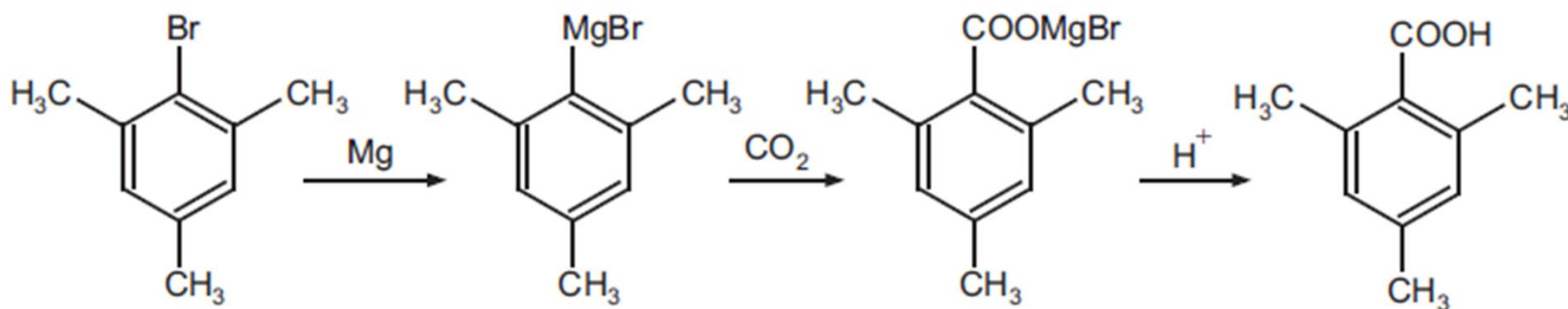
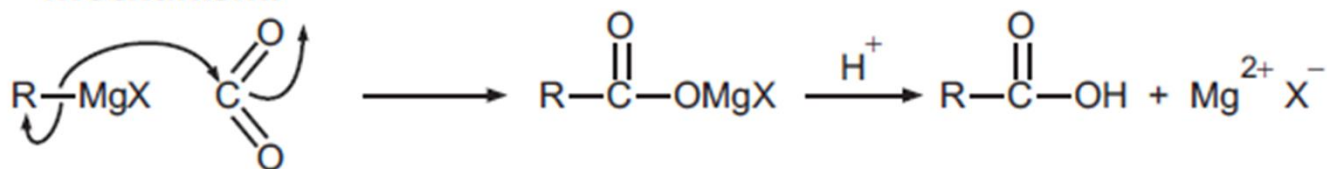


4. Carbonation of Grignard reagent:

Grignard reagent adds to the carbon-oxygen double bond of carbon dioxide to form magnesium salt of the carboxylic acid. This magnesium carboxylate on acidification produces carboxylic acid.



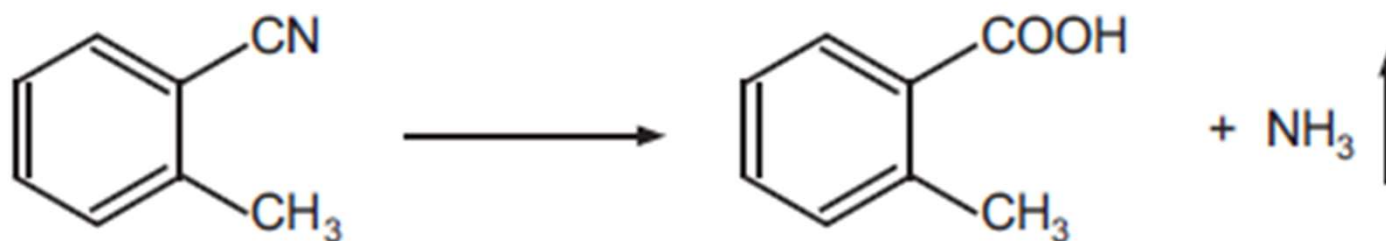
Mechanism:



5. Hydrolysis of nitriles and cyanohydrins:

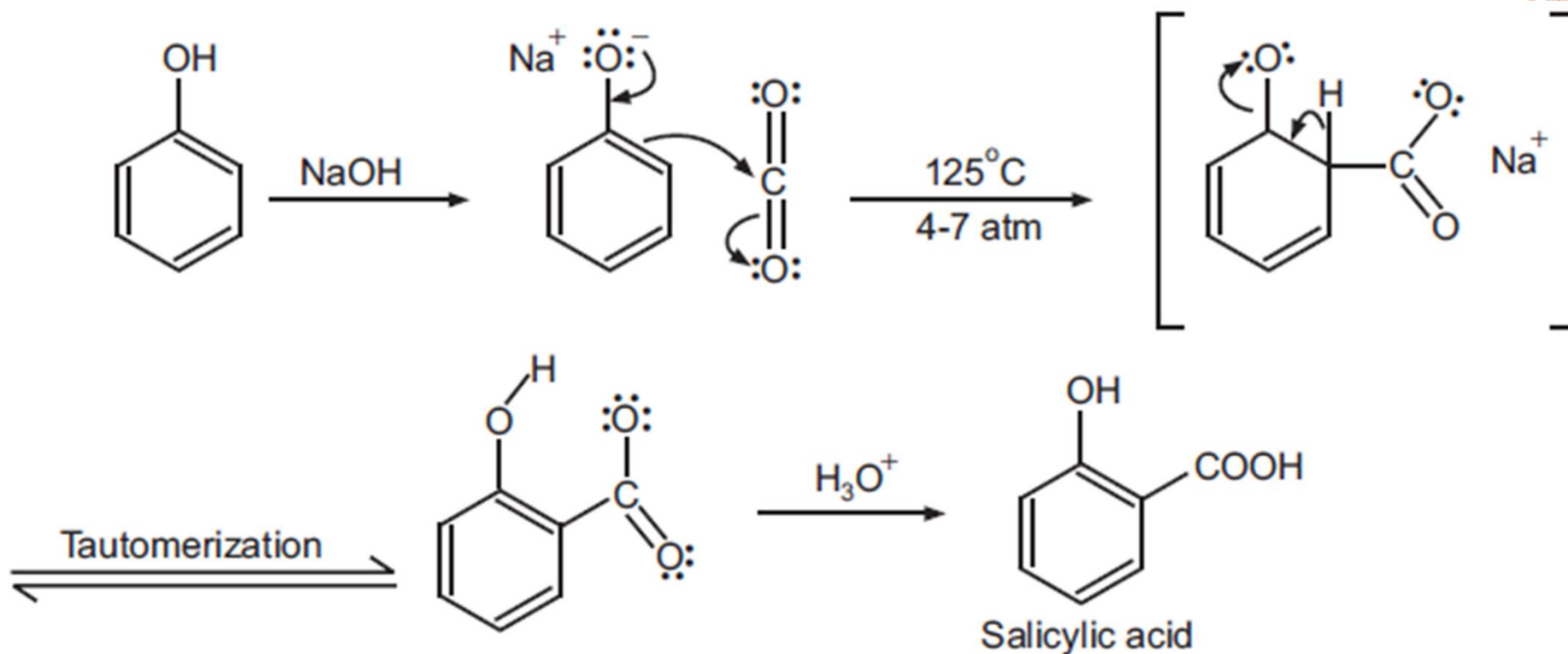
Hydrolysis of nitriles yields carboxylic acid.

Aromatic nitriles are prepared from diazonium salts since, aryl halides are less reactive. These nitriles are hydrolysed to give carboxylic acids.



6. Special methods for phenolic acids:

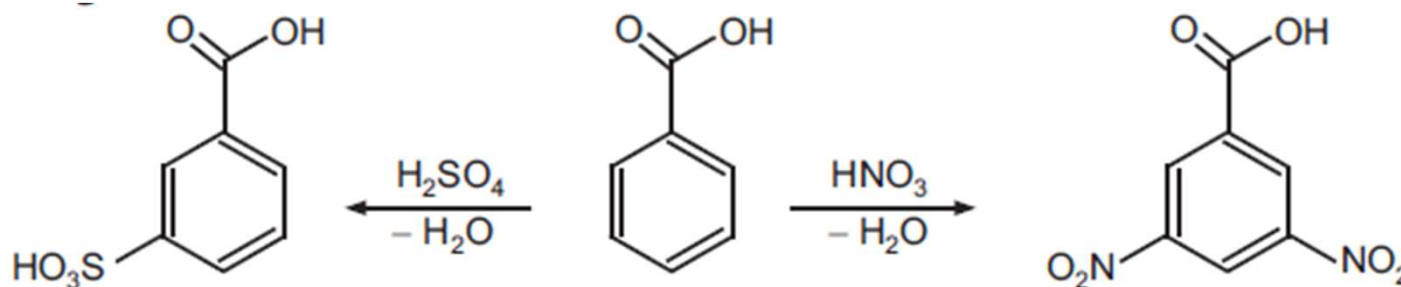
Example: Kolbe Schmidt reaction



IMPORTANT REACTIONS OF BENZOIC ACID

Reactions of benzoic acid can occur at either the **aromatic ring** or the **carboxylic group**.

1. Aromatic ring



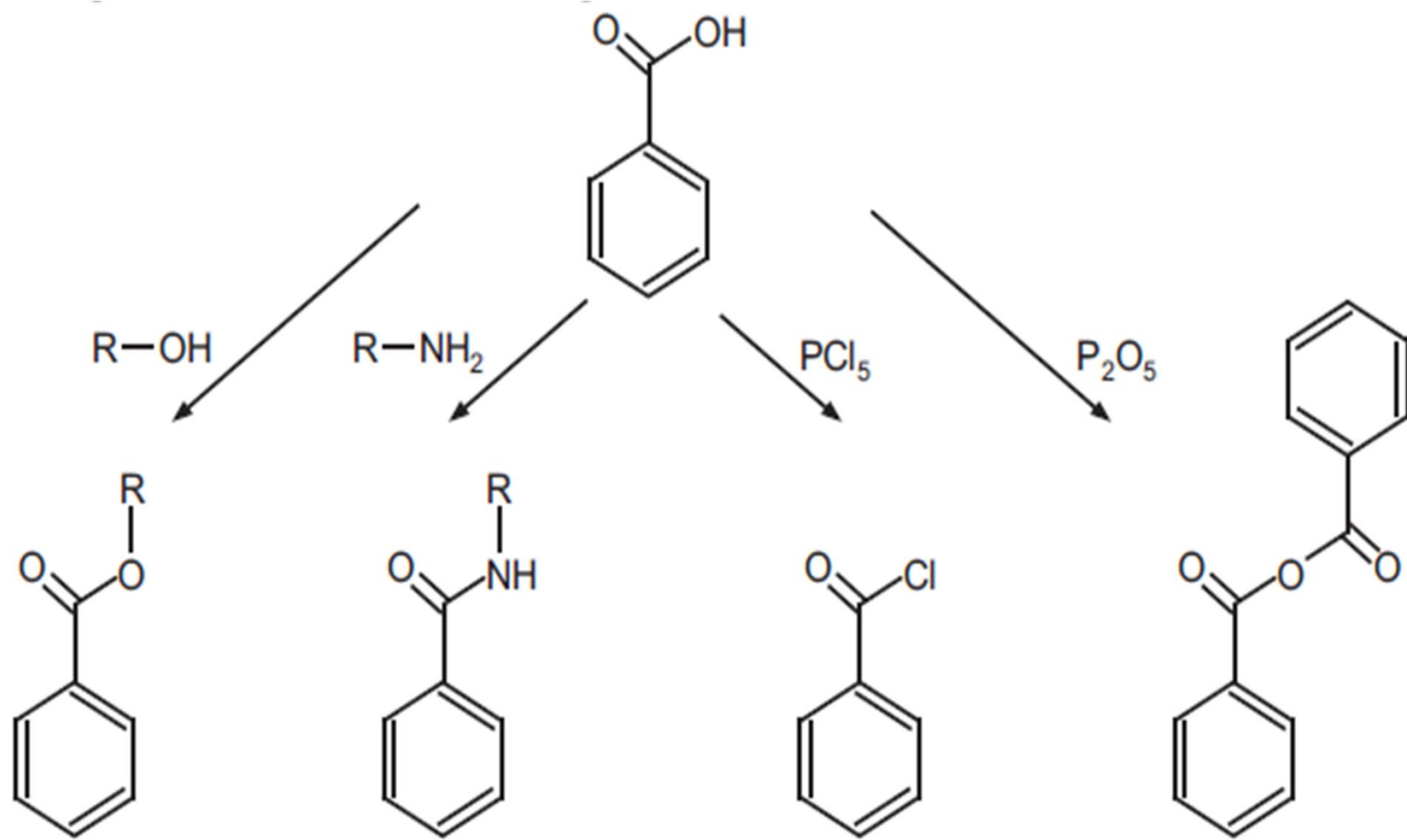
Electrophilic aromatic substitution reaction will take place mainly in the *meta-position* to the electron-withdrawing carboxylic group. The second substitution reaction (on the right) is slower because the first nitro group is deactivating. Conversely, if an activating group (electron-donating) was introduced (e.g., alkyl), a second substitution reaction would occur more readily than the first and the disubstituted product might not accumulate to a significant extent.

2. Carboxylic group

All the reactions mentioned for **carboxylic acids** are also possible for **benzoic acid**.

- ✓ Benzoic acid esters are the product of the acid catalysed reaction with alcohols.
- ✓ Benzoic acid amides are more easily available by using activated acid derivatives (such as benzoyl chloride) or by coupling reagents used in peptide synthesis like DCC and DMAP.
- ✓ The more active benzoic anhydride is formed by dehydration using acetic anhydride or phosphorus pentoxide.

- ✓ Highly reactive acid derivatives such as acid halides are easily obtained by mixing with halogenation agents like phosphorus chlorides or thionyl chloride.
- ✓ Ortho-esters can be obtained by the reaction of alcohols under acidic water free conditions with benzonitrile.
- ✓ The copper catalysed decarboxylation of benzoate to benzene may be effected by heating in quinoline. Alternatively, Hunsdiecker decarboxylation can be achieved by forming the silver salt and heating.



Benzoic acid ester

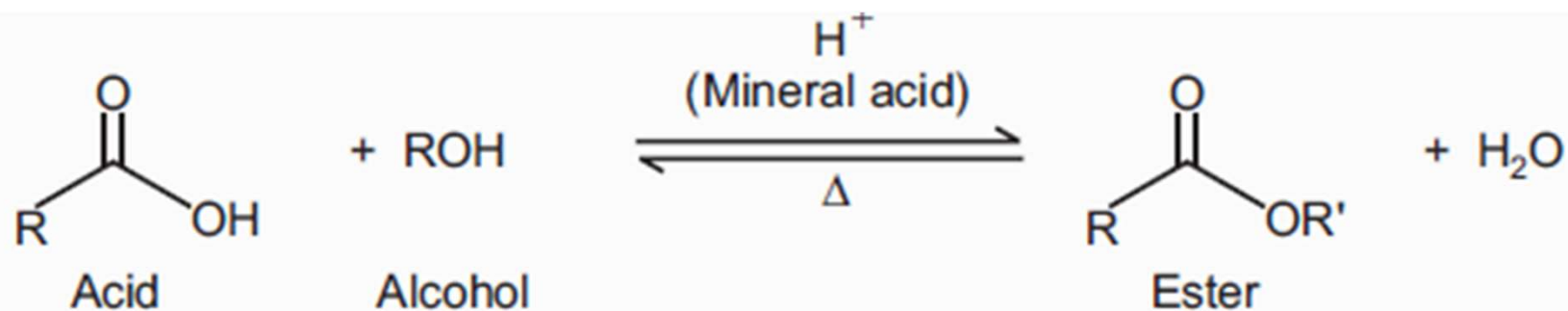
Benzoic acid amide

Benzoyl chloride

Benzoic acid anhydride

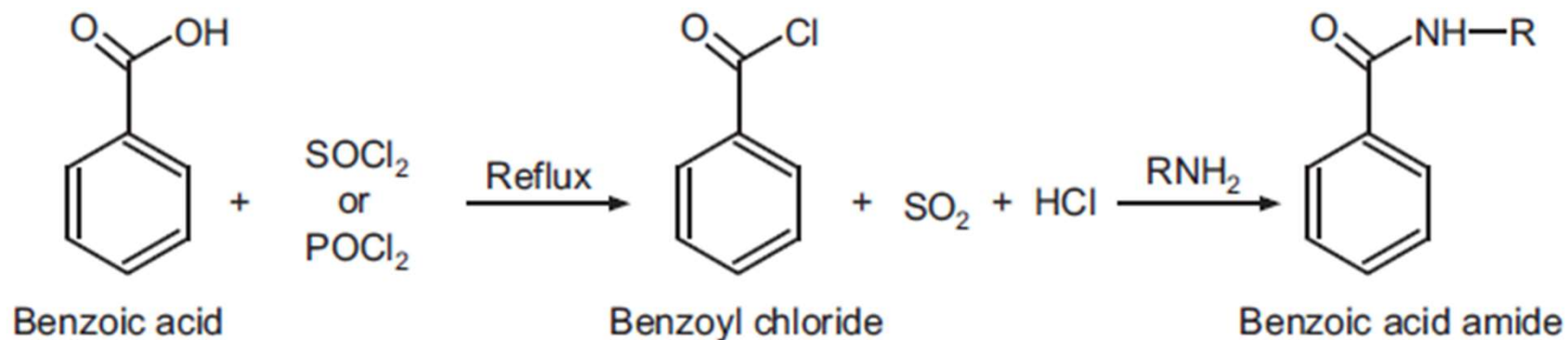
1. Production of Esters

Benzoic acid reacts with alcohols to produce esters. For example, with ethyl alcohol (C₂H₅OH), benzoic acid forms ethyl benzoate, an ester (C₆H₅CO-O-C₂H₅). Some esters of benzoic acid are plasticizers.



2. Production of an Acid Halide

With phosphorus pentachloride (PCl_5) or thionyl chloride (SOCl_2), benzoic acid reacts to form benzoyl chloride ($\text{C}_6\text{H}_5\text{COCl}$), which is classified as an acid (or acyl) halide. Benzoyl chloride is highly reactive and is used to form other products. For example, it reacts with ammonia (NH_3) or an amine (such as methylamine, $\text{CH}_3\text{-NH}_2$) to form an amide (benzamide, $\text{C}_6\text{H}_5\text{CONH}_2$).

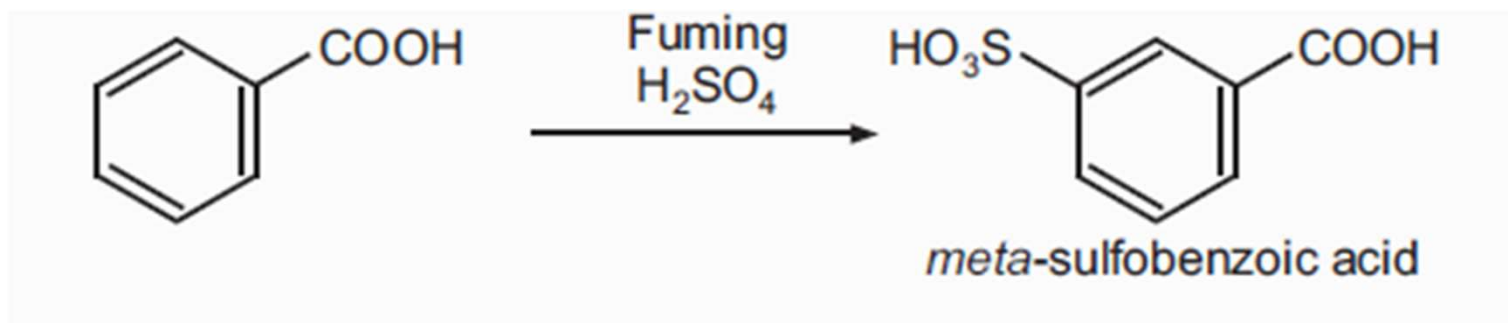


3. Sulfonation

Reaction of benzoic acid with fuming sulfuric acid (H_2SO_4) leads to sulfonation of the aromatic ring, in which the functional group SO_3H replaces a hydrogen atom on the aromatic ring.

The product is mostly *meta-sulfobenzoic acid* ($\text{SO}_3\text{H}-\text{C}_6\text{H}_4-\text{COOH}$).

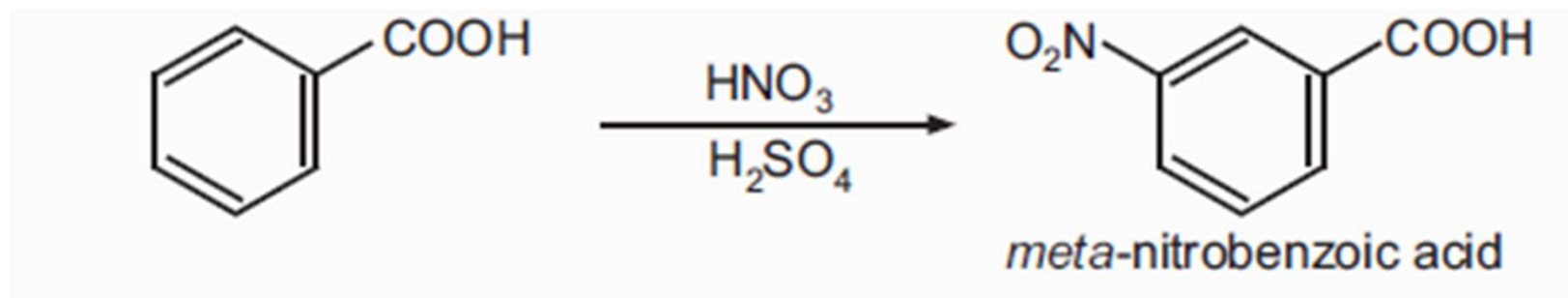
The prefix "meta" indicates that the functional group is attached to the third carbon atom relative to the point of attachment of the carboxyl group.



4. Nitration

Benzoic acid reacts with concentrated nitric acid (HNO_3), in the presence of sulfuric acid as a catalyst, leading to nitration of the ring.

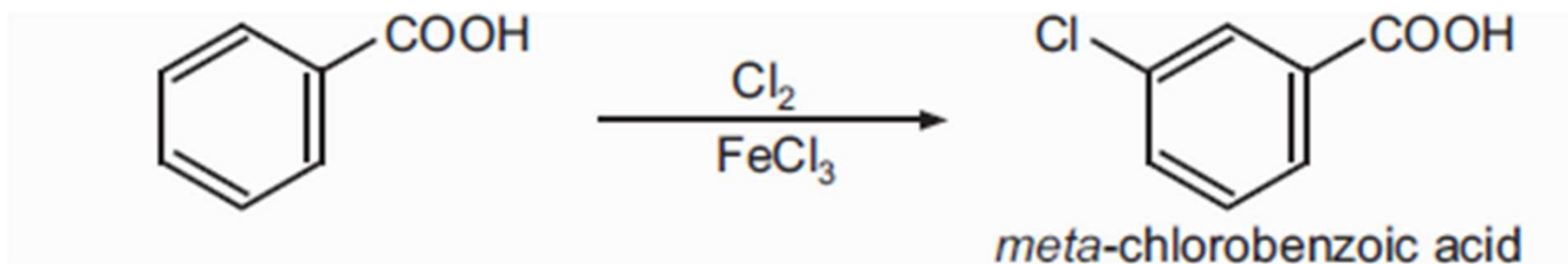
The initial product is mostly *metanitrobenzoic acid* ($\text{NO}_2\text{-C}_6\text{H}_4\text{-COOH}$), in which the functional group NO_2 is attached to the ring at the *meta position relative to the carboxyl group*.



5. Halogenation

In the presence of a catalyst such as ferric chloride (FeCl_3), benzoic acid reacts with a halogen such as chlorine (Cl_2) to form a halogenated molecule such as *metachlorobenzoic acid* ($\text{Cl-C}_6\text{H}_4\text{COOH}$).

In this case, a chlorine atom is attached to the ring at the *meta position relative to the carboxyl group*



6. Conversion to alcohol

Carboxylic acids can be reduced using lithium aluminium hydride to form the corresponding alcohol. An alkoxide intermediate is formed and the alcohol is liberated by hydrolysis. LiAlH_4 is a good reducing agent and gives excellent yield. But it is very costly and hence can be used only for the reduction of small quantities of compounds.

Hence, as an alternative to direct reduction, acids can be converted to alcohols by first converting them to esters and then reducing these esters using various other reagents.

