

6.6: PREPARING CARBOXYLIC ACIDS

OBJECTIVES

After completing this section, you should be able to

- describe in detail the methods of preparing carboxylic acids discussed in previous chapters:
 - the oxidation of alkylbenzenes.
 - the oxidative cleavage of alkenes.
 - the oxidation of primary alcohols and aldehydes.
- discuss, in detail, the hydrolysis of nitriles:
 - write an equation to illustrate the preparation of a carboxylic acid through nucleophilic attack by cyanide ion on an alkyl halide and hydrolysis of the nitrile which results.
 - identify the carboxylic acid formed from the hydrolysis of a given nitrile, or from the reaction of a given alkyl halide with cyanide ion followed by hydrolysis of the resulting nitrile.
 - identify the alkyl halide needed to prepare a given carboxylic acid by the formation and subsequent hydrolysis of a nitrile.
 - identify the reagents needed to convert a given alkyl halide into a carboxylic acid containing one more carbon atom.
- discuss, in detail, the carboxylation of Grignard reagents:
 - write an equation describing the formation of a carboxylic acid from a Grignard reagent.
 - identify the carboxylic acid obtained through the treatment of a given Grignard reagent with carbon dioxide followed by dilute acid.
 - identify the Grignard reagent (or the alkyl halide required to form the Grignard reagent) that must be used to produce a given carboxylic acid by reaction with carbon dioxide.
 - write the detailed mechanism for the formation of a carboxylic acid using a Grignard reagent.

STUDY NOTES

Review the methods of obtaining carboxylic acids presented in earlier sections:

- oxidation of aromatic compounds—Section 16.9.
- oxidative cleavage of alkenes—Section 8.8.
- oxidation of primary alcohols and aldehydes—Sections 17.7 and 19.3.

Carboxylic acids can be prepared using a wide variety of reactions. Many carboxylic acid derivatives such as esters, amides, and anhydrides can undergo hydrolysis to form the parent carboxylic acids. The most common methods for synthesizing carboxylic acids can be separated into three major groups.

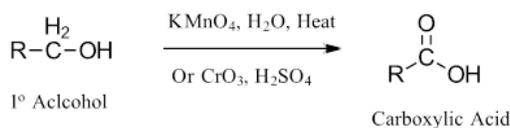
- Oxidations
- Carboxylation of Grignard Reagents
- Hydrolysis of Nitriles

1) FORMING CARBOXYLIC ACIDS THROUGH OXIDATIONS

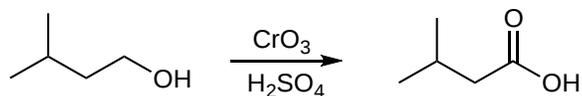
The carbon atom of a carboxyl group has a high **oxidation state**. It is not surprising, therefore, that many of the chemical reactions used for their preparation are oxidations. Such reactions have been discussed in previous sections of this text.

OXIDATION OF 1° ALCOHOLS

The oxidation of 1° alcohols to carboxylic acids can be performed with a wide variety of oxidizing agents including potassium permanganate (KMnO_4) and Jones reagent (CrO_3 & H_2SO_4). One of the main synthetic limitations of alcohol oxidations is that the necessary oxidizing agents often react with other oxidizable functional groups, such as aldehydes, alkyl arenes, and other alcohols. Because alcohols are often readily available this reaction is the most common oxidative reaction for creating simple carboxylic acids.



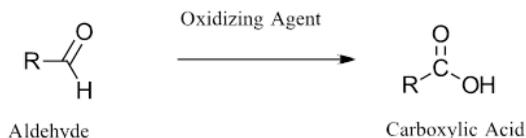
EXAMPLE



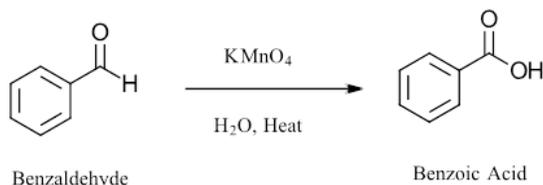
Oxidation of 3-methylbutan-1-ol to 3-methylbutanoic acid

OXIDATION OF ALDEHYDES

In a similar fashion as 1° alcohols, aldehydes are also converted to carboxylic acids using a wide variety of oxidizing agents including potassium permanganate and Jones reagent.



EXAMPLE

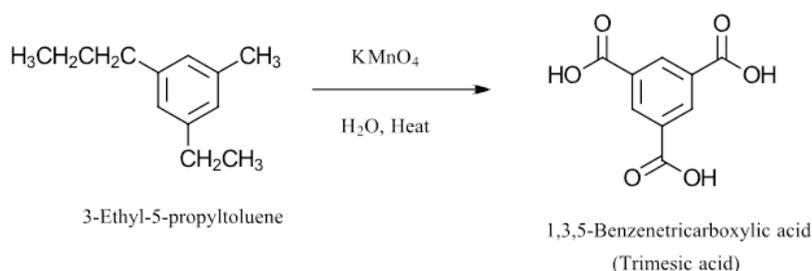


OXIDATION OF ALKYL ARENE SIDE-CHAINS

Primary and secondary carbons directly attached to an aromatic ring can be converted to carboxylic acids by reaction with strong oxidizing agents including potassium permanganate and Jones reagent. Tertiary carbons attached to an aromatic ring are not affected by these reactions. It should be noted that alkyl groups are ortho, para directors and after oxidation the carboxylic acid formed is a meta director.

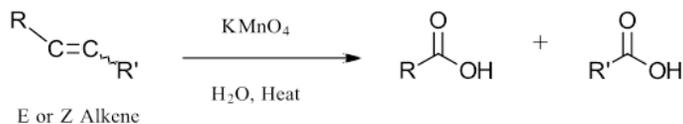


EXAMPLE

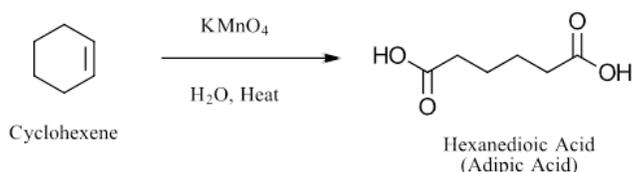


OXIDATIVE CLEAVAGE OF ALKENES

Alkenes can undergo oxidative cleavage to form carboxylic acids by reacting with hot alkaline KMnO_4 .

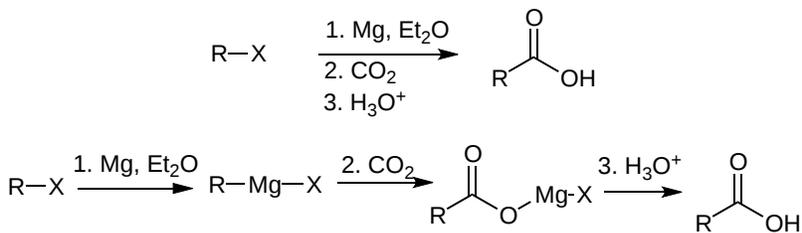


EXAMPLE

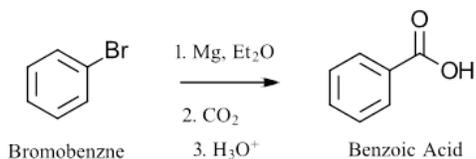


2) CARBOXYLATION OF GRIGNARD REAGENTS

In this method, an electrophilic halide is first transformed into a strongly nucleophilic Grignard reagent. The Grignard reagent adds to the C=O bond of carbon dioxide (an electrophile) to yield the salt of a carboxylic acid called a halomagnesium carboxylate. This intermediate is then treated with a strong aqueous acid to form the carboxylic acid. Most alkyl or aryl halides can be used for this synthesis of carboxylic acids. The main limitation is that no functional groups incompatible with Grignard reagents can be present such as O-H, N-H, S-H, or C=O bonds.

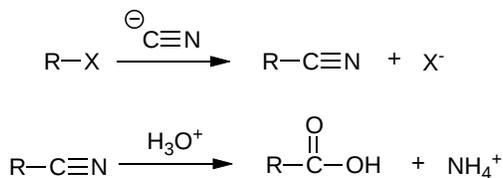


EXAMPLE



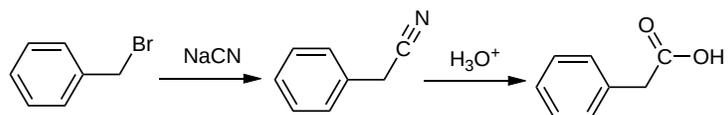
3) HYDROLYSIS OF NITRILES

Hydrolysis of nitriles to carboxylic acids requires two steps. First, an alkyl halide is reacted with a nucleophilic cyanide anion to form a nitrile intermediate by an S_N2 reaction. Subsequent hydrolysis of the nitrile is typically performed by heating with an acidic or basic aqueous solution and uses a mechanism discussed later in this chapter. Due to the requirements of the S_N2 reaction, only primary and secondary alkyl halides may be used for this reaction. Tertiary alkyl halides typically produce an alkene through E2 elimination reaction and aryl halides usually do not react.

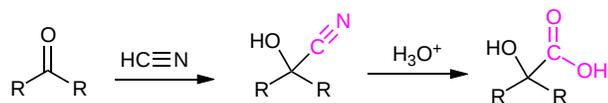


Two steps of nitrile formation and hydrolysis

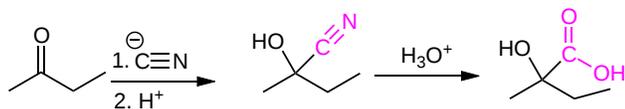
EXAMPLE



Aldehydes and ketones can be converted to cyanohydrins through nucleophilic addition of a cyanide anion to the carbonyl. The -CN group of the cyanohydrin can also be hydrolyzed to form an alpha hydroxy carboxylic acid.



EXAMPLE



conversion of butan-2-one to 2-hydroxy-2-methylbutanoic acid

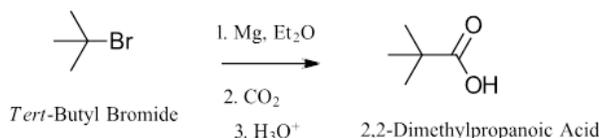
WORKED EXAMPLE: CHOOSING A SYNTHESIS PATHWAY TO A CARBOXYLIC ACID

Thus far this chapter has discussed three main methods for the creation of a carboxylic acid functional group: the oxidation of a 1° alcohol, the carboxylation of a Grignard reagent, and the hydrolysis of a nitrile. Select one of these three methods to perform the following transformation. Briefly explain why the other two methods would be unsuccessful.

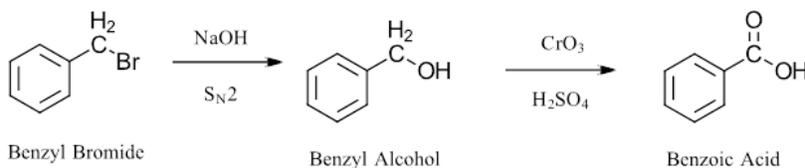
- Tert-Butyl Bromide → 2,2-Dimethylpropanoic acid.
- Benzyl Bromide → Benzoic Acid
- 3-Bromo-1-propanol → 4-Hydroxybutanoic acid

SOLUTIONS

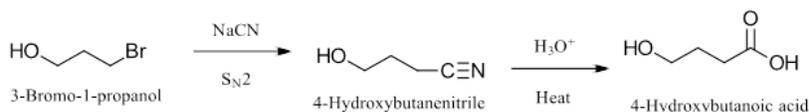
a) The product contains one more carbon than the reactant so the oxidation of a 1° alcohol would be an ineffective method. Also, the reactant contains a tertiary halide, so the S_N2 reaction required to form a nitrile would not be possible. The carboxylation of a Grignard reagent would be the most effective method because it allows for the addition of a carbon, it is not severely affected by the sterics of the tertiary halide, and there are no incompatible functional groups.



b) The product and reactant have the same number of carbons so both the carboxylation of a Grignard reagent and hydrolysis of a nitrile would be ineffective for this conversion. Benzyl bromide is a primary alkyl halide which can easily be converted to a primary alcohol by an S_N2 reaction with NaOH. Once formed, the primary alcohol can be converted to a carboxylic acid using an oxidation reaction.



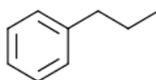
c) The product contains one more carbon than the reactant so the oxidation of a primary alcohol would not be an effective method. Also, the carboxylation of a Grignard reagent would not be an effective method because the presence of an incompatible alcohol functional group in the reactant. The reactant contains a primary halogen which can readily be converted to a nitrile by an S_N2 reaction with NaCN. The resulting nitrile can be converted to a carboxylic acid through hydrolysis.



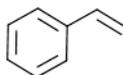
EXERCISES

1) Show how the following molecules can be used to synthesize benzoic acid:

a)



b)

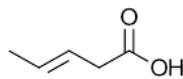


c)

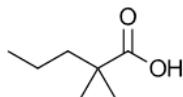


2) Please give the structure of the bromide required to make the following using the carboxylation of a Grignard reagent:

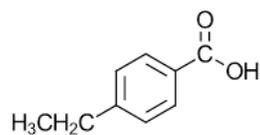
a)



b)

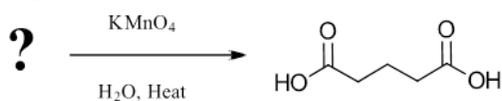


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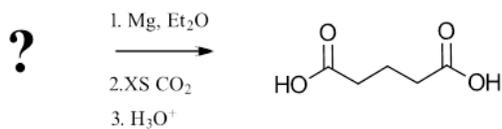


3) Please give the possible reactants for the following reactions:

a) There are at least four possible answers for question a.



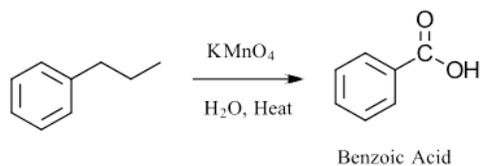
b)



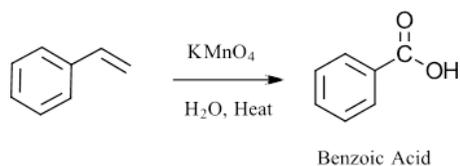
SOLUTIONS

1)

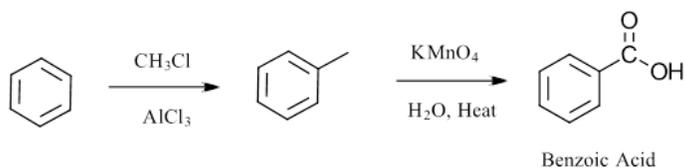
a)



b)

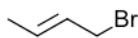


c)

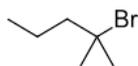


2)

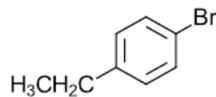
a)



b)

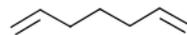
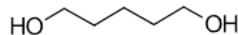
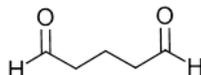


c)

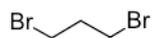


3)

a)



b)



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