# Grignard Synthesis of Benzoic Acid[1]

Organometallic compounds are versatile intermediates in the synthesis of alcohols, carboxylic acids, alkanes, and ketones, and their reactions form the basis of some of the most useful methods in synthetic organic chemistry. They readily attack the carbonyl double bonds of aldehydes, ketones, esters, acyl halides, and carbon dioxide. The use of organometallic reagents can produce the synthesis of highly specific carbon-carbon bonds in excellent yields. Among the most important organometallic reagents are the alkyl- and arylmagnesium halides, which are almost universally called Grignard reagents after the French chemist Victor Grignard, who first realized their tremendous potential in organic synthesis. Their importance in the synthesis of carbon-carbon bonds was recognized immediately after the report of their discovery in 1901. In 1912, Victor Grignard received the Nobel Prize in chemistry for his work on the reaction that bears his name, a carbon-carbon bond-forming reaction by which almost any alcohol may formed from appropriate alkyl halides and carbonyl compounds. The Grignard reagent is easily formed by reaction of an alkyl halide, in particular a bromide, with magnesium metal in anhydrous diethyl ether. Although the reaction can be written and thought of as simply : RBr + Mg = RMgBr. It appears that the structure of the material in solution is rather more complex. There is evidence that dialkylmagnesium is present, that is, 2 R-MgBr = R-Mg-R + MgBr$_2$, and that the magnesium atoms, which have the capacity to accept two electron pairs from donor molecules to achieve a four-coordinated state, are solvated by the unshared pairs of electrons on ether. Grignard reagents, like all organometallic compounds, are substances containing carbonmetal bonds. Because metals are electropositive elements, carbon-metal bonds have a high degree of ionic character, with a good deal of negative charge on the carbon atom. This ionic character gives organometallic compounds a high degree of carbon nucleophilicity.

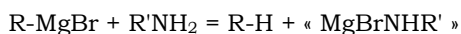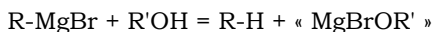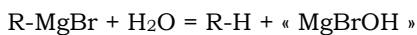$$\overset{-\delta}{R} - \overset{+\delta}{Mg} - \overset{-\delta}{X}$$
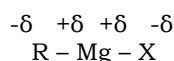
The Grignard reagent is a strong base and a strong nucleophile. As a base, it will react with all protons that are more acidic than those found on alkenes and alkanes.
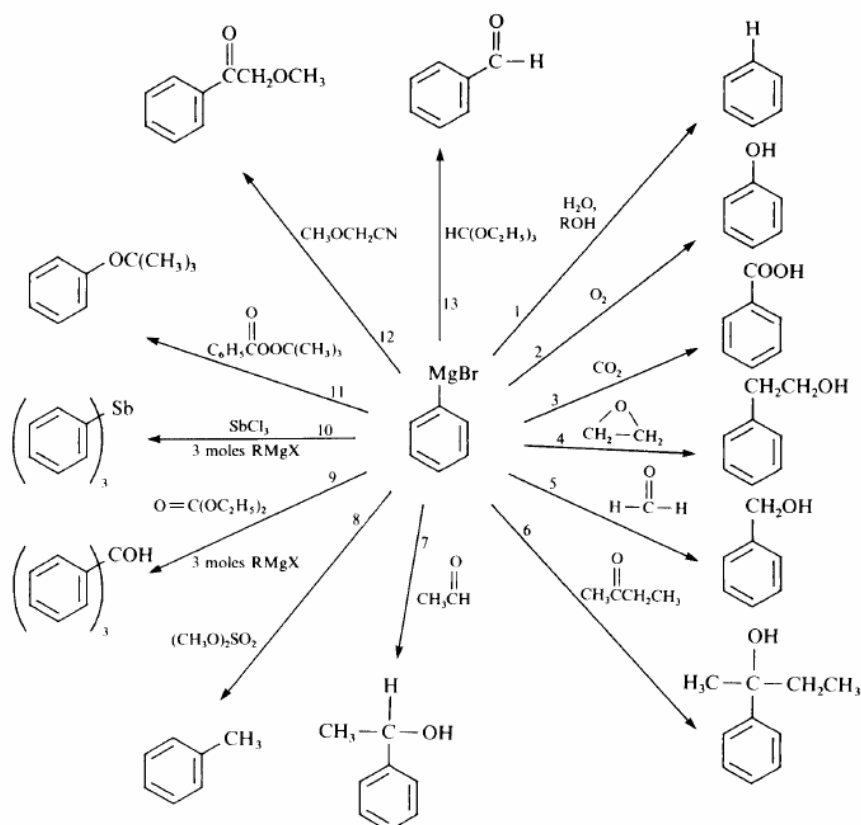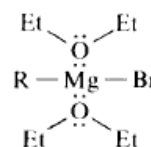
Thus Grignard reagents react readily with water, alcohols, amines, thiols, etc., to regenerate the alkane.

$$R\text{-}MgBr + H_2O = R\text{-}H + \text{« } MgBrOH \text{ »}$$
$$R\text{-}MgBr + R'OH = R\text{-}H + \text{« } MgBrOR' \text{ »}$$
$$R\text{-}MgBr + R'NH_2 = R\text{-}H + \text{« } MgBrNHR' \text{ »}$$

Such reactions are generally undesirable and are referred to as reactions that "kill" the Grignard. In the absence of acidic protons, Grignard reagents undergo a wide variety of nucleophilic addition reactions, especially with compounds containing polar C=O bonds. The resulting carbon-carbon bond formation yields larger and more complex molecules; and because a variety of different organic (R or Ar) groups can be introduced into organic structures, a wide array of organic compounds can be produced. Some reactions of Grignards are shown below. The starting material for preparing the Grignard reagent can contain no acidic protons. The reactants and apparatus must all be completely dry; otherwise, the reaction will not start. If proper precautions are taken, however, the reaction proceeds smoothly. The magnesium metal, in the form of metallic turnings, has a coat of oxide on the outside. A fresh surface can be exposed by gently bending or crimping a the turnings under the absolutely dry ether in the presence of the organic halide with a glass stirring rod. Be careful not to break the stirring rod. Reaction will begin at the exposed surface, as evidenced by a slight turbidity in the solution and evolution of bubbles. Once the exothermic reaction starts, it proceeds easily, the magnesium dissolves, and a solution of the Grignard reagent is formed. The solution is often turbid and gray due to impurities in the magnesium. The reagent is not isolated but is reacted immediately with, most often, an appropriate carbonyl compound, to give, in another exothermic reaction, the magnesium alkoxide. In a simple acid-base reaction this alkoxide is reacted with acidified ice water to give the covalent, ether-soluble alcohol and the ionic water-soluble magnesium salt, Mg^{2+} or $Mg(OH)$ depends on the pH. Formation of a Grignard reagent takes place in a heterogeneous reaction at the surface of solid magnesium metal, and the surface area and reactivity of the magnesium are crucial factors in the rate of the reaction. It is thought that the alkyl or aryl halide reacts with the surface of the metal to produce a carbon-free radical and a magnesium-halogen bond. The free radical R•, then reacts with the •MgX to give the Grignard reagent, RMgX. the Grignard reagent by exposing an unoxidized metallic surface and providing a larger reactive surface area. For an alkyl halide, this procedure will usually be all that is necessary to initiate the reaction quickly; and, in many instances, breaking just one magnesium turning suffices. When an aryl halide is used, grinding a few magnesium turnings and adding a small iodine crystal can promote the heterogeneous reaction at the surface of the magnesium. There is some question about iodine's exact function; it may react with the metal surface to provide a more reactive interface or it may activate the aryl halide. Some of the color changes that one sees are due to the presence of iodine. The proper selection of solvent is crucial in carrying out a

reaction involving a Grignard reagent. Diethyl ether is the most frequently used solvent because it is inexpensive and promotes good yields. The yields of Grignard reagents are highest when a large amount of ether is present and when pure, finely divided magnesium metal is used. The magnesium atom in a Grignard reagent has a coordination number of four. The alkyl magnesium halide already has two covalent bonds to magnesium. The other two sites can be occupied by ether molecules. These complexes are quite soluble in ether. In the absence of the solvent, the reaction of magnesium and the alkyl halide takes place rapidly but soon stops because the surface of the metal becomes coated with the organomagnesium halide. In the presence of a solvent, the surface of the metal is kept clean and the reaction proceeds until all of the limiting reagent is consumed. As indicated earlier, the presence of water or other acids inhibits the initiation of the reaction and destroys the organometallic reagent once it forms. All glassware and reagents must be thoroughly dry before beginning a Grignard experiment. Oven-drying of the glassware is essential when the laboratory atmosphere is humid. When the humidity in the laboratory is low, as it is during the winter heating season, air-drying the glassware overnight will usually be sufficient for macroscale preparations. The glassware for microscale reactions must always be dried in an oven just prior to beginning the reaction because even trace amounts of moisture become significant at this scale. Commercially available anhydrous ether, alkyl halides, and aryl halides are sufficiently pure for most Grignard reactions. Keep the ether container tightly closed except when actually pouring the reagent, and do not let your ether stand in an open container, because water from the air will dissolve into it. The mechanism of the Grignard reaction with aldehydes and ketones is actually quite complex, but it can easily be rationalized as a simple nucleophilic addition reaction. The hydrolysis step is important in a Grignard synthesis. It is common to use an aqueous mineral acid, such as sulfuric or hydrochloric acid, to expedite hydrolysis. Not only does this cause the reaction to go more readily, but Mg(II) is converted from the much less manageable hydroxide or alkoxide salts to water-soluble sulfates or chlorides. For preparing labile products, such as tertiary alcohols, the weaker acid ammonium chloride is an excellent alternative. Strong acids, such as sulfuric acid, may cause tertiary alcohols to dehydrate. The great versatility of this reaction lies in the wide range of reactants that undergo reaction with the Grignard reagent. In the present microscale experiment we shall carry out another common type of Grignard reaction, the formation of a carboxylic acid from 1 mole of the reagent and 1 mol. of carbondioxide. The primary impurity in the present experiment is biphenyl, formed by the reaction of phenylmagnesium bromide with unreacted bromobenzene. The most effective way to lessen this side reaction is said to be to add the bromobenzene slowly to the reaction mixture so that it will react with the magnesium and not be present in high concentration to react with previously formed Grignard reagent. The impurity is easily eliminated, since it is much more soluble in hydrocarbon solvents than benzoic acid.

Experimental. Before you begin this experiment, your apparatus must be thoroughly cleaned and dried with a heat gun. If your Grignard reaction fails to start, you have probably not heeded this advice. The diethyl ether must be anhydrous and the bromobenzene has been dried over calcium chloride. The magnesium is of a very high purity. For this experiment : do not use grease on glass joints, do not add boiling chips and no external heating is needed.

ETHER IS EXTREMELY FLAMMABLE.
NO NAKED FLAME SHOULD BE USED BY YOU OR ANYONE WORKING NEAR YOU.
BE SAFETY CONSCIOUS.
ETHER MUST ON <u>NO ACCOUNT</u> BE POURED DOWN A SINK DRAIN
USE THE ORGANIC WASTE BOTTLE FOR DISPOSAL.

In a 250 mL round-bottom flask place 2.3 g of magnesium metal and possibly a crystal of iodine (iodine reacts with the inactive oxide coating on magnesium metal exposing a fresh surface) and assemble a water condenser vertically (reflux position) on it. Into a clean dry dropping funnel are added 10.0 mL of bromobenzene and 20 mL of anhydrous diethyl ether and the separatory funnel is stoppered and held on a clamp. A gentle stream of water is maintained through the condenser. A drying-tube charged with calcium chloride is fitted on top of the condenser. Watch for development of small bubbles on the Mg surface. The reaction should start within 3-5 minutes and become quite vigorous. To the remaining ether-bromobenzene mixture, add another 30 mL of anhydrous ether (this mixture must be ready at the time the reaction starts) and add this mixture down the condenser in 3-5 mL portions so as to keep the reaction alive and refluxing well. Do not allow the reaction to become too quiescent. Occasionally swirl the flask to help mixing of contents. When the whole mixture of bromobenzene and ether is added and the reaction is over, the ether will stop boiling by itself. However, it is normal to find a few pieces of unreacted magnesium in the flask. Immediately proceed to the next step.

Note: If crushing the magnesium with a glass rod failed to start your reaction, you have at some stage allowed the ingress of moisture. You must dismantle the apparatus and start again – but take proper care to have everything dry. Do not throw any Mg metal or $CaCl_2$ into liquid organic waste containers ! $CaCl_2$ and any waste Mg metal are to be put into the proper SOLID waste containers.

The reaction between phenyl magnesium bromide and carbon dioxide is simply a nucleophilic addition of a phenyl carbanion to the positively polarized carbon atom of CO_2. (The initial product is the MgBr salt of Benzoic acid and the acidification liberates the free acid.) Slowly, add dry-ice (20 g) into the reaction mixture while swirling the flask. When all the dry-ice has disappeared, slowly add 20 mL of diethylether, then 100 g of ice and then 20 mL of dilute hydrochloric acid (5 M) is added and the mixture carefully stirred with a glass rod. Benzoic acid is liberated from its MgBr salt, and dissolves in the ether. Pour the mixture into a separatory funnel, shake well (careful: venting is needed) and allowed to settle. Drain out the lower aqueous layer and discard. Into the separatory funnel containing the ether solution of benzoic acid, add 2 ×30 mL of NaOH at 10%wt and shake well. Draw off the lower alkaline layer into a beaker, and, while stirring vigorously, make it very strongly acidic (pH approx. = 1) by the slow addition of concentrated hydrochloric acid. Cool the solution in an ice bath and collect and collect your product of benzoic acid by suction filtration through a Büchner funnel. Keep it under suction for 15 min. Weight your product, record mass, % yield and melting point. Discard the left over ether phase from separatory funnel into the HALOGENATED waste container at the front fume hood.

Recrystallization. The solubility of benzoic acid in water is 68 g.L^{-1} at 95 °C and 1.7 g.L^{-1} at 0 °C. Dissolve the acid in very hot water. Let the solution cool slowly to room temperature; then cool it in ice for several minutes before collecting the product by vacuum filtration on the Hirsch funnel. Use the ice-cold filtrate in the filter flask to complete the transfer of benzoic acid from the reaction tube. Turn the product out onto a piece of filter paper, squeeze out excess water, and allow it to dry thoroughly. Once dry, weigh it, calculate the percentage yield, and determine the melting point along with the melting point of the crude material. Obtain an IR (KBr pellet) of your product and compare it with a reference IR. Place your product in a neatly labeled vial with your name(s) and submit to your instructor.

Post lab Questions

1. Write the reaction for the preparation of benzoic acid.

2. Why is water so detrimental to a Grignard reaction? Give a balanced equation for the formation of a side product often produced during Grignard reactions using phenyl-magnesium bromide.

3. Fill in the table

Product	Amount recovered (g)	% Yield	Melting point °C	Appearance
Benzoic acid				

4. Compare the observed melting point with that reported in the literature and comment on the purity of the product.

5. In the procedure after the addition of carbon dioxide, 5M HCl was added and the aqueous layer was discarded; then 10%wt. NaOH was added to the reaction and the ether phase discarded and then again HCl was added. What is the purpose of all these acid and base additions? Complete the equations and briefly explain the chemical reactions taking place.

6. The primary impurity in the present experiment is biphenyl. Show how it is produced.

7. Analyze the IR spectrum of benzoic acid which you obtained in the laboratory. Write your peak assignments on the spectrum. Identify the –OH and C=O absorptions, and the absorptions characteristic of an aromatic ring. Attach your spectrum.

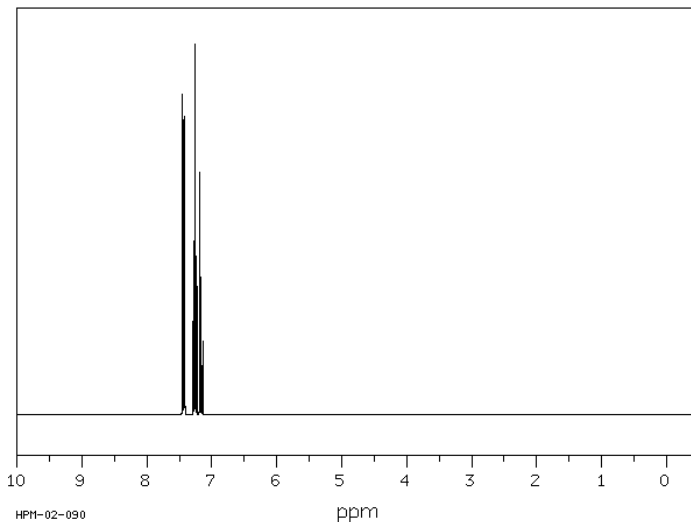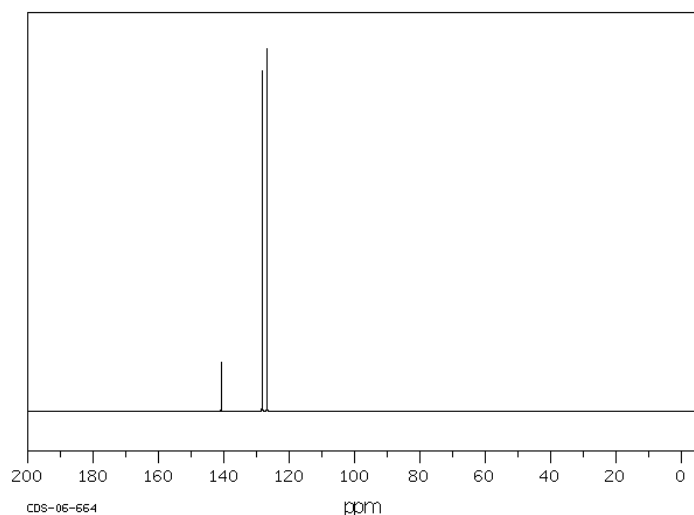8. Analyze the ^{13}C and ^{1}H NMR spectra of benzoic acid.

CDS-04-578
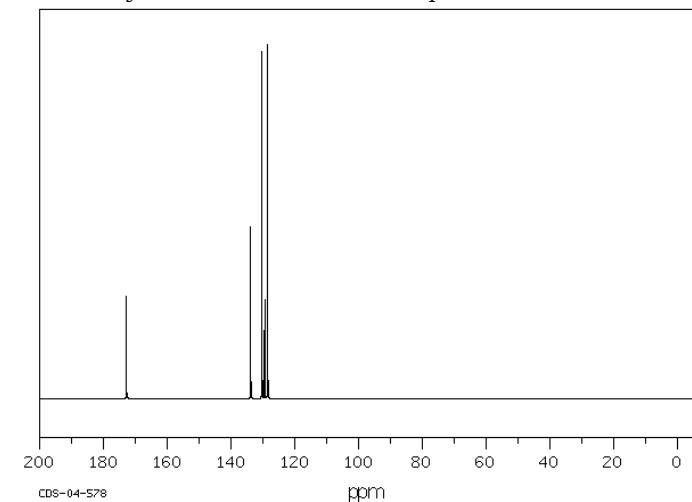
Five signals, in ppm : 172.77 ; 133.83 ; 130.28 ; 129.44 ; 128.49
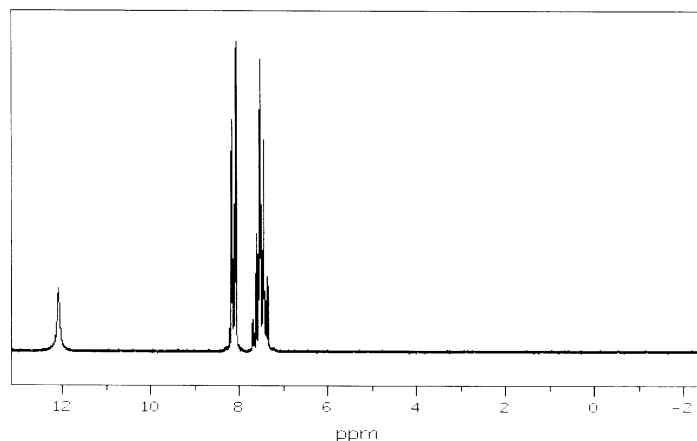
Four signals, in ppm : 12.09 ; 8.12 ; 7.62 ; 7.45.

13. Identify a by-product by the ^1H and ^{13}C NMR spectra.

CDS-06-664   ppm   HPM-02-090   ppm

14. Analyze the mass spectrum of bromobenzene shown below and specifically answering the following.

    14.1. The molecular weight of bromobenzene is 157 amu. Explain the appearance of the m/e 156 and 158 signals of about equal intensity.

    14.2. Suggest a structure for the cation responsible for the m/e 77 signal.

    14.3. Calculate the theoretical height of m/e 78 signal.