Grignard Synthesis of Benzoic Acid

Advanced Preparation: It is imperative that all equipment and reagents be absolutely dry**. One lab period before you plan to run the reaction, you should place the glassware to be used—two reaction tubes, two shorty vials, and a stirring rod—can be dried in a 110 °C oven to dry, along with the magnesium turnings.

Prelab Exercise: Prepare a flow sheet for the preparation of benzoic acid. Through a knowledge of the physical properties of the solvents, reactants, and products, show how the products are purified. Indicate which layer in separations should contain the product.

Introduction

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 be 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

$$\text{RBr + Mg} \rightarrow \text{RMgBr}$$

it appears that the structure of the material in solution is rather more complex. There is evidence that dialkylmagnesium is present, that is,

$$2 \text{R-MgBr} \leftrightarrow \text{R-Mg-R} + \text{MgBr}_2$$

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.

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.

$$\text{R-MgBr + H}_2\text{O} \rightarrow \text{R-H + MgBrOH}$$

$$\text{R-MgBr + R'}\text{OH} \rightarrow \text{R-H + MgBrOR'}$$

$$\text{R-MgBr + R'NH}_2 \rightarrow \text{R-H + MgBrNHR'}$$

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 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, such as

\[
\begin{align*}
R-MgBr^+ & \quad \rightarrow \quad R'-\overset{\text{O}}{C}R'' \\
R^{\prime \prime} & \quad + \quad MgBr^+ \\
\end{align*}
\]

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:

\[
\begin{align*}
R' \overset{\text{O}}{C}R'' & \quad + \quad HCl^- \\
\rightarrow \quad R' \overset{\text{O}}{C}R'' & \quad + \quad MgBrCl \\
\end{align*}
\]

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 carbon dioxide.

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. The synthesis of benzoic acid must be accomplished in one lab period. So plan accordingly!
Cautions: Ether is extremely flammable; do not work with this solvent near flames or strongly heated hot plates or sand baths. Some reagents are added slowly and dropwise to keep exothermic reactions from generating too much heat and boiling over. Ether boils readily at 37°C, the same temperature as your body.

Step 1 – Preparation of Phenylmagnesium Bromide (Phenyl Grignard Reagent)

\[
\text{Bromobenzene} \quad \text{MW 157.02} \\
\text{bp 156 °C} \\
\text{den 1.491} \\
\text{n}^2_{20} \text{D 1.5590}
\]

\[
\text{Magnesium} \quad \text{At. wt 24.31}
\]

\[
\text{Phenylmagnesium bromide} \quad \text{(not isolated, used in situ)}
\]

- **Advance Preparation:** It is imperative that all equipment and reagents be absolutely dry. One lab period before you plan to run the reaction, you should place the glassware to be used-two reaction tubes, two shorty vials, and a stirring rod-can be dried in a 110°C oven to dry, along with the magnesium turnings. **Use anhydrous ether as solvent.** Rinse syringe and needle in dry anhydrous ether. If it appears to be dirty, obtain an unused syringe needle and syringe from stockroom. Alternatively, if the glassware, syringe, septa, and magnesium appear to be perfectly dry, they can be used without special drying. The plastic and rubber-ware should be rinsed with anhydrous ether prior to use. Do not place plastic ware in the oven. New, sealed packages of syringes can be used without prior drying. The ether used throughout this reaction must be absolutely dry (use the anhydrous ether on the hooded shelf in the lab). **Don’t use the ether under your hood.** However, ether extractions of aqueous solutions can be carried out with the wet ether in your hood.

- The container already on the hooded shelf is a 50-mL septum-capped bottle. This method of dispensing the solvent has three advantages: The ether is kept anhydrous, the exposure to oxygen is minimized, and there is little possibility of its catching fire. Ether is extremely flammable; do not work with this solvent near flames.

- To remove ether from a septum-capped bottle, inject a volume of air into the bottle equal to the amount of ether being removed. Pull more ether than needed into the syringe, and then push the excess back into the bottle before removing the syringe. Try not to hold the syringe barrel in your warm hands as this will cause the ether to vaporize and squirt out of the syringe. As the fluid gets lower in the bottle, the short needle may not reach the fluid. In this case, turn the bottle upside down.

- Remove a reaction tube from the oven and immediately cap it with a small white septum (in Organic Lab Equipment Kit). In the operations that follow, keep the tube capped except when it is necessary to open it. After it cools to room temperature, add about 2 mmol (about 50 mg) of magnesium turnings. Record the weight of magnesium used to the nearest milligram. We will make it the limiting reagent by using a 5% molar excess of bromobenzene (about 2.1 mmol.). (See below.)

[Note: If your first attempt at this experiment failed, you can try activating your magnesium with iodine. Add a small crystal of iodine to your dry magnesium metal, close with the septum, and insert a needle through this. **Do not add any ether!** Take the reaction tube and a test tube holder to desk 77 and use the Bunsen burner located there to heat the magnesium iodine mixture until you see iodine vapor rise in the tube. **Allow the reaction tube to cool to room temperature and continue as you did before.**]

- Using a dry syringe, add to the magnesium by injection through the septum 0.5 mL of anhydrous diethyl ether. Your laboratory instructor can demonstrate transfer from the storage container used in your laboratory.

- Into an oven-dried shorty vial weigh about 2.1 mmol (about 330 mg) of dry (stored over molecular sieves) bromobenzene. Using a syringe, add to this vial 0.7 mL anhydrous diethyl ether, and **immediately,** with the same syringe, remove all the solution from the vial. This can be done virtually quantitatively so you do not need to rinse the vial. Immediately cap the empty vial to keep it dry for later use. Inject about 0.1 mL of the bromobenzene-ether mixture into the reaction tube and mix the contents by flicking the tube. Pierce the septum with another needle for pressure relief.
• Once the reaction has started, the bromobenzene-ether solution is added slowly from the syringe. The empty needle is for pressure relief, but if condensation is complete (aided by the damp pipe cleaner), it will not be needed. Once the reaction slows down, stir it with the magnetic stirring bar.

• The reaction will not ordinarily start at this point, so remove the septum, syringe, and empty syringe needle and crimp or bend the magnesium turnings with a dry stirring rod. You can do this easily in the confines of the 10 mm diameter reaction tube while it is placed on a hard surface. There is little danger of poking the stirring rod through the bottom of the tube. Immediately replace the septum, syringe, and empty syringe needle (for pressure relief). The reaction should start within seconds. The formerly clear solution becomes cloudy and soon begins to boil as the magnesium metal reacts with the bromobenzene to form the Grignard reagent, phenylmagnesium bromide.

• If the reaction does not start within 1 min, begin again with completely different, dry equipment (syringe, syringe needle, reaction tube, etc.). Once the Grignard reaction starts, it will continue. To prevent the ether from boiling away, wrap a pipe cleaner around the top part of the reaction tube. Dampen this with water or, if the room temperature is very hot, with alcohol.

• To the refluxing mixture add slowly and dropwise over a period of several minutes the remainder of the solution of bromobenzene in ether at such a rate that the reaction remains under control at all times. After all the bromobenzene solution is added, spontaneous boiling of the diluted mixture may be slow or become slow. At this point, add a 1/2 " magnetic stirring bar to the reaction tube and stir the reaction mixture with a magnetic stirrer. If the rate of reaction is too fast, slow down the stirrer. The reaction is complete when none or a very small quantity of the metal remains. Check to see that the volume of ether has not decreased. If it has, add more anhydrous diethyl ether. The phenylmagnesium bromide will now be converted to benzoic acid. Since the solution of the Grignard reagent deteriorates on standing, the next step should be started at once.
Step 2 - Preparation: Benzoic Acid

- Push one end of your dry 1' x 1/16' teflon tubing through a small white septum (in Organic Lab Equipment Kit) using a toothpick to guide the tubing (ask T.A. for help). Crush a small piece of Dry Ice (solid carbon dioxide found in grey bin at the North end of Lab 215, near the windows) and fill a reaction tube 1/3 full with the crushed dry ice. Place the septum with the tubing through it onto the Dry Ice reaction tube. As the Dry Ice sublimes, \( \text{CO}_2 \) gas will come out of the Teflon tube. Remove the septum from the reaction tube containing the phenyl magnesium bromide solution and inserting the Teflon tube into it. Allow the \( \text{CO}_2 \) gas to bubble through the solution for about 15 min.

- At the end of the 15-min period, hydrolyze the intermediate bromomagnesium carboxylate salt as follows. Cool the tube in ice, and add to it dropwise with vigorous pipet mixing between each drop, 2 mL of 3 N hydrochloric acid. Two homogeneous layers of approximately equal volume should result. Add more ether (it need not and should not be anhydrous since your are adding it to water) to the reaction tube if not. Remove a drop of the ether layer for TLC analysis. Any bubbling seen at the interface or in the lower layer is leftover magnesium reacting with the hydrochloric acid. Remove the aqueous layer, and pipet mix the ether layer with 1 mL of water in order to remove any remaining acid or magnesium salts. Discard the lower water layer. Extract the benzoic acid into a basic aqueous layer by adding to the ether solution 0.7 mL of 3 M sodium hydroxide solution, pipet mixing the layers thoroughly, and withdrawing the aqueous layer, which is placed in a very small beaker or 20-mL vial. The extraction of the ether layer is repeated with another 0.5-mL portion of 3M NaOH and finally with 0.5 mL of water. Now that the basic extraction of the benzoic acid from the ether layer is complete, the ether containing mainly the by-product diphenyl formed during the preparation of the phenylmagnesium bromide, can be discarded.

- The combined aqueous extracts are heated gently and briefly to about 50 °C (You may use a beaker of hot tap water bath or a lab neighbor’s sand bath) to drive off dissolved ether from the aqueous solution and which is then made acidic by the addition of concentrated hydrochloric acid (mix thoroughly before testing with indicator paper). Cool the mixture thoroughly in an ice bath. Collect the benzoic acid on the Hirsch funnel, and wash it with about 1 mL of ice water while on the funnel. A few crystals of this crude material are saved for a melting-point determination, and the remainder of the product is recrystallized from boiling water.

- The solubility of benzoic acid in water is 68 g/L at 95 °C and 1.7 g/L 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.

**Product Analysis:** Analyze sample according to Assignment sheet and instructions on Sample Preparation in Lab Guide.

**Cleaning Up:** Combine all aqueous layers, dilute with a large quantity of water, and flush the slightly acidic solution down the drain.

**Post lab Questions**

1. Suggest an alternate synthesis that can be used to make benzoic acid from readily available starting materials.
2. In the synthesis of benzoic acid, benzene is often detected as an impurity. How does this come about?
3. If the ethyl ether used in the Grignard reaction is wet, what byproduct would be formed?
Synthetic Experiment PreLab Grading Sheet

Name(s): ____________________________

TA: ________________________________

Date: ________________________________

PreLab For Exp't #: **101**

**Title: Grignard Synthesis of Benzoic Acid**

<table>
<thead>
<tr>
<th>Date, Name, Desk #, Experiment # &amp; Title(abbreviated after 1st pg), Section &amp; TA Name</th>
<th>Possible Points</th>
<th>Missed Points</th>
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<td>Completeness of Chemical Data Table(s)</td>
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<tr>
<td>PreLab Exercise</td>
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<tr>
<td>Spectral Features Comparison (IR, NMR)</td>
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<tr>
<td>Work-up - Explanation of the product isolation and purification process</td>
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Date Handed in: ________________

General Comments: ____________________________

**Total Points:** ______
# Synthetic Experiment Final Report Grading Sheet

Name: ____________________________

TA: ______________________________

Date: ______________________________

Final Report For Exp't #: **101**

**Title: Grignard Synthesis of Benzoic Acid**

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<tr>
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<tr>
<td>Data: Weighing data, molecular weights, moles, density, volumes, analysis conditions. (Examples: IR - KBr weight; NMR solvent)</td>
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<td>Purity: Give melting point (pure and impure) or other indicators of purity.</td>
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<th><strong>RESULTS AND DISCUSSION</strong> - Overall organization, readability, completeness</th>
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<td>Assignment and discussion of all major IR or NMR peaks in terms of proving the correct product was formed.</td>
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See Lab Guide Chapter 3, Section 3.4 for guidelines in annotating spectra and Ch 11 for help with interpretation.

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<th><strong>POSTLAB QUESTIONS</strong></th>
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Date Handed in: _______________________

General Comments: _______________________

**Total Points:** ______