Expt 5: Synthesis of Benzoic Acid Using the Grignard Reaction

INTRODUCTION

The Grignard reaction is one of the most general methods for carbon-carbon bond formation in all of organic chemistry. In the first stage of this procedure, an organic halide reacts with magnesium metal to form an organomagnesium compound, which is known as a Grignard reagent. It is important to recognize that this is yet another example of an organic redox reaction. More specifically, the carbon atom that was initially bonded to the halide is reduced by two electrons, and the magnesium is oxidized by two electrons. Even though the magnesium formally "inserts" into the carbon-halogen bond, this is actually a stepwise process, as shown below:

In the first step, a single electron is transferred from magnesium metal to the organic halide (in this case, bromobenzene). This results in the formation of a radical anion: this intermediate is a radical (because it contains an unpaired electron) and an anion (since the electron gives it a net negative charge). After transferring a single electron, the magnesium ion is in an unstable +1 oxidation state, and so it combines with the carbon radical to form the organomagnesium (Grignard) reagent. Note that the formation of the magnesium-carbon bond could occur either by direct radical combination or via electron transfer; in either case the magnesium atom in the Grignard reagent attains the preferred +2 oxidation state; Moreover, since formation of the Grignard reagent occurs through radical intermediates, by-products arising from radical coupling are sometimes observed.

By forming the Grignard reagent, we have effectively reversed the polarity of the bond to carbon. Since carbon has a higher electronegativity than the metal magnesium, the C-Mg sigma bond is highly polarized, placing a partial negative charge on carbon. As a result, Grignard reagents act as carbanion equivalents, and they are both strong nucleophiles and strong bases. This means that great care must be taken to exclude even relatively weak acids (such as water or alcohols) from the reaction mixture in order to avoid the formation of by-products arising from proton transfer.
Grignard reagents are almost always synthesized in ethereal solvents such as diethyl ether or tetrahydrofuran (THF) for two very important reasons: (1) ethers do not generally react with Grignard reagents (i.e. they are stable to strong bases and nucleophiles) and (2) the lone pairs on oxygen help to stabilize the partial positive charge on magnesium and facilitate formation of the Grignard reagent.

Once formed, Grignard reagents can react with a wide variety of carbonyl-containing compounds to form new carbon-carbon bonds in a general process known as nucleophilic addition. The C=O bond is highly polarized, making carbonyl compounds electrophilic at carbon. If the Grignard reagent reacts with an aldehyde, ketone or ester, the ultimate product is an alcohol. However, Grignard reagents can also react with one of the carbonyl groups in carbon dioxide (CO₂) to form carboxylic acids, as shown below:

One way to carry out this reaction is to bubble carbon dioxide gas into a solution of the Grignard reagent. However a more convenient alternative is to simply pour the Grignard reagent onto dry ice (solid CO₂). The immediate product of nucleophilic addition is actually a magnesium carboxylate, i.e. the magnesium salt of a carboxylic acid. In order to obtain the desired carboxylic acid, this intermediate must be treated with a strong acid, such as aqueous HCl, during the work-up process. The addition of acid also serves to decompose any residual magnesium metal and causes the resulting magnesium salts to dissolve in the aqueous layer, to facilitate purification.

**EXPERIMENTAL OVERVIEW:**

In this experiment, you will prepare the Grignard reagent phenyl magnesium bromide and use it to synthesize benzoic acid in a carboxylation reaction. The overall reaction scheme is shown below:
It is extremely important that all of the glassware used in this experiment is dry. In an effort to remove as much water as possible, you will be using equipment that has been pre-dried in an oven.

After acidification of the crude mixture at the end of the reaction, the benzoic acid in the organic layer may be contaminated with unreacted bromobenzene and other organic by-products. Therefore, we will use the acid/base properties of benzoic acid to separate it from these organic by-products in a technique known as liquid/liquid extraction. More specifically, deprotonating benzoic acid forms a water-soluble carboxylate anion, leaving the other organic by-products in the organic layer. Subsequent isolation and acidification of the aqueous layer re-precipitates the benzoic acid, which can then be isolated by vacuum filtration. The residual impurities in the organic layer will then be analyzed and identified using gas chromatography/mass spectrometry (GC/MS). Finally, you will record the mass, melting point range and infrared spectrum of your benzoic acid during the next lab period.

**REAGENT/PRODUCT TABLE:**

<table>
<thead>
<tr>
<th>Reagents</th>
<th>MW (g/mol)</th>
<th>MP (°C)</th>
<th>BP (°C)</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>bromobenzene</td>
<td>157.01</td>
<td>-31</td>
<td>156</td>
<td>1.491</td>
</tr>
<tr>
<td>magnesium</td>
<td>24.31</td>
<td>648</td>
<td>1090</td>
<td></td>
</tr>
<tr>
<td>carbon dioxide (dry ice)</td>
<td>44.01</td>
<td>-78.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diethyl ether</td>
<td>74.12</td>
<td>-116</td>
<td>34.6</td>
<td>0.706</td>
</tr>
<tr>
<td><strong>Products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>benzoic acid</td>
<td>122.12</td>
<td>122-123</td>
<td>249</td>
<td></td>
</tr>
</tbody>
</table>

**FOR YOUR SAFETY:**

1. Wear gloves when handling bromobenzene and benzoic acid
2. Diethyl ether is volatile and highly flammable; try to keep all vials and containers capped.
3. Phenyl magnesium bromide is a strong nucleophile and a strong base. It reacts vigorously with water, so be sure to wear gloves when pouring it onto the dry ice.
EXPERIMENTAL PROCEDURE:

PART I: Preparation of Phenyl Magnesium Bromide

1. Obtain the following items that have been pre-dried in an oven for you: 1 small sample vial and cap, 1 large sample vial and cap, one 5" Pasteur pipette, one Claisen adapter, and one 5 mL conical vial without cap containing a spin vane.

2. Measure out approximately 75 mg of magnesium turnings using the tweezers provided and record this mass in your notebook. Transfer the magnesium turning to the 5 mL conical vial containing the spin vane.

3. Obtain a drying tube packed with indicating silica gel desiccant pellets, and set up the apparatus as described in Section A.5 of Appendix A and shown in Figure A.5A. Place the vial in the aluminum block on the stirring hot plate.

4. Take the large, dry sample vial to your instructor who will fill it about two-thirds full of anhydrous ether. Tightly cap it, and label it as “ether vial”.

5. For use in Step 7, clean the syringe in the Microscale Kit by drawing several portions of acetone into it (with needle attached). Carefully remove the plunger and place the barrel end of the syringe over the heavy-walled tubing attached to the house vacuum, and pull air through the syringe for a minute to remove the acetone. Carefully reinsert the plunger.

6. Pre-weigh the small dry sample vial, with cap, that was dried in the oven. Place 0.34 mL of bromobenzene (density = 1.491 g/mL) and then reweigh to determine the mass of bromobenzene that have added. Using the pre-dried Pasteur pipette, add ~2 mL of anhydrous ether to this vial from the “ether vial”, cap it, and shake it gently to dissolve the bromobenzene in the ether. If you wish to, you may label this small vial as "bromobenzene-ether." (It will be used immediately in the next step though.)

7. Using the clean, dry syringe (Step 5a), transfer all the bromobenzene-ether mixture to the conical vial containing the Mg turnings. This may be done by drawing the bromobenzene-ether mixture into the syringe, inserting the needle through the rubber septum on the reaction apparatus, and injecting the mixture. It will be necessary to refill the syringe several times to get all the bromobenzene-ether mixture into the conical vial, and this should be done as quickly as possible.

8. Turn on the magnetic stirrer (setting 5-6, no heat), and stir the mixture gently. The reaction has started when the solution turns light yellow (or darker) color; another indication that the reaction has started is the formation of a brownish-gray, cloudy solution and sometimes even a trace of white precipitate (magnesium hydroxide). If none of these changes are observed after 5-10 min, consult your instructor. [Side Note: it may be necessary to add iodine to your reaction to facilitate the formation of the Grignard. If this is done, then you will see an
immediate color change to a deep red (from the iodine) that will fade to a white color. After this, the usual Grignard observations should occur.

9. As soon as the reaction has started (gold-yellow stage of Grignard formation), use the syringe from your kit and add about 1 mL of ether\(^1\) from the “ether vial” to the conical vial. If the reaction becomes too vigorous, as evidenced by vigorous boiling, you should place the conical vial in a beaker of cold tap water until the boiling has subsided some but do not cool it until the boiling stops. [Side Note: this has never been an issue with microscale Grignard reactions.] The volume of the reaction mixture should be about 4 mL that can be estimated from the volume markings on the conical vial. If not, add more ether from the “ether vial” to the reaction mixture using the syringe so the volume is at least 4 mL.

10. Allow the reaction mixture to stir for an additional 5-10 min, during which time most or all of the magnesium metal should be gone. Any residual Mg metal will be dissolved when HCl is added in Step 11.

**Carboxylation of Phenyl Magnesium Bromide; Hydrolysis of Reaction Mixture**

11. Allow the reaction mixture to cool to room temperature. Take a clean, dry 30- or 50-mL small beaker to your instructor to get Dry-ice. Do not weigh the Dry-ice, as you will be given an excess of it. Remove the conical vial from the rest of apparatus attached to it, and immediately carefully pour its contents onto the Dry-Ice. (Be prepared – this Grignard reagent is a strong nucleophile and a reactive electrophile – the force of this carboxylation reaction will surprise you.) Rinse the conical vial with about 1-mL of anhydrous ether and add it to the beaker.

12. Hydrolyze the reaction mixture by slowly adding about 3 mL of 6\(M\) HCl to the beaker, swirling to remove the remnants of Dry-ice. The beaker will be very cold and may need to warm back to room temperature to dissolve all the unreacted Dry-ice. Add an additional 8-10 mL of ether to beaker, and stir the mixture with a stirring rod. You should now have two distinct layers—an aqueous layer containing inorganic salts and HCl, and an ether layer containing benzoic acid and neutral organic compounds. Both layers should be clear, although the ether layer is typically light yellow in color. If any solid is present, add an additional 2-mL of 6\(M\) HCl and stir again.

\(^1\)For adding this 1-mL of ether, you may use the syringe without cleaning and drying it.
13. Pour the contents of the beaker into a clean large sample vial from your locker. To rinse the beaker, add 1-2 mL of ether to the beaker, swirl it, and transfer it to the vial.

**Isolation of Benzoic Acid**

14. Turn on the hot plate to a setting of about 4 for use later.

15. Cap the vial (from Step 13) and invert it gently several times to mix the layers. Vent several times by loosening and re-tightening the cap.

16. Allow the layers to separate. Remove the lower aqueous layer with a pipette, and leave the upper ether layer in the vial. The separation will require you to hold the vial at a slight angle to aid in removal of the entire lower layer. Put the aqueous layer in a small beaker (mark it as “acid layer”) but don’t discard any layers until you are certain you have obtained benzoic acid.

17. Add about 4 mL of 5% NaOH solution to the organic ether layer in the vial, cap it, and shake it gently; vent it several times by loosening and re-tightening the cap. Allow the layers to separate, and remove the lower aqueous layer with a pipette. Save this layer in a different 30- or 50- mL beaker labeled “basic layer-product”.

18. Repeat Step 17 two more times, each with 4 mL portions of 5% NaOH. Combine all the basic NaOH extracts from the bottom layers in the same beaker. Save the upper ether layer remaining in the vial and label it “ether layer”.

19. Add a small scoop of decolorizing charcoal to the beaker containing the basic NaOH layers and heat it gently on the hot plate, with stirring or swirling, for about 2 minutes to remove traces of ether dissolved in the aqueous layer. The solution should not boil, although the bubbles of escaping ether fumes will be observed initially.

20. Using a glass funnel and fluted filter paper, gravity filter the contents of the beaker containing the decolorized solution into another clean, small beaker. Add about 2 mL of water to this beaker that contained the NaOH layers from Step 19, swirl around, rinsing the inside of the beaker as best as possible. Pour this through the filter paper as well. The filter funnel does not have to be pre-warmed because the product is contained in solution as its water-soluble sodium salt and thus will not crystallize in the funnel.

21. Cool the beaker containing the filtrate from Step 20 to room temperature by placing it on the bench for a couple minutes. With stirring, add about 4 mL of 6 M HCl to the beaker. This converts sodium benzoate into benzoic acid, and you should observe the formation of a white precipitate of benzoic acid. Use pH paper to determine that the solution is pH ~ 1. (Check the pH by adding a drop of solution on the tip of a stirring to a piece of pH paper. DO NOT dip the pH paper in the
solution.) If the solution is not pH 1, add HCl drop wise and with stirring until the solution is the proper acidity.

22. Cool the beaker in an ice-water bath. Collect the benzoic acid by vacuum filtration on a Hirsch funnel (Section A.2, Figure A.2). Add 1 mL of ice water to the beaker, swirl to rinse, and pour over the solid on the funnel. Repeat with an additional 1 mL portion of ice-water. Support the Hirsch funnel in a beaker and allow it to dry in your locker until the next lab period.

23. Transfer the dry benzoic acid to a dry, pre-weighed sample vial, and determine the weight and percent yield of the product. Determine the MP range (reported MP of benzoic acid: 122°C) and hand in the product in properly labeled vial.

PREPARATION OF ETHER LAYER FOR ANALYSIS OF ORGANIC BY-PRODUCTS (TLC AND/OR GC/MS)

24. Add a small amount of anhydrous magnesium sulfate to the vial labeled “ether layer” and gently swirl the solution. Continue adding small amounts of magnesium sulfate until some of it is free-flowing. When the ether layer is sufficiently dried, it should be completely clear.

25. Remove the drying agent using the technique of gravity filtration (fluted filter paper and clean, dry glass funnel), and collect the filtrate in a clean and dry sample vial. Label the vial “dried ether layer” along with your name and course section number.

26. If asked to, fill the GC vial that has been provided for you at least half full with a sample of the dried ether layer and submit this GC vial to your instructor for GC/MS analysis. You will receive a GC printout and mass spectra for each of the organic by-products during the next lab period.

27. Store the vial that contains the remainder of your ether layer in your drawer for TLC analysis in the next lab period. Make sure that the vial is tightly capped so the ether does not evaporate.

WASTE DISPOSAL

1. Place the acid layer from Step 16, any unused acid from Step 16 and the filtrate from Step 21 in the “aqueous acid waste” bottle.

2. Dispose of any excess ether in the “organic waste” container.

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2If instructed to do so, the benzoic acid may be recrystallized from a minimum volume of hot water.
Part II: THIN-LAYER CHROMATOGRAPHY OF THE ETHER LAYER

In CHEM 331, we analyzed a mixture of compounds by Thin Layer Chromatography (TLC). You should re-read your lab procedure from that chromatography experiment and the relevant chapters in Zubrick (Ch. 27 and 28) before doing this part of the experiment (TLC notes posted online, as well). An important difference in this lab is that the compounds we are trying to analyze are colorless and so cannot be seen if we just look at the TLC plate. In fact, many common organic substances are white solids and so this is not an unusual problem. There are various ways to “visualize” colorless compounds, including chemical staining methods. The simplest technique using TLC plates in which the silica stationary phase contains a fluorescent indicator molecule. Fluorescence is observed when molecules emit light after absorbing light of the higher energy. In this case, when UV radiation (254 nm) is used to illuminate the TLC plate, the stationary phase fluoresces visible light of a yellow-green color. If there is a compound absorbed onto the stationary phase, it (usually) suppressed (or quenches) the fluorescence and therefore appears as a dark spot against the bright background. Certain organic molecules, not the ones in this lab, also display fluorescence and so may appear as bright spots against the background.

We can therefore mark the position of the spot on the plate with a pencil when illuminated and analyze the TLC plate as we did previously.

We will analyze our ether layer for the presence of biphenyl and bromobenzene by TLC. Biphenyl is a by-product of the Grignard formation (caused by a radical termination step during the formation of the Grignard reagent) and bromobenzene could be present if the Grignard formation did not go to completion. We are unable to analyze for benzene (formed if any acidic protons are present during Grignard formation) because it is too volatile and evaporates quickly. This is general feature of TLC that volatile liquid compounds cannot be observed. Each TLC plate will be run with standards spotted on your plate along with your ether layer. Standard solutions of both biphenyl and bromobenzene will be provided for you. You will develop the TLC plate using petroleum ether as the eluting solvent.

Below is a quick reminder of the major points of running a TLC plate.

- Mark the baseline position on the TLC plate provided with a pencil, about 1 cm from the bottom of the plate.
• Using a clean micropipette for each compound (biphenyl, bromobenzene, your ether layer), spot each solution on the base line, ensuring that the spots are equally spaced and are not too close to the edges.
• Set up your developing chamber with petroleum ether as your elution solvent. Remember that the depth of the solvent must be less than the distance of your spot to the bottom of the TLC plate.
• Use tweezers to carefully place the TLC plate in the developing tank, being careful not to entirely the solvent at an angle. Be sure not to touch the side of the chamber with your TLC plate!
• Cover the developing chamber with the glass plate.
• When the solvent is approximately 1 cm from the top of the plate, remove the plate using tweezers. Grab the TLC plate at the solvent front, remove the plate from the chamber and mark the position of the solvent front with a pencil before the solvent evaporates.
• Let the plate dry then visualize it under the UV lamp as shown by the instructor. Outline any spots you see with a pencil while the light is shining on it.
• Bring the plate back to your bench and make an exact “life-size” copy of it in your notebook by tracing all around the plate and transcribing the positions of the baseline, solvent front and spots as precisely as you can.
• Measure the distances from the baseline to the solvent front and then from the baseline to the center of any spots. Use these values to calculate the $R_f$ values for any spots that are observed.

Dispose of your ether layer and any petroleum ether used from the TLC plates in the organic waste container. You may place your TLC plates in the trash once you have copied them into your notebook and are certain you no longer have use for them.

**CALCULATIONS**

1. Calculate the moles of Mg metal used.
2. Calculate the moles of bromobenzene used.
3. Determine which compound is your limiting reagent.
4. Calculate the theoretical yield of benzoic acid
5. Calculate the percent yield of benzoic acid.
6. Calculate the $R_f$ values for any spots on your TLC plates.
Date: Wed Dec 16 11:11:33 2009 (GMT-05:00)  bromobenzene

Scans: 4

Resolution: 4.000