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Grignard Reaction - Synthesis of Substituted Benzoic Acids

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The Grignard Reaction

Introduction:
Despite more than a century of organic chemistry, the formation of C–C bonds is still one of the most difficult transformations that we encounter today. Fortunately, the ability of carbon to make bonds not only to C, H, N, O, S, and P (those elements found extensively in the living world), but also to metals of Group I, II, and the d block has allowed us to make considerable advances in C–C bond formation. Organometallic species such as these have striking reactivities that allow organic chemists to overcome some of the challenges associated with forming C–C bonds.

The advent of organometallic chemistry really began with the pioneering work of Victor Grignard, who found that treating a bromoalkane with magnesium metal resulted in the formation of an organometallic adduct where magnesium inserted into the C–Br bond. While making a metal-carbon bond was not new, Grignard found that these reagents (now bearing his name) could react with electrophiles like carbonyl compounds to generate new C–C bonds, an achievement that won him a share of the Nobel Prize in Chemistry in 1912. The reason this occurs is that the Grignard reagent is strongly polarized, placing a partial negative charge on the carbon directly attached to the metal. The magnesium itself had a partial positive charge and the bromide has a partial negative charge.

This finding was important because of its synthetic utility. For years, the easiest way to create alcohols was accomplished by reacting a Grignard reagent with a ketone or aldehyde. Primary, secondary, and tertiary alcohols can be prepared by judiciously choosing the carbonyl compound and bromoalkane, many of which are easy to make themselves. For example, consider the alcohol below:

How many different ways can you think of to make this compound using a Grignard reagent and a carbonyl compound? And what bromoalkane would you use to react with MgBr₂ to make the Grignard reagent? It might be easier to think about this in the reverse direction. There are three ways:

![Diagram of Grignard reaction](image-url)
The Grignard Reaction

In this week’s experiment, you will be performing a modification of the Grignard reaction. You will each be given a unique aryl bromide, from which you will generate the Grignard reagent and react it with dry ice to create a substituted benzoic acid derivative. Solid carbon dioxide is a carbonyl compound that is also reactive towards Grignard reagents. Instead of an alcohol, the product is a carboxylic acid.

\[
\begin{align*}
&1. \text{Mg}^2+, \text{Et}_2\text{O} \\
&2. \text{CO}_2(s) \\
&3. \text{HCl(aq)} \\
&\rightarrow
\end{align*}
\]

Why is the Grignard reaction an important one to learn? This reaction requires enormous attention to detail, an important skill to learn in experimental science. You must work extremely efficiently because the Grignard reagent is very moisture- and air-sensitive, basic, and reactive. Furthermore, generating the Grignard reagent will take patience, so be sure to make careful observations. A successful Grignard reaction is a good indication of future success as a chemist and an important part of your undergraduate training.

In this experiment, you will also be introduced to a new purification technique called liquid-liquid extraction (or extraction) that will allow you to separate organic-soluble compounds from aqueous material. We will also review how to properly dry an organic solution so that it is free of residual water. Finally, you will isolate the benzoic acid as a white solid by vacuum filtration, a technique you have already learned. Analysis by \(^1\)H NMR, IR, and LC/MS will be used for characterization.

References:
1. www.nobelprize.org
Grignard Reaction

**Equipment:**
Microscale glassware kit
Claisen head
25 and 50 mL beakers
10 mL graduated cylinder
1 mL syringes and needles
2.5 or 5 mL syringes
20 mL syringe and long needle (3)
Pasteur pipets
Capillary tubes
Cotton
Rubber septa
Balloon
Scintillation vials and caps
NMR tubes
Heated in oven prior to lab:
10 mL round-bottomed flask
5 mL conical vial
3 mL conical vial
Claisen head
50 mL Erlenmeyer flask

**Chemicals:**
Bromobenzene
4-Bromotoluene
1-Bromonaphthalene
4-bromoanisole
Dry ice
Anhydrous diethyl ether
Diethyl ether
Calcium chloride
Magnesium ribbon
Iodine chips
6 M Hydrochloric acid (4 x 500 mL)
5% Sodium hydroxide (2 x 500 mL)
Methanol (2 x 200 mL)
Deionized water
CDCl₃

Preparation of the Grignard reagent: Place 0.15 g shiny magnesium ribbon into a dry round-bottomed flask. Quickly scratch the ribbon with a spatula to create a rough surface. Add a spin vane to the flask and assemble the apparatus as shown in the figure below. Be sure to seal off the Claisen head from the atmosphere with a rubber septum.

**Grignard Reaction Apparatus**

![Grignard Reaction Apparatus Diagram]

Transfer 20 mL of anhydrous diethyl ether into a 50 mL Erlenmeyer flask and cap to avoid exposure to the atmosphere. This will be your source of anhydrous diethyl ether for the remaining of the experiment.

In a dry 5 mL conical vial, add 6.5 mmol of your aryl bromide as a liquid via syringe. Add 4.0 mL of anhydrous diethyl ether to the vial via syringe. Stir to mix and then withdraw 1.6 mL of this solution and add it directly to the round-bottomed flask containing the magnesium ribbon (you will use the remainder of the aryl bromide solution later). Using a hot plate or a heating mantle, gently warm the solution with stirring no higher than the boiling point of diethyl ether. You should notice bubbling occurring at the metal surface. Try heating for a while before doing the following troubleshooting: add a small crystal of iodine to the flask and gently heat, add more aryl bromide solution, or withdraw a small sample of the Grignard reagent from someone else and inject it into your reaction mixture (make sure this person has the same substrate!).

If you have successfully generated the Grignard reagent, the solution should be a cloudy brownish-gray mixture. Add the remainder of the aryl bromide solution over a period of 15 minutes. It may be necessary to heat the mixture occasionally to ensure continuous generation of the Grignard reagent, however addition of the aryl bromide solution should make the mixture boil without application of external heat. Do not let the reaction boil too vigorously, though. If this happens, remove it from the heat or add the aryl bromide solution slower and allow it to cool periodically. By now, the magnesium ribbon should become consumed. When all of the aryl bromide solution has been added,
rinse the 5 mL conical vial with 2 mL anhydrous diethyl ether and add it to the reaction mixture. If any diethyl ether has been lost during the addition due to boiling, add more until your volume is approximately 6 mL. DO NOT LET YOUR REACTION GO DRY. After letting the reaction mixture stir for 30 minutes, nearly all of the magnesium should have disappeared, at which point you should cool the mixture to room temperature and proceed to the next step.

**Synthesis of a benzoic acid derivative:** When the Grignard reagent is cool, quickly obtain 4 g of crushed dry ice (~1 pellet) in a beaker. It is not important that the exact amount is measured. What is critical is that this is done fast to avoid condensation of water onto the surface of the dry ice. IMMEDIATELY add the entire solution of Grignard reagent to the dry ice via a Pasteur pipet as quickly as possible, leaving the unreacted magnesium behind. Bubbling will occur as CO₂ reacts and is sublimed. Rinse the flask with another 2-3 mL of anhydrous diethyl ether. Swirl the reaction mixture occasionally until all of the dry ice has sublimed. The reaction mixture should be a viscous syrup or frothy solid.

**Workup:** Slowly add 10 mL 6.0 M HCl (aq.) to the beaker with swirling. Any remaining magnesium will react to form hydrogen gas. If you still have solid remaining, add a little more HCl solution or more diethyl ether. You should now have two layers since diethyl ether and water are not miscible. Transfer this solution to a Falcon tube and rinse the beaker with diethyl ether.

Remove the bottom layer from the Falcon tube and place in a separate beaker (this will be discarded). The top layer (diethyl ether) contains your product and impurities. Add 4 mL 5% NaOH (aq.) to the Falcon tube, and cap and invert (be careful to release the pressure after each inversion by gently removing the cap). Remove the lower aqueous phase and place in another beaker (this time it should be saved). Repeat with a second and third portion of 5% NaOH (aq.), collecting the bottom layer each time in the same beaker as the material to be saved. For the second and third wash, you may be able to shake the sample instead of inverting it.

To the combined aqueous extracts, add 10 mL 6.0 M HCl (aq.) and a white precipitate should result. Stir the mixture to fully precipitate the solid. Additional cooling to 0 °C may be necessary. Collect your crystals on a Hirsch funnel by vacuum filtration. Rinse the beaker with cold water (4 mL total) and then wash the crystals. Transfer the crystals to a tared vial and warm in an oven for 10 minutes to dry the solid of remaining water.

**Analysis:** Obtain a yield of your benzoic acid derivative. Measure the IR spectrum of the benzoic acid, submit a ¹H NMR (in ~0.7 mL CDCl₃) and an LC/MS (<1 mg in 1.5 mL MeOH). Submit your sample in a scintillation vial labeled with your name and structure to your TF, who will save your benzoic acid derivative for potential use next semester!

**Pre-Lab Exercise:**
1. Why is it necessary that the glassware be dried in an oven prior to your arrival?
2. What is an emulsion? Name a few ways to destroy an emulsion.
3. a) A student extracts an organic compound from an aqueous solution using diethyl ether. Which layer is on top? b) A student washes a reaction mixture in dichloromethane with water to remove aqueous impurities. Which layer is on top? c) A student washes a reaction mixture in acetonitrile with water to remove aqueous impurities, but notices that two layers are not created. Why not?

4. Why does the magnesium metal need to be scraped before use?

5. When ketones are reacted with Grignard reagents, tertiary alcohols are formed. When aldehydes are reacted with Grignard reagents, secondary alcohols are formed. What carbonyl compound would you use to prepare a primary alcohol using a Grignard reagent?

6. Explain the following observation:

7. How would you prepare each of the following compounds using the Grignard reaction?

Post-Lab Assignment: Organic Syntheses Preparation, due in Lab one week after you complete the experiment. The answers to Pre-Lab Exercise questions 1, 2, and 4 (above) should be answered somewhere in your discussion paragraph where appropriate. Describe the overall success of the reaction and comment on its rate by referring to your TLCs. Interpret your NMR and IR data and how you would expect this data to change from starting material to product.