

Experiment 2. The Grignard Reaction: Preparation of Benzoic Acid

References: Brown & Foote, Chapters 15.1, 16.6, 17.5

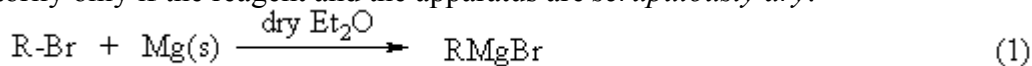
INTRODUCTION:

The chemical reactions used in the synthesis of organic compounds can be divided into two groups: functional group transformation and carbon-carbon bond formation. Most of the experiments that you have carried out thus far (in 2OA3) have involved the manipulation of functional groups. In this experiment you will form a carbon-carbon bond by attaching a phenyl group to the carbonyl atom of carbon dioxide.

BACKGROUND:

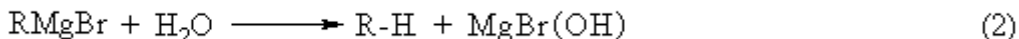
General Principles of the Grignard Reaction

The Grignard reaction is one of the more important classical methods for forming carbon-carbon bonds. It is a two step process: first the Grignard reagent is prepared and then it is reacted with a suitable carbonyl-containing compound. Grignard reagents are prepared (eq. 1) from alkyl halides by treatment with magnesium metal in the presence of dry ether. The reaction proceeds satisfactorily only if the reagent and the apparatus are *scrupulously dry*.



The alkyl magnesium halide is soluble in the Ether solution and is used in this medium. The solubility results from the solvation of the organometallic compound by the ether. Hydrocarbon solvents are not useful in the preparation of Grignard reagents because they cannot solvate the product.

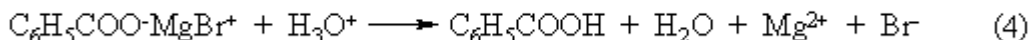
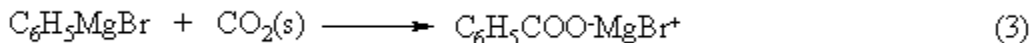
If the solvent is "wet" (i.e. contains traces of water), the Grignard reagent is destroyed as fast as it is formed (eq. 2). Thus the importance of using dry ether and dry glassware cannot be over emphasized.



Besides reacting with H₂O, Grignard reagents also react with (and are decomposed by) carboxylic acids, alcohols, amines, ammonium salts and other compounds which are slightly acidic. The Grignard is not only a potent nucleophile, it is a very strong base since it is the conjugate base of a very weak acid (pK_a of benzene ~44). Grignard reagents will also react with O₂, but in the present experiment, the oxygen-free atmosphere is obtained by keeping the ether solution warm during the preparation of the reagent. Ether is sufficiently volatile that a blanket of ether vapour above the solution keeps the reagent reasonably well insulated from contact with air. If a very high yield of product is desired, it is preferable to carry out the reaction in a nitrogen atmosphere.

Preparation of Benzoic Acid using the Grignard Reaction

In this experiment, the alkyl magnesium halide will be in the form of phenyl magnesium bromide ($R = C_6H_5$ in eq. 1), which you will prepare from bromobenzene. The phenyl magnesium bromide will be quenched with solid carbon dioxide (eq. 3) and then benzoic acid is isolated from the acidified reaction mixture (eq. 4).



PRE-LAB PREPARATION:

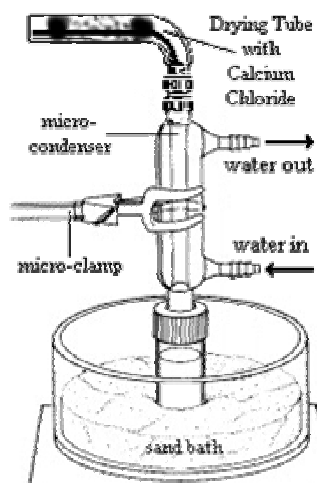
1. Write a mechanism for the reaction of phenylmagnesium bromide with carbon dioxide (using curly arrows, etc.).
2. What is the molar ratio of CO_2 to Grignard reagent used in this experiment? Why do you use an excess of CO_2 ?
3. Show how ether solvates the grignard reagent by Lewis Acid/Lewis Base interactions.

EXPERIMENTAL PROCEDURE:

CAUTION: *Ether is very flammable.* Do NOT use ether if there is a flame in the lab.

1. Preparation of Phenyl Magnesium Bromide (Grignard Reagent)

a) Start heating a sand bath on maximum.



b) Set up a reflux apparatus using a 10 mL cylindrical vial and a condenser fitted with a calcium chloride drying tube. **Make sure that the flask and condenser are DRY before you assemble your apparatus.**

b) Add your 0.5" magnetic stir bar, 0.17 g Mg turnings and ONE small crystal of iodine to the flask, and then reassemble the apparatus.

c) *Without* cooling water in the condenser, heat the vial by rotating it gently in a sand bath, so that most of the walls of the flask have been heated. This can be done by holding the apparatus firmly in both hands, and moving the apparatus around in the sand bath.

Continue to the point of generating a purple vapour.

The heating should have removed any film of moisture on the surface of the magnesium or the flask. When the flask cools, dry air will be sucked into the apparatus through the drying tube, so do not

disassemble the apparatus until it has completely cooled.

d) Prepare a communal ice bath for the bench-row in case any of the reactions to be carried out become too vigorous.

e) Remove the vial from the condenser, add 3 mL of *absolute dry ether* to the vial (*there are two types of ether on the bench, one is a specially prepared dry or "absolute" ether, the other is ordinary ether to be used for extraction*), and 0.75 mL (1.1 g) of bromobenzene, swirl the flask to

mix the ether and bromobenzene and reassemble the apparatus and set the magnetic stirrer operating.

f) Immediately, attach your condenser to the cooling water and start stirring the reaction.

g) If you have followed directions carefully (i.e., everything was clean and dry) the reaction should begin immediately or after slight warming with your hands placed against the bottom of the flask (the stirring action of the magnetic stirrer also helps). You will recognize that the reaction has begun by the appearance of a cloudiness in the ether and eventual boiling of the ether.

If the reaction does not start, the following steps should be carried out:

1. Using a dry stirring rod, crush a piece of magnesium firmly against the bottom of the flask (take care not to break the flask!). The reaction should begin, if not try 2.

2. Warm the flask gently on a heating mantle, with swirling. Remove the heat and see if boiling continues. If not try 1 again. If still no reaction, go to 3.

3. Add a couple of drops of 1,2-dibromoethane. If there is still no action, go to 4.

4. Tough Luck: try again but this time **dry** everything. [If you use a water, acetone sequence to dry your flask, make sure you do a final rinse with ether to remove the last traces of acetone. Acetone undergoes a pinacol reduction with Mg and this appears to inactivate the Mg surface to organometallic formation.]

g) As soon as you are sure that the reaction is starting, add an additional 2 mL of absolute ether through the top of the condenser. The reaction mixture should continue to boil but if it should become sluggish apply *gentle* heat with a heating mantle until all but the tiniest flakes of the magnesium has disappeared (periodically stop the stirrer to check how much Mg remains; this may take up to 30 min.). If at any point during the process you appear to be losing ether from your reaction mixture, add a few more mL of ether through the top of the condenser via a dropping pipette, to keep the volume above half full. You have now prepared a solution of phenyl magnesium bromide in ether and it should be used immediately in the next step.

NOTE: at the end of the day, discard the CaCl_2 in your drying tube into the "Inorganic Solid Waste". If you don't, after a few days you will be left with a "brick-like" mass of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ which is very tedious to remove.

2. Reaction of Phenyl Magnesium Bromide with Carbon Dioxide

a) Just before you are ready to use it, place finely divided (crushed) solid carbon dioxide (approx. 4 g) in a beaker.

b) With vigorous stirring, slowly add the prepared solution of the Grignard reagent. Stir until the mixture becomes thick and sticky.

c) When the solid carbon dioxide has all gone, slowly add a mixture of water (7 mL), ice (7 g) and concentrated hydrochloric acid (1.0 mL). Mix thoroughly.

3. Isolating the Benzoic Acid

a) Add the mixture to a separating funnel.

b) Extract the aqueous phase with *two portions* of ether (7 mL each). ie. keep the top layers.

c) Combine the ether layers and extract them with three portions (4 mL each) of 1.0 M *or* 5% NaOH (whichever is available). ie. keep the bottom layers.

d) Combine the NaOH extracts and acidify with concentrated hydrochloric acid to pH 2 (Congo

Red paper is turned blue). Make sure the reaction mixture is reasonably cool as benzoic acid has appreciable solubility in warm water.

NOTE: IF NO precipitate forms, then likely some ether is present on the surface of your benzoic acid solution. Gently blow off the ether on the acidified solution until crystals appear. Continue to cool in ice bath until precipitation is complete.]

e) Collect the precipitate by vacuum filtration.

f) Dry the product as thoroughly as possible, and then weigh it.

g) Calculate the % yield of the crude product.

NOTE: The ether layer contains neutral non-polar compounds such as unreacted bromobenzene and biphenyl. It should be discarded into the HALOGENATED ORGANIC WASTE bottle.

4. Purifying the Benzoic Acid

The benzoic acid will be purified by recrystallizing it from hot water. If you have less than 0.2g, check with your TA before recrystallizing.

a) Put the benzoic acid in a clean beaker (keep a small portion aside for the MP determination of the crude product).

b) Add enough hot water to *just* dissolve the solid

c) Allow the solution to cool to room temperature, and then put it into an ice bath.

d) collect the crystals by vacuum filtration.

e) Dry the product as thoroughly as possible and re-weight it.

f) Calculate the % yield of the purified product.

5. Characterization of the Benzoic Acid

a) Obtain and label an IR spectrum of your recrystallized product.

b) Measure the melting points of your crude and recrystallized products and record them.

c) Dispose your benzoic acid in the SOLID WASTE jar provided.