Macroscale Synthesis of Triphenylmethanol via a Grignard Reaction

Important: We will do experiments 4, 5, and 7 in Chapter 38. We will use new techniques in this experiment and include the use of ground glass equipment, a water-cooled condenser, and a separatory funnel. Review the use of a separatory (sep) funnel in Chapter 7.

Note that these handouts are not stand-alone procedures. These are simply suggestions that should be incorporated into your prelab outline, which is based mainly on the lab text.

This is a multistep synthesis. Great care must be used throughout to ensure obtaining a sufficient quantity of material to proceed to subsequent steps. A four-step reaction wherein each step gives a 70% yield will result in a 24% overall yield (.7 x .7 x .7 x .7). Imagine a 15 step synthesis, which is common in many syntheses of complex products. Assuming a 70% yield at each step, one would obtain a 0.5 % yield of final product. Translated into grams, assuming that the MW of the starting material is 1/2 that of final product, **to obtain 1 g of final product**, one would have to **start with 16,384 g of starting material**! Percent yields are indeed important.

Summary: You will add bromobenzene to a flask containing anhydrous diethyl ether and magnesium, initiate the reaction by scratching the surface of the magnesium, and once the reaction begins, dilute the solution with more ether. The exothermic reaction will cause the ether to boil and the water-cooled condenser will condense the ether vapor and return the liquid ether to the flask, thereby preventing the ether from evaporating. The process of returning condensed vapor to a flask is called refluxing. A drying tube is used to protect the contents of the flask from water vapor. If the reaction gets out of control, it can be moderated by cooling in an ice-water bath.

Caution: diethyl ether is **extremely flammable**.

Reaction Failure Warning: Water is very detrimental to this experiment until you purposely add it later in the procedure. Even though water may not be visible on glassware, enough may be adsorbed onto the surface to prevent the reaction from working. Therefore, any glassware to be used in the formation and reaction of the Grignard reagent cannot be washed with water on the same day that the experiment is run. In all operations be very careful to NOT allow water to contact the equipment or reagents or solvent and be especially careful to not allow the reagent and solvent containers to become contaminated with water. Even your fingers are moist enough to contaminate the glassware. Do not handle anything that will come into contact with the reaction mixture (such as the stirring end of the stirring rod) with your bare fingers.

Experiment 4: Preparation of the Grignard

Get together the following equipment, which has been dried in a 130 °C oven and desiccator cooled:

- A 10 mL and 25 OR 50 mL graduated cylinder
- a 100 mL round-bottomed (RB) flask
- a drying tube
- a jacketed water condenser and 2 pieces of condenser tubing (caution: these may have water inside and if you are not careful you may get the other equipment wet)

- a glass stirring rod
- and a corked 50 mL Erlenmeyer flask.

Apparatus: The apparatus will be set up as in Fig. 38.8 but with the following modifications: The heating device will not be present but the flask should be clamped above the benchtop in case the ice bath is needed. For added security, clamp the condenser as well.

Condenser Prep: Just so you know about how much to turn on the water valve when the time comes, turn the valve slightly, just until a very slow steady flow begins. Note that the amount to turn the valve is very slight. Remember this for later. Make sure the pieces of tubing will be long enough to reach the water source and trough. Slip the rubber tubing onto the condenser (slightly wetting the end of the tubing allows it to be pushed onto the condenser more easily, but don't slop the water around). Connect the tubing from the lower condenser connection to the water source. Run the upper tubing directly into the cup sink in the fume hood, being sure that it is pushed far enough into the sink to prevent its coming out when the water is turned on. Do not turn on the water yet (moisture may condense on the inside of the condenser). For added security to prevent flooding, loosely attach a small clamp holder to the end of the drain tube. This will prevent the tube from being easily pulled out of the drain,

Drying Tube Prep: Yours will be an angled drying tube. This is okay. (Cotton at both ends will prevent the drying agent from succumbing to gravity.) Place a small loose plug of cotton into the drying tube to block the inner opening, and using the powder funnel and spoon while working right over the large plastic container (to catch stray calcium chloride pellets), slowly (so as not to clog the funnel) add enough anhydrous calcium chloride pellets to half-fill the tube, add another piece of loosely-packed cotton, then finally the one-holed stopper.

Measure Reagents and Solvents: Measure out the magnesium ($Mg^{(0)}$) onto weighing paper and add it to the RBF. Using a small 3-pronged clamp, clamp the flask securely to a ring stand. Attach the condenser (do NOT use grease on the ground glass connections), and place the drying tube on the top of the condenser. Do not turn on the water just yet. Pour directly (no pipets) into the larger graduated cylinder 25 mL of anhydrous diethyl ether (DO NOT USE TBME. It does not complex very well with the magnesium and as such the Grignard will not form). Add the diethyl ether to the 50 mL Erlenmeyer flask and cork it. Pour directly (no pipets) into the larger graduated cylinder 15 mL of anhydrous diethyl ether and add it to the $Mg^{(0)}$ in the RB flask. Using the attached pipet, measure out 9 mL of bromobenzene into the small graduated cylinder.

Prepare an ice-water bath and have it handy in case the reaction becomes too vigorous. Note that a mixture of ice and water is much more effective at cooling a flask than ice alone. If the reaction needs moderation, just cool the bottom of the RB flask slightly. Do this only as a last resort and only for a very short period. Otherwise the reaction may stop. In all cases keep the ice-water bath away from the reaction set-up and be very careful to not spill water near the reaction set-up or equipment being used. Keep your hands very dry.

Note: that when you finally begin running water through the condenser, turn the water on very slowly at first, give it time to fill the tubing and condenser, and watch the rate of flow out of the drain tube. The flow rate should be the minimum needed to keep a constant light trickle. Anything greater runs the risk of popping the tubing open or causing some other havoc.

Starting the Reaction: normally the reaction will not start until the surface of the $Mg^{(0)}$ has been scratched. Nevertheless, be prepared in case the reaction does start right away. Once the reaction starts in earnest

(solution turns a pale brown, becomes cloudy and you see bubbles forming at the metal surface), add the remaining ether and swirl thoroughly as before and start the water running through the condenser as described above.

Using a short-tipped pipet, transfer the bromobenzene through the top of the condenser. Using the same pipet, use a half-pipet full of ether from your 50 mL Erlenmeyer to rinse the bromobenzene out of the graduated cylinder and through the top of the condenser. It does not matter if a little bromobenzene gets into the ether in the Erlenmeyer – this will be added to the reaction mixture later anyway. Swirl the flask to mix the solution well.

Most people will need to do the following: Move the flask down so its bottom touches the ring stand base, remove the condenser, and using the dry stirring rod, gently scratch a piece of $Mg^{(0)}$ by pushing it very carefully against the RB flask and twisting. IT IS VERY EASY TO POKE A HOLE THROUGH THE FLASK so pick a piece of $Mg^{(0)}$ that is resting on the bottom of the flask, so the benchtop provides solid backing. Scratch a couple of pieces of $Mg^{(0)}$ in this way then replace the condenser, swirl the flask and observe the mixture. (The $Mg^{(0)}$ will not actually be crushed into small pieces but by mashing a few pieces some of the oxide surface will be scratched, allowing bare metal to come into contact with the bromobenzene-ether solution. Once the reaction begins, the oxide coating will no longer hinder the reaction.) Reaction is evidenced by cloudiness, color change, or bubbling (or a combination of the three). Some reactions will begin right away and others may take some time (as much as 10-15 minutes). Swirl the flask as before and observe carefully, looking for the telltale signs of reaction (cloudiness, color change, eventual small bubbles, then more rapid bubbling). Swirl throughout. Once the reaction has clearly begun, reattach the condenser, add the remaining ether and swirl to mix well. Position the apparatus high enough so that the ice-water bath can easily be used if needed.

Once the reaction speeds up sufficiently, begin running cool water through the condenser, taking extreme care to not open the valve too much. Remember, a slight trickle of water is all that is required. Because the water pressure can change, it is wise to check the flow occasionally during reaction, and to readjust the flow if necessary. The condenser should feel cool to the touch.

Start the flow of cold water through the condenser as follows: turn on the water very slightly, give it a moment, and look for flow through the condenser and eventually out the exit tube into the sink. If water does not begin to flow, turn it up slightly more and wait a bit. Eventually you want to see a very slow but steady trickle of water exiting the tubing into the sink. Too fast a flow will burst the tubing and very likely ruin your and your neighbor's experiments. Be careful. Once water has flowed for a while, feel the outside of the condenser to see that it is cool and if necessary turn up the flow slightly. The water pressure in the building may change during the reaction so check the flow occasionally.

What to do if the reaction does not start: after scratching the $Mg^{(0)}$ give it time. Some reactions will begin right away and others will begin only after as much as 10 minutes. Be patient. Warm the flask with your hand. Loosen the clamp and swirl the flask to mix the contents. If after 10 minutes, the reaction has not begun, with your TA watching, remove the condenser and carefully scratch a little more $Mg^{(0)}$ (dry stirring rod) then replace the condenser and give it some more time. Watch closely for signs of reaction. If all else fails, start another reaction using dry equipment. Do NOT use suggestions 3 and 4 for starting the Grignard (3, iodine and 4, previously made Grignard).

Allow the reaction to proceed at a reasonable rate. What is reasonable? If boiling becomes so fast that ether vapors are coming out of the top of the condenser, cool the flask a little with the cold bath, but do not cool it so much that the reaction stops. A rate that allows condensing vapors to reach no further than about half-way up the condenser is reasonable. In the beginning, when reaction is vigorous, the content will mix by

itself. Later, when the reaction subsides, occasionally swirl the flask well to mix the contents to allow the reaction to go to near completion. Some Mg° will likely remain even at the end of the reaction.

Throughout the reaction, some diethyl ether may evaporate. Note the approximate volume of liquid and as you proceed add anhydrous diethyl ether if necessary to replace what was lost.

Turn on the hot plate to about 125 °C. When the reaction no longer boils very much on its own, even after swirling, carefully warm the flask by lowering it so that the bottom just rests inside the heating well. Remember that ether boils at 35 °C. Gently boil the mixture for 5-10 minutes at a rate such that the condensing vapors go no higher than the lowest part of the condenser. Allow the flask to cool to room temperature (RT). If a significant amount of ether evaporates during this heating step, replace it with more anhydrous ether. Some $Mg^{(0)}$ will remain.

Exp. 5. Addition of Methyl Benzoate. Rather than adding the methyl benzoate/ether solution (make sure it is well mixed) using a separatory funnel, simply pipet the solution in small amounts (half a pipet full) through the top of the condenser (remove drying tube), with swirling after each addition. This reaction is also exothermic, so do not add the methyl benzoate too rapidly, and be sure to swirl well after each addition. Have the ice-water bath handy.

Exp. 7 Reaction Completion. Using the heating well in the same way as above, gently reflux the mixture for 30 minutes, replacing any losses of ether as necessary.

Acid Hydrolysis. The hydrolysis of the alkoxide involves adding aqueous acid, so any additional ether which is used at this point need not be anhydrous. The hydrolysis step is also exothermic so some ether will evaporate. If evaporation is significant more ether should be added (note that the ether will eventually be evaporated so if too much is added more time will be required for evaporation). The ice should help to minimize evaporation. After refluxing the mixture for 30 minutes, allow the flask to cool unaided to RT, then transfer the contents to a 250 mL Erlenmeyer flask which contains the ice and sulfuric acid. Do this by pouring/pipeting back and forth from the RB flask to the 250 mL Erlenmeyer. This is the messy step. Use a glass funnel to help. It is helpful when pouring the reaction mixture, which contains solid (what is the solid?), to swirl and suspend as much solid as possible so that as much of the solid as possible is transferred to the Erlenmeyer during the pouring. Eventually all solid will react and dissolve so that finally there will be two liquid layers (ether and aqueous) and NO solid in the Erlenmeyer or RB flasks (a little remaining $Mg^{(0)}$ is okay). Any solid left behind in the RB flask represents lost product and will result in a decreased yield. Do a final rinse of the RB flask with a small amount of fresh ether and 10% sulfuric acid.

This is the stopping point for the day. Do not go on. It will be rushed and mistakes can be made. Write your name clearly on the Erlenmeyer flask and set it into the hood, uncorked. We will stopper it later, after the reaction has clearly ceased.

Before leaving, using soap/water and a little acetone, clean the RB flask, condenser, stoppers, drying tube, and the 25 mL (or 50 mL) graduated cylinder and place them into the collection bin. Empty the $CaCl_2$ from the drying tube into the appropriate container.

Week 2 - Extraction and Recrystallization:

Extraction. Carry out the extraction procedure using the sep funnel (review use in the lab text). Most likely all the solvent will have evaporated. See the note below. After the extraction, filter off the drying agent.
Recrystallization. Add the hexanes and concentrate down (in hood) the solution until crystals just start to form, let it cool slowly and crystallize (give it time, complete crystallization is slow), cool in ice, then isolate crystals via suction filtration. Leave the solid so it can dry and obtain a melting point in LUH.

Waste Disposal: Place the acidic, aqueous and the saturated sodium chloride layers into the aqueous acidic waste container. Dispose of hexanes, recrystallization solvents (save filtrates until you are sure you have product), and TLC solvents in the nonhalogenated liquid waste container. Used calcium chloride pellets go into the container labeled as such.

Note:

When you return for week 2: You will find that all of the ether has evaporated and the Erlenmeyer flask will contain the aqueous layer plus solid product. If enough water has evaporated solid magnesium salts may be present too. The amount of water should be about 75 mL (don't measure this in a graduated cylinder – just approximate – any transfers result in loss of product) so if the level is much below this add more water up to about 75 mL. Add about 35 mL ether to redissolve the solid (a little more if needed, no need for anhydrous—dissolution is slow so do not add too much ether – stir and give it time). Swirl and stir until all solid is dissolved and proceed with the sep funnel extraction (try out the sep funnel operation with plain water first to get the hang of it). Be sure to save a small amount of the ether solution for TLC analysis. (If solid is present in the solution in the sep funnel it may be that ether has evaporated enough so there is not enough to dissolve all of the product. If this is the case add a little (but not a lot) more ether and shake further.) Add hexanes and concentrate it down (in hood) until crystals just start to form, let it cool slowly and crystallize (give it time, complete crystallization is slow), cool in ice then vacuum filter.

Determine the weight, % yield, and MP of the product (has to be dry) and analyze the various samples by TLC. In the TLC analysis, pure biphenyl should be run alongside the crude and pure triphenylmethanol. The product should also be analyzed by IR spectroscopy.

Answer questions 1-3 on page 505