

Macroscale Grignard Synthesis of Triphenylmethanol. Reactions of Triphenylmethanol.

IMPORTANT: Everyone will do Chapter 38, Exp's 4, 5, and 7 and Chapter 33, Exp's 1, 2, and 8. New techniques will be used in this experiment. These include use of ground glass equipment, a water-cooled condenser, and a separatory funnel. Read about the use of a separatory (sep) funnel in Chapt 7. When you have a moment in the lab period before the sep funnel is needed, to become familiar with its operation, do a trial run with the sep funnel using only water. The new techniques will be demonstrated.

Treat this experiment as one three-week, 30 point experiment. 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 reaction. 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 ($.7 \times .7 \times .7 \times .7$). 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 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 as in this case 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.

Warning. Water is very detrimental to this experiment until you purposely add it later in the procedure. Even though HOH 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.

Exp 4. Grignard Preparation

Get together the following equipment, which has been oven-dried:

CAUTION: it will be very HOT. A 10 mL and 25 OR 50 mL graduated cylinder, a 100 mL 3-necked round-bottomed (RB) flask, 2 glass stoppers, a drying tube, a condenser, 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: a three-necked flask will be used, with two of the necks stoppered with ground glass stoppers. The heating device will not be present but the flask should be clamped above the benchtop in case the ice bath is needed. The other two openings in the flask will be stoppered with ground-glass stoppers.

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).

Drying Tube Prep: 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°) onto weighing paper and add it to the RB flask and using a small 3-pronged clamp, clamp the flask securely to a ring stand. Stopper the two outer openings, place the condenser into the center opening (do NOT use grease on the ground glass connections), and place the drying tube on the top of the condenser. Do not yet turn on the water. Pour directly (no pipets) into the larger graduated cylinder 25 mL of absolute ether, add it to the 50 mL Erlenmeyer flask and cork it. Pour directly (no pipets) into the larger graduated cylinder 15 mL of anhydrous ether and add it to the Mg° in the RB flask. Using the attached pipet, measure out 9 mL of bromobenzene into the small grad cylinder.

Prepare an ice-water bath and have it handy in case the reaction becomes overzealous. 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 the end of the exit tube. The flow rate should be the minimum needed to keep a steady stream of water flowing. 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° has been scratched. Nevertheless be prepared in case the reaction does start right away. Once the reaction starts in earnest add the remaining ether and swirl thoroughly as before and start the water running through the condenser as described below.

Remove one stopper from the flask and using a short-tipped pipet transfer the bromobenzene directly onto the ether in the bottom of the flask taking care to not dribble it along the side of the flask or onto the opening. 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 into the reaction flask. 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. Replace the stopper and 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 one of the stoppers from the RB flask, and using the dry stirring rod, gently scratch a piece of Mg° 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° that is resting on the bottom of the flask, so the benchtop provides solid backing. Scratch a couple of pieces of Mg° in this way then replace the stopper, swirl the flask and observe the mixture. (The Mg° 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 – maybe 5-10 minutes. Swirl the flask as before and observe carefully, looking for the telltale signs of reaction (cloudiness, color change, eventually small bubbles, then more rapid bubbling). Swirl throughout. Once the reaction has clearly begun, 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 awhile 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° give it time. Some reactions will begin right away and others will begin only after 5 or 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 reaction has not begun, with an instructor watching, remove a stopper and carefully scratch a little more Mg° (dry stirring rod) then replace the stopper 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).

At this point you can relax a bit.

- 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 ether if necessary to replace what was lost.

- Turn on the heating mantle and set it to a very low voltage. To do this, turn it up to 30-40 then back it down to about 10 or to the point where the lamp just stays lit. When the reaction no longer boils very much on its own, even after swirling, carefully warm the flask by lowering it, not right into the mantle but above it just to the point where the ether boils gently. Remember that ether boils at 35° and if you lower the flask too close to the heat the ether may boil violently and evaporate. Gently boil the ether for five or ten 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° 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) via the top of the condenser, with swirling after each addition. This reaction too is exothermic so do not add the ester too rapidly and be sure to swirl well after each addition. Have the ice-water bath handy.

Exp. 7 Reaction Completion. Using the heating mantle in the same way as above, gently reflux the mixture for 1/2 hour, 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 1/2 hour, allow the flask to cool, 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° is ok). 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.

Depending upon the amount of time you have left in the lab period you can stop at one of three places.

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

(1) If there is less than about an hour left in the lab period, this is a good point at which to stop for the day. 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. If you still have an

hour or so left, you may continue with the next part. Most people will have time to continue and it is best to get at least the next step completed.

(2) If you have enough time and wish to continue, complete the Extraction.

Extraction. Carry out the extraction procedure using the sep funnel as described in the book. 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 more ether and shake further. If time is short, after the sep funnel extraction and drying with CaCl_2 , decant the ether solution into a tared Erlenmeyer flask (as small as possible but that will not be filled more than halfway), write your name on the flask, cork it and leave it in the fume hood.

(3) If you still have half an hour and wish to continue, complete the Recrystallization.

Recrystallization. As described in the text, after drying with CaCl_2 and decanting the drying agent, add the 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. Leave the solid to dry until next time.

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.

Week 2. Depending upon where you left off last week, you will do one of the following:

1- If you have already finished the extraction and recrystallization during Week 1 skip down to "Determine the weight, % yield, etc" below.

2- If you stopped last time after doing the extraction but before doing the recrystallization:

you will find that most or all of the ether has evaporated. Redissolve the solid in about 35 mL ether (a little more if needed, no need for anhydrous – dissolution is slow so do not add too much ether – stir and give it time), add hexanes, and continue as described in the text (concentrate solution down (in hood) until crystals just start to form, let cool slowly and crystallize (give it time, complete crystallization is slow), cool in ice, vacuum filter the crystals then skip down to "Determine the weight, % yield, etc" below.

3- If you stopped last time before doing the extraction you will find that most or all of the ether has evaporated and the Erlenmeyer flask will contain the aqueous layer plus solid product and 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 grad 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 as a fluorolube mull.

Chapter 33. Reactions of Triphenylmethyl Carbocation. Note that boiling sticks can be used only in nonreactive solutions, e.g, in a recrystallization. When reagents that are reactive to wood are used (e.g., H₂SO₄ and HBr), a boiling stone must be used instead. Exp 1 (microscale). Change: use 2 mL of methanol instead of 3. Before trying to filter the product, be sure that it has crystallized well. Allow it to cool for a sufficient time (let it stay in an ice bath while you go on to the next exp), scratch the inside of the tube with a glass stirring rod, and if necessary, add water dropwise (only as a last resort) with stirring to decrease the solubility of the product. Change: after squeezing out as much water as possible between sheets of filter paper, the crystals will still be damp. Do not weigh and calculate a % yield of crude product as stated. Instead, save a little crude aside for a mp comparison, then recrystallize the damp material and weigh and calculate the % yield for the recrystallized material after it is dry (how do you know when something is dry? - dry to constant weight - methanol should dry quite rapidly). Compare the MPs of crude and recrystallized material (after they have completely dried). Exp 2. The 0.2 mL of HBr will be dispensed with a buret (4 small graduations). Change: again, do not weigh and calculate the % yield of crude material - it will still be damp. Instead, squeeze out as much water as possible between sheets of filter paper as before, and then, after saving a little aside for a mp comparison, recrystallize the remainder of the product and weigh and calculate the % yield for the recrystallized material after it is dry (constant weight - hexanes will dry rapidly, but residual water will linger). Compare the MPs of crude and purified material. The Beilstein test will be done but must be done away from any flammable solvents. Specific instructions will be given for use of burners. Under no circumstance light a burner without the express permission of your instructor. Analyze compound 1 (Exp 8) by IR spectroscopy as a fluorolube mull.

Waste Disposal: Place aqueous acidic filtrates into the container labeled as such. All organic solvents go into the Nonhalogenated Liquid Waste container. When you are finished with the products place them into the Solid Waste container.

Week 3 of the Grignard Synthesis. Finish up if necessary. Remember to always include an "Experimental Section" kept in the style of J Am Chem Soc or J Org Chem in your report.

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Questions.

Do questions 1.) and 2.) on p. 505.

3.) Draw the structure of the product that would result if 2-propanol were substituted for methanol in Exp 1 of Reactions of Triphenylmethanol.

4.) Draw four resonance structures of the triphenylmethyl carbocation. How many can be drawn?