

Experiment 16 —

Grignard Chemistry: Synthesis of Triphenylmethanol

Pre-lab preparation. (1) Write the balanced equation for the reaction that you will be carrying out, including structures of the reactant and product. (2) Determine the quantities of reagents in the usual way. The procedure will give you the proportions; figure out the masses and volumes before coming to lab. (3) Write the mechanism of the reaction. Two equivalents of Grignard reagent react with one of ester. The first part is a carbonyl substitution — Grignard adds to the carbonyl group to make a tetrahedral intermediate, then the carbonyl group is regenerated as the leaving group, methoxide, is expelled. The second part is a carbonyl addition. (4) Write the reaction of your Grignard reagent, PhMgBr, with water. This is what will happen if your flask is wet. Another side reaction is the formation of biphenyl (Ph–Ph). We'll think more about this later. (5) Sketch the apparatus that you will be using, and explain how the apparatus satisfies the five criteria (a - e) stated in the first paragraph of the procedure. (6) Explain briefly what each step of the extraction does. Keep in mind that each step of a liquid-liquid extraction leaves some residual material in the other layer. (e.g., in extracting an ether solution with water, after draining off the aqueous layer, some water remains with the ether layer, either dissolved in the ether or as droplets on the sides of the sep funnel).

Students sometimes get the impression that nitration (last week's experiment) is some sort of "rite of passage" on the way to becoming an Organic Chemist. Bah. The Real Rite of Passage is the Grignard reaction. If you can do this, avoid filling the lab with ether fumes, avoid setting fire to the instructor or TA, and — even more important — get the reaction to work, you will be a *bona fide* Budding Organic Chemist.

Background. Developed by the French chemist Victor Grignard in the early 1900s, organomagnesium halides, R–MgX, quickly became some of the most important reagents in the synthetic organic chemist's repertoire. Grignard was awarded the 1912 chemistry Nobel prize for the development of these versatile reagents and exploration of their reactions.

Grignard reagents are prepared by the reaction of organo halides and magnesium metal. The reaction happens on the surface of the Mg and involves single-electron transfers, radical ions, surface-bound species, and possibly free radicals as well. The result is an overall insertion of Mg into the C–X bond. Because the divalent Mg is electron-deficient, solvation by electron-donating ethers is normally required to stabilize these reagents during their formation, storage, and reactions.

Their polar carbon-metal covalent bond causes Grignard reagents to behave as *carbanion* equivalents. They are extremely strong bases as well as excellent nucleophiles. Because these compounds are such strong bases, they must be prepared and handled in environments free of water and other proton sources like alcohols and amines. Dry solvents and glassware are essential to the success of any reaction that involves a Grignard reagent.

In this experiment, you will allow two equivalents of phenylmagnesium bromide, PhMgBr, to react with methyl benzoate, PhCO₂Me, to produce triphenylmethanol, Ph₃COH. The first equivalent of Grignard reagent does a carbonyl substitution; the ketone produced then undergoes a carbonyl addition with the second equivalent.

Determine the quantities of bromobenzene, magnesium metal, and methyl benzoate needed to prepare a theoretical yield of 9.65g of triphenylmethanol. Methyl benzoate should be your limiting reagent; use 10% more than the stoichiometric quantity of Mg and 15% more than the stoichiometric quantity of bromobenzene. We'll check your calculations before you begin.

Procedure. This reaction will require (a) the controlled addition of PhBr to a stirred mixture of Mg metal in dry ether, Et₂O, and then a similar controlled addition of PhCO₂Me. We may need to (b) cool the mixture if the reaction becomes too vigorous, or we may need to warm it (what's the bp of ether?) to keep it going and to ensure that it has gone to completion. At the same time as the additions, we'll need to be able to (c) condense the vapor of the boiling Et₂O, and (d) stir the reaction mixture. And all this needs to happen with (e) everything protected from atmospheric moisture. This means that we can't very well use an Erlenmeyer with a stirring rod like we have in the past, nor can we keep switching flask accessories — remember, we need to condense Et₂O, stir, and add reagents all at once, in a dry environment.

A solution that meets all these requirements well enough for our purposes is a 3-necked flask with ground-glass joints. On the center neck will be a stoppered *addition funnel*. On one side neck will be a *condensor* topped with a "drying tube" — a calcium chloride-filled tube that is open to the outside. This allows the reaction to "breathe", but any air that it "inhales" gets dried by the CaCl_2 . On the other side neck will be a stopper. You can use this as an access port to add Mg and Et_2O directly to the reaction flask.

As you go, record in your notebook what you actually did and what you observed in enough detail that someone else can follow this and repeat the procedure.

Put two small graduated cylinders in the oven to dry them (what sizes? Check the volumes of solvent and reagents and find out). The plastic bases on some of the cylinders will melt in the oven, so be sure to remove these.

Assemble the glassware as described above. Don't attach the rubber tubing to the condenser yet, but you'll need to remember to do this and get the water going before you start the reaction. Place the magnesium "turnings" and a magnetic stir bar in the flask. Remember that heating anything in a closed system could lead to disaster, so *check carefully that your apparatus has no sealed spaces* — think about it — if you heat a particular part of the apparatus, where will the hot air go? If there's no vent, the pressure increase will blow the apparatus apart — if you're lucky it will fail at a joint and the airborne glassware will break when it lands on the benchtop or floor. Unlucky is what happens when no joints can come apart and the pressure causes the glass itself to fail — violently. *Check your set-up with the lab instructor or TA*, then flame-dry the apparatus. Be careful not to roast the Mg; you only need to heat the glassware enough to drive off the moisture on the inside surface. You'll see the water vapor recondensing on nearby cooler surfaces as you go. Work from the bottom of the flask, chasing moisture up the necks and out the top of the addition funnel and out the condenser. You're not going to be able to reach the inner tube of the condenser with the flame — we'll have to live with the bit of moisture on that surface. If you now leave the set-up open as it cools, moisture will reenter the apparatus. Don't do that. But if you stopper everything, cooling will create a vacuum, and moist air will rush in as soon as you remove a stopper. So don't do that either. The apparatus and Mg will appreciate being able to inhale nice *dry air* as they cool. Figure it out and make it happen.

Now would be a good time to retrieve your dry graduated cylinders. Cover the opening with aluminum foil to restrict air circulation, and let them cool. You'll need to use these at several stages of the procedure, so keep them covered with foil to minimize the amount of moisture that gets in. How much do the cylinders and rxn glassware (and Mg) have to cool before you add the ether?

Because diethyl ether is so volatile and flammable, this will be kept in an undisclosed location until everyone is finished flame-drying their set-ups. *When all flames are out and all burners have been put away*, the instructor or TA will fetch the ether. Please keep in mind that *anhydrous ether* is expensive. The air in the room is not anhydrous. If you leave the cap off of the Et₂O, within minutes enough atmospheric moisture will enter that the whole can will be trashed.

Have an ice bath ready, but do not cool the reaction mixture unless the reaction becomes too vigorous. This will be obvious from the rate of reflux. Get 15 ml of Et₂O. Add about half to the Mg turnings, and the other half to the addition funnel. Then add the bromobenzene to the addition funnel. You may have to swirl this to get a homogeneous solution. Start the magnetic stirrer, and then add about 1/4 of the bromobenzene solution. The reaction will probably begin on its own within 5 to 10 min — the solution may become slightly cloudy, and the ether will begin boiling. Once it gets going, you can add the remainder of the PhBr solution, in portions, so that the reaction maintains a nice reflux rate. Once all the PhBr is in and the reaction is still going, add another 25 ml of Et₂O, a few ml at a time, via the addition funnel. This dilution will help keep the reaction under control. Your job now is to ensure that it keeps going, in a controlled manner, until the Mg is consumed. Cool with ice if necessary, but don't overcool it or it may stop.

If your reaction doesn't get going, don't despair because this is a common problem with making Grignard reagents. Organic chemistry lore includes the following possible remedies: (a) Warm the flask with your hands. (What's the bp of Et₂O? What's your body temp?) (b) Carefully crush the Mg with a glass stirring rod. Don't break the flask or the stirring rod. (c) Add a tiny crystal of I₂. (d) Add a little (1/4 ml) of the PhMgBr solution from someone nearby whose reaction worked. (e) If nothing has worked, ask Prof. S to toss in a few gray beard hairs

— this may do the trick. Once it's started, follow the procedure described in the previous paragraph.

Once there are no more than a few tiny specks of Mg left, you're ready for the next step. If you lost much ether, add a little more to bring the volume up to what it should be, then figure out how you lost so much ether. Is your condenser water flowing? Is there a loose joint? In the addition funnel, make a solution of the methyl benzoate in 15 ml of Et₂O. You didn't forget to close the stopcock, did you? Which should be added first, the more dense liquid or the less dense liquid? If you have two layers, remove the addition funnel and gently rock or swirl it to get a homogenous solution.

Cool the flask briefly in an ice bath, then add the methyl benzoate solution dropwise. You may see a white precipitate during the addition. What do you think that is? You should be able to do this addition at a moderately rapid rate; go slow at first, and keep an eye on the reflux rate — this will give you an indication of how much heat is being generated. Rinse the addition funnel with a few ml of dry ether. To ensure completion of the reaction, heat the reaction mixture to a gentle reflux with a warm water bath for 30 min.

Combine about 50 ml of ice and 50 ml of 10% sulfuric acid, and carefully pour the reaction mixture into this (use a flask, *not* a beaker). Swirl the mixture for a few minutes. (What is the purpose of this step?) Note that any remaining bits of Mg metal will be destroyed by the acid. Use a separatory funnel *in a fume hood* to separate the layers. Be sure to vent this frequently — your hand will warm the ether and increase its vapor pressure, and any acid-base reactions that occur in the funnel will also increase the temperature. Keep track of where your product is, and don't discard anything until you're sure you have it. Wash the ether layer with 25 ml of water, 25 ml of 5% NaOH (don't combine that solution with the acid — use a separate flask) and 10 ml of saturated NaCl ("brine"), then dry it over MgSO₄. After a few minutes, remove the drying agent. To encourage the product to crystallize, add 25 ml of alkane solvent (this could be "hexanes", "ligroin", or "petroleum ether" — these are all mixtures of alkanes), and heat on a steam bath, with a "boiling stick", to drive off the lower boiling solvent. Once crystals of product begin to appear, cool and isolate the solid in the usual way. Which solvent should you use to rinse the crystals?

Let the crystals air-dry until your next lab period. Then, you will determine the yield, measure the melting point, and perhaps do some other fun experiments.

Your report, due next week, should include a discussion of what you observed during the procedure. Did a precipitate form and then disappear during the addition of the ester? What was that? Did something go wrong? If so, what were the possible chemical consequences? For example, perhaps you noticed droplets of water inside your condenser during the reaction, and they gradually got rinsed down into the reaction mixture — how might that have impacted the reaction? Keep in mind that you had an excess of certain reagents (which ones?), so maybe something like this wasn't a complete disaster.

The pre-lab part of this document noted two potential side reactions. Are there others? Were all the side products isolated along with the Ph_3COH ? (hint: no) If not, at what stage of the procedure do you think these side-products were separated from the Ph_3COH ? You also used some reagents in excess. What happened to the excess? At what stage of the procedure were these separated from the product?

It was mentioned in the pre-lab that formation of biphenyl is a side reaction. One way this can form is by reaction of bromobenzene with the Grignard during the initial stage of the procedure. Write this reaction. (The mechanism is unclear, but it's not a simple nucleophilic substitution.) Another way that biphenyl might be formed is by reaction of PhMgBr with atmospheric oxygen. How do you think this happens? We can think of the Grignard as " Ph^- ", so it's obvious that two of these can't just come together and make a bond... what accepts the extra electrons? Hmmm... The best way to prevent this is by running the reaction under an inert atmosphere of N_2 or Ar gas. In your case, ether fumes blanketed the reaction mixture, and this served the same purpose. In previous years this reaction was run with mechanical stirring — a motor attached to a glass shaft with a teflon paddle on the end stirred the mixture vigorously. That procedure resulted in large amounts of biphenyl that coated the inner surface of the flask. Why do you think more biphenyl was produced by that procedure?

Adapted from *Organic Experiments*, L.F. Fieser and K.L. Williamson; 7th ed, 1992; pp. 319-27.