Synthesis of 1-Phenylethanol: A Grignard Reaction

W. H. Bunnelle, L. A. Meyer, R. E. Glaser

Introduction

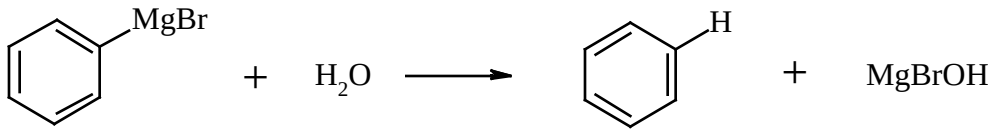
The Grignard reaction is one of the most useful reactions in organic chemistry. The reaction allows the creation of a carbon-carbon bond between an alkyl halide and a carbonyl compound, and is quite useful for the construction of large molecules from two smaller ones. This reaction is discussed in more detail in Wade, 4/e, Chapter 10, pp 433-443. One of the real virtues of the reaction is that it is very general – nearly any type of alkyl halide can be converted to a Grignard reagent, and these will react with virtually any carbonyl compound.

Preparation of the Grignard Reagent

Usually, Grignard reagents are prepared from the corresponding alkyl bromide or chloride:

$$R\text{-}X \xrightarrow[\text{ether}]{\text{Mg}} R\text{-}MgBr \qquad X = Br, Cl \text{ or } I$$

Iodides will react, but these starting materials are generally not as easy to prepare as are the chlorides and bromides. The one real restriction on the preparation and use of Grignard reagents is that they are very strong bases and, thus, they are easily destroyed by any source of protons. In general, any compound with H attached to a heteroatom (O, N, or S) is incompatible with the Grignard reagent, since a rapid acid-base reaction will take place, as illustrated by the reaction of phenylmagnesium bromide with water:



This means that Grignard reagents cannot be prepared from compounds containing reactive functional groups such as OH, NH_2, carbonyl groups, etc., which will react with the organometallic system as soon as it is formed. Likewise, solvents containing these functional groups must be avoided, since they will destroy the Grignard reagent. Usually, diethyl ether is used as a reaction solvent for Grignard reactions. Ether is polar enough to keep the Grignard reagent in solution, but does not react with the organometallic. Protection from moisture is a particular concern: since water is present in the atmosphere, we must design a reaction set-up which protects the reagent from moisture. This apparatus is illustrated in Figure 1. Basically, a modified reflux set-up is used. The reaction takes place in the round-bottom flask. Since the reaction is exothermic, and the heat produced is sufficient to boil the ether solvent, a reflux condenser must be included. In fact, the reaction is so vigorous that it must be controlled by slow (dropwise) addition of the alkyl halide to the magnesium metal. This addition is most conveniently accomplished through use of the separatory funnel, which holds the alkyl halide. The stopcock can be adjusted to maintain the proper rate of addition. (When used this way, the separatory funnel is more properly called an addition funnel.) Since the reaction flask has only one neck, provisions must be made for attachment of both the addition funnel and the condenser. This is achieved by using a Claisen adapter, that is, a “y”-shaped adapter. The addition funnel is best placed in the straight neck of the

Claisen adapter, with the condenser set in the curved neck. That way, the alkyl halide will drop directly into the reaction flask without dribbling along the walls of the apparatus. It is probably a good idea to support the addition funnel with an iron ring. Now, the liquid in the addition funnel will prevent any air from entering the system that way (until the addition is complete, at which time the stopcock will be closed). We cannot stopper the top end of the condenser, since we would then have a closed system, but something must be done to prevent moisture from entering through the condenser. A simple device called a drying tube is fitted to the top of the condenser with the thermometer adapter. The drying tube is simply a plastic or glass tube, filled with anhydrous $CaCl_2$ pellets. Any air which enters the apparatus must pass through the drying agent, where the moisture is removed.

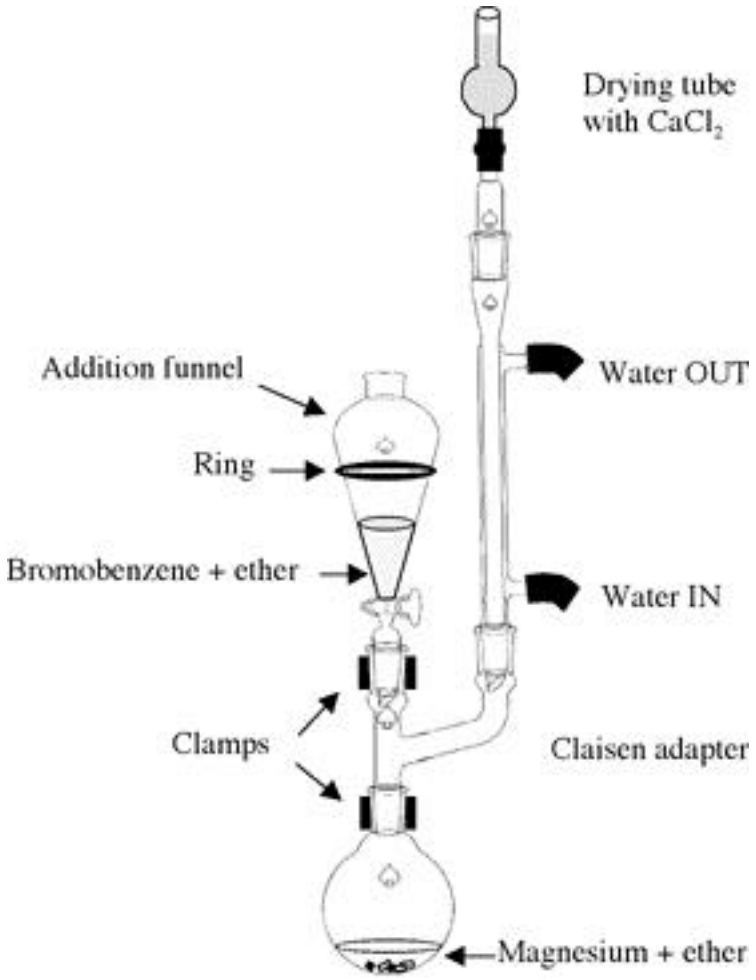


Figure 1. The apparatus for preparation of the Grignard reagent. During the flaming out process, the addition funnel is replaced with a glass stopper, and only the magnesium metal (no ether) is present in the flask.

Air-dried glassware inevitably has a thin layer of moisture adsorbed on the surface. Of course, this poses a problem for the preparation of Grignard reagents, since the moisture present will destroy an equivalent quantity of the organometallic. This film of moisture can be removed by a process called "flaming out" the apparatus. The reaction apparatus is completely assembled except for a glass stopper in place of the addition funnel. The flame from a torch is played across the entire outer surface of the apparatus. This will vaporize the water vapor from the inner surface of the glass, and as the atmosphere inside the apparatus heats up, it will expand and tend to drive the moisture up the condenser and onto the drying tube. Since moisture will tend to condense on a cool surface, it is important to get the entire glass surface heated. (Exception: The ground joints

should not be heated directly; peripherally at best). The flame is repeatedly brushed across the outer glass surface until it is warm – often, it is possible to see the evaporating mist. The heating process should be repeated twice more to ensure that moisture is adequately removed. The magnesium metal to be used in the reaction can be placed in the reaction flask prior to the 'flame out' process. This will ensure that moisture adhering to the metal surface is removed before reaction. In this case, however, care must be taken to avoid heating the metal too strongly. Surface oxidation of the metal is accelerated at higher temperature, and excessive heating may even cause ignition of the metal. After the third flame-out cycle, the apparatus is allowed to cool to room temperature. The flow of cooling water through the condenser is begun.

Dry ether is added to the magnesium metal in the reaction flask, and a solution of bromobenzene in ether is placed in the addition funnel, which is now fitted to the apparatus. A portion of the bromobenzene is then added to the reaction flask. Ideally, the reaction will begin spontaneously, evidenced by the development of cloudiness and a noticible exotherm which eventually will cause the ether solvent to boil. The reaction usually takes a few minutes to start, and initiation of the reaction can often be assisted by warming the bottom of the reaction flask with the palm of your hand, and gentle swirling of the flask. The mixture sometimes turns a yellow-brown color as the reaction proceeds.

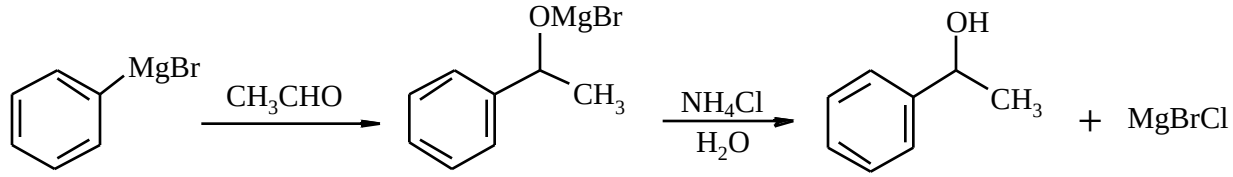
Frequently, the formation of the Grignard reagent is slow to start. There are several tricks to get a sluggish reaction started. The first thing to try is to crush a few pieces of the magnesium with a glass stirring rod. Often, a slow-starting reaction is caused by a thin coating of oxide on the surface of the magnesium; the idea here is to expose a fresh surface of clean metal where the reaction can begin. The flask can be removed from the rest of the apparatus for the short time it takes to do this. With one hand cupped around the outside of the flask for support, the glass rod is used to grind a piece of magnesium against the inner wall of the flask. This is repeated for two or three pieces of the metal, and the mixture is examined closely for signs of reaction. It is very important to provide proper support on the outer surface of the flask during this operation. It is surprisingly easy to punch the glass rod right through the wall of the flask, if such support is not given. This crushing procedure will get 95% of the reactions to start. If this method fails, check with your TA. It is sometimes helpful to add a small crystal of iodine to the reaction mixture. This reacts with magnesium metal to make MgI_2, in the process cleaning the metal surface. Another useful method is to add a small amount of reacting Grignard solution to the flask. For this purpose, a small-scale Grignard reaction can be initiated in a test-tube, and when that reaction commences, it is poured into the reaction flask. This "jump start" will normally take care of the most recalcitrant systems.

Once the reaction begins, and the ether is boiling at a steady reflux, the remainder of the bromobenzene solution is added dropwise through the addition funnel. The rate of the addition is controlled to maintain a steady refluxing of the ether, without allowing the reaction to become too violent. In case the reaction gets too vigorous, it can be moderated by cooling the flask with an ice bath. The addition should take about 20-30 minutes for completion.

The Grignard Reaction

At the end of the metallation reaction, the refluxing will subside and most of the magnesium metal should be consumed. It is possible to store solutions of Grignard reagents, so long as they are kept free from moisture and oxygen. More often, as in this case, they are used directly in the next reaction. The reaction of the Grignard reagent with ethanal (acetaldehyde) is easy to carry out using the same reaction apparatus. A solution of the acetaldehyde in ether is placed in the addition funnel, and added dropwise to the Grignard reagent. The reaction is quite exothermic and the flask should be cooled in an ice-water bath to moderate the reaction. During the addition, which should take about 10-15 minutes, the reaction mixture sets to a thick sludge due to precipitation of the magnesium salt of the alcohol, and the apparatus should be rocked gently several times during the addition to ensure reasonable mixing.

Reaction of the Grignard reagent with the aldehyde leads first to the magnesium alkoxide salt. Treatment of this salt with aqueous acid causes hydrolysis of the Mg-O bond and liberates the free alcohol.



A convenient mild acid to use here is a saturated aqueous solution of NH_4Cl, which converts the magnesium to a water-soluble salt (MgBrCl). Separation of the ether layer, followed by drying and removal of the solvent by distillation, provides the crude alcohol. The alcohol could be purified by vacuum distillation, but we will evaluate the purity of the crude product instead. The mass of the crude alcohol should be measured, and the percent yield calculated. An IR spectrum of the alcohol should be recorded, and the major, diagnostic peaks assigned.

Experiment 11

A Grignard reaction of phenylmagnesium bromide with ethanal will be used to prepare 1-phenylethanol. The crude product will be characterized by IR spectroscopy.

Safety: Ethyl ether is extremely flammable, and will not be permitted in the lab while flames are in use. Flames will be extinguished 20 minutes after the start of the lab period, and will not be permitted thereafter. Make certain that your apparatus has cooled completely before adding any ether. Ethanal is quite volatile and it is toxic (a narcotic). This material will be dispensed as a solution in ether. Bromobenzene is a skin irritant; if spilled on the skin, it should be washed off immediately with soap and water.

Nomenclature: Ether aka diethyl ether, ethanal aka acetaldehyde, 1-phenylethanol aka *sec*-phenethanol.

The reaction will be run in a 250 ml round-bottom flask, fitted with a Claisen adapter, addition funnel, condenser and drying tube as in Figure 1. All glassware must be clean and dry. Do not use acetone to rinse your glassware: Acetone reacts with the Grignard reagent, and poses a fire hazard during the flaming out process. The addition funnel is set aside, and the straight neck of the Claisen adapter closed with a glass stopper. Do not connect the condenser hoses at this time. Magnesium turnings (2.0 g) are placed in the flask, and the apparatus flamed out as described in the text. Dry the system thoroughly, but take care to avoid strong heating of the magnesium metal or direct heating of the ground joints. Let the apparatus cool completely before proceeding further.
Connect the condenser hoses and begin the flow of water through the jacket. Prepare a solution of 8.0 ml of bromobenzene in 60 ml of dry ether and place in the addition funnel. Run about 15 ml (1/4th) of this solution into the reaction flask, and wait for the reaction to begin before adding any more. Warm the flask with the palm of your hand, and crush a few of the magnesium pieces to help initiate the reaction. The first sign of reaction is the development of turbidity in the solution, and a slow bubbling at the metal surface. This will develop rapidly to a steady, rolling boil as the reaction begins in earnest. After the initial burst of reaction has tailed off somewhat (but before boiling stops all together), begin the dropwise addition of the remainder of the bromobenzene solution. The rate of addition should be adjusted so as to sustain a steady reflux without losing any ether out of the top of the condenser. The addition normally takes about 20 - 30 minutes. After the addition is complete, the stopcock of the addition funnel should be closed, and the mixture allowed to stand until the reaction has subsided.

The addition funnel is charged with a solution of ethanal in dry ether (20 ml of a 4.0 M solution), and the reaction flask is cooled in an ice water bath. The aldehyde solution is added dropwise to the Grignard reagent, with frequent, gentle rocking of the apparatus to ensure good mixing. The addition normally takes 10 - 15 minutes. The reaction mixture is then allowed to stand for 5 minutes more, and finally quenched by cautious addition (through the addition funnel) of 20 ml of saturated aqueous NH_4Cl. The layers are separated (the addition funnel becomes a separatory funnel once again; it may be necessary to add up to 15 ml of water to dissolve the salts), and the ether layer is washed with 20 ml of saturated NaCl solution, and dried over Na_2SO_4.
The solvent is removed by simple distillation into a tared distilling flask. Don't forget to add a couple of boiling chips. Distill as much ether as possible. The last traces of solvent can be removed from the residue by the following procedure. The distilling flask is fitted with the vacuum adapter, which is then stoppered. A vacuum hose is fitted to the adapter as illustrated in Figure 2, and this is connected to a vacuum source. Swirl the flask and warm gently in a boiling water bath while pumping - the last bit of ether will be removed within a few minutes. Disconnect the vacuum adapter, determine the yield of the product, and record its IR spectrum.

Waste: Aqueous waste, including any magnesium salts, go in the container provided. The distilled ether should be returned to the bottle labeled "recovered ether." Nothing else goes in this bottle!

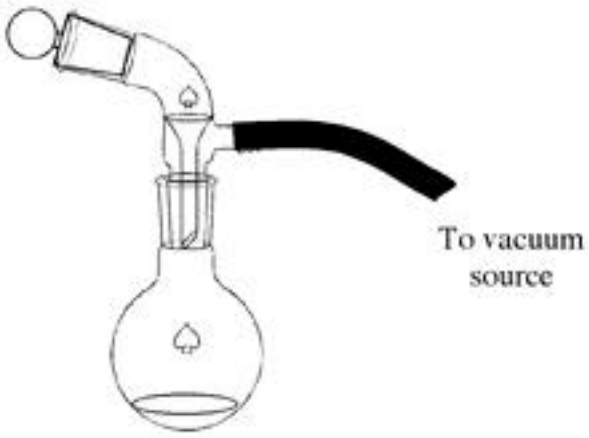


Figure 2. The apparatus for vacuum evaporation of the last traces of solvent.

Post-laboratory Questions

1. What is the limiting reagent for the overall transformation of bromobenzene to 1-phenylethanol?

2. A common byproduct of the formation of a Grignard reagent (RMgBr) is the coupling product R-R. In the present case, formation of phenylmagnesium bromide might be accompanied by the production of biphenyl, C_6H_5—C_6H_5, which would carry through the rest of the synthesis unchanged. The IR spectra of pure biphenyl and pure 1-phenylethanol can be found on the web sites referenced in the "Infrared Spectroscopy" section of experiment 3. Find a transmittance spectra in one of these web sites, for both biphenyl and 1-phenylethanol, and include them in your report. Can you identify a band which would be diagnostic for the presence of any biphenyl impurity in 1-phenylethanol? Based on the IR spectrum of your product, what can you say about its purity?

3. Suggest another Grignard reaction which would lead to 1-phenylethanol.

4. The last traces of ether are removed under vacuum (~30 Torr). Estimate the boiling temperature of 1-phenylethanol at 30 Torr. Is there a danger of losing the 1-phenylethanol during this treatment?