

Synthesis of 1-Phenylethanol: A Grignard Reaction

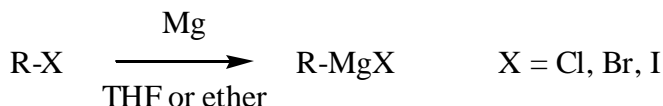
W. H. Bunnelle, L. A. Meyer, R. E. Glaser (Version 3)

Introduction

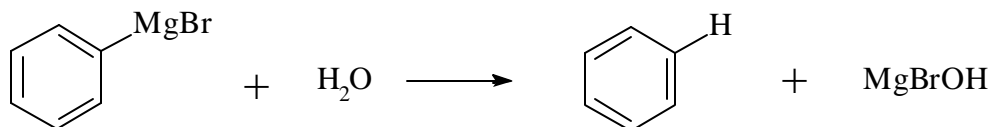
The Grignard reaction is one of the most useful reactions in organic chemistry. The reaction allows the creation of a carbon-carbon bond between an alkyl halide and a carbonyl compound, and is quite useful for the construction of large molecules from two smaller ones. This reaction is discussed in more 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:



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, NH₂, 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. Tetrahydrofuran (THF) and diethyl ether are most commonly used as reaction solvents for Grignard reactions. They are polar enough to keep the Grignard reagent in solution, but do 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 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, a Claisen adapter is used to attach both the addition funnel and the condenser. 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). A simple device called a

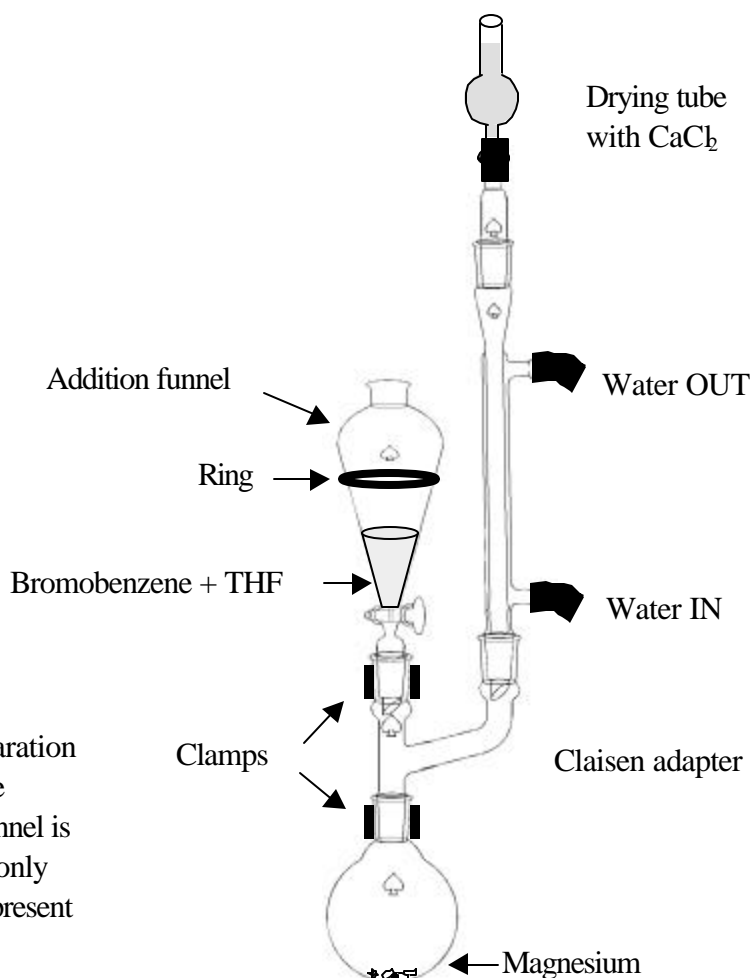


Figure 1. The apparatus for preparation of the Grignard reagent. During the flaming out process, the addition funnel is replaced with a glass stopper, and only the magnesium metal (no THF) is present in the flask.

drying tube is fitted to the top of the condenser with the thermometer adapter, to prevent moisture from entering through the condenser. 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.

Air-dried glassware inevitably has a thin layer of moisture adsorbed on the surface. This poses a problem for the preparation of Grignard reagents, since the moisture present will destroy an equivalent quantity of the organometallic. The 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.

A solution of bromobenzene in THF is placed in the addition funnel, which is now fitted to the apparatus. A portion of the bromobenzene/THF solution is then added to the reaction flask. Ideally, the reaction will begin spontaneously, evidenced by the development of cloudiness and a noticeable exotherm which eventually will cause the THF 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.

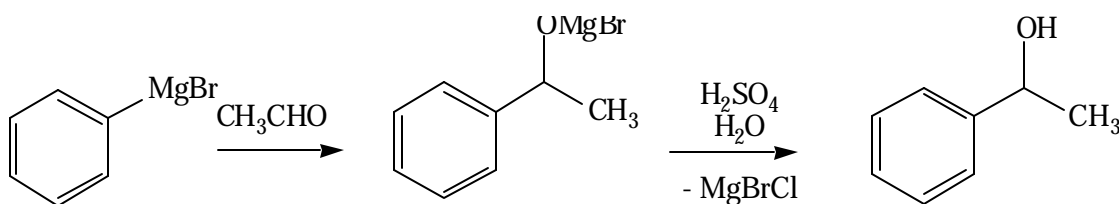
Frequently, the formation of the Grignard reagent is slow to start. There are several tricks to get a sluggish reaction started. The first thing to try is to crush the magnesium in a mortar and pestle prior to flame-out. Often, a slow-starting reaction is caused by a thin coating of oxide on the surface of the magnesium; the idea here is to expose a fresh surface of clean metal where the reaction can begin. If this method fails, check with your TA. It is sometimes helpful to add a few drops of 1,2-dibromoethane, which reacts rapidly with magnesium to form ethylene, thus providing a clean surface on the metal for the reaction to start. A small crystal of iodine also serves the same purpose. 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 THF 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 THF, 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 THF 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.



Separation of the organic 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: 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 THF. Ethanal is quite volatile and it is toxic (a narcotic). This material will be dispensed as a solution in THF. Bromobenzene is a skin irritant; if spilled on the skin, it should be washed off immediately with soap and water. Ethyl ether is extremely flammable.

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 dry and reasonably clean (Check with your TA and he/she will tell you if you need to wash it). 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. The magnesium turnings (2.0 g) are crushed with a mortar and pestle, and placed in the flask. The apparatus is 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 THF 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. 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 THF 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 4.5 mL ethanal and 15.5 mL THF (this is a 4.0 M ethanal solution in THF), 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.

Pour the reaction mixture into a 250 ml Erlenmeyer flask containing 25 ml 10 % sulfuric acid and 15 g ice. Rinse the reaction flask with 5 ml THF followed by 5 ml 10 % sulfuric acid, and combine these rinses with the reaction mixture. Transfer the mixture into a separatory funnel leaving the magnesium and ice behind. Rinse the Erlenmeyer flask with 30 mL ether and combine with the mixture in the separatory funnel. The layers are separated (It may be necessary to add up to 15 ml of water to dissolve remaining salts), and the ether/THF layer is washed with 20 ml of saturated NaCl solution, and dried over 1-2 g of Na_2SO_4 (add more Na_2SO_4 if solution is not clear).

Filter the dried ether/THF solution through a small cotton plug into a tared round-bottom flask and remove the solvent using a rotary evaporator under vacuum. Your TA will demonstrate how to operate. Determine the yield of the product, and record its IR spectrum.

Post-laboratory Questions

1. What is the limiting reagent for the overall transformation of bromobenzene to 1-phenylethanol?
2. What peak in the IR spectrum most clearly demonstrate the presence of alcohol product? If the product had unreacted aldehyde remaining, what IR peak would indicate the presence of this contaminant?
3. Suggest another Grignard reaction which would lead to 1-phenylethanol.