

19. The Grignard Reaction

A. Introduction

The Grignard reaction is an extremely valuable reaction in organic chemistry because it allows for the formation of carbon-carbon bonds. The reaction was discovered by the French chemist Victor Grignard. He was awarded the 1912 Nobel Prize in Chemistry for his work.

A Grignard reaction involves the use of a Grignard reagent, which is an alkyl, aryl, or vinyl halide that has magnesium inserted between the carbon halogen bond. The reagents are quite easily prepared by adding magnesium metal to a solution of the alkyl, aryl, or vinyl halide. Some representative Grignard reagents are shown in figure 1a. Addition of magnesium into the bond changes electronic character of the carbon that was previously bonded to the halogen. For example, in bromobenzene, the carbon bears a partial positive charge because of inductive electron withdrawal by the bromine. In contrast, the addition of magnesium changes this character as shown in figure 1b. The magnesium metal bears a partial positive charge while the adjacent carbon bears a partial negative charge. The negative character on the carbon makes it a strong nucleophile. It may actually be helpful to think of the Grignard reagent as an ion-pair where the carbon bears a negative charge and MgBr bears a positive charge.

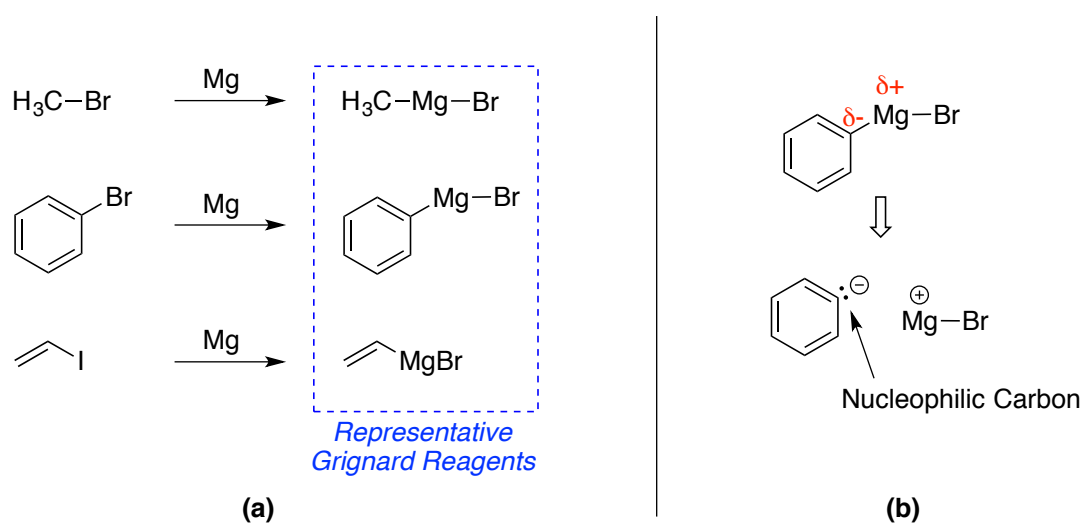


Figure 1: Grignard Reagents

The nucleophilic Grignard reagent reacts readily with a variety of electrophiles, most notably carbonyl compounds. In the case of aldehydes and ketones, one equivalent of Grignard reagent can react with the aldehyde or ketone to provide 2° and 3° alcohols, respectively (figure 2 a&b). When esters and acid chlorides are reacted with Grignard reagents, however, two equivalents of reagent are necessary. This results in the addition of two R groups to the carbonyl carbon and formation of a tertiary alcohol (figure 2 c&d). The second addition of Grignard reagent is possible with esters and acid chlorides due to the presence of a leaving group (OR, Cl) attached to the carbonyl carbon.

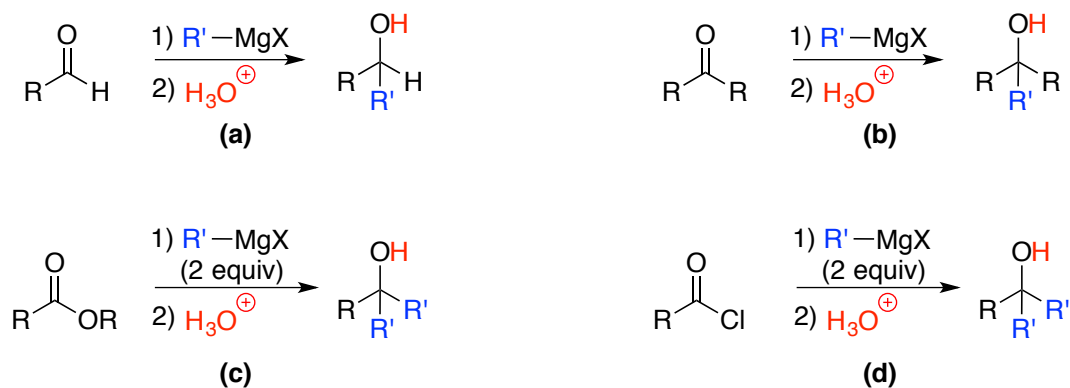


Figure 2. Grignard Reactions with Carbonyl Compounds

In this laboratory experiment, you will be reacting the ester methyl benzoate with phenyl magnesium bromide. Because the carbonyl compound is an ester, two equivalents of Grignard reagent will be used, allowing for the addition of two phenyl groups to the carbonyl carbon. The mechanism for this reaction is shown in figure 3. In the first step, the nucleophilic Grignard reagent adds to the electrophilic carbonyl carbon of the ester to provide a tetrahedral intermediate. This unstable intermediate then collapses to reform the carbon-oxygen double bond along with loss of CH_3O^- . The resulting product is an electrophilic ketone, which is attacked by a second equivalent of Grignard reagent providing another tetrahedral intermediate. This intermediate does not contain a leaving group, thus the reaction cannot continue further. Upon acidic workup, the negatively charged oxygen is protonated to provide the tertiary alcohol product.

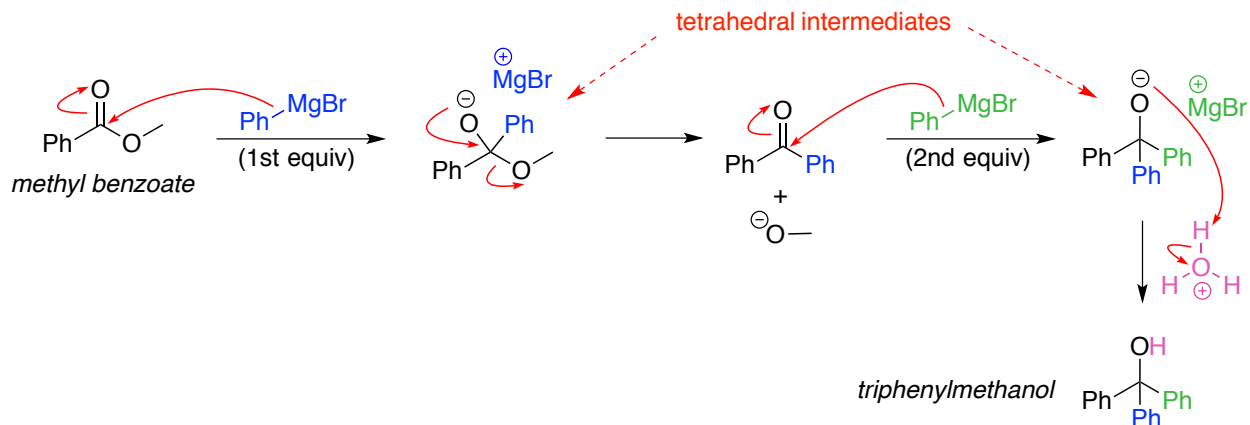


Figure 3. Mechanism for Grignard Addition to an Ester

Reaction Solvent

In addition to being a strong nucleophile, Grignard reagents are extremely basic and react rapidly with protic molecules. It is therefore imperative that the solvent used for a Grignard reaction be aprotic and anhydrous (completely free of water). Typical solvents for Grignard reactions include anhydrous diethyl ether and tetrahydrofuran (THF). If traces of water are present in the reaction solvent or on the glassware being used, the Grignard reagent will react with the water and be destroyed. If this undesired reaction consumes the Grignard reagent, it will be unavailable for reaction with the carbonyl compound. Figure 4 shows the fate of a Grignard reaction reacting with a protic solvent such as water.

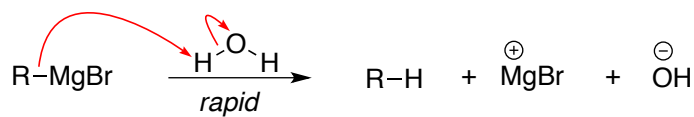


Figure 4. Reaction of a Grignard Reagent with Water

Formation of the Grignard Formation

It is often difficult to get the reaction between magnesium and the organohalide to start. Upon extended exposure to oxygen in the air, a thin layer of magnesium oxide can surround the surface of the magnesium, which prevents the metal from inserting between the carbon-halogen bond. Typically, a small amount of I_2 or 1,2-dibromoethane is added to the magnesium metal to help “activate” it. These activators react with the magnesium at areas of the metal where the oxide layer most thin. This opens up reactive sites on the metal where it can subsequently react with the desired organohalide. In this experiment, 1,2-dibromoethane will be used as the initiator. It is an especially reactive alkyl halide and the organic product is ethylene gas, which escapes out of the reaction flask (figure 5).

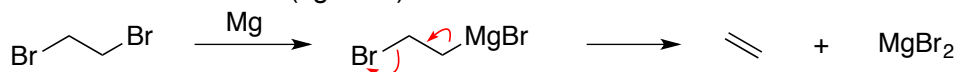


Figure 5. Activation of the Magnesium Metal with 1,2-Dibromoethane

B. Experimental Procedure

Upon first entering the lab, place a 10-mL round bottomed flask, spin vane, water condenser, and Claisen head in a 110 °C oven. The glassware should be left in the oven for 10-20 min to remove residual moisture. Following the quiz and pre-lab lecture, carefully remove the glassware from the oven. When the glassware is cool enough to handle, assemble the reaction apparatus as shown in figure 6. Try to assemble the apparatus while it is still warm. Use black screw caps/connectors with O-rings to connect the various pieces of glassware together. Be sure to include a septum at the top of the Claisen head and at the top of the condenser. Clamp the entire apparatus just above the stir plate. The entire system is to be maintained under a positive nitrogen pressure, which is accomplished using a nitrogen line branched off to a nitrogen bubbler. Your TA will explain thoroughly how to set up the nitrogen lines. Leaks tend to appear at the junction between the dry tubing and the needles. It is often necessary to use parafilm to help form a seal between the needle and tubing.

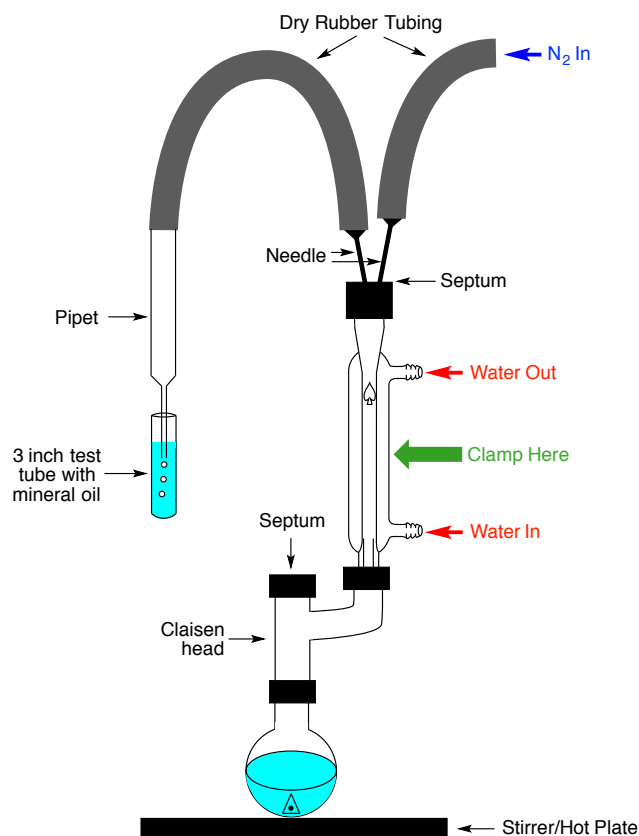


Figure 6. Grignard Reaction Assembly

Weigh out approximately 54 mg of magnesium. The magnesium is provided in the form of a ribbon that can be cut into several small pieces with scissors. Once measured out, the magnesium should be transferred to the round bottom flask, which is to be quickly reconnected to the rest of the apparatus. Based on the amount of magnesium *actually* measured out, complete the reagent table below (Table 1).

Table 1. Reagents Used in the Grignard Reaction

Reagent	MW	Equiv.	Sample Data		Actual Data	
			Mass	Mmol	Mass	Mmol
Magnesium (Initially)	24.3	2.2	53.5 mg	2.20		
1,2-Dibromoethane	187.9	0.2	3 drops	0.20	3 drop	0.20
Magnesium (Left)*	24.3	2	48.6 mg	2.00		
Bromobenzene	157.0	2.5	393 mg	2.50		
Methyl Benzoate	136.2	1	136 mg	1.00		

*The magnesium (left) is determined by taking the mmol of magnesium initially obtained and subtracting the mmol reacted away (0.20 mmol) upon introduction of the 1,2-dibromoethane.

Obtain three 1-dram vials along with the corresponding screw caps. In **vial 1**, dissolve methyl benzoate in 1.0 mL of anhydrous diethyl ether. In **vial 2**, dissolve bromobenzene in 1.5 mL of anhydrous diethyl ether. In **vial 3**, dissolve three drops of 1,2-dibromoethane in 0.5 mL of anhydrous diethyl ether along with 10 drops of the bromobenzene solution from vial 2. Cap each vial tightly to prevent the solvent from evaporating.

Flush the entire apparatus with nitrogen for ~5 min. First, ensure you have no leaks by adjusting the nitrogen flow so that there is a steady stream of bubbles exiting the bubbler. Next, loosen the lock nut with the septum on the Claisen head to allow nitrogen gas to escape. Allow the system to purge for ~5 min. During this time, you should have the spin vane stirring to help move the nitrogen gas through the system. After the nitrogen purge, tighten the lock nut/septum and decrease the flow of nitrogen through the system.

Using a syringe and needle, transfer the contents of **vial 3** to the round bottomed flask by injecting the solution through the septum in the Claisen head. The reaction should initiate and turn cloudy with the evolution of gas. After a few min, the solution should become clear. Once the reaction is underway, add the contents of **vial 2** over 5 min via syringe. The reaction is exothermic and you should observe the ether solvent boiling in the flask. Once boiling ceases, heat the flask using the hot-plate on a low setting (remember the boiling point of ether is 35 °C) until the ether begins to reflux. Allow the reaction mixture to stir at reflux until all of the magnesium has reacted away.

Next, add the contents of **vial 1** over 2 min via syringe, then heat the solution to reflux with stirring for 30 min. If the volume of ether in the flask drops significantly, add additional anhydrous ether through the septum.

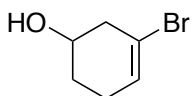
Remove the reaction from heat and allow it to cool slightly. Turn off the nitrogen line and disconnect the round-bottomed flask from the apparatus. Cool the flask containing the reaction mixture in an ice bath. To the cooled solution, add 1 mL of water slowly then add 3 M aqueous HCl dropwise until all of the solids dissolve. Using pH paper, check to ensure that the aqueous layer is acidic. *At this point, the reaction can be stopped and finished up during the next lab period if necessary.*

Transfer the entire reaction mixture to a 5 mL conical vial using a pipet. Wash the flask with 1 mL of diethyl ether and transfer this solution to the 5 mL vial. Add a spin vane to the conical vial and stir the solution rapidly for 1 min on the stir-plate to affect extraction of the organic components into the ether layer. Stop stirring and allow the layers to separate. Carefully pipet out and discard the lower aqueous layer. Add 1.5 mL of water and stir the solution rapidly to wash the ether layer. Again, allow the layers to separate and discard the lower aqueous layer. Finally, add 1 mL of saturated aqueous sodium chloride (brine), stir, allow the layers to separate, and discard the lower aqueous layer.

Dry the organic layer by passing it through a drying tube prepared from a small pipet plugged with cotton containing 3-4 cm of anhydrous Na_2SO_4 . Collect the dried organic solution into a conical vial. Rinse the drying tube with ~ 0.5 mL of ether and collect this solution in the vial. Using a stream of nitrogen and gentle heating if necessary, evaporate the solvent to provide an oil. Add 1 mL of hexane to precipitate out a solid product. Warm the solution for a few minutes to dissolve impurities. Remove the vial from heat and cool the solution in an ice bath. Collect the solid product by Hirsch filtration washing the solid with a bit of hexane. Calculate the yield, determine the melting point, and record an IR spectrum of the solid product.

C. Pre-Lab Questions

1. A Grignard reagent is prepared by reacting *trans*-1-bromo-1-butene with magnesium. What are the products of the reaction when this reagent is reacted with:
 - a. Ethanol
 - b. Acetone
 - c. Ethyl Acetate ($\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$) [assume excess Grignard reagent]
 - d. Deuterium Oxide (D_2O)
2. A student tried to prepare a Grignard reagent from the organohalide shown below. This student was not successful. Explain why.



3. Toward the end of the procedure, you are instructed to remove the reaction flask from the apparatus and add 1 mL of water. Why is it not necessary to carry out this step under the nitrogen atmosphere?

D. Post-Lab Questions

1. Look up the literature melting point range for triphenylmethanol. How does your experimental melting point compare?
2. What key IR stretches are present in your reaction product?
3. If you were to obtain an NMR spectrum of your product to accompany your IR data, which type of NMR experiment do you think would be most useful, ^1H or ^{13}C ? Explain.
4. What ketone starting material will react with PhMgBr to provide triphenylmethanol?