Experiment 47

Nucleophilic Addition to Carbonyl: Grignard Reaction with a Ketone

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PURPOSE OF THE EXPERIMENT

Demonstrate the formation of a carbon-carbon bond using the addition of a Grignard reagent to a ketone. Perform the reaction under anhydrous reaction conditions.

BACKGROUND INFORMATION

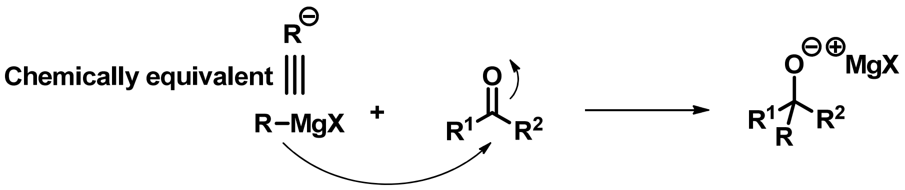
Victor Grignard had investigated the reaction of organic halides with magnesium at the turn of the twentieth-century. For this work, he received the 1912 Nobel Prize in Chemistry. In the history of organic chemistry, the Grignard reaction has stood out due to its broad substrate scope, operational simplicity, and versatility.

Common non-metals such as oxygen, nitrogen, and the halogens are more electronegative than carbon. As a result, a carbon bonded to these atoms has a partial positive character. When magnesium is inserted between the carbon and a halogen, however, the polarity is reversed because carbon is more electronegative than magnesium. This process transforms carbon from an electrophilic atom to a nucleophilic one, as shown in Equation 1. The Grignard reaction was the first reaction to generate the use of carbon as a nucleophile to make carbon-carbon bonds.

(Eq. 1)

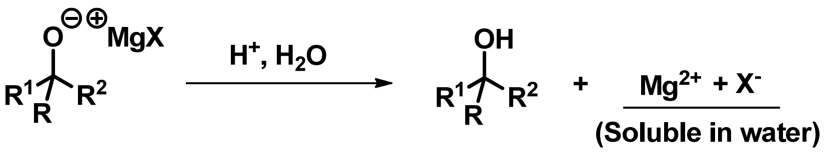
The structure of a Grignard reagent in solution has been the subject of intense studies. In fact, a Grignard reagent cannot be isolated without a solvent present. The non-bonded electrons from the oxygen in an ether solvent or the nitrogen in an amine solvent are necessary to stabilize a Grignard reagent. The standard way of indicating a Grignard reagent, RMgX, is not an accurate representation of the larger aggregation in solution. The stoichiometry works, however, as if RMgX were the actual reactive species. For simplicity, chemists continue to use this designation.

The nucleophilic carbon of a Grignard reagent rapidly adds to the carbonyl carbon of an aldehyde or ketone, as shown in Equation 2. A Grignard reagent can also react with esters, acid chlorides, nitriles, expoxides, and carbon dioxide.



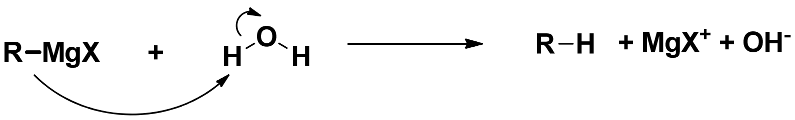
(Eq. 2)

Hydrolysis of the resulting complex with aqueous acid produces an alcohol (Equation 3). The reaction of Grignard reagent with formaldehyde produces a primary alcohol. With any other aldehyde, the Grignard reaction produces a secondary alcohol. with a ketone, the Grignard reaction produces a tertiary alcohol.



(Eq. 3)

The greatest practical challenge in preparing a Grignard reagent is to keep water out of the reaction. The negative charge of the carbon in the Grignard reagent makes the carbon very basic. Water can donate a proton to the carbon, destroying the nucleophilic character of the Grignard reagent (Equation 4). Several precautions should be taken in the procedure to exclude water: the reaction flask should be flame-dried before adding solvent; a N_2 ballon keeps wet air from entering the apparatus; the diethyl ether solvent should be specially dried and packaged to guarantee that it is anhydrous.



(Eq. 4)

EXPERIMENTS **Addition of allylmagnesium bromide into 9-fluorenone to form 9-allyl-9H-fluoren-9-ol**

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	*mp* (°C)	bp (°C)	*density (g/mL)*
Allyl bromide	0.5 mL	120.98		71	1.43
Magnesium (turnings)	~ ~~170~~200 mg	24.31			
1,2-Dibromoethane*	0.05mL	187.86			2.18
9-Fluorenone	360mg	182.20	48		
NH_4Cl (saturated in water)	~ 4mL				
diethyl ether anhydrous					
water, distilled	~6mL				

*Addition of 1,2-dibromoethane is optional.

PROCEDURE

Caution: Wear lab coats and safety goggles at all times while in the lab. Wearing contact lens is strictly prohibited.

1. Drying the Apparatus

Note 1. Use of manifolder and doing flame-drying should be guided by your TA

All equipment and reagents must be *absolutely dry*.

Dry a clean, reflux condenser and two necked round-bottom flask (RBF) in a oven (~80 °C) for at least 30 min.

To a 50 mL two necked ~~round-bottom flask~~ (RBF) add a magnetic stirring bar and magnesium turnings. Be aware of magnesium turnings which sticks to mouth of RBF, it can cause RBF to break during vacuum pump process. Close the side neck of RBF with a rubber septum. Connect the RBF with reflux condenser. Then apparatus is connected to a high vacuum pump through a manifolder for 10 mins. ~~Under the vacuum, perform the flame-drying for the RBF.~~

Note 2. Ask your TA how to prepare a N_2 balloon.

When the RBF is cooled to room temperature, the flask is released from the manifolder under N_2 atmosphere by attaching N2 balloon and immediately close the top of condenser with a rubber septum as shown in Figure 1. Connect water line to the reflux condenser and flow the water before the addition of reagents. C**onfirm the direction of water flow in and out correctly and make sure the water flow out to the sink.**

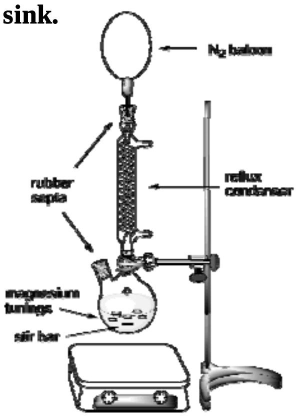


Figure 1. Reflux apparatus for the Grignard reaction

2. Preparing the Allyl magnesium bromide Reagent

Caution: Diethyl ether is highly flammable and toxic. Do not use it near flames or other heat sources. *Make sure that all burners in the laboratory are extinguished before opening the container of diethyl ether*. Prevent eye, skin, and clothing contact. Use a ***fume hood***.

Add 4 mL of anhydrous diethyl ether to the flask using a disposable syringe to the side neck of RBF. The mixture starts vigorous stirring. (Optional : Add the 1,2-dibromoethane slowly dropwise using a disposable syringe and bubbling in the mixture can be observed.) Then add the allylbromide slowly by dropwise using a disposable syringe. Place the ice-bath or water-bath to the reaction flask ~~when the vigorous boiling is observed~~.

Note 3. Instead of using 1,2-dibromoethane or iodine, ground magnesium tuning using a mortar and a pestle can be used.

The preparation of Grignard reagent completes when only a few remnants of metal remain (normally takes 30 mins). Check to see whether the volume of ether has not decreased. If it has, add more anhydrous ether. Since the solution of Grignard reagent decomposes on standing, the next step should be started immediately.

3. 9-Allyl-9H-fluoren-9-ol from 9-Fluorenone

To a 25 mL one neck RBF, add 9-fluorenone and close the neck with a rubber septum. Evacuate the air using manifolder for 10 mins and attaching N_2 balloon in the RBF. Add 5 mL of anhydrous diethyl ether using disposable syringe. Dissolve 9-fluorenone in diethyl ether and take the whole solution using the disposable syringe. Using the syringe, transfer a 9-fluorenone solution dropwise into the prepared Grignard reagent solution through the side-neck septum. The resulting mixture was stirred for 30-40 mins. Take the reaction mixture using capillary and develop the TLC for checking the reaction completed or not.

Prepare an ice bath or water bath and place it on the flask. Remove the side-neck rubber septum and add 4 mL diethyl ether, 4 mL saturated aq. NH_4Cl solution and 6 mL distilled water in sequence with vigorous stirring.

Remove the RBF from the apparatus. Then gradually pour the reaction mixture into a separatory funnel (rinse the flask with ether three-times), and shake it. Allow the layers to separate. Drain the aqueous layer from the separatory funnel into a beaker. Collect the organic layer into the Erlenmeyer flask. Pour the aqueous layer again to separatory funnel and repeat the extraction for two times in same sequence.

Add anhydrous magnesium sulfate ($MgSO_4$) to the ether solution for drying the solution. Equipped the flask with a stopper and allow the solution to dry for 5 mins. Then filter the solution through a glass filter into a tared RBF. The collected ether layer is evaporated by using a rotary evaporator and evacuate the solvent until the solid obtain.

4. Characterizing the product by ^{1}H NMR

Rinse the solid product with hexane. And filter the solid product using Buchner funnel or glass funnel with aspirator. Rinse with the hexane a few times and dr~~ied~~y it. Weighing the blank vial first and transfer the solid product to vial.

Confirm your product by ^{1}H NMR and assigned each peaks with simple explanation. Finally, calculate the yield of product in percentage.

Post-Laboratory Questions

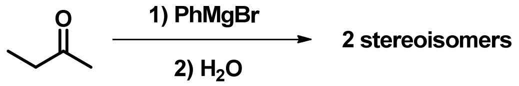
1. Although this reaction underwent well, suggest the method to improve the reaction yield or reaction rates in this experiment. (You can change the reagent but the product must be same.)

2. The purification of product is important in chemical reaction.

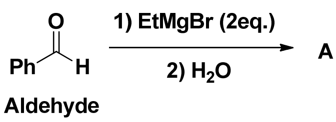
a) We used excess amount of allylmagnesium bromide in this experiment. However, the final product did not contain anything from allylmagnesium bromide except 9-allyl-9H-fluoren-9-ol. Explain this with brief reason.

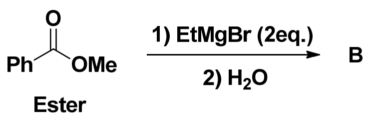
b) If the starting material (9-Fluorenone) is still present, we could separate it from the product using the above procedure. Explain how they were separated and suggest other methods to separate the product from the reaction mixture.

3. Draw all stereoisomers of product in this reaction.

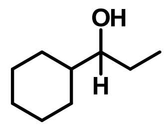


4. Expect the products of each reaction and explain the reason why two reactions showed different products.





5. Suggest the way to synthesize the given compound with appropriate Grignard reagent and carbonyl compound. (There can be various ways to synthesize it.)



Pre-Laboratory Questions

Only handwriting! No typing.

1. Summarize MSDS of all chemicals used in this experiment.

2. Explain the reason why we should perform a flame-drying of all glass wares before preparing the Grignard reagent.

3. Explain the function of 1,2-dibromoethane or iodine in the preparation of the Grignard reagent using the mechanism of Grignard reagent preparation.

4. Show the chemical reaction of this experiment <u>in structural formula</u>. Assign the nucleophile and the electrophile, respectively. (The reaction is 9-fluorenone with allylmagnesium bromide. Draw both reactants and products.)

5. Expect the R_f value of <u>product</u> compared to the starting material. Is it higher or lower than 9-fluorenone? Explain with brief reasoning.