

Fig. 20-1



Experiment 20

GRIGNARD SYNTHESIS OF A DEUTERATED COMPOUND

Francois Auguste Victor Grignard (1871-1935)

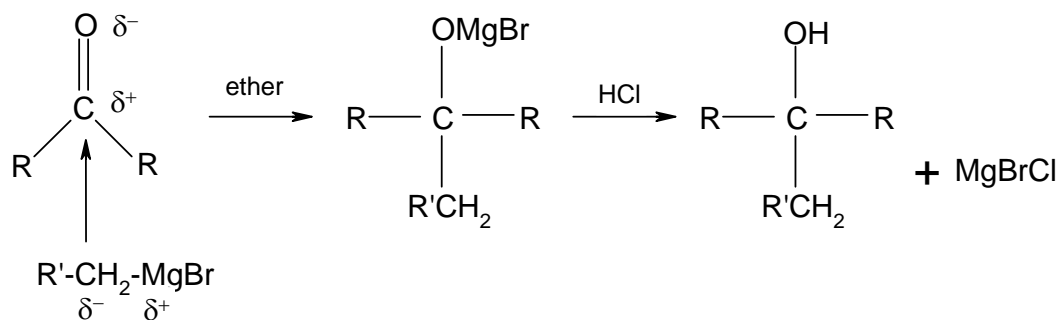
http://nobelprize.org/nobel_prizes/chemistry/laureates/1912/grignard-bio.html

Text Topics and New Techniques

Grignard reaction (**glassware must be dried several hours prior to starting**). For a possibly “greener” solvent, see: Teixeira, J. M.; Byers, J. N.; Perez, M. G.; Olman, R. W. *J. Chem. Ed.*, **2010**, 87, 714-716.

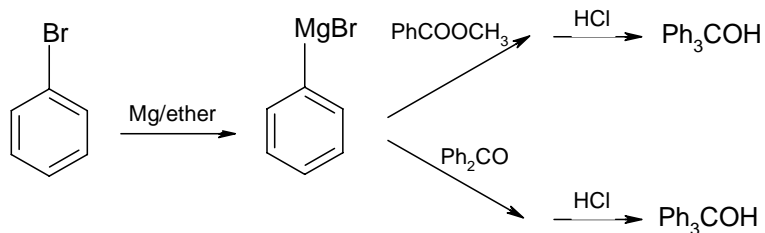
Discussion

Reactions that form carbon - carbon bonds are of the utmost importance in organic synthesis. Included among carbon - carbon bond forming reactions are the Diels-Alder, Friedel-Crafts and Wittig reactions and the use of acetylide, cyanide and the conjugate bases of carbonyl and carboxyl compounds as nucleophiles. Perhaps the most versatile of all use organomagnesium reagents commonly known as Grignard reagents. Grignard reagents and the similar but even more reactive organolithium reagents have the advantage that a carbon metal bond is polar covalent in nature with the partial negative charge on the carbon. This means that the Grignard reagent undergoes reactions that might be expected of carbon nucleophiles. In other words, because of its partial negative charge, the carbon bonded to the magnesium attacks sites that are susceptible to attack by nucleophiles such as the partially positively charged carbon of carbonyl and carboxyl groups. A typical reaction between a Grignard and a symmetrical ketone is illustrated below.

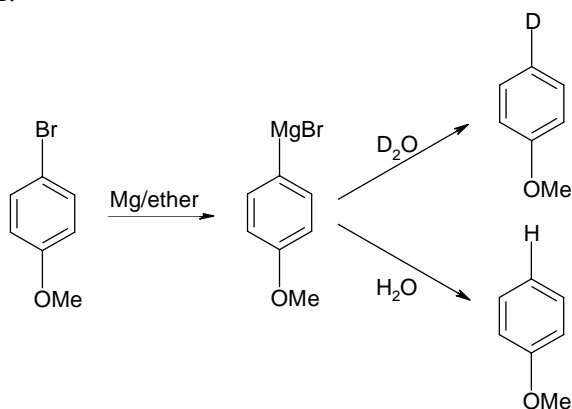


Fortunately, it is relatively easy to make Grignard reagents from alkyl chlorides or bromides. It does need to be recognized, however, that Grignard reagents will not form if even traces of water are present and the glassware to be used needs to be dried preferably in an oven for several hours before use.

To give students experience with the preparation and reactions of Grignard reagents, many organic laboratory texts include the preparation of triphenylmethanol. This is accomplished by the preparation of the Grignard from bromobenzene and subsequent reaction with either methyl benzoate or benzophenone. Both reactions afford triphenylmethanol in good yield and differ primarily in the mole ratio of Grignard to carboxyl or carbonyl required.



Instead of preparing triphenylmethanol, a different preparation was selected for this experiment. The first reaction in today's experiment will be similar to the first reaction illustrated above except that 4-bromoanisole will be used in place of bromobenzene. The Grignard reagent produced will then be reacted (or quenched) with deuterium oxide. Because it is extremely difficult to exclude all the water, the product will be a mixture of 4-deuteroanisole and anisole. Your goal will be to determine the ratio of the two in your product mixture using H-nmr.



Techniques

Because Grignard reagents do not form in the presence of water, all necessary glassware should be placed in a 105°C oven several hours or overnight prior to the time the experiment is to be performed. The usual glassware for a Grignard includes a round bottom flask equipped with a magnetic stirring bar, a reflux condenser and a dropping funnel. Be sure to remove all plastic parts before insertion into the oven. Dry ether is by far the most commonly used solvent for Grignards although tetrahydrofuran is also used. A freshly opened can is strongly recommended as once an ether container has been opened, it will begin to accumulate moisture from the air and also to air oxidize to a potentially explosive peroxide. "Dry" ether once opened should never be stored for prolonged periods of time.

The magnesium used for Grignards should be specially prepared Grignard magnesium. Although Grignard reactions are often difficult to start, once started, they are exothermic. An ice bath should be kept within arm's reach to cool the reaction should it start refluxing too fast. As the instructions call for use of a magnetic stirrer and a heating mantle for gentle refluxing, the mantle and stirrer unit should be mounted on a lab jack so they can quickly be lowered and replaced by the ice bath if necessary. Drying tubes packed with calcium chloride should be placed in the top of the condenser and the dropping funnel.



Fig. 20-2

Procedure

Be sure there are no flames any time during this experiment in your laboratory. Diethyl ether has a very low flash point temperature. Set up your dried glassware as illustrated above using a 100 mL round bottom flask. A 3 necked flask can also be used. Assemble the system so that the flask is in a heating mantle on a magnetic stirrer unit with a stirring bar in the flask. Add 1.2 g of magnesium turnings to the flask. Transfer 5 mL of 4-bromoanisole and 10 mL of dry ether to the dropping funnel. Turn on the water in the condenser and set the magnetic stirrer to a vigorous level. Add about a third of the halide solution to the magnesium. An exothermic reaction should start within a few minutes and cause the reaction to gently boil. If after several minutes, the reaction has not started, try crushing a couple pieces of the magnesium with a glass stirring rod being careful not to break the flask. If this doesn't start the reaction, try warming it or adding a crystal of iodine or a couple drops of iodomethane. Cool only if boiling becomes too vigorous.

After the reaction has clearly started, add the remaining halide-ether solution dropwise from the dropping funnel over a period of several of minutes at a rate that maintains a gentle reflux. After the addition is complete, add an additional 5 mL of ether to the reaction mixture via the dropping funnel. Allow the reaction to continue until only specks of the magnesium remain. After the reaction slows down, gently reflux the mixture for about 10 minutes.

After the Grignard reaction is complete and has cooled to room temperature solution, cool the Grignard reagent with an ice bath. Add 1.5 mL of D₂O (or see **Option** below) to the dropping funnel and add the D₂O to the Grignard reagent at a rapid dropwise rate. The solution should vigorously react during the addition. Stir the mixture for about 10 minutes and add 10 mL of a saturated ammonium chloride aqueous solution. After this addition is complete add an additional 10 mL of water to the mixture and stir to dissolve all solids.

Add about 25 mL of technical grade ether to the mixture and transfer the mixture to a separatory funnel. After shaking, discard the aqueous layer. Wash the ether layer with about 10 mL of water followed by 10 mL of saturated aqueous sodium chloride solution. Dry the ether layer over sodium sulfate. Decant the ether layer into a round bottom flask, wash the sodium sulfate with a small amount of ether and combine the ether layers and rotary evaporate off the ether. Using a small scale distillation apparatus, distill the product. Determine the H-nmr of the product and compare it to the H-nmr of anisole. Determine the percent of the product that has deuterium in the para position of anisole.

The analysis of the H-nmr to determine the ratio of the deuterated anisole to anisole requires a careful integration of the aromatic region of the spectrum. Because the Aldrich site (<http://www.sigmaaldrich.com/>) enables the user to zoom the aromatic region, it is probably the site of choice to prepare for this experiment. After finding anisole, click on the *Safety and Documentation* section to locate the H-nmr.

Option - Instead of adding D₂O to the Grignard reagent, transfer about 20 g of crushed dry ice to a small beaker. Slowly and carefully pour the Grignard reagent onto the dry ice. After the reaction is complete and the excess dry ice has sublimed, add 25 mL of 3 M HCl to the beaker to hydrolyze the salt. Use a separatory funnel to separate the organic phase from the aqueous phase. Wash the aqueous phase with a small amount of ether and add the ether to the organic phase. Properly dispose of the aqueous phases. In a separatory funnel containing the organic phase, carefully add 10% sodium hydroxide solution to extract the acid product into the aqueous phase. Wash the organic layer a second time with base and combine the two base layers. Properly dispose of the organic phase. Carefully acidify the aqueous layer with 3 M HCl and then add ether to extract the acid product into the ether. Repeat the ether extraction and combine the ether layers. Dry the ether layer over anhydrous sodium sulfate and evaporate the ether. Recrystallize the product if necessary and identify using physical and spectroscopic properties.

Extension - It might be interesting and enlightening to compare the rates of electrophilic substitution of anisole and 4-deuteroanisole and other substituted aromatic compounds. For qualitative rate studies of bromination reactions, see for example:

<http://www.chemistry.sfu.ca/assets/uploads/file/Course%20Materials%2009-2/chem286/EAS.pdf>

<http://www.xula.edu/chemistry/department/organic/Labbook/EASprocedure.pdf>

Mohrig, J. R.; Morrill, T. C.; Hammond, C. N.; Neckers, D. C.; *Experimental Organic Chemistry*, Freeman, **1998**, pp. 214-217.

Schoffstall, A. M.; Gaddis, B. A.; Druelinger, M. L. *Microscale and Miniscale Organic Chemistry Laboratory Experiments*, McGraw-Hill, **2000**, pp. 292-294.

References

Pasto, D.; Johnson, C.; Miller, M. *Experiments and Techniques in Organic Chemistry*, Prentice-Hall, **1992**, pp. 448-456.

Prelaboratory Preparation - *Experiment 20*

First, be sure to list all the goals of the experiment. Prepare a table for insertion of useful and observed data such as molecular mass, mass, moles, melting points, percent yields and recoveries. Determine which reagent is the limiting reagent. Inspect and zoom on the aromatic region of anisole at the Aldrich site (<http://www.sigmaaldrich.com/> in the *Safety and Documentation* section under anisole) and determine how you will use the H-nmr to determine the ratio of deuterated anisole to anisole.

Observations

Report all relevant observations including, masses and spectra.

Conclusions

This section should include the following:

1. Were the goals of the experiment achieved? Explain your answer.
2. Based on the limiting reagent, what was the percent recovery?
3. How could the percent yield and recovery have been improved?
4. Give the ratio of deuterated anisole to anisole as determined by H-nmr.
5. Discuss how you determined the percent of deuteration and suggest methods for improving the percentage.
6. If you performed the option, what was the product structure? Explain how you arrived at your conclusion.