

14

Formation and reaction of a Grignard reagent

14.1 Introduction

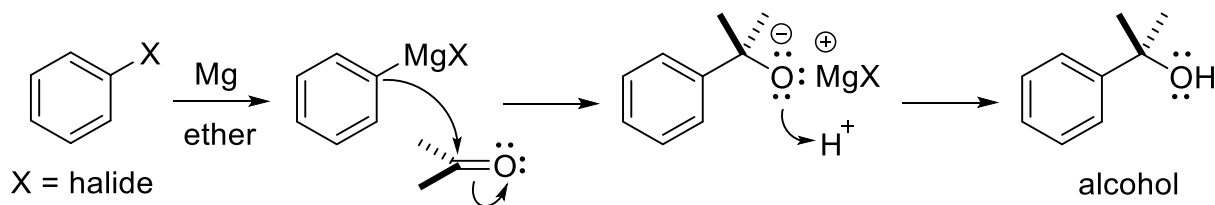
The study and use of compounds featuring carbon-metal bonds (**organometallic chemistry**) is a major area of synthetic chemistry. Metal atoms are less electronegative than carbon and so the polarity of a C-M bond is reversed in comparison to C-H, C-X (X= halogen), C-N etc. found in a typical organic compound *i.e.* the carbon atom is **nucleophilic** rather than electrophilic. Reactions involving organometallic compounds are widely used in industrial organic and pharmaceutical synthesis.

An organomagnesium halide such as phenylmagnesium bromide (PhMgBr) is commonly referred to as a **Grignard reagent**. Other examples of organometallic compounds familiar from CHEM 343/345 include organolithium reagents (RLi) and lithium diorganocuprates (R₂CuLi, Gilman reagents). Organometallic compounds are widely used as both stoichiometric reagents and catalysts to enable organic transformations that are difficult or impossible to accomplish with classical organic reagents.

A Grignard reagent is formed by reaction of magnesium metal with an organic halide in diethyl ether. The halide can be iodine (most reactive), bromine or chlorine (least reactive). Recall that you studied the reactivity of a series of C-X bonds in Chapter 5.

The stoichiometric reaction of Grignard reagents with carbonyl compounds is a common method for the formation of **carbon-carbon single bonds** and an important route for the synthesis of alcohols. The type of carbonyl compound used determines the type of alcohol produced; aldehydes afford secondary alcohols, while ketones and esters yield tertiary alcohols. Primary alcohols can be prepared from the Grignard reaction of formaldehyde (CH₂O).

The simplified mechanism of the Grignard reaction with acetone (Scheme 1) involves attack by the nucleophilic carbon atom of the Grignard reagent at the carbonyl carbon atom to form a new C-C bond. Acidic work-up converts the alkoxide species to the corresponding alcohol.



Scheme 1 Simplified mechanism for the Grignard reaction

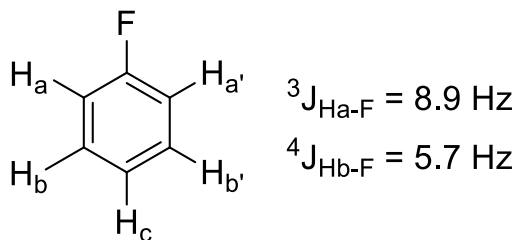
The source of the reactivity of the Grignard reagent is the highly polarized C-Mg bond. These reagents are reactive not only toward carbonyl compounds but also water and oxygen, and care must be taken during their preparation. The solvents and chemicals used to prepare Grignard reagents in a research lab must be rigorously anhydrous, and elaborate glassware is often used to ensure that the reagent does not react with air or water. The experiment that you will perform does not require rigorously anhydrous conditions but the Grignard reagent is still protected from atmospheric moisture and oxygen by a blanket of ether vapor.

In this experiment, you will work with a partner to generate a Grignard reagent and react it *in situ* (i.e. without isolating it) with solid carbon dioxide. Following work-up, the corresponding carboxylic acid will be isolated and purified.

Pre-lab question

- 1) This experiment involves the formation of a Grignard reagent from 1-bromo-4-fluorobenzene and its subsequent reaction with solid carbon dioxide. There are two possible sites on 1-bromo-4-fluorobenzene for insertion of the Mg atom into a C-X bond, and thus two different Grignard reagents that could be formed.
 - a) Draw each of the possible Grignard reagents.
 - b) Draw the resulting product of a reaction between each of the possible Grignard reagents with CO_{2(s)}, followed by acidic workup.
- 2) The ¹⁹F and ⁷⁹Br/⁸¹Br nuclei are NMR active. The presence of these nuclei in a molecule can result in additional coupling in the ¹H-NMR spectrum. The ⁷⁹Br and ⁸¹Br nuclei each have a spin quantum number $I = 3/2$ but both have large quadrupole moments which make their nuclei almost undetectable in a normal ¹H-NMR experiment. In contrast, the ¹⁹F nucleus has a spin quantum number $I = 1/2$ (same as ¹H and ¹³C nuclei) and is 100% abundant in naturally-occurring fluorine atoms. These properties make ¹⁹F-NMR data easy to obtain, and allow ¹⁹F-¹H and ¹⁹F-¹³C coupling to be observed in ¹H- and ¹³C-NMR spectra. This “extra” coupling can be a powerful diagnostic tool for structural determination of ¹⁹F containing molecules.

Use the J_{HF} coupling constants shown below (J_{CF} coupling constants can be found on the course website) to predict the ¹H-NMR coupling pattern of each possible substituted benzoic acid product obtained from the Grignard reaction.

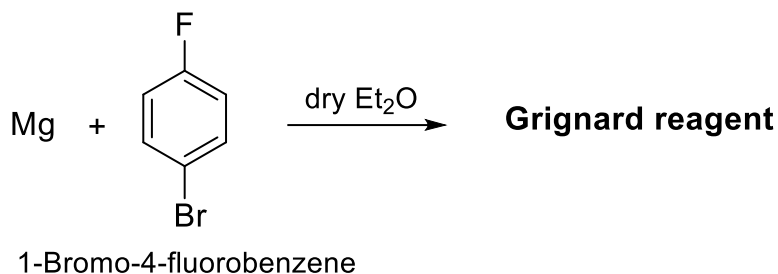


14.2 Procedure

Work in pairs.

Preparation of the Grignard reagent is followed immediately by reaction with CO₂.

Preparation of the Grignard reagent



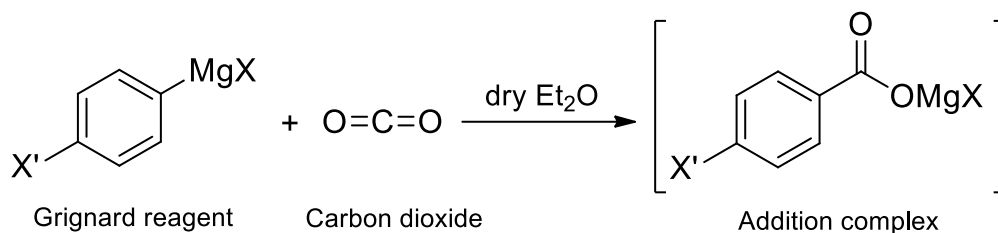
All glassware and materials should be dry.

Equip a 25 mL round bottom flask containing a stir bar with an air-condenser attached to a water condenser. Place a drying tube packed with blue Drierite atop the water condenser.

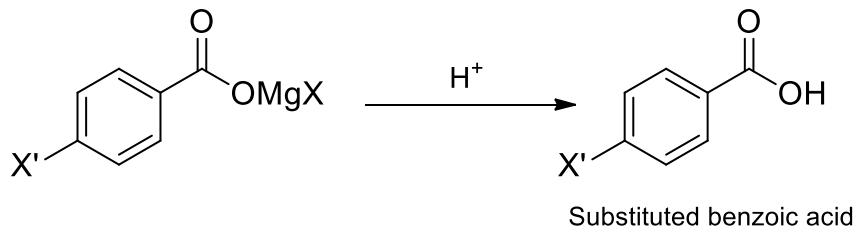
Remove the condenser unit and add to the flask Mg turnings (0.12 g, 4.94 mmol), and anhydrous diethyl ether (7 mL, use diethyl ether from the metal can). Add 1-bromo-4-fluorobenzene (0.50 mL, 0.80 g, 4.57 mmol, dispensed *via* an Eppendorf pipette) to a glass vial and dilute with anhydrous diethyl ether (2 mL). Add the aryl halide solution to the reaction flask via a Pasteur pipette with stirring, followed by 3 drops of 1,2-dibromoethane.

Reflux the reaction mixture for 30 minutes, stirring the mixture rapidly during the process. The start of the reaction is indicated by a slight turbidity of the solution. The mixture will become progressively more turbid as the reaction proceeds, eventually becoming pale yellow. After the reflux time allow the reaction mixture to cool to room temperature.

Reaction of the Grignard reagent with CO₂



X/X' = halide



Transfer the Grignard reagent solution to a beaker. Fill a small glass sample vial with crushed solid CO₂ and add it slowly piece-wise to the Grignard reagent solution with rapid stirring. Stir until all of the CO₂ has reacted and then allow the mixture to warm to room temperature. With stirring, add water (10 mL) followed by aq. 6 M HCl solution (3 mL) drop-wise. Add diethyl ether (10 mL, wash-bottle ether is fine for this process) and continue to stir until most of the solids have dissolved.

Transfer the two-phase mixture to a separatory funnel and shake vigorously to further extract the product into the organic layer. Isolate the organic layer and extract the aqueous layer again with diethyl ether (5 mL). Combine the organic layers and extract them with aq. 5 % NaOH solution (2 x 10 mL portions).

Remove any solids in the basic extract by filtration. Acidify the extract to ~pH 3 by drop-wise addition of aq. 6M HCl solution. This process should require 3-5 mL of acid solution.

Isolate the product by vacuum filtration on a small plastic filter funnel and rinse it with 2 x 5 mL water. Allow the product to air-dry by pulling vacuum on it for ~15 min. Report the mass and % yield of the product, and submit a sample for ¹H-NMR analysis. Obtain an IR spectrum of the dry product.

Lab Report

In addition to answering the post-lab questions your report should include a fully interpreted ^1H -NMR spectrum of your product.

Post-lab questions

- 1) Predict the ^1H -NMR chemical shifts of the ^1H -nuclei in each of the possible benzoic acid products. Use either WebMO calculations (B3LYP/6-31G(d)) or the Curphy-Morrison additivity constants (or both – you could compare them!). Show all work for the Curphy-Morrison prediction.
- 2) Use your experimental ^1H -NMR and ^{19}F -NMR spectra to explain whether the C-F or C-Br bond of 1-bromo-4-fluorobenzene is more reactive toward insertion of Mg. Rationalize your answer by discussing the differences in C-X bond strength.
- 3) Explain why the reaction mixture was treated with aq. 6M HCl solution following addition of CO_2 . Include balanced chemical equations in your answer.
- 4) Explain why the reaction mixture was treated with treated with 5% aq. NaOH solution followed by aq. 6M HCl solution during the purification stage. Include balanced chemical equations in your answer.

CHEM 344 Grignard Reaction

Name:

TA:

Lab Partner:

Mass of purified product (g)_____

% Yield of purified product (show calculation below)_____

WebMO job numbers: _____ (opt+vib freq) _____ (NMR)
 _____ (opt+vib freq) _____ (NMR)

CHEM 344 Grignard Reaction

Name

Lab Partner

Prelab

Descriptive title
Balanced reaction
Answers to pre-lab questions
Reagent table
Concise outline of procedure

Total ____/7

Report

Observations ____/3

Total ____/3

Report Total ____/10

Results

Interpretation of ¹H-NMR & IR data ____/6

Post-lab question 1 ____/4

Post-lab question 2 ____/4

Post-lab question 3 ____/3

Post-lab question 4 ____/3

Results Total ____/20

Final Total ____/30