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Laboratory Experiment

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Use of ^{1}H, ^{13}C, and ^{19}F-NMR Spectroscopy and Computational Modeling To Explore Chemoselectivity in the Formation of a Grignard Reagent

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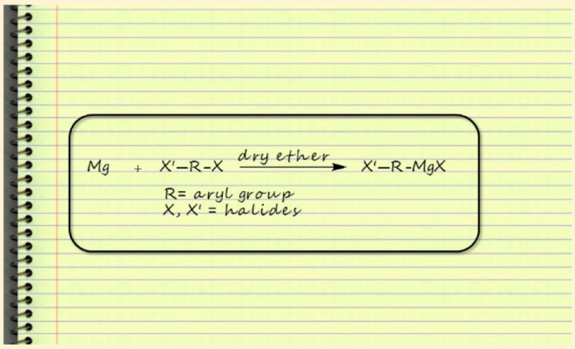
Supporting Information

ABSTRACT: A discovery-based Grignard experiment for a second-year undergraduate organic chemistry course is described. The exclusive Grignard reagent formed by the reaction of 1-bromo-4-fluorobenzene (**1**) with Mg is 4-fluorophenylmagnesium bromide (**2**), which is treated with either benzophenone or CO_2 to produce the corresponding fluorinated alcohol (**3**) or benzoic acid (**4**), respectively. The use of a dihalogenated Grignard reagent requires students to discern its reactivity for synthesis. Students predict the chemoselectivity of Grignard reagent formation based on the C−X bond energies of **1** and investigate their predictions by analysis of ^{1}H, ^{13}C, and ^{19}F NMR, EI−MS, and IR data of **3** and **4**. Empirical parameters and DFT calculations are used to predict the ^{1}H and ^{13}C NMR chemical shifts of **4** and the hypothetical brominated analogue.



KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Laboratory Instruction, Inquiry-Based/Discovery Learning, Aldehydes/Ketones, Carboxylic Acids, Computational Chemistry, Grignard Reagents, NMR Spectroscopy*

INTRODUCTION

The generation and use of organomagnesium halides (Grignard reagents) are two of the more important and well-studied areas of organic chemistry.[1] These nucleophilic organometallic compounds have found broad use in the formation of carbon−carbon σ-bonds either via reaction with an electrophile or through transition metal-mediated coupling reactions. Accordingly, the study of Grignard reagents is a cornerstone of introductory organic undergraduate lecture and laboratory courses. Experiments involving the generation and reaction of various Grignard reagents have been described for use in the instructional laboratory.[2] All of these protocols employ a monohalogenated compound (typically an aryl bromide) as the starting material, and thus, the site of oxidative addition of Mg to the C−X bond to form the Grignard reagent is unambiguous. Currently absent from this palette of exercises is a reaction in which students are faced with the potential formation of two distinct Grignard reagents from the same molecule and thus two different isolable products from the subsequent reaction of the Grignard reagent with an electrophile.

To address this issue, a discovery-based laboratory experiment was developed that uses commercially available 1-bromo-4-fluorobenzene (**1**) (Scheme 1) as the starting material for the Grignard reagent. Although **1** possesses two carbon−halogen bonds, Mg inserts only into the C−Br bond, and thus, 4-fluorophenylmagnesium bromide (**2**) is the exclusive Grignard reagent formed. Compound **2** is treated in situ with either benzophenone or carbon dioxide to produce the corresponding fluorinated alcohol ((4-fluorophenyl)-diphenylmethanol, **3**) or carboxylic acid (4-fluorobenzoic acid, **4**), respectively. The reaction proceeds in standard glassware and requires no special precautions beyond those typically employed for the generation of a simple Grignard reagent. Students predict the structure of the Grignard reagent (and thus the product) and test their predictions by analysis of ^{1}H, ^{13}C, and ^{19}F NMR and IR spectra and EI−MS data obtained from **3** or **4**. Furthermore, students use computational molecular modeling to calculate the trend of homolytic C−X bond dissociation energies (X = F, Cl, Br) in simple halobenzenes and to predict ^{1}H and ^{13}C NMR chemical shifts of the potential products for comparison with experimental values.

This laboratory experiment has been successfully completed by >1000 students in two separate introductory organic laboratory courses at Winona State University and University of Wisconsin-Madison. The main pedagogical goal of the experiment is to foster a data-driven discussion of bonding and reactivity in simple organic molecules. In addition, NMR spectroscopic characterization of products **3** and **4** provides students with experience in analyzing ^{19}F NMR data and unusual coupling phenomena in ^{1}H and ^{13}C spectra.

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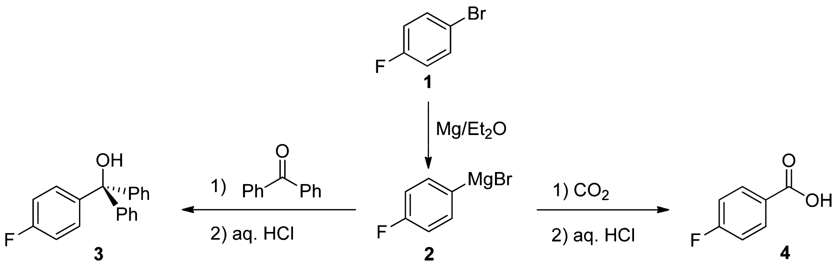
Scheme 1. Generation and Reaction of Grignard Reagent 2



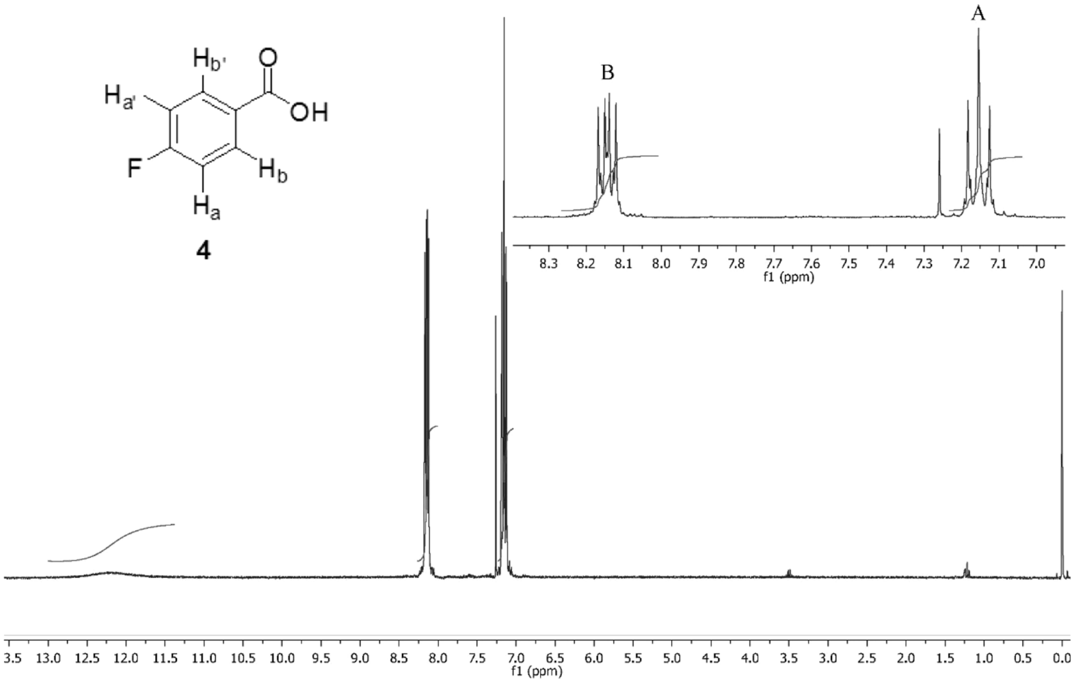


Figure 1. ^{1}H NMR ($CDCl_3$) spectrum of **4**.

■ EXPERIMENTAL OVERVIEW

The generation of Grignard reagent **2** and its subsequent reaction with benzophenone or CO_2 (Scheme 1) are performed by pairs of students as follows. Magnesium turnings are weighed into a dry round-bottom flask equipped with a reflux condenser and $CaCl_2$ drying column, and anhydrous diethyl ether is added. Preparation of **2** from **1** and Mg turnings in anhydrous diethyl ether is carried out using standard procedures. Upon cooling to room temperature, the electrophilic substrate (either benzophenone or solid CO_2) is added to the solution of **2**. The mixture is stirred, followed by acidification with HCl (aq). The organic products are then extracted into diethyl ether. Product **3** is isolated by evaporation of the dried ether extract. The residue is triturated with petroleum ether and purified by recrystallization from 2-propanol or petroleum ether. Product **4** is purified by base extraction with aq. 5% NaOH solution, followed by neutralization with aqueous acid and isolation by vacuum filtration. Both products are characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, EI–MS, and IR data (see the Supporting Information for a detailed description of the experimental procedure).

Computational molecular modeling is increasingly employed in the undergraduate organic curriculum.[3,4] The current lab exercise provides opportunity for computational analysis of the substrate **1** and possible products of the Grignard reaction of **2** with CO_2. At UW-Madison, students performed density functional (DFT) calculations to explore the C–X bond distances and bond dissociation energies in a series of halobenzenes (X = F, Cl, Br).[5] Students also used a combination of DFT calculations and empirically derived Curphy–Morrison additivity parameters[6] to predict the ^{1}H and ^{13}C NMR chemical shifts of **4** and 4-bromobenzoic acid (**5**), the alternate product of the Grignard reaction of **2** with CO_2. All DFT calculations were performed in the Gaussian 09 program via the WebMO interface using B3LYP/6-31G(d) (see the Supporting Information for references and computational details).

■ HAZARDS

Magnesium turnings, diethyl ether, petroleum ether, 2-propanol, and **1** are flammable. Diethyl ether, petroleum ether, 2-propanol, and **1** are skin and respiratory irritants. Fresh anhydrous ether should be used to ensure reaction initiation and avoid potential peroxide hazards. Solid CO_2 can cause burns and expand upon sublimation; do not cap storage vials containing solid CO_2. Hydrochloric acid solution is corrosive and may cause skin burns and eye damage. Magnesium sulfate and benzophenone should be handled with caution. Chloroform-*d* is a potential carcinogen and skin irritant. Solid and

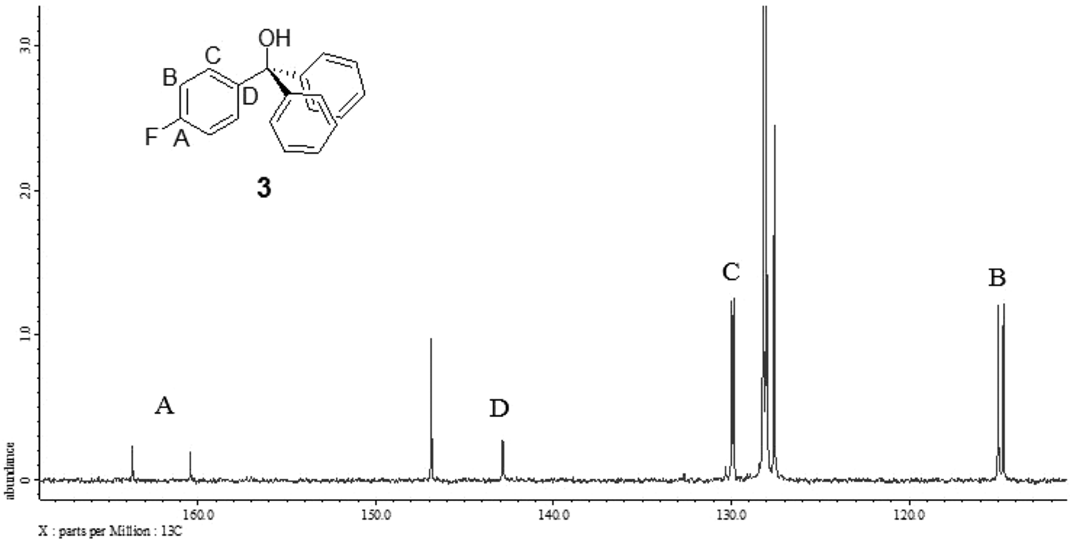


Figure 2. ^{13}C NMR ($CDCl_3$) spectrum of **3**. Methanolic carbon = 81.9 ppm.

liquid waste should be disposed into appropriately labeled containers. Goggles, disposable gloves, and a lab coat should be worn at all times, and the procedures should be performed in a fume hood or similarly ventilated workspace. Hazards of products **2**, **3**, and **4** are unknown, and they should be handled cautiously to avoid exposure.

The molecular modeling component has no hazards.

RESULTS AND DISCUSSION

Two variations of this Grignard reaction have been carried out in second-year undergraduate organic laboratory courses. Products **3** and **4** were successfully synthesized from **1** by approximately 700 and 500 students, respectively. Two consecutive 4 h lab periods are required for the synthesis, purification, and characterization of **3**, whereas **4** is prepared and isolated in a single 4 h lab period. For **3**, students acquired all spectroscopic data. For product **4**, students submitted samples for NMR spectroscopy and retrieved data outside of scheduled class time. NMR spectroscopy was carried out on a 300 MHz spectrometer. With rare exception, each pair of students successfully isolated the appropriate product. The average yield of recrystallized **3** was in the range of 30–40%, whereas **4** was isolated in 60–65% yield following protonation of the conjugate base formed during basic extraction.

The Grignard synthesis of **3** and **4** enables students to experimentally explore the concept of chemoselectivity. Structural characterization by various spectroscopic data provides students with definitive evidence that the C–Br bond of **1** is more reactive toward Mg than the C–F bond and that the formation of the Grignard reagent **2** is completely chemospecific. Both products contain a fluorine atom, and thus, the ^{1}H and ^{13}C NMR spectra of these compounds display $^{1}H–^{19}F$ and $^{13}C–^{19}F$ coupling. Because of the presence of $^{1}H–^{19}F$ coupling ($^{3}J_{HF}$ = 9.0 Hz, $^{4}J_{HF}$ = 5.4 Hz), the aromatic regions of the ^{1}H NMR spectra of **3** and **4** display more complex splitting patterns than the AA′XX′ or AA′BB′ patterns typically observed in *para*-substituted aromatic rings.[7] The spectrum of **3** (Supporting Information) contains several overlapping signals from the two nonfluorinated phenyl groups, but the signal due to *ortho*-$^{1}H–^{19}F$ coupling is well-resolved (at 7.0 ppm) and distinguishable from the other aromatic ring ^{1}H signals due to the shielding effect of the ^{19}F atom. The ^{1}H NMR spectrum of **4** (Figure 1) features two well-resolved resonances that display an AA′MM′X (X = ^{19}F) pattern arising from $^{1}H–^{19}F$ coupling in addition to the usual $^{1}H–^{1}H$ coupling. The presence of $^{13}C–^{19}F$ coupling in the $^{13}C\{^{1}H\}$-NMR spectra of **3** (Figure 2) and **4** (Supporting Information) requires students to analyze the presence of four well-resolved doublets. Because students are accustomed to observing singlets in $^{13}C\{^{1}H\}$-NMR spectra, the doublets present another opportunity to highlight coupling arising from a nucleus other than ^{1}H and ^{13}C.

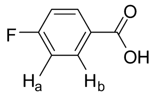
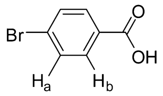
In addition to highlighting $^{1}H–^{19}F$ and $^{13}C–^{19}F$ coupling, **3** and **4** were analyzed by ^{19}F-NMR spectroscopy (Supporting Information). The magnetic properties and 100% abundance of the fluorine nucleus allow students to observe ^{19}F NMR data and determine that a fluorine atom is present in the product and subsequently determine the identity of the initially formed Grignard reagent. The ^{19}F NMR spectra of **3** and **4** consist of a singlet at δ −115.5 and δ −104.4, respectively.

EI–MS is also used to determine the structure of each product. In addition to the m/z value of the molecular ions derived from **3** and **4** (m/z = 278 and 140 respectively), the absence of the characteristic $^{79}Br/^{81}Br$ isotope pattern in each mass spectrum confirm that the C–Br bond is not present in either product. The infrared spectra of **3** and **4** clearly show the expected absorptions due to the tertiary alcohol and the carboxylic acid functional groups. Careful analysis of the fingerprint region shows a band at 1292 cm^{-1}, suggestive of C–F stretching. The totality of the spectroscopic data clearly conveys to students that the C–F bond is retained in **3** and **4** and provides compelling evidence that the Grignard reagent was formed by oxidative addition of Mg into the C–Br bond. Representative student NMR, MS, and IR spectroscopic data for **3** and **4** are included in the Supporting Information.

COMPUTATIONAL MODELING

Computational molecular modeling of the homolytic C–X bond dissociation energies of model halobenzenes Ph–X (X = F, Cl, Br),[5] in combination with the spectroscopic data and background knowledge of the Grignard reaction, allowed students to predict correctly that the C–Br bond of **1** was most likely to undergo oxidative addition of Mg, which thus

Table 1. Predicted ^{1}H-NMR Chemical Shifts for 4 and 5[abc]

	4-Fluorobenzoic acid **(4)**			4-Bromobenzoic acid **(5)**		
						
	Empirical Prediction (ppm)[a]	Comp. Prediction (ppm)[b]	Exp. (ppm)[8,c]	Empirical Prediction (ppm)[a]	Comp. Prediction (ppm)[b]	Exp. (ppm)
H_a	7.2	6.8	7.15	7.5	7.2	7.62
H_b	8.1	8.1	8.15	7.9	7.9	7.96

[a] Curphy−Morrison[6] empirical parameters. [b] Computational prediction using WebMO/Gaussian 09 at a B3LYP/6-31G(d) level. [c] This work and ref 8.

explains the observed chemospecificity inherent in the formation of **2**. Students also used DFT calculations and empirical Curphy−Morrison parameters[6] to predict the ^{1}H and ^{13}C NMR chemical shifts of **4** and **5**, the alternate product of the Grignard reaction of **2** with CO_2 (Table 1). The combination of theoretical and empirical data analysis allowed students to eliminate **5** as a likely product from the reaction of **2** with CO_2 and provided multiple avenues for students to interpret the experimental ^{1}H and ^{13}C NMR spectra of **4**.

Students successfully demonstrated an understanding of the Grignard reaction, which was assessed via the content of lab reports, by responses to specific questions in lab quizzes and course exams. Exam questions required students to demonstrate conceptual understanding of Grignard reactions. Instructions for the lab report and sample exam-style questions are included in the Supporting Information.

SUMMARY

The generation and reaction of **2**, derived from the dihalobenzene **1**, adds a number of valuable components to the traditional Grignard reaction laboratory exercise. In addition to providing practical experience in handling a mildly reactive organometallic species, the exercise allowed students to experimentally determine and rationalize the relative reactivity of the C−F and C−Br bonds in **1** toward insertion of Mg. Specifically, students analyzed and compared experimental spectroscopic, empirical, and theoretical data to determine the outcome of the reaction of Grignard reagent **2** with benzophenone or CO_2. Furthermore, the NMR spectroscopic characterization of products **3** and **4** introduced students to ^{19}F-coupled NMR spectroscopy. Finally, the synthesis of **3** and **4** provided an entry point for the discussion of fluorinated organic molecules, an area of significant current interest.[9]

ASSOCIATED CONTENT

Supporting Information

Student laboratory manual chapter, instructor notes, experimental procedures and spectroscopic data, and details of computational molecular modeling exercises. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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