

Preparation of an Ester-Containing Grignard Reagent by Halogen–Metal Exchange

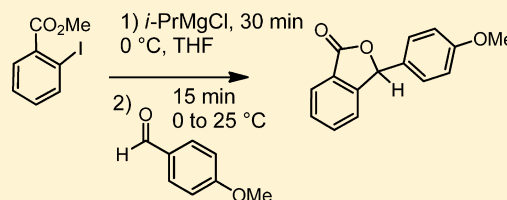
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S Supporting Information

ABSTRACT: In this experiment, students carry out a halogen–metal exchange reaction of methyl 2-iodobenzoate with isopropylmagnesium chloride in THF at 0 °C to afford 2-carbomethoxyphenylmagnesium chloride, which is treated with *p*-methoxybenzaldehyde to give a lactone (phthalide) product. This reaction introduces students to the modern method of preparation of Grignard and organolithium reagents by halogen–metal exchange rather than by using metallic magnesium or lithium, which is rarely done in a research laboratory. It also demonstrates that Grignard reagents bearing reactive functionality can be prepared and utilized in synthesis, although students are still often taught otherwise. The IR spectrum of the crude product provides semiquantitative information on the success of the reaction because the lactone product and starting material ester and aldehyde have very different carbonyl absorptions, demonstrating the power of this technique to distinguish between functional groups. The product can be purified by chromatography, recrystallization, or trituration, which allows students to compare different purification methods in terms of time required, yield, and purity of product.

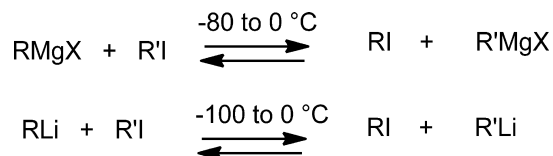
KEYWORDS: Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Organometallics, IR Spectroscopy, NMR Spectroscopy



Undergraduate organic chemistry courses teach students that Grignard and organolithium reagents are prepared from organic halides and magnesium in ether at reflux or lithium in an alkane solvent. These reactions are widely used on an industrially scale but are not as useful on a small scale in the research laboratory. In research laboratories, organic graduate students routinely make organometallic reagents by deprotonation and halogen–metal exchange, and rarely make them directly from metallic magnesium or lithium.

Unfortunately, undergraduate organic chemistry courses do not cover halogen–metal exchange well.¹ RMgCl or RLi will react very rapidly with R'X to give RX and R'MgCl or R'Li at temperatures as low as –100 °C! (Scheme 1). This reaction is

Scheme 1. Halogen–Metal Exchange of Grignard and Organolithium Reagents with Organic Halides



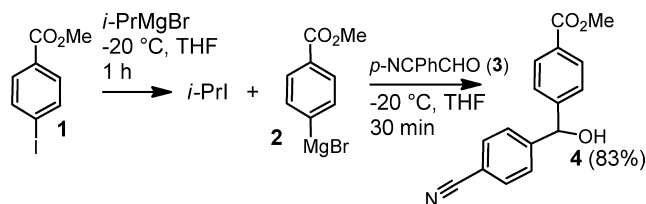
fastest for X = I, slower for X = Br and Cl, and does not proceed for X = F. This homogeneous reaction is much faster and more reproducible than the slow heterogeneous formation of RMgX or RLi from organic halides and magnesium or lithium.

This reaction is an equilibrium reaction and the position of the equilibrium is determined by the ability of the R or R' group to stabilize the partial negative charge of the organometallic reagent. The stability of a Grignard or organolithium reagent, which drives the equilibrium, corresponds to the ability of the carbon to stabilize partial negative charge, which corresponds to the $\text{p}K_{\text{a}}$ of RH. sp^2 Hydrogens ($\text{p}K_{\text{a}}$ 40–45) are more acidic than sp^3 hydrogens ($\text{p}K_{\text{a}}$ 50 to 60), so the equilibrium for the reaction of iodobenzene with an alkylmagnesium reagent to give an sp^2 phenylmagnesium reagent and an sp^3 alkyl iodide lies far to the right. Tertiary hydrogens (R_3CH , $\text{p}K_{\text{a}}$ 60) are less acidic than secondary hydrogens, which are less acidic than primary hydrogens, which are less acidic than methane ($\text{p}K_{\text{a}}$ 50). Therefore, the least stable and most reactive organolithium reagent for halogen–metal exchange is *t*-butyllithium, which has been widely used for this purpose for more than 40 years. However, *t*-butyllithium is too pyrophoric to be used safely in an undergraduate teaching laboratory.

Over the past 20 years, the use of Grignard reagents for halogen–metal exchange reactions has been developed by Paul Knochel and others.² The most reactive, readily available Grignard reagent is isopropylmagnesium chloride. Grignard reagents are less pyrophoric than organolithium reagents and can be safely used in an undergraduate laboratory with standard precautions.

Remarkably, Knochel found that Grignard reagents, which are less reactive than organolithium reagents, are compatible at low temperature with some carbonyl groups, again contrary to what undergraduates are sometimes taught in organic chemistry classes. For instance, reaction of methyl 4-iodobenzoate (**1**) (Scheme 2) with isopropylmagnesium bromide in tetrahy-

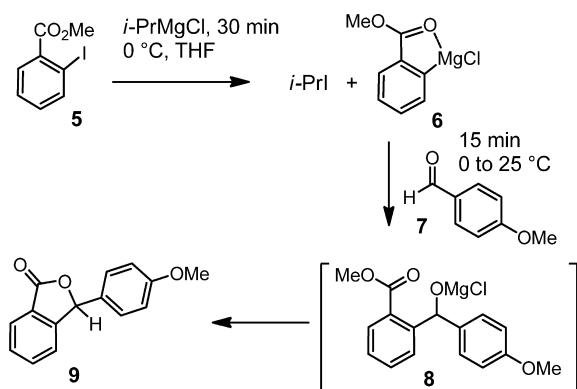
Scheme 2. Halogen–Metal Exchange Reaction of Methyl 4-Iodobenzoate (1**) at $-20\text{ }^{\circ}\text{C}$**



drofuran (THF) at $-20\text{ }^{\circ}\text{C}$ affords the aryl Grignard reagent **2**, which can be trapped with *p*-cyanobenzaldehyde (**3**) to give the secondary alcohol **4** in 83% yield.³ However, it is difficult to carry out this reaction in an undergraduate laboratory because it is necessary to work at $-20\text{ }^{\circ}\text{C}$, which requires either expensive cryogenic equipment or very carefully maintaining the temperature with a dry ice bath.

Fortunately, the analogous reaction with methyl 2-iodobenzoate (**5**) (Scheme 3) and isopropylmagnesium

Scheme 3. Halogen–Metal Exchange Reaction of Methyl 2-Iodobenzoate (5**) at $0\text{ }^{\circ}\text{C}$**



chloride in THF to give **6** can be run at $0\text{ }^{\circ}\text{C}$ using an ice bath for cooling.⁴ This reaction can thus be carried out easily in an undergraduate laboratory. Care is needed with reagent stoichiometry, reaction temperature, and most importantly keeping the reaction mixture free of oxygen and water. Binding of the magnesium to the ester speeds up halogen–metal exchange of **5** and chelation of the product Grignard reagent to the ester stabilizes **6**. Addition of *p*-methoxybenzaldehyde (anisaldehyde, **7**) to the solution of Grignard reagent **6** gives the secondary alkoxide **8** that cyclizes to form 3-(4-methoxyphenyl)-1(3*H*)-isobenzofuranone γ -lactone (phthalide **9**). Thus, the ortho ester group (**1**) facilitates halogen–metal of **5**, (**2**) stabilizes Grignard reagent **6**, and (**3**) provides an adjacent electrophile so that alkoxide **8** cyclizes spontaneously to form γ -lactone **9**. During workup, the organic layer is washed with aqueous hydrochloric acid to facilitate lactonization of any residual hydroxy ester or hydroxy acid.

NMR spectroscopy is the main characterization tool in organic research laboratories, but IR spectroscopy is more

widely used in teaching laboratories because of instrument cost, ease of use, and acquisition time issues. Analysis of the IR spectrum of the crude product mixture quickly establishes the success or failure of the reaction because the carbonyl groups of the starting ester **5**, starting aldehyde **7**, and product γ -lactone **9** absorb at different frequencies. The carbonyl stretch of the product γ -lactone **9** occurs at a much higher frequency, 1760 cm^{-1} ,⁵ than those of the starting materials *p*-methoxybenzaldehyde (**7**) ($1684\text{--}1698\text{ cm}^{-1}$)⁶ and methyl 2-iodobenzoate (**5**) (1731 cm^{-1})⁶ and byproduct methyl benzoate (1724 cm^{-1}),⁶ which might be formed by protonation of Grignard reagent **6**. These peaks can easily be distinguished using modern FT-IR spectrometers, so that students can easily determine the success of their reaction prior to purification.

EXPERIMENTAL PROCEDURE

Students work in pairs. An oven-dried Schlenk flask (25 mL) containing a stir bar and methyl 2-iodobenzoate (**5**) (1 mmol) is evacuated and filled with nitrogen twice. Anhydrous THF (4 mL) is added, the mixture is cooled to $0\text{ }^{\circ}\text{C}$ in an ice bath, isopropylmagnesium chloride solution (2.0 M in THF) (1 mmol) is added, and the reaction is stirred for 30 min at $0\text{ }^{\circ}\text{C}$. A solution of *p*-methoxybenzaldehyde (anisaldehyde, **7**) (1 mmol) in anhydrous THF (1 mL) is added by syringe to the aryl Grignard reagent, the ice bath is removed, and the reaction is stirred 15 min. Workup gives crude **9** as at least a semisolid. Students obtain an IR spectrum of the crude product. Students purify **9** by flash chromatography on silica gel eluting with 3:1 hexanes/EtOAc, recrystallization from EtOH, or trituration with ether or hexanes. The melting point of **9** is obtained. Students obtain a ^1H NMR spectrum of their purified product in CDCl_3 and analyze it in their report. A detailed procedure is in the Supporting Information.

HAZARDS

Eye protection and gloves should be worn throughout. Care is needed in handling isopropylmagnesium chloride, even though the quantities used are small. It must be stored in a closed container in a dry place. In contact with water it releases flammable gases that may ignite spontaneously. It forms explosive peroxides with oxygen. It causes skin burns and eye damage. Handling organic solvents in open containers should be performed in a fume hood. Hexanes, THF, diethyl ether, ethanol, and ethyl acetate are highly flammable and should not be inhaled or ingested. There is a danger of serious damage to health by prolonged exposure through inhalation of *n*-hexane, including a possible risk of impaired fertility. *n*-Hexane is a neurotoxin. Diethyl ether and THF can form explosive peroxides. CDCl_3 is toxic; avoid inhalation, ingestion, and skin or eye contact. Silica gel is an inhalation hazard. Methyl 2-iodobenzoate, *p*-methoxybenzaldehyde, and phthalide **9** have not been fully tested for toxicity and should therefore be handled with care avoiding inhalation or skin contact.

RESULTS AND DISCUSSION

This experiment was carried out one time by 12 pairs of students in an upper-division undergraduate organic chemistry laboratory course and was completed in a single 4 h laboratory period. The halogen–metal exchange reaction introduced students to the modern method of preparation of Grignard reagents by halogen–metal exchange rather than by using metallic magnesium, which is rarely done in a research

laboratory. The use of isopropylmagnesium chloride is not as hazardous as the use of organolithium reagents for halogen–metal exchange. The reaction also demonstrated that Grignard reagents bearing a reactive ester group can be prepared and utilized in synthesis, although students are still often taught otherwise. The reaction proceeded in 30 min at 0 °C in an ice bath, making it easy to carry out in a teaching laboratory. Preparation of the solution of *p*-methoxybenzaldehyde in anhydrous THF in an open vial simplified the procedure without significantly reducing the yield. The crude product that all students isolated was a solid or a semisolid, which indicated that the reaction was successful. The IR spectra that students obtained of the crude product showed a large peak at 1755–1760 cm^{−1} for the carbonyl stretch for **9** and small or no peaks for ester **5** at 1730 cm^{−1} and aldehyde **7** at 1690 cm^{−1}. This provided semiquantitative information on the success of the reaction and demonstrated the power of this technique to distinguish between functional groups. Students purified **9** by chromatography, recrystallization, or trituration, which allowed them to compare different purification methods in terms of time required, yield, and purity based on melting point; the melting point for **9** reported in SciFinder ranges from 110 to 125 °C with most in the range of 114–119 °C.⁷ Flash chromatography was the slowest procedure, and gave the highest yield of product with a slightly lower melting point. Recrystallization from 95% ethanol was more rapid and gave purer product based on melting point, but in lower yield. Trituration with ether or precipitation by adding hexane to a solution in small amounts of dichloromethane was the most rapid and gave purer product based on melting point, but again in lower yield. At 400 MHz, the six different aromatic protons are well resolved in the ¹H NMR spectrum (a representative student spectrum is shown in Figures S1 and S2 in the Supporting Information). The 4-methoxyphenyl group absorbs as an AA'BB' (apparent AB) pattern. The other aromatic protons absorb as an ABCD pattern that is almost first-order at 400 MHz. Students could, therefore, fully analyze the NMR spectrum.

Pedagogically, this experiment is designed to do the following: (1) illustrate how to perform reactions under inert atmosphere conditions on a semimicroscale using the same techniques used in a research laboratory; (2) provide opportunities for students to explore multiple ways of purification (chromatography, recrystallization, and trituration) and to evaluate their effectiveness in terms of time required, yield, and purity; (3) illustrate the power of IR spectroscopy to distinguish between different carbonyl groups; (4) allow students to practice assigning coupling patterns in ¹H NMR spectra; and (5) instruct students on halogen–metal exchange as a modern procedure for preparing reactive organometallic reagents and to give them an introduction to the compatibility of these reagents with some other functional groups under low temperature conditions. Surprisingly, there appears to be only a single example of halogen–metal exchange in laboratory experiments in this Journal.¹

All student groups were able to carry out the reaction successfully, obtaining solid lactone crude product in good yield and purity as judged by IR spectroscopy. Students were allowed to choose which purification technique to use and were required to analyze all the different techniques used in their reports, which they did very effectively. The lab reports demonstrated that students understood and appreciated the power of the halogen–metal exchange technique that was basis

of this experiment. They were able to analyze the IR spectra properly and to assign the coupling pattern in the ¹H NMR spectrum fully.

■ ASSOCIATED CONTENT

Supporting Information

Representative student ¹H NMR, ¹³C NMR, and IR spectral data for lactone **9**; instructor notes, including examples of student results with various purification procedures and details of chemicals and equipment used; editable student handout. This material is available via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Brandeis University Chemistry Department is thanked for funding this project. The efforts of the undergraduate students who successfully completed this experiment in CHEM 49a at Brandeis University are gratefully acknowledged, as are the helpful suggestions of the teaching assistants in the course.

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