Grignard Reaction of an Epoxide[1]

A Mechanistic Study

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The reaction of epoxides with organometallic reagents is an important method for C–C bond formation (*1*). Alkynyllithium and organocopper reagents are routinely used for regioselective ring-opening of substituted epoxides at the less substituted carbon to afford the corresponding alcohols (*2*). However, since Grignard reagents (*3*) are an equilibrium mixture of RMgX, R_2Mg, and MgX_2, all of which can react with epoxides, their reactions with substituted epoxides are complicated by various side reactions that often lead to a mixture of products (*4*). For example, disubstituted epoxides such as isobutylene oxide and aryl-substituted epoxides such as styrene oxide (**1**) tend to rearrange prior to C–C bond formation (*4*). Tiffeneau and Fourneau reported that the reaction of **1** with alkylmagnesium bromides yields 1-phenyl-2-alkanols (**5**, Fig. 1, pathway B) (*5*); presumably, the $MgBr_2$ present catalyzes the rearrangement of **1** to phenylacetaldehyde (**9**), which then undergoes Grignard addition. More recently, Deniau et al. reported that this reaction yields a mixture of 1-phenyl-2-alkanol (**5**) and 2-phenyl-1-alkanol (**2**) (Fig. 1, pathways B and A, respectively) (*6*).

Kharasch and Clapp have demonstrated that *the order of addition has a dramatic effect on the product ratio for the reaction of* ***1*** *with PhMgBr* (*7*). Addition of **1** to an ether solution of PhMgBr ("normal" addition) gives 2,2-diphenylethanol (**3**) along with a smaller amount of 1,2-diphenylethanol (**6**). However, when PhMgBr is added to an ether solution of **1** ("inverse" addition), the product of rearrangement (**6**) predominates and **3** is the minor product. It should be noted that **6** could also arise from direct alkylation of the unsubstituted epoxide carbon of **1** (Fig. 1, pathway C; R = Ph). However, this could only be a very minor source of **6**, because Deniau et al. isolated products arising from only pathways A and B, and Rose and Taylor reported similar results for the reaction of **1** with vinylmagnesium bromide (*8*); moreover, via either mode of addition, they detected less than 1% of **8**, formed via pathway C.

Undergraduate laboratory experiments that are less "cookbook" and more "discovery-based" or that present students with a puzzle are becoming increasingly common (*9*).[2] We find that a modification of Kharasch's protocol is an excellent vehicle for a discovery-based experiment in which students are introduced to epoxide chemistry, share their laboratory data, and make mechanistic conclusions from their experimental results.

After a general discussion of epoxide reactivity and presentation of the results of Deniau et al. and Rose and Taylor on the reaction of **1** with Grignard reagents, students are asked to predict the products of the reaction of **1** with PhMgBr and *experimentally* determine the effect of altering the mode of reactant addition on the ratio of isomeric alcohols formed. The class is divided into two groups: one performs the normal addition while the other performs the inverse addition. A second lab period is devoted to the preparation of "authentic" samples of **3** and **6** by $NaBH_4$ reduction of diphenylacetaldehyde and deoxybenzoin, respectively.[3] Each student performs the reduction on only one substrate. Students compare TLC analyses of their Grignard reaction mixtures and authentic alcohol samples (students share small amounts of their samples) to establish not only that they have two major products from the reaction but that they are indeed **3** and **6**, as predicted in class. Selected students (in our case, chemistry majors) are asked to obtain carefully integrated ^1H NMR spectra of randomly selected student samples containing the mixture of products from both normal and inverse additions, as well as of the alcohol samples from both hydride reductions. Copies of all spectra are made available to the class. With spectra of authentic **3** and **6** at hand, students can easily distinguish the nonaromatic protons of **3** and **6** found in the ^1H NMR spectra of the mixtures and can estimate the ratio of alcohol isomers from the integration of their respective peaks. During a follow-up session, the class discusses and analyzes their combined results in order to rationalize the effect of reagent addition on the ratio of alcohol isomers.

Experimental Procedure

This experiment was performed by 60 students enrolled in the second-semester organic chemistry laboratory at Fordham University. A single 4-h lab period was used for the preparation of PhMgBr and its reaction with **1**. A second lab period was used for the hydride reductions and TLC and NMR analyses of the Grignard reaction mixture. All reagents for this experiment were used as received from the supplier (Aldrich Chemical Co.), without additional purification. TLC analyses were performed using Hard Layer Silica Gel GHLF UNIPLATES with inorganic binder (available from Analtech, Inc.) and Riedel-deHaen TLC plates, silica gel (60 F 254), 0.2 mm

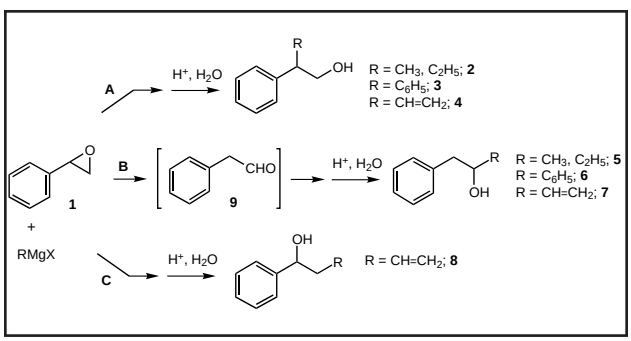

Figure 1. Possible pathways for the reaction of styrene oxide (**1**) with a Grignard reagent.

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thickness on aluminum (available from Aldrich) with 10:1 (v/v) petroleum ether:ethyl acetate as eluent. ^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer and ^{13}C NMR spectra were recorded on JEOL FX90Q and Bruker spectrometers. The protocol was adapted from a procedure reported by Kharasch and Clapp (*7*). Styrene oxide is a cancer suspect agent and is somewhat corrosive, but is not highly toxic. Its LD_{50} is 1500–2000 mg/kg, making it less poisonous than diethyl ether (LD_{50} = 1215 mg/kg) (*10*). However, *students should be required to wear gloves and warned against touching styrene oxide or inhaling its vapors.* Handling is minimized by distributing preweighed samples in capped vials. Diethyl ether, ethanol, petroleum ether, and ethyl acetate are flammable liquids; magnesium and sodium borohydride are flammable solids.

Reaction of Styrene Oxide with PhMgBr; "Normal" Addition

Styrene oxide (500 mg; 4.16 mmol) dissolved in 5 mL of anhyd ether was added dropwise from an addition funnel, over ca. 5 min, into a 25-mL round-bottomed flask containing PhMgBr freshly prepared from 1.34 g (8.53 mmol) of bromobenzene and 200 mg (8.23 mmol) of magnesium turnings in 5 mL of anhyd ether. The reaction mixture was swirled periodically during the addition. After addition was complete the mixture was heated to reflux for 10 min, cooled to room temperature, and treated with 10 mL of 10% H_2SO_4. The aqueous layer was extracted once with 10 mL of ether. The ether extract was dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to afford 646 mg (78%; the average yield) of a clear, pale yellow oil (ratio **3**:**6** is approx. 2:1).

Reaction of Styrene Oxide with PhMgBr; "Inverse" Addition

A solution of PhMgBr in 10 mL of anhyd ether (prepared as described above) was added dropwise from an addition funnel over 10 min to a solution of styrene oxide (500 mg; 4.16 mmol) in anhyd ether (10 mL). After addition was complete the mixture was heated to reflux for 10 min and worked up as described above to afford 735 mg (89%; the average yield) of a clear, amber oil (ratio of **3**:**6** is approx. 1:3).

$NaBH_4$ Reduction of Diphenylacetaldehyde

A solution of diphenylacetaldehyde (511 mg; 2.60 mmol) dissolved in 95% ethanol (5 mL) was treated with $NaBH_4$ (106 mg; 2.80 mmol). After periodically swirling the reaction mixture over 10 min, the solution was diluted with water (4 mL) and heated to its boiling point over a steam bath. The mixture was then diluted with more water (10 mL) and extracted once with ether (15 mL). The ether extract was dried over anhyd $MgSO_4$ for 10–15 minutes and filtered. The solvent was removed on a rotary evaporator to afford 282 mg (55%; the average yield) of **3** as a viscous liquid that partially solidified upon standing:

> ^{1}H NMR ($CDCl_3$) δ 7.24 (s, 10 H, C_6H_5), 4.10 (m, 3H, $CHCH_2$), 1.95 (m, 1 H, OH, D_2O exchangeable);
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> ^{13}C NMR ($CDCl_3$) δ 140.31, 127.37, 127.09, 125.47, 64.85 (C1), 52.50 (C2).

Student samples were homogeneous by TLC analysis.

*$NaBH_4$ Reduction of Deoxybenzoin (*11*)*

A solution of deoxybenzoin (500 mg; 2.55 mmol) dissolved in 95% ethanol (5 mL) was treated with $NaBH_4$ (100 mg; 2.64 mmol). After periodically swirling the reaction mixture over 10 min, the solution was diluted with water (4 mL) and heated to its boiling point over a steam bath. The mixture was then diluted with more water (2 mL) and cooled to room temperature. Precipitation was induced by scratching the inner surface of the flask with a sturdy glass stirring rod. After addition of more water (5 mL) and cooling in an ice water bath, 400 mg (79%; the average yield; mp 61–65 °C) of a white solid was collected by vacuum filtration. Crystallization from petroleum ether (ca. 2–4 mL) afforded 380 mg (75%) of **6** as a white solid; mp 64–65.5 °C (mp 66 °C [*11a*]):

> ^{1}H NMR ($CDCl_3$) δ 7.10 (m, 10 H, C_6H_5), 4.60 (t, 1H, C**H**OH), 2.85 (d, 2 H, CH_2), 2.30 (m, 1 H, OH, D_2O exchangeable);
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> ^{13}C NMR ($CDCl_3$) δ 142.75, 136.95, 128.34, 127.15, 126.28, 125.25, 124.77, 74.00 (C1), 44.81 (C2).

The average yield of purified **6** students obtained was 300 mg (59%). Student samples were homogeneous by TLC analysis.

Results and Discussion

The preparation of PhMgBr is typical of that described in any number of textbook protocols; we found flame-drying the apparatus to be unnecessary, provided that glassware was completely free of water. Students encountered no difficulties in either the Grignard reagent preparation or its reaction with **1** by either mode of addition. The $NaBH_4$ reductions of diphenylacetaldehyde and deoxybenzoin cleanly afford their respective alcohols in very short reaction times and good yields; **3** is a low-melting solid that can be characterized by mp determination of its 3,5-dinitrobenzoate derivative (mp 135 °C [*7*], recrystallization from methanol), while characterization of **6** can be accomplished by recrystallization from petroleum ether followed by mp determination. TLC analyses are straightforward, as the R_f's of **3** and **6** are wide enough apart (0.20 and 0.36, respectively), and students were instructed to co-spot their Grignard reaction mixtures along with authentic alcohol samples on the same plate in order to identify the spots. ^{1}H NMR peak integration is ideal for establishing the ratio of **3** to **6** present in both reaction mixtures. Although the aromatic protons of **3** and **6** overlap at ca. 7 ppm, the methylene and methine protons of **3** are fortuitously chemical shift equivalent and appear at 4.1 ppm, while the methylene protons of **6** appear as a doublet at 2.9 ppm and the methine proton appears as a triplet at 4.6 ppm. ^{13}C NMR analysis can also be used to detect the presence of both isomers; the spectrum of the mixture of **3** and **6** afforded by normal addition displays intense peaks at 65 and 53 ppm (C-1 and C-2 of **3**, respectively) with small, yet clearly noticeable peaks at 74 and 45 ppm (C-1 and C-2 of **6**, respectively). The same peaks are displayed in the spectrum of the mixture of alcohols afforded by inverse addition, but with opposite intensities. Again, students can make peak assignments for the mixtures by comparing them to spectra of their authentic samples. From the student-generated data, it is clear that normal addition primarily affords **3**, whereas inverse addition primarily affords **6**. For normal addition, the large excess of Grignard reagent consumes most of the epoxide at once, allowing only a small amount of **9** to accumu-

late. The slow addition of Grignard reagent during inverse addition presumably permits a greater contact time between **1** (which is in large excess) and the Lewis acid component of the Grignard reagent (most likely MgX_2), allowing the concentration of **9** to increase before the addition of more nucleophile (*8*).

This "mechanistic investigation" provides the benefits of a discovery-based experiment (*9*) while emphasizing the importance of concentration effects in chemical reactions. Most students are surprised to learn that the outcome of a reaction can be altered simply by changing the order of reactant addition! The Grignard synthesis is performed to probe the reactivity of **1**, not merely for the sake of illustrating a textbook reaction. Students must *analyze* their products (instead of just submitting them for a grade) in order to obtain the data necessary for making mechanistic conclusions. The preparations of **3** and **6** by hydride reduction also serve a specific purpose: independent synthesis to obtain proof of structure. Moreover, students sample the benefits of collaborative work (and dividing up the tasks allows more data to be generated). Plausible extensions and variations of this experiment are numerous and all would serve as both an interesting alternative to more traditional undergraduate Grignard experiments and a suitable introduction to epoxide chemistry.[4]

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Notes

1. Presented at the 29th Middle Atlantic Regional Meeting of the American Chemical Society, Division of Chemical Education; Washington, DC; 24 May 1995.

2. Two mechanism-oriented undergraduate experiments involving the reaction of Grignard reagents with a conjugated ketone (*12a*) and a conjugated nitrile (*12b*) have recently been described in this *Journal*.

3. Alternatively, students can be given commercial samples of **3** (Aldrich) and **6** (Chem Services).

4. Despite the fact that epoxide chemistry is routinely discussed in organic chemistry lecture texts, there are very few published undergraduate experiments that focus on either the reactions or the preparation of epoxides (*13*).

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