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Laboratory Experiment

Discovery-Based Bromination of Alcohols: An Organic Chemistry Experiment Supporting Spectroscopic Analysis and Mechanistic Reasoning

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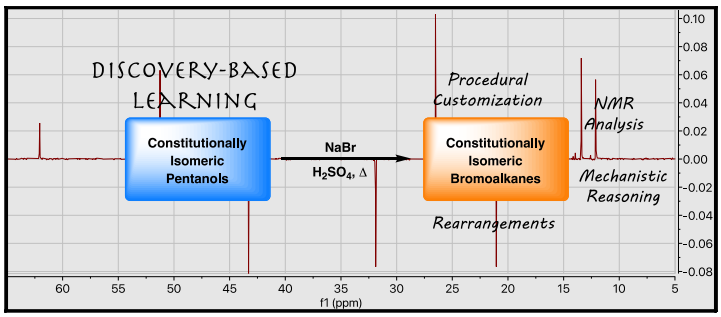

ABSTRACT: The bromination of six isomeric alcohols is adapted to a discovery-based organic chemistry laboratory experiment, whereby students are provided an alcohol starting material and are charged with determining the product or product mixture produced using relevant spectroscopic data. The experiment solidifies NMR analysis skills while reinforcing the mechanistic reasoning that supports the study of organic reactions. The laboratory is highly customizable and can be adapted to align with available instrumentation to best meet the needs of students, and it has been successfully implemented at three separate universities.

KEYWORDS: *Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Inquiry-Based/Discovery Learning, Alcohols, Nucleophilic Substitution, Mechanisms of Reactions, NMR Spectroscopy, Constitutional Isomers*

INTRODUCTION

Inexpensive alcohols are often halogenated in the laboratory to provide useful synthetic intermediates capable of further functionalization. Alcohol bromination can be accomplished with gaseous hydrogen bromide, phosphorus tribromide, or a sulfuric acid/hydrobromic acid aqueous mixture.[1] In many cases, this reaction leads to rearrangement products by way of carbocation intermediates. This phenomenon was studied extensively in the 1940s and 1950s.[2,3] We have developed an organic chemistry laboratory experiment, typically used in the second semester of our curricula, leveraging the bromination of constitutionally isomeric alcohols toward strengthening students' NMR data analysis and mechanistic reasoning skills.

A thorough examination of spectroscopic techniques supporting the experimental study of organic chemistry is a necessary component of any curricula. This spectroscopy unit, however, is somewhat disconnected from the major organic chemistry content areas describing methods of synthesizing organic compounds, and the new content does not implicitly reinforce mechanistic principles that scaffold organic reactions together. To strengthen and reinforce the mechanistic principles underpinning organic reactions while solidifying NMR analysis skills, we have developed a discovery-based[4−6] bromination of isomeric alcohols experiment expanding on a previous report.[7] Discovery-based experiments (also sometimes called guided-inquiry[4,5]) could be characterized as those that provide students with a tested procedure producing a predetermined, yet unspecified, outcome. During these experiments, therefore, the students must "discover" the experimental outcome once they have obtained the necessary data. Some survey and assessment data have indicated that discovery-based approaches may lead to greater laboratory enjoyment, a sense of achievement, and better learning outcomes.[4−6] As such, many discovery-based laboratories[7−34]

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have been developed in the past few decades to replace more traditional expository experiments, where students simply verify expected experimental outcomes.

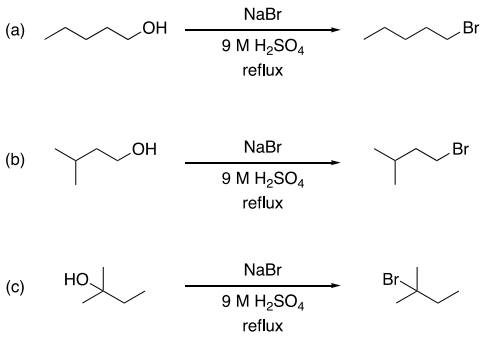
SETTING AND LABORATORY DEVELOPMENT

This laboratory was primarily developed at the University of Wisconsin−River Falls (UWRF) and was subsequently used at Bethel University and Villanova University. The laboratory has been customized to the different universities related to the availability of instrumentation and other factors, but the main text below will describe the standard experimental sequence performed at UWRF. A "procedural customization" section has been added before the experiment summary to highlight the supporting units that have been used in other academic settings.

OVERVIEW OF EXPERIMENT

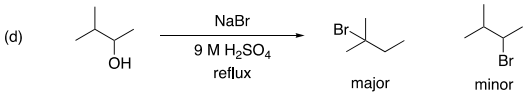
This laboratory experiment highlights the reactions of alcohols that students typically learn in the second half of Organic Chemistry I. At the beginning of the lab, each group is assigned an isomeric alcohol that they will submit to the laboratory manual's experimental protocol describing its conversion to an undefined alkyl halide. Specifically, students react their alcohol with sodium bromide in 9 M sulfuric acid[1] to produce one or more alkyl bromides. While students have encountered this reaction type in the classroom (more commonly shown as alcohols reacting with H−Br directly), this laboratory provides them an opportunity to run the reaction in person, predict the reaction outcome, use spectroscopic methods to determine their product structure, and compare the actual outcome to their expectation. The six isomeric alcohol starting materials produce a mixture of expected and unexpected outcomes. The simplest outcome involves the bromide replacing the hydroxyl group without rearrangement, which is observed for (a) the primary alcohol, 1-pentanol, producing 1-bromopentane via an expected S_N2 pathway, (b) the primary alcohol, 3-methyl-1-butanol, producing 1-bromo-3-methylbutane via an expected S_N2 pathway, and (c) the tertiary alcohol, 2-methyl-2-butanol, producing 2-bromo-2-methylbutane via an expected S_N1 pathway (Scheme 1).

Scheme 1. Alcohols Producing Direct Bromide Substitution



Complexity increases modestly as (d) the secondary alcohol, 3-methyl-2-butanol, produces a product mixture of major 2-bromo-2-methylbutane and minor 2-bromo-3-methylbutane (Scheme 2). The major product 2-bromo-2-methylbutane presumably forms via an S_N1 pathway with subsequent expected carbocation rearrangement prior to bromide addition.

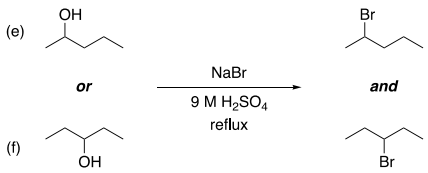
Scheme 2. 3-Methyl-2-butanol Produces Major Alkyl Bromide Product via Expected Rearrangement



^{13}C NMR and distortionless enhancement of polarization transfer (DEPT) NMR data need to be examined closely to see evidence of 2-bromo-3-methylbutane, as the signals are miniscule when compared to the 2-bromo-2-methylbutane signals. Once amplitude of the spectra are increased, however, five clear signals are visible and match the expectation for 2-bromo-3-methylbutane. Of note for this minor product are the two diastereotopic methyl signals, which many students expect to produce a single signal.

The final two starting materials, secondary alcohols (e) 2-pentanol and (f) 3-pentanol, both produce the same mixture of products, 2-bromopentane and 3-bromopentane, via an expected S_N1 pathway that gives rise to an unexpected 2° → 2° carbocation rearrangement, which often confounds students (Scheme 3). Students analyze their products using decoupled ^{13}C NMR and DEPT NMR, and the spectra allow them to determine the reaction outcomes.

Scheme 3. Alcohols Produce Unexpected Product Mixture



While the use of H_2SO_4/NaBr for bromination of alcohols has been classically used in expository teaching laboratory experiments[35−37] and was later modified to the previously noted discovery-based approach,[7] the current experiment enhances former protocols in the following ways:

1. Students "discover" reaction outcomes more independently as the number of starting material alcohols has been expanded to six (former experiment used three alcohols).
2. Use of DEPT NMR allows students to conclusively assign methyl, methylene, methine, and quaternary carbon signals.
3. All reactions use identical conditions for halogenation providing a simpler procedural setup (former experiment[7] chlorinated one alcohol using Lucas' Reagent).
4. ^1H NMR and GC-MS have been used in supporting units to more thoroughly characterize products including the examination of product ratios for reactions producing mixtures.
5. Bromopentane products are comparatively less volatile and hazardous (former experiment's 1-bromopropane is a low boiling health hazard).

The experiment is meant to be used early in the second-semester organic chemistry laboratory sequence, as that is the time that NMR often intersects with reaction analysis and mechanistic reasoning. The pedagogic learning outcomes include (1) student use of ^{13}C NMR data to identify unknown reaction products; (2) student use of DEPT NMR data to

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accurately assign ^{13}C NMR signals as methyl, methylene, methine, or quaternary in support of their proposed products; (3) student ability to use NMR software to acquire and analyze their own NMR data; and (4) student inference of reaction type (S_N1 versus S_N2) and necessary mechanistic steps (including rearrangements) through the identification of reaction outcomes.

HAZARDS

Sulfuric acid is corrosive to body tissue and can cause eye and respiratory burns. Preparation of 9 M sulfuric acid from a concentrated solution is highly exothermic, and it is suggested that this solution be prepared beforehand by lab support staff. Sodium bromide can cause mild eye and skin irritation. All alcohol starting materials are highly flammable liquids that can cause eye, skin, and respiratory irritation. All product alkyl bromides are highly flammable liquids that cause eye, skin, and respiratory irritation. Chloroform-*d* causes eye and skin irritation and has been shown to be a reproductive toxin and mutagen in animal studies. Sodium sulfate is a mild eye and skin irritant.

LABORATORY PARTICIPANTS AND PRACTICAL CONSIDERATIONS

At UWRF, this experiment was commonly performed by sections of ∼20 students working in pairs. In this setting, the six alcohol starting materials are used and four of them are run in duplicate. Students are not initially made aware of the duplicate groups, which means that individual lab partners are able to "discover" the result seemingly single handedly. The reaction is completed and analyzed over a two-week period (each session 2 h and 50 min). In the first week, students run, workup, and purify their reaction after which they prepare their NMR sample. The ^{13}C and DEPT NMR experiments are queued to run at the end of the first lab session, allowing them to return in the second week to fully acquired data. In the second week, students spend around 1.5−2 h analyzing their NMR data to determine their product structures using NMR software (Bruker's Topspin at UWRF). As this is their first time using the software to analyze ^{13}C or DEPT spectra, this time allotment is to allow them to become comfortable with the software as they will be using it repeatedly throughout the semester.

Immediately following the data analysis, the class reports out their reaction outcomes while describing what data allowed them to come to their specific conclusion. Before this occurs, the instructor makes students aware of any duplicate reaction groups so that the information can be delivered as a collective 4-person group. This discussion session informing students of the experimental outcomes of each alcohol is important, as students are required to write out mechanisms of three representative reactions (1-pentanol, 2-methyl-2-butanol, and 3-methyl-2-butanol) as part of their laboratory writeup. Upon completion of the lab, students write a laboratory report in which they tabulate their NMR data, assign the signals to their products, discuss how their data informed them of their reaction outcome, and summarize their experiment to address any errors and how different factors may have impacted their yield (grading rubric provided in the Supporting Information). This lab report format allowed for assessment of the pedagogic goals. This experiment has been run with roughly 90 students each year at UWRF from Fall 2017−Present. The average score of 156 students throughout the Fall 2017−Spring 2020 academic years was an 89 ± 3%. The most recent section to perform this experiment had product yields averaging 51.5 ± 6.0% ranging from 3−4.5 g of product.

EXPERIMENTAL SUMMARY

An assigned alcohol (4.0 g, 45.4 mmol) is added to a mixture of sodium bromide (7.00 g, ∼68 mmol) and 9.0 M sulfuric acid (12 mL). The mixture is refluxed for 25 min. After it is cooled, the flask is equipped for simple distillation and the distillate is collected until the drip rate slows considerably. The distillate is washed with saturated sodium bicarbonate followed by saturated brine. The organic layer is then transferred to a preweighed collection vial for the determination of yield and preparation of an NMR sample. The student handout, which has a more thorough procedure describing the experiment, is available in the Supporting Information. The student handout also lists (1) learning objectives, (2) background reading from the accompanied lecture textbook, and (3) green chemistry principles that apply to the experiment to inform students of sustainability efforts.

RESULTS AND DISCUSSION

Upon successful isolation of the product bromoalkanes, students are generally able to independently identify the product using ^{13}C and DEPT NMR. To prepare them for this, students are instructed during the 25 min reflux to (1) predict the product of these reactions and (2) sketch expected ^{13}C and DEPT spectra for their predicted products. Any confusion during the NMR analysis laboratory component is usually resolved by asking students to compare their actual data with the sketches of their expected spectra.

Representative Data

While students are informed during the prelab lecture that some of the starting materials may provide product mixtures upon reaction completion, this result is typically the most challenging for students to interpret. Both 2-pentanol and 3-pentanol create the same product mixture of 2-bromopentane and 3-bromopentane upon reacting (albeit in different product ratios), and this mixture is analyzed using decoupled ^{13}C NMR, DEPT 45 (shows $CH/CH_2/CH_3$ as (+) signals), DEPT 90 (shows only CH as (+) signals), and DEPT 135 (shows CH/CH_3 as (+) signals and CH_2 as (−) signals). The students are instructed to stack their data into a single spectrum, displaying everything simultaneously (Figure 1). For the mixture of 2-bromopentane and 3-bromopentane, 8 signals are expected (5 for 2-bromopentane and 3 for 3-bromopentane). These aliphatic signals are completely resolved and occur at 12.1, 13.4, 21.0, 26.5, 31.8, 43.2, 51.6, and 62.4 ppm (Figure 1). The DEPT-135 allows for conclusive assignment of 21.0, 31.8, and 43.2 as methylene signals. The DEPT-90 allows for conclusive assignment of 51.6 and 62.4 as methine signals. Leftover signals 12.1, 13.4, and 26.5 by default must be methyl signals, as they are positive in the DEPT-135 spectrum and absent from the DEPT-90 spectrum. While these data alone do not allow students to assign the specific signals corresponding to 2-bromopentane versus 3-bromopentane, when product ratio information is gathered and a comparison of ^{13}C NMR spectra for the reaction of 2-pentanol versus 3-pentanol is performed (and compared with literature values), the assignments indicated in Figure 1 can be made conclusively. This definite signal assignment, however, was not a graded

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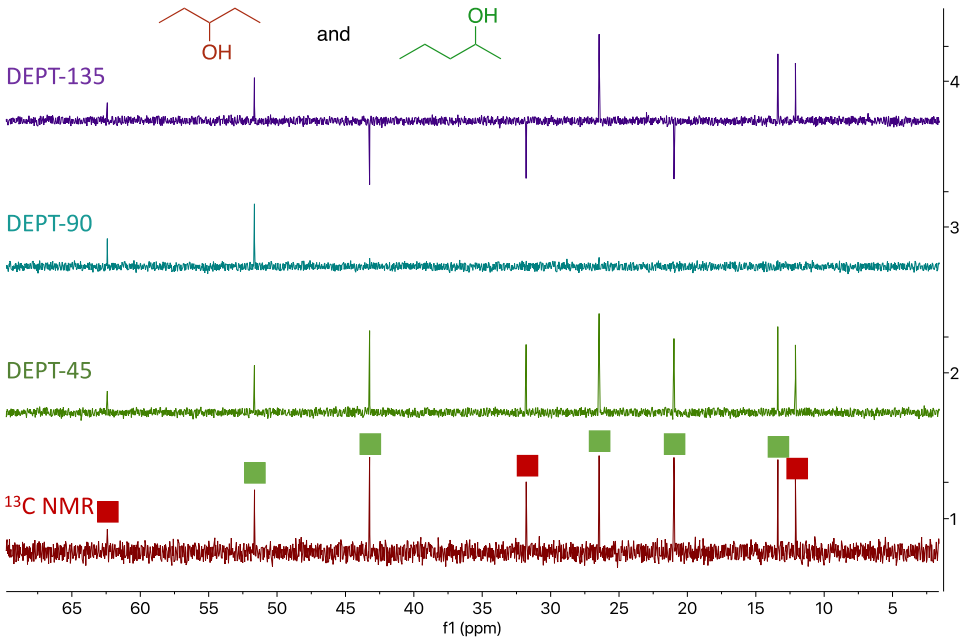

Figure 1. Representative student ^{13}C, DEPT-45, DEPT-90, and DEPT-135 spectra stacked in this order (bottom to top) for a mixture of 2-bromopentane and 3-bromopentane produced from reaction of 2-pentanol. Signals with a green box are from 2-bromopentane and signals with a red box are from 3-bromopentane.

component of the standard laboratory report. Instead, students were required to classify the signals as indicating methyl, methylene, methine, or quaternary carbons. Student data for the remaining alcohols are broken down in a similar manner in the Supporting Information.

Assessment of Learning Goals

Once students have completed the experiment, they prepare a lab report in a format described by the rubric in the Supporting Information. To organize NMR data, students are required to generate a table (1) assigning chemical shift numbers ascending letter codes (e.g., lowest chemical shift assigned "A"), (2) describing the signals as a methyl, methylene, methine, or C_{quat}, and (3) noting, to the extent possible, which signals correspond to which carbons in their product or product mixture, which is drawn as part of the table. This writeup allows students to demonstrate that they can identify unknown reaction products, assign their signals using ^{13}C and DEPT NMR data, and use NMR software to acquire and analyze their individual products, three of our pedagogic learning goals. The average score from a typical semester on this lab report component was a 91%, demonstrating that our students successfully identified their reaction product, tabulated the data, and assigned signals correctly. Beyond accurately presenting the NMR data in table format, students were required to explain how their spectroscopic data informed them of their reaction outcome in writing as part of the discussion section. The average score for this section was an 87%, which suggests that describing the data in writing was modestly more challenging for our students than putting it into table format. To assess the ability of students to infer the reaction type by knowing the reaction outcomes, they were required to write out the mechanisms for the reactions of 1-pentanol, 2-methyl-2-butanol, and 3-methyl-2-butanol. Students had moderate success in this task, with an average score of 76%. They were generally able to infer whether the reaction was unimolecular, bimolecular, or required a carbocation rearrangement, which was the major learning goal related to this task, but those that struggled experienced challenges concerning mechanistic principles. Specifically, arrow pushing was occasionally seen in the reverse direction or various arrows were simply missing. Overall, this experiment accomplished the pedagogic goals and students seemed to enjoy the process.

CUSTOMIZATION OPPORTUNITIES

As this procedure has now been completed at UWRF, Bethel University, and Villanova University, each of those institutions have made slight procedural modifications over time to best meet the needs of their students and align with available instrumentation.

Inclusion of GC-MS for Product Characterization

GC-MS has been included for further characterization of the reaction products. This supporting data allowed students to (1) use mass spectrometry as an additional method of verifying product structure, (2) demonstrate bromine incorporation into the product using isotopic ratios (Figure 2A), and (3) determine approximate product ratios when multiple products were formed (Figure 2B). Full GC-MS data is provided in the Supporting Information.

Inclusion of ^{1}H NMR for Product Characterization

While the ^{1}H NMR spectra of all products or product mixtures have some number of overlapping signals or multiplets, ^{1}H NMR can still be included for full product characterization. Additionally, ^{1}H NMR has been used as an additional means of examining product ratios. As the methine signals in 2-bromopentane and 3-bromopentane are completely resolved, they can be used to calculate the approximate product ratio (Figure 2C). Gratifyingly, the integration ratio very closely

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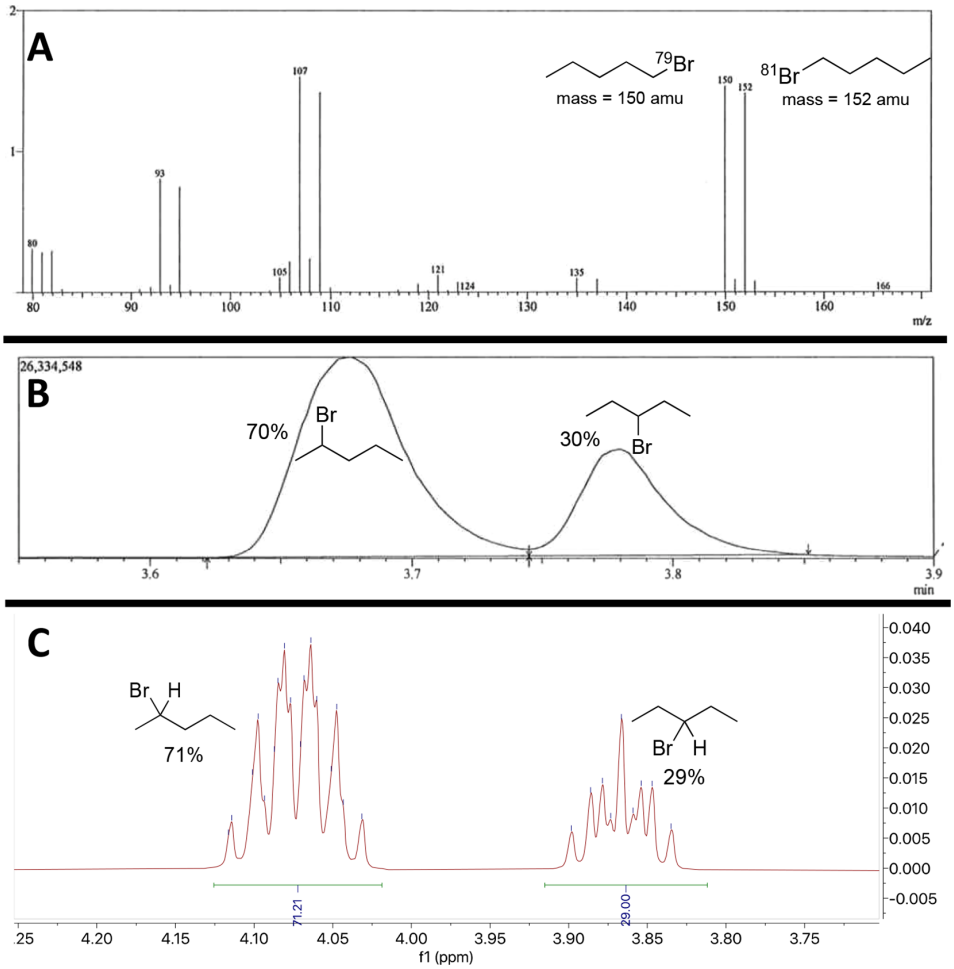

Figure 2. Customization of the experiment can occur in a variety of ways. (A) Mass spectrometric analysis of 1-bromopentane shows a clear M + 2 signal in a roughly 1:1 ratio demonstrating bromine incorporation. (B) GC analysis of the 2-pentanol reaction products shows a 70:30 ratio of 2-bromopentane to 3-bromopentane. (C) ^{1}H NMR analysis of the 2-pentanol reaction products shows a 71:29 ratio of 2-bromopentane to 3-bromopentane.

matches the GC-MS data even though these products were prepared by different students at different institutions (Bethel and Villanova).

Single Lab Period Completion

If this lab were implemented after students had sufficient training time with the NMR processing software, it could be completed in a single lab period. When the lab was being adapted to a chemistry majors only lab section with a four-hour experiment window, it was modified in this way. One potential complication of moving the lab to a single week could be the lack of time to acquire ^{13}C NMR data, as hundreds or thousands of scans are often required to obtain resolved carbon signals given ^{13}C's low natural abundance. Since this protocol allows for the easy synthesis of multigram quantities of these alkyl bromides, however, students were informed to make NMR samples with 100−300 mg quantities of their product. This allowed clear ^{13}C NMR spectra to be acquired in as few as 16 scans, allowing all students to obtain NMR data for analysis before the lab period expired.

Inclusion of Other Isomeric Alcohols

When the lab was being designed, the intention was to include all saturated isomeric five carbon alcohols as starting materials to allow for student "discovery" to occur relatively independently. After performing the reaction with previously unmentioned 2-methyl-1-butanol and 2,2-dimethyl-1-propanol, however, it was noted that these alcohols required procedural modifications that would have resulted in procedural heterogeneity and the creation of complex mixtures of products. Despite these challenges, these alcohols could be included in lab curricula to demonstrate different alcohol substitution phenomena. For example, 2,2-dimethylpropanol, also known as neopentyl alcohol, is often provided as an example in organic chemistry texts to demonstrate the impact of sterics on substitution reaction rates. Although the alcohol is primary, being vicinal to the *tert*-butyl group decreases the rate of bimolecular substitution chemistry. This concept is demonstrated by the fact that none of the direct halogen substitution, which would presumably form 1-bromo-2,2-dimethylpropane via an S_N2 reaction, is observed when neopentyl alcohol is subjected to the reaction conditions.

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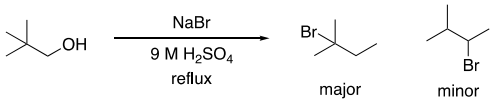
Instead, this primary alcohol provides a mixture of rearranged products 2-bromo-2-methylbutane and 2-bromo-3-methylbutane (Scheme 4). While low yield and substantial leftover unreacted alcohol is noted if neopentyl alcohol is subjected to the standard reaction conditions, significant product formation can be achieved by increasing the reflux time to 45 min (from 25 min) and including a modified extraction technique that washes the organic layer with concentrated sulfuric acid to remove unreacted alcohol starting material.

Scheme 4. Neopentyl Alcohol Undergoes Bromination with Procedural Modifications



While inclusion of neopentyl alcohol provides significant enrichment to the laboratory experience, the procedural complications and unequal distribution of challenge for the students who would have been assigned this alcohol led to its exclusion from our typical laboratory experiment. The reaction of 2-methyl-1-butanol had similar types of complications and was also excluded. The procedural modifications and spectra of these reactions are included in the Supporting Information to allow adapting departments to include these examples if deemed a good fit.

SUMMARY

The discovery-based bromination of saturated isomeric five-carbon alcohols has been adapted successfully to the organic chemistry laboratory sequence at the University of Wisconsin–River Falls, Bethel University, and Villanova University. The protocol is streamlined, allowing for an identical experimental setup across all six isomeric alcohol starting materials, and this allows students to "discover" their reaction outcomes seemingly independently, as there are a limited number of repeat starting materials. This experiment allows students to apply and practice their understanding of spectroscopic techniques toward the analysis of unknown reaction products. Upon identification of their isomeric bromoalkane product, the laboratory reinforces mechanistic reasoning skills via the proposal of reaction mechanisms by the students. The experiment is highly customizable allowing individual departments to adopt the protocol and include more or less spectroscopy to closely match instrumentation availability and student needs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.1c00544.

Notes for instructors (PDF)
Notes for instructors(DOCX)
Student handouts (PDF)
Student handouts (DOCX)

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Notes

The authors declare no competing financial interest.

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