ORGANIC

UNDERGRADUATE EXPERIMENT

The Regioselective Epoxidation of Carvone

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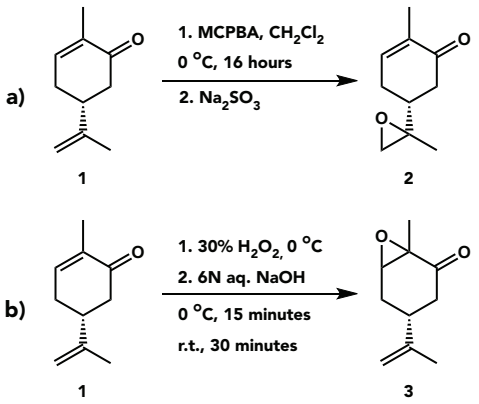
INTRODUCTION

For most undergraduate students, the laboratory component can be the most important portion of their organic chemistry courses due to its impact on strengthening the theoretical material taught in lecture halls. After first year general chemistry courses, students have become familiar with basic laboratory techniques such as solubility, polarity, extraction/isolation techniques, *etc.* However, in the latter years of a students' chemistry education, they are exposed to increasingly complex and more specific concepts. This includes organic transformations (*e.g.*, Fischer esterification, chemiluminescent reaction, aldol condensation, Friedel-Crafts acylation and alkylation, etc.), characterization techniques using analytical methods (*e.g.*, ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, infrared spectroscopy, high-performance liquid chromatography, *etc.*) and many more. Specifically, nuclear magnetic resonance (NMR) is an extremely important characterization technique available to chemists in determining atom connectivity and relative spatial orientation, chemical environment, functional group identification, among other things.

Because of the significance of NMR, it is important for undergraduate students to gain hands-on experience with this technique, as it is increasingly likely for them to encounter it in future industrial or educational environments. Unfortunately, traditional high-field NMR spectrometers are inherently expensive as these require regular maintenance, use of cryogens, and extensive training for operation of the instruments. With the advent of benchtop technology, students can access NMR with ease, gathering and interpreting their own spectra within a laboratory session.

Regioselective epoxidations, while important transformations in organic synthesis, are not commonly studied in most organic chemistry laboratories.[1-5] This reaction involves the formation of a strained oxirane ring from an alkene functionality, which is highly susceptible to nucleophilic attack, making it a valuable intermediate in many organic processes.[1,3] Selective reactions are important to synthetic chemists, and the sample experiment presented herein explores two different regioselective reactions to form epoxides.[1,4-6] In order

to showcase this selectivity, the naturally occurring compound (R)-(-)-carvone (**1**) was chosen due to its molecular structure containing both an electron-rich alkene and an α,β-unsaturated carbonyl functionality.[1,3] The two reactions performed in this sample experiment are based on work published by Mak *et al*. in *The Journal of Chemical Education*.[1] The two regioselective reactions are outlined in **Scheme 1**, where **1** is either treated with the peroxy acid 3-chloroperbenzoic acid (MCPBA), to form carvone-7,8-oxide (**2**), or with alkaline hydrogen peroxide to obtain carvone-1,2-oxide (**3**).



Scheme 1. *Reaction scheme for the epoxidation of carvone **1** with **a)** MCPBA to obtain **2** and **b)** 30% H_2O_2 and aqueous 6N sodium hydroxide to obtain **3**.*

As shown in these two reactions, both alkene groups behave differently under their respective reaction conditions. To understand the reason for the regioselectivity, we must also understand the different chemical environments of each alkene group in **1**. In general, alkenes are electron rich moieties and often act as nucleophiles in reactions, which is true for the transformation in **Scheme 1a**. As the isopropenyl alkene group is electron rich and MCPBA is an electron deficient peroxy acid, the isopropenyl alkene acts as a nucleophile. However, in **Scheme 1b**, nucleophilic attack from the peroxide anion on the α,β-unsaturated carbonyl leads to the formation of an enolate anion, which is stabilized under alkaline conditions, before ultimately leading to peroxide formation.[1]

By comparing the 60 MHz ^{1}H and ^{13}C{^{1}H} NMR spectra of the final products (**2** and **3**) with the starting material (**1**), we were able to confirm the formation of these products and illustrate the benefits of incorporating benchtop NMR into undergraduate teaching laboratories. Furthermore, this experiment highlights key benefits in regioselective reactions and also offers the characterization of like-products by students using benchtop NMR analysis.

Procedure

Materials

(*R*)-(-)-carvone (98%), 3-chloroperbenzoic acid (≥77%), dichloromethane (≥99.8%), anhydrous methanol (99.8%), sodium sulfite (≥98%), sodium carbonate (≥99.5%), magnesium sulfate (≥99.5%), hydrogen peroxide (30% w/w in H_2O) and sodium hydroxide (≥98%) were purchased from MilliporeSigma and used without further purification.

Instrumentation

All NMR data was obtained using a Nanalysis 60PRO instrument. The ^{1}H experiments were performed using the following acquisition parameters: spectral width, 40 ppm; spectral center, 10 ppm; number of points, 8192; number of scans, 16; dummy scans, 0; interscan delay, 1 second; pulse angle, 90°; receiver gain, auto. The ^{13}C{^{1}H} experiments were performed using the following acquisition parameters: spectra width: 220 ppm; spectral center, 100 ppm; number of points, 4096; number of scans, 4096; interscan delay, 0 seconds; pulse angle, 30°; receiver gain, auto. All spectra were manually corrected for phase and baseline distortions using the MestReNova software (v14.1.1).

Synthesis

*Carvone-7,8-oxide (**2**)*

(*R*)-(-)-carvone (1.00 g, 6.68 mmol, 1.0 equiv.) was dissolved in dichloromethane (DCM, 8 mL) in a 25 mL round-bottomed flask and cooled to 0 °C in an ice bath. To that mixture, a solution of 3-chloroperbenzoic acid (MCPBA, 1.69 g, 9.80 mmol, 1.5 equiv.) in DCM (8 mL) was added dropwise over a period of 20 minutes. The formation of a precipitate was immediately observed upon addition, and the resulting mixture was allowed to stir in the ice bath for 3 hours. The reaction mixture was moved to a freezer set to 0 °C and left to settle overnight (16 hours). A 10% sodium sulfite solution (1 mL) was added once the mixture had returned to room temperature, and the reaction was allowed to stir for 5 minutes. The mixture was gravity filtered and the solid was washed with DCM (2 x 4 mL). The washes were combined with the filtrate and washed with 10% sodium carbonate (3 x 15 mL) and a saturated salt solution (15 mL). The organic layers were collected, combined, dried with anhydrous magnesium sulfate and filtered by gravity filtration. The filtrate was concentrated in vacuo and yielded a clear, pale yellow colored liquid. No further purification was necessary.

*Carvone-1,2-oxide (**3**)*

(*R*)-(-)-carvone (1.00 g, 6.68 mmol) was dissolved in methanol (8 mL) in a 25 mL round-bottomed flask and cooled to 0 °C in an ice bath. A solution of 6N aqueous sodium hydroxide was prepared in the meantime. To the carvone and methanol mixture, 30% w/w hydrogen peroxide was added dropwise over a period of 5 minutes. Then, 6N aqueous sodium hydroxide was added dropwise to the solution over a period of 5 minutes and the mixture was allowed to stir at 0 °C for 15 minutes. The solution was taken out of the ice bath and allowed to stir at room temperature for 30 minutes. To the resulting mixture, DCM (10 mL) was added and the organic layer was washed with water (3 x 15 mL), a saturated salt solution (15 mL), and dried with anhydrous magnesium sulfate. The solution was gravity filtered and the filtrate was concentrated in vacuo, yielding a clear liquid. No further purification was necessary.

Results and Discussion

The ^{1}H and ^{13}C{^{1}H} NMR spectra of the two final products (**2** and **3**) were collected and compared with the spectrum of the starting material (**1**). These spectra are shown in **Figure 1** and **Figure 2**.

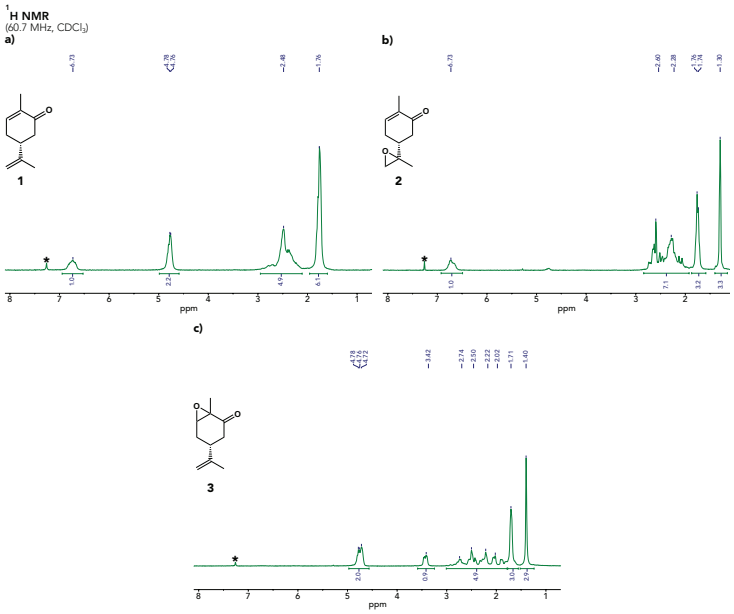


Figure 1. *^{1}H (60.7 MHz) NMR spectra of* ***a)*** *carvone (**1**),* ***b)*** *carvone-7,8-oxide (**2**), and* ***c)*** *carvone-1,2-oxide (**3**). The asterisk represents the residual solvent peak for chloroform-d.*

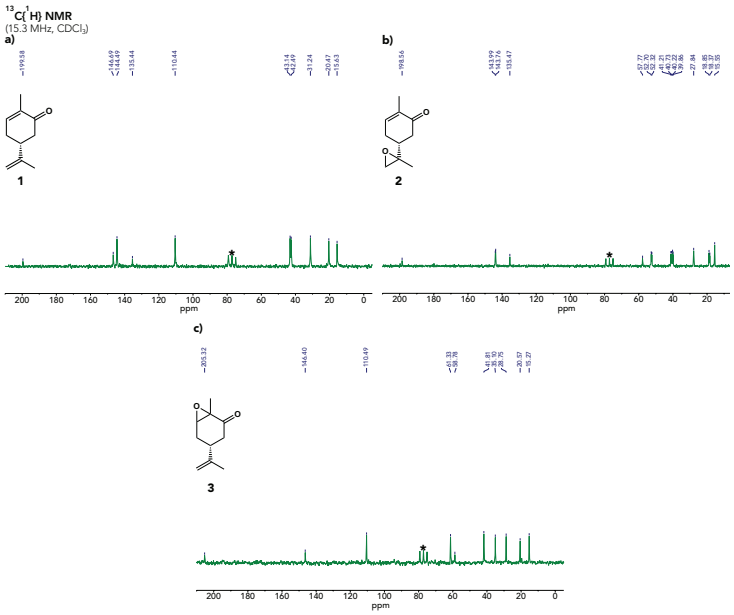


Figure 2*. ^{13}C{^{1}H} (15.3 MHz) NMR spectra of* ***a)*** *carvone (**1**),* ***b)*** *carvone-7,8-oxide (**2**), and* ***c)*** *carvone-1,2-oxide (**3**). The asterisk represents the residual solvent peak for chloroform-d.*

In the ^{1}H NMR spectrum of **1**, there are 4 major regions. These are: a peak centered at 6.73 ppm, related to the α,β–unsaturated carbonyl proton; a peak centered at 4.77 ppm, related to the isopropenyl double bond; a peak centered at 2.48 ppm, related to the CH and CH_2 groups; and a peak centered at 1.76 ppm, related to the two methyl groups on the molecule. We would normally expect to see **2** separate peaks for the methyl groups, however, they are coincidentally equivalent at low-field and appear as a singlet that integrate to 6 protons.

Upon comparison of carvone **1** with epoxidized carvone **2**, we notice two significant differences which aid in determining if the final product, **2**, was successfully synthesized. First, the peaks of the isopropenyl double bond centered at 4.78 ppm in the NMR spectrum of **1** do not appear in the NMR spectrum of **2** as the double bond has undergone the selective epoxidation via MCPBA, forming the oxirane ring. The second significant difference between the two spectra can be observed for the methyl groups of both carvones **1** and **2**. In the NMR spectrum of **1**, the methyl groups are not fully resolved. After the epoxidation of the isopropenyl double bond, the methyl groups in **2** are in very different chemical environments relative to each other, and we are able to resolve both peaks at 1.3 ppm and 1.75 ppm.

For the reaction via a basic peroxide route, when comparing the two ^{1}H spectra, we once again notice some significant differences. For carvone **3**, as a result of the formation of an oxirane ring on the α,β-unsaturated carbonyl, we no longer observe the peak centered at 6.73 ppm in carvone **1**, but we retain the isopropenyl alkene peak centered at 4.76 ppm. Contrary to carvone **1**, where the methyl groups are overlapping, the formation of the oxirane ring causes the methyl of the α,β-unsaturated carbonyl to be in a completely different chemical environment relative to the methyl of the isopropenyl alkene peak. This results in the methyl of the α,β-unsaturated carbonyl giving rise to a peak centered at 1.40 ppm.

In the ^{13}C{^{1}H} NMR spectra, the signals related to the isopropenyl and α,β-unsaturated carbonyl alkene carbons are the major peaks of interest. In the ^{13}C{^{1}H} spectrum of **1**, the α,β-unsaturated carbonyl carbons appear at 135.44 ppm and 144.49 ppm for the α and β positions, respectively, whereas the isopropenyl carbon and the vinylic carbon of this alkene appear at 146.69 ppm and 110.44 ppm, respectively. It is important to note that both of these reactions form diastereomers, as reported by Mak *et al.* in the *Journal of Organic Chemistry*, wherein they observed a ratio of diastereomers of 1:1.33 for carvone **2** and 19:1 for carvone **3**. **1** In carvone **2**, we also observe the diastereomeric signals in a similar ratio (**Figure 2b**), however, in carvone **3**, we do not observe the unique diastereomeric signals. This difference in diastereomer formation might be due to the base-catalyzed reaction generating carvone **3** in a stereoselective manner, possibly because of steric relief during the transition state favoring a trans configuration of the oxirane ring relative to the isopropenyl group.[7]

When comparing the ^{13}C{^{1}H} NMR spectra of the reaction from carvone **1** with MCPBA to carvone **2**, apart from the diastereomeric peaks, we observe a significant difference in the chemical shift of the carbon peaks associated with the isopropenyl group. The isopropenyl C*q* and vinylic CH carbons shift from 146.69 ppm and 110.44 ppm in carvone **1** to 57.77 ppm and 52.32/52.70 ppm, respectively in carvone **2**. For the α,β-unsaturated carbonyl carbons, we do not observe a significant chemical shift difference from carvone **1** to carvone **2**, where the α and β carbons appear at 135.46 ppm and 143.99/143.76 ppm, respectively.

Upon epoxidation of the α,β-unsaturated carbonyl using hydrogen peroxide in a basic media to obtain carvone **3** from carvone **1**, the most significant chemical shift changes in the ^{13}C{^{1}H} NMR spectrum of carvone **3** is understandably the carbons of the α, β-unsaturated carbonyl. The formation of the oxirane ring in this position causes the alpha and beta carbons to shift from 135.44 ppm and 144.49 ppm to 58.78 ppm and 61.33 ppm, respectively. Due to this reaction being selective, the isopropenyl group is not affected and therefore,

does not show a significant change in chemical shift. In carvone **3**, the isopropenyl carbon and vinylic carbon appear at 146.40 ppm and 110.49 ppm, respectively, which is similar to that of carvone **1**.

Conclusion

With the incorporation of benchtop NMR spectroscopy into higher level organic chemistry courses, students are able to build a stronger foundation of NMR knowledge and add this experience to their resumé. Students can directly collect their own spectra within a laboratory period and gain knowledge in interpreting this data. In this sample experiment, students fine-tune their NMR ability by discerning the spectrum of like-molecules, which gives them first-hand experience of NMR in scenarios outside of school. Specifically, this sample experiment explores the regioselective epoxidation of carvone via two different routes: by use of MCPBA, which epoxidizes carvone **1** at the isopropenyl alkene region to make **2**, and through a basic peroxide reaction that selectively reacts at the α,β-unsaturated carbonyl to produce **3**. The ^{1}H and $^{13}C\{^{1}H\}$ spectra of all 3 compounds were collected and compared to ensure a successful synthesis. As benchtop NMR is readily accessible to students, it is easily incorporated into undergraduate laboratories, allowing for students to obtain first-hand characterization skills in their undergraduate degree.

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