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Laboratory Experiment

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Synthesis of Methyl Cyclopentanecarboxylate: A Laboratory Experience in Carbon Rearrangement

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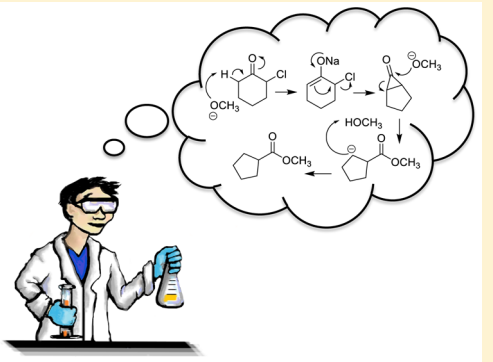
Supporting Information

ABSTRACT: We present a novel guided inquiry second semester organic chemistry laboratory rearrangement experiment. Students performed the Favorskii Rearrangement to obtain methyl cyclopentanecarboxylate in good yields. The students learned about the individual steps of the Favorskii mechanism and were required to propose a complete reaction mechanism and product structure. The students then confirmed the structure of the product by NMR and IR spectroscopy. This experiment provides students with experience in running organic chemistry reactions, structure determination, spectroscopy, general problem solving, and drawing rearrangement mechanisms.



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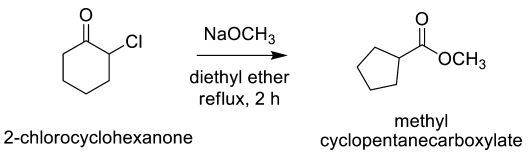
Organic chemistry lecture students often struggle to predict reaction products with complex mechanisms, such as those involving carbon rearrangements and ring-contraction. Perhaps the best way to determine the product of a reaction is through running the reaction, obtaining and interpreting spectra, and combining these interpretations with one's mechanistic predictions. A great place for students to practice prediction and confirmation of reaction products is in the organic chemistry laboratory, where they can execute the chemical reaction, isolate the product, obtain and interpret spectra, and use their mechanistic understanding to determine the product structure. Additionally, hands-on experience in running organic reactions helps make the concepts more tangible.

Often in organic laboratory courses, students follow "cookbook" procedures and do not spend enough time thinking about mechanisms. Researchers have studied mechanistic reasoning and success in organic chemistry and have found a correlation between improved mechanistic reasoning and students' success in the classroom.[1−3] They suggest more instructors should promote mechanism-based learning, as many students struggle through organic chemistry without a basic understanding of reaction mechanisms.[2] A mechanistic reasoning-based, carbon rearrangement organic laboratory experiment, in which students use mechanistic reasoning and spectroscopy to determine the product structure, is an excellent opportunity for students to improve their laboratory technique alongside their mechanistic reasoning skills. Complex mechanisms involving ring contraction, such as the Favorskii Rearrangement, tend to be difficult for students to predict. Rearrangement-based experiments are one of the most effective ways to teach such difficult concepts.[4−7]

Currently, there are reported laboratory experiments involving rearrangement products.[7−13] However, most of these experiments include the use of boron trifluoride etherate,[12] which is extremely toxic. Other similar experiments involve expensive Lewis acids[13] that are not compatible with typically large undergraduate student laboratory sections. There are also very few rearrangement experiments that involve ring contraction[14] or expansion.

Herein, we report a rearrangement laboratory experiment for the second semester second-year undergraduate organic chemistry laboratory course that is based on guided inquiry pedagogy. Our new laboratory experiment involves the ring contraction of 2-chlorocyclohexanone via Favorskii Rearrangement in the presence of sodium methoxide, producing methyl cyclopentanecarboxylate (Scheme 1). The Favorskii Rearrange-

Scheme 1. Rearrangement of 2-Chlorocyclohexanone to Methyl Cyclopentanecarboxylate



2-chlorocyclohexanone — methyl cyclopentanecarboxylate

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ment is not typically covered in lecture, so students are exposed to a new organic reaction mechanism and must truly rely upon their cognitive ability to deduce a complex mechanism based upon their understanding of how similar species typically react, combined with their ability to interpret spectra. Students perform the reaction, isolate the product and analyze it via NMR and IR spectroscopy. They are also given a mechanism problem set to complete, with reactions that are similar to each individual step of the Favorskii mechanism. The overall pedagogical goals of this experiment are to improve their ability to determine the structure of an unknown compound based on spectroscopic data and also improve their mechanistic reasoning skills. In this way, students experience an important organic chemistry process through the course of the experiment: performing a reaction and attempting to predict its mechanism, isolating and characterizing the product, and revising mechanistic/product predictions based on experimental data.

EXPERIMENTAL SECTION

Students were provided with a laboratory handout (see Supporting Information) containing the experimental procedure and the structure of the starting material a week prior to beginning this experiment. Students were required to calculate the amounts, number of moles, and equivalents for each reagent and record the calculations in their lab notebooks before class. The experiment began with a short prelab lecture, during which the instructor reviewed safety information and general reaction setup. After the short prelab lecture, students set up their reactions (see Supporting Information for details).

Each student ran the reaction individually, and the experiment requires two 3 h laboratory periods to complete. Set-up is relatively quick and easy, but the reaction stir time is 2 h (most of the 3 h lab period), so much of the "pre-lab lecture" was saved until after all students had set up their reactions. Once all students had initiated their reaction, they reconvened to continue with the lecture portion of the lab experiment and discussed concepts of ^{13}C NMR spectroscopy, APT (attached proton test), and assignment of diastereotopic protons in ^{1}H NMR. Students were also given a problem set (five questions) related to the mechanism steps of the Favorkii reaction. The students were instructed to complete the problem set (see Supporting Information) individually, and after 30 min, the instructor collected their answers to assess their ability to complete the mechanism steps related to the Favorkii reaction. The instructor reviewed the questions with the class and the students were then asked to propose a mechanism and product for the experiment at hand based on the given reagents and what they learned from the problem-set mechanisms. These attempts at the Favorkii mechanism were not discussed in class, as the product would not be characterized until the next laboratory period. The problem set attempts were collected, and at the end of the reaction period, the students stopped the reaction and stored the resulting mixtures until the next lab period.

The students completed the workup, isolation, and characterization via IR and ^{1}H NMR (run on a 90 MHz NMR in class by each student) on Day 2 of the laboratory experiment (see Supporting Information for experimental details and representative spectra). Additionally, the instructor combined several student samples to collect an additional APT NMR spectra (run outside of class on a 400 MHz instrument) to aid in product determination. The students were directed to propose a plausible mechanism and structure of the product in their laboratory reports.

HAZARDS

The students performed all chemical reactions and workup in a fume hood. Students should wear safety glasses, lab coats, and gloves when working with the reagents. 2-Chlorocyclohexanone can cause irritation to the eyes, skin, and respiratory tract when inhaled. Sodium methoxide is corrosive to the skin and eyes. Diethyl ether is an extremely flammable liquid and vapor. The product, methyl cyclopentane carboxylate, can cause irritation in contact with eyes and skin. The NMR solvent, deuterated chloroform, is toxic orally and by inhalation, causes skin and eye irritation, and is carcinogenic.

RESULTS AND DISCUSSION

One of the major goals of designing this undergraduate laboratory experiment was to give students guided practice in predicting the product and mechanism of a reaction, while demonstrating to the students how experimentation/data facilitate the problem-solving process. Another of our goals was to be able to guide them through the process of mechanistic/product prediction in a stepwise fashion, such that both students and professor could observe students' progress and compare their abilities to predict products (a) through mechanistic predictions only, (with the help of problem-set guidance) and then (b) combining problem set guidance with characterization data. We hypothesized that most students would be better able to predict the product, and therefore mechanism, with the help of the characterization data, and we used the answers they gave on problem sets to compare (a) what percentage of students were able to successfully predict the product/mechanism at the beginning of the experiment, and (b) were able to improve their predictions after data had been collected.

This laboratory experiment has been performed by 72 students over four laboratory sections, all students were able to individually synthesize, isolate, and characterize the expected product, within two 3-h laboratory periods with reasonable yields (generally between 30−70%). The experimental procedures have been adapted from literature methods[15] and optimized such that the reaction is straightforward to perform, and the desired product can be obtained at acceptable purity (typically between 70−90% purity by NMR) with minimal purification. In one section, the students attempted to further purify the product by simple distillation (product boiling point is 82 °C). The distillation glassware we have available in our laboratory is best suited for scales larger than 1 g, so we initially chose to have the students run the reaction on a 2 g scale in an effort to make workup and purification easier. However, the distillation resulted in drastically lower yields and did not improve the purity of the product. In subsequent laboratory sections we did not direct the students to distill the product and, therefore, have been able to reduce the amount of starting material to scales ranging from 0.5−1 g based on instructor preference.

The ^{1}H NMR spectra were collected by the students on a 90 MHz NMR in class, and they were also given a ^{1}H NMR spectrum obtained by the instructor using a 400 MHz instrument. The ^{1}H NMR spectrum of the product is simple yet offers an opportunity for students to learn about diastereotopic protons. With minimal guidance from the

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instructor and use of contributing information from the IR spectrum and problem set mechanisms, 75% of the students were able to analyze the chemical shifts and integration of the ^{1}H NMR spectra to determine the basic ring structure of the product and the presence of a methyl ester. The guidance from the instructor consisted mainly of delineating which peaks were arising from their products and which were arising from impurities, since the students do not yet have the expertise to make such distinctions. Also, for some spectra, the instructor helped the student normalize the integral values appropriately, since the 90 MHz NMR does not always give the level of resolution and proper integration to allow the students to do this on their own. With those distinctions made, 10 of 14 students in the most recent laboratory section were able to detect symmetry in the molecule, assign the five-membered ring and methyl ester, and determine the overall product structure before leaving the laboratory on Day 2. Although the spectral indications of symmetry and basic ring structure, combined with the students' mechanistic reasoning, were enough for most students to assign the structure, students reported that specific identification of individual diastereotopic proton signals was mainly done using the 400 MHz spectrum, in which these peaks are better resolved. This was a good opportunity for students to compare the resolution available from a 90 MHz vs 400 MHz instrument. The remaining four students deduced the product structure at home using the ^{1}H NMR and IR spectra they obtained, combined with the additional spectra provided by the instructor.

The product from several students was collected and used to obtain APT spectra on a 400 MHz NMR instrument, which was distributed to all students after the lab period to aid them in characterization (to be discussed in their lab reports). The APT spectrum of the product was simple to interpret with five signals observed due to symmetry. This was a good opportunity to introduce APT spectroscopy and its ability to distinguish different types of carbons. The students were very comfortable working with the APT spectrum toward determination of the chemical structure of the product and did well in using it to support the product structure assignment in lab reports.

The mechanism of this reaction is challenging as it contains multiple steps, including deprotonation, intramolecular nucleophilic attack, attack at a carbonyl carbon, ring contraction, and protonation. These individual mechanistic steps are commonly used in the second semester organic chemistry course, though combining them into one complete mechanism, such as the Favorskii mechanism, can be challenging for undergraduates. We improved the learning experience by providing a carbon rearrangement problem set to the students. The handout helps the students learn the representative mechanisms for each step of the Favorskii reaction, and were expected to use this information to write the complete Favorskii reaction mechanism (given the starting reagents) and draw the product. The handout was designed in order to (1) help students work through the mechanism and predict the product and (2) probe the students' mechanistic reasoning skills as they perform the experiment.

The handout was given to the students at the beginning of the experiment during the prelab discussion, and students were instructed to complete the handout, individually and with no aid from the instructor. The students' initial attempts at the handout provided insight into their mechanistic abilities (see Supporting Information for examples). Students had the most issues with the enol formation (57% students were correct on Attempt 1) and subsequent enol attack of an alkyl halide (43% students correct). Additionally, many students (75%) attempted to use protonated carbonyls as electrophiles or methanol as a nucleophile, which is inappropriate in basic solution. Despite these errors in protonation state, which are common for second-year organic chemistry students, they do tend to use nucleophiles and electrophiles correctly in general. As expected, only 14% of the students were able to correctly draw the Favorskii mechanism without running the experiment and using spectroscopic data. The handouts were turned in and the instructor briefly discussed the four representative mechanism steps (the instructor did not discuss the actual Favorskii mechanism with the students during the prelab discussion) and the students then performed the experiment.

During the second laboratory period, once students had isolated their products and collected NMR and IR data, the students were again given the same carbon-rearrangement handout and instructed to complete the handout. The student's answers on the four mechanism problems improved with 90% of the students providing the correct response for each mechanism problem. Fifty percent of the students were able to provide the correct mechanism for the reaction they performed before leaving the laboratory on day 2 (although we observed that some students still continued to use methanol as the nucleophile, rather than methoxide). Having observed the class as they interpreted spectra and worked on solving the reaction mechanism after finishing the experiment, we believe that the students seemed more engaged and invested in understanding the mechanism and determining their product structure than they would have been in a lecture setting and that their critical thinking and problem solving abilities were heavily exercised.

The students responded well to the mechanism challenge and could solve the mechanism with little help from the instructor. Only a few students needed significant hints, and the instructor observed the students closely to see their problem-solving processes and make sure they worked individually, for the most part. For most students, the most difficult part of solving the mechanism seemed to be in determining the first step. Once the students learned the first step involves deprotonation of the α carbon of the carbonyl, *opposite* the leaving group, most students were able to correctly complete the mechanism. Upon performing the reaction and isolating the product, the students seemed more determined to solve the mechanism than they would have been in a lecture setting.

CONCLUSION

We have successfully implemented a novel, second semester organic chemistry laboratory rearrangement experiment that involves the proposal of the reaction mechanism and spectroscopic identification of the product. The reagents for this experiment were relatively safe and inexpensive, the experimental procedure was easy to follow, and the students were able to obtain, isolate, and characterize the product in two laboratory periods. The students gained experience in structure determination via IR and ^{1}H NMR spectroscopy, as well as ^{13}C NMR, APT, and analysis of diastereotopic protons. The students also gained experience in proposing and drawing mechanisms, particularly rearrangement mechanisms, which can be challenging for students at the undergraduate level.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00588.

Sample student handout and instructor notes with experimental details and sample spectra. (PDF)

Sample student handout and instructor notes with experimental details and sample spectra. (DOCX)

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Notes

The authors declare no competing financial interest.

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