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Laboratory Experiment

Transmutation of Scent: An Evaluation of the Synthesis of Methyl Cinnamate, a Commercial Fragrance, via a Fischer Esterification for the Second-Year Organic Laboratory

Jacob H. Steele, Marie X. Bozor, and Gregory R. Boyce*

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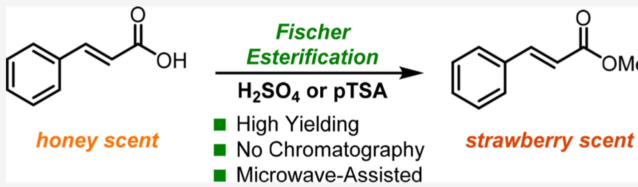
ABSTRACT: The synthesis of a commercial fragrance, methyl cinnamate, via Fischer esterification was evaluated for use as a second-year organic chemistry course. The experiment utilizes *trans*-cinnamic acid, a commercial flavoring that possesses a mild honey floral odor, as an inexpensive starting material. Both the starting material and the product are listed as GRAS (Generally Recognized as Safe) for use in foods and fragrances. The high-yielding experiment enables students to explore concepts of flavor and fragrances, transmutation of scent, catalysis, green chemistry, NMR spectroscopy, thin layer chromatography (TLC), and acid−base extractions. In addition to the commonly employed sulfuric acid catalyst, alternative conditions were developed using *p*-toluenesulfonic acid monohydrate as an easier to handle catalyst, and conditions for performing both reactions under microwave irradiation are also reported. The experiment was analyzed in a second-year organic chemistry laboratory over six semesters.



KEYWORDS: *Esters, Second-Year Undergraduate, Organic Chemistry, Synthesis, Green Chemistry, Hands-On Learning/Manipulatives*

INTRODUCTION

Fischer esterification is a hallmark of the second-year undergraduate organic chemistry laboratory. The reaction converts a carboxylic acid to an ester in the presence of refluxing acid and is typically run for 1 h in an educational laboratory setting. It is common for the Fischer esterification experiment to synthesize fragrant esters to increase student interest and impact. Some examples of fragrant esters synthesized by the Fischer esterification in an educational context include methyl salicylate (wintergreen), isoamyl acetate (banana), octyl acetate (orange), hexyl acetate (pear), and isobutyl propionate (tropical/fruity) (Figure 1).[1] Some limitations of these experiments include high boiling point alcohols that can be challenging to remove without column chromatography or a distillation and that several examples that do not go to completion in a single lab period. Additionally, long alkyl chain fragrant esters, like octyl acetate, have ^{1}H NMR spectra that can be challenging for second-year undergraduate students to interpret. Combinatorial and qualitative laboratories focusing on fragrant ester synthesis can address some of these issues and are highly effective for solving unknown compounds and characterizing different fragrance profiles by scent.[1] These laboratories that focus on odor identification typically do not isolate the ester from the crude mixture, which can limit their efficacy in second-year organic chemistry laboratories where learning objectives usually include the isolation, yield determination, and characterization by NMR and IR spectroscopy and thin-layer chromatography (TLC). We sought a Fischer esterification

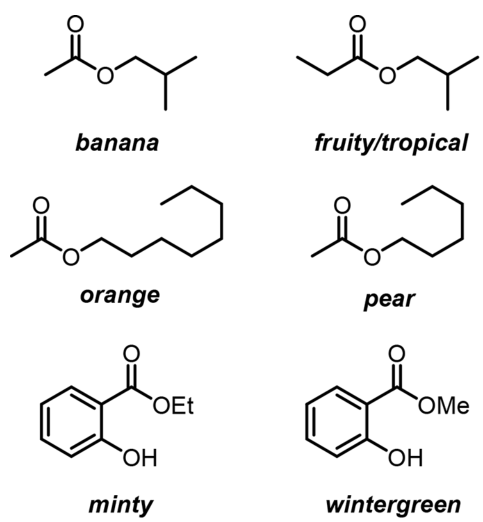


Figure 1. Common fragrant esters synthesized by Fischer esterification.

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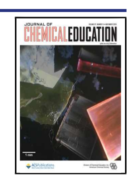


experiment that would provide a high yield of a fragrant ester in high purity during one lab period with no purification necessary aside from an acid−base extraction. The experiment would also need to produce TLC and ^{1}H NMR results that allow for second-year students to confidently interpret the results. We also hoped to incorporate the concept of transmutation of scent where one pleasant-smelling compound could be synthesized from another and microwave-assisted synthesis to integrate concepts that are not well covered in traditional undergraduate organic chemistry curricula.

Cinnamate esters are known for their pleasant fragrance and are derived from commercially available *trans*-cinnamic acid. *trans*-Cinnamic acid is a natural product found in cinnamon and honey that is classified as a generally recognized as safe (GRAS) flavor and fragrance with a mild butter/honey odor, thus making it an appealing starting material for educational laboratories.[2] A recent report synthesized several of these esters as an unknown identification experiment in the second-year organic laboratory.[3] Methyl cinnamate is a natural product and a commercial fragrance possessing a potent strawberry scent. This compound has been synthesized previously in an educational context via a Horner−Wadsworth−Emmons Wittig reaction under aqueous conditions,[4] and ethyl cinnamate, a similar but less potent fragrance, has been synthesized via Fischer esterification[1f] and under solvent-free Wittig conditions.[5] The synthesis of methyl cinnamate from *trans*-cinnamic acid by Fischer esterification has been reported in the literature under a variety of conditions. The most common method employs refluxing methanol and with excess concentrated sulfuric acid and is typically run for over 12 h.[6] Additionally, a textbook, *Experimental Organic Chemistry*, has reported a student-level procedure for this transformation along with sample IR and NMR spectra for characterization.[7] To our knowledge, no assessment of the reaction's success in an organic chemistry laboratory course has been reported nor has the reaction optimization for the protocol been reported. The goal of this study was to further investigate this Fischer esterification to determine the effectiveness of the experiment in a student laboratory environment with respect to the specified learning outcomes and evaluate students' perceptions of the experiment. Student data was collected over three years in sections of the second-semester undergraduate organic chemistry laboratory at Florida Gulf Coast University. We also report the use of *p*-toluenesulfonic acid (pTSA) as a more effective and safer catalyst for the reaction along with conditions for the microwave-assisted synthesis of methyl cinnamate.

■ PEDAGOGICAL GOALS

The experiment introduces the concept of transmutation of scent and the synthesis of commercially relevant chemicals in the context of Fischer esterification. The concept of transmutation of scent provides students with a sensory experience to heighten the impact of the lab. This experiment is an example of green chemistry in that it is high-yielding and provides high atom economy while avoiding the generation of hazardous waste. The experiment provides an alternative to the commonly performed fragrance laboratories, including the synthesis of wintergreen that provides a 25% yield.[8] The learning outcomes were assessed by observation of the practical laboratory skills as well as the content provided in the postlaboratory reports. The specific learning outcomes for the students are the following:

- Understand the concept of catalysis.
- Interpret the ^{1}H NMR of methyl cinnamate.
- Perform an acid−base extraction and identify which components were removed from the organic layer to provide the pure product.
- Monitor the completion of the reaction by TLC.
- Understand green chemistry principles and metrics such as *E* factor.[9]
- Understand the structure−activity relationships between chemicals and fragrance.
- Perform a microwave-assisted synthesis and understand the use of modern instrumentation in chemical industry.

■ OPTIMIZATION OF THE REACTION

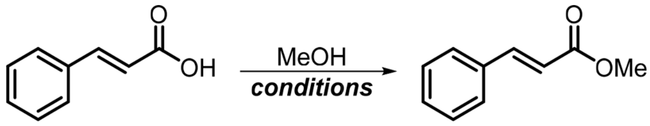
Due to the caustic properties of concentrated sulfuric acid, we desired to limit the amount used through an optimization screen as well as determine if a safer acid could be employed, with the best results summarized in Table 1. The optimization screen demonstrated that excess sulfuric acid was not necessary and that the reaction could be run catalytically with 75 mol % of sulfuric acid to provide a 94% yield in 1 h (entry 1). If the reaction is run for 1.5 h, 50 mol % of sulfuric acid can be used to achieve a 99% yield (see Supporting Information). Further reductions in catalyst loading resulted in a lower yield, as described in the Supporting Information. A series of Lewis and Brønsted acids were also screened to find a suitable surrogate for concentrated sulfuric acid, and pTSA was identified as a capable alternative. The optimized conditions for pTSA provide a 91% yield at a 50 mol % catalyst loading (entry 2). pTSA is an appealing option for educational lab settings since it is a solid that is easier to handle compared to the more corrosive concentrated sulfuric acid solution.

We also sought to incorporate a microwave-assisted organic synthesis option since it provides several advantages over conventional heating conditions. It can significantly reduce reaction times, decrease solvent usage, and increase yields while also using less energy than conventional heating.[10] The use of microwave reactors in the undergraduate lab curriculum also provides students the opportunity to work with modern equipment that is standard in the chemical industry and useful in teaching concepts of green chemistry.[11] Optimization of methyl cinnamate synthesis with both catalysts allowed for a reduction in both the catalyst loading and solvent usage. The reaction vessel was heated at 110 °C for 2 min followed by a cool-down period to less than 55 °C to provide a 97% yield using 50 mol % concentrated sulfuric acid in 0.45 M methanol (entry 3). The alternative pTSA catalyst can also be utilized under microwave conditions, providing a 91% yield in 2 min with 50 mol % pTSA in 0.45 M methanol (entry 4). The reaction was diluted with diethyl ether, neutralized with a saturated sodium bicarbonate solution, and rinsed with brine. The organic layer was then dried with magnesium sulfate, and the solvent was evaporated to provide pure methyl cinnamate. A detailed procedure for the conventional and microwave experiments and the optimization screen for the Fischer esterification are provided in the Supporting Information.

■ OVERVIEW OF THE LABORATORY EXPERIMENT

This experiment is designed for a second-year undergraduate organic chemistry laboratory course but is amenable for use in general chemistry and high school laboratories. The synthesis of methyl cinnamate can be completed in a single 2−3 h

Table 1. Optimized Conditions for the Synthesis of Methyl Cinnamate from *trans*-Cinnamic Acid under Conventional and Microwave Heating



Entry	Heating	Catalyst	Mol %	*M*	Temp. (°C)	Time (min)	Yield (%)
1	Conventional	H_2SO_4	75	0.2	Reflux	60	94
2	Conventional	pTSA	50	0.2	Reflux	60	91
3	Microwave	H_2SO_4	50	0.45	110 °C	2	97
4	Microwave	pTSA	50	0.45	110 °C	2	91

laboratory period by students working individually or in groups. Students are required to complete a prelaboratory assignment in their notebook and complete an online quiz to ensure that they understand the safety considerations and the general topics covered in the experiment. After the experiment, each student submits a laboratory report further analyzing their results and the concepts covered in the experiment.

EXPERIMENT

The experiment consists of a reaction setup, an acid–base extraction, a TLC analysis to monitor the completion of the reaction, and structural determination by NMR. If a microwave reactor is available, the conventional heating and microwave-assisted protocols can be run simultaneously and compared. After an overview of the experiment and procedure by the instructor, the students added *trans*-cinnamic acid and methanol to a round-bottom flask. A catalytic amount of either concentrated sulfuric acid or pTSA is added to the solution. The addition of sulfuric acid is ideally performed in a fume hood via a glass dropper. The reaction is then refluxed for 1 h. If a microwave reactor is available, the microwave-assisted synthesis is run at 110 °C for 2 min. Both procedures are run with no precautions to remove air or moisture from the reaction. After the reaction cools to room temperature, the completion of the reaction can be observed via TLC (20% ethyl acetate/hexanes; UV or $KMnO_4$ stain). The reaction typically provides a spot-to-spot conversion, where the methyl cinnamate has a R_f value of 0.74 and the cinnamic acid starting material has a R_f value of 0.10. The reaction is neutralized with saturated sodium bicarbonate solution, and the product is extracted with diethyl ether. The organic layer was washed with brine and dried with magnesium sulfate, and the solvent was evaporated to provide methyl cinnamate. The acid–base extraction also serves to remove any residual cinnamic acid from the organic layer so that no further purification is required. The fragrant white solid was then characterized by ^{1}H NMR.

HAZARDS

Safety goggles, closed-toed shoes, and long pants covering the ankles should be worn at all times during the experiment. Sulfuric acid is corrosive, toxic, and must be handled with care. pTSA can cause skin irritation. *trans*-Cinnamic acid can cause irritation to the skin, eyes, and respiratory tract. *trans*-Cinnamic acid and methyl cinnamate are listed as GRAS (Generally Recognized as Safe) for use in foods and fragrances. Ether is a highly flammable organic solvent and should be kept away from an ignition source. Ethyl acetate, hexanes, and methanol are flammable organic solvents and can cause skin, eye, and respiratory irritation. Potassium permanganate is corrosive and a strong oxidant that reacts violently with combustible or reducing materials. Students should wear gloves when handling sulfuric acid and the $KMnO_4$ stain. Deuterated chloroform is toxic and a suspected carcinogen. To smell cinnamic acid or methyl cinnamate, it is important to use the proper wafting technique to not harm the mucous membranes in the nose.

RESULTS AND DISCUSSION

The experiment was performed by six classes of a second-year organic chemistry laboratory course over 6 academic terms. Each class consisted of roughly 23 students per section, with a total of 138 students working in groups of two. Students had previously been introduced to separatory funnel extractions and how to set up a reflux condenser in prior experiments in this course while the Fischer esterification was already introduced in the lecture. All groups were able to successfully complete the experiment and obtain methyl cinnamate in high purities. The only noticeable impurity was residual diethyl ether from inadequate evaporation. The average yield for the experiment was 68% with a range of 34–98%. The most common issues were inadequate heating of the reaction mixture and the addition of the incorrect amount of sulfuric acid from the glass dropper. When the experiment was performed by an undergraduate research student in a research lab setting, the yield was consistently >90%. Prior to the experiment, the students were required to read a prelaboratory write-up, complete a prelaboratory quiz, and create a bulleted laboratory procedure to ensure that they understood the relevant concepts and safety precautions. After the laboratory period, a lab report was assigned to reflect on the concepts covered in the experiment. The completion of the reaction was analyzed by TLC, and the purity of the product was analyzed by ^{1}H NMR spectroscopy. Spectroscopic data acquisition was performed by the instructor but could be performed by the students if desired.

The ^{1}H NMR spectrum of methyl cinnamate (Figure 2) provides an interesting and appropriate level spectrum for second-year organic chemistry students. The diagnostic peak for the reaction is the readily identifiable methyl ester peak at 3.80 ppm. Due to the conjugation of the *trans*-alkene with the electron-withdrawing ester group, H_c of the *trans* alkene is deshielded at 7.70 ppm, leading to a 1.24 ppm separation from H_b at 6.44 ppm. The *trans* geometry of the alkene provides an opportunity to discuss *J* values for vicinal couplings ($^3J_{HH}$) in alkenes. The *J* value for H_b and H_c is 16 Hz, which is common for *trans*-alkenes, while *cis*-alkene vicinal coupling constants are smaller, typically around 5–10 Hz. Since vicinal coupling

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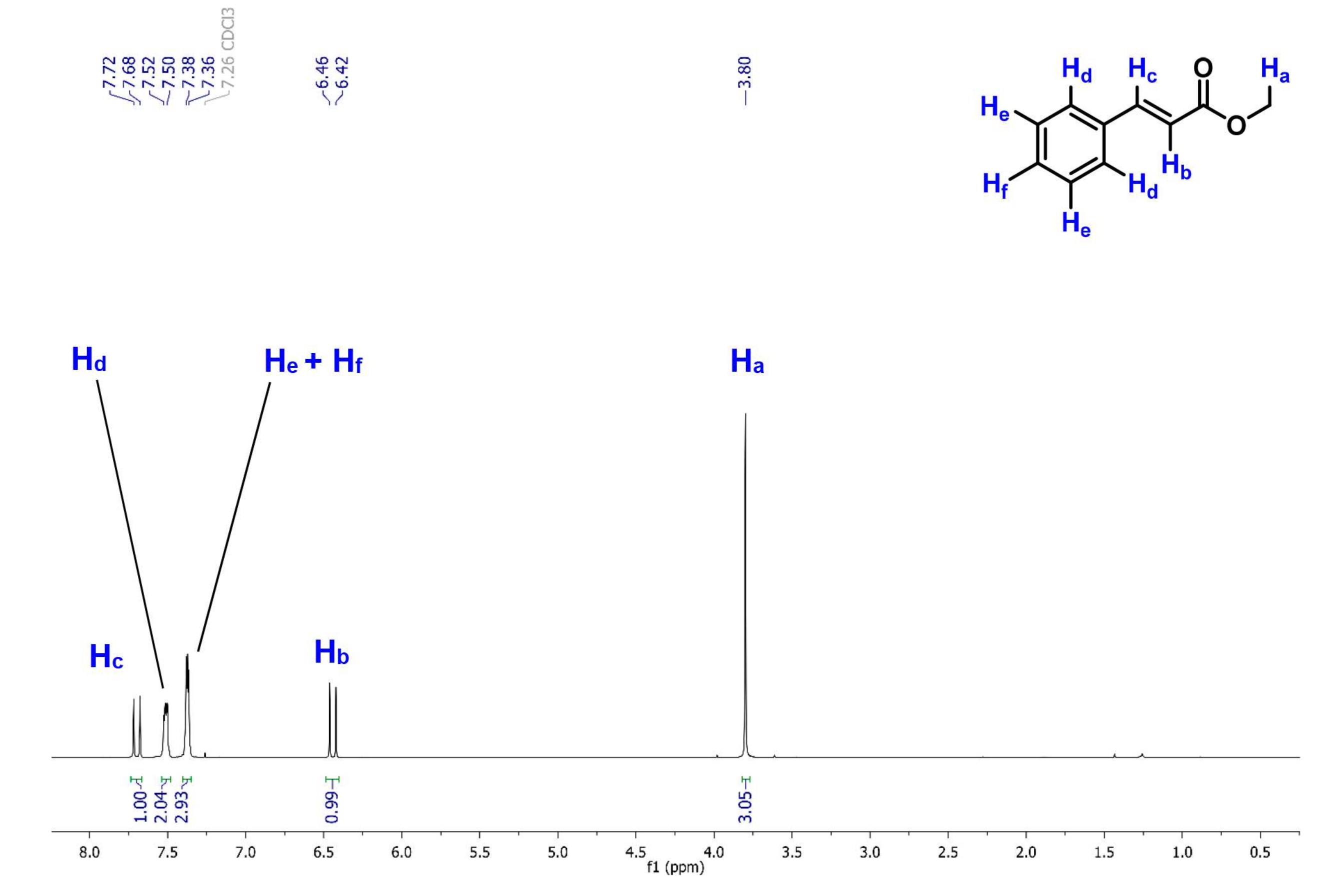

Figure 2. Student-obtained ^{1}H NMR spectrum of methyl cinnamate at 400 MHz in $CDCl_3$.

constants are very reliable for determining stereochemistry, it would also be possible to have the students solve for the geometry of the alkene using this *J* value if desired. The *ortho* protons (H_d) of the phenyl group at 7.52−7.50 ppm are also deshielded due to the conjugation with the electron-withdrawing system, leading to a clear distinction from the meta and para protons (H_e and H_f) at 7.38−7.36 ppm.

The pedagogical goals were assessed in the lab reports by determining the percent yield, interpreting the ^{1}H NMR, explaining the purpose of the base in the liquid−liquid extraction, explaining the purpose of the catalyst, and providing the mechanism for the Fischer esterification. A quantitative assessment of the 130 postlaboratory reports provided the following statistics:

- 93% of students correctly calculated the percent yield for their experiment.
- 91% of students correctly interpreted the ^{1}H NMR spectrum.
- 86% of students provided the correct mechanism for the reaction.
- 59% of students commented on the distinct strawberry smell of methyl cinnamate when discussing the physical characteristics of the product.

These data collectively demonstrate that significant learning occurred in the experiment. It also demonstrates that the ^{1}H NMR spectrum was an appropriate level for students in the Organic Chemistry II laboratory course. While only 59% of students mentioned the distinct strawberry scent, this was not requested in the instructions for the postlaboratory report, which highlights the impact the fragrance had on the majority of the students' sensory experience of the lab.

An indirect assessment of the effectiveness of the experiment from the student's perspective was examined by a voluntary, anonymous Likert-scale student survey, with the results presented in Figure 3. Of the 107 students that answered the survey,[12] a large majority of the students (96%) believed that the lab was effective at improving their knowledge of the course content from the lecture. In this context, course content means the Fischer esterification reaction and spectroscopy. To assess whether the transformation of *trans*-cinnamic acid to methyl cinnamate was an effective experiment, the students were asked if they believed this experiment had real-world applications. A significant majority (89%) stated that the synthesis of the commercial fragrance had real-world applications. A student wrote in the free-response portion of the survey that this experiment "allowed me to [relate] organic chemistry to real life examples." As to whether the experiment was an effective example of green chemistry, 97% of students answered favorably. Finally, 93% of students agreed that the completion of the reaction can be determined by scent and by the ^{1}H NMR spectrum. In the free-response portion of the survey, several students mentioned that they appreciated the pleasant smell of the final product. Student feedback included comments such as "this is a fun lab that you could actually enjoy by the scent that was created. I always enjoy labs with synthesis that you can identify the product by a certain characteristic" and "smelled strawberry fruity. Almost like a fruit roll-up."

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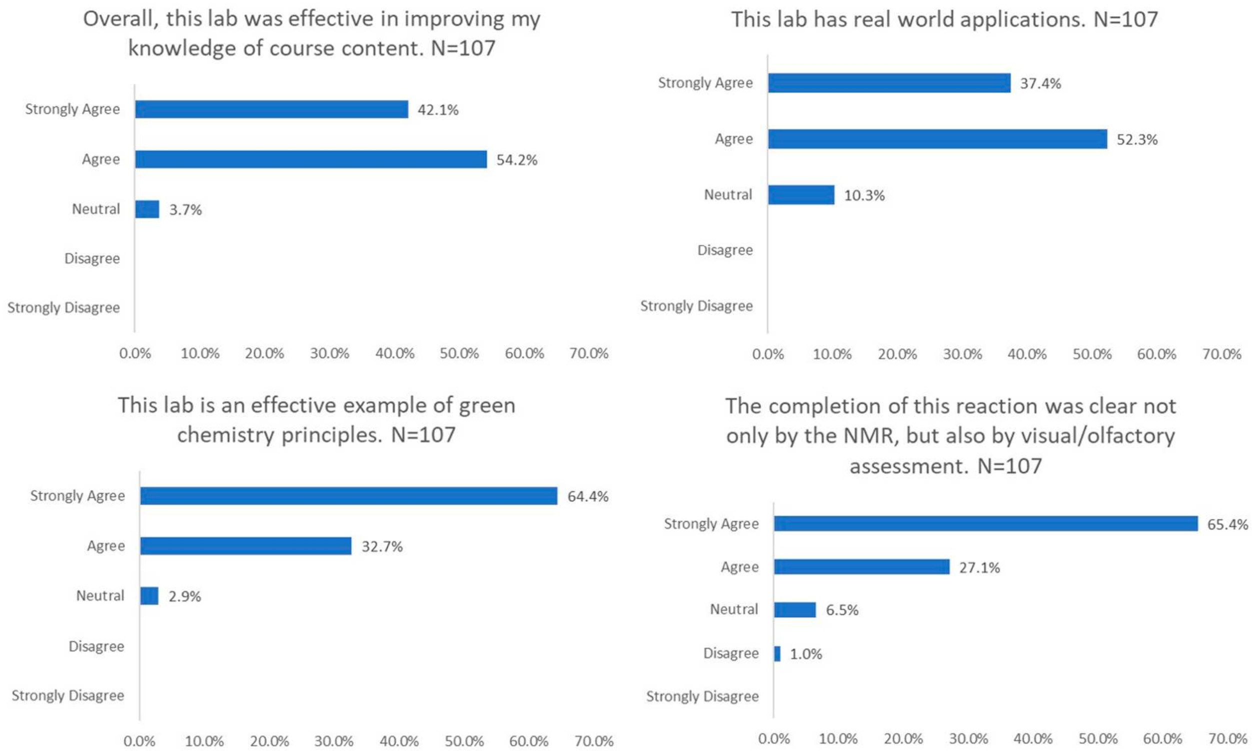

Figure 3. Likert data for the students' perception of the experiment on their knowledge of the course content and interest.

A sampling of additional students' free-response comments is provided in the Supporting Information.

DISCUSSION TOPICS

The described undergraduate laboratory experience provides an opportunity to cover several important topics in modern organic chemistry through the traditional Fischer esterification module. The experiment provides an opportunity to discuss semiochemicals and the use of fragrant organic compounds in signaling.[13] The transmutation of the scent aspect provides an opportunity to highlight the complex and sometimes unpredictable relationship between structure and odor.[14] Since both the starting material and the products are used in flavors and fragrance, a discussion of how organic chemistry is utilized in the flavors and fragrance industry also serves as an excellent discussion topic. Particularly, the synthesis of fragrances and the structural features that affect scent and GRAS ingredients can be discussed. The use of TLC provides the opportunity to review TLC analysis and how the polarity of compounds affect their R_f values. This is also a good opportunity to explain how TLC is used to monitor reaction completion by the disappearance of the starting material and emergence of the product spot since the reaction provides such a clean conversion. Particularly, if the experiment is run at a general chemistry or high school level, the use of NMR can lead to a broader discussion on the use of NMR spectroscopy in society. A discussion of the relationship between NMR and magnetic resonance imaging (MRI) and the Nobel Prize awarded for the use of MRI in medicine would be appropriate.[15] Finally, this experiment adheres to several of the principles of green chemistry that can be discussed.[16] The reaction provides a high atom economy while being promoted by catalytic amounts of either sulfuric acid or pTSA, which minimizes the production of toxic waste. If a microwave reactor is employed, the protocol's energy efficiency can be discussed, as microwaves transfer energy more efficiently to the reacting molecules than conventional heating, leading to fast reaction times.[11] If the pTSA variant is used, the use of safer chemical alternatives can be discussed.

CONCLUSION

The described experiment introduces the concepts of flavors and fragrance, the transmutation of scent, green chemistry, and catalysis in the context of Fischer esterification for the second-year organic chemistry laboratory curriculum. The experiment exposes students to the concepts and techniques of acid−base extraction, ^{1}H NMR spectroscopy, microwave-assisted synthesis, and thin layer chromatography (TLC) through a real-world synthesis example of a commercial flavor and fragrance. The option to use a microwave reactor to accelerate the reaction rate and minimize solvent and catalyst usage or to employ pTSA as an easier to handle solid catalyst are additional benefits of this experimental protocol. Due to the sensory experience of the lab, the relatively nontoxic setup, and inexpensive starting materials, this experiment may also be amendable for high school and introductory general chemistry courses.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.0c00861.

Experimental procedures, characterization data, optimization conditions, instructor notes, selected student comments, chemical and equipment lists, and additional references (PDF, DOCX)

■ AUTHOR INFORMATION

Corresponding Author

Gregory R. Boyce − *Department of Chemistry and Physics, Florida Gulf Coast University, Fort Myers, Florida 33965, United States*; orcid.org/0000-0002-5295-3378; Phone: 239-590-1471; Email: gboyce@fgcu.edu; Fax: 239-590-7200

Authors

Jacob H. Steele − *Department of Chemistry and Physics, Florida Gulf Coast University, Fort Myers, Florida 33965, United States*

Marie X. Bozor − *Department of Chemistry and Physics, Florida Gulf Coast University, Fort Myers, Florida 33965, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jchemed.0c00861

Notes

The authors declare no competing financial interest.

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