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Microwave-Assisted Esterifications: An Unknowns Experiment Designed for an Undergraduate Organic Chemistry Laboratory

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Abstract The utilization of microwaves in synthetic chemistry provides a mechanism for the efficient heating of reactions, offering benefits such as rapid reaction rates and increased yields. Here, we present an undergraduate organic chemistry lab that utilizes microwave technology to perform esterification with alcohol unknowns. This experiment would normally require over an hour for reflux and apparatus assembly; however, with microwave technology we are able to develop a generic methodology to accomplish the esterification reaction in five minutes, demonstrating the efficiency of the microwave and allowing more time for product analysis and characterization. Moreover, the integration of an unknowns aspect to the laboratory implements the problem-solving laboratory approach and confers the ability to solidify principles of NMR spectroscopy as well as product purification techniques.

Keywords: *undergraduate laboratory experiment, hands-on learning, microwave irradiation, esterification*

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1. Introduction

In the past 30 years microwaves have found widespread use in organic chemistry [1]. Microwave irradiation directly interacts with both the solvent and reactants, providing a mechanism for the efficient heating of reactions [2]. Overall, microwave reactors offer key advantages, such as the ability to significantly reduce reaction times and increase product yields [2]. While the traditional Fisher esterification is a hallmark of organic chemistry laboratories, translating this reaction to a microwave setting perfectly illustrates these advantages and exposes students to modern techniques in synthetic organic chemistry. Through utilization of microwave technology, the standard one-hour (or longer) reaction time can be reduced to five minutes and affords product in comparable yields. Previous reports of microwave-assisted esterification laboratories have been presented [3]; however, this experiment is novel in the development of a general procedure that facilities high yielding reactions and the incorporation of an unknowns aspect to the experiment to further develop organic laboratory skills. Furthermore, introducing an unknowns aspect into undergraduate laboratory experiments is useful in order to avoid a "cookbook approach" to lab exercises. This approach to learning can be defined as Problem Solving Learning (PSL) and is used to foster critical problem solving skills, creativity, and complex thinking in students [4,5].

Esters are compounds derived from the reaction of an acid and an alcohol. The Fisher esterification is a staple of many undergraduate organic laboratory courses due to its synthetic utility and its relevance to course materials. Moreover, it is a reaction that typically does not require extremely hazardous chemicals and long reaction times [6]. Certain organic esters display a characteristic fragrance that is easily recognized and found in many artificial fruit flavorings [7]. The sensory component of the laboratory is an additional feature that engages students and confers a purpose to the laboratory beyond simply performing a reaction. In this experiment, a direct esterification reaction will be performed in the microwave reactor. Due to the use of microwave technology, there is no reaction apparatus setup and breakdown that comes with the standard esterification reaction, and the undergraduate student is able to focus on purification and unknown product analysis.

1.1. Learning Objectives

1. To increase knowledge and afford hands-on experience with an esterification reaction.
2. To provide exposure to modern synthetic techniques, specifically microwave reactors.
3. To afford a practical application of proton NMR, and solidify concepts associated with the technique through the identification of unknown spectra.

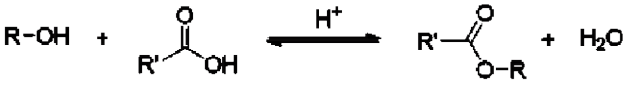
4. To provide a mechanism for the students to develop critical thinking and problem solving skills through the use of a PSL approach.

Each student is introduced to the mechanism of the esterification provided in the manual to provide a hands-on understanding of the reaction. This experiment allows the undergraduate researcher the opportunity to become familiar with modern technologies employed in organic synthesis by utilization of a microwave reactor. Due to the prevalence of these reactors in various laboratories, this experience provides a valuable exposure of the undergraduates to alternative mechanisms of heating and the concepts related to microwave technologies. Instead of remaining idle during at typical thermal esterification reaction to reach completion (often 1 h), the reaction time is significantly reduced to five minutes, allowing for time efficiency and the ability to re-emphasize important laboratory techniques such as acid-base extractions and ^{1}H NMR characterization. Furthermore, this experiment confers the undergraduate with a lesson in product purity through the interpretation of NMR spectra. While a similar experiment has previously been reported [3], the introduction of an unknowns aspect coupled with the use of a CEM Discover microwave reactor and a generalized procedure for all alcohols have been found to increase the efficacy of the laboratory. Most notably, the identification of an unknown product has been found to increase the engagement of the students and enhance learning outcomes.

2. Materials and Methods

2.1. Experimental Overview

The synthesis of esters may be carried out by numerous methods. When using acid and an alcohol, the reaction is referred to as a direct esterification (Scheme 1). These reactions are also known as ester condensations due to the fact that water is always a byproduct of the reaction.



Scheme 1.

In this experiment an ester will be synthesized using a direct esterification reaction, utilizing an unknown alcohol, acetic acid, and a catalytic amount of sulfuric acid. These reactions are generally in equilibrium, leading to yields of only 50-70%, and often take several hours. By performing this reaction in the microwave and using excess acetic acid, the reactions are driven to completion- increasing the yield, and the drastically reducing the rate of the reaction. Moreover, the minimal scale utilized in the microwave represents a higher cost-efficiency and affords minimal waste relative to standard reflux experiments described in the literature.

This experiment will incorporate several key laboratory skills for the undergraduate researcher including microwave synthesis, acid-base extraction, filtration, and NMR characterization. Another interesting variation on the lab would include the simultaneous synthesis of the unknown both under thermal and microwave conditions to truly illustrate the advantages of the microwave.

2.2. Student Procedure

2.2.1. Laboratory Setup

A microwave esterification protocol was adapted from a previously reported CEM microwave experiment, but translated to a more general protocol for the use of various alcohols under identical conditions [8]. Laboratory set-up includes the preparation of the unknown alcohols: octanol, propanol, isoamyl alcohol, and benzyl alcohol. These should be labeled with a specific unknown number and placed in the laboratory for student use. Each alcohol yields a corresponding ester, with a distinct fruity smell (Figure 1).

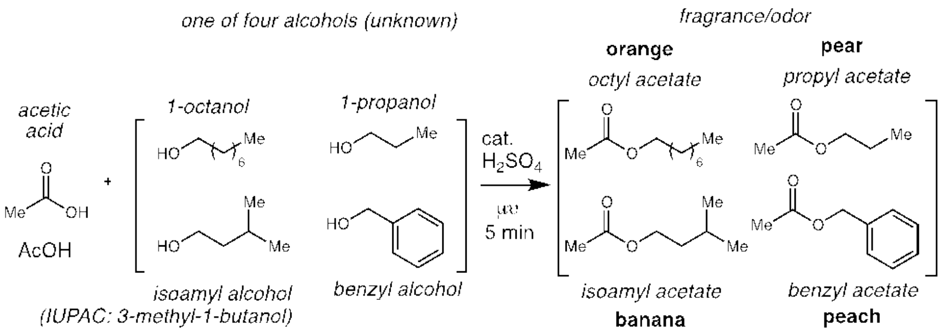


Figure 1. Protocol for the microwave esterification including the alcohols used as unknowns and the corresponding synthesized esters. Each produced ester displays a distinct fruity smell; isoamyl acetate-banana, propyl acetate-pear, benzyl acetate-peach, and octyl acetate-orange

2.2.2. Synthetic Protocol

Students work in pairs and should require a two-hour time period for this lab. At the beginning of lab, each pair should select an unknown alcohol and measure 0.75 mL of their unknown into a dry 10 mL microwave vial using either a transfer or automated pipette. Acetic acid (1 mL) is then added, followed by five drops of sulfuric acid. Increased yields were found when 5-10 silica beads were added to the vial to adsorb water created during the direct esterification reaction. The removal of water facilitates pre- and post-lab discussions involving Le Chatelier's principles and driving forces within reactions. Due to the single-sample nature of the CEM Discover, once the reaction is assembled, students sign up for the use of the microwave. While they are waiting, students begin the analysis of the NMRs provided to identify which spectrum corresponds to which unknown. When ready, the students place the vial in a CEM Discover microwave reactor, and irradiate the reaction in temperature mode to a temperature of 130˚C for 5:00 minutes. Pre-set conditions can be pre-programmed into the microwave reactor, or for a greater hands-on experience, students can program the settings themselves.

Upon reaction completion, the students perform an extraction using a solution of 10% sodium bicarbonate and diethyl ether. The sodium bicarbonate should be added first (10 mL) to a 125 mL separatory funnel, and the reaction mixture added in portions. The reaction should be effervescent, as the excess acid is quenched by the sodium bicarbonate. Diethyl ether should then be added (15 mL), shaken, and once the layers have separated, the organic layer should be collected. To the organic layer, the students should add an additional 5 mL of sodium bicarbonate, separate, and again collect the organic layer. This step should be repeated once more. Once completed, the organic layer is dried with anhydrous $MgSO_4$ and filtered by gravity into a dry, pre-weighed, round-bottom flask (there should be no use of flame in the same room as the diethyl ether due to its extreme flammability). Using a rotary evaporator, the students then remove the solvent *in vacuo*, and again weigh the flask to determine weight and yield of their unknown ester. The actual procedure is provided in the Supplementary Information.

2.2.3. Identification of Unknown

The four potential ester products each exhibit a distinct 'fruity' smell. Using a glass rod, the students transfer a drop of their unknown ester to a paper towel and gently waft the scent so as to identify the fruit smell. . However, students should truly identify their unknown product through utilizing ^{1}H NMR characterizations either taken by the student or provided in the manual (Figure 2). Actual NMR spectra can further the learning experience by facilitating discussion on residual solvent peaks, and potential starting material contamination of the spectrum. To increase the proton NMR analysis, integrations are not provided, instead challenging students to identify products based on the number of unique protons and their splitting patterns.

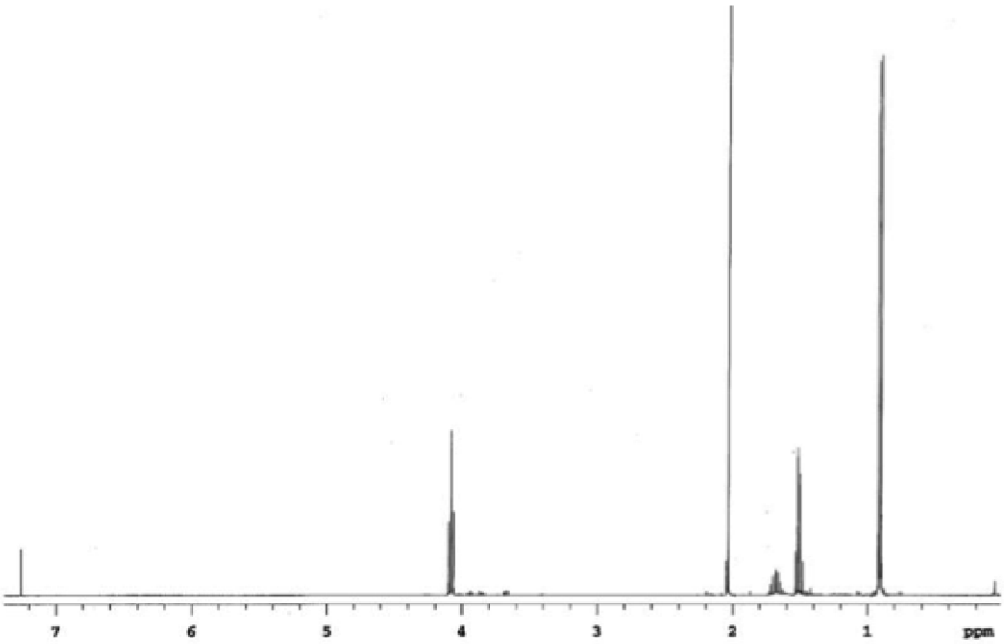


Figure 2. Sample ^{1}H NMR obtained by the laboratory students. Pictured is Unknown Product 4, or isoamyl acetate. The ^{1}H NMR is either obtained by the student or provided in the manual. Determining product structure from the ^{1}H NMR allows the student to accurately identify what alcohol was reacted with the acetic acid

Students should evaluate the ^{1}H NMR spectra to determine the unknown starting material, and use both the ^{1}H NMR characterization and the scent of their product to determine the ester product they have prepared. They can then determine the molecular weight and percent yield of their product for the lab report. Due to the ability of the microwave to drastically decrease reaction time, the students have more laboratory time devoted to ^{1}H NMR characterization and discussion of fundamental laboratory purification principles.

2.2.4. Hazards

Goggles should be worn at all times for this lab. As diethyl ether is extremely flammable, open flames should not be used during the laboratory period; thus, glassware should be dried beforehand. Acetic acid can cause slight skin irritations, and sulfuric acid can be extremely harmful if in contact with eyes. Reaction set-up and the extraction should be performed in a well-ventilated hood, with the separatory funnel always facing away from the student. A teaching assistant or supervisor should check student's rotovap set-up to assure there is no cracked glassware and the vacuum system is properly closed.

3. Results and Discussion

This experiment has been employed as second semester undergraduate organic chemistry lab for 3 years. Each year has approximately 16 sections each containing 22 students, and the students work in pairs. The microwave has proven to be useful in the formation of the desired unknown ester, drastically reducing the standard esterification reaction rate and producing similar or higher yields than those typically formed with the one-hour reaction time. By using an unknown alcohol and producing an unknown ester, this experiment focuses on product analysis and problem solving on behalf of the student researcher. Overall, students appreciate the opportunity to work with modern technology and enjoy being able to identify an organic compound based on a familiar smell. The ^{1}H NMR analysis allows the student to refresh their interpretation abilities from the previous semester, and become familiar with solvent or impurities common in actual NMR spectra. This experiment effectively prepares them for further research in a faculty research lab or future analysis in industry through solidification of purification techniques and proton NMR analysis. Moreover, the use of an unknown alcohol provides a mechanism to more actively engage the student as they must utilize chemical and sensory tools to determine what was made during the lab, and translate the product back into its reactants.

4. Conclusions

A direct esterification reaction was translated to a CEM Discover microwave reactor, reducing the standard one-hour reaction time to five minutes and affording a similar yield. This exposes the students to new methods of organic synthesis and incorporates modern technologies into traditional laboratories. By reducing the reaction time, the undergraduate student can devote more time to the identification of the unknown ester. Furthermore, valuable lessons are learned on purity of compounds in relation to product NMRs. Finally, the product identification aspect of the laboratory challenges students to employ critical thinking skills, and aids to solidify a strong foundation of the reaction mechanism and proton NMR analysis.

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