Synthetic efforts towards the development of a microwave synthesis of isobutyl propionate ester.

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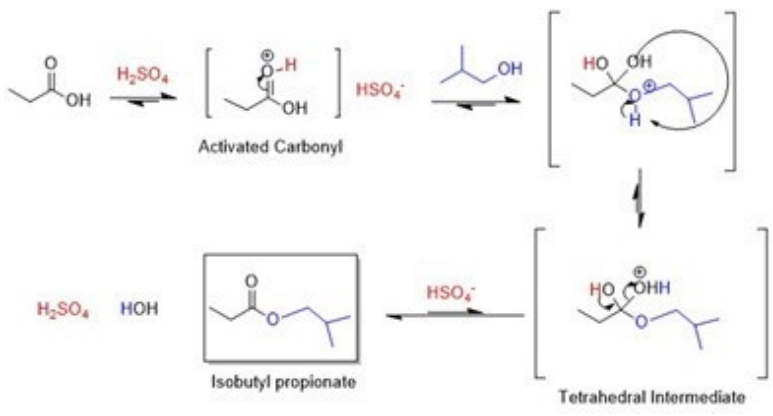
ABSTRACT

Environmental risks are physical, biological, and chemical factors that harm ecosystems and human health. In order to reduce environmental risks, there first must be a coordinated effort to collect the best available scientific information. Thus, conducting research is important for the development of environmentally friendly pathways to synthesize products that are used in our everyday lives. This study investigates the use of a greener methodology in the synthesis of small organic molecules that have industrial applications. Isobutyl propionate, an ester compound that is widely used in food and beverage industries as a rum flavor, was the primary focus of this study. One of the directions demonstrated in literature is a solvent-free approach, for example the use of an enzyme catalysts or dried Dowex H^+/NaI ion exchange resin results in high yields of simple esters. Removal of solvent minimizes the hazardous waste production for each kg of product. In our research plan we focused on testing applicability of utilizing microwave energy to synthesize isobutyl propionate. Microwave synthesis allows for a more efficient heat transfer and as a result minimizes energy waste per kg of product obtained. Here in we report our findings on synthesis, isolation, and analysis of purity of the target ester. All reactions were performed using a single mode Biotage® Initiator+ synthesizer under varied temperature and time reaction conditions. Infrared spectroscopy (IR) and nuclear magnetic resonance spectroscopy (NMR) were used to analyze product formation and the composition of reaction mixtures. While collected data demonstrate applicability of microwave energy to obtain the desired ester compound, further investigation will have to be undertaken to optimize the method.

INTRODUCTION

Our research project rises from an idea we can accomplish an environmentally friendly and commercially viable synthesis of esters by using a solvent-free microwave synthetic pathway. Esters, due to their olfactory qualities, are used in industry as food additives and flavorings for a myriad of products such as, ethyl acetate as nail polish remover and glue while also naturally occurring in wine or methyl salicylate in root beer and Raglex™ oientments.[1,2] These esters are synthetically derived from a Fischer condensation of an alcohol and an organic carboxylic acid with an acid catalyst activating the acidic carbonyl. A typical reaction and the curved-arrow mechanism are summarized and illustrated in Scheme 1. Color coding indicates the contribution of different reagents to the final product structure. The reaction received then name of Fischer esterification to honor the scientist, Hermann Emil Fischer, who discovered its mechanism.



Scheme 1. Illustration of a general ester synthesis and the underlying mechanism. The reaction can produce a variety of esters using variable combinations of acid and alcohols. Different variations of starting materials, e.g., acid anhydrides or acid chlorides also could be used. Prior to the product formation the key tetrahedral intermediate participates in equilibrium, therefore, presence of acid catalyst is essential for the reaction to occur. This reaction can be carried out at a room temperature over a prolonged time but most commonly is conducted under reflux.

The reaction is typically done with one or both reactants in a liquid phase and an extremely concentrated strong acid allowing for no excess water to be present in the system during the reaction. This shifts the equilibrium further towards the desired products and is only limited by the stoichiometric production of water as a byproduct of the reaction. In addition, a prolonged heating is required to ensure the maximum product is obtained. Though attractive commercially from the cost perspective and product yields, this methodology creates significant amounts of organic waste and results in a substantial heat loss during the reflux portion of the experiment. Careful maintenance of the reflux temperature throughout the entirety of the synthesis also provides an additional complication, especially when large quantities need to be synthesized. We hypothesized that use of microwave energy would improve heat transfer during the reaction. During microwave heating the energy of magnetron is transferred directly to the reacting molecules (Figure 1).

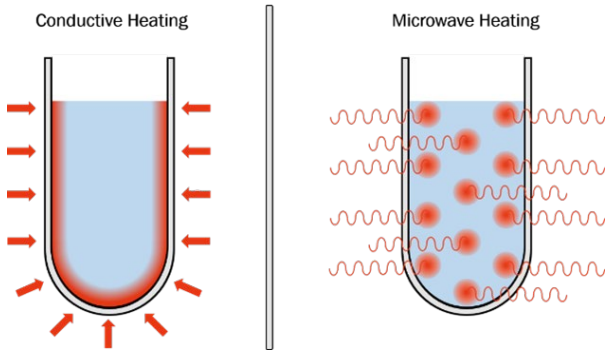


Figure 1. Conventional heating compared to microwave heating. The image was adopted from CEM corporation (accessed on May 28, 2021 at http://cem.com).[3] In a conventional heating (illustrated on the left) the heat is transferred from the walls of a vial towards the middle of the reaction mixture. As a result, the reaction medium experiences the highest temperature on walls, but the temperature quickly drops as molecules travel. Mixing can increase homogeneity of heating to some extent; however, the limitation of effective heat transfer remains. During microwave heating (on the right) the energy is delivered directly to reacting molecules decreasing energy waste.

In this project we investigated two objectives: 1) minimization of solvent use during synthesis and purification; and 2) application of microwave energy towards ester synthesis. Our target compound in this study was isobutyl propionate. Previously the use of a solid phase enzyme catalyst and a gaseous phase reaction substrate has been investigated and shown to be a successful method, achieving 92% yields at experimentally found ideal conditions.[4] Most notable of these conditions is that 11 g of enzyme were used at a remarkably low 50 ºC. This method, though extremely effective, would be difficult to implement given that the reaction vessel was constructed by the research team rather than being a commercially available item. Thus, the expense incurred by the development of an industry scale reaction vessel would be impractical.

Another development of green synthesis was reported by P.A. Turhanen et al. when utilizing dried Dowex H^+/NaI ion exchange resin as a media to conduct synthesis of simple esters at mild temperatures. In this solvent-free methods esters were isolated with yields between 70-82% and high purity.[5] Though successful in synthesis and isolation of esters, the general availability of the equipment used and/or reagents needed present a significant barrier to application of this technology for an industrial green ester synthesis. Previously *King et al.*[6] reported use of MARS batch reactor towards microwave synthesis, however to the best of our knowledge there have been no reports on using Biotage® Initator+ towards that goal. Here in we report our findings on applicability of using the single mode microwave reactor towards the solvent-free microwave synthesis of simple esters as a straightforward and environmentally sustainable synthetic pathway.

MATERIALS AND METHODS

Standard samples of reactant grade isobutanol, propionic acid, and concentrated sulfuric acid were provided by instructor and used without further purification. The ester, isobutyl propionate, was synthesized using an acid catalyzed Fischer esterification in a Biotage Initiator+ microwave synthesizer. Microwave Biotage 2–5 mL single-use vials were supplied by instructor's research laboratory. Common glassware, common and deuterated solvents were provided in teaching laboratory space. Nuclear magnetic resonance (NMR) data were collected NMR spectrometer at University of Wisconsin - La Crosse located in Prairie Springs Science Center and analyzed using Bunker Topspin 4.1.1. software. Infrared (IR) data were collected for neat samples using FT-IR spectrometers with ATR utility attachment available in teaching laboratory space and analyzed using Omnic software.

PROCEDURE

General Synthesis. Reactions were carried out using a standard 2–5 mL Biotage microwave reaction vial in an excess of isobutanol, 0.02 mol, and a half molar equivalent of organic acid, 0.01 mol, with 20 drops of acid catalyst

being added along with a stir bar before being crimped shut and transferred to the reactor. The conversion of energy transfer from a conventional prolonged reflux reaction to microwave heating using built-in Biotage Wizard software. The reaction times were varied from two to ten minutes while the temperature was maintained at 219 °C.

General Isolation. Upon cooling, the reaction vials were opened, and the ester layer was removed, and the remaining excess alcohol and water being discarded in liquid waste container. Sodium sulfate was used to dry remaining water from the ester layer. The crude mixtures were analyzed for product conversion without further purification.

RESULTS AND DISCUSSION

All data are given below regarding the optimization of experimental procedure using the target compound of isobutyl propionate. A comparison of reagent quantities and product yields is provided in Table 1. One of the goals of this project was to attempt estimation of the ideal amount of time in the microwave reactor that would produce the cleanest product of isobutyl propionate using propionic acid, isobutyl alcohol and sulfuric acid catalyst. We tested three different reaction times: two, five, and ten minutes. Overall, we were able to produce the target compound in moderate yield with minimum purification required. Although the difference between isolated yield is small our data indicate that carrying our reaction at five and ten minutes is conducive towards product formation. In some of the cases the separation of layers was complicated (entries 3 and 6) and prevented us from estimating an accurate isolated product yield. Further investigation will be required to understand the reasoning behind this experimental observation and to overcome this limitation.

Table 1. Mass of starting materials, molar ratio, and yield of each experiment.

Entry	*Time, min*	*Mass of acid, g*	*Mass of alcohol, g*	*Molar ratio (acid:alcohol)*	*Yield, %*
1	2	0.747	1.528	1:2	69.7
2	2	0.748	1.480	1:2	72.8
3	5	0.750	1.480	1:2	62.3*
4	5	0.763	1.457	1:2	76.6
5	10	0.757	1.480	1:2	70.6
6	10	0.748	1.532	1:2	84.1*

*Non-isolated product yield is listed. The percent yield is calculated based on the estimation using ^{1}H NMR integral ratios of OCH_2 signal of the ester product to that one of starting alcohol and total mass of crude mixture.

Infrared (IR) spectroscopy, a characterization method used to determine the presence of functional groups in a chemical sample, was used for experiments 1, 2, 4 and 5. This technique uses infrared radiation to excite the molecules of a compound and generate a spectrum based on the energy absorbed. Different types of bonds absorb different frequencies of radiation and thus the identity of functional groups in a compound can be determined. This method was useful in assessing whether or not the target compound, isobutyl propionate, could be present in each experiment. Although IR spectroscopy is not a deterministic method to confirm the presence of a compound, it does provide functional group data that can be matched with the functional groups present in the target compound. In this study, the presence of a carbonyl signal at 1700 cm^{-1} in the IR spectra provided evidence that isobutyl propionate may have been formed in each experiment. Figure 2 below shows the IR spectrum for experiment 1, which was similar to the IR spectra for experiments 2, 4, and 5 in that they all showed a carbonyl signal.

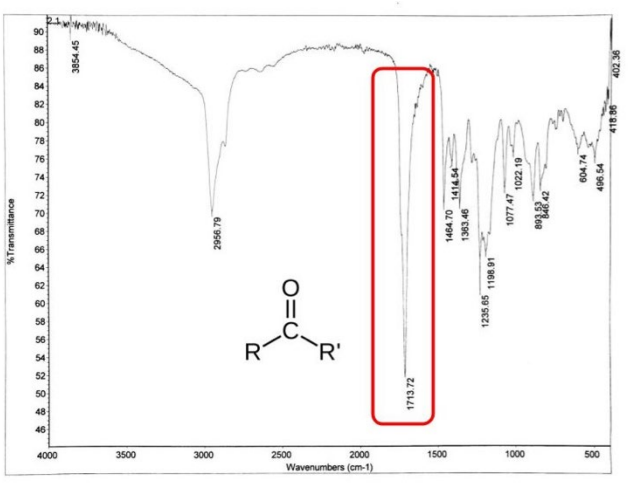
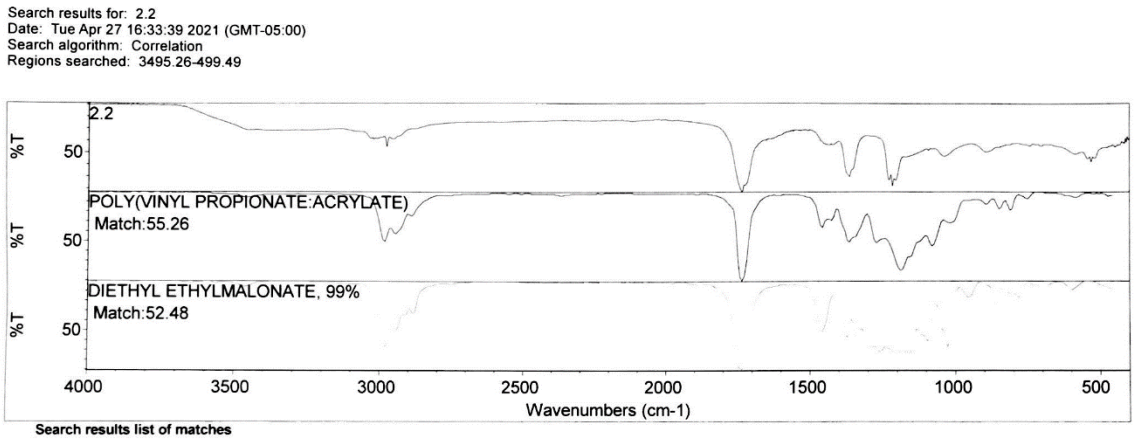


Figure 2. Infrared (IR) spectrum from experiment 1 showing the presence of a carbonyl functional

group (C=O) in the product. The illustration of the molecular representation of carbonyl group using a ketone is shown to the side.

In addition to IR spectroscopy, a database search was done to determine what compound(s) most closely matched with the compound(s) formed in each experiment. The database search showed a 50-60% match to 3-nonanone (for experiment 1) or polyvinyl propionate (for experiments 2, 4, and 5). Although the database search does not confirm the presence of isobutyl propionate, it does provide evidence that the product of each experiment contained a carbonyl functional group and was likely an ester compound. Figure 3 below shows the database search for experiment 2, which shows a 55% match to polyvinyl propionate, a carbonyl-containing ester. This database search shows similar results as that of the other experiments.



Search results list of matches

	Index	Match	Compound Name	Library Name
1	15	55.26	POLY(VINYL PROPIONATE:ACRYLATE)	Hummel Polymer Sample Library
2	15	52.48	DIETHYL ETHYLMALONATE, 99%	Aldrich Condensed Phase Sample Library
3	20	52.33	URETHANE ALKYD, LINSEED OIL-RICH	Hummel Polymer Sample Library
4	54	51.75	2-Butanone; Methyl ethyl ketone	HR Specta IR Demo
5	3	50.99	(Dimethylamino)acetone; 1-Dimethylamino-2-propanone	HR Specta IR Demo
6	1	50.92	ACETOCHLORO-A-D-GLUCOSAMINE	Sigma Biological Sample Library
7	56	50.73	2-Pentanone	HR Specta IR Demo
8	16	49.19	POLY(VINYL PROPIONATE/ACETATE)	Hummel Polymer Sample Library
9	729	48.68	Synthetic polyurethane rubber	HR Nicolet Sampler Library
10	49	48.65	POLY(VINYL CHLORIDE:MMA)	Hummel Polymer Sample Library

Figure 3. Infrared (IR) spectroscopy database search from experiment 2 showing a match to an ester compound. All libraries available on the instrument were selected to ensure a comprehensive search. Although, the sample preparation for the database samples is different than the one applied in our project it is not sufficient to alter the probability of the search to the appreciable extend.

Nuclear Magnetic Resonance (NMR) spectroscopy, a characterization method used to determine the content, purity, and molecular structure of chemical compounds, was used for experiments 1, 2, 4, and 5. This spectroscopic technique observes local magnetic fields surrounding atomic nuclei and detects NMR signals with sensitive radio receivers. This method was useful in assessing whether or not the target compound, isobutyl propionate, was produced in each experiment. Although it was possible to acquire ^{1}H and ^{13}C NMR spectra due to a substantial difference in acquisition time (2 and 40 minutes respectively) only ^{1}H NMR data were collected. All of the samples were prepared using a standard technique to ensure a valid comparison of signal-to-noise ratio. The ^{1}H NMR spectra for each experiment showed that isobutyl propionate was produced in each reaction in moderate yields. However, each experiment also included a mix of starting materials and impurities, including aromatic compounds. For the purpose of assessing the original goal of whether or not the target compound was produced, the aromatic region of the NMR spectra was disregarded. There were no probable explanations for the appearance of aromatic peaks other than the use of contaminated glassware, which may have contained leftover chalcone compounds from previous experiments. Despite the presence of impurities in each experiment, isobutyl propionate was detected and therefore

its synthesis was successful. The impurities, as well as evidence for the presence of the target compound, are discussed in further detail below.

Here, impurities are discussed in further detail, specifically regarding experiments 1 and 2 which reacted in the microwave reactor for two minutes. The ^{1}H NMR spectrum for experiment 1 (shown in purple in Figure 4) showed unknown peaks around 5.0 ppm and 7.0 ppm. The ^{1}H NMR spectrum for experiment 2 (shown in red in Figure 4) showed more intense aromatic signals and an unknown quartet at 4.2 ppm. These extra peaks were not present in the ^{1}H NMR spectra of experiments 4 and 5, which reacted in the microwave reactor for five and ten minutes, respectively. This provides evidence that setting the microwave reactor to two minutes was the least efficient method in producing a cleaner product, whereas five and ten minutes resulted in somewhat cleaner ^{1}H NMR spectra.

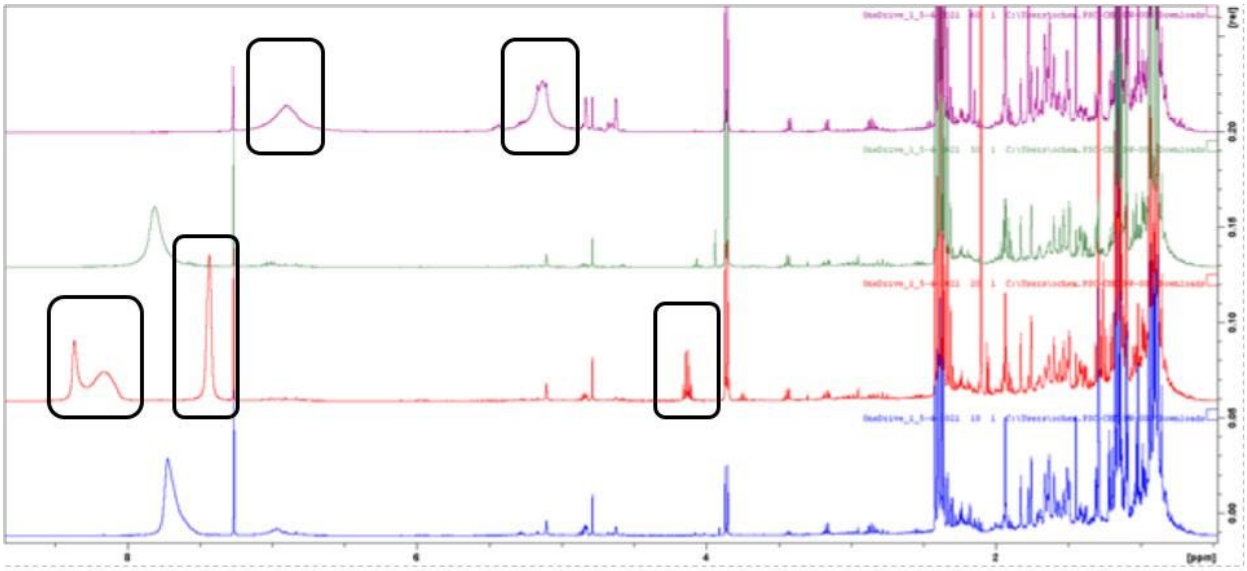


Figure 4. ^{1}H NMR spectra for experiments 1 (purple), 2 (red), 4 (blue), and 5 (green) are provided using stacking option of Topspin software. The enhancement of signals to demonstrate the remaining identified impurity signals is applied. The signals corresponding to impurities in experiments 1 and 2 are selected.

Here, evidence for the formation of the expected product, isobutyl propionate, is discussed in further detail. The splitting pattern for the product is shown on Figure 5. As demonstrated later in Figure 6 below, spectra obtained for experiments 1, 2, 4, and 5 contained a doublet for a CH_2 group at 3.9 ppm, which is split by a neighboring CH group. This is called multiplicity, or coupling, which refers to the appearance of a group of symmetric peaks representing a hydrogen atom. When a hydrogen, or proton, is coupled, the number of neighboring hydrogens is one less than the number of peaks in the multiplet (see Figure 5).

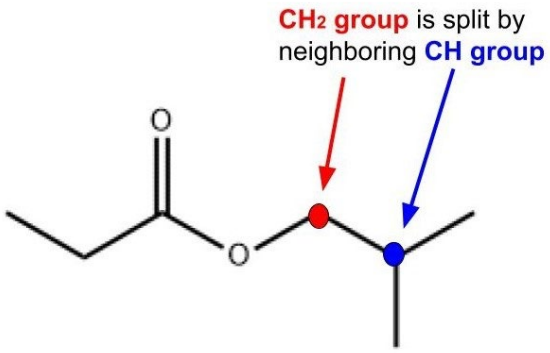


Figure 5. Splitting pattern of CH_2 group in isobutyl propionate.

To facilitate the comparison of spectral data we analyzed them on the same scale using Topspin software stacking capabilities (Figure 6). To maintain a similar concentration between experiments all samples for 1H NMR analysis were prepared using a standard 25 mg mass measurement and dissolution in a consistent volume of deuterated chloroform ($CDCl_3$). No filtration was applied as samples appeared as homogenous liquids.

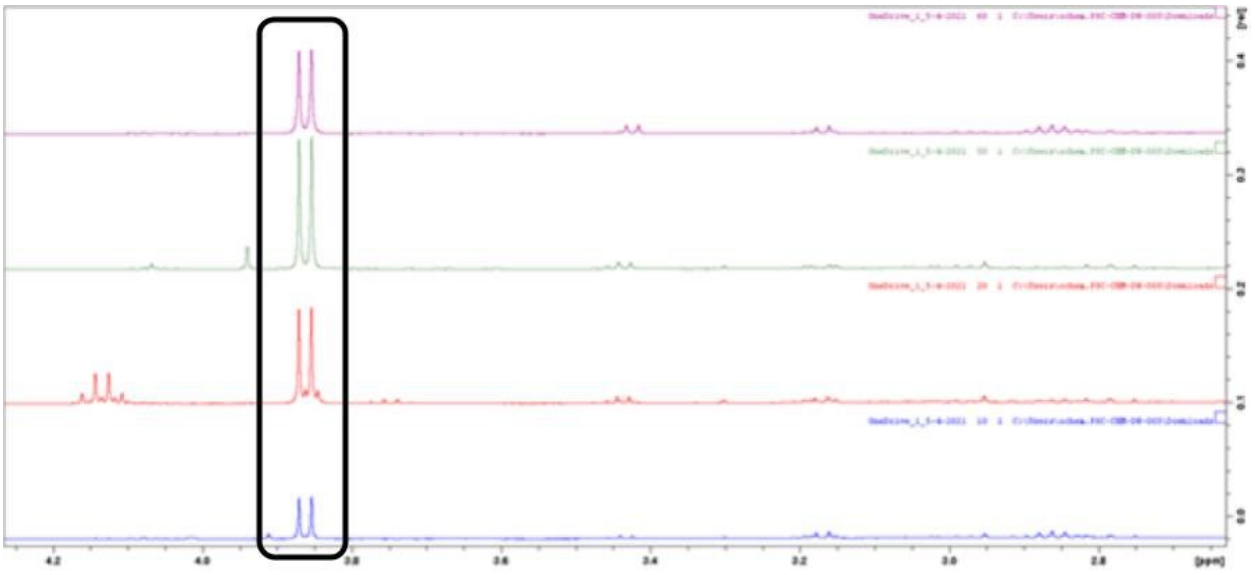


Figure 6. Expanded view of ^{1}H NMR spectra aliphatic region (2.8 to 4.2 ppm). Experiments are stacked to illustrate the product formation and experimental differences, for experiments 1 (purple), 2 (red), 4 (blue), and 5 (green)

This OCH_2 signal is consistent with the expected ^{1}H NMR of isobutyl propionate, shown in Figure 7 below, and provides evidence that the expected product was formed in each experiment. The computational software is fairly accurate in predicting the exact location and splitting of the signals. Although, we could have used a previously reported experimental spectrum of our target compound for consistency of comparison within our project and complexity of ^{1}H NMR data for reaction mixtures the NMR predictor was chosen as a standard.

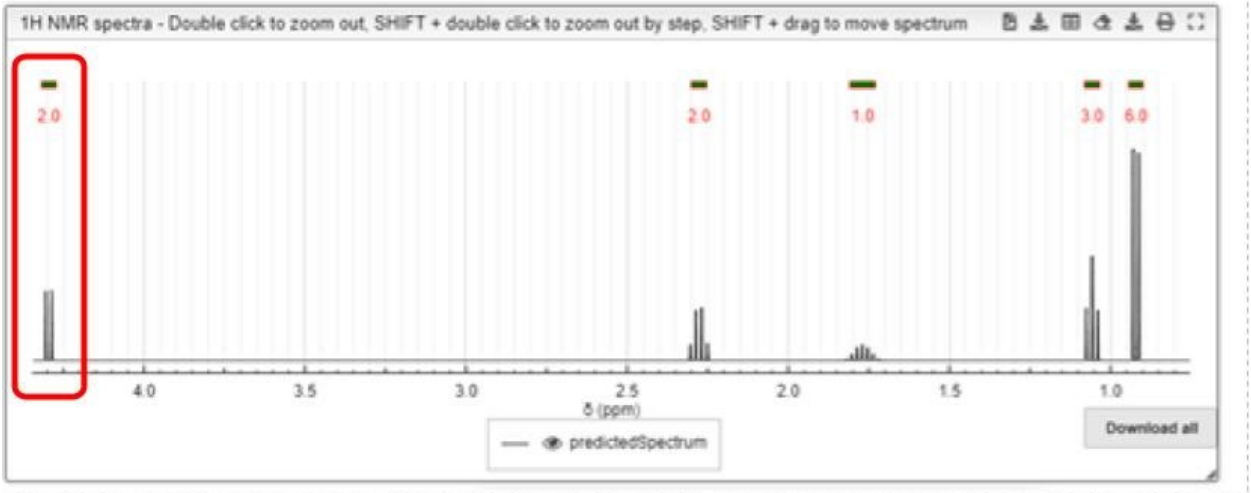


Figure 7. Predicted ^{1}H NMR spectrum for the expected product, with OCH_2 peak highlighted in red.

Other important peaks shown in the observed NMR spectra (see Figure 8 below) include a quartet at 2.3 ppm for a CH_2 group, which is split by a neighboring methyl group and is next to a carbonyl. This peak overlaps with another quartet from one of the starting materials, propionic acid. Also, there is a triplet at 1.1 ppm for a CH_3 group, which is split by the neighboring CH_2 group. Furthermore, there is a doublet at 0.8 ppm for the two identical methyl groups located on the isobutyl group of isobutyl propionate, which is split by the neighboring CH group. The last expected peak, a nonet at 2.3 ppm, is less obvious in the NMR spectra of each experiment because it is smaller and is overlapping with impurity peaks. Overall, the observed peaks are consistent with those shown in the expected NMR spectrum of isobutyl propionate (shown in Figure 7 above). Therefore, there is sufficient data to determine that the expected product, isobutyl propionate, is present in each experiment.

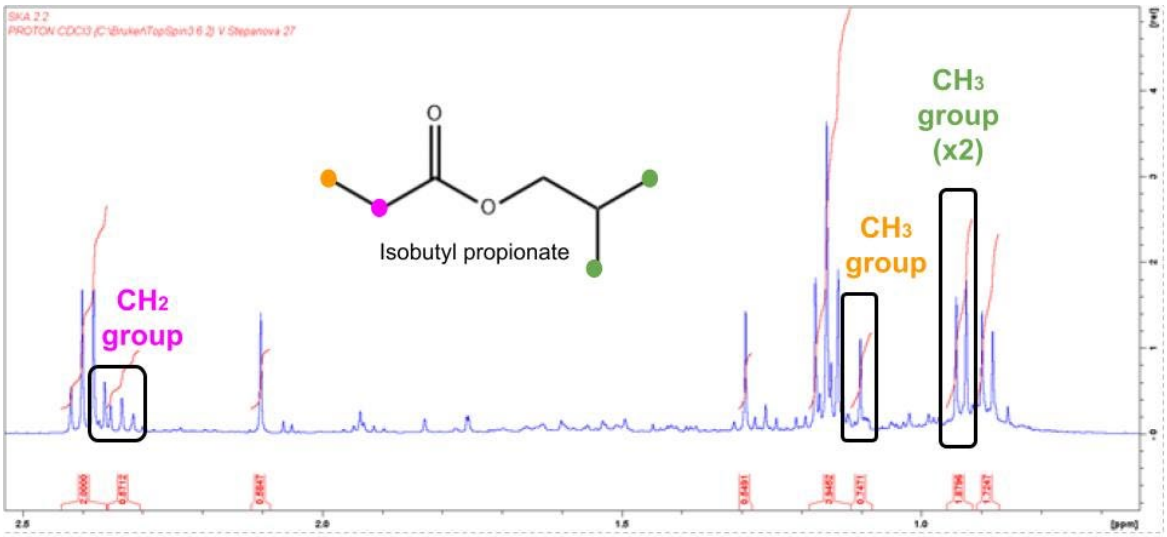


Figure 8. [1]H NMR spectrum of the aliphatic region for experiment 2, product peaks are circled. The color coding is used to match the desired target product structure and the observed chemical signals in the spectrum.

Next, impurities are discussed in further detail. The NMR spectra revealed the presence of both starting materials, propionic acid, and isobutyl alcohol, in differing quantities in the final product. This resulted in overlapping signals between the impurities and the expected ester product. Another impurity was acetone, which appeared as a singlet at 2.1 ppm, shown in Figure 9 below.

The NMR peaks for the starting material propionic acid, which was shown to be in excess in the final product, is shown in Figure 9 below. There is a quartet for a CH_2 group at 2.4 ppm, which is split by the neighboring CH_3 group in propionic acid. There is also a triplet for a CH_3 group at 1.1 ppm, which is split by the neighboring CH_2 group. These peaks are similar to those shown in Figure 10 of the predicted NMR for propionic acid and provides evidence that an excess of propionic acid was used in each experiment.

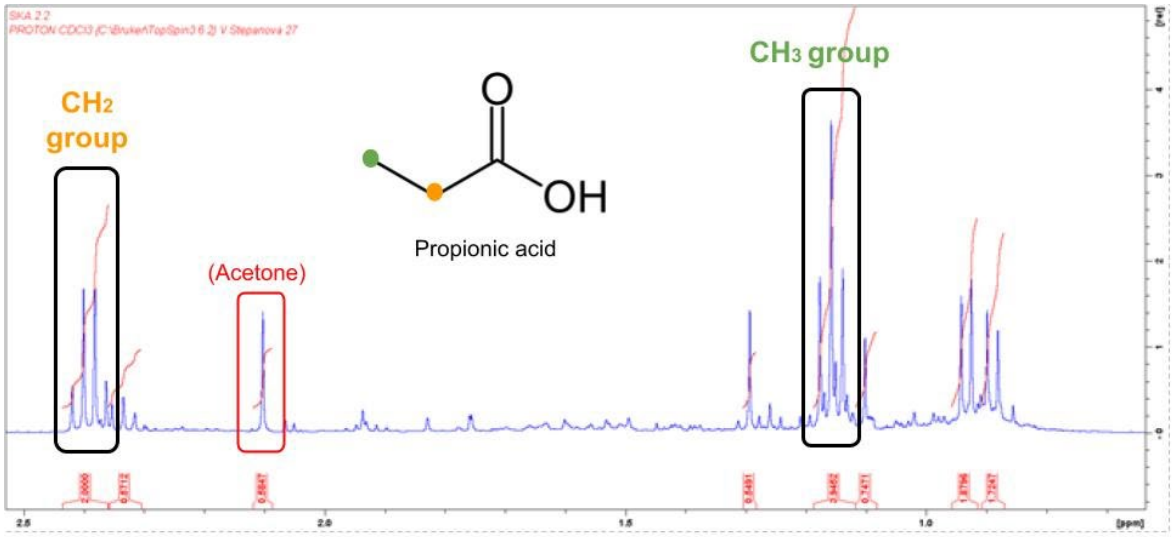


Figure 9. [1]H NMR spectrum of the aliphatic region for experiment 2, product peaks are circled.

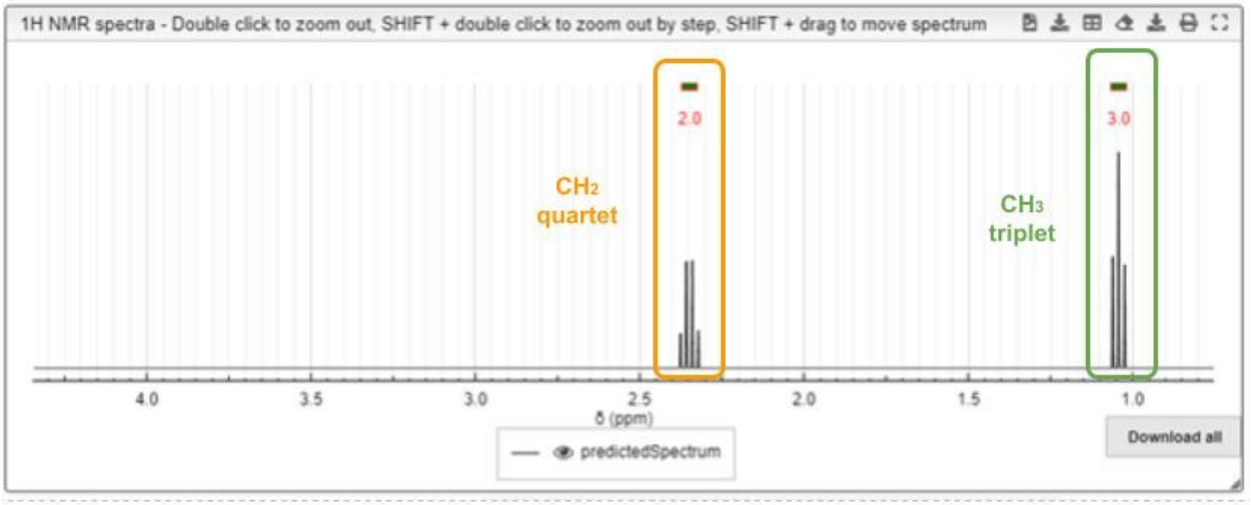


Figure 10. Predicted NMR spectrum of propionic acid. Due to the limitations, the predictor omits acidic hydrogens.

The identification of ^{1}H NMR peaks for the starting material isobutyl alcohol, which was shown to be present in small quantities in the final product, is shown in Figure 11 below. The unique signal appears as a small doublet at 3.4 ppm for a CH_2 group, which is split by the neighboring CH group in isobutyl alcohol. This peak was assigned an integration value of 0.14 relatively to the integration of product peaks at their expected values (e.g. OCH_2 at 2.0). Figure 12 below shows another doublet at 0.8 ppm for the two identical methyl groups on isobutyl alcohol. A substantial expansion was required to discover and identify the impurity of the starting alcohol. Overall, the placement of these two peaks is consistent with the predicted peaks of isobutyl alcohol with small changes potentially due to the concentration difference and presence of residual water in the sample. The integration values do not appear to match, which is most likely due to overlapping of various peaks from several different compounds. This observation is important to illustrate the simplicity of our approach. Although the reaction was conducted in an excess of alcohol the production of stochiometric quantities of water during the synthesis of target ester allows for a straightforward removal of remaining alcohol. Miscibility of isobutyl alcohol with formed water is sufficient enough that a simple decanting of top ester layer results only in a relatively small impurity of this starting material in the collected spectrum.

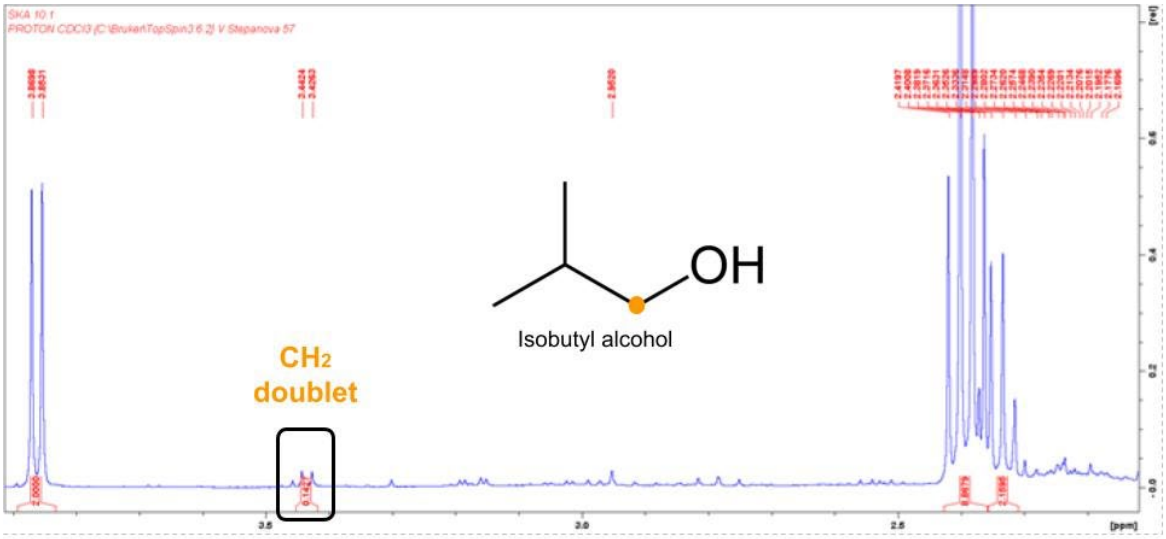


Figure 11. Expanded NMR spectrum of the aliphatic region, from 1.5 to 4.0 ppm, from experiment 5, which showed similar peaks to the spectra from experiments 1, 2, and 4. The circled region shows the observed peak for the starting material isobutyl alcohol.

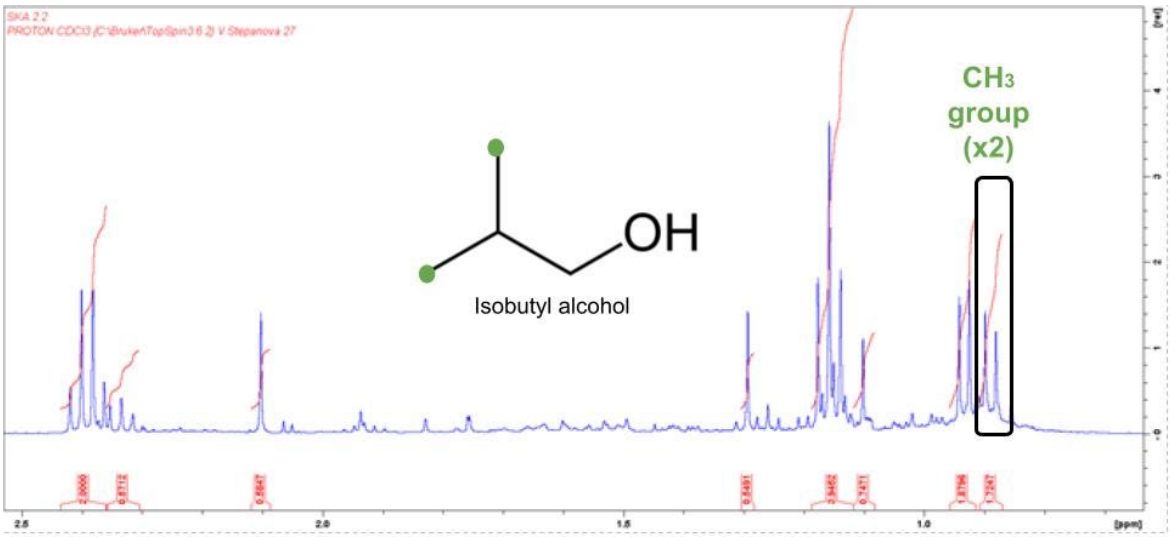


Figure 12. Expanded NMR spectrum of the aliphatic region, from 0 to 2.5 ppm, from experiment 2, which showed similar peaks to the spectra from experiments 1, 4, and 5. The circled region shows the observed peak for the starting material isobutyl alcohol.

Based on the integration data, the molar ratio of each compound in the final product was calculated to be 1 (isobutyl propionate) to 0.07 (isobutyl alcohol) to 4 (propionic acid). Therefore, each experiment resulted in about 19.7% isobutyl propionate, 1.4% alcohol and 78.9% acid. Overall, the expected product was produced in moderate yields in each experiment, and the experiments that ran for five or ten minutes resulted in less impurities than the experiments that ran at two minutes.

CONCLUSION

The study was successful in that the expected product, isobutyl propionate, was produced under solvent-free, microwave assisted conditions. Longer reaction time generally resulted in higher yield and simplified isolation of mixtures. The separation and purification of the product presented substantial limitation for isolation of a pure product in high yields. Further investigation will be needed to identify the most effective combination of microwave synthetic parameters and purification procedure.

ACKNOWLEDGMENT

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