**Article**

# Kinetic monitoring and Fourier-Transform Infrared (FTIR) spectroscopy of the green oxidation of (-)-menthol to (-)-menthone

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## SUMMARY

**Green chemistry involves reducing the production of hazardous substances in chemical processes to be more sustainable, thereby decreasing pollution and other environmental damage. Solvent is a major contributor of waste in organic synthesis, so the greenness of a chemical reaction can be improved by changing the solvent. The oxidation of (-)-menthol to (-)-menthone in different solvent systems was monitored using Fourier-transform infrared (FTIR) spectroscopy. Our study conducted this reaction in solvent systems of acetic acid and other solvents as replacements for acetonitrile: acetone, ethyl acetate, and dichloromethane. Solvent choice was determined based on the principles of green chemistry, and kinetics and yield of the reactions in different solvents were investigated. Through FTIR spectroscopy, the products of all the reactions were characterized as (-)-menthone. Since a limiting factor in hypochlorite-mediated oxidations of alcohols to carbonyls is the solubility of the hypochlorite salt, we hypothesize that the most polar solvent systems will give the fastest reaction rate and highest yields. Our hypothesis was incorrect, as the reaction time was shortest and product yield was greatest for the oxidation performed in ethyl acetate and acetic acid, which are less polar than acetonitrile. The green oxidation of (-)-menthol to (-)-menthone was optimized in this solvent system.**

## INTRODUCTION

Green chemistry is defined as the design of chemical operations that utilize the most economical usage of reagents by maximizing yields, exploring safer methodology to conduct chemical reactions, and reducing unnecessary byproducts and hazardous waste (1). The concept of green chemistry is important because it reduces pollution on a molecular scale and reduces the harmful effects of hazardous byproducts and reagents on people and the environment by increasing the safety and efficiency of chemical processes. Here, we investigated the oxidation of (-)-menthol to (-)-menthone in a variety of solvent systems, which were selected based on the distribution of cost, availability, and sustainability.

In 2014, reactions involving the oxidation of alcohols were used in 10.4% of medicinal chemistry papers and appeared in 46% of manuscripts regarding the chemical synthesis of natural products (2). It is clear that oxidation of alcohols is an important step in the diversification and synthesis of natural products. Therefore, an efficient and green oxidation would be beneficial in the large-scale synthesis of complex chemical compounds. The initial reaction procedure developed by Nwaukwa and Keehn used a solvent system of acetonitrile and acetic acid (3). The principles of green chemistry were important to further optimize these initial conditions to conduct a greener reaction overall.

(-)-Menthol is a natural product that can be extracted from peppermint (*Mentha piperita*). The compound is a chiral crystalline white solid with a strong peppermint odor. (-)-Menthol is a biologically active compound and also has industrial uses in cosmetics and perfumes because of its minty fragrance (4). (-)-Menthol is a useful test substrate for other reactions in industry given its structural simplicity. (-)-Menthone, another biologically active compound, shares similar characteristics with (-)-menthol, most notably its slight peppermint odor (5).This molecule also has similar uses in the cosmetic and perfume industries. Menthone's natural form is a colorless, viscous liquid, and it can be obtained by oxidation of the secondary alcohol in (-)-menthol to a ketone (**Figure 1**) (6). (-)-Menthone, a reported natural product, is a useful synthetic intermediate, which can be used in a variety of other chemical reactions. It is a versatile chiral building block for the
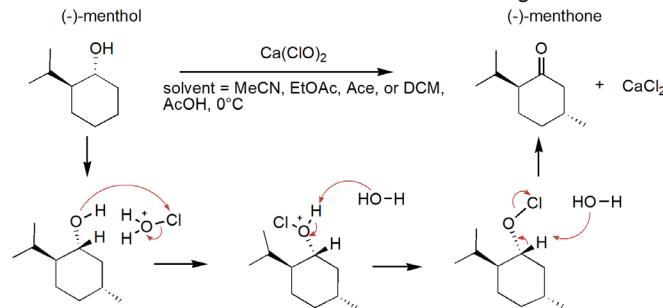


**Figure 1. Reaction mechanism of (-)-menthol to (-)-menthone oxidation tested in four different solvent systems.** The arrow pushing mechanism of the calcium hypochlorite oxidation is depicted.

| Oxidation Reaction | Reagents | Atom Economy | Molecular Weight of discarded reagents | Hazardous byproducts |
|---|---|---|---|---|
| Dess-Martin (7) | Dess-Martin Periodinane | 26.58% | 424.14 g/mol | Iodinane |
| Swern (8) | Oxalyl chloride, DMSO, triethylamine | 33.35% | 306.25 g/mol | Carbon monoxide, dimethyl sulfide |
| Jones (9) | Chromium trioxide, Sulfuric acid | 43.53% | 198.07 g/mol | Chromium (IV) oxide |
| Corey-Kim (10) | N-chlorosuccinimide, Dimethyl sulfide, triethylamine | 34.04% | 296.85 g/mol | dimethyl sulfide |
| Calcium Hypochlorite (3) | Calcium hypochlorite | 51.55% | 142.98 g/mol | None |

**Table 1.** Comparison of atom economy of oxidation reactions with different mild oxidizing agents.



**Figure 2. Chemical structures of reagents and byproducts of common oxidation reactions**. The byproducts of four other common reactions to oxidize secondary alcohols to ketones were compared to a calcium hypochlorite oxidation.

synthesis of other compounds.

There are a number of reactions that can efficiently oxidize secondary alcohols into ketones; we focused on optimizing green conditions for this transformation. Calcium hypochlorite was chosen as a mild oxidizing agent because it is relatively inexpensive, and involves minimal production of hazardous byproducts. Hypochlorite salts can perform oxidations with high atom economy, as it produces only calcium chloride as a byproduct, which can be removed through an extraction rather than via column chromatography, thereby minimizing the use of solvent in the purification process (**Table 1**). Most suffer from the coproduction of other substances during an oxidation reaction, many of which are themselves highly reactive, toxic, or challenging to remove (**Figure 2**).

A limitation in hypochlorite-mediated oxidations of alcohols to carbonyls is the solubility of the hypochlorite salt, so more polar solvent systems for these reactions will result in faster reaction rates and higher yields. The oxidation of (-)-menthol to (-)-menthone was tested in a variety of solvents, chosen based on their polarity and relative greenness. All the reactions produced the desired product, (-)-menthone, confirmed by Fourier-transform infrared (FTIR) spectroscopy. The reaction performed in ethyl acetate, the least polar solvent, completed first with the greatest yield as opposed to the reaction with acetonitrile, so our hypothesis was incorrect.

## RESULTS
### Solvent optimization

The solvents screened for the oxidation reaction included acetonitrile, ethyl acetate, acetone, or dichloromethane, which are of different polarities (**Table 2**). We hypothesized that the most polar solvent systems will result in the fastest reaction rate and highest yield because the solubility of the hypochlorite salt, a limiting factor, will be greater. All reactions were conducted at room temperature and in an ice bath. The starting material, (-)-menthol, was first characterized through Fourier-transform infrared (FTIR) spectroscopy, with a broad

O-H stretch at 3250 cm-1, representing an alcohol, and 3 medium C-H stretches from 2850 to 2950 cm$^{-1}$ (**Figure 3**). Reasonable yields of (-)-menthone were produced from every reaction with an average yield of 75%. During synthesis, reaction progress was tracked by thin-layer chromatography (TLC) because the polarity of the alcohol in (-)-menthol is greater than the polarity of the ketone in (-)-menthone,. The silica gel plate used in TLC shows the less polar spot for the (-)-menthone traveled farther along the plate than the spot for (-)-menthol, verifying the alcohol to ketone transformation. The products were characterized by FTIR spectroscopy, which showed the lack of a broad alcohol stretch at 3250 cm$^{-1}$ and the appearance of a ketone stretch at 1706cm$^{-1}$ in the spectrum of the product (**Figure 4**). The other IR spectra includes all products from (-)-menthol oxidations; all products have 3 matching C-H stretches near or at 2955, 2928, and 2870cm-1 in their spectra and strong C=O peaks at 1706cm$^{-1}$ (**Figure 3**). The 3 C-H and C=O stretches in IR spectra of all products near 3000cm$^{-1}$ and 1700cm$^{-1}$ match the strong C-H stretches at 2953cm$^{-1}$, 2926cm$^{-1}$, and 2869cm$^{-1}$, and the strong C=O stretch at 1706cm$^{-1}$ in the IR spectrum of isolated (-)-menthone, confirming that (-)-menthone was produced (**Figure 5**). The spectra of (-)-menthone from the oxidation conducted in dichloromethane contains the same

| Solvent used with acetic acid | Relative Cost (lowest - highest) | 'Greenness' Score (GSK solvent guide) | Relative Polarity (least - most polar) | Production of (-)-Menthone |
|---|---|---|---|---|
| Acetonitrile (MeCN) | 4 | Some known issues | 0.46 | Yes |
| Ethyl acetate (EtOAc) | 2 | Few known issues | 0.308 | Yes |
| `Acetone (Ace) | 3 | Some known issues | 0.355 | Yes |
| Dichloromethane (DCM) | 1 | Major known issues | 0.309 | Yes (with an impurity) |

**Table 2.** Comparison of each solvent tested in oxidation reaction of (-)-Menthol to (-)-Menthone.
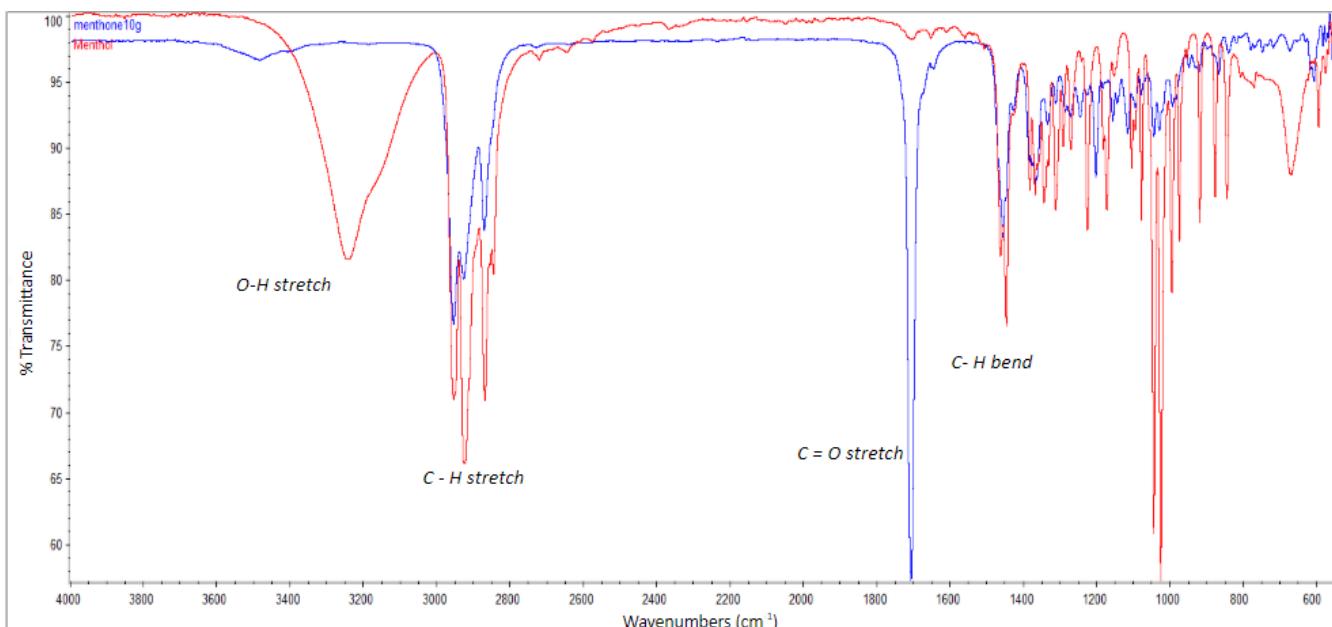
**Figure 3. IR Spectra of (-)-menthol. (-)**-menthol is seen in red with broad O-H stretch at 3250 cm$^{-1}$ and 3 medium C-H stretches from 2850 to 2950 cm$^{-1}$ and (-)-menthone (blue) with strong C=O peak at 1706cm$^{-1}$.
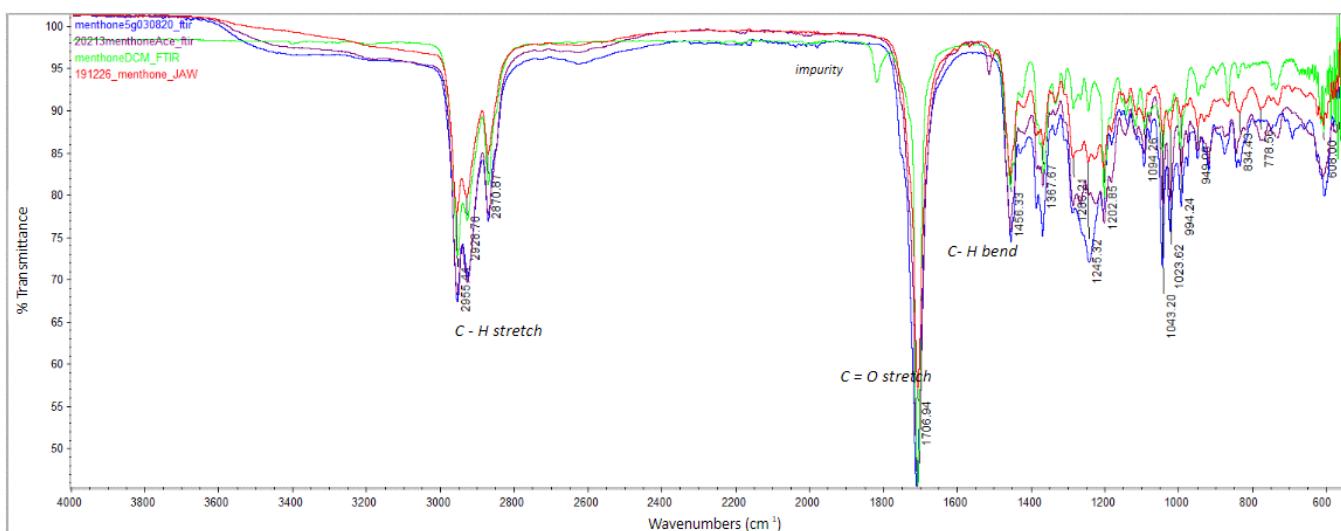


**Figure 4. IR Spectra of product from all (-)-menthol oxidation.** The oxidation product from reaction performed in DCM (green), (-)-menthone from oxidation in acetone (purple), (-)-menthone from oxidation in acetonitrile (red), (-)-menthone from oxidation in ethyl acetate (blue) with C-H stretches near/at 2955, 2928, and 2870cm$^{-1}$ and strong C=O peaks at 1706cm$^{-1}$.

major stretches as the other products, but includes a weak peak at 1800cm$^{-1}$, suggesting an impurity in the product (**Figure 4**). The yields of the reactions are also reported (**Figure 6**). Because there was an impurity in the reaction in dichloromethane (DCM), yield of that reaction was not taken. All four reactions had at least two trials, once at room temperature and once in an ice bath, so each solvent was tested for percent yield twice and the kinetics experiments were done twice total. The solvents acetonitrile and ethyl acetate were tested two more times beyond the initial two trials. Overall, the greatest yield of (-)-menthone was produced in the reaction with ethyl acetate, the least polar

solvent, which does not support our hypothesis.

### Kinetics Study

Two kinetics studies were conducted for this reaction: at room temperature and in an ice bath. The completion of each reaction was monitored using thin-layer chromatography. At room temperature, there was no significant difference in kinetics of the reactions in different solvent systems, with all the reactions completing within minutes of each other, so this data was not recorded. The reactions in an ice bath were performed on a smaller scale than the reactions at room temperature due to a decreasing supply of the starting
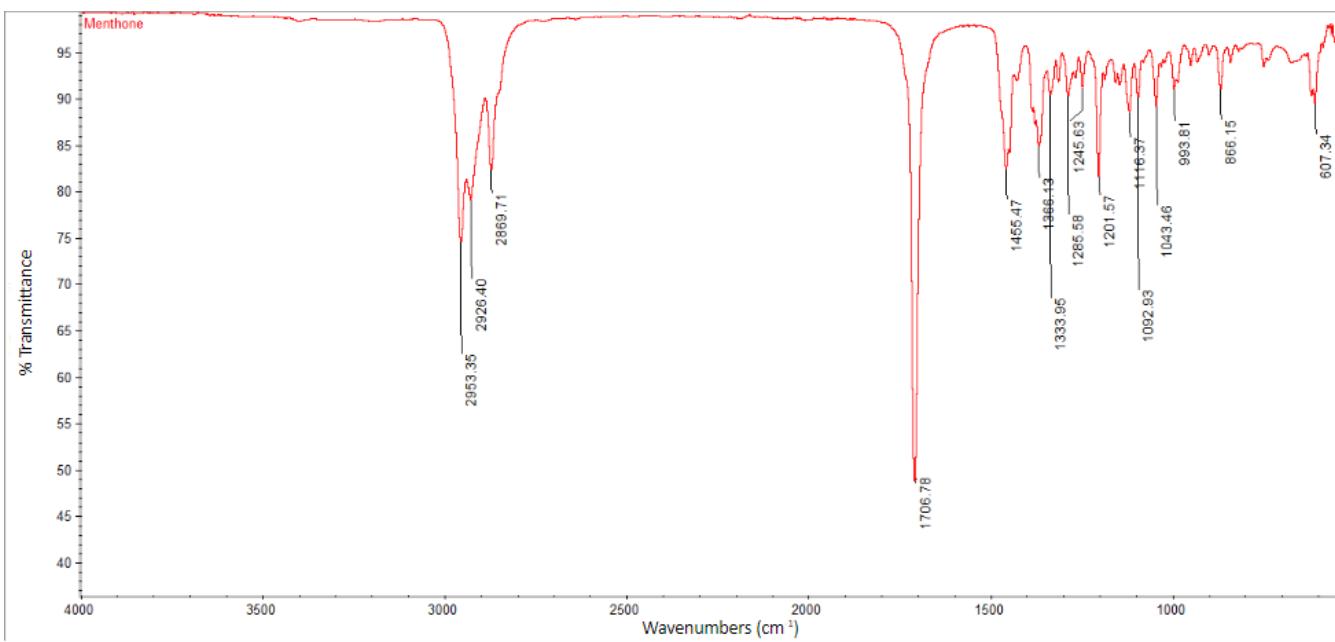
**Figure 5. IR Spectrum of isolated (-)-menthone.** Strong C-H stretches at 2953cm$^{-1}$, 2926cm$^{-1}$, and 2869cm$^{-1}$ and strong C=O stretch at 1706cm$^{-1}$ are observed.

material, so comparisons between the reaction times cannot be made. Of the reactions performed in an ice bath, the oxidation in the solvent system of ethyl acetate and acetic acid completed first in 18 minutes, followed by the reactions in dichloromethane and acetic acid, acetonitrile and acetic acid, and acetone and acetic acid, respectively (**Figure 6**). This also contradicts our initial hypothesis of the reaction completing fastest in the most polar solvent because the reaction completed fastest in ethyl acetate, the least polar of all the solvent systems. Still, from these results, it appears that this reaction works to produce (-)-menthone with a relatively green solvent system and a green oxidant.

## DISCUSSION
### Optimization of solvent scope & kinetics study

The oxidation of (-)-menthol to (-)-menthone converts a secondary alcohol into a ketone (**Figure 1**). The initial solvent system for this reaction reported by Nwaukwa and coworkers is acetonitrile and acetic acid (3). Solvents that were considered in place of acetonitrile included dichloromethane, ethyl acetate, and acetone (**Figure 1**). In a paper by Byrne et al., GlaxoSmithKline's, Pfizer's, and Sanofi's solvent selection guides were compared, providing a comprehensive assessment of certain solvents (12). Green solvents are evaluated based on their environmental, health, and safety (EHS) effects and energy demand. Based on the updated GSK's solvent sustainability guide and the solvent selection guides from Pfizer and Sanofi, ethyl acetate and acetone were considered more green replacements for acetonitrile (13). Furthermore, ethyl acetate and acetone cost less than acetonitrile. Although dichloromethane was not recommended as a green solvent in comparison, it was chosen in our study due to its widespread availability. While changing the solvent system, we also compared the kinetics of the reaction. Each reaction condition was then assessed on the basis of yield and reaction time. In all conditions screened, acetic acid was added as a green acid source to catalyze the reaction.

We report the synthesis of (-)-menthone from (-)-menthol in four different solvent systems, acetonitrile and acetic acid, ethyl acetate and acetic acid, acetone and acetic acid, and dichloromethane and acetic acid. This was confirmed by Fourier-transform infrared (FTIR) spectroscopy. We initially hypothesized that the more polar solvents would give higher yields due to better solubility of the hypochlorite salt. Contrary to initial expectations, the oxidation reaction conducted in ethyl acetate gave the greatest yield of (-)-menthone and completed the fastest, so this solvent system was confirmed as the most efficient. We believe the reaction progressed fastest in ethyl acetate because it can harbor a greater concentration of the active oxidizing agent, hypochlorous acid. Therefore, the oxidation of (-)-menthol to (-)-menthone using calcium hypochlorite is optimal in a solvent system of acetic acid and ethyl acetate. Although the reaction in dichloromethane did take considerably less time compared to the reactions in acetone and acetonitrile, attempts to oxidize (-)-menthol consistently contained an impurity that we were not able to characterize, but was detected by FTIR.

We did face certain experimental limitations in that only two trials were run for each experiment reaction, and the kinetics study results for the reactions at room temperature could not be fully quantified. Due to a decreasing supply of (-)-menthol, the reactions for the experiment in an ice bath were run at a smaller scale, which made it difficult to compare to the reactions at room temperature. Also, the product was
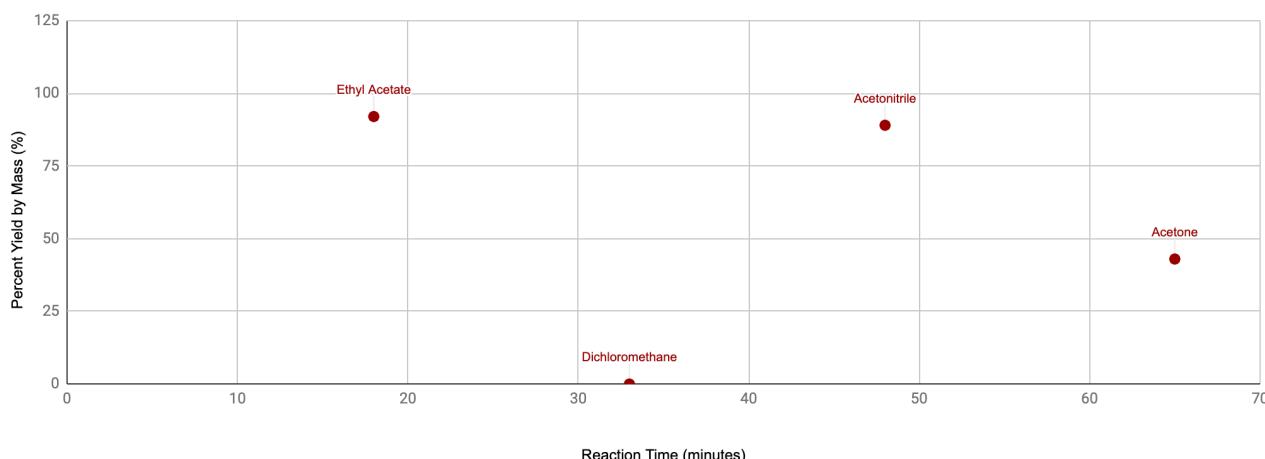
**Figure 6. Percent yield by mass of each oxidation reaction product vs. time for completion.** Each data point is labeled according to the solvent the reaction was completed in. (The percent yield for the reaction in DCM was not taken due to an impurity, so its data point shows as 0% yield).

initially extracted in DCM, which is not considered a "green" solvent. Instead, the solvent-based extraction could be performed with cyclohexane or better, ethyl acetate, both of which are organic solvents that are not miscible with water. This change would contribute to an even more green reaction.

Despite these setbacks, data was still collected although it did not support our hypothesis. The oxidation reaction of (-)-menthol to (-)-menthone conducted in a solvent system of ethyl acetate and acetic acid resulted in the greatest yield, with the least amount of time for the reaction to complete. The product of our reaction was characterized through FTIR to monitor the conversion of the alcohol on (-)-menthol to a ketone. The transformation of the alcohol to ketone was confirmed through IR spectra of the products, which either contained or did not contain the peak for the functional group. Considering that the natural product is the stereoisomer (-)-menthol, the product of its oxidation was (-)-menthone. To further characterize the product, we can use proton nuclear magnetic resonance spectroscopy (1H NMR) and a polarimeter to measure optical rotation, which will provide more information about the structure of the products. Further, the impurity produced in DCM may be a higher frequency carbonyl, and this could be investigated by tracking the reaction progress of the reaction mixture with FTIR and determining which compounds were formed during the reaction.

Ultimately, our research optimizes an oxidation reaction by utilizing a green solvent system, green oxidant, and column-free purification. Further, the reaction can be scaled-up easily while using greener solvents for extractions. As a more sustainable chemical reaction, this work contributes to the promotion and development of green chemistry principles in the future.

## METHODS

### Oxidation of (-)-menthol to (-)-menthone

In a beaker, (-)-menthol (1g, 0.0064 mol, 1 equivalence) was dissolved in a solvent system of concentrated acetic acid (5mL, 0.084 mol) and then 1 molar equivalent of acetonitrile, ethyl acetate, acetone, or dichloromethane. The dissolved solution was added dropwise to a cooled solution of calcium hypochlorite (0.09g, 0.0064 mol, 1 equivalence) and water in a round bottom flask equipped with a Teflon stir bar. The reaction was stirred in an ice bath, and reaction progress was monitored by thin-layer chromatography (TLC) in a solvent system of hexane to ethyl acetate (90:10). Since the polarity of the alcohol in (-)-menthol, the starting material, is greater than the polarity of the ketone in (-)-menthone, the assumed product, TLC can be used to track this reaction. The silica gel plate visually shows how the less polar spot for the product would have traveled farther along the plate than the spot for starting material, thus confirming the alcohol to ketone transformation. The TLCs were visualized using a potassium permanganate stain. Upon completion, water was added, and the product was extracted in four portions of DCM (4x30mL). The organic layers were washed with a saturated sodium carbonate aqueous solution, combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford (-)-menthone as light-yellow colored oil with a slight peppermint odor. The product was then characterized with FTIR. IR spectra were collected on a Thermo Nicolet iS5 Fourier-transform infrared (FTIR) spectrometer equipped with an iD5 attenuated total reflectance (ATR) sample assembly. IR spectra were processed on OMICS software from Thermo Scientific. Then, after taking the mass of the final product, percent yield of the reaction was determined by dividing the mass of the product by the mass of the starting material used and then multiplying by 100. The percent yield for each reaction was calculated based on the assumption that the final product following the extractions is pure. This

assumption was made because no solvent peaks were found in the IR spectra of the products. The percent yield reported in Figure 6 was the greater yield of each reaction between the initial two trials.

### Kinetics Study

The oxidation reaction described above was conducted for all solvent systems simultaneously at a 1-gram scale at room temperature. Four stir plates were arranged side by side and solutions of 1g of (-)-menthol (1g, 0.0064 mol, 1 equivalence) were dissolved into solvent systems of acetic acid and the solvents in Table 2 in the specified quantities. Each solution was added dropwise to a round bottom flask containing 1g of calcium hypochlorite (0.09g, 0.0064 mol, 1 equivalence) and 13.33 mL of water over a period of 10 minutes at room temperature. Reaction progress was monitored by TLC immediately, 15 minutes, 30 minutes, 1 hour, and 2 hours after stirring began.

The (-)-menthol oxidation reaction was also performed on a 100mg scale with (-)-menthol (0.01g, 0.00064 mol, 1 equivalence) and calcium hypochlorite (0.009g, 0.00064 mol, 1 equivalence) in an ice bath for all solvent systems. These reactions were performed in vials in an ice bath. Reaction progress was monitored by TLC immediately after the reactions were stirred, until up to 1.5 hours when the last reaction completed.

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