

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

Anvi Surapaneni<sup>1,6</sup>, Atri Surapaneni<sup>1,6</sup>, Jeslyn Wu<sup>2,6</sup>, Ayush Bajaj<sup>1,6</sup>, Katrina Reyes<sup>3,6</sup>, Rohan Adwankar<sup>4,6</sup>, Ananya Vittaladevuni<sup>5,6</sup>, Edward Njoo<sup>6</sup>

<sup>1</sup>The Quarry Lane School, 6363 Tassajara Rd, Pleasanton, CA 94588

<sup>2</sup>Mission San Jose High School 41717 Palm Ave, Fremont, CA 94539

<sup>3</sup>American High School 36300 Fremont Blvd, Fremont, CA 94536

<sup>4</sup>Irvington High School 41800 Blacow Rd, Fremont, CA 9453

<sup>5</sup>Dougherty Valley High School 10550 Albon Road, San Ramon CA 94582

<sup>6</sup>Center for Advanced Study at Aspiring Scholars Directed Research Program, Fremont, California

**ABSTRACT:** 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. 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, while acetonitrile is the most polar solvent. The green oxidation of (-)-menthol to (-)-menthone was optimized in this solvent system.

## Introduction:

In 2014, reactions involving the oxidation of alcohols were used in 10.4% of medicinal chemistry papers and appear in 46% of manuscripts regarding the chemical synthesis of natural products<sup>1</sup>. It is clear that oxidations of alcohols are an important step in the diversification and synthesis of natural products. For example, the oxidation of a secondary alcohol is used in the synthesis of a nominal harziane diterpenoid very recently reported by Höning and coworkers; other isolated harziane diterpenoids have been shown to possess antifungal and cytotoxic activity.<sup>2</sup> Therefore, an efficient and green oxidation would be beneficial in the large scale synthesis of complex chemical compounds. 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.<sup>3</sup> 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, in a safe and efficient process. Here, we investigate the oxidation of (-)-menthol to (-)-menthone in a variety of solvent systems, which were selected based on the distribution of cost, availability, and sustainability. The initial reaction procedure developed by Nwaukwa and coworkers used a solvent system of acetonitrile and acetic acid.<sup>4</sup> The principles of green chemistry were important in optimization of conditions to conduct this reaction.

(-)-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.<sup>5</sup> Menthol is a useful test substrate for other reactions in industry given its simplicity. (-)-Menthone, another biological-

ly active compound, shares similar characteristics with menthol, most notably its slight peppermint odor.<sup>6</sup> This molecule also has similar uses in the cosmetics and perfumes industries; however, menthone's natural form is a colorless, viscous liquid. Menthone can be obtained by oxidation of the secondary alcohol in menthol to a ketone [Fig. 1].<sup>7</sup> (-)-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 syntheses of other compounds.

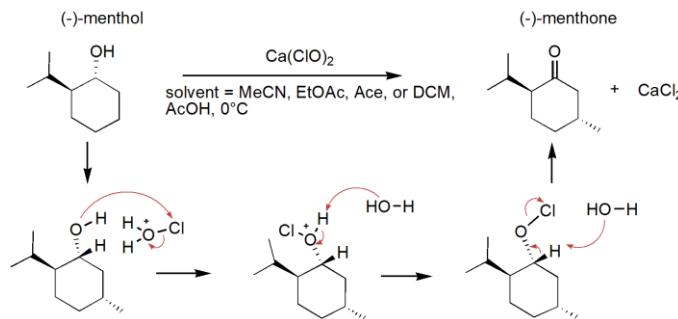


Figure 1: Reaction mechanism of (-)-menthol oxidation to (-)-menthone in four different solvent systems

There are a number of reactions that can be conducted to efficiently oxidize secondary alcohols into ketones; we focused on optimizing green conditions for this transformation. Calcium hypochlorite was chosen as a mild oxidizing agent; 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. A comparison of other mild oxidation reagents commonly used are indicated in 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 [Fig. 2].

Oxi-dation Reac-tion	Reagents	Atom Econ-omy	Molecular Weight of discarded reagents	Hazardous byproducts
Dess-Martin <sup>8</sup>	Dess-Martin Perio-dinane	26.58 %	424.14 g/mol	Iodinane
Swern <sup>9</sup>	Oxalyl chloride, DMSO, triethyl-amine	33.35 %	306.25 g/mol	Carbon monoxide, dimethyl sulfide
Jones <sup>10</sup>	Chromium triox-ide, Sul-furic acid	43.53 %	198.07 g/mol	Chromium (IV) oxide
Co-rey-Kim <sup>11</sup>	N-chlorosuc cinimide, Dimethyl sulfide, triethyl-amine	34.04 %	296.85 g/mol	dimethyl sulfide
Calcium Hypo-chlorite <sup>4</sup>	Calcium hypo-chlorite	51.55 %	142.98 g/mol	None

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

Oxidation Reaction	Reagents	Byproducts
Dess-Martin	Dess-Martin Periodinane	Iodane
Swern	Oxalyl chloride DMSO Triethylamine	Carbon monoxide Dimethyl sulfide
Jones	Chromium trioxide Sulfuric acid	Chromium (IV) oxide
Corey-Kim	Dimethyl sulfide Triethylamine N-chlorosuccinimide	Dimethyl sulfide
Calcium Hypochlorite	Calcium Hypochlorite	Calcium chloride

Figure 2: Structures of reagents and byproducts of common oxidation reactions

## Results:

### Optimization of solvent scope:

The solvents screened for the oxidation reaction included acetonitrile, ethyl acetate, acetone, or dichloromethane, which are also of different polarities. All reactions were conducted at room temperature and in an ice bath. The starting material, (-)-menthol, was first characterized through infrared spectroscopy, with a broad O-H stretch at  $3250\text{ cm}^{-1}$ , representing an alcohol, and 3 medium C-H stretches from 2850 to  $2950\text{ cm}^{-1}$  [Fig. 3] as shown in red. Reasonable yields of (-)-menthone were produced from every reaction, an average of 75% yield. The products were characterized by infrared spectroscopy, which showed the lack of a broad alcohol stretch at  $3250\text{ cm}^{-1}$  and the appearance of a ketone stretch at  $1706\text{ cm}^{-1}$  in the spectrum of the product shown in blue [Fig. 4]. The other IR spectra includes all the products from the menthol oxidations with the (-)-menthone from the oxidation performed in DCM in green, acetone in

purple, acetonitrile in red, and the ethyl acetate reaction in blue. All products have 3 matching C-H stretches near or at  $2955$ ,  $2928$ , and  $2870\text{ cm}^{-1}$  in their spectra and strong C=O peaks at  $1706\text{ cm}^{-1}$  [Fig. 3]. The 3 C-H and C=O stretches in IR spectra of all products near  $3000\text{ cm}^{-1}$  and  $1700\text{ cm}^{-1}$  match the strong C-H stretches at  $2953\text{ cm}^{-1}$ ,  $2926\text{ cm}^{-1}$ , and  $2869\text{ cm}^{-1}$  and the strong C=O stretch at  $1706\text{ cm}^{-1}$  in the IR spectrum of isolated (-)-menthone, confirming that (-)-menthone was produced [Fig. 5]. The spectra of (-)-menthone from the oxidation conducted in dichloromethane, contains the same major stretches as the other products, but includes a weak peak at  $1800\text{ cm}^{-1}$ , suggesting an impurity in the product, which is shown in green [Fig. 4]. Also, the yields of the reactions are reported in a corresponding table, Table 3. Because there was an impurity in the reaction in 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 % 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.

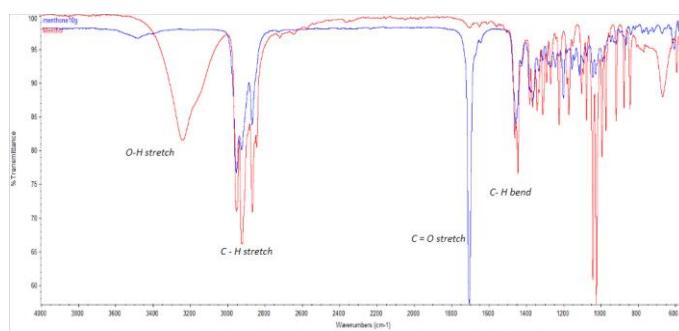


Figure 3: IR Spectra of menthol (red) and (-)-menthone (blue)

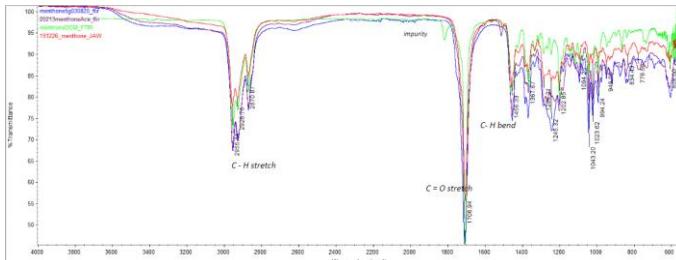


Figure 4: IR Spectra of product from all menthol oxidations with the oxidation product from reaction performed in DCM (green), (-)-menthone from oxidation in acetone (purple), (-)-menthone from oxidation in acetonitrile (red), (-)-menthone from oxidation in ethyl acetate (blue)

Ethyl acetate (EtOAc )	2	Few known issues	0.308	Yes
Ace-tone (Ace)	3	Some known issues	0.355	Yes
Di-chloro me-thane (DCM)	1	Major known issues	0.309	Yes (with an impuri-ty)

Table 2: Comparison of each solvent tested in oxidation reaction of (-)-Menthol to (-)-Menthone

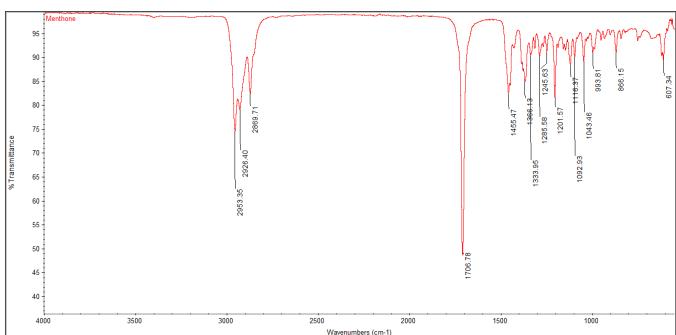


Figure 5: IR Spectrum of isolated (-)-menthone

Solvent used with acetic acid	Relative Cost (lowest - highest)	'Green ness' Score (GSK solvent guide)	Relative Polarity <sup>12</sup> (least - most polar)	Production of (-)-Menthone
Ace-tonitrile (MeCN )	4	Some known issues	0.46	Yes

#### 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. Because the reactions in an ice bath were performed on a smaller scale than the reactions at room temperature, 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. Then, the reactions in dichloromethane and acetic acid, acetonitrile and acetic acid, and in acetone and acetic acid completed, respectively as shown in Table 3. From these results, it is clear that this reaction works to produce (-)-

menthone with a green solvent system, a green oxidant, and a column-free purification.

Solvent used with acetic acid	Time of Reaction Completion (min.)	Percent yield by mass
Acetonitrile (MeCN)	48	89%
Ethyl acetate (EtOAc)	18	92%
Acetone (Ace)	65	43%
Dichloromethane (DCM)	33	—

**Table 3:** Comparison of solvent choice in the oxidation reaction with reaction time and percent yield of reaction

## Discussion:

### *Optimization of solvent scope & kinetics study:*

The oxidation of (-)-menthol to (-)-menthone converts a secondary alcohol into a ketone [Fig. 1]. The initial solvent system for this reaction reported by Nwaukwa and coworkers is acetonitrile and acetic acid. Solvents that were considered in place of acetonitrile included dichloromethane, ethyl acetate, and acetone [Fig. 1]. In a paper by Byrne and coworkers, GlaxoSmithKline's, Pfizer's, and Sanofi's solvent selection guides were compared, providing a comprehensive assessment of certain solvents.<sup>13</sup> 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 as more “green” replacements for acetonitrile.<sup>14</sup> 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 4 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. Overall, this reaction 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. This reaction produces (-)-menthone with a green solvent system, a green oxidant, and a column-free purification. Also, the product was 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 oxidation reaction.

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 ( $^1\text{H}$  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.

## 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 (-)-menthone, 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 (FT-IR) 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 per-

cent yield reported in Table 3 was the greater yield of each reaction between the initial two trials.

#### Kinetics Study:

The oxidation reaction as laid out previously 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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