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Research Article

Green Oxidation of Menthol in Multigram Scale Based on Calcium Hypochlorite

Mariana Falcão Lopes Princisval Carlos, Marcus Vinicius Nora de Souza*

Instituto de Tecnologia em Fármacos Farmanguinhos, FIOCRUZ Fundação Oswaldo Cruz, Rio de Janeiro 21041-250, Brazil
E-mail: mvndesouza@gmail.com

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Abstract: The oxidation reaction stands as a fundamental process in organic synthesis, holding significant importance in generating various value-added chemical products. Oxidative processes are pivotal realms for both industrial and academic exploration. Present-day scientific and research pursuits emphasize the imperative need for chemistry to evolve towards absolute sustainability, prioritizing safety, intelligence, and environmental friendliness—thus aligning with the principles of green chemistry. This work aims to report a green oxidation procedure of menthol to menthone in multigram scale, using calcium hypochlorite as reagent, that can be use in academy research or practical class.

***Keywords*:** green chemistry; menthone; synthesis

1. Introduction

The mint genus (Mentha) is part of the Lamiaceae family, encompassing 42 species, fifteen hybrids, as well as various subspecies, varieties, and cultivars. Among the cultivated varieties, two are widely recognized for their menthol content: *Mentha x piperita L. (MP) and Mentha arvensis L. (MA)*. Mints are renowned for their relatively high essential oil (EO) content [1,2].

EO are multicomponent mixtures of secondary plant volatiles made from various plant sections that are steam- or hydro-distilled. The primary components of EO are categorized as mono- and sesquiterpenes, which include alcohols, ketones, esters, hydrocarbons, aldehydes, and ethers. EO are oily, limp liquids that are soluble in lipids, ethanol, and nonpolar organic solvents but insoluble in water [3].

Menthol and menthone, two of the most widely produced and marketed EOs globally, are the main components shared by MP and MA. Menthol (20–60%), menthone (5–35%), menthyl acetate (1–20%), and menthofuran (0.1–15%) are the primary ingredients of MPEO, whereas menthol (greater than 60%) and menthone (4–18%) are the primary ingredients of MAEO, as illustrated in Figure 1 [4].

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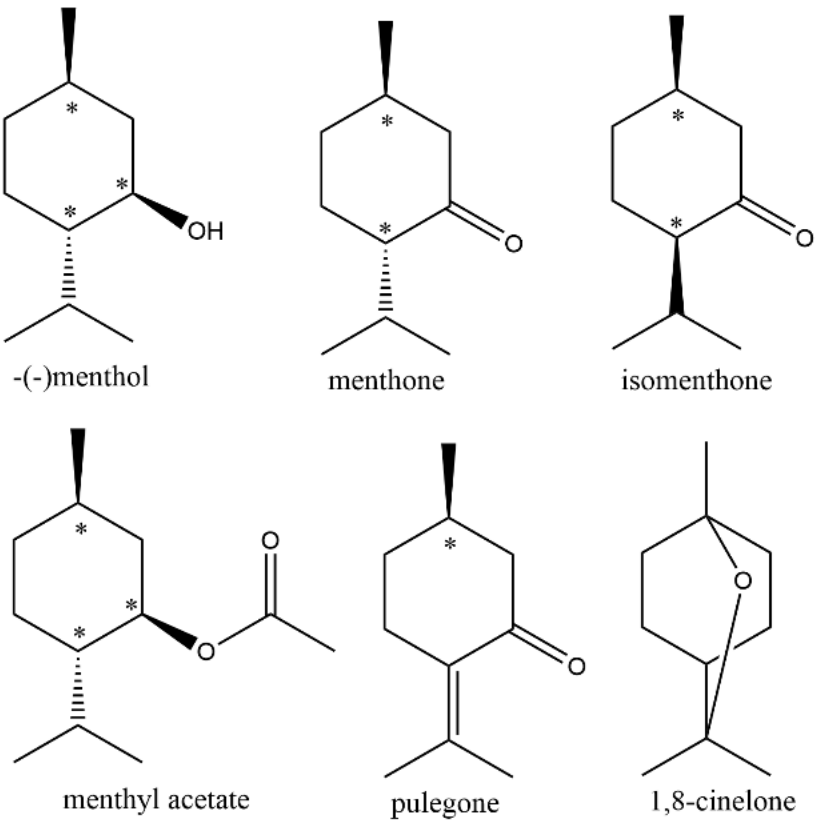


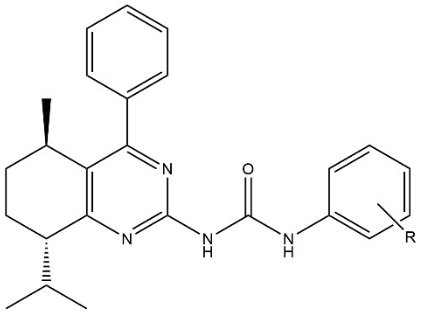
Figure 1. Structures of the majority components of MPEO.

Mentha piperita, commonly referred to as peppermint, has been used to treat several illnesses, including irritable bowel syndrome, migraines, and heartburn. The primary component of peppermint leaves is terpenes, a class of naturally occurring substances that includes monoterpenes, sesquiterpenes, and other compounds., however, menthol (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexan-1-ol is the dominant constituent among terpenes [5,6]. Due to its structure, menthol is a monocyclic monoterpene alcohol with three chiral carbons; it can be used to synthesize bioactive compounds; thus, this compound and its derivatives have a wide range of applications in medicine and agrochemistry [7].

Second only to menthol in terms of dominance, menthone, also known by its chemical name, 5-methyl-2-(1-methylethyl) cyclohexanone, is a major component of peppermint oil. Menthone's biological qualities, including its antibacterial, antifungal, antibiofilm, and anti-inflammatory effects, have come to light [8].

One example of this property is the study by Zao et al [9] wich evidenced antibacterial activities of menthone against methicillin resistant *Staphylococcus aureus* MRSA, the minimal inhibitory concentration (MIC) was reported 3.5 µg/mL and minimal bactericidal concentration (MBC) of 7.1 µg/mL. This study also reported that the mechanism of action involved the alteration of membrane structural components and corresponding properties.

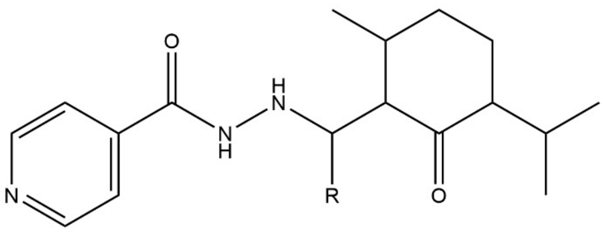
One more example of the importance of these compound derivatives is the study by Huang et al [10], where the authors synthesized a few unique menthone compounds with pyrimidine and urea moieties to investigate more effective anticancer medicines generated from natural products. Using the standard methyl thiazolytetrazolium assay, the in vitro antitumor activity was evaluated. The results indicated that the best compounds against Hela, MGC-803, MCF-7, and A549 were 4i, 4g, 4s, and 4m (Figure 2), with IC50 values of 6.04 ± 0.62 µM, 3.21 ± 0.67 µM, 19.09 ± 0.49 µM, and 18.68 ± 1.53 µM, respectively. Emphasizing the derivative 4i, it was found by Western blot assays and network pharmacology prediction results that drug 4i may inhibit Hela cells by blocking the PI3K/Akt/mTOR signaling pathway [10].



4g: R = 4-Cl 4m: R = 3,5-Me
4i: R = 4-Br 4s: R = 4-NO_2

Figure 2. Structures of the most efficient synthesized compounds by Huang et al. 2022 [10].

Another example of the biological activity of menthone derivatives is the study by Al-Khattaf et al [11], which uses menthone as a precursor of possible synthesized drugs. The authors synthesized twelve compounds derived from menthone and highlighted three of them. The compound 1g showed significantly higher antibacterial activity against gram positive bacteria of *E. faecalis* (1g - MIC = 2 µg/mL), and gram-negative bacteria of *P. aeruginosa* (1g - MIC = 0.25 µg/mL) than standard ciprofloxacin. The compound 1c exhibited high antifungal activity in contradiction of *M. audouinii* (1c - MIC = 4 µg/mL) and compound 1b exhibited high antifungal activity in contradiction of *C. albicans* (1b - MIC = 0.25 µg/mL) compared to clotrimazole. Therefore, the authors concluded that 1b, 1c, and 1g (Figure 3) could serve as a novel class of antimicrobial agents [11].



R= 1b: -Ph-Cl; 1c: -Ph-OH;1g :

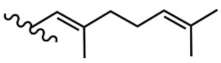


Figure 3. Structures of the most efficient synthesized compounds by Al-Khattaf et al 2021 [11].

As seen in the examples above, these compounds are important, because in addition to having different biological activities, they can also be precursors of new compounds with good pharmacological potential, justifying them being continuously targeted in research.

These days, protecting and preserving the environment is a top priority for society, which is encircled by a system centered on the development of civilization and economic growth through the exploitation of natural resources and various industrial processes, some of which require the use and handling of hazardous chemicals. As a result of these environmental changes, environmental protection becomes crucial [12].

The industrial sector generates a great quantity of hazardous chemical waste; however, education is the sector that generates the greatest variety of these, which results in a diversification of chemical residues that can produce different risks of exposure, difficulty in handling, and environmental impacts [13,14].

With this, the concept of green chemistry began to appear. It was first formulated at the beginning of the 1990s and can be defined as the "design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances"[15,16]. Several terms have been introduced and associated with the concept of green chemistry, such as eco-efficiency, sustainable chemistry, atom efficiency or atom economy, and renewable energy sources[17].

Green chemistry is generally based on the 12 principles proposed by Anastas and Warner, Figure 4. The 12 principles are design guidelines to help researchers achieve sustainability. Nowadays, these 12 principles of green chemistry are considered as fundamentals to contributing to sustainable development[15,18,19].

Figure 4. The 12 principles of green chemistry.

According to the previous assertions, the green synthesis of menthone is an experiment of oxidation of the alcohol function of menthol using a sanitizing agent as oxidant, since the classical methods of menthone synthesis via menthol oxidation pass by the use of extremely toxic reagents such as chromic acid[20] or by the use of very expensive reagents such as Dess-Martin periodinane[21].

The concept of green chemistry exerts significant influence because it goes beyond confines of research laboratories, and has touched industry, education, the environment, and the general public. Considering this, the present work intends to collaborate with the dissemination of the large-scale green synthesis of menthone that correlates with the precepts of green chemistry employing both simple operating conditions as well as technical characterization/identification which is accessible in the laboratories.

2. Materials and Methods

2.1 *Materials*

The reagents employed in this study for synthesizing menthone included anhydrous acetonitrile (99.8% purity, VETEC), menthol (analytical standard, VETEC), glacial acetic acid (ACS reagent, ≥99.7% purity, Merck), and commercially obtained calcium hypochlorite from DOMCLOR. All reagents were used lacking prior treatment. Menthol was also obtained commercial for comparation.

2.2 *Experimental Procedure*

A solution of calcium hypochlorite was previously prepared with 7 g of $Ca(ClO)_2$ in 40 mL of water (0 °C). 10 g of menthol was dissolved in 50 mL of acetic acid and acetonitrile (3:2), this solution was slowly added into the salt solution. After that, the final solution was left under magnetic stirring at room temperature for 1 h (Figure 5) during the hour more 40 mL of water was added to the solution. The product was extracted with dichloromethane (2× 30 mL), dried with magnesium sulfate anhydrous and evaporated.

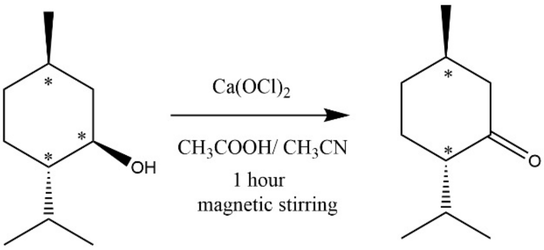


Figure 5. Synthesis of menthone from menthol oxidation.

3. Results and Discussion

The conversion of alcohols to ketones is an extremely common and important reaction in organic chemistry because this compound has a high reaction potential and can be used to produce several derivatives[22]. The oxidation reaction of menthone is well reported in literature, but some reactions still use toxic or expensive reagents, such as, chromic acid (methodology described by Haunt 1985)[20] or Dess-Martin periodinane[21]. The development of this reaction constitutes an active area for both academic and industrial research, especially when performed on an industrial scale[23].

This study utilized calcium hypochlorite as the oxidizing agent, chosen for its superior environmental friendliness, ease of handling, and cost-effectiveness compared to alternative options. It is easy to find commercially, and it was not necessary to use analytical reagents to proceed with the reaction. Its aqueous solution provides a higher concentration of the hypochlorite species than the one present in household bleaches, the reagent used was found in a swimming pool product.

The reaction was tested with an increase in the mass of the starting material, in this case menthol. This procedure was carried out to analyze whether the reaction would show good reproducibility, continuing with good yield even with the increase in mass. Table 1 shows the increase in the amount of menthol and the yield obtained in each of the procedures. The progress of the reaction was monitored by the change in the color of the final solution—which presented a light-yellow color—and by TLC, using hexane: ethyl acetoacetate (6:1). No additional purification procedures were required, as only one spot appeared on the TLC. The final product was also subjected to ^{13}C and ^{1}H NMR d 1H NMR analysis, revealing spectra free from impurities.

Table 1. Yields of synthesized products with increasing mass of the starting reagent.

Menthol (g)	Menthone (g)	Yield (%)
1.0	0.8	88
2.5	1.9	85
5.0	4.2	81
10.0	8.8	88

According to Table 1, the reaction using 10 g of menthol was successful, obtaining a yield of 88% with no need for further purification, which was a positive point of the procedure. Another point is that the reaction occurred at room temperature, making it, in addition to being ecologically correct, an alternative that can be used in the industrial field.

In addition to 10 g, the starting reagent was also increased to 12 g and 15 g. However, the yields obtained in these reactions did not increase significantly, indicating that 10 g was the optimal maximum increase for this reaction.

The structure of menthone was confirmed using IR and RMN, even though this substance is well known in literature. The IR spectra showed an intense peak at 1711 cm^{-1} regarding the carbonyl group, and the disappearance of the broad band related to the absorption of the O-H bond, present in the IR of menthol, as can be seen in Figure 6.

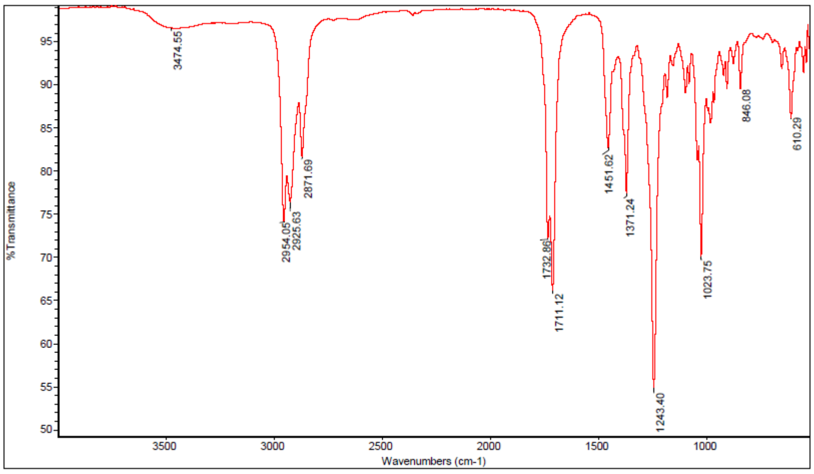


Figure 6. IR spectrum of synthesized menthone.

4. Conclusions

This work shows an environment friendly procedure, alternative to menthol oxidation, as the use of calcium hypochlorite is safe and effective, giving a yield of 82%. The proposal discussed can also be considered in the educational field of experimental organic chemistry, because it can provide students with the understanding of several experimental techniques such as filtration, liquid extraction, and distillation in a rotary evaporator.

The use of reagents of low toxicity such as menthol, the low cost, and the ease of purchase makes this proposal good for research and industries, combined with the green conditions, are some of the strengths of the methodology.

It can also be noted that despite being an eco-friendly reaction with good yield, there are some limitations. For instance, when scaling up the reaction, beyond a certain quantity of mass (in this case 10 g), even with gradual increments, there is no significant increase in yield. Another point is the need to prepare the aqueous solution of calcium hypochlorite beforehand and in a short time, as a solution prepared too long ago is not efficient as an oxidizing agent.

This work intends to collaborate with the dissemination of the green synthesis of menthone, correlated with the precepts of green chemistry, using simple operating conditions and characterization techniques which can be accessible in the didactic field and industry, such as thin layer chromatography, infrared spectroscopy, and formation of derivatives.

Author Contributions

Mariana F. P. L. Carlos: Investigation; Writing original draft, editing. Marcus Vinicius Nora de Souza: Conceptualization; Supervision; Writing, review, and editing.

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Conflict of interest

The authors declare that there is no conflict of interest in this study.

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