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Synthesis of menthol esters with fatty acids, a comparison between Fischer and Steglich esterification

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Abstract:
Menthol esters are a class of organic compounds used in many branches of the chemical industry, such as the cosmetics industry (easy to dissolve, emulsify and accelerate absorption into the skin), pharmaceuticals (in the controlled release mechanisms of menthol and fatty acids) and food (preserving certain properties of menthol), but also in the perfume industry (releasing the menthol fragrance upon hydrolysis of the ester bond). In the present work, we present the production of several esters of menthol (a saturated cyclic secondary cyclic alcohol) with fatty acids (carboxylic acids with long linear aliphatic chain and even number of carbon atoms) by Steglich esterification, namely esters of menthol with caprylic acid – C8:0 (to obtain menthyl octanoate), lauric acid – C12:0 (to obtain menthyl laurate) and palmitic acid – C16:0 (to obtain menthyl palmitate).

Keywords: organic synthesis, menthol esters, purification, analysis

1. INTRODUCTION

Esterification is a chemical process of ester formation from a carboxylic acid and an alcohol. The mechanism of the classical esterification process (Fischer) is nucleophilic substitution by addition-elimination and takes place in three steps: protonation of the carbonyl group, attack of the nucleophile, water elimination and deprotonation.

There are several methods of obtaining esters, among which can be listed: Fischer esterification (traditional method), Steglich esterification and biocatalytic esterification (enzyme-catalyzed and with the most satisfactory yield of obtaining the product of interest) [1–5].

Unlike Fischer esterification, where the reaction to obtain the ester is catalyzed by sulphuric acid (which can carbonize the reaction medium) and takes place at equilibrium (an additional azeotropic distillation operation is required to capture water, to shift the equilibrium to the right and increase the yield of ester), Steglich esterification is advantageous because it consists in obtaining the ester by an irreversible reaction catalyzed by N,N'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) [6].

The mechanism of Steglich esterification is shown in **Figure 1**.

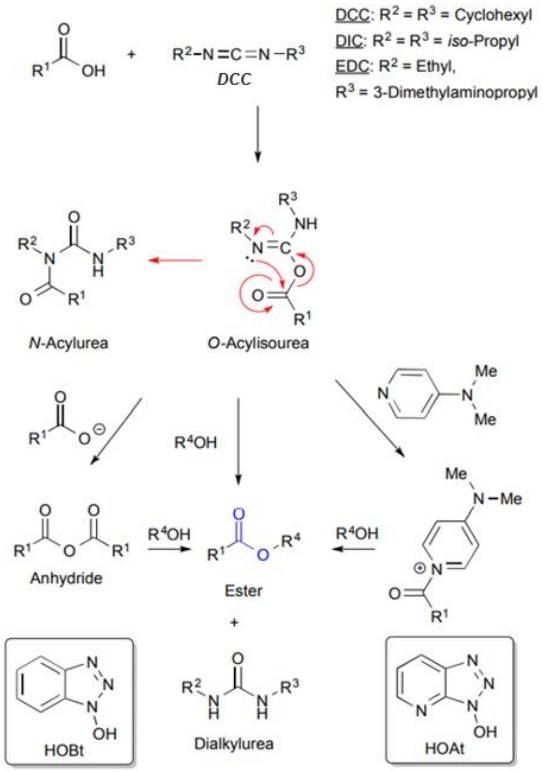


Figure 1. Steglich esterification mechanism [6].

2. MATERIALS AND METHODS

2.1. Materials

The materials used in this research were selected to ensure the accuracy and reproducibility of the results. All reagents and chemicals used were of high purity (minimum 99%) and were purchased from reputable suppliers in the field, certified for product quality and consistency. The equipment and instruments used were calibrated according to international standards and maintained to ensure an optimal level of measurement accuracy. In addition, all materials were stored under conditions specified by the manufacturer to prevent degradation or contamination, thus ensuring the reliability of the experiments.

2.2. Organic synthesis methods

2.2.1. Fischer esterification working procedure

For the Fischer esterification, menthol (0.01 moles), fatty acid (0.01 moles), CH_3Cl (25 mL) and H_2SO_4 (1 mL) are introduced into a round-bottomed flask with heating (oil bath) and magnetic stirring. This is connected to an azeotropic distillation apparatus (to remove the azeotropic mixture between the formed water and CH_3Cl from the reaction medium and shift the chemical equilibrium to the right) and allowed to reflux for 3 hours [7]. After the addition of the catalyst (H_2SO_4), a yellowish coloration is observed, which becomes darker over 3 hours. Neutralize with $NaHCO_3$ and extract with water (**Figure 2**).

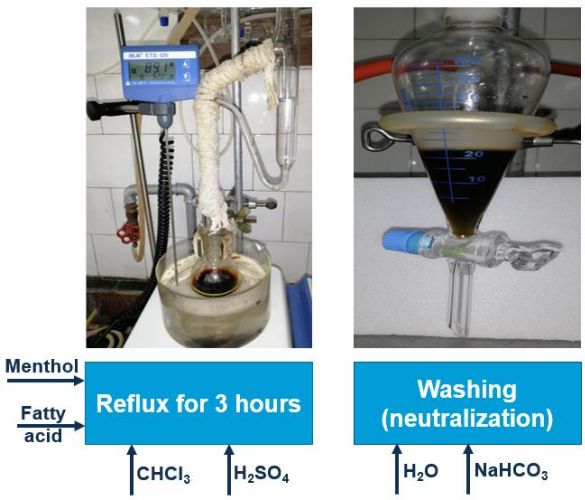


Figure 2. Fischer esterification process scheme.

2.2.2. Steglich esterification working procedure

To perform the Steglich esterification, menthol (0.01 moles), fatty acid (0.01 moles), DMAP (0.001 moles) and CH_2Cl_2 (10 mL) are placed in a round-bottomed flask fitted with magnetic stirring. Cool the mixture on an ice bath to 0-3°C, add DCC (0.01 moles), close the flask with a stopper and shake for 5 minutes. Then remove the ice bath, leaving the shaking at room temperature for another 3 hours. Vacuum filtration follows by washing the flask with CH_2Cl_2, removing the dicyclohexylurea (DCU) formed [6]. The resulting mixture was then evaporated under low pressure using a rotary evaporator, removing traces of DCU, water and CH_2Cl_2. The reaction mass was washed with 0.5N HCl solution and saturated $NaHCO_3$ solution, forming an emulsion and separating the organic phase from the aqueous phase overnight [8]. The organic phase was subjected to drying with anhydrous $MgSO_4$, filtration (removing the formed $MgSO_4 \cdot 7H_2O$ crystallohydrate) and evaporation (removing the remaining CH_2Cl_2), yielding the crude reaction product (**Figure 3**).

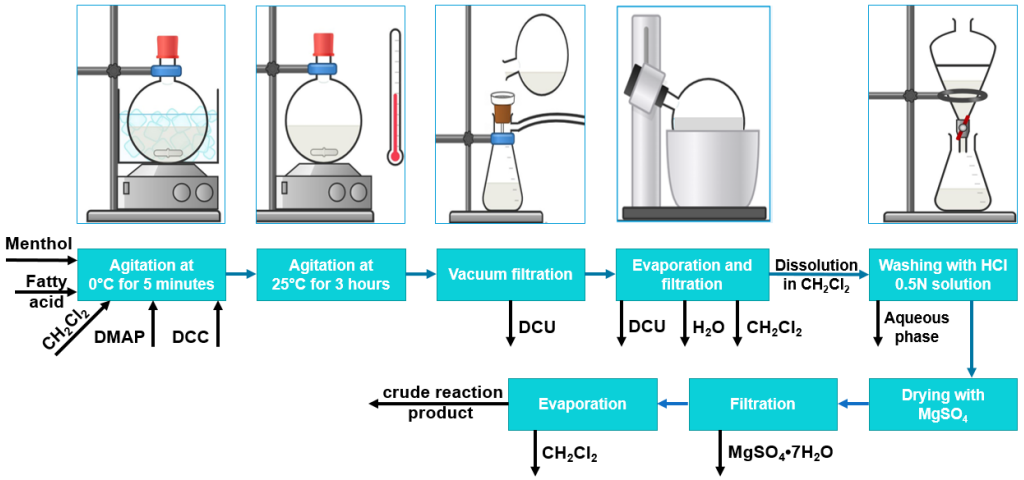


Figure 3. Steglich esterification process scheme.

2.3. Purification methods

Once the actual esterification reaction is complete, the crude reaction product is purified. First, separation is carried out on a chromatographic column filled with silica gel (used as stationary phase) [5]. The column was filled with 30g of silica gel and primed with petroleum ether (PE). The reaction mass was deposited on 7.8g of silica gel. It was eluted with various mixtures of ethyl ether (EE) and PE (used as mobile phase), the polarity of the mobile phase was gradually increased (by gradually increasing the

concentration of EE in the mixture from 1 to 10%) and the fractions were separated [9]. The fractions obtained were analyzed using thin layer chromatography (silica gel plates), bromcresol green solution as developer and EE:EP mixture (1:1) as mobile phase for the chromatographic tank. Finally, spots were identified by UV lamp (**Figure 4**).

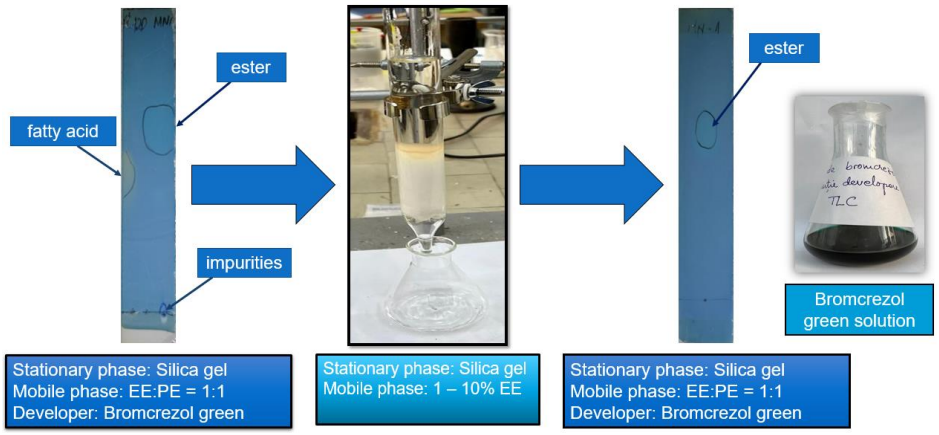
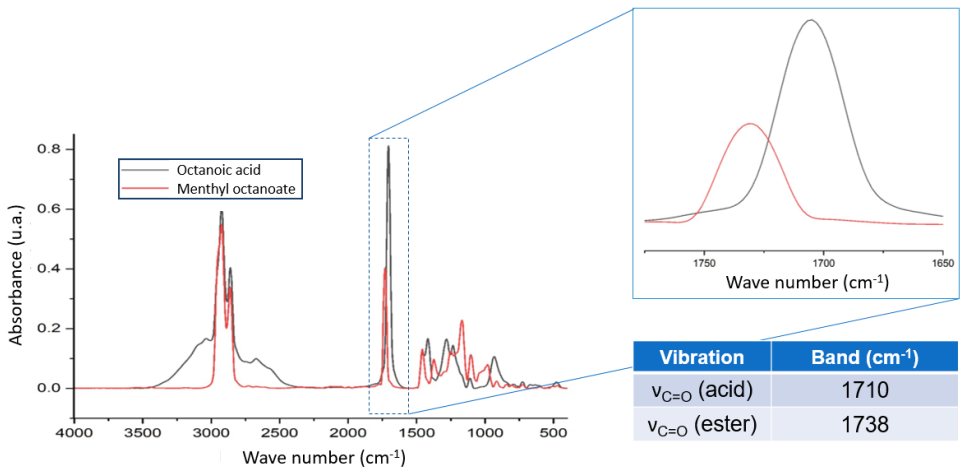


Figure 4. Scheme of the purification process of the reaction product.

2.4. Analysis methods

2.4.1. Infrared spectroscopy (IR)

Once the ester obtained is of high purity, its chemical structure is analyzed by IR spectroscopy, which provides information about the functional groups (**Figure 5**).



Vibration	Band (cm^{-1})
$\nu_{C=O}$ (acid)	1710
$\nu_{C=O}$ (ester)	1738

Figure 5. IR spectrum of menthyl octanoate superimposed on that of octanoic acid.

We observe that the ester band no longer records the specific hydrogen bonding signals and that the vibration of the carbonyl group has shifted from the carboxylic acid band to the ester band [5].

2.4.2. Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H-NMR)

By diluting the ester in deuterated chloroform ($CDCl_3$), we obtain by ^{1}H-NMR spectroscopy information about the protons and their order in its chemical structure (**Figure 6**) [5,8].

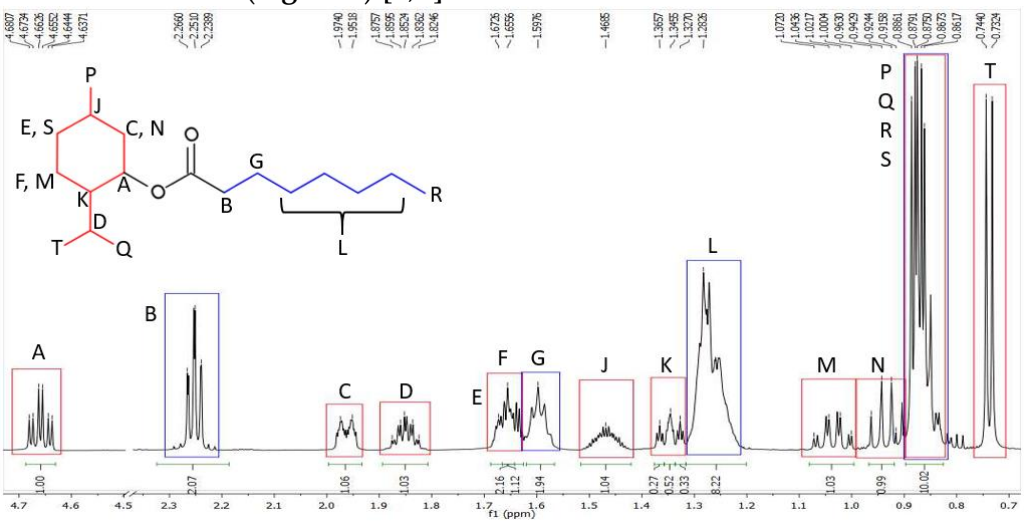
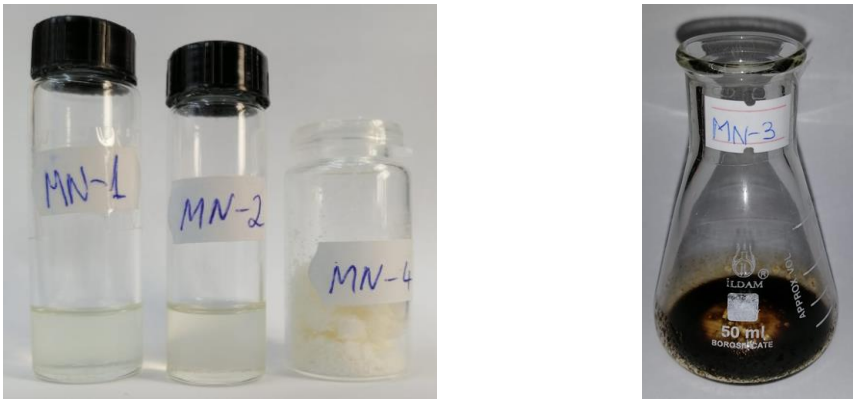


Figure 6. ^{1}H-NMR spectrum of menthyl octanoate.

3. RESULTS AND DISCUSSION

3.1. Results

The result of the Fischer esterification was a dark-colored reaction mass (sample MN-3) with high viscosity and an unpleasant, pungent odor. After purification and spectral analysis the results remained inconclusive. On the other hand, Steglich esterification yielded two colorless, slightly viscous and odorless liquid products (samples MN-1 and MN-2) and an odorless white solid product (sample MN-4). There is a clear difference in the appearance of the products produced by the two methods (**Figure 7**).



(**a**) (**b**)

Figure 7. Appearance of Steglich esterification products (**a**) and Fischer (**b**).

Steglich esterification is advantageous and accessible in the laboratory because the resulting esters are easy to purify, their chemical structure has been validated by analytical methods (IR and ^{1}H-NMR) and the yield is satisfactory, the results of which are shown in Table 1.

Table 1. Final results of Steglich esterification.

Code of the obtained sample	Ester obtained	Final results	
		Aspect	Yield (%)
MN-1	Menthyl octanoate	colorless liquid	75
MN-2	Menthyl laurate	colorless liquid	76
MN-4	Menthyl palmitate	white solid	78

3.2. Discussion

There is no clear delimitation between the different areas of use of organic compounds. They overlap, and a minimum of knowledge in each area can lead both to increased efficiency in the realization of a chemical process and to improved research in organic chemistry by acquiring a common language with specialists in other fields with whom we need to collaborate. Research into the branch of menthyl esters can give rise to a multi- and interdisciplinary approach [10].

4. CONCLUSION

Fischer esterification is difficult to use in laboratory practice and does not give conclusive results, the main obstacles being the reversibility of the reaction and the risk of carbonization.

Three esters of menthol with fatty acids were obtained by the Steglich method in satisfactory yields (~80%). The structures of the obtained compounds were confirmed by spectroscopy (IR and ^{1}H-NMR). The stability of menthol esters increases with fatty acid chain length.

Steglich esterification remains the most accessible and promising method for obtaining esters chemically in the laboratory.

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