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Bulletin of Chemical Reaction Engineering & Catalysis, 19 (2) 2024, 350-360

Research Article

Utilization of Silica Gel for the Synthesis of Geranyl Laurate and Citronellyl Laurate

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Received: 17th May 2024; Revised: 20th June 2024; Accepted: 21st June 2024
Available online: 8th July 2024; Published regularly: August 2024

Abstract

Geraniol and citronellol are monoterpenoid alcohols with diverse pharmacological activities. This research focuses on synthesized of geranyl laurate and citronellyl laurate using silica gel as an esterification catalyst. The FTIR peak spectra of silica gel showed that Si−OH, Si−O−Si group were observed. XRD showed that the silica gel is an amorphous phase. The reaction was conducted under reflux using a Dean–Stark trap. The reaction was monitored by TLC and then the product was purified using column chromatography. This work reported that silica gel can be utilized as a catalyst for preparing geranyl laurate and citronellyl laurate which proven by the spectra of FTIR, ^{1}H-NMR, and ^{13}C-NMR of the geranyl laurate and citronellyl laurate formed. The IR spectra of geranyl laurate and citronellyl laurate showed the presence of a carbonyl group (C=O) at 1744-1745 cm^{-1} and C−O from ester at 1170-1176 cm^{-1}. The peak number and its chemical shift on ^{1}H-NMR and ^{13}C-NMR spectra further verified the structure of geranyl laurate and citronellyl laurate. In conclusion, silica gel can be utilised as a catalyst for preparing geranyl laurat and citronellyl laurate. Therefore, a silica gel-based catalyst is promising to be developed for esterification applications.

Keywords: Silica Gel; Esterification; Dean-Stark Trap; Geranyl laurate; Citronellyl laurate

How to Cite: K.N. Rosalina, T. Wukirsari, S. Hudiyono, S. Handayani (2024). Utilization of Silica Gel for the Synthesis of Geranyl Laurate and Citronellyl Laurate. *Bulletin of Chemical Reaction Engineering & Catalysis*, 19 (2), 350-360 (doi: 10.9767/bcrec.20159)

Permalink/DOI: https://doi.org/10.9767/bcrec.20159

1. Introduction

Indonesia has an area of around 9 million km^2 with very high biodiversity. The country is home to a quarter of the world's flowering plants, totaling around 20,000 species. Among these, 40% are unique to Indonesia, representing endemic or native species [1]. Essential oils from various plants widely used commercially for cosmetics and perfumes [2]. Essential oils consist of natural products with diverse and complex organic structures. Terpenes and terpenoids are the major constituents of essential oils [3].

Geraniol and citronellol are examples of important monoterpenoid alcohols that have been widely reported to possess several bioactivities. Geraniol can be isolated from the essential oil of aromatic plants such as *Rosa damascena* (Rosaceae), *Monarda fistulosa* (Lamiaceae), and *Pelargonium graveolens* (Geraniaceae) [4]. A rose-like fragrance of geraniol has led to its widespread use as an active ingredient in commercial products [5]. Geraniol also exhibited pharmacological activities, such as anticancer activity against colo-205 cancer (IC_{50} = 20 µM) [6], antibacterial activity against most of Candida and Staphylococcus (MIC values ≤600 µg/mL) [7], anti-inflammatory [8], and neuroprotective activity [9]. Another prominent monoterpenoid alcohol is citronellol. Citronellol is found in the essential oil of plants belonging to the genus Cymbopogon. Previous studies have revealed the antibacterial activity of citronellol against *Candida albicans* at a concentration of 6.25%, whereas citronellol at a concentration of 25% inhibited the growth

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Streptococcus mutans and *Streptococcus sobrinus* [10]. Citronellol also showed antidiabetic activity [11] and anticancer activity against A549, NCI-H23, BT-20, and PC3 cell lines with IC_{50} range of 60-69 μM [12].

A large number of drugs are derived from natural products. The structure of monoterpenoid alcohol such as geraniol and citronellol can be modified into its ester form. Widiyarti *et al.* [13,14] have reported the synthesis and anticancer activity against murine leukemia (P388) of geranyl butyrate (IC_{50} = 22.345 μg/mL), geranyl caproate (IC_{50} = 27.996 μg/mL), geranyl caprylate (IC_{50} = 32.298 μg/mL), and citronellyl caproate (IC_{50} = 38.49 μg/mL). However, the esterification of geraniol and citronellol with lauric acid has never been carried out. Lauric acid contributes 45–53% of coconut oil's total fatty acid composition. The abundance of coconut oil production in Indonesia reach 2.8 million tons in 2021 [15].

Esterification stands out as a crucial process in organic synthesis [16]. These reactions are reversible and have low reaction rate. Therefore, various catalysts are often employed in this reversible reaction. Both homogeneous and heterogeneous catalysts have been utilized to conduct esterification reactions [17]. Homogeneous acid catalysts have been used since 1895 to catalyze Fischer esterification [18]. Organic and inorganic acids, such as H_2SO_4, HCl, HI, and p-toluene sulfonic acid, are widely adopted in esterification techniques in commercial applications. The disadvantages of homogenous acid catalysts are toxic, corrosive, and difficult to remove from the end-product [17]. Moreover, homogeneous acid catalysts may react with other acid-sensitive functional groups such as carbon-carbon double bonds. The acid catalyst can change the configuration of carbon-carbon double bonds. Therefore, a homogenous acid catalyst is unsuitable for the esterification of geraniol and citronellol because these compounds contain carbon-carbon double bonds.

Currently, there is substantial interest in heterogeneous catalysts in research due to their benefit. The heterogeneous catalytic has several advantages over the homogeneous catalytic including easy separation, catalyst recycling/reuse, and less energy requirement [19]. Several heterogeneous catalysts using silica gel as the support structure provide impressive chemical and thermal stability, a large surface area, and better solid acidic site accessibility. Silica gel as a catalyst has been employed in various reactions [20]. Heterogeneous silica-based catalysts have been used for amidation reactions [21−23], hydrogenation [24], and alkylation [25]. The utilization of silica gel as catalyst for esterification reaction have not been reported. In this research silica gel was challenged to catalyze esterification of geraniol and citronellol using lauric acid. The silica gel was expected preserving the configuration of carbon-carbon double bonds in monoterpenoid alcohol. This research has potential for subsequent development in the production of oleochemicals.

2. Materials and Methods

2.1 Materials

The materials used in this study were lauric acid, geraniol, citronellol, and silica gel 60 (0.063-0.200 mm) for catalyst and column chromatography were purchased from Merck (Darmstadt, Germany); p-xylene 99% (Loba Chemie); 2',7'-dichlorofluorescein, whatman filter paper (grade 42) was purchased from Merck. TLC silica gel 60 F254 were purchased from Sigma-Aldrich; toluene and ethyl acetate with technical grade.

2.2 Characterization of Silica Gel

Silica gel as a catalyst was characterized by FTIR and XRD. The functional groups of the silica gel were measured using FTIR (SHIMADZU IR Prestige-21) in the range of 4000–400 cm^{-1}. FTIR analysis used KBr powder as a blank. Diffraction patterns were measured using XRD (Malvern Panalytical) at an angle in the 2θ range from 10° to 90° with operating conditions, a voltage of 40 kV, and a current of 30 mA using Cu-Kα radiation (1.54 Å).

2.3 Synthesis of Geranyl Laurate and Citronellyl Laurate

Lauric acid and geraniol were added to a flat-bottom flask in a 1:1 equimolar ratio. A 20 mL of p-xylene was added to the flat-bottom flask as a solvent and 20% silica gel as a catalyst. Then, the mixture was refluxed with a Dean-Stark trap for 16 h at 138 °C. The reaction was monitored by TLC using toluene-ethyl acetate (95:5). The reaction was stopped and cooled, then the silica gel was separated by gravity filtration using paper filter Whatman no.42. The solvent was evaporated and the residue was purified by column chromatography using toluene-ethyl acetate (97.5:2.5) and liquid-liquid extraction with K_2CO_3 and *n*-hexane. The same procedure was applied to synthesize citronellyl laurate except for adding citronellol as the starting material. The product was characterized by FTIR (SHIMADZU IR Prestige-21), ^{1}H-NMR (Bruker Avance Neo-Ascend 500 MHz), and ^{13}C-NMR (Bruker Avance Neo-Ascend 125 MHz).

3. Results and Discussion

3.1 Silica Gel Catalyst

The silica gel used as a catalyst was characterized by FTIR and characteristic wavenumbers were obtained for the siloxane functional group (Si−O−Si) and the silanol functional group (Si−OH) as shown in Figure 1. FTIR spectrum recorded of silica gel, broadband appears at range 3700-3000 cm^{-1} and peak at 1643 cm^{-1} corresponds to the vibration and stretching O−H band. In the literature, the −OH stretching vibrations of the Si−OH group absorb in the same region as the alcohols, 3700-3200 cm^{-1} [26].

The broad band between 1300-1096 cm^{-1} is associated with the asymmetric stretching vibrations of the Si−O bond. These vibrations typically occur at wavenumbers of 1110-830 cm^{-1} [26]. The Si−O−Si vibration was indicated by the present of a peak at 793 cm^{-1}, while the peak at 479 cm^{-1} indicated Si−O rocking vibrations. These observed vibrations are consistent with the literature, where symmetric stretching vibrations of Si−O−Si usually appear around 800 cm^{-1}, and Si−O bending vibrations appear in the region around 500-470 cm^{-1} [26].

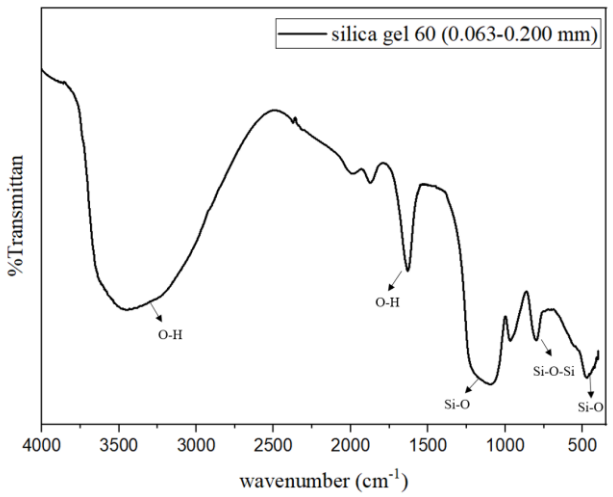


Figure 1. FTIR spectrum of silica gel 60 (0.062-0.200 nm).

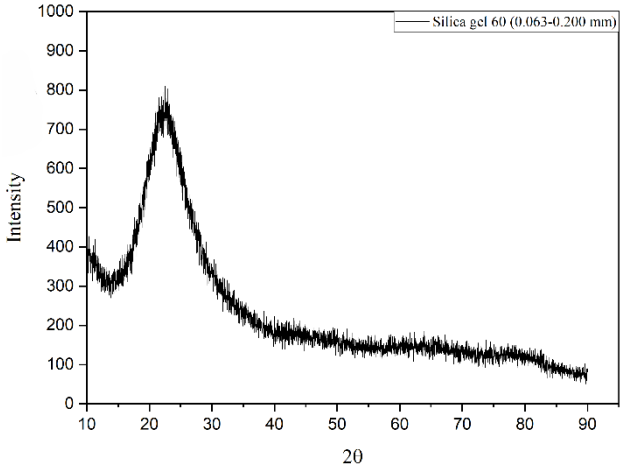


Figure 2. XRD of silica gel 60 (0.062-0.200 nm).

The XRD patterns of silica gel are shown in Figure 2. It is clearly seen that the patterns of diffraction peak at 22°, indicating the typical amorphous structure of silica gel. Previous research stated that the silica gel diffraction at the peak of the angle widened at an angle of 2θ = 23° [27]. Based on the typical peak at the angle, it showed an amorphous structure.

3.2 Synthesis of Ester Products

Synthesis of geranyl laurate and citronellyl laurate was carried out under reflux with a Dean-Stark trap using silica gel as a catalyst. The purpose of using the Dean-Stark apparatus for esterification reactions was to facilitate the efficient removal of water produced as a byproduct during the reaction. Removal of water shifted the equilibrium towards the formation of products and prevented hydrolisis of the desired ester product. A solvent having a higher boiling point than water (*p*-xylene, b.p. = 138°C) was chosen to aid the removal of water. *p*-Xylene has been reported by Poras *et al.* [23] for removal the water during the amidation reaction under the same condition. Yang *et al.* explained that the amidation reaction using *p*-xylene as a solvent gave better yields compared to using toluene [28]. As a result, geranyl laureate and citronellyl laurate can be obtained in higher yield

The esterification reaction for 16 h without a catalyst did not show the formation of product as indicated by TLC (Figure 3a). Figure 3a exhibited that the spot of reaction mixture at the same position as the starting material, no new spot was observed. On the other hand, utilization of silica gel as catalyst showed the spot of product was

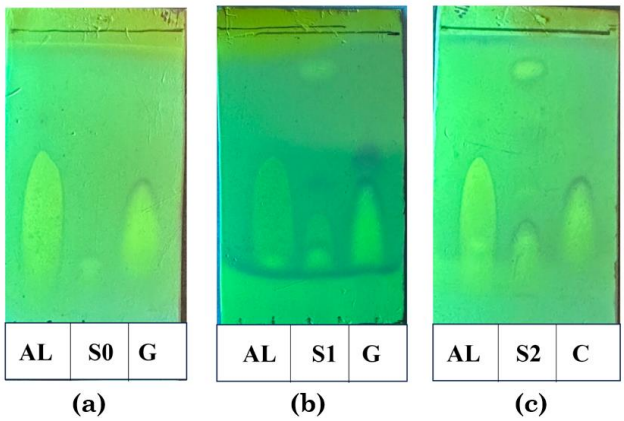


Figure 3. The TLC profile of esterification reaction for the synthesis of geranyl laurate without catalyst (a) and using silica gel catalyst (b) & (c) (notes: LA = lauric acid; S0-2 = reaction mixture, G = geraniol C = citronellol).

faintly visible on TLC after 8 h of reaction. The spots were visualized using 2',7'-dichlorofluorescein, a non-destructive staining agent. Therefore, the reaction was continued for 16 h to obtain more product. TLC profile in Figures 3b and 3c indicated that geranyl laurate and citronellyl laurate have been formed. Toluene-ethyl acetate (95:5) was used as the eluent system

The spot of the esterification product appeared as new spots with higher Rf value compared to its starting material. Ester group (−COOR) of geranyl laurate and citronellyl laurate have lower polarity compared to the hydroxyl and carboxyl group of its starting material. After 16 h of reaction, the spot of starting materials can be detected on the TLC profile. This data described that the reaction did not work perfectly.

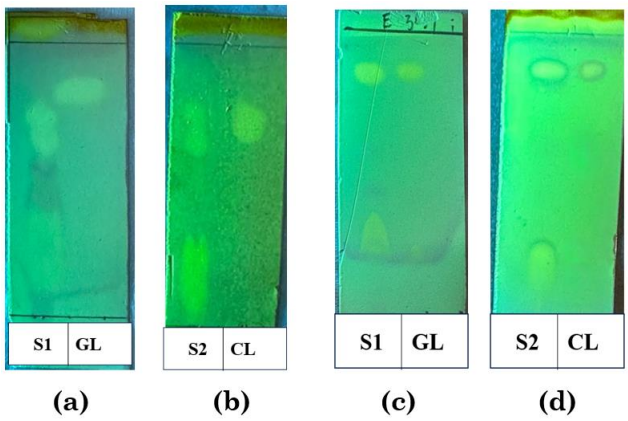


Figure 4. The TLC profile of the before and after purification using column chromatography (a) & (b) and using liquid-liquid extraction (c) & (d). (Notes: S1, S2 = before purification, GL = purified geranyl laurate, CL= purified citronellyl laurate).

Separation using column chromatography was employed to obtain pure geranyl laurate and citronellol laurate. Silica gel was used as the stationary polar phase and the mobile phase consisted of toluene:ethyl acetate (97.5:2.5). Normal phase column chromatography was selected based on the low polarity of ester as the target compound. Low polarity compound has low affinity with the stationary phase and elute quickly through the column [29]. In this research, isocratic elution was used because the separating compounds have large differences of Rf value. TLC profile before and after purification of geranyl laurate and citronellyl laurate can be seen in Figures 4a dan 4b. Geranyl laurate and citronellyl laurate were obtained in low yield, i.e. 18.63 % and 12.91%, respectively.

Besides purification using a column, liquid-liquid extraction was also performed for comparison (Figures 4c and 4d). The liquid-liquid extraction was carried out using *n*-hexane-K_2CO_3. Extraction with K_2CO_3 was done to remove any remaining lauric acid residues in the organic phase [30]. The purification by liquid-liquid extraction showed a higher yield than purification by column chromatography, i.e. 42,89% for geranyl laurate and 43,58% for citronellyl laurate. This finding indicated that part of the sample was adsorbed onto the silica during column chromatography.

The presence of a single spot after purification using column chromatography and liquid-liquid extraction confirmed the geranyl laurate and citronellyl laurate can be separated from the starting materials. Both geranyl laurate and citronellyl laurate were colorless oils at room temperature, in contrast to lauric acid which is solid at room temperature. This difference of physical form proved that the esterification reaction has occurred.

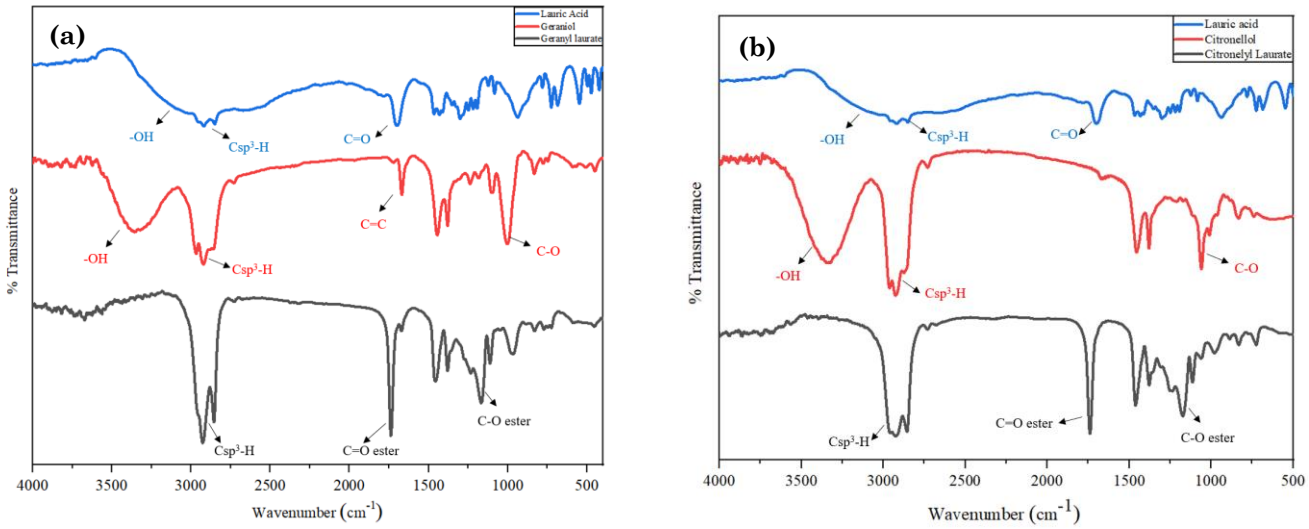


Figure 5. FTIR spectra of geranyl laurate (a) and citronellyl laurate (b) compared with starting material.

3.3 FTIR Spectra of Geranyl Laurate and Citronellyl Laurate

Figure 5 displays the IR spectra of lauric acid, geraniol, and citronellol compared to their ester products. The lauric acid IR spectrum showed a single sharp peak at 1707 cm^{-1} that can be attributed to the carbonyl group (C=O). Additionally, a characteristic very broad peak absorption at 3329 cm^{-1} indicated the presence −OH of carboxyl group. On the other hands, −OH group of geraniol and citronellol appeared as broad and intense peak at region 3300 cm^{-1}. The IR spectra of geraniol and citronellol also exhibited a vibration of Csp^3−H at region 2900 cm^{-1}, vibration of C=C at region 1600 cm^{-1}, and vibration of C−O at region 1000 cm^{-1}.

The peak absorption of −OH was not observed in the IR spectra of the geranyl laurate and citronellyl laurate as ester products. This IR analysis confirmed that geranyl laurate and citronellyl laurate were successfully synthesized. The structure of geranyl laurate and citronellyl laurate was also verified by the appearance of C=O peak absorption (1745 cm^{-1}) at higher frequency than C=O peak absorption of lauric acid (1707 cm^{-1}). The increase of peak absorption C−O at 1170 cm^{-1} also confirmed the structure of geranyl laurate and citronellyl laurate. This data was consistent with the literature. The intense C=O stretching vibration of ester occurs at higher frequencies (1750 cm^{-1} to 1735 cm^{-1}) than that of carboxyl group (1720 cm^{-1} to 1706 cm^{-1}) and the C−O peak absorption at the 1210 cm^{-1} to 1163 cm^{-1} region [26].

3.4 ^{1}H-NMR and ^{13}C-NMR Spectra of Geranyl Laurate

Spectrum ^{1}H-NMR (500 MHz) of the geranyl laurate (Figure 6) showed the high purity of geranyl laurate. The peaks in the downfield area (δ_H 4.59, 2H, d) represented the proton of C-10 methylene group attached to an electronegative oxygen atom. Doublet multiplicity on C-10 due to the interaction with the proton of C-9 methine group. The vinylic proton at C-9 and C-4 was also observed in the downfield area with triplet multiplicity at region δ_H 5 ppm. The vinylic proton or alkene proton occupied a chemical shift at 4-7 ppm [26]. The vinylic proton at C-9 (δ_H 5.34, 1H, t, J = 7.2 Hz) was less shielded than the vinylic proton at C-4 (5.08, 1H, t, J = 6.9 Hz) because of the presence of an electronegative oxygen atom.

The peak at δ_H 2.29 ppm (2H, t, J = 7.6 Hz) represented the methylene group CH_2 at C-12 next to the carbonyl group. The interaction between protons of C-12 with 2 protons from the methylene group of C-13 gave the triplet multiplicity. The proton of allylic methylene (CH_2)

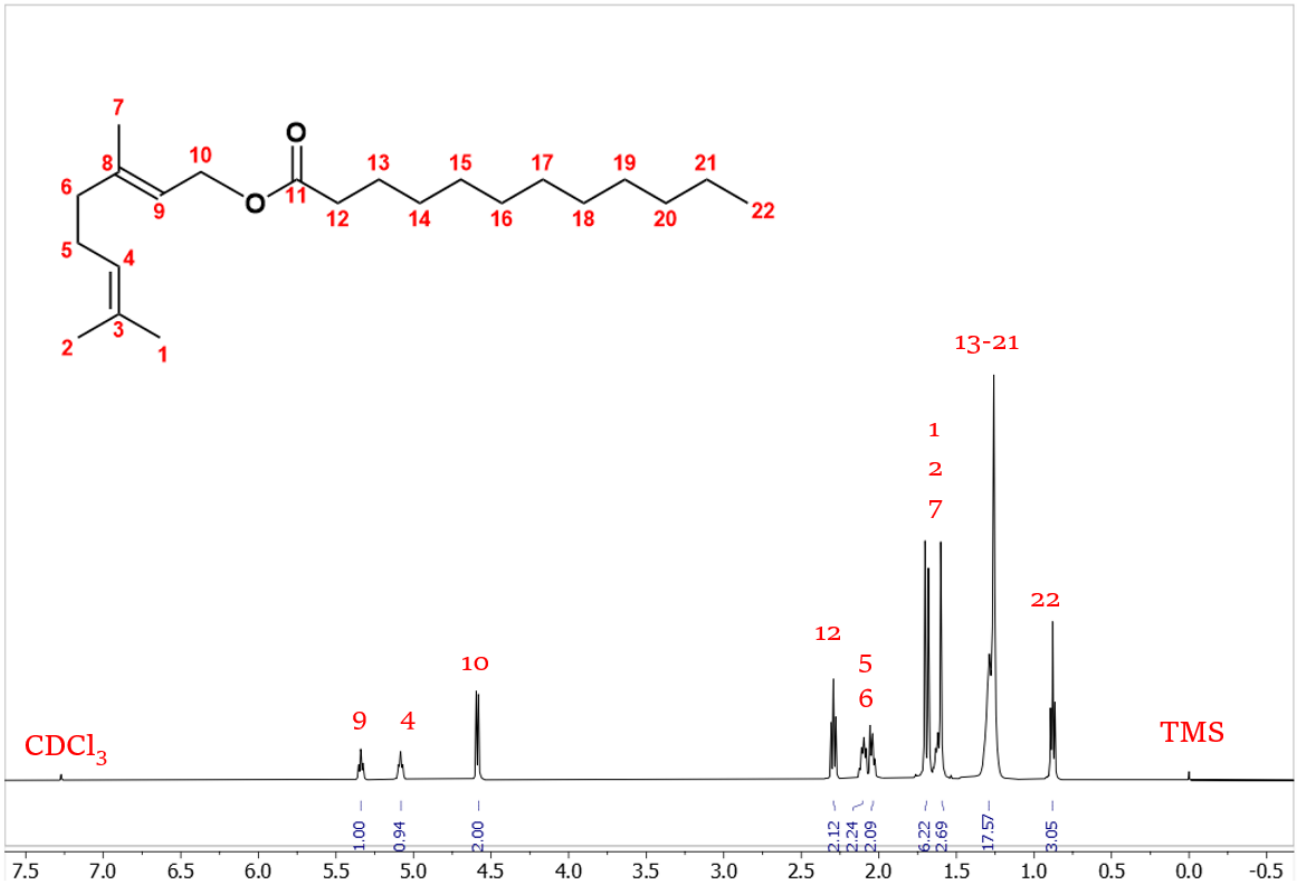


Figure 6. Spectrum ^{1}H-NMR of geranyl laurate.

C-5 and C-6 appeared at upfield area δ_H 2.10 ppm and δ_H 2. 04 ppm, respectively. On the other hand, the protons of allylic methyl C-1, C-2, and C-7 were detected as a singlet peak at δ_H 1.60 ppm (3H, s), 1.68 ppm (3H, s), and 1.70 ppm (3H, s), respectively. The most shielded protons of terminal methyl C-22 appeared as triplets at δ_H 0.88 ppm (3H, t, J = 7.4 Hz).

^{13}C-NMR spectrum of synthesized geranyl laurate is shown in Figure 7. Based on ^{13}C-NMR spectrum of geranyl laurate, there were 22 carbon signals. Three signals at region δ_C 77.04 ppm indicated the signal of $CDCl_3$ as the solvent for NMR analysis. The most downfield peak at δ_C 173.85 ppm exhibited the presence of the ester carbonyl group (C-11). According to Günther, the signal of the carbonyl ester group is within the range of 160-180 ppm [31]. The carbon next to the oxygen atom of ester (C-10) was detected at δc 61.13 ppm. The carbon signal between 60-90 ppm proved the presence of a C-sp3 group that binds oxygen [26].

The signal of vinylic carbon (C-sp2) C-3, C-4, C-8, and C-9 can be seen at δc 131.74, 123.77, 142.01, and 118.47 ppm, respectively. Based on the literature, the signal of alkene carbon appears in the 100-140 ppm area [31]. The C-sp^3 methylene carbon appeared at δc 39.53 (C-6), 34.38 (C-12), 31.91 (C-13), 29.60 (C-14), 29.47 ppm (C-15), 29.33 (C-16), 29.27 (C-17), 29.16 (C-18), 26.31 (C-5), 25.65 (C-19), 25.02 (C-20), and 22.68 ppm (C-21). Terminal methyls were observed in the upfield area at δc 17.65 ppm (C-1 and C-2), 16.43 (C-7), and 14.09 ppm (C-22).

3.5 ^{1}H-NMR and ^{13}C-NMR Spectra of Citronellyl Laurate

Figure 8 displays spectrum ^{1}H-NMR (500 MHz) of the citronellyl laurate. The chemical shift of protons from C-10 δ_H 4.09 ppm (2H, t, J = 7.0 Hz) represented the methylene group in the downfield region due to interaction with the more electronegative oxygen atom. According to Silverstein, the peak of methylene groups that interact with oxygen atoms can be detected at around 3-4 ppm [26]. The neighboring protons (C-9) appeared at δ_H 1.54 ppm (2H, m). The signal of vinylic proton from the methine group C-4 at δ_H 5.09 (1H, t, J = 7.1 Hz) was located in the downfield area due to its proximity to sp2 carbon. The proton of allylic methylen (C-5) was observed at δ_H 1.99 ppm (2H, m, J = 8.4 Hz).

The multiplet signal of the C-8 methine group (δ_H 1.47, 1H, m) indicated the presence of 7 neighboring protons. Proton signals from methylene of C-6 and C14-C21 were observed at δ_H 1.45-1.26 (m, 18H). Methyl signals appeared at

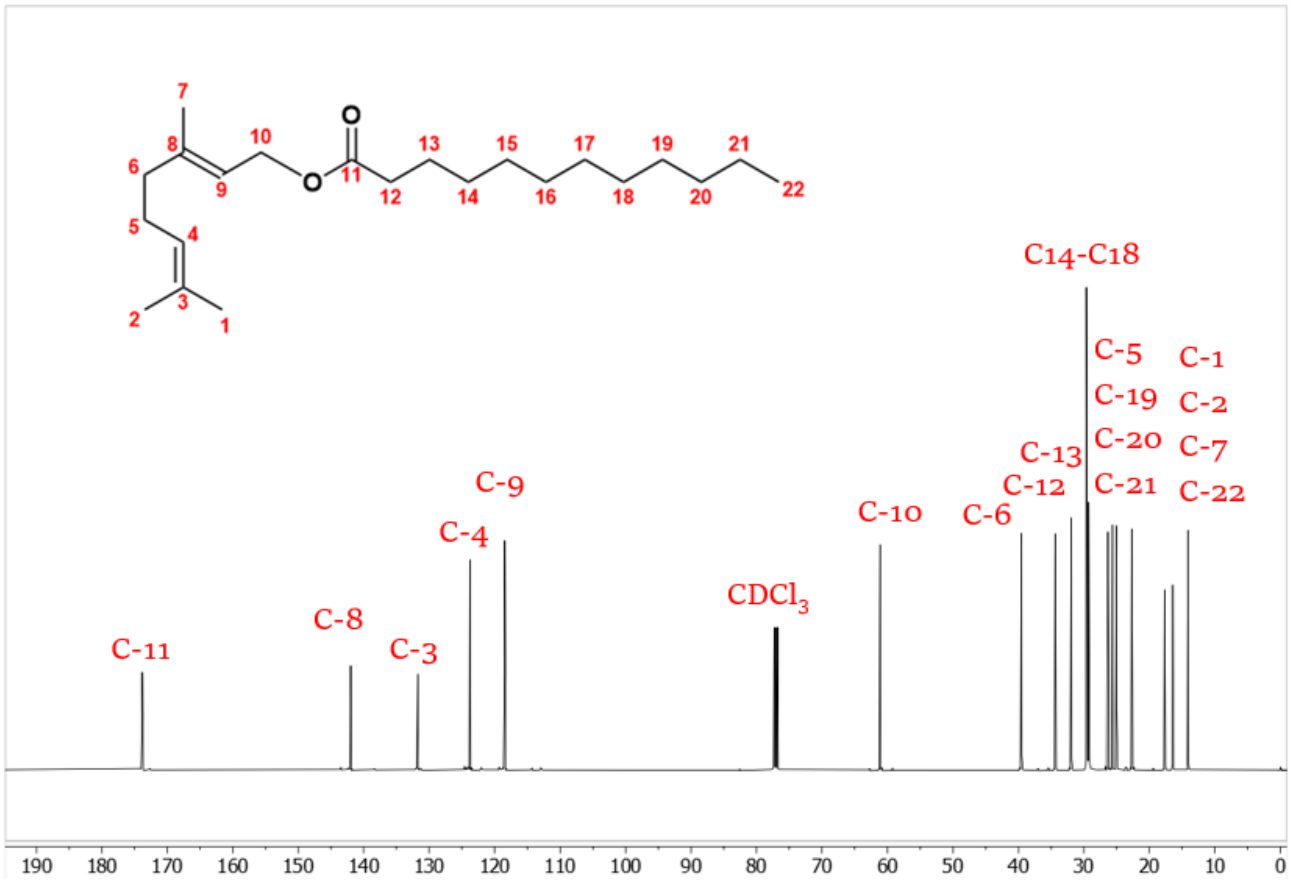


Figure 7. Spectrum ^{13}C-NMR of geranyl laurate

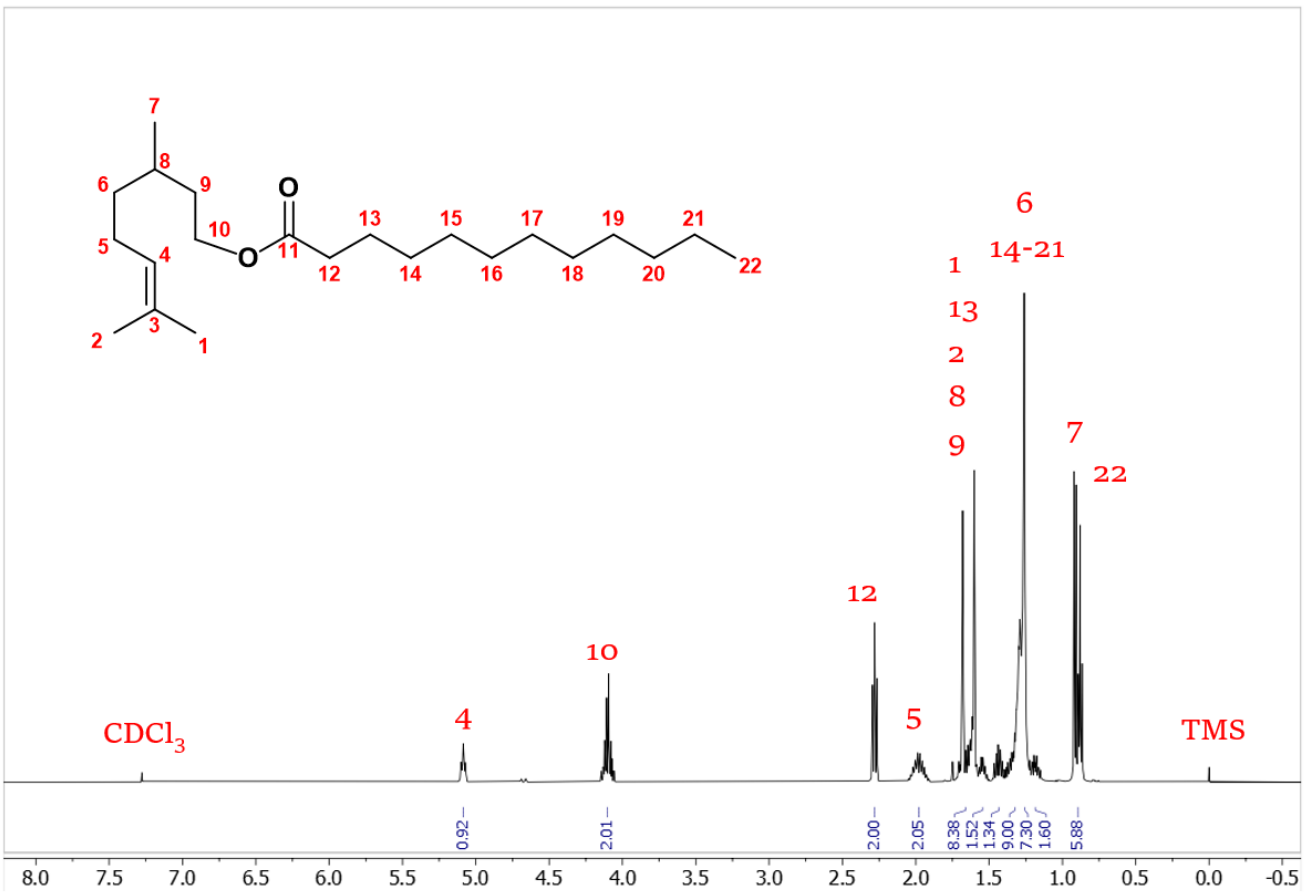


Figure 8. Spectrum ^{1}H-NMR of citronellyl laurate.

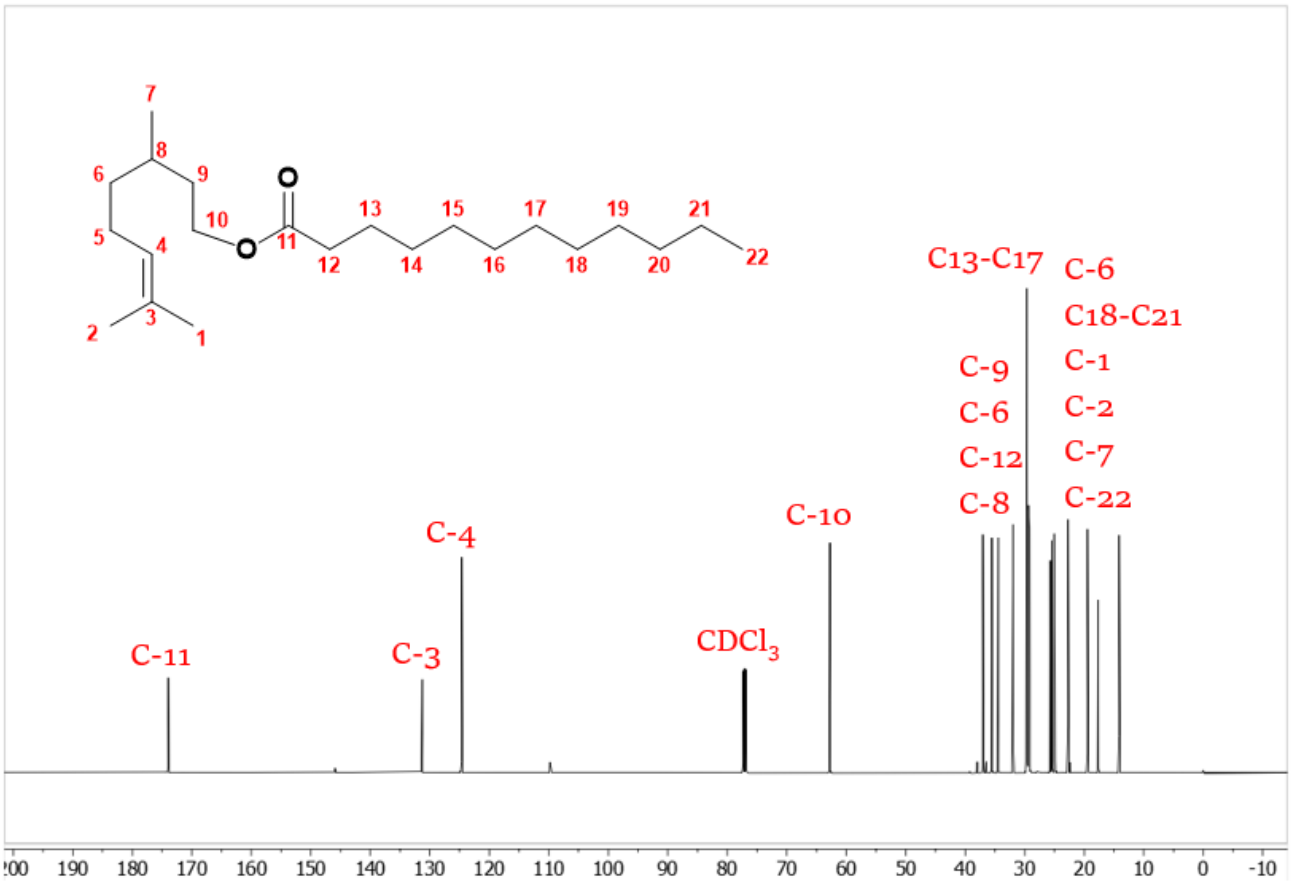
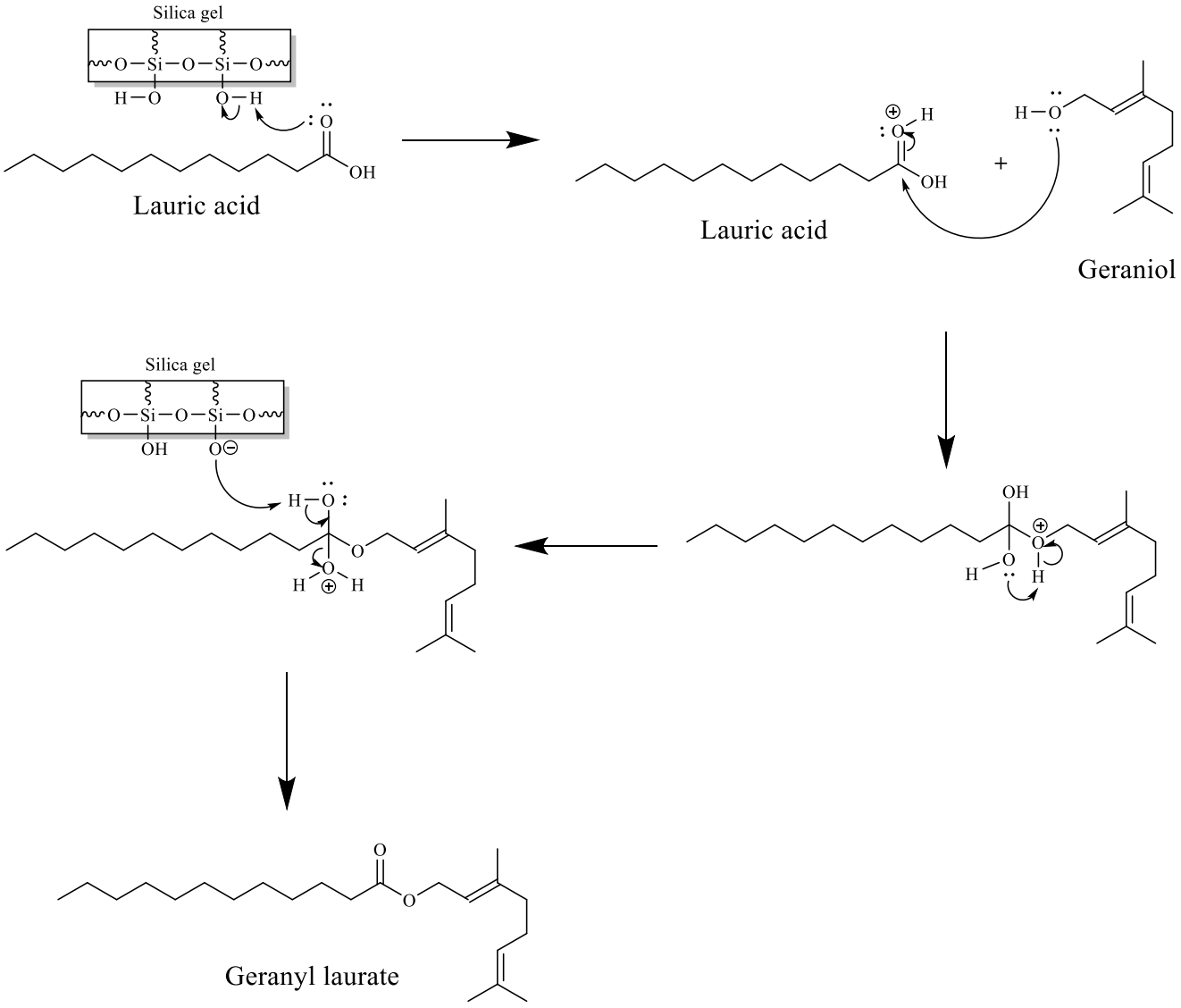


Figure 9. Spectrum ^{13}C-NMR of citronellyl laurate.

δ_H (ppm) 0.88 (3H, t), 0.91 (3H, s), 1.60 (3H, s), and 1.68 (3H, s) belonging to C-22, C-7, C-2, and C-1, respectively.^{13}C-NMR spectrum in Figure 9 confirmed the structure of citronellyl laurate. Similar to geranyl laurate, ^{13}C-NMR spectrum of citronellyl laurate also exhibited 22 carbon signals. The carbonyl ester group (C-11) can be seen in the most downfield area (δc 173.94 ppm) as mentioned by Günther [31]. The presence of an ester group was also verified by the appearance of carbon signal C-10 at δc 62.76 ppm. The signal at δc 124.62 and 131.28 ppm represented the signal of C-sp^2 carbon (C-4 and C-3). The multiple signals of C-sp^3 carbon can be detected at δc 14-37 ppm. The peak at δc 31.96 ppm showed the existence of methine carbon (C-8). The methylene carbon was pointed by the peaks at δc 37.07 (C-9), 35.5 (C-6), 34.35 (C-12), 29.65 (C-13), 29.54 (C-14), 29.52 (C-15), 29.32 (C-16), 29.21 (C-17), 25.72 (C-5), 25.44 (C-18), 25.07 (C-19), 22.72 (C-20), and 19.52 ppm (C-21). The peaks of methyl were displayed at δc 19.44 (C-1 and C-2), 17.65 (C-7), and 14.13 ppm (C-22).

3.6 Mechanism of Esterification with Silica Gel as Catalyst

While not a strong acid, the surface of silica gel can possess some mild acidic sites [32]. These sites might slightly activate the carboxylic acid group, making it a more effective electrophile and potentially contributing to a catalytic effect. The proposed mechanism of the esterification reaction using a silica gel as a catalyst is shown in Scheme 1 for geranyl laurate formation and Scheme 2 for citronellyl laurate formation. In the first step, protonation of the carbonyl oxygen in lauric acid using silica gel as a catalyst gives a delocalized carbocation which improves the carbonyl carbon to a much better electrophile. The carbonyl carbon is vulnerable to nucleophilic attack by the alcohol group (geraniol and citronellol) in the second step. The π bond breaks when a lone pair of oxygen makes a bond with the carbonyl carbon. These π bond electrons ascend to the oxygen and displace the positive charge. This gives us the oxonium ion. An activated complex is produced in the third



Scheme 1. Propose mechanism of geranyl laurate formation using a silica gel.

stage when a proton is transferred from the oxonium ion to one of the OH groups. Subsequent 1,2-elimination of water, in the fourth step, leads to the protonated ester. A lone pair of oxygen forms the π bond which will expel water as a good leaving group. In the last step, deprotonation gives the final product (geranyl laurate and citronellyl laurate).

4. Conclusions

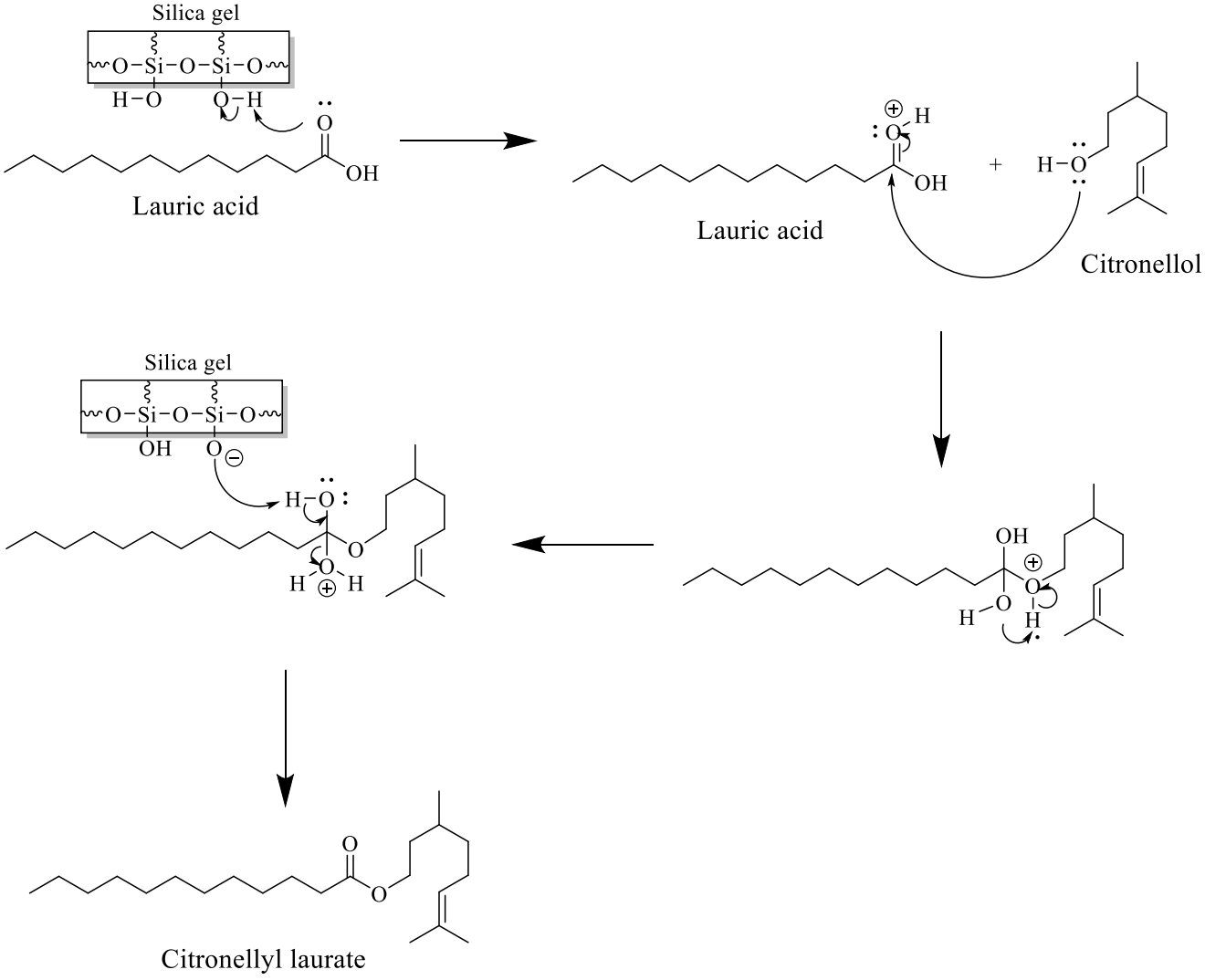
This report explained silica gel was able to catalyze the synthesis of geranyl laurate and citronellyl laurate. Silica gel surfaces have some mild acidic sites. These sites mildly activate the carboxylic acid group, increase its electrophilicity, and catalyze the esterification reaction. The formation of geranyl laurate and citronellyl laurate was proved by TLC, FTIR, ^{1}H-NMR, and ^{13}C-NMR. The yield of geranyl laurate was 18.63% and citronellyl laurate was 12.91% using column chromatography. The purification with liquid-liquid extraction showed a higher yield for geranyl laurate (42.89%) and citronellyl laurate (43.58%). Silica gel-based catalysts can be developed for esterification.

Acknowledgement

The authors would like to express their gratitude to FMIPA Universitas Indonesia for the financial support provided through Hibah Publikasi Pascasarjana, FMIPA, Universitas Indonesia Year 2024.

CRediT Authors Statement

Author contribution: K.N. Rosalina: writing - original draft, writing - review & editing, formal analysis, investigation, and visualization. T. Wukirsari: conceptualization, methodology, and supervision. S. Hudiyono: supervision. S. Handayani: supervision. All authors have read and agreed to the published version of the manuscript.



Scheme 2. Propose mechanism of citronellyl laurate formation using a silica gel.

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