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Synthesis of 2-(4-Allyl-2-Methoxy Phenoxy)-N,N-Bis(2-Hydroxyethyl) Acetamide from the Transformation of Eugenol Isolated from Clove Oil

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Abstract. Eugenol as the main component of clove oil has been isolated through NaOH salting procedure followed by H_2SO_4hydrolysis, n-hexane partitioning and purification with vacuum distillation. 71% (v/v) eugenol was produced used gas chromatography analysis(purity : 97.70%). 2-(4-allyl-2-methoxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound has the potential as antibacterial or substances for medicine in pharmaceutical can be synthesized from eugenol isolated through alkoxylation, esterification and followed by amidase. Alkoxylation was done using Williamson method through NaOH transformation of hydroxyl functional group in eugenol to form sodium eugenolate then with α-monochloroacetate substitution in reflux condition, eugenyl acetate was produced. The acid produced was extracted with ether/Na_2CO_3, followed by recrystallization using hot water and produced 70.52% solid form. Eugenyl acetate esterification with methanol in benzene solvent with H_2SO_4 catalyst in reflux condition produced methyl eugenol acetate liquid with 81.36% of yield. Amidase of methyl eugenol acetate with diethanolamine and sodium methoxide catalyst with methanol solvent in reflux condition. After purification, 2-(4-allyl-2-methoxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound in solid form is produced with 72.99% yield. Eugenol isolated, eugenyl acetate and methyl eugenol acetate had their structures analyzed with FT-IR spectroscopy while 2-(4-allyl-2-methoxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound was analysed using FT-IR and ^{1}H-NMR.

Keyword: Eugenol, etherification, eugenyl acetate, esterification, methyl eugenol acetate, amidase, 2-(4-allyl-2-methoxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide.

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1 Introduction

Clove oil is an essential oil from cloves plant (*Syzygium aromaticum*) in the family *Myrtaceae* which is planted a lot in Indonesia, India and Madagascar (Alma, et, al, 2007). Eugenol is the main component to determine the quality of clove oil, in which the content reaches 70 – 96%

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(Kardiman, 2005). The higher eugenol compound in the clove oil, the higher its quality and value. SNI 06-2387-2006 standard is a minimum of 78% eugenol in clove oil (BSN, 2006).

Eugenol is a phenolic compound with molecular formula of $C_{10}H_{12}O_2$. It contains a number of functional groups such as allyl ($-CH_2-CH=CH_2$), phenol (-OH) and methoxy ($-OCH_3$) which allow eugenol as the base material to synthesize other compounds as eugenol derivatives with various activities and potentially more valuable (Anwar, 1994). Eugenol and the derivatives have strategic roles in various industries like pharmaceutical, cosmetics, food and drinks, cigarette, pesticides, fishery, mining, active packaging and any other chemical industries (Pramod,et al, 2010). Therefore eugenol from clove oil can be used as the raw material for pesticides, also several studies that this compound and the derivatives are effective to control nematode, pathogenic fungi, bacteria, insects as pests or as medicine in pharmacology (Wiratno, 2009).

Eugenol and its derivatives have strategic roles in many industries has led to a big market opportunity that supported by the abundance of clove oil in Indonesia, therefore eugenol isolation and the synthesis of the derivatives need to be developed. With the expansion of agroindustry for eugenol processing and followed by its derivatives, it is expected that Indonesia does not only cover its own industrial needs but also able to become the main supplier for world's needs for eugenol and the derivatives compound. Several studies with eugenol have been done, especially the derivatives compound from eugenol. For examples allyl group transformation from eugenol to become aldehyde in vanillin used as additives in food, also hydroxyl transformation to alkyl, acyl or acetyl from eugenol like methyl eugenol, eugenyl benzoate and acetyl eugenol that can be used as bio-additive material in diesel fuel (Sastohamidjojo, 2004). The synthesis of 4-allyl-2-methoxy-6-amino phenol from eugenol nitration produces 4-allyl-2-methoxy-6-nitro phenol that is followed by reduction of nitro group to become amines. This compound is expected to have functions in medicine for pharmaceutical or for agricultural uses (Sudarma, et al, 2009). Similarly synthesis of amino methyl derivatives compound with anti-cancer activities from the reaction between eugenol with aniline from Mannich reaction (Rudianto, et al, 2014). Several amides and alkanolamides either aliphatic or aromatic derivatives are used widely as antibacterial, emulsifier, intermediates for synthesis of medicine like antibiotic (Dorge, 1982).

Based on the description above, the researcher is interested in synthesizing eugenol derivatives compound through etherification of hydroxyl group in eugenol from clove oil with α-monochloroacetate to produce eugenyl acetate and followed by esterification reaction by methanol to produce methyl eugenol acetate. Next, through amidase using diethanolamide to produce 2-(4-allyl-2-methoxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound.

2. Materials and Methods

Clove oil used was bought from chemical store in Medan for technical grade product. While the other materials, such as: diethanolamine, monochloroacetate acid, NaOH pellet, Na_2CO_3, diethyl ether, HCl 6N, saturated NaCl, chloroform, methanol, silica gel GF_{254}, H_2SO4, $NaOCH_3$, anhydrousNa_2SO_4, n-hexane, benzene are practical grade (P.A.) by E. Merch.

2.1. Eugenol Isolation from Clove Oil

20.8 gram of solid NaOH was dissolved in 200 ml aquadest in a 1 L beaker glass. Next, 100 ml of clove oil was added gradually and stirred continuously with a magnetic stirrer. The mixture was poured into a separatory funnel and was extracted with n-hexane until two layers of solutions were formed. The lower layer (aqueous phase) was hydrolyzed after separation by adding 25% H_2SO_4 until pH=3 was reached. Then it was extracted with n-hexane solvent. The n-hexane fraction was washed with water, dried by adding anhydrous $Na_2SO_4$and filtered. The filtrate was evaporated using a rotary evaporator and eugenol was produced. Then the compound was purified using vacuum distillation. Finally, the distillate produced was analyzed using gas chromatography and FT-IR spectroscopy.

2.2. The Synthesis of Eugenyl Acetate

88 gram (0.041 mol) of eugenol was put into 250 ml Erlenmeyer flask. Then, 14 ml of aquadest and 6 gram (0.15 mol) of solid NaOH were added. The mixture was homogenized by stirring. Next, 6 gram (0.063 mol) of monochloroacetate acid was added, with a continuous stirring, the mixture is heated in a boiling water bath until a solidified mixture was formed. The solid produced was chilled and acidified using HCl 6N until pH $\leq$ 4 was reached. After that, it was extracted with 100 ml of ether, the ether layer was washed with 30 ml of aquadest and extracted with 4 gram of Na_2CO_3 dissolved in 30 ml of aquadest. HCl 6N was added into carbonate solution until pH = 2, and the mixture was chilled, filtered, dried and was recrystallized using hot water. The solid obtained was put to dry in an oven at 50^{o}C. Finally, eugenyl acetate was obtained and it was weighed and analyzed using FT-IR spectroscopy.

2.3. The Synthesis of Methyl Eugenol Acetate

5 gram (0.024 mol) of eugenyl acetate, 10 ml of methanol absolute and 20 ml of benzene were put into a 250 ml of three neck flash and stirred with a magnetic stirrer. A set of reflux equipment was assembled and 2 ml of H_2SO_4(c) was added and stirred at cold state. The mixture was refluxed for 5 hours, then, excess benzene and methanol were evaporated using a rotary evaporator. The precipitate was dissolved into 25 ml of n-hexane and washed twice with 5 ml of aquadest. The n-hexane layer was dried using anhydrous Na_2SO_4 and filtered. The solvent in the

filtrate was evaporated using a rotary evaporator. Methyl eugenol acetate produced was weighed and analyzed using an FT-IR spectrophotometer.

2.4. The Synthesis of 2-(4-Allyl-2-Methoxy Phenoxy)-N,N-Bis(2-Hydroxyethyl) Acetamide.

4 gram (0.018 mol) of methyl eugenol acetate was added into a 250 ml three neck flask, 2 ml (0.020 mol) of diethanolamine was added and stirred. A set of reflux equipment was assembled and 2 gram of CH_3Ona in 10 ml of methanol was added. The mixture was refluxed with continuous stirring for 5 hours. Then, the product was evaporated in a rotary evaporator. The precipitate obtained was extracted with 50 ml of diethyl ether and washed by 5 ml of saturated NaCl for 3 times. The upper layer of the mixture was added with anhydrous $CaCl_2$ and filtered. The filtrate was dried with anhydrous Na_2SO_4 and filtered. The solvent in the filtrate was evaporated using a rotary evaporator. Next, the precipitate obtained, 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide, was weighed and analyzed using TLC and followed by analysis using FT-IR and ^{1}H-NMR spectrophotometer.

3. Results And Discussion

3.1. Eugenol Isolation from Clove Oil

The isolation of eugenol from clove oil has produced 71% of yield with 97.70% purity based on gas-liquid chromatography analysis. The separation of eugenol from the oil was done by the formation of Na-eugenolate salt with the addition of NaOH to eugenol which aims for solubility in polar solvent and the compound can be separated from other non-polar components in clove oil except eugenol. Na-eugenolate was then hydrolyzed to release eugenol by using 25% H_2SO_4 untuk pH = 3 was reached. Eugenol can be separated from the liquid phase by using n-hexane in the extraction process. The physical properties for purified eugenol in vacuum distillation at 111^{o}C and 5 mmHg pressure involves density at 1.0634 g/ml, reflective index of 1.5364 with clove aroma and yellowish color liquid. The reactions occurred during the isolation process were salt formation and followed by hydrolysis with H_2SO_4 (**Figure 1**). FT-IR spectroscopy spectrum of eugenol gave peaks at wavelengths (v) of 3512 cm-1 that shows -OH group, 3010 cm-1 that gives C-H sp2 in allyl and aromatic ring, 2976 cm-1 for C-H sp3 in methoxy group. Then, v = 1641 cm-1 shows C=C bonds in central benzene and allyl group. Furthermore, absorbance band in v = 1300 – 1100 cm-1 is a stretching vibration of C-O-C which is a methoxy with central benzene core (**Figure 2**).

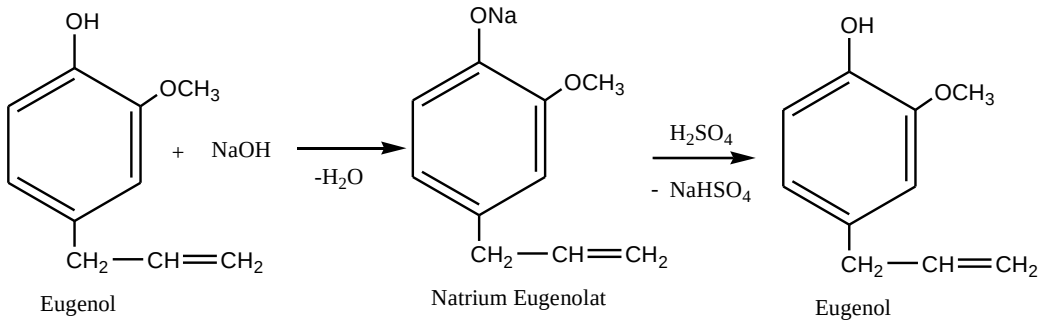

Figure 1. Isolation reaction of eugenol from clove oil

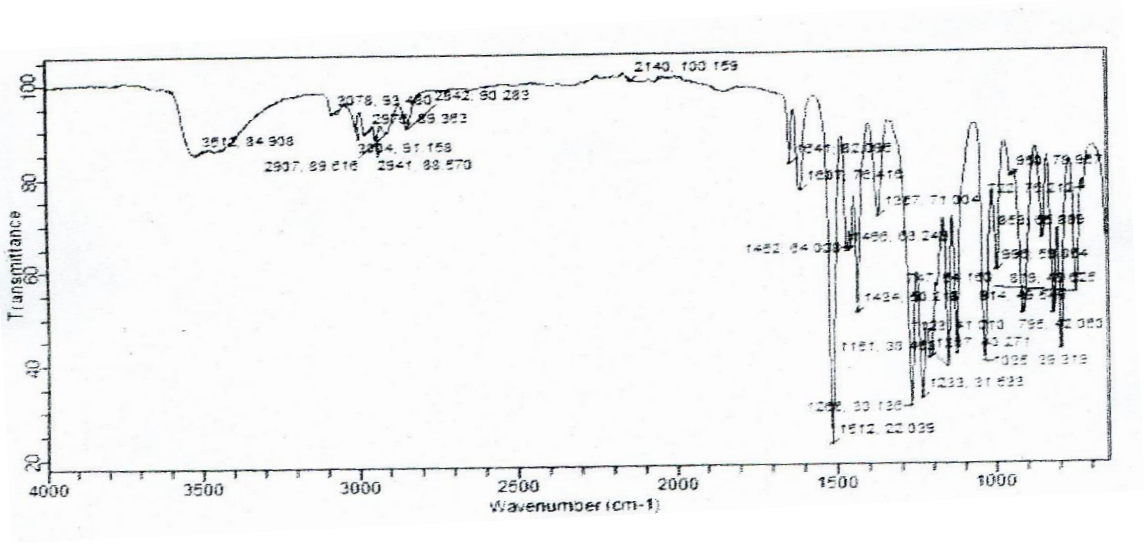

Figure 2. FT-IR spectrum of eugenol isolated from clove oil

3.2. The Synthesis of Eugenyl Acetate

From 6.88 gram, (0.041 mol) of eugenol used in the study, 6.02 gram (70.52%) of eugenyl acetate was formed in white solid form. The reaction for eugenyl acetate synthesis started by the improvement of nucleophilicity from element O in -OH groups from eugenol to become -Ona in Na-eugenoxide that followed by nucleophilic substitution reaction with α-monochloroacetate that produces eugenyl acetate (**Figure 5**). FT-IR spectroscopy spectrum analysis for eugenyl acetate gave expanded peaks at wave number (v) = 3425 cm^{-1} that showed -OH vibration from COOH group of eugenyl acetate. Then the appearance of vibration peak at 1751 cm^{-1} showed C=O vibration in COOH group (**Figure 3**).

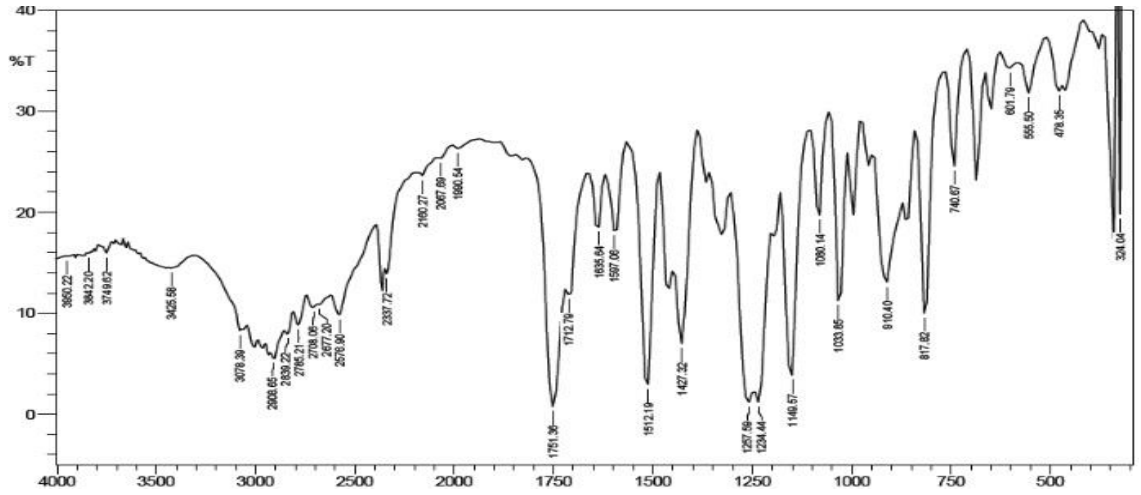

Figure 3. FT-IR spectrum of Eugenyl Acetate

3.3. The Synthesis of Methyl Eugenol Acetate

From 5 gram (0.024 mol) of eugenyl acetate used, 4.335 gram (81.362%) of methyl eugenol acetate in clear yellowish liquid was formed. In this step, methyl eugenol acetate was an intermediate to synthesis amide compound in a low temperature as it is easier to form amide compounds derives from methyl esther than a direct amidase to carboxylate group (Figure 5). FT-IR spectrum of methyl eugenol acetate supports that the compound produced showed a disappearance of -OH group vibration at v = 3425.58 cm-1 when in compare to eugenyl acetate spectrum. Moreover, there were changes of vibrational peaks for C=O group at v=1751.36 cm^{-1} in eugenyl acetate to 1767.53 cm^{-1}. This is dues to the substitution of the functional group attached to C=O to OCH_3 from OH. The energy needed to vibrate C=O group from $CooCH_3$ is bigger than that in COOH therefore the wave number in C=O from $COOCH_3$ is bigger (**Figure 4**).

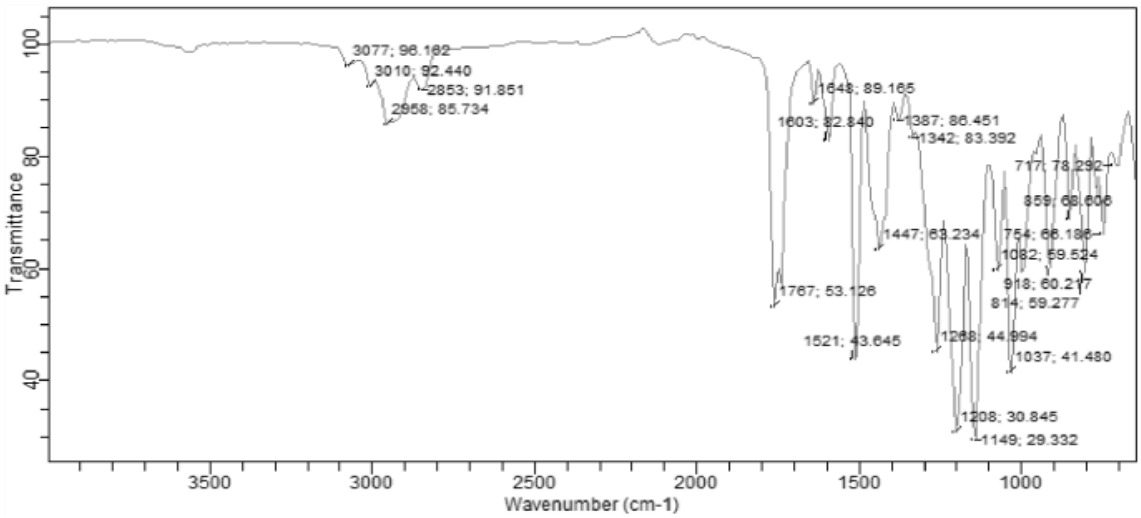

Figure 4. FT-IR spectrum for methyl Eugenol Acetate

3.4. The Synthesis of 2-(4-Allyl-2-Methoxy Phenoxy)-N,N-Bis(2-Hydroxyethyl) Acetamide

From 4 gram of methyl eugenol acetate used, 3.876 gram (72.99%) of 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound was formed which is a yellow solid. In amide reaction, the carboxylic group from eugenyl acetate was transformed to methyl ester. Therefore, amination was easier in order to produce amide compounds such as 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound (**Figure 5**). The amidase of carboxylate group normally takes place at high temperature with decarboxylation occur. FT-IR spectroscopy analysis of the compound synthesized showed the disappearance of C=O vibration group from ester at 1752.38 cm^{-1} wavelength to 1591.91 cm^{-1} in amide and supported by the reappearance of 3487.30 cm^{-1} wavelength which show the vibration of -OH group from ethanolamine (**Figure 6**).

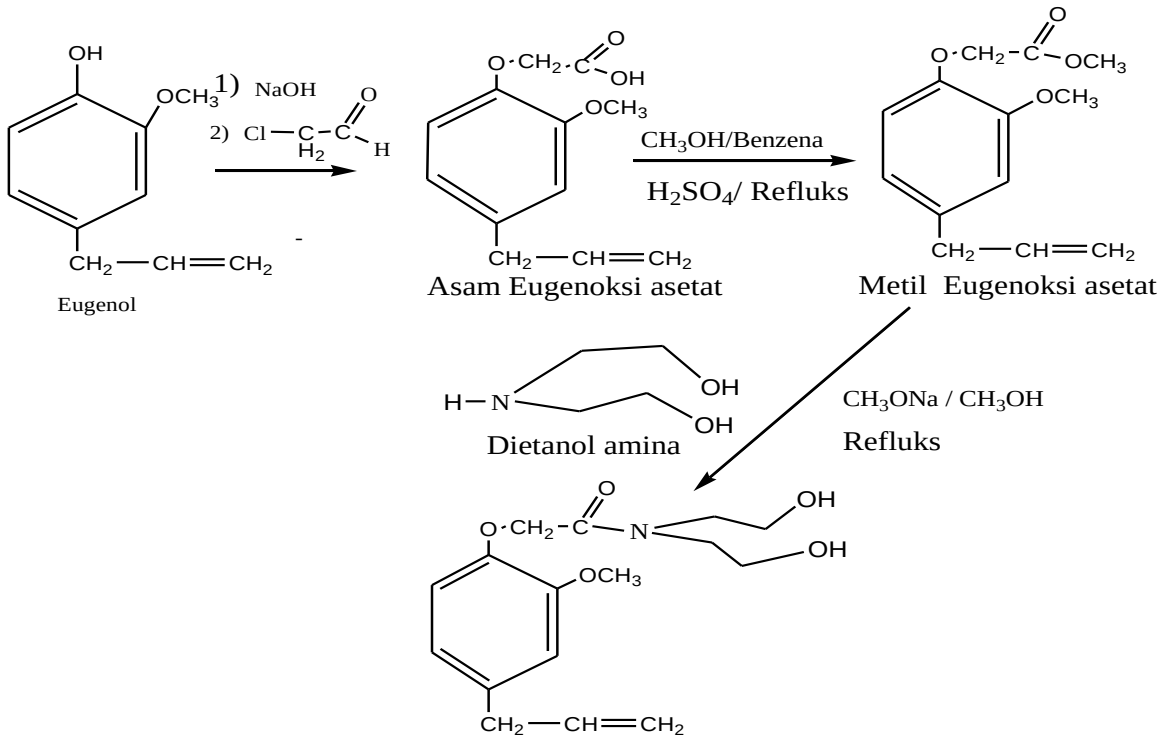

Figure 5. The synthesis reaction of 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound from eugenol

^{1}HNMR spectroscopy analysis of 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound (**Figure 7**) showed 8 protons environments with chemical shifting (δ) of : (1) δ = 2.7 ppm (t) for 4 protons -CH_2-N, (2) δ = 3.6 ppm (t) for 4 protons -CH_2-OH, (3) δ = 3.8 ppm (s) for 3 protons -O-CH_3, (4) δ c = 4.3 ppm (s) for 2 protons -CH=O, (5) δ = 4.8 ppm (s) for 2 protons -OH, (6) δ = 5.0 ppm (m) for 2 protons of allyl (-CH2-), (7) δ = 5.9 ppm (m) for 1 proton of allyl (-C=CH-) and δ = 6.8 ppm (m) for 3 protons of unsubstituted central benzene

core. The chemical shifting of allyl groups were multiplet as protons were coupling in allyl groups and therefore they form multiple signals. Similarly, this happened to protons in element C that attached to central benzene.

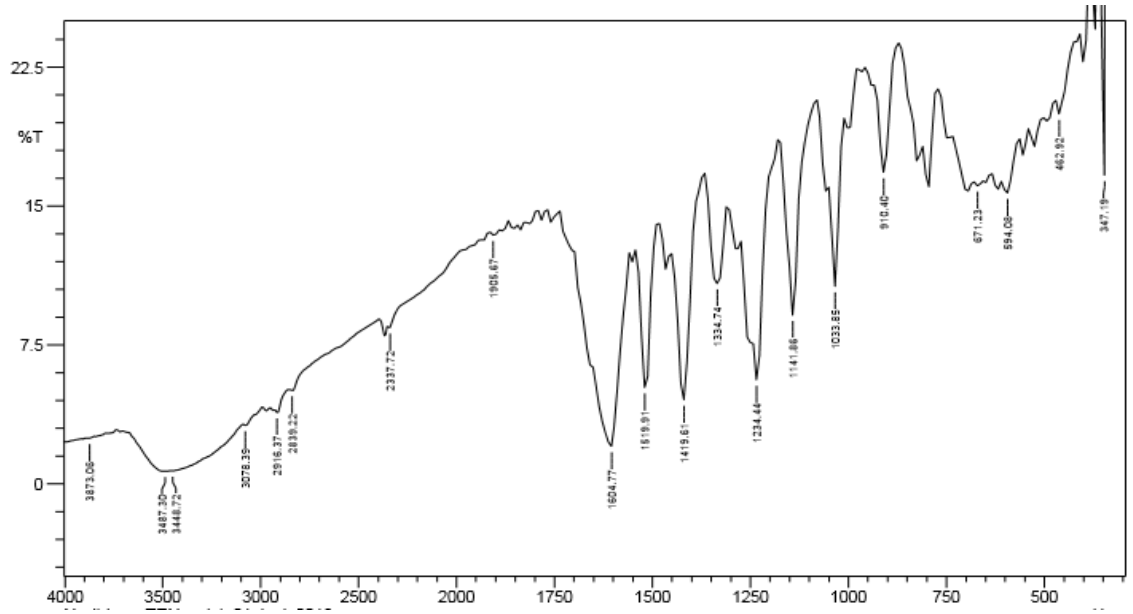

Figure 6. FT-IR spectrum for 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide

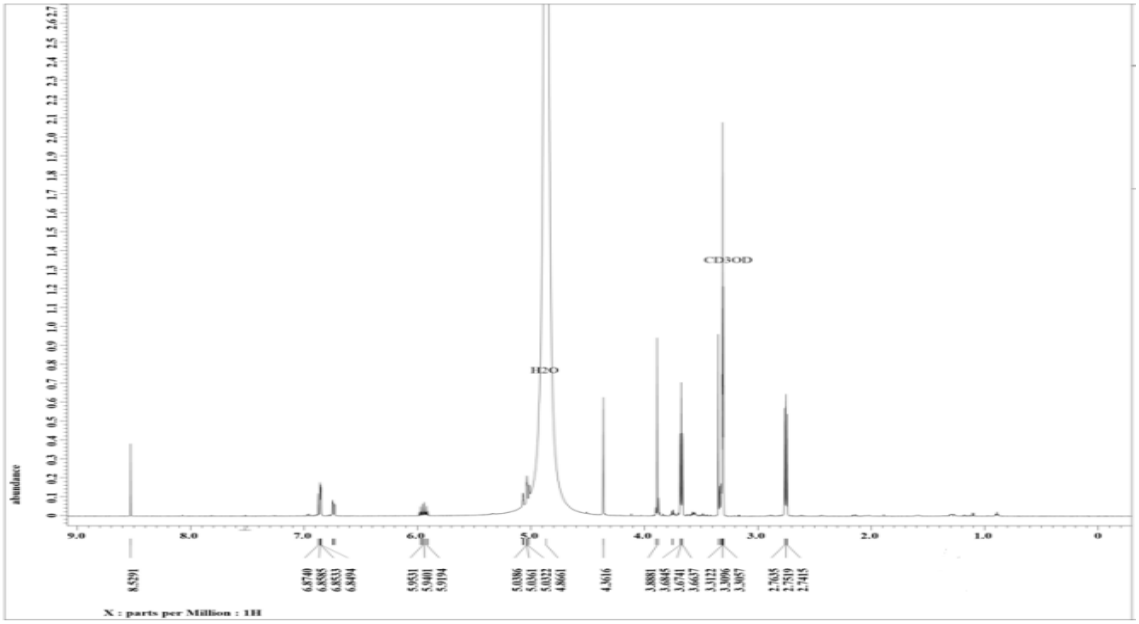

Figure 7. [1]HNMR spectrum for 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide

4. Conclusion

71% of eugenol can be isolated from clove oil and 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound can be synthesized from eugenol with 3 steps, such as alkoxylation, esterification and amidase. This can be concluded that:

1. The synthesis of eugenyl acetate from alkoxylation of eugenol in NaOH solution and with Williamson etherification reaction with α-monochloroacetate has given 70.52% yield.

2. Methyl eugenol acetate synthesized through the esterification of eugenyl acetate with methanol in benzene and H_2SO_4 (c) catalyst in reflux condition has produced 81.36% of yield.

3. Amidase of methyl eugenol acetate was done to produce 2-(4-allyl-2-metxy phenoxy)-N,N-bis(2-hydroxyethyl) acetamide compound with diethanolamine in methanol with $NaOCH_3$ catalyst and has yielded 72.99% of the compound.

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