Synthesis of 4-(2-Chloropropyl)-2-Methoxyphenol from Eugenol and Ketoprofen by Hydrohalogenation Reaction using HCl Catalyst

A Yugatama¹, A H Ramelan², R Niruri¹ and N F Aisiah¹

¹Pharmacy Department, Faculty of Mathematics and Natural Sciences, SebelasMaret University, Indonesia
²Physics Department, Faculty of Mathematics and Natural Sciences SebelasMaret University

Email: adiyugatama.apt@gmail.com

Abstract. Eugenol is a phenolic compound that has hydroxy and allyl groups in its structure. Eugenol can be transformed into its derivative through esterification and addition reactions. Esters can be synthesized through Fischer esterification reactions using concentrated HCl as catalyst. The use of HCl as catalyst in esterification of eugenol may form 4-(2-chloropropyl)-2-methoxyphenol from hydrohalogenation reaction between the allyl eugenol and HCl. The purpose of this study was to determine the formation of a 4-(2-chloropropyl) 2-methoxyphenol compound as a result of hydrohalogenation reaction eugenol and ketoprofen using HCl as catalyst and to find out the identification of the compound. The results showed that synthesis of 4-(2-chloropropyl)-2-methoxyphenol compound as eugenol derivative was formed by hydrohalogenation reactions. The compound was identified based on the results of the analysis using FTIR, GC-MS, and HPLC instruments.

1. Introduction

Essential oils are bioactive compounds derived from plants. Essential oils have been widely used because of the various benefits they have such as fragrances, flavorings in food and beverage products [1]. Some essential oils have also been used in the medical field because of the pharmacological activities they have. One of the many essential oils found in Indonesia is clove oil (Syzygium aromaticum). The main content (70-96%) of clove oil is eugenol [2]. Eugenol has activities as analgesics, local anesthetics, anti-inflammatory, anti-oxidant, antibacterial and antifungal [3, 4, 5, 6].

Eugenol is a phenolic compound that has allyl (-CH₂-CH=CH₂), hydroxy (-OH), and methoxy (-OCH₃) groups. These functional groups make eugenol can be transformed into its derivate through various reactions such as esterification in its hydroxy group and addition in its vinyl group (-CH = CH₂) [7]. The hydroxy group of eugenol can be modified into an ester compound through the Fischer esterification reaction. Fischer Esterification is an ester formation reaction using a strong acid as catalyst (HCl and H₂SO₄) [8].

The use of HCl as catalyst in the esterification reaction is to activate the carbonyl group on ketoprofen through a protonation process so that it can be reacted with eugenol to form a ketoprofen eugenol ester compound, but HCl can also react with the vinyl group in eugenol to form alkyl chloride compounds through addition reactions. This reaction is also referred to as hydrohalogenation reaction[9]. The hydrohalogenation reaction of HCl in vinyl eugenol forms a 4-(2-chloropropyl)-2-
methoxyphenol compound. Addition reactions to vinyl eugenol groups can forming eugenol derivate namely 4-(2,3 dichloropropyl)-2-methoxyphenol compound [10]. This proves that the vinyl eugenol group can undergo an addition reaction.

The antimicrobial effects of phenolic compounds can be increased by the addition of halogen atoms in their structure. The addition of halogen atoms can increase eugenol’s lipophilicity. This is important in increasing the antimicrobial activity of eugenol derivative compounds [11]. The aim of this study were to synthesize and identify the compounds formed in the hydrohalogenation reaction process of eugenol and ketoprofen using HCl as catalyst and determine the possibility of the formation of 4-(2-chloropropyl)-2-methoxyphenol compounds which may have potential activity as a new drug.

2. Experimental

2.1. Materials
Eugenol (PT. Indesso), Ketoprofen (PT. KalbeFarma), HCl p.a, methanolp.a, N-Hexanp.a, ethyl acetate p.a, chloroformp.a, petroleum ether, sodium bicarbonate, aquadest, analytical scale (Mettler Toledo), micropipette (Thermo), UV-Vis spectrophotometry (Genesys™), FTIR spectrophotometer (Shimadzhu FTIR-8201 PC), HPLC (Waters) with UV-Vis detector and C-18 column, GCMS (Shimadzu QP-2010 SE) with Rtx-5MS column.

2.2. Synthesis of 4-(2-Chloropropyl-2-Methoxyphenol)
2.2.1. HCl
2.2.2. Synthesis of 4-(2-Chloropropyl-2-Methoxyphenol)
2.2.3. Identification of Synthesis Product
2.3. Identification of Synthesis Product
2.3.1. FTIR
Sample was dropped on 200 mg KBr pellets. The sample was analyzed in the mid infrared area (4000–400 cm⁻¹). FTIR spectra results were analyzed based on the functional groups contained in the compound.

2.3.2. GCMS
Sample was analyzed using helium gas as mobile phase and Rtx-5MS column (30 m x 0.25 mm). The column temperature was programmed from 80°C to 300°C. The rate of increase in temperature was 10°C/minute. The ion source temperature was set at 250°C and the interface temperature was 300°C. GC-MS spectra was analyzed based on the fragmentation formed.

2.3.3. HPLC
100 mg sample was dissolved in 10 mL of methanol. The solution was diluted with methanol to obtain a sample concentration of 10 μg/mL. The sample was analyzed using C-18 column (150 mm x 4.6 mm) as stationary phase and methanol:water (65:35) as the mobile phase with flow rate of 1 mL/min. The sample injection volume was 20 μL. The detector used was a UV-Vis detector at 261 nm.

3. Result and Discussions
3.1. Synthesis of 4-(2-Chloropropyl-2-Methoxyphenol)
double bond which have the most hydrogen atoms [12]. The mechanism of the hydrohalogenation reaction is presented in Figure 1.

The double bond in vinyl group of eugenol is a nucleophile that can bind with hydrogen atoms from HCl. H atom from HCl will bind to C atoms which have more hydrogen atoms according to Markovnikov's rules and form more stable carbocations on secondary carbon atoms. The more substituents in the carbocation, more stable the carbocation will be [13]. Cl atom from HCl which is a strong nucleophile will bind to positively charged carbocations. The result of the synthesis obtained was 5.744 ± 0.116 g samples in the form of liquid that was not soluble in water, but soluble in organic solvents such as ethanol, methanol, and chloroform.

![Figure 1](image1.png)

**Figure 1.** The reaction mechanism of 4-(2-chloropropyl)-2-methoxyphenol compounds

3.2. Identification of Synthesis Product
3.2.1. FTIR

The FTIR spectrum of the sample (Figure 2) shows the presence of C-Cl bonds which is characterized by stretching vibration in the absorption area of 800 - 400 cm\(^{-1}\), namely at 721 cm\(^{-1}\). The absorption peak at the area of 3517 cm\(^{-1}\) shows the presence of O-H vibrations which have absorption areas at 3550 - 3500 cm\(^{-1}\). Absorption in 1275 cm\(^{-1}\) indicates the presence of vibrations of C-O phenol. The presence of aromatic groups in the sample is characterized by absorption in the area of 3100-3000 cm\(^{-1}\) which shows stretching vibration of = CH aromatic at 3062 cm\(^{-1}\) and is supported by absorption at 1453 cm\(^{-1}\) which indicates the presence of C = C aromatic bond [14].

![Figure 2](image2.png)

**Figure 2.** FTIR Spectrum of 4-(2-Chloropropyl)-2-Methoxyphenol
3.2.2. GCMS

Based on the GC-MS chromatogram profile (Figure 3) there are three dominant peaks that appear at the retention time of 7.648; 10.211; and 17.603 with a percentage area of 75.14%, 6.24% and 14.66%, respectively. The peaks at 7.648 and 17.603 minutes showed the results of analysis with fragmentation patterns that corresponded to eugenol and ketoprofen as the starting material of the synthesis process with m/z values of 164 and 254 corresponding to the molecular mass (Mr) of eugenol and ketoprofen.

The peak at 10.211 minute has an m/z value of 200. Spectral data shows molecular ion peaks at m/z 200 followed by fragmentation peaks at m/z 165, 137, 122, 94 and 77. The pattern of fragmentation from the peak indicates the formation of 4-(2-chloropropyl)-2-methoxyphenol compounds with the molecular formula C_{10}H_{13}ClO_2. The compound is a derivative compound of eugenol as a result of the hydrohalogenation reaction of eugenol with HCl. The m/z 200 value is in accordance with Mr of 4-(2-chloropropyl)-2-methoxyphenol.

![Figure 3. GCMS Chromatogram of Synthesis Product](image)

![Figure 4. Mass Spectrum of Eugenol (A), Ketoprofen (B), and 4-(2-Chloropropyl)-2-methoxyphenol (C)](image)
3.2.3. HPLC

The HPLC chromatogram (Figure 6) showed that there were 2 peaks with a retention time that resembles the starting material of synthesis, ketoprofen and eugenol. There was a new peak that appears at the retention time of 20.786 minute. The peak was the peak of the compound from the reaction formed in the synthesis process, namely 4-(2-chloropropyl)-2-methoxyphenol with an area of 25.305. Based on the results of the analysis using Chemdraw, 4-(2-chloropropyl)-2-methoxyphenol compounds have a greater partition coefficient (LogP) than eugenol which is 2.77. This compound is more lipophilic than eugenol. The addition of halogen atoms to the structure of eugenol will increase the lipophilicity of derivative compounds [11].
4. Conclusion

4-(2-chloropropyl)-2-methoxyphenol compounds can be synthesized as a result of eugenol hydrohalogenation reaction. Identification of 4-(2-chloropropyl)-2-methoxyphenol compounds based on data from FTIR analysis shows the presence of C-Cl bond at 721 cm$^{-1}$, -OH vibration at 3515 cm$^{-1}$, -CO absorption at 1269 cm$^{-1}$, and absorption of C=C aromatic at 1453 cm$^{-1}$, analysis using GC-MS shows peaks with m/z of 200 and fragmentation patterns that correspond to fragmentation of 4-(2-chloropropyl)-2-methoxyphenol compounds, the HPLC chromatogram shows the appearance of a new peak that is different from the starting material used.

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References

[1] Rau JS and Karuppayil SM 2013 J. Indcrop. 62 250-264
[2] Cortes-Rojas D F, Souza C R F and Oliveira W P 2014 Asian Pac. J. Trop. Biomed. 4(2) 90-96
[3] Farias MD, Oliveira PS, Dutra FSP, Fernandes T J, Pereira C M P, Oliveira S Q, Stefanello FM, Lencina C L and Barschak A G 2014 J. Pharm. Pharmacol. 66(5) 733–746
[4] Hemalatha R, Nivetha P, Mohanapriya C, Sharmila G, Muthukumaran C and Gopinath M 2016 J. Food Sci. Technol. 53(2) 1189-1198
[5] Thosar N, Basak S, Bahadure RN and Rajurkar M 2013 Eur. J. Dent. 7(suppl 1) S71-S77
[6] Venkadeswaran K, Thomas PA and Geraldine P 2016 Biomed. Pharmacother. 80 276–288
[7] Wang Y, Wang X, Xie Y and Zhang K 2018 Cellulose 25 3703-3731
[8] Alhassan G, Merza J and Ghenim R 2018 J. Chem. Pharm. Res. 10(10) 71-79
[9] Solomons TWG and Fryhle CB 2011 Organic Chemistry (New Jersey: John Wiley & Sons Inc.)
[10] Heredia D A, Larghi E L and Kaufman T S 2016 Eur. JOC 2016(7) 1397-1404
[11] Martins RM, Farias MD, Nedel F, Pereira C M P, Lencina C and Lund R G 2016 Med. Chem. Res. 25 2360-2367
[12] Esfandiarfard K, Mai J and Ott S 2017 J. Am. Chem. Soc. 139(8) 2940-2943
[13] Sudarma IM, Yuanita E and Suana IW 2013 *Indo.J.Chem.* **13**(2) 181-184

[14] Stuart B. 2004 *Infrared Spectroscopy: Fundamental and Applications* (New Jersey: John Wiley & Sons)