



Unexpected Dimer from Demethylation Reaction of Eugenol under Acidic Conditions

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Abstract. Eugenol is an alkenyl phenol compound obtained as an essential oil from different parts of the clove such as its leaves and flowers. The essential oil from cloves can contain up to 90% eugenol, which is mainly responsible for its aroma. Eugenol is an interesting compound due to its simplicity and richness in functionalities, making it a valuable building block in synthesis. One of the key steps in eugenol transformation is demethylation to produce a hydroxycavicol. Demethylation is commonly carried out using a nucleophilic or an acidic method. In this study, a simple yet reliable nucleophilic method for demethylation using lithium chloride (LiCl) was attempted. The product was characterized by NMR, FTIR and HRMS spectroscopy. The absence of a methoxy signal at 3.5-4 ppm in the ^1H NMR spectrum suggests that demethylation was successful. The HRMS result showed m/z 149.0596, confirming the formation of product. The demethylation reaction under acidic conditions formed a dimer of eugenol with the methoxy group still intact. This was supported by the ^1H NMR data, which showed methoxy signals at 3.85 and 3.82 ppm and integration in the aromatic region, which suggests a dimer structure.

Keywords: clove essential oil; demethylation; dimerization; eugenol; natural products.

1 Introduction

The clove is a traditional spice that has been cultivated in eastern Indonesia for centuries. Cloves have a characteristic aroma and originate from the flower buds of a plant in the family of Myrtaceae, called *Syzygium aromaticum*, which is native to the Maluku Islands, Indonesia. Its essential oil can contain up to 90% of eugenol, an aromatic compound mainly responsible for the aroma of the clove [1].

Eugenol is a potential building block for several biologically active compounds, such as an hepatoprotective Sylibinin [2] and aromatic vanillin [3]. Eugenol possesses conjugated terminal alkenyl groups that can be converted by oxidation or reduction to dienophile and precursor in olefin metathesis [4]. Compounds with alkenyl phenol moiety and its derivatives have been used in developing

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microelectronic devices, thermo copolymers and other advanced materials. This compound has also been used in the modification of co-monomers in polymer synthesis. Addition of a small amount of alkenyl phenol into a growing polymer produces a polymer that has better resistance to light [5].

Due to its abundance and cheap supply from renewable sources, transformations of eugenol into many compounds have been developed. One of the key steps in eugenol transformation is a simple but reliable method for demethylation, which provides hydroxycavicol units. Hydroxycavicol or 4-allylcatechol is a chemical compound with high antioxidant property that is naturally found in the leaves of the herbal plant *Piper betle* Linn [6,7].

Demethylation of aryl methyl ethers is commonly done using nucleophilic and acidic methods. Among the reagents reported for the demethylation of methyl ether are Lewis acids, such as aluminium trichloride (AlCl_3) and ethyl silane (EtSH) [8], lithium chloride (LiCl) [9], boron tribromide (BBr_3) [10] and lithium iodide (LiI) [11].

2 Experiments

The experiments, which were sensitive to moisture or involving sensitive compounds, were carried out under a positive pressure of nitrogen and in a flame-dried apparatus equipped with a rubber septum sealed with parafilm. The reaction mixtures were stirred with teflon-coated magnetic stirring bars unless otherwise stated. All experiments were monitored by analytical thin-layer chromatography. Solvents were removed using a rotary evaporator under ~ 30 mmHg of pressure and heated with a water bath at 30°C or higher.

2.1 Materials

Eugenol was obtained from PT. Indesso Utama Kencana and used without further purification. Sodium hydroxide and ammonium nitric were obtained from Sigma Aldrich and prepared as 5M solution. HBr solution (48%), glacial acetic acid, lithium chloride, dimethyl formamide, sodium sulphate anhydrate and sodium carbonate were obtained from Sigma Aldrich. The solvents, i.e. *n*-hexane, ethyl acetate and dichloromethane, were obtained from Merck and freshly distilled prior to use.

2.2 Instruments and Equipment

Infrared spectra were obtained on a Shimadzu IR Prestige-21 FTIR spectrometer. Solid samples were analyzed as transparent KBr pellets, while liquid samples were either examined directly without solvent between NaCl salt plates or as a solution in dichloromethane using NaCl liquid cells. Mass

spectrometry was recorded on a Waters LCT XE ESI-TOF (Electrospray Ionization Time of Flight) spectrometer. MS and HRMS are stated in units of mass of charge ratio (m/z).

Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy was conducted on an Agilent DD2 and JEOL ECA 500 MHz NMR spectrometer. Chemical shifts are reported as δ with reference to tetramethylsilane (δ 0.00) in units of parts per million (ppm). The deuterated solvent used in the measurement was chloroform-*d* (CDCl_3), which provided the residual solvent signal as internal standard (^1H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.04, triplet).

Multiplicities are stated as: s (singlet), d (doublet), m (multiplets), br (broad), dd (doublet of doublets), and ddt (doublet of doublet of triplets). Coupling constants (J) are indicated in Hertz (Hz). The number of protons (n) in the spectrum for a given resonance is denoted by $n\text{H}$.

2.3 Procedure

2.3.1 Demethylation of Eugenol using LiCl

Eugenol (7 mL, 45 mmol, 1 equiv.) was dissolved in 49 mL dimethylformamide. Lithium chloride (3.9 g, 91 mmol, 2 equiv.) was then added, followed by refluxing the reaction mixture for 48 hours under positive flow of nitrogen. After completion, 10 mL of water was added and the reaction mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried using sodium sulphate anhydrate, filtered through filter paper, and the dichloromethane was removed using rotary evaporator. To obtain the reaction product, the crude mixture was purified by passing through a column chromatography using *n*-hexane-ethyl acetate (9:1) as eluent. The isolated product was a white solid (1.353 g, 18.1%). Rf *n*-hexane-ethyl acetate (8:2) = 0.37; UV 244 and 286 nm; ^1H -NMR (500 MHz, CDCl_3) δ 6.82 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 1.4 Hz, 1H), 6.63 (d, J = 8.6 Hz, 1H), 5.92 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.07 (dd, J = 13.1, 5.7 Hz, 1H), 3.26 (d, J = 6.7 Hz, 2H); ^{13}C -NMR (125 MHz, CDCl_3) δ 143.3, 141.5, 137.6, 133.5, 121.2, 116.0, 115.7, 39.8; IR(KBr) 14421, 1521, 1606, 3356, 3329 and 3300; ESI-HRMS (M-H, $\text{C}_9\text{H}_{10}\text{O}_4$), calculated: 149.0603, obtained: 149.0596.

2.3.2 Demethylation of Eugenol using HBr

Eugenol (2.3 mL, 14.8 mmol, 1 equiv.) was dissolved in a mixture of glacial acetic acid (25 mL) and bromic acid 48% (25 mL). The mixture was stirred at ambient temperature for 5 minutes. After that, the temperature was increased to

110 °C and the stirring was continued for 30 minutes. After completion, the reaction mixture was poured into 25 mL of cold water. After that, 25 mL of saturated sodium carbonate solution was added. The mixture was extracted with ethyl acetate (3 x 50 mL), the combined organic layers were dried using sodium sulphate anhydrate and filtered, and the solvent was removed under vacuo. The crude product was purified by column chromatography with dichloromethane-*n*-hexane (3:7) as eluent. The product obtained was a yellowish liquid (27 mg, 1.1%). ¹H NMR (500 MHz, CDCl₃) δ 6.80 (d, *J* = 1.4 Hz, 1H), 6.67 (s, 1H), 6.78 (d, *J* = 1.4 Hz, 1H), 6.54 (s, 1H), 3.13 (d, *J* = 9.7 Hz, 2H), 2.97 (d, *J* = 9.6 Hz, 2H), 5.64 (m, 1H), 5.46 (m, 1H), 4.27 – 4.08 (m, 4H), 3.85 (s, 3H), 3.82 (s, 3H).

3 Result and Discussion

3.1 Demethylation with LiCl

Demethylation with LiCl is based on a nucleophilic reaction, where oxygen atoms in the methoxy group act as nucleophiles, while the lithium chloride is an electrophile that accepts electrons. In this case, LiCl served as activator of the methoxy group. The TLC profile of the reaction showed only one major product. Demethylation of eugenol **1** using LiCl to form hydroxycavicol **2** is shown in Figure 1.

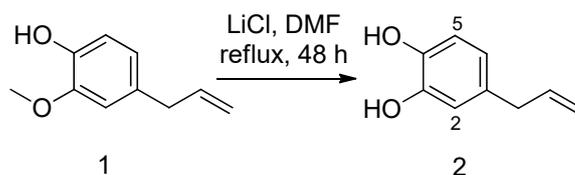


Figure 1 Demethylation reaction of eugenol with LiCl.

However, upon isolation and purification by chromatography, a low yield was obtained (18.1%) due to the unstable nature of the hydroxycavicol product. This is expected with the natural antioxidant property of the hydroxycavicol compounds [7]. Characterization of the pure product was carried out by NMR spectroscopy, of which the result is shown in Table 1. The proton NMR data showed 3 signals in the aromatic region, which correspond to trisubstituted aromatic compounds. The signals at 6.82 ppm and 6.63 ppm were observed as doublets with ortho coupling while the signal at 6.73 ppm appeared as a doublet with meta coupling. The signals at 5.92, 5.07 and 3.26 ppm are characteristic of the allyl group, which remained intact under the reaction conditions.

Data from the ¹³C-NMR spectrum of the demethylated product showed 8 signals corresponding to 9 carbon atoms. Two carbons in the aromatic region appeared

as one signal. There was no observable methoxy carbon, which indicates that the demethylation reaction was successful.

Table 1 NMR Data for Hydroxycavicol in CDCl₃.

No. C	δ_C ppm	δ_H ppm (multiplicity, J Hz)
1	137.6	-
2	116.0	6.73 (d, 1.4, 1H)
3	141.5	-
4	143.3	-
5	115.7	6.82 (d, 8.5, 1H)
6	116.0	6.63 (d, 8.6, 1H)
7	39.8	3.26 (d, 6.7, 2H)
8	133.5	5.92 (ddt, 16.9, 10.2, 6.7, 1H)
9	121.2	5.07 (dd, 13.1, 5.7, 2H)

Characterization of the hydroxycavicol was done using FTIR spectroscopy. There was no absorbance at 1120 cm⁻¹, which indicates the absence of C-O bonds corresponding to the methoxy group. On the other hand, absorbance was observed at 3200 cm⁻¹ and 1600 cm⁻¹, which corresponds to the O-H in the hydroxyl group and the C=C of the aromatic ring, respectively.

A mass spectrometry experiment was carried out to complement the NMR and FTIR analysis. An *m/z* value of 149.0596 corresponding to the M-H value of hydroxycavicol was obtained as compared to the calculated value of 149.0603, which confirms the formation of product.

3.2 Demethylation with HBr

Demethylation using bromic acid 48% was carried out in glacial acetic acid that served as protic solvent. After rigorous chromatographic purification, product **3** was isolated. Characterization of the pure product was carried out by ¹H NMR spectroscopy, of which the result is shown in Table 2.

Based on the NMR data, methoxy signals appeared at 3.85 and 3.82 ppm, which suggests that the demethylation reaction was unsuccessful. The proton signals at 2.97 and 3.13 ppm indicates protons bonded to the alkene group and the signal at 4.27-4.08, which appeared as a multiplet, indicates the presence of allyl groups. The signals appeared in two sets, which suggests a dimer compound.

The multiplicities of the signals in the aromatic region also suggest that product **3** was a dimer. Two signals at chemical shifts 6.67 and 6.54 ppm were observed as a singlet. Other than that, signals that appeared as a doublet (meta) appeared at chemical shifts 6.80 and 6.78 ppm, which indicates the possibility of substitution at C5 on the aromatic ring. Since the signals observed were

symmetrical, the possible product was a dimer of eugenol with a structure as shown in Figure 2.

Table 2 ^1H NMR Data for Product 3 in CDCl_3 .

No. C	δ_{H} ppm (multiplicity, J Hz)
1, 1'	-
2	6.80 (d, 1.4, 1H)
2'	-
3	-
3'	6.67 (s, 1H)
4, 4'	-
5, 5'	-
6	6.78 (d, 1.4, 1H)
6'	6.54 (s, 1H)
7	3.13 (d, 9.7, 2H)
7'	2.97 (d, 9.6, 2H)
8	5.64 (m, 1H)
8'	5.46 (m, 1H)
9, 9'	4.27 – 4.08 (m, 4H)
(O-CH ₃)	3.85 (s, 3H)
(O-CH ₃)	3.82 (s, 3H)

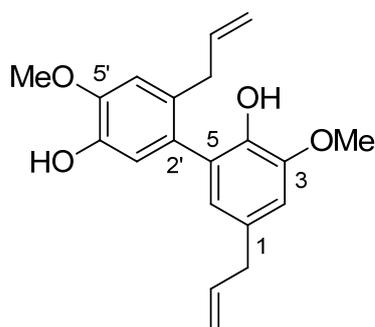


Figure 2 Proposed structure of dimer product 3.

The formation of a dimer may follow a radical mechanism aided by oxygen impurities. When the reaction was carried out under nitrogen, no dimer product was observed. Synthesis of dieugenol has been reported by Ogata, *et al.* [12] by treatment with peroxide aided by FeSO_4 catalyst, which proceeded through a radical oxidative coupling mechanism. These conditions provide a dimer with both substituents at the ortho position. Alkene and hydroxyl groups react very slowly with oxygen to produce traces of organic peroxides, which promote a free radical chain reaction. The presence of HBr and oxygen in the reaction system may result in the peroxide effect, which generates a stabilized allylic

radical, leading to the formation of dimeric product **3** [13]. The proposed radical mechanism for the formation of the dimer is presented in Figure 3.

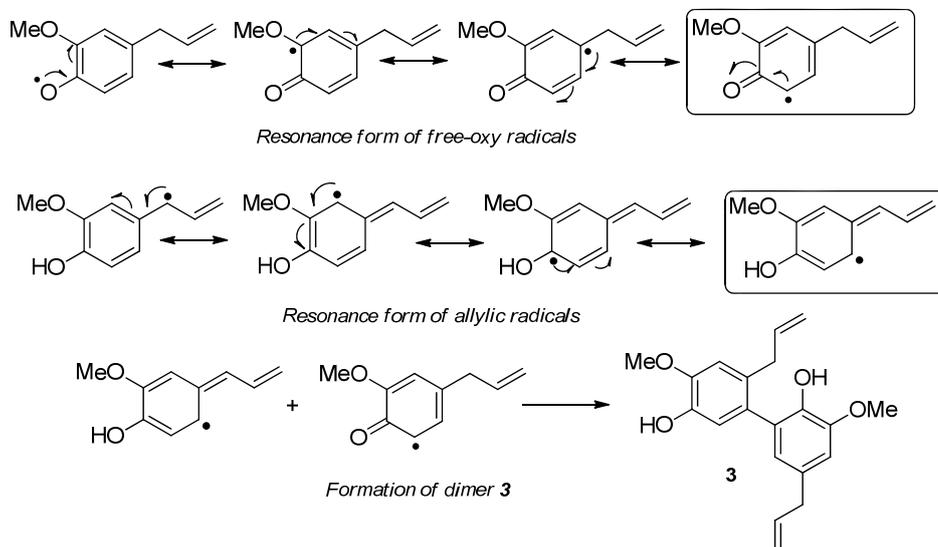


Figure 3 Proposed mechanism for dimer formation.

4 Conclusion

Demethylation of eugenol using lithium chloride was accomplished to generate hydroxycavicol **2**. The product was purified by chromatographic methods and intensively characterized using NMR, FTIR and HRMS spectroscopy, which confirmed the structure of a hydroxycavicol compound. The attempted demethylation reaction under acidic conditions, however, did not produce a demethylated product but a dimeric product. This structure was concluded based on the multiplicities and coupling constant in the aromatic region based on the ^1H NMR data. The proposed radical mechanism involves oxidative coupling and the peroxide effect due to the presence of HBr and oxygen in the reaction. The dimeric product was not observed when the reaction was carried out under nitrogen.

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