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Synthesis of Eugenyl Cinnamate from Clove Oil (*Syzygium aromaticum*) via Bromination-Dehydrobromination Methods

Anita Alni,[1*] Shinta Ellisya Fauzia ,[1] Didin Mujahidin[1]

[1]Division of Organic Chemistry, Faculty of Mathematics and Natural Sciences, Institut Teknologi Bandung, Jalan Ganesa 10 Bandung, Jawa Barat, Indonesia 40132

[*]Corresponding e-mail: alni@chem.itb.ac.id

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ABSTRACT

Synthesis of bioactive materials based on Indonesian natural products as precursors are potential to achieve a sustainable supply of modern medicines. Eugenyl cinnamate is a crucial building block in many bioactive compounds such as hepatoprotective silibinin. This research features simple synthesis of eugenyl cinnamate from eugenol, an essential oil presents as major constituent of clove oil (*Syzygium aromaticum*). The transformations were carried out via protection of hydroxyl group, bromination, and dehydrobromination reactions of eugenol (**1**) consecutively. The products of the synthesis were purified by gravity column chromatography and were characterized by FTIR and NMR spectroscopy. Benzylation of eugenol was carried out under basic condition with high yield (94.3%). Characterization by spectroscopic methods showed that eugenyl benzyl ether (**2**) was formed. Bromination of eugenyl benzyl ether yielded three products, namely: dibromo (**3a** and **3b**), and tri-bromo eugenyl benzyl ether (**3c**). Compound **3a** and **3b** were epimers based on intensive NMR analysis (^{1}H, ^{13}C and DEPT). These epimers were separable using simple gravitational colomn chromatography. To improve the selectivity of the reaction, protecting group was changed to acetyl to yield eugenyl acetyl ether (**4**). Bromination of (**4**) yielded the desired dibromo product (**5**). The dehydrobromination reaction of compound **5** with cinnamic acid yielded the eugenyl cinnamate (**6**) with yield of 23.2%.

Keywords: Eugenol, bromination, eugenyl cinnamate, photocatalysis, epimers

INTRODUCTION

Synthesis of bioactive materials based on Indonesian natural products as precursors are potential to be developed to achieve a sustainable supply of modern medicines. Synthesis of bioactive molecules often requires varieties of building blocks and catalyst originated from petroleum refining and cracking processes [1]. The absence of petroleum refining and fine chemicals industry in Indonesia requires these precursors to be highly dependent on import, and lengthy processing time is required until the chemicals arrive at laboratories. On the other hand, Indonesian biodiversity could provide abundant sources of building blocks intact with desired functional groups for the target molecules [2]. Bio-based fine chemicals could offer larger variety of building blocks range from simple to complicated chiral structures as compared to petroleum-based compounds [3].

Eugenol is major constituent of clove oil distilled from *Syzygium aromaticum*, a tree plant originated from Maluku Island Indonesia. These region has produced cloved oil for decades and exported as raw material. Distilled oil from the flowers of clove could contain up to 88% of eugenol which could be further purified through fractional distillation [4].

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Phenylpropene group in eugenol open feasibility to access numerous amounts of bioactive compounds. The use of eugenol as building block is not entirely new, various targets have been accomplished using eugenol as starting material [5]. In this research, eugenyl cinnamate was synthesized from eugenol which could be further used as building block to synthesize hepatoprotective silibinin [6]. Eugenyl cinnamate was also reported to have anti-schistosomal activity by inducing cytoplasmic vacuoles and death in schistosomula of worm *Schistosoma mansoni* [7]. Previous route to synthesize eugenyl cinnamate has also been reported by Holzgrabe et al. via transformation of isolated bornyl caffeate [7].

EXPERIMENT

Compounds which are sensitive to moisture were handled accordingly and stored in ambience brown bottles. Procedures that involve moisture sensitive compounds were carried out under a positive pressure of nitrogen and in glassware that were flame-dried equipped with sealed rubber septum. Teflon-coated magnetic stirring bars were used to stir the reaction mixtures unless otherwise stated. All experiments were monitored by analytical thin layer chromatography. Solvents were removed using rotary evaporator under ~50 mmHg of pressure and heated in a water bath at 40 ^{o}C or above.

Chemicals and instrumentation

Eugenol was obtained from PT. Indesso Utama Kencana and used without further purification. Benzyl chloride, Potassium carbonate, sodium sulphate, bromine, sodium thiosulphate and cinnamic acid were obtained from Sigma and used without further purification. Solvents such as dimethyl sulfoxide, acetonitrile, ethyl acetate, n-hexane, chloroform and acetone were from Merck. Analytical thin layer chromatography was performed using Merck 60 F_{254} pre-coated silica gel plates (0.25 mm thickness). Visualization was conducted using UV light (254 nm). Flash column chromatography was performed using Merck Silica Gel 60 (70-230 mesh) and freshly distilled solvents.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were measured on Agilent DD2 and JEOL ECA 500 MHz NMR spectrometer. Chemical shifts were reported as δ with the reference to tetramethysilane (δ 0.00) in units of parts per million (ppm). Deuterated solvent used in the measurement was chloroform-d ($CDCl_3$) which provided residual solvent signal as an internal standard (1H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.04, triplet). Multiplicities were stated as: s (singlet), d (doublet), m (multiplets), br (broad), dd (doublet of doublets), and ddt (doublet of doublet of triplets) accordingly. Coupling constants (J) were indicated in Hertz (Hz). The number of protons (n) in the spectrum for a given resonance was denoted by nH. NMR spectrums are provided as supplementary document.

Procedures

4-Allyl-1-(benzyloxy)-2-methoxybenzene (2)

Eugenol (3.29 g, 20 mmol, 1 equiv.) and 50 mL of acetonitrile were added into a three-neck round bottom flask with attached condenser and rubber septum. 6.92 g (50 mmol, 2.5 equiv.) of K_2CO_3 was added and the reaction mixture was stirred for 10 minutes at room temperature. Benzyl chloride (4.6 mL, 40 mmol, 2 equiv.) was added dropwise and the reaction mixture was refluxed for 24 h. Upon completion, 50 mL of water was added, and the reaction mixture was extracted by ethyl acetate (3 x 50 mL). To the combined organic layer was added Na_2SO_4 and the mixture was filtered, and the filtrate was evaporated. The crude product was

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purified using column chromatography with ethyl acetate: *n*-hexane (5:95) as eluent (94.27% yield, R_f 0.41, pale yellow oil).

^{13}C NMR (125 MHz, Chloroform-d) δ 149.6, 146.5, 137.6, 137.4, 133.3, 128.5, 127.8, 127.3, 120.4, 115.7, 114.2, 112.4, 71.2, 56.0, 39.9. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.46 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.31 (tt, *J* = 7.3, 2.2 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 1.9 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.97 (m, 1H), 5.15 (s, 2H), 5.12-5.06 (m, 2H), 3.89 (s, 3H), 3.34 (d, *J* = 6.7 Hz, 2H).

4-Allyl-1-(acetyloxy)-2-methoxybenzene (4)

A 5.0 mL of acetyl chloride (2 equiv.) was added into a three-neck round bottom flask and was heated to reflux. 5.4 g of Eugenol (1 equiv.) was added dropwise. The reaction was monitored using thin layer chromatography for 1 hour. After completion, 10 mL saturated sodium bicarbonate solution was added. The organic layer was extracted using ethyl acetate and concentrated in vacuo. Eugenyl acetate 4 was subjected to subsequent reaction without further purification.

1-(Benzyloxy)-4-(2,3-dibromopropyl)-2-methoxybenzene (3a-c)

Eugenyl benzyl ether (447 mg, 1.92 mmol, 1 equiv.) was added into round bottom flask filled with 4 mL chloroform. The mixture was stirred at 0 ^{o}C (in an ice bath). After that, 0.15 mL (1.5 equiv.) of Br_2 in chloroform was added dropwise until the color of solution remain brownish yellow. The mixture was continued to stir for 1 hour followed by addition of 10 mL of saturated sodium thiosulphate solution. The mixture was extracted with ethyl acetate (3x 10 mL). To the combined organic layer was added Na_2SO_4, and then was filtered. The filtrate was concentrated in vacuo. The crude product was purified by column chromatography with *n*-hexane: ethyl acetate: chloroform (93.5:1.5:5) as eluent. Three products were obtained and characterized as follow:

3a, A pale yellow oil, R_f 0.31, ^{13}C NMR (125 MHz, Chloroform-d) δ 148.8, 148.1, 136.3, 129.2, 128.7, 128.1, 127.4, 117.9, 114.9, 114.2, 71.2, 56.2, 51.2, 42.9, 37.2. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.45 (dd, *J* = 10, 5 Hz, 2H), 7.40 (t, *J* = 10 Hz, 2H), 7.34 (tt, *J* = 5, 10 Hz, 1H), 7.08 (s, 1H), 6.88 (s, 1H), 5.11 (s, 2H), 4.5 (m, 1H), 3.89 (s, 3H), 3.86 (dd, *J* = 10, 5 Hz, 1H), 3.75 (dd, *J* = 10, 5 Hz, 1H), 3.62 (dd, *J* = 15, 5 Hz, 1H), 3.07 (dd, *J* = 15, 10 Hz, 1H).

3b, A pale yellow oil, R_f 0.38, ^{13}C NMR (125 MHz Chloroform-d) δ 149.4, 147.4, 137.1, 129.7, 128.6, 127.8, 127.3, 121.7, 113.8, 113.2, 71.0, 56.0, 52.6, 41.5, 36.1. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.46 (dd, *J* = 10, 5 Hz, 2H), 7.38 (t, *J* = 5 Hz, 2H), 7.32 (tt, *J* = 10, 5 Hz, 1H), 6.86 (d, *J* = 10, 1H), 6.86 (d, *J* = 5, 1H), 6.78 (dd, *J* = 10, 5 Hz, 1H), 5.11 (s, 2H), 4.35 (m, 1H), 3.91 (s, 3H), 3.82 (dd, *J* = 10, 5 Hz, 1H), 3.62 (dd, *J* = 10, 9 Hz, 1H), 3.40 (dd, *J* = 15, 5 Hz, 1H), 3.12 (dd, *J* = 15, 9 Hz, 1H).

3c, A pale yellow oil, R_f 0.47, ^{13}C NMR (125 MHz, Chloroform-d) δ 149.6, 147.9, 137.0, 132.5, 128.6, 127.9, 127.3, 119.5, 113.8, 111.4, 70.9, 56.1, 48.5, 35.7. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.45 (d, *J* = 10 Hz, 2H), 7.38 (t, *J* = 10 Hz, 2H), 7.32 (t, *J* = 10Hz, 1H), 6.88 (d, *J* = 10 Hz, 1H), 6.78 (d, *J* = 5, 1H), 6.72 (dd, *J* = 10, 5 Hz, 1H), 5.16 (s, 2H), 3.91 (s, 3H), 3.77 (dd, *J* = 10, 5 Hz, 2H), 3.71 (dd, *J* = 10, 5 Hz, 2H), 3.31 (qi, *J* = 10 Hz, 1H).

(*E*)-3-(4-Acetoxy-3-methoxyphenyl)allyl cinnamate (6)

Dibromo eugenyl acetate (78.4 mg, 0.21 mmol, 1.0 equiv.) was added into a round bottom flask followed by the addition of 2.0 mL of DMSO, 35.2 mg of cinnamic acid (0.23 mmol, 1.1 equiv.) and 59.9 mg K_2CO_3 (0.4 mmol, 2.0 equiv.). The reaction mixture was stirred

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at room temperature for 24 hours. The crude product was purified by column chromatography using *n*-hexane: ethyl acetate (9:1) as eluent. The product **6** (17.5 mg, pale yellow oil 23.19%, R_f 0.41) was characterized by spectroscopic methods.

^{13}C NMR (125 MHz, Chloroform-d) δ 169.1, 166.7, 151.1, 145.2, 139.6, 135.3, 134.3, 133.6, 130.4, 128.9, 128.1, 123.6, 122.9, 119.4, 117.8, 110.2, 65.0, 55.9, 20.7. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.75 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.43 – 7.37 (m, 3H), 7.04 – 6.98 (m, 3H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.33 (m, 1H), 4.88 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.86 (s, 3H), 2.33 (s, 3H).

RESULT AND DISCUSSION

Synthesis of eugenyl cinnamate included the transformation of an allyl group in eugenol [7]. However, other than an active allyl group, eugenol also contained an active phenol group that can affect the electrophilic substitution of the bromide into the aromatic ring. Hence, protection of the phenol group was required before the bromination reaction to prevent the formation of aryl bromide [8]. Schematic representation of the multistep synthesis is shown in Figure 1.

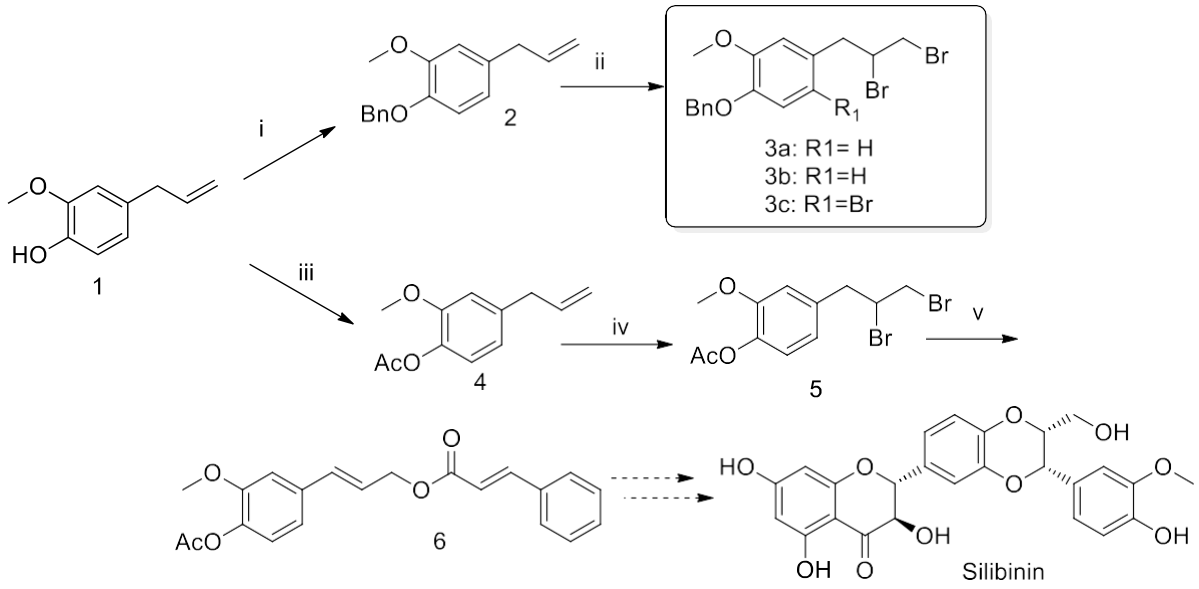

Figure 1. Synthesis of eugenyl cinnamate from eugenol. Conditions: (i) BnCl (2 equiv.), K_2CO_3 (2.5 equiv), CH_3CN, reflux 24 hours; (ii) Br_2 (1.5 equiv), $CHCl_3$, 0^o C, 1 hour; (iii) AcCl (2 equiv.); (iv) Br_2 (1 equiv.), AcOH; (v) Cinnamic acid (1.1 equiv), K_2CO_3 (2 equiv.), DMSO, rt, 24 hour.

Benzylation was carried out by reacting eugenol with benzyl chloride with K_2CO_3 as base in acetonitrile [9]. Potassium carbonate deprotonated the acidic hydrogen of phenolic group of eugenol. The phenolate anion was stabilized by the resonance of the aromatic system. The product of this reaction, eugenyl benzyl ether (**2)** was obtained in high yield (94.27%).

The ^{13}C NMR spectrum showed 15 signals where two signals at chemical shift of 127.3 and 128.5 ppm had double intensity which corresponded to two carbons each. This support the structure of product **2** that consist of 17 carbon atoms. Signal at the chemical shifts of 55.6 and 71.2 ppm corresponded to carbon in methyl and metylene ether respectively. Methylene ether

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appeared downfield as compared to the methyl ether due to the bond with aromatic ring and caused deshielding effect. Benzylic carbon appears at δ 127.3, 127.8, and 128.5 ppm. These signals showed symmetry in which two carbons that were at *ortho* position to methylene were equivalent, so as two carbons at *meta* position.

The ^{1}H NMR spectrum showed that there were 18 hydrogen atoms based on the integration of the signals. Signal at δ 5.15 ppm (s, 2H) corresponded to methylene bonded to aromatic group. Signal at δ 6.60-7.60 ppm corresponded to aromatic proton which consisted of two aromatic rings. Signals at chemical shift of 6.83, 6.76, and 6.68 ppm were aromatics proton from eugenol which appear upfield as compared to signals of benzyl protecting group which appear at chemical shift of 7.46, 7.37, and 7.31 ppm. This data confirmed the structure of compound **2**.

Bromination towards compound **2** was carried out by dropwise addition of Br_2 solution in chloroform. Upon addition, the mixture changed color into brown, which quickly disappeared that indicated that addition to double bond has occurred. The addition of Br_2 solution was stopped when permanent yellowish brown color was observed. At the end of the reaction, saturated sodium sulphate solution was added to reduce the unreacted Br_2 in solution. Bromination towards compound **2** produced three compounds which were separated using column chromatography namely product **3a**, **3b** and **3c** with the yield of 18.56%, 15.47%, and 14.30% respectively. The remaining starting material was also recovered.

The ^{13}C NMR spectrum of **3c** showed 15 carbons. Two signals at δ 127.4 and 128.7 ppm corresponded to two carbons each which suggested there were 17 carbon atoms. Signals at chemical shift of 35-60 ppm which indicated carbon bonded to halogen (-C-Br) in place of terminal alkene signals. This suggested that alkene group in benzyl ether **2** has undergone addition reaction to form a dibromo compound. The ^{1}H NMR spectrum of **3c** indicated 17 hydrogen atoms. Two signals appeared as singlet at δ 7.08 (s, 1H) and 6.88 ppm (s, 1H). These signals corresponded to aromatic proton hence indicated bromination has occurred at the aromatic region. Singlet multiplicity suggested that proton at δ 7.08 ppm does not have neighbor at *ortho* or *meta* position, hence electrophilic substitution had occurred at the position *meta* to the benzyloxy or *ortho* towards the allyl group. The methoxy substituents on benzyl ether **2** were electron donor that activated the aromatic ring (*ortho-para* directing). The allyl group was deactivating; hence substitution was directed towards meta position. In addition, steric hindrance of the methoxy group directed the substitution reaction to occur at *para* position to the methoxy group.

The ^{13}C NMR spectrum of **3a** showed 15 signals. Two signals at δ 127.3 and 128.6 ppm corresponded to two carbons each, hence suggested that compound **3a** consist of 17 carbon atoms. Terminal alkene signals were absent, replaced by signals at δ 35-60 ppm which corresponded to C-Br, and confirmed that addition had occurred. The ^{1}H NMR spectrum of **3a** showed signals corresponded to 18 hydrogens. Signals at aromatics region were observed at δ 6.86, 6.86, and 6.78 ppm which suggested there was no substitution at the aromatic ring. As compared to spectrum of its precursor **2**, the disappearance of terminal alkene signals at δ 5.97 ppm (m, 1H) and 5.12-5.06 ppm (m, 2H) replaced by methyne and methylene signals at δ 4.35 and 3.9-3.00 ppm supported the ^{13}C NMR that bromination has occurred to produce compound **3a**.

The ^{13}C NMR spectrum of compound **3b** showed 14 signals in which two of them corresponded to two signals each. This suggested that compound **3b** consisted of 16 carbon atoms. As compared to its precursor (compound **2**) the terminal alkene signals were absent, replaced by signals at δ 35-60 ppm which corresponded to C-Br which suggested that

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bromination had occurred to form a dibromo product. Signals at the aromatics region suggested that there was no aromatic substitution. The DEPT NMR experiment showed that signal at δ 35.8 ppm had twice as much intensity corresponded to two methylene groups. This suggested there were 17 carbon atoms in compound **3b** instead of 16 as suggested by ^{13}C NMR spectrum.

Further analysis of the ^{13}C NMR and ^{1}H NMR spectra suggested that compound **3a** and **3b** had similar structure; however, these compounds were separated by column chromatography and showed different chemical shifts for the propyl group in the NMR spectrum. Conformation analysis of compounds **3a** suggested that the methyne group was between Br and H hence appear at downfield position as compared to compound **3b** (**Figure 2**). Based on this data, compound **3a** and **3b** are epimers. The formation of epimers from bromination had been reported previously [10].

Figure 2. Newman projection of compound **3a** and **3b**

Due to the formations of side products and low conversion of starting materials, alternative protecting group was used. Eugenol was protected with acetyl group based on reported procedure to yield acetyl ether **4** [9]. Compound 4 was subjected to bromination without further purification to yield compound **5** with 64 % yield. Finally, compound **5** was subjected to reaction with cinnamic acid to form the target product (eugenyl cinnamate **6**). K_2CO_3 was used as base to deprotonate the acid and further react with the dibromo compound to produce compound **6** with 23.19% yield. The reaction was carried out in DMSO to better solvate the cinnamate anion and react with the dibromo compound **5**.

The ^{13}C NMR spectrum of compound **6** showed 19 signals, in which signals at δ 128.1 and 128.9 ppm corresponded to two carbons each, suggesting there were 21 carbons in compound **6**. Signals at δ 166.7 and 169.1 ppm corresponded to two carbonyl esters. Signals at δ 117.8, 122.9, 133.6, and 145.2 ppm suggested two alkene groups were present. The ^{1}H NMR spectrum showed 20 hydrogen atoms. Signals at δ 7.75, 6.69, 6.50 and 6.33 ppm indicated proton bonded to alkene group. Structure of compound **6** was confirmed based on ^{1}H NMR and ^{13}C NMR analysis.

Eugenyl cinnamate **6** could be utilized as building block in many bioactive compounds, hence the route to synthesize it from abundantly available natural products could provide cheaper access to medicine.

CONCLUSION

Synthesis of eugenyl cinnamate **6** was accomplished *via* bromination-dehydrobromination methods. The syntheses were carried out in three steps with good yield (23.2 %). Bromination towards benzyl eugenyl ether **2** produced three products including brominated aromatic ring **3c**, and two epimeric dibromo compounds **3a** and **3b** that were separable using gravitational column chromatographic method. Bromination towards acetyl eugenyl ether 4 yielded single product (compound **5**) hence this route was pursued.

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Dehydrobromination was carried out in the presence of base using cinnamic acid as substituent and yielded the desired eugenyl cinnamate ester **6**.

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CONFLICT OF INTEREST

Authors declare no conflict of interests.

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