FeCl₃-catalyzed Synthesis of Dehydrodiisoeugenol

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Abstract

Dehydrodiisoeugenol (DDIE) synthesis has been performed by modifying a method recommended by Leopold with a different ratio of isoeugenol and FeCl₃ (1.9:1). FeCl₃ was chosen as catalyst due to its efficiency and environment-friendly property. This modification yielded 22.93 % of product. The product, a white crystalline form, was characterized using thin layer chromatography, melting point, UV, IR, HRMS, and NMR spectroscopy, as well as HPLC, employing pure DDIE as the standard. TLC chromatogram showed Rf 0.32 using n-hexane/ethyl acetate (8:2). The crystals melted at 138-139 °C, while its UV maximum was detected at λ 273 nm. IR spectrum showed a specific broad O-H stretch at 3437.15 cm⁻¹, C-H aromatic and C-H alkene at 3163.26 and 3024.38 cm⁻¹, C-H alkyl stretch at 2951.09 and 2927.94 cm⁻¹. An overtone peak of aromatic was detected at 2100 to 1700 cm⁻¹. C-O peak was detected at 1126.43 cm⁻¹. HPLC showed that this compound was eluted at 11.886 minutes after it was injected to a C18 column 250 x 4 mm using a mixture of methanol and double distilled water (73:27) for mobile phase. HRMS spectra predicted that the molecular structure is C₂₀H₂₂O₄ as showed by abundance peak at *m/z* 327.1595 of [M+H]⁺. ¹H-NMR and ¹³C-NMR indicated that the synthesized compound contains 13 types of proton and 20 types of carbon. Herein we reported that white needle-like crystals of DDIE using FeCl₃ as catalyst had been synthesized, moreover the decreasing of the catalyst reduced the yield of the product.

Keywords: antidiabetic, anti-inflammatory, diabetes, DDIE, Myristica fragrans Houtt, nutmeg, PPARy

1. Introduction

Dehydrodiisoeugenol (DDIE) (Fig.1) is a chemical compound contained in fruit and seed of nutmeg (*Myristica fragrans* Houtt).



Fig. 1. Chemical structure of DDIE (a) and isoeugenol (b)

Built using ChemDrawUltra 8.0.3 of ChemOffice 2004 (www.cambridgesoft.com)

DDIE showed anti-inflammatory (Li and Yang, 2012) and antidiabetic activity on PPAR γ receptor (Lestari, 2012). Previous study determined that the level of DDIE, myristicin, and safrole in the ethanol extract of nutmeg seeds was 4.662 %, 17.226 %, and 10.979 %, respectively using RP-HPLC (Saputri, 2014). Isolation of bioactive compounds from

plants is a wholesome-work therefore this research was aimed to synthesize DDIE by employing FeCl₃ as catalyst.

The coupling of two phenoxy radicals leads to new asymmetric stereo-centers. The reaction can lead to pure enantiomers or mixtures if stereo-control exists due to a catalyst and/or matrix and/or chiral auxiliarities in the starting compound. The coupling will form a very reactive quinone methide intermediate, which could react quickly with a suitable nucleophile and leads finally to a stable dimeric structure called lignin or dilignol (Setälä, 2008).

Leopold categorized eight groups of lignin compound with different elements, whereas DDIE was categorized in group VII. Leopold method in which 50 g of isoeugenol, as the starting material, was reacted with a few crystals of DDIE, had successfully yielded 30 % of the product. This reaction was catalyzed by $FeCl_3$ with ratio of isoeugenol- $FeCl_3$ 1.4:1 (Leopold, 1950). In his paper, Leopold did not provide detailed information, either of the amount of DDIE that he had used for the reaction or the characterization analysis of the product.

 $FeCl_3$ was chosen in this reaction, due to its efficiency and green catalyst property in modern organic synthesis (Diaz et al, 2006). The use of $FeCl_3$ as catalyst were reported for arylation of benzyl alcohols and benzyl carboxylates (Zhan and Liu, 2006), benzylation of 1,3-dicarbonyl compounds (Komeyama et al, 2007) and the synthesis of 1-substituted-1H-1,2,3,4-tetrazoles. The latter mentioned that an excess of $FeCl_3$, as catalyst, did not lead to a substantial improvement in the yield while decreasing the catalyst reduced it (Darvish and Khazraee, 2015).

2. Materials and Methods

2.1 Materials

Isoeugenol 99.0 % (Sigma Aldrich-USA) was purchased in Maebashi-Japan, while the other materials were purchased in Jakarta-Indonesia: DDIE standard 500 µg/mL (Kimia Farma-Indonesia), methanol HPLC grade 99.9% (J.T. Baker-USA), ethanol analytical grade 99 % (Merck Millipore-Germany), double-distilled water (IPHA-Indonesia), FeCl₃ analytical grade (Merck Millipore-Germany), *n*-hexane analytical grade 96% (Merck Millipore-Germany), ethyl acetate analytical grade 99.5 % (Merck Millipore-Germany), KBr analytical grade (Merck-Germany).

2.2 Synthesis of DDIE

This compound was synthesized by modifying a method recommended by Leopold (Leopold, 1950):

1 mL of isoeugenol 99.0 % oily solution was slowly added by stirring, into a mixture of 12.06 mL ethanol 95% and 5.36 mL of double-distilled water, until the two immiscible liquids dissolved. Into this mixture, 5 mL of FeCl₃ 35% (isoeugenol: FeCl₃ = 1.9 : 1) was added and stirred until a yellowish-green precipitate formed (Fig.2a). Then, 230 μ L of 500 μ g/mL DDIE standard was poured into the solution. The mixture was kept at 5°C for 24 hours. The white crystalline formed (Fig.2b) was vacuum-filtered and washed with 45% ethanol.

2.3 Thin Layer Chromatography

A few mg of the white crystalline product was dissolved in methanol and eluted on silica gel F_{254} (Merck) using a mixture of *n*-hexane-ethyl acetate (8:2) as eluent. Both isoeugenol 99.0 % and DDIE standard were used as comparison.

2.4 UV Spectroscopy

2 mg of the white crystalline product was dissolved in 100 ml of double-distilled water to get 20μ g/ml. This solution was measured its absorbance against water in UV-1700 Pharma (Shimadzu) spectrophotometer.

2.5 IR Spectroscopy

2 mg of the white crystalline product was dispersed in 198 mg of previously dried KBr. The disc was measured its %T using FTIR IRAffinity-1 (Shimadzu).

2.6 HPLC

 $20 \ \mu$ l of $20 \ \mu$ g/ml solution was injected to C18 column, 250 mm x 4 mm of HPLC 1525 Binary HPLC Pump (Waters) instrument, using a mixture of methanol and double-distilled water (73:27) as mobile phase. Flow rate was set at 1 ml/min. The UV detector was set at 282 nm.

2.7 HRMS

A few mg of the white crystalline product was dissolved in a mixture of acetone and 0.1 % formic acid in acetonitrile-water (1:1). The solution was ionized by heating it at 300 °C after it was injected to a capillary column of HRMS (Waters LCT Premier XE). TOF was used as detector.

2.8 NMR

10 mg of the white crystalline product was dissolved in CDCl₃ and injected in ¹H-NMR (Agilent), ¹³C-NMR (Agilent). Spectrum was recorded at 500 MHz and 125 MHz Agilent, respectively, and analyzed using VnmrJ 3.2 software.

3. Result and Discussion

Leopold, who performed a synthesis of DDIE, had modified a method described by Erdtman. He used a ratio of isoeugenol-FeCl₃ 1.4:1, and yielded 30 % of product (Leopold, 1950). No detailed reaction or spectra were provided in this paper.

In our project, we modified Leopold method by using lesser amount of FeCl₃ (ratio of isoeugenol-FeCl₃ is 1.9:1). The yellowish-green precipitate (Fig.2) that was slowly formed, was kept at 5°C for 24 hours after it had been reacted with 230 μ l of DDIE standard priorly.



Fig. 2. Yellowish-green precipitate of isoeugenol-FeCl₃ (a) and the white crystalline product (b)

The phenolic group of isoeugenol when it was reacted with $FeCl_3$, formed a coloured ferric-phenolate intermediate (Fig.3).



Intermediate



(b)

Fig. 3. Proposed scheme for isoeugenol reaction with FeCl₃ (built using ChemDrawUltra 8.0.3) (a); Erdtman's scheme for DDIE synthesis (b). Reaction 3b was copied from Davin et al (2008)

Furthermore Davin and his colleagues (2008), reviewed a scheme reaction on FeCl₃-catalyzed coupling of isoeugenol to give 8-5'-linked-dehydrodiisoeugenol (Fig.3b) proposed by Erdtman. In his review, Davin traced back the work of Hogar Erdtman who investigated the coupling of allylphenol and isoeugenol, which in the presence of FeCl₃, could afford the racemic dehydrogenated products, DDIE (Fig.3b) linked through the 8-5' positions. This coupling initially generated the intermediate quinone methide, whose subsequent intramolecular ring closure afforded (\pm)-DDIE (Davin et al, 2008).

TLC assay showed that the synthesis product was eluted at Rf 0.32 (Fig.4).



Fig. 4. TLC spots of (a) isoeugenol; (b) DDIE; and (c) synthesis product

The synthesis product's polarity character resembled to that of DDIE standard (Fig.4b and 4c), while the oily solution of isoeugenol (Fig.4a) eluted with the nonpolar solvent faster than the other two compounds, hence it resulted a higher Rf value.

The synthesis product melted in the range between 138-139°C, compared to Leopold's 132-133°C.



Fig. 5. UV spectrum of (a) DDIE standard; (b) synthesis product; (c) a mixture of DDIE standard-synthesis product (1:1); (d) overlay spectra of (a), (b), and (c)

Both DDIE (Fig.5a) and the synthesis product (Fig.5b) showed maxima at 275 and 273 nm, respectively. This maximum confirmed the λ_{max} prediction of Woodward-Fieser rules, that the chromophore structure of DDIE (Fig.1a) is the aromatic ring with –OH substituent which base value is 270 nm (Pavia et al, 2009; Silverstein et al, 1999).



Fig. 6. IR spectrum of synthesis product

IR spectrum of the product (Fig.6) showed a specific broad O-H stretch at 3437.15 cm⁻¹, C-H aromatic and C-H alkene at 3163.26 and 3024.38 cm⁻¹, C-H alkyl stretch at 2951.09 and 2927.94 cm⁻¹. An overtone peak of aromatic was detected at 2100 to 1700 cm⁻¹. C-O peak was detected at 1126.43 cm⁻¹. These peaks resembled those of DDIE standard.



Fig.7. HPLC chromatogram of (a) DDIE standard; (b) synthesis product; (c) a mixture of DDIE standard-synthesis product (1:1)

Furthermore, HPLC chromatogram indicated a similar character of DDIE ($R_t = 11.693 \text{ min}$, Fig.7a) and the synthesis product ($R_t = 11.886 \text{ min}$, Fig.7b). Both compounds were eluted slowly due to their hydrophobic character, e.g. aromatics and methyls in the molecule (Fig.1a).

The synthesis product was further analyzed using HRMS with TOF detector, compared to DDIE, $C_{20}H_{22}O_4$ (MW = 326.15186 g/mol). A strong intensity (> 70 %) base molecular peak which indicated (M+H)⁺ was detected at *m/z* 327.1595 (Fig.8). This peak was predicted belonged to DDIE.



Fig. 8. HRMS spectrum of the synthesis product

The synthesis product was examined under a polarization microscope (Olympus BX53) with 400x magnification, and the solid needle-like crystals could be seen in Fig.9.



Fig. 9. Needle-like crystals of the synthesis product in 400x magnification



Fig. 11. ¹³C-NMR spectrum of the synthesis product

The last characterization of the synthesis product was performed using ¹H-NMR (Fig.10) and ¹³C-NMR (Fig.11) which shows the synthesized compound contains 13 types of proton and 20 types of carbon. 2D ¹H-NMR (CDCl₃/TMS) indicated: δ 1.37 (d, 3H, CH₃), δ 1.86 (t, 3H, CH₃), 3.42-3.47 (m, 1H, CH), 3.87 (s, 3H, CH₃-O), 3.89 (s, 3H, CH₃-O), 5.09 (d, 1H, CH), 5.64 (br s, 1H, Ar-OH), 6.35 (d, 1H, C17), 6.76 (s, 1H, C16), 6.79 (s, 1H, C14), 6.87-6.91 (m, 2H, CH₃, CH), 6.97 (s, 1H, CH₃), while 2D ¹³C-NMR (CDCl₃) indicated: δ 17.7 (C9), 18.5 (C19), 45.7 (C8), 56.0 (CH₃-O) 56.1 (CH₃-O), 93.9 (C7), 109.0 (C2), 109.3 (C12), 113.4 (C16), 114.2 (C5), 120.1 (C-6), 123.6 (C18), 131.0 (C17). 132.2 (C11), 132.1 (C1), 133.4 (C15), 144.2 (C13), 145.9 (C4), 146.7 (C14), 146.8 (C3).

4. Conclusion

Herein we reported that white needle-like crystals of DDIE using FeCl₃ as catalyst had been synthesized; moreover the decreasing of the catalyst reduced the yield of the product.

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