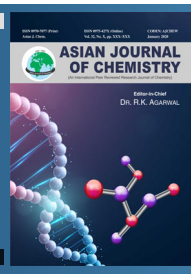
Asian Journal of Chemistry; Vol. 32, No. 1 (2020), 17-20

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22114



Nitration of Methyl Eugenol Derived from Clove Oil

I.M. SUDARMA*, A. SHOFIATI and M.G. DARMAYANTI

Department of Chemistry, University of Mataram, Jl. Majapahit 62, Mataram 83125, Indonesia

*Corresponding author: Tel/Fax: +62 370 646506; E-mail: sud_arma@yahoo.co.id

Received: 4 April 2019; *Accepted*: 6 July 2019; *Published online*: 18 November 2019; AJC-19663

No report is available in literature for the nitration of methyl eugenol. The main goal of this work is to find an efficient method for the synthesis of 5-nitro-methyl eugenol. 5-Nitro-methyl eugenol is of considerable importance in the production of other fine chemicals such as 5-amino-methyl eugenol for further chemical synthesis and has also possible to enhance its biological properties and other applications. The methyl eugenol can be prepared from methylation of eugenol which can be isolated from clove oil. In an attempt to synthesize nitro-methyl eugenol in high yield, three different nitration methods of methyl eugenol have been applied. Method (a) gave 5.97 %, (b) 84.37 % and (c) 11.40 %. Method (b) using a nitrating consisting mixture of HNO_3 and H_2SO_4 under mild condition has been found to give 5-nitro-methyl eugenol in good yield.

Keywords: Nitration, Methyl eugenol, 5-Nitro-methyl eugenol.

INTRODUCTION

Methyl eugenol (ME) is a yellowish oil [4-allyl-l,2-dimethoxy-benzene] is found in more than 450 species of plants from 80 families including both angiosperm and gymnosperm families [1]. Methyl eugenol has been used for antifungal [2], anti-bacterial [3], nematicidal [4], anti-inflamation [5], anticancer [6] and food flavouring [7].

In continuation of our work to enhance the biological activity and applicable use of easily isolated natural products such as eugenol, cinnamaldehyde and methyl eugenol, previously, in this connection we have reported an efficient method on nitration of eugenol [8]. Our goal is to afford suitable method for the nitration of methyl eugenol. Nitration of methyl eugenol is attractive and rewarding area of research and of course will give different results compare to eugenol. The nitration of organic compounds may be achieved with many nitrating reagents and is a useful method in organic synthesis [9].

Methyl eugenol is an aromatic compound similar to eugenol with three substituents (2-methoxy and one allyl). These substituents lead the regioselectivity for further reaction such as nitration. The regioselectivity is governed by interaction between the substituent and the reagent, steric hindrance, electronic and solvent effects [10]. Those effects will give low to moderate yields of nitro-methyl eugenol due to competition reaction of the substituents. Thus, investigation a convenient and efficient method for the regioselective synthesis of nitro-methyl eugenol is desirable.

There are three reaction approaches could be applied for nitration of methyl eugenol *e.g.*, (a) nitration based on benzene, methyl eugenol has benzene moiety on its structure that possible undergo nitration reaction [11]; (b) nitration reaction depend on dimethoxybenzene, methyl eugenol has dimethoxybenzene which is also possible go through nitration reaction [12]; (c) nitration reaction on the basis of eugenol, methyl eugenol is derivative of eugenol that experience with nitration process [8].

EXPERIMENTAL

The plant materials (clove bud) were collected from the cultivated plant at Gangga village, North Lombok, West Nusa Tenggara, Indonesia. All the chemical reagents were purchased with the highest commercially available purity (Merck and Sigma) and were used without further purification. The material used included: dichloromethane, hexane, methanol, acetic acid, sodium hydroxide pellet, anhydrous sodium carbonate, nitric acid, sulfuric acid, sodium nitrite, potassium sulfate, ammonium nitrite, acetonitrile, analytical thin layer chromatography, silica gel chromatography.

GC-MS were recorded on GC-MS QP-2010 Ultra, Merk Shimadzu. GC Parameters were setup as follows, oven temperature (°C) = 60.0, oven equilibrium time (min) = 0.50; injection temperature (°C) = 280.0; interface temperature (°C) = 300.0; column length (m) = 30; column diameter (mm) = 0.25; column pressure (kPa) = 100; column flow (mL/min) = 1.6; linear velocity = 46.4; split ratio = 22; total flow (mL/min) = 40.2; program time (min) = 27.00. MS parameter, start *m/z* = 33.00 end *m/z* = 550.00; scan interval (s) = 0.50; scan speed (amu/s) = 1000.

The original ^{1}H NMR, spectra were generally recorded in $CDCl_3$ on a Bruker spectrometer at 400 MHz.

Preparation of extract and isolation of eugenol: Clove bud (100 g) were air dried and extracted with dichloromethane for 2 × 24 h. The extract was filtrated and evaporated with rotary evaporator to afford yellowish oil (40.4 g, 40.4 %). Column chromatography was employed to isolate eugenol from the clove oil (10 g). Gradient elution starting with hexane and increased by the following hexane/dichloromethane ratios: 4/1, 3/2, 1/1 and 0/100). Twenty fractions were collected from elution. Fractions shown to be identical by thin layer chromatography were combined and evaporated in rotary evaporator. Fractions containing eugenol were combined affording yellowish oil (8.26 g) (82.6 %). This oil was identified as eugenol by gas chromatography-mass spectrometry (GC-MS) analyses, $M^{+\bullet}$ 164, calculated for $C_{10}H_{12}O_2$ Major fragments: 149 ($M^{+\bullet} - CH_3$), 131, 121, 103, 91, 77 (C_6H_6, base peak); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 6.82 (1H, d, ArH), 6.67 (1H, d, ArH), 6.66 (1H, s, ArH), 5.91(2H, m, -CH_2-), 5.53 (2H, m, ArOH and -HC=), 5.05 (2H, m, =CH_2), 3.81 (3H, s, $ArOCH_3$).

Synthesis of methyl eugenol: A 100 mL three-neck flask equipped with condenser and magnetic stirrer was charged with eugenol (5 g) was then added NaOH (2 g in 20 mL of distilled water) and stirred for 15 min. 4 mL of dimethyl sulfate was added drop-wise and stirring for 0.5 h. The mixture was refluxed at 103 °C for 1 h. Worked up was adapted as method by Riyanto *et al.* [13] to afford yellowish oil. GC-MS) analyses, $M^{+\bullet}$ 178, calculated for $C_{11}H_{14}O_2$ Major fragments: 163 ($M^{+\bullet}$-CH_3), 147 ($M^{+\bullet} - OCH_3$), 135, 115, 107, 91, 77 (C_6H_6). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 6.82 (1H, d, ArH), 6.67 (1H, d, ArH), 6.66 (1H, s, ArH), 5.91(2H, m, -CH_2-), 5.50 (1H, m, -HC=), 5.05 (2H, m, =CH_2), 3.81 (3H, s, $ArOCH_3$), 3.77(3H, s, $ArOCH_3$).

Synthesis of 5-nitromethyl eugenol

Method (a): Nitration of methyl eugenol using nitration of benzene approaches: A 50 mL round bottomed flask with magnetic stirrer was charged with 0.01 M (5 mL) H_2SO_4 and 0.5 g methyl eugenol was stirred for 5 min (solution A). 70 % HNO_3 (10 mL) was mixed with 0.01 M (10 mL) H_2SO_4 (solution B). The (solution B) was added slowly to the solution A and stirred at room temperature for 1 h then refluxed for 20 min. Worked up as method Sudarma *et al.* [8] to afford yellowish oil (0.72 g). GC-MS analyses gave (5.97 %), $M^{+\bullet}$ 223, calculated for $C_{11}H_{13}NO_4$ Major fragments: 163 ($M^{+\bullet} - CH_3$), 147 ($M^{+\bullet} - OCH_3$), 135, 115, 107, 91, 77 (C_6H_6).

Method (b): Nitration of methyl eugenol using nitration of dimethoxybenzene approaches: In a 25 mL beaker there were added methyl eugenol (1 g), acetic acid (4 mL) and stirring with a magnetic stirrer in an ice bath there was added, drop by drop a nitrating mixture consisting of 0.5 mL 65 % HNO_3 and 0.5 mL H_2SO_4. A yellow solid immediately started forming. After the addition the mixture was left stirring for 45 min and then it was poured in 30 mL of cold water. The solids were filtered and washed with 2 × 5 mL of ethanol. The product was recrystallized from 30 mL of ethanol and gave 0.86 g of crystalline mass of "green-olive-yellow" kind of colour. GC-MS analyses gave (84.37 %), $M^{+\bullet}$ 223, calculated for $C_{11}H_{13}NO_4$ Major fragments: 163 ($M^{+\bullet} - CH_3$), 147 ($M^{+\bullet} - OCH_3$), 135, 115, 107, 91, 77 (C_6H_6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (1H, s); 6.85 (1H, s);); 5.98 (1H, m); 5.14 (2H, m); 3.91(3H, s, OCH_3); 3.89 (3H, s, OCH_3); 3.76 (2H, d, *J* 6.4 Hz).

Method (c): Nitration of methyl eugenol using nitration of eugenol approaches: A round bottomed flask (50 mL) with magnetic stirrer was charged methyl eugenol (1 g) and acetonitrile (20 mL) then stirred for 5 min. Potassium hydrogen sulphate (0.64 g) and ammonium nitrate (1.4 g) were added and stirred at room temperature for 0.5 h and refluxed for 5 h. Worked up as method Baghernejad *et al.* [14] to afford yellowish to reddish oil. GC-MS analyses gave (11.40 %), $M^{+\bullet}$ 223, calculated for $C_{11}H_{13}NO_4$ major fragments: 163 ($M^{+\bullet} - CH_3$), 147 ($M^{+\bullet} - OCH_3$), 135, 115, 107, 91, 77 (C_6H_6).

RESULTS AND DISCUSSION

Eugenol as a starting material for synthesis of nitro-methyl eugenol was extracted and isolated from clove bud of *Syzygium aromaticum*. Extraction with dichloromethane gave a yellowish clove oil (40.4 %) and this crude oil was fractionated by column chromatography to give eugenol which was confirmed by GC-MS and ^{1}H NMR analysis. The GC-MS result showed eugenol peak with the retention time of 12.407 min (Fig. 1).

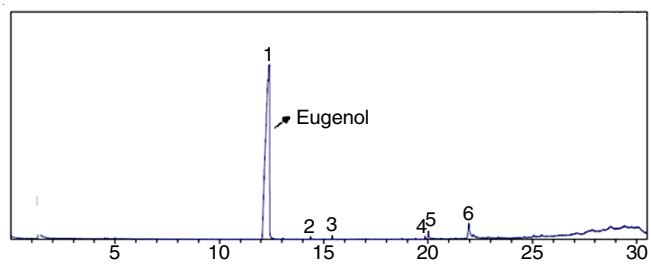


Fig. 1. Chromatogram of isolated eugenol

Eugenol is a simple phenol which is potentially reactive towards electrophilic aromatic substitution. This is because the hydroxy group, (-OH), is a strongly activating, *ortho*- or *para*- directing substituent. Protection of phenols is one of the most common synthetic strategies utilized to mask hydroxyl functionalities during multistep synthetic procedures. Procedures of *o*-methylation are widely employed for the protection and purification of various natural and synthetic products. Eugenol could be easily methylated by dimethyl sulfate in high yield [13]. The GC-MS result showed methyl eugenol peak (86.58 %) with the retention time of 9.928 min (Fig. 2).

Nitration of benzene derivatives with electron donating substituent such as methoxy leads to substitution at *o*- and *p*-positions according to a statistical distribution. Structurally the methyl eugenol is similar to dimethoxybenzene will effect

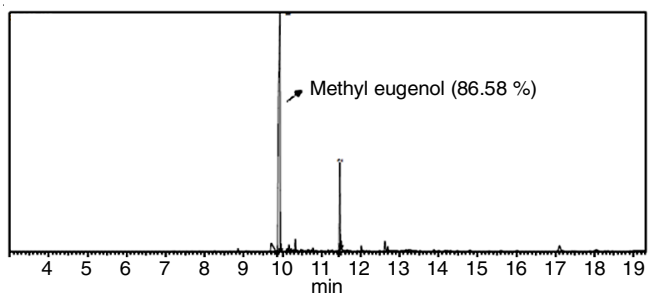


Fig. 2. Chromatogram of methyl eugenol

further substitution reaction such as nitration. The methyl eugenol has two methoxyl groups at 1 and 2 positions on its benzene moiety with electron donating substituent. These two methoxyl group will compete each other to designate -NO_2 at right position. There are three possible positions at benzene moiety of methyl eugenol to designate -NO_2 group *i.e.* at 3, 5 and 6 positions (Fig. 3).

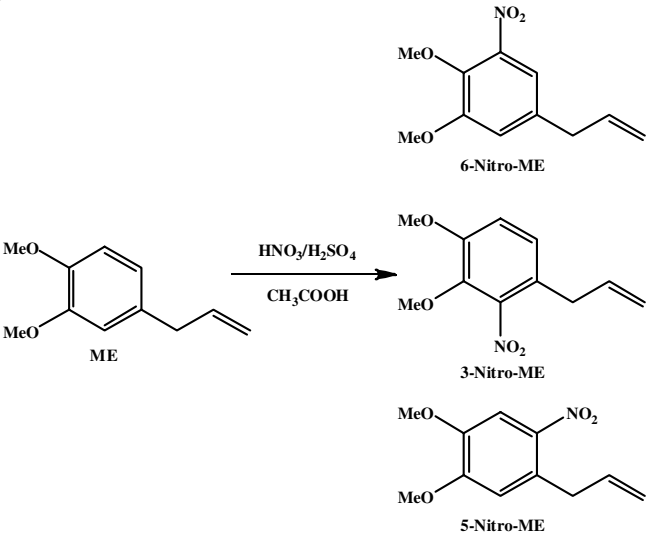


Fig. 3. Proposed nitration reaction of methyl eugenol

Position 3 and 6 were excluded due to steric hindrance by cloud of MeO- and position 5 was desirable, it was due to free steric hindrance and easier to approach by –NO_2. Besides the steric hindrance, the position of –NO_2 was controlled by the two MeO- groups at the benzene moiety. Competition reaction between two MeO- groups nullified *ortho* position for both and only *para* position at carbon number 5 qualified for –NO_2.

Preliminary studied showed that the nitration of methyl eugenol with method (a) which was based on benzene approach gave low yield (5.97 %) (Fig. 4). Oxidation reaction occurred when the methyl eugenol was refluxed with HNO_3 and H_2SO_4. This reaction was vigorous and producing nitro-methyl eugenol at retention time 11.518 min and a lot of unidentified impurities.

Method (b) which was depended on dimethoxybenzene approach used CH_3COOH as a catalyst is desirable to overcome the vigorous reaction in method (a). This reaction was quite mild and providing high yield of nitro-methyl eugenol (84.37 %). The GC-MS result showed nitro-methyl eugenol peak (84.37 %) with the retention time of 11.537 min (Fig. 5). The

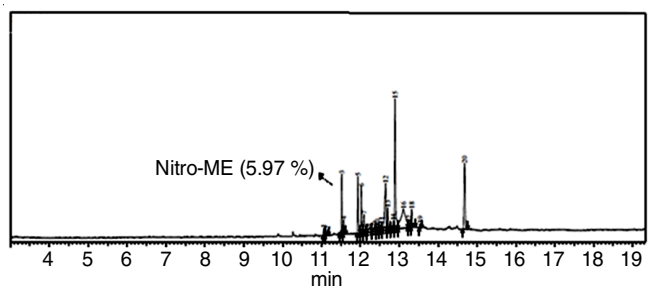


Fig. 4. Chromatogram of nitration of methyl eugenol using method (a)

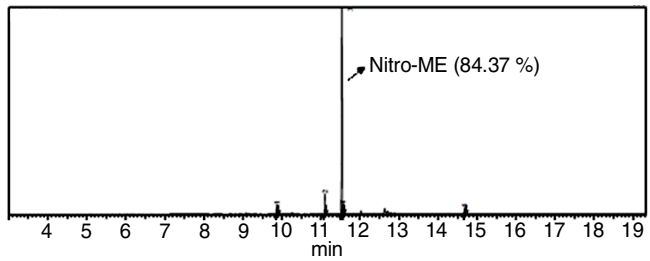


Fig. 5. Chromatogram of nitration of methyl eugenol using method (b)

impurity components was dominated by unreacted methyl eugenol (6.04 %) and unidentified compounds.

Method (c) on the basis of eugenol approach produced low yield of nitro-methyl eugenol (11.40 %). Replacement of HNO_3 with NH_4NO_3 and H_2SO_4 by $KHSO_4$ in method (b) gave no significance yield (Fig. 6).

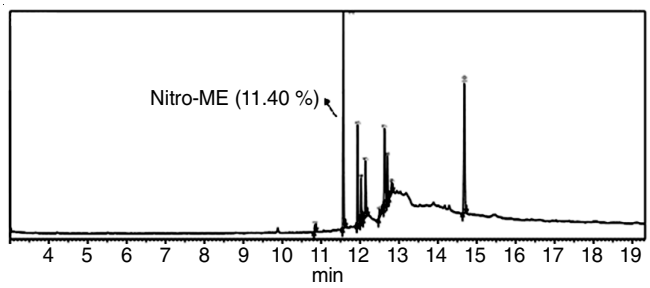


Fig. 6. Chromatogram of nitration of methyl eugenol using method (c)

The GC-MS result showed nitro-methyl eugenol peak (11.40 %) with the retention time of 11.569 min. The impurity components were dominated by unidentified compounds. Reaction condition of these three different methods was presented in Table-1.

TABLE-1
NITRATION OF METHYL EUGENOL
WITH THREE DIFFERENT METHODS

Method	Condition	5-Nitro-methyl eugenol yield (%)
a	70 % HNO_3/0.01 M H_2SO_4, room temp., 1 h, refluxed 20 min	5.97
b	CH_3COOH/65 % HNO_3/H_2SO_4, room temp., 45 min, cold H_2O	84.37
c	NH_4NO_3/$KHSO_4$, CH_3CN, room temp., 0.5 h, refluxed 5 h	11.40

The low cost and the availability of the reagents, easy, clean work-up and high yield make method (b) attractive for 5-nitro-methyl eugenol synthesis.

Conclusion

Method (b) was believed to be a suitable method for the synthesis of 5-nitro-methyl eugenol.

ACKNOWLEDGEMENTS

This research was supported by the Ministries of Research, Technology and Higher Education Republic of Indonesia through "Penelitian Berbasis Kompetensi" Research Grant 2018 for the financial support.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. K.H. Tan and R. Nishida, *J. Insect Sci.*, **12**, 1 (2012); https://doi.org/10.1673/031.012.5601.
2. P. Sudhakar, P. Latha, Y. Sreenivasulu, B.V. Reddy, T. M. Hemalatha, M. Balakrishna and K.R. Reddy, *Indian J. Exp. Biol.*, **47**, 63 (2009).
3. P.G. Rossi, L. Bao, A. Luciani, J. Panighi, J.M. Desjobert, J. Costa, J. Casanova, J.M. Bolla and L. Berti, *J. Agric. Food Chem.*, **55**, 7332 (2007); https://doi.org/10.1021/jf070674u.
4. I.K. Park, J. Kim, S.G. Lee and S.C. Shin, *J. Nematol.*, **39**, 275 (2007);
5. Y.K. Choi, G.S. Cho, S. Hwang, B.W. Kim, J.H. Lim, J.C. Lee, H.C. Kim , W.K. Kim and Y.S. Kim, *Free Radic. Res.*, **44**, 925 (2010); https://doi.org/10.3109/10715762.2010.490837.
6. L. Yin, Z. Sun, Q. Ren, X. Su and D. Zhang, *J. BUON*, **23**, 1174 (2018).
7. R.L. Smith, T.B. Adams, J. Doull, V.J. Feron, J.I. Goodman, L.J. Marnett, P.S. Portoghese, W.J. Waddell, B.M. Wagner, A.E. Rogers, J. Caldwell and I.G. Sipes, *Food Chem. Toxicol.*, **40**, 851 (2002); https://doi.org/10.1016/S0278-6915(02)00012-1.
8. I.M. Sudarma, N. Wazni, N. Wildawaty, E. Yuanita and I.W. Suana, *Asian J. Chem.,* **26**, 173 (2014).
9. M.A. Zolfigol, E. Ghaemi and E. Madrakian, *Molecules*, **6**, 614 (2001); https://doi.org/10.3390/60700614.
10. R.O.C. Norman and R. Taylor, Electrophilic Substitution in Benzenoid Compounds, Elsevier: Amsterdan, p. 301 (1965).
11. G. Booth, Nitro Compounds, Aromatic, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH: Weinheim, edn 6 (2007).
12. C. Waterlot, B. Haskiak and D. Couturier, *J. Chem. Res.*, 106 (2000); https://doi.org/10.3184/030823400103166788.
13. Riyanto, H. Sastrohamidjojo and E. Fariyatun, *IOSR J. Appl. Chem.*, **9**, 105 (2016).
14. B. Baghernejad, M.M. Heravi, H.A. Oskooie and Y.S. Beheshtiha, *Gazi Univ. J. Sci.*, **22**, 169 (2009).