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An Efficient Method on Nitration of Eugenol Using NH_4NO_3 and $KHSO_4$

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The main objective of this research was to find new method for the synthesis of nitro-eugenol. Nitro-eugenol is of considerable importance in the production of other fine chemicals such as amino-eugenol for further chemical synthesis and has also been reported to possess antibacterial, antioxidant and anticancer properties. In an attempt to synthesize nitro-eugenol in high yield, some different nitration methods of eugenol have been applied. An efficient method using NH_4NO_3 in the presence of $KHSO_4$ as a catalyst has been found to give nitro-eugenol in good yield.

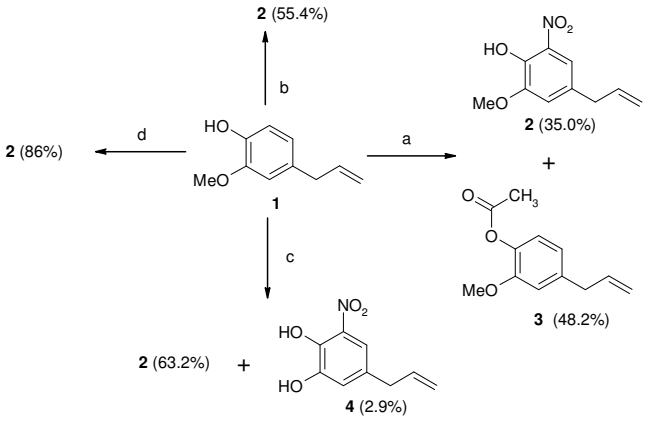
Keywords: Nitration, Eugenol, Nitro-eugenol, NH_4NO_3, $KHSO_4$.

INTRODUCTION

Eugenol (4-allyl-2-methoxyphenol) (**1**), a main constituent of the essential oil obtained from commonly consumed spices such as *Syzygium aromaticum* (clove). has been used for antibacterial[1], acaricidal[2], antihelicobacter[3] and antiproliferative[4]. It is used in the form of a paste or mixture as dental cement, filler and restorative material. Plant oils, including clove, may be used in livestock to inhibit microbial fermentation in waste products. Clove oil may be found in high concentration licorice (glycyrrhizin) products to prevent gel formation in an aqueous solution[5].

Eugenol is considered as a phenolic compound which undergo electrophilic aromatic substitution reactions through nitration. Nitration of organic compounds has long been a very active and rewarding area of research and is the subject of a large body of literature or methods. Nitration is the most important method for introduction of nitrogen functionality on aromatic ring. The nitration of aromatic compounds may be achieved with many nitrating reagents and is a very useful method in organic synthesis and also, nitro compounds find use in many industrial applications[6]. Nitro compounds can be reduced easily to the corresponding amino derivatives.

Eugenol is an aromatic compound similar to benzene with three substituents (hydroxy, methoxy and allyl). These substituents lead the regioselectivity for further reaction of eugenol. The regioselectivity is governed by steric hindrance, interaction between the substituent and the reagent, electronic effects and solvent effects[7]. Those effects will give low to moderate yields of nitro-eugenol synthesis. Thus, a convenient method for the regioselective synthesis of nitro-eugenol is desirable. Eugenol has been investigated and reported for further chemical transformation[8-11] and chemical transformation methods of this compound to nitro-eugenol (**2**) derivative was investigated. Herein, we report our results on the regiospecific nitration of eugenol using several reagents and solvents (**Scheme-I**).



Scheme-I: Synthesis methods of nitro-eugenol (**2**). Conditions: (a) HNO_3/CH_3COOH, rt. 1 h, refluxed 20 min, (b) HNO_3/dilute H_2SO_4, heated 55 ºC, 20 min, (c) $NaNO_3$/$KHSO_4SiO_2$/H_2O (1:1) CH_2Cl_2 rt. 5.5 h, (d) NH_4NO_3/$KHSO_4$, CH_3CN, rt. 0.5 h, refluxed 5 h

Our objective in undertaking this work was to overcome the limitation and draw-back of the reported methods, to reach good or high yielding one pot synthesis of nitro-eugenol using

a combination of reagents and solvents, to consider the rules of green chemistry to implement nitration in ecofriendly conditions.

EXPERIMENTAL

Unless otherwise stated, all chemical reagents were purchased with the highest commercially available purity (Merck and Sigma) and were used without previous purification. The material used included: clove, dichloromethane, hexane, nitric acid, glacial acetic acid, sulfuric acid, sodium nitrite, potassium sulphate, silica gel, ammonium nitrite, acetonitrile, sodium hydroxide, methanol, anhydrous sodium carbonate analytical thin layer chromatography.

GC-MS were recorded on GC-MS QP-5050A, BC-17A and MS 5050A Merk Shimadzu. GC Parameters were setup as follows, oven temp (ºC) = 60.0, oven equil. time (min) = 0.50; injection temp. (ºC) = 280.0; interface temp (ºC) = 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, ^{13}C NMR and DEPT spectra are directly reproduced throughout. The were generally recorded in $CDCl_3$ on a Bruker spectrometer at 400 MHz.

Procedure

Extraction and GC-MS analysis: Dried leaves of *Syzygium aromaticum* (250 g) was grounded to fine particles and percolated with dichloromethane (500 mL) and kept for 24 h and then the liquid extract was filtered and evaporated to afford yellowish oil (20.02 g, 8 %). This oil was analyzed by GC-MS and ^{1}H NMR to confirm the presence of eugenol.

Isolation of eugenol: Eugenol was obtained from the clove oil leaves, according to standard procedure[12] and identified by GC-MS and NMR analyses. M^+. 164, calcd. (%) for $C_{10}H_{12}O_2$ major fragments: 49 (M^+. -CH_3), 131, 121, 103, 91, 77 (C_6H_6, base peak). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.35 (2H, d, *J* = 6.6 Hz, H1'); 3.93 (3H, s, OCH_3); 5.13 (2H, m, H3'); 5.50 (1H, s, OH); 5.91 (1H, m, H2'); 6.5 - 6.96 (3H, aromatic protons).

Method (a): Nitration of eugenol using HNO_3/CH_3COOH: A 50 mL round bottomed flask with magnetic stirrer was charged with 70 % nitric acid (10 mL) and glacial acetic acid (10 mL) then stirred for 5 min. Eugenol 0.5 g (3.05 mmol) was dissolved in glacial acetic acid (5 mL) and added slowly to the solution of nitric acid and acetic acid and stirred at room temperature for 1 h and then refluxed for 20 min. Water (50 mL) was added and the mixture stirred strongly until all organic material had precipitated. The mixture was then filtered to afford a yellow residue. The residue dissolved with dichloromethane and water (50 mL) was added then the organic layer filtered and dried with anhydrous sodium carbonate. Dichloromethane was evaporated to give 0.65 g yellowish oil. After chromatography column gave the desired compound (**2**) (0.22 g, 35.0 %) and compound (**3**) (0,30 g, 48.2 %). Compound (**2**) (oil): $M^{+\cdot}$ 209, calcd. (%) for $C_{10}H_{11}NO_4$ major fragments: 195 ($M^{+\cdot}$ -CH_2), 178, 163, 147, 131, 119, 103, 91 (base peak). IR (KBr, ν_{max}, cm^{-1}, film): 3232 (O-H), 3084 (C=CH-Ar), 3014 (CH=CH_2), 2936, 2829, 1634 (C=C), 1547 (NO_2), 1399, 1327, 1260 (C-O), 1127 (C-O), 1066, 999, 912, 764. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.35 (2H, d, *J* = 6.6 Hz, H1'); 3.93 (3H, s, OCH_3); 5.13 (2H, m, H3'); 5.91 (1H, m, H2'); 6.96 (1H, s, H3); 7.50 (1H, d, *J* = 0.9 Hz, H5); 10.67 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 39.4 (C1'); 56.7 (OCH_3); 115.1 (C5); 117.1 (C3'); 118.6 (C3); 131.2 (C4); 133.6 (C6); 135.9 (C2'); 144.9 (C1); 149.8 (C2). Compound (**3**) (oil): $M^{+\cdot}$ 206, calcd. (%) for $C_{12}H_{14}O_3$. Major fragments: 164 ($M^{+\cdot}$ -$COCH_3$) (base peak), 149, 147, 131, 119, 103, 91. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.31 (3H, s, CH_3CO_2-); 3.38 (2H, d, *J* = 6.7 Hz, H1'); 3.82 (3H, s, OCH_3); 5.10 (2H, m, H3'); 5.97 (1H, m, H2'); 6.77 (2H, m, H3 and H5); 6.95 (1H, d, *J* = 7.9 Hz, H6).

Method (b): Nitration of eugenol using HNO_3/dilute H_2SO_4: A 50 mL round bottomed flask with magnetic stirrer was charged with H_2SO_4 0.01 M (5 mL) and eugenol 0.5 g (3.05 mmol) then stirred for 5 min (solution A). 70 % HNO_3 (10 mL) was mixed with H_2SO_4 0.01 M (10 mL) (solution B). (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 b to afford yellowish oil (0.72 g). Purified by chromatography column gave the desired compound (**2**) (0.353 g, 55.4 %).

Method (c): Nitration of eugenol using $NaNO_3$/$KHSO_4$: Eugenol (1.0 g, 6.10 mmol) was dissolved in dichloromethane (25 mL) and was added to a mixture which contained 4.5 g (33 mmol) of potassium hydrogen sulphate, 3 g (35.3 mmol) of sodium nitrate and 3.5 g of wet silica to 50 % P/P; the mixture was left with constant stirring at room temperature for 4 h. The complete disappearance of the starting product was confirmed by thin layer chromatography (TLC) (dichloromethane: *n*-hexane 1:3). The reacted mixture was filtered through silica and the solid was washed with dichloromethane and the solvent evaporated in vacuum to give a reddish oil. Pure product was obtained after chromatographic column (5:1-3:1 dichloromethane in hexane), which gave of the desired compound (**2**) (956 mg, 75 % yield). Carrasco *et al.*, reported (**Scheme-I**), their method produced compund (**2**) (63.2 %) and compound (**4**) (2.9 %).

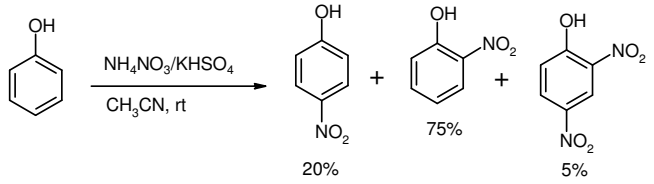
Method (d): Nitration of eugenol using NH_4NO_3/$KHSO_4$: A round bottomed flask (50 mL) with magnetic stirrer was charged 1.00 g eugenol (6.10 mmol) and acetonitrile (20 mL) then stirred for 5 min. Potassium hydrogen sulphate (0.64 g) and ammonium nitrate (1.4 g) were added and stirred at room temperature for 0.5 h then refluxed for 5 h. Worked up as method Bita Baghernejad *et al.*[13] to afford yellowish to redish oil (1.1 g, pure by tlc analysis).

RESULTS AND DISCUSSION

Eugenol is an aromatic compound which has similar properties to benzene. Nitration of benzene derivatives with electron donating substituent such as phenol leads to substitution at the *o*- and *p*-positions according to a statistical distribution. Simple phenol undergo electrophilic aromatic substitution reactions by nitration and an *ortho* nitro group onto phenols is desirable (**Scheme-II**)[12].

TABLE-1
NITRATION OF EUGENOL WITH DIFFERENT METHODS

No.	Method	Conditions	Nitro-eugenol yield (%)
1	a	HNO_3/CH_3COOH, rt. 1 h, refluxed 20 min	35.0
2	b	HNO_3/dilute H_2SO_4, heated 55 ºC, 20 min	55.4
3	c	$NaNO_3/KHSO_4$ SiO_2/H_2O (1:1) CH_2Cl_2 rt. 5.5 h	63.5 -75.0
4	d	$NH_4NO_3/KHSO_4$, CH_3CN, rt. 0.5 h, refluxed 5 h	86.0



Scheme-II: Nitration of simple phenol

Structurally eugenol is similar to phenol but its has two more substituents (methoxy and allyl) will give effect for further substitution reaction. Preliminary studied showed that nitration of eugenol with method (a) gave very low yield. Competitive reaction occurred when CH_3COOH used as a catalyst due to the formation of ester by CH_3COOH with phenolic group of eugenol. Based on this reason, new different methods have to be develop to afford high yields of nitro-eugenol (Table-1).

Concentrated nitric acid can effect nitration but it is not as reactive as a mixture of nitric acid with sulfuric acid. Method (b) used dilute sulfuric acid as catalyst is desirable to overcome the competitive reaction of CH_3COOH in method (a) but it was still to give low yield.

As far green chemistry concerns, sulfuric acid in any form is notorious and its safe disposal is one of the problems and concerns of chemical industries and therefore its replacement with safer reagent is favourable[13]. The replacement of concentrated nitric acid with $NaNO_3$ and sulfuric acid with $KHSO_4$ as a safer reagent might result in more efficient, selective and high yielding nitration with a more reasonable mechanism for generation of NO_2^+. Nitration can also be carried out in organic solvents. In these solvents the formation of NO_2^+ is often the rate controlling step.

$$NaNO_3 + KHSO_4 \longrightarrow HNO_3 + Na^+ + KSO_4^-$$

$$HNO_3 + KHSO_4 \longrightarrow NO_2^+ + H_2O + KSO_4^-$$

The nitration reaction of eugenol with method (c), in the presence of inorganic acidic salt $KHSO_4$, $NaNO_3$ and wet SiO_2 (50 % w/w) in dichloromethane performed under mild and heterogeneous conditions at room temperature to give the products in moderate yields. A combination of sodium nitrate and inorganic acidic salt can act as a solid HNO_3 equivalent and wet SiO_2 acts as a reaction medium providing a heterogeneous effective surface area for *in situ* generation of HNO_3 in low concentrations[6].

Among the solvents used such as acetic acid (method a), CH_2Cl_2 (method c) and CH_3CN (method d), the latter gave the best yields of the nitro-eugenol at reflux temperature. The replacement of $NaNO_3$ in method (c) with NH_4NO_3 in method (d) also gave significance yield. The low cost and the availability of the reagents, easy and clean work-up and high yield make method d attractive for nitro-eugenol synthesis.

Conclusion

Method (d) using green, available, inexpensive and easy to handle $NH_4NO_3/KHSO_4$ reagent was believed to be a suitable method for the synthesis of nitro eugenol.

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REFERENCES

1. S.A. Burt and R.D. Reinders, *Lett. Appl. Microbiol*., **36**, 162 (2003).
2. S.I. Kim, J.H. Yi, J.- Tak and Y.-J. Ahn, *Vet. Parasitol*, **120**, 297 (2004).
3. Y. Li, C. Xu, Q. Zhang, J.Y. Liu and R.X. Tan, *J. Ethnopharmacol.*, **98**, 329 (2005).
4. M. Pisano, G. Pagnan, M. Loi, M.E. Mura, M.G. Tilocca, G. Palmieri, D. Fabbri, M.A. Dettori, G. Delogu, M. Ponzoni and C. Rozzo, *Mol. Cancer*, **6**, 8 (2007).
5. http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-clove.html.
6. M.A. Zolfigol, E. Ghaemi and E. Madrakian, *Molecules*, **6**, 614 (2001).
7. R.O.C. Norman and R. Taylor, Electrophilic Substitution in Benzenoid Compounds, Elsevier, Amsterdan, p. 301 (1965).
8. H. Carrasco A, L. Espinoza C, V. Cardile, C. Gallardo, W. Cardona, L. Lombardo, K. Catalán M, M. Cuellar F and A. Russo, *J. Braz. Chem. Soc*., **19**, 543 (2008).
9. I.M. Sudarma, M. Ulfa and Sarkono, *Indo. J. Chem*., **9**, 84 (2009).
10. I.M. Sudarma, M. Ulfa and Sarkono, *Indo. J. Chem*., **9**, 267 (2009).
11. I.M. Sudarma, Proceeding International Conference on Medicinal Plant, WMCU, Surabaya, Vol. 1, 1-6 (2010).
12. J. Mannoppo (2008); http://molucasablog.blogspot.com/2010/06/isolasi-eugenol-dari-bunga-cengkeh-dan.html.
13. B. Baghernejad, M.M. Heravi, H.A. Oskooie and Y.S. Beheshtiha, *Gazi Univ. J. Sci.*, **22**, 169 (2009).