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Competitive Reaction of –OH and –NH_2 Functional Groups on Synthesis of Bioactive *ortho*-Cetamol Derivative (4-Allyl-2-methoxy-N-acetyl-*o*-amino phenol) from Amino-Eugenol

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The main aim of this research was to develop new or novel compounds with potential biological activity from readily accessed natural products, in particular eugenol (**1**). A new *ortho*-cetamol derivative (4-allyl-2-methoxy-N-acetyl-*o*-amino phenol) was synthesized from amino-eugenol which was prepared by series reactions from eugenol (4-allyl-2-methoxy-phenol). Eugenol has been transformed to its nitro eugenol (**2**) in good yield by adding potassium hydrogen sulfate and ammonium nitrate. The nitro group of eugenol reduced smoothly to amino-eugenol (**3**) by treating with zinc and formic acid. Reaction of amino eugenol with acetyl chloride in the presence of sodium carbonate produced 2-acetato-5-allyl-3-methoxy-aniline (**4**) (16.16 %) and 4-allyl-2-methoxy-N-acetyl-*o*-aminophenol (**5**) (58.58 %) and competitive reaction occured between –OH and –NH_2 groups of amino-eugenol during the acylation reaction due to steric hindrance.

Keywords: Competitive reaction, Steric hindrance, *ortho*-Cetamol, Amino-eugenol.

INTRODUCTION

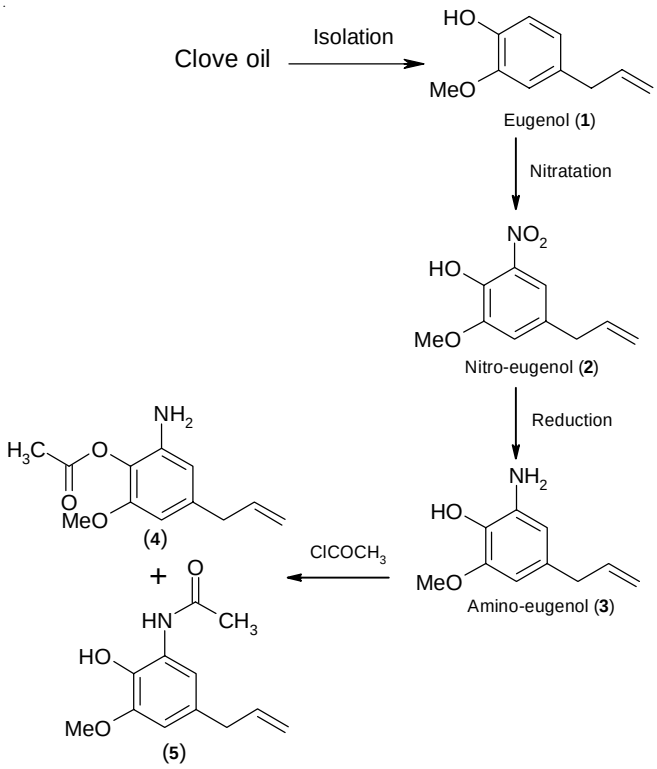
Amino-eugenol (4-allyl-2-methoxy-6-amino phenol) was derived from bioactive eugenol which was isolated from clove oil. Cloves (*Syzygium aromaticum*) are harvested primarily in Indonesia, Madagascar and Zanzibar, India, Pakistan and Sri Lanka. According to FAO, Indonesia produced almost 80 % of the world's clove output in 2005. Cloves contain eugenol (4-allyl-2-methoxyphenol), a main constituent of the essential oil and have been used for antibacterial[1], acaricidal[2], anti-helicobacter[3] and antiproliferative[4]. Eugenol is considered as a phenolic compound similar to benzene with three substituents (hydroxy, methoxy and allyl) which undergo electrophilic aromatic substitution reactions through nitration[5]. Nitro-eugenol is of considerable importance in the production of other fine chemicals such as amino-eugenol for further chemical synthesis. Amino-eugenol has two functional groups namely –OH and –NH_2 which could be easily acylated by chloroacetyl to produce an ester (–O-acetyl) and an amide (N-acetyl). N-Acetylation of amines is a common important chemical reaction in organic synthesis[6].

N-Acetyl eugenol (*ortho*-cetamol) has two functional groups which are similar to *para*-cetamol with different position (*ortho* and *para*) on their benzene ring. These functional groups may have similar biological effect to paracetamol which is a commonly used analgesic and antipyretic drug and is being used since more than six decades. It has been proved to be an excellent and effective drug for pain relief and control of fever in adults and children. Some novel alkylated *meta*-cetamol compounds showed antimicrobial and anthelmintic activities[7]. Therefore, there has been an impetus and effort in search for discovery and development of newer pharmacologically active paracetamol derivatives. Hence we made an attempt to synthesize a new *ortho*-cetamol derivative from amino-eugenol which was prepared by series reaction from natural isolated eugenol (**Scheme-I**).

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, methanol, sodium hydroxide pellet, acetonitrile, ammonium nitrite, potassium hydrogen sulfate, zinc powder, formic acid, silica gel, sodium carbonate anhydrous, acetyl chloride, analytical thin layer chromatography.

Instrumentation: GC-MS were recorded on GC-MS QP-5050A, BC-17A and MS 5050A Merk Shimadzu. GC parameters were setup as follows: Oven temp.: 60 °C, Oven equil. time: 0.5 min; Injection temp.: 280 °C; Interface temp.: 300 °C; Column length: 30 m; Column diameter: 0.25 mm;



Scheme-I: Synthesis of *ortho*-cetamol (**5**) from amino-eugenol

Column pressure: 100 kPa; Column flow: 1.6 mL/min; Linear velocity: 46.4; Split ratio: 22; Total flow: 40.2 mL/min; Program time: 27 min. MS parameter, Start *m/z* = 33.00 End *m/z* = 550.00; Scan interval (sec.) = 0.50; Scan speed (amu/sec) = 1000. The original ^{1}H NMR, ^{13}C NMR and DEPT spectra are directly reproduced throughout. They were generally recorded in $CDCl_3$ on a Bruker spectrometer at 400 MHz.

Procedure

Extraction and GC-MS analysis: Dried clove (100 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 (8.5 g) (8.50 %). This oil was analyzed by GC-MS and ^{1}H NMR to confirm the presence of eugenol.

Isolation of eugenol (1)[10]: Eugenol was obtained from the clove oil, according to standard procedure and identified by GC-MS and NMR analyses. $M^{+\cdot}$ 164, calcd. for $C_{10}H_{12}O_2$ Major fragments: 49 ($M^{+\cdot}$ –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).

Preparation of nitro-eugenol (2)[10]: A round bottomed flask (50 mL) with magnetic stirrer was charged 1 g eugenol (6.10 mmol) and acetonitrile (20 mL) then stirred for 5 min. Potassium hydrogen sulfate (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 a method by Baghernejad *et al.*[8] to afford yellowish to reddish oil (1.1 g, pure by TLC analysis). GC-MS, $M^{+\cdot}$ 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). FTIR (ν_{max}, cm^{-1}): 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).

Preparation of amino-eugenol (3)[11]: Nitro-eugenol (620 mg, 2.97 mmol) was dissolved in methanol (10 mL) and the solution stirred with zinc powder (1 g) and formic acid (2.5 mL) for 10 min. Worked up as Gowda *et al.*[9], to afford the desired amino eugenol compound (452 mg, 2.52 mmol, 85 % yield). GC-MS: $M^{+\cdot}$ 179, calcd. for $C_{10}H_{13}NO_2$ Major fragments: 164, 152, 136, 118, 106, 91 (base peak). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.21 (2H, d, CH_2), 3.48 (1H, s, NH); 3.68 (1H, s, NH), 3.85 (3H, s, OCH_3); 5.05 (2H, m, CH_2), 5.25 (1H, s, OH); 5.91 (1H, m, H2'); 6.18 (1H, s, ArH), 6.25 (1H, s, ArH). FTIR (ν_{max}, cm^{-1}): 3389 (O-H), 3306 (NH_2), 2943 (C=CH-Ar), 2848 (CH=CH_2), 1608 (C=C), 1131 (C-O).

Acylation of amino eugenol: To stirred solution of amino eugenol (200 mg, 1.12 mmol) and sodium carbonate (400 mg, 3.78 mmol) in dry dichloromethane (20 mL) cooled to 0 °C, chloro acetyl chloride (0.4 mL, 5 mmol) was added dropwise. Stirring was continued below 5 °C for another 15 min and then the mixture was stirred further at room temperature for 1 h. Distilled water (25 mL) was added to the solution, then the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The dichloromethane was combined and dried. Evaporation of the solution to dryness gave gum (205 mg) and further purification gave *ortho*-cetamol (4-allyl-2-methoxy-N-acetyl-*o*-amino phenol) (**5**) (145mg, 0.656 mmol, 58.58 %), $M^{+\cdot}$ 221, calcd. for $C_{12}H_{15}NO_3$ Major fragments: 179 ($M^{+\cdot}$ –$COCH_3$, characteristic for amino-eugenol), 164 ($M^{+\cdot}$ –$NHCOCH_3$, characteristic for eugenol), 147, 136, 118, 91 and 77. FTIR (ν_{max}, cm^{-1}): 3309 (O-H), 3084 (C=CH-Ar), 3014 (CH=CH_2), 2930 (C-H), 1657 (NCO), 1514 (-NH-), 1267 (C-N) and 2-aceto-5-allyl-3-methoxy-anilin (**4**) (40 mg, 0.18 mmol, 16.16 %), GCMS: $M^{+\cdot}$ 221, calcd. for $C_{12}H_{15}NO_3$ Major fragments: 203, 179, 164, 147, 136, 118, 91 and 77. FTIR (ν_{max}, cm^{-1}): 3306 (NH_2), 2943 (C=CH-Ar), 2848 (CH=CH_2), 1714 (C=O), 1608 (C=C), 1131 (C-O).

RESULTS AND DISCUSSION

In the synthetic approach based on chemical transformation of amino-eugenol in **Scheme-I**, as a first step required nitro-eugenol (**2**) as a precursor. This was prepared by isolation of eugenol (**1**) from clove oil then converted to nitro-eugenol (**2**) in good yield using potassium hydrogen sulfate and ammonium nitrate[5]. The structure of the isolated eugenol (**1**) and nitro-eugenol (**2**) were confirmed by their mass spectrum and ^{1}H NMR. The GC-MS analysis of (**1**) showed the molecular ion at *m/z* 164, consistent with the molecular formula $C_{10}H_{12}O_2$. The ^{1}H NMR spectrum of (**1**) confirmed 12 protons, with the methoxy singlet at 3.93 ppm; three aromatic proton of benzene ring at 6.5 - 6.96 ppm; one phenolic proton at 5.50 ppm; and the remaining five allyl proton at 3.35, 5.13 and 5.91 ppm. The GC-MS analysis of (**2**) showed molecular ion at *m/z* 209, calculated for $C_{10}H_{11}NO_4$ The FT-IR of (**2**) gave a

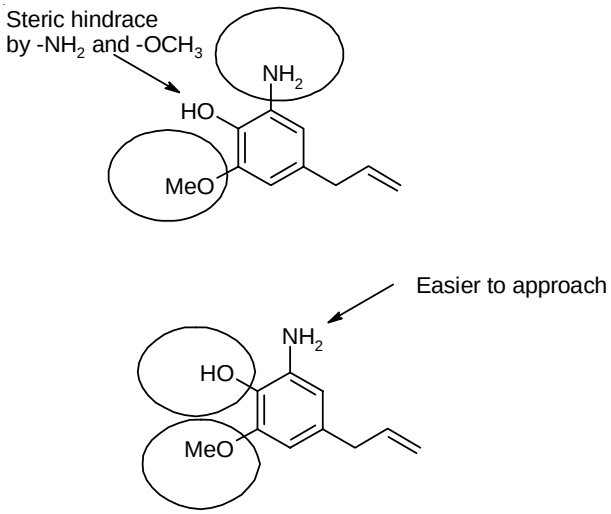
characteristic –OH phenol dan nitro groups stretching bands at frequency 3232 (O-H) and 1547 (NO_2). The ^{1}H NMR. spectrum of (**2**) gave signal –OH shifted downfield at 10.67 ppm due to the formation of hydrogen bonding between hydrogen from –OH with oxygen from NO_2.

Further step is preparation of amino-eugenol (**3**) from nitro-eugenol (**2**) to the corresponding amine. Typical reducing agent such as zinc and formic acid, has been used for the reduction of nitro aromatic. The structure of amino-eugenol (**3**) was confirmed spectroscopically. The GC-MS analysis observed molecular ion at *m/z* 179 consistent with the molecular formula $C_{10}H_{13}NO_2$. Comparison of the ^{1}H NMR spectra of (**2**) and (**3**) revealed that the chemical shifts of the protons were very similar except the amino group of (**3**) showed a two protons singlet at 3.48 and 3.68 ppm. The remaining protons were assigned to the phenolic as a signal at 5.25 ppm, a methoxy at 3.85 ppm, the protons of methylene which attached on benzene ring at 3.21 ppm and a methylene terminal at 5.05 ppm. An olefinic proton gave signal at 5.91 ppm and two aromatic protons gave signal at 6.18 and 6.25 ppm. In the FT-IR spectrum of (**3**) a characteristically sharp bands for the amino group was present at 3306 cm^{-1}.

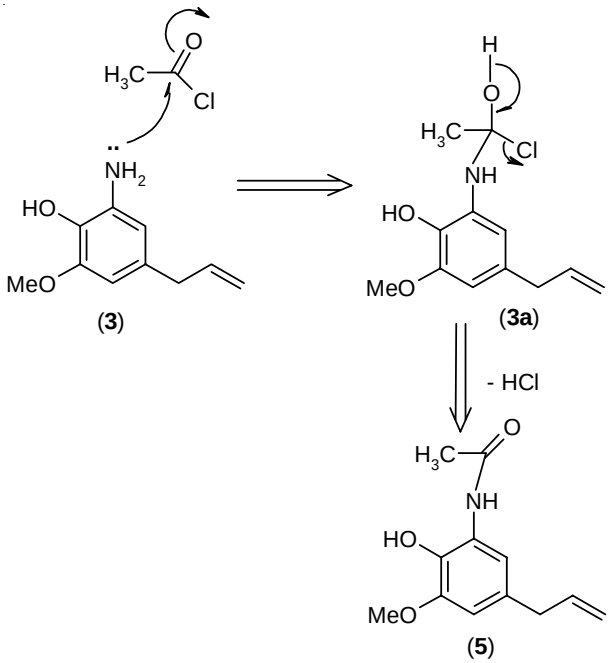
Final step for the synthesis of *ortho*-cetamol (**5**) is acylation of amino-eugenol, the simplest and most used method for the transformation of amines to be acetamides is N-acylation of an amine with an acid halide or anhydride in the presence of base. The chemical transformation of the amino-eugenol (**3**) to *ortho*-cetamol (**5**) was prepared by stirring amino-eugenol (**3**) in dichloromethane with anhydrous sodium carbonate and the acetyl chloride. All prepared derivatives were characterized using GC-MS, FTIR and their formation mechanism. The GC-MS analysis showed two isomers present namely the 4-allyl-2-methoxy-N-acetyl-*o*-amino phenol or *ortho*-cetamol (**5**) and 2-aceto-5-allyl-3-methoxy-anilin (**4**) which have the same molecular ion at *m/z* 221, corresponding to the molecular formula $C_{12}H_{15}NO_3$.

In the FT-IR of (**4**) and (**5**) (Table-1) showed significant different, compound (**4**), a characteristically sharp band for amine group occurred at 3306 cm^{-1} and strong absorption at 1714 cm^{-1} for carbonyl of acetyl group and compound (**5**), a characteristically sharp band for the amide carbonyl group was present at 1657 cm^{-1} and broad band for hydroxy group was present at 3309 cm^{-1}.

Competitive reaction occured on this reaction due to the presence of two reactive functional groups such –OH and –NH_2 which could undergo substitution reaction with acetyl chloride. *ortho*-Cetamol (**5**) was favourable formed (yield 58.58 %) than 2-aceto-5-allyl-3-methoxy-anilin (**4**) (yield 16.16 %) due to effect of steric hindrance. Amino group (-NH_2) on amino eugenol (**3**) was less hindered than hydroxy group (-OH) so more easily attack or approach by acyl chloride. On the other hand the hydroxy group is shading by two neighbouring functional groups (-OCH_3 and –NH_2) so difficult to approach by acyl chloride.



Mechanistically, the formation of *ortho*-cetamol (**5**) can be explained as follows: amino group of amino eugenol (**3**) has two lone pair electron as a nucleophilic will attack the carbonyl of acetyl chloride to produce intermediate (**3a**) and elimination of HCl would then afford compound (**5**).



Scheme-II: Mechanism the formation of *ortho*-cetamol (**5**)

TABLE-1
MS, FTIR AND YIELD OF 2-ACETO-5-ALLYL-3-METHOXY-ANILIN (**4**) AND 4-ALLYL-2-METHOXY-N-ACETYL-*O*-AMINO PHENOL (**5**)

Compd.	MS	FTIR	Yield (%)
4	221, 203, 179, 164, 147, 136, 118, 91, 77	**3306** (NH_2, sharp), 2943 (C=CH-Ar), 2848 (CH=CH_2), **1714** (C=O), 1608 (C=C), 1131 (C-O)	16.16
5	221, 179, 164, 147, 136, 118, 91, 77	**3309** (O-H, broad), 3084 (C=CH-Ar), 3014 (CH=CH_2), 2930 (C-H), **1657** (NCO), 1514 (-NH-), 1267 (C-N)	58.58

Conclusion

In current research, a new *ortho*-cetamol (**5**) derivative was synthesized from amino-eugenol (**5**) which was prepared by series reactions from eugenol (4-allyl-2-methoxy-phenol) and is a promising lead molecule for the development of new drug.

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