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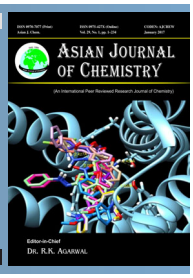

N,N-Dimethylation of Nitro-eugenol to its New 4-Allyl-2-(dimethylamino)-6-methoxyphenol *via* Eschweiler–Clarke Methylation Reaction

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Eugenol is a main constituent of essential oil and can be extracted and isolated from clove (*Syzygium aromaticum*). Eugenol has widely biological activities such as antiseptic and anesthetic. Eugenol can be used as a fine chemical for further synthesis of new or novel compounds. The main aim of this research was to develop new or novel compounds with potential biological activity such as 4-allyl-2-(dimethylamino)-6-methoxyphenol from eugenol (**1**). Derivatization of eugenol to its nitro derivative (**2**) can be achieved by treated with ammonium nitrate and potassium bisulphate. One-pot synthesis method *via* the Eschweiler–Clarke methylation of nitroeugenol using formaldehyde, formic acid, Zn catalyst, gave the *N,N*-dimethylation of nitro moiety. The result was then analyzed by GC-MS and NMR. The GC-MS analyses showed peak with *m/z* of 207 (59.51 %) and consistent with the molecular formula $C_{12}H_{17}O_2N$. The ^{1}H NMR was in accordance with the proposed structure which showed 17 protons corresponded to 4-allyl-2-(dimethylamino)-6-methoxyphenol (**3**).

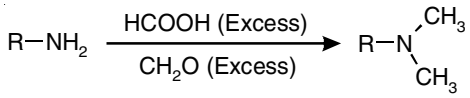
Keywords: Nitro-eugenol, One-pot synthesis, Eschweiler–Clarke methylation, Schiff base.

INTRODUCTION

It has been reported that eugenol was isolated from clove (*Syzygium aromaticum*) can be used as a fine chemical for further synthesis of new or novel compounds [1-5]. In continuation of our work on chemical transformation of eugenol, method of *N,N*-dimethylation of nitroeugenol (4-allyl-2-methoxy-6-nitrophenol) using formaldehyde catalyzed with zinc powder and formic acid was performed. This synthesis involved direct reduction of nitro-eugenol compound without isolating the intermediate of primary amine and make the synthesis is more efficient compare to the normal synthesis of amine.

Common methods for preparation of methylated amines include nucleophilic attack of methylating reagents, for example, methyl iodide or dimethyl sulfate, or methylation with formaldehyde in the presence of a reducing reagent, for example, formic acid, metal hydrides or hydrogen gas and nitro compounds. The aromatic nitro compounds could be transformed into dimethyl amines directly in the presence of a simple iron catalyst without ligand [6]. The *N*-methylation of amines and nitro compounds with CO_2/H_2 can be realized with up to 97 % yield under relatively mild reaction conditions. *N*-Formylation becomes the main reaction if the reaction was performed under milder conditions or using $Pd/ZnZrO_x$ as the catalyst [7].

The Eschweiler–Clarke methylation is a chemical reaction whereby a primary (or secondary) amine is methylated using excess formic acid and formaldehyde according to the following reaction:



It is named for the German chemist Wilhelm Eschweiler (1860-1936) and the British chemist Hans Thacher Clarke (1887-1972) [8].

A facile synthesis of *N,N*-dimethylanilines from primary aromatic amines and dimethyl carbonate has been achieved for the first time in the presence of diphenylammonium triflate. *N,N*-dimethylanilines were selectively obtained in high yields [9]. A series of TiO_2 supported nano-Pd catalysts (Pd/TiO_2) were prepared and used for the *N,N*-dimethylation of different amines and nitro compounds with methanol under UV irradiation at room temperature [10].

EXPERIMENTAL

Unless otherwise stated, all chemical reagents were purchased with the highest commercially available purity (Merck and Sigma). The materials used were: dried clove buds, distilled

water, dichloromethane (DCM), sodium hydroxide, anhydrous sodium sulphate, *n*-hexane, acetonitrile, ammonium nitrate, potassium bisulphate, ethanol, formaldehyde, formic acid, zinc powder, methanol and silica gel 60 mesh.

General procedure:

Preparation of cloves: Dried clove buds were ground into fine particles for extraction.

Cloves extraction: Extraction of cloves was done by using Sudarma *et al.* method [1]. Approximately 250 g of clove powder were macerated with 1,750 mL dichloromethane and stored away from light for 2 × 24 h. The result then filtered and the filtrate was collected. The filtrate was evaporated with rotary evaporator to obtain the extract. Afterwards, the solvent-free extract was weighed and tested with thin layer chromatography (TLC).

Eugenol isolation: Clove oil (5 g) were dissolved in dichloromethane (15 mL). The mixture was added with NaOH (1.22 g), which had been dissolved with H_2O (9.15 mL). Mixture was stirred with magnetic stirrer for 15 min in room temperature. Two layers were formed where the water phase in the top layer was separated from the organic phase in the bottom layer. The water phase that contains eugenol salt was acidified with concentrated HCl to pH 3. The bottom layer (A) was then separated from the top layer with separation funnel. The remaining top layer then extracted with 15 mL dichloromethane and the bottom layer (B) was collected and combined with the previous bottom layer (A). The extraction with dichloromethane was done three times. The mixture was washed with water to neutral pH. The bottom layer (crude eugenol) was collected and added with anhydrous Na_2SO_4. The crude eugenol then filtered with dichloromethane:*n*-hexane (1:1) mixture and evaporated with rotary evaporator.

Nitration of eugenol [11]: Eugenol (1.6 g) was dissolved in acetonitrile (20 mL) and stirred with magnetic stirrer. Solution of NH_4NO_3 (1.4 g) and $KHSO_4$ (0.64 g) was added to the mixture. Mixture then refluxed for 5 h and filtered with filter paper to obtain the filtrate (A). The remaining precipitation was washed by acetonitrile (20 mL) and filtrate (B) was obtained, which then combined with (A). Afterwards, filtrate was dried with anhydrous Na_2SO_4 and filtered. Filtrate was evaporated with rotary evaporator to obtain the liquor, which then was tested with TLC. Compounds in liquor were separated by using column chromatography with eluents as follow: *n*-hexane 100 %, *n*-hexane:dichloromethane (1:1) and dichloromethane 100 %. Fractions obtained then were identified by TLC. Fractions with the same spot were combined and evaporated. The result then tested for purity with TLC.

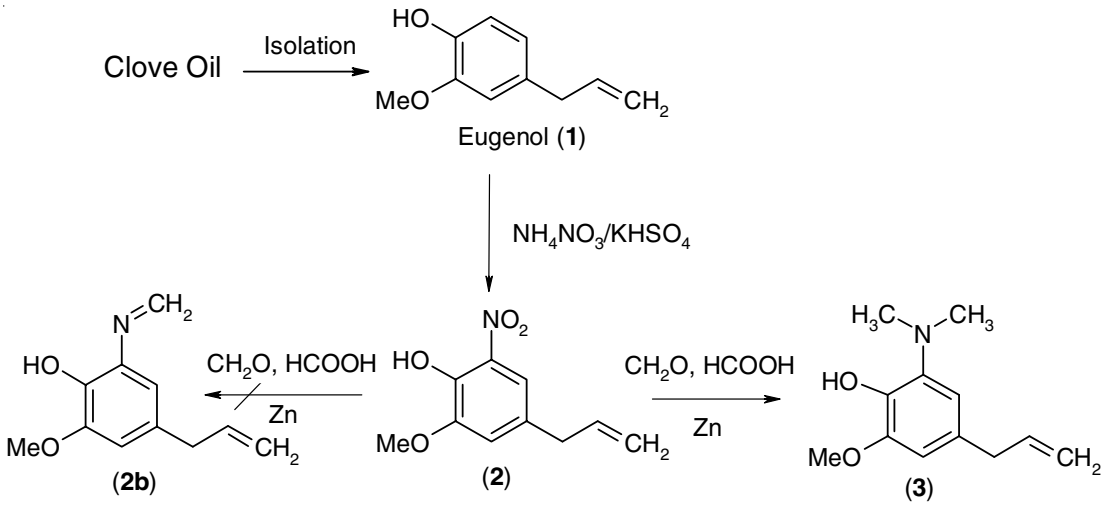
Synthesis of amine [12]: A mixture of nitroeugenol (0.72 mmol), formaldehyde (0.72 mmol) and Zn powder (7.32 mmol) was dissolved in 25 mL of ethanol. Formic acid (4.5 mmol) was then added to the mixture. Reaction was heated at 65 °C for approximately 4.5 h and filtered while hot. Filtrate was extracted with dichloromethane (3 × 25 mL) and the organic phases were combined, which then dried with Na_2SO_4. Mixture was filtered and evaporated. Afterwards, the obtained product was analyzed by using GC-MS.

RESULTS AND DISCUSSION

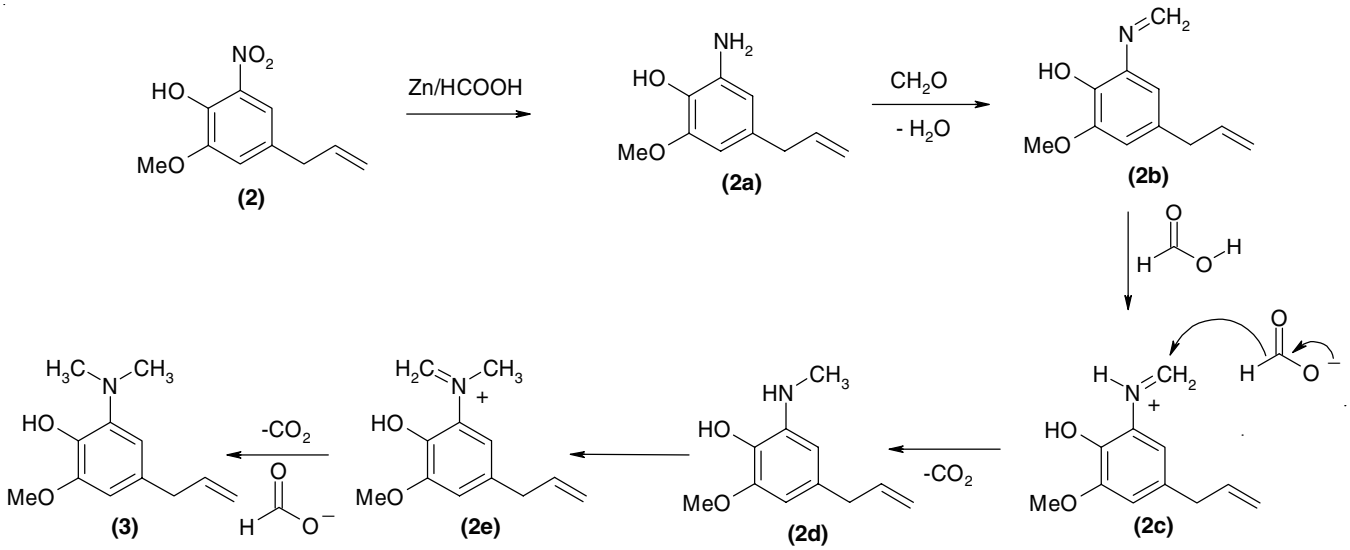
Herein, we reported derivatization of eugenol isolated from clove (*Syzygium aromaticum)* to its new *N,N*-dimethylamino derivative *via* Eschweiler-Clarke methylation of nitro-eugenol. Eschweiler-Clarke methylation normally used a primary (or secondary) amine, aldehyde and formic acid, but in this one pot synthesis the nitro compound (nitro-eugenol) was used instead of amine compound and make this method more efficient because one step reaction was eliminated.

One pot reaction of nitro-eugenol (**2**) and formaldehyde, formic acid and zinc catalyst expected to afford Schiff base (**2b**), in fact this compound was not present and fortunately unexpected of *N,N*-dimethyl amine derivative or 4-allyl-2-(dimethylamino)-6-methoxyphenol (**3**) was formed due to further reaction occurred on Schiff base moiety or imine of **2d** by formic acid. The formic acid acts as a source of hydride and reduces the imine to a secondary amine and the second methylation occurred on secondary amine to form final products (**3**) (**Scheme-I**).

GC-MS analyses of one pot reaction of nitro-eugenol with formaldehyde and formic acid gave eugenol (25.02 %), unreacted nitro-eugenol (5.13 %) and *N,N*-dimethylamino derivative (59.51 %) (Fig. 1).



Scheme-I: Synthesis of new *N,N*-dimethylamino derivative (**3**) from eugenol (**1**)



Scheme-II: Formation of 4-allyl-2-(dimethylamino)-6-methoxyphenol (**3**)

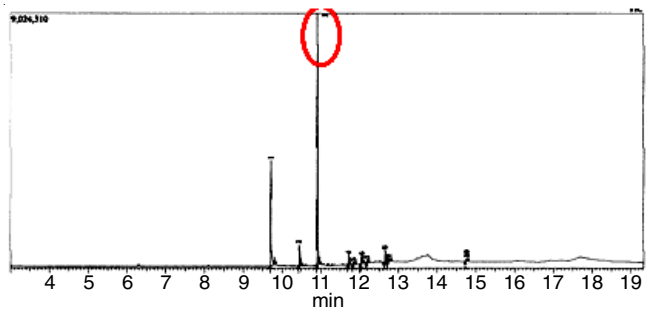


Fig. 1. GC-MS analysis the reaction of nitro-eugenol with formaldehyde, formic acid and Zn catalyst

The GC-MS analysis showed peak 3 as a major *N,N*-dimethylamino derivative which has molecular ion at *m/z* 207 corresponding to the molecular formula $C_{12}H_{17}NO_2$. Further purification of *N,N*-dimethylamino by chromatography gave brown gum. Analysis of (**3**) by NMR spectroscopy provided valuable information to establish its structure [13]. The ^{1}H NMR was in accordance with the proposed structure which showed 17 protons corresponding to two N-methyl singlet at δ 2.71, one methoxy singlet at δ 3.85, one methylene doublet at δ 3.31, one methylene multiplet at δ 5.06, one olefinic at δ 5.94 and two aromatik protons singlet at δ 6.49 and 6.55, one hydroxy at δ 3.47.

The formation mechanism of 4-allyl-2-(dimethylamino)-6-methoxyphenol (**3**) could be explained as follow (**Scheme-II**): nitro-eugenol (**2**) was reduced by Zn/formic acid to afford intermediated unisolated amino-eugenol (**2a**). The first methylation of the amine begins with imine or Schiff base (**2b**) formation with formaldehyde. The Zn/formic acid acts as a source of hydride and reduces the imine to a secondary amine (**2d**). The driving force is the elimination of the gas carbon dioxide. The second methylation occurs with the secondary amine (**2d**) attacked poor electrons of carbonyls group of formaldehyde followed by condensation of H_2O to form intermediate (**2e**) which was further reduced to the final product 4-allyl-2-(dimethylamino)-6-methoxyphenol (**3**) by Zn/formic acid.

The reaction of nitro-eugenol (**2**) with formaldehyde, formic acid and Zn catalyst gave also side products eugenol (**1**) and unreacted nitro eugenol (**3**). The occurance of the products was due to elimination of amino group by acid. This acid could be reacted with amino group through nucleophilic substitution reaction.

Conclusion

Nitro-eugenol prepared from nitration of eugenol could be transformed to 4-allyl-2-(dimethylamino)-6-methoxyphenol *via* the Eschweiler–Clarke methylation in moderate yield.

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