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One-Pot Synthesis of 5-Allyl-8-hydroxy-7-methoxy-2-methylquinoline

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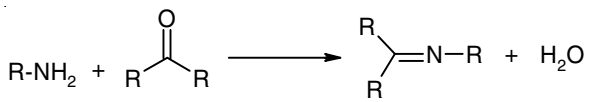
The main aim of this research was to develop novel Schiff base compounds from readily accessed natural products, in particular eugenol (**1**). A new 5-allyl-8-hydroxy-7-methoxy-2-methylquinoline was synthesized *via* one-pot Schiff base reaction of nitro-eugenol with acetaldehyde. Normally Schiff base was prepared directly from primary amine and aldehyde, but in this paper it was prepared directly from nitro compound such as nitro-eugenol and acetaldehyde with three different catalyst namely: Fe/HCl or Zn/formic acid or Sn/HCl in ethanol. These catalysts were used to optimize the yield of Schiff base without isolating the primary amine. Nitro eugenol (**2**) was synthesized in good yield by adding potassium hydrogen sulfate and ammonium nitrate. This nitro-eugenol was treated with Fe/HCl or Zn/formic acid or Sn/HCl in ethanol under refluxed condition to afford 5-allyl-8-hydroxy-7-methoxy-2-methylquinoline (**3**) (73.49 %), (43.50 %) and (40.14 %) respectively.

Keywords: One-pot synthesis, Schiff base, Quinoline ring, Nitro-eugenol, Fe catalyst.

INTRODUCTION

Previously it has been reported that eugenol can be used as a fine chemical for further synthesis of new or novel compounds [1-4]. In continuation of our work on chemical transformation of eugenol, one-pot synthesis of Schiff base compounds derived from nitro-eugenol catalyzed by Fe/HCl, Zn/formic acid or Sn/HCl were reported. 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 Schiff base. A Schiff base is a nitrogen analogue of an aldehyde or ketone in which the C=O group is replaced by C=N-R group. Normally Schiff base is synthesized from a primary amine and carbonyl compounds. It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme:



Novel one-pot synthesis of Schiff base compounds derived from different diamine and aromatic aldehyde catalyzed by P_2O_5/SiO_2 under free-solvent condition at room temperature has been reported by Devidas *et al.* [5]. Other author reported that mild and convenient one pot synthesis of Schiff bases in the presence of P_2O_5/Al_2O_3 as new catalyst under solvent-free conditions [6]. Schiff bases are very important class of compounds due to their wide range of biological activities and even industrial applications [7]. Schiff bases are also interesting range of applications in various fields of science [8]. Many Schiff bases are known to be medicinally important and are used to design medicinal compounds [9].

Aromatic primary amine such as aniline undergoes Schiff base reaction with aldehyde to form quinoline ring. Quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Indeed some of the quinoline derivatives are oldest compounds, which have been utilized for the treatment of a variety of diseases [10]. In this paper, an effort in search for design and synthesis of newer biologically active Schiff base derivative from eugenol are presented.

EXPERIMENTAL

The material used included: clove, dichloromethane, hexane, methanol, acetaldehyde, ethanol, sodium hydroxide pellet, acetonitrile, ammonium nitrite, potassium hydrogen sulfate, iron powder, zinc powder, tin powder, hydrochloric acid, formic acid, sodium carbonate anhydrous, analytical thin layer chromatography, silica gel chromatography.

General procedure: Dried clove buds were ground into fine particles (powder) for extraction. Approximately 250 g of clove powder were percolated with 1,750 mL dichloromethane and stored away from light for 2 × 24 h. The result

then filtered and the filtrate was evaporated with rotary evaporator to obtain the clove oil (57.42 g, 22.97 %).

Isolation of eugenol: 21.9 g of clove oil were dissolved in 65.7 mL dichloromethane. The mixture was added with 5.36 g NaOH, which had been dissolved with 39 mL H_2O. Mixture was stirred with magnetic stirrer for 1 h at room temperature. Two layers were formed where the aqueous phase in the top layer was separated from the organic phase in the bottom layer. The aqueous phase that contains eugenol salt was acidified with concentrated HCl to pH 3. The organic layer was then separated from the aqueous layer with separation funnel. The remaining aqueous layer then extracted with 15 mL dichloromethane (3×). The crude eugenol then filtered with dichloromethane:*n*-hexane (1:1) through silica gel mixture and evaporated with rotary evaporator to afford eugenol (18.33 g, 83.7 %).

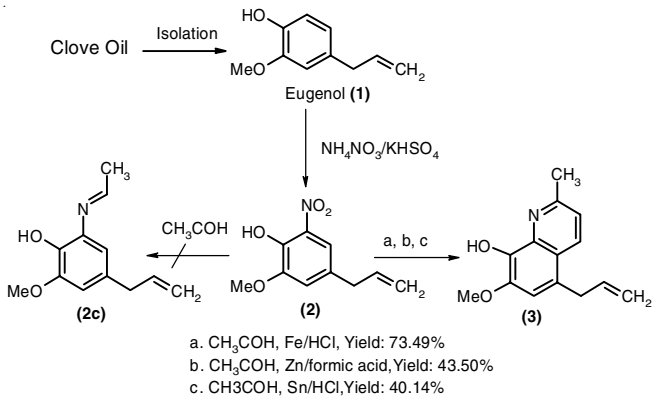
Nitration of eugenol: Nitration reaction was conducted by the method of Baghernejad *et al.* [11]. Approximately 1.6 g of eugenol was dissolved in 20 mL acetonitrile with magnetic stirrer. Solution of 1.4 g NH_4NO_3 and 0.64 g $KHSO_4$ was added to the mixture. Mixture then refluxed for 5 h and filtered with filter paper to obtain the filtrate (A). The remaining precipitation was washed by 20 mL acetonitrile 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 Schiff base: This reaction was conducted by adopting method from Rao *et al.* [12]. A mixture of nitroeugenol (0.72 mmol), acetaldehyde (0.72 mmol) and Fe powder (7.32 mmol) was dissolved in 25 mL of ethanol-H_2O (2:1 v/v). Hydrochloric 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, evaporated and analyzed by using GC-MS and NMR. Zinc and tin catalysts were performed in similar manner as above method.

RESULTS AND DISCUSSION

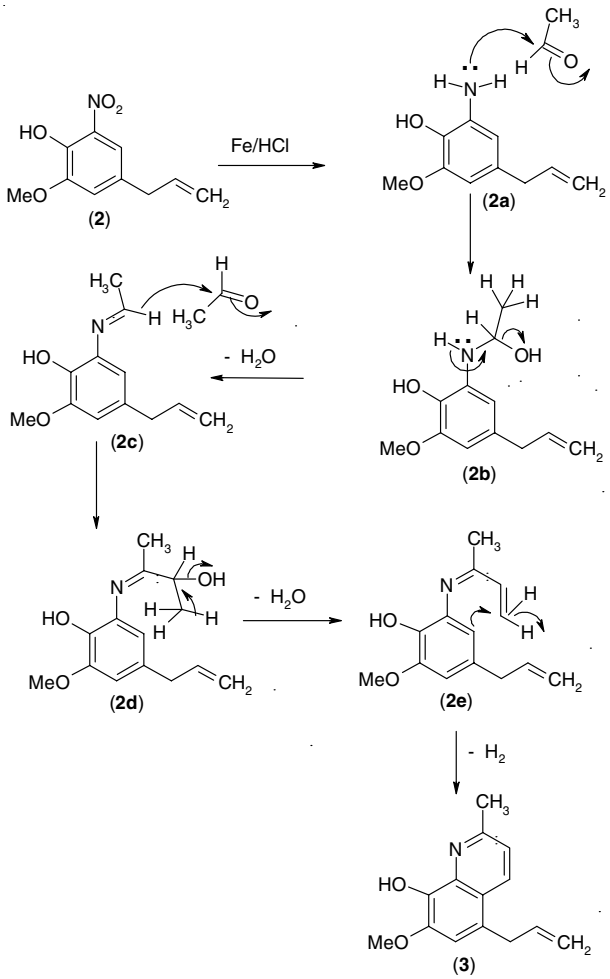
Schiff base was normally synthesized from a primary amine and aldehyde functional groups. The primary amine groups as an intermediate could be easily prepared by reduction of nitro compounds with metal catalysts. In this one pot synthesis, isolation of amino eugenol as the primary amine from reduction of nitro eugenol was not performed make this method more efficient because one step reaction was eliminated.

One pot synthesis of Schiff base from nitro eugenol (**2**) and acetaldehyde expected to afford Schiff base (**2c**). In fact this compound was not present and fortunately unexpected 5-allyl-8-hydroxy-7-methoxy-2-methylquinoline (**3**) was formed due to further substitution reaction occurred on Schiff base moiety of (**2c**) by acetaldehyde and followed by oxidation reactions (**Scheme-I**).



Scheme-I: Synthesis of new ring quinoline derivative (**3**) from natural isolated eugenol

The formation mechanism of 5-allyl-8-hydroxy-7-methoxy-2-methylquinoline (**3**) could be explained as follows (**Scheme-II**): First, nitro-eugenol (**2**) was reduced by Fe/HCl or Zn/formic acid or Sn/HCl to afford intermediated unisolated amino-eugenol (**2a**). Second, donor electron on nitrogen atom of $–NH_2$ attacked poor electrons of carbonyls group of acetaldehyde to form intermediate (**2b**). Elimination or condensation of H_2O gave intermediate (**2c**), which was further reacted with acetaldehyde to afford intermediate (**2d**). Elimination or condensation of H_2O gave intermediate (**2e**). Stabilize through cyclization or 6 member ring formation gave the final product (**3**).



Scheme-II: Formation mechanism of compound **3**

The 5-allyl-8-hydroxy-7-methoxy-2-methylquinoline (**3**) was characterized by GC-MS and NMR spectroscopy. GC-MS showed molecular ion at *m/z* 229 consistent with the molecular formula $C_{14}H_{15}NO_2$. Analysis of compound **3** by NMR spectroscopy provided valuable information to establish its structure. ^{13}C NMR was in accordance with the proposed structure which showed 14 peaks corresponding to 2 methyl at δ 25.03 and 57.33, 2 methylene at δ 36.37 and 116.38, 4 methine at δ 115.88, 120.31, 133.03, 137.04 and 6 quartenary carbons at δ 120.38, 126.39, 137.91, 138.64, 143.30, 157.27. ^1H NMR spectrum of compound **3**, the methyl and the methoxyl were ascribed to the signal at δ 2.69 and 4.03, the two methylene protons gave signal at δ 3.71 and 5.04. The remaining olefinic and aromatic protons appeared at δ 6.03, 7.16, 7.18 and 8.11. The DEPT and ^1H data enabled assignments of the proton position (Fig. 1).

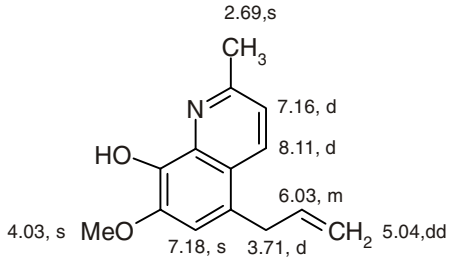


Fig. 1. ^1H NMR spectroscopic assignments for compound **3**

To optimize the yield of 5-allyl-8-hydroxy-7-methoxy-2-methylquinoline (**3**), three different metal catalysts namely Fe, Zn and Sn powder were investigated. These metals were used to reduce nitro-eugenol become amino-eugenol. In most cases a modifier is used with the catalyst to enhance reduction selectivity. In general, metals tend to make good reducing agents because they can only be oxidized. The reducing ability of the metal is given by the activity series.

Li > K > Ca > Na > Mg > Al > Zn > Cr > Fe >
Ni > Sn > Pb > H_2 > Cu > Hg > Ag > Pt > Au
most active least active

Based on GC-MS analyses, Fe-catalyzed reduction gave the highest yield (73.49 %), followed by Zn/formic acid (43.50 %) and Sn/HCl (40.14 %). Iron powder proved superior to stannous chloride with high tolerance of sensitive functional groups and high yields of the desired aryl amines in relatively short reaction times [12,13].

Conclusion

Fe-catalyzed reduction gave the highest yield (73.49 %) of a new 5-allyl-8-hydroxy-7-methoxy-2-methylquinoline *via* one-pot reaction of nitro-eugenol with acetaldehyde.

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