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Note

An expeditious synthesis of syringaldehyde from *para*-cresol

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Syringaldehyde is prepared from *p*-cresol *via* a three step reaction sequence in overall yield of 63-67%. The synthesis involves selective bromination followed by high pressure and temperature methoxilation and catalytical oxidation. The use of copper chloride in different oxidation state as a catalyst in two key steps *i.e.* methoxilation in aromatic ring (by cuprous chloride) and oxidation of aromatic methyl to aldehyde (by cupric chloride) underscore fidelity of the process.

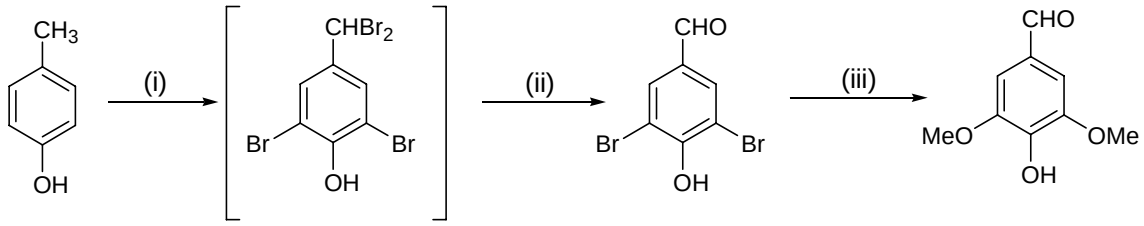
Keywords: *p*-Cresol, bromination, methoxilation, cupper chloride-diethylamine complex, catalytic oxidation, syringaldehyde

Syringaldehyde is an important constituent of many plant isolates[1] and has widespread occurrence in wood products. It can be easily converted to trimethoxybenzaldehyde which is an essential intermediate of the antibacterial drug trimethoprim[2]. It is also used in the colorimetric determination of free chlorine in water[3]. Syringaldehyde is generally manufactured from gallic acid through a multistep reaction sequence[4]. Other raw materials include vanillin[5], pyrogallol[6], *p*-hydroxybenzaldehyde[7], *etc*. Most of the starting materials mentioned above are not economically viable in the production of syringaldehyde. Therefore, with the aim of exploring the possibility of utilizing an alternative chemical which is cheap and easily available, the current study considers the use of *p*-cresol as a starting material. *p*-Cresol is a by-product of the petroleum industry, therefore available in abundance. Manchand *et al.*[8] earlier reported a practical synthesis of syringaldehyde from *p*-cresol *via* the formation of an intermediate 3,5-dibromo-4-hydroxybenzaldehyde in moderate yield. Subsequently, Ya-Fei Ji *et al*.[9] reported an important method for the preparation of the tetrabromo intermediate to increase the yield of 3,5-dibromo-4-hydroxybenzaldehyde. The intermediate 3,5-dibromo-4-hydroxybenzaldehyde was converted to syringaldehyde (**Figure 1**) through methoxylation in an autoclave at elevated pressure and temperature and finally to trimethoxybenzaldehyde in 72.4% yield.

Results and Discussion

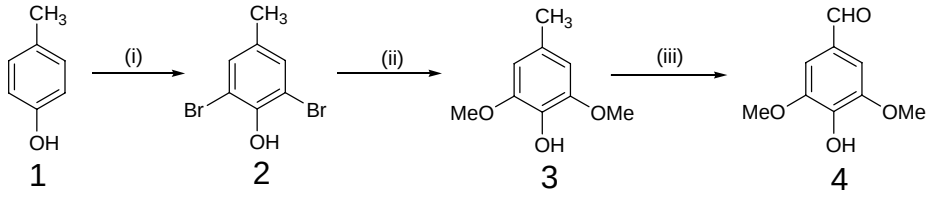
In this communication is reported an alternative approach to the synthesis of syringaldehyde with overall yield of 59-67%, which is environment friendly, facile and more efficient. A cheaper, easy to handle catalyst cuprous chloride (generated *in situ* from cupric chloride) has been successfully used over two successive steps *e.g*. methoxilation and oxidation of aromatic methyl group. In the proposed scheme *p*-cresol **1** was first converted to 4-methyl-2,6-dibromophenol **2** in almost 96-97% yield under controlled condition. The addition of bromine to *p*-cresol proceeded through an exothermic reaction, where slow addition and controlled temperature (20-25°C) produced the best results. In presence of acetic acid as a solvent, the yield of dibromo product could be further improved to ~98-99.5% without the formation of tetrabromo derivative. Methoxilation of dibromo product **2** was carried out in the presence of cuprous chloride catalysis. The aforesaid catalyst was prepared by heating cupric chloride under anhydrous conditions in a round bottom flask over a gas flame, indicated by the change of color from greenish blue to light gray, possibly due to the formation of cuprous chloride[10]. The reaction-mixture comprising 4-methyl-2,6-dibromophenol **2**, cuprous chloride (obtained from activated cupric chloride) in dry DMF and freshly prepared sodium methoxide in methanol was heated at a 85-90°C under inert atmosphere, furnishing 4-methyl-2,6-dimethoxyphenol **3** in 82% yield. In order to avoid the use of DMF which is difficult to recover, high pressure (90 lb) and temperature (112-14°C) conditions in an autoclave were employed. Therefore, attempts were made to methoxylate **2** under pressure with methanol as a solvent and activated cupric chloride as a catalyst. However, despite best efforts and varying the parameters of temperature and pressure the yield of **3** could not be improved beyond 74%.

In the final step, oxidation of methyl to aldehyde function was successfully achieved by oxidising



(i) Br_2/o-$C_6H_4Cl_2$; (ii) H_3O^+, $NaOCH_3$; (iii) Cu_2Cl_2/CH_3OH

Figure 1



(i) Br_2, AcOH; (ii) CuCl/DMF /MeONa/MeOH; (iii) $CuCl_2$/ DEA/MeOH, O_2

Scheme I

4-methyl-2,6-dimethoxyphenol **3** with a cupric chloride-diethylamine (1:1) complex[11] in methanol in presence of molecular oxygen continuously bubbled through the reaction-mixture at a constant rate. In this step, smooth conversion of 4-methyl-2,6-dimethoxy-phenol to syringaldehyde **4** was achieved in 84% yield along with the formation of some unidentified side products **(Scheme I)**. Air oxidation in place of oxygen prolonged the reaction time with reduced over all yield. The efforts to improve the oxidation of 4-methyl-2,6-dimethoxyphenol in presence of various other cupric chloride-secondary amine complexes such as piperidine, pyrrolidine, *etc*. were not successful. Syringaldehyde could be easily recovered from the dried reaction-mixture by triturating it with hexane and recrystallizing the pure product from ethyl acetate as pale yellow needles.

Experimental Section

Melting points were determined in capillaries using Buchi technical apparatus (Buchi-510) and are uncorrected. ^{1}H NMR spectra in $CDCl_3$ were recorded on a T-60 Varian 60 MHz spectrometer with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ, ppm). Reagents and solvents used were of LR grade. Silica gel coated aluminium plates from M/s Merck were used for TLC.

Synthesis of 2,6-dibromo-4-methyl phenol, 2

(i) A four necked round bottomed flask equipped with a condenser fitted with a calcium chloride drying tube, a thermometer, a dropping funnel and a mechanical stirrer was charged with *p*-cresol **1** (54.0 g, 0.50 mole). Bromine (52 mL, 1.0 mole) was added dropwise with continuous stirring for a period of 1 hr while maintaining the temperature between 20-25°C by external cooling. After the addition of bromine the reaction-mixture was further stirred for 2 hr at RT. The mixture was extracted with chloroform (3 × 60 mL), the combined organic layer and lower phase first washed with 5% aq. sodium carbonate solution and thereafter several times with cold water till neutral and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure furnished 128.4 g (96.5%) of the pale yellow-white solid **2**, m.p. 49°C (lit. m.p. 48°C) (ref 12).

(ii) The same reaction when carried out in acetic acid (250 mL) at 15°C after usual work-up yielded **2** in 98.55% yield.^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s, -CH_3), 7.30 (2H, s, Ar-H).

Synthesis of 2,6-dimethoxy-4-methylphenol, 3

(i) Freshly cut sodium metal pieces (34.5 g, 1.5 mole) were added to stirred dry methanol (400 mL) under anhydrous conditions. The mixture was

externally heated to a gentle reflux till all the sodium was consumed to form sodium methoxide. Part of the methanol (about 150 mL) was slowly distilled out. To the concentrated methanolic sodium methoxide solution in a mechanically stirred vessel fitted with a reflux condenser and a thermometer, 79.2 g (0.3 mole) of 2,6-dibromo-4-methylphenol **2** and cuprous chloride (activated cupric chloride) in dry DMF (300 mL) were added. Activated cupric chloride was separately prepared by heating (17.5 g, 0.10 mole) it in a round bottom flask over a flame under anhydrous conditions till the greenish blue colour of cupric chloride turned greyish. The reaction-mixture in inert atmosphere was heated externally with stirring and the temperature of the mixture raised to 85-88°C when colour of the solution starts changing from greenish blue to brownish red. The stirring was continued further for 2.5 hr at 88-90°C. The reaction-mixture was then cooled to RT and poured into crushed ice. It was then acidified with dilute hydrochloric acid to *p*H 3-4. The product was extracted with dichloromethane (3 × 200 mL). The crude product (50.0 g) was obtained as a viscous brown liquid after usual work-up and complete removal of the solvent. The crude product comprised 84% of the desired product *i.e.* 2,6-dimethoxy-4-methylphenol **3** as estimated by GC on SGE-BPX5 fused silica column.

(ii) The reaction was carried out in the absence of DMF in an autoclave, and the mixture heated to 112-14°C at a pressure of 6 atmosphere (90 lb) with constant stirring for a period of 3 hr. After cooling to RT, the reaction-mixture was processed as described above to obtain 2,6-dimethoxy-4-methylphenol **3** in 72% yield. ^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s, -CH_3), 3.87(6H, s, 2 × -OCH_3), 6.40 (2H, s, Ar-H).

Synthesis of 3,5-dimethoxy-4-hydroxybenzaldehyde (syringaldehyde), 4

Crude 2,6-dimethoxy-4-methylphenol **3** (41.0 g, 0.20 mole, 84% purity) dissolved in methanol (200 mL) and a solution comprising of freshly prepared complex (1:1) from cupric chloride (3.40 g, 0.02 mole) and diethylamine (1.46 g, 0.02 mole) dissolved in 70 mL of methanol were mixed together in a round bottom flask fitted with a mechanical stirrer. Purified oxygen gas was bubbled through the solution at a rate of 55 mL/min and the mixture was stirred at RT. The progress of the reaction was monitored by TLC. Supply of oxygen was stopped after about 3 hr when all of **3** was consumed. The reaction-mixture was filtered to remove undissolved impurities and the filtrate was concentrated upto 5 mL. It was then poured over crushed ice and acidified with dilute hydrochloric acid. The product was extracted with dichloromethane (3 × 100 mL) from the aqueous solution. The combined dichloromethane portions were washed free of acid and concentrated under reduced pressure to afford crude reddish brown product. Pure syringaldehyde **4** was obtained by repeated crystallization from hexane as pale yellow needles (33.2 g, yield 91%) m.p. 107-8°C (Lit. m.p. 109-10°C) (ref. 13). ^{1}H NMR ($CDCl_3$): δ 4.00 (6H, s, 2 × -OCH_3), 7.20 (2H, s, Ar-H), 9.96 (1H, s, CH=O).

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