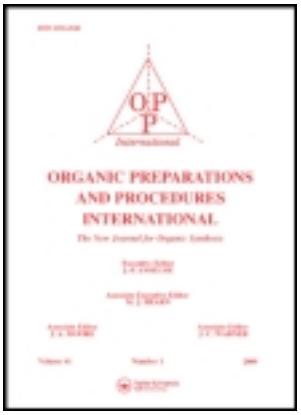

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An Alternate Preparation of 3,4,5-Trimethoxyphenol

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OPPI BRIEF

An Alternate Preparation of 3,4,5-Trimethoxyphenol

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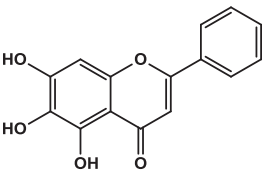
3,4,5-Trimethoxyphenol (**4**) is an important intermediate for the preparation of *baicalein*, a natural product possessing significant pharmacological activities and whose derivatives and analogs are under current investigation. [1–7]



Scheme 1
Structure of baicalein

Of the many methods for its preparation,[8–11] the simplest employs the Baeyer-Villiger rearrangement of commercially available and expensive 3,4,5-trimethoxybenzaldehyde followed by hydrolysis to produce **4** in 46% yield. However, the reaction conditions are very harsh and employ catalysts or reagents that are toxic and environmentally unfriendly. The methylation of 2,6-dimethoxyhydroquinone also gave **4** albeit in poor yields (<5%) because of the poor regioselectivity of the reaction as would be expected.[12] More recently, inexpensive and commercially available 3,4,5-trimethoxybenzoic acid (**1**) has been used as a source of **4** *via* substitutive *ipso* nitration to 3,4,5-trimethoxynitrobenzene followed by reduction to the aniline, diazotization and hydrolysis.[13] As part of our program for the development of natural biological compounds and in the investigation on their structure-activities relationships,[14,15] we now report an alternative and efficient process to

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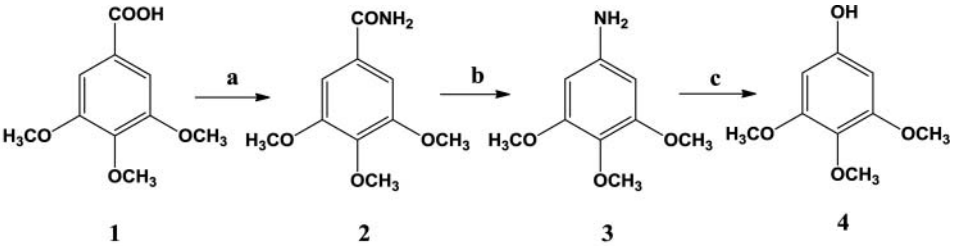
prepare aniline **3** from **1** and improved the yield of the conversion of **3** to **4** from 56% to 80%.



Conditions: (a) $SOCl_2$, DMF, CH_2Cl_2, 45°C; NH_3-H_2O, 0°C (b) NaOCl, NaOH, H_2O, r.t.→100°C (c) $NaNO_2$, 10% H_2SO_4, 10–15°C; 10% H_2SO_4, $CuSO_4$, 100°C.

Scheme 2

In conclusion, the process is concise, safe, easily performed and can be scaled-up. The overall yield of **4** from **1** was 58%. Avoidance of highly toxic and expensive reagents makes the procedure cost-effective and environment friendly.

Experimental Section

All reactions were monitored by TLC on silica gel GF_{254} with mixed solvents (hexane : ethyl acetate, 2:1) as developer. ^{1}H NMR spectra were measured at 500 MHz ($CDCl_3$/TMS) on a Bruker Dr ×500 spectrometer and chemical shift are reported in ppm (δ) relative to TMS as internal standard. Mass spectra were determined (FABMS) on VG Auto Spec-3000 spectrometer and reported as m/z. Melting points are uncorrected.

3,4,5-Trimethoxybenzamide (2)

To a mixture of 3,4,5-trimethoxybenzoic acid **1** (106.0 g, 0.5 mol) in 200 ml CH_2Cl_2, 0.2 ml DMF and 45 ml $SOCl_2$ were added. The reaction mixture was stirred at 45°C for 3 h and the gases generated were absorbed in an aqueous alkali solution. Then, the solvent CH_2Cl_2 and excess $SOCl_2$ were evaporated under reduced pressure to give a pale-yellow solid residue of 3,4,5-trimehoxybenzoyl chloride, which was dissolved in 100 ml dry acetone at room temperature and slowly added into 92 ml 25% ammonia at 0°C under vigorous stirring. The mixture was stirred for another 1 h at 0°C and the solid was collected and recrystallized from water to give colorless needles (95.0 g, 90% yield), mp. 173–175°C, *lit.*[6]174–176°C. ^{1}H NMR: δ7.06 (s, 2H), 3.92 (s, 6H), 3.91(s, 3H). MS (m/e): 211(M^+).

3,4,5-Trimethoxyaniline (3)

To 600 ml of 12% commercial sodium hypochlorite solution and 600 ml 2 M NaOH, compound **2** (160.0 g, 0.75 mol) was added in portions over 30 minutes. The reaction mixture was vigorously stirred below 25°C until TLC showed that compound **2** had disappeared; the reaction mixture was then heated to 100°C under stirring. After the reaction was complete,

it was cooled and the solid was collected and saved. The filtrate was extracted with CH_2Cl_2 (2 × 2000 ml) and the extracts were dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to give a solid. This solid was combined the solid above and recrystallized from water to give compound **3** as white crystals (109.7 g, 80% yield), mp. 111–113°C, *lit.*[13]110–110.5°C. ^{1}H NMR: δ5.95(s, 2H), 3.82(s, 6H), 3.77(s, 3H). MS (m/e): 183(M^+).

3,4,5-Trimethoxyphenol (4)

To a solution of 3,4,5-trimethoxyaniline (**3**, 91.5 g, 0.5 mol) in 2000 ml of 10% H_2SO_4 cooled to 15°C was added dropwise a solution of $NaNO_2$ (35.0 g, 0.5 mol) in 200 ml water over 30 minutes. Once the addition was complete, the reaction mixture was stirred for another 2–3 h at 10–15°C and then the diazonium salt solution (**CAUTION**!) was slowly added dropwise into a boiling solution of 1500 ml 10% H_2SO_4 and 200 g $CuSO_4$ over 2 h. The reaction mixture was stirred for another 10 minutes and then cooled to room temperature and extracted with CH_2Cl_2 (2 × 2000 ml). The extracts were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give a solid. The residue were recrystallized from petroleum-ethyl acetate (1:1) to give compound **4** as white crystals (73.0 g, 80% yield), mp. 145–147°C, *lit.*[9] 144–145°C. ^{1}H NMR: δ 6.09(s, 2H), 3.80(s, 6H), 3.76(s, 3H). MS (m/e): 184(M^+).

Note: The 10% H_2SO_4 aqueous waste solution containing $CuSO_4$ should be recovered and use repeatedly.

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