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Note

Synthesis of methyl 2-methoxy-5-hydroxycinnamate, a metabolite of *Murraya paniculata*

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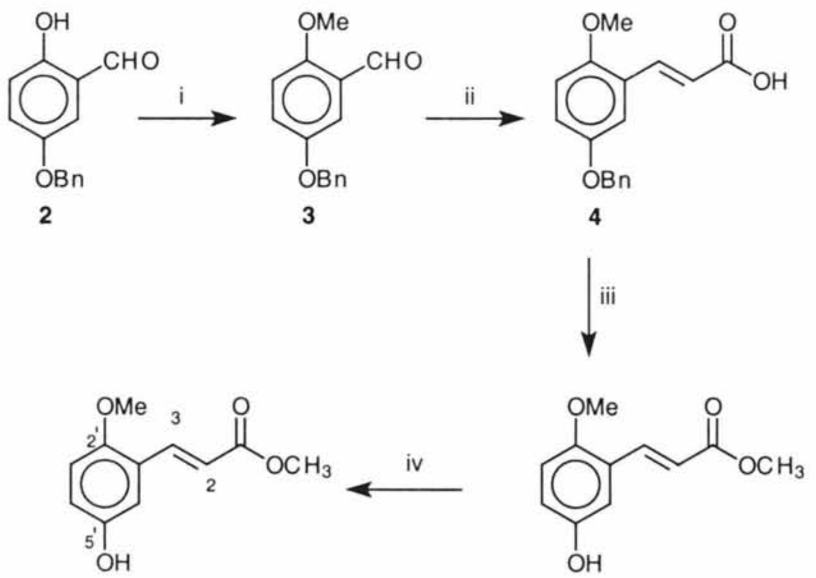
Methyl 2-methoxy-5-hydroxycinnamate **1** has been obtained from 2-hydroxy-5-benzyloxybenzaldehyde **2** in four steps with an overall yield of 26%.

Methyl 2-methoxy-5-hydroxycinnamate **1** was isolated as one of the new metabolites from the leaves of *Murraya paniculata*[1]. The leaves and roots of this plant have been used in folk medicine for the treatment of stomachache and toothache, as a stimulant and in gout, etc. The leaves passess antibiotic activity against *Mycococcus pyogenes* and *Escherichia coli*[1]. Due to our interest on phenylpropanoids[2-5], we have synthesized **1** and the results are reported in this note.

2-Hydroxy-5-benzyloxybenzaldehyde **2** on methylation with methyl iodide in the presence of K_2CO_3 yielded 2-methoxy-5-benzyloxybenzaldehyde **3** in 78% yield. **3** on condensation with malonic acid under Knoevenagel-Doebner conditions[6] gave 2-methoxy-5-benzyloxycinnamic acid **4** in 69% yield. **4** on esterification with MeOH gave methyl 2-methoxy-5-benzyloxycinnamate **5** in 90% yield. Debenzylation of **5** was carried out using $AlCl_3$ and N, N-dimethylaniline[7] to give the title compound **1** in 54% yield (**Scheme I**). This is the first report on the synthesis of **1**. The spectral data of synthetic **1** are in agreement with those reported for natural **1**. Thus, **1** was obtained starting from **2** in four steps with an overall yield of 26%.

Experimental Section

Melting points were determined on a MEL Temp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FTIR Spectrometer; ^{1}H NMR spectra on a Bruker 400 MHz or 300 MHz NMR spectrometer; and mass spectra on a Finnigan MAT 95S mass spectrometer. TLC was carried out on silica gel (ACME) layers. Petroleum ether is the fraction of bp 60-80°C.



(i) Methyl iodide, acetone, K_2CO_3, reflux, 18h, 78% (ii) Malonic acid, pyridine, piperidine, Δ, 2h, 69% (iii) CH_3OH, H^+, reflux, 5h, 90% (iv) $AlCl_3$, N, N-dimethylaniline, CH_2Cl_2, rt, 1h, 54%

2-Methoxy-5-benzyloxybenzaldehyde 3. To a solution of **2**[8] (0.5 g, 2.18 mmoles) in acetone (5 mL) were added methyl iodide (1.6 mL, 10.5 mmoles) and potassium carbonate (1.0 g, 7.24 mmoles) and refluxed on a water-bath for 18 hr. After the completion of reaction, the reaction mixture was filtered to remove potassium carbonate and the solvent was evaporated. The residue obtained was recrystallised from the pet. ether-ethyl acetate mixture to give **3** (0.41 g, 78%), m.p. 78-80°C; IR(KBr): 2870, 1677, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.88 (3H, s), 5.04 (2H, s), 6.93 (1H, d, *J*=9.0), 7.20 (1H, dd, *J*=9.0, 3.1), 7.42-7.34 (6H, m), 10.44 (1H, s).

2-Methoxy-5-benzyloxycinnamic acid 4. A mixture of **3** (0.4 g, 1.64 mmoles), malonic acid (0.34 g, 3.28 mmoles), pyridine (0.75 mL) and piperidine (0.01 mL) was heated on a water-bath for 2 hr. After completion of reaction, the reaction mixture was poured into 1 *N* HCl (10 mL). The precipitated solid was filtered, dried and recrystallised from methanol to give **4**, (0.32 g, 69%), m.p. 142-43°C; IR(KBr): 3442, 1690, 1496, 1260 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ 3.80 (3H, s), 5.10 (2H, s), 6.55 (1H, d, *J*=9.0), 7.06 (1H, dd, *J*=9.0, 2.8), 7.30-7.46 (6H, m), 7.79 (1H, d, *J*=16.1).

Methyl 2-methoxy-5-benzyloxycinnamate 5. A solution of **4** (0.17 g, 0.50 mmoles) in methanol (2.5 mL) was treated with Conc. HCl (0.01 mL) under reflux for 5 hr. After the completion of reaction, the solvent was evaporated and diluted with ethyl acetate (20 mL). The solution was successively washed with sat. sodium bicarbonate solution, brine and water. The solvent was evaporated and the residue obtained was chromatographed over silica gel to give 5 (0.16 g, 90%), m.p. 81-82°C; ^1H NMR (200 MHz, $CDCl_3$); δ 3.79 (3H, s), 3.85 (3H, s), 5.10 (2H, s), 6.42(1H, d, *J*=16.0), 6.78 (1H, d, *J*=9.0), 6.90 (1H, dd, *J*=9.0, 2.0), 7.08 (1H, d, *J*=2.0), 7.31-7.42 (5H, m), 7.90 (1H, d, *J*=16.0).

Methyl 2-methoxy-5-hydroxycinnamate 1. To a mixture of **5** (0.2 g, 0.74 mmoles), N, N-dimethylaniline (0.2 g, 1.63 mmoles) and dichloromethane (5 mL), was added anhydrous aluminium chloride (0.5 g, 2.9 mmoles) at 0°C and the same temperature was maintained for further 30 min. The reaction mixture was then allowed to warm up to room temperature and kept at rt for 30 min. After the completion of reaction, the reaction mixture was quenched with 1*N* HCl (5 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with saturated sodium bicarbonate solution, brine and water, successively, dried and the solvent was evaporated. The residue obtained was charomatographed over silica gel column using mixtures of pet. ether and ethyl acetate to give **1** (0.08 g, 54%), m.p. 89-90°C; IR(KBr): 3370, 1696, 1501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.82 (6H, s, 2×–OCH_3), 6.47(1H, d, *J*=16.1, H-2), 6.79 (1H, d, *J*=8.9, H-3′), 6.86 (1H, dd, *J*=8.9, 3.0, H-4′), 7.01(1H, d, *J*=3.0, H-6′), 7.94 (1H, d, *J*=16.1 H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4 (C-1), 152.3(C-2′), 149.6 (C-3), 140.3 (C-5′), 123.8(C-1′), 118.5(C-4′), 118.2 (C-3′), 115.0(C-2), 112.6(C-6′), 56.0(2′-OCH_3), 51.8 (COOCH_3); EIMS: m/z% 208 (M^+, 29), 177 (100), 162(21), 134(23), 121(8), 77(8).

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