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Synthesis of Methyl 3-(2,4,5-Trimethoxyphenyl)-Propionate, an Antifungal and Larvicidal Constituent of *Cordia alliodora*†

MULABAGAL VANISREE, JAKKA KAVITHA
and GOTTUMUKKALA V. SUBBARAJU*
Laila Impex R&D Centre, Unit I, Phase III, Jawahar Autonagar, Vijayawada-520 007, India
E-mail: subbaraju@nettlinx.com

Methyl 3-(2,4,5-trimethoxyphenyl)-propionate (1) has been synthesized starting from 2,4,5-trimethoxybenzaldehyde in three steps with an overall yield of 68%.

Key words: Synthesis, methyl 3-(2,4,5-trimethoxyphenyl)-propionate, antifungal, larvicidal, *Cordia alliodora*.

Methyl 3-(2,4,5-trimethoxyphenyl)-propionate **(1)** was isolated recently as a new antifungal and larvicidal constituent of the root bark of *Cordia alliodora*[1]. It exhibited antifungal properties against phytopathogenic mold, *Cladosporium cucumerinum* and also showed a marked activity against the larvae of the yellow-fever-transmitting mosquito, *Aedes aegypti*[1]. In a continuing study on the synthesis of phenylpropanoids[2–7], we have synthesized **(1)** starting from commercially available 2,4,5-trimethoxybenzaldehyde **(2)** in three steps with an overall yield of 68% and the results are reported in this note.

Melting points were determined on an MEL temperature apparatus and are uncorrected. UV spectra were recorded on a Shimadzu 240 spectrometer, IR spectra on a Perkin-Elmer BX FTIR spectrometer, ^{1}H NMR spectra on a Bruker 300 MHz NMR spectrometer and mass spectra on a VG micromass spectrometer. TLC was carried out on silica gel (ACME) layers. Petroleum ether is the fraction of b.p. 60–80°C.

3-(2,4,5-Trimethoxyphenyl)-2-propenoic acid (3): A mixture of 2,4,5-trimethoxybenzaldehyde (2, 2.0 g, 10.2 mmoles), malonic acid (3.0 g, 28.8 mmoles), pyridine (3.0 mL, 48.1 mmoles) and piperidine (0.4 mL) was heated on a water bath (80–90°C) for 4.5 h. After the completion of reaction, the reaction mixture was poured into 2 N HCl (40 mL). The precipitated solid was filtered and recrystallized from methanol to give **(3)** (1.93 g, 80%), m.p. 151–152°C; UV (MeOH): 284, 343 nm; IR (KBr): 2945 (br), 1684, 1598, 1515, 1291, 1200 cm^{-1}.

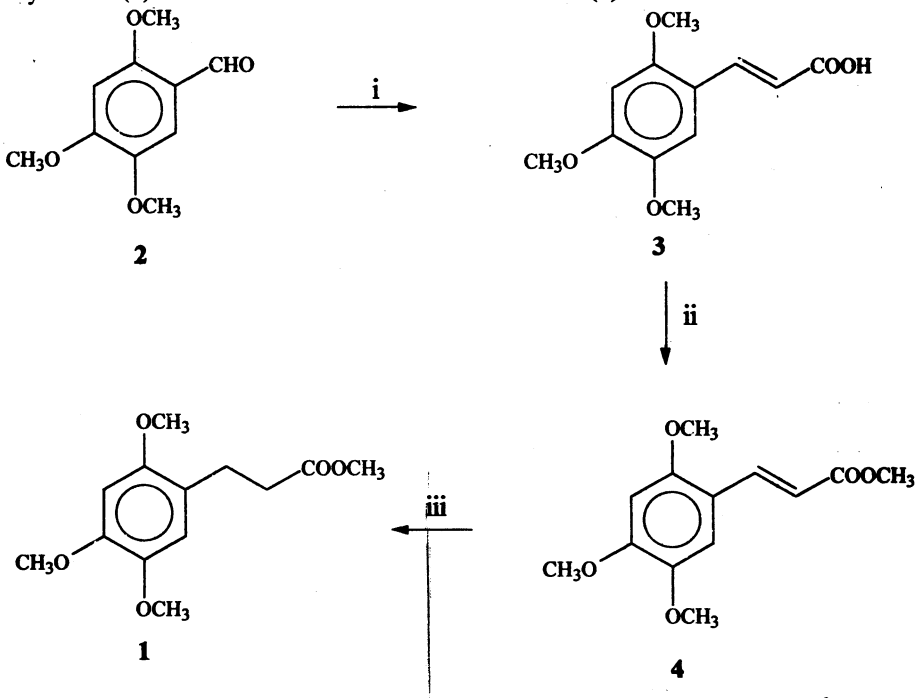
Methyl 3-(2,4,5-trimethoxyphenyl)-2-propenoate (4): To a solution of **(3)** (1.0 g, 4.2 mmoles) in methanol (15 mL) was added conc. HCl (0.2 mL) and refluxed on a water bath for 3 h. After the completion of reaction, the solvent was removed *in vacuo* and diluted with ethyl acetate (20 mL). The organic layer was washed with saturated sodium bicarbonate solution, brine and water, successively. The ethyl acetate layer was dried over anhydrous sodium sulphate and passed through a small column of silica gel to give **(4)** (0.94 g, 89%), m.p.

†Laila Impex communication # 13.

96–98°C [Ref. 8: m.p. 90–92°C]; UV (MeOH): 285, 345 nm; IR (KBr): 1716, 1627, 1610, 1517, 1296, 1045, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.78 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 6.31 (1H, d, J = 16 Hz), 6.46 (1H, s), 6.98 (1H, s), 7.90 (1H, d, J = 16 Hz).

Methyl 3-(2,4,5-trimethoxyphenyl) propionate (1): To a stirred solution of **(4)** (0.6 g, 2.4 mmoles) in ethyl acetate (15 mL) under hydrogen atmosphere was added Pd-C (10%, 0.25 g, 2.4 mmoles) in portion-wise for about 30 min. After the completion of reaction, the reaction mixture was filtered to remove the catalyst and recrystallized using a mixture of pet. ether and ethyl acetate to give **(1)** as a low melting solid (0.58 g, 96%), m.p. 41–43°C; UV (MeOH): 218, 227, 288 nm; IR (KBr): 1735, 1515, 1449, 1212, 1037 cm^{-1}; ^1H NMR 300 MHz, $CDCl_3$): δ 2.54 (2H, t, J = 7.6 Hz), 2.84 (2H, t, J = 7.6 Hz), 3.65 (3H, s), 3.80 (3H, s), 3.81 (3H, s), 3.86 (3H, s), 6.45 (1H, s), 6.68 (1H, s). EIMS: m/z $[M]^+$: 253 (100), 239 (25), 182 (12), 181(78), 151 (29).

Condensation of **2** with malonic acid under Knoevenagel-Doebner conditions[9] gave 3-(2,4,5-trimethoxyphenyl)-2-propenoic acid **(3)** in 80% yield. Esterification of **(3)** with MeOH in presence of conc. HCl gave methyl 3-(2,4,5-trimethoxyphenyl)-2-propenoate **(4)** in 89% yield. Hydrogenation of **(4)** using Pd-C (10%) as a catalyst afforded the title compound, **(1)**, in 96% yield (Scheme-1). This is the first report on the synthesis of **(1)** and the spectral and physical data of synthetic **(1)** corroborated well with those of natural **(1)**.



Scheme-1. (i) Malonic acid, pyridine, piperidine, heat, 4.5 h, 80%; (ii) MeOH, H+, reflux, 3.0 h, 89%; (iii) Pd-C, H2, ethyl acetate, 0.5 h, 96%

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