Synthesis of vinyl caffeate, an antioxidant from *Perilla frutescens* Britton var. *crispa* (Thunb.)

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Mercuric acetate mediated *trans* vinylation has been used as a key step in the synthesis of vinyl caffeate 1. The title compound has been obtained from 3,4-dihydroxybenzaldehyde in four steps with an overall yield of 20%.

Caffeic acid and its derivatives have been reported as antioxidant compounds. Vinyl caffeate 1 was isolated, recently, as one of the antioxidant principles of *Perilla frutescens* Britton var. *crispa* (Thunb.), a Japanese medicinal plant. Due to our interest on compounds having C₆-C₃ units, we have synthesized 1 for the first time and the results are reported in this note.

Condensation of 3,4-dibenzyloxybenzaldehyde 3, obtained from 3,4-dihydroxybenzaldehyde 2, with malonic acid under Knoevenagel-Doebner conditions gave 3,4-dibenzyloxycaffeic acid 4 in 98% yield. Mercurate mediated *trans* vinylation of 4 with vinyl acetate afforded vinyl 3,4-dibenzylcaffeate 5, in 48% yield. Debenzylation of 5 was carried out using AlCl₃ and *N*,*N*-dimethylaniline to give the title compound 1 in 46% yield (Scheme I). Thus, 1 was obtained starting from 3,4-dihydroxybenzaldehyde in four steps with an overall yield of 20%. The spectral data of synthetic 1 agree well with those reported for natural 1.

Experimental section

Melting points were determined on a MEL Temp apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV 240 spectrophotometer, IR spectra on a Perkin-Elmer 1600 FT-IR spectrometer. ¹H NMR spectra were recorded on a Varian Gemini 400 MHz or Jeol JNM EX 90 MHz NMR spectrometer and Mass Spectra on VG micromass 70-70H mass spectrometer. TLC was carried out on silica gel (ACME) layers. Petroleum ether is the fraction of bp 60-80 °C. 3,4-Dihydroxybenzaldehyde was prepared from vanillin using AlCl₃/pyridine in 84% yield.

3,4-Dibenzyloxybenzaldehyde 3. A mixture of 3,4-dihydroxybenzaldehyde (2, 1.5 g, 10.8 mmoles), benzyl bromide (3.0 mL, 25.2 mmoles), potassium carbonate (2.0 g, 14.5 mmoles) and acetone (15 mL) was kept under reflux for 7 hr. After this period, the reaction mixture was filtered to remove potassium carbonate and the solvent was removed. The residue obtained was recrystallised from a mixture of ethyl acetate and pet. ether to give 3 as a white crystalline solid, 3.25 g (94%), mp 86-88 °C (lit. mp 87-89 °C). Rf = 0.71 (pet. ether-ethyl acetate, 4:1); UV (MeOH):

![Scheme I](image)

1) BnBr, K₂CO₃, Acetone, reflux, 7 hr, 94%; ii) Malonic acid, Pyridine, Piperidine, Δ, 3 hr, 96%; iii) Vinyl acetate, Hg(OAc)$_₂$, H₂SO₄, 50 °C, 2 hr, 48%; iv) AlCl₃, *N*,*N*-dimethylaniline, CH₂Cl₂, Room Temperature, 2 hr, 46%.
214, 234, 289 and 315 nm; IR (KBr): 2817, 2726 and 1677 cm⁻¹; ¹H NMR (CDCl₃, 90 MHz) : δ 5.20 (s, 2H), 5.25 (s, 2H), 6.95 (d, 1H, J = 8.5 Hz), 7.01-7.45 (m, 12H) and 9.70 (s, 1H).

3,4-Dibenzyll caffeic acid 4. A mixture of 3 (2.5 g, 7.8 mmoles), malonic acid (2 g, 19.2 mmoles), pyridine (4 mL, 49.4 mmoles) and piperidine (0.2 mL) was heated on a water bath for 3 hr. The reaction mixture was poured into excess dil. HCl (100 mL, 2.0 N). The precipitated solid was filtered and recrystallised from methanol to give 4, 2.77 g (98%)

Vinyl 3,4-dibenzyl caffeate 5. A mixture of 4 (0.2 g, 0.55 mmoles), vinyl acetate (0.6 mL, 7.1 mmoles) and mercuric acetate (0.02 g, 0.06 mmoles) was kept under stirring in nitrogen atmosphere at room temperature for 2 hr. After completion of the reaction, the reaction mixture was quenched with 1N HCl (5 mL) and extracted with ethyl acetate (20 mL), the organic layer was washed with sodium bicarbonate solution, brine and water successively, and the solvent was evaporated. The residue obtained was chromatographed over silica gel column using mixtures of chloroform and methanol (95:5) as eluant to give 5, 0.05 g (46%), mp 132-134 °C.

References