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## Note

# SYNTHESIS OF N-[3-(3,4-DIMETHOXY- PHENYL)PROPANOYL]PYRROLE, A METABOLITE OF *PIPER* *BRACHYSTACHYUM*

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N-[3-(3,4-Dimethoxyphenyl)propanoyl]pyrrole (**1**) has been synthesized in three steps starting from veratraldehyde (**2**) with an overall yield of 66%.

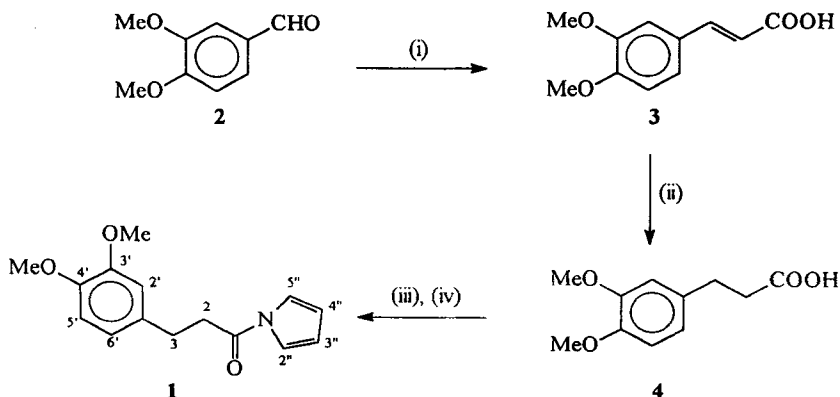
*Keywords:* N-[3-(3,4-Dimethoxyphenyl)propanoyl]pyrrole; *Piper brachystachyum*; 1-acylpyrrole

## INTRODUCTION

The genus *Piper* (Piperaceae) is a rich source of a variety of secondary metabolites, particularly, piperine type alkaloids [1]. During a comparative phytochemical study on several Indian *Piper* species, a new alkaloid, N-[3-(3,4-dimethoxyphenyl)propanoyl]pyrrole (**1**) was isolated from *Piper brachystachyum* [2]. Due to our interest on phenylpropanoids [3–5], we have synthesized **1** and the details are presented below.

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SCHEME 1  $\text{CH}_2(\text{COOH})_2$ , pyridine, piperidine, 80–90°C, 3 h, 95%; (ii) Pd–C (10%),  $\text{HCOONH}_4$ , methanol, reflux, 2 h, 91%; (iii)  $\text{SOCl}_2$ ; (iv) **5**, pyrrole, tetrabutylammonium bromide,  $\text{NaOH}$ , 95°C, 1.5 h, 76%.

## RESULTS AND DISCUSSION

Condensation of veratraldehyde (**2**) with malonic acid under Knoevenagel–Doebner conditions [6] gave 3-(3,4-dimethoxyphenyl)propenoic acid (**3**) in 95% yield. Hydrogenation of **3** using Pd–C (10%) [7] gave 3-(3,4-dimethoxyphenyl)propanoic acid (**4**) in 91% yield. Acylation of pyrroles under usual conditions with acids, esters or anhydrides leads to the formation of 2 and 3-acylated products rather than N-acylated compounds [8]. Therefore, the desired N-acylation of pyrrole using 3-(3,4-dimethoxyphenyl)propanoyl chloride (**5**) (prepared from **4**) was carried out under phase transfer catalysis [9] to give the title compound (**1**) in 76% yield. Thus, **1** was obtained starting from **2** in three steps (Scheme 1) with an overall yield of 66%. The spectral data of synthetic **1** agree well with those reported for natural **1**.

## EXPERIMENTAL SECTION

### General Experimental Procedures

Melting points were determined on a Mel Temp apparatus and are uncorrected. UV spectra were recorded on a Shimadzu 240 Spectrometer. IR spectra were measured on a Perkin-Elmer 1600 FT-IR spectrometer.  $^1\text{H}$ NMR spectra were recorded on a JEOL 400 MHz or JEOL JNM EX 90 MHz NMR spectrometer and Mass spectra on a VG micromass 70-70H mass

spectrometer. TLC was carried out on silica gel (ACME) layers. Petroleum ether is the fraction of b.p. 60–80°C.

*3-(3,4-Dimethoxyphenyl)propenoic acid (3)* A mixture of veratraldehyde (**2**, 1.00 g, 6.02 mmol), malonic acid (1.26 g, 12.0 mmol), pyridine (1.2 ml, 15.5 mmol) and piperidine (0.2 ml) was heated on a water bath (80–90°C) for 3 h. After the completion of reaction, the reaction mixture was poured into 2 N HCl (15 ml). The precipitated solid was filtered and recrystallized from methanol to give **3**, 1.16 g (95%), m.p. 178–180°C (Ref. [10] m.p. 181–183°C); UV  $\lambda_{\max}$  (MeOH) 298, 350 nm; IR (KBr)  $\nu_{\max}$  1685  $\text{cm}^{-1}$ .

*3-(3,4-Dimethoxyphenyl)propanoic acid (4)* A mixture of **3** (0.5 g, 2.4 mmol), Pd–C (10%, 0.2 g), ammonium formate (0.3 g, 4.75 mmol) and methanol (5 ml) was refluxed on a water bath for 2 h. After the completion of reaction, the reaction mixture was filtered to remove the catalyst and the solvent was evaporated. The residue obtained was recrystallized from a mixture of chloroform and methanol to give **4**, 0.46 g (91%), m.p. 90–91°C (Ref. [10] 96–98°C) UV  $\lambda_{\max}$  (MeOH) 208, 229 nm; IR (KBr)  $\nu_{\max}$  2926, 1699  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (90 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.72 (2H, d,  $J=7.3$  Hz), 2.91 (2H, d,  $J=7.3$  Hz), 3.88 (6H, s), 6.81 (3H, m).

*3-(3,4-Dimethoxyphenyl)propanoyl chloride (5)* This was prepared from **4** (0.5 g, 2.3 mmol) using thionyl chloride (0.9 ml, 4.6 mmol) and the acid chloride obtained after removal of excess thionyl chloride was used in the following reaction without further purification.

*N-[3-(3,4-Dimethoxyphenyl)propanoyl]pyrrole (1)* To a mixture of pyrrole (0.07 ml, 1.0 mmol), tetrabutylammonium bromide (4 mg, 0.01 mmol), and methylene chloride (10 ml), powdered NaOH (0.1 g, 2.5 mmol), under stirring was added **5** (0.35 g, 1.5 mmol) in portion wise in about 20 min. The reaction mixture was then heated on a water bath at 95°C for 1.5 h. After the completion of reaction, the reaction mixture was cooled to room temperature and diluted with methylene chloride (20 ml) and washed with saturated sodium bicarbonate solution, brine and water successively, dried over anhydrous sodium sulphate and the solvent was evaporated. The residue obtained was chromatographed over silica gel column using mixtures of petroleum ether and ethyl acetate (95:5) as eluant to give **1**, 0.205 g (76%), m.p. 92–94°C (Ref. [2] m.p. 108°C); UV  $\lambda_{\max}$  (MeOH) 206, 232 nm; IR (KBr)  $\nu_{\max}$  3364, 2925, 1714, 1510, 1263  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.03–3.14 (4H, m, H-2, H-3), 3.85 (3H, s,  $\text{OCH}_3$ ), 3.86 (3H, s,  $\text{OCH}_3$ ), 6.27 (2H, t,  $J=2.2$  Hz, H-3'', H-4''), 6.78–6.85 (3H, m, H-2', H-5', H-6'), 7.29 (2H, brs, H-2'', H-5'');  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.8 (C=O), 149.0 (C-3'), 147.7 (C-4'), 132.8 (C-1'), 120.2 (C-6'), 119.0 (C-2'', C-5''), 113.2 (C-3'', C-4''), 111.9 (C-5'), 111.4 (C-2'), 56.0 ( $-\text{OCH}_3$ ), 55.8

(-OCH<sub>3</sub>), 36.7 (C-2), 30.1 (C-3); EIMS *m/z* [M<sup>+</sup>] 259 (39), 185 (34), 151 (100), 107 (17), 69 (25).

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