First total synthesis of two new amide alkaloids from *Piper boehmeriaefolium*

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3-(3,4,5-Trimethoxyphenyl)propanoylpyrrole and 3-(3,5-dimethoxy-4-hydroxyphenyl)propanoylpyrrole, two new amide alkaloids, were prepared from 3,4,5-trimethoxybenzaldehyde via 3,4,5-trimethoxycinnamic acid and the corresponding dihydroacid. This route is simple and the reaction conditions are mild.

Keywords: amide alkaloids, 3-(3,4,5-trimethoxyphenyl)propanoylpyrrole, 3-(3,5-dimethoxy-4-hydroxyphenyl)propanoylpyrrole

Phytochemical investigations of *Piper* species have revealed the occurrence of amides which are reported to possess various ACAT inhibitory,[1] cytotoxic,[2–3] antimycobacterial,[4–5] insecticidal,[6–7] antiprotozoan,[8] analgesic,[9] and antidepressant[10] activities.

3-(3,4,5-Trimethoxyphenyl)propanoylpyrrole **1** and 3-(3,5-dimethoxy-4-hydroxyphenyl)propanoylpyrrole **2**, two new amide alkaloids, were first isolated from *Piper boehmeriaefolium* in 2011.[11] The total synthesis of **1** and **2** has not only theoretical importance but potential medical prospect. The synthesis of **1** and **2** has not been reported so far. We report here a facile approach (Scheme 1) as illustrated in the total synthesis of **1** and **2**.

Results and discussion

Our synthetic approach, depicted in Scheme 1, began with 3,4,5-trimethoxybenzaldehyde **3**. 3,4,5-Trimethoxycinnamic acid **4** was prepared in 89% yield using Knoevenagel–Doebner reaction conditions starting from **3** and malonic acid and pyridine in the presence of Piperidine as a catalyst. Subsequent catalytic hydrogenation of **4** in tetrahydrofuran gave 3,4,5-trimethoxyhydrocinnamic acid **5** in 94% yield. In the next step, the direct N-acylation of pyrrole with the carboxylic acid **5** afforded the title compound **1** in 82% yield. The second title compound **2** was prepared in 53% yield by the monodemethylation of **1** using a standard literature procedure using $AlCl_3$.[12]

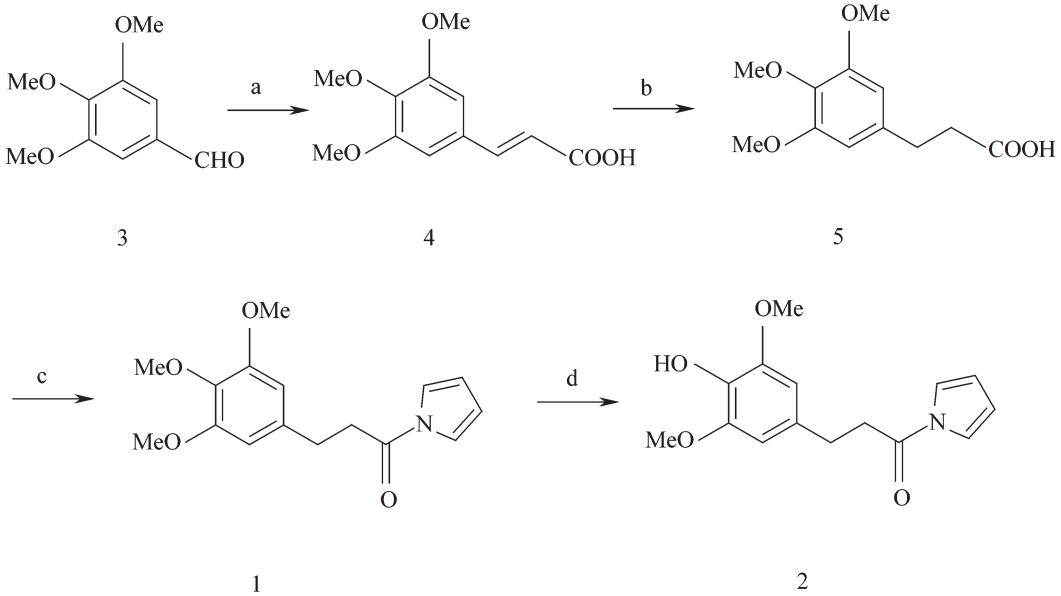
In summary, we have developed a concise and efficient synthetic method for preparation of two new amide alkaloids **1** and **2**. This route is simple and the reaction conditions are mild.

Experimental

Reagents and solvents were obtained from commercial suppliers. Melting points were determined on a X-4 melting-point apparatus and are uncorrected. NMR spectroscopy was performed on a Bruker Avance 400-MHz (^{1}H, 400 MHz; ^{13}C, 100 MHz) instrument. Mass spectra (EI-MS) were determined on a Thermo Finnigan LCQ-Advantage.

3,4,5-Trimethoxycinnamic acid (**4**): Piperidine (3 mL) was added to a mixture of **3** (9.8 g, 0.05 mol) and malonic acid (7.8 g, 0.075 mol) in pyridine (100 mL). The mixture was stirred at 80 °C until the reaction was completed using TLC to monitor the reaction. The reaction mixture was concentrated under vacuum to afford a residue, which was dissolved in EtOAc (100 mL) and washed with 5% HCl (30 mL × 2) and distilled water (30 mL × 2) respectively. It was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was recrystallised from CH_3OH–H_2O to give **4** (10.59 g, 89%) as colourless crystals; m.p. 125–126 °C (lit.[13] 126–127 °C); ^{1}H NMR ($CDCl_3$) δ: 12.10 (s, 1H), 7.62 (d, *J* = 15.9 Hz, 1H), 6.78 (s, 2H), 6.36 (d, *J* = 15.9 Hz, 1H), 3.89 (s, 6H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 171.5, 153.6, 148.7, 139.7, 130.9, 116.5, 105.8, 60.3, 56.1; EI-MS (*m/z*, %): 238 ([M] $^+$, 100), 223 (46), 181 (11), 163 (25).

3,4,5-Trimethoxyhydrocinnamic acid (**5**): A suspension of **4** (4.76 g, 0.02 mol) and 0.3 g 5% Pd/C in 50 mL THF was hydrogenated at room temperature and 30 psi. Uptake ceased after 3 h. After filtering, the filtrate was rotary evaporated to produce a residue that was recrystallised from water to give **5** (4.51 g, 94%) as white crystals; m.p. 103–104 °C (lit.[14] 104–105 °C); ^{1}H NMR ($CDCl_3$) ; 8.65 (s, 1H), 6. 44 (s, 2H), 3. 87 (s, 6H), 3. 85 (s, 3H), 2.80 (t, *J* = 7.4 Hz, 2H),



3 4 5 1 2

Scheme 1 a, Malonic acid, pyridine, piperidine, 80 °C, 89%; b, H_2, 5% Pd/C, THF, 94%; c, DCC, DMAP, DCM, 82%; d, $AlCl_3$, CH_2Cl_2, 53%.

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2.63 (t, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 174.2, 153.5, 135.8, 135.7, 105.3, 61.4, 56.1, 34.3, 30.5; EI-MS (*m/z*, %): 240 ([M]$^+$, 100), 225 (42), 181 (83), 151 (19), 137 (27).

3-(3,4,5-Trimethoxyphenyl)propanoylpyrrole (**1**): A stirred solution of DCC (2.06 g, 0.01 mol) in CH_2Cl_2 (20 mL) was added to a solution of pyrrole (1.34 g, 0.02 mol), DMAP (1.22 g, 0.01 mol) and carboxylic acid **5** (2.4 g, 0.01 mol) in CH_2Cl_2 (50 mL) at 0 °C under a nitrogen atmosphere were added The solution was warmed to rt and stirred for 6 h, then the mixture was filtered. The solvent was distilled off and the residue was purified by silica gel chromatography on silica gel to give **1** (2.37 g, 82%) as a white solid; m.p. 51–53 °C (lit.[11] 52–53 °C); ^{1}H NMR ($CDCl_3$) δ: 7.30 (s, 2H), 6.43 (s, 2H), 6.28 (t, J = 2.4 Hz, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.13 (m, 2H), 3.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 169.1, 152.4, 135.7, 135.5, 118.1, 112.7, 60.1, 53.8, 35.9, 30.2; EI-MS (*m/z*, %): 289 ([M]$^+$, 83), 222 (11), 194 (21), 181 (100).

3-(3,5-Dimethoxy-4-hydroxyphenyl) propanoylpyrrole (**2**): Anhydrous aluminium chloride (2.66 g, 20 mmol) was added to a solution of **1** (1.45 g, 5 mmol) in dry CH_2Cl_2 (20 mL) was added. The mixture was sonicated for 20 min, quenched with sat. NH_4Cl, and then washed with water and brine. The aqueous solution was extracted with CH_2Cl_2. The organic phase was dried and concentrated. The residue was purified by silica gel chromatography on silica gel to give **2** (0.73 g, 53%) as white solid; m.p. 88–90 °C (lit.[11] 89–90 °C); ^{1}H NMR ($CDCl_3$) δ: 7.25 (s, 2H), 6.42 (s, 2H), 6.20 (t, J = 2.2 Hz, 2H), 5.63 (s, 1H), 3.78 (s, 6H), 3.06 (t, J = 7.5 Hz, 2H), 2.96 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 168.9, 146.1, 132.8, 130.5, 118.2, 112.3, 54.4, 36.1, 29.8; EI-MS (*m/z*, %): 275 ([M]$^+$, 100), 208 (21), 180 (36), 167 (86).

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