Supporting information for

Efficient Synthesis of Imidazoles From Aldehydes and 1,2-Diketones Using Microwave Irradiation

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General procedure for the preparation of 2,4,5-trisubstituted imidazoles (2-(4-fluorophenyl)-4,5-dipheny-limidazole):
Benzil (42 mg, 0.2 mmol), 4-fluorobenzaldehyde (25 mg, 0.2 mmol), and ammonium acetate (154 mg, 2.0 mmol) were combined and dissolved in 1.0 mL of HOAc in a 2 mL Smithsynthesizer™ reaction vial (Part #352016) containing a magnetic stir bar. The reaction vessel was heated in the Smithsynthesizer™ reactor cavity for 5 min at 180 °C, after which the vessel was rapidly cooled to 40 °C by the unit. The reaction mixture was added dropwise to a 0 °C concentrated NH_4OH solution and immediately formed a white precipitate which was collected by filtration and washed with H_2O. The solid was dried in a vacuum oven for 18 h at 50 °C to afford 2,4,5-triphenylimidazole as a bright white solid (61 mg, 97%). Analytical LCMS: single peak (2.411 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (400, DMSO-d_6) δ 12.69 (s, 1H), 8.14 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.55–7.21 (m, 12H); HRMS *m/z* 315.1304 ($C_{21}H_{15}FN_2 + H^+$ requires 315.1292).

Representative analytical data for entries in Table 2:
Entry 3: Analytical LCMS: single peak (2.536 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (400, DMSO-d_6) δ 12.50 (s, 1H), 8.02 (d, J = 8.9 Hz, 1H), 8.02 (d, J = 8.9 Hz, 1H), 7.54 (m, 2H), 7.49 (m, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.36 (m, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.21 (m, 1H), 7.05 (m, 2H), 3.82 (s, 3H); HRMS *m/z* 327.1483 ($C_{22}H_{18}N_2O + H^+$ requires 327.1492).
Entry 5: Analytical LCMS: single peak (2.273 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (400, DMSO-d_6) δ 12.42 (s, 1H), 11.99 (s, 1H), 8.65 (d, J = 5.6 Hz, 2H), 7.93 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.79 (m, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.47 (m, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.43–7.23 (m, 5H), 7.16 (t, J = 7.6 Hz, 1H); HRMS *m/z* 413.1771 ($C_{28}H_{20}N_4 + H^+$ requires 413.1761).

Representative analytical data for entries in Table 3:
Entry 1: Analytical LCMS: single peak (2.361 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (400, DMSO-d_6) δ 12.87 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 7.84 (s, 1H), 7.73 (s, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 6.4 Hz, 1H), 7.41 (m, 1H), 6.96 (d, J = 3.2

Hz, 1H), 6.75 (d, J = 3.2 Hz, 1H), 6.67 (m, 1H), 6.58 (m, 1H); HRMS *m/z* 277.0974 ($C_{17}H_{12}N_2O_2 + H^+$ requires 277.0972).
Entry 3: Analytical LCMS: single peak (2.537 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (400, DMSO-d_6) δ 12.50 (s, 1H), 8.05 (d, J = 7.2 Hz, 2H), 7.45–7.38 (m, 6H), 7.35 (t, J = 7.2 Hz, 1H), 7.01 (m, 2H), 6.89 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H); HRMS *m/z* 357.1610 ($C_{23}H_{20}N_2O_2 + H^+$ requires 357.1598).
Entry 5: Analytical LCMS: single peak (2.738 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (400, DMSO-d_6) δ 12.56 (s, 1H), 8.06 (d, J = 7.2 Hz, 2H), 7.48–7.43 (m, 4H), 7.39–7.36 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H), 2.29 (s, 3H); HRMS *m/z* 325.1714 ($C_{23}H_{20}N_2 + H^+$ requires 325.1699).

Lepidiline B:
Acetaldehyde (34 µL, 0.6 mmol), 2,3-butanedione (53 µL, 0.6 mmol), and ammonium acetate (462 mg, 6.0 mmol) were combined and dissolved in 3.0 mL of HOAc in a 5 mL Smithsynthesizer™ reaction vial (Part #352016) containing a magnetic stir bar. The reaction vessel was heated in the Smithsynthesizer™ reactor cavity for 5 min at 180 °C, after which the vessel was rapidly cooled to 40 °C by the unit. The reaction mixture was added dropwise to a 0 °C concentrated NH_4OH solution and was diluted with 20 mL H_2O before being extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford 2,4,5-trimethylimidazole as a crystalline solid (50 mg, 76%). Analytical LCMS: single peak (0.3 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (400, $CDCl_3$) δ 2.31 (s, 3H), 2.11 (s, 6H).
Benzyl chloride (127 mg, 1.0 mmol), 2,4,5-trimethylimidazole (22 mg, 0.2 mmol), and Et_3N (141 µL, 1.0 mmol) were combined and dissolved in 1.0 mL of CH_3CN in a 2 mL Smithsynthesizer™ reaction vial (Part #352016) containing a magnetic stir bar. The reaction vessel was heated in the Smithsynthesizer™ reactor cavity for 5 min at 180 °C, then rapidly cooled to 40 °C by the unit before being purified directly by HPLC to afford lepidiline B (25 mg, 43%) identical in all respect to properties reported for the natural product.[1] Analytical LCMS: single peak (2.441 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (DMSO-d_6) δ 7.43–7.34 (m, 6H), 7.16 (d, J = 7.2 Hz, 4H), 5.45 (s, 4H), 2.64 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 143.7, 134.4, 129.0 (2C), 128.1, 126.5 (2C), 125.9 (2C), 47.9, 10.2, 8.3 (2C); HRMS *m/z* 291.1885 ($C_{20}H_{23}N_2Cl - Cl^-$ requires 291.1856).

Trifenagrel:
Benzil (42 mg, 0.2 mmol), 2-[2-(dimethylamino)ethoxy]benzaldehyde[2] (39 mg, 0.2 mmol), and ammonium acetate (154 mg, 2.0 mmol) were combined and dissolved in 1.0 mL of HOAc in a 2 mL Smithsynthesizer™ reaction vial (Part #352016) containing a magnetic stir bar. The reaction vessel was heated in the Smithsynthesizer™ reactor cavity for 5 min at 180 °C, after which the vessel was rapidly cooled to 40 °C by the unit. The reaction mixture was added dropwise to a 0 °C concentrated NH_4OH solution and immediately formed a white precipitate which was collected by filtration and washed with H_2O. The solid was dried in a vacuum oven for 18 h at 50 °C to afford analytically

pure trifenagrel (76 mg, 99%). Analytical LCMS: single peak (2.109 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >95% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (300, $CDCl_3$) δ 12.21 (s, 1H), 8.47 (dd, J = 1.8, 7.8 Hz, 1H), 7.65 (d, J = 7.2 Hz, 2H), 7.48 (d, J = 6.3 Hz, 2H), 7.40–7.26 (m, 8H), 7.11 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 4.23 (dd, J = 5.1, 6.0 Hz, 2H), 2.67 (dd, J = 5.1, 5.4 Hz, 2H), 1.97 (s, 6H); HRMS *m/z* 384.2070 ($C_{25}H_{25}N_3O + H^+$ requires 384.2070).

(1) Cui, B.; Zheng, B. L.; He, K.; Zheng, Q. Y. *J. Nat. Prod*. **2003**, *66*, 1101.
(2) Phillips, A. P.; White, H. L.; Rosen, S. Eur. Patent 58890(A1), 1982.