Phosphine-Mediated Coupling of Gramines with Aldehydes: A Remarkably Simple Synthesis of 3-Vinylindoles

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Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen with magnetic stirring. Solvents were purified prior to use by the Glass Contour solvent purification system. Organic solutions were concentrated *in vacuo* below 35 °C at approximately 25 mm Hg. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and potassium permanganate solution or ceric ammonium molybdate solution followed by heating. Melting points were measured with a Bibby Sterilin Stuart SMP10 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) or Bruker AMX-400 (400 MHz) spectrometer and are reported in ppm using tetramethylsilane as an internal standard (0.00 ppm). Data are reported as br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker Avance-400 (100 MHz) or Bruker AMX-400 (100 MHz) spectrometer and are reported in ppm using the solvent as the internal standard (CDCl₃ at 77.23 ppm, DMSO-*d*₆ at 39.52 ppm, CD₃CN at 1.32 and 118.26 ppm). High-resolution mass spectra were obtained on a Thermo Finnigan MAT 95 XL Magnetic Sector spectrometer with electrospray ionization at the State University of New York at Buffalo Mass Spectrometry Facility.

General procedure. To a solution of 174 mg (1.00 mmol) of gramine (**1**) in 2.0 mL of dry acetonitrile was added 0.10 mL of benzaldehyde (1.00 mmol) and 0.37 mL of *n*-Bu₃P (1.50 mmol) at room temperature. The reaction mixture was gently refluxed (oil bath temperature 90 °C) for 24 hours after which time TLC (silica gel, 2:1 hexanes/EtOAc) indicated consumption of starting benzaldehyde. The reaction mixture was concentrated *in vacuo*, taken up in 10 mL of (3:1 hexanes/EtOAc), filtered through a 2-cm pad of silica gel (the pad washed with 30 mL of 3:1 hexanes/EtOAc), and concentrated *in vacuo*. The residue was recrystallized (CH₂Cl₂/hexane) and the mother liquor was flash chromatographed (hexanes/EtOAc, 4:1) to provide 194 mg (73% combined yield) of (*E*)-3-(2-phenylethenyl)-1*H*-indole (**6**) as a white crystalline solid: mp 192-193 °C [Lit.¹ 193-194 °C]; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 16.4 Hz, 1H), 7.19-7.28 (m, 4H), 7.31-7.41 (m, 5H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.99-8.01 (d, *J* = 7.1 Hz, 1H), 8.16 (br s, 1H).

1-((1H-Indol-3-yl)methyl)-3-styryl-1H-indole (7): mp 159-160 °C; IR (CHCl₃) 3409, 3051, 3032, 1632, 1597, 1528, 1458, 1419, 1392, 1338, 1315, 1165, 957, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.41 (s, 2H), 6.97-7.34 (m, 14H), 7.44-7.48 (m, 4H), 7.95 (br s, 1H), 7.99 (d, *J* = 0.7 Hz, *J* = 7.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 42.1, 110.2, 111.6, 111.8, 114.3, 118.9, 120.4 (2C), 120.6, 122.0, 122.4, 122.8, 123.5, 124.9, 125.8 (2C), 126.6 (2C), 126.7, 127.7, 128.8 (2C), 136.6, 137.5, 138.9; HRMS (DEI): Exact mass calcd for C₂₅H₂₀N₂ (M⁺) 348.1621. Found 348.1610.

3-(4-Methylstyryl)-1H-indole (8).² Following **General procedure**, **8** was obtained in 83% yield from 174 mg (1.00 mmol) of gramine and 0.12 mL of 4-methylbenzaldehyde (1.00 mmol). Characterization data: colorless solid, mp 214-215 °C (CH₂Cl₂/Hexane) [Lit.² 215-216 °C]; ¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 3H), 7.11 (d, *J* = 16.5 Hz, 1H), 7.15-7.30 (m, 6H), 7.34-7.43 (m, 4H), 7.99 (d, *J* = 7.4 Hz, 1H), 8.13 (br s, 1H).

3-(4-Methoxystyryl)-1H-indole (9).¹ Following **General procedure**, **9** was obtained in 77% yield from 174 mg (1.00 mmol) of gramine and 0.13 mL of 4-methoxybenzaldehyde (1.00 mmol). Characterization data: colorless solid, mp 198-199 °C (CH₂Cl₂/Hexane) [Lit.¹ 146-147 °C]; ¹H NMR (400 MHz, CDCl₃) δ 3.84 (s, 3H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 16.4 Hz, 1H), 7.18-7.27 (m, 4H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.39 (d, *J* = 7.1 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 8.14 (br s, 1H).

3-(4-Chlorostyryl)-1H-indole (10).² Following **General procedure**, **10** was obtained in 73% yield from 174 mg (1.00 mmol) of gramine and 140 mg of 4-chlorobenzaldehyde (1.00 mmol). Characterization data: white crystalline solid, mp 214-215 °C (CH₂Cl₂/Hexane); ¹H NMR (400 MHz, CDCl₃) δ 7.08 (d, *J* = 16.4 Hz, 1H), 7.23-7.28 (m, 4H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 5.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 7.5 Hz, 1H), 8.20 (br s, 1H).

Methyl 4-((E)-2-(1H-indol-3-yl)vinyl)benzoate (11). Following **General procedure**, **11** was obtained in 80% yield from 174 mg (1.00 mmol) of gramine and 164 mg of methyl 4-formylbenzoate (1.00 mmol). Characterization data: yellow crystalline solid, mp 224-225 °C (CH₂Cl₂/Hexane); IR (CHCl₃) 3375, 3097, 3036, 2160, 2029, 1975, 1709, 1632, 1597, 1570, 1528, 1504, 1458, 1427, 1277, 1250, 1177, 1107, 953, 852 744 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.84 (s, 3H), 7.13-7.18 (m, 3H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 16.5 Hz, 1H), 7.68-7.72 (m, 3H), 7.91 (d, *J* = 8.2 Hz, 2H), 8.04 (d, *J* = 7.6 Hz, 1H), 11.46 (br s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 51.9, 112.0, 113.5, 120.0 (2C), 121.8, 122.0, 125.1, 125.4 (2C), 125.7, 126.7, 127.4,

129.6 (2C), 137.1, 143.6, 166.1; HRMS (DEI): Exact mass calcd for C₁₈H₁₅NO₂ (M⁺) 277.1097. Found: 277.1097.

3-((E)-2-(Phenanthren-9-yl)vinyl)-1H-indole (12).

Following **General procedure**, **12** was obtained in 74% yield from 174 mg (1.00 mmol) of gramine and 206 mg of 9-phenanthrenecarboxyaldehyde (1.00 mmol). Characterization data: yellow crystalline solid, mp 209-211 °C (CH₂Cl₂/Hexane); IR (CHCl₃) 3414, 3055, 3036, 1632, 1528, 1454, 1419, 1385, 1338, 1246, 1099, 953, 741 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.20-7.23 (m, 2H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.60-7.66 (m, 3H), 7.74-7.76 (m, 2H), 7.87-7.91 (m, 2H), 8.04 (d, *J* = 5.7 Hz, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 8.18 (s, 1H), 8.79 (d, *J* = 3.5 Hz, 1H), 8.89 (d, *J* = 5.8 Hz, 1H), 11.44 (br s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 111.9, 114.1, 119.7, 119.8, 119.8, 121.8, 122.2, 122.7, 123.3, 124.5, 125.3, 125.7, 126.2, 126.4, 126.6, 126.9, 126.9, 128.3, 129.1, 130.0, 130.2, 131.7, 134.4, 137.0; HRMS (DEI): Exact mass calcd for C₂₄H₁₇N (M⁺) 319.1356. Found 319.1349.

3-((E)-2-(1H-indol-3-yl)vinyl)benzonitrile (13).

Following **General procedure**, **13** was obtained in 71% yield from 174 mg (1.00 mmol) of gramine and 131 mg of 3-cyanobenzaldehyde (1.00 mmol). Characterization data: yellow crystalline solid, mp 143-144 °C (CH₂Cl₂/Hexane); IR (CHCl₃) 3410, 3101, 3059, 3036, 2230, 1632, 1589, 1574, 1520, 1477, 1454, 1404, 1323, 1269, 1250, 1223, 1095, 968, 895, 822, 795, 737 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.08 (d, *J* = 16.5 Hz, 1H), 7.19-7.30 (m, 3H), 7.37 (d, *J* = 16.5 Hz, 1H), 7.39-7.48 (m, 4H), 7.71 (d, *J* = 7.3 Hz, 1H), 7.77 (s, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 8.28 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 111.8, 113.0, 115.2, 119.3, 120.3, 121.1, 123.0, 123.2, 124.7, 125.1, 125.6, 129.3, 129.6, 129.8, 130.0, 137.1, 140.1; HRMS (DEI): Exact mass calcd for C₁₇H₁₂N₂ (M⁺) 244.0995. Found 244.0986.

3-(2,6-Dimethoxystyryl)-1H-indole (14).

Following **General procedure**, **14** was obtained in 63% yield from 174 mg (1.00 mmol) of gramine and 166 mg of 2,6-dimethoxybenzaldehyde (1.00 mmol). Characterization data: white thick oil; IR (CHCl₃) 3402, 3051, 3001, 2959, 2939, 2905, 2835, 1701, 1620, 1581, 1454, 1431, 1338, 1250, 1107, 1034, 972, 775, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.87 (s, 6H), 6.58 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.19-7.24 (m, 4H), 7.46 (d, *J* = 16.8 Hz, 1H), 7.77 (d, *J* = 16.8 Hz, 1H), 8.03 (br s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 56.1, 104.4, 111.4, 116.1, 117.2, 117.6, 120.3, 120.6, 122.5, 123.2, 125.7, 126.1, 127.2, 137.1, 158.5; HRMS (DEI): Exact mass calcd for C₁₈H₁₇NO₂ (M⁺) 279.1254. Found 279.1251.

4-((E)-2-(1H-indol-3-yl)vinyl)phenylmethanol (15).

Following **General procedure**, **15** was obtained in 76% yield from 174 mg (1.00 mmol) of gramine and 136 mg of 4-hydroxymethylbenzaldehyde³ (1.00 mmol).

Characterization data: yellow crystalline solid, mp 212-213 °C (CH₂Cl₂/Hexane); IR (CHCl₃) 3386, 3283, 3028, 2914, 2871, 1457, 1186, 956, 937, 750, 741 cm⁻¹; ¹H NMR (400 MHz, CD₃CN) δ 3.14 (s, 1H), 4.57 (s, 1H), 7.12-7.23 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 16.6 Hz, 1H), 7.46-7.48 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 7.7 Hz, 1H), 9.44 (br s, 1H); ¹³C NMR (100 MHz, CD₃CN) δ 64.6, 112.8, 115.5, 120.8, 121.0, 122.9, 123.2, 125.1, 126.2, 126.4, 126.5 (2C), 128.2 (2C), 138.2, 138.7, 141.4; HRMS (DEI): Exact mass calcd for C₁₇H₁₅NO (M⁺) 249.1148. Found 249.1141.

3-((*E*)-2-(Pyridin-3-yl)vinyl)-1*H*-indole (16).¹ Following **General procedure**, **16** was obtained in 69% yield from 174 mg (1.00 mmol) of gramine and 0.10 mL of 3-pyridinecarboxaldehyde (1.00 mmol). Characterization data: yellow crystalline solid, mp 194-195 °C (CH₂Cl₂) [Lit.¹ 195-196 °C]; ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, *J* = 16.5 Hz, 1H), 7.25-7.29 (m, 4H), 7.36-7.43 (m, 3H), 7.83 (td, *J* = 1.7 Hz, *J* = 7.9 Hz, 1H), 8.00 (dd, *J* = 1.6 Hz, *J* = 6.7 Hz, 1H), 8.38 (br s, 1H), 8.00 (dd, *J* = 1.4 Hz, *J* = 4.7 Hz, 1H), 8.73 (d, *J* = 1.9 Hz, 1H).

3-((*E*)-2-(Thiophen-2-yl)vinyl)-1*H*-indole (17). Following **General procedure**, **17** was obtained in 87% yield from 174 mg (1.00 mmol) of gramine and 93 μL of 2-thiophenecarboxaldehyde (1.00 mmol). Characterization data: yellow crystalline solid, mp 199-200 °C (CH₂Cl₂/Hexane, decomp.); IR (CHCl₃) 3387, 1620, 1535, 1508, 1458, 1416, 1338, 1281, 1234, 1099, 949, 856, 814, 748, 694 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.01 (s, 1H), 7.10-7.17 (m, 4H), 7.31-7.33 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 11.34 (s, 1H); ¹³C NMR (100 MHz, *d*₆-DMSO) δ 111.9, 113.1, 117.1, 119.7, 119.8, 121.8, 122.3, 123.0, 124.3, 124.9, 126.4, 127.8, 137.0, 144.0; HRMS (DEI): Exact mass calcd for C₁₄H₁₁NS (M⁺) 225.0607. Found 225.0611.

3-((*E*)-2-(Furan-2-yl)vinyl)-1*H*-indole (18).¹ Following **General procedure**, **18** was obtained in 76% yield from 174 mg (1.00 mmol) of gramine and 80 μL of 3-furaldehyde (1.00 mmol). Characterization data: yellow crystalline solid, mp 192-193 °C (CH₂Cl₂/Hexane); ¹H NMR (400 MHz, CD₃CN) δ 6.34 (d, *J* = 3.1 Hz, 1H), 6.46 (t, *J* = 1.6 Hz, 1H), 6.96 (d, *J* = 16.4 Hz, 1H), 7.14-7.21 (m, 2H), 7.24 (d, *J* = 16.4 Hz, 1H), 7.45-7.47 (m, 3H), 7.92 (d, *J* = 7.8 Hz, 1H), 9.42 (br s, 1H).

3-((*E*)-3,3-Dimethylbut-1-enyl)-1*H*-indole (19). Following **General procedure**, **19** was obtained in 32% yield from 174 mg (1.00 mmol) of gramine and 0.57 mL of pivaldehyde (5.00 mmol). Characterization data: thick colorless oil; IR (CHCl₃) 3360, 2959, 2905, 2866, 1705, 1647, 1616, 1531, 1458, 1427, 1362, 1338, 1242, 1103, 744 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.22 (s, 9H), 6.33 (d, *J* = 16.3 Hz, 1H), 6.53 (d, *J* = 16.3 Hz, 1H), 7.17 (d, *J* = 2.3 Hz, 1H), 7.24 (qd, *J* = 0.8 Hz, *J* = 7.0 Hz, 2H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.95 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 30.1, 33.7, 111.5, 115.7, 117.0, 120.1, 120.2, 122.3, 122.5, 125.9, 136.9, 139.5; HRMS (DEI): Exact mass calcd for C₁₄H₁₇N (M⁺) 199.1356. Found 199.1353.

1-((1H-Indol-3-yl)methyl)-3-((E)-3,3-dimethylbut-1-enyl)-1H-indole was isolated in 15% yield. Characterization data: white solid, mp 75-76 °C (Hexane/Ethyl acetate); IR (CHCl₃) 3348, 2956, 2916, 2850, 1701, 1612, 1462, 1354, 1246, 1173, 1099, 744 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.11 (s, 9H), 5.33 (s, 2H), 6.20 (d, *J* = 16.4 Hz, 1H), 6.43 (d, *J* = 16.4 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 7.04-7.08 (m, 2H), 7.14-7.26 (m, 4H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.81 (br s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 30.1, 33.6, 41.9, 110.0, 111.5, 112.1, 114.2, 117.1, 118.9, 119.8, 120.2, 120.4, 122.0, 122.7, 123.4, 126.1, 126.6, 126.7, 136.5, 137.3, 138.8; HRMS (DEI): Exact mass calcd for C₂₃H₂₄N₂ (M⁺) 328.1934. Found 328.1928.

3-(2-Cyclopropylvinyl)-1H-indole (20). Following **General procedure**, **20** was obtained in 55% yield (*E:Z* = 71:29) from 174 mg (1.00 mmol) of gramine and 0.11 mL of cyclopropanecarbaldehyde (1.50 mmol). Characterization data: yellow amorphous solid; IR (CHCl₃) 3392, 3074, 3051, 2999, 1531, 1458, 1423, 1230, 1095, 949, 798, 741 cm⁻¹. **E-20**: ¹H NMR (400 MHz, CD₃CN) δ 0.49-0.52 (m, 2H), 0.78-0.81 (m, 2H), 1.56-1.58 (m, 1H), 5.76 (dd, *J* = 8.7 Hz, *J* = 16.0 Hz, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 7.08-7.25 (m, 2H), 7.42-7.46 (m, 2H), 7.79 (d, *J* = 7.9 Hz, 1H), 9.08 (br s, 1H); ¹³C NMR (100 MHz, CD₃CN) δ 7.2, 15.4, 112.4, 115.3, 120.3, 120.4, 121.0, 122.7, 123.7, 126.2, 131.5, 137.8; HRMS (DEI): Exact mass calcd for C₁₃H₁₃N (M⁺) 183.1043. Found 183.1030.

3-(But-1-enyl)-1H-indole (21). Following **General procedure**, **21** was obtained in 11% yield (*E:Z* = 86:14) from 174 mg (1.00 mmol) of gramine and 0.40 mL of propanal (5.00 mmol) as an amorphous solid; IR (CHCl₃) 3389, 2960, 2930, 2871, 1456, 1249, 1099, 957, 750, 741 cm⁻¹. **E-21**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.08 (t, *J* = 7.4 Hz, 3H), 2.21 (q, *J* = 7.2 Hz, 2H), 6.16 (td, *J* = 6.5 Hz, *J* = 16.0 Hz, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 7.36-7.40 (m, 2H), 7.76 (d, *J* = 7.9 Hz, 1H), 11.06 (br s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 14.6, 26.5, 112.0, 113.9, 119.5, 119.8, 121.7, 122.5, 124.3, 125.6, 127.7, 137.2; HRMS (DEI): Exact mass calcd for C₁₂H₁₃N (M⁺) 171.1043. Found 171.1042.

2-Methyl-3-styryl-1H-indole (23). Following **General procedure**, **23** was obtained in 55% yield from 140 mg (0.74 mmol) of 2-methylgramine (**22**)⁴ and 74 μL of benzaldehyde (0.74 mmol). Characterization data: yellow crystalline solid, mp 190-191 °C (CH₂Cl₂/Hexane); IR (CHCl₃) 3402, 3032, 2912, 1632, 1458, 1427, 1308, 1246, 953, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 3H), 7.07 (d, *J* = 16.4 Hz, 1H), 7.15-7.21 (m, 4H), 7.25 (d, *J* = 16.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.61 (br s, 1H), 7.94 (d, *J* = 7.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 12.4, 110.8, 111.1, 119.8, 120.6, 121.8, 121.9, 125.4, 125.8, 126.6, 126.7, 128.8, 134.8,

135.7, 139.2; HRMS (DEI): Exact mass calcd for C₁₇H₁₅N (M⁺) 233.1199. Found 233.1199.

¹ De Silva, S. O.; Snieckus, V. *Can. J. Chem.* **1974**, *52*, 1294–1306

² Tewari, R. S.; Gupta, K. C. *Indian J. Chem., Sect B* **1976**, *14B*, 419–421.

³ Mak, C. C.; Bampos, N.; Darling, S. L.; Montalti, M.; Prodi, L.; Sanders, J. K. M. *J. Org. Chem.* **2001**, *66*, 4476–4486.

⁴ Bennett, R.; Maggiolo, A.; Shah, T. *J. Heterocycl. Chem.* **1981**, *18*, 391–394.

— 0.00028

17

DMSO- d_6 , 100 MHz

CDCl₃, 400 MHz

20 (71:29 *E:Z*)
CD₃CN, 400 MHz