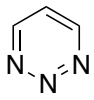
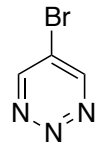
Inverse Electron Demand Diels–Alder Reactions of 1,2,3-Triazines: Pronounced Substituent Effects on Reactivity and Cycloaddition Scope

Erin D. Anderson and Dale L. Boger*

Department of Chemistry and the Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037

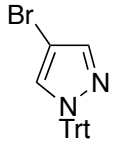


1,2,3-Triazine (1).[S1,S2] Hydroxylamine-*O*-sulfonic acid (43.3 g, 383 mmol) was added to a stirring solution of pyrazole (**5**, 8.68 g, 128 mmol) in 3.7 M NaOH (207 mL). The internal reaction temperature was monitored and kept below 60 °C. After 30 min, the reaction mixture was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with saturated aqueous NaCl (75 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The concentrated product was taken up in CH_2Cl_2 (352 mL). H_2O (132 mL) was added and the reaction mixture was cooled to 0 °C. $NaIO_4$ (54.5 g, 255 mmol, 2.0 equiv) was added and the reaction mixture was stirred at 0 °C for 12 h. After 12 h, the reaction mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. Recrystallization (ether) provided **1** (2.54 g, 25%) as a light brown or tan solid: mp 66 °C (ether) (literature 70 °C)[S2]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.08 (d, J = 5.2 Hz, 2H), 7.44 (t, J = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 149.8, 117.8; IR ν_{max} 3107, 3048, 1542, 1409, 1333, 979, 934, 817, 765, 651 cm^{-1}; ESI-TOF HRMS *m/z* 82.0400 ([M + H]$^+$, $C_3H_3N_3$ + H^+ requires 82.0400).

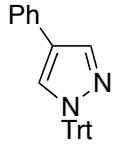


5-Bromo-1,2,3-triazine (4).[S3] Hydroxylamine-*O*-sulfonic acid (2.54 g, 22.5 mmol) was added to a stirring solution of 4-bromopyrazole (**7**, 1.10 g, 7.48 mmol) in 3.7 M NaOH (12 mL). The internal reaction temperature was monitored and kept below 60 °C. After 30 min, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (25 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The concentrated product was taken up in CH_2Cl_2 (20 mL). H_2O (7.6 mL) was added and the reaction mixture was cooled to 0 °C. $NaIO_4$ (2.94 g, 13.7 mmol, 2.0 equiv) was added and the reaction mixture was stirred at 0 °C for 12 h. After 12 h, the reaction mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (25 mL),

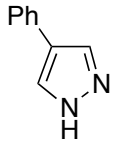
dried (Na_2SO_4), and concentrated on a rotary evaporator. Flash chromatography (SiO_2, 20% EtOAc/hexanes) provided **4** (1.06 g, 89%) as a light brown solid: mp 112 °C (EtOAc) (violent decomposition) (literature 125–126 °C)[S3]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 151.8, 123.7; IR ν_{max} 3062, 2998, 1504, 1350, 1321, 1142, 1005, 952, 934, 853, 796, 759, 733, 657, 602, 431 cm^{-1}; ESI-TOF HRMS *m/z* 159.9498 ($[M + H]^+$, $C_3H_2BrN_3 + H^+$ requires 159.9505).



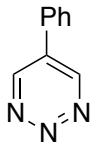
4-Bromo-1-trityl-1*H*-pyrazole (8). *t*-BuOK (1.38 g, 12.3 mmol, 1.2 equiv) and TrtCl (3.15 g, 11.3, mmol, 1.1 equiv) were added sequentially to a stirring solution of 4-bromopyrazole, (**7**, 1.51 g, 10.3 mmol) in DMF (14.4 mL) under Ar at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 1 h. The reaction mixture was poured into EtOAc/H_2O (50 mL/50 mL). The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated on a rotary evaporator. Recrystallization (THF/hexanes) provided **9** (3.55 g, 89%) as a white crystalline solid: mp 186–188 °C (hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, J = 0.8 Hz, 1H), 7.39 (d, J = 0.8 Hz, 1H), 7.32 (m, 9H), 7.13 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.6, 140.2, 132.3, 130.1, 127.9, 127.8, 92.4, 79.34; IR ν_{max} 1443, 952, 745, 696, 634, 606 cm^{-1}; ESI-TOF HRMS *m/z* 411.0471 ($[M + Na]^+$, $C_{22}H_{17}BrN_2 + Na^+$ requires 411.0467).



4-Phenyl-1-trityl-1*H*-pyrazole (10). $PhB(OH)_2$ (0.477 g, 3.91 mmol, 1.1 equiv), $Pd(PPh_3)_4$ (0.416 g, 0.36 mmol, 0.1 equiv), and 5 M aqueous K_2CO_3 (1.42 mL, 7.12 mmol, 2.0 equiv) were added sequentially to a stirring solution of **9** (1.39 g, 3.56 mmol) in DME/H_2O (18 mL/8 mL) under Ar. The reaction mixture was warmed at 85 °C and stirred for 12 h. After 12 h, the reaction mixture was concentrated on a rotary evaporator. The residue was taken up in EtOAc (50 mL), washed with H_2O (15 mL) and saturated aqueous NaCl (15 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. Recrystallization (THF/hexanes) provided **10** (1.30 g, 94%) as a white crystalline solid: mp 155–156 °C (hexanes) (literature 149 °C)[S9]: ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.80 (s, 1H), 7.67 (s, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.36 (m, 11H), 7.25 (m, 6H); ^{13}C NMR (acetone-d_6, 400 MHz) δ 143.1, 137.2, 132.6, 130.2, 129.1, 128.8, 127.7, 126.3, 125.5, 121.6, 78.8; IR ν_{max} 1487, 1443, 1358, 1157, 902, 872, 747, 692, 668, 640, 623, 501 cm^{-1}; ESI-TOF HRMS *m/z* 409.1676 ($[M + Na]^+$, $C_{28}H_{22}N_2 + Na^+$ requires 409.1675).

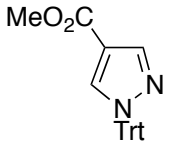


4-Phenyl-1*H*-pyrazole (11). Compound **10** (293 mg, 0.76 mmol) was stirred in 1.25 M HCl in MeOH:CH_2Cl_2 (4.4 mL: 3.7 mL) at 40 °C for 1 h. After 1 h, toluene (2 mL) was added and the reaction mixture was concentrated. Recrystallization (THF/hexanes) provided **11** (103 mg, 94%) as a white crystalline solid: mp 228–230 °C (hexanes) (literature 234–235 °C)[S10]; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.06 (s, 2H), 7.62 (m, 2H), 7.36 (m, 2H), 7.21 (m, 1H); ^{13}C NMR (acetone-d_6, 400 MHz) δ 132.5, 130.6, 128.7, 125.9, 125.0, 121.2; IR ν_{max} 2660, 869, 819, 755, 688, 502 cm^{-1}; ESI-TOF HRMS *m/z* 145.0754 ([M + H]$^+$, $C_9H_8N_2$ + H$^+$ requires 145.0760).

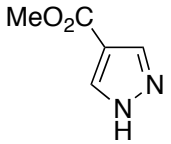


5-Phenyl-1,2,3-triazine (2).[S4] Hydroxylamine-*O*-sulfonic acid (587 mg, 5.19 mmol, 3.0 equiv) in H_2O (1.6 mL) was added dropwise to a stirring solution of **11** (251 mg, 1.73 mmol) in 3.7 M NaOH (2.8 mL) and EtOH (13 mL). The internal reaction temperature was monitored and kept below 60 °C. The reaction mixture was stirred for 30 min at room temperature. After 30 min, the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The concentrated product was taken up in CH_2Cl_2 (5.1 mL). H_2O (1.8 mL) was added and the reaction mixture was cooled to 0 °C. $NaIO_4$ (740 mg, 3.46 mmol, 2.0 equiv) was added and the reaction mixture was stirred at 0 °C for 12 h. After 12 h, the reaction mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. Flash chromatography (SiO_2, 50% EtOAc/hexanes) provided **2** (247 mg, 91%) as a tan solid: mp 139–140 °C (ether) (literature 139–141 °C)[S4a]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.31 (s, 2H), 7.73 (m, 2H), 7.60 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.3, 131.3, 130.9, 130.0, 129.6, 127.2; IR ν_{max} 3049, 1562, 1514, 1494, 1450, 1365, 1353, 1319, 1304, 1001, 985, 944, 919, 777, 697, 664, 628, 551, 480 cm^{-1}; ESI-TOF HRMS *m/z* 158.0716 ([M + H]$^+$, $C_9H_7N_3$ + H$^+$ requires 158.0713).

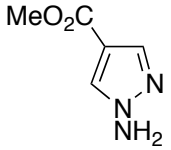
This procedure was carried out on scales up to 3.5 g with yields from 82-91%.



Methyl 1-Trityl-1*H*-pyrazole-4-carboxylate (13). A solution of 1.7 M *t*-BuLi in pentane (4.4 mL, 6.6 mmol, 2.2 equiv) was added to a stirring solution of **9** (1.17 g, 3.02 mmol) in THF (30 mL) under Ar at −78 °C. The resulting bright orange solution was immediately quenched with methyl chloroformate (0.627 g, 6.64 mmol, 2.2 equiv). The reaction mixture was allowed to warm to room temperature, diluted with EtOAc (60 mL), washed with saturated aqueous NaCl (25 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. Recrystallization (THF/hexanes) provided **13** (0.525 g, 47%) as a white solid: mp 164–165 °C (hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, J = 0.8 Hz, 1H), 7.93 (d, J = 0.4 Hz, 1H), 7.32 (m, 9H), 7.13 (m, 6H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.6, 142.4, 135.7, 130.1, 128.0, 127.9, 113.5, 79.5, 51.4; IR ν_{max} 1721, 1552, 1442, 1244, 1212, 1153, 1016, 872, 761, 745, 696, 670, 635 cm^{-1}; ESI-TOF HRMS *m/z* 391.1413 ($[M + Na]^+$, $C_{24}H_{20}N_2O_2 + Na^+$ requires 391.1417).

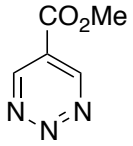


Methyl 1*H*-Pyrazole-4-carboxylate (14). Compound **13** (1.34 g, 3.64 mmol) was stirred in 1.25 M HCl in MeOH:CH_2Cl_2 (21 mL:18 mL) at 40 °C for 3 h. After 3 h, toluene (10 mL) was added and the reaction mixture was concentrated. Trituration with toluene provided **14** (417 mg, 91%) as a white crystalline solid: mp 128–130 °C (toluene) (literature 136–137 °C)[S11]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (s, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 136.5, 114.8, 51.5; IR ν_{max} 2837, 1707, 1527, 1436, 1399, 1326, 1241, 1195, 1153, 999, 946, 885, 849, 796, 762, 604, 502 cm^{-1}; ESI-TOF HRMS *m/z* 127.0505 ($[M + H]^+$, $C_5H_6N_2O_2 + H^+$ requires 127.0502). This compound is also now commercially available.

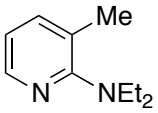


Methyl 1-Amino-1*H*-pyrazole-4-carboxylate (15). NaH (60% dispersion in mineral oil, 55.2 mg, 1.38 mmol, 1.2 equiv) was added to a stirring solution of **14** (145 mg, 1.15 mmol) in DMF (2.7 mL). The resulting grey suspension was stirred at room temperature for 45 min. After 45 min, NH_2Cl[S6] (ca. 0.15 M in ether, 10.7 mL) was added to the reaction mixture while maintaining an Ar sparge. The reaction mixture was stirred at room temperature for 30 min. After 30 min, the reaction was quenched with the addition of saturated aqueous $Na_2S_2O_4$ (3 mL), diluted with water (25 mL), and extracted with ether (5 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated on a rotary evaporator. Flash chromatography (SiO_2, ether) provided **15** (151 mg, 93%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (s, 1H), 7.80 (s, 1H), 5.33 (bs, 2H), 3.82 (s, 3H); ESI-TOF HRMS *m/z* 142.0615 ($[M + H]^+$, $C_5H_7N_3O_2 + H^+$ requires 142.0611).

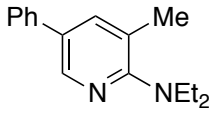
Amination with *O*-(4-nitrobenzoyl)hydroxylamine: A solution of $KOBu^t$ (174 mg, 1.55 mmol, 1.1 equiv) in NMP (1.7 mL) was added to a stirring solution of **14** (177 mg, 1.41 mmol) in NMP (18.7 mL). The resulting light pink solution was stirred at room temperature for 20 min. After 20 min, a solution of *O*-(4-nitrobenzoyl)hydroxylamine (182 mg, 1.62 mmol, 1.15 equiv) in NMP (11.0 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h. After 2 h, the reaction mixture was treated with saturated aqueous NaCl (7%, 60 mL) and ethyl acetate (60 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (60 mL). The combined organic layers were washed with aqueous sodium bicarbonate (5%, 45 mL), H_2O (45 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. Flash chromatography (SiO_2, ether) provided **15** (149 mg, 75%) as a white solid.



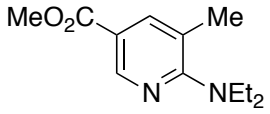
Methyl 1,2,3-Triazine-5-carboxylate (3).[S5] Compound **15** (335 mg, 2.37 mmol) was taken up in CH_2Cl_2 (50 mL) and cooled to 0 °C. $NaIO_4$ (1.02 g, 4.75 mmol, 2.0 equiv) in H_2O (50 mL) was cooled to 0 °C and added to the stirring solution of **15** at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After 2 h, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. Compound **16** was extremely sensitive to moisture and was handled only in oven-dried glassware under an atmosphere of Ar. Flash chromatography (oven-dried SiO_2, ether) provided **3** (272 mg, 81%) as a yellow oil: ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.53 (s, 2H), 4.05 (s, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 178.7, 149.8, 130.1, 54.8; IR ν_{max} 2953, 1712, 1626, 1562, 1435, 1396, 1366, 1293, 1232, 1197, 1143, 1030, 1011, 963, 916, 839, 802, 768 cm^{-1}; ESI-TOF HRMS *m/z* 140.0454 ($[M + H]^+$, $C_5H_5N_3O_2 + H^+$ requires 140.0454).



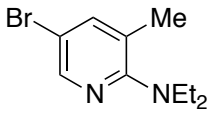
2-Diethylamino-3-methylpyridine (17). Compound **16a**[S7] (100 mg, 0.90 mmol) was added to a stirring solution of **1** (48.7 mg, 0.60 mmol) in $CHCl_3$ (0.6 mL) at 25 °C. The reaction mixture was stirred at 60 °C for 3 h, concentrated and purified by column chromatography (SiO_2, 30% EtOAc/hexanes) to afford **17** (63.4 mg, 64%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (dd, J = 4.8, 1.2 Hz, 1H), 7.38 (ddd, J = 7.3, 1.9, 0.7 Hz, 1H), 6.80 (dd, J = 7.3, 4.8 Hz, 1H), 3.19 (q, J = 6.8 Hz, 4H), 2.25 (s, 3H), 1.07 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.5, 144.9, 139.0, 125.9, 117.0, 45.0, 18.8, 13.1; IR ν_{max} 2968, 1586, 1469, 1448, 1422, 1376, 1354, 1254, 1193, 1102, 779 cm^{-1}; ESI-TOF HRMS *m/z* 165.1392 ($[M + H]^+$, $C_{10}H_{16}N_2 + H^+$ requires 165.1386).



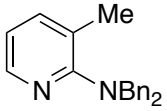
2-Diethylamino-3-methyl-5-phenylpyridine (18). Compound **16a** (35.6 mg, 0.32 mmol) was added to a stirring solution of **2** (33.2 mg, 0.21 mmol) in $CHCl_3$ (0.2 mL) at 25 °C. The reaction mixture was stirred at room temperature for 3 h, concentrated, and purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to provide **18** (35.0 mg, 69%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (d, J = 2.0 Hz, 1H), 7.61 (m, 1H), 7.55 (m, 2H), 7.33 (m, 1H), 3.27 (q, J = 6.8 Hz, 4H), 2.33 (s, 3H), 1.13 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.7, 143.0, 138.3, 137.8, 129.8, 128.8, 127.0, 125.3, 45.0, 19.0, 13.2; IR ν_{max} 2967, 1600, 1470, 1427, 1376, 1256, 1126, 898, 756, 694 cm^{-1}; ESI-TOF HRMS *m/z* 241.1701 ([M + H]$^+$, $C_{16}H_{20}N_2$ + H$^+$ requires 241.1699).



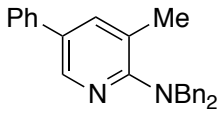
Methyl 6-(Diethylamino)-5-methylnicotinate (19). Compound **16a** (17.8 mg, 0.16 mmol) was added to a stirring solution of **3** (15.0 mg, 0.11 mmol) in $CHCl_3$ (0.1 mL). The reaction mixture was stirred for 5 min at room temperature, concentrated, and purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) to provide **19** (17.2 mg, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.72 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 2.2, 0.4 Hz, 1H), 3.89 (s, 3H), 3.41 (q, J = 6.8 Hz, 4H), 2.31 (s, 3H), 1.17 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6, 163.4, 147.3, 140.3, 121.1, 117.2, 51.7, 44.3, 20.1, 13.4; IR ν_{max} 2360, 2340, 1717, 1602, 1291, 1265, 420 cm^{-1}; ESI-TOF HRMS *m/z* 223.1447 ([M + H]$^+$, $C_{12}H_{18}N_2O_2$ + H$^+$ requires 223.1441).



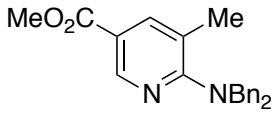
5-Bromo-2-Diethylamino-3-methylpyridine (20). Compound **16a** (32.2 mg, 0.29 mmol) was added to a stirring solution of **4** (30.8 mg, 0.19 mmol) in $CHCl_3$ (0.2 mL). The reaction mixture was stirred for 15 min at room temperature, concentrated, and purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) to provide **20** (43.4 mg, 93%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.70 (s, 1H), 7.87 (s, 1H), 3.87 (s, 3H), 3.38 (q, J = 7.2 Hz, 4H), 2.28 (s, 3H), 1.14 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.2, 145.5, 141.3, 127.5, 112.1, 45.0, 18.8, 13.11; IR ν_{max} 2970, 1469, 1424, 1378, 1355, 1258, 1133 cm^{-1}; ESI-TOF HRMS *m/z* 243.0492 ([M + H]$^+$, $C_{10}H_{15}N_2Br$ + H$^+$ requires 243.0491).



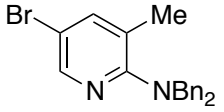
2-Dibenzylamino-3-methylpyridine (21). Compound **16b** (221 mg, 0.94 mmol) was added to a stirring solution of **1** (50.9 mg, 0.63 mmol) in $CHCl_3$ (0.6 mL) at 25 °C. The reaction mixture was stirred at 60 °C for 12 h, concentrated and purified by column chromatography (SiO_2, 40% EtOAc/hexanes) to afford **21** (72.5 mg, 40%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (ddd, J = 4.8, 1.9, 0.5 Hz, 1H), 7.46 (ddd, J = 7.3, 1.9, 0.8 Hz, 1H), 7.34–7.24 (m, 10H), 6.88 (dd, J = 7.3, 4.8 Hz, 1H), 4.40 (s, 4H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 161.3, 145.2, 139.4, 139.0, 128.2, 128.1, 126.7, 125.6, 118.0, 54.5, 18.7; IR ν_{max} 1584, 1446, 1418, 1358, 1220, 784, 736, 694 cm^{-1}; ESI-TOF HRMS *m/z* 289.1693 ([M + H]$^+$, $C_{20}H_{20}N_2$ + H$^+$ requires 289.1699).



2-Dibenzylamino-3-methyl-5-phenylpyridine (22). Compound **16b** (127 mg, 0.54 mmol) was added to a stirring solution of **2** (56.2 mg, 0.36 mmol) in $CHCl_3$ (0.4 mL). The reaction mixture was stirred at 60 °C for 3 h, concentrated, and purified by flash chromatography (SiO_2, 40% EtOAc/hexanes) to provide **22** (86.5 mg, 66%) as a light yellow solid: mp 56–60 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.45 (d, J = 2.5 Hz, 1H), 7.69 (dd, J = 2.5, 1.0 Hz, 1H), 7.59 (m, 2H), 7.47 (m, 2H), 7.39–7.32 (m, 9H), 7.27 (m, 2H), 4.46 (s, 4H), 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.5, 143.3, 139.0, 138.1, 138.0, 130.7, 128.8, 128.21, 128.19, 127.2, 126.8, 126.5, 125.0, 54.4, 18.9; IR ν_{max} 1450, 1358, 1214, 903, 739, 694, 519 cm^{-1}; ESI-TOF HRMS *m/z* 365.2002 ([M + H]$^+$ $C_{26}H_{24}N_2$ + H$^+$ requires 365.2012).

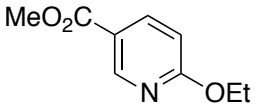


Methyl 6-(Dibenzylamino)-5-methylnicotinate (23). Compound **16b** (37.7 mg, 0.16 mmol) was added to a stirring solution of **3** (15.2 mg, 0.11 mmol) in $CHCl_3$ (0.1 mL). The reaction mixture was stirred for 15 min at room temperature, concentrated, and purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to provide **23** (31.6 mg, 83%) as a dark yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.76 (d, J = 2.5 Hz, 1H), 7.99 (s, 1H), 7.30 (m, 10H), 4.59 (s, 4H), 3.92 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 163.5, 147.5, 140.9, 138.4, 128.4, 127.9, 127.0, 121.4, 118.5, 53.3, 51.8, 19.8; IR ν_{max} 1716, 1600, 1430, 1297, 1227, 698 cm^{-1}; ESI-TOF HRMS *m/z* 347.1758 ([M + H]$^+$, $C_{22}H_{22}N_2O_2$ + H$^+$ requires 347.1754).



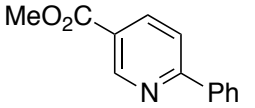
2-Dibenzylamino-5-bromo-3-methylpyridine (24). Compound **16b** (49.0 mg, 0.21 mmol) was added to a stirring solution of **4** (22.1 mg, 0.14 mmol) in $CHCl_3$ (0.6 mL). The reaction mixture was stirred for 15 min at room temperature, concentrated, and

purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) to provide **24** (13.1 mg, 25%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (s, 1H), 7.50 (s, 1H), 7.24 (m, 10H), 4.29 (s, 4H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.0, 145.9, 141.6, 138.6, 128.25, 128.18, 127.4, 126.9, 113.2, 54.5, 18.7; IR ν_{max} 2361, 2340, 1453, 1421, 1360, 1222, 741, 698 cm^{-1}; ESI-TOF HRMS *m/z* 367.0801 ($[M + H]^+$, $C_{20}H_{19}BrN_2 + H^+$ requires 367.0804).



Methyl 6-Ethoxynicotinate (27). From alkyne **25**: Compound **25** (45 μL, 0.25 mmol, 50% w/w in hexanes) was added to a stirring solution of **3** (7.0 mg, 0.05 mmol) in xylenes (0.1 mL). The reaction mixture was warmed to 140 °C for 24 h, cooled, and concentrated. Flash chromatography (SiO_2, 20% EtOAc/hexanes) provided **27** (5.6 mg, 62%) as an off-white solid: mp 48–50 °C (EtOAc) (literature 51–52 °C)[S12]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.78 (d, *J* = 1.5 Hz, 1H), 8.11 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.5, 165.8, 150.0, 139.4, 119.3, 110.6, 62.4, 51.9, 14.4; IR ν_{max} 2990, 2360, 1713, 1601, 1492, 1438, 1288, 1124, 848, 778 cm^{-1}; ESI-TOF HRMS *m/z* 182.0805 ($[M + H]^+$, $C_9H_{11}NO_3 + H^+$ requires 182.0812).

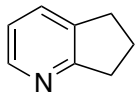
From ketene acetal **38**: Hunig's base (25 μL, 0.15 mmol, 0.8 equiv) and compound **38** (25 μL, 0.19 mmol, 1.0 equiv) were added sequentially to a stirring solution of **3** (26.0 mg, 0.19 mmol) in dioxane at 60 °C under Ar. The reaction mixture was stirred at 60 °C for 30 min and then purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) to provide **27** (33.7 mg, 99%) as an off-white solid.



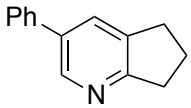
Methyl 6-Phenylnicotinate (28). From alkyne **26**: Compound **26** (77 μL, 0.7 mmol) was added to a stirring solution of **3** (20.0 mg, 0.14 mmol) in xylenes (0.2 mL). The reaction mixture was warmed to 140 ºC, stirred for 24 h, cooled, and concentrated. Flash chromatography (SiO_2, 40% EtOAc/hexanes) provided **28** (18.0 mg, 59%) as a tan solid: mp 108–110 °C (literature 118 °C)[S13]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.29 (s, 1H), 8.35 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.06 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.50 (m, 3H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 160.9, 150.9, 138.3, 137.9, 129.9, 128.9, 127.3, 124.2, 119.8, 52.3; IR ν_{max} 1715, 1596, 1438, 1288, 1268, 1118, 752 cm^{-1}; ESI-TOF HRMS *m/z* 214.0866 ($[M + H]^+$, $C_{13}H_{11}NO_2 + H^+$ requires 214.0863).

From enol ether **39**: Compound **39** (162 μL, 0.79 mmol) was added to a stirring solution of **3** (22.0 mg, 0.16 mmol) in xylenes (0.2 mL). The reaction was warmed to 140 °C, stirred for 24 h, and purified by flash chromatography (SiO_2, 40% EtOAc/hexanes) to yield **28** (16.1 mg, 48%) as a tan solid.

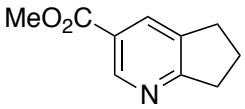
From enol ether **40**: Compound **40** (134 μL, 0.5 mmol, 0.5 M in CH_2Cl_2) was added to a stirring solution of **3** (14.0 mg, 0.1 mmol) in xylenes (0.2 mL). The reaction was warmed to 140 °C, stirred for 24 h, and purified by flash chromatography (SiO_2, 40% EtOAc/hexanes) to yield **28** (10.5 mg, 49%) as a tan solid.



Cyclopenta[*b*]pyridine (30). Compound **29a** (160 μL, 1.10 mmol) was added to a stirring solution of **1** (59.5 mg, 0.73 mmol) in $CHCl_3$ (1 mL). The reaction mixture was stirred at 25 °C for 5 min and then warmed at 60 °C for 14 h. The reaction mixture was concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexanes) to afford **30** (42.1 mg, 48%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (d, J = 5.0 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.89 (m, 1H), 2.90 (t, J = 9.0 Hz, 2H), 2.81 (t, J = 8.5 Hz, 2H), 2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.3, 147.2, 136.6, 131.7, 120.7, 34.0, 30.5, 22.8; IR ν_{max} 2953, 1577, 1418, 1089, 786, 722 cm^{-1}; ESI-TOF HRMS *m/z* 120.0810 ([M + H]$^+$, $C_8H_9N + H^+$ requires 120.0808).

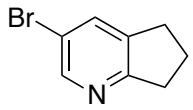


3-Phenylcyclopenta[*b*]pyridine (31). Compound **29a** (35 μL, 0.24 mmol) was added to a stirring solution of **2** (24.8 mg, 0.16 mmol) in $CHCl_3$ (0.3 mL). The reaction mixture was stirred at room temperature for 5 min, and then warmed to 60 °C for 14 h. After 14 h, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexanes) to provide **31** (27.2 mg, 88%) as an off-white solid: mp 76–77 °C (EtOAc) (literature 82–83 °C)[S14]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56 (s, 1H), 7.67 (s, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 3.05 (t, J = 7.5 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.17 (q, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.6, 146.2, 138.5, 137.0, 134.3, 130.6, 128.9, 127.5, 127.1, 33.8, 30.6, 23.3; IR ν_{max} 1460, 1447, 1385, 907, 761, 693, 507 cm^{-1}; ESI-TOF HRMS *m/z* 196.1126 ([M + H]$^+$, $C_{14}H_{13}N + H^+$ requires 196.1121).

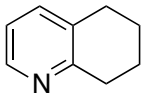


Methyl Cyclopenta[*b*]pyridine-3-carboxylate (32). Compound **29a** (29 μL, 0.20 mmol) was added to a stirring solution of **3** (18.7 mg, 0.13 mmol) in $CHCl_3$ (0.2 mL). The reaction mixture was stirred at room temperature for 5 min and then warmed to 45 °C for 30 min. After 30 min, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to provide **32** (20.0 mg, 84%) as a tan solid: mp 45–47 °C (EtOAc): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.96 (s, 1H), 8.07 (s, 1H), 3.92 (s, 3H), 3.06 (t, J = 9.5 Hz, 2H), 2.98 (t, J = 9.0 Hz, 2H), 2.17 (q, J = 9.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 166.4, 149.3, 137.0, 132.8, 123.8, 52.2, 34.4, 30.4, 23.1; IR -

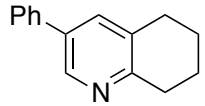
ν_{max} 2951, 1710, 1596, 1431, 1392, 1315, 1287, 1270, 1191, 1115, 771 cm^{-1}; ESI-TOF HRMS *m/z* 178.0864 ($[M + H]^+$, $C_{10}H_{11}NO_2 + H^+$ requires 178.0863).



3-Bromocyclopenta[*b*]pyridine (33). Compound **29a** (46 µL, 0.32 mmol) was added to a stirring solution of **4** (34.1 mg, 0.21 mmol) in $CHCl_3$ (0.4 mL) at 0 °C. The reaction was stirred at 0 °C for 5 min and then warmed to 45 °C. After 45 min, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to provide **33** (16.7 mg, 40%) as a tan solid: mp 65–67 °C (EtOAc): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1H), 7.61 (d, *J* = 1.0 Hz, 1H), 2.94 (q, *J* = 9.5 Hz, 4H), 2.14 (q, *J* = 9.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3, 148.3, 139.2, 134.7, 118.2, 33.6, 30.6, 23.4; IR ν_{max} 2951, 2923, 1428, 1384, 1202, 1115, 1084, 895, 875, 704, 647, 517, 420 cm^{-1}; ESI-TOF HRMS *m/z* 197.9907 ($[M + H]^+$, $C_8H_8BrN + H^+$ requires 197.9913).

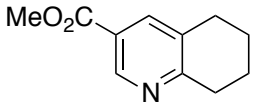


5,6,7,8-Tetrahydroquinoline (34). Compound **29b** (162 µL, 1.01 mmol) was added to a stirring solution of **1** (54.0 mg, 0.67 mmol) in $CHCl_3$ (1.3 mL). The reaction mixture was stirred at room temperature for 5 min and then warmed to 60 °C for 14 h. After 14 h, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 50% ether/hexanes) to provide **34** (25.4 mg, 29%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.29 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.29 (d, *J* = 9.5 Hz, 1H), 6.96 (m, 1H), 2.88 (t, *J* = 8.0 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 1.86 (m, 2H), 1.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.2, 146.6, 136.6, 132.1, 120.7, 32.4, 28.6, 22.9, 22.6; IR ν_{max} 2930, 1573, 1446, 1423, 182, 727 cm^{-1}; ESI-TOF HRMS *m/z* 134.0962 ($[M + H]^+$, $C_9H_{11}N + H^+$ requires 134.0964).

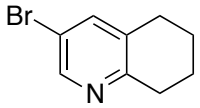


3-Phenyl-5,6,7,8-tetrahydroquinoline (35). Compound **29b** (35 µL, 0.22 mmol) was added to a stirring solution of **2** (22.6 mg, 0.14 mmol) in $CHCl_3$ (0.3 mL). The reaction mixture was stirred at room temperature for 5 min and then warmed to 60 °C for 14 h. After 14 h, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 5% acetone/toluene) to provide **35** (15.0 mg, 50%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.59 (s, 1H), 7.56 (m, 3H), 7.46 (m, 2H), 7.38 (m, 1H), 2.98 (t, *J* = 6.5 Hz, 2H), 2.84 (t, *J* = 6.5 Hz, 2H), 1.93 (m, 2H), 1.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.2, 145.0, 138.1, 135.2, 134.0, 132.1, 128.9, 127.7, 127.0, 32.1, 28.9, 23.1,

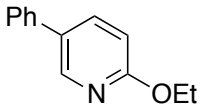
22.7; IR ν_{max} 2931, 1460, 763, 697 cm^{-1}; ESI-TOF HRMS *m/z* 210.1281 ($[M + H]^+$, $C_{15}H_{15}N + H^+$ requires 210.1277).



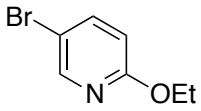
Methyl 5,6,7,8-Tetrahydroquinoline-3-carboxylate (36). Compound **29b** (68 μL, 0.42 mmol) was added to a stirring solution of **3** (39.0 mg, 0.28 mmol) in $CHCl_3$ (0.6 mL). The reaction mixture was stirred at room temperature for 5 min and then warmed to 60 °C and stirred for 14 h. After 14 h, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, EtOAc) to provide **36** (48.0 mg, 90%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.90 (d, *J* = 2.0 Hz, 1H), 7.93 (d, *J* = 1.0 Hz, 1H), 3.89 (s, 3H), 2.94 (t, *J* = 8.0 Hz, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 1.88 (m, 2H), 1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 162.8, 147.7, 137.5, 132.0, 123.3, 32.7, 28.5, 22.7, 22.4; IR ν_{max} 2900, 1720, 1600, 1433, 1403, 1294, 1272, 1217, 1151, 1109, 767 cm^{-1}; ESI-TOF HRMS *m/z* 192.1021 ($[M + H]^+$, $C_{11}H_{13}NO_2 + H^+$ requires 192.1019).



3-Bromo-5,6,7,8-tetrahydroquinoline (37). Compound **29b** (51 μL, 0.32 mmol) was added to a stirring solution of **4** (33.8 mg, 0.21 mmol) in $CHCl_3$ (0.4 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and then warmed to 45 °C for 30 min. After 30 min, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 50% EtOAc/hexanes) to provide **37** (30.3 mg, 68%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.39 (d, *J* = 2.5 Hz, 1H), 7.50 (t, *J* = 1.5 Hz, 1H), 2.86 (t, *J* = 8.5 Hz, 2H), 2.75 (t, *J* = 8.0 Hz, 2H), 1.88 (m, 2H), 1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.0, 147.6, 138.9, 134.2, 117.2, 32.0, 28.6, 22.8, 22.3; IR ν_{max} 2935, 2860, 1445, 1394, 987 cm^{-1}; ESI-TOF HRMS *m/z* 212.0065 ($[M + H]^+$, $C_9H_{11}BrN + H^+$ requires 212.0069).



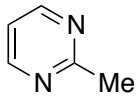
2-Ethoxy-5-phenylpyridine (41). Compound **38** (175 μL, 1.3 mmol, 5.0 equiv) was added to a stirring solution of **2** (41.9 mg, 0.27 mmol) in xylenes. The reaction mixture was warmed to 140 °C, stirred for 24 h, and purified by flash chromatography (SiO_2, CH_2Cl_2) to provide **41** (50.4 mg, 95%) as a light yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.40 (dd, *J* = 2.6, 0.8 Hz, 1H), 7.81 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.55 (2H, m), 7.47 (2H, m), 6.83 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.44 (q, *J* = 6.8 Hz, 2H), 1.46 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.3, 145.0, 138.0, 137.4, 130.0, 128.9, 127.2, 126.6, 110.9, 61.8, 14.7; IR ν_{max} 1601, 1468, 1283, 1037, 767, 694 cm^{-1}; ESI-TOF HRMS *m/z* 200.1072 ($[M + H]^+$ $C_{13}H_{13}NO + H^+$ requires 200.1070).



5-Bromo-2-ethoxypyridine (42). Compound **38** (270 μL, 2.06 mmol) was added to a stirring solution of **4** (66.0 mg, 0.41 mmol) in dioxane (0.4 mL). The reaction mixture was warmed to 100 °C and stirred for 24 h. After 24 h, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexanes) to provide **42** (32.9 mg, 39%) as a light brown solid: mp 25 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (d, J = 3.0 Hz, 1H), 7.61 (dd, J = 9.0, 3.0 Hz), 6.62 (d, J = 9.0 Hz, 1H), 4.31 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 162.7, 147.5, 141.0, 112.7, 111.4, 62.1, 14.5; IR ν_{max} 1583, 1301, 1372, 1349, 1278, 1243, 1035, 824 cm^{-1}; ESI-TOF HRMS *m/z* 201.9861 ([M + H]$^+$, C_7H_8BrNO + H^+ requires 201.9862).

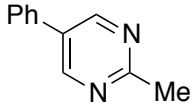
Amidines. The free base of dienophile **44a** was obtained by treatment of the HCl salt with NaOMe in MeOH.[S8]

The free base of dienophiles **44b**–**44m** were obtained by treating a solution of the HCl salt in CH_2Cl_2 with aqueous KOH (2.0 M). The aqueous layer was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated.



2-Methylpyrimidine (45). Compound **44a** (78.0 mg, 1.34 mmol) was added to a stirring solution of **1** (99.0 mg, 1.22 mmol) in CD_3CN (0.6 mL). Rapid gas evolution followed the addition of **44a**. The reaction mixture was stirred for 5 min at 25 °C to afford **45** (93%). Because of the volatility of **45**, the conversion was determined by integral ratios of ^{1}H NMR in CD_3CN relative to the integral value of the internal standard (anisole). ^{1}H NMR (CD_3CN, 400 MHz) δ 8.65 (d, J = 4.8 Hz, 2H), 7.21 (t, J = 4.4 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (CD_3CN, 400 MHz) δ 168.3, 157.4, 117.8, 25.0; ESI-TOF HRMS *m/z* 95.0608 ([M + H]$^+$, $C_5H_6N_2$ + H^+ requires 95.0604).

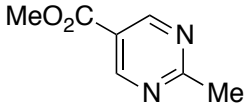
Compound **44b** (70 μL, 0.7 mmol) was added to a stirring solution of **1** (51.2 mg, 0.63 mmol) in CD_3CN (0.2 mL). The reaction mixture was warmed to 80 °C and stirred for 24 h to afford **45** (63%, 99% brsm).



2-Methyl-5-phenylpyrimidine (46). Compound **44a** (47.9 mg, 0.83 mmol) was added to a stirring solution of **2** (61.0 mg, 0.75 mmol) in CH_3CN (0.5 mL). The reaction mixture was stirred at 5 min at room temperature and then warmed to 45 °C and stirred for 5 min. The reaction mixture was then concentrated and purified by flash

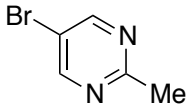
chromatography (SiO_2, CH_2Cl_2) to provide **46** (126 mg, 98%) as an off-white solid: mp 63 °C (CH_2Cl_2) (literature 57–58 °C)[S15]: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (s, 2H), 7.52–7.39 (m, 5H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 154.8, 134.3, 130.9, 129.1, 128.4, 126.6, 25.5; IR ν_{max} 1581, 1540, 1443, 1377, 763, 749, 298, 651, 549, 493, 421 cm^{-1}; ESI-TOF HRMS *m/z* 171.0917 ([M + H]$^+$ $C_{11}H_{10}N_2$ + H^+ requires 171.0917).

Compound **44b** (73.8 mg, 0.85 mmol) was added to a stirring solution of **2** (121 mg, 0.77 mmol) in CH_3CN (0.5 mL). The reaction mixture was stirred at 5 min at room temperature and then warmed to 80 °C and stirred for 24 h. The reaction mixture was then concentrated and purified by flash chromatography (SiO_2, CH_2Cl_2) to provide **46** (124 mg, 94%) as an off-white solid.

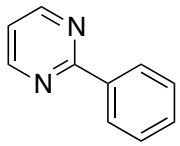


Methyl 2-Methylpyrimidine-5-carboxylate (47). Compound **44a** (13.4 mg, 0.23 mmol) was added to a stirring solution of **3** (29.0 mg, 0.21 mmol) in CH_3CN (0.2 mL). The reaction mixture was stirred at room temperature for 10 min, concentrated, and then purified by flash chromatography (SiO_2, 50% EtOAc/hexanes) to provide **47** (19.5 mg, 62%) as a yellow solid: mp 54–56 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.16 (s, 2H), 3.96 (s, 3H), 2.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 164.4, 158.1, 121.2, 52.5, 26.4; IR ν_{max} 1714, 1587, 1555, 1428, 1301, 1256, 1126, 1031, 945, 763, 490 cm^{-1}; ESI-TOF HRMS *m/z* 153.0656 ([M + H]$^+$ $C_7H_8N_2O_2$ + H^+ requires 153.0659).

Compound **44b** (14.8 mg, 0.17 mmol) was added to a stirring solution of **3** (21.0 mg, 0.15 mmol) in CH_3CN (0.2 mL). The reaction mixture was stirred at room temperature for 15 min, concentrated, and then purified by flash chromatography (SiO_2, 50% EtOAc/hexanes) to provide **47** (15.6 mg, 68%) as a yellow solid.

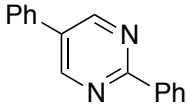


5-Bromo-2-methylpyrimidine (48). Compound **44a** (12.2 mg, 0.21 mmol) was added to a stirring solution of **4** (31.2 mg, 0.20 mmol) in CH_3CN (0.2 mL). The reaction mixture was stirred at room temperature for 10 min, concentrated, and purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to provide **48** (15.7 mg, 47%) as a yellow solid: mp 59–60 °C (EtOAc): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.69 (s, 2H), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 157.5, 117.5, 25.3; IR ν_{max} 1539, 1428, 1261, 1114, 1009, 927, 739, 637, 470 cm^{-1}; ESI-TOF HRMS *m/z* 172.9716 ([M + H]$^+$ $C_5H_5BrN_2$ + H^+ requires 172.9709).



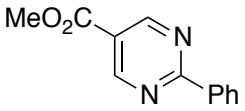
2-Phenylpyrimidine (49). Compound **44c** (108 mg, 0.90 mmol) was added to a stirring solution of **1** (36.5 mg, 0.45 mmol) in dioxane (0.5 mL). The reaction was stirred at 25 °C for 6 h. The reaction mixture was concentrated and purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) to afford **49** (64.3 mg, 91%) as a white solid: mp 34–36 ºC (EtOAc) (literature 36–37 ºC)[S16]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79 (d, J = 4.0 Hz, 2H), 8.45 (m, 2H), 7.50 (m, 3H), 7.16 (t, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 157.2, 137.5, 130.7, 128.5, 128.1, 119.0; IR ν_{max} 1552, 1410, 1314, 1027, 824, 808, 739, 685, 637, 447 cm^{-1}; ESI-TOF HRMS *m/z* 157.0766 ([M + H]$^+$, $C_{10}H_8N_2$ + H$^+$ requires 157.0760).

Compound **44d** (160 mg, 1.07 mmol) was added to a stirring solution of **1** (58.1 mg, 0.72 mmol) in DMF (0.7 mL). The reaction mixture was warmed to 100 °C and stirred for 6 h. The reaction mixture was concentrated and purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) to afford **49** (18.1 mg, 16%) as a white solid.



2,5-Diphenylpyrimidine (50). Compound **44c** (32.4 mg, 0.27 mmol) was added to a stirring solution of **2** (38.5 mg, 0.24 mmol) in dioxane (0.3 mL). The reaction mixture was stirred at room temperature for 6 h. After 6 h, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) to provide **50** (50.2, 88%) as an off-white solid: mp 177–180 °C (EtOAc) (literature 182–184 °C)[S16]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.03 (s, 2H), 8.50 (m, 2H), 7.64 (m, 2H), 7.56–7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 155.2, 137.3, 134.5, 131.6, 130.7, 129.4, 128.7, 128.6, 128.1, 126.7; IR ν_{max} 1536, 1433, 1376, 910, 741, 652, 571, 505 cm^{-1}; ESI-TOF HRMS *m/z* 233.1076 ([M + H]$^+$, $C_{16}H_{12}N_2$ + H$^+$ requires 233.1073).

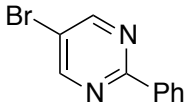
Compound **44d** (38.8 mg, 0.26 mmol) was added to a stirring solution of **2** (27.4 mg, 0.17 mmol) in DMF (0.2 mL). The reaction mixture was warmed to 100 °C and stirred for 24 h. After 24 h, the reaction mixture was purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) to provide **50** (19.5 mg, 48%) as an off-white solid.



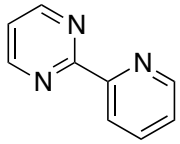
Methyl 2-Phenylpyrimidine-5-carboxylate (51). Compound **44c** (18.5 mg, 0.15 mmol) was added to a stirring solution of **3** (20.0 mg, 0.14 mmol) in dioxane (0.2 mL). The reaction mixture was stirred at room temperature for 5 min, concentrated, and then

purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to provide **51** (30.5 mg, 99%) as a white solid: mp 159–161 °C (EtOAc) (literature 161–163 °C)[S17]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.31 (s, 2H), 8.52 (m, 2H), 7.53 (m, 3H), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2, 164.4, 158.4, 136.6, 131.8, 129.0, 128.7, 121.5, 52.5; IR ν_{max} 2946, 1714, 1580, 1539, 1420, 1384, 1291, 1240, 1198, 1128, 958, 941, 824, 756, 743, 691, 649, 506 cm^{-1}; ESI-TOF HRMS *m/z* 215.0818 ($[M + H]^+$, $C_{12}H_{10}N_2O_2 + H^+$ requires 215.0815).

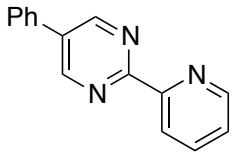
Compound **44d** (9.0 mg, 0.06 mmol) was added to a stirring solution of **3** (7.0 mg, 0.05 mmol) in DMF (0.1 mL). The reaction mixture was warmed to 100 °C, stirred for 24 h, concentrated, and then purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to provide **51** (7.5 mg, 70%) as a white solid.



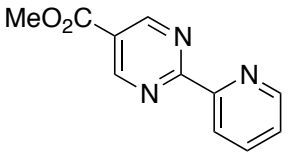
5-Bromo-2-phenylpyrimidine (52). Compound **44c** (14.6 mg, 0.12 mmol) was added to a stirring solution of **4** (17.7 mg, 0.11 mmol) in CH_3CN (0.2 mL) at –20 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 10 min. After 10 min, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) to provide **52** (10.4 mg, 40%) as a white solid: mp 83–84 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.84 (s, 2H), 8.41 (m, 2H), 7.50 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 157.8, 136.4, 131.1, 128.7, 128.2, 118.3; IR ν_{max} 2921, 1527, 1416, 1370, 1314, 1119, 1069, 1003, 922, 742, 690, 637, 470, 416 cm^{-1}; ESI-TOF HRMS *m/z* 234.9862 ($[M + H]^+$ $C_{10}H_7BrN_2 + H^+$ requires 234.9865).



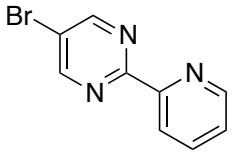
2-(Pyridin-2-yl)pyrimidine (53). Compound **44e** (91.2 mg, 0.75 mmol) was added to a stirring solution of **1** (55.5 mg, 0.69 mmol) in dioxane (0.7 mL). The reaction was stirred at room temperature for 5 min and then warmed to 60 °C for 2 h, concentrated, and purified by PTLC (SiO_2, 10% MeOH/CH_2Cl_2) to afford **53** (104.8 mg, 98%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.92 (d, J = 4.8 Hz, 2H), 8.85 (m, 1H), 8.52 (m, 1H), 7.87 (m, 1H), 7.41 (m, 1H), 7.32 (t, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 157.6, 154.5, 149.9, 136.9, 124.9, 123.4, 120.3; IR ν_{max} 1551, 1480, 758, 664, 634 cm^{-1}; ESI-TOF HRMS *m/z* 158.0713 ($[M + H]^+$, $C_9H_7N_3 + H^+$ requires 158.0713).



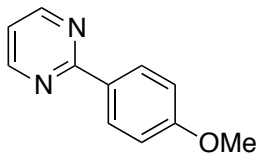
5-Phenyl-2-(pyridin-2-yl)pyrimidine (54). Compound **44e** (50.9 mg, 0.42 mmol) was added to a stirring solution of **2** (44.1 mg, 0.28 mmol) in dioxane (0.3 mL). The reaction was stirred at room temperature for 15 min, concentrated, and purified by PTLC (10% MeOH/CH_2Cl_2) to provide **54** (65.3 mg, 99%) as a white solid: mp 158–160 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.08 (d, J = 0.5 Hz, 2H), 8.83 (m, 1H), 8.52 (dd, J = 6.2, 0.8 Hz, 1H), 7.84 (m, 1H), 7.62 (m, 2H), 7.50 (m, 2H), 7.44 (m, 1H), 7.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.2, 155.4, 154.3, 150.1, 136.8, 134.1, 132.8, 129.3, 128.9, 126.8, 124.8, 123.3; IR ν_{max} 1533, 1438, 1422, 1376, 759, 719, 694, 650, 617, 524 cm $^{-1}$; ESI-TOF HRMS *m/z* 234.1026 ($[M + H]^+$, $C_{15}H_{11}N_3 + H^+$ requires 234.1026).



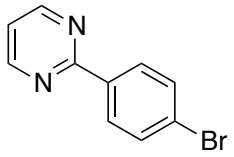
Methyl 2-(Pyridin-2-yl)pyrimidine-5-carboxylate (55). Compound **44e** (19.4 mg, 0.16 mmol) was added to a stirring solution of **3** (21.0 mg, 0.15 mmol) in dioxane (0.2 mL). The reaction mixture was stirred at room temperature for 5 min, concentrated, and purified by PTLC (EtOAc) to provide **55** (32.2 mg, 99%) as an off-white solid: mp 164 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.43 (s, 2H), 8.89 (m, 1H), 8.61 (m, 1H), 7.91 (m, 1H), 7.46 (m, 1H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 164.6, 159.3, 154.1, 150.8, 137.6, 126.1, 124.9, 123.2, 53.2; IR ν_{max} 1714, 1581, 1545, 1419, 1384, 1307, 1286, 1255, 1243, 1197, 1133, 1080, 1031, 990, 768, 646, 506 cm^{-1}; ESI-TOF HRMS *m/z* 216.0768 ($[M + H]^+$, $C_{11}H_9N_3O_2 + H^+$ requires 216.0767).



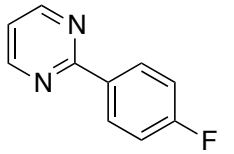
5-Bromo-2-(pyridin-2-yl)pyrimidine (56). Compound **44e** (24.2 mg, 0.2 mmol) was added to a stirring solution of **4** (29.8 mg, 0.18 mmol) in dioxane (0.2 mL). The reaction mixture was stirred at room temperature for 5 min, concentrated, and purified by PTLC (SiO_2, 90% EtOAc/hexanes) to provide **56** (43.9 mg, 99%) as a white solid: mp 124–126 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.95 (s, 2H), 8.84 (m, 1H), 8.50 (d, J = 10.0 Hz, 1H), 7.87 (m, 1H), 7.43 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.8, 158.3, 153.8, 150.3, 137.1, 125.3, 123.6, 120.0; IR ν_{max} 2921, 1528, 1408, 1365, 1121, 1096, 1008, 991, 932, 759, 689, 636, 618, 489, 424, 409 cm^{-1}; ESI-TOF HRMS *m/z* 235.9818 ($[M + H]^+$, $C_9H_6BrN_3 + H^+$ requires 235.9818).



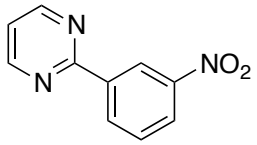
2-(4-Methoxyphenyl)pyrimidine (57). Compound **44f** (52.9 mg, 0.35 mmol) was added to a stirring solution of **1** (25.4 mg, 0.31 mmol) in CH_3CN (0.3 mL). The reaction mixture was stirred at 25 °C. Complete color change was observed 1 min after addition of **44f**. The reaction mixture was then warmed to 60 °C for 2 h, concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexane) to afford **57** (53.9 mg, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.73 (d, J = 4.5 Hz, 2H), 8.39 (d, J = 8.5 Hz, 2H), 7.08 (t, J = 5.0 Hz, 1H), 6.99 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 161.9, 157.1, 130.2, 129.7, 118.3, 113.9, 55.3; IR ν_{max} 1604, 1581, 1563, 1551, 1512, 1407, 1324, 1245, 1165, 1024, 848, 795, 641, 589 cm^{-1}; ESI-TOF HRMS *m/z* 187.0872 ($[M + H]^+$, $C_{11}H_{10}N_2O + H^+$ requires 187.0866).



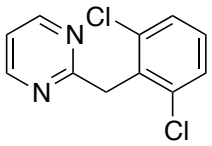
2-(4-Bromophenyl)pyrimidine (58). Compound **44g** (89.7 mg, 0.45 mmol) was added to a stirring solution of **1** (33.2 mg, 0.41 mmol) in CH_3CN (0.5 mL). The reaction mixture was stirred at 25 °C. Complete color change was observed 20 min after addition of **44g**. The reaction mixture was then warmed to 60 °C for 4 h, concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexane) to afford **58** (95.9 mg, 99%) as a white solid: mp 128–132 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77 (d, J = 4.0 Hz, 2H), 8.31 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7, 157.2, 136.4, 131.7, 129.7, 125.5, 119.2; IR ν_{max} 1563, 1550, 1406, 1171, 1064, 1006, 806, 785, 767, 707, 639, 621, 543, 440, 431 cm^{-1}; ESI-TOF HRMS *m/z* 234.9872 ($[M + H]^+$, $C_{10}H_7BrN_2 + H^+$ requires 234.9865).



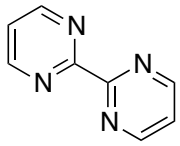
2-(4-Fluorophenyl)pyrimidine (59). Compound **44h** (30.7 mg, 0.22 mmol) was added to a stirring solution of **1** (16.4 mg, 0.20 mmol) in CH_3CN (0.3 mL). The reaction mixture was stirred at 25 °C. Complete color change was observed 5 min after addition of **44h**. The reaction mixture was then warmed to 60 °C for 2 h, concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexane) to afford **59** (34.8 mg, 99%) as a light yellow solid: mp 49–51 °C (EtOAc) (literature 54–56 °C)[S16]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (d, J = 4.8 Hz, 2H), 8.45 (m, 2H), 7.17 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 163.8, 163.4, 157.2, 133.73, 133.70, 130.3, 130.2, 118.9, 115.6, 115.4; IR ν_{max} 1601, 1552, 1510, 1412, 1213, 1154, 818, 791, 580 cm^{-1}; ESI-TOF HRMS *m/z* 175.0672 ($[M + H]^+$, $C_{10}H_7FN_2 + H^+$ requires 175.0666).



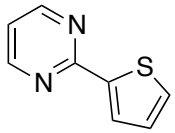
2-(3-Nitrophenyl)pyrimidine (60). Compound **44i** (66.1 mg, 0.40 mmol) was added to a stirring solution of **1** (29.5 mg, 0.36 mmol) in CH_3CN (0.4 mL). Complete color change was observed 5 min after addition of **44i**. The reaction mixture was then warmed to 60 °C for 5 h, concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexane) to afford **60** (72.9 mg, 99%) as a light yellow solid: mp 139–141 °C (EtOAc) (literature 143–144 °C)[S16]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.27 (s, 1H), 8.82 (d, J = 4.8 Hz, 2H), 8.75 (d, J = 7.6 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.25 (t, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4 157.4, 148.7, 139.3, 133.8, 129.5, 125.1, 123.2, 120.1; IR ν_{max} 1564, 1518, 1477, 1412, 1346, 1320, 1073, 797, 782, 731, 685, 672, 633, 454 cm^{-1}; ESI-TOF HRMS *m/z* 202.0611 ([M + H]$^+$, $C_{10}H_7N_3O_2$ + H^+ requires 202.0611).



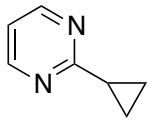
2-(2,6-Dichlorobenzyl)pyrimidine (61). Compound **44j** (70.5 mg, 0.35 mmol) was added to a stirring solution of **1** (25.6 mg, 0.32 mmol) in CH_3CN (0.6 mL). Complete color change was observed 5 min after addition of **44j**. The reaction mixture was then warmed to 60 °C for 2 h, concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexane) to afford **61** (67.7 mg, 90%) as a yellow solid: mp 88–90 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (s, 2H), 7.33 (m, 2H), 7.12 (m, 2H), 4.70 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 157.1, 136.3, 134.3, 128.4, 128.0, 118.6, 40.8; IR ν_{max} 1560, 1434, 1412, 1087, 926, 769, 629 cm^{-1}; ESI-TOF HRMS *m/z* 239.0140 ([M + H]$^+$, $C_{11}H_8Cl_2N_2$ + H^+ requires 239.0137).



2,2'-Bipyrimidine (62). Compound **44k** (32.0 mg, 0.26 mmol) was added to a stirring solution of **1** (19.3 mg, 0.24 mmol) in CH_3CN (0.3 mL). Complete color change was observed 10 min after addition of **44k**. The reaction mixture was then warmed to 60 °C for 5 h, concentrated and purified by PTLC (SiO_2, 10% MeOH/CH_2Cl_2) to afford **62** (37.4 mg, 99%) as a white solid: mp 103–105 °C (EtOAc) (literature 112–114 °C)[S18]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.93 (d, J = 4.8 Hz, 4H), 7.36 (t, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0, 157.8, 121.4; IR ν_{max} 1549, 1388, 1138, 816, 766, 636, 617, 506, 469, 423 cm^{-1}; ESI-TOF HRMS *m/z* 159.0669 ([M + H]$^+$, $C_8H_6N_4$ + H^+ requires 159.0665).



2-(Thiophen-2-yl)pyrimidine (63). Compound **44l** (61.8 mg, 0.49 mmol) was added to a stirring solution of **1** (36.1 mg, 0.45 mmol) in CH_3CN (0.5 mL). Complete color change was observed 1 min after addition of **44l**. The reaction mixture was then warmed to 60 °C for 2 h, concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexane) to afford **63** (68.5 mg, 95%) as a white solid: mp 80–82 °C (EtOAc) (literature 79–80 °C)[S19]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.67 (d, J = 4.8 Hz, 2H), 8.00 (dd, J = 2.8, 0.8 Hz, 1H), 7.47 (dd, J = 4.0, 1.2 Hz, 1H), 7.14 (m, 1H), 7.06 (t, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.5, 157.1, 143.1, 129.9, 128.9, 128.3, 118.4; IR ν_{max} 1551, 1527, 1432, 1396, 1209, 1048, 853, 809, 792, 703, 629 cm^{-1}; ESI-TOF HRMS *m/z* 163.0327 ($[M + H]^+$, $C_8H_6N_2S + H^+$ requires 163.0324).



2-Cyclopropylpyrimidine (64). Compound **44m** (20.5 mg, 0.24 mmol) was added to a stirring solution of **1** (18.0 mg, 0.22 mmol) in CH_3CN (0.3 mL). Complete color change was observed instantaneously after addition of **44m**. The reaction mixture was then warmed to 60 °C for 1 h, concentrated and purified by flash chromatography (SiO_2, 40% EtOAc/hexane) to afford **64** (25.4 mg, 95%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, J = 4.4 Hz, 2H), 7.02 (t, J = 4.8 Hz, 1H), 2.22 (m, 1H), 1.12–1.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 156.7, 117.8, 18.2, 10.8; IR ν_{max} 1559, 1440, 1371, 1230, 909, 795 cm^{-1}; ESI-TOF HRMS *m/z* 121.0763 ($[M + H]^+$, $C_7H_8N_2 + H^+$ requires 121.0760).

References

(S1) Okatani, T.; Koyama, J.; Tagahara, K. *Heterocycles* **1989**, *9*, 1809.

(S2) Neunhoeffer, H.; Clausen, M.; Vötter, H.; Ohl, H.; Krüger, C.; Angermund, K. *Liebigs Ann. Chem.* **1985**, 1732.

(S3) ^{1}H NMR was consistent with previous report: Ohsawa, A.; Kaihoh, T.; Itoh, T.; Okada, M.; Kawabata, C.; Yamaguchi, Y.; Igeta, H. *Chem. Pharm. Bull.* **1988**, *36*, 3838.

(S4) ^{1}H NMR was consistent with previous reports: (a) Itoh, T.; Nagata, K.; Kaihoh, T.; Okada, M.; Kawabata, C.; Arai, H.; Ohnishi, H.; Yamaguchi, K.; Igeta, H.; Ohsawa, A.; Iitaka, Y. *Heterocycles* **1992**, *33*, 631. (b) Mättner, M.; Neunhoeffer, H. *Synlett* **2003**, 413.

(S5) ^{1}H NMR was consistent with previous reports: Neunhoeffer, H.; Bopp, R.; Diehl, W. *Liebigs Ann. Chem.* **1993**, 367.

(S6) Hynes, J.; Doubleday, W. W.; Dyckman, A. J.; Godfrey, J. D.; Grosso, J. A.; Kiau, S.; Leftheris, K. *J. Org. Chem.* **2004**, *69*, 1368.

(S7) Verkruijsse, H.; Bos, H.; de Noten, L.; Brandsma, L. *J. Royal Netherlands Chem. Soc.* **1981**, *100*, 244.

(S8) Crossland, I.; Grevil, F. *Acta Chem. Scand.* **1981**, *35b*, 605.

(S9) Ichikawa, H.; Ohno, Y.; Usami, Y.; Arimoto, M. *Heterocycles* **2006**, *68*, 2247.

(S10) Reger, D. L.; Gardinier, J. R.; Grattan, T. C.; Smith, M. R.; Smith, M. D. *New J. Chem.* **2003**, *27*, 1670.

(S11) Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 3994.

(S12) Newkome, G. R.; Kohli, D. K.; Kawato, T. *J. Org. Chem.* **1980**, *45*, 4509.

(S13) Bordin, F.; Baccichetti, F.; Gianfranco, F. *Annali di Chimica* **1965**, *55*, 882.

(S14) Taylor, E. C. *J. Org. Chem.* **1991,** *56*, 1807.

(S15) Majumder, S. *Tetrahedron* **2010**, *66*, 3152.

(S16) Zheng, X.; Song, B.; Bin, X. *Eur. J. Org. Chem.* **2010**, *23,* 4376.

(S17) Schwan, T. J. *J. Heterocyclic Chem.* **1977**, *14*, 695.

(S18) Vlad, G.; Horvath I. T. *J. Org. Chem.* **2002,** *67*, 6550.

(S19) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358.