The Use of *N*-Protected Amino Acids in the Minisci Radical Alkylation

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Supporting Information

General

All reactions were carried out under a nitrogen atmosphere. Solvents and reagents were used as purchased without purification or drying. The starting materials are commercially available: 3-chloro-6-methylpyridazine, *N*-benzoylalanine and 2-phthalimidopropionic acid were purchased from Lancaster; 3-chloro-6-phenylpyridazine and 3-chloro-6-methoxypyridazine were purchased from Aldrich; *N*-phthaloyl-DL-valine and *N*-phthaloyl-DL-leucine were purchased from Senn Chemicals and *N*-benzoyl-β-alanine was purchased from Sigma. Ammonium persulfate was purchased from Aldrich and kept refrigerated. It has been noted that this material should be stored cold as poor yields may otherwise result.[1] Thin layer chromatography was performed on Merck KGaA silica gel $60F_{254}$ glass precoated plates (250 μm thickness) and visualized by shortwave light. Melting points were determined on a MEL-TEMPII apparatus fitted with a Fluke 50S thermocouple and are uncorrected. Infrared absorption spectra were recorded as thin films on polyethylene card using a Nicolet Magna-IR spectrometer 550 or as a solid on a Nicolet Nexus-670 FTIR operating in Attenuated Total Reflectance mode. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX400 NMR using chloroform unless stated otherwise. Mass spectrometry was performed on a Hewlett Packard Series 1100 MSD. HPLC analysis was conducted on an Agilent 1100 series instrument operating in reverse phase mode using a Zorbax RX-C8 column and MeCN/0.01%formic acid buffer elution. Elemental analyses were carried out by Qualitative Technologies Inc., Whitehouse, NJ.

All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, MS and/or combustion analysis/HRMS. The regiochemical assignment for compounds **8a**, **8b**, **9c** and **9d** was made by a combination of nOe, chemical shift and 2D NMR techniques.

Characterization data for compounds **6a-6f**, **6h, 8a, 8b, 9c, 9d, 10, 11, 14-16**.

***N*-[(3,6-dichloropyridazin-4-yl)methyl]benzamide (6a):** mp 148-149 °C; IR 3315, 1649, 1133 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.12 (bt, *J* = 5.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.81 (s, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.0 Hz, 2H), 4.51 (d, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 167.4, 156.3, 155.7, 142.7, 133.9, 132.2, 129.3, 128.9, 128.0, 40.5; MS (CI) *m/z* 284 (3%), 282 (8, M+H), 248 (24), 246 (71), 145 (35), 143 (100); Anal. Calcd for $C_{12}H_9N_3Cl_2O$: C, 51.09; H, 3.22; N, 14.89; Cl, 25.13. Found: C, 51.03; H, 3.11; N, 14.82; Cl, 25.22.

Benzyl (3,6-dichloropyridazin-4-yl)methylcarbamate (6b): oil; IR 3322, 3033, 1712, 1514, 1133 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 350 K) δ 7.72 (t, *J* = 1.0 Hz, 1H), 7.70 (bs, 1H), 7.34 (m, 5H), 5.09 (s, 2H), 4.34 (dd, *J* = 5.9, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO, 350 K) δ 156.2, 155.5, 142.6, 137.3, 129.0, 128.8, 128.3, 128.0, 66.5, 41.6; MS (CI) *m/z* 316 (2%), 313 (12), 312 (17, M+H) 223 (65), 220 (100) 188 (26), 186 (81); Anal. Calcd for $C_{13}H_{11}N_3Cl_2O_2$: C, 50.02; H, 3.55; N, 13.46; Cl, 22.72. Found: C, 50.37; H, 3.32; N, 13.31; Cl, 22.62.

***N*-[(3,6-dichloropyridazin-4-yl)methyl]-4-methylbenzenesulfonamide (6c):** mp 152-153.5 °C; IR 3352, 1404, 1367, 1315, 1159, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dm, *J* = 8.2 Hz, 2H), 7.60 (t, *J* = 1.0 Hz, 1H), (d, *J* = 8.2 Hz, 2H), 5.34 (bt, *J* = 6.7 Hz, 1H), 4.23 (dd, *J* = 6.7, 1.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 154.6, 144.8, 139.5, 136.3, 130.2, 128.6, 127.1, 43.2, 21.6; MS (CI) *m/z* 336 (3%), 334 (12), 332 (20, M+H) 178 (69), 176 (100); Anal. Calcd for $C_{12}H_{11}N_3Cl_2O_2S$: C, 43.39; H, 3.34; N, 12.65; Cl, 21.34. Found: C, 43.52; H, 2.97; N, 12.65; Cl, 21.18.

2-[(3,6-dichloropyridazin-4-yl)methyl]-1*H*-isoindole-1,3(2H)-dione (6d): mp 211-214 °C; IR 1708, 1394, 1371 1314, 1141 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.16 (d, *J* = 1.0 Hz, 1H), 7.86 (m, 4H), 4.81 (d, *J* = 1.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 168.1, 156.5, 155.2, 140.0, 135.0, 132.5, 129.4, 123.8, 38.5; MS (CI) *m/z* 312.0 (12%), 310.9 (11), 307.9 (100, M+H), 274.0 (9), 272.1 (26), 143.1 (13); Anal. Calcd for $C_{13}H_7N_3Cl_2O$: C, 50.67; H, 2.29; N, 13.64. Found: C, 50.98; H, 2.12; N, 13.29.

***tert*-Butyl (3,6-dichloropyridazin-4-yl)methylcarbamate (6e):** mp 95-97 °C; IR 3390, 1685, 1507, 1142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 5.10 (bs, 1H), 4.38 (d, *J* = 6.2 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 155.7, 155.1, 141.2, 127.9, 81.1, 41.3, 28.3; MS (CI) *m/z* 226 (12%), 223 (63), 222 (100) 188 (13), 186 (41); Anal. Calcd for $C_{10}H_{13}N_3Cl_2O$: C, 43.18; H, 4.71; N, 15.11; Cl, 25.49. Found: C, 43.32; H, 4.44; N, 15.15; Cl, 25.43.

***N*-[(3,6-dichloropyridazin-4-yl)methyl]acetamide (6f):** mp 139-140 °C; IR 3301, 1666, 1369 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.47 (bt, *J* = 5.6 Hz, 1H), 7.74 (t, *J* = 1.0 Hz, 1H), 4.27 (dd, *J* = 5.7, 1.0 Hz, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 170.7, 156.3, 155.7, 142.9, 128.9, 39.8, 22.9; MS (CI) *m/z* 222 (3%), 220 (5, M+H), 186 (11), 184 (29), 145 (36), 143 (100); Anal. Calcd for $C_7H_7N_3Cl_2O$: C, 38.21; H, 3.21; N, 19.10; Cl, 32.22. Found: C, 38.09; H, 2.95; N, 18.94; Cl, 32.31.

***N*-[(3,6-dichloropyridazin-4-yl)methyl]-*N*-methylbenzamide (6h):** mp 102-103 °C; IR 1638, 1532, 1382, 1283 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 350 K) δ 7.81 (s, 1H), 7.47 (m, 5H), 4.70 (s, 2H), 3.06 (3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 156.5, 155.6, 139.3, 134.5, 130.7, 128.8, 128.0, 127.3, 48.5, 38.8; MS (CI) *m/z* 298 (6%), 295 (6, M+H), 262 (35), 260 (100); Anal. Calcd for $C_{13}H_{11}N_3Cl_2O$: C, 52.72; H, 3.74; N, 14.19; Cl, 23.94. Found: C, 52.82; H, 3.35; N, 14.23; Cl, 24.02.

***N*-[(3-chloro-6-methylpyridazin-4-yl]methyl]benzamide (8a):** mp 93-94 °C; IR 3295, 1648, 1533, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.84 (dm, *J* = 7.1 Hz, 2H), 7.57 (tt,

J = 7.4, 1.3 Hz, 1H), 7.49 (tm, *J* = 7.4 Hz, 2H), 7.37 (s, 1H), 6.85 (brs, 1H), 4.68 (dd, *J* = 6.1, 0.7 Hz, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 160.1, 154.1, 137.4, 133.2, 132.2, 128.8, 127.8, 127.2, 40.5, 21.6; MS (CI) *m/z* 264 (5%), 262 (14, M+H), 226 (84), 123 (100); HRMS [M + H] calcd for $C_{13}H_{13}ClN_3O$, 262.0747; found, 262.0743. Anal. Calcd for $C_{13}H_{12}N_3ClO$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.60; H,4.56; N, 15.76.

***N*-[(3-chloro-6-phenylpyridazin-4-yl)methyl]benzamide (8b):** mp 190-192 °C; IR 3380, 1653, 1527, 907 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.13 (bt, *J* = 5.3 Hz, H), 8.13 (s, 1H), 8.06 (m, 2H), 7.93 (m, 2H), 7.55 (m, 4H), 7.50 (ct, *J* = 7.6 Hz, 2H), 4.62 (d, *J* = 5.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 167.3, 158.9, 155.2, 139.5, 135.3, 134.1, 132.1, 130.9, 129.7, 128.9, 127.9, 127.4, 125.6, 40.6; MS (CI) *m/z* 348 (6%), 346 (16, M+Na), 326 (23), 324 (62, M+H), 288 (94), 185 (100); Anal. Calc'd for $C_{18}H_{14}N_3ClO$: C, 66.77; H, 4.36; N, 12.98; Cl, 10.95. Found: C, 66.70; H, 4.07; N, 12.98; Cl, 11.20.

***N*-[(6-chloro-3-methoxypyridazin-4-yl)methyl]benzamide (9c):** mp 180-182 °C; IR 3269, 1638, 1531, 1356, 992 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.02 (bt, *J* = 5.6 Hz, 1H), 7.91 (dd, *J* = 7.1, 0.9 Hz, 2H), 7.56 (tt, *J* = 7.0, 1.1 Hz, 1H), 7.49 (m, 4H), 4.41 (dd, *J* = 5.6, 0.9 Hz, 2H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 167.2, 162.9, 151.0, 134.1, 133.3, 132.0, 128.8, 127.9, 127.8, 55.6, 37.5; MS (CI) *m/z* 280 (32%), 278 (100, M+H), 175 (4), 173 (10); Anal. Calcd for $C_{13}H_{12}N_3ClO_2$: C, 56.22; H, 4.36; N, 15.13; Cl, 12.77. Found: C, 56.33; H, 4.28; N, 15.08; Cl, 12.84.

***N*-[(6-chloro-3-isopropoxypyridazin-4-yl)methyl]benzamide (9d):** oil; IR 3305, 1647, 1531, 1413, 1336, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dm, *J* = 7.5 Hz, 2H), 7.55 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.47 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.30 (t, *J* = 1.1 Hz, 1H), 6.94 (brt, *J* = 6.2 Hz, 1H), 5.55 (quintet, *J* = 6.1 Hz, 1H), 4.56 (dd, *J* = 6.2, 1.1 Hz, 2H), 1.42 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 162.2, 150.8, 133.6, 132.2, 131.3, 128.8, 128.0, 127.1, 71.2, 38.2, 22.0; MS (CI) *m/z* 330 (1), 328 (4, M + Na), 308 (1), 306 (M + H), 266 (36), 264 (100); HRMS [M + H] calcd for $C_{15}H_{17}ClN_3O_2$, 306.1009; found, 306.1009.

***N*-[2-(3,6-dichloropyridazin-4-yl)ethyl]benzamide (10):** mp 147-148 °C; IR 3291, 1634, 1552, 1311, 1143 cm^{-1}; ^{1}H NMR (400 MHz, d_6-dmso) δ 8.52 (br d, *J* = 5.7 Hz, 1H), 7.94 (s, 1H), 7.70 (dt, *J* = 7.1, 1.5 Hz, 2H), 7.47 (m, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 2H), 3.59 (q, *J* = 6.3 Hz, 2H), 2.96 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 157.0, 155.9, 142.2, 133.9, 131.8, 130.8, 128.6, 127.2, 38.0, 32.7; MS (CI) *m/z* 295 (1%, M+H), 177 (69), 175 (M-$BzNH_2$), 157 (16); HRMS [M + H] calcd for $C_{13}H_{12}Cl_2N_3O$, 296.0357; found, 296.0363.

5-(3,6-dichloropyridazin-4-yl)pyrrolidin-2-one (11): mp 135-137 °C; IR 3180, 3102, 1658, 1318, 1135 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.49 (br s, 1H), 5.03 (dd, *J* = 8.7, 5.0 Hz, 1H), 2.87 (m, 1H), 2.46 (m, 2H), 1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 156.8, 154.4, 144.7, 125.9, 53.9, 29.1, 27.8; MS (CI) *m/z* 236 (7%), 234 (51), 232 (100, M+H), 196 (32), 151 (32), 148 (43); HRMS [M + H] calcd for

$C_8H_8Cl_2N_3O$, 232.0044; found, 232.0047. Anal. Calcd for $C_8H_7N_3Cl_2O$: C, 41.4; H, 3.04; N, 18.11. Found: C, 41.08; H, 2.93; N, 17.01.

2-[1-(3,6-dichloropyridazin-4-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (14): mp 135-136 °C; IR 1707, 1381, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (complex dd, *J* = 5.4, 3.2 Hz, 2H), 7.85 (s, 1H), 7.77 (complex dd, *J* = 5.4, 3.2 Hz, 2 H), 5.69 (q, *J* = 7.1 Hz, 1H), 1.87 (d, *J* = 7.1 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 156.4, 155.4, 140.7, 134.6, 131.4, 129.6, 123.8, 45.5, 16.5; MS (CI) *m/z* 343.9 (3%, M+Na), 326 (8), 323 (65), 322 (100, M+H), 288 (7), 286 (23); Anal. Calcd for $C_{14}H_9N_3Cl_2O_2$: C, 52.20; H, 2.82; N, 13.04; Cl, 22.02. Found: C, 52.28; H, 2.43; N, 12.77; Cl, 22.02.

2-[1-(3,6-dichloropyridazin-4-yl)-2-methylpropyl]-1*H*-isoindole-1,3(2*H*)-dione (15): needles, mp 176-178 °C; IR 1776, 1713, 1386, 1340, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.29 (d, *J* = 11.4 Hz, 1H), 3.04 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 156.6, 156.2, 139.4, 134.6, 131.1, 130.8, 123.7, 56.3, 28.5, 1.9, 19.4; MS (CI) *m/z* 374 (1%), 372 (2, M+Na), 354 (11), 352 (64), 350 (100, M+H), 312 (11), 310 (68), 308 (99) 187 (22), 185 (66); HRMS [M + H] calcd for $C_{16}H_{14}Cl_2N_3O_2$, 350.0463; found, 350.0456. Anal Calcd for $C_{16}H_{13}Cl_2N_3O_2$: C, 54.87; H, 3.74; N, 12.00. Found: C, 54.82; H, 3.71; N, 13.53.

2-[1-(3,6-dichloropyridazin-4-yl)-3-methylbutyl]-1*H*-isoindole-1,3(2*H*)-dione (16): A modified experimental procedure was used to prepare this compound. A vigorously stirred mixture of *N*-phthaloyl-DL-leucine (92 g, 35.2 mmol), 3,6-dichloropyridazine (2.0 g, 13.4 mmol), $AgNO_3$ (0.45 g, 2.68 mmol), sulfuric acid (0.53 g, 5.4 mmol) and water (70 mL) was heated to 85 ºC before a solution of ammonium persulfate (9.79 g, 43.0 mmol) in water (20 mL) was added over 15 min. After aging for 10 min, IPAc (100 mL) was added, the reaction cooled to 20 ºC and then NH_4OH used to give a pH of 10 in the aqueous layer. The layers were separated and the aqueous layer extracted with IPAc (50 mL). The combined organic layers were washed with 1M $KHCO_3$ (50 mL aq sol), dried ($MgSO_4$) and then filtered through a glass fiber disk before concentration under reduced pressure. Column chromatography on silica gel (CH_2Cl_2/hexane elution increasing to 100% CH_2Cl_2 elution) afforded the title compound (2.80 g, 57%) as an oil; IR 1774, 1713, 1371, 1139 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.86 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.2 Hz, 2H), 5.69 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.55 (ddd, *J* = 13.9, 10.8, 4.5 Hz, 1H), 1.81 (ddd, *J* = 13.9, 9.3, 4.8 Hz, 1H), 1.54 (m, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 156.3, 155.5, 140.9, 134.7, 131.3, 129.9, 123.8, 48.6, 39.0, 25.3, 23.1, 21.5; MS (CI) *m/z* 368 (11%, M+H), 366 (69), 364 (100), 310 (12), 308 (17), 199 (23); HRMS [M + H] calcd for $C_{17}H_{16}Cl_2N_3O_2$, 364.0620; found, 364.0623.

4-*tert*-butyl-3,6-dichloropyridazine: mp 38-40 ºC, lit. mp 39-41 ºC.[2]

[1] Samaritoni, J. G.; Babbitt, G. *J. Heterocyclic Chem.* **1991**, *28*, 583.
[2] Crossland, I. *Acta Chem. Scand.* **1968**, *22*, 2700.