Mild and Practical Method for the α -Arylation of Nitriles with Heteroaryl Halides

Artis Klapars, Jacob H. Waldman,* Kevin R. Campos, Mark S. Jensen, Mark McLaughlin, John Y. L.*

Chung, Raymond J. Cvetovich, Cheng-yi Chen

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

Supporting Information

Contents:

General Considerations	S1
6-Cyano-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid <i>tert</i> -butyl ester	S1
General Procedure for Coupling of Nitriles with Heteroaryl Halides	S2
Examples for Coupling of Nitriles with Heteroaryl Halides	S3
References	S6

General Considerations. Toluene and acetonitrile were dried using 3 Å molecular sieves. Hexamethyldisilazide bases and other reagents were purchased from Aldrich and used directly. Flash chromatography was performed with E.Merck silica gel (230-400 mesh, 60 Å).

6-Cyano-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (1). A 100 mL round bottom flask was charged with (3*S**,4*R**)-3-cyanomethyl-4-(toluene-4-sulfonyloxy)-pyrrolidine-1-

carboxylic acid *tert*-butyl ester (5.43 g, 14.3 mmol) and THF (35 mL), and cooled to -20 °C. A 1.0M solution of NaHMDS in THF (15.7 mL, 15.7 mmol) was added over 10 min while the temperature was kept between -25 °C and -20 °C. The reaction mixture was allowed to reach room temperature for 1h. The thick, brown slurry was quenched with water (140 mL; mild exotherm) and extracted with 3×200 mL dichloromethane. The light yellow organic phase was dried (Na₂SO₄); concentrated, the residue was filtered through a silica plug eluting with hexane-MTBE (1:1) and concentrated again to afford 2.87 g (96% yield) of an amber oil that slowly solidified. According to NMR spectrum, this material was >95% pure mixture of the nitrile diastereomers in ~1:1 ratio. The mixture of diastereomers could be used directly in the subsequent coupling reaction or alternatively it could be separated by flash chromatography on silica gel (hexane-ethyl acetate 2:1 to neat ethyl acetate).

The convex isomer (1*R**,5*S**,6*R**) eluted first and was further purified by crystallization from heptane. Mp 72-73 °C; IR (neat) 2240, 1698, 1415, 1388, 1172, 1117 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.78-3.60 (m, 2H), 3.38 (d, *J* = 11.6 Hz, 2H), 2.17 (m, 2H), 1.43 (s, 9H), 1.24 (t, *J* = 3.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 154.5, 119.7, 80.3, 47.2 (br), 47.0 (br), 28.3, 25.2 (br), 24.4 (br), 6.8; Anal. Calc'd for C₁₁H₁₆N₂O₂: C, 63.44; H, 7.74; N, 13.45; Found: C, 63.40; H, 7.72; N, 13.40. The relative stereochemistry of the diastereomer was confirmed by a gradient NOE experiment. Irradiation of the signal at 1.24 ppm (CH next to nitrile) produced NOE enhancement of signals at 2.17 ppm (0.2%, bridgehead CH) and 3.38 ppm (0.5%, pyrrolidine CH₂).

The concave isomer (1*R**,5*S**,6*S**) eluted second and was further purified by crystallization from heptane-ethyl acetate. Mp 103-104 °C; IR (neat) 2234, 1684, 1412, 1367, 1179, 1121 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.84 (d, *J* = 11.7 Hz, 1H), 3.76 (d, *J* = 11.7 Hz, 1H), 3.61-3.53 (m, 2H), 2.03 (m, 2H), 1.69 (t, *J* = 7.6 Hz, 1H), 1.46 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 153.7, 116.1, 80.1, 46.0, 45.7, 28.4, 22.9, 22.2, 8.2; Anal. Calc'd for C₁₁H₁₆N₂O₂: C, 63.44; H, 7.74; N, 13.45; Found: C, 63.55; H, 7.84; N, 13.37. The relative stereochemistry of the diastereomer was confirmed by a gradient NOE experiment. Irradiation of the signal at 1.69 ppm (CH next to nitrile) produced NOE enhancement of signal at 2.03 ppm (1%, bridgehead CH) and <0.1% enhancement of the pyrrolidine CH₂ signals.

General procedure for coupling of nitriles with heteroaryl halides (Table 4): An oven dried Schlenk tube with magnetic stir bar was evacuated and backfilled with nitrogen three times and charged with nitrile (1.00 mmol), aryl halide (1.00 mmol) and dry toluene. The reaction mixture was cooled to 0

°C and the hexamethyldisilazide base (1.00 mmol for tertiary nitriles and 2.00 mmol for primary and secondary nitriles) was added dropwise over 5 min. For X = F, a 0.47 M solution of KHMDS in toluene was used. For X = Cl or Br, a 1.0 M solution of NaHMDS in THF was used. Total reaction volume was 3 mL. The solution was then stirred at 0 °C for 1 hr then at rt overnight. Reaction completion was checked by TLC analysis and the reaction mixture was filtered through a syringe filter (0.45 µm) to remove particulate matter and purified by silica gel column chromatography to afford the coupled products.

(5)¹: Synthesized from cyclopropanecarbonitrile (67 mg) and 2-fluoro-5-bromopyridine (176 mg) to afford 168 mg (75%) of a white crystalline solid: mp 93.5 – 94.5 °C; IR (film) 2238.92, 1574.74, 1558.40, 1466.66, 1124.13, 1004.95, 667.76 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.50 (m, 1H), 7.81 (dd, 1H, *J* = 8.4, 2.4 Hz), 7.62 (dd, 1H, *J* = 8.4, 0.7 Hz), 1.80 (m, 2H), 1.73 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 153.5, 150.8, 139.3, 122.3, 121.7, 118.9, 20.3, 15.2; Anal. Calc'd for C₉H₇N₂Br: C, 48.46; H, 3.16; N, 12.56; Found: C, 48.19; H, 2.97; N, 12.24.

(6): Synthesized from isobutyronitrile (69 mg) and 2,5-dibromopyridine (236 mg) to afford 212 mg (94%) of colorless solid: mp = 90.0 – 91.0 °C; IR (film) 2983.73, 2239.66, 1470.81, 1365.30, 1122.78, 1007.79, 835.50 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.64 (d, 1H, *J* = 2.4 Hz), 7.85 (dd, 1H, *J* = 8.4, 2.4 Hz), 7.50 (d, 1H, *J* = 8.4 Hz), 1.72 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 158.3, 150.8, 139.8, 123.8, 121.4, 119.9, 39.2, 27.8; [MH⁺] Calc'd for C₉H₁₀N₂Br: 225.0018; Found: 225.0027.

(7): Synthesized from isobutyronitrile (69 mg) and 2-chloro-3-fluoropyridine (132 mg) to afford 142 mg (87%) of a colorless oil: IR (film) 2990.34, 2240.26, 1597.29, 1440.66, 1249.30, 1192.77, 1088.60, 807.98 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.40 (m, 1H), 7.45 (m, 1H), 7.32 (m, 1H), 1.80 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 158.9, 156.3, 146.9, 146.8, 144.7, 144.7, 125., 125.0, 124.5, 124.4, 123.1, 37.0, 36.9, 26.2, 26.2; ¹⁹F NMR (377 MHz, CDCl₃) δ -119.25; [MH⁺] Calc'd for C₉H₁₀N₂F: 165.0828; Found: 165.0830.

(8a): Synthesized from 2-cyanobutane (89 mg) and 2-fluoropyridine (98 mg) to afford 90 mg (56%) of a colorless oil: IR (film) 2974.43, 2238.77, 1588.61, 1471.67, 1432.67, 788.71, 749.28 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.59 (m, 1H), 7.70 (td, 1H, *J* = 7.9, 1.9 Hz), 7.56 (d, 1H, *J* = 8.0 Hz),

7.20 (ddd, 1H, $J = 7.4, 4.7, 0.9$ Hz), 2.12 (m, 1H), 1.95 (m, 1H), 1.70 (s, 3H), 0.91 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 158.7, 149.8, 137.1, 123.3, 122.7, 120.9, 45.4, 34.0, 26.2, 9.9; $[\text{MH}^+]$ Calc'd for $\text{C}_{10}\text{H}_{13}\text{N}_2$: 161.1079; Found: 161.1073.

(8b)²: Synthesized from 1-phenyl-1-cyanopropane (145 mg) and 2-fluoropyridine (98 mg) to afford 202 mg (91%) of a colorless oil: IR (film) 2976.34, 1586.73, 1466.51, 1431.01, 755.95, 701.12 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.63 (m, 1H), 7.66 (td, 1H, $J = 7.8, 1.6$ Hz), 7.52 (m, 3H), 7.36 (m, 1H), 7.28 (m, 1H), 7.20 (m, 1H), 2.75 (m, 1H), 2.48 (m, 1H), 1.05 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 158.4, 149.5, 139.3, 137.2, 128.9, 128.0, 126.7, 122.8, 122.4, 122.0, 55.3, 32.5, 10.2; $[\text{MH}^+]$ Calc'd for $\text{C}_{15}\text{H}_{15}\text{N}_2$: 223.1235; Found: 223.1241.

(9)³: Synthesized from either 1-cyanopropane (70 mg, 1.0 eq.) and 2-fluoropyridine (97 mg, 1.0 eq.), or 1-cyanopropane (70 mg, 1.0 eq.) and 2-chloropyridine (227 mg, 2.0 eq.) to afford 129 mg (88%) and 90 mg (61%), respectively, of a colorless oil: IR (film) 2972.52, 2242.72, 1590.70, 1472.83, 1436.19, 994.81, 751.16 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, 1H, $J = 4.7$ Hz), 7.70 (td, 1H, $J = 7.7, 1.7$ Hz), 7.40 (d, 1H, $J = 7.9$ Hz), 7.21 (ddd, 1H, $J = 7.5, 4.8, 0.8$ Hz), 3.91 (dd, 1H, $J = 8.1, 6.1$ Hz), 2.03 (m, 2H), 1.05 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 155.3, 150.0, 137.3, 123.0, 121.8, 120.1, 41.4, 27.7, 11.5; $[\text{MH}^+]$ Calc'd for $\text{C}_9\text{H}_{11}\text{N}_2$: 147.0922; found: 147.0924.

(10)³: Synthesized from 2-methyl-1-cyanopropane (83 mg, 1.0 eq.) and 2-chloropyridine (114 mg, 1.0 eq.) using either 1.0 eq. or 2.0 eq. of NaHMDS to afford 33 mg (31%) and 114 mg (71%), respectively, as a colorless oil: IR (film) 2966.45, 2241.36, 1590.79, 1471.61, 1435.80, 752.54 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.55 (dm, 1H, $J = 4.8$ Hz), 7.69 (td, 1H, $J = 7.7, 1.8$ Hz), 7.38 (m, 1H), 7.21 (ddd, 1H, $J = 7.6, 4.9, 1.0$ Hz), 3.85 (d, 1H, $J = 5.8$ Hz), 2.38 (d sept, 1H, $J = 6.0, 6.7$ Hz), 1.07 (d, 3H, $J = 6.8$ Hz), 0.97 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 154.8, 149.9, 137.1, 122.9, 122.4, 119.1, 47.4, 32.7, 21.1, 18.5; $[\text{MH}^+]$ Calc'd for $\text{C}_{10}\text{H}_{13}\text{N}_2$: 161.1079; Found: 161.1079.

(11)⁴: Synthesized from acetonitrile (41 mg) and either 2-fluoropyridine (97 mg) or 2-chloropyridine (114 mg) to afford 103 mg (87%) and 18 mg (15%), respectively, as a yellow oil: IR (film) 2250.92, 1592.89, 1475.74, 1437.20, 1411.46, 996.85, 758.47 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.55 (m, 1H), 7.70 (td, 1H, $J = 7.7, 1.9$ Hz), 7.38 (d, 1H, $J = 7.9$ Hz), 7.23 (m, 1H), 3.90 (s, 2H); ^{13}C

NMR (100 MHz, CDCl₃) δ 150.6, 150.0, 137.5, 123.1, 122.3, 117.1, 26.7; [MH⁺] Calc'd for C₇H₇N₂: 119.0609; Found: 119.0608.

(**12**)⁵: Synthesized from isobutyronitrile (69 mg) and 1-chloroisoquinoline (164 mg) to afford 196 mg (98%) as a white crystalline solid: mp 67.7 – 69.0 °C; IR (film) 3054.85, 2988.85, 2938.91, 2360.88, 2339.20, 2232.72, 1560.31, 1502.60, 1327.07, 1006.56, 828.55, 749.48 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.69 (m, 1H), 8.45 (d, 1H, *J* = 5.6 Hz), 7.84 (m, 1H), 7.68 (m, 2H), 7.58 (d, 1H, *J* = 5.6 Hz), 2.00 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 156.6, 140.9, 137.2, 130.0, 128.2, 127.5, 125.3, 125.2, 125.0, 121.6, 37.6, 28.1; Anal. Calc'd for C₁₃H₁₂N₂: C, 79.56; H, 6.16; N, 14.27; Found: C, 79.34.; H, 6.04; N, 14.13.

(**13**)⁶: Synthesized from isobutyronitrile (69 mg) and 2-chloropyrazine (115 mg) to afford 95 mg (65%) as a colorless oil: IR (film) 2240.10, 1473.07, 1403.16, 1122.10, 1016.61, 852.43 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.88 (m, 1H), 8.55 (m, 2H), 1.76 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 155.2, 144.2, 144.1, 141.8, 123.1, 37.8, 27.6; [MH⁺] Calc'd for C₈H₁₀N₃: 148.0875; Found: 148.0874.

(**15**): Synthesized from isobutyronitrile (69 mg) and 3-chloro-6-phenylpyridazine (191 mg) to afford 76 mg (52%) as a white crystalline solid: mp 117.0 – 118.0 °C; IR (film) 3055.77, 2988.37, 2237.25, 1265.85, 757.18, 701.63 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (m, 2H), 7.92 (d, 1H, *J* = 8.9 Hz), 7.83 (d, 1H, *J* = 8.9 Hz), 7.51 (m, 3H), 1.90 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.4, 158.8, 135.7, 130.6, 129.3, 127.2, 124.8, 124.7, 123.4, 38.8, 28.0; [MH⁺] Calc'd for C₁₄H₁₄N₃: 224.1190; Found: 224.1188.

(**16**)⁷: Synthesized from isobutyronitrile (69 mg) and 2-chlorobenzoxazole (154 mg) to afford 166 mg (89%) as a white crystalline solid: mp 90.0 – 91.0 °C; IR (film) 2997.65, 2239.51, 1613.95, 1569.40, 1455.45, 1284.43, 1126.83, 944.31, 752.80, 763.78 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.78 (m, 1H), 7.58 (m, 1H), 7.40 (m, 2H), 1.95 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 163.5, 151.1, 140.6, 125.9, 124.9, 120.6, 120.5, 110.9, 33.9, 26.1; [MH⁺] Calc'd for C₁₁H₁₁N₂O: 187.0869; Found: 187.0871.

(17)⁸: Synthesized from isobutyronitrile (69 mg) and 2-chlorobenzothiazole (170 mg) to afford 177 mg (88%) as a colorless crystalline solid: mp 45.0 – 47.0 °C; IR (film) 2985.77, 2360.71, 2339.69, 1507.90, 1457.18, 1438.79, 1244.45, 1043.53, 760.80, 730.15 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.1 Hz), 7.51 (td, 1H, *J* = 7.3, 1.2 Hz), 7.42 (td, 1H, *J* = 8.1, 1.2 Hz), 1.95 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 152.9, 135.1, 126.7, 125.9, 123.6, 122.3, 121.9, 38.0, 28.3; Anal. Calc'd for C₁₁H₁₀N₂S: C, 65.32; H, 4.98; N, 13.85; Found: C, 65.09; H, 4.85; N, 13.80.

References:

-
- ¹ Fukuda, Y. PCT Int. Appl. 2005005420, 2005.
 - ² Carver, D. R.; Greenwood, T. D.; Hubbard, J. S.; Komin, A. P.; Sachdeva, Y. P.; Wolfe, J. F. *J. Org. Chem.* **1983**, 48, 1180.
 - ³ Bernhart, C. A.; Condamine, C.; Demarne, H.; Roncucci, R.; Gagnol, J. P.; Gautier, P. J.; Serre, M. A. *J. Med. Chem.* **1983**, 26, 451.
 - ⁴ Skerlj, R. T.; Bogucki, D.; Bridger, G. J. *Synlett* **2000**, 10, 1488.
 - ⁵ Endo, T.; Saeki, S.; Hamana, M. *Chem. Pharm. Bull.* **1981**, 29, 3105.
 - ⁶ Akkerman, A. M.; van Leeuwen, G. C. Michels, J. F. FR Patent 1404514, 1965.
 - ⁷ Ikeguchi, M.; Ito, K. Sawaki, M.; Morishima, Y. PCT Int. Appl. 9413665, 1994.
 - ⁸ Ikeguchi, M.; Sawaki, M.; Yoshii, H.; Maeda, K.; Morishima, Y. *Nippon Noyaku Gakkaishi* **2000**, 25, 107.