Synthesis of *N*-Heteroaryl-7-Azabicyclo[2.2.1]heptane Derivatives via Palladium-Bisimidazol-2-ylidene Complex Catalyzed Amination Reactions

Jie Cheng, Mark L. Trudell*

Department of Chemistry, University of New Orleans, New Orleans, LA 70148

Email:mtrudell@uno.edu

Supporting Information

Mailing Address: Mark L. Trudell, Department of Chemistry,
University of New Orleans
New Orleans, LA 70148

Telephone: (504) 280-7337
FAX: (504)-280-6860
Email: mtrudell@uno.edu

General Information

- All heteroaryl halides (Aldrich) NaOtBu (Aldrich) and Pd2(dba)3 (Strem) were used as received. 1,4-Dioxane (Aldrich) was dried by distillation over Na/benzophenone prior to use.
- Flash chromatography was performed on silica gel 60 (230-400 mesh) (Natland International Corp.).
- ^{1}H and ^{13}C NMR spectra were recorded for the free bases on aVarian-400 MHz spectrometer at ambient temperature in $CDCl_3$ (Cambridge Isotope Laboratories Inc.)
- C,H, N analyses were determined for the corresponding oxalatesalts.
- Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected.

Aminations of heteroaryl halides with 7-azabicyclo[2.2.1]heptane hydrochloride (1). *General Procedure*. A Schlenk tube, flame-dried in vacuo, was placed under an Ar atmosphere on a vacuum line. The tube was charged with $Pd_2(dba)_3$ (18mg, 0.02mmol), DiIper salt **6** (30mg, 0.04mmol), Na^{t}OBu (270mg, 2.8mmol) and dioxane (5mL). The Schlenk tube was sealed and heated to 80°C for 0.5 h. The heteroarylhalide (1 mmol) and 7-azabicyclo[2.2.1]heptane hydrochloride (**1**) (160mg, 1.2mmol) were added and the temperature was increased to 100-110°C. After 20-40 h, the mixture was then allowed to cool to room temperature. The mixture was diluted with water then extracted with diethyl ether. The extracts were combined, washed with saturated brine solution, and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash chromatography (hexane/ethyl acetate).

7-(2-Pyridinyl)-7-azabicyclo[2.2.1]heptane (**4**): mp 112-114 °C (oxalate salt). ^{1}HNMR δ 8.15 (1H, dd, J = 6, 1.6 Hz), 7.42 (1H, tt, J = 8.8, 2 Hz), 6.66, (1H, d, J = 8.8Hz), 6.62 (1H, t, J = 6Hz); 4.44 (2H, t, J = 2.4 Hz), 1.79-1.75 (4H, m). 1.45 (4H, d, J = 6.8 Hz). ^{13}C NMR δ 159.5, 148.3, 137.4, 114.2, 110.1, 57.1(2), 29.1 (4). MS *m/z* (CI, %): 175 (100, $M+H^+$), 176 (30, $M+2H^+$), 145(10). FTIR (film) ν 3403, 1669, 1593, 779 cm^{-1}. Anal Calcd. for $C_{11}H_{14}N_2 \bullet C_2H_2O_4$: C, 59.06; H, 6.10; N, 10.60. Found: C, 59.08; H, 6.16; N, 10.45.

7-(3-Pyridinyl)-7-azabicyclo[2.2.1]heptane (**7**a): mp 108-110 °C (oxalate salt). ^{1}HNMR δ 8.20 (1H, d, J = 2.8 Hz), 7.97 (1H, dd, J = 4.8, 1.6 Hz), 7.10-7.06 (1H, m), 7.02 (1H, dd, J = 8, 4.4 Hz), 4.11 (2H, t, J = 2.4 Hz), 3.96(1H, t, J = 9.6 Hz), 3.16 (1H, t, J = 14.4 Hz), 1.73-1.70 (4H, m), 1.38 (4H, d, J = 4.4 Hz). ^{13}C NMR δ 144.2, 140.3, 138.9, 123.6, 123.1, 1, 57.8(2), 28.5 (4). CIMS *m/z* (%) 175 (100, $M+H^+$), 176(15, $M+2H^+$), 145(10), 100(13). FTIR (film) ν 3376, 1647, 1580, 808, 708, 615 cm^{-1}. Anal Calcd. for $C_{11}H_{14}N_2 \bullet C_2H_2O_4$: C, 59.06; H, 6.10; N, 10.60. Found: C, 59.31; H, 6.07; N, 10.54

7-(4-Pyridinyl)-7-azabicyclo[2.2.1]heptane (**7b**): mp 200 °C (dec, oxalate salt). ^{1}HNMR δ 8.19 (2H, d, J = 6Hz), 6.62 (2H, d, J = 6Hz), 4.19(2H, t, J = 2Hz), 1.73 (4H, dd, J = 7.2, 2 Hz), 1.43(4H, d, J=6.8Hz). ^{13}C NMR δ 153.9, 150.2(2), 110.8 (2), 57.0(2), 28.8 (4). CIMS δ *m/z* (%): 175 (100, $M+H^+$), 176(28, $M+2H^+$),145 (10). FTIR (film) ν 3399, 1642, 1583, 809 cm^{-1}. Anal Calcd. for $C_{11}H_{14}N_2 \bullet C_2H_2O_4 \bullet 0.75\ H_2O$: C, 56.21; H, 6.35; N, 10.08. Found: C, 56.32; H, 6.23; N, 9.81.

7-(2-Methoxy-5-pyridinyl)-7-azabicyclo[2.2.1]heptane (**7**c): mp 166-168 °C (oxalate salt). ^{1}HNMR δ 7.74 (1H, d, J = 3.2 Hz), 7.19 (1H, dd, J=8.8, 3.2 Hz), 6.60 (1H, d, J=9.2 Hz), 4.06 (2H, quintet, J=2.4 Hz), 1.76 (4H, m), 1.40 (4H, d, J=7.2 Hz). ^{13}C NMR δ158.2, 138.8, 134.2, 128.9, 110.8, 58.8 (2), 53.4, 28.7 (4). CIMS *m/z* (%): 205 (100), 206 (16). FTIR (film) ν 3414, 1606, 1567, 1279, 1033, 824, 672. cm^{-1}. Anal Calcd. for $C_{12}H_{16}N_2O \bullet C_2H_2O_4 \bullet H_2O$: C, 53.84; H, 5.81; N, 8.57. Found: C, 53,94; H, 5.67; N, 8.25.

7-(3-Iodo-6-pyridinyl)-7-azabicyclo[2.2.1]heptane (**7**d): mp 136-138 °C (free base). ^{1}H NMR δ 8.30 (1H, d, J=2.4 Hz), 7.64 (1H, dd, J = 8.4, 2.4 Hz), 6.51 (1H, d, J = 8.8Hz), 4.40, (2H, t, J = 2.4Hz), 1.78-1.75 (4H, m), 1.46 (4H, d, J = 7.2Hz). ^{13}C NMR δ 158.4, 154.2, 145.1, 112.4, 78.9, 57.3(2), 29.2(4). CIMS *m/z* (%) 301 (100, $M+H^+$), 175 (30). FTIR (film) ν 3744, 1648, 1566, 1461, 821 cm^{-1}. Anal Calcd. for $C_{11}H_{13}N_2I$: C, 44.02; H, 4.37; N, 9.33. Found: C, 44.33; H, 4.44; N, 9.09.

7-(3-Quinolinyl)-7-azabicyclo[2.2.1]heptane (**7**e): mp 128-130 °C (oxalate salt). ^{1}H NMR δ: 8.78 (1H, d, J = 2.8 Hz), 7.98 (1H, dd, J = 8, 0.8Hz), 7.59 (1H, dd, J=8, 2Hz), 7.45-7.37 (2H, m),

7.31 (1H, d, J = 2.8Hz), 4.27 (2H, t, J = 2Hz), 1.77 (4H, dd, J=8.4, 2Hz), 1.41 (4H, d, J = 6.8Hz). ^{13}CNMR δ 144.4, 142.7, 141.7, 129.0, 128.9, 126.7, 126.2, 125.8, 117.1, 58.1(2), 28.5(4). CIMS *m/z* (%) 225 (100, M+H$^+$), 226(25, M+2H$^+$), 195 (15). FTIR (film) ν 3390, 1596, 876, 752 cm^{-1}. Anal Calcd. for $C_{15}H_{16}N_2 \bullet C_2H_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.02; H, 5.83; N, 8.83.

7-(3-Isoquinolinyl)-7-azabicyclo[2.2.1]heptane (**7**f): mp 154-156 °C (oxalate salt). ^{1}H NMR δ 8.78 (1H, s), 8.10 (1H, dd, J = 8.4, 0.8 Hz), 8.04 (1H, s), 7.82 (1H, d, J = 7.6 Hz), 7.58 (1H, dt, J = 8, 1.2 Hz), 7.48 (1H, dt, J = 7.2, 1.2 Hz), 4.18 (2H, quintet, J = 2.4Hz), 1.91 (4H, dd, J = 8.4, 2Hz), 1.42 (4H, dd, J = 7.2, 1.2 Hz). ^{13}C NMR δ 145.7, 138.2, 130.7, 130.6, 129.2, 128.9, 127.7, 126.8, 123.4, 60.2(2), 29.0(4). CIMS *m/z* (%): 225 (100, M+H$^+$), 226(65, M+2H$^+$). FTIR (film) ν 3384, 1580, 853. cm^{-1}. Anal Calcd. for $C_{15}H_{16}N_2 \bullet C_2H_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.22; H, 5.86; N, 8.89.

7-(4-Tolyl)-7-azabicyclo[2.2.1]heptane (**7**g): mp 177-178 °C (oxalate salt). ^{1}H NMR δ 7.02 (2H, d, J = 8.4 Hz), 6.82 (2H, d, J = 8.4 Hz), 4.17 (2H, quintet, J = 2 Hz) 1.84 (4H, d, J = 8.4 Hz), 1.45 (4H, d, J = 6.8 Hz), ^{13}C NMR δ 145.8, 129.8(2), 128.4, 116.7(2), 58.3(2), 28.8 (4), 20.6. CIMS *m/z* (%) 188 (100, M+H$^+$), 189(30, M+2H$^+$), 158(15). IR (film): 3336, ν 1617, 1512, 819. cm^{-1}. Anal Calcd. for $C_{13}H_{14}N_2 \bullet 1.5C_2H_2O_4$: C, 59.62; H, 6.25; N, 4.34. Found: C, 59.31; H, 6.26; N, 4.25

7-(2-Chloro-5-pyridinyl)-7-azabicyclo[2.2.1]heptane (**8**):^{1}H NMR δ 7.99 (1H, d, J = 2.4 Hz), 7.14 (1H, s), 7.13 (1H, m), 4.16 (2H, t, J = 2.4 Hz), 1.78 (4H, m), 1.48 (4H, d, J = 6.8Hz). ^{13}C NMR δ 143.6, 141.1, 138.2, 126.7, 124.3, 58.5(2), 28.7(4). CIMS *m/z* (%) 209 (100), 211 (35), 100 (20). FTIR (film) ν 3407, 1638, 1553, 830 cm^{-1}.