Furanyl cyclic amines: a diastereoselective synthesis of 2,6-*syn*-disubstituted piperidines under thermodynamic control

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(±)-7a

N-Tosyl-*t*-butyl-carbamate (1.00 g, 3.70 mmol) and triphenylphosphine (970 mg, 3.70 mmol) were sequentially added to a stirred solution of the starting alcohol (0.5 g, 2.50 mmol) in THF (20 mL). Diisopropylazodicarboxylate (DIAD, 750 mg, 728 µL, 3.70 mmol) was added dropwise at room temperature and the mixture was stirred at this temperature for 1 hour. The solvent was removed under vacuum and the isolated material was purified by column chromatography on silica gel, eluting with a gradient from ether to 1:1 ether:ethyl acetate, affording a clear oil (883 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$):

7.78 (2 H, d, J = 8.2 Hz), 7.30 (2 H, d, J = 8.2 Hz), 4.58 (1 H, m), 3.66 (4 H, m), 3.62 (2 H, m), 3.48 (2 H, m), 2.44 (3 H, s), 2.37 (2 H, m), 2.06 (1 H, m), 1.82-1.63 (3 H, m), 1.44 (3 H, d, J = 8.2 Hz), 1.35 (9 H, s)

^{13}C NMR (100 MHz, $CDCl_3$):

171.36, 150.73, 143.86, 137.87, 129.20, 127.75, 84.06, 66.93, 66.73, 54.93, 46.06, 41.91, 34.59, 32.53, 27.95, 22.55, 21.58, 19.65

MS (TOF ES^{+}): 931 ([M_2Na^+], 100%), 909 ([M_2H^+], 18%), 477 ([MNa^+], 40%), 455 ([MH^+]), 18%), 377 ([M-Boc+Na^{+}], 45%), 355([M-Boc+H^{+}], 73%)

ACC-MASS: $C_{22}H_{34}N_2O_6S$ [MH^+] requires 455.2216. Observed: 455.2216

IR (ν, cm^{-1}): 2923, 1725, 1646, 1436, 1352, 1275, 1153, 1116, 1088, 671

(±)-8a

A solution of *n*-butyllithium (1.6 M, hexanes, 6.86 mL, 11.0 mmol) was added dropwise to a solution of furan (1.12 mL, 15.45 mmol) in THF (12 mL) at -10 °C under argon and was maintained at that temperature for 1 hour before being cooled to -78 °C. A solution of the starting amide (±)-7a (1.0 g, 2.21 mmol) in THF (2.0 mL) was added dropwise. After 1 hour the reaction mixture was transferred via cannula to a stirring flask of methanol (50 mL) at -78 °C. After stirring for 5 minutes, sodium borohydride (250 mg, 6.6 mmol) was added and the solution was allowed to warm to room temperature and stirred for 12 hours. Most of the solvent was removed under vacuum and the residue was taken up in water (50 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL) and dried over magnesium sulphate. The solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel to afford the product (±)-**8a** as a colourless oil (715 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$):

ppm 7.76 (2 H, d, *J* = 7.3 Hz), 7.33 (1 H, s) 7.27 (2 H, d, *J* = 7.3 Hz), 6.30 (1 H, m), 6.20 (1 H, m), 4.64 (1 H, dd, *J* = 10.84, 6.6 Hz), 4.53 (1 H, m), 2.41 (3 H, s), 2.18 (1 H, m), 1.99 (1 H, m), 1.86 (2 H, m), 1.70 (1 H, m), 1.30-1.26 (2 H, m), 1.41 (3 H, d, *J* = 6.8 Hz), 1.33 (9 H, s)

^{13}C NMR (100 MHz, $CDCl_3$):

156.73, 156.70, 150.70, 150.68, 143.71, 143.70, 141.71, 137.87, 137.85, 129.07, 127.70, 110.04, 110.02, 105.69, 105.68, 83.89, 83.87, 67.45, 67.41, 55.28, 55.19, 35.19, 35.15, 34.58, 34.51, 27.87, 27.86, 22.96, 22.89, 21.47, 19.70, 19.67

MS (TOF ES$^+$): 892 ([$M_2NH_4^+$], 100%), 460 ([MNa^+], 13%)

ACC-MASS: $C_{22}H_{31}NO_6SNa$ [MNa^+] requires 460.1770. Observed: 460.1787

IR (ν, cm^{-1}): 2934, 1725, 1369, 1354, 1279, 1257, 1151, 1088, 1007, 989, 728, 670

(±)-9

Potassium carbonate (242 mg, 1.75 mmol) was added to a solution of the starting boc-carbamate (±)-8a (59 mg, 0.18 mmol) in methanol (3.5 mL). The mixture was heated to 100 °C (external temperature) with stirring under argon and maintained at this temperature for 24 hours. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine and dried over magnesium sulphate. The solvent was removed under vacuum and the crude residue was purified by column chromatography on silica gel, eluting with a gradient from petrol(40-60):ether 1:1 to ether. The product was isolated as a colourless oil (35 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$):

7.74 (2 H, d, J = 8.15), 7.35 (2 H, d, J = 0.99), 7.28 (2 H, m), 6.31 (1 H, dd, J = 1.87, 2.98), 6.18 (1 H, d, J = 3.16), 4.57 (2H, m), 3.29 (1 H, m), 2.41 (3H, m), 1.70 (2 H, m), 1.45-1.20 (5 H, m), 1.01 (3H, m)

^{13}C NMR (100 MHz, $CDCl_3$):

156.60, 143.18, 141.83, 138.13, 129.59, 127.00, 110.12, 110.11, 105.76, 105.73, 67.42, 67.40, 49.77, 49.74, 36.99, 34.93, 21.63, 21.61, 21.46, 21.41, 21.36

MS (TOF ES$^+$): 677 ([M_2Na^+], 100%), 692 ([$M_2NH_4^+$], 72%), 360 ([MNa^+], 65%), 320 ([M-OH$^-$], 65%)

ACC-MASS: $C_{17}H_{23}NO_4SNa$ [MNa^+] requires 360.1246. Observed: 360.1243

IR (ν, cm^{-1}): 3272, 2928, 2598, 1427, 1318, 1155, 1092, 1009, 884, 815, 739, 707, 664

(±)-*syn*-10a

p-Toluenesulfonic acid hydrate (5.0 mg, 9 mol%) was added to a solution of the starting material (100 mg, 0.30 mmol) in deuterochloroform (50 mL) and the mixture was stirred rapidly at room temperature under an argon atmosphere. The progress of the reaction was monitored by ^{1}H NMR of small aliquots (which were subsequently returned to the pot). After 72 hours the reaction mixture was added to hexane (50 mL) and the resulting suspension was applied directly to a column packed with silica gel which had been wetted with hexane. Elution with a solvent gradient from petrol(40-60) to petrol(40-60):ether 1:1 afforded the major diastereomer as a white solid (77 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$):

7.79 (2 H, d, J = 8.23 Hz), 7.36 (1 H, m), 7.29 (2 H, d, J = 8.23), 6.32 (1 H, dd, J = 3.13, 1.83 Hz), 6.22 (1 H, d, J = 3.13 Hz), 5.32 (1 H, d, J = 6.06), 4.10 (1 H, m), 2.43 (3 H, s), 2.19 (1 H, d, J = 2.19 Hz), 1.88 (1 H, qt, J = 13.23, 3.69 Hz), 1.66-1.34 (4 H, m), 0.88 (3 H, d, J = 7.10 Hz)

^{13}C NMR (100 MHz, $CDCl_3$):

154.50, 142.79, 141.53, 138.68, 129.51, 127.07, 110.44, 106.91, 48.27, 48.09, 29.46, 26.14, 21.50, 19.02, 14.85

MS (TOF ES$^+$): 661 ([M_2Na^+], 100%), 383 (77%), 342 ([MNa^+], 13%), 320 ([MH^+], 52%)

ACC-MASS: $C_{17}H_{21}NO_3SNa$ [MNa^+] requires 342.1140. Observed: 342.1140

IR (ν, cm^{-1}): 2946, 1331, 1166, 1141, 1104, 1016, 996, 971, 914, 816, 724, 657