Simple Conversion of Aromatic Amines into Azides

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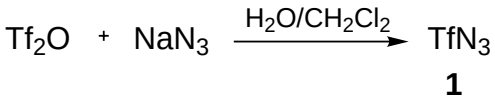
Experimental Section

General Considerations. All materials were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography was carried out on precoated silica gel plates (Kieselgel 60 F254, E. Merck & Co, Germany). Flash column chromatography was performed using silica gel (230-400 mesh) from E.M. Science. All NMR spectra were recorded on a Varian Mercury 400MHz instrument with chemical shifts reported relative to residual deuterated solvent peaks. Chemical shifts (δ) are in ppm; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet) or m (multiplet); coupling constants (*J*) are reported in hertz. IR spectra were recorded on a Nicolet MAGNA-IR 550 spectrometer with OMINIC FT-IR software installed. GC/Mass spectra were recorded on a ThermoFinnigan AS2000 c.u. Instrument.

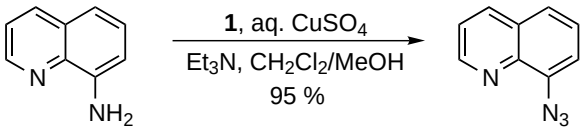
A typical procedure is described below.

Preparation of 1:



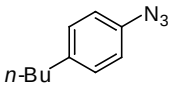
A solution of NaN_3 (3.5g, 54mmol) in water (8mL) and CH_2Cl_2 (3mL) was cooled to 0°C in an ice-water bath. To this vigorously stirred solution, Tf_2O (2.54g, 1.51mL, 9mmol) was added dropwise through a syringe. After stirred at 0°C for 2 hours, the organic phase was separated and the aqueous phase was extracted with 3mL CH_2Cl_2. The combined organics were washed with 10mL saturated aqueous $NaHCO_3$ and saved for use in the next step. (***Note****: Although we have not experienced any problem in handling this compound, precaution should be taken due to its explosive nature. See reference 7(b) in text.*)

Amine to Azide conversion:

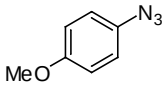


8-aminoquinoline (432.2mg, 3mmol) was dissolved in CH_2Cl_2 (2mL) in a 50mL round- bottomed flask. Et_3N (909mg, 1.25mL, 9mmol) and a solution of $CuSO_4$ (24mg, 0.15mmol $CuSO_4$ in 0.5mL H_2O) were added to the flask consecutively. Freshly prepared dichloromethane solution of TfN_3 was then added and the solution was brought to homogeneity by adding MeOH (ca. 2mL). The resulting solution was stirred at room temperature and the progress of the reaction was monitored by TLC. After the reaction was done, it was poured into saturated

aqueous $NaHCO_3$ (30mL) and extracted with CH_2Cl_2 (3x30mL). The combined organics were washed with 30mL brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (CH_2Cl_2) to obtain the pure product as dark brownish solid (485mg, 95%). R_f = 0.33 (CH_2Cl_2); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 8.87 (dd, J_1=8.0Hz, J_2=2.0Hz, 1H), 8.37 (dd, J_1=8.0Hz, J_2=2.0Hz, 1H), 7.73 (dd, J_1=8.4Hz, J_2=1.2Hz, 1H), 7.57 (dd, J_1=8.0Hz, J_2=4.0Hz, 1H), 7.49 (t, J=8.0Hz, 1H), 7.31 (dd, J_1=8.0Hz, J_2=1.2Hz, 1H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 148.9, 141.3, 136.4, 135.1, 128.7, 126.5, 124.6, 122.0, 119.0; IR (KBr pellet): 2119cm^{-1}. GCMS Calcd for $C_9H_6N_4$ 170.06, found 169.9 $[M]^+$, 142 $[M-N_2]^+$.

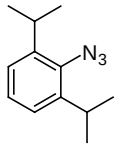


4-butyl-1-azido-benzene: clear yellow oil (481mg, 93%). R_f = 0.60 (1:9, CH_2Cl_2/hexane); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 7.19-6.96 (AB quartet, J_1=8.8Hz, J_2=2.4Hz, 4H), 2.51 (t, J=7.6Hz, 2H), 1.48 (m, 2H), 1.24 (m, 2H), 0.85 (t, J=7.2Hz, 3H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 139.1, 136.4, 129.5, 118.6, 34.2, 33.2, 21.7, 13.8; IR (KBr pellet): 2109cm^{-1}. GCMS Calcd for $C_{10}H_{13}N_3$ 175.11, found 174.9 $[M]^+$, 146.9 $[M-N_2]^+$.

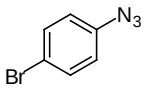


4-methoxy-1-azido-benzene: pale yellow solid (400mg, 90%). R_f = 0.31 (1:3, CH_2Cl_2/hexane); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 7.01-6.93 (AB quartet,

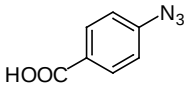
J_1=9.2Hz, J_2=2.4Hz, 4H), 3.72 (s, 3H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 156.5, 131.2, 119.9, 115.1, 55.3; IR (KBr pellet): 2105cm^{-1}. GCMS Calcd for $C_7H_7N_3O$ 149.06, found 148.9 $[M]^+$, 120.8 $[M\text{-}N_2]^+$.



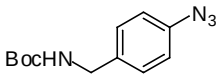
2,6-diisopropyl-1-azido-benzene: clear orange oil (550mg, 91.7%). R_f = 0.80 (1:9, CH_2Cl_2/hexane); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 7.16 (m, 3H), 3.26 (m, *J*=6.8Hz, 2H), 1.18 (d, *J*=6.8Hz, 12H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 142.1, 134.3, 126.8, 123.8, 28.4, 23.2; IR (KBr pellet): 2125cm^{-1}. GCMS Calcd for $C_{12}H_{17}N_3$ 203.14, found 202.9 $[M]^+$, 175.0 $[M\text{-}N_2]^+$.



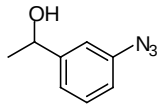
4-azido-bromobenzene: clear yellow oil (503mg, 85.1%). R_f = 0.70 (1:9, CH_2Cl_2/hexane); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 7.55-7.03 (AB quartet, J_1=8.8Hz, J_2=2.4Hz, 4H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 138.7, 132.5, 121.1, 116.9; IR (KBr pellet): 2090cm^{-1}. GCMS Calcd for $C_6H_4BrN_3$ 196.96, found 196.7, 198.7 $[M]^+$, 168.7, 170.7 $[M\text{-}N_2]^+$.



4-azido-benzoic acid: Extraction was done between 1N HCl and CH_2Cl_2, pale yellow solid (430mg, 88%). R_f = 0.50 (1:9, MeOH/CH_2Cl_2); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 12.9 (s, 1H), 7.95-7.17 (AB quartet, J_1=8.4Hz, J_2=1.6Hz, 4H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 167.1, 144.5, 131.8, 127.9, 119.8; IR (KBr pellet): 2106cm^{-1}. GCMS Calcd for $C_7H_5N_3O_2$ 163.04, found 162.9 $[M]^+$, 134.8 $[M\text{-}N_2]^+$.

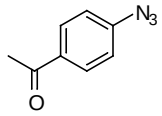


4-azido-N-Boc-benzylamine: white solid (358mg, 96.2%). R_f = 0.35 (CH_2Cl_2); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 7.41 (t, J=6.4Hz, 1H), 7.27-7.05(AB quartet, J_1=8.4Hz, J_2=2.0Hz, 4H), 4.08 (d, J=6.4Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 155.5, 137.5, 137.0, 128.4, 118.8, 77.7, 42.8, 28.3; IR (KBr pellet): 2116cm^{-1}. GCMS Calcd for $C_{12}H_{16}N_4O_2$ 248.13, found 248.0 $[M]^+$.

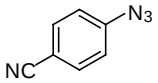


Rac-3-azido-α-methylbenzyl alcohol: clear yellow oil (470mg, 96.1%). R_f = 0.25 (CH_2Cl_2); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 7.34 (t, J=8.0Hz, 1H), 7.14 (d, J=7.6Hz, 1H), 7.08 (t, J=1.2Hz, 1H), 6.94 (ddd, J_1=7.6Hz, J_2=2.4Ha, J_3=0.8Hz, 1H), 5.27 (d, J=4.0Hz, 1H), 4.72 (m, 1H), 1.30 (d, J=6.4Hz, 3H); ^{13}C NMR

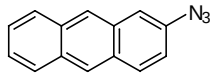
(100.6MHz, DMSO-d_6, δ, ppm): 149.6, 138.8, 129.5, 122.1, 117.0, 115.5, 67.6, 25.9; IR (KBr pellet): 2110cm^{-1}. GCMS Calcd for $C_8H_9N_3O$ 163.07, found 162.9 $[M]^+$, 134.8 $[M-N_2]^+$.



4-azido-acetophenone: off-white solid (71mg, 14.6%, recovered starting material 303mg, 74.8%). R_f = 0.60 (CH_2Cl_2); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 7.97-7.12 (AB quartet, J_1=8.4Hz, J_2=2.0Hz, 4H), 2.54 (s, 3H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 196.1, 143.9, 133.3, 130.0, 119.0; IR (KBr pellet): 2100cm^{-1}. GCMS Calcd for $C_8H_7N_3O$ 161.06, found 160.8 $[M]^+$, 132.8 $[M-N_2]^+$.



4-azido-benzonitrile: white solid (30mg, 6.95%, recovered starting material 278mg, 79%). R_f = 0.20 (1:3, CH_2Cl_2/hexane); ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 7.85-7.26 (AB quartet, J_1=8.4Hz, J_2=1.6Hz, 4H); ^{13}C NMR (100.6MHz, DMSO-d_6, δ, ppm): 144.3, 133.8, 120.0, 118.3, 107.0; IR (KBr pellet): 2110cm^{-1}. GCMS Calcd for $C_7H_4N_4$ 144.04, found 143.8 $[M]^+$, 115.8 $[M-N_2]^+$.



2-azidoanthracene: 2-aminoanthracene (76mg, 0.4mmol) was dissolved in 2ml THF, then the typical procedure was followed; yellow solid (69mg, 78%). R_f = 0.5

(1:6, CH_2Cl_2/hexane); ^1H NMR (400MHz, DMSO-d_6, δ, ppm): 8.59 (s, 1H), 8.53 (s, 1H), 8.15 (d, *J*=9.6Hz, 1H), 8.06 (m, 2H), 7.81 (d, *J*=2.4Hz, 1H), 7.51 (dd, J_1=8.8Hz, J_2=2.4Hz, 1H); ^{13}C NMR (100.6MHz, $CDCl_3$, δ, ppm): 137.0, 132.5, 131.9, 131.5, 130.6, 128.4, 128.1, 127.6, 126.7, 126.4, 126.1, 125.5, 125.2, 119.4, 115.2; IR (KBr pellet): 2118cm^{-1}. GCMS Calcd for $C_{14}H_9N_3$ 219.08, found 220.9 $[M]^+$, 192.9 $[M-N_2]^+$.