Base and solvent dependency of an oxidative retro-alkylation of secondary and tertiary benzylamines

*Antonio Feula and John S. Fossey**
School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK
j.s.fossey@bham.ac.uk

Experimental

Commercially available solvents and reagents were used without further purification. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AVIII300 NMR spectrometer and at 400 MHz on a AV400 NMR spectrometer, ^{13}C{^{1}H} NMR spectra at 100 MHz on a Bruker AVIII400 NMR spectrometer, are proton decoupled and were recorded at room temperature unless otherwise stated, data was processed with Mestrec version 5.2.5-4731 and Topspin 2.0 (Version of: Nov 9th 2006). Chemical shifts (δ) are reported in ppm relative to TMS (δ 0.00) for the ^{1}H NMR and to chloroform (δ 77.0) for the ^{13}C NMR measurements, coupling constant *J* are expressed in Hertz, the pendant technique was used for ^{13}C NMR assignment. Mass spectra were recorded with electrospray MS Waters LCT Time of Flight Mass Spectrometer and with EI (GC/MS) Waters GCT Premier Time of Flight Mass Spectrometer. Infrared Spectra were recorded on a PerkinElmer 100FT-IR spectrometer at room temperature.

General Procedures

General procedure A:

Caesium carbonate (3 equiv.) and iodine (1 equiv.) were added to amine in acetonitrile. Consumption of starting material was monitored by TLC. When the reaction was deemed completed solvent was removed *in vacuo*. To the residue thus obtained an aqueous solution of sodium thiosulfate was added, the compound was extracted with ethylacetate (x 3), washed with water, dried over magnesium sulphate and dried *in vacuo* to deliver the corresponding imine.

General procedure B:

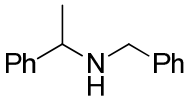
The imine was stirred at 60 ℃ in 3 M hydrochloric acid for one hour. Diethyl either was added and the aqueous layer was neutralised with 2 M NaOH and extracted with chloroform (x 3). The solvent was dried over magnesium sulphate and removed *in vacuo*, the product was obtained with no need of further purification.

General procedure C:

Caesium carbonate (3 equiv.) and iodine (1 equiv.) were added to the amine in DMSO:H_2O (5:1). Consumption of starting material was monitored by TLC. When the reaction was completed diethyl ether and a solution of sodium thiosulfate were added, the organic layer was washed with water (x 3) and the solvent was dried over magnesium sulfate and removed *in vacuo*, to deliver the corresponding amine.

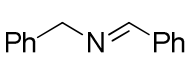
Synthesis

Synthesis of *N*-benzyl-1-phenylethanamine (1b)



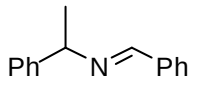
General procedure **C** was used: *N*-Benzyl-*N*-ethyl-1-phenylethanamine (0.21 mmol, 50 mg), caesium carbonate (0.63 mmol, 205 mg), iodine (0.63 mmol, 159 mg), 5:1 DMSO:water (12 mL), yield = 44 mg, >99%. IR 3062, 3026, 2974, 1493, 1451, 1372, 1302, 1238; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.47 (3H, *d*, *J* = 6.6, Me), 1.73 (1H, *br*, NH), 3.69 (1H, *d*, *J* = 13.2, NHC*H*HPh), 3.77 (1H, *d*, *J* = 13.2, NHCH*H*Ph), 3.91 (1H, *q*, *J* = 6.6, PhC*H*NH), 7.30-7.48 (10H, *m*, ArH); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), 24.65 (CH_3), 51.79 (CH_2), 57.63 (CH), 126.83 (CH), 126.96 (CH), 127.06 (CH), 128.26 (CH), 128.48 (CH), 128.60 (CH), 140.79 (C), 145.72 (C). High-resolution MS calcd for $C_{15}H_{17}N$: 211.1361; found: 211.1360.

Synthesis of (*E*)-*N*-benzylidene-1-phenylmethanamine (3a)



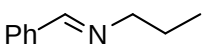
General procedure **A** was used: Dibenzylamine (0.25 mmol, 50 mg), caesium carbonate (0.76 mmol, 248 mg), iodine (0.25 mmol, 63 mg) and acetonitrile (10 mL), yield = 49 mg, >99 %. IR 3062, 3027, 2871, 2839, 1642, 1580, 1495, 1451, 1378, 1292; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.67 (2H, *s*, PhCH_2), 7.13-7.31 (8H, *m,* PhH), 7.68-7.74 (2H, *m,* PhH), 8.18 (1H , *s*, C*H*=N); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), 65.23 (CH_2), 127.25 (CH), 128.26 (CH), 128.59 (CH), 128.78 (CH), 128.86 (CH), 131.0 (CH), 136.53 (C), 139.75 (C), 162.04 (CH). M/z: (ES^+) 196.1 $[M + H]^+$.

Synthesis of (*E*)-*N*-benzylidene-1-phenylethanamine (3b**)**



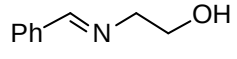
General procedure **A** was used: *N*-Benzyl-1-phenylethanamine (0.24 mmol, 50 mg), caesium carbonate (0.71 mmol, 237 mg), iodine (0.24 mmol, 61 mg), acetontrile (10 mL), yield = 49 mg, >99%. IR 3061, 3026, 2971, 2926, 2866, 1645, 1492, 1450, 1380, 1292; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.51 (3H, *d*, *J* = 6.6, Me), 4.45 (1H, *q*, *J* = 6.6, PhC*H*CH_3), 7.11-7.36 (8H, *m*, PhH), 7.68-7.71 (2H, *m*, PhH), 8.27 (1H, s, C*H*=N); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), 24.93 (CH_3), 69.78 (CH), 126.69 (CH), 126.87 (CH), 128.31 (CH), 128.47 (CH), 128.57 (CH), 130.61 (CH), 136.48 (C), 145.26 (C), 159.48 (CH). High-resolution MS calcd for $C_{15}H_{15}N$: 209.1204; found: 209.1199.

Synthesis of (*E*)-*N*-benzylidenepropan-1-amine (3e**)**



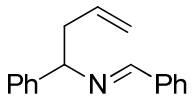
General procedure **A** was used: *N*-Benzylpropan-1-amine (0.67 mmol, 100 mg), caesium carbonate (2.01 mmol, 656 mg), iodine (0.67 mmol, 170 mg), magnesium sulphate (3.35 mmol, 400 mg), acetontrile (15 mL), yield = 98 mg, >99 %. IR 2962, 2931, 2874, 1645, 1580, 1451, 1379, 1338; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.85 (3H, *t*, *J*= 7.4, C*H*$_3$), 1.56-1.68 (2H, *m*, C*H*$_2$CH$_3$), 3.46 (2H, *td*, *J*= 6.9 & 1.1, NC*H*$_2$), 7.27-7.29 (3H, *m,* PhH), 7.60-7.63 (2H , *m,* PhH), 8.14 (1H, *s*, C*H*=N); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), 11.88 (CH_3), 24.10 (CH_2), 65.33 (CH_2), 128.03 (CH), 128.55 (CH), 130.43 (CH), 136.40 (C), 160.74 (CH). m/z: (EI$^+$) 146.1 [M + H]$^+$.

Synthesis of (*E*)-2-(benzylideneamino)ethanol (3f**)**



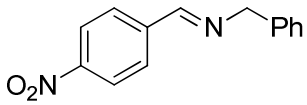
General procedure **A** was used: 2-(Benzylamino)ethanol (0.44 mmol, 67 mg), caesium carbonate (1.33 mmol, 434 mg), iodine (0.44 mmol, 112 mg), acetonitrile (10 mL), yield= 65 mg >99%. IR 3345, 3062, 3029, 2878, 1645, 1450, 1382, 1294; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 3.75-3.78 (2H, *m*, C*H*$_2$OH), 3.91-3.94 (2H, *m*, NC*H*$_2$CH$_2$), 4.53 (1H, *br*, OH), 7.40-7.45 (3H, *m*, PhH), 7.72-7.74 (2H, *m*, PhH), 8.33 (1H, s, C*H*=N); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), 62.33 (CH_2), 63.32 (CH_2), 128.21 (CH_2), 128.64 (CH), 130.90 (CH), 135.81 (C), 163.27 (CH). M/z: (ES$^+$) 149.1 [M + H]$^+$.

Synthesis of (*E*)-*N*-benzylidene-1-phenylbut-3-en-1-amine (4a**)**



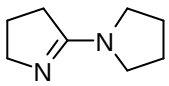
General procedure **A** was used: *N*-Benzyl-1-phenylbut-3-en-1-amine (0.42 mmol, 100 mg), caesium carbonate (1.26 mmol, 410 mg), iodine (0.42 mmol, 106 mg), magnesium sulphate (2.10 mmol, 253 mg), CH_3CN (10 mL), yield = 78 mg, 79%. IR 3062, 3027, 2977, 2903, 2847, 1642, 1493, 1452, 1414, 1380, 1310, 1292; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.60-2.65 (2H, *m*, PhCHC*H*$_2$), 4.27 (1H, $_{apt}$*t*, $_{obs}$*J* = 7.5, PhC*H*CH$_2$), 4.91-5.01 (2H, *m*, CH=C*H*$_2$), 5.58-5.72 (1H, *m*, C*H*=CH$_2$), 7.17-7.39 (8H, *m*, ArH), 7.69-7.72 (2H, *m*, PhH), 8.23 (1H, s, C*H*=N); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) 43.15 (CH_2), 75.32 (CH), 117.15 (CH_2), 126.98 (CH), 127.07 (CH), 128.31 (CH), 128.39 (CH), 128.49 (CH), 130.56 (CH), 135.47 (CH), 136.33 (C), 143.85 (C), 160.01 (CH). High-resolution MS calcd for $C_{17}H_{17}N$: 235.1361; found: 235.1355.

Synthesis of (*E*)-*N*-(4-nitrobenzylidene)-1-phenylmethanamine (4d**)**



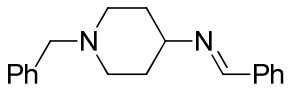
General procedure **A** was used: *N*-Benzyl-1-(4-nitrophenyl)methanamine (0.16 mmol, 40 mg), caesium carbonate (0.49 mmol, 160 mg,), iodine (0.16 mmol, 41 mg,), acetonitrile (10 mL), yield = 38 mg, >99%. IR 3000, 2934, 2904, 2835, 1636 1509, 1372, 1342, 1243; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.75 (2H, *s*, PhC*H*$_2$), 7.13-7.28 (5H, *m*, PhH), 7.80 (2H, *d*, *J* = 8.9, ArH), 8.11 (2H, *d*, *J* = 8.9, ArH), 8.32 (1H, *s*, C*H*=N); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), 65.19 (CH_2), 123.85 (CH), 127.32 (CH), 128.10 (CH),128.67 (CH), 128.95 (CH), 138.57 (C), 141.67 (C), 149.08 (CH), 159.49 (CH). m/z: (ES$^+$) 241.1 [M + H]$^+$.

Synthesis of 5-(pyrrolidin-1-yl)-3,4-dihydro-2H-pyrrole (6**)**



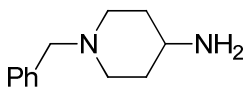
General procedure **A** was used: Pyrrolidine (1.41 mmol, 100 mg), caesium carbonate (4.22 mmol, 1.38 g), iodine (358 mg, 1.41 mmol), acetonitrile (15 mL), yield = 97 mg, >99%. IR 3392, 2973, 2920, 1677, 1503, 1454, 1421, 1343, 1300, 1259; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.01-2.08 (4H, *m,* N=CNCH$_2$C*H*$_2$), 2.25 (2H, *quin*, *J* = 7.6, N=CCH$_2$C*H*$_2$), 2.94 (2H, *t*, *J* = 7.6, N=CC*H*$_2$), 3.62 (2H, *t*, *J* = 6.4, N=CNC*H*$_2$), 3.74-3.79 (4H, *m*, C=NC*H*$_2$ & N=CNC*H*$_2$); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), 20.68 (CH_2), 25.24 (CH_2), 25.30 (CH_2), 31.95 (CH_2), 47.44 (CH_2), 51.13 (CH_2), 51.86 (CH_2), 165.51 (C). M/z: (ES$^+$) 139.1 [M + H]$^+$.

Synthesis of (*E*)-1-benzyl-*N*-benzylidenepiperidin-4-amine



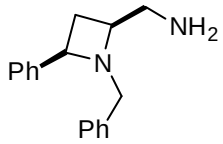
General procedure **A** was used: *N*,1-Dibenzylpiperidin-4-amine (100 mg, 0.36 mmol), caesium carbonate (348 mg, 1.07 mmol), iodine (91 mg, 0.36 mmol), acetonitrile (15 mL), yield = 98 mg, 99%. IR 3060, 3026, 2937, 2804, 2760, 1639, 1450, 1389, 1293; ^{1}H NMR (δ; 400 MHz, $CDCl_3$); 1.67-1.70 (2H, *m*, CH=NCHC*H*$_2$), 1.79-1.88 (2H, *m,* CH=NCHC*H*$_2$), 2.12 (2H, *t*, *J* = 10.8, NC*H*$_2$CH$_2$), 2.87-2.91 (2H, *m*, NC*H*$_2$CH$_2$), 3.18 (1H, *m*, CH=NC*H*), 3.50 (2H, *s*, NC*H*$_2$Ph), 7.17-7.34 (8H, *m*, PhH), 7.64-7.66 (2H, *m*, PhH), 8.25 (1H, *s*, C*H*=N); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) 33.49 (CH_2), 52.08 (CH_2), 63.16 (CH_2), 67.54 (CH), 126.99 (CH), 128.12 (CH), 128.22 (CH), 128.56 (CH), 129.15 (CH), 130.48 (CH), 136.51 (C), 138.56 (C), 159.11 (CH). High-resolution MS calcd for $C_{19}H_{23}N_2$: 279.1861; found: 279.1869.

Synthesis of 1-benzylpiperidin-4-amine (11**)**



General procedure **B** was used: (*E*)-1-Benzyl-*N*-benzylidenepiperidin-4-amine (0.090 mmol, 25 mg), yield = 17 mg, >99%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.33-1.45 (2H, *m*, NH$_2$CHC*H*$_2$), 1.59 (2H, *br*, N*H*$_2$) 1.76-1.81 (2H, *m,* NH$_2$CHC*H*$_2$), 2.02 (2H, *td*, *J* = 11.7 & 2.4, NC*H*$_2$CH$_2$NH$_2$), 2.60-2.70 (1H, *m*, C*H*NH$_2$), 2.80- 2.86 (2H, *m*, NC*H*$_2$CH$_2$NH$_2$), 3.49 (2H, *s*, NC*H*$_2$Ph), 7.21-7.35 (5H, *m*, PhH); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) 35.94 (CH_2), 48.77 (CH), 52.43 (CH_2), 63.08 (CH_2), 126.91 (CH), 128.14 (CH), 129.10 (CH), 138.56 (C). m/z: (EI$^+$) 190.1 [M + H]$^+$.

Synthesis of ((*cis*)-1-benzyl-4-phenylazetidin-2-yl)methanamine (13**)**



Procedure: Caesium carbonate (0.82 mmol, 268 mg) and iodine (0.27 mmol, 70 mg), were added to *N*-benzyl-1-((*cis*)-1-benzyl-4-phenylazetidin-2-yl)methanamine (0.27 mmol, 89 mg), in acetonitrile (15 mL). Consumption of starting material was monitored by TLC. When the reaction was deemed completed solvent was removed *in vacuo*. To the residue thus obtained a solution of $Na_2S_5O_3$ was added, the compound was extracted with EtOAc, washed with water, dried over magnesium sulfate and dried *in vacuo* to deliver the corresponding imine. The imine was stirred in a suspension of silica in ethyl acetate for 1 h and the hydrolysed product purified by flash chromatography. Yield= 61 mg, 89%. IR 3393, 2924, 1603, 1493, 1453, 1356, 1215, 1157; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.15 (1H, $_{apt}q$, $_{obs}J$= 11.1, PhCHCH*H*), 2.40-2.52 (2H, *m*, PhCHC*H*H and NCHCH*H*NH_2), 2.90 (1H, *dd*, *J* = 13.2 & 1.8, NCHC*H*HNH_2), 3.53 (1H, *d*, *J* = 12.3, NC*H*HPh), 3.60-3.61 (1H, *m*, C*H*CH_2NH), 3.90 (1H, *d*, *J* = 12.3, NCH*H*Ph), 4.19 (1H, $_{apt}t$, $_{obs}J$ = 8.2, PhC*H*CH_2), 6.15 (2H, *br*, NH_2), 7.17-7.35 (10H, *m*, PhH); ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), 29.80 (CH_2), 40.99 (CH_2), 57.74 (CH), 59.91 (CH_2), 65.40 (CH), 127.02 (CH), 127.99 (CH), 128.54 (CH), 128.63 (CH), 129.27 (CH), 129.51 (CH), 135.73 (C), 140.13 (C). High-resolution MS calcd for formula $C_{17}H_{21}N_2$: 253.1705; found: 253.1696.