Exploring a benzyloxyaniline linker utilising ceric ammonium nitrate (CAN) as a cleavage reagent: Solid Phase synthesis of *N*-unsubstituted β-lactams and secondary amides

Kirsteen H. Gordon and Shankar Balasubramanian*

University Chemical Laboratory, University of Cambridge, Cambridge, CB2 1EW, UK

Supplementary Information

Resin bound N-Boc aniline **2**. To a suspension of NaH (340 mg, 8.4 mmol) in DMF (20 ml) at 0 ^{o}C was added **1** (1.760 g, 8.4 mmol) in DMF (10 ml). The mixture was warmed to rt and stirred for 1 h, then cannulated into TentaGel bromomethyl resin (10 g, 2.8 mmol) pre-swollen in DMF (20 ml). The resin was stirred for 12 h then was filtered and washed (DMF, THF:1M HCl, THF:H_2O, THF, DCM) then dried to afford **2**: ^{1}H NMR (400 MHz, MAS) δ 1.50 (s, $(CH_3)_3$), 3.82 (s, CH_2), 6.82-6.84 (d, *p*-ArH), 7.30 (d, *p*-ArH); ^{13}C gel phase NMR (100 MHz) δ 28.7, 67.8, 79.6, 114.9, 120.3, 134.7, 153.3, 154.6; FTIR (CH_2Cl_2) υ cm^{-1} 1718

Resin bound aniline **3**. Resin **2** was stirred with 20 % TFA in DCM for 12 h then was filtered and washed with DCM. The resin was neutralised with portions of DCM:Et_3N and was washed again with DCM and dried to afford **3**: ^{1}H NMR (400 MHz, MAS) δ 3.80 (s, CH_2), 6.61-6.64 (d, *p*-ArH), 6.71-6.74 (d, *p*-ArH); ^{13}C gel phase NMR (100 MHz) δ 68.1, 115.2, 115.8, 140.6, 151.5; FTIR (CH_2Cl_2) υ cm^{-1} 3448, 3373

General procedure for synthesis of β-lactams 6a-f.

To resin **3** (200 mg, 0.068 mmol) in DCM (2 ml) with 4Å molecular sieves at rt was added aldehyde (0.68 mmol, 10 eq). The mixture was stirred for 0.5 h then was filtered and washed with anhydrous DCM (2 x 2 ml). The resin was re-suspended in DCM (2 ml) and a second

portion of aldehyde (0.68 mmol, 10 eq) was added. After 0.5 h, the resin was filtered and washed as previously, then suspended in DCM (2 ml) and cooled to 0 ^{o}C. Et_3N (93 µl, 0.68 mmol, 10 eq) was added, followed by the drop-wise addition of phenoxyacetyl chloride (47 µl, 0.34 mmol, 5 eq). The mixture was allowed to warm to rt and was stirred for 18 h. The resin was filtered, washed (DCM, THF:sat. $NaHCO_3$, THF:H_2O, THF, DCM) and dried.

Resin bound β-lactam **6a**: As described in the general procedure using *trans*-hexenal: ^{13}C NMR (100 MHz) 60.9, 67.7, 81.4, 115.3, 116.2, 118.6, 122.4, 123.7, 127.5, 128.8, 129.3, 130.3, 132.7, 133.1; FTIR (CH_2Cl_2) υ cm^{-1} 1759

Resin bound β-lactam **6b**. As described in the general procedure using *p*-nitrobenzaldehyde: ^{13}C NMR (100 MHz) δ 61.0, 67.7, 81.2, 155.2, 155.4, 118.6, 122.6, 123.5, 123.9, 129.1, 129.4; FTIR (CH_2Cl_2) υ cm^{-1} 1761, 1493, 1348

Resin bound β-lactam **6c**. As described in the general procedure using *m*-chlorobenzaldehyde: ^{13}C NMR (100 MHz) δ 61.23, 67.7, 81.1, 115.2, 115.6, 118.7, 121.8, 122.3, 126.3, 128.1, 128.9, 129.3, 129.6, 131.0; FTIR (CH_2Cl_2) υ cm^{-1} 1759

Resin bound β-lactam **6d**: As described in the general procedure using *o*-bromobenzaldehyde: ^{13}C NMR (100 MHz) 60.9, 67.7, 81.4, 115.3, 116.2, 118.6, 122.4, 123.7, 127.5, 128.8, 129.3, 130.3, 132.7, 133.1; FTIR (CH_2Cl_2) υ cm^{-1} 1759

Resin bound β-lactam **6e**. As described in the general procedure using trimethylacetaldehyde: ^{13}C NMR (100 MHz) δ 27.2, 64.2, 67.7, 80.6, 114.5, 114.9, 116.0, 122.2, 129.6; FTIR (CH_2Cl_2) υ cm^{-1} 1751

Resin bound β-lactam **6f**. As described in the general procedure using *p*-anisaldehyde: ^{13}C NMR (100 MHz) δ 53.7, 61.7, 67.7, 81.2, 113.8, 115.1, 115.6, 118.8, 122.1, 125.6, 129.4; FTIR (CH_2Cl_2) υ cm^{-1} 1754

General procedure for cleavage of solid phase β-lactams 7a-7f.

To resin bound β-lactams **6** (200 mg, 0.068 mmol) in MeCN (2 ml) at rt was added CAN (186 mg, 0.34 mmol, 5 eq) in H_2O (0.5 ml). The resin was stirred for 0.5 h then was washed with portions of DCM and H_2O. The organic layer was removed from the combined filtrates and the aqueous layer was re-extracted with two further portions of DCM. The combined organics were washed with 10 % Na_2SO_3 (until the aqueous phase remained clear), sat. $NaHCO_3$ and brine, then dried ($MgSO_4$). Concentration yielded pale orange solids which were eluted (EtOAc/hexane) through a silica plug.

cis-4-(1-pentenyl)-3-phenoxy-azetidin-2-one **7a**. As described in the general procedure using resin **6a**: ^{1}H NMR (400 MHz) δ 0.79 (t, 3H, CH_3, *J* = 7.4), 1.26-1.33 (m, 2H, CH_2), 1.95-2.02 (m, 2H, CH_2), 4.44 (dd, 1H, H-4, *J* = 8.0, 4.6), 5.31 (dd, 1H, H-3, *J* = 4.6, 2.3), 5.55 (dd, 1H, CH=, *J* = 15.4, 8.1), 5.77 (dt, 1H, CH=, *J* = 15.4, 6.8), 6.05 (br s, 1H, NH), 6.94-7.00 (m, 2H, Ph), 7.24-7.28 (m, 3H, Ph); IR (CH_2Cl_2) υ cm^{-1} 3407, 1778; HRMS (EI): [M^+] calculated for $C_{14}H_{17}NO_2$: 231.1259, found 231.1254 HPLC purity (UV 220 nm) 98 %

cis-4-(4-nitrophenyl)-3-phenoxy-azetidin-2-one **7b**. As described in the general procedure using resin **6b**: ^{1}H NMR (400 MHz) δ 5.17 (d, 1H, H-4, *J* = 4.7), 5.58 (dd, 1H, H-3, *J* = 4.7, 2.2), 6.36 (br s, 1H, NH), 6.76 (d, 2H, OPh, *J* = 8.0), 6.96 (t, 1H, OPh, *J* = 7.5), 7.15-7.19 (m, 2H, OPh), 7.55 (d, 2H, *p*-NO_2 ArH, *J* = 8.6), 8.18 (d, 2H, *p*-NO_2 ArH, *J* = 8.6); IR (CH_2Cl_2) υ cm^{-1} 3408, 1787; HRMS (EI): [M^+] calculated for $C_{15}H_{12}N_2O_4$: 284.0797, found 284.0792; HPLC purity (UV 220 nm) 93 %;

cis-4-(3-chlorophenyl)-3-phenoxy-azetidin-2-one **7c**. As described in the general procedure using resin **6c**: ^{1}H NMR (400 MHz) δ 5.02 (d, 1H, H-4, *J* = 4.7), 5.52 (dd, 1H, H-3, *J* = 4.7, 2.6), 6.25 (br s, 1H NH), 6.79 (d, 2H, OPh, *J* = 8.4), 6.93 (t, 1H, OPh, *J* = 7.4), 7.16-7.20 (m, 2H, OPh), 7.24-7.29 (m, 3H, *m*-Cl ArH), 7.38 (s, 1H, *m*-Cl ArH); IR (CH_2Cl_2) υ cm^{-1} 3404,

1785; HRMS (EI): [M^+] calculated for $C_{15}H_{12}NO_2Cl$: 273.0557, found 273.0542 ; HRMS (EI M^+) calculated ; HPLC purity (UV 220 nm) 98 %

cis-4-(2-bromophenyl)-3-phenoxy-azetidin-2-one **7d**. As described in the general procedure using resin **6d**: ^{1}H NMR (400 MHz) δ 5.44 (d, 1H, H-4, *J* = 4.9), 5.56 (dd, 1H, H-3, *J* = 4.8, 3.3), 6.29 (br s, 1H, NH), 6.89 (2H, d, OPh, *J* = 7.8), 6.95 (1H, t, *o*-Br ArH, *J* = 7.4), 7.17-7.19 (m, 3H, OPh), 7.38 (t, 1H, *o*-Br ArH, *J* = 7.3), 7.51-7.54 (m, 2H, *o*-Br ArH); IR (CH_2Cl_2) υ cm^{-1} 3404, 1782; HRMS (ES): [MH^+] calculated for $C_{15}H_{12}NO_2Br$: 318.0117, found 318.0124; HPLC purity (UV 220 nm) 99 %;

cis-3-phenoxy-4-isobutyl-azetidin-2-one **7e**. As described in the general procedure using resin **6e**: ^{1}H NMR (400 MHz) δ 1.07 (s, 9H, $(CH_3)_3$), 3.66 (d, 1H, H-4, *J* = 5.2), 5.29 (dd, 1H, H-3, *J* = 5.2, 2.0), 6.03 (s, 1H, NH), 7.00-7.02 (m, 1H, OPh), 7.04-7.11 (m, 2H, OPh), 7.28-7.32 (m, 2H, OPh); IR (CH_2Cl_2) υ cm^{-1} 3411, 1766; HRMS (EI): [MH^+] calculated for $C_{13}H_{17}NO_2$: 219.1259, found 219.1249; HPLC purity (UV 220 nm) 96 %

cis-4-(4-methoxyphenyl)-3-phenoxy-azetidin-2-one **7f**. As described in the general procedure using resin **6f**: ^{1}H NMR (400 MHz) δ 3.78 (s, 3H, OCH_3), 5.00 (d, 2H, H-4, *J* = 4.6), 5.46 (dd, H-3, *J* = 4.6, 2.5), 6.21 (br s, 1H, NH), 6.77-6.79 (m, 2H, *p*-OCH_3 ArH), 6.82-6.85 (m, 2H, *p*-OCH_3 ArH), 6.89-6.92 (m, 1H, OPh), 7.13-7.18 (m, 2H, OPh), 7.28-7.31 (m, 2H, OPh); IR (CH_2Cl_2) υ cm^{-1} 3406, 1782; HRMS (EI): [MH^+] calculated for $C_{16}H_{15}NO_3$; 269.1052, found 269.1042; HPLC purity (UV 220 nm) 97 %

General procedure for synthesis of secondary amines 8a-e.

To resin **3** (500 mg, 0.15 mmol) in DCM (6 ml) with 4Å molecular sieves at rt was added aldehyde, R^1CHO (1.5 mmol, 10 eq). The mixture was stirred for 0.5 h then was filtered and washed with anhydrous DCM (2 x 5 ml). The resin was re-suspended in DCM (6 ml) and a second portion of aldehyde, R^1CHO (1.5 mmol, 10 eq) was added and stirred for another 0.5 h.

The resin was filtered and washed with anhydrous DCM (2 x 5 ml) then was suspended in THF (3 ml). $NaBH_4$ (29 mg, 0.75 mmol, 5 eq) in MeOH (3 ml) was added by cannulation. Bubbling was observed and the reaction was stirred for 10 h before addition of 1 M HCl. The resin was filtered, washed (H_2O:THF, THF, DCM) then dried.

General procedure for synthesis of secondary amides 9a-e.

To resin **8** (400 mg, 0.12 mmol) and DMAP (cat.) in DCM at rt was added Et_3N (164 µl, 1.2 mmol, 10 eq) then acid chloride, R^2COCl (0.6 mmol, 5 eq). The mixture was stirred for 10 h then was filtered, washed (THF:H_2O, THF:1M HCl, THF, DCM) and dried.

General procedure for cleavage of secondary amides 10a-e.

To resin **9** (200 mg, 0.05 mmol) in MeCN (2 ml) at rt was added CAN (160 mg, 5 eq) in H_2O (1 ml). The mixture was stirred for 1 h then was filtered and washed with portions of H_2O and DCM. The organic layer was separated and the aqueous phase was extracted with two portions of DCM. The combined organics were washed with 10 % Na_2SO_3 (until the aqueous phase remained clear), sat. $NaHCO_3$ and brine, then were dried and concentrated to yield crude product which was filtered through a plug of silica.

N-(4-nitrobenzyl)isobutyramide **10a**. As described in the general procedure using resin **9a** afforded **10a**: ^{1}H NMR (400 MHz) δ 0.97 (d, 6H, 2 x CH_3, *J* = 6.4), 2.11-2.20 (m, 3H, CH_2N and CH), 4.55 (d, 2H, CH_2CO, *J* = 6.2), 5.86 (br s, 1H, NH), 7.44 (d, 2H, *p*-NO_2 ArH, *J* = 8.8), 8.19 (d, 2H, *p*-NO_2 ArH, *J* = 8.8); ^{13}C NMR (100 MHz) δ 22.5, 26.2, 42.8, 46.0, 123.9, 128.3, 146.1, 172.6; IR (CH_2Cl_2) υ cm^{-1} 3446, 1674, 1522, 1348; HRMS (EI): [M^+] calculated for $C_{12}H_{16}N_2O_3$: 236.1161, found 236.1164; HPLC purity (UV 220 nm) 96 %

N-(4-methylbenzyl)isobutyramide **10b**. As described in the general procedure using resin **9b** afforded **10b**: ^{1}H NMR (400 MHz) δ 0.96 (d, 6H, CH_3 x 2, *J* =6.5), 2.06 (d, 2H, CH_2CO, *J* =

6.9), 2.10-2.19 (m, 1H, CH), 2.33 (s, 3H, CH_3), 4.40 (d, 2H, CH_2NHCO, *J* = 5.6), 5.88 (br s, 1H NH), 7.09-7.18 (m, 4H, Ar); ^{13}C NMR (100 MHz) δ 21.1, 22.5, 26.2, 43.4, 46.2, 127.9, 129.4, 135.4, 137.2, 172.2; IR (CH_2Cl_2) υ cm^{-1} 3442, 1668; HRMS (ES): [MNa^+] calculated for $C_{13}H_{19}NO$: 228.1361, found 228.1364; HPLC purity (UV 220 nm) 93 %

N-(2-bromobenzyl)isobutyramide **10c**. As described in the general procedure using resin **9c** afforded **10c**: ^1H NMR (400 MHz) δ 0.94 (d, 6H, CH_3 x 2, *J* = 6.5), 2.06 (d, 2H, CH_2O, *J* = 6.2), 2.09-2.15 (m, 1H, CH), 4.51 (d, 2H, CH_2NHCO, *J* = 6.0), 5.87 (br s, 1H, NH), 7.14-7.16 (m, 1H, Ar), 7.26-7.30 (m, 1H, Ar), 7.39-7.41 (dd, 1H, Ar, *J* = 7.6, 1.7), 7.53-7.56 (dd, 1H, Ar, *J* = 8.0, 1.2); ^{13}C NMR (100 MHz) δ 22.5, 26.2, 43.8, 46.0, 123.8, 127.7, 129.2, 130.6, 132.8, 137.5, 172.3; IR (CH_2Cl_2) υ cm^{-1} 3452, 1671; HRMS (ES): [MNa^+] calculated for $C_{12}H_{16}NOBr$: 292.0296, found 292.0313; HPLC purity (UV 220 nm) 94 %

N-neopentylbenzamide **10d**. As described in the general procedure using resin **9d** afforded **10d**: ^1H NMR (400 MHz) δ 0.98 (s, 9H, $(CH_3)_3$), 3.27 (d, 2H, CH_2N, *J* = 6.4), 6.21 (br s, 1H, NH), 7.40-7.49 (m, 3H, Ph), 7.75-7.77 (m, 2H, Ph); ^{13}C NMR (100 MHz) δ 27.3, 32.2, 51.0, 126.8, 128.6, 131.3, 135.1, 167.7; IR (CH_2Cl_2) υ cm^{-1} 3454, 1662; HRMS (ES): [MNa^+] calculated for $C_{12}H_{17}NO$: 214.1200 observed 214.1208; HPLC purity (UV 220 nm) 95 %