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Expedient synthesis of substituted (S)-N-(α-methylbenzyl)aziridines

Sean P. Bew,* David L. Hughes, Vladimir Savic, Katy M. Soapi and Martin A. Wilson

School of Chemical Sciences & Pharmacy, University of East Anglia, Norwich, NR4 7TJ, UK

s.bew@uea.ac.uk

General

All reactions described as being carried out under nitrogen / argon were performed using flame-dried apparatus which were allowed to cool under an inert atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl under nitrogen. HMDS and triethylamine were dried by distillation from calcium hydride under nitrogen. All other reagents were used as supplied unless otherwise specified. Organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent removed on a rotary evaporator *in vacuo*. Column chromatography refers to flash column chromatography and was carried out on silica gel (Fluka Silica Gel 60 70-230 Mesh, Cat N^o 60741). TLC was carried out using Merck plates (aluminium coated with 0.2 mm silica gel 60 F_{254}). Plates were visualised either by UV light (254 nm) and / or iodine absorbed on silica gel.

Characterisation

^{1}H-NMR spectra were recorded on either an Oxford Gemini 300 (300 MHz) or 400 (400 MHz) spectrometers. Chemical shifts (δ_H) are reported in parts per million (p.p.m.) and are referenced to the residual solvent peak. *J* values are given in Hertz. ^{13}C-NMR spectra were recorded at 75.45 MHz on the Oxford Gemini 300 MHz spectrometer or at 100.55 MHz on the Oxford Gemini 400 MHz spectrometer. Chemical shifts (δ_C) are quoted in p.p.m. and referenced using residual solvent signals. Low resolution (*m/z*) and high resolution mass spectra were obtained by the EPSRC National Mass Spectrometry Service at the University of Wales, Swansea. Major peaks are listed with intensities quoted as percentages of the base peak. Optical rotation values were measured on a Perkin-Elmer 241-polarimeter using the sodium D line and solvent indicated.

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General procedure for conjugate addition of (*S*)-*N*-(α-methylbenzyl)hydroxylamine to activated carbon-carbon double bonds.

To a stirred suspension of (*S*)-*N*-(α-methylbenzyl)hydroxylamine oxalate **5** in dry THF (1g / 25 mL) under an atmosphere of argon at room temperature was added 1.0 eq^{n} of triethylamine. The mixture was stirred for 5 min, and then 1.0 eq^{n} of the appropriate Michael acceptor was added in one portion. Stirring was continued until all the starting hydroxylamine had been consumed. (determined by TLC using 1:1 hexane : EtOAc). The solvent was removed *in vacuo* and the residue dissolved / suspended in diethyl ether allowing it to be filtered through a plug of silica using diethyl ether as the eluent. The resulting filtrate was concentrated to dryness *in vacuo* affording the desired product.

(*S*)-3-[Hydroxy-(1-phenyl-ethyl)-amino]-propionic acid *tert*-butyl ester (Entry 1, Table 1): $[\alpha]_D^{22}$ -16.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s), 1.37 (3H, d, *J* = 6.6 Hz), 2.44 (2H, t, *J* = 6.8 Hz), 2.75 (2H, br), 3.66 (1H, q, *J* = 6.6 Hz), 6.08 (1H, brs), 7.14 – 7.26 (5H, m); δ_C (75 MHz, $CDCl_3$) 19.6, 27.9, 34.2, 52.7, 67.5, 80.2, 127.3, 127.9, 128.3, 142.5, 172.5; *m/z* (CI/NH_3) 266.2 ($[M+H]^+$, 34%), 250.3 (100); HRMS: found (ES^+) $[M+H]^+$, 266.1748. $C_{15}H_{23}NO_3$ requires $[M+H]^+$, 266.1751.

(*S*)-*N*-(2-Benzenesulfonyl-ethyl)-*N*-(1-phenyl-ethyl)-hydroxylamine (Entry 5, Table 1): $[\alpha]_D^{22}$ -20.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* = 6.6 Hz), 2.76 – 2.92 (2H, m), 3.29 – 3.40 (2H, m), 3.56 (1H, q, *J* = 6.6 Hz), 5.40 (1H, brs), 7.09 – 7.20 (5H, m), 7.38 – 7.54 (3H, m), 7.75 (2H, d, *J* = 7.1 Hz); δ_C (75 MHz, $CDCl_3$) 19.4, 50.2, 53.7, 67.5, 127.5, 127.6, 127.8, 128.4, 129.1, 133.6, 139.3, 141.8; *m/z* (CI/NH_3) 306.2 ($[M+H]^+$, 12%), 290.2 (100), 291.2 (22), 288.2 (20), 186.1 (11), 174.1 (10), 148.1 (34), 134.1 (13), 122.1 (13); HRMS: found (ES^+) $[M+H]^+$, 306.1158. $C_{16}H_{19}NO_3S$ requires $[M+H]^+$, 306.1158.

General procedure for acylation of Michael addition products.

To a stirred solution of the appropriate *N*-substituted free OH hydroxylamine in dry THF (0.2 M) at 0 °C under a nitrogen atmosphere was added 1.0 eq^{n} of triethylamine. After 10 min, 1.0 eq^{n} of trimethylacetyl cyanide was added and the reaction mixture allowed to warm to ambient temperature, the reaction being monitored by TLC analysis (4 : 1 hexane : EtOAc). When TLC analysis indicated that all the starting

material had been consumned the solvents were removed *in vacuo* and the residue redissolved in diethyl ether. The diethyl ether solution was subsequently filtered through a silica plug and the silica eluted with further aliquots of diethyl ether. The diethyl ether filtrates were concentrated to dryness *in vacuo* and the crude product was purified via column chromatography on silica gel (gradient from 9 : 1 to 4 : 1 hexane : EtOAc).

General procedure for the one-pot synthesis of *O*-pivaloyl hydroxylamines.

To a stirred suspension of (*S*)-*N*-(α-methylbenzyl)hydroxylamine oxalate **5** in dry THF (1g /25 mL) under an atmosphere of argon at room temperature was added 2.5 eq^n of triethylamine. The mixture was stirred for 5 minutes at ambient temperature and then 1.0 eq^n of the Michael acceptor was added in one portion. Stirring was continued until all the starting material (*S*)-*N*-(α-methylbenzyl)hydroxylamine had been consumed (determined using TLC analysis 1 : 1 hexane : EtOAc). The reaction mixture was cooled to 0 °C and 1.0 eq^n of trimethylacetyl cyanide was added. After stirring for 1 hour at 0°C the solvent was removed *in vacuo* and the residue redissolved in diethyl ether. The diethyl ether solution was filtered through a silica plug eluting with more diethyl ether. The resulting filtrates were concentrated to dryness *in vacuo* and the reaction product purified via column chromatography using silica gel (gradient from 9 : 1 to 4 : 1 hexane : EtOAc).

(*S*)-3-[*N*-(*O*-trimethylacetyl)-*N*-(1-phenyl-ethyl)-amino]-propionic acid *tert*-butyl ester 8: $[\alpha]_D^{22}$ -7.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.00 (9H, s), 1.35 (12H, m), 2.27 – 2.44 (2H, m), 2.91 – 2.99 (1H, m), 3.07 (1H, br), 3.93 (1H, q, *J* = 6.6 Hz), 7.14 – 7.29 (5H, m); δ_C (100 MHz, $CDCl_3$) 20.0, 27.4, 28.3, 33.2, 38.8, 51.8, 67.2, 80.8, 127.7, 128.0, 128.5, 141.8, 171.4, 176.7; *m/z* (CI/NH_3) 350.3 ($[M+H]^+$, 23%), 250.2 (100); HRMS: found (ES^+) $[M+H]^+$, 350.2322. $C_{20}H_{31}NO_4$ requires $[M+H]^+$, 350.2326.

(*S*)-*N*-(2-Benzenesulfonyl-ethyl)-*N*-(1-phenyl-ethyl)-*O*-trimethylacetylhydroxyl amine 10: $[\alpha]_D^{22}$ -5.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s), 1.28 (3H, m), 3.05 – 3.33 (4H, m), 3.89 (1H, q, *J* = 6.4 Hz), 7.13 – 7.20 (5H, m), 7.45 (2H, t, *J* = 7.6 Hz), 7.56 (1H, t, *J* = 7.6 Hz), 7.76 (2H, d, *J* = 8.0 Hz); δ_C (75 MHz, $CDCl_3$) 19.6, 26.9, 38.4, 49.2, 53.3, 66.8, 127.6, 127.9, 127.9, 128.5, 129.4, 134.0, 138.9, 140.8, 176.6; *m/z* (CI/NH_3) 390.2 ($[M+H]^+$, 4%), 290.1 (100); HRMS: found (ES^+) $[M+H]^+$, 390.1736. $C_{21}H_{27}NO_4S$ requires $[M+H]^+$, 390.1734.

General procedure for cyclisation of *O*-pivaloyl hydroxylamines.

To a stirred solution of dry HMDS in dry THF (1.3 M) at 0 °C under a nitrogen atmosphere was added 1.0 eq^n of n-BuLi (1.6 M in hexanes). After 30 minutes, this solution was transferred *via* cannular into a THF solution of 1.0 eq^n of the appropriate *O*-pivaloyl hydroxylamine (0.1 M) at -40 °C under a nitrogen atmosphere. The reaction was stirred at -40 °C until it was judged to be complete (normally 2 to 3 hours) as determined by TLC analysis (4 : 1 hexane : EtOAc). The reaction was quenched at -40°C with saturated aqueous ammonium chloride and the reaction products extracted with diethyl ether. The extracts were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified *via* column chromatography on silica gel (using either 9 : 1 or 4 : 1 hexane : EtOAc).

***tert*-Butyl (2*S*, 1'*S*)-1-(1'-phenyl-ethyl)-aziridine-2-carboxylate 3:** $[\alpha]_D^{22}$ -78.5 (*c* 0.8, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 1.43 – 1.51 (13H, m), 2.05 – 2.10 (2H, m), 2.50 (1H, q, *J* = 6.4 Hz), 7.22 – 7.41 (5H, m); δ_C (75 MHz, $CDCl_3$) 23.2, 28.0, 33.6, 38.9, 69.8, 81.2, 127.0, 127.2, 128.4, 143.9, 170.2; *m/z* (CI/NH_3) 248.2 ($[M+H]^+$, 100%), 122.1 (23); HRMS: found (ES^+) $[M+H]^+$, 248.1644. $C_{15}H_{21}NO_2$ requires $[M+H]^+$, 248.1645.

2-Benzenesulfonyl-(2*R*, 1'*S*)-1-(1'-phenyl-ethyl)-aziridine 14: $[\alpha]_D^{22}$ +32.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, d, *J* = 6.4 Hz), 1.74 (1H, d, *J* = 5.9 Hz), 2.46 (1H, q, *J* = 6.4 Hz), 2.49 (1H, d, *J* = 2.6 Hz), 2.94 (1H, dd, *J* = 2.6, 5.9 Hz), 7.18 – 7.25 (5H, m), 7.51 – 7.55 (2H, m), 7.59 – 7.62 (1H, m), 7.94 – 7.97 (2H, m); δ_C (75 MHz, $CDCl_3$) 22.5, 32.8, 55.2, 68.6, 126.7, 127.6, 128.6, 129.0, 129.1, 134.0, 138.0, 142.7; *m/z* (CI/NH_3) 288.1 ($[M+H]^+$, 100%), 148.1 (61), 52.2 (92), 44.2 (29); HRMS: found (ES^+) $[M+H]^+$, 288.1051. $C_{16}H_{17}NO_2S$ requires $[M+H]^+$, 288.1053.

2-Benzenesulfonyl-(2*S*, 1'*S*)-1-(1'-phenyl-ethyl)-aziridine 14: $[\alpha]_D^{22}$ -40.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.8 Hz), 1.86 (1H, d, *J* = 6.0 Hz), 2.45 (1H, q, *J* = 6.8 Hz), 2.70 (1H, d, *J* = 2.8 Hz), 2.95 (1H, dd, *J* = 2.8, 6.0 Hz), 6.83 – 7.02 (5H, m), 7.15 – 7.23 (2H, m), 7.34 – 7.42 (1H, m), 7.49 – 7.55 (2H, m); δ_C (75 MHz, $CDCl_3$) 22.0, 32.4, 54.0, 69.4, 126.9, 127.5, 128.2, 128.4, 128.9, 133.5, 137.9, 141.5; *m/z* (CI/NH_3) 288.2 ($[M+H]^+$, 100%), 148.1 (18); HRMS: found (ES^+) $[M+H]^+$, 288.1056. $C_{16}H_{17}NO_2S$ requires $[M+H]^+$, 288.1053.

Methyl (2*S*, 1'*S*)-1-(1'-phenyl-ethyl)-aziridine-2-carboxylate 16: $[\alpha]_D^{22}$ -100.1 (*c* 1.18, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.50 (3H, d, *J* = 6.6 Hz), 1.63 (1H, d, *J* = 6.5 Hz), 2.16 (1H, d, *J* = 3.1 Hz), 2.24 (1H, dd, *J* = 3.1, 6.5 Hz), 2.57 (1H, q, *J* = 6.6 Hz), 3.78 (3H, s), 7.25 – 7.43 (5H, m); δ_C (75 MHz, $CDCl_3$) 22.9, 33.8, 37.9, 52.1, 69.8, 126.9, 127.3, 128.3, 143.3, 171.4.

Table 2

Entry	Temperature	3 : 12	Yield of 3 & 12
1	-100°C	77 : 13	100%
2	-78°C	75 : 25	66%
3	-60°C	87 : 13	45%
4	-40°C	91 : 9	52%
5	-20°C	90 : 10	93%
6	0°C	83 : 17	100%

Table 3

Entry	Base	3 : 12	Yield of 3 & 12
1	NaH	no rxt of **8**	0%
2	Bemp	no rxt of **8**	0%
3	n-BuLi	83 : 17	60%
4	*t*-BuOK	72 : 28	42%
5	LDA	45 : 55	100%
6	LHMDS	93 : 7	100%
7	NaHMDS	74 : 26	79%
8	KHMDS	66 : 34	100%
9	Li diphenylamide	56 : 44	100%

Table 4

Entry	Solvent	3 : 12	Yield of 3 & 12	μ
1	THF	93 : 7	100%	5.8
2	Ether	85 : 15	67%	3.8
3	Toluene	86 : 14	59%	1.0
4	TBDME	89 : 11	60%	4.1
5	DMF	-	Messy rxt	10.8
6	DCM	-	Messy rxt	5.2
7	MeCN	-	Messy rxt	11.8
8	Pyridine	-	Messy rxt	7.9
9	Anisole	-	Messy rxt	4.2
10	DME	-	Messy rxt	6.1