3-Hydroxypyrrolidines from epoxysulfonamides and dimethylsulfoxonium methylide†

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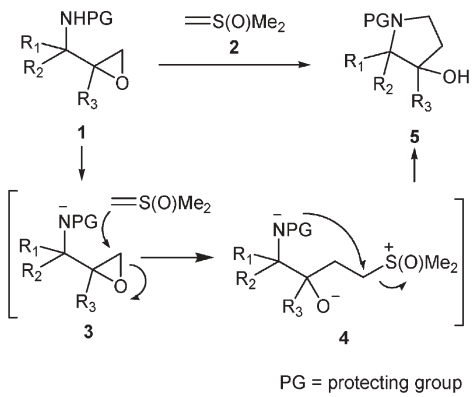
***N*-Tosyl-protected 3-hydroxypyrrolidines are prepared by reaction of dimethylsulfoxonium methylide with readily available epoxysulfonamides.**

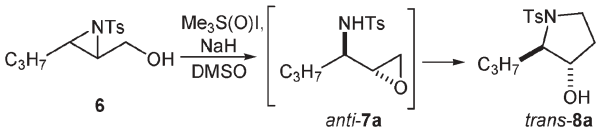
The 3-hydroxypyrrolidine motif **5** is found in a range of naturally occurring bioactive alkaloids,[1] pharmaceuticals[2] and drug intermediates,[3] and a number of synthetic approaches to 3-hydroxypyrrolidines have been developed.[3,4] In connection with our interest in the reactions of sulfur ylides with three-membered heterocycles,[5] and stimulated by a report in 2004 by Borhan and co-workers concerning the synthesis of 3-hydroxytetrahydrofurans from epoxy alcohols using dimethylsulfoxonium methylide **2**,[6] we considered whether 3-hydroxypyrrolidines **5** could be obtained from aminoepoxides **1** using ylide **2**[7] (Scheme 1).



Scheme 1 3-Hydroxypyrrolidines **5** from aminoepoxides **1**.

For the chemistry shown in Scheme 1 to succeed, regioselective ring-opening of the epoxide by the ylide **2** should be followed by 5-*exo*-*tet* cyclisation in preference to oxetane[8] formation. It was anticipated that a suitably acidifying *N*-protecting group (*e.g.* PG = RSO_2) would assist pyrrolidine formation, because the amino functionality would then likely be deprotonated under the reaction conditions[9] (as shown in intermediates **3** and **4**). Potential complications[10] due to aziridine formation from intermediate **3** by aza-Payne rearrangement should be avoided by using epoxysulfonamides **1** (PG = RSO_2), since the latter are commonly accessed by base-induced aza-Payne rearrangement of *N*-tosyl 2-aziridinemethanols;[11] another synthetically useful route to epoxysulfonamides **1** (PG = RSO_2) proceeds by epoxidation of allylic sulfonamides.[12]

Direct application of Borhan's conditions [$Me_3S(O)I$ (10 equiv.), NaH (10 equiv.), DMSO, 85 °C, 24 h][6] to 2-aziridinemethanol **6**[13] gave the desired 3-hydroxypyrrolidine **8a** (44%), likely by way of (deprotonated) epoxysulfonamide **7a** from *in situ* aza-Payne rearrangement (Scheme 2). However, the potential restriction to using 2-aziridinemethanols as starting materials, together with the requirement for a large excess of the ylide **2**[14] and prolonged reaction time, led us to focus on optimising conditions for 3-hydroxypyrrolidine synthesis from epoxysulfonamides.[15,16]



Scheme 2 3-Hydroxypyrrolidine **8a** from aziridinemethanol **6**.

Epoxysulfonamide **7a**† (0.1 M in DMSO) was completely consumed within 70 min following reaction with ylide **2** [3 equiv., generated from $Me_3S(O)I$ and NaH] at 80 °C, however 3-hydroxypyrrolidine **8a** was obtained in only 30% yield, with no other products being isolated. Generating ylide **2** from $Me_3S(O)I$ (3 equiv.) and *n*-BuLi (3 equiv.) in THF proved more encouraging, giving 3-hydroxypyrrolidine **7a** in 60% yield after 16 h at rt (Table 1, entry 1); reduced reaction times at rt gave lower yields of **8a**, with starting epoxide **7a** being recovered. Lowering the concentration of epoxide **7a** to 0.02 M slightly reduced the efficiency of the reaction (entry 2). A modest improvement in the yield of **7a** to 65% was obtained by refluxing the reaction mixture for 70 min (entry 3).[17] The yield of **8a** fell when lowering the amount of ylide **2** (to 2 equiv.) either directly (51%, entry 4), or by deprotonating epoxide **7a** with NaH (1 equiv.) first (52%). Using NaHMDS as the base also had a detrimental effect on the yield of **8a**. However, switching solvent to DMPU gave a significant increase in yield of **8a** (87%, entry 5) and, more usefully, this improvement was also observed when using DMPU as an additive (up to 20 equiv.) in THF (entries 6–9). Under the latter conditions, 2 h at reflux was optimal (70 min or 3 h gave slightly reduced yields of **8a**).

A series of epoxysulfonamides **7**, prepared in two steps from the corresponding allylic alcohols by Sharpless aziridination[13] followed by aza-Payne rearrangement[11] [KH (4 equiv.), THF, −78 °C to 0 °C, 2 h],† were then subjected to the optimised conditions

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† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for all new epoxysulfonamides and 3-hydroxypyrrolidines, and ^1H and ^{13}C NMR spectra for 3-hydroxypyrrolidines. See DOI: 10.1039/b606583j

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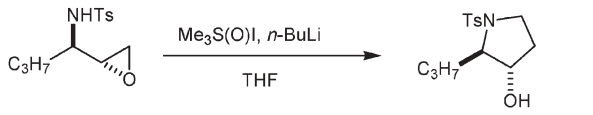
Table 1 Optimisation of 3-hydroxypyrrolidine **8a** synthesis from epoxysulfonamide **7a**



anti-**7a** *trans*-**8a**

Entry[a]	DMPU (equiv.)	Temperature/°C	Time/h	Yield (%)
1	—	rt	16	60
2[b]	—	rt	16	50
3	—	Reflux	1.2	65
4[c]	—	Reflux	1.2	51
5	Neat	80 °C	2	87
6	5	Reflux	2	69
7	10	Reflux	2	75
8	15	Reflux	2	83
9	20	Reflux	2	86

[a] 0.1 M in epoxide **7a** with *n*-BuLi (3.3 equiv.) and $Me_3S(O)I$ (3 equiv.) used unless indicated otherwise. [b] 0.02 M in epoxide **7a**. [c] *n*-BuLi (2.3 equiv.) and $Me_3S(O)I$ (2 equiv.) used.

developed above (Table 1, entry 9) to give the corresponding 3-hydroxypyrrolidines **8** in 72–88% yield (Table 2).§

Either *trans*- or *cis*-2-substituted-3-hydroxypyrrolidines **8** could be prepared in good yield, starting from the corresponding *anti*- or *syn*-epoxysulfonamides **7** (entries 1–4). The simple 3-hydroxypyrrolidine **8c** (entry 5), 2-aryl-3-hydroxypyrrolidines **8d** and **8e** (entries 6 and 7), tertiary alcohol-containing pyrrolidine **8f** (entry 8) and 2,2-disubstituted-3-hydroxypyrrolidine **8g** (entry 9) were all accessible using this methodology. The relative stereochemistries of 3-hydroxypyrrolidines **8** were generally determined by NOE experiments. In the case of 2-aryl-3-hydroxypyrrolidine **8e**, the structure was supported by X-ray crystallographic analysis (Fig. 1).[18]

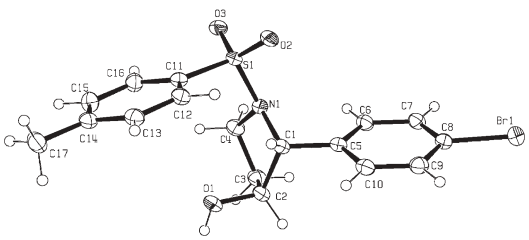
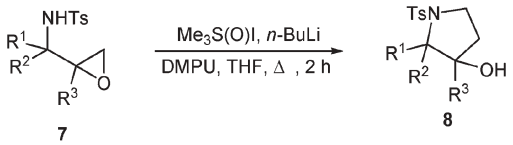


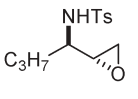
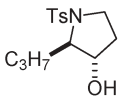
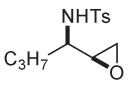
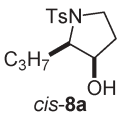
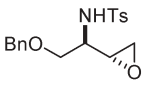
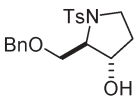
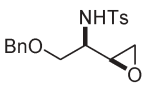
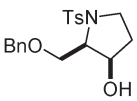
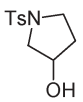
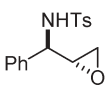
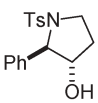
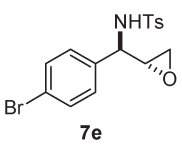
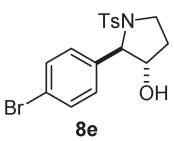
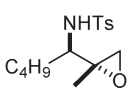
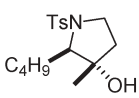
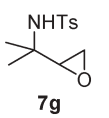
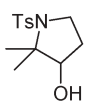
Fig. 1 X-Ray structure of 3-hydroxypyrrolidine **8e** with thermal ellipsoids at the 40% probability level.

Both spiro- and *cis*-fused hydroxypyrrolidines **10a** and *cis*-**10b** could be made using this chemistry (Table 3, entries 1 and 2). Interestingly, the more strained *trans*-fused [4.3.0] system *trans*-**10b** was also successfully generated (entry 3). Epoxysulfonamides **9a** and *syn*-**9b** were prepared by epoxidation (the latter in a highly diastereoselective manner)[12] of the corresponding allylic sulfonamides.†

It has also been found possible to extend the methodology to a 2,3-disubstituted epoxide, when one of the substituents supports the ring-opening process. Thus, 2,3,4-trisubstituted pyrrolidine **12** was formed in 77% yield from epoxysulfonamide **11**† (Scheme 3). The relative stereochemistry was assigned from NOE experiments.

Table 2 3-Hydroxypyrrolidines **8** from epoxysulfonamides **7**

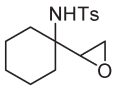
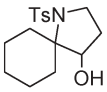
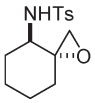
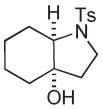
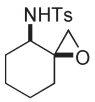
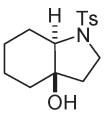


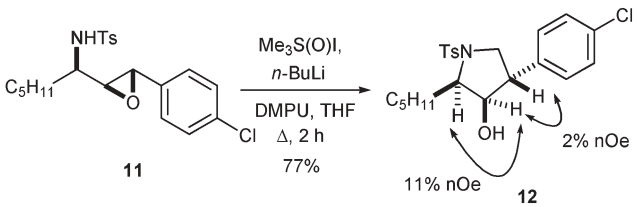
Entry	Epoxide **7**	Pyrrolidine **8**	Yield (%)
1	 *anti*-**7a**	 *trans*-**8a**	86
2	 *syn*-**7a**	 *cis*-**8a**	83
3	 *anti*-**7b**	 *trans*-**8b**	74
4	 *syn*-**7b**	 *cis*-**8b**	76
5	 **7c**	 **8c**	72
6	 **7d**	 **8d**	88
7	 **7e**	 **8e**	82
8	 **7f**	 **8f**	80
9	 **7g**	 **8g**	72

In summary, we have established a process of useful generality for the conversion of epoxysulfonamides to stereodefined 3-hydroxypyrrolidines. The method uses readily available reagents and occurs under experimentally straightforward conditions. Additional studies in the area of epoxysulfonamides and sulfonium ylides are currently underway.

We thank the EPSRC and GlaxoSmithKline for an Industrial CASE award (M. J. F.). We also thank the Royal Society for an International Incoming Fellowship (Z. X.) and a Sino-British Fellowship Trust award (C. L.) and the EPSRC National Mass Spectrometry Service Centre for mass spectra.

Table 3 Spiro- and fused-hydroxypyrrolidines **10** from epoxysulfonamides **9**

Entry	Epoxide **9**	Pyrrolidine **10**	Yield (%)
1	 **9a**	 **10a**	81
2	 *anti*-**9b**	 *cis*-**10b**	69
3	 *syn*-**9b**	 *trans*-**10b**	66



Scheme 3 Preparation and determination of stereochemistry of trisubstituted hydroxypyrrolidine **12**.

Notes and references

§ *Typical procedure for synthesis of 3-hydroxypyrrolidines from epoxysulfonamides*: *n*-BuLi (1.6 M in hexanes 0.38 mL, 0.61 mmol) was added dropwise to a stirred suspension of $Me_3S(O)I$ (123 mg, 0.56 mmol) in THF (1.4 mL) at −78 °C and stirred at this temperature for 15 min, and then at 0 °C for 15 min. The mixture was re-cooled to −78 °C and a solution of *anti*-**7a** (0.19 mmol) in THF (0.5 mL) was added dropwise, followed by DMPU (0.45 mL, 3.74 mmol) and the reaction then warmed to rt over 5 min and heated to reflux. After 2 h, 5% aq. NH_4Cl (10 mL) and EtOAc (10 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (60% Et_2O in petrol) to give the corresponding *trans*-**8a** (45 mg, 86%) as a colourless oil; R_f 0.18 (70% Et_2O in petrol); IR (neat)/cm^{-1} 3510br, 2960s, 1599s, 1494s, 1336s, 1156s; ^1H NMR (400 MHz) δ 7.74 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 4.05 (d, J = 3 Hz, 1H), 3.49–3.44 (m, 2H), 3.24 (ddd, J = 10.5, 9.5, 7 Hz, 1H), 2.41 (s, 3H), 2.06–1.97 (m, 1H), 1.77–1.67 (m, 3H), 1.50–1.33 (m, 2H), 1.26 (br, 1H), 0.94 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz) δ 143.4, 134.2, 129.5, 127.7, 74.8, 69.1, 46.2, 37.3, 32.4, 21.5, 19.5, 14.0; MS *m/z* (CI) 301 (M + NH_4^+, 100), 284 (68), 130 (50), 48 (33), 86 (29), 72 (30); HRMS calcd for $C_{14}H_{25}N_2O_3S$ (M + NH_4^+) 301.1586, found 301.1577.

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17 Using $Me_3S(O)Cl$ as a source of ylide **2** under these conditions gave an identical yield of **8a**.

18 Crystallographic data for **8e**: $C_{17}H_{18}BrNO_3S$, M_r = 396.30, crystal size 0.04 × 0.04 × 0.20 mm, colourless needles, crystal system triclinic, a = 7.4856(4), b = 9.7383(5), c = 11.5200(6) Å, α = 95.766(2), β = 96.244(2), γ = 92.306(3)°, V = 829.49(8) Å^3, Z = 2, D_c = 1.587 mg m^{-3}, F_{000} = 404, T = 150 K, space group $P\bar{1}$, Z = 2, μ = 2.617 mm^{-1}, 10663 reflections were measured, R = 0.0423, wR = 0.0507. CCDC 602881. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606583j.

