Rapid and Selective Synthesis of Substituted 1,2,5-Thiadiazolidine 1,1-Dioxides

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Abstract: The reaction of *N*,*N*-dimethylsulfamoyl aziridines with primary amines gives direct access to substituted 1,2,5-thiadiazolidines in a regioselective manner. Furthermore, the product from reaction with 4-methoxybenzyl amine can be subsequently manipulated to give the alternative nitrogen substitution pattern in a controlled fashion.

Key words: heterocycles, aziridines, cyclic sulfamides, regioselective

As part of a progamme to develop potent and selective inhibitors of γ-secretase for the treatment of Alzheimer's disease, we identified a series of cyclic sulfamides[1] with the general structure shown in Figure 1. We herein report an improved synthesis of substituted 1,2,5-thiadiazolidines, which facilitates rapid exploration of structure–activity relationships for this class of compounds.

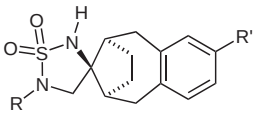
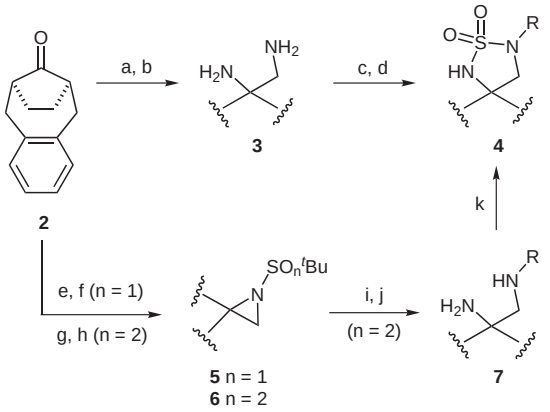


Figure 1

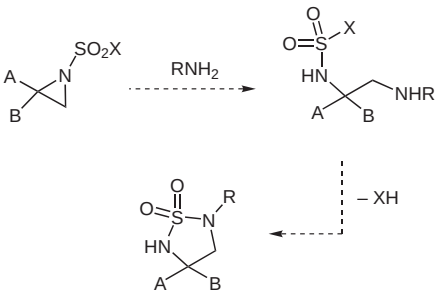
Our initial approach introduced the nitrogen substituent, R, by alkylation of the parent heterocycle, which in turn was prepared by reaction of the appropriate diamine with sulfamide (Scheme 1).[2]

However, in some cases bis-alkylation led to a significant reduction in yield of the required product, despite the use of stoichiometric amounts of electrophile. This led us to examine aziridine opening with primary amines as an alternative method to create and control the desired substitution pattern of the final heterocycle. Ellman and others[3] have demonstrated the utility of the *tert*-butylsulfinyl group in amine synthesis. An attractive feature is that it can be removed under mild conditions, but opening of a *tert*-butylsulfinyl aziridine[4] with an amine requires somewhat elevated temperatures.[5] Therefore, we first targeted the *tert*-butylsulfonyl analogue. In accordance with literature precedent,[6] the reaction of **6** with an amine proceeds smoothly and with complete regiocontrol, but removal of a *tert*-butylsulfonyl group requires strongly acidic conditions that are often incompatible with many functional groups.



Scheme 1 *Reagents and conditions:* a) NH_4OH, NaCN, NH_3, MeOH, 0 °C, 70%; b) $LiAlH_4$, THF, r.t., 77%; c) $SO_2(NH_2)_2$, pyridine, reflux, 85%; d) NaH, RBr, DMF, r.t.; e) (±)-*t*-BuS(O)NH_2, $Ti(OEt)_4$, THF, reflux, 72%; f) $Me_3S(O)I$, NaH, DMSO, 81%; g) *t*-$BuSO_2NH_2$, $TiCl_4$, Et_3N, $(ClCH_2)_2$, reflux, 83%; h) $Me_3S(O)I$, NaH, DMSO, 48%; i) RNH_2, DMSO, 100 °C, 55–90%; j) CF_3SO_3H, anisole, CH_2Cl_2, 0 °C to r.t.; k) $SO_2(NH_2)_2$, pyridine, reflux, 36–67%, 2 steps.

We speculated that it may be possible to activate aziridine opening with a sulfonyl group in which the *tert*-butyl group is replaced with a moiety that could function as a leaving group, thus facilitating in situ cyclisation to give the cyclic sulfamide in one step (Scheme 2). This would give the desired heterocycle directly, with the required substitution pattern, and negate the need for harsh conditions in either the opening of the aziridine or removal of the activating group.



Scheme 2

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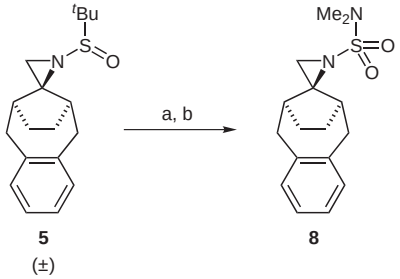
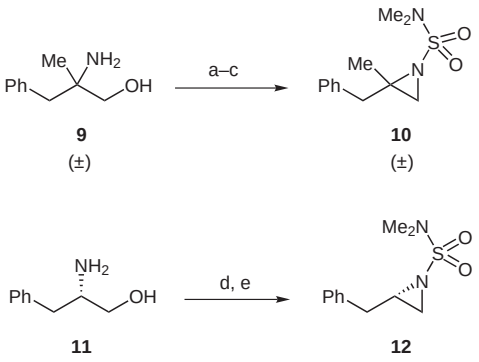
To test this possibility we chose to examine the reactivity of *N*,*N*-dimethylsulfamoyl aziridines (X = NMe_2). These may be accessed from the *tert*-butylsulfinyl aziridine by deprotection with HCl in methanol followed by reaction with dimethylsulfamoyl chloride (Scheme 3). Alternatively, they can be constructed from an amino alcohol in a straightforward manner as shown in Scheme 4. The dimethylsulfamoyl group can be introduced either following Mitsunobu reaction[7] or prior to conversion of the alcohol to a leaving group. Both options serve as effective routes to the desired heterocycle.



Scheme 3 *Reagents and conditions:* a) HCl, dioxane, MeOH, 0 °C, 76%; b) Me_2NSO_2Cl, Et_3N, CH_2Cl_2, r.t., 63%.

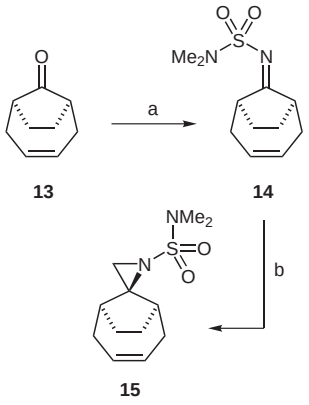


Scheme 4 *Reagents and conditions:* a) Me_2NSO_2Cl, Et_3N, CH_2Cl_2, r.t., 91%; b) MsCl, Et_3N, CH_2Cl_2, r.t., 86%; c) NaH, THF, 0 °C, 83%; d) DIAD, PPh_3, PhMe, reflux, 62%; e) Me_2NSO_2Cl, Et_3N, CH_2Cl_2, r.t., 78%.

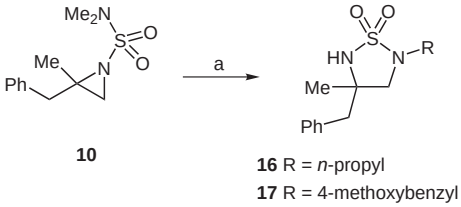
A more concise synthesis of *N*,*N*-dimethylsulfamoyl aziridines,[8] starting from a carbonyl group, was developed through adaptation of the sulfinyl imine chemistry described in Scheme 1. Substituting dimethylsulfamide for *tert*-butylsulfinamide affords the *N*,*N*-dimethylsulfamoyl imine in modest yield[9] (Scheme 5); subsequent reaction with trimethylsulfoxonium ylide[10] proceeds well to give the activated aziridine in comparable overall yield to the other routes described.

We found that simply heating **10** in DMSO at 100 °C with five equivalents of a primary amine affords the desired cyclic sulfamide directly and in good yield (Scheme 6).

Aziridines **12** and **15** were then employed to test a range of amines in this transformation (Table 1). Good yields and regioselectivity were observed with allylic, benzylic and sterically demanding aliphatic amines. Aliphatic amines with heteroatoms, and heteroaromatic benzylic

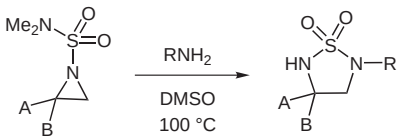


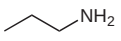
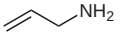
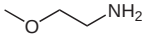
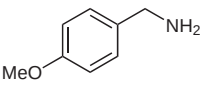
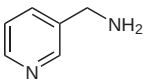
Scheme 5 *Reagents and conditions:* a) $Me_2NSO_2NH_2$, $Ti(OEt)_4$, THF, reflux, 50%; b) $Me_3S(O)I$, NaH, DMSO, 87%.



Scheme 6 *Reagents and conditions:* a) RNH_2, DMSO, 100 °C (**16**: 80%; **17**: 90%).

Table 1 Reaction of Aziridines **12** and **15** with Amines[11]



Entry	RNH_2		
1		**18a**, 87%	**19a**, 87%[12]
2		**18b**, 78%	**19b**, 66%
3		**18c**, 72%	**19c**, 67%
4		**18d**, 66%	**19d**, 77%
5		**18e**, 79%	**19e**, 81%
6		**18f**, 76%	**19f**, 64%
7		**18g**, 60%	**19g**, 66%

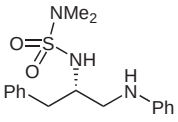
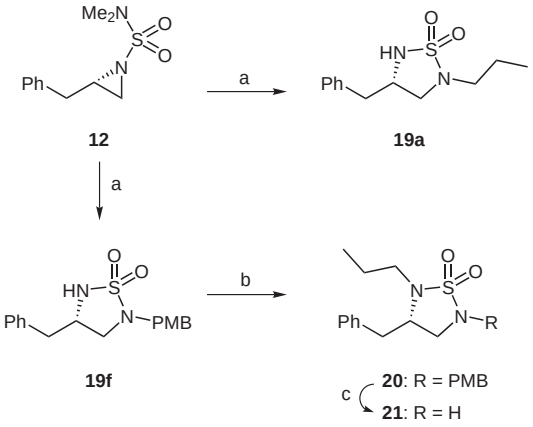


Figure 2 Structure of the product from the reaction of **12** with aniline.

amines also performed well. Interestingly, the reaction of **12** with aniline, under the standard conditions, failed to give the desired cyclic sulfamide. Instead, the product of simple aziridine opening (Figure 2) was isolated in good yield (90%).

The product from reaction with 4-methoxybenzylamine can be further manipulated to access alternatively substituted analogues (Scheme 7). The sulfamide reacts smoothly with simple alkyl halides after deprotonation with sodium hydride,[13] and the 4-methoxybenzyl group can then be removed by treatment with trifluoroacetic acid at room temperature.[14]



Scheme 7 *Reagents and conditions:* a) RNH_2, DMSO, 100 °C (**19a**: 87%; **19f**: 64%); b) NaH, THF, *n*-PrBr, 96%; c) TFA, 99%.

In conclusion, we have developed a novel reaction of *N*,*N*-dimethylsulfamoyl aziridines with primary amines to furnish substituted 1,2,5-thiadiazolidines in a regioselective manner. Furthermore, we have shown that the product from reaction with 4-methoxybenzyl amine can be subsequently manipulated to give access to any desired nitrogen substitution pattern in a controlled fashion.

Acknowledgment

The authors would like to thank Dr. I. J. Collins, Mr. M. P. Ridgill and Miss L. Farnsworth for contributions to the work described in Schemes 1 and 2, Miss M. Bettati for assistance with ee determination by chiral HPLC, and Mr. S. Thomas for accurate mass determinations.

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(9) ***N′*-{Bicyclo[4.2.1]non-3-en-9-ylidene}-*N*,*N*-dimethylsulfamide (14).** Titanium(IV) ethoxide (12.6 mL, 60 mmol) was added to a solution of bicyclo[4.2.1]non-3-en-9-one[15] (**13**, 2.72 g, 20 mmol) and *N*,*N*-dimethylsulfamide (12.4 g, 100 mmol) in dry THF (20 mL) at r.t. under N_2. The dark red solution was stirred and heated at reflux for 16 h, then allowed to cool to r.t. The reaction mixture was poured into brine (120 mL) with rapid stirring. After 20 min the solid was removed by filtration through Hyflo®, washing with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined extracts were washed with half-sat. aq $NaHCO_3$, then dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography (silica, 5% EtOAc–isohexane) to give the title compound (2.4 g, 50%) as a colourless solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.48–1.68 (2 H, m), 1.94–2.13 (2 H, m), 2.17–2.38 (3 H, m), 2.56–2.65 (1 H, m), 2.83 (6 H, s), 2.88–2.94 (1 H, m), 3.73–3.80 (1 H, m), 5.54–5.72 (2 H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.8, 29.8, 33.3, 34.9, 39.0, 42.4, 46.8, 125.8, 127.9. MS (ES^+): *m*/*z* = 243 [MH^+].

(10) **(1′*R*,2*R*,6′*S*)-*N*,*N*-dimethyl-1*H*-spiro{aziridine-2,9′-bicyclo[4.2.1]non[3]ene}-1-sulfonamide (15).** NaH (60% disp., 600 mg, 15 mmol) was added portionwise to a stirred solution of trimethylsulfoxonium iodide (3.3 g, 15 mmol) in dry DMSO (25 mL) at r.t. under nitrogen. After 1 h, a solution of imine **14** (2.4 g, 10 mmol) in dry DMSO (25 mL) was added. After 1 h the reaction was quenched with H_2O (50 mL), then extracted with EtOAc (3 × 50 mL). The combined extracts were washed with H_2O (2 × 50 mL), brine (50 mL) then dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography (silica, 10% EtOAc–isohexane) to give the title compound (2.2 g, 87%)

as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55–1.61 (2 H, m), 1.93–1.97 (2 H, m), 2.09–2.18 (4 H, m), 2.39 (2 H, s), 2.65 (2 H, dd, *J* = 3.7, 13.2 Hz), 2.92 (6 H, s), 5.57 (2 H, br s). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 28.4, 34.1, 39.2, 41.3, 44.0, 58.4, 127.5. MS (ES^+): *m/z* = 257 [MH^+]. HRMS: *m/z* calcd for $C_{12}H_{21}N_2O_2S$ [MH^+]: 257.1324; found: 257.1322.

(11) **Typical Procedure for Aziridine Opening.** A solution of the aziridine (1 mmol) and the amine (5 mmol) in dry DMSO (15 mL) was stirred and heated at 100 °C for 16 h under N_2. After cooling to r.t. the mixture was diluted with an equal volume of H_2O, then extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL) then dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography (silica, EtOAc–isohexane) to give the cyclic sulfamide.

(12) **Data for (4*S*)-4-Benzyl-2-propyl-1,2,5-thiadiazolidine-1,1-dioxide (19a).** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (3 H, t, *J* = 7.4 Hz), 1.62 (2 H, sext, *J* = 7.3 Hz), 2.83–2.93 (2 H, m), 2.97–3.05 (2 H, m), 3.07 (1 H, dd, *J* = 9.2, 7.1 Hz), 3.42 (1 H, dd, *J* = 9.2, 6.8 Hz), 3.95 (1 H, sext., *J* = 7.0 Hz), 4.43 (1 H, br d, *J* = 6.2 Hz), 7.20 (2 H, d, *J* = 7.0 Hz), 7.26–7.35 (3 H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 11.8, 21.6, 41.1, 48.9, 53.8, 54.0, 127.7, 129.3, 129.5, 136.5. HRMS: *m/z* calcd for $C_{12}H_{19}N_2O_2S$ [MH^+]: 255.1167; found: 255.1176. $[\alpha]_D^{22}$ –35 (*c* 1, MeOH). The ee was determined to be >99% by chiral HPLC (CHIRALPAK AD-H, 15% EtOH–isohexane, 1 mL/min). The ee for the aziridine **12** was also found to be >99% by chiral HPLC (CHIRALPAK AS-H, 7% EtOH–isohexane, 1 mL/min).

(13) **(3*S*)-3-Benzyl-5-(4-methoxybenzyl)-2-propyl-1,2,5-thiadiazolidine-1,1-dioxide (20).** NaH (60% disp, 96 mg, 2.4 mmol) was added to a stirred solution of (4*S*)-4-benzyl-2-(4-methoxybenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (**19f**, 665 mg, 2 mmol) in dry DMF (20 mL) at 0 °C under N_2. After 1 h, *n*-propyl bromide (220 μL, 2.4 mmol) was added. The reaction was quenched with H_2O after a further hour, then partitioned between EtOAc (50 mL) and H_2O (50 mL). The aqueous layer was extracted with EtOAc (50 mL). The combined extracts were washed with brine (50 mL), then dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography (silica, 10% EtOAc–isohexane) to give the cyclic sulfamide (718 mg, 96%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (3 H, t, *J* = 7.4 Hz), 1.69 (2 H, sext, *J* = 7.4 Hz), 2.71 (1 H, dd, *J* = 9.1, 13.5 Hz), 2.78 (1 H, dd, *J* = 6.6, 9.3 Hz), 2.90 (1 H, dt, *J* = 13.6, 7.7 Hz), 3.03–3.10 (2 H, m), 3.24 (1 H, dt, *J* = 13.9, 7.0 Hz), 3.48–3.52 (1 H, m), 3.79 (3 H, s), 3.93 (1 H, d, *J* = 13.6 Hz), 4.19 (1 H, d, *J* = 13.6 Hz), 6.85 (2 H, d, *J* = 8.6 Hz), 7.08 (2 H, d, *J* = 6.7 Hz), 7.21–7.28 (5 H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 11.8, 22.0, 40.0, 49.8, 50.0, 50.5, 55.7, 58.9, 114.5, 127.3, 127.4, 129.2, 129.6, 130.4, 136.5, 159.9. HRMS: *m/z* calcd for $C_{20}H_{27}N_2O_3S$ [MH^+]: 375.1742; found: 375.1736.

(14) **(3*S*)-3-Benzyl-2-propyl-1,2,5-thiadiazolidine-1,1-dioxide (21).** A solution of (3*S*)-3-benzyl-5-(4-methoxybenzyl)-2-propyl-1,2,5-thiadiazolidine-1,1-dioxide (**20**, 562 mg, 1.5 mmol) in TFA (3 mL) was stirred at r.t. for 2 h. The mixture was then concentrated in vacuo. The residue was taken up in EtOAc (25 mL). The organic layer was washed with brine (25 mL), then dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography (silica, 10–20% EtOAc–isohexane) to give the cyclic sulfamide (378 mg, 99%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (3 H, t, *J* = 7.4 Hz), 1.69 (2 H, sext, *J* = 7.4 Hz), 2.79 (1 H, dd, *J* = 8.6, 13.6 Hz), 2.92 (1 H, dt, *J* = 7.8, 13.6 Hz), 3.06 (1 H, dd, *J* = 5.2, 13.6 Hz), 3.13–3.21 (2 H, m), 3.34 (1 H, dt, *J* = 7.1, 11.7 Hz), 3.61–3.68 (1 H, m), 4.54 (1 H, t, *J* = 7.2 Hz), 7.19–7.34 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 21.2, 39.0, 44.5, 47.8, 62.3, 126.8, 128.5, 128.9, 135.6. HRMS: *m/z* calcd for $C_{12}H_{19}N_2O_2S$ [MH^+]: 255.1167; found: 255.1154.

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