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General synthesis of *n*-membered cyclic sulfamides

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Abstract—A general method for the synthesis of *n*-membered cyclic sulfamides (cyclosulfamides) is described. An application to the synthesis of constrained peptidal cyclic sulfamide is illustrated.

1. Introduction

Cyclic sulfamides are attractive molecules with potential application in medicinal chemistry. They have been shown to display promising value as cyclic scaffolds for peptidomimetics in the design of protease inhibitors such as HIV protease,[1] serine protease[2] and metalloprotease.[3]

The reported strategies for the synthesis of cyclosulfamides are based either on the incorporation of the sulfamoyl moiety reacting sulfuryl chloride[4] or sulfonyl urea ($H_2NSO_2NH_2$)[1d,5] on vicinal diamines, or by intramolecular cyclization of linear sulfamides using reductive cross-coupling reaction[6] or ring-closing metathesis synthesis.[7] Others processes leading to fused ring cyclic sulfamides have been also described.[8]

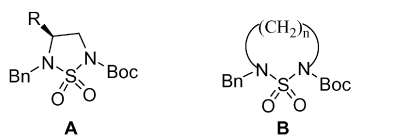
In our previous studies,[9] we described a convenient access to a series of five-membered cyclic sulfamides *N*,*N*′-disubstituted by orthogonal protections **A** (Fig. 1), starting from aminoacids and chlorosulfonylisocyanate. These heterocycles could be useful as a starting point for the construction of an array of peptidomimetic scaffolds. Following our synthetic effort to design new cyclic sulfamides, we decided to explore the possibility for ring extension. So we wish to report herein a general method allowing the preparation of cyclic sulfamides with different sizes (**B** Fig. 1).

2. Results and discussion

As outlined in Scheme 1, the different heterocycles were prepared in a two-step reaction sequence starting from *N*-benzyl-*N*′-*tert*-butoxycarbonylsulfamide **1**. This requisite substrate was prepared by sulfamoylation of benzylamine as previously described.[10] Regiospecific *N*-alkylation of **1** was carried out in heterogeneous system using potassium carbonate in acetone to afford compounds **2** in moderate to good yields for $n>3$. In the case of $n=2$ or 3, cyclized products were directly obtained under these experimental conditions. Alternatively, a synthetic approach using Mitsunobu reaction could be applied starting from bromoalcohol.[9b] Compounds **2a**–**k** are obtained in good yields.

In the next stage of the synthesis, compounds **2** were subjected to cyclization in diluted basic medium under solvent reflux to afford cyclosulfamides **3**. This approach in two steps permits us to obtain final cyclosulfamides in satisfactory yield. Synthesis in one step has also been envisioned, but in this case cyclosulfamides were obtained in bad yields after fastidious purifications.

Identification of all isolated products **2** and **3** was accomplished with the aid of ^1H and ^{13}C NMR spectroscopies



R= H, Me, iBu, iPr, Bn n= 2,3,4,5,6,7,8,9,10,11,12

Figure 1.

Keywords: cyclic sulfamides; cyclisation; sulfamides; peptidomimetic scaffold.

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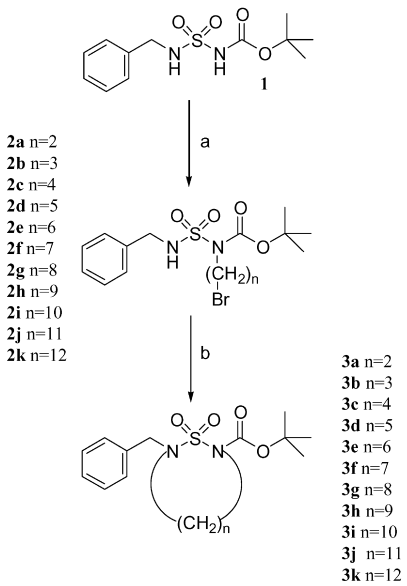


Scheme 1. General synthesis of *n*-membered cyclosulfamides. *Reagents and conditions*: (a) dibromoalkane 1 equiv., K_2CO_3 3 equiv., acetone for $n>3$ or bromoalcohol 1 equiv., PPh_3 1.1 equiv., DIAD 1.1 equiv., THF; (b) NaOH 1.5 equiv. DMSO.

and mass spectrometry. Structural proof was obtained by X-ray analysis of compound **3b**.[11] (Fig. 2)

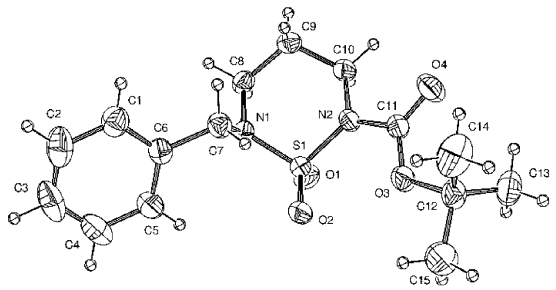
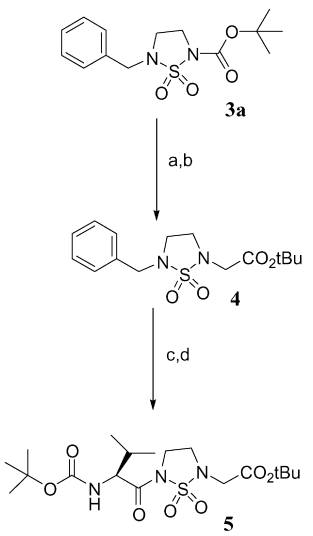


Figure 2. X-Ray crystal structure of compound **3b**.

A sequential deprotection protocol was next used for the introduction of conformation constraint in various peptide chains. As proof of this concept we choose to prepare a constrained dipeptidal cyclic sulfamide (Scheme 2) where amino acid where sequentially coupled on each side of sulfamide function. Selective cleavage of the *tert*-butoxycarbonyl protection under TFA conditions and the coupling with *tert*-butyl bromoacetate in the presence of DBU gave compound **4** in good yield. Attempts to incorporate the amino acid moiety employing Mitsunobu reaction (PPh_3/DIAD or $P(Bu_3)$/ADDP) with an α-hydroxyester did not permit the isolation of the expected compound. Alternatively, debenzylation using Pd(0)-catalyzed hydrogenolysis in ethanol, followed by peptidic coupling with *N*-Boc protected valine afforded the pseudopeptide **5** in good yield (Scheme 2).

3. Conclusion

In summary, we have shown that facile formation of *n*-membered *N*,*N*′-protected cyclic sulfamides can be carried out in two steps by an inter- and intramolecular



Scheme 2. Example of preparation of constrained dipeptidal cyclic sulfamide. *Reagents and conditions*: (a) TFA, CH_2Cl_2; (b) *tert*-butylbromoacetate, DBU; (c) ammonium formate, Pd/C, EtOH; (d) Boc-Val-OH, BOP, DMF.

N-alkylation. We also demonstrate the useful application of these cyclic sulfamides in the preparation of pseudo peptides. This flexible strategy is amenable to a number of variations (cycle size, nature of amino acid, length of peptide) and further work are currently being pursued to incorporate these cyclic sulfamides scaffold into peptidic sequences of biological interest.

4. Experimental

4.1. General

All commercial chemicals and solvents were used as received. Melting points were determined in open capillary tubes on a Buchi apparatus and are uncorrected. ^1H and ^{13}C spectra were respectively recorded in a 250 MHz and 400 MHz Bruker spectrometers. Chemicals shifts are reported in δ units (ppm). All coupling constants J are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and combination of these signals. Electron Ionization mass spectra (30 eV) were recorded in positive or negative mode on a Water MicroMass ZQ. High-resolution mass spectra were measured on a Jeol SX102 mass spectrometer and recorded in FAB positive mode. All reactions were monitored by TLC on silica Merck 60 F_{254} precoated aluminium plates and were developed by spraying with ninhydrin solution. Columns chromatographies were performed on Merck silica gel (230–400 mesh).

4.2. General procedure for the synthesis of *N*′-benzyl-*N*′-bromoalkyl-*N*′-*tert*-butoxycarbonylsulfamide

Method A: using heterogeneous system K_2CO_3/Acetone ($n>3$). A mixture of 1 equiv. of *N*-benzyl-*N*′-*tert*-butoxycarbonyl sulfamide and 1 equiv. of dibromoalkane was stirred at 60°C with 3 equiv. of K_2CO_3 in acetone during 24 h. After filtration, and concentration, the residue was purified by chromatography on silica gel.

Method B. Using Mitsunobu conditions. 1 equiv. of *N*-benzyl-*N'*-*tert*-butoxycarbonyl sulfamide and 1 equiv. of bromoalcohol were dissolved in the minimum of THF. 1.1 equiv. of PPh_3 and 1.1 equiv. of DIAD were successively added. The mixture was stirred 3 h at room temperature, and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

4.2.1. *N*-Benzyl-*N'*-bromoethyl-*N'*-tert-butoxycarbonyl sulfamide 2a. Yield: 65%; mp: 97–98°C; ^{1}H NMR ($CDCl_3$) δ: 7.35 (m, 5H, Ar-H), 5.6 (t, 1H, J=6.5 Hz, NH), 4.2 (d, 2H, J=6.1 Hz, CH_2Ar), 3.95 (t, 2H, J=7 Hz, CH_2Br), 3.45 (t, 2H, J=7.2 Hz, CH_2N), 1.5 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 151.7, 135.7, 129.3, 128.7, 85.2, 48.6, 48.3, 29.4, 28.4; MS (ESI+, 30 eV): 416 $[M+Na]^+$; HRMS calcd for $C_{14}H_{21}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 393.0484, found 393.0481.

4.2.2. *N*-Benzyl-*N'*-bromopropyl-*N'*-*tert*-butoxycarbonyl sulfamide 2b. Yield: 69%; mp: 106–107°C; ^{1}H NMR ($CDCl_3$) δ: 7.35 (s, 5H, Ar-H), 4.38 (s, 2H, CH_2Ar), 3.98 (t, 2H, J=5.7 Hz, CH_2Br), 3.42 (t, 2H, J=5.9 Hz, CH_2N), 1.8 (m, 2H, CH_2), 1.55 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 152.1, 135.8, 129.2, 128.5, 84.8, 48.5, 46.8, 33.1, 30.2, 28.4; MS (ESI+, 30 eV): 430 $[M+Na]^+$; HRMS calcd for $C_{15}H_{23}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 407.0640, found 407.0640.

4.2.3. *N*-Benzyl-*N'*-bromobutyl-*N'*-*tert*-butoxycarbonyl sulfamide 2c. Yield: 65%; mp: 98–99°C; ^{1}H NMR ($CDCl_3$) δ: 7.35 (m, 5H, Ar-H), 5.6 (t, 1H, J=6.8 Hz, NH), 4.15 (d, 2H, J=6.1 Hz, CH_2Ar), 3.6 (t, 2H, J=7 Hz, CH_2Br), 3.4 (t, 2H, J=6.3 Hz, CH_2N), 1.85 (m, 4H, CH_2), 1.5 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 151.9, 135.5, 128.9, 128.2, 84.3, 48.3, 46.9, 33.1, 29.8, 28.4, 28.1; MS (ESI+, 30 eV): 444 $[M+Na]^+$; HRMS calcd for $C_{16}H_{25}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 421.0797, found 421.0795.

4.2.4. *N*-Benzyl-*N'*-bromopentyl-*N'*-*tert*-butoxycarbonyl sulfamide 2d. Yield: 63%; mp: 65–68°C; ^{1}H NMR ($CDCl_3$) δ: 7.29 (m, 5H, Ar-H), 5.56 (t, 1H, NH), 4.11 (d, 2H, J=6.3 Hz, CH_2Ar), 3.55 (t, 2H, J=7.3 Hz, CH_2Br), 3.37 (t, 2H, J=6.6 Hz, CH_2N), 1.46 (s, 9H, ^{t}Bu), 1.4–1.9 (m, 6H, $3CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.2, 135.9, 129.2, 128.6, 84.4, 48.5, 47.8, 33.8, 32.5, 29.3, 28.4, 25.5; MS (ESI+, 30 eV): 458 $[M+Na]^+$; HRMS calcd for $C_{17}H_{27}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 435.0953, found 435.0950.

4.2.5. *N*-Benzyl-*N'*-bromohexyl-*N'*-*tert*-butoxycarbonyl sulfamide 2e. Yield: 58%; mp: 43–45°C; ^{1}H NMR ($CDCl_3$) δ: 7.30 (m, 5H, Ar-H), 5.56 (t, 1H, NH), 4.10 (d, 2H, J=6.2 Hz, CH_2Ar), 3.52 (t, 2H, J=7.0 Hz, CH_2Br), 3.32 (t, 2H, J=7.4 Hz, CH_2N), 1.42 (s, 9H, ^{t}Bu), 1.2–1.8 (m, 8H, $4CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.2, 135.9, 129.2, 128.6, 84.3, 48.5, 48.0, 34.0, 32.9, 29.9, 28.4, 28.1, 26.1; MS (ESI+, 30 eV): 472 $[M+Na]^+$; HRMS calcd for $C_{18}H_{29}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 449.1010, found 449.1012.

4.2.6. *N*-Benzyl-*N'*-bromoheptyl-*N'*-*tert*-butoxycarbonyl sulfamide 2f. Yield: 40%; mp: 52–54°C; ^{1}H NMR ($CDCl_3$) δ: 7.4 (m, 5H, Ar-H), 5.6 (t, 1H, NH), 4.1 (d, 2H, J=6.2 Hz, CH_2Ar), 3.6 (t, 2H, J=7.3 Hz, CH_2Br), 3.4 (t, 2H, J=6.7 Hz, CH_2N), 1.5 (s, 9H, ^{t}Bu), 1.2–1.8 (m, 10H, $5CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.3, 135.9, 129.2, 128.6, 84.2, 48.5, 48.1, 34.2, 33.0, 30.0, 28.7, 28.4, 26.7; MS (ESI+, 30 eV): 486 $[M+Na]^+$; HRMS calcd for $C_{19}H_{31}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 463.1266, found 463.1262.

4.2.7. *N*-Benzyl-*N'*-bromooctyl-*N'*-*tert*-butoxycarbonyl sulfamide 2g. Yield: 58%; mp: oil; ^{1}H NMR ($CDCl_3$) δ: 7.2 (m, 5H, Ar-H), 5.5 (t, 1H, NH), 4.1 (d, 2H, J=5.3 Hz, CH_2Ar), 3.5 (t, 2H, J=7.4 Hz, CH_2Br), 3.35 (t, 2H, J=6.7 Hz, CH_2N), 1.4 (s, 9H, ^{t}Bu), 1.2–1.8 (m, 12H, $6CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.3, 135.8, 129.1, 128.5, 84.3, 48.5, 48.1, 34.3, 33.1, 30.0, 28.8, 28.5, 28.4, 26.6; MS (ESI+, 30 eV): 500 $[M+Na]^+$; HRMS calcd for $C_{20}H_{33}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 477.1423, found 477.1420.

4.2.8. *N*-Benzyl-*N'*-bromononyl-*N'*-*tert*-butoxycarbonyl sulfamide 2h. Yield: 47%; mp: 57–58°C; ^{1}H NMR ($CDCl_3$) δ: 7.35 (m, 5H, Ar-H), 5.6 (t, 1H, NH), 4.15 (d, 2H, J=6.2 Hz, CH_2Ar), 3.6 (t, 2H, J=7.2 Hz, CH_2Br), 3.4 (t, 2H, J=6.9 Hz, CH_2N), 1.5 (s, 9H, ^{t}Bu), 1.3–1.8 (m, 14H, $7CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.3, 136.0, 129.2, 128.5, 84.1, 48.5, 48.2, 34.3, 33.1, 30.1, 29.6, 29.4, 29.0, 28.4, 26.9; MS (ESI+, 30 eV): 514 $[M+Na]^+$; HRMS calcd for $C_{21}H_{35}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 491.1579, found 491.1579.

4.2.9. *N*-Benzyl-*N'*-bromodecyl-*N'*-*tert*-butoxycarbonyl sulfamide 2i. Yield: 43%; mp: 38–40°C; ^{1}H NMR ($CDCl_3$) δ: 7.2 (m, 5H, Ar-H), 5.5 (t, 1H, J=6.2 Hz, NH), 4.1 (d, 2H, J=6.2 Hz, CH_2Ar), 3.5 (t, 2H, J=7.4 Hz, CH_2Br), 3.36 (t, 2H, J=6.8 Hz, CH_2N), 1.8 (m, 2H, CH_2), 1.5 (m, 2H, CH_2), 1.4 (s, 9H, ^{t}Bu), 1.2 (m, 12H, $6CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.3, 135.8, 129.3, 128.8, 84.3, 48.6, 48.1, 34.4, 33.2, 30.3, 29.8, 29.5, 29.3, 29.1, 28.5, 28.4, 26.9; MS (ESI+, 30 eV): 528 $[M+Na]^+$; HRMS calcd for $C_{22}H_{37}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 505.1736, found 505.1730.

4.2.10. *N*-Benzyl-*N'*-bromoundecyl-*N'*-*tert*-butoxycarbonyl sulfamide 2j. Yield: 46%; mp: 31–33°C; ^{1}H NMR ($CDCl_3$) δ: 7.3 (m, 5H, Ar-H), 5.55 (t, 1H, NH), 4.1 (d, 2H, J=6.3 Hz, CH_2Ar), 3.6–3.3 (m, 4H, CH_2Br and CH_2N), 1.9 (m, 2H, CH_2), 1.5 (s, 9H, ^{t}Bu), 1.1–1.5 (m, 16H, $8CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.2, 135.9, 129.1, 128.7, 84.2, 48.5, 48.2, 34.5, 33.2, 30.3, 29.8, 29.5, 29.3, 29.1, 28.6, 28.4, 26.8; MS (ESI+, 30 eV): 542 $[M+Na]^+$; HRMS calcd for $C_{23}H_{39}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 518.1813, found 518.1810.

4.2.11. *N*-Benzyl-*N'*-bromododecyl-*N'*-*tert*-butoxycarbonyl sulfamide 2k. Yield: 45%; mp: 45–47°C; ^{1}H NMR ($CDCl_3$) δ: 7.4 (m, 5H, Ar-H), 5.6 (t, 1H, J=7 Hz, NH), 4.15 (d, 2H, J=6.2 Hz, CH_2Ar), 3.6 (t, 2H, J=7.6 Hz, CH_2Br), 3.4 (t, 2H, J=6.8 Hz, CH_2N), 1.9 (m, 2H, CH_2), 1.5 (s, 9H, ^{t}Bu), 1.2–1.8 (m, 18H, $9CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.3, 136.0, 129.2, 128.6, 84.1, 48.5, 48.2, 34.4, 33.2, 30.2, 29.8, 29.5, 29.1, 28.5, 28.4, 26.9; MS (ESI+, 30 eV): 556 $[M+Na]^+$; HRMS calcd for $C_{24}H_{41}BrN_2O_4S+H^+$: m/z $[M+H]^+$ 533.2049, found 532.2046.

4.3. General procedure for cyclization of compounds 2

A diluted solution of 1 equiv. of pure compound **2**, 0.1 equiv. of tetrabutylammonium iodide and 5 equiv. of

K_2CO_3 in acetone was warmed 18 h. The reaction was then filtered and the filtrate concentrated under reduced pressure. The residue was chromatographed on a silica gel column.

4.3.1. 2-Benzyl-5-*tert*-butoxycarbonyl-1,2,5-thiadiazolidine-1,1-dioxide 3a. Yield: 80%; mp: 83–84°C; ^{1}H NMR ($CDCl_3$) δ: 7.3 (m, 5H, Ar-H), 4.20 (s, 2H, CH_2Ar), 3.7 (t, 2H, J=6.4 Hz, CH_2), 3.19 (t, 2H, J=6.5 Hz, CH_2), 1.5 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 149.8, 134.5, 129.2, 128.8, 85.0, 50.9, 43.3, 42.9, 28.4; MS (ESI+, 30 eV): 335 $[M+Na]^+$; HRMS calcd for $C_{14}H_{20}N_2O_4S+H^+$: m/z $[M+H]^+$ 313.1222, found 313.1222.

4.3.2. 2-Benzyl-6-*tert*-butoxycarbonyl-1,2,6-thiadiazine-1,1-dioxide 3b. Yield: 85%; mp: 107–108°C; ^{1}H NMR ($CDCl_3$) δ: 7.3 (m, 5H, Ar-H), 4.32 (s, 2H, CH_2Ar), 3.92 (t, 2H, J=5.8 Hz, CH_2NBoc), 3.4 (t, 2H, J=5.8 Hz, CH_2), 1.5 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 152.2, 135.6, 129.2, 128.9, 84.3, 52.4, 47.5, 28.4, 19.9; MS (ESI+, 30 eV): 349 $[M+Na]^+$; HRMS calcd for $C_{15}H_{22}N_2O_4S+H^+$: m/z $[M+H]^+$ 327.1379, found 327.1379.

4.3.3. 2-Benzyl-7-*tert*-butoxycarbonyl-1,2,7-thiadiazepine-1,1-dioxide 3c. Yield: 75%; mp: 90–91°C; ^{1}H NMR ($CDCl_3$) δ: 7.3 (s, 5H, Ar-H), 4.5 (s, 2H, CH_2Ar), 3.7 (m, 2H, CH_2NBoc), 3.25 (m, 2H, CH_2NBn), 1.8–1.7 (m, 4H, $2CH_2$), 1.5 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 153.2, 136.3, 129.2, 128.4, 84.1, 52.1, 46.0, 28.7, 28.4, 24.2; MS (ESI+, 30 eV): 363 $[M+Na]^+$; HRMS calcd for $C_{16}H_{24}N_2O_4S+H^+$: m/z $[M+H]^+$ 341.1535, found 341.1532.

4.3.4. 2-Benzyl-8-*tert*-butoxycarbonyl-1,2,8-thiadiazocine-1,1-dioxide 3d. Yield: 58%; mp: 92–95°C; ^{1}H NMR ($CDCl_3$) δ: 7.3 (m, 5H, Ar-H), 4.4 (s, 2H, CH_2Ar), 3.4 (t, 2H, J=6.8 Hz, CH_2NBoc), 3.05 (t, 2H, J=5.1 Hz, CH_2NBn), 1.65–1.5 (m, 6H, $3CH_2$), 1.5 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 153.3, 134.9, 129.2, 128.6, 84.3, 52.4, 46.8, 32.8, 32.2, 29.3, 28.4; MS (ESI+, 30 eV): 377 $[M+Na]^+$; HRMS calcd for $C_{17}H_{26}N_2O_4S+H^+$: m/z $[M+H]^+$ 355.1692, found 355.1688.

4.3.5. 2-Benzyl-9-*tert*-butoxycarbonyl-1,2,9-thiadiazonine-1,1-dioxide 3e. Yield: 60%; mp: 123–126°C; ^{1}H NMR ($CDCl_3$) δ: 7.2 (m, 5H, Ar-H), 4.8 (s, 2H, CH_2Ar), 3.8 (t, 2H, J=5.5 Hz, CH_2NBoc), 3.2 (t, 2H, J=5.9 Hz, CH_2NBn), 1.65–1.45 (m, 8H, $4CH_2$), 1.40 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 151.6, 133.9, 129.2, 128.4, 83.3, 51.5, 48.0, 34.0, 32.9, 29.9, 28.4, 28.1; MS (ESI+, 30 eV): 391 $[M+Na]^+$; HRMS calcd for $C_{18}H_{28}N_2O_4S+H^+$: m/z $[M+H]^+$ 369.1848, found 369.1842.

4.3.6. 2-Benzyl-10-*tert*-butoxycarbonyl-1,2,10-thiadiazecine-1,1-dioxide 3f. Yield: 60%; mp: 131–135°C; ^{1}H NMR ($CDCl_3$) δ: 7.3 (m, 5H, Ar-H), 4.7 (s, 2H, CH_2Ar), 3.85 (t, 2H, J=5.5 Hz, CH_2NBoc), 3.25 (t, 2H, J=5.9 Hz, CH_2NBn), 1.65–1.40 (m, 8H, $4CH_2$), 1.5 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 154.3, 136.5, 129.2, 128.6, 84.5, 51.5, 48.1, 34.3, 33.2, 30.4, 28.8, 28.4; MS (ESI+, 30 eV): 405 $[M+Na]^+$; HRMS calcd for $C_{19}H_{30}N_2O_4S+H^+$: m/z $[M+H]^+$ 383.2005, found 383.2001.

4.3.7. 2-Benzyl-11-*tert*-butoxycarbonyl-1,2,11-thiadiazoundecine-1,1-dioxide 3g. Yield: 30%; mp: 125–128°C; ^{1}H NMR ($CDCl_3$) δ: 7.3 (m, 5H, Ar-H), 4.7 (s, 2H, CH_2Ar), 3.84 (t, 2H, J=6.9 Hz, CH_2NBoc), 3.42 (t, 2H, J=6.1 Hz, CH_2NBn), 1.8 (m, 2H, CH_2), 1.60 (s, 9H, ^{t}Bu), 1.4–1.20 (m, 8H, $4CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.3, 135.4, 129.1, 128.2, 84.2, 52.5, 48.1, 34.4, 33.4, 30.1, 28.8, 28.5, 28.4, 26.2; MS (ESI+, 30 eV): 419 $[M+Na]^+$; HRMS calcd for $C_{20}H_{32}N_2O_4S+H^+$: m/z $[M+H]^+$ 397.2161, found 397.2160.

4.3.8. 2-Benzyl-12-*tert*-butoxycarbonyl-1,2,12-thiadiazododecine-1,1-dioxide 3h. Yield: 62%; mp: 99–102°C; ^{1}H NMR ($CDCl_3$) δ: 7.4 (m, 5H, Ar-H), 4.7 (s, 2H, CH_2Ar), 3.85 (t, 2H, J=7.9 Hz, CH_2NBoc), 3.2 (t, 2H, J=8 Hz, CH_2NBn), 1.6 (m, 4H, $2CH_2$), 1.4 (s, 9H, ^{t}Bu), 0.95 (m, 10H, $5CH_2$); ^{13}C NMR ($CDCl_3$) δ: 153.3, 136.2, 129.2, 128.2, 84.6, 51.5, 48.2, 34.2, 33.3, 30.3, 29.4, 29.0, 28.4, 27.1; MS (ESI+, 30 eV): 433 $[M+Na]^+$; HRMS calcd for $C_{21}H_{34}N_2O_4S+H^+$: m/z $[M+H]^+$ 411.2318, found 411.2312.

4.3.9. 2-Benzyl-13-*tert*-butoxycarbonyl-1,2,13-thiadiazotridecine-1,1-dioxide 3i. Yield: 60%; mp: 72–75°C; ^{1}H NMR ($CDCl_3$) δ: 7.2 (m, 5H, Ar-H), 4.4 (s, 2H, CH_2Ar), 3.5 (t, 2H, J=7.4 Hz, CH_2NBoc), 3.1 (t, 2H, J=7.9 Hz, CH_2NBn), 1.8 (m, 4H, $2CH_2$), 1.4 (s, 9H, ^{t}Bu), 1.20 (m, 12H, $6CH_2$); ^{13}C NMR ($CDCl_3$) δ: 152.1, 137.1, 128.9, 128.4, 83.5, 53.0, 49.5, 48.5, 34.3, 33.2, 29.7, 28.6, 28.4, 27.0, 26.9; MS (ESI+, 30 eV): 447 $[M+Na]^+$; HRMS calcd for $C_{22}H_{36}N_2O_4S+H^+$: m/z $[M+H]^+$ 425.2474, found 425.2469.

4.3.10. 2-Benzyl-14-*tert*-butoxycarbonyl-1,2,14-thiadiazotetradecine-1,1-dioxide 3j. Yield: 40%; mp: 81–84°C; ^{1}H NMR ($CDCl_3$) δ: 7.4 (m, 5H, Ar-H), 4.7 (s, 2H, CH_2Ar), 3.8 (t, 2H, J=6.2 Hz, CH_2NBoc), 3.4 (t, 2H, J=6.7 Hz, CH_2NBn), 1.8–1 (m, 18H, $9CH_2$), 1.5 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ: 154.2, 136.2, 129.1, 128.8, 84.2, 52.3, 48.5, 34.6, 33.7, 30.2, 29.7, 29.5, 29.3, 29.1, 28.7, 28.4, 26.9; MS (ESI+, 30 eV): 461 $[M+Na]^+$; HRMS calcd for $C_{23}H_{38}N_2O_4S+H^+$: m/z $[M+H]^+$ 439.2631, found 439.2625.

4.3.11. 2-Benzyl-15-*tert*-butoxycarbonyl-1,2,15-thiadiazopentadecine-1,1-dioxide 3k. Yield: 40%; mp: 95–98°C; ^{1}H NMR ($CDCl_3$) δ: 7.3 (m, 5H, Ar-H), 4.5 (s, 2H, CH_2Ar), 3.68 (t, 2H, J=7.4 Hz, CH_2NBoc), 3.2 (t, 2H, J=7.5 Hz, CH_2NBn), 1.8 (m, 4H, $2CH_2$), 1.7–1.4 (m, 10H, $5CH_2$), 1.3 (s, 9H, ^{t}Bu), 0.9 (m, 6H, $3CH_2$); ^{13}C NMR ($CDCl_3$) δ: 153.3, 136.2, 129.2, 128.1, 84.8, 52.5, 48.1, 34.2, 33.3, 30.2, 29.8, 29.5, 29.1, 28.5, 28.4, 27.0; MS (ESI+, 30 eV): 475 $[M+Na]^+$; HRMS calcd for $C_{24}H_{40}N_2O_4S+H^+$: m/z $[M+H]^+$ 453.2787, found 453.2781.

4.4. Preparation of compound 4

Compound **3a** was dissolved in a 20% solution of TFA in CH_2Cl_2 and stirred at room temperature until TLC analysis indicated the disappearance of the starting material. The solution was then concentrated under vacuum, and the residue purified by column chromatography with silica gel (eluent: CH_2Cl_2) to give the expected deprotected compound in 90% yield. (mp: 37–39°C; ^{1}H NMR ($CDCl_3$) δ: 7.4 (m, 5H, Ar-H), 4.6 (t, 1H, NH), 4.2 (s, 2H, CH_2Ar), 3.5

(q, 2H, J=6.4, 13 Hz, CH_2NH), 3.3 (t, 2H, J=6.7 Hz, CH_2NBn); MS (ESI+, 30 eV): 235 $[M+Na]^+$). This compound was then treated at room temperature with a solution of DBU (1.5 equiv.) in anhydrous THF. After 15 minutes, *tert*-butyl bromoacetate (1 equiv.) was added and the reaction mixture was stirred 4 h at room temperature, then concentrated under vacuum and purified by chromatography on silica gel. Compound **4** was obtained as a white powder in 76% yield; mp: 55–58°C; ^1H NMR ($CDCl_3$) δ: 7.4 (m, 5H, Ar-H), 4.2 (s, 2H, CH_2Ar), 3.8 (s, 2H, NCH_2CO), 3.55 (t, 2H, J=6.3 Hz, CH_2NBn), 3.25 (t, 2H, J=6.7 Hz, CH_2N), 1.5 (s, 9H, ^{t}Bu); MS (ESI+, 30 eV): 349 $[M+Na]^+$.

4.5. Preparation of compound 5

To a solution of compound **4** in ethanol was added ammonium formate (5 equiv.) and Pd/C. The mixture was refluxed until total disappearance of the starting material (TLC monitoring). The reaction mixture was then filtered through celite, and the filtrate concentrated. The residue was purified by chromatography on silica gel to give the N-debenzylated intermediate in 85% yield. (mp: 108–111°C; ^1H NMR ($CDCl_3$) δ: 4.5 (t, 1H, NH), 4.8 (s, 2H, NCH_2CO), 3.6 (m, 4H, CH_2N and CH_2NH), 1.5 (s, 9H, ^{t}Bu); MS (ESI+, 30 eV): 259 $[M+Na]^+$). To a solution of the above compound in DMA (*N*,*N*-dimethyl acetamide) was added N-Boc Valine (1 equiv.), BOP (1.5 equiv.) and DIEA (1.5 equiv.). The mixture was stirred at room temperature overnight then poured in water and extracted twice with ethyl acetate. The combined extracts were washed twice with $NaHCO_3$, followed by brine, dried and concentrated. The residue was purified by chromatography to give **5** as a white powder in 60% yield; mp: 118–123°C; ^1H NMR ($CDCl_3$) δ: 5.6 (d, 2H, J=8.4 Hz, NH), 4.7 (m, 1H, C×H), 4.1 (2m, 2H, CH_2NCO), 3.8 (s, 2H, NCH_2CO), 3.65 (t, 2H, J=6.8 Hz, CH_2N), 2.2 (m, 1H, –CH–), 1.45 and 1.5 (2 s, 18H, ^{t}Bu), 1.1 (d, 2H, J=10.2 Hz, CH_3), 0.9 (d, 2H, J=10.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 172.9, 169.1, 157.9, 82.5, 60.4, 56.1, 51.1, 46.6, 45.7, 33.8, 32.4, 31.0, 30.7, 22.4, 19.2; MS (ESI+, 30 eV): 458 $[M+Na]^+$; HRMS calcd for $C_{17}H_{33}N_3O_6S+H^+$: m/z $[M+H]^+$ 408.2168, found 408.2162.

4.6. X-Ray structural analysis of 3b

$C_{15}H_{22}N_2O_4S$, M_w=326.41, triclinic, $P-1$, a=6.259(2) Å, b=9.422(2) Å, c=14.375(9) Å, α=82.68(1), β=82.82(2), γ=81.28(2), V=826.3(3) Å^{-3}, Z=2, D_x=1.312 Mg m^{-3}, λ(Mo Kα)=0.71073 Å, μ=2.15 cm^{-1}, $F(000)$=348, T=293 K. The sample (0.24×0.18×0.18 mm) is studied on an automatic diffractometer CAD4 NONIUS with graphite monochromatized Mo Kα radiation (Fair, C. K. (1990) MolEN, An Interactive Intelligent System for Crystal Structure Analysis, User Manual, Enraf-Nonius, Delft, The Netherlands.). The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$=54°, scan $\omega/2\theta$=1, t_{max}=60 s, range HKL: H 0,5; K-11,11; L-18,18) gives 2978 unique reflections from which 2255 with $I>2.0\sigma(I)$. After Lorenz and polarization corrections (Spek, A. L. (1997) HELENA. Program for the handling of CAD4-diffractometer output SHELX(S/L), Utrech, The Netherlands.) the structure was solved with SIR-97 (Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna. R. *J. Appl. Crystallogr.* **1998**, *31*, 74.) which reveals the non hydrogen atoms of the compound. After anisotropic refinement a Fourier Difference reveals many hydrogene atoms. The whole structure was refined with SHELXL97 (Sheldrick, G. M. (1997). SHELX97. Program for the Refinement of Crystal Structures, Univ. of Göttingen, Germany.) by the full-matrix least-square techniques (use of F square magnitude; x, y, z, β_{ij} for S, O, N and C atoms, x, y, z in riding mode for H atoms; 200 variables and 2978 observations; calc $w=1/[\sigma^2(Fo^2)+(0.061P)^2+0.19P]$ where $P=(Fo^2+2Fc^2)/3$ with the resulting R=0.035, R_w=0.096 and S_w=1.001 (residual $\Delta\rho\leq$0.22 eÅ^{-3}). (International Tables for X-ray Crystallography (1992). Vol. C. Ed. A. J. C. (Kluwer Academic Publishers, Dordrecht)). Ortep views realized with PLATON98 (Spek, A. L. (1998) PLATON. A multipurpose crystallographic tool, Utrecht University, Utrecht, The Netherlands).

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