Abstract: The sulfamide functional group is increasingly relevant in both medicinal and bioorganic chemistry. We report here practical access to a series of N2,N5-substituted five-membered cyclosulfamides. The five-membered heterocyclic motif was prepared starting from proteogenic amino acids and chlorosulfonyl isocyanate via the Mitsunobu reaction. Selected chemical and spectral properties and the antimicrobial evaluation of these compounds are detailed.

Keywords: Amino acids, cyclic sulfamides, cyclization, Mitsunobu reaction, propionylation, constrained peptides.

Introduction

The synthesis and reactivity of heterocyclic compounds containing sulfanyl moieties have attracted much interest in recent years because of the interesting chemical and biological properties associated with their structural similarities with biomolecules containing carbonyl groups. Cyclosulfamides have enjoyed popularity in the field of medicinal chemistry as nonhydrolyzable components in peptidomimetics [1-2], agonists of the 5-HT1D receptor (regulating serotonin levels) [3], HIV and serine protease inhibitors [4-7], and constrained di- and tripeptides [8]. The reported strategies for the synthesis of cyclosulfamides are based either on the incorporation of the sulfamoyl moiety by reacting...
sulfuryl chloride [9] or sulfonyl urea [10] with vicinal diamines, or ring-closing metathesis syntheses [11]. Recently, Johnson and co-workers reported the synthesis of N-Arylcyclosulfamides starting from sulfuryl chloride and chloroethyl-amine [12]. In previous publications [13-15], we have described a convenient access to a series of five and n-membered cyclic sulfamides B and N,N'-disubstituted orthogonally protected ones A (Figure 1), starting from natural amino acids, chloroethylamine and chlorosulfonylisocyanate (CSI) followed by 5-exo-tet closure with base. These heterocycles could be useful starting points for the construction of an array of peptidomimetic scaffolds and constrained di and-tripeptides. CSI has been found to be versatile reagent of great interest in synthetic heterocyclic chemistry [16]. In this case, CSI contains the required sulfonyl group and one of the nitrogens of the 1,2,5-thiadiazolidine1,1-dioxides.

**Figure 1.** Cyclosulfamide structures

In continuation of our efforts to design and synthesize new cyclic sulfamides, we have extended our studies to a series of new heterocyclic constrained peptides containing sulfamide groups C and D (Figure 1). The derivatization of amino acids allowed the introduction N-C* moieties with a well-defined configuration. Herein, we describe the synthesis and the preliminary results of the biological evaluation of a series of these new heterocycles containing sulfamido groups.

**Results and Discussion**

As outlined in Scheme 1, the different heterocyles 1b-5b were prepared in a two-step reaction sequence starting from (tert-butyloxycarbonylsulfonyl) L-amino acid methyl esters 1-5. These compounds were synthesized by sulfamoylation of aminoester derivatives (Ala, Val, Leu, Asp, Glu) as previously described [17-19].

**Scheme 1.** General synthesis of N², N⁵ cyclosulfamides

Reagents and conditions: (a) Chloroethanol (1 equiv.), PPh₃ (1 equiv.), DEAD (1 equiv.), THF; (b) K₂CO₃ (1.5 equiv.), DMSO.
In these Boc-sulfamides 1-5, the Boc (t-butyloxycarbonyl) group increases the acidity of the adjacent NH group and allows an expedient regiospecific alkylation under Mitsunobu conditions [20-21] using chloroethanol, which provides the N-substituted Boc–sulfamides 1a-5a in good yields. The cyclization reaction of these N,N'-sulfamides 1a-5a under basic conditions in DMSO gives N2,N5-substituted cyclosulfamides 1b-5b in satisfactory yields.

Selective cleavage of the t-butyloxycarbonyl protective group with trifluoroacetic acid gives compounds 1c-5c in good yield (Scheme 2). N2,N5-Cyclosulfamides 1d-5d were readily prepared in quantitative yield from the cyclosulfamides 1e-5e by treatment with propionyl chloride in the presence of triethylamine. These compounds can be used in asymmetric aldol reactions. Also, attempts to incorporate the amino acid moiety employing the Mitsunobu reaction using an α-hydroxy ester (L(-)ethyl lactate) allowed us to obtain two constrained dipeptidal cyclic sulfamides 1e-2e in moderate yields with inversion of the configuration.

**Scheme 2.** Preparation of constained dipeptide cyclic sulfamides

\[
\begin{align*}
1b-5b & \xrightarrow{a} 1c-5c \\
1b-5b & \xrightarrow{b} 1d-5d \\
1b-5b & \xrightarrow{c} 1e-2e
\end{align*}
\]

*Reagents and conditions:* (a) TFA, CH2Cl2; (b) propionyl chloride (1 equiv.), TEA (1 equiv.), CH2Cl2; (c) (L)-(-) ethyl lactate (1 equiv.), PPh3 (1 equiv.), DEAD (1 equiv.), THF.

The structures of all compounds were unambiguously confirmed by the usual spectroscopic methods: 1H- and 13C-NMR spectroscopy, mass spectrometry and IR spectra.

**Biological Activity**

The bacterial strains used in this study were *Staphylococcus aureus* and *Escherichia coli* species. They were isolated from an aquatic medium, followed by successive isolations carried out periodically in specific media in order to obtain strains as pure as possible. The solid media of MacConkey and Chapman have been used for *Escherichia coli* and *Staphylococcus aureus*, respectively. Microscopic study, after Gram coloration, was carried out after incubation at 37°C for 24 hours. The biochemical characteristics of each strain have been determined using a classic biochemical gallery. Finally, the pathogenic power of *Staphylococcus aureus* has been confirmed by showing that the coagulase of this strain was hemolytic, *in vitro*, towards rabbit or human plasma.
In vitro evaluation of the bacterial sensitivity of the strains to cyclosulfamides 4a and 4d:

To draw the antibiogram, the dilution in a liquid medium method was chosen. It is based on putting inoculums of each studied strain in contact with increasing concentrations of the cyclosulfamides 4b and 4d. In a glucose medium, each bacterial inoculum (100 µL per suspension) was distributed in a series of tubes (macro-dilution method) containing increasing sulfamide concentrations [22]. The bacterial inoculum corresponding to the two studied strains, was previously prepared from a colony that was collected from a solid medium and then put in suspension in a glucose medium for 18 hours at 37°C. After the incubation of the whole tubes at 37°C for 24 hours, the MIC (minimal inhibited concentration) of each of the two cyclosulfamides with respect to each strain (Escherichia coli and/or Staphylococcus aureus) was measured as indicated by the tube that contained the lower concentration of the product and where no apparent bacterial growth is noticed. The results of the in vitro evaluation of the sensitivity of the bacteria Escherichia coli and Staphylococcus aureus towards cyclosulfamides 4b and 4d are presented in Tables 1 and 2, respectively.

**Table 1.** Strain sensitivity towards cyclosulfamide 4b

| µg/mL | 2   | 3   | 5   | 8   | 10  | 15  | 20  | 30  | 40  | 50  | 80  | 100 |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| strain | E. coli | +   | +   | +   | MIC | -   | -   | -   | -   | -   | -   | -   |
|        | S. aureus | +   | +   | +   | +   | +   | +   | +   | +   | +   | +   | +   |

**Table 2.** Strain sensitivity towards cyclosulfamide 4d

| µg/mL | 2   | 3   | 5   | 8   | 10  | 15  | 20  | 30  | 40  | 50  | 80  | 100 |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| strain | E. coli | +   | MIC | -   | -   | -   | -   | -   | -   | -   | -   | -   |
|        | S. aureus | +   | +   | +   | +   | +   | +   | +   | +   | +   | +   | +   |

No inhibitory effect on the growth of the Staphylococcus aureus strain was observed in the presence of cyclosulfamide 4b. The cyclosulfamide 4d, also tested in this study, similarly showed no significant antimicrobial activity towards S. aureus. It is therefore clear that this species is resistant to these particular compounds. In contrast, however, a significant bacteriostatic effect has been observed towards Escherichia coli, with no growth being observed in tubes containing sulfamide concentrations.
of 4b equal or greater than 8 µg/mL, while cyclosulfamide 4d also showed a marked antimicrobial activity with regards to *Escherichia coli* and a MIC of 3µg/mL was obtained for this molecule.

**Conclusions**

We have established a new synthetic strategy to prepare peptidic structures constrained with a cyclosulfamide moiety. The \(N^2,N^3\)-unsymmetric cyclic sulfamides can be prepared in three steps (alkylation, cyclization, deprotection). We have also demonstrated the useful application of these cyclic sulfamides in the preparation of pseudopeptides. The preliminary results of antimicrobial activity are encouraging. Further biological evaluation of the resulting compounds and their incorporation into biomolecule analogues are currently in progress.

**Acknowledgements**

This work was partially supported by the National Agency for Research in Health (ANDRS, Project N°05/05/00039), CNEPRU Project E2301/02/04 and Applied Organic Chemistry Laboratory (F.N.R. 2000) National Research Fund (Algerian Research Ministry, MERS). Fruitful discussions with Ms. Hadjira Mesbah (Faculty of Sciences) are greatly appreciated.

**Experimental**

**General**

All commercial chemicals and solvents were used as received. Melting points were determined in open tubes on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer. Microanalyses were performed in the Microanalysis Laboratory of ENSCM (Montpellier). \(^1\)H and \(^13\)C- Nuclear Magnetic Resonance spectra were determined on a Brüker AC 250 spectrometer. Chemical shifts are recorded in ppm (δ) and coupling constants in Hertz, relative to tetramethydsilane used as internal standard. Multiplicity is indicated as s (singlet), d (doublet), q (quadruplet), m (multiplet) and combinations of these signals. Fast-atom bombardment mass spectra (FAB) were recorded in positive or negative mode with glycerol (G), thioglycerol (GT), or 3-nitrobenzyl alcohol (NOBA) as matrix. Optical rotations for solutions in CHCl\(_3\) were measured with a POLAX model 2L digital polarimeter. All reactions were monitored by Thin Layer Chromatography (TLC) on silica gel Merck 60 F\(_{254}\) precoated aluminium plates, developed by spraying with ninhydrin solution. Column chromatography was performed using silica gel 60 (230-400 mesh).

**General synthetic procedure for carbamoylation–sulfamoylation:**

A solution of N-chlorosulfonyl tert-butylcarbamate (0.05 mol) was prepared by addition of tert-butanol (4.8 mL in 50 mL of dried dichloromethane) into a solution of CSI (7.1 g in the same solvent). The resulting solution of Boc-sulfamoyl chloride (25 mL) and triethylamine (17.40 g, 17.1 mL, 85 mmol) in dichloromethane (100 mL) was added into a suspension of amino ester (0.05 mol) in the same solvent (120 mL) at 0°C. The reaction was complete in 45 minutes. The reaction mixture was then
diluted with dichloromethane (100 mL) and washed with two portions of 0.1 N HCl solution. The organic layer was dried (Na₂SO₄) and concentrated in vacuo to give the crude product, which was purified by column chromatography eluting with dichloromethane to give compounds 1-5 in 75-80% yield. The synthesis by this general method of compounds 1-4 from CSI, tert-butyl alcohol and the methyl esters of the amino acids L-alanine, L-valine, L-leucine and L-aspartic acid was previously described [18-19].

(S)-Dimethyl [N-(N-tertiobutoxycarbonyl)-sulfamoyl] glutamate (5). Yield=76%; TLC: Rₓ=0.34 (CHCl₃-MeOH 9:1); m.p=105-106°C; [α]D =+17 (c=1; MeOH). IR (KBr) ν cm⁻¹: 1744, 1706 (C=O), 1380 and 1160 (SO₂), 3305 and 3353 (NH). ¹H-NMR (CDCl₃) δ ppm: 7.72 (s, 1H), 5.55 (d, J=8.4 Hz, 1H), 4.42 (m, 1H), 3.72-3.80 (2s, 6H), 3.00 (ddd, J=16.5, 6.4, 6.4 Hz, 2H), 3.20 (ddd, J=16.5, 6.4, 6.4 Hz, 2H), 2.20 (m, 2H), 1.50 (s, 9H); ¹³C-NMR (CDCl₃) δ ppm: 173, 171, 151, 85, 56, 53, 52, 48, 41, 29, 28, 27; M.S: (NOBA, FAB<0): 353 [M-H]⁻, 253, 707. M=354; Anal. Calcd. for C₁₂H₂₂N₂O₈S: C, 40.67; H, 6.21; N, 7.90; S, 9.03; found C,40.73; H, 6.24; N, 7.94; S, 8.92.

General procedure for the synthesis of N-Boc, N’-(2-chloroalkyl) sulfamides 1a-5a

A solution of N-tert-butoxycarbonylsulfamoylamino esters 1-5 (30 mmol), triphenyl-phosphine (7.6 g) and chloroethanol (2.4g; 2 mL) in THF (25 mL) was added dropwise (20 min, 5°C) to a solution of equimolar quantities of diethyl (diisopropyl) azodicarboxylate (5.22 g or 6.06 g) in the same solvent (25 mL). The reaction medium was stirred under an atmosphere of dry nitrogen for about 45 min. TLC revealed that the substituted compound formed is less polar than its precursor (UV, ninhydrin). Oxydoreduction compounds were removed by filtration after precipitation into diethyl ether. The filtrate was concentrated and the crude residue was purified by column chromatography eluting with dichloromethane. Substituted compounds 1a-5a were recovered in 65-75% yield.

(S) Methyl [N,N’-tert-butoxycarbonyl, N’-chloroethyl)sulfamoyl] alaninate (1a). Yield=65%; TLC: Rₓ=0.52 (CHCl₃); m.p.=88-90 °C; [α]D =-17 (c=1, MeOH); IR (KBr) ν cm⁻¹: 1744, 1706 (C=O), 1380 and 1160 (SO₂), 3305 (NH). ¹H-NMR (CDCl₃) δ ppm: 5.55 (d, J=8.4 Hz, 1H), 4.42 (m, 1H), 3.70 (s, 3H), 3.65 (t, J=6.8 Hz, 2H), 3.95 (t, J=6.8 Hz, 2H), 1.50 (s, 9H ), 1.30 (d, J=7.2 Hz, 3H); ¹³C-NMR (CDCl₃) δ ppm: 170, 150, 84, 54, 52 49, 29, 27, 25; M.S: (NOBA, FAB<0): 343 [M-H]⁻, 243, 687. M=344-346; Anal. Calcd. for C₁₁H₂₁N₂O₆SCl: C, 38.31; H, 6.09; N, 8.12; S, 9.28; found: C,38.33; H, 6.09; N, 8.09; S, 9.22.

(S) Methyl [N-(N’-tert-butoxycarbonyl, N’-chloroethyl)sulfamoyl] valinate (2a). Yield=68%; TLC: Rₓ=0.65 (CHCl₃); m.p.=60-62 °C; [α]D =-9 (c=1; MeOH); IR (KBr) ν cm⁻¹: 1730, 1700 (C=O), 1390 and 1160 (SO₂), 3310 (NH). ¹H-NMR (CDCl₃) δ ppm: 5.80 (d, J=8.42 Hz, 1H), 3.95 (t, J=6.8 Hz, 2H), 3.87 (m, 1H), 3.68 (s, 3H), 3.65 (t, J=6.8 Hz, 2H), 2.10 (m, 1H ), 1.52 (s, 9H ), 0.98 (2d, J=6.9 Hz, 6H, 2CH₃); ¹³C-NMR (CDCl₃) δ ppm: 172, 152, 85.55, 52, 48, 41, 28, 27, 22; M.S: (NOBA, FAB>0): 373 [M+H]⁺, 273, 747. M=372-274; Anal. Calcd. for C₁₃H₂₅N₂O₆SCl: C, 41.88; H, 6.71; N, 7.51; S, 8.59; found: C, 41.93; H, 6.74; N, 7.46; S, 8.51.
(S) Methyl [N-(N’-tert-butyloxycarbonyl, N’-chloroethyl)-sulfamoyl] leucinate (3a). Yield=75%; TLC: Rf =0.60 (CHCl3); m.p.=67-69°C; [α]D=−23 (c=1; MeOH); IR (KBr) v cm−1: 1740, 1712 (C=O), 1390 and 1160 (SO2), 3267 (NH); 1H-NMR (CDCl3) δ ppm: 5.80 (d, J=8.8 Hz, 1H), 3.95 (t, J=6.8 Hz, 2H), 3.87 (q, J=6.8 Hz, 1H), 3.68 (s, 3H), 3.65 (t, J=6.8 Hz, 2H), 1.87 (m, 2H), 1.55 (s, 9H), 1.48 (m, 1H), 0.98-0.88 (2d, J=3.9 Hz, 6H); 13C-NMR (CDCl3) δ ppm: 172, 152, 85, 56, 53, 48, 43, 41, 28, 25, 24, 22; M.S: (NOBA, FAB>0): 387 [M+H]+, 287, 773. M=386-388; Anal. Calcd. for C14H27N2O6SCl: C, 43.46; H, 6.98; N, 7.24; S, 8.28; found: C, 43.49; H, 6.94; N, 7.20; S, 8.21.

(S) Methyl [N-(N’-tert-butyloxycarbonyl, N’-chloroethyl)-sulfamoyl] aspartate (4a). Yield=70%; TLC: Rf =0.67 (CHCl3); oil; [α]D=−33 (c=1; MeOH); IR (KBr) ν cm−1: 1755, 1715 (C=O) 1370 and 1130 (SO2), 3269 (NH); 1H-NMR (CDCl3) δ ppm: 5.85 (d, J=8.4 Hz, 1H), 4.30 (q, J=8.4 Hz, 1H), 3.90 (t, J=6.7 Hz, 2H), 3.70-3.80 (2s, 6H), 3.68 (t, J=6.7 Hz, 2H), 3.50 (2dd, J= 4.1, 8.4 Hz, 2H), 1.50 (s, 9H); 13C-NMR (CDCl3) δ ppm: 171, 170, 150, 85, 55, 51, 52, 49, 42, 28, 27; M.S: (NOBA, FAB>0): 407 [M+H]+, 307, 805. M=406-404; Anal. Calcd. for C13H23N2O8SCl: C,38.75; H, 5.71; N, 6.95; S, 7.95; found: C, 38.73; H, 5.74; N, 6.94; S, 7.92.

(S) Methyl [N-(N’-tert-butyloxycarbonyl, N’-chloroethyl)-sulfamoyl] glutamate (5a). Yield=72%; TLC: Rf =0.65 (CHCl3); oil; [α]D=−21 (c=1; MeOH); IR (KBr) ν cm−1: 1746, 1715 (C=O) 1395 and 1156 (SO2), 3310 (NH); 1H-NMR (CDCl3) δ ppm: 6.10 (d, J=8.5 Hz, 1H), 4.30 (m, 1H), 3.90 (t, J=6.7 Hz, 2H), 3.68 (t, J=6.9 Hz 2H), 2.48 (m, 2H), 2.10 (m, 2H), 1.50 (s, 9H); 13C-NMR (CDCl3) δ ppm: 173, 171, 151, 85, 56, 53, 52, 48, 41, 29, 28, 27; M.S: (NOBA, FAB>0): 417 [M+H]+, 317, 833. M=416-418; Anal. Calcd. for C14H25N2O8SCl: C, 40.33; H, 6.02; N, 6.72; S, 7.68; found: C, 40.42; H, 6.04; N,6.75; S, 7.62.

General procedure for preparation of N-Boc-N-substituted)-1,2,5-thiadiazolidine 1,1-dioxides 1b-5b.

Cyclization with K2CO3 in DMSO

The 2-chloroalkyl compounds (10 mmol) were dissolved in dimethysulfoxide (DMSO) and anhydrous K2CO3 (1.5 equiv.) was added in one portion. The resulting mixture was stirred at room temperature for 8 h, diluted with dichloromethane (200 mL) and acidified with 5% HCl. The organic layer was washed with water, dried (Na2SO4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel. Recrystallization of the crude product from CH2Cl2-petroleum ether (1:5) afforded the pure expected cyclosulfamides 1b-5b in 82-92% yields.

(N2-(2’S)-Propionic acid methyl ester, N5-tert-butyloxycarbonyl)-1,2,5-thiadiazolidine 1,1-dioxide (1b). Yield=86%; TLC: Rf =0.58 (CHCl3); Mp=132-134°C; [α]D=−34. (c=1; MeOH); IR (KBr) ν cm−1: 1746, 1715 (C=O), 1395 and 1156 (SO2), 3310 (NH); 1H-NMR (CDCl3) δ ppm: 4.15 (q, J=7.8 Hz, 1H), 3.80 (t, J=6.4 Hz 2H), 3.70 (s, 3H), 3.65 (t, J=6.4 Hz, 2H), 1.50 (d, J=7.8 Hz, 1H), 1.52 (s, 9H); 13C-NMR (CDCl3 δ ppm: 172, 150, 84, 56, 52, 43, 39, 28, 27; M.S: (NOBA, FAB<0): 307 [M-H]−, 207; M=308; Anal. Calcd. for C11H20N2O6S: C, 42.85; H, 6.49; N, 9.09; S, 10.39; found: C, 42.83; H, 6.44; N, 9.04; S, 10.32.
(N\(^2\)-(2'S)-3'-methylbutyric acid methyl ester, N\(^5\)-tert-butyloxycarbonyl)-1,2,5-thiadiazolidine-1,1-dioxide (2b). Yield=90%; TLC: R\(_f\) =0.60 (CHCl\(_3\)); m.p.=154-155° C; [\(\alpha\)]\(_D\) =-38 (c=1; MeOH); IR (KBr) \(\nu\) cm\(^{-1}\): 1745, 1718 (C=O), 1390 and 1160 (SO\(_2\)); \(^1\)H-NMR (CDCl\(_3\) \(\delta\) ppm: 4.15 (d, J=7.2 Hz, 1H), 3.95 (t, J=6.4 Hz, 2H), 3.80 (t, J=6.4 Hz, 2H), 3.70 (s, 3H), 2.20 (m, 1H), 1.57 (s, 9H), 1.30 (d, J= 7.2 Hz, 3H), 0.98 (2d, J=6.9 Hz, 6H); \(^1\)C-NMR (CDCl\(_3\) \(\delta\) ppm: 172, 149, 84, 56, 53, 43, 39, 28, 26, 23, 22; M.S: (NOBA, FAB>0): 337 [M+H] \(^+\), 237; M=336; Anal. Calcd. for C\(_{13}\)H\(_{24}\)N\(_2\)O\(_6\)S: C, 46.43; H, 7.14; N, 8.33; S, 9.52; found: C, 46.48; H, 7.17; N, 8.34; S, 9.44.

(N\(^2\)-(2'S)-4'-Methylpentanoic acid methyl ester, N\(^5\)-tert-butyloxycarbonyl)-1,2,5-thiadiazolidine-1,1-dioxide (3b). Yield= 87%; TLC: R \(_f\) =0.58 (CHCl\(_3\)); m.p.=138-139° C; [\(\alpha\)]\(_D\) =-53 (c=1; MeOH) ; IR (KBr) \(\nu\) cm\(^{-1}\): 1747, 1728 (C=O), 1360 and 1120 (SO\(_2\) ); \(^1\)H-NMR (CDCl\(_3\) \(\delta\) ppm: 4.30 (t, J=8.4 Hz), 3.95 (t, J=6.4 Hz, 2H), 3.72 (s, 3H), 3.55 (t, J=6.4 Hz, 2H), 1.55-1.65 (m, 3H), 1.51 (s, 9H), 0.95-1.00 (2d, J=6.9 Hz, 6H) ; \(^1\)C-NMR (CDCl\(_3\) \(\delta\) ppm: 171, 149, 86, 54, 53, 43, 39, 37, 28, 25, 23, 21 ; M.S: (NOBA, FAB>0): 351 [M+H] \(^+\), 251 ; M=350; Anal. Calcd. for C\(_{14}\)H\(_{26}\)N\(_2\)O\(_6\)S: C, 48.00; H, 7.43; N, 8.00; S, 9.14; found: C, 48.07; H, 7.48; N, 7.94; S, 9.07.

(N\(^2\)-(2'S)-Bis(1',3'-methoxycarbonyl)ethyl),N\(^5\)-tert-butyloxycarbonyl)-1,2,5-thiadiazolidine-1,1-dioxide (4b). Yield=82%; R \(_f\) =0.61(CHCl\(_3\)); oil; [\(\alpha\)]\(_D\) =+38 (c=1; MeOH); IR (KBr) \(\nu\) cm\(^{-1}\): 1754, 1751, 1710 (C=O) 1390 and 1150 (SO\(_2\)); \(^1\)H-NMR (CDCl\(_3\) \(\delta\) ppm: 4.30 (m, 1H), 3.70-3.80 (2s, 6H), 3.95 (t, J=6,4 Hz), 3.55 (t, J=6.4 Hz, 2H), 3.50 ( ddd, J=17.2, 7.1, 4.5 Hz, 2H), 1,50 (s, 9H); \(^1\)C-NMR (CDCl\(_3\) \(\delta\) ppm: 177, 171, 150, 85, 57 53, 52, 43, 39, 28, 25; M.S: (NOBA, FAB>0): 367 [M+H] \(^+\), 267; M=366; Anal. Calcd. for C\(_{13}\)H\(_{22}\)N\(_2\)O\(_8\)S : C, 42.62; H, 6.01; N, 7.65; S, 8.74; found : C, 42.63; H, 6.04; N, 7.69; S, 8.69.

Deprotection

A solution of trifluoroacetic acid (50% in dried dichloromethane; 3 equiv) was added dropwise into a stirred solution of N,N'-substituted cyclosulfamides 1b-5b (20 mmol) in dried dichloromethane (15 mL) at 0°C. The reaction medium was stirred during two hours, concentrated under reduced pressure and coevaporated with diethyl ether. The residue was purified by flash chromatography. Elution with CH\(_2\)Cl\(_2\)-MeOH (95:5) gave deprotected cyclic sulfamides 1c-5c in 85%-90% yield.

\(N\(^2\)-(2'S)-(Propionic acid methyl ester) 1,2,5-thiadiazolidine 1,1-dioxide (1c). Yield=90%; TLC: R\(_f\) =0.45 (CHCl\(_3\)); m.p.=124-125° C; [\(\alpha\)]\(_D\) =-34. (c=1; MeOH); IR (KBr) \(\nu\) cm\(^{-1}\): 1751 (C=O) 1375 and 1160 (SO\(_2\)), 3345 (NH); \(^1\)H-NMR (CDCl\(_3\) \(\delta\) ppm: 6.24 (t, J=6.7 Hz, 1H), 4.15 (q, 1H, J=7,8 Hz, 1H),
To a stirring solution of N-substituted cyclosulfamide 1c-5c (20 mmol), in dichloromethane (50 mL) was added triethylamine (1.1 equiv., 22 mmol, 2.22 g, 1.60 mL), and catalytic quantities of dimethylaminopyridine (DMAP). Propionyl chloride (1.5 equiv., 30 mmol, 2.41 g, 2.57 mL) diluted in the same solvent (15 mL) was added slowly to the resulting solution. When the addition was completed, the reaction mixture was stirred under an atmosphere of dry nitrogen. TLC reveals the formation of a substituted compound less polar than its precursor. The reaction mixture was concentrated in vacuo. The residue diluted with dichloromethane (50 mL), acidified with 0.1 N HCl solution and washed with water. The organic layer was dried with (Na2SO4) and concentrated under
reduced pressure to give the crude product. The residue was purified on silica gel by column chromatography eluting with dichloromethane to give the N², N⁵ substituted cyclosulfamides 1d-5d in 75-90% yields.

\[N²-(2'S')-(propionic acid methyl ester), N⁵-propionyl\] 1,2,5-thiadiazolidine 1,1-dioxide (1d). Yield=90%; TLC: Rf=0.59 (CHCl₃); m.p.=88-89°C; [α]D=-17 (c=1; MeOH); IR (KBr) ν cm⁻¹: 1750-1715 (C=O), 1375 and 1160 (SO₂); \(^1\)H-NMR (CDCl₃) δ ppm: 4.15 (q, J=7.8 Hz, 1H), 3.80 (t, J=6.2 Hz, 2H), 3.70 (s, 3H), 3.65 (t, J=6.7 Hz, 2H), 2.85 (q, J=7.4 Hz, 2H), 1.50 (d, 3H, J=7.8 Hz), 1.15 (t, 3H, J=7.4 Hz, 3H); \(^1^3\)C-NMR (CDCl₃) δ ppm: 172, 170, 56, 53, 41, 39, 29, 28, 12; M.S: (NOBA, FAB>0): 265 [M+H]⁺, 208; M=264; Anal. Calcd. for C₉H₁₆O₅N₂S: C, 40.91; H, 6.06; N, 10.60; S, 12.12; found: C, 40.98; H, 6.17; N, 10.65; S, 12.05.

\[N²-(2'S')-(3'-methylbutyric acid methyl ester), N⁵-propionyl\] 1,2,5-thiadiazolidine 1,1-dioxide (2d). Yield=88%; TLC: Rf=0.62 (CHCl₃); m.p.=94-95°C; [α]D=-14 (c=1; MeOH). IR (KBr) ν cm⁻¹: 1748-1712 (C=O), 1389-1163 (SO₂); \(^1\)H-NMR (CDCl₃) δ ppm: 4.15 (d, J=7.2 Hz, 1H), 3.95 (t, J=6.7 Hz, 2H), 3.8 (t, J=6.7 Hz, 2H), 2.85 (q, 2H, J=7.4 Hz, 2H), 1.30 (m, 1H), 1.16 (t, J=7.4 Hz, 3H), 0.98 (2d, J=6.9 Hz, 6H); \(^1^3\)C-NMR (CDCl₃) δ ppm: 172, 170, 56, 53, 43, 39, 26, 28, 23, 22, 13; M.S: (NOBA, FAB>0): M=373 [M+H]⁺, 174, 745; M=372; Anal. Calcd. for C₁₁H₂₀N₂O₅S; C, 45.20; H, 6.85; N, 9.59; S, 10.96; found: C, 45.23; H, 6.19; N, 9.54; S, 10.89.

\[N²-(2'S')-4'-methylpentanoic acid methyl ester), N⁵-propionyl\] 1,2,5-thiadiazolidine 1,1-dioxide (3d). Yield=85%; TLC: Rf=0.65 (CHCl₃); m.p.=106-108°C; [α]D=+54 (c=1; MeOH); IR (KBr) ν cm⁻¹: 1747-1718 (C=O), 1362 and 1125 (SO₂); \(^1\)H-NMR (CDCl₃) δ ppm: 4.10 (m, 1H), 3.92 (t, J=6.7 Hz, 2H), 3.75 (t, J=6.7 Hz, 2H), 3.72 (s, 3H), 2.85 (q, J=7.4 Hz, 2H), 1.55-1.65 (m, 12H), 1.15 (t, J=7.4 Hz, 3H), 0.98-1.00 (2d, J=6.9 Hz, 6H); \(^1^3\)C-NMR (CDCl₃) δ ppm: 175, 170, 57, 53, 41, 39, 28, 29, 25, 23, 21, 12; M.S: (NOBA, FAB>0): M=307 [M+H]⁺, 250; M=306; Anal. Calcd. for C₁₂H₂₂O₇N₂S: C, 47.06; H, 7.19; N, 9.15; S, 10.46; found: C, 47.12; H, 7.25; N, 9.08; S, 10.42.

\[N²-(2'S')-bis(1',3'-methoxycarbonylethyl), N⁵-propionyl\] 1,2,5-thiadiazolidine 1,1-dioxide (4d). Yield=80%; TLC: Rf=0.67 (CHCl₃); m.p.=106-108°C; [α]D=-87 (c=1; MeOH); IR (KBr) ν cm⁻¹: 1749, 1718 (C=O), 1362 and 1125 (SO₂); \(^1\)H-NMR (CDCl₃) δ ppm: 4.30 ( 2d, J=7.3, 4.6 Hz, 1H), 3.70-3.80 (2s, 6H), 3.85 (t, J=6.8 Hz, 2H), 3.72 (s, 3H), 3.50 (ddd, J=J=17.2, 7.3, 4.6 Hz, 2H); \(^1^3\)C-NMR (CDCl₃) δ ppm: 173, 172, 165, 57, 53, 52, 43, 40, 29, 25, 12; M.S: (NOBA, FAB>0): M=323 [M+H]⁺, 266. M=322; Anal. Calcd. for C₁₁H₁₈O₇N₂S: C, 40.99; H, 5.54; N, 8.69; S, 9.34; found: C, 41.03; H, 5.64; N, 8.80; S, 9.30.

\[N²-(2'S')-bis(1',4'-methoxycarbonylpropyl), N⁵-propionyl\] 1,2,5-thiadiazolidine 1,1-dioxide (5d). Yield=75%; TLC: Rf=0.51 (CHCl₃); m.p.=87 (c=1; MeOH); IR (KBr) ν cm⁻¹: 1745, 1738 and 1715 (C=O), 1380 and 1150 (SO₂); \(^1\)H-NMR (CDCl₃) δ ppm: 4.30 ( 2d, J=7.3, 4.6 Hz, 1H), 3.70-3.80 (2s, 6H), 3.85 (t, J=6.8 Hz, 2H), 3.60 (t, J=6.8 Hz, 2H), 3.50 (ddd, J=17.2, 7.3, 4.6 Hz, 2H); \(^1^3\)C-NMR (CDCl₃) δ ppm: 173, 172, 165, 57, 53, 52, 43, 40, 29, 25, 12; M.S: (NOBA, FAB>0): M=322 [M+H]⁺, 266. M=322; Anal. Calcd. for C₁₂H₂₂O₇N₂S: C, 42.86; H, 5.95; N, 8.33; S, 9.52; found: C, 42.92; H, 9.87; N, 8.28; S, 9.43.
Alkylation via the Mitsunobu Reaction

To a stirring solution of N-substituted cyclosulfamide 1d-2d (3.23 mmol) in THF (2 mL) was slowly added DEAD (3.23 mmol, 0.5 mL) via dropwise addition. A solution consisting of (L)-(-)-ethyl lactate (3.23 mmol, 0.37 mL) and PPh₃ (3.23 mmol, 847 mg) in THF (3 mL), was slowly transferred via cannula into the cyclosulfamide solution. The reaction medium was stirred under an atmosphere of dry nitrogen for about 45 min. TLC reveals (UV, ninhydrin) the formation of a substituted compound less polar than its precursor. Oxydoreduction compounds were removed by filtration after precipitation into diethylether. The filtrate was concentrated and the crude residue was purified by column chromatography eluting with dichloromethane. N,N'-Substituted cyclosulfamides 1e-2e were recovered in 65-75% yield.

\[ \text{[N}^2-(2S)-(\text{Methoxycarbonyl}ethyl), \ N^5-(2'R)-(\text{propionic acid ethyl ester})-1,2,5\text{-thiadiazolidine 1,1-dioxide (1e). Yield=65%; TLC: Rf=0.61 (CHCl}_3); \ m.p.=88-89^\circ \text{C}; [\alpha]_D^0=-65 (c=1; MeOH); \text{IR (KBr) } \gamma \text{ cm}^{-1}: \ 1750-1731 \ (\text{C}=\text{O}), \ 1360 \text{ and } 1152 \ (\text{SO}_2); \text{¹H-NMR (CDCl}_3) \delta \text{ ppm: 4.76 (q, J=7.3, 1H), 4.65 (q, J=7.2, 1H), 4.15 (q, J=7.2 Hz, 1H), 3.80 (t, J=6.7 Hz, 2H), 3.70 (s, 3H), 3.65 (t, J=6.7 Hz, 2H),1.44 (d, J=7.2, 3H), 1.39 (d, J=7.1 Hz, 3H), 1.28 (t, J=7.2, 3H); \text{¹C-NMR (CDCl}_3 \delta \text{ ppm: 172, 170, 56, 55, 53, 50, 41, 39, 29, 28, } 12; \text{ M.S: (NOBA, FAB>0): M}=309 \ [\text{M+H}]^+. \text{ M}=308; \text{ Anal. Calcd. for C}_{11}H_{20}N_2O_6N_2S: C, 42.86, H, 6.49, N, 9.09. S,10.03. Found: C, 40.86, H,6.13, N,9.47. S, 10.03.} \]

\[ \text{[N}^2-(2S)-(3-Methylmethoxycarbonylpropyl), \ N^5-(2'R)-\text{propionic acid ethyl ester})-1,2,5\text{-thiadiazolidine-1,1-dioxide (2e). Yield =75%; TLC: Rf =0.61 (CHCl}_3); \ m.p.=80-81^\circ \text{C}; [\alpha]_D^0= -12.0 (c=0.5, CHCl}_3); \text{IR (KBr) } \gamma \text{ cm}^{-1}: \ 1745, 1729, 1346, 1145; \text{¹H-NMR (CDCl}_3) \delta \text{ ppm: 4.70 (q, J=7.3 Hz, 1H), 4.20 (q, J=7.1 Hz, 2H), 3.90 (d, J=3.3 Hz, 1H), 3.80-3.60 (m, 4H), 3.70 (s, 3H), 2.12 (m, 1H), 1.39 (d, J=7.1 Hz, 3H), 1.26 (t, J=7.3 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H ), 0.88 (d, J=6.9 Hz,3H); \text{¹C-NMR (CDCl}_3 \delta \text{ ppm: 172, 169, 56, 55, 53, 52, 50, 41, 39, 28, 22, 21, 14; M.S: (NOBA, FAB>0): M}=337 \ [\text{M+H}]^+. \text{ M}=336; \text{ Anal. Calcd. for C}_{13}H_{24}N_2O_6S: C, 46.43; H, 7.14; N, 8.33; C, 9.52. Found: C, 46.49; H, 7.18; N, 8.34; S, 9.43.} \]

References

1. Groutas, W. C.; Kuang, R.; Venkataraman, R.; Epp, J.B.; Ruan, S.; Prakash, O. Biochemistry 1997, 36, 4739-4750.
2. Groutas, W. C.; Kuang, R.; Ruan, S.; Epp, J. B.; Venkataraman, R.; Truong, T. M. Bioorg. Med. Chem. 1998, 8, 661-671.
3. Castro, J. L.; Baker, L.; Guiblin, A. R.; Hobbs, S. C.; Jenkins, M. R.; Russel, M. G. N.; Beer, M. S.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J. J. Med. Chem. 1994, 37, 3023-3032.
4. Bäkbro, K.; Löwgren, S.; Österlund, K.; J. Atepo, J.; Unge, T.; Hultén, J.; Bonham, N. M.; Schaal, W.; Karlén, A. Hallberg, A. J. J. Med. Chem. 1997, 40, 898-902.
5. Hultén, J.; Bonham, N. M.; Nilstroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Aqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A. J. Med. Chem. 1997, 40, 885-897.
6. Schaal, W.; Kalsson, A.; Ahlsén, G.; Andersson, H. O.; Danielson, U. H.; Classon, B.; Unge, T.; Samuelsson, B.; Hultén, A.; Hallberg, A. J.; Karlén, A. J. Med. Chem. 2001, 44, 155-164.
7. (a) Lai, Z.; Gan, X.; Wei, L.; Alliston, K. R.; Yu, H.; Li, Y.H.; W. C. Groutas, W. C. *Arch. Biochem. Biophys.* 2004, 429, 191-197; (b) Groutas, W. C.; Epp, J. B.; Kuang, R.; Ruan, S.; Chong, S.L.; Venkataraman, R.; Tu, J.; He, S.; Fu, Q.; Y.H. Li.; Truong, T. M.; Vu, N. *Arch. Biochem. Biophys.* 2001, 385, 162 -169.

8. Boudjabi, S.; Dewynter, G.; Voyer, N.; Toupet, L.; Montero, J.L *Eur. J. Org. Chem.* 1999, 2275-2283.

9. M. Knollmuller, M. *Monatsh. Chem.* 1970, 101, 1443-1448.

10. Ahn, K. H.; Yoo, D. J.; Kim, J. S.; *Tetrahedron Lett.* 1992, 33, 6661-6664.

11. Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, D. J.; Klien, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* 2000, 56, 9782-9790; (b) Jun, J. H.; Dougherty, J. M.; Probst, D. A.; Jiménez, M. S.; Hanson, P. R. *Tetrahedron* 2003, 59, 8901-8912.

12. Johnson, P. D.; Jewell, S. A.; Romero, D.L. *Tetrahedron Lett.* 2003, 44, 5483-5485.

13. Regainia, Z.; Abdaoui, M.; Aouf, N.; Dewynter, G.; Montero, J. L. *Tetrahedron* 2000, 56, 381-387.

14. Regainia, Z.; Winum, J.Y.; Smain, F.T.; Toupet, L.; Aouf, N.; Montero, J. L. *Tetrahedron* 2003, 59, 6051-6056.

15. Berredjem, M.; Djebbar, H.; Regainia, Z.; Aouf, N.; G. Dewynter, G.; J.-Y. Winum, J. Y.; Montero, J. L. *Phosphorus, Sulfur Silicon* 2003, 178, 693-705.

16. Dhar, N.D.; Murthy, K. S. *Synthesis* 1986, 437-449

17. Dewynter, G.; Aouf, N.; Regainia, Z.; Montero, J.L. *Tetrahedron* 1996, 52, 993-1004.

18. Dewynter, G.; Aouf, N.; Criton, M.; Montero, J. L. *Tetrahedron* 1993, 49, 65-76.

19. Aouf, N.; Dewynter, G.; Montero, J. L. *Tetrahedron Lett.* 1991, 32, 6545-6546.

20. Mitsunobu. O. *Synthesis* 1981, 1-29.

21. Hughes, D. L. *Org. React.* 1992, 42, 335-380.

22. Laverdière, M.; Sabath, L.D. *J. Med.* 1977, 44, 73-88.

*Sample availability:* Available from the authors.

© 2005 by MDPI (http:www.mdpi.org). Reproduction is permitted for noncommercial purposes.