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Cyclosulfamides as Constraint Dipeptides: The Synthesis and Structure of Chiral Substituted 1,2,5-Thiadiazolidine 1,1-Dioxides: Evaluation of the Toxicity

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Cyclosulfamides as Constraint Dipeptides: The Synthesis and Structure of Chiral Substituted 1,2,5-Thiadiazolidine 1,1-Dioxides: Evaluation of the Toxicity

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A general synthesis for the preparation of chiral N-N′ *substituted 1,2,5-thiadiazolidine 1,1-dioxides has been developed beginning with proteogenic amino acid, sulfuryl chloride, and dibromoethane. The selected chemistry and spectral properties of these compounds are examined. Overall, routes described are applicable to the synthesis of a variety of constrained dipeptidal sulfamides representing novel peptidomimetic scaffolds.*

Keywords Amino acids; constraints peptides; cyclic sulfamides

A cyclic sulfamide (1,2,5-thiadiazolidine 1,1-dioxides) motif is used as new type of peptidic constraint to lock two consecutive amide nitrogens by a sulfonyl bridge. Peptidomimetic analogs have found wide application as bioavailable and potent mimetics of naturally occurring biologically active peptides.[1]

Major efforts have thus been devoted to the development of agonists or antagonists of these peptides that could be used as a drug with high

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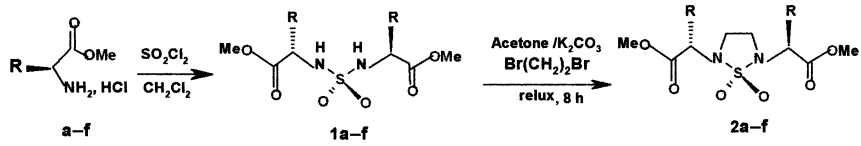
specificity and low toxicity. In the field of medicinal chemistry, a cyclic sulfamide is one of the most important structural motifs that exist in many pharmaceutically useful compounds. For example, some sulfamides, including cyclic ones, are known to be effective HIV[2] and serine protease inhibitors,[3] as both agonists and antagonists of serotonin,[4] histamine receptors,[5] and constrained di- and tripeptides.[6] Furthermore, cyclic sulfamides have also been used as effective chiral auxiliaries in asymmetric aldol reactions.[7] However, most reported methods for the synthesis of cyclic sulfamides rely on the reaction of amines with sulfuryl chloride or isocyanate chlorosulfonyl under drastic reaction conditions.[8] Our aim is to develop a new type of constraint that conserves the peptidic scaffold while inducting a rigid fold that orients the side chain of a dipeptide unit into specific spacial relationship. Recently, we reported the synthesis and the reactivity of new cyclosulfamides.[9] We now report the successful extension of this work to the synthesis of constrained dipeptide incorporation into cyclosulfamides.

To do so, we envisioned the linkage of two consecutive amide nitrogens by a dibromoethane reagent to create a cyclosulfamide dipeptide constraint (Figure 1).



SCHEME 1 ae = **a**: Ala; **b**: Val; **c**: Leu; **d**: Phe; **e**: Asp; **f**: Glu.

Three methods have been used for access to symmetric and unsymmetric cyclosulfamides. The routes to the symmetric sulfamides **2a–f** center on the coupling of four equivalents of an amino ester with sulfuryl chloride (SO_2Cl_2) (Scheme 1). Routes to unsymmetric sulfamide **6** feature the sequential coupling of an alcohol then an aminoester to

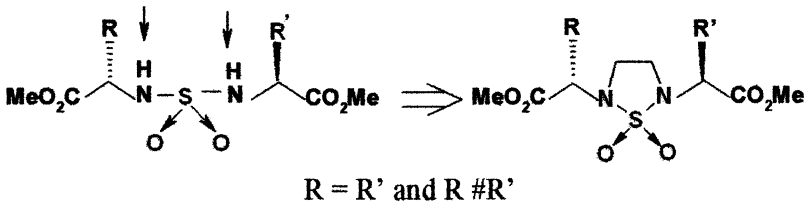
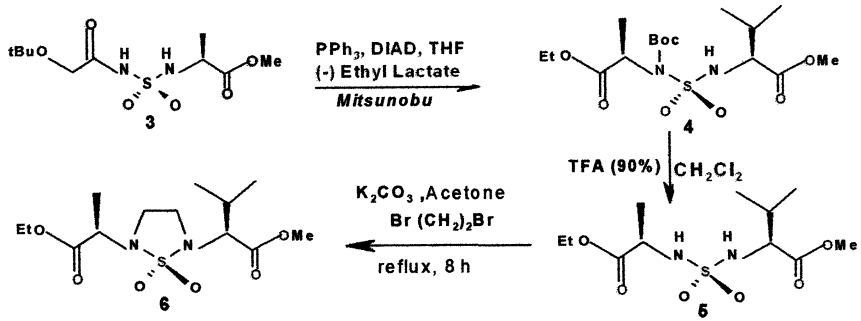


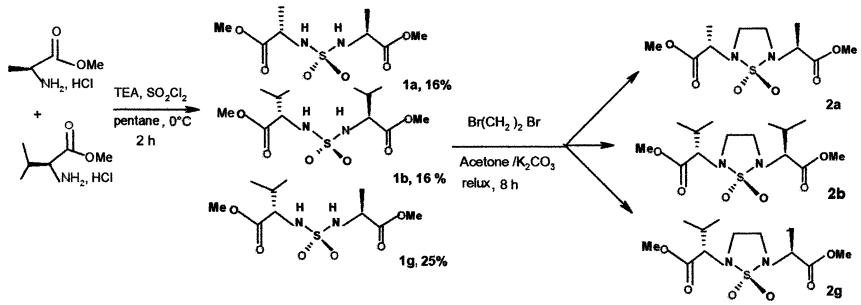
FIGURE 1 Predictable constraints induced by the insertion of cyclosulfamide in a peptidic structure.

chlorosulfonyl isocyanate ($OCNSO_2Cl$), followed by a Mitsunobu reaction (Scheme 2).



SCHEME 2

These two methods have been reviewed.[10] In addition, attempts to directly couple aminoesters (Ala,Val) derivatives with SO_2Cl_2 were successful. By this method, we could obtain simultaneously symmetric and unsymmetric sulfamides with an acceptable yield (Scheme 3).



SCHEME 3

RESULTS AND DISCUSION

The way to the amino-ester derived C2-symmetric sulfamides **1a–f** is outlined in Scheme 1. The symmetric sulfamides **1a–f** were prepared in 75–85% yields by the treatment of 4 equivalents of α-amino esters with sulfuryl chloride in pentane or dichloromethane. It was found that the use of 2 equiv of α-amino ester as base to neutralize the liberated HCl gave a product superior in purity to that obtained by a prior generation of a pyridine-sulfuryl chloride adduct followed by the treatment with aminoesters **a–f**. The treatment of *N*,*N*′-disubstituted sulfamides compounds **1a–f** in acetone with a large excess of 1,2-dibromoethane under basic conditions (potassium carbonate K_2CO_3) and reflux gave symmetric cyclosulfamides **2a–f** in excellent yields (Scheme 1).

Unsymmetric cyclic sulfamides have been shown to be HIV protease inhibitors.[11]

The cyclic unsymmetric sulfamide **6** can be prepared in four steps starting from a sulfonyl carbamate to differentate its two nucleophilic N-H sites. In this route, we utilize the pKa difference of the sulfonyl carbamate N-H and sulfamide N-H in a selective Mitsunobu/deprotection sequence first developed by our group[12] and later exploited by others.[13] Thus, sulfonyl carbamate **3** is utilized in a regioselective Mitsunobu reaction[14] to generate, after deprotection, the unsymmetric sulfamide **5** dipeptidal scaffold in good yield (Scheme 2).

The cyclization was carried out under basic conditions with dibromoethane, which produces the unsymmetric *N*,*N*′ substituted cyclosulfamide **6**.

In this work, we developed also a new and efficient method in one step for access to unsymmetric and symmetric sufamides. This strategy utilizes two amino ester (Valine, Alanine) derivatives, which were condensed with sulfuryl chloride in triethylamine/pentane or dichloromethane (**1a, 1b, 1g**) as outlined in Scheme 3.

The unsymmetric and symmetric sulfamide Alanine and Valine derivatives (**1a**, **1b**, **1g**) can be prepared in one steep starting from two aminoester chlorhydrates (Ala, Val) simultaneously. In addition, attempts to directly couple amino esters (Ala, Val) with SO_2Cl_2 in pentane at 0°C for 2 h were successful. By this method, we have obtained three compounds: two symmetric sulfamides (Ala, Val) derivatives **1a**, **1b** in a 16% yield and the mixed sulfamide **1g** in a 25% yield. TLC reveals (ninhydrin) unsymmetric sulfamide formation. This latter is more polar than its analogue symmetrical descended from the Valine and is less polar than that coming from Alanine. This method has the advantage to lead in a single step to both symmetric and unsymmetric sulfamides. The crude residue was separated by column chromatography eluted with dichloromethane. The products were obtained in acceptable yields.

Structures of all compounds were unambiguously confirmed by usual spectroscopic methods: IR, ^{1}H NMR, and mass spectrometry. The *N*-*N*′-sulfonyl bis-L-aminoesters **1a–g** were characterized by the presence in IR spectra of bands at 3280 ± 20 cm^{-1} (NH) and by an intense absorption at 1730 ± 10 cm^{-1} for the carbonyl group. NH appeared in the NMR spectra in the form of a doublet at 5 ± 1 ppm. This signal disappears in cyclized compounds and shows a signal for ethylene protons at 3.5–4 ppm. For the resulting compounds containing the five-membered ring **2a–g**, IR spectra showed bands at 1730 ± 10 cm^{-1} (C=O) and near 1350 and 1185 cm^{-1} (SO_2).

For the compounds (**4–6**), the disappearance of the (C=O) absorption and (NH) bands in IR confirm the removal the Boc group and the cy-

clization. Deprotection and cyclization were equally followed in NMR by the dissapearance of the signal of the *ter*-butyl and NH protons.

Evaluation of Toxicity of Studied Molecules on the Respiratory Metabolism of Living Organisms: *The protists cilia*

The toxicity of synthesized molecules was determined by the respiratory kinetics test.[15] The microorganism used in the present investigation was an unicellular biflagellar algae (*Tetraselmis suecica*) whose energizing features are identical to that of mammal cells. The used protists were provided from cultures at an exponential phase of growth and were kept at 20°C under continuous light. A polarographic method was used to estimate to the respiratory activity of protozoan via an electrode Hansatech type. Sulfamides were chosen as molecules under the following conditions: control cells (in water), control-aceton (in order to dissolve molecules **1g**, **1a**, and **1f**), cotrimoxazol (marketed Shape, used like positive control), and **1b** and **1e** molecules (dissolved in water). All molecules were tested at a 100 mM concentration. It is the aim of the present experimental investigation to evaluate the short-term toxicity of the tested molecules, and kinetics over 15 minutes were recorded. The results, thus obtained, are summarized in Figure 2.

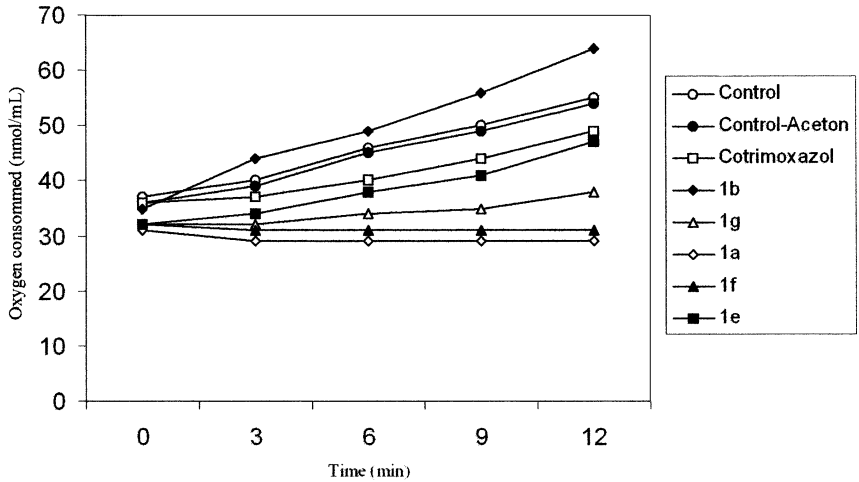


FIGURE 2 The kinetic of action of molecules on the respiratory activity of *Tetraselmis suecica*. (O): Control; (●): control-aceton, (□): treated with Cotrimoxazol; (♦): treated with **1b**; (△): treated with **1g**; (◇): treated with **1a**; (▲): treated with **1f**, and (■) treated with **1e**.

It is clear that the respiratory activity of control cells, control-aceton-cells, and cotrimoxazol treated-cells incease with time, reaching 55 nmol/mL after 15 min. The inhibition of 20% is observed after the treatment with the 1e molecule. A more important inhibition is obtained the after the treatment with the the 1 g molecule. The respiratory activity is completely stopped in the presence of both **1f** and 1a molecules. An important stimulation of the respiratory activity was observed in the presence of the **1**b molecule, which reaches about 20% in relation to the control.

In conclusion, it is evident from these results that two of the studied molecules (**1a** and **1f**) are strongly toxic, whereas the **1b** molecule seems to have small toxic effects. In the same way all other molecules seem to be rather less toxic. The **1f** and **1a** molecules could constitute excellent potentially cytotoxic agents, particilarly in antitumorous therapy.

EXPERIMENTAL SECTION

Melting points were determined in open tubes on an electrothermal digital apparatus and are uncorrected. FTIR spectra were recorded on a Perkin-Elmer spectrophotometer. Elemental analysis was determined on a Perkin-Elmer 240 C elemental analyzer, and the results were in an acceptable range. Proton Magnetic Resonances were determined with an AC 250 Bruker spectrometer (Université de Constantine Algérie). Mass spectra (electrospry method) were recorded on a Finnigan MAT TSQ-700. Optical rotations were measured in a 1-cm cell on a Polax polarimeter. TLC was performed on silica gel 60 F_{254} (Merck). Column chromatography was performed on silica gel 60. All solvents used for reactions were anhydrous.

General Procedure for the Synthesis of *N,N′*-Disubstituted Sulfamides—Symmetric Derivatives

A solution of sulfuryl chloride (10 mmol, 1.35 g) in pentane (30 mL) was added dropwise to an ice-cooled, stirred solution of (40 mmol) α-amino ester in pentane (80 mL) cooled to 0°C. The reaction mixture was stirred for 15 min, after which cold water (200 mL) was added, and the reaction mixture was stirred for additional 15 min. The mixture was extracted with of CH_2Cl_2 (200 mL); the organic phase was washed with 120 mL of 1M HCl, followed with water (120 mL), and dried with Na_2SO_4, and the solvent was removed under reduced pressure to give the crude sulfamide as a colorless, viscous gum. Aquerous fractions were combined, made basic with 30% (v/v) aqueous NaOH, and extracted with 2×60 mL of CH_2Cl_2. The combined organic extracts were

washed with 100 mL of water and dried with Na_2SO_4. The solvent was removed under reduced pressure to recover the excess of α-amino acid ester. The crude residue was purified by column chromatography eluted with dichloromethane, yield (81%) of *N,N′* bis sulfonyl aminoesters as a white powder.

N,*N′*-Sulfonyl bis L-Alanine Dimetyl ester **1a**, *N*,*N′*-Sulfonyl bis L-valine dimetyl ester **1b**, *N*,*N′*-Sulfonyl bis L-leucine dimetyl ester **1c**, and *N*,*N′*-Sulfonyl bis L-phenylalanine dimetyl ester **1d** were prepared according to the literature procedure, see ref. 10.

N,N′-Sulfonyl Bis-L-Aspatic Dimetyl Ester 1e

Yield = 78%; R_f = 0.61 in (CH_2Cl_2); m.p. = 80–82°C; $[\alpha]_D$ = +17 (c = 1, MeOH).

FTIR (KBr, ν cm^{-1}) 3294, 2966, 1735, 1360, 1164. ^{1}**H NMR** ($CDCl_3$, δ ppm): 5.90 (d, J = 8.4 Hz, 2H), 4,42 (m, 2H), 3.72–3.80 (2s, 12 H), 3.20–2.80 (ddd, J = 17.2, 4.3, 8.3 Hz, 4H).

MS (ESI): 385 [M + H]+, 407 [M + 23]+, 100%.

M = 384 ($C_{12}H_{20}$ $N_2O_{10}S$); Calcd %, C, = 37.50; H, = 5.21; N, = 7.29 found C, 37.55; H, 5.23; N, 7.23.

N,N′-Sulfonyl Bis-L-Glutamic Dimethyl Ester 1f

Yield = 80%; R_f = 0,65 in (CH_2Cl_2); m.p. = 73–75°C; $[\alpha]_D$ = +45 (c = 1, MeOH).

FTIR (KBr, ν m^{-1}), 3290, 2976, 1734, 1364, 1160. ^{1}**H NMR** ($CDCl_3$, δ ppm): 5.40 (d, J = 8.8 Hz, 2H), 4.42 (m, 2H), 3.69–3.80 (2s, 12H,), 2.50 (m, 4H), 1.80–2.30 (2m, 4H).

MS (ESI + 1): 413 [M + H]+, 435 [M + 23]+, 100%

$C_{14}H_{24}N_2O_{10}S$ M, 412 Calcd% C, 40.77; H, 5.82; N, 6.79; found % C, 40.82; H, 5.86; N, 6.71.

N-[[(1S) 1-Methoxycarbonyl-Ethyamino] Sulfonyl]-L-Valine Methyl Ester 1g

Yield = 25%; R_f = 0.62 (CH_2Cl_2); m.p. = 67–69°C; $[\alpha]_D$ = −132.3 (c = 1 MeOH).

FTIR (KBr, ν cm^{-1}): 3282, 1732, 1338, 1141. ^{1}**H NMR** ($CDCl_3$, δ ppm): 5.10 (m, 2H), 4.15 (m, 1H), 3.90 (dd, J = 4.6, 5.1 Hz, 1H), 3.70 (1s, 6H), 2.10 (m, 1H), 1.40 (d, J = 7.1 Hz, 3H), 0,98 (d, J = 6.8 Hz, 3H), 0,88 (d, J = 6.9 Hz, 3H).

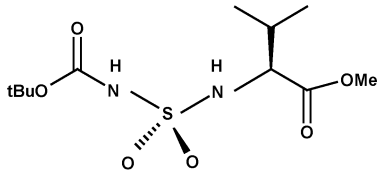
MS (ESI + 1): 413 [M + H]+, 435 [M + 23]+, 100%.

$C_{10}H_{20}$ N_2O_6S M = 296 Calcd % C, 40.54; H, 6.76; N, 9.46. Found % C, 40.59; H, 6.78; N, = 9.44.

(*Ter*-Butyloxycarbonylsulfonyl) L-valine methyl ester **3** was prepared using literature procedure; see ref. 8.

N-Ter-butyloxycarbonyl-N′[[-1-ethoxycarbonyl-ethylamino] Sulfonyl]-L-valine Methyl Ester 4

A solution of Boc-sulfamide **3** (1.00 g, 3.23 mmol) (Scheme 4), valine amino ester derivative, and diethyl azodicarboxylate (508 μL, 3.23 mmol) in THF (10 mL) was added dropwise (15 mn, 5°C) to a solution of equimolar quantities of triphenylphosphine (2.52 g) and L-ethyl lactate (847 mg, 3.23 mmol) in THF (2 mL). The reaction medium was stirred under atmosphere of dry nitrogen for about 45 min. TLC reveals the formation of a substituted compound (ninhydrine) less polar than its precuseur. Oxydoreduction compounds (Ph_3P=O, $EtCO_2$-NH-NH-CO_2Et) were removed by filtration after precipitation into diethylether. The solution was concentrated under reduced pressure to leave a crude oil. The crude residue was purified by the column chromatography eluted with dichloromethane. (5:1 hexane/EtOAc), yield 1.07g (81%) of Boc-protected sulfamide as yellow oil.



$C_{11}H_{22}0_6N_2S$ M=310 (1g, 3.23mmol]

SCHEME 4

Yield = 80%; R_f = 0.60 (CH_2Cl_2); $[\alpha]_D$ = + 68.8 (c = 1.00 $CHCl_3$).

FTIR (neat, ν m^{-1}): 3297, 1742, 1708, 1695, 1349, 1139. **^{1}H NMR** ($CDCl_3$, δ ppm): 6.15 (d, J = 7.6 Hz, 1H), 4.89 (q, J = 6.9 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H); 4.09 (dd, J = 6.9, 4.0 Hz, 1H), 3.77 (s, 3H), 2.15 (m, 1H), 1.57 (d, J = 16.9 Hz, 3H), 1.50 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0,88 (d, J = 6.9 Hz, 3H). **MS** (ESI): 409 [M − H]+, 433 [M + 23]+, 100%.

$C_{16}H_{30}N_2O_8S$ M = 410 Calcd % C, 46.83; H, 7.32; N, = 6.83. Found % C, 46.89; H, 7.38; N, 6.85.

N-[[(1R)-1-ethoxycarbonyl-ethylamino]sulfonyl]-L-valine Methyl Ester 5

A solution of trifluoroacetic acid (3 Eq., 4.17 g, 2.82 mL, 3.66 mmol) in dichloromethane (v/v) was added dropwise to the Boc-sulfamide **4**

(500 mg, 1.22 mmol) dissolved in the same solvent (50 mL). The reaction medium was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL), washed with $NaHCO_3$, and dried (Na_2SO_4). The organic layer was concentrated under reduced pressure and coevaporated with diethyl ether. Residue was recrystallized from dichloromethane; the deprotected sulfamide **5** was obtained in good yield.

Yield = 90%; R_f = 0,60 (CH_2Cl_2); m.p. = 80–81°C; $[\alpha]_D = -129.2$ (c = 0.5 $CHCl_3$).

FTIR (KBr, ν cm^{-1}): 3282, 1732, 1742, 1349, 1139. ^{1}**H NMR** ($CDCl_3$, δ ppm): 4.98 (t, J = 10.1, 8.9 Hz, 1H), 4.22 (q, J = 7.1 Hz, 1H), 4.05 (m, 1H); 3.80 (dd, J = 10.2, 4.9 Hz, 1H), 3.70 (s, 3H), 2.08 (m, 1H), 1.37 (d, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0,88 (d, J = 6.9 Hz, 3H).

MS (ESI): 333 [M + 23]+, 100%.

C_{11} H_{22} N_2O_6S M, 310 Calcd % C, 42.58; H, 7.10; N, 9.03; found % C, 42.59; H, 7.18; N, 9.04.

General Procedure for the Cyclization of Symmetric and Dissymmetric Derivatives

The *N*, *N*′-disubstituted sulfamides compounds (10 mmol) were dissolved in dry acetone, and K_2CO_3 (1.5 equiv., anhydrous) was added in one fraction. The resulting mixture was stirred at r.t. for 8 h, diluted with dichloromethane (200 mL), and acidified with 5% HCl. The organic layer was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel chromatography (eluant H_2Cl_2) to afford the cyclosulfamides **2a–g** derivatives in a 70–80% yield.

2,2′-(2S,2S′)- [2,2′-Bis-Propionic Acid Dimethyl Ester]-1,2,5-thiadiazolidine 1,1-Dioxide 2a

Yield = 78%; R_f = 0.64 (CH_2Cl_2); mp = 68–70°C; $[\alpha]_D = -132.3$ (c = 1, MeOH).

FTIR (KBr, ν cm^{-1}): 1740, 1349, 1137. ^{1}**H NMR** ($CDCl_3$, δ ppm): 4.12 (q, J = 7.1 Hz, 2H); 3.85 (m, 2H), 3.75. (s, 6H), 3.60 (m, 2H), 1.40 (d, J = 7.1 Hz, 6H).

MS (ESI): 411 [M + 23]+ 100%.

$C_{10}H_{18}$ $N_2O_6N_2S$ M, 294 Calcd % C, 40.81; H, 6.12; N, 9.52. Found % C, 40.86; H, 6.13; N, 9.47.

2,2′-(2S, 2S′)-[3,3′-Dimethyl Bis-butyric Acid Dimethyl Ester]-1,2,5-Thiadiazolidine1,1-Dioxide 2b

Yield = 75%; R_f = 0,65 (CH_2Cl_2); m.p. = 90–92; $[\alpha]_D$ = +45.3 (C g/L concentration = 1, MeOH).

FTIR (KBr, ν cm^{-1}): 1739, 1375, 1180. ^{1}**H NMR** ($CDCl_3$, δ ppm): 4.05 (d, 3.0 Hz, 2H), 3.90 (m, 2H), 3.80 (s, 6H), 3.60 (m, 2H), 2.10 (m, 2H), 0.95–1.05 (2d, J = 6.6, 6.6 Hz, 12H).

MS (ESI): 373[M + 23]+ 100%.

$C_{14}H_{26}$ N_2O_6S M = 350 Calcd % C, 48.00, H, 7.43; N, 8.00. found % C, 48.05; H, 7.47; N, 7.97.

2,2′-(2S, 2S′)-[4,4′-Dimethyl Bis-Pentanoic Acid Dimethyl Ester]-1,2,5-Thiadiazolidine 1,1dioxide 2c

Yield = 80%; R_f = 0, 61 (CH_2Cl_2); m.p. = 115–117°C; $[\alpha]_D$ = − 54.3 (c = 1, MeOH).

FTIR (KBr, ν cm^{-1}): 1740, 1375, 1180. ^{1}**H NMR** ($CDCl_3$, δ ppm): 4.10 (t, J = 5.2 Hz, 2H); 4.00 (m, 2H), 3.80 (s, 6H), 3.60 (m, 2H), 1.64 (m, 6H), 1.05–0.95 (2d, J = 6.8, 6.8 Hz, 12H).

MS (ESI): 379 [M + H]+, 401 [M + 23]+.

$C_{16}H_{30}$ N_2O_6S M = 378 Calcd % C, 50.79; H, 7.93; N, 7.40; found % C, 50.81; H, 7.96; N, 7.38.

2,2′-(2S, 2S′)-[3,3′-Diphenyl Bis-Propionic Acid Dimethyl Ester]-1,2,5-Thiadiazolidine 1,1-Dioxide 2d

Yield = 80%; R_f = 0,70 (CH_2Cl_2); m.p. = 60–62°C; $[\alpha]_D$ = − 89.3 (c = 1, MeOH).

FTIR (KBr, ν cm^{-1}): 1738, 1349, 1170. ^{1}**H NMR** ($CDCl_3$, δ ppm): 7.30–7.20 (m, 10H), 4.50 (t, J = 7.5 Hz, 2 H), 3.95 (m, 2H), 3.80 (m, 4H), 3.75 (s, 6H), 3.20–2.90 (ddd, J = 14.2, 7.8, 7.4 Hz, 4H).

MS (ESI): 447 [M + H]+, 469[M + 23]+ 100%.

$C_{22}H_{26}$ N_2O_6S M, 446 Calcd % C, 59.19; H, 5.83; N, 6.28. found % C, 59.22; H, 5.89; N, 6.24.

N,N′-Bis [2,2′-(2S,2S′)-bis (1,2-(Metoxycarbonyl) Ethyl]-1,2,5-Thiadiazolidine 1,1-Dioxide 2e

Yield = 76%; R_f = 0.65 (CH_2Cl_2); Yellow oil; $[\alpha]_D$ = − 25.3 (c = 1, MeOH).

FTIR (film, ν cm^{-1}): 1741, 1356, 1185. ^{1}**H NMR** ($CDCl_3$, δ ppm): 4.70 (t, J = 7.1 Hz, 2H), 3.75–3.70. (2s, 12H); 3.50–3.65 (m, 4H), 3.15–3.90 (ddd, J = 17.2, 7.1, 4.5 Hz, 4H).

MS (ESI): 411 [M + H]+, 433[M + 23]+ 100%.

$C_{14}H_{22}$ $N_2O_{10}S$ M = 410 Calcd % C, 40.97; H, 5.36; N, 6.83; found % C, 40.99; H, 5.39; N, 6.80.

N,N′-Bis[2,2′-(2S,2S′)-bis (1,2-(metoxycarbonyl) Propyl]-1,2,5-Thiadiazolidine1,1-dioxide 2f

Yield = 80%; R_f = 0.65 ($CHCl_3$); Yellow oil; $[\alpha]_D = -65.3$ (c = 1, MeOH).

FTIR (film, ν cm^{-1}): 1740, 1356, 1185. ^{1}**H NMR** ($CDCl_3$, δ ppm): 4.35 (2d, J = 5.3, 5.3 Hz, 2H), 3.70–3.80 (2s, 12H), 3.80–3.90 (m, 4Hcycle), 2.50 (m, 4H), 1.90–2.30 (2m, 4H).

MS (ESI + 1): 461 [M + 23]+ 100%.

$C_{16}H_{26}$ $N_2O_{10}S$ M = 438 Calcd % C, 43.83; H, 5.93; N, 6.39; found % C, 43.89; H, 5.99; N, 6.32.

N^2-[(2S)–(3-Methyl methoxycarbonyl-propyl)], *N*^{5}-[(2′S)-propionic Acid Methyl Ester]-1,2,5-thiadiazolidine 1,1-dioxide 2g

Yield = 78%; R_f = 0.62 (CH_2Cl_2); m.p. = 57–58° C; $[\alpha]_D = -129.2$ (c = 1, $CHCl_3$).

FTIR (KBr, ν cm^{-1}): 1734, 1346, 1145. ^{1}**H NMR** ($CDCl_3$, δ ppm) : 4.22 (q, J = 7.1Hz, 1H), 3.90 (d, J = 3.3 Hz, 1H); 3.75–3.70 (2s, 6H), 3.80–3.60 (m, 4H), 2.08 (m, 1H), 1.37 (d, J = 7.1 Hz, 3H), 0,98 (d, J = 6.8 Hz, 3H), 0,88 (d, J = 6.9 Hz,3H).

MS (ESI + 1): 323 [M + H]+, 345 [M + 23]+, 100%.

$C_{12}H_{22}$ N_2O_6SM = 322 Calcd% C, 47.72; H, 6.83; N, 8.69; found% C, 47.69; H, 6.88; N, 8.64.

N^2-[(2S)–(3-Methyl methoxycarbonyl-propyl)], *N*^{5}–[(2′R)-Propionic Acid Ethyl Ester]-1,2, 5-Thiadiazolidine1,1-dioxide 6

Yield = 76%; R_f = 0,60 (CH_2Cl_2); m.p. =80–81°C; $[\alpha]_D = -12.0$ (c = 0,5, $CHCl_3$).

FTIR (KBr, ν cm^{-1}): 1745, 1734, 1346, 1145. ^{1}**H NMR** ($CDCl_3$,δ 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).

MS (ESI + 1): 413 [M+H] +, 435 [M+23] +, 100%.

$C_{13}H_{24}N_2O_6S$ M = 336; Calcd% C, 46.43; H, 7.14; N, 8.33; found% C, 46.49; H, 7.18; N, 8.34.

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