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Synthesis of 1,2,5-Thiadiazolidines 1,1-dioxides (*Cyclosulfamides*) Starting from Amino Acids and Chlorosulfonyl Isocyanate

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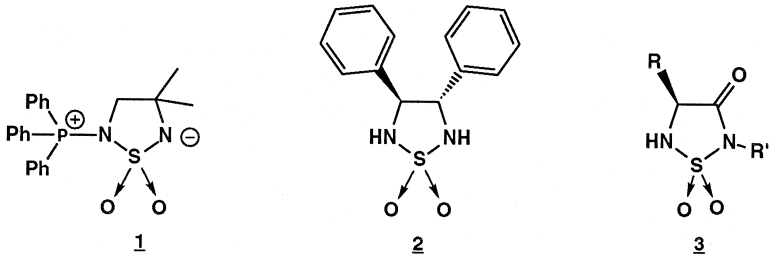
Abstract—We report here a practical access to a series of five-membered cyclosulfamides (1,2,5-thiadiazolidines 1,1-dioxides) N^2 substituted by the BOC group. These compounds are synthesized starting from chlorosulfonyl isocyanate and nitrogen mustards or amino acids. The derivatization of amino acids can lead to an alkyl group on C-4 with a well-defined configuration; in this case the N^5 position was protected by a benzyl group. These compounds are valuable tools for asymmetric synthesis. © 2000 Elsevier Science Ltd. All rights reserved.

The introduction of the sulfamido group $-NH-SO_2-NH-$ into a heterocyclic structure can lead to interesting new chemical and/or pharmacological potentialities. Thus (Fig. 1) the betaine-containing compound **1** can be used in a Mitsunobu-like reaction,[1] the chiral inductor **2** was proposed in asymmetric synthesis in connection with Oppolzer's sultame model,[2] sulfahydantoins such as **3** were developed by our group as key intermediates for the synthesis of constrained peptides,[3] and others have demonstrated their antiprotease potentialities.[4] Moreover many related syntheses of these kind of products have been reported in the last 10 years because of their pharmacological properties.[5]



1 2 3

Figure 1.

The general access described in previous work for the synthesis of the five-membered *cyclosulfamides* proceeds via the reaction of a *vic*-diamine with sulfuryl chloride or the sulfamide $H_2NSO_2NH_2$.[6] However, those approaches can be limited by drastic reaction conditions, the formation of polycondensation side products and the preparation of the diamine itself. We considered a preparation starting from natural amino acids and chlorosulfonyl isocyanate (CSI) (Fig. 2), inspired by our previously described synthesis of sulfahydantoins **3**.[7] Chlorosulfonyl isocyanate has been found to be a versatile reagent in organic synthesis[8] with a great interest in heterocyclic chemistry.[9] In this case CSI contains the required sulfonyl group and one of the nitrogens of 1,2,5-thiadiazolidine 1,1-dioxides.

We report here a convenient access to a series of such five-membered cyclosulfamides **23**–**29**, N^2 substituted by the BOC group. The derivatization of amino acids allowed the introduction of an alkyl group on C-4 with a well-defined configuration; for these compounds N^5 was protected by a benzyl group, removable by hydrogenolysis.

Keywords: chlorosulfonyl isocyanate; nitrogen mustards; amino acids; Mitsunobu reaction; cyclosulfamides; 4-substituted-1,2,5-thiadiazolidine 1,1-dioxides.

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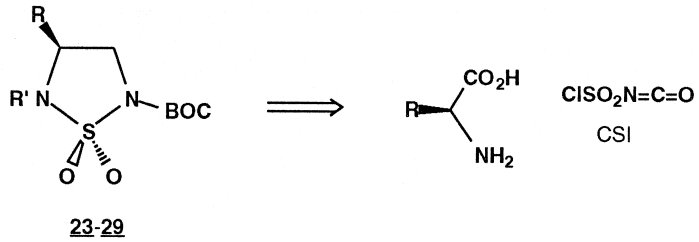


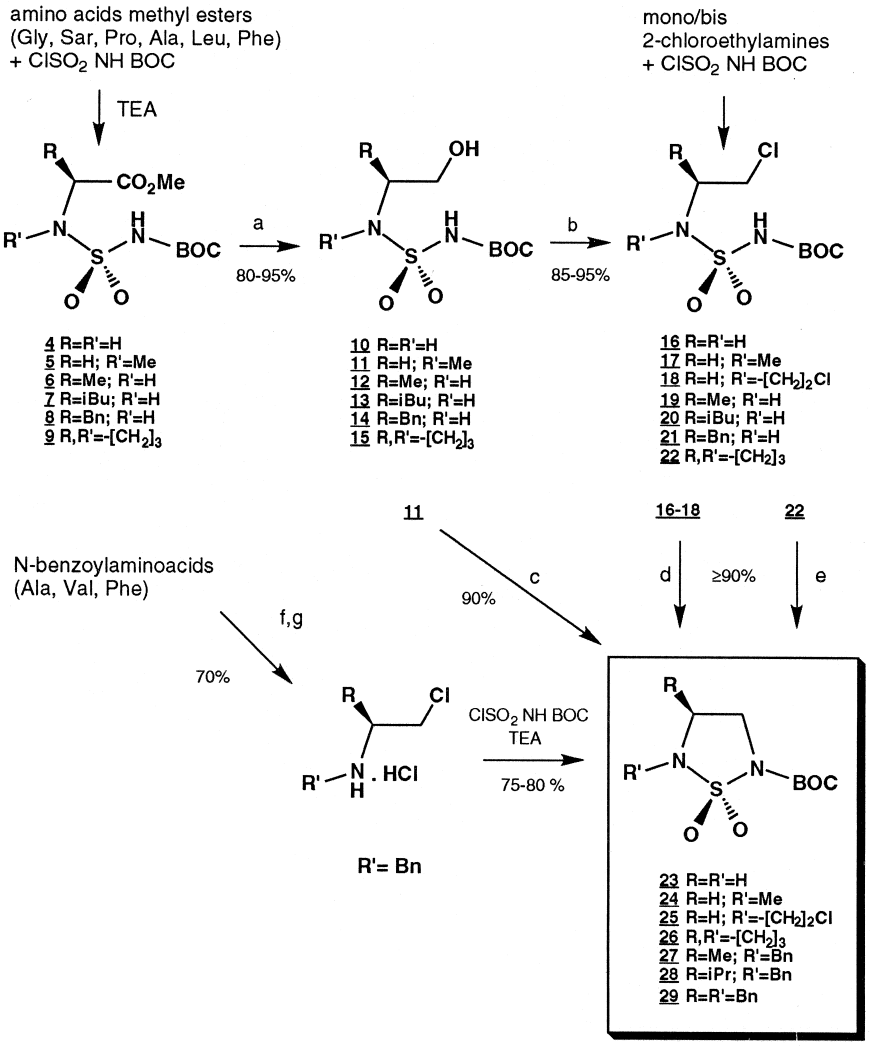
Figure 2.

Results and Discussion

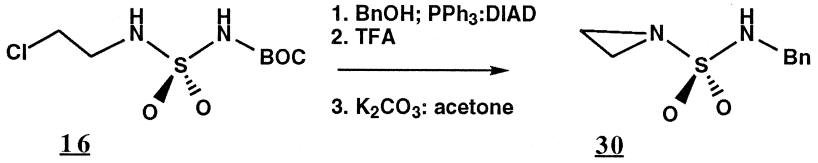
In the synthesis of sulfahydantoins **3**, starting from MeO_2C–CHR–NH–SO_2NHR' (sulfamoylaminoesters)[3,10] the 5-*exo-trig* ring closure was governed by: (1) the steric constraints around R–CHα; indeed the bulky character of R favored the cyclization, and (2) the nature of the *N*-sulfamic substituent (R′=H or alkyl); a EWG such as BOC group led only to the saponification of methyl ester by a closure–reopening mechanism. The cyclization was carried out under strongly basic conditions (NaOH:dioxane or *t*BuOK:*t*BuOH) and occurred with retention of configuration.

Starting from the same precursors, *N*-BOC-sulfamoyl-aminoacid esters **4**–**9** (Scheme 1), chemoselective reduction using potassium borohydride gave aminoalcohol BOC-sulfamates **10**–**15**; then chlorination using PPh_3:CCl_4 furnished the corresponding 2-chloroethyl derivatives in an overall 80% yield. Among them, **16** and **18** (R′=H or CH_2CH_2Cl) were directly synthesized by reaction of the corresponding mustards with BOC-sulfamoyl chloride.

Attempted cyclization of aminoalcohol BOC-sulfamates in Mitsunobu conditions[11] was only decisive for the sarcosinol derivative **11**; *cyclosulfamides* **23**–**25** were obtained in high



Scheme 1. (a) KBH_4; $MeOH/H_2O$; (b) PPh_3, CCl_4; (c) PPh_3, DIAD, THF; (d) K_2CO_3, DMSO; (e) CuBr, $CuCO_3$, DMF; (f) $LiAlH_4$, THF; (g) $SOCl_2$, CH_2Cl_2.



Scheme 2.

yield by treatment of **16**–**18** with K_2CO_3 in DMSO (or triethylamine in acetonitrile). In these series, the presence of the BOC group—activating the sulfamide nitrogen nucleophilicity—was required for a 5-*exo-tet* closure; indeed the replacement of BOC by a benzyl group directed the reaction towards the formation of sulfonylaziridines[12] by a 3-*exo-tet* cyclization (Scheme 2).

Starting from the constrained prolinol-related structure **22**, the fused-bicyclic compound **26** can be obtained following Goldberg's procedure:[13] K_2CO_3 was used as base, Cu and CuBr were added in stoichiometric amount and the reaction mixture was heated in acetonitrile. Contrary to sulfahydantoins, the formation of the related dioxothiadiazolidine was radically hindered by the presence of a bulky group on the CH* for the derivatives **19**–**21**. So we envisioned the preparation of the expected chiral cyclosulfamides starting from *N*-substituted Ala, Val, Phe. Benzoylation of amino acids, followed by reduction using $LiAlH_4$, and chlorination using thionyl chloride gave in overall 80% yield the chiral 1-substituted *N*-benzyl 2-chloroethylamine hydrochlorides. In the alkaline conditions of the sulfonylation by *N*-BOC sulfamoyl chloride (excess of triethylamine in dichloromethane), the subsequent cyclization was spontaneously carried out and gave the chiral N^1-BOC, N^5-Bn thiadiazolidine **27**–**29**. Such orthogonal protecting groups can be independently removed in appropriate conditions (40% trifluoroacetic acid in dichloromethane for the BOC group; Pd–C and ammonium formate for the benzyl group).[14]

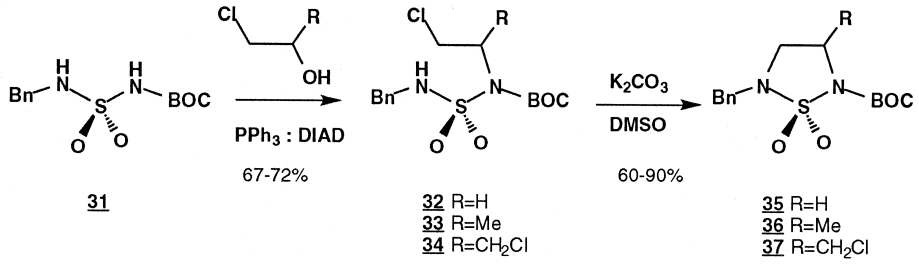
An alternative synthesis for 3-substituted regioisomers was developed starting from N^1-BOC, N^3-Bn-sulfamide **31** and selected 2-haloalcohols, by two successive alkylations (Scheme 3), leading to the derivatives **35**–**37**.

The structure of all the compounds were unambigously confirmed by usual spectroscopic methods. For the resulting compounds containing the five-membered ring, IR spectra showed bands at $1700\pm10\ cm^{-1}$ (C=O) and near 1350 and 1185 cm^{-1} (SO_2). ^1H NMR spectra of the chiral compounds showed an AB system due to the diastereotopic benzylic protons at 4.30 ppm ($\Delta\delta$=0.2 ppm, ^2J=−15.1 Hz). Interestingly, this anisochrony was more emphasized ($\Delta\delta$=0.45 ppm) for the derivatives **36** and **37**, in which the benzyl group was nevertheless more distant from the asymmetric carbon. We imputed this effect to the relative position of the benzyl and alkyl substituents: due to the sp^3 hybridization of the concerned nitrogen, both groups are located in *trans* position in the 4,5-series but can adopt a *cis* constrained position for the 3,5-derivatives.

In conclusion, the synthesis of 1,2,5-thiadiazolidines 1,1-dioxides can be easily performed starting from chlorosulfonyl isocyanate and nitrogen mustards derived from amino acids. Heterocyclic closure was performed in alkaline (or SN/redox) conditions by internal nucleophilic substitution on chloromethyl (or hydroxymethyl) group by an *N*-BOC-sulfamoyl anion. The derivatization of amino acids can lead to an alkyl group on C-4 with a well-defined configuration; for these cyclosulfamides the N^5 was substituted by a benzyl group. Accordingly, the chiral series contain two orthogonal *N*-protecting groups. In perspective, the removal of those groups (Boc and Bn) by acidic treatment and/or hydrogenolysis will furnish deprotected forms of these heterocycles. The biological evaluation of the resulting compounds, their use as tools in asymmetric synthesis and their incorporation in biomolecules analogues are currently in progress.

Experimental

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer spectrophotometer. Microanalyses were performed in the microanalysis laboratory of ENSCM (Montpellier). Proton Nuclear Magnetic Resonance was determined with an AC 250 Bruker spectrometer. Chemical shifts are expressed in parts per million, with TMS as reference. The multiplicity was indicated as: s (singlet), d (doublet), t (triplet), q (quadruplet),



Scheme 3.

m (multiplet) and combination of these signals. Fast-atom bombardment mass spectra (FAB-MS) were recorded in positive or negative mode on a JEOL DX 300 spectrometer with the G, GT, or NOBA as matrix. Optical rotations were measured in a 1 cm cell on a Perkin–Elmer polarimeter. Thin Layer Chromatography (TLC) was performed on precoated aluminum sheets of silica gel 60-F_{254} (Merck). Column chromatography was performed with silica gel 60.

Carbamoylation–sulfamoylation: general procedure

To a stirred solution of 5 mL of chlorosulfonyl isocyanate (CSI) (8.15 g, 57.6 mmol) in 100 mL of anhydrous dichloromethane at 0°C were added 57.6 mmol of absolute *tert*-butyl alcohol in the same solvent. After being stirred for 30 min, the resulting solution of BOC-sulfamoyl chloride and 24 mL of triethylamine (17.40 g, 171.85 mmol) in 100 mL of dichloromethane were added dropwise to 57.60 mmol of a suspended aminoacid ester (or 2-chloroethylamine/bis-2-chloroethylamine) hydrochloride in 120 mL of dichloromethane. The reaction temperature did not rise above 5°C. The resulting reaction solution was allowed to warm up to rt over 2 h. The reaction mixture was diluted with 100 mL of dichloromethane, washed with 0.1N HCl solution and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give the crude product. Recrystallization from CH_2Cl_2 at low temperature afforded the expected compounds in 65–75% yield.

Methyl esters of [*N*-(*N*-BOC)-sulfamoyl] amino acids. The synthesis of the compounds, starting from CSI *tert*-butyl alcohol and methyl esters of amino acids (glycine, L-alanine, L-valine, L-leucine and L-phenylalanine) has been previously reported.[10]

Methyl [*N*-(*N*-BOC)-sulfamoyl]-sarcosinate 5. Yield=65%; R_f=0.76 (CH_2Cl_2–MeOH 9:1); foam; IR (film, ν cm^{-1}): 1728, 1718 (C=O, methyl ester and *t*-butyl carbamate), 1360 and 1175 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.62 (s, 1H, exch, NHBOC), 4.14 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.04 (s, 3H, NCH_3), 1.49 (s, 9H, tBu). MS (NOBA, FAB>0): 283, $[M+H]^+$; 172. Anal ($C_9H_{18}N_2O_6S$): calcd % C 38.29; H 6.38; N 9.93; found % C 38.26; H 6.43; N 9.87.

[(*S*)(−)] Methyl [*N*-(*N*-BOC)-sulfamoyl]-prolinate 9. Yield=75%; R_f=0.58 (CH_2Cl_2–MeOH 95:5); Mp 132–134°C; $[\alpha]_D$=−9.5 (*c*=1, MeOH); IR (KBr, ν cm^{-1}): 1730, 1712 (C=O, methyl ester and *t*-butyl carbamate), 1359 and 1170 (SO_2). ^1H NMR (DMSO-d_6, δ): 7.50 (s, 1H, exch, NHBOC), 4.64 (m, 1H, C*H), 3.57 (s, 3H, OCH_3), 3.16 (m, 2H, β-CH_2), 1.90 (m, 4H, 2×CH_2), 1.46 (s, 9H, *t*Bu) MS (NOBA, FAB>0): 309, $[M+H]^+$. Anal: ($C_{11}H_{20}N_2O_6S$); calcd % C 42.86; H 6.49; N 9.09; found % C 42.99; H 6.56; N 9.03.

N-(N-BOC)-sulfamoyl]-β-aminoalcohols: general procedure[15]

Methyl BOC-sulfamoylaminoesters (13.40 mmol) in 100 mL of THF was added dropwise to a suspension of $NaBH_4$ (46 mmol) in 120 mL of THF–water (4:1, v/v) at 0°C. When the addition was complete, the reaction was allowed to warm up overnight to rt. The TLC showed the formation of a more polar compound (UV, ninhydrin). The reaction mixture was acidified slowly with HCl 5% and concentrated in vacuo. The aqueous layer was extracted with ethyl acetate (3×150 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Recrystallization of the crude product in AcOEt–hexane (1:4) or column chromatography eluted with CH_2Cl_2/MeOH (90:10) afforded analytically pure products in 80–95% yields.

[*N*-(*N*-BOC)-sulfamoyl]-glycinol 10. Yield=80%; R_f=0.17 (CH_2Cl_2–MeOH 95:5); Mp 70°C; IR (KBr, ν cm^{-1}): 3450 (OH), 3250 (NH), 1712 (C=O), 1354 and 1136 (SO_2). ^1H NMR (DMSO-d_6, δ): 10.80 (s, 1H, exch, NHBoc), 7.36 (t, 1H, *J*=5.74 Hz, exch, NH), 4.70 (s broad, 1H, exch, OH), 3.44 (m, 2H, CH_2OH), 2.90 (q, 2H, NCH_2), 1.40 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 241, $[M+H]^+$; 140. Anal ($C_7H_{16}N_2O_5S$): calcd % C 35.00; H 6.66; N 11.66; found % C 35.05; H 6.69; N 11.60.

[*N*-(*N*-BOC)-sulfamoyl] sarcosinol 11. Yield=87%; R_f=0.28 (CH_2Cl_2–MeOH 95:5); foam; IR (film, ν cm^{-1}): 3430 (OH), 3225 (NH), 1715 (C=O), 1330 and 1165 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.78 (s, 1H, exch, NHBOC), 5.50 (t, 1H, NCH_2), 3.82 (t, 2H, CH_2OH), 3.02 (s, 3H, CH_3), 1.50 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 255, $[M+H]^+$; 154. Anal ($C_8H_{18}N_2O_5S$): calcd % C 37.80; H 7.08; N 11.02; found % C 37.83; H 6.97; N 11.06.

[*N*-(*N*-BOC)-sulfamoyl] alaninol 12. Yield=89%; R_f=0.18 (CH_2Cl_2–MeOH 95:5); Mp 120–123°C; IR (KBr, ν cm^{-1}): 3500 (OH), 3300 (NH), 1705 (C=O), 1334 and 1156 (SO_2). ^1H NMR (DMSO-d_6, δ): 10.82 (s, 1H, exch, NHBOC), 7.32 (d, 1H, *J*=5.74 Hz, exch, NH), 4.72 (s broad, 1H, exch, OH), 3.38 (m, 2H, CH_2OH), 1.45 (s, 9H, *t*Bu), 1.10 (d, 1H, *J*=6.0 Hz, CH_3). MS (NOBA, FAB>0): 255, $[M+H]^+$; 232; 199; 155. Anal ($C_8H_{18}N_2O_5S$): calcd % C 37.80 H 7.08; N 11.02; found % C 35.95; H 7.18; N 10.97.

[*N*-(*N*-BOC)-sulfamoyl]-leucinol 13. Yield=86%; R_f=0.40 (CH_2Cl_2–MeOH 95:5); Mp 100–101°C; IR (KBr, ν cm^{-1}): 3450 (OH), 3255 (NH), 1708 (C=O), 1344 and 1166 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.90 (s, 1H, exch, NHBOC), 5.6 (d, 1H, exch, NH), 3.74 (m, 1H, C*H), 3.55 (m, 2H, CH_2OH), 2.41 (s broad, 1H, exch, OH), 1.76 (m, 1H, CH), 1.49 (s, 9H, *t*Bu), 1.36 (m, 2H, CH_2), 0.80 (2d, 6H, 2×CH_3). MS (NOBA, FAB>0): 297, $[M+H]^+$; 240. Anal ($C_{11}H_{24}N_2O_5S$): calcd % C 44.60 H 8.11; N 9.46; found % C 44.84; H 8.08; N 9.30.

[*N*-(*N*-BOC)-sulfamoyl]-phenylalaninol 14. Yield=95%; R_f=0.29 (CH_2Cl_2–MeOH 95:5); Mp: 140–142°C; IR (KBr, ν cm^{-1}): 3380 (OH), 3225 (NH), 1702 (C=O), 1348; 1176 (SO_2). ^1H NMR (DMSO-d_6, δ): 10.84 (s, 1H, exch, NHBOC), 7.48 (d, 1H, exch, NH), 7.29 (m, 5H, ArH), 4.75 (s, 1H, exch, OH), 3.33 (m, 3H, CH_2+C*H), 2.84–2.72 (2dd, 2H, J_{vic}=5.50 Hz and J_{gem}=−11.50 Hz, CH_2Ph), 1.43 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 331, $[M+H]^+$; 275. Anal ($C_{14}H_{22}N_2O_5S$): calcd % C 50.90 H 6.66; N 8.48; found % C 50.84; H 6.82; N 8.30.

[*N*-(*N*-BOC)-sulfamoyl]-prolinol 15. Yield=85%; R_f=0.36 (CH_2Cl_2–MeOH 95:5); Mp: 108–110°C; IR (KBr, ν cm^{-1}): 3500 (OH), 3250 (NH), 1708 (C=O), 1340 and 1154 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.65 (s, 1H, exch, NHBOC), 4.11 (s br., 1H, exch, OH), 3.86 (m, 1H, C*H), 3.64 (m, 2H, CH_2OH), 3.38 (m, 2H, CH_2), 2.20 (m, 4H, 2×CH_2), 1.48 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 281, $[M+H]^+$; 225. Anal ($C_{10}H_{20}N_2O_5S$): calcd % C 42.86; H 7.14; N 10.00; found % C 42.90; H 7.18; N 9.88.

General procedure for the synthesis of N^1-BOC,N^3-(2-chloroalkyl) sulfamides

A solution of BOC-sulfamoylaminoalcohols (5.35 mmol), triphenylphosphine (16.05 mmol) and CCl_4 (16.05 mmol) in 100 mL of anhydrous acetonitrile was refluxed for 8 h.[16] After cooling to room temperature, the solution was concentrated in vacuo. The residue was triturated with diethyl ether (3×150 mL). Triphenyl phosphine oxide which precipitates in the combined organic layers, was removed by filtration. The filtrate was concentrated and the residue purified on silica gel (CH_2Cl_2) to afford the methylene chloride derivatives in 85–95% yield.

N^1-BOC,N^3-(2-chloroethyl) sulfamide 16. Yield=85%; R_f=0.76 (CH_2Cl_2–MeOH 95:5); Mp: 132°C; IR (KBr, ν cm^{-1}): 3325 and 3250 (NH), 1705 (C=O), 1350, 1140 (SO2). ^1H NMR ($CDCl_3$, δ): 7.35 (s, 1H, exch, NHBOC), 5.65 (t, 1H, exch, NH), 3.68 (t, 2H, *J*=6.0 Hz, CH_2Cl), 3.42 (q, 2H, *J*=6.0 Hz, CH_2NH), 1.52 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 259–261, $[M+H]^+$, 158–160 $[M+H]^+$−BOC ($C_7H_{15}ClN_2O_4S$).

N^1-BOC,N^3-methyl,N^3-(2-chloroethyl) sulfamide 17. Yield=85%; R_f=0.76 (CH_2Cl_2–MeOH 95:5); Mp: 132°C; IR (KBr, ν cm^{-1}): 3325 and 3250 (NH), 1705 (C=O), 1350, 1140 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.35 (s, 1H, exch, NHBOC), 5.65 (t, 1H, exch, NH), 3.68 (t, 2H, *J*=6.0 Hz, CH_2Cl), 3.42 (q, 2H, *J*=6.0 Hz, CH_2NH), 1.52 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 273–275, $[M+H]^+$. Anal ($C_8H_{17}ClN_2O_4S$): calcd % C 35.23 H 6.23; N 10.27; found % C 35.29; H 6.26; N 10.23.

N^1-BOC,N^3,N^3-bis(2-chloroethyl) sulfamide 18. Yield=85%; R_f=0.88 (CH_2Cl_2–MeOH 95:5); Mp: 83–84°C; IR (KBr, ν cm^{-1}): 3300 (NH), 1710 (C=O), 1360 and 1145 (SO_2).^1H NMR ($CDCl_3$, δ): 7.30 (s, 1H, exch, NH), 3.79 (m, 8H, 2×CH_2CH_2Cl), 1.54 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 320, 322, 324 $[M+H]^+$ ($C_9H_{18}Cl_2N_2O_4S$).

N^1-BOC,N^3-methyl,N^3-(2-chloroethyl) sulfamide 19. Yield=96%; R_f=0.76 (CH_2Cl_2–MeOH 95:5); IR (KBr, ν cm^{-1}): 3225 (NH), 1705 (C=O), 1335 and 1153 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.05 (s, 1H, exch, NH), 3.62 (s, 4H, 2×CH_2), 2.98 (s, 3H, CH_3), 1.44 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 273–275, $[M+H]^+$; 237; 172 ($C_8H_{17}ClN_2O_4S$).

N^1-BOC,N^3-[(2-chloro-1-isobutyl) ethyl] sulfamide 20. Yield=90%; R_f=0.80 (CH_2Cl_2–MeOH 95:5); Mp: 165°C; IR (KBr, ν cm^{-1}): 3330 and 3225 (NH), 1700 (C=O), 1355 and 1163 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.24 (s, 1H, exch, NHBOC), 5.28 (d, 1H, exch, NH) 3.76 (m, 2H, CH_2Cl), 3.64 (m, 1H, C*H), 1.74 (m, 1H, CH), 1.58 (m, 2H, CH_2), 1.52 (s, 9H, *t*Bu), 0.85 (2d, 6H, 2×CH_3). MS (NOBA, FAB>0): 315, 317; $[M+H]^+$; 214 ($C_{11}H_{23}ClN_2O_4S$).

N^1-BOC,N^3-[(2-chloro-1-benzyl) ethyl] sulfamide 21. Yield=95%; R_f=0.95 (CH_2Cl_2–MeOH 95:5); Mp: 115–117°C; IR (KBr, ν cm^{-1}): 3250 (NH), 1702 (C=O), 1325 and 1143 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.58 (s, 1H, exch, NHBOC), 7.20 (m, 6H, ArH+NH), 3.91 (m, 1H, C*H), 3.55 and 3.42 (2dd, 2H, *J*=4.42, 7.04 Hz, CH_2Cl), 3.21 and 2.82 (2dd, 2H, *J*=5.0, 8.70 Hz, CH_2Ph), 1.42 (s, 9H, *t*Bu) ($C_{14}H_{21}ClN_2O_4S$).

N^1(*N*-BOC-sulfamoyl)-2-(2-chloroethyl) pyrrolidine 22. Yield=86%; R_f=0.88 (CH_2Cl_2–MeOH 95:5); Mp: 79–80°C; $[\alpha]_D$=−5.5 (*c*=1, MeOH); IR (KBr, ν cm^{-1}): 3250 (NH), 1702 (C=O), 1325 and 1170 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.10 (s br,1H, exch, NHBOC), 4.38 (m, 1H, C*H) 3.70 and 3.50 (2dd, 2H, J_{vic}=3.50 Hz and J_{gem}=−7.89 Hz, CH_2Cl), 3.48, 2.02, 1.89 (3m, 3×2H, 3 CH_2 pyrr), 1.46 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 299–301, $[M+H]^+$; 263, $[M+H]^+$−HCl; 198 $[M+H]^+$−BOC ($C_{10}H_{19}ClN_2O_4S$).

Cyclization with K_2CO_3 in DMSO: general procedure

The 2-chloroalkyl compounds (10 mmol) were dissolved in dimethylsulfoxide (DMSO) and K_2CO_3 (1.5 equiv., anhydrous), was added in one fraction. 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 (Na_2SO_4) and concentrated in vacuo. Recrystallization of the crude product in CH_2Cl_2/petroleum ether (1:5) afforded pure expected cyclosulfamides **23**–**25** and **34** and **35**.

N^2-BOC-1,2,5-thiadiazolidine 1,1-dioxide 23. Yield=90%; R_f=0.67 (CH_2Cl_2–MeOH 95:5); Mp: 143°C; IR (KBr, ν cm^{-1}): 3300 (NH), 1695 (C=O), 1360 and 1145 (SO_2). ^1H-NMR ($CDCl_3$, δ): 4.76 (t, 1H, exch, NH), 3.92 (t, 2H, *J*=6.42 Hz, CH_2), 3.54 (q, 2H, *J*=7.61 Hz, CH_2NH), 1.52 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 223, $[M+H]^+$; 167; 122 ($C_7H_{14}N_2O_4S$).

N^2-BOC-N^5-methyl-1,2,5-thiadiazolidine 1,1-dioxide 24. 5 g (22.32 mmol) of **11** in 10 mL of anhydrous CH_2Cl_2 are added dropwise to a solution of triphenylphosphine (8.75 g, 33.48 mmol) and diisopropylazodicarboxylate (DIAD) (6.77 g, 33.48 mmol) in the same solvent. The reaction medium was stirred under atmosphere of dry nitrogen for 20 min. Oxidoreduction products were removed by filtration after precipitation with diethyl ether. The filtrate was concentrated and the residue was purified by column chromatography eluted with CH_2Cl_2. Cyclic sulfamide **24** was obtained as a white solid.

Yield=90%; R_f=0.77 (CH_2Cl_2–MeOH 95:5); Mp: 84°C; IR (KBr, ν cm^{-1}): 1705 (C=O), 1310 and 1170 (SO_2). ^1H NMR ($CDCl_3$, δ): 3.76 (t, 2H, CH_2), 3.28 (t, 2H, *J*=6.43 Hz, CH_2), 3.46 (s, 3H, CH_3), 1.48 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 237, $[M+H]^+$; 136. Anal ($C_8H_{16}N_2O_4S$).

N^2-BOC-N^5-(2-chloroethyl)-1,2,5-thiadiazolidine 1,1-dioxide 25. Yield=96%; R_f=0.70 (CH_2Cl_2–MeOH 95:5); Mp:

73–75; IR (KBr, ν cm^{-1}): 1690 (C=O), 1330 and 1155 (SO_2). ^1H NMR ($CDCl_3$, δ): 3.76, 3.67, 3.45, 3.39 (4t, 8H, 4 CH_2), 1.48 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 285–287; $[M+H]^+$; 249; 184 ($C_9H_{17}ClN_2O_4S$).

N^2-BOC-pyrrolidino[1,2-*c*]-1,2,5-thiadiazolidine 1,1-dioxide 26. A mixture of **22** (2 g, 6.67 mmol) in 50 mL of acetonitrile and 1.40 g (10 mmol) of K_2CO_3 was stirred at room temperature for 15 min. 0.43 g (6.67 mmol) of Cu and 0.96 g (6.67 mmol) of CuBr were added and the mixture was heated under reflux for 24 h. After cooling to rt, the reaction mixture was filtered and concentrated in vacuo. The residue diluted with 200 mL of CH_2Cl_2, was acidified with 1N HCl solution. The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified on silica gel (CH_2Cl_2/AcOEt 8:2). Bicyclic compound **26** was obtained as a colorless solid.

Yield=80%; R_f=0.72 (CH_2Cl_2–MeOH 95:5); Mp: 68–70°C; $[\alpha]_D$=−17 (*c*=1, MeOH); IR (KBr, ν cm^{-1}): 1710 (C=O), 1310 and 1145 (SO_2). ^1H NMR ($CDCl_3$, δ): 4.17 (td,1H, *J*=2.81, 4.58 Hz, C*H), 3.94 and 3.40 (2dd, 2H, *J*=1.72, 2.74 and 7.24 Hz, CH_2), 3.75 and 3.40 (2 dd, 2H, *J*=2.30, 4.22 and 6.51 Hz, CH_2 pyrr), 2.24 and 1.59 (2m, 2H, CH_2 pyrr), 2.05 (m, 2H, CH_2 pyrr), 1.55 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 263, $[M+H]^+$; 192; 57 ($C_{10}H_{18}N_2O_4S$).

***N*-Benzoyl-aminoacid esters.** To a solution of aminoacid ester hydrochloride (10^{-2} mol) and aqueous solution of K_2CO_3 2N (2.5×10^{-2} mol) in $CHCl_3$ (200 mL) was added dropwise benzoyl chloride (1.405 g, 10^{-2} mol). The reaction medium was stirred vigorously and heated at reflux for 3 h. The reaction was quenched with water and the compound was extracted twice with $CHCl_3$ (2×100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford *N*-benzoylaminoesters as a white powder in quantitative yields.

***N*-Benzylaminoalcohols.** A solution of *N*-benzoylaminoester (20 mmol) in anhydrous THF (20 mL) was added slowly to a mixture of lithium aluminium hydride (1.15 g, 30 mmol) in the same solvent (60 mL) and the medium was refluxed with stirring for 3.5 h. The reaction mixture was cooled on ice and the lithium aluminium complex was decomposed by the slow addition of THF–water (4:1, 20 mL). The resulting mixture was stirred for 1 h and then filtered through Celite. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The reaction product has been used in crude form.

Substituted mustards. To a refluxing solution of *N*-benzylaminoalcohol (14.60 mmol) in $CHCl_3$ (50 mL) was slowly added a solution of thionyl chloride (60 mL, 126 mmol) in 30 mL of $CHCl_3$. When the addition was completed, the reflux was continued for 2 h. The reaction mixture was concentrated in vacuo to give the crude product as a white powder.

N^2-BOC-N^5-benzyl-4-substituted-1,2,5-thiadiazolidine 1,1-dioxides. Sulfamoylation of *N*-benzyl-2-chloroalkylamines hydrochlorides with BOC-sulfamoyl chloride in triethylamine (2 equiv.) was carried out according to the general procedure. The residue was purified by flash chromatography. Elution with CH_2Cl_2/MeOH (95:5) gave cyclic sulfamides in 75–80% yield as colorless solids.

N^2-BOC-4-methyl-N^5-benzyl-1,2,5-thiadiazolidine 1,1-dioxide 27. Yield=75%; R_f=0.40 (CH_2Cl_2); Mp: 95–97°C; IR (KBr, ν cm^{-1}): 1708 (C=O), 1330 and 1150 (SO_2); $[\alpha]_D$=+25 (*c*=1, $CHCl_3$). ^1H NMR ($CDCl_3$, δ): 7.40 (m, 5H, ArH), 4.30 (2d, 2H, *J*=−15.17 Hz, CH_2Ph), 3.88 and 3.50 (2dd, 2H, *J*=2.75, 5.55 Hz, CH_2), 3.50 (m, 1H, C*H), 1.60 (s, 9H, *t*Bu), 1.25 (d, 3H, *J*=6.28 Hz, CH_3). MS (NOBA, FAB>0): 327, $[M+H]^+$; 226; 91. Anal ($C_{15}H_{22}N_2O_4S$): calcd % C 55.21; H 6.75; N 8.58; found % C 55.30; H 6.73; N 8.51.

N^2-BOC-4-isopropyl-N^5-benzyl-1,2,5-thiadiazolidine 1,1-dioxide 28. Yield=75%; R_f=0.72 (CH_2Cl_2–MeOH 95:5); Mp: 82–84°C; IR (KBr, ν cm^{-1}): 1715 (C=O), 1340 and 1160 (SO_2); $[\alpha]_D$=+5 (*c*=1, $CHCl_3$). ^1H NMR ($CDCl_3$, δ): 7.40 (m, 5H, ArH), 4.30 (2d, 2H, *J*=−14.63 Hz, CH_2Ph), 3.90 and 3.50 (2dd, 2H, J_{vic}=3.16 Hz, and J_{gem}=−12.8 Hz, CH_2), 3.50 (m, 1H, C*H), 1.58 (s+m, 10H, CH+*t*Bu), 1.22 (d, 6H, *J*=5.93 Hz, CH_3). MS (NOBA, FAB>0): 355, $[M+H]^+$; 91 ($C_{17}H_{26}N_2O_4S$).

N^2-BOC-N^5, 4-dibenzyl-1,2,5-thiadiazolidine 1,1-dioxide 29. Yield=74%; R_f=0.62 (CH_2Cl_2); Mp: 104°C; IR (KBr, ν cm^{-1}): 1710 (C=O), 1335; 1150 (SO_2); $[\alpha]_D$=−30 (*c*=1, $CHCl_3$). ^1H NMR ($CDCl_3$, δ): 7.30 (m, 10H, ArH), 4.25 (2d, 2H, *J*=−14.69 Hz, NCH_2Ph), 3.50 (m, 3H, C*H+CH_2Ph), 3.08 and 2.60 (2dd, 2H, CH_2), 1.52 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 403, $[M+H]^+$; 91 ($C_{21}H_{26}N_2O_4S$).

***N*-(*N*-Benzylsulfamoyl) aziridine 30.** Yield=90%; R_f=0.62 (CH_2Cl_2–MeOH 95:5); foam. ^1H NMR ($CDCl_3$, δ): 7.28 (m, 5 H, ArH), 4.62 (t, 1H, NH, exch), 4.34 (d, 2H, CH_2Ph), 2.18 (s br, 4H, 2×CH_2*azir)*. MS (NOBA, FAB>0): 425 $[dimer+H]^+$, 213, $[M+H]^+$; 91 ($C_9H_{12}N_2O_2S$).

The preparation of N^1-BOC-N^3-benzylsulfamide **31** has been previously reported[10] and reactions with chloroethanol, 1-chloro-2-propanol and 1,3-dichloro-2-propanol under Mitsunobu conditions were performed following the procedure described for compound **23**.

N^1-BOC-N^3-benzyl,N^3(2-chloroethyl) sulfamide 32. Yield=69%; R_f=0.75 (CH_2Cl_2–MeOH 95:5); Mp: 60°C; IR (KBr, ν cm^{-1}): 1708 (C=O), 1355; 1150 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.30 (s, 5 H, ArH), 5.50 (t,1H, NH, exch), 4.25 (s, 2H, CH_2Ph), 4.08 (t, 2H, CH_2N), 3.76 (t, 2H, CH_2Cl), 1.48 (s, 9H, *t*Bu). MS (EI pos): 349, $[M+H]^+$ ($C_{14}H_{21}N_2ClO_4S$).

N^1-BOC-N^3-benzyl,N^3[(2-chloro,1-methyl) ethyl] sulfamide 33. Yield=72%; R_f=0.81 (Et_2O–hexane); Mp: 66°C; IR (KBr, ν cm^{-1}): 1702 (C=O), 1355; 1165 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.39 (m, 5 H, ArH), 5.68 (t, 1H, NH, exch), 4.69 (m, 1H, CH), 4.28 (m, 2H, CH_2Ph), 3.97, 3.66 (2m, 2H, CH_2Cl), 1.58 (s, 9H, *t*Bu),1.52 (d, 3H, CH_3). MS (NOBA, FAB>0): 363–365, $[M+H]^+$ ($C_{15}H_{23}N_2ClO_4S$).

N^1-BOC-N^3-benzyl,N^3[(2-chloro,1-chloromethyl) ethyl] sulfamide 34. Yield=67%; R_f=0.65 (CH_2Cl_2); Mp: 112°C; IR (KBr, ν cm^{-1}): 1697 (C=O), 1350; 1155 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.30 (s, 5 H, ArH), 5.52 (t, 1H, NH, exch), 4.76 (m, 1H, CH), 4.28 (d, 2H, J=6.08 Hz, CH_2Ph), 3.85 (m, 4H, 2×CH_2Cl), 1.48 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 397–399–401, $[M+H]^+$ ($C_{15}H_{22}Cl_2N_2O_4S$).

N^1-BOC-N^5-benzyl-1,2,5-thiadiazolidine 1,1-dioxide 35. Yield=90%; R_f=0.60 (CH_2Cl_2–MeOH 95:5); Mp: 84°C; IR (KBr, ν cm^{-1}): 1720 (C=O), 1335; 1170 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.36 (s, 5 H, ArH), 4.20 (s, 2H, CH_2Ph), 3.77 (t, 2H, CH_2NBOC), 3.19 (t, 2H, CH_2NBn), 1.57 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 313, $[M+H]^+$.

N^2-BOC-3-methyl-N^5-benzyl-1,2,5-thiadiazolidine 1,1-dioxide 36. Yield=94%; R_f=0.60 (Et_2O–hexane); Mp: 88°C; IR (KBr, ν cm^{-1}): 1715 (C=O), 1330; 1155 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.33 (m, 5 H, ArH), 4.12 (m, 1H, CH-Me), 3.97, 4.31 (2d, 2H, J=−14.0 Hz, CH_2Ph), 2.37, 3.25 (2dd, 2H, J=3.5, 6.5 Hz, CH_2 ring), 1.52 (s, 9H, *t*Bu), 1.34 (d, 3H, J=6.0 Hz, CH_3). MS (NOBA, FAB>0): 327, $[M+H]^+$; 226; 91.

N^2-BOC-3-chloromethyl-N^5-benzyl-1,2,5-thiadiazolidine 1,1-dioxide 37. Yield=58%; R_f=0.60 (CH_2Cl_2); Mp: 54°C; IR (KBr, ν cm^{-1}): 1708 (C=O), 1345; 1165 (SO_2). ^1H NMR ($CDCl_3$, δ): 7.31 (s, 5 H, ArH), 4.36 (d, 1H, J=−13.60 HZ, CH-Ph), 4.17 (m, 1H, C^*H), 3.97 (d, 1H, CH-Ph), 3.75, 3.55 (2dd, 2H, J=3.40, 10.30 Hz, CH_2 ring), 3.24 (m, 2H, CH_2Cl), 1.52 (s, 9H, *t*Bu). MS (NOBA, FAB>0): 360–362, $[M+H]^+$.

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