Synthesis and Applications of β-Aminoethanesulfonyl Azides

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Received 15 July 2005; revised 22 August 2005

Abstract: A very efficient method for the synthesis of β-aminoethanesulfonyl azides is descibed. These aliphatic sulfonyl azides are accessible starting from a variety of protected amino acids, including those having functionalized side chains. Furthermore, these sulfonyl azides can be coupled to thio acids, and can be substituted with different aliphatic amines.

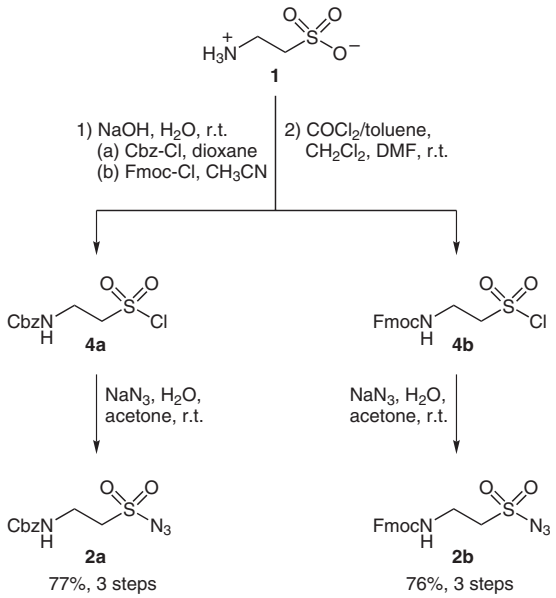
Key words: sulfonyl azide, sulfonyl chloride, amino acid, sulfonamides

There is a continuous interest in easily accessible and versatile building blocks. One of the main objectives in our group is the preparation of peptidomimetics using different building blocks derived from amino acids. Previously we described the efficient synthesis of β-aminoethanesulfonyl chlorides starting from natural amino acids.[1] These sulfonyl chlorides have been successfully employed for use in peptide–peptidomimetic hybrides,[2] synthetic receptors,[3] ligands for catalysis,[4] cyclic sulfonamides,[5] and oligopeptidosulfonamides.[6] In a different project, using β-aminoethanesulfonyl chlorides, we embarked on the sulfonyl azide moiety. Little is described in the literature about the use of the sulfonyl azide moiety in biologically active compounds, while a sulfonyl azide can interact by hydrogen bonding and electrostatic interactions. In one example the sulfonyl azide moiety has successfully been used in selective cyclooxygenase-2 inhibitors.[7]

For synthetic applications mostly aromatic sulfonyl azides are described in the literature, which were mainly used in thermolysis reactions,[8] azidations,[9] diazo-transfer reactions,[10] and reactions with alkenes.[11] Only few papers describe reactions other than diazo-transfer reactions[10a] with aliphatic sulfonyl azides. One describes the thermolytic reaction between pentylsulfonyl azide and cyclohexane, affording an *N*-cyclohexylsulfonamide.[8f] The Staudinger reaction between an aliphatic sulfonyl azide derived from isoborneol and racemic tertiary phosphines yielded stable phosphinimines, which were hydrolyzed to form chiral phosphines.[12] Recently Shangguan et al. described a new and very interesting reaction of a sulfonyl azide with a thioacid, which afforded an *N*-acyl sulfonamide.[13] If this reaction is selective and also works with amino acid based sulfonyl azides, it might be possible to use it for chemical ligation by coupling a peptido-peptidosulfonyl azide with a peptide thio acid.

Synthesis of sulfonyl azides in the literature is generally performed starting from sulfonyl chlorides.[8,12] An aqueous solution of acetone is mostly used as solvent, in which both the sulfonyl chloride and sodium azide dissolve. The β-aminoethanesulfonyl chlorides earlier prepared by us were protected with either the Fmoc group or the Cbz group.[1] Since the Cbz group is more stable under many reaction conditions, we decided to start with the preparation of a Cbz-protected β-aminoethanesulfonyl azide derived from glycine (Scheme 1).

For this purpose, taurine (**1**) was Cbz-protected and subsequently reacted with phosgene to give Cbz-protected taurylsulfonyl chloride (**4a**).[1]



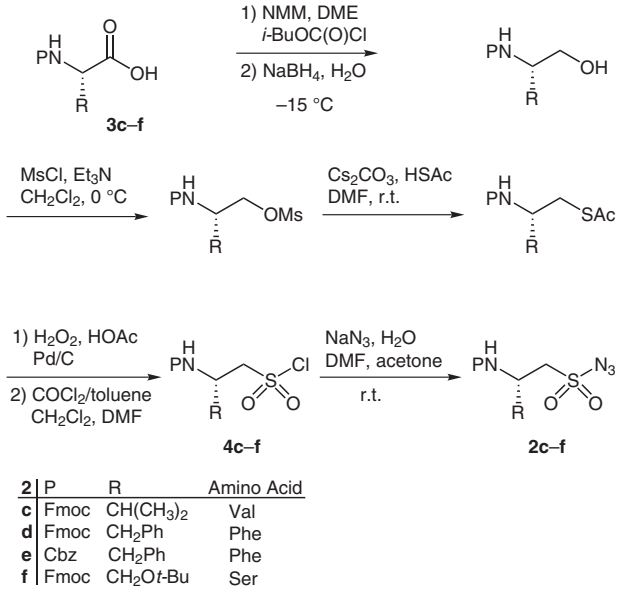
Scheme 1

The first attempt for reaction of Cbz-protected taurylsulfonyl chloride with NaN_3 in an acetone–water mixture resulted in a fast and clean conversion to sulfonyl azide **2a** in 90% yield (77% from taurine). In this procedure a solution of the sulfonyl chloride in acetone was added to an aqueous solution of NaN_3. After these promising results, we wondered whether the Fmoc group would be stable under these reaction conditions. For this purpose the azide-substitution reaction was repeated with Fmoc-protected taurylsulfonyl chloride (**4b**).[1] Unfortunately the

SYNTHESIS 2006, No. 3, pp 0455–0460
Advanced online publication: 11.01.2006
DOI: 10.1055/s-2006-926273; Art ID: Z13805SS

yield of Fmoc-protected sulfonyl azide **2b** was only 49% due to Fmoc cleavage, which was clearly visible on TLC. During the reaction a white precipitate formed, which probably was sulfonyl chloride. To prevent Fmoc cleavage, it is very important that the azide anions react directly with the sulfonyl chloride, which is difficult when the sulfonyl chloride is not completely dissolved. Thus, after addition of more acetone and inversion of the addition sequence, Fmoc-protected sulfonyl azide **2b** was obtained in 90% yield (Table 1).

Now that both Fmoc- and Cbz-protected glycine-derived sulfonyl azides were successfully prepared, the next step was the preparation of β-aminoethanesulfonyl azides with different side chains, including functionalized side chains. Fmoc-protected β-aminoethanesulfonyl chlorides **4c–f** were prepared following a procedure which was previously described by our group, starting from Fmoc- and Cbz-protected amino acids **3** (Scheme 2).[1]



2	P	R	Amino Acid
c	Fmoc	$CH(CH_3)_2$	Val
d	Fmoc	CH_2Ph	Phe
e	Cbz	CH_2Ph	Phe
f	Fmoc	CH_2O*t*-Bu	Ser

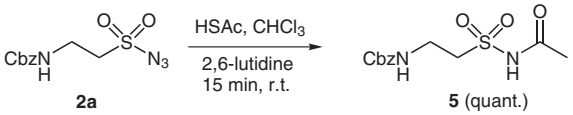
Scheme 2

Table 1 Yields of Sulfonyl Azides **2a–f**

Amino Acid	Sulfonyl Azide **2**	Yield (%)
Cbz-Gly-OH	**a**	90
Fmoc-Gly-OH	**b**	92
Fmoc-Val-OH	**c**	79
Fmoc-Phe-OH	**d**	99
Cbz-Phe-OH	**e**	90
Fmoc-Ser(*t*-Bu)-OH	**f**	74

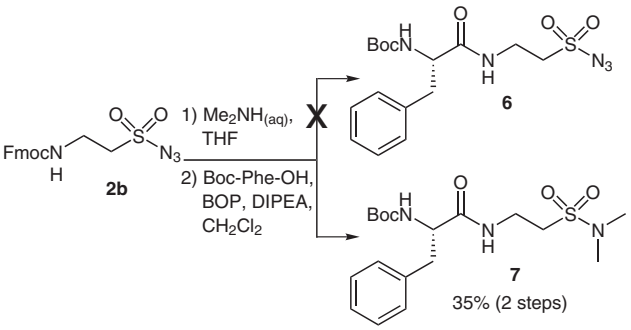
Due to solubility problems in the initial experiments, the procedure used for **2b** was slightly altered by changing the solvent ratio and by addition of DMF. Fmoc-protected sulfonyl chlorides **4c–d** were smoothly converted to the corresponding sulfonyl azides in good to excellent yields (79–99%) (Table 1). Cbz-phenylalanine-derived sulfonyl azide was also efficiently prepared in high yield (90%), following the procedure used for **2a**. For preparation of a functionalized sulfonyl chloride, **4f**, derived from Fmoc-Ser(*t*-Bu)-OH, was selected.[1] Sulfonyl azide **2f** was prepared in 74% yield, using the standard procedure.

As a first application we studied the reaction of sulfonyl azides with thio acids. The reaction is fast and gives *N*-acyl sulfonamides in high yields. As a proof of principle Cbz-protected sulfonyl azide **2a** was reacted with thioacetic acid in chloroform (Scheme 3).



Scheme 3

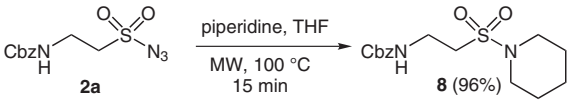
N-Acyl sulfonamide **5**[14] was obtained in quantitative yield after only 15 minutes reaction time. This reaction was so promising that we prepared a set of *N*-acyl sulfonamides from sulfonyl azides **2a–f** and different thio acids, including peptide-based thio acids to explore the scope of the reaction and for use as a new chemical ligation reaction.[14] We found that the reaction was high-yielding and indeed can be used to couple sulfonyl azides to peptide thio acids. For use as a chemical ligation reaction N-terminal deprotected sulfonyl azides were required, to which amino acids or peptides can be coupled. For this purpose the N-terminus of Fmoc-tauryl sulfonyl azide **2b** was deprotected with a large excess of dimethylamine in THF (Scheme 4).



Scheme 4

Boc-Phe-OH was directly coupled to the resulting free amine using (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane. Instead of Fmoc-deprotection followed by coupling, the sulfonyl azide underwent a substitution reaction by dimethylamine leading to **7**, and no coupling product **6** retaining the sulfonyl azide moiety was found. In attempts to selectively remove the Fmoc group, different amounts of either dimethylamine or piperidine were used. In all re-

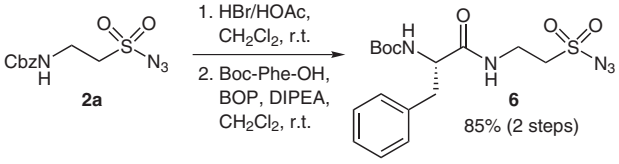
actions, both Fmoc cleavage and azide substitution were observed. At lower amounts of the amine, the Fmoc cleavage was slightly favored over the substitution. Since substitution of the *sulfonyl* azide always occurred, we became interested in exploring the scope of this reaction. To our knowledge, in contrast to *acyl* azides, this reaction has never been described in the literature. A series of test reactions was carried out with Cbz-tauryl sulfonyl azide **2a**, using different amines (benzylamine, methylamine, dimethylamine, piperidine) in different amounts (2–40 equivalents). All amines were capable of substitution, but at least ten equivalents were needed for complete conversion at room temperature overnight. Heating accelerated the reaction, but the best improvement was found using microwave irradiation. As a proof of principle Cbz-tauryl sulfonyl azide **2a** was reacted with four equivalents of piperidine in tetrahydrofurane at 100 °C with microwave irradiation (Scheme 5).



Scheme 5

After only 15 minutes reaction time, sulfonamide **8** was isolated in 96% yield, showing that our sulfonyl azides can be substituted by amines.

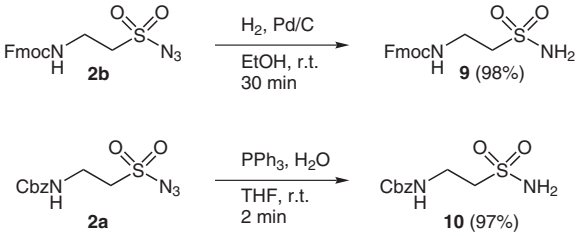
Since Fmoc cleavage of sulfonyl azides was not possible, we decided to cleave the Cbz group. For this purpose, sulfonyl azide **2a** was treated with HBr/HOAc, and the HBr salt of the amine was transformed into the HCl salt using an ion exchange resin (Scheme 6).



Scheme 6

Subsequently, Boc-Phe-OH was coupled using BOP to give peptido-peptidosulfonyl azide **6** in 85% yield, showing that the N-terminus of our sulfonyl azides can be used for coupling amino acids and probably peptides. This example also shows that the sulfonyl azide moiety is stable under both strong acidic (HBr/HOAc) and basic (DIPEA) conditions. Furthermore, under these coupling conditions no substitution products were found from nucleophilic attack of the free amine at the sulfonyl azide.

For a different project, primary sulfonamides were needed. It was envisioned that these could be obtained by reduction of the sulfonyl azides. Thus, after treatment of Fmoc-protected sulfonyl azide **2b** with hydrogen and palladium on carbon (Scheme 7), sulfonamide **9** was obained in 98% yield. Due to the instability of the Cbz protecting group under these conditions, a Staudinger reduction was attempted. In the literature a similar reduction is described; treatment of the sulfonyl azide with a tertiary phosphine for 12 h at 60° in THF, affords a phosphinimine. The phosphinimine is then hydrolyzed using 3 M sulfuric acid in refluxing dioxane for 12 h.[12] Since these conditions are quite harsh, it was decided to first try the common Staudinger conditions.[15] Thus, Cbz-protected sulfonyl azide **2a** was treated with triphenylphosphine and water in tetrahydrofuran. To our surprise, sulfonamide **10** was obtained in 97% yield after only two minutes reaction time at room temperature. We also tried to isolate the phosphinimine intermediate by repeating the Staudinger reaction in the absence of water. On TLC the intermediate was indeed formed but slowly hydrolyzed to the sulfonamide, indicating its moisture sensitivity.



Scheme 7

In conclusion, we have developed a very efficient method for the preparation of β-aminoethanesulfonyl azides starting from different amino acids, including those containing functionalized side chains. These sulfonyl azides were remarkably stable, but could be easily substituted by amines, using microwave irradiation to give sulfonamides. The sulfonyl azides were also successfully converted to *N*-acyl sulfonamides by reaction with thio acids. Amino acids – and probably peptides – can be coupled to the N-terminus, providing access to peptido-peptidosulfonyl azides for use in chemical ligation. The chemistry of sulfonyl azides is currently under further investigation.

Fmoc-protected amino acids were purchased from MultiSynTech GmbH (Witten, Germany). Peptide-grade solvents for synthesis were purchased from Biosolve (The Netherlands). Dowex 2 × 8 (Cl-form) was purchased from Fluka. Reactions were carried out at ambient temperature unless stated otherwise. TLC analysis was performed on Merck pre-coated silica gel 60 F-254 (0.25 mm) plates. Spots were visualized with UV light, ninhydrin, or Cl_2-TDM.[16] Solvents were evaporated under reduced pressure at 40 °C. Column chromatography was performed on ICN silica gel 60 (32–63 m). Melting points were measured on a Büchi melting point apparatus and are uncorrected. Electrospray mass spectra were recorded on a Shimadzu LCMS-QP-8000 spectrometer. Elemental analyses were carried out at Kolbe Mikroanalytisches Laboratorium (Mülheim an der Ruhr, Germany). Microwave-assisted reactions were carried out in a Biotage Initiator. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian G-300 spectrometer. For ^{1}H NMR, TMS or DMSO (2.50 ppm) were used as internal standards; for ^{13}C NMR, $CDCl_3$ and THF-d_8 (67.4 ppm) were used. ^{13}C NMR spectra were recorded using the attached proton test (APT) pulse sequence. The ^{13}C NMR spectrum of **9** was recorded on a Varian Inova-500 spectrometer.

Sulfonyl Azides 2a–f; General Procedure

A solution of NaN_3 (195 mg, 3.00 mmol) in H_2O (10 mL) was added dropwise to a solution of the sulfonyl chloride **4a–f** (3 mmol) in acetone (15 mL) and DMF (15 mL). The reaction was stirred at r.t. for up to 1 h. After evaporation of acetone, H_2O (200 mL) was added and the product precipitated. The mixture was filtered and the residue was washed with 5% $NaHCO_3$ soln (10 mL), H_2O (50 mL), and dried in vacuo. Sulfonyl azides **2a–f** were all obtained as white solids.

2a (Cbz-Tau-N_3)

The reaction (16.9 mmol scale) was carried out using H_2O (90 mL) and acetone (90 mL) as solvents. The acetone solution of the sulfonyl chloride was added dropwise to the aq solution of NaN_3. Instead of precipitation, the reaction was worked up by evaporation of acetone, followed by re-dissolving in EtOAc (250 mL) and washing with 5% $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL). Drying over Na_2SO_4 and evaporation of EtOAc afforded the sulfonyl azide.

Yield: 4.3 g (90%); R_f = 0.63 (MeOH–CH_2Cl_2, 1:99); mp 78 °C.

IR (KBr): 2150 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.55 (m, 2 H, CH_2SO_2), 3.72 (m, 2 H, NCH_2), 5.12 (s, 2 H, CH_2Ph), 5.36 (br s, 1 H, NH), 7.35 (s, 5 H, Ar-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.7 (NCH_2), 55.2 (CH_2SO_2), 67.2 (OCH_2Ph), 128.1, 128.4, 128.6, 135.9 (Ar-C), 156.1 [C=O (Cbz)].

ESI-MS: *m*/*z* (%) = 285 $[M + H]^+$, 307 $[M + Na]^+$, 323 $[M + K]^+$, 569 $[2M + H]^+$.

Anal. Calcd for $C_{10}H_{12}N_4O_4S$: C, 42.25; H, 4.25; N, 19.71. Found: C, 42.32; H, 4.21; N, 19.66.

2b (Fmoc-Tau-N_3)[17]

The preparation (2.95 mmol scale) was carried out in the absence of DMF.

Yield: 1.02 g (92%); R_f = 0.54 (MeOH–CH_2Cl_2, 1:99); mp 118 °C.

IR (KBr): 2141 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (m, 2 H, CH_2SO_2), 3.71 (m, 2 H, NCH_2), 4.21 [t, 1 H, CH (Fmoc)], 4.44 [d, 2 H, CH_2 (Fmoc)], 5.33 (br s, 1 H, NH), 7.29–7.78 [m, 8 H, Ar-CH (Fmoc)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.7 (NCH_2), 47.1 [CH (Fmoc)], 55.2 (CH_2SO_2), 67.1 [CH_2 (Fmoc)], 120.0, 124.4, 124.9, 127.1, 127.8, 141.3, 143.6 [Ar-C (Fmoc)], 156.1 [C=O (Fmoc)].

ESI-MS: *m*/*z* (%) = 473 $[M + H]^+$, 395 $[M + Na]^+$, 411 $[M + K]^+$, 745 $[2M + H]^+$.

Anal. Calcd for $C_{17}H_{16}N_4O_4S$: C, 54.83; H, 4.33; N, 15.04. Found: C, 54.71; H, 4.25; N, 14.92.

2c (Derived from Fmoc-valine)[17]

Scale: 1.1 mmol; yield: 0.36 g (79%); R_f = 0.54 (MeOH–CH_2Cl_2, 1:99); mp 158 °C.

IR (KBr): 2139 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 [2 d, 6 H, $CH(CH_3)_2$], 2.04 [m, 1 H, $CH(CH_3)_2$], 3.49 (dd, 1 H, CH^aSO_2, J_{gem} = 14.7 Hz, J_{vic} = 3.7 Hz), 3.60 (dd, 1 H, CH^bSO_2, J_{gem} = 14.7 Hz, J_{vic} = 8.1 Hz), 4.01 (m, 1 H, NCH), 4.22 [t, 1 H, CH (Fmoc)], 4.45 [m, 2 H, CH_2 (Fmoc)], 5.04 (d, 1 H, NH), 7.29–7.77 [m, 8 H, Ar-CH (Fmoc)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 19.2 [$CH(CH_3)_2$], 31.5 [$CH(CH_3)_2$], 47.2 [CH (Fmoc)], 53.0 (NCH), 57.0 (CH_2SO_2), 66.9 [CH_2 (Fmoc)], 119.0, 125.0, 127.1, 127.7, 141.3, 143.6, 143.7 [Ar-C (Fmoc)], 155.7 [C=O (Fmoc)].

ESI-MS: *m*/*z* (%) = 415 $[M + H]^+$, 437 $[M + Na]^+$, 453 $[M + K]^+$.

Anal. Calcd for $C_{20}H_{22}N_4O_4S$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.77; H, 5.28; N, 13.39.

2d (Derived from Fmoc-phenylalanine)[17]

The reaction (3.0 mmol scale) was carried out using H_2O (30 mL), acetone (20 mL), and DMF (40 mL) as solvents.

Yield: 1.37 g (99%); R_f = 0.56 (MeOH–CH_2Cl_2, 1:99); mp 168 °C.

IR (KBr): 2131 (s) cm^{-1}.

^{1}H NMR (300 MHz, THF-d_8,): δ = 2.95 (dd, 1 H, CH^aPh, J_{gem} = 13.6 Hz, J_{vic} = 5.8 Hz), 3.03 (dd, 1 H, CH^bPh, J_{gem} = 13.6 Hz, J_{vic} = 8.2 Hz), 3.71 (dd, 1 H, CH^aSO_2, J_{gem} = 14.7 Hz, J_{vic} = 3.9 Hz), 3.88 (dd, 1 H, CH^bSO_2, J_{gem} = 14.7 Hz, J_{vic} = 8.6 Hz), 4.19 [m, 2 H, NCH, CH (Fmoc)], 4.40 [m, 2 H, CH_2 (Fmoc)], 7.01 (d, 1 H, NH), 7.15–7.81 [m, 13 H, Ar-CH (Fmoc, Ph)].

^{13}C NMR (75 MHz, THF-d_8): δ = 40.0 (CH_2Ph), 48.3, 50.3 [NCH, CH (Fmoc)], 58.4 (CH_2SO_2), 66.7 [CH_2 (Fmoc)], 120.6, 125.9, 127.4, 127.7, 128.3, 129.3, 130.3, 138.5, 142.3, 145.3 [Ar-C (Fmoc, Ph)], 156.4 [C=O (Fmoc)].

ESI-MS: *m*/*z* (%) = 463 $[M + H]^+$, 485 $[M + Na]^+$, 501 $[M + K]^+$, 925 $[2M + H]^+$.

Anal. Calcd for $C_{24}H_{22}N_4O_4S$: C, 62.32; H, 4.79; N, 12.11. Found: C, 62.40; H, 4.75; N, 12.03.

2e (Derived from Cbz-phenylalanine)

The reaction (3.8 mmol scale) was carried out using H_2O (19 mL) and acetone (50 mL) as solvents. The reaction and workup were performed using the same procedure as for **2a**.

Yield: 1.28 g (90%); R_f = 0.48 (MeOH–CH_2Cl_2, 1:99); mp 141 °C.

IR (KBr): 2137.57 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.02 (m, 2 H, $CHCH_2Ph$), 3.47 (dd, J_{gem} = 14.8 Hz, J_{vic} = 4.4 Hz, 1 H, $CHCH^aSO_2$), 3.71 (dd, J_{gem} = 14.8 Hz, J_{vic} = 7.7 Hz, 1 H, $CHCH^bSO_2$), 4.32 (m, 1 H, NCH), 5.09 (s, 2 H, OCH_2Ph), 5.23 (d, 1 H, NH), 7.15–7.38 [m, 10 H, Ar-CH (Cbz, Ph)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.3 ($CHCH_2Ph$), 49.1 (NCH), 57.2 (CH_2SO_2), 67.0 (OCH_2Ph), 127.3, 128.0, 128.2, 128.5, 128.9, 129.2, 135.9, 136.0 [Ar-C (Ph, Cbz)], 155.4 [C=O (Cbz)].

ESI-MS: *m*/*z* (%) = 375 $[M + H]^+$, 397 $[M + Na]^+$, 413 $[M + K]^+$, 749 $[2M + H]^+$.

Anal. Calcd for $C_{17}H_{18}N_4O_4S$: C, 54.53; H, 4.85; N, 14.96. Found: C, 54.60; H, 4.78; N, 14.87.

2f (Derived from Fmoc-Ser(*t*-Bu)-OH)[17]

Scale: 1.62 mmol; yield: 0.55 g (74%); R_f = 0.73 (MeOH–CH_2Cl_2, 1:99); mp 103 °C.

IR (KBr): 2137 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 [s, 9 H, $C(CH_3)_3$], 3.51, 3.64 (2 m, 4 H, CH_2SO_2, *t*-$BuOCH_2$), 4.23 [t, 1 H, CH (Fmoc)], 4.35–4.51 [m, 3 H, CH_2 (Fmoc), NCH], 5.33 (br d, 1 H, NH), 7.30–7.78 [m, 8 H, Ar-CH (Fmoc)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4 [$C(CH_3)_3$], 47.1, 47.6 [NCH, CH (Fmoc)], 55.9 (CH_2SO_2), 61.7 (*t*-$BuOCH_2$), 67.0 [CH_2 (Fmoc)], 73.8 [$C(CH_3)_3$], 120,0, 124.9, 125.0, 127.1, 127.8, 141.3, 143.6 [Ar-C (Fmoc)], 155.5 [C=O (Fmoc)].

ESI-MS: *m*/*z* (%) = 459 $[M + H]^+$, 481 $[M + Na]^+$, 497 $[M + K]^+$, 917 $[2M + H]^+$.

Anal. Calcd for $C_{22}H_{26}N_4O_5S$: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.49; H, 5.66; N, 12.06.

Peptido-peptidosulfonyl azide 6

To a solution of sulfonyl azide **2a** (284 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added a solution of HBr in HOAc (33%, 6 mL). While stirring for 30 min at r.t., a white precipitate formed. After removal of the solvents in vacuo, the residue was dissolved in H_2O (10 mL), and Dowex 2 × 8 (0.60 g, Cl-form) was added. Stirring for 5 min at r.t., followed by filtration and concentration in vacuo, afforded the HCl-salt (188 mg) in quantitative yield. To the HCl-salt was subsequently added CH_2Cl_2 (40 mL), Boc-Phe-OH (265 mg, 1.00 mmol), BOP (464 mg, 1.05 mmol), and DIPEA (385 μL, 2.21 mmol). The mixture was stirred overnight at r.t. The pH was kept at approx. 8 by addition of DIPEA during the reaction. After concentration, the residue was suspended in EtOAc (100 mL) and was washed with 1.0 M $KHSO_4$ (3 × 50 mL), brine (50 mL), 5% $NaHCO_3$ soln (3 × 50 mL), and brine (50 mL). Drying over Na_2SO_4, followed by column chromatography (EtOAc–hexanes–HOAc, 44.5:44.5:1), afforded **6** as a white solid.

Yield : 336 mg (85%); R_f = 0.39 (EtOAc–hexanes, 1:1); mp 72 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 [s, 9 H, $C(CH_3)_3$], 3.06 (d, 2 H, $CHCH_2Ph$), 3.30–3.51 (2 m, 4 H, CH_2SO_2), 3.72 (m, 2 H, $NCH_2CH_2SO_2$), 4.35 [m, 1 H, NCHC(O)], 5.01 [d, 1 H, NHBoc], 6.63 (s, 1 H, $NHCH_2CH_2SO_2$), 7.18–7.35 [m, 5 H, Ar-CH].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 [$C(CH_3)_3$], 33.8 ($NHCH_2CH_2$), 38.2 (CH_2Ph), 54.6 (CH_2SO_2), 55.8 [$NCHC(O)$], 80.5 [$C(CH_3)_3$], 127.1, 128.3, 128.7, 129.2, 129.4, 136.3 (Ar-C), 155.4 [C=O (Boc)], 172.0 [$CHC(O)NH$].

ESI-MS: *m*/*z* (%) = 364.05 [M – *t*-Bu + Na]$^+$, 420.20 [M + Na]$^+$, 461.10 [M + CH_3CN + Na]$^+$.

Anal. Calcd for $C_{16}H_{23}N_5O_5S$: C, 48.35; H, 5.83; N, 17.62. Found: C, 48.22; H, 5.69; N, 17.77.

Peptido-peptidosulfonamide 7

To a solution of sulfonyl azide **2b** (372 mg, 1.00 mmol) in THF (10 mL) was added aq 40% solution Me_2NH (5.1 mL). After stirring for 1 h at r.t., the reaction mixture was concentrated in vacuo and co-evaporated with toluene (3 × 20 mL). To the residue was added Boc-Phe-OH (265 mg, 1.00 mmol), BOP (443 mg, 1.00 mmol), CH_2Cl_2 (6 mL), and DIPEA (0.36 mL, 2.2 mmol). After stirring for 1.5 h at r.t., the mixture was concentrated and dissolved in EtOAc (20 mL). After washing with 1.0 M $KHSO_4$ (4 × 10 mL), 1.0 M NaOH (2 × 10 mL), H_2O (10 mL), and brine (10 mL), the organic layer was dried over Na_2SO_4 and concentrated. Column chromatography (EtOAc–hexanes, 1:2) afforded **7** as a white solid.

Yield: 141 mg (35%); R_f = 0.33 (EtOAc–hexanes, 1:2); mp 123 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 2.84–3.08 [m, 10 H, $N(CH_3)_2$, $CHCH_2Ph$, CH_2SO_2), 3.65 (m, 2 H, $NCH_2CH_2SO_2$), 4.38 [m, 1 H, NCHC(O)], 5.12 [s, 1 H, NHBoc], 6.79 (s, 1 H, $NHCH_2CH_2SO_2$), 7.18–7.32 [m, 5 H, Ar-CH].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 [$C(CH_3)_3$], 33.6 ($NHCH_2CH_2$), 37.2 [$N(CH_3)_2$], 38.3 (CH_2Ph), 46.9 (CH_2SO_2), 55.7 [$NCHC(O)$], 80.0 [$C(CH_3)_3$], 126.9, 128.5, 129.2, 136.5 (Ar-C), 155.2 [$(CH_3)_3CC$=O], 171.6 [$CHC(O)NH$].

ESI-MS: *m*/*z* (%) = 300.05 [M – Boc + H]$^+$, 344.15 [M – *t*-Bu + H]$^+$, 422.35 [M + Na]$^+$, 438.35 [M + K]$^+$.

Peptidosulfonamide 8

To a solution of sulfonyl azide **2a** (142 mg, 0.500 mmol) in THF (5 mL) was added piperidine (198 μL, 2.00 mmol). The mixture was irradiated with microwaves for 15 min at 100 °C. After evaporation of the solvent, the residue was dissolved in EtOAc (20 mL) and washed with 5% $NaHCO_3$ soln (10 mL), 1.0 M $KHSO_4$ soln (10 mL), and brine (10 mL). Drying over Na_2SO_4 and concentration in vacuo afforded **8** as a clear yellowish oil.

Yield : 157 mg (96%); R_f = 0.39 (EtOAc–hexanes, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (m, 6 H, $NCH_2CH_2CH_2CH_2$), 3.06 (t, 2 H, SO_2CH_2), 3.20 (m, 4 H, 2 × $NCH_2CH_2CH_2$), 3.65 (m, 2 H, $NCH_2CH_2SO_2$), 5.10 (s, 2 H, OCH_2Ph), 5.61 (m, 1 H, NH), 7.34 [m, 5 H, Ar-CH (Cbz)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5, 25.4 ($NCH_2CH_2CH_2CH_2$), 35.4 ($NCH_2CH_2SO_2$), 46.4 ($NCH_2CH_2CH_2$), 48.4 (SO_2CH_2), 66.7 (OCH_2Ph), 127.9, 128.0, 128.4, 136.1 [Ar-CH (Cbz)], 156.1 [C=O (Cbz)].

ESI-MS: *m*/*z* (%) = 349.05 [M + Na]$^+$.

Peptidosulfonamide 9

To a solution of sulfonyl azide **2b** (186 mg, 0.500 mmol) in EtOH (10 mL) was added a cat. amount of Pd/C (10%). The mixture was stirred for 30 min under H_2 (balloon). Filtration over Hyflo Super Cel medium (Fluka), followed by evaporation of the solvent, afforded **9** as a white solid.

Yield: 169 mg (98%); R_f = 0.60 (MeOH–CH_2Cl_2, 1:9); mp 126 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.76 (m, 1 H, NH), 3.10 (m, 2 H, CH_2SO_2), 3.60 (m, 2 H, NCH_2), 4.22 [t, 1 H, CH (Fmoc)], 4.25 [d, 2 H, CH_2 (Fmoc)], 6.92 (br s, 2 H, NH_2), 7.31–7.91 [m, 8 H, Ar-CH (Fmoc)].

^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD, 9:1): δ = 35.6 (NCH_2), 46.8 [CH (Fmoc)], 53.9 (CH_2SO_2), 66.5 [OCH_2 (Fmoc)], 119.6, 124.7, 126.7, 127.4, 141.0, 143.4 [Ar-CH (Fmoc)], 156.8 [C=O (Fmoc)].

ESI-MS: *m*/*z* (%) = 347.35 [M + H]$^+$, 369.15 [M + Na]$^+$, 410.15 [M + CH_3CN + Na]$^+$.

Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09. Found: C, 59.07; H, 5.15; N, 7.97.

Peptidosulfonamide 10

A mixture of sulfonyl azide **2a** (56.9 mg, 0.200 mmol), PPh_3 (52.5 mg, 0.200 mmol), THF (3 mL), and H_2O (2 mL) was stirred at r.t. After 2 min the sulfonyl azide was completely dissolved and the evolution of N_2 had stopped. The mixture was concentrated in vacuo and EtOAc (20 mL) was added. After washing with 1.0 M $KHSO_4$ (10 mL) and brine (10 mL), the organic layer was dried over Na_2SO_4 and concentrated. Column chromatography (MeOH–CH_2Cl_2, 4:96) afforded sulfonamide **10** as a white solid.

Yield: 50.1 mg (97%); R_f = 0.21 (MeOH–CH_2Cl_2, 5:95); mp 78 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.13 (t, 2 H, CH_2SO_2), 3.38 (m, 3 H, NCH_2, NH), 5.03 (s, 2 H, $PhCH_2$), 6.93 (br s, 2 H, NH_2), 7.36 [m, 5 H, Ar-CH (Cbz)].

^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.8, 35.9 (NCH_2), 54.1 (CH_2SO_2), 65.7 (OCH_2Ph), 128.0, 128.1, 128.6, 137.2 [Ar-CH (Cbz)], 156.1, 156.2 [C=O (Cbz)].

ESI-MS: *m*/*z* (%) = 281.15 [M + Na]$^+$, 322.15 [M + CH_3CN + Na]$^+$.

Acknowledgment

We thank Mr. C. Versluis from the Department of Biomolecular Mass Spectrometry for recording some of the mass spectra.

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