An Efficient Synthesis of *N*-Protected β-Aminoethanesulfonyl Chlorides: Versatile Building Blocks for the Synthesis of Oligopeptidosulfonamides

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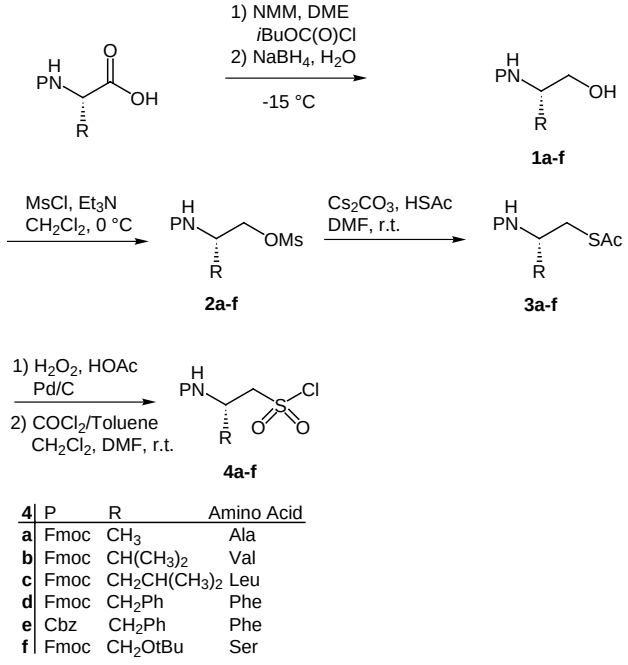
Abstract: A very efficient method for the synthesis of β-aminoethanesulfonyl chlorides is described. These aliphatic functionalized sulfonyl chlorides are accessible starting from a variety of protected amino acids, including those having functionalized side chains.

Key words: sulfonamides, sulfonyl chloride, amino acid, thioacetate, oxidation

There is still a growing interest in easily accessible building blocks, especially for combinatorial chemistry applications. We are interested in building blocks for the synthesis of peptoid-[1], urea-,[2] peptoidsulfonamide-,[3] and peptidosulfonamide-[4]peptidomimetics. Building blocks for peptidosulfonamides have been successfully applied to the synthesis of receptor molecules,[5] catalysts[6] and oligopeptidosulfonamides.[7] For combinatorial chemistry purposes, in which libraries of considerable size and purity are required, convenient and efficient syntheses of building blocks are indispensable. This is also a requirement for the solid phase synthesis of oligopeptidosulfonamides of considerable length,[7] perhaps ultimately leading to proteinosulfonamides. Originally, peptidosulfonamides were synthesized by the reaction of a β-aminoethanesulf*i*nyl chloride with an amine, and subsequent oxidation to the sulfonamide.[4a-f] The oxidation step did not always result in high yields and was difficult to optimize for use in solid phase synthesis.[4f] This problem was circumvented by the β-aminoethanesulf*o*nyl chloride approach in which Boc-[4g,8] or Fmoc-protected[4g] β-aminoethanesulfonyl chlorides have been employed. Using these Fmoc-protected aminoethanesulfonyl chlorides, we were able to synthesize oligopeptidosulfonamides on the solid phase as well as peptide-peptidosulfonamide hybrids.[4h] However, the route leading to these Boc- and Fmoc-protected sulfonyl chlorides was very cumbersome and only afforded impure compounds. Fmoc-protected sulfonyl chlorides are especially attractive for solid phase synthesis, because the efficiency of the synthesis can be monitored by formation of the dibenzofulvene-adduct after Fmoc-cleavage.[9] In the previously reported sulfonyl chloride syntheses,[4g,8] the Boc-group had to be cleaved in order to generate a soluble intermediate for the introduction of the sulfonate using aqueous sodium sulfite. Clearly the aim was to eliminate this tedious substitution step, of which the success was very much dependent on the solubility of the intermediate and which required an additional de/reprotection step. Therefore, the idea was to avoid the substitution step in water by preparation of a thioacetate precursor of the sulfonate.

To this end, Fmoc-protected amino acids (Ala, Val, Leu, Phe) were reduced to the corresponding alcohols **1a**–**d** (Scheme 1) using a method described by Rodriguez et al.[10] The alcohols were obtained as pure solids in high yields and did not require further purification. The mesylates **2a**–**d** were obtained in high yields (Table) by reaction of alcohols **1a**–**d** with methanesulfonyl chloride in



4	P	R	Amino Acid
a	Fmoc	CH_3	Ala
b	Fmoc	$CH(CH_3)_2$	Val
c	Fmoc	$CH_2CH(CH_3)_2$	Leu
d	Fmoc	CH_2Ph	Phe
e	Cbz	CH_2Ph	Phe
f	Fmoc	CH_2OtBu	Ser

Scheme 1

Table Yields of Compounds **2–4**

	Yield (%)		
Amino Acid	**2**	**3**	**4**
FmocAlaOH (**a**)	86	72	62
FmocValOH (**b**)	92	58	60
FmocLeuOH (**c**)	91	60	59
FmocPheOH (**d**)	94	64	68
CbzPheOH (**e**)	80	86	87[a]
FmocSer(*t*-Bu) (**f**)	97	54	82[a]

[a] Yields obtained using the sodium acetate method.

dichloromethane and Et_3N (Table) and could be purified by crystallization. The next three steps were crucial for the success of this approach. The first step was the introduction of the thioacetate group, which was carried out by adding the mesylates **2a**–**d** to a mixture of thioacetic acid (HSAc) and Cs_2CO_3 in DMF. Although a slight excess of Cs_2CO_3 is needed for overnight completion and a clean conversion, a large excess of Cs_2CO_3 had to be avoided to prevent cleavage of the Fmoc-group. Nevertheless, the slight basicity of the mixture was sufficient for cleavage of a small amount of the Fmoc-groups. After stirring overnight followed by workup and column chromatography, thioacetates **3a**–**d** were obtained in 58–72% yield on a 14–31 mmol scale.

Originally, it was attempted to synthesize the thioacetates **3a**–**d** directly from alcohols **1a**–**d** by a Mitsunobu reaction. It was found that this reaction was faster than the substitution reaction using the mesylate. However, purification was usually very tedious, and not reproducible on a larger scale (>10 mmol), due to formation of the Michael adduct of thioacetic acid and DIAD in addition to triphenyl phosphinoxide. Next, thioacetates **3a**–**d** were oxidized to the corresponding sulfonic acids using aqueous hydrogen peroxide (30% w/w) and acetic acid. After stirring overnight, the excess of peroxide was destroyed by addition of 10% Pd/C, followed by filtration, evaporation to dryness, and removal of residual water in the crude sulfonic acids by co-evaporation with toluene. The third and most crucial step is the conversion of the sulfonic acid to the corresponding sulfonyl chloride. Originally triphosgene was used but this was difficult to remove during purification. The sulfonyl chlorides that were prepared in this way invariably contained some unreacted triphosgene, which was not detectable on ^{13}C NMR and TLC. This residual triphosgene caused serious problems in the couplings reactions. Apart from incomplete coupling, isocyanates were formed, which upon reaction with the amine gave urea byproducts (dimers). Although almost all triphosgene could be removed using ethyl acetate/hexanes mixtures instead of dichloromethane over a silica plug, the yields of the sulfonyl chlorides were reduced as well. This problem was completely remedied by using a phosgene solution in toluene instead of triphosgene. Excess of phosgene can easily be removed by evaporation in vacuo, which simplifies the purification. The phosgene reactions proceeded similar to the triphosgene reactions, and after completion, the reaction mixture was concentrated, followed by a short silica plug (CH_2Cl_2) affording the sulfonyl chlorides **4a**–**d** in 59–68% yield at a 6–18 mmol scale, starting from thioacetates **3a**–**d**.

This procedure was also suitable for the preparation of sulfonyl chlorides containing the Cbz-protecting group, e.g., **4e**, which were required for a different project. Reduction to the alcohol **1e** and synthesis of the mesylate **2e** proceeded similar to **1d** and **2d**, respectively. However, the Cbz-protected thioacetate **3e** was obtained in a yield of 86% as compared to 64% for **3d**. This difference is probably due to some Fmoc cleavage in the latter compound (vide supra). The synthesis of sulfonyl chloride **4e** proceeded as expected, showing, albeit not surprising, that our new method for the synthesis of Fmoc-protected β-aminoethanesulfonyl chlorides is even better for Cbz-protected amino acids.

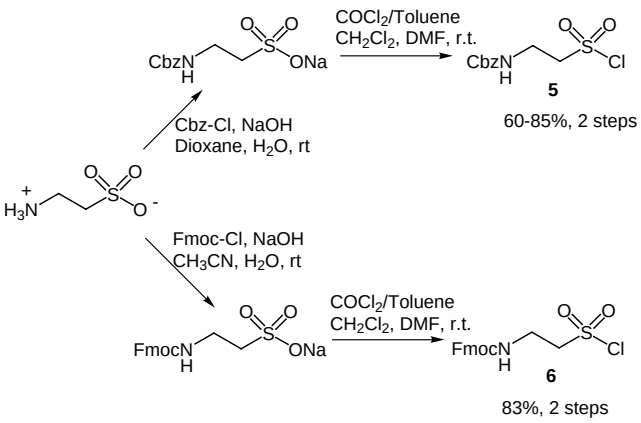
For the preparation of oligopeptidosulfonamides with functional side chains and peptidomimetic libraries of considerable diversity, β-aminoethanesulfonyl chlorides derived from functionalized amino acids are needed. So far, virtually only nonfunctionalized β-aminoethane-sulfonyl chlorides[4-8] are reported. To our knowledge, only the synthesis of a sulfonyl chloride having an ethyl-ester in the side chain was reported.[11] Chiral vinylogous sulfonyl chlorides have been described[12] starting from serine and tyrosine, but these are not compatible with solid phase synthesis using the Fmoc strategy. We envisioned that by carefully adjusting the conditions, the above described method could be adapted to the preparation of functionalized β-aminoethanesulfonyl chlorides, i.e., containing acid labile protecting groups. As a test case, the synthesis of the sulfonyl chloride derived from Fmoc-Ser(*t*-Bu)-OH was undertaken. It was assumed that if it was possible to convert this amino acid with the acid labile *tert*-butyl ether to the corresponding sulfonyl chloride, then it should also be possible to synthesize other functionalized β-aminoethanesulfonyl chlorides.

Reduction of Fmoc-Ser(*t*-Bu)-OH to the corresponding alcohol **1f** followed by conversion to mesylate **2f**, and synthesis of the thioacetate afforded **3f** in a good yield (overall: 47%, Table) without any problems. As more or less anticipated, a problem occurred during the oxidation step. After completion of the reaction and destruction of excess of peroxide, it was found that during the evaporation of the solvents (acetic acid, water), part of the *tert*-butyl groups were cleaved. Probably, the mixture became too acidic due to concentration of the sulfonic acid. This problem was solved by addition, after completion of the oxidation, of solid sodium acetate,[13] in order to convert the sulfonic acid in situ to its sodium-salt, thus preventing the reaction mixture from becoming too acidic. As a result, the thioacetate derived from serine, i.e., **3f**, could be easily converted to the desired sulfonyl chloride **4f** in a yield of 82%.

In order to investigate if the addition of sodium acetate could improve the yields of other sulfonyl chlorides as well, Cbz-protected sulfonyl chloride **4e** was synthesized from **3e** using sodium acetate. Indeed the yield of sulfonyl chloride **4e** was increased from 50% to 87%, thus showing that reducing the acidity by addition of sodium acetate was also favorable for the preparation of a sulfonyl chloride containing the more stable Cbz-group when compared to a *t*-Bu-.

The simplest aminoethanesulfonyl chloride, i.e., taurylsulfonyl chloride is derived from taurine and was earlier synthesized[14] by treatment of *N*-protected taurine with triphosgene.[4g] It was assumed that the above described method using phosgene might be also efficient for the

synthesis of *N*-protected taurylsulfonyl chlorides. Indeed, the phosgene method was very high yielding and reproducible, even on a large scale (100 mmol) (Scheme 2). Thus after *N*-protection sulfonyl chlorides **5** and **6** were obtained in high yields (60−85%).



Scheme 2

In conclusion, we have developed a highly efficient method for the convenient synthesis of β-aminoethanesulfonyl chlorides, in principle starting from any conceivable Fmoc- and Cbz-protected amino acid, including those having functionalized side chains. The method features the synthesis of a sodium sulfonate from a thioacetate, which is followed by synthesis of the sulfonyl chloride using phosgene.

Under present investigation is extension of the scope towards other functionalized amino acids, and to evaluate if this procedure could be fully applied to tryptophane, histidine, etc., which might be sensitive to the oxidation step.

Fmoc-protected amino acids were purchased from Alexis Corporation (Läufelfingen, Switzerland) and Cbz-protected amino acids from Advanced Chemtech Europe (Machelen, Belgium). Peptide grade solvents for synthesis were purchased from Biosolve (The Netherlands). *N*-methylmorpholine (NMM) was distilled from CaH_2. 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[15]. Solvents were evaporated under reduced pressure at 40 °C. Column chromatography was performed on Merck Kieselgel 60 (40−63 µm). Mps were determined using a Gallenkamp melting point apparatus no. 889339, and were 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). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian G-300 spectrometer. Chemical shifts are reported in ppm relative to TMS (0 ppm) for the ^{1}H NMR and to $CDCl_3$ (77 ppm) for the ^{13}C NMR as internal standards. ^{13}C NMR spectra were recorded using the attached proton test (APT) pulse sequence.

Alcohols 1a−f; General Procedure:

Alcohols **1a**−**f** were synthesized according to Rodriguez et al.[10] The described method afforded the alcohols **1a**−**f** in high yields (85−95%). Reactions were carried out up to 150 mmol scale.

Mesylates 2a−f; General Procedure[16]

To a solution of alcohol **1a**−**f** (18 mmol) in CH_2Cl_2 (60 mL) was added Et_3N (3.0 mL, 21.6 mmol). After cooling to 0 °C, methanesulfonyl chloride (MsCl, 1.67 mL, 21.6 mmol) was added dropwise. Stirring was continued for 1−4.5 h at r.t., followed by addition of CH_2Cl_2 (60 mL). The mixture was washed with a $KHSO_4$ (1 M, 60 mL), H_2O (60 mL), and brine (30 mL). After drying (Na_2SO_4) and evaporating the solvent in vacuo, the mesylate was crystallized from CH_2Cl_2/hexanes.

2a

The reaction was carried out on a 37 mmol scale using 2.5 times the amount of solvent of the general procedure due to the poor solubility of Fmoc-alaninol in CH_2Cl_2. Crystallization (EtOAc/hexanes) afforded white crystals. R_f = 0.24 (EtOAc/Hexanes, 1:1); mp = 139 °C.

^{1}H NMR ($CDCl_3$): δ = 1.27 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 3.00 (s, 3H, SO_2CH_3), 4.05 (m, 1H, $CHCH_3$), 4.22 [m, 3H, $MsOCH_2$, CH (Fmoc)], 4.43 [m, 2H, CH_2 (Fmoc)], 4.86 (br s, 1H, NH), 7.19−7.78 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 17.1 ($CHCH_3$), 37.4 (SO_2CH_3), 46.1 (NCH), 47.2 [CH (Fmoc)], 66.8 [CH_2 (Fmoc)], 71.7 ($MsOCH_2$), 120.0, 125.0, 127.1, 127.7, 141.3, 143.8 [Ar-C (Fmoc)], 155.8 [C=O (Fmoc)].

ESI MS: *m/z* = 398.05 $[M+Na]^+$.

Anal. Calcd for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73. Found: C, 60.76; H, 5.38; N, 3.74.

2b

Scale: 18 mmol; white crystals; R_f = 0.45 (EtOAc/Hexanes, 1:1); mp = 141 °C.

^{1}H NMR ($CDCl_3$): δ = 0.97 [2d, *J* = 6.6 and 7.0 Hz, 6H, $CH(CH_3)_2$], 1.87 [m, 1H, $CH(CH_3)_2$], 2.98 (s, 3H, SO_2CH_3), 3.69 (m, 1H, NCH), 4.27 [m, 3H, $MsOCH_2$, CH (Fmoc)], 4.46 [d, 2H, CH_2 (Fmoc)], 4.85 (br d, 1H, NH), 7.19−7.78 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 18.6, 19.3 [$CH(CH_3)_2$], 29.0 [$CH(CH_3)_2$], 37.4 (SO_2CH_3), 47.2 [CH (Fmoc)], 55.5, 55.6 (NCH), 67.0 [CH_2 (Fmoc)], 69.4 ($MsOCH_2$), 120.0, 125.0, 127.1, 127.7, 141.3, 143.8 [Ar-C (Fmoc)], 156.1 [C=O (Fmoc)].

ESI MS: *m/z* = 426.15 $[M+Na]^+$.

Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.24; N, 3.47. Found: C, 62.54; H, 5.88; N, 3.43.

2c

Scale: 18 mmol; white crystals; R_f = 0.51 (EtOAc/Hexanes, 1:1); mp = 119 °C.

^{1}H NMR ($CDCl_3$): δ = 0.93 [2d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$], 1.40 [m, 2H, $CH_2CH(CH_3)_2$], 1.64 [m, 1H, $CH(CH_3)_2$], 3.00 (s, 3H, SO_2CH_3), 3.99 (m, 1H, NCH), 4.22 [m, 3H, $MsOCH_2$, CH (Fmoc)], 4.45 [d, 2H, CH_2 (Fmoc)], 4.78 (br d, 1H, NH), 7.29−7.78 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 21.9, 22.9 [$CH(CH_3)_2$], 24.6 [$CH(CH_3)_2$], 37.3 (SO_2CH_3), 40.0 [$CH_2CH(CH_3)_2$], 47.2 [CH (Fmoc)], 48.5 (NCH), 66.6 [CH_2 (Fmoc)], 71.4 ($MsOCH_2$), 120.0, 125.0, 127.1, 127.7, 141.3, 143.7 [Ar-C (Fmoc)], 155.8 [C=O (Fmoc)].

ESI MS: *m/z* = 440.00 $[M+Na]^+$.

Anal. Calcd for $C_{22}H_{27}NO_5S$: C, 63.29; H, 6.52; N, 3.35. Found: C, 63.08; H, 6.12; N, 3.34.

2d

Scale: 78.3 mmol; white crystals; R_f = 0.11 (CH_2Cl_2); mp = 149 °C.

^{1}H NMR ($CDCl_3$): δ = 2.93 (m, 2H, CH_2Ph), 2.99 (s, 3H, SO_2CH_3), 4.22 [m, 4H, $MsOCH_2$, CH (Fmoc), NCH], 4.39 [d, *J* = 6.6 Hz, 2H, CH_2 (Fmoc)], 5.02 (br d, 1H, NH), 7.20−7.78 [m, 13H, Ar-CH (Ph, Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 37.1 (CH_2Ph), 37.3 (SO_2CH_3), 47.1 [CH (Fmoc)], 51.4 (NCH), 66.8 [CH_2 (Fmoc)], 69.6 ($MsOCH_2$), 120.0, 125.0, 127.1, 127.7, 128.8, 129.2, 136.3, 141.3, 143.7 [Ar-C (Ph, Fmoc)], 155.6 [C=O (Fmoc)].

ESI MS: *m/z* = 474.35 $[M+Na]^+$.

Anal. Calcd for $C_{25}H_{25}NO_5S$: C, 66.50; H, 5.58; N, 3.10. Found: C, 66.39; H, 5.65; N, 2.96.

2e

Scale: 83.4 mmol; white crystals, R_f = 0.67 (5% MeOH/CH_2Cl_2); mp = 101 °C.

^{1}H NMR ($CDCl_3$): δ = 2.96 (m, 5H, SO_2CH_3, $CHCH_2$Ph), 4.15 (m, 3H, $MsOCH_2$, NCH), 5.08 (m, 3H, OCH_2Ph, NH), 7.33 [m, 10H, Ar-CH (Ph, Cbz)].

^{13}C NMR ($CDCl_3$): δ = 37.0 (CH*C*H_2Ph), 37.2 (SO_2CH_3), 51.3 (NCH), 66.9 (OCH_2Ph), 69.4 ($MsOCH_2$), 127.0, 128.1, 128.2, 128.5, 128.8, 129.2, 136.3 [Ar-C (Ph, Cbz)], 155.6 [C=O (Cbz)].

ESI MS: *m/z* = 386.15 $[M+Na]^+$.

Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.49; H, 5.82; N, 3.85. Found: C, 59.38; H, 5.89; N, 3.76.

2f

Scale: 42.5 mmol; colorless oil; Rf = 0.11 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.19 [s, 9H, $C(CH_3)_3$], 3.01 (s, 3H, SO_2CH_3), 3.41 (dd, J_{gem} = 8.8 Hz, J_{vic} = 5.5 Hz, 1H, *t*-BuOCH^a), 3.54 (dd, J_{gem} = 9.2 Hz, J_{vic} = 3.3 Hz, 1H, *t*-BuOCH^b), 4.06 (m, 1H, NCH), 4.26 [m, 3H, $MsOCH_2$, CH (Fmoc)], 4.42 [m, 2H, CH_2 (Fmoc)], 5.23 (br d, 1H, NH), 7.30−7.78 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 27.3 [C(*C*H_3)$_3$], 37.2 (SO_2CH_3), 47.1 [CH (Fmoc)], 50.0 (NCH), 59.5 (*t*-BuO*C*H_2), 66.9 [CH_2 (Fmoc)], 67.9 ($MsOCH_2$), 73.5 [*C*(CH_3)$_3$], 120.0, 125.0, 127.0, 127.7, 141.3, 143.7 [Ar-C (Fmoc)], 155.8 [C=O (Fmoc)].

ESI MS: *m/z* = 470.35 $[M+Na]^+$.

Thioacetates 3a−f; General Procedure[16]

HSAc (1.18 mL, 16.8 mmol) was added to a suspension of Cs_2CO_3 (2.96 g, 9.1 mmol) in DMF (70 mL). The mesylate **2a**−**f** (14 mmol) was added in one portion to the formed solution and stirring was continued at r.t. for 18 h, during which the reaction flask was covered with aluminium foil. The mixture was poured into distilled H_2O (300 mL), and extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with H_2O (400 mL), $NaHCO_3$ (5% w/w, 400 mL), and brine (200 mL). Drying (Na_2SO_4) followed by concentration in vacuo afforded the crude product, which was purified by column chromatography (CH_2Cl_2).

3a

Scale: 30 mmol; white solid; R_f = 0.73 (EtOAc/hexanes, 1:1); mp = 134 °C.

^{1}H NMR ($CDCl_3$): δ = 1.20 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 2.34 [s, 3H, C(O)*C*H_3], 3.04 (d, *J* = 6.2 Hz, 2H, SCH_2), 3.93 (m, 1H, NCH), 4.20 [t, *J* = 7.0 Hz, 1H, CH (Fmoc)], 4.36 [m, 2H, CH_2 (Fmoc)], 4.94 (br d, 1H, NH), 7.27−7.76 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 20.2 ($CHCH_3$), 30.5 [C(O)CH_3], 34.7 (SCH_2), 47.1 [NCH, CH (Fmoc)], 66.5 [CH_2 (Fmoc)], 119.9, 125.0, 126.9, 127.6, 141.2, 143.8 [Ar-C (Fmoc)], 155.6 [C=O (Fmoc)], 195.8 (SC=O).

ESI MS: *m/z* = 378.05 $[M+Na]^+$.

Anal Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.51; H, 6.04; N, 3.79.

3b

Scale: 14 mmol; white solid; R_f = 0.20 (CH_2Cl_2); mp = 121 °C.

^{1}H NMR ($CDCl_3$): δ = 0.96 (2d, *J* = 6.6 Hz, 6H, $CHCH_3)_2$), 1.81 [m, 1H, $CH(CH_3)_2$], 2.32 [s, 3H, C(O)CH_3], 3.04 (m, 2H, SCH_2), 3.64 (m, 1H, NCH), 4.21 [t, *J* = 7.0 Hz, 1H, CH (Fmoc)], 4.37 [m, 2H, CH_2 (Fmoc)], 4.82 (br d, 1H, NH), 7.28−7.77 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 18.0, 19.2 [$CH(CH_3)_2$], 30.6 [$CH(CH_3)_2$], 31.6 (SCH_2), 32.2 [C(O)CH_3], 47.2 [CH (Fmoc)], 56.7 (NCH), 66.6 [CH_2 (Fmoc)], 119.9, 125.0, 125.1, 127.0, 127.6, 141.2, 143.9, 144.0 [Ar-C (Fmoc)], 156.3 [C=O (Fmoc)], 196.3 (SC=O).

ESI MS: *m/z* = 406.10 $[M+Na]^+$.

Anal. Calcd for $C_{22}H_{25}NO_3S$: C, 68.90; H, 6.57; N, 3.65. Found: C, 68.96; H, 6.58; N, 3.59.

3c

Scale: 15 mmol; white solid; R_f = 0.21 (CH_2Cl_2), mp = 79 °C.

^{1}H NMR ($CDCl_3$): δ = 0.91 [d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$], 1.36 [m, 2H, $CH_2CH(CH_3)_2$], 1.64 [m, 1H, $CH(CH_3)_2$], 2.33 [s, 3H, C(O)CH_3], 2.98 (dd, J_{gem} = 13.9 Hz, J_{vic} = 7.3 Hz, 1H, SCH^a), 3.09 (dd, J_{gem} = 13.9 Hz, J_{vic} = 4.8 Hz, 1H, SCH^b), 3.90 (m, 1H, NCH), 4.21 [t, *J* = 7.0 Hz, 1H, CH (Fmoc)], 4.39 [m, 2H, CH_2 (Fmoc)], 4.70 (br d, 1H, NH), 7.28−7.77 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 22.1, 23.0 [$CH(CH_3)_2$], 24.8 [$CH(CH_3)_2$], 30.6 [C(O)CH_3], 34.2 (SCH_2), 43.6 [$CH_2CH(CH_3)_2$], 47.2 [CH (Fmoc)], 49.3 (NCH), 66.5 [CH_2 (Fmoc)], 119.9, 125.0, 127.0, 127.6, 141.3, 143.8, 144.0 [Ar-C (Fmoc)], 155.9 [C=O (Fmoc)], 195.8 (SC=O).

ESI MS: *m/z* = 420.20 $[M+Na]^+$.

Anal. Calcd for $C_{23}H_{27}NO_3S$: C, 69.49; H, 6.85; N, 3.52. Found: C, 69.26; H, 6.80; N, 3.38.

3d

Scale: 31 mmol; white solid, R_f = 0.23 (CH_2Cl_2); mp = 83 °C.

^{1}H NMR ($CDCl_3$): δ = 2.33 [s, 3H, C(O)*C*H_3], 2.78−3.09 (m, 4H, SCH_2, CH_2Ph), 4.04 (m, 1H, NCH), 4.17 [t, *J* = 7.0 Hz 1H, CH (Fmoc)], 4.32 [m, 2H, CH_2 (Fmoc)], 4.95 (br s, 1H, NH), 7.16−7.76 [m, 13H, Ar-CH (Fmoc, Ph)].

^{13}C NMR ($CDCl_3$): δ = 30.6 [C(O)*C*H_3], 32.6 (SCH_2), 40.5 (CH_2Ph), 47.2 [CH (Fmoc)], 52.6 (NCH), 66.6 [CH_2 (Fmoc)], 119.9, 125.0, 126.7, 127.0, 127.6, 128.6, 129.3, 137.0, 141.2, 143.8 [Ar-C (Fmoc, Ph)], 155.7 [C=O (Fmoc)], 195.7 (SC=O).

ESI MS: *m/z* = 454.15 $[M+Na]^+$.

Anal. Calcd for $C_{26}H_{25}NO_3S$: C, 72.36; H, 5.84; N, 3.25. Found: C, 72.28; H, 5.92; N, 3.16.

3e

Scale: 20 mmol; purified by crystallization (CH_2Cl_2/hexanes); white needles; R_f = 0.59 (EtOAc/hexanes, 1:1); mp = 85 °C.

^{1}H NMR ($CDCl_3$): δ = 2.33 [s, 3H, C(O)CH_3], 2.95 (m, 4H, CHC*H*$_2$Ph, SC*H*$_2$), 4.06 (m, 1H, NCH), 4.92 (br d, 1H, NH), 5.07 [s, 2H, CH_2 (Cbz)], 7.33 [m, 10H, Ar-CH (Ph, Cbz)].

^{13}C NMR ($CDCl_3$): δ = 30.5 [C(O)*C*H_3], 32.6 (SCH_2), 40.3 (CH*C*H_2Ph), 52.5 (NCH), 66.5 [CH_2 (Cbz)], 126.7, 127.9, 128.0, 128.4, 128.5, 129.3, 136.5, 137.0 [Ar-C (Ph, Cbz)], 155.7 [C=O (Cbz)], 195.9 (SC=O).

ESI MS: *m/z* = 366.10 $[M+Na]^+$.

Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.55; H, 6.23; N, 3.96.

3f

Scale: 35 mmol; white crystalline solid; R_f = 0.18 (CH_2Cl_2); mp = 78 °C.

^{1}H NMR ($CDCl_3$): δ = 1.19 [s, 9H, $C(CH_3)_3$], 2.35 [s, 3H, $C(O)CH_3$], 3.37 (d, *J* = 6.6 Hz, 2H, SCH_2), 3.44 (m, 2H, *t*-$BuOCH_2$), 3.92 (m, 1H, NCH), 4.25 [m, 1H, CH (Fmoc)], 4.38 [m, 2H, OCH_2 (Fmoc)], 5.25 (br d, 1H, NH), 7.30−7.78 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 27.4 [$C(CH_3)_3$], 30.6 [$C(O)CH_3$], 31.0 (SCH_2), 47.2 [CH (Fmoc)], 51.3 (NCH), 62.5 (*t* $BuOCH_2$), 66.8 [CH_2 (Fmoc)], 73.2 [$C(CH_3)_3$], 120.0, 125.1, 127.0, 127.6, 141.3, 143.9 [Ar-C (Fmoc)], 155.9 [C=O (Fmoc)], 196.0 (SC=O).

ESI MS: *m/z* = 450.25 $[M+Na]^+$.

Anal. Calcd for $C_{24}H_{29}NO_4S$: C, 67.42; H, 6.84; N, 3.28. Found: C, 67.65; H, 6.61; N, 3.08.

Sulfonyl Chlorides 4a−f; General Procedure[16]

A mixture of H_2O_2 [30% w/w in H_2O (5 mL)] and HOAc (10 mL) was added to a solution of thioacetate **3a**−**f** (4.9 mmol) in HOAc (5 mL). After stirring overnight at r.t., 10% Pd/C (25 mg) was added to destroy the excess of peroxide. For synthesis of the sodium sulfonate, NaOAc (1.1 equiv) was added before adding the Pd/C, followed by 1 h of stirring at r.t. Filtration over Hyflo, concentration, and co-evaporation with toluene (3 × 30 mL) afforded the crude sulfonic acid or sodium sulfonate. Under a N_2 atm, CH_2Cl_2 (30 mL) was added followed by a phosgene solution in toluene (20% m/m, 4 mL) and DMF (0.6 mL). If necessary, after 1 h additional phosgene solution (1−2 mL) was added for completion of the reaction. After stirring for 2 h at r.t., the mixture was concentrated and the product was purified through a silica plug (CH_2Cl_2), followed by precipitation in CH_2Cl_2/hexanes, and filtration. The product was dried (P_2O_5) and stored under Ar.

4a

Scale: 9.1 mmol; white solid; R_f = 0.20 (CH_2Cl_2); mp = 149 °C.

^{1}H NMR ($CDCl_3$): δ = 1.48 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 3.86 (dd, 1H, SO_2CH^a), 4.14 (dd, 1H, SO_2CH^b), 4.22 [t, 1H, CH (Fmoc)], 4.32 (m, 1H, NCH), 4.46 [m, 2H, CH_2 (Fmoc)], 5.09 (d, 1H, NH), 7.30−7.78 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 19.6 (CH_3), 44.4 (NCH), 47.1 [CH (Fmoc)], 66.8 [CH_2 (Fmoc)], 69.4 (SO_2CH_2), 120.0, 125.0, 127.1, 127.8, 141.3, 143.6 [Ar-C (Fmoc)], 155.2 [C=O (Fmoc)].

ESI MS: *m/z* = 402.10, 404.15 $[M+Na]^+$: due to chlorine isotopes.

Anal. Calcd for $C_{18}H_{18}ClNO_4S$: C, 56.92; H, 4.78; N, 3.69. Found: C, 56.90; H, 4.42; N, 3.75.

4b

Scale: 16.3 mmol; white solid; R_f = 0.56 (EtOAc/hexanes, 1:2); mp = 168 °C.

^{1}H NMR ($CDCl_3$, 50 °C): δ = 0.96 [m, 6H, $CH(CH_3)_2$], 2.09 [m, 1H, $CH(CH_3)_2$], 3.87−4.06 (m, 3H, SO_2CH_2CH), 4.22 [t, 1H, CH (Fmoc)], 4.46 [m, 2H, CH_2 (Fmoc)], 5.04 (br s, 1H, NH), 7.28−7.77 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 18.2, 19.3 [$CH(CH_3)_2$], 31.3 [$CH(CH_3)_2$], 47.2 [CH (Fmoc)], 53.8 (NCH), 66.8 [CH_2 (Fmoc)], 67.0 (SO_2CH_2), 120.0, 125.0, 127.1, 127.7, 141.3, 143.6, 143.7 [Ar-C (Fmoc)], 155.6 [C=O (Fmoc)].

ESI MS: *m/z* = 430.05, 432.05 $[M+Na]^+$: due to chlorine isotopes.

Anal. Calcd for $C_{20}H_{22}ClNO_4S$: C, 58.89; H, 5.44; N, 3.43. Found: C, 58.82; H, 5.54; N, 3.33.

4c

Scale: 18.2 mmol; white solid; R_f = 0.26 (CH_2Cl_2); mp = 144 °C.

^{1}H NMR ($CDCl_3$): δ = 0.94 [m, 6H, $CH(CH_3)_2$], 1.43−1.78 [m, 3H, $CH_2CH(CH_3)_2$], 3.85 (dd, 1H, J_{gem} = 14.3 Hz, J_{vic} = 4.0 Hz, SO_2CH^a), 4.07 (dd, J_{gem} = 14.3 Hz, J_{vic} = 6.1 Hz, 1H, SO_2CH^b), 4.21 [m, 2H, NCH, CH (Fmoc)], 4.46 [m, 2H, CH_2 (Fmoc)], 5.01 (d, 1H, NH), 7.29−7.78 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 21.5, 22.8 [$CH(CH_3)_2$], 24.7 [$CH(CH_3)_2$], 42.1 [$CH_2CH(CH_3)_2$], 47.0 (NCH), 47.2 [CH (Fmoc)], 66.7 [CH_2 (Fmoc)], 69.0 (SO_2CH_2), 120.0, 125.0, 127.1, 127.8, 141.3, 143.6 [Ar-C (Fmoc)], 155.3 [C=O (Fmoc)].

ESI MS: *m/z* = 444.00, 446.15 $[M+Na]^+$: due to chlorine isotopes.

Anal. Calcd for $C_{21}H_{24}ClNO_4S$: C, 59.78; H, 5.73; N, 3.32. Found: C, 60.20; H, 5.83; N, 3.18.

4d

Scale: 5.6 mmol; white solid; R_f = 0.21 (CH_2Cl_2); mp = 175 °C (dec.).

^{1}H NMR (THF-d_8): δ = 2.87 (dd, J_{gem} = 13.6 Hz, J_{vic} = 5.1 Hz, 1H, CH^aPh), 2.98 (dd, J_{gem} = 13.6 Hz, J_{vic} = 8.1 Hz, 1H, CH^bPh), 4.05−4.33 [m, 6H, SO_2CH_2, NCH, CH (Fmoc), CH_2 (Fmoc)], 6.96 (d, 1H, NH), 7.06−7.68 [m, 13H, Ar-CH (Fmoc, Ph)].

^{13}C NMR (THF-d_8, Int. ref. = 67.4 ppm): δ = 39.8 (CH_2Ph), 48.3, 50.9 [NCH, CH (Fmoc)], 66.7, 68.3 [SO_2CH_2, CH_2 (Fmoc)], 120.7, 126.0, 126.0, 127.6, 127.8, 128.4, 129.4, 130.3, 138.4, 143.4 [Ar-C (Fmoc, Ph)], 145.4 [C=O (Fmoc)].

ESI MS: *m/z* = 478.05, 480.25 $[M+Na]^+$: due to chlorine isotopes.

Anal. Calcd for $C_{24}H_{22}ClNO_4S$: C, 63.22; H, 4.86; N, 3.07. Found: C, 63.16; H, 4.61; N, 2.94.

4e

Scale: 11.4 mmol; white solid; R_f = 0.30 (CH_2Cl_2); mp = 126 °C.

^{1}H NMR ($CDCl_3$): δ = 3.09 (m, 2H, $CHCH_2Ph$), 3.87 (dd, J_{gem} = 14.3 Hz, J_{vic} = 4.0 Hz, 1H, SO_2CH^a), 4.13 (dd, J_{gem} = 14.3 Hz, J_{vic} = 7.0 Hz, 1H, SO_2CH^b), 4.39 (m, 1H, NCH), 5.09 (dd, *J* = 14.1 Hz, 2H, OCH_2Ph), 5.22 (br d, 1H, NH), 7.15−7.39 [m, 10H, Ar-CH (Ph, Cbz)].

^{13}C NMR ($CDCl_3$): δ = 39.1 ($CHCH_2Ph$), 49.8 (NCH), 67.1 (OCH_2Ph), 69.0 (SO_2CH_2), 127.4, 128.1, 128.3, 128.5, 129.0, 129.2, 135.7, 135.9 [Ar-C (Ph, Cbz)], 155.3 [C=O (Cbz)].

ESI MS: *m/z* = 390.10, 392.05 $[M+Na]^+$: due to chlorine isotopes.

Anal. Calcd for $C_{17}H_{18}ClNO_4S$: C, 55.51; H, 4.93; N, 3.81. Found: C, 55.38; H, 5.06; N, 3.74.

4f

The thioacetate **3f** was first dissolved in THF (8 mL), before adding HOAc. NaOAc (8.8 mmol) was added after completion of the oxidation. The chloride was purified by column chromatography, and was not precipitated. Scale: 8.0 mmol; white solid. R_f = 0.29 (CH_2Cl_2); mp = 119 °C.

^{1}H NMR ($CDCl_3$): δ = 1.21 [s, 9H, $C(CH_3)_3$], 3.52 (dd, J_{gem} = 9.2 Hz, J_{vic} = 4.4 Hz, 1H, *t*-$BuOCH^a$), 3.67 (dd, J_{gem} = 9.2 Hz, J_{vic} = 2.9 Hz, 1H, *t*-$BuOCH^b$), 4.02 (m, 2H, SO_2CH_2), 4.24 [m, 1H, CH (Fmoc)], 4.47 [m, 3H, OCH_2 (Fmoc), NCH], 5.42 (br d, 1H, NH), 7.31−7.79 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 27.3 [$C(CH_3)_3$], 47.1 [NH (Fmoc)], 48.1 (NCH), 61.4 (*t*-$BuOCH_2$), 65.3 (SO_2CH_2), 66.9 [CH_2 (Fmoc)], 73.9 [$C(CH_3)_3$], 120.0, 124.9, 125.0, 127.0, 127.7, 141.2, 143.6 [Ar-C (Fmoc)], 155.3 [C=O (Fmoc)].

ESI MS: *m/z* = 474.15, 475.90 $[M+Na]^+$: due to chlorine isotopes.

Anal. Calcd for $C_{22}H_{26}ClNO_5S$: C, 58.47; H, 5.80; N, 3.10. Found: C, 58.26; H, 5.91; N, 2.97.

Cbz-taurylsulfonyl Chloride (5)

Taurine (6.26 g, 50 mmol) was dissolved in a solution of NaOH (1 M, 50 mL) in H_2O. Then simultaneously, under vigorous stirring, a solution of Cbz-chloride (10.6 mL, 75 mmol) in dioxane (65 mL) and a solution of NaOH (1 M, 75 mL) in H_2O were added dropwise. After stirring for 1 h, the reaction mixture was extracted with EtOAc (2×200 mL) to remove excess of Cbz-chloride. Concentration of the aqueous layer in vacuo followed by co-evaporation with toluene (150 mL), EtOH (150 mL), and CH_2Cl_2 (3×150 mL) afforded the crude sodium sulfonate salt, which was dried (P_2O_5). Subsequently, a phosgene solution in toluene (20% w/w, 50 mL) and DMF (4 mL) were added to a suspension of the sodium sulfonate in CH_2Cl_2 (350 mL). The reaction mixture was concentrated after stirring for 1 h at r.t. Purification by silica gel column chromatography (CH_2Cl_2) afforded Cbz-taurylsulfonyl chloride as a white solid in 60% yield (2 steps). On a larger scale (150 mmol) yields up to 85% were reached.

R_f = 0.27 (CH_2Cl_2); mp = 47 °C.

^{1}H NMR ($CDCl_3$): δ = 3.85 (m, 4H, $SO_2CH_2CH_2$), 5.12 (br s, 2H, CH_2Ph), 5.44 (br s, 1H, NH), 7.35 (s, 5H, Ar-CH).

^{13}C NMR ($CDCl_3$): δ = 36.3 (NCH_2), 64.6 (SO_2CH_2), 67.3 (CH_2Ph), 128.1, 128.4, 128.6, 135.8 (Ar-C), 156.1 [C = O (Cbz)].

ESI MS: *m/z* = 278.01, 280.01 $[M+H]^+$, 299.94, 301.97 $[M+Na]^+$: due to chlorine isotopes.

Anal. Calcd for $C_{10}H_{12}ClNO_4S$: C, 43.25; H, 4.36; N, 5.04; S, 11.54. Found: C, 43.33; H, 4.37; N, 5.01; S, 11.42.

Fmoc-taurylsulfonyl Chloride (6)

A solution of taurine (3.13 g, 25 mmol) in H_2O (50 mL) was adjusted to pH 8.5 by the addition of NaOH (1 M) in H_2O. Subsequently, a solution of Fmoc-chloride (7.75 g, 30 mmol) in CH_3CN (100 mL) was added, during which the pH was kept at 8−8.5 by addition of small amounts of 1 M NaOH. The reaction mixture was stirred for approximately 1 h. After addition of H_2O (150 mL), excess of Fmoc-chloride was removed by washing with EtOAc (2×150 mL). Concentration of the aqueous layer under reduced pressure followed by co-evaporation with toluene (3×150 mL), EtOH (3×150 mL), and CH_2Cl_2 (3×150 mL) afforded the crude sodium sulfonate salt, which was dried (P_2O_5). Subsequently, a phosgene solution in toluene (20% m/m, 20 mL) and DMF (3 mL) were added to a suspension of the sodium sulfonate in CH_2Cl_2 (200 mL). If necessary, more phosgene solution (5 mL) was added after 1 h to complete the reaction. The reaction mixture was concentrated after stirring for 2 h at r.t. Purification by silica gel column chromatography (CH_2Cl_2) under an elevated N_2 pressure afforded Fmoc-taurylsulfonyl chloride as a white solid in 83% yield (2 steps).

R_f = 0.16 (CH_2Cl_2); mp = 95 °C.

^{1}H NMR ($CDCl_3$): δ = 3.84 (m, 4H, $SO_2CH_2CH_2$), 4.20 [t, 1H, CH (Fmoc)], 4.44 [d, 2H, CH_2 (Fmoc)], 5.35 (br s, 1H, NH), 7.28−7.77 [m, 8H, Ar-CH (Fmoc)].

^{13}C NMR ($CDCl_3$): δ = 36.3 (NCH_2), 47.1 [CH (Fmoc)], 64.6 (SO_2CH_2), 67.1 [CH_2 (Fmoc)], 128.1, 128.4, 128.6, 135.8 (Ar-C), 156.1 [C=O (Fmoc)].

ESI MS: *m/z* = 388.03, 390.03 $[M+Na]^+$: due to chlorine isotopes.

Anal. Calcd for $C_{17}H_{16}ClNO_4S$: C, 55.81; H, 4.41; N, 3.83; S, 8.76. Found: C, 55.91; H, 4.28; N, 3.66; S, 8.55.

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