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Synthesis of *N*-phthalimido β-aminoethanesulfonyl chlorides: the use of thionyl chloride for a simple and efficient synthesis of new peptidosulfonamide building blocks

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Abstract—*N*-Phthalimido β-aminoethanesulfonyl chlorides, new building blocks for the synthesis of peptidosulfonamide peptidomimetics, were prepared in a straightforward manner from amino acids. In the crucial synthetic step, sulfonic acids or their sodium salts were converted into the corresponding sulfonyl chlorides using an excess of refluxing thionyl chloride or thionyl chloride/DMF. This simple and effective chlorinating method is also applicable to β-aminoethane sulfonic acids and their sodium salts with other *N*-protecting groups.

Bioisosteric replacement of a peptide bond with various surrogates is a widespread strategy for improving biological activity, physicochemical properties, and stability of peptides.[1–3] In the past, a wide variety of modified peptides have been developed (e.g., azapeptides, depsipeptides, retro and retro-inverso peptides, phospha- peptides, ureidopeptides, etc.).[4] Among these, peptidosulfonamides have been recognized as building blocks, not only for preparing peptidomimetics, but also for developing enzyme inhibitors, catalysts, foldamers, tweezers, etc.[5–22] Due to the intrinsic chemical instability of α-peptidosulfonamides, most of the studies of peptides containing the SO_2NH junction are limited to β-peptidosulfonamides (Fig. 1).[23] These possess a geometry similar to the tetrahedral intermediate formed during peptide bond cleavage.[24] Their polarity and hydrogen-bond donation capability are greater than those of the corresponding natural peptides.[13] Additionally, the stability of peptidosulfonamide peptidomimetics toward degradation by proteases is significantly increased.[25]

In principle, two types of β-aminosulfonic acid mimics of naturally occurring α-amino acids are possible: one having the side chain on the α-carbon with respect to the sulfonyl moiety and one with the side chain on the β-carbon atom (Fig. 1). Most of the research in this field has been devoted to β-substituted β-sulfonopeptides. Originally, peptidosulfonamides were synthesized by coupling β-aminoethanesulfinyl chlorides with C-protected amino acids, followed by oxidation of the resulting sulfinamides to sulfonamides.[8,9,24] The oxidation step did not always result in satisfactory yields.[9] In the most general approach *N*-protected β-sulfonyl chlorides are used to prepare sulfonopeptides. They are usually obtained from *N*-protected β-sulfonic acids or their sodium salts, using chlorinating agents such as PCl_5,[26,27] phosgene,[17,18,20] or triphosgene.[9,11,13] The *N*-protected β-sulfonic acids are conveniently prepared from readily available *N*-protected α-amino acid esters, which are reduced to alcohols, mesylated, then converted into the corresponding thioacetates, and finally oxidized to the target sulfonic acids.[18] In these procedures Cbz, Fmoc, and Boc *N*-protecting groups have been used.

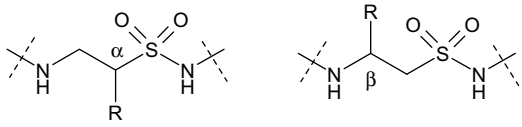

Figure 1. α- and β-substituted β-aminoethane sulfonamide mimics of natural amino acids.

Keywords: Peptidomimetics; Peptidosulfonamides; β-Aminosulfonyl chlorides.
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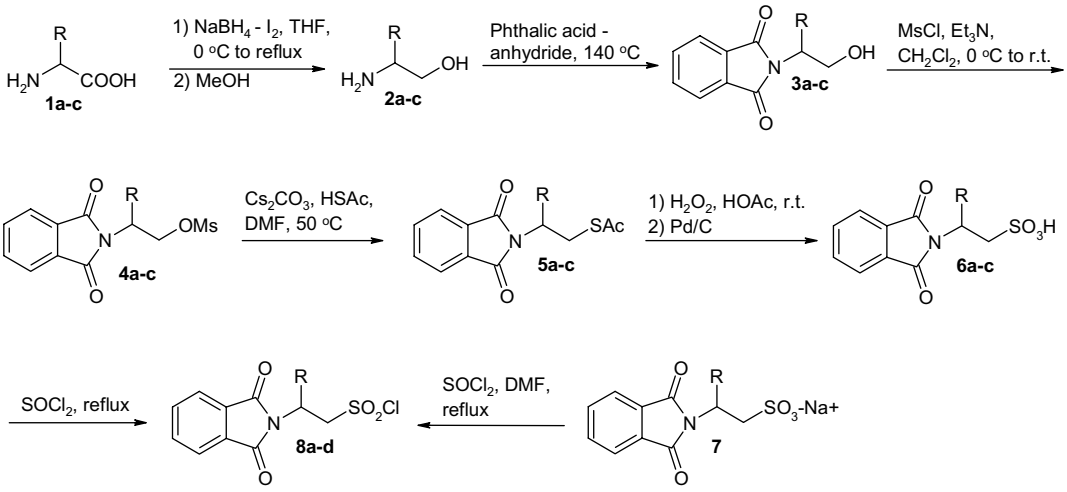


Scheme 1. Synthesis of *N*-phthalimido β-aminoethanesulfonyl chlorides **8a**–**d**.

As a part of our research on peptidosulfonamide enzyme inhibitors we wanted to introduce a new protection strategy using the *N*-phthalimido protecting group (Scheme 1). We started the synthesis with free amino acids **1** (Ala, Val, Phe), which were reduced to aminoalcohols **2** using the $NaBH_4$–I_2 system[28] and phthaloylated with phthalic anhydride to give *N*-phthalimido protected aminoalcohols **3** in high yield. In the next three steps, we slightly modified the procedure of Brouwer et al.[18] The protected aminoalcohols **3** were mesylated with methanesulfonyl chloride and Et_3N in dichloromethane. In the next step, mesylates **4** were added to a mixture of thioacetic acid and Cs_2CO_3 in DMF and stirred at 50 °C for 24 h. If the reaction was carried at room temperature, as described originally,[18] the yields were low and irreproducible. Furthermore, a slight excess of Cs_2CO_3 was needed for clean conversion. Although we used more vigorous conditions we did not notice any cleavage of the phthalimido group as was reported in the case of the Fmoc *N*-protecting group.[18] Thioacetates **5** were then oxidized to the corresponding sulfonic acids **6** using aqueous hydrogen peroxide and acetic acid and, after 24 h at rt, the excess of peroxide was destroyed by adding 10% Pd/C. The resulting crude sulfonic acids **6** were finally refluxed in excess thionyl chloride to give sulfonyl chlorides **8a**–**c** in high yields on a 7–35 mmol scale (Table 1).[29] We did not observe any racemization of compounds **2**–**6** and **8** during this procedure. The optical purity of all products was confirmed by optical rotation. In addition, sulfonyl chlorides **8a**–**c** were coupled with enantiomerically pure amino acids (e.g., L-Ala(OBzl)) and the products were examined by ^{1}H NMR (data not shown). No multiplication of ^{1}H NMR signals, due to possible formation of diastereomers, was observed which provided further evidence that the procedure described in this paper is racemization free.

The reaction of sulfonic acid sodium salt **7** with an excess of refluxing thionyl chloride was also examined (Table 1). The reaction proved to be sluggish, most probably because of the low solubility of sulfonic acid sodium salts in thionyl chloride. Nevertheless, the corresponding sulfonyl chloride **8d** could be obtained by a slight modification of the procedure in which a small amount of dry DMF was added to the reaction mixture to achieve clean and rapid chlorination of sodium salt **7** (Scheme 1).[30]

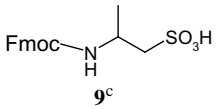
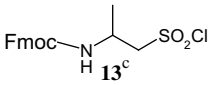
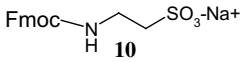
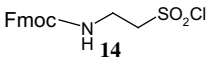
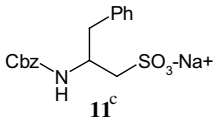
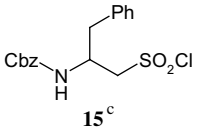
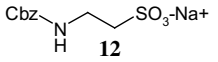
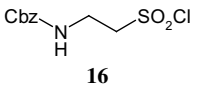
The crucial step in the synthesis of peptidosulfonamides is the conversion of sulfonic acids to the corresponding sulfonyl chlorides. β-Substituted β-aminoethane sulfonyl chlorides are usually obtained from sulfonic acids or their salts using triphosgene[9,11,13] or phosgene[17,18,20] as chlorinating agents. Both agents give sulfonyl chlorides in high yields but also suffer from some drawbacks. Triphosgene is not detectable by ^{1}H NMR and TLC which makes purification of sulfonyl chlorides very difficult. In addition, it was reported that residual triphosgene caused serious problems in the subsequent coupling reactions, thus lowering overall yields.[18] These problems were overcome by replacing triphosgene with phosgene which can be easily removed by evaporation in vacuum. However, phosgene is toxic on acute inhalation exposure and severe respiratory effects have been reported in humans.[32] To circumvent these problems we sought

Table 1. Yields of compounds **3**–**5** and **8**

Starting amino acids **1**	R	Yield (%)			
		3	**4**	**5**	**8**
L-Ala (**a**)	CH_3	86	96	82	85[a]
L-Val (**b**)	$CH(CH_3)_2$	75	90	71	67[a] (<20)[b]
D-Phe (**c**)	CH_2Ph	96	84	80	62[a] (<20)[b]
Tau (**d**)[c]	H	—	—	—	<20 (89)[d]

[a] Overall yields from the conversion of thioacetates **5a**–**c** into sulfonyl chlorides **8a**–**c** (two steps).
[b] Yields from the $SOCl_2$ procedure, applying the corresponding sodium salts of **6**.
[c] The sulfonic acid sodium salt **7** was prepared as described.[31]
[d] Yield from the $SOCl_2$ /DMF procedure.

Table 2. Synthesis of Fmoc- and Cbz-protected β-aminoethane sulfonyl chlorides from the corresponding sulfonic acids or their salts

Starting material[a]	Product[b]	Chlorinating agent	Yield (%)
 **9**[c]	 **13**[c]	$SOCl_2$	70
 **10**	 **14**	$SOCl_2$	85
 **11**[c]	 **15**[c]	$SOCl_2$/DMF	58
 **12**	 **16**	$SOCl_2$/DMF	75

[a] The sulfonic acids or their sodium salts were prepared as described.[18]
[b] The compounds were previously prepared by the procedure using phosgene.[18]
[c] (*S*)-enantiomers.

a different chlorinating agent which would be suitable for activating the sulfonic acid group.

Thionyl chloride has been reported to chlorinate *N*-protected taurine, however the reaction was carried out in dichloromethane solution, starting from the tetrabutyl ammonium salt.[12] Using excess refluxing $SOCl_2$ or $SOCl_2$/DMF we achieved smooth and convenient conversion of β-substituted β-aminoethane sulfonic acids **6a–c** or sulfonic acid sodium salt **7** into the corresponding sulfonyl chlorides **8a–d**. Since the broad applicability of thionyl chloride as a chlorinating reagent for the synthesis of peptidosulfonamide building blocks has not been reported, we investigated the generality of this interesting reaction by using a series of sulfonic acids or their sodium salts **9–12** which were *N*-protected with either Fmoc- or Cbz-protecting groups. The sulfonic acids or their sodium salts were refluxed in an excess of either $SOCl_2$ or $SOCl_2$/DMF for 4 h to give sulfonyl chlorides **13–16** in high yields on the 7–15 mmol scale (Table 2).

To conclude, the synthesis of *N*-phthalimido β-aminoethanesulfonyl chlorides is presented, which are new building blocks for the synthesis of peptidosulfonamides, an emerging group of peptidomimetics. In the crucial step, sulfonic acids or their sodium salts were converted into the corresponding sulfonyl chlorides using an excess of either $SOCl_2$ or $SOCl_2$/DMF. This simple and effective chlorinating method is also applicable to β-aminoethane sulfonic acids with other *N*-protecting groups.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.011.

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29. The structures of all compounds were confirmed by ^{1}H NMR, IR, and mass spectroscopy. For all new compounds satisfactory elemental analyses data were obtained. A typical procedure for preparing compounds **8a–c** is as follows:
(*S*)-2-Phthalimidopropanol (**3a**): Phthalic anhydride (20.00 g, 135 mmol) and (*S*)-alaninol (9.66 g, 129 mmol) were fused at 140 °C for 7 h. The reaction mixture was cooled to rt and the resulting solid dissolved in ethyl acetate (200 ml). The solution was washed successively with saturated aqueous $NaHCO_3$ (60 ml), H_2O (60 ml), citric acid (10% w/w, 60 ml) and brine (60 ml). Drying (Na_2SO_4), followed by concentration in vacuo, afforded compound **3a** (22.70 g, 86%) as a white solid: R_f = 0.48 ($CHCl_3$/MeOH = 9/1); mp 79–82 °C (lit.[33] mp 77 °C); $[\alpha]_D^{23}$ +32.7 (*c* 0.312, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, 3H, *J* = 7.1 Hz, CH_3), 2.70 (br s, 1H, OH), 3.91 (dd, 1H, *J* = 11.8, 3.8 Hz, CH_2), 4.05 (dd, 1H, *J* = 11.7, 7.5 Hz, CH_2), 4.45–4.63 (m, 1H, CH), 7.70–7.78 (m, 2H, Pht-H), 7.82–7.90 (m, 2H, Pht-H); FAB MS: *m*/*z* = 206 $(M+H)^+$.
(2*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl methanesulfonate (**4a**): To a solution of alcohol **3a** (9.76 g, 48 mmol) in CH_2Cl_2 (150 ml) was added Et_3N (8.0 ml, 57 mmol). After cooling to 0 °C, methanesulfonyl chloride (4.5 ml, 57 mmol) was added dropwise. Stirring was continued overnight at rt, followed by addition of CH_2Cl_2 (100 ml). The mixture was washed with $NaHCO_3$ (5% w/w, 2 × 100 ml), H_2O (2 × 100 ml), and brine (80 ml). The organic phase was dried over Na_2SO_4, filtered and evaporated. The mesylate **4a** was crystallized from ethyl acetate/hexane. Crystallization afforded white crystals (12.90 g, 96%): R_f = 0.64 ($CHCl_3$/MeOH = 9/1); mp 71–74 °C; $[\alpha]_D^{23}$ +34.0 (*c* 0.315, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.53 (d, 3H, *J* = 6.8 Hz, CH_3), 2.99 (s, 3H, CH_3), 4.45 (dd, 1H, *J* = 9.8, 4.4 Hz, CH_2), 4.68–4.90 (m, 2H, CH_2 + CH), 7.71–7.80 (m, 2H, Pht-H), 7.82–7.91 (m, 2H, Pht-H); IR (KBr, cm^{-1}) 3012, 1771, 1709, 1467, 1354, 1170,1042, 992, 821, 719, 517; FAB MS: *m*/*z* = 284 $(M+H)^+$; Anal. Calcd for $C_{12}H_{13}NO_5S$: C, 50.87; H, 4.63; N, 4.94. Found: C, 51.16; H, 4.70; N, 4.96.
S-[(2*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl) propyl] ethanethioate (**5a**): Thioacetate (3.6 ml, 51 mmol) was added to a suspension of Cs_2CO_3 (15.25 g, 47 mmol) in DMF (70 ml). The mesylate **4a** (12.05 g, 43 mmol) was added in one portion to the resulting solution and stirring was continued at 50 °C for 24 h, prior to which the reaction flask was covered with aluminum foil. The mixture was poured into distilled H_2O (250 ml), and the aqueous phase extracted with EtOAc (3 × 150 ml). The combined organic layers were washed with H_2O (150 ml), $NaHCO_3$ (5% w/w, 150 ml), and brine (150 ml). The organic phase was dried over Na_2SO_4, filtered, and evaporated. The resulting residue was purified by column chromatography (EtOAc/hexane = 1/1) to afford **5a** as a white solid (9.20 g, 82%): R_f = 0.40 (EtOAc/Hex = 1/1); mp 54–57 °C; $[\alpha]_D^{23}$ +170.1 (*c* 0.332, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.58 (d, 3H, *J* = 6.9 Hz, CH_3), 2.30 (s, 3H, CH_3), 3.40 (dd, 1H, *J* = 13.9, 5.5 Hz, CH_2), 3.52 (dd, 1H, *J* = 13.9, 9.7 Hz, CH_2), 4.42–4.58 (m, 1H, CH), 7.68–7.78 (m, 2H, Pht-H), 7.80–7.90 (m, 2H, Pht-H); IR (KBr, cm^{-1}) 3453, 2976, 1698, 1466, 1356, 1106, 944, 884, 714, 630; FABMS: *m*/*z* = 264 $(M+H)^+$; Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.29; H, 4.89; N, 5.23.
(2*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-propanesulfonyl chloride (**8a**): A mixture of H_2O_2 (30% w/w in H_2O, 30 ml) and HOAc (60 ml) was added to a solution of thioacetate **5a** (9.05 g, 34.4 mmol) in HOAc (30 ml). After stirring for 24 h at rt, 10% Pd/C was added to destroy the excess peroxide. Filtration, concentration, and coevaporation with toluene (2 × 20 ml) and ether (2 × 20 ml) under reduced pressure afforded the crude sulfonic acid **6a**. The sulfonic acid **6a** was dried at 40 °C for 48 h in vacuo over P_2O_5 and NaOH and afterwards refluxed in $SOCl_2$ (20 ml) for 7 h. Excess $SOCl_2$ was removed by evaporation, followed by coevaporation with toluene and ether under reduced pressure. The resulting residue was purified through a silica plug (CH_2Cl_2) to afford a white solid **8a** (8.41 g, 85%). Analytical samples of the product were precipitated from CH_2Cl_2/hexane: R_f = 0.65 (CH_2Cl_2/acetone = 18/1); mp 83–85; $[\alpha]_D^{23}$ +78.1 (*c* 0.310, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.66 (d, 3H, *J* = 7.2 Hz), 3.97 (dd, 1H, *J* = 14.5, 3.6 Hz, CH_2), 4.77 (dd, 1H, *J* = 14.3, 9.8 Hz, CH_2), 5.13–5.28 (m, 1H, CH), 7.72–7.81 (m, 2H, Pht-H), 7.84–7.93 (m, 2H, Pht-H); IR (KBr, cm^{-1}) 3467, 1776, 1711, 1374, 1169, 1062, 860, 724, 605, 525; EI MS: 287, 289 (M^+); Anal. Calcd for $C_{11}H_{10}ClNO_4S$: C, 45.92; H, 3.50; N, 4.87. Found: C, 46.18; H, 3.52; N, 4.68.
30. A typical procedure: To a cooled (ice bath) mixture of sulfonic acid sodium salt **7** (5.00 g, 17.9 mmol) and excess thionyl chloride (10 ml) was added DMF (1 ml) dropwise. The mixture was heated at reflux for 5 h. The chlorinating species was removed by evaporation, followed by coevaporation with toluene and ether under reduced pressure. The residue was dissolved in EtOAc (100 ml) and washed with H_2O (60 ml), saturated aqueous $NaHCO_3$ (60 ml) and brine (50 ml). The organic phase was dried over Na_2SO_4, filtered, evaporated, and the residue purified through a silica plug (CH_2Cl_2) to afford sulfonyl chloride **8d** as a white solid (4.90 g, 89%); mp 160–162 °C (lit.[31] mp 159–162 °C).
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