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A practical solid phase synthesis of oligopeptidosulfonamide foldamers

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Abstract

Oligopeptidosulfonamide foldamers were efficiently synthesized on the solid phase using Fmoc protected β-aminoethanesulfonylchlorides in the presence of *N*-methylmorpholine. © 2000 Published by Elsevier Science Ltd.

The term 'foldamer' was coined by Gellman[1,2] to designate the class of β-peptides, which has been shown to fold into defined three dimensional structures similar to those of natural peptides.[3] Other foldamer classes[2] include, for example, the vinylogous peptides, but also oligomers in which the peptide amide bond is replaced by another moiety such as the sulfonamide moiety, leading to oligopeptidosulfonamides or 'β-sulfonopeptides' and vinylogous sulfonopeptides.[2] In the recent past we[4] and others[5] have synthesized oligopeptidosulfonamides consisting of up to three residues. Clearly, it will be very interesting to see if oligopeptidosulfonamides containing a large number of residues adopt defined structures.[2] In order to realize the synthesis of such large oligomers a solid phase procedure is indispensable. An absolute prerequisite for the development of a practical solid phase method is the easy availability of the necessary building blocks. Recently, we have described an efficient synthesis of *N*-protected β-aminoethane sulfonylchlorides[6] as versatile building blocks for the synthesis of oligopeptidosulfonamides. Here we describe the use of these sulfonyl chlorides in a practical and convenient solid phase synthesis procedure towards oligopeptidosulfonamide foldamers.

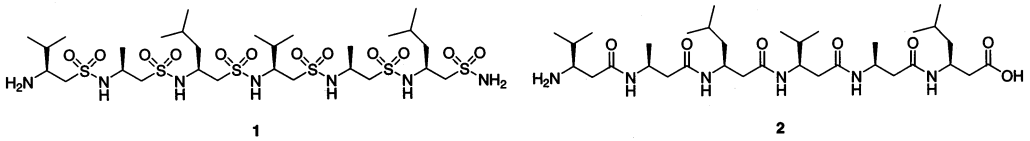

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Figure 1. Oligopeptidosulfonamide analogue **1** of the β-hexapeptide **2** of Seebach et al.[7]

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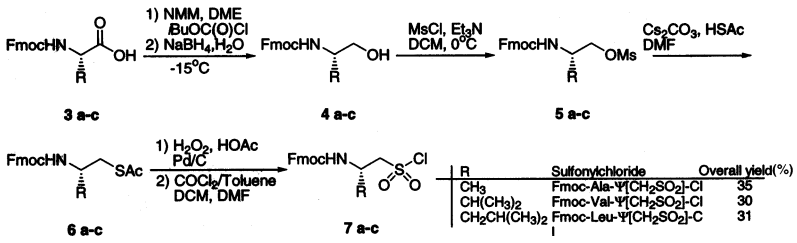
As a first target molecule we chose the oligopeptidosulfonamide analogue **1** of the β-hexapeptide **2** of Seebach[7] et al. (Fig. 1). This β-peptidosulfonamide **1** was assembled on Argogel™-Rink-NH-Fmoc resin in an iterative manner (Scheme 2). Each cycle consisted of a deprotection and a coupling step. Deprotection of the Fmoc group was achieved each time with a 20% solution of piperidine in NMP. The required Fmoc protected β-aminoethane sulfonylchlorides **7a–c** were prepared in four steps starting from Fmoc protected amino acids, as was described recently[6] (Scheme 1). In short, Fmoc amino acids **3a–c** were reduced to the corresponding amino alcohols **4a–c** using sodium borohydride. This was followed by mesylation to **5a–c** and subsequent substitution to the thioacetates **6a–c**. Oxidation with hydrogen peroxide in acetic acid gave the sulfonic acids, which were immediately converted into the sulfonylchlorides **7a–c**. Three different sulfonyl chlorides were prepared in overall yields of 30–35% corresponding to an average yield of 79% per reaction.



Scheme 1. Synthesis of the required Fmoc-protected β-aminoethanesulfonylchlorides[6]

For the solid phase procedure the Fmoc protecting group was cleaved from the Rink-linker with piperidine to give the free amine, which was treated with an excess (4 equiv.) of Fmoc-Leu-ψ[CH_2SO_2]-Cl and (6 equiv.) *N*-methylmorpholine (NMM) to introduce the first β-aminoethanesulfonamide residue to give **9**. Introduction of the second β-aminoethanesulfonamide residue i.e. Fmoc-Ala-ψ[CH_2SO_2]-Cl was performed in an identical manner and led to **10**. Repetition of the deprotection and coupling cycle for an additional four times ultimately led to the hexa-β-peptidosulfonamide attached to the solid support,[8] i.e. **11**. *N*-methylmorpholine was used as a base in each of the coupling reactions. These proceeded smoothly and to a very high degree of completion, as was clearly observed by the bromophenol blue (BPB) test, which was negative after each coupling and blue colored beads were absent.[9] This observation was corroborated by measuring the total absorbance of the piperidine–dibenzofulvene adduct (λ_{max} 301 nm) obtained after cleavage of the Fmoc group after each coupling step.[10] It was found that the loading of the growing oligopeptidosulfonamide decreased only slightly with each coupling step (Fig. 2).

After removal of the last Fmoc group, the oligopeptidosulfonamide was cleaved from the resin with a mixture of TFA and water. Mass spectral studies (ES-MS) unambiguously showed the presence of the desired oligopeptidosulfonamide **1** in the reaction product, but probably the low absorbance of the sulfonamide moiety prevented a clear detection of the oligopeptidosulfonamide in the HPLC analysis. To circumvent this problem an additional UV-detectable group was introduced. The *p*-nitro-benzenesulfonyl- (*p*-NBS) and the benzyloxycarbonyl- (Cbz) protective groups were selected for this purpose. The use of an aromatic sulfonyl chloride allowed detection while at the same time gave rise to an 'all' sulfonamide structure. In contradistinction a Cbz group was introduced solely for the purpose of purification, since it is UV-detectable and can be cleanly removed afterwards to give the pure oligopeptidosulfonamide **1**.

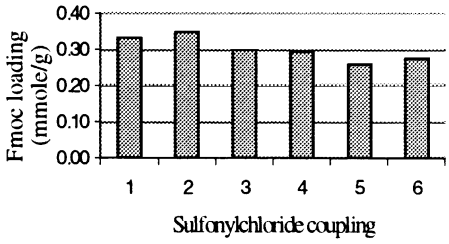
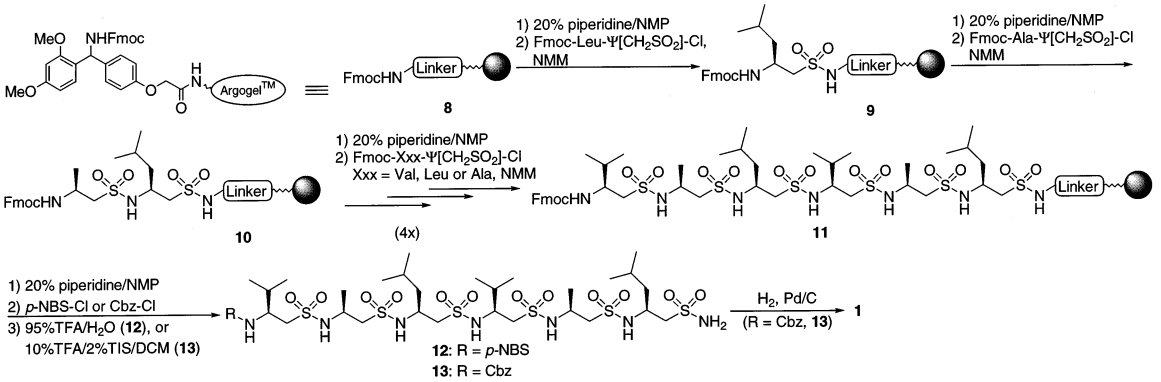


Figure 2.

Both protective groups were introduced after cleavage of the last Fmoc group by treatment with *p*-NBS-chloride or Cbz-chloride in the presence of excess NMM. After acidolytic cleavage, followed by purification by silica gel column chromatography, the desired oligopeptidosulfonamides **12** and **13** were obtained in excellent overall yields of 54 and 66%, respectively. These correspond to excellent average yields of 96 and 97%, respectively, per synthesis step (Scheme 2). Hydrogenolysis of the Cbz group in the presence of 10% Pd/C gave, after precipitation from methanol and diethyl ether and lyophilization, the desired compound **1** as a white powder (HCl-salt) in 54% yield. The oligopeptidosulfonamides **1**, **12** and **13** have all been characterized by UV, IR, NMR[11] and mass spectral analysis.[11]



Scheme 2. Solid phase synthesis of oligopeptidosulfonamide foldamers

Preliminary circular dichroism (CD) studies so far did not indicate the presence of a defined helical secondary structure in solution, as has been observed for the corresponding oligo-β-peptides. This might be explained by the poor UV absorbance of the backbone sulfonamide moieties preventing the observation of a defined structure by this method. Alternatively, oligopeptidosulfonamides of this length and/or with these residues may fail to assume a defined structure. Clearly, we have to take recourse to other techniques to investigate the 'foldamer behavior' of these oligopeptidomimetics. Those techniques include, for example, temperature dependent NMR spectroscopy and exchange rate determination of sulfonamide protons for deuterium.[3a]

In conclusion, we have described both a practical and efficient solid phase synthesis of oligopeptidosulfonamide foldamers using Fmoc protected β-aminoethanesulfonylchloride building blocks. The use of the Fmoc strategy is completely compatible with the Fmoc strategy used for the construction of peptides and therefore β-peptide-peptidosulfonamide hybrids are easily accessible.

Under present investigation is the construction and structure of larger oligopeptidosulfonamide foldamers, as well as oligopeptidosulfonamides containing functionalized aminosulfonic acid residues, which might ultimately lead to construction of proteinaceous sulfonamides.

Acknowledgements

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8. A typical procedure is as follows: 0.35 g of Argogel™-Rink-NH-Fmoc resin (loading 0.30 mmol/g), swollen in NMP, was shaken three times, each time for 10 minutes, with 2.1 mL of a 20% solution of piperidine in NMP (v/v). Subsequently, the resin was successively washed five times, each time for 2 minutes, with NMP and DCM. Then, the resin was shaken with four equivalents of Fmoc-Leu-$\psi[CH_2SO_2]$-Cl and six equivalents NMM in 2.1 mL DCM for 18 hours at room temperature to introduce the Fmoc protected peptidosulfonamide building block. Finally, the resin was washed five times, each time for 2 minutes, with DCM, followed by the BPB test. The resin is then ready for the next deprotection/coupling cycle.
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11. For example, the *p*-NBS protected oligopeptidosulfonamide **12**: 600 MHz ^{1}H NMR (CD_3OH, $T=268$ K, Watergate CD_3OH suppression): δ 0.85–0.95 (m, 24H, 8×CH_3, 2×Val^s, 2×Leu^s), 1.26 (d, 3H, CH_3 Ala^s, $J=6.8$ Hz), 1.35 (d, 3H, CH_3 Ala^s, $J=6.7$ Hz), 1.44–1.55 (m, 4H, 2×CH_2CH$(CH_3)_2$ 2×Leu^s), 1.77 (m, 2H, C$H(CH_3)_2$ 2×Leu^s), 1.97 (m, 1H, C$H(CH_3)_2$ Val^s), 2.07 (m, 1H, C$H(CH_3)_2$ Val^s), 2.96 (dd, 1H, CH_2SO_2 Val^s, $J_{gem}=14.5$ Hz, $J_{vic}=5.6$ Hz), 3.08 (dd, 1H, CH_2SO_2 Ala^s, $J_{gem}=14.3$ Hz, $J_{vic}=5.1$ Hz), 3.13 (dd, 1H, CH_2SO_2, Val^s, $J_{gem}=14.6$ Hz, $J_{vic}=7.1$ Hz), 3.19–3.35 (m, 7H, CH_2SO_2 Leu^s, Ala^s, Val^s), 3.41 (dd, 1H, CH_2SO_2 Ala^s, $J_{gem}=14.2$ Hz, $J_{vic}=7.4$ Hz), 3.49 (dd, 1H, CH_2SO_2 Leu^s, $J_{gem}=14.4$ Hz, $J_{vic}=6.5$ Hz), 3.60 (m, 1H, NCH Ala^s), 3.73 (m, 1H, NCH Val^s), 3.83 (m, 1H, NCH Val^s), 3.92 (m, 2H, NCH Leu^s (2×)), 3.99 (m, 1H, NCH Ala^s), 6.90

(bs, 2H, SO_2NH_2), 7.02 (d, 1H, NH Ala^s, $J=8.2$ Hz), 7.07 (d, 1H, NH Leu^s, $J=9.0$ Hz), 7.18 (bd, 1H, NH Leu^s), 7.25 (d, 1H, NH Val^s, $J=9.0$ Hz), 7.28 (bd, 1H, NH Ala^s), 7.80 (d, 1H, NH Val^s, $J=8.9$ Hz), 8.10 (d, 2H, Ar-CH, $J=9.0$ Hz), 8.39 (d, 2H, Ar-CH, $J=9.0$ Hz). 150 MHz ^{13}C NMR (CD_3OH): δ 16.77, 17.48, 18.74 and 19.15 (CH_3 Val^s); 22.12 and 22.29 (CH_3 Leu^s); 23.09, 23.23, 23.26 and 23.40 (CH_3 Ala^s and CH_3 Leu^s); 25.37 and 25.47 ($CH(CH_3)_2$ Leu^s); 32.86 and 35.54 ($CH(CH_3)_2$ Val^s); 46.65 and 46.75 ($CH_2CH(CH_3)_2$ Leu^s); 47.44 (NCH Ala^s), 49.78 and 49.92 (NCH Leu^s); 55.78 (CH_2SO_2 Val^s), 55.99 and 56.34 (NCH Val^s); 56.64 (CH_2SO_2 Val^s), 60.52, 60.89, 60.98 and 61.06 (CH_2SO_2 Ala^s, Leu^s); 125.27 and 129.54 (Ar-CH); 148.49 and 151.28 (Ar-C). ESI-MS found: m/z 1091.2689 $[M+Na]^+$, calcd 1091.2692.