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Peptidomimetic building blocks for the synthesis of sulfonamide peptoids

Jeroen van Ameijde and Rob M. J. Liskamp *

Department of Medicinal Chemistry, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Sorbonnelaan 16, PO Box 80082, 3508 TB Utrecht, The Netherlands

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Abstract

There is a constant demand for novel building blocks for combinatorial chemistry applications. A one-pot synthesis of a novel class of peptidomimetic building blocks to be used for the preparation of sulfonamide peptoids, is presented here. Furthermore, it is shown that these compounds can be incorporated in a peptide sequence.

Keywords: peptidomimetics; sulfonamides; Michael reaction; combinatorial chemistry.

There is a constant need for new building blocks in order to increase diversity in combinatorial libraries. Peptidomimetics are particularly interesting, because they can be used to mimic biologically active peptides.[1] A wide variety of peptidomimetic building blocks has been developed in the past: e.g. peptoids,[2] sulfonamides,[3] ureapeptidomimetics,[4] and hydrazinopeptidomimetics.[5]

In this communication we present a convenient synthesis of a novel type of peptidomimetic building block to be used for the preparation of *sulfonamide peptoids*. The general structure of these compounds is shown in Fig. 1. As can be seen, these compounds actually mimic beta amino acids, which are currently receiving considerable interest in the literature.[6]

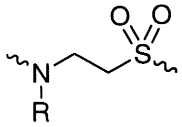

Fig. 1. General structure of a sulfonamide peptoid

The synthesis of these compounds was first investigated via an analogous route to the one which we developed earlier for peptoid peptidomimetics[2b,c] (Scheme 1, route 1). Therefore, the first step in the route towards building blocks for sulfonamide peptoids involved refluxing 2-bromoethylsulfonate **1** and two equivalents of amine **2** in water for 48 h. The formation of product could be monitored on TLC. Isolation of the substitution product **3** turned out to be very difficult because of the zwitter-ionic nature of

* Corresponding author. Tel: (31)30-2537396; fax: (31)30-2536655; e-mail: r.m.j.liskamp@pharm.uu.nl (R. M. J. Liskamp)

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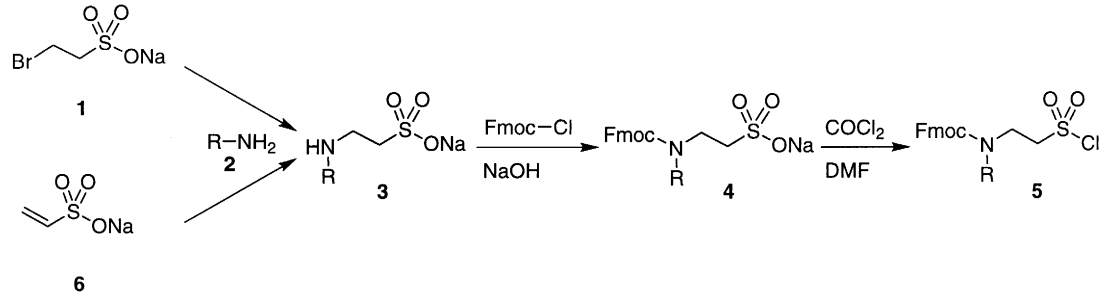
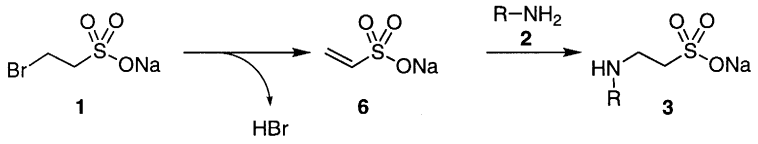
this compound. Therefore, it was decided to remove excess amine **2** by extraction into dichloromethane under basic conditions. The aqueous phase, containing inter alia the substitution product **3**, was used directly in the second step: a standard Fmoc-protection under Schotten–Baumann conditions. As it turned out to be impossible to extract the resulting Fmoc protected monomer **4** into an organic phase even under strongly acidic conditions, it was decided to use the crude product in the final step of the synthesis, after evaporation of the solvent and careful drying. This final step involved the treatment of the sulfonate **4** with a solution of phosgene in toluene, in the presence of *N*,*N*-dimethylformamide. The resulting sulfonyl chloride **5** (a sulfonamide peptoid monomer) could be easily isolated and purified by column chromatography. The overall yield of this virtually one-pot procedure was ca. 35%.



Scheme 1. Synthesis of sulfonamide peptoid monomers

It was then assumed that the first step in the synthesis could be replaced by a Michael addition of amine **2** to vinylsulfonate **6** (Scheme 1, route 2). The advantage of this procedure is that only one equivalent of amine **2** could be employed because no hydrogen bromide is formed. Using this procedure the three-step synthesis of sulfonamide peptoid monomers could be carried out in one pot.† Yields were comparable to those achieved using the first method, viz. 25–40% (Table 1).

Surprisingly, it was found that the different starting materials (**1** and **6**) in both routes showed similar R_f-values on TLC. We therefore suspected that the substitution reaction carried out in the first approach actually proceeds via an elimination–addition tandem reaction (Scheme 2). This was confirmed by an NMR experiment: a sample of bromide **1** in D_2O decomposed quite rapidly into vinylsulfonate **6**.

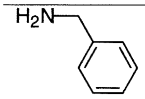
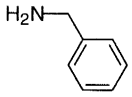
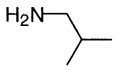
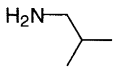
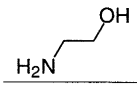


Scheme 2. Mechanism of substitution of 2-bromoethylsulfonate

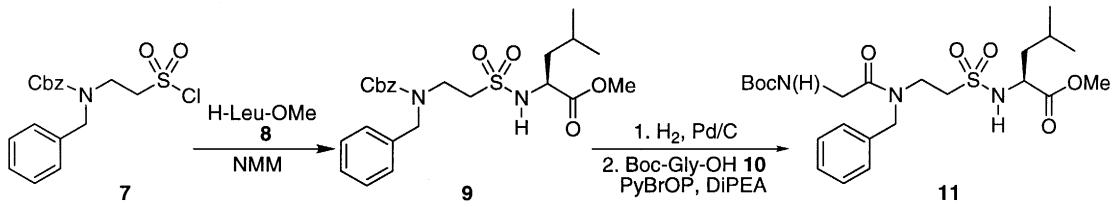
The second procedure was employed for the convenient synthesis of a number of sulfonamide peptoid monomers containing either the Fmoc- or Cbz-protecting group. The synthetic procedure for Cbz-protected sulfonamide peptoids is identical to that of the Fmoc-protected monomers, except that Cbz–Cl was used instead of Fmoc–Cl at the amine-protection step. The results of these syntheses are summarized in Table 1.

† General procedure: To 4.43 ml (10 mmol) of a 25% solution of vinylsulfonate in water, 10 mmol of amine and water (6 ml) were added. The resulting mixture was refluxed for 48 h. After cooling to room temperature, dioxane (10 ml) was added, and the pH was adjusted to 8.5. Fmoc–Cl (2.59 g, 10 mmol) was added, and the pH of the reaction mixture was kept at 8–8.5 with 1N NaOH. The solvents were then evaporated, and the crude product was dried in vacuo over P_2O_5. A 20% solution of phosgene in toluene (12 ml), dichloromethane (20 ml), and DMF (2.5 ml) were added, and this mixture was stirred at room temperature for 3 h. After filtration, the solvents were evaporated, and column chromatography (eluent: DCM) afforded the pure sulfonylchloride.

Table 1
Results of the syntheses of sulfonamide peptoid building blocks

Amine	Protection	Monomer	Yield
	Fmoc	Fmoc-NPhe-ψ[CH_2SO_2Cl]	30%
	Cbz	Cbz-NPhe-ψ[CH_2SO_2Cl]	35%
	Fmoc	Fmoc-NLeu-ψ[CH_2SO_2Cl]	33%
	Cbz	Cbz-NLeu-ψ[CH_2SO_2Cl]	40%
	Cbz	Cbz-NIle-ψ[CH_2SO_2Cl]	37%
	Cbz	Cbz-NHse(Cbz)-ψ[CH_2SO_2Cl]	25%

As an illustration of the applicability of these novel peptidomimetic building blocks, it was attempted to incorporate a sulfonamide peptoid monomer in a small peptide (Scheme 3). First, Cbz-NPhe-Ψ[CH_2SO_2Cl] **7** was coupled to Leucine methylester **8** using *N*-methylmorpholine as a base (73%). Then, after Cbz deprotection by palladium(0)-catalyzed hydrogenolysis, Boc-protected glycine **10** was coupled to sulfonamide **9** using PyBrOP.[7] This coupling reagent was previously employed successfully in the synthesis of peptoid peptidomimetics[2b,c] (54%). It is expected that the yields of these coupling reactions can be improved using solid phase synthesis, in which excess of starting material is used.



Scheme 3. Incorporation of a sulfonamide peptoid residue in a peptide

In conclusion, a convenient route for the synthesis of interesting novel peptidomimetic building blocks is presented to be used for the preparation of sulfonamide peptoids. Both Fmoc- and Cbz-protected monomers are accessible, so these compounds can be used in solution as well as in solid phase synthesis. The applicability was illustrated by incorporating a sulfonamide peptoid in a small peptide.

References

1. (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1993**, 33, 1699. (b) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244.
2. (a) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banvill, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlet, P. A. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 9367. (b) Kruijtzer, J. A. W.; Liskamp, R. M. J. *Tetrahedron Lett.* **1995**, *36*, 6969. (c) Kruijtzer, J. A. W.; Hofmeijer, L. J. F.; Heerma, W.; Versluis, C.; Liskamp, R. M. J. *Chem. Eur. J.* **1998**, *4*, 1570.

3. See, for example: (a) Decicco, C. P.; Seng, J. L.; Kennedy, K. E.; Covington, M. B.; Welch, P. K.; Arner, E. C.; Magolda, R. L.; Nelson, D. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2231. (b) Choy, N.; Choi, H.; Won, H. J.; Kim, C. R.; Yoon, H.; Kim, S. C.; Lee, T. G.; Koh, J. S. *J. Med. Chem.* **1997**, *7*, 2635. (c) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *J. Org. Chem.* **1995**, *60*, 5157. (d) Benedetti, F.; Berti, F.; Colombatti, A.; Ebert, C.; Linda, P.; Tonizzo, F. *Chem. Commun.* **1996**, 1417. (e) Paik, S.; White, E. H. *Tetrahedron* **1996**, 5303. (f) Gude, M.; Piarulli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *47*, 8589. (g) De Bont, D. B. A.; Dijkstra, G. D. H.; Den Hartog, J. A. J.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3035.
4. (a) Burgess, K.; Linthicum, D. S.; Shin, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 907. (b) Burgess, K.; Ibarzo, J.; Linthicum, D. S.; Russell, D. H.; Shin, H.; Shitangkoon, A.; Totani, R.; Zhang, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 1556.
5. (a) Barré, C.; Le Grel, P.; Robert, A.; Bandy-Flock, M. *J. Chem. Soc., Chem. Commun.* **1994**, 607. (b) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539.
6. (a) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta.* **1998**, *81*, 187. (b) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V. *Helv. Chim. Acta.* **1998**, *81*, 932.
7. Coste, J.; Frerot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967.