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Approaches to the Synthesis of Ureapeptoid Peptidomimetics

John A.W. Kruijtzer, Dirk J. Lefeber and Rob M.J. Liskamp*

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

Abstract: ureapeptoid peptidomimetics can be composed from Boc-protected N-substituted ethylenediamines. The best approach is to synthesize these from chloroacetonitrile followed by conversion to the corresponding crystalline *p*-nitrophenyl carbamates in order to prepare the ureapeptoids. © 1997 Elsevier Science Ltd.

Recent years have shown the development of several new classes of oligomeric peptidomimetics. Noteworthy examples include peptoids[1], the oligocarbamates[2], the oligourea peptidomimetics[3] and hydrazinopeptides[4], the oligosulfones[5] as well as the (α-β unsaturated)peptidosulfonamides[6]. By combining these classes of peptidomimetics, the diversity of compounds can be increased enormously thus obtaining 'hybrid' peptidomimetics, which might be very useful for the development of lead compounds from peptides.

In this communication we describe an approach for the preparation of a class of hybrid peptidomimetics denoted as 'ureapeptoids'. A ureapeptoid can be considered as a hybrid of a peptoid and a urea peptidomimetic (Fig. 1). Peptoids can be obtained by the submonomer[1a] and monomer method[7]. A monomer approach for the preparation of ureapeptidomimetics was described by Burgess et al.[3a], whereas a submonomer approach was presented recently by Schultz et al.[3d]. Based on our earlier developed monomer approach[7a] for the preparation of peptoids, we envisioned the preparation of a ureapeptoid based on synthons **1** or **2**.

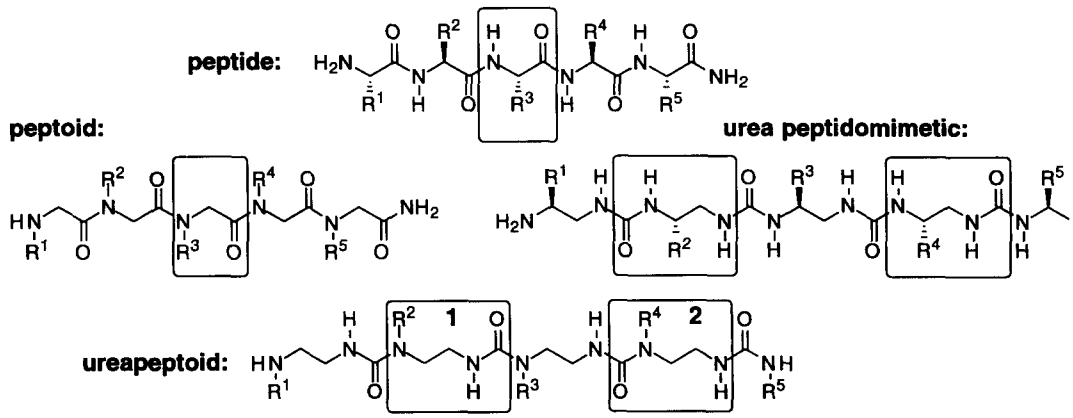
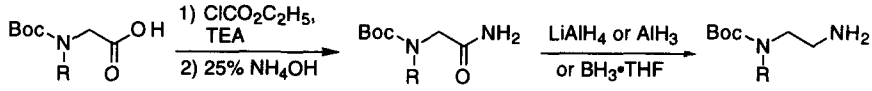


Figure 1. Structures of a peptide, peptoid, urea peptidomimetic and a ureapeptoid. Possible synthons of these oligomers are depicted in the frames.

Both possible synthons **1** and **2** are derived from a mono N-substituted ethylenediamine, which was readily accessible using the previously described method[7a] for the preparation of peptoid monomers. Thus, starting from ethyl bromoacetate compounds **3a-c** were obtained in three steps (overall yields 87-98 %). Reaction with ethyl chloroformate[8] and aqueous ammonia gave the corresponding amides **4a-c** in high yields. Several attempts have been undertaken to reduce the primary amides to the corresponding primary amines **5a-c**

with $LiAlH_4$, AlH_3[9] or $NaBH_4/CoCl_2$[10] but the yields (0-30%) were disappointing. The low yields were partly due to removal of the Boc-group during the reduction step. The best result (ca 60%) was obtained using diborane[11] in THF using 1N $KHSO_4$ instead of 6N HCl in the work-up to avoid removal of the Boc-group. Unfortunately, this modified procedure was not reproducible.

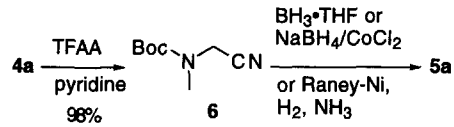


3a R = Me
3b R = *i*-Bu
3c R = Bzl

4a-c **5a-c**

Scheme 1. Synthesis and reduction of Boc-protected peptoid amides

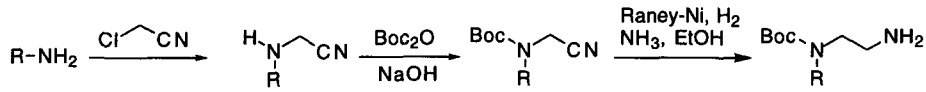
Therefore, an alternative approach was based on the assumption that reduction of nitriles is generally easier to accomplish, using milder and more selective reducing agents than reduction of primary amides. To evaluate this, nitrile **6** was synthesized in 98% yield from **4a** by dehydration with trifluoroacetic anhydride in pyridine[12] (Scheme 2) to serve as a model compound in reduction experiments.



Scheme 2. Synthesis and reduction of nitrile **6**.

Disappointingly, using diborane[11b] in THF the corresponding amine **5a** was obtained in a yield of only 20%. By using the $NaBH_4/CoCl_2$[10,13] mixture the yield increased to 57%. But the work-up procedure, *i.e.* liberation of the amine from the amine-borohydride complex was tedious. The best results were obtained by catalytic hydrogenation of **6** in a Parr apparatus using Raney-Nickel[14] to afford amine **5a** in 67% yield.

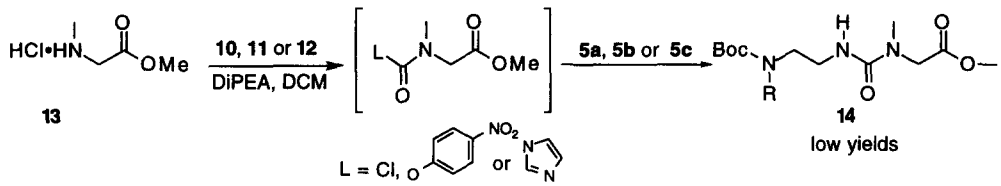
This convenient catalytic reduction of the nitrile function allowed a considerable simplification of the synthesis of the required Boc-protected N-substituted ethylenediamines[15]. Thus, by employing chloroacetonitrile these N-substituted diamines **5b-d** are accessible in just three steps in good overall yields (61% - 76%) (scheme 3).



7a R = *i*-Bu	**8a** 85%	**9a** 88%	**5b** 93%
7b R = Bzl	**8b** 88%	**9b** 99%	**5c** 87%
7c R = CH_2-*p*-C_6H_4O*t*Bu	**8c** 95%	**9c** 91%	**5d** 70%

Scheme 3. Synthesis of Boc-protected ureapeptoid monomers.

These Boc-protected N-substituted diamines can then be used in the preparation of ureapeptoids using *e.g.* *p*-nitrophenyl chloroformate[16a] **10**, triphosgene[16b] **11** and CDI **12**.

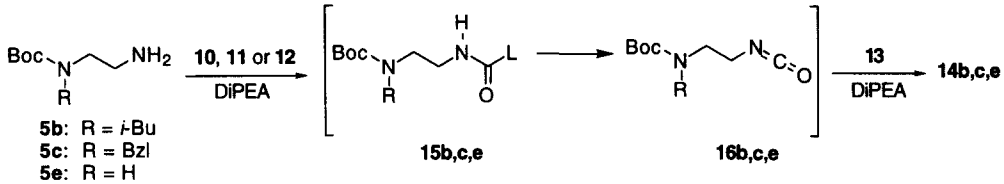


13 **14** low yields

Scheme 4

In order to determine which method was preferable, syntheses of ureapeptoid dimers were carried out. In the first attempts, the methyl ester **13** of H-NAla-OH *i.e.* sarcosine was treated with **10**, **11** or **12**, followed by treatment with the diamines **5a-c** (Scheme 4). This procedure only gave the desired dimers in low yields even after prolonged reaction times. We reasoned that these results were likely caused by the impossibility of secondary amines to form an isocyanate intermediate (*vide infra*).

A better approach is the reverse procedure *i.e.* treatment of diamine **5b**, **5c** and **5e** with **10**, **11** or **12**, followed by treatment with sarcosine methyl ester **13**. In order to avoid formation of the symmetrical dimer, the Boc-protected primary amine was added dropwise to **10, 11** or **12** in order to obtain the intermediate carbamate **15** and subsequent isocyanate **16**. These were not isolated but immediately converted to ureapeptoid dimers by addition of sarcosine methyl ester **13** (Scheme 5).



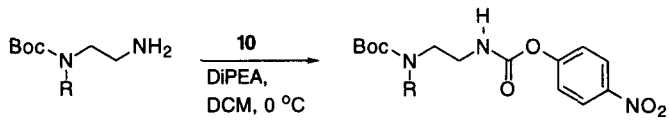
Scheme 5. Synthesis of ureapeptoid dimers **14** using active carbamates.

The results using the latter approach are summarized in Table 1. Furthermore, it was found that the *p*-nitrophenyl carbamates (Scheme 5: **15**: L = pNO_2Ph) are actually quite stable and can be isolated by crystallization.

Table 1. Yields (%) of the coupling reactions by activated primary amines.

dimer	*p*-nitrophenyl chloroformate **10**	triphosgene **11**	CDI **12**
14b	56	5	7
14c	68	38	70
14e	70	45	70

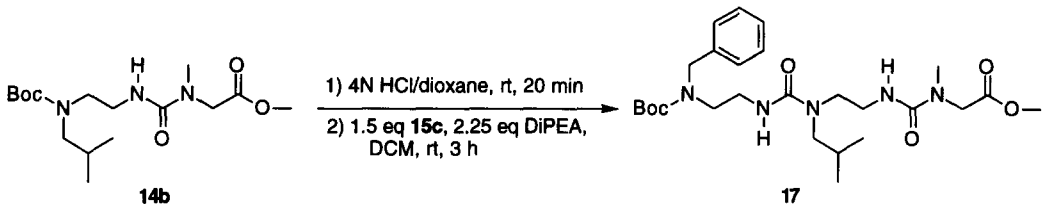
Thus, *p*-nitrophenyl carbamates **15** were obtained by addition of the appropriate primary amine in DCM to a *p*-nitrophenyl chloroformate solution in DCM containing **one** equivalent of DiPEA to afford after extractive work-up and recrystallization the carbamates in good to excellent yields (Scheme 6). So far, all synthesized activated carbamates were solids which are easy to handle.



Scheme 6. Synthesis of *p*-nitrophenyl carbamates.

Addition of carbamate **15b** to **13** in DCM with three equivalents of DiPEA gave the desired dimer **14b** in excellent yield (93%), thus showing that even a better yield was obtained without isolation of the carbamate (see Table 1: 56%).

This convenient *p*-nitrophenyl carbamate coupling procedure was used to synthesize a ureapeptoid trimer in solution (Scheme 7). The Boc-group of **14b** was removed with 4N HCl/dioxane to yield the secondary amine which was reacted with **15c** using DiPEA as a base in DCM to afford the ureapeptoid trimer **17** in 64% yield[17].



14b 17

Scheme 7. Synthesis of a ureapeptoid trimer.

In conclusion, we have shown that N-protected ureapeptoid monomers *i.e.* mono Boc-protected N-substituted ethylenediamines can be conveniently prepared. Moreover, the *p*-nitrophenyl carbamates are versatile building blocks for the construction of ureapeptoids as was illustrated by the preparation of ureapeptoid dimers and a trimer in solution. Under present investigation is the synthesis of larger ureapeptoids as well as the implementation of their solid-phase synthesis.

REFERENCES AND NOTES

1. (a) Simon, R.J.; Kania, R.S.; Zuckermann, R.N.; Huebner, V.D.; Jewell, D.A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C.K.; Spellmeyer, D.C.; Tan, R.; Frankel, A.D.; Santi, D.V.; Cohen, F.E.; Bartlett, P.A. *Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 9367-9371; (b) Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 543-544.
2. Cho, C.Y.; Moran, E.J.; Cherry, S.R.; Stephans, J.C.; Fodor, S.P.A.; Adams, C.L.; Sundaram, A.; Jacobs, J.W.; Schultz, P.G. *Science* **1993**, *261*, 1303-1305.
3. (a) Burgess, K.; Linthicum, D.S.; Shin, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 907-909; 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*, 1556-1564; (b) Hutchins, S.M.; Chapman, K.T. *Tetrahedron Lett.* **1994**, *35*, 4055-4058; (c) Hutchins, S.M.; Chapman, K.T. *Tetrahedron Lett.* **1995**, *36*, 2583-2586; (d) Kim, J-M.; Bi, Y.; Paikoff, S.J.; Schultz, P.G. *Tetrahedron Lett.* **1996**, *37*, 5305-5308.
4. (a) Barré, C.; Le Grel, P.; Robert, A.; Baudy-Floc'h, M. *J. Chem. Soc. Chem. Comm.* **1994**, 607; (b) Han, H.; Janda, K.D. *J. Am. Chem. Soc.* **1996**, *118*, 2539-2544.
5. (a) Moran, E.J.; Wilson, T.E.; Cho, C.Y.; Cherry, S.R.; Schultz, P.G. *Biopolymers Peptide Science* **1995**, *37*, 213-219; (b) Sommerfield, T.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 553-554.
6. (a) Moree, W.J.; Schouten, A.; Kroon, J.; Liskamp, R.M.J. *Int. J. Pept. Protein Res.* **1995**, *45*, 501-507; (b) Moree, W.J.; van der Marel, G.A.; Liskamp, R.M.J. *J. Org. Chem.* **1995**, *60*, 5157-5169; (c) Genari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2067-2068; (d) De Bont, D.B.A.; Moree, W.J.; Liskamp, R.M.J. *Bioorg. Med. Chem.* **1996**, *4*, 667-672; (e) Gude, M.; Piarulli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *47*, 8589-8592; (f) De Bont, D.B.A.; Dijkstra, G.D.H.; Den Hartog, J.A.J.; Liskamp, R.M.J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3035-3040.
7. (a) Kruijtzer, J.A.W.; Liskamp, R.M.J. *Tetrahedron Lett.* **1995**, *36*, 6969-6972; (b) Kruijtzer, J.A.W. *Thesis* **1996** Utrecht University, The Netherlands; Kruijtzer, J.A.W.; Liskamp, R.M.J. *manuscript in preparation.*
8. Kawamoto, I.; Endo, R.; Ishikawa, K.; Kojima, K.; Miyauchi, M.; Nakayama, E. *Synlett.* **1995**, 575-577.
9. Yoon, N.M.; Brown, H.C. *J. Am. Chem. Soc.* **1968**, *90*, 2927-2938.
10. Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *20*, 4555-4558.
11. (a) Brown, H.C.; Heim, P. *J. Org. Chem* **1973**, *38*, 912-916; (b) Brown, H.C.; Choi, Y.M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153-3163.
12. Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, *28*, 1813-1816.
13. Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801-6802.
14. (a) Ravikumar, V.T. *Synth. Commun.* **1994**, *24*, 1767-1772; (b) Schwoegler, E.J.; Adkins, H. *J. Am. Chem. Soc.* **1939**, *61*, 3499-3502.
15. The Glycine ureapeptoid monomer viz. N-Boc-ethylenediamine is commercially available, Fluka AG Switzerland.
16. (a) Gante, *J. Chem. Ber.* **1965**, *98*, 3334-3339; (b) Majer, P.; Randad, R.S. *J. Org. Chem.* **1994**, *59*, 1937-1938.
17. Unfortunately, part of **17** cyclized to the corresponding C-terminal hydantoin which was isolated in 23% yield.

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