Application of carbodiimide mediated Lossen rearrangement for the synthesis of α-ureidopeptides and peptidyl ureas employing *N*-urethane α-amino/peptidyl hydroxamic acids†

N. Narendra, Gundala Chennakrishnareddy and Vommina V. Sureshbabu*

Received 24th March 2009, Accepted 20th May 2009
First published as an Advance Article on the web 7th July 2009
DOI: 10.1039/b905790k

Application of the Lossen rearrangement to the synthesis of N-urethane protected α-peptidyl ureas and ureidopeptides is reported. The carbodiimide mediated rearrangement of *N*-Boc/Z/Fmoc protected α-amino/peptide hydroxamic acids into isocyanates and coupling of the latter with the amino acid esters/peptide esters have been accomplished in a single-pot to obtain good yields of urea products. Synthesis of the ureidoalanine derivatives *via* the hydroxamate derivatives of N-protected aspartic acid has also been carried out using the same procedure.

Introduction

Research in peptide therapeutics has been revisited during recent years following the developments in the chemistry of peptidomimetics. Chemical modification of the peptide backbone has turned into a powerful tool to overcome the intrinsic inadequacies of peptide drugs.[1] The urea linkage is one of the common types of amide-bond surrogate to be inserted into the peptide backbone. *N*,*N*-Substituted ureas, *N*,*N*′-linked ureas and ureidopeptoids are being explored for novel applications in medicinal[2] as well as structural chemistry.[3] Ureido analogs of angiotensin,[4] [Leu]enkephaline,[5] gasrtin antagonists,[6] Tat derived oligomers binding TAR RNA[7], aspartic peptidases[8] and protease inhibitors like microbial alkaline protease,[9] HIV-1 protease,[10] aspartic acid proteases,[11] γ-secretase[12] and several other classes of enzyme inhibitors[13] have been prepared and studied for improved biological properties. Urea functionality has been utilized to create highly organized hydrogen bonded molecular assemblies including protein secondary structure mimics[14–16] and hydrogen bonded molecular self-assemblies.[17,18] Non-proteinogenic amino acids like L-albizziine contain urea linkages.[19] Consequently, it is important that efficient methods to synthesize peptides bearing a ureido bond are available.

Currently, ureidopeptides are synthesized using the following methods: a) Coupling of amine with isocyanates that are obtained by the reaction of α-amino acid esters with phosgene or triphosgene.[20] Alternatively, several coupling agents like *N*,*N*′-carbonyldiimidazole,[21] *N*,*N*′-disuccinimido carbonate,[22] 1,1′-carbonylbisbenzotriazole[23] and also treatment of the primary amines with PPh_3-CCl_4-TEA system[24] have been used for the insertion of ureido bond into peptide backbone; b) Curtius or oxidative Hoffmann rearrangement for insertion of the ureido bonds at the C-terminus of *N*-protected α- or β-amino acid.

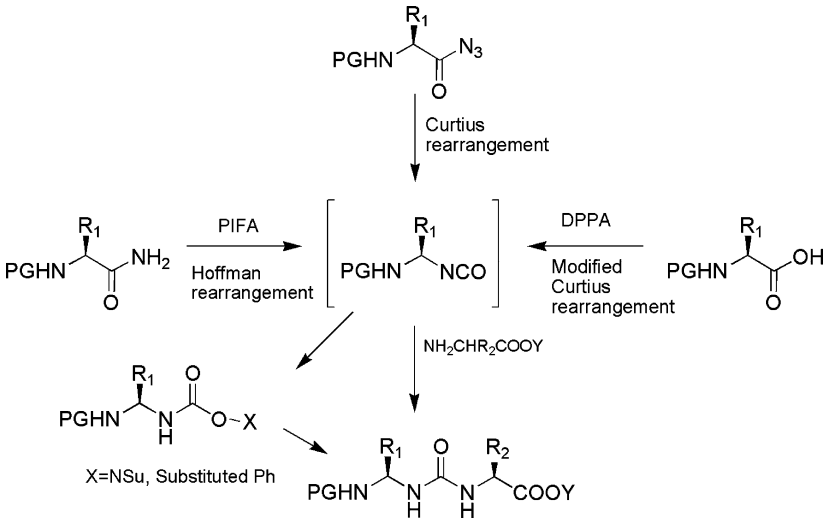
Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr B. R. Ambedkar Veedhi, Bangalore, 560001, India. E-mail: hariccb@rediffmail.com

† Electronic supplementary information (ESI) available: General experimental procedure for the preparation of N^{α}-protected amino/peptide hydroxamic acid and characterization data. See DOI: 10.1039/b905790k

For preparation of peptidyl ureas through Curtius rearrangement, the N-protected α-amino acid azides are heated at reflux in toluene and the resulting isocyanates are coupled with amino acid/ester.[25] The isocyanates obtained from N-protected α/β amino acid azides are also converted into methyl/ethyl carbamates[26] that are in turn used as activated monomers for urea synthesis. Synthesis of α-peptidyl ureas through diphenylphosphoryl azide (DPPA) mediated modified Curtius rearrangement has been recently reported[27] (Scheme 1). β-Peptidyl ureas are also synthesized in solution and solid phase by using the monomers obtained by coupling the amines resulting from reduction of the N-protected α-amino nitriles/amides or β-amino alkyl azides or by other methods.[28] The bis[trifluroacetoxy]phenyliodine (PIFA) mediated oxidative Hoffmann rearrangement of N-urethane protected amino amides also yields peptidyl ureas.[29] Both main chain and side chain primary amide groups have been transformed into isocyanate moiety *via* this method in a single step and coupled with amino component.[30]

In spite of their routine use, both the Curtius and Hoffmann rearrangements present their own limitations. The azide method, although compatible with common *N*-protecting groups,[31] is synthetically less attractive—particularly for large scale reactions—due to the instability of acyl azides and their explosive nature under the high temperature conditions used for accomplishing the rearrangement. Furthermore, this method furnishes impressive yields of ureas with Fmoc chemistry while it does not quantitatively yield Boc protected ureas mainly due to the instability of Boc-amino acid azides. The PIFA mediated conversion of amides to isocyanates uses stable amides as starting materials and involves milder conditions. But, in addition to the high cost of PIFA, the reaction requires higher equivalents of a base and therefore becomes incompatible with Fmoc chemistry. Consequently, its application to Fmoc chemistry has resulted in describing limited examples with invariably less yields.[29] Moreover, when PIFA is used, the trifluoroacetic acid byproduct formed during the reaction can catalyze the hydrolysis of isocyanate thus reducing the yields of urea and can also deprotect the Boc group.[32]

The isocyanates, on the other hand, can also be produced through the Lossen rearrangement of hydroxamic acids. Here,



Scheme 1 Outline of the present methods followed for urea bond insertion.

the isocyanates are generated from the activated hydroxamates through the displacement of *N*-hydroxyl group followed by the C→N migration. Reagents such as *p*-toluenesulfonyl chloride,[33] *N*,*O*-bis-(ethoxycarbonyl)hydroxylamine,[34] methanesulfonyloxycarbamate,[35] several acylating agents[36] and carbodiimides[37] have been used to accomplish the rearrangement. The reported applications of this rearrangement include degradation of the carboxyl group of oligosaccharide derivatives *via* an isocyanate intermediate.[38] In peptide chemistry, the application of this reaction is limited to very few early reports on carboxyl terminal determination in peptides[39] and mechanistic studies relating to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) mediated conversion of hydroxamic acid into amines.[40] The formation of an isocyanate as a common byproduct through the Lossen rearrangement of the *N*-hydroxy succinimidyl esters and carbonates has been documented.[41]

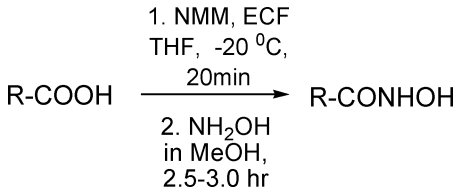
A feature of this reaction, especially suited for peptide chemistry is its ability to be executed under mild and neutral conditions when the rearrangement is effected using *N*,*N*-dicyclohexylcarbodiimide (DCC) or EDC. Consequently, the reaction becomes compatible with all the three urethanes, Boc, Z and Fmoc and tolerable by most side chain protecting groups that are labile towards either acid or base. In spite of these inherent advantages, the application of this rearrangement to the synthesis of peptidomimetics has not been explored.[31] With the intention of developing a new and facile method to α-peptidyl urea synthesis, we considered demonstrating the application of Lossen rearrangement in the peptidomimetic chemistry.

Studies on the reaction were initiated with the preparation of the hydroxamic acid from the corresponding N-protected α-amino acids. The amino acid derived hydroxamic acids, apart from being synthetically useful compounds, are also biologically active in and of themselves.[42] Several procedures have been reported for the synthesis of N-protected amino/peptide hydroxamic acids. These include hydroxaminolysis of N-protected amino acid esters,[43] resin bound amino/peptide acids[44] and N-protected amino acid derived oxazolidinones.[45] Hydroxamates have also been prepared by the reaction of hydroxyl amine with amino acids in presence of cyanuric chloride,[46] tetramethylfluoroformamidinium hexafluorophosphate (TFFH)[47] and alkyl chloroformates.[48] Coupling of N-protected amino acids with *O*-benzylhydroxylamine followed by hydrogenolysis has also yielded hydroxamic acids.[49] The *N*-Boc and Z-α-amino hydroxamic acids employed as starting materials in the present study were prepared as stable solids in high yields by treating the corresponding mixed anhydride solutions with a neutral methanolic solution of hydroxyl amine prepared by neutralizing $NH_2OH.HCl$ with methanolic KOH (Table 1). Out of the two Fmoc protected hydroxamic acids, Fmoc-Val-NHOH was prepared starting from stable Fmoc-Val-Cl,[50] while the Fmoc-Glu(O^{t}Bu)-NHOH was obtained through the mixed anhydride method (Table 1). The easy and quantitative preparation of hydroxamic acids from amino acid and peptide acids and their long shelf-life place them as better starting materials compared to the amino acid azides.

Rearrangement of the hydroxamic acid was effected by treating Boc-Phe-NHOH (chosen as model compound) with a solution of EDC in CH_2Cl_2 at rt for about 30 min. This was followed by the addition of amino acid ester (H-Val-OMe) and continuing the stirring for another 4–5 h provided the dipeptidyl urea **1c** in 72% yield. The effect of the two carbodiimides, EDC and DCC on the yield of the urea could be observed with EDC producing about 5–10% higher yield than DCC. Also, during purification, while the urea adduct of EDC could be removed by aqueous work up, DCU was tediously removed either through column chromatography or repeated recrystallization with DMSO-water.

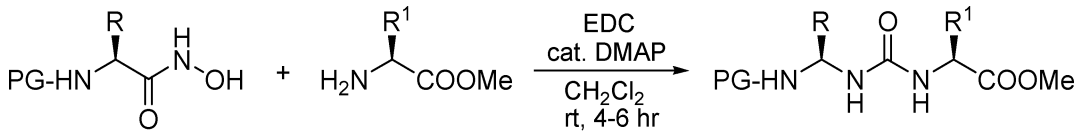
However with both the carbodiimides, addition of a catalytic amount of 4-dimethylaminopyridine (DMAP) increased the yields. For instance, when the reaction of Boc-Phe-NHOH was carried out in the presence of 0.1 equivalent of DMAP, the yield of **1c** rose to 82%. Once the optimized reaction condition was described, the reaction was repeated by using EDC to obtain the Boc and Z protected dipeptidyl ureas, **1a–g** and **2a–d** in good yields. However, when the reaction was carried out using N-Fmoc protected hydroxamic acids, comparably less yields of the peptidyl ureas **3a** and **3b** were observed. This was reasoned out to the reduced solubility of the N-Fmoc protected α-amino hydroxamic acids in CH_2Cl_2 (Table 2).

Table 1 Preparation of N^{α}-protected amino/peptide hydroxamic acids



R-CONHOH	Yield (%)	Ref.	R-CONHOH	Yield (%)
Boc-Val-NHOH	92	46b	Z-Ala-Ile-NHOH, **4a**	92
Boc-Phe-NHOH	96	43a,44a,46a–b,47	Z-Leu-Phe-NHOH, **4b**	88
Boc-Ser(OBzl)-NHOH	91	49	Z-Phe-Leu-NHOH, **4c**	94
Z-Ala-NHOH	95	43b,46a	Boc-Val-Leu-NHOH, **4d**	90
Z-Val-NHOH	91	46a,47	Boc-Val-Pro-NHOH, **4e**	84
Z-Phg-NHOH	93	New compd.	Boc-Phe-Phg-NHOH, **4f**	91
Fmoc-Glu(O^{t}Bu)-NHOH	90	New compd.	Boc-Val-Ala-Leu-NHOH, **4g**	81
Fmoc-Val-NHOH	90	50	Boc-Phg-Phe-NHOH, **4i**	89

Table 2 Preparation of peptidyl ureas from N^{α}-protected amino acid hydroxamates and various amino acid esters



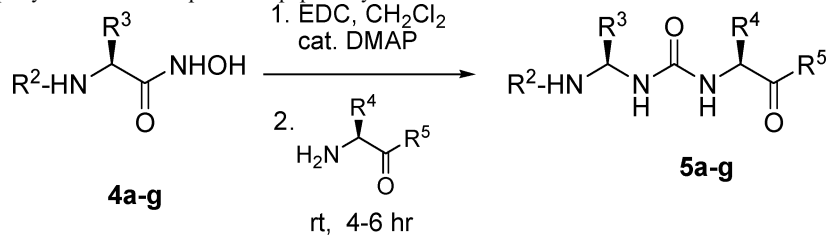
PG=Boc:**1a-g**; PG=Cbz:**2a-d**; PG=Fmoc: **3a-b**

Entry	R	R^1	Yield (%)
1a	$CH(CH_3)_2$	H	79
1b	$CH_2C_6H_5$	$CH_2CH(CH_3)_2$	78
1c	$CH_2C_6H_5$	$CH(CH_3)_2$	82
1d	$CH(CH_3)_2$	CH_3	81
1e	$CH(CH_3)_2$	$CH_2C_6H_5$	81
1f	$CH(CH_3)_2$	$C(CH_3)C_6H_5$	79
1g	CH_2OBzl	H	76
2a	CH_3	H	79
2b	$CH(CH_3)_2$	CH_3	77
2c	(L)-C_6H_5	*R*-$C(CH_3)C_6H_5$	80
2d	(L)-C_6H_5	*S*-$C(CH_3)C_6H_5$	79
3a	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$	68
3b	$C_2H_4COOtBu$	H	69

The reaction was explored for the inclusion of the ureido bond in between the oligopeptide sequences. The dipeptides, Boc-Val-Leu-OH, Z-Phe-Leu-OH, Z-Leu-Phe-OH and Z-Ala-Ile-OH were converted into their hydroxamate derivatives by following the procedure outlined in Table 1, and reacted with amino acid methyl esters in the presence of EDC to obtain the ureido bond linked tripeptide esters **5a–d** in about 75% yield. Boc-Val-Leu-NHOH and Boc-Val-Pro-NHOH were coupled respectively to dipeptide and tripeptide esters in the presence of EDC to afford the corresponding ureido analogs of tetrapeptide **5e** and pentapeptide **5f**. Finally, the hexapeptide sequence Boc-Val-Ala-Leu-ψ[NH-CO-NH]-Val-Ala-Leu-OMe was synthesized. For this, Boc-Val-Ala-Leu-NHOH was subjected to the rearrangement using EDC and coupled with the amino free tripeptide ester to yield the ureido bond possessing oligopeptides **5g** in 68% yield (Table 3).

To study the possibility of epimerization during the reaction, two epimeric dipeptidyl ureas were synthesized *via* the present method by reacting Z-L-Phg-NHOH, separately with optically pure *R* and *S* 1-phenylethylamine. The ^{1}H-NMR analysis of the crude sample of the dipeptidyl urea Z-L-Phg-ψ(NHCONH)-*R*-(+)-phenylethylamine **2c** and Z-L-Phg-ψ(NHCONH)-*S*-(–)-phenylethylamine **2d** containing *R*-1-phenylethylamine and *S*-1-phenylethylamine residues revealed the methyl group peaks at δ values 1.36, 1.38 and 1.38 and 1.39 ppm respectively. Further, the NMR spectrum of the epimeric mixture of **2c** and **2d** (Fig. 1) prepared by using the racemic mixture of 1-phenylethylamine contained the methyl group resonances at δ values 1.36, 1.38 and 1.39. Optical purities of the oligopeptidyl ureas synthesized from peptide hydroxamic acids were also evaluated. The ^{1}HNMR spectrum of the two tripeptidyl ureas **5h** and **5i**, obtained by reacting Boc-L-Phe-L-Phg-NHOH **4f** separately with (*R*) and (*S*) 1-phenylethylamine, contained single methyl groups at δ values 1.38, 1.40; and 1.47 and 1.49 respectively, while the equimolar mixture of the epimers **5h** and **5i**, prepared by reacting racemic 1-phenylethylamine with **4f**, showed the methyl group doublets at 1.46 and 1.38. Further, the ^{1}HNMR of tripeptidyl ureas

Table 3 Synthesis of peptidyl ureas from N$^{\alpha}$-protected peptide hydroxamic acids



Entry	R^2	R^3	R^4	R^5	Yield (%)
5a	Z-Ala	$CH(CH_3)C_2H_5$	$CH_2CH(CH_3)_2$	OMe	78
5b	Z-Leu	$CH_2C_6H_5$	CH_3	OMe	80
5c	Z-Phe	$CH_2CH(CH_3)_2$	$CH(CH_3)C_2H_5$	OMe	74
5d	Boc-Val	$CH_2CH(CH_3)_2$	$CH_2C_6H_5$	OMe	71
5e	Boc-Val	$CH_2CH(CH_3)_2$	$CH(CH_3)_2$	Leu-OMe	75
5f	Boc-Val	$-(CH_2)_3-$	$CH(CH_3)_2$	Ala-Leu-OMe	71
5g	Boc-Val-Ala	$CH_2CH(CH_3)_2$	$CH(CH_3)_2$	Ala-Leu-OMe	68

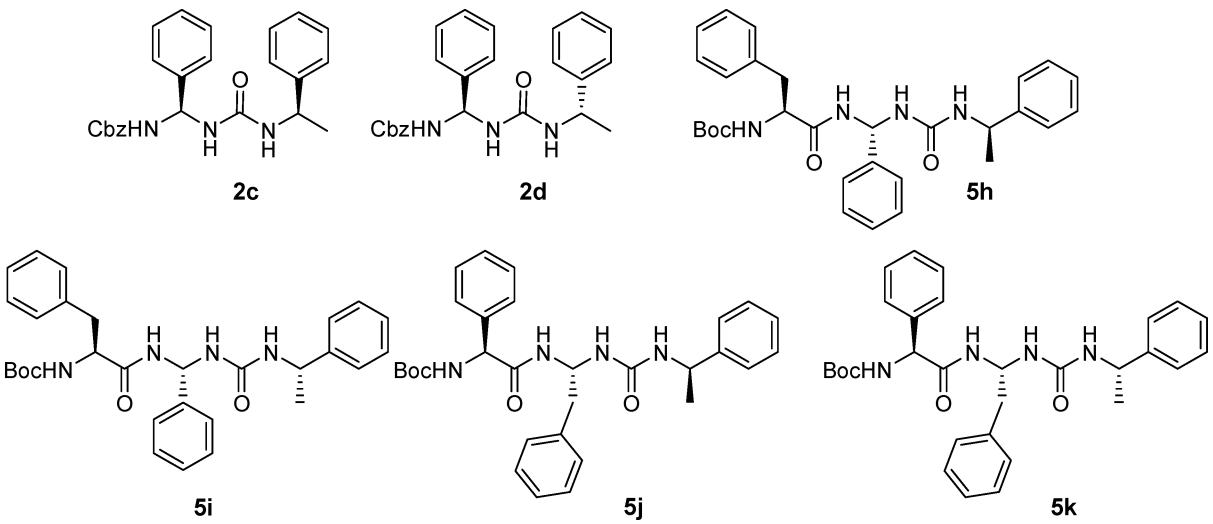
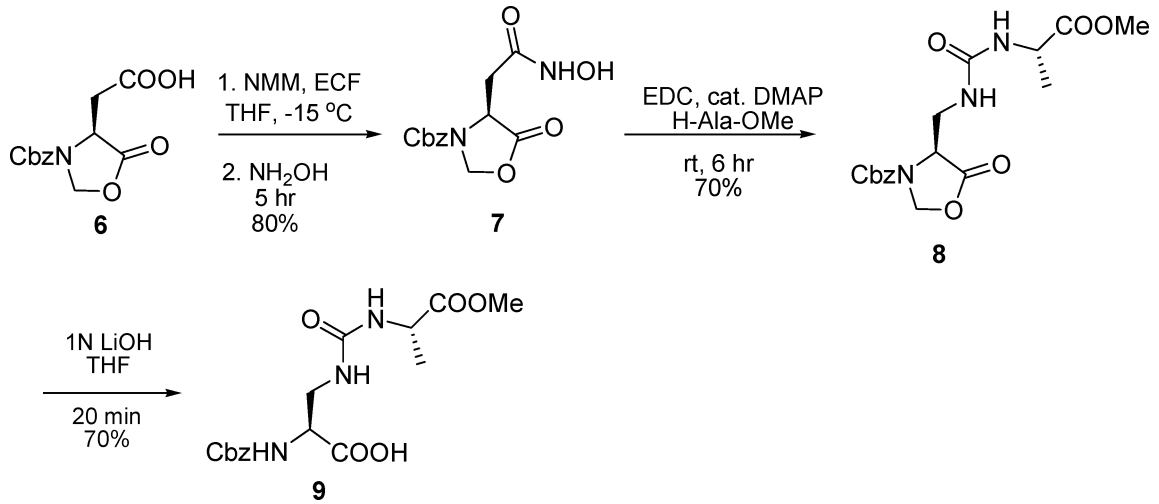


Fig. 1 Peptidylureas studied for epimerization.

5j and **5k** containing (*R*) and (*S*) 1-phenylethylamine residues respectively, synthesized similarly from Boc-L-Phg-L-Phe-NHOH **4i** contained distinct doublets at δ values 1.25, 1.27; and 1.21 and 1.23 respectively. Again the equimolar mixture of the epimers **5j** and **5k**, obtained by reacting racemic 1-phenylethylamine with **4g** had two doublets at 1.22 and 1.26. The appearance of only one distinct doublet for each sample of the compounds **2c** and **2d**; **5h** and **5i**; **5j** and **5k**, and the methyl group resonances separated by 0.04–0.09 ppm for the equimolar mixtures of the epimers in the ^{1}HNMR spectra confirmed that the compounds analyzed were optically pure and the synthesis of peptidyl ureas through the present protocol proceeds with retention of configuration.

Ureidoalanine derivatives which are structurally similar to L-albizziine in possessing an ueriodo group in the side chain are widely used as drug components.[51] Conventionally they are prepared by coupling of the isocyanates with N$^{\alpha}$-protected 2,3-diaminopropionic acid ester,[52] or coupling ω-isocyanates from *N*-Boc-5-oxazolidinones with different amines.[53] We envisioned that the application of the afore-described Lossen rearrangement conditions would lead to simple and practical synthesis of ureidoalanine derivatives *via* a safe and simple method devoid of the use of acid azides. Accordingly, the Z-Asp-oxazolidinone **6** was prepared in 91% yield through the reported method.[54] It was then converted into the hydroxamate **7** by treating the corresponding mixed anhydride solution with hydroxyl amine. The resulting hydroxamic acid, obtained in 80% yield, was found to be stable at ambient temperature for a very long time. It was then subjected to the rearrangement using the EDC and coupled with amino acid ester under similar reaction conditions described above. The ureido compound **8** was isolated in about 70% yield and was completely characterized. Saponification of the oxazolidinone with 1 N LiOH for 30 min yielded the *N*$^{\alpha}$-Z-ureidoalanine **9** (Scheme 2).

In conclusion, we have demonstrated that N-urethane protected α-amino acid and peptide acid derived hydroxamic acids easily undergo Lossen rearrangement effected by carbodiimide to yield isocyanates which in presence of α-amino acid/peptide esters produce good yields of peptidyl ureas. The reaction is carried out under mild conditions, neutral reaction medium, and applicable to all commonly employed urethane type N-protecting groups.



Scheme 2 Synthesis of ureidoalanine derivative.

Ureido bonds can also be easily inserted in the amino acid side chains by reacting the corresponding hydroxamates with amines under the same protocol. The reaction can be easily scaled up.

Experimental section

General procedure for the preparation of peptidyl ureas

To a solution of 201.3 mg (1.05 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 12.2 mg (0.1 mmol) of 4-dimethylaminopyridine (DMAP) in dry CH_2Cl_2 or tetrahydrofuran was added the finely ground powder of N^{α}-urethane protected amino/peptide hydroxamic acid (1.0 mmol) in small portions at rt. The reaction mixture was stirred for 20 min and then amino-free amino acid/peptide acid ester (1.0 mmol) was added. The resulting mixture was stirred at rt for 4–5 h until completion (as monitored by TLC). The solvent was removed *in vacuo* and the residue was dissolved in EtOAc. The organic layer was washed with 10% citric acid solution, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the product, which was purified by column chromatography using $CHCl_3$/MeOH.

Boc-Val-Ala-Leu-NHOH, 4g. Mp 158–159 °C; ^{1}H NMR ($CDCl_3$, DMSO-d_6, 200 MHz) δ 0.81–1.01 (m, 12H), 1.20–1.31 (m, 4H), 1.45 (s, 9H), 1.62–1.95 (m, 3H), 4.25 (m, 1H), 4.42–4.55 (m, 1H), 7.20 (br, 1H); ^{13}C NMR ($CDCl_3$, DMSO-d_6, 100 MHz) 18.4, 19.0, 22.0, 22.9, 28.6, 32.0, 41.3, 48.9, 51.2, 52.5, 79.6, 158.2, 169.8, 172.2, 173.4 6; HRMS *m/z* 439.2528 (M + Na^+), calcd for $C_{19}H_{36}N_4O_6Na$ 439.2533.

Boc-Val-ψ[NH-CO-NH]-Gly-OMe, 1a. Mp 165–167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (m, 6H), 1.46 (s, 9H), 2.05 (m, 1H), 3.69 (s, 3H), 4.05 (m, 1H), 4.32–4.50 (br, 2H), 5.10 (br, 1H), 6.00 (br, 1H), 9.50 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 28.2, 30.8, 41.7, 42.0, 52.1, 60.0, 72.1, 79.7, 156.6, 158.8, 172.2; HRMS *m/z* 326.1698 (M + Na^+), calcd for $C_{13}H_{25}N_3O_5Na$ 326.1692.

Z-Val-ψ[NH-CO-NH]-Ala-OMe, 2b. Mp 182–184 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.89–1.05 (m, 6H), 1.40 (d, J = 5.6 Hz, 3H), 2.10 (m, 1H), 3.75 (s, 3H), 4.22 (m, 1H), 5.10 (s, 2H), 5.41 (br, 1H), 6.45 (br, 1H), 7.30–7.45 (m, 5H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 17.7, 18.2, 18.8, 19.1, 31.2, 48.8, 52.4, 53.6, 60.3, 63.7, 67.0, 128.2, 128.5, 136.2, 154.1, 156.3, 170.8; HRMS *m/z* 374.1685 (M + Na^+), calcd for $C_{17}H_{25}N_3O_5Na$ 374.1692.

Fmoc-Glu(OtBu)-ψ[NH-CO-NH]-Gly-OMe, 3b. Mp 196–198 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 1.35 (s, 9H), 2.02 (m, 2H), 2.23 (t, 2H), 3.67 (s, 3H), 4.01 (s, 2H), 4.38 (t, 1H), 4.66 (d, 2H), 5.54 (t, 1H), 6.05 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) 27.7, 30.3, 31.1, 41.2, 46.7, 51.5, 57.8, 65.3, 79.6, 120.1, 125.2, 127.0, 127.6, 140.7, 143.8, 155.0, 156.6, 171.5, 171.6; MALDI-TOF *m/z* 534.3 (M + Na^+), calcd for $C_{27}H_{33}N_3O_7Na$ 534.2.

Z-Ala-Ile-ψ[NHCONH]-Leu-OMe, 5a. Mp 190–192 °C; ^{1}H NMR ($CDCl_3$, DMSO-d_6, 200 MHz) δ 0.85–1.05 (m, 12H), 1.26 (d, J = 6.6 Hz 3H), 1.44–1.87 (m, 4H), 3.64 (s, 3H), 4.05–4.12 (m, 1H), 4.23–4.29 (m, 1H), 4.92–4.96 (m, 1H), 5.03 (s, 2H), 6.27–6.37 (m, 1H), 6.76–6.80 (br, 2H), 7.31 (br, 5H), 7.84–7.88 (br, 2H); ^{13}C NMR ($CDCl_3$, DMSO-d_6, 100 MHz) δ 11.0, 14.0, 18.5, 21.5, 22.5, 24.4, 24.9, 40.1, 41.5, 50.1, 50.8, 51.5, 60.5, 66.5, 127.1, 127.5, 128.1, 136.8, 155.5, 156.7, 171.5, 174.2; HRMS *m/z* 501.2684 (M + Na^+), calcd for $C_{24}H_{38}N_4O_6Na$ 501.2689.

Acknowledgements

The authors thank Professor Fred Naider, CUNY, New York for useful discussions and the Department of Science and Technology, New Delhi for financial support (grant no. SR/S1/OC-26/2008). GC thanks CSIR, New Delhi for a Senior Research Fellowship.

References

1 (*a*) T. K. Sawyer, *in Peptide-Based Drug Design Controlling Transport and Metabolism*, Eds.: M. D. Taylor, G. L. Amidorn, Oxford University Press, New York, 1995, pp. 332; (*b*) P. A. Wender, D. J. Mitchell, K. Pattabiram, E. T. Pelkey, L. Steinman and J. B. Rothbard, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 13003; (*c*) R. M. J. Liskamp, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 633.

2 A. P. Kozikowski, J. Zhang, F. Nan, P. A. Petukhov, E. Grajkowska, J. T. Wroblewski, T. Yamamoto, T. Bzdega, B. Wroblewska and J. H. Neale, *J. Med. Chem.*, 2004, **47**, 1729.
3 (*a*) D. Seebach, A. K. Beck and D. J. Bierbaum, *Chem. Biodiversity*, 2004, **1**, 1111; (*b*) R. P. Cheng, S. H. Gellman and W. F. De-Grado, *Chem. Rev.*, 2001, **101**, 3219; (*c*) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev.*, 2001, **101**, 3893; (*d*) S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173.
4 Y. E. Antsan, N. A. Makarova and G. I. Chipens, *Sov. J. Bioorg. Chem. (Engl. Transl.)*, 1982, **3**, 185.
5 K. Kawasaki, M. Maeda, J. Watanabe and H. Kaneto, *Chem. Pharm. Bull.*, 1988, **36**, 1766.
6 M. Rodriguez, P. Dubreuil, J. P. Bali and J. Martinez, *J. Med. Chem.*, 1987, **30**, 758.
7 (*a*) N. Tamilarasu, I. Huq and T. M. Rana, *J. Am. Chem. Soc.*, 1999, **121**, 1597; (*b*) C. Y. Cho, E. J. Moran, S. R. Cherry, J. C. Stephans, S. P. Fodor, C. L. Adams, A. Sundaram, J. W. Jacobs and P. G. Schultz, *Science*, 1993, **261**, 1303.
8 N. A. Dales, R. S. Bohacek, K. A. Satyshur and D. H. Rich, *Org. Lett.*, 2001, **3**, 2313.
9 R. J. Broadbridge, R. P. Sharma and M. Akhtar, *Chem. Commun.*, 1998, 1449.
10 P. Y. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, Y. N. Wong, C. H. Chang, P. C. Weber, D. A. Jackson, T. R. Sharpe and S. Erickson-Viitanen, *Science*, 1994, **263**, 380.
11 E. K. Kick and J. A. Ellman, *J. Med. Chem.*, 1995, **38**, 1427.
12 (*a*) P. Bakshi and M. S. Wolfe, *J. Med. Chem.*, 2004, **47**, 6485; (*b*) D. P. Getman, G. A. de Crescenzo, R. M. Heintz, K. L. Reed, J. J. Talley, M. L. Bryant, M. Clare, K. A. Houseman, J. J. Marr and R. A. Mueller, *J. Med. Chem.*, 1993, **36**, 288.
13 A. P. Kozikowski, J. Zhang, F. P. Nan, A. Petukhov, E. Grajkowska, J. T. Wroblewski, T. Yamamoto, T. Bzdega, B. Wroblewska and J. H. Neale, *J. Med. Chem.*, 2004, **47**, 1729.
14 J. S. Nowick, *Acc. Chem. Res.*, 1999, **32**, 287 and references cited therein.
15 A. Violette, S. Fournel, K. Lamour, O. Chaloin, B. Frisch, J. -P. Briand, H. Monteil and G. Guichard, *Chem. Biol.*, 2006, **13**, 531.
16 (*a*) C. Didierjean, J. -P. Briand, A. Aubry and G. Guichard, *Angew. Chem., Int. Ed.*, 2002, **41**, 1895; (*b*) A. Violette, M. C. Averlant-Petit, V. Semetey, C. Hemmerlin, R. Casimir, R. Graff, M. Marraud, J. -P. Briand, D. Rognan and G. Guichard, *J. Am. Chem. Soc.*, 2005, **127**, 2156.
17 (*a*) V. Semetey, D. Rognan, C. Hemmerlin, R. Graff, J. -P. Briand, M. Marraud and G. Guichard, *Angew. Chem., Int. Ed.*, 2002, **41**, 1893; (*b*) D. Ranganathan, C. Lakshmi and I. Karle, *J. Am. Chem. Soc.*, 1999, **121**, 6103; (*c*) D. Ranganathan, S. Kurur, K. P. Madhusudanan and I. L. Karle, *Tetrahedron Lett.*, 1997, **38**, 4659.
18 (*a*) P. S. Corbin, S. C. Zimmerman, P. A. Thiessen, N. A. Hawryluk and T. J. Murray, *J. Am. Chem. Soc.*, 2001, **123**, 10475; (*b*) T. Moriuchi, T. Tamura and T. Hirao, *J. Am. Chem. Soc.*, 2002, **124**, 9356.
19 (*a*) R. Gmelin, G. Strass, G. Z. Hasenmaier and B. Naturforsch, *Chem. Sci.*, 1958, **13**, 252; (*b*) M. Famulok, *J. Am. Chem. Soc.*, 1994, **116**, 1698.
20 J. S. Nowick, D. L. Holmes, G. Noronha, E. M. Smith, T. M. Nguyen and S. -L. Huang, *J. Org. Chem.*, 1996, **61**, 3929 and references cited therein.
21 X. Zhang, J. Rodrigues, L. Evans, B. Hinkle, L. Ballantyne and M. Pena, *J. Org. Chem.*, 1997, **62**, 6420.
22 K. Takeda, Y. Akagi, A. Saiki, T. Tsukahara and H. Ogura, *Tetrahedron Lett.*, 1983, **24**, 4569.
23 A. R. Katritzky, D. P. M. Pleynet and B. Yang, *J. Org. Chem.*, 1997, **62**, 4155.
24 S. Porwanski, S. Menuel, X. Marsura and A. Marsura, *Tetrahedron Lett.*, 2004, **45**, 5027.
25 For the preparation of isocyanates derived from N^{α}-Fmoc-amino acids under reflux, ultrasonication and microwave conditions see: (*a*) B. S. Patil, G. R. Vasanthakumar and V. V. Sureshbabu, *J. Org. Chem.*, 2003, **68**, 7274; For the synthesis of N^{α}-Fmoc-peptide isocyanates and their use in the synthesis of α-oligopeptidyl ureas see:; (*b*) V. V. Sureshbabu, B. S. Patil and R. Venkatramanarao, *J. Org. Chem.*, 2006, **71**, 7697.
26 For the use of active methyl carbamates see: (*a*) B. S. Patil and V. V. Sureshbabu, *Lett. Pept. Sci.*, 2003, **10**, 93; (*b*) L. Fischer, V. Semetey, J. M. Lozano, A. P. Schaffner, J. P. Briand, C. Didierjean and G. Guichard, *Eur. J. Org. Chem.*, 2007, **15**, 2511; For the use of ethyl carbamates as monomers see:; (*c*) G. Guichard, V. Semetey, M. Rodriguez and J. P. Briand, *Tetrahedron Lett.*, 2000, **41**, 1553; (*d*) G. Guichard, V. Semety, C. Diderjean, A. Aubry, J. P. Briand and M. J. Rodriguez, *J. Org. Chem.*, 1999, **64**, 8702.
27 V. V. Sureshbabu, G. Chennakrishnareddy and N. Narendra, *Tetrahedron Lett.*, 2008, **49**, 1408.
28 (*a*) J. A. W. Kruijtzer, D. J. Lefeber and R. M. J. Liskamp, *Tetrahedron Lett.*, 1997, **38**, 5335; (*b*) A. Boeijien, J. V. Ameijde and R. M. J. Liskamp, *J. Org. Chem.*, 2001, **66**, 8454; (*c*) K. Burgess, D. S. Linthicum and H. Shin, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 907; (*d*) A. Boeijen and R. M. J. Liskamp, *Eur. J. Org. Chem.*, 1999, 2127; (*e*) K. Burgess, J. Ibarzo, D. S. Linthicum, D. H. Russell, H. Shin, A. Shintangkoon, R. Totani and A. J. Zhang, *J. Am. Chem. Soc.*, 1997, **119**, 1556; (*f*) J. M. Kim, Y. Bi, S. J. Paikoff and P. G. Schultz, *Tetrahedron Lett.*, 1996, **37**, 5305; (*g*) K. T. Chapman and S. M. Hutchins, *Tetrahedron Lett.*, 1994, **35**, 4055.
29 A. C. Myers, J. A. Kowalski and M. A. Lipton, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5219.
30 (*a*) R. H. Boutin and G. M. Loudon, *J. Org. Chem.*, 1984, **49**, 4277; (*b*) A. S. Radhakrishna, M. E. Parham, R. M. Riggs and G. M. Loudon, *J. Org. Chem.*, 1979, **44**, 1746.
31 For the study on selection of N-protecting group, side reactions, applications in the synthesis of retro-inverso peptides see: (*a*) M. D. Fletcher and M. M. Campbell, *Chem. Rev.*, 1998, **98**, 763; (*b*) *Houben-Weyl: Synthesis of Peptides & Peptidomimetics*, M. Goodman, A. Felix, L. Moroder, C. Toniolo, Eds.; Georg Thieme Verlag: Stuttgart, New York, 2003; Vol. E22c and references cited therein; (*c*) *Peptides: Chemistry and Biology*, N. Sewald, H. D. Jakubke, Eds.; Wiley-VCH Verlag GmbH, D-69469 Weinheim, 2002; (*d*) M. Chorev, *Biopolymers (Peptide Science)*, 2005, **80**, 67.
32 E. A. Englund, H. N. Gopi and D. H. Appella, *Org. Lett.*, 2004, **6**, 213.
33 (*a*) G. Zvilichovsky, *J. Org. Chem*, 1969, **34**, 486; (*b*) J. Pihuleac and I. Bauer, *Synthesis*, 1989, 61.
34 R. Anilkumar, S. Chandrasekhar and M. Sridhar, *Tetrahedron Lett.*, 2000, **41**, 5291.
35 J. A. Stafford, S. S. Gonzales, D. G. Barrett, E. M. Suh and P. L. Feldman, *J. Org. Chem.*, 1998, **63**, 10040.
36 (*a*) T. Shioiri, in *Comprehensive Organic Synthesis*, B. M. Trost, Ed.; Pergamon: Oxford, 1991; Vol. 6, p 795, and references therein; (*b*) M. A. Stolberg, R. C. Tweit, G. M. Steinberg and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, 1955, **77**, 765.
37 J. Abrahamsson and E. Hadler, *Tetrahedron Lett.*, 1976, **17**, 3615.
38 P. W. Needs, N. M. Rigby, S. G. Ring and A. J. MacDougall, *Carbohydrate Res.*, 2001, **333**, 47.
39 M. J. M. Miller, F. E. DeBons and G. M. Loudon, *J. Org. Chem.*, 1977, **42**, 1750.
40 D. G. Hoare, A. Olson and D. E. Jr Koshland, *J. Am. Chem. Soc.*, 1968, **90**, 1638.
41 A. Isidro-Llobet Baringo, X. Just-Baringo, A. Ewenson, M. Alvarez and F. Albericio, *Biopolymers (Peptide Science)*, 2007, **88**, 733.
42 (*a*) S. Murahashi, T. Oda, S. Sugahara and Y. Masui, *J. Org. Chem.*, 1990, **50**, 1744; (*b*) T. R. Burke, M. R. Fesen, A. Mazumdr, J. Wang, A. M. Carithers, D. Grunberger, J. Drisscoll, K. Kohn and Y. Pommier, *J. Med. Chem.*, 1995, **38**, 4171.
43 (*a*) A. Massaro, A. Mordini, G. Reginato, F. Russso and M. Taddei, *Synthesis*, 2007, 3201; (*b*) A. R. Ritter and M. J. Miller, *J. Org. Chem.*, 1994, **59**, 4602.
44 For the solid phase synthesis of amino acid/peptide hydroxamic acids see: (*a*) E. Thouin and W. D. Lubell, *Tetrahedron Lett.*, 2000, **41**, 457; (*b*) S. M. Dankwardt, *Synlett*, 1998, 761; (*c*) L. S. Richter and M. C. Desai, *Tetrahedron Lett.*, 1997, **38**, 321.
45 G. V. Reddy, *Synth. Commun.*, 1999, **29**, 3613.
46 (*a*) G. Giacomelli, A. Porcheddu and M. Salaris, *Org. Lett.*, 2003, **5**, 2715; (*b*) K. Ahlford, A. B. Zaitsev, J. Ekstrom and H. Adolfsson, *Synlett*, 2007, 2541.
47 A. El-Faham, S. N. Khattab and M. Abdul-Ghani, *ARKIVOC*, 2006, **xiii**, 57.
48 (*a*) E. Hofmann and I. Faiferman, *J. Org. Chem.*, 1964, **29**, 748; (*b*) A. S. Reddy, M. S. Kumar and G. R. Reddy, *Tetrahedron Lett.*, 2000, **41**, 6285; For other related references on hydroxamic acids see: (*c*) K. Nagarajan, S. Rajappa, P. Rajagopalan and P. K. Talwalkar, *Indian J. Chem., Sect. B*, 1991, **30**, 222; (*d*) M. C. Pirrung, J. Cao and J. Chen, *J. Org. Chem.*, 1995, **60**, 5790; (*e*) M. C. Pirrung and J. H. L. Chau, *J. Org. Chem.*, 1995, **60**, 8084; (*f*) B. H. Lee and M. J. Miller, *J. Org. Chem.*, 1983, **48**, 24.
49 P. F. Vogt, M. J. Miller, M. J. Mulvihill, S. Ramamurthy, G. C. Savela and A. R. Ritter, *Enantiomer*, 1997, **2**, 367.

50 G. R. Vasanthakumar and V. V. Sureshbabu, *Tetrahedron Lett.*, 2003, **44**, 4099 and references cited therein.
51 (*a*) J. R. Piper, G. S. McCaleb, J. A. Montgomery, F. A. Schmid and F. M. Sirotnak, *J. Med. Chem.*, 1985, **28**, 1016; (*b*) C. Lherbet, M. Morin, R. Castonguay and J. W. Keillor, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 997.
52 D. R. Sargent and C. G. Skinner, *J. Med. Chem.*, 1971, **14**, 465.
53 (*a*) H. Teng, Y. He, L. Wu, J. Su, X. Feng, G. Qiu, S. Liang and X. Hu, *Synlett*, 2006, 877; Using 5-oxazolidinones as internally and bidentately protected intermediates for ω-COOH modification avoids intramolecular trapping of the generated isocyanate by the α-amine see: (*b*) J. Spengler, C. Bottcher, F. Albericio and K. Burger, *Chem. Rev.*, 2006, **106**, 4728.
54 J. M. Scholtz and P. A. Bartlett, *Synthesis*, 1989, 542.

