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A facile and one-pot synthesis of N^{α}-Fmoc/Bsmoc/Boc/Z-protected ureidopeptides and peptidyl ureas employing diphenylphosphoryl azide [DPPA]

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Abstract

Diphenylphosphoryl azide (DPPA) mediated one-pot synthesis of N^{α}-Fmoc/Bsmoc/Boc/Z-protected ureidopeptides and peptidyl ureas as well as phenyl/succinimidyl (N^{α}-urethane protected) methyl carbamates starting from N^{α}-protected amino acids is reported. The formation of an azide, its rearrangement and coupling with an amino component is accomplished in a sequence of one-pot operations. The protocol has incorporated urea linkages in a sterically hindered peptide.

Keywords: Diphenylphosphoryl azide; Ureidopeptides; Peptidyl ureas; Curtius rearrangement; One-pot synthesis

1. Introduction

Peptide backbone modification has developed into a powerful tool to introduce desired structural motifs and to enhance biological properties in peptidomimetics.[1] The urea linkage is the most common type of peptide bond surrogate to be introduced into peptide sequences.[2,3] The metabolic stability and unique bonding properties of the NH–CO–NH– moiety have resulted in its inclusion in potent peptidyl conjugates and bioactive oligomers. Some examples of peptidomimetics containing a urea moiety with elevated biological properties are the TAR-binding fragment of the Tat protein,[4,5] HIV-1 proteases,[6] γ-secretase,[7] aspartic acid protease,[8] microbial alkaline proteinase inhibitors,[9] and aspartic peptidases.[10] The ureido analogs of [Leu^5]enkephalin,[11] angiotensins,[12] gastrin antagonists, and protease inhibitors[13,14] have been prepared. Natural products containing urea linkages are also known.[15] In addition, urea linkages have been used as scaffolds to obtain new generation molecules like dendrimers and self-assembling organic nanotubes.[16] In this context, the development of rapid and simplified synthetic procedures for the insertion of a ureido linkage into peptide sequences continues to receive attention.[17]

Current strategies to synthesize N^{α}-protected urea-linked peptides are predominantly based on Curtius and Hoffmann rearrangements. Sureshbabu et al., reported an elegant procedure for the synthesis of Fmoc protected α-ureido peptides,[18] oligoureas,[19] and a variety of substituted phenyl-(9-fluorenylmethoxycarbonylamino)methyl carbamates[20] through the classical Curtius rearrangement employing a series of isocyanates derived from stable N^{α}-Fmoc amino acid azides.[21] Guichard and co-workers, reported the stepwise synthesis of *N*,*N*′-urea-linked oligomers using *O*-succinimidyl (N^{α}-urethane protected) methyl carbamates.[17] Lipton and co-workers, employed bis[trifluoroacetoxy]phenyliodine (PIFA) for synthesizing ureidopeptides from N^{α}-protected amino and peptide amides via Hoffmann rearrangement.[22] Appella and co-workers used the same reagent to prepare 2,3-diaminopropionic acid starting from Boc-Asn.[23]

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The synthesis of ureidopeptides through classical Curtius rearrangement[24] involves a multi-step protocol whereby an acid azide is prepared via a mixed anhydride or acid chloride, its isolation and rearrangement into an isocyanate followed by coupling with an amine. This protocol has considerable limitations such as the isolation of potentially explosive acid azides, which cause handling problems, and the inherently unstable isocyanates, especially those derived from Bsmoc, Boc, and *Z*-amino acids, which can undergo partial degeneration even before coupling with the amine. On the other hand, the protocol using bis[trifluoroacetoxy]phenyliodine is particularly useful in Boc and Z chemistry. Its utility in Fmoc chemistry is not satisfactory due to the necessity of higher equivalents of bases. Therefore, a simple, improved, and scalable protocol which produces higher yields of the urea and which also tolerates different urethane protecting groups is desirable.

DPPA is used as an azide transfer reagent in organic synthesis.[25–33] Despite its extensive applications, to the best of our knowledge, there are no reports on the synthesis of N^{α}-urethane protected ureidopeptides and peptidyl ureas using DPPA.[17,34,35] Herein, the properties of DPPA as a carboxy activating and azido group transfer reagent are exploited in obtaining ureido peptidomimetics. This protocol has advantages over previous methods as it circumvents the pre-activation of the carboxylic group before reaction with azide donors and isolation of unstable acid azides and isocyanates. In addition, the complete sequence of functional group transformations can be accomplished in one-pot.

2. Results and discussions

In a typical reaction, a solution of N^{α}-Fmoc/Bsmoc/Boc/*Z*-amino acid or peptide acid in THF was maintained at 0 °C. To this, equimolar quantities of diisopropylethylamine (DIEA) and DPPA were added successively. The reaction mixture was stirred at 0 °C for 20 min followed by addition of the amino acid ester. The resulting reaction mixture was subjected to reflux/ultrasonication/microwave irradiation. The in situ generated isocyanate immediately reacted with the amino acid ester to afford the required ureas **1a–4b** and **5a–d** (Scheme 1, Table 1). IR analysis of the reaction mixture without addition of the amino/phenol component revealed a distinct isocyanate peak at around 2300 cm^{-1}. Product isolation in most cases was straightforward as they precipitated from the reaction mixture as solids. However, some of the Boc, Bsmoc, and *Z*-ureidopeptides did not precipitate and required a simple work-up. The Fmoc-ureidopeptides/carbamates were recrystallized as pure crystalline solids using DMSO/water (8:2). When the reaction was carried out under microwave irradiation, the N^{α}-protected amino acids were dissolved in a minimum amount of THF and then diluted with toluene

Scheme 1. Synthesis of N^{α}-protected urea esters.

Table 1
N^{α}-Fmoc/Bsmoc/Boc/Z-protected ureidopeptides and peptidyl ureas

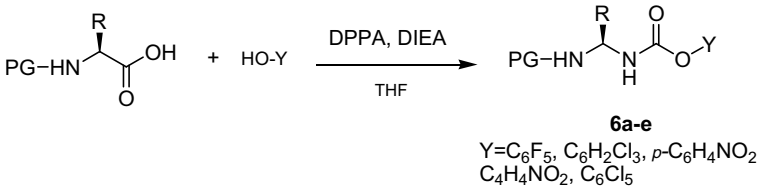
Entry	R^1	R^2	R^3	Y	Mp (°C)	Yield (%) Method			Mass
						A	B	C	
1a	Fmoc	$CH_2OCH_2C_6H_5$	CH_3	CH_3	184	94	95	79	518.2[a]
1b	Fmoc	$CH_2CH_2COO^tBu$	$CH_2C_6H_5$	Bn	147	89	85	71	616.2[a]
1c	Fmoc	$(CH_2)_4NHBoc$	$CH(CH_3)_2$	CH_3	180	92	95	80	597.3[a]
1d	Fmoc	$CH_2SCH_2NHCOCH_3$	H	Bn	175	72	78	70	577.2[a]
2a[c]	Bsmoc	$CH_2SCH_2C_6H_5$	CH_3	CH_3	148	78	83	75	534.1[a]
2b	Bsmoc	$CH_2C_6H_5$	$CH(CH_3)_2$	Et	182	70	75	74	530.2[a]
3a	Boc	$CH_2OCH_2C_6H_5$	H	CH_3	123	78	77	72	382.2[a]
3b	Boc	$CH_2COOCH_2C_6H_5$	CH_3	Et	140	80	75	70	438.2[a]
3c	Boc	CH_3	$CH(CH_3)_2$	CH_3	170	90	80	75	318.2[a]
4a	Z	$CH_2C_6H_5$	CH_3	CH_3	169	86	80	70	400.2[a]
4b	Z	$CH(CH_3)_2$	$CH_2C_6H_5$	Bn	197	92	89	82	504.2[a]
5a	Fmoc-Leu	CH_3	$CH_2C_6H_5$	CH_3	147	90	85	—	624.3[b]
5b	Fmoc-Ser(OBn)	$CH_2C_6H_5$	CH_3	Bn	173	91	92	—	764.3[b]
5c	Boc-Pro	$CH(CH_3)_2$	$CH(CH_3)C_2H_5$	Bn	175	75	78	—	556.3[b]
5d	Z-Val	$CH(CH_3)CH_2CH_3$	$CH(CH_3)_2$	Bn	192	80	85	—	592.3[b]

[a] ESI MS [M+H].
[b] MALDI TOF [M+Na].
[c] HRMS: found, 556.1185 (M+Na); calcd, 556.1188 (M+Na).

due to its better compatibility in microwave synthesis. Also, replacing THF with other solvents such as CH_2Cl_2, $CHCl_3$, and DMF gave no significant changes in the product yields. A number of N^{α}-Fmoc/Boc/Z-protected ureidodipeptide esters were synthesized in 71–94% yields. Ureidopeptides, **2a**,**b**, containing the highly base-sensitive Bsmoc group were also prepared in good yields. Urea-linked dipeptides with at least one side-chain functionalized amino acid were synthesized in about 75% yields via the described procedure. Moreover, NMR analysis of the products revealed the entire protocol to be free from epimerization.[36] Though all the three described methods worked well for the synthesis of ureidopeptides, better results were obtained when the reaction was carried out under thermal and ultrasonication in terms of purity and yield.

The protocol was also useful to synthesize N^{α}-urethane protected amino methyl carbamates, which are known to be stable precursors for insertion of a urea moiety. When N-protected amino acids were subjected to similar reaction conditions with the addition of phenol/*N*-hydroxysuccinimide, carbamates **6a**–**e** were obtained in yields of 78–95% (Scheme 2, Table 2). It is noteworthy that our attempts to prepare these carbamates in a one-pot reaction using PIFA resulted in lower yields.

Finally, the versatility of the reported protocol for the insertion of a urea linkage in large peptides was demonstrated by the incorporation of the –NH–CO–NH– moiety between the 4th and 5th positions of the β-sheet octapeptide Boc-Leu-Aib-Val-β-Ala-γ-Abu-Leu-Aib-Val-OMe.[37] The octapeptide length was maintained constant by replacing γ-Abu with β-Ala. The synthesis of **9** (Scheme 3) was accomplished by coupling of Boc-Leu-Aib-Val-β-Ala-OH **7** with β-Ala-Leu-Aib-Val-OMe **8** in the presence of an equimolar quantity of DPPA and DIEA under ultrasonication. After simple work-up and recrystallization, **9** was obtained in 84% yield and characterized using ^{1}H NMR and MALDI-mass spectrometry.

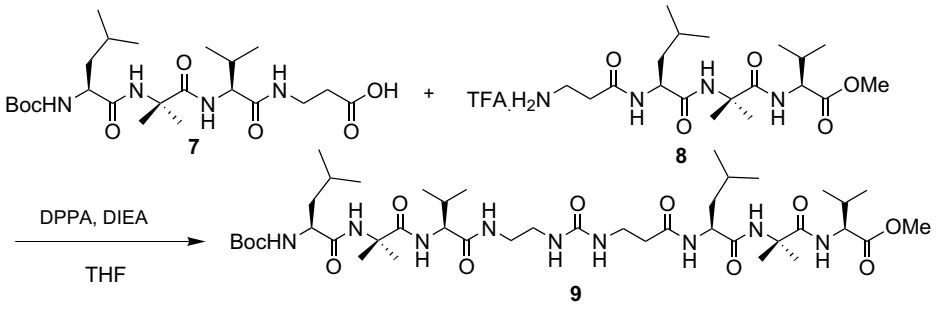


Scheme 2. Synthesis of N^{α}-protected active methyl carbamates.

Table 2
Active phenyl/succinimidyl N^{α}-Fmoc/Boc/Z-protected methyl carbamates

Entry	PG	R	Y	Mp (°C)	Yield (%) Method		Mass[a] [M+H]
					A	B	
6a	Fmoc	$CH_2C_6H_5$	C_6F_5	163	92	90	569.16
6b	Fmoc	$CH(CH_3)C_2H_5$	$C_6H_2Cl_3$[b]	116	95	91	547.10
6c	Fmoc	CH_2COO^tBu	*p*-$C_6H_4NO_2$	136	87	89	548.25
6d	Boc	$CH_2CH(CH_3)_2$	$C_4H_4NO_2$[c]	107	79	78	344.16
6e	Z	$CH(CH_3)CH_2CH_3$	C_6Cl_5	162	85	83	526.95

[a] ESI MS.
[b] 2,4,5-Trichlorophenyl.
[c] *N*-Hydroxysuccinimidyl.



Scheme 3. Synthesis of urea linkage-containing octapeptide **9**.

3. Conclusion

In conclusion, we have developed a useful one-pot protocol for the incorporation of a urea moiety in N^{α}-urethane protected peptides employing DPPA. Fmoc/Bsmoc/Boc/Z-protected ureidopeptide esters and various active carbamates have been prepared in good yields without epimerization.

4. General experimental procedure for the preparation of ureido peptides, methyl carbamates, and peptidyl ureas

4.1. Method A: thermal

To a solution of N^{α}-protected amino acid/peptide acid (1.0 mmol) in THF, DPPA (1.0 mmol) and DIEA (1.0 mmol) were added successively at 0 °C and the reaction stirred for 20 min. To this, amino acid ester salt (1.0 mmol) neutralized with *N*-methylmorpholine (NMM) (1.0 mmol) in THF was added and the reaction mixture refluxed for about 30 min until completion (as monitored by TLC). The precipitated crude ureido peptides were isolated by simple filtration and recrystallized using DMSO/water (8:2). In the case of several Boc/Z/Bsmoc-protected products, simple workup was required. The solvent was removed in vacuo and the reaction mixture was taken into ethyl acetate. The organic layer was washed with 10% citric acid solution, $NaHCO_3$ (10%) solution, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the product, which was recrystallized from DMSO/ water (8:2).

4.2. Method B: ultrasonication at ambient temperature

To a solution of N^{α}-protected amino acid/peptide acid (1.0 mmol) in THF, DPPA (1.0 mmol) and DIEA (1.0 mmol) were added at 0 °C and the reaction stirred for 20 min. To this, amino acid ester (1.0 mmol) neutralized with NMM (1.0 mmol) in THF was added and the reaction mixture was subjected to ultrasonic irradiation (35 kHz, ELMA, TRANSSONIC 310/H) at ambient temperature for 20 min, until the reaction was complete. The resulting products were isolated using the procedure described in method A.

4.3. Method C: microwave irradiation

To a solution of N^{α}-protected amino acid/peptide acid (1.0 mmol) in THF/toluene mixture, DPPA (1.0 mmol) and DIEA (1.0 mmol) were added at 0 °C and the reaction stirred for 20 min. To this, amino acid ester (1.0 mmol) neutralized with NMM (1.0 mmol) in THF was added and then the reaction mixture was exposed to microwave irradiation (Samsung M1739N oven with a frequency of 2450 MHz, at 60% of the total power output, i.e., 720 W) until the reaction was complete. The reaction was worked up as described in method A.

5. Selected spectral data

5.1. N^{α}-Boc-Ser (OBn)-ψ(NH–CO–NH)-Gly-OMe (**3a**)

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.35 (s, 9H), 3.60 (s, 3H), 3.52–3.75 (m, 4H), 4.48 (s, 2H), 5.32 (m, 1H), 6.23 (m, 2H), 6.82 (t, $J = 10.4$ Hz, 1H), 7.30–7.42 (m, 5H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.5, 51.7, 57.7, 63.7, 65.0, 71.9, 78.0, 126.6, 129.3, 130.5, 138.0, 155.3, 156.8, 174.5. ESI MS: *m*/*z* 382.2 $[M+H]^+$. Anal. Calcd for $C_{18}H_{27}N_3O_6$: C, 56.68; H, 7.15; N, 11.02. Found: C, 56.38; H, 7.20; N, 11.10.

5.2. N^{α}-Z-Phe-ψ(NH–CO–NH)-Ala-OMe (**4a**)

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.50 (d, $J = 6.2$ Hz, 3H), 2.92 (d, $J = 6.7$ Hz, 2H), 3.52 (s, 3H), 4.12 (m, 1H), 4.80 (s, 2H), 5.21 (br m, 1H), 6.45 (d, $J = 7.2$ Hz, 1H), 6.57 (d, $J = 7.4$ Hz, 1H), 7.10–7.40 (m, 10H), 7.79 (d, $J = 6.9$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.0, 41.2, 50.2, 51.1, 63.5, 65.3, 126.0, 127.4, 127.6, 128.0, 128.6, 129.0, 129.8, 138.6, 141.2, 156.1, 158.5, 171.9. ESI MS: *m*/*z* 400.2 $[M+H]^+$.

5.3. Fmoc-Leu-Ala-ψ(NH–CO–NH)-Phe-OMe (**5a**)

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85–0.90 (m, 6H), 1.17 (d, $J = 6.3$ Hz, 3H), 1.35 (m, 2H), 1.40–1.60 (m, 1H), 2.95 (d, $J = 6.7$ Hz, 2H), 3.15 (m, 2H), 3.60 (s, 3H), 3.95 (m, 1H), 4.20–4.45 (m, 3H), 5.36 (br, 1H), 6.50 (m, 2H), 7.15–7.50 (m, 9H), 7.75 (d, $J = 7.1$ Hz, 2H), 7.90 (d, $J = 7.1$ Hz, 2H), 8.15 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.5, 22.0, 23.7, 25.0, 37.9, 41.5, 47.6, 49.5, 52.3, 54.0, 65.3, 67.3, 120.1, 125.3, 126.7, 127.3, 127.9, 128.5, 129.3, 137.8, 141.5, 144.0, 156.7, 169.1, 172.1, 173.6. MALDI-TOF MS: *m*/*z* observed 623.3 [M+Na].

5.4. Bsmoc-Phe-ψ(NH–CO–NH)-Val-OEt (**2b**)

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (d, $J = 7.8$ Hz, 6H), 1.13 (t, $J = 8.1$ Hz, 3H), 1.81 (m, 1H), 2.98 (m, 2H), 4.28 (s, 2H), 4.48 (m, 2H), 4.51 (m, 1H), 6.12 (d, $J = 6.5$ Hz, 1H), 6.30 (m, 1H), 6.9–7.7 (m, 10H), 9.0 (m, 2H) ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.12, 18.24, 38.23, 41.35, 58.91, 60.12, 69.22, 70.15, 112.53, 118.75, 125.29, 126.21, 127.21, 128.12, 129.82, 132.82, 133.53, 135.58, 139.23, 141.20, 155.45, 160.52, 175.18. HRMS: found, 529.1881 [M+Na]; calcd, 529.1883 [M+Na].

5.5. p-Nitrophenyl-{1-(9-fluorenylmethoxycarbonylamino)-2-[tert-butoxycarbonyl]methyl}carbamate (**6c**)

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45 (s, 9H), 2.45 (m, 2H), 4.20–4.35 (m, 4H), 6.65 (d, $J = 7.4$ Hz, 1H), 7.20–8.14 (m, 13H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.0, 37.9, 47.3, 49.1, 66.7, 81.6, 120.1, 121.8, 125.1, 127.0, 127.7, 141.4, 143.8, 144.6, 153.7, 155.6, 156.8, 171.3. MS

(MALDI-TOF) *m/z* observed: 570.0 $[M+Na]^+$, 586.2 $[M+K]^{+\cdot}$ Anal. Calcd for $C_{29}H_{29}N_3O_8$: C, 63.61; H, 5.34; N, 7.67. Found: C, 63.52; H, 5.22; N, 7.56.

5.6. Compound 9

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75–0.95 (m, 24H), 1.39 (s, 9H), 1.52 (m, 6H), 1.62 (m, 2H), 1.69–1.85 (m, 12H), 1.97 (m, 1H), 2.28 (m, 2H), 2.98 (m, 2H), 3.15–3.21 (m, 3H), 3.85–3.97 (m, 2H), 4.03–4.15 (m, 3H), 4.59 (m, 1H), 6.87–6.96 (m, 2H), 7.01–7.22 (m, 3H), 7.59–7.85 (m, 3H), 8.15 (s, 1H), 8.21 (s, 1H). MALDI-TOF MS: *m/z* observed 906.5 [M+Na], 922.5 [M+K]. HRMS: found, 906.5653 [M+Na]; calcd, 906.5640 [M+Na].

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References and notes

1. Nowick, J. S.; Smith, E. M.; Pairish, M. *Chem. Soc. Rev.* **1996**, *25*, 401–415.
2. Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380–384.
3. Burgess, K.; Shin, H.; Linthicum, D. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 907–909.
4. Wang, X.; Huq, I.; Rana, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 6444–6445.
5. Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303–1305.
6. Navia, M. A.; Fitzgerald, P. M. D.; McKeever, B. M.; Leu, C.-T.; Heimbach, J. C.; Herber, W. K.; Sigal, I. S.; Darke, P. L.; Springer, J. P. *Nature* **1989**, *337*, 615–620.
7. Bakshi, P.; Wolfe, M. S. *J. Med. Chem.* **2004**, *47*, 6485–6489.
8. Kick, E. K.; Ellman, J. A. *J. Med. Chem.* **1995**, *38*, 1427–1430.
9. Broadbridge, R. J.; Sharma, R. P.; Akhtar, M. *Chem. Commun.* **1998**, 1449–1450.
10. Dales, N. A.; Bohacek, R. S.; Satyshur, K. A.; Rich, D. H. *Org. Lett.* **2001**, *3*, 2313–2316.
11. Kawasaki, K.; Maeda, M.; Watanabe, J.; Kaneto, H. *Chem. Pharm. Bull.* **1988**, *36*, 1766–1771.
12. Vegner, R. E.; Chipens, G. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1975**, *45*, 431–434.
13. Rodriguez, M.; Dubreuil, P.; Bali, J. P.; Martinez, J. *J. Med. Chem.* **1987**, *30*, 758–763.
14. Guerlavais, V.; Boegglin, D.; Mousseaux, D.; Oiry, C.; Heitz, A.; Deghengi, R.; Locatelli, V.; Torsello, A.; Ghe, C.; Catapano, F.; Muccioli, G.; Galleyrand, J.-C.; Fehrentz, J.-A.; Martinez, J. *J. Med. Chem.* **2003**, *46*, 1191–1203.
15. Teng, H.; He, Y.; Wu, L.; Su, J.; Feng, X.; Qiu, G.; Liang, S.; Hu, X. *Synlett* **2006**, 877–880.
16. Semetey, V.; Didierjean, C.; Briand, J.-P.; Aubry, A.; Guichard, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1895–1898.
17. Fischer, L.; Semetey, V.; Lozano, J.-M.; Schaffner, A. P.; Briand, J.-P.; Didierjean, C.; Guichard, G. *Eur. J. Org. Chem.* **2007**, *15*, 2511–2525.
18. Patil, B. S.; Vasanthakumar, G. R.; Sureshbabu, V. V. *J. Org. Chem.* **2003**, *68*, 7274–7280.
19. Sureshbabu, V. V.; Patil, B. S.; Venkatramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697–7705.
20. Patil, B. S.; Sureshbabu, V. V. *Lett. Pept. Sci.* **2003**, *10*, 93–97.
21. Sureshbabu, V. V.; Ananda, K.; Vasanthakumar, G. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4328–4331.
22. Myers, A. C.; Kowalski, J. A.; Lipton, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219–5222.
23. Englund, E. A.; Gopi, H. N.; Appella, D. H. *Org. Lett.* **2004**, *6*, 213–215.
24. Smith, P. A. S. *Org. React.* **1946**, *3*, 337–449.
25. Jacobi, P. A.; Zheng, W. *Tetrahedron Lett.* **1993**, *34*, 2581–2584.
26. Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett.* **1998**, *39*, 7235–7238.
27. Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4308–4310.
28. Kedrowski, B. L. *J. Org. Chem.* **2003**, *68*, 5403–5406.
29. Yamada, S.; Ikota, N.; Shioiri, T.; Tachibana, S. *J. Am. Chem. Soc.* **1975**, *97*, 7174–7175.
30. Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.
31. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18*, 1977–1980.
32. Richter, L. S.; Andersen, S. *Tetrahedron Lett.* **1998**, *39*, 8747–8750.
33. Daisuke, S. D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2006**, *47*, 7219–7223.
34. *Houben-Weyl: Synthesis of Peptides & Peptidomimetics*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Georg Thieme: Stuttgart, New York, 2003; Vol. E22c; and references cited therein.
35. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.
36. The racemization study was carried out through ^{1}H NMR analysis of the ureas prepared by coupling Fmoc-Ser(Bn)OH with optically pure *R* or *S*-1-phenylethylamine and its racemate. The methyl resonances of the phenylethylamine residue in Fmoc-Ser(Bn)-ψ(NH–CO–NH)-*R*-(+)-1-phenylethylamine and Fmoc-Ser(Bn)-ψ(NH–CO–NH)-*S*-(−)-1-phenylethylamine were observed as distinct doublets at δ 1.30, 1.32 and δ 1.29, 1.31, respectively, with separation of 0.02 ppm in DMSO-d_6 solution. For Fmoc-Ser(Bn)-ψ(NH–CO–NH)-*R*,*S*-(±)-1-phenylethylamine, the corresponding methyl resonances were observed as two doublets at δ 1.32, 1.30 and δ 1.31, 1.29. This clearly showed that there was no formation of an epimeric mixture (absence of two $-CH_3$ doublets when optically pure phenylethylamines were coupled) during the reaction. Instead, the reaction resulted in optically pure product.
37. Karle, I. L.; Pramanik, A.; Banerjee, A.; Bhattacharjya, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 9087–9095.