Carbonyldiimidazole (CDI) Mediated Synthesis of N^{α}-Protected Amino Acid Azides: Application to the One-pot Preparation of Ureidopeptides

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Abstract: Synthesis of N^{α}-protected amino acyl azides starting from corresponding acids *via* the carbonyldiimidazole (CDI) activation is described. The protocol is extended for a one-pot preparation of ureido peptides that circumvents the isolation of acyl azide and isocyanate intermediates. The reaction was accomplished without using any additives and base. The protocol is simple, clean, high yielding and free from racemization.

Keywords: Acyl azide, CDI, one-pot reaction, ureidopeptides.

INTRODUCTION

N-Protected amino acid azides are well known and efficient acylating agents in peptide chemistry. They were first reported by Curtius during his efforts to develop mild, racemization free route for peptide synthesis [1]. Acid azide method, frequently used in the segment condensation of peptide fragments by the divergent approach, is still practiced by the peptide chemists especially for the coupling of bifunctional amino acids His, Thr, Trp and Ser [2]. The total synthesis of bovine pancreatic ribonuclease (RNase) A with 124 amino acids was carried out using acid azide method by Haruaki Yajima [3]. They are the building blocks for the synthesis of partially modified retro-inverso peptides, gem-diaminoalkylamines, β-amino acids, β-amino alcoholss [4]. In general, acyl azides are extensively used in organic synthesis for the preparation of amides, nitriles, and heterocycles and also in cycloaddition reactions [5].

Curtius rearrangement is an important application of acyl azides, which describes their degradation into isocyanate through a concerted mechanism. Isocyanates are reactive intermediates employed in the synthesis of polyurethanes, used as precursors to agrochemicals, adhesives, *etc* [6]. In particular, amino acid derived isocyanates are useful intermediates for the synthesis of artificial β-sheets, various pharmacologically important scaffolds such as ureas, carbamates, and formamides [7]. Insertion of urea moiety in place of amide bond has lead to ureidopeptidomimetics some of which are screened as HIV-1 protease inhibitors, $[Leu]^5$ enkephalin analogs, angiotensins, γ-secretaries that have shown increased metabolic stability [8].

The protocols generally employed to access acyl azides involve reaction of an azide ion with activated carboxy acids such as acid chlorides, mixed anhydrides, oxazolidinones [9]. Subhas Bose *et al.*, reported the synthesis of acyl azides by a reaction of NaN_3 with aldehydes using Dess-Martin periodinane [10]. Katritzky's group developed a method for the synthesis of acyl azides from corresponding acyl benzotriazole intermediate [11]. Sureshbabu *et al*., reported the preparation of Fmoc-amino acid azides from corresponding acid chlorides or mixed anhydrides [7,12]. However the acid chloride method is obsolete in case of Boc/Z amino acids because the corresponding acid chlorides degrade to Leuch's anhydride [9] and most of the other protocols are less advantageous due to multi-step reactions, long duration, and use of toxic reagents. On the other hand, though a plethora of protocols are available for the synthesis of urea derivatives such as reaction of amines with carbonyl transfer agents, active carbamates or the generation of isocyanates using phosgene/phosgene equivalents followed by reaction with an amine [13], the one involving generation of isocyanates through curtius rearrangement of acyl azides followed by their aminolysis is of much synthetic interest. This is the protocol of choice especially for *N*-protected α-ureido peptidomimetics. Previously, we had demonstrated one pot preparation of ureido peptides from corresponding acids using diphenylphosphoryl azide (DPPA) and Deoxoflour/$TMSN_3$ [14]. The *in situ* generated acyl azides have played a key role in these experiments. Recently our group reported the synthesis of acyl azides employing peptide-coupling reagents such as EDC, HBTU in high yields [15]. In view of the wide spread applications of acyl azides, development of a mild protocol for their preparation is still of interest.

With the continued interest in this area and our knowledge over various classes of carbonyl transfer reagents, we became interested towards a mild reagent of this class-carbonyldiimidazole (CDI) which is also known for its ability to activate carboxyl group [16]. It was envisioned that it could be a useful reagent for generation of acyl azides from corresponding acids. CDI possesses several advantages over the traditional coupling agents such as low cost, high yield and purity of the products and racemization free coupling. Fustero *et al*., carried out total synthesis of tetramic acid using CDI as carbonyl transfer reagent [17]. Figueiredo group employed it as hydroxy group activator for the synthesis of

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0929-8665/11 $58.00+.00

substituted azetidines [18]. The protease inhibitor GE 20372 and MAPI containing urea linkage were synthesized by Zhang and coworkers [19]. It was also employed for the aqueous phase synthesis of peptides and peptide thioesters [20]. Recently Dube's group employed CDI as a promoter for the Lossen rearrangement of various hydroxamic acids to isocyanates [21]. Larrivee and others demonstrated CDI mediated amidation of acyl imidazoles in presence of diazabicycloundecene (DBU) as catalyst [22]. Despite such wide spread application, there are no reports on the utility of CDI for the synthesis of acyl azides. With an aim to demonstrate the newer application of this reagent, we now, report the synthesis of acyl azides and then, a one-pot preparation of ureido derivatives through CDI mediated carboxy activation.

RESULTS AND DISCUSSION

In the first part of our work, *N*-protected amino acyl azides were synthesized from corresponding acids. In a typical reaction, a chilled solution of Fmoc-Ala-OH **1a** in THF was treated with equimolar quantity of CDI. After 15 min, NaN_3 (dissolved using a few drops of DMSO) was added and the reaction was continued for another 20 min. The resulting acyl azide **3a** was isolated after a simple workup as pure solid in a yield exceeding 90%. Imidazole byproduct was removed completely in aqueous workup. Initial characterization by IR revealed the presence of a strong peak at 2135 cm^{-1} corresponding to the acyl azide. Further analyses through mass and NMR studies confirmed the product (Scheme **1**).

The acyl azide formation is a two-step process involving first, the activation of carboxy group as acyl imidazole (imidazolide) **2** followed by its azidolysis. The IR analysis of the isolated imidazolide had a signal at 1650 cm^{-1}, which underwent rapid azidolysis on addition of NaN_3/DMSO. The reaction was monitored by subjecting an aliquot of reaction mixture to IR analysis in frequent intervals of time. Complete disappearance of imidazolide peak confirmed the completion of reaction which took only about 20 min.

The importance of the protocol lies in the fact that the method doesn't require the addition of an organic base, which usually is the case in typical coupling reactions during carboxyl group activation, thus circumventing the base catalyzed side reactions including racemization. The efficacy of the protocol was demonstrated by preparing some other Fmoc-protected amino acid azides **3a-d** as well. Encouraged by this result, the protocol was extended to synthesize a few Z-protected amino acid azides **3e-h** including one bifunctional amino acid derived acyl azide **3f** also. In addition, two dialkyl amino acid azides Boc-Aib-N_3 **3i** and Boc-Gpn-N_3 **3j** were also prepared (Table **1**).

As a second objective, we undertook an one-pot synthesis of ureidopeptides. For this, the solution of Fmoc-Ala-N_3 prepared as described previously, was subjected to ultrasonication for 10 min without isolation. The *in situ* generated isocyanate was treated with leucinyl methyl ester (obtained by deprotonation of the corresponding hydrochloride salt using Zn dust) [23] under ultrasonication. The reaction was complete in 15 min to afford the desired urea **4a**. This was evident by TLC analysis and precipitation of insoluble urea adduct from the reaction mixture. An excess of hexane was added and the product was collected by filtration. A simple recrystallization afforded **4a** in good yield with excellent purity as a stable solid (Scheme **2**).

The sequence of Curtius rearrangement was confirmed by carrying out a separate experiment without adding amine component to the reaction mixture. The acyl azide generated by the reaction of NaN_3/DMSO with *N*-protected amino acid derived imidazolide, underwent Curtius transformation on subjecting to ultrasonication to afford the corresponding isocyanate. This was confirmed through IR spectroscopy (2245 cm^{-1}) and complete disappearance of acyl azide peak was observed after 10 min. The protocol was extended for the synthesis of few other Fmoc-protected ureas **4a-c**, as well as Boc/Z-protected ureidopeptides **4d-h**. All the products were obtained in excellent yield and purity (Table **2**). The case studies carried out on specimen examples of ureidopeptides confirmed that the entire protocol is free from racemization [24].

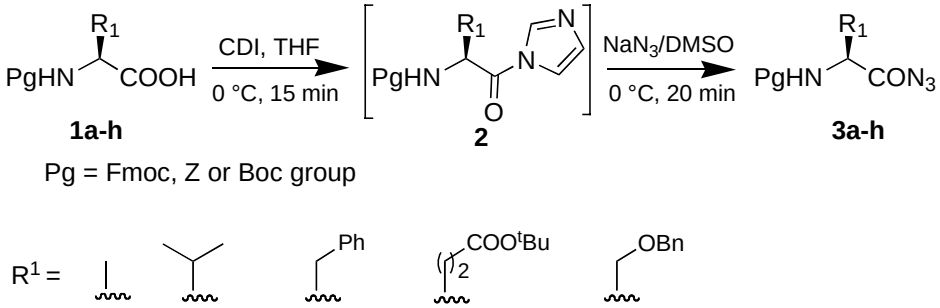
CONCLUSION

In summary, a simple route for the preparation of N^{α}-protected amino acyl azides is reported employing CDI as carboxy activating agent and the protocol is extended for an one-pot synthesis of ureidopeptides. The reaction is simple, mild and high yielding.

EXPERIMENTAL PROCEDURE

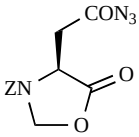
General

All solvents were distilled prior to use and reagents were used as received from Sigma-Aldrich. Melting points were determined on a Buchi model 150 melting point apparatus in open capillaries and are uncorrected. IR spectra were re-

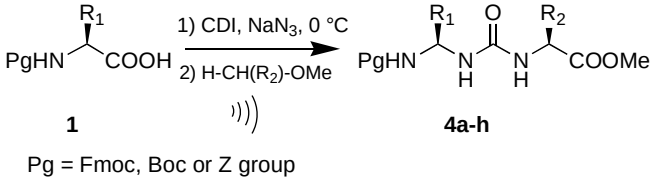


Scheme (1). Synthesis of urethane protected amino acyl azides.

Table 1. List of Urethane Protected Acyl Azides

Entry	Acyl Azide	Yield (%)	Mp (°C)	HRMS $[M+Na]^+$ Obsd./Calcd.
3a	Fmoc-Ala-N_3	89	162 (163) [7a]	359.1123/359.1120
3b	Fmoc-Val-N_3	87	168 (169) [7a]	387.1425/387.1433
3c	Fmoc-Glu(^{t}Bu)-N_3	78	169(168-170)[7a]	473.17/473.18[a]
3d	Fmoc-Ser(OBn)-N_3	75	146	481.1285/481.1278[b]
3e	Z-Phe-N_3	88	145 (146) [11]	347.1093/347.1120
3f		76	Gum	327.0712/327.0705
3g	Z-Val-N_3	70	Gum	249.13/249.11[a]
3h	Z-Gpn-N_3	74	Gum	353.1595/353.1590
3i	Boc-Aib-N_3	78	Gum	251.15/251.11[a]
3j	Boc-Gpn-N_3	77	Gum	335.1489/335.1485[b]

[a] ESI-MS; [b] $[M+K]^+$



Scheme (2). One-pot synthesis of ureido peptides.

corded on a Nicolet model impact 400 D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). ^{1}H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. High-resolution mass spectra (HR-MS) were recorded on Q- Tof micromass mass spectrometer. The ultrasound bath (Elma, T 310/H) was German made and operated at 35 kHz.

General Procedure for 3a-j: To a solution of *N*-protected amino acid (1.0 mmol) in THF (10.0 mL), was added CDI (162 mg, 1.0 mmol) at 0 °C and the reaction mixture was stirred for 15 min. To this, NaN_3 (1.1 mmol, 72 mg) in DMSO (1-2 drops) was added and the stirring was continued for another 20 min. The solvent was removed under vacuum and diluted with CH_2Cl_2 (20 mL). The organic layer was washed with 5% Na_2CO_3 solution (2 x 10 mL), water (2 x 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated *in vacuo* to afford the product in 88-90% yield.

General procedure for 4a-g: To a chilled solution of *N*-protected amino acid (1.0 mmol) in THF (10 mL), CDI (162 mg, 1.0 mmol) was added and the reaction mixture was stirred for 15 min. NaN_3 (72 mg, 1.1 mmol in few drops of DMSO) was added and the stirring was continued for 20 min. Then the reaction mixture was ultrasonicated for 10 min, amino acid ester (1.1 mmol, obtained by neutralizing its hydrochloride salt with Zn dust) was added and the ultrasonication was continued for another 15 min. Urea product, which precipitated out from the reaction mixture, was filtered and recrystallized using DMSO-water system. Otherwise, the product was isolated through simple work up.

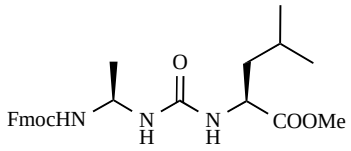
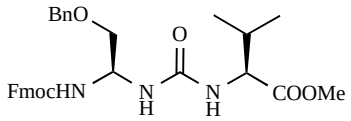
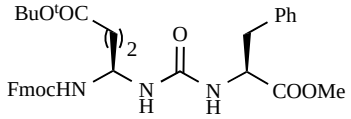
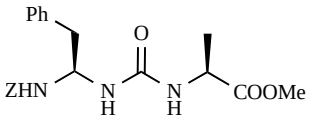
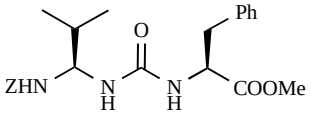
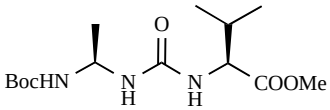
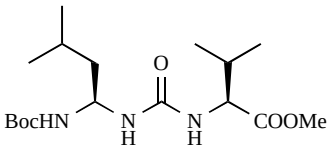
Spectral Characterization Data

(*S*)-(9*H*-Fluoren-9-yl)methyl 1-azido-1-oxopropan-2-ylcarbamate {Fmoc-Ala-N_3} (3a): IR (KBr): 1698, 2135 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): white solid; δ (ppm) 1.42 (3H, d, *J* = 7.2 Hz), 3.88 (1H, m), 4.35 (1H, t, *J* = 3.8 Hz), 4.48 (2H, d, *J* = 6.8 Hz), 6.89 (1H, br), 7.3-7.9 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.6, 47.5, 51.9, 67.5, 120.5, 125.4, 127.6, 128.3, 141.8, 144.1, 150.6, 180.9.

(*S*)- (9*H*-Fluoren-9-yl)methyl 1-azido-3-methyl-1-oxobutan-2-ylcarbamate {Fmoc-Val-N_3} (3b): IR (KBr): 1701, 2138 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): white solid; δ (ppm) 0.93 (6H, d, *J* = 6.2 Hz), 2.15 (1H, m), 3.99 (1H, br), 4.12 (1H, t, *J* = 3.8 Hz), 4.25 (2H, d, *J* = 6.4 Hz), 5.89 (1H, br), 7.22-7.75 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.7, 31.4, 47.7, 61.2, 67.6, 125.4, 125.5, 127.6, 128.23, 141.8, 144.2, 156.8, 180.1.

(*S*)-*tert*-Butyl-4(((9*H*-fluoren-9-yl)methoxy)carbonyl)-5-azido-5-oxopentanoate {Fmoc-Glu(O^{t}Bu)-N_3} (3c): IR (KBr): 1695, 2136 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): white solid; δ (ppm) 1.38 (9H, s), 1.79-1.82 (2H, m), 2.10 (1H, br),

Table 2. List of Urethane Protected Ureidopeptides

Entry	Urea	Yield (%)	Mp (°C)	HRMS $[M+Na]^+$ Found/Calcd.
4a		94	200 (199)[7b]	476.2153/473.2161
4b		89	167- 168	568.2432/568.2424
4c		88	135	640.2432/640.2425[b]
4d		89	168 (169) [15a]	422.1681/422.1692
4e		91	188	450.23/420.20[a]
4f		92	172 (170) [15a]	340.1845/340.1848
4g		79	174-175 (175) [14]	398.2052/398.2057[b]

[a] ESI-MS; [b] $[M+K]^+$

2.18-2.25 (2H, m), 3.87 (1H, m), 4.12-4.27 (3H, m), 7.33-7.89 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 27.7, 31.3, 38.5, 46.5, 51.5, 65.5, 79.6, 127.2, 127.4, 127.6, 129.0, 140.6, 142.5, 155.8, 168.0, 171.5.

(*S*)-(9*H*-Fluoren-9-yl)methyl 1-azido-3-(benzyloxy)-1-oxopropan-2-ylcarbamate {Fmoc-Ser(OBn)-N_3} (3d): IR (KBr): 1697, 2142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): white solid; δ (ppm) 3.28 (2H, s), 3.65 (2H, d, *J* = 4.6 Hz), 4.15 (1H, t, *J* = 3.8 Hz), 4.27 (2H, d, *J* = 6.4 Hz), 4.65 (1H, m), 6.95 (1H, br), 7.22-7.81 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.5, 47.6, 52.5, 68.5, 69.8, 127.0, 127.6, 128.1, 128.4, 128.7, 128.9, 129.2, 137.5, 141.1, 143.8, 156.1, 171.9.

(*S*)-Benzyl 1-azido-1-oxo-3-phenylpropan-2-ylcarbamate {Z-Phe-N_3} (3e): IR (KBr): 1695, 2132 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): white solid; δ (ppm) 2.51 (2H, d, *J* = 5.6 Hz), 3.67 (1H, m), 5.09 (2H, s), 6.98 (1H, br), 7.13-7.35 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 38.1, 57.2. 67.6, 128.1, 128.6, 128.9, 129.1, 129.3, 129.7, 135.9, 136.7, 156.4, 179.8.

(*S*)-Benzyl 4-(2-azido-2-oxoethyl)-5-oxooxazolidine-3-carboxylate {Z-Asp(oxa)-N_3} (3f): IR (film): 1712, 2146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): gum; δ (ppm) 2.89 (2H, d, *J* = 6.4 Hz), 4.01 (1H, t, *J* = 4.2 Hz), 5.16 (2H, s), 5.65 (2H, s), 7.19-7.21 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 55.6, 67.7, 79.0, 128.5, 128.9, 129.2, 136.9, 153.3, 172.6, 180.3.

(*S*)-Benzyl 1-azido-3-methyl-1-oxobutan-2-ylcarbamate {Z-Val-N_3} (3g): IR (film): 1702, 2142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): gum; δ (ppm) 0.92 (6H, d, *J* = 6.4 Hz), 2.18 (1H, m), 3.95 (1H, br), 5.36 (2H, s), 6.23 (1H, br), 7.22-7.70 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.5, 30.4, 53.5, 67.8, 127.2, 127.8, 128.9, 139.9, 155.8, 179.5.

Benzyl 1-(azidocarbonyl)cyclohexylcarbamate {Z-Gpn-N_3} (3h): IR (film): 1699, 2141 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): gum; δ (ppm) 1.18-1.25 (10H, m), 2.35 (2H, s), 2.89 (2H, br), 5.25 (2H, s), 6.99 (1H, br), 7.19-7.21 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 24.7, 28.8, 37.5, 39.3, 41.8, 65.6, 126.9, 127.5, 128.9, 139.8, 155.6, 171.3.

***tert*-Butyl 1-azido-2-methyl-1-oxopropan-2-ylcarbamate {Boc-Aib-N_3} (3i):** IR (film): 1694, 2138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$,): gum; δ (ppm) 1.39 (9H, s), 1.47 (6H, s), 5.02 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.5, 28.9, 52.3, 79.3, 155.6, 180.1.

***tert*-Butyl 1-(azidocarbonyl)cyclohexylcarbamate {Boc-Gpn-N_3} (3j):** IR (film): 1702, 2138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): gum; δ (ppm) 1.36 (9H, s), 1.19-1.43 (10H, m), 2.33 (2H, s), 2.92 (2H, br), 6.95 (1H, br); ^{13}C NMR (100MHz, $CDCl_3$,): δ (ppm) 21.5, 24.3, 27.5, 28.3, 36.4, 39.2, 42.5, 78.6, 156.5, 171.9.

(*S*)-Methyl 2-(3-((*S*)-1-(((9*H*-fluoren-9-yl)methoxy) carbonyl)ethyl)uriedo)-4-methylpentanoate {Fmoc-Ala-*ψ*[NHCONH]-Leu-OMe} (4a): IR (film): 1649, 1698, 1739 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): white solid; δ (ppm) 0.92 (6H, d, *J* = 6.4 Hz), 1.17 (3H, d, *J* = 6.4 Hz), 1.32 (2H, m), 1.52 (1H, m), 3.61 (3H, s), 3.67-3.82 (2H, m), 4.12 (2H, d, *J* = 7.2 Hz), 4.21 (1H, t, *J* = 4.4 Hz), 5.01 (1H, d, *J* = 7.2 Hz), 5.35 (1H, br), 6.98 (1H, br), 7.25-7.81 (8H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.2, 22.3, 23.2, 40.1, 47.2, 48.8, 50.4, 61.6, 66.5, 120.1, 124.6, 127.2, 127.6, 141.5, 143.8, 155.5, 156.6, 171.5.

(*S*)-Methyl 2-(3-((*S*)-1-(((9*H*-fluoren-9-yl)methoxy) carbonyl)-2-(benzyloxy)ethyl)uriedo)-3-methylbutanoate {Fmoc-Ser(OBn)-*ψ*[NHCONH]-Val-OMe} (4b): IR (KBr): 1648, 1701, 1738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): white solid; δ (ppm) 0.94 (6H, d, *J* = 6.4 Hz), 2.18 (1H, m), 3.28 (2H, s), 3.62 (2H, d, *J* = 4.6 Hz), 3.68 (3H, s), 3.98-4.02 (2H, m), 4.12 (2H, d, *J* = 7.4 Hz), 4.27 (1H, t, *J* = 4.2 Hz), 5.82 (1H, br), 6.51-6.72 (2H, m), 7.33-7.75 (13H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.5, 31.4, 47.3, 50.5, 52.5, 61.9, 65.9, 68.3, 69.8, 120.5, 125.6, 127.1, 127.4, 127.9, 128.8, 129.1, 136.9, 141.5, 144.7, 155.5, 156.9, 171.1.

(*S*)-*tert*-Butyl-4(((9*H*-fluoren-9-yl)methoxy)carbonyl)-4-(3-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)ureido)butanoate {Fmoc-Glu(O^{t}Bu)-*ψ*[NHCONH]-Phe-OMe} (4c): IR (KBr): 1644, 1692, 1731 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): white solid; δ (ppm) 1.42 (9H, s), 2.1 (2H, t, *J* = 7.2 Hz), 2.52 (2H, m), 2.87 (2H, d, *J* = 6.8 Hz), 3.65 (3H, s), 4.15 (1H, t, *J* = 4.4 Hz), 4.29 (2H, d, *J* = 7.2 Hz), 4.40-4.47 (2H, m), 5.65 (1H, d, *J* = 6.0 Hz), 6.75-6.91 (2H, m), 7.54-7.85 (13H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 27.8, 35.3, 37.7, 46.5, 51.8, 54.3, 61.5, 62.4, 66.6, 73.5, 119.8, 124.6, 126.1, 126.8, 127.2, 128.6, 129.2, 137.6, 141.1, 143.6, 155.3, 156.6, 170.8, 171.4.

(*S*)-Methyl 2-(3-((*S*)-1-(benzyloxycarbonyl)-2-phenylethyl)ureido)propanoate {Z-Phe-*ψ*[NHCONH]-Ala-OMe} (4d): IR (KBr): 1647, 1699, 1734 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): white solid; δ (ppm) 1.42 (3H, d, *J* = 7.2 Hz), 2.72 (2H, d, *J* = 5.2 Hz), 3.56 (3H, s), 3.89 (2H, m), 5.25 (2H, s), 6.76-6.98 (3H, m), 7.12-7.19 (10H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.9, 36.5, 42.8, 45.7, 52.5, 62.3, 125.6, 126.3, 127.1, 127.8, 128.3, 128.9, 138.5, 139.9, 155.5, 156.5, 171.1.

(*S*)-Methyl 2-(3-((*S*)-1-(benzyloxycarbonyl)-2-methylpropyl)ureido)-3-phenylpropanoate {Z-Val-*ψ*[NHCONH]-Phe-OMe} (4e): IR (KBr): 1652, 1701, 1738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): white solid; δ (ppm) 0.78 (6H, d, *J* = 5.6 Hz), 1.75 (1H, m), 2.89 (2H, d, *J* = 7.4 Hz), 3.56 (3H, s), 4.51-4.82 (2H, m), 5.25 (2H, s), 5.69 (1H, br), 6.96 (2H, m), 7.19-7.21 (10H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.8, 25.6, 36.8, 41.2, 48.5, 52.5, 65.9, 125.6, 126.9, 127.1, 127.9, 128.2, 128.8, 139.1, 141.6, 155.6, 156.9, 169.9.

(*S*)-Methyl 2-(3-((*S*)-1-(*tert*-butoxycarbonyl)ethyl) uriedo)-3-methylbutanoate {Boc-Ala-*ψ*[NHCONH]-Val-OMe} (4f): IR (KBr): 1649, 1705 1739 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): white solid; δ (ppm) 0.84 (6H, d, *J* = 6.0 Hz), 1.25 (3H, d, *J* = 7.2 Hz), 1.36 (9H, s), 2.12 (1H, m), 3.64 (3H, s), 4.25-4.37 (2H, m), 4.76 (1H, br), 6.22–6.58 (2H, br); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.6, 17.7, 27.6, 31.9, 47.5, 51.2, 62.5, 75.4, 154.6, 156.2, 173.6.

(*S*)-Methyl 2-(3-((*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl)ureido)-3-methylbutanoate

{Boc-Leu-*ψ*[NHCONH]-Val-OMe} (4g): IR (KBr): 1645, 1702 1738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): white solid; δ (ppm) 0.93 (12H, m), 1.21 (2H, m), 1.38 (9H, s), 1.72 (1H, m), 2.12 (1H, m), 3.63 (3H, s), 4.21 (1H, m), 4.32 (1H, m), 5.03 (1H, br), 6.41-6.53 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.8, 18.5, 23.7, 31.0, 46.9, 52.9, 55.1, 58.3, 63.1, 76.3, 155.8, 156.3, 172.6.

ACKNOWLEDGEMENT

We thank University Grant Commission (UGC) [Grant No. 37-79/2009 (SR)], New Delhi, India for financial support.

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[24] To check the possibility of racemization both during the preparation of acyl azide and ureidopeptides, two diasteriomeric ureidopeptides were prepared by treating Z-Val-CON_3 with *R* or *S*-1-phenylethylamine and its racemate. The Methyl resonances of the phenylethylamine residue in Z-Val-*ψ*(NHCONH)-*R*-(+)-1-phenylethylamine and Z-Val-*ψ*(NHCONH)-*S*-(-)-1-phenylethylamine were observed as distinct doublets at δ 1.30, 1.32 and δ 1.29, 1.31, respectively. For Z-Val-*ψ*(NHCONH)-*R,S*-(±)-1-phenylethylamine, the corresponding methyl resonances were observed as two doublets at δ 1.33, 1.31 and 1,32, 1.30. 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.

Received: October 21, 2010 **Revised: May 5, 2011** **Accepted: May 6, 2011**