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Pentafluorophenyl-(*tert*-butoxycarbonylamino)methylcarbamates: Synthesis, isolation and application to the synthesis of ureidopeptides

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The one-pot synthesis of pentafluorophenyl-(*tert*-butoxycarbonylamino)methyl carbamates starting from *N*-Boc amino acids is described. Ultrasound mediated concomitant rearrangement and coupling reactions have resulted in the production of good yields of the active methyl carbamates. The carbamates have been employed as monomeric building blocks for the synthesis of dipeptidyl urea esters/acids. All the compounds obtained have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Keywords: Boc-amino acids, Curtius rearrangement, ultrasonication, concomitant synthesis, pentafluoro phenyl-(*tert*-butoxycarbonylamino)methylcarbamates, peptidyl ureas

Peptidyl ureas find a varied range of applications in biological as well as structural chemistry[1]. As drugs, they are used as HIV-1 protease inhibitors[2,3], CCK-B receptor antagonists[4] and endothelin antagonists[5] and secretagogues[6,7]. Ureido bonds are introduced into peptide backbone to obtain conformationaly controlled well-defined structures[8] and to stabilize secondary structural elements like turns, helices, or sheets, *via* non covalent interactions[9,10].

The first synthesis of ureido analogues of biologically active peptide (angiotensin II) was described more than two decades ago by Chipens *et al.*[11-13] Traditional methods for the synthesis of ureidopeptides include the reaction of amino acid esters with isocyanates or with phosgene[14,15], carbonyldiimidazole[16] and disuccinimido carbonate[17]. Since the usage of phosgene raises safety concerns, reagents like *bis*(4-nitrophenyl)carbonate[18], triphosgene [bis(trichloromethyl)carbonate][19], di-*tert*-butyldicarbonate[20], 1,1-carbonylbis benzotriazole[21], *S,S*-dimethyldithiocarbonate[22] and trihaloacetylchlorides[23] have been used as safer alternatives. The solid phase synthesis of oligourea related to [Leu]enkephalin has been reported *via* conversion of *N*-Fmoc-β-amino alky azides into the corresponding amine and reacting the later with nitrophenylchloroformate to obtain 4-nitrophenylcarbamate as reactive monomers[24]. Similar strategy has also been adopted for urea synthesis with Boc-chemistry[25].

The isocyanates obtained from the Curtius rearrangement of acyl azides[26] can be trapped by a variety of nucleophiles including amines and alcohols to prepare ureas and carbamates respectively. A number of methods has been developed based on this principle to insert urea bonds from the C-terminus of amino acid and peptides. In all these cases, the acyl azides obtained from carboxylic acid derivatives like hydrazides[27], acyl chlorides[28] and mixed anhydrides[29,30] are isolated and rearranged in separate steps. However, since the acyl azides are well-known to be unstable with limited shelf-life, one-pot processes that allow the direct conversion of carboxylic acids into reactive carbamates have become very popular[31,32]. Guichard *et al*., have demonstrated an efficient solid phase synthesis of oligoureas using *O*-succinimidyl-(9*H*-fluroren-9-ylmethoxycarbonylamino/*tert*-butoxycarbonylamino)ethylcarbamates, as activated monomers. These carbamates were prepared by coupling the isocyanates obtained from the rearrangement of *N*-Fmoc/Boc-protected-β-amino acid azides, with N-hydroxysuccinimide[33]. They have also prepared *O*-succinimidyl-(Boc/Fmoc/Z amino)methyl carbamates from the corresponding N-protected α-amino acids[34].

The application of commercially available, stable, pentafluorophenyl ester of N^{α}-urethane protected amino acids in solid phase as well as solution phase peptide coupling reaction is well documented in literature[35]. The pentafluorophenyl derivatives are

highly reactive and remain in usable form for long durations. The Boc-pentaflurophenyl esters have been used successfully for assembling decamers in solution phase[36,37].

Herein is reported the ultrasonication assisted efficient single-pot concomitant synthesis of pentafluorophenyl-(*tert*-butoxycarbonylamino)methyl carbamates **3** and their ready conversion into dipeptidyl urea esters **5a-h** and dipeptidyl urea acids **5i-n**. The direct conversion of the acid azide into methyl carbamate has resulted in the increased yields of carbamates. Unlike the previously reported procedures which carry out the reaction under conventional high temperature reflux, the present method uses ultrasound to accomplish the reaction at RT. This is of significant practical advantage as it enables the convenient handling of acid azides that are known to be explosive at high temperatures.

Results and Discussion

N-Boc-protected amino acids **1** were first converted to their acyl azides **2** by reaction of their mixed anhydrides [generated by treatment with EtOCOCl / *N*-methylmorpholine (NMM)] with aqueous NaN_3 at -10 to -15°C. After a simple workup, the resulting azide was dissolved in toluene along with equimolar amounts of pentafluorophenol and NMM and then subjected to ultrasound for about 15-25 min at ambient temperature. The rearrangement of the acid azide along with the concomitant coupling of the generated isocyanate with the phenol resulted directly in the methyl carbamate **3**. After the reaction, the product **3** precipitated out from the toluene solution and was filtered. A single recrystallization using DMSO-water was sufficient to obtain the analytically pure compounds. The entire reaction sequence, as shown in **Scheme I**, was complete within 60 min. All the methyl carbamates **3** made were characterized by IR, ^{13}C NMR and mass spectrometry. The pentafluorophenyl-(*tert*-butoxycarbonylamino)methylarbaates **3a-m** had in their IR spectrum a characteristic sharp peak at 1745-1755 cm^{-1}.

The physical constants of **3a-m** are given in **Table I**. The methyl carbamates were found stable for long periods of storage at ambient temperature with no noticeable degradation or change in spectral behavior.

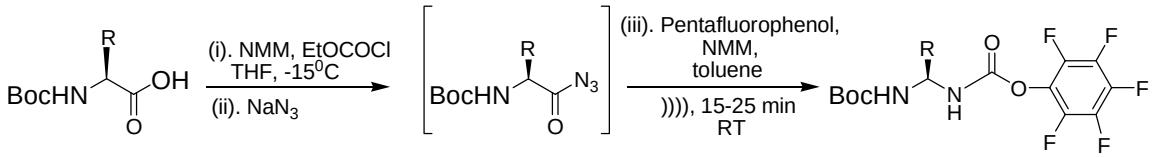
The usefulness of methyl carbamates **3** as reactive monomers for the urea synthesis was then demonstrated. Ureidopeptide esters (**Scheme II**) as well as ureidopetide acids were synthesized by reacting amino acid esters and *N, O bis*-TMS [amino acids] with **3**. The reaction proceeded rapidly with the disappearance of all starting materials within 30 min. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was triturated in water (to remove side product pentafluorophenol formed during the reaction) and purified by recrystallization. The ureas **6a-h** were obtained as pure compounds in good yields.

Epimerization during the two reactions *viz*., synthesis of carbamates **3** and their conversion into ureas was studied using NMR spectroscopy. The pentafluorophenyl methyl carbamate derived from L-phenylalanine *via* the above method was reacted with optically pure 1-phenylethylamines (both the + and – isomers, **7a** and **7b**) and with a racemic sample in separate experiments (**Scheme III**). The urea adducts Boc-Val-ψ(NH-CO-NH)-*R*-(+)-1-phenylethylamine **8a**, Boc-Val-ψ(NH-CO-NH)-*S*-(-)-1-phenylethylamine **8b** and Boc-Val-ψ(NH-CO-NH)-*R*,*S*-(±)-1-phenylethylamine **8c** thus obtained were subjected to ^1H NMR analysis. Their ^1H NMR spectra revealed distinct doublets for CH_3 group in case of ureas obtained by coupling enantiomerically pure 1-phenylethylamine. On the other hand, the adduct obtained from the racemic mixture of 1-phenylethylamine had two methyl group doublets. This clearly showed that the synthesis of active carbamate as well as their conversion to ureas was free from epimerization. The ^1H NMR spectra of **8a** [δ 1.28 and 1.30 (CH_3, d)]; **8b** [δ 1.27 and 1.29 (CH_3, d)] and for **8c** [δ 1.28, 1.29, 1.29 and 1.306 (CH_3, d)] are given in the **Figure 1**.

Experimental Section

Materials and Methods

The melting points were recorded in open capillary tubes and are uncorrected. The reactions were carried out using a sonic bath (35 kHz, Elma, T 310/H German make) at ambient temperature. Infrared spectra were recorded on a Nicolet Impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). Specific rotations were recorded on Rudolf Research Autopol IV automatic polarimeter. Elemental analyses were carried out using Perkin Elmer Analyser and the samples were dried for 24 hr under vacuum before analysis. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Mass spectra were recorded on MALDI-TOF (Kratos) and ESI-MS.



1a-m **2a-m** **3a-m**

Compd	R	Compd	R	Compd	R
3a	CH_3	**3e**	$CH(CH_3)C_2H_5$	**3j**	CH_2COOBn
3b	H	**3f**	$CH_2C_6H_5$	**3k**	$(CH_2)_2COOBn$
3c	$CH(CH_3)_2$	**3g/3h**	L-C_6H_5/ D-C_6H_5	**3l**	-$(CH2)_{3}$-
3d	$CH_2CH(CH_3)_2$	**3i**	CH_2OBn	**3m**	$(CH_2)_2SCH_3$

Scheme I

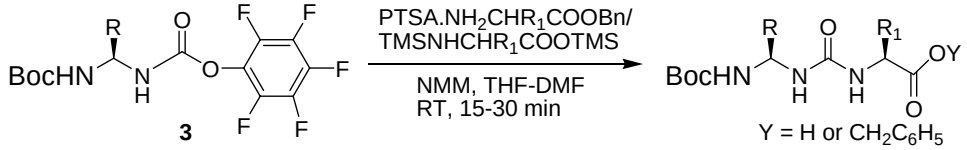
Table I — Physical constants of pentafluorophenyl-(*tert*-butoxycarbonylamino) methyl carbamates

Compd	Yield (%)	m.p. (ºC)	$[\alpha]_D^{25}$ (c1,DMF)	Elemental analysis Found (Calcd..) (%)			Spectral data
				C	H	N	
3a	88	123	+1.6	45.20 (45.41	4.14 4.08	7.80 7.57)	^{1}H NMR (DMSO-d_6): δ 1.21 (9H, s), 1.52 (3 H, t, *J*=10.1 Hz), 5.10 (1H, m), 5.92 (1H, br), 6.36 (1H, br); ^{13}C NMR (DMSO-d_6): δ 23.2, 31.2, 55.8, 76.5, 141.2, 142.3, 143.8, 149.6, 165.1, 172.2.
3b	87	120	-	43.55 (43.83	3.78 3.68	7.60 7.86)	^{1}H NMR (DMSO-d_6): δ 1.29(9 H, s), 4.98, 6.0 (1H, br), 6.31(1H, br); ^{13}C NMR (DMSO-d_6): δ 31.5, 54.3 76.3, 141.1, 142.5, 143.6, 149.6, 165.4, 172.0.
3c	89	126	-9.2	48.00 (48.25	4.90 4.81	7.10 7.03)	^{1}H NMR (DMSO-d_6): δ 1.10 (6 H, d, *J*=8.5 Hz), 1.27 (9 H, s), 2.91 (1H, m), 5.23(1H, m), 5.82 (1H, br), 6.29(1H, br); ^{13}C NMR (DMSO-d_6): δ 17.3, 29.1, 31.3, 58.2, 76.4, 141.3, 142.2, 144.0, 150.1, 165.3, 172.4.
3d	85	122	-8.5	49.62 (49.52	5.20 5.13	6.84 6.79)	^{1}H NMR (DMSO-d_6): δ 1.11 (6H, d, *J*=7.8 Hz), 1.32 (9 H, s), 1.69 (2H, m), 1.85 (1H, m), 5.25(1H, m), 6.10 (1H, br), 6.29 (1H, br); ^{13}C NMR (DMSO-d_6): δ 22.3, 23.1, 31.4, 43.8, 58.7, 76.2, 141.1, 142.5, 143.1, 149.6, 165.0, 172.3.
3e	84	125	-8.8	49.70 (49.52	5.10 5.13	6.74 6.79)	^{1}H NMR (DMSO-d_6): δ 0.98 (3H, t, *J*=10.9 Hz), 1.16 (3H, d, *J*=8.1 Hz), 1.25 (2H, m), 1.31 (9 H, s) , 2.86, 5.31(1H, m), 5.95 (1H, br), 6.31(1H, br); ^{13}C NMR (DMSO-d_6): δ 12.1, 12.9, 22.3, 31.2, 40.3, 57.8, 76.6, 141.5, 142.6, 143.4, 149.5, 164.9, 172.1.
3f	88	143	-6.3	53.70 (53.82	4.10 4.29	6.54 6.28)	^{1}H NMR (DMSO-d_6): δ 1.29(9 H, s), 3.21 (2H, m), 5.50(1H, m), 5.92 (1H, br), 6.10 (1H, br), 7.12-7.29 (5H, m); ^{13}C NMR (DMSO-d_6): δ 31.6, 44.3, 59.8, 76.4, 125.1 127.1, 127.8, 135.8, 141.3, 142.2, 143.9, 149.6, 165.1, 172.2.
3g	85	126	-2.5	52.68 (52.78	4.10 3.96	6.34 6.48)	^{1}H NMR (DMSO-d_6): δ 1.26 (9 H, s), 5.48(1H, m), 5.82 (1H, br), 6.21(1H, br), 7.05-7.21 (5H, m); ^{13}C NMR (DMSO-d_6): δ 31.5, 56.2, 76.6, 126.9, 128.1, 128.6, 139.3, 141.2, 142.4, 144.1, 150.1, 165.4, 172.0.
3h	87	130	+2.8	52.84 (52.78	4.20 3.96	6.44 6.48)	^{1}H NMR (DMSO-d_6): δ 1.26 (9 H, s), 5.48(1H, m), 5.82 (1H, br), 6.21(1H, br), 7.05-7.21 (5H, m); ^{13}C NMR (DMSO-d_6): δ 31.5, 56.2, 76.6, 126.9, 128.1, 128.6, 139.3, 141.2, 142.4, 144.1, 150.1, 165.4, 172.0.
3i	88	127	-5.1	52.71 (52.95	4.40 4.44	5.44 5.88)	^{1}H NMR (DMSO-d_6): δ 1.22 (9 H, s), 3.82 (2H, m), 4.68 (2H, s), 5.63(1H, m), 5.99(1H, br), 6.18 (1H, br), 7.11-7.23 (5H, m); ^{13}C NMR (DMSO-d_6): δ 31.3, 56.9, 72.1, 76.3, 78.3, 127.0, 127.6, 127.9, 137.9, 141.1, 142.2, 143.7, 149.8, 165.2, 172.1.
3j	89	142	-4.8	52.54 (52.39	4.10 4.20	5.44 5.55)	^{1}H NMR (DMSO-d_6): δ 1.30 (9 H, s), 2.89 (2H, m), 5.10 (2H, s), 5.85(1H, m), 5.90(1H, br), 6.08(1H, br), 7.02-7.21(5H, m); ^{13}C NMR (DMSO-d_6): δ 31.4, 38.9, 57.1, 70.1, 76.4, 127.1, 127.9, 128.1, 138.3, 141.2, 142.4, 143.5, 150.0, 165.5, 172.3, 175.6.

—Contd

Table I — Physical constants of pentafluorophenyl-(*tert*-butoxycarbonylamino) methyl carbamates— *Contd*

Compd	Yield (%)	m.p. (ºC)	$[\alpha]_D^{25}$ (c1,DMF)	Elemental analysis Found (Calcd..) (%)			Spectral data
3k	88	117	-5.3	53.34 (53.29	4.14 4.47	5.30 5.40)	^{1}H NMR (DMSO-d_6): δ 1.32 (9 H, s), 2.45 (2H, m), 2.68 (2H, t, *J*=10.9 Hz), 5.13 (2H, s), 5.80(1H, m), 5.92 (1H, br), 6.10 (1H, br), 7.0-7.22 (5H, m); ^{13}C NMR (DMSO-d_6): δ 28.3, 31.3, 35.2, 57.3, 69.9, 76.5, 127.0, 127.3,1 28.1, 137.6, 141.4, 142.3, 143.4, 149.9, 165.5, 172.1, 173.8.
3l	82	132	-7.9	48.84 (48.61	4.30 4.08	6.90 7.09)	^{1}H NMR (DMSO-d_6): δ 1.30 (9 H, s), 1.58 (2H, m), 1.89 (2H, m), 3.30 (2H, m), 5.52 (1H, m), 5.81 (1H, br); ^{13}C NMR (DMSO-d_6): δ 22.3, 30.1, 31.2, 43.8, 55.8, 76.6, 141.2, 142.5, 143.4, 149.8, 165.2, 172.3.
3m	85	105	+5.9	44.84 (44.76	4.50 4.23	6.60 6.52)	^{1}H NMR (DMSO-d_6): δ 1.29 (9 H, s), 2.19 (3H, s), 3.10 (2H, m), 5.89 (1H, m), 5.91(1H, br), 6.31(1H, br); ^{13}C NMR (DMSO-d_6): δ 19.3, 31.3, 44.8, 57.9, 76.7, 141.1, 142.3, 143.5, 149.9, 165.2, 172.3.



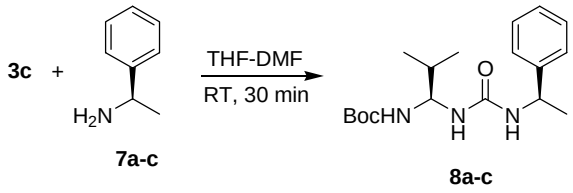
Compd	R	R_1	Y
6a	$CH_2CH(CH_3)_2$	CH_3	$CH_2C_6H_5$
6b	CH_2OBn	H	$CH_2C_6H_5$
6c	$(CH_2)_2COOBn$	H	$CH_2C_6H_5$
6d	$CH(CH_3)_2$	CH_3	$CH_2C_6H_5$
6e	$(CH_2)_2COOBn$	CH_3	H
6f	$CH(CH_3)_2$	CH_3	H
6g	CH_2OBn	CH_3	H
6h	CH_2OBn	$CH(CH_3)_2$	H

Scheme II

All solvents were freshly distilled prior to use. Amino acid methyl ester hydrochlorides were prepared by using methanol and thionyl chloride and amino acid benzyl ester *p*-toluene sulfonate were prepared by reported procedure[38].

General procedure for the synthesis of pentafluorophenyl-(*tert*-butoxycarbonylamino)methyl carbamates 3a-m. Boc-*α*-amino acid **1** (1 mmol) was dissolved in THF (5 mL) and cooled to –20°C. After addition of *N*-methylmorpholine (1.1 mmol) and ethyl chloroformate (1.1 mmol), the mixture was stirred at –20 °C for 15 min and allowed to warm to -5°C. It was treated with an aqueous solution of NaN_3 (2.5 mmol in 2 mL of water) for 5 min. After removal of the solvent under reduced pressure, the resulting residue was diluted with CH_2Cl_2 (15 mL), washed with 5% citric acid solution (3×5 mL), 5% sodium bicarbonate solution (3×5 mL), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the acyl azide **2**, which was used without further purification. The acyl azide was taken in toluene (5 mL), pentafluorophenol (1 mmol) and NMM (1.1 mmol) were successively added. It was sonicated in an ultrasound bath for about 15-25 min at ambient temperature. After the completion of the reaction, the carbamates which crystallized out from the toluene solution were collected by filtration. All the carbamates **3** made have been fully characterized. The physical and spectral data are given in **Table I**.

General procedure for the synthesis of N^{α}-Boc-protected dipeptidylurea esters 6a-h. To a stirred solution of amino acid benzyl ester *p*-toluenesulfonate salt **4** (1.3 mmol) in THF- DMF (2:1, 5 mL), NMM (1.2 mmol) and pentafluorophenyl methylcarbamate **3** (1 mmol) were added successively and stirred at RT till the completion of the reaction. After the



Scheme III

completion of the reaction, the solvent was evaporated under reduced pressure and the residue was taken into water, filtered and purified by recrystallization from DMSO-water to afford the pure urea esters **6a-h** as crystalline off-white solids.

General procedure for the synthesis of N^{α}-Boc-protected dipeptidylurea acids 6i-h. To a stirred suspension of amino acid (1 mmol) in CH_2Cl_2 (5 mL) was added freshly distilled TMS-Cl (2.2 mmol) and TEA (2.2 mmol) and refluxed for 2 hr. To the reaction mixture, methyl carbamate 3 (1 mmol) in THF-DMF (2:1, 5 mL) was added and stirred for 30 min at RT. After the completion of the reaction, the solvent was evaporated under reduced pressure and the residue was filtered, triturated in water (to remove side product formed during the reaction) and purified by recrystallization from DMSO-water (7:3) or ethyl acetate and hexane (2:1) to afford the pure urea acids 6i-h as a crystalline off-white solids.

Boc-Leu-ψ(NH-CO-NH)-Ala-OBn, **6a**. Yield: 70%; m.p. 130-32ºC; ^{1}H NMR (DMSO-d_6): δ 0.93 (6H, d, *J*= 7.3 Hz), 1.16 (3H, d, *J*= 7.7 Hz), 1.35 (11H, s), 1.65 (1H, m), 3.8-3.9 (2H, m), 5.1 (2H, s), 5.35 (1H, d, *J*= 8.2 Hz), 6.3 (1H, d), 6.5 (1H, d, *J*= 7.9 Hz), 7.2-7.4 (5H, m); ^{13}C NMR (DMSO-d_6): δ 17.5, 22.1, 23.3, 24.5, 28.6, 48.9, 51.2, 61.9, 78.1, 126.9, 127.6, 129.1, 137.5, 155.0, 156.8, 175.5; ESI-MS: *m/z* 408.8 $[M+H]^+$. Anal. Calcd. for $C_{21}H_{33}N_3O_5$: C, 61.90; H, 8.16; N, 10.31. Found: C, 61.80; H, 7.82; N, 10.10%.

Boc-Ser(Bn)-ψ(NH-CO-NH)-Gly-OBn, **6b**. Yield: 76%; m.p. 127-28ºC; ^{1}H NMR (DMSO-d_6): δ 1.3-1.45 (18H, s), 3.7-3.85 (5H, m), 4.9 (2H, s), 5.35 (1H, d, *J*= 7.9 Hz), 6.3-6.4 (2H, m), 6.5 (1H, d, *J*= 8.0 Hz), 7.2-7.45 (5H, m); ^{13}C NMR (DMSO-d_6): δ 27.9, 28.3, 51.9, 61.3, 61.9, 65.3, 77.5, 78.1, 126.9, 128.6, 129.1, 137.5, 155.0, 156.8, 175.5; ESI-MS: *m/z* 425.5 $[M+H]^+$. Anal. Calcd. for $C_{21}H_{33}N_3O_6$: C, 59.56; H, 7.85; N, 9.92. Found: C, 61.10; H, 8.09; N, 10.22%.

Boc-Glu(OBn)-ψ(NH-CO-NH)-Gly-OBn, **6c**. Yield: 71%; m.p.131-32ºC; ^{1}H NMR (DMSO-d_6): δ 1.35 (9H, s), 2.6 (2H, m), 2.95 (2H, t, *J*= 9.5 Hz), 3.85 (3H, m), 4.95 (4H, s), 5.3 (1H, d, *J*= 7.6 Hz), 6.3-6.45 (2H, m), 7.3–7.55 (10H, m); ^{13}C NMR (DMSO-d_6): δ 27.5, 38.9, 41.2, 53.5, 57.5, 61.3, 62.5, 78.3, 126.9, 127.7, 129.4, 137.9, 155.2, 156.8, 174.5; ESI-MS: *m/z* 501.7 $[M+H]^+$. Anal. Calcd. for $C_{26}H_{33}N_3O_7$: C, 62.51; H, 6.66; N, 8.41. Found: C, 62.20; H, 6.52; N, 8.38%.

Boc-Val-ψ(NH-CO-NH)-Ala-OBn, **6d**. Yield: 70%; m.p. 152-54ºC; ^{1}H NMR (DMSO-d_6): δ 0.93 (6H, t, *J*= 9.5 Hz), 1.17 (3H, d, *J*= 8.3 Hz), 1.35 (9H, s), 1.85 (1H, m), 3.7-3.8 (2H, m), 4.95 (2H, s), 5.2 (1H, d, *J*= 7.7 Hz), 6.35-6.4 (2H, m), 7.3–7.5 (5H, m); ^{13}C NMR (DMSO-d_6): δ 17.5, 18.9, 19.5, 28.9, 51.0, 59.2, 61.5, 78.1, 126.9, 127.7, 129.4, 137.9, 155.1, 157.8, 174.5; ESI-MS: *m/z* 395.4 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{31}N_3O_5$: C, 61.05; H, 7.94; N, 10.68. Found: C, 61.20; H, 8.02; N, 10.38%.

Boc-Glu(OBn)-ψ(NH-CO-NH)-Ala-OH, **6e**. Yield: 70%; m.p. 140-41ºC; ^{1}H NMR (DMSO-d_6): δ 1.15 (3H, d, *J*=7.1 Hz), 1.31 (9H, s), 2.5 (2H, m), 2.85 (2H, m), 3.45 (1H, m), 3.9 (1H, m), 5.1 (2H, s), 5.3 (1H, d, *J*=7.9 Hz), 6.2 (1H, br), 6.5 (1H, d, *J*= 8.2 Hz), 7.3–7.4 (5H, m), 8.25 (1H, d); ^{13}C NMR (DMSO-d_6): δ 17.7, 28.1, 38.5, 40.3, 50.0, 50.3, 62.5, 74.3, 126.7, 128.5, 129.5, 137.2, 155.2, 156.5, 158.2, 175.8; MS (FAB^+): *m/z* 424.3. Anal. Calcd. for $C_{20}H_{29}N_3O_7$: C, 56.73; H, 6.90; N, 9.92. Found: C, 56.66; H, 6.50; N, 10.50%.

Boc-Val-ψ(NH-CO-NH)-Ala-OH, **6f**. Yield: 71%; m.p. 146-48ºC; ^{1}H NMR (DMSO-d_6): δ 0.93 (6H, t, *J*= 9.1 Hz), 1.16 (3H, d, *J*= 7.5 Hz), 1.3 (9H, s), 1.85 (1H, m), 3.8-3.9 (2H, m), 5.2 (1H, d, *J*= 7.8 Hz), 6.2-6.35 (2H, m), 8.15 (1H, d, *J*=8.0 Hz); ^{13}C NMR (DMSO-d_6): δ 17.4, 18.7, 19.5, 28.1, 29.4, 49.5, 58.1, 75.3, 155.2, 156.8, 176.5; MS (FAB^+): *m/z* 303.9. Anal. Calcd. for $C_{13}H_{25}N_3O_5$: C, 51.47; H, 8.31; N, 13.85. Found: C, 52.08; H, 8.57; N, 13.50%.

Boc-Ser(Bn)-ψ(NH-CO-NH)-Ala-OH, **6g**. Yield: 67%; m.p. 117-19ºC; ^{1}H NMR (DMSO-d_6): δ 1.16 (3H, d, *J*=7.9 Hz), 1.2-1.35 (18H, s), 3.35 (2H, d, *J*= 7.3 Hz), 3.75-3.9 (2H, m), 5.25 (1H, d, *J*= 7.9 Hz), 6.2-6.35 (2H, m), 8.25 (1H, d, *J*=8.3 Hz); ^{13}C NMR (DMSO-d_6): δ 17.4, 27.0, 28.3, 49.1, 51.7, 62.5, 74.7, 75.1, 155.1, 156.8, 174.5; MS (FAB^+): *m/z* 348.3. Anal. Calcd. for $C_{15}H_{29}N_3O_6$: C, 51.86; H, 8.41; N, 12.10. Found: C, 51.50; H, 7.92; N, 12.38%.

Boc-Ser(Bn)-ψ(NH-CO-NH)-Val-OH, **6h**. Yield: 68%; m.p. 135-37ºC; ^{1}H NMR (DMSO-d_6): δ 0.91 (6H, t, *J*=8.5 Hz), 1.35 (9H, s), 1.85 (1H, m), 3.45 (2H, d, *J*= 7.7 Hz), 3.7-3.85 (2H, m), 4.9 (2H, s), 5.15 (1H, d, *J*=8.0 Hz), 6.2-6.35 (2H, m), 7.2-7.35 (5H, m), 8.15 (1H, d, *J*= 8.3 Hz); ^{13}C NMR (DMSO-d_6):

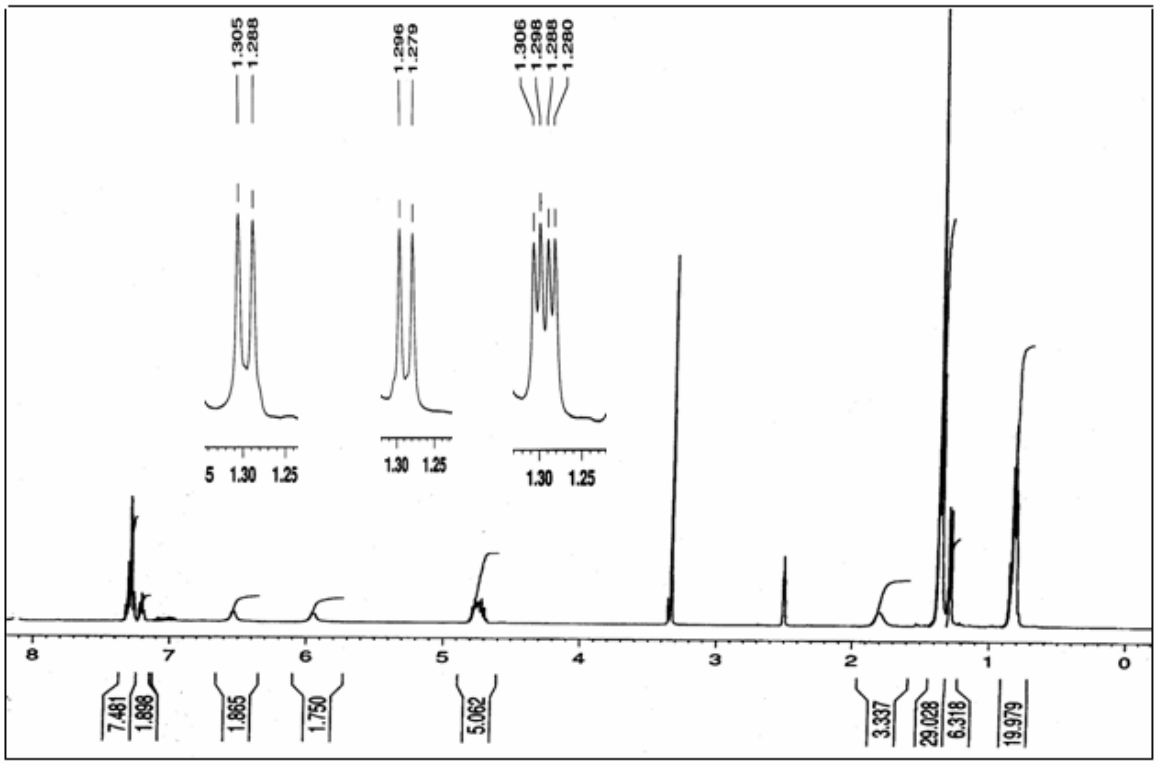


Figure 1 — ^{1}H NMR spectrum of Boc-Val-ψ(NH-CO-NH)-*R*-(+)-1-phenylethylamine: Inset figure shows splitting pattern of CH_3 group of 1-phenylethylamine in urea adducts *R*-(+)-1-phenylethylamine **8a**, *S*-(-)-1-phenylethylamine **8b** and *R*,*S*-(±)-1-phenylethylamine **8c**

δ 18.5, 19.5, 28.3, 29.7, 49.0, 52.1, 62.3, 63.1, 75.5, 126.5, 128.7, 129.3, 137.1, 154.7, 156.8, 176.5; MS (FAB$^+$): *m/z* 410.1. Anal. Calcd. for $C_{20}H_{31}N_3O_6$: C, 58.66; H, 7.63; N, 10.26. Found: C, 58.78; H, 8.07; N, 10.20%.

Test for racemization. To a solution of pentafluorophenyl-1-{[(*tert*-butloxycarbonyl)amino]-2-methyl propyl}carbamate (1 mmol) derived from N^{α}-Boc-valine was added *R*-(+), *S*-(-) and *R*,*S*-(±)-1-phenylethylamine (0.121 g, 1 mmol) in separate experiments. After the completion of the reaction, the residue was triturated with water, filtered and purified by recrystallization to obtain the diastereomerically pure urea adducts **8a-c**.

Boc-Val-ψ(NH-CO-NH)-*R*-(+)-1-phenylethylamine, **8a**. Yield: 72%; m.p. 141-42°C; $[\alpha]_D^{25}$: + 28.6 (c 1, DMSO); ^{1}H NMR (DMSO-d_6): δ 0.8-0.9 (6H, m), 1.28-1.30 (3H, d), 1.35 (9H, s), 1.85 (1H, m), 3.3 (1H, m), 4.7-4.8 (2H, m), 5.95 (1H, br), 6.55 (1H, br), 7.2-7.35 (5H, m); MS (FAB$^+$): *m/z* 336.1. Anal. Calcd. for $C_{18}H_{29}N_3O_3$: C, 64.45; H, 8.71; N, 12.53. Found: C, 64.78; H, 8.23; N, 12.59%.

Boc-Val-ψ(NH-CO-NH)-*S*-(-)-1-phenylethylamine, **8b**. Yield: 72%; m.p. 137-39°C; $[\alpha]_D^{25}$: - 29.3 (c 1, DMSO-d_6); ^{1}H NMR (DMSO-d_6): δ 0.8-0.9 (6H, m), 1.27-1.29 (3H, d), 1.35 (9H, s), 1.85 (1H, m), 3.32 (1H, m), 4.7-4.8 (2H, m), 5.95 (1H, br), 6.5 (1H, br), 7.2-7.35 (5H, m); MS (FAB$^+$): *m/z* 336.2. Anal. Calcd. for $C_{18}H_{29}N_3O_3$: C, 64.45; H, 8.71; N, 12.53. Found: C, 64.58; H, 8.13; N, 12.29%.

Boc-Val-ψ(NH-CO-NH)-*R*, *S*-(±)-1-phenylethylamine, **8c**. Yield: 72%; m.p. 138-40°C; ^{1}H NMR (DMSO-d_6): δ 0.8-0.9 (6H, m), 1.28-1.30 (3H, two d), 1.35 (9H, s), 1.85 (1H, m), 3.3 (1H, m), 4.7-4.8 (2H, m), 5.95 (1H, br), 6.55 (1H, br), 7.2-7.35 (5H, m); MS (FAB$^+$): *m/z* 336.0. Anal. Calcd. for $C_{18}H_{29}N_3O_3$: C, 64.45; H, 8.71; N, 12.53. Found: C, 64.48; H, 8.53; N, 12.50%.

Conclusion

Pentafluorophenyl-(*tert*-butoxycarbonylamino) methyl carbamates **3** were prepared in high yields from their corresponding *N*-Boc-protected α-amino acid azides through the ultrasonication assisted Curtius rearrangement followed by the concomitant coupling with pentafluorophenol. All the methyl carbamates prepared were stable solids with extended shelf-life. They were readily and quantitatively

converted into dipeptidyl urea esters/acids by reacting with amino acid esters/*bis* TMS amino acids. The NMR analysis of the synthesis of active carbamates and their conversion into ureas has revealed both the protocols to be epimerization free.

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