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Efficient Synthesis of *N*-Fmoc-Aminoalkoxy Pentafluorophenyl Carbonates: Application for the Synthesis of Oligopeptidyl Carbamates

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Abstract: *N*-Fmoc-β-Aminoalkoxy pentafluorophenyl carbonates have been synthesized through the reaction of *N*-Fmoc-β-aminoalkoxy carbonyl chloride with pentafluorophenol. The reaction was clean and high yielding, and the products have been fully characterized using infrared, NMR, and mass spectroscopy. Their utility as efficient building blocks for the preparation of *N*-Fmoc-oligopeptidyl carbamate esters and acids has been demonstrated. The method exemplifies a simple protocol for the efficient preparation of oligopeptidyl carbamates in solution phase.

Keywords: *N*-Fmoc-β-Aminoalkoxy carbonyl chlorides, carbonates, oligopeptidyl carbamates, pentafluorophenol

INTRODUCTION

The urethane moiety (Fig. 1)[1,2] has vital roles in several bioactive molecules, and the synthetic peptidyl carbamates are under various clinical and therapeutical studies.[3–10] Among the various reports on the synthesis of oligopeptides, Cho et al. have employed[4] the stepwise solid-phase synthesis of linear and cyclic peptidyl carbamates using the active *p*-nitrophenyl carbonates as building blocks.

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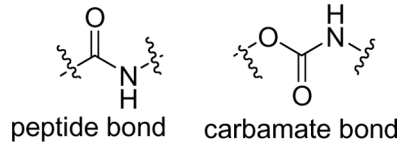


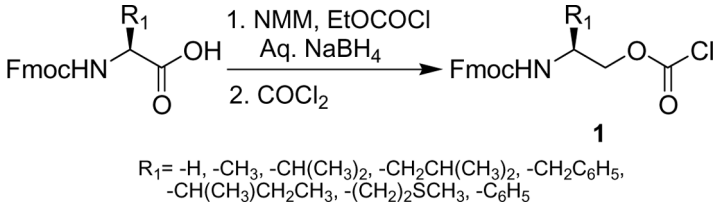
Figure 1. Insertion of carbamate bond as peptide bond isostere.

These carbonates were prepared by the reaction of Fmoc-β-amino alcohol with *p*-nitrophenyl chloroformate. A similar strategy was reported by Warrass et al. utilizing benzotriazolyl carbonate monomers prepared by using dibenzotriazolyl carbonates (DBTC).[6] Alsina et al. used the succinimidyl carbonates synthesized by treating β-amino alcohol with disuccinimidyl carbonate (DSC).[11] Some of these active carbonates were not isolated but prepared and used in situ, whereas some others were found to be stable only up to a limited period of time and hence cannot be stored for longer times. In addition, some of these protocols are less attractive from the synthetic standpoint because of the use of excess reagent, longer reaction time (24 h), and lower yields. Recently, our group reported the synthesis of *N*-Fmoc aminoalkoxy pentachlorophenyl carbonates and demonstrated their utility as monomers for the synthesis of the oligocarbamate esters.[12] To improve the reactivity and applications of such active carbonate monomers, we proceeded with synthesizing highly reactive pentafluorophenyl carbonates as oligocarbamate building blocks. Accordingly, we herein describe the synthesis of *N*-Fmoc-β-aminoalkoxy pentafluorophenyl carbonates and their utility as efficient building blocks for the oligopeptidyl carbamate synthesis.

RESULTS AND DISCUSSION

The *N*-Fmoc-β-amino alcohols were prepared by the reduction of the in situ–generated amino acid–derived mixed anhydride using $NaBH_4$. The conversion of the *N*-protected amino alcohols into their aminoalkoxy carbonyl chlorides was brought out by the reaction with phosgene.[12,13] When phosgene was bubbled into a solution of *N*-Fmoc-β-amino alcohol at $-20^{\circ}C$, the corresponding *N*-Fmoc-aminoalkoxy carbonyl chloride **1** was formed in about 1.5 h, which was isolated as a solid powder (Scheme 1).

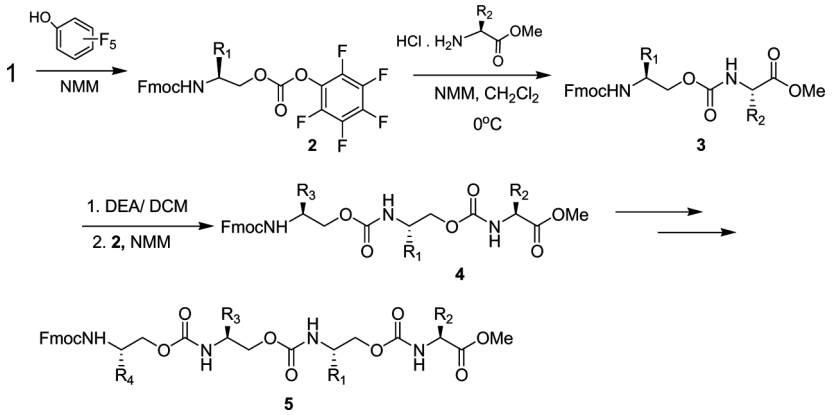
These intermediates were further utilized for the preparation of peptidyl carbamate. Hence, a reaction of Fmoc-β-aminoalkoxy carbonyl chloride **1** with the amino acid ester in the presence of *N*-methylmorpholine (NMM) yielded dipeptides **3** possessing carbamate linkages in place



Scheme 1. Synthesis of Fmoc-amino alkoxy carbonyl chloride from amino acid.

of the amide bond within 2 h. In spite of the good reactivity of *N*-Fmoc-aminoalkoxy carbonyl chlorides with the nucleophiles, their poor shelf stability and moisture sensitivity put a barrier on their handling. Their conversion into stable compounds with retention of the reactivity can be achieved by treating with a substituted phenol, resulting in active carbonates. Among the various choices, pentafluorophenol (Pfp) was selected because it has been considered as the best auxiliary in routine peptide synthesis. Compared to the contemporary reagents—pentachlorophenol, *p*-nitrophenol, trichlorophenol, *N*-hydroxysuccinimide—the Pfp is advantageous because of its high reactivity. The pentafluorophenyl carbonates **2** were prepared by the reaction of Pfp with *N*-Fmoc-β-aminoalkoxy carbonyl chloride **1** in the presence of NMM (Scheme 2).

The *N*-Fmoc-β-aminoalkoxy pentafluorophenyl carbonates **2** were also utilized for the synthesis of *N*-Fmoc-dipeptidyl carbamate esters **3**. For this, **2** was treated with an amino acid methyl ester hydrochloride salt neutralized with NMM at 0°C (Scheme 2). The reaction was complete



Scheme 2. Synthesis of active carbonate **2** and its utility in making di- and oligopeptidyl carbamates.

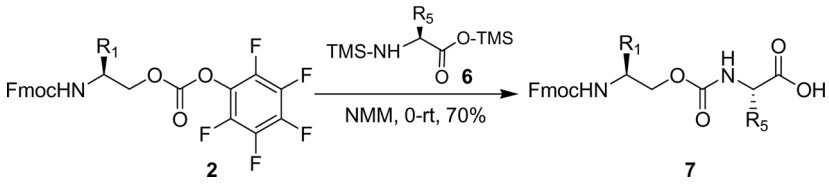
Table 1. List of *N*-Fmoc-peptidyl carbamate esters **3, 4, 5** and acids **7**

Entry	Dipeptidyl carbamates	Yield (%)	M.p. (°C)	HRMS (M+Na) (obsd./calcd.)
3a	*N*-Fmoc-Ala^c-Val-OMe	88	112	477.2009 (477.2002)
3b	*N*-Fmoc-Met^c-Ala-OMe	94	113	509.1728 (509.1722)
3c	*N*-Fmoc-Ile^c-Leu-OMe	86	109	533.2620 (533.2628)
4a	*N*-Fmoc-Ala^c-Leu^c-Ala-OMe	78	88	592.2633 (592.2635)
4b	*N*-Fmoc-Met^c-Ile^c-Phe-OMe	77	118	728.2986 (728.2982)
5a	*N*-Fmoc-Ala^c-Gly^c-Ile^c-Ala-OMe	63	112	679.2949 (679.2955)
5b	*N*-Fmoc-Ile^c-Phe^c-Gly^c-Ala-OMe	58	132	755.3272 (755.3268)
7a	*N*-Fmoc-Ala^c-Leu-OH	76	—	477.2008 (477.2002)
7b	*N*-Fmoc-Val^c-Ile-OH	75	—	505.2310 (505.2315)

within 20–25 min. No column purification was required, and all the *N*-Fmoc-peptidyl carbamate esters **3a–c** were obtained as white solid powders after precipitation from hexane–ethyl acetate (8:2) in about 85–96% yield and were found to be more than 99% pure as analyzed by (HPLC) high-performance liquid chromatography.

The utility of the active carbonates **2** was further demonstrated for the synthesis of several *N*-Fmoc-oligopeptidylcarbamates. The Fmoc group from the dipeptidyl carbamate ester **3** was removed using 20% DEA/CH_2Cl_2 in 0.5 h, and the resulting free amino peptidyl carbamate ester was reacted with **2** (Scheme 2) to obtain the tripeptidyl carbamate esters (**4a** and **b**) in good yield and purity. Similarly, a few tetrapeptidyl carbamate esters were also prepared (**5a** and **b**, Table 1).

Finally, **2** was also employed for the synthesis of peptidyl carbamate acids **7**. This would readily give free terminal carboxylic acid end in the peptidyl carbamates so that the further chain extension/modification could be easily accomplished (Scheme 3). An amino acid was converted to its bis-TMS derivative[14] by refluxing it in CH_2Cl_2 with trimethylsilyl chloride (TMS-Cl) and *N*-ethyldiisopropylamine (DIEA) and was reacted with **2** at 0°C. The resulting *N*-Fmoc-peptidyl carbamate acids **7a** and **b** were isolated as pure ones after a workup, and the yields were more



Scheme 3. Preparation of dipeptidyl carbamate acids **7**.

than 70% (Table 1). All the synthesized compounds were free from racemization as evident by HPLC analysis. Our attempt to prepare dipeptidyl carbamate acids **7** from **1** was not satisfactory, giving rise to only about 10% conversion into the desired products. In these cases, much of the alcohol was recovered.

CONCLUSION

In summery, we have demonstrated a simple and efficient route for the synthesis of shelf-stable *N*-Fmoc-β-aminoalkoxy pentafluorophenyl carbonates starting from the corresponding aminoalkoxy carbonyl chlorides and pentafluorophenol. They have been employed as efficient monomeric building blocks for the synthesis of oligopeptidyl carbamate esters/acids. The reactions were clean and high yielding, and all the compounds were isolated and fully characterized.

EXPERIMENTAL

Melting points were determined using the capillary method and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet model impact 300D Fourier Transform (FT)–IR spectrometer (KBr pellets, $3\,cm^{-1}$ resolution). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400-MHz spectrometer. Mass spectra were recorded on HRMS. All solvents were freshly distilled prior to use. Amino acid methyl ester hydrochlorides were prepared by using methanol and thionyl chloride. Unless or otherwise mentioned, all amino acids used have an L-configuration. Thin-layer chromatographic (TLC) analysis was carried out using the precoated silica-gel G_{254} plates.

General Procedure for the Synthesis of *N*-Fmoc-β-Aminoalkoxy Pentafluorophenyl Carbonates 2

A solution of pentafluorophenol (1.2 mmol) in dry CH_2Cl_2 (10 mL) was added to a stirred solution of *N*-Fmoc-β-aminoalkoxy carbonyl chloride **1** (1 mmol) at 0°C in dry CH_2Cl_2 followed by NMM (1.5 mmol). After the completion of the reaction, citric acid (10%, 10 mL) was added, and the resulting layers were separated. The organic layer was washed with aqueous sodium carbonate solution (10%, 10 mL × 2), water (10 mL × 3), and brine (10 mL). Finally, it was dried over anhydrous sodium sulfate

and concentrated under vacuum to obtain the desired compound as a white solid.

Data

N-Fmoc-Ala-ψ(CH_2–O–CO–O)-Pfp **2a**

Mp: 99°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (d, 3H, $J = 6.6$ Hz), 3.60 (m, 1H), 4.19 (t, 1H), 4.31 (m, 2H), 4.40 (d, 2H, $J = 7.0$ Hz), 5.10 (d, 1H, $J = 6.6$ Hz), 7.3–7.7 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 17.2, 46.0, 47.2, 66.8, 72.1, 120.0, 124.9, 127.0, 127.7, 131.1, 132.1, 141.3, 143.8, 155.5, 170.1; IR (KBr) 1710, 1782 cm^{-1}. HRMS calcd. for $C_{25}H_{18}F_5NNaO_5$: 530.1003; found 530.1009 $[M + Na]^+$.

N-Fmoc-Val-ψ(CH_2–O–CO–O)-Pfp **2b**

Mp: 101°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (d, 6H, $J = 4.4$ Hz), 1.87 (m, 1H), 3.86 (m, 1H), 4.19–4.51 (m, 5H), 4.92 (d, 1H, $J = 7.1$ Hz), 7.31–7.79 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 18.3, 31.7, 47.0, 52.9, 66.8, 70.5, 120.0, 124.9, 127.0, 127.7, 131.1, 132.7, 141.3, 142.4, 143.8, 150.9, 155.5, 171.5; IR (KBr) 1705, 1782 cm^{-1}. HRMS calcd. for $C_{27}H_{22}F_5NNaO_5$: 558.1316; found 558.1314 $[M + Na]^+$.

N-Fmoc-Ile-ψ(CH_2–O–CO–O)-Pfp **2c**

Mp: 92°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.77 (t, 3H), 0.85 (d, 3H), 1.33 (m, 2H), 1.52 (m, 1H), 3.74 (m, 1H), 4.21 (t, 1H), 4.36 (d, 2H $J = 3.1$ Hz), 4.42 (d, 2H, $J = 8$ Hz), 4.9 (d, 1H, $J = 9.3$ Hz), 7.29 (m, 2H), 7.4–7.7 (m, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 11.1, 14.0, 15.3, 25.2, 35.8, 36.9, 47.3, 54.1, 54.6, 66.7, 70.3, 119.9, 124.9, 125.6, 127.0, 127.6, 136.5, 138.5, 139.1, 141.3, 142.5, 143.8, 151.3, 156.0, 170.2; IR (KBr): 1698, 1787 cm^{-1}. HRMS calcd. for $C_{28}H_{24}F_5NNaO_5$: 572.1472; found 572.1465 $[M + Na]^+$.

N-Fmoc-Leu-ψ(CH_2–O–CO–O)-Pfp **2d**

Mp: 103°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (d, 6H, $J = 7.2$ Hz), 1.63 (m, 3H), 2.75 (m, 1H), 4.19 (t, 1H, $J = 6.9$ Hz), 4.34 (m, 2H), 4.40 (m, 2H), 4.91(d, 1H, $J = 7.1$ Hz), 7.25–7.80 (m, 8H); ^{13}C NMR ($CDCl_3$,

200 MHz): δ 11.3, 15.1, 25.2, 38.8, 47.3, 57.3, 66.7, 71.2, 119.9, 124.9, 127.0, 127.7, 131.0, 132.0, 132.7, 141.3, 143.6, 150.5, 155.6, 168.9; IR (KBr) 1710, 1783 cm^{-1}. HRMS calcd. for $C_{28}H_{24}F_5NNaO_5$: 572.1472; found 572.1479 $[M + Na]^+$.

N-Fmoc-Phe-ψ(CH_2–O–CO–O)-Pfp **2e**

Mp: 110°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.90 (d, 2H, $J = 5.0$ Hz), 3.71 (m, 1H), 4.19 (t, 1H, $J = 13.5$ Hz), 4.30 (m, 2H), 4.40 (d, 2H, $J = 7.0$ Hz), 5.41 (d, 1H), 7.20–7.80 (m. 13H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 37.3, 47.2, 51.1, 66.8, 70.4, 119.9, 124.9, 127.0, 127.7, 127.8, 129.1, 131.1, 132.1, 136.2, 138.6, 142.4, 143.7, 151.1, 155.6, 172.1; IR (KBr) 1705, 1782 cm^{-1}. HRMS calcd. for $C_{31}H_{22}F_5NNaO_5$: 606.1316; found 606.1320 $[M + Na]^+$.

N-Fmoc-Gly-ψ(CH_2–O–CO–O)-Pfp **2f**

Mp: 114°C; ^{1}H NMR ($CDCl_3$, 300 MHz): 3.20 (m, 2H), 4.19 (t, 1H, $J = 13.0$ Hz), 4.30 (m, 2H), 4.39 (d, 2H, $J = 6.9$ Hz), 4.91 (br, 1H), 7.30–7.80 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 39.5, 47.1, 66.8, 71.8, 120.0, 124.9, 127.0, 127.7, 132.1, 132.2, 132.3, 143.8, 150.9, 155.6, 169.8; IR (KBr) 1715, 1780 cm^{-1}. HRMS calcd. for $C_{24}H_{16}F_5NNaO_5$: 516.0846; found 516.0852 $[M + Na]^+$.

N-Fmoc-Met-ψ(CH_2–O–CO–O)-Pfp **2 g**

Mp: 107°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.82 (m, 2H), 1.95 (s, 3H), 2.21 (t, 2H, $J = 12.9$ Hz), 2.70 (m, 1H), 3.81 (m, 1H), 4.18 (t, 1H, $J = 14.0$ Hz), 4.32 (d, 2H), 4.41 (d, 2H, $J = 7.2$ Hz), 7.21–7.80 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 15.0, 29.3, 32.7, 47.2, 54.1, 66.7, 70.5, 119.8, 124.0, 124.8, 127.7, 131.6, 132.1, 132.7, 141.3, 142.4, 150.7, 155.6, 171.1; IR (KBr) 1705, 1785 cm^{-1}. HRMS calcd. for $C_{27}H_{22}F_5NNaO_5S$: 590.1037; found 590.1031 $[M + Na]^+$.

N-Fmoc-Asp(OBzl)-ψ(CH_2–O–CO–O)-Pfp **2h**

Mp: 129°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.97 (m, 3H), 4.12–4.45 (m, 5H), 4.91 (d, 2H, $J = 6.0$ Hz), 5.01(s, 1H), 7.01–7.80 (m, 13H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 40.6, 47.3, 52.0, 63.2, 66.4, 71.0, 119.8, 124.9, 127.0, 127.7, 128.8, 129.1, 131.1, 132.1, 132.7, 135.2, 137.0, 141.3, 142.4, 151.2, 155.6, 171.2, 171.8; IR (KBr) 1710, 1779 cm^{-1}. HRMS calcd. for $C_{33}H_{24}F_5NNaO_7$: 664.1371; found 664.1380 $[M + Na]^+$.

N-Fmoc-L-Phg-ψ(CH_2–O–CO–O)-Pfp **2i**

Mp: 106°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.19 (t, 1H, $J = 13.0$ Hz), 4.40 (m, 5H), 4.92 (d, 1H, $J = 7.2$ Hz), 7.11–7.80 (m, 13H); ^{13}C NMR ($CDCl_3$, 200 MHz): 47.2, 54.4, 66.8, 70.4, 119.9, 124.9, 127.0, 127.7, 128.8, 129.1, 131.6, 132.1, 132.4, 136.2, 141.3, 142.4, 143.7, 151.2, 155.8, 169; IR (KBr) 1705, 1780 cm^{-1}. HRMS calcd. for $C_{30}H_{20}F_5NNaO_5$: 592.1159; found 592.1157 $[M + Na]^+$.

Synthesis of *N*-Fmoc Peptidyl Carbamate Ester 3

A solution of amino acid methyl ester hydrochloride (1.2 mmol) neutralized with NMM (1.5 mmol) was added to a solution of **2** (1 mmol) in dry CH_2Cl_2 (12 mL) at 0°C, and the reaction mixture was stirred at same temperature for 30 min. Citric acid (10%, 10 mL) was added, and the layers were separated. The organic layer was washed with sodium carbonate solution (10%, 10 mL × 2), water (10 mL × 2), and brine (10 mL) and dried over anhydrous sodium sulfate. The crude was purified by column chromatography using 30% EtOAc in hexane.

Data

N-Fmoc-Ala-ψ(CH_2–O–CO–NH)-Val-OMe **3a**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81 (d, 6H, $J = 6.1$ Hz), 1.17 (d, 3H, $J = 6.9$ Hz), 1.75 (m, 1H, $J = 6.8$ Hz), 2.52 (m, 1H), 3.53 (br, 1H), 3.74 (s, 3H), 4.11 (m, 2H), 4.19 (t, 1H), 4.34 (d, 2H, $J = 6.2$ Hz), 4.89 (d, 1H, $J = 6.1$ Hz), 5.33 (s, 1H), 7.30–7.77 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 17.3, 18.2, 42.1, 42.7, 47.4, 49.1, 52.3, 66.7, 67.9, 120.0, 125.1, 127.1, 127.8, 141.4, 144.0, 155.6, 156.7, 173.4; IR (KBr) 1715, 1777 cm^{-1}.

N-Fmoc-Met-ψ(CH_2–O–CO–NH)-Ala-OMe **3b**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.2 (d, 3H, $J = 5.8$ Hz), 1.47 (d, 3H, $J = 6.9$ Hz), 1.94–2.75 (m, 6H), 3.71 (s, 3H), 4.10–4.41 (m, 5H), 5.13–5.2 (br, 2H), 7.13–7.79 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 14.6, 18.7, 26.1, 30.9, 35.2, 47.2, 52.1, 54.2, 63.9, 66.8, 120.0, 125.0, 127.1, 127.2, 141.3, 144.0, 155.6, 156.4, 172.7; IR (KBr) 1698, 1789 cm^{-1}.

N-Fmoc-Ile-ψ(CH_2–O–CO–NH)-Leu-OMe **3c**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81–0.98 (m, 14H), 1.51 (m, 4H), 3.21 (br, 2H), 3.72 (s, 3H), 4.12–4.39 (m, 5H), 5.14–5.28 (br, 2H), 7.1–7.79 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 18.5, 22.4, 24.8, 32.4, 38.2, 41.2, 47.4, 48.8, 52.4, 54.9, 55.8, 64.2, 66.8, 120.0, 125.0, 127.2, 127.2, 141.3, 144.0, 155.6, 156.4, 172.9; IR (KBr) 1715, 1781 cm^{-1}.

General Procedure for the Synthesis of Oligopeptidyl Carbamates 4, 5

A solution of **3** (1 mmol) in a mixture of DEA/CH_2Cl_2 (1:1, 10 mL) was stirred for 30 min, and the reaction mixture was concentrated under reduced pressure to remove DEA completely. The resulting free amino peptidyl carbamate was isolated after trituration of the residue with ether (15 mL). It was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0°C. A solution of **2** in dry CH_2Cl_2 was added followed by NMM (1.2 mmol). After the completion of the reaction (TLC), the reaction mixture was washed with 10% citric acid solution, water (10 mL × 2), and brine. The crude was purified by column chromatography using 35% hexane–EtOAc to get the tripeptidyl carbamate ester as a solid. Similar steps were repeated to obtain the tetrapeptidyl carbamates.

Data

N-Fmoc-Ala-ψ(CH_2–O–CO–NH)-Leu-ψ(CH_2-O-CO-NH)-Ala-OMe **4a**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (d, 6H, $J = 7.3$ Hz), 1.26 (m, 6H, $J = 6.8$ Hz), 1.42 (m, 3H), 2.42 (m, 1H), 3.53 (br, 1H), 3.72 (s, 3H), 4.11 (m, 2H), 4.20–4.35 (m, 6H), 5.33–5.68 (m, 3H), 7.30–7.79 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 17.3, 18.2, 18.5, 25.3, 35.6, 46.7, 46.9, 49.1, 51.2, 60.8, 62.7, 66.7, 68.2, 119.9, 125.1, 127.1, 127.8, 141.4, 144.0, 155.6, 156.3, 156.7, 172.8; IR (KBr) 1710, 1778, 1780 cm^{-1}.

N-Fmoc-Met-ψ(CH_2–O–CO–NH)-Ile-ψ(CH_2–O–CO–NH)-Phe-OMe **4b**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (d, 6H, $J = 7$ Hz), 1.97–2.2 (m, 7H), 1.44 (m, 3H), 2.51 (m, 1H), 3.1 (br, 2H), 3.35 (m, 1H), 3.70 (s, 3H), 4.12 (m, 1H), 4.3–4.6 (m, 7H), 5.6–5.8 (m, 3H), 7.1–7.7 (m, 13H): ^{13}C NMR ($CDCl_3$, 200 MHz): 14.8, 17.4, 19.2, 22.3, 24.5, 32.1, 41.1, 47.3, 48.8, 52.3, 54.8, 59.2, 64.5, 66.8, 68.2, 72.1, 120.0, 125.0, 127.1, 127.2, 127.7,

128.6, 129.6, 135.7, 141.2, 144.7, 155.6, 156.1, 157.2, 172.0; IR (KBr) 1705, 1768, 1778 cm^{-1}.

N-Fmoc-Ala-ψ(CH_2–O–CO–NH)-Gly-ψ(CH_2–O–CO–NH)-Ile-ψ (CH_2–O–CO–NH)-Ala-OMe **5a**

^{1}H NMR ($CDCl_3$, 300 MHz): 0.87 (d, 6H, $J = 7.3$ Hz), 1.26 (m, 6H, $J = 6.8$ Hz), 1.42 (m, 3H), 2.42 (m, 1H), 3.14–3.38 (m, 4H), 3.53 (br, 1H), 3.72 (s, 3H), 4.11 (m, 2H), 4.20–4.35 (m, 7H), 5.33 (br, 3H), 7.30–7.79 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 17.3, 18.2, 18.5, 22.1, 25.3, 35.6, 42.6, 46.7, 46.9, 49.1, 51.2, 60.8, 62.7, 66.7, 68.2, 119.9, 125.1, 127.1, 127.8, 141.4, 144.0, 155.6, 156.3, 156.7, 168.2, 172.8; IR (KBr) 1710, 1777, 1780 cm^{-1}.

N-Fmoc-Ile-ψ(CH_2–O–CO–NH)-Phe-ψ(CH_2–O–CO–NH)-Gly-ψ (CH_2–O–CO–NH)-Ala-OMe **5b**

^{1}H NMR ($CDCl_3$, 300 MHz): 0.95 (d, 6H, $J = 6.8$ Hz), 1.15 (d, 3H, $J = 5.8$ Hz), 1.50–1.81 (m, 3H), 3.12–3.32 (m, 8H), 3.71 (s, 3H), 4.11 (m, 2H), 4.41–4.62 (m, 6H), 5.25 (br, 3H), 6.1 (s, 1H), 7.30–7.80 (m, 13H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 14.7, 18.6, 20.8, 22.3, 22.5, 35.6, 37.3, 46.7, 47.0, 49.1, 52.3, 54.0, 66.7, 67.9, 70.1, 120.0, 125.1, 127.1, 127.8, 128.5, 128.6, 138.0, 141.4, 144.0, 155.4, 155.5, 156.9, 167.2, 171.2, 173.9; IR (KBr) 1700, 1778, 1785 cm^{-1}.

Synthesis of *N*-Fmoc-Peptidyl Carbamate Acid 7

Initially, an amino acid was converted to its Bis TMS derivative **6**. TMS-Cl (2.5 mmol), followed by TEA (2.5 mmol), and was added to a suspension of amino acid (1 mmol) in CH_2Cl_2 refluxed for 3 h. The mixture was cooled to rt and was added to a stirred solution of **2** in CH_2Cl_2 at 0°C. After 1 h, the reaction mixture was concentrated, and the residue was taken into a solution of sodium carbonate. The aqueous layer was washed with ether (10 mL × 2), followed by acidification using dilute HCl. The precipitate was extracted into ethyl acetate (15 mL), and the organic layer was washed with water (10 mL × 3), followed by brine wash (15 mL). The solvent was removed under reduced pressure to afford the desired compound as gummy solids.

Data

N-Fmoc-Ala-ψ(CH_2–O–CO–NH)-Leu-OH **7a**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (d, 6H, $J = 6.4$ Hz), 1.2 (d, 3H, $J = 5.8$ Hz), 1.45 (m, 3H), 3.68–3.7 (m, 4H), 4.20–4.42 (m, 4H), 5.10–5.2 (br, 2H), 7.10–7.80 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 22.3, 22.9, 38.3, 41.1, 47.4, 48.8, 49.7, 52.3, 64.7, 66.7, 120.0, 125.0, 127.0, 127.3, 127.9, 128.6, 129.2, 135.7, 141.4, 144.0, 155.6, 156.4, 172.8; IR 1707, 1778 cm^{-1}.

N-Fmoc-Val-ψ(CH_2–O–CO–NH)-Ile-OH **7b**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.8–0.9 (m, 12H), 1.58 (m, 4H), 3.31 (br, 1H), 4.12–4.39 (m, 5H), 5.2 (m, 2H), 5.32 (br, 1H), 7.5–7.79 (m, 8H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 18.5, 22.4, 24.8, 32.4, 41.2, 48.8, 54.9, 64.2, 66.8, 120.0, 125.0, 127.2, 141.3, 144.0, 155.6, 156.4, 168.9, 172.9; IR 1710, 1780 cm^{-1}.

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