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The first example of linear peptides containing a *N*-trifluoroethylated backbone amide linkage and the surprising solution dynamics observed by ^{19}F NMR

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Abstract

The α-amino group of (L)phenylalanine methyl ester was trifluoroethylated using (2,2,2-trifluoroethyl)phenyliodonium *N*,*N*-bis(trifluoromethylsulfonyl)imide. A dipeptide Gly(L)Phe containing a trifluoroethylated peptide bond was synthesized by removing the α-amino proton of N^{α}-trifluoroethyl (L)phenylalanine methyl ester followed by coupling with N^{α}-phthaloyl glycine acid fluoride. The dipeptide was further coupled with (L)leucine methyl ester under conventional carboxyl activation conditions to provide two diastereomers of the tripeptide Gly(D,L)Phe(L)Leu. The solution dynamic behavior of the tripeptide was investigated as a function of solvents, by NOESY and variable temperature (VT) ^{19}F NMR experiments.

Keywords: (2,2,2-Trifluoroethyl)phenyliodonium *N*,*N*-bis(trifluoromethylsulfonyl)imide; Trifluoroethylation; Peptide bonds; Solution dynamic behavior; ^{19}F NMR; Conformational study

1. Introduction

Selective trifluoroethylation of bioactive compounds has been investigated since the early 1960s [1–5]. However, the progress in this research area is much slower compared to selective fluorination of bioactive compounds, such as amino acids and peptides [6,7]. In the past decade, we have focused on the synthesis and applications of the novel trifluoroethylating agent $CF_3CH_2I(C_6H_5)N(SO_2CF_3)_2$. The chemo selectivity of this agent was demonstrated by trifluoroethylation of the functionalities of α-amino acids [8–10]. The CF_3CH_2– group was introduced at the *N*-terminus of leucine and methionine enkephalins to improve the lipophilicity of these brain peptides. The nucleophilicity of the trifluoroethylated *N*-terminus was shown in intramolecular cyclization reactions [11]. Herein we report our results on the incorporation of the CF_3CH_2– group into peptide bonds of model linear peptides, which leads to unanticipated conformational behavior in solution as observed by ^{19}F NMR. The fluorine labeled peptides illustrate the potential of the fluoroalkyl groups to both affect and act as a probe of the solution dynamics of small peptides.

2. Results and discussion

Converting a secondary amide bond to a trifluoroethylated tertiary counterpart can be carried out by two potential synthetic routes: pre-trifluoroethylation and post-trifluoroethylation. In the early 1970s, Steinman et al. [2] prepared 1-trifluoroethyl-5-phenyl-1,4-benzodiazepin-2-one (**II** in Scheme 1) in low yields by first removing proton from 1 position of parent compound (**I**) and then reacting with trifluoroethyl iodide. This reaction could not be substantially improved by altering the reaction conditions or by the use of trifluoroethyl benzenesulfonate or trifluoroethyl trichloromethanesulfonate (triclate) as the alkylating agents.

The possibility of introducing the trifluoroethyl group at an earlier stage in the synthesis of (**II**) was then investigated. Based on Dickey's research [12], trifluoroethylation of anilines with 2-chloro-1,1,1-trifluoroethane by autoclave reactions, and Hansen's work [13], trifluoroethylation of diethylamine with trifluoroethyl trifluoromethanesulfonate (triflate), Steinman

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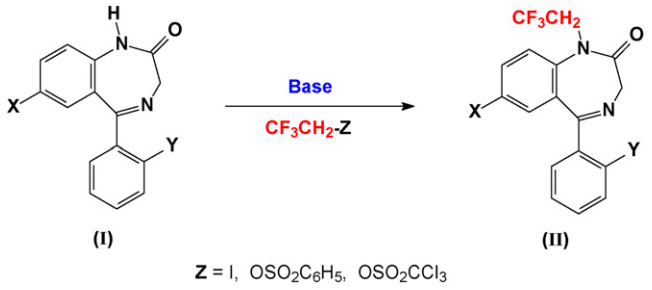


Scheme 1.

et al. [2] prepared and used triclate to obtain the secondary *N*-trifluoroethylated anilines and aminobenzophenones. These were then coupled directly with bromoacetyl bromide and phthalimidoacetyl chloride to form desired tertiary amide functionalities.

In the late 1990s, Claremon et al. [14a] and Selnick et al. [14b] used excess trifluoroethyl iodide with 5-phenyl-1,4-benzodiazepin-2-one (**I**, X = H, Y = H) in the presence of Cs_2CO_3 in DMF at 50 °C to obtain 1-trifluoroethyl-5-phenyl-1,4-benzodiazepin-2-one (**II**, X = H, Y = H) in 60–68% yields. To obtain a trifluoroethylated peptide bond, we tried the reaction of both *N*-phthaloyl and *C*-methyl ester protected Gly-(L)Phe dipeptide under the same reaction conditions, but the reaction failed.

We then turned our attention to introducing CF_3CH_2– group to the α-amino nitrogen of amino acids at an earlier stage followed by a coupling reaction with an amino acid fluoride, but failed in the coupling step. Our earlier research showed that the lack of nucleophilicity of the trifluoroethylated α-amino nitrogen of amino acids in the conventional linear peptide coupling reactions was caused by both steric and electronic effects of the CF_3CH_2– group [9,10]. However, a trifluoroethylated α-amino group could form an amide bond in an intramolecular cyclization reaction leading to cyclic dipeptide formation [11]. We reasoned that deprotonating the α-amino group would lead to reactivity.

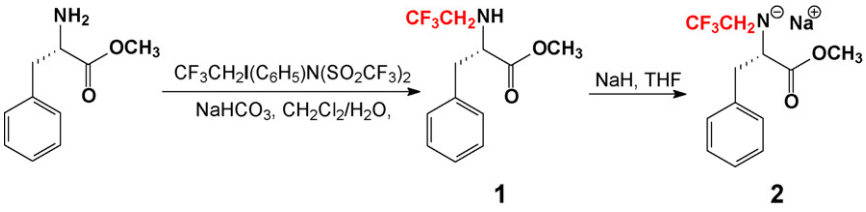
Trifluoroethylating agent (2,2,2-trifluoroethyl)phenyliodonium triflate was initially synthesized by Umemoto and Gotoh [15] and used to trifluoroethylate different nucleophiles during 1980s [16]. In 1994, the same trifluoroethylating agent was prepared using the modified method by Resnati and used for *N*-trifluoroethylation of amino alcohols under dry conditions [17]. In this research, novel trifluoroethylating agent (2,2,2-trifluoroethyl)phenyliodonium *N*,*N*-bis(trifluoromethylsulfonyl)imide was synthesized [8] and used for *N*-trifluoroethylation of α-amino acids.

The reaction of (L)phenylalanine methyl ester with $CF_3CH_2I(C_6H_5)N(SO_2CF_3)_2$ in two phase solvents CH_2Cl_2/H_2O resulted in N^{α}-trifluoroethyl (L)phenylalanine methyl ester **1** (Scheme 2), which was then deprotonated at the α-amino position to provide ionic intermediate **2**.

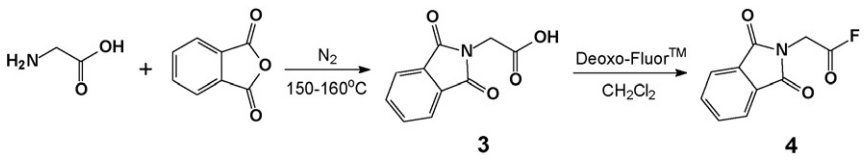
Glycine was protected with phthalic anhydride to form N^{α}-phthaloyl glycine **3** (Scheme 3), which was converted to acid fluoride **4** using Deoxo-Fluor™.

Coupling between ionic intermediate **2** and acid fluoride **4** formed the desired peptide bond (Scheme 4). After basic hydrolysis and acidification, dipeptide **5** was obtained.

Dipeptide **5** was further coupled with (L)leucine methyl ester under conventional carboxyl activation conditions to give tripeptide **6** (Scheme 5).



Scheme 2.



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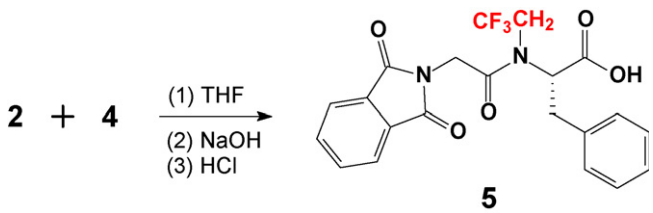
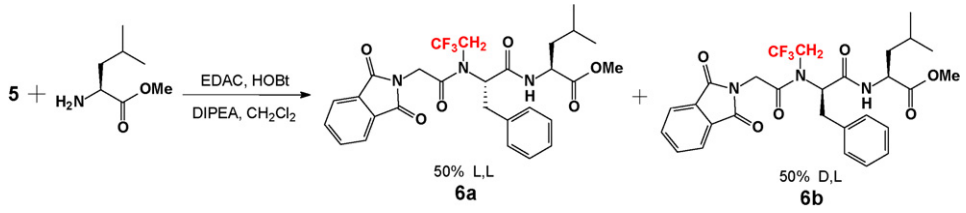


Scheme 4.



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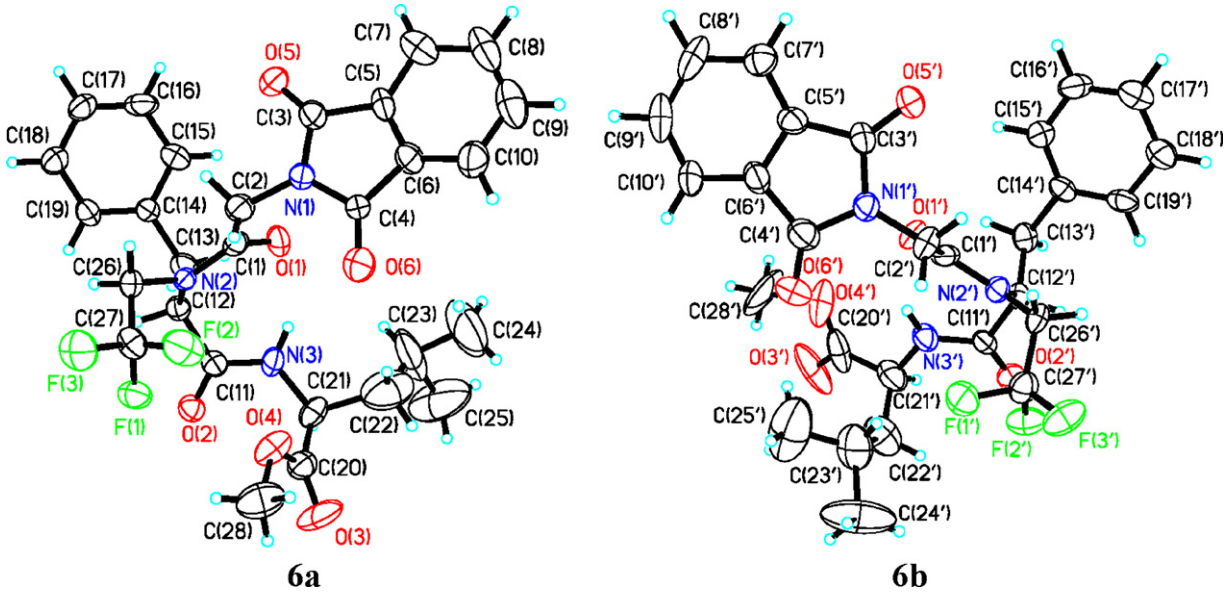


Fig. 1. Crystal structures of tripeptide **6**.

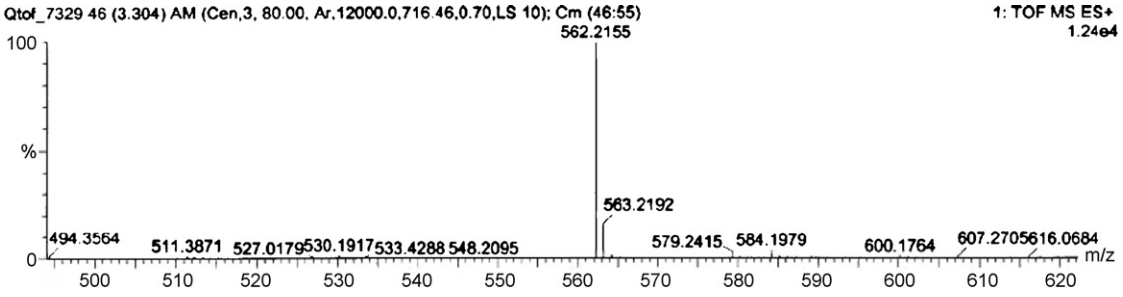


Fig. 2. HRMS of tripeptide **6**, formula $(M + H)$ $C_{28}H_{31}N_3O_6F_3$, calc 562.2165, found 562.2155.

Tripeptide **6** was characterized by crystal structure analysis (Fig. 1) and HRMS (Fig. 2).

From the crystal structures of tripeptide **6**, it was clear that the tripeptide was obtained in diastereomeric forms. Both secondary peptide bond and trifluoroethylated tertiary peptide bond of each diastereomer assumed the sterically favored *Z* conformation about the C(=O)–N bond in the solid state.

Initially, when tripeptide **6** was subjected to NMR characterization, four well resolved triplets were observed in ^{19}F NMR spectra shown in Fig. 3. In different deuterated solvents, the relative intensities of four triplets changed dramatically. However, it was found that the ratio of $(A_1 + A_2)/(B_1 + B_2)$ was constant in different NMR solvents and was always 1. Therefore, it was inferred that triplets A_1 and A_2 belonged to one diastereomer of tripeptide **6**, B_1 and B_2 belonged to another diastereomer, and full racemization at α-carbon of (L)phenylalanine occurred at the carboxyl activation step during the coupling reaction with (L)leucine methyl ester. Presumably, full racemization at the α-carbon was facilitated by the attachment of the electron withdrawing CF_3CH_2– group to the adjacent nitrogen, although the effect of *N*-methylation of peptides on the base-catalyzed epimerization at the adjacent C_α position was also observed [18,19].

The ^{19}F NMR spectra of tripeptide **6** revealed that in solution each diastereomer existed in two different conformations. The equilibrium between two corresponding conformers was affected by the polarity of solvents.

The exchange between two conformations for each diastereomer of tripeptide **6** was further verified by a 2D ^{19}F NOESY experiment shown in Fig. 4. A 2D ^{1}H NOESY

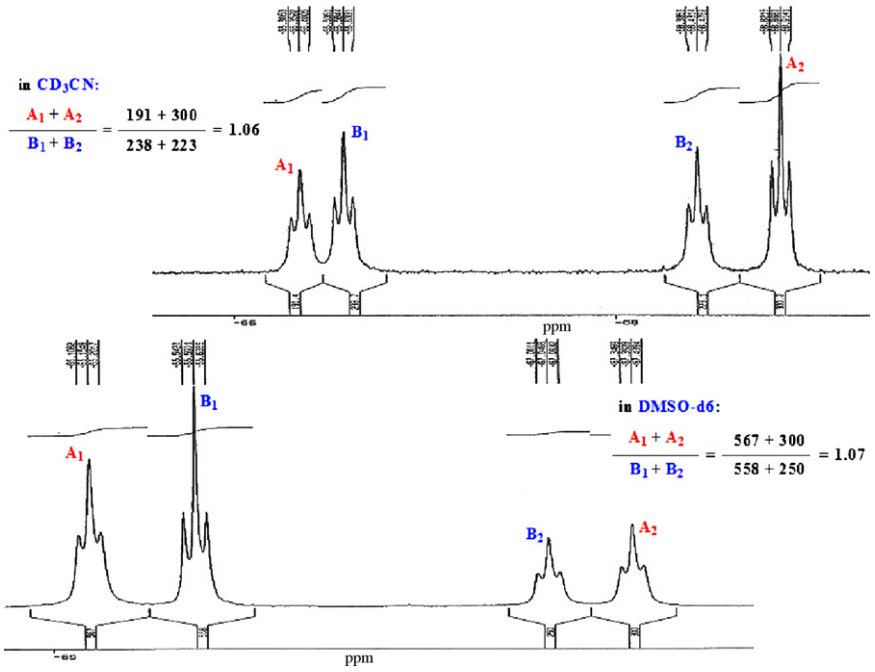


Fig. 3. ^{19}F NMR spectra of diastereomeric tripeptide **6** in CD_3CN (top) and DMSO-d_6 (bottom) (188.31 MHz, 21 °C).

experiment was also carried out (Fig. 5, zoomed in NH proton region), in which each pair of negative cross peaks (in dotted line) represented the conformational exchange.

In *N*-monosubstituted amides shown in Scheme 6(a), both rotamers could always be detected in formamides (R^1 = H) [20]; whereas in higher amides (R^1 = Alkyl) only the form *Z*, in which the R^1 and R^2 were *trans* to each other, was found in most cases [20–22]. Therefore the exchange peaks in 2D ^1H NOESY spectrum (Fig. 5, NH proton region) reflected the rotation (*Z* and *E* exchange) about the trifluoroethylated tertiary amide bond shown in Scheme 6(b) instead of the secondary amide bond to which the NH proton belonged. This was further verified by the consistency of the integration ratios of the four triplets in ^{19}F NMR spectra (Figs. 3 and 4) and that of the four doublets in the ^1H NMR spectrum (Fig. 5, NH proton region) obtained in the same solvent DMSO-d_6 at the same temperature.

In unsymmetrically *N*,*N*-disubstituted amides, LaPlanche and Rogers [23] found that the bulkier substituent (R^2) on nitrogen was *trans* to the acetyl methyl group (R^1) of acetamides, in the preferred isomer. *N*-Alkylation of a linear peptide increased the proportion of *cis* (R^2 *cis* to R^1) peptide present [19,24]. This is even more evident in our case, presumably because the CF_3CH_2– group is an electron withdrawing group which decreases the double bond character of the amide bond and makes its rotation easier.

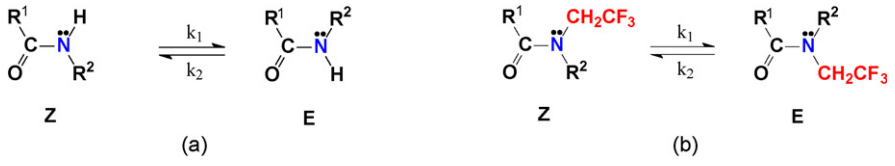
The dynamic behavior of tripeptide **6** was further investigated by variable temperature ^{19}F NMR experiments from 25 °C up to 128 °C in DMSO-d_6 (Fig. 6).

At *ca*. 88 °C, the resonances of the trifluoroethyl groups of the two conformers from each diastereomer of tripeptide **6** coalesced. This suggested the rotation around the trifluoroethylated tertiary peptide bond (*Z* and *E* exchange) shown in Scheme 6(b). At the higher temperatures, the signals from two diastereomers of tripeptide **6** gradually merged and sharpened indicating that the inversion at the trifluoroethylated α-amino nitrogen became faster on the NMR time scale.

In summary, the trifluoroethyl group has been introduced into peptide bonds by deprotonating trifluoroethylated α-amino group followed by the coupling reaction with acid fluoride. The introduction of CF_3CH_2– group facilitates peptide bond rotation and results in different conformations. The solution dynamic behavior of the corresponding linear peptides can be investigated using a variety of ^{19}F NMR techniques.

3. Experimental

Trifluoroethylating agent $CF_3CH_2I(Ph)N(SO_2CF_3)_2$ was synthesized [8]. Other reagents and solvents were obtained from commercial suppliers and used without further purification. NMR spectra were obtained on Bruker AC-200, Bruker Avance 300, JEOL ECX-300, and JEOL Eclipse+ 500



Scheme 6. *Z* and *E* exchange: (a) about secondary amide bond and (b) about trifluoroethylated tertiary amide bond ($R^2 > -CH_2CF_3$).

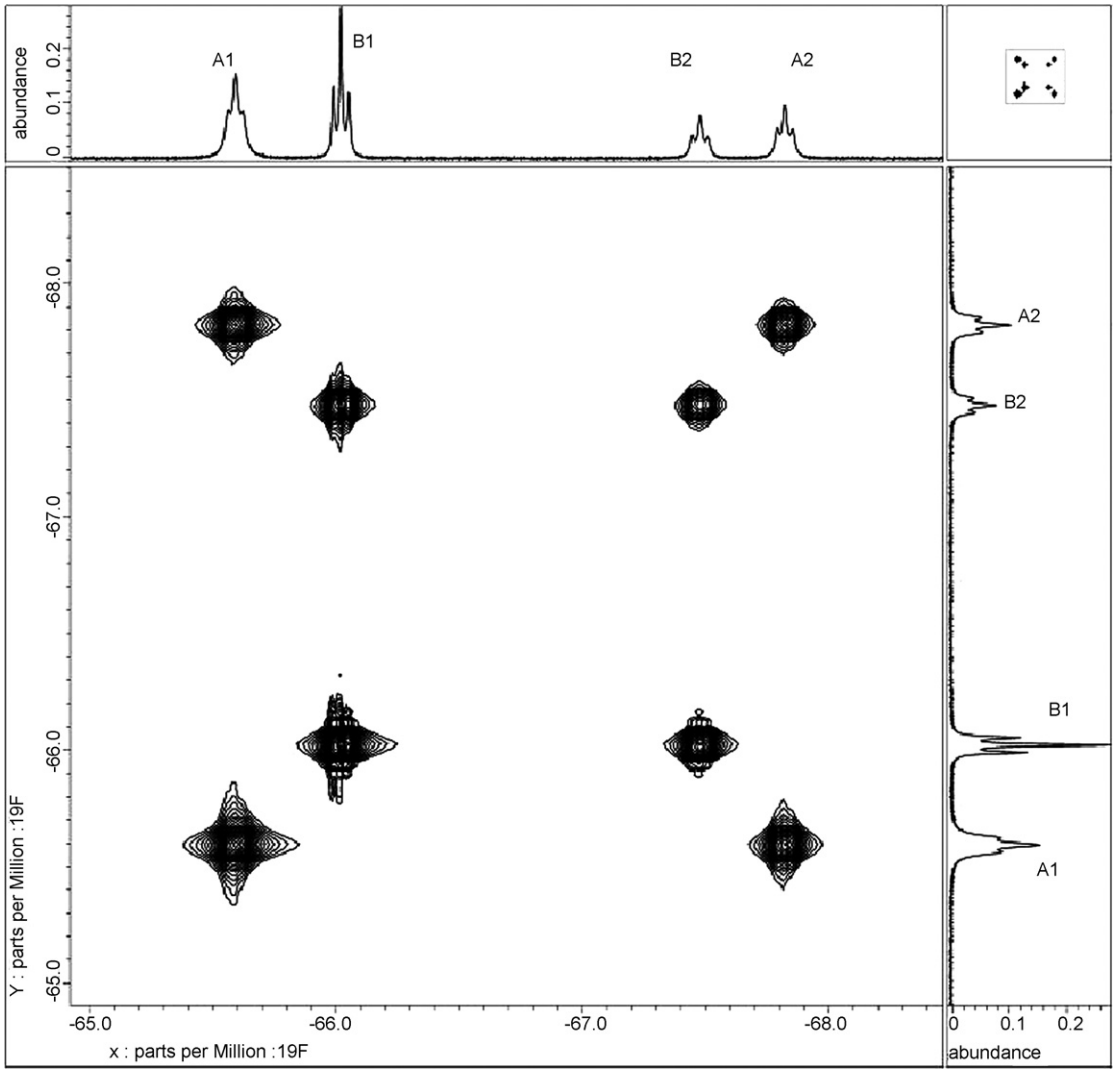


Fig. 4. 2D ^{19}F NOESY spectrum of diastereomeric tripeptide **6** in DMSO-d_6 (282.78 MHz, 21 °C).

spectrometers. Chemical shifts are given in ppm relative to $CFCl_3$ for ^{19}F, and relative to deuterated solvents used for ^{1}H and ^{13}C NMR. Melting points are uncorrected.

3.1. N^{α}-Trifluoroethyl (L)phenylalanine methyl ester *1*

(L)Phenylalanine methyl ester hydrochloride (2.157 g, 10.00 mmol) was suspended in CH_2Cl_2 (70 mL). Water (70 mL) and Na_2CO_3 (7.0 g) were added. The mixture was stirred for 30 min. The clear organic layer was separated. $NaHCO_3$ (1.008 g, 12.00 mmol), water (70 mL) and trifluoroethylating agent $CF_3CH_2I(Ph)N(SO_2CF_3)_2$ (6.237 g, 11.00 mmol) were added with stirring at room temperature. After 3 h, the CH_2Cl_2 layer was again separated and washed with 3 × 100 mL of water. The organic solvent was evaporated. The obtained residue was subjected to column chromatography using 10–30% acetone in hexanes to give 2.523 g (9.658 mmol, 96.6%) of compound **1**.

Compound **1**: colorless oil. ^{19}F NMR (188.31 MHz, CD_3CN): −71.76 (3F, t, J = 9.75 Hz). ^{1}H NMR (200.13 MHz, CD_3CN): 2.91–2.94 (2H, m), 2.96–3.19 (1H, m), 3.19–3.40 (1H, m), 3.53–3.72 (1H, m), 3.61 (3H, s), 7.16–7.34 (5H, m).

3.2. Deprotonated ionic intermediate *2*

N^{α}-Trifluoroethyl (L)phenylalanine methyl ester **1** (0.784 g, 3.00 mmol) and NaH (95%, 0.106 g, 4.20 mmol) were dissolved/suspended in dry THF (15 mL). The reaction mixture was refluxed under N_2 protection for 24 h. The conversion of N^{α}-trifluoroethyl (L)phenylalanine methyl ester to the corresponding N^{α}-deprotonated anionic intermediate **2** was 93.6% based on ^{19}F NMR.

Intermediate **2**: ^{19}F NMR (188.31 MHz, $(CD_3)_2CO$): −71.24 (3F, t, J = 8.66 Hz).

3.3. N^{α}-Phthaloyl glycine *3*

Glycine (1.137 g, 15.00 mmol) and phthalic anhydride (2.244 g, 15.00 mmol) were grinded together thoroughly. The mixture was heated at 150–160 °C for 30 min under N_2 protection. The crude product was crystallized from CH_3OH/

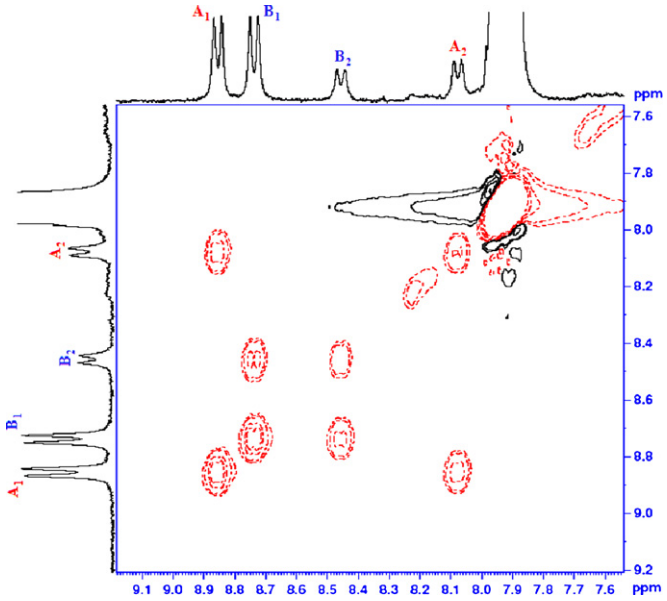


Fig. 5. 2D ^{1}H NOESY spectrum of **6** in DMSO-d_6 (NH proton region, 300.13 MHz, 21 °C).

H_2O yielding 2.911 g (14.18 mmol, 94.6%) of N^{α}-phthaloyl glycine **3**.

Compound **3**: white solid; mp 193–196 °C. ^{1}H NMR (200.13 MHz, CD_3CN): 4.35 (2H, s), 7.75–7.87 (4H, mc).

3.4. N^{α}-Phthaloyl glycine acid fluoride **4**

N^{α}-Phthaloyl glycine **3** (0.615 g, 3.00 mmol) was suspended in dry CH_2Cl_2 (15 mL) under N_2 protection. The suspension was cooled in an ice bath with stirring. [Bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor^{TM}, 0.68 mL, 3.6 mmol) was added dropwise through a syringe. The reaction was continued at 0 °C for 1 h and at room temperature for 2.5 h. Ice cooled water (20 mL) was added. The mixture was stirred vigorously for 10 min. The organic layer was separated and dried with anhydrous Na_2SO_4. The solvent was evaporated, and the obtained residue was dried under vacuum at 40 °C for 1 h. The conversion of N^{α}-phthaloyl glycine **3** to N^{α}-phthaloyl glycine acid fluoride **4** was 92.4% based on ^{1}H NMR.

Compound **4**: colorless semi-crystalline solid. ^{19}F NMR (188.31 MHz, CD_3CN): 32.99 (1F, t, J = 3.77 Hz). ^{1}H NMR

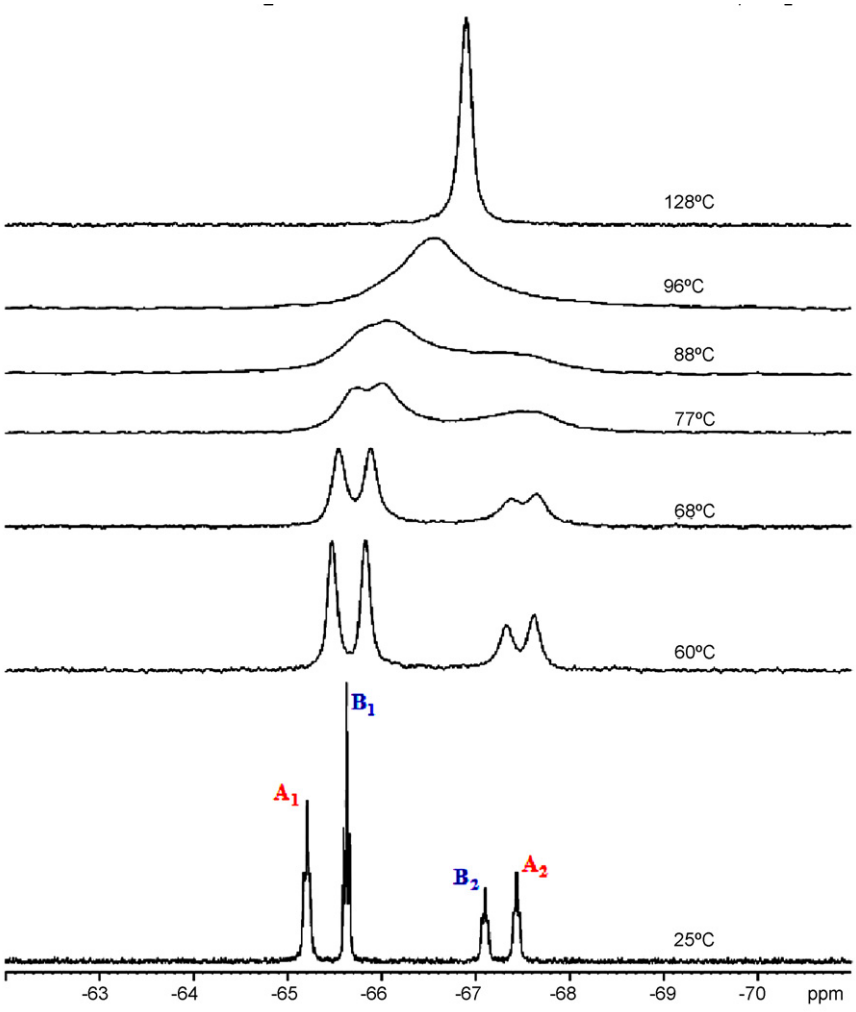


Fig. 6. Variable temperature ^{19}F NMR spectra of tripeptide **6** in DMSO-d_6 (282.38 MHz).

(200.13 MHz, CD_3CN): 4.65–4.68 (2H, d, J = 3.76 Hz), 7.79–7.92 (4H, mc).

3.5. Dipeptide **5**

Intermediate **2** (1.87 mmol, 10.0 mL of reaction solution from 3.2) was added dropwise into 5 mL of dry THF containing 2.77 mmol of N^{α}-phthaloyl glycine acid fluoride **4** with stirring at 60 °C. The reaction mixture was refluxed for 16 h. Aqueous 2 M NaOH solution (15 mL) was added and the mixture was stirred for 10 h at room temperature. The reaction mixture was cooled in an ice bath and acidified with conc. HCl to pH 4.5. After evaporating solvents, the obtained residue was suspended in 15 mL of CH_2Cl_2 and washed with 15 mL of H_2O twice. The organic layer was separated and the solvent was evaporated. The obtained residue was subjected to column chromatography with 5–20% MeOH in $CHCl_3$ as eluent to yield 0.487 g (1.12 mmol, 59.9%) dipeptide **5**.

Compound **5**: white solid. ^{19}F NMR (188.31 MHz, CD_3CN, for major isomer): −69.94 (3F, t, J = 9.15 Hz). ^{1}H NMR (500.16 MHz, CD_3CN, for major isomer): 3.10–3.23 (2H, m), 3.23–3.32 (1H, m), 3.91–4.01 (1H, mc), 4.08–4.14 (1H, dd, J = 5.05 Hz, J = 5.05 Hz), 4.30–4.60 (2H, mc), 7.22–7.41 (5H, m), 7.82–7.93 (4H, mc). ^{13}C NMR (125.77 MHz, CD_3CN, for major isomer): 34.1, 39.4, 39.7, 49.7 (q, J = 34.2 Hz), 64.7, 123.4, 125.6 (q, J = 290.2 Hz), 128.8, 129.1, 129.5, 132.1, 134.5, 137.8, 167.2, 167.8, 169.9.

3.6. Tripeptide **6**

Dipeptide **5** (0.362 g, 0.830 mmol), (L)leucine methyl ester (0.185 g, 1.00 mmol), HOBt (0.160 g, 1.16 mmol) and EDAC·HCl (0.227 g, 1.16 mmol) were suspended in 15 mL of CH_2Cl_2. The reaction mixture was stirred and cooled at 0 °C. DIPEA (0.42 mL, 1.9 mmol) was added in one portion through a syringe. The reaction was continued at 0 °C for 2 h and at room temperature for 14 h.

The reaction mixture was washed with 20 mL of 0.5 M HCl, 20 mL of 0.1 M $NaHCO_3$, and 3 × 20 mL of H_2O, respectively. The organic layer was separated, and the solvent was evaporated. The obtained crude product was subjected to column chromatography twice using 1–5% MeOH in $CHCl_3$ and 20–30% acetone in hexanes, respectively, yielding 0.437 g (0.780 mmol, 93.4%) of tripeptide **6**.

Compound **6**: white solid; mp 147–149 °C. HRMS (ESI) for $(M + H)^+$: $C_{28}H_{31}N_3O_6F_3$; calc: 562.2165; found: 562.2155.

Crystallographic data of tripeptide **6**: formula, $C_{28}H_{30}N_3O_6F_3$; M = 561.21; monoclinic; C_2; T = 253(2) K; a = 24.800(5), b = 8.0711(16), c = 29.210(6) Å, β = 106.60(3)°; V = 5603.2(19) Å^3; D_{calc} = 1.331 g cm^{-3}; Z = 8; μ = 0.107 mm^{-1}; empirical absorption correction (0.9696–0.9926); Mo Kα radiation with graphite monochromator, λ = 0.71073 Å; Rigaku AFC-8S diffractometer; 22,997 measured reflections (R_{int} = 13.58%); 9892 reflections used with $I > 2\sigma(I)$; $2\theta_{max}$ = 50.10°; 724 parameters; non-H atoms refined anisotropically; H atoms fixed in calculated positions (C–H = 0.96 Å); full-matrix least-squares on F^2 refinement; R = 8.15%/$R_w(F^2)$ = 18.64%. CCDC 609,457.

Acknowledgments

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