Ionic Liquid Supported Peptide Synthesis Demonstrated by the Synthesis of Leu⁵-Enkephalin

Weishi Miao and Tak Hang Chan*

Department of Chemistry, McGill University, Montreal, Quebec
Canada H3A 2K6

Email: tak-hang.chan@mcgill.ca

Supporting information

Table of Contents

1. Table of Contents	S1
2. General Experimental and the loading step	S2
3. The peptide forming step	S3
4. Determination of degree of racemization in loading and peptide forming steps	S6
5. The peptide liberation step	S7
6. ¹ H NMR spectra of ionic liquid supported peptide 2a , 4a , 7 , 9 and 11	S9
7. Mass spectra of ionic liquid supported peptide 2a , 4a , 7 , 9 and 11	S10

EXPERIMENTAL

General. All reagents were obtained commercially and were used without further purification unless otherwise noted. Solvents were reagent grade and if necessary, were dried by standard procedures. ^1H NMR and ^{13}C NMR spectra were recorded on 300 or 400 MHz NMR spectrometers at 20 °C. Chemical shifts for protons are reported in parts per million and referenced to residual protium in acetone- d_6 (δ 2.06) or methanol- d_4 (δ 3.30). Carbon chemical shifts are reported in parts per million relative to the carbon resonance of the methyl group of acetone- d_6 (δ 29.8) or methanol- d_4 (δ 49.0). The doubling of peaks in the NMR spectra of ionic liquid supported peptides **3a**, **6** and **8** are due to the counterion exchanges between BF_4^- and TFA^- . Optical rotations were determined by digital polarimeter. Degree of racemization and purity of final product were determined by analytical HPLC using chiral analytical columns with 2-propanol in hexanes as the eluent, and a semi-prep column with $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{TFA}$ as eluent system. Mass spectroscopic data (FAB) were obtained at the McGill University Mass Spectrometry Facility.

The esterification (loading) step. To a mixture of ionic liquid **1** (1.07g, 5 mmol), Boc-leucine (L- or D-form, 2.31g, 10 mmol) and dimethylaminopyridine (0.25g, 2 mmol) in dry acetonitrile (25 mL) was added dicyclohexylcarbodiimide (1M in CH_2Cl_2 , 10 mL, 10 mmol). The mixture was stirred vigorously for 18 h at room temperature under nitrogen and filtrated through a plug of celite. The celite plug was rinsed with acetonitrile and, the combined organic phase was concentrated in vacuum. The crude residue was washed firstly with ether (20 mL $\times$ 3), then dissolved in CH_2Cl_2 and washed with 2M HCl (10 mL $\times$ 3). The organic phase was dried over Na_2SO_4 and concentrated to afford **ionic liquid supported Boc-leucine 2a (L-isomer) or 2b (D-isomer)** 1.95g (91%) as pale yellow oils. ^1H NMR (300 MHz, Acetone- d_6) δ 9.08 (s, 1H), 7.80 (s, 1H), 7.71 (s, 1H), 6.41 (d, br, J = 7.8 Hz, 1H), 4.66-4.64 (m, 2H), 4.60-4.43 (m, 2H), 4.20-4.13

(m, 1H), 4.04 (s, 3H), 1.68-1.53 (m, 3H), 1.39 (s, 9H), 0.91 (d, $J = 6.0$ Hz, 3H), 0.89 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, Acetone- d_6) δ 173.2, 156.4, 138.0, 124.4, 123.6, 79.3, 63.4, 53.0, 49.3, 40.7, 36.6, 28.5 (3C), 25.4, 23.1, 21.6; HRMS (FAB) calcd. for $\text{C}_{17}\text{H}_{30}\text{N}_3\text{O}_4$ (M^+) 340.2237, found 340.2236.

The peptide forming step (deprotection and coupling). To a solution of ionic liquid supported Boc-peptide (2 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The reaction was stirred at room temperature under nitrogen for 0.5h. Upon concentration under reduced pressure, the residue was washed twice with ether and dried on vacuum line to yield the deprotected ionic liquid supported peptide as TFA salt. The residue was then dissolved together with the next Boc-protected amino acid (3 mmol) and PyBOP (3 mmol) in CH_3CN (35 mL). DIPEA (6 mmol) was added dropwise and the resulting reaction mixture was stirred at 35°C under nitrogen atmosphere for 8 h. The solvent was removed under vacuum and the residue was washed firstly with ether (20 mL $\times$ 3), then dissolved in CH_2Cl_2 and washed with water (10 mL $\times$ 3). The organic phase was dried over Na_2SO_4 and concentrated to afford the ionic liquid supported Boc-peptide which was of sufficient purity and could be used directly for the next cycle of peptide synthesis. The product could be further purified, if desired, by dissolving the compound in acetone, filtered through a short pad of silica gel, and evaporation of the solvent.

Ionic liquid supported leucine TFA salt 3a: ^1H NMR (400 MHz, Acetone- d_6) δ 9.20 (s, 0.55H), 9.12 (s, 0.45H), 7.85 (s, 1H), 7.68 (s, 1H), 5.02-4.98 (m, 0.45H), 4.75-4.58 (m, 4H), 4.27-4.25 (m, 0.55H), 4.05 (s, 3H), 1.90-1.87 (m, 2H), 1.73-1.70 (m, 1H), 0.95 (d, $J = 6.0$ Hz, 3H), 0.93 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, Acetone- d_6) δ 169.4 (0.55C), 167.7 (0.45C), 138.0 (0.55C), 137.8 (0.45C), 124.4, 123.6 (0.45C), 123.5 (0.55C), 65.1 (0.45C), 64.9 (0.55C), 52.2, 48.9, 39.8 (0.55C), 39.4 (0.45C), 36.4, 25.1 (0.45C), 24.8 (0.55C), 22.7 (0.45C), 22.3 (0.55C), 22.1 (0.55C), 21.6 (0.45C); HRMS (FAB) calcd. for $\text{C}_{24}\text{H}_{44}\text{N}_6\text{O}_4\text{BF}_4$ ($2\text{M}^+ + \text{BF}_4^-$) 567.3450, found 567.3453.

Ionic liquid supported Leu-Boc-phenylalanine 4a: foam-like pale yellow solids; ^1H NMR (400 MHz, Acetone- d_6) δ 9.04 (s, 1H), 7.81 (s, 1H), 7.70 (s, 1H), 7.67 (d, br, J = 6.8 Hz, 1H), 7.29-7.20 (m, 5H), 6.20 (d, br, J = 8.0 Hz, 1H), 4.69-4.66 (m, 2H), 4.64-4.52 (m, 2H), 4.44-4.37 (m, 2H), 4.08 (s, 3H), 3.19-2.91 (m, 2H), 1.72-1.58 (m, 3H), 1.35 (s, 9H), 0.92 (d, J = 6.0 Hz, 3H), 0.89 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, Acetone- d_6) δ 172.9, 172.4, 156.5, 138.2, 132.6, 129.9 (2C), 128.8 (2C), 127.0, 124.5, 123.5, 79.4, 63.4, 56.6, 51.6, 49.4, 40.4, 38.3, 36.7, 28.4 (3C), 25.2, 23.2, 21.6; HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{39}\text{N}_4\text{O}_5$ (M^+) 487.2920, found 487.2920. Treatment with trifluoroacetic acid afforded the **ionic liquid supported Leu-phenylalanine TFA salt 6:** ^1H NMR (300 MHz, Acetone- d_6) δ 9.33 (s, br, 0.6H), 9.25 (s, br, 0.4H), 7.87 (s, br, 1H), 7.72 (s, br, 0.6H), 7.67 (s, br, 0.4H), 7.28-7.25 (m, 5H), 5.38-5.33 (m, 0.4H), 4.70-4.50 (m, 4H), 4.40-4.34 (m, 1.6H), 4.07 (s, 1.8H), 4.00 (s, 1.2H), 3.55-3.26 (m, 2H), 1.82-1.70 (m, 2H), 1.58-1.53 (m, 1H), 0.92 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, Acetone- d_6) δ 172.2, 172.0, 138.7 (0.6C), 138.5 (0.4C), 136.5 (0.6C), 135.6 (0.4C), 130.5 (0.8C), 130.4 (1.2C), 129.3 (1.2C), 129.2 (0.8C), 128.0 (0.6C), 127.9 (0.4C), 124.5, 123.6 (0.4C), 123.5 (0.6C), 63.6 (0.4C), 63.5 (0.6C), 54.9, 52.1 (0.6C), 52.0 (0.4C), 49.5 (0.6C), 49.4 (0.4C), 40.3 (0.4C), 39.9 (0.6C), 38.2 (0.6C), 37.4 (0.4C), 36.6, 25.2 (0.6C), 25.1 (0.4C), 23.1, 21.6 (0.4C), 21.5 (0.6C); HRMS (FAB) calcd. for $\text{C}_{21}\text{H}_{31}\text{N}_4\text{O}_3$ (M^+) 387.2395, found 387.2396.

Ionic liquid supported Leu-Phe-Boc-glycine 7: foam-like pale yellow solids; ^1H NMR (300 MHz, Acetone- d_6) δ 9.04 (s, 1H), 7.78 (t, J = 1.8 Hz, 1H), 7.66 (t, J = 1.8 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.30-7.18 (m, 5H), 6.46 (m, 1H), 4.73-4.65 (m, 3H), 4.54-4.51 (m, 2H), 4.45-4.38 (m, 1H), 4.06 (s, 3H), 3.78-3.61 (m, 2H), 3.24-3.00 (m, 2H), 1.71-1.56 (m, 3H), 1.39 (s, 9H), 0.90 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, Acetone- d_6) δ 171.7 (2C), 170.3, 156.7, 137.7, 137.5, 129.4 (2C), 128.6 (2C), 126.8, 124.1, 123.0, 79.3, 63.1, 54.9, 51.3, 48.9, 44.4, 39.9, 37.4, 36.2, 28.0 (3C), 24.7, 22.7, 21.2; HRMS

(FAB) calcd. for $C_{28}H_{42}N_5O_6$ (M^+) 544.3134, found 544.3135. Treatment with trifluoroacetic acid afforded the **ionic liquid supported Leu-Phe-glycine TFA salt 8**: 1H NMR (300 MHz, Acetone- d_6) δ 9.13 (s, 1H), 7.80 (s, 1H), 7.68 (s, 1H), 7.32-7.20 (m, 5H), 4.66-4.50 (m, 7H), 4.41-4.39 (m, 1H), 4.06 (s, 3H), 3.25-2.96 (m, 2H), 1.77-1.68 (m, 2H), 1.59-1.54 (m, 1H), 0.92 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, Acetone- d_6) δ 172.4, 172.3, 172.2, 138.4 (0.5C), 138.3 (0.5C), 138.2 (0.5C), 138.0 (0.5C), 130.0 (2C), 128.94 (1C), 128.91 (1C), 127.22 (0.5C), 127.17 (0.5C), 124.57 (0.5C), 124.54 (0.5C), 123.44 (0.5C), 123.40 (0.5C), 63.4, 56.8 (0.5C), 56.6 (0.5C), 51.6 (0.5C), 51.5 (0.5C), 49.5 (0.5C), 49.3 (0.5C), 42.8, 39.9 (0.5C), 39.8 (0.5C), 38.4 (0.5C), 38.3 (0.5C), 36.6, 25.2 (0.5C), 25.16 (0.5C), 23.17 (0.5C), 23.15 (0.5C), 21.5 (0.5C), 21.4 (0.5C); HRMS (FAB) calcd. for $C_{23}H_{34}N_5O_4$ (M^+) 444.2609, found 444.2611.

Ionic liquid supported Leu-Phe-Gly-Boc-glycine 9: foam-like pale yellow solids; 1H NMR (300 MHz, Acetone- d_6) δ 9.09 (s, 1H), 8.12 (m, br, 1H), 7.80 (t, J = 1.8 Hz, 1H), 7.68 (t, J = 1.8 Hz, 1H), 7.64 (m, 1H), 7.61 (m, 1H), 7.30-7.21 (m, 5H), 6.57 (m, 1H), 4.76-4.59 (m, 3H), 4.54-4.51 (m, 2H), 4.40-4.33 (m, 1H), 4.08 (s, 3H), 3.82-3.75 (m, 4H), 3.33-2.95 (m, 2H), 1.89-1.55 (m, 3H), 1.43 (s, 9H), 0.94 (d, J = 6.0 Hz, 3H), 0.89 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, Acetone- d_6) δ 171.9, 171.8, 171.6, 169.8, 156.9, 138.0, 137.8, 129.1 (2C), 128.6 (2C), 126.7, 124.1, 123.0, 79.4, 63.1, 55.6, 51.4, 48.9, 44.6, 43.8, 39.9, 37.3, 36.3, 28.2 (3C), 24.7, 22.9, 21.2; HRMS (FAB) calcd. for $C_{30}H_{45}N_6O_7$ (M^+) 601.3348, found 601.3350. Treatment with trifluoroacetic acid afforded the **ionic liquid supported Leu-Phe-Gly-glycine TFA salt 10**: 1H NMR (400 MHz, Acetone- d_6) δ 9.10 (s, 1H), 7.81 (s, 1H), 7.70 (s, 1H), 7.28-7.20 (m, 5H), 4.75-4.67 (m, 5H), 4.58-4.50 (m, 2H), 4.43-4.38 (m, 1H), 4.08 (s, 3H), 3.89-2.87 (m, 2H), 3.23-3.04 (m, 2H), 1.65-1.58 (m, 3H), 0.92 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, Acetone- d_6) δ 171.9, 171.7, 137.9, 129.4, 129.3 (2C), 128.4 (2C), 126.7, 124.0, 123.0, 63.0, 55.8, 50.8, 49.3, 48.9, 43.5, 39.7, 37.3, 36.3, 24.8, 22.7, 21.2.; HRMS (FAB) calcd. for $C_{25}H_{37}N_6O_5$ (M^+) 501.2826, found 501.2825.

Ionic liquid supported Leu-Phe-Gly-Gly-Boc-tyrosine 11: foam-like pale yellow solids; ^1H NMR (400 MHz, Acetone- d_6) δ 9.08 (s, 1H), 8.21 (s, br, 1H), 8.07 (s, br, 1H), 7.80 (s, 1H), 7.68 (d, $J = 7.2$ Hz, 1H), 7.67 (s, 1H), 7.56 (d, $J = 7.2$ Hz, 1H), 7.34-7.20 (m, 5H), 7.15 (d, $J = 8.0$ Hz, 2H), 6.90 (d, $J = 8.0$ Hz, 2H), 6.49 (d, $J = 7.2$ Hz, 1H), 4.76-4.56 (m, 3H), 4.54-4.51 (m, 2H), 4.40-4.33 (m, 2H), 4.08 (s, 3H), 3.96-3.66 (m, 4H), 3.31-2.91 (m, 4H), 1.85-1.70 (m, 2H), 1.62-1.55 (m, 1H), 1.36 (s, 9H), 1.30 (s, 9H), 0.94 (d, $J = 6.0$ Hz, 3H), 0.89 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, Acetone- d_6) δ 174.0, 171.9, 171.7, 171.3, 169.8, 156.4, 154.5, 138.1, 137.8, 132.2, 129.9(2C), 129.3 (2C), 128.6 (2C), 126.7, 124.1, 124.0 (2C), 122.9, 79.6, 77.9, 63.2, 57.2, 56.0, 51.4, 48.5, 44.0, 43.8, 39.8, 37.4, 37.0, 36.3, 28.6 (3C), 28.1 (3C), 24.8, 22.9, 21.2; HRMS (FAB) calcd. for $\text{C}_{43}\text{H}_{62}\text{N}_7\text{O}_9$ (M^+) 820.4605, found 820.4609.

Determination of degree of racemization in the loading and peptide forming steps.

Preparation of ionic liquid supported Leu-Phe-Boc 4a-d: **4a-d** were prepared from the reactions of ionic liquid supported leucine **2a-b** (L- and D-enantiomer) with Boc-L-phenylalanine and Boc-DL-phenylalanine using the general procedure for peptide formation (page S3). **4a:** L, L-epimer, **4b:** D, L-epimer, **4c:** L, DL-epimers and **4d:** D, DL-epimers.

Methyl N-(tert-Butyloxycarbonyl)-phenylalanyl-leucinate 5a-d: **4a** (0.1 mmol) from the previous step was dissolved in ammonia-saturated methanol (2 mL). The resulting solution was then stirred at room temperature overnight. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel 230-400 mesh, hexane-ethyl acetate gradient) to afford dipeptide product **MeO-Leu(L)-Phe(L)-Boc 5a-(L, L)**. In the same manner, dipeptides **MeO-Leu(D)-Phe(L)-Boc 5b-(D,L)**, **MeO-Leu(L)-Phe(DL)-Boc 5c-(L,DL)** and **MeO-Leu(D)-Phe(DL)-Boc 5d-(D,DL)** were also prepared. HPLC analysis: Diacel Chiralcel

OD-H column, 5% isopropanol in hexane, 0.5 mL/min, $\lambda = 220$ nm, t_R (L, L-epimer): 13.3 min, t_R (D, L-epimer): 13.4 min; t_R (L, D-epimer): 15.7 min; t_R (D, D-epimer): 22.2 min; Diacel Chiralcel OD-J column, 5% isopropanol in hexane, 0.3 mL/min, $\lambda = 220$ nm, t_R (L, L-epimer): 16.0 min, t_R (D, L-epimer): 17.4 min.

MeO-Leu(L)-Phe(L)-Boc 5a-(L, L)¹: white solids, m.p. 101-103 °C (lit.¹: m.p. 101-104 °C). ¹H NMR (400 MHz, Acetone-*d*₆) δ 7.52 (d, $J = 7.6$ Hz, 1H), 7.26-7.18 (m, 5H), 6.07 (d, $J = 8.0$ Hz, 1H), 4.56-4.50 (m, 1H), 4.42-4.38 (m, 1H), 3.68 (s, 3H), 3.20-2.88 (m, 2H), 1.75-1.68 (m, 1H), 1.62-1.58 (m, 2H), 1.35 (s, 9H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.91 (d, $J = 6.4$ Hz, 3H). HPLC analysis showed no detectable amount of D, L-epimer, L, D-epimer and D, D-epimer.

MeO-Leu(D)-Phe(L)-Boc 5b-(D,L)¹: colorless crystals, m.p. 136-138 °C. ¹H NMR (400 MHz, Acetone-*d*₆) δ 7.44 (d, $J = 7.2$ Hz, 1H), 7.28-7.18 (m, 5H), 6.06 (d, $J = 8.0$ Hz, 1H), 4.48-4.42 (m, 1H), 4.41-4.35 (m, 1H), 3.66 (s, 3H), 3.11-2.93 (m, 2H), 1.55-1.52 (m, 3H), 1.36 (s, 9H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.87 (d, $J = 6.4$ Hz, 3H). HPLC analysis showed no detectable amount of L, L-epimer, L, D-epimer and D, D-epimer.

The peptide liberation step. To a mixture of the ionic liquid supported pentapeptide **11** (180 mg, 0.2 mmol) in THF/H₂O (1:2, v/v, 3.0 ml) was added 1M NaOH aqueous solution (0.2 mL). The mixture was stirred at room temperature for 5 h. The volatile component was removed under reduced pressure and the residue solution was acidified to pH 5-6. The precipitate was washed twice with distilled water and dried on the vacuum line to give 120 mg (85%) of **Boc-pentapeptide 12** as foam-like pale yellow solids. ¹H NMR (400 MHz, Acetone-*d*₆) δ 8.01 (s, br, 1H), 7.80 (s, br, 1H), 7.65 (d, $J = 6.8$ Hz, 2H), 7.30-7.15 (m, 5H), 7.17 (d, $J = 8.0$ Hz, 2H), 6.89 (d, $J = 8.0$ Hz, 2H), 6.43 (d, $J = 7.2$ Hz, 1H), 4.76-4.74 (m, 1H), 4.52-4.47 (m, 1H), 4.42-4.39 (m, 1H), 4.01-3.74 (m, 4H), 3.28-2.90 (m, 4H), 1.79-1.65 (m, 3H), 1.35 (s, 9H), 1.30 (s, 9H), 0.94

(d, $J = 6.0$ Hz, 3H), 0.92 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, Acetone- d_6) δ 173.5, 173.2, 171.4, 170.0, 169.0, 156.1, 154.3, 138.0, 132.6, 130.0 (2C), 129.6 (2C), 128.4 (2C), 126.5, 124.0 (2C), 79.2, 77.8, 56.8, 54.9, 51.1, 43.5, 43.1, 40.8, 37.9, 37.3, 28.7 (3C), 28.2 (3C), 25.0, 23.0, 21.5; HRMS (FAB) calcd. for $\text{C}_{37}\text{H}_{53}\text{N}_5\text{O}_9\text{Na}$ (M+Na) 734.3741, found 734.3742. Boc protected oligopeptide **12** (117 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (1.5 mL), then TFA (1.5 mL) and several drops of anisole were added. The mixture was stirred at ambient temperature under nitrogen atmosphere for 0.5 h. Evaporation and washing with ether gave **Leu⁵-enkephalin TFA salt 14^{II}** (109mg, 99%) as pale yellow solids, m.p. 148-152 °C (authentic sample m.p. 150-153 °C); $[\alpha]^{20}_{\text{D}} = 25.0$ (c 0.8, 95% AcOH), authentic sample $[\alpha]^{20}_{\text{D}} = 25.6$ (c 0.9, 95% AcOH); HPLC $t_{\text{R}} = 16.0$ min, (authentic sample $t_{\text{R}} = 15.7$ min), Agilent Zorbax SB-CN Semi-prep column; eluent, 0-5 min, H_2O -0.05% TFA (v/v), 6-15 min, 0-60% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ -0.05% TFA (v/v/v), 16-23 min, 60-100% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ -0.05% TFA (v/v/v); post time, 7 min; flow rate, 3.0 ml/min; ^1H NMR (400 MHz, Methanol- d_4) δ 7.24-7.21 (m, 4H), 7.18-7.15 (m, 1H), 7.08 (d, $J = 8.4$ Hz, 2H), 6.77 (d, $J = 8.4$ Hz, 2H), 4.71-4.67 (m, 1H), 4.42-4.39 (m, 1H), 4.07 (t, $J = 7.2$ Hz, 1H), 3.96-3.72 (m, 4H), 3.19-2.92 (m, 4H), 1.71-1.61 (m, 3H), 0.94 (d, $J = 6.0$ Hz, 3H), 0.90 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, Methanol- d_4) δ 175.1, 173.1, 171.0, 170.6, 170.4, 158.0, 138.0, 131.3 (2C), 130.2 (2C), 129.2 (2C), 127.5, 125.8, 116.8 (2C), 56.2, 55.6, 52.3, 43.9, 43.4, 41.7, 39.0, 37.7, 26.0, 23.2, 22.0; HRMS (FAB) calcd. for $\text{C}_{28}\text{H}_{37}\text{N}_5\text{O}_7\text{Na}$ (M+Na) 578.2592, found 578.2591.

FIGURE 1 ^1H NMR spectra of ionic liquid supported peptide **2a**, **4a**, **7**, **9** and **11**

FIGURE 2 Mass spectra of ionic liquid supported peptide **2a**, **4a**, **7**, **9** and **11**

^I Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055-3056.

^{II} a) Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929-932; b) vilkas, E.; vilkas, M.; Sainton, J. *Int. J. Pept. Protein Res.* **1980**, *15*, 29-31; c) Carpino, L. A.; Gao, H.-S.; Ti, G.-S.; Segev, D. *J. Org. Chem.* **1989**, *54*, 5887-5897.