Monatshefte für Chemie - Chemical Monthly
https://doi.org/10.1007/s00706-020-02670-x

ORIGINAL PAPER

Synthesis of novel proline-based imidazolium ionic liquids

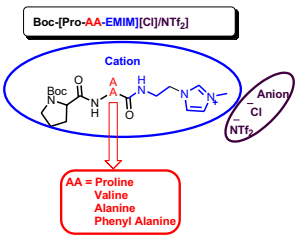
Snehkrishn A. Chaubey[1] · **Niranjan Patra**[1] · **Roli Mishra**[1]

Received: 28 April 2020 / Accepted: 10 August 2020

Abstract

A series of eight novel proline functionalized dipeptide imidazolium ionic liquids (DPILs), i.e. Boc-[Pro-Pro-EMIM], Boc-[Pro-Val-EMIM], Boc-[Pro-Ala-EMIM], Boc-[Pro-Phe-EMIM] containing [Cl] and [NTf_2] anions were synthesized via a facile reaction of 2-chloroethylamine with four different dipeptides (Boc-Pro-Pro-OH, Boc-Pro-Val-OH, Boc-Pro-Ala-OH, and Boc-Pro-Phe-OH) followed by reaction with 1-methylimidazole and subsequent anion exchange. The synthesized ILs revealed similar characteristics of a conventional imidazolium ILs. The synthesized ILs were investigated by ^{1}H NMR, ^{13}C NMR, FT-IR, mass spectroscopy, TGA, and DSC. TGA revealed an improved thermal stability for NTf_2 over chloride ion. DSC revealed a melting temperature less than 100 °C.

Graphic abstract



Keywords Proline · Dipeptide ionic liquids · Imidazolium · Amino acid-based ionic liquids · Physicochemical properties

Introduction

Amino acid-based ionic liquids (AAILs) have drawn tremendous attention of researchers due to their potential structural and biocompatible properties [1–5]. Amino acids (AAs) can be easily converted into cations and anions in ILs since they have side chains/functional groups as well as chiral properties which can define their wide range of physicochemical and biological properties. These properties make them suitable to find applications as electrochemical sensors, super capacitors, biocatalytic reactions, biosensors, bio preservation as well as protein solubilization, stabilization and crystallization [6], miscibility with water and/or organic solvents [7], melting point [8–12]. AAILs have also been shown to have excellent CO_2 absorption and membrane transport properties [13–18].

There are quite a few reports in which amino acids have been used as cations [19]. Amino acids and their ester salts [AAE] [NO_3/Sac] based ionic liquids have been reported by Kou et al. [20]. In most cases, synthesized AAILs and amino acids are used as anions [21, 22]. Various imidazolium-based AAILs have been synthesized using 20 natural amino acids and imidazole. All the synthesized [EMIM][AA] ILs are stable up to 200 °C except the [EMIM][CYS]. Recently, AAILs with amino acids as the anions and phosphonium, choline, ammonium, and imidazolium as the cations have been reported [23, 24] to have interesting physicochemical and biological activities.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00706-020-02670-x) contains supplementary material, which is available to authorized users.

✉ Roli Mishra
roli.mishra@iar.ac.in; rolimishra2@gmail.com

[1] Department of Engineering and Physical Sciences, Institute of Advanced Research, Gandhinagar 382426, India

Published online: 10 September 2020

Subsequently, several other amino acid-based ILs have been synthesized such as glycine-based ILs [25], *N*-heterocyclic amino acid-derived ILs [26], valine, leucine, and alanine-based chiral imidazolium ILs [27], 4-HO-Pro-Val tagged 1-methylimidazolium ionic liquids as catalyst for asymmetric aldol reactions [28]. Amino acid choline-based ionic liquids (AACBILs), i.e. choline alanine ([CH][Ala]), choline β-alanine ([CH][β-Ala]), and choline phenylalanine ([CH][Phe]) were explored using the quantum mechanical calculations and also molecular dynamics simulations in both gas and liquid phases [29]. The properties of the [EMIM][GLY] ionic liquid with respect to fullerenes, graphene, and carbon nanotubes were studied using molecular dynamics simulations [30]. Amino acid (AAs) based ionic liquids (ILs) containing amino acids as anions, namely [TMA][AA] and [TBP][AA] showed good CO_2 absorption activity [31].

Presently the most commonly used amino acid-based ionic liquids contain amino acids as anions. There is limited evidence of amino acid-based ionic liquids where amino acids are used as cations instead of anions. Amino acid-based ionic liquids with L-proline as cations have been reported as chiral separation ligands [32]. Further, Xiao et al. synthesized poly-L-cysteine-bearing imidazolium salts; Hu et al. presented L-glutamate-based polypeptide ILs; while Guillen et al. depicted (*S*)-histidine-bearing imidazolium ILs [33–35]. L-Valine-based alkyl chain-appended 1,2,3-triazolium room temperature chiral ILs (CILs) with iodide and hexafluorophosphate anions were synthesized and characterized [36]. The longer alkyl chain containing CILs displayed facile self-aggregation, whereas both short and long alkyl chains containing CILs showed pre-micellar aggregation. Herein, we report a facile approach to synthesize a novel peptide-based imidazolium ILs in which peptides are present as cations. These peptide-based imidazolium ILs exhibit improved thermal and structural properties. To the best of our knowledge, this is the first report of synthesis on proline-based dipeptide imidazolium ILs.

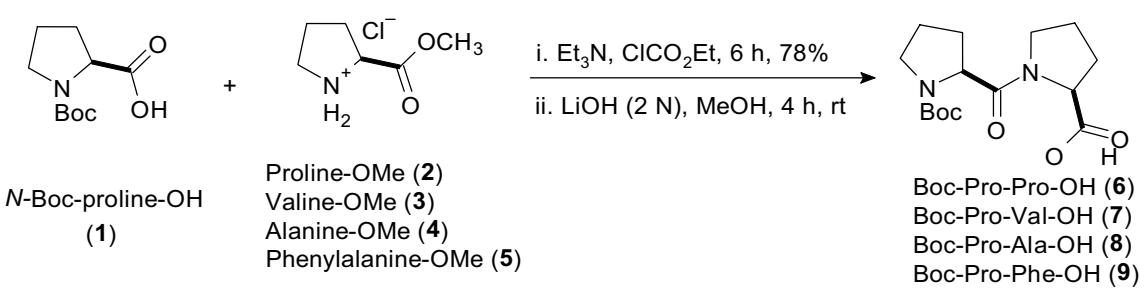
Results and discussion

Syntheses of dipeptide-based imidazolium ionic liquids were carried out as shown in Schemes 1 and 2. Boc-Pro-OH was coupled with H-Pro-OMe.HCl/H-Val-OMe HCl/H-Ala-OMe.HCl/H-Phe-OMe.HCl using ethyl chloroformate. The resulting dipeptides were hydrolyzed with NaOH to produce dipeptides **6–9** with free carboxylic acid (Scheme 1).

Subsequently these peptides **6–9** with free carboxylic acid were coupled with chloroethylamine hydrochloride using ethyl chloroformate and triethylamine to yield 2-chloroethylamide containing dipeptides Boc-Pro-Pro-2-chloroethylamide, Boc-Pro-Pro-2-chloroethylamide, Boc-Pro-Val-2-chloroethylamide, Boc-Pro-Ala-2-chloroethylamide (**10–13**), respectively. Quaternization of 1-methylimidazole with Boc-Pro-Pro-2-chloroethylamide, Boc-Pro-Pro-2-chloroethylamide, Boc-Pro-Val-2-chloroethylamide, Boc-Pro-Ala-2-chloroethylamide (**10–13**) furnished Boc-[Pro-Pro-EMIM][Cl]/Boc-[Pro-Val-EMIM]-[Cl]/Boc-[Pro-Ala-EMIM][Cl]/Boc-[Pro-Phe-EMIM][Cl] (**14–17**, Scheme 2). Then, the halide ion of these salts was exchanged with $LiNTf_2$ (trifluoromethanesulfonimide lithium salt) to yield dipeptide-based imidazolium ionic liquids with NTf_2 anion **18–21** (Scheme 2).

The structure and purity of the synthesized DPILs were confirmed with ^{1}H NMR, ^{13}C NMR, FT-IR, and ESI spectroscopy. FT-IR spectra of the DPILs exhibited a characteristic absorption band for amide N–H symmetric stretching around at 3320–3255 cm^{-1}. The aliphatic $–CH_2$ and $–CH_3$ (aliphatic C–H stretching) bands appeared at 2837–2950 cm^{-1} region. The presence of the amide carbonyl group (CO–NH) was indicated by a strong band at 1643 cm^{-1}. The presence of C–N bond stretching in the region of 1165–1249 cm^{-1} was due to the formation of quaternary nitrogen of imidazole ring while peaks at 1643, 1563 cm^{-1} were due to –C = N bond of five-membered imidazolium ring. Additionally, the peaks at 1417 cm^{-1} were due to –C = C– bond and imidazolium ring. In IR spectrum of DPILs **18–21** with anion [NTf_2], the band at

Scheme 1

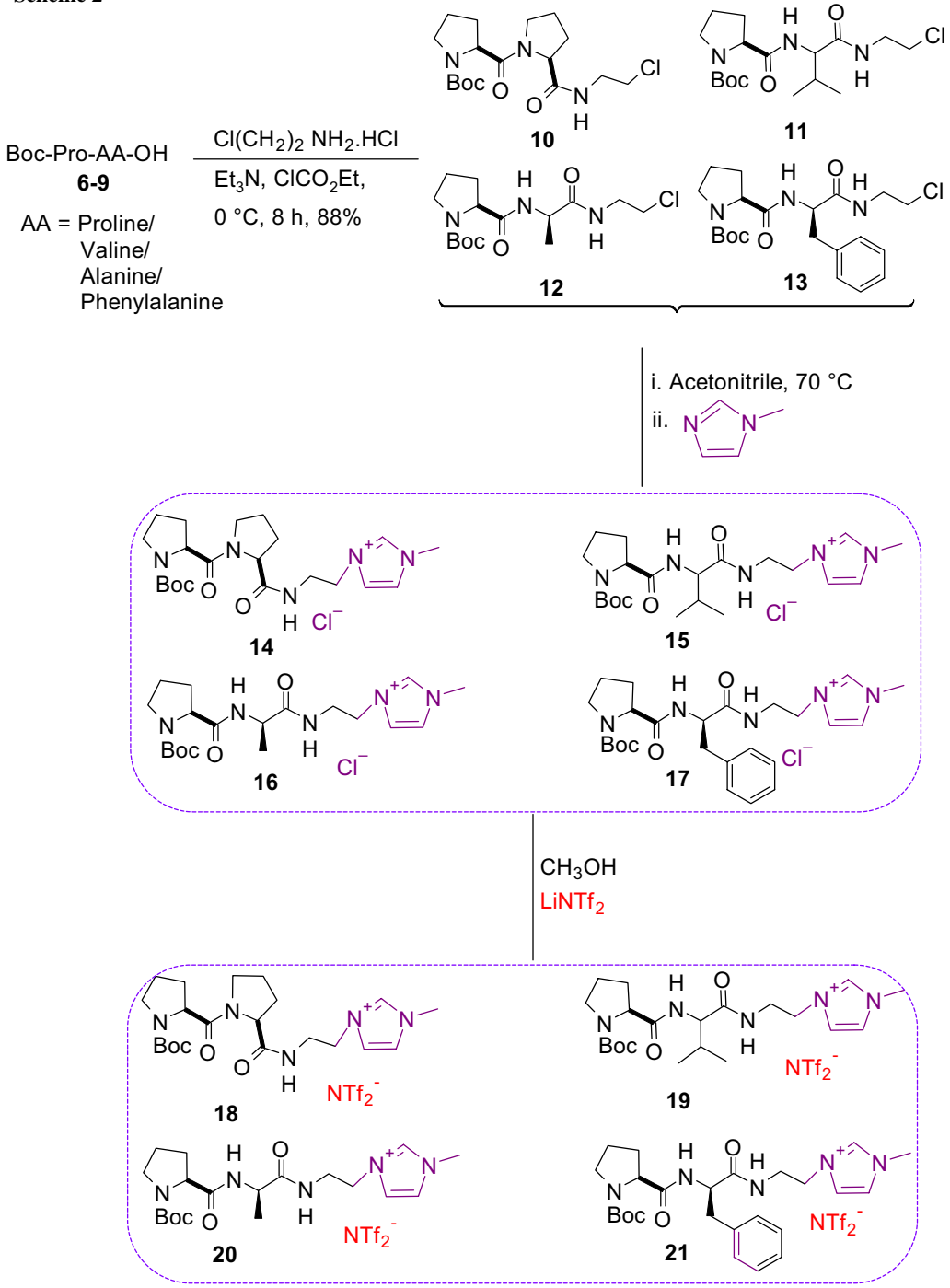


N-Boc-proline-OH (**1**)

Proline-OMe (**2**)
Valine-OMe (**3**)
Alanine-OMe (**4**)
Phenylalanine-OMe (**5**)

Boc-Pro-Pro-OH (**6**)
Boc-Pro-Val-OH (**7**)
Boc-Pro-Ala-OH (**8**)
Boc-Pro-Phe-OH (**9**)

Scheme 2



1120–1470 cm^{-1} corresponds to the SO_2 symmetric, CF_3 and SO_2 asymmetric stretching vibrations.

In ^1H NMR spectra of DPIL **14**, two methylenic protons (N–CH = CH = N) of imidazole ring appeared as multiplet from $\delta = 7.79$ to 7.73 ppm while for DPILs **15**, **16** methylenic protons appeared as multiplet from 7.98 to 7.78 ppm and in DPIL **17** two methylenic protons of imidazole ring appeared as multiplet from 8.08 to 8.33 ppm, respectively. The single proton (N = CH–N) in imidazole ring appeared as a multiplet in the range of 8.95–9.23 ppm for compound **14**, 9.2–9.12 ppm for DPILs **15**, **16**, and 9.08–9.25 for DPIL **17**. For DPIL **17**, the five aromatic protons appeared as multiplet in the range of 7.76–7.17 ppm. The 9H protons of *tert*-butyl chain of Boc in all ILs **14–17** were observed in the region of 1.29–1.40 ppm. – CH_3 group attached via imidazole ring displayed doublet peak for IL **14** at 3.85 ppm with coupling constant $J = 7.0$ Hz and singlet at 3.86 and 3.75 ppm for **15**, **16**, and **17**.

^{13}C NMR signals in the range of $\delta = 48.1–48.7$ ppm displayed the formation of quaternary nitrogen in DPILs **14**–**17**. The two carbons (−CH=CH−) of imidazole ring in ILs appeared in the range of 123.2–123.3 ppm, while third carbon as −N–C=N− appeared in the range of 137.1–137.8 ppm. The two carbon peaks in DPILs **18**–**21** at 124 ppm and 117 ppm corresponding to the anion [NTf_2], while ^{19}F peak for anion [NTf_2] was found at −78.676, −78.678, −78.683, and −78.675 ppm in DMSO. ESI–MS positive mode spectra of the synthesized DPILs **14**–**17** exhibited the molecular ion peaks at *m/z* = 421.2852, 423.2817, 395.2613, and 471.3048, confirming their molecular masses.

The water content of the DPILs viz. Boc-[Pro-Pro-EMIM], Boc-[Pro-Val-EMIM], Boc-[Pro-Ala-EMIM], and Boc-[Pro-Phe-EMIM] measured by coulometric titration system were 0.02, 0.02, 0.04, and 0.02%, respectively. The water content was constantly kept as low as possible by continuously working under high vacuum environment since the presence of water could lower the maximum solubility significantly.

The entire synthesized DPILs showed good solubility in polar solvents like H_2O, DMSO, CH_3OH, C_2H_5OH, and CH_3CN. Thus the synthesized peptide-based ionic liquids which eliminate the use of traditional solvent vehicles may have immense potential for effective formulation of poorly water-soluble drugs.

Thermal properties of proline-based dipeptide imidazolium ionic liquids **14**–**21** were measured by TGA and DSC are summarized in Table 1. The temperature-ramped TGA experiments were performed in triplicate for each ionic liquid in order to validate the reproducibility of the T_{onset} measurement. TGA revealed a clear improvement in thermal stability of the NTf_2 (bis(trifluoromethane)sulfonimide) (Fig. 1b) as compared to the Cl (Fig. 1a) because NTf_2 anion formed stronger hydrogen bond due to the presence of highly electronegative fluorine atom. TGA results obtained for the ionic liquid Boc-[Pro-Pro-EMIM][NTf_2] (**18**) showed the percent mass and the rate of mass loss as a function of the temperature. The thermal degradation of the compound was monitored as a large mass loss at

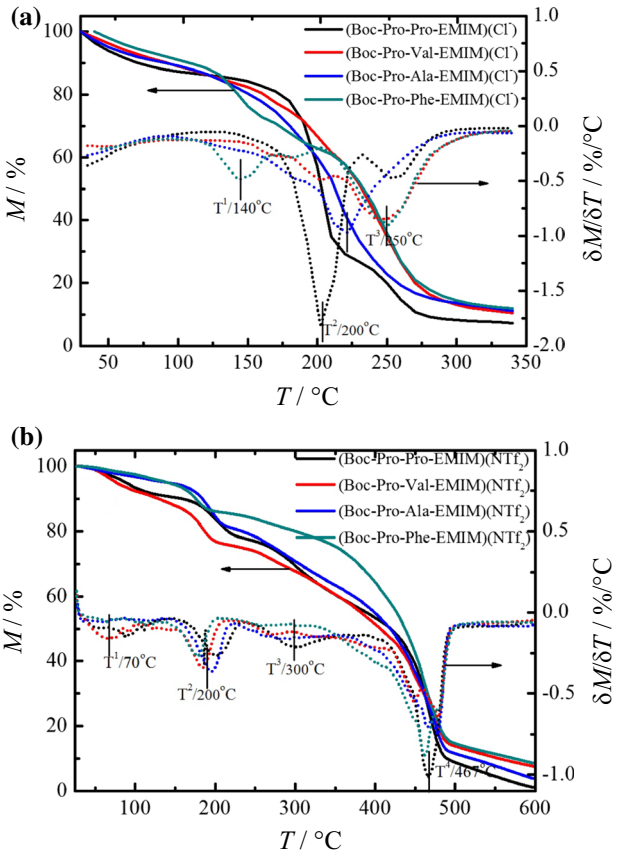


Fig. 1 TGA (solid line) and DTG (dotted line) of synthesized ionic liquid containing chloride and bis(trifluoromethyl)sulfonamide anions

385 °C (48.71%) due to decomposition of anion in dipeptide linkage.

Figure 2 shows the DSC curves of different dipeptide-based ionic liquids **14**–**17**. Figure 2a revealed a T_g of −42, −36, −34, and −21 °C for chloride anion-based peptide ionic liquids. A broad endothermic peak appeared at 95.30, 64.66, and 94.80 °C appears to be the melting point of the corresponding ILs. Thus it proves the ionic liquid characteristics of compounds **14**, **15**, **17**. That Boc-[Pro-Ala-EMIM][Cl] does not show any endothermic melting peak which reveals an amorphous nature of the compound.

Table 1 Thermophysical properties of synthesized proline-based dipeptide imidazolium ionic liquids (DPILs) **14**–**21**

Thermal properties	Compounds							
	14	**15**	**16**	**17**	**18**	**19**	**20**	**21**
T^{decom}/°C[a]	200	190	175	195	385	300	300	390
M.p. /°C[b]	95.30	64.66	ND	94.80	76	102	76.33	72
T_g^{onset}/°C[c]	−34	−42	−21	−36	ND	ND	ND	ND

ND not detected

[a]Onset of decomposition temperature monitoring by TGA (10 °C/min)

[b]Melting point

[c]Glass transition temperature

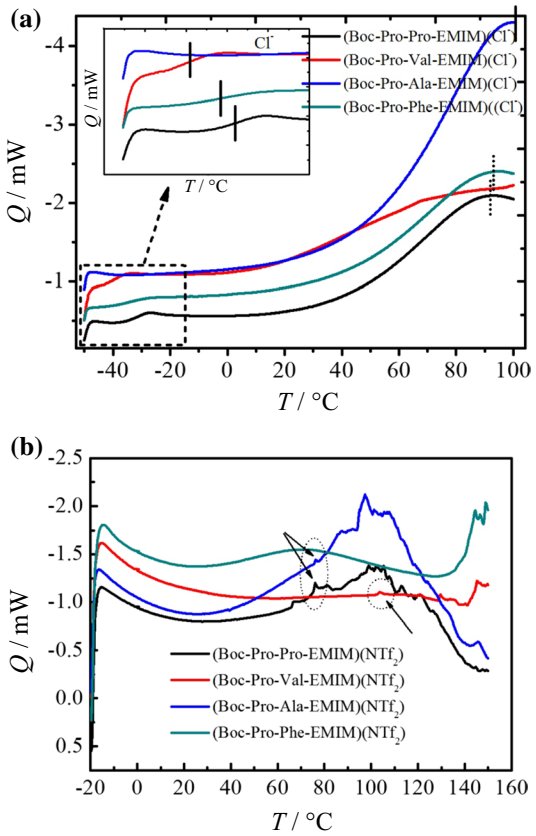


Fig. 2 DSC curve of synthesized ionic liquid containing chloride and bis(trifluoromethyl)sulfonamide anions

The bis(trifluromethanesulfonyl)imide (NTf_2) anion-based peptide ionic liquids DSC was performed from − 20 to 110 °C. Figure 2b does not reveal any T_g in the measured temperature zone which might appear by lowering the starting temperature in DSC. Dipeptide ionic liquids Boc-[Pro-Pro-EMIM][NTf_2], Boc-[Pro-Ala-EMIM)][NTf_2], and Boc-[Pro-Phe-EMIM][NTf_2] in Fig. 2b shows clear endothermic melting peaks at 76, 76.33, and 72 °C.

The results of DSC further prove and validate to be room temperature ionic liquids. The relatively straightforward synthetic procedure and the presence of chiral centers in the precursors are a remarkable advantage in our approach.

Conclusions

We have synthesized a series of novel dipeptide ionic liquids based on proline dipeptide and functionalized methylimidazolium having excellent yields and purity. The synthesized compounds were visibly transparent viscous liquids at room temperature. All the synthesized dipeptide ionic liquids Boc-[Pro-Pro-EMIM][Cl]/[NTf_2], Boc-[Pro-Val-EMIM][Cl]/[NTf_2], Boc-[Pro-Ala-EMIM][Cl]/[NTf_2], and Boc-[Pro-Phe-EMIM][Cl]/[NTf_2] exhibited improved thermal stabilities. The entire synthesized DPILs showed good solubility in polar solvents. Furthermore, the good yields, mild conditions, and suitable facile procedure confirmed that this method would play a vital role in synthesis of more diverse peptide-based chiral ionic liquids. Currently, we are investigating the effects of these peptide ionic liquids in organocatalyst reactions and design of tandem processes.

Experimental

All the reagents were commercially available and were used without further purification. All amino acids used were of the L-series. Solvents were purified according to the literature protocol and freshly distilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker NMR spectrometer at 400 MHz and 100 MHz, respectively. The Fourier transform infrared (FT-IR) spectra of the DPILs were recorded on a JASCO- 4700 FT-IR spectrophotometer in an attenuated total reflectance (ATR) mode. All spectra were obtained with accumulation of 32 scans in the wave number range of 4000–600 cm^{-1}. Moisture content was analyzed by Karl Fischer (Metrohm 860 KF coulometer) in solution combi columat fritles (500 cm^3) coulometric titration System. TGA was carried out using a thermogravimetric analyzer (TA SDT Q600) in nitrogen at a heating rate of 10 °C min^{-1} from 25 to 600 °C. DSC was performed in a METLER TOLEDO DSC1 from − 50 to 100 °C for chloride anion ionic liquids and − 20 to 160 °C for NTf_2 anion ionic liquids in an N_2 atmosphere.

Synthesis of dipeptide functionalized ILs

In a round bottom flask, 2.15 g Boc-Pro-OH (10 mmol) was taken and dissolved in 20 cm^3 anhydrous DCM. Then, 2.78 cm^3 Et_3N (20 mmol) was added to it followed by 1.14 cm^3 ethyl chloroformate (12 mmol). The reaction mixture was stirred at − 5 °C under nitrogen atmosphere for 30 min. The L-proline methyl ester hydrochloride (1.65 g, 10 mmol) was taken in another round bottom flask and dissolved in ~ 5 cm^3 DMF at 0 °C. Et_3N (1.52 cm^3, 11 mmol) was added to it and stirred at room temperature for 10 min. The free amino acid methyl ester in DMF was directly added to the freshly prepared mixed anhydride. Then, the reaction mixture was stirred at − 5 °C for 30 min and was brought to room temperature and stirred for 8–14 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with 100 cm^3 ethyl acetate, the organic layer was extracted using 50 cm^3 water, and the organic phase was washed with 50 cm^3 brine. The ethyl acetate layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to afford

Boc-Pro-Pro-OMe. The residue was then purified using column chromatography as reported in literature protocol [37].

The dipeptide methyl ester (Boc-Pro-Pro-OMe) was dissolved in methanol. Aqueous NaOH (2 M, 1.5 eq) was then added dropwise. The reaction mixture was stirred at room temperature for 4–6 h. The progress of the reaction was measured by TLC. After completion of the reactions, organic solvent was removed on a rotary evaporator and the pH of the aqueous solution was adjusted to 2–3 with 1 N HCl. The aqueous layer was washed twice with ethyl acetate. The organic layer was dried with $MgSO_4$and was concentrated to give desired crude product which was purified by silica gel (230–400 mesh) column chromatography eluting with a solution of ethyl acetate/hexane.

The dipeptides **7**, **8**, and **9** were prepared from the same procedure as the preparation of compound **6**.

(*S*)-1-[(*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carbonyl]pyrrolidine-2-carboxylic acid (Boc-Pro-Pro-OH, 6, $C_{15}H_{24}N_2O_5$) Yield: 65%; m.p.: 91 °C; column: EtOAc/hexane; TLC: $R_f = 0.24$ (EtOAc/hexane 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.65–4.15$ (m, 2H), 3.81–3.75 (m, 1H), 3.63–3.34 (m, 3H), 2.24–1.82 (m, 8H), 1.47–1.39 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.7$, 175.8, 155.9, 154.7, 154, 81.0, 80.4, 59.4, 59.3 (rotamer), 58.9, 58.6 (rotamer), 57.8, 57.6 (rotamer), 46.8, 46.7 (rotamer), 30.8, 30.0, 29.7, 29.4, 28.4, 28.3 (rotamer), 28.2, 28.1 (rotamer), 24.9, 24.2, 24.1,23.6 ppm.

(*S*)-1-[(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutanoyl]pyrrolidine-2-carboxylic acid (Boc-Pro-Val-OH, 7, $C_{15}H_{26}N_2O_5$) Yield: 78%; m.p.: 98 °C; column: EtOAc/hexane; TLC: $R_f = 0.20$ (EtOAc/hexane 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$ (br, s, 1H), 7.28 (br, s,1H), 7.01 (br, s, 1H), 4.49–4.41 (m, 1H), 4.25 (d, 1H, $J = 13.9$ Hz), 3.64–3.34 (m, 3H), 2.17–2.01 (m, 1H), 1.90–1.83 (m, 2H), 1.47–1.37 (m, 9H), 1.29–1.28 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.4$, 175.3, 173.0, 172.4, 155.8, 155.1, 80.7, 61.3, 59.7, 57.1, 48.1, 47.0, 31.9, 28.3, 24.6, 23.7, 20.7, 19.1 ppm.

(*S*)-2-[(*S*)-1-Carboxyethylcarbamoyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (Boc-Pro-Ala-OH, 8, $C_{13}H_{22}N_2O_5$) Yield: 69%; m.p.: 114 °C; column: EtOAc/hexane; TLC: $R_f = 0.36$ (EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$ (br, s,1H), 6.91 (br, s, 1H), 4.41 (dd, 1H, $J = 13.9$ Hz, 5.6 Hz), 4.13 (dd, 1H, $J = 13.9$ Hz, 5.6 Hz), 2.99 (dd, 1H, $J = 13.9$ Hz, 5.6 Hz), 2.94 (dd, 1H, $J = 13.9$ Hz, 5.6 Hz), 2.24–2.04 (m, 1H), 1.87 (br s, 2H), 1.60–1.24 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.3$, 172.9, 155.3, 80.9, 61.0, 59.8, 48.1, 47.1, 31.1, 136.1, 129.3, 128.4, 127.0, 81.4, 80.7, 61.0, 60.0, 52.9, 46.9, 31.1, 28.3, 24.5, 23.7 ppm.

1-(*S*)-2-[(*S*)-1-Carboxy-2-phenylethylcarbamoyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (Boc-Pro-Phe-OH, 9, $C_{19}H_{26}N_2O_5$) [38, 39] Yield: 74%; m.p.: 121 °C; column: EtOAc/hexane; TLC: $R_f = 0.32$ (EtOAc/hexane 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.77$ (br, s, 1H), 7.27–7.23 (m, 2H), 7.20–7.14 (m, 3H), 6.86 (br s, 1H), 4.86 (br s, 1H), 4.22 (br s, 1H), 3.35–3.24 (m, 2H), 3.06 (dd, 1H, $J = 13.9$ Hz, 5.6 Hz), 2.17 (m, 1H), 1.86 (m, 1H), 1.74 (br s, 2H), 1.39 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.0$, 172.9, 155.3, 136.1, 129.3, 128.4, 127.0, 81.4, 80.7, 61.0, 60.0, 52.9, 46.9, 37.5, 30.8, 29.7, 28.2, 24.3, 23.3 ppm.

Synthesis of the Boc-dipeptide-2-chloroethylamide 10

To the suspension of 0.312 g dipeptide Boc (Pro-Pro)-OH (**6**, 1 mmol) in 10 cm^3 CH_2Cl_2, 0.278 cm^3 Et_3N (2 mmol) was added at 10 °C. Then 0.286 cm^3 ethyl chloroformate (3 mmol) was added dropwise and stirred for 30 min at 0 °C. The 2-chloroethylamine hydrochloride salt (0.139 g, 1.2 mmol) was dissolved in 2–3 cm^3 DMF at 0 °C. Et_3N (0.167 cm^3, 11 mmol) was added to it and stirred at room temperature for 30 min. The free 2- chloroethylamine in DMF was directly added to freshly prepare mixed anhydride of Boc (Pro-Pro)-OH and stirred for 8–14 h at room temperature. Progress of reaction was monitored by TLC. The mixture was diluted with 50 cm^3 ethyl acetate and the solution was washed with water and saturated brine solution. The organic layer was dried over Na_2SO_4 and concentrated on rotary evaporator. The residue was purified by flash column chromatography on silica gel to give Boc-Pro-Pro-2-chloroethylamide (**10**).

The compounds **11**, **12**, and **13** were prepared using the same procedure as the preparation of compound **10**.

2-[2-(2-Chloroethylcarbamoyl)pyrrolidine-1-carbonyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (Boc-Pro-Pro-2-chloroethylamide, 10, $C_{17}H_{28}ClN_3O_4$) Yield: 57%; m.p.: 81 °C; column: EtOAc/hexane; TLC: $R_f = 0.60$ (EtOAc/hexane 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.51$ (br, s, 1H), 7.32 (br, s, 1H), 6.52 (br, s, 1H), 5.33(s, 1H), 4.84–3.38 (m, 8H), 1.89 (m, 4H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.7$, 80.9, 60.7, 59.9, 59.0, 47.0, 44.9, 43.7, 42.2, 41.2, 39.1, 31.1, 29.7, 28.5, 24.6, 23.8 ppm.

2-[1-(2-Chloroethylcarbamoyl)-2-methylpropylcarbamoyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (Boc-Pro-Val-2-chloroethylamide, 11, $C_{17}H_{30}ClN_3O_4$) Yield: 87%; m.p.: 113 °C; column: EtOAc/hexane; TLC: $R_f = 0.52$ (EtOAc/hexane 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$ (br, s, 1H), 7.02 (br, s, 1H), 6.28 (br, s, 1H), 4.33–4.22 (m, 3H), 3.59–3.42 (m, 8H), 2.36–1.85 (m, 8H), 1.47 (s, 9H), 0.96–0.89 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 172.2, 80.8, 77.1, 60.8, 58.4, 47.3,43.2, 41.3, 31.3, 29.1, 24.2, 19.4, 18.8, 17.0 ppm.

2-[1-(2-Chloroethylcarbamoyl)ethylcarbamoyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (Boc-Pro-Ala-2-chloroethylamide, 12, $C_{15}H_{26}ClN_3O$) Yield: 80%; m.p.: 69 °C; column: EtOAc/hexane; TLC: R_f = 0.29 (EtOAc/hexane 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (br, s, 1H), 7.21 (br, s, 1H), 7.01 (br, s, 1H), 6.83 (br, s, 1H), 4.49 (m, 1H), 3.64–3.34 (m, 6H), 2.17–1.83 (m, 5H), 1.45–1.37 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 80.7, 77.1, 60.6, 49.0, 47.3, 42.9, 41.4, 31.0, 29.7, 29.3, 28.9, 28.5, 28.4, 24.6, 17.7 ppm.

2-[1-(2-Chloroethylcarbamoyl)-2-phenylethylcarbamoyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (Boc-Pro-Phe-2-chloroethylamide, 13, $C_{21}H_{30}ClN_3O_4$) Yield: 85%; colorless liquid; column: EtOAc/hexane; TLC: R_f = 0.56 (EtOAc/hexane 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (br, s, 1H), 7.98 (m, s, 1H), 7.31–7.07 (m, 9H), 6.73 (s, 1H), 6.52 (s, 1H), 4.89–4.05 (m, 6H), 3.54–3.06 (m, 13H), 2.28 (s, 1H), 1.43–137 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 171.8, 170.9, 155.6, 136.4, 129.2, 128.6, 127.1, 80.7, 77.0, 60.9, 60.4, 59.7, 54.2, 53.2, 47.2, 42.5, 41.5, 38.9, 37.3, 29.5, 28.3, 24.4, 23.5, 21.0 ppm.

Synthesis of the (Boc-dipeptide ethyl methylimidazolium) chloride (14)

To 0.372 g Boc-Pro-Pro-2-chloroethylamide (**10**, 1 mmol), 0.82 g N-methylimidazole (1.1 mmol) was added and the mixture was stirred at 75 °C for ~ 24 h. After completion of the reaction, the solvent was removed by decantation and the obtained viscous solution was purified by column chromatography on silica gel using acetone and methanol as eluent to furnished yellowish color viscous liquid product **14**.

The compounds **15**, **16**, and **17** were prepared from the same procedure as the preparation of compound **14**.

1-[2-[[1-(1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl]amino]ethyl]-3-methyl-3*H*-imidazol-1-ium chloride (Boc-(Pro-Pro-EMIM)(Cl), 14, $C_{21}H_{34}ClN_5O_4$) Yield: 70%; column: acetone (100%); TLC: R_f = 0.55 (EtOAc/methanol 50/50); FT-IR (ATR): $\overline{\nu}$ = 3255, 2982, 2837, 2361, 1643, 1563, 1417, 1249, 1165, 1017 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.23–8.95 (m, 1H, Im), 8.33–8.16 (m, 1H, Im), 7.79–7.73 (m, 1H, Im), 7.69 (s, 1H, NH), 4.40–4.38 (m, 1H, Pro), 4.24–4.19 (m, 3H), 3.85 (d, 3H, J = 5.6 Hz, NCH_3), 3.57–3.37 (m, 6H, Pro), 2.10–1.72 (m, 8H, Pro), 1.39–1.32 (m, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.2, 171.1, 153.2, 137.2, 122.9, 78.3, 59.6, 57.4, 48.2, 46.6, 35.6, 29.5, 29.3, 28.3, 27.8, 24.6, 23.7, 23.2 ppm.

1-[2-[2-[(1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl]-amino)-3-methylbutyrylamino]ethyl]-3-methyl-3*H*-imidazol-1-ium chloride (Boc-(Pro-Val-EMIM)(Cl), 15, $C_{21}H_{36}ClN_5O_4$) Yield: 74%; column: acetone (100%); TLC: R_f = 0.55 (EtOAc/methanol 50/50); FT-IR (ATR): $\overline{\nu}$ = 3262, 2972, 2834, 2361, 1652, 1538, 1412, 1239, 1165, 1126, 1021, 920 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.2–9.12 (m, 1H, Im), 8.51–8.34 (m, 1H, Im), 7.98–7.78 (m, 1H, Im), 7.60 (s, 1H, NH), 6.89 (s, 1H, NH), 4.31–4.22 (m, 3H, CH_2 and Val), 4.05–3.95 (m, 1H, Pro), 3.86 (s, 3H, NCH_3), 3.58–3.28 (m, 4H), 2.13–2.09 (m, 1H, Val), 1.92–1.74 (m, 4H), 1.40–1.29 (m, 9H, Boc), 0.83–0.74 (m, 6H, Val) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 153.6, 137.4, 128.1, 123.3, 122.6, 120.5, 78.6, 58.8, 48.4, 46.6, 35.7, 32.8, 30.9, 29.9, 29.3, 28.0, 23.9, 23.1, 21.1, 19.1, 18.3 ppm.

1-[2-[2-[(1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl)-amino]propionylamino]ethyl]-3-methyl-3*H*-imidazol-1-ium chloride (Boc-(Pro-Ala-EMIM)(Cl), 16, $C_{19}H_{32}ClN_5O_4$) Yield: 60%; column: acetone (100%); TLC: R_f = 0.55 (EtOAc/methanol 50/50); FT-IR (ATR): $\overline{\nu}$ = 3233, 2983, 2837, 2361, 1650, 1544, 1416, 1248, 1165, 1018 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.18–9.07 (m, 1H, Im), 8.67–8.34 (m, 1H, Im), 8.18–7.99 (m, 1H, Im), 7.78–7.71 (m, 2H), 7.64 (s, 1H, NH-Im), 7.13–7.12 (s, 1H, NH), 6.91 (s, 1H, NH), 4.30–4.10 (m, 3H, Ala), 3.87–3.86 (m, 2H), 3.66 (s, 1H), 3.61–3.11 (br, s, water) 2.10–1.72 (m, 3H, Ala-CH_3), 1.39–1.11 (m, 9H, Boc) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5, 153.7, 137.4, 127.9, 123.0, 120.5, 78.6, 59.3, 48.3, 46.6, 35.7, 32.9, 30.9, 29.8, 28.0, 24.0, 23.2, 18.1, 17.4 ppm.

1-[2-[2-[(1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl)-amino]-3-phenylpropionylamino]ethyl]-3-methyl-3*H*-imidazol-1-ium chloride (Boc-(Pro-Phe-EMIM)(Cl), 17, $C_{25}H_{36}ClN_5O_4$) Yield: 74%; m.p.: 121 °C; column: EtOAc/hexane 4:6); TLC: R_f = 0.55 (EtOAc/methanol 50/50); FT-IR (ATR): $\overline{\nu}$ = 3255, 2950, 2837, 2360, 1651, 1557, 1414, 1243, 1165, 1018 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25-9.08 (m, 1H, Im), 8.80–8.68 (m, 1H, Im), 8.33–8.08 (m, 1H, Im), 8.23 (s, 1H, NH), 7.76–7.17 (m, 1H, Ar), 7.36 (s, 1H, NH), 7.30–7.17 (m, 4H, Ar), 4.50–4.36 (m, 1H), 4.26- 3.92 (m, 4H, CH_2), 3.75 (s, 3H, CH_3, Im), 3.57–3.22 (m, 4H, Pro & CH_2), 3.04–2.80 (m, 2H, Ar-CH_2), 2.09–1.58 (m, 4H, Pro), 1.29–1.12 (d, 9H, Boc) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.0, 153.6, 138.0, 137.4, 129.1, 128.0, 126.2, 124.6, 123.3, 122.6, 121.6, 78.7, 59.3, 54.2, 48.5, 46.6, 35.7, 33.8, 30.8, 29.7, 27.9, 23.8, 22.9 ppm.

Anion exchange procedure

The aqueous solution of Boc-(Pro-Pro-EMIM)(Cl) (**14**, 0.5 mmol) was dissolved in methanol and added to

bis(trifluoromethane)sulfonimide lithium salt (0.5 mmol) in methanol. The reaction mixture was stirred at room temperature for 2–3 h. The precipitates appeared in the reaction mixture was filtered to get corresponding ionic salts of Boc-(Pro-Pro-EMIM)(NTf_2) (**18**). The desired pure products were dried in vacuum for 24 h.

The compounds Boc-(Pro-Val-EMIM)(NTf_2) (**19**), Boc-(Pro-Ala-EMIM)(NTf_2) (**20**), and Boc-(Pro-Phe-EMIM)(NTf_2) (**21**) were prepared from the same procedure as the preparation of compound Boc-(Pro-Pro-EMIM)(NTf_2) (**18**). All the final products were obtained in high yield and purity levels.

1-[2-[[1-(1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl]amino]ethyl]-3-methyl-3*H*-imidazol-1-ium bis(trifluoromethylsulfonyl)imide (Boc-(Pro-Pro-EMIM)(NTf_2), 18, $C_{23}H_{34}F_6N_6O_8S_2$) Yield: 95%; FT-IR (ATR): $\overline{\nu}$ = 3334, 2945, 2908, 2832, 2163, 1987, 1678, 1451, 1417, 1352, 1197, 1134, 1020, 616, 571, 528, 509 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.93 (m, 1H, Im), 8.05–8.04 (m, 1H, Im), 7.69–7.76 (d, 2H, NH-Im), 4.39–4.36 (m, 1H, Pro), 4.20–4.15 (m, 4H), 3.83 (d, 3H, NCH_3), 3.73 (s, 1H), 3.61–3.43 (m, 4H, Pro), 2.49–1.66 (m, 10H, Pro), 1.39–1.32 (m, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.5,153.2, 137.1, 124.3, 122.7, 121.1, 117.9, 114.7, 78.5, 59.6, 57.6, 48.3, 46.5, 35.6, 29.2, 28.0, 24.6, 23.3 ppm; ^{19}F NMR (376 MHz, DMSO-d_6): δ = − 78.676 ppm.

1-[2-[2-[(1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl)-amino]-3-methylbutyrylamino]ethyl]-3-methyl-3*H*-imidazol-1-ium bis(trifluoromethylsulfonyl)imide (Boc-(Pro-Val-EMIM)(NTf_2), 19, $C_{23}H_{36}F_6N_6O_8S_2$) Yield: 97%; FT-IR (ATR): $\overline{\nu}$ = 3371, 2975, 1661, 1530, 1419, 1183, 1053, 743, 608, 506, 459 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.04–8.94 (m, 1H, Im), 8.28–8.10 (m, 1H, Im), 7.92–7.68 (m, 3H, Im), 7.14 (s, 1H, NH), 6.94 (s, 1H, NH), 4.21 (br, s, 2H, CH_2 & Val), 3.98–3.91 (m, 1H, Pro), 3.83 (s, 2H, NCH_3), 3.65 (s, 1H), 3.49–3.35 (br, d, 3H), 2.07–1.85 (m, 3H, Val), 1.38–1.27 (m, 9H), 0.78–0.77 (m, 6H, Val) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 137.2, 127.4, 123.0, 120.9, 117.8, 59.2, 57.9, 48.3, 46.5, 35.6, 33.0, 29.8, 28.0, 19.0, 17.7 ppm; ^{19}F NMR (376 MHz, DMSO-d_6): δ = − 78.678 ppm.

1-[2-[2-[(1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl)-amino]propionylamino]ethyl]-3-methyl-3*H*-imidazol-1-ium bis(trifluoromethylsulfonyl)imide (Boc-(Pro-Ala-EMIM)(NTf_2), 20, $C_{21}H_{32}F_6N_6O_8S_2$) Yield: 91%; FT-IR (ATR): $\overline{\nu}$ = 3321, 2944, 2832, 1678, 1450, 1416, 1354, 1197, 1136, 1021, 617, 571, 516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.01 (m, 1H, Im), 8.57–8.39 (m, 1H, Im), 8.15–8.05 (m, 2H, Im), 7.69–6.67 (d, 2H, Im-NH), 4.49–7.26 (m, 1H, NH), 4.21–4.07 (m, 4H, Pro), 3.96–3.34 (m, water), 2.07–1.76 (m, 3H, Ala-CH_3), 1.38–1.12 (m, 9H, Boc) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5, 136.9, 123.3, 122.4, 117.8, 59.3, 48.4, 46.4, 35.6, 34.5, 28.1, 28.0 ppm; ^{19}F NMR (376 MHz, DMSO-d_6): δ = − 78.683 ppm.

1-[2-[2-[(1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl)amino]-3-phenylpropionylamino]ethyl]-3-methyl-3*H*-imidazol-1-ium bis(trifluoromethylsulfonyl)imide (Boc-(Pro-Phe-EMIM)(NTf_2), 21, $C_{27}H_{36}F_6N_6O_8S_2$) Yield: 96%; FT-IR (ATR): $\overline{\nu}$ = 3748, 3318, 2944, 2832, 2511, 1996, 1767, 1692, 1451, 1415, 1198, 1117, 1021, 675, 616, 515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.96–8.92 (m, 1H, Im), 8.5 (s, 1H, Im), 8.30 (m, 1H, Im), 8.06–7.90 (m, 1H, NH), 7.66 (s, 1H, Ar), 7.48 (s, 1H), 7.38(s, 1H), 7.25–7.19 (m, 4H, Ar), 4.45 (br, 1H), 4.18–4.17 (br, 2H, CH_2), 4.03 (br, 1H, CH), 3.95–3.78 (m, 4H, CH_2-Pro), 3.02–2.76 (m, 2H, Ar-CH_2), 2.09–1.90 (m, 1H, Pro), 1.65–1.61 (br, 2H), 1.38–1.15 (m, 9H, Boc) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 136.7, 129.0, 128.0, 126.3, 123.4, 122.4, 121.0, 40.2, 117.8, 59.3, 35.7, 34.5, 28.0 ppm; ^{19}F NMR (376 MHz, DMSO-d_6): δ = − 78.675 ppm.

Acknowledgements We gratefully acknowledge financial support from the Department of Science and Technology-SERB New Delhi, (SERB/F/8435/2015-16). The author also thanks RSIC CDRI, Lucknow and IISc, Bangalore for the spectral analysis.

References

1. Greaves TL, Drummond CJ (2008) Chem Rev 108:206
2. Köddermann T, Wertz C, Heintz A (2006) Chem Phys Chem 7:1944
3. Endres F, El Abedin SZ (2006) Phys Chem Chem Phys 8:2101
4. Dupont J, Suarez PAZ (2006) Phys Chem Chem Phys 8:2441
5. Lungwitz R, Spange S (2008) New J Chem 32:392
6. Dupont J (2004) J Braz Chem Soc 15:341
7. Huddleston JG, Visser AE, Reichert WM, Willauer HD, Broker GA, Rogers RD (2001) Green Chem 3:156
8. Preiss U, Verevkin SP, Koslowski T, Krossing I (2011) Chem Eur J 17:6508
9. Holbrey JD, Seddon KR (1999) J Chem Soc Dalton Trans. https://doi.org/10.1039/A902818H
10. Shirota H, Mandai T, Fukazawa H, Kato T (2011) J Chem Eng Data 56:2453
11. Wilkes JS, Zaworotko MJ (1992) J Chem Soc Chem Commun 965
12. Aparicio S, Atilhan M, Karadas F (2010) Ind Eng Chem Res 49:9580
13. Yu H, Wu YT, Jiang YY, Zhou Z, Zhang ZB (2009) New J Chem 33:2385
14. Kasahara S, Kamio E, Ishigami T, Matsuyama H (2012) Chem Commun 48:6903
15. Jiang YY, Wang GN, Zhou Z, Wu YT, Geng J, Zhang Z-B (2008) Chem Commun 4:505
16. Zhang J, Zhang S, Dong K, Zhang Y, Shen Y, Lv X (2006) Chem Eur J 12:4021
17. Goodrich BF, de la Fuente JC, Gurkan BE, Lopez ZK, Price EA, Huang Y, Brennecke JF (2011) J Phys Chem B 115:9140

18. Giammona G, Cavallaro G, Pitarresi G, Pedone E (2000) Colloid Polym Sci 278:69
19. Kirchhecker S, Espositom D (2016) Curr Opin Green Sustain Chem 2:28
20. Tao G-H, He L, Liu W-S, Xu L, Xiong W, Wang T, Kou Y (2006) Green Chem 8:639
21. Fukumoto K, Yoshizawa M, Ohno H (2005) J Am Chem Soc 127:2398
22. Ohno H, Fukumoto K (2007) Acc Chem Res 40:1122
23. Egorova KS, Gordeev EG, Ananikov VP (2017) Chem Rev 117:7132
24. Egorova KS, Seitkalieva MM, Posvyatenko AV, Ananikov VP (2015) Toxicol Res 4:152
25. He L, Tao G-H, Parrish DA, Shreeve JM (2009) J Phys Chem B 113:15162
26. Wasserscheid P, Bösmann A, Bolm C (2002) Chem Commun. https://doi.org/10.1039/b109493a
27. Bao W, Wang Z, Li Y (2003) J Org Chem 68:591
28. Kucherenko AS, Perepelkin VV, Zhdankina GM, Kryshtal GV, Srinivasan E, Inani H, Zlotin SG (2016) Mendeleev Commun 26:388
29. Moosavi M, Banazade N, Torkzadeh M (2019) J Phys Chem B 123:4070
30. Herrera C, Alcalde R, García G, Atilhan M, Aparicio S (2015) J Phys Chem C 119:27080
31. Guzmán J, Ortega-Guevara C, García de León R, Martínez-Palou R (2017) Chem Eng Technol 40:2339
32. Mu X, Qia L, Zhang H, Shen Y, Qiao J, Maa H (2012) Talanta 97:349
33. Xiao J, Li M, Liu W, Li Y, Ling Y, Tang H (2017) Eur Polym J 88:340
34. Hu Q, Deng Y, Yuan Q, Ling Y, Tang H (2014) J Polym Sci Part A: Polym Chem 52:149
35. Guillen F, Brégeon D, Plaquevent J-C (2006) Tetrahedron Lett 47:1245
36. Mishra R, Pandey S, Trivedi S, Pandey S, Pandey PS (2014) RSC Adv 4:33478
37. Porte V, Thioloy M, Pigoux T, Métro T-X, Martinez J, Lamaty F (2016) Eur J Org Chem 21:3505
38. Bonnamour J, Métro T-X, Martinez J, Lamaty F (2013) Green Chem 15:1116
39. Bhuyan BJ, Mugesh G (2012) Org Biomol Chem 10:2237