Ecofriendly microwave-assisted preparation, characterization and antitumor activity of some propylimidazolium-based ionic liquids derivatives

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Abstract

An ecofriendly and efficient preparation of a set of a new 1-propylimidazolium-based ionic liquids (1–20) has been manufactured by using both microwave irradiation and conventional procedure. Different spectral analysis (FT-IR, mass spectra, NMR and elemental analysis) were utilized to examine the structures of the newly prepared ILs. The in vitro antitumor activities of all ILs (1–20) were investigated, using viability assay, towards HEPG-2, MCF7 and CACO2 Cells. Among all tested ILs, the 3-(3-phenylpropyl)-1-propyl-1H-imidazol-3-ium tetrafluoroborate (13) showed better activity towards human hepatocellular carcinoma (HEPG-2) and colon carcinoma (CACO2), while the 3-(3-phenoxypropyl)-1-propyl-1H-imidazol-3-ium tetrafluoroborate (20) exhibited low IC50 values against human breast adenocarcinoma (MCF7) compared to the standard drug (5-fluorouracil (5-FU)). Generally, all ILs 1–20 derivatives showed moderate cytotoxic activity against all tested cell lines.

1. Introduction

The large use of organic solvents in chemical reactions has been a big issue in both chemical industries and labs due to their effects on many aspects including flammability, toxicity, volatility, safety, environmental pollution and human health. Alternatives to organic solvents are needed to be approached to solve these problems [1–3]. Green chemistry has appeared as a good competitor to traditional organic solvents in terms of producing compounds with little impact to the environment in addition to increasing yields of products through optimizing preparation process [1,4,5]. One of the intensive rapidly studying research area in green chemistry is ionic liquids (ILs) [1,6,7]. This can be accomplished to their exceptional physical properties which include low flammability and volatility, high polarity, poor coordinating nature, water miscibility and their capability of dissolving a wide range of inorganic and organic solutes [1,6,7].

ILs are salts made of organic cations such as pyridinium, imidazolium and quaternary ammonium cations coupled with anion moieties such as bis(trifluoromethyl)sulfonyl imide (CF3SO2)2N−, hexafluorophosphate (PF6−), tetrafluoroborate (BF4−), trifluoroacetate (CF3COO−), nitrate (NO3−) and halides (Cl−, Br−, I−) [8–12]. Among the organic cations, imidazolium is the most widely used due to its low viscosity and its high ionic conductivity. Whereas, BF4− is the favoured anion owing to its low cost and its competitive characteristic [8]. The exceptional physical and chemical properties of ionic liquids made them suitable for a large number of applications such as solvents for organic reactions and catalysis [13,14], generation materials with high conductivity [15], as electrolytes in electrochemistry [16,17], as antimicrobial agents [18,19], as anticorrosion coatings [20,21], as matrices for mass spectrometry [22], as stationary phases for chromatography [23,24], in supportive immobilization of enzymes [25,26], as antibacterial agent [11], in solar cells and fuel [27,28], in technologies of nanomaterials [29,30], and in separation technologies [31,32].

Recently, microwave-assisted reactions in organic synthesis (MAOS) have received more attention as ecofriendly green processing technologies [33]. The use of such environmentally processes led to a significant enhancement in reaction rates and yields [33–36]. Consequently, the goal of the current study is to prepare a new family of 1-propylimidazolium-based room temperature ionic liquids (RTILs) by using microwave irradiation and conventional procedure, which were used as antitumor agents. A comparative study on biological activities of human pathogens (HEPG-2, MCF-7 and CACO2) of the prepared ILs were made to evaluate their antitumor activities in order to recognize the relationship between their toxicities and structures.
2. Materials and methods

2.1. Experimental

Unless otherwise stated, all solvent and chemical reagents were purchased from commercial suppliers and used without any purification. 1H, 13C, 19F, 11B and 31P nuclear magnetic resonance (NMR) were recorded on a Bruker AV 400 (400 MHz) using CDCl3 as the solvent at room temperature. IR absorption spectra were recorded on a Schimadzu 8201 PC using NaCl disc within the wavenumber range of 4000–400 cm⁻¹, FTIR spectrophotometer (νmax in cm⁻¹). The elemental analyses were recorded using the 2400 Series II CHNS/O analyzer. A Bruker MALDI TOF MS was applied to record mass spectra. A controllable single-mode microwave reactor (CEM Corp, Matthews, NC, USA), CEM Discover, was used for the microwave-assisted reactions for synthetic use. The reactor is facilitated with a magnetic stirrer, a plethora of pressure and a control of temperature and power. The temperature and power were in the range of 60–250°C and 15–300 W, respectively. The reactor has a maximum operating pressure of 2·10⁶ Pa.

2.2. Synthesis

2.2.1. Preparation of 1-propylimidazolium halides 1–5 using conventional method

An appropriate alkyl halide (1.1 eq) was added to a solution of 1-propylimidazole (1 eq) in toluene at room temperature. The reaction temperature was raised to 80°C and lift to stir for 18 h. The separation of oil from the homogenous mixture of alkyl halide and 1-propylimidazole in toluene was the evidence of the completion of the reaction. The obtained viscous IL was extracted by removing solvent and carefully washed with 10 ml of ethyl acetate (3 times). Finally, the resultant IL was dried at a reduced pressure to remove volatile organic solvents.

2.2.2. Preparation of propylimidazolium halides 1–5 under microwave irradiation:

Under microwave irradiation, an appropriate alkyl halide (1 eq) and 1-propylimidazole (1 eq) were added together in a Teflon reaction vial. The reaction mixture was then exposed to irradiation at 80°C for 20 min. The desired IL was then obtained as outlined earlier in the conventional procedure.

2.2.3. Anion metathesis reaction leading to ILs 6–20 using conventional method:

The ILs 1–5 (1 eq) was dissolved in DCM and then NaBF₄, KPF₆ or CF₃CO₂Na (1.2 eq) was added. The mixture lift to stir under reflux for 3 h. The product was then isolated by solvent extraction. The resultant product was filtered followed by removing solvent under reduced pressure to produce the desired ILs (6–20).

2.2.4. Anion metathesis reaction leading to 6–20 under microwave irradiation:

In a microwave reactor vessel, imidazolium-halides salts 1–5 (1 eq) and 1 eq of NaBF₄, KPF₆ or CF₃CO₂Na were added together and dissolved in a small amount of DCM. The reaction mixture was performed for 10 min at 70°C. The ILs (6–20) were collected as outlined in the conventional method.

3. Results and discussion

3.1. Synthesis

Based on interesting results published recently, we focused on the preparation of a new family of RTILs (1–20) by using microwave irradiation and conventional procedure in order to test them for antitumor activities [37–39]. As shown in Scheme 1, 1-propylimidazolium-based ionic liquids (1–5) have been synthesized through the reaction of 1-propylimidazole in toluene with a suitable alkyl bromide at 80°C for 18 h. The quaternization reaction was performed via the nucleophilic attack of the Sp²-N imidazole atom on the alkyl bromide in order to produce the desired imidazolium bromides (1–5). The resultant products were obtained as oils in moderate yields ranging between 71 and 74% (Table 1).

Microwave irradiation (MW) was used as an eco-friendly technology for the synthesis of 1-propylimidazolium-based derivatives (1–5). It is believed that MW technology is beneficial for boosting the percentage yields relative to the conventional methods. The reaction progress was monitored where the reaction mixture turned from a clear homogeneous solution into two aqueous phases. The formation of the two phases is ascribed to the insolubility of the resultant ILs in toluene. The impact of the MW strategy on the outcome yield was noticeable, and the reaction time was shorter when compared to the conventional strategy. Table 1 summarizes the percentage yields of the two different strategies.

The quaternization reaction of 1-propylimidazol with benzylbromide produced 3-benzyl-1-propyl-1H-imidazol-3-ium bromide (1) which was chosen as a reference IL in order to assert the spectroscopic data of the synthesized 1-propylimidazolium-based ILs (1–5). The 1H NMR spectra of product 1 showed a triplet, multiplet and triplet peaks at 0.92, 1.91 and 4.24 ppm, respectively, which correspond to the protons on the methyl and the two methylenes of the propyl group. It also showed a singlet peak at 5.60 ppm for the methylene protons of NCH₂Ph. The aromatic region showed a singlet peak at 10.52 ppm, which is referred to the most acidic imidazolium proton. The peaks of the other two imidazolium protons and the phenyl protons are located at 7.28–7.52 ppm.
Scheme 1. Synthesis of novel propylimidazolium-based ionic liquids derivatives 1–5.

Table 1. Comparison between the prepared ILs (1–5) under microwave irradiation (MW) and conventional procedure (CP).

| Compound | RBr      | CP Yield (%) | CP Time (h) | MW Yield (%) | MW Time (min) |
|----------|----------|--------------|-------------|--------------|---------------|
| 1        | Ph(CH₂)Br | 74           | 18          | 84           | 20            |
| 2        | Ph(CH₂)₂Br| 72           | 18          | 86           | 20            |
| 3        | Ph(CH₂)₃Br| 73           | 18          | 85           | 20            |
| 4        | PhO(CH₂)₂Br| 71          | 18          | 87           | 20            |
| 5        | PhO(CH₂)₃Br| 72          | 18          | 87           | 20            |

The ¹³C NMR spectrum of product 1 exhibited a peak at 10.7 ppm for the CH₃ group and three peaks of CH₂ at 23.6, 51.5 and 53.1 ppm. The signals positioned at the aromatic area between 122.0 and 136.6 ppm are attributed to the carbons on the imidazolium and phenyl rings. ¹³C-DEPT-NMR was used to confirm the formation of the target ILs 1.

FT-IR spectrum was applied to confirm the success of the N-alkylation reaction of 1-propylimidazole (1–5). The FT-IR spectrum of compound 1 displayed absorption peaks at around 3080, 2940, 1600 and 1550 cm⁻¹ indicating the existence of C–H Ar, C–H Al, C=Na n d C=C, respectively. Finally, the mass spectroscopy of the IL 1 exhibited a main peak at 201.28 corresponding to the desired mass ions [M-Br]⁺.

The following step involved the anion exchange of 3-benzyl-1-propyl-1H-imidazol-3-ium bromide using an aqueous solution of sodium trifluoroacetate (CF₃COONa), sodium tetrafluoroborate (NaBF₄) and potassium hexafluorophosphate (KPF₆) (Scheme 2). Single mode system MW activation, with a control of temperature and power during the reaction process, was used for the anions exchange metathesis of tetrafluoroborate, hexafluorophosphate and trifluoroacetate. As presented in Table 2, the yields obtained by the microwave irradiation method, within a short period of time, were slightly higher than that of the conventional procedure. It is noted that the yields were not affected by exchanging the anion agents.

NMR spectroscopy was the most efficient analysis for monitoring the anions exchange metathesis reactions. The NMR spectra of ILs 6–20 exhibited a slight shift in the ¹H and ¹³C NMR to those reported for their precursors 1–5. It is worth mention that the highest chemical shift in ¹H NMR spectra is ascribed to the most acidic hydrogen on the imidazolium ring. Moreover, the ¹¹B-, ¹⁹F-, ³¹P-NMR and FTIR spectra confirmed that the anions exchange metathesis reactions were performed successfully. The bromine anion exchange of compound 1 using NaBF₄ produced the IL 6. The ¹¹B NMR and ¹⁹F NMR spectra of IL 6 showed a singlet peak at 0.91 ppm and a singlet peak at -150.43 ppm, respectively, which proved the incorporation of the boron and fluorine atoms in the BF₄⁻ anion. In the ³¹P and ¹⁹F NMR spectrums of compound 7, the existence of multiplet peaks at -157.45 to -131.06 ppm.

Table 2. Comparison between the anions exchange metathesis of ILs (6–20) under MW and CP.

| Ionic liquid | R     | MY     | CP Yield (%) | CP Time (h) | MW Yield (%) | MW Time (min) |
|--------------|-------|--------|--------------|-------------|--------------|---------------|
| 6            | (CH₂)Ph | NaBF₄ | 94           | 3           | 98           | 10            |
| 7            | KPF₆  |       | 95           | 3           | 99           | 10            |
| 8            | CF₃COONa |       | 95           | 3           | 98           | 10            |
| 9            | (CH₂)₂Ph | NaBF₄ | 93           | 3           | 98           | 10            |
| 10           | KPF₆  |       | 93           | 3           | 97           | 10            |
| 11           | CF₃COONa |       | 94           | 3           | 97           | 10            |
| 12           | (CH₂)₂Ph | NaBF₄ | 93           | 3           | 98           | 10            |
| 13           | KPF₆  |       | 94           | 3           | 98           | 10            |
| 14           | CF₃COONa |       | 93           | 3           | 98           | 10            |
| 15           | (CH₂)₃OPh | NaBF₄ | 95           | 3           | 99           | 10            |
| 16           | KPF₆  |       | 94           | 3           | 98           | 10            |
| 17           | CF₃COONa |       | 92           | 3           | 98           | 10            |
| 18           | (CH₂)₃OPh | NaBF₄ | 94           | 3           | 97           | 10            |
| 19           | KPF₆  |       | 92           | 3           | 99           | 10            |
| 20           | CF₃COONa |       | 94           | 3           | 98           | 10            |

[^a]: 3 h, Reflux, in DCM;[^b]: 10 min, 70°C, Power (300W).
and two singlets at $-72.88$ and $-70.99$ ppm, respectively, proved the existence of the phosphorous and fluorine atoms in the PF$_6^-$ anion. The anion metathesis reaction with CF$_3$COONa has also been carried out and produced IL 8, as was also proved by its $^{19}$F NMR spectrum, which displayed a singlet peak at $-75.35$ ppm corresponding to the CF$_3$COO$^-$ anion. Spectroscopic data of the synthesized RTILs (1–20) are shown in the experimental part.

### 3.2. Cytotoxic activity of ILs 1–20

**In vitro** cytotoxicity screening were performed for the newly synthesized ILs (1–20) towards CACO2 (colon carcinoma), HepG-2 (human hepatocellular carcinoma) and MCF-7 (human breast adenocarcinoma) using a viability assay. The measurement of cell growth and viability was in agreement with the stated reports [40]. All results are presented in Table 3. The experimental data showed a decrease in cell survival as dose was increased. The data exhibited moderate cytotoxic activity by IC$_{50}$ range: 30.9–490 µg/mL. The presented results clearly demonstrated that 3-(3-phenylpropyl)-1-propyl-1H-imidazol-3-ium tetrafluoroborate (13) showed the highest activity against specific cancer cell (HEPG-2 and CACO2) with IC$_{50}$ values of 30.9, 49.6 µg/mL, respectively, compared to the tested standard drug 5-FU which are 12.1 and 13.3 µg/mL, respectively. Furthermore, 3-(3-phenoxypropyl)-1-propyl-1H-imidazol-3-ium tetrafluoroborate (20) showed moderate anticancer activity against all cancer cell lines. However, this compound 20 showed the unique activity against MCF7 cell line among all tested ILs with IC$_{50}$ value of 105 µg/mL.

| Sample Code | IC$_{50}$ values (µg/mL) |
|-------------|--------------------------|
|             | HepG-2 Cells | MCF-7 Cells | CACO2 Cells |
| 1           | 225 ± 8.3    | 375 ± 7.6   | 153 ± 6.2   |
| 2           | 81.2 ± 2.2   | 232 ± 5.3   | 109 ± 3.2   |
| 3           | 97.2 ± 2.7   | 465 ± 9.4   | 107 ± 3.4   |
| 4           | 112 ± 3.1    | 182 ± 4.1   | 119 ± 2.7   |
| 5           | 61.5 ± 1.8   | 479 ± 9.7   | 91.2 ± 1.9  |
| 6           | 381 ± 8.9    | 490 ± 10.6  | 421 ± 8.1   |
| 7           | 494 ± 10.3   | 446 ± 9.1   | 445 ± 9.5   |
| 8           | 332 ± 6.4    | 386 ± 8.3   | 191 ± 6.2   |
| 9           | 142 ± 5.6    | 192 ± 4.6   | 151 ± 3.8   |
| 10          | 60.1 ± 1.1   | 401 ± 8.9   | 98.2 ± 3.1  |
| 11          | 231 ± 6.8    | 202 ± 4.7   | 217 ± 6.7   |
| 12          | 55.5 ± 1.9   | 246 ± 7.1   | 88 ± 3.1    |
| 13          | 30.9 ± 0.6   | 211 ± 5.9   | 49.6 ± 1.8  |
| 14          | 60.6 ± 1.3   | 201 ± 6.4   | 99.4 ± 3.3  |
| 15          | 124 ± 4.1    | 487 ± 10.6  | 122 ± 3.9   |
| 16          | 73.4 ± 3.6   | 384 ± 8.7   | 121 ± 4.1   |
| 17          | 109 ± 4.2    | 297 ± 7.6   | 107 ± 3.7   |
| 18          | 310 ± 8.3    | 363 ± 8.6   | 241 ± 7.4   |
| 19          | 93.1 ± 3.4   | 216 ± 4.8   | 124 ± 3.4   |
| 20          | 102 ± 3.2    | 105 ± 2.7   | 115 ± 3.5   |
| 5-FU        | 121.1 ± 0.11 | 27.8 ± 0.09 | 13.3 ± 0.14 |

IC$_{50}$ values show the average of three repetitions.
4. Conclusion

In conclusion, the preparation of the 20 novel ILs was effectively performed using both conventional procedure and green microwave-assisted method. It was found that the synthesis of the ILs (1–20) by using the simple and efficient microwave-assisted method has significantly improved the yields of the resultant ILs in a short reaction time. The chemical structures of the synthesized ILs (1–20) were confirmed by FT-IR, mass spectra, $^{1}H$, $^{13}C$, $^{11}B$, $^{19}F$, and $^{31}P$-NMR. All these newly synthesized ILs were screened for their antitumor activity against HEPG-2, MCF7 and CACO2 Cells. The obtained results showed that ILs 13 exposed the best activity towards HEPG-2 and CACO2, while the ILs 20 exhibited the lowest IC50 values for MCF7 compared to the standard drug (5-FU). Generally, all tested ILs 1–20 showed moderate activities against all tested cell lines.

Contributions

The author conceived and designed the experiments; performed the experiments and analysed the data; wrote the paper. The biological tests were carried out at The Regional Center for Mycology & Biotechnology at Al-Azhar University, Egypt.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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