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Full Paper

Preparation of Second Generation Ionic Liquids by Efficient Solvent-Free Alkylation of *N*-Heterocycles with Chloroalkanes

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Abstract: Non-conventional techniques, such as microwave (MW) and power ultrasound (US) as well as combined MW/US irradiation, have been used to promote one-pot synthesis of second-generation ionic liquids (ILs), cutting down reaction times and improving yields. However, the use of chloroalkanes in the alkylation of *N*-heterocycles requires more drastic conditions if results are to match those obtained with more reactive alkyl halides. The present paper describes a series of MW- or MW/US-promoted IL preparations starting from chloroalkanes and classic heterocycles (1-methylimidazole, pyridine and 1-methylpyrrolidine). When reactions were carried out under conventional heating in an oil bath they required longer reaction times and gave poorer yields. ^{1}H-NMR analysis and ion-exchange chromatography showed that the present solventless procedure afforded ILs of satisfactory purity. The observed high yields (usually 70-98% isolated), and short reaction times showed that a straightforward access to ILs can be also achieved with the use of alkyl chlorides, resulting in a considerable reduction of costs.

Keywords: Ionic liquids, chloroalkanes, one-pot reaction, microwaves, ultrasound.

Introduction

The increasing interest in ionic liquids (ILs) is documented by the increasing publication rate of papers dealing with their applications; this number was roughly about 20 papers per year around 1995, rising to some 300 papers per year around 2001 [1] and it rose further to 2,500 in 2006. Although scientific indicators predict a brilliant future for ILs, some major hurdles remian to be addressed before their industrial use becomes routine, particularly regarding production costs, possible safety hazards, as well as technical problems to be solved before preparative scale-up can be undertaken.

Second-generation ILs are halogen-free and stable in the presence of air and moisture [2, 3]. They are usually prepared through two successive steps: 1) the alkylation of a nitrogen-bearing compound (Menshutkin reaction) to yield first-generation halogenated ILs; 2) the exchange of halide with a different anion (metathesis). Non-conventional techniques, such as irradiation with microwaves (MW) [4] and power ultrasound (US) [5], whether used alone or in combination [6, 7], have considerably improved the synthesis of ILs, cutting down reaction times and improving yields [8-14]. The recent introduction of efficient, solventless, one-pot synthetic protocols [15-18] should certainly make ILs cheaper and thus encourage a wider employ of these innovative reaction media. We present here another significative contribution to this end showing that alkyl iodides and bromides can be effectively replaced by the corresponding chlorides, which are much cheaper and readily available, albeit much less reactive.

Results and Discussion

In a recent paper [17] we described the synthesis of 1-octyl-3-methylimidazolium hexafluorophosphate ([C8mim][PF_6]), starting from chlorooctane and working under simultaneous MW/US irradiation in a cooled reactor. The reaction temperature was 140°C after an initial step (10 min) at 120°C to avoid overshooting the final temperature. The reaction was continued at 140°C for 20 min to afford the IL in nearly quantitative yield (98%, Table 1, entry 1a). It was by means of an efficient cooling system that we could raise the MW energy input enough to sufficiently increase the reactivity of the alkyl chloride without causing any attendant decomposition. In the present work we extended our investigation to several other ILs by changing the heterocycle, the chloroalkane and the anion source. With the aim to compare the effects of the different energy sources on the kinetics of this reaction we carried it out at the same temperature under MW irradiation only (Table 1, entry 1b), under conventional heating plus US irradiation (Table 1, entry 1c) and under conventional heating alone for up to four hours (Table 1, entries 1d and 1e). Although longer reaction times were required, even under the last-mentioned conditions good yields were achieved (84%). When the reaction mixture, being heated in an oil bath, was irradiated with a 20 kHz US probe, the yield rose from 47 to 62% after one hour (Table 1, entry 1c).

We obtained 1-octyl-3-methylimidazolium tetrafluoroborate ([C8mim][BF_4]) (95% yield) (Table 1, entry 2) in 30 min (two irradiation steps). The preparation of 1-octyl-3-methylimidazolium triflate ([C8mim][OTf]) (Table 1, entry 3) and 1-octyl-3-methylimidazolium *bis*(trifluoromethanesulfon)imide ([C8mim][NTf_2]) (Table 1, entry 4) took longer times (yields 65% and 72%, respectively, see Table 1).

When the state-of-the-art is considered [3], these results represent a significant progress towards an easier access to ILs.

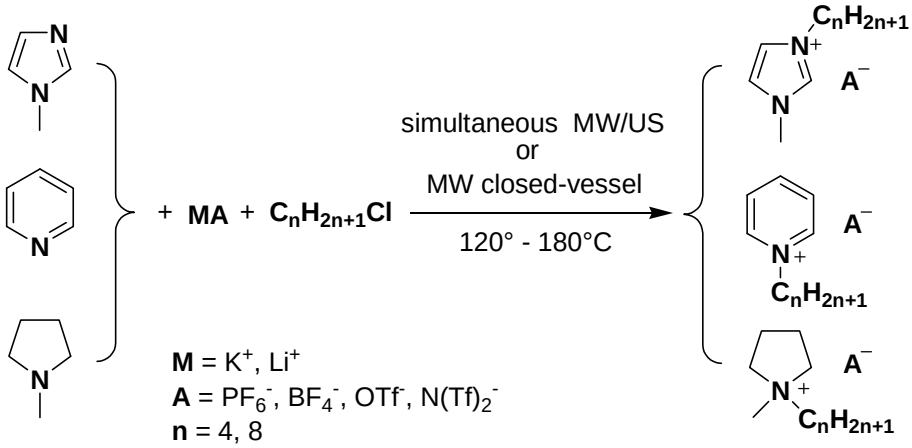
Table 1. ILs synthesis under simultaneous MW/US irradiation in a cooled reactor or under conventional heating in an oil bath. Reagents: 1-methylimidazole (1-mim) and 1-chlorooctane.

Entry	Anion source	Irradiation time (min)	MW power (W)	US power (W)	Temperature (°C)*	Yield (%)
1a	KPF_6	**10/20	90	40	120/140	98
1b	KPF_6	60	60	-	140	88
1c	KPF_6	60 (oil bath)	-	40	140	62
1d	KPF_6	60 (oil bath)	-	-	140	47
1e	KPF_6	240 (oil bath)	-	-	140	84
2	KBF_4	**10/20	75	40	120/140	95
3	KOTf	**10/45	85	45	120/140	65
4	$LiN(Tf)_2$	**10/90	110	45	120/140	72

*Measured by optical-fibre thermometer. **Two temperature steps.

After these outstanding results, we applied the same MW/US procedure to the synthesis of ILs with 1-butyl-3-methylimidazolium and *N*-octylpyridinium cations. In either case, however, because higher temperatures were necessary to achieve *N*-alkylation [180°C for pyridine (pyr) and 140°C for 1-methylimidazole], operative difficulties arose in the use of the combined MW/US reactor. In fact the reaction temperature could not exceed the boiling points of pyridine and 1-chlorobutane (115°C and 78°C, respectively) because the MW/US combined reactor is an "open vessel" system. Scheme 1 summarizes the overall synthetic strategy.

Scheme 1. General synthetic procedure.



While the syntheses of 1-butyl-3-methylimidazolium and *N*-octylpyridinium chlorides, attempted with this system (at 75°C and 100°C, respectively), were unsuccessful (Table 2, entries 2 and 5), excellent yields were obtained under MW irradiation in a closed vessel at 180°C (98% C4mimCl and 85% C8PyCl; see Table 2, entries 3 and 6). *N*-Alkylation of 1-methylpyrrolidine also was strongly temperature-dependent. The same reaction was carried out under MW irradiation in a closed vessel at 120°C, 160°C and 180°C (two-step temperature increases; Table 2, entries 8, 9 and 10). At 120°C, no IL was formed, while at 180°C a quantitative yield was obtained. The *N*-alkylation of 1-methyl-imidazole, pyridine and 1-methylpyrrolidine was carried out under conventional heating in a closed vessel (Table 2, entries 1, 4 and 7). Reaction yields were comparable with those obtained under MW irradiation, while reaction times were considerably longer.

Table 2. *N*-alkylation of heterocycles under conventional heating, simultaneous MW/US irradiation or MW in a closed vessel.

Entry	Heterocycle*	Alkyl halide	Irradiation time (min) (1 or 2 steps)	MW power (W)	US power (W)	Temperature (°C)	Yield (%)
1	1-mim	1-ClC_4	**60/240	-	-	140/180	95
2	1-mim	1-ClC_4	150	120***	30	75	<5
3	1-mim	1-ClC_4	10/30	85	-	120/180	98
4	pyr	1-ClC_8	**60/240	-	-	140/180	80
5	pyr	1-ClC_8	180	60***	25	100	<5
6	pyr	1-ClC_8	10/30	85	-	120/180	85
7	1-mpyr	1-ClC_8	**60/240	-	-	140/180	88
8	1-mpyr	1-ClC_8	10/60	40	-	80/120	0
9	1-mpyr	1-ClC_8	15/50	80	-	120/160	20
10	1-mpyr	1-ClC_8	15/50	90	-	120/180	99

*1-mim: 1-methylimidazole; pyr: pyridine; 1-mpyr: methylpyrrolidine.

** Reactions were carried out in a pressure-resistant Pyrex tube, heated in an oil bath.

*** Cooled reactor [8].

Successively we applied the MW procedure (closed vessel) to the one-pot synthesis of several 1-butyl-3-methylimidazolium and *N*-octylpyridinium second-generation ILs. The alkyl chloride, heterocycle and anion source were placed in a pressure-resistant reactor and irradiated with MW under vigorous magnetic stirring. The reaction temperature was raised up to 180°C after an initial step (10-15 min) at 120°C, which allowed the heterogeneous system to gain a more regular heating ramp. The reaction was then continued at 180°C for 30-50 min (Table 3).

[C4mim][PF_6], [C4mim][BF_4] and [C4mim][OTf] (Table 3, entries 1, 2 and 3, respectively) were obtained in good yields (72-90%), while a slightly lower yield (62%) was found for [C4mim][N(Tf)2]

(Table 3, entry 4). This result can probably be justified by the lower polarization degree of the N(Tf)2-anion, hence its lower sensitivity to MW.

Good yields (>60%) were also achieved for [C8Py][PF6], [C8Py][BF4] and [C8Py][OTf] (Table 3, entries 5, 6 and 7, respectively) while [C8Py][NTf2] (Table 3, entry 8) could not be synthesized in one-pot with this procedure. Although the peculiar behaviour of the reaction with $LiN(Tf)_2$ had already been observed [15], we have no explanation for this failure, considering the good results achieved with 1-mim (see Table 1). The low boiling point of 1-methylpyrrolidine (1-mpyr) (80°C) forced us to use the closed-vessel system exclusively. A comparison of reactions carried out at different temperatures showed that it was necessary to reach 180°C in order to obtain a quantitative yield for 1-methyl-1-octylpyrrolidinium chloride (Table 2, entry 10). Yields close to 80% were achieved in less than 1 h for different 1-methyl-1-octylpyrrolidinium ILs (Table 3, entries 9 -11).

Table 3. MW-assisted one-pot RTIL synthesis (closed vessel)*.

Entry	Heterocycle**	Alkyl halide	Anion source	Irradiation steps (min)	MW power (W)	Yield (%)
1	1-mim	$1\text{-}ClC_4$	KPF_6	15/30	60	90
2	1-mim	$1\text{-}ClC_4$	KBF_4	10/30	55	72
3	1-mim	$1\text{-}ClC_4$	KOTf	15/40	65	75
4	1-mim	$1\text{-}ClC_4$	$LiN(Tf)_2$	10/30	65	62
5	pyr	$1\text{-}ClC_8$	KPF_6	15/50	65	83
6	pyr	$1\text{-}ClC_8$	KBF_4	10/40	60	68
7	pyr	$1\text{-}ClC_8$	KOTf	10/50	55	60
8	pyr	$1\text{-}ClC_8$	$LiN(Tf)_2$	15/50	65	traces
9	1-mpyr	$1\text{-}ClC_8$	KPF_6	15/35	95	85
10	1-mpyr	$1\text{-}ClC_8$	KBF_4	10/45	113	81
11	1-mpyr	$1\text{-}ClC_8$	KOTf	10/45	104	79

*Carried out with two temperature steps, 120° and 180°C.

**1-mim: 1-methylimidazole; pyr: pyridine; 1-mpyr: methylpyrrolidine.

Conclusions

In summary, we have developed a simple, efficient and rapid one-pot procedure to synthesize second generation Ils, which made it possible to use poorly reactive but inexpensive alkyl chlorides. MW/US combined irradiation and closed-vessel MW have proven to be advantageous activation techniques that dramatically increase yields and purity levels of products, cutting down reaction times. Low-boiling chloroalkanes and heterocycles required the closed-vessel MW procedure. Under conventional heating in pressure-resistant Pyrex tubes, the reaction occurred in longer reaction times, often with acceptable yields.

Synthesized ILs were purified during the workup (extraction from water with organic solvents or washes with water or diethyl ether). Isolated yields of ILs were calculated as mean values from three experiments. Through ^{1}H-NMR [19], we could establish a >95% purity degree (for organic impurities) and through ion-exchange chromatography we evaluated inorganic impurities, such as free halide content in second generation ILs (falling in the range 200-2500 ppm).

Experimental

General

Commercially available reagents were used without further purification. Reactions were carried out in a closed vessel in a professional multimode oven (Microsynth - Milestone, BG - Italy). For simultaneous MW/US irradiation the oven was equipped with a US probe featuring a pyrex® horn (frequency 21.4 kHz, tip diameter 17 mm) developed in the author's laboratory at the University of Turin in collaboration with Danacamerini sas (TO - Italy) [7]. The reactor was efficiently cooled by circulation of a MW-inert liquid (Galden H270, Solvay-Solexis, MI - Italy) refrigerated at 2°C by a chiller. The US probe (20 kHz, max power 250 W) with a titanium horn is commercially available from Danacamerini sas. IR spectra were recorded on a Shimadzu FT-IR8001 spectrophotometer; ^{1}H- and ^{13}C-NMR spectra on a Bruker Avance 300 spectrometer, respectively at 300 and 75MHz (25°C). Chemical shifts were calibrated to the $CDCl_3$ residual peak (7.27 for ^{1}H- and 77.16 for ^{13}C NMR).

General procedure

1-Methylimidazole, pyridine or 1-methylpyrrolidine (40 mmol), the appropriate salt for anion exchange (40 mmol) and the chloroalkane (40 mmol) were placed either in a 100 mL two-necked round-bottomed flask (for simultaneous MW/US irradiation) or in a pressure-resistant reactor (Milestone) for MW irradiation in a closed vessel. Reactions under conventional heating in a thermostatted oil bath were carried out in a pressure-resistant Pyrex tube while for US irradiation a titanium horn was inserted in the flask containing the reaction mixture. Reaction times, operating power and temperatures are reported in the tables. The reaction mixtures were poured into acetone (100 mL) and filtered on a Celite® pad, then the solvent was removed under vacuum. Hydrophobic ILs were washed with water (4x20 mL) and diethyl ether (4x20 mL), to be finally dried under vacuum at 90°C (3 h). Hydrophilic ILs were dissolved in water (50 mL) and extracted with dichloromethane (4x25 mL); solvents were removed under vacuum and products washed with diethyl ether (4x20 mL) to be finally dried at 90°C under vacuum (3 h). All products were analyzed by ^{1}H- and ^{13}C-NMR, IR spectroscopy as well as ion-exchange chromatography thereby confirming their structures and a satisfying degree of purity. Yield values are averages from the results of two/three experiments.

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Sample Availability: Samples of all the compounds described herein are available from the authors.