

Product as Reaction Solvent: An Unconventional Approach for Ionic Liquid Synthesis

Cinzia Chiappe,^{*,†} Andrea Mezzetta,[†] Christian Silvio Pomelli,[†] Monica Puccini,[‡] and Maurizia Seggiani^{*,‡}

[†]Department of Pharmacy, University of Pisa, via Bonanno 33, 56126 Pisa, Italy

[‡]Department of Civil and Industrial Engineering, University of Pisa, Largo L. Lazzarino, no. 1, 56126 Pisa, Italy

ABSTRACT: Ionic liquids (ILs) are considered a promising class of potentially environmentally friendly solvents for use in a variety of applications. However, they are generally synthesized by batch in unsustainable solvents. ILs to be really “green” compounds for widespread use should be also synthesized in a benign manner. Here, we report an unconventional procedure to prepare [Bmim]Cl, as a typical IL, using the same product as solvent. This approach guarantees a high reaction rate assuring at the same time a high product purity degree. The comparison with three sustainable polar molecular solvents, having a sufficiently high boiling point (1-butanol, methylisobutylketone, and water), was also performed showing all of the potentialities of the proposed procedure.

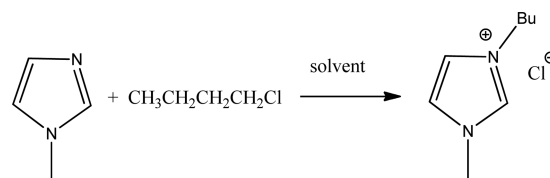
KEYWORDS: ionic liquid synthesis, purity, process efficiency, [Bmim]Cl

INTRODUCTION

Ionic liquids (ILs) are salts with melting temperatures below 100 °C, usually constituted by a large and asymmetric organic cation associated with an organic or inorganic anion. Due to their ionic character, ILs exhibit peculiar physicochemical properties, including a negligible vapor pressure, low flammability, high thermal and chemical stabilities, broad liquid temperature range, and high solvation ability for organic, inorganic, and polymeric compounds.^{1–3} The ability of some specific ILs to dissolve important biopolymers, such as cellulose, chitin, and keratin, has become an area of intense activity in the last 10 years.^{4–6} For their unique properties, which can be moreover tailored through an appropriate cation and anion selection, ILs have been proposed as solvents, media, electrolytes, or additives in the most diverse applications: organic synthesis, catalysis, extraction processes, electrochemistry, nanotechnology, and so on.^{2,7–11} The high potentiality showed by ILs in different strategic areas of research is expected to lead to an increasing demand. Currently, ILs are mainly produced in batch reactors and various companies already supply a portfolio of ILs, however, at relatively high prices, at least when compared with molecular solvents. The costs depend on various factors including the production scale, type of reactor, and process. The production process affects actually not only the IL price but also their environmental impact: synthesis requires normally large amounts of organic solvents. It is indeed usually carried out through one or two-step processes: the alkylation of a N-, P-, or S-containing organic compound, for example, N-methylimidazole (MIM), giving normally a halide based IL, followed by an eventual anion exchange (metathesis reaction). The alkylation step, that is, the Menshutkin reaction in the case of tertiary amines, is however characterized by high energy demand and long reaction times, in particular when less expensive but also less reactive chloroalkanes are used.

In 2007 Kralish et al., using MIM and chlorohexane as a model system, suggested the solvent-free process at 70 °C in a batch reactor as the best procedure in terms of energy demand, toxicological aspects, and costs to synthesize 1-hexyl-3-methylimidazolium chloride.¹² However, the solvent-free process is very slow with chloroalkanes at this temperature. For example, when MIM was reacted at 70 °C with chlorobutane (BuCl), 50 h was necessary to reach 90% conversion into the expected 1-butyl-3-methylimidazolium chloride, [Bmim]Cl (Scheme 1).¹³

Scheme 1. [Bmim]Cl Synthesis via the Menshutkin Reaction



Although an increase in reaction temperature generally has positive effects in terms of reaction times, this rate enhancement is accompanied by the formation of colored contaminants arising from N-methylimidazole decomposition and polymerization. Nonconventional techniques, such as microwave, have been also used^{14,15} to promote 1,3-dialkylimidazolium halide synthesis under solvent-free conditions, being able to drastically reduce reaction times and guarantee a good quality of the product. However, to date, microwave chemistry is mainly restricted to the laboratory scale, with equipment capable of producing a few grams of material, although the development

Received: September 7, 2016

Published: November 29, 2016



Table 1. Solvent and Pressure Effect on the Reaction Time for the Synthesis of [Bmim]Cl

	solvent	MIM:BuCl ratio	T (°C)	P (bar)	time (h)	conversion (%)	IL color
lab-scale synthesis	H ₂ O	1:1.3	100	1	220	81	colorless
	1-butanol	1:1.3	120	1	96	99	orange
	MIBK	1:1.3	120	1	49	99	dark yellow
	[Bmim]Cl	1:1.3	120	1	24	98.5	pale yellow
autoclave	[Bmim]Cl	1:1.1	100	4	18	99	colorless
	[Bmim]Cl	1:1.1	120	4	14	99	pale yellow

of microwave flow (micro)reactors could favor the scale up of these processes.

Therefore, reactions in solvent are generally preferred, in particular whenever the IL purity is an important target. Although a large number of media have been employed for the alkylation reaction, including also not exactly environmental friendly solvents, Welton et al. have recently reported¹⁶ an improved procedure to synthesize [Bmim]Cl using ethyl acetate as reaction medium, which is able to guarantee the formation of a pure and uncolored product. The process requires, however, long reaction times (3 days at 45 °C followed by 4 days at 75 °C).

Actually, the Menshutkin reaction can be carried out also in ILs, and though with reactive alkylating agents (bromides and iodides) the ionic environment has only a moderate kinetic effect, significant increases in reaction rate with respect to the classical molecular polar aprotic solvents have been observed when chloroalkanes have been used as alkylating agents.¹⁷

Therefore, to evaluate the possibility to identify new conditions able to guarantee a higher reaction rate, assuring at the same time a high product purity degree, the unusual approach to synthesize [Bmim]Cl in [Bmim]Cl itself was investigated in the range of temperature 100–120 °C. The comparison with three environmentally friendly molecular solvents, having a sufficiently high boiling point, 1-butanol (BuOH, 117.7 °C), methylisobutylketone (MIBK, 117–118 °C), and water (100 °C), was also performed.

RESULTS AND DISCUSSION

The reaction of MIM with BuCl was preliminarily carried out in three conventional solvents (water, BuOH, MIBK) and in [Bmim]Cl using batchwise-operating stirred lab-scale glass reactors at atmospheric pressure or under pressure (4 bar) in an autoclave. The two reagents were mixed together with the selected solvent obtaining a single or two-phase system (see [Experimental Section](#)). In all cases, conversion was monitored over time at constant temperature. BuCl was generally used in excess, typically 1.3 mol per mol of MIM, owing to its low solubility in the reaction mixtures and its relatively low boiling point (79 °C at 1 bar). Only when the reaction was carried out in autoclave (4 bar), the excess was reduced to 1.1 mol per mol of MIM. Syntheses were conducted at 100 or 120 °C. [Table 1](#) summarized the operating conditions and results.

MIM alkylation in both protic solvents (water, BuOH) required long reaction times also at refluxing temperature: 99% MIM conversion was achieved in 96 h in 1-butanol, whereas a conversion of only 81% was obtained after 220 h in water. Moreover, whereas the product formed in water was practically colorless, an orange IL was obtained in BuOH. A yellow colored IL was obtained also in MIBK, but in this case only 49 h were sufficient to achieve 99% conversion.

On the contrary, [Bmim]Cl was the sole medium able to ensure at 120 °C a high conversion in a significantly lower time

(24 h), giving a pale yellow compound. Reactions carried out in this medium on a larger scale in the batchwise-operating stirred lab-scale glass reactor (1 L) gave comparable results. Moreover, a practically uncolored IL was obtained in [Bmim]Cl at 100 °C even if, as expected, a longer reaction time (40 h) was necessary to reach 99% conversion.

It is noteworthy that a significant process improvement was obtained working at this temperature under pressure, in autoclave at 4 bar. Under these conditions, despite the fact that only a small excess of BuCl was used (ca. 10%), a 95% conversion was achieved in 8 h and 99% in 18 h, affording a practically uncolored product, as shown in [Figure 1](#).

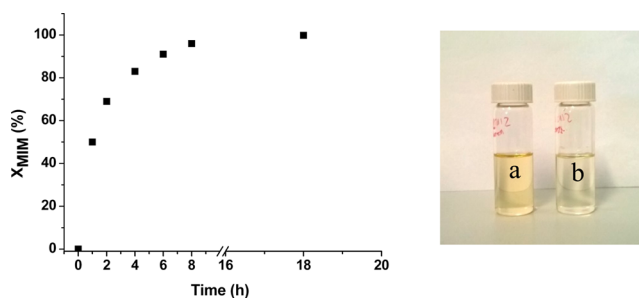


Figure 1. Left: X_{MIM} as a function of reaction time obtained in autoclave using [Bmim]Cl as solvent. Right: [Bmim]Cl obtained at 100 °C in open vessel (a) and at 100 °C in autoclave at 4 bar (b).

The present data clearly show that [Bmim]Cl is an appropriate medium for its own synthesis, increasing the reaction rate with respect to molecular solvents and assuring a high product quality. The colorless liquid, after the removal of the excess of BuCl at reduced pressure and storage in a freezer overnight, solidifies indeed into a white product corresponding to pure [Bmim]Cl (NMR, UV).

However, to better identify the more sustainable conditions to obtain a high-quality IL, initially a solvent-free reaction at 100 °C and 4 bar pressure in autoclave was also carried out. In autoclave, with a chlorobutane saturated atmosphere, the negative effect of oxygen on MIM decomposition could result mitigate. In agreement with this hypothesis, a yellow colored (but not orange!) [Bmim]Cl was obtained after 8 h (conversion >98%).

Furthermore, for the reaction carried out in [Bmim]Cl, we investigated the possibility to reduce the amount of IL used as solvent. Experiments carried out at 120 °C in stirred lab-scale glass reactors at atmospheric pressure using a quarter of the amount of IL employed in the previously described comparative experiments allowed to obtain a pale yellow IL, after 24 h. It is noteworthy that in this case the quantity of IL used as solvent is ca. 20% (w/w) of the finally recovered amount of [Bmim]Cl; therefore in an eventual in continuous process, the IL used as solvent is in large measure renewed at

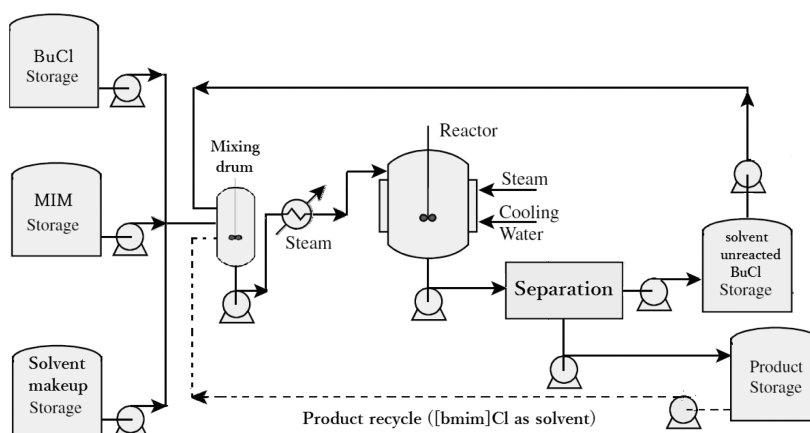


Figure 2. Process flow diagram for [Bmim]Cl production using organic solvent (BuOH) or [Bmim]Cl as reaction medium.

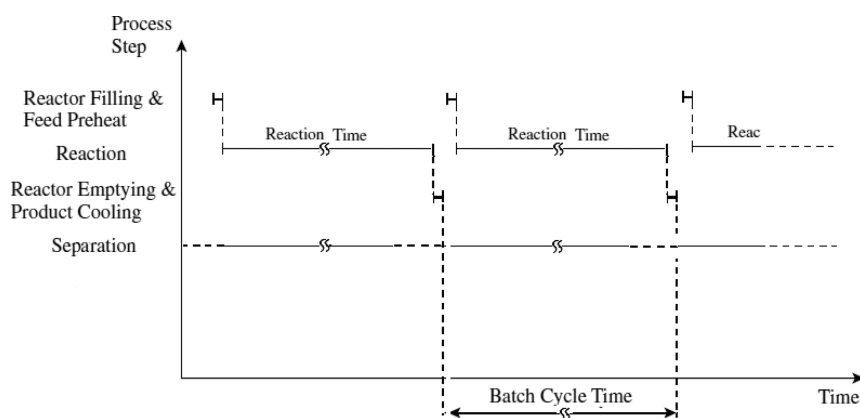


Figure 3. Gantt chart for a batch [Bmim]Cl production process with the separation step overlapped to the reaction step.

each cycle so reducing eventual problems arising by prolonged exposure at high temperatures. Moreover, stability experiments carried out in our laboratory by heating continuously [Bmim]Cl at 120 °C for 80 days show that the recovered liquid was practically unchanged; IR and NMR spectra were identical to those of the starting material.

In view of a large-scale production of [Bmim]Cl, the marked reduction of the reaction time on going from organic solvents to [Bmim]Cl should significantly reduce the IL production cost. To support this statement, Figure 2 shows a simple process flow diagram that can be considered for an industrial batch [Bmim]Cl production using BuOH (a typical molecular organic solvent) or [Bmim]Cl as solvent.

The two reagents (MIM and BuCl) and the solvent (BuOH or [Bmim]Cl) are withdrawn from the storage using pumps and sent to a mixing drum. Then, the reaction mixture is transferred into a heat exchanger (where it is preheated to 120 °C) and finally to a steam heated batch reactor. At the end of the reaction, cooling water is circulated through the reactor jacket, and the reactor effluent is withdrawn using a pump and transferred to a phase separator, when [Bmim]Cl is the solvent, or to a homogeneous mixture separation system (batch distillation, extraction, etc.) when BuOH is employed. Subsequently, the product ([Bmim]Cl) is sent to the storage, while the unreacted BuCl and the recovered solvent, if present, are sent to an intermediate storage and, then, recycled to the reactor.

Figure 3 shows the related Gantt or time event chart.

The first two steps, pumping for reactor filling and feed preheating, are both semicontinuous, whereas reactor heating, reaction heating, and subsequently cooling are in batch. The pumping step to empty the reactor and to charge the separation system are again semicontinuous, as well as the phase separation step. For a process of this type, the batch cycle time is the interval between successive batches of production. Since a high utilization of equipment is one of the goals of each batch process design, as shown in Figure 3, separation and reaction steps have been overlapped. This operative strategy allows indeed a significant decrease of the batch cycle time. However, since in this case the reaction itself represents the limiting step of the whole process, the marked reduction of reaction time obtained using [Bmim]Cl as solvent further reduces markedly the batch cycle time. Practically, this means that a higher rate of production can be obtained using an equipment (pumps, heat exchanger, batch reactor, separator, storages, etc.) having the same size of that employed for the reaction carried out in molecular solvents or, alternatively, if an increase of the production capacity of the plant is not required, the size of the equipment to obtain the same production can be markedly reduced.

It is also relevant that working with [Bmim]Cl as solvent under a slight overpressure (4 bar) at 120 °C a further reduction of reaction time can be obtained, with analogous benefits in terms of capital cost savings. It is to remark that owing to the low operating overpressure the savings, due to the further reduction of equipment size or to the increase of the hourly production, will be greater than the small increases of

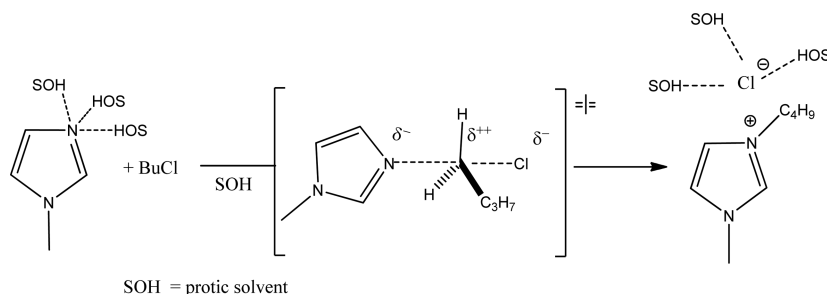


Figure 4. Reagent and TS solvation by protic solvents.

operating/capital costs related to the pumping of the reagent mixture at 4 bar and to the reactor sealing systems.

In addition, it is noteworthy that the use of [Bmim]Cl as solvent offers also advantages in the product isolation step. Since BuCl, generally used in excess, is only partially soluble in [Bmim]Cl, when the reaction is carried out in this medium at the end of the process two-phases are present and therefore the separation of product can be carried out in a simple gravity settler resulting less expensive (lower operating/capital costs) compared to the operations required for the single-phase liquid mixture (such as distillation, extraction, etc..) when BuOH is the solvent. Moreover, an eventual flash distillation of the small amount of BuCl dissolved in [Bmim]Cl is facilitated by the fact that the IL vapor pressure is practically negligible.

Finally, some mechanistic considerations arise from the observed solvent effect on reactivity. In particular, the higher reaction rate observed in [Bmim]Cl and MIBK, with respect to BuOH and water, clearly shows that this reaction, characterized by charge increase on going from reagents to the transition state (TS), is positively affected by solvent dipolarity/polarizability whereas its eventual hydrogen bond ability plays an opposite role. This behavior is in agreement with a substitution reaction occurring through an *early* TS, in which solvent hydrogen bonding to leaving group (chloride ion) is not important, whereas the solvent–reagent interaction (in particular, with MIM) decreases reactivity (Figure 4). In the Menschutkin reaction, only when the C-leaving group bond breaking in the TS is advanced (*late* TS), both solvent dipolarity and hydrogen bond donor ability contribute to increase the reaction rate.

It is to note that, also in molecular solvents, experiments carried out on trimethylamine and nitrobenzyl chloride indicated that the transition state for the Menschutkin reaction does not resemble the products of reaction but lies somewhere between the reactants and an ion pair, probably nearer to the reactants than to the ion pair (*early* TS). The “anomalous” effect of aliphatic alcohols on the rate of Menschutkin reactions was indeed attributed to the fact that the transition states resemble comparatively nonpolar solutes and are therefore destabilized by aliphatic alcohols, as compared with the dipolar aprotic solvents which may affect stabilization through nonspecific interactions.¹⁸

It is also to note that, although the ability of [Bmim]⁺ cation to act as a hydrogen bond donor has been several times evidenced,^{19,20} data here reported confirm that this feature strongly depends on the counteranion and decreases on the increasing anion hydrogen bond acceptor ability.²¹ The well-known strong cation–anion interactions, characterizing the [Bmim]⁺ cation and chloride anion, evidently disfavors the ability of both the coupled ions to interact with added

compounds, in particular with neutral species such as MIM, and makes [Bmim]Cl a proper solvent for its self-synthesis.

Last but not least, a comparison with the kinetic study carried out under solvent-free conditions¹³ might be also interesting. After 20–25% conversion, the reaction of MIM and BuCl under solvent-free conditions should be indeed practically in the same conditions of our process.¹³ However, the relatively long times necessary to have a high conversion and the low quality of the product obtained in the absence of solvent, in particular at high temperatures, show the important role exerted by the solvent ([Bmim]Cl itself) in the first part of the reaction. Probably, under solvent-free conditions, the moderate polarity of the reagents is unable to stabilize efficiently the TS, thus increasing the reaction time. On the other hand, the solvent-free system, having also a reduced ability to dissipate heat, favors side reactions giving colored byproducts.

CONCLUSIONS

The use of [Bmim]Cl as a reaction medium to synthesize [Bmim]Cl itself allows to isolate the expected product with a high-purity degree in a substantially shorter time, completely avoiding the use volatile organic solvent (VOC). The efficiency of the process is considerably higher than the conventional procedures using organic solvents or water as shown by comparing separation procedures, plant size, and batch cycles. In addition, it has been shown that, working with [Bmim]Cl as solvent under a slight overpressure (4 bar) and at 120 °C, a further reduction of reaction time can be obtained, with consequent benefits in terms of costs. Finally, it is to note that the same approach can be applied to the synthesis of other ILs, including chloride salts having different cations and bromide-based ILs.

EXPERIMENTAL SECTION

All chemicals (1-methylimidazole, MIM, 99%, 1-chlorobutane, BuCl, 99+ %, 1-butanol BuOH, 99%, methylisobutylketone, MIBK, 99%) were purchased from Alpha Aesar. NMR spectra were recorded on a Bruker Avance III 300 spectrometer (250 MHz).

The synthesis of [Bmim]Cl from 1-methylimidazole and chlorobutane was carried out as follows.

Lab-Scale Synthesis. MIM (27 g) and BuCl (40 g) in a molar ratio of 1:1.3 were added to the selected solvent (water, BuOH, MIBK, or [Bmim] Cl, 61 g) in a 250 mL round-bottomed flask equipped with a reflux condenser and magnetic stirrer. A single or two-phase system was obtained depending on solvent: in BuOH, reagents and product are soluble in the reaction medium, and the process occurs in a single phase; in MIBK, the second phase is formed during the progress of the reaction (the product is insoluble in the reaction medium); in

water and [Bmim]Cl, the reaction product and MIM are almost completely miscible with the solvent, while BuCl is only partially miscible and forms a second phase.

The reaction mixture was heated to the required temperature (100 or 120 °C) under magnetic stirring. During the course of the reaction some samples were collected and analyzed by ¹H NMR. The samples were quickly analyzed. Typically, the time duration between sample withdraw and NMR analysis was less than 5 min; further conversion during this time was negligible due to the relatively slower kinetic rates at ambient conditions. The conversion over time was determined by following the disappearance of the reactant and appearance of the product peaks on the NMR spectrum.

Batch Reactor Synthesis. Synthesis of [Bmim]Cl was carried also in a 1 L thermostatically controlled batch jacketed reactor equipped with a reflux condenser, mechanical stirrer, dropping funnel, and thermocouple. MIM (120 g) and BuCl (190 g) in molar ratio 1:1.3 were added to the selected solvent (MIBK or [Bmim]Cl, 250 g) and heated up to reaction temperature under stirring. During the course of the reaction some samples were collected and analyzed by ¹H NMR, as reported above.

Autoclave Reactor Synthesis. MIM (7 g) and BuCl (8.8 g) in molar ratio 1:1.1 were added to [Bmim]Cl (15 g) in a 150 mL stainless steel autoclave equipped with magnetic stirrer. The reactor was pressurized to 4 bar using an inert gas (nitrogen) and heated up to the reaction temperature (100 or 120 °C) under stirring. In this case, the reactions, carried out in parallel in a Eyela Process Station PPV-4060 reactor equipped with four autoclaves HIP-60, were stopped at different times, and the mixtures were analyzed by ¹H NMR, as reported above.

At the end of the reaction (99% conversion), after the removal of the excess of BuCl at reduced pressure, the colorless liquid was cooled to room temperature and subsequently placed in a freezer overnight to obtain a white precipitate, [Bmim]Cl.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: cinzia.chiappe@unipi.it.

*E-mail: maurizia.seggiani@unipi.it.

ORCID

Cinzia Chiappe: 0000-0001-6615-908X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We would like to acknowledge the kind support in the framework of the COST Action EXIL—Exchange on Ionic Liquids (CM1206). C.C. would like to thank the University of Pisa for support (PRA _2015_0015).

REFERENCES

- (1) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*, 2nd ed; Wiley-VCH: Weinheim, 2008.
- (2) Hallett, J. P.; Welton, T. Room-temperature ionic liquids: solvents for synthesis and catalysis. 2. *Chem. Rev.* **2011**, *111*, 3508.
- (3) Chiappe, C.; Pieraccini, D. Ionic liquids: solvent properties and organic reactivity. *J. Phys. Org. Chem.* **2005**, *18*, 275.
- (4) Chiappe, C.; Cevasco, G. Are ionic liquids a proper solution to current environmental challenges? *Green Chem.* **2014**, *16*, 2375.

- (5) Tran, C. D.; Mututuvuri, T. M. Cellulose, Chitosan, and Keratin Composite Materials. Controlled Drug Release. *Langmuir* **2015**, *31*, 1516.
- (6) Wang, H.; Gurau, G.; Rogers, R. D. Ionic liquid processing of cellulose. *Chem. Soc. Rev.* **2012**, *41*, 1519–1537.
- (7) Plechkova, N. V.; Seddon, K. R. Application of ionic liquids in the chemical industry. *Chem. Soc. Rev.* **2008**, *37*, 123.
- (8) Sun, X.; Luo, H.; Dai, S. Ionic Liquids-Based Extraction: A Promising Strategy for the Advanced Nuclear Fuel Cycle. *Chem. Rev.* **2012**, *112*, 2100.
- (9) Zhang, S.; Ueno, K.; Dokko, K.; Watanabe, M. Recent Advances in Electrolytes for Lithium–Sulfur Batteries. *Adv. Energy Mater.* **2015**, *5*, 1500117.
- (10) Zhang, Q.; Shreeve, J. N. M. Energetic Ionic Liquids as Explosives and Propellant Fuels: A New Journey of Ionic Liquid Chemistry. *Chem. Rev.* **2014**, *114*, 10527.
- (11) MacFarlane, D. R.; Tachikawa, N.; Forsyth, M.; Pringle, J. M.; Howlett, P. C.; Elliott, G. D.; Davis, J. H.; Watanabe, M.; Simon, P.; Angell, C. A. Energy Application of Ionic liquids. *Energy Environ. Sci.* **2014**, *7*, 232–250.
- (12) Kralisch, D.; Reinhardt, D.; Kreisel, G. Implementing objectives of sustainability into ionic liquids research and development. *Green Chem.* **2007**, *9*, 1308.
- (13) Große Böwing, A.; Jess, A. Kinetics of single- and two-phase synthesis of the ionic liquid 1-butyl-3-methylimidazolium chloride. *Green Chem.* **2005**, *7*, 230.
- (14) Khadilkar, B. M.; Rebeiro, G. L. Microwave-Assisted Synthesis of Room-Temperature Ionic Liquid Precursor in Closed Vessel. *Org. Process Res. Dev.* **2002**, *6*, 826.
- (15) Cravotto, G.; Calcio Gaudino, E.; Boffa, E.; Lévêque, J. M.; Estager, J.; Bonrath, W. Preparation of Second Generation Ionic Liquids by Efficient Solvent-Free Alkylation of N-Heterocycles with Chloroalkanes. *Molecules* **2008**, *13*, 149.
- (16) Clough, C.; Griffith, J.; Sulaiman, M. R.; Corbett, P.; Welton, T. Alkylation of 1-Methylimidazole with 1-Chlorobutane; the ionic liquid 1-Butyl-3-methylimidazolium Chloride. *CHEMSPIDER*, [10.1039/SP747](https://chemspider.org/entry/10.1039/SP747).
- (17) Bini, R.; Chiappe, C.; Pomelli, C. S.; Parisi, B. Effect of Ionic Liquids on the Menschutkin Reaction: An Experimental and Theoretical Study. *J. Org. Chem.* **2009**, *74*, 8522.
- (18) Abraham, M. H. Substitution at Saturated Carbon. Part VIII. Solvent Effects on the Free Energy of Trimethylamine, the Nitrobenzyl Chlorides, and the Trimethylamine-Nitrobenzyl Chloride Transition States. *J. Chem. Soc. B* **1971**, *0*, 299.
- (19) Jessop, P. G.; Jessop, D. A.; Fu, D.; Phan, L. Solvatochromic parameters for solvents of interest in green chemistry. *Green Chem.* **2012**, *14*, 1245.
- (20) Ab Rani, M. A.; Brant, A.; Crowhurst, L.; Dolan, A.; Lui, M.; Hassan, N. H.; Hallett, J. P.; Hunt, P. A.; Niedermeyer, H.; Perez-Arlandis, J. M.; Schrems, M.; Welton, T.; Wilding, R. Understanding the polarity of ionic liquids. *Phys. Chem. Chem. Phys.* **2011**, *13*, 16831.
- (21) Chiappe, C.; Pomelli, C. S.; Rajamani, S. Influence of structural variations in cationic and anionic moieties on the polarity of ionic liquids. *J. Phys. Chem. B* **2011**, *115*, 9653.