

*Invited Review*

## Synthesis of Ionic Liquids Using Non Conventional Activation Methods: An Overview

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**Summary.** The synthesis of ionic liquids under non conventional activation methods is historically reviewed and completed with the recent developments of “one-pot” synthesis and combination of these activation methods.

**Keywords.** Anions; Cations; Ionic liquids; Microwave; Ultrasound.

### Introduction

The first ionic liquid was synthesized in 1914 but it is in the last decade that these compounds have attracted worldwide attention as a potential alternative to organic solvents. Their remarkable chemical and physical characteristics encouraged both academic and industrial chemists to explore their use in such diverse domains as chemical analysis [1], separation [2], electrochemistry [3], engineering fluids [4], performance additives [5], and synthesis [6]. Ionic liquids (ILs) consist of organic cations (bearing charged nitrogen, sulfur or phosphorus atoms) coupled with either organic or inorganic anions. They resemble molten inorganic salts, with the capital difference that they are liquid at room temperature or

at least below 100°C. Besides being very polar, they often are non-coordinating and their vapour pressures are barely measurable, which enable them to be re-used several times. However, the properties of ILs can be tuned according to their use.

In the 1980s ILs had almost exclusive employment in electrochemistry owing to their exceptional ionic structure. The poor chemical stability towards water and air of the few ILs known at this time was however a major hindrance in regard to other applications being developed. Moreover, the classical method for their synthesis was excessively time-consuming. The emergence in the following decades of a new concern for environmental problems aroused chemists to think in terms of pollution, long-term toxicity, sustainability, and renewable materials for the design of new chemical processes. Nowadays, it is no longer a minority trend, and it results in the concept of “Green Chemistry”. “Green Chemistry” codified a set-up of rules to attempt to conciliate the increasing use of man-made chemicals with the respect and care of future generations and the preservation of ecosystems. In this context tremendous efforts have been exerted to develop and to improve the synthesis of [7] a new generation of ILs (“second-generation ionic liquids”), with even more

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interesting properties. At present, the most common classes of ILs are alkylammonium, alkyipyridinium, and *N,N'*-dialkylimidazolium salts [6].

Industry has not yet shown a great interest in using ILs but this should happen soon. Indeed, great economic and environmental benefits should arise from the use of these reaction media that are better than conventional organic solvents. Indeed, they lead to easier product's recovery, they can act both as solvent and catalyst, and they can be recycled. However, their toxicity and long term stability are still not well controlled and this remains problematic for industrial purposes [8]. Up to date factual information concerning the industrial use of ILs has been scanty, although a marked boost in the relevant literature has occurred at the turn of the century. Indeed, the publication rate of articles dealing with ILs was roughly about 20 papers a year in 1995 whereas in 2001, this rate increased up to 300 papers a year [9]. In spite of scientific indicators that assume a successful future for ILs, some major hurdles are still in the way before their industrial use becomes routine, *viz.*

1. Safety from the health and environmental standpoints have to be established.
2. Analysis of economic benefits has to be carried out.
3. Swift and cheap production of ILs have to be finalized.
4. New applications in production.
5. Application as solvent in new analytic methods (head space GC).
6. Synthesis of halogen-free and/or chiral ILs.

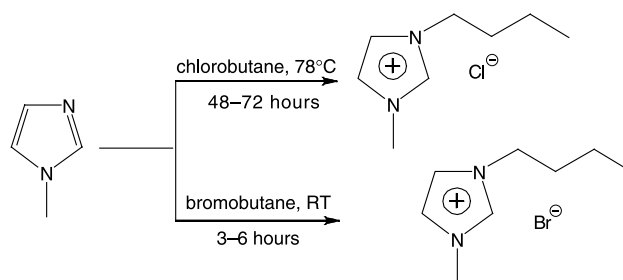
The subject of the present review is to answer the questions of easy, cheap, and fast synthesis of ILs. Indeed, the classic synthetic procedure for ILs production is not satisfactory [10]. Non-conventional activation methods, arising from the academic research in the early eighties, became popular almost in the same time than the advent of second-generation ionic liquids. Microwave (MW) [11] and ultrasound (US) [12] are nowadays the best known and most used non-conventional activation techniques at a laboratory scale. Industry also shows a growing interest in the application of MW and, to a lower extent, US technologies. MWs act by a rapid and dielectric heating of polar materials whereas US brings out interesting chemical and physical effects by the physical phenomenon of cavitation. US has been used for many years by organic chemists and bio-

chemists to enhance reaction rates, decrease reaction times, and avoid harsh experimental conditions [13, 14]. Laboratories engaged in the synthesis, the characterization, and the use of ILs have been quick to take advantage of the great potential of these methods in order to improve, to speed-up, and to simplify their preparation. Owing to their ionic nature, ILs strongly absorb MW radiations. Moreover, MW- and US-promoted reactions have been successfully carried out in non-conventional media such as ILs. Thus, throughout the "Green Chemistry principles", a synergy was born between non-conventional methods and non-conventional media in a way to make ILs preparation easier.

### Synthesis of First-Generation or Halogenated ILs

The first generation of ILs is accessible through a  $S_N2$  mechanism by quaternarization of the heteroatom (nitrogen or phosphorus) of an organic heterocycle, for example, an imidazole derivative. Classically, the synthesis of ILs based on 1-butyl-3-methylimidazolium cation [*bmim*]<sup>+</sup> can last from a few hours for the bromide to a few days for the chloride. Bromide-based ILs are easily accessible, but alkyl bromides are much more expensive and less available than alkyl chlorides. As chloride is a worse nucleophile compared to bromide, some energy is necessary to increase the reaction rate. This accounts for the various reaction times and experimental conditions required to prepare [*bmim*]Cl and [*bmim*]Br, as shown in Scheme 1.

First-generation ILs do not have many applications because they all are hydrophilic and relatively unstable in the presence of air and moisture. Second-generation ILs that are obtained by anion metathesis from the former generation are more interesting. Indeed, these compounds are hydrophobic and ex-



Scheme 1

hibit remarkable properties, that is why improving the synthesis of first-generation ILs has become such an important target.

In 2001, *Varma et al.* [15] reported the first MW-assisted neat preparation (open vessel) of several imidazolium-based ILs using an excess of alkyl halide. The authors found that the reactivity trend was  $I > Br > Cl$ , alkyl chlorides being slow to react. This procedure led to a drastic decrease of the reaction time, from a few days down to a few minutes in the most impressive instances. The IL that begins to form under MW irradiation increases the polarity of the medium, and consequently the rate of MW absorption. However, the use of alkyl halides in an open vessel is somehow hazardous, and the purity of products is also unsatisfactory. Moreover, use of an open vessel under intense heating to synthesize very hygroscopic compounds entails strong water absorption, forbidding any possible scale-up, as products have to be dried under high vacuum prior to use. The authors, also finding that continuous irradiation led to a partial decomposition of cationic moieties, intermittently irradiated and mixed the reaction mixture. They repeated the alternate irradiation-mixing procedure until the formation of a clear single phase was obtained. Nevertheless, *Chan et al.* [16] pointed out that this procedure was difficult to reproduce in a common household reactor and that an overheating of the reaction mixture generated vapours and led to product's decomposition; a short-circuit of the MW reactor was sometime observed. Indeed, they reported a marked overheating under continuous irradiation and also emphasised that runaway reactions were fairly common with solvent-free systems, in which effective heat dissipation by the solvent did not play any role. According to them some of these problems could be avoided either with the use of focused MW, allowing a more precise control of both temperature and radiation intensity, or by the dispersal of reactants on inert solid supports. In the case under discussion, overheating could be exacerbated because the halide salt is more polar than the starting materials, and consequently absorbs MW more strongly. They suggested a simple modification of the *Varma's* procedure allowing large-scale preparation of first-generation ILs in an unmodified household MW reactor. They then immersed the reactor containing the starting materials in a tank of water that had been preheated to 60°C and placed the entire system in an unmodified house-

hold reactor equipped with five power levels. This set-up prevented both the overheating and the danger of runaway reactions. At the beginning of the reaction, the overall polarity of the starting materials is lower than the one of the water mantle. The MW absorption is therefore unequally distributed between the two compartments and the water heats up to around 80°C. When enough IL has formed, the overall polarity of the reaction mixture overtakes the one of water, so that the former absorbs more strongly MWs and the formation rate of the ionic compound increases. The effects of MW power levels and duration of heating were examined to optimize the reaction conditions. The reaction batch was mixed in between each irradiation step and the alternate irradiation/mixing was repeated until a clear single phase was formed. The authors noted that the first irradiation step was of key importance as an overheating at this stage or a too long irradiation time initiated the decomposition of the reaction mixture. This step had to be shortened and conducted at a lower power level than successive ones. *Chan et al.'s* modification probably yielded purer ILs than those previously obtained, but it seemed to work only with alkyl bromides [16]. Indeed, if it erased some problems, it was unfit for the preparation of ILs from alkyl chlorides, as the required heating was much stronger than for bromides.

All the aforementioned MW-assisted methods used modified or unmodified household reactors that did not allow any effective control of power, hence of temperature and/or pressure of the reacting system. It is no wonder if the reproducibility of results obtained with such reactors is unpredictable, which is a serious obstacle to establish a generalized MW-assisted method. Finally, an excess (10–300% molar) of alkyl halide was necessary for the reaction to be completed, which decreased the greenness of the process. In addition, large amounts of organic solvents had to be used to remove non converted starting materials and reaction by-products. *Rebeiro et al.* [17] improved the procedure in a modified CEM microwave digester (MARS-S) by using a closed vessel with an upper cooling system fitted to the top, at least when pressure was unnecessary. The advent of multimode and monomode reactors – *i.e.* with MWs directly focused on the target reactor – allowed reactions to be controlled in a very strict manner with a monitoring of temperature, power, and pressure (Fig. 1).



**Fig. 1.** Professional multimode MW reactor MARS-S (CEM)

The authors noticed that the higher the temperature inside the reactor, hence the pressure in closed vessels, the shorter the reaction time. A further advantage of this procedure was the diversification of starting chemicals and the use of fine power control. Thus, the authors claimed that the method could be generalized, using several nitrogen-based organic structures together with different alkyl bromides and chlorides. Table 1 summarizes some of their key results.

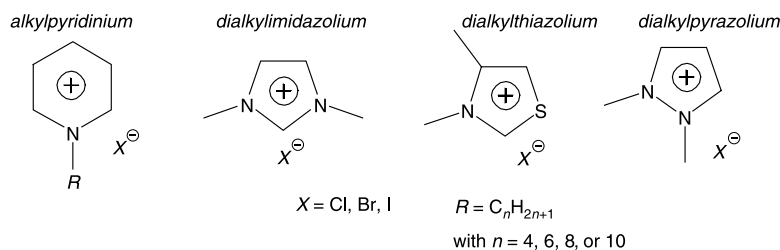
These data are consistent with the reactivity trend highlighted by Varma *et al.* [15] for alkyl halides and show that a general procedure for the preparation of first-generation ILs could be developed under MW irradiation, even though results with lutidine did not appear to be optimized. In 2003 Deetlefs *et al.* [18]

reported a method for the preparation of a very large number of nitrogen-based first-generation ILs. This work conformed to Green Chemistry guidelines as it was carried out under solvent-free conditions, took a very short time, and had high atom efficiency. It covered a large scale of concentrations (50 mM–2 M) in either sealed or open vessels, thanks with a fine control of power and reaction time. By using a very small molar excess of alkyl halides (1–2%) it avoided the use of large amounts of solvents for purification. Compared to classical methods of synthesis, MW-based techniques clearly proved more efficient because of their speed, their low amounts of solvent or their solvent-free conditions and finally, their applicability to a broad spectrum of nitrogen-based precursors. Figure 2 presents a comprehensive view of ILs synthesised by Deetlefs *et al.* [18].

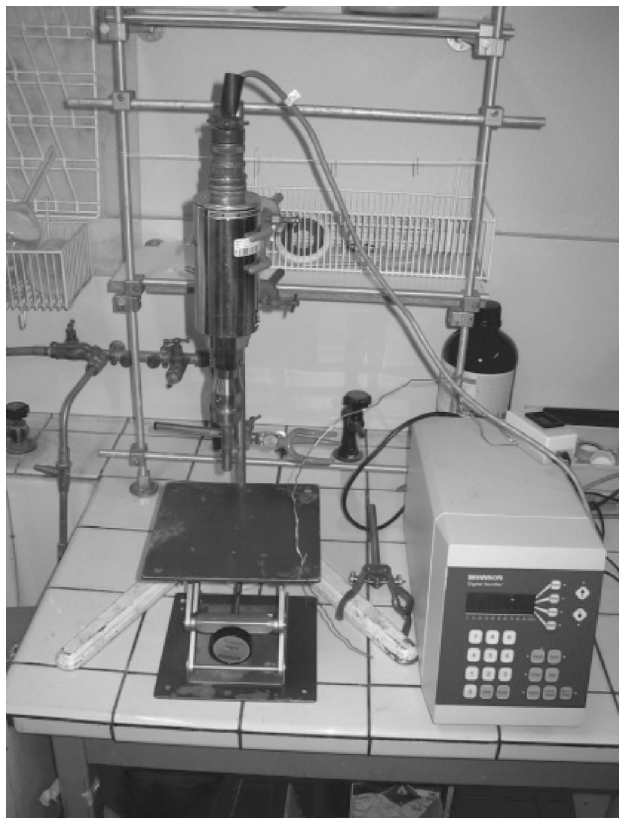
US technology has been approached to a lesser extent in the preparation of first-generation ILs, once again by Varma *et al.* [19]. To our best knowledge, this is the only paper dealing with the preparation of first-generation ILs under US irradiation. Besides generating highly reactive intermediates, such as radical species, in heterogeneous systems US may cause physical effects, such as micro-emulsion, mass transport, and reduction of particle size [20]. The passage of low frequency (20–40 kHz) sound waves also heats up the reacting system.

**Table 1.** Synthesis of first generation ILs in a professional MW multimode reactor

Amine	RX	Time/min	$T/^{\circ}\text{C}$	$P/\text{bar}$	Yield/%
1-Methylimidazole	1-Bromobutane	2.5 + 0	105	/	99
1-Methylimidazole	1-Chlorobutane	2 + 22	150	3.93	91
Pyridine	1-Bromopropane	1 + 2	120	2.00	86
Pyridine	1-Chloropropane	5 + 85	150	5.45	56
2,6-Lutidine	1-Bromobutane	5 + 55	200	12.41	58
2,6-Lutidine	1-Chlorobutane	5 + 55+	200	12.41	10
		(5 + 25)	230	13.17	
Pyridine	2-Phenethyl chloride	5 + 55	200	3.86	98



**Fig. 2.** Preparation of first-generation ILs in a professional multimode MW reactor



**Fig. 3.** Professional 20 kHz Ultrasonic probe (BRANSON “Digital Sonifier”)

Varma *et al.* used the combination of all these subsequent effects to design a neat US-assisted procedure to be carried out in a closed vessel [19]. As the quaternarization step of the nitrogen heterocycles involves an ionic pathway ( $\text{S}_{\text{N}}2$ ), US not only heats up the starting materials and initiates the reaction, but also provides an efficient mixing that is particularly effective on heterogeneous systems and generally

**Table 2.** Ultrasonic preparation of first-generation ILs

Alkyl halide <sup>a</sup>	Time/h	Yield/%	Time/h <sup>d</sup>	Yield/% <sup>d</sup>
1-Bromopropane	2	95 <sup>b</sup>	2	0
1-Bromobutane	2	94 <sup>b</sup>	6	0
1-Bromooctane	2	93 <sup>b</sup>	6	0
1-Chlorobutane	6	24 <sup>b</sup>	6	0
	2	86 <sup>c</sup>	2	0
1-Chlorohexane	6	31 <sup>b</sup>	6	0
	0.5	89 <sup>c</sup>	2	0
1-Chlorooctane	6	42 <sup>b</sup>	6	0
	0.25	93 <sup>c</sup>	2	0

<sup>a</sup> Alkyl halide/methylimidazole: 1.1/1; <sup>b</sup> ultrasonic bath;

<sup>c</sup> ultrasonic probe (20 kHz); <sup>d</sup> silent conditions (mechanical stirring)

overcomes the high viscosity of ILs. For example, when 1-methylimidazole and bromo- or chlorobutane are mixed together, the resulting system is homogeneous. However, as the IL starts to form, it separates out as a second phase. Because of its high viscosity, the resulting heterogeneous system cannot be efficiently mixed by common stirring devices, which accounts for the long reaction times that generally result from this arrangement. Table 2 shows a comparison of results obtained with and without US irradiation.

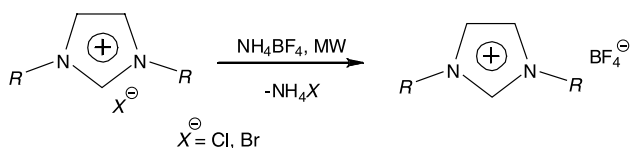
Using an ultrasonic bath for alkyl bromides or iodides and an ultrasonic probe for alkyl chlorides, the authors achieved a solvent-free procedure resulting in shorter reaction times and lower reaction temperatures when compared with conventional methods. In addition, they reported that products were generally purer. Although this method was designed only for dialkylimidazolium salts and was not developed for a variety of nitrogen-based cations as was the case for MW-assisted methods, its results prove that US is also effective in improving the preparation of first-generation ILs.

### Synthesis of Second-Generation ILs

The successful application of non-conventional activation methods for the synthesis of first-generation ILs being established, several research groups adapted them to synthesize second-generation ILs. These comprise ILs owning even more remarkable physical and chemical properties, and offering new perspectives of application. One of the most promising property is recycling and re-use. This important family of ILs is accessed by exchanging the halide anions of first-generation ILs with bulkier ones, most commonly bis(trifluoromethanesulfonyl) imide ( $\text{NTf}_2^-$ ), hexafluorophosphate ( $\text{PF}_6^-$ ), tetrafluoroborate ( $\text{BF}_4^-$ ), and trifluoromethanesulfonate ( $\text{CF}_3\text{SO}_3^-$ ). The classic method used for this exchange or metathesis requires 24–48 h at room temperature in acetone and in a heterogeneous system. The product is then purified and large amounts of organic molecular solvents are required to remove the resulting mineral salts together with not converted starting materials. Finally the IL is dried under high vacuum for a few hours. When all steps (synthesis, purification, and drying) are added up, this procedure is quite time-consuming and priceless when considering that industry-affordable ILs are

possibly reusable solvents, a major economic obstacle to a general use of ILs. Although, several attempts were made to improve the synthetic route using different reagents such as  $\text{HPF}_6$  or  $\text{HBF}_4$ , none of them really conformed to the principles of “Green Chemistry”. Another drawback was the outlay required to remove impurities and water, neither being permissible in a “general” solvent that should cope with water, air, acids, bases, and electrochemical processes. Adding new chemicals to speed up the reaction may also complicate purification. Non-conventional activation methods offer an acceptable means toward a faster production of purer ILs, resulting in a higher space-time-yield and a decrease of costs. Once again, *Varma et al.* published in 2002 [21] a MW-assisted preparation of  $\text{BF}_4$ -based dialkylimidazolium ILs. Starting from bromide or chloride precursors with a  $\text{C}_4$ – $\text{C}_8$  side chain and the ammonium  $\text{BF}_4$  salt, they used in solvent-free conditions the previously described procedure [15] with the same unmodified household reactor (Scheme 2).

They repeated the treatment until a fine precipitate of ammonium halide was formed. Surprisingly, they did not try to generalize this interesting method with other commercially available salts such as  $\text{NH}_4\text{PF}_6$

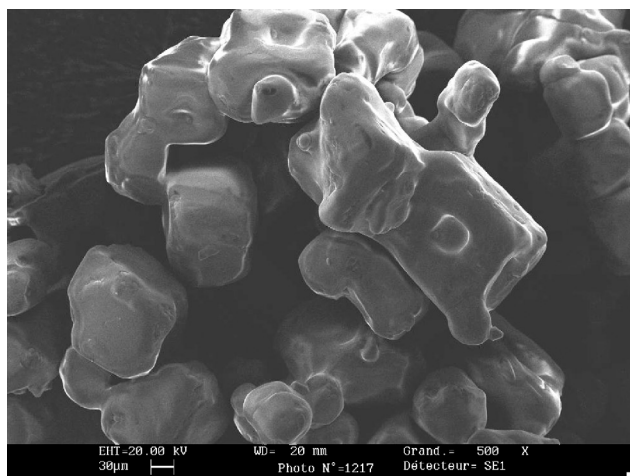


**Scheme 2**

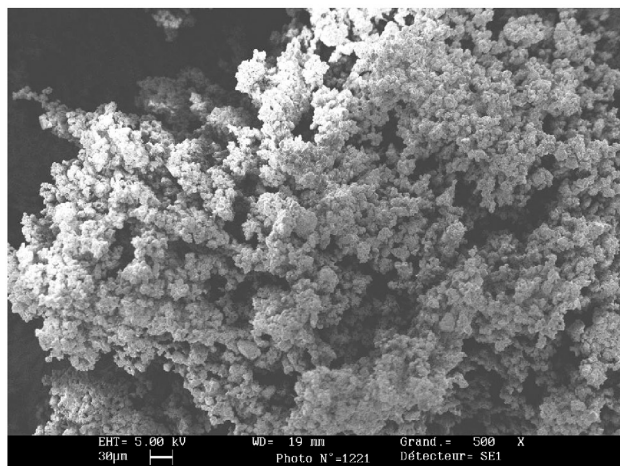
or  $\text{NH}_4\text{OTf}$ , possibly because they met with experimental problems, as ammonium salts are not very stable under heating.

The above-quoted results indicate that a MW based procedure is the best choice for the preparation of first-generation ILs, as the starting system is homogeneous. This conclusion does not hold for the metathesis reaction, which under conventional conditions usually takes place at room temperature in a heterogeneous system. In this case there is no need for a rapid heating to increase the reaction rate. However, a really efficient mixing of the heterogeneous system is needed. To this purpose US is well suited, as the mechanical effects of cavitation cause a marked reduction of particle size, resulting in a micro-emulsion and an enhancement of mass transport. We took these considerations into account in designing a generalized US-assisted procedure for the synthesis of second-generation ILs. In 2002 *Lévêque et al.* [22] described a mild, efficient, and swift method to access several  $\text{C}_4$ – $\text{C}_8$  dialkylimidazolium-based ILs with  $\text{PF}_6$ ,  $\text{BF}_4$ ,  $\text{OTf}$ , and  $\text{N}(\text{Tf})_2$  anions, working in acetone under low-frequency US (20–30 kHz). The vigorous US-induced mixing of the solid–liquid–liquid reaction system markedly reduced the particle size of the ammonium salts that correspondingly increased the reaction rate (Fig. 4).

Reaction time was decreased from 24–48 to 1–2 h; moreover, the increased reaction rate minimized side-reactions, resulting in a higher overall purity of products. For hydrophobic ionic moieties, only water was used to remove resulting mineral salts; the

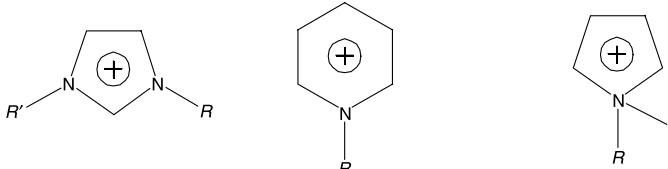


Before sonication



After sonication

**Fig. 4.** Reduction of particle size of ammonium  $\text{BF}_4$  by US (20 kHz)



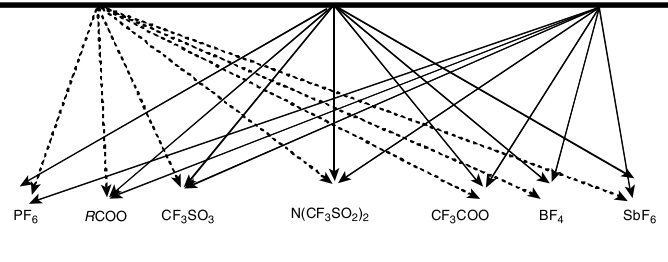
	1-alkyl-3-alkyl imidazolium	N-alkyl pyridinium	N-alkyl-N-methyl pyrrolidinium
Example	1-butyl-3-methyl-imidazolium	1-butylpyridinium	2-butyl-N-methyl-pyrrolidinium
Name of the cation	<i>bmim</i>	<i>C4pyr</i>	<i>bmpyrrol</i>
Counter anion	chloride	bromide	chloride
Full Name	<i>bmimCl</i>	<i>C4pyrBr</i>	<i>bmpyrrolCl</i>
possible counter-anions			

Fig. 5. Overview of the US-assisted preparation of second-generation ILs

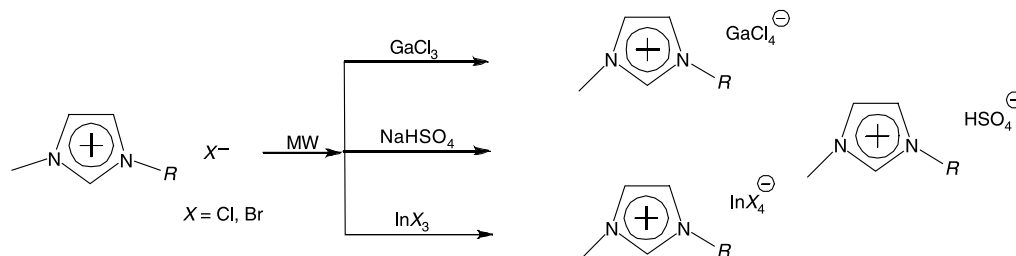
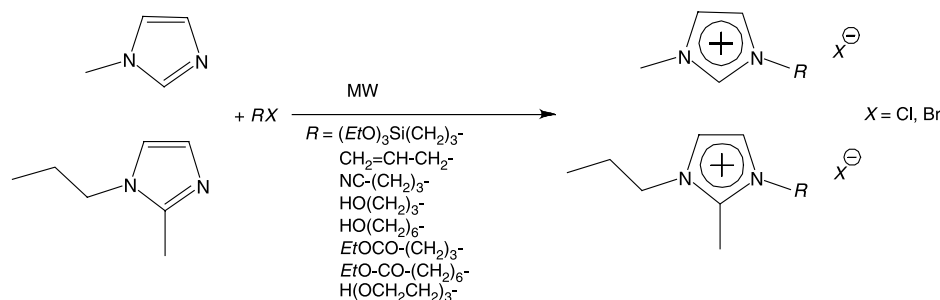
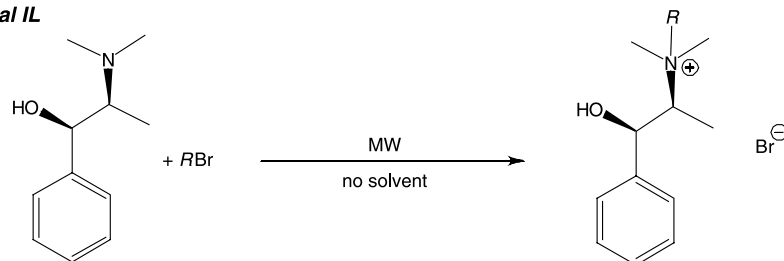
reacted mixture was first poured into water and then extracted with a suitable organic solvent. Finally, the product was dried under high vacuum to remove water *prior to* use. For hydrophilic ones, the mixture was first poured into a minimum of dichloromethane and then washed several times with water and the product dried under high vacuum. In 2006 the procedure was extended to other amines and anions, proposing a standardized method [23] as shown in Fig. 5.

### Synthesis of Third-Generation ILs

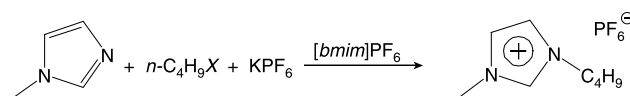
A third generation of ILs, known as Task-Specific Ionic Liquids (TSIL), recently emerged [24]. These compounds are designed for specific tasks as solvent and/or catalyst to be used in a particular chemical process. For their preparation a procedure under MW irradiation can be rapidly developed according to the characteristics of the starting materials and the homogeneous/heterogeneous nature of their mixture. As already pointed out, MW irradiation

will work better on a homogeneous system. Many research groups are equipping their laboratories with professional reactors to access a multitude of known and unknown ILs. Figure 6 presents a non-exhaustive overview of published MW-assisted preparations.

An easy access to ILs containing organometallics or functionalized side chains opens an exciting vista of enhanced reactivities [25]. The design of chiral ILs derived from biomass might achieve a breakthrough in the field of stereochemistry by replacing with recyclable ILs not only molecular organic solvents, but also expensive chiral catalysts. In many reactions re-usable ILs may play many roles. ILs containing organometallics or functionalized side chains have already proved applicable to catalytic systems [26] and water treatment [27]. Examples have also been reported of chiral induction by ILs obtained from biomass or otherwise, although so far observed *ee%* values are too low to warrant industrial applications [28]. Many groups are currently pursuing the search for a more effective recyclable

**Anion metathesis****Side chain functionalization****Design of chiral IL****Fig. 6.** Overview of some procedures for the synthesis of ILs under MW irradiation

solvent/chiral dual inductor. Basically no synthesis limit exists to design any structure of IL, as long as the products remain liquid at least below 100°C.

**Scheme 3****One-Pot or Three-Component Synthesis of ILs**

Another goal of “Green Chemistry” is to reduce the number of synthesis steps and also to decrease the solvent amount required for both synthesis and work-up. A three-component, one-step synthesis of second-generation ILs would be very advantageous not only in terms of environmental impact but also in terms of time consumption and industrial access. However, to the best of our knowledge only one report of such a synthesis was published in the literature, and that was using conventional activation [29]. In this paper *Xu et al.* described a one-pot synthesis of various imidazolium-based second-generation ILs using the target compounds themselves as

reaction media [29]. One-pot synthesis of 1-butyl-3-methylimidazolium hexafluorophosphate  $[bmim]PF_6$  follows as described in Scheme 3.

Although these results are interesting from the standpoint of eco-chemistry, reactions were quite long, especially when alkyl bromides and chlorides were used: it took 15 h to obtain  $[bmim]PF_6$  from the corresponding bromide IL and 35 h from the chloride. As pointed out, US is known to accelerate not only the quaternarization of nitrogen but also anion metathesis through the reduction of particle size. Our team applied US to one-pot synthesis for a rapid access to second-generation room-temperature ILs



**Table 3.** One-pot, US-assisted synthesis of room-temperature ILs

Amine <sup>a</sup>	PF <sub>6</sub> salt	Alkyl halide	T/°C <sup>b</sup>	Time/min	Yield/% <sup>c</sup>
1-Methylimidazole	KPF <sub>6</sub>	1-Bromooctane	85	120	85
1-Methylimidazole	KPF <sub>6</sub>	1-Bromopentane	87	180	87
Pyridine	KPF <sub>6</sub>	1-Bromooctane	81	180	86
1-Methylpyrrolidine	KPF <sub>6</sub>	1-Bromooctane	80	40	86
1-Methylimidazole	KOTf	1-Bromooctane	83	180	90
Pyridine	KOTf	1-Bromooctane	85	180	75
1-Methylimidazole	KBF <sub>4</sub>	1-Bromooctane	80	180	78

<sup>a</sup> Amine/potassium salt/alkyl halide 1 eq./1 eq./1 eq., ultrasonic irradiation: 20 kHz, acoustic power 0.99 W cm<sup>-3</sup>; <sup>b</sup> temperature increased because of ultrasound, a cryostat was used to counter heating; <sup>c</sup> isolated yield

[30]. Several ILs families were synthesized in much shorter times than under thermal activation. Some of our results are given in Table 3.

Yields up to 87% and good purities were obtained with various families of anions, cations, and alkyl bromides; reaction times were much shorter compared to those reported by *Xu et al.* and these neat syntheses fully comply with “Green Chemistry” rules [29].

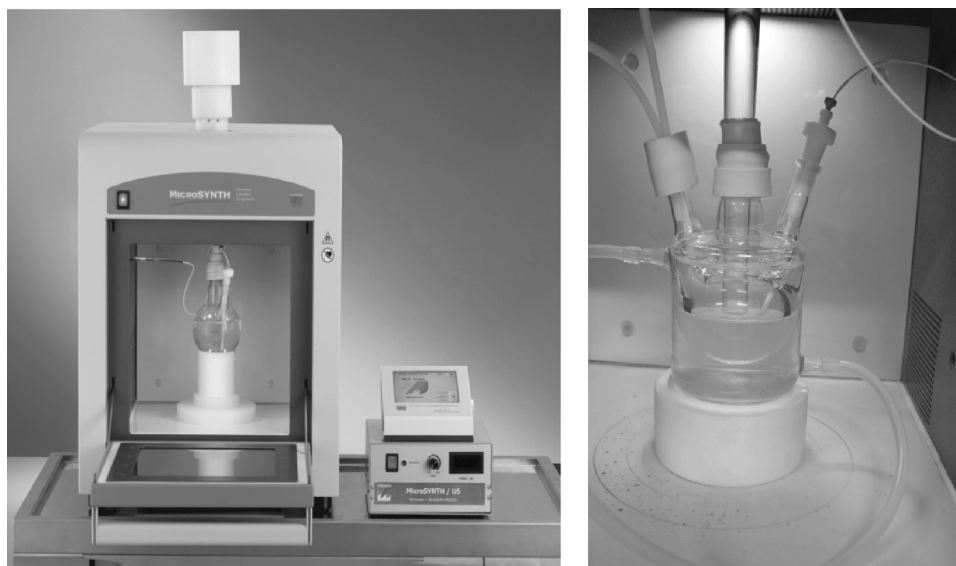
Very recently *Cravotto et al.* proposed an improved method [31], combining MW and US irradiations, for one-pot synthesis of room-temperature ILs. As discussed above, MW and US can speed up both steps of IL synthesis. Recent advances showed that simultaneous US/MW irradiation, being practically hazard-free, represents an emerging technological innovation that deserves widespread attention in fine-chemical research [32]. A US-probe prototype with

horn that does not absorb MW [33] made it possible to cumulate the benefits of expeditious MW heating and of particle-size reduction effected by US. Figure 7 shows the combination of US probe and MW reactor.

Results from this innovative patented protocol were excellent: high yields of second-generation ILs were obtained in very short reaction times (3–25 min, depending on the kind of IL targeted). Some results of this study are given in Table 4.

One of the main obstacles to large-scale commercialization and industrial use of ILs is the lack of performance data in industrial conditions, as well as lack of toxicological data.

Several efficient and rapid ways of access to ILs under conventional and non-conventional activations have been developed on laboratory scale. The next



**Fig. 7.** Multimode microwave reactor (Milestone BG-Italy) combined with a Pyrex ultrasonic horn (Danacamerini TO-Italy), also with a cooling system (on the right)

**Table 4.** One-pot synthesis of ILs under combined MW/US activation

Amine <sup>a</sup>	PF <sub>6</sub> salt	Alkyl halide	T/°C <sup>b</sup>	MW power/W	US power/W	Time/min	Yield/% <sup>c</sup>
1-Methylimidazole	KPF <sub>6</sub>	1-Bromooctane	120	35	45	3	93
1-Methylimidazole	KPF <sub>6</sub>	1-Bromobutane	90	25	35	10	80
Pyridine	KPF <sub>6</sub>	1-Bromooctane	110	20	40	10	95
1-Methylimidazole	LiN(Tf) <sub>2</sub>	1-Bromooctane	140	45	45	25	94

<sup>a</sup> Amine/potassium salt/alkyl halide 1 eq./1 eq./1 eq., ultrasonic irradiation: 20 kHz, acoustic power 0.99 W/mL; <sup>b</sup> temperature increased because of ultrasound, a cryostat was used to counter heating; <sup>c</sup> isolated yield

step will be process design based on chemical properties and thermodynamic data obtained with pilot plants. Scale-up is necessary to fully understand the behaviour of these compounds and to build up, in a second phase, their large-scale use. However, before this, a thorough toxicological study of these compounds must be carried out. It would also be interesting to develop eco-friendly, and/or biodegradable ILs. Although the industrial use of non-conventional activation methods is still very limited, their rapid development not only in organic synthesis but also in cosmetics, food, water treatment, *etc.* will certainly create a diffuse awareness of their advantages from an ecologic standpoint. Moreover, the numerous ways to synthesize ILs developed in the last two decades under both conventional and non conventional activation methods should lead to their scaling-up for industrial purposes.

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### References

- [1] Pandey S (2006) *Anal Chem Act* **556**: 38
- [2] a) Luo H, Dai S, Bonnesen PV, Buchanan III AC (2006) *J Alloys Compounds* **418**: 195; b) Meindersma G, Podt A (JG), de Haan AB (2005) *Fuel Proc Tech* **87**: 59
- [3] a) de Souza RF, Padilha JC, Goncalves RS, Rault-Berthelot J (2006) *Electrochem Comm* **8**: 211; b) Villagran C, Aldous L, Lagunas MC, Compton RG, Hardacre C (2006) *J Electroanal Chem* **588**: 27; c) Zhang S, Hou Y, Huang W, Shan Y (2005) *Electrochim Acta* **50**: 4097; d) Lagrost C, Carrié D, Vaultier M, Hapiot P (2003) *J Phys Chem* **107**: 745
- [4] a) Wong HT, Han S, Livingston AG (2006) *Chem Engin Sci* **61**: 1338; b) Basheer C, Vetrichelvan M, Suresh V, Lee HK (2006) *Tetrahedron Lett* **47**: 957
- [5] Weyershausen B, Lehmann K (2005) *Green Chem* **7**: 15
- [6] For reviews see a) Taubert A, Li Z (2007) *Dalton Trans*: 723; b) Chowdhury S, Mohan RS, Scott JL (2007) *Tetrahedron* **63**: 2363; c) Welton T (1999) *Chem Rev* **99**: 2071
- [7] Wilkes JS, Zaworotko MJ (1992) *J Chem Soc Chem Commun*: 965
- [8] a) Zhao D, Liao Z, Zhang Z (2007) *Clean* **35**: 42; b) Docherty KM, Kulpa CF Jr (2005) *Green Chem* **7**: 185
- [9] Wilkes JS (2002) Introduction. In: Wassercheid P, Welton T (eds) *Ionic Liquids in Synthesis*. Wiley-VCH, Weinheim, Germany, p 1
- [10] Davis JH (2002) Synthesis and Purification of Ionic Liquids. In: Wassercheid P, Welton T (eds) *Ionic Liquids in Synthesis*. Wiley-VCH, Weinheim, Germany, p 7
- [11] Loupy A (ed) (2006) *Microwaves in Organic Synthesis*. Wiley-VCH, Weinheim, Germany
- [12] Cravotto G, Cintas P (2006) *Chem Soc Rev* **35**: 180
- [13] a) Lidström P, Tierny J, Wathey B, Westman J (2001) *Tetrahedron* **57**: 9225; b) Loupy A (2004) *CR Chimie* **7**: 103; c) Loupy A (ed) (2006) *Microwaves in Organic Synthesis*. Wiley-VCH, Weinheim, Germany
- [14] Mason TJ (ed) (1990, 1991, 1993, 1995, 1999, 2001) *Advances in Sonochemistry*, Vol. 1–6. JAI Press Ltd, London, England
- [15] Varma RS, Namboodiri VV (2001) *Chem Comm*: 643
- [16] Law MC, Wong KY, Chan TH (2002) *Green Chem* **4**: 328
- [17] Khadilkar BM, Rebeiro GL (2002) *Org Proc Res Develop* **6**: 826
- [18] Deetlefs M, Seddon KR (2003) *Green Chem* **5**: 181
- [19] Namboodiri VV, Varma RS (2002) *Org Lett* **4**: 3161
- [20] a) Luche JL (ed) (1998) *Synthetic Organic Sonochemistry*. Plenum Press, New-York; b) Luche JL (1990) *Ultrasonically Promoted Carbonyl Addition Reactions*. In: Mason TJ (ed) *Advances in Sonochemistry*, Vol. 1, JAI Press Ltd, London, England, p 119; c) Ando T, Kimura T (1991) *Ultrasound Organic Synthesis Involving Non Metal Solids*. In: Mason TJ (ed) *Advances in Sonochemistry*, Vol. 2. JAI Press Ltd, London, England, p 211
- [21] Namboodiri VV, Varma RS (2002) *Tetrahedron Lett* **43**: 5381
- [22] Lévêque JM, Luche JL, Pétrier C, Roux R, Bonrath W (2002) *Green Chem* **4**: 357
- [23] Lévêque JM, Desset S, Suptil J, Fachinger C, Draye M, Bonrath W, Cravotto G (2006) *Ultrason Sonochem* **13**: 189
- [24] For examples see a) Zhang ZC (2006) *Adv catal* **49**: 153; b) Forbes DC, Weaver KJ (2004) *J Mol Cat A: Chem* **214**: 129; c) Kamal A, Chouhan G (2005) *Tetrahedron*

- Lett **45**: 1489; d) Davis JH Jr (2004) Chem Lett **9**: 1072; e) Bates ED, Mayton RD, Ntai I, Davis JH Jr (2002) J Am Chem Soc **124**: 926; f) Fraga-Dubreuil J, Bazureau JP (2001) Tetrahedron Lett **42**: 6097
- [25] Wassercheid P, Welton T (eds) (2002) Ionic Liquids in Synthesis. Wiley-VCH, Weinheim, Germany
- [26] Lee SG (2006) Chem Comm: 1049
- [27] a) Germani R, Mancini MV, Savelli G, Spreti N (2007) Tetrahedron Lett **48**: 1767; b) Vijayaraghavan R, Vedaraman N, Surianarayanan M, MacFarlane DR (2006) Talanta **69**: 527; c) Heitzman B, Young BA, Rausch DJ, Rickert P, Stepinski DC, Dietz ML (2006) Talanta **69**: 527
- [28] a) Ni B, Garre S, Headley AD (2007) Tetrahedron Lett **48**: 1999; b) Guo HM, Niu HY, Xue MX, Guo QX, Cun LF, Mi AQ, Jiang YZ, Wang JJ (2006) Green Chem **8**: 682; c) Vo Thanh G, Pegot B, Loupy A (2004) Eur J Org Chem: 1112; d) Vo Thanh G, Gori D, Loupy A (2004) Tetrahedron Lett **45**: 6425
- [29] Xu DQ, Liu BY, Luo SP, Xu ZY, Shen YC (2003) Synthesis **17**: 2626
- [30] Estager J, L  v  que JM, Cravotto G, Boffa L, Bonrath W, Draye M (2007) Synlett (in press)
- [31] Cravotto G, Boffa L, Estager J, L  v  que JM, Draye M, Bonrath W, US Patent application No 60/800,011
- [32] Cravotto G, Cintas P (2007) Chem Eur J **13**: 1902
- [33] a) Cravotto G, Buffa C, Omiccioli G (2006) Patent application TO A 000766; b) Cravotto G, Omiccioli G, Buffa C, Dal Lago G (2004) Patent Application VR A000167