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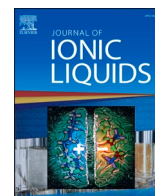
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## Easy to scale up synthesis of a high-purity piperidinium based ionic liquid combining both sustainability and cost-effectiveness

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### ABSTRACT

Ionic liquids have attracted much attention these last years because they have been identified as a new class of media offering interesting opportunities to transfer the traditional chemical processes to new, clean and eco-friendly technologies. But in order for these compounds to achieve their commercial potential, it must be demonstrated that they can be produced in hundreds of kilograms at a time in a benign simple and highly efficient way. However, the main applications in which they are involved require a high degree of purity. In the context of the circular economy and with the aim of developing a generic, straightforward, economical and eco-friendly method for high-purity piperidinium-based ionic liquids preparation, we investigate here the experimental conditions of determining step of the synthesis *i.e.* the Menshutkin reaction. This enables use to offer a high-yield and high-quality protocol, that is easy to scale up and that combines sustainability with cost-effectiveness.

### Introduction

Ionic liquids (ILs), *i.e.* molten salts with melting points less than 100 °C at atmospheric pressure, (Hagiwara and Ito, 2000) have attracted much attention these last years. (R.D Rogers and Seddon, 2003; Chatel et al., 2018; Lei et al., 2017) Indeed, these almost non-flammable, non-volatile and recyclable solvents have been identified as a new class of media offering interesting opportunities to transfer the traditional chemical processes to new, clean and eco-friendly technologies. (R.D. Rogers and Seddon, 2003) Their original and interesting properties, such as good thermal, (Meine et al., 2010) chemical and electrochemical stabilities, (Qingbo et al., 2016) tunable polarity and basicity/acidity, (Yang et al., 2018) wide electrochemical window, (Hapiot and Lagrost, 2008) etc., endow ILs with interesting prospects in various industrial applications, such as solvents for the syntheses, catalysis, analytical separations, extractions, electrochemistry, lubrication for example. (Durga and Mishra, 2016; Gutowski, 2018) From an application point of view major concern in the preparation of ionic liquids is their purity (Srouf et al., 2013), especially when they are

involved in analytical purposes. Another issue that needs to be addressed to achieve efficient commercial synthesis and make these compounds available on an industrial scale is their production and commercialization costs. (Shamsuri and Abdullah, 2010) Indeed, their preparation often involves high E factor processes making them circuitously prohibitively expensive. (Deetlefs and Seddon, 2010) But in order for these compounds to achieve their commercial potential, it must be demonstrated that they can be produced in hundreds of kilograms at a time. (Rakita, 2003) Finally, in the current context of green chemistry it is highly desirable to develop environmentally benign, simple and highly efficient syntheses. (Zakeri et al., 2017)

Based on green chemistry principles and the use of green metrics, Deetlefs and Seddon discussed the greenness of some typical laboratory ionic liquid preparations; (Deetlefs and Seddon, 2010) their conclusion was: 'Green, but not green enough'. Since this paper, efforts have been made to improve ionic liquid synthesis by using methods reducing their environmental impact. In a previous work (Chatel et al., 2012) we revisited the synthesis of lipophilic piperidinium-, pyrrolidinium-, imidazolium and pyridinium- bis(trifluoromethanesulfonyl)imide ionic

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liquids used for indium electrodeposition, (Traore et al., 2011) and the protocols were advantageously optimized as highlighted by their greatly decreased E-factor. Unfortunately, the main drawback of these protocols was a lack of purity of the ionic liquid. Indeed, first generation ethylpiperidine-based ionic liquid (Chatel et al., 2012) for example, was obtained as a white, lightly yellow, hygroscopic powder, probably due to the presence of degradation products formed during the quaternization reaction of ethylpiperidine, impacting the purity of the second generation one. Significant time and efforts have then to be devoted to the purification of the quaternized intermediate prior to anion exchange, (Ward et al., 2007) discrediting the greenness and the performance of the experiment. Indeed, the purity of ionic liquids is key condition for their use in electrochemistry for example. (Ignat'ev et al., 2012) The standard protocols published in the literature for the synthesis of piperidinium based ionic liquids usually result in lightly yellow materials whereas ammonium cation-based liquids should appear water-white when pure. In addition, the transparency of the ionic liquid does not guarantee its purity; and most of the time, even if the ionic liquid appears transparent, its use in electrochemistry can reveal the presence of impurities even at extremely low concentrations. Unfortunately, a low concentration of impurity on a laboratory scale quickly becomes problematic on an industrial scale. Main studies devoted to the synthesis of pure ionic liquids are focused on the anionic metathesis step. In this work, the efforts are concentrated on the Menshutkin reaction, which control is then shown to be crucial for the purity of the ionic liquid. Indeed, the importance of the control of the Menshutkin reaction was already shown for synthesis of co-crystals in high yield and purity (Pfrunder et al., 2012). In addition, facing global challenges concerning climate change, resource and raw materials scarcity and/or criticality, the security, population growth, and increasing consumption requires moving to a sustainable circular economy (Lee and Cha, 2021). In that context and with the goal of devising a generic, simple, cost-effective, and environmentally friendly method for the preparation of a high-purity piperidinium-based ionic liquid, we describe here a high-yield and high-quality protocol, that is easy to scale up and that combines both sustainability and cost advantages.

## Results and discussion

The search for new synthesis protocols of new ionic liquids or existing ionic liquids, from available, inexpensive, and low toxicity precursors, and respecting of the 12 principles of green chemistry as much as possible is a very active field of research today.

Quaternization reactions are known to be exothermic or endothermic depending on whether their transition states are structurally similar to the products or the reagents. (Haddon et al., 2016) In a process intensification study, Waterkamp et al. (Waterkamp et al., 2007) reported the adiabatic temperature for a run-away reaction and the heat of reaction for 1-methylimidazole and 1-bromobutane to be at least 48 °C and -96 kJ mol<sup>-1</sup> respectively. Of course, this temperature released can be the cause of degradations, and then impurities in the final product, but can be partially dissipated by the solvent; this point is very important for obtaining pure products. As demonstrated by Menshutkin the rate of SN<sub>2</sub> reactions is heavily influenced by the polarity of the solvent. (Menschutkin, 1890; Schleicher and Scurto, 2009) For polar aprotic solvents, an increase in the polarity of the solvent results in an increase in the rate of the Menshutkin reaction (Schleicher and Scurto, 2009), while it decreases the rate for typical SN<sub>2</sub> reactions (Solà et al., 1991). The effect of a polar solvent on a Menshutkin reaction is to position the transition state earlier in the reaction coordinate, then lowering the energy barrier and decreasing the endothermicity of the process. (Solà et al., 1991) Indeed, Menshutkin reaction is endothermic; and while SN<sub>2</sub> reactions involving a charged nucleophile can be seen as a migration of charge, the Menshutkin reaction can be considered as a creation of two charges of opposite sign followed by their subsequent separation, favored by the presence of a polar solvent. (Solà et al., 1991) In a study

dedicated to solvents effects upon Menshutkin reaction, Acevedo et al. (Acevedo and Jorgensen, 2010) confirmed that the reaction coordinate is particularly sensitive to the polarity of the solvent, insofar as the more polar aprotic and protic solvents allow considerably earlier transition structures compared to the nonpolar solvents. Nevertheless, Struebing et al. (Struebing et al., 2013) were unable to explain the large increase of rate constant of the reaction of phenacyl bromide with pyridine in nitromethane ( $\epsilon=36.56$  at 298 K,  $k = 6.09 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ) compared to that in acetonitrile ( $\epsilon = 35.59$  at 298 K,  $k = 4.70 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ) solely with the small increase of 0.97 in solvent's polarity. Therefore, polarity of the solvent is not its only determining property to increase the rate of a Menshutkin reaction.

## Synthesis

Even if most of the impurities contained in the ionic liquids originate from their preparation (Stark et al., 2008), the first potential source is linked to the purity of the precursors. In our work, all the precursors were distilled prior to synthesis to ensure a high quality of the ionic liquids.

Fine-tuning the Menshutkin reaction - Initially, 1 eq. of *N*-ethylpiperidine was refluxed with 1 eq. of *n*-bromobutane in acetonitrile to form the *N*-butyl-*N*-ethylpiperidinium bromide. A study of the kinetic of the reaction showed that the yield of *N*-butyl-*N*-ethylpiperidinium bromide increased with the reaction time (Table 1).

In Table 1, after 24 h of reaction, 93 % of the first-generation ionic liquid is obtained. Unfortunately, the yellowish color of the powder highlights the presence of impurities; the reaction was then stopped after 16 h of stirring to get a white powder. Acetonitrile presents an interesting relative polarity ( $E_T^N$ ) of 0.460 (Reichardt, 2003) but is considered as problematic according to the CHEM21 solvent guide of classical solvents. (Prat et al., 2016) To increase the sustainability of the reaction, we switched to acetone that is slightly less polar ( $E_T^N = 0.355$ ) (Reichardt, 2003) than acetonitrile but that is recommended by the CHEM21 solvent guide of classical solvents. (Prat et al., 2016)

In Table 2, after 72 h of reflux in acetone an excellent yield of 95 % was observed but the powder obtained was yellowish, highlighting the presence of impurities. 48 h of reflux were required to obtain 78 % of *N*-butyl-*N*-ethylpiperidinium bromide as a white powder.

In addition to solvent polarity, thermal properties such as heat transfer play an important role. In heat transfer analysis, thermal diffusivity  $\alpha$  measures the ability of a medium to conduct thermal energy relative to its ability to store thermal energy. It is expressed as the thermal conductivity divided by density and specific heat capacity at constant pressure (Eq. 1).

$$\alpha = \frac{\lambda}{\rho \times C_p} \quad (1)$$

With  $\alpha$  the thermal diffusivity (m<sup>2</sup>.s<sup>-1</sup>),  $\lambda$  the thermal conductivity (W.m<sup>-1</sup>.K<sup>-1</sup>),  $C_p$  the heat capacity (J.g<sup>-1</sup>.K<sup>-1</sup>),  $\rho$  the density (g.cm<sup>-3</sup>).

Thus, with values of  $9.19 \times 10^{-8} \text{ m}^2 \cdot \text{s}^{-1}$  (at 299.19 K) for acetone (Fujii et al., 1997) and  $12.03 \times 10^{-8} \text{ m}^2 \cdot \text{s}^{-1}$  (at 303.15 K) for acetonitrile (Shokouhi et al., 2013), the thermal diffusivity of acetonitrile is higher

**Table 1**

Yield of *N*-butyl-*N*-ethylpiperidinium bromide as a function of the reaction time with acetonitrile as solvent.

Entry	Times <sup>a</sup> , h	Yield <sup>b</sup> , %	Appearance
1	8	42	White powder
2	16	79	White powder
3	24	93	Yellowish powder

<sup>a</sup> Reaction mixture was stirred at 80 °C.

<sup>b</sup> Yields were determined after purification.

Conditions of the reactions: 0.1 mol of *N*-ethylpiperidine, 0.1 mol of *n*-bromobutane, 40 mL of acetonitrile,  $C_p$  of acetonitrile = 91.60 J.K<sup>-1</sup>.mol<sup>-1</sup>.

**Table 2**

Yield of *N*-butyl-*N*-ethylpiperidinium bromide as a function of the reaction time with acetone as solvent.

Entry	Times <sup>a</sup> , h	Yield <sup>b</sup> , %	Appearance
4	24	34 <sup>c</sup>	White powder
5	48	78	White powder
6	72	95	Yellowish powder

<sup>a</sup> Reaction mixture was stirred at 50 °C.

<sup>b</sup> Yields were determined after purification.

<sup>c</sup> % of conversion.

Conditions of the reactions: 0.1 mol of *N*-ethylpiperidine, 0.1 mol of *n*-bromobutane, 40 mL of acetone,  $C_p$  of acetone = 125.45 J.K<sup>-1</sup>.mol<sup>-1</sup>.

than that of acetone, which probably contributes to the higher kinetic of the reaction.

Finally, Table 1 and Table 2 clearly show that the temperature of the reaction is a key parameter to control the kinetic of the Menshutkin reaction (Shaik et al., 1994), that is strongly endothermic. Temperature is also a key parameter to control the purity (Burrell et al., 2007) of the resulting ionic liquid that is sensitive to the duration of reaction too. The purity of the reaction product depends on the temperature and duration of the reaction. Due to the absence of conjugates, a colorless compound is expected. The yellowish powders obtained after purification can then be taken as an indication of the presence of impurities, that are not detected by NMR.

After vigorous stirring in hot acetonitrile or acetone for 16 or 48 h respectively, the solid was cooled, filtered and washed with iced acetone, yielding the first-generation ionic liquid as a crystalline, slightly hygroscopic white solid.

Metathesis - The first generation's ionic liquid was then stirred with lithium bis(trifluoromethanesulfonyl)imide in water at room temperature, quantitatively leading to the perfectly colorless hydrophobic *N*-butyl-*N*-ethylpiperidinium bis(trifluoromethanesulfonyl)imide (BEPipNTf<sub>2</sub>) in 96 % yield. LiBr was recovered from the aqueous phase after evaporation of water. The raw product was then recrystallized, yielding 67 % of isolated LiBr. However, this step was not optimized, so recovery of this valuable material can be further improved. Indeed, lithium bromide is a very versatile compound, which is used for the treatment of psychiatric disorders, for example as a mood stabilizer (Shorter, 2009). Due to its highly hygroscopic property, it is widely used as a desiccant in air-conditioning systems and industrial drying systems (Lizarte et al., 2012). Its stability and relative safety make it a reactive of choice for various organic transformations (Rudravar 2005). In addition, several government including the UK, Russia, USA, etc., have classified Li as an energy-critical metal due to its increasing demand for Li-ion battery production, (Benson et al., 2017) thus highlighting the need for recycling processes. Moreover, a recent analysis (Greim et al., 2020) clearly shows that the criticality of Li takes the form of a long-term supply shortage. Thus, with the aim of moving towards a sustainable circular economy, achieving a balance between Li supply and demand throughout this century depends on the existence of such sustainable recycling solutions. In the proposed process, lithium can be re-used after its recovery without further transformation. Finally, the solvents, acetone and water, are recycled by distillation for reuse, helping to reduce the environmental footprint of the protocol.

### Physicochemical properties

#### Purity determination

Electrochemical analysis - There are four main classes of common potential impurities in ionic liquids; water, organics from non-distilled starting precursors and unreacted starting materials, or halides and metals. (Clare et al., 2009)

A variety of spectroscopic methods are available for the determination of the purity of ionic liquids, but electrochemistry is a very powerful

tool with low detection limits, depending on the impurity, for providing a very quick indication. In addition, BEPipNTf<sub>2</sub> being synthesized to serve as solvent and electrolyte in an electrochemical device for metal electrodeposition, its electrochemical stability window plays a crucial role. (Mousavi et al., 2015) This electrochemical stability window is then determined by the reduction potential of its cation and the oxidation potential of its anion. (Murugesan et al., 2014) A simple voltammogram can provide both purity and electrochemical stability informations. Indeed, the electrochemical window can be negatively affected by the presence of impurities such as halide impurities. (Haerens et al., 2012; Sun et al., 2005)

Fig. 1 shows the linear voltammogram of BEPipNTf<sub>2</sub> recorded on glassy carbon (C<sub>g</sub>) having an anodic limiting potential (E<sub>AL</sub>) of 2.0 V and cathodic limiting potential (E<sub>CL</sub>) of -2.7 V, resulting in a wide 4.7 V potential window that should be, if needed, predicted by a method developed by Maginn, Brennecke et al. (Zhang et al., 2014) The linear voltammogram restricted to low current values, presented in the inset of Fig. 1, clearly shows that the synthesized liquid ionic is of high purity compared to the commercially available one (dotted line). More specifically, the current recorded for potential values higher than 0.6 V vs Ag<sup>+</sup>/Ag, usually attributed to halide oxidation reaction, is lower than the one recorded in the commercial ionic liquid of 99.5 % purity, which guaranties a purity of our ionic liquid in halides higher than 99.5 %.

Water content by Karl-Fischer titration - Water, that is the most common impurity in ionic liquids, can be easily identified using <sup>1</sup>H NMR or infrared spectroscopy, but it can be accurately quantified within few minutes without sample preparation using a Karl-Fischer titration. This rapid experiment requiring only small product samples enabled us to determine a water content of less than 10 ppm in the home-made BEPipNTf<sub>2</sub>.

NMR experiments - NMR experiments have led to the structural characterization of the ionic liquid and can generally give product purity up to 95 %. However, as it does not identify compounds present at less than 1 % (Claridge et al., 2008), it was not useful for assessing ionic liquid purity. Consequently, the purity of the second-generation ionic liquid was monitored by electrochemical analysis, while the presence of impurities in the first-generation ionic liquid was identified by a slight coloring of the compound.

#### Physicochemical properties of *N*-butyl-*N*-ethylpiperidinium bis(trifluoromethanesulfonyl)amide

There is very limited literature data on the physicochemical

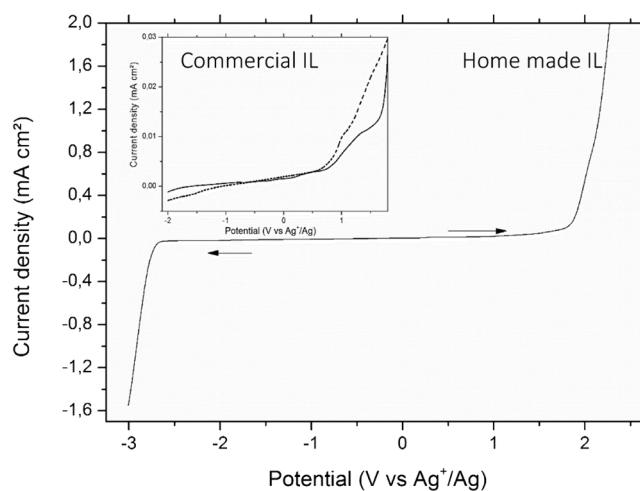


Fig. 1. Linear voltammogram of neat BEPipNTf<sub>2</sub> on C<sub>g</sub> disk working electrode at T = 60 °C, Carbon rod auxiliary electrode, and a Ag<sup>+</sup>/Ag reference scanned at 5 mV s<sup>-1</sup>, O<sub>2</sub>/H<sub>2</sub>O levels < 1 ppm. Inset comparison with BEPipNTf<sub>2</sub> purchased from Solvionic (dotted line) in the low current range.

properties of piperidinium based ionic liquids. However, transport properties are fundamental engineering data that are essential for the design of electrochemical processes. The density, viscosity, refractive index, and conductivity of BEPipNTf<sub>2</sub> were determined as a function of water content measured by Karl Fischer coulometric titration, and the results are summarized in Table 3.

In Table 3, the density ( $d$ ) of 1.36 g.cm<sup>-3</sup> measured at 25 °C is comparable to that of *N*-butyl-*N*-methylpiperidinium bis(trifluoromethanesulfonyl)imide (BMPipNTf<sub>2</sub>) (1.34 g.cm<sup>-3</sup> at 20 °C) and published in the literature. (Le et al., 2012) The water content of BMPipNTf<sub>2</sub> is not indicated by the authors, but it has been shown to have a negligible effect on the density. (Watanabe et al., 2016) In contrast, the presence of water has been shown to strongly decrease the viscosity of an ionic liquid. (Jacquemin et al., 2006) It is therefore difficult to compare the viscosity determined for BEPipNTf<sub>2</sub> with that of BMPipNTf<sub>2</sub> published in the literature. The conductivity of the BEPipNTf<sub>2</sub>, that is temperature dependent, would probably be higher than that of BMPipNTf<sub>2</sub> if determined at 25 °C. Finally, the BEPipNTf<sub>2</sub> refractive index (Bhattacharjee et al., 2014) is in the same order of magnitude as that of BMPipNTf<sub>2</sub> measured at 25 °C.

### Green chemistry metrics

**Green motion** – The French group MANE is a worldwide leader in the fragrance and flavor industry. A few years ago, it developed an interesting tool for evaluating the environmental impact of products combining health, safety, and environmental aspects in setting a metric that enables to rate a product and its specific process. (Phan et al., 2015) This tool allows assigning a coefficient of 0 to 100 to ingredients based on their respect of the principles of Green Chemistry. This coefficient of "greenness" is obtained via a multi-criteria methodology based on the following approach: the twelve principles are grouped into seven fundamental concepts that are raw material, solvent, hazard and toxicity of reagents, reaction, process, hazard and toxicity of the final product, and waste. For each concept, different criteria are defined. The more these criteria have a negative impact on the environment, the lower the rating will be, while the closer the score is to 100, the greener the product. Based on these individual scores, a general score from 0 to 100 is attributed to the whole manufacturing process, the GREEN MOTION™ rating. Available for perfumers and flavorists from 2012, MANE's GREEN MOTION™ is also applicable to all types of manufacturing: pharmaceutical, fine chemicals, natural product extraction, bio-transformations. A value of 50 in the GREEN MOTION™ rating has been arbitrarily attributed as a 'green limit'. The GREEN MOTION™ tool is available on-line (MANE Flavor and Fragrance, 2020) for rating the overall safety of a product and its impact on the environment and the health on the people producing or using it.

The objective of this work was to propose a good yielding and high-quality protocol, that is easy to scale up and that combines both sustainability and cost profit.

The Green Motion assessment tool was then used to rate the *N*-butyl-*N*-ethylpiperidinium bis(trifluoromethanesulfonyl)imide and its

**Table 3**  
Physicochemical constants of BEPipNTf<sub>2</sub><sup>a</sup> and BMPipNTf<sub>2</sub><sup>b</sup>.

IL	Density g.cm <sup>-3</sup>	Viscosity mPa.s	Refractive index	Conductivity mS.cm <sup>-1</sup>
BEPipNTf <sub>2</sub> <sup>a</sup>	1.36 <sup>c</sup>	216.27 <sup>c</sup>	1.4347 <sup>d</sup>	0.8 <sup>d</sup>
BMPipNTf <sub>2</sub> <sup>b</sup>	1.34 <sup>d</sup>	173 <sup>c</sup>	1.42928 <sup>c</sup>	0.6 <sup>c</sup>
	Murugesan et al., 2014	Murugesan et al., 2014	Claridge et al., 2008	Murugesan et al., 2014

The water content of the ionic liquid was.

<sup>a</sup> less than 10 ppm or.

<sup>b</sup> was not given. Temperature:.

<sup>c</sup> at 25 °C,.

<sup>d</sup> at 20 °C.

process of production.

Green motion assessment in Fig. 2 attributes a global value that is over the 'green minimum limit' arbitrarily set by MANE to evaluate the greenness. Analysis of each criterion shows that the grades attributed to waste, process, reaction, final product impact and solvent are higher than 50 and between 60 for the final product impact and 87 for the waste. Unfortunately, the raw material criterion presents a grade of zero because all the reactants used for the synthesis are petro-based reagents. Similarly, the hazard and toxicity criteria are rated zero, as no studies have yet been carried out on the final product to prove that it is safe for Human and Environment. Indeed, this product is still not commercially available.

GSK's reagent guides – In 2008, Pfizer proposed a green chemistry tool for rapid reagents selection based on three criteria: greenness, utility and scalability (Alfonsi et al., 2008). Through a complementary approach, GSK developed then a guide encouraging green reagent selection over a wide range of chemical transformations (Adams et al., 2013). The sustainability and greenness of our process using acetone was thus evaluated using the metric proposed by GSK40.

An EHS (Environmental, Health, Safety) score was calculated for *N*-ethylpiperidine (*N*-Epip), 1-bromooctane (1-BO) and lithium bis(trifluoromethanesulfonyl)imide (LiNTf<sub>2</sub>) by considering the presence or absence of certain risk phrases associated with each of them, followed by the geometric mean of the three scores attributed (Ward and Masters, 2014). The results are summarized in Table 4.

Then, an overall clean chemistry score was calculated by taking the geometric mean of scores attributed to the assessing aspects of the process that are ease of work-up, use of co-reagents, stoichiometry, and atom efficiency (AE) (Table 5).

Finally, the overall "Greenness" score was calculated by taking the geometric mean of the EHS and overall clean chemistry scores. Thus, for the synthesis of *N*-butyl-*N*-methylpiperidinium bis(trifluoromethanesulfonyl)imide in acetone, the overall "greenness" score ((EHS x Clean Chemistry) = (7.4 x 6.1)<sup>1/2</sup>) is 6.7.

Since in GSK's reagent guides (Adams et al., 2013) classify a reagent as "green" if its overall "greenness" score is superior to 6, it is possible to classify the synthesis of *N*-butyl-*N*-methylpiperidinium bis(trifluoromethanesulfonyl)imide in acetone described in this work as a green synthesis.

Environmental Factor (E-factor) - mass of waste/mass of product (kg waste per kg product) - and Reaction Mass Efficiency (RME) have been then calculated. E-factor that has been proposed by R. Sheldon (Sheldon, 1992; Sheldon, 2017) is the actual amount of waste produced in a process. It takes into account the waste of all the chemicals used, whether for synthesis but also for the various treatments. It takes the



**Fig. 2.** GREEN MOTION™ assessment of *N*-butyl-*N*-ethylpiperidinium bis(trifluoromethanesulfonyl)imide synthesis.

**Table 4**

ESH Scores for the chemical used for the synthesis of *N*-butyl-*N*-methylpiperidinium bis(trifluoromethanesulfonyl)imide in acetone.

Chemical	Health	Safety	Environment	ESH Score
<i>N</i> -ethylpiperidine	7	4	10	6.5
1-bromobutane	10	4	4	5.4
LiNTf <sub>2</sub>	4	10	7	6.5

$$\text{Overall EHS} = ((\text{EHS (N-Epip)}) \times \text{EHS (1-BO)}) \times \text{EHS (LiNTf}_2))^{1/3} = 6.1.$$

**Table 5**

Assessment of Chemistry Scores.

Work-up	Co-reagent	Other issues	AE	Stoichiometry
10	10	7	4.6	7

$$\text{Overall clean chemistry score} = (10 \times 10 \times 7 \times 4.6 \times 7)^{1/5} = 7.4.$$

product yield into account as well. A greater negative environmental impact is expressed by a higher E factor that means more waste too. That means, an E-factor as close as possible to zero is desirable. E-factor can be calculated for a one step as well as multi-step processes, and its ideal value is zero. The concepts of Atomic Economics (AE) and Factor E have prompted the chemical industry and academic research around the world to take a more concrete look at waste production.

In their original publication, Sheldon and co-authors defined waste as “everything but the desired product”, except for water. In our work, by considering that water is not a waste and acetone is recycled without loss, an E-factor of 0.20 is found. Nevertheless, the present trend in the pharmaceutical industry is to consider water as a waste, which leads to an increase of the E-factor to 2.30. Finally, if the protocol is considered in its entirety, that is to say if the loss of LiBr as well as that of water, ethanol and acetone during recycling are taking into account, the E-factor is increased to 3.62. Unfortunately, despite its large success and ease of evaluation, the E-factor exhibits some limitations. For example, it does not reflect the environmental impact of waste in terms of environmental hazard and depletion. Furthermore, it does not consider energy-related waste. In that context, Hollmann et al. have defined the *E*<sup>+</sup>-factor, which is the E-factor plus a hidden E-factor contribution due to CO<sub>2</sub>-emissions caused by electricity generation for example. (Tieves et al., 2019) Nevertheless, these E-factor values demonstrate the considerable waste reduction by recycling the solvents by reducing the number of isolations of intermediates along a given pathway by telescoping or concatenating one reaction into the next.

The reaction mass efficiency (Andraos and Sayed, 2007; Andraos, 2005) (RME) measures the efficiency with which a given reactant mass ends up in the desired product; it is the ratio of the actual yield to the mass of all the reagents and is based on the law of conservation of mass. The RME and E-factor are simply connected through equation 3 that allows easy calculation of either indicator once one of them is known. That means, RME as close as possible to 1 is desirable. It considers the use of solvent in the reaction and the workup and purification phases following the reaction.

$$\text{RME} = 1 / (1 + \text{E} - \text{factor}) \quad (2)$$

Thus, in the present work, by considering that water is not a waste and acetone is recycled a RME of 0.83 can be calculated. It is decreased to 0.30 when water is considered as a waste, and to 0.20 when the process is considered in its entirety. The literature suggests that RME is a better and more useful metric than AE in the evaluation of reaction performance.

These calculations show the limitations of E-factor and RME for analyzing the greenness of the process as a whole.

## Conclusions

This work describes a very good yielding protocol for the synthesis of high-quality *N*-butyl-*N*-methylpiperidinium bis(trifluoromethanesulfonyl)imide, which is easy to scale up, combines both sustainability and cost profit and can be used for the synthesis of a wide range of ionic liquids. In this work, it is shown that the control of purity of an ionic liquid can be monitored through the control of kinetic and solvent effects, that are investigated. Besides, the results obtained using ‘the green motion’ proposed by MANE and ‘reagent guides’ proposed by GSK, show that the process can be considered as sustainable. In addition, lithium, which is considered as an energy-critical metal, is recycled as LiBr at the end of the process for its possible marketing, maximizing thus the contribution of the entire process to the circular economy. This approach is easily implemented for the synthesis of various piperidinium, pyrrolidinium, imidazolium, etc. based ionic liquids.

Finally, from a fundamental point of view, this synthesis procedure gave us a unique opportunity in a further work to diagnose the plasma formed during the implosion of cavitation bubbles induced by sonication under Ar of this high purity [BEPip][NTf<sub>2</sub>] and to follow the temporal evolution of the sonoluminescence spectra obtained. The intense sonoluminescence (SL) produced as long as absorption of SL light by the sonolysis degradation products (thus still pure) does not prevent from simulating the emissions made it possible to determine the temperatures derived from the molecular emissions and to characterize the plasma formed in the acoustic cavitation bubbles during collapses (Pflieger et al., 2019; Pflieger et al., 2022).

## Experimental section

The Mentschukin’s reaction was performed under Argon. Solvents were dried by conventional methods and stored under Argon over molecular sieves (4 Å). (Hagiwara and Ito, 2000) *N*-Ethylpiperidine and 1-bromobutane were purchased from Aldrich and distilled immediately prior to use. Lithium Bis(trifluoromethyl)imide salt was purchased from abcr and used as received. Commercial *N*-Butyl-*N*-ethyl-piperidinium Bis(trifluoromethanesulfonyl)imide used for electrochemical characterization in Fig. 1 was purchased from Solvionic (99.5 % purity).

NMR experiments were performed with a Bruker AVANCE 400 III HD spectrometer at Laboratoire d’Electrochimie et Physicochimie des Matériaux et des Interfaces of the University Grenoble-Alpes (France). <sup>1</sup>H NMR spectra were referenced to residual protiated solvents (7.26 ppm for CDCl<sub>3</sub> and 4.79 ppm for D<sub>2</sub>O) and <sup>13</sup>C chemical shifts are reported relative to deuterated solvent (δ = 77.0 ppm for CDCl<sub>3</sub>). <sup>2</sup><sup>19</sup>F NMR data are reported relative to CFCl<sub>3</sub> and <sup>7</sup>Li NMR spectra were referenced to LiCl as an external reference, respectively. 2D NMR experiments (COSY, HSQC) were performed to complete the assignments. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), m (multiplet), bs (broad singlet).

High Resolution Mass Spectrometry (HRMS) experiments were performed using a Synapt G2-S (Waters) spectrometer at the Laboratoire de mesures physiques of the University of Montpellier.

Refractive index and viscosity were measured using an Anton Paar Abbemat 550 refractometer and an Anton Paar Lovis 200 M microviscosimeter. Density was performed with a vibrating U-tube Mettler Toledo RM50 densimeter.

Conductivities of RTILs were measured using a Tacussel Electronique CDRV62 conductimeter/resistivitimeter with a platinum 2-electrode cell (Materials Mates). The cell was calibrated with 5 × 10<sup>-3</sup> to 3.3 × 10<sup>-2</sup> KCl solutions, and the data were recorded at a frequency of 62 Hz.

Electrochemical experiments for electrochemical window determination were performed in an argon filled glove box (Mbraun Labstar; O<sub>2</sub>/H<sub>2</sub>O levels < 1 ppm) using a BIOLOGIC VSP300 potentiostat. A three-electrode set up with a 0.196 cm<sup>2</sup> surface glassy carbon (C<sub>g</sub>) disk working electrode, a Carbon rod auxiliary electrode, and Ag<sup>+</sup>/Ag reference electrode was used (reference solution: 10 mM AgCF<sub>3</sub>SO<sub>3</sub> in

BMICF<sub>3</sub>SO<sub>3</sub>).

The water content of the ionic liquids was measured by Karl Fischer coulometric titration (Metrohm 831KF coulometer) using Hydranal 34,843 Coulomat AG-H (Fluka) as titrant. Two distinct techniques are used for the determination of water by the Karl Fischer method, depending on the amount of water contained in the test sample. The volumetric method is used for quantities of water if the order of a few mg, and the coulometric method for the quantities of water of the order of a few µg. During this work, the quantities of sample and therefore of water injected being low, the coulometric method was chosen for the hygroscoy determination.

#### *N-Butyl-N-ethyl-piperidinium bromide salt*

Freshly distilled 1-bromobutane (148.2 mL, 189.1 g, 1.38 mol) was added to a solution of *N*-Ethylpiperidine (190.5 mL, 157.0 g, 1.38 mol) in dry acetone (400 mL). The resulting mixture was vigorously stirred and heated at 50 °C for 48 h. After cooling, the solution was placed at -20 °C for 24 h. The resulting white precipitate was then filtrated, washed with cold acetone (3 × 100 mL) and dried under vacuum overnight to afford the expected product as a white powder in 80 % (276.2 g, 1.10 mol) yield.

Recycling of acetone: acetone was recycled by distillation over KMnO<sub>4</sub>.

Note: For some experiments, acetone was replaced by acetonitrile. In this case, the mixture of *N*-Ethylpiperidine (190.5mL, 157.0g, 1.38mol) and bromobutane (148.2mL, 157.0g, 1.38mol) in acetonitrile (400mL) was heated at 80 °C for 16h. After cooling, the brominated salt crystallizes in fine needles. The precipitate was then filtrated off, washed with cold acetone (3 × 100mL) and dried under vacuum overnight. Finally, the expected compound was obtained as a white crystalline powder in 78% (269.3 g, 1.07 mol) yield.

<sup>1</sup>H NMR (400.13MHz, CDCl<sub>3</sub>, 298 K): δ 1.05 (t, 3H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, 3 *J* = Hz), 1.36 (t, 3H, NCH<sub>2</sub>CH<sub>3</sub>, 3 *J* = Hz), 1.48 (sex, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, 3 *J* = Hz), 1.71–1.79 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.95 (bs, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.33–3.37 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.39–3.45 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.47 (q, 2H, NCH<sub>2</sub>CH<sub>3</sub>, 3 *J* = Hz) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100.61 MHz, CDCl<sub>3</sub>, 298 K): δ 6.94 (s, CH<sub>2</sub>CH<sub>3</sub>), 13.37 (s, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 19.51 (s, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 19.55 (s, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 21.07 (s, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 23.01 (s, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 54.03 (s, CH<sub>2</sub>CH<sub>3</sub>), 57.76 (s, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 59.00 (s, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>) ppm. HRMS (ESI<sup>+</sup>): calcd for C<sub>11</sub>H<sub>24</sub>N [M]<sup>+</sup> 170.1909, found 170.1909.

#### *N-Butyl-N-ethyl-piperidinium bis(trifluoromethanesulfonyl)imide*

To a solution of *N*-Butyl-*N*-ethyl-piperidinium bromide salt (260.6g, 1.04mol) in distilled water (350mL) was added lithium bis(fluoromethanesulfonyl)imide (298.6g, 1.04mol). The mixture was stirred at room temperature overnight. The organic layer was separated and washed with distilled water (4 × 150mL). The colorless organic solution was then dried under vacuum at 80 °C for 24h and was stored under dry Argon. Yield: 96 % (449.7g, 0.99mol).

The water content was measured by Karl Fischer titration and was less than 10ppm. IR (ATR): 2926.7 and 2877.29 (CH stretch.), 1480.8 and 1460.1 (CH bend.), 1348 (SO<sub>2</sub> asym.stretch.), 1174.3 (CF<sub>3</sub>), 1133.1 (SO<sub>2</sub> sym.stretch.), 1050.6 (SN) cm<sup>-1</sup>. <sup>1</sup>H NMR (400.13MHz, CDCl<sub>3</sub>, 298K): δ 0.99 (t, 3H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, 3*J*=7.2Hz), 1.30 (t, 3H, NCH<sub>2</sub>CH<sub>3</sub>, 3*J*=7.2Hz), 1.40 (sex, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, 3 *J* = 7.2Hz), 1.57–1.65 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 1.72 (quin, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, 3*J*=6.0Hz), 1.86 (bs, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.16–3.20 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.31 (t, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, 3*J*=6.0Hz), 3.36 (q, 2H, NCH<sub>2</sub>CH<sub>3</sub>, 3*J*=7.2Hz) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100.61MHz, CDCl<sub>3</sub>, 298K): δ 7.03 (s, NCH<sub>2</sub>CH<sub>3</sub>), 13.42 (s, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 19.61 (s, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 20.86 (s, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 23.26 (s, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 23.33 (s, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 53.80 (s,

NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 58.11 (s, NCH<sub>2</sub>CH<sub>3</sub>), 59.02 (s, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 119.99 (q, CF<sub>3</sub>, 1*J* (C-F) = 321.4Hz) ppm. F{<sup>1</sup>H} NMR (376.49MHz, CDCl<sub>3</sub>, 298K): δ -79.01 (s, CF<sub>3</sub>) ppm. HRMS (ESI<sup>+</sup>) calcd for C<sub>11</sub>H<sub>24</sub>N [M]<sup>+</sup> 170.1909, found 170.1909.

#### *LiBr recovery*

After metathesis reaction, the aqueous layers were combined, and water was evaporated under reduced pressure. The white raw product was then recrystallized three times in EtOH. LiBr was dried under vacuum for 48h at 110 °C. Yield: 67% (0.66mol, 57.6g). <sup>1</sup>H NMR (400.13MHz, CDCl<sub>3</sub>, 298 K): no organic compounds were detected. <sup>7</sup>Li NMR (155.50MHz, CDCl<sub>3</sub>, 298K): δ 2.84 (s, LiBr) (2.85ppm for LiBr commercial source) ppm.

#### **CREdIT authorship contribution statement**

**Manuel Lejeune:** Investigation, Methodology, Resources. **Micheline Draye:** Visualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Sophie Legeai:** Funding acquisition, Writing – review & editing. **Stéphanie Michel:** Resources. **Guilhem Arrachart:** Funding acquisition, Writing – review & editing. **Stéphane Pellet-Rostaing:** Funding acquisition, Project administration.

#### **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### **Data availability**

No data was used for the research described in the article.

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