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# Synthesis of aryl azides: A probe reaction to study the synergetic action of ultrasounds and ionic liquids

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#### ABSTRACT

The combined effect of ultrasounds and ionic liquids was used to perform the synthesis of aryl azides by nucleophilic aromatic substitution in ionic liquid/[1-butyl-3-methylimidazolium][N<sub>3</sub>] binary mixtures. The ultrasounds efficiency was analyzed as a function of the substrate and of the ionic liquid structure. In the first case, both  $6\pi$  and  $10\pi$  electrons aryl halides were considered. As far as the ionic liquid structure is concerned, both aromatic and aliphatic ionic liquids were taken into account. Among aromatic cations, the effects due to different ability in giving hydrogen bond or  $\pi$ - $\pi$  interactions were considered. The use of a geminal ionic liquid having an aromatic spacer was examined too.

On the whole, collected data evidence an activating effect on the target reaction by the combined use of ultrasounds and ionic liquids. The structural order degree of the ionic liquid seems to be the main factor affecting the ultrasounds efficiency. Furthermore, the effects due to changes in the anion structure seem to be more significant than those due to changes in the cation structure.

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## 1. Introduction

Since their enunciation, the fifth and the sixth principle of Green Chemistry represented a clear request for the scientific community to tune up new processes having low energetic requirements and to use, when possible, solvents or any other auxiliary substances having low environmental impact [1]. The significant ferment that such a request has generated is testified by the large number of papers focused on the use of alternative reaction media, such as water [2–4], supercritical fluids [5] and ionic liquids [6,7]. In addition, the use of alternative catalytic methods of irradiation such as microwaves [8] and ultrasounds [9,10] has been investigated.

During the years, further development of research activity in this field has been geared to identify the right combination of solvent medium and catalytic methodology in order to achieve the best results of synthetic processes with the full environmental care. In this context, during the last few years interesting data have been obtained by the combined use of ultrasounds (US) and ionic liquids (ILs).

As far as ILs are concerned as reaction media, the results obtained allowed to outline the positive effects they may exert on a given reaction in terms of rate, selectivity and yield [11,12]. It has been frequently reasserted that ILs cannot be considered as continuous media, such as conventional organic solvents [13,14]. As matter of fact, they show peculiar properties such as low vapor pressure, low flammability and a certain structural order degree, which markedly determine the aforementioned effects. Among these properties, the negligible vapor pressure is the one that makes them suitable reaction media for US irradiation. Although a precise correlation between cavitation energy and vapor pressure has not been reported, it is well known that rates of sonochemical reaction can be increased by lowering the vapor pressure of the solvent [15,16]. Under this light, the synergetic action of ILs and US has been used in the study of the Suzuky [17] and the Heck [18] reactions, alcohols acetylation [19], the synthesis of xanthene derivatives [20], 2,4-diaryltriazoles [21], oximes [22], quinoline derivatives [23] and so on.

In order to have a deeper understanding of such a synergetic action, we studied the aryl azides formation by  $S_NAr$  under US activation, using IL/[bmim][N<sub>3</sub>] binary mixtures as solvent media. This reaction was chosen because in conventional organic solvents aryl azides are not generally obtained by  $S_NAr$  from corresponding aryl halides. On the other hand, satisfactory results were obtained in IL solution and using [bmim][N<sub>3</sub>] as the nucleophile source [24,25]. Previous literature reports have outlined the positive effect of US irradiation on the  $S_NAr$  reaction [26,27]; thus, in our opinion, the above reaction could be a suitable probe to verify whether the combined action of US and ILs has a further favorable effect.

Obviously, the interest in this investigation is also due to the fact that the obtained products are key intermediates in organic synthesis. Indeed, it is well known that aryl azides are useful synthones in order to obtain various heterocycles having applications in pharmaceutical, agricultural and materials chemistry [28,29].





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The substrates chosen for this work (see Fig. 1) differ for the aromatic ring structure. In particular,  $6\pi$  electrons (five- and sixmembered ring) and  $10\pi$  electrons (bicyclic ring) derivatives were considered. In order to have information about the effect of IL nature on the US activation, the 2-bromo-5-nitrothiophene was chosen as model substrate and the formation of the relevant azide was studied at 298 K in different IL/[bmim][N<sub>3</sub>] binary mixtures (see Fig. 1). This investigation allowed us to achieve a better knowledge of the relationships between the IL nature and the US action. This could impart to the study a predictive and, if possible, a practical value, helping to choose the suitable IL media to carry out a reaction under US irradiation.

In particular, ILs differing for the cation ability in giving hydrogen bond or  $\pi$ - $\pi$  interactions such as [bmim][NTf<sub>2</sub>] and [bm<sub>2</sub>im] [NTf<sub>2</sub>] [where bm<sub>2</sub>im = 1-butyl-2,3-dimethylimidazolium and NTf<sub>2</sub> = bis(trifluoromethansulfonyl)imide] or [bmim][NTf<sub>2</sub>] and [bmpyrr][NTf<sub>2</sub>] (where bmpyrr = N-butyl-N-methylpyrrolidinium) were used. In addition, the effect due to a different extent of  $\pi$  contact surface area for the cation was also evaluated, by using the [Bzmim][NTf<sub>2</sub>] and the [Bzbim][NTf<sub>2</sub>] as solvent media (where Bzmim = 1-benzyl-3-methylimidazolium and Bzbim = 1-benzyl-3-butylimidazolium).

The latter ILs differ for the length of the alkyl chain, which is a further parameter able to affect both the nature of the cation–cation interactions and the structural order degree of IL. The influence due to a different nature of the cation structure was also analyzed by using a geminal IL, namely the 3,3'-di-n-butyl-1,1'-(1,3-phenyl-enedimethylene)diimidazolium bis[bis(trifluoromethansulfonyl) imide] [m-Xyl-(bim)<sub>2</sub>][NTf<sub>2</sub>]<sub>2</sub>.

As a matter of fact, it has been recently reported that this IL of third generation has a higher structural order degree than the corresponding monocationic [bmim][NTf<sub>2</sub>], as a consequence of the more extensive cation–cation interaction [30]. The use of geminal ionic liquids could be quite interesting. Indeed, despite some recent papers have had their synthesis and the study of their properties as main subject [31,32], only few examples have been reported about their use as reaction media [33,34]. Furthermore, in order to optimize their applications, it could be rather interesting to have a better knowledge of the relationships existing between their structure and the effect they exert on the outcome of a given reaction. Under this perspective, the comparison with data collected in [Bzmim][NTf<sub>2</sub>] and [Bzbim][NTf<sub>2</sub>] solution could give useful information.

It is well known that both cohesive forces and structural order degree are markedly affected by the size, shape and coordination ability of the anion [35]. This is the reason why ILs differing for the anion nature, such as [bmim][BF<sub>4</sub>], [bmim][PF<sub>6</sub>], [bmim][NTf<sub>2</sub>] and [bmim][SbF<sub>6</sub>] were also used.

Finally, in order to have a comparison with conventional organic solvents, the synthesis of the 2-azido-5-nitrothiophene, both under silent and US activation, was studied also in MeOH solution using  $[bmim][N_3]$  as nucleophile source.

# 2. Experimental details

#### 2.1. Materials

 $[bmim][BF_4]$ ,  $[bmim][PF_6]$ , 1,4-dioxane, NaN<sub>3</sub> and aryl halides were purchased and used without further purification. [bmim]



Fig. 1. Structure of the used substrates and ionic liquids.

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[NTf<sub>2</sub>], [bm<sub>2</sub>im][NTf<sub>2</sub>], [bmpyrr][NTf<sub>2</sub>], [bmim][SbF<sub>6</sub>], [Bzmim] [NTf<sub>2</sub>], [Bzbim][NTf<sub>2</sub>], [*m*-Xyl-(bim)<sub>2</sub>][NTf<sub>2</sub>]<sub>2</sub> were prepared according to previously reported procedures [30,36,37]. All ionic liquids were dried before use on a vacuum line at 70 °C for at least 2 h, stored in a dryer under argon and over calcium chloride. The 2-bromo-5-nitrofurane (**2**) [38] and the 2-bromo-3-nitrothiophene (**4**) [39] were prepared according to previous reports.

<sup>1</sup>H NMR spectra were collected on a 300 MHz spectrometer. All spectra were recorded in CDCl<sub>3</sub> solution.

#### 2.1.1. 1-Benzyl-3-butylimidazolium bromide

Butylimidazole (3.68 g, 29.6 mmol) was dissolved in 2-propanol (50 mL). The obtained solution was placed in an oil bath at 85 °C. Benzylbromide (5.08 g, 29.6 mmol) was dissolved in 2-propanol (50 mL) and the solution was added, dropwise, to the butylimidazole solution. The reaction mixture was stored at 85 °C for 24 h. After cooling, the solution was concentrated in vacuo and the obtained yellow oil was washed several times with diethyl ether. The obtained bromide salt was dissolved in anhydrous dichloromethane (100 mL) and stirred overnight at room temperature, in the presence of active charcoal (1% in weight). After filtration on neutral alumina and concentration in vacuo, the corresponding bromide was obtained.

Yellow oil (yield 91%).  $\delta_{H}$  (300 MHz; CDCl<sub>3</sub>) 10.70 (s, 1H, H-2), 7.56 (m, 2H, H4–H5), 7.39 (m, 5H, Ph), 5.67 (s, 2H, CH<sub>2</sub>-Ph), 4.36 (t, <sup>3</sup>J 7.5, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.93 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.42 (m, 2H, CH<sub>2</sub> CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.99 (t, <sup>3</sup>J 7.5, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

$$\begin{split} &\delta_C\,(300~\text{MHz};\,\text{CDCl}_3)\,137.45\,(\text{C2}~\text{im}),\,133.47\,(\text{C1}~\text{Ph}),\,129.87\,(\text{C2-C6}~\text{Ph}),\,129.82\,(\text{C3-C5}~\text{Ph}),\,129.45\,(\text{C4}~\text{Ph}),\,122.43\,(\text{C5}~\text{im}),\,122.27\,(\text{C4}~\text{im}),\,53.67\,(\text{CH}_2\text{-Ph}),\,50.37\,(\text{CH}_2\text{CH}_2\text{CH}_3),\,32.46\,(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3),\,19.81\,(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3),\,13.83\,(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3). \end{split}$$

# 2.1.2. 1-Benzyl-3-butylimidazolium bis(trifluoromethansulfonyl)imide

The 1-benzyl-3-butylimidazolium bromide (7.59 g, 25.7 mmol) was dissolved in dichloromethane (40 mL). The obtained solution was placed in an ice bath and lithium bis(trifluoromethansulfonyl)imide (7.52 g, 26.2 mmol) was added. The reaction mixture was stirred at room temperature for 48 h. Then, it was filtered to remove the LiBr salt and the organic solution was washed with water, until the aqueous phase was halide free (by means of a silver nitrate test). The ionic liquid, obtained after concentration in vacuo, was dissolved in dichloromethane (100 mL) and treated with active charcoal (1% in weight) overnight. Then, the solution was filtered through a pad of neutral alumina and concentrated in vacuo to give the ionic liquid.

Table 1

Yields in azido derivatives of (1) and (8) obtained through nucleophilic aromatic substitution at different volumes of [bmim][BF<sub>4</sub>]/1,4-dioxane binary mixture at 298 K under ultrasounds irradiation.<sup>a</sup>

Entry	Substrate	$V_{\text{solvent mixture}}$ (µL)	Co-solvent (%, v:v)	Yield % <sup>b</sup>
1	1 <sup>c</sup>	600	25	76
2	1 <sup>c</sup>	130	23	78
3	1 <sup>c</sup>	100	0	73
4	1 <sup>c</sup>	65	23	75
5	8 <sup>d</sup>	600	25	71
6	8 <sup>d</sup>	130	23	78
7	8 <sup>d</sup>	100	0	69
8	8 <sup>d</sup>	65	23	70

<sup>a</sup> All reaction were carried out by using 1.44 mmol of substrate and 1.8 mmol of  $[bmim][N_3]$ .

<sup>b</sup> Isolated yield after column chromatography. Yields were reproducible within 2%.

<sup>d</sup> Reaction time = 4 h.

Pale yellow oil (yield 80%).  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 8.97 (s, 1H, H-2), 7.47 (m, 5H, Ph), 7.33 (d, <sup>3</sup>*J* 19.5, 2H, H4–H5), 5.40 (s, 2H, CH<sub>2</sub>-Ph), 4.25 (t, <sup>3</sup>*J* 7.5, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.91 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.43 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.02 (t, <sup>3</sup>*J* 7.2, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

 $\delta_{C}~(300~\text{MHz};~\text{CDCl}_3)~135.53~(C2~\text{im}),~132.21~(C1~\text{Ph}),~129.74~(C2-C4~\text{Ph}),~129.57~(C3-C5~\text{Ph}),~128.82~(C4~\text{Ph}),~122.32~(C5~\text{im}),~122.26~(C4~\text{im}),~120.02~(CF_3SO_2N),~53.62~(CH_2-\text{Ph}),~50.06~(CH_2CH_2CH_2CH_3),~31.87~(CH_2CH_2CH_2CH_3),~19.31~(CH_2CH_2CH_2CH_3),~13.17~(CH_2CH_2CH_2CH_3).$ 

#### 2.2. Reaction conditions

The reactions were carried out in a thermostated ultrasonic cleaning bath (VWR International USC-900) operating at a frequency of 45 kHz. The tank dimensions were  $495 \times 130 \times 150$  mm, with a liquid holding capacity of 8.6 L. The ultrasonic cleaner had an output power of 0–200 W through digital adjustment. The reactions were carried out in a round-bottomed flask of 20 mL capacity suspended at the center of the cleaning bath, 5 cm below the surface of the liquid.

#### 2.2.1. General procedure for aryl azides synthesis

An amount of 1.44 mmol of aryl halide was dissolved in 0.3 mL of 1,4-dioxane. The obtained solution was added dropwise to a thermostated mixture of 1.8 mmol of [bmim][N<sub>3</sub>] in IL solution (1.2 mL). In all cases the reaction mixture was irradiated in the water bath of the ultrasonic cleaner at the temperature and for the time indicated in Tables 1-3. The composition of the reaction mixture was examined time by time by TLC. In some cases, the reaction was quenched at a suitable time to avoid the formation of overwhelming by-products. Then, the reaction mixture was extracted several times with diethyl ether. After solvent elimination, the residues were separated by flash chromatography on neutral alumina. The pure aryl azides obtained were characterized by IR, <sup>1</sup>H NMR spectra and melting points. In the case of 4-halopyridines, an equimolar amount of hydrochloric acid was added to the reaction mixture in diethyl ether solution. After solvent elimination, the composition of the mixture was determined by <sup>1</sup>H NMR.

Table 2

Yields in azido derivatives of Aryl Halides obtained through nucleophilic aromatic substitution in  $[bmim][BF_4]/[bmim][N_3]$  binary mixtures under ultrasounds irradiation or under silent conditions.<sup>a</sup>

_						
	Entry	Substrate	Temperature (K)	US yield % <sup>b</sup> (Time)	Silent yield % <sup>b</sup> (Time)	Silent yield % <sup>b,c</sup> (Time)
	1	1	298	74 (20 min)	54 (20 min)	62 (2 h)
	2	2	298	67 (5 min)	61 (5 min)	73 (30 min)
	3	3	298	54 (30 min)	83 (30 min)	83 (30 min)
	4	4	298	73 (20 min)	54 (20 min)	58 (2 h)
	5	5	313	6 (16 h)	<2 (16 h)	13 (72 h)
	6	6	323	22 (6 h)	13 (6 h)	19 <sup>d</sup> (24 h)
	7	7	298	9 <sup>e</sup> (12 h)	<2 (12 h)	20 <sup>e</sup> (24 h)
	8	8	298	71 (4 h)	16 (4 h)	86 (24 h)
	9	9	323	7 <sup>f</sup> (8 h)	<2 (8 h)	52 <sup>f</sup> (72 h)

<sup>a</sup> All reaction were carried out by using 1.44 mmol of substrate and 1.8 mmol of  $[bmim][N_3]$ .

<sup>b</sup> Isolated yield after column chromatography. Yields were reproducible within 2%.

<sup>c</sup> See Ref. [24].

- <sup>d</sup> Reaction temperature = 333 K.
- <sup>e</sup> Yields calculated in the reaction mixture by <sup>1</sup>H NMR (see Section 2).

<sup>f</sup> In the case of 2-chloroquinoline, according to Ref. [24], the tetrazole derivative of 2-azidoquinoline was obtained.

<sup>&</sup>lt;sup>c</sup> Reaction time = 20 min.

#### Table 3

Yields in 2-azido-5-nitrothiophene obtained through nucleophilic aromatic substitution in different binary mixtures  $IL/[bmim][N_3]$  at 298 K under ultrasounds irradiation (20 min) or silent conditions (2 h).<sup>a</sup>

Entry	Solvent	US yield % <sup>b</sup>	Silent yield % <sup>b</sup>
1	MeOH	11 (25) <sup>c</sup>	20
2	[bmim][BF <sub>4</sub> ]	76	62 <sup>d</sup>
3	[bmim][PF <sub>6</sub> ]	84	63
4	[bmim][SbF <sub>6</sub> ]	63	69
5	[bmim][NTf <sub>2</sub> ]	70	57 <sup>d</sup>
6	[bm <sub>2</sub> im][NTf <sub>2</sub> ]	74	55 <sup>d</sup>
7	[bmpyrr][NTf <sub>2</sub> ]	75	69 <sup>d</sup>
8	[Bzmim][NTf <sub>2</sub> ]	74	72
9	[Bzbim][NTf <sub>2</sub> ]	64	65
10	$[m-Xyl-(bim)_2][NTf_2]_2$	74	71

 $^{a}$  All reaction were carried out by using 1.44 mmol of substrate and 1.8 mmol of [bmim][N\_3].

<sup>b</sup> Isolated yield after column chromatography. Yields were reproducible within 2%.

<sup>c</sup> Reaction time = 2 h.

<sup>d</sup> See Ref. [24].

#### 3. Results and discussion

#### 3.1. Optimization of experimental conditions

Our primary goal was the optimization of the experimental conditions. Preliminary runs were carried out using the 2-bromo-5nitrothiophene as the model substrate. The choice of this substrate was due to its high reactivity, which was previously verified on studying the formation of aryl azides in IL/[bmim][N<sub>3</sub>] binary mixtures at 298 K [24].

We first tried to work with an output power of 100 W. Data collected in [bmim][BF<sub>4</sub>] solution show that the better yield in the 2-azido-5-nitrothiophene was obtained after 40 min of irradiation (yield = 76%). Further increases in irradiation time resulted in no improvement. By irradiating with an output power of 200 W for 20 min a similar result was obtained (yield = 76%). In order to verify if the obtained yield was the limit value, we carried out the US irradiation for 40 min and 2 h (the reaction time under silent conditions) [24]. In both cases no significant changes in yield were obtained (yield = 76% for 40 min and 77% for 2 h). Similarly, under silent conditions, yield did not improve significantly after 2 h [24]. Good reproducibility of experimental results was verified. In particular, the 2-azido-5-nitrothiophene was obtained with small differences in yield (2% in yield).

The first comparison between these data and those previously collected under silent conditions, evidences two important features. In agreement with the frequently claimed ultrasounds activation of organic reactions, [9,10,17–23] the target reaction proceeded in a shorter reaction time (20 min versus 2 h) and with significantly higher yield (76% for US; 62% for silent). Furthermore, bearing in mind what previously sanctioned by the Green Chemistry principles, the ultrasounds activation seems to be quite advantageous from an environmental point of view, as testified by a lower waste of energy [E = 57.3 kcal for US irradiation (P = 200 W; t = 20 min) and 722 kcal for silent (P = 420 W, (output power of the magnetic stirrer); t = 2 h)].

#### 3.2. Solvent composition

Among the factors that must be taken into account in tuning up a synthetic strategy, the amount of solvent used as well as its nature plays an important role. In order to respect the Green Chemistry principles, both modern industry and academy are trying to decrease the amount of solvent used, promoting a sort of "solvent economy" tendency. Under this perspective, in order to verify if the combined system now used (ILs and US) may follow this tendency, we used the [bmim][BF<sub>4</sub>] as solvent medium and we tried to decrease the volume used in each experiment. Because all experiments in this work were carried out using 1,4-dioxane as cosolvent (see Section 2), we decreased the volume of the solvent mixture used, keeping constant the nucleophile:substrate molar ratio. We used two model substrates, namely the 2-bromo-5-nitrothiophene (1) and the 4-chloroquinoline (8), which were chosen for their significantly different solubilities in our solvent media. Data collected are reported in Table 1.

Also in this case the US activation positively affects our reaction system. Indeed, irrespective of the substrate used, the decrease in solvent volume does not induce any significant decrease in yields. In both cases it seems that the best experimental conditions are fulfilled using a solvent volume as large as 130  $\mu$ L (entries 2 and 6, Table 1). Once again, according to previously collected data [24], the cosolvent plays a favorable role. Indeed, the absence of cosolvent (entries 3 and 7, Table 1) induces a decrease in yields [40]. This result perfectly agrees with report by Srinivasan et al. [17] about the favorable effect exerted by MeOH in the US promoted Suzuki cross-coupling reaction in IL, which was ascribed to the homogeneity of the reaction mixture.

Under magnetic stirring, by using the best experimental conditions found out for US irradiation ( $V_{solvent} = 130 \mu$ L) and **1** as substrate, yield was lower despite a higher reaction time (yield = 62%, 2 h). However, since a meaningful comparison with results previously obtained has to be made, all reactions mentioned in the subsequent sections were conducted by using the same solvent composition described elsewhere [24].

#### 3.3. The effect of the substrate nature

In Table 2 yields collected for different substrates, under US irradiation in  $[bmim][BF_4]$  solution, are reported. For a useful comparison, we reported data collected at silent conditions by using two different reaction times. In particular, together with data previously reported [24], the ones collected by using the same reaction times used under US irradiation are also showed.

These data must be analyzed as a function of the nature of the substrate and the reaction temperature. Under US irradiation we used the lowest temperature that allowed to achieve a higher yield compared to that obtained under silent conditions; moreover, we used the lowest reaction time allowing the completion or limiting yield to be reached. A maximum temperature value of 323 K was used.

The comparison between data collected, at the same reaction time, under US and silent conditions, shows that in all cases considered the US irradiation exerts a positive effect. Indeed, independently of the used substrate an increase in yields can be detected and this trend results more significant in the case of the 2-bromo-5-nitrothiophene (1), 2-bromo-3-nitrothiophene (4) and 4-chloropyridine (8).

As far as the comparison with data previously collected at silent conditions [24] is concerned, shorter reaction times were used. Furthermore, in some cases yields were comparable to those obtained under silent conditions [24]. For instance, positive effects of the combined action IL/US were detected in the case of the 2-bromo-5-nitrothiophene (1), 2-bromo-3-nitrothiophene (4) and 1-bromo-2-nitrobenzene (6) (see entries 1, 4 and 6, Table 2). Indeed, in these cases the US activation allowed to obtain comparable or higher yields than the ones previously collected [24], using shorter reaction times (1, 4 and 6) or also a lower reaction temperature (6). By contrast, in the case of 2-bromo-5-nitrofurane (2), 2-bromo-5-nitrothiazole (3), 4-bromopyridine (7) and 4-chloroquinoline (8) (see entries 2, 3, 7 and 8, Table 2) significantly lower

yields were obtained with respect to the ones previously collected under silent conditions [24]. In order to explain these results, we tested the stability of the starting materials and of the corresponding azides to US irradiation. The US irradiation of **2** and **3**, in the absence of [bmim][N<sub>3</sub>], for 5 min and 30 min, respectively, allowed to recover only 73% and 69% of the substrate, respectively. On the grounds of these results, a certain sensitivity of the starting materials to US irradiation may be hypothesized. This should induce a decrease in the amount of substrate available for the reaction, and consequently in the reaction yield. By contrast, in the case of (**7**), the low yield in 4-azidopyridine could be ascribed to the high vapor pressure of both substrate and product.

As far as the reaction temperature is concerned, comparison with data previously obtained [24] indicates that in some cases the synergetic favorable effect of US/IL becomes less significant when a higher reaction temperature is needed. As a matter of fact. both the 1-bromo-4-nitrobenzene (5) and the 2-chloroquinoline (9) (see entries 5 and 9, Table 2) give significantly lower yields under US irradiation. Different literature reports have evidenced the unfavorable effect on the outcome of US irradiation deriving from a temperature increase [41-42]. On this purpose, even Khosropour et al. evidenced no improvement in yields, as a consequence of the temperature increase, on studying the US promoted synthesis of 2,4-diarylthiazoles in [bmim][BF<sub>4</sub>] solution [21]. Probably, a higher reaction temperature might induce a decrease in the order degree of the IL supramolecular structure [43]. As a consequence, weaker interactions should occur and, on the whole, a less efficient cavitation process takes place (see later).

#### 3.4. The IL effect

In order to get further information about the effect of IL nature on the US activation, the formation of 2-azido-5-nitrothiophene, at 298 K, was studied in different IL solutions. As we mentioned previously, in order to have a comparison with conventional organic solvents, the target reaction was also studied in MeOH solution. Moreover, for drawing a meaningful comparison with results previously collected, all silent reactions were conducted for 2 h, a time after which no significant increase in yields had been detected for the synthesis of 2-azido-5-nitrothiophene in the same reacting system [24].

Data collected are reported in Table 3, together with data previously obtained under silent conditions at 298 K.

Analysis of data collected in MeOH solution shows that US irradiation induces no significant improvement on the studied reaction. Indeed, the obtained yields under ultrasounds irradiation, at two different reaction times (20 min and 2 h) resulted lower or comparable to the one collected under silent conditions.

A different behavior was observed in IL solutions. In all the cases considered, indeed yields were higher than those collected in MeOH solution. Furthermore, with the only exception of [bmim][SbF<sub>6</sub>] solution, yields collected in different IL solutions under US activation resulted higher than those previously collected under silent conditions [24]. However, also in [bmim][SbF<sub>6</sub>], a comparable yield was obtained in a significantly lower reaction time.

For a better understanding of the obtained results in IL solution, data collected in Table 3 must be analyzed both as a function of the IL anion and cation structure.

#### 3.4.1. The IL anion effect

Analysis of collected data as a function of the IL anion structure shows that yields decrease along the series:  $[bmim][PF_6] > [b$  $mim][BF_4] > [bmim][NTf_2] > [bmim][SbF_6]. This trend, with the$  $exception of [bmim][SbF_6], is quite similar to the one previously$ obtained under silent conditions [24]. However, in the latter case a less relevant IL anion effect had been detected. Indeed, yields varied in a narrower range.

Data collected herein cannot be explained on the grounds of the IL anion symmetry. Indeed, the two anions having the highest symmetry ( $[PF_6^-]$  and  $[SbF_6^-]$ ) give rise to the highest and the lowest yield, respectively. We have previously obtained a similar result, on studying the copper(II) catalyzed mononuclear rearrangement of heterocycles [44], and the obtained result was ascribed to the highest structural organization of [bmim][PF\_6]. This might be invoked also in the present study to explain our experimental results.

In order to verify this hypothesis, all parameters accounting for cation–anion, cation–cation and ion pairs interactions, such as  $\beta$ , the cohesive pressure and the extent of IL aggregation degree should be taken into account. Firstly, we analyzed the cohesive pressure of the different ILs used in this work. This parameter has been defined as a measure of the strength of the interactions among solvent molecules. In some cases it has been invoked to rationalize the ILs effect on the reaction course or on the ion pairs stabilities in IL solution [45–47]. In our case, the cohesive pressure significantly decreases on going from [bmim][PF<sub>6</sub>] to [bmim][NTf<sub>2</sub>]  $(ced = 6774, 6632 and 4523 atm for [bmim][PF_6], [bmim][BF_4] and$ [bmim][NTf<sub>2</sub>])[48] and this trend perfectly parallels the one detected for yields. On the other hand, the  $\beta$  values (as a measure hydrogen bond acceptor ability of the anion) for the ILs used in this work change along the series:  $[bmim][BF_4] > [bmim][PF_6] > [b$ mim][NTf<sub>2</sub>] > [bmim][SbF<sub>6</sub>] [49]. Therefore, with the only exception of [bmim][PF<sub>6</sub>], changes in this parameter reflect the ones observed for yields. In the case of [bmim][PF<sub>6</sub>], a significant contribution to the activating effect of the US irradiation might also derive from its largest viscosity. Indeed, Fuchigami et al. underlined in a recent paper that the synergetic action of US and IL may be a consequence of the favored mass transport in these viscous solvent media [50].

Taking into account the cation-anion interaction, it should be hypothesized that a stronger interaction should induce a higher structural order degree for the solvent system. This, in turn, favors the occurrence of those supramolecular interactions which overall allow to assimilate aromatic ILs to supramolecular fluids [51,52]. As far as the extent of IL aggregation degree is concerned, by using resonance light scattering investigation we have previously evidenced a decrease in the aggregation degree of bmim<sup>+</sup>-ILs that parallels the changes in yields obtained in this work [53].

As we stated previously, the effectiveness of US irradiation in conventional organic solvents increases on decreasing the solvent vapor pressure, as a consequence of an easier cavitation process [54]. The vapor pressure of a solvent accounts for the strength of its intermolecular interactions. Therefore, an IL having strong interactions could be compared to a conventional solvent having a low vapor pressure, and consequently, it should be a solvent system more efficient in promoting the US irradiation. As a confirmation, the efficiency of US irradiation, evaluated as the difference between the yields obtained under US activation and silent conditions ( $\Delta_{yield}$ ), decreases on decreasing the structural order degree of the solvent system ( $\Delta_{yield} = 21$ , 14 and 13% for [bmim][PF<sub>6</sub>], [bmim][BF<sub>4</sub>], [bmim][NTf<sub>2</sub>]).

#### 3.4.2. The IL cation effect

The analysis of data collected as a function of IL cation structure shows that, in all cases considered, comparable or higher yields were obtained under US irradiation than under silent condition [24]. As a consequence of the significant structural changes in the used IL cations, quite articulate trends were observed in both conditions. However, there are two important differences with results previously discussed about IL anion structure, that have to be taken into account. First, under US irradiation the range of yields is narrower than that under silent conditions ( $\Delta_{yield} = 17\%$  and 11% for silent and US, respectively). Second, under US irradiation the decrease in reaction time does not correspond to an increase in yield (see entry 9 of Table 3) in some cases. On the whole, these data seem to indicate a less significant influence of change in IL cation structure on the effectiveness of cavitation process.

Comparison between data collected under silent conditions and US irradiation, for butyl-methyl-substituted cations (namely bmim<sup>+</sup>, bm<sub>2</sub>im<sup>+</sup> and bmpyrr<sup>+</sup>, see entries 5–7 of Table 3), indicates that the positive effect of US irradiation increases along the series [bmpyrr][NTf<sub>2</sub>] < [bmim][NTf<sub>2</sub>] < [bm<sub>2</sub>im][NTf<sub>2</sub>] ( $\Delta_{yield} = 6\%$ , 13% and 19% for [bmpyrr][NTf<sub>2</sub>], [bmim][NTf<sub>2</sub>] and [bm<sub>2</sub>im][NTf<sub>2</sub>], respectively), according to a larger efficiency of the cavitation process in a more organized IL. On the other hand, a larger order degree of aromatic ILs with respect to the aliphatic ones, and the consequent effects it has on the outcome of a reaction, have been frequently outlined [55–57].

The substitution of a butyl or methyl group with a benzyl group on the imidazolium ring, ([Bzmim][NTf<sub>2</sub>] and [Bzbim][NTf<sub>2</sub>]) causes a slight yield increase and decrease, respectively under US irradiation, while the rate of the process is still dramatically increased.

The use of a geminal IL, such as  $[m-Xyl-(bim)_2][NTf_2]_2$ , even promotes the outcome of the target reaction at silent conditions (see entry 10 of Table 3), as accounted for by the comparison with yields obtained in [Bzbim][NTf\_2] solution. Furthermore, US irradiation induces also a moderate increase in yields. However, it is worth noting the significant difference in yields occurring in  $[m-Xyl-(bim)_2][NTf_2]_2$  and in [Bzbim][NTf\_2] solution ( $\Delta_{yield} = 10\%$ ).

#### 4. Conclusions

The whole of collected data shows that the combined use of US irradiation and ILs exerts a positively favorable effect on the synthesis of aryl azides by  $S_NAr$ . In particular, in all the cases considered a significant decrease of reaction time was detected under US activation. In our opinion, this constitutes an important result both from a synthetic and environmental point of view. As a matter of fact, it involves a lower energy waste than classical magnetic stirring. Furthermore, the US irradiation allows to fit the "solvent economy" tendency, by decreasing the volume of solvent used, and consequently by reducing the amount of auxiliary substances to be dispersed in the environment.

However, a honest evaluation of collected data also require to highlight the negative aspects of the studied combined action (US/IL). Indeed, as well as other catalytic methods of irradiation, the substrate and/or product sensitivity to the amount of energy provided to reaction mixture has to be taken into account.

Among the different factors which can affect the outcome of the target reaction, a significant role is played by the structural order degree of the used IL. On the whole, collected data seem to indicate that this IL property is largely changed by modifying the anion, whereas changes in the cation properties seem to have only a minor effect. In general, the most organized solvent systems prove to be the best candidates for US irradiation. This could be a consequence of the most significant solvent–solvent interactions favoring the cavitation process on the whole. However, likewise conventional organic solvents, the US efficiency in IL media decreases when higher reaction temperatures are needed. This is probably a consequence of the weakening of cation–cation and cation–anion interactions, resulting in less organized solvent media.

Finally, to the best of our knowledge, this is one of the few literature reports about the use of a geminal IL for the study of organic reactions, and the first case in which the effect of US irradiation has been analyzed for a IL of third generation too.

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