

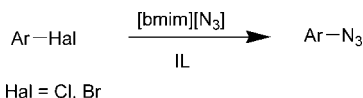
Ionic Liquids/[bmim][N₃] Mixtures: Promising Media for the Synthesis of Aryl Azides by S_NAr

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The nucleophilic aromatic substitution of some activated aryl or heteroaryl halides has been performed in ionic liquid solution, using the 1-butyl-3-methylimidazolium azide as a nucleophile. The reaction course was studied varying the structures of both substrates and ionic liquids. In particular, in the latter case, the reaction of 2-bromo-5-nitrothiophene was carried out in five different ionic liquids ([bmim][BF₄], [bmim][PF₆], [bmim][NTf₂], [bm₂im][NTf₂], and [bmpyr][NTf₂]). Finally, for all the substrates considered, a comparison with data obtained in MeOH solution in the presence of NaN₃ was also performed. Data collected indicate that in some cases it is possible to obtain aromatic or heteroaromatic azide derivatives in satisfactory yield by means of a S_NAr reaction using [bmim][N₃] as the nucleophile.

Introduction

Azides are useful intermediates in organic synthesis. They undergo 1,3-dipolar cycloaddition, and they are frequently used to synthesize various nitrogen-containing compounds.¹ Different synthetic procedures are usually used to prepare alkyl and aryl azides. The former ones can be obtained by nucleophilic aliphatic substitution,² by heating the proper alkyl halide with sodium azide in DMSO or DMF. The latter ones are generally prepared by treatment of diazonium salts with an azide anion.³ Nucleophilic displacement by an azide anion can be ac-

complished only provided that the aromatic ring is sufficiently activated. On the other hand, harsh conditions might induce the loss of nitrogen or other decomposition processes. Under this light, the search for mild conditions for aryl azide synthesis could represent a useful tool in the field of organic chemistry.

It is well-known that in the tune up of a synthetic method a crucial role is played by solvent. The possibility to change solvent nature as a function of the studied reaction is very important. This justifies the growing interest in ionic liquids (ILs) shown by the scientific community in the past decade.⁴ Besides their low vapor pressure and nonflammability, for which they have been claimed green solvents for industrial applications,

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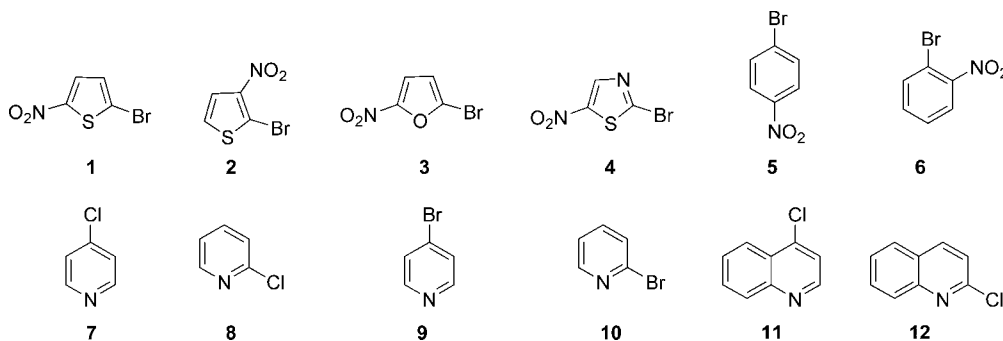
(1) (a) Blass, B. E.; Coburn, K. R.; Faulkner, A. L.; Seibel, W. L.; Srivastava, A. *Tetrahedron Lett.* **2003**, *44*, 2153–2155. (b) Li, Z.; Seo, T. S.; Ju, J. *Tetrahedron Lett.* **2004**, *45*, 3143–3146. (c) Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Adv. Synth. Catal.* **2006**, *348*, 2437–2442. (d) Holub, J. M.; Jang, H.; Kirshenbaum, K. *Org. Biomol. Chem.* **2006**, *4*, 1497–1502. (e) Aureggi, V.; Sedelmeier, G. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 8440–8444. (f) Bosch, L.; Villarasa, J. *Agew. Chem., Int. Ed. Engl.* **2007**, *46*, 3926–3930. (g) Li, P.; Wang, L. *Lett. Org. Chem.* **2007**, *4*, 23–26. (h) Wang, Z.-X.; Zhao, Z.-G. *J. Heteroat. Chem.* **2007**, *44*, 89–92. (i) Sreedhar, B.; Reddy, P. S. *Synth. Commun.* **2007**, *37*, 805–812.

(2) (a) Goutare, R.; Care, A.; Tan, L.; Leboeuf, M. *Bull. Soc. Chim. Fr.* **1962**, 646. (b) Reist, E. J.; Spencer, R. R.; Baker, B. R.; Goodman, L. *Chem. Ind. (London)* **1962**, 1794. (c) Biffin, M. E. C.; Miller, J.; Paul, D. B. In *The Chemistry of Azido Group*; Patai, S., Ed.; John Wiley & Sons: New York, 1971; Chapter 2. (d) Stark, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199. (e) Landini, D.; Maia, A.; Montanari, F.; Rolla, F. *J. Org. Chem.* **1983**, *48*, 3774–3777. (f) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368. (g) Ito, M.; Koyakumar, K.; Ohta, T.; Takaya, H. *Synthesis* **1995**, 376–378. (h) Sasson, R.; Rozen, S. *Org. Lett.* **2005**, *7*, 2177–2179. (i) Sing, P. N. D.; Klima, R. F.; Muthukrishnan, S.; Murthy, R. S.; Sankaranayanan, J.; Stanlecker, H. M.; Patel, B.; Gudmundsdóttir, A. D. *Tetrahedron Lett.* **2005**, *46*, 4213–4217. (j) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697–6700. (k) Li, J.-J. *Synlett* **2007**, 505–506.

(3) (a) Ritchie, C. D.; Wright, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 2429–2432. (b) Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1972**, *94*, 4966–4971. (c) Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571–2572. (d) Avemaria, F.; Zimmermann, V.; Bräse, S. *Synlett* **2004**, 1163–1166. (e) Liu, C.-Y.; Knochel, P. *J. Org. Chem.* **2007**, *72*, 7106–7115.

(4) (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083. (b) Wasserscheid, P.; Keim, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3772–3789. (c) Rogers, R. D.; Seddon, K. R. *Ionic Liquids: Industrial Application to Green Chemistry*; ACS Symposium Series 818, American Chemical Society: Washington, DC, 2002. (d) Rogers, R. D.; Seddon, K. R. *Ionic Liquids as Green Solvents. Progress and Prospects*; ACS Symposium Series 856, American Chemical Society: Washington, DC, 2003. (e) Rogers, R. D.; Seddon, K. R.; Volkov, S. *Green Industrial Application of Ionic Liquids*; NATO Science Series II: Mathematics, Physics and Chemistry, Kluwer: Dordrecht, 2003; Vol. 92. (f) Chiappe, C.; Pieraccini, D. *J. Phys. Org. Chem.* **2005**, *18*, 275–297. (h) Rogers, R. D.; Seddon, K. R. *Ionic Liquids III A: Fundamentals, Progress, Challenges and Opportunities*; ACS Symposium Series 901, American Chemical Society: Washington, DC, 2005. (i) Harper, J. B.; Kobrak, M. N. *Mini-Rev. Org. Chem.* **2006**, *3*, 253–269. (j) Malhotra, S. V. *Ionic Liquids in Organic Synthesis*; ACS Symposium Series 950, American Chemical Society: Washington, DC, 2005. (k) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363–2389. (l) *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2008.

CHART 1. Structures of Used Substrates



their peculiar characteristic is the ionic nature. The high number of possible cation–anion combinations allows us to modulate the properties of these solvents, as a function of the target reaction. As a consequence, ILs frequently affect the outcome of a reaction, giving yields and selectivities higher than molecular solvents, under mild conditions too.⁵

A particular class of ILs is constituted by the ones whose anion may promote the target reaction.⁶ Among these ILs, we focused our attention on 1-butyl-3-methylimidazolium azide ([bmim][N₃]) and its reactivity. Only few reports have considered until now the effect that non-nucleophilic ionic liquids may exert on the anion activation.^{7,8} To the best of our knowledge, ILs such as [alkmim][N₃] have been used to study the nucleophilic substitution on some alkyl sulfonates in solution of non-nucleophilic ILs.⁸ The [bmim][N₃], having a reactive anion, could promote the formation of aryl azides starting from aryl halides. On the other hand, some recent reports have outlined that ILs are solvent media capable of catalyzing nucleophilic aromatic substitution (S_NAr).⁹

Here, we report a systematic study of reactivity of some activated aryl or heteroaryl halides (Chart 1) in the presence of [bmim][N₃], in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) solution at 298 K. Substrates were chosen for

their different aromatic ring structures. In particular, 6 π electron (five- and six-membered rings) and 10 π electron (bicyclic ring) derivatives were considered.

To get information about the effect of the ionic liquid structures on this nucleophilic aromatic substitution, the 2-bromo-5-nitrothiophene was chosen as a model substrate, and its reactivity was analyzed in the presence of five ILs, namely, [bmim][X] (where X = BF₄⁻, PF₆⁻, and NTf₂⁻, NTf₂⁻ = bis(trifluoromethylsulfonylimide)), [bmpyrr][NTf₂], and [bm₂im][NTf₂] (where bmpyrr = butyl-methylpyrrolidinium and bm₂im = 1-butyl-2,3-dimethylimidazolium). The used ILs are different for symmetry, size, and coordination ability of the anion but also for cation ability to give H-bond, π – π , and cation– π or more generally ion–quadrupole type interactions.¹⁰

Finally, to have a comparison with azide anion reactivity in conventional organic solvents, the target reaction has also been carried out in methanol solution, using NaN₃ as a nucleophile source.

Results and Discussion

IL Effect. First, to evaluate the nucleophilicity of [bmim][N₃] under our experimental conditions, we analyzed the reactivity of benzyl bromide. The study of this nucleophilic aliphatic substitution allowed us to have a comparison with some previously reported data about alkyl azide synthesis. Data show that [bmim][N₃] in [bmim][BF₄] solution (yield = 96.1%, conversion = 96.1%)¹¹ is a better nucleophile than NaN₃ in MeOH solution (yield = 39.5%, conversion = 39.5% for the same reaction time). Furthermore, the yield obtained in [bmim][N₃]/[bmim][BF₄] mixture is higher than the one previously reported by using the [bmim][PF₆]/H₂O/NaN₃ mixture.¹²

In light of this result, we used **1** as a model substrate to study the effect of IL nature on the target reaction. In Table 1, yield

(5) (a) Kaar, J. L.; Jesionowski, A. M.; Berberich, J. A.; Moulton, R.; Russell, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 4125–4131. (b) Maruyama, T.; Yamamura, H.; Kotani, T.; Kamiya, N.; Goto, M. *Org. Biomol. Chem.* **2004**, *2*, 1239–1244. (c) Sasaki, K.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2004**, *45*, 7043–7047. (d) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751–760. (e) Akiyama, T.; Suzuki, A.; Fuchibe, K. *Synlett* **2005**, 1024–1026. (f) Ranu, B. C.; Jana, R. *J. Org. Chem.* **2005**, *70*, 8621–8624. (g) Conte, V.; Floris, B.; Galloni, P.; Mirruzzo, V.; Scarso, A.; Sordi, D.; Strukul, G. *Green Chem.* **2005**, *7*, 262–266. (h) Laali, K. K.; Sarca, V. D.; Okazaki, T.; Brock, A.; Der, P. *Org. Biomol. Chem.* **2005**, *3*, 1034–1042. (i) Man, B. Y. W.; Hook, J. M.; Harper, J. B. *Tetrahedron Lett.* **2005**, *46*, 7641–7645. (j) Lindén, A. A.; Johansson, M.; Hermans, N.; Bäckvall, J.-E. *J. Org. Chem.* **2006**, *71*, 3849–3853. (k) Chiappe, C.; Piccioli, P.; Pieraccini, D. *Green Chem.* **2006**, *8*, 277–281. (l) Yoshino, T.; Imori, S.; Togo, H. *Tetrahedron* **2006**, *62*, 1309–1317. (m) Duan, Z.; Gu, Y.; Deng, Y. *J. Mol. Catal. A: Chem.* **2006**, *246*, 70–75. (n) van Rantwijk, K. F.; Sheldon, R. A. *Chem. Rev.* **2007**, *107*, 2757–2785. (o) Ma, X.; Zhou, Y.; Zhang, J.; Zhu, A.; Jiang, T.; Han, B. *Green Chem.* **2008**, *10*, 59–66. (p) Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P.; Kondaji, G.; Nagaiah, K. *Catal. Commun.* **2008**, *9*, 590–593.

(6) (a) Ranu, C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049–3052. (b) Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2005**, *46*, 1489–1491. (c) Xu, J. M.; Liu, B. K.; Wu, W. B.; Qian, C.; Wu, Q.; Lin, X. F. *J. Org. Chem.* **2006**, *71*, 3991–3993. (d) Xu, J.-M.; Qian, C.; Liu, B.-K.; Wu, Q.; Lin, X.-F. *Tetrahedron* **2007**, *63*, 986–990. (e) Ranu, B.; Banerjee, S.; Jana, R. *Tetrahedron* **2007**, *63*, 776–782. (f) Gong, K.; Wang, H.-L.; Fang, D.; Liu, Z.-L. *Catal. Commun.* **2008**, *9*, 650–653.

(7) (a) Lancaster, N. L.; Welton, T.; Young, G. B. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2267–2270. (b) Wheeler, C.; West, K. N.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **2001**, 887–888. (c) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281–4285. (d) Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* **2003**, *68*, 6710–6715. (e) Lancaster, N. L.; Welton, T.; Young, G. B. *J. Org. Chem.* **2004**, *69*, 5986–5992.

(8) (a) Landini, D.; Maia, A. *Tetrahedron Lett.* **2005**, *46*, 3961–3963. (b) Betti, C.; Landini, D.; Maia, A. *Tetrahedron* **2008**, *64*, 1689–1695.

(9) (a) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Venkat Narsaiah, A. *Tetrahedron Lett.* **2003**, *44*, 2217–2220. (b) D’Anna, F.; Frenna, V.; Noto, R.; Pace, V.; Spinelli, D. *J. Org. Chem.* **2006**, *71*, 5144–5150. (c) Newington, I.; Perez-Arlandis, J. M.; Welton, T. *Org. Lett.* **2007**, *9*, 5247–5250.

(10) (a) Hanke, C. G.; Johansson, A.; Harper, J. B.; Lynden-Bell, R. M. *Chem. Phys. Lett.* **2003**, *374*, 85–90. (b) Holbrey, J. D.; Reichert, W. M.; Nieuwenhuyzen, M.; Sheppard, O.; Hardacre, C.; Rogers, R. D. *Chem. Commun.* **2003**, 476–477. (c) Harper, J. B.; Lynden-Bell, R. M. *Mol. Phys.* **2004**, *102*, 85–94. (d) Deetlefs, M.; Hardacre, C.; Nieuwenhuyzen, M.; Sheppard, O.; Soper, A. K. *J. Phys. Chem. B* **2005**, *109*, 1573–1598. (e) Lachwa, J.; Bento, I.; Duarte, M. T.; Lopes, J. N. C.; Rebelo, L. P. N. *Chem. Commun.* **2006**, 2445–2447. (f) Lynden-Bell, R. M.; Del Pópolo, M. G.; Youngs, T. G. A.; Kohanoff, J.; Hanke, C. G.; Harper, J. B.; Pinilla, C. C. *Acc. Chem. Res.* **2007**, *40*, 1138–1145. (g) Hardacre, C.; Holbrey, J. D.; Nieuwenhuyzen, M.; Youngs, T. G. A. *Acc. Chem. Res.* **2007**, *40*, 1146–1155.

(11) The “yield” represents the extent of conversion to azide, and the “conversion” represents the extent of substrate consumption.

(12) Lourenço, N. M. T.; Afonso, C. A. M. *Tetrahedron* **2003**, *59*, 789–794.

TABLE 1. Yield and Conversion Values Relative to Nucleophilic Aromatic Substitution of the 2-Bromo-5-nitrothiophene (1) in the Presence of [Na][N₃] or [bmim][N₃], in MeOH and IL Solution

entry	solvent	nucleophile	[Nuc]/[Sub]	time (h)	conversion ^a (%)	yield ^a (%)	difference (%)
1	MeOH	NaN ₃	1	168	82.7	43.9	38.8
2	[bmim][BF ₄] ^b	NaN ₃	1	70	66.9	52.6	14.3
3	[bmim][BF ₄] ^b	[bmim][N ₃]	1	22	64.0	57.9	6.1
4	[bmim][BF ₄] ^b	[bmim][N ₃]	1.22	2	65.9	61.6	4.3
5	[bmim][BF ₄] ^b	[bmim][N ₃]	1.22	0.5 ^c	65.0	65.0	0.0
6	[bmim][BF ₄] ^d	[bmim][N ₃]	1.22	2	67.2	66.9	0.3
7	[bmim][PF ₆] ^b	[bmim][N ₃]	1.22	2	63.3	63.3	0.0
8	[bmim][NTf ₂] ^b	[bmim][N ₃]	1.22	2	66.3	56.9	9.4
9	[bm ₂ im][NTf ₂] ^b	[bmim][N ₃]	1.22	2	55.6	54.7	0.9
10	[bm ₂ im][NTf ₂] ^b	[bm ₂ im][N ₃]	1.22	2	71.3	68.9	2.4
11	[bmpyr][NTf ₂] ^b	[bmim][N ₃]	1.22	2	70.6	68.6	2.0

^a After column chromatography. ^b V_{IL} = 1.2 mL, V_{1,4-dioxane} = 0.3 mL. ^c At 313 K. ^d Neat [bmim][BF₄].

and conversion values obtained under different experimental conditions are reported. Furthermore, in the last column, differences between conversion and yield are also reported to evaluate how “clean” the reaction is.

As shown by reaction time, conversion, and yield values, the azide anion is a better nucleophile in [bmim][BF₄] than in MeOH solution (entries 1 and 2). The azide anion nucleophilicity which is higher in ILs than in conventional organic solvents has been previously detected by Landini et al.⁸ and also by Afonso et al.,¹⁰ studying nucleophilic aliphatic substitution. It is well-known that nucleophilic aromatic substitution is heavily affected by solvent nature.¹³ In our case, the two solvents considered have comparable polarity ($E_{NR} = 217.2$ and 217.7 for MeOH and [bmim][BF₄], respectively)¹⁴ but different H-bond donor abilities ($\alpha = 1.05$ and 0.627 for MeOH and [bmim][BF₄], respectively).¹⁵ This can have a composite effect on the reaction under examination. Indeed, on one hand, H-bond donor ability may assist the reaction by favoring the departure of the bromine leaving group. On the other hand, it may also disfavor the reaction as a consequence of the nucleophile stabilization by coordination.

Under this light, the different reactivities of the nucleophile in the two solvent media could be the result of a negative H-bond donor effect. Alternatively, ILs such as [bmim][BF₄] have been described as polymeric supramolecular fluids,¹⁶ able to include reagents in their partially ordered structure rather than to solvate them. Consequently, the higher reactivity in these solvent media could be also ascribed to less considerable solvation effects.

The analysis of collected data in IL solution shows that the reactivity of the azide ion depends on the counterion. Indeed, in the presence of [bmim][N₃], the 2-azido-5-nitrothiophene was obtained in higher yield and in a shorter time than by using NaN₃ (entries 2 and 3). Probably, Coulomb interactions, which

are maximized in these solvent media, lower the reactivity of the nucleophile when the counterion is the smaller Na⁺ cation. Furthermore, the shorter reaction time seems to make the reaction cleaner (entries 2 and 3).

The target reaction is favored by increasing the nucleophile/substrate ratio (entries 3 and 4), as shown from the significant decrease in the reaction time. Bearing in mind that the reaction proceeds through an addition–elimination mechanism,¹⁷ the increase in nucleophile concentration favors the first reaction step and, on the whole, the product formation. On the other hand, a temperature increase induces a further decrease in the reaction time (entries 4 and 5). However, we chose to carry out the reactions at 298 K (see after) because significant differences in both yield and conversion values were not detected.

We have also analyzed the effect due to the presence of a cosolvent because all reactions were studied in the presence of 1,4-dioxane (see Experimental Section) to facilitate substrate solubilization. Data reported in Table 1 indicate that the cosolvent presence has a limited effect on both conversion and yield (entries 4 and 6). Under this light, practical reasons induced us to carry out the reaction in the presence of 1,4-dioxane. However, the scarce relevance of cosolvent presence perfectly agrees with data recently obtained by us, about the properties of [bmim][BF₄]/1,4-dioxane binary mixtures,¹⁸ outlining that the data collected in the binary mixture can be referred to a partially organized solvent medium, such as neat IL.

Several literature reports evidenced that significant changes in the outcome of a reaction could be afforded as a function of the ions constituting IL. Under this light, we carried out the target reaction in solution of ILs having different cation or anion properties. By analogy with previous discussion about the comparison between [bmim][BF₄] and MeOH, the effect of IL cations may be rather composite. Indeed, cations having an acidic H atom, such as bmim⁺ (H2 of imidazolium) and bm₂im⁺ (CH₃ of imidazolium), may assist bromine departure in the transition state, favoring the reaction. However, they can also coordinate the nucleophile, decreasing its reactivity. On the whole, collected data show that the latter effect is prevalent. Indeed, both yield and conversion increase on going from an aromatic cation (entries 8 and 9) to an aliphatic one (entry 11). Further confirmation to the positive effect due to the decrease in the cation H-bond donor ability can be found comparing both yield and conversion values obtained in [bm₂im][NTf₂]/

(13) (a) Terrier, F. *Nucleophilic Aromatic Displacement: The influence of the nitro group*; in *Organic Nitro Chemistry Series*; Ferrer, H., Ed.; VCH Publishers: New York, 1991. (b) Nudelmann, N. S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups*; Patai, S., Ed.; J. Wiley & Sons Ltd.: London, 1996; Chapter 29. (c) Alvaro, C. E. S.; Nudelmann, N. S. *Arkivoc* **2003**, (x), 95–106.

(14) Carmichael, A. J.; Seddon, K. R. *J. Phys. Org. Chem.* **2000**, *13*, 591–595.

(15) (a) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1990. (b) Crowhurst, L.; Mawdsley, P. R.; Perez-Arlandis, J.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2003**, *5*, 2790–2794.

(16) (a) Dupont, J. J. *Braz. Chem. Soc.* **2004**, *15*, 341–350. (b) Consorti, C. S.; Suarez, P. A. Z.; de Souza, R. F.; Burrow, R. A.; Farrar, D. H.; Lough, A. J.; Loh, W.; da Silva, L. H. M.; Dupont, J. J. *Phys. Chem. B* **2005**, *109*, 4341–4349. (c) Canongia Lopes, J. N. A.; Padua, A. A. H. *J. Phys. Chem. B* **2006**, *110*, 3330–3335.

(17) (a) Meisenheimer, J. *Justus Liebigs Ann. Chem.* **1902**, *323*, 205. (b) Terrier, F. *Chem. Rev.* **1982**, *82*, 77–152.

(18) D'Anna, F.; Frenna, V.; La Marca, S.; Noto, R.; Pace, V.; Spinelli, D. *Tetrahedron* **2008**, *64*, 672–680.

TABLE 2. Yield and Conversion Values Relative to Nucleophilic Aromatic Substitution of Aryl Halides in the Presence of [Na][N₃] or [bmim][N₃], in MeOH and [bmim][BF₄] Solution, at [Nuc]/[Sub] = 1.22

entry	substrate	conditions	time (h)	conversion ^a (%)	yield ^d (%)	difference (%)
1	1	b	168	82.7	43.9	38.8
2		c	2	65.9	61.6	4.3
3	2	b	92	51.4	26.7	24.7
4		c	2	58.8	58.2	0.6
5	3	b	0.5	36.6	14.0	22.6
6		c	0.5	82.8	82.8	0
7	4	b	2.5	51.3	51.3	0
8		c	2.5	73.1	73.1	0
9	5	b	24 ^b	0	0	
10		c	72 ^c	89.6	13.4	76.2
11	6	b	24 ^b	0	0	
12		c	24 ^b	33.6	19.0	14.6
13	7	b	24	0	0	
14		c	24	67.4 ^e	15.4 ^e	52.0
15	8	b	72 ^d	0	0	
16		c	72 ^d	0	0	
17	9	b	24	0	0	
18		c	24	69.0 ^e	20.2 ^e	48.8
19	10	b	48 ^d	0	0	
20		c	72 ^d	0	0	
21	11	b	24	81.1	46.2	34.9
22		c	24	86.3	86.3	0
23	12	b	72 ^d	0	0	
24		c	72 ^d	71.4	51.8	19.6

^a After column chromatography. b = MeOH/NaN₃. c = [bmim][BF₄]/[bmim][N₃]. V_{IL} = 1.2 mL. V_{1,4-dioxane} = 0.3 mL. ^b At 333 K. ^c At 313 K. ^d At 323 K. ^e Determined by ¹H NMR.

[bmim][N₃] and [bm₂im][NTf₂]/[bm₂im][N₃] mixtures (entries 9 and 10). In the latter case, a higher reactivity of the azide anion, as a consequence of a lower cation H-bond donor ability, gives rise to higher conversion and yield values.

The anion effect (entries 4, 7, and 8) seems to be less important than the cation one and could be mainly ascribed to ion symmetry, which in turn induces a higher cross-linking degree of the solvent medium. Indeed, both yield and cleanness of the reaction are slightly higher in the presence of [PF₆⁻] and [BF₄⁻] than in the presence of [NTf₂⁻], indicating a certain importance of the structural organization of IL.¹⁹ A similar trend was previously found by Chiappe et al. on studying nucleophilic aliphatic substitution of alkyl tosylate in the presence of NaN₃.^{7d}

Substrate Structure. In Table 2, yield and conversion values relative to nucleophilic aromatic substitution, as a function of different substrates, collected in [bmim][BF₄] and in MeOH solution, are reported. Also, in this case, to have an evaluation of reaction cleanness, differences between yield and conversion values are reported in the last column of the table. In some cases, significant differences were detected. In general, both in MeOH and in IL solution, these values are higher when a higher reaction time was needed. In these cases, the TLC analysis of reaction mixture, time by time, indicated the formation of some byproducts more polar than azides, which were not characterized.

Data reported in the table show that, in all cases considered, the azide anion is a better nucleophile in [bmim][BF₄] than in MeOH solution. Indeed, in MeOH solution, lower yield values and higher reaction times were recorded (see, for example, entries 3–6, 23, and 24). Furthermore, it is noteworthy that in

some cases (see, for example, entries 9–14, 17, 18, 23, and 24) the reaction proceeds only in the [bmim][BF₄]/[bmim][N₃] mixture.

By analogy with what was previously said, in general the reaction becomes less clean on going from [bmim][BF₄] to MeOH solution, accordingly to reaction time increase. Data collected here allow us to draw some conclusions about the sensitivity of the target reaction to substrate structure, leaving group nature, and isomer reactivity.

Most of the substrates considered in this work give the corresponding azide derivatives at 298 K. Higher temperature values were used in the presence of benzene derivatives (**5**, **6**) (entries 9–12), 2-halopyridines (**8**, **10**) (entries 15 and 16 and 19 and 20), and 2-chloroquinoline (**12**) (entries 23 and 24). Positive results were obtained only in [bmim][BF₄] solution, for **5**, **6**, and **12**. In the latter case, according to literature reports, we did not obtain the 2-azidoquinoline, but the corresponding tetrazole derivative.²⁰

In IL solution, along the series of five-membered heteroaryl halides, both yield and conversion values increase on going from thiophene (**1**) up to furane derivative (**3**). A more variegated situation was detected in MeOH solution. The comparison between data relative to thiophene (**1**) and thiazole (**4**) derivatives evidences the activating effect due to the presence of the aza-group (entries 1 and 2 and 7 and 8). Further confirmation to the activating effect of the aza-group in [bmim][BF₄] solution can be achieved by comparing data relative to 1-bromo-4-nitrobenzene (**5**) and to 4-bromopyridine (**9**) (entries 9 and 10 and 17 and 18). In the latter case, the 4-bromopyridine, in IL solution, gives a higher yield at a lower temperature and in a shorter reaction time (entries 10 and 18). The aza-group effect, comparable to the presence of a nitro group on the aromatic ring, is more significant in IL solution than in MeOH solution.

Several different reports have outlined the importance of π – π interactions in determining reactivity in imidazolium-based ILs.²¹ These interactions seem to be important also in our case. Indeed, data reported in Table 2 show that in IL solution the 2-bromo-5-nitrothiophene (**1**) reacts faster than the 1-bromo-4-nitrobenzene (**5**) (entries 2 and 10), according to its higher π electron density, which should favor the occurrence of π – π interactions.²² The thiophene derivative gives higher yield also in MeOH solution, according to the previously reported higher reactivity of thiophene derivatives versus S_NAr with respect to benzene derivatives.²³ However, the large differences detected in IL solution, in both yield and reaction time values, are more significant than usually detected in conventional organic solvents.

Also, the comparison between data relative to 4-chloropyridine (**7**) and 4-chloroquinoline (**11**) (entries 14 and 22) shows that, in IL solution, higher yields at lower temperatures can be detected in the presence of a substrate having a more extended π system and consequently a better ability to give π – π interactions. Probably, on going from 6 π to 10 π electron systems, the increase in the contact surface area favors once more the occurrence of these activating interactions.²²

(20) Wentrup, C.; Winter, H. W. *J. Am. Chem. Soc.* **1980**, *102*, 6159–6161.

(21) (a) Iwata, K.; Kakita, M.; Hamaguchi, H. *J. Phys. Chem. B* **2007**, *111*, 4914–4919. (b) D'Anna, F.; Frenna, V.; Pace, V.; Noto, R. *Tetrahedron* **2006**, *62*, 1690–1698. (c) D'Anna, F.; Frenna, V.; Noto, R.; Pace, V.; Spinelli, D. *J. Org. Chem.* **2006**, *71*, 9637–9642.

(22) Steed, W. J.; Atwood, J. L. In *Supramolecular Chemistry*; Wiley-VCH: Weinheim, 2000; pp 26–28.

(23) (a) Spinelli, D.; Dell'Erba, C.; Salvemini, A. *Ann. Chim. (Rome, Italy)* **1962**, *92*, 1156–1166. (b) Chapman, N. B.; Parker, R. E.; Soanes, P. W. *J. Chem. Soc.* **1954**, 2109–2114.

(19) McLean, A. J.; Muldoon, M. J.; Gordon, C. M.; Dunkin, I. R. *Chem. Commun.* **2002**, 1880–1181.

The effect of π - π interactions also allows us to explain why 2-halopyridines (**8** and **10**) (see also before), differently from 2-chloroquinoline, do not give the corresponding azides (entries 15, 16, 19, 20, 23, and 24). Indeed, in the presence of 2-halopyridines, a steric hindrance to the nucleophile attack could be hypothesized as a consequence of the π - π stacking. This negative effect could be less important in the presence of 2-chloroquinoline that, having a more extended contact surface area, could show a different arrangement of aromatic rings interacting in the π - π stacking.

Finally, a comparison between data relative to 4-bromo- (**9**) and 4-chloropyridine (**7**) (entries 14 and 18) seems to indicate that the target reaction is barely affected by leaving group nature, with bromide giving a slightly higher yield than chloride. This latter result underlines the minor relevance of the H-bond between the IL cation and the leaving group. This confirms that also in IL solution the rate-determining step is the nucleophile attack on the aromatic system.

Conclusions

In conclusion, the results obtained in this work outline that the [bmim][N₃] in IL solution is a suitable source of nucleophile to favor aryl azides formation by S_NAr. Differently from what was detected in MeOH solution, in the presence of NaN₃, in most cases, the reaction proceeds with a shorter reaction time and in a cleaner way.

The reactivity of the azide nucleophile in IL solution is affected by the hydrogen bond donor ability of the cation. Indeed, a negative H-bond donor solvent effect has been evidenced. On the other hand, the IL anion effect seems to be less important and might be prevalently ascribed to its symmetry, which induces a higher structural order degree in the solvent system. Finally, conversion and yield values collected in [bmim][BF₄] solution, as a function of different substrates, show that the reactivity is positively affected by π - π interactions between imidazolium ions and aromatic substrate. In particular, for 6 π electron systems, the occurrence of these interactions is favored by higher electron density, while in 10 π electron systems the increase in contact surface area has been proven to be the determinant factor.

Experimental Section

Materials. [bmim][BF₄], [bmim][PF₆], 1,4-dioxane, NaN₃, and aryl halides were purchased and used without further purification. [bmim][NTf₂], [bm₂mim][NTf₂], [bmpyr][NTf₂], [bmim][N₃], and [bm₂mim][N₃] were prepared according to previously reported procedures.^{8,24} 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-3-nitrothiophene (**2**)²⁵ and 2-bromo-5-nitrofurane (**3**)²⁶ were prepared according to previous reports.

General Procedure for Aryl Azide 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 thermostatted mixture of 1.8 mmol of [bmim][N₃] in [bmim][BF₄] solution (1.2 mL). 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 byproduct. For the less reactive substrates, the reaction was followed for at least 24 h. Then, the reaction mixture was extracted several times with diethyl ether. After solvent elimination, the residues were separated by flash chromatography on neutral aluminum oxide.

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 ¹H NMR.

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Supporting Information Available: IR, ¹H NMR, and ¹³C NMR spectra of 2-azido-5-nitrothiazole. References about azides. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(24) (a) Schröder, U.; Wadhawan, J. D.; Compton, R. G.; Marken, F.; Suarez, P. A.; Consorti, C. S.; de Souza, R. F.; Dupont, J. *New J. Chem.* **2000**, *24*, 1009–1015. (b) Cammarata, L.; Kazarian, S. G.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2001**, *3*, 5192–5200.

(25) Carpanelli, C.; Leandri, G. *Ann. Chim. (Rome, Italy)* **1961**, *51*, 181–194.

(26) Nazarova, Z. N.; Novikov, V. N. *Zh. Obshch. Khim.* **1961**, *31*, 263–267.