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Aryl Azides Formation Under Mild Conditions: A Kinetic Study in Some Ionic Liquid Solutions

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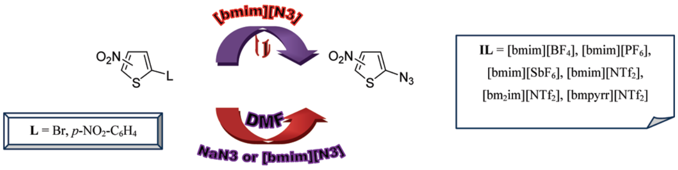

The kinetics of nucleophilic aromatic substitution of three nitrothiophene derivatives in different [1-butyl-3-methylimidazolium][N_3]/ionic liquid binary mixtures was studied spectrophotometrically at 298 K. Ionic liquids differing for cation structure (imidazolium or pyrrolidinium) and for size, shape, and coordination ability of the anion ([BF_4^-], [PF_6^-], [SbF_6^-], and [NTf_2^-]) were used. Furthermore, in order to have a comparison with conventional organic solvents, the target reaction was also carried out in DMF solution at increasing concentration of NaN_3 or [bmim][N_3]. Data collected show that the reaction occurs faster in DMF than in ionic liquid solution. Furthermore, as a consequence of the ability of all solvent media to favor the leaving group departure, a simple linear dependence of the pseudo-first-order kinetic constant from nucleophile concentration was detected. The results of this kinetic investigation once more underline that ionic liquids are able to exert peculiar effects that can be understood also considering their three-dimensional organization.

Introduction

The wide interest that in the past decade the scientific community has shown toward ionic liquids[1] (ILs) has been largely due to the great versatility in cation−anion combination. The right choice of the cation−anion pair allows the modulation of physicochemical properties, such as density and viscosity,[2] but also structural properties of these solvent media such as the order degree, which is markedly controlled both by cation−anion and cation−cation interactions.[3] Furthermore, in some cases the right cation−anion combination can allow one to obtain a "task specific" IL, i.e., an IL having a reactive ion that can act not only as solvent medium, but also as catalyst of a given reaction.[4] After the pioneering work of Rogers et al. geared to the synthesis of task specific

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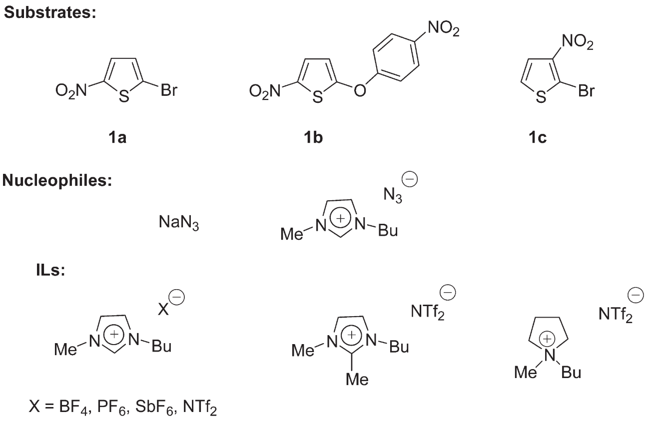
ILs to be used in the extraction of metal ions from aqueous solutions,[5] several different papers have been published about this topic.[6] On this purpose, glycerylimidazolium-based ILs have been recently prepared to be used in palladium-catalyzed reactions.[7] Similarly, benzimidazolium ILs have been used as Brønsted acids for the acetalization of aromatic aldehydes.[8] On the other hand, among ILs characterized by the presence of a reactive anion, it suffices to remember the use of the 1-butyl-3-methylimidazolium hydroxide ([bmim][OH]) for the aza-Michael addition reaction[9] or the use of [bmim][SCN] for the synthesis of alkyl thiocyanates.[10] More recently dialkylimidazolium azides have been used and their catalytic efficiency in the formation of alkyl azides has been studied in different IL solutions.[11]

It is worth remembering that aryl azides are generally prepared by treatment of diazonium salts with azide anion.[12] Nucleophilic displacement by an azide anion can only be accomplished provided that the aromatic ring is sufficiently activated.[13] On the other hand, harsh conditions might induce loss of nitrogen or other decomposition processes. Then, the obtaining of aryl azides under mild conditions and the analysis of factors affecting the rate of the reaction could represent a useful topic in the field of organic chemistry.

In the framework of our interest for ILs properties,[14] we recently demonstrated that, unlike conventional organic solvents, the [bmim][X]/[bmim][N_3] binary mixtures are suitable reaction media for the synthesis of aromatic azides by S_NAr under mild conditions.[15]

CHART 1. Structures of Substrates, Nucleophiles, and ILs Used



To obtain deeper insights into the knowledge of the properties of such binary mixtures, we studied the formation of aryl azides by S_NAr from a kinetic point of view. In our opinion this investigation could have important advantages. First, as largely reported in literature, aryl azides are useful intermediates for the synthesis of heterocyclic compounds, which in turn have several applications in the field of materials, pharmaceutical, and agricultural chemistry.[16] Furthermore, it is well-known that the S_NAr is largely affected by solvent properties.[17] This reaction has been frequently used to study the peculiar features of conventional organic solvents, their binary mixtures, and, more recently, IL solutions.[14c,15,18] As a consequence, it could be a suitable probe reaction to pursue our aim.

We took into account as substrates some substituted nitrothiophenes (Chart 1), namely the 2-bromo-5-nitrothiophene (**1a**), the 2-*p*-nitrophenoxy-5-nitrothiophene (**1b**), and the 2-bromo-3-nitrothiophene (**1c**).

These substrates were chosen on the grounds of the different leaving group ability, the different position of the substituents, which could induce a different substrate activation for the target reaction, and the higher reactivity than the corresponding nonhetero aromatic systems. The kinetic investigation was carried out spectrophotometrically in different IL solutions, at 298 K, using increasing concentrations of [bmim][N_3] (0.010−0.06 M) and following the aryl azides formation at suitable wavelengths.

Both aliphatic and aromatic ILs were used (Chart 1). In particular, chosen ILs differed for the cation ability to give hydrogen bond and $\pi-\pi$ interactions, namely [bmim][NTf_2] and

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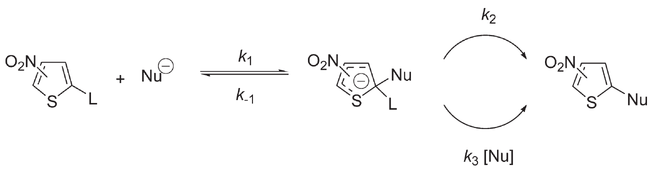
CHART 2. General Scheme of S_NAr on Nitrothiophene



[bm$_2$im][NTf$_2$] or [bmim][NTf$_2$], [bm$_2$im][NTf$_2$], and [bmpyrr]-[NTf$_2$], respectively (where bmim = 1-butyl-3-methylimidazolium, bm$_2$im = 1-butyl-2,3-dimethylimidazolium, bmpyrr = *N*-butyl-*N*-methylpyrrolidinium, and NTf$_2$ = bis(trifluoromethanesulfonyl)imide).

Furthermore, as the size, shape, and coordination ability of the anion play a significant role in determining the IL structural organization,[19] the kinetic investigation was also carried out in ILs differing for the nature of the anion, such as the [bmim][BF$_4$], [bmim][PF$_6$], [bmim][SbF$_6$], and [bmim]-[NTf$_2$].

Finally, in order to have a comparison with conventional organic solvents, the target reaction was also studied in DMF solution, using different concentrations of both NaN_3 or [bmim][N$_3$] (0.01−0.06 M).

Results and Discussion

The general scheme of S_NAr processes on nitrothiophenes is reported in Chart 2, whereas the observed rate constant, k_{obs}, is given by eq 1

$$k_{obs} = (k_1k_2[\mathrm{Nu}] + k_1k_3[\mathrm{Nu}]^2)/(k_{-1} + k_2 + k_3[\mathrm{Nu}]) \quad (1)$$

Simplified kinetic expression can be calculated as a function of the nature of the solvent, the leaving group, and the nucleophile used. In particular, if $(k_2 + k_3\,[\mathrm{Nu}]) \gg k_{-1}$, eq 2 can be derived

$$k_{obs} = k_1[\mathrm{Nu}] = k_{II}[\mathrm{Nu}] \quad (2)$$

The reactivity of the studied substrates was previously investigated in the presence of anionic nucleophiles (sodium thiophenate) both in methanol and in 1,4-dioxane/water solution.[20] In both cases a linear dependence of k_{obs} from the nucleophile concentration was detected. This indicates that the rate of consumption of the intermediate is greater than the rate at which it is produced and underlines the solvent ability to favor the leaving group departure.

Data collected by us in the presence of azide nucleophile, both in DMF and in IL solution,[21] actually evidenced for the title reaction a simple linear dependence of the observed pseudo-first-order rate constant (k_{obs}) on the nucleophile concentration (see eq 2). The second-order rate constants (k_{II}) for substrates **1**, as a function of solvent medium and nucleophile source, are reported in Table 1 (complete data at different azide concentration are available in the Supporting Information, Tables 2−4).

First, we tried to evaluate how the different nature of the counterion of the azide nucleophile (Na^+ or bmim$^+$) affected the reactivity in DMF solution. In our opinion such a comparison could be interesting because the DMF is well-known as a solvent able to solvate only cationic species, consequently favoring the S_N reaction. As can be seen from data reported in Table 1 (entries 1 and 2), k_{II} values increase on going from NaN_3 to [bmim][N$_3$], according to the increase in the cation size and the decrease in the positive charge density. These results seem to indicate the occurrence of a less intimate ion pair for the [bmim][N$_3$]. Consequently, weaker interaction between the azide anion and the bmim$^+$ cation could be presumed, which favors on the whole the nucleophilic power of the azide anion.

The reactivity in DMF solution decreases along the series **1b** > **1a** > **1c** in the presence of both NaN_3 and [bmim][N$_3$]. The higher reactivity of **1b** reflects the reactivity sequence previously detected in conventional organic solvents[20b] and in IL solution[14c] in the presence of neutral nucleophiles. On the other hand, the higher reactivity of **1a** with respect to **1c** agrees with the reactivity trend previously detected for the same substrates in methanol or dioxane/water solution, by using sodium thiophenate as the nucleophile.[20a] In conventional organic solvents for thiophene derivatives these results evidenced a trend quite similar to the one detected for benzene derivatives,[22] notwithstanding the higher bond localization. These results were rationalized on the grounds of the negative effect due to the presence of the *o*-nitro group.

Comparison among data collected in DMF and in ILs solution evidences that the target reaction proceeds faster in the former solvent medium. The lower reactivity of the azide anion in ILs solution than in aprotic polar solvent, such as DMSO, was also detected by Maia et al., on studying the nucleophilic aliphatic substitution of *n*-alkyl methanesulfonates.[11c] On the grounds of the Hughes−Ingold rules,[23] the decrease in reactivity on going from DMF to ILs solution could be ascribed to the increase in solvent polarity. Indeed, all ILs used show higher E_T (30) values than for DMF (E_T (30) = 43.2 kcal/ mol for DMF;[24] E_T(30) = 48.1−52.7 kcal/ mol for ILs used[25]). In the studied reaction, the charge is more delocalized during the activation process, thus an increasing solvent polarity should reduce k_{II} values.

However, even if the E_T(30) trend explains the change in reactivity on going from DMF to ILs, the same parameter does not allow the rationalization of the reactivity sequence in IL solution. Indeed, the E_T(30) values change along the series[25] [bmim][BF$_4$] < [bmim][SbF$_6$] < [bmim][PF$_6$] < [bmim][NTf$_2$] < [bmpyrr][NTf$_2$] < [bm$_2$im][NTf$_2$], whereas in general k_{II} values change as follows: [bmpyrr][NTf$_2$] < [bm$_2$im][NTf$_2$] < [bmim][BF$_4$] < [bmim][NTf$_2$] < [bmim]-[PF$_6$] < [bmim][SbF$_6$]. Probably, in order to rationalize data collected in ILs solution, the combined effect due to different factors should be taken into account.

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[21] All kinetic measurements were carried out by using 1,4-dioxane as cosolvent (ca. 13% by volume, see the Experimental Section). However, on the grounds of our previous results[14e] we are confident that these binary mixtures could be compared to those in neat IL.

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TABLE 1. Second Order Rate Constants (k_{II}) for the Nucleophilic Aromatic Substitution of 1a−c in DMF and in Ionic Liquid Solution at 298 K

entry	solvent	nucleophile	k_{II} (M^{-1} s^{-1})^{a,b} **1a**	k_{II} (M^{-1} s^{-1})^{a,b} **1b**	k_{II} (M^{-1} s^{-1})^{a,b} **1c**
1	DMF	NaN_3	0.0332(0.002)	0.989(0.037)	0.0262(0.0007)
2	DMF	[bmim][N_3]	0.0395(0.001)	1.21(0.01)	0.034(0.001)
3	[bmim][BF_4]	[bmim][N_3]	0.00223(0.0001)	0.129(0.005)	0.00619(0.00028)
4	[bmim][PF_6]	[bmim][N_3]	0.00182(0.0001)	0.136(0.009)	0.00498(0.00019)
5	[bmim][SbF_6]	[bmim][N_3]	0.000517(0.00001)	0.0573(0.0035)	0.00364(0.00013)
6	[bmim][NTf_2]	[bmim][N_3]	0.00159(0.00005)	0.071(0.003)	0.00543(0.00022)
7	[bm_2im][NTf_2]	[bmim][N_3]	0.00304(0.00018)	0.124(0.007)	0.00710(0.00018)
8	[bmpyrr][NTf_2]	[bmim][N_3]	0.00400(0.00001)	0.312(0.0099)	0.0194(0.0008)

[a] Standard deviations are given in parentheses. [b] Observed kinetic constant values were reproducible within ±5%.

We tried also to analyze our reactivity data using the linear solvation energy relationship (LSER) by Kamlet and Taft.[26] However, attempts to carry out any multiparametric correlation gave unsatisfactory results, indicating that classical solvent parameters are somehow unsuitable in order to rationalize our results. In perfect agreement with previous observations, particular care must be used when considering the concept of liquid polarity in IL solution.[27] First, as the used nucleophile was a charged species, a negative effect on its reactivity deriving from the IL cation ability to give hydrogen bond should be claimed. Indeed, all ILs used in this work have larger α values than DMF.[25] Moreover, particularly in the presence of aromatic ILs, a further deactivating effect must be taken into account. On this purpose, different literature reports have shown that these solvent media are able to interact with aromatic substrates by means of $\pi-\pi$, π−cation, and π−quadrupole interactions.[28] In some cases, these interactions significantly affect the reactivity of aromatic substrates in IL solution.[14a−d,g,29] In particular, as far as S_NAr is concerned, a recent report in literature evidences as in aromatic ILs, on going to intermediate, the decrease of significant interactions between the starting material and the solvent accounts for the favorable entropic effect.[30] If these interactions are operating also in our case, they should induce a higher stabilization of the initial state with respect to the transition state leading to the intermediate, decreasing on the whole the reaction rate.

As far as data collected in ILs solution is concerned as a function of the substrate, the reactivity changes along the series **1b** > **1c** > **1a**. Thus, considering k_{II} values relevant to 2-X-5-nitrothiophenes, also in this case a higher reaction rate was detected for the 2-*p*-nitrophenoxy-5-nitrothiophene. However, larger reactivity ratios ($k_{II,\mathbf{1b}}/k_{II,\mathbf{1a}}$) are observed in IL solution than in DMF ($k_{II,\mathbf{1b}}/k_{II,\mathbf{1a}} = 45-110$ in IL and ~30 in DMF solution). This trend is in perfect agreement with the reactivity−selectivity principle. Nevertheless, in our opinion some other factors should be considered.

On the grounds of the previous discussion (see above), the reactivity of a substrate such as **1b**, having an aromatic leaving group, should be particularly disfavored in a solution of aromatic ILs. However, an opposite effect also should be considered. Indeed, ILs have been frequently described as well-organized hydrogen-bonded polymeric supramolecules.[31] As a consequence of the feeble but cooperative interactions working in these solvent media, the response of the solvent to perturbation induced by the solute is restricted and slower than that detected for molecular liquids.[32] Under this light, the solute may also be forced into a preorganized structure. In our case, this effect could favor the coplanarity between two aromatic rings. As a consequence, reactivity ratios ($k_{II,\mathbf{1b}}/k_{II,\mathbf{1a}}$) detected in IL solution could be a result of a fine balance between the increased electron-withdrawing effect of the *p*-nitrophenoxy group (conjugation of oxygen lone pair with phenyl ring) and the decreased electrophilic character of the thiophene ring carbon atom (conjugation of another oxygen lone pair with thiophene ring). In DMF solution, where aromatic rings have a higher freedom of rotation around the C−O bond, an "allenic" situation could be hypothesized. This one should induce a maximization of two above effects, so generating lower reactivity ratios.

The comparison between reactivity data corresponding to **1a** and **1c** highlights a different behavior in ILs solution than in DMF solution. In this case, independently from the IL used, a higher reactivity for the ortho-substituted substrate (**1c**) was observed. The reactivity ratio ($k_{\mathbf{1c}}/k_{\mathbf{1a}}$) ranges from 2.3 in [$bm_2im$][$NTf_2$] up to 4.9 in [bmpyrr][$NTf_2$]. We also determined a similar trend on studying the reactivity of these substrates in IL solutions, in the presence of neutral nucleophiles.[14c] In that case, the low reactivity ratios allowed us to leave out the hypothesis of the occurrence in IL solution of a built-in solvation phenomenon. This kind of solvation cannot operate in this case. Therefore, the whole of the results collected by us about the reactivity of thiophene derivatives

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in IL solution seems to indicate the occurrence of a *hyper*-ortho effect, similar to the one detected previously in conventional organic solvents.[33] This effect should activate the substrate, as a consequence of the larger electron-withdrawing power of the *o*-nitro group. Also in this case, the organizing ability of solvent media (see above) may induce a higher coplanarity between the thiophene ring and nitro group, favoring on the whole its electronic effect.

The last point to be analyzed is the effect due to the different structure of IL cation and anion. Several literature reports evidenced that significant changes in the outcome of a reaction could be afforded as a function of ions constituting ILs. Analysis of data relevant to [NTf$_2$]-based ILs shows that the reactivity of the studied substrates is significantly affected by the cation structure of IL. In general, the rate constant values increase along the following series: [bmim][NTf$_2$]<[bm$_2$im][NTf$_2$]<[bmpyrr][NTf$_2$]. The cation
effect on the target reaction may be rather composite.

First, the nature of the cation (aliphatic or aromatic) must be considered. As we said previously, the target reaction should be affected by the positive effect that an aliphatic cation, such as bmpyrr$^+$, could exert on the activation energy, as a consequence of the lower stabilization of the reagents. Second, the cation ability to give a hydrogen bond also should be taken into account. Indeed, cations having more acidic protons, such as bmim$^+$ (H2 of the imidazolium ring) and bm$_2$im$^+$ (CH$_3$ of the imidazolium ring), may coordinate the leaving group, favoring the electrophilic character of C2 and, on the whole, the reaction course. On the other hand, these cations can also coordinate the nucleophile, decreasing its reactivity. This latter effect was considered the factor determining the reactivity sequence of anionic nucleophiles in nucleophilic aliphatic substitution.[11c] In our case, data collected show that the deactivation of the nucleophile does not contribute to a large extent to the changes in the reaction rate.

As far as the effects due to different anion structure are concerned ([bmim$^+$]-based ILs), k_{II} values reported in Table 1 show that the reactivity increases on going from [bmim][SbF$_6$] to [bmim][BF$_4$], according to the increase in coordination ability of the anion (β = 0.146 and 0.376 for [bmim][SbF$_6$] and [bmim][BF$_4$], respectively).[34] This result seems to underline a certain importance of the structural organization of IL, as a consequence of the cross-linking degree of the solvent medium. We previously detected a similar trend, on studying from a qualitative point of view the aryl azide formation in the [bmim][N$_3$] binary mixtures,[15] and our results agreed with data collected by Chiappe et al. on studying nucleophilic aliphatic substitution of alkyl tosylate in the presence of NaN$_3$.[35]

Conclusions

Collected data show that the task specific IL [bmim][N$_3$] is a suitable source of nucleophile to obtain aryl azides from the corresponding aryl halides under mild conditions. In DMF solution the driving force of the process is the lower positive density charge of the bmim$^+$ cation, giving rise to a less intimate ion pair and consequently to a more reactive nucleophile.

On the other hand, kinetic data collected in IL solution indicate that different structural features of [bmim][N$_3$]/IL binary mixtures should be taken into account in order to rationalize reactivity results in these solvent media. In particular, among different factors, once more the structural order degree of the binary mixture and its organizing ability seem to play a significant role in determining the reactivity of the studied substrates.

Experimental Section

Materials. Commercial 1,4-dioxane, 2-bromo-5-nitrothiophene, [bmim][BF$_4$], and [bmim][PF$_6$] were purchased and used without further purification. Substrates **1b** and **1c** were prepared according to a procedure reported previously.[14c,36] The ILs [bmim][NTf$_2$], [bm$_2$im][NTf$_2$], [bmpyrr][NTf$_2$], and [bmim][SbF$_6$] were prepared by anion metathesis of the corresponding chlorides with NaSbF$_6$ or LiNTf$_2$, according to reported procedures.[37] [bmim][N$_3$] was prepared as previously reported.[11]

All ionic liquids were dried on a vacuum line at 60 °C for at least 2 h before use, then stored in a dryer under argon and over calcium chloride.

Kinetic Measurements and Calculations. UV−vis spectra and kinetic measurements were carried out by using a spectrophotometer equipped with a Peltier temperature controller, able to keep the temperature constant within 0.1 deg. The sample for a typical kinetic run was prepared by mixing into a quarz cuvette (optical path 0.2 cm) 500 μL of a [bmim][N$_3$] solution in IL with 75 μL of a concentrated solution of substrate in 1,4-dioxane, previously thermostated. The substrate concentration was constant and equal to 2.0×10^{-4} M; the [bmim][N$_3$] ranged from 0.01 to 0.06 M. At the working wavelength, all ILs binary mixtures were spectroscopically transparent. The reactions were studied over at least three half-lives. In all cases, the correlation coefficients were higher than 0.9998. The apparent first-order rate constants obtained were reproducible within ±5%. All kinetic data were analyzed by means of the KALEIDAGRAPH 4.0 software package.

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Supporting Information Available: Rate constants collected at different azide concentrations at 298 K. This material is available free of charge via the Internet at http://pubs.acs.org.

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