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PII: S0040-4020(15)00642-0

DOI: 10.1016/j.tet.2015.05.003

Reference: TET 26718

To appear in: *Tetrahedron*

Received Date: 30 January 2015

Revised Date: 20 April 2015

Accepted Date: 1 May 2015

Please cite this article as: D'Anna F, Millan D, Noto R, The ionic liquid effect on the Boulton-Katritzky reaction: a comparison between substrates of different structure, *Tetrahedron* (2015), doi: 10.1016/j.tet.2015.05.003.

Graphical Abstract

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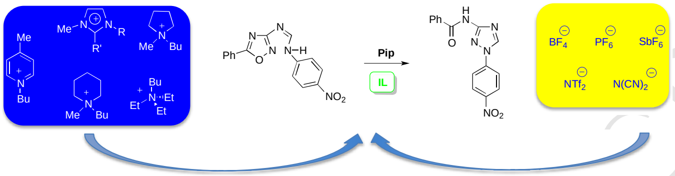

Tetrahedron
journal homepage: www.elsevier.com

The ionic liquid effect on the Boulton-Katritzky reaction: a comparison between substrates of different structure

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Dedicated to Prof. Alan Katritzky for his significant contribution in heterocyclic chemistry

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Ionic Liquids
MRH reaction
Base catalysis

ABSTRACT

The mononuclear rearrangement of heterocycles, also called Boulton-Katritzky reaction, was studied in ionic liquid solution using *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N'*-(4-nitrophenyl)-formamidine as substrate. The investigation was carried out using piperidine as basic catalyst and several ionic liquids differing in both cation and anion structure. Kinetic data collected were compared with the ones previously reported using (*Z*)-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole to have information about the effect due to the different structure of the alkyl chain borne on the substrate. Furthermore, data were analysed on the grounds of polarity, Kamlet-Taft solvent parameters, but taking also in consideration the structural features of the solvent used.

On the whole, the results obtained seem to indicate that the "ionic liquid effect" can be explained considering the structural features of the constituent ions, their effect on the structure of solvent media and their ability to interact with the transition state of the target reaction.

1. Introduction

Reactivity in ionic liquid (IL) solutions has been one of the topics investigated since their first development in the middle of 1990s. The so-called "IL effect" has been frequently claimed, including two different observations. The first one has a mere kinetic nature and takes into account the effect that ILs are able to exert on rate of reactions without affecting mechanism.[1-6] In the second one, a change in the outcome of reactions is detected.[7-14]

In some cases, the "IL effect" has been rationalized on the grounds of their solvent properties, as assessed using classical solvent descriptors such as polarity and Kamlet-Taft solvent parameters describing a classical solvent effect.[9,15,16] However, it is worth mentioning that together with the classical "IL effect" a supramolecular "IL effect" has also been claimed. This picture takes in consideration the ionic lattice persisting in these ionic media in the liquid state and stemming from Coulomb interactions. This provides a certain structural order degree that, in the presence of an aromatic cation or anion, is further increased by the occurrence of π-π or cation-π interactions.[17,18] On the grounds of the above considerations, ILs have been described as supramolecular fluids and reactivity in IL solution has been explained bearing in mind their ability to act as confined reaction media. Their kinetic effect is mainly ascribed to supramolecular interactions established with ground or transition state.[19-21] In this light, the supramolecular "IL effect" can also result from entropic effects occurring in these media but which do not operate in conventional organic solvents (COS).[22-27]

However, notwithstanding different papers and current thoughts about reactivity in IL solution, this topic is still the object of intense debate. This arises from the possibility of varying IL properties by simply changing the cation or anion structure, but also from dissimilar effects that the same IL might exert on different reactions. The above considerations confirm what was proposed at the end of 1990 by Armstrong et al. about the probability that effects observed could be a function not only of the IL nature, but also of the substrate or reaction used as probe.[28]

In the framework of our interest in studying ILs properties and applications, we have performed in IL solution some classical organic reactions.[29-31] Among these, we have paid attention to the mononuclear rearrangement of heterocycles (MRH), also called the Boulton-Katritzky reaction.[32-35] This reaction is an azole-azole interconversion widely studied in conventional solvents using both basic[36] and acidic catalysts.[37]

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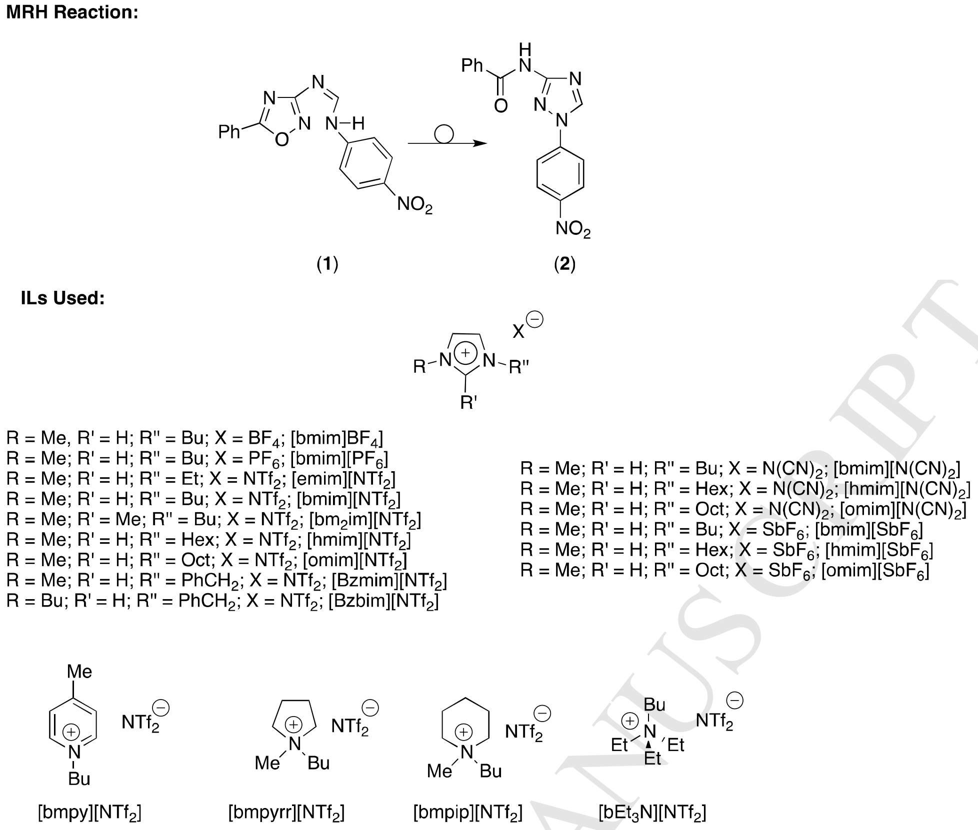

Scheme 1. Representation of reaction studied and ILs used.

Data collected by us, considering the base catalysed rearrangement of (*Z*)-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in solution of mono-,[32,33] di-,[34] and task specific dicationic ILs,[35] demonstrated the positive effect exerted on the above reaction by aromatic ILs. These ones, being able to establish π-π and π-dipole interactions, stabilize the cyclic quasi-aromatic transition state of the reaction and favour its outcome. Together with solvent and catalyst properties, the above reaction is heavily affected by the nature of the side chain borne on the starting oxadiazole ring. Indeed, it determines properties of the final heterocycle and consequently acts on the nature of the transition state.[36,38]

In light of the above considerations, the main goal of this paper is to have a better understanding of the "IL effect" on the MRH reaction. To pursue this aim, considering the significant role played by side chain structure of the substrate, we studied the MRH reaction of the *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N'*-(4-nitrophenyl)-formamidine (**1**) into the corresponding 1-aryl-3-benzoylamino-1,2,4-triazole (**2**) (Scheme 1). Bearing in mind data previously reported by us, this study could reveal information about side chain effect on the MRH reaction, never investigated so far in IL solutions. As base catalyst, we used piperidine (Pip) and we performed a kinetic investigation at 298 K under pseudo-first order conditions. In particular, the catalyst concentration ranged from 0.002 M up to 0.02 M, whereas substrate concentration stayed constant and was equal to 0.0002 M. The investigation was carried out by means of UV-vis measurements at 340 nm.

The target reaction was studied in nineteen different ILs (Scheme 1). Both aliphatic and aromatic ILs were used. As far as aromatic ILs are concerned, we tried to evaluate the relevance of different factors such as the nature of the aromatic cation (imidazolium and pyridinium), cation acidity as accounted for the presence of a methyl group on C2 of the imidazolium ion ([bmim$^+$] and [bm$_2$im$^+$]), and the effect deriving from the presence of a different alkyl chain length on the imidazolium ion. Furthermore, we also used benzylimidazolium-based ILs to assess the effect due to the extension of π-surface area of the cation on the outcome of the reaction. The role played by the anion was tested using [bmim$^+$]-based ILs having anions differing in size, shape and coordination ability such as [BF$_4^-$], [PF$_6^-$], [SbF$_6^-$], [NTf$_2^-$] and [N(CN)$_2^-$]. The target reaction was also performed in [NTf$_2^-$]-based ILs having different aliphatic cations such as [bmpyrr$^+$], [bmpip$^+$] and [bEt$_3$N$^+$]. Comparison between pyrrolidinium and piperidinium based ILs could allow us to assess the relevance of geometry and flexibility of a cyclic cation. On the other hand, the use of ammonium-based IL could give information about the role played by the increase in conformational freedom of the cation on going from cyclic to acyclic structures.

Kinetic data were analysed on the grounds of classical solvent parameters. Furthermore, the structural order degree of solvents used was evaluated performing Resonance Light Scattering (RLS) measurements.

2. Results and discussion

Comparison between reactivity in COS and IL solutions. The MRH reaction of (**1**) was previously studied in ACN solution at 313 K, using different basic catalysts such as piperidine (Pip), triethylamine (TEA) and DABCO.[36] Results reported indicate that the triazole formation occurred only using tertiary amines. Indeed, in the presence of Pip, the formation of *p*-nitroaniline and 3-amino-5-phenyl-1,2,4-oxadiazole was observed as a consequence of the hydrolysis of the imino bond in the side chain. Furthermore, at 313 K in ACN solution and using TEA as catalyst, the plot of experimental rate constant *versus* TEA concentration showed a downward curvilinear trend. The above trend was ascribed to the occurrence of a two step mechanism in which the triazole formation took place only after the preliminary formation of a base-substrate ion pair.

In some IL solutions we observed specific behaviour. Indeed, in [SbF$_6$]-based ILs, the reaction was very slow (more than a week was needed to have a conversion lower than 40 %) and k_{obs} detected did not show a regular trend as a function of amine concentration. On the other hand, in [bmpy][NTf$_2$] solution, we observed a change in the colour of the reaction mixture from pale yellow to pale red, probably indicating the occurrence of secondary processes.

In all other IL solutions, unlike ACN solution, we observed the triazole formation, as accounted for by UV-vis spectra recorded as a function of time (see Fig. 1 of Supplementary data) and TLC analysis of the reaction mixtures at the end of the reaction. Furthermore, in all cases, the plot of k_{obs} as a function of Pip concentration showed a linear trend. Fit of experimental trend according to equation (1):

$$k_{obs} = i + k_{II}\,[\mathrm{Pip}] \qquad (1)$$

allowed calculation of second-order rate constants (k_{II}) reported in Table 1 (k_{obs} values as a function of Pip concentration are summarized in Table 1 of Supplementary data). Moreover, in the above cases we detected negative intercept values that, on the grounds of previous reports, were ascribed to the occurrence of an acid-base interaction between Pip and IL cation.[32]

Table 1. Second-order rate constants for the MRH of (**1**) in IL solution at 298 K and IL mole fractions (X_{IL}) in the reaction mixtures

Entry	IL	X_{IL}	k_{II} (M^{-1} s^{-1})[a]
1	[bmim][BF$_4$]	0.70	0.177 (0.006)
2	[bmim][PF$_6$]	0.69	0.044 (0.003)
	[N(CN)$_2$]-based ILs		
3	[bmim][N(CN)$_2$]	0.68	0.240 (0.010)
4	[hmim][N(CN)$_2$]	0.64	0.397 (0.020)
5	[omim][N(CN)$_2$]	0.61	0.034 (0.001)
	[NTf$_2$]-based ILs		
6	[bmim][NTf$_2$]	0.58	0.071 (0.002)
7	[emim][NTf$_2$]	0.60	0.026 (0.002)
8	[hmim[NTf$_2$]	0.56	0.018 (0.001)
9	[omim][NTf$_2$]	0.53	0.026 (0.001)
10	[bm$_2$im][NTf$_2$]	0.57	0.029 (0.001)
11	[Bzmim][NTf$_2$]	0.48	0.054 (0.003)
12	[Bzbim][NTf$_2$]	0.47	0.070 (0.003)
13	[bmpyrr][NTf$_2$]	0.48	0.061 (0.002)
14	[bmpip][NTf$_2$]	0.47	0.060 (0.003)
15	[bEt$_3$N][NTf$_2$]	0.46	0.0016 (0.0001)

[a] Standard deviations are given in parenthesis.

Linear dependence of k_{obs} on Pip concentration shows that, unlike from data collected in ACN solution, the rate of reaction does not tend to a limiting value. This evidence, together with triazole formation as the only reaction product, allows stating that the ionic solvent media were able to induce a change in the outcome of the target process.

Reactivity in IL solution. In IL solution, second order rate constants range from 0.400 M^{-1} s^{-1} down to 0.0016 M^{-1} s^{-1}, with the largest value detected in [hmim][N(CN)$_2$] and the lowest one detected in [bEt$_3$N][NTf$_2$] solution. The above range allows a certain dependence of reaction rate from the nature of the IL used. To understand the origin of this dependence, we first considered the polarity of the ILs used. Indeed, data previously reported for MRH reactions in COS revealed that, with the catalyst being the same, reaction rates increase with solvent polarity. In Table 2 of the Supplementary data, polarity parameters ($E_T(30)$ and E_{NR}) for ILs used are reported. Furthermore, in Fig. 2 of Supplementary data plots of $\log k_{\mathrm{II}}$ versus $E_T(30)$ or E_{NR} are displayed. As accounted for by E_{NR} values, analysis of the above plots indicates that IL polarity does not allow rationalizing of reactivity data. Indeed, for this parameter, we obtained a very scattered plot with no obvious trend. This could be the result of very narrow range of E_{NR} values ($215.3 < E_{NR} < 218.2$ kJ/mol) that does not account for large differences detected in reactivity data.

A different situation was observed as far as $E_T(30)$ values were concerned. Indeed, in this case, the plot of $\log k_{\mathrm{II}}$ as a function of $E_T(30)$ values did not show a clear trend (Fig. 2b of Supplementary data), but a careful look at two different areas of the plot ($50.5 < E_T(30) < 53.0$ kcal/mol and $68.8 < E_T(30) < 70.2$ kcal/mol, Fig. 2c-d of Supplementary data) shows an increase in $\log k_{\mathrm{II}}$ with solvent polarity. Interestingly, the above area identify two IL classes, the first one comprising imidazolium salts, with the exception of $[bm_2im][NTf_2]$, and the second one including $[N(CN)_2]$- and benzylimidazolium based ILs. In both cases, an increase of $\log k_{\mathrm{II}}$ with solvent polarity was detected. The above trends seem to indicate that, unlike COS, solvent polarity in this case does not allow an univocal treatment of reactivity data, unless in the IL group, sub-groups formed by ILs having a similar structure are considered.

In light of the above results, we tried to analyse the "IL effect" using Kamlet-Taft descriptors.[39] These descriptors are reported in Table 2 of the Supplementary data. Furthermore, in Fig. 3 of the Supplementary data, plots of $\log k_{\mathrm{II}}$ as a function of α, β or π^* are displayed. It is worth remembering that the above parameters account for solvent microscopic properties, such as hydrogen bond donor ability (α), hydrogen bond acceptor ability (β) and dipolarity or polarizability (π^*). Analysis of the above plots indicates that these parameters are not able to explain the reactivity trend observed, if taken alone. In view of this, we tried to apply a linear solvation energy relationship (LSER):

$$\log k_{\mathrm{II}} = \mathrm{const} + a\cdot\alpha + b\cdot\beta + c\cdot\pi^* \qquad (2)$$

Such an approach has been successfully applied in IL solution to explain the data collected for different organic reactions. [16,9,15]

In our case, multiparametric analysis did not give satisfactory results. Indeed, taking in consideration all ILs used, we obtained the eq. 3:

$$\log k_{\mathrm{II}} = -3.97 + 2.51\ (2.26)\cdot\alpha + 0.46\ (0.50)\cdot\beta + 0.06\ (0.22)\cdot\pi^* \qquad R^2 = 0.368 \quad n = 15 \qquad (3)$$

detecting a very poor correlation, as indicated by the correlation coefficient and standard deviations. On the other hand, dissecting ILs on the grounds of cation nature and taking into account only imidazolium based ILs, the correlation coefficient slightly improved as accounted for by eq. 4:

$$\log k_{\mathrm{II}} = -6.37 + 4.85\ (2.75)\cdot\alpha + 0.29\ (0.50)\cdot\beta + 0.14\ (0.23)\cdot\pi^* \qquad R^2 = 0.513 \quad n = 12 \qquad (4)$$

but without giving good results. On the whole, the above results obtained seem to indicate that factors other than solvent microscopic properties as evaluated by α, β and π^* parameters affect the reaction studied.

According to a previous report,[40] we also tried to correlate reactivity data with IL mole fraction in the reaction mixtures (X_{IL} values are reported in Table 1). In our case, this parameter range from $0.46 < X_{IL} < 0.70$. However, perusal of data reported in Table 1 seems to indicate a scarce influence of IL amount on the outcome of the reaction.

A different way to analyse data collected is to take into consideration structural features of the cation and anion and try to correlate changes in reactivity with the variations they are able to induce on the crystal lattice of ILs.

Anion Effect. To evaluate the role played by the different nature of the anion, we took into account $[bmim^+]$-based ILs. As stated, the anions used differ in size, shape, cross-linking and coordination ability. Furthermore, as the cation is the same, the anion also determines the viscosity of the solvent media, with the highest viscosity detected for $[bmim][PF_6]$ and the lowest for $[bmim][NTf_2]$ (η = 450 and 52 cP for $[bmim][PF_6]$ and $[bmim][NTf_2]$, respectively).[41] Among the anions used, $[BF_4^-]$ and $[PF_6^-]$ have high symmetry and a significant cross-linking ability. On the other hand, both $[N(CN)_2^-]$ and $[NTf_2^-]$ are trigonal, but the former has the highest basicity and coordination ability (see Table 2 of Supplementary data).

Analysis of the k_{II} values reported in Table 1 shows that the reactivity decreases along the following order: $[N(CN)_2^-] > [BF_4^-] > [NTf_2^-] > [PF_6^-]$. The above trend perfectly recalls that for β values (β = 0.942, 0.327, 0.263 and 0.202 for $[bmim][N(CN)_2]$, $[bmim][BF_4]$, $[bmim][NTf_2]$ and $[bmim][PF_6]$, respectively), indicating that the anion coordination ability plays a significant role in determining the reactivity trend observed. This result closely agrees with the one we collected performing the MRH reaction in IL solution and using the (*Z*)-phenylhydrazone of the 3-benzoyl-5-phenyl-1,2,4-oxadiazole as substrate.[33] In that case, we ascribed the effect observed to the anion ability to stabilize the transition state and to increase the nucleophilicity of the NH phenylhydrazonic. It is worth noting that, if this effect is also operative in this case, it seems less relevant. Indeed, reactivity ratios significantly decreased on going from (*Z*)-phenylhydrazone to arylformamidine ($k_{\mathrm{II,[bmim][BF4]}}$: $k_{\mathrm{II,[bmim][NTf2]}}$: $k_{\mathrm{II,[bmim][PF6]}}$ = 20: 2.7: 1 for (*Z*)-phenylhydrazone and 4: 2.5: 1 for arylformamidine, respectively), indicating a lower sensitivity of the latter transition state to the anion nature.

The reactivity trend obtained could also be analysed, taking into account the structural organization of ILs used. Indeed, data previously collected for MRH reaction performed in IL solution indicated that, for aromatic ILs, a further stabilizing effect of the transition state could derive from solvents ability to establish π-π interactions.[32] Obviously, the relevance of the above effect should increase in parallel with the structural organization degree of the solvent. On this subject, an evaluation of ILs organization could be obtained using Resonance Light Scattering (RLS) measurements that accounts for the presence of aggregates in solution and allows having an assessment of their sizes.[42,43] It is worth remembering that RLS intensities (I_{RLS}) are proportional to the square of aggregates volume. In the case of ILs, as a consequence of differences in size of the cation or anion, similar

I_{RLS} values could be detected for aggregates formed by a different number of IL units. I_{RLS} values detected at 522 nm for all ILs used are reported in Table 3 of the Supplementary data. Analysis of I_{RLS} values for [bmim$^+$]-base ILs shows that the size of the aggregates decreased along the following trend: [bmim][N(CN)$_2$] > [bmim][PF$_6$] > [bmim][BF$_4$] > [bmim][NTf$_2$]. With the only exception of [bmim][PF$_6$], the above trend foresees a structural order degree decreasing in parallel with the reactivity trend. The discrepancy observed in the case of [bmim][PF$_6$] could be ascribed to the presence of a different number of IL units constituting aggregates, as a consequence of the biggest anion size. Alternatively, it could be also due to the high viscosity of this IL that could hamper contact between reagents and slow down the rate of reaction.

Irrespective of any effect exerted by the IL anion, it is important to explain why, the arylformamidine rearrangement feels less of a positive effect exerted by a more ordered solvent system with respect to (*Z*)-phenylhydrazone. In our opinion, it could be ascribed to the different aromaticity of triazoles obtained from (*Z*)-phenylhydrazone and arylformamidine. Indeed, on the grounds of DFT calculations, transition states of MRH reaction have been described as cyclic and quasi-aromatic.[44] On the other hand, aromaticity indexes[45-47] account for a lower aromaticity of 1,2,4-triazole with respect to 1,2,3-triazole (in the case of Bird aromaticity index I = 81 and 88 for 1,2,4- and 1,2,3-triazole, respectively).[45] In turn, the different aromaticity of products should derive from a different aromaticity of the corresponding transition states that in the case of the arylformamidine could be less stabilized by IL ability of giving π-π interactions.

Cation Effect. For the cation effect, we first analysed data collected using [NTf$_2$]-based ILs. Comparison between second-order rate constants collected in [bmim][NTf$_2$] and [bm$_2$im][NTf$_2$] (entries 6 and 10 of Table 1) shows that the rate of reaction decreases in parallel with cation ability to give hydrogen bond. We observed a similar trend analysing the reactivity of (*Z*)-phenylhydrazone.[33] Furthermore, in two cases we also detected similar reactivity ratios ($k_{II,[bmim][NTf2]}/k_{II,[bm2im][NTf2]}$ = 2.5[33] and 2.0 for arylformamidine and (*Z*)-phenylhydrazone, respectively).

[NTf$_2$]-based ILs also allow evaluation of the effect deriving from different alkyl chain length on the imidazolium ion. In Fig. 1, the trend of k_{II} values is shown as a function of different alkyl chain length and different anion nature. Rate constant firstly increases with alkyl chain length until reaching a maximum value after which it significantly decreases.

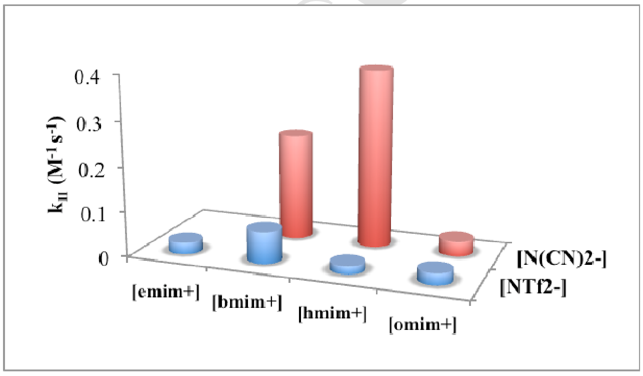

Figure 1. Plot of k_{II} values as a function of alkyl chain length.

The presence of a longer alkyl chain could induce different effects. The first one due to the increase in van der Waals interactions that should induce a parallel increase in the order degree of solvent media favouring the progress of the reaction. The above favourable effect could be counterbalanced by a concomitant rise in solvent viscosity and alkyl chain conformational freedom. These latter effects could become operative beyond a certain length and disfavour the reaction as a consequence of decrease in structural order degree and hindrance of contact between reagents. It is worth remembering that the different packing of solvent system as a function of alkyl chain length has been frequently considered able to induce different solvation of reagents through cation or alkyl chain.[48,49] On the grounds of the above considerations, it can be stated that the maximum reaction rate represents the best balance among above factors. However, a careful analysis of data displayed in Fig. 1 indicates that the role played by alkyl chain length is also affected by the IL anion. Indeed, for [NTf$_2$]-based ILs, the highest reaction rate was detected in the presence of the butyl chain; whereas for [N(CN)$_2$]-based ILs it was obtained for the hexylimidazolium derivative.

It is worth mentioning that we previously detected a similar situation studying the base-catalysed Kemp elimination reaction in some [NTf$_2$]- and [SbF$_6$]-based ILs.[19] To explain the above results, the dependence of ILs viscosity on the anion nature and size of aggregates present in the ILs used should be taken into account. In Fig. 2, the plot of I_{RLS} is reported as a function of alkyl chain length for [NTf$_2$]- and [N(CN)$_2$]-based ILs.

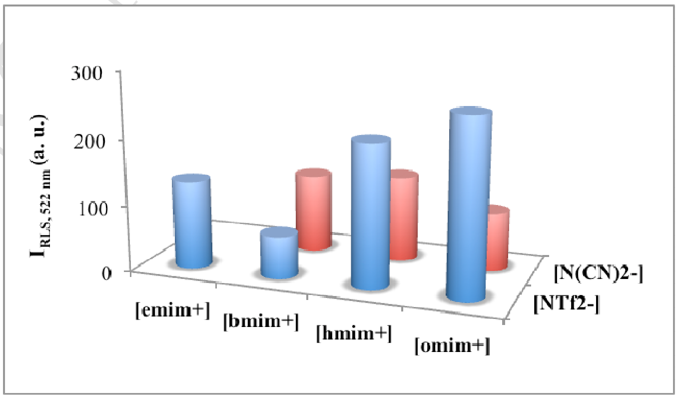

Figure 2. Plot of RLS intensity as a function of alkyl chain length for [NTf$_2$] and [N(CN)$_2$]-based ILs.

A careful analysis of data collected shows that, in the case of [NTf$_2$]-based ILs, the size of aggregates decreases going from [emim][NTf$_2$] to [bmim][NTf$_2$], but increases going to [omim][NTf$_2$]. The above trend does not parallel the reactivity trend. According to reactivity data, RLS measurements foresee the presence of more extended aggregates in [hmim][N(CN)$_2$].

It is well known that viscosity increases with alkyl chain length and comparison between values previously reported for [bmim][NTf$_2$] and [bmim][N(CN)$_2$] demonstrates that [N(CN)$_2$]-based ILs are less viscous than [NTf$_2$]-based ILs (η = 52 and 31.8 cP for [bmim][NTf$_2$] and [bmim][N(CN)$_2$], respectively).[50] On the grounds of the above statements, data collected seems to indicate that in [NTf$_2$]-based ILs, the reactivity observed was a balance between viscosity and structural order degree effect. On the other hand, in [N(CN)$_2$]-based ILs, where structural organization plays a more significant role with respect to viscosity, the first factor prevails giving rise to the highest reaction rate in the highest ordered solvent media.

A further parameter to analyse is the extension of π-surface area of the cation on going from imidazolium to benzylimidazolium based ILs. Unlike data collected for (*Z*)-phenylhydrazone, an increase in π-surface area of the cation did not induce significant changes in reactivity. Indeed, reactivity stayed constant on going from [bmim][NTf_2] to [Bzbim][NTf_2] (entries 6 and 12 of Table 1) and slightly decreased on going from [bmim][NTf_2] to [Bzmim][NTf_2] (entries 6 and 11 of Table 1). This result could be further support to the hypothesis concerning a lower sensitivity of transition states deriving from arylformamidine to IL ability to give π-π interactions.

The last topic to take into consideration is the effect exerted by the aliphatic or aromatic nature of the IL cation. Comparison of the data collected in [bmim][NTf_2], [bmpyrr][NTf_2], [bmpip][NTf_2] and [bEt_3N][NTf_2] (entries 6 and 12-15 of Table 1) shows that reactivity decreases along the following series: [bmim][NTf_2] > [bmpyrr][NTf_2] ≈ [bmpip][NTf_2] >> [bEt_3N][NTf_2]. It is worth noting that the most significant change was detected on going from [$bmim^+$]-based ILs to ammonium IL, whereas only a modest decrease was obtained on going from [bmim][NTf_2] to aliphatic but cyclic cations such as [$bmpyrr^+$] and [$bmpip^+$]. It is worth noting that a similar trend has been recently detected by Guirado et al. studying the reduction of 9-fluorenone in IL solution.[51] In this case, the quite similar E^0 values obtained in [bmpyrr][NTf_2] and [bmpip][NTf_2] were ascribed to similar pre-organization and steric hindrance of cations.

In our case, the similar k_{II} values collected in the above ILs show that the target reaction does not feel the effect due to a different cation shape and geometry. This result is different from the one detected performing Kemp elimination reaction in the same ILs.[19] Furthermore, in the above case as well as studying aryl azides formation in ILs,[52] we also detected an inverse trend for k_{II} values collected in [bmim][NTf_2] and [bEt_3N][NTf_2] solution. Indeed, we observed a significant increase in the rate of reaction on going from aromatic to aliphatic IL. In the current case, the significantly low reactivity detected in [bEt_3N][NTf_2] solution could be ascribed to its tetrahedral structure that, compared to other "bidimensional" aliphatic cations, could hinder the base approach or the formation of stabilizing interactions with the transition state of the target reaction.

Finally, comparison with data previously collected for (*Z*)-phenylhydrazone in [bmim][NTf_2] and [bmpyrr][NTf_2] further supports the idea that the transition state deriving from the present substrate is less sensitive to the positive effect deriving from cation aromaticity as accounted for by different reactivity ratios ($k_{II,[bmim][NTf2]}$: $k_{II,[bmpyrr][NTf2]}$ = 44 and 1.2 in the case of (*Z*)-phenylhydrazone and arylformamidine, respectively).

3. Conclusions

The main goals of this paper were the study of the "IL effect" on the MRH reaction and analysis of the influence of the side chain structure borne on the starting 1,2,4-oxadiazole. As for the "IL effect", data collected show that these solvent media are able to positively act on the mechanism of the reaction and, differently from COS, allow the obtainment of 1,2,4-triazole derivative using Pip as basic catalyst. Probably, this is a consequence of the organized structure of ILs that, providing confined environments, hamper that base attack along directions favouring substrate hydrolysis. Anion symmetry being the same ([PF_6^-] and [SbF_6^-]), the above effect seems to be a function of anion size as demonstrated by the poor reactivity detected in [bmim][SbF_6].

Quite interestingly, we have verified that the side chain structure present on the 1,2,4-oxadiazole ring plays a significant role in determining the "IL effect" observed. Indeed, unlike data we previously collected in the case of (*Z*)-phenylhydrazone, arylformamidine rearrangement results less affected by the structural order degree of IL and its ability to establish π-π interactions with the target transition state. Probably, this can be mainly ascribed to differences in aromaticity of 1,2,4- and 1,2,3-triazole derivatives obtained as reaction products.

Finally, one of the main questions we wished to solve was the possibility to apply LSER relationship to this classical organic reaction performed in IL solution. Unlike some previous reports,[16,1] the above approach fails in the attempt to rationalize the data collected. Among other things, kinetic data show how in some cases cations having a different structure give rise to quite similar reactivities. Probably, this indicates that the reactivity of the arylformamidine in IL solution is a result of the balance among different factors such as polarity, cation and anion structural features and repercussions they have on the IL lattice. All these factors act on the transition state stabilization and cannot be represented by a single equation.

4. Experimental Section

Materials. Commercial 1,4-dioxane, [bmim][BF_4], [bmim][PF_6], 4-nitroaniline, *N*,*N*-diethyl-*p*-nitroaniline, Nile Red and Reichardt's dye 30 were purchased and used without further purification. Substrates **1** and **2** were prepared according to a previously reported procedure.[53] [bmim][NTf_2], [bm_2im][NTf_2], [emim][NTf_2], [hmim][NTf_2], [omim][NTf_2], [bmpy][NTf_2], [Bzbim][NTf_2], [Bzmim][NTf_2], [bmpyrr][NTf_2], [bmpip][NTf_2], [bEt_3N][NTF_2], [bmim][SbF_6], [hmim][SbF_6] [omim][SbF_6], [bmim][$N(CN)_2$], [hmim][$N(CN)_2$], [omim][$N(CN)_2$], were prepared by anion metathesis of the commercially available corresponding chloride with $NaSbF_6$, $LiNTf_2$, or $NaN(CN)_2$ according to a previously reported procedure.[54]

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

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 K. The sample for a typical kinetic run was prepared by mixing into a quarz cuvette (optical path 0.2 cm), 500 μL of IL, 50 μL of a solution of substrate in 1,4-dioxane and then 25 μL of a concentrated solution of amine in 1,4-dioxane, previously thermostated. The substrate concentration was constant and equal to $2.0 \cdot 10^{-4}$ M; the piperidine concentration ranged from $0.2–2.0 \cdot 10^{-3}$ M. 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 analysed by means of the KALEIDAGRAPH 4.0 software package.

Determination of solvent parameters. The determination of solvent parameters was carried out by mixing into a quarz cuvette (optical path 0.2 cm), 500 μL of IL and 75 μL of a concentrated solution of spectroscopic probe in 1,4-dioxane. The concentration of the probe was equal to $2.0 \cdot 10^{-4}$ M. The obtained solution was thermostated at 298 K.

RLS measurements. Resonance Light Scattering measurements were carried out on a spectrofluorophotometer employing a synchronous scanning mode in which the emission and excitation monochromators were preset to identical wavelengths. The RLS spectrum was recorded from 300 to 600 nm setting both excitation and emission slit widths at 1.5 nm.

Acknowledgments

We thank University of Palermo (2012-ATE-0405) and MIUR (FIRB 2010 RBFR10BF5V) for financial support. D.M thanks project ICM-P10-003-F CILIS, granted by ‘‘Fondo de Innovación para la Competitividad’’ from Ministerio de Economía, Fomento y Turismo, Chile.

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Supplementary Material

Supplementary material for this article: tables of kinetic data, polarity parameters, Kamlet-Taft solvent parameters, I_{RLS} values as a function of ionic liquid, plots of logk_{II} as a fuction of polarity or Kamlet-Taft solvent parameters are available.

Supplementary Data for

The ionic liquid effect on the Boulton-Katritzky reaction: a comparison between substrates of different structure

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Figure 1. UV-vis spectra collected as a function of time collected at 298 K, in [bmim][BF_4] solution and in the presence of Pip (0.014 M).

Figure 2. Plots of logk_{II} as a function of polarity parameters and Kamlet-Taft solvent parameters.

Table 1. Observed Rate Constants (k_{obs}) for the MHR reaction of (1) in IL solution, at 298 K, as a function of Pip concentration.

Table 2. Polarity parameters ($E_T(30)$ and E_{NR}) and Kamlet-Taft solvent parameters corresponding to ILs used.

Table 3. I_{RLS} detected at 522 nm as a function of ionic liquid.

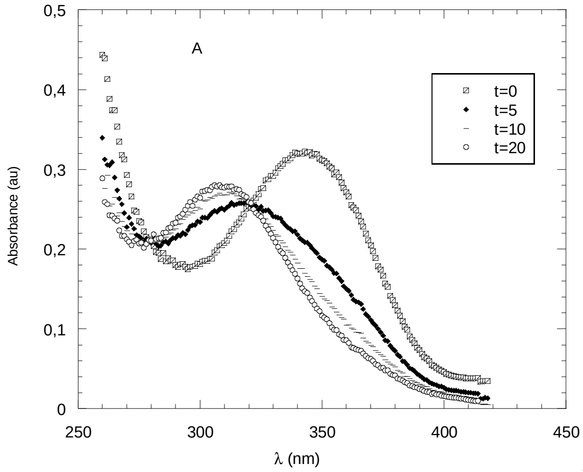
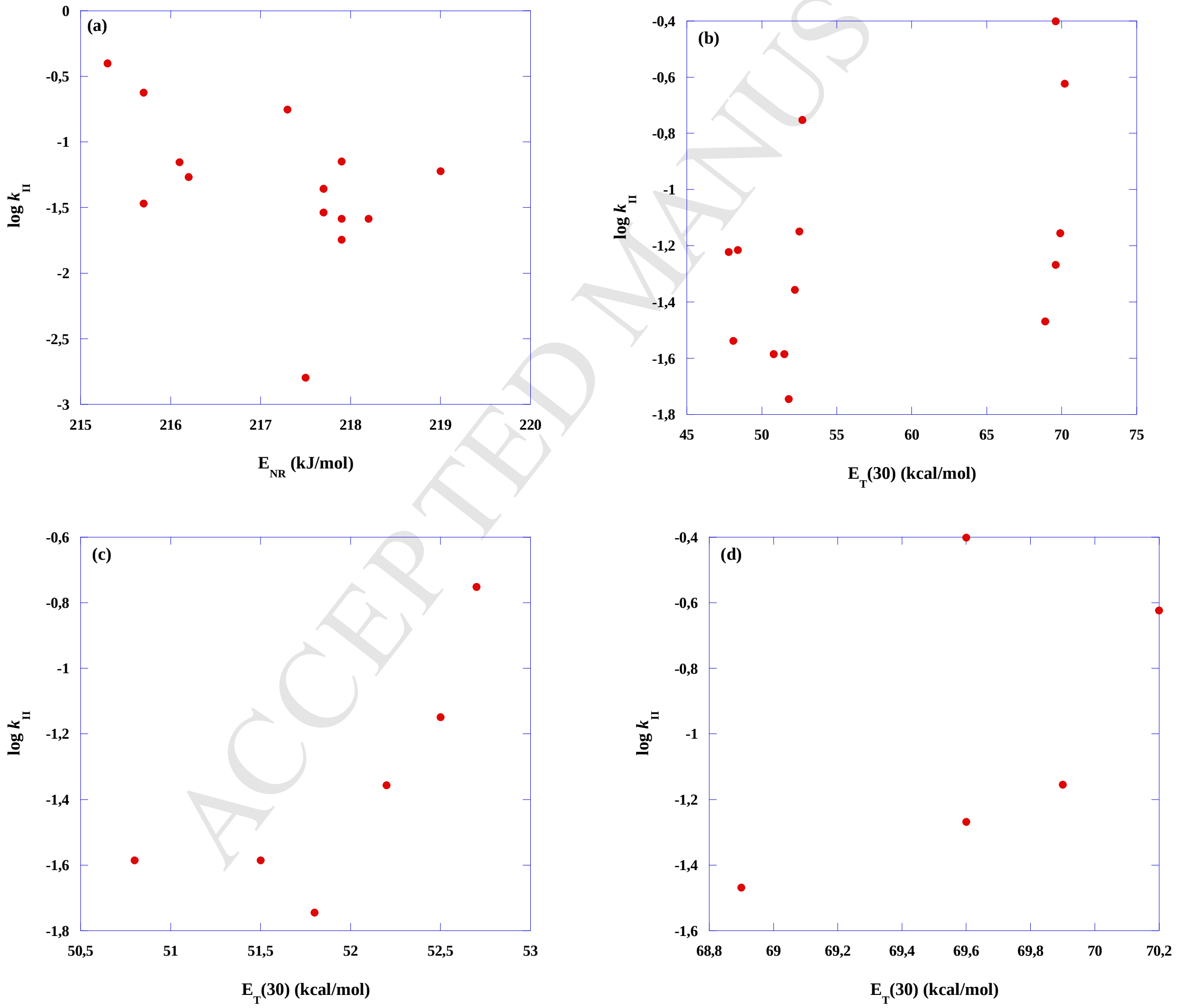


Figure 1. UV-vis spectra collected as a function of time collected at 298 K, in [bmim][BF_4] solution and in the presence of Pip (0.014 M).



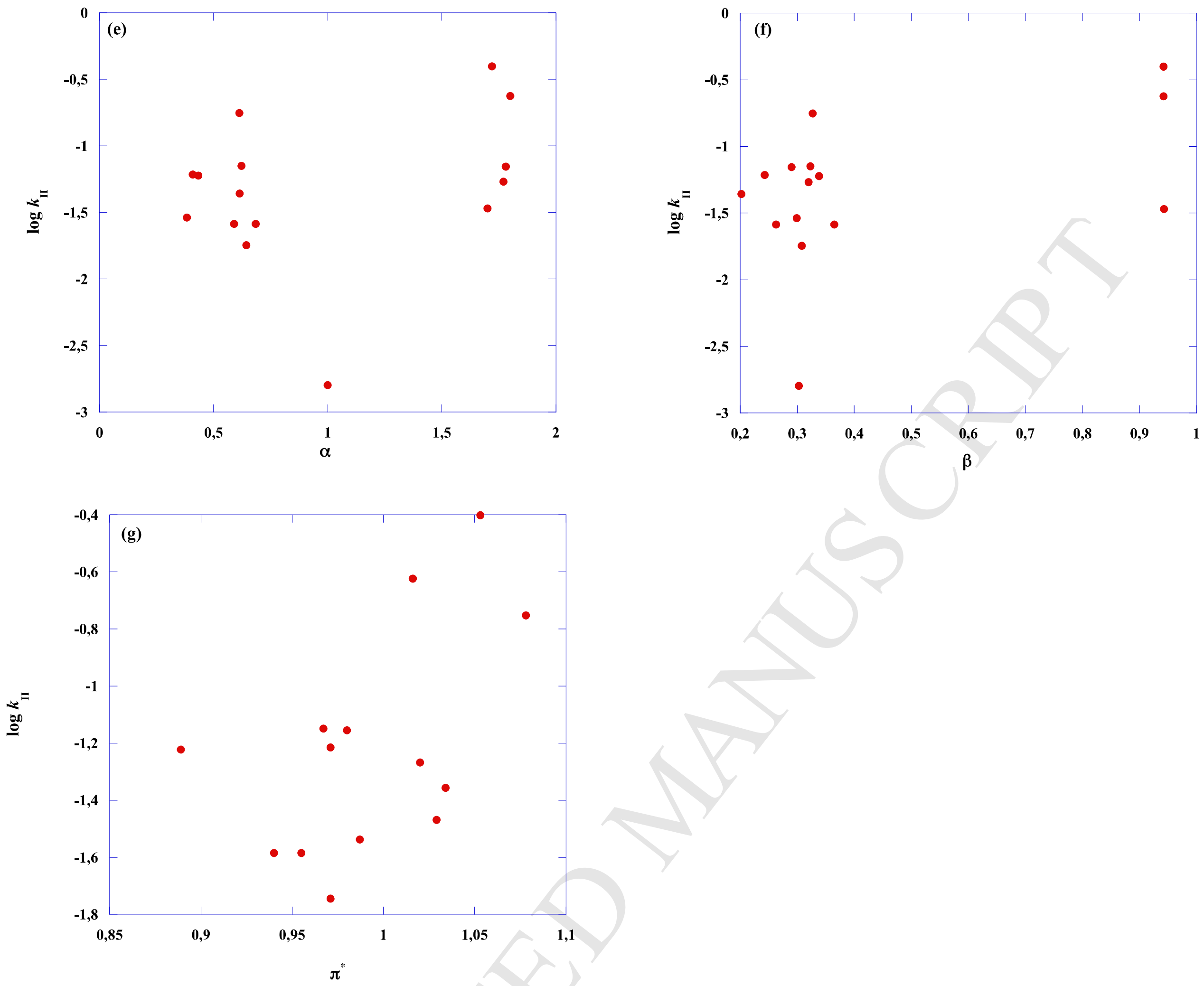


Figure 2. Plots of logk_{II} as a function of: (a) E_{NR} values; (b) $E_T(30)$; (c) $E_T(30)$ in the range 50.5 < $E_T(30)$ < 53.0 kcal/mol; (d) 68.8 < $E_T(30)$ < 70.2 kcal/mol; (e) α ; (f) β; (g) π*.

Table 1. Observed Rate Constants (k_{obs}) for the MHR reaction of (**1**) in IL solution, at 298 K, as a function of Pip concentration.

IL	[Pip] (M)	$10^3\ k_{obs}$ (s^{-1})^{a}
[bmim][BF$_4$]	0.002	0.510
	0.004	0.506
	0.007	1.270
	0.010	1.820
	0.014	2.480
	0.018	3.320
[bmim][PF$_6$]	0.002	0.048
	0.004	0.146
	0.007	0.177
	0.010	0.369
	0.014	0.612
	0.018	0.707
[N(CN)$_2$]-based ILs		
[bmim][N(CN)$_2$]	0.002	0.353
	0.004	1.132
	0.007	1.650
	0.010	2.800
	0.014	3.380
	0.018	4.210
[hmim][N(CN)$_2$]	0.002	0.622
	0.004	1.966
	0.007	2.780
	0.010	4.320
	0.014	5.220
	0.018	7.000
[omim][N(CN)$_2$]	0.004	0.0084
	0.007	0.0589
	0.010	0.1840
	0.014	0.3330
	0.018	0.4630
[NTf$_2$]-based ILs		
[bmim][NTf$_2$]	0.002	0.155
	0.004	0.360
	0.007	0.462
	0.010	0.690
	0.014	0.977
	0.018	1.320
[emim][NTf$_2$]	0.002	0.033
	0.004	0.082
	0.007	0.140
	0.010	0.196
	0.014	0.320
	0.018	0.463
[hmim][NTf$_2$]	0.002	0.035
	0.004	0.069
	0.007	0.116
	0.010	0.165
	0.014	0.252
[omim][NTf$_2$]	0.002	0.046
	0.004	0.096
	0.007	0.140
	0.010	0.217
	0.014	0.365
	0.018	0.448

$[bm_2im][NTf_2]$	0.002	0.069
	0.004	0.143
	0.007	0.212
	0.010	0.289
	0.014	0.433
	0.018	0.531
$[Bzmim][NTf_2]$	0.002	0.052
	0.004	0.159
	0.007	0.271
	0.010	0.463
	0.014	0.753
	0.018	0.865
$[Bzbim][NTf_2]$	0.002	0.067
	0.004	0.240
	0.007	0.413
	0.010	0.670
	0.014	0.860
	0.018	1.130
$[bmpyrr][NTf_2]$	0.002	0.123
	0.004	0.248
	0.007	0.360
	0.010	0.588
	0.014	0.870
	0.018	1.070
$[bmpip]$ $[NTf_2]$	0.002	0.020
	0.004	0.080
	0.007	0.240
	0.010	0.460
	0.014	0.690
	0.018	0.780
$[bEt_3N][NTf_2]$	0.004	0.009
	0.007	0.012
	0.010	0.018
	0.014	0.025
	0.018	0.030

[a] Rate constants were reproducible within ± 5%.

Table 2. Polarity parameters ($E_T(30)$ and E_{NR}) and Kamlet-Taft solvent parameters corresponding to ILs used.

Entry	**IL**	**$E_T(30)$ (kcal/mol)**	**E_{NR} kJ/mol)**	**α**	**β**	**π^***
1	[bmim][BF_4]	52.7[a]	217.3[a]	0.613[a]	0.327[a]	1.078[a]
2	[bmim][PF_6]	52.2[a]	217.7[a]	0.614[a]	0.202[a]	1.034[a]
	[$N(CN)_2$]-based ILs					
3	[bmim][$N(CN)_2$]	70.2[b]	215.7[b]	1.800[b]	0.942[b]	1.016[b]
4	[hmim][$N(CN)_2$]	69.6[b]	215.3[b]	1.730[b]	0.942[b]	1.053[b]
5	[omim][$N(CN)_2$]	68.9[b]	215.7[b]	1.700[b]	0.943[b]	1.029[b]
	[NTf_2]-based ILs					
6	[bmim][NTf_2]	51.5[a]	218.2[a]	0.622[a]	0.263[a]	0.955[a]
7	[emim][NTf_2]	52.5[a]	217.9[a]	0.684[a]	0.323[a]	0.967[a]
8	[hmim][NTf_2]	51.8[a]	217.9[a]	0.643[a]	0.308[a]	0.971[a]
9	[omim][NTf_2]	50.8[a]	217.9[a]	0.590[a]	0.365[a]	0.940[a]
10	[bm_2im][NTf_2]	48.1[a]	217.7[a]	0.384[a]	0.299[a]	0.987[a]
11	[Bzmim][NTf_2]	69.6[c]	216.2[c]	1.770[c]	0.320[c]	1.020[c]
12	[Bzbim][NTf_2]	69.9[c]	216.1[c]	1.780[c]	0.290[c]	0.980[c]
13	[bmpyrr][NTf_2]	48.4[a]		0.409[a]	0.243[a]	0.971[a]
14	[bmpip][NTf_2]	47.8[a]	219.0[a]	0.433[a]	0.338[a]	0.889[a]
15	[bEt_3N][NTf_2]		217.5[a]	0.999[a]	0.303[a]	0.948[a]

[a]From Ref. [1]; [b]Determined in this work; [c]From Ref. [2]

Table 3. I_{RLS} detected at 522 nm as a function of ionic liquid.

Entry	**IL**	**I_{RLS}**
1	[bmim][BF_4]	78.5
2	[bmim][PF_6]	98.1
3	[bmim][$N(CN)_2$]	119
4	[hmim][$N(CN)_2$]	129
5	[omim][$N(CN)_2$]	87.4
6	[bmim][NTf_2]	63.1
7	[emim][NTf_2]	133
8	[hmim] [NTf_2]	214
9	[omim][NTf_2]	264
10	[bm_2im][NTf_2]	63.1
11	[Bzmim][NTf_2]	152
12	[Bzbim][NTf_2]	248
13	[bmpyrr][NTf_2]	76.4
14	[bmpip][NTf_2]	263
15	[bEt_3N][NTf_2]	102

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