

Nucleophilic Displacement Reactions in Ionic Liquids: Substrate and Solvent Effect in the Reaction of NaN₃ and KCN with Alkyl Halides and Tosylates[†]

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Room-temperature ionic liquids have been used as environmentally benign solvents for the preparation of primary and secondary alkyl azides and nitriles under solid-RTIL phase-transfer conditions. The reaction of primary, secondary, and tertiary halides or tosylates with KCN and NaN₃ has been investigated in three ionic liquids ($[bmim][PF_6]$, $[bmim][N(Tf)_2]$, and $[hpyr][N(Tf)_2]$). The observed nucleofugacity scales for the reaction of NaN₃ are similar to those reported for the same process in cyclohexane, indicating that in these solvents it is possible to evidence the intrinsic ability to depart of leaving groups. Changes in the nature of the IL cation or anion determine significant modifications in reactivity of the investigated substrates. Reactivity has been interpreted considering a gradual shift of the mechanism from concerted S_N2 (primary substrates) to stepwise $S_{\rm N}1$ (tertiary substrate, 3), through the nucleophilically assisted formation of an ion pair intermediate, in the case of 2d.

Introduction

The term ionic liquids (ILs) has been introduced in recent years to describe a class of organic salts that are liquid in their pure state at or near room temperature. These liquids possess several properties, such as low melting point, negligible vapor pressure, low coordinating ability, and excellent thermal and chemical stability, which make them attractive alternatives to traditional solvents in a wide range of chemical processes,¹ in liquidliquid extractions,² and for ultralow volatility liquid matrixes.³ Several excellent reviews describe many organic reactions that have successfully been performed with high yields using these liquids as solvents.¹ However, physical and chemical properties of some of these solvents have only recently been investigated,⁴ and few data have been reported to explain how the bulky properties and the microscopic dynamic of these new reaction media may affect reactivity.⁵ It is well-known that the selection of the solvent is one of the most important features for the success of a planned reaction; solvent can affect equilibria and rate-determining reac-

tion times, as well as product distribution. Since ionic liquids have properties completely different from the molecular solvents, it is evident that they may have dramatic effects on reactions occurring within them. Considering the number of available ionic liquids, and the possibility to tailor new ionic liquids, surely the chemist needs in addition to his intuition some general rules to facilitate the choice. We have therefore decided to study some typical organic reactions, such as electrophilic additions⁶ and nucleophilic substitutions reactions, to understand how the properties of these solvents may affect chemical reactivity. In particular, in this work we have investigated the possibility to obtain azides and nitriles from alkyl halides and tosylates by a nucleophilic substitution reaction using NaN₃ or KCN in three ionic liquids, [bmim][PF₆], [bmim][N(Tf)₂], and [hpyr][N(Tf)₂] (where bmim = 1-butyl-3-methylimidazolium, hpyr =1-hexylpyridinium, PF_6 = hexafluorophosphate, and $N(Tf)_2 = bis(trifluoromethylsulfonyl)imide).$



 $X = PF_6$ or $[(CF_3)SO_2]_2N$

[†] In memory of Professor Serena Catalano (1945–2002).

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It is worthy of note that, although many types of reactions have been investigated in ILs, only few examples of nucleophilic substitution reactions have been reported.^{7–9} The versatile reactivity and the synthetic usefulness of the azido and cyano group is well documented, and there are several methods available for the preparation of these compounds. The most common methods utilize alkyl halides via the nucleophilic substitution with alkali metal azides or cyanides (mainly NaN₃ or KCN) in various solvents.¹⁰ However, these methodologies often suffer from complex procedures, long reaction times, and low yields, not to mention the usual purification problems and the difficulties associated with azide isolation from solvents (DMF or DMSO). To improve the yields and to facilitate the product isolation, nucleophilic displacement reactions are often carried out under phase-transfer catalysis (PTC) conditions,¹¹ which favor the contact between the reagents and provide activation of the nucleophilic anion. Unfortunately, in conventional PTC the organic solvents used are environmentally undesirable species. Recently, Eckert et al. have demonstrated the possibility to use of $[bmim][PF_6]$ as a catalyst and solvent for the cyanide displacement of benzyl chloride. Furthermore, when this work was under review, Afonso et al. have reported a study about the use of the same IL as a catalyst and solvent for several nucleophilic substitution reactions under aqueous-IL phase-transfer conditions.¹²

In this paper, we present new data about the reactions of primary, secondary, and tertiary halides and tosylates with KCN and NaN_3 in three ionic liquids having different properties in order to provide additional insight on the mechanism of nucleophilic displacement reactions under solid-RTILs PTC conditions.

Results and Discussion

Methodology. To evaluate how the IL properties affect the nucleophilic substitution reactions three different ionic liquids were used in this study; [bmim][PF₆], $[bmim][N(Tf)_2]$, and $[hpyr][N(Tf)_2]$. The $[bmim]^+$ ILs have been chosen since they are largely used in synthesis and their physicochemical properties are significantly different.^{4,13} For these ILs, in addition to the bulk physical properties (viscosity, density and so on), some chemical properties (dipolarity, hydrogen bond ability, and so on) that may be important to rationalize the solventsubstrate interactions have been recently reported.¹³ The third IL has been chosen to evaluate the specific effects

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that imidazolium cation can have on the nucleophilic substitution reactions.

Since it is well-known¹⁴ that the presence of impurities (unreacted base and halides) markedly affect the physicochemical properties of RTILs, and that halides can compete with added nucleophilic anions (CN^{-} and N_{3}^{-}), particular attention was paid to the purity of the ILs used (see the Experimental Section). Furthermore, considering that the presence of water can have dramatic effects on reactivity, all ILs were subjected to a drying procedure (2 h at 80 °C under vacuo) before use. The water content of the dried ILs was determined by Karl-Fisher titration: [bmim][PF₆] 348 \pm 25 ppm, [bmim][N(Tf)₂] 152 \pm 20 ppm, [hpyr][N(Tf)₂] 120 ± 10 ppm.

To obtain information about the ability of ILs to affect substitution reactions simple primary and secondary long chain alkyl halides or tosylates (1a-d and 2a-c) and a tertiary halide, 1-iodoadamantane (3), were chosen as substrates, while KCN and NaN3 were used as nucleophile sources. The reactions were carried out in screw cup vials, in a recirculating heated bath, and were stirred with magnetic stir bars. The substrate concentration was 0.5 M, and the amount of KCN or NaN₃ was three times the stoichiometric amount of alkyl halide or tosylate. While the substrates were completely soluble in the ionic liquids, solid KCN or NaN₃ was present in the system at all times. Therefore, before introducing the substrate, the salt was stirred overnight in the ionic liquid in order to reach an equilibrium concentration. Reactions were carried out at 80 °C, under stirring, and at prefixed times were stopped by product extraction with Et_2O . The product distribution was determined by NMR and GC-MS analysis, and conversions were evaluated by GC after addition of a proper amount of an internal standard. All the reactions were carried out at least in triplicate. Table 1 illustrates the reaction with NaN₃ while Table 2 reports data related to reaction with KCN. It is worth noting that the addition of water (5 equiv) did not affect the reaction of primary and secondary substrates with NaN₃ while it gave higher yields of the substitution product in the reaction of KCN. In contrast, substrate 3 gave always in the presence of water relevant amounts of the corresponding alcohol. These results show therefore that anhydrous conditions are not necessary to obtain the corresponding azides and nitriles, at least in the case of primary and secondary substrates. Anyway, since one of the aims of this investigation was to obtain information about the relative reactivity of different substrates under identical conditions, the reactions of substrates 1, 2, and **3** were carried out simultaneously using the same batch of solvent (Scheme 1).

Determination of Solvent Properties and Nucleofugacity. Table 1 shows that the reaction of primary and secondary halides or tosylates with NaN3 provides corresponding azido derivatives as the sole products. Primary tosylate **1d** reacts rapidly with NaN₃ in all examined ILs although conversion depends on the solvent. The solvent influence on the reaction rates is strictly related to the nature of the leaving group. In the case of the tosyl group reaction rates increase in the order $[bmim][N(Tf)_2]$ < [hpyr][N(Tf)₂] < [bmim][PF₆]; thus, the highest rate is

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TABLE 1. Reaction of Substrates $1{-}3$ with NaN_3 in ILs at 80 $^\circ\text{C}$

auk atuat a		aalaaant	time	$conv^a$	product
substrate		solvent	(n)	(%)	selectivity
					4
C ₈ H ₁₇ Cl	1a	[bmim][PF ₆]	7	7	100
C ₈ H ₁₇ Br	1b	$[bmim][PF_6]$	7	30	100
$C_8H_{17}I$	1c	[bmim][PF ₆]	7	20	100
C ₈ H ₁₇ OTs	1d	[bmim][PF ₆]	3	99	100
					5/6
sec-C7H15Br	2b	[bmim][PF ₆]	7	56	100:0
sec-C ₈ H ₁₇ OTs	2d	[bmim][PF ₆]	3	100	>95:<5
					7
AdI	3	[bmim][PF ₆]	7	42	90
					4
C ₈ H ₁₇ Cl	1a	[bmim][N(Tf) ₂]	7	15	100
C ₈ H ₁₇ Br	1b	[bmim][N(Tf) ₂]	7	75	100
C ₈ H ₁₇ I	1c	[bmim][N(Tf) ₂]	7	42	100
C ₈ H ₁₇ OTs	1d	[bmim][N(Tf) ₂]	7	100	100
C ₈ H ₁₇ OTs	1d	[bmim][N(Tf) ₂]	3	60	100
					5/6
sec-C7H15Br	2b	[bmim][N(Tf) ₂]	7	40	100:0
sec-C ₈ H ₁₇ OTs	2d	[bmim][N(Tf) ₂]	3	90	90:10
					7
AdI	3	[bmim][N(Tf) ₂]	7	55	90
					4
C ₈ H ₁₇ Cl	1a	[hpyr][N(Tf) ₂]	7	6	100
C ₈ H ₁₇ Br	1b	[hpyr][N(Tf) ₂]	7	60	100
$C_8H_{17}I$	1c	[hpyr][N(Tf) ₂]	7	25	100
C ₈ H ₁₇ OTs	1d	[hpyr][N(Tf) ₂]	7	90	100
C ₈ H ₁₇ OTs	1d	[hpyr][N(Tf) ₂]	3	88	100
					5/6
sec-C7H15Br	2b	[hpyr][N(Tf) ₂]	7	50	100:0
sec-C ₈ H ₁₇ OTs	2d	[hpyr][N(Tf) ₂]	3	100	90:10
					7
AdI	3	[hpyr][N(Tf) ₂]	7	31	90

^{*a*} Each value represents the mean of at least three determinations. Average error: $\pm 5\%$. Isolated yields, given by the sum of substrates and product(s), were always >90%.

observed in the most viscous [bmim][PF₆]. The situation is completely different in the case of halides 1a-c for which the highest rates are observed in [bmim][N(Tf)₂]; the IL has the higher hydrogen bond acidity.¹³ The reactivity scale as a function of the leaving group is, however, the same in the three ILs: $OTs > Br > I \gg Cl$. It is well-known that in molecular solvents the reactivity sequence depends on the solvent, being mainly affected by the ability of the medium to solvate both the entering group and the activated complex. The nucleophilicity scale for nucleophilic substitution by N₃⁻ in a series of *n*-octyl derivatives is indeed I > Br > OTs > Cl in DMSO and $OTs > I > Br \gg Cl$ in cyclohexane.^{10c} This behavior has been explained^{10c} considering that on going from the polarizable DMSO to nonpolar, nonpolarizable cyclohexane the solvation of the entering group and activated complex becomes unimportant. Therefore, in cyclohexane better than in any other solvent the observed reaction rates reflect not only the intrinsic nucleophilicity of the entering group but also the nucleofugacity of the leaving group. The reactivity sequence found in the three ILs, which exactly corresponds to that calculated¹⁵ for S_N2 reactions in gas phase, seems to suggest the absence of strong specific interactions between the examined ILs and the activated complex.

Related to this reaction, the high reactivity of the secondary substrates, which is comparable or higher than

TABLE 2. Reaction of Substrates 1-3 with KCN in ILs at 80 °C

			time	conv ^a	product
substrate		solvent	(h)	(%)	selectivity
					8
C ₈ H ₁₇ Cl	1a	[bmim][PF ₆]	7	5	100
C ₈ H ₁₇ Br	1b	[bmim][PF ₆]	7	18	100
C ₈ H ₁₇ Br	1b	$[bmim][PF_6] + water$	7	95	100
C ₈ H ₁₇ I	1c	$[bmim][PF_6]$	7	95	100
C ₈ H ₁₇ OTs	1d	$[bmim][PF_6]$	7	95	100
					9/6
sec-C7H15Br	2b	[bmim][PF ₆]	7	14	>95:nd ^b
sec-C ₈ H ₁₇ OTs	2d	$[bmim][PF_6]$	7	100	0:100
					10
AdI	3	$[bmim][PF_6]$	7		\mathbf{nd}^{b}
					8
C ₈ H ₁₇ Cl	1a	[bmim][N(Tf) ₂]	7	4	100
C ₈ H ₁₇ Br	1b	$[bmim][N(Tf)_2]$	7	7	100
C ₈ H ₁₇ I	1c	$[bmim][N(Tf)_2]$	7	37	100
C ₈ H ₁₇ OTs	1d	$[bmim][N(Tf)_2]$	7	75	100
					9/6
sec-C7H15Br	2b	[bmim][N(Tf) ₂]	7	8	>95:nd ^b
sec-C ₈ H ₁₇ OTs	2d	$[bmim][N(Tf)_2]$	7	>90	0:100
					10
AdI	3	[bmim][N(Tf) ₂]	7		\mathbf{nd}^{b}
					8
C ₈ H ₁₇ Cl	1a	[hpyr][N(Tf) ₂]	7	0	
C ₈ H ₁₇ Br	1b	[hpyr][N(Tf) ₂]	7	10	100
$C_8H_{17}I$	1c	[hpyr][N(Tf) ₂]	7	50	100
C ₈ H ₁₇ OTs	1d	[hpyr][N(Tf) ₂]	7	31	100
					9/6
sec-C7H15Br	2a	[hpyr][N(Tf) ₂]	7	10	>95:nd ^b
sec-C ₈ H ₁₇ OTs	2b	[hpyr][N(Tf) ₂]	7	100	0:100
					10
AdI	3	[hpyr][N(Tf) ₂]	7		nd ^b

^{*a*} Each value represents the mean of at least three determinations. Average error: \pm 5%. Isolated yields, given by the sum of substrate and product(s), were always >90%. ^{*b*} nd = not detected.

SCHEME 1



that of the corresponding primary substrates, should be noted. Secondary alkyl substrates generally react by an $S_N 2$ mechanism, except that $S_N 1$ mechanism may become important at high solvent polarity. Thus, they are generally enclosed in the borderline region between $S_N 1$ and $S_N 2$ mechanisms. Alternative interpretations have been

given of this borderline region. For example, Sneen¹⁶

MY = NaN₃, KCN

X: **a** = CI, **b** = Br, **c** = I, **d** = OTs

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SCHEME 2

$$Nu^{+} R^{-}X \xrightarrow{k_{1}} \left[Nu^{-}R^{-}X \right]^{-} \xrightarrow{k_{p}} R^{-}Nu^{+}X^{-}$$

SCHEME 3



considered four possible mechanisms to explain the stereochemical and kinetic behavior of substitution reactions: S_N1 , S_N2 , concurrent S_N1 and S_N2 , and substitution at the stage of intimate ion pairs. In this latter situation, products are formed by a dipolar reaction on a reversible formed ion pair. However, Sneen's interpretations and his conclusions have been criticized extensively. Considering the S_N1 and S_N2 reactions as "limiting" behavior, subsequently, the S_N2(intermediate) mechanism has been proposed to account for relatively weakly nucleophilically assisted processes showing ion-pair characteristics.¹⁷ The term S_N2(intermediate) should emphasize the possibility that an S_N2 reaction may proceed via a nucleophilically solvated ion pair intermediate, which is energetically more feasible than Sneen's ion pairs mechanism. The pentacoordinate intermediate proposed by this mechanism is an ion pair similar to the activated complex in the one stage $S_N 2$ reaction (Scheme 2).¹⁷

Also, this mechanism has not been without criticism and alternative reaction pathways have been proposed. To explain the reaction mechanism in the borderline situation it has been proposed that ion pairs could be formed by heterolysis of the bond between carbon and leaving group before the rate-determining nucleophilic attack, and "internal return" to starting materials occurs more rapidly than the attack of the nucleophile.¹⁸ Alternatively, a preassociation mechanism with yet another timing association of the nucleophile with the substrate occurring before the rate-limiting step has been considered.¹⁹ On the basis of this model, as suggested¹⁹ by Jancks, a clear distinction between the different mechanisms can be made considering the lifetime of the intermediate rather than on the character of the transition state. When the intermediate does not exist, or it is too unstable to diffuse away through the solvent, the reaction must occur through a preassociation mechanism in which the reactants are assembled in an encounter complex before the first bonding-making and bondingbreaking step occurs. The preassociation mechanism can be either concerted, with no intermediate, or stepwise, with intermediate. Scheme 3 reports for a substitution reaction in which Nu^- is the nucleophile the classical $S_N 1$

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SCHEME 4



mechanism (upper pathway) and two mechanism involving preassociation: the concerted (lower pathway), and the stepwise (central pathway). When the sandwich intermediate complex (Nu[•]–R^{•+}X⁻) break down to reactants faster than Nu⁻ diffuse away from it, i.e., $k_{-i} > k_{-d}$ the lowest energy pathway will be the preassociation mechanisms.

It is evident from this brief summary that to establish the reaction mechanism in the case of nucleophilic substitution on secondary substrates is not easy. Their reactions in molecular solvents have been object of extensive discussions. However, the high reactivity of the secondary substrates with respect the primary ones, observed for the reaction of NaN₃ in all examined ILs, is in disagreement with a concerted S_N2 mechanism. Among the remaining possible reaction pathways, the distinction between a free intermediates mechanism (S_N1) and the more concerted processes (S_N2, S_N2(intermediate), preassociation) can be made on the basis of known^{19b} criteria:

(i) The reaction of the free intermediate R^+ with Nu^- is often diffusion controlled; therefore, the observation of different rates with different nucleophiles under the same conditions rules out rate determining diffusion controlled trapping of the intermediate.^{19b} In our experiments substrate **2b** quickly reacts with N_3^- but, under the same conditions, does not react with CN^- . This excluded a diffusion-controlled trapping of a free secondary carbocation.

(ii) A free intermediate must show constant partitioning, regard less of its source, in its reaction with different nucleophiles.^{19b} In our experiments, substrate **2d** gives, in the same solvent and at the same temperature, the substitution product with N_3^- and an elimination product with CN^- .

(iii) A free carbocation intermediate gives generally racemization having the same reactivity on both sides of the trigonal carbon.^{19b} The reaction of the optically pure tosyl derivative of (*S*)-2-hexanol (**11**) with NaN₃ in the three examined ionic liquids gives the corresponding (*R*)-2-azidohexane²⁰ (**12**) through a process characterized by a practically complete inversion (ee > 93%, determined by GC on a chiral column) (Scheme 4).

Analogously, the triflate ester of diacetone-D-glucose (13) gives by reaction with NaN₃, in [bmim][PF₆] at 80 °C, exclusively the azido derivative²¹ (14) having D-allo configuration which arises from complete inversion (Scheme 5).

It is worth noting that when the same reaction was carried out in DMF a ca. 1:1 mixture of azido derivative **14** and elimination product **15** was obtained. Thus, IL reduces elimination in favor of substitution.

Finally, 2-bromoadamantane practically does not react with NaN_3 in all the three ILs under reaction conditions which give a conversion >50% from **2b**. This halide is a

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typical secondary alkyl substrate for which nucleophilic assistance is hindered by the cage structure and it is generally used as model for "limiting" behavior. Substitution can occur exclusively through S_N1 mechanism (Scheme 6).

In conclusion, all of the results exclude the involvement of a free carbocation intermediate in the reaction of secondary substrates with NaN₃ in the examined ILs suggesting a more concerted mechanism. We therefore retain that the reaction proceeds through the rear-side nucleophilic attack of azide with a S_N2 mechanism in the case of primary substrates. This mechanism gradually shifts toward a pure S_N1, which surely occurs in the case of the bridgehead cage compound **3**, passing through the nucleophilically assisted formation of an ion pair intermediate in the case of **2d**. It is noteworthy that the reactions of primary and secondary substrates might occur even with preassociation.²²

Theoretical calculations indicate the presence of an encounter complex nucleophile–substrate (or –product), corresponding to an energy minimum before and after the energy maximum, on the reaction coordinate for the $S_N 2$ substitution process in gas phase.²³ In solution, generally the complexes become less important on increasing solvent polarity due to the solvation of the anion. However, if the energy of solvation of N_3^- anion is much smaller in the ionic liquid than in water or protic solvents, as recently suggested^{5a} for Br⁻, the formation of the encounter complex, and therefore, the preassociation mechanism, might become much more favorable in these solvents than in the molecular ones.

Related to the reaction of KCN, it is noteworthy that, as expected, our primary substrates react slower with KCN than benzyl chloride⁷ in all investigated ionic liquids. The reaction is furthermore much more sensitive than that of NaN₃ to the nature of the solvent and to the presence of water and, maybe in agreement with this feature, the higher conversions have been obtained in [bmim][PF₆], the IL containing the higher amount of water. It is also worth noting that the nucleofugacity scale becomes with this nucleophile OTs > I > Br \gg Cl in [bmim]⁺ ILs and I > OTs > Br \gg Cl in [hpyr][N(Tf)₂]. This seems to indicate the presence of more specific interactions solvent nucleophile and/or solvent activated

complex in the CN⁻ reaction, which probably occur through a transition state characterized by a more advanced C-X breaking. Finally, secondary bromide 2b reacts slower with CN^- than with N_3^- , while tosylate 2d gives under the same conditions exclusively the corresponding elimination product(s). The reactivity order of **2b** $(N_3^- \gg CN^-)$ is opposite to that observed in molecular solvents for displacement reactions on methyl halides, but the same as for nucleophilic reactions with carbocations.²⁴ This behavior confirms the large amount of carbocation character of the transition state. Furthermore, the different elimination/substitution ratio found in the reaction of **2b** and **2d** with KCN strongly supports the involvement of ion pair intermediates in the reaction of secondary substrates. For the first-order S_N1 reactions the leaving group has nothing to do with the competition between elimination and substitution. Analogously in S_N2 reactions the elimination/substitution ratio is not greatly dependent on leaving group and, in particular, when OTs is the leaving group generally there is much more substitution.²⁵ Only in the case of ion-pair intermediates leaving group can affect this ratio.

Finally, the data of secondary substrates show that in the examined ILs CN^- anion is a hard anion prone to abstract a proton giving the elimination adduct, while the N_3^- anion is a softer anion which interacts preferentially with an sp₃ carbon to give a substitution product. Since elimination in the 1-adamantyl nucleus is highly improbable, due to the large amount of strain which would be present in the resulting bridgehead olefin, iodide **3** gives neither the corresponding nitrile, nor the elimination product, but a complex mixture of unidentified products or the corresponding alcohol in the presence of water.

Conclusions

In conclusion, this work further confirms the preliminary report indicating that ionic liquids may be used as solvents for nucleophilic substitution reactions between organic compounds and inorganic salts.^{7,8,12} Furthermore, it shows for the first time that it is possible to obtain in these media primary, secondary, and tertiary azides, without problems of purification and isolation. It is worth noting that in the reaction of NaN3 elimination does not compete with substitution even in the case of the sterically hindered substrates, as the triflate ester of diacetone-D-glucose. This behavior is in contrast with that observed in DMF. Furthermore, the data obtained under strictly comparable conditions show that the course of the substitution reactions depends on the nature of the nucleophile, on the nature of the leaving group and on the properties of the reaction medium. Changes in the nature of IL cation or anion determine significant modifications in the reactivity of the same substrates with the same nucleophile. Although ILs should be considered polar solvents (polarity measured¹³ using dye probes ranges between that of short-chain alcohols and acetonitrile-DMSO) the results reported in this work indicate that concerted or rear-side nucleophilically assisted reac-

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tions (with or without preassociation) are preferred with respect the formation of free ionic intermediates. Ionic liquids seem therefore to behave as ionizing but not dissociating solvents. Work is in progress to assess the ionic intermediates stability in these new reaction media.

Experimental Section

General Remarks. ¹H and ¹³C NMR spectra were recorded in CDCl₃. GC-MS spectra were carried out on a 30 m DB5 capillary column using an instrument equipped with an ion trap detector. GC analysis were carried out using an ECONO-CAP EC-5 column (30 m) or a 25 m Chiraldex GTA column. 1-Chlorooctane (99%), 1-bromooctane (99%), 1-iodooctane (98%), 1-octanol (99%), 2-octanol (97%), 2-bromoheptane, 2-bromoadamantane (98%), 1-iodoadamantane (98%), (S)-(+)-2-hexanol (99%), and diacetone-D-glucose (98%) were used without purification. [bmim][PF₆], [bmim][N(Tf)₂], and [hpyr][N(Tf)₂] were prepared following the reported procedures:²⁶ attention was paid to the elimination of bases and Cl- ions which may be present in the solvents as impurities. To eliminate the eventually present traces of unreacted bases [bmim][Cl] and [hpyr][Cl] were carefully recrystallized. The presence of 1-methylimidazole in [bmim][Cl] was checked using the recently reported²⁷ colorimetric method. To remove chloride anion, after metathesis reactions, all ILs were washed several times with deionized water until no chloride was found in the aqueous phase (silver nitrate test in the aqueous phase). The purity of imidazolium salts was finally checked by UV measuring the absorption spectra between 240 and 400 nm. Purified [bmim]+ salts (containing $Cl^- < 0.1$ ppm) have practically no absorption band in the 250-300 nm region.²⁸ After drying (2 h at 80 °C under vacuo) the water amount in ILs was determined by Karl Fisher technique using an apparatus composed of a stand titrator and a coulometer. 3-O-(Trifluoromethanesulfonyl)-1,2: 5,6-di-O-isopropylidene-α-D-glucofuranose was prepared as previously reported.²⁹

Synthesis of Tosyl Derivatives of Primary and Secondary Alcohols. General Procedure. To a solution of *p*-toluensulfonyl chloride (5 g, 0.027mol) in 25 mL of dichloromethane, containing a catalytic amount of pyridine (0.5 mL), was added the proper alcohol (1-octanol, 2-octanol, or (S)-(+)-2-hexanol) (0.018 mol). The reaction was followed by TLC. At the end of the reaction, the pyridinium chloride (visible as long white needles) was removed by filtration, and the resulting filtrate was washed with an aqueous solution of HCl (0.1 N), then with NaHCO₃ (aq), and finally with water until neutralization. The organic layer was then dried (MgSO₄) and filtered, and the solvent was removed by distillation at reduced pressure.

Substitution Reactions. General Procedures. Reactions were carried out in a screw cup with Teflon-faced rubber septum vials under magnetic stirring. To a suspension of KCN or NaN₃ (3 mmol) in 2 mL of ionic liquid, stirred overnight at 80 °C, was added a proper amount of substrate (1 mmol). The mixture was stirred at 80 °C for the times reported in Tables 1 and 2, and then the products were extracted with Et₂O (1 mL × 5). The combined organic layers were dried (MgSO₄) and diluted to an exactly known volume. A portion of this solution, exactly measured, was analyzed by GC–MS after addition of an appropriate amount of an internal standard (benzonitrile or 1-chlorohexane). The remaining solution was analyzed by NMR after removal of the solvent by distillation in vacuo.

The reaction of 3-O-(trifluoromethanesulfonyl)-1,2:5,6-di-Oisopropylidene- α -D-glucofuranose with NaN₃ in DMF at 80 °C was carried out using the same procedure described above. Products were extracted as previously reported.²¹

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Supporting Information Available: ¹H and ¹³C NMR spectra of **1d**, **2d**, (*S*)-2-hexyltosylate, 1-azodooctane, 1-cyanooctane, (*R*)-2-azidohexane, 2-azidoheptane, and 2-azidooctane. This material is available free of charge via the Internet at http://pubs.acs.org.

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