Ionic liquids as exceedingly convenient solvents for the Friedel–Crafts monoalkylation of electron-rich arenes with paraformaldehyde using HCl as catalyst

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Friedel–Crafts hydroxyalkylation of 2-methoxynaphthalene, anisole and 2-methylfuran with paraformaldehyde has been carried out in *N*-ethyl-*N*′-methylimidazolium chloride (1^+Cl^-) or *N*-butyl-*N*′-methylimidazolium hexafluorophosphate ($2^+PF_6^-$) or ethanol using concentrated aqueous HCl as catalyst. The results have shown an extraordinary activity and selectivity towards the formation of the corresponding hydroxymethyl derivative using $2^+PF_6^-$ as solvent. This sharply contrasts with the case of the ethanol as solvent wherein the reaction is much slower and diarylation products are largely formed.

KEY WORDS: ionic liquid; Brönsted acid catalyst; Friedel–Crafts; benzylic alcohols

1. Introduction

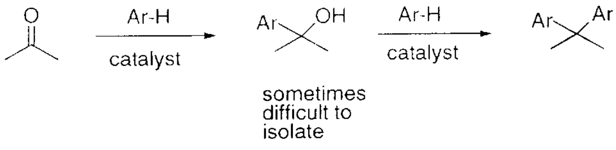
There is no doubt that the nature of the reaction medium, particularly physicochemical properties of the solvent such as polarity, viscosity, ability to form hydrogen bonds, etc., plays an important role in the reaction rate and selectivity of the chemical transformations occurring therein. Recently, there been much interest in the use of ionic liquids as solvents [1,2]. It has been proposed that these solvents would be a suitable medium to develop the new green chemistry [3,4]. This proposal is mainly based on the low vapour pressure and immiscibility of ionic liquids with other common organic solvents that would allow eventually their recovery once the reaction is complete. Ionic liquids as solvents combine the ability to dissolve organic substrates with high polarity.

Despite its promising possibilities, examples reporting organic reactions carried out in ionic liquids are still scarce [5–14]. In an elegant approach, Lewis acid-catalysed reactions including Friedel–Crafts alkylations have been performed in ionic liquids having chloride as counter anion by dissolving $AlCl_3$ [1–3,15]. Depending on the amount of $AlCl_3$, different $Al_xCl_y^-$ chloroaluminates are formed that act as the true catalytic species for the reaction. Reported examples of the use of ionic liquid containing $AlCl_3$ have the problem that total absence of humidity is required to avoid hydrolysis of the chloroaluminates [1,2,16]. Given that ionic liquids are highly hygroscopic solvents, the requisite of absence of humidity complicates the reaction procedure. Herein we report for the first time a Brönsted acid-catalysed Friedel–Crafts alkylation using ionic liquids as solvents that do not require work-up under dry conditions. In fact, the catalytically active species is HCl that is added to the ionic liquid from a concentrated aqueous solution. We have found that the activity of the reaction is much higher in ionic liquids as solvent, and in addition high selectivity towards monoalkylation is observed, contrasting with the results in ethanol wherein diarylation generally predominates. These results clearly exemplify the possibilities of ionic liquids as solvents in catalytic organic reactions, even if some water is present in the medium.

2. Results and discussion

The reaction investigated in the present study consists in the Friedel–Crafts hydroxyalkylation of electron-rich aromatic compounds with paraformaldehyde [17]. In this reaction the primary product is the corresponding hydroxymethyl derivative. But most commonly this benzylic alcohol reacts under the reaction conditions, whereby a diarylmethane is finally formed. Scheme 1 shows the general reaction process for the hydroxyalkylation with carbonylic compounds as alkylating reagents.

To compare the efficiency of ionic liquids as solvent for this hydroxyalkylation reaction we have selected



Scheme 1. Products formed in the Friedel–Crafts condensation of electron-rich arenes with carbonylic compounds.

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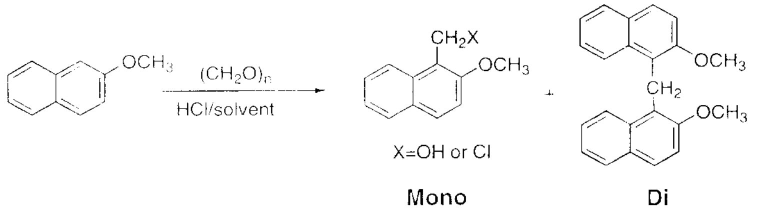
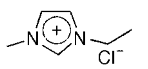
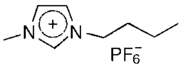
Table 1

Results of the hydroxyalkylation of 2-methoxynaphthalene (0.11 mmol) by paraformaldehyde (see the arene/$(CH_2O)_n$ ratio) catalysed by HCl (0.15 ml) from a concentrated aqueous solution (33 wt%) at 40 °C in three different solvents



$ArH/(CH_2O)_n$	Solvent	Time (h)	MB (%)[a]	Conv. (%)[b]	Selectivity (%)[c,d]	
					Mono	Di
1 : 5	Ethanol	16	84	52	0	100
1 : 10		16	>98	90	0	100
1 : 5		24	>98	33	90	9
1 : 10		24	>98	32	98	2
1 : 5		3	98	100	94	6
1 : 10		0.20	98	100	97	3

[a] Mass balance = $(n_{ArH} + n_{mono} + 2n_{di}) \times 100/n_{ArHo}$.

[b] Conversion = $(n_{ArHo} - n_{ArH}) \times 100/n_{ArHo}$.

[c] Selectivity to mono = $n_{mono} \times 100/(n_{mono} + n_{di})$.

[d] Selectivity to di = $n_{di} \times 100/(n_{mono} + n_{di})$.

2-methoxynaphthalene, anisole and 2-methylfuran as aromatic compounds. The real catalyst of the reaction is HCl. Known amounts of concentrated HCl were added to the ionic liquid. To determine the influence of the nature of the ionic liquid two different imidazolium salts (1^+Cl^- and $2^+PF_6^-$, see table 1) were tested and the results compared to those obtained with ethanol. The relevant reaction conditions, the conversions achieved and the selectivities measured for the hydroxymethylation of 2-methoxynaphthalene are collected in table 1.

The most salient feature from table 1 is the totally different selectivity in the products obtained in ethanol as compared to ionic liquids. While in ethanol, as was observed in many other solvents, the monoalkylation product is absent, this monoalkylated product is obtained in a high selectivity in the case of ionic liquids 1^+Cl^- and $2^+PF_6^-$. Depending on the nature of the counterion, variable proportions of the hydroxymethyl or chloromethyl derivatives were obtained. The relative yield of the latter increased when the ionic liquid was saturated with NaCl.

Also remarkable is the difference in the initial reaction rates depending on the solvent. Particularly relevant is the fact that the activity of HCl in $2^+PF_6^-$ is dramatically higher than in 1^+Cl^- when the chloride is a counter anion. In fact the reaction is complete almost immediately upon addition of HCl to a mixture of the reagents in $2^+PF_6^-$. While there is not a simple explanation for this notable difference in activity, the same influence of the counter anion has already been observed in other reactions carried out in ionic liquids. This is the case for totally different reactions as, for instance, epoxidations of alkenes and the nucleophilic ring aperture of the epoxides [18,19]. Also in these cases PF_6^- as counter anion was found to be much more convenient than Cl^-.

Given that the reaction in $2^+PF_6^+$ is very fast, the primary benzylic product of the hydroxyalkylation undergoes a consecutive alkylation at a much lower reaction rate and, therefore, at much longer reaction times the selectivity towards monoalkylation decreases. Figure 1 shows the corresponding time–conversion

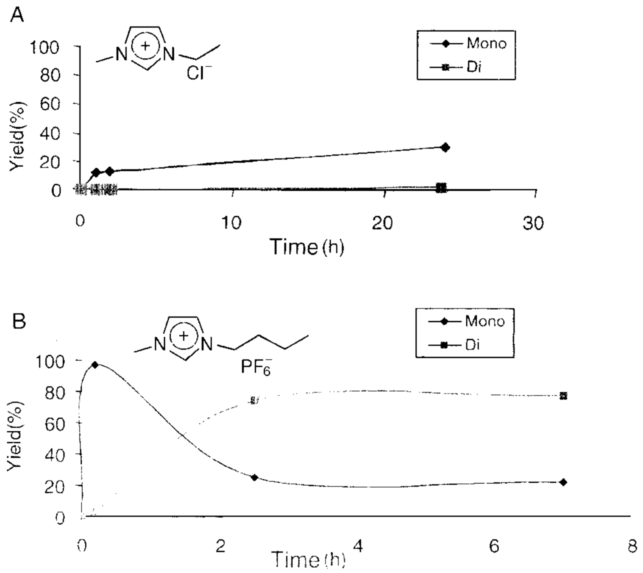
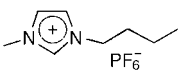
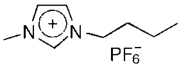


Figure 1. Yield *versus* time for the formation of mono and dialkylated products in the reaction of 2-methoxynaphthalene (0.11 mmol) with paraformaldehyde (10 equivalents) in ionic liquids (1.00 g) at 40 °C using aqueous concentrated HCl (0.15 ml) as catalyst: (A) in 1^+Cl^- and (B) $2^+PF_6^-$.

Table 2
Results of the reaction of anisole or 2-methylfuran (0.11 mmol) with paraformaldehyde (10 equivalents) at 40 °C using aqueous concentrated HCl (0.15 ml) as catalyst

Substrate	Solvent	Time (h)	Conversion[a] (%)	Selectivity (%)	
				Mono	Di
Anisole		0.75	100	77[b]	23
	Ethanol	20	60	60[b]	40
2-Methylfuran		0.75	100	100	0
	Ethanol	20	<5	—	—

[a] Mass balances were higher than 95% in all cases.
[b] Mixture of ortho/para positional isomers.

plot for the reaction of 2-methoxynaphthalene in 1^+Cl^- and $2^+PF_6^-$ under the conditions studied.

The above findings were expanded by studying two other electron-rich arenes, namely anisole and 2-methylfuran. The comparison between the activity and selectivity for the hydroxyalkylation with these two arenes attained either in $2^+PF_6^-$ or in ethanol is summarised in table 2. While in the case of 2-methylfuran only 5-alkylation takes place, as expected for anisole a mixture of ortho/para positional isomers is formed.

As can be seen there, the trends observed for 2-methoxynaphthalene are also apparent in table 2: (i) much higher conversion in $2^+PF_6^-$ than in ethanol at the same reaction time; and (ii) higher selectivity to monoalkylation as opposed to ethanol wherein only the diaryl product is detected.

In summary, in the reported use of ionic liquids for related Friedel–Crafts reactions using $AlCl_3$ as Lewis acid the presence of water deactivates significantly the activity of the catalyst [1,2,4,15,16]. Herein we have found that a Brönsted acid-catalysed reaction such as the Friedel–Crafts hydroxyalkylation of arenes can be performed conveniently in ionic liquids even in the presence of water. In addition, we have found in ionic liquids an exceedingly good selectivity towards monoalkylation, that is, a highly reactive compound. In contrast, under the same conditions working in ethanol only dialkylation occurs. Our report constitutes a good example of the possibilities that ionic liquids offer as solvents in HCl catalysed reactions.

3. Experiments

The ionic liquids 1^+Cl^- and $2^+PF_6^-$ and the 2-methoxynaphthalene and 2-methylfuran were commercial samples and used as received. Known amounts of the arene (0.11 mmol) and the corresponding equivalent amount of paraformaldehyde were dissolved in the appropriate solvent (1.00 g). Then, concentrated HCl (33 wt%) was added (0.15 ml) and the mixture stirred magnetically at 40 °C using a thermostated oil bath. The course of the reaction was periodically followed by analysing weighted aliquots of the reaction mixture. Proportional weights (approximately 1 : 4) of nitrobenzene were added as internal standard, then the mixture was diluted with CH_2Cl_2 (1 ml) and analysed by GC (Varian 3300 chromatograph equipped with a 30 m capillary column of crosslinked 5% phenylmethylsilicone). In the case of ionic liquids, the final reaction mixture was submitted to continuous liquid–liquid extraction using diethyl ether as solvent (EtO_2 is not miscible with ionic liquids). The structure of the products was determined in some cases by comparison with authentic samples [20,21] obtained by alternative methods and in others by GC-MS spectroscopy (HP-5 MS apparatus, same column as for GC). The corresponding MS spectra were compatible with the proposed structure.

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