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Activation of Nucleophilic Fluorination by Salts in Ionic Liquids and in Sulfolane

Stéphane Anguille,[a] Maxime Garayt,[a] Vincent Schanen,[b] and René Grée[a, c,*]

[a] ENSCR, Laboratoire de Synthèse et Activation de Biomolécules, CNRS UMR 6052, Avenue du Général Leclerc, 35700 Rennes Beaulieu, France
[b] Rhodia Recherches et Technologies, Centre de Recherche de Saint Fons, 85 Avenue des Frères Perret, BP 62, 69192 Saint-Fons Cedex, France
[c] Université de Rennes 1, Laboratoire de Synthèse et Electrosynthèse Organiques, CNRS UMR 6510, Avenue du Général Leclerc, 35042 Rennes Cedex, France
Fax: (+33)-(0)2-23-23-69-78; e-mail: rene.gree@univ-rennes1.fr

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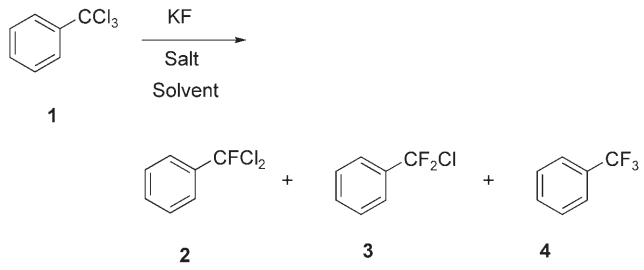
Abstract: The nucleophilic substitution of $PhCCl_3$ by KF in imidazolium-type RTILs is faster than in classical organic solvents but it is strongly dependent upon the nature of the counteranion. The addition of bromide salts in substoichoimetric amounts to the [bmim][PF_6] solvent strongly accelerates this reaction. Furthermore, it has been discovered that addition of KPF_6 to the reaction mixtures strongly activates the nucleophilic fluorination by KF, not only in the [bmim][NTf_2] or [bmim][PF_6] ionic liquids but also for the reactions performed in sulfolane.

Keywords: fluorides; fluorination; halogen exchange; ionic liquids; nucleophilic substitution; salt effect

The room temperature ionic liquids (RTILs) are attractive new reaction media, due to their unique physical and chemical properties.[1] Many types of organic and organometallic reactions, as well as biotransformations, have already been performed in these solvents and in some cases the RTILs offer distinctive advantages in terms of reactivity and selectivity. In addition, these RTILs can be very often recycled and reused.[2] Furthermore, they can be employed to immobilize the reagents and/or the catalysts as task specific ionic liquids (TSILs).[3]

Various aspects of the nucleophilic substitution reactions have already been studied in RTILs. The halide nucleophilicity in ionic liquids has been established on the basis of kinetic data.[4] Different types of nucleophilic substitutions have been performed, for instance, with cyanide or azide anions.[5] The hydrolysis of halogen derivatives has also been reported in ionic liquids,[6] as well as cleavage reactions of ethers,[7] or the formation of carbonates.[8] Recently, it has been demonstrated that nucleophilic fluorination on aliphatic systems can be successfully performed in ionic liquids, or with polymer-supported ionic liquids.[9] Examples of aromatic nucleophilic fluorinations have also been described in the literature.[10] However, it must be mentioned that various nucleophiles, including the basic fluoride anion, can decompose the imidazolium salts which are often used as RTILs.[11] Using α,α,α-trichlorotoluene as a model substrate, we have established previously that ionic liquids offer significant improvements in terms of reactivity and selectivity during the nucleophilic fluorination with KF, as compared to classical organic solvents such as sulfolane or DMSO, for instance.[12] The purposes of this paper are (1) to report a systematic study of the reaction of KF with trichlorotoluene in different imidazolium-derived ionic liquids and to demonstrate the key role of the nature of the RTIL anion in this process, (2) to establish that various bromide salts, added in substoichiometric amounts, strongly activate the nucleophilic fluorination in [bmim][PF_6], and (3) to demonstrate that KPF_6 is also a potent activator of the nucleophilic fluorination, not only in ionic liquids but also in sulfolane.

The trichlorotoluene **1** has been selected as the model compound in our studies.[13] It will allow us to study the selectivity of the reaction since it could afford not only the monofluorinated compound **2** but also the difluorinated derivative **3** or the trifluorinated derivative **4** (Scheme 1). Furthermore, since all these derivatives hydrolyse very quickly into the benzoyl fluoride (PhCOF, **5**), the presence of water will be easily detected in these fluorinations. In all reactions we used high quality potassium fluoride (spray-dried KF) as nucleophilic fluorinating agent. The different butylmethylimidazolium salts have been prepared, and dried, following literature procedures.[14]



Scheme 1. Fluorination of trichlorotoluene.

In a first set of experiments, performed at 150 °C with 2 equivalents of KF at a 0.25 molar concentration in the solvent, we compared the fluorination reactions in three different ionic liquids and in sulfolane. The results are given in Figure 1 (for the conversion of **1**) and in Figure 2 (for the yield in **2**).

Under these conditions, the reaction is extremely slow in sulfolane, affording the compound **2** in only 3 % yield after 5 h. On the contrary, the fluorination is easily performed in [bmim][PF_6], affording a good yield in **2** (87 %) after 5 h. Furthermore, the selectivity is excellent since the amount of **3** is very low (less than 5 %) and both the trifluoro derivative **4** and the benzoyl fluoride **5** are not detected. A comparison of the halide-derived ionic liquids leads to some interesting observations. The fluorination occurs also in [bmim]Cl but the reaction remains relatively slow and the yield in **2** is only 30 % after 5 h. The use of [bmim]Br led to an unusual behaviour in comparison with the other solvents: in this ionic liquid the rate is faster but the yield is quickly stabilised at around 60 %, while all the trichlorotoluene is consumed. These results demonstrate that bromide salts can strongly activate the nucleophilic fluorination of **1**.[15] Therefore we checked if [bmim]Br, in substoichiometric amounts, could also improve the fluorination in the [bmim][PF_6] solvent. The results are given in Figure 3 and, indeed, under the same reaction conditions, with only 0.2 equivalents of [bmim]Br, a 20 % increase in the yield of **2** (to 88 %) was observed after 2 h. Furthermore, the selectivity remained good since **3** was obtained only in 6 % yield without any traces of **4** or **5**.

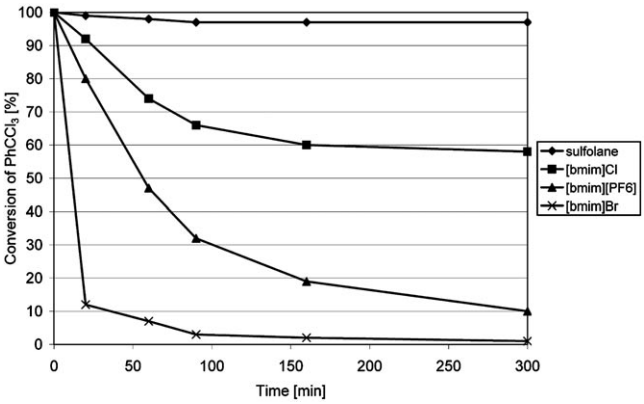


Figure 1. Fluorination in three ionic liquids and sulfolane (conversion of **1**, GC analysis).

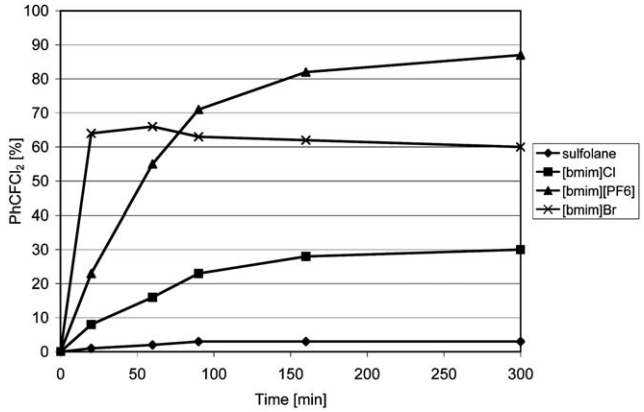


Figure 2. Fluorination in three ionic liquids and sulfolane (formation of **2**, GC analysis).

This activation is also observed, as expected, by using tetramethylammonium and tetramethylphosphonium bromides (Table 1). In all cases and under the same reaction conditions, improvements in yields (up to 40 %), are observed. However the use of less hygroscopic phosphonium salts is recommended since,

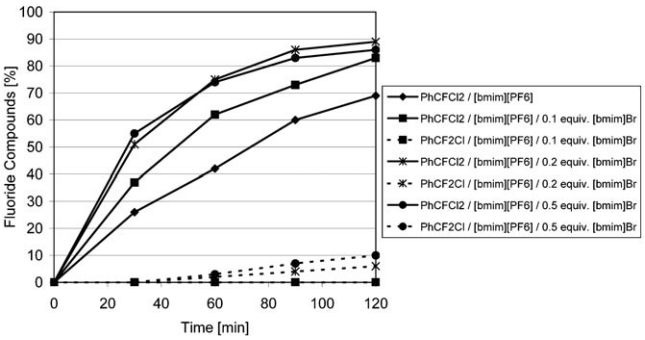


Figure 3. Activation of the fluorination by using various amounts of [bmim]Br (GC analysis).

Table 1. Activation by ammonium and phosphonium bromides in [bmim][PF_6] (0.25 M, 150 °C, 1 h, 2 equivalents of KF, GC analysis).

	2 (%)	**3** (%)	**4** (%)	**5** (%)
[bmim][PF_6]	40	/	/	/
Me_4NBr (2.0 equivs.)	75	10	traces	2
Me_4NBr (1.0 equivs.)	50	traces	/	15
Me_4NBr (0.1 equivs.)	67	traces	/	traces
Me_4PBr (2.0 equivs.)	71	12	/	/
Me_4PBr (1.0 equivs.)	80	5	/	/
Me_4PBr (0.2 equivs.)	69	1	/	/

under these conditions, they do not afford any benzoyl fluoride **5**.[16]

It is known that quaternary ammonium salts catalyse the fluorination reactions performed under phase-transfer catalysis and, in that case, it is strongly dependent upon the water content.[17] Such a phenomenon could explain, at least in part, the results obtained here in the RTILs. However, another possible explanation for the activation observed in the presence of bromide ions is given in Scheme 2.

A first nucleophilic substitution by Br^- affords the bromodichlorotoluene **6** as a reactive intermediate which can be trapped by F^- to give the fluorinated product **2**. In the presence of larger quantities of Br^-, further substitution reactions on compound **2** (and/or **6**) can occur in the same way, leading ultimately to the difluoro derivative **3** and to the trifluorotoluene **4**. In agreement with that hypothesis, the reactions performed in pure [bmim]Br afforded larger quantities of these two compounds. Furthermore, a GC-MS analysis of the reaction mixture obtained during the fluorination reaction in pure [bmim]Br allowed the characterisation of a $[PhCBrCl]^+$ ion, in agreement with the intermediacy of compound **6**.

The higher reactivity observed in [bmim][PF_6] as compared to other ionic liquids, such as [bmim][NTf_2], led us to study the effect of the PF_6 counteranion on the fluorination of **1** (Figure 4). The addition of 4 equivalents of KPF_6 to the reaction mixture in [bmim][PF_6] afforded little change in reactivity with a slight increase (8%) in the yield of **2**. On the contrary, in [bmim][NTf_2], a significant increase in the yield (up to 25%) was observed. More surprisingly in sulfolane, a very important change occurred with a 65% increase to give a 68% yield in **2**!

Furthermore, an increase of the concentration of KPF_6 in the ionic liquid (while keeping the substrate **1** at a constant 0.125 M concentration) induced a further increase in the rate of the formation of compound **2**. With 8.2 equivalents of KPF_6 the reaction is finished in less than 2 h, affording an excellent yield in **2** (Figure 5).

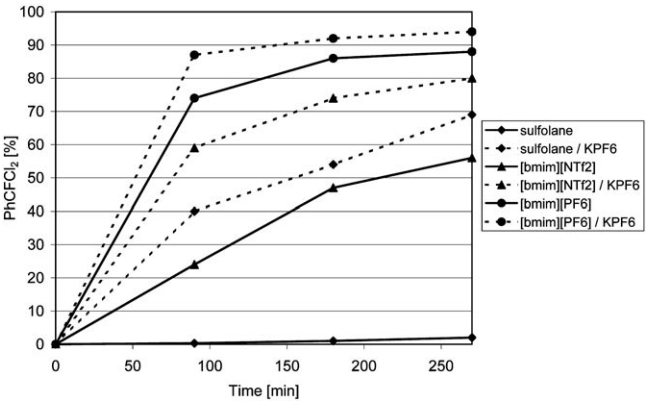


Figure 4. Activation of fluorination by KPF_6 in ionic liquids and sulfolane (GC analysis).

Finally, we have found that by using only 0.2 or 0.5 equivalents of KPF_6 in sulfolane at high concentrations, excellent results are obtained in the monofluorination of **1** (Figure 6). Under the optimised reaction conditions (1.1 equivalents of KF with 0.5 equivalents

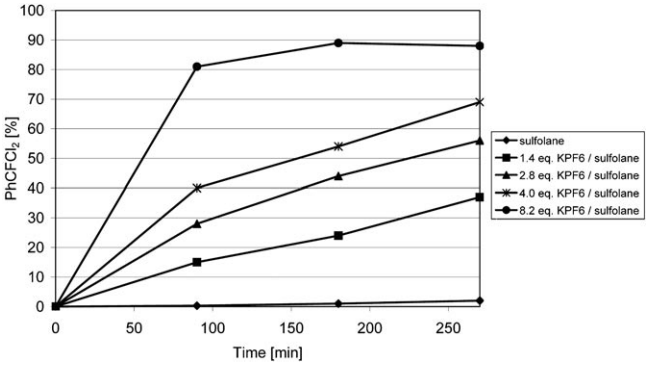
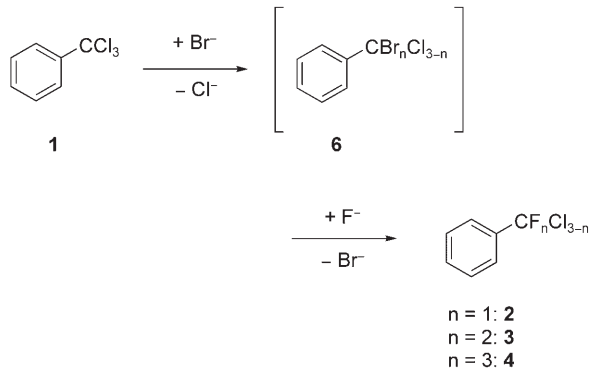


Figure 5. Effect of the amount of KPF_6 on the fluorination by KF in sulfolane (GC analysis).



Scheme 2. Activation by Br^- during the fluorination of trichlorotoluene.

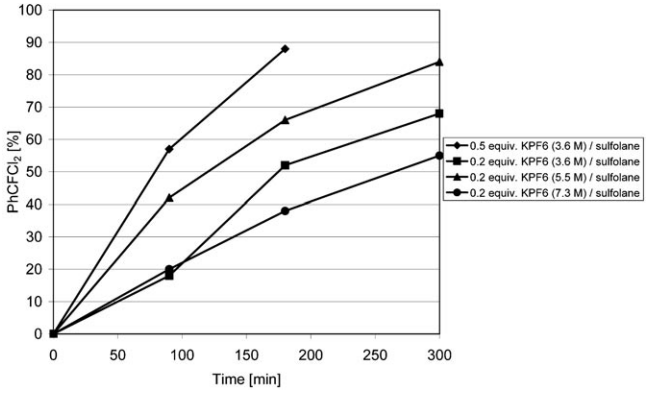


Figure 6. Effect of the concentration of KPF_6 in sulfolane, on the fluorination by KF (GC analysis).

of KPF_6 at a 3.6 M concentration in sulfolane), the monofluorinated derivative **2** is obtained in over 85% yield after only 3 h at 150 °C. Excellent results are also obtained in 5 h with 0.2 equivalents of KPF_6 at 5.5 M in sulfolane.

This new method for nucleophilic fluorination appears very attractive from the synthetic point of view but the reasons leading to this unusual activation by KPF_6 are not clear at this stage. Further studies and, in particular, in depth physicochemical experiments dealing with the structure and properties of the ionic species in solution, will be necessary before suggesting a rationale for this process. Finally, a very unusual activation of the fluorination by KF has been demonstrated both in ionic liquids and in sulfolane.

This study confirms that the nucleophilic fluorination can be successfully performed in ionic liquids. Furthermore, it has been shown that such fluorination processes can be activated by bromide salts. Finally, a very unusual activation by KPF_6, both in ionic liquids and in sulfolane, has been discovered.

Experimental Section

The butylmethylimidazolium salts were prepared and dried following literature procedures.[13] The ionic liquids were dried under vacuum (≈ 3 mm Hg) at 70 °C during 24 h before their use; the sulfolane was also kept under vacuum (≈ 3 mm Hg) at 60 °C during 24 h before being used. Spray-dried potassium fluoride (RHODIA), ammonium bromide, phosphonium bromide and potassium hexafluorophosphate were dried under vacuum (≈ 3 mm Hg) at 70 °C during 24 h before being used in the reactions.

Representative Procedure for the Fluorination Reactions Performed in Ionic Liquids

To potassium fluoride (58 mg, 1 mmol) in a 5 mL flask was added the ionic liquid (4 mL). The reaction mixture was stirred during 12 h under vacuum at 70 °C and then the temperature was increased to 150 °C during 10 min to remove all traces of water. After the transfer of argon to the reaction flask, the trichlorotoluene **1** was added *via* a syringe to the reaction mixture at 150 °C. After the appropriate reaction time, the samples were removed from the reaction mixture *via* a syringe and extracted with diethyl ether. The contents of the organic phases were analyzed by GC (HP 5890 A, SE-30 capillary column) using authentic samples of compounds **1** to **5** as references.

Representative Procedure for the Fluorination Reactions Performed in Sulfolane

To potassium fluoride (58 mg, 1 mmol) in a 5 mL flask was added the sulfolane (4 mL). The reaction mixture was stirred during 12 h under vacuum at 60 °C. After the transfer of argon to the reaction flask, the temperature was increased to 150 °C and the trichlorotoluene **1** was added *via* a syringe. After the appropriate reaction time, the samples were removed from the reaction mixture *via* a syringe and extracted with diethyl ether. The contents of the organic phases were analysed by GC (HP 5890 A, SE-30 capillary column) using authentic samples of compounds **1** to **5** as references.

Acknowledgements

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