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Solvent free nucleophilic introduction of fluorine with [bmim][F]

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ABSTRACT

1-*n*-Butyl-3-methylimidazolium fluoride ([bmim][F]) proved very efficient fluorinated reagent for nucleophilic substitution over sulfonate esters and alkyl halides. Preparation of the ionic liquid as well as its use as the reagent has been performed to be the more eco-friendly as possible. No organic solvent is needed for the fluoride introduction, reaction times are reduced by using microwave as the heating source, and the ionic liquids carefully recycled. Furthermore, no special care has to be taken as the presence of water in [bmim][F] was not deleterious to the transformation yield.

Introduction

The increasing interest in fluorine chemistry stems from the ability of this halogen to dramatically change the physical, chemical, and biological properties of many organic compounds. Its unique properties such as its small size, high electronegativity, conformational, and structural modifications account for this enthusiasm.[1] Late and selective fluorination of organic molecules has become a very important target in various fields of research (pharmaceuticals, agrochemicals, materials,...).[2] Apart from the recent transition metal catalyzed mediated fluorinations, two main methods for the nucleophilic introduction of this halogen are currently used.[3] The first, is a fluorodeoxygenation, carried out on substrates bearing hydroxyl or carbonyl groups, using diethylaminosulfur trifluoride (DAST) or improved analogues. The second approach is the nucleophilic displacement of a leaving group by the fluoride ion. This seminal strategy which employs cheap and readily available alkali metal fluorides suffers however from two major drawbacks due to the intrinsic properties of the reagents: a limited solubility in organic solvent and a strongly tamed nucleophilicity due to the close solvatation of fluoride, emphasized by its high hygroscopic properties. As a consequence, the procedure described in initial publications required hazardous and harsh reagents or disadvantageous reaction conditions.[4] In order to avoid the problem of a solvated fluoride ion, phase transfer type protocol and reagents (e.g., crown ether, tetraalkylammonium fluoride, anhydrous tetrabutylammonium...) have been successfully proposed to enhance the nucleophilic character of the fluoride anion.[5] These molecules remain nevertheless somewhat hygroscopic and exhibit an enhanced basicity which sometimes causes side reactions such as elimination process.

Polar aprotic solvents (acetonitrile and dimethylformamide), are frequently employed for nucleophilic displacement reactions.[6] Recently, ionic liquids (ILs) have been proposed as a promising alternative. Due to their very distinctive characteristics (e.g., good solubility for many organic and inorganic compounds and recyclability)[7] these salts have been the subject of intense research as effective reaction solvents[8] including nucleophilic substitution.[9,10] In particular, they have been shown to be efficient promoters for nucleophilic fluorination.[11] In 2002, Chi et al. reported the synthesis of fluoroalkanes from alkyl mesylates or alkyl halides using KF in various ILs.[12] The use of 1-*n*-butyl-3-methylimidazolium salt ([bmim][X]) helped to reduce reaction time as well as the amount of byproduct. One of the main drawbacks of this methodology is the occurrence of side reactions which result in the degradation of the ILs.[13] The enhanced basicity of metal fluorides can lead to Hoffman elimination on side chains of the cationic part of the system. This phenomenon then required the design of more elaborated ILs in order to preserve their integrity and their recycling properties.[14] An important breakthrough was recently reported by Chae and co-workers[15] This group showed that ILs can be used as both solvents and reagents for the synthesis of primary and secondary organohalides starting from sulfonate esters. Under the reported conditions, the anionic moiety of [bmim][X] (X = Cl, Br, I, OAc, SCN) reacted as nucleophilic entities. Surprisingly, this methodology has not been extended to the key introduction of a fluorine atom. This is probably due to the poor accessibility of [bmim][F]. Contrary to conventional synthesis of ionic liquids, [bmim][F] cannot be obtained readily by simple quaternization of

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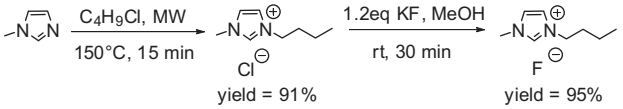


Scheme 1. Synthesis of [bmim][F].

N-alkylimidazoles with alkyl fluoride, because of the strong C–F bond. This particular IL was identified for the first time as a decomposition product during the eating of the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate.[16] Only two synthetic methods have been since described. They both proceed according to a two-step protocol: the classical preparation of N-alkylimidazoles [bmim][Cl]or[I] is followed by an anion exchange either with the help of a resin[17] or by anion metathesis conducted with expensive AgF.[18] We were intrigued by a single example which described the use of KF in substoichiometric ratio for the in situ formation of [bmim][F]. The resulting crude IL was reacted directly with *n*-octyl *p*-toluenesulfonate to give rise to *n*-octyl fluoride, as revealed by gas chromatography analysis.[18b]

This result not only reinforces the great potential of [bmim][F] as a fluorinating agent but also highlights the need for a reliable method of preparation. This is the topic of this present paper. Herein, we report a cheap synthesis of [bmim][F], its application as a nucleophilic fluorinating reagent and finally its recyclability. We have tried to solve most of the reactivity problems mentioned in the introduction. In particular, the opportunity to get a fine balance between reactivity and stability of our reagent was carefully examined.

Results and discussion

In order to access the target molecule, the precursor [bmim][Cl] was prepared according to the literature via solvent-free N-alkylation of 1-methylimidazole with 1-chlorobutane in closed vessels under monomode microwave irradiation, as well as all the reactions described in this Letter (Scheme 1).[19] Since the dielectric properties of ionic liquids allow them to absorb microwaves very efficiently, they are highly suitable for the microwave assisted organic synthesis.[20] The second step, the anion exchange of azolium halides, was carried out with potassium fluoride. The choice of KF was clearly motivated by the low price of this compound, compared to AgF or CsF. The anion metathesis was carried out at room temperature, with methanol as the solvent and using a slight excess (1.2 equiv) of KF.[21] No special precautions had to be taken for the transformation. Methanol was used without further purification and the potassium fluoride was not dried prior to its introduction into the reaction mixture.

The fluorinated IL was isolated in a good yield of 95% and its purity, as well as the anion exchange, was carefully verified through various analytic methods. Close examination of NMR spectra revealed, in addition to a slight shifting of all the signals, the intriguing disappearance of the peak of the hydrogen located in position C(2) that is between the two nitrogens. We assume that this phenomenon can be explained by a hydrogen bond with the fluorine anion. This hypothesis as well as the structure of synthesized [bmim][F] was ascertained by X-ray analysis (Fig. 1).[22] This diagram revealed that the cations are associated by an overlapping of the alkyl tails. The fluoride and the hydrogen attached to C-2 of the imidazolium ring are closed together (1.96 Å) which confirms the existence of a hydrogen bond between them. Importantly, this diagram showed the presence of one molecule of water per anion. This fact accounts for the stability of our IL but fortunately is not deleterious for the reactivity of our compound as depicted in the following study.

The nucleophilic fluorination of 3-phenylpropyl *p*-tolenesulfonate was investigated as model reaction (Table 1). During this study no particular handling precautions were required.

To our delight, the fluorination occurred in a good yield of 66% in only 10 min, when 3-phenylpropyl *p*-toluenesulfonate was stirred with 2 equiv of [bmim][F] at 80 °C (entry 1). Increasing the temperature had no influence on the yield whereas the use of 3 equiv of fluorinated agent resulted in a slight increase of the yield to 77% (entries 2 and 3). In order to find the best compromise between

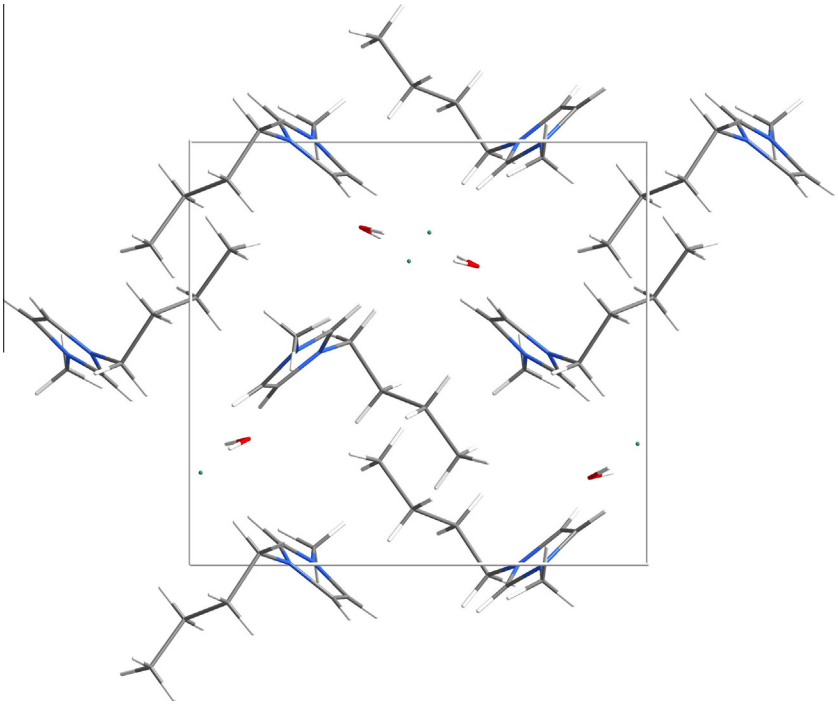
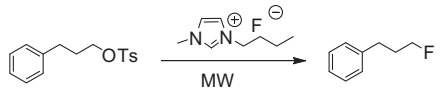


Figure 1. Molecular packing diagram of 1-butyl-3-methylimidazolium fluoride monohydrate.

Table 1
Fluorination of 3-phenylpropyl *p*-toluenesulfonate with [bmim][F]



Entry	Time (min)	Temperature (°C)	BMIMF (equiv)	Yield[a] (%)
1	10	80	2	66
2	10	100	2	66
3	10	80	3	77
3	30	80	1	49
4	30	80	2	84
5	30	80	3	95 (85)[b]
6[c]	360	80	5	83

[a] Yield determined ^{19}F NMR with internal reference.
[b] Isolated yield.
[c] Reaction conducted under conventional heating.

Table 2
Fluorination reaction on various substrates with [bmim][F]

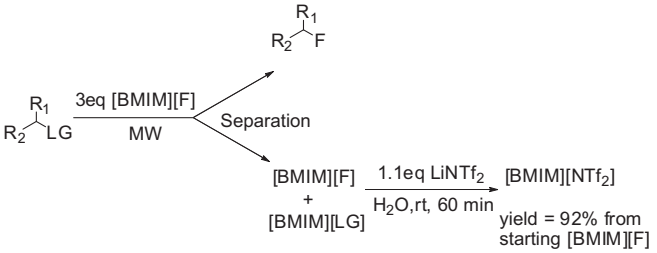
Entry	Substrate	Time (min)	Temperature (°C)	Yield[a] (%)
1	$C_6H_5O(CH_2)_2OTs$	30	80	78
2	$C_6H_5(CH_2)_3OMs$	30	80	85
3	$C_8H_{17}OTs$	30	80	73
4	$C_8H_{17}OMs$	30	80	76
5	$C_6H_5(CH_2)_3Br$	30	80	64
6	$C_8H_{17}Br$	30	80	52
7	$C_8H_{17}I$	60	80	60
8	$C_6H_5CH_2Br$	30	80	70
9	$C_6H_5CH_2Cl$	30	80	68
10	$(4\text{-Me})C_6H_4CH_2Br$	30	80	70
11	$(4\text{-MeO})C_6H_4CH_2Cl$	30	80	73
12	$(4\text{-F})C_6H_4CH_2Br$	30	80	74
13	$(4\text{-}NO_2)C_6H_4CH_2Br$	30	80	34
14	$C_6H_5CH_2CN$	180	120	n.r
15	$C_6H_{13}CH(OTs)CH_3$	60	100	43
16	$C_6H_{13}CH(OMs)CH_3$	75	100	46
17	$C_6H_{13}CH(Br)CH_3$	120	100	14

[a] Yield determined ^{19}F NMR with internal reference.

the conversion and the number of equivalents of reagent engaged, the reaction time was raised. Thirty minutes of microwave irradiation was enough to obtain a complete conversion and to deliver the 1-fluoro-3-phenyl propane in a good isolated yield, (85%, entry 5). As a comparison, with conventional heating, 6 h were needed with 5 equiv of ILs to obtain a comparable yield (entry 6).

Encouraged by these results, we attempted the fluorination reaction on various substrates with different leaving groups in order to evaluate the scope and limitations of [bmim][F] (Table 2). The previously optimized conditions (30 min at 80 °C under microwave irradiation) were successfully applied to a wide range of substrates.[23] Primary aryl- and alkyl-sulfonate (tosyl and mesyl) groups were displaced with a good yield to give rise to the desired molecules (entries 1–4). If the leaving group is a halogen (Br or I), the yields were slightly lower but still reasonable (entries 5–7) for alkyl chains but remain high when they are on benzylic position. Benzyl bromides and also chlorides were easily substituted by [bmim][F] (entries 8–13). The functionalization of the aromatic part, even by a fluorine atom, was not detrimental to the yield, except for the nitro group. Unfortunately, a cyano group proved unreactive. No displacement of this moiety has been observed and the starting material is totally recovered even after three hours at elevated temperatures. This result is not surprising, as a cyano group is a poorer leaving group compared to sulfonate according to previously reported example.[24]

We also noticed the sensitivity of this reaction to steric hindrance. When the substrate was a fatty or a secondary alkyl halide, acceptable yields were obtained with sulfonates, providing an increase of the temperature and the reaction time (entries 15–17). It is important to point out that the yield matches with the conversion for these last transformations. No elimination products were observed. This could be explained by the F–H hydrogen bond which insured the inherent nucleophilicity and reduced the basicity of the fluoride anion.



Scheme 2. Recycling of the IL.

As part of our eco-friendly process, the recycling of the cationic core of our reagent was undertaken (Scheme 2).

After the completion of the fluorination process, the desired compound was extracted with pentane. The resulting crude solution was then a mixture of unreacted [bmim][F] and [bmim][X] (X = Cl, Br, I, OMs, OTs). The composition of the anionic part was related to the substrate engaged in reaction. This chemical diversity precluded the full regeneration of [bmim][F]. Regarding the case of tosyl or mesyl anion, the reaction is unfavorable due to hard/soft metathesis consideration.[25] To address this limitation, $LiNTf_2$ rapidly appeared as the best candidate to insure a total conversion toward a unique and useful known IL. The mixture of ILs was dissolved in water and after addition of 1.1 equiv of lithium salt, [bmim][F] and [bmim][X] were both fully converted into [bmim][NTf_2] which formed a lower phase during the reaction. After the separation of the two phases, pure [bmim][NTf_2] was recovered in a yield of up to 92%. This IL could be used later on as reaction media for other organic syntheses.[8b,7m]

Conclusion

We have shown that 1-*n*-butyl-3-methylimidazolium fluoride could be easily synthetized using cheap potassium fluoride without any special care. We have demonstrated its potential as a fluorinating agent to provide soft nucleophilic substitution. No solvent, special precautions or complex or hazardous additional reagents are necessary for this transformation. The use of microwave irradiation allows a short reaction time avoiding as a consequence the formation of byproducts like the competitive elimination product. The resulting mixture of ILs is entirely recycled in a very green and easy way. Further developments of this new reagent and other applications are under study in our laboratory.

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21. *Preparation of 1-n-butyl -3-methyl imidazolium fluoride:* To a solution of 1-methyl-3-(*n*-butyl) imidazolium chloride (5.0 g, 29 mmol) in methanol (38 mL) was added in one portion a solution of potassium fluoride (2.5 g, 43.5 mmol, 1.5 equiv) in methanol (42 mL). After one hour at room temperature, the insoluble potassium chloride was removed by filtration and washed with methanol (50 mL). The liquid phase was concentrated under reduced pressure. Dichloromethane (20 mL) was added and the precipitate formed was removed by filtration. The liquid phase was concentrated under reduced pressure to afford the desired product as a yellow waxy solid (95%, 4.3 g, 28 mmol). ^{19}F NMR ($CDCl_3$, 188 MHz) (ppm) δ: −123.0 (1F, s); ^{1}H NMR ($CDCl_3$, 200 MHz) (ppm) δ: 0.82 (t, J = 6 Hz, 3H), 1.28 (sextuplet, J = 6 Hz, 2H), 1.76 (quintuplet, J = 6 Hz, 2H), 3.94 (s, 3H), 4.15 (t, J = 6 Hz, 2H), 7.49–7.34 (m, 2H,); ^{13}C NMR (D_2O, 75 MHz) (ppm) δ: 12.6, 18.7, 31.2, 35.6, 48.8, 122.2, 123.4, 135.8.
22. Crystal data: $C_8H_{17}FN_2O$, M_w = 176.24, orthorhombic, space group $P2_12_12_1$; dimensions: a = 8.4486(5) Å, b = 10.4370(6) Å, c = 11.3144(5) Å, V = 997.68(9) Å^3; Z = 4; μ = 0.09 mm^{-1}; 13878 reflections measured at 200 K; independent reflections: 1670 [1432 Fo > 4σ (Fo)]; data were collected up to a 2Θmax value of 60° (100% coverage). Number of variables: 119; R_1 = 0.036, wR_2 = 0.094, S = 1.06; highest residual electron density 0.13 e Å^{-3}.
23. *General procedure for fluorination:* The starting substrate (0.5 mmol) and 1-*n*-butyl-3-methyl imidazolium fluoride (1.5 mmol, 3 equiv) were stirred for 30 min at 80 °C under microwave irradiation. The mixture was cooled to room temperature and the fluorinated compound was extracted with diethyl ether (3 × 5 mL). Organic layers were mixed and concentrated under reduced pressure. For NMR ^{19}F determination, chlorodifluoroanisole (88 mg, 0.5 mL) was introduced as internal reference in 0.75 mL of acetone-d_6. The product could also be purified by chromatography on silica gel to afford the desired product.
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