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New Method of Fluorination Using Potassium Fluoride in Ionic Liquid: Significantly Enhanced Reactivity of Fluoride and Improved Selectivity

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Organic compounds with low fluorine content have received much interest because of their physiological properties.[1] Many efforts have been made to increase the potency of biologically active compounds by replacing hydrogen with a fluorine atom. The nucleophilic displacement of various sulfonates and halides by fluoride is the typical method for the introduction of a single fluorine atom into aliphatic organic compounds.[2] Alkali metal fluoride such as potassium fluoride is the traditional reagent for this type of reaction.[3] However, its limited solubility in organic solvent and low nucleophilicity require generally vigorous conditions. Thus, a number of metal fluoride reagents such as KF/18-crown-6,[4] polymer supported fluoride,[5] "spray-dried" KF,[6] and calcium fluoride supported on alkali metal fluoride[7] have been reported to solve these problems. 18-Crown-6 derivatives have been largely used to enhance the solubility and nucleophilicity of KF in organic media.[4] However, these above-mentioned processes are generally less efficient than those using tetraalkylammonium fluorides. Tetrabutylammonium fluoride (TBAF) is the most popular reagent for the nucleophilic fluorination.[8] Despite its good solubility and reactivity, the fluorination using tetraalkylammonium fluorides has some drawbacks which are that these reagents also cause the elimination of alkyl halides, the formation of alkyl sulfonates to alkenes, and the hydroxylation to alcohols because "naked" fluoride can act not only as a nucleophile but also as a base.[8a] DeShong et al. recently developed the fluorinating reagent, tetrabutylammonium triphenyldifluorosilicate (TBAT), which is less basic than TBAF, free from anhydrous condition, yet, less nucleophilic.[9] However, TBAT still requires long reaction time due to its relative low reactivity. Moreover, it is relative expensive and causes too much chemical waste considering its large molecular weight as compared with that of KF.

Ionic liquids (see Figure 1) have recently been regarded as an eco-friendly alternative to replace volatile organic solvents in current chemical processing, due to their unique physical and chemical properties.[10] It has also been reported that ionic liquids containing imidazolium cations can act as powerful media in some catalytic organic reactions not only the for facilitation of catalyst recovery and but also for the acceleration of reaction rate and improvment of selectivity.[11] In this report, we present a highly efficient method for the synthesis of fluoroalkanes from alkyl mesylate or alkyl halides by a nucleophilic substitution reaction using KF and ionic liquids such as [bmim][X].[12] In this method, ionic liquids play an important role in significantly enhancing the reactivity of KF as well as reducing formation of byproducts, for example, alkenes, alcohols, or both.[13]

Table 1 illustrates the fluorination reaction of 2-(3-methanesulfonyloxypropoxy)naphthalene (**1**) with KF in the presence of [bmim][BF_4] under various reaction conditions. Whereas the fluorination of the mesylate **1** with KF in an organic solvent such as CH_3CN at 100 °C occurred hardly even after 24 h (entry 10), the same reaction in [bmim][BF_4] as a reaction solvent was completed within 2 h, affording the wanted product **2a** (85%) together with the alkene byproduct **2c** (10%) (entry 1). Very interestingly, however, the addition of water (5 equiv) completely eliminated the formation of the undesired alkene **2c** and thus gave higher yield of **2a** (92%, entry 2). Moreover, entries 3 and 4 show that the use of acetonitrile as a cosolvent does not affect the reactivity of the fluorination. The presence of a proper amount of cosolvent was rather desirable (94% yield of **2a** in entry 4[14]). When an excess of water (10% of total reaction volume) was added, the hydroxylation of the mesylate **1** to alcohol **2b** (6%) took place, although the fluoroalkane **2a** was still a major product (88%) (entry 5). This result means that our fluorination method using [bmim][BF_4] does not require anhydrous conditions. In addition, as shown in entries 6−9, the use of lesser amounts of [bmim][BF_4] had little influence on the reactivity of fluorination. It should be here noted that the use of catalytic amounts (0.5 equiv) of [bmim][BF_4] was also enough to almost complete the reaction over 12 h. A comparison of entries 9 and 11 demonstrates that when using only catalytic amounts of the ionic liquid [bmim][BF_4] fluorination proceeded much faster than using 2 equiv of 18-crown-6.

To find the optimal ionic liquid and cosolvent, we next carried out the fluorination of **1** under the same conditions as for entry 4 in Table 1, except for the use of the four other ionic liquids instead of [bmim][BF_4], and two other cosolvents instead of acetonitrile. In entries 1 and 2 (Table 2), using [bmim][PF_6] and [bmim][SbF_6],

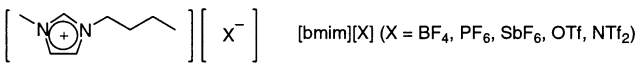
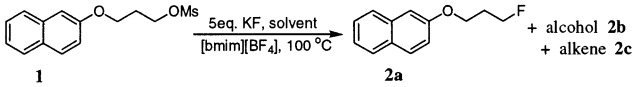


Figure 1. Ionic liquids.

Table 1. Fluorinations of Mesylate **1** with KF under Various Reaction Conditions[a]



1 **2a**

entry	[bmim][BF_4] mL (equiv)	CH_3CN (mL)	H_2O (μL)	raction time (h)	yield of product (%)[b] 1	2a	2b	2c
1	5	−	0	2	−	85	−	10
2	5	−	90 (5 equiv)	1.5	−	92	−	−
3	3.2	1.6	90	1.5	−	93	trace	−
4	1.6	3.2	90	1.5	−	94	−	−
5	3	1.5	500	1.5	−	88	6	−
6	1	4	90	1.5	−	92	−	−
7	0.57 (3)	4.4	90	3	−	91	trace	−
8	0.19 (1)	4.8	90	6	−	89	trace	−
9	0.1 (0.5)	5	90	12	trace	84	8	trace
10	−	5	0	24	86	trace	−	−
11	18-crown-6 (2)	5	0	24	53	40	−	−

[a] All reactions were carried out on a 1.0 mmol reaction scale of mesylate **1** using 5 mmol of KF at 100 °C. [b] Isolated yield.

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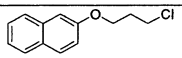
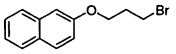
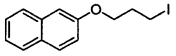
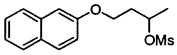
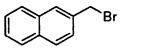
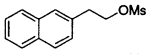
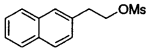
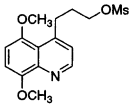
Table 2. Fluorinations of Mesylate **1** with KF in Various Ionic Liquids and Cosolvents[a]

				yield of product (%)[b]			
entry	ionic liquid	cosolvent	reaction time (h)	**1**	**2a**	**2b**	**2c**
1	[bmim][PF_6]	CH_3CN	2	–	90	trace	–
2	[bmim][SbF_6]	CH_3CN	2	–	93	–	–
3	[bmim][OTf]	CH_3CN	4	–	79	15	–
4	[bmim][NTf_2]	CH_3CN	5	61	35	trace	–
5	[bmim][BF_4]	1,4-dioxane	1.5	–	91	–	–
6[c]	[bmim][BF_4]	*t*-BuOH	1.5	–	85	trace	–

[a] All reactions were carried out under the same condition as entry 4 in Table 1. [b] Isolated yield. [c] 7% of the *tert*-butoxylated compound was detected by ^{1}H NMR.

Table 3. Fluorinations of Various Alkyl Halides and Mesylates Using KF in [bmim][BF_4][a]

entry	Compound	temp (°C)	reaction time (h)	yield[b] (%)	comment
1		110	24	66	18% alcohol 10% alkene
2		100	4	83	13% alkene
3		100	3	76	19% alkene
4		100	2	74	18% alkenes
5[c]		90	1.5	93	trace alcohol
6		100	1.5	54	39% alkene
7[d]		100	2.0	76	9% alkene 10% alcohol
8		60	2	73	
9		100	1.5	95	

[a] Unless otherwise noted, all reactions were carried out under the same condition as entry 4 in Table 1. [b] Isolated yield. [c] Entry 5 was performed in 10 g of reaction scale. [d] The reaction was carried out under the condition of entry 5 in Table 1.

we obtained results similar to those obtained with [bmim][BF_4] (Table 1, entry 4). However, the fluorination using [bmim][OTf] gave slightly lower yield (79%) (entry 3). 1,4-Dioxane could also be used as a cosolvent in the fluorination reaction, while *tert*-butyl alcohol was not a proper cosolvent because the *tert*-butoxylation of **1** to 2-(3-*tert*-butoxypropoxy)naphthalene took place in 7% (entry 6).

Table 3 illustrates that the fluorination of primary, secondary, and benzylic halides or mesylates using 5 equiv of KF in the presence of [bmim][BF_4] under the same conditions as for entry 4 in Table 1 (with the exception of entry 7), provides corresponding fluorocompounds in comparable or better yields than other methods previously reported.[4,5,8,9] The fluorination of primary chloro-, bromo-, and iodoalkane under these conditions provided **2a** in good yield (66, 83, and 76%, entries 1−3, respectively) with minimal byproducts. The fluorination reaction of a secondary mesylate (entry 4) also proceeded smoothly, affording the corresponding fluoride in 74% isolated yield, whereas secondary halides or mesylates predominantly underwent the elimination under the other previously reported conditions. A benzylic fluoride was produced in good yield by the fluorination of the bromide (entry 5). It is difficult to introduce the fluorine to haloethyl or alkanesulfonylethyl aromatic compounds because the elimination of these to styrenes is the dominant reaction.[15] However, as shown in entry 6, the fluorination of 2-(2-mesylethyl)naphthalene to 2-(2-fluoroethyl)naphthalene proceeded predominantly and provided the corresponding fluoride in 54% yield with alkene in 39% yield. Interestingly, as shown in entry 7 (Table 3), the reaction using an excess amount of water (10% of total reaction volume, the conditions of entry 5 in Table 1) gave a significantly improved yield (75%) and reduced the elimination product. This result suggests that the control of the amount of water in the fluorination in the presence of ionic liquid can suppress the elimination and provide a high yield of the desired fluoroproduct. The fluorination of α-bromoacetophenone also afforded α-fluoroacetophenone in good yield (entry 8). In the final example, a 5,8-dimethoxy-4-fluoropropylquinoline[16] was produced in 95% isolated yield by the fluorination of the mesylate (entry 9).

In summary, we have demonstrated facile nucleophilic fluorination of some halo- and mesylalkanes to the corresponding fluoroalkanes using KF in the presence of an ionic liquid and water. The ionic liquid-water system could not only enhance the reactivity of KF significantly but also reduce the formation of byproducts. Further studies on the development of a more efficient protocol (lower reaction temperature, shorter reaction time, etc.) for nucleophilic fluorination using ionic liquids are in progress in our laboratories. Applications of this fluorination method to ^{18}F labeling for diagnostic agents are also under investigations.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra including characterization of all compounds and ionic liquid information (PDF). This material is available free of charge via a Internet at http://pubs.acs.org.

References

(1) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320. (b) Filler, R. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Ed.; Studies in Organic Chemistry 48; Elsevier; New York, 1993; pp 1−23.
(2) For reviews on nucleophilic fluorination, see: (a) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647−667. (b) Mascaretti, O. A. *Aldrichimica Acta* **1993**, *26*, 47−58.
(3) Forche, D. In *Methoden der Organischen Chemie Houben-Weyl*; Mueller, E., Ed.; George Thieme Verlag: Stuttgart, 1962; Vol. 5/3.
(4) Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* **1974**, *96*, 2250−2252.
(5) Colonna, S.; Re, A.; Gelbard, G.; Cesarotti, E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2248−2252.
(6) Ishikawa, N.; Kitazume, T.; Yamazaki, T.; Mochida, Y.; Tatsumo, T. *Chem. Lett.* **1981**, 761−764.
(7) (a) Clark, J. H.; Hyde, A. J.; Smith, D. K. *J. Chem. Soc., Chem. Commun.* **1986**, 791−793. (b) Ichihara, J.; Matsuo, T.; Hanafusa, T.; Ando, T. *J. Chem. Soc., Chem. Commun.* **1986**, 793−794.
(8) (a) Cox, D. P.; Terpinsky, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216−3219. (b) Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Welch, M. J. *J. Org. Chem.* **1987**, *52*, 658−664.
(9) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995,** *117*, 5166−5167.
(10) For recent reviews on ionic liquids, see: (a) Sheldon, R. *Chem. Commun.* **2001**, 2399−2407. (b) Wasserscheid, P.; Kein, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772−3789. (c) Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2083.
(11) (a) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.-g.; Choi, J. H. *Chem. Commun.* **2001**, 1122−1123. (b) Song, C. E.; Shim, W. H.; Roh, E. J.; Choi, J. H. *Chem. Commun.* **2000**, 1695−1696. (c) Song, C. E.; Roh, E. J. *Chem. Commun.* **2000**, 837−838.
(12) 1-*n*-Butyl-3-methylimidazolium cation [bmim] and its counteranions: tetrafluoroborate [BF_4], hexafluorophosphate [PF_6], hexafluoroantimonate [SbF_6], triflate [OTf], and bis(trifluoromethanesulfonyl)imide [NTf_2] are used.
(13) Dermeik, S.; Sasson, Y. *J. Org. Chem.* **1985**, *50*, 879−882.
(14) **Typical Procedure.** KF (290 mg, 5 mmol) was added to the mixture of 2-(3-methanesulfonyloxypropoxy)naphthalene (**1**, 280 mg, 1.0 mmol), [bmim][BF_4] (1.6 mL), and H_2O (90 μL, 5 mmol) in acetonitrile (3.2 mL). The mixture was stirred over 1.5 h at 100 °C. The reaction mixture was extracted from the ionic liquid phase with ethyl ether (7 mL × 3). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc/hexanes) to obtain 192 mg (94%) of 2-(3-fluoropropoxy)naphthalene (**2a**).
(15) Gerdes, J. M.; Keil, R. N.; Shulgin, A. T.; Mathis, C. A. *J. Fluorine Chem.* **1996**, *78*, 121−129.
(16) Kim, D. W.; Choi, H. Y.; Lee, K.-J.; Chi, D. Y. *Org. Lett.* **2001**, *3*, 445−447.

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