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Oxidative desulfurization–fluorination reaction promoted by [bdmim][F] for the synthesis of difluorinated methyl ethers

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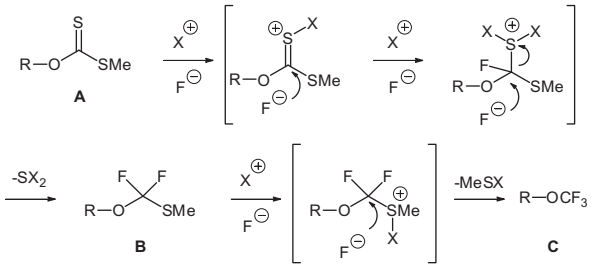
ABSTRACT

A new ionic liquid [bdmim][F] has been prepared and fully characterized. Its potential as a fluoride source for the desulfurization–fluorination process has been evaluated with success. The carbon–sulfur double bond of xanthates and thiocarbonates has been difluorinated to give rise to small libraries of halogenated ketals and thioketals.

Introduction

α-Fluorinated methyl ethers are a highly important class of emergent and promising moieties for various applications, particularly in materials, and in agrochemical and pharmaceutical sciences.[1] The perfluorination of the carbon adjacent to the oxygen atom often results in an increased lipophilicity of the molecule as well as a profound modification of the electronic and steric parameters.[2] These remarkable properties associated with a still challenging preparation of α-fluorinated ethers have stimulated many synthetic works in recent years.[3] Two approaches are at the disposal of the chemist: the direct introduction of a perfluorinated methyl group starting from a hydroxyl group or the construction of the perfluorinated ether moiety from a properly designed organic function. These two methods are complementary in terms of target molecules as well as their respective scope and limitations. The second approach, which is also the seminal one, is versatile as it allows the transformation of the same precursor to either difluoromethyl- or trifluoromethyl ethers by simply tuning the reaction parameters. Nevertheless, it often requires harsh conditions or toxic reagents difficult to handle such as CCl_4/HF, SF_4, SbF_5, MoF_6, BrF_3, XeF_2.[4] In the early 90s Hiyama et al. developed a promising methodology, the oxidative desulfurization–fluorination reaction. Indeed, by treatment of dithiocarbonates A (xanthate esters) with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in hydrogen fluoride–pyridine (Olah's reagent[5]) as both reagent and solvent, trifluoromethyl ethers C are obtained (Scheme 1).[6] Whereas by using $TBAH_2F_3$[7] the difluoro(methylthio)methyl ethers B are isolated in moderate yields as the sole products.[6a,b] The common mechanism may be interpreted as a successive bromonium formation with sulfur atoms followed by iterative nucleophilic introduction of fluorine substituents.

Recently, ionic liquids (ILs) have been proposed as promising alternatives to many organic solvents. Due to their very distinctive characteristics (e.g., good solubility for many organic and inorganic compounds and recyclability),[8] these salts rapidly proved to be efficient solvents for various chemical transformations[9] including nucleophilic fluorination.[10] Amine–$(HF)_n$ (Onium Poly-Hydrogen Fluorides) are intrinsically also ionic liquids.[11] They have been used to alleviate the volatility and toxicity of neat anhydrous HF and also as stable and useful substitutes for hydrogen fluoride in fluorination of organic compounds.[12] Nevertheless, their availability, preparation, or in some case difficult handling, still



Scheme 1. Mechanism of the oxidative desulfurization–fluorination.

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remain as limitations. In this context, we assume that an ionic liquid containing a single fluoride ion may be a solution to these difficulties. We have indeed recently disclosed an easy access to 1-*n*-butyl-3-methylimidazolium fluoride [bmim][F] and showed its potential as a fluorinating agent for mild nucleophilic substitutions.[13]

Results and discussion

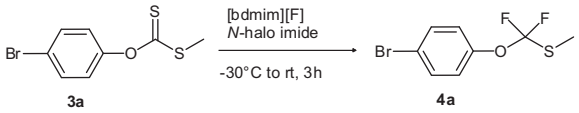
As part of our program devoted to the use of fluorinated ionic liquids, we were really intrigued by their use as a source of fluoride in a desulfurization–fluorination process, instead of Olah's reagent. Herein, we report a practical synthesis of a new fluorinated ionic liquid and its application as a fluoride source in an oxidative desulfurization–fluorination reaction for the preparation of difluorinated ethers. The first tryouts were conducted with [bmim][F] as both reagent and solvent and were quickly disappointing as the IL proved incompatible with various oxidative reagents (DBH, NBS, Br_2, etc.). The mixing of the two partners resulted in a strong exothermic phenomenon, fumes and complete degradation of the IL. We assume that the acidic proton position C2 of the imidazole ring is responsible for this unwanted side reaction. This position is sensitive and can particularly be easily halogenated.[14] To circumvent the problem, we focused our attention on the synthesis of the unknown 1-*n*-butyl-2,3-dimethylimidazolium fluoride ([bdmim][F]). The synthesis was achieved in two steps (Scheme 2). The precursor [bdmim][Cl] was prepared according to the literature via solvent-free N-alkylation of 1,2-dimethylimidazole with 1-chlorobutane in closed vessels under monomode microwave irradiation.[15] The second step, the anion exchange of azolium halides, was carried out with potassium fluoride in methanol as the solvent.[16] The desired IL was prepared on a multigram scale and isolated in pure form without any purification steps and with an almost quantitative yield.

The structure of [bdmim][F] was ascertained by X-ray analysis (Fig. 1). This diagram revealed that the cationic parts of the IL are associated by π-stacking with a distance of 3.405 Å between the imidazole ring. The fluoride anion is spatially close to the hydrogen attached to the C-4 of the imidazole ring. As expected, this is different from the [bmim][F] case for which the fluoride anion formed a hydrogen bond with the hydrogen at the C-2 position. This diagram showed a close association of one molecule of water and one molecule of methanol per anion which precluded the possibility of convenient removal all these two compounds. We assume furthermore that presence of water accounts for the stability of our IL.[10d]

Optimization of the oxidative desulfurization–fluorination process started with *S*-methyl *O*-4-bromophenyl dithiocarbonate **3a** as model substrate on a 0.4 mmol scale (Table 1).

The *N*-bromosuccinimide (NBS) was firstly chosen as the oxidizing agent. All the reagents were mixed at −30 °C without

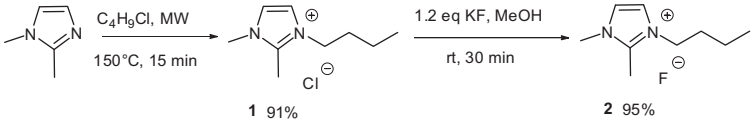
Table 1
Perfluorination of *S*-methyl *O*-4-bromophenyl dithiocarbonate **3a**



3a **4a**

Entry	BDMIMF (equiv)	*N*-Halo imide (equiv)	Additive (equiv) and/or solvent	Yield[a] (%)
1	5	NBS (6)	/	14
2	10	NBS (6)	/	20
3	10	NBS (6)	KF(3)/MeOH (1 ml)	19
4	10	NBS (6)	CsF(3)/MeOH (1 ml)	17
5	10	NBS (9)	CH_2Cl_2 (4 ml)	31
6	10	NBS (9)	CH_2Cl_2 (7 ml)	24
7	20	NBS (9)	CH_2Cl_2 (4 ml)	22
8	10	NBS (12)	CH_2Cl_2 (4 ml)	45 (40)[b]
9	10	DBH (9)	CH_2Cl_2 (4 ml)	<5
10	10	NIS (9)	CH_2Cl_2 (4 ml)	<5
11	10	NCS (9)	CH_2Cl_2 (4 ml)	/
12	10	Selectfluor (9)	CH_2Cl_2 (4 ml)	/

[a] Yield determined ^{19}F NMR with 4-(chloro-difluoro-methoxy)-phenylamine as internal reference.
[b] Isolated yield.



1 91% **2** 95%

Scheme 2. Synthesis of [bdmim][F].

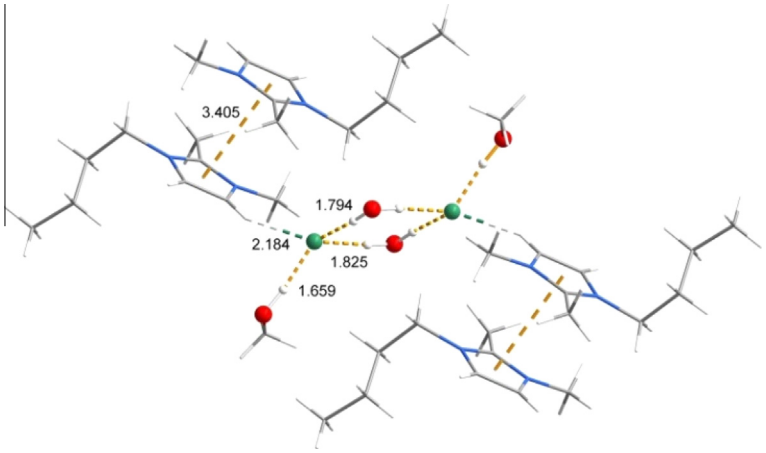


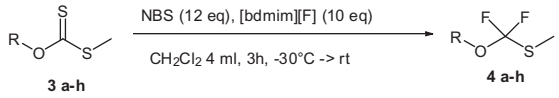
Figure 1. Molecular packing diagram of 1-butyl-2,3-dimethylimidazolium fluoride monohydrate.

any particular handling precautions and the reaction was then left to stir at room temperature for 3 h. We were pleased to achieve, in poor but very encouraging yields, the formation of difluoro derivative **4a**. With 10 equiv of IL, the yield was slightly improved (entry 2). Addition of a supplementary source of fluoride, such as KF or CsF dissolved in methanol, was not beneficial (entries 3 and 4). The increase in the number of equivalents of NBS (to a maximum of 12) allowed the isolation of **4a** with an acceptable yield of 40% (entries 5–8). The presence of a minimum amount of dichloromethane (4 ml) was added to simply avoid stirring problems. The use of other *N*-halo imides proved inefficient, giving rise either to complete degradation of the substrate (entries 9 and 10) or to no conversion at all (entries 11 and 12).

Whatever the conditions employed, no trifluoromethyl ether was even formed, only the difluoro(methylthio)methyl ethers were. As a first conclusion, [bdmim][F] appears not as an equivalent of HF–pyridine but more like an analogue of $TBAH_2F_3$, the latter being often prepared with HF. In this context, we were happy to describe the fluorination of a xanthate with simple IL as a fluoride source.

Encouraged by these results, the scope and limitations of the reactivity of [bdmim][F] were thus evaluated with a set of xanthates (Table 2).[17]

Table 2
Synthesis of difluoro(methylthio)methyl ethers **4** from xanthate **3**



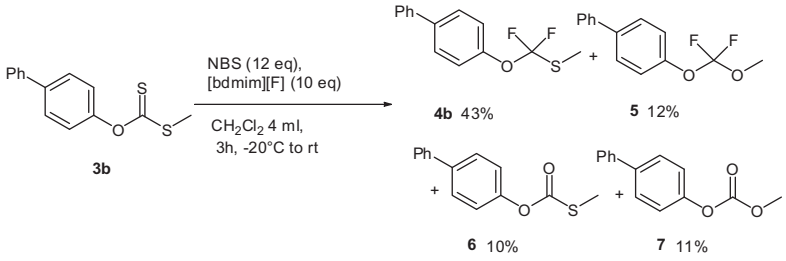
Entry	R	Product	Yield[a] (%)
1	(**3a**) 4-Br–C_6H_4–	**4a**	45 (41)[b]
2	(**3b**) 4-Ph–C_6H_4–	**4b**	52 (43)[b]
3	(**3c**) 4-Me–C_6H_4–	**4c**	40 (25)[b]
4	(**3d**) 4-MeO–C_6H_4–	**4d**	38 (27)[b]
5	(**3e**) 3-MeO_2C–C_6H_4–	**4e**	43 (30)[b]
6	(**3f**) 4-IsoPr–C_6H_4–	**4f**	48 (36)[b]
7	(**3g**) Ph–$(CH_2)_3$–	**4g**	36
8	(**3h**) $C_{16}H_{33}$–	**4h**	29

[a] Yield determined ^{19}F NMR with 4-(chloro-difluoro-methoxy)-phenylamine as internal reference.
[b] Isolated yield.

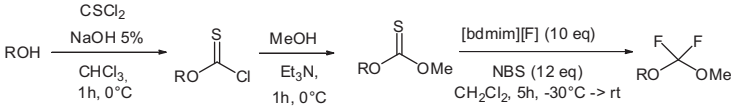
The previously optimized conditions (12 equiv of NBS, 10 equiv of [bdmim][F]) were successfully applied to a wide range of substrates to give rise to the corresponding difluoro(methylthio)methyl ethers **4a–f** with correct yields for aromatic compounds (entries 1–6) to low yields for aliphatic series (entries 7 and 8). The compounds are nevertheless isolated in similar or better yields compared to the literature. As the conversion was always almost total, a careful investigation of the numerous side-products formed during this process was conducted with xanthate **3b** and enabled us to isolate and characterize most of them (Scheme 3).

Despite the large excess of brominating agent, aromatic rings did not suffer from ring halogenation even with an electron-donating group attached to the aromatic moiety. The undesired molecules were presumably formed because of the presence of water and methanol in the [bdmim][F]. The presence of *S*-methyl *O*-4-biphenyl thiocarbonate **6**, isolated with 10% yield can indeed be explained by hydrolysis side reaction whereas carbonate **7** may result in the nucleophilic attack of methanol. More the more surprisingly was the isolation of the 4-[difluoro(methyloxy)methoxy]biphenyl **5** in which the methylthio was substituted by a methoxy group once again due to the presence of methanol in the IL. This observation turned our attention to the possibility of finding adequate conditions and/or substrates to improve the yield of the formation of such rare difluorinated ketals.

Only a few methods leading to the difluoromethylenedioxy group (OCF_2O) have been reported.[18] Those types of compounds have been prepared mainly by reacting various nucleophilic fluoride reagents (e.g., BrF_3, HF, AgF, $Bu_4NH_2F_3$) with either dichlorodioxomethylene derivatives or thiocarbonates. The synthesis of asymmetrical aryl–alkyl difluoromethylenedioxy compounds requires quite harsh conditions outlining the urgent need for a more practical preparation. The *O*,*O*-aryl-methylthiocarbonates, substrates for fluoro-desulfurization process, were prepared by an adaptation of the described methods without further optimization. These thiocarbonates were then engaged in reaction in the presence of [bdmim][F] (10 equiv) and NBS (12 equiv), following our previous protocol[17] (Scheme 4). Compound **9a** was chosen for the first attempt because the ketal **10a** was already described. To our delight, we were able to isolate the pure molecule **10a** albeit in rather low yields in spite of a total conversion. We assume those side reactions as partial hydrolysis may occur during the process.



Scheme 3. Synthesis of 4-(difluoro(methylthio)methoxy) biphenyl **4b** from xanthate **3b**.



8a 68% R= 3-NO_2-C_6H_4-	**9a** 67% yield	**10a** (38%)[a] 24%
8b 72% R = 4-MeO-C_6H_4-	**9b** 71% yield	**10b** (38%)[a] 29%
8c 50% R= 4-Ph-C_6H_4-	**9c** 30% yield	**5** (36%)[a] 24%
8d 40% R= 2-Naphyl-CH_2-	**9d** 32% yield	**10d** - (37%)[a] 33%
8e 90% R= 4-Br-C_6H_4-	**9e** 73% yield	**10e** - (38%)[a] 15%

[a] Yield determined ^{19}F NMR with 4-(chloro-difluoro-methoxy)-phenylamine as internal reference.

Scheme 4. Formation of asymmetric aryl–alkyl difluoromethylenedioxy derivatives.

Our procedure was furthermore nicely extended to four substrates. Unknown difluorinated ketals **5**, **10b**,**d**,**e** have been then isolated and fully characterized. They are stable on pure form and can be totally recovered even after two weeks on the bench. We are convinced that our methodology, easy to implement, is fully complementary of other synthetic methods which need reagents that are inconvenient to handle.

Because of the large excess of [bdmim][F] needed for the reaction and for eco-friendly concerns, the valorization of the cationic core was lastly undertaken. After the completion of the fluorination process, the desired difluorinated compound was extracted with diethyl ether. The resulting mixture of ILs was dissolved in water and of 1.1 equiv of lithium bistriflimide was added. ILs were fully converted into [bdmim][NTf_2], which formed a lower phase during the reaction. After the separation of the two phases, pure [bdmim][NTf_2] was recovered with a yield of up to 95% from starting [bdmim][F]. This IL could be used later on as reaction media for other organic syntheses.[8m,9b]

Conclusion

In conclusion, a new ionic liquid [bdmim][F] was prepared on a multi gram scale and fully characterized. Its use as a nucleophilic source of fluoride proved very efficient in the desulfurization–fluorination process. Without any particular precaution, we were able to achieve the difluorination of xanthates and thiocarbonates without the use of HF–pyridine or $TBAH_2F_3$. This methodology only employed stable and non-toxic reagents to achieve the preparation of promising new compounds. Synthetic opportunities offered both by these difluorinated ethers and by this IL are under current development in our laboratory and will be reported in due course.

Acknowledgments

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16. *Preparation of 1,2-dimethyl-3-(n-butyl) imidazolium fluoride* (**2**): A solution of potassium fluoride (2.5 g, 43.5 mmol, 1.5 equiv) in methanol (42 mL) was added, at room temperature, in one portion to a solution of 1,2-dimethyl-3-(*n*-butyl)imidazolium chloride (5.45 g, 29 mmol, 1 equiv) in methanol (38 mL). After one hour stirring, the insoluble KCl was removed by filtration and washed with methanol (50 mL). The liquid phase was concentrated under vacuum. Dichloromethane (20 mL) was then added and the resulting precipitate was removed by filtration. The solution was concentrated under vacuum to afford the desired product as orange crystals (4.8 g, 28 mmol, 95% yield). Melting point: 19–22 °C. ^{1}H NMR (200 MHz, MeOD): δ = 0.99 (t, ^3J = 7.3 Hz, 3H), 1.40 (tq, ^3J = 7.3 Hz, 2H), 1.81 (tt, ^3J = 7.6 Hz, 3H), 2.65 (s, 3H), 3.84 (s, 3H), 4.18 (t, ^3J = 7.4 Hz, 3H), 7.49–7.61 (m, 2H) ppm. ^{13}C NMR (50 MHz, MeOD): δ = 9.5, 13.9, 20.6, 32.8, 35.4, 49.2, 49.9, 122.2, 123.7, 145.9 ppm. ^{19}F NMR (188 MHz, MeOD): δ = −151.0 ppm.
17. *General procedure for preparation of α-difluorinated ethers:* At −30 °C, to a solution of [bdmim][F] (689 mg, 4 mmol, 10 equiv) dissolve in dichloromethane (2 mL) were successively added NBS (855 mg, 4.8 mmol, 12 equiv) then dropwise a solution of xanthate (0.4 mmol, 1 equiv) in dichloromethane (2 mL). The solution was stirred at room temperature for 3 h and the mixture was concentrated under vacuum to remove dichloromethane. Diethyl ether (10 mL) was added and the mixture was

stirred for 10 min. The ether phase and the ionic liquid phase were separated. This procedure was carried out six times in order to extract completely the product. Organic phases were combined and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel to afford the desired product.

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