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Ionic Liquid-Mediated Hydrofluorination of *o*-Azaxylylenes Derived from 3-Bromooxindoles

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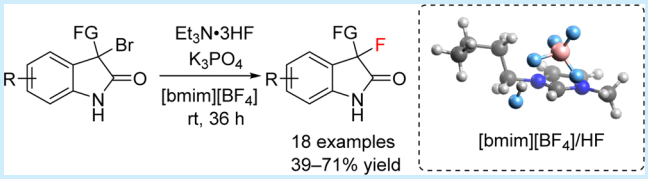
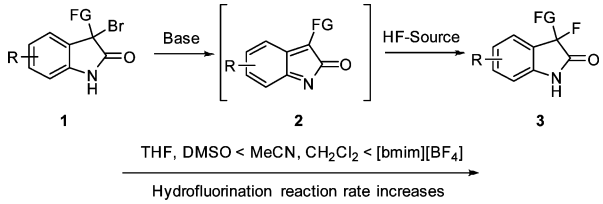
S *Supporting Information*

ABSTRACT: The hydrofluorination reaction of 3-bromooxindole using mild HF reagents in an ionic liquid is described. This transformation can operate at room temperature to give a series of 3-substituted 3-fluorooxindole derivatives including racemic BMS 204352 (MaxiPost). The mechanistic study about interactions between HF and 3-butyl-1-methylimidazolium tetrafluoroborate [bmim][BF_4] is also discussed on the basis of energy calculations.



Nucleophilic fluorination reactions for the synthesis of organofluorines are very important in agrochemical,[1] pharmaceutical,[2] and radiopharmaceutical industries.[3] This importance has driven research interest in the development of a method for the incorporation of fluorine atoms into organic molecules. Therefore, versatile methods for alkyl,[4] allyl,[5] and aryl fluoride synthesis[6] have recently been developed. In addition, deoxyfluorination of alcohols has also been explored extensively.[7] Among them, S_N2 fluorination reaction of alkyl halide or tosylate using alkali fluorides in polar aprotic solvents is the most general method for synthesizing primary and secondary alkyl fluorides. Numerous approaches using the phase-transfer system, alcohol additives,[8] ionic liquids,[9] crown ethers,[10] and bulky ammonium salts[11] to promote the poor nucleophilicity of fluoride ion have been reported. Despite these advances, the tertiary alkyl−F bond, which is difficult to form via the nucleophilic fluorination reactions, remains a challenge. Fluoride is a small ion that has high electronegativity with decreasing nucleophilicity. It also tightly solvates with protic solvents to decrease the nucleophilicity. Therefore, the nucleophilic fluorination reactions have significant limitations in terms of high-temperature conditions, limited substrates, and solvents. However, recently, progress in this research has been seen in the development of methods for forming sp^3 C−F bonds. Gilmour and Jacobsen developed 1,2-difluorination of alkenes by the combination system with nucleophilic fluorine sources/an oxidant/an aryl iodide catalyst, independently.[12] Nishikata disclosed site-selective tertiary alkyl−fluorine bond formation of α-bromoamides using CsF under copper catalysis.[13] An iron(II)-catalyzed aminofluorination of inactive olefins using a fluorine ion formed by a complex of Et_3N·3HF and XtalFluor-E to afford β-fluoro amino products was reported by Xu.[14] To the best of our knowledge, an operationally simple method for hydrofluorination to yield tertiary alkyl−F bonds is rare.[15] Herein, we disclose an ionic liquid-mediated hydrofluorination of *o*-azaxylylene intermediates **2** generated in situ from 3-bromooxindoles **1**, giving the 3-fluorooxindole products **3** (Scheme 1). In this study, the mechanistic study of interactions between HF and 3-butyl-1-methylimidazolium tetrafluoroborate [bmim][BF_4] is also discussed on the basis of energy calculations.

Scheme 1. Hydrofluorination of 3-Bromooxindole Derivatives



The oxindole scaffold can be found in a tremendous number of natural compounds as well as in biological active compounds.[16] The incorporation of fluorine atom into the oxindole nucleus is valuable in medicinal chemistry. Since the potential of 3-bromooxindoles as precursors of highly reactive electrophilic *o*-azaxylylenes was reported in 1964,[17] a tremendous number of reactions with C, O, N, and S nucleophiles have been developed.[18] Given nucleophiles for hydrofluorination of *o*-azaxylylenes, hydrogen fluoride is the classical nucleophilic fluorinating reagent, but it must be

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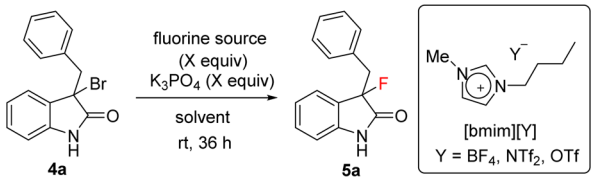
handled carefully due to its hazardous gas. Currently available HF-based reagents such as Olar's reagent (HF−pyridine), Et_3N−HF, and poly(hydrogenfluoride)complex are less toxic and easier to handle. Accordingly, we envisaged that an operationally simple electrophilic fluorination of *o*-azaxylylene intermediates is enabled by the use of such HF-based reagents.

We initially examined the hydrofluorination of 3-benzyl-3-bromooxindole (**4a**) as a model substrate employing HF-based reagents as a fluorine source in the presence of base (Table 1).

Table 1. Optimization of Hydrofluorination of 5a



entry	fluorine source	*X* (equiv)	solvent	yield[a] (%)
1	$Et_3N{\cdot}3HF$	2	THF	ND
2	$Et_3N{\cdot}3HF$	2	DMSO	ND
3[b]	$Et_3N{\cdot}3HF$	2	MeOH	ND
4	$Et_3N{\cdot}3HF$	2	CH_2Cl_2	29
5	$Et_3N{\cdot}3HF$	2	MeCN	31
6	$Et_3N{\cdot}3HF$	5	MeCN	31
7	$Et_3N{\cdot}3HF$	2	[bmim][BF_4]	41
8	$Et_3N{\cdot}3HF$	5	[bmim][BF_4]	52 (58)[c]
9[d]	$Et_3N{\cdot}3HF$	5	[bmim][BF_4]	ND
10	Py·HF	3	[bmim][BF_4]	3
11	DMPU·HF	3	[bmim][BF_4]	13
12	KF	2	[bmim][BF_4]	31
13	CsF	2	[bmim][BF_4]	35
14	$Et_3N{\cdot}3HF$	5	[bmim][NTf_2]	53
15	$Et_3N{\cdot}3HF$	5	[bmim][OTf]	21

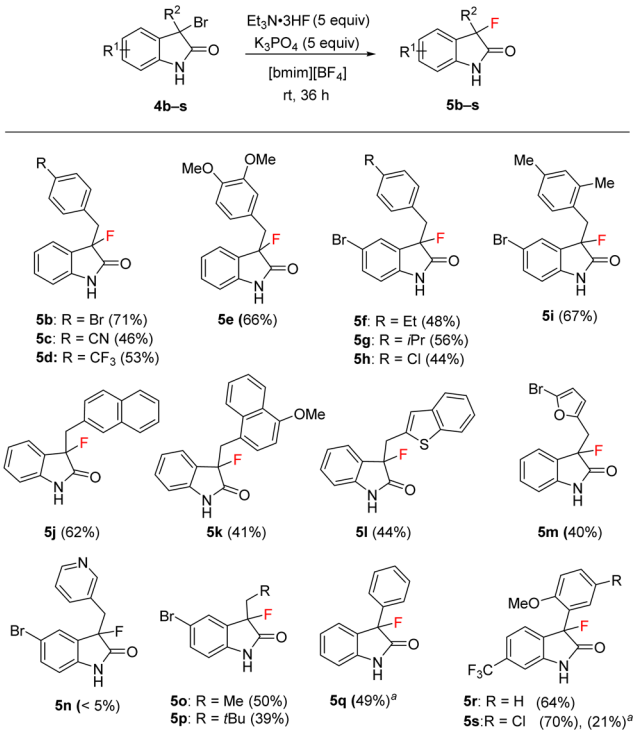
[a]Determined by ^{19}F NMR with fluorobenzene as an internal standard. [b]3-Methoxyoxindole as a main product was obtained in 55% yield (see the Supporting Information for details). [c]Yield in parentheses for the reaction performed on a 1 mmol scale. [d]Conducted in absence of K_3PO_4. ND = not determined, Py = pyridine, DMPU = *N*,*N*′-dimethylpropyleneurea.

The mixture of **4a** and 2 equiv of $Et_3N{\cdot}3HF$ and K_3PO_4 in various solvents at room temperature was stirred for 36 h. Extensive experiments revealed that the yield of product **5a** was greatly affected by the used solvent. Neither THF nor DMSO was effective (entries 1 and 2). A protic solvent, MeOH, was employed as a nucleophile to predominantly give a corresponding 3-methoxyoxindole in 55% isolated yield (entry 3). The fluorination reactions in dichloromethane or MeCN produced the product **5** in 29% or 31% yield (entries 4 and 5). In MeCN, the increased yield was not observed by addition of a large excess amount of fluorine source and base (entry 6). Ionic liquids containing imidazolium cations have been widely recognized as a useful reaction media not only the for an ecofriendly recyclable solvent to replace volatile organic solvents but also the for acceleration of reaction rate and improvement of selectivity. It has also been reported for various ionic liquid-mediated chemical transformations including S_N2 fluorination reactions and halofluorination of alkenes.[9] Therefore, an ionic liquid [bmim][BF_4] as a reaction medium was employed to this reaction. As expected, ionic liquid-mediated hydrofluorination of **4a** increased to 41% yield (entry 7). In addition to use of [bmim][BF_4], addition of excess amount of $Et_3N{\cdot}3HF$ and base (5.0 equiv) provided a higher yield of **5a** (52%, entry 8). The reaction scale was increased from 0.1 to 1.0 mmol to 58% yield. The absence of base resulted in no product, which suggests that base is necessary for dehydrobromination of **4a** to generate *o*-azaxylylene intermediates (entry 9). Upon screening of fluorine sources including alkali fluorides, we found that $Et_3N{\cdot}3HF$ is the most proper nucleophile in comparison to HF reagents based on pyridine and DMPU (entries 10 and 11). Moreover, KF and CsF were evaluated, and use of them afforded the fluorinated product in 31% and 35% yield, respectively (entries 12 and 13).

We next investigated the influence of counterions of ionic liquids (entries 14 and 15). When [bmim][NTf_2] was used, we obtained a result similar to that using [bmim][BF_4]. The hydrofluorination reaction in [bmim][OTf] gave a lower yield (21%). Subsequently, we executed the recycling of solvent with the optimized conditions in hand. After the reaction was completed, **5a** and byproducts were extracted with diethyl ether from the ionic liquid followed by filtration through a Millipore millex-lg. After drying under vacuum, [bmim][BF_4] could be reused for this hydrofluorination reaction. We have performed three runs and obtained similar yields.

We investigated the scope of 3-bromooxindole derivatives (Scheme 2). 3-Benzyl-3-bromooxindoles **4b−e** bearing different electronic substituents (R = Br, CN, CF_3, OMe) and 3-benzyl-3,5-dibromooxindoles bearing different electronic substituents (R = Me, Et, *i*Pr, Cl) were tolerable, giving the corresponding products in 44−71% yields. The reactions of **4j−m** bearing naphthalene, benzothiophene, and furan moieties provided the corresponding products **5j−m** in 40−62% yields. Compound **5n** bearing a pyridine ring was not an efficient substrate for this hydrofluorination reaction. Syntheses of

Scheme 2. Scope of Hydrofluorination of Various 3-Bromooxindoles



[a]MeCN was used instead of [bmim][BF_4].

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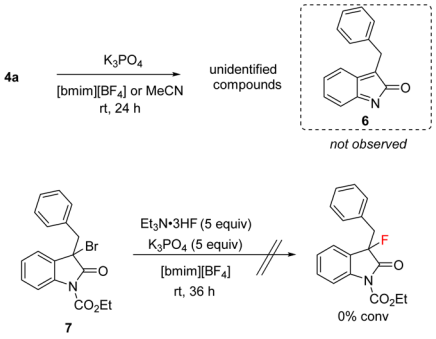
aliphatic substituted 3-fluorooxindoles **5o**,**p** were successful. The presence of a bulky *tert*-butyl group resulted in a slightly lower yield of **5p** (39%). The hydrofluorination of 3-bromo-3-phenyloxindole (**4q**) favored MeCN as the reaction medium over ionic liquid. The hydrofluorination of **4q** in MeCN proceeded and gave the desired product **5n** in 49% yield. In the case of [bmim][BF_4], rapid decomposition of **4q** was observed. BMS 204352 (MaxiPost), a potassium channel opener for the treatment of stork, was developed.[19] The structure is characterized by an important three-component aromatic oxindole and a fluorine atom at the 3-position of oxindole. A large number of synthetic methods of BMS 204352 have been reported to date. Most of those approaches for the incorporation of fluorine atom are the electrophilic fluorination reactions with electrophilic reagents such as Selectfluor and NFSI. We thus attempted an approach for synthesis of BMS 204352 through the nucleophilic fluorination reaction. The hydrofluorination of 3-bromooxindole **4s** and the an analogue **4r** with $Et_3N{\cdot}3HF$ in [bmim][BF_4] proceeded smoothly to give the corresponding product **5r** and racemic BMS 204352 (**5s**) in 64 and 70% yield, respectively. When MeCN was used instead of [bmim][BF_4], the yield of **5s** was decreased to 21%.

In order to further understand this transformation, we also carried out experiments as shown in Scheme 3. To examine in

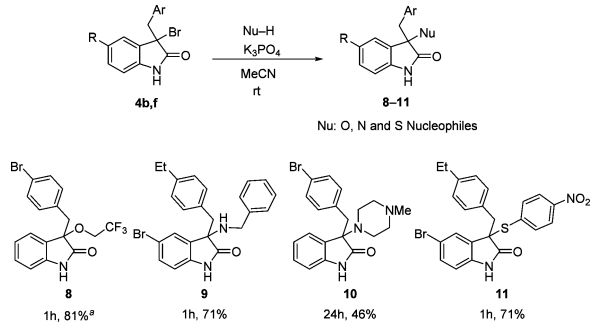
Scheme 3. Control Experiments with 4a and 7



situ generation of reactive *o*-azaxylylene intermediate **6**, the reaction of **4a** in [bmim][BF_4] or MeCN in the presence of K_3PO_4 without HF reagents was performed. The intermediate **6** would be formed in situ, but the evident decomposition of **4a** was merely observed due to its instability. Additionally, the reaction of *N*-(ethoxycarbonyl)-3-bromooxindole **7** as a substrate under standard conditions was performed, it did not proceed at all. To this end, when a variety of O, S, and N nucleophiles were used instead of HF reagents, these reaction without ionic liquids successfully provided access to the corresponding products (Scheme 4). Overall, these results show that the intermediate **6** plays an important role as an electrophile to react with HF reagent. As illustrated in Table 1, ionic liquids have effects on the hydrofluorination of 3-bromooxindole derivatives, gaining the higher yield of fluorinated products, in contrast to the corresponding reactions in common organic solvents.

We thus hypothesized that ionic liquids aid H−F bond cleavage to accelerate the reaction with *o*-azaxylylene. Hydrogen bonds associated with interaction between HF and [bmim][BF_4] in optimized geometry at the MPW1K/6-311++G** level of theory are calculated (Figure 1).[20] The results show that the C2-acidic proton of [bmim] binds to the fluoride of HF, which seems to partially decrease its nucleophilicity.

Scheme 4. Scope of Nucleophiles



[a]Nucleophile 2,2,2-trifluoroethanol was used as a solvent.

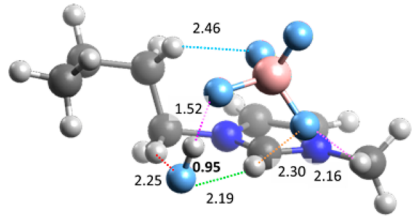


Figure 1. Hydrogen bonds in optimized geometry of HF and [bmim][BF_4].

Interestingly, the bond length of HF is enlarged at 0.95 Å from 0.91 Å. The reason is that a counterpart [BF_4] of the imidazolium cation plays a role as a Brønsted base in drawing the hydrogen of HF. Relevant reports about DFT studies of the chelation of CsF with ionic liquids suggest that a counteranion of ionic liquids neutralizes the Coulombic influence of Cs^+ on F^-, enhancing S_N2 fluorination reactions. The argument is very similar to that of our calculation results. Taken together, these results support a mechanism including the formation of electrophilic *o*-azaxylylenes from 3-bromooxindole derivatives and ionic liquid-mediated H−F bond activation.

In summary, we have developed the ionic liquid-mediated hydrofluorination of *o*-azaxylylenes in situ generated from 3-bromooxindoles using mild HF-based reagents under mild conditions. In these reactions, synthesis of fluorinated compounds for industrial purposes with nucleophilic is noteworthy in terms of cost and atom economy because the nucleophilic reagents such as alkaline fluorides and HF-based reagents are usually less expensive than electrophilic reagents. This operationally simple method provides access to a series of 3-fluorooxindole compounds which would be biologically relevant compounds. Moreover, the mechanistic study based on energy calculations revealed the enlargement of the H−F bond length. Applications with synergetic effects of HF/[bmim][BF_4] in nucleophilic fluorination reactions are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00887.

General experimental procedures and characterization date for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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