Research Article

A New Air-stable Fluorinating Reagent, IF_5-pyridine-HF

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1. Introduction

Hypervalent iodine fluorides have been used as oxidants as well as fluorinating reagents. Among them, iodotoluene difluoride (*p*-$TolIF_2$), is the most popular fluorinating reagent because it can be prepared without hazardous F_2 gas, and stable enough to be used without special knowledge and techniques.[1]

On the other hand, iodine pentafluoride (IF_5) is not as popular as *p*-$TolIF_2$ because F_2 gas is used in its preparation and it decomposes in air by moisture emitting corrosive HF. Therefore, we studied fluorination reactions using the hypervalent iodine reagent *p*-$TolIF_2$.[1b,1e-g] After several years, we became interested in IF_5 because it is more reactive than *p*-$TolIF_2$, even though more hazardous than *p*-$TolIF_2$. During the studies using IF_5, we found that IF_5 can be used for the introduction of a fluorine atom into the α-position of a sulfur group in sulfides,[2] and desulfurizing difluorination of benzylic sulfides.[3] We also found a unique fluorination reaction of aryl alkyl sulfide with IF_5 where poly-fluorination took place under migration of the arylsulfanyl group.[4] Thus, we showed that IF_5 can be used as a fluorinating reagent, and moreover, a unique new fluorination reaction was developed using IF_5. However, a serious drawback of IF_5 is that it is difficult to obtain. Its instability made its commercial availability difficult. Therefore, we made a new stable fluorinating reagent from IF_5.

2. Development of IF_5-pyridine-HF

To make a stable fluorinating reagent from IF_5, many additives were investigated. When pyridine-HF (1:1 complex) was added to IF_5, a white solid was formed.[5] The white solid is moisture-stable and non-hygroscopic, and therefore, can be handled in air without decomposition. The white solid was poorly soluble in non-polar solvents such as hexane and CH_2Cl_2, and soluble in polar solvents, such as acetonitrile. Next, the white solid was applied to several fluorination reactions, and found to be a suitable fluorinating reagent.

The precise structure of the white solid is unclear, because its X-ray crystal structure analysis is still unsuccessful. However, the weight of the generated white solid is 95% of the total weight of the starting materials used in its synthesis. Therefore, the proposed molecular formula, IF_5-pyridine-HF, should be correct.

3. Fluorination reactions using IF_5-pyridine-HF

3-1. Fluorination of sulfide at α-position

When a sulfide (**1**) was added to a suspension of IF_5-pyridine-HF in CH_2Cl_2, the mixture changed to dark red color and fluorination took place at the α-position of the sulfur group to give a fluorinated product (**2**)[5] (eq. 1). In the reaction of **1** with IF_5, three fluorine atoms were introduced under the same conditions,[4] whereas only one fluorine atom was introduced in the reaction with IF_5-pyridine-HF. Therefore, IF_5-pyridine-HF was found to be less reactive than IF_5 itself.

3-2. Desulfurizing difluorination of benzylic sulfide[5]

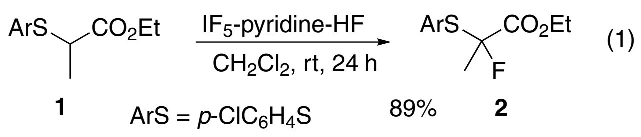
In the reaction of a benzylic sulfide having an electron-withdrawing group (**3**), the fluorination at the α-position of the sulfur group, followed by the substitution of a fluoride with the sulfur group took place to give a *gem*-difluoride (**4**) (eq. 2).

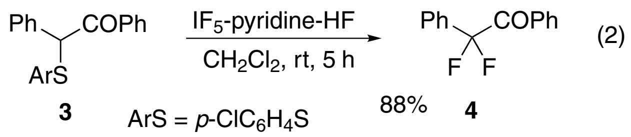
3-3. Synthesis of *gem*-difluoride from aldehyde dithioacetal and ketone dithioketal[5]

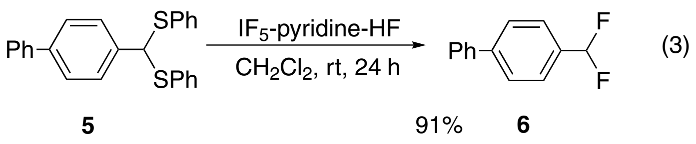
When an aldehyde dithioacetal (**5**) was reacted with IF_5-pyridine-HF, a *gem*-difluoride (**6**) was formed (eq. 3). The dithioacetal or dithioketal of a carbonyl compound without α-hydrogen can be applied to this reaction. When the dithioketal of a ketone has an α-hydrogen, a *poly*-fluorination reaction occurred as shown in section 3-11.

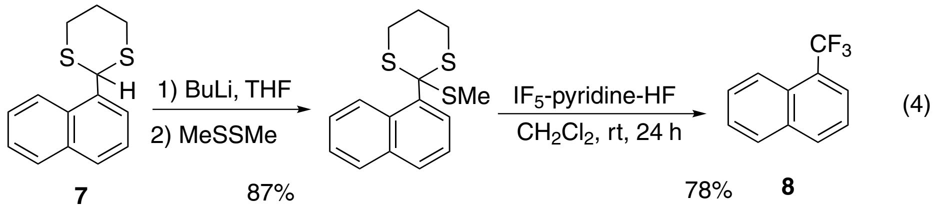
3-4. Introduction of a trifluoromethyl group into an aromatic ring[5]

The introduction of a methylsulfanyl group into an aromatic aldehyde dithioacetal (**7**), followed by the reaction with IF_5-pyridine-HF gave a trifluoromethylated aromatic compound (**8**) (eq. 4).









3-5. Synthesis of (methylsulfanyl)difluoromethyl ether and trifluoromethyl ether from alcohol and phenol dithiocarbonates[6]

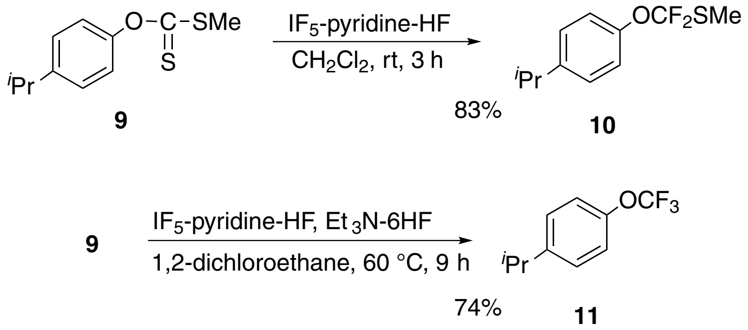
When a dithiocarbonate (**9**) was reacted with IF_5-pyridine-HF, the corresponding (methylsulfanyl)difluoromethyl ether (**10**) was selectively formed. On the other hand, when the reaction was carried out in the presence of Et_3N-6HF, the corresponding trifluoromethyl ether (**11**) was selectively formed (eq. 5).

This reaction can be applied to the dithiocarbonate of aliphatic alcohols, and a liquid crystal material having a trifluoromethoxy group (**12**) was synthesized (eq. 6).

3-6. Fluoromethyl ether synthesis[7]

(Methylsulfanyl)methyl ether is known as a protecting group of hydroxy groups. A (methylsulfanyl)methyl ether of phenol (**13**) was converted to the corresponding fluoromethyl ether (**14**) by the reaction with IF_5-pyridine-HF (eq 7). This reaction can be applied to the (methylsulfanyl)methyl ether of phenols and aliphatic alcohols.

A fluoromethyl ether of an amino acid derivative (**15**), a potential PET tracer, was prepared by the reaction with IF_5-pyridine-HF (eq. 8).



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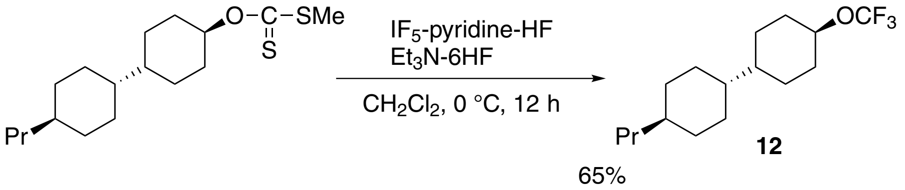

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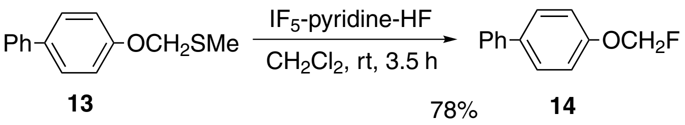

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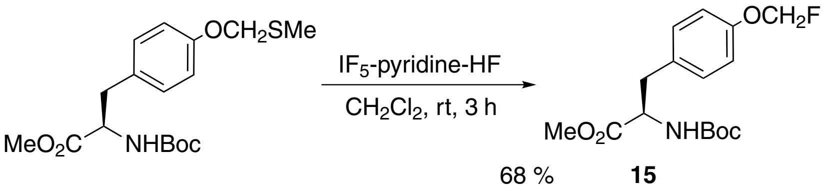

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3-7. Glycosyl fluoride synthesis[8]

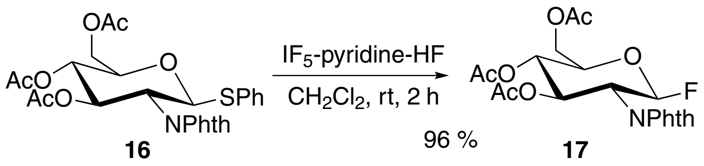
Glycosyl fluoride is used as a key intermediate for *poly*-saccharide synthesis, and has been prepared from the corresponding (phenylsulfanyl)glycoside by the reaction with a fluorinating reagent and an oxidant. On the other hand, the application of IF_5-pyridine-HF alone was sufficient to convert (phenylsulfanyl)glycoside (**16**) to the corresponding glycosyl fluoride (**17**) (eq. 9). This reaction can be used for the synthesis of furanose, pyranose, and disaccharide derivatives.

3-8. Generation of “IF” species and its application to the iodofluoroalkane synthesis[9]

The “IF” species has been conveniently generated by several methods, such as by the reaction of I_2 with F_2, and used for the addition reaction to alkenes without isolation.[10] When IF_5-pyridine-HF was reduced with a reductant such as I_2, KI, and Sn, the “IF” species was generated (eq. 10). When the reaction was carried out in the presence of an alkene, the corresponding iodofluorination product (**18**) was formed. The reaction proceeded regioselectively (eq. 11).

3-9. Generation of “IF” species part 2, and its application to iodofluoroalkene synthesis[11]

When the “IF” species was generated in the presence of an alkyne, the corresponding iodofluoroalkene was formed. In the conventional method, the expected iodofluoroalkene was obtained from an internal alkyne, however, in the reaction with a terminal alkyne, the corresponding iodofluoroalkene was formed in poor yield, and the formation of a by-product was observed.[12] On the other hand, in the reaction with IF_5-pyridine-HF, the iodofluoroalkene was formed regio- and stereoselectively from the terminal alkyne as well as from the internal alkyne by using *p*-hydroquinone as the reductant (eq. 12).



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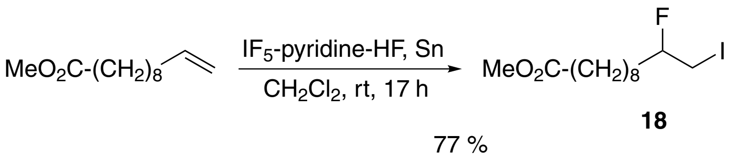
$$\mathrm{IF_5\text{-}pyridine\text{-}HF} \xrightarrow[\mathrm{CH_2Cl_2}]{\text{reductant}} \text{"I-F" species} \qquad (10)$$



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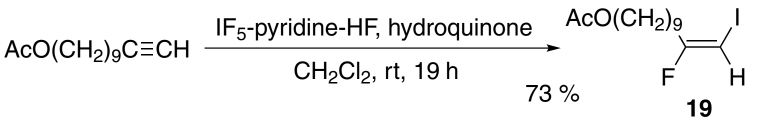

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3-10. Iodoazidation of alkene[13]

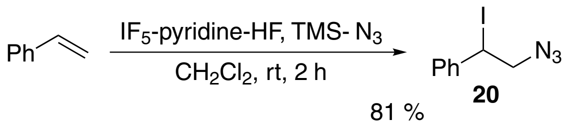
When IF$_5$-pyridine-HF was reacted with Me$_3$SiN$_3$, and then an alkene was added, the iodoazidation of the alkene took place. In the reaction with a terminal alkene, the *anti*-Markovnikov type adduct (**20**) was formed selectively (eq. 13). The reaction with cyclohexene gave a mixture of *cis*- and *trans*-adducts. These results indicated that the reaction proceeded through a radical mechanism, and IF$_5$-pyridine-HF acted as an oxidant.

3-11. Poly-fluorination of sulfide[14]

When an alkyl aryl sulfide was reacted with IF$_5$, *poly*-fluorination took place under migration of the ArS group to give the corresponding *poly*-fluorinated product.[4] On the other hand, in the reaction with IF$_5$-pyridine-HF, only the *mono*-fluorinaton of the aryl alkyl sulfide took place under the same conditions (section 3-1). However, the introduction of an electron-donating group into the aryl group and by carrying out the reaction at a higher temperature, the *poly*-fluorination of the sulfide could be achieved even by the reaction with IF$_5$-pyridine-HF (eq. 14).

In the reaction of IF$_5$-pyridine-HF with the dithioketal of a ketone with an α-hydrogen (**21**), the corresponding *poly*-fluorinated product (**22**) was also formed (eq. 15).

In both the reactions, the same intermediate (**23**) should be formed (**Scheme 1**).



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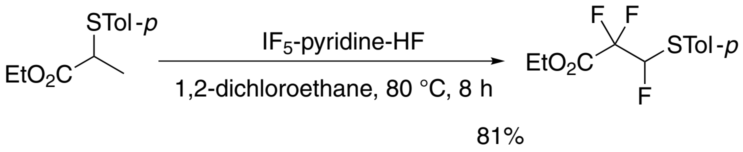

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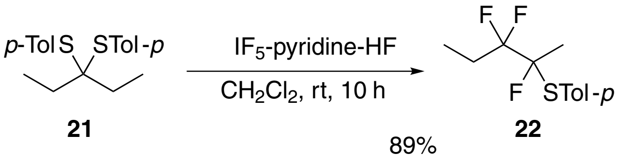

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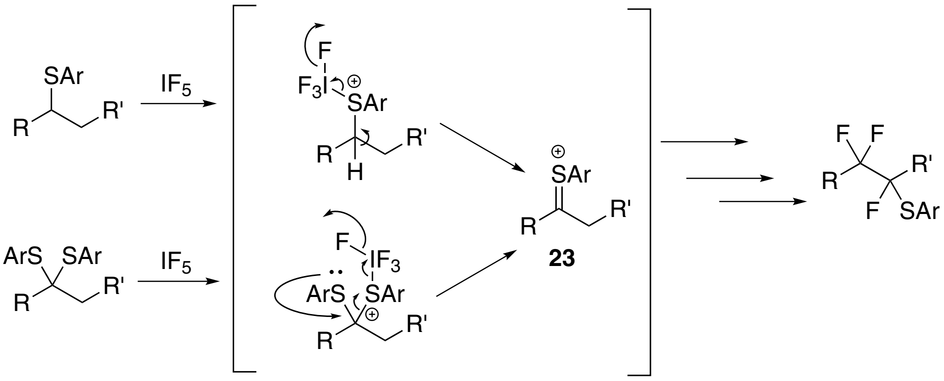

Scheme 1.

4. Conclusion

We prepared a new fluorinating reagent, IF_5-pyridine-HF, which has advantages of unusual stability and ease of use. We also developed several reactions using IF_5-pyridine-HF. We hope that IF_5-pyridine-HF will be used by many chemists.

Acknowledgment

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References

1) (a) W. B. Motherwell, *Aldrichimica Acta* **1992**, *25*, 71. (b) M. Sawaguchi, S. Hara, N. Yoneda, *J. Fluorine Chem.* **2000**, *105*, 313. (c) S. Hara, In *Advances in Organic Synthesis,* K. K. Laali, Ed.; Bentham Science Publishers, **2006**, p. 49. (d) S. A. P. Quintiliano, *Synlett* **2007**, 1797. (e) M. Yoshida, S. Hara, *J. Synth. Org. Jpn.* **2008**, *66*, 44. (f) S. Hara, *SIS Letters* **2009**, *10*, 2. (g) S. Hara, In *Up-to-date Chemistry & Technological Application for Iodine,* M. Yokoyama, Ed.; CMC Publishing, **2011**, p. 196.
2) S. Ayuba, N. Yoneda, T. Fukuhara, S. Hara, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1597.
3) T. Fukuhara, S. Hara, *Synlett* **2009**, 198.
4) (a) S. Ayuba, T. Fukuhara, S. Hara, *Org. Lett.* **2003**, *5*, 2873. (b) T. Fukuhara, S. Hara, *J. Org. Chem.* **2010**, *75*, 7393.
5) S. Hara, M. Monoi, R. Umemura, C. Fuse, *Tetrahedron* **2012**, *68*, 10145.
6) T. Inoue, C. Fuse, S. Hara, *J. Fluorine Chem.* **2015**, *179*, 48.
7) M. Kunigami, S. Hara, *J. Fluorine Chem.* **2014**, *167*, 101.
8) M. Kunigami, S. Hara, *Carbohydr. Res.* **2015**, *417*, 78.
9) S. Yano, S. Hara, *Synthesis* **2015**, *47*, 2839.
10) (a) S. Rozen, M. Brand, *J. Org. Chem.* **1985**, *50*, 3342. (b) S. Rozen, M. Brand, *Tetrahedron Lett.* **1980**, *21*, 4543.
11) H. Ukigai, S. Hara, *Tetrahedron Lett.* **2016**, in press.
12) P. Conte, B. Panunzi, M. Tingoli, *Tetrahedron Lett.* **2006**, *47*, 273.
13) T. Hiraoka, S. Yano, S. Hara, *Synthesis* **2016**, in press.
14) T. Inoue, S. Nakabo, S. Hara, *J. Fluorine Chem.* **2016**, *184*, 22.

Introduction of the author:

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1974-1976: Master of Engineering at Kyoto University
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1994-2001: Associate Professor at Faculty of Engineering, Hokkaido University
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1989: Incentive Award in Synthetic Organic Chemistry, Japan
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New fluorination reactions, Synthesis of organofluorine compounds

TCI Related Products

P2140	IF_5-Pyridine-HF	1g	5g	25g
D0714	Dimethyl Disulfide (= MeSSMe)	25g	100g	500g
T0801	Trimethylsilyl Azide (= TMS-N_3)	5g	25g	100g