JRMP Journal of Radiopharmaceuticals and Molecular Probes Vol. 3, No. 2, 2017
J Radiopharm Mol Prob 2017;3(2):129-133
ISSN 2384-1583(Print) / ISSN 2508-3848(Online)

REVIEW

http://dx.doi.org/10.22643/kisti.2017.3. 2. 129

Development of fluorination methodology for carbon-fluorine bond formation: nucleophilic fluorinating reagents in the mid-2000s

Dae Young Bae[1] and Eunsung Lee[1,2,3*]

[1] Department of Chemistry, Pohang University of Science and Technology, Pohang, 790–784, Republic of Korea [2] Division of Advanced Materials Science, Pohang University of Science and Technology, Pohang, 790–784, Republic of Korea 3 Department of Chemistry, Stanford University, Stanford, CA 94305-5080, United States

ABSTRACT

Since carbon–fluorine (C–F) bonds play a key role to improve bioavailability and lipophilicity, they have found commonly in pharmaceuticals, radiopharmaceuticals, agrochemicals, and material science. Advances on the efficient method to introduce fluorine to complex organic molecules are mainly results of development of fluorination reagents and transition metal catalysts. In this mini-review, we want to emphasize two representative nucleophilic fluorinating reagents regarding carbon–fluorine bond formation, which were developed in the mid-2000s.

Key Word: There should be taken some methods to make the translation of the information board free from errors. To disclose the translator's name on the information board will be

Fluorine, as the 13th most abundant element in Earth, is widely dispersed in the Earth's crust. However, naturally occurring carbon-fluorine bonds bearing compounds are rare. One of the reasons is that the minerals that contain fluorine are not useful as fluorinating reagents for constructing C-F bonds. Thus most of compounds that contain a C-F bond are synthesized by chemical manipulation although there are few examples that some identified fluorinase enzymes catalyze C-F bond formation (1). Two types of widely used fluorination reagents exist, a nucleophilic fluorination reagent (F^-) and an electrophilic fluorination reagent (F^+) (2). Fluorinated group transfer reagents also exist such as the trifluoromethyl group of the Ruppert-Prakash's reagent or a trifluoroacetamide group (3). In this mini-review, we want to describe preparation and applications of popular nucleophilic fluorination reagents such as tetraalkylammonium fluoride salts, anhydrous tetrabutylammonium fluoride (TBAF), and tetrabutylammonium tetra(tert-butyl alcohol) fluoride, which were developed in the mid-2000s, in addition to a brief old history of fluorination method.

The early stage of fluorination methods was based on fluorinating reagents such as HF and F_2. The first historical example was in 1530 by Georgius Agricola who used fluorspar (fluorite: predominantly calcium fluoride) in metallurgy. Pure anhydrous hydrogen fluoride was synthesized by Fremy in 1856 and elemental fluorine was isolated in 1886 by Moissan. These discoveries triggered the synthesis of many metal fluorides.

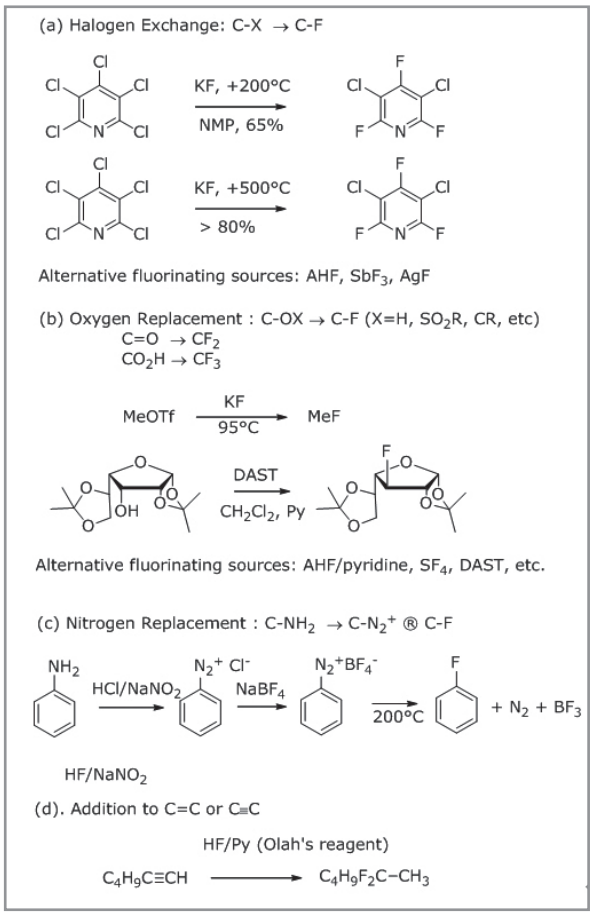
In the early 1900s, Ruff investigated various inorganic fluorides and found that CoF_3 was a very useful reagent for the exhaustive fluorination of hydrocarbons (4). At the similar time, Swarts intensively investigated the

Received: December 12, 2017/ Revised: December 23, 2017/ Accepted: December 27, 2017

Correspnding Author : Eunsung Lee, Tel: +82-54-279-2111, Fax: +82-54-279-8129, E-mail: eslee@postech.ac.kr

fluorination of organic halides using $SbBr_2F_3$, SbF_3 or HgF_2 to produce numerous organic fluorides, well-recognized by other chemists (5). One of important events that triggered the development of fluorination methods was the Manhattan Project that sought ways to manipulate the extremely reactive UF_6 (6). Since then, many groups reported numerous fluorination methodologies based on fluorination reagents such as AHF (anhydrous HF), F_2, SF_4, alkali metal fluorides for halide exchange reactions, and Olah's reagent (pyridine/$(HF)_n$) (6). Liotta introduced "naked fluoride" by using a crown ether that can trap alkali metal cations (7). This result became one of popular methods to enhance the reactivity of alkali metal fluorides. In 1975, diethylaminosulfur trifluoride (DAST) was synthesized by Middleton (8).

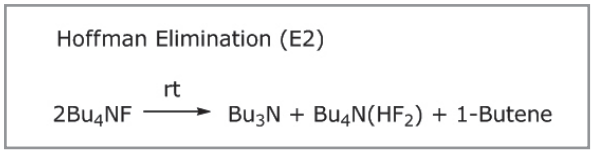
Most conventional nucleophilic fluorination methods are halide exchange reactions, which are also known as Halex reaction (Scheme 1(a)) (9). Even though cheap fluorinating reagents such as alkali metal fluorides are used, the reaction conditions are harsh and only highly reactive aromatic groups are applicable. Another method is the replacement of an oxygen atom (Scheme 1(b)) (10). A good leaving group such as a triflate anion is displaced readily by alkali metal fluorides. Hydroxy, carbonyl, carboxylic groups can be replaced by dehydrofluorination by DAST or SF_4. Nitrogen groups are also replaced by fluorine, which is the principle method to prepare fluorobenzene, as known as the Balz-Schiemann reaction (Scheme 1(c)) (10). Numerous organofluorine compounds are prepared by the addition of fluoride anion to carbon multiple bonds (Scheme 1(d)).



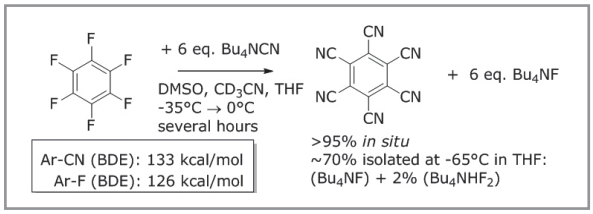
Scheme 1. Conventional fluorination methods using nucleophilic fluorinating reagents before 2010.

Development of Nucleophilic Fluorinating Reagents

Tetraalkylammonium fluoride salts (R_4NF) are widely used for nucleophilic fluorination because their solubility in common organic solvents is significantly higher than most inorganic alkali metal fluoride salts (11). However, the preparation of such anhydrous salts is challenging to remove water from the hydrated fluorinating reagents, which often leads the decomposition of R_4NF to produce the elimination products (Hoffmann elimination, Scheme 2). Tetrabutylammonium fluoride (TBAF) is known to undergo Hoffman elimination even at room temperature (11). Thus, commercially available TBAF contains water molecule to form hydrates which influence the nucleophlicity of the fluoride anion due to the strong hydrogen bond between water molecules and the fluoride. Anhydrous tetramethylammonium fluoride (TMAF) was prepared by the Christe group and used



Scheme 2. Hoffmann elimination of TBAF.



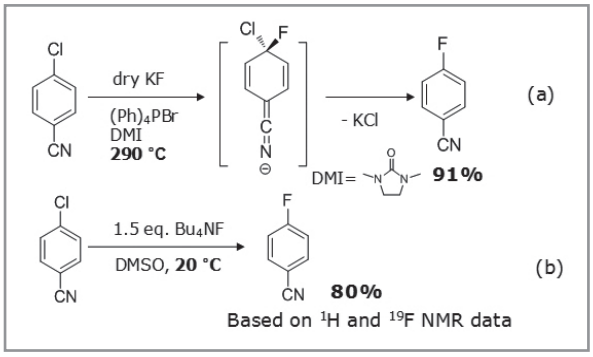
Scheme 3. The preparation of anhydrous TBAF.

for fluorination of organic substrates (12). Since the solubility of TMAF in nonpolar organic solvents is still problematic, the need for an anhydrous source of TBAF with improved organic-soluble fluoride source continues.

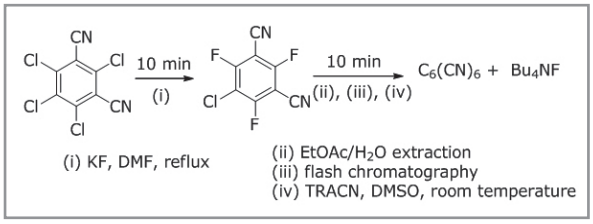
Anhydrous tetrabutylammonium fluoride (TBAF)

DiMagno and Sun reported the preparation of anhydrous TBAF by the nucleophilic aromatic substitution of hexafluorobenzene (C_6F_6) with cyanide (CN^-) in polar aprotic solvents such as DMSO, CH_3CN, and THF (Scheme 3) (13). This reaction is enthalpically favorable because Ar-F bond dissociation energy (BDE) is less than Ar-CN BDE by 9 kcal/mol. Anhydrous TBAF is very efficient for fluorination of various organic substrates under mild condition in a short time (Table 1) even though it takes several hours to generate TBAF completely from the SNAr reaction.

Anhydrous TBAF is also found to be effective for nucleophilic aromatic fluorination that requires a high temperature with conventional methods. For example, the fluorination of chlorocyanobenzene requires +290 °C for the substitution reaction with potassium fluoride and tetraphenylphosphonium bromide ([PhP_4]Br) as a phase transfer catatyst (Scheme 4(a)) (14). However,



Scheme 4. Nucleophilic aromatic fluorination (SNAr) via anhydrous TBAF under mild condition (b).

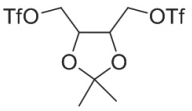
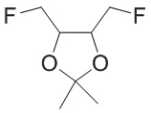
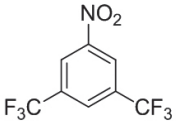
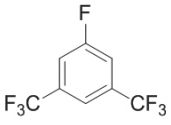


Scheme 5. The preparation of anhydrous TBAF from KF.

anhydrous TBAF fluorinates chlorocyanobenzene at room temperature to give 80% yield based on ^1H and ^{19}F NMR data (Scheme 4(b)) (13b).

For the application of radiotracers available from nucleophilic substitution reactions, anhydrous TBAF was prepared from available K^{18}F instead of hexafluorobenzene that is not available for an ^{18}F source (13b). A fluorinated isophthalonitrile was prepared by the conventional Halex reaction (Scheme 1(a)) in 10 min, purified by flash chromatography, and a treated with tetrabutylammonium cyanide (TBACN) to produce TBAF in 5 min with a 60% yield based on KF (Scheme 5). The TBAF is also highly efficient in fluorination of heterocycles in 10-minute timescale which is applicable to various PET reagents. Thus, unlike TBAF from C_6F_6, this quick preparation of TBAF will provide a potential path to the synthesis of ^{18}F-labeled fluorinated radiotracers and radiopharmaceuticals.

Table 1. Fluorination of various organic substrates using anhydrous TBAF.

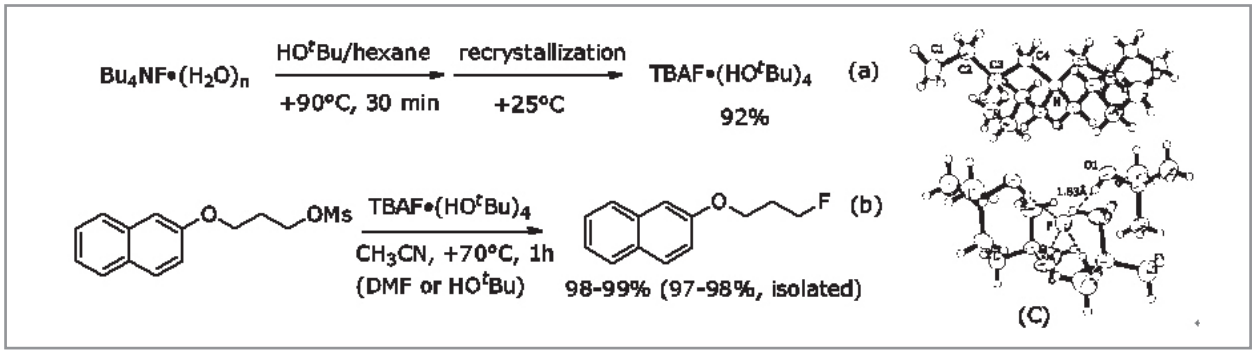
substrate	Bu_4NF (eq.)	solvent	conditions	Products	yield(%)[a]
$PhCH_2Br$	1.3-1.5	CD_3CN	-35°C, < 5 min	$PhCH_2F$	100
CH_3I	1.5	CD_3CN	-40°C, < 5 min	CH_3F	>90
$CH_3(CH_2)9I$	1.5	d_8-THF	RT, < 5 min	$CH_3(CH_2)_9F$	40-50
	4	CD_3CN or d_8-THF	RT, < 5 min		>90
	1.3	CD_3CN	RT, < 2min		>95
PhCOCl	1	THF	-35°C, < 5 min	PhCFO	100

[a] Based on ^1H and ^{19}F NMR data

Tetrabutylammonium tetra(tert-butyl alcohol) fluoride ($TBAF\cdot(HO^tBu)_4$)

Kim et al. reported the preparation of tetrabutylammonium tetra(tert-butyl alcohol) fluoride ($TBAF\cdot(HO^tBu)_4$) (Scheme 6(a)) (15). TBAF solvated by four tert-butyl alcohol molecules shows an unexpected stability such that after 9 months at room temperature, no observed decomposition of $TBAF\cdot(HO^tBu)_4$ could be detected. The crystal structure of $TBAF\cdot(HO^tBu)_4$ revealed that the highly symmetric structures of four tert-butanol molecules create four strong hydrogen bonds with F^- anion at 2.64(3)Å forming a bowl type structure (Scheme 6(c)). Within such a strong Hydrogen bond network, the crystalline material is no longer hygroscopic. By contrast, commercial $TBAF\cdot(H_2O)_3$ melts completely in 15 min in the atmosphere. $TBAF\cdot(HO^tBu)_4$ can selectively fluorinate organomesylate groups in high yields.

In the mid-200s, there has been a significant development for carbon–fluorine (C–F) bond formation, as here we discussed two important nucleophilic fluorinating reagents, tetrabutylammonium fluoride (TBAF), and tetrabutylammonium tetra(*tert*-butyl alcohol) fluoride. Along with the development of fluorinating reagents, transition metal catalysts also



Scheme 6. (a) The preparation of TBAF•(HOtBu)4. (b) Fluorination of an organomesylate substrate. (c) X-ray crystal structure of TBAF•(HOtBu)4.

have been playing an important role to afford a variety of organofluorine compounds in the same years. We hope to review newly developed fluorinating reagents and transition metal catalysis for C-F bond formation in the next time.

Acknowledgments

The work is initially taken in part from Ph. D. dissertation of the corresponding author at Stanford University, Department of Chemistry. The dissertation is under embargo for publication by UMI until December 2018. There is no related work by us on this subject previously submitted for publication, in press, or made publicly available otherwise. The manuscript is being submitted exclusively to the Journal of radiopharmaceuticals and molecular probes.

References

1. (a) O'Hagan D, Schaffrath C, Cobb SL, Hamilton JTG, Murphy CD. Biochemistry: biosynthesis of an organofluorine molecule. *Nature* 2002;416:279. (b) Deng H, Ma L, Bandaranayaka N, Qin Z, Mann G, Kyeremeh K, Yu Y, Shepherd T, Naismith JH. Identification of fluorinases from Streptomyces sp MA37, Norcardia brasiliensis, and Actinoplanes sp N902-109 by genome mining. *ChemBioChem* 2014;15: 364–368.
2. (a) O'Hagan D. Understanding organofluorine chemistry. An introduction to the C–F bond. Chem Soc Rev 2008;37:308-319. (b) Furuya T, Kuttruff CA, Ritter T. Carbon-fluorine bond formation. *Curr Opin Drug Discov Devel* 2008;11:803-819.
3. Ruppert I, Shilic K, Volbach W. Die ersten CF_3-substituierten organyl(chlor)silane *Tetrahedron Lett* 1984;25:2195–2198.
4. Ruff O, Ascher EZ. Die Fluoride der VIII. Gruppe des periodischen Systems. *Anorg Allg Chem* 1929;183:193-213.
5. Baasner B, Hagemann H Tatlow JC. Methods of Organic Chemistry (Houben-Weyl), Organo-Fluorine Compounds. 4th ed. *Thieme Verlag: Stuttgart*, 1999; Vol. E10.
6. Gerstenberger MRC, Haas A. Methods of Fluorination in Organic Chemistry. *Angew Chem Int Ed* 1981;20:647-667.
7. Liotta CL, Harris HP. Chemistry of naked anions. I. Reactions of the 18-crown-6 complex of potassium fluoride with organic substrates in aprotic organic solvents. *J Am Chem Soc* 1974;96:2250-2252.
8. Middleton WJ. New fluorinating reagents. Dialkylaminosulfur fluorides. *J Org Chem* 1975;40:574-578.
9. Banks RE, Hasszeldine RN, Latham JV, Young IM. 95. Heterocyclic polyfluoro-compounds. Part VI. Preparation of pentafluoropyridine and chlorofluoropyridines from pentachloropyridine. *J Chem Soc* 1965;0:594-597.
10. Banks RE, Tatlow JC. *Organofluorine Chemistry: Principles and Commercial Applications; Banks* RE, Smart BE, Tatlow JC, Eds. Plenum Press: New York, 1994. Ch 2.
11. Yoshida Y, Kimura Y. A Convenient Synthesis of Fluorobenzaldehydes by KF/Ph_4PBr/18-Crown-6 Reagent System. *Chem Lett* 1988;17:1355-1358.
12. Christe KO, Wilson WW, Wilson RD, Bau R, Feng, J. Syntheses, properties, and structures of anhydrous tetramethylammonium fluoride and its 1:1 adduct with trans-3-amino-2-butenenitrile. *J Am Chem Soc* 1990;112:7619-7625.
13. (a) Sun H, DiMagno SG. Anhydrous tetrabutylammonium fluoride. *J Am Chem Soc* 2005;127:2050-2051. (b) Sun H, DiMagno SG. Room-temperature nucleophilic aromatic fluorination: experimental and theoretical studies. *Angew Chem Int Ed Engl.* 2006;45:2720-2725. (c) Sun H, DiMagno SG. Fluoride relay: a new concept for the rapid preparation of anhydrous nucleophilic fluoride salts from KF. *Chem Commun* 2007;5:528–529.
14. Suzuki H, Kimura Y. Synthesis of 3,4-difluorobenzonitrile and monofluorobenzonitriles by means of halogen-exchange fluorination. *J Fluorine Chem* 1991;52:341-351.
15. Kim DW, Jeong HJ, Lim ST, Sohn MH. Tetrabutylammonium tetra(tert-butyl alcohol)-coordinated fluoride as a facile fluoride source. *Angew Chem Int Ed Engl.* 2008;47:8404–8406.