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DIMETHYLSULFONIUM SALTS AS SUBSTRATES IN AROMATIC NUCLEOPHILIC SUBSTITUTION WITH FLUORIDE IONS

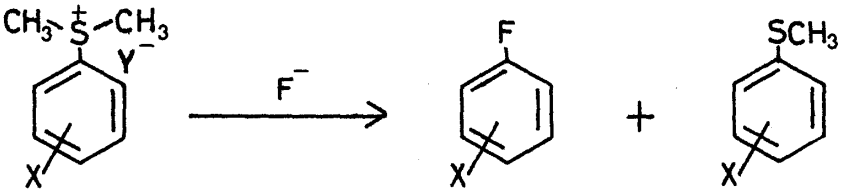
Minoru Maeda,* Toshimitsu Fukumura, and Masaharu Kojima
Faculty of Pharmaceutical Sciences, Kyushu University,
Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan

Phenyldimethylsulfonium salts activated by electron-withdrawing substituents undergo nucleophilic substitution with fluoride ion to give aryl fluorides.

KEYWORDS ——— fluorination; nucleophilic displacement; activated aromatic dimethylsulfonium; fluoride

Aromatic fluorination still commands the attention of synthetic organic chemists, in spite of several methods available, owing to recent interest in the synthesis of ^{18}F-labeled radiopharmaceuticals and their growing applications. Attention has been focused on leaving groups attached to aromatic rings in displacement reactions with fluoride ion, which, in principle, has the specially synthetic potential for producing ^{18}F-labeled aryl fluorides with high specific activity. Recent works involve the Wallach triazene reaction[1) and the nucleophilic displacement of activated halogeno- or nitro-aromatics.[2) However, there is still a need for developing new and fast reactions for the preparation of ^{18}F-labeled aromatics. The leaving group efficiency in the nucleophilic displacement of activated aromatic compounds increases in the order $Cl < NO_2 \simeq F < Me_3N^+ < Me_2S^+$, as evidenced by kinetic studies.[3) The first example involving aromatic displacement of a trimethylammonium group by fluoride ion has been reported by Horwitz _et al._,[4) and more recently the utility of this group as a leaving group in ^{18}F-labeling has been also reported.[5) We now wish to report the first nucleophilic displacement of activated aromatic dimethylsulfonium groups by fluoride ion.

_p_-Nitrophenyldimethylsulfonium methylsulfate (**1**) reacted with two molar equivalents of fluoride ion to afford _p_-fluoronitrobenzene (**2**) in 48-72% yield with the thioether (**3**), depending on the fluorinating agents and solvents used (Table I). The reaction was complete in only 10 min at 100°C in dry dimethyl sulfoxide (DMSO) or N,N-dimethylformamide (DMF), giving more than 50% yield of the fluoro compound (**2**). Higher temperature leading to the more rapid reaction disfavored the formation of the fluoro compound because of the increased loss of the methyl function. Other dipolar aprotic solvents such as acetonitrile, hexamethylphosphoric triamide (HMPA) and propylene carbonate were not so useful. When dry cesium fluoride in DMSO or DMF was replaced by tetra-_n_-butylammonium fluoride (TBAF) trihydrate, the yield of **2** was unchanged and the demethylation process was considerably suppressed;[6) the use of TBAF dried _in vacuo_[7) in the place of its trihydrate had no



(1) X = *p*-NO$_2$ Y = CH$_3$SO$_4$ (2) X = *p*-NO$_2$ (3) X = *p*-NO$_2$
(4) X = *p*-NO$_2$ Y = ClO$_4$
(5) X = *o*-NO$_2$ Y = CH$_3$SO$_4$ (6) X = *o*-NO$_2$ (7) X = *o*-NO$_2$
(8) X = *p*-CN Y = CH$_3$SO$_4$ (9) X = *p*-CN (10) X = *p*-CN
(11) X = *p*-COCH$_3$ Y = CH$_3$SO$_4$ (12) X = *p*-COCH$_3$ (13) X = *p*-COCH$_3$
(14) X = *p*-CH$_3$ Y = ClO$_4$ (15) X = *p*-CH$_3$

Table I. Fluorination of Activated Aromatic Sulfonium Salts by Fluoride Ion

Substrate[a]	Fluorinating agent	Solvent	Products[b] (% yield)	
(1)	CsF	DMSO	(2) (66)	(3) (20)
	RbF	DMSO	(2) (51)	(3) (34)
	TBAF[c]	DMSO	(2) (66)	(3) (6)
	TBAF[c]	CH$_3$CN	(2) (48)	(3) (22)
	CsF	DMF	(2) (72)	(3) (19)
	TBAF[c]	DMF	(2) (69)	(3) (3)
(4)	CsF	DMSO	(2) (51)	(3) (37)
(5)	CsF	DMSO	(6) (47)	(7) (21)
	TBAF[c]	DMSO	(6) (34)	(7) (25)
	CsF	DMF	(6) (56)	(7) (25)
(8)	CsF	DMSO	(9) (32)	(10) (61)
	TBAF[c]	DMF	(9) (41)	(10) (54)
	CsF	DMF	(9) (26)	(10) (65)
(11)	CsF	DMSO	(12) (2)	(13) (46)
	CsF	DMF	(12) (3)	(13) (51)
(14)	CsF	DMSO		(15) (66)

a) Reactions were carried out at 100°C for 10 min with a substrate concentration of 6.3×10^{-2}M. b) Yields were measured by HPLC. The identity of the products was established by comparing their retention volumes or the ^{1}H-NMR spectra with authentic samples. c) Commercial tetra-*n*-butylammonium fluoride trihydrate was used without drying.

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significant effect on the reaction. Addition of three molar equivalents of water to a dry cesium fluoride-DMF system, however, resulted in the markedly decreased formation of **2** (30%). The use of perchlorate instead of methylsulfate as the counter ion did not have much influence on the yield of **2**.

Similar treatment of the *o*-nitro and *p*-cyano substituted compounds (**5** and **8**) gave a 26-56% yield of the corresponding fluoro compound. On the other hand, the demethylation process was the predominant reaction on treatment of the *p*-acetyl compound (**11**) and only a poor yield (*ca*. 2%) of the corresponding fluoro compound was obtained. When *p*-methylphenyldimethylsulfonium (**14**) was utilized as the substrate, the displacement was completely suppressed. The result shows that the nucleophilic displacement of the dimethylsulfonium group by fluoride ions depends strongly on the activating substituent on an aromatic ring and increases in the order consistent with the well-known electron-withdrawing power. The sulfonium salt itself underwent demethylation to give the thioether in almost 50% yield when simply heated in dry DMSO or DMF at 100°C for 10 min.8) Therefore, adding the sulfonium compound to a solution of the fluorinating agent in a desired solvent was required for the success of the displacement of dimethylsulfonium group by fluoride ions. This new fluorination provides an alternative method for preparing nitro- and cyano-substituted fluoro-aromatics. It is advantageous because of the rapidity of its reaction under relatively mild conditions, and because TBAF trihydrate as a fluorinating agent can be used without drying.

It has been reported that, in aromatic dimethylsulfonium compounds, nucleophiles such as iodide and thiocyanate attack the methyl group, whereas hydroxide and methoxide ions displace the sulfonium groups.9) Similar treatment of **1** with other halide anions (potassium iodide, sodium bromide or potassium chloride) under the same conditions gave the thioether (**3**) in nearly quantitative yield, suggesting that only a strong hard ion causes the direct displacement of the sulfonium group.

This particular leaving group of dimethylsulfonium moiety in activated aromatics may be applied also to the radiosynthesis of aromatic precursors for ^{18}F-labeled radiopharmaceuticals, although separation of the undesired thioether from the reaction mixture is necessary.

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