Heterocycles, Vol. 60, No. 1, 2003, pp. 15 - 22
Received, 7th October, 2002, Accepted, 18th November, 2002, Published online, 25th November, 2002

ELECTROLYTIC PARTIAL FLUORINATION OF ORGANIC COMPOUNDS. 66. ANODIC FLUORINATION OF (THIAZOL-2-YL)ACETONITRILES[1]

Sayed M. Riyadh and Toshio Fuchigami*

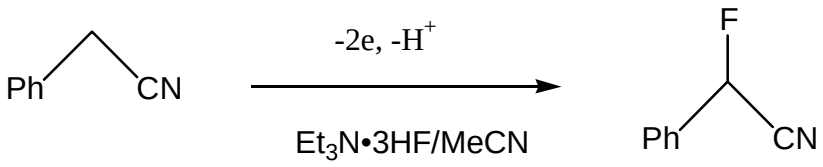
Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226-8502 Japan
Tel./Fax +81-45-924-5406; E-mail: fuchi@echem.titech.ac.jp

Abstract- Electrochemical partial fluorination of (4-arylthiazol-2-yl)acetonitriles was carried out to afford the corresponding (4-aryl-5-fluoro-5*H*-thiazol-2-ylidene)acetonitriles as main products in addition to (4-aryl-5-fluorothiazol-2-yl)acetonitriles and (4-arylthiazol-2-yl)fluoroacetonitriles. AM1 calculations were conducted to compare the stability of the fluorinated products.

An increasing interest has recently been paid to the chemistry of various fluorine-containing heterocycles due to their unique physical properties, specific chemical reactivities, and their remarkable biological activities.[2] In fact, many selectively fluorinated analogues of biologically important compounds have exhibited dramatic enhancement in their biological activity.[3] Recently, electrochemical fluorination methodology has been established as a unique and useful tool for selective direct fluorination of organic molecules.[4,5] Nevertheless, very few examples of anodic partial fluorination of heterocyclic compounds have been reported to date, however, the yields and/or selectivities are generally quite low.[6-11]

Previously, it was found that anodic fluorination of 2-thiazolyl sulfides gave *gem*-difluorothiazoline derivatives while cyanomethyl 2-thiazolyl sulfide afforded cyanofluoromethyl 2-thiazolyl sulfide owing to the strongly electron-withdrawing effect of the cyano group.[12] In this work, we explored the anodic fluorination of (thiazol-2-yl)acetonitriles devoid of a sulfur atom. Incidentally, Leaurent and his co-workers reported that anodic fluorination of phenylacetonitrile afforded 40% yield of α-fluorophenylacetonitrile.[13] In this reaction, a fluorine atom was introduced to the α-position to the electron-withdrawing cyano group as shown in Scheme 1.

We expected that cyanomethylheteroaromatics may be anodically fluorinated in a similar manner. With these facts in mind, in this work, we attempted the anodic fluorination of (4-arylthiazol-2-yl)acetonitriles devoid of a sulfur atom.

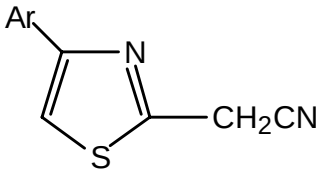


(40%)

Scheme 1

The oxidation potentials E_p^{ox} of (4-arylthiazol-2-yl)acetonitriles (**1~5**)[14] were measured by cyclic voltammetry in a divided cell with a Pt anode in 0.1 M $Bu_4N•BF_4$/anhydrous acetonitrile using SCE as a reference electrode. These (4-arylthiazol-2-yl)acetonitriles exhibited irreversible oxidation peaks (E_p^{ox}), which are listed in Table 1.

Table 1. Oxidation Potentials (E_p^{ox}) of (4-Arylthiazol-2-yl)acetonitriles (1~5)



1~5 Ar = 4-XC_6H_4

No.	X	E_p^{ox} (V *vs* SCE)[a]
1	H	1.94
2	Cl	2.05
3	CN	2.2
4	NO_2	2.3
5	MeO	1.9

[a] Substrate (0.01 M) in 0.1 M $Bu_4N•BF_4$/ MeCN; Sweep rate 100 mv/s.

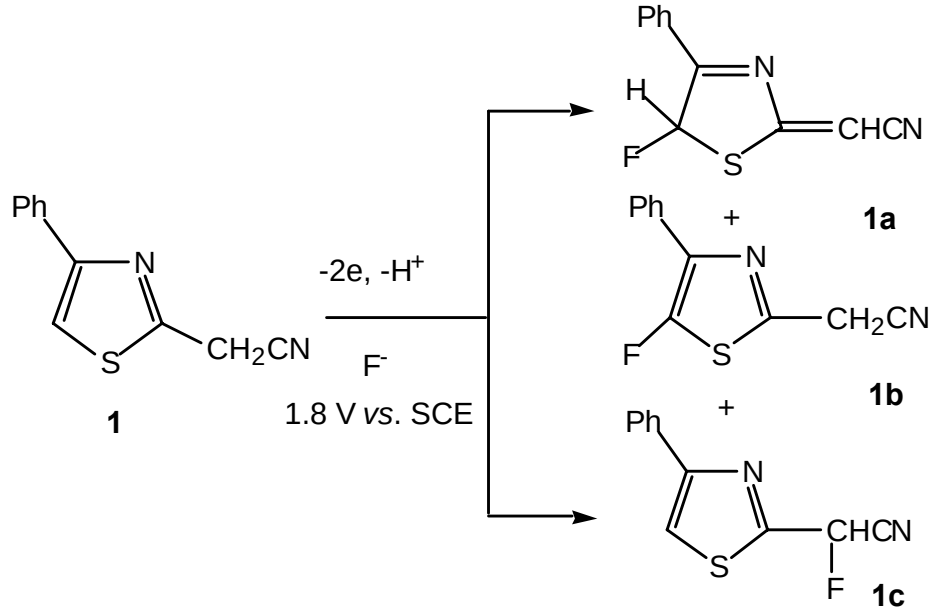
Typical anodic fluorination conditions are as follows: Electrolysis was conducted under controlled potential using a platinum anode and cathode (3 x 3 cm^2) in 0.3 M solution of a fluoride salt in dimethoxyethane (30 mL) containing (4-arylthiazol-2-yl)acetonitriles (**1~5**) (1 mmol) by using an H-type divided cell with a glass diaphragm under a nitrogen atmosphere at ambient temperature. After the electrolysis, the resulting electrolytic solution was passed through a short column of silica gel using ethyl acetate as an eluent. The collected solution was evaporated under vacuum. Then, the yield of the

fluorinated product was calculated by means of ^{19}F NMR by using a known amount of monofluorobenzene as an internal standard. The yield was calculated on the basis of the integral ratio between the monofluorobenzene and the fluorinated product. After that, the fluorinated product was isolated by column chromatography on silica gel using a hexane/ethyl acetate eluent (5:1).

At first, anodic fluorination of (4-phenylthiazol-2-yl)acetonitrile (**1**) as a model compound was examined. The electrolytic results are summarized in Table 2.

Unlike the case of phenylacetonitrile,[24] the fluorination took place regioselectively at the 5-position of the

Table 2. Anodic Fluorination of (4-Phenylthiazol-2-yl)acetonitrile 1



Run	Supporting Electrolyte	Solvent	Cell[a]	F/mol	Yield (%)[b]		
					1a	**1b**	**1c**
1	$Et_4NF•4HF$	DME	UD	6[c]	12	3	2
2	$Et_4NF•4HF$	DME	D	6	22	2	2
3	$Et_4NF•4HF$	DME	D	8	31	2	2
4	$Et_4NF•4HF$	DME	D	10	41	3	3
5	$Et_4NF•5HF$	DME	D	10	45(42)	2	2
6	$Et_4NF•5HF$	DME	UD	10	20	2	2
7	$Et_4NF•5HF$	MeCN	D	10	8	2	2

[a] D = divided cell, UD = undivided cell.

[b] Determined on the basis of ^{19}F NMR; isolated yield is shown in parenthesis.

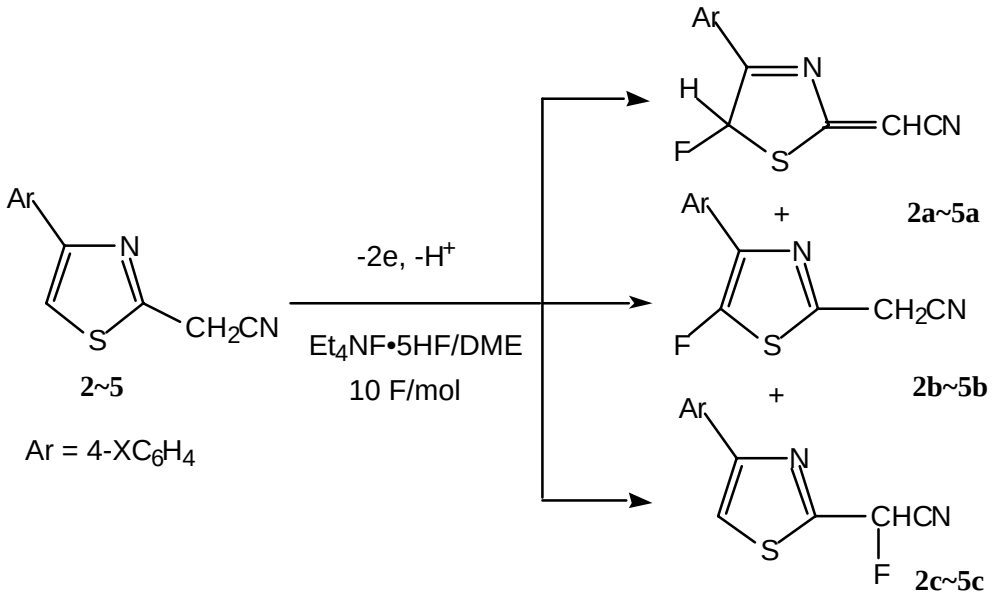
[c] Under constant current.

thiazole ring to afford (5-fluoro-4-phenyl-5*H*-thiazol-2-ylidene)acetonitrile (**1a**) as a main product and two isomeric fluorinated products, (5-fluoro-4-phenylthiazol-2-yl)acetonitrile (**1b**) and fluoro(4-phenylthiazol-2-yl)acetonitrile (**1c**) as minor products regardless of electrolytic conditions.

When the electrolysis was conducted at constant current, the overall fluorinated yield was significantly low (Run 1). On the other hand, constant potential electrolysis (1.8 V *vs* SCE) improved the fluorination yield. The yield was increased with an increase of the charge passed till 10 F/mol (Runs 2-4). $Et_4NF•5HF$ was found to be the best choice for the electrochemical fluorination of (4-phenylthiazol-2-yl)acetonitrile (**1**) (Run 5). The overall fluorination yield decreased significantly when an undivided cell (Run 6) or acetonitrile (Run 7) was used. It is quite interesting that nonaromatic **1a** was isolated as a major product while its aromatic tautomer (**1b**) was minor.

Next, anodic fluorination of various (4-arylthiazol-2-yl)acetonitriles (**2~5**) was attempted by constant potential electrolysis. The fluorination proceeded smoothly to afford three kinds of fluorinated products

Table 3. Anodic Fluorination of (4-Arylthiazol-2-yl)acetonitriles (2~5)



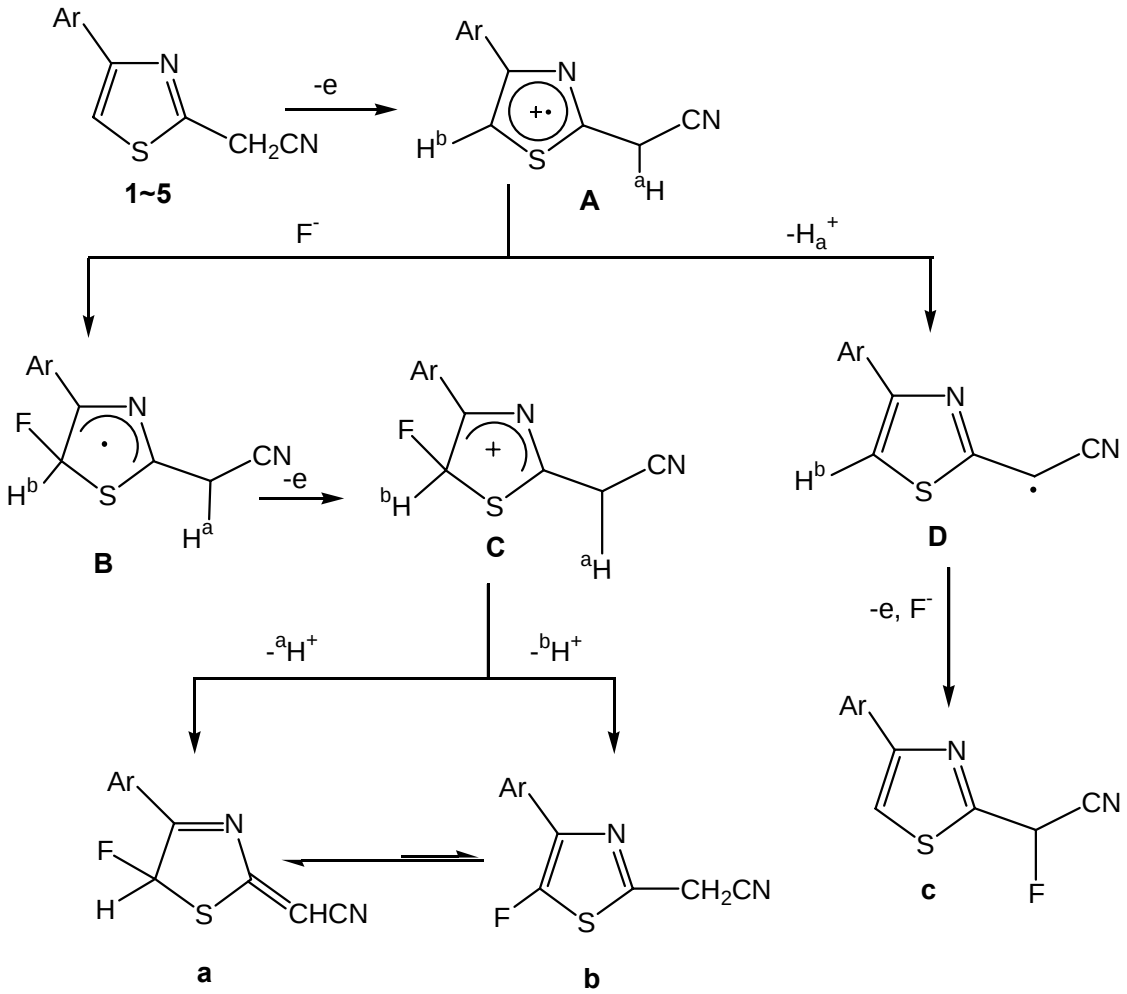
Run	Compound No.	X	Applied Potential V *vs*. SCE	Yield (%)[a]		
				a	**b**	**c**
1	**1**	H	1.8	45 (42)	2	2
2	**2**	Cl	1.9	42(37)	3	3
3	**3**	CN	2.1	40(35)	5	8(6)
4	**4**	NO_2	2.2	38(33)	8(6)	12(10)
5	**5**	MeO	1.85	48(33)	-	-

[a] Determined on the basis of ^{19}F NMR; isolated yields are shown in parentheses.

as shown in Table 3.

The product selectivity was appreciably affected by the substituents on the phenyl ring at the 4-position. For example, incorporation of an electron-withdrawing group to the *para*-position of the phenyl ring considerably increased the formation of both (4-aryl-5-fluorothiazol-2-yl)acetonitriles (**2b~4b**) and α-side-chain fluorinated products (**2c~4c**) (Runs 2-4). This may be due to increase in the acidic character of cyanomethyl protons and a thiazole ring proton. On the other hand, incorporation of an electron-donating group led to the exclusive formation of [5-fluoro-4-(4-methoxyphenyl)-5*H*-thiazol-2-ylidene]acetonitrile (**5a**) (Run 5), which seems to be due to decrease in the acidic character of cyanomethyl protons and the thiazole ring proton.

A possible reaction mechanism for anodic fluorination of (4-arylthiazol-2-yl)acetonitriles (**1~5**) is depicted in Scheme 2.



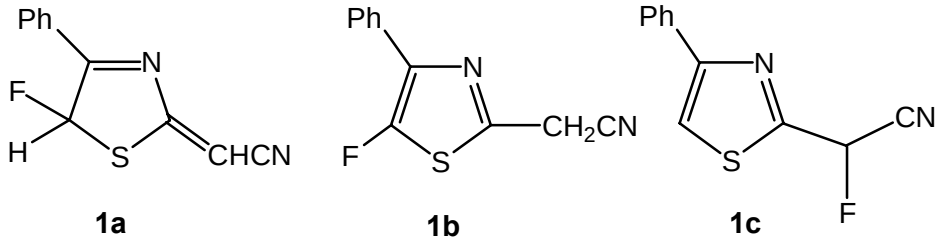
Scheme 2

The one-electron oxidation takes place from the thiazole ring to generate the radical cation (**A**), which reacts with a fluoride ion at the position α to the sulfur atom to generate radical (**B**). Further one-electron

oxidation of **B** forms the cationic intermediate (**C**). Deprotonation of a cyanomethyl group (H_a) produces (5-fluoro-5*H*-thiazol-2-ylidene)acetonitriles (**a**) as major products. On the other hand, elimination of the α–proton (H_b) to the sulfur atom affords (5-fluorothiazol-2-yl)acetonitriles (**b**) as minor products.

Moreover, deprotonation of the cyanomethyl group (H_a) of the radical cation (**A**) generates the corresponding radical (**D**) followed by further oxidation and successive reaction with a fluoride ion to afford the corresponding fluoro(thiazol-2-yl)acetonitriles (**c**) as minor products. Regardless of the substituents on the phenyl ring of (4-arylthiazol-2-yl)acetonitriles, (**1a**~**5a**) were formed as major products.

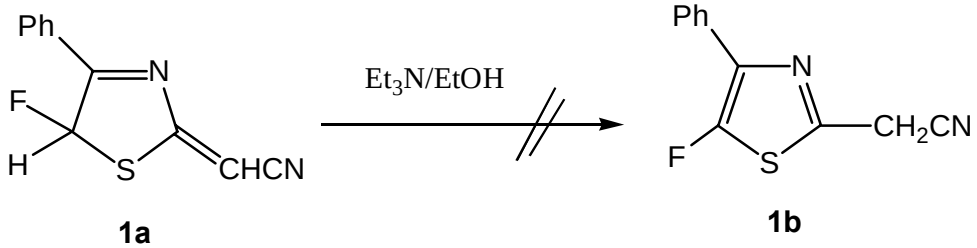
In order to compare the stability of **1a**~**5a**[15] with **1b**~**5b**[16] and **1c**~**5c**,[17] the heat of formation (ΔH_f) of (**1a**~**1c**) as the model compounds was calculated. The calculations were carried out with the MOPAC 2000 program using AM1. As shown in Figure 1, **1a** was found to be thermodynamically most stable although **1a** is not aromatic.



	1a	1b	1c
Heat of Formation (ΔH_f) (kcal/mol)	-63.64	-53.93	-53.32

Figure 1

Moreover, treatment of **1a** with Et_3N in ethanol at room temperature resulted in no formation of **1b** (Scheme 3). These facts clearly suggest that the tautomeric equilibrium between **a** and **b** must be much more favorable toward the tautomers **a** with an *exo* double bond. Since the non-fluorinated starting material (**1**) does not have a tautomer corresponding to **1a**, a fluorine atom should affect the stability of both **1a** and **1b**. However, the reason is not clear at present.



Scheme 3

Recently, we found the similar results in the anodic fluorination of 3-benzylchromone: (*E*)-3-benzylidene-2,3-dihydro-2-fluorochroman-4-one was formed solely and the corresponding aromatic 2-fluorochromone was not formed.[29]

In summary, novel electrochemical fluorination of (4-arylthiazol-2-yl)acetonitriles (**1~5**) has been established, and (5-fluoro-5*H*-thiazol-2-ylidene)acetonitriles were mainly obtained instead of (5-fluorothiazol-2-ly)acetonitriles. AM1 calculation disclosed that the former non aromatic products were thermodynamically more stable than the latter aromatic ones.

ACKNOWLEDGEMENT

This work was financially supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We are grateful to Morita Chemical Industries Co., Ltd., for generous gifts of fluoride salts. We also thank Dr. H. Ishii for his valuable suggestions.

REFERENCES AND NOTES

1. Part 65: S. M. Riyadh, H. Ishii, and T. Fuchigami, *Tetrahedron*, in press.
2. (a) K. Burger, U. Wucherpfennig, and E. Brunner, *Adv. Heterocycl. Chem*., 1994, **60**, 1. (b) *Biomedicinal Aspects of Fluorine Chemistry*, ed. by R. Filler and Y. Kobayashi, Kodansha, Tokyo, 1982.
3. J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, USA, 1991.
4. (a) T. Fuchigami, In *Organic Electrochemistry*, 4th ed.; ed.by H. Lund and O. Hammerich, Dekker, New York, 2001, pp. 1035-1050. (b) T. Fuchigami, In *Advances in Electron-Transfer Chemistry*; ed. By P. S. Mariano, JAI Press, CT, 1999, pp. 41-130. (c) T. Fuchigami, Y. Hou, and K. M. Dawood, *Rev. Heteroatom Chem*., 1999, **19**, 67.
5. M. Noel, V. Suryanarayanan, and S. Chellammal, *J. Fluorine Chem*., 1997, **83**, 31.
6. K. Makino and H. Yoshioka, *J. Fluorine Chem*., 1988, **39**, 435.
7. J. R. Ballinger and F. W. Teare, *Elctrochim. Acta*, 1985, **30**, 1075.
8. G. P. Gambaretto, M. Napoli, C. Franccaro, and L. Conte, *J. Fluorine Chem.*, 1982, **19**, 427.
9. J. H. Meurs and W. Eilenberg, *Tetrahedron*, 1991, **47**, 705.
10. M. Sono, N. Morita, Y. Shizuri, and M. Tori, *Tetrahedron Lett.*, 1994, **35**, 9237.
11. A. Konno, M. Shimojo, and T. Fuchigami, *J. Fluorine Chem*., 1998, **87**, 137.
12. S. M. Riyadh and T. Fuchigami, *J. Org. Chem*., in press.
13. E. Laurent, B. Marquet, and R. Tardivel, *Tetrahedron*, 1989, **45**, 4431.

14. V. H. Schaefer and K. Gewald, *J. Prakt. Chemie*., 1974, **316**, 684.

15. **1a**: oil. ^{1}H NMR δ 5.42 (d, 1 H, *J* = 6 Hz), 7.54 (d, 1 H, *J* = 58 Hz), 7.41-7.67 (m, 3 H), 8.18 (m, 2 H). ^{19}F NMR δ –59.7 (dd, *J* = 58, 6 Hz). MS *m/z*, 218 (M^+). Anal. Calcd for $C_{11}H_7N_2FS$: C, 60.53; H, 3.23; N, 12.84; S, 14.69. Found: C, 60.38; H, 3.51; N, 12.62; S, 14.54. **2a**: oil. ^{1}H NMR δ 6.12 (d, 1 H, *J* = 6 Hz), 7.28 (d, 1 H, *J* = 57 Hz), 7.72 (d, 2 H, *J* = 8 Hz), 8.09 (d, 2 H, *J* = 8 Hz). ^{19}F NMR δ –61.7 (dd, *J* = 57, 6 Hz). MS *m/z*, 252 (M^+). Anal. Calcd for $C_{11}H_6N_2ClFS$: C, 52.28; H, 2.39; N, 11.09; S, 12.69. Found: C, 52.53; H, 2.67; N, 10.89; S, 12.57. **3a**: mp 42 ^{o}C. ^{1}H NMR δ 6.12 (d, 1 H, *J* = 6 Hz), 7.38 (d, 1 H, *J* = 57 Hz), 7.85 (d, 2 H, *J* = 8 Hz), 8.21 (d, 2 H, *J* = 8 Hz). ^{19}F NMR δ –62.7 (dd, *J* = 57, 6 Hz). MS *m/z*, 243 (M^+). Anal. Calcd for $C_{12}H_6N_3FS$: C, 59.25; H, 2.49; N, 17.27; S, 13.18. Found: C, 59.34; H, 2.72; N, 16.98; S, 12.83. **4a**: oil. ^{1}H NMR δ 6.22 (d, 1 H, *J* = 6 Hz), 7.48 (d, 1 H, *J* = 57 Hz), 7.94 (d, 2 H, *J* = 9 Hz), 8.29 (d, 2 H, *J* = 9 Hz). ^{19}F NMR δ –63.5 (dd, *J* = 57, 6 Hz). MS *m/z*, 263 (M^+). Anal. Calcd for $C_{11}H_6N_3O_2FS$: C, 50.19; H, 2.30; N, 15.96; S, 12.18. Found: C, 50.31; H, 2.48; N, 15.72; S, 11.98. **5a**: oil. ^{1}H NMR δ 5.97 (d, 1 H, *J* = 6 Hz), 7.09 (d, 1 H, *J* = 57 Hz), 7.71 (d, 2 H, *J* = 8 Hz), 8.11 (d, 2 H, *J* = 8 Hz). ^{19}F NMR δ –61.7 (dd, *J* = 57, 6 Hz). MS *m/z*, 248 (M^+). Anal. Calcd for $C_{12}H_9N_2OFS$: C, 58.05; H, 3.65; N, 11.28; S, 12.92. Found: C, 58.29; H, 3.81; N, 11.19; S, 12.77.

16. **1b**: ^{19}F NMR δ –68.14 (s). **2b**: ^{19}F NMR δ –68.21 (s). **3b**: mp 45 ^{o}C. ^{1}H NMR δ 4.31 (s, 2 H), 7.72 (d, 2 H, *J* = 8 Hz), 8.11 (d, 2 H, *J* = 8 Hz). ^{19}F NMR δ –63.86 (s). MS *m/z*, 243 (M^+). Anal. Calcd for $C_{12}H_6N_3FS$: C, 59.25; H, 2.49; N, 17.27; S, 13.18. Found: C, 59.34; H, 2.62; N, 16.98; S, 12.88. **4b:** oil. ^{1}H NMR δ 4.08 (s, 2 H), 8.09 (d, 2 H, *J* = 9 Hz), 8.29 (d, 2 H, *J* = 9 Hz). ^{19}F NMR δ –63.8 (s). MS *m/z*, 263 (M^+). Anal. Calcd for $C_{11}H_6N_3O_2FS$: C, 50.19; H, 2.30; N, 15.96; S, 12.18. Found: C, 49.86; H, 2.11; N, 15.76; S, 12.03.

17. **1c**: ^{19}F NMR δ –92.37 (d, *J* = 54 Hz). **2c**: ^{19}F NMR δ –92.95 (d, *J* = 54 Hz). **3c**: mp 50 ^{o}C. ^{1}H NMR δ 6.53 (d, 1 H, *J* = 54 Hz), 7.36 (d, 2 H, *J* = 8 Hz), 7.61 (s, 1 H), 8.27 (d, 2 H, *J* = 8 Hz). ^{19}F NMR δ –94.52 (d, *J* = 54 Hz). MS *m/z*, 243 (M^+). Anal. Calcd for $C_{12}H_6N_3FS$: C, 59.25; H, 2.49; N, 17.27; S, 13.18. Found: C, 59.17; H, 2.32; N, 16.98; S, 12.94. **4c**: oil. ^{1}H NMR δ 6.35 (d, 1 H, *J* = 54 Hz), 7.48 (d, 2 H, *J* = 9 Hz), 7.94 (s, 1 H), 8.39 (d, 2 H, *J* = 9 Hz). ^{19}F NMR δ –94.81 (d, *J* = 54 Hz). MS *m/z*, 263 (M^+). Anal. Calcd for $C_{11}H_6N_3O_2FS$: C, 50.19; H, 2.30; N, 15.96; S, 12.18. Found: C, 49.94; H, 2.18; N, 15.69; S, 11.94.

18. K. M. Dawood and T. Fuchigami, *J. Org. Chem*., 2001, **66**, 7691.