Pergamon

TETRAHEDRON

Tetrahedron 57 (2001) 8817–8821

Electrolytic partial fluorination of organic compounds. Part 57: Regioselective anodic monofluorination of nitrogen-containing heterocyclic propargyl sulfides☆

Sayed M. Riyadh, Hideki Ishii and Toshio Fuchigami*

Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Miduri-Ku, Yokohama 226-8502, Japan

Received 18 July 2001; accepted 27 August 2001

Abstract—Anodic fluorination of various nitrogen-containing heterocyclic propargyl sulfides using $Et_4NF\cdot nHF$ (n=3,4) or $Et_3N\cdot 3HF$ as a supporting electrolyte and fluoride ion source in dimethoxyethane provided the corresponding monofluorinated products in moderate yields. Fluorination took place selectively at the position α to the sulfur atom of the sulfides and the heterocyclic moieties were not fluorinated at all.

1. Introduction

Pyridyl propargyl sulfides are effective antifungal agents and have been found to be surprisingly effective in protecting finished paint from mildew attack for an extended period.[2] Benzothiazolyl propargyl sulfides are useful as potent antagonists of the Bradykinin B-2 receptors[3] as well as antitumor[4] and antiprofilative.[5] They are also well-known to exhibit antimicrobial activity.[6] Many potent clinical important antitumor drugs having a quinoline moiety have been discovered.[7] A large number of quinoline derivatives are involved in manufacturing a wide variety of medicines and pharmaceuticals.

On the other hand, the development of highly efficient and selective synthetic methods of organofluorine compounds continues to be of crucial importance in the field of medicinal and agricultural chemistries due to their unique and pronounced biological properties.[8] The relationships between molecular structures and biological activities suggest that introduction of fluorine atom(s) into an aromatic ring or its side-chain may have a great enhancement or change of biological activities. However, conventional chemical fluorination processes are not always easy to undertake and very often require hazardous reagents.[9]

On the other hand, anodic fluorination has been proved to be more convenient access to accomplish such objects.[10] Previously, we found that electron-withdrawing groups markedly promoted anodic α-fluorination of sulfides.[11] Since an acetylenic group has also an electron-withdrawing effect, it was expected that heterocyclic sulfides having an α-acetylenic group would be anodically fluorinated.

With these facts in mind, we have comparatively studied anodic fluorination of nitrogen-containing heterocyclic propargyl sulfides such as 2-pyridyl, 4-pyridyl, 2-pyrimidyl, 2-quinolyl, 2-benzothiazolyl, and 2-(5-chlorobenzothiazolyl) propargyl sulfides **1–6** in dimethoxyethane (DME) and acetonitrile (MeCN) containing various fluoride salts. It was found that such nitrogen-containing heterocyclic propargyl sulfides gave the corresponding α-fluorinated products selectively where the fluorine atom was regioselectively introduced into the position α to the sulfur atom. Fluorination at the acetylenic group or heterocyclic ring did not take place at all.

2. Results and discussion

2.1. Preparation of heterocyclic sulfides

The reaction of appropriate heterocyclic thiols with propargyl bromide in the presence of K_2CO_3 or NaOH afforded the corresponding heterocyclic propargyl sulfides **1–6** in good yields as shown in Scheme 1.

2.2. Oxidation potentials of heterocyclic propargyl sulfides

In order to investigate the effect of heterocyclic rings on the oxidation potentials of sulfides, the anodic peak potentials of heterocyclic propargyl sulfides **1–6** were measured by

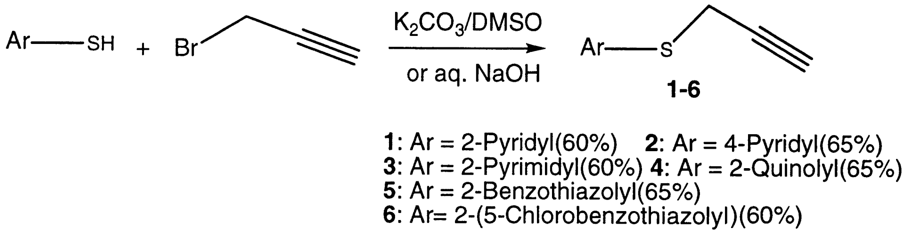
---

☆ See Ref. 1.

Keywords: selective fluorination; electrochemical fluorination; α-fluoro heterocyclic sulfide.

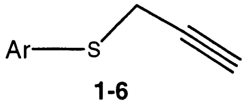
* Corresponding author. Tel./fax: +81-45-924-5406;
e-mail: fuchi@echem.titech.ac.jp

0040–4020/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(01)00866-3



Scheme 1.

Table 1. Oxidation potentials (peak potentials, E_p^{ox}) of heterocyclic propargyl sulfides **1–6**



1-6

Sulfides		E_p^{ox} (V vs SSCE)
No.	Ar	
1	2-Pyridyl	1.92
2	4-Pyridyl	1.90
3	2-Pyrimidyl	2.2
4	2-Quinolyl	1.92
5	2-Benzothiazolyl	1.95
6	2-(5-Chlorobenzothiazolyl)	2.04
–	Methyl 2-pyridyl sulfide	1.74

Substrate (1 mmol) in 0.1 M $Bu_4N{\cdot}BF_4$/MeCN. Sweep rate: 100·V/s.

cyclic voltammetry in an anhydrous acetonitrile solution containing Bu_4NBF_4 (0.1 M) using platinum electrodes and SSCE as a reference electrode. All these sulfides showed irreversible oxidation peaks, the first oxidation peak potentials E_p^{ox} of the heterocyclic propargyl sulfides **1–6** are summarized in Table 1.

Pyridyl propargyl sulfides **1**,**2** and 2-quinolyl propargyl sulfide **4** showed almost the same oxidation potentials. The oxidation potential of propargyl 2-pyrimidyl sulfide **3** was higher than those of **1**,**2** and **4** due to the effect of two electron-withdrawing nitrogen atoms in the pyrimidyl ring. 2-(5-Chlorobenzothiazolyl) propargyl sulfide **6** has a more positive oxidation potential compared with unsubstituted 2-benzothiazolyl propargyl sulfide **5** due to the electron-withdrawing effect of a chlorine atom. The oxidation potential of sulfide **1** is much higher than that of 2-pyridyl methyl sulfide in spite of no α-electron-withdrawing group in **1**. This may suggest that the electron-transfer would take place at the sulfur atom of heterocyclic sulfides.

2.3. Anodic monofluorination of heterocyclic propargyl sulfides

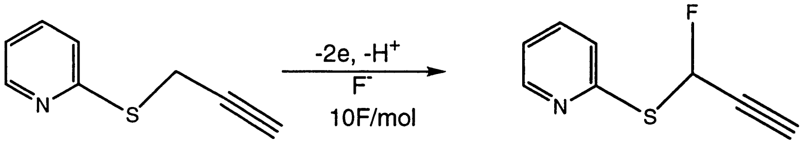
Firstly, the anodic fluorination of 2-pyridyl propargyl sulfide **1** as a model compound was investigated under various electrolytic conditions. The results are summarized in Table 2.

As shown in Table 2, anodic fluorination of **1** proceeded to give the corresponding α-monofluorinated product **7** in a moderate yield. $Et_3N{\cdot}3HF$/DME was found to be suitable as a fluoride salt/electrolytic solvent system (run 4). In our previous work, acetonitrile was suitable for anodic fluorination of 2-pyridyl sulfides having various electron-withdrawing group.[12] However, acetonitrile was not effective for the anodic fluorination of 2-pyridyl propargyl sulfide (run 1).

It is known that anodic fluorination of pyridine takes place at the pyridine ring.[13] We also found anodic fluorination at the pyridine ring of isonicotinic acid ester.[14] Therefore, it should be noted that fluorination took place exclusively at the α-position to the sulfur atom of simple 2-pyridyl propargyl sulfide **1**.

Next, we extended the anodic fluorination to other heterocyclic propargyl sulfides **2–4** using $Et_3N{\cdot}3HF$/DME. As shown in Table 3, the anodic fluorination proceeded regardless of the nature of heterocyclic rings. Anodic fluorination of 4-pyridyl propargyl sulfide **2** proceeded smoothly in a manner similar to the 2-pyridyl analogue and gave almost same yield of α-monofluorinated product **8**. As, 2-pyrimidyl

Table 2. Anodic monofluorination of 2-pyridyl propargyl sulfide **1** under various electrolytic conditions

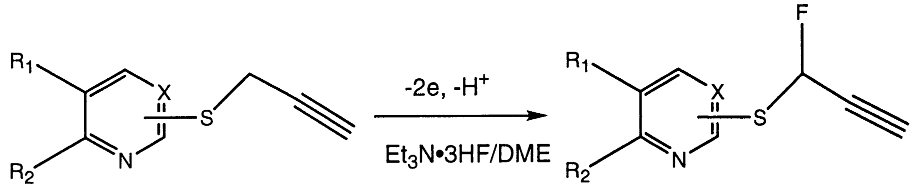


1 **7**

Run	Supporting electrolyte	Solvent	Yield[a] (%)
1	$Et_4NF{\cdot}4HF$	MeCN	15
2	$Et_4NF{\cdot}4HF$	DME	35
3	$Et_4NF{\cdot}3HF$	DME	40
4	$Et_3N{\cdot}3HF$	DME	55 (50)[b]

[a] Calculated on the basis of ^{19}F NMR.
[b] Isolated yield.

Table 3. Anodic monofluorination of heterocyclic propargyl sulfides **2–4**



2-4 **8-10**

	Sulfides			Charged passed (F/mol)		Yield[a] (%)
	No.	X	R_1,R_2			
4-Pyridyl	(**2**)	CH	H,H	10	**8**	58(55)[b]
2-Pyrimidyl	(**3**)	N	H,H	12	**9**	60(55)[b]
2-Quinolyl	(**4**)	CH	$(CH{=}CH)_2$	12	**10**	35(30)[b,c]

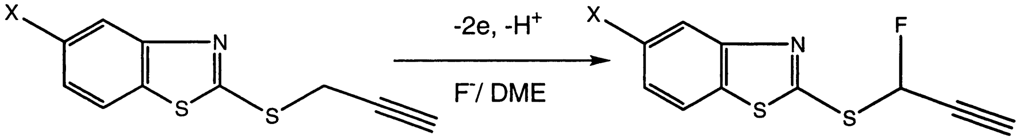
[a] Determined by ^{19}F NMR.
[b] Isolated yield.
[c] A large amount of the starting material **4** was recovered.

propargyl sulfide **3** has a higher oxidation potential compared with the pyridyl analogus **1** and **2**, a larger amount of electricity was required to complete the electrolysis to give the corresponding α-monofluorinated product **9** in moderate yield. In contrast, anodic fluorination of 2-quinolyl propargyl sulfide **4** under the same electrolytic conditions provided much lower yield of the α-monofluorinated product **10**. In this case, a large amount of starting material **4** was recovered.

Moreover, anodic fluorination of 2-benzothiazoly propargyl sulfide **5** was carried out using three kinds of fluoride salts as shown in Table 4. Among the supporting fluoride salts used, $Et_4NF{\cdot}3HF$ gave the best result (run 3). Anodic fluorination of 5-chloroderivative **6** using $Et_4NF{\cdot}3HF$ gave higher fluorination yield than that of **5** (run 4). This substituent effect on the anodic fluorination is similar to the anodic fluorination of 2-benzothiazolyl sulfides having various electron-withdrawing groups such as ester, ketone, and cyano groups.[15]

The high regioselectivity in the anodic fluorination of heterocyclic sulfides **1**–**6** can be explained in terms of the facile elimination of an α-proton of the fluorosulfonium ion intermediate[16] due to a strong electron-withdrawing propargyl group as shown in Scheme 2.

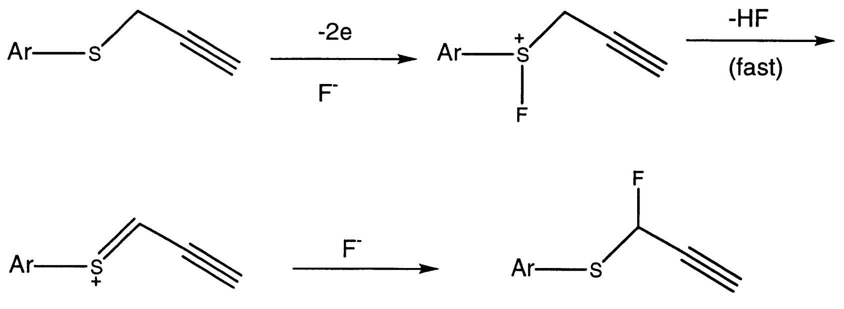
Table 4. Anodic monofluorination of 2-benzothiazolyl and 2-(5-chlorobenzothiazolyl) propargyl sulfides **5**,**6**



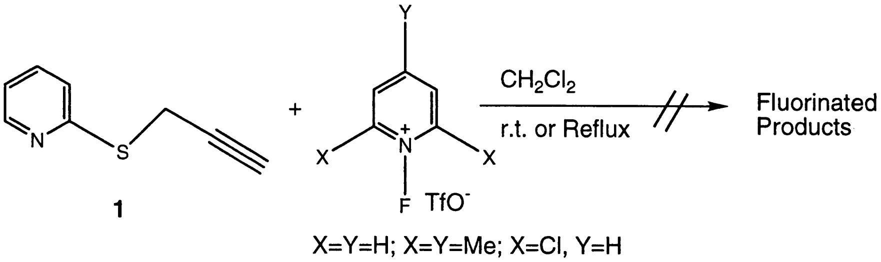
5, 6 **11, 12**

Run	X	Compound no.	Supporting electrolyte	Charged passed (F/mol)	Yield[a] (%)
1	H	**5**	$Et_4NF{\cdot}4HF$	10	7
2	H	**5**	$Et_3N{\cdot}3HF$	10	15
3	H	**5**	$Et_4NF{\cdot}3HF$	10	22(20)[b]
4	Cl	**6**	$Et_4NF{\cdot}3HF$	12	35(30)[b]

[a] Determinated by ^{19}F NMR.
[b] Isolated yield.



Scheme 2.



Scheme 3.

It is well-known that fluorinated sulfides can be prepared from the corresponding sulfides using XeF_2 or DAST. However, the former reagent is costly and the latter one requires the corresponding sulfoxides as the substrate. Recently, *N*-fluoropyridinium triflates and tetrafluoroborate have been shown to be alternative fluorination reagents of activated methylenes and benzenes.[17] However, fluorination of 2-pyridyl sulfide **1** as a model compound with various types of *N*-fluoropyridinium triflates in dichloromethane either at room temperature or under reflux resulted in no formation of the desired fluorinated product (Scheme 3). Therefore, the electrochemical fluorination is more advantageous than the conventional chemical method for such heterocyclic sulfides.

3. Conclusion

In summary, we have successfully carried out anodic monofluorination of nitrogen-containing heterocyclic propargyl sulfides. We have found that this fluorination is greatly affected by the ring system of starting sulfides as well as supporting fluoride salts.

4. Experimental

Caution. $Et_4NF\cdot3HF$ is toxic and if in contact with skin causes serious burn, so proper safety precautions should be taken all the time, it is therefore, recommended to protect hands with rubber gloves.

Materials. 4-Pyridyl propargyl sulfide **2**,[2] 2-benzothiazolyl propargyl sulfide **5**,[3] and 2-(5-chlorobenzothiazolyl) propargyl sulfide **6**[3] were prepared according to the literatures.

4.1. Preparation of propargyl sulfides 1,3

To a stirred solution of 2-mercaptopyridine or 2-mercaptopyrimidine (0.01 mol) in 50 ml of DMSO containing 1.5 g (0.012 mol) of K_2CO_3, was added propargyl bromide (0.01 mol), and the reaction mixture was stirred at room temperature for 2 h. The product was purified by column chromatography on silica gel (hexane/AcOEt=1:1) to provide the desired product.

4.1.1. 2-Pyridyl propargyl sulfide (1). ^{1}H NMR δ 2.2 (t, 1H, J=2.8 Hz), 3.9 (d, 2H, J=2.8 Hz), 7.18 (t, 1H, J=8 Hz), 7.46 (d, 1H, J=7 Hz), 7.52 (t, 1H, J=8 Hz), 8.44 (d, 1H, J=7 Hz). MS *m*/*z* 149 (M^+), 148 (M^+-H). Anal. Calcd for C_8H_7NS: C, 64.39; H, 4.73; N, 9.39. Found: C, 64.31; H, 4.57; N, 9.31.

4.1.2. 2-Pyrimidyl propargyl sulfide (3). ^{1}H NMR δ 2.16 (t, 1H, J=3 Hz), 3.91 (d, 2H, J=3 Hz), 6.98 (t, 1H, J=5 Hz), 8.54 (d, 2H, J=5 Hz). MS *m*/*z* 150 (M^+), 149 (M^+-H). Anal. Calcd for $C_7H_6N_2S$: C, 55.97; H, 4.03; N, 18.65. Found: C, 55.85; H, 4.18; N, 18.43.

4.1.3. Preparation of 2-quinolyl propargyl sulfide (4). To a solution of 2-mercaptoquinoline (0.01 mol) dissolved in 50 ml of 2 M sodium hydroxide solution was added propargyl bromide (0.01 M), the reaction mixture was stirred at room temperature for 2 h. The product was purified by column chromatography on silica gel (eluent: hexane/AcOEt (2:1)) to give the pure product. ^{1}H NMR δ 2.19 (t, 1H, J=2.5 Hz), 4.17 (d, 2H, J=2.5 Hz), 7.25 (d, 1H, J=7 Hz), 7.45 (t, 1H, J=6 Hz), 7.67 (t, 1H, J=8 Hz), 7.73 (d, 1H, J=8 Hz) 7.95 (t, 2H, J=7 Hz). MS *m*/*z* 199 (M^+), 198 (M^+-H). Anal. Calcd for $C_{12}H_9NS$: C, 72.33; H, 4.55; N, 7.03. Found: C, 72.29; H, 4.69; N, 6.97.

4.2. Anodic fluorination of heterocyclic propargyl sulfides

The electrolyses were carried out with platinum plate electrodes (3×3 cm^2) in $Et_4NF\cdot nHF$ (n=3,4) or $Et_3N\cdot3HF$/DME or MeCN (30 ml) containing a sulfide **1–6** (1 mmol) using an undivided cell under nitrogen atmosphere at room temperature. Constant current (5 mA/cm^2) was passed until the starting material **1–6** was consumed (checked by TLC). After the electrolysis, the electrolytic solution was passed through a short column filled with silica gel using AcOEt as an eluent to remove fluoride salts. The eluent was evaporated under reduced pressure, and the residue was further purified by column chromatography on silica gel using an appropriate solvent as the eluent.

4.2.1. α-Fluoro-2-pyridyl propargyl sulfide (7). Eluent: hexane/AcOEt (1: 2). ^{1}H NMR δ 3.02 (dd, 1H, J=2.5, 3 Hz), 7.45 (d, 1H, J=52 Hz), 7.28 (t, 1H, J=8 Hz), 7.56 (d, 1H, J=7 Hz), 7.62 (t, 1H, J=8 Hz), 8.54 (d, 1H, J=7 Hz). ^{19}F NMR δ −67.5 (dd, J=2.5, 52 Hz). MS *m*/*z* 167 (M^+), 166 (M^+-H). HRMS *m*/*z* calcd for C_8H_6FNS: 167.0205. Found 167.0105. Anal. Calcd for C_8H_6FNS: C, 57.47; H, 3.62; N, 8.38. Found: C, 57.19; H, 3.86; N, 8.04.

4.2.2. α-Fluoro-4-pyridyl propargyl sulfide (8). Eluent: hexane/AcOEt (1: 2). ^{1}H NMR δ 2.83 (dd, 1H, J=2.6, 3.1 Hz), 6.31 (d, 1H, J=47 Hz), 7.11 (d, 2H, J=5 Hz), 8.27 (d, 2H, J=5 Hz). ^{19}F NMR δ −63.8 (dd, J=2.6, 47 Hz). MS *m*/*z* 167 (M^+), 166 (M^+-H). Anal. Calcd for C_8H_6FNS: C, 57.47; H, 3.62; N, 8.38. Found: C, 57.26; H, 3.88; N, 8.15.

4.2.3. α-Fluoro-2-pyrimidyl propargyl sulfide (9). Eluent: benzene. ^1H NMR δ 3.02 (dd, 1H, J=2, 4 Hz), 7.1 (t, 1H, J=5 Hz), 7.4 (d, 1H, J=48 Hz), 8.61 (d, 2H, J=5 Hz). ^{19}F NMR δ −67.2 (dd, J=2, 48 Hz) MS *m*/*z* 168 (M^+), 167 (M^+-H). HRMS *m*/*z* calcd for $C_7H_5FN_2S$: 168.0157. Found 168.0127.

4.2.4. α-Fluoro-2-quinolyl propargyl sulfide (10). Eluent: hexane/AcOEt (10: 1). ^1H NMR δ 3.01 (dd, 1H, J=2, 2.2 Hz), 7.26 (d, 1H, J=7 Hz), 7.49 (t, 1H, J=6 Hz), 7.67 (t, 1H, J=8 Hz), 7.73 (t, 1H, J=8 Hz), 7.81 (d, 1H, J=52 Hz), 8.01 (d, 2H, J=7 Hz). ^{19}F NMR δ −67.7 (dd, J=2, 52 Hz) MS *m*/*z* 217 (M^+), 216 (M^+-H). HRMS *m*/*z* calcd for $C_{12}H_8FNS$: 217.0361. Found 217.0312.

4.2.5. α-Fluoro-2-benzothiazolyl propargyl sulfide (11). Eluent: hexane/AcOEt (10: 1). ^1H NMR δ 3.07 (dd, 1H, J=2, 2.5 Hz), 7.25 (t, 1H, J=8 Hz), 7.35 (t, 1H, J=8 Hz), 7.45 (d, 1H, J=53 Hz), 7.65 (d, 1H, J=8 Hz), 7.85 (d, 1H, J=8 Hz). ^{19}F NMR δ −68.5 (dd, J=2, 53 Hz). MS *m*/*z* 223 (M^+), 222 (M^+-H). HRMS *m*/*z* calcd for $C_{10}H_6FNS_2$: 222.9926. Found 222.9920.

4.2.6. α-Fluoro-2-(5-chlorobenzothiazolyl) propargyl sulfide (12). Eluent: hexane/AcOEt (10: 1). ^1H NMR δ 3.09 (dd, 1H, J=2, 2.5 Hz), 7.24 (d, 1H, J=52 Hz), 7.31 (d, 1H, J=10 Hz), 7.67 (d, 1H, J=10 Hz), 7.88 (s, 1H). ^{19}F NMR δ −68.1 (dd, J=2, 52 Hz). MS *m*/*z* 258 (M^+), 257 (M^+-H). Anal. Calcd for $C_{10}H_5ClFNS_2$: C, 46.60; H, 1.96; N, 5.43. Found: C, 46.46; H, 2.3; N, 5.38**.**

Acknowledgements

This research was 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, Japan.

References

1. Part 56: Shaaban, R. M.; Fuchigami, T. *Tetrahedron Lett.*, submitted for publication.
2. Brandman, H. A.; Freudewald, J. E.; Manowitz, M.; Nikawitz, E. J.; Sharpell, F. H. U.S. 4,170,704. *Chem. Abst.*, **1980**, *92*, 41776a.
3. Heitsch, H.; Wagner, A.; Scholkens, B. A.; Wirth, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 327–332.
4. Chua, M. S.; Shi, D. F.; Wrigley, S.; Bradshaw, T. D.; Hutchinson, I.; Shaw, P. N.; Barrett, D. A.; Stanley, L. A.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 381–392.
5. Easmon, J.; Heinisch, G.; Hofmann, J.; Langer, T.; Grunicke, H. H.; Fink, J.; Purstinger, G. *Eur. J. Med. Chem.* **1997**, *32*, 397–408.
6. Sutoris, V.; Foltinova, P.; Blockinger, G. *Chem. Zvesti.* **1997**, *31*, 92.
7. (a) Deady, L. W.; Kaye, A. J.; Finaly, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 2040. (b) Scharping, C. E.; Duke, C. C.; Holder, G. M.; Larden, D. *Carcinogenesis* **1993**, *14*, 1041. (c) Moron, J.; Rautureau, M.; Huel, C.; Pierre, A.; Berthier, L. K.; Atassi, G.; Bisagni, E. *Anti-cancer Drug Des.* **1993**, *8*, 399. (d) Yamato, M.; Takeuchi, Y.; Chang, M. R.; Hashigaki, K. *Chem. Pharm. Bull.* **1992**, *40*, 528. (e) Takeuchi, Y.; Chang, M. R.; Hashigaki, K.; Tashiro, T.; Tsuruo, T.; Tsukagoshi, S.; Yamato, M. *Chem. Pharm. Bull.* **1992**, *40*, 1481.
8. (a) Smart, B. E., Ed. *Chem. Rev.* **1996**, 96. (b) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996.
9. Huddlicky, M., Pavlath, A. E., Eds.; *Chemistry of Organic Fluorine Compounds*; American Chemical Society: Washington, DC, 1995; Vol. II.
10. (a) Childs, W. V.; Christensen, L.; Klink, F. W.; Kolpin, C. F. In *Organic Electrochemistry*; Lund, H., Baizer, M. M., Eds.; 3rd ed., Marcel Dekker: New York, 1991; Chapter 26. (b) Fuchigami, T. In *Organic Electrochemistry*; Lund, H., Hammerich, O., Eds.; 4th ed., Marcel Dekker: New York, 2001; Chapter 25. (c) Sawaguchi, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *Isr. J. Chem.* **1999**, *39*, 151.
11. (a) Fuchigami, T.; Shimojo, M.; Nakagawa, K. *J. Org. Chem.* **1990**, *55*, 6070. (b) Shaaban, M. R.; Ishii, H.; Fuchigami, T. *J. Org. Chem.* **2000**, *65*, 8685. (c) Riyadh, S. M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* **2001**, *42*, 3009.
12. Erian, A. W.; Konno, A.; Fuchigami, T. *J. Org. Chem.* **1995**, *60*, 7654.
13. Ballinger, J. R.; Teare, F. W. *Electrochem. Acta* **1985**, *30*, 1075.
14. Fuchigami, T.; Shimojo, M.; Konno, A. *J. Fluorine Chem.* **1997**, 87.
15. Hou, Y.; Higashiya, S.; Fuchigami, T. *J. Org. Chem.* **1997**, *62*, 9173.
16. Fuchigami, T.; Konno, A.; Nakagawa, K.; Shimojo, M. *J. Org. Chem.* **1994**, *59*, 5937.
17. (a) Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn* **1986**, *59*, 3625. (b) Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995**, *60*, 6563.