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Electrolytic partial fluorination of organic compounds. Part 56: Highly regioselective anodic mono- and difluorination of *s*-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives†

Mohamed R. Shaaban and Toshio Fuchigami*

Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226-8502, Japan

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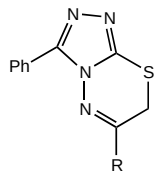
Abstract—Constant potential anodic oxidation of *s*-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives in DME containing $Et_4NF{\cdot}4HF$ using an undivided cell provided the corresponding 7-monofluorinated products predominantly in good to moderate yields. 7,7-Difluorination was also anodically achieved. © 2002 Elsevier Science Ltd. All rights reserved.

Broad biological and pharmacological activities of various thiadiazines fused with an *s*-triazole ring have been extensively studied,[2] especially, *s*-triazolo[3,4-*b*][1,3,4] thiadiazines have been shown to possess a wide spectrum of bioactivities[3] such as anti-inflammatory, analgesic, and anti-fungal activities.[4] On the other hand, much interest has been paid to partially fluorinated heterocyclic compounds due to their unique chemical, physical and biological properties.[5] Therefore, development of efficient methods for selective fluorination of heterocycles is of much importance. Recently, we have shown that electrolytic oxidation in the presence of fluoride salts is effective in partial fluorination of various organic compounds,[6] which is more convenient compared to the conventional chemical fluorination methods. In addition, we have successfully achieved anodic ring fluorination of some heterocyclic systems.[7] Although several papers dealing with the selective anodic fluorination of heterocycles have been published,[8] direct ring fluorination of heterocyclic compounds fused with a heterocyclic ring has never been reported except for one example.[9] In this paper, we wish to report a novel synthesis of ring-fused fluoroheterocycles by direct selective fluorination of *s*-triazolo[3,4-*b*][1,3,4]thiadiazines. The oxidation potentials of *s*-triazolo[3,4-*b*][1,3,4]thiadiazines **1a–d** were measured by cyclic voltammetry in which an anhydrous acetonitrile solution containing $Bu_4N{\cdot}BF_4$ (0.1 M), platinum electrodes, and a saturated NaCl calomel electrode (SSCE) as a reference electrode were used. All these compounds showed irreversible waves in cyclic voltammograms, and their first peak oxidation potentials are listed in Table 1.

It is of interest that the oxidation potentials of 6-aryl derivatives **1b–d** are much lower than that of 6-methyl derivative **1a**. This is in sharp contrast to that of the

Table 1. Oxidation potentials (peak potentials, E_p^{ox}) of *s*-triazolo[3,4-*b*][1,3,4]thiadiazines **1a–d**[a]



1a-d

Substrate		E_p^{ox} (V versus SSCE)
No.	R	
1a	CH_3	2.24
1b	C_6H_5	1.79
1c	p-$NO_2C_6H_4$	1.89
1d	p-$CH_3OC_6H_4$	1.71
$PhSCH_3$		1.41[b]
$PhSCH_2Ph$		1.43[b]
n-$C_7H_{15}SCH_2CO_2Et$		1.90[b]
$PhCH_2SCH_2CO_2Et$		1.91[b]

[a] Substrate (1 mmol) in 0.1 M $Bu_4N{\cdot}BF_4$/MeCN. Sweep rate: 100 mV/s.

[b] In 0.1 M $NaClO_4$/MeCN. Sweep rate: 100 mV/s.

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

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oxidation potentials of benzyl sulfides are slightly higher than those of the corresponding alkyl sulfides[10] (Table 1). Additionally, the substituents on the 6-phenyl group considerably affect the oxidation potentials, suggesting that the initial electron transfer would take place at the C=N bond in the thiadiazine ring.

A typical anodic fluorination of **1a** was carried out using a platinum anode and cathode (3×3 cm^2) in the presence of 0.4 M $Et_4NF{\cdot}4HF$ or $Et_3N{\cdot}3HF$ in DME or MeCN (15 ml) for 0.5 mmol of the substrate at room temperature. After the starting material was completely consumed (monitored by TLC), the electrolysis solution was passed through a short column of silica gel, and then the fluorinated products were isolated and purified by preparative TLC or column chromatography on silica gel using benzene/ethyl acetate (1:1) as an eluent.[11–13]

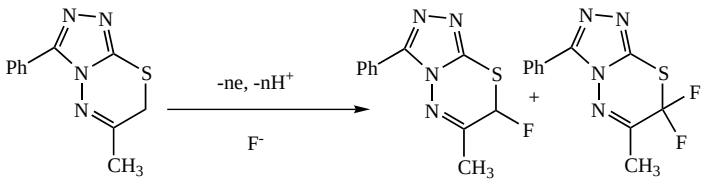
As shown in Table 2, constant current electrolysis of **1a** was sluggish in MeCN as the solvent probably because of passivation (run 3), but the use of DME provided the fluorinated products in moderate to good yields regardless of the supporting fluoride salts. In either case, the fluorine substitution occurred regioselectively on the 7-carbon adjacent to the sulfur atom of the thiadiazine ring, without on the metyl and/or the phenyl groups, to form a mixture of mono and difluorinated products (**2a** and **3a**[12]). Conversely, monofluorination of **1a** to **2a** was best effected using $Et_4NF{\cdot}4HF$ under constant potential electrolysis conditions (run 5). The other monofluorinated compounds **2b–d**[13] were similarly prepared from the corresponding heterocycles in moderate yields under identical conditions as shown in Table 3.

Because of potential unique biological activities of *gem*-difluoromethylene compounds, we explored some efficient conversion methods to difluorinated materials **3**. When a large excess amount of electricity was passed under the constant current electrolysis conditions, difluorinated compound **3a** was obtained in a reasonable yield (41%) as a sole product (Table 2, run 7). Alternatively, an 84% yield of **3a** was obtained by fluorination of the monofluorinated compound **2a** under the conditions shown in Scheme 1. Other difluorinated derivatives, **3b** and **3c** were similarly prepared in moderate yields. Although electrosynthesis of *gem*-difluorinated heterocycles from chlorodifluoromethyl compounds using mediators has been reported,[14] the current method is easier in terms of the electrolytic procedure.

The fluorination reaction seems to be initiated by electron transfer from the C=N bond to generate the corresponding radical cation **A** followed by deprotonation to form a radical intermediate **B** as shown in Scheme 2. Further oxidation of **B** followed by the reaction with a fluoride ion affords **2**. If the initial electron transfer takes place from the sulfur atom, the oxidation potentials of **1a** and **1b** should be almost same in consideration to the oxidation potentials of benzyl and alkyl sulfides (Table 1). However 6-aryl derivatives, **1b–d** are much more easily oxidized than a 6-methyl derivative **1a**. Therefore, the initial reaction involving electron transfer from the sulfur atom can be ruled out.

In summary, we have developed novel synthesis of mono- and difluorinated heterocyclic compounds fused with a heterocyclic ring, *s*-triazolo[3,4-*b*][1,3,4]thiadiazines, using regioselective anodic ring

Table 2. Anodic mono- and difluorination of 6-methyl-3-phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines (**1a**) under various electrolytic conditions

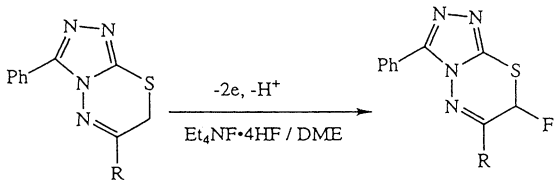


1a **2a** **3a**

Run	Supporting electrolyte	Solvent	Charge passed (F/mol)	Yield (%)[a]	
				2a	**3a**
1	$Et_3N{\cdot}3HF$	DME	3[b]	42	0
2	$Et_3N{\cdot}3HF$	DME	4.5[c]	34	1
3	$Et_3N{\cdot}3HF$	MeCN	6	3	8
4	$Et_3N{\cdot}3HF$	DME	8	34	27
5	$Et_4NF{\cdot}4HF$	DME	3[b]	81(74)	0
6	$Et_4NF{\cdot}4HF$	DME	6	15	30
7	$Et_4NF{\cdot}4HF$	DME	8	0	41
8	$Et_4NF{\cdot}3HF$	DME	8	6	36
9	$Et_3N{\cdot}5HF$	DME	8	14	32

[a] Calculated on the basis of ^{19}F NMR and the isolated yield is indicated in parentheses.
[b] Constant potential electrolysis was used.
[c] A considerable amount of starting material (ca. 40%) was recovered.

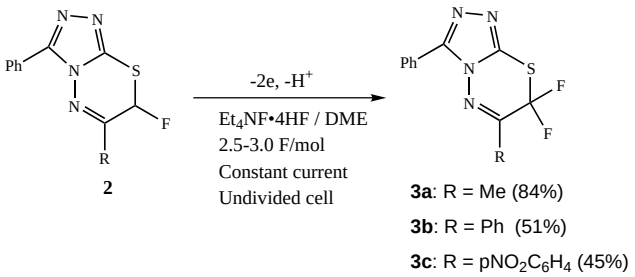
Table 3. Anodic monofluorination of *s*-triazolo[3,4-*b*][1,3,4]thiadiazines **1a–d** using constant potential electrolysis



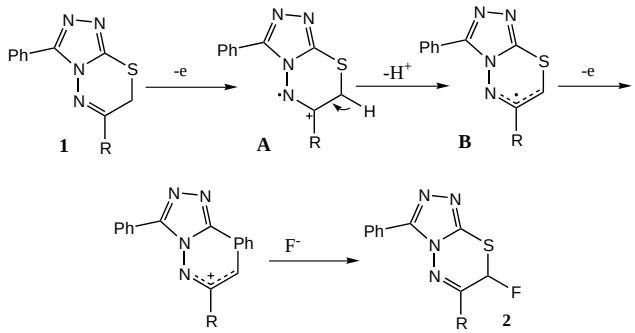
1a-d 2a-d

Substrate		Applied potential (V versus SSCE)	Charge passed (F/mol)	Yield (%)[a]
No.	R			
1a	CH_3	2.24	3	81 (74)
1b	C_6H_5	1.79	2	67 (61)
1c	p-$NO_2C_6H_4$	1.89	2.5	68 (58)
1d	p-$CH_3OC_6H_4$	1.71	4	40 (36)

[a] Calculated on the basis of ^{19}F NMR and the isolated yield is indicated in parentheses.



Scheme 1.



Scheme 2.

monofluorination. In this reaction, the electron transfer takes place initially from an imino group to result in the regioselective fluorination at α to the sulfur atom. This fluorination may be applicable to various heteroatom compounds other than sulfides.

Acknowledgements

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11. Compound **2a**: mp 50°C; ^{1}H NMR: δ 2.55 (s, 3H), 5.98 (d, 1H, $J=50$ Hz), 7.51 (m, 3H), 8.08 (d, 2H, $J=7.25$ Hz); ^{19}F NMR: δ −74.73 (d, $J=50.50$ Hz); MS m/z 248 (M^+). Anal. calcd for $C_{11}H_9FN_4S$: C, 53.21; H, 3.65; F, 6.65; N, 22.57; S, 12.92. Found: C, 53.50; H, 3.90; F, 6.54; N, 22.45; S, 12.88.
12. Compound **3a**: mp 42°C; ^{1}H NMR: δ 2.53 (s, 3H), 7.51 (m, 3H), 8.05 (d, 2H, $J=7.25$ Hz); ^{19}F NMR: δ −0.02 (s); MS m/z 266 (M^+). Anal. calcd for $C_{11}H_8F_2N_4S$: C, 49.62; H, 3.03; F, 14.27; N, 21.04; S, 12.04. Found: C, 49.81; H, 2.93; F, 14.02; N, 20.61; S, 11.79.
13. Compound **2b**: mp 63°C; ^{1}H NMR: δ 6.86 (d, 1H, $J=50$ Hz), 7.43 (m, 6H), 7.87 (m, 2H), 8.09 (d, 2H, $J=7.3$ Hz); ^{19}F NMR: δ −68.90 (d, $J=50.50$ Hz); MS m/z 310 (M^+). Anal. calcd for $C_{16}H_{11}FN_4S$: C, 61.92; H, 3.57; F, 6.12; N, 18.05; S, 10.33. Found: C, 61.81; H, 3.77; F, 5.87; N, 17.76; S, 10.02.

    Compound **2c**: mp 48°C; ^{1}H NMR: δ 6.86 (d, 1H, $J=50$ Hz), 7.63 (m, 5H), 7.89 (m, 2H), 8.19 (d, 2H, $J=7.3$ Hz); ^{19}F NMR: δ −68.89 (d, $J=50$ Hz); MS m/z 355 (M^+). Anal. calcd for $C_{16}H_{10}FN_5O_2S$: C, 54.08; H, 2.84; F, 5.35; N, 19.71; S, 9.02. Found: C, 54.22; H, 2.78; F, 5.67; N, 19.76; S, 8.92.

    Compound **2d**: mp 39°C; ^{1}H NMR: δ 3.89 (s, 3H), 6.86 (d, 1H, $J=50$ Hz), 7.05 (d, 2H, $J=7.3$ Hz), 7.51 (m, 3H), 7.87 (d, 2H, $J=7.3$ Hz), 8.15 (d, 2H, $J=7.3$ Hz); ^{19}F NMR: δ −69.06 (d, $J=50.50$ Hz); MS m/z 340 (M^+). Anal. calcd for $C_{17}H_{13}FN_4OS$: C, 59.99; H, 3.85; N, 16.46. Found: C, 60.27; H, 4.10; N, 16.48.
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