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ELECTROLYTIC PARTIAL FLUORINATION OF ORGANIC COMPOUNDS. 59. HIGHLY REGIOSELECTIVE ANODIC MONOFLUORINATION OF 2*H*-1,4-PYRIDO[3,2-*b*]-1,4-OXAZIN-3(4*H*)-ONE DERIVATIVES[1]

Norio Iwayasu, Mohamed R. Shaaban, and Toshio Fuchigami*

Department of Electronic Chemistry, Tokyo Institute of Technology
Nagatsuta, Midori-ku, Yokohama 226-8502 Japan
Tel +81 45 924 5406; Fax+81 45 924 5489;
E-mail fuchi@echem.titech.ac.jp

Abstract - Regioselective anodic fluorination of *2H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one derivatives was successfully carried out in dimethoxyethane containing Et_4NF-4HF using an undivided cell to provide the corresponding α-monofluorinated products in moderate yields.

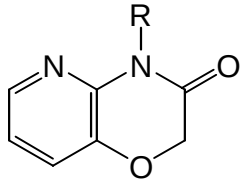
Partially fluorinated heterocyclic compounds have attracted much interest because of their potent biological and pharmacological activities in addition to their role in development of new functional materials.[2-4] On the other hand, broad biological and pharmacological activities of various fused heterocyclic compounds have been extensively studied.[5] Recently, *2H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one derivatives have shown various biological activities. Among them, the important effects are analgesic and antinociceptive activities.[6] Many fluorinated analogues of biologically active molecules have exhibited dramatic enhancement in their properties. However, direct selective fluorination of heterocyclic rings is not always straightforward. Recently, anodic fluorination has been shown to be more elegant and applicable than conventional fluorination methods.[7] So far, limited examples of anodic fluorination of oxygen - containing heterocyclic compounds have been reported.

Morpholines,[8] furan,[9] and benzofuran[9] were anodically fluorinated; however, the yield and/or selectivity are low due to the instability of the fluorinated products. We have successfully carried out anodic monofluorination of various heterocyclic sulfides and anodic ring fluorination of different heterocyclic systems.[10] Although several papers[11] dealing with the selective anodic fluorination of heterocycles have been published, direct ring fluorination of heterocyclic compounds fused with a heterocyclic ring has not been reported except for one example.[12]

In this paper, we wish to report for the first time a successful anodic monofluorination of *2H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one derivatives as a highly regioselective route to introduce a fluorine atom directly into the position α to the ring oxygen atom of a fused hetercyclic system.

At first, the oxidation potentials of *2H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one derivatives (**1**) were measured by cyclic voltammetry (CV). An anhydrous acetonitrile solution containing Bu_4NF-BF_4 (0.1 M), platinum electrodes and saturated NaCl calomel electrode (SSCE) as a reference electrode were used in this CV measurement. All these compounds showed irreversible waves in their cyclic voltamograms. The first peak oxidation potentials are listed in Table 1.

Table 1. Oxidation Potentials (Peak Potentials, E_p^{ox}) of *2H*-1,4-Pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one Derivatives[a]



1

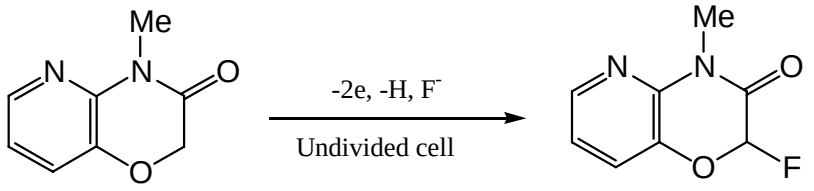
Substrate		Ep^{ox}
No	R	(V vs. SSCE)
1a	Me	1.60
1c	CH_2COOEt	1.64
1d	CH_2Ph	1.69
1e	H	1.63

[a] Substrate (1 mmol) in 0.1 M Bu_4N-BF_4/MeCN. Sweep rate: 100 mV/s.

As shown in Table 1, the oxidation potentials of *2H*-1,4-pyrido[3,2-*b*]- 1,4-oxazin-3(4*H*)-one (**1a, c, d, e**) are relatively low and the substituents at the nitrogen atom affect appreciably the oxidation potentials.

Typical anodic fluorination conditions are as follows: Electrolysis was carried out at a constant current (5 mA/cm^2) with platinum plates (3x3 cm^2) as the anode and cathode in 0.4 M Et_4NF-4HF/DME (15 mL) containing 20 mmol of 4-methyl-*2H*-1,4-pyrido[3,2-*b*]- 1,4-oxazin-3(4*H*)-one (**1a**) using an undivided cell. The temperature was kept at ambient temperature during the electrolysis. After the starting material (**1a**) was completely consumed (monitored by TLC), the electrolysis solution was passed through a short column filled with silica gel to remove fluoride salts, and then the fluorinated product (**2a**)[12] was isolated and purified using column chromatography on silica gel using benzene as an eluent. The results are summarized in Table 2.

Table 2. Anodic Monofluorination of 4-Methyl-2*H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (1a) Under Various Electrolytic Conditions



1a **2a**

Run	Supporting Electrolyte	Solvent	Charge passed (F/mol)	Yield(%)[a] of **2a**
1	Et_4NF-4HF	DME	3	63(45)
2	Et_4NF-4HF	DME	3[b]	53
3	Et_4NF-3HF	DME	2[c]	31
4	Et_3N-5HF	DME	3	13
5	Et_3N-3HF	DME	4	10
6	Et_4NF-4HF	MeCN	3	27
7	Et_3N-3HF	MeCN	2	5

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

[b] Constant potential electrolysis (+2.28 V vs SSCE).

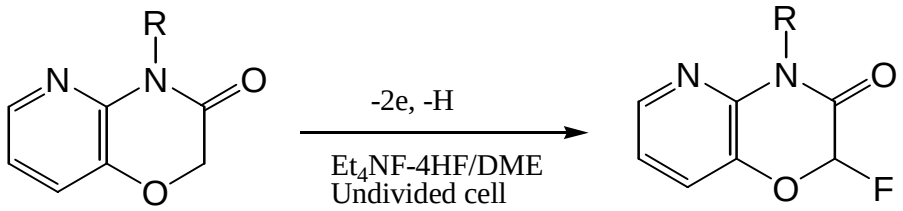
[c] A divided cell was used.

As shown in Table 2, anodic fluorination proceeded to give the monofluorinated product,

and a fluorine atom was selectively introduced into the position α to the oxygen atom. The yield was greatly affected by both the solvents and the supporting fluoride salts used. DME was suitable for the fluorination while acetonitrile was not. The use of Et_4NF-4HF provided the best yield (Run 1), while Et_3N-5HF and Et_3N-3HF were not effective. The constant potential electrolysis resulted in little lower yield (Run 2).

We extended the fluorination to the other *2H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one derivatives (**1b-d**) using a Et_4NF-4HF/DME electrolytic solution. The results are summarized in Table 3. Monofluorinated products (**2b-d**)[13-15] were predominantly formed in moderate yields regardless of N-substituents.

Table 3. Anodic Monofluorination of 2*H*-1,4-Pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one Derivatives (1a-d) Using Et_4NF-4HF/DME



1a-d **2a-d**

Run	R	Charge passed (F/mol)	Yield(%)[a]	
1a	Me	2	**2a**	63(45)
1b	Et	2	**2b**	71(60)
1c	CH_2COOEt	2	**2c**	56(40)
1d	CH_2Ph	2.5	**2d**	63(51)

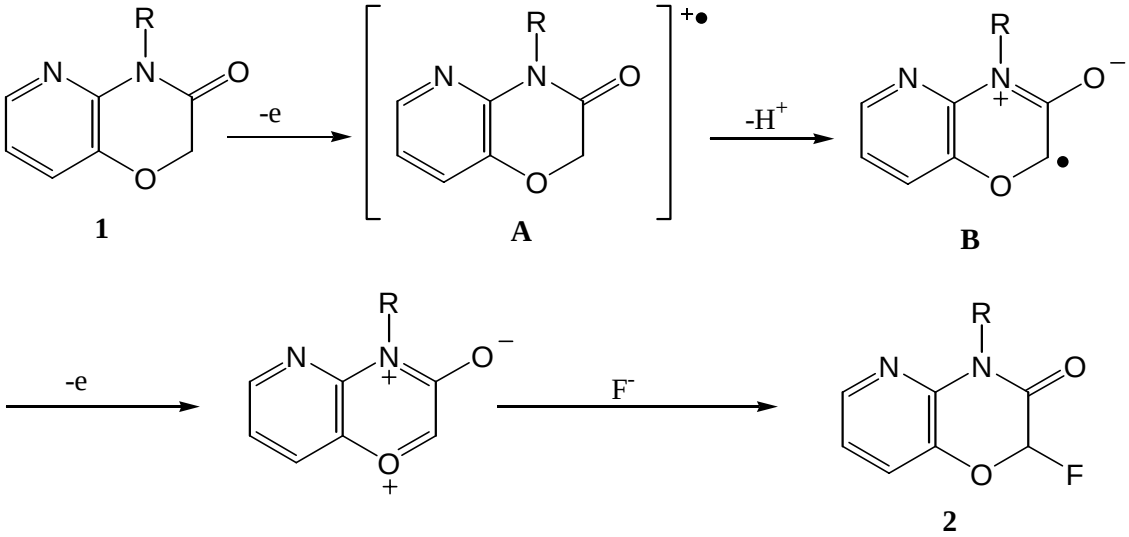
[a] Calculated on the basis of ^{19}F NMR spectrometry and the isolated yields are shown in parentheses.

It was found that no fluorination took place at the benzylic position of **1d** although the anodic benzylic substitution easily takes place. Therefore, it is noted that the anodic fluorination is highly regioselective.

Since the substituents at the nitrogen atom appreciably affect the oxidation potentials of **1**, the fluorination reaction seems to be initiated by electron transfer from the nitrogen atom of the heterocyclic ring to generate the corresponding radical cation (**A**) followed by deprotonation to from the more stable radical (**B**), which is stabilized by a capto-dative

effect. Further one- electron oxidation of (**B**) followed by the reaction with a fluoride ion affords **2**.

Scheme 1



In summary, we have successfully carried out anodic monofluorination at the position α to the ring oxygen atom of *2H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one derivatives. This is the first report of successful regioselective anodic direct fluorination of oxygen- and nitrogen-containing heterocyclic compounds fused with a heterocyclic ring.

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13. **2a**: mp 65°C; ^{1}H NMR ($CDCl_3$): δ 3.56 (s, 3 H), 6.05 (d, 1 H, J = 51.78 Hz), 7.06 (dd, 1 H, J = 4.9, 7.9 Hz), 7.44 (d, 1 H, J = 7.9 Hz), 8.15 (d, 1 H, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$): δ 26.95, 101.75 (d, 1 H, J = 235.85 Hz), 119.46, 124.73, 142.73, 158.20; ^{19}F NMR δ -49.70 (d, J = 51.78 Hz); MS (*m/z*) 182 (M^+),153, 135, 121, 106,93, 79; Anal. Calcd for $C_9H_8NO_2F$: C, 52.75; H, 3.87; N, 15.38. Found: C, 52.58; H, 4.13; N, 15.34.
14. **2b**: mp 41°C; ^{1}H NMR ($CDCl_3$): δ 1.13 (t, 3 H, J = 7.1 Hz), 4.26 (q, 2 H, J = 7.1 Hz), 6.14 (d,1 H, J =51.79), 7.05 (dd, 1 H, J = 4.8, 7.9 Hz), 7.44 (d, 1 H, J = 7.9 Hz), 8.18 (d, 1 H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$): δ 12.91, 35.46, 100.77 (d, 1 H, J = 235.32 Hz), 119.36, 124.81, 136.06, 139.29, 142.73, 158.30; ^{19}F NMR δ -50.10 (d, J = 51.79 Hz); MS (*m/z*) 196 (M^+),168, 153, 120, 106, 92, 78,.

15. **2c**: mp 84°C; ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3 H, *J* = 7.25 Hz), 4.24 (q, 2 H, *J* = 7.25 Hz), 4.87 (d, 1 H, *J* = 17.4 Hz), 4.90 (d, 1 H, *J* = 17.4 Hz), 6.10 (d, 1 H, *J* = 51.44 Hz), 7.08 (dd, 1 H, *J* = 4.8, 8 Hz), 7.48 (d, 1 H, *J* = 8 Hz), 8.11 (d, 1 H, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$): δ 14.09, 40.93, 61.60, 101.55 (d, 1 H, *J* = 235.85 Hz), 119.82, 124.00, 135.88, 138.94, 142.64, 158.30, 167.12; ^{19}F NMR δ -49.90 (d, *J* = 51.44 Hz); MS (*m/z*) 254 (M^+), 208, 182, 181, 154, 153, 134, 105, 94, 78; Anal. Calcd for $C_{12}H_{12}NO_4F$: C, 51.97; H, 4.36; N, 11.02. Found: C, 51.72; H, 4.57; N, 10.84.
16. **2d**: mp 92°C; ^{1}H NMR ($CDCl_3$): δ 5.31 (d, 1 H, *J* = 17.4 Hz), 5.50 (d, 1 H, *J* = 17.4 Hz), 6.15 (d, 1 H, *J* = 51.78 Hz), 7.02 (dd,1 H, *J* = 4.8, 7.9 Hz), 7.03-7.35 (m, 5H), 7.42 (d,1 H, *J* = 7.9 Hz), 8.17 (d,1 H, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$): δ 42.45, 100.98 (d, 1 H, *J* = 235.85 Hz), 119.98, 124.21, 128.32, 136.54, 139.76, 142.54, 158.32; ^{19}F NMR δ -50.13 (d, *J* = 51.78 Hz); MS (*m/z*) 258 (M^+), 230, 209, 210, 182, 181, 154, 153, 127, 105, 91, 79, 65; Anal. Calcd for $C_{15}H_{12}NO_2F$: C, 65.11; H, 4.29; N, 10.85. Found: C, 64.77; H, 4.37; N, 10.68.