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Electrolytic partial fluorination of organic compounds. Part 61: The first example of direct α-fluorination of protected α-amino acids†,‡

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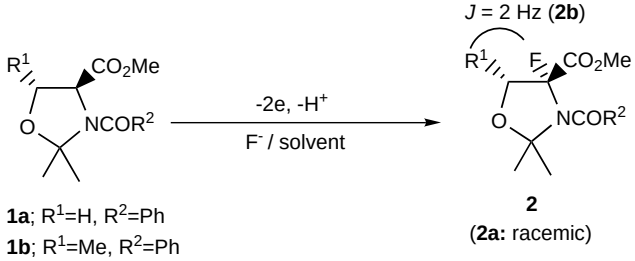
Abstract—Regioselective anodic α-monofluorination of oxazolidines **1** derived from α-amino acid was successfully carried out. This is the first example of the successful, direct α-fluorination of protected amino acids. Anodic fluorination of methyl *N*-acetyl pyroglutamate also provided the corresponding α-fluorinated product in moderate yield, while the anodic fluorination of an open-chain α-amino acid, *N*-(carboethoxy)methylphathalimide, was unsuccessful.

It is well known that the introduction of fluorine atom(s) into organic molecules sometimes enhances or greatly changes their biological activities. There have been many reports on the preparation of fluorine-containing amino acids.[2] However, few studies have been reported on the preparation of α-fluoro-α-amino acid derivatives,[3] although unique biological properties are expected for α-fluoro-α-amino acids.[4] To our best knowledge, there have been no reports on direct α-fluorination of either protected or unprotected α-amino acids so far. Several examples of partial anodic α-fluorination of organonitrogen compounds such as lactams were reported; however, silyl[5a] and sulfenyl[5b] leaving groups on their α-position or two carbonyl groups on the same nitrogen atom (*N*-acyl lactams) are necessary.[6] It was reported that the yields of anodic fluorination of *N*-methyl lactams were quite low.[7]

In this paper, we report successful anodic fluorination of 1,3-oxazolidines **1** derived from L-serine and L-threonine to give α-fluorinated products in good yields (Scheme 1). This is the first example of direct partial α-fluorination of α-amino acid derivatives.

Anodic fluorination of **1** was carried out under various conditions as shown in Table 1. [8] The fluorination was successfully carried out without any mediator, although anodic methoxylation at the α-position of protected α-amino acids requires a halide ion mediator (Cl^-, Br^-, I^-).[9] Although dimethoxyethane (DME) has recently been shown to be an effective solvent for anodic fluorination of various heterocycles,[10] the use of DME did not give any fluorinated products, and a large amount of **1a** was recovered (run 1). This is mainly due to the predominant anodic oxidation of DME owing to the much higher oxidation potential of **1** compared with that of DME.

On the other hand, acetonitrile (MeCN) was found to be effective for the fluorination of **1a** regardless of supporting fluoride salts, and the corresponding 4-fluorinated product **2a**[11] was obtained in moderate yield of 66% (run 2). Anodic fluorination in nitromethane required the least amount of electricity to complete the electrolysis; however, the yield was much lower than that obtained in MeCN (run 4). A graphite anode as well as a platinum anode was also effective for the fluorination of **1a** (run 3). 1,3-Oxazolidine **1b** was also



1a; R^1=H, R^2=Ph
1b; R^1=Me, R^2=Ph

2
(**2a:** racemic)

Scheme 1.

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† For Part 60, see Ref. 1.

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Table 1. Anodic fluorination of 1,3-oxazolidines **1**

Run	Substrate	Solvent	Anode material	Electrolyte	Electricity (F/mol)	Yield (%)[a]
1	**1a**	DME	Pt	$Et_4NF{\cdot}4HF$	4	0[b]
2	**1a**	MeCN	Pt	$Et_4NF{\cdot}4HF$	3	66 (56)
3	**1a**	MeCN	Graphite	$Et_4NF{\cdot}4HF$	4	64
4	**1a**	$MeNO_2$	Pt	$Et_4NF{\cdot}4HF$	2.5	42
5	**1a**	MeCN	Pt	$Et_3N{\cdot}3HF$	4	56
6	**1a**	MeCN	Pt	$Et_4NF{\cdot}4HF$	3	62
7	**1b**	MeCN	Pt	$Et_4NF{\cdot}4HF$	3	(73, 81% de)
8	**1b**	MeCN	Graphite	$Et_4NF{\cdot}4HF$	4	(66, 76% de)
9[c]	**1b**	MeCN	Pt	$Et_4NF{\cdot}4HF$	5	(32, 76% de)

[a] Determined by ^{19}F NMR. The figures in parentheses are isolated yields.
[b] Starting material was not consumed.
[c] Electrolysis was carried out at −22°C.

fluorinated similarly at a platinum anode in $Et_4NF{\cdot}4HF$/MeCN to provide **2b**[12] in good yield with high diastereoselectivity (run 7). Even when the anodic fluorination of **1b** was conducted at low temperature, −22°C, the diastereoselectivity of **2b** did not increase and the yield decreased drastically (run 9). It was reported that anodically oxidative decarboxylation in methanol of chiral oxazolidine-4-carboxylates gave optically active methoxylated products and its optical purity strongly depended on anode materials.[13] However, as shown in Table 1 (runs 7 and 8), anode materials did not affect the stereoselectivity significantly.

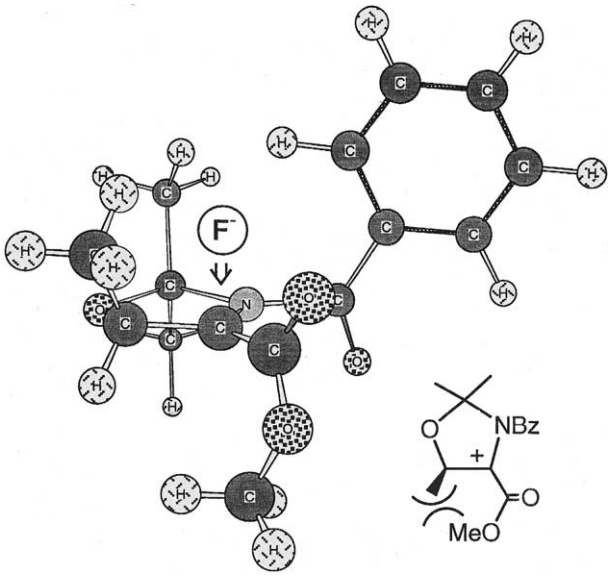
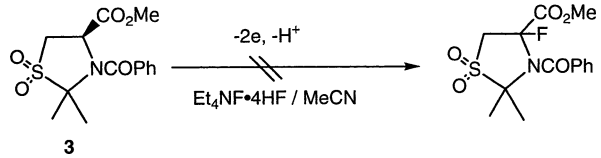


Figure 1.



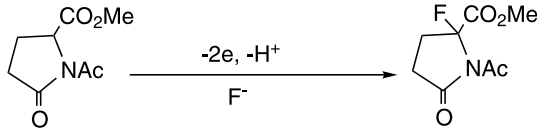
3

Scheme 2.

The stereochemistry of the major diastereomer of **2b** was determined by long-range coupling between the fluorine atom and methyl protons in the ^1H NMR. The stereoselectivity was explained as follows. The carbomethoxy group on the cationic carbon atom would be fixed to be at the opposite side of the adjacent methyl group due to their steric repulsion. Therefore, a fluoride ion should attack **1b**$^+$ from the less hindered *re* face as shown in Fig. 1.

In sharp contrast, anodic fluorination of 3-benzoyl-4-carbomethoxy-1,1-dioxothiazolidine **3**, an analogue of **1**, did not proceed at all (Scheme 2). Next, we carried out anodic fluorination of cyclic amino acids such as *N*-benzoylproline methylester and methyl *N*-acetylpyroglutamate **4**. Although the proline derivative did not undergo fluorination, **4** gave the α-fluorinated product **5**[14] in low yield under the same conditions. Recently, Yoneda et al. reported that pulse electrolysis in $Et_3N{\cdot}5HF$/MeCN at low temperature below 0°C was suitable for efficient anodic α-fluorination of *N*-acyllactams.[6] We also attempted the anodic fluorination of **4** by alternating the polarity of the electrodes every 5 s at 0°C, and the yield increased significantly to ca. 60% (Scheme 3). In contrast, fluorination of *N*-(carboethoxy)methylphthalimide **6**, which can be considered to be an open-chain analogue of **4**, did not proceed at all (Scheme 4).

The oxidation potentials (decomposting potentials) of the starting compounds measured by linear sweep voltammetry (LSV) are shown in Table 2. The sulfone

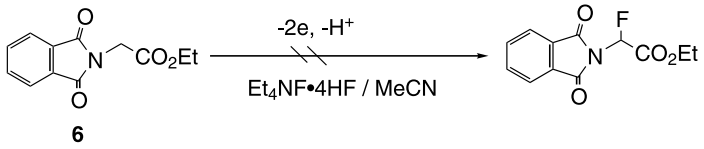


4 **5**

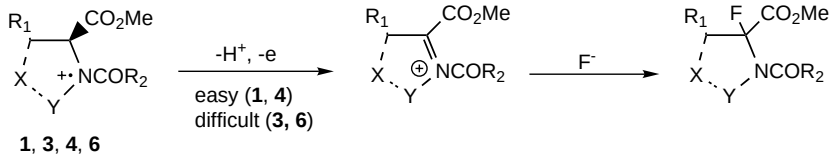
Pulse electrolysis in $Et_3N{\bullet}5HF$ (5mL) - MeCN (10mL), 3.5 F/mol, 0 : 58%(isolated yield)

$Et_4NF{\bullet}4HF$ (5mmol) - MeCN (10mL), 4.5 F/mol, r.t.: 19% (^{19}F-NMR yield)

Scheme 3.



Scheme 4.



Scheme 5.

Table 2. Oxidation potentials (decomposition potential) of amino acid derivatives[a]

Substrate	E_d^{ox} (V versus SCE)
1a	2.3
1b	2.3
3	2.4
4	2.8
6	2.7

[a] Determined by LSV with scanning rate 50 mV/s using a Pt anode in 0.1 M Bu_4NBF_4/MeCN containing a substrate (20 mM).

derivative **3** has ca. 0.1 V higher oxidation potential than **1a** and **1b**. Anodic fluorination of **4**, which possesses much higher oxidation potential than **1a** and **1b**, proceeded smoothly, while open-chain type **6** having a lower oxidation potential than **4**, was not fluorinated at all. These results indicated that oxidation potential is not crucial for the successful fluorination reaction. It is known that anodic α-methoxylation of carbamate[15] and amine[16] proceeds through *ECEC* mechanism and the deprotonation step of the cation radical intermediate is the rate-determining step. Therefore, the successful anodic fluorination would be related with the easiness of the elimination of an α-proton of radical cations of **1** and **4** (Scheme 5). However, further mechanistic study is necessary.

In summary, we have illustrated the first example of successful, direct α-fluorination of α-amino acid derivatives using an electrochemical method.

Acknowledgements

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8. Electrolysis was carried out at a platinum anode and cathode (2×2 cm^2, each) in solvent (10 mL) containing 5 mmol of fluoride salt and 1 mmol of substrate using an undivided glass cell. Constant current (50 mA/cm^2) was passed until the starting material was consumed. After the electrolysis, the resulting electrolytic solution was passed through a short column chromatography on silica gel using ethyl acetate to remove the fluoride salt. The eluent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (hexane to hexane/AcOEt).
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11. **2a**: ^1H NMR δ 1.76 (3H, s), 1.85 (3H, s), 3.31 (3H, s,), 4.20 (1H, dd, $J=51$ Hz, 10 Hz), 4.28 (1H, dd, $J=37$ Hz, 13 Hz), 7.34–7.53 (5H, m); ^{19}F NMR δ −33.76 (m); anal. calcd for $C_{14}H_{16}FNO_4$: C, 59.78; H, 5.73; N, 4.98. Found: C, 59.39; H, 5.66; N, 5.00%.

12. **2b**: mp 94–96°C; ^{1}H NMR (*trans* and *cis* mixture) δ 1.23 (3H, d, $J=6$ Hz, *trans*), 1.26 (3H, s, *trans*), 1.32 (3H, dd, $J=6$ Hz, 2 Hz, *cis*), 1.81 (3H, s), 1.82 (3H, s), 3.29 (3H, s, *cis*), 3.52 (3H, s, *trans*), 4.33 (1H, dq $J=18$ Hz, 6 Hz, *cis*), 4.52 (1H, dq, $J=19$ Hz, 6 Hz, *trans*), 7.34–7.54 (5H, m); ^{19}F NMR δ −48.71 (m, *trans* and *cis* mixture); anal. calcd for $C_{15}H_{18}FNO_4$: C, 61.01; H, 6.14; N, 4.74. Found: C, 60.75; H, 6.09; N, 4.66%.
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14. **5**: ^{1}H NMR δ 2.35–2.51 (2H, m), 2.53 (3H, s), 2.63–2.77 (1H, m), 2.84–2.98 (1H, m), 3.68 (3H, s); ^{19}F NMR δ −48.99 (dd, $J=25$ Hz, 19 Hz); HRMS m/z: calcd for $C_8H_{10}FNO_4$: 203.0594. Found: 203.0585.
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