Functionalization Including Fluorination of Nitrogen-Containing Compounds Using Electrochemical Oxidation

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Nitrogen-containing compounds have been subjected to electrochemical oxidation with Et_3N–3HF as an electrolyte. Caffeine afforded 8-fluorocaffeine as a sole product in 40.3% yield. Guanosine tetraacetate and uridine triacetate gave the fluorinated compounds in 17.5 and 4.6% yields, respectively. Similar electrochemical oxidation of caffeine with methanol, KCl, or KCN afforded 8-methoxycaffeine, 8-chlorocaffeine, or 8-cyanocaffeine, respectively.

Key words electrochemistry; oxidation; fluorination; lactam; nucleoside; caffeine

When fluorine atoms are introduced into steroid hormones, quinolone antibacterial drugs, and pyrimidinic antineoplastic drugs, the compounds often show a significant increase in effect and a large change in action spectrum.[1] In recent years, many fluorinated medicines have appeared on the market. Since very few fluorinated compounds are found as natural products,[2] the development of synthetic methodology to make fluorinated compounds is very important. Various electrophilic and nucleophilic fluorinating reagents have been reported recently.[3] 8-Fluorocaffeine has been prepared using SF_4, which is a nucleophilic fluorinating reagent, in three steps (22% overall yield)[4] and electrophilic fluorination of uracil using CF_3OF in two steps (84% overall yield) has been reported.[5] However, these fluorinating reagents are difficult to use owing to their poisonous nature and the need for careful handling. On the other hand, electroorganic reactions can generate various active reactants by changing the voltage, electrode, solvent, and/or electrolyte. Nitrogen atoms in organic compounds have an unshared electron pair which is easily oxidized on the anode to afford a radical cation regioselectively.[6] The radical cation would be trapped by a fluoride anion as a nucleophile. Compounds containing nitrogens, especially heterocycles, are common in nature and play important biological roles. Although electrolysis of nucleic acids has been reported,[7] only degradation compounds have been produced. Electrochemical introduction of an oxygen function into lactam compounds is known,[6] but anodic fluorination at a position next to a nitrogen atom of the amide has not been reported. We now report in detail a simple partial fluorination and functionalization of nitrogen-containing compounds using electrochemical oxidation.

Results and Discussion

Nitrogen-containing compounds were oxidized using constant-potential electrolysis (CPE), constant-current electrolysis (CCE) or alternating current electrolysis with a supporting electrolyte in an undivided cell equipped with a glassy carbon plate or platinum wire electrode and saturated calomel electrode (SCE) at room temperature. When the starting material was consumed (checked by TLC), the procedure was stopped and the mixture was worked up as usual. The product was purified by silica gel column chromatography.

Anodic Oxidation of Testosterone-2,4-Dinitrophenylhydrazone (1) Since testosterone (**3**), which has an enone group, requires a high oxidation potential for anodic functionalization, we attempted electrolysis of the hydrazone **1**, which can be prepared easily from testosterone (**3**). When anodic oxidation of **1** was carried out in methanol using $LiClO_4$ as an electrolyte, the 5-methoxylated compound **2** was obtained in 38.5% yield. The molecular formula of compound **2** was determined as $C_{26}H_{34}O_6N_4$ by HRMS. The presence of a methoxyl (δ_H 3.25; δ_C 50.6), a hydroxyl (δ_H 3.67; 3450 cm^{-1}), and a 2,4-dinitrophenyl (δ_H 7.69, 8.48, 8.76) group was inferred from the ^1H- and ^{13}C-NMR and IR spectra. Since the signal of a proton at C-4 appeared at 7.03 (1H, s), the double bond remained between C-3 and C-4 or C-4 and C-5. The above data indicated that methanol had been introduced into the starting material. As the hydroxyl group at C-17 was unattached, the methoxyl group must have been introduced at the C-5 position with concomitant migration of the double bond as a result of oxidation at the nitrogen atom. Although compound **2** is a single product, the stereochemistry was not determined. When Et_3N–3HF was used as an electrolyte, an inseparable mixture of 5-fluorinated compounds **4a** and **4b**, and testosterone (**3**) were produced in 6.4 and 39.3% yields, respectively. The molecular ion peak of 5-fluorinated **4** was increased by 18 atomic mass units from that of the starting material **1** in the mass spectrum. The ^{19}F-NMR spectrum showed the existence of a fluorine atom in **4**. In the ^{13}C-NMR spectrum, a doublet with a large coupling constant due to C–F (165.2 Hz), three sets of doublets with medium coupling constants due to C–C–F (14.9—25.6 Hz), and five sets of doublets with small coupling constants due to C–C–C–F (0.8—11.4 Hz) were observed. Therefore, fluorine had been introduced at C-5 of **4a**, **b**. The ratio of **4a** and **4b** was 3 : 1 as judged from the ^{13}C-NMR spectrum.

Anodic Oxidation of *N*-Methyl-ε-caprolactam (5) and

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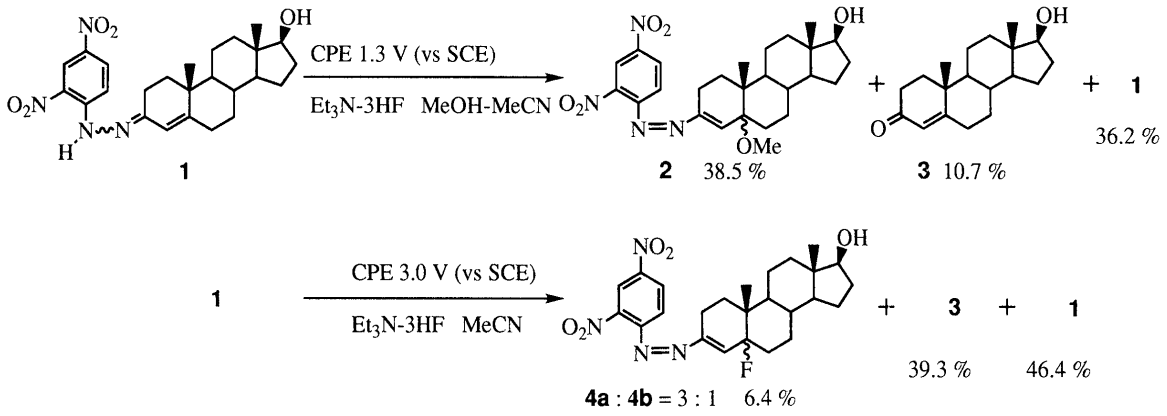


Chart 1

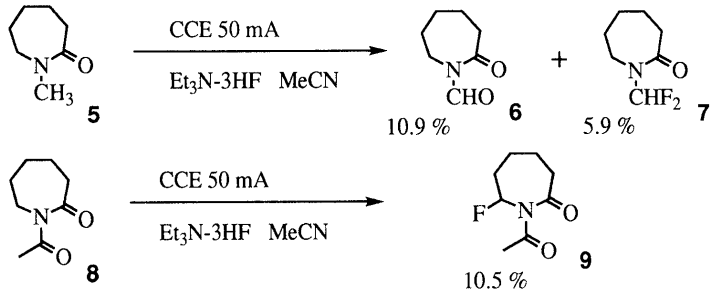


Chart 2

***N*-Acetyl-ε-caprolactam (8)** We chose *N*-methyl-ε-caprolactam (**5**), which has a methyl and a methylene group attached to nitrogen of the amide, and *N*-acetyl-ε-caprolactam (**8**), which has an electron-poor nitrogen atom attached to two carbonyl groups, as model amides. *N*-Methyl-ε-caprolactam (**5**) was oxidized in acetonitrile with Et_3N–3HF to afford *N*-formyl-ε-caprolactam (**6**),[8,9] presumably *via* attack of water in the reaction system, and the difluorinated compound **7**. The molecular ion peak of compound **7** was observed at *m/z* 163.0842 ($C_7H_{11}ONF_2$) in the high-resolution mass spectrum. The ^{1}H-NMR spectrum showed disappearance of the *N*-methyl group signal and the presence of a triplet signal having a large coupling constant (61.1 Hz) due to substitution of two fluorine atoms. The ^{13}C- and ^{19}F-NMR spectra also supported the structure **7**. On the other hand, oxidation of *N*-acetyl-ε-caprolactam (**8**) was carried out in the same way to afford the monofluorinated compound **9** as a sole product. In the ^{1}H-NMR spectrum of compound **9**, the signal of the methylene group attached to the amide nitrogen disappeared. A proton signal at δ_H 6.87 (d) having a large coupling constant (45.5 Hz) with the fluorine atom, and a carbon signal at δ_C 90.1 (d) having a large coupling constant (202.8 Hz) with the fluorine atom were observed. It is known that the regioselectivity of oxidation of lactams (γ-, δ-, and ε-) depends upon the ring size of the substrate.[10] When *N*-methyl-ε-caprolactam (**5**) was used, substitution of fluoride occurred at the exocyclic α-carbon atom next to the nitrogen atom, as expected. It is noteworthy that oxidative fluorination can occur at an endocyclic α-carbon atom next to the electron-poor nitrogen atom. With these results in mind, we next attempted the anodic oxidation of more complicated heterocycles such as purines or pyrimidines in order to obtain fluorinated nucleosides.

Anodic Oxidation of Xanthines[11] Caffeine (**10**) belongs to the xanthine group of compounds and has pharmacological activities itself. Its derivatives, methoxycaffeine (**11**) and chlorocaffeine (**12**), are topoisomerase II inhibitors.[12] We examined anodic functionalization, including methoxylation, cyanation, chlorination, and fluorination. The results of anodic oxidation of caffeine in various solvents and electrolytes are summarized in Table 1. Constant-potential oxidation of caffeine (**10**) in methanol (entry 1) afforded 8-methoxycaffeine (**11**)[13] as a result of an attack by a methoxide anion even in the presence of a fluoride anion. On the other hand, electrolysis of caffeine with KCl as an electrolyte in acetonitrile gave 8-chlorocaffeine (**12**)[14] (entry 3). When KCN was used as an electrolyte in acetonitrile, 8-cyanocaffeine (**13**)[4] was formed (entry 4). Finally, optimization of fluorination was attempted. When only KF was used as an electrolyte in acetonitrile, 8-cyanocaffeine (**13**) was produced (entry 5). When 18-crown-6 was added under the above conditions, 8-fluorocaffeine (**14**)[4] was isolated in poor yield (entry 9). Although constant-potential electrolysis was successful with Et_3N–3HF in acetonitrile, the reaction rate was very slow (entry 10). Finally, caffeine (**10**) was fluorinated by using Et_3N–3HF as an electrolyte in acetonitrile under alternating current to give 8-fluorocaffeine (**14**) in 40.3% yield (entry 11).

Anodic Oxidation of Nucleosides[11] When guanosine tetraacetate (**15**) was oxidized using Et_3N–3HF as an electrolyte in acetonitrile under similar conditions (*vide supra*), 8-fluoroguanosine tetraacetate (**16**) was produced in 17.5% yield. In the same electrolyte and solvent, ox-

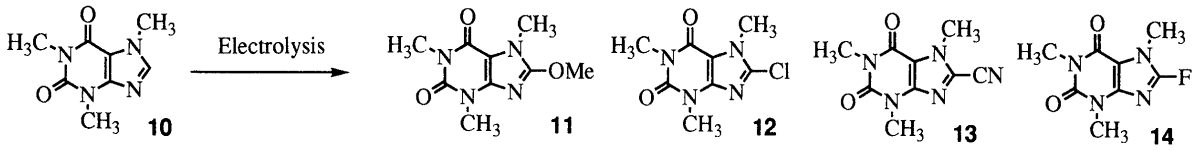


Chart 3

Table 1. The Results of Anodic Oxidation of Caffeine (**10**) under Various Conditions

Entry	Solvent	Electrolyte	Electrode	Potential (V *vs.* SCE)	Time (h)	Products	Yield (%)
1	MeOH	KF	+C−Pt	1.5	2.5	**11**	43.0
2	MeOH	$LiClO_4$	+C−Pt	2.0	2.0	**11**	6.2
3	MeCN	KCl	+C−Pt	1.5	11.5	**12**	42.7
4	MeCN	KCN	+C−Pt	1.5	5.0	**13**	10.5
5	MeCN	KF	+C−Pt	2.0	5.0	**13**	4.3
6	H_2O	KF	+C−Pt	1.4—1.5	2.2	Complex mixture	
7	THF	KF, 18-crown-6	+C−Pt	1.5—1.8	2.5	Complex mixture	
8	DMF	KF, 18-crown-6	+C−Pt	2.0—1.7	7.0	Complex mixture	
9	MeCN	KF, 18-crown-6	+C−Pt	1.5—2.2	5.0	**14**	1.4
10	MeCN	Et_3N–3HF	+C−Pt	2.0	8.0	**14**	15.0
11	MeCN	Et_3N–3HF	+Pt−Pt	5.0[a]	17.0	**14**	40.3

a) Cell voltage (AC 60 Hz).

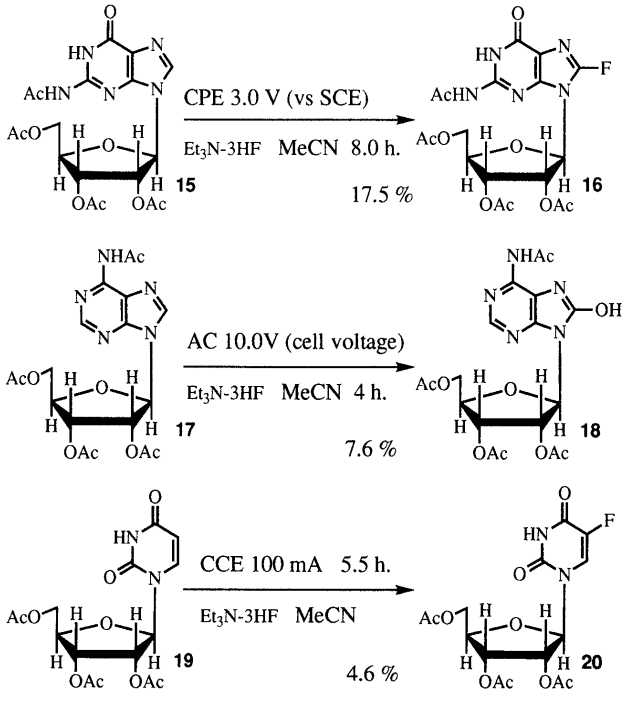


Chart 4

idation of adenine tetraacetate (**17**) afforded 8-hydroxyadenine tetraacetate (**18**)[15] in 7.6% yield instead of fluorinated compounds. With alternating current, uridine triacetate (**19**) was oxidized with Et_3N–3HF as an electrolyte in acetonitrile to afford 5-fluorouridine triacetate (**20**)[16] in 4.6% yield.

In Chart 5, two possible mechanisms for fluorination of purines are presented. Scheme 1 is based on the oxidation of the oxygen atom, and Scheme 2 on the oxidation of the nitrogen atom. In the case of caffeine, both mechanisms may operate. However, in the case of purine nucleoside only Scheme 2 can reasonably explain the position of fluorination. Oxidation potentials of ketones are higher than those of amines in general. In the case of lactams, the position next to the nitrogen rather than the oxygen atom is functionalized regioselectively. Therefore functionalization of lactams, xanthines, purines, and pyrimidines can be explained consistently in terms of direct oxidation of the nitrogen atom as in Scheme 2.

In conclusion, we have succeeded in simple partial fluorination and functionalization of nitrogen-containing compounds using electrochemical oxidation. Although the yield of fluorination is not high, the present method requires only one step and it is therefore advantageous for the functionalization of some heterocycles having biological activity, as fluorinated compounds in general are synthesized in not less than two steps.

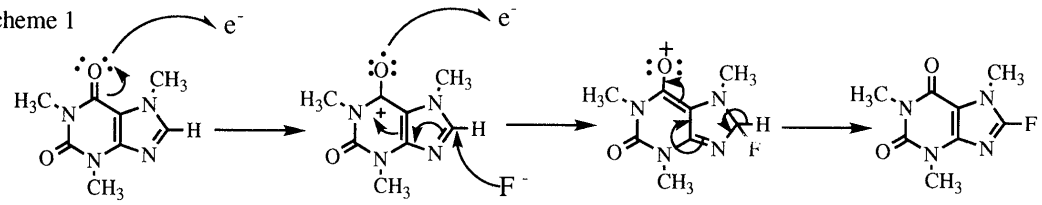
Experimental

^1H-, ^{13}C-, and ^{19}F-NMR spectra were recorded on a Varian Unity 200 spectrometer. The solvent used for NMR spectra was $CDCl_3$ unless otherwise stated, and *J*-values are given in Hz. ^{19}F-NMR chemical shifts are given in ppm upfield from trifluoroacetic acid as an internal standard. IR spectra were measured on a JASCO FT-IR5300 spectrophotometer. Mass spectra were measured on a JEOL JMS AX-500 spectrometer. Silica gel 60 for column chromatography was purchased from Merck. Solvents used in oxidation reactions were dried by treatment with molecular sieves 4A.

General Procedure A solution of nitrogen-containing compounds and supporting electrolyte in solvents was placed in a flask equipped with a glassy carbon plate or platinum wire anode, platinum wire cathode, saturated calomel electrode (SCE), and nitrogen inlet. The solution was oxidized using constant-potential electrolysis (CPE), constant-current electrolysis (CCE) or alternating current electrolysis (ACE) until only a trace of starting material remained, as judged by TLC. The reaction mixture was diluted with AcOEt and water. The layers were separated, and the organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was immediately chromatographed over silica gel with a gradient of AcOEt in hexane (0—100%) to afford functionalized compounds.

Anodic Methoxylation of Testosterone-2,4-dinitrophenylhydrazone (1) Conditions: testosterone-2,4-dinitrophenylhydrazone (**1**) (115.9 mg), $LiClO_4$ (506.7 mg), MeCN (20 ml), MeOH (20 ml), glassy carbon anode (CPE) (1.3 V *vs.* SCE) (2.7 h). Products: testosterone-2,4-dinitrophenylhydrazone (**1**) (41.9 mg, 36.2%), testosterone (**3**) (7.6 mg,

Scheme 1



Scheme 2

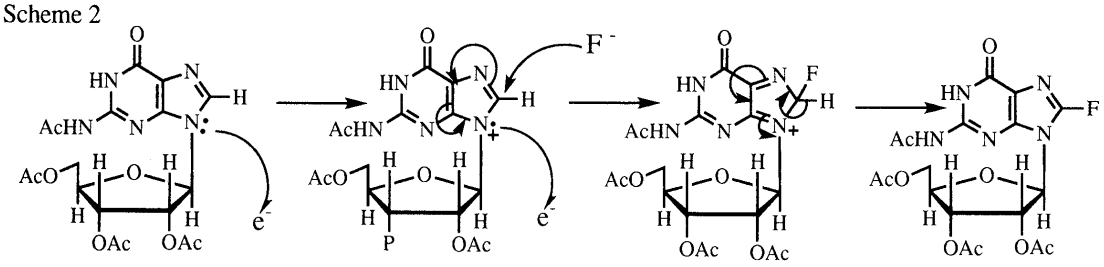


Chart 5

10.7%), methoxyazo compound **2** (47.5 mg, 38.5%).

Compound **2**: Red scales, mp 105—107 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, s), 0.91 (3H, s), 3.25 (3H, s), 3.67 (1H, t, J=8.8 Hz), 7.03 (1H, s), 7.69 (1H, d, J=9.0 Hz), 8.48 (1H, dd, J=9.0, 2.5 Hz), 8.76 (1H, d, J=2.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.2, 16.0, 20.2, 21.1, 23.3, 25.1, 25.6, 26.3, 30.5, 34.9, 36.7, 39.8, 44.8, 49.4, 50.6, 75.5, 75.9, 81.8, 119.9, 120.0, 127.6, 146.6, 147.3, 148.9, 150.5, 157.9. IR (film) cm^{-1}: 3450, 2960, 1620, 1550, 1460, 1360, 1080. MS m/z: 498 (M^+), 481, 468 (base), 449, 431, 421, 303. HRMS m/z: 498.2450 (Calcd for $C_{26}H_{34}O_6N_4$: 498.2478).

Anodic Fluorination of Testosterone-2,4-dinitrophenylhydrazone (1) Conditions: testosterone-2,4-dinitrophenylhydrazone (**1**) (155.5 mg), Et_3N–3HF (1 ml), MeCN (30 ml), platinum anode (CPE) (3.0 V *vs.* SCE) (3.5 h). Products: testosterone-2,4-dinitrophenylhydrazone (**1**) (72.1 mg, 46.4%), testosterone (**3**) (37.6 mg, 39.3%), fluoroazo compounds (mixture of **4a** and **4b**) (10.3 mg, 6.4%).

Compounds **4a** and **4b**: Red scales, mp 117—120 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, s), 0.95 (3H, s), 3.84 (1H, m), 6.90 (1H, br s), 7.66 (1H, d, J=8.8 Hz), 8.50 (1H, dd, J=8.8, 1.8 Hz). ^{13}C-NMR ($CDCl_3$) major peaks δ: 11.2 (CH_3), 15.5 (CH_3 (18), d, $J_{C\text{-}C\text{-}C\text{-}F}$=3.5 Hz), 20.0 ($CH_2$ (7 or 1), d, $J_{C\text{-}C\text{-}C\text{-}F}$=3.5 Hz), 20.9 ($CH_2$), 23.3 ($CH_2$), 25.4 ($CH_2$), 26.8 ($CH_2$ (1 or 7), d, $J_{C\text{-}C\text{-}C\text{-}F}$=2.3 Hz), 30.5 ($CH_2$), 30.9 ($CH_2$ (6), d, $J_{C\text{-}C\text{-}F}$=25.6 Hz), 34.6 (CH), 36.6 (CH_2), 38.9 (C (10), d, $J_{C\text{-}C\text{-}F}$=19.5 Hz), 43.2 (C), 45.5 (CH (9), d, $J_{C\text{-}C\text{-}C\text{-}F}$=0.8 Hz), 50.5 (CH), 81.8 (CH), 94.7 (C (5), d, $J_{C\text{-}F}$=165.2 Hz), 119.8 (CH), 120.1 (CH), 127.8 (CH), 143.9 (CH (4), d, $J_{C\text{-}C\text{-}F}$=14.9 Hz), 146.6 (C), 147.6 (C), 148.7 (C), 158.1 (C (3), d, $J_{C\text{-}C\text{-}C\text{-}F}$=11.4 Hz). Minor peaks δ: 11.0 (CH_3), 16.0 (CH_3 (18), d, $J_{C\text{-}C\text{-}C\text{-}F}$=6.1 Hz), 19.1 ($CH_2$ (7 or 1), d, $J_{C\text{-}C\text{-}C\text{-}F}$=2.7 Hz), 21.6 ($CH_2$), 23.3 ($CH_2$), 27.2 ($CH_2$), 28.0 ($CH_2$ (1 or 7), d, $J_{C\text{-}C\text{-}C\text{-}F}$=9.9 Hz), 30.5 ($CH_2$), 32.7 ($CH_2$ (6), d, $J_{C\text{-}C\text{-}F}$=23.2 Hz), 34.7 (CH), 36.3 (CH_2), 39.2 (C (10), d, $J_{C\text{-}C\text{-}F}$=19.1 Hz), 43.0 (C), 44.2 (CH (9), d, $J_{C\text{-}C\text{-}C\text{-}F}$=3.1 Hz), 50.5 (CH), 81.6 (CH), 94.5 (C (5), d, $J_{C\text{-}F}$=161.0 Hz), 119.7 (CH), 120.1 (CH), 127.7 (CH), 145.0 (CH (4), d, $J_{C\text{-}C\text{-}F}$=16.8 Hz), 146.9 (C), 147.7 (C), 148.4 (C), 159.2 (C (3), d, $J_{C\text{-}C\text{-}C\text{-}F}$=11.8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −62.2 (m). IR (film) cm^{-1}: 3430, 2960, 1550, 1360. MS m/z: 486 (M^+, base), 468, 451, 432, 291. HRMS m/z: 486.2292 (Calcd for $C_{25}H_{31}O_5N_4F$: 486.2278).

Anodic Oxidation of *N*-Methyl-ε-caprolactam (5) Conditions: *N*-methyl-ε-caprolactam (**5**) (281.1 mg), Et_3N–3HF (1 ml), MeCN (20 ml), glassy carbon anode (CCE, 50.0 mA) (5.0 h). Products: *N*-formyl-ε-caprolactam (**6**)[8,9] (34.2 mg, 10.9%), *N*-difluoromethyl-ε-caprolactam (**7**) (21.2 mg, 5.9%).

N-Formyl-ε-caprolactam (**6**)[8,9]: A colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.79 (6H, br s), 2.69 (2H, m), 3.79 (2H, m), 9.39 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 23.5 (CH_2), 28.6 (CH_2), 29.5 (CH_2), 38.2 (CH_2), 40.2 (CH_2), 162.2 (CH), 177.8 (C). IR (film) cm^{-1}: 2932, 1720, 1700. MS m/z: 142 $(M+1)^+$, 113 (base), 98, 85, 67, 55, 41.

N-Difluoromethyl-ε-caprolactam (**7**): A colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (6H, br s), 2.57 (2H, d, J=8.0 Hz), 3.47 (2H, d, J=6.5 Hz), 7.33 (1H, t, $J_{H\text{-}C\text{-}F}$=61.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 23.2 (CH_2), 29.1 (CH_2), 29.8 (CH_2), 37.4 (CH_2), 41.3 (CH_2), 109.2 (CH, t, $J_{C\text{-}F}$= 240.5 Hz), 176.4 (C). ^{19}F-NMR ($CDCl_3$) δ: −29.9 (d, J=61.1 Hz). IR (film) cm^{-1}: 2938, 1694, 1414. MS m/z: 163 (M^+), 144, 131, 115, 106, 96, 84, 68, 55 (base). HRMS m/z: 163.0842 (Calcd for $C_7H_{11}ONF_2$: 163.0809).

Anodic Fluorination of *N*-Acetyl-ε-caprolactam (8) Conditions: *N*-acetyl-ε-caprolactam (**8**) (281.1 mg), Et_3N–3HF (1 ml), MeCN (20 ml), platinum anode (CCE, 50.0 mA) (8.0 h). Products: ε-fluoro-*N*-acetyl-ε-caprolactam (**9**) (24.3 mg, 7.0%).

ε-Fluoro-*N*-acetyl-ε-caprolactam (**9**): A colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (6H, m), 2.67 (3H, d, J=0.4 Hz), 2.83 (2H, m), 6.87 (1H, ddd, J=45.5, 6.3, 1.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 22.2 (CH_2, d, $J_{C\text{-}F}$=3.5 Hz), 23.3 (CH_2), 27.0 (CH_2), 32.0 (CH_2, $J_{C\text{-}F}$=25.6 Hz), 39.2 (CH_2, d, $J_{C\text{-}F}$=3.8 Hz), 90.1 (CH, d, $J_{C\text{-}F}$=202.8 Hz), 172.9 (C, s), 177.2 (C, d, $J_{C\text{-}F}$=2.8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −79.54 (dd, J=45.7, 35.2 Hz). IR (film) cm^{-1}: 2946, 1728, 1417. CI-MS m/z: 174 $(M+1)^+$, 172 (base), 154 $(M+1-HF)^+$, 141, 130. HR-CI-MS m/z: 174.0946 (Calcd for $C_8H_{13}O_2NF$: 174.0930).

Anodic Methoxylation of Caffeine (10) Conditions: caffeine (**10**) (231.8 mg), KF (1.2 g), MeOH (30 ml), glassy carbon anode (CPE, 1.5 V *vs.* SCE) (2.5 h). Product: 8-methoxycaffeine (**11**)[13] (115.1 mg, 43.0 %).

8-Methoxycaffeine (**11**)[13]: Colorless needles, mp 179—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.36 (3H, s), 3.50 (3H, s), 3.68 (3H, s), 4.14 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 27.5 (CH_3), 29.5 (CH_3), 57.6 (CH_3), 103.3 (C), 146.0 (C), 151.4 (C), 154.5 (C), 156.0 (C). IR (film) cm^{-1}: 2950, 1700, 1660, 1530. MS m/z: 224 (M^+, base), 209, 181, 167, 139.

Anodic Chlorination of Caffeine (10) Conditions: caffeine (**10**) (202.0 mg), KCl (1.2 g), 18-crown-6 (1.0 g), MeCN (40 ml), glassy carbon anode (CPE, 1.5 V *vs.* SCE) (10.5 h). Products: caffeine (**10**) (19.2 mg), 8-chlorocaffeine (**12**)[14] (101.4 mg, 42.8%).

8-Chlorocaffeine (**12**)[14]: Colorless needles, mp 187—189 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.39 (3H, s), 3.54 (3H, s), 3.96 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 27.9 (CH_3), 29.7 (CH_3), 32.6 (CH_3), 108.1 (C), 138.8 (C), 146.9 (C), 151.1 (C), 154.4 (C). IR (film) cm^{-1}: 1705, 1659. MS m/z: 228 (M^+, base), 199, 193, 171, 143, 128.

Anodic Cyanation of Caffeine (10) Conditions: caffeine (**10**) (205.0 mg), KCN (1.6 g), and 18-crown-6 (1.5 g), MeCN (40 ml), glassy carbon anode (CPE, 1.5 V *vs.* SCE) (5.0 h). Products: caffeine (**10**) (36.6 mg), 8-cyanocaffeine (**13**)[4] (25.9 mg, 11.2%).

8-Cyanocaffeine (**13**)[4]: Colorless needles, mp 150—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (3H, s), 3.58 (3H, s), 4.18 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 28.3 (CH_3), 29.9 (CH_3), 34.0 (CH_3), 109.5 (C), 109.8 (C), 124.8 (C), 147.5 (C), 151.2 (C), 154.7 (C). IR (film) cm^{-1}: 2247, 1657, 1595, 1547. MS m/z: 219 (M^+, base), 190, 186, 162, 134, 119, 107.

Anodic Fluorination of Caffeine (10) Conditions: caffeine (**10**) (207.7 mg), Et_3N–3HF (1 ml), MeCN (20 ml), platinum electrodes (ACE, 5.0 V cell voltage, 60 Hz) (17.0 h). Products: caffeine (**10**) (9.7 mg), 8-fluorocaffeine (**14**)[4] (91.4 mg, 40.3%).

8-Fluorocaffeine (**14**)[4]: Colorless needles, mp 159—161 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.40 (3H, s), 3.52 (3H, s), 3.85 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 27.9 (CH_3), 29.9 (CH_3), 30.6 (CH_3), 103.8 (C, $J_{C\text{-}N\text{-}C\text{-}F}$=3.0 Hz), 144.4

(C, $J_{C\text{-}N\text{-}C\text{-}F}$=13.7 Hz), 151.5 (C), 152.2 (C, $J_{C\text{-}F}$=254.7 Hz), 155.0 (C). ^{19}F-NMR ($CDCl_3$) δ: −31.4 (m). IR (film) cm^{-1}: 2950, 1720, 1660, 1450. MS *m/z*: 212 (M^+), 183, 155, 140, 127 (base), 112, 100.

Anodic Fluorination of Guanosine Tetraacetate (15) Conditions: guanosine tetraacetate (**15**) (1.0 g), Et_3N–3HF (3.0 ml), MeCN (50 ml), platinum electrodes (ACE, 10.0 V cell voltage, 60 Hz) (7.5 h). Products: guanosine tetraacetate (**15**) (216.9 mg), fluoroguanosine tetraacetate (**16**) (235.1 mg, 17.5%).

Fluoroguanosine Tetraacetate (**16**): Colorless scales, mp 101—105 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.11 (3H, s), 2.16 (3H, s), 2.32 (3H, s), 4.36—4.52 (2H, m), 4.58—4.74 (1H, m), 5.76 (1H, dd, J=5.1, 4.2 Hz), 5.91 (1H, d, J=5.1 Hz), 5.99 (1H, t, J=5.1 Hz), 9.36 (1H, br s), 12.05 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 20.4 (CH_3), 20.6 (CH_3), 20.9 (CH_3), 24.2 (CH_3), 63.1 (CH_2), 70.9 (CH), 72.3 (CH), 80.0 (CH), 85.5 (CH), 115.7 (C, $J_{C\text{-}N\text{-}C\text{-}F}$=12.5 Hz), 145.8 (C, $J_{C\text{-}N\text{-}C\text{-}F}$=3.8 Hz), 147.7 (C, $J_{C\text{-}N\text{-}C\text{-}N\text{-}C\text{-}F}$=2.7 Hz), 149.0 (C, $J_{C\text{-}F}$=249.1 Hz), 154.6 (C, $J_{C\text{-}C\text{-}N\text{-}C\text{-}F}$=2.3 Hz), 169.5 (C), 169.8 (C), 171.7 (C), 172.1 (C). ^{19}F-NMR ($CDCl_3$) δ: −30.9 (m). IR (film) cm^{-1}: 3167, 1748, 1686, 1231. MS *m/z*: 469 (M^+), 294, 259 (base), 212, 198. HRMS *m/z*: 469.1231 (Calcd for $C_{18}H_{20}O_9N_5F$: 469.1245).

Anodic Hydroxylation of Adenosine Tetraacetate (17) Conditions: adenosine tetraacetate (**17**) (321.9 mg), Et_3N–3HF (2.0 ml), MeCN (30 ml), platinum electrodes (ACE, 10.0 V cell voltage, 60 Hz) (4.0 h). Products: adenosine tetraacetate (**17**) (28.5 mg), 8-hydroxyadenosine tetraacetate (**18**)[15] (25.2 mg, 7.6%).

8-Hydroxyadenosine tetraacetate (**18**)[15]: Colorless scales, mp 106—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 2.13 (3H, s), 2.15 (3H, s), 2.28 (3H, s), 4.28 (1H, dd, J=10.8, 6.0 Hz), 4.37 (1H, td, J=6.0, 2.7 Hz), 4.50 (1H, dd, J=10.8, 2.7 Hz), 5.82 (1H, t, J=6.0 Hz), 6.12 (1H, d, J=3.8 Hz), 8.35 (1H, s), 9.07 (1H, br s), 9.51 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 23.8 (CH_3), 63.3 (CH_2), 70.5 (CH), 72.1 (CH), 79.2 (CH), 84.5 (CH), 108.5 (C), 137.7 (C), 150.4 (s ×2), 150.7 (CH), 169.7 (C), 170.0 (C), 170.1 (C), 170.7 (C). IR (film) cm^{-1}: 3314, 1744, 1703, 1227. MS *m/z*: 451 (M^+), 332, 289, 276, 259, 139 (base).

Anodic Fluorination of Uridine Triacetate (19) Conditions: uridine triacetate (**19**) (217.5 mg), Et_3N–3HF (1.0 ml), MeCN (30 ml), platinum anode (CCE, 100 mA) (5.5 h). Products: uridine triacetate (**19**) (10.7 mg), fluorouridine triacetate (**20**)[16] (10.4 mg, 4.6%).

Fluorouridine triacetate (**20**)[16]: Colorless needles, mp 126—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s), 2.13 (3H, s), 2.18 (3H, s), 4.37 (3H, br s), 5.30 (1H, br s), 5.32 (1H, br d, J=3.2 Hz), 6.07 (1H, dt, J=3.2, 1.6 Hz), 7.62 (1H, d, J=5.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 20.4 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 62.9 (CH_2), 70.0 (CH), 72.8 (CH), 80.1 (CH), 87.2 (CH), 123.3 (CH, $J_{C\text{-}C\text{-}F}$=33.5 Hz), 140.8 (C, $J_{C\text{-}F}$=239.6 Hz), 148.7 (C), 156.4 (C, $J_{C\text{-}C\text{-}F}$=26.0), 169.6 (C), 169.7 (C), 170.0 (C). ^{19}F-NMR ($CDCl_3$) δ: −87.2 (br d, J=5.3 Hz). IR (film) cm^{-1}: 3266, 1740, 1227. FAB-MS *m/z*: 427 $(M+K)^+$, 411 $(M+Na)^+$.

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