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Functionalisation Including Fluorination of Caffeine, Guanosine Tetraacetate, and Uridine Triacetate using Electrochemical Oxidation

Masakazu Sono*, Naoko Toyoda, Yoshikazu Shizuri, and Motoo Tori

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro cho, Tokushima 770, Japan

Abstract:. The title compounds have been subjected to electrochemical oxidation with Et_3N-3HF as an electrolyte. Caffeine afforded 8-fluorocaffeine as a sole product in 43% yield. Guanosine tetraacetate and uridine triacetate gave the fluorinated compounds in 7.3 and 4.8 % yield, respectively. Similar electrochemical oxidation of caffeine with methanol, KCl or KCN yielded 8-methoxycaffeine, 8-chlorocaffeine, or 8-cyanocaffeine, respectively.

One of the methods for development of new drugs is the modification of functional groups existing in biologically active compounds. Especially when the fluorine atom is introduced, compounds often show a significant increase in effect and a large change in effective spectrum.[1] In recent years many fluorinated medicines have appeared on the market. As very few fluorinated compounds are present in Nature,[2] the development of synthetic methodology to make fluorinated compounds is very important. Although various electrophylic and nucleophilic fluorinating reagents have been reported recently,[3] these are often difficult to be used owing to their poisonous nature and difficult handling. Although the electrolysis of nucleic acids have been reported,[4] only degradation compounds have been produced. We now report our simple and efficient partial fluorination and functionalization of caffeine (1), guanosine tetraacetate (2), and uridine triacetate (3) using electrochemical oxidation.

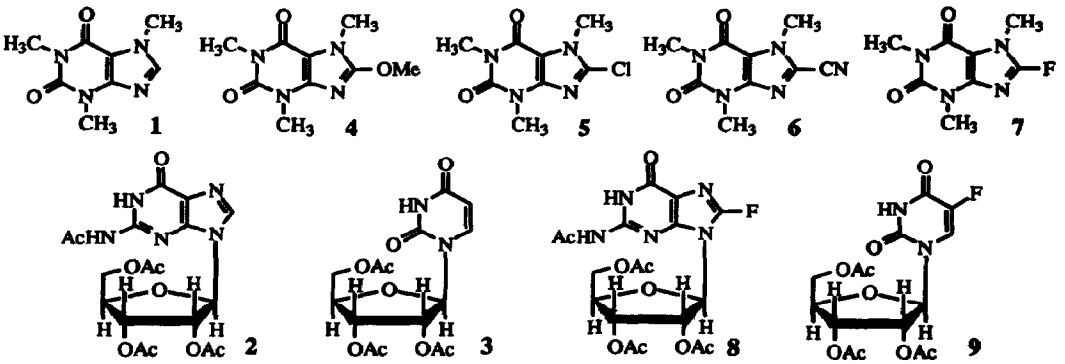
Anodic oxidation of heterocyclic compounds (ca. 1 mmol) in acetonitrile (20 ml) containing Et_3N-3HF (ca. 1 ml) as supporting electrolyte was carried out in an undivided cell equipped with a platinum wire electrode under constant potential conditions at room temperature. When the starting material was consumed (checked by TLC), the electricity was stopped and the mixture was worked up as usual and purified by silica gel chromatography. The results are summarized in Table 1. First of all the xanthine compound, caffeine (1), was oxidized electrochemically under several conditions. Constant potential oxidation of caffeine (1) in methanol (Entry 1) afforded 8-methoxycaffeine (4)[5] in 43 % yield. On the other hand electrolysis of caffeine (1) with KCl as an electrolyte in acetonitrile gave 8-chlorocaffeine (5)[6] in 47 % yield (Entry 2). These two compounds, (4 and 5), have been known to have topoisomerase II inhibitory activity.[7] When KCN was used as an electrolyte in acetonitrile, 8-cyanocaffeine (6)[8] was formed (Entry 3). Caffeine (1) was fluorinated by using Et_3N-3HF as an electrolyte in acetonitrile to give 8-fluorocaffeine (7)[8, 9] (42 % yield) (Entry 4). When guanosine tetraacetate (2) was oxidized using Et_3N-3HF as an electrolyte in acetonitrile under similar conditions, 8-fluoroguanosine tetraacetate (8)[10] was produced in 7.3 % yield (Entry 5). Uridine triacetate (3) was also oxidized using Et_3N-3HF as an electrolyte in acetonitrile to afford 5-fluorouridine triacetate (9)[11, 12] in 4.8 % yield (Entry 6).

Although the yield of fluorination is not so 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 by not less than two steps. These are the first examples of electrolytic fluorination of this class of compounds. Further investigation from a mechanistic and pharmacological aspect is underway.

Table 1. Electrochemical oxidation of caffeine (1) and related compounds.

Entry	Substrate	Solvent	Conditions electrolyte	Potential (vs. SCE)	Time	Products	Yield
1	1	MeOH	KF	1.5 V	2.5 h	(4)	43.0 %
2	1	MeCN	KCl	1.5 V	11.5 h	(5)	42.7 % (47.2 %)[a]
3	1	MeCN	KCN	1.5 V	5.0 h	(6)	13.6 %
4	1	MeCN	Et_3N-3HF	5.0 V[b]	17.0 h	(7)	40.3 % (42.2 %)[a]
5	2	MeCN	Et_3N-3HF	3.0 V	10.0 h	(8)	6.3 % (7.3 %)[a]
6	3	MeCN	Et_3N-3HF	C.C.E. 100 mA	5.5 h	(9)	4.6 % (4.8 %)[a]

a: Based on consumed starting material. b: Cell voltage (AC 60 Hz).



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9. **7**: MS: 212 (M^+), 183, 155, 140, 127 (base), 112, 100; δ_H ($CDCl_3$): 3.40 (3H, s), 3.52 (3H, s), 3.85 (3H, s); δ_C ($CDCl_3$): 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); δ_F ($CDCl_3$, TFA): -31.4 (s); IR(film): 2950, 1720, 1660, 1450. cm^{-1}.
10. **8**: HRMS, Found: 469.1231. Calcd for $C_{18}H_{20}O_9N_5F$: 469.1245; δ_H ($CDCl_3$): 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, brs), 12.05 (1H, brs); δ_C ($CDCl_3$): 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); δ_F ($CDCl_3$, TFA): -30.9 (s); IR(film): 3167, 1748, 1686, 1231 cm^{-1}.
11. **9**: FABMS: 427 $(M+K)^+$, 411 $(M+Na)^+$; δ_H ($CDCl_3$): 2.11 (3H, s), 2.13 (3H, s), 2.18 (3H, s), 4.37 (3H, brs), 5.30 (1H, brs), 5.32 (1H, brd, *J*=3.2 Hz), 6.07 (1H, dt, *J*=3.2, 1.6 Hz), 7.62 (1H, d, *J*=5.3 Hz); δ_C ($CDCl_3$): 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); δ_F ($CDCl_3$, TFA): -87.2 (brd, *J*=5.3Hz); IR(film): 3266, 1740, 1227 cm^{-1}.
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