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PRELIMINARY NOTE

Direct Fluorination of Biologically Interesting Compounds Using N-Fluoro-3,5-Dichloropyridinium Triflate

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SUMMARY

N-fluoro-3,5-dichloropyridinium triflate was used for the direct fluorination of biologically important aromatic compounds.

Fluorinated analogues of biologically important organic molecules have proved to be valuable biochemical and pharmacological agents [1]. Consequently there is a constant search for new selective and efficient ways for introducing fluorine into these molecules. Umemoto et al. recently have introduced N-fluoropyridinium triflates as stable electrophilic fluorinating agents [2]. As part of our ongoing interest in preparation of fluorinated biologically active molecules, especially catecholamines [3], we have examined the reaction of N-fluoro-3,5-dichloropyridinium triflate (1) with several

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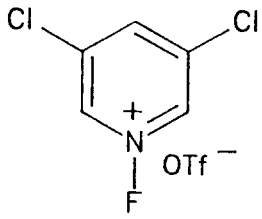
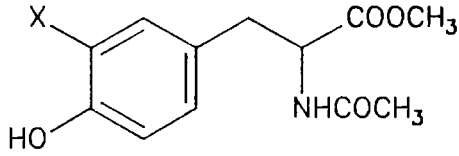
aromatic compounds. Reaction of N-acetyltyrosine methyl ester (2) with 1 for 8 hr at room temperature in CH_2Cl_2/CH_3CN 9/1 gave 3-fluoro-N-acetyltyrosine methyl ester (3) in 65% yield [4]. The substitution ortho to the hydroxy group is in accordance with an electrophilic fluorination mechanism.

Reaction of 17β-estradiol (4) and 1 (CH_2Cl_2/CH_3CN 9/1, 12 hr, room temperature) provided a one to one mixture of 2-fluoro-17β-estradiol (5) and 4-fluoro-17β-estradiol (6) in 60% isolated yield [5]. No fluorinated product was obtained when the percentage of CH_3CN was increased in an attempt to obtain a better dissolution of the starting material.

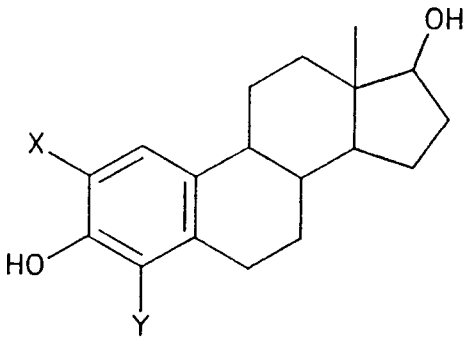


1



2 X = H

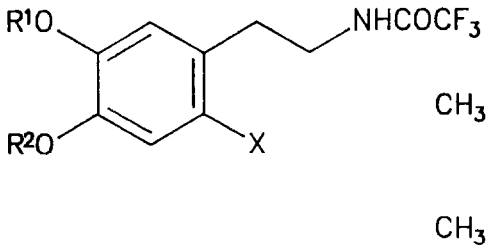
3 X = F

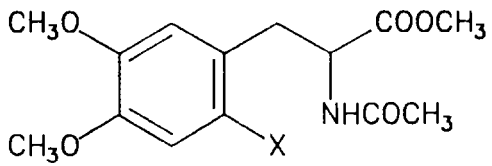


4 X = H, Y = H

5 X = F, Y = H

6 X = H, Y = F





	R^1	R^2	X
7	H	H	H
8	H	CH_3	H
9	CH_3	H	H
10	CH_3	CH_3	H
11	CH_3	CH_3	F

12 X = H

13 X = F

An attempt to fluorinate N-trifluoroacetyl dopamine (7) using the same procedure resulted in a rapid consumption of fluorination reagent and production of oxidation products. Similar results were obtained when one of the hydroxyl groups was protected as a methoxy group as in 8 or 9. However a moderate yield (20%) of the 6-fluoro derivative 11 [6] was isolated when a fully protected dopamine derivative was treated with 1 (35 C, CH_2Cl_2, 10 hr). The regioselectivity observed is in accordance with an electrophilic reaction pathway.

The protected dopa derivative 12 exhibited a similar behavior - the 6-fluoro isomer 13 was the only fluorinated product obtained (35 C, CH_2Cl_2, 8 hr, 30%).

Compound	^{19}F nmr	^{1}H nmr
3	-140.3 (t, J=12 Hz)	(CD_3OD/TMS) 1.91(s,3), 2.8-3 (m,2), 3.67(s,3), 4.59(dd, J_1=8.8 Hz, J_2=5.7 Hz, 1), 6.77- 6.84(m, 2), 6.89(dd, J_1= 12.9 Hz, J_2=1.7 Hz, 1)
5	-141.1 (dd, J_1=12 Hz J_2=10 Hz)	(CD_3OD/TMS) 0,77(s, 3), 3.65(t, J=8.4Hz, 1), 6.57(d, J=10 Hz, 1), 6.91(d, J=12 Hz, 1)
6	-142.4 (d, J=8.6 Hz)	(CD_3OD/TMS) 0.77(s,3), 3.65(t, J=8.4 Hz, 1), 6.68(t, J=8.6 Hz, 1), 6.88(d, J=8.6 Hz, 1)
11	-127.1 (dd, J_1= 9Hz, J_2=5 Hz, 1) -77.2(s, 3)	($CDCl_3$/TMS) 2.87(t, J=6.9 Hz, 2), 3.60(t, J=6.9 Hz, 2), 3.84(s, 3), 3.86(s, 3), 6.62(d, J=5 Hz, 1), 6.65(d, J=9.2 Hz, 1)
13	-126.3 (dd, J_1=11 Hz, J_2=7 Hz)	($CDCl_3$/TMS) 2.01(s,3), 3.24(M,2), 3.66 (s,3), 3.82(s,3), 3.84(s,3), 4.78(m,1), 6.55(d, J=7 Hz, 1), 6.62(d, J=11 Hz, 1)

A typical fluorination reaction is as follows: 400 mg (1.68 mmol) of 2 and 632 mg (2 mmol) of 1 were stirred under nitrogen in 10 ml of dry CH_2Cl_2/CH_3CN (9:1). After 8 hr the starting material and reagent were consumed (verified by KI paper and

TLC). The reaction mixture was poured over 10 ml of water, neutralized with $NaHCO_3$, and separated. The organic layer was washed with 10 ml of water, dried (Na_2SO_4) and concentrated under reduced preasure. The crude product was purified by silica gel vacuum column chromatography with 60% ethyl acetate in petrol ether (bp 35-60 C) as eluent. 280 mg (1.1 mmol) of 3 were obtained (65% yield).

The present study demonstrates the utility of 1 for the fluorination of biologically important molecules containing oxygenated aromatic rings. With the catecholamines, the main advantages of this procedure are the high regioselectivity, mild reaction conditions and stability of the reagent.

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