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Fluorination of Pyrrolic Compounds with Xenon Difluoride

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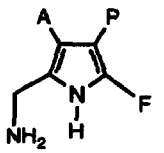
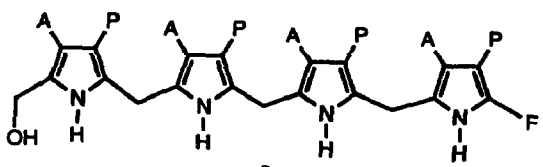
Abstract: Direct fluorination of the pyrrole ring with electron-withdrawing groups, such as, -CHO, -COR, -COOR, -$CONR_2$, using xenon difluoride under mild conditions leads to the corresponding fluoropyrroles in 25-54% yields. It was found that fluorination takes place only at the α-position of the pyrrole even when the β-position is also free.

In connection with our syntheses of fluorinated porphobilinogen (PBG) **1** and hydroxymethylbilane (HMB) **2** as potential inhibitors of the enzymes PBG deaminase and uro'gen III cosynthase respectively,[1,2] we required an efficient method for preparing fluoropyrrole compounds. Although it has been known for some time that fluorine often has profound and unexpected effects on biological activity, general methods for the direct introduction of fluorine into pyrrole rings,[3] which are frequently found in natural products, are not available, due to the high reactivity of pyrroles towards electrophiles and the oxidizing power of electrophilic fluorinating reagents, nor can fluorine be introduced into the pyrrole ring by the classic Balz-Schiemann reaction.[4] We report herein the first preparation of fluoropyrroles by direct fluorination of the pyrrole ring without N-H protection, using xenon difluoride as fluorinating reagent.



1

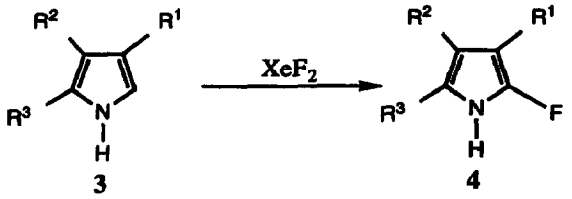


2

A=CH_2COOH, P=CH_2CH_2COOH

As illustrated in Scheme 1, a series of α-free substituted pyrrole compounds **3a-3i** were reacted with xenon difluoride to give the expected products **4a-4i**. In a typical experiment, the α-unsubstituted pyrrole was dissolved in degassed acetonitrile or dichloromethane under a nitrogen atomosphere and xenon difluoride (1.2 equiv) added with stirring at 0°C. The resulting mixture was warmed gradually to room temperature. Slow Xe gas evolution was observed and the reaction was monitored for the disappearance of xenon difluoride using KI-starch paper. The mixture was poured into water and extracted with dichloromethane. The extract was dried with anhydrous sodium sulfate and the solvent evaporated to give the crude product which was purified by chromatography on silica gel. The results are listed in Table 1.

Scheme 1



3 4

	R^1	R^2	R^3		R^1	R^2	R^3
3a	H	H	CHO	**3b**[5]	CH_2CH_2COOMe	CH_2COOMe	CHO
3c	H	H	$COOCH_2Ph$	**3d**[6]	CH_2CH_2COOMe	CH_2COOMe	$COOCH_2Ph$
3e[6]	CH_2COOMe	CH_2CH_2COOMe	$COOCH_2Ph$	**3f**	H	H	$COCCl_3$
3g[7]	H	H	$CONMe_2$	**3h**[8]	CH_2CH_2COOMe	CH_2COOMe	CH_3
3i[8]	CH_2COOMe	CH_2CH_2COOMe	CH_2OAc				

Table 1. Results of the reaction of substituted pyrroles (**3a-i**) with xenon difluoride

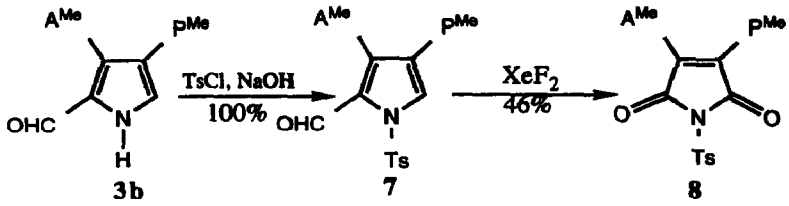
Entry	Product	Solvent	Temp.(°C)	Reaction (h)	Yield (%)[a]	δ_F(ppm)[b]
1	**4a**[9]	CH_3CN	0-25	6	35	-126.59
2	**4b**[9]	CH_3CN	0-25	6	32	-130.60
3	**4c**[9]	CH_3CN	0-25	7	37	-131.41
4	**4d**[9]	CH_2Cl_2	0-25	4	33	-135.54
5	**4e**[9]	CH_2Cl_2	0-25	2.5	25	-135.62
6	**4f**[9]	CH_2Cl_2	0-25	8	33	-125.26
7	**4g**[9]	CH_2Cl_2	0-25	2	54	-135.80
8	**4h**	CH_2Cl_2	-78-25	1	0	
9	**4i**	CH_2Cl_2	-78-25	1	0	

(a). Isolated yields based on **3**. (b). ^{19}F-NMR chemical shifts are reported in ppm upfield from trichlorofluoromethane as internal standard in $CDCl_3$ as solvent.

Because xenon difluoride is both a strong electrophile and oxidizing reagent, the successful fluorination of the pyrrole ring depends on its electronic properties as shown in Table 1. When the pyrrole ring is substituted by electron-withdrawing groups, such as, -CHO, -COR, -COOR, $-CONR_2$, the corresponding fluorinated products are obtained in 25-54% yields, whereas substrates with electron-rich pyrrole rings (as **3h** or **3i**), gave complicated mixtures in which no fluoropyrrole was detected by ^{19}F-NMR in the reaction temperature range from -78°C to 25°C. This indicates that only the less nucleophilic pyrrole rings could be fluorinated by xenon difluoride. Introduction of a second electron-withdrawing group into the pyrrole ring, however, led

only to oxidized product. For example, N-tosylated **3b** gave only the oxidized compound **8** in 46% yield under the same reaction conditions (Scheme 2).

Scheme 2



3b **7** **8**

A^{Me}=CH_2COOMe, P^{Me}=CH_2CH_2COOMe

Interestingly, when the β-position of the substituted pyrroles is also free as in **3a**, **3c**, **3f** and **3g**, it was found that the fluorination only took place at the α-position, no β-fluorinated pyrroles being detected, thus, revealing a satisfactory regioselectivity of the reaction, presumably due to greater electrophilicity of the α-position of the pyrrole compared with the β-position.

Although in the case of **3a** or **3b** small amounts of oxidized by-products were observed , xenon difluoride tolerated the aldehyde group during fluorination of pyrrole ring, providing a short route to the target molecules. We have also tried several other fluorinating reagents, for example, N-fluoropyridium triflate[10] and p-toluyl-N-fluoro-N-propyl sulfonamide.[11] However, no desired fluoropyrroles were obtained under a range of reaction conditions.

In conclusion, direct fluorination of the pyrrole ring using xenon difluoride as fluorinating reagent could provide a simple, efficient method for the direct synthesis of a wide range of novel fluoropyrroles.

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9. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker-WM300MHz spectrometer with TMS as internal standard, $CDCl_3$ as solvent, chemical shift in ppm, coupling constants J in Hz. Compound **4a**: ^{1}H-NMR δ 10.63 (br., s, 1H, N-H), 9.32 (d, J_{H-F} = 3.3, 1H, CHO), 6.90 (t, J = 4.5, 1H, H-C(4)), 5.77 (t, J = 4.5, 1H, H-C(3)); ^{13}C-NMR δ 178.85 (CHO), 153.26 (d, J_{C-F} = 274, C-2), 124.38, 122.73, 91.30 (d, $^{2}J_{C-F}$ = 11, C-3); EI-MS m/e 113 (M^+, 100), 84 (32), 57 (14). Compound **4b**: ^{1}H-NMR δ 9.47 (br., s, 2H, N-H and CHO), 3.77 (s, 2H, CH_2COOMe), 3.72, 3.67 (2 s, 2x3 H, 2 COO*Me*), 2.73 (t, ^{3}J = 6.8, 2H, CH_2CH_2COOMe), 2.57 (t, ^{3}J = 6.8, 2H, CH_2CH_2COOMe); ^{13}C-NMR δ 176.78 (CHO), 173.04 (COO), 170.69 (COO), 150.67 (d, J_{C-F} = 274, C-2), 127.77, 120.93, 103.68 (C-3), 52.48 (OCH_3), 51.72 (OCH_3), 33.59, 29.64, 17.32. HRMS (EI) Calcd for C12H14FNO5 (M^+) 271.0856, Found 271.0851. Compound **4c**: ^{1}H-NMR δ 9.35 (br., s, 1H, N-H), 7.50-7.32 (m, 5H, H-Ph), 6.84-6.81 (m, 1H, H-C(4)), 5.64-5.60 (m, 1H, H-C(3)), 5.30 (s, 2H, CH_2Ph); ^{13}C-NMR δ 1600.62 (COO), 149.52 (d, J_{C-F} = 268, C-2), 135.99, 128.59 (2C), 128.27 (2C), 115.72, 113.63, 89.33 (d, $^{2}J_{C-F}$ = 10, C-3), 70.50 (CH_2Ph); EI-MS m/e 219 (M^+, 25), 112 (7), 91 (100), 84 (4). Compound **4d**: ^{1}H-NMR δ 8.87 (br., s, 1H, N-H), 7.35-7.30 (m, 5H, H-Ph), 5.23 (s, 2H, CH_2Ph), 3.80 (s, 2H, CH_2COOMe), 3.62, 3.58 (2 s, 2x3 H, 2 COO*Me*), 2.67 (t, ^{3}J = 7.8, 2H, CH_2CH_2COOMe), 2.50 (t, ^{3}J = 7.8, 2H, CH_2CH_2COOMe); ^{13}C-NMR δ 173.14 (COO), 171.45 (COO), 160.33 (COO), 146.23 (d, J_{C-F} = 266, C-2), 135.78, 128.57, 128.38, 128. 34, 118. 24, 102.20 (d, $^{2}J_{C-F}$ = 9, C-3), 66.12 (CH_2Ph), 51.99, 51.99 (OCH_3), 51.70 (OCH_3), 33.85, 30.61, 17.49; EI-MS m/e 377 (M^+, 24), 345 (5), 333 (10), 256 (26), 224 (52), 192 (47), 150 (21), 91 (100). Compound **4e**: ^{1}H-NMR δ 9.21 (br., s, 1H, N-H), 7.31-7.27 (m, 5H, H-Ph), 5.20 (s, 2H, CH_2Ph), 3.62, 3.54 (2 s, 2x3 H, 2 COO*Me*), 3.37 (s, 2H, CH_2COOMe), 2.89 (t, ^{3}J = 8.0, 2H, CH_2CH_2COOMe), 2.47 (t, ^{2}J = 8.0, 2H, CH_2CH_2COOMe); ^{13}C-NMR δ 173.51 (COO), 171.52 (COO), 160.46 (COO), 146.79 (d, J_{C-F} = 267, C-2), 135.79, 130.66, 128.64, 128.44, 128.38, 109.47, 96.10 (d, $^{3}J_{C-F}$ = 8.4, C-3), 66.20 (CH_2Ph), 51.52, 51.52 (OCH3), 50.79 (OCH_3), 34.37, 27.41, 20.67; EI-MS m/e 376 ($(M-H)^+$, 24), 305 (72), 283 (22), 219 (15), 199 (20), 168 (23). Compound **4f**: ^{1}H-NMR δ 9.48 (br., s, 1H, N-H), 7.35-7.29 (m, 1H, H-C(4)), 5.82-5.78 (m, 1H, H-C(3)); ^{13}C-NMR δ 172.67 (CO), 152.16 (d, J_{C-F} = 274, C-2), 122.21 (C-4), 114.88 (CCl_3), 110.45 (C-5), 91.90 (d, $^{2}J_{C-F}$ = 9, C-3); EI-MS m/e 229 ($(M-H)^+$, 8), 182 (3), 166 (9), 128 (32), 112 (100), 84 (15). Compound **4g**: ^{1}H-NMR δ 11.11 (br., s, 1H, N-H), 6.39 (t, J = 4.0, 1H, H-C(4)), 5.54 (t, J = 4.0, 1H, H-C(3)), 3.23 (s, br, 6H, $N(CH_3)_2$); ^{13}C-NMR δ 162.28 ($CONMe_2$), 149.29 (d, J_{C-F} = 262, C-2), 116.42, 112.48, 87.64, 37.92; EI-MS m/e 156 ($M,^+$ 100), 138 (3), 128 (5), 112 (54), 84 (20).
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