Journal of Fluorine Chemistry, 39 (1988) 435–440

Received: March 15, 1988; accepted: April 9, 1988

PRELIMINARY NOTE

Selective Fluorination of Ethyl 1-Methylpyrazole-4-carboxylates with Poly(Hydrogen Fluoride)-Amine Complex under Electrolytic Anodic Oxidation

Kenzi MAKINO** and Hirosuke YOSHIOKA*

The Institute of Physical and Chemical Research (RIKEN)
Wako, Saitama 351-01 (Japan)

SUMMARY

Fluorination of ethyl 1-methylpyrazole-4-carboxylate (1a) and its 3-chloro analogue (1b) with poly(hydrogen fluoride)-pyridine-triethylamine complex under electrolytic anodic oxidation yielded new ethyl 1-methyl-5-fluoropyrazole-4-carboxylate (2a), ethyl 1-fluoromethyl-5-fluoropyrazole-4-carboxylate (3a) and their 3-chloro analogues (2b) and (3b). Major factors controlling selectivities and yields for the fluorinated pyrazole-4-carboxylates are described.

Selective fluorination of common organic carbonyl compounds or N-heterocycles at the activated carbon atom(s) under

** Permanent Address; Central Research Institute, Nissan Chemical Ind., Ltd., Tsuboi-cho, Funabashi, Chiba 274 (Japan)

0022-1139/88/$3.50

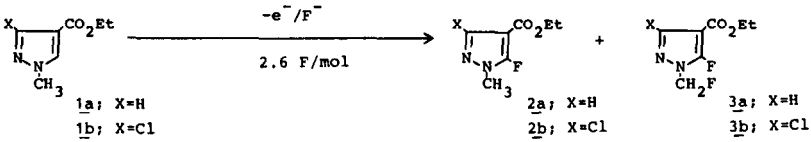
electrolytic conditions is one of the most attractive but yet rarely attempted research areas, and there exist only a few relevant reports. For example, Laurent et al. lately reported the formation of mono- and difluorinated (4-methoxyphenyl)acetone and ethyl (4-methoxyphenyl)acetate [1], and fluoroindane derivatives [2], by anodic oxidation of corresponding substrates in the presence of triethylamine trishydrofluoride. Ballinger et al. also reported recently the formation of 2-fluoropyridine by electrolysis of pyridine with tetramethylammonium fluoride bishydrofluoride as supporting electrolyte as well as fluoride source [3]. In connection with our consecutive works on the selective fluorination of various N-heterocycles under mild conditions [4-6], we now wish to report a new method for the selective fluorination of ethyl 1-methylpyrazole-4-carboxylate (1a) and its 3-chloro analogue (1b) by the electrolysis with a modified poly(hydrogen fluoride)-amine complex, which may provide us with a direct pathway leading to a variety of new heterocycles containing a limited number of fluorine atoms.

First, we found that the electrolysis of 1a with 70% poly(hydrogen fluoride)-pyridine, hereinafter HF-Py, which was potentiostatically conducted in acetonitrile in a beaker cell equipped with Pt electrodes at +2.50 V against a Ag-AgCl reference electrode, yielded after feeding of 2.6 F/mole the 5-fluoro derivative (2a) as minor product together with the 1-fluoromethyl-5-fluoro derivative (3a) as the major in a ratio of 1 : 3 in a low combined yield (See run 1 in Table 1). The selectivity for 2a was notably improved by increasing the amount of triethylamine added to the HF-Py media. The yield was maximized up to 40% in a 83% selectivity for 2a when 0.6 volume

equivalent of triethylamine (vs. HF-Py) was added (See run 3)[A], and the selectivity became complete in run 4 but with sharp decrease in the yield when one volume equivalent of triethylamine was applied to the media. Acetonitrile appears to be an unique solvent for the current fluorination, showing a sharp contrast to the negative case with THF in run 5. Moreover, the modification of HF-Py with di-n-isopropylamine resulted in a nearly equal result to that seen for triethylamine, and N,N-diethylaniline gave a better selectivity for 2a in a similar yield (See run 6). Triethylamine trishydrofluoride as applied to this electrolysis in place of the modified HF-Py media also gave a similar result but in a lower yield for 2a (See run 10). It is evident that modification of the HF-Py

TABLE 1

Potentiostatical Electrofluorination of Ethyl 1-Methylpyrazole-4-carboxylate (1a) and Its 3-Chloro Analogue (2b) with HF-Py-Amine at Pt or C Anode.



1a; X=H
1b; X=Cl

2a; X=H
2b; X=Cl

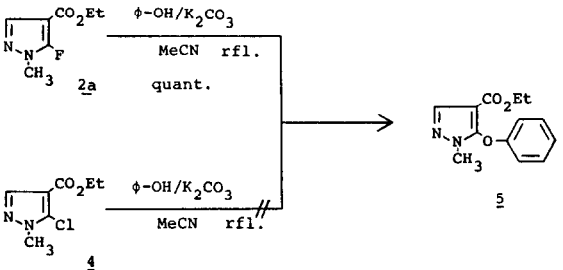
3a; X=H
3b; X=Cl

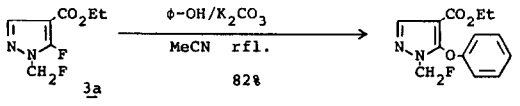
Run	Substrate	Anode	Electrolyte	Solvent	Reaction Potential(V)	Molar Ratio 2a : 3a / 2b : 3b	Yield(%) 2a+3a / 2b+3b
1	1a	Pt	HF-Py[1]	MeCN	+2.50	25 : 75	16
2	1a	Pt	HF-Py-Et_3N(0.3)[2]	MeCN	+2.50	57 : 43	23
3	1a	Pt	HF-Py-Et_3N(0.6)	MeCN	+2.50	83 : 17	40
4	1a	Pt	HF-Py-Et_3N(1.0)	MeCN	+3.00	100 : 0	18
5	1a	Pt	HF-Py-Et_3N(0.6)	THF	+2.70	100 : 0	2
6	1a	Pt	HF-Py-Et_2N-ϕ(0.6)	MeCN	+2.50	92 : 8	39
7	1a	C	HF-Py-Et_3N(0.6)	MeCN	+2.10	97 : 3	31
8	1b	Pt	HF-Py-Et_3N(0.6)	MeCN	+2.80	69 : 31	26
9	1b	C	HF-Py-Et_3N(0.6)	MeCN	+2.10	98 : 2	47
10	1a	Pt	3HF·Et_3N	MeCN	+2.70	93 : 7	29

[1] 70% HF-Py was used. [2] Volume ratio of triethylamine to HF-Py.

with an amine controls essential outcome of this electrolytic fluorination. As we stated in our previous work [7], the added amine may affect the nucleophilicity of fluoride anions in the media, and thus the nucleophilic fluorination after or concerted with the anodic oxidation becomes sharply governed. The selectivity for 2a and the combined yield of 2a and 3a were also dependent on the reaction potential applied to the media and the best selectivity was attained at +2.40 V that is nearly the lowest potential applicable under this condition. Better results for selective preparation of 2a as well as the 3-chloro analogue (2b) were obtained when carbon electrodes were employed, in which a lower potential (+2.10 V) was applicable to the fluorination of 1a and 1b (See runs 7 and 9).

Finally, it is noteworthy that the fluorine atom in 2a was shown to be nucleophilically more active than chlorine atom in the 5-chloro analogue (4), while the N-fluoromethyl group in 3a





was stable enough to remain intact on the treatment affording the 1-fluoromethyl-5-phenoxypyrazole (6).

NOTE

A typical reaction procedure is described (Run 3 in Table 1): To a solution of 70% HF-Py (5 ml) in 15 ml of dry MeCN, was added Et_3N (3 ml) at room temperature under stirring in nitrogen. After stirring for 15 min, 1a (308 mg, 2 mmol) was added at room temperature and potentiostatically treated at +2.50 V until passing 2.6 F/mol (ca. 4 h). After the addition of aqueous 25% KF (30 ml), the mixture was extracted three times with 20 ml of AcOEt. The AcOEt solution was washed two times with saturated aqueous $NaHCO_3$, two times with 5% HCl and three times with water, and dried on anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel with $CHCl_3$ as eluent to give 33% of 2a and 7% of 3a respectively. 2a: Colorless oil. IR (neat): 3570, 2960, 1717, 1588, 1550, 1443, 1409, 1380, 1352, 1290, 1240, 1194, 1170, 1108, 1050, 1013, 981, 868, 834, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34(3H, t, J=7.1 Hz), 375(3H, d, J= 1.5 Hz), 4.30(2H, q, J=7.1 Hz), 7.75(1H, d, J=2.6 Hz); ^{19}F NMR ($CDCl_3$) δ -127.4(=C-F); MS m/z 172(M^+), 144, 127(base peak). 3a: Colorless oil. IR(neat): 3570, 2975, 1720, 1608, 1519, 1464, 1430, 1389, 1358, 1280, 1219, 1148, 1098, 1054, 1010, 973, 884, 867, 835, 794, 773 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.36(3H, t, J=7.1 Hz), 4.33(2H, q, J=7.1 Hz), 5.96(2H, d d, J=51.9, 0.9 Hz), 7.89(1H, d d, J=2.6, 1.3 Hz); ^{19}F NMR($CDCl_3$) δ -169.3 (N-CH_2F), -125.4(=C-F); MS m/z 190(M^+), 171, 162, 145(base peak).

The chloro analogues 2b and 3b were similarly prepared as indicated in run 8. 2b: mp 64-65 °C. IR(KBr): 2975, 1720, 1560, 1438, 1379, 1279, 1253, 1182, 1088, 1030, 1012, 888, 830, 771 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.35(3H, t, J=7.1 Hz), 3.73(3H, d, J=1.3 Hz), 4.33(2H, q, J=7.1 Hz); ^{19}F NMR($CDCl_3$) δ -118.7(=C-F); MS m/z 206(M^+), 178, 161(base peak), 134. 3b: Colorless oil. IR(neat): 2970, 1722, 1590, 1523, 1459, 1420, 1385, 1358, 1289, 1220, 1170, 1077, 1014, 895, 847, 775 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.37(3H, t, J=7.1 Hz), 4.36(2H, q, J=7.1 Hz), 5.91(2H, d d, J=51.5, 0.9 Hz); ^{19}F NMR($CDCl_3$) δ -169.2($N-CH_2F$), -116.7(=C-F); MS m/z 224(M^+), 205, 196, 179(base peak).

1 E. Laurent, B. Marquet, R. Tardivel, and H. Thiebault, J. Fluorine Chem., 29 (1985) 193.

2 E. Laurent, H. Lefranc, and R. Tardivel, J. Fluorine Chem., 35 (1987) 54.

3 J. R. Ballinger, F. W. Teare, B. M. Bowen, and E. S. Garnett, Electrochim. Acta, 30 (1985) 1075.

4 K. Makino and H. Yoshioka, Heterocycles, 26 (1987) 1215.

5 K. Makino and H. Yoshioka, J. Fluorine Chem., 35 (1987) 677.

6 K. Makino and H. Yoshioka, J. Fluorine Chem., 37 (1987) 119.

7 S. Kanemoto, M. Shimizu, and H. Yoshioka, Tetrahedron Lett., 28 (1987) 663.