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CONTROLLED, REGIOSPECIFIC OXIDATION OF PYRIDINE CARBOXYLIC ACIDS AND ESTERS WITH ELEMENTAL FLUORINE

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Abstract: Pyridine carboxylic acid salts or esters in water or water-acetonitrile mixtures were treated with elemental fluorine to give the corresponding 2-pyridones.

Elemental fluorine is a potent oxidizer, but aside from fluorinations, has seldom been used for the controlled oxidation of organic substances.[1,2] Recently, Rozen[3] has described the use of acetyl hypofluorite as a reagent to synthesize pyridinols from pyridines via 2-acetoxypyridines, although even with this reactive fluorinating agent and oxidizer, pyridines bearing electron-withdrawing groups at C-2(6) failed to react. One of us reported earlier the use of F_2 to prepare 2-fluoro substituted pyridines directly from substituted pyridines in $CF_2ClCFCl_2$.[4] We now report that the direct fluorination of pyridine carboxylic acids and esters can be used to prepare the corresponding 2-pyridones in one step. As shown by the examples in Table 1, the direct aqueous fluorination method is distinguished from acetyl hypofluorite oxidations in that the pyridones are formed directly and the reaction works well even for pyridines bearing electron-withdrawing groups at C-2(6). The results are novel as they represent the controlled, regiospecific transformation of C-H to C-OH in one step using F_2 as the primary oxidant.

While esters of pyridine and quinoline carboxylic acids were conveniently fluorinated at 0-25°C in water-acetonitrile mixtures, pyridine carboxylic acids were fluorinated in water in the form of their potassium salts. Yields for the pyridones compare favorably with the usual two-step sequence involving peracid oxidation to the N-oxide, followed by treatment with acetic anhydride. For example, 6-hydroxy-2,3-dicarbomethoxypyridine (entry 4) was prepared in 27.5% overall yield by the two-step sequence,[5] compared to 56% for the one-step fluorination procedure.

Somewhat surprisingly, 2-fluoropyridine acids or esters could not be detected by NMR at any time after F_2 treatment, and in fact were shown to be stable to the reaction conditions. Thus, while 2-fluoro-4-carbomethoxypyridine could not be detected following the fluorination of methyl isonicotinate in water-acetonitrile, fluorination of the latter, mixed with the former, gave methyl 2-hydroxyisonicotinate and unreacted methyl 2-fluoro-isonicotinate. Therefore, the pyridones were not formed by hydrolysis of the corresponding 2-fluoropyridines.

TABLE 1 Direct Aqueous Fluorination Of Pyridine Acids And Esters

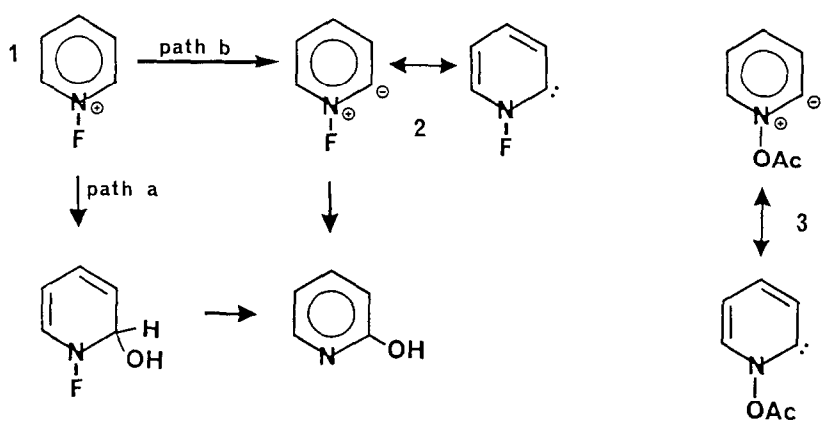
Entry	Reactant	Conditions	Product	Yield[a]
1	4-COOH	H_2O, 0°C, 2 equiv. KOH, 10% F_2 in N_2	2-OH-4-COOH	62%
2	3-COOH	"	2-OH-3-COOH 2-OH-5-COOH	73%[b]
3	2-COOH	"	2-OH-6-COOH	51%
4	2,3-$(COOCH_3)_2$	2:1 CH_3CN/H_2O 0°C, 10% F_2 in N_2	2-OH-5,6-$(COOCH_3)_2$	56%
5	3,5-$(COOCH_3)_2$	"	2-OH-3,5-$(COOCH_3)_2$	60%
6	quinoline-4-$COOCH_3$	as above, 25°C	2-OH-4-$COOCH_3$-quinoline	75%

(a) Recrystallized yields. (b) Combined yield of isomers (ratio about 1:1).

A more likely reaction pathway involves the intermediacy of N-fluoropyridinium cations (1). These could be formed directly by reaction with F_2. Alternatively, F_2 has been shown to react rapidly with water to give HOF[6], which could also react to form the N-fluoropyridinium cation 1 (in analogy with its proposed formation from CH_3COOF)[3].

Two possibilities exist for the conversion of 1 into the observed products (Scheme). In analogy with the mechanism proposed for acetyl hypofluorite oxidations,[3] direct attack of water or hydroxide on 1 could be considered (path a). Umemoto, however, has suggested that N-fluoropyridinium cations are readily deprotonated to form a carbene (path b) which reacts with CH_2Cl_2 to form 2-chloropyridines and with nitriles to form amides of 2-aminopyridine.[7] 2-Chloropyridines were also formed in the reaction of acetyl hypofluorite with pyridines in the presence of CH_2Cl_2, but the reaction of 1 with CH_2Cl_2 was suggested.[8] Although we have no evidence which allows us to determine which pathway is correct, it is worth noting the similarity between the results of Umemoto and those of Quarroz who has shown that the N-oxides of picolinic acids react with tertiary amines and acetic anhydride to give 2-chloropyridines in the presence of CH_2Cl_2,[9] and amides of 2-amino pyridines in the presence of nitriles.[10] It is likely that these reactions proceed through carbene intermediates 3 (following acetylation and decarboxylation), and are thus mechanistically similar with path b.

Scheme 1



Experimental

Dimethyl 1,6-dihydro-6-oxo-pyridine-2,3-dicarboxylate

A solution of 3.0 g (15.4 mmol) dimethyl pyridine-2,3-dicarboxylate in 30 mL 2:1 acetonitrile:water was cooled to 0°C. F_2 (11 cc/min) diluted with N_2 (80 cc/min) was bubbled in subsurface for 20 min (total F_2 8.8 mmol). After flushing the system with N_2 for 30 min at room temperature, the solution was refluxed for 2 h. Solvent was removed under vacuum to give a solid which was redissolved in dichloromethane. The dichloromethane solution

was washed with brine, and dried ($MgSO_4$). Evaporation of the solvent gave a yellow powder which was recrystallized from toluene, affording 1.05 g (56%) white needles, mp 162-163 °C (lit.[5] 159-161 °C). This material was converted into the corresponding diacid in 90% yield by refluxing in aqueous 5% NaOH for 3 h (mp 248 °C (dec.); ^1H NMR (DMSO-d_6) δ 9.9 (bs, 3 H), 7.9 (d, J=10 Hz, 1 H), 6.5 (d, J=10 Hz, 1 H); Anal. Calcd. for $C_7H_5NO_5$: C, 45.91; H, 2.76; N, 7.65; Found: C, 45.64; H, 2.81; N, 7.38%); IR (KBr) 3100-2400 (broad), 1760, 1730, 1665, 1440, 1300, 1260, and 1135 cm^{-1}.

2-Hydroxyisonicotinic acid

Isonicotinic acid (5 g, 41 mmol) was dissolved in 50 mL water containing 6.7 g KOH. A mixture of F_2 in N_2 (F_2 at 10 cc/min, N_2 at 90 cc/min; 74 mmol F_2) was bubbled into the mixture at ice-bath temperature for a total of 3.5 h. The pH of the solution at this time was about 6. After warming to room temperature, the resultant liquid-solid mixture was treated with 3 mL conc. HCl, and stirred overnight. Filtration provided 4.0 g crude product which was recrystallized from 50% acetic acid (3.5 g, 62% yield), mp 328 °C (dec). Anal. Calcd. for $C_6H_5NO_3$: C, 51.80; H, 3.60; N, 10.07%; Found: C, 51.80; H, 3.69; N, 9.96%. NMR (DMSO-d_6) δ 10.65 (bs, 2 H), 7.45 (d, J=7 Hz, 1 H), 6.8 (d, J=1.5 Hz), 6.55 (dd, J=1.5, 7 Hz, 1 H).

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