OXYGENATION OF THE UNACTIVATED PYRIDINE SYSTEM BY ACETYL HYPOFLUORITE MADE DIRECTLY FROM F_2

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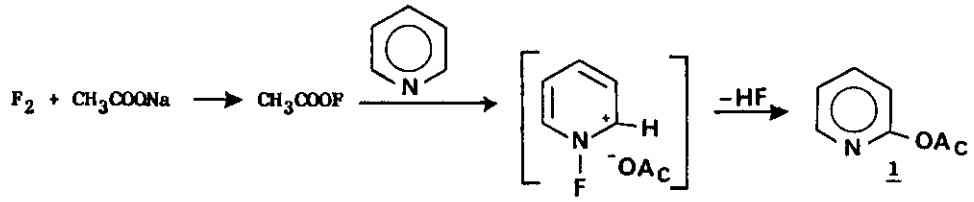
Abstract — Acetyl hypofluorite was found capable of activating the usually unreactive pyridine by substituting the hydrogen at the 2 position by an acetoxy group which then was hydrolyzed to the corresponding pyridinone. Substituents at 3, 4 or 5 position do not interfere with the reaction, but compounds with substituents at 2 (with the exception of aromatic ones) either do not react or produce tars. The reaction conditions are very mild and the yields are very good for this kind of substitution. Quinolines and pyrazines also react very satisfactorily.

Professor Barton, to whom this article is dedicated, was one of the first to develop the unorthodox chemistry of electrophilic fluorination using the only commercially available fluoroxy reagent - CF_3OF.[1] Later it was realized that F_2 itself could also be employed directly,[2] as well as indirectly,[3] toward this end. Although routine use of fluorine in organic chemistry was very rare, it was not surprising to see it used for fluorination purposes, in the same way as chlorine, for example, was used for chlorination and peroxy reagents for oxygenation. Recently however, the first halogen has proved itself to be more than merely a fluorinating agent and we have used it as a tool for difficult to perform aromatic brominations,[4] iodinations,[5] epoxidations,[6] olefinations,[2b] and hydroxylations forming eventually fluorine free compounds. We describe here yet another novel transformation of this kind, namely acetoxylation of the pyridine system at the 2 position, using acetyl hypofluorite - AcOF[7] made in-situ from F_2.[8]

Direct regiospecific substitution of a hydrogen on the pyridine nucleus by an oxygenated moiety in reasonable yields is a formidable task. Nucleophilic attack on the ring with KOH gave only traces of the 1H-2-pyridinone[9] while autoclave reaction of $CuSO_4$ with pyridine derivatives at 300 °C yielded the corresponding pyridinones in less than 7%.[10] The only practical way up to now has been the preparation of the corresponding N-oxide

followed by a rearrangement facilitated by prolonged heating either with acetic anhydride[11] or with some strong Lewis acid such as $SbCl_5$.[12] We found that acetyl hypofluorite offers a new, efficient and very mild route for achieving that goal of activating this inert heterocyclic system. Thus when a $CFCl_3$ or a chloroform solution of pyridine was added to a cold solution of AcOF a fast reaction was observed and in a few minutes 2-acetoxypyridine (1) was obtained in higher than 85% yield.

One potential way to turn the pyridine ring into a chemically active species is to temporarily destroy its aromaticity, perform a reaction and then restore it. We believe that this is exactly what AcOF is doing.[13] The oxygen bound fluorine is a very strong electrophile and it bonds itself to the lone pair of the nitrogen atom. Because of its extremely high electronegativity, a positive center is induced at the 2 and 4 positions. The fluorine atom destabilizes these positive centers, shorten their life time and since, the acetoxy residue is near only to the 2 position, the ion pair collapses rapidly forming the N-fluoro cyclohexadiene system A which stabilizes itself by HF elimination and aromatic restoration.[14] It is worth noting that neither radical scavengers such as nitrobenzene derivatives nor radical initiators such as benzoyl peroxide have any affect on the outcome of the reaction in agreement with its proposed ionic mechanism. Reactions of somewhat similar nature were recently described.[15]



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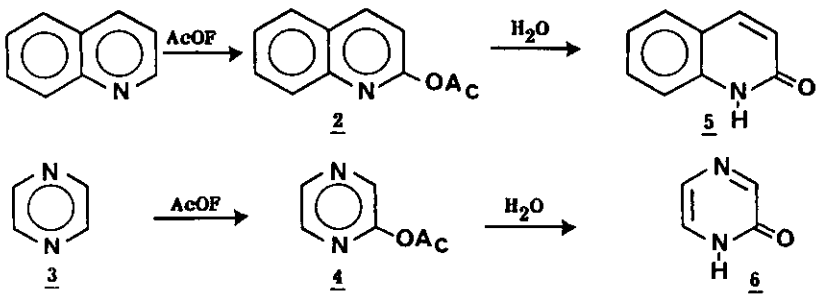
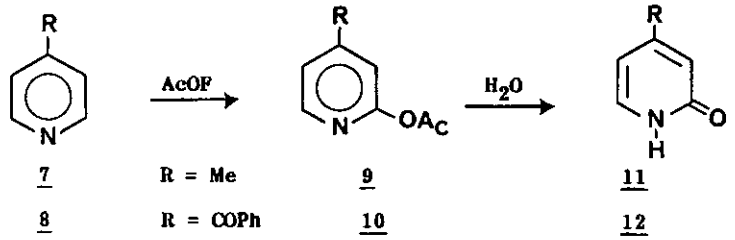
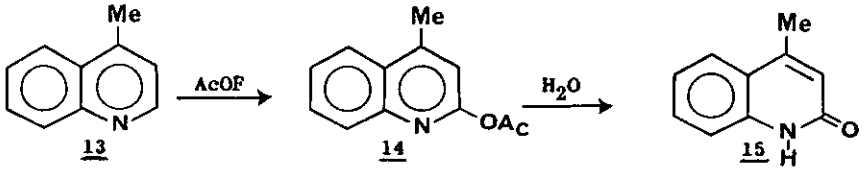
This fast reaction is not confined to the pyridine ring. The 1,2-π-region in quinoline has more olefinic character than that in pyridine itself reflected in a faster reaction producing 2-acetoxy quinoline (2) in higher than 90% yield. On the other hand, the system of the pyrazine molecule (3) is more electron deficient than that of the pyridine making it practically unreactive at -78 °C, but when warmed up to -40 °C a fast reaction took place and an 80% yield of 2-acetoxypyrazine (4) was obtained. Most acetates described in this paper are unknown compounds, but can be easily hydrolyzed to the usually known and more stable 1H-2-one derivatives (5 and 6 for quinoline and pyrazine skeletons). It should be noted at this point that most reactions could be carried at room temperature as well, but since AcOF decomposes at relatively high temperatures, the yields might be slightly affected.



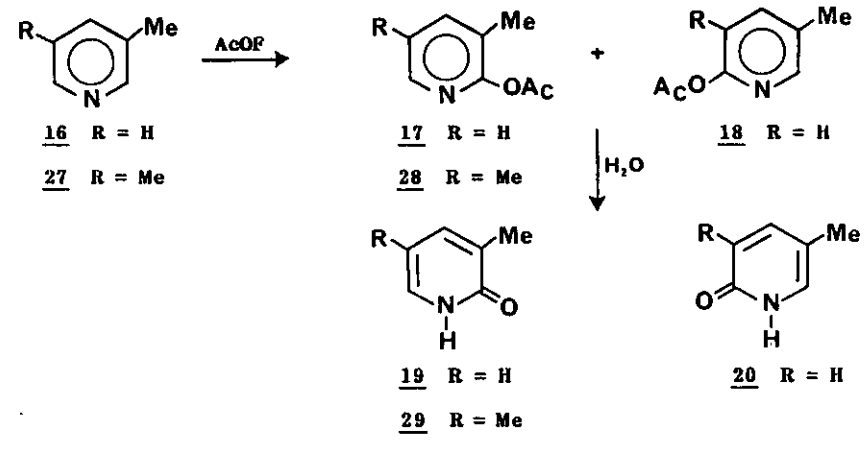
The described oxygenating reaction is equally efficient with various substituted pyridines as for example compounds with electron donating or withdrawing groups at the 4 position. Thus 4-methyl-(7) and 4-benzoylpyridine (8), produced the 2-acetoxy derivatives 9 and 10 in yields of up to 90% which were quantitatively hydrolyzed to the corresponding pyridinones 11 and 12. Similar reaction was also observed with 4-methylquinoline (13) which was eventually converted to 4-methyl-1H-2-quinolinone (15) in 65% overall yield.





Two potential isomers can be formed when the pyridine nucleus is substituted at the 3-position. When this substituent is a methyl as in 16, two isomers in a ratio of 1:1 were indeed formed, isolated and identified as 2-acetoxy-3-methyl- (17) and 2-acetoxy-5-methylpyridine (18) which again were easily hydrolyzed to 19 and 20. When however, 3-acetyl- (21) or 3-fluoropyridine (22) were reacted with AcOF, the corresponding 2-acetoxy isomers 23 and 24 and their hydrolysis products 25 and 26 were formed exclusively. The regiospecificity of these reactions can be rationalized by examining the two resonance forms A and B of the corresponding N-fluoro intermediate. In both cases the nonbonding electrons of either the carbonyl or the fluorine atom at the 3 position will be a part of an extended conjugation only when the carbocation is at C-2 (A). The reaction proceeds smoothly also when both the 3 and the 5 positions are occupied as demonstrated by 3,5-

dimethylpyridine (27) forming in good yield the 2-acetoxy-3,5-dimethylpyridine (28).



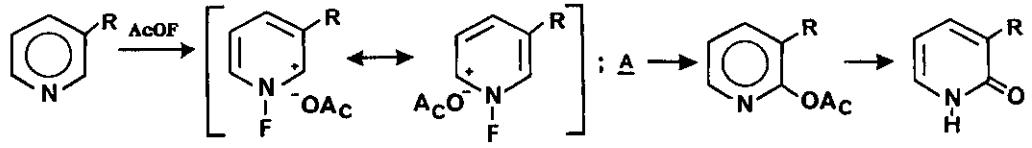
16 R = H
27 R = Me

17 R = H
28 R = Me

18 R = H

19 R = H
29 R = Me

20 R = H



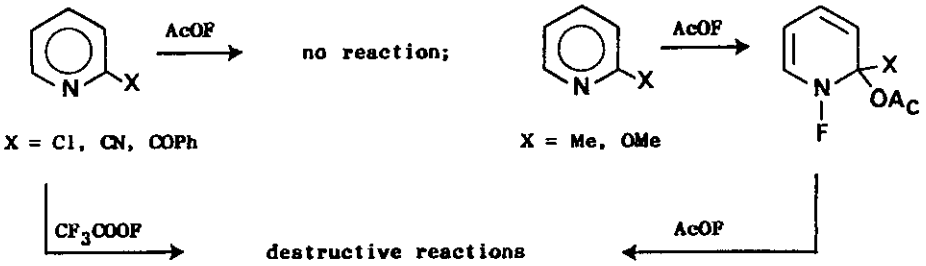
21 R = Ac
22 R = F

23 R = Ac
24 R = F

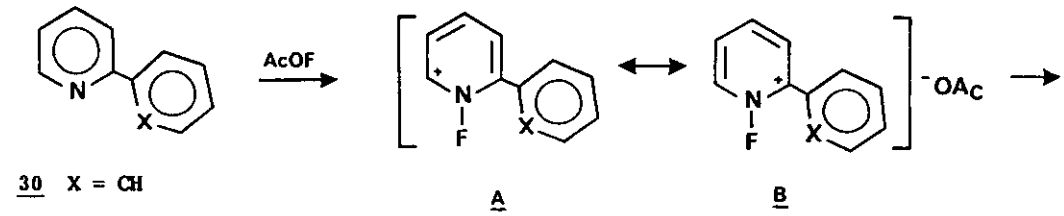
25
26

While substitution at 3,4 or 5 positions does not affect the activation of the pyridine ring by acetyl hypofluorite, substitution at C-2 does. The proposed mechanism is based on the initial attack of the electrophilic fluorine of AcOF on the nitrogen's lone pair electrons. If however the basicity of the pyridine heteroatom becomes too low, no N-F bond would be formed and hence no reaction would take place. This indeed is the case with 2-chloro-, 2-cyano- or 2-benzoylpyridine which were fully recovered after long treatment with AcOF even at room temperature. Although the efficiency of an electron withdrawing group is highest when located at the 2 position, it still can affect the outcome of the reaction when more remotely situated. Thus, we have reacted 8-nitroquinoline with AcOF, but again only the starting material was fully recovered. When however these heterocycles are treated with the more powerful electrophilic agent trifluoroacetyl hypofluorite - CF_3COOF,[3b] the oxygen bound fluorine reacts immediately with the nitrogen lone pair, but an additional fast reaction with another molecule of CF_3COOF follows before restoration of the aromaticity can take place, resulting in an inseparable mixture of many compounds none of them having aromatic protons. On the other hand compounds with electron donating substituents at the 2 position such as 2-methyl- or 2-methoxypyridine react with acetyl hypofluorite, but since the resulting positive charge is stabilized mainly at C-2 the

adduct does not have an easy pathway for HF elimination and again the resulting diene reacts further with the reagent to give eventually a mixture of many non aromatic compounds.

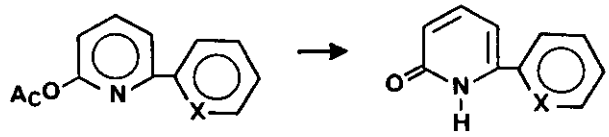


If however, we put at C-2 a substituent which would encourage a transition state with a positive center at C-6 instead of at C-2, there would be no reason for a clean acetoxylation not to take place after all. Such is the case, for example, with 2-phenylpyridine (30). From the two possible resonance structures A and B, A is obviously the dominant one because of the extended conjugation. This leads indeed to the formation of 2-phenyl-6-acetoxypyridine (31) in a quite respective yield.



30 X = CH
32 X = N

A B



31 X = CH 34
33 X = N 35

Similar factors govern the reaction of 2,2-bipyridine (32) with acetyl hypofluorite, although the yield of the resulting 2-pyridyl-6-acetoxypyridine (33) is somewhat lower than for 31, apparently because the electrophilic fluorine can attack both nitrogen atoms. Here again the acetoxy derivatives were easily hydrolyzed to the corresponding

pyridinones 34 and 35.

In conclusion, we have shown that a molecule with a highly reactive pole, such as electrophilic fluorine, can accomplish chemical transformations even on very unreactive systems such as the pyridine family employing extremely mild conditions. In a broader sense, after a whole century since the discovery of fluorine, we hope organic chemists will start to consider this element and reagents derived in situ from it, as a "legitimate" way for performing a broad spectrum of chemical transformations.

EXPERIMENTAL

^{1}H Nmr spectra were recorded with a Bruker WH-360 spectrometer with $CDCl_3$ as a solvent. They are reported in ppm downfield from Me_4Si serving as an internal standard. Mass spectra were measured with a Du Pont 21-491B spectrometer. Ir spectra were recorded as neat films, in $CHCl_3$ solution or in KBr pellets on a Perkin-Elmer 177 spectrometer and the wave-length reported in cm^{-1} units.

General Procedure for Work with Fluorine. A description of the setup and the procedure for working with elemental fluorine has previously been described[3b]. It is worth repeating that F_2 and AcOF should be treated with care since they are strong oxidizers. The work should be conducted in an efficient hood or in a well ventilated area. The toxicity of AcOF is not yet known, but some fluoroxy reagents are suspected to be strong poisons. If elementary precautions are taken, work with fluorine and its derivatives is safe and relatively simple.

Preparation of AcOF has already been described by us.[3c] The reactions were carried by addition of a cold (-75 °C) $CHCl_3$ or $CFCl_3$ solution of the substrate to the cold AcOF solution. The reactions were usually carried out on scales of 30-40 mmols using 1.5-2 fold excess of AcOF with conversions higher than 95%. They were usually monitored by TLC or nmr and lasted from a few minutes to one hour. If a very slow or no reaction was observed, the mixture was allowed to warm up to -40 °C or even to room temperature. The reaction was terminated by pouring into 500 ml of thiosulfate solution, washing the organic layer with $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent. The crude product was usually purified by vacuum flash chromatography using Silicagel 60-H (Merck) and 20 -30% EtOAc in petrol ether as eluent. Compounds in the Table which are not referenced are new to the best of our knowledge and their analytical data, including microanalysis for the corresponding pyridinones, are in excellent agreement with the assigned structures. All the acetates were quantitatively hydrolyzed to the corresponding pyridinones by adding a

few drops of water to the neat material and stirring the mixture at 50 °C for half an hour.

TABLE

Compnd	Reactn Temp.(°C)	yield (%)	mp[a] (°C)	ref	spectral properties
1	-75	85		16	ir 1760; nmr 2.3 (3H, s)
2	-75	96		17	ir 1770; nmr 2.36 (3H, s)
4	-40	80			ir 1770; nmr 8.5 (2H, m); 8.4(1H,dd,J_1 = 2.5, J_2 = 1.5 Hz); 2.4 (3H, s).
6			186 (EtOH)	18	nmr (DMSO) 7.96 (1H, d, J = 1.5 Hz); 7.31 (1H, d, J = 4Hz); 7.4 (1H,dd, J_1 = 4, J_2 = 1.5 Hz).
9	-40	75			ir 1770; nmr 8.1 (1H, d, J = 5 Hz); 6.85 (1H, d, J = 5 Hz); 6.7 (1H, s); 2.32 (3H, s); 2.25 (3H, s).
10	-75	90			ir 1760, 1655; nmr 8.35 (1H, d, J = 5 Hz); 7.7- 7.3 (6H, m); 7.21 (1H, s); 2.37 (3H, s).
11			130 (EtOAc)	19	ir 1660; nmr 7.3 (1H, d, J = 3.5 Hz); 6.4 (1H, d, J = 1.5 Hz); 6.17 (1H, dd, J_1 = 3.5, J_2 = 1.5 Hz); 2.23 (3H, s).
12			160 (EtOAc)		ir 1650 (br peak); nmr 7.84 (2H, m); 7.63 (1H m); 7.53 (3H, m); 6.84 (1H, s); 6.66 (1H, dd, J_1 = 6.5, J_2 = 1.3 Hz); ms m/z 199 (M^+); 105 (M - COPh)$^+$.
14	-75	65	75 (PE/EtOAc)		ir 1770; nmr 7.99 (2H, bt, J = 8 Hz); 7.71 (1H, td, J_1 = 8, J_2 = 1.3 Hz); 7.56 (1H, td, J_1 = 8, J_2 = 1.3 Hz); 7.06 (1H, bs); 2.72 (3H, s); 2.39 (3H, s); ms m/z 201 (M^+).
15			223 (acetone)	20	ir 1650; nmr 7.7 (1H, d, J = 8 Hz); 7.5 (1H, t, J = 8 Hz); 7.3 (1H, d, J = 8 Hz); 7.2 (1H, t, J = 8 Hz); 6.4 (1H, s); 2.42 (3H, s).
17+ 18[b]	-40	75[c]			ir 1775; nmr 2.33 (two Ac); 2.3 and 2.19 (two Me).
19			140	19	ir 1660; nmr 7.34 (1H, d, J = 6.5 Hz); 7.3 (1H, d, J = 6.5 Hz); 6.23 (1H, t, J = 6.5 Hz); 2.17 (3H, s).
20			185 (EtOAc)	19	ir 1655; nmr 7.36 (1H, dd, J_1 = 9.1, J_2 = 2.5 Hz);

					7.22 (1H, bs); 6.56 (1H, d, J = 9.1 Hz); 2.11 (3H, s).
24	-75	70			ir 1770; nmr 8.17 (1H, dd, J_1 = 4.7, J_2 = 1.4 Hz); 7.54 (1H, dd, J_1 = 9.5, J_2 = 1.4 Hz); 7.26 (1H, ddd, J_1 = 9.5, J_2 = 4.7, J_3 = 3.1 Hz); 2.37 (3H, s); ^{19}F nmr[d] -131 (dd, J_1 = 10, J_2 = 3.1 Hz).
25[e]	-40[f]	70[f]	157 (EtOAc/ EtOH)		ir 1670, 1640; nmr 8.14 (1H, dd, J_1 = 7.2, J_2 = 2 Hz); 7.82 (1H, dd, J_1 = 7.2, J_2 = 2 Hz); 6.42 (1H, t, J = 7.2 Hz); 2.6 (3H, s); ms m/z 137 (M^+); 122 (M - Me)$^+$; 94 (M - Ac)$^+$.
26			165 (EtOAc)	21	ir 1655; nmr 7.37 (1H, ddd, J_1 = 10, J_2 = 9.7, J_3 = 1.5 Hz); 7.22 (1H, bd, J = 5.6 Hz); 6.14 (1H, ddd, J_1 = 9.7, J_2 = 5.6, J_3 = 3.4 Hz); ^{19}F nmr[d] -133 (dd, J_1 = 10, J_2 = 3.4 Hz).
28	-40[g]	75			ir 1770; nmr 8.03 (1H, s); 7.42 (1H, s); 2.34 (3H, s); 2.3 (3H, s); 2.16 (3H, s).
29			117 (PE)	22	ir 1665; nmr 7.2 (1H, s); 7.09 (1H, s); 2.15 (3H, s); 2.06 (3H, s).
31	-75	75			ir 1760; nmr 7.96 (2H, d, J = 11 Hz); 7.82 (1H, t, J = 7.8 Hz); 7.63 (1H, d, J = 7.8 Hz); 7.43 (3H, m); 7.61 (1H, d, J = 7.8 Hz); 2.37 (3H, s); ms m/z 213 (M^+); 170 (M - Ac)$^+$.
33	-75				nmr 8.70 - 7.10 (7H, m); 2.38 (3H, s); ms m/z 214 (M^+).
34[h]			198	23	ir 1640; nmr 7.65 (2H, m); 7.48 (4H, m); 6.54 (1H, d, J = 10 Hz); 6.47 (1H, dd, J_1 = 7, J_2 = 1 Hz).
35[h]		135			ir 1655; nmr 8.65 (1H, dd, J_1 = 3.5, J_2 = 1.3 Hz); 7.83 - 7.25 (4H, m); 6.81 (1H, dd, J_1 = 7, J_2 = 0.7 Hz); 6.65 (1H, dd, J_1 = 9, J_2 = 0.7 Hz).

Notes to the Table: a) unless a mp is given the compound is a liquid; b) these two acetates were not separated, but were hydrolyzed directly to the pyridinones 19 and 20. c) combined yield of 17 and 18 (1:1 ratio); d) in ppm upfield from $CFCl_3$ which served as an internal standard; e) the 2-acetyl derivative was not isolated and the product was directly hydrolyzed; f) this is the acetoxylation reaction yield and temp; g) unusually slow reaction; completed in about 3 hours; h) unlike all other pyridinones the hydrolysis

leading to these compounds needed an acidic medium and longer reaction time.

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