Preparation of 2-Fluoropyridines via Base-Induced Decomposition of *N*-Fluoropyridinium Salts[1]

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N-Fluoropyridinium salts with either BF_4^-, SbF_6^-, or PF_6^- as a counteranion were treated with excess base such as triethylamine at room temperature to give 2-fluoropyridine in good yield. This method was successfully applied to the preparation of 2-fluoropyridine derivatives possessing electron-donating or -withdrawing substituents using substituted *N*-fluoropyridinium tetrafluoroborates. Pyridine-F_2 compounds produced through reactions of pyridines with molecular fluorine were also treated with a base to give 2-fluoropyridines but in low yields. These reactions are considered to occur through a carbene mechanism as follows: a novel N-F-containing cyclic carbene (**3**), generated from the *N*-fluoropyridinium salts by 2-proton abstraction, reacts with fluorine atoms from counteranions such as BF_4^-, SbF_6^-, or PF_6^-, followed by elimination of F^- from the N-F moiety, to yield 2-fluoropyridines. Previously reported findings in reactions of pyridines with molecular fluorine are explained on the basis of this mechanism.

Introduction

The reaction of pyridine and 2-fluoropyridine with molecular fluorine was first noted by Simons to result in the formation of a certain amount of 2-fluoropyridine (**2a**) and 2,6-difluoropyridine, respectively.[2] According to Meinert, pyridine reacts with molecular fluorine diluted with nitrogen in $CFCl_3$ at −80 °C to give pyridine-F_2 compound as a colorless precipitate, which violently undergoes decomposition at >−2 °C to leave a red-brown oil containing **2a**.[3] Quite recently, Van Der Puy reported the direct fluorination of substituted pyridines using molecular fluorine to give the corresponding 2-fluoropyridines, but in yields quite low considering the amounts of pyridines used.[4] In the present study, as a new method for preparing 2-fluoropyridines, the fluorination of pyridines was conducted by base-induced decomposition of *N*-fluoropyridinium salts with BF_4, SbF_6, or PF_6 counteranion.

Results and Discussion

We recently synthesized *N*-fluoropyridinium triflate and its analogues as selective fluorinating agents with variable fluorinating power, which react with carbon nucleophiles by "F^+" transfer.[5,6] It is of interest that a very different base-initiated reaction has been found to occur on treating *N*-fluoropyridinium salts with nitrogen or oxygen bases such as amines or alkoxides in solvents.[7] As an intermediate reactive species for the base-initiated reaction, we propose a unique singlet carbene produced by 2-proton abstraction by bases.[7] Carbon and nitrogen or oxygen nucleophiles appear to differ primarily with respect to the high stability of C-F bonds compared to N-F or O-F bonds.

The novel base-initiated reaction led unexpectedly to a substitution reaction at the 2-position of the pyridine ring by solvents that usually are unreactive.[7,8] *N*-Fluoropyridinium salts **1** can easily be prepared in good yields from pyridines by using molecular fluorine diluted with nitrogen and a metal salt of a strong acid or Lewis acid.[5] These reactions should, therefore, be applicable to the preparation of 2-fluoropyridines provided a fluorine source is available in the reaction system. On treating *N*-fluoropyridinium tetrafluoroborates, hexafluoro-

Scheme I

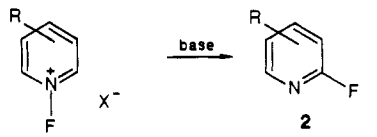

Table I. Preparation of 2-Fluoropyridine (2a) from *N*-Fluoropyridinium Salts

run[a]	1 (R = H), X =	base (equiv)[b]	temp	time[c]	yield[d] of **2a**, %
1	BF_4	Et_3N (1)	rt[f]	5 min	66
2	BF_4	Et_3N (2)	rt	5 min	69
3	BF_4	Et_3N (3)	rt	5 min	73
4	BF_4	Et_3N (5)	rt	5 min	75
5	BF_4	Et_3N (10)	rt	5 min	79
6	BF_4	pyridine (10)	rt	5 min	58
7[e]	BF_4	KF (9)	40 °C	7 day	26
8	BF_4	n-$Bu_4N^+F^-$ (2.6)	rt	5 min	80
9	SbF_6	Et_3N (10)	rt	5 min	78
10	PF_6	Et_3N (10)	rt	5 min	74

[a] *N*-Fluoropyridinium salts were added by portions into the base under stirring at room temperature. [b] Figures in parentheses mean the equivalency of the used bases to the *N*-fluoropyridinium salts. [c] Figures mean the time for additional stirring after the addition of the *N*-fluoropyridinium salts to the bases. [d] GC yields except for run 6 and 8, which were ^{19}F NMR yields. [e] THF was used as a solvent. [f] rt = room temperature.

(1) Umemoto, T.; Tomizawa, G. Japanese Patent Appl., Sept 18, 1986.
(2) Simons, J. H. *Fluorine Chemistry*, Simons, J. H., Ed.; Academic Press Inc.: New York, 1950; Vol. 1, pp 420-421.
(3) Meinert, H. *Z. Chem.* **1965**, *5*, 64.
(4) Van Der Puy, M. *Tetrahedron Lett.* **1987**, *28*, 255.
(5) Umemoto, T.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 3271.
(6) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465.
(7) Umemoto, T.; Tomizawa, G. *Tetrahedron Lett.* **1987**, *28*, 2705.
(8) Recently, Rozen et al. reported 2-chlorination, bromination, or oxygenation of pyridines by the action of acetyl hypofluorite in halocarbon solvents such as methylene chloride and methylene bromide or alcohol solvents (Hebel, D.; Rozen, S. *J. Org. Chem.* **1988**, *53*, 1123). The base-initiated reaction of *N*-fluoropyridinium acetates, produced through reactions of pyridines with acetyl hypofluorite, by action of their own basic counter anion AcO^- may be suggested as a reaction mechanism, since the similar reaction is caused by treating *N*-fluoropyridinium triflate with sodium acetate (1 equiv) as a base in methylene chloride at room temperature to give 2-chloropyridine (40%) along with 2-pyridyl triflate (3%) and 2-fluoropyridine (2%). But 2-pyridyl acetate which was produced in 15% yield in Rozen's case was not detected in this case.

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Table II. Preparation of 2-Fluoropyridine Derivatives 2

$$1\ (X = BF_4) \xrightarrow[\text{room temperature, 5 min}]{\text{base (10 equiv)}} 2$$

run[a]	1 (X = BF_4), R =	base	product 2	yield,[b] %	^{19}F NMR[c]
1	4-methyl	Et_3N	2-fluoro-4-methyl	80	69.8
2	3,5-dimethyl	Et_3N	2-fluoro-3,5-dimethyl	87	77.3
3	3,5-dimethyl	Py[d]	2-fluoro-3,5-dimethyl	30	77.3
4	4-*tert*-butyl	Et_3N	4-*tert*-butyl-2-fluoro	91, 72[e]	69.0
5	4-*tert*-butyl	Py	4-*tert*-butyl-2-fluoro	24	69.0
6	2-methoxy	Et_3N	2-fluoro-6-methoxy	75	70.5
7	2-methoxy	Py	2-fluoro-6-methoxy	10	70.5
8	4-phenyl	Et_3N	2-fluoro-4-phenyl[g]	40[f]	67.8
9	4-(methoxycarbonyl)	Et_3N	2-fluoro-4-(methoxycarbonyl)	69	66.4
10	4-(methoxycarbonyl)	Py	2-fluoro-4-(methoxycarbonyl)	49	66.4
11	3-(ethoxycarbonyl)	Et_3N	3-(ethoxycarbonyl)-2-fluoro	48[h]	61.7
			5-(ethoxycarbonyl)-2-fluoro	7[h]	61.5
12	2-chloro	Et_3N	2-chloro-6-fluoro	72[i]	66.1
13	3,5-dichloro	Et_3N	3,5-dichloro-2-fluoro	62	73.6
14	3,5-dichloro	Py	3,5-dichloro-2-fluoro	70	73.6
15	3,5-dichloro	Et_2NH	3,5-dichloro-2-fluoro	73	73.6
16	3,5-bis(CF_3)	Et_3N	3,5-bis(CF_3)-2-fluoro	99	60.8[j]
17	3-cyano	Et_3N	3-cyano-2-fluoro	51	60.0
18	3-cyano	Py	3-cyano-2-fluoro	49	60.0
19	2-cyano	Py	2-cyano-6-fluoro	79	63.4
20	4-nitro	Et_3N	2-fluoro-4-nitro	21	61.7
21	4-nitro	Py	2-fluoro-4-nitro	31	61.7

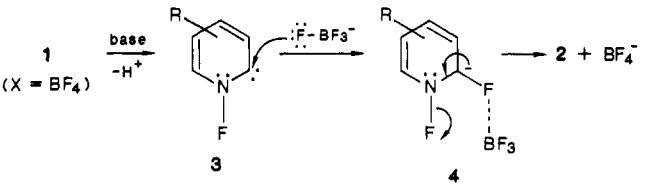
[a] Reaction conditions and the procedure were the same as for run 5 in Table I, except that in runs 6–8 the amine was added into the salts. [b] GC yields based on the *N*-fluoropyridinium salts, unless otherwise noted. [c] ^{19}F chemical shifts of 2- or 6-F were given in ppm upfield from internal $CFCl_3$ in $CDCl_3$. [d] Py = pyridine. [e] Isolated yield based on the *N*-fluoropyridinium salt. [f] Isolated yield based on the starting pyridine derivative. [g] ^{19}F NMR analysis showed that the product was contaminated by a small amount of 2-fluoro-4-(fluorophenyl)pyridine. [h] GC yields based on the starting pyridine derivatives. [i] As byproducts, 2,6-dichloropyridine (1%), 2,6-difluoropyridine (2.5%), and 2-chloropyridine (3%) were found. [j] Two singlets at 62.3 ppm (CF_3) and 63.4 (CF_3) were observed.

antimonates, or hexafluorophosphates (1, X = BF_4, SbF_6, or PF_6) with a base in the absence of a solvent at room temperature, an exothermic reaction was found to occur immediately to afford selectively 2-fluoropyridines **2** in good yields (Scheme I).

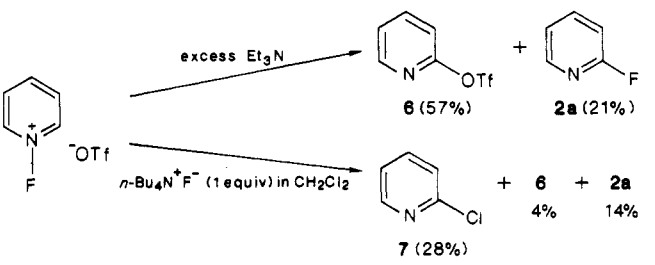
Table I shows the conditions under which *N*-fluoropyridinium salts reacted with bases and the results obtained. The same results were obtained regardless of the counteranion, BF_4^-, SbF_6^-, or PF_6^-, used. An excess of triethylamine (Et_3N) as the base provided higher yields. The yield of **2a** increased with the amount of Et_3N and thus apparently Et_3N serves not only as a base but also as a solvent for solid *N*-fluoropyridinium salts. The use of liquid tetrabutylammonium fluoride gave similar results. With KF in THF, **2a** was obtained in low yield and a long reaction time was required, possibly due to the very low solubility of KF in THF (run 7).

As seen in Table II, our reaction was successfully applied to the 2-fluorination of various pyridine derivatives, each having electron-withdrawing or -donating substituents. It is evident that this method is effective for the direct preparation of 2-fluoropyridines from pyridines. The well-known Balz–Schiemann reaction[9] (thermal decomposition of pyridinediazonium tetrafluoroborates) or Finger reaction[10] (Cl–F exchange reaction of 2-chloropyridines with F^-) requires 2-aminopyridines or 2-chloropyridines as starting materials. The latter also requires a naked fluoride anion, high temperature, and long reaction time and thus is of limited application to the preparation of 2-fluoropyridine or fluoropyridines having electron-withdrawing substituents.

Scheme II



Scheme III



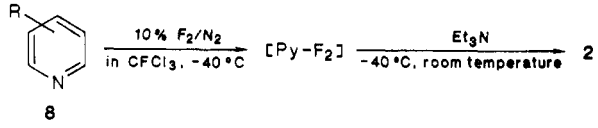
The present 2-fluorination of *N*-fluoropyridinium salts is thought to proceed through a carbene mechanism as follows:[7] the unique singlet carbene **3**, generated from **1** by the action of a base, reacts with a fluorine atom from either BF_4^-, SbF_6^-, or PF_6^- to yield **2** via transient intermediate **4** followed by elimination of F^- with the simultaneous regeneration of the counteranion, as shown by Scheme II. *N*-Fluoropyridinium salts do not undergo addition–elimination reactions with nucleophiles.[7]

Treating triflate **5** with excess Et_3N under the conditions of run 5 in Table I gave a large amount of 2-pyridyl triflate (**6**) (57%) and a small yield of **2a** (21%). Treatment of **5** with tetrabutylammonium fluoride (1 equiv) in methylene chloride at room temperature for 5 min gave 2-chloropyridine (**7**) (28%) as the main product, along with **2a** (14%) and **6** (4%). Chloride **7** was formed by the

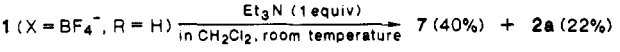
(9) (a) Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186. (b) Roe, A. *Org. React.* **1949**, *5*, 193. (c) A recent paper: Fukuhara, T.; Kikuchi, T.; Yoneda, N.; Suzuki, A. The 11th Japanese National Meeting on Fluorine Chemistry, Oct 17, 1986, Nagoya, Japan, Abstract pp 74–75.

(10) (a) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034. (b) Finger, G. C.; Starr, L. D.; Dickerson, D. R.; Gutowsky, H. S.; Hamer, J. *J. Org. Chem.* **1963**, *23*, 1666. (c) Ishikawa, N. *Yuki Gosei Kagaku Kyokai Shi* **1967**, *25*, 808. (d) A recent paper: Ogawa, T.; Takaoka, A.; Ishikawa, N. The 11th Japanese National Meeting on Fluorine Chemistry, Oct 17, 1986, Nagoya, Japan, Abstract pp 86–87.

Scheme IV



reaction of carbene **3** with methylene chloride solvent.[7] The yield of **2a** from **1** (X = BF_4, R = H) using ammonium fluoride without a solvent was the same as that using Et_3N (runs 8 and 5, Table I). Thus, the fluorine atom of products **2** in Scheme I does not come directly from N–F but from one of the counteranions, BF_4^-, SbF_6^-, or PF_6^-, nor is the fluoride anion of the ammonium fluoride the source of fluorine but rather it serves as the base. This is in good agreement with the carbene mechanism described above. A small amount of **2a** in the reactions of Scheme III is formed by reaction of carbene **3** with F^- and/or attack of intermediate onium salts by F^- as indicated in our previous paper.[7] Borate **1** (X = BF_4, R = H) was treated with Et_3N (1 equiv) in methylene chloride to yield chloride **7** (40%) and fluoride **2a** (22%), thus indicating that carbene **3** reacts with the solvent more easily than with BF_4^-.



It may appear strange that reaction of *N*-fluoropyridinium moieties with amines, even in an excess of the latter, failed to result in the formation of any products (Scheme I). In this regard, the proposed carbene has been shown not to react with strongly electron-donating nucleophiles such as amines.[7]

The higher yields with Et_3N compared to pyridine in the case of electron-donating substituents (runs 2–7, Table II) presumably reflect the requirement for a stronger base. A 7:1 mixture of two 2-fluoro isomers was obtained in the fluorination of ethyl nicotinate, with 3-(ethoxycarbonyl)-2-fluoropyridine as the main product (run 11, Table II). Thus, the more acidic protons at C-2 were replaced preferentially. The exclusive 2-fluorination of 3-cyanopyridine (runs 17 and 18) may be explained on the basis of the great difference in acidity between 2- and 6-protons due to the high electronegativity of the cyano group.

Pyridine–F_2 was prepared in situ at low temperature; subsequent treatment with excess Et_3N gave **2a** in 22–35% overall GC yields. The yields of substituted 2-fluoropyridines **2** were similarly low (Table III, Scheme IV). In consideration of this and the unstable and potentially explosive nature of pyridine–F_2 compounds[3,4] this method is undesirable.

Pyridine–Cl_2, –Br_2, –I_2 and –IBr compounds have been shown to be molecular complexes with a linear nitrogen–halogen–halogen atom structure.[11] However, pyridine–F_2 compounds should have ionic structures in the *N*-fluoropyridinium fluoride salt form,[3,5] since a fluorine atom has extremely poor two-coordinating ability[12] and the stable covalent N–F bond is formed easily.[5] Thus, the counteranion displacement reaction of pyridine–F_2, prepared in $CFCl_3$ at –78 °C, with sodium triflate in CH_3CN–$CFCl_3$ (2:1) at –40 °C occurred readily to give *N*-fluoropyridinium triflate (**5**) (32%) and sodium fluoride.

The ^1H NMR spectrum of the pyridine–F_2 in CH_3CN at room temperature, prepared by first dissolving solid pyridine–F_2, which was produced by treating pyridine with 10% F_2/N_2 in $CFCl_3$ at –78 °C followed by evaporating the reaction mixture to dryness at less than –40 °C, in dry CH_3CN at –40 °C, showed a doublet of doublets at 9.22 ppm and two multiplets at 8.70 and 8.30 ppm, as was also noted for the *N*-fluoropyridinium moiety of *N*-fluoropyridinium triflate and its analogues.[5] Complex peaks of essentially the same size were also noted in the range of 8.1–6.8 ppm, possibly due to decomposition products. The ^{19}F NMR spectrum showed three peaks at –48.3 (weak), 67.9 (weak), and 173 (strong) ppm. The first corresponded to the N–F chemical shift (ca. –48.5 ppm) of *N*-fluoropyridinium salts, the second to that of 2-fluoropyridine, a decomposition product, and the third to F^- or HF. Since F^- makes a tight hydrogen bond with HF, it appears quite likely that *N*-fluoropyridinium fluoride, stabilized by HF, is present and may be expressed as $[C_5H_5N\text{–}F]^+F^-(HF)_n$. The hydrogen fluoride is probably produced by side reactions that occur by the extremely reactive molecular fluorine or decomposition of pyridine–F_2 itself.

Table III. Reaction of Substituted or Unsubstituted Pyridine–F_2 with Et_3N[a]

run	8, R =	temp, °C	product 2	yield,[b] %
1[c]	H	–78 → rt[d]	2-fluoro (**2a**)	35
2	H	–30 → rt	2-fluoro (**2a**)	22–30
3	4-Me	–40 → rt	2-fluoro-4-methyl	26
4	4-t-Bu	–40 → rt	4-*tert*-butyl-2-fluoro	47
5	2-OMe	–40 → rt	2-fluoro-6-methoxy	24
6	4-COOMe	–40 → rt	2-fluoro-4-(methoxycarbonyl)	24
7	3-COOEt	–40 → rt	3-(ethoxycarbonyl)-2-fluoro	22
			5-(ethoxycarbonyl)-2-fluoro	9

[a] Ten equimolar amount of Et_3N to the pyridines was used. [b] GC yields based on the starting pyridines. [c] Reaction of pyridine with 10% F_2/N_2 was carried out at –78 °C. [d] rt = room temperature.

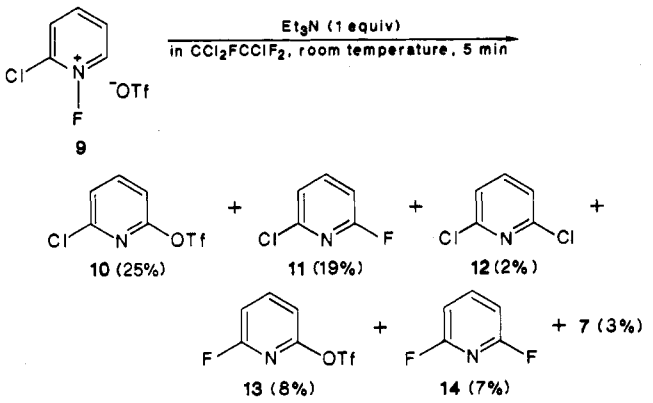
The ^1H and ^{19}F NMR spectra at room temperature of a pyridine–F_2 solution prepared by treating pyridine with 10% F_2/N_2 in CH_3CN at –40 °C was in complete agreement with that of HF-stabilized *N*-fluoropyridinium fluoride, except for an unidentified small peak at –57.4 ppm in the ^{19}F NMR. Cooling of an acetonitrile solution to –40 °C followed by treatment with $BF_3{\cdot}OEt_2$ gave tetrafluoroborate **1** (X = BF_4, R = H) in 31% yield.

From the data presented above, **2** from pyridine–F_2 compounds by our method results from base-initiated reactions of *N*-fluoropyridinium salts and the carbenes **3** thus formed react with the counteranion F^- ($F^-HN^+Et_3$) to give **2**.

The unusual results reported previously are explained well by those presented in this paper. Simons found that, on reacting liquid pyridine with molecular fluorine at –40 °C, a dark brown solid separated from the solution and underwent exothermic decomposition on warming to 0 °C to give **2a**.[2] Reactions of *N*-fluoropyridinium salts with a base gave similar results. The formation of **2a** is understandable by the carbene mechanism: unreacted pyridine acts as a base toward *N*-fluoropyridinium fluoride and the resulting carbene reacts with F^-. That pyridine–F_2 may fluorinate pyridine to give **2a**, as suggested by Simons,[2,13] is not possible as evident from the fact that treatment of *N*-fluoro-3-(ethoxycarbonyl)pyridinium tetrafluoroborate with pyridine afforded 3-(ethoxycarbonyl)-2- and -6-fluoropyridines, but not **2a**. If the suggestion of Simons were correct, the *N*-fluoro-3-(ethoxycarbonyl)pyridinium salt should be capable of fluorinating pyridine to give **2a**, since the *N*-fluoropyridinium salt possessing an electron-withdrawing group has a greater

(11) Hassel, O. *Proc. Chem. Soc.* **1957**, 250.
(12) Smart, B. E. *Supplement D; The Chemistry of Halides, Pseudo-Halides and Azides*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1983; Part 1, pp 616–618.
(13) Simons, J. H. U.S. Patent 2,447,717, 1948.

Scheme V



fluorinating power than pyridine–F_2, an unsubstituted *N*-fluoropyridinium salt.[6] Although Meinert et al. reported the fluorination of uracil by pyridine–F_2 at −30 °C to give 5-fluorouracil quantitatively,[14] we could never detect 5-fluorouracil by the same treatment but recovered uracil almost quantitatively.

The formation of **2** from the decomposition of pyridine–F_2 compounds, as reported by Meinert[3] and Van Der Puy,[4] may also be explained as follows: pyridine–F_2 compounds, i.e., *N*-fluoropyridinium fluorides, undergo 2-proton abstraction by their own basic counteranion F^- on being warmed to room temperature to generate the carbenes **3**, which abstract fluorine atoms from the resulting HF to give **2**.

This carbene mechanism is strongly supported by the fact that the decomposition of the pyridine–F_2 compound in $CFCl_3$–CH_2Cl_2 (1:1) solvent gave chloride **7** (7%), which was a chlorine abstraction product from methylene chloride solvent, besides fluoride **2a** (31%).

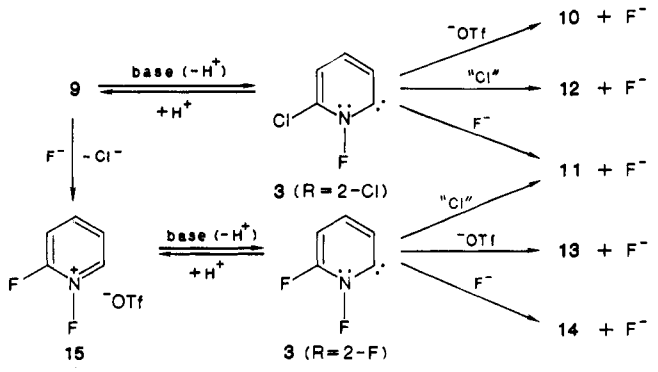
In the case of Van Der Puy, who allowed pyridines to react with 0.4 or lesser molar amounts of molecular fluorine in 1,1,2-trichlorotrifluoroethane, unreacted starting pyridines may possibly act as the bases in carbene reactions. This would explain why, in his experiments, electron-withdrawing groups apparently stabilize pyridine–F_2 compounds against thermal decomposition, since these groups decrease the basicity of pyridines.

Van Der Puy also suggests that the decomposition of pyridine–F_2 compounds most likely occurs as a result of the addition of F_2 to the most electron-rich C=N bond. He detected 2,6-dichloropyridine (**12**) and 2,6-difluoropyridine (**14**) as byproducts in addition to 2-chloro-6-fluoropyridine (**11**) as the major product in the reaction of 2-chloropyridine (**7**) with molecular fluorine.

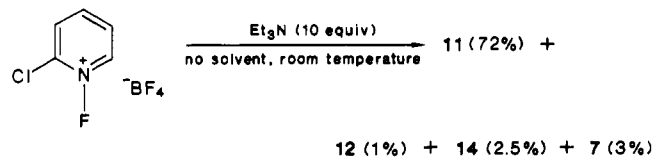
We carried out the decomposition of *N*-fluoro-2-chloropyridinium triflate (**9**) with Et_3N (1 equiv) in 1,1,2-trichlorotrifluoroethane solvent and precisely determined the reaction products, which are shown in Scheme V.

Chloro triflate **10** and chloro fluoride **11** are easily explained by the carbene mechanism, but fluoro triflate **13** and difluoride **14** cannot be explained simply by the carbene mechanism alone. Fluoro triflate **13** strongly indicates the possibility that *N*-fluoro-2-fluoropyridinium triflate (**15**) is formed as an intermediate, since the pyridyl triflate **13** is one of the products characteristic of base-initiated reactions of *N*-fluoropyridinium triflates.[7] Byproducts **13** and **14** can be explained by the carbene reaction with TfO^- and F^- of *N*-fluoro-2-fluoropyridinium salt **15** produced by a substitution reaction of *N*-fluoro-2-chloropyridinium salt **9** with the generated fluoride anion (Scheme VI).

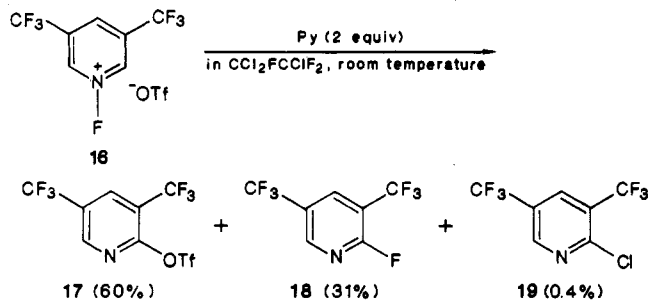
Scheme VI



Scheme VII



Scheme VIII



Dichloride **12** can be explained as a result of the carbene reaction of intermediate **3** (R = 2-Cl) with chlorine sources; the trichlorotrifluoroethane solvent used, chloride anions generated in the conversion of **9** to **15** (Scheme VI), or other molecules of **9**. Although halogenated hydrocarbons such as methylene chloride act as the halogen source in the base-initiated reactions,[7] the trichlorotrifluoroethane solvent is excluded as the chlorine source by the following two facts: (1) the base-initiated reaction of *N*-fluoro-2-chloropyridinium tetrafluoroborate (**1**, R = 2-Cl, X = BF_4) without the solvent gave 1% of dichloride **12** (Scheme VII), which is very close to 2% of the case using the solvent (Scheme V), and (2) a chlorine abstraction product was not detected even when *N*-fluoro-2-cyanopyridinium tetrafluoroborate (**1**, R = 2-CN, X = BF_4), which was expected to be activated more than 2-chloro salt **1** (R = 2-Cl, X = BF_4), was treated with Et_3N (1 equiv) in the trichlorotrifluoroethane solvent. The whole mechanism is shown in Schene VI except for **7**, which was probably formed by the reduction–oxidation between the salt **9** and Et_3N.

However, *N*-fluoro-3,5-bis(trifluoromethyl)pyridinium triflate (**16**) in which the 2- and 6-reaction sites are activated by the nearest electronegative trifluoromethyl groups gave chlorine abstraction product **19** (0.4%) as shown in Scheme VIII. These results indicate that the carbene is sufficiently activated by electron-withdrawing substituents at 3- and 5-positions to permit reaction with much less reactive 1,1,2-trichlorotrifluoroethane molecules.

Accordingly, major product chloro fluoride **11** and byproducts dichloride **12** and difluoride **14** in the reaction

(14) Meinert, H.; Cech, D. *Z. Chem.* **1972**, *12*, 292.

of 2-chloropyridine (7) with molecular fluorine, as reported by Van Der Puy, can be explained by our mechanism; 11 and 12 were formed by the carbene reaction of the intermediate 3 (R = 6-Cl) and 14 resulted from the formation of *N*-fluoro-2-fluoropyridinium fluoride as an intermediate followed by the carbene reaction.

Experimental Section

General. Melting points were uncorrected. ^{1}H NMR spectra were measured on a Varian EM 390 NMR spectrometer, a Varian XL-100 NMR spectrometer, or a Bruker AM-400 NMR spectrometer. ^{19}F NMR spectra were obtained on a Hitachi R-20B NMR spectrometer. ^{19}F NMR chemical shifts were given in ppm upfield from trichlorofluoromethane as an internal standard. IR spectra were measured on a JASCO A-202 diffraction grating infrared spectrometer. Mass spectra were recorded on a Hitachi RMU-6MG spectrometer at 70 eV. GC analyses were carried out on an Okura Model-802 gas chromatograph with a column (3 m × 2 mm) packed with PEG-6000 (15%) on Uniport B.

Materials. A 20% F_2/N_2 cylinder (F_2/N_2 = 2/8) was purchased from Kanto Denka Kagaku Company in Japan. Since the content of hydrogen fluoride in the molecular fluorine was very low (0.2–0.3%), fluorine was used without a NaF trap. Other commercially available chemicals were used without further purification, unless otherwise noted.

Preparation of *N*-Fluoropyridinium Salts. *Caution!* Since molecular fluorine is a highly oxidizing and toxic gas, the experimenter should familarize him- or herself with the precautions necessary for the safe handling of molecular fluorine.[15] The use of diluted fluorine in an inert gas (N_2 or Ne) is considerably safer than pure fluorine.

Apparatus. The apparatus used for the fluorination consisted of a 20% F_2/N_2 cylinder, a N_2 cylinder, two flow meters (Hastings mass flow meters Model CST), a Pyrex glass reactor, and valves made of stainless steel or brass. The cylinders, the flow meters, and the valves were connected with stainless steel or copper tubes. The 20% F_2/N_2 cylinder was equipped with a pressure regulator (Takachiho F_2 regulator Model 7630H) that was designed for fluorine service. The glass reactor was connected to the outlet of further diluted molecular fluorine (10% F_2/N_2) by using a Viton tube. The gas outlet of the reactor was connected to a granular alumina trap which neutralized the fluorine gas.

Typical Procedure. A 10% F_2/N_2 mixture was bubbled at a flow rate of 50 mL/min into a solution of 0.80 g (10.1 mmol) of pyridine and 1.70 g (10.1 mmol) of sodium hexafluorophosphate in 30 mL of dry acetonitrile on a cooling bath of −40 °C with vigorous stirring. The total amount of F_2 used was 30 mmol. After nitrogen was flowed to remove an excess of fluorine, the reaction mixture was warmed to room temperature, filtered through Celite to remove sodium fluoride formed, and evaporated to dryness at room temperature. The resulting solid was recrystallized from acetonitrile–methylene chloride to give 2.04 g (83%) of *N*-fluoropyridinium hexafluorophosphate. **1a** (R = H, X = BF_4), **1b** (R = H, X = SbF_6), **1c** (R = H, X = PF_6), **1d** (R = 4-Me, X = BF_4), **1e** (R = 3,5-diMe, X = BF_4), **1f** (R = 4-t-Bu, X = BF_4), **1g** (R = 2-MeO, X = BF_4), **1h** (R = 2-Cl, X = BF_4), **1i** (R = 3,5-diCl, X = BF_4), **1j** (R = 4-COOMe, X = BF_4), **1k** [R = 3,5-bis(CF_3), X = BF_4], **1l** (R = 3-CN, X = BF_4), **1m** (R = 2-CN, X = BF_4), and **1n** (R = 4-NO_2, X = BF_4) were prepared in 78, 81, 83, 70, 75, 81, 71, 83, 79, 88, 66, 83, 78, and 86% isolated yields, respectively. *N*-Fluoropyridinium tetrafluoroborates having an electron-withdrawing substituent(s), **1h** and **1j–n**, were prepared by using lithium tetrafluoroborate instead of sodium tetrafluoroborate. In the case of **1i**, BF_3·OEt_2 was used instead of metal tetrafluoroborates. Their melting points and ^{19}F NMR chemical shifts (acetonitrile-d_3) corresponding to N–F are as follows: **1d**, mp 57–60 °C, −40.2 ppm; **1e**, mp 170–173 °C, −46.5 ppm; **1f**, mp 143–145 °C, −40.0 ppm; **1g**, mp 102–103 °C, −0.5 ppm; **1h**, mp 128–130 °C, −39.0 ppm; **1i**, mp 208–209 °C, −52.7 ppm; **1j**, mp 75–76 °C, −51.6 ppm; **1k**, mp 219–222 °C dec, −55.1 ppm; **1l**, mp 144–149 °C dec, −53.0 ppm; **1m**, mp 114–116 °C, −47.9 ppm; **1n**, mp 125–128 °C, −54.8 ppm. In the experiments of runs 8 and 11 in Table II, crude *N*-fluoropyridinium salts obtained according to the above method using sodium tetrafluoroborate were utilized for the next reaction without further purification.

Preparation of 2-Fluoropyridines 2 from Salts 1. Typical Procedure. Ground crystals of *N*-fluoro-4-*tert*-butylpyridinium tetrafluoroborate (1.90 g, 7.89 mmol) were added by portions into 8 mL (79 mmol) of triethylamine under stirring at room temperature in a period of ca. 30 min. A vigorous exothermic reaction occurred immediately each time a portion of the *N*-fluoropyridinium salt was added. After all of the salt was added, the solution was stirred for an additional 5 min. The GC analysis of the reaction mixture showed that 4-*tert*-butyl-2-fluoropyridine was produced in a 91% yield. The reaction mixture was acidified with 1% hydrochloric acid and extracted with pentane. The organic layer was dried with anhydrous magnesium sulfate and filtered, and the evaporation of the solvent gave 0.87 g (72%) of 4-*tert*-butyl-2-fluoropyridine as an oil (purity by GC analysis, >98%).

The structures of the products were determined by comparison of authentic samples or spectral analyses. The spectral data (NMR, mass, and IR) of 2-fluoro-4-(methoxycarbonyl)pyridine and 2-fluoro-3,5-dimethylpyridine were in agreement with those reported previously.[4] The fluorine chemical shifts of 2-fluoropyridine derivatives are shown in Table II. Other spectral data are as follows. 2-Fluoro-4-methylpyridine: ^{1}H NMR ($CDCl_3$) δ 8.06 (1 H, d, *J* = 5 Hz, 6-H), 6.97 (1 H, double multiplet, *J* = 5 Hz, 5-H), 6.72 (1 H, bs, 3-H), 2.40 (3 H, s, CH_3); mass spectrum, *m/e* 111 (M^+). 4-*tert*-Butyl-2-fluoropyridine: ^{1}H NMR ($CDCl_3$) δ 8.12 (1 H, d, *J* = 5 Hz, 6-H), 7.20 (1 H, double multiplet, *J* = 5 Hz, 5-H), 6.90 (1 H, s, 3-H), 1.33 (9 H, s, t-Bu); mass spectrum, *m/e* 153 (M^+). 2-Fluoro-6-methoxypyridine: ^{1}H NMR ($CDCl_3$) δ 7.60 (1 H, ddd, *J* = 7.5, 7.5, 7.5 Hz, 4-H), 6.57 (1 H, dd, *J* = 7.5, 1.5 Hz, 3-H or 5-H), 6.42 (1 H, dd, *J* = 7.5, 2.5 Hz, 5-H or 3-H), 3.90 (3 H, s, CH_3); mass spectrum, *m/e* 127 (M^+). 2-Fluoro-4-phenylpyridine: ^{1}H NMR ($CDCl_3$) δ 8.23 (1 H, d, *J* = 5 Hz, 6-H), 7.70–7.30 (6 H, m, Ph and 5-H), 7.07 (1 H, d, *J* = ca. 1 Hz, 3-H); mass spectrum, *m/e* 173 (M^+). 3-(Ethoxycarbonyl)-2-fluoropyridine: ^{1}H NMR ($CDCl_3$) δ 8.42 (2 H, m, 4- and 6-H), 7.32 (1 H, m, 5-H), 4.42 (2 H, q, *J* = 6 Hz, CH_2), 1.42 (3 H, t, *J* = 6 Hz, CH_3); IR (neat) 1735 cm^{-1} (CO). 5-(Ethoxycarbonyl)-2-fluoropyridine: ^{1}H NMR ($CDCl_3$) δ 8.87 (1 H, d, *J* = 2 Hz, 2-H), 8.40 (1 H, ddd, *J* = 8, 8, 2 Hz, 5-H), 6.98 (1 H, dd, *J* = 8, 3 Hz, 4-H), 4.40 (2 H, q, *J* = 6 Hz, CH_2), 1.40 (3 H, t, *J* = 6 Hz, CH_3). 3,5-Dichloro-2-fluoropyridine: ^{1}H NMR ($CDCl_3$) δ 8.06 (1 H, m, 6-H), 7.83 (1 H, double multiplet, *J* = 8 Hz, 4-H); mass spectrum, *m/e* 165 (M^+). 3,5-Bis(trifluoromethyl)-2-fluoropyridine: ^{1}H NMR ($CDCl_3$) δ 8.75 (1 H, bs, 6-H), 8.32 (1 H, d, *J* = 8.4 Hz, 4-H); mass spectrum, *m/e* 233 (M^+). 3-Cyano-2-fluoropyridine: ^{1}H NMR ($CDCl_3$) δ 8.47 (1 H, m, 6-H), 8.10 (1 H, m, 4-H), 7.33 (1 H, m, 5-H); IR (neat) 2250 cm^{-1} (CN); mass spectrum, *m/e* 122 (M^+). 2-Cyano-6-fluoropyridine: ^{1}H NMR ($CDCl_3$) δ 8.08 (1 H, ddd, *J* = 7.5, 7.5, 7.5 Hz, 4-H), 7.70 (1 H, dd, *J* = 7.5, 1.5 Hz, 3-H), 7.28 (1 H, dd, *J* = 7.5, 2.2 Hz, 5-H); mass spectrum, *m/e* 122 (M^+). 2-Fluoro-4-nitropyridine: ^{1}H NMR ($CDCl_3$) δ 8.54 (1 H, d, *J* = 5.5 Hz, 6-H), 7.95 (1 H, dd, *J* = 5.5, 2 Hz, 5-H), 7.69 (1 H, dd, *J* = 2, 2 Hz, 3-H); IR (KBr) 1545, 1360 cm^{-1} (NO_2); mass spectrum, *m/e* 142 (M^+).

Reaction of Pyridine–F_2 Compounds with Et_3N. Typical Procedure. Pyridine (248 mg, 3.13 mmol) was dissolved in 5 mL of trichlorofluoromethane, and a 10% F_2/N_2 mixture was bubbled into the solution at −40 °C at a rate of 40 mL/min under stirring. The total amount of F_2 used was 9.39 mmol. Pyridine–F_2 compound separated from the solution as a solid. After removal of an excess of fluorine by flowing nitrogen, 4.4 mL (31 mmol) of Et_3N was added into the reaction mixture at the temperature shown in Table III and the reaction mixture was gradually warmed to room temperature in a period of ca. 30 min under stirring. The yields were determined by the GC analysis of the reaction mixtures and the results are shown in Table III.

Reaction of *N*-Fluoropyridinium Salt with a Base in a Solvent. Typical Procedure. Into a solution of 1 mmol of *N*-fluoropyridinium salt in 2 mL of dry methylene chloride was dropwise added 1 mmol of triethylamine under stirring at room temperature. An exothermic reaction occurred immediately on adding the amine. After being stirred for an additional 5 min,

(15) *Inorganic Syntheses*; Shreeve, J. M., Ed.; John Wiley & Sons, Inc.: New York, 1986; Vol. 24, Chapter 1, pp 22–27.

the reaction mixture was analyzed by GC. The structural assignment of the products was carried out by the comparison of authentic samples or by spectral analyses of the isolated products.

2-Pyridyl triflate (6): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1 H, d, J = 8.2 Hz, 3-H), 7.41 (1 H, dd, J = 7.4, 4.8 Hz, 5-H), 7.92 (1 H, dd, J = 8.2, 4.8 Hz, 4-H), 8.40 (1 H, d, J = 4.8 Hz, 6-H); ^{19}F NMR ($CDCl_3$) 73.13 (s); IR (neat) 1420 (SO_2), 1210, 1135 cm^{-1}; mass spectrum, m/e 227 (M^+). Anal. Found C, 31.47; H, 1.88; N, 6.03. Calcd for $C_6H_4F_3O_3S$: C, 31.73; H, 1.77; N, 6.17.

2-Chloro-6-[[(trifluoromethyl)sulfonyl]oxy]pyridine (10): oil; ^{1}H NMR ($CDCl_3$) δ 7.15 (1 H, d, J = 7.8 Hz, 3-H), 7.49 (1 H, d, J = 7.8 Hz, 5-H), 7.89 (1 H, dd, J = 7.8, 7.8 Hz, 4-H); ^{19}F NMR ($CDCl_3$) 73.0 (s, CF_3); IR (neat) 1423 (SO_2), 1215, 1135 cm^{-1}; mass spectrum, m/e 263, 261 (M^+). Anal. Found: C, 27.42; H, 1.16; N, 5.26. Calcd for $C_6H_3ClF_3NO_3S$: C, 27.53; H, 1.15; N, 5.35.

2-Fluoro-6-[[(trifluoromethyl)sulfonyl]oxy]pyridine (13): oil; ^{1}H NMR ($CDCl_3$) δ 7.10 (1 H, dd, J = 7.8, 2.3 Hz, 3-H), 7.17 (1 H, d, J = 7.8 Hz, 5-H), 8.04 (1 H, ddd, J = 7.8, 7.8, 7.8 Hz, 4-H); ^{19}F NMR ($CDCl_3$) 67.0 (1 F, bs, 2-F), 74.6 (3 F, s, CF_3); IR (neat) 1430 (SO_2), 1220, 1140 cm^{-1}; mass spectrum, m/e 245 (M^+). Anal. Found: C, 29.16; H, 1.27; N, 5.55. Calcd for $C_6H_3F_4NO_3S$: C, 29.39; H, 1.22; N, 5.71.

3,5-Bis(trifluoromethyl)-2-[[(trifluoromethyl)sulfonyl]oxy]pyridine (17): oil; ^{1}H NMR ($CDCl_3$) δ 8.83 (1 H, bs, 6-H), 8.37 (1 H, bs, 4-H); ^{19}F NMR ($CDCl_3$) 62.8 (3 F, s, CF_3), 63.3 (3 F, s, CF_3), 73.4 (3 F, s, SO_2CF_3); IR (in $CDCl_3$) 1425 (SO_2), 1350, 1220, 1160, 1130 cm^{-1}; mass m/e 363.9660 (M^+) (calcd for $C_8H_2NF_9O_3S$ 363.9645).

Reaction of Pyridine-F_2 with Sodium Triflate or BF_3·OEt_2. With Sodium Triflate. A 10% F_2/N_2 mixture was introduced at a flow rate of 30 mL/min just above the surface of a solution of pyridine (3 mmol) in 6 mL of $CFCl_3$ on a cooling bath of -78 °C under stirring. As the fluorine was introduced, a white or creamy solid formed. Total amount of F_2 used was 4.5 mmol. After nitrogen was flowed at a rate of 15 mL/min for 30 min, a solution of 0.518 g of sodium triflate in 12 mL of dry CH_3CN was added carefully, the temperature being kept below -40 °C, and the reaction mixture was stirred for 2 h on a cooling bath of -40 °C. The mixture was warmed to room temperature, filtered through Celite to remove sodium fluoride, and evaporated up to dryness without heating. The resulting solid was sufficiently washed with 2 mL of dry tetrahydrofuran to give 0.235 g (32%) of **5**.

With BF_3·OEt_2. Pyridine (3 mmol) was fluorinated with 10% F_2/N_2 in 6 mL of dry CH_3CN in the same manner as above. F_2 used was 9 mmol. After the fluorination, the homogeneous reaction solution was warmed to room temperature and left for 1 h. The NMR spectra of this acetonitrile solution are discussed in Results and Discussion section. Then the solution was cooled on a bath of -40 °C and BF_3·OEt_2 (3 mmol) was added into it under stirring. After stirring for 1 h at -40 °C, 50 mL of diethyl ether was added into the solution at -40 °C. The resulting solid was collected by filtration and washed with 2 mL of dry tetrahydrofuran to give 0.203 g of the solid, which was recrystallized from dry CH_3CN-Et_2O to give 0.172 g (31%) of **1** (X = BF_4, R = H).

Registry No. **1** (X = BF_4, R = 3-CO_2Et), 116241-52-2; **1a**, 107264-09-5; **1b**, 107264-12-0; **1c**, 107264-10-8; **1d**, 116241-53-3; **1e**, 116241-63-5; **1f**, 116241-55-5; **1g**, 116241-56-6; **1h**, 119071-51-1; **1i**, 109705-15-9; **1j**, 116241-51-1; **1k**, 119071-53-3; **1l**, 119071-53-3; **1m**, 119071-55-5; **1n**, 116241-58-8; **2** (R = 3,5-Me_2), 111887-71-9; **2** (R = 4-*t*-Bu), 116241-60-2; **2** (R = 6-OMe), 116241-61-3; **2** (R = 4-Ph), 116241-62-4; **2** (R = 4-CO_2Me), 455-69-6; **2** (R = 3-CO_2Et), 113898-56-9; **2** (R = 3,5-$(Cl)_2$), 823-56-3; **2** (R = 3-CN), 3939-13-7; **2** (R = 2-cyano-6-fluoro), 3939-15-9; **2** (R = 4-NO_2), 18614-46-5; **2** (R = 4-Me), 461-87-0; **2** (R = 5-CO_2Et), 116241-59-9; **2a**, 372-48-5; **5**, 107263-95-6; **6**, 65007-00-3; **7**, 109-09-1; **8** (R = H), 110-86-1; **8** (R = 4-Me), 108-89-4; **8** (R = 3,5-$(Me)_2$), 591-22-0; **8** (R = 4-*t*-Bu), 3978-81-2; **8** (R = 2-OMe), 1628-89-3; **8** (R = 4-Ph), 939-23-1; **8** (R = 4-CO_2Me), 2459-09-8; **8** (R = 3,5-$(Cl)_2$), 2457-47-8; **8** (R = 3,5-bis(CF_3)), 20857-47-0; **8** (R = 3-Cn), 100-54-9; **8** (R = 2-CN), 100-70-9; **8** (R = 4-NO_2), 1122-61-8; **8** (R = 3-CO_2Et), 614-18-6; **9**, 119071-56-6; **10**, 119071-57-7; **11**, 20885-12-5; **12**, 2402-78-0; **13**, 119071-58-8; **14**, 1513-65-1; **16**, 119071-59-9; **17**, 119071-60-2; **18**, 119071-61-3; **19**, 70158-60-0.

Synthesis of Side-Chain Derivatives of 2,2′-Bipyridine

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General and versatile synthetic methods have been developed for the preparation of a large variety of 2,2′-bipyridines bearing a single functionalized side chain in the 4-position.

Introduction

Few organic ligands have received more attention than 2,2′-bipyridine (bpy) and its analogues (e.g. 1,10-phenanthroline).[1] A large proportion of the recent interest in this ligand stems from the very interesting photophysical and photochemical properties exhibited by several of its transition metal complexes, in particular those of ruthenium,[2] osmium,[3] and rhenium.[4] As more elaborate systems exploiting such properties have started to emerge, especially in redox electrocatalysis and solar energy conversion, it has become increasingly desirable to find ways to link the metal complexes covalently to a variety of auxiliary molecules and/or to polymeric substrates.[5] Regarding the former, one of the currently most active areas of research involves the synthesis of chromophore-quencher systems, where an attempt at achieving improved charge separation is made by attaching suitable electron-transfer acceptors (such as 4,4′-bipyridinium ion) and/or donors (such as phenothiazine) to $Ru(bpy)_3^{2+}$ and related species.[6] Another area of growing interest is to be found

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