# Synthesis of 2-Substituted Pyridines by the Reaction of N-Fluoropyridinium Fluoride with Trimethylsilyl Derivatives

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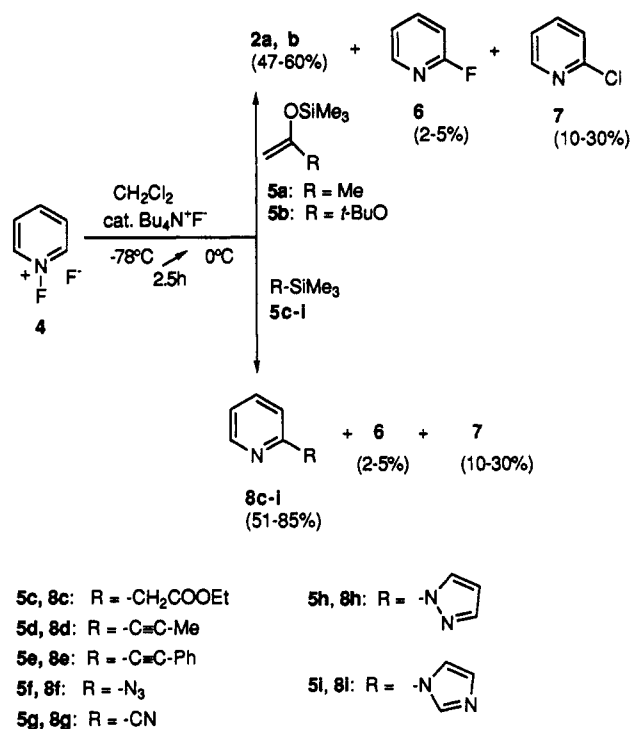*Department of Chemistry, Georgia State University, Atlanta, Georgia 30303*

N-Fluoropyridinium salts, such as 1a,b, have been used with limited success for fluorination of organic compounds.[1] These reactions usually produce a complicated mixture of products including various substituted pyridines which are often derived from the reaction with solvent. Attempts have been made to develop these observations into practical methods for the synthesis of substituted pyridines. Conditions have been found for the preparation of 2-fluoro,[2] 2-chloro,[3,4] and 2-bromopyridine,[3,4] and for the introduction of hydroxy,[5] substituted-oxy,[6,7] amido,[8] phosphonio,[9] and arsonio[9] functions at position 2 of pyridine. Examples of a successful introduction of a carbon substituent at the pyridine ring by using a similar approach are rare. Inefficient syntheses of 2-[1-(alkylthio)alkyl]pyridines[10] (yields 20–27%), 2-phenylpyridine[8] (33%), 2-(furan-2-yl)pyridine[8] (17%), 2-(furan-3-yl)pyridine[8] (13%), regioselective alkylations of 1 at position 2 by malonate anions and derivatives[11] (11–27%), and the preferential alkylations of 1 at position 4 by nitro group-stabilized anions[12] (41–47%) have been described. Additional examples are provided in eq 1 by our previously unreported syntheses of ketone 2a and ester 2b from 1

1a: X = OTf
1b: X = BF4

2a: R = Me (35% from 1a)
2b: R = t-BuO (45% from 1a)

3 (32–40%)   (1)
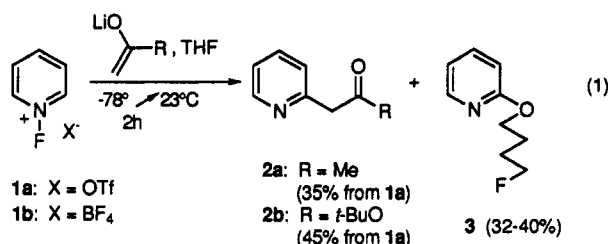
and the corresponding lithium enolates. Modest yields of 2a and 2b were obtained with 1a as the starting material. The mixtures were heterogeneous with the less-soluble tetrafluoroborate salt 1b, which resulted in an even lower

Scheme I

5c, 8c: R = -CH2COOEt
5d, 8d: R = -C≡C-Me
5e, 8e: R = -C≡C-Ph
5f, 8f: R = -N3
5g, 8g: R = -CN

5h, 8h: R = -N(pyrazolyl)

5i, 8i: R = -N(imidazolyl)

efficiency. Ether 3[8] was a byproduct in all these reactions conducted in THF.[13]

In this paper we present a novel general strategy to the synthesis of 2-substituted pyridines, which is based on the reaction of N-fluoropyridinium fluoride (4) with various trimethylsilyl derivatives 5 (Scheme I). The desired major products 2 and 8 are easily separated by flash chromatography from varying amounts of 2-fluoropyridine (6) and 2-chloropyridine (7).

The salt 4 is conveniently generated[14,15] *in situ* by bubbling elemental fluorine diluted with argon through a solution of pyridine in dichloromethane at −78 °C and then allowed to react with 5. Compounds 5 are electrophilic counterattack reagents.[16] Their reaction with fluoride ion generates the corresponding anionic species which undergo a subsequent reaction with the N-fluoropyridinium cation. The yields of products 2 and 8 are good, and the efficiency is further improved by ca. 5% by conducting the reaction in the presence of a catalytic amount of anhydrous tetrabutylammonium fluoride.

As can be seen from comparison of eq 1 and the first two entries in Scheme I, the yields of 2a and 2b are greater for the latter reactions. Interestingly, all these reactions of the lithium enolates and trimethylsilyl derivatives gave the C-substituted pyridines 2a,b exclusively. The corresponding O-substituted isomers were not observed by GC–MS analysis of crude mixtures. By contrast, 2-(isopropenyloxy)pyridine is the sole isomer (25%) formed upon treating 1a with acetone in the presence of triethylamine.[8]

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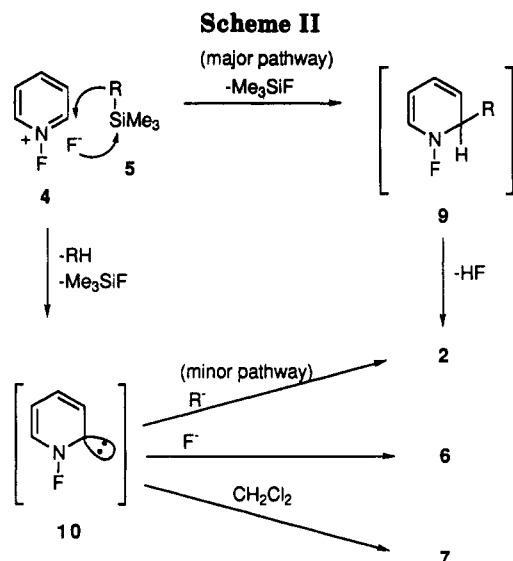(7) Rozen, S.; Hebel, D. Heterocycles 1989, 28, 249.
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Scheme II

A nucleophilic addition at the position 2 of the *N*-fluoropyridinium cation to form an adduct[11] **9** and a proton abstraction to form a carbene[2,8,11] **10** have been proposed previously to account for the observed transformations of *N*-fluoropyridinium salts (Scheme II). Because the carbon 2 is the most electrophilic site and the proton attached to this carbon is the most acidic proton in the cation, these mechanistic proposals are consistent with the preferential formation of 2-substituted pyridines in most cases studied, as already discussed. In particular, carbene **10** is a likely precursor to **3** in the reaction with THF and to **6** and **7** in the respective reactions with fluoride ion and dichloromethane. On the other hand, a major reaction pathway in the synthesis of **2** and **8** from **4** and silicon reagents **5** apparently involves the intermediacy of adduct **9**. It can be suggested that the interaction of fluoride ion with the silicon atom of **5** takes place in close proximity to the *N*-fluoropyridinium cation because this cation is ion-paired with the fluoride. The increased nucleophilicity[17] of R⁻ upon ion pairing with the large *N*-fluoropyridinium cation may play a role. This suggestion is consistent with the observed slightly increased efficiency of the synthesis of **2** and **8** when conducted in the presence of tetrabutylammonium fluoride.

In summary, we have described a new practical method for the synthesis of 2-substituted pyridines from *N*-fluoropyridinium fluoride generated *in situ* and readily available silicon reagents. The method is general and efficient. More importantly, its experimental simplicity is far superior to most of the multistep preparations of **2** and **8** described previously. The procedure is safe if conducted properly, and we have tested it numerous times at a 5-fold greater scale than that described in the Experimental Section. It must be cautioned, however, that elemental fluorine is a strong oxidizing agent. *Dichloromethane will burn freely and ether solvents will explode at 23 °C on contact with the commercial 10% mixture of fluorine and an inert gas.*[18] With dichloromethane as the solvent, we have deliberately increased the temperature during the generation of **4** and encountered no safety problems with a large excess of fluorine

even at –15 °C. In a typical experiment, however, the low temperature of the mixture is easily maintained not to exceed –60 °C. Since the reagent **4** may decompose violently upon warming,[15] it is extremely important that this reagent is allowed to react with an excess of the silyl derivative **5** at the low temperature.

Experimental Section

Molecular fluorine diluted with argon (1:9) was obtained from Air Products and Chemicals, Inc. A system for the generation of *N*-fluoropyridinium fluoride[14,15] (**4**) consisted of a standard glass flask, all-Teflon connectors and tubing, and an all-glass flow meter to estimate the amount of fluorine passed through the mixture. *N*-Fluoropyridinium triflate[15] (**1a**), *N*-fluoropyridinium tetrafluoroborate[15] (**1b**), enol trimethylsilyl ethers (**5a**) of acetone[19] and (**5b**) of *tert*-butyl acetate,[20] ethyl (trimethylsilyl)acetate[21] (**5c**), 1-(trimethylsilyl)propyne[22] (**5d**), 1-phenyl-2-(trimethylsilyl)acetylene[22] (**5e**), trimethylsilyl azide[23] (**5f**), trimethylsilyl cyanide[24] (**5g**), 1-(trimethylsilyl)pyrazole[25] (**5h**), and 1-(trimethylsilyl)imidazole[25] (**5i**) were prepared as described. Dichloromethane was distilled from phosphorus pentoxide under a nitrogen atmosphere immediately before use. All products reported previously were identified by spectral comparison (GC-MS and ^{1}H NMR) with the authentic samples.

Reactions of *N*-Fluoropyridinium Triflate (1a) with Lithium Enolates of Acetone and *tert*-Butyl Acetate. Lithium enolates (10 mmol) in THF (20 mL) were generated as described.[26] The solution was cooled to –78 °C under a nitrogen atmosphere and treated dropwise with a solution of **1a** (1.24 g, 5 mmol) in THF (10 mL). The resultant pale yellow mixture was stirred at –78 °C for 1 h and then allowed to reach 23 °C within the next 1 h. After the KI/starch test[11] showed the absence of **1a**, the mixture was concentrated and treated with CH₂Cl₂ (50 mL), and the solution was filtered from inorganic salts. Flash chromatography on silica gel with hexanes gave 2-[(4-fluorobutyl)oxy]pyridine[8] (**3**) as an oil (yield 32–40%) and then (pyridin-2-yl)acetone[27] (**2a**, 240 mg, 35%) or ester **2b** was eluted with hexanes/CH₂Cl₂ (1:1).

***tert*-Butyl (Pyridin-2-yl)acetate (2b):** An oil; yield 436 mg (45%); ^{1}H NMR (CDCl₃/TMS, 270 MHz) δ 1.35 (s, 9H), 5.62 (s, 2H), 7.15–7.30 (m, 2H), 7.87 (t, J = 8.8 Hz, 1H), 8.36 (d, J = 5.4 Hz, 1H); ^{13}C NMR (CDCl₃/TMS, 68 MHz) δ 27.8, 65.7, 81.4, 122.8, 124.1, 136.4, 141.2, 149.6, 170.4; MS *m/z* 57 (100), 92 (31), 120 (28), 193 (M+, 5). Anal. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.61; H, 7.90; N, 7.19.

Synthesis of 2a,b and 8c-i from *N*-Fluoropyridinium Fluoride (4) and Silicon Reagents 5a-i. An excess of the fluorine gas (15–20 mmol) was bubbled through a solution of pyridine (0.79 g, 10 mmol) in dichloromethane (25 mL) at such a rate that the initial temperature of –78 °C did not rise above –50 °C. The resultant white suspension of **4** was flushed with nitrogen (<–50 °C) to remove molecular fluorine, and then treated dropwise (<–50 °C) with a solution of a trimethylsilyl derivative **5a-i** (20 mmol) in dichloromethane (10 mL) and a solution of anhydrous tetrabutylammonium fluoride (25 mg) in dichloromethane (1 mL). The resultant yellow mixture was stirred at –50 °C for 1 h, then allowed to reach 0 °C within the next 1 h, and finally stirred for 0.5 h at 0 °C, after which time the KI/

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starch test[11] showed the absence of **4**. The mixture was passed through a thin layer of silica gel, and the gel was washed with dichloromethane. The solutions were combined, washed with water, dried (MgSO$_4$), and concentrated. Silica gel chromatography (hexanes) gave a mixture of 2-fluoropyridine (**6**) and 2-chloropyridine (**7**). Subsequent elution with hexanes/ether (1:1) furnished **2a,b** or **8c-i**: (pyridin-2-yl)acetone[27] (**2a**, 47%, an oil), *tert*-butyl (pyridin-2-yl)acetate (**2b**, 60%, an oil), ethyl (pyridin-2-yl)acetate[28] (**8c**, 55%, an oil), 2-(propyn-1-yl)pyridine[29]

(**8d**, 54%, an oil), 2-(phenylethynyl)pyridine[29,30] (**8e**, 61%, an oil), 2-azidopyridine[31] (**8f**, 85%, mp 155–156 °C, reported[31] mp 154–156 °C), 2-cyanopyridine[32] (**8g**, 51%, an oil), 2-(pyrazol-1-yl)pyridine[33] (**8h**, 54%, mp 39–40 °C, reported[33] mp 38–40 °C), 2-(imidazol-1-yl)pyridine[33] (**8i**, 52%, mp 38–40 °C, reported[33] mp 38–40 °C.

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