A Highly Regioselective Reaction of *N*-Fluoropyridinium Salts with Stabilized Sulfur, Oxygen, and Nitrogen Nucleophiles: A Convenient Route to 2-Substituted Pyridines

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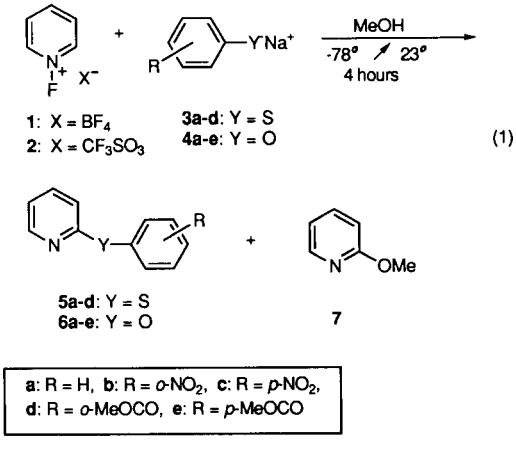
Received May 10, 1993

Dedicated to the memory of Dr. Roland K. Robins

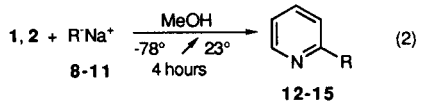
2-Substituted pyridines are efficiently obtained by the reactions of *N*-fluoropyridinium tetrafluoroborate or triflate with anions derived from benzenethiols, phenols, azoles, cyanamide, and with azide anion. The results are consistent with a nucleophile addition at the position 2 of the *N*-fluoropyridinium cation as the major reaction pathway.

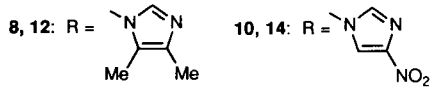
J. Heterocyclic Chem., **30**, 1361 (1993).

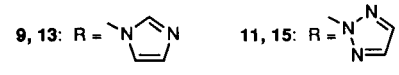
In spite of the immense interest in 2-substituted pyridines as ligands for metals [1,2] and building blocks in organic synthesis [3,4] including the preparation of biologically active agents [5-7], few efficient methods for the introduction of a substituent at the position 2 of the pyridine ring are available. The more general approaches involve displacement of a nucleofugal group, usually a halogen [8,9], Ullman reaction [1,10], Reissert-Henze [11] and related conversions [12,13], and transformations of a group already present at the position 2 of the pyridine [14].



Reactions of readily available *N*-fluoropyridinium salts [15-17], such as **1**, **2** (eq 1), have been used with limited success in the preparation of the desired pyridine derivatives. Conditions have been found for the synthesis of 2-fluoro [18], 2-chloro [19,20], and 2-bromopyridine [19,20], and for the introduction of hydroxy [21], amido [22], phosphonio [23], and arsonio [23] functions at the position 2 of pyridine. On the other hand, the reported syntheses of 2-[1-(alkylthio)alkyl]pyridines [24], 2-phenylpyridine [22], 2-(furan-2-yl)pyridine [22], 2-(furan-3-yl)pyridine [22], regioselective alkylations of **2** at position 2 by malonate anions [25], and the preferential alkylations of **2** at position 4 by anions derived from nitroalkanes [26], all are highly inefficient. As a rule, these transformations of **1**, **2** produce a complicated mixture of products which are often derived from the reaction with solvent.

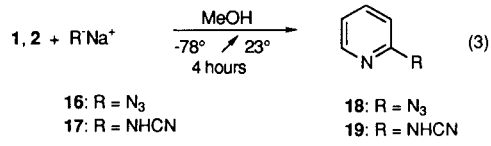






In this paper we report efficient syntheses of 2-(arylthio)pyridines **5a-d**, 2-(aryloxy)pyridines **6a-e** (eq 1), 2-(heteroaryl)pyridines **12-15** (eq 2), and two additional derivatives **18**, **19** (eq 3) by the reactions of **1** or **2** with the corresponding *S*-, *O*-, and *N*-centered nucleophiles. The reactions are conveniently conducted in anhydrous methanol to give the desired compounds **5**, **6**, **12-15**, **18**, and **19** in a 40-80% yield, varying amounts of 2-methoxypyridine (**7**, 15-40%), and other minor products. For example, 2-(phenylthio)pyridine (**5a**, 48%) was accompanied by **7** (30%), and diphenyl disulfide (15%). The formation of the corresponding disulfides was suppressed in the reactions of **3b-d** with **1** or **2**, as shown by gc-ms analyses of crude mixtures and subsequent preparative separations by silica gel chromatography. The gc-ms analyses also revealed that the 2-substituted pyridines were the sole isomers in all cases studied. This result demonstrates that the reactions of equations 1-3 are highly regioselective. Virtually identical results were obtained for the reactions conducted with **1** and **2**, which indicates that a counterion of the *N*-fluoro-

pyridinium cation does not play a role. Similar results were also obtained with lithium, sodium, and potassium salts of the nucleophilic reagents.



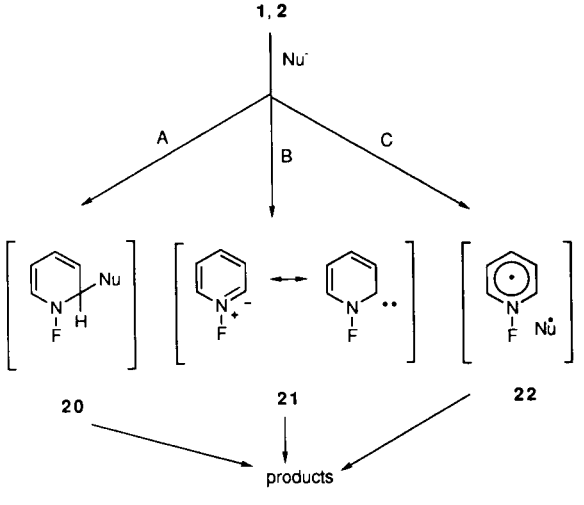
16: R = N_3
17: R = NHCN

18: R = N_3
19: R = NHCN

Anhydrous methanol is the optimized solvent in spite of the fact that its use always results in the formation of **7** as a by-product. A rapid flash chromatography is sufficient, however, for isolation of the desired products **5**, **6**, **12-15**, **18**, and **19** in analytically pure forms. Considerably more complicated mixtures of products were observed for the reactions conducted in other solvents. For example, the use of hexanes gave a substantial amount of tar, and 2-fluoropyridine was the major low molecular weight product for the reactions of **1**. The use of either tetrahydrofuran or ethyl ether also resulted in lower yields of the target compounds. *N*,*N*-Dimethylformamide was found to react violently with **1** and **2** to give 2(1*H*)-pyridone, a large number of unidentified products, and tar. Finally, the reactions conducted in acetonitrile followed by quenching with water produced *N*-(2-pyridyl)acetamide [22] as the major product.

The treatment of either **1** or **2** with sodium methoxide in methanol gave **7** in an 80% yield. With other alcohols the corresponding 2-alkoxypyridines were also formed efficiently. Aliphatic mercaptide ions and mercaptanes, on the other hand, were oxidized to the corresponding disulfides. It has also been reported that the treatment of **2** with a large excess of diethylamine does not produce 2-(diethylamino)pyridine at all [22].

Scheme I



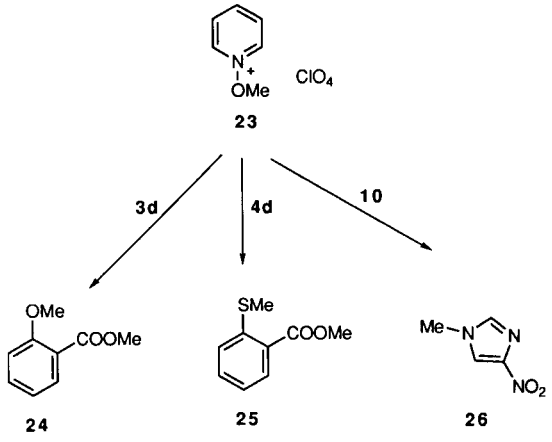
Three mechanistic pathways A-C (Scheme I) have been proposed previously [15,25] to account for the formation of substituted pyridines in the reactions of *N*-fluoropyridinium salts. These are: (A) a nucleophile addition to the most electropositive position 2 of the *N*-fluoropyridinium cation to form an intermediate adduct **20**, (B) a proton abstraction from the cation to form a carbene **21**, and (C) a single electron transfer (SET) from a reagent to the cation to form a radical pair **22**. We believe that the major mechanism for all successful reactions of equations 1-3 involves the nucleophile addition reaction (pathway A). This suggestion comes from analysis of the effect of the nucleophile structure on the efficiency of the reaction. More specifically, a general correlation can be seen that greater yields of 2-substituted pyridines are obtained with nucleophiles stabilized by an electron withdrawing group. Thus, the yields of **5b-d** (68-80%) are greater than that for the phenylthio derivative **5a** (48%), and a similar relationship is seen for **6b-e** (68-80%) when compared to the unsubstituted phenoxy compound **6a** (56%). In a similar way the yields of imidazole derivatives **12** (40%), **13** (43%), and **14** (65%) parallel the electronic effects [27] of the substituents, CH_3, H, NO_2. Since the electron-withdrawing substituents decrease basicity of the anionic reagents, these correlations are not consistent with the involvement of carbene **21** (pathway B) as major reaction intermediate. It is also known that the stabilized anions are less likely to be involved in a SET process (pathway C) than their counterparts without an electron-withdrawing group [27]. While the SET process may be involved as a minor pathway in the reactions of unsubstituted benzenethiolate anion **3a** with **1** or **2**, as evidenced by the formation of a small amount of diphenyl disulfide, this reaction pathway is even less important with the substituted thiolates **3b-d**. As already noted, the formation of the corresponding disulfides is virtually suppressed for the latter reactions. By contrast, the alkylthiolate anions with a high electron density at the sulfur atom can be involved in free radical processes [27], and they are oxidized by **1** or **2** to disulfides. The radical pathway C, on the other hand, is an unlikely mechanism for reactions of alkoxide and phenoxide ions, because these anions are poor single-electron donors [27]. Relatively little is known about the reactivity of nitrogen-centered anions such as **8-11** (eq 2) and **16**, **17** (eq 3). It should be strongly emphasized, however, that all these species are stabilized anions. They are nucleophilic and, at the same time, weakly basic.

In summary, the efficient synthesis of 2-substituted pyridines in the reactions of **1** or **2** with stabilized anions is fully consistent with a nucleophile addition reaction (pathway A) as the major reaction pathway. The involvement of the pathways B and C is minimized by electron delocalization in these stabilized anions.

This synthetic method is especially suitable for the preparation of pyridines with a sterically hindered substituent, such as **5d**, **6d**, and 2-(heteroaryl)pyridines, such as

14. We have attempted the preparation of these compounds by using two classical approaches, without any success in either case. In the first attempts, heating of a mixture of 2-bromopyridine with an excess of a sodium salt **3d**, **4d**, or **10** in methanol under reflux conditions for 24 hours and followed by a standard workup gave an almost quantitative recovery of 2-bromopyridine. In the attempted Reissert-Henze reactions (Scheme II) *N*-methoxypyridinium perchlorate (**23**) was allowed to react with the same reagents under similar conditions. Again, a gc-ms analysis of crude mixtures revealed the lack of the expected pyridines **5d**, **6d** or **14**. Workup of the mixtures gave the corresponding methyl derivatives **24-26** (yields of 25-27%) as the sole low molecular weight products.

Scheme II



EXPERIMENTAL

Methanol was allowed to react with sodium and then distilled under a nitrogen atmosphere immediately before use. *N*-Fluoropyridinium tetrafluoroborate (**1**) was prepared as described [18] and the triflate salt **2** was obtained from Aldrich. The gc-ms analyses were conducted on an HP 5890 Series II Gas Chromatograph equipped with an on-column injector, a poly(dimethylsiloxane)-coated capillary column (25 m x 0.32 mm), and a 5970 Mass Selective Detector operating at 70 eV. Melting point (Pyrex capillary) are not corrected. The ^{1}H nmr spectra were obtained at 270 MHz at 25° in deuteriochloroform solutions with tetramethylsilane as an internal reference. Coupling constants smaller than 1.5 Hz are not reported. Known compounds **5a** [28], **6a** [29], **7** (Aldrich), **12** [1], **13** [10], **14** [30], **15** [6], **18** [31], and **19** [32] were identified by comparison of melting points and spectral data (^{1}H nmr and ms) with those of the authentic samples. Compounds **24** (Aldrich), **25** [33], and **26** [34] were identified in a similar manner.

General Procedure for Preparation of 2-Substituted Pyridines **5**, **6**, **12-15**, **18** and **19**.

With the exception of sodium azide (**16**) a nucleophilic reagent **3a-d**, **4a-e**, **8-11**, **17** (2 mmoles) was generated from sodium methoxide (2 mmoles) in methanol (10 ml) and a benzenethiol, a phenol, a heterocycle, and cyanamide (2 mmoles), respectively, under a nitrogen atmosphere. This solution was cooled to -78° and then treated dropwise with stirring with a solution of an *N*-fluoropyridinium salt **1**, **2** (1 mmole) in methanol (2 ml). The resultant yellow mixture was stirred at -78° for 1 hour under a nitrogen atmosphere, then allowed to reach 23° within the next 1 hour, and finally stirred at 23° for 2 hours. Workup included concentration of the mixture on a rotary evaporator to 5 ml, treatment of the residue with ether (30 ml) to precipitate inorganic salts, and then filtration. Concentration of the ether solution was followed by chromatography on silica gel with hexanes/ether (4:1) as an eluent. Solid compounds were additionally crystallized from cyclohexane.

2-(Phenylthio)pyridine, **5a**.

This compound was obtained in a 48% yield, an oil. The reported yield [28] was 47%.

2-[(2-Nitrophenyl)thio]pyridine, **5b**.

This compound had mp 59-60°, yield 72%; ^{1}H nmr δ 7.16 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.28-7.48 (m, 4H), 7.60 (t, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.60 (d, J = 4.6 Hz, 1H); ms: m/z 78 (35), 111 (66), 155 (100), 232 (21, M$^+$).

Anal. Calcd. for $C_{11}H_8N_2O_2S$: C, 56.88; H, 3.47; N, 12.06. Found: C, 56.69; H, 3.55; N, 12.01.

2-[(4-Nitrophenyl)thio]pyridine, **5c**.

This compound had mp 102-103°, yield 80%; ^{1}H nmr δ 7.20 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.31-7.50 (m, 4H), 7.64 (t, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.68 (d, J = 4.6 Hz, 1H); ms: m/z 78 (41), 111 (72), 155 (100), 232 (29, M$^+$).

Anal. Calcd. for $C_{11}H_8N_2O_2S$: C, 56.88; H, 3.47; N, 12.06. Found: C, 56.74; H, 3.51; N, 12.15.

2-[(2-Methoxycarbonylphenyl)thio]pyridine, **5d**.

This compound was obtained as an oil, yield 58%; ^{1}H nmr δ 3.87 (s, 3H), 7.12 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.25-7.46 (m, 4H), 7.58 (t, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 4.6 Hz, 1H); ms: m/z 51 (15), 78 (28), 186 (100), 245 (25, M$^+$).

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.59; H, 4.47; N, 5.65.

2-(Phenoxy)pyridine, **6a**.

This compound was obtained in a 56% yield, an oil. The reported yield [29] was 69%.

2-[(2-Nitrophenyl)oxy]pyridine, **6b**.

This compound had mp 122-123°, yield 76%; ^{1}H nmr δ 7.20 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.25-7.46 (m, 4H), 7.66 (t, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.70 (d, J = 4.6 Hz, 1H); ms: m/z 78 (34), 95 (100), 139 (75), 216 (27, M$^+$).

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.02; H, 3.70; N, 12.91.

2-[(4-Nitrophenyl)oxy]pyridine, **6c**.

This compound had mp 147-149°, yield 80%; ^{1}H nmr δ 7.26 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.35-7.57 (m, 4H), 7.70 (t, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 8.70 (d, J = 4.6 Hz, 1H); ms: m/z 78 (42), 95 (100), 139 (67), 216 (21, M$^+$).

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.98; H, 3.81; N, 13.03.

2-[(2-Methoxycarbonylphenyl)oxy]pyridine, **6d**.

This compound was obtained as an oil, yield 68%; ^{1}H nmr δ 3.92 (s, 3H), 7.14 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.30-7.54 (m, 4H), 7.60 (t, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 8.56 (d, J =

4.6 Hz, 1H); ms: m/z 78 (21), 95 (61), 152 (27), 170 (100), 229 (25, M^+).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.02; H, 4.78; N, 6.04.

2-[(4-Methoxycarbonylphenyl)oxy]pyridine, **6e**.

This compound was obtained as an oil, yield 72%; ^{1}H nmr δ 4.12 (s, 3H), 7.12 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.32-7.58 (m, 4H), 7.72 (t, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.60 (d, J = 4.6 Hz, 1H); ms: m/z 78 (26), 95 (77), 152 (21), 170 (100), 229 (31, M^+).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.92; H, 4.91; N, 6.07.

2-(4,5-Dimethylimidazol-1-yl)pyridine, **12**.

This compound was obtained in a 40% yield, mp 93-94°. The reported yield [1] was 63%.

2-(Imidazol-1-yl)pyridine, **13**.

This compound was obtained in a 43% yield, mp 38-40°. The reported yield [10] was 40%.

2-(4-Nitroimidazol-1-yl)pyridine, **14**.

This compound was obtained in a 65% yield, mp 180-181°. The reported yield [30] was 42%.

2-(1,2,3-Triazol-2-yl)pyridine, **15**.

This compound was obtained in a 60% yield, mp 92-93°. The reported yield [6] was 50%.

2-Azidopyridine, **18**.

This compound was obtained in a 80% yield, mp 155-156°. The reported yield [31] was 21%.

2-(Cyanamino)pyridine, **19**.

This compound was obtained in a 48% yield, mp 143-144°. The reported yield [32] was 42%.

Acknowledgment.

We thank NIH NIAID (grant AI27196) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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