Facile Synthesis of 2-[1-(Alkylthio)alkyl]pyridines and Phenyl-Substituted Derivatives

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The title compounds **5** are produced in the reaction of *N*-fluoropyridinium tetrafluoroborate (**1**) with sulfides **2**. The proposed mechanism involves single-electron transfer from **2** to **1** followed by transformations of the resultant radical intermediates.

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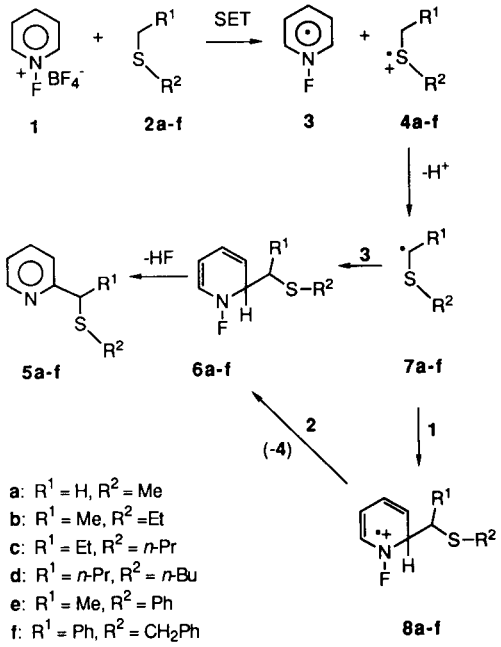
Alkyl and aryl 2-pyridylmethyl sulfides and their derivatives are of immense pharmaceutical interest. Many compounds of this class possess antisecretory and antiulcer activities [1-3] or are antiinflammatory agents [4,5]. The known sulfides have been prepared from pyridines substitued with a hydroxymethyl, chloromethyl, aminomethyl or carbaldehyde function at the 2-position [1-7]. Only relatively simple derivatives have been synthesized because the chemistries used are not general in scope.

In this paper we present a novel approach to the synthesis of alkyl or aryl 2-pyridylmethyl sulfides and their substituted derivatives of a general structure **5** (Scheme I). The method is based on an apparent free-radical alkylation (*vide infra*) of *N*-fluoropyridinium tetrafluoroborate (**1**) with sulfides **2**. The reaction is regioselective in that it produces a 2-substituted pyridine exclusively. Although a mixture of **5** with other products is formed, a simple flash chromatography is sufficient for isolation of **5** in an analytically pure form.

Scheme I



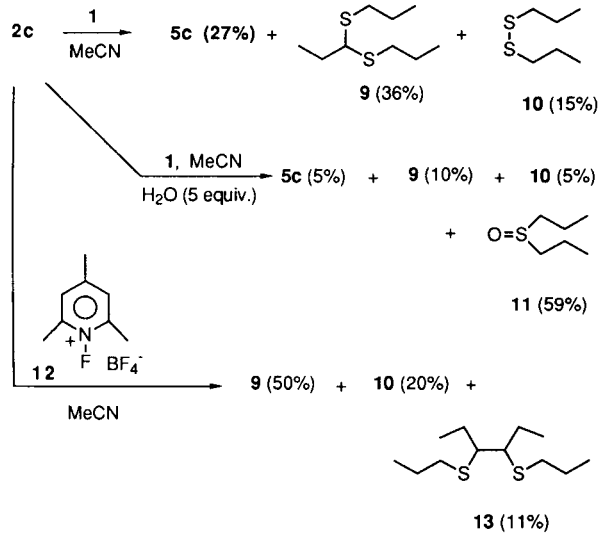
Product **5a** gave virtually identical ^{1}H nmr and mass spectra with those of the compound obtained by treatment of 2-(chloromethyl)pyridine with sodium methanethiolate [7]. New compounds **5b-f** gave satisfactory elemental analyses and their spectral data were fully consistent with the given structures. In particular, the 2-substitution of the pyridine ring in all compounds **5a-f** was evident from a one-proton doublet at δ 8.40 $\pm$ 0.1. This lowest-field absorption pattern is characteristic for C6-H of 2-substituted pyridines [8]. The methine proton adjacent to the pyridine and the sulfur atom gave the nmr absorption at δ 3.20 $\pm$ 0.02 for aliphatic derivatives **5b-d** and δ 3.54 $\pm$ 0.02 for phenyl derivatives **5e,f**, as expected. Molecular ion peaks were observed in the mass spectra of all compounds **5a-f**.

We suggest that the reaction is initiated by single-electron transfer (SET) from **2** to **1** to give a radical cation **4** and a radical **3** [9,10]. A subsequent loss of proton from **4** [11] produces a nucleophilic radical **7** which then undergoes a coupling reaction with a fluorine-substituted electrophilic radical **3** [12] to give a dihydropyridine **6**. Alternatively, the suggested intermediate product **6** may be formed in an addition reaction of the nucleophilic species **7** with cation **1** followed by a one-electron reduction of the resultant, transient radical cation **8** by sulfide **2**. Elimination of hydrogen fluoride [13] from **6** would produce **5**, the observed product. The suggested mechanistic pathways are in agreement with other findings that nucleophilic alkyl radicals selectively attack the most electrophilic position 2 of the pyridine nucleus or pyridinium cation [13,14].

Sulfide **2c** was selected to conduct mechanistic studies under different reaction conditions. A gc-ms analysis of the mixture obtained in dry acetonitrile under an inert atmosphere revealed, in addition to **5c**, the presence of two other major products, a dithioacetal **9** and a disulfide **10** (Scheme II). Compounds **5c**, **9**, and **10** were successfully separated by silica gel chromatography. On the other

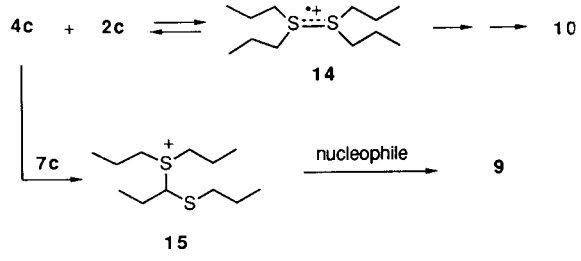
hand a sulfoxide **11** was the major product and the formation of **5c**, **9**, and **10** was suppressed in the reaction of **2c** with **1** conducted in the presence of water (5 equivalents) under otherwise identical conditions. The sulfoxide **11** was also the major product of the reaction of **2c** with **1** conducted in anhydrous acetonitrile but in the presence of oxygen. In the last experiment, *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**12**), which cannot undergo an addition reaction to the C-2 position, was substituted for **1**. Sulfide **2c** was treated with the reagent **12** in a dry solvent under an inert atmosphere. Under these conditions the yields of **9** and **10** were greater than in the similar first reaction with **1**, and a new product **13** was formed. Again, the mixture was separated into analytically pure components by using silica gel chromatography.

Scheme II



The formation of all these products is fully consistent with the suggested involvement of radical intermediates. It is known that sulfides are readily oxidized to radical cations under proper conditions [15,16], and these intermediate species are stabilized by interaction with a free sulfide to form a complex such as **14** [17] (Scheme III). The complex formation increases lifetime of the radical cation **4c** and thus allows for deprotonation of **4c** to give a radical **7c**, the suggested precursor to **5c**. The radical **7c** cannot undergo an addition reaction with methyl-substituted reagent **12**, as suggested for the reagent **1**-mediated reaction. As a result, a recombination of **7c** is observed to give product **13**. The competing formation of dithioacetal **9** can be explained by coupling of **4c** with **7c** followed by a nucleophilic displacement of a propyl group from the resultant sulfonium cation **15**. With **14**, a similar nucleophilic reaction followed by oxidation and then the reaction with a nucleophile again may lead to disulfide **10**. Fluoride ion or pyridine may serve as the nucleophiles [18]. Indeed, a control reaction of methyldipropylsulfonium iodide (**16**), a model compound for **15**, with tetrabutylammonium fluoride as the source of fluoride ion, furnished dipropyl sulfide (**2c**) in quantitative yield. Treatment of this sulfonium salt with pyridine in acetonitrile gave a similar result [19].

Scheme III



The formation of sulfoxide **11** for the reaction conducted in the presence of water can be explained by hydration of the intermediate radical cation **4c**. Sulfoxide **11** can also be formed from **4c** in the presence of oxygen [15], as observed.

In summary, we have shown a useful method for homolytic alkylation of a pyridinium system with sulfides to give 2-substituted pyridines [20]. Alkyl radicals for the alkylation of pyridine or a pyridinium cation can be generated by electrolysis of carboxylic acids, thermal decomposition of acid anhydrides or salts, and in related reactions [14]. These methods, however, may not be suitable for the generation of free radicals such as **7** derived from sulfides. The synthetic utility of our method is further stressed by a facile preparation of the reagent **1** [21] and a simple workup for the isolation of pyridine derivatives **5** [26].

EXPERIMENTAL

Sulfides **2a-f** were obtained from Aldrich. Authentic samples of **5a** [7], **9** [22], **10** [23], **11** [24], and **13** [25] were synthesized as described. The *N*-fluoropyridinium salts **1** and **12** were prepared as described [21], crystallized from anhydrous acetonitrile, and stored over phosphorus pentoxide. Acetonitrile was distilled from phosphorus pentoxide under a nitrogen atmosphere immediately before use. The gc-ms analyses were conducted on an H-P 5890 Series II Gas Chromatograph equipped with an on-column injector, a poly(dimethylsiloxane)-coated capillary column (25 m x 0.32 mm), and 5970 Mass Selective Detector operating at 70 eV. Preparative chromatography was conducted on a column slurry-packed with silica gel in hexanes. Compounds **9**, **10**, and **13** were separated with hexanes as an eluent. Compounds **5a-f** and **11** were then eluted with mixtures of hexanes/ether, 4:1 and 2:1, respectively. A single elution with the former mixture of solvents is sufficient to obtain pure compound **5a-f** when isolation of other products is not desired. 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 2 Hz are not reported.

General Procedure for Preparation of 2-Substituted Pyridines **5a-f**.

A solution of the reagent **1** (1.84 g, 10 mmoles) in dry acetonitrile (15 ml) was stirred at −35° under a nitrogen atmosphere and treated dropwise with a solution of a sulfide **2a-f** (10 mmoles) in acetonitrile (5 ml). The mixture was stirred at −35° for 1 hour and then at 23° until the reagent **1** was consumed (4-6 hours) as indicated by the inability of the mixture to oxidize potassium iodide to iodine in a standard potassium iodide-starch test. Then the mixture was concentrated to 5 ml on a rotary evaporator, treated with sodium hydrogen carbonate, and extracted with dichloromethane (3 x 25 ml). The extract was dried with sodium sulfate and concentrated. Chromatography as described above gave product **5a-f** as an oil.

2-[(Methylthio)methyl]pyridine, **5a**.

This compound [7] was obtained in a 25% yield; ^{1}H nmr: δ 2.54 (s, 3H), 3.34 (s, 2H), 7.06 (d, J = 8.0 Hz, 1H), 7.32 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 8.50 (d, J = 4.6 Hz, 1H); ms: m/z 48 (100), 93 (72), 125 (27), 139 (M^+, 47). The spectral data were not presented in [7].

2-[1-(Ethylthio)ethyl]pyridine. **5b**.

This compound was obtained in a 21% yield; ^{1}H nmr: δ 1.02 (t, J = 6.6 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H), 2.68 (q, J = 6.6 Hz, 2H), 3.22 (q, J = 6.6 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.28 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 8.46 (d, J = 4.6 Hz, 1H); ms: m/z 61 (100), 93 (76), 107 (33), 167 (M^+, 61).

Anal. Calcd. for $C_9H_{13}NS$: C, 64.62; H, 7.83; N, 8.37. Found: C, 64.36; H, 7.74; N, 8.33.

2-[1-(Propylthio)propyl]pyridine, **5c**.

This compound was obtained in a 27% yield; ^{1}H nmr: δ 0.90-1.48 (m, 10H), 2.54 (t, J = 6.6 Hz, 2H), 3.20 (t, J = 6.6 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 8.42 (d, J = 4.6 Hz, 1H); ms: m/z 43 (100), 61 (79), 93 (67), 137 (29), 195 (M^+, 49).

Anal. Calcd. for $C_{11}H_{17}NS$: C, 67.63; H, 8.77; N, 7.17. Found: C, 67.69; H, 8.72; N, 7.18.

2-[1-(Butylthio)butyl]pyridine, **5d**.

This compound was obtained in a 22% yield; ^{1}H nmr: δ 0.84-1.56 (m, 14H), 2.48 (t, J = 6.6 Hz, 2H), 3.18 (t, J = 6.6 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 8.44 (d, J = 4.6 Hz, 1H); ms: m/z 57 (100), 61 (75), 89 (44), 93 (76), 135 (45), 167 (43), 223 (M^+, 25).

Anal. Calcd. for $C_{13}H_{21}NS$: C, 69.90; H, 9.48; N, 6.27. Found: C, 69.72; H, 9.52; N, 6.34.

2-[1-(Phenylthio)ethyl]pyridine. **5e**.

This compound was obtained in a 20% yield; ^{1}H nmr: δ 1.34 (d, J = 6.8 Hz, 3H), 3.52 (q, J = 6.8 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.12-7.26 (m, 5H), 7.32 (dd, J = 8.0 Hz, J = 4.6 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 8.50 (d, J = 4.6 Hz, 1H); ms: m/z 93 (65), 109 (100), 199 (64), 215 (M^+, 51).

Anal. Calcd. for $C_{13}H_{13}NS$: C, 72.51; H, 6.08; N, 6.50. Found: C, 72.56; H, 6.05; N, 6.54.

2-[α-(Benzylthio)-2-benzyl]pyridine, **5f**.

This compound was obtained in a 22% yield; ^{1}H nmr: δ 3.32 (s, 2H), 3.56 (s, 1H), 6.88-7.34 (m, 12H), 7.52 (t, J = 8.0 Hz, 1H), 8.38 (d, J = 4.6 Hz, 1H); ms: m/z 123 (100), 169 (75), 213 (43), 291 (M^+, 37).

Anal. Calcd. for $C_{19}H_{17}NS$: C, 78.31: H, 5.88; N, 4.81. Found: C, 78.13; H, 5.96; N, 4.87.

Acknowledgment.

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[19] The sulfonium iodide **16** precipitated from a solution of iodomethane and dipropyl sulfide (**2c**) in ether. Compound **16** was allowed to react with tetrabutylammonium fluoride or pyridine under the general conditions of solvent, concentration, and time, described for the synthesis of **5**. Analyses of the two reaction mixtures by gc-ms, ^{1}H nmr, and preparative chromatography, all revealed the presence of **2c** as the only sulfur-containing product. Demethylation of **16** by fluoride ion in the presence of a much more nucleophilic iodide ion can be explained by irreversible formation of fluoromethane. Due to high energy of a carbon-fluorine bond, alkyl fluorides do not react with sulfides.

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[26] Slightly lower yields of **5a-f** were obtained for the reactions of *N*-fluoropyridinium trifluoromethanesulfonate than with **1** under otherwise identical conditions. The trifluoromethanesulfonate salt is hygroscopic.