Attempted Syntheses of Aminofluorothiophenes

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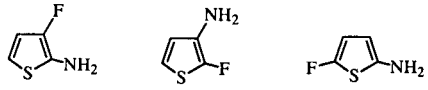
Received April 22, 1999

It appeared that a key intermediate for 2-amino-3-fluorothiophene (**1**), methyl 3-fluorothiophene-2-carboxylate (**5**), had been prepared by a Schiemann reaction of the 3-diazonium salt (**6**) in xylenes. This report was not correct. Gomberg coupling products **7** with *o*-xylene are actually formed. We were able to prepare **5** by using special conditions for the Schiemann reaction. The hydrazide derivative of **5** failed to give **1** under Curtius reaction conditions. Two new acetamidofluorothiophene compounds were prepared using Selectfluor™ as the fluorinating agent, but no aminofluorothiophenes **1-3** or salts could be obtained by acidic hydrolysis of either amide.

J. Heterocyclic Chem., **36**, 1247 (1999).

In an attempt to make fluoroquinolone antibiotics [1] with fluorothiophene substituents at position 1, we required aminofluorothiophenes such as 2-amino-3-fluorothiophene **1**, 3-amino-2-fluorothiophene **2**, or 2-amino-5-fluorothiophene **3** (Figure 1).



1 **2** **3**

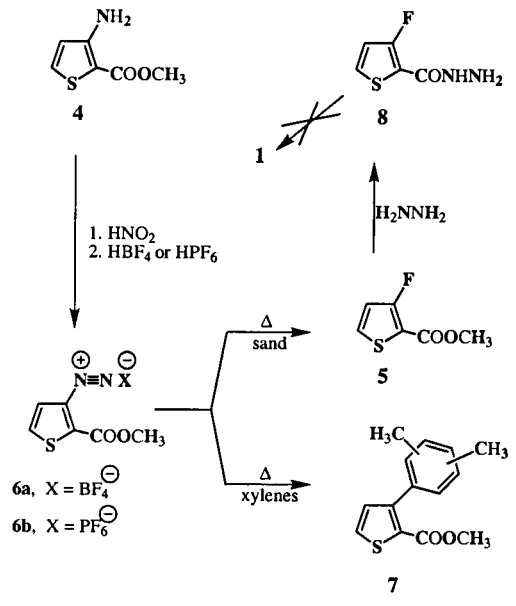
Figure 1

Aminothiophenes have long been noted for their instability [2-6]. In addition, reports on attempted introduction of fluorine into a thiophene nucleus using the Schiemann reaction were negative [7,8]. There is only one report, by Corral, *et al.* for a Schiemann reaction on a thiophene ring [9], in which the authors have claimed that methyl 3-amino-2-thiophenecarboxylate **4** gave a normal Schiemann reaction (Scheme 1).

The claimed product of this reaction, **5**, could have been used as a precursor to make **1**.

We conducted the reaction exactly according to the recipe by Corral, *et al.*, and obtained a solid product with a similar mp (115° *vs* 112°); but our ^{1}H nmr of this compound showed two "extra" peaks at 7.15 ppm and 2.04 ppm. The mass spectrum showed a molecular ion mass of 246. These data, accompanied with elemental analyses, revealed that the product of this reaction, instead of being compound **5**, carries a xylene ring at position 3 (compound **7**, Scheme 1). In fact this compound is the product of a Gomberg reaction between the diazonium salt **6** and xylenes. If this were the case, since we had used mixed xylenes, one would expect to get all possible isomers from all three isomers of xylene. A gc-ms of an extract from the

Scheme 1



reaction mixture (before any further purification) showed 7 major peaks, of which 6 peaks showed the same molecular ion peaks (246) (Figure 2).

In order to find the exact structure of compound **7**, the reaction was repeated in *o*-, *p*-, and *m*-xylene separately. Only *o*-xylene gave a solid product, which was composed of two components with the same molecular weight (246). These are the two possible isomers for the Gomberg reaction between compound **6** and *o*-xylene (**7a** and **7b** in Scheme 2). Of these two isomers, compound **7b** showed the exact ^{1}H nmr as the product from the original reaction. We find it odd that Corral, *et al.*, reported only the "thiophenic protons" in their ^{1}H nmr data. Their elemental assays cannot be explained.

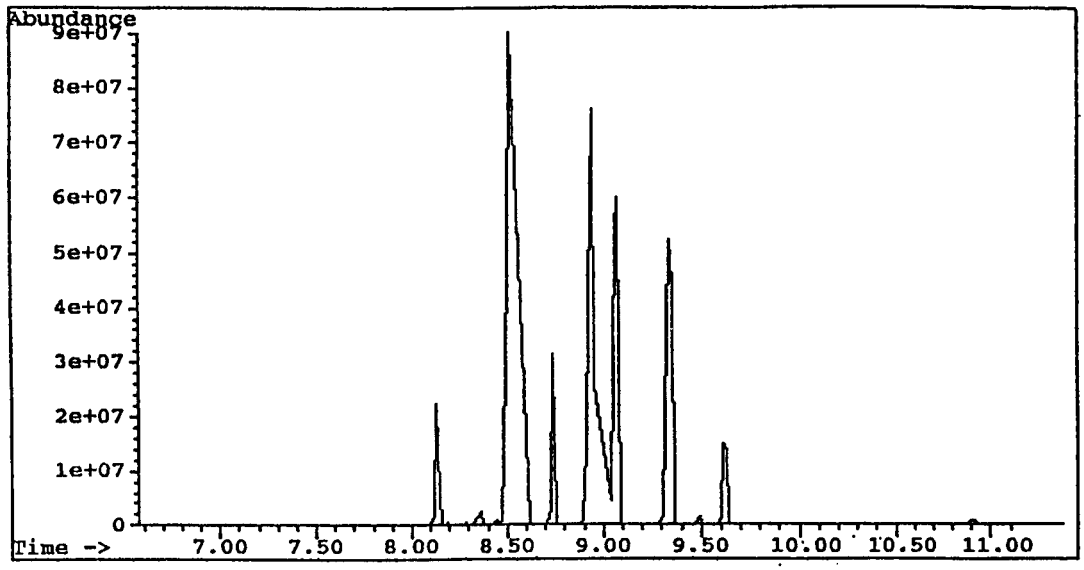
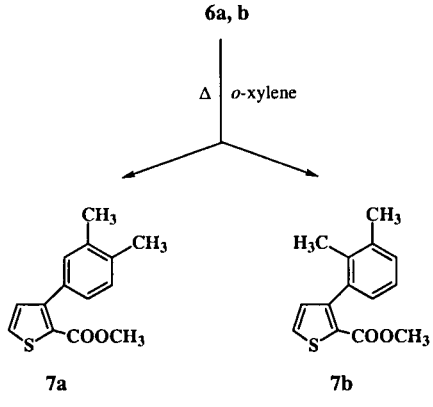


Figure 2.

In addition to the thermal decomposition in xylenes, several other versions of the Schiemann reaction were tried on compound **6**, such as $Et_3N.3HF$/ultrasound [10], $Et_3N.3HF$/Freon™ 113, Cu/acetone [11], 70% HF [12] and HF-pyridine [13], but none of them was successful. Eventually when a mixture of **6** and "sand" was heated under vacuum (0.1-1 torr) a crystalline product began to sublime out of the mixture, and in fact compound **5** was at hand in 30% yield, representing the first successful Schiemann reaction on any type of thiophene ring. Data from ^1H nmr, ^{13}C nmr, ^{19}F nmr, ms and elemental analysis support the structure of compound **5** obtained from this reaction.

Scheme 2



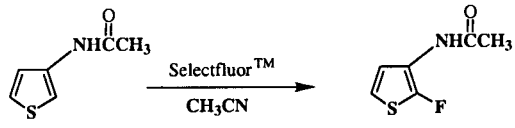
7a **7b**

3-Fluorothiophene-2-carboxylic hydrazide **8** was prepared from compound **5**, but attempts to conduct a Curtius reaction on **8** using the Smith method [14] were unsuccessful.

Ring fluorination of acetanilide by electrophilic substitution with Selectfluor™, a species with an N-F function, was reported [15]. For this model compound we found that 20 minutes at reflux in acetonitrile was optimum. Under these conditions, acetamidothiophenes decomposed and we found that 1-10 minutes at 20° was optimum. Some decomposition occurred even at -20°, the lowest temperature at which reaction took place.

In an attempt to make **2**, 3-acetamidothiophene **9** [16], was treated with Selectfluor™ [17] and 3-acetamido-2-fluorothiophene **10** was obtained (Scheme 3).

Scheme 3



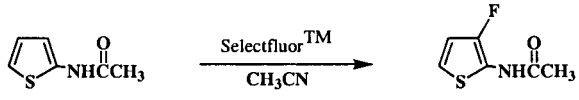
9 **10**

Treatment of 2-acetamidothiophene **11** [18] with Selectfluor™ gave 2-acetamido-3-fluorothiophene **12** (Scheme 4). The position of the fluorine on the 2-acetamidothiophene can be determined by several criteria. The 4-fluoro isomer is eliminated by the presence of a $^3J_{H\text{-}H}$. This is too large to be a $^4J_{H\text{-}H}$ value. The choice is then left to determine whether the pair of protons is at the 3, 4, or the 4, 5 positions. The $^3J_{H\text{-}F}$ for the proton adjacent to the fluorine establishes the relative assignment of position of the protons, but does not determine whether the fluorine is at the 3- or the 5-position. The protons are correlated to their carbons using a ^1H-^{13}C 2D-nmr HETCOR experiment. The SoftShell C-13 NMR module is used to calculate the ring carbon chemical shifts for the 3-fluoro- and the 5-fluoro-2-acetamidothiophenes. The C-13 NMR Module calculates on the basis of empirically determined substituent constants based on a very large data set. It generally matches a calculated shift to better than 5 ppm

of the experimentally determined value. It is assumed here that errors due to solvent effects will be smaller than errors due to mismatch of the incorrect structure. The calculation for the 3-fluoro isomer gives a mean absolute error between experimental and calculated shift values of 1.9 ppm. The largest single absolute error is 4.1 ppm. The calculation for the 5-fluoro isomer gives a mean absolute error of 23.9 ppm with the largest single absolute error of 39.9 ppm. Thus empirically based ^{13}C shift calculations indicate that the isomer obtained is the one with fluorine at the 3-position. This can be further confirmed by comparing $^{3}J_{H3\text{-}H4}$ and $^{3}J_{H4\text{-}H5}$ for a series of fluorothiophenes [20] and 2-substituted-5-fluorothiophenes [21]. It has been found that the $^{3}J_{H3\text{-}H4}$ has a range of 3.85-4.60 ppm for these compounds while the range for $^{3}J_{H4\text{-}H5}$ coupling is 5.33-6.02 Hz. The experimental compound has a $^{3}J_{H\text{-}H}$ coupling of 6.0 Hz supporting protons at the 4,5-positions and the fluorine at the 3-position.

Since **1** and **2** as free bases are unstable [6], acidic hydrolysis was tried on compounds **10** and **12** in order to obtain the hydrochloride salts of **1** and **2**. In both cases the hydrolysis was unsuccessful and an hydrogen sulfide odor was indicative of thiophene ring decomposition.

Scheme 4



11 **12**

In conclusion, although Selectfluor™ has proven to be highly effective for the fluorination of acetanilide [15], it was found incompatible with acetamidothiophenes and the fluorinated derivatives were obtained in very low yields. In the case of 3-acetamidothiophene, fluorination is directed to position 2 since both intrinsic reactivity of the thiophene ring and the activating effect of acetamido group are in favor of position 2. In the other case (2-acetamidothiophene) it seems that the activating effect of the acetamido group outweighs the intrinsic reactivity of the thiophene ring (which is in favor of position 5) and fluorination is directed to position 3.

EXPERIMENTAL

The methyl 3-aminothiophenecarboxylate **4**, was obtained from Aldrich (cat. # 23,290-4). Melting points were determined with a Thomas-Hoover capillary melting point apparatus and needed no correction. Evaporations were carried out with a rotary evaporator at 20-30 torr pressure. The reactions were monitored by tlc performed on Silica Gel™ plates (Whatman Diamond MK6F Silica Gel™ 60A) using chloroform for development and short-wave uv for visualization. Chromatographic purification by means of an Ace-Kauffman column means that a solid sample was extracted with hot solvent, passing through absorbent into refluxing solvent in a special apparatus [19]. Infrared spectra were obtained with a Perkin-Elmer Spectrum 1000 FT-IR instrument. The ^{1}H NMR spectra were recorded at 60 MHz on a Varian EM360L spectrometer except when otherwise indicated. The ^{13}C and ^{19}F nmr spectra were recorded at 200 MHz on a Varian XL200 spectrometer except when otherwise indicated. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane for ^{1}H and ^{13}C NMR and fluorotrichloromethane for ^{19}F NMR as the internal standard. The ^{1}H-^{13}C 2D-nmr HETCOR experiments were run using software supplied by Varian Instruments. The pulse sequence used BIRD pulses for suppression of homonuclear proton couplings. Empirically based ^{13}C nmr shift calculations were obtained from SoftShell International's C-13 nmr Module which runs in their ChemWindow drawing package [22]. The gc chromatograms and mass spectra were determined with a Hewlett Packard 5890 series II gas chromatograph (30-m x 0.32-mm RTX-200 column, Restek Co., Catalog # 15064) with a Hewlett-Packard 5971A mass detector utilizing electron impact ionization. The hplc was carried out on a Milton Roy® HPLC system consisting of ConstaMetric® 3000 series isocratic pump, and a SpectoMonitor® 3100 variable wavelength uv/vis detector at 254 nm wavelength. Elemental assays were carried out by Oneida Research Services, Whitesboro, NY 13492 or Microanalysis, Wilmington, DE 19808.

Methyl 3-(*o*-Xylen-3-yl)thiophene-2-carboxylate (**7b**).

A suspension of methyl 3-diazothiophene-2-carboxylate tetrafluoroborate **6a** (10.24 g, 40 mmoles, [9]) or methyl 3-diazothiophene-2-carboxylate hexafluorophosphate **6b** (12.56 g, 40 mmoles, [9]) in dry xylenes (100 ml, Fisher X3S-4) was boiled under reflux at 135-140° for 4 hours. The solvent was evaporated. To the residue was added 10% sodium carbonate solution (100 ml) and the mixture was extracted with ether. The ethereal extract was washed with water and dried over anhydrous magnesium sulfate. Solvent was evaporated and a brown liquid was obtained which solidified after a few hours. This solid was recrystallized from absolute ethanol to give 0.28 g (from the fluoroborate derivative, 4.4%) and 0.24 g (from the fluorophosphate derivative, 4%) of methyl 3-(*o*-xylen-3-yl)thiophene-2-carboxylate **7b**, mp 115-117°; ir (potassium bromide): 1680 (C=O), 1210 cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.58 (1H, d, J = 4.98 Hz, 5-H), 7.20-7.14 (1H, high order d, $J_{H4\text{-}H5}$ = 7.1 Hz, $J_{H6\text{-}H5}$ = 7.6 Hz, xylene 5-H), 7.10-7.06 (2H, high order dd, xylene 4-H and 6-H), 6.89 (1H, d, J = 4.98 Hz, 4-H), 3.70 (3H, s, OCH_3), 2.05 (6H, s, xylene CH_3 groups); ms: m/z 246 ($M^{+\cdot}$), 231(M – CH_3), 215 (M – OCH_3), 187 (M – $COOCH_3$), 171.

Anal. Calcd. for $C_{14}H_{14}O_2S$ (246.32): C, 68.27; H, 5.73; S, 13.01. Found: C, 67.01; H, 5.77; S, 12.97.

Reaction of Methyl Thiophene-2-carboxylate-3-diazonium Salt **6a** or **6b** with *m*- or *p*-Xylene.

The reaction conditions above for **7b** gave no crystalline product in these cases.

Reaction of Methyl Thiophene-2-carboxylate-3-diazonium Salt **6a** or **6b** with *o*-Xylene.

The reaction conditions above for **7b** gave a mixture of 60% **7a** and 40% **7b** in this case which were determined by gc-ms; ^{1}H nmr for **7a** (deuteriochloroform): δ 7.65 (1H, d, J = 5 Hz, 5-H), 7.15 (3H, s, xylene aromatic Hs), 6.94 (1H, d,

J = 5 Hz, 4-H), 3.75 (3H, s, OCH_3), 2.33 (6H, s, xylene CH_3 groups).

Methyl 3-Fluorothiophene-2-carboxylate (**5**).

A mixture of either methyl 3-diazothiophene-2-carboxylate tetrafluoroborate **6a** (7.68 g, 0.03 mole) or methyl 3-diazothiophene-2-carboxylate hexafluorophosphate **6b** (9.42 g, 0.03 mole) and 40 g of sand was heated in a round-bottomed flask at 160° under vacuum distillation (1.5-1 mm Hg) conditions. When the head thermometer showed 75-80°, a pale yellow liquid product distilled and solidified inside the condenser. Distillation was stopped when a dark yellow liquid began to distill. Then the solid was scraped out of the condenser and allowed to remain in the fume hood for a few hours to get rid of boron trifluoride gas. This compound was then recrystallized from methanol/water to give methyl 3-fluorothiophene-2-carboxylate **5** (1.54 g from the tetrafluoroborate derivative, 32% yield and 1.45 g from the hexafluorophosphate, 30% yield), mp 51-53°; ir (thin film on a sodium chloride plate): 1715 (C=O), 1554, 1450, 1090, 773 cm^{-1}; ^1H nmr (200 MHz) (deuteriochloroform): δ 7.43-7.40 (1H, dd, J_{H5-H4} = 5.5 Hz, J_{F-H4} = 3.8 Hz, 4-H), 6.86-6.84 (1H, dd, J_{H4-H5} = 5.5 Hz, J_{F-H5} = 0.54 Hz, 5-H), 3.89 (3H, s; OCH_3), ^{13}C nmr (deuteriochloroform): δ 161.8 (C-3), 130.0 (C=O), 129.9 (C-5), 118.5 (C-4), 118.1 (C-2), 51.9 (OCH_3); ^{19}F nmr (deuteriochloroform): δ -115.4 (1F, d, J_{H4-F} = 3.7), ms: m/z 160 ($M^{+\bullet}$), 129 (M – OCH_3), 101 (M – $COOCH_3$).

Anal. Calcd. for $C_6H_5FO_2S$ (160.16): C, 44.99; H, 3.15; F, 11.86; S, 20.02. Found: C, 44.84; H, 3.24; F, 11.70; S, 20.05.

3-Fluorothiophene-2-carboxylic Hydrazide (**8**).

A solution of 3 ml of 87% aqueous hydrazine hydrate (2.62 g of hydrazine hydrate, 0.05 mole) and 1.25 ml of absolute ethanol was brought to gentle boiling. To this solution was added methyl 3-fluorothiophene-2-carboxylate **5** (4.0 g, 0.025 mole) during a period of 45 minutes. The reaction mixture was heated under reflux for 15 more minutes. After the reaction mixture had cooled to room temperature, the crystals were collected and washed with ether to give 3.14 g (78%) of 3-fluorothiophene-2-carboxylic hydrazide **8**, mp 136-140°; ir (thin film on a sodium chloride plate): 3188, 3090, 1654 (C=O), 1534, 763 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.93-7.66 (1H, t, J = 4 Hz, 4-H), 7.23-7.05 (1H, d, J = 6 Hz, 5-H), 6.33-4.66 (3H, br s, NH, NH_2); ms: m/z 160 ($M^{+\bullet}$).

Anal. Calcd. for $C_5H_5FN_2OS$ (160.17): C, 37.50; H, 3.15; F, 11.86; N, 17.49; S, 20.02. Found: C, 37.74; H, 3.16; F, 11.46; N, 17.73; S, 19.47.

3-Acetamido-2-fluorothiophene (**10**).

Selectfluor™ (6.37 g, 0.018 mole, Aldrich 43,947-9) was dissolved in acetonitrile (180 ml, Fisher A 996-4) at 70°. At ~20° this solution was treated under nitrogen with 3-acetamidothiophene **9** (2.54 g, 0.018 mole, [15]). The resulting solution was stirred for 10 minutes (after 10 minutes a negative KI-starch test was obtained). Then it was poured into ethyl ether (400 ml), washed with water (3 x 250 ml), then with a saturated solution of sodium bicarbonate (250 ml), dried over anhydrous magnesium sulfate, filtered and evaporated at 20°. A brown liquid was obtained which solidified after a few hours. The solid was extracted from a small Ace-Kauffman column packed with 6 cm of Silica Gel, Merck, grade 10181 (Aldrich 24,217-9) using diethyl ether as the eluent to give 0.63 g of yellow solid which was still impure. This solid was sublimed at 70-75° and 1 torr; thus 0.14 g (5%) of a white powder was obtained which still showed two spots on tlc. Further purification was carried out by preparative thin layer chromatography on Alumina GF (Uniplate™, 500 μm, 20 x 20 cm, Analtech cat # 04012), using 20:1 toluene and dimethylacetamide as eluent to give **10** at R_f of 0.47, mp 107.5-110°; ir (thin film on a sodium chloride plate): 3246, 1658 (C=O), 1441, 707 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 7.29-7.27 (1H, dd, J_{H4-H5} = 6.30 Hz, J_{F-H5} = 3.26 Hz, 5-H), 7.10-7.0 (1H, br s, NH), 6.55-6.53 (1H, dd, J_{H5-H4} = 6.30 Hz, J_{F-H4} = 4.41 Hz, 4-H), 2.10 (3H, s, $COCH_3$); ^{19}F nmr (400 MHz, deuteriochloroform): δ -147.9 (1F, dd, J_{H4-F} = 4.6 Hz, J_{H5-F} = 3.3 Hz, 2-F); ms: m/z 159 ($M^{+\bullet}$), 117, 90, 63.

Anal. Calcd. for C_6H_6FNOS (159.178): C, 45.27; H, 3.80; F, 11.93; N, 8.80; S, 20.14. Found: C, 44.88; H, 4.01; F, 12.27; N, 7.96; S, 19.18.

2-Acetamido-3-fluorothiophene (**12**).

Selectfluor™ (14.16 g, 0.04 mole, Aldrich 43,947-9) was dissolved in acetonitrile (280 ml, Fisher A 996-4) at 70°. At ~20° this solution was treated under nitrogen with 2-acetamidothiophene **11** (5.64, 0.04 mole, [17]). The reaction was almost instant (negative KI-starch test was obtained right after adding **11**). Then it was poured into diethyl ether (500 ml), washed with water (3 x 300) then a saturated solution of sodium bicarbonate (300 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. A brown liquid was obtained which solidified after a few hours. This solid was extracted from a small Ace-Kauffman column packed with 6 cm of Silica gel, Merck, grade 10181 (Aldrich 24,217-9) using diethyl ether as the eluent to give 1.35 g of a yellow impure solid which was then sublimed at 70-80° and 1 torr twice to give 0.35 g of a white powder which was still impure. A solution of 30 mg of this compound in 1 ml methanol was applied to a preparative hplc using an Alltima (Alltech) semipreparative C-8 reverse-phase column (94020296, 10 μm, 100 Å, 1.0 x 25 cm) and elution with 10% methanol in water at 3ml/minute. In general, 3 peaks were observed: t_{R1} = 36.1 minutes, assigned to 2-acetamidothiophene **11**, t_{R2} = 40.2 minutes, assigned to 2-acetamido-3-fluorothiophene **12** and t_{R3} = 80.5 minutes, which due to its minute amount we were not able to identify. The mp of **12** was 128-129.5°; ir (thin film on a sodium chloride plate): 3223, 1649 (C=O), 1399, 730; ^1H nmr (200 MHz, deuteriochloroform): δ 7.58 (1H, br s, NH), 6.98 (1H, dd, J_{H5-H4} = 6.0 Hz, J_{F-H4} = 4.6, 4-H), 6.87 (1H, d, J_{H4-H5} = 6.0 Hz, 5-H); ^{13}C nmr (200 MHz, dimethyl-d_6 sulfoxide): δ 166.9 (C=O), 144.7 (d, J_{F-C3} = 249.2 Hz, C-3), 119.1 (d, J_{F-C2} = 14.0 Hz, C-2), 115.6 (d, J_{F-C4} = 9.7 Hz, C-4), 114.6 (d, J_{F-C5} = 23.6, C-5), 22.2 (CH_3); ^{19}F nmr (200 MHz, deuteriochloroform): δ -141.7 (1F, d, J_{H4-F} = 4.7 Hz); ms: m/z 159 ($M^{+\bullet}$), 117, 90, 63.

Anal. Calcd. for C_6H_6FNOS (159.178): C, 45.27; H, 3.80; F, 11.93; N, 8.80; S, 20.14. Found: C, 45.00; H, 3.79; F, 11.54; N, 8.29; S, 19.25.

Acknowledgements.

The authors wish to thank James E. Hall of Zeneca Pharmaceutical Inc. for determining 400 MHz nmr spectra and Rick S. Hock and Nisit Kittipongpatana for their help with hplc.

F. Kobarfard thanks Shaheed Beheshti University, Tehran, Iran, for doctoral fellowships and Department of Chemistry & Biochemistry of USP for teaching assistantships.

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