A Facile and Improved Synthesis of 3-Fluorothiophene

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Abstract: A new efficient and convenient route to 3-fluoro-thiophene in four steps and 49% overall yield is reported. The fluorine atom was successfully introduced into the thiophene ring in 67% yield using the Schiemann reaction on 2-methoxycarbonyl-thiophene-3-diazonium tetrafluoroborate. The product, methyl 3-fluorothiophene-2-carboxylate was saponified and the 3-fluo-rothiophene-2-carboxylic acid was decarboxylated to afford 3-fluo-rothiophene in 93% yield.

Key words: heterocycles, fluorine substitution, nucleophilic aromatic substitution, 3-fluorothiophene, Schiemann reaction

3-Fluorothiophene (**1**) is a simple compound, but reported rather infrequently in the literature. It has proven to be a molecule whose synthesis is far from straightforward. It is an important compound which, if there were a simple and efficient synthesis, would be used to a much greater extent in a number of diverse areas. For example, in conjugated polymers,[1–3] antistatic agents,[4] and various oligomers.[2,5] There are also numerous reported bioactive substances which have substituted 3-fluorothiophene rings including, for example, herbicides,[6] xanthine oxidase inhibitors,[7] and compounds for sleep modulation therapy.[8] The synthesis of **1** is challenging due to the higher reactivity of the 2-position of the thiophene ring relative to the 3-position and the difficulty of introducing a fluorine substituent. Although there are a number of syntheses reported for the preparation of 3-fluorothiophene (**1**), most suffer from some problems such as low yields, lengthy steps, dangerous or expensive reagents, or insufficient experimental data. These include an early report on the attempted synthesis of fluorothiophene using the Schiemann reaction, which involves the thermal decomposition of an aryldiazonium tetrafluoroborate to produce the corresponding fluoroaromatic compound,[9] which was not successful[10] even though the reported Schiemann reaction was an adaption of the synthesis of fluorobenzene taken from *Organic Syntheses*.[11] Other methods include a report using metal–halogen interchange of 3-bromothiophene followed by reaction with perchloryl fluoride,[12] which is a dangerous material,[13–15] direct fluorination of thiophene to give a mixture of 2- and 3-fluorothiophene,[16–18] and reports of the introduction of fluorine into the 3-position of the thiophene ring using Sandmeyer and Schiemann reactions.[19–21]

The fluorinated thiophene, methyl 3-fluorothiophene-2-carboxylate (**2**), has been produced by the Schiemann reaction of diazonium salt **3**[20,22] and, additionally, the corresponding 3-fluorothiophene-2-carboxylic acid (**4**) has been made from thiophene-2-carboxylic acid using *n*-butyllithium and the expensive and highly hygroscopic *N*-fluorobenzenesulfonimide in a large excess.[21,23]

Finally, 3-fluorothiophene (**1**) has also been prepared using a lengthy procedure in low yield (8.3% overall). In one step involving cesium fluoride mediated fluorination of 3-chloro-2-cyanothiophene (**5**), purification was said to be rather difficult.[24] We tried this synthetic route, and attempts to convert **5** to **6** (Scheme 1) provided a mixture of compounds, as shown by ^{1}H NMR spectroscopy and TLC, which we were unable to identify or separate. Interestingly, ^{19}F NMR spectroscopy of the mixture showed two doublets at –119.01 ppm and –119.03 (*J* = 4.6 Hz), but assignment of these bands to a particular product is not possible at this time.
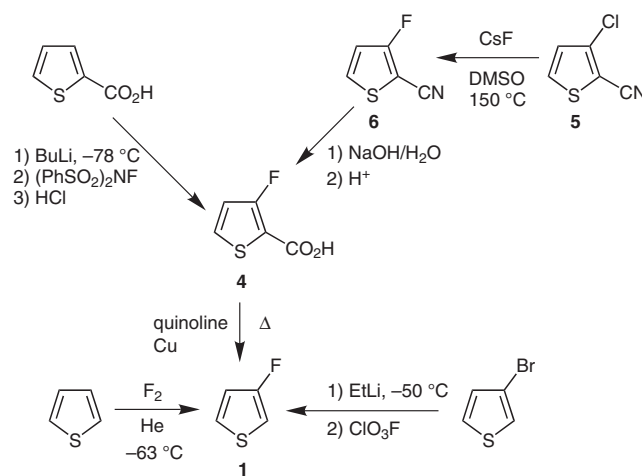
Scheme 1 Reported syntheses of 3-fluorothiophene (**1**)

Our successful synthesis of 3-fluorothiophene (**1**) involves the use of the special conditions for the Schiemann reaction as reported by Kobarfard[20] and Sampson[22] to give **3** as shown in Scheme 2. This involves heating the diazonium fluoroborate salt mixed with sand. The starting material for the synthesis of methyl 3-fluorothiophene-2-carboxylate (**2**), methyl 3-aminothiophene-2-carboxylate (**7**), was diazotized using sodium nitrite and tetrafluoroboric acid to give the corresponding diazonium salt, 2-methoxycarbonylthiophene-3-diazonium tetrafluoroborate (**3**) in 93% yield. A mixture of **3** and sand was then heated un-
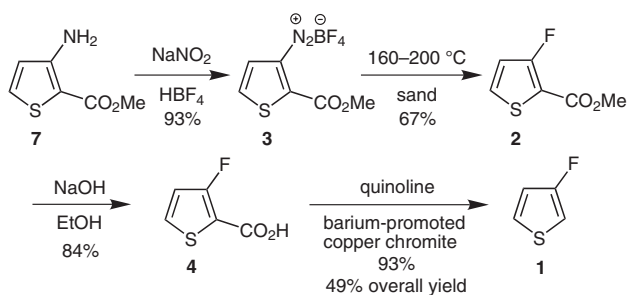
Scheme 2   Synthesis of 3-fluorothiophene (**1**)

der vacuum (0. 1 Torr) and when the oil-bath temperature reached 160 °C a crystalline product started to sublime and was trapped with a liquid nitrogen cold finger. Also, a pale yellow liquid was further distilled and solidified inside the distillation apparatus. The solid and the solidified liquid were mixed to yield methyl 3-fluorothiophene-2-carboxylate (**2**) in a good yield of 67% after precipitation from methanol. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectroscopy supported the structure of the product, methyl 3-fluorothiophene-2-carboxylate (**2**).

3-Fluorothiophene-2-carboxylic acid (**4**) was obtained in 84% yield by the hydrolysis of **2** using sodium hydroxide. The decarboxylation of **4** was carried out in a fashion similar to another reported substituted thiophenecarboxylic acid decarboxylation[25] using barium-promoted copper chromite in quinoline. Finally, 3-fluorothiophene (**1**) was obtained in 93% yield by direct distillation from the reac-

tion mixture. The overall yield in the four steps from **7** to **1** was 49%. It should be mentioned that metal-catalyzed decarboxylation and decarboxylative coupling of aromatic and heteroaromatic carboxylic acids is of current interest and that includes not only copper-catalyzed reactions[25,26,27a] but other metals as well.[27b] The purity of **1** was greater than approximately 97% as shown by the ^{1}H NMR spectrum (Figure 1).

All reactions were carried out in dried glassware. All solvents were dried over 3 Å molecular sieves. Anhyd DMSO (>99.9%) was obtained in Sure/Seal bottles from Aldrich Chemical Co. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a JEOL Eclipse 500 NMR spectrometer at 500.16 MHz, 125.76 MHz and 470.62 MHz, respectively, using CDCl$_3$ solvent with tetramethylsilane as an internal standard for ^{1}H, residual CHCl$_3$ for ^{13}C, and CFCl$_3$ for ^{19}F NMR spectra. Chemical shifts are reported in ppm (δ) and coupling constants in Hz. Flash chromatography was performed using flash silica gel 32–63 µm, 60 Å.

3-Chloro-2-cyanothiophene (**5**)[24] and 2-methoxycarbonylthiophene-3-diazonium tetrafluoroborate (**3**)[19] were prepared as described in the literature.

Attempted Preparation of 3-Fluoro-2-cyanothiophene (6)[24]
3-Chloro-2-cyanothiophene (**5**; 2.15 g, 0.015 mol) was dissolved in DMSO (40 mL), and CsF (4.0 g, 0.026 mol) was added to the solution. The mixture was refluxed for 24 h. After cooling, the mixture was diluted with CH$_2$Cl$_2$ (100 mL). About 1 g of charcoal was added to the mixture and then the mixture was stirred for 20 min and filtered. The solution was washed with H$_2$O (4 × 20 mL), and aq. sat. NaHCO$_3$ (2 × 20 mL), and dried (MgSO$_4$). The solvent was re-
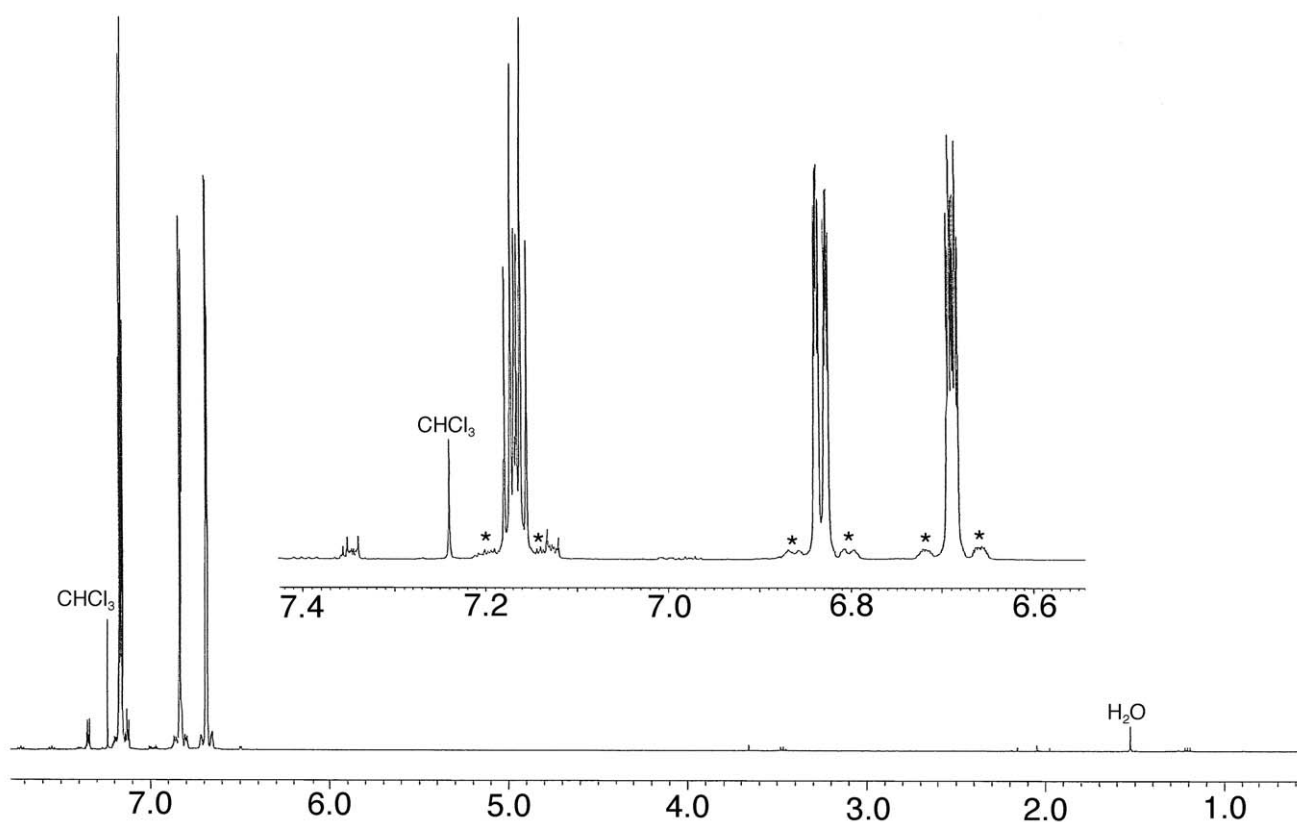

Figure 1   ^{1}H NMR spectrum of **1**; * indicates spinning side bands

moved with a rotary evaporator to produce white crystals (0.7 g). TLC showed this to be a mixture of many compounds.

^{19}F NMR (CDCl$_3$/CFCl$_3$): δ = –119.01 (d, J = 4.6 Hz), –119.03 (d, J = 4.6 Hz).

Methyl 3-Fluorothiophene-2-carboxylate (2)[20]
A mixture of 2-methoxycarbonylthiophene-3-diazonium tetrafluoroborate (**3**;[19] 15.4 g, 0.060 mol) and sand (80 g) in a round-bottomed flask was attached to a distilling head connected to another round-bottomed flask and a Dewar type condenser cooled with liquid N$_2$. The mixture was heated and when the temperature reached 160 °C (oil-bath temperature) under vacuum (0.1 Torr), the product **3** sublimed and was trapped on the inner surface of the condenser; then at ca. 200 °C a pale yellow liquid distilled and solidified in the round-bottomed flask. The products inside the condenser and the round-bottomed flask were combined and this was washed repeatedly with MeOH until it all dissolved. The product **2** was collected as a pale yellow solid upon the addition of H$_2$O (15 mL). The product was filtered and air dried to give 6.4 g (67%) of **2**; mp 48–50 °C (Lit.[20] mp 51–53 °C).

^{1}H NMR (CDCl$_3$): δ = 7.42 (dd, J = 5.5 Hz, J$_{H,F}$ = 3.8 Hz, 1 H), 6.86 (d, J = 5.5 Hz, 1 H), 3.89 (s, 3 H) [Lit.[20] ^{1}H NMR (CDCl$_3$): δ = 7.42 (dd, J = 5.5, 3.8 Hz, 1 H), 6.85 (dd, J = 5.5, 0.5 Hz, 1 H), 3.89 (s, 3 H)].

^{13}C NMR (CDCl$_3$): δ = 160.9 (d, J$_{C,F}$ = 3.8 Hz), 160.2 (d, ^{1}J$_{C,F}$ = 276.4 Hz) 130.1 (d, J$_{C,F}$ = 10.5 Hz), 118.5 (d, J$_{C,F}$ = 24.9 Hz), 112.5 (d, J$_{C,F}$ = 10.1 Hz), 51.9 (s) [Lit.[20] ^{13}C NMR (CDCl$_3$): 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 (CDCl$_3$/CFCl$_3$) (H-coupled): δ = – 115.4 (d, J = 3.5 Hz) [Lit.[20] ^{19}F NMR (CDCl$_3$/CFCl$_3$): δ = – 115.4 (d, J = 3.7 Hz)].

Anal. Calcd for C$_6$H$_5$FO$_2$S: C, 44.99; H, 3.15. Found: C, 44.75; H, 3.00.

3-Fluorothiophene-2-carboxylic Acid (4)
This compound was prepared from **3** in 84% yield as described in the literature.[19]

^{1}H NMR (CDCl$_3$): δ = 10.7 (br s, 1 H),7.52 (dd, J = 5.5 Hz, J$_{H,F}$ = 3.8 Hz, 1 H), 6.85 (d, J = 5.5 Hz, 1 H) [Lit.[23] ^{1}H NMR (CDCl$_3$): δ = 10.7 (s), 7.53 (dd, J = 5.5, 3.6 Hz), 6.90 (d, J = 5.4 Hz); Lit.[24] ^{1}H NMR (CDCl$_3$): δ = 7.85 (dd, J = 5.5, 4.2 Hz), 7.12 (d, J = 5.4 Hz)].

3-Fluorothiophene (1)
The decarboxylation of 3-fluorothiophene-2-carboxylic acid (**4**) was carried out similar to a reported substituted thiophenecarboxylic acid decarboxylation.[25] 3-Fluorothiophene-2-carboxylic acid (**4**; 1.68 g, 80 mmol) was dissolved in quinoline (10 mL) in a single-necked round-bottomed flask connected to a distillation apparatus. Barium-promoted copper chromite (1.24 g, 40 mmol) was added to the solution and the temperature was raised to 200 °C (oil-bath). The highly volatile product **1** was distilled at 30–32 °C (distilling head temperature) and collected in a cold receiver (ice-bath); yield: 0.80 g (93%). Based on integration of the vertically expanded ^{1}H NMR spectrum the purity can be estimated as >97% (Figure 1).

^{1}H NMR (CDCl$_3$): δ = 7.17 (dt, J = 5.4, 3.4 Hz, 1 H), 6.83 (ddd, J = 5.4, 1.5 Hz, 0.9 Hz, 1 H), 6.69 (ddd, J = 3.4, 1.5, 1.1 Hz, 1 H) [Lit.[24] ^{1}H NMR (CDCl$_3$): δ = 7.15 (ddd, J = 5.4, 3.4, 3.4 Hz, 1 H), 6.85 (ddd, J = 5.5, 2.4, 1.1 Hz, 1 H), 6.70 (ddd, J = 3.4, 2.4, 1.1 Hz, 1 H)].

^{13}C NMR (CDCl$_3$): δ = 158.5 (d, ^{1}J$_{C,F}$ = 257.7 Hz), 124.8 (d, J$_{C,F}$ = 9.1 Hz), 117.2 (d, J$_{C,F}$ = 26.9 Hz), 103.1 (d, J$_{C,F}$ = 21.1 Hz)

[Lit.[24] ^{13}C NMR (CDCl$_3$): δ = 158.5 (d, J = 257.5 Hz), 124.8 (d, J = 9.2 Hz), 117.3 (d, J = 26.9 Hz), 103.2 (d, J = 21.1 Hz)].

^{19}F NMR (CDCl$_3$/CFCl$_3$): δ = –131.0 (d, J = 2.3 Hz) [Lit.[24] ^{19}F NMR (CDCl$_3$/CFCl$_3$): δ = –131.0 (d, J = 3.2 Hz)].

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