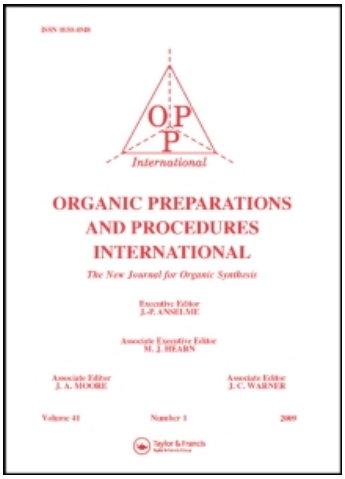

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A FACILE SYNTHESIS OF 3-FLUOROTHIOPHENE-2-CARBOXYLIC ACID

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A FACILE SYNTHESIS OF 3-FLUOROTHIOPHENE-2-CARBOXYLIC ACID

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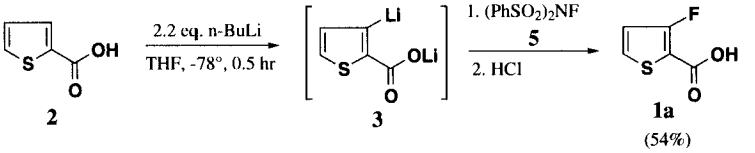
In connection with an ongoing project in our laboratory, we required a convenient synthesis of 3-fluorothiophene-2-carboxylic acid (**1a**). This compound has previously been prepared by three research groups. In one synthesis, 3-fluorothiophene (**1b**) was lithiated with butyllithium, and the resulting 2-lithio carbanion was carboxylated with carbon dioxide.[1] The requisite 3-fluorothiophene itself was prepared from 3-bromothiophene (**1c**) *via* halogen/lithium exchange followed by fluorination with perchloryl fluoride, which is both hazardous and expensive.[1,2] An alternative and apparently attractive approach involved diazotization of methyl 3-aminothiophene-2-carboxylate (**1d**), followed by a Schiemann reaction in xylene.[3] However, in our hands the only product isolated (in >90% yield) was the azo compound **1e** which arose from coupling of the diazonium salt with the solvent xylene. The most recent synthesis of 3-fluorothiophene-2-carboxylic acid (**1a**, 32% overall yield) required four steps starting with 3-chlorothiophene (**1f**).[4] We now report a convenient, one-step synthesis of **1a** from thiophene-2-carboxylic acid (**2**).

1 a, X = CO_2H, Y = F
b, X = H, Y = F
c, X = H, Y = Br
d, X = CO_2Me, Y = NH_2
e, X = CO_2Me, Y = 2,4-$(CH_3)_2C_6H_3N_2$
f, X = H, Y = Cl

Electrophilic fluorination of carbanions using N-fluorosulfonamides,[5] N-fluorosulfonimides[6] and N-fluorosultams[7] has been shown in recent years to be effective for the preparation of a broad variety of fluorinated organic substrates. Since C-H lithiation of thiophene-2-carboxylic acid takes place regiospecifically at position 3 through intramolecular chelation control,[8] it appeared that direct electrophilic fluorination of this carbanion might represent a facile method for the preparation of **1a**. Indeed, treatment of **2** with 2.2 equivalents of n-butyllithium in THF at -78° for 30 minutes smoothly gave the dianion **3**. To this solution of the dianion was added 1.5 equivalents of N-fluorodibenzenesulfonamide at -78°. The mixture was stirred for 4-5 hours and then allowed to warm to room temperature overnight to produce 3-fluorothiophene-2-carboxylic acid (**1a**) in 54% isolated yield in a single step from commercially available **2**.



EXPERIMENTAL SECTION

Melting points are uncorrected. NMR spectra were determined in the solvents indicated below using TMS as the internal standard. Reagents and solvents were purchased from Aldrich: solvents were dried and purified according to standard procedures.[9]

3-Fluorothiophene-2-carboxylic Acid.- To a precooled (-78°) solution of 2-thiophenecarboxylic acid (**2**, 1.28 g, 10 mmol) in tetrahydrofuran (50 mL) was added n-BuLi (8.8 mL, 22.0 mmol, 2.2 eq) at -78°, with stirring. After the reaction mixture had been stirred for 30 minutes, a solution of N-fluorodibenzenesulfonamide (4.73 g, 15.0 mmol, 1.5 eq) in tetrahydrofuran (40 mL) was added at -78°. Stirring was continued at -78° for 5 hrs, and then at room temperature overnight. After recooling to 0°, the reaction was quenched with 6N HCl (5 mL) and diluted with 50 mL of Et_2O. The two layers were separated, the aqueous layer was back-extracted with 2x20 mL of Et_2O, and the combined ethereal extracts were dried over anhydrous $MgSO_4$. Removal of solvent gave the crude product which was purified by silica gel chromatography (eluent 10-20% EtOAc in hexane) to give compound **1a** (789 mg, 54%), mp. 172-173°, lit.[1] mp. 175-176°. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, J = 5.5 Hz, 1H), 7.52 (dd, J_1 = 5.5 Hz, J_2 = 3.7 Hz, 1H). ^{1}H NMR (270 MHz, acetone-d_6): δ 7.03 (d, J = 5.6 Hz, 1H), 7.79 (dd, J_1 = 5.6 Hz, J_2 = 4.0 Hz, 1H). ^{13}C NMR (68 MHz, acetone-d_6): δ 113.8 (d, J = 11.0 Hz), 119.4 (d, J = 25.0 Hz), 132.0 (d, J = 10.0 Hz), 160.8 (d, J = 3.0 Hz), 161.5 (d, J = 274.0 Hz). HRms: Calcd for $C_5H_3FO_2S$: 146.9837. Found: 146.9838.

Anal. Calcd. for $C_5H_3FO_2S$: C, 41.10; H, 2.07. Found: C, 41.36; H, 2.16

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THE ALKYLATION OF COUMARIN AT C-3 OF 4-HYDROXYCOUMARIN‡

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Several important natural compounds have an alkyl chain at C-3 on 4-hydroxycoumarin.[1] Compounds comprising 4-hydroxycoumarin nucleus are reported to have anthelmintic, hypnotic, insecticidal, antifungal activities and anticoagulant effect.[2] In an attempt to synthesize 3-geranyl-coumarin, which is one of the natural coumarins,[3] 4-hydroxycoumarin was treated with geranyl bromide in the presence of K_2CO_3, and the desired product was formed in low yield. Two major byproducts were the O-alkylated and 3-C alkylated compounds.[4] We have shown that the alkylation of the 4-hydroxycoumarin ambident anion in conjuction with a small counter ion led to O-alkylation, while in the presence of a larger counter ion, C-3 alkylated products were obtained as the main product.[5] Alkylation of 4-hydroxycoumarin (**1**) with reagents capable of forming stable carbonium ion intermediates yielded 3-alkylated products as well as O-alkylated products.[6,7]