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Reaction of Thioglycolate with α-Fluoro-β-(Phenylthio)enones (or -enals): Synthesis of Substituted α-Carboxy-γ-Fluorothiophenes

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Abstract: A new synthetic method to substituted α-carboxy-γ-fluorothiophenes **2F** is reported. They were prepared by the reaction between two equivalents of methyl thioglycolate anion and α-fluoro-β-(phenylthio)enones (or -enals) **1F**, in DMSO (70°C) in yields ranging from 41% to 85%. We show from the reaction of (*Z*)-α-fluoro-β-(phenylthio)but-enone **1aF**, that cyclisation to fluorothiophene **2aF** occurs *via* the formation of stable enolates of α-fluoro-β-(dithianyl)butanone.
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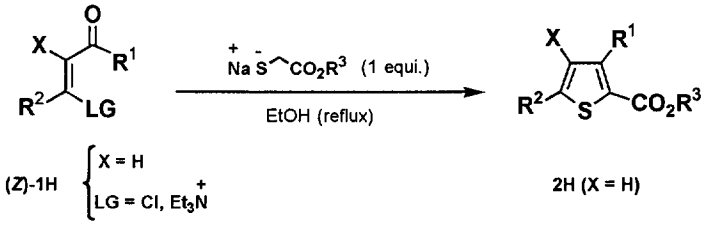
Many investigations have been carried out to discover new synthetic pathways to fluorine-containing five-membered aromatic heterocycles[1] with the aim to modify their chemical or physical properties. From this point of view, fluorothiophenes should be potent intermediates to access to pharmacological or agrochemical active products[2]. Moreover, the electrochemical polymerisation of β-substituted thiophenes can provide electricity conducting materials[3] and a recent studie has indicated that films of β-fluorothiophene exhibited interesting electrochemical characteristics[4].

α-Fluoro and β-fluorothiophenes were previously obtained by direct fluorination of their respective hydrogeno analogues using fluorine[5], or by electrophilic fluorination of thienyllithiums with $FClO_3$ reagent[6]. Unfortunately, the first method gave a mixture of α-fluoro and β-fluoro isomers while the second one was hazardous due to the unstability of perchlorylfluoride . More recently, Lemaire and coworkers[7] have published a one gram scale synthesis of β-fluorothiophene involving the nucleophilic fluorination of the α-cyano-β-chlorothiophene with CsF, followed by an hydrolysis of the cyano group and a subsequent decarboxylation. Nevertheless, the generality of this process has not been examined.

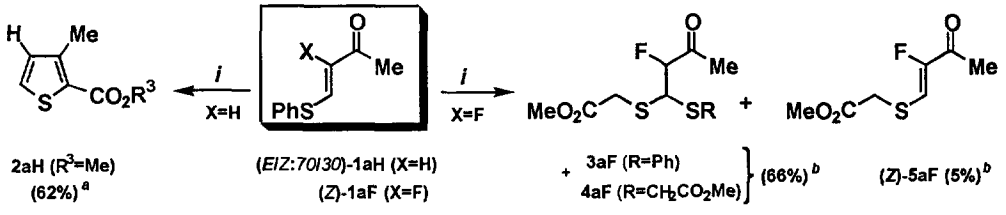
Preparations of monofluorothiophenes have curiously not been reported by reactions involving fluorinated 1,3-bis electrophilic precursors while several syntheses of hydrogeno analogues have been described, using this methodology[2]. Specially, substituted α-carboalcoxy thiophenes **2H** were obtained by condensation between the sodium salt of alkyl thioglycolates (1 equivalent) and the (*Z*) isomer of β-leaving group-substituted enones **1H** (LG=chloro or triethylammonium) in refluxing ethanol[8] (Scheme 1).



Scheme 1

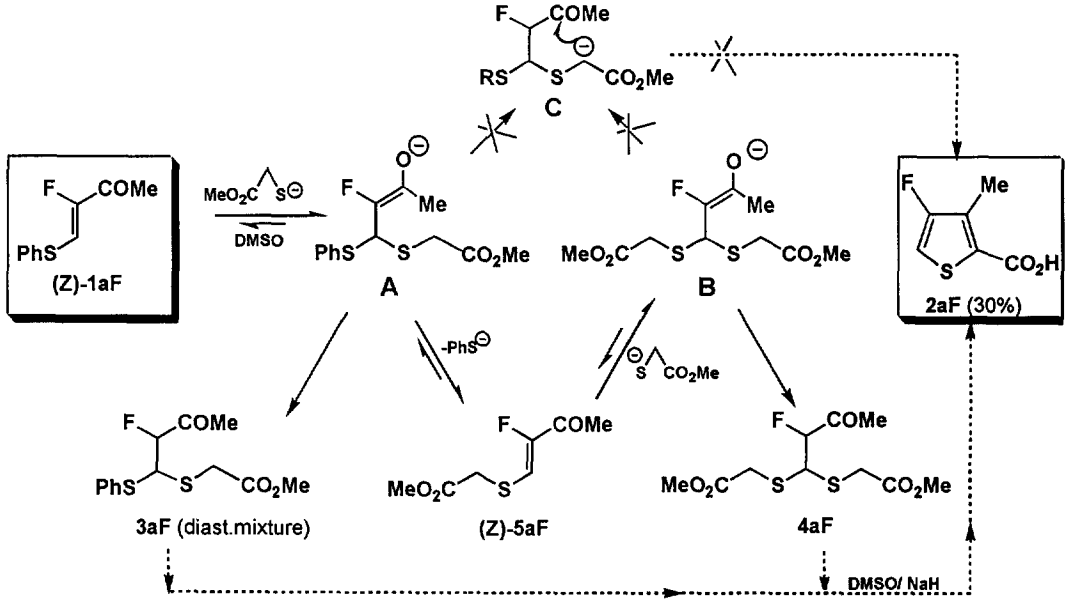
Having found that α-fluoro-β-(phenylthio)enones or enals **1F** (R^1=H, alkyl, Ph; X=F; LG=S-Ph) can be readily prepared from their respective hydrogeno-analogues **1H** (X=H)[9], the depicted reaction in scheme 1 has been applied to our α-fluorinated compounds.

In a first experiment, we have verified from the unfluorinated thioenone (*E/Z:70/30*)-**1aH** that the use of major (*E*)-β-thio enone instead pure (*Z*)-chloro derivative did not generate some stereochemical or leaving group problems. The treatment of (*E/Z:70/30*)-**1aH** by one equivalent of methylthioglycolate (in boiling MeOH) afforded the desired α-carbomethoxythiophene **2aH** in isolated yield (62%) quite similar with those observed from β-chloroenones[8] (Scheme 2). Under the same conditions the corresponding fluoro analogue (*Z*)-**1aF** gave only a complex mixture in which unusual **3aF** and **4aF** dithians[10] were identified[11] as the major products, accompanied with slight amounts of the fluorovinylsulfide (*Z*)-**5aF** resulting from a nucleophilic conjugate addition-elimination with classical retention of configuration[12].



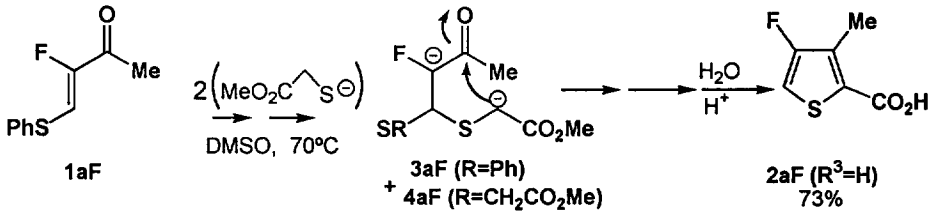
Scheme 2

It should be noted that the same result was observed when the reaction was carried out, in aprotic solvent as DMSO (Scheme 3) at 70°C instead refluxing MeOH, but other aprotic condition as DMF/Et_3N[8b] furnished an unidentified complex mixture. Moreover, the α-carboxy-β-methyl-γ-fluorothiophene **2aF** (R^3=H) was isolated in moderate yield (~30%) when the mixture consisting largely of **3aF** and **4aF** was treated with one equivalent of NaH in DMSO (70°C). These results involve the formation of two intermediary enolates **A** and **B** in which the expected prototropy, giving the fluorothiophene **2aF** *via* **C**, could not take place because of low basicity of the resulting anions or its unsuited conformation. So, an excess of base was necessary to obtain the cyclisation.



Scheme 3

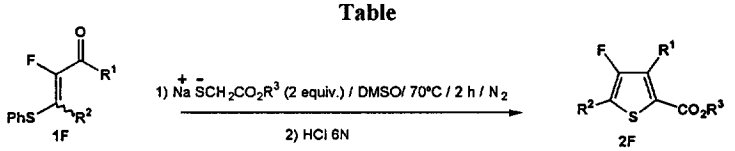
Consequently, **1aF** was conveniently converted to **2aF** (R^3=H) in satisfactory yield (Table: run 1) using two equivalents of methylthioglycolate towards enone in DMSO, leading us to propose the plausible mechanism described in scheme 4 (thiolates anions could undergo the saponification of the methyl ester group).



Scheme 4

Other α-carboxy γ-fluorothiophenes **2F** were then synthesised[13] in the same conditions, in good yields starting from α-fluoroenones (Table: run 2, 3) and rather moderate yields from α-fluoroenals (run 4, 5). Condensation of **1aF** or **1cF** with ethylthioglycolate instead methylester afforded the α-carboethoxy-γ-fluorothiophene **2aF** (R^3=Et) and **2cF** (R^3=Et) respectively, without any saponified products (run: 6, 7).

Table



Run	Substrats: (*E*/*Z*)-1F	R^1	R^2	Products: 2F isolated yields	^{19}F NMR (188.2 MHz, $CFCl_3$ CD_3COCD_3,) δ, *J* (Hz)
1	(*Z*)-**1aF** [a]	Me	H	**2aF** (R^3=H) 73%	-126.8 (s)
2	(*50/50*)-**1bF** [a]	Me	Me	**2bF** (R^3=H) 54%	-132.8 (q, $^4J_{HF}$=1.5)
3	(*50/50*)-**1cF** [a]	Ph	Me	**2cF** (R^3=H) 85%	-131.1 (q, $^4J_{HF}$=1.5)
4	(*68/32*)-**1dF** [a]	H	Me	**2dF** (R^3=H) 41%	-131.8 (q, $^4J_{HF}$=1.4)
5	(*22/78*)-**1eF** [a]	H	*t*-Bu	**2eF** (R^3=H) 44%	-125.6 (s)
6	(*100/0*)-**1aF** [b]	Me	H	**2aF** (R^3=Et) 71%	-127.6 (s)
7	(*50/50*)-**1cF** [b]	Ph	Me	**2cF** (R^3=Et) 79%	-131.6 (q, $^4J_{HF}$=2.1)

[a] *Condensation with NaS-CH_2-CO_2Me;* [b] *Condensation with NaS-CH_2-CO_2Et*

In conclusion, γ-fluorothiophenes have been obtained *via* an unclassical nucleophilic vinylic substitution mechanism.The first enolic intermediates can be trapped by an acidic hydrolysis to give saturated dithianes or cyclised to fluorothiophenes with an excess of base. The fluor-carbanion lone pair repulsion increasing the negative charge density on oxygen-atom associated with the nucleofugacity of the thio groups SR seem responsible of this particular situation[14].

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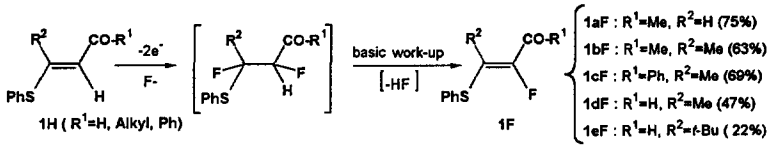

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3aF + **4aF**: ^{19}F NMR (188.2 MHz, $CDCl_3$, $CFCl_3$): -180.9 (dd, $^2J_{HF}$=50.2, $^3J_{HF}$=19.8); -193.7 (dd, $^2J_{HF}$ =48.9, $^3J_{HF}$=31.5); -200.3 (dd, $^2J_{HF}$=50.3, $^3J_{HF}$=15.9). MS were recorded on a Nermag R10-10S (70 eV) coupled with a capillary GC (DELSI DI 700 chromatograph-DB5 column: 30mx0.25mm: **3aF**: (diast mixture) m/z (%) 302 (M^+, 43), 175 (48), 134 (51), 133 (30), 131 (25), 109 (21), 59 (57), 43(100). **4aF**: MS: m/z (%) 278 (M^+, 34), 263 (36), 207 (31), 205 (20),133 (17), 131 (12), 59 (59), 45(33), 43 (100). **(Z)-5aF**: ^{19}F NMR: -123,5 (d, $^3J_{HF}$= 32,8). MS: m/z (%): 192 (M^+, 31), 160 (21), 133 (25), 132 (24), 119 (87), 89 (11), 59 (17), 46 (11), 45 (52), 43 (100).
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13) Selected spectral and analytical data of fluoro thiophenes: **2aF** (**R^3=H**): solid (mp: 141-143°C, unrecrystallised). ^{1}H NMR (200 MHz, CD_3COCD_3, TMS): 2.45 (s, CH_3); 6.99 (s, 1H); 10.96 (broad s, 1H). ^{13}C NMR (50.3 MHz, CD_3COCD_3, TMS): 11.7 (s, CH_3); 110.5 (d, CH, $^2J_{CF}$=20.1); 125.2 (s, C_q); 135.8 (d, C_q, $^2J_{CF}$=22.5); 156.6 (d, CF, $^1J_{CF}$=260.8); 168.0 (d, CO_2H, $^4J_{CF}$=2.6). Anal.Calc. for $C_5H_5O_2SF$: C, 45.00; H, 3.15; S, 20.02; F, 11.86. Found: C, 45.73; H, 3.23; S, 19.78; F, 11.26. **2bF** (**R^3=H**): solid (mp: 109-110°C sublimated). ^{1}H NMR: 2.36 (d, CH_3, $^4J_{HF}$ =1.5); 2.41 (d, CH_3, $^4J_{HF}$=0.7); 7.26 (broad s, 1H). ^{13}C NMR:10.6 (s, CH_3); 12.0 (s, CH_3); 117.9 (s, C_q); 123.3 (d, C_q,$^2J_{CF}$=18.2); 134.6 (d, C_q, $^2J_{CF}$=22.9); 154.2 (d, CF, $^1J_{CF}$=255.3); 164.1 (s, CO_2H). Anal. Calc. for $C_7H_7O_2SF$: C, 48.27 H, 4.05; S 18.41; F 10.9. Found: C, 48.29 H, 4.18; S, 18.75; F, 10.03. **2cF** (**R^3=H**): solid (mp: 179-181°C, petroleum ether/Et_2O). ^{1}H NMR: 2.38 (d, CH_3, $^4J_{HF}$=1.5); 7.35 (m, 5H); 8.61 (broad s, 1H). ^{13}C NMR: 11.6 (s, CH_3); 124.1 (d, C_q, $^3J_{CF}$=4.8); 124.5 (d, C_q, $^2J_{CF}$=18.4); 129.0 (s, $2CH_{arom}$); 129.5 (s, $1CH_{arom}$); 131.2 (d, $2CH_{arom}$, $^4J_{CF}$=1.2); 133.3 (d, C_i,$^3J_{CF}$=2.6); 137.8 (d, C_q, $^2J_{CF}$=20.6); 153.3 (d, CF, $^1J_{CF}$=257.8); 163.6 (d, CO_2H, $^4J_{CF}$=3.0). Anal.Calc. for $C_7H_7O_2SF$: C, 61.01 H, 3.84; S 13.54; F 8.04. Found: C, 61.07; H, 3.85; S, 12.97; F, 7.81. **2dF** (**R^3=H**): solid (mp: 159-160°C, petroleum ether/Et_2O). ^{1}H NMR: 2.38 (d, CH_3, $^4J_{HF}$=1.4); 7.42 (s, 1H); 9.88 (broad s, 1H).^{13}C NMR: 9.3 (s, CH_3); 121.6 (d, CH, $^2J_{CF}$=25.7); 124.3 (d, C_q, $^2J_{CF}$=18.7); 127.5 (d, C_q, $^3J_{CF}$=8.0); 153.3 (d, CF, $^1J_{CF}$=255.2); 161.3 (d, CO_2H, $^4J_{CF}$=2.8). **2eF** (**R^3=H**): solid (mp: 168-170°C, petroleum ether/Et_2O). ^{1}H NMR: 1.42 (s, *t*-Bu); 7.50 (s, 1H); 8.00 (broad s, 1H). ^{13}C NMR: 31.0 (d, $3CH_3$, $^4J_{CF}$=2.2); 35.0 (d, C_q, $^3J_{CF}$=2.9); 124.6 (d, CH, $^2J_{CF}$=27.2), 127.8 (d, C_q, $^3J_{CF}$=8.7); 141.3 (d, C_q, $^2J_{CF}$=13.7); 153.7 (d, CF, $^1J_{CF}$=256.4); 162.9 (d, CO_2H, $^4J_{CF}$=2.6). Anal. Calc. for $C_9H_{11}O_2SF$: C, 53.45 H, 5.48; S 15.85; F 9.39. Found: C, 53.84; H, 5.62; S, 16.35; F, 8.95. **2aF** (**R^3=Et**): liquid. ^{1}H NMR: 1.38 (t, CH_3, $^3J_{HH}$=6.5); 2.42 (s, CH_3); 4.34 (q, CH_2, $^3J_{HH}$=6.5); 6.87 (s, 1H). ^{13}C NMR ($CDCl_3$): 14.3 (s, CH_3); 17.0 (s, CH_3); 61.1 (s, CH_2); 108.4 (d, CH, $^2J_{CF}$=20.2), 126.1 (s, C_q); 134.0 (d, C_q, $^2J_{CF}$=22.7); 156.5 (d, CF, $^1J_{CF}$=260.4); 162.1 (d, CO_2-, $^4J_{CF}$=2.8). **2cF** (**R^3=Et**): solid (mp: 57-59°C, petroleum ether). ^{1}H NMR: 1.19 (t, CH_3, $^3J_{HH}$=7.1); 2.41 (d, CH_3, $^4J_{HF}$=2.1); 4.19 (q, CH_2, $^3J_{HH}$=7.1); 7.40 (s, 5H). ^{13}C NMR ($CDCl_3$): 10.6 (s, CH_3); 14.1 (s, CH_3); 61.0 (s, CH_2), 123.2 (C_q, d, $^2J_{CF}$=18.5), 127.8 (s, $2CH_{arom}$); 128.4 (s, CH_{arom}); 129.2 (d, C_{arom}, $^3J_{CF}$=8.8), 129.8 (d, $2CH_{arom}$, J_{CF}=1.0), 131.9 (d, C_q, $^3J_{CF}$=2.5), 136.6 (d, C_q, $^2J_{CF}$=20.9), 152.2 (d, CF, $^1J_{CF}$=258.5), 161.4 (d, CO_2-, $^4J_{CF}$=3.0).
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