Effects of Substituents on the Chlorination of Methyl 3-Hydroxythiophene-2-carboxylate and on the Reaction of the Resulting Chlorinated Products with Active Hydrogen Containing Compounds

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The title tandem reactions that produce 5-substituted compounds of methyl 3-hydroxythiophene-2-carboxylate can also be applied with a minor modification to the 4-alkyl and 4-aryl derivatives thereof. On the other hand, 5-alkyl and 5-aryl derivatives that undergo a similar smooth chlorination behave in the second reaction in a different manner.

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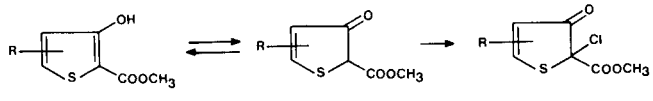
Due to the existence of keto-enol tautomerism methyl 3-hydroxythiophene-2-carboxylates **1** might be chlorinated at position **2** affording the corresponding 2-chloro-4-thiolen-3-one derivatives **2**.



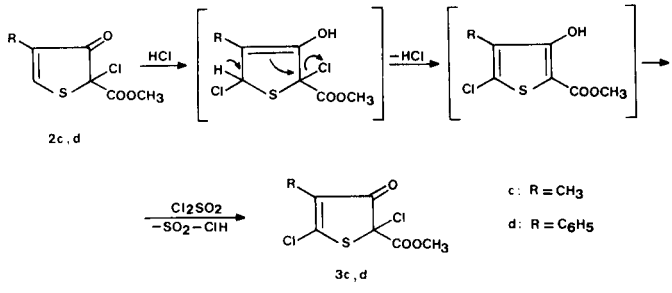
1 **2**

a: R = H d: R = 4-C_6H_5
b: R = 4-Br e: R = 5-CH_3
c: R = 4-CH_3 f: R = 5-C_6H_5

As a matter of fact compounds **1a** (R = H) and **1b** (R = 4-Br) have been shown to react readily in dichloromethane solution at room temperature with one equivalent of sulphuryl chloride to yield the corresponding compounds **2a,b** [1]. However, when strong attracting substituents R such as 4-NO_2, 4-$COCH_3$ or 4-$COOCH_3$ were present in compounds **1** the corresponding compounds **2** could not be obtained in that way [2]. This may be due to a further enhancement of the already strong enolic character of **1a** produced by these substituents. Therefore, it was considered worthwhile to study the effect of electron releasing substituents R on this reaction.

When compounds **1c** (R = 4-CH_3) and **1d** (R = 4-C_6H_5) were made to react in dichloromethane with one equivalent of sulphuryl chloride, in addition to the anticipated corresponding compounds **2c,d**, the dichlorinated derivatives **3c,d** were obtained. These last compounds must originate from the former ones and the hydrogen chloride evolved in the chlorination reaction according to the mechanism outlined in Scheme I.

Scheme 1



2c,d

c: R = CH_3
d: R = C_6H_5

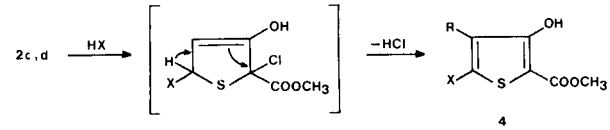
3c,d

Therefore **2c,d** appeared to add hydrogen chloride much faster than **2a,b**. As no hydrogen chloride evolved in the chlorination of **1c,d** by one equivalent of *N*-chlorosuccinimide in carbon tetrachloride at reflux, **2c,d** were prepared in this manner in excellent yields and no traces of **3c,d** were found.

On the other hand, compounds **1e** (R = 5-CH_3) and **1f** (R = 5-C_6H_5) were chlorinated both by sulphuryl chloride and by *N*-chlorosuccinimide affording only the corresponding compounds **2e** and **2f** in good yields.

As previously described for **2a,b** [1,2,3,4] compounds **2c,d** added a number of HX compounds such as thiols, alcohols, azoles, *etc.*, having an active hydrogen bond to a heteroatom. These 1,4-addition reactions which are catalyzed, or autocatalyzed, by acids take place as outlined in Scheme II.

Scheme II

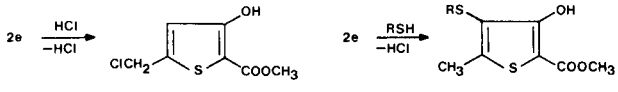


4

Examples of the addition of several types of HX compounds to **2c,d** producing compounds **4** in good yields (60-90%) are given in Experimental. Thus, the initial scope of these tandem reactions is now broadened to 4-alkyl and 4-aryl derivatives of **1a**.

Even though compounds **2e,f** were not expected to react as **2a-d**, some of the above reactions were tried with them. Reaction of **2e** with hydrogen chloride led to compound **5** in good yield by an unknown mechanism.

Scheme III



5 **6**

Whereas reaction of **2e** with thiolic compounds RSH led to compounds **6**. The supposed mechanism is considered to be a free radical chain addition [5] of RSH to the double bond of **2e** followed by stabilization of the adduct by loss of hydrogen chloride as before. A similar addition of benzenothiol to **2a** had already been reported as a secondary reaction [2] and butanothiol had also been found to add similarly in a secondary reaction to **2a** [6].

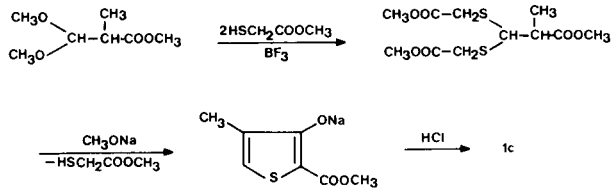
On the other hand no reaction took place between **2f** and hydrogen chloride and in the reaction with 1-butanothiol, **2f** acting as an oxidant was reconverted to **1f** according to the Scheme IV.

Scheme IV

$$2\ \mathbf{2f} + 2\ C_4H_9SH \rightarrow 2\ \mathbf{1f} + (C_4H_9S)_2 + 2\ HCl$$

Although starting compounds **1c-f** are known compounds, **1c** could not be prepared in acceptable yield as described [7]. Therefore it was synthethized from methyl 3,3-dimethoxy-2-methylpropionate [8,9] by a new procedure shown in Scheme V.

Scheme V



EXPERIMENTAL

Melting points were determined in a Buchi 530 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian EM-390 spectrometer and are reported in δ values with tetramethylsilane as the internal standard. MN 5160 silica gel 60 (230-400 mesh) was used for "flash" chromatography.

Compounds **1d** [7], **1e** [10] and **1f** [10] were obtained by described methods.

General Procedure for the Chlorination of Compounds **1c-f** by Sulphuryl Chloride.

Sulphuryl chloride (0.9 ml, 10 mmoles) was added to a solution of the corresponding **1c-f** (8 mmoles) in dichloromethane (10 ml). When gas evolution was ended (1-6 hours), the solvent was removed *in vacuo* and the residue was either recrystallized or flash chromatographed (silica gel, hexane/ethyl acetate 5/1).

Methyl 2,5-Dichloro-4-methyl-3-oxo-2,3-dihydrothiophene-2-carboxylate (**3a**).

This compound was collected (0.4 g, 25%) as the faster moving compound (Rf = 0.64) in the flash chromatography of the product of **1c** chlorination, colourless solid, mp 85-86° (hexane); ir (potassium bromide): 1760 (C=O) and 1710 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 1.98 (3H, s, CH_3), 3.82 (3H, s, $COOCH_3$); ms: (m/e) 241 M$^+$.

Anal. Calcd. for $C_7H_6Cl_2O_3S$: C, 34.85; H, 2.48; S, 13.27. Found: C, 34.89; H, 2.46; S, 13.32.

Methyl 2-Chloro-4-methyl-3-oxo-2,3-dihydrothiophene-2-carboxylate (**2c**).

This compound was collected (0.9 g, 56%) as the second moving compound (Rf = 0.31) in the flash chromatography of the product of **1c** chlorination, colourless solid, mp 52-54° (hexane/ethyl acetate): ir (potassium bromide): 1740 (C=O), 1690 cm^{-1} (ester (C=O); ^{1}H-nmr (deuteriochloroform): 1.90 (3H, s, CH_3); 3.80 (3H, s, $COOCH_3$), 7.95 (1H, s, H-5); ms: (m/e) 206.5 M$^+$.

Anal. Calcd. for $C_7H_7ClO_3S$: C, 40.67; H, 3.38; S, 15.49. Found: C, 40.71; H, 4.06; S, 16.01.

Methyl 2-Chloro-5-methyl-3-oxo-2,3-dihydrothiophene-2-carboxylate (**2e**).

This compound was obtained as a white solid in 87% yield by recrystallization from hexane-ethyl acetate of the product of **1e** chlorination, mp 89-91°; ir (potassium bromide): 1680 (C=O), 1740 cm^{-1} (ester (C=O); ^{1}H-nmr (deuteriochloroform): 2.37 (3H, s, CH_3); 3.82 (3H, s, $COOCH_3$), 6.00 (1H, s, H-4); ms: (m/e) 206.5 M$^+$.

Anal. Calcd. for $C_7H_7ClO_3S$: C, 40.67; H, 3.38; S, 15.49. Found: C, 40.82; H, 3.35; S, 15.66.

Methyl 2-Chloro-5-phenyl-3-oxo-2,3-dihydrothiophene-2-carboxylate (**2f**).

This compound was obtained as a white solid in 73% yield by recrystallization from hexane-ethyl acetate of the product of **1f** chlorination, mp 77-78°; ir (potassium bromide): 1670 (C=O), 1710 cm^{-1} (ester (C=O); ^{1}H-nmr (deuteriochloroform): 3.86 (3H, s, $COOCH_3$), 7.36 (5H, m, ArH), 7.92 (1H, s, H-4); ms: (m/e) 268.5 M$^+$.

Anal. Calcd. for $C_{12}H_9ClO_3S$: C, 53.63; H, 3.35; S, 11.91. Found: C, 53.81; H, 3.39; S, 12.38.

Methyl 2,5-Dichloro-4-phenyl-3-oxo-2,3-dihydrothiophene-2-carboxylate (**3b**).

This compound was collected (0.5 g, 24%) as the faster moving compound (Rf = 0.32) in the flash chromatography of the product of **1d** chlorination. Colourless solid, mp 114-115° (hexane): ir (potassium bromide): 1750 (C=O), 1720 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 3.85 (3H, s, $COOCH_3$), 7.41 (5H, m, PhH); ms: (m/e) 303 M$^+$.

Anal. Calcd. for $C_{12}H_8Cl_2O_3S$: C, 47.52; H, 2.64; S, 10.56. Found: C, 47.63; H, 2.68; S, 10.71.

Methyl 2-Chloro-4-phenyl-3-oxo-2,3-dihydrothiophene-2-carboxylate (**2d**).

This compound was collected (1.3 g, 61%) as the second moving compound (Rf = 0.22) in the flash chromatography of the product of **1d** chlorination. Colourless solid, mp 65-67°C (hexane/ethyl acetate): ir (potassium bromide): 1740 (C=O), 1685 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 3.83 (3H, s, $COOCH_3$), 7.28-7.70 (5H, m, PhH); 8.41 (1H, s, 5-H); ms: (m/e) 268.5 M$^+$.

Anal. Calcd. for $C_{12}H_9ClO_3S$: C, 53.63; H, 3.35; S, 11.91. Found: C, 53.79; H, 3.40; S, 12.15.

General Procedure for the Chlorination of Compounds **1c-f** by *N*-Chlorosuccinimide.

A stirred mixture of the corresponding **1c-f** (8 mmoles) and

N-chlorosuccinimide (1.6 g, 12 mmoles) in carbon tetrachloride (8 ml) was heated at reflux for a night (15 hours). Succinimide was filtered off from the cooled solution, the solvent removed *in vacuo*, and the residue recrystallized. Proceeding in this manner, **2c** was obtained in 84% yield, **2d** in 87% yield, **2f** in 63% yield and **2e** in 77% yield.

Addition of methanol to **2c** and **2d**.

A solution of compound **2c** or **2d** (9 mmoles) in methanol (15 ml) was left at room temperature, or heated at reflux, for the time required (tlc). The solution was cooled in freezer, the crystallized solid filtered and recrystallized.

Methyl 3-Hydroxy-5-methoxy-4-methylthiophene-2-carboxylate.

This compound was obtained from **2c** after 8 hours at room temperature as a white solid in 69% yield, mp 91-93° (hexane); ir (potassium bromide): 1650 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 1.90 (3H, s, CH_3), 3.81 (3H, s, $COOCH_3$), 3.90 (3H, s, OCH_3), 9.92 (1H, s, OH).

Anal. Calcd. for $C_8H_{10}O_4S$: C, 47.52; H, 4.95; S, 15.84. Found: C, 47.71; H, 4.97; S, 16.32.

Methyl 3-Hydroxy-5-methoxy-4-phenylthiophene-2-carboxylate.

This compound was obtained from **2d** in 60% yield after 2 days at room temperature and in 78% yield after 3 hours heating at reflux as a white solid, mp 63-65% (methanol); ir (potassium bromide): 1650 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): 3.82 (3H, s, OCH_3), 3.93 (3H, s, $COOCH_3$), 7.20-7.65 (5H, m, ArH), 10.51 (1H, s, OH).

Anal. Calcd. for $C_{13}H_{12}O_4S$: C, 59.09; H, 4.54; S, 12.12. Found: C, 59.01; H, 4.57; S, 12.62.

Addition of Hydrogen Chloride to **2c** and **2d**.

A solution of compound **2c** or **2d** (9 mmoles) in acetic acid (10 ml) was saturated with dry hydrogen chloride and left at room temperature for the time required (tlc). The solvent was removed *in vacuo* and the residue was either recrystallized or silica gel chromatographed (solvent hexane/ethyl acetate 5:1).

Methyl 5-Chloro-3-hydroxy-4-methylthiophene-2-carboxylate.

This compound was obtained from **2c** after 2 days in 78% yield by recrystallization of the residue from hexane as a white solid, mp 72-74°; ir (potassium bromide): 3300 (OH) and 1670 cm^{-1} (ester C=O); ^{1}H-nmr: 2.07 (3H, s, CH_3), 3.82 (3H, s, $COOCH_3$), 9.71 (1H, s, OH).

Anal. Calcd. for $C_7H_7ClO_3S$: C, 40.67; H, 3.38; S, 15.49. Found: C, 40.81; H, 3.42; S, 15.65.

Methyl 5-Chloro-3-hydroxy-4-phenylthiophene-2-carboxylate.

This compound was obtained from **2d** after 3 days in 63% yield by flash chromatography as a white solid, mp 77-78°; ir (potassium bromide): 3200 (OH) and 1660 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 3.80 (3H, s, $COOCH_3$), 7.23-7.42 (5H, m, ArH), 9.92 (1H, s, OH).

Anal. Calcd. for $C_{12}H_9O_3SCl$: C, 53.63; H, 3.35; S, 8.68. Found: C, 54.02; H, 3.51; S, 8.72.

Addition of Thiolic Compounds to **2c** and **2d**.

To a solution of **2c** or **2d** (9 mmoles) in acetic acid (10 ml) containing concentrated sulphuric acid (0.48 ml, 9 mmoles) the thiolic compound (10 mmoles) was added and the whole left at room temperature for 15 hours. The reaction mixture was poured into ice water and extracted with diethyl ether. The extract was dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was either recrystallized or flash chromatographed (silica gel, hexane/ethyl acetate 5:1).

Methyl 5-Acetylthio-3-hydroxy-4-methylthiophene-2-carboxylate.

This compound was obtained from **2c** and thioacetic acid in 75% yield as a white solid, mp 112-114° (hexane); ir (potassium bromide): 3300 (OH), 1700 ($SCOCH_3$) and 1680 cm^{-1} (ester C=O); ^{1}H-nmr: 2.05 (3H, s, CH_3), 2.37 (3H, s, $SCOCH_3$), 3.81 (3H, s, $COOCH_3$), 9.59 (1H, s, OH).

Anal. Calcd. for $C_9H_{10}O_4S_2$: C, 43.90; H, 4.06; S, 26.01. Found: C, 43.79; H, 4.12; S, 26.95.

Methyl 5-Butylthio-3-hydroxy-4-methylthiophene-2-carboxylate.

This compound was obtained from **2c** and 1-butanothiol in 62% yield as a colourless liquid, bp 146° (0.2 mm, Hg); ir (potassium bromide): 3300 (OH) and 1650 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 0.87 (3H, t, J = 9, CH_3), 120-170 (4H, m, CH_2CH_2), 2.02 (3H, s, CH_3), 2.81 (2H, t, J = 9, S-CH_2), 3.80 (3H, s, $COOCH_3$), 9.63 (1H, s, OH).

Anal. Calcd. for $C_{11}H_{16}O_3S_2$: C, 50.76; H, 6.5; S, 24.61. Found: C, 51.12; H, 6.23; S, 25.08.

Methyl 3-Hydroxy-4-methyl-5-phenylthiothiophene-2-carboxylate.

This compound was obtained from **2c** and thiophenol in 83% yield as a white solid, mp 95-97° (hexane); ir (potassium bromide): 3250 (OH) and 1660 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): 2.10 (3H, s, CH_3), 3.82 (3H, s, $COOCH_3$), 7.25 (5H, m, ArH), 9.65 (1H, s, OH).

Anal. Calcd. for $C_{13}H_{12}O_3S_2$: C, 55.71; H, 4.28; S, 22.85. Found: C, 55.86; H, 4.33; S, 22.91.

Methyl 5-Acetylthio-3-hydroxy-4-phenylthiophene-2-carboxylate.

This compound was obtained from **2d** and thioacetic acid in 71% yield as a white solid, mp 75-76° (hexane); ir (potassium bromide): 3200 (OH), 1710 ($SCOCH_3$) and 1660 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 2.29 (3H, s, $SCOCH_3$), 3.87 (3H, s, $COOCH_3$), 7.32 (5H, m, ArH), 9.76 (1H, s, OH).

Anal. Calcd. for $C_{14}H_{12}O_4S_2$: C, 54.54; H, 3.89; S, 10.38. Found: C, 54.61; H, 3.86; S, 10.39.

Methyl 5-Butylthio-3-hydroxy-4-phenylthiophene-2-carboxylate.

This compound was obtained from **2d** and 1-butanothiol in 62% yield after flash chromatography as a white solid, mp 60-62° (methanol); ir (potassium bromide): 1640 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 0.83 (3H, t, J = 9, CH_3), 1.21 (4H, m, CH_2-CH_2), 2.85 (2H, t, J = 9, S-CH_2), 3.92 (3H, s, $COOCH_3$), 7.32-7.58 (5H, m, ArH), 9.92 (1H, s, OH).

Anal. Calcd. for $C_{16}H_{18}O_3S$: C, 73.84; H, 6.92; S, 12.30. Found: C, 73.89; H, 6.97; S, 12.51.

Methyl 3-Hydroxy-4-phenyl-5-phenylthiothiophene-2-carboxylate.

This compound was obtained from **2d** and thiophenol in 68% yield after flash chromatography as a white solid, mp 81-83° (methanol); ir (potassium bromide): 3300 (OH) and 1660 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 3.89 (3H, s, $COOCH_3$), 7.17-7.52 (10H, m, ArH), 9.94 (1H, s, OH).

Anal. Calcd. for $C_{18}H_{14}O_3S_2$: C, 63.15; H, 4.09; S, 9.35. Found: C, 63.38; H, 4.07; S, 9.71.

Addition of Azoles to **2c** and **2d**.

To a solution of **2c** or **2d** (9 mmoles) in chloroform (15 ml) the corresponding azole (18 mmoles) was added and the solution was left at room temperature for the time required (tlc). The reaction mixture was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue recrystallized.

Methyl 3-Hydroxy-4-methyl-5-pyrazolylthiophene-2-carboxylate.

This compound was obtained from **2c** and pyrazole in 81% yield as a white solid, mp 125-126° (acetone); ir (potassium bromide): 1650 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 2.20 (3H, s, CH_3); 3.84 (3H, s, $COOCH_3$), 6.45 (1H, m, H-4 pyrazole), 7.71 (2H, m, H-3 and H-5 pyrazole), 9.67 (s, 1H, OH).

Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.42; H, 4.20; N, 11.76; S, 13.44. Found: C, 50.53; H, 4.31; N, 11.81; S, 14.24.

Methyl 3-Hydroxy-5-imidazolyl-4-methylthiophene-2-carboxylate.

This compound was obtained from **2c** and imidazole in 78% yield as a white solid, mp 72-74° (acetone); ir (potassium bromide): 1690 cm^{-1} (ester C=O); ^{1}H-nmr: 2.16 (s, 3H, CH_3); 3.94 (s, 3H, $COOCH_3$), 7.12 (2H, m, H-4 and H-5 imidazole), 7.66 (1H, s, H-2 imidazole), 9.70 (s, 1H, OH).

Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.42; H, 4.20; N, 11.76; S, 13.44. Found: C, 50.47; H, 4.23; N, 11.72; S, 13.41.

Methyl 3-Hydroxy-4-phenyl-5-pyrazolylthiophene-2-carboxylate.

This compound was obtained from **2d** and pyrazole in 71% yield as a white solid, mp 121-122° (*i*-prOH); ir (potassium bromide): 1640 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 3.89 (3H, s, $COOCH_3$), 6.18 (1H, m, H-4 pyrazole), 7.08 (1H, d, J = 2, H-5 pyrazole), 7.32 (5H, m, ArH), 7.51 (1H, m, H-3 pyrazole), 9.92 (s, 1H, OH).

Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 60.00; H, 4.00; N, 9.33; S, 10.66. Found: C, 60.31; H, 4.08; N, 9.32; S, 10.74.

Methyl 3-Hydroxy-5-imidazolyl-4-phenylthiophene-2-carboxylate.

This compound was obtained from **2d** and imidazole in 68% yield as a white solid, mp 170-172° (methanol); ir (potassium bromide): 1690 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 3.82 (3H, s, $COOCH_3$), 7.00 (2H, m, H-4 and H-5 imidazole), 7.2-7.4 (5H, m, ArH), 7.42 (1H, s, H-2 imidazole), 10.72 (1H, s, OH).

Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 60.00; H, 4.00; N, 9.33; S, 10.66. Found: C, 60.82; H, 4.12; N, 9.36; S, 10.61.

Addition of benzenosulphinic and Hydrazoic Acids.

To a stirred solution of **2c** or **2d** (9 mmoles) in acetic acid (15 ml) the corresponding sodium benzenosulphinate (18 mmoles) or azide (18 mmoles) was added and left at room temperature for the time required (tlc). The solvent was removed *in vacuo* and the residue was partitionated between water and ethyl acetate. After removal of the solvent the residue was recrystallized.

Methyl 5-Benzenesulphonyl-3-hydroxy-4-methylthiophene-2-carboxylate.

This compound was obtained from **2c** and sodium benzenosulphonate in 58% yield as a white solid, mp 136-138° (isopropyl alcohol); ir (potassium bromide): 3300 (OH); 1700 (C=O) and 1140 cm^{-1} (SO_2); ^{1}H-nmr (DMSO-d_6): 2.20 (3H, s, CH_3); 3.90 (3H, s, $COOCH_3$), 7.52 (3H, m, ArH), 7.95 (2H, m, ArH), 9.48 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{14}O_5S_2$: C, 57.75; H, 3.74; S, 8.55. Found: C, 57.76; H, 3.74; S, 8.61.

Methyl 5-Azido-3-hydroxy-4-methylthiophene-2-carboxylate.

This compound was obtained from **2c** and sodium azide in 77% yield as a white solid, mp 76-77° (methanol); ir (potassium bromide): 2100 (N_3) and 1660 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 1.94 (3H, s, CH_3); 3.83 (3H, s, $COOCH_3$), 9.78 (1H, s, OH).

Anal. Calcd. for $C_7H_7N_3O_3S$: C, 39.43; H, 3.28; N, 19.71; S, 15.02. Found: C, 39.87; H, 3.34; N, 19.98; S, 16.39.

Methyl 5-Benzenesulphonyl-3-hydroxy-4-phenylthiophene-2-carboxylate.

This compound was obtained from **2d** and sodium benzenosulphinate in 70% yield as a white solid, mp 115-117° (isopropyl alcohol); ir (potassium bromide): 1600 (ester C=O) and 1470 cm^{-1} (SO_2); ^{1}H-nmr (DMSO-d_6): 3.94 (3H, s, $COOCH_3$), 7.1-7.3 (10H, m, ArH), 9.47 (1H, s, OH).

Anal. Calcd. for $C_{18}H_{14}O_5S_2$: C, 57.75; H, 3.74; S, 8.55. Found: C, 57.76; H, 3.74; S, 8.61.

Methyl 5-Azido-3-hydroxy-4-phenylthiophene-2-carboxylate.

This compound was obtained from **2d** and sodium azide in 71% yield as a white solid, mp 85-86° (methanol); ir (potassium bromide): 2100 (N_3) and 1650 (ester C=O); ^{1}H-nmr (deuteriochloroform): 3.79 (3H, s, $COOCH_3$), 7.32 (5H, m, ArH), 9.85 (1H, s, OH).

Anal. Calcd. for $C_{12}H_9N_3O_3S$: C, 52.36; H, 3.27; N, 15.27; S, 11.63. Found: C, 52.31; H, 3.29; N, 15.31; S, 11.68.

Addition of Thiolic Compounds to **2e**.

The procedure employed was that used for the addition to **2c** and **2d**.

Methyl 4-Butylthio-3-hydroxy-5-methylthiophene-2-carboxylate.

This compound was obtained from **2e** and 1-butanothiol in 57% yield after flash chromatography, as an oil; ir (potassium bromide): 1650 (ester C=O); ^{1}H-nmr (deuteriochloroform): 0.86 (3H, t, J = 7.5, CH_3), 1.47 (4H, m, CH_2-CH_2), 2.51 (3H, s, CH_3), 2.79 (2H, t, J = 7.5, CH_2-S), 3.82 (3H, s, $COOCH_3$), 9.83 (1H, s, OH).

Anal. Calcd. for $C_{11}H_{16}O_3S_2$: C, 50.76; H, 6.15; S, 24.61. Found: C, 50.82; H, 6.19; S, 25.45.

Methyl 4-Acetylthio-3-hydroxy-5-methylthiophene-2-carboxylate.

This compound was obtained from **2e** and thioacetic acid in 52% yield, after flash chromatography, as a white solid, mp 87-89°; ir (potassium bromide): 1710 ($SCOCH_3$) and 1680 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 2.45 (6H, s, CH_3 and $SCOCH_3$), 3.91 (3H, s, $COOCH_3$), 9.73 (1H, s, OH).

Anal. Calcd. for $C_9H_{10}O_4S_2$: C, 43.90; H, 4.06; S, 20.01. Found: C, 44.12; H, 4.10; S, 26.18.

Reaction of **2e** and Hydrogen Chloride.

The procedure used was that employed for the addition of hydrogen chloride to **2a** and **2b**.

Methyl 5-Chloromethyl-3-hydroxythiophene-2-carboxylate.

This compound was obtained after 1 day time in 83% yield after flash chromatography as a white solid, mp 46-48° (isopropyl alcohol); ir (potassium bromide): 3300 (OH) and 1750 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 3.88 (s, 3H, $COOCH_3$), 4.52 (s, 2H, CH_3Cl), 6.27 (s, 1H, H-4), 9.53 (s, 1H, OH); ms: (m/e) 206.5 M^+.

Anal. Calcd. for $C_7H_7ClO_3S$: C, 40.67; H, 3.38; S, 15.49. Found: C, 40.79; H, 3.42; S, 16.13.

Reaction of **2f** with 1-Butanothiol.

Using the procedure for the addition of thiolic compounds to **2c** and **2d**, compound **1f**, mp 92-93° was isolated in 54% yield after flash chromatography.

Methyl 3-Hydroxy-4-methylthiophene-2-carboxylate (**1c**).

A mixture of methyl 3,3-dimethoxy-2-methylpropionate (81 g, 0.5 mole), methyl thioglycolate (106 g, 1 mole) and boron trifluoride etherate (2.0 ml) was slowly heated to 130° in an oil bath. When near the theoretical quantitiy of methanol (32 g) was distilled off, 625 mg (1.25 moles) a 2*N* solution of sodium methoxide in methanol were added to the stirred cold reaction mixture and the whole left overnight. Methanol was removed *in vacuo* and the residue was stirred with water (100 ml) and filtered. The solid was washed successively with water (30 ml) and dichloromethane (30 ml). A stirred suspension of this solid in water was acidified with 4*N* hydrochloric acid and extracted with dichloromethane. The residue from the evaporated extract distilled at 84° (2 mm, Hg) yielding 56 g (65%) of a colourless liquid that crystallize on standing; ir (potassium bromide: 3225 (OH) and 1640 cm^{-1} (ester C=O); ^{1}H-nmr (deuteriochloroform): 2.05 (s, 3H, CH_3), 3.80 (s, 3H, $COOCH_3$), 7.96 (s, 1H, H-5), 9.58 (s, 1H, OH).

Anal. Calcd. for $C_7H_8O_3$: C, 48.83; H, 4.65; S, 18.60. Found: C, 48.91; H, 4.69; S, 19.16.

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REFERENCES AND NOTES

[1] C. Corral and J. Lissavetzky, *J. Chem. Soc., Perkin Trans. I*, 2711 (1984).

[2] C. Corral and J. Lissavetzky, *J. Chem. Res., (S)*, 168; *(M)*, 1444 (1986).

[3] C. Corral and J. Lissavetzky, *Synthesis*, 847, (1984).

[4] C. Corral, M. B. El-Ashmawy, J. Lissavetzky and I. Manzanres, *J. Hetercyclic Chem.*, **24**, 1301 (1987).

[5] α-Haloketones have been shown to activate free radical chain additions to double bonds; F. Rist and W. E. Waughan, U.S. Patent 2,299,911; *Chem Abstr.*, **37** 1722 (1943).

[6] C. Corral and I. Manzanares, unpublished results.

[7] J. Brelivet, P. Apprion and J. Teste, *Bull. Soc. Chim. France*, 1344 (1971).

[8] N. C. Deno, *J. Am. Chem. Soc.*, **69**, 2233 (1947).

[9] P. Biever, *Ann. Chim.*, **9**, 674 (1954).

[10] H. Fiesselmann and F. Thoma, *Chem. Ber.*, **89**, 1907 (1956).