A Convenient Synthesis of 2,3,4,5-Functionalised Thieno[2,3-*b*]thiophenes

Geoffroy Sommen, Alain Comel, Gilbert Kirsch*

Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique, Faculté des Sciences, Ile du Saulcy, 57045 Metz Cedex, France
E-mail: kirsch@sciences.univ-metz.fr

Received 5 December 2002; revised 18 January 2003

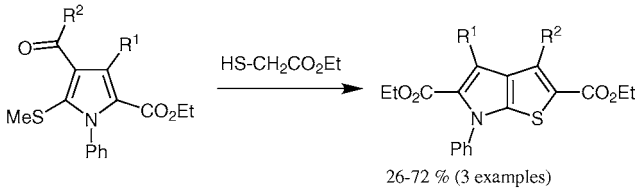
Abstract: A two steps simple synthesis of 2,3,4,5-functionalised thieno[2,3-*b*]thiophenes **2**–**6** from ketene dimethylthioacetals is described.

Key words: bicyclic compounds, chemoselectivity, cyclisation, heterocycles, thiols

Substituted thieno[2,3-*b*]thiophenes and the methods of their preparation are known since the 50s. One of the most recent synthetic pathways for their preparation is based on the cyclisation of ketene dithioacetals, obtained from carbon disulfide, in basic media.[1a–e] The ketene dithioacetal dipotassium salt intermediates are reacted generally with the same methylene active halide or in combination with methyl iodide in order to obtain 5-methylsulfanylthiophenes.[1c,e] The use of two different halides should lead to a mixture of symmetrical and unsymmetrical thieno[2,3-*b*]thiophenes barely separable and is not reported in the literature.

We have described[2] recently the formation of thiophenes from ketene phenylaminomethylthioacetals using ethyl thioglycolate in a basic medium (K_2CO_3/EtOH). The ability of thioglycolate to replace a methylsulfanyl group of ketene dimethylthioacetals has been investigated and we have selectively prepared 5-methylsulfanylthiophenes in excellent yields (Scheme 1, Table 1).

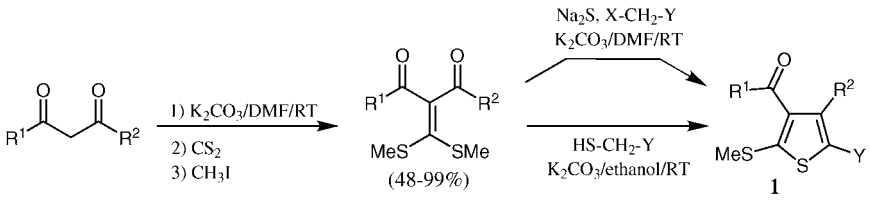
According to our recent work on 5-methylsulfanylpyrroles[3] (see Scheme 2), we decided to remove the remaining methylsulfanyl group with a second equivalent of ethyl thioglycolate under previous conditions, although this way leads only to symmetrical thieno[2,3-*b*]thiophenes that can be prepared following a much easier one-pot procedure.[4]



Scheme 2

Other methylene active thiols can be used but they are not commercially available and their preparation reduces significantly the applications of the method, even if the yields observed for each step were good to excellent with ethyl thioglycolate.

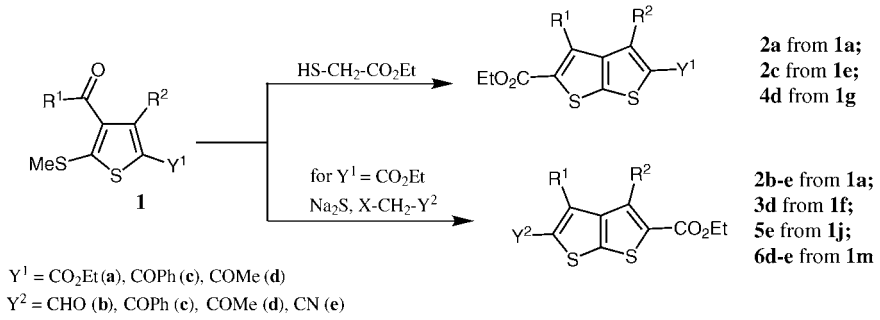
Finally, we chose to use Na_2S and a halide in order to prepare 5-methylsulfanylthiophenes bearing a group other than the ethoxycarbonyl group obtained with the use of ethyl thioglycolate (see Scheme 1). This strategy allowed us to avoid the tedious synthesis and use of other thiols for the formation of thiophenes **1**. This reaction is generally well known and used for the preparation of thiophenes[5] but was not described for such compounds. Various expected thiophenes have been successfully isolated in moderate to good yields. The decrease in yield can be in particular attributed to the formation of symmetrical sulfide. At this stage, two different ways can lead to unsymmetrical thieno[2,3-*b*]thiophenes. The first one consists in reacting the thiophenes **1**, obtained from a ketene dimethylthioacetal and the appropriate halide in the presence of sodium sulfide, with ethyl thioglycolate and potassium carbonate as the condensation promoter. The second one is almost the same, ethyl thioglycolate and the system halide/sodium sulfide being exchanged in the two steps of this synthetic path (see Schemes 1 and 3). These two different ways have been investigated (see Table 2) but we preferred the second one for practical reasons.



Scheme 1

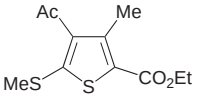
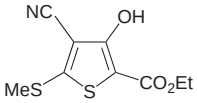
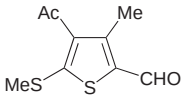
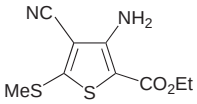
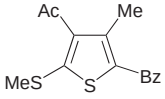
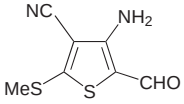
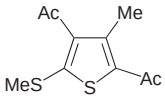
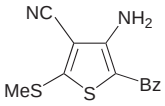
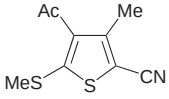
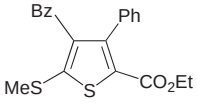
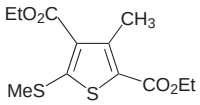
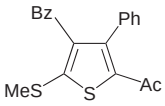
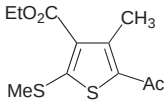
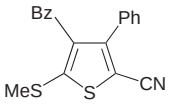
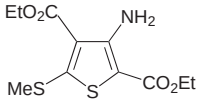
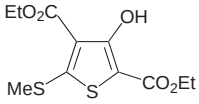
Synthesis 2003, No. 5, Print: 01 04 2003.
Art Id.1437-210X,E;2003,0,05,0735,0741,ftx,en;Z15402SS.pdf.

ISSN 0039-7881



Scheme 3

Table 1 Synthesis of Thiophenes **1**

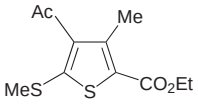
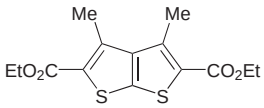
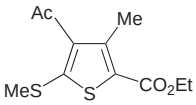
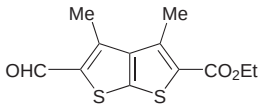
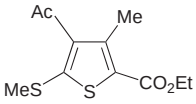
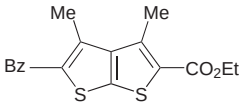
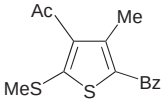
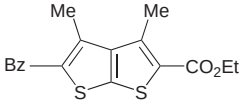
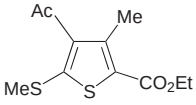
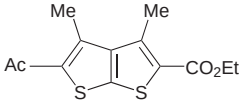
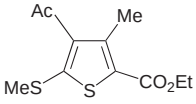
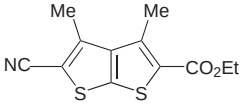
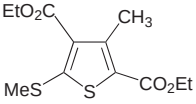
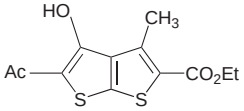
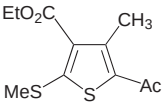
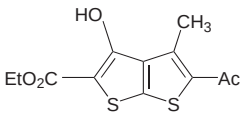
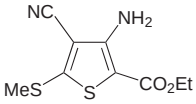
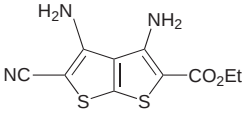
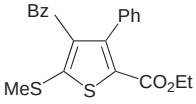
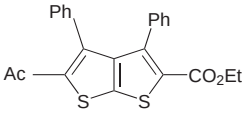
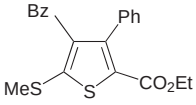
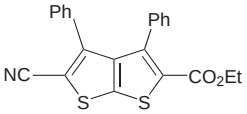
Entry	Compound	Yield (%)	Entry	Compound	Yield (%)
1a		95[a] or 60[b]	**1i**		43[a,c]
1b		17[b]	**1j**		95[a]
1c		68[b]	**1k**		17[b]
1d		43[b]	**1l**		15[b]
1e		37[b]	**1m**		75[a]
1f		65[a]	**1n**		80[b]
1g		50[b]	**1o**		96[b]
1h		43[a,c]	**1p**		64[a]

[a] Obtained with ethyl thioglycolate.
[b] Obtained with Na_2S/appropriate halide.
[c] Separated by acid and base treatment.

We have noticed that the yields obtained with ethyl thioglycolate are generally significantly higher than with Na_2S and we systematically used thioglycolate, for practical reasons, in one of the two steps needed for the preparation of the thieno[2,3-*b*]thiophenes. We did not investigate whether or not the thioglycolate has to be used in the first or second step of our synthetic method but compound **2c** has been obtained in similar overall yields using thioglycolate in the first step (**2c** from **1a**) or in the second one (**2c** from **1e**). Nevertheless, we demonstrated that thieno[2,3-*b*]thiophenes could be obtained in two different manners using our strategy.

Finally, we focused on compounds **3d** and **4d** both prepared from ethyl acetoacetate (unsymmetrical starting

Table 2 Synthesis of Thieno[2,3-*b*]thiophenes **2**–**6** from Thiophenes **1**

Entry	Starting Compound	Reagents	Product	Yield (%)
2a		ethyl thioglycolate or Na_2S/ethyl bromoacetate		73 47
2b		Na_2S/chloroacetaldehyde		61
2c		Na_2S/bromoacetophenone		55
2c		ethyl thioglycolate		96
2d		Na_2S/chloroacetone		85
2e		Na_2S/chloroacetonitrile		69
3d		Na_2S/chloroacetone		85
4d		ethyl thioglycolate		93
5e		Na_2S/chloroacetonitrile		81
6d		Na_2S/chloroacetone		86
6e		Na_2S/chloroacetonitrile		85

material). In this particular case, we clearly demonstrated that the order of the sequence Na_2S/chloroacetone/ethyl thioglycolate allowed to fully control the substituents in the 2 and 5 position of the resulting thieno[2,3-*b*]thiophenes. Our synthetic way appeared to be regiospecific which greatly simplified the purification process.

In summary, we have described the first general and selective access to 2,3,4,5 functionalised thieno[2,3-*b*]thiophenes using a two steps strategy based on the reactivity of ketene dithioacetals towards thiols or equivalents (Na_2S/halides).

Ketene Dithioacetals; General Procedure

A 250 mL three-necked round-bottom flask equipped with magnetic stirrer, condenser and septum was charged with a solution of 1,3-diketone (100 mmol) in DMF (100 mL). Dried K_2CO_3 (13.8 g, 100 mmol) was added and the mixture was stirred for 2 h at r.t. CS_2 (18.0 mL, 300 mmol) was added and the mixture was stirred for 2 h at r.t. MeI (12.5 mL, 200 mmol) was then added and the mixture was stirred for 4 h before being poured onto H_2O (400 mL). The precipitated crude product was purified by filtration followed by crystallisation from EtOH. When the product was an oil, the organic phase was extracted with Et_2O (3×100 mL). The combined organic extracts were washed with H_2O (2×100 mL), dried (MgSO4), and concentrated in vacuo.

Thiophenes 1; General Procedures

Method A, Using Ethyl Thioglycolate: A 100 mL three-necked round-bottom flask equipped with magnetic stirrer, condenser and septum was charged with a solution of ethyl thioglycolate (1.1 mL, 10 mmol) in EtOH (30 mL). A dithioacetal (10 mmol) and dried K_2CO_3 (1.38 g, 10 mmol) was added in one portion. The mixture was stirred under reflux for 6 h and then the reaction was quenched with H_2O (100 mL). The precipitated crude product was purified by filtration followed by crystallisation in EtOH.

Method B, Using Na_2S: A 100 mL three-necked round-bottom flask equipped with magnetic stirrer, condenser and septum was charged with a solution of Na_2S (2.40 g, 10 mmol) in DMF (30 mL). This mixture was heated to 50 °C until dissolution and then an appropriate dithioacetal (10 mmol) was added. After stirring for 1 h at 50 °C the alkylating agent (10 mmol) was added and stirred for 0.5 h. Dried K_2CO_3 (1.38 g, 10 mmol) was added and the mixture was stirred for 6 h at 50 °C. The reaction was quenched with H_2O (100 mL) and the crude product precipitated was purified by filtration followed by crystallisation from EtOH.

Ethyl 4-Acetyl-3-methyl-5-methylsulfanylthiophene-2-carboxylate (1a)

Mp 79 °C.

IR (KBr): 1701, 1706 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.36 (t, 3 H, *J* = 7.2 Hz), 2.55 (s, 3 H), 2.57 (s, 3 H), 2.73 (s, 3 H), 4.31 (q, 2 H, *J* = 7.2 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.6 (CH_3), 14.7 (CH_3), 17.6 (CH_3), 30.3 (CH_3), 60.2 (CH_2), 123.3 (C), 136.3 (C), 139.9 (C), 145.3 (C), 156.3 (C), 160.6 (CO_2), 193.2 (CO).

Anal. Calcd for $C_{11}H_{14}O_3S_2$: C, 51.14; H, 5.46. Found: C, 51.21; H, 5.36.

4-Acetyl-3-methyl-5-methylsulfanylthiophene-2-carbaldehyde (1b)

Mp 100 °C.

IR (KBr): 1659, 1633 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.56 (s, 3 H), 2.60 (s, 3 H), 2.72 (s, 3 H), 9.96 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.9 (CH_3), 18.7 (CH_3), 31.2 (CH_3), 123.2 (C), 134.3 (C), 135.5 (C), 136.8 (C), 147.2 (C), 180.6 (CHO), 193.9 (CO).

Anal. Calcd for $C_9H_{10}O_2S_2$: C, 50.44; H, 4.70. Found: C, 50.46; H, 4.68.

1-(5-Benzoyl-4-methyl-2-methylsulfanylthiophen-3-yl)ethanone (1c)

Mp 104 °C.

IR (KBr): 1611, 1636 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 2.55 (s, 3 H), 2.57 (s, 3 H), 7.38–7.88 (m, 5 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.2 (CH_3), 18.7 (CH_3), 31.3 (CH_3), 128.0 (2 CH), 128.4 (CH), 128.5 (C), 128.9 (C), 132.4 (2 CH), 133.8 (C), 139.5 (C), 144.6 (C), 188.7 (CO), 195.2 (CO).

Anal. Calcd for $C_{15}H_{14}O_2S_2$: C, 62.04; H, 4.86. Found: C, 62.19; H, 4.69.

1-(4-Acetyl-3-methyl-5-methylsulfanylthiophen-2-yl)ethanone (1d)

Mp 80 °C.

IR (KBr): 1649, 1648 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 2.54 (s, 3 H), 2.60 (s, 3 H), 2.69 (s, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 16.3 (CH_3), 18.4 (CH_3), 30.2 (CH_2), 31.3 (CH_2), 134.6 (C), 139.1 (C), 144.3 (C), 155.1 (C), 189.9 (CO), 195.6 (CO).

Anal. Calcd for $C_{10}H_{12}O_2S_2$: C, 52.60; H, 5.30. Found: C, 52.55; H, 5.28.

4-Acetyl-3-methyl-5-methylsulfanylthiophene-2-carbonitrile (1e)

Mp 114 °C.

IR (KBr): 2206, 1637 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.47 (s, 3 H), 2.56 (s, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.4 (CH_3), 17.1 (CH_3), 30.5 (CH_3), 113.1 (CN), 122.2 (C), 123.4 (C), 142.7 (C), 149.4 (C), 192.7 (CO).

Anal. Calcd for $C_9H_9NOS_2$: C, 51,16; H, 4,29; N, 6,63. Found: C, 51.18; H, 4.26; N, 6.63.

Diethyl 3-Methyl-5-methylsulfanylthiophene-2,4-dicarboxylate (1f)

Mp 89 °C.

IR (KBr): 1682, 1630 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, 3 H, *J* = 7.1 Hz), 2.58 (s, 3 H), 2.82 (s, 3 H), 4.28 (q, 2 H, *J* = 7.1 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.3 (CH_3), 15.4 (CH_3), 17.9 (CH_3), 60.7 (CH_2), 60.8 (CH_2), 123.8 (C), 127.1 (C), 148.5 (C), 157.9 (C), 161.7 (CO_2), 163.6 (CO_2).

Anal. Calcd for $C_{12}H_{16}O_4S_2$: C, 49.98; H, 5.59; N, 4.62. Found: C, 50.02; H, 5.63; N, 4.58.

Ethyl 2-Acetyl-3-Methyl-5-methylsulfanylthiophene-4-carboxylate (1g)

Mp 87 °C.

IR (KBr): 1725, 1698 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1,39 (t, 3 H, *J* = 7.2 Hz), 2.50 (s, 3 H), 2.58 (s, 3 H), 2.72 (s, 3 H), 4,36 (q, 2 H, J = 7.2 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.2 (CH_3), 16.0 (CH_3), 18.0 (CH_3), 60.9 (CH_2), 127.8 (C), 134.5 (C), 146.7 (C), 158.3 (C), 163.6 (CO_2), 189.8 (CO).

Anal. Calcd for $C_{11}H_{14}O_3S_2$: C, 51.14; H, 5.46. Found: C, 51.23; H, 5.40.

Diethyl 3-Amino-5-methylsulfanylthiophene-2,4-dicarboxylate (1h)

Mp 103 °C.

IR (KBr): 3502, 3353, 1685, 1663 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.2 Hz), 1.40 (t, 3 H, *J* = 7.2 Hz), 2.55 (s, 3 H), 4.26 (q, 2 H, *J* = 7.2 Hz), 4.36 (q, 2 H, *J* = 7.2 Hz), 6.84 (s, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.5 (CH_3), 14.8 (CH_3), 17.0 (CH_3), 59.8 (CH_2), 60.7 (CH_2), 114.0 (C), 155.4 (C), 155.5 (C), 160.4 (C), 163.3 (CO_2), 163.4 (CO_2).

Anal. Calcd for $C_{11}H_{14}O_3S_2$: C, 45.66; H, 5.22; N, 4.84. Found: C, 45.56; H, 5.20; N, 4.70.

Ethyl 4-Cyano-3-hydroxy-5-methylsulfanylthiophene-2-carboxylate (1i)

Mp 110 °C.

IR (KBr): 3292, 2222, 1664 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30 (t, 3 H, *J* = 7.2 Hz), 2.74 (s, 3 H), 4.34 (q, 2 H, *J* = 7.2 Hz), 9.86 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.3 (CH_3), 17.4 (SCH_3), 61.7 (CH_2), 100.0 (C), 102.0 (C), 111.3 (CN), 159.3 (C), 163.7 (CO_2), 164.3 (C).

Anal. Calcd for $C_9H_9NO_3S_2$: C, 44.43; H, 3.73; N, 5.76. Found: C, 44.26; H, 3.78; N, 5.66.

Ethyl 3-Amino-4-cyano-5-methylsulfanylthiophene-2-carboxylate (1j)
Mp 147 °C.

IR (KBr): 3445, 3339, 2220, 1672 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, 3 H, *J* = 7.2 Hz), 2.64 (s, 3 H), 4.30 (q, 2 H, *J* = 7.2 Hz), 5.76 (s, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.4 (CH_3), 16.8 (CH_3), 60.2 (CH_2), 112.7 (CN), 148.7 (C), 154.2 (C), 159.5 (C), 162.1 (C), 163.6 (CO_2).

Anal. Calcd for $C_9H_{10}N_2O_2S_2$: C, 44.61; H, 4.16; N, 11.56. Found: C, 44.65; H, 4.13; N, 11.57.

4-Amino-5-formyl-2-methylsulfanylthiophene-3-carbonitrile (1k)
Mp 173 °C.

IR (KBr): 2208, 1609 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.71 (s, 3 H), 7.47 (s, 2 H), 9.66 (s,1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 16.9 (CH_3), 97.5 (C), 110.8 (C), 110.9 (CN), 142.5 (C), 155.2 (C),165.1 (CHO).

Anal. Calcd for $C_7H_6N_2OS_2$: C, 42.40; H, 3.05; N, 14.13. Found: C, 42.38; H, 3.06; N, 14.21.

4-Amino-5-benzoyl-2-methylsulfanylthiophene-3-carbonitrile (1l)
Mp 209 °C.

IR (KBr): 2200, 1603 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.23 (s, 3 H), 7.45–7.61 (m, 5 H), 7.93 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 39.7 (CH_3), 90.6 (C), 112.6 (CN), 123.8 (2 CH), 125.4 (2 CH), 127.4 (CH), 128.2 (C), 138.0 (C), 156.4 (C), 163.9 (C), 180.5 (CO).

Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21. Found: C, 57.03; H, 3.74; N, 10.14.

Ethyl 4-Benzoyl-5-methylsulfanyl-3-phenylthiophene-2-carboxylate (1m)
Mp 96 °C.

IR (KBr): 1712, 1637 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (t, 3 H, *J* = 7.2 Hz), 2.59 (s, 3 H), 4.20 (q, 2 H, *J* = 7.2 Hz), 7.19–7.60 (m, 10 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.5 (CH_3), 61.1 (CH_2), 126.9 (CH), 127.4 (2 CH), 127.9 (CH), 128.1 (2 CH), 129.1 (CH), 129.4 (2 CH), 129.5 (CH), 133.0 (2 CH), 134.1 (C), 137.3 (C), 142.2 (C), 147.9 (C), 192.7 (CO_2), 205.6 (CO).

Anal. Calcd for $C_{21}H_{18}O_3S_2$: C, 65.94; H, 4.74. Found: C, 65.79; H, 4.74.

1-(4-Benzoyl-5-methylsulfanyl-3-phenylthiophen-2-yl)ethanone (1n)
Mp 134 °C.

IR (KBr): 1659, 1639 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.93 (s, 3 H), 2.59 (s, 3 H), 7.19–7.60 (m, 10 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 19.1 (CH_3), 28.9 (CH_3), 127.1 (CH), 128.2 (2 CH), 128.5 (2 CH), 129.5 (2 CH), 129.8 (2 CH), 133.1 (CH), 134.4 (C), 137.2 (C), 140.0 (C), 140.1 (C), 146.0 (C), 150.3 (C), 191.1 (CO), 192.5 (CO).

Anal. Calcd for $C_{20}H_{16}O_2S_2$: C, 68.15; H, 4.58. Found: C, 68.06; H, 4.44.

4-Benzoyl-5-methylsulfanyl-3-phenylthiophene-2-carbonitrile(1o)
Mp 89 °C.

IR (KBr): 2204, 1651 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.58 (s, 3 H), 7.19–7.60 (m, 10 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 19.4 (CH_3), 113.5 (CN), 127.0 (CH), 127.6 (C), 128.3 (2 CH), 128.4 (2 CH), 128.5 (C), 128.7 (2 CH), 129.1 (CH), 129.4 (2 CH), 132.1 (C), 133.3 (C), 136.5 (C), 152.1 (C), 191.4 (CO).

Anal. Calcd for $C_{19}H_{13}NO_2S_2$: C, 68,03; H, 3,91; N, 4,18. Found: C, 68.13; H, 3.71; N, 4.10.

Diethyl 3-Hydroxy-5-methylsulfanylthiophene-2,4-dicarboxylate (1p)
Mp 96 °C.

IR (KBr): 1688, 1659 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.15 (t, 3 H, *J* = 7.1 Hz), 1.25 (t, 3 H, *J* = 7.1 Hz), 2.45 (s,3 H), 4.02 (q, 2 H, *J* = 7.1 Hz), 4.14 (q, 2 H, *J* = 7.1 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.9 (CH_3), 14.0 (CH_3), 16.5 (CH_3), 60.5 (CH_2), 61.3 (CH_2), 102.2 (C), 114.3 (C), 154.6 (C), 162.0 (C), 163.3 (CO_2), 167.0 (CO_2).

Anal. Calcd for $C_{11}H_{14}O_5S_2$: C, 45.50; H, 4.86. Found: C, 45.46; H, 4.76.

Thieno[2,3-*b*]thiophenes 2–6; General Procedure
Method A, Using Ethyl Thioglycolate: A 100 mL three-necked round-bottom flask equipped with magnetic stirrer, condenser and septum was charged with a solution of ethyl thioglycolate (1.1 mL, 10 mmol) in EtOH (30 mL). The appropriate 5-methylsulfanylthiophene **1** (10 mmol) and dried K_2CO_3 (1.38 g, 10 mmol) was added in one portion. The mixture was stirred under reflux for 6 h and then the reaction was quenched with H_2O (100 mL). The precipitated crude product was purified by filtration followed by crystallisation from EtOH.

Method B, Using Na_2S: A 100 mL three-necked round-bottom flask equipped with magnetic stirrer, condenser and septum was charged with a solution of Na_2S (2.40 g, 10 mmol) in DMF (30 mL). This mixture was heated to 50 °C until dissolution, before adding the appropriate thiophene **1** (10 mmol). After stirring for 1 h at 50 °C, the alkylating agent (10 mmol) was added. The mixture was stirred for 0.5 h and then dried K_2CO_3 (1.38 g, 10 mmol) was added. The mixture was stirred for 6 h at 50 °C and the reaction was quenched with H_2O (100 mL). The precipitated crude product was purified by filtration followed by crystallisation from EtOH.

Diethyl 3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate (2a)
Mp 142 °C (Lit.[4] mp 142 °C).

IR (KBr): 2987, 2941, 1703 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (t, 6 H, *J* = 7.1 Hz), 2.86 (s, 6 H), 4.35 (q, 4 H, *J* = 7.1 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.4 (2 CH_3), 21.2 (2 CH_3), 61.0 (2 CH_2), 130.7 (2 C), 138.9 (C), 142.6 (2 C), 152.1 (C), 176.3 (2 CO_2).

Anal. Calcd for $C_{14}H_{16}O_4S_2$: C, 53.82; H, 5.16. Found: C, 53.98; H, 5.28.

Ethyl 5-Formyl-3,4-dimethylthieno[2,3-*b*]thiophene-2-carboxylate (2b)
Mp 133 °C.

IR (KBr): 1668, 1709 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (t, 3 H, *J* = 7.2 Hz), 2.84 (s, 3 H), 2.86 (s, 3 H), 4.34 (q, 2 H, *J* = 7.2 Hz), 10.11 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.2 (CH_3), 14.5 (CH_3), 14.6 (CH_3), 61.2 (CH_2), 140.7 (C), 141.5 (C), 142.0 (C), 147.6 (C), 148.7 (C), 162.2 (CO_2), 181.9 (CHO).

Anal. Calcd for $C_{12}H_{12}O_2S_2$: C, 53.71; H, 4.51. Found: C, 53.69; H, 4.45.

Ethyl 5-Benzoyl-3,4-dimethylthieno[2,3-*b*]thiophene-2-carboxylate (2c)
Mp 181 °C.

IR (KBr): 1642, 1710 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.2 Hz), 2.65 (s, 3 H), 2.89 (s, 3 H), 4.36 (q, 2 H, *J* = 7.2 Hz),7.45–7.88 (m, 5 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.2 (CH_3), 14.3 (CH_3), 15.7 (CH_3), 61.0 (CH_2), 128.3 (2 CH_{arom}), 129.1 (2 CH_{arom}), 132.4 (CH_{arom}), 137.4 (C), 138.9 (C), 139.3 (C), 140.8 (C), 145.6 (C), 147.8 (C), 149.0 (C), 162.4 (CO_2), 181.6 (CO).

Anal. Calcd for $C_{18}H_{16}O_3S_2$: C, 62.76; H, 4.68. Found: C, 62.60; H, 4.60.

5-Acetyl-3,4-dimethylthieno[2,3-*b*]thiophene-2-carboxylate (2d)
Mp 154 °C.

IR (KBr): 1666, 1705 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (t, 3 H, *J* = 7.2 Hz), 2.55 (s, 3 H), 2.88 (s, 3 H), 2.94 (s, 3 H), 4.35 (q, 2 H, *J* = 7.2 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8 (CH_3), 14.0 (CH_3), 14.9 (CH_3), 61.1 (CH_2), 130.2 (C), 139.2 (C), 139.4 (C), 141.0 (C), 144.8 (C), 147.9 (C), 162.2 (CO), 191.3 (CO).

Anal. Calcd for $C_{13}H_{14}O_3S_2$: C, 55.29; H, 5.00. Found: C, 55.22; H, 4.99.

Ethyl 5-Cyano-3,4-dimethylthieno[2,3-*b*]thiophene-2-carboxylate (2e)
Mp 171 °C.

IR (KBr): 2206, 1716 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.31 (t, 3 H, *J* = 7.2 Hz), 2.64 (s, 3 H), 2.77 (s, 3 H), 4.31 (q, 2 H, *J* = 7.2 Hz).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 13.8 (CH_3), 14.3 (CH_3), 15.2 (CH_3), 61.2 (CH_2), 114.3 (CN), 130.7 (C), 139.7 (C), 144.4 (C), 144.5 (C), 145.7 (C), 153.3 (C), 162.0 (CO_2).

Anal. Calcd for $C_{12}H_{11}NO_2S_2$: C, 54.32; H, 4.18; N, 5.28. Found: C, 54.41; H, 4.40; N, 5.25.

Ethyl 5-Acetyl-4-hydroxy-3-methylthieno[2,3-*b*]thiophene-2-carboxylate (3d)
Mp 93 °C.

IR (KBr): 1717, 1688 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (t, 3 H, *J* = 7.2 Hz), 2.47 (s, 3 H), 2.74 (s, 3 H), 4.42 (q, 2 H, *J* = 7.2 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.6 (CH_3), 14.8 (CH_3), 17.3 (CH_3), 60.2 (CH_2), 121.4 (C), 123.4 (C), 126.6 (C),148.0 (C), 149.5 (C), 161.0 (COH), 162.8 (CO_2), 200.8 (CO).

Anal. Calcd for $C_{12}H_{12}O_4S_2$: C, 50,69; H, 4,25. Found: C, 50.56; H, 4.29.

Ethyl 5-Acetyl-3-hydroxy-4-methylthieno[2,3-*b*]thiophene-2-carboxylate (4d)
Mp 136 °C.

IR (KBr): 1725, 1671 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (t, 3 H, *J* = 7.2 Hz), 2.47 (s, 3 H), 2.74 (s, 3 H), 4.42 (q, 2 H, *J* = 7.2 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.2 (CH_3), 16.2 (CH_3), 29.7 (CH_3), 61.3 (CH_2), 130.5 (C), 136.0 (C), 136.2 (C), 138.5 (C), 146.8 (C), 161.8 (COH), 163.6 (CO_2), 190.3 (CO).

Anal. Calcd for $C_{12}H_{12}O_4S_2$: C, 50,69; H, 4,25. Found: C, 50.50; H, 4.26.

Ethyl 3,4-Diamino-5-cyanothieno[2,3-*b*]thiophene-2-carboxylate (5e)
Mp 219 °C.

IR (KBr): 2197, 1656 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.27 (t, 3 H, *J* = 7.2 Hz), 4.23 (q, 2 H, *J* = 7.2 Hz), 6.90 (s, 2 H), 7.09 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 14.6 (CH_3), 59.9 (CH_2), 115.9 (CN), 126.9 (C), 128.2 (C), 147.0 (C), 148.2 (C), 148.8 (C), 150.8 (C), 163.7 (CO_2).

Anal. Calcd for $C_{10}H_9N_2O_2S_2$: C, 44.61; H, 4.16; N, 11.56. Found: C, 44.65; H, 4.13; N, 11.57.

Ethyl 5-Acetyl-3,4-diphenylthieno[2,3-*b*]thiophene-2-carboxylate (6d)
Mp 92 °C.

IR (KBr): 1712, 1637 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (t, 3 H, *J* = 7.2 Hz), 2.60 (s, 3 H), 4.19 (q, 2 H, *J* = 7.2 Hz), 7.11–7.59 (m, 10 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8 (CH_3), 19.3 (CH_3), 60.9 (CH_2), 126.6 (CH), 127.1 (2 CH), 127.5 (CH), 128.0 (2 CH), 128.8 (CH), 129.2 (2 CH), 129.3 (2 CH), 133.9 (C), 137.0 (C), 137.1 (C), 140.4 (C), 147.7 (C), 147.8 (C), 160.8 (C), 192.4 (CO_2), 200.9 (CO).

Anal. Calcd for $C_{23}H_{18}O_3S_2$: C, 67.95; H, 4.46. Found: C, 67.81; H, 4.42.

Ethyl 5-Cyano-3,4-diphenylthieno[2,3-*b*]thiophene-2-carboxylate (6e)
Mp 180 °C.

IR (KBr): 2213, 1719 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (t, 3 H, *J* = 7.2 Hz), 4.19 (q, 2 H, *J* = 7.2 Hz), 6.91–7.04 (m, 10 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.7 (CH_3), 61.3 (CH_2), 109.1 (C), 113.7 (CN), 125.8 (2 C), 126.7 (2 C), 127.9 (C), 128.1 (C), 128.5 (C), 128.9 (2 C), 128.6 (2 C), 129.0 (C), 130.4 (C), 133.2 (C), 133.4 (C), 147.6 (C), 142.0 (C), 161.1 (CO_2).

Anal. Calcd for $C_{22}H_{15}NO_2S_2$: C, 67.84; H, 3.88; N, 3.60. Found: C, 67.80; H, 3.90; N, 3.61.

References

(1) (a) Mashraqui, S. H.; Hariharasubrahmanian, H.; Kumar, S. *Synthesis* **1999**, 2030. (b) Mashraqui, S. H.; Hariharasubrahmanian, H. *Synth. Commun.* **2000**, *30*, 1695. (c) Augustin, M.; Rudorf, W. D.; Schmidt, U. *Tetrahedron* **1976**, *32*, 3055. (d) Dalgaard, L.; Jansen, L.; Lawesson, S. O. *Tetrahedron* **1974**, *30*, 93. (e) Gompper, R.; Kutter, E.; Töpfl, W. *Liebigs Ann. Chem.* **1962**, *659*, 90.

(2) Sommen, G.; Comel, A.; Kirsch, G. *Tetrahedron Lett.* **2002**, *43*, 257.

(3) Sommen, G.; Comel, A.; Kirsch, G. *Tetrahedron*, submitted.

(4) Comel, A.; Kirsch, G. *J. Heterocycl. Chem.* **2001**, *38*, 1167.

(5) *The Chemistry of Heterocyclic Compounds*, Part 2, Vol. 44; Gronowitz, S., Ed.; Wiley: New York, **1986**, ; and references cited therein.