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THE SYNTHESIS OF 2-(ALKYLTHIO)- AND 2-(ARYLTHIO)-3-CYANOTHIOPHENES. THE NUCLEOPHILIC DISPLACEMENT OF THE ALKYLSULFINYL GROUP BY THIOLS.

J.M.Luteijn* , H.Dolman and H.C.Wals

DUPHAR Research Laboratories, Synthesis Department Crop Protection
P.O.Box 2, 1380 AA Weesp, The Netherlands.

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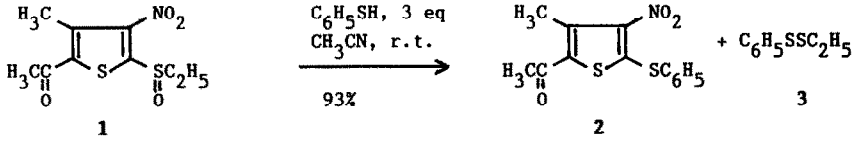
Abstract - The nucleophilic substitution of activated 2-(alkylsulfinyl)thiophenes with alkyl- or arylmercaptans gives the corresponding 2-(alkylthio)- or 2-(arylthio)- substituted thiophenes. When thiolate anion is used instead of thiol, sulfoxide reduction is the main reaction.

Generally 2-alkylthio-3-cyanothiophenes are easily prepared by the Gompper reaction[1]. Sometimes, however, the preparation of 3-cyanothiophenes with at the 2 position a thioether substituent containing an activated methylene group, gives poor yields because of further ring closure reactions at the cyano group[2]. Furthermore the Gompper reaction cannot be used for the synthesis of 2-(arylthio)thiophenes.

Since a series of 2-(alkylthio)- and 2-(arylthio)-3-cyanothiophenes were needed as intermediates in the synthesis of novel thiophene derivatives of biological interest, it was desirable to develop a general and convenient method for the preparation of the title thiophenes. In the course of an earlier research program, dealing with the synthesis of 2-(alkylsulfinyl)-3-nitrothiophenes[3], we discovered the high reactivity of the alkylsulfinyl group towards nucleophilic displacement with thiols.

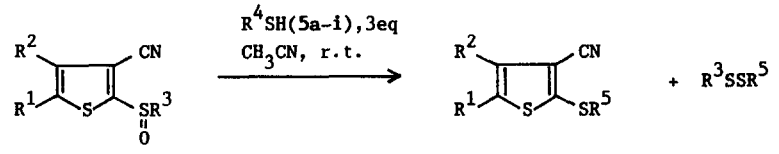
Treatment of **1** with thiophenol gave substitution product **2** and disulfide **3**. The reaction takes place readily under neutral conditions at room temperature. The formation of a sulfenic acid intermediate is believed to be involved, leading directly, or indirectly via a thiolsulfinate, to the formation of a disulfide after reaction with thiol[4].



1 **2** **3**

It has been demonstrated that substitution reactions on thiophenes with various nucleophiles proceed readily when the ring is activated by a nitro group[5,6]. In view of the ease of the reaction outlined above we were interested to study the scope of the reaction with respect to the less strongly activated 3-cyanothiophenes.

Therefore a series of 2-(alkylsulfinyl)thiophenes **4a-d** was allowed to react with various thiols. The reactions were carried out at room temperature in acetonitrile with 3 equivalents of thiol. After 3 - 8 hours the thiophenes **6a-j** could be isolated. In most cases yields were moderate to good (see Table). We have no explanation for the poor yield of **6e** from the reaction of **4d** with mercaptoethanol. The disulfides that arise from further reactions of the alkylsulfinyl leaving group with thiol, were not isolated.



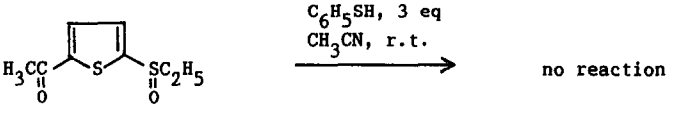
4a–d 6a–j

4	R^1	R^2	R^3
a	COC_6H_5	Cl	C_2H_5
b	$COCH_3$	C_6H_5	C_2H_5
c	CN	Cl	CH_3
d	CN	OCH_3	CH_3

5	R^4
a	$CH_2CH_2N(CH_3)_2$.HCl
b	$CH_2CH_2N(CH_2CH_3)_2$.HCl
c	C_6H_5
d	$C_{10}H_{21}$-n
e	CH_2CH_2OH
f	$CH_2C_6H_5$
g	$CH_2CO_2C_2H_5$
h	C_3H_7-i
i	C_6H_4Cl-p

6	R^1	R^2	R^5
a	COC_6H_5	Cl	$CH_2CH_2N(CH_3)_2$
b	$COCH_3$	C_6H_5	$CH_2CH_2N(CH_2CH_3)_2$
c	CN	Cl	C_6H_5
d	CN	OCH_3	$C_{10}H_{21}$-n
e	CN	OCH_3	CH_2CH_2OH
f	CN	OCH_3	$CH_2C_6H_5$
g	CN	OCH_3	$CH_2CO_2C_2H_5$
h	CN	OCH_3	C_3H_7-i
i	CN	OCH_3	C_6H_4Cl-p
j	CN	OCH_3	C_6H_5

Activation by two strongly electron withdrawing groups is necessary for the reaction to take place. This is shown by the fact that the less activated thiophene **7** does not react with thiophenol under the conditions described above.



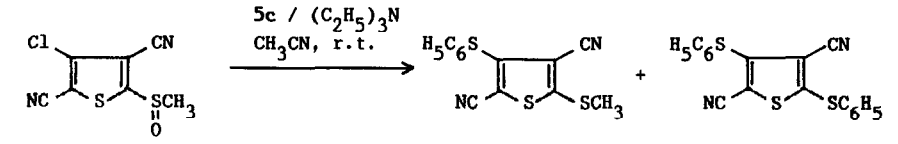
7

It is noteworthy to mention that in all cases the not ionized form of the thiols was used in the reaction. The not ionized thiol group of simple low molecular weight thiols is considered to be only weakly nucleophilic[7], and therefore nucleophilic substitution reactions are generally carried out with thiolate anions instead of thiols[8]. Interestingly, when **4c** was reacted with thiophenolate anion, (generated by the addition of triethylamine to thiophenol) the reaction took a completely different course. Nucleophilic displacement of chlorine and reduction of the sulfoxide gave **8** as the main product. Product **9** was formed as a result of nucleophilic attack at both the sulfinyl group and the chlorine atom. Reaction of **4d** with 4-chlorothiophenolate anion under the same conditions gave the reduction product **10** and the substitution product **6i**, both in low yields.

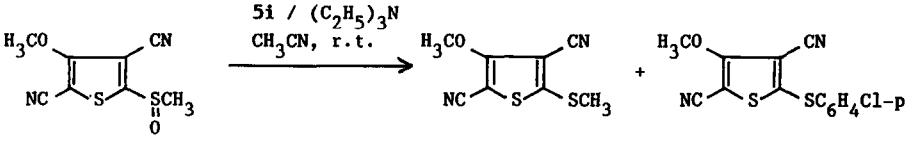
Table. Compounds **6a-j** prepared.

Prod. No.	Start. Mat.	Yield[a] (%)	m.p.(°C)[b] (Solvent)	Molecular Formula[c]	IR(KBr)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ (ppm), J (Hz)
6a	**4a,5a**	71	117-119 (i-PrOH)	$C_{16}H_{15}ClN_2OS_2$ (350.9)	2222, 1623, 1490, 1399	2.30(s,6H);2.71(t,J=7,2H); 3.28(t,J=7,2H);7.4-7.8(m,5H)
6b	**4b,5b**	89	90-92 (i-PrOH)	$C_{19}H_{22}N_2OS_2$ (358.5)	2213, 1632, 1364	1.06(t,J=7,6H);1.96(s,3H); 2.60(q,J=7,4H);2.88(t,J=7,2H); 3.28(t,J=7,2H);7.3-7.7(m,5H)
6c	**4c,5c**	84	90-92 (EtOH)	$C_{12}H_5ClN_2S_2$ (276.8)	2219, 1507, 1361	7.5-7.7(m)
6d	**4d,5d**	92	42 (Petr.Et)	$C_{17}H_{24}N_2OS_2$ (336.5)	2231, 2209, 1545, 1403	0.88(t,J=7,3H);1.2-1.3(m,14H); 1.76(m,2H);3.09(t,J=7,2H); 4.31(s,3H)
6e	**4d,5e**	21	92-94 (i-Pr_2O)	$C_9H_8N_2O_2S_2$ (240.3)	3489(br), 2210, 1541, 1390	2.6(br,1H);3.29,(t,J=6,2H); 3.94(t,J=6,2H);4.32(s,3H)
6f	**4d,5f**	40	84-86 (EtOH)	$c_{14}H_{10}N_2OS_2$ (286.4)	2211, 2201, 1540, 1388	4.26(s,2H);4.27(s,3H); 7.3(m,5H)
6g	**4d,5g**	92	67-69 (i-Pr_2O)	$C_{11}H_{10}N_2O_3S_2$ (282.3)	2229, 2203, 1733, 1542, 1393	1.3(t,J=7,3H);3.80(s,2H); 4.26(q,J=7,2H);4.32(s,3H)
6h	**4d,5h**	45	72-74 (i-Pr_2O)	$C_{10}H_{10}N_2OS_2$ (238.3)	2227, 2211, 1546, 1388	1.44(d,J=7,6H);3.61(m,1H); 4.32(s,3H)
6i	**4d,5i**	83	104-107 (EtOH)	$C_{13}H_7ClN_2OS_2$ (306.8)	2228, 2209, 1545, 1388	4.29(s,3H);7.4-7.6(m,4H)
6j	**4d,5c**	90	110 (i-PrOH)	$C_{13}H_8N_2OS_2$ (272.3)	2228, 2209, 1541, 1388	4.28(s,3H);7.5-7.7(m,5H)

[a]Isolated yield after purification
[b]Uncorrected
[c]Satisfactory microanalyses obtained: C ±0.17; H ±0.14; N ±0.39; S ±0.45
[d]Recorded on a Nicolet 60 SX Infrared Spectrometer
[e]Recorded on a Bruker WP 200 Spectrometer.



4c 8 (48%) 9 (27%)



4d 10 (29%) 6i (20%)

The reduction of sulfoxide to thioether in nucleophilic displacement reactions has been mentioned previously[9,10]. In the reactions of **4a-d** with the not ionized thiols **5a-i** however, no sulfoxide reduction was observed.

In two recent papers a very similar nucleophilic displacement reaction of 2-(alkylsulfinyl)- and 2-(arylsulfinyl)benzimidazoles with thiols was described[4,11]. The formation of sulfoxide reduction products is not mentioned in these papers.

We believe that the reactions described above offer a useful method for the synthesis of 2-(thio-substituted)-3-cyano- or 3-nitrothiophenes. The method is particulary suited for the synthesis of 2-(arylthio)thiophenes, starting from the corresponding alkylthio compounds (Gompper reaction[1]), followed by simple sulfoxidation and reaction with an arylmercaptan (for example **6c,i,j**). Furthermore, the neutral reaction conditions make this synthesis a convenient method for the introduction of thioether side chains that contain an activated methylene group (**6g**).

EXPERIMENTAL PART.

Compound **7** was prepared in 52 % yield by reaction of 2-acetyl-5-bromothiophene with sodium ethylthiolate in ethanol, followed by sulfoxidation with 3-chloroperbenzoic acid in CH_2Cl_2.[3]

Silica gel (Kieselgel 60, 70 - 230 mesh, Merck) was used for column chromatography with CH_2Cl_2 as the eluent.

Mass spectra were recorded on a Kratos MS 30 spectrometer.

2-Acetyl-3-methyl-4-nitro-5-phenylthiothiophene (2).

Thiophenol (**5c**, 3.1 mL, 30 mmol) is added to a stirred solution of **1**[3] (2.61 g, 10 mmol) in acetonitrile (50 mL) and stirring is continued for 3 h. The reaction mixture is concentrated under reduced pressure and the resulting oil is taken up in ethanol (10 mL). After standing thiophene **2** precipitates; yield 2.72 g (93%); m.p. 160 - 163 °C.

$C_{13}H_{11}NO_3S_2$	calc.	C 53.22	H 3.78	N 4.77	S 21.86
(293.4)	found	C 53.15	H 3.87	N 4.79	S 21.80

IR (KBr): ν = 1667, 1525, 1396, 1321, 1240 cm^{-1} .

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.40(s,3H,$COCH_3$); 2.78(s,3H,CH_3); 7.5-7.7(m,5H_{arom}).

The mother liquor is concentrated and dissolved in CH_2Cl_2. The solution is washed with 2 normal NaOH (100 mL) and with H_2O until neutral and dried (Na_2SO_4). The solvent is evaporated and the residue is chromatographed to afford ethylphenyl disulfide (3)[12] as an oil; yield 1.41g (83 %).
MS: (70 eV): m/e= 170 (M^+), 78.
^{1}H-NMR($CDCl_3$/TMS): δ = 1.30(t,J=7,3H,$SCH_2\underline{CH_3}$); 2.74(q,J=7,2H,$SC\underline{H_2}CH_3$);
7.1-7.7(m,5H_{arom}).

2-Benzoyl-3-chloro-4-cyano-5-ethylsulfinylthiophene (4a).
A cold solution of KOH (32 g, 0.57 mol) in H_2O (15 mL) is added slowly to a well stirred ice cooled solution of malonitrile (16.5 g, 0.25 mol) and CS_2 (22.5 mL, 0.37 mol) in DMF (150 mL). The temperature of the reaction mixture is maintained between 0 and 10 °C. After 20 min iodoethane (39 g, 0.25 mol) is added. After stirring for 30 min 2-bromoacetophenone (50 g, 0.25 mol) is added, followed by KOH (2.5 g, 4.5 mmol). The temperature of the reaction mixture rises to 55 °C. The mixture is cooled to 45 - 50 °C and stirring is continued for 1 h. The mixture is poored into ice-water (200 mL) and the solid precipitate is filtered off by suction, washed and dried. This affords the crude 3-amino-2-benzoyl-4-cyano-5-ethylthiothiophene; yield 59.6 g (83%); m.p. 117-119 °C. This product is used in the next reaction without further purification.
3-Amino-2-benzoyl-4-cyano-5-ethylthiothiophene is added to a mixture of $CuCl_2$ (13.5 g, 0.1 mol) in dry CH_3CN (200 mL) and isoamylnitrite (20 mL, 0.15 mol) with stirring at 65 °C under N_2, at such a rate that the temperature of the reaction mixture is maintained at 65 °C. After stirring for 1 h the mixture is concentrated and the residue is taken up in CH_2Cl_2 (100 mL) and washed with 6 normal HCl (2 times 100 mL). The organic layer is washed with saturated aqueous $NaHCO_3$ solution (100 ml), dried ($MgSO_4$) and concentrated. Column chromatography affords 2-benzoyl-3-chloro-4-cyano-5-ethylthiothiophene; yield 13.6 g (63%); m.p. 88-90 °C.
A solution of this compound (3.1 g, 10 mmol) in CH_2Cl_2 (200 mL) is cooled with an ice-salt bath to -5 °C. 3-Chloroperbenzoic acid (83%) (2.0 g, 9.65 mmol) is added portionwise with stirring to this solution. After 6 h solid $NaHCO_3$ (5 g) is added and the mixture is stirred for 1 h. The reaction mixture is filtered and the filtrate is concentrated to give a yellow solid. Recrystallization from diisopropyl ether gives **4a**; yield 3.0 g (92%); m.p. 110 °C.

$C_{14}H_{10}ClNO_2S_2$	calc.	C 51.93	H 3.11	N 4.33	S 19.80
(323.8)	found	C 51.87	H 2.99	N 4.23	S 19.87

IR (KBr): ν= 2227, 1656, 1500, 1246, 1067 cm^{-1}
^{1}H-NMR ($CDCl_3$/TMS): δ = 1.41(t,J=7,3H,$S(O)CH_2\underline{CH_3}$);
3.30(q,J=7,2H,$S(O)C\underline{H_2}CH_3$); 7.7-7.81(m,5H_{arom}).

2-Acetyl-4-cyano-5-ethylsulfinyl-3-phenylthiophene (4b).
2-Acetyl-4-cyano-5-ethylthio-3-phenylthiophene is prepared according to the previously described procedure[2].
A solution of this compound (2.87 g, 10 mmol) in CH_2Cl_2 (40 mL) is cooled in an ice-salt bath to -5 °C. 3-Chloroperbenzoic acid (83%) (2.08 g, 10 mmol) is added to this solution. After standing overnight the solution is washed with a saturated $NaHCO_3$ solution (40 mL), with H_2O until neutral, dried (Na_2SO_4) and concentrated. The solid residue is crystallized from isopropanol to give **4b**; yield 2.36 g (78%); m.p. 117-119 °C.

$C_{15}H_{13}NO_2S_2$	calc.	C 59.38	H 4.32	N 4.62	S 21.13
(303.4)	found	C 59.18	H 4.22	N 4.71	S 21.05

IR (KBr): ν= 2218, 1667, 1363, 1265, 1069 cm^{-1}.
^{1}H-NMR($CDCl_3$/TMS): δ = 1.40(t,J=7,3H,$S(O)CH_2\underline{CH_3}$); 2.00(s,3H,$COCH_3$);
3.24(q,J=7,2H,$S(O)C\underline{H_2}CH_3$); 7.40-7.56(m,5H_{arom}).

3-Chloro-2,4-dicyano-5-methylsulfinylthiophene (4c)
A cold solution of KOH (50 g, 0.89 mol) in H_2O (30 mL) is added slowly with stirring to an ice cold solution of malonitrile (26.5 g, 0.40 mol) and CS_2 (45 mL, 0.75 mol) in DMF (250 mL). The temperature of the

reaction mixture is maintained between 0 and 10 °C. After stirring for 10 min iodomethane (60 g, 0.42 mol) is added, after another 30 min followed by chloroacetonitrile (30.5 g, 0.40 mol). Powdered KOH is added (4.0 g, 70 mmol) and the temperature is allowed to rise to 40 °C. After stirring for 1 h H_2O is added (500 mL). The precipitate is filtered off and the filter cake is washed with H_2O and dried to give the crude 3-amino-2,4-dicyano-5-methylthiothiophene; yield 54.5 g (70%); m.p. 144 °C.

To a solution of this compound (12.5 g, 64 mmol) in acetonitrile (100 mL) is added CuCl (1g), concentrated HCl (25 mL) and a saturated aqueous NaCl solution (30 mL). This mixture is cooled to -2 °C and a solution of $NaNO_2$ (20 g, 0.23 mol) in H_2O (20 mL) is added slowly with stirring. After 3 h the mixture is filtered and the filtrate is concentrated. The residue is extracted with CH_2Cl_2 (2 times 50 mL). The extract is washed with aqueous K_2CO_3 solution (50 mL) and with H_2O until neutral, dried (Na_2SO_4) and concentrated. The residue is chromatographed to give 3-chloro-2,4-dicyano-5-methylthiothiophene; yield 6.6 g (48%), m.p. 144°C.

A solution of this compound (3.6 g, 17 mmol) in CH_2Cl_2 (100 mL) is cooled to -5 °C. 3-Chloroperbenzoic acid (83%) (3.15 g, 15 mmol) is added portionwise with stirring to this solution. After standing overnight the reaction mixture is washed with aqueous $NaHCO_3$ (2 times 25 mL), with H_2O until neutral and dried (Na_2SO_4). The solution is concentrated and chromatographed to give **4c**; yield 1.85 g (48%); m.p. 148°C.

$C_7H_3ClN_2OS_2$	calc.	C 36.45	H 1.31	N 12.14	S 27.80
(230.7)	found	C 36.37	H 1.41	N 12.12	S 27.92

IR (KBr): ν = 2237, 2226, 1505, 1402, 1364, 1070 cm^{-1}.

^{1}H-NMR($CDCl_3$/TMS): δ = 3.17(S(O)CH_3).

2,4-Dicyano-3-methoxy-5-methylsulfinylthiophene (4d).

A mixture of ethyl cyanoacetate (226 g, 2.0 mol) and CS_2 (170 g, 2.23 mol) in DMF (1.2 L) is cooled to 0 °C. To this mixture is added slowly with stirring a cold solution of KOH (260 g, 4.64 mol) in H_2O (120 mL). The temperature of the reaction mixture is maintained between 0 and 10 °C. After 15 min chloroacetonitrile (152 g, 2.0 mol) is added and the mixture is warmed to 30 °C. A cold solution of KOH (130 g, 2.32 mol) in H_2O (60 mL) is added slowly. After 30 min the mixture is cooled to 5 °C and iodomethane (282 g, 2.0 mol) is added. A thick precipitate is formed. Finally the reaction flask is swirled by hand to assure mixture of the contents. H_2O (100 mL) is added, followed by concentrated HCl (220 mL). The mixture is poured into H_2O (2 L), the precipitate is isolated by suction and washed with H_2O and ether and dried to give 2,4-dicyano-4-hydroxy-5-methylthiothiophene; yield 280 g (70 %); m.p. 200 °C (dec).

A mixture of this compound (6.0 g, 3.1 mmol), iodomethane (10 mL, 16 mmol), K_2CO_3 (10 g, 7.2 mmol) and benzyltriethylammonium chloride (0.5 g) is refluxed in CH_3CN (200 mL). After 2 h the reaction mixture is filtered. The filtrate is concentrated and the residue is taken up in CH_2Cl_2 (50 mL), washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), with H_2O until neutral and dried (Na_2SO_4). The solution is concentrated and the residue is recrystallized from isopropanol to give 2,4-dicyano-4-methoxy-5-methylthiothiophene; yield 4.0 g (62%); m.p. 132 °C.

A solution of this compound (3.8 g, 18.1 mmol) in CH_2Cl_2 (100 mL) is cooled to 0 °C. 3-Chloroperbenzoic acid (83%) (3.9 g, 18.7 mmol) is added portionwise with stirring to this solution. After 1 h the solution is washed with a saturated aqueous solution of $NaHCO_3$ (40 mL) and with H_2O until neutral. The solution is dried (Na_2SO_4) and concentrated. The residue is recrystallized from diisopropyl ether to give **4d**; yield 3.75 g (91%); m.p. 132-135 °C.

$C_8H_6N_2O_2S_2$	calc.	C 42.47	H 2.67	N 12.38	S 28.34
(226.3)	found	C 42.44	H 2.82	N 12.33	S 28.56

IR (KBr): ν = 2239, 2220, 1544, 1472, 1380, 1250, 1056 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.08(s,3H,S(O)CH_3); 4.39(s,3H,OCH_3).

Thiophenes 6a-j; General procedure.

To a stirred solution of cyanothiophene 4 (10 mmol) in CH_3CN (50 mL) is added all at once thiol 5 (30 mmol, 3 eq.). Stirring is continued for 3-8 h. The solvent is removed under reduced pressure and the residue is recrystallized. In the case of **6a,b** the residue is taken up in CH_2Cl_2 , washed with saturated $NaHCO_3$ solution (50 mL) and with H_2O (50 mL), dried and concentrated. Recrystallization of the residue gave the

pure samples.

In the case of **6h** the crude product is purified by column chromatography, followed by recrystallization.

Reaction of 3-chloro-2,4-dicyano-5-methylsulfinylthiophene (4c) with thiophenolate anion.

To a stirred suspension of **4c** (6.92 g, 30 mmol) in CH_3CN (75 mL) is added thiophenol (**5c**, 3.1 mL, 30 mmol, 1 eq.), immediately followed by triethylamine (4.2 mL, 30 mmol). The reaction mixture becomes clear. Stirring is continued for 1 h. The reaction mixture is concentrated under reduced pressure, taken up in CH_2Cl_2 (50 mL), washed with saturated aqueous Na_2CO_3 solution (25 mL) and with H_2O until neutral and dried (Na_2SO_4). The solvent is removed and the residue is chromatographed. This affords **8**; yield 4.17 g (48%) and **9**; yield 2.82 g (27 %).

2,4-Dicyano-5-methylthio-3-phenylthiothiophene (8).

M.p. 120 - 122 °C.

$C_{13}H_8N_2S_3$	calc.	C 54.14	H 2.80	N 9.71	S 33.35
(288.4)	found	C 54.17	H 2.84	N 9.89	S 33.38

IR (KBr): ν = 2218, 1577, 1475, 1398 cm^{-1}.

^{1}H-NMR($CDCl_3$/TMS): δ = 2.70(s,3H,SCH_3); 7.3-7.6(m,5H_{arom}).

2,4-Dicyano-3,5-diphenylthiothiophene (9).

M.p. 118 - 120 °C.

$C_{18}H_{10}N_2S_3$	calc.	C 61.69	H 2.88	N 7.99	S 27.44
(350.5)	found	C 61.62	H 2.89	N 8.16	S 27.35

IR (KBr): ν = 2226, 2214, 1472, 1398 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.3 - 7.7 (m,H_{arom}).

Reaction of 2,4-dicyano-3-methoxy-5-methylsulfinylthiophene (4d) with 4-chloro-thiophenolate anion.

To a stirred suspension of **4d** (2.26 g, 10 mmol) in CH_3CN (50 mL) is added a mixture of 4-chlorothiophenol (**5i**, 4.34 g, 30 mmol, 3 eq.) and triethylamine (4.2 mL, 30 mmol, 3 eq.) The reaction mixture becomes clear. Stirring is continued for 3 h. The solvent is removed and the residue is taken up in CH_2Cl_2. The solution is washed with 2 normal NaOH (3 times 100 mL) and with H_2O until neutral, dried (Na_2SO_4) and concentrated. The residue is chromatographed to afford **10** (0.61 g, 29%) and **6i** (0.61 g, 20 %).

2,4-Dicyano-3-methoxy-5-methylthiothiophene (10).

M.p. 133 - 135 °C.

$C_8H_6N_2OS_2$	calc.	C 45.69	H 2.88	N 13.32	S 30.50
(210.3)	found	C 45.73	H 2.88	N 13.26	S 30.65

IR (KBr): ν = 2225, 2213, 1548, 1458 cm^{-1} .

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.68(s,3H,SCH_3); 4.32(s,3H,OCH_3).

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