A One-Step Synthesis of Thiophene Derivatives

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Several methods for the preparation of thiophenes have been reported and their application in the synthesis of useful compounds has been widely studied[1-13]. Most thiophenes from

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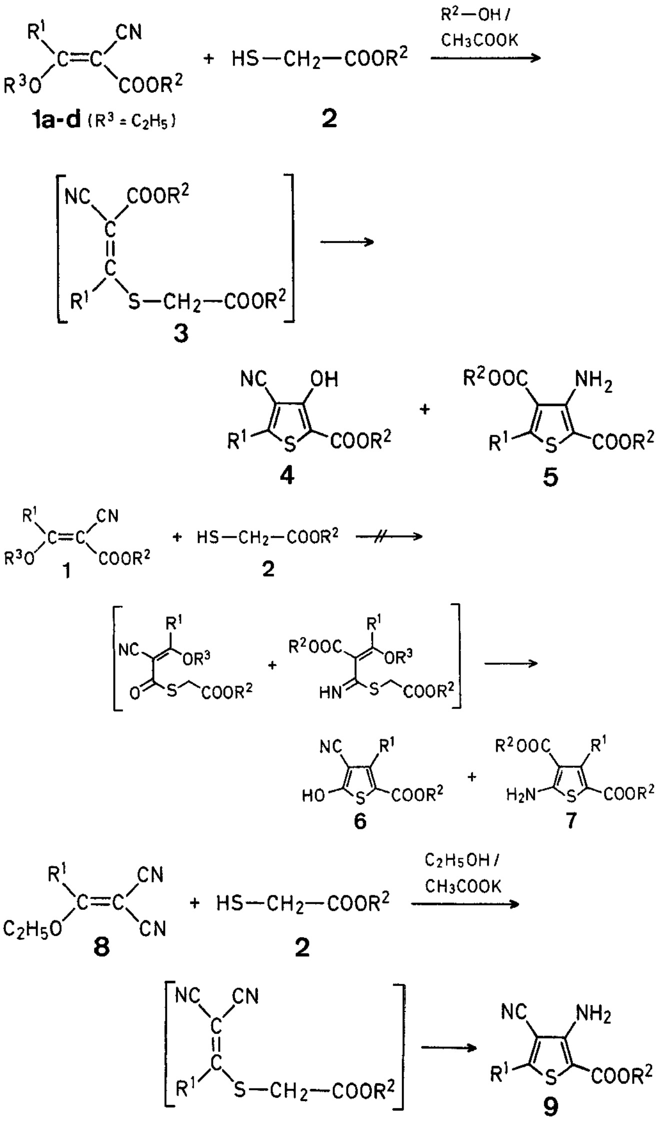
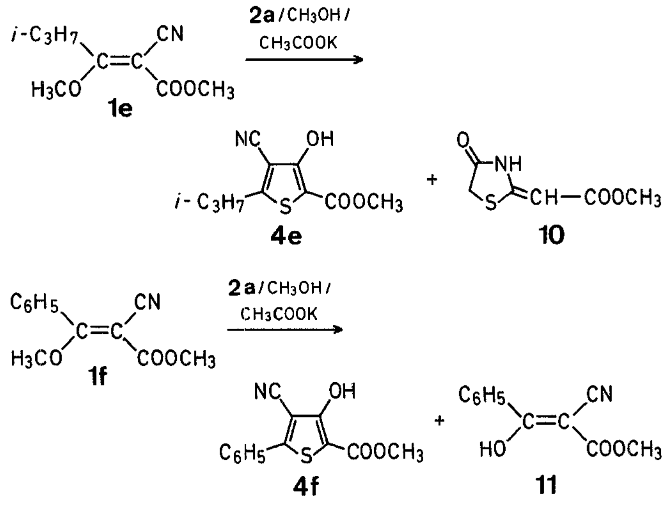
two-component pathways are formed by reaction of 3-thionate salts of acrylic esters or acrylonitriles with halogen compounds. We now report the first one-step synthesis of 3-hydroxy- or 3-aminothiophenes (**4**, **5**, or **9**) from 3-alkoxy-2,3-unsaturated nitriles (**1** or **8**) and mercaptoacetic esters (**2**) in a refluxing alcohol (Scheme **A**).



Scheme A

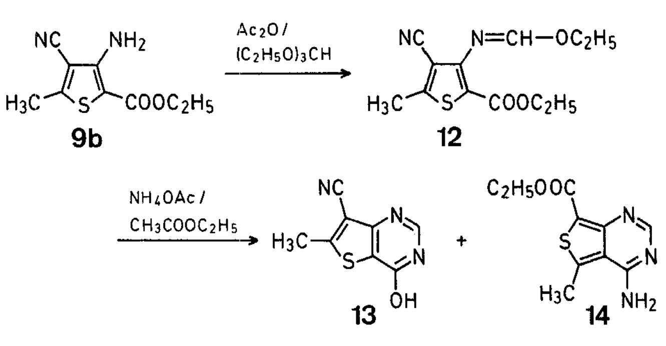
Reaction of nitriles **1a-d** with mercaptoacetic esters **2** in the presence of potassium acetate in an appropriate alcohol gave the 5-alkyl-2-alkoxycarbonyl-4-cyano-3-hydroxythiophenes (**4a-d**) and 5-alkyl-2,4-dialkoxycarbonyl-3-aminothiophenes (**5a-d**) in good yields. No isomeric 5-hydroxy- (**6**) and 5-aminothiophenes (**7**) were formed as proved by the isolation of the intermediate **3a** in the reaction of the nitrile **1a** with the mercapto ester **2a**. The intermediate **3a** was easily converted into the thiophenes **4a** and **5a** under alkaline conditions. 3-Aminothiophenes (**9**) were prepared in high yields from the dinitrile **8** and the mercapto ester **2** (Scheme **A**).

On the other hand, an analogous reaction between **1e** (or **1f**)[14], and **2a** did not give the corresponding 3-aminothiophene **5e** (or **5f**), but **4e** (or **4f**) and **10** [or methyl 2-cyano-3-hydroxycinnamate (**11**)] as shown in Scheme **B**. 3-Ethoxy-2-methoxycarbonyl- (or -2-cyano-)-acrylonitrile (**1**; $R^1=H$, $R^2=CH_3$, $R^3=C_2H_5$ or **8**; $R^1=H$) reacted with **2a** under the same conditions to form only 2-methoxycarbonylmethylene- (or 2-cyanomethylene)-4-thiazolidinone (**10**).



Scheme B

The 3-aminothiophene **9b** was converted into a mixture of 7-cyano-4-hydroxy-6-methylthieno[3,2-*d*]pyrimidine (**13**) and 4-amino-7-ethoxycarbonyl-5-methylthieno[3,4-*d*]pyrimidine (**14**) via the intermediate **12** by treatment with triethyl orthoformate and ammonium acetate (Scheme **C**).



Scheme C

Thiophene Derivatives 4, 5, and 9 from 1 or 8 and 2; General Procedure:

A mixture of the 3-alkyl-3-alkoxyacrylonitrile (**1** or **8**; 10 mmol) and the mercaptoacetic ester (**2**; 10 mmol) in a suitable alcohol (**2a**: methanol, **2b**: ethanol, 10 ml) containing potassium acetate (15 mmol) is heated under reflux for 0.5-2 h. The crystals which precipitate during the reaction are collected by filtration. In the reaction of **1** with **2**, the resultant precipitate is dissolved in hot water, and the solution is acidified with concentrated hydrochloric acid to pH 5. The crystals thus formed are collected by filtration, washed with water, and recrystallized from methanol (**4a**, **c**) or ethanol (**4b**, **d**).

Alternatively, the filtrate is evaporated under reduced pressure, the precipitate formed is isolated by suction, washed well with water, and recrystallized from methanol (**5c**) or ethanol (**5b**, **d**).

However, the white product (**5a**) containing intermediate **3a** is isolated by column chromatography on silica gel using 3 : 2 v/v hexane/ethyl acetate as eluent to give **3a** and **5a**.

In the reaction of **8** with **2**, the resultant precipitate is washed with water and recrystallized from tetrahydrofuran to give **9**.

Methyl 2-cyano-3-methoxycarbonylmethylthio-crotonate (**3a**); yield: 0.3 g (13%); m.p. 129–130 °C.

$C_9H_{11}NO_4S$	calc.	C 47.16	H 4.84	N 6.11	S 13.96
(229.2)	found	47.10	4.77	6.09	14.03

I.R. (Nujol): $\nu=2225$, 1725, 1684, 1525 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): $\delta=2.55$ (s, 3 H); 3.72 (s, 3 H); 3.77 (s, 3 H); 4.19 ppm (s, 2 H).

Cyclization of Methyl-2-cyano-3-methoxycarbonylmethylthio-crotonate (3a):

A mixture of **3a** (2.3 g, 10 mmol) and potassium carbonate (1.3 g, 10 mmol) in methanol (20 ml) is heated under reflux for 30 min, and worked up as above to give **4a**; yield: 0.85 g (43%) and **5a**; yield: 0.71 g (31%).

Reaction of 1e with 2a:

A mixture of **1e** (1.83 g, 10 mmol), **2a** (1.06 g, 10 mmol), potassium acetate (1.47 g, 15 mmol), and methanol (10 ml) is refluxed for 7 h. The crystalline matter separates out during the reaction. After cooling, the precipitate is collected and dissolved in hot water. The solution is acidified with concentrated hydrochloric acid to pH 5. The resultant white precipitate is collected, washed with water, and recrystallized from methanol to give **4a** (Tables).

The water-insoluble material is recrystallized from methanol/dimethyl sulfoxide to afford **10**; yield: 1.2 g (69%); m.p. 176–177 °C.

$C_6H_7NO_3S$	calc.	C 41.62	H 4.08	N 8.09	S 18.49
(173.1)	found	41.70	4.29	7.85	18.13

I.R. (Nujol): $\nu = 3260, 1750, 1710, 1658, 1570\ cm^{-1}$.

^1H-N.M.R. (DMSO-d_6): $\delta = 3.50$ (s, 3H); 3.70 (s, 2H); 5.35 (s, 1H); 11.26 ppm (br, 1H).

Table 1. Thiophenes **4**, **5**, and **9** prepared

Product	R^1	R^2	Yield [%]	m.p. [°C]	Molecular formula[a] or Lit. m.p.
4a	CH_3	CH_3	28	137–138°	$C_8H_7NO_3S$ (197.1)
4b	CH_3	C_2H_5	28	149–151°	150°[10]
4c	C_2H_5	CH_3	35	115–116°	$C_9H_9NO_3S$ (211.2)
4d	C_2H_5	C_2H_5	47	70–71°	$C_{10}H_{11}NO_3S$ (225.2)
4e	i-C_3H_7	CH_3	18	118–119°	$C_{10}H_{11}NO_3S$ (225.2)
4f	C_6H_5	CH_3	77	168–169°	$C_{13}H_9NO_3S$ (259.2)
5a	CH_3	CH_3	37	129–130°	$C_9H_{11}NO_4S$ (229.2)
5b	CH_3	C_2H_5	23	75–76°	73°[10]
5c	C_2H_5	CH_3	25	96–97°	$C_{10}H_{13}NO_4S$ (243.2)
5d	C_2H_5	C_2H_5	31	72–73°	$C_{12}H_{17}NO_4S$ (271.3)
7a	CH_3	CH_3	97	202–204°	$C_8H_8N_2O_2S$ (196.2)
7b	CH_3	C_2H_5	88	140–141°	140°[9]
7c	C_2H_5	CH_3	83	152–154°	$C_9H_{10}N_2O_2S$ (210.2)
7d	C_2H_5	C_2H_5	87	111–113°	$C_{10}H_{12}N_2O_2S$ (224.3)

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.18, N ±0.27, S ±0.31.

Reaction of 1f with 2a:

A mixture of **1f** (1.09 g, 5 mmol), **2a** (0.53 g, 5 mmol), potassium acetate (0.74 g, 7.5 mmol) and methanol (10 ml) is heated under reflux for 1 h. After cooling, the precipitate is collected and dissolved in hot water. The pH of the aqueous solution is adjusted with concentrated hydrochloric acid to about 5. The product thus formed is separated, washed with water, and recrystallized from methanol to give **4f** (Tables).

The reaction filtrate is concentrated and poured into a water (10 ml). The solution is acidified with hydrochloric acid. The product thus formed is collected, washed with water, and then recrystallized from methanol to give *methyl 2-cyano-3-hydroxycinnamate* (**11**); yield: 0.12 g (12%); m.p. 77–78 °C.

$C_{11}H_9NO_3$	calc.	C 65.02	H 4.42	N 6.89
(203.3)	found	64.73	4.28	6.67

I.R. (Nujol): $\nu = 2230, 1660, 1610, 1595, 1565\ cm^{-1}$.

^1H-N.M.R. ($CDCl_3$): $\delta = 3.95$ (s, 3H); 7.5–8.1 (m, 5H); 14.04 ppm (br, 1H).

Preparation of 2-Methoxycarbonylmethylene-(or 2-cyanomethylene)-4-thiazolidinone:

A mixture of 3-ethoxy-2-methoxycarbonyl-(or -2-cyano)-acrylonitrile (10 mmol) and **2a** (1.06 g, 10 mmol) is dissolved in ethanol (10 ml) containing potassium acetate (0.98 g, 10 mmol), and heated under reflux for 1 h. A crystalline matter precipitates out during the reaction. The crystals are filtered, washed with water, and then recrystallized from ethanol/dimethyl sulfoxide to afford *2-methoxycarbonylmethylene-4-thiazolidinone* (**10**); yield: 0.53 g (31%): m.p. 176–177 °C [or *2-cyanomethylene-4-thiazolidinone*; yield: 0.60 g (43%); m.p. 196–210 °C (dec.)].

2-Cyanomethylene-4-thiazolidinone:

$C_5H_4N_2OS$	calc.	C 42.86	H 2.88	N 20.00	S 22.84
(140.1)	found	42.65	2.83	20.27	22.51

I.R. (Nujol): $\nu = 3120, 2070, 2215, 1750, 1720, 1590\ cm^{-1}$.

^1H-N.M.R. (DMSO-d_6): $\delta = 4.00$ (s, 2H); 4.90 (s, 1H); 11.72 ppm (br, 1H).

4-Cyano-2-ethoxycarbonyl-3-ethoxymethyleneamino-5-methylthiophene (12):

A mixture of **9b** (2.1 g, 10 mmol), triethyl orthoformate (8.9 g, 60 mmol), and acetic anhydride (1.0 g, 10 mmol) is heated under reflux for 5 h. The reaction mixture is concentrated and cooled in an ice-box. The crystals formed are recrystallized from chloroform; yield: 2.3 g (86%); m.p. 89–90 °C.

$C_{12}H_{14}N_2O_3S$	calc.	C 54.13	H 5.30	N 10.52	S 12.02
(266.3)	found	54.06	5.22	10.41	12.26

Table 2. I.R. and N.M.R. Spectra of Thiophenes **4**, **5**, and **9**

Compound	I.R. (nujol) ν [cm^{-1}]					^1H-N.M.R. (DMSO-d_6) δ [ppm]		
	ν_{O-H}	ν_{N-H}	$\nu_{C\equiv N}$	$\nu_{C=O}$	$\nu_{C=C}$	R^1	R^2	OH or NH_2
4a	3300		2230	1675	1570	2.60 (s)	3.80 (s)	10.35 (br)
4b	3325		2240	1685	1567	2.59 (s)	1.31 (t), 4.30 (q)	10.68 (br)
4c	3320		2240	1670	1560	1.29 (t), 2.99 (q)	3.86 (s)	10.11 (br)
4d	3300		2240	1670	1560	1.31 (t), 2.97 (q)	1.31 (t), 4.30 (q)	10.50 (br)
4e	3330		2235	1665	1570	1.33 (d), 3.33 (sept)	3.75 (s)	9.90 (br)
4f	3315		2245	1667	1557	7.4–7.7 (m)	3.77 (s)	10.80 (br)
5a		3500, 3480		1685, 1655	1585	2.55 (s)	3.73 (s), 3.82 (s)	6.97 (s)
5b		3490, 3375		1690, 1658	1590	2.58 (s)	1.28 (s), 4.23 (q) 1.34 (s), 4.30 (q)	6.91 (s)
5c		3480, 3370		1690, 1650	1590	1.23 (t), 3.09 (q)	3.79 (s), 3.88 (s)	6.98 (s)
5d		3490, 3370		1690, 1658	1590	1.23 (t), 3.07 (q)	1.26 (t), 4.22 (q) 1.32 (t), 4.31 (q)	6.90 (s)
7a		3430, 3360	2225	1678	1615	2.58 (s)	3.82 (s)	6.94 (s)
7b		3435, 3350	2230	1680	1620	2.58 (s)	1.28 (t), 4.30 (q)	6.89 (s)
7c		3450, 3350	2240	1678	1620	1.28 (t), 2.97 (q)	3.82 (s)	6.90 (s)
7d		3470, 3360	2235	1670	1610	1.28 (t), 2.98 (q)	1.28 (t), 4.31 (q)	5.50 (br)

I.R. (Nujol): $\nu = 2230, 1715, 1645, 1545\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 1.25$ (t, 3H); 1.37 (t, 3H); 2.67 (s, 3H); 4.27 (q, 2H); 4.40 (q, 2H); 8.21 ppm (s, 1H).

7-Cyano-4-hydroxy-6-methylthieno[3,2-*d*]pyrimidine (13) and 4-Amino-7-ethoxycarbonyl-5-methylthieno[3,4-*d*]pyrimidine (14):

To a solution of **12** (2.66 g, 10 mmol) and ethyl acetate (10 ml), ammonium acetate (0.92 g, 12 mmol) is added, and then the mixture is stirred under reflux for 3 h. The solution is concentrated under reduced pressure. The resultant precipitate is collected, washed with water, and dissolved in ethanol (5 ml). The ethanol-insoluble precipitate is recrystallized from ethanol/tetrahydrofuran to give **13**; yield: 0.34 g (18%); m.p. 299–300 °C.

$C_8H_5N_3OS$	calc.	C 50.26	H 2.64	N 21.99	S 16.74
(191.1)	found	49.97	2.73	21.85	16.73

I.R. (Nujol): $\nu = 3450, 3110, 1670, 1655, 1595\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.75$ (s, 3H); 8.21 (s, 1H); 12.62 ppm (br, 1H).

The ethanol solution is concentrated, and the solid formed is filtered, recrystallized from ethanol to afford **14**, yield: 0.57 g (24%); m.p. 220–222 °C.

$C_{10}H_{11}N_3O_2S$	calc.	C 50.63	H 4.64	N 17.72	S 13.49
(237.2)	found	50.78	4.55	17.59	13.60

I.R. (Nujol): $\nu = 3320, 1695, 1665, 1570\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 1.29$ (t, 3H); 2.93 (s, 3H); 4.26 (q, 2H); 7.40 (br, 2H), 8.12 ppm (s, 1H).

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