A NEW ROUTE FOR THE SYNTHESIS OF 3-METHOXYTHIOPHENES

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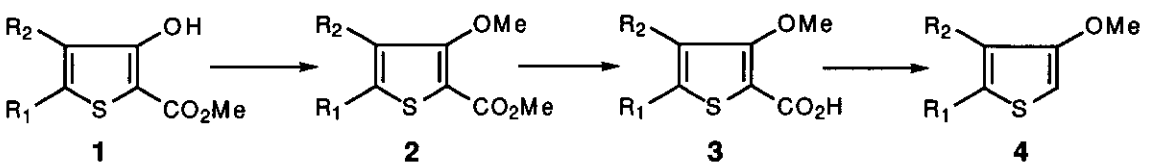
Abstract—A new synthesis of 4-substituted, 5-substituted and 4,5-disubstituted 3-methoxythiophenes is reported. The reaction takes place in three steps in nealy quantitative yields starting from methyl 3-hydroxythiophene-2-carboxylates.

We were interested in the synthesis of a series of 3-methoxy thiophene derivatives (**4**) with additional electron releasing groups for the study of their reactivity in Diels-Alder reaction conditions towards dimethyl acetylenedicarboxylate. The synthesis of 3-methoxythiophene by the Gronowitz method[1] (Copper catalyzed Williamson reaction with 3-bromothiophene, sodium methoxide and cupric oxide), cannot be extended for the preparation of many 3-methoxythiophene derivatives because of the difficulty or the impossibility of synthesis of the starting bromothiophenes.

This fact led us to design an alternative route starting from methyl 3-hydroxythiophene-2-carboxylates (**1**), which due to the presence of the ester group in position 2 of the thiophene nucleus are stable enol compounds, differently to other 3-hydroxythiophenes.

In this paper we describe an easy and versatile method for the synthesis of 3-methoxythiophene derivatives (**4**) in nearly quantitative yields in three steps starting from compounds (**1**) (Scheme), in similar manner to that described for the synthesis of the dimethyl ether of thiotetronic and α-halothiotetronic acids.[2]



Scheme

1-4	R_1	R_2
a	H	Me
b	H	SMe
c	H	Ph
d	Me	H
e	SMe	H
f	Me	Me
g	SMe	Me

Compounds (**1**) can be synthesized in very good yields.[3-7] Compounds (**2**) are obtained by heating compounds (**1**) (0.1 mol) for 12 h with dimethyl sulfate (0.12 mol) in boiling acetone (200 ml) in the presence of anhydrous potassium carbonate (0.12 mol) (Table 1).

Table 1. Synthesis of compounds (**2**)

Prod.	Yield (%)	Molecular Formula	Analysis Calcd/Found C	H	S	mp [°C] (solvent) or bp [°C] (Torr.)	Ir υ (cm^{-1}) CO	^{1}H Nmr (TMS, δ)[a]
2a	82	$C_8H_{10}O_3S$	51.61 51.43	5.37 5.39	17.20 17.35	oil	1690	2.37 (s, 3H, CH_3), 3.82 (S, 3H, CO_2CH_3), 3.89 (s, 3H, OCH_3), 7.12 (s, 1H, H-5)
2b	88	$C_8H_{10}O_3S_2$	44.04 44.14	4.59 4.71	29.36 29.33	oil	1710	2.39 (s, 3H, SCH_3), 3.72 (s, 3H, CO_2CH_3), 3.94 (s, 3H, OCH_3), 7.15 (s, 1H, H-5)
2c	85	$C_{13}H_{12}O_3S$	62.90 62.64	4.84 4.93	12.90 13.14	93-95 (methanol)	1710	3.79 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 7.43 (m, 6H, 5 benzene protons and 1H, H-5)
2d	83	$C_8H_{10}O_3S$	51.61 51.74	5.38 5.41	17.20 17.32	70-71 (n-hexane)	1700	2.41 (s, 3H, CH_3), 3.78 (s, 3H, CO_2CH_3), 3.91 (s, 3H, OCH_3), 6.52 (s, 1H, H-4)
2e	85	$C_8H_{10}O_3S_2$	44.04 44.13	4.59 4.47	29.36 29.56	oil	1700	2.41 (s, 3H, CH_3), 3.76 (s, 3H, CO_2CH_3), 3.92 (s, 3H, OCH_3), 6.58 (s, 1H, H-4)
2f	80	$C_9H_{12}O_3S$	54.00 54.13	6.00 6.15	16.00 16.29	43-44 (methanol)	1710	1.94 (s, 3H, CH_3), 2.27 (s, 3H CH_3), 3,84 (s, 3H, CO_2CH_3), 3.97 (s, 3H, OCH_3)
2g	82	$C_9H_{12}O_3S_2$	46.55 46.63	5.17 5.19	27.59 27.61	oil	1690	1.98 (s, 3H, CH_3), 2.41 (s, 3H, SCH_3), 3.84 (s, 3H, CO_2CH_3), 3.94 (s, 3H, OCH_3)

[a] The spectra were recorded using $CDCl_3$ as solvent.

Alkaline hydrolysis of compounds (**2**) (0.1 mol) by refluxing them until total disolution with 1N sodium hydroxide (0.15 mol) and acidification to pH 3 with 1N hydrogen chloride gave compounds (**3**) (Table 2).

Table 2. Synthesis of compounds (**3**)

Prod.	Yield (%)	Molecular Formula	Analysis Calcd/Found C	H	S	mp [°C] (solvent) or bp [°C] (Torr.)	Ir υ (cm^{-1}) CO	^{1}H Nmr (TMS, δ)[a]
3a	94	$C_7H_8O_3S$	48.83 49.12	4.65 4.72	18.60 18.87	127-129 (benzene)	1660	2.14 (s, 3H, CH_3), 3,86 (s, 3H, OCH_3), 6.99 (s, 1H, H-5)

3b	92	$C_7H_8O_3S_2$	41.18 41.36	3.92 3.94	31.37 31.12	137-139 (toluene)	1650	2.43 (s, 3H, SCH_3), 3.81 (s, 3H, OCH_3), 7.17 (s, 1H, H-5)
3c	97	$C_{12}H_{10}O_3S$	61.54 61.69	4.27 4.31	13.67 13.94	150-151 (toluene)	1670	3.81 (s, 3H, OCH_3), 7.47 (m, 6H, 5 benzene protons and 1H, H-5)
3d	91	$C_7H_8O_3S$	48.84 49.03	4.65 4.72	18.60 18.83	162-163 (toluene)	1650	2.42 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.81 (s, 1H, H-4)
3e	90	$C_7H_8O_3S_2$	41.18 41.32	3.92 3.98	31.37 31.52	117-118 (methanol)	1650	2.54 (s, 3H, SCH_3), 3.82 (s, 3H, OCH_3), 6.98 (s, 1H, H-4)
3f	95	$C_8H_{10}O_3S$	51.61 51.83	5.38 5.39	17.20 1731	126-128 (benzene)	1640	1.94 (s, 3H, CH_3), 2.38 (s, 3H, SCH_3), 3.84 (s, 3H, OCH_3)
3g	90	$C_8H_{10}O_3S_2$	44.04 44.21	4.59 4.61	29.36 29.63	127-129 (benzene)	1660	1.94 (s, 3H, CH_3), 2.38 (s, 3H, SCH_3), 3.84 (s, 3H, OCH_3)

[a] The spectra were recorded using DMSO-d_6 as solvent.

These compounds were thermally decarboxylated «in vacuo» by heating them above their melting points until the CO_2 evolution ceased (Table 3).

Table 3. Synthesis of compounds (**4**)

Prod.	Yield (%)	Molecular Formula	Analysis Calcd/Found C	H	S	mp [°C] (solvent) or bp [°C] (Torr.)	^{1}H Nmr (TMS, δ)[a]
4a	87	C_6H_8OS	56.25 56.31	6.25 6.29	25.00 25.83	85-87 (8)	2.02 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.10 (d, 1H, J≈3.0 Hz, H-2), 6.73 (d, 1H, J≈3.0 Hz, H-5)
4b	92	$C_6H_8OS_2$	45.00 45.13	5.00 5.08	40.00 40.17	120-122 (8)	2.31 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 6.13 (d, 1H, J≈3.0 Hz, H-2), 6.74 (d, 1H, J≈3.0 Hz, H-5)
4c	92	$C_{11}H_{10}OS$	69.47 69.72	5.26 5.29	16.84 17.13	98-100 (8)	3.81 (s, 3H, OCH_3), 6.32 (d, 1H, J≈2.0 Hz, H-5), 7.15 (d, 1H, J≈2.0 Hz, H-2), 7.70 (m, 5H, benzene proton)
4d	91	C_6H_8OS	56.25 56.43	6.25 6.31	25.00 25.15	65-67 (8)	2.32 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 5.96 (d, 1H, J≈1.0 Hz, H-2), 6.69 (d, 1H, J≈1.0 Hz, H-4)
4e	98	$C_6H_8OS_2$	45.00 45.24	5.00 5.12	40.00 40.28	110-111 (8)	2.39 (s, 3H, SCH_3), 3.71 (s, 3H, OCH_3), 6.10 (d, 1H, J≈1.0 Hz, H-2), 6.69 (d, 1H, J≈1.0 Hz, H-4)
4f	94	$C_7H_{10}OS$	51.61 51.83	5.38 5.39	17.20 17.31	119-121 (8)	1.98 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 5.94 (s, 1H, H-2)
4g	89	$C_7H_{10}OS_2$	44.09 44.21	4.59 4.61	29.36 29.63	132-134 (8)	2.11 (s, 3H, CH_3), 2.34 (s, 3H, SCH_3), 3.69 (s, 3H, OCH_3), 6.18 (s, 1H, H-2)

[a] The spectra were recorded using $CDCl_3$ as solvent.

EXPERIMENTAL

Melting points were measured on a Büchi 510 apparatus and are uncorrected. Ir spectra were recorded on a Shimadzu-435 Ir Spectrophotometer. ^{1}H Nmr on a Bruker AM (200 MHz) Spectrometer and mass spectra on a Vacuum generator V 12-250. All the reagents used were of commercial grade and used as such. Mycroanalyses were made on a Perkin-Elmer 240 analyzer.
The starting materials were prepared according to the references: compounds (**1a-c**),[3] compound (**1d**),[4] compound (**1e**),[5] compound (**1f**)[6] and compound (**1g**).[7]

Methyl 3-methoxythiophene-2-carboxylates (2). General Procedure

Dimethyl sulfate (13.2 g, 0.12 mol) was added to a stirred mixture of the corresponding compound (**1**) (0.1 mol) and anhydrous potassium carbonate (16.6 g, 0.12 mol) in acetone (200 ml). The reaction mixture was heated at reflux temperature for 12 h and then evaporated to dryness. The residue was treated with water and the product extracted with CH_2Cl_2 (200 ml). Evaporation of the organic solvent *in vacuo* led to the compounds (**2**) (Table 1).

3-Methoxythiophene-2-carboxylic acids (3). General Procedure

A suspension of compounds **2** (0.1 mol) in 150 ml (0.15 mol) of 1N NaOH solution was heated to reflux for 30 min until total disolution. After cooling, the reaction mixture was acidified with 1N HCl to pH3 and the solid product so formed was extracted with EtOAc (200 ml). Evaporation of the organic solvent *in vacuo* led to the compounds (**3**) (Table 2).

3-Methoxythiophenes (4). General Procedure

Compounds (**3**) were heated at reduced pressure (11 Torr.) 30°C above their melting points. After the evolution of CO_2 had ceased, the resulting oil was distilled (Table 3).

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