

## SYNTHESIS OF 4-SUBSTITUTED METHYL 3-(2,3-EPOXY)PROPOXYTHIOPHENE-2-CARBOXYLATES

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**Abstract**—The synthesis of 4-substituted methyl 3-hydroxythiophene-2-carboxylates is reported. The selective *O*-alkylation by two methods of these compounds gives the correspondent epoxy derivatives.

In connection with our ongoing work on the synthesis of potential antidepressant drugs<sup>1</sup> we were interested in the preparation of the title compounds (**5**) (specially 4-thiomethyl derivative (**5a**)).

In this paper, we describe the synthesis of the 4-substituted alkyl-3-hydroxythiophene-2-carboxylate derivatives (**4**) using a simple modification of the Fiesselmann procedure and their selective *O*-alkylation to the title compounds (**5**).

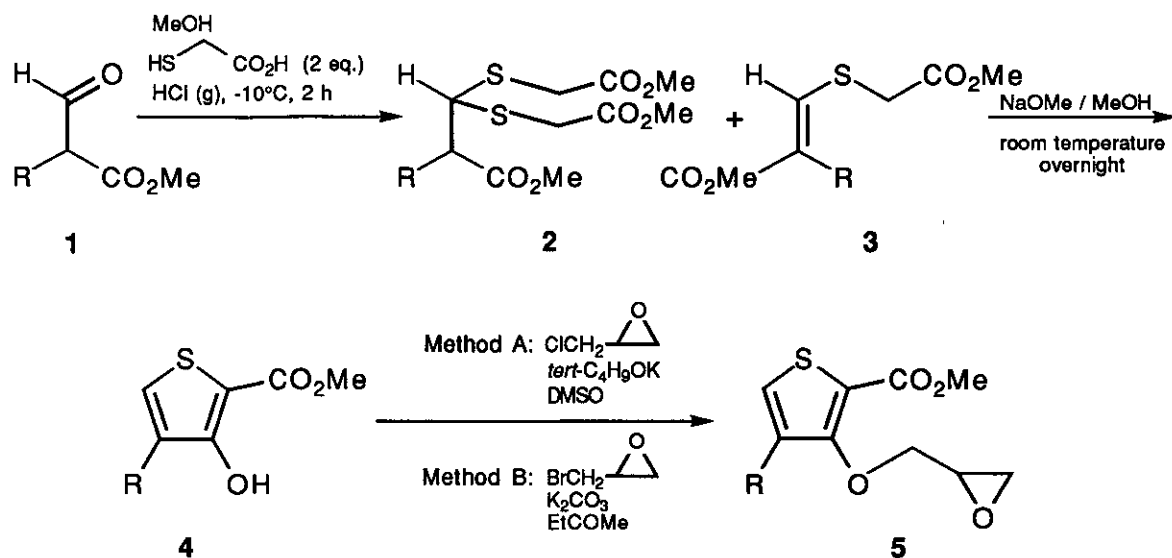
Some 4-substituted alkyl-3-hydroxythiophene-2-carboxylates can be obtained by several different methods, a known procedure being the electrophilic substitution reactions<sup>2</sup> of alkyl 3-hydroxythiophene-2-carboxylates; however this useful procedure for the introduction of groups like bromine, nitro, acetyl, chloroacetyl<sup>3,4</sup> is not suitable for the synthesis of compounds (**4a-f**).

The Fiesselmann procedure is also a common route for the synthesis of 5- and 4,5-substituted alkyl 3-hydroxythiophene-2-carboxylates,<sup>5</sup> but there are only a few references<sup>6-9</sup> of the 4-substituted derivatives, which are not easily available for the readers. Brelivet *et al.* have published an application of this method for the synthesis of several alkyl 3-hydroxythiophene-2-carboxylates, among which the only 4-substituted compound was 4-methyl derivative (**4c**).<sup>10</sup> However neither the spectroscopic data nor the exact yield are reported.

These facts and our recent publication of a simple modification of the Fiesselmann method to obtain in only two steps and in high yields different condensed derivatives of alkyl 3-hydroxythiophene-2-carboxylates<sup>11</sup> prompted us to apply this procedure, with slight changes (only two steps using thioglycolic acid instead of methylthioglycolate and a shorter time of bubbling HCl), to the synthesis of 4-substituted compounds (**4a-c, e, f**) and to publish the results and the experimental conditions in a detailed manner.

The starting materials are the  $\alpha$ -formyl esters (**1**) instead of the  $\beta$ -oxo esters used in the Fiesselmann procedure as depicted in the Scheme, except for the case of **4d**. This compound was synthesized as described in the literature<sup>12</sup> by a specific method not applicable for the rest of the hydroxy derivatives (**4a-f**). Compounds (**1**) were obtained in good yields by a Claisen condensation of the corresponding esters and methyl formate excepts for the case of **1c** (21% yield).

The first step was carried out by bubbling a hydrogen chloride stream for 2 hours (less than 2 hours for the bicyclic derivatives) into an alcohol solution of the corresponding compound (**1**) and anhydrous thioglycolic acid kept at  $-10^{\circ}\text{C}$  (when the thioglycolic esters are used, the yields decreased remarkably) (Table 1).



SCHEME 1

1-5	R
a	SMe
b	Ph
c	Me
d	allyl
e*	SBu <sup>n</sup>
f*	SPh

\*Only Compounds 1-4

The isolated crude products were mixtures of compounds (2) and (3) which were submitted to cyclization under the conditions described in the Scheme (Scheme 1, Table 1) to yield compounds (4).

Compounds (2a-b and 3a-b) were separated by flash column chromatography to confirm their structures, the triester derivatives (2) being the majority of the mixture. The proximity of their R<sub>f</sub> values and the easier work up encouraged us to use the crude product for the cyclization reactions.

The attempts of transformation of the sulfides (3a-b) into compounds (4) in Dieckmann cyclization conditions were unsuccessful. This fact may suggest the E configuration of the unsaturated compounds (3) that hinders the Dieckmann reaction, in contrast to the Z one observed for the bicyclic derivatives.<sup>11</sup>

The yields obtained from the  $\alpha$ -formyl esters show the validity of this method, although the yield for compound (1c) was low (23%) (this compound could not be synthesized by Kroll<sup>7</sup> using the classical Fiessemann conditions, probably due to the instability of methyl 2-formylpropionate (1c). This fact prompted us to design another way for the synthesis of 1c using the dimethylacetal of 1c as starting material,<sup>13</sup> and boron trifluoride as catalyst. This is a general method useful for the synthesis of 4-alkyl-3-hydroxythiophene-2-carboxylates that avoids the use of the unstable alkyl 2-formylalkanoales.

Table 1  
4 Substituted methyl 3-Hydroxythiophene-2-carboxylates (4)

Prod. <sup>a</sup>	Yield (%) <sup>b</sup>	Molecular Formula	Analysis Calcd/Found			mp [°C] (solvent) or bp [°C] (Torr.)	I <sub>r</sub> v (cm <sup>-1</sup> )		<sup>1</sup> H Nmr (CDCl <sub>3</sub> /TMS δ)
			C	H	S		OH	CO	
4a	61	C <sub>7</sub> H <sub>8</sub> O <sub>3</sub> S <sub>2</sub>	41.15 41.21	3.95 3.93	31.38 31.59	104-106 (methanol)	3200	1640	2.37 (s, 3H, SCH <sub>3</sub> ), 3.86 (s, 3H, OCH <sub>3</sub> ), 7.12 (s, 1H, H-5 thiophene), 9.69 (s, 1H, OH)
4b <sup>c</sup>	75	C <sub>12</sub> H <sub>10</sub> O <sub>3</sub> S	61.51 61.75	4.30 4.17	13.68 13.99	82-83 (methanol)	3250	1650	3.87 (s, 3H, OCH <sub>3</sub> ), 7.30-7.77 (m, 6H, aromatic), 10.10 (s, 1H, OH)
4c <sup>d</sup>	23	C <sub>7</sub> H <sub>8</sub> O <sub>3</sub> S	48.82 48.63	4.68 4.51	18.62 18.42	73-75 (0.5)	3200	1640	2.05 (s, 3H, CH <sub>3</sub> ), 3.87 (s, 3H, OCH <sub>3</sub> ), 6.96 (s, 1H, H-5 thiophene), 9.58 (s, 1H, OH)
4e	69	C <sub>10</sub> H <sub>14</sub> O <sub>3</sub> S <sub>2</sub>	48.77 48.49	5.73 5.48	26.03 25.85	33-35 (methanol)	3250	1650	0.78-0.86 (t, 3H, J=7.2 Hz, CH <sub>3</sub> ), 1.13-1.66 (m, 4H, CH <sub>2</sub> ), 2.76-2.97 (t, 2H, J=7.2 Hz, SCH <sub>2</sub> ), 3.85 (s, 3H, OCH <sub>3</sub> ), 7.08 (s, 1H, H-5 thiophene), 9.68 (s, 1H, OH)
4f	56	C <sub>12</sub> H <sub>10</sub> O <sub>3</sub> S <sub>2</sub>	54.12 54.41	3.78 3.56	24.08 24.35	62-64 (methanol)	3250	1650	3.80 (s, 3H, OCH <sub>3</sub> ), 7.20-7.33 (m, 6H, aromatic), 9.70 (s, 1H, OH)

a The yields obtained using methyl thioglycolate were (4a) (36%); (4b) (46%); (4c) (12%); (4e) (36%); and (4f) (27%).

b Yields bases on starting materials (1).

c This compound was synthesized by Kroll<sup>7</sup> in a 73% yield with a mp 84°C (no more experimental analytical or spectroscopic data are referred).

d This compound could not be synthesized by Kroll;<sup>7</sup> Brelivet *et al.*,<sup>10</sup> described the product, bp 60°C (0.05 Torr.), neither yield nor spectroscopic data. The molecular formulè is mistaken.

The selective *O*-alkylation of compounds (4) only made for compounds (4a-d), was carried out by two methods. One is previously employed for the alkylation reactions<sup>14,15</sup> (Method A, Table 2), using epichlorohydrin and potassium *tert*-butoxide in dimethyl sulfoxide, being not useful for the *O*-alkylation of compound (4d) because of the double bond isomerization. The other one (Method B, Table 2) is that using ethyl methyl ketone/potassium carbonate and epibromohydrin. This method is useful for all these compounds (including 4d) and allows an easier and cleaner work up and the yields obtained are better than those by the A method.

Table 2  
4 Substituted 3-(2,3-Epoxy)propoxythiophene-2-carboxylates (5)

Prod.	Yield (%) Method		Molecular Formula	Analysis Calcd/Found			mp [°C] (solvent)	Ir $\nu$ (cm <sup>-1</sup> ) CO	<sup>1</sup> H Nmr (CDCl <sub>3</sub> /TMS) $\delta$ , J (Hz)
	A	B		C	H	S			
5a	62	85	C <sub>10</sub> H <sub>12</sub> O <sub>4</sub> S <sub>2</sub>	46.14 46.35	4.65 4.68	24.63 25.01	oil <sup>a</sup>	1720	2.37 (s, 3H, SCH <sub>3</sub> ), 2.86 (m, 2H, OCH <sub>2</sub> ), 3.35 (m, 1H, CH), 3.85 (s, 3H, OCH <sub>3</sub> ), 4.15 (dd, 1H, J <sub>1a-1b</sub> =11.9, J <sub>1b-2</sub> =5.9, OCH <sub>2</sub> ), 4.42 (dd, 1H, J <sub>1a-1b</sub> =11.9, J <sub>1a-2</sub> =2.9, OCH <sub>2</sub> ), 7.19 (s, 1H, H-5 thiophene)
5b	57	82	C <sub>15</sub> H <sub>14</sub> O <sub>4</sub> S	62.06 62.17	4.86 4.81	11.04 11.24	74-76 (isopropanol)	1720	2.81 (m, 2H, OCH <sub>2</sub> ), 3.36 (m, 1H, CH), 3.80 (s, 3H, OCH <sub>3</sub> ), 4.10 (dd, 1H, J <sub>1a-1b</sub> =11.9, J <sub>1b-2</sub> =5.9, OCH <sub>2</sub> ), 4.42 (dd, 1H, J <sub>1a-1b</sub> =11.9, J <sub>1a-2</sub> =2.9, OCH <sub>2</sub> ), 7.02 (s, 1H, H-5 thiophene), 7.30-7.60 (m, 5H, phenyl),
5c	69	81	C <sub>10</sub> H <sub>12</sub> O <sub>4</sub> S	52.61 52.41	5.30 5.38	14.04 14.25	oil <sup>a</sup>	1700	2.42 (s, 3H, CH <sub>3</sub> ), 2.86 (m, 2H, OCH <sub>2</sub> ), 3.35 (m, 1H, CH), 3.80 (s, 3H, OCH <sub>3</sub> ), 4.07 (dd, 1H, J <sub>1a-1b</sub> =11.9, J <sub>1b-2</sub> =5.9, OCH <sub>2</sub> ), 4.37 (dd, 1H, J <sub>1a-1b</sub> =11.9, J <sub>1a-2</sub> =2.9, OCH <sub>2</sub> ), 6.57 (s, 1H, H-5 thiophene)
5d	—	87	C <sub>12</sub> H <sub>14</sub> O <sub>4</sub> S	56.68 56.47	5.55 5.47	12.61 12.49	oil <sup>a</sup>	1710	2.68 (m, 2H, OCH <sub>2</sub> ), 3.21-3.46 (m, 3H, CH epoxy and CH <sub>2</sub> ), 3.80 (s, 3H, OCH <sub>3</sub> ), 4.07 (dd, 1H, J <sub>1a-1b</sub> =11.9, J <sub>1b-2</sub> =5.9, OCH <sub>2</sub> ), 4.37 (dd, 1H, J <sub>1a-1b</sub> =11.9, J <sub>1a-2</sub> =2.9, OCH <sub>2</sub> ), 5.06 (d, 2H, J=15.0, CH=CH <sub>2</sub> ), 5.80 (m, 1H, CH), 7.02 (s, 1H, H-5 thiophene)

a These compounds were purified by a column flash chromatography (see experimental part).

## EXPERIMENTAL

Melting points were measured on a Büchi 510 apparatus and are uncorrected. Ir spectra were recorded on a Shimadzu-435 Ir spectrophotometer; <sup>1</sup>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. The plates and silica gel (230-240 mesh) were from E. Merck, Darmstadt. Mycroanalyses were made on a Perkin-Elmer 240 analyzer.

### Methyl $\alpha$ -formylpropanates (1). General Procedure

A solution of the corresponding acetate (0.1 mol) in methyl formate (9.6 g, 0.16 mol) was added to a suspension of Na (3.68 g, 0.16 mol) in anhydrous Et<sub>2</sub>O (60 ml). The reaction mixture was stirred at room temperature until the total disappearance of the Na. The solid formed was filtered, washed with Et<sub>2</sub>O (50 ml) and dissolved in H<sub>2</sub>O. This solution was acidified and the oil formed was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated at reduced pressure and the oily residue was distilled or recrystallized.

Methyl 2-methylthio-3-oxopropionate (**1a**); yield 78%; bp 45-47°C/20 Torr. Anal. Calcd for C<sub>5</sub>H<sub>8</sub>O<sub>3</sub>S: C, 40.53; H, 5.44; S, 21.64. Found: C, 40.41; H, 5.36; S, 21.95.

Methyl 2-butylthio-3-oxopropionate (**1e**); yield 85%; bp 63-65°C/20 Torr. Anal. Calcd for C<sub>8</sub>H<sub>14</sub>O<sub>3</sub>S: C, 50.50; H, 7.42; S, 16.85. Found: C, 50.22; H, 7.31; S, 17.03.

Methyl 2-phenylthio-3-oxopropionate (**1f**); yield 83%; mp 57-59°C/MeOH. Anal. Calcd for C<sub>10</sub>H<sub>10</sub>O<sub>3</sub>S: C, 57.13; H, 4.79; S, 15.25. Found: C, 57.32; H, 4.93; S, 15.57.

Compounds (**1b**)<sup>16</sup> and (**1b**)<sup>17</sup> were prepared according to known procedures.

### 4 Substituted Methyl 3-Hydroxythiophene-2-carboxylates (4). General Procedure

A solution of the  $\alpha$ -formylpropanate (**1**) (0.1 mol) in absolute MeOH (100 ml) was cooled at -10°C and a stream of HCl gas was bubbled into the system until saturation. Then, thioglycolic acid (18.4 g, 0.2 mol) was added and the bubbling of HCl was continued at -10°C for 2 h. The mixture was left at room temperature for 4 h. The solvent was evaporated at reduced pressure and the residue neutralized with 5% NaHCO<sub>3</sub> solution and extracted with Et<sub>2</sub>O (200 ml). The organic phase was separated, washed with water (200 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated and the resultant product, a mixture of compounds (**2** and **3**), was used in crude in the next step (compounds (**2a,b** and **3a,b**) were purified to confirm their structures as mentioned below).

To the above crude product was added a 2N methanolic solution of NaOMe (120 ml, 240 mmol) and the reaction mixture was left overnight at room temperature. The solvent was evaporated at reduced pressure and the residue treated with ice cold water (150 ml). The mixture was acidified with 2N HCl. CH<sub>2</sub>Cl<sub>2</sub> (150 ml) was added and the organic layer separated was washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated and the resultant products were purified by distillation or crystallization (Table 1).

### Separation of compounds (**2a,b** and **3a,b**)

A portion (1 g) of the crude products resulting in the first step of the above reaction was chromatographed by flash chromatography on a silica gel column (45 × 10 cm, 230-240 mesh) using hexane/EtOAc (5:1) as eluent to obtain the following compounds.

#### Reaction of compound (**1a**)

Methyl 3,3-bis(methoxycarbonylmethylthio)-2-methylthiopropionate (**2a**) as an oil. Rf 0.51.

Ir (film):  $\nu$  1690, 1645. <sup>1</sup>H Nmr (CDCl<sub>3</sub>):  $\delta$  = 2.24 (s, 3H, SCH<sub>3</sub>), 3.40 (d, 1H, J=7.0 Hz, CH), 3.49 (s, 2H, SCH<sub>2</sub>), 3.51 (s, 2H, SCH<sub>2</sub>), 3.82 (s, 6H, 2OCH<sub>3</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 4.38 (d, 1H, J=7.0 Hz, CH). Ms: m/z (%) 342 (M<sup>+</sup>, 8), 262 (100). Anal. Calcd for C<sub>11</sub>H<sub>18</sub>O<sub>6</sub>S<sub>3</sub>: C, 38.89; H, 5.30; S, 28.08. Found: C, 39.12; H, 5.36; S, 28.37.

Methyl 3(methoxycarbonylmethylthio)-2-methylthioacrylate (**3a**) as an oil. Rf 0.62.

Ir (film):  $\nu$  1700, 1635. <sup>1</sup>H Nmr (CDCl<sub>3</sub>):  $\delta$  = 2.28 (s, 3H, SCH<sub>3</sub>), 3.46 (s, 2H, SCH<sub>2</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 7.21 (s, 1H, OH). Ms: m/z (%) 236 (M<sup>+</sup>, 32), 134 (100). Anal. Calcd for C<sub>8</sub>H<sub>12</sub>O<sub>4</sub>S<sub>2</sub>: C, 40.66; H, 5.12; S, 27.13. Found: C, 40.38; H, 5.07; S, 27.29.

### Reaction of compound (1b)

Methyl 3,3-bis(methoxycarbonylmethylthio)-2-phenylpropionate (2b) as an oil. Rf 0.56.

Ir (film):  $\nu$  1690, 1645.  $^1\text{H Nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  = 3.31 (d, 1H,  $J=6.9$  Hz, CH), 3.46 (s, 2H, SCH<sub>2</sub>), 3.48 (s, 2H, SCH<sub>2</sub>), 3.81 (s, 6H, 2OCH<sub>3</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 4.58 (d, 1H,  $J=6.9$  Hz, CH), 7.15-7.45 (m, 5H, aromatic). Ms:  $m/z$  (%) 372 ( $\text{M}^+$ , 14), 267 (100). Anal. Calcd for  $\text{C}_{16}\text{H}_{20}\text{O}_6\text{S}_2$ : C, 51.60; H, 5.41; S, 17.22. Found: C, 51.34; H, 5.38; S, 17.43.

Methyl 3-(methoxycarbonylmethylthio)-2-phenylacrylate (3b) as an oil. Rf 0.68.

Ir (film):  $\nu$  1690, 1650.  $^1\text{H Nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  = 3.50 (s, 2H, SCH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 3.84 (s, 3H, CH<sub>3</sub>), 7.13-7.40 (m, 5H, aromatic), 7.47 (s, 1H, CH). Ms:  $m/z$  (%) 266 ( $\text{M}^+$ , 41), 74 (100). Anal. Calcd for  $\text{C}_{13}\text{H}_{14}\text{O}_4\text{S}$ : C, 58.63; H, 5.30; S, 12.04. Found: C, 58.53; H, 5.27; S, 12.31.

### 4-Substituted Methyl 3-(2,3-epoxy)propoxythiophene-2-carboxylate (5). General Procedure

Method A. Epichlorohydrin (2.3 g, 0.024 mol) was added dropwise to a stirred solution of the corresponding methyl 3-hydroxythiophene-2-carboxylate (0.01 mol), *tert*-BuOK (1.4 g, 0.012 mol) in DMSO (17 ml). The reaction mixture was treated at 100°C during 2-3 h and the solvent was distilled off at 0.1 Torr. The residue was extracted with hot hexane. The solvent was evaporated and the epoxy derivatives formed were purified by crystallization or chromatography on a silica gel column using hexane/EtOAc (5:1) as eluent (Table 2).

Method B. Anhydrous  $\text{K}_2\text{CO}_3$  (1.4 g, 0.01 mol) was added to a stirred solution of the corresponding methyl 3-hydroxythiophene-2-carboxylate (0.01 mol) in ethyl methyl ketone (30 ml) and the stirring was continued for 10 min until the potassium salt of the hydroxy compounds (4) were formed. Then epibromohydrin (1.9 g, 0.013 mol) was added and the mixture was heated at reflux temperature overnight. The solvent was evaporated and cold water (20 ml) was added. The mixture was extracted with EtOAc (25 ml) and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was distilled off and the epoxy derivatives formed were purified by crystallization or chromatography on a silica gel column using (hexane/EtOAc) (5:1) as eluent (Table 2).

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