Synthesis of [*b*]-Condensed Alkyl 3-Hydroxythiophene-2-carboxylates

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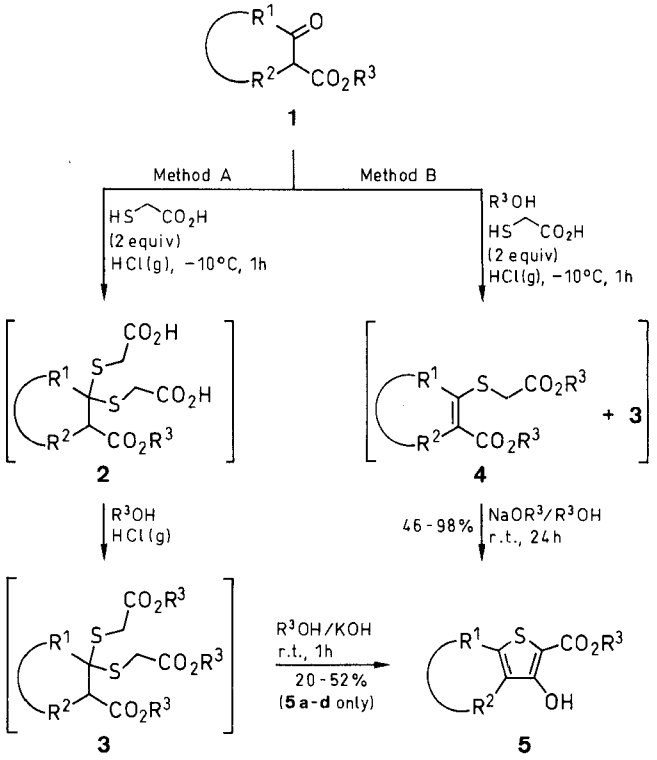
A simple modification of the Fiesselmann procedure for the synthesis of bicyclic alkyl 3-hydroxythiophene-2-carboxylates allow higher yields in only two steps.

Our interest in the study of 3-thienyloxypropanolamines as β-adrenergic blocking agents[1,2] and platelet aggregation inhibitors[3] prompted us to continue the study of new bicyclic products of this type. The title compounds **5** appear as good intermediates for their synthesis and, in this paper, a modification of the Fiesselmann procedure, the most common route for the synthesis of alkyl 3-hydroxythiophene-2-carboxylates, and its application to the preparation of the new compounds **5a–h** is described.

In the only published paper on this procedure,[5] it is stated that it must be carried out in three steps in order to obtain good yields (Scheme, Method A). The initial condensation reaction of linear or cyclic β-oxo esters **1** and thioglycolic acid, catalyzed by hydrogen chloride, must be performed in the absence of solvents. The isolated resulting thioketals **2** are esterified to the triester **3** by the corresponding alcohol, using hydrogen chloride as a catalyst. Finally, the cyclization of the isolated triesters **3** to compounds **5** is achieved by means of alcoholic potassium hydroxide.

Nevertheless, when the above procedure was applied to the synthesis of the new bicylic thiophene compounds **5a–h**, only moderate or very poor yields were obtained (Table, Method A). In order to get better results some variations in the procedure were tried, which finally allowed an easier synthesis of these compounds in only two steps with much better yields. It was considered that, given this type of cyclic β-oxo esters, even if unsaturated sulfides **4** were formed,[5] they should necessarily have the *Z*-configuration and they would be able to undergo the final cyclization, leading, in every case, to the thiophene derivatives **5**. Thus (Scheme, Method B), the first step was carried out by bubbling a hydrogen chloride stream for 4 hours into an alcoholic solution of the appropriate cyclic β-oxo ester and anhydrous thioglycolic acid kept at −10 °C. The isolated crude product so obtained (probably a mixture of **4** and **3**) was submitted to cyclization in the second step, by treatment with the corresponding sodium alkoxide in an alcoholic solution maintained under nitrogen atmosphere, to give compounds **5a–j** (Method B, Table).

The results obtained following the above mentioned modifications in the Fiesselmann procedure, when cyclic β-oxo esters were used as starting materials, show that, in these cases, such modifications allow an easier and shorter workup affording the final products **5** in much better yields. The structures of all the new compounds were established on the basis of their analytical and spectroscopic data (Table).



1–5	R^1	R^2	R^3
a	$-(CH_2)_5-$		Et
b	$-(CH_2)_6-$		Et
c	$-CH(Me)(CH_2)_2-$		Me
d	$-CH(Me)(CH_2)_3-$		Me
e	$-(CH_2)_2CH(Me)CH_2-$		Me
f	$-(CH_2)_2SCH_2-$		Me
g	$-(CH_2)_3S-$		Et
h	$-CH_2SCH_2S-$		Et
i	$-CH_2SCH_2-$		Me
j	$-(CH_2)_2S-$		Me

Scheme

After completion of this work we found out that in two doctoral theses[6,7] from the University of Erlangen-Nürnberg, made available to Gronowitz,[8] the above modifications appear to have been used with success in several cases. It was felt, however, that the reporting of our results in this paper should be expedient, in order to avoid misconceptions on the Fiesselmann reaction.

Melting points were measured on a Gallenkamp capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 IR spectrophotometer and ^1H NMR on a Bruker AM (200 MHz) spectrometer. All reagents used were of commercial grade and used as such. The thioglycolic acid and the starting cycloalkanones were purchased from Fluka Chemical Co. TLC plates and silica gel (230–240 mesh) were from E. Merck, Darmstadt. Microanalyses were made on a Perkin-Elmer 240 analyzer.

Table. Compounds **5** Prepared

Product	Yield (%)[a] Method A	Yield (%)[a] Method B	mp (°C) (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR ν (cm^{-1}) OH	IR ν (cm^{-1}) CO	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
5a	45	86	32–34 (EtOH)	$C_{12}H_{16}SO_3$ (240.2)	3300–3180	1650	1.55–1.74 (m, 4H), 1.82–1.94 (m, 2H), 2.60–2.66 (m, 2H), 2.73–2.79 (m, 2H), 9.81 (s, 1H, OH)[c]
5b	52	75	19–20 (EtOH)	$C_{13}H_{18}SO_3$ (254.2)	3295–3195	1655	1.39–1.44 (m, 4H), 1.60–1.69 (m, 4H), 2.59–2.65 (m, 2H), 2.77–2.83 (m, 2H), 9.73 (s, 1H, OH)[c]
5c	48	91	44–46 (MeOH)	$C_{10}H_{12}SO_3$ (212.2)	3275	1670	1.25 (d, 3H, J = 6.87, CH_3), 1.89–2.06 (m, 1H), 2.54–2.82 (m, 3H), 3.23–3.35 (m, 1H), 9.69 (s, 1H, OH)[d]
5d	20	87	38–40 (MeOH)	$C_{11}H_{14}SO_3$ (226.2)	3300	1660	1.27 (d, 3H, J = 6.72, CH_3), 1.22–1.51 (m, 1H), 1.57–1.80 (m, 1H), 1.87–2.08 (m, 2H); 2.30–2.62 (m, 2H), 2.31–2.93 (m, 1H); 9.63 (s, 1H, OH)[d]
5e	–[e]	81	60–62 (MeOH)	$C_{11}H_{14}SO_3$ (226.2)	3300	1655	1.08 (d, 3H, J = 6.43, CH_3), 1.46–1.56 (m, 1H), 1.84–2.09 (m, 3H), 2.61–2.63 (m, 1H), 2.68–2.77 (m, 2H), 9.65 (s, 1H, OH)[d]
5f	–[e]	46	51–53 (MeOH)	$C_9H_{10}S_2O_3$ (230.21)	3500–3350	1635, 1585	2.88–2.94 (m, 2H, 6-CH_2), 2.97–3.04 (m, 2H, 7-CH_2), 3.59 (t, 2H, J = 1.32, 4-CH_2), 9.64 (s, 1H, OH)[d]
5g	–[e]	54	68–70 (EtOH)	$C_{10}H_{12}S_2O$ (244.2)	–	1650, 1560	2.14–2.26 (m, 2H, 6-CH_2), 2.77–2.83 (m, 2H, 5-CH_2), 2.98–3.04 (m, 2H, 7-CH_2), 9.73 (s, 1H, OH)[c]
5h	–[e]	62	150–152 (EtOH)	$C_9H_{10}S_3O_3$ (262.3)	3275	1675, 1555	3.88 (s, 2H, 5-CH_2), 4.15 (s, 2H, 7-CH_2), 9.75 (s, 1H, OH)[c]
5i	–	98	140–142 (MeOH)	139[7]	3320–3230	1665, 1540	3.92–3.98 (m, 2H, 4-CH_2), 4.10–4.15 (m, 2H, 6-CH_2), 9.61 (s, 1H, OH)[d]
5j	–	85	164–166 (MeOH)	170[7]	3290	1665, 1540	3.13–3.21 (m, 2H, 5-CH_2), 3.71–3.79 (m, 2H, 6-CH_2), 9.60 (s, 1H, OH)[d]

[a] Yield based on starting materials.
[b] Satisfactory microanalyses obtained: C ± 0.28, H ± 0.16, S ± 0.36.
[c] The compounds showed the expected ^1H NMR data for the $CO_2CH_2CH_3$ group.
[d] The products showed the signal corresponding to CO_2CH_3.
[e] No noticeable quantity of the product could be isolated.

The cyclic β-keto esters **1** were prepared according to known methods: 2-ethoxycarbonylcycloheptanone (**2a**),[9] 2-ethoxycarbonylcyclooctanone (**2b**),[9] 2-methoxycarbonyl-5-methylcyclopentanone (**2c**),[10,11] 2-methoxycarbonyl-6-methylcyclohexanone (**2d**),[9,12] 3-methoxycarbonyltetrahydro-1,4-thiapyrone (**2f**),[13], 2-ethoxycarbonyltetrahydro-1,3-thiapyrone (**2g**),[14] 4-ethoxycarbonyl-1,3-dithiacyclohexan-5-one (**2h**),[15] 3-oxo-2-methoxycarbonyltetrahydrothiophene (**2i**)[16] and 3-oxo-4-methoxycarbonyltetrahydrothiophene (**2j**).[16]

The new compound 2-ethoxycarbonyl-4-methylcyclohexanone (**2e**) was obtained from 4-methylcyclohexanone by the same procedure used for the synthesis of **2d**;[9] yield: 60%; bp 124–126°C/14 Torr.

2e:

$C_{10}H_{16}O_3$ (180.1) calc. C 65.24 H 8.69
found 65.09 8.78

IR (film): ν = 1740, 1710, 1650, 1610 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.80–0.98 (m, 3H, CH_3), 1.22 (t, 3H, J = 5.9 Hz, (OCH_2CH_3)), 1.65–1.90 (m, 8H, ring CH_2 + CH), 4.15 (q, 2H, J = 5.9 Hz, OCH_2).

[*b*]-Condensed Alkyl 3-Hydroxythiophene-2-carboxylates 5; General Procedures:

Method A: A mixture of the β-oxo ester **1a–h**, (0.1 mol) and freshly distilled thioglycolic acid (0.2 mol) was cooled at −10°C and a stream of HCl gas was bubbled into the system for 1 h. The organic phase was extracted with CH_2Cl_2 (200 mL), washed with water (200 mL) and dried (Na_2SO_4). The solvent was evaporated and the product **2a–h** thus obtained was dissolved in absolute alcohol (1 mol) and a stream of gaseous HCl was bubbled until turbidity. The mixture was left at r.t. until separation of two phases (≃ 90 h) which were decanted. The alcohol and HCl were removed from the organic layer by distillation. The residue was extracted with CH_2Cl_2 and the extract washed with water and dried (Na_2SO_4). The solvent was evaporated and the crude product **3** used in the following reaction.

Compound **3** (0.1 mol) was added to a 2 N KOH/alcoholic solution (175 mL). The mixture was stirred for 1 h at r.t. and the solvent evaporated. Cold water (175 mL) was added and the mixture acidified with 2 N HCl. The organic product was extracted with Et_2O (175 mL), washed with water and dried (Na_2SO_4). The final product **5a–h** was purified by recrystallization from an appropriate solvent (Table).

Method B: A solution of the β-oxo ester **1a–j** (0.1 mmol) in absolute EtOH (500 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 4 h. The mixture was left at r.t. for 90 h. The solvent was evaporated at reduced pressure and the residue neutralized with 5% $NaHCO_3$ solution, and extracted with Et_2O (200 mL). The organic phase was separated, washed with water (200 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was directly used in the next step.

To the above crude product was added a 2 N solution of the corresponding sodium alkoxide in the corresponding alcohol (175 mL) and kept under N_2 for 24 h. The solvent was evaporated at reduced pressure and the residue treated with ice-cold water (175 mL). The mixture was acidified with ice-cold 2 N HCl until pH = 1. Et_2O (175 mL) was added and the organic layer separated, washed with water (175 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product **5** chromatographed on a silica gel

column (45 × 10 cm, 230–240 mesh) using hexane/EtOAc (10:1) as eluent. The final products **5a–j** were purified by crystallization from an appropriate solvent (Table).

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