

Claisen condensation of dimethyl 2,3-thiophenedicarboxylate with methyl acetate and acetonitrile

M. STRUHÁRIK and P. HRNČIAR

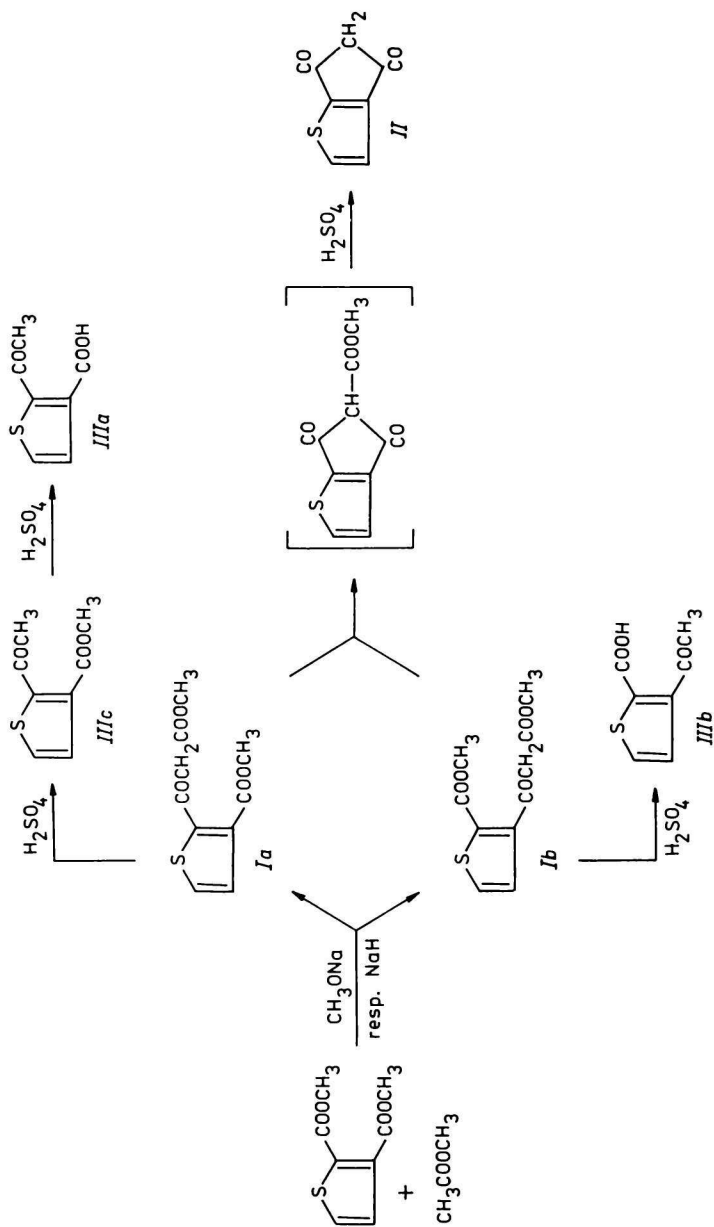
*Department of Organic Chemistry, Faculty of Natural Sciences,
Komenský University, CS-842 15 Bratislava*

Received 17 January 1984

Claisen condensation of dimethyl 2,3-thiophenedicarboxylate with methyl acetate has been carried out. It was found that practically only the first step of the reaction proceeded on the carbon of the methoxycarbonyl group in the position 2 of the thiophene ring, while 4,5-dihydro-6*H*-cyclopenta[*b*]thiophene-4,6-dione (*II*) was formed only in a low yield. Higher yields of β -diketone (*II*) were not achieved by changing the reaction conditions. Also the reaction with acetonitrile proceeded on the carbon of the methoxycarbonyl group in the position 2 of the thiophene ring and the cyclic product has not been isolated. The compounds obtained were characterized by their IR, ^1H NMR, and ^{13}C NMR spectra.

Проведена конденсация по Клайзену диметил-2,3-тиофендикарбоксилата с метилацетатом. Обнаружено, что практически только первая стадия реакции проходит по атому углерода метоксикарбонильной группы в положении 2 тиофенового кольца, в то время как 4,5-дигидро-6*H*-циклопента[*b*]тиофен-4,6-дион (*II*) образовывался лишь с малым выходом. Более высокие выходы β -дикетона (*II*) не удалось достичь и при изменении реакционных условий. Аналогично и реакция с ацетонитрилом проходила по углероду метоксикарбонильной группы в положении 2 тиофенового кольца и циклический продукт не был выделен. Полученные соединения были охарактеризованы своими ИК, ^1H ЯМР и ^{13}C ЯМР спектрами.

It is known that 1,3-indandione can be prepared by Claisen condensation of diester of phthalic acid with ethyl acetate under catalysis of sodium ethoxide [1]. Aiming to prepare the thiophene analogue of 1,3-indandione, i.e. 4,5-dihydro-6*H*-cyclopenta[*b*]thiophene-4,6-dione (*II*) in a similar way, we carried out the Claisen condensation of dimethyl 2,3-thiophenedicarboxylate with methyl acetate. The reaction conditions were the same as in the preparation of 1,3-indandione from diethyl phthalate and ethyl acetate catalyzed with sodium ethoxide [2] or the reaction was performed in benzene and tetrahydrofuran under catalysis of sodium hydride. We have found that the reaction of dimethyl 2,3-thiophenedicarboxylate with methyl acetate did not result in β -diketone *II* unambiguously as in the



Scheme 1

reaction of diethyl phthalate with ethyl acetate, where 1,3-indandione was formed in 70 % yield. Therefore, after acidification with sulfuric acid the reaction products were chromatographically separated and identified by IR, ^1H NMR, and ^{13}C NMR spectra as well as by elemental analysis.

Analysis of the products revealed that, practically, only the first step of the reaction proceeded and the main product of the reaction was methyl 3-(3-methoxycarbonyl-2-thienyl)-3-oxopropanoate (*Ia*) (Scheme 1). In addition to this compound we have isolated from the reaction mixture 4,5-dihydro-6*H*-cyclopenta[*b*]-thiophene-4,6-dione (*II*), a condensation product of *Ia* and methyl 3-(2-methoxycarbonyl-3-thienyl)-3-oxopropanoate (*Ib*), respectively, as well as 2-acetyl-3-thiophenecarboxylic acid (*IIIa*) and 3-acetyl-2-thiophenecarboxylic acid (*IIIb*), which were formed by hydrolysis and decarboxylation of *Ia* and *Ib*. The compounds *IIIa* and *IIIb*, known from the literature [3], helped to assign the structures of positional isomers *Ia* and *Ib*, because *IIIa* was obtained by ketone-forming cleavage with 40 % sulfuric acid from *Ia* and isolation of *IIIb*, though in a trace amount, gave evidence about the presence of the isomer *Ib* in the reaction mixture. Isolation of the compound *IIIc* indicated that hydrolysis of the ester group of the β -keto ester grouping in *Ia* proceeded more readily than that of the other ester group, while the ratio of *Ia*/*IIIc* depended on the conditions of acidification of the reaction mixture.

In order to obtain β -diketone *II* in higher yields, we changed the reaction conditions (reaction time, temperature, amount of the catalyst). Besides, the reaction was performed in benzene and tetrahydrofuran under catalysis of NaH. The results of these reactions are reviewed in Table 1. To elevate the reaction temperature and thus the yield of β -diketone *II*, we accomplished the Claisen condensation of dimethyl 2,3-thiophenedicarboxylate also with ethyl acetate (at 80 °C) and phenyl acetate (at 120 °C). The increased temperature did not lead to increased yield of β -diketone *II*.

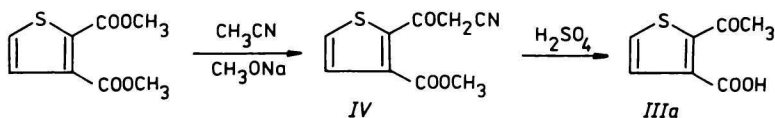
We attempted to prepare β -diketone *II* also from the product of the first step of the reaction, i.e. from the compound *Ia*. We carried out the Dieckmann condensation of the compound *Ia* in benzene under catalysis of NaH. The β -diketone *II* was isolated in 15 % yield and methyl 2-acetyl-3-thiophenecarboxylate, formed by partial hydrolysis and subsequent decarboxylation of the compound *Ia*, in 60 % yield. On the other hand, Dieckmann condensation of the compound *IIIc* (obtained by hydrolysis and subsequent esterification of *Ia*), carried out in boiling xylene under catalysis of potassium triphenylmethanide, has not afforded any β -diketone *II* and the starting keto ester has not been obtained either. In this reaction several compounds were formed in low yields, therefore, we have not dealt with their further identification.

Further we carried out Claisen condensation of dimethyl 2,3-thiophenedicarboxylate with acetonitrile (Scheme 2) where 3-(3-methoxycarbonyl-2-thienyl)-3-

Table 1

Review of experimental results

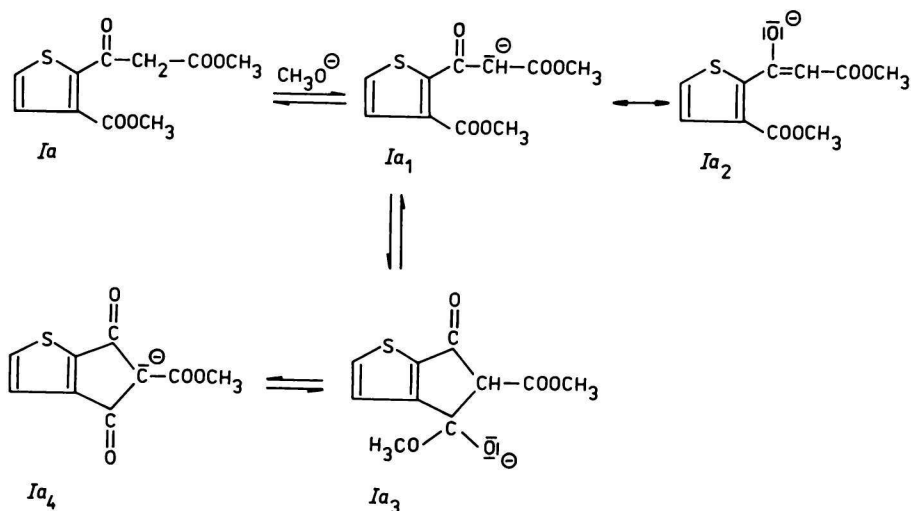
Catalyst	Medium	Temperature/°C	Reaction time/h	Yield/%					
				<i>II</i>	<i>Ia</i>	<i>Ib</i>	<i>IIIa</i>	<i>IIIb</i>	<i>IIIc</i>
CH ₃ ONa	CH ₃ COOCH ₃	40—50	20	9	54	0	3	1	0
CH ₃ ONa	CH ₃ COOCH ₃	20—30	40	2	71	0	3	1	0
NaH	C ₆ H ₆	20	20	10	30	0	8	4	5
NaH	THF	20	20	10	28	0	10	2	6



Scheme 2

-oxopropanenitrile (IV) was isolated in 55 % yield as the first-step reaction product. Its structure was proved by hydrolysis and decarboxylation in 30 % H_2SO_4 at 140°C during 12 h, when 2-acetyl-3-thiophenecarboxylic acid (IIIa) was formed in high yield. The desired cyclic product from the second step of the reaction has not been isolated. The reaction with acetonitrile proceeded selectively on the carbon of the methoxycarbonyl group in the position 2 of the thiophene ring similarly as in the case of methyl acetate.

The reaction between dimethyl 2,3-thiophenedicarboxylate and ester of acetic acid stops in the first step giving the ester Ia, though this has more acid hydrogens in the position 2 than the ester of acetic acid and forms the anion faster (Ia_1 , Ia_2 , Scheme 3). Consequently, the reaction should proceed further on similarly as in the case of diethyl phthalate. The explanation why it is not so lies in that the anion Ia_3 is formed rather difficultly due to geometrical reasons. The anion Ia_3 , which is unstable, turns to Ia_1 and only a small part to Ia_4 which gives the compound II on acidification (Scheme 3). The second reason may be in that the negative charge is more shifted towards the oxygen (structure Ia_2 , Scheme 3). We take the first reason for a more probable one.



Scheme 3

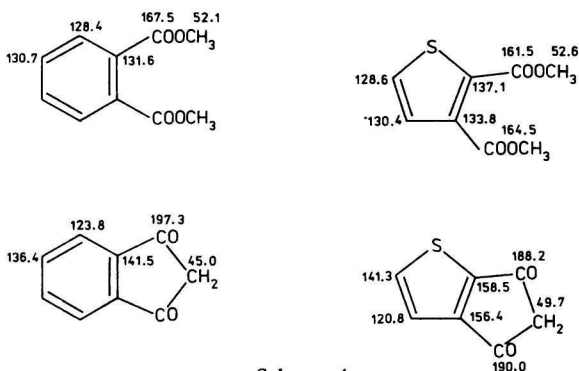
It follows from the ^1H NMR, ^{13}C NMR, and IR spectra that 4,5-dihydro-6*H*-cyclopenta[*b*]thiophene-4,6-dione (*II*) occurs in CCl_4 , CHCl_3 , and pyridine in the dioxo form only. 1,3-Indandione and other cyclic β -dicarbonyl compounds occurring in dioxo forms exhibit two absorption bands in the region of basic stretching vibrations. The more intensive one at lower wavenumbers belongs to asymmetric vibration and the weaker one at higher wavenumbers to symmetric vibrations of the coupled 1,3-dicarbonyl system. In comparison to 1,3-indandione, the positions of the ν_s and ν_{as} absorption bands were observed at lower wavenumbers with *II* (for 1,3-indandione $\tilde{\nu}_{as} = 1723\text{ cm}^{-1}$, $\tilde{\nu}_s = 1756\text{ cm}^{-1}$; for 4,5-dihydro-6*H*-cyclopenta[*b*]thiophene-4,6-dione $\tilde{\nu}_{as} = 1713\text{ cm}^{-1}$ and $\tilde{\nu}_s = 1747\text{ cm}^{-1}$). The difference between the wavenumbers of symmetric and asymmetric stretching vibrations $\Delta\tilde{\nu} = \tilde{\nu}_s - \tilde{\nu}_{as}$ was in the case *II* (34 cm^{-1}) only by 1 cm^{-1} bigger than in the case of 1,3-indandione (33 cm^{-1}). According to the observations of Fayat and Foucaud [4] the $\Delta\tilde{\nu}$ values can be taken for the measure of degree of vibration coupling and, in the first approximation, they depend on the magnitude of the angle between the two vibrating C=O bonds in the cyclic system. The $\Delta\tilde{\nu}$ values obtained indicate that this angle is approximately the same with both 1,3-indandione and β -diketone *II*. This is interesting because the other angles between the atoms of the fused β -dicarbonyl system will be evidently different with regard to transition from six-membered to five-membered aromatic ring. The geometry of the compound *II* will be studied later.

The ^1H NMR spectrum of β -diketone *II* revealed a singlet of hydrogens of the methylene group at $\delta = 3.45\text{ ppm}$ contrary to 1,3-indandione at $\delta = 3.23\text{ ppm}$. The doublet at $\delta = 7.96\text{ ppm}$ was assigned to hydrogen attached to carbon in the position 2 and that at $\delta = 7.37\text{ ppm}$ in the position 3 of the thiophene skeleton.

The ^1H NMR spectrum of methyl 3-(3-methoxycarbonyl-2-thienyl)-3-oxopropanoate (*Ia*) showed that this compound occurred in keto-enol equilibrium, while the ratio of keto and enol forms depended on polarity of the solvent (in CDCl_3 19 % enol form, in CCl_4 13 % enol form).

The ^1H NMR spectrum of methyl 2-acetyl-3-thiophenecarboxylate (*IIIc*) proved that this compound occurred exclusively in the keto form, contrary to the compound *Ia*.

It followed from the ^{13}C NMR spectral measurements that the signal belonging to the carbon of the methylene group appeared at higher δ (49.7 ppm) than the corresponding one in 1,3-indandione ($\delta = 45.0\text{ ppm}$). On the other hand, the carbons of the carbonyl groups in β -diketone *II* had the δ values lower (188.2 ppm , 190.0 ppm) than that in 1,3-indandione ($\delta = 197.3\text{ ppm}$). For comparison we present the ^{13}C NMR spectra of the starting dimethyl ester of phthalic acid and 2,3-thiophenedicarboxylic acid (Scheme 4). It is evident from the values presented that the fused grouping $-\text{CO}-\text{CH}_2-\text{CO}-$, in comparison to two ester groups, affected the chemical shifts of carbons in the thiophene skeleton more



Scheme 4

significantly than in benzene skeleton, which points to larger electron-density transfer on carbons of the thiophene ring.

Experimental

The starting dimethyl 2,3-thiophenedicarboxylate was prepared according to the literature [5]. Infrared spectra of the synthesized compounds were recorded with a Specord 75 IR (Zeiss, Jena) spectrophotometer calibrated with polystyrene foil; the measuring accuracy was $\pm 1 \text{ cm}^{-1}$. ^1H NMR spectra were measured with a Tesla 487 apparatus at the working frequency 80 MHz. ^{13}C NMR spectra were taken on a Jeol FX-100 spectrometer with working frequency 25 MHz.

A. Claisen condensation of dimethyl 2,3-thiophenedicarboxylate with methyl acetate catalyzed with sodium methoxide

Sodium (0.92 g; 0.040 mol) was powdered by a stirrer in boiling xylene (20 cm^3). After cooling xylene was poured off, sodium was washed with a small amount of dry diethyl ether and dimethyl 2,3-thiophenedicarboxylate (4.00 g; 0.020 mol) was added immediately. The mixture was heated to 40 $^\circ\text{C}$ and dry methyl acetate (7 cm^3) with two drops of absolute methanol was added under stirring during 60 min. The reaction mixture was then stirred under reflux (oil bath 50–60 $^\circ\text{C}$) for 20 h, while another methyl acetate (30 cm^3) was added gradually so that the formed paste became homogeneous. Then methyl acetate was evaporated directly in the reaction vessel and the yellow salt was dissolved in water (50 cm^3) at 70 $^\circ\text{C}$. Then 70 % H_2SO_4 (4 cm^3) was added dropwise and the mixture was heated at 70 $^\circ\text{C}$ for 5 min. After cooling the reaction mixture was extracted with CHCl_3 (3 \times 20 cm^3), the combined extracts were dried with anhydrous Na_2SO_4 , chloroform was evaporated, and the residue (yellow-brown oil) was fractionated on silica gel (L 100/250) using benzene–ethyl acetate (volume ratio = 10:1) as the eluant.

The yield of methyl 3-(3-methoxycarbonyl-2-thienyl)-3-oxopropanoate (*Ia*) was 2.60 g (54 %), yellow oil $n(\text{D}, 20^\circ\text{C}) = 1.5496$. For $\text{C}_{10}\text{H}_{10}\text{O}_5\text{S}$ ($M_r = 242.17$) w_i (calculated):

49.59 % C, 4.13 % H, 13.22 % S; $w_i(\text{found})$: 49.08 % C, 3.96 % H, 13.50 % S. $^1\text{H NMR}$ (CDCl_3 , TMS) δ/ppm : keto 3.73 (s, 3H, 2- CH_3), 3.90 (s, 3H, 3- CH_3), 4.10 (s, 2H, CH_2), 7.40 (d, 1H), 7.54 (d, 1H), enol 3.78 (s, 3H, 2- CH_3), 3.90 (s, 3H, 3- CH_3), 4.03 (s, 1H, CH), 7.21 (d, 1H), 7.44 (d, 1H), 12.37 (s, 1H, OH); keto/enol = 13/3. $^1\text{H NMR}$ (CCl_4 , TMS) δ/ppm : keto 3.65 (s, 3H, 2- CH_3), 3.87 (s, 3H, 3- CH_3), 3.98 (s, 2H, CH_2), 7.34 (d, 1H), 7.46 (d, 1H), enol 3.76 (s, 3H, 2- CH_3), 3.87 (s, 3H, 3- CH_3), 3.91 (s, 1H, CH), 7.16 (d, 1H), 7.39 (d, 1H), 12.39 (s, 1H, OH); keto/enol = 7/1. IR (CCl_4) $\tilde{\nu}/\text{cm}^{-1}$: 1744, 1727, 1665 $\nu(\text{C=O})$, 1654 $\nu(\text{C=C})$.

The second fraction isolated ($R_f \sim 0.4$) in 0.28 g (9 %) yield was 4,5-dihydro-6*H*-cyclopenta[*b*]thiophene-4,6-dione, white needles (crystallization from CCl_4), m.p. = 13° °C. For $\text{C}_7\text{H}_4\text{O}_2\text{S}$ ($M_r = 152.12$) $w_i(\text{calculated})$: 55.26 % C, 2.63 % H, 21.05 % S; $w_i(\text{found})$: 55.21 % C, 2.57 % H, 21.21 % S. $^1\text{H NMR}$ (CDCl_3 , TMS) δ/ppm : 3.45 (s, 2H, CH_2), 7.37 (d, 1H), 7.96 (d, 1H). $^1\text{H NMR}$ (pyridine, HDMSO) δ/ppm : 3.44 (s, 2H, CH_2), 7.17 (d, 1H), 7.92 (d, 1H). IR (CCl_4) $\tilde{\nu}/\text{cm}^{-1}$: 1747 $\nu(\text{C=O})$, 1713 $\nu(\text{C=O})_{\text{as}}$.

In trace amounts were also isolated 2-acetyl-3-thiophenecarboxylic acid (*IIIa*) and 3-acetyl-2-thiophenecarboxylic acid (*IIIb*).

When changing the reaction temperature to 20 °C during addition of methyl acetate and to 30 °C during further 40 h, after acidification 3.48 g (71 %) *Ia* and 0.07 g (2 %) *II* were isolated.

B. Claisen condensation of dimethyl 2,3-thiophenedicarboxylate with methyl acetate catalyzed with sodium hydride

a) provided in benzene

To the suspension of NaH (0.24 g; 0.010 mol) in absolute benzene (4 cm^3), prepared in the atmosphere of nitrogen, the mixture of dimethyl 2,3-thiophenedicarboxylate (1.00 g; 0.005 mol), absolute benzene (4 cm^3), methyl acetate (2 cm^3), and absolute DMSO (1 cm^3) was added dropwise at room temperature. The mixture was shortly heated to reflux and stirred at room temperature for 20 h. Then benzene and methyl acetate were distilled off, the residue was dissolved in water (10 cm^3) at 70 °C, 70 % H_2SO_4 (2 cm^3) was added dropwise and it was stirred at 70 °C for 5 min. After cooling the reaction mixture was extracted with CHCl_3 (3 \times 10 cm^3), the combined extracts were washed with water (2 \times 10 cm^3), dried with anhydrous Na_2SO_4 , chloroform was distilled off and the residue was fractionated chromatographically (see A). Yield of *Ia* 0.36 g (30 %), *II* 0.08 g (10 %).

b) provided in tetrahydrofuran

To the suspension of NaH (0.24 g; 0.010 mol) in absolute THF (18 cm^3), prepared in the atmosphere of nitrogen, dimethyl 2,3-thiophenedicarboxylate (1.00 g; 0.005 mol) was added and then absolute methyl acetate (3 cm^3) was added dropwise within 5 min. The mixture was stirred at room temperature for 20 h, then THF was distilled off and the residue was worked up similarly as described under *a*). Yield of *Ia* 0.34 g (28 %), *II* 0.07 g (10 %).

*C. Dieckmann condensation of methyl
3-(3-methoxycarbonyl-2-thienyl)-3-oxopropanoate (Ia)*

To the suspension of NaH (0.12 g; 0.005 mol) in absolute benzene (5 cm³), prepared in the atmosphere of nitrogen, the mixture of *Ia* (1.21 g; 0.005 mol), absolute benzene (12 cm³), absolute DMSO (1 cm³) was added dropwise with stirring at room temperature. After the addition was complete, the mixture was shortly heated to reflux and then stirred at room temperature for another 15 h. Benzene was distilled off and water (25 cm³) was added to the residue. After heating to 70 °C, 70 % H₂SO₄ (2 cm³) was added dropwise and the mixture was stirred at 80 °C for 15 min. After cooling the reaction mixture was extracted with CHCl₃ (3 × 10 cm³), the combined extracts were washed with water (2 × 10 cm³), dried with anhydrous Na₂SO₄, chloroform was distilled off and the residue was fractionated chromatographically (see A). Yield of *II* 0.11 g (15 %), *IIIc* 0.55 g (60 %).

D. Hydrolysis of methyl 3-(3-methoxycarbonyl-2-thienyl)-3-oxopropanoate (Ia)

To *Ia* (3.30 g; 0.0136 mol) 40 % H₂SO₄ (35 cm³) was added and heated under stirring at the temperature of the oil bath 110–115 °C for 3 h. After cooling the content of the flask including the formed crystals was poured off onto the filtration equipment (the compounds stuck to the bottom were isolated), sucked, dissolved in ether, dried with anhydrous Na₂SO₄ and crystallized from ether.

Yield of 2-acetyl-3-thiophenecarboxylic acid (*IIIa*) was 2.01 g (87 %), colourless crystals of m.p. = 108 °C. For C₈H₆O₃S (*M_r* = 170.11) *w_i*(calculated): 49.41 % C, 3.53 % H, 18.82 % S; *w_i*(found): 49.02 % C, 3.61 % H, 18.75 % S. ¹H NMR (CDCl₃, TMS) δ/ppm: 2.80 (s, 3H, CH₃), 7.69 (d, 1H), 7.95 (d, 1H).

E. Esterification of 2-acetyl-3-thiophenecarboxylic acid (IIIa)

The compound *IIIa* (1.40 g; 0.0082 mol) was dissolved in absolute methanol (30 cm³), *p*-toluenesulfonic acid (0.20 g) was added and refluxed for 16 h. Then methanol was evaporated to approximately 10 cm³, water (50 cm³) was added and the mixture was extracted with CHCl₃ (3 × 20 cm³). The combined extracts were washed with water (2 × 10 cm³), dried with anhydrous Na₂SO₄ and chloroform was distilled off. Yellow oil (1.60 g) was obtained and purified chromatographically on silica gel (L 100/250) using benzene as the eluant. The first fraction contained the pure product. The yield of methyl 2-acetyl-3-thiophenecarboxylate (*IIIc*) was 1.15 g (76 %), colourless oil, *n*(D, 20 °C) = 1.5481. For C₈H₈O₃S (*M_r* = 184.12) *w_i*(calculated): 52.17 % C, 4.34 % H, 17.39 % S; *w_i*(found): 52.25 % C, 4.29 % H, 17.85 % S. ¹H NMR (CDCl₃, TMS) δ/ppm: 2.61 (s, 3H, 2-CH₃), 3.92 (s, 3H, 3-CH₃), 7.33 (d, 1H), 7.46 (d, 1H). IR (CCl₄) $\bar{\nu}$ /cm⁻¹: 1729, 1687 ν (C=O).

F. Claisen condensation of dimethyl 2,3-thiophenedicarboxylate with acetonitrile

To powdered sodium (0.23 g; 0.010 mol) (see A) dimethyl 2,3-thiophenedicarboxylate (1.00 g; 0.005 mol) was added and then absolute acetonitrile (8 cm³) with a drop of dry methanol was added dropwise at the temperature of the oil bath (60 °C) during 30 min. The mixture was stirred under reflux for 20 h, then acetonitrile was distilled off, the yellow salt was dissolved in water (12 cm³) at 70 °C and concentrated HCl (3 cm³) was added dropwise. The mixture was extracted with CHCl₃ (3 × 10 cm³), the combined extracts were dried with anhydrous Na₂SO₄, chloroform was distilled off and the residue was fractionated on silica gel (L 100/250) using the mixture of benzene—ethyl acetate (volume ratio = 3 : 1) as the eluant. The first fraction contained 0.57 g (55 %) of 3-(3-methoxycarbonyl-2-thienyl)-3-oxopropenenitrile (IV) which was crystallized from the mixture of THF-petroleum ether; colourless crystals of m.p. = 101—102 °C. For C₉H₇O₃NS (*M_r* = 209.14) *w_i*(calculated): 51.67 % C, 3.35 % H, 15.31 % S; *w_i*(found): 52.08 % C, 3.31 % H, 15.72 % S. ¹H NMR ((CD₃)₂CO, HDMSO) δ/ppm: keto 3.87 (s, 3H, CH₃), 4.44 (s, 2H, CH₂), 7.42 (d, 1H), 7.85 (d, 1H), enol 3.95 (s, 3H, CH₃), 4.30 (s, 1H, CH), 7.37 (d, 1H), 7.67 (d, 1H); keto/enol = 21/4. IR (CHCl₃) $\tilde{\nu}$ /cm⁻¹: 1720, 1677 ν (C=O), 1630 ν (C=C), 2200 ν (C≡N).

References

1. Wislicenus, W., *Ber.* 20, 593 (1887).
2. Teeters, W. O. and Shriner, R. L., *J. Amer. Chem. Soc.* 55, 3027 (1933).
3. Pirson, P., Schonne, A., and Christiaens, L., *Bull. Soc. Chim. Belg.* 79, 575 (1970).
4. Fayat, C. and Foucaud, A., *Bull. Soc. Chim. Fr.* 1970, 4491.
5. Binder, D. and Stanetty, P., *Synthesis* 1977, 200.

Translated by A. Kardošová