

## The Synthesis of Thiophenes by the Spontaneous Cyclisation of Thionated $\gamma$ -Diketones

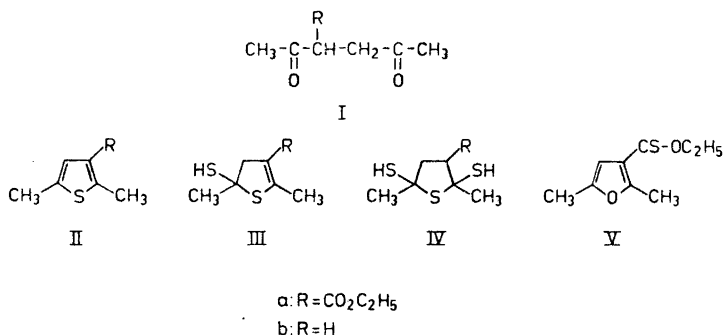
FRITZ DUUS\*

*Department of Chemistry, Aarhus University, 8000 Aarhus C, Denmark*

The acid catalysed reactions of some  $\gamma$ -diketones with  $H_2S$  at  $-35^\circ C$  are described. The spontaneous intramolecular cyclisation of the primarily formed intermediate enethiols leads to the formation of thiophenes, which were isolated as the main products. A similar cyclisation reaction of transiently formed *gem*-dithiols gives rise to the formation of 2-mercapto-2,3-dihydrothiophenes and 2,5-dimercaptotetrahydrothiophenes, which were isolated as by-products. The structures of the latter compounds are discussed on the basis of the NMR spectra.

In connection with the study of the thione-enethiol tautomerism of  $\beta$ -thio-ketoesters<sup>1</sup> several  $\alpha$ -substituted  $\beta$ -thio-ketoesters were prepared by the acid catalysed action of  $H_2S$  on the corresponding  $\beta$ -ketoesters at low temperatures ( $-60^\circ$  to  $-40^\circ C$ ).<sup>1</sup> Ethyl  $\alpha$ -acetylacetoacetate (Ia), when subjected to these reaction conditions, neither gave the related  $\beta$ -thio-ketoester, nor the related *gem*-dithiol.<sup>1</sup> Instead two cyclic compounds, IIa and IIIa, were isolated from the reaction mixture by preparative layer chromatography (PLC) in yields of 57 %, and 17 %, respectively. The thiophene IIa was not an unexpected product, as an early known synthetic route to thiophenes in fact is based on the thionation of  $\gamma$ -diketones, and the subsequent, spontaneous cyclisation of the thionated intermediate.<sup>2</sup> The thionation agents generally used are  $P_2S_3$ <sup>3</sup> and  $P_2S_5$ .<sup>4</sup> However, according to a recent paper,<sup>5</sup> the action of  $P_2S_5$  on Ia (and, generally, on  $\gamma$ -diketones containing an ester group as in Ia) does not lead to the formation of IIa, but rather to the furanoic thionoester V. Thus, the present ester group evidently promotes the enolization process to such a degree that cyclisation of Ia, through dehydration, occurs prior to thionation. The subsequent conversion of the furanoic ester to the corresponding thionoester is expected under the reaction conditions.<sup>5,6</sup>

\* Present address: Department of Chemistry, Odense University, Niels Bohrs Allé, 5000 Odense, Denmark.



Apparently, H<sub>2</sub>S has been used as thionation agent only in one case, in which acetylacetone (Ib) on treatment with H<sub>2</sub>S at 325°C in the catalytic presence of Al<sub>2</sub>O<sub>3</sub> was reported to give 2,5-dimethylthiophene (IIb) in a yield of 35 %.<sup>7</sup> Consequently, Ib was exposed to treatment with H<sub>2</sub>S in acid ethanol at a temperature < -35°C. From the crude reaction product mixture, pure IIb was isolated by simple distillation in a yield of 33 %. A higher boiling fraction contained the hitherto unknown di- and tetrahydrothiophenes IIIb and IVb, which were separated by PLC and isolated in yields of 3.3 % and 15 %, respectively. Thus, the hereby presented experimental method appears to represent a new, useful synthetic route to substituted thiophenes.

Obviously, the mercaptodihydrothiophenes IIIa and IIIb, and the dimercaptotetrahydrothiophene IVb are cyclisation products of intermediately formed *gem*-dithiols. The last named compounds are very often reaction products, when ketones are subjected to the actual reaction conditions and the enethiolisation process of the primarily formed thiones is not especially favourable, or impossible.<sup>1,8,9</sup> IIIa, IIIb, and IVb are all stable compounds which can be distilled at reduced pressure without detectable evolution of H<sub>2</sub>S. Moreover, no decomposition occurred when IIIa was kept in acidic ethanol solution at room temperature for 20 h. Reflux of IIIa in the same medium for 4 h resulted only in partial (27 %) conversion to IIa. Therefore, the possibility that the unsaturated heterocycles were formed by stepwise H<sub>2</sub>S elimination from the more saturated compounds within the same series (*i.e.* IV → III → II) under the reaction conditions seems most unlikely. Rather, the product distribution reflects the relative stability of the equilibrated, transient open-chain thiones and *gem*-dithiols. The complete absence of IVa among the reaction products is not surprising, as evidently in this special case H<sub>2</sub>S elimination is energetically favourable due to the emergence of a carbonyl-conjugated double bond.<sup>10</sup> Further, the successive formation of transient β-thioketo- and especially β,β-dimercaptoesters from Ia is very probably less prevalent due to the enforcing effect of the ester groups on competing enolisation and enethiolisation processes.

Presumably both of the two geometrical isomers of the compounds III were formed. They are, however, NMR-spectroscopically indistinguishable (Table 1). Possessing two chiral centers, IVb can occur in three stereo-isomeric forms of

Table 1.  $^1\text{H}$  NMR chemical shifts (ppm,  $\delta$ -values) and coupling constants (Hz, in brackets) of synthesised heterocyclic compounds. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).<sup>a</sup> Unless stated to the contrary, the solvent is  $\text{CS}_2$ .

	$\text{CH}_3-\overset{\textstyle  }{\underset{\textstyle  }{\text{C}}}-$	$-\text{SH}$	$-\text{CH}_2-$	$\text{CH}_3-\overset{\textstyle  }{\text{C}}=$	$-\text{CH}=\text{}$
IIa <sup>b</sup>				2.33 (dq) [1.1/0.5] 2.58 (qd) [0.5/0.25]	6.86 (qq) [1.1/0.25]
IIb				2.34 (m <sup>c</sup> )	6.34 (m <sup>c</sup> )
IIIa <sup>d</sup>	1.84 (d) [0.85]	2.74 (q) [0.85]	3.24 (qd <sup>e</sup> ) [1.8]	2.24 (t) [1.8]	
IIIb	1.83 (d) [0.9]	2.70 (q) [0.9]	2.90 (dq) [2.6/2.1]	1.90 (td) [2.1/1.6]	5.09 (tq) [2.6/1.6]
IVb	1.89 <sup>f</sup> (s) 1.77 <sup>g</sup> (d) [0.7]	2.51 <sup>f</sup> (s) 2.63 <sup>g</sup> (q) [0.7]	2.0–3.0 (m <sup>h</sup> )		
IVb <sup>i</sup>	1.72 <sup>f</sup> (s) 1.57 <sup>g</sup> (d) [0.7]	2.39 <sup>f</sup> (s) 2.57 <sup>g</sup> (q) [0.7]	1.8–2.8 (m <sup>h</sup> )		

<sup>a</sup> In combinations, the first mentioned multiplicity symbol refers to the greater coupling.

<sup>b</sup> Ester group protons: 4.15 (q), and 1.28 (t),  $J = 7$  Hz.

<sup>c</sup> The multiplicity of the sharp signal is observable only on the 50 Hz scale, and cannot be further specified without a better resolution.

<sup>d</sup> Ester group protons: 4.06 (q), and 1.24 (t),  $J = 7$  Hz.

<sup>e</sup> The doublet reflects the magnetical non-equivalence of the methylene protons (separation  $\sim 6$  Hz).

<sup>f</sup> Form A $\equiv$ D,L-form.

<sup>g</sup> Form B $\equiv$ meso-forms.

<sup>h</sup> Two overlapping AA'BB' patterns.

<sup>i</sup> Solvent:  $\text{C}_6\text{D}_6$ .

which the D- and L-forms can be expected to be mutually indistinguishable (by NMR), but distinguishable from the meso-form. In fact, the NMR spectrum of IVb shows two distinct methyl signals as well as two mercapto-proton signals. The individual affiliations of the former signals to exclusively one or the other of the latter was unambiguously manifested from the signal intensities and existing couplings (Table 1). Although the mercapto-proton signals appear within the complex region of the two overlapping AA'BB' patterns of the methylene protons, they are nevertheless easily extracted due to the characteristic low-field displacements, which occur on replacing the solvent  $\text{CS}_2$  by  $\text{CD}_3\text{CN}$ . It is evident that the D,L-forms possess a dipole moment vector different from that of the meso-form. According to Ledaal,<sup>11</sup> the preferred or

“average” shape of the collision complex of a solute molecule and a solvent benzene molecule is determined by the alignment of the six-fold symmetry axis of the benzene molecule and the “averted” dipole moment vector of the solute molecule. In a magnetic field, the solute molecule will be exposed to the diamagnetic anisotropy associated with the induced ring currents in the benzene molecule, and shielding (or deshielding) of the solute protons will occur. Based on  $C_6D_6$ -induced NMR solvent shifts ( $\Delta\delta_{CH_3}$  (A) = +0.17,  $\Delta\delta_{SH}$  (A) = +0.12,  $\Delta\delta_{CH_3}$  (B) = +0.20,  $\Delta\delta_{SH}$  (B) = +0.06 ppm; + denotes upfield shift), the A- and B-form signals (Table 1) are tentatively assigned to the D,L- and the meso-form, respectively.

### EXPERIMENTAL

$^1H$  NMR spectra of 20 % (vol.) solutions were recorded at 60 MHz on a Varian A-60 spectrometer at  $37 \pm 2^\circ C$ . TMS was used as internal reference standard. Coupling constants were measured on the 50 Hz scale.

IR spectra were recorded as 5 % solutions in  $CCl_4$  on a Beckman IR 18 spectrophotometer.

PLC was carried out on  $20 \times 40$  cm glass sheets with a 3 mm coating of Kieselgel PF <sup>254-1-366</sup> (Merck). Elution was performed with a mixture of ether and light petroleum (1:19). Boiling points are uncorrected. Yields refer to the isolated, pure products. Elemental analyses were carried out on the microanalytical laboratory of Løvens Kemiske Fabrik, Ballerup, Denmark.

*2,5-Dimethyl-3-ethoxycarbonylthiophene (IIa)*, and *2,5-dimethyl-2-mercapto-4-ethoxy-carbonyl-2,3-dihydrothiophene (IIIa)*: 18.6 g (0.1 mol) of ethyl  $\alpha$ -acetylacetoacetate (Ia) were dissolved in 225 ml of 99 % ethanol, and the solution was cooled to  $-50^\circ C$ .  $H_2S$  gas was passed through the solution for 1 h, followed by dry HCl gas also for 1 h, during which the temperature of the solution raised to  $-35^\circ C$ . Finally,  $H_2S$  gas was passed through the solution at the latter temperature for additionally  $3\frac{1}{2}$  h. The reaction mixture was poured into a mixture of light petroleum (200 ml) and ice-water (400 ml) with manual stirring. The layers were separated, and the organic layer was washed with water, and dried ( $CaSO_4$ ). After removed of light petroleum, the remaining oil (17.8 g) was subjected to PLC (13 sheets, 3 elutions). Two bands appeared. The combined 13 upper bands ( $R_F'' = 0.68$ ) gave, after extraction with ether and subsequent evaporation of the latter, 10.5 g (57 %) of pure IIa, b.p.<sub>12</sub>  $115^\circ$ ,  $n_D^{25}$  1.5128 (lit.<sup>12</sup> b.p.<sub>8</sub>  $106-109^\circ$ ,  $n_D^{20.5}$  1.5142); IR,  $\nu[C=O]$ :  $1715\text{ cm}^{-1}$  (s);  $\nu[C=C]$ :  $1560\text{ cm}^{-1}$  (m),  $1500\text{ cm}^{-1}$  (m). (Found: C 58.72; H 6.57; S 16.82. Calc. for  $C_9H_{12}O_2S$ : C 58.69; H 6.57; S 17.38.)

Similarly, the 13 lower bands [ $R_F'' = 0.47$ ] gave 3.7 g (17 %) of pure IIIa, b.p.<sub>0.17</sub>  $82^\circ$ ,  $n_D^{25}$  1.5451; IR,  $\nu[S-H]$ :  $2550\text{ cm}^{-1}$  (w),  $\nu[C=O]$ :  $1710\text{ cm}^{-1}$  (s);  $\nu[C=C]$ :  $1651\text{ cm}^{-1}$  (s). (Found: C 50.00; H 6.51; S 28.79. Calc. for  $C_9H_{14}O_2S_2$ : C 49.54; H 6.47; S 29.33.)

*2,5-Dimethylthiophene (IIb)*, *2,5-dimethyl-2-mercapto-2,3-dihydrothiophene (IIIb)*, and *2,5-dimethyl-2,5-dimercaptotetrahydrothiophene (IVb)*: 17.1 g (0.15 mol) of acetylacetone were dissolved in 250 ml of 99 % ethanol, and treated with  $H_2S$  and HCl as described above (second  $H_2S$ -supply:  $2\frac{1}{2}$  h). Otherwise following the work-up procedure described above, 14.8 g of a colourless oil were obtained after the removal of light petroleum. Distillation through a Vigreux-column gave three fractions:

(1)  $32-38^\circ/12\text{ mmHg}$ , (2)  $38-110^\circ/12\text{ mmHg}$ , and (3)  $110-112^\circ/12\text{ mmHg}$ .

Redistillation of the first fraction gave 5.7 g (33 %) of pure IIb, b.p.  $138^\circ$ ,  $n_D^{25}$  1.5103 (lit.<sup>3</sup> b.p.  $135.5-136^\circ$ ,  $n_D^{19}$  1.51418).

The second fraction ( $\sim 0.5$  g) contained mainly IIb, but was not further characterized.

The third fraction (8.2 g) was subjected to PLC (8 sheets, one elution). The combined bands ( $R_F = 0.65$ ) gave 730 mg (3.3 %) of pure IIIb, b.p.<sub>0.6</sub>  $34-36^\circ$ ; IR,  $\nu[S-H]$ :  $2545\text{ cm}^{-1}$  (w),  $\nu[C=C]$ :  $1640\text{ cm}^{-1}$  (m). (Found: C 49.18; H 6.91; S 43.51. Calc. for  $C_9H_{10}S_2$ : C 49.31; H 6.90; S 43.79.)

The combined bands ( $R_F = 0.45$ ) gave 4.1 g (15 %) of pure IVb, b.p.<sub>0.6</sub>  $69^\circ$ ,  $n_D^{25}$  1.5690; IR,  $\nu[S-H]$ :  $2540\text{ cm}^{-1}$  (m). (Found: C 40.13; H 6.83; S 52.84. Calc. for  $C_8H_{12}S_3$ : C 40.00; H 6.71; S 53.29.)

*Attempted elimination of H<sub>2</sub>S from IIIa.* 1.2 g of IIIa was dissolved in 20 ml of 0.5 N ethanolic HCl, and the solution was refluxed for 4 h. After cooling, the solvent was evaporated, and the remaining oil (0.97 g) was examined by NMR. The spectrum showed the presence of only IIa and IIIa, in percentages of 27, and 73, respectively (calculated from signal integrals).

## REFERENCES

1. Duus, F. *Tetrahedron* **28** (1972) 5923.
2. Paal, C. *Ber.* **18** (1886) 551.
3. Buu-Hoi, N. P. and Nguyen-Hoan. *Rec. Trav. Chim.* **67** (1948) 309.
4. Farrar, M. W. and Levine, R. *J. Am. Chem. Soc.* **72** (1950) 4433.
5. Trebaul, C. and Teste, J. *Bull. Soc. Chim. France* **1970** 2272.
6. Trebaul, C. *Bull. Chim. France* **1971** 1102.
7. Yur'ev, Yu. K. and Makarov, N. V. *Zh. Obshch. Khim.* **28** (1958) 885.
8. Demuynck, M. and Vialle, J. *Bull. Soc. Chim. France* **1967** 1213.
9. Bleisch, S. and Mayer, R. *Chem. Ber.* **100** (1967) 93.
10. Duus, F. and Lawesson, S.-O. *Tetrahedron* **27** (1971) 387.
11. Ledaal, T. *Tetrahedron Letters* **1968** 1683.
12. Schulte, K. E., Reisch, J. and Bergenthal, D. *Chem. Ber.* **101** (1968) 1540.

Received July 15, 1972.