Studies in sulfur heterocycles. Part 15.[1] Condensed heterocycles derived from thieno[2,3-*c*]- and thieno[3,2-*c*]-thiopyrans

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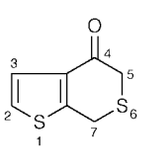
Several tricyclic compounds obtained by annelation of five- and six-membered nitrogen heterocycles onto thieno-[2,3-*c*]- and thieno[3,2-*c*]-thiopyran are reported. New expedient syntheses of 7*H*-thieno[2,3-*c*]thiopyran-4(5*H*)-one and 4*H*-thieno[3,2-*c*]thiopyran-7(6*H*)-one are also reported.

In the earlier papers of this series[1] a number of tricyclic compounds consisting of five- or six-membered heterocycles annelated to benzo[*b*]thiophene were reported. We report herein the synthesis of compounds in which the heterocycles are annelated to thieno[2,3-*c*]- and thieno[3,2-*c*]-thiopyrans. These compounds, structurally similar to the compounds reported earlier in this series, the benzene ring being replaced by a thiopyran moiety, are interesting as they have a core system which is an analogue of biologically active 1*H*-2-benzothiopyran[2] and of compounds in which the benzene ring of the latter is replaced by other heterocycles.[3] Polycyclic compounds obtained by annelating indole or quinoline to 1*H*-2-benzothiopyran have been reported[4] and linear tricyclic compounds obtained by annelation of a pyrimidine ring onto thieno[3,2-*c*]thiopyran have shown antibacterial and antiparasitic activities.[5] Being novel π-systems, thieno[2,3-*c*]- and thieno[3,2-*c*]-thiopyrilium salts have been objects of theoretical studies[6] *e.g.* Hückel molecular orbital (HMO) calculation of electron densities, which were useful in the interpretation of ^{1}H NMR data of these compounds.

Results and discussion

The two key intermediates in these syntheses *viz.* 7*H*-thieno-[2,3-*c*]thiopyran-4(5*H*)-one (**1**) and 4*H*-thieno[3,2-*c*]thiopyran-7(6*H*)-one (**2**) were synthesized earlier[7] by cyclizing the corresponding 2-(2- or 3-thienylmethylsulfanyl)acetic acids (**3**).



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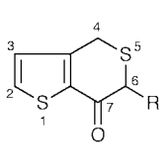
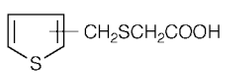


2 R = H



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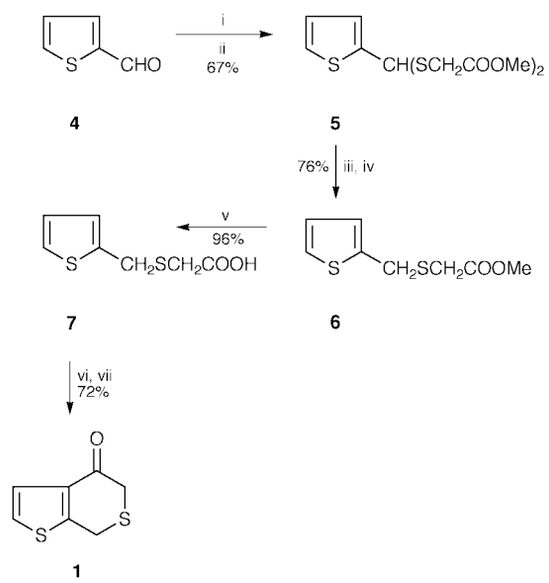
Difficult accessibility of the starting thiols and their instability necessitated the development of more expedient approaches to these compounds. A possible access to **2** from the corresponding β-oxo ester (see later), elegantly synthesized by Scrowston and Shaw,[8] was surprisingly not exploited. The use of unstable thiols in the preparation of the acids **3** was circumvented in the following way. The ketone **1** was synthesized from the easily available thiophene-2-carbaldehyde (**4**) in excellent overall yield (Scheme 1).



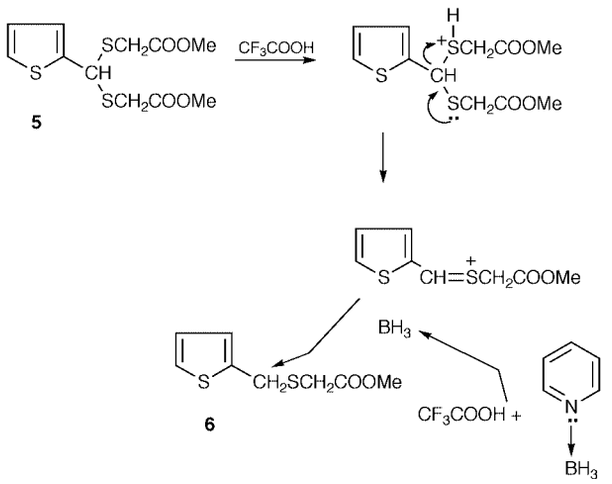
Scheme 1 *Reagents*: i) $HSCH_2COOMe$; ii) anhy. $AlCl_3$–CH_2Cl_2; iii) trifluoroacetic acid–CH_2Cl_2; iv) pyridine–borane; v) methanolic KOH; vi) $SOCl_2$–ether, vii) $SnCl_4$–CS_2.

Treatment of carbaldehyde **4** with methyl mercaptoacetate in dichloromethane in the presence of anhydrous aluminium chloride afforded 2-[bis(methylsulfanylacetyl)methyl]thiophene (**5**) in 67% yield. Selective removal of one of the acetal groups in the latter was achieved with pyridine–borane in the presence of trifluoroacetic acid, presumably according to the mechanism shown in Scheme 2.

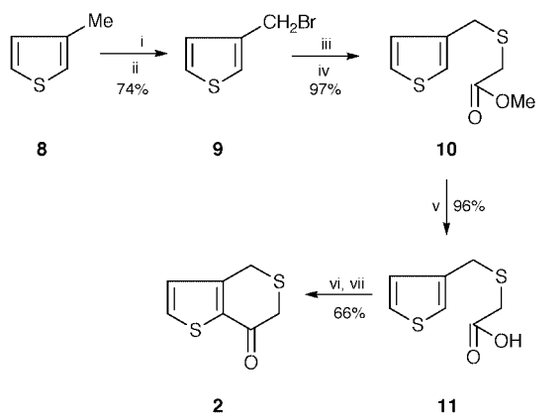
Hydrolysis of the ester group in **6** and the cyclization of the resulting acid **7** were carried out in the usual way.

The ketone **2** was synthesized from 3-methylthiophene (**8**) (Scheme 3) also in good overall yield. Side chain bromination of **8** proceeded in 74% yield to afford 3-bromomethylthiophene (**9**)[9] sufficiently pure for the next step. Treatment of **9** with methyl mercaptoacetate in the presence of sodium methoxide afforded methyl 2-(3-thienylmethylsulfanyl)acetate (**10**) in 97% yield. Hydrolysis of the ester function and cyclization of the resulting acid were accomplished in the usual way.

With the two ketones in hand, the desired tricyclic compounds were synthesized as described below. Advantage is taken of the highly acidic character of the methylene protons in

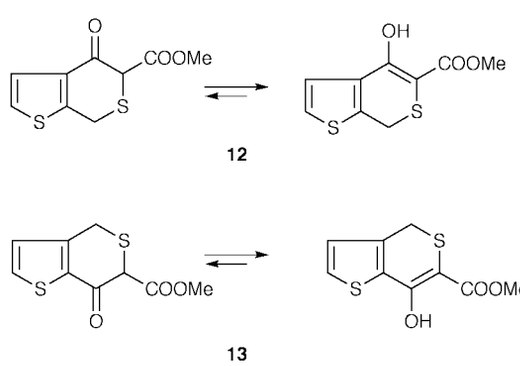


Scheme 2



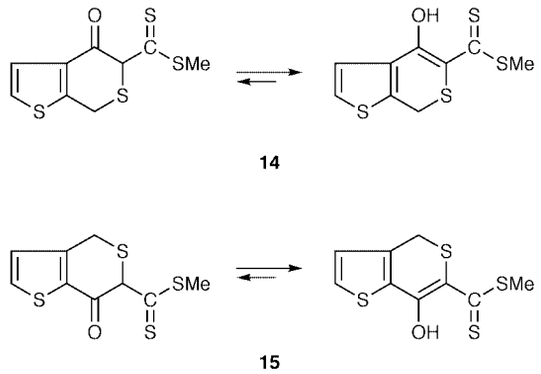
Scheme 3 *Reagents*: i) *N*-bromosuccinimide; ii) AIBN–CCl_4; iii) NaOMe–MeOH; iv) $HSCH_2COOMe$; v) methanolic KOH; vi) $SOCl_2$–ether; vii) $SnCl_4$–CS_2.

the 5- and 6-positions in the ketones **1** and **2**, as they are flanked by the carbonyl function and ring sulfur atom. The β-oxo esters **12** and **13** were obtained from **1** and **2** respectively upon treatment with dimethyl carbonate in the presence of oil-free sodium hydride in benzene. The β-oxo ester **12** exists entirely in

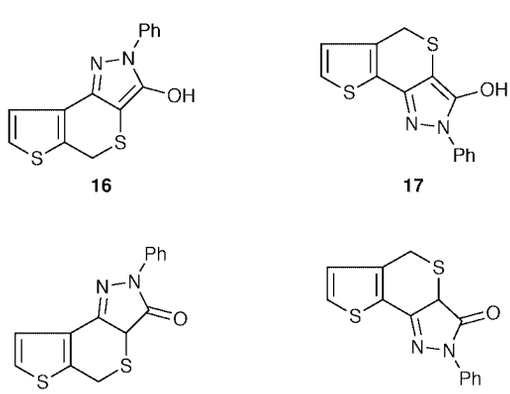


the enolic form in the solid phase. The IR spectrum (KBr disc) showed ν_{max} 3400 cm^{-1} (enolic OH) and no carbonyl absorption. In chloroform solution, **12** exists as a 1:1 mixture of the keto and the enol tautomers as inferred from the integral ratios of H-5 and enolic OH (δ 5.59 and 12.16) in the NMR spectrum, recorded as a $CDCl_3$ solution. Typically the signals due to H_2-7 in the keto and enol forms are present as an AB quartet centred at (δ 4.2 and 3.5, J 17.1 Hz) and a singlet respectively. Similar observations were made by others[8] with the β-oxo ester **13**.

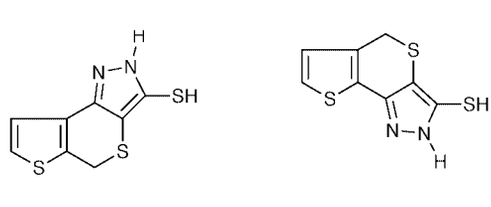
The ketones **1** and **2** also reacted with dimethyl trithiocarbonate in dry benzene in the presence of potassium *tert*-butoxide to give the β-oxo dithioesters **14** and **15**, which from spectroscopic evidence, exist mostly in the enolic form.



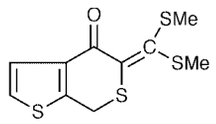
The β-oxo esters **12** and **13** reacted smoothly with phenylhydrazine in hot methanol to afford the tricyclic compounds 3-hydroxy-2-phenyl-2,5-dihydrothieno[3′,2′:4,5]thiopyrano-[3,2-*c*]pyrazole (**16**) and 3-hydroxy-2-phenyl-2,5-dihydrothieno-[2′,3′: 4,5]thiopyrano[3,2-*c*]pyrazole (**17**) in 75 and 74% yields respectively. While these compounds existed in the enolic forms as evident from the ^1H NMR (δ 7.98, enolic OH) and IR (no carbonyl absorption) data, it is interesting to note that the corresponding benzo analogues are reported[8] to exist entirely as the pyrazolone tautomer.



The β-oxo dithioesters **14** and **15** reacted with hydrazine hydrate in refluxing ethanol to afford the tricyclic compounds 3-mercapto-2,5-dihydrothieno[3′,2′:4,5]thiopyrano[3,2-*c*]-pyrazole (**20**) and 3-mercapto-2,5-dihydrothieno[2′,3′:4,5]thiopyrano[3,2-*c*]pyrazole (**21**) in 75% yields. Spectroscopic data showed that these compounds existed as enethiol tautomers.



The β-oxo dithioesters upon methylation (MeI–K_2CO_3–dry acetone) were converted into 5-[bis(methylsulfanyl)methylidene]-7*H*-thieno[2,3-*c*]thiopyran-4(5*H*)-one (**22**) and 6-[bis-(methylsulfanyl)methylidene]-4*H*-thieno[3,2-*c*]thiopyran-7(6*H*)-one (**23**) in high yields. Oxoketene dithioacetals of this type are three carbon fragments which have been extensively used[10] as



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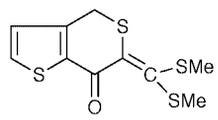

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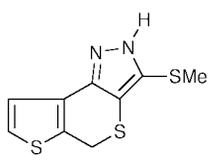
versatile intermediates in organic synthesis. Earlier we have used[11] this type of intermediate for annelation of five- and six-membered heterocycles onto an existing benzo[*b*]thiophene core. In a similar manner compounds **22** and **23** were used in the annelations reported below.

Annelation of five-membered nitrogen heterocycles *e.g.* pyrazole and pyrimidine onto the existing thienothiopyran core could be achieved through reaction of suitable bifunctional nucleophiles with the 1,3-electrophilic centres in the oxoketone dithioacetals. In refluxing ethanol, hydrazine hydrate reacted with **22** and **23** affording tricyclic compounds 3-methylsulfanyl-2,5-dihydrothieno[3′,2′ : 4,5]thiopyrano[3,2-*c*]-pyrazole (**24**) and 3-methylsulfanyl-2,5-dihydrothieno[2′,3′ :



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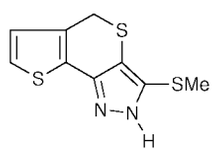

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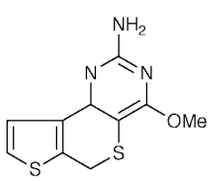

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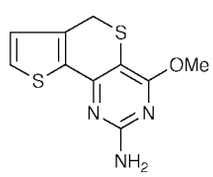

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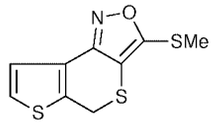
4,5]thiopyrano[3,2-*c*]pyrazole (**25**), both in 72% yield, while refluxing with guanidine hydrochloride in the presence of methanolic sodium methoxide 2-amino-4-methoxy-6*H*-thieno-[3′,2′ : 4,5]thiopyrano[3,2-*d*]pyrimidine (**26**) and 2-amino-4-methoxy-6*H*-thieno[2′,3′ : 4,5]thiopyrano[3,2-*d*]pyrimidine (**27**) were obtained respectively. Cyclization takes place in both cases with simultaneous expulsion of methanethiol. During the formation of **26** and **27**, the sodium methoxide needed for the liberation of guanidine from its hydrochloride was also responsible for the displacement of the SMe function in the pyrimidine ring by a methoxy group. Hydroxylamine hydrochloride being an asymmetric bifunctional nucleophile, reacted with the 1,3-electrophilic centres in **22** and **23** affording two regioisomeric isoxazoles in each case. The regiocontrol of the annelation reaction is governed by the pH of the reaction medium. Formation of the oxime followed by cyclization with simultaneous expulsion of methanethiol under basic conditions (sodium methoxide–methanol) to afford 3-methylsulfanyl-5*H*-thieno[3′,2′ : 4,5]thiopyrano[3,2-*c*]isoxazole (**28**) and 3-methylsulfanyl-5*H*-thieno[2′,3′ : 4,5]thiopyrano[3,2-*c*]isoxazole (**29**) from **22** and **23**.

Protonation of the carbonyl function of the oxoketone dithioacetal in acidic pH is encouraged by stabilization of the protonated species by charge delocalization. Nucleophilic attack by hydroxylamine at the positive centre in **30b** results in the species **31** which undergoes cyclization to afford 3-methylsulfanyl-5*H*-thieno[3′,2′ : 4,5]thiopyrano[2,3-*d*]isoxazole (**32**) and 3-methylsulfanyl-5*H*-thieno[2′,3′ : 4,5]thiopyrano[2,3-*d*]-isoxazole (**33**).



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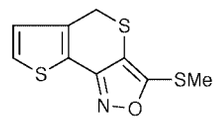

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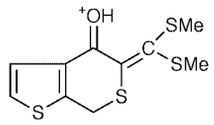
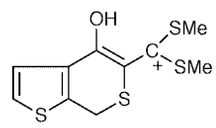
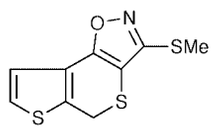


30a



30b



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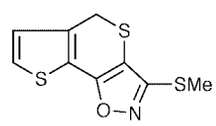

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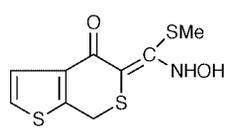

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Experimental

Melting points (uncorrected) were recorded in open capillaries on a hot stage apparatus. IR spectra were recorded on a Perkin-Elmer 298 spectrometer, for solids in potassium bromide discs and for liquids by placing a thin layer of the sample between two potassium bromide discs. ^{1}H, ^{13}C and DEPT(135) NMR spectra were recorded in $CDCl_3$ solutions unless otherwise stated, on Varian EM-360, JEOL FX-100 and Bruker DPX-300 spectrometers. Chemical shifts (δ) are expressed in ppm using tetramethylsilane as internal standard. Coupling constant (J) values are given in Hz.

Commercially available solvents were distilled prior to use. Light petroleum (bp 60–80 °C) was used. Anhydrous sodium sulfate was used as drying agent.

2-[Bis(methoxycarbonylmethylsulfanyl)methyl]thiophene 5

A solution of thiophene-2-carbaldehyde (11.2 g, 100 mmol) and methyl mercaptoacetate (21.24 g, 200 mmol) in dichloromethane (150 ml) was stirred at room temperature, to which anhydrous aluminium chloride (5.6 g, 42 mmol) was added in small portions under cooling. The reaction mixture turned turbid as the reaction proceeded. After the addition, the mixture was further stirred for another 10–15 min and was then hydrolysed with water (20 ml). The resulting mixture was extracted with dichloromethane, washed with water and dried. The solvent was removed under reduced pressure to obtain **5** as a yellow liquid which was purified by column chromatography [ethyl acetate–light petroleum (1 : 9) as eluent]. Yield 67%; bp 90–95 °C/0.5 mmHg (Found: C, 42.92; H, 4.65. $C_{11}H_{14}O_4S_3$ requires C, 43.11; H, 4.60%); ν_{max}/cm^{-1} 1735 (COOMe); δ_H 7.28 (dd, 1H, H-5, J 5 and 4.8), 7.13 (d, 1H, H-3, J 5), 6.92 (dd, 1H, H-4, J 5 and 4.8), 5.63 (s, 1H, Ar-C*H*-SS), 3.70 (s, 6H, two OCH_3), 3.25–3.54 (q, 4H, two S-CH_2-CO); δ_C 170.52 (*C*OOMe), 142.58 (*C*-2), 127.30 (*C*-5), 127.05 (*C*-3), 126.66 (*C*-4), 52.88 (O*C*H$_3$), 49.17 (Ar-*C*H-SS), 33.95 (S-*C*H$_2$-CO).

Methyl 2-(2-thienylmethylsulfanyl)acetate 6

Trifluoroacetic acid (148 ml) was added dropwise to a stirred solution of **5** (18.6 g, 0.06 mol) and dichloromethane (180 ml)

under cooling (ice–salt). After stirring for 30 min, pyridine–borane (16.2 ml) was added dropwise to the cold reaction mixture and stirred for a further 30 min at 0 °C. The solvent was removed under reduced pressure and the residue made alkaline with 10% sodium hydroxide solution followed by extraction with ether. The combined extracts were washed with brine, dried and the solvent removed. The residue was chromatographed over silica gel [ethyl acetate–light petroleum (1 : 19) as eluent] to afford **6** as a colourless liquid. Yield 76%; bp 75–80 °C/0.5 mmHg (Found: C, 47.61; H, 5.30. $C_8H_{10}O_2S_2$ requires C, 47.5; H, 4.98%); ν_{max}/cm^{-1} 1725 (COOMe); δ_H 7.20 (dd, 1H, H-5′, *J* 5 and 4.8), 6.94 (d, 1H, H-3′, *J* 5), 6.89 (dd, 1H, H-4′, *J* 5 and 4.8), 4.03 (s, 2H, Ar-CH_2-S), 3.70 (s, 3H, OCH_3), 3.14 (s, 2H, S-CH_2-CO); δ_C 171.05 (*C*OOMe), 140.70 (*C*-2′), 127.51 (*C*-5′), 127.10 (*C*-3′), 125.82 (*C*-4′), 52.78 (O*C*H$_3$), 32.48 (Ar-*C*H$_2$-S), 31.13 (S-*C*H$_2$-CO).

3-Bromomethylthiophene 9

To a solution of 3-methylthiophene (17.64 g, 0.18 mol) in carbon tetrachloride (300 ml) was added *N*-bromosuccinimide (27 g, 0.15 mol) and AIBN (0.2 g). The mixture was heated under reflux with vigorous stirring for 1 h and then for another 4 h in the presence of light (tungsten lamp, 200 W). Succinimide separated upon cooling (ice bath), was filtered and the residue washed with carbon tetrachloride (50 ml). The highly lachrymatory oil left upon removal of solvent was 3-bromomethylthiophene (lit.[9] bp 70–100 °C/2 mmHg) and was sufficiently pure for the next step. Yield 74%; $\delta_H(CCl_4)$ 7.30–7.02 (m, 3H, aromatic protons), 4.5 (s, 2H, CH_2Br).

Methyl 2-(3-thienylmethylsulfanyl)acetate 10

Methyl mercaptoacetate (13.78 g, 0.13 mol) in dry methanol (100 ml) was added dropwise to a solution of sodium methoxide [prepared from sodium (3.1 g, 0.13 mol) in dry methanol (20 ml)] under magnetic stirring and external cooling (ice bath). After 15 min 3-bromomethylthiophene (23.5 g, 0.13 mol) in dry methanol (100 ml) was added slowly to the reaction mixture. After stirring overnight at room temperature, the solvent was removed under reduced pressure, the residue poured into crushed ice and extracted with ether. The organic layer was washed with water, dried and the solvent evaporated to afford **10** as a colourless liquid, which was purified by column chromatography [ethyl acetate–light petroleum (1 : 19) as eluent]. Yield 97% (Found: C, 47.66; H, 5.39. $C_8H_{10}O_2S_2$ requires C, 47.5; H, 4.98%); ν_{max}/cm^{-1} 1740 (COOMe); δ_H 7.22 (m, 1H, H-2′), 7.11 (d, 1H, H-5′, *J* 5), 7.01 (d, 1H, H-4′, *J* 5), 3.83 (s, 2H, Ar-CH_2-S), 3.70 (s, 3H, OCH_3), 3.07 (s, 2H, S-CH_2-CO); δ_C 170.66 (*C*OOMe), 137.33 (*C*-2′), 128.11 (*C*-5′), 126.12 (*C*-4′), 123.17 (*C*-3′), 52.22 (O*C*H$_3$), 31.99 (Ar-*C*H$_2$-S), 30.77 (S-*C*H$_2$-CO).

General procedure for the hydrolysis of esters

A methanolic potassium hydroxide [prepared by dissolving potassium hydroxide (64 g) in a minimum quantity of water followed by the addition of methanol (300 ml)] solution of the substrate (16 g, 0.078 mol) was stirred for 24 h at room temperature. Removal of methanol under reduced pressure and acidification of the residue was followed by ether extraction. The ethereal extract was washed with 5% sodium bicarbonate solution and the aqueous layer was acidified followed by ether extraction. The organic layer was washed with water, dried and the evaporation of the solvent afforded the crude acid.

2-(2-Thienylmethylsulfanyl)acetic acid 7. Obtained as a low melting point solid which was purified by sublimation (110 °C/0.01 mmHg). Yield 96% (Found: C, 44.45; H, 4.15. $C_7H_8O_2S_2$ requires C, 44.65; H, 4.28%); ν_{max}/cm^{-1} 1700 (COOH), 3100 (OH); δ_H 11.29 (br s, 1H, COO*H*), 7.21 (dd, 1H, H-5′, *J* 5), 6.97 (dd, 1H, H-3′, *J* 5), 6.91 (dd, 1H, H-4′, *J* 5), 4.06 (s, 2H, Ar-CH_2-S), 3.16 (s, 2H, S-CH_2-CO); δ_C 177.49 (*C*OOH), 140.37 (*C*-2′), 127.81 (*C*-5′), 127.2 (*C*-3′), 126.07 (*C*-4′), 32.45 (Ar-*C*H$_2$-S), 31.19 (S-*C*H$_2$-CO).

2-(3-Thienylmethylsulfanyl)acetic acid 11. Obtained as a low melting solid which was purified by sublimation (120 °C/0.01 mmHg). Yield 96% (Found: C, 44.55; H, 4.21. $C_7H_8O_2S_2$ requires C, 44.65; H, 4.28%); ν_{max}/cm^{-1} 1705 (COOH), 3100 (OH); δ_H 11.67 (br s, 1H, COO*H*), 7.29 (m, 1H, H-2′), 7.17 (d, 1H, H-5′, *J* 5), 7.06 (d, 1H, H-4′, *J* 5), 3.97 (s, 2H, Ar-CH_2-S), 3.16 (s, 2H, S-CH_2-CO); δ_C 176.74 (*C*OOH), 137.02 (*C*-2′), 128.11 (*C*-5′), 126.32 (*C*-4′), 123.46 (*C*-3′), 31.96 (Ar-*C*H$_2$-S), 30.81 (S-*C*H$_2$-CO).

General procedure for the cyclization of 2-(thienylmethylsulfanyl)acetic acids

The acid (10 g, 0.053 mol), thionyl chloride (20 ml, 0.25 mol) and dry ether (100 ml) were refluxed under stirring for 2 h. Solvent and excess thionyl chloride were removed under vacuum and the crude acid chloride (10.98 g, 0.053 mol) was dissolved in carbon disulfide (220 ml). Stannic chloride (15.255 g, 0.058 mol) in carbon disulfide (30 ml) was added to the reaction mixture which was kept at −10 °C, under vigorous stirring. After the addition was complete, a reddish mass was formed which was further stirred for 2 h at 0 °C, followed by the addition of ice–HCl and extraction with dichloromethane. The organic layer was washed with water, dried and solvent removed to afford the crude product as an off white solid which was purified by column chromatography [ethyl acetate–light petroleum (1 : 9) as eluent] and crystallized from ether–light petroleum.

7*H*-Thieno[2,3-*c*]thiopyran-4(5*H*)-one 1. Yield 72%; mp 40–41 °C; ν_{max}/cm^{-1} 1660 (CO) (Found: C, 49.28; H, 3.60. $C_7H_6OS_2$ requires C, 49.38; H, 3.55%); δ_H 7.42 (d, 1H, H-2, *J* 5), 7.06 (d, 1H, H-3, *J* 5), 3.99 (s, 2H, Ar-CH_2-S), 3.46 (s, 2H, S-CH_2-CO); δ_C 187.55 (*C*O), 151.68 (*C*-8), 136.16 (*C*-9), 126.76 (*C*-2), 123.12 (*C*-3), 35.94 (Ar-*C*H$_2$-S), 26.19 (S-*C*H$_2$-CO).

4*H*-Thieno[3,2-*c*]thiopyran-7(6*H*)-one 2. Yield 66%; mp 68–70 °C; ν_{max}/cm^{-1} 1660 (CO) (Found: C, 49.30; H, 3.61. $C_7H_6OS_2$ requires C, 49.38; H, 3.55%); δ_H 7.59 (d, 1H, H-2, *J* 5), 6.97 (d, 1H, H-3, *J* 5), 3.85 (s, 2H, Ar-CH_2-S), 3.48 (s, 2H, S-CH_2-CO).

General procedure for the synthesis of β-dithioesters

Dimethyl trithiocarbonate (4.2 g, 0.03 mol) was stirred with a solution of the ketone (4 g, 0.0235 mol) in benzene in the presence of potassium *tert*-butoxide (with a catalytic amount of *N*,*N*-dimethylformamide) for 1 h at 0 °C and 8 h at room temperature. The residue left after removal of the solvent was poured into crushed ice and extracted with dichloromethane; the organic layer was washed with water and dried. The crude residue obtained as a red solid after evaporation of the solvent was purified by column chromatography [ethyl acetate–light petroleum (1 : 19) as eluent] and crystallized from ether–light petroleum.

Methyl 4-oxo-4,5-dihydro-7*H*-thieno[2,3-*c*]thiopyran-5-carbodithioate 14. Yield 92%; mp 96–98 °C (Found: C, 41.40; H, 3.35. $C_9H_8OS_4$ requires C, 41.51; H, 3.1%); ν_{max}/cm^{-1} 3400 (enolic OH); δ_H 15.85 (s, 1H, O*H*), 7.59 (d, 1H, H-2, *J* 5), 6.93 (d, 1H, H-3, *J* 5), 3.90 (s, 2H, Ar-CH_2-S), 2.63 (s, 3H, S-CH_3); δ_C 213.32 (*C*SSMe), 161.20 (*C*O), 142.82 (*C*-9), 133.64 (*C*-8), 133.09 (*C*-2), 127.19 (*C*-3), 109.04 (*C*-5, keto form), 60.54 (*C*-5, enol form), 28.16 (*C*-7), 19.73 (S*C*H$_3$).

Methyl 7-oxo-6,7-dihydro-4*H*-thieno[3,2-*c*]thiopyran-6-carbodithioate 15. Yield 97%; mp 110–111 °C (Found: C, 41.44; H, 3.64. $C_9H_8OS_4$ requires C, 41.51; H, 3.1%); ν_{max}/cm^{-1} 3400

(enolic OH); δ_H 15.86 (s, 1H, O*H*), 7.61 (d, 1H, H-2, *J* 6), 6.95 (d, 1H, H-3, *J* 6), 3.92 (s, 2H, Ar-CH_2-S), 2.67 (s, 3H, S-CH_3); δ_C 212.9 (*C*SSMe), 160.73 (*C*O), 142.32 (*C*-8), 133.19 (*C*-9), 132.57 (*C*-2), 126.68 (*C*-3), 108.57 (*C*-6 keto form), 60.52 (C-6 enol form), 27.68 (*C*-4), 19.22 (S*C*H_3).

General procedure for the synthesis of oxoketene dithioacetals

Potassium carbonate (1.38 g, 10 mmol) was added to a solution of β-dithioester (2.6 g, 10 mmol) in dry acetone (80 ml). After refluxing for 3 h, the reaction mixture was cooled to 0 °C and methyl iodide (2.13 g, 15 mmol) was added dropwise at that temperature under magnetic stirring for 2 h followed by 10 h stirring at room temperature. The solid was filtered, the solvent removed under reduced pressure and the residue poured into crushed ice. After extraction with ether, the organic layer was washed with water and dried. Removal of solvent afforded the crude material as an orange solid which was purified by column chromatography [ethyl acetate–light petroleum (1 : 9) as eluent] and recrystallized from ether–light petroleum mixture.

5-[Bis(methylsulfanyl)methylidene]-7*H*-thieno[2,3-*c*]thiopyran-4(5*H*)-one 22. Yield 95%; mp 74–75 °C (Found: C, 43.88; H, 3.55. $C_{10}H_{10}OS_4$ requires C, 43.76; H, 3.67%); ν_{max}/cm^{-1} 1600 (CO); δ_H 7.57 (d, 1H, H-2, *J* 5), 6.93 (d, 1H, H-3, *J* 5), 4.03 (s, 2H, Ar-CH_2-S), 2.51 (s, 6H, two S-CH_3); δ_C 176.96 (*C*O), 152.34 (*C*-5), 145.75 (*C*(SMe)$_2$), 139.61 (*C*-9), 134.24 (*C*-2), 127.73 (*C*-3), 126.74 (*C*-8), 28.98 (Ar-*C*H$_2$-S), 19.65 (S*C*H$_3$).

6-[Bis(methylsulfanyl)methylidene]-4*H*-thieno[3,2-*c*]thiopyran-7(6*H*)-one 23. Yield 95%; mp 88–90 °C (Found: C, 43.92; H, 3.51. $C_{10}H_{10}OS_4$ requires C, 43.76; H, 3.67%); ν_{max}/cm^{-1} 1600 (CO); δ_H 7.59 (d, 1H, H-2, *J* 5), 6.95 (d, 1H, H-3, *J* 5), 4.04 (s, 2H, Ar-CH_2-S), 2.53 (s, 6H, two S-CH_3); δ_C 176.57 (*C*O), 151.96 (*C*-6), 145.35 [*C*(SMe)$_2$], 139.22 (*C*-8), 133.84 (*C*-2), 127.33 (*C*-3), 126.35 (*C*-9), 28.58 (Ar-*C*H$_2$-S), 19.26 (S*C*H$_3$).

General procedure for the synthesis of β-oxoesters

Dimethyl carbonate (1.35 g, 15 mmol) reacted with ketone (1.7 g, 10 mmol) in dry benzene in the presence of sodium hydride (1.6 g, 20 mmol) under cooling (ice bath) and was stirred for 1 h at 0 °C and 8 h at room temperature. The solvent was removed under reduced pressure and the residue poured into crushed ice. After extraction with ether, the organic layer was washed with water and dried. Removal of solvent afforded the crude material as a light yellow solid which was recrystallized from ether–light petroleum.

Methyl 4-oxo-4,5-dihydro-7*H*-thieno[2,3-*c*]thiopyran-5-carboxylate 12. Yield 55%; mp 130–132 °C (Found: C, 47.25; H, 3.60. $C_9H_8O_3S_2$ requires C, 47.35; H, 3.53%); ν_{max}/cm^{-1} 3400 (enolic OH); δ_H 12.16 (s, 1H, O*H*), 7.54 (d, 1H, H-2, *J* 5), 6.85 (d, 1H, H-3, *J* 5), 5.59 (s, 1H, H-5), 3.87 (AB quartet, 2H, Ar-CH_2-S, *J* 17), 3.73 (s, 3H, OCH_3).

Methyl 7-oxo-6,7-dihydro-4*H*-thieno[3,2-*c*]thiopyran-6-carboxylate 13. Yield 58%; mp 166–168 °C (Found: C, 47.22; H, 3.61. $C_9H_8O_3S_2$ requires C, 47.35; H, 3.53%); ν_{max}/cm^{-1} 3400 (enolic OH); δ_H 12.09 (s, 1H, O*H*), 7.42 (d, 1H, H-2, *J* 5), 6.78 (d, 1H, H-3, *J* 5), 5.52 (s, 1H, H-6), 3.79 (AB quartet, 2H, Ar-CH_2-S, *J* 17), 3.67 (s, 3H, OCH_3).

3-Hydroxy-2-phenyl-2,5-dihydrothieno[3′,2′ : 4,5]thiopyrano-[3,2-*c*]pyrazole 16

Compound **12** (114 mg, 0.5 mmol) together with phenylhydrazine (54 mg, 0.5 mmol) was refluxed in magnesium dried ethanol (5 ml) for 8 h. After removal of solvent the residue was treated with ice-cold water (15 ml) and extracted with ether. The extract was dried and solvent removed to afford the crude product. Column chromatography over silica gel [ethyl acetate–light petroleum (1 : 9) as eluent] afforded **16** as a yellow oil. Yield 75% (Found: C, 58.85; H, 3.60; N, 9.65. $C_{14}H_{10}N_2OS_2$ requires C, 58.72; H, 3.52; N, 9.78%); ν_{max}/cm^{-1} 3420 (OH); δ_H 7.98 (s, 1H, O*H*), 7.70 (d, 1H, H-7, *J* 5), 7.52 [dd, 2H, aromatic protons (H-2′ and 6′), *J* 7.5 and 3.8], 7.36–7.46 [m, 3H, aromatic protons (H-3′, 4′ and 5′)], 7.21 (d, 1H, H-8, *J* 5), 3.65 (s, 2H, Ar-CH_2-S).

3-Hydroxy-2-phenyl-2,5-dihydrothieno[2′,3′ : 4,5]thiopyrano-[3,2-*c*]pyrazole 17

Compound **17** was obtained in the same manner as compound **16**. Yield 74% (Found: C, 58.85; H, 3.60; N, 9.65. $C_{14}H_{10}N_2OS_2$ requires C, 58.72; H, 3.52; N, 9.78%); ν_{max}/cm^{-1} 3420 (OH); δ_H 7.83 (s, 1H, O*H*), 7.60 (d, 1H, H-7, *J* 5), 7.00–7.50 (m, 6H, C_6H_5 and H-6), 3.53 (s, 2H, Ar-CH_2-S).

3-Mercapto-2,5-dihydrothieno[3′,2′ : 4,5]thiopyrano[3,2-*c*]-pyrazole 20

β-Dithioester (**14**) (260 mg, 1 mmol) together with hydrazine hydrate (1 mmol equiv.) was refluxed in magnesium dried ethanol (5 ml) for 2 h, after which solvent removal under reduced pressure and trituration of the residue with ether afforded **20** as a yellow solid which was recrystallized from ether–light petroleum. Yield 75%; mp 218–220 °C (decomp.) (Found: C, 42.70; H, 2.85; N, 12.15. $C_8H_6N_2S_3$ requires C, 42.45; H, 2.67; N, 12.37%); ν_{max}/cm^{-1} 2980 (NH); δ_H([$^2H_6$]-DMSO) 13.6 (S*H*), 7.76 (s, 1H, N*H*), 7.6 (d, 1H, H-7, *J* 5), 7.12 (d, 1H, H-8, *J* 5), 4.05 (s, 2H, Ar-CH_2-S).

3-Mercapto-2,5-dihydrothieno[2′,3′ : 4,5]thiopyrano[3,2-*c*]-pyrazole 21

Compound **21** was obtained in the same manner as compound **20**. Yield 75%; mp 228–230 °C (decomp.) (Found: C, 42.71; H, 2.96; N, 12.19. $C_8H_6N_2S_3$ requires C, 42.45; H, 2.67; N, 12.37%); ν_{max}/cm^{-1} 2980 (NH); δ_H([$^2H_6$]-DMSO) 13.5 (S*H*), 7.75 (s, 1H, N*H*), 7.55 (d, 1H, H-7, *J* 5), 7.10 (d, 1H, H-6, *J* 5), 4.03 (s, 2H, Ar-CH_2-S).

3-Methylsulfanyl-2,5-dihydrothieno[3′,2′ : 4,5]thiopyrano[3,2-*c*]-pyrazole 24

Oxoketene dithioacetal (**22**) (275 mg, 1 mmol) together with hydrazine hydrate (1 mmol equiv.) was refluxed in magnesium dried ethanol (5 ml) for 5 h, after which solvent removal under reduced pressure and trituration of the residue with ether afforded **24** as a yellow solid which was recrystallized from ether–light petroleum. Yield 72%; mp 132–134 °C (decomp.) (Found: C, 45.10; H, 3.28; N, 11.54. $C_9H_8N_2S_3$ requires C, 44.97; H, 3.35; N, 11.66%); ν_{max}/cm^{-1} 3010 (NH); δ_H([$^2H_6$]-DMSO) 8.47 (s, 1H, N*H*), 7.46 (d, 1H, H-7, *J* 5), 7.02 (d, 1H, H-8, *J* 5), 4.03 (s, 2H, Ar-CH_2-S), 2.39 (s, 3H, SCH_3).

3-Methylsulfanyl-2,5-dihydrothieno[2′,3′ : 4,5]thiopyrano[3,2-*c*]-pyrazole 25

Compound **25** was obtained in the same manner as compound **24**. Yield 72%; mp 148–150 °C (decomp.) (Found: C, 45.05; H, 3.25; N, 11.55. $C_9H_8N_2S_3$ requires C, 44.96; H, 3.35; N, 11.66%); ν_{max}/cm^{-1} 3010 (NH); δ_H([$^2H_6$]-DMSO) 8.46 (s, 1H, N*H*), 7.44 (d, 1H, H-7, *J* 5), 7.01 (d, 1H, H-6, *J* 5), 4.01 (s, 2H, Ar-CH_2-S), 2.38 (s, 3H, SCH_3).

3-Methylsulfanyl-5*H*-thieno[3′,2′ : 4,5]thiopyrano[3,2-*c*]-isoxazole 28

Hydroxylamine hydrochloride (0.139 g, 2 mmol) was added to a magnetically stirred solution of sodium methoxide [prepared from sodium (57 mg, 2.5 mmol) in dry methanol (10 ml)]. After being stirred for 15 min, the reaction mixture was treated with

22 (0.14 g, 0.5 mmol) and then refluxed for 8 h. After this, the solvent was evaporated and the residue was treated with ice-cold water and extracted with ether. The extract was dried and evaporated to afford the crude product which was chromatographed over neutral alumina [ethyl acetate–light petroleum (1 : 9) as eluent] to afford **28** as yellow oil. Yield 75% (Found: C, 44.90; H, 3.08; N, 5.64. $C_9H_7NOS_3$ requires C, 44.78; H, 2.92; N, 5.80%); δ_H 7.44 (d, 1H, H-7, *J* 5), 6.99 (d, 1H, H-8, *J* 5), 4.02 (s, 2H, Ar-CH_2-S), 2.54 (s, 3H, SCH_3).

3-Methylsulfanyl-5*H*-thieno[2′,3′ : 4,5]thiopyrano[3,2-*c*]-isoxazole 29

Compound **29** was obtained in the same manner as compound **28**. Yield 75% (Found: C, 44.95; H, 3.12; N, 5.65. $C_9H_7NOS_3$ requires C, 44.78; H, 2.92; N, 5.80%); δ_H 7.44 (d, 1H, H-7, *J* 5), 6.99 (d, 1H, H-6, *J* 5), 3.98 (s, 2H, Ar-CH_2-S), 2.55 (s, 3H, SCH_3).

3-Methylsulfanyl-5*H*-thieno[3′,2′ : 4,5]thiopyrano[2,3-*d*]-isoxazole 32

Sodium acetate (0.164 g, 2 mmol), acetic acid (6 ml) and a solution of hydroxylamine hydrochloride (0.139 g, 0.5 mmol) in water (4 ml) were added to **22** (0.14 g, 0.5 mmol) dissolved in benzene (6 ml) and made homogeneous by the addition of ethanol (6 ml). The reaction mixture was then refluxed for 30 h. After evaporation of the solvent the residue was poured into crushed ice and extracted with dichloromethane, the organic layer was washed with water, dried and evaporated. Chromatography of the residue on neutral alumina afforded **32** as a light yellow liquid. Yield 65% (Found: C, 44.65; H, 2.82; N, 5.68. $C_9H_7NOS_3$ requires C, 44.78; H, 2.92; N, 5.80%); δ_H 7.44 (d, 1H, H-7, *J* 5), 6.99 (d, 1H, H-8, *J* 5), 4.02 (s, 2H, Ar-CH_2-S), 2.60 (s, 3H, SCH_3).

3-Methylsulfanyl-5*H*-thieno[2′,3′ : 4,5]thiopyrano[2,3-*d*]-isoxazole 33

Compound **33** was obtained in the same manner as compound **32**. Yield 65% (Found: C, 44.62; H, 3.15; N, 5.92. $C_9H_7NOS_3$ requires C, 44.78; H, 2.92; N, 5.80%); δ_H 7.44 (d, 1H, H-7, *J* 5), 6.99 (d, 1H, H-6, *J* 5), 4.01 (s, 2H, Ar-CH_2-S), 2.59 (s, 3H, SCH_3).

2-Amino-4-methoxy-6*H*-thieno[3′,2′ : 4,5]thiopyrano[3,2-*d*]-pyrimidine 26

Guanidine hydrochloride (50 mg) and **22** (140 mg, 0.5 mmol) were added to a solution of sodium methoxide [prepared from sodium (25 mg, 1 mmol) in dry methanol (10 ml)] and the mixture was refluxed for 8 h. Removal of solvent from the mixture by distillation left a residue which was triturated with water to give **26** as a liquid which was purified by column chromatography [ethyl acetate–light petroleum (1 : 9) as eluent]. Yield 70% (Found: C, 47.67; H, 3.71; N, 16.61. $C_{10}H_9N_3OS_2$ requires C, 47.79; H, 3.61; N, 16.72%); δ_H 7.52 (d, 1H, H-8, *J* 5), 7.23 (d, 1H, H-9, *J* 5), 4.99 (s, 2H, NH_2), 4.03 (s, 2H, Ar-CH_2-S), 3.4 (s, 3H, OCH_3).

2-Amino-4-methoxy-6*H*-thieno[2′,3′ : 4,5]thiopyrano[3,2-*c*]-pyrimidine 27

Compound **27** was obtained in the same manner as compound **26**. Yield 70% (Found: C, 47.65; H, 3.74; N, 16.58. $C_{10}H_9N_3OS_2$ requires C, 47.79; H, 3.61; N, 16.72%); δ_H 7.52 (d, 1H, H-8, *J* 5), 7.23 (d, 1H, H-7, *J* 5), 4.99 (s, 2H, NH_2), 3.97 (s, 2H, Ar-CH_2-S), 3.39 (s, 3H, OCH_3).

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