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Routes to Building Blocks for Heterocyclic Synthesis by Reduction of Ketene Dithioacetals

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Abstract: Two general methods have been developed permitting the effective reduction of ketene dithioacetals to give substituted dithianes. Reduction with magnesium in methanol is less reliable than reduction with zinc in acetic acid. The greater inconsistency of magnesium in methanol has been investigated by a cyclic voltammetric study of the substrates. The utility of the dithianes has been successfully illustrated by cyclisations to afford, after deprotection, a variety of heterocyclic aldehydes.
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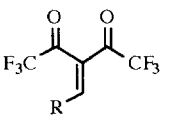
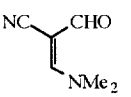
The central role of β-dicarbonyl compounds and their equivalents in the synthesis of many heterocyclic skeletons including pyrimidines has stimulated over many years an interest[1] in the synthesis of novel C_3 building blocks. Condensation of the two carbonyl groups of the appropriate β-dicarbonyl compound with amidines, ureas or guanidines affords[2] substituted pyrimidines. Similarly five-membered heterocycles are obtained[3] using hydrazines or hydroxylamine. With the need to synthesize diversely substituted heterocycles more complex acyclic building blocks have been designed so that the appropriate substituents might be introduced directly through reaction with bis-nucleophiles. The building blocks (1-6) are typical in leading[4] by successive 1,4-addition and further reaction to both 5- and 6-ring heterocycles. Each of the building blocks (1-6) carries a latent aldehyde group but because 1,4-addition is the favoured pathway such building blocks fail to give heterocyclic aldehydes. An alternative route to heterocyclic aldehydes might be based on cyclisations of the dithianes (7). Here if bis-nucleophiles reacted with electrophilic sites X and Y, then deprotection of the dithiane would develop a novel route to such aldehydes. As the dithianes (7) are not well described, in this paper we report both the preparation of a range of diversely substituted dithianes and illustrate their successful transformation to heterocyclic aldehydes.



(1) R = Et_2N
(2) R = OEt
(3) R = SEt



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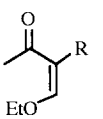
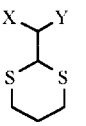


(5) R = CN
(6) R = COOEt



(7)

TABLE Reduction of Ketene Dithioacetals

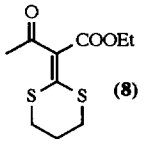
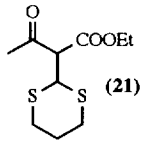
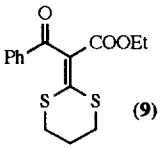
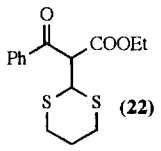
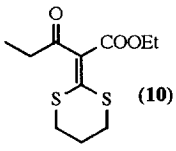
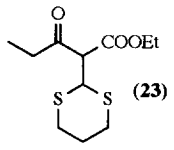
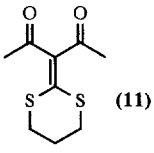
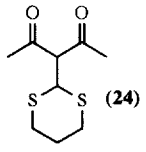
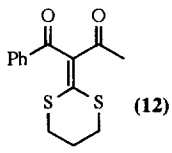
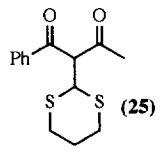
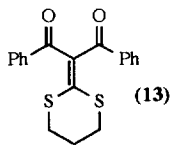
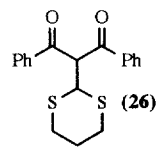
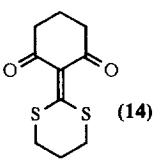
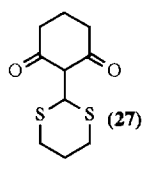
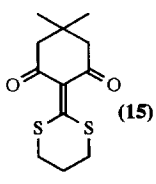
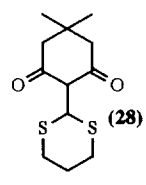
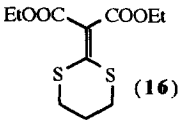
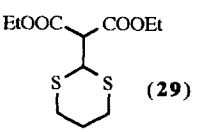
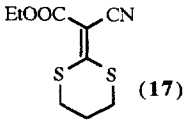
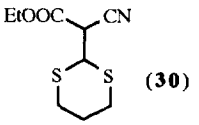
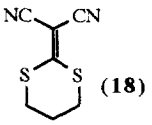
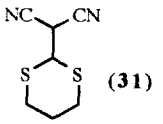
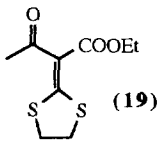
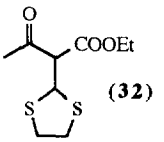
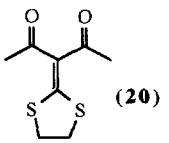
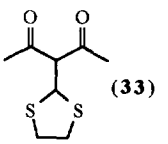
Substrate	Reducing Agent	Product	Yield (%)
 **(8)**	Mg/MeOH	 **(21)**	87
	Zn/AcOH		84
 **(9)**	Mg/MeOH	 **(22)**	43
	Zn/AcOH		59
 **(10)**	Mg/MeOH	 **(23)**	0
	Zn/AcOH		43
 **(11)**	Mg/MeOH	 **(24)**	92
	Zn/AcOH		87
 **(12)**	Mg/MeOH	 **(25)**	18
	Zn/AcOH		43
 **(13)**	Mg/MeOH	 **(26)**	45
	Zn/AcOH		50
 **(14)**	Mg/MeOH	 **(27)**	51
	Zn/AcOH		53
 **(15)**	Mg/MeOH	 **(28)**	66
	Zn/AcOH		71

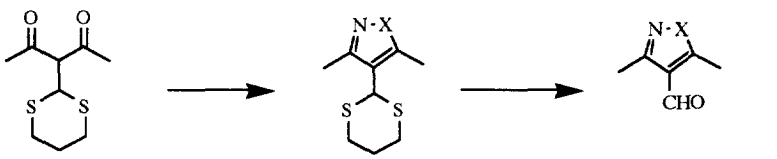
TABLE Continued Reduction of Ketene Dithioacetals

Substrate	Reducing Agent	Product	Yield (%)
 (16)	Mg/MeOH	 (29)	76
	Zn/AcOH		71
 (17)	Mg/MeOH	 (30)	77
	Zn/AcOH		70
 (18)	Mg/MeOH	 (31)	80
 (19)	Mg/MeOH	 (32)	44
	Zn/AcOH		52
 (20)	Mg/MeOH	 (33)	42
	Zn/AcOH		45

Although there are possible routes[5] to the building blocks (7) by a nucleophilic displacement based on 2-chlorodithiane or by use of the dithiane anion[6] with a halogenated β-dicarbonyl compound, we have developed a new route based on reduction of ketene dithioacetals. The required ketene dithioacetals are readily prepared by reaction of carbon disulfide with the enolate anion of the appropriate β-dicarbonyl compound and subsequent alkylation. The ketene dithioacetals were prepared by two methods, the older established procedure[7] in dimethylformamide and the more recently described[8] method on alumina. The reduction of ketene dithioacetals has been described[9] under a variety of conditions. Reduction with lithium aluminium hydride[10] affords β-hydroxydithioacetals, but reduction with diisobutyl aluminium hydride, 9-borabicyclo[3,3,1]nonane or catechol borane[11] gives products by 1,4-reduction. Conversely reduction with sodium borohydride in the presence of nickel chloride[12] leads to reductive loss of sulfur. In a series of papers illustrating the use of magnesium in methanol or ethanol Pak et al[13] have reported not only reductive desulfonylations but also 1,4-reduction of conjugated esters and ketones. The electrochemical reduction[14] of ketene dithioacetals again leads to loss of sulfur. We have studied the reduction of 13 ketene dithioacetals (8 -20) with zinc in acetic acid and magnesium in methanol. We find that under these dissolving metal conditions 1,4-reduction to give saturated dithianes (21-33) is very efficient. As shown in the Table both reaction conditions permit preparation of the required dithianes in

good yield. It is important to use a cyclic ketene dithioacetal. In contrast to the efficient reductions to give dithianes and dithiolanes, elimination of the alkylthiol precluded efficient reduction of acyclic dithioketals. In no case do we observe products of over reduction. However in the case of the use of magnesium in methanol we observe an interesting dependence of the efficiency of reduction with the structure of the ketene dithioacetal. In contrast reduction with zinc in acetic acid is efficient in all cases and is the method of choice.

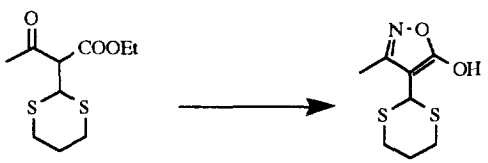
Surprisingly it was found that the ketene dithioacetal (10) using magnesium in methanol was not reduced, in contrast to the lower homologue (8), which was efficiently reduced. Although the synthetic failure could be avoided by use of zinc in acetic acid, we chose to examine further the behaviour of the two ketene dithioacetals (8) and (10). The $E_{1/2}$ reduction were measured by cyclic voltammetry and the values for both the ketene dithioacetals (8 -1.60eV) and (10 -1.63eV) were very similar. It is clear that the relative electron affinities, a thermodynamic parameter of the ketene dithioacetals, are so similar that a kinetic factor must explain the differences in behaviour. In view of this unexpected difference we checked their relative reactivities. A mixture of the two ketene dithioacetals were dissolved in methanol and magnesium was added. On work up it was found that the ketene dithioacetal (8) was smoothly reduced to the dithiane (21). In contrast the second ketene dithioacetal (10) was recovered substantially unchanged. Electron transfer to the ketene dithioacetals is likely to be assisted by complexation with a Lewis acid. Magnesium ion could be complexed with the two carbonyl functionalities and hence assist reduction. The measurement of the $E_{1/2}$ values in the presence of added magnesium ion confirms this view. Magnesium ion leads to a positive shift of the observed cathodic waves.



(24) **(34)** X = NH **(38)** X = NH

(35) X = NPh **(39)** X = NPh

(36) X = O **(40)** X = O



(21) **(37)**

Reduction is therefore likely by electron transfer from the cathode to a magnesium ion ketene dithioacetal complex. However the same shift (120mV) is observed for the two ketene dithioacetals and therefore the relative ease of electron transfer is too similar to account for the marked difference in behaviour of the ketene dithioacetals (8) and (10). A probable explanation of the relative reactivities of the ketene dithioacetals (8) and (10) is extra steric constraints in the case of (10). If such factors inhibit magnesium coordination at the two carbonyl centres,

then a significant reactivity difference can be expected. However in practice, use of zinc in acetic acid avoids this kinetic difficulty and then reduction of ketene dithioacetal (10) proceeds reliably.

The value of the dithianes is illustrated by the conversion of the dithianes (21) and (24) to heterocyclic dithianes. By condensation with hydrazine the dithiane (24) affords the pyrazole (34). Similarly with phenylhydrazine and hydroxylamine hydrochloride the dithiane (24) affords the pyrazole (35) and the isoxazole (36) respectively. Similarly the ester (21) with hydroxylamine hydrochloride gives the isoxazole (37). The deprotection of the heterocyclic dithianes with N-bromosuccinimide[15] gave the desired heterocyclic aldehydes (38-40) in good yield. Our results establish the ease of synthesis of substituted dithianes by dissolving metal reductions of ketene dithioacetals. Whilst the use of magnesium and methanol is generally effective, zinc and acetic acid has the advantage of greater reliability. With the access to the dithianes established the illustrative examples given in this paper show that such dithianes are effective building blocks for the direct synthesis of heterocyclic aldehydes.

Experimental

Preparation of Ketene Dithioacetals

Method A: To a stirred solution of the 1,3-dicarbonyl compound (10.0mmol) and potassium carbonate (4.14g, 30mmol) in DMF (20ml) at room temperature was added carbon disulfide (1.14g, 15.0mmol) followed by 1,3-dibromopropane (2.42g, 12.0mmol) over 20min. The resulting mixture was stirred for a further 7h before ice-water (20ml) was added.In many cases a solid was recovered by filtration, dried in a desiccator and recrystallised to afford the following products. In other cases an oil was obtained. Then the mixture was extracted with dichloromethane (3 x 25ml), the combined organic phases were washed with water (20ml), dried and the solvent removed *in vacuo*. The crude product was purified by chromatography (silica gel) and elution with light petroleum: ethyl acetate (9:1) afforded the following products.

Method B: A solution of the 1,3-dicarbonyl compound (10.0mmol) in carbon disulfide (0.91g) was adsorbed on to alumina / potassium fluoride (2mmol of fluoride per gram of alumina, 16g) in a stoppered flask. After 1h 1,3-dibromopropane (2.1g, 10.4mmol) was added and the contents of the flask were mixed well by shaking. After 24h acetonitrile (50ml) was added and the suspension filtered through celite. The filtrate was dried over $MgSO_4$ and the solvent removed *in vacuo*. Again solid products were purified by recrystallisation from ethanol and liquid products were purified by column chromatography as described above.

Using the above methods the following ketene dithioacetals were prepared:

Ethyl 2-(1,3-dithian-2-ylidene)-3-oxobutanoate (8) by method A in 69% yield and method B in 65% yield as pale yellow crystals m.p. 60-62°C (lit[16] m.p. 59-60°C).

Ethyl 2-(1,3-dithian-2-ylidene)-3-oxo-3-phenylpropionate (9) by method A in 67% yield and method B in 48% yield as pale yellow crystals m.p. 102-104°C (known compound[17] but m.p. not reported).

Ethyl 2-(1,3-dithian-2-ylidene)-3-pentanoate (10) by method A in 81% yield and method B in 73%

yield as a pale yellow oil, δH 1.11 (3H, t J 7.4, CH_3), 1.33 (3H, t J 7.0 OCH_2CH_3), 2.23 (2H, m, CH_2), 2.59 (2H, q J 7.4, CH_2), 2.91 (2H, t J 7.0, SCH_2), 2.96 (2H, t J 7.0, SCH_2) and 4.29 (2H, q J 7.0, OCH_2); δC 8.60 (CH_3), 14.29 (OCH_2CH_3), 23.97 (CH_2), 29.31 (SCH_2), 29.45 (SCH_2), 35.00 (CH_2CO), 61.39 (OCH_2), 128.35 (*C*CO), 165.46 (C=*C*S), 167.43 (CO, ester) and 197.81 (CO, ketone); ν_{max} 3019, 1701, 1684 and 1467cm.$^{-1}$; λ_{max} 322nm (ε 16,800), found M^+ 260.056 $C_{11}H_{16}O_3S_2$ requires 260.057 m/z 260 (34), 231 (100), 215 (14), 203 (21), 187 (10) and 159 (32).

3-(1,3-Dithian-2-ylidene)-pentane-2,4-dione (**11**) by method A in 74% yield and method B in 52% yield as pale yellow crystals m.p. 79-80°C (lit[18] m.p. 79-80°C).

2-(1,3-Dithian-2-ylidene)-1-phenylbutane-1,3-dione (**12**) by method A in 70% yield and method B in 61.5% yield as pale yellow crystals m.p. 113-115°C (lit[19] m.p. 116°C).

2-(1,3-Dithian-2-ylidene)-1,3-diphenylpropane-1,3-dione (**13**) by method A in 84% yield and method B in 80% yield as pale yellow crystals m.p. 126-128°C; δH 2.33 (2H, quin. J 7.4, CH_2), 2.98 (4H, t J 7.4, SCH_2), 7.19 (4H, m, aromatic), 7.30 (2H, m, aromatic), 7.59 (4H, m, aromatic); δC 24.97 (CH_2), 29.89 (SCH_2), 128.36, 129.10, 132.49 and 133.98 (*C*CO and aromatic), 139.21 (aromatic), 173.49 (C=*C*S), and 191.58 (CO); ν_{max} 2930, 1615 and 1450cm.$^{-1}$; found M^+ 340.061 $C_{19}H_{16}O_2S_2$ requires 340.059, m/z 340 (60).

2-(1,3-Dithian-2-ylidene)-cyclohexane-1,3-dione (**14**) by method A in 45% yield and method B in 38% yield as pale yellow crystals m.p. 220-222°C; δH 1.97 (2H, quin. J 7.1, CH_2), 2.36 (2H, quin J 7.3, CH_2), 2.60 (4H, t J 7.1, CH_2CO), 2.89 (4H, t J 7.3, SCH_2); δC 18.87 (CH_2), 24.96 (CH_2), 31.78 (SCH_2), 38.75 (CH_2CO), 129.97 (*C*CO) 192.60 (C=*C*S) and 194.80 (CO); ν_{max} 2946, 1654 and 1607cm.$^{-1}$; λ_{max} 351nm (ε 18,200) 299 (ε 6300) and 244nm (ε 14,000) found M^+ 228.028 $C_{10}H_{12}O_2S_2$ requires 228.028 m/z 228 (100), 195 (50), 181 (21) and 168 (15).

5,5-Dimethyl-2-(1,3-dithian-2-ylidene)-cyclohexane-1,3-dione (**15**) by method A in 67% yield as pale yellow crystals m.p. 195-197°C (lit[20] m.p. 196-198°C).

Diethyl (1,3-dithian-2-ylidene)-1-propanedioate (**16**) by method A in 93% yield and method B in 59% yield as golden yellow crystals m.p. 58-59°C (lit[16] m.p. 59-60°C).

Ethyl (1,3-dithian-2-ylidene)-cyanoacetate (**17**) by method A in 91% yield and method B in 68% yield as pale orange crystals m.p. 94-95°C (lit[16] m.p. 93-94°C).

2-(1,3-Dithian-2-ylidene)-propanedinitrile (**18**) by method A in 63% yield and method B in 66% yield

as orange-beige crystals m.p. 134-135°C (lit[21] m.p. 133-133.5°C).

Ethyl 2-(1,3-dithiolan-2-ylidene)-3-oxo-butanoate (19) To a stirred solution of ethyl 3-oxo-butanoate (1.30g) in DMF (20ml) at room temperature was added carbon disulfide (1.14g) followed by 1,2-dibromoethane (2.26g) dropwise over 20min. The resulting mixture was stirred for a further 7h and then ice-water (20ml) was added. After filtration, the residue was dried in a desiccator and recrystallised from ethanol to give as pale ivory crystals the title compound (2.04g) in 88% yield, m.p. 81-83°C (lit[22] m.p. 82-83°C).

3-(1,3-Dithiolan-2-ylidene)-pentane-2,4-dione (20) To a stirred solution of pentane-2,4-dione (1.00g) and potassium carbonate (4.14g) in DMF (20ml) at room temperature was added carbon disulfide (1.14g) followed by 1,2-dibromoethane (2.26g) dropwise over 20min. The resulting mixture was stirred for a further 7h and then ice-water (20ml) was added. After filtration, the residue was dried in a desiccator and recrystallised from ethanol to give as pale brown crystals the title compound (1.52g) in 75% yield, m.p. 140-142°C (lit[22] m.p. 141-143°C).

Reduction of Ketenedithioacetals

Method A: To a chilled (5°C) stirred solution of the ketenedithioacetal (10mmol) in dry methanol (20ml) was added magnesium turnings (0.81g, 35mmol). The mixture was stirred for 24h before aqueous hydrochloric acid (1M, 25ml) was added. The solution was extracted with dichloromethane washed with brine (50ml) and water (50ml), dried and the solvent was removed *in vacuo*. The crude product was purified by chromatography [silica gel, light petroleum and ethyl acetate (9:1) as eluent]. Solids were recrystallised from ethanol.

Method B To a stirred solution of the ketenedithioacetal (10mmol) in acetic acid (25ml) was added zinc dust (6.54g, 50mmol). After 48h the mixture was filtered through celite which was washed well with acetic acid. The solvent was removed from the combined filtrates *in vacuo* and the residue was dissolved in water (20ml). This aqueous solution was extracted with dichloromethane (3 x 25ml) and the combined organic phases were dried and then concentrated *in vacuo*. The crude product was purified by chromatography [silica gel, light petroleum and ethyl acetate (9:1) as eluent]. Solids were recrystallised from ethanol.

Using the above methods the following reduction products of ketenedithioacetals were obtained:

Ethyl 2-(1,3-dithian-2-yl)-3-oxobutanoate (21) by method A in 87% yield and by method B in 84% yield. This ester has been previously described[23].

Ethyl 2-(1,3-dithian-2-yl)-3-oxo-3-phenylpropionate (22) by method A in 43% yield and by method B in 59% yield as an ivory white solid, m.p. 78-80°C; δH 1.21 (3H, t J 7, CH_3), 2.03 (2H, m, CH_2), 2.80 (4H, m, SCH_2), 4.18 (2H, q J 7, OCH_2), 4.73 (1H, d J 11, CH), 5.10 (1H, d J 11, CHS), 7.50 (2H, t J 7.4, H_m), 7.62 (1H, t J 7.4, H_p) and 8.08 (2H, d J 7.4, H_o); δC 14.12 (CH_3), 25.34 (CH_2), 27.41 (SCH_2), 27.53 (SCH_2), 42.24 (CHS), 58.60 (CHCO), 62.24 (OCH_2), 128.92, 129.05, 134.13, 136.49 (aromatic), 166.42 (CO, ester) and 191.40 (CO, ketone); ν_{max} 2906, 1737 and 1689cm.$^{-1}$; found M^+ 310.069

$C_{15}H_{18}O_3S_2$ requires 310.070, m/z 310 (100), 281 (62), 265 (21), 233 (34).

Ethyl 2-(1,3-dithian-2-yl)-3-oxobutanoate (23) as a pale yellow oil by method A in 0% yield and by method B in 43% yield; δH 1.09 (3H, t J 7, CH_3), 1.28 (3H, t J 7.4, CH_3), 2.03 (2H, m, CH_2), 2.62 (2H, q J 7.4, CH_2CO), 2.77 (2H, m, SCH_2), 2.95 (2H, m, SCH_2), 4.20 (1H, d J 11.4, CHCO), 4.21 (2H, q J 7.4, OCH_2), 4.46 (1H, d J 11.4, CHS); δC 7.58 (CH_3), 14.18 (CH_3), 25.25 (CH_2), 27.64 (SCH_2), 27.66 (SCH_2), 36.27 (CH_2CO), 41.78 (CHS), 62.09 (OCH_2), 63.28 (CHCO), 166.56 (CO, ester) and 202.09 (CO, ketone); ν_{max} 2983, 1745 and 1714cm.$^{-1}$; found M^+ 262.073 $C_{11}H_{18}O_3S_2$ requires 262.073, m/z 262 (28), 233 (100), 217 (51), 188 (29), 187 (10) and 114 (21).

3-(1,3-Dithian-2-yl)-pentane-2,4-dione (24) as colourless crystals m.p. 81-83°C (lit.[24] m.p. 94°C) by method A in 92% yield and by method B in 87% yield.

3-(1,3-Dithian-2-yl)-1-phenylbutane-1,3-dione (25) as golden yellow crystals m.p. 110-112°C by method A in 18% yield and by method B in 43% yield; δH 2.03 (2H, m, CH_2), 2.23 (3H, s, CH_3), 2.84 (4H, m, SCH_2), 4.80 (1H, d J 11.4, CH), 5.18 (1H, d J 11.4, CHS), 7.50 (2H, t J 7.4, H_m), 7.61 (1H, t J 7.4, H_p) and 8.06 (2H, d J 7.4, H_o); δC 25.20 (CH_2), 27.26 (CH_3), 27.67 (SCH_2), 27.96 (SCH_2), 42.85 (CHS), 67.40 (CHCO), 129.07, 129.12, 134.31, 136.73 (aromatic), 192.95 (CO) and 200.24 (CO); ν_{max} 2963, 1717 and 1676cm.$^{-1}$; found M^+ 280.060 $C_{14}H_{16}O_2S_2$ requires 280.059, m/z 280 (5), 237 (100), 175 (44), 163 (18), 119 (15) and 105 (58).

2-(1,3-Dithian-2-yl)-1,3-diphenylpropane-1,3-dione (26) as a golden oil by method A in 45% yield and by method B in 50% yield; δH 1.96 (1H, m, CH), 2.09 (1H, m, CH), 2.90 (4H, m, SCH_2), 5.10 (1H, d J 11.0, CHS), 5.84 (1H, d J 11.0, CHCO), 7.45 (4H, t J 7.7, H_m), 7.57 (2H, t J 7.4, H_p) and 8.03 (4H, d J 7.0, H_o); δC 25.41 (CH_2), 29.53 (SCH_2), 42.33 (CHS), 60.97 (CHCO), 129.01, 129.10, 134.04, 136.72 (aromatic) and 191.91 (CO); ν_{max} 2903, 1700 and 1662cm.$^{-1}$; found M^+ 342.073 $C_{19}H_{18}O_2S_2$ requires 342.074, m/z 342 (42), 265 (100), 237 (23) and 161 (15).

2-(1,3-Dithian-2-yl)-3-hydroxycyclohex-2-enone (27) as a pale yellow oil by method A in 51% yield and by method B in 53% yield; δH 1.94 (2H, m, CH_2), 1.97 and 2.07 (2H, m, CH_2), 2.27 (2H, t J 7.0, CH_2), 2.40 (2H, t J 7.0, CH_2), 2.80 (2H, m, SCH_2), 3.01 (2H, m, SCH_2), 5.67 (1H, s, CHS), 8.01 (1H, bs, OH); δC 16.41 (CH_2), 24.81 (CH_2), 30.61 (CH_2), 31.58 (SCH_2), 36.81 (CH_2CO), 38.39 (CHS), 110.41 (=CCO), 174.29 (=COH) and 194.76 (CO); ν_{max} 3338, 2964, 1652 and 1609cm.$^{-1}$; found M^+ 230.045 $C_{10}H_{14}O_2S_2$ requires 230.046, m/z 230 (76), 197 (54), 156 (100) and 110 (21).

5,5-Dimethyl-2-(1,3-dithian-2-yl)-3-hydroxycyclohex-2-enone (28) as a silvery grey solid m.p. 128-130°C) by method A in 66% yield and by method B in 71% yield; δH 1.02 (6H, s, CH_3), 1.80 and 2.10

(2H, m, CH_2), 2.22 (2H, s, CH_2), 2.35 (2H, s, CH_2), 2.82 (2H, m, SCH_2), 3.00 (2H, m, SCH_2), 5.68 (1H, s, CHS), 7.98 (1H, bs, OH); δC 24.87 (CH_2), 28.23 (CH_3), 31.56 (SCH_2), 31.75 (CMe_2), 38.11 (CH), 43.13 (CH_2CO), 50.10 (CH_2), 111.76 (=CCO), 175.10 (=COH) and 194.49 (CO); ν_{max} 3342, 2960, 1648 and 1612cm.$^{-1}$; found M^+ 258.073 $C_{12}H_{18}O_2S_2$ requires 258.075, m/z 258 (95), 225 (60), 184 (100) and 117 (25).

Diethyl (1,3-dithian-2-yl)propanedioate (29) as a pale green oil by method A in 76% yield and by method B in 71% yield. This ester has been previously described[25].

Ethyl (1,3-dithian-2-yl)cyanoacetate (30) as white crystals m.p. 62-64°C by method A in 77% yield and by method B in 70% yield; δH 1.28 (3H, t J 7.4, CH_3), 1.99 (2H, m, CH_2), 2.74 (2H, m, SCH_2), 3.02 (2H, m, SCH_2), 4.02 (1H, d J 7.4, CHCO), 4.25 (2H, q J 7.4, OCH_2), 4.32 (1H, d J 7.4, CHS); δC 14.12 (CH_3), 24.47 (CH_2), 27.54 (SCH_2), 27.69 (SCH_2), 42.29 (CHS), 44.90 (CHCO), 63.63 (OCH_2), 114.86 (CN) and 163.52 (CO); ν_{max} 2985, 2241 and 1748cm.$^{-1}$; found M^+ 231.038 $C_9H_{13}O_2S_2$ requires 231.039.

2-(1,3-Dithian-2-yl)propanedinitrile (31) as pale brown crystals m.p. 104-106°C by method A in 80% yield; δH 1.84 and 1.94 (2H, m, CH_2), 2.74 (2H, m, SCH_2), 3.02 (2H, m, SCH_2), 4.37 (1H, d J 11.0, CHS), 5.82 (1H, d J 11.0, CHCN); δC 23.94 (CH_2), 24.81 (CHCN), 28.96 (SCH), 30.04 (SCH_2) and 113.26 (CN) ; ν_{max} 2928 and 2329cm.$^{-1}$; found M^+ 184.013 $C_7H_8N_2S_2$ requires 184.013.

Ethyl 2-(1,3-dithiolan-2-yl)-3-oxo-butanoate (32) as a pale yellow oil by method A in 44% yield and by method B in 52% yield. This ester has been previously described[26].

3-(1,3-Dithiolan-2-yl)-pentane-2,4-dione (33) as pale yellow crystals m.p. 49-51°C (lit.[26] m.p. 50-52.5°C) by method A in 42% yield and by method B in 45% yield.

4-(1,3-Dithian-2-yl)-3-hydroxy-5-methylisoxazole (37)

To a stirred solution at room temperature of the ester (**21**) (2.48g) in ethanol (10ml) was added hydroxylamine hydrochloride (0.7g) in water (1ml). The mixture was heated under reflux for 2 hours, cooled and poured into water (30ml). The solution was extracted with diethyl ether (3 x 25ml), the combined organic extracts were dried and the solvent was removed *in vacuo*. The crude product was purified by column chromatography [silica gel, eluent light petroleum: ethyl acetate (7:3) to afford in 48% yield the title compound (**37**) (1.04g) as bright orange crystals, m.p. 110-112°C (ethanol) δH 1.63 (1H, m) and 2.06 (1H, m) (CH_2), 2.31 (3H, s, CH_3), 2.81 (2H, m, SCH_2), 3.06 (2H, m, SCH_2), 3.31 (1H, bs, OH) and 5.10 (1H, s, CHS); δC 11.26 (CH_3), 24.61 (CH_2), 31.15 (SCH_2), 38.35 (CH), 93.67, 161.80 and 169.52; ν_{max} 2722, 1674 and 1580cm.$^{-1}$; found M^+ 217.023 $C_8H_{11}NO_2S_2$ requires 217.023 m/z 217 (8), 143 (40), 119 (69) and 106 (100).

3,5-Dimethyl-4-(1,3-dithian-2-yl)-1*H*-pyrazole (34)

To a stirred solution at room temperature of the dione (**24**) (2.18g) in ethanol (10ml) was added hydrazine hydrate (0.5g). The mixture was heated under reflux for 30min., cooled and poured into brine (20ml). The solution was extracted with diethyl ether (3 x 25ml), the combined organic extracts were dried and the solvent was removed *in vacuo*. The crude product was purified by column chromatography [silica gel, eluent light petroleum: ethyl acetate (7:3) to afford in 81% yield the title compound (**34**) (1.73g) as white crystals, m.p. 159-161°C (ethanol); δH 1.89 (1H, m) and 2.16 (1H, m) (CH_2), 2.39 (6H, s, CH_3), 2.87 (2H, m, SCH_2), 3.00 (2H, m, SCH_2), 5.18 (1H, s, CHS) and 6.47 (1H, bs, NH); δC 11.72 (CH_3), 25.26 (CH_2), 32.55 (SCH_2), 41.56 (CH), 113.68 and 143.31; ν_{max} 3012 and 1546cm.$^{-1}$; found M^+ 214.061 $C_9H_{14}N_2S_2$ requires 214.062 m/z 214 (94), 140 (100) and 139 (86).

3,5-Dimethyl-4-(1,3-dithian-2-yl)-1-phenylpyrazole (35)

To a stirred solution at room temperature of the dione (**24**) (2.18g) in ethanol (10ml) was added phenylhydrazine (1.08g). The mixture was heated under reflux for 3 h. cooled and poured into brine (20ml). The solution was extracted with diethyl ether (3 x 25ml), the combined organic extracts were dried and the solvent was removed *in vacuo*. The crude product was purified by column chromatography [silica gel, eluent light petroleum: ethyl acetate (7:3) to afford in 45% yield the title compound (**35**) (1.31g) as a red oil; δH 1.84 (1H, m) and 2.09 (1H, m) (CH_2), 2.36 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.86 (2H, m, SCH_2), 3.01 (2H, m, SCH_2), 5.21 (1H, s, CHS) and 7.35-7.5 (5H, m, aromatic); δC 11.72 (CH_3), 14.36 (CH_3), 26.13 (CH_2), 33.16 (SCH_2), 42.61 (CH) and 115.16, 126.14, 129.03, 129.82, 139.46, 143.31 and 146.21 (aromatic); ν_{max} 1562cm.$^{-1}$; found M^+ 290.094 $C_{15}H_{18}N_2S_2$ requires 290.094 m/z 290 (86), 216 (100) and 213 (56).

3,5-Dimethyl-4-(1,3-dithian-2-yl)-isoxazole (36)

To a stirred solution at room temperature of the dione (**24**) (2.18g) in ethanol (10ml) was added hydroxylamine hydrochloride (0.7g). The mixture was heated under reflux for 2 h. cooled and poured into brine (30ml). The solution was extracted with diethyl ether (3 x 25ml), the combined organic extracts were dried and the solvent was removed *in vacuo*. The crude product was purified by column chromatography [silica gel, eluent light petroleum: ethyl acetate (7:3) to afford in 99% yield the title compound (**36**) (2.13g) as colourless needles m.p. 54-56°C (ethanol); δH 1.88 (1H, m) and 2.15 (1H, m) (CH_2), 2.35 (3H, s, CH_3), 2.50 (3H, s, CH_3), 2.86 (2H, m, SCH_2), 3.01 (2H, m, SCH_2) and 5.06 (1H, s, CHS); δC 10.16 (CH_3), 11.04 (CH_3), 23.46 (CH_2), 31.59 (SCH_2), 39.71 (CH) and 112.49, 159.12 and 168.26 (aromatic); ν_{max} 2902, 1627 and 1451cm.$^{-1}$; found C, 49.9; H, 6.0; N, 6.39; $C_9H_{13}NOS_2$ requires C, 50.2; H, 6.05; N, 6.51.

3,5-Dimethyl-4-formyl-1H-pyrazole (38)

To a stirred solution of the pyrazole (**34**) (2.14g) in acetonitrile (30ml) was added N-bromosuccinimide (12.46g) in 80% aqueous acetonitrile (20ml) at -5°C. The temperature was raised to 30°C over 10min. before sodium sulfite (2M, 30ml) was added and the solution was extracted with hexane:dichloromethane (1:1, 3 x 30ml). The

combined organic extracts were washed with brine (40ml) and water (40ml), dried and the solvent was removed in vacuo to afford a crude reaction product, which was purified by column chromatography [silica gel, eluent light petroleum: ethyl acetate (9:1)] to give the title compound (**38**) (1.20g) in 97% yield as a colourless oil, δH 2.25 (6H, s) (CH_3), 6.73 (1H, bs, NH), (1H, s, CHO); δC 11.23 (CH_3), 94.05 (C4), 148.83 (C3 and 5) and 185.29 (CO); ν_{max} 3117, 1708, 1670 and 1580 $cm.^{-1}$; found M^+ 124.064 $C_6H_8N_2O$ requires 124.064. m/z 124 (M^+, 100), 95 (43) and 80 (38).

3,5-Dimethyl-4-formyl-1-phenylpyrazole (39)

By the above procedure the title compound (**39**)[27] was obtained in 94% yield.

3,5-Dimethyl-4-formylisoxazole (40)

By the above procedure the title compound (**40**)[28] was obtained in 78% yield.

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