Synthesis of New Dithiolethione Derivatives: 5-(1-hydroxyiminoalkyl)-1,2-dithiole-3-thiones and 5-acyl-1,2-dithiole-3-thiones

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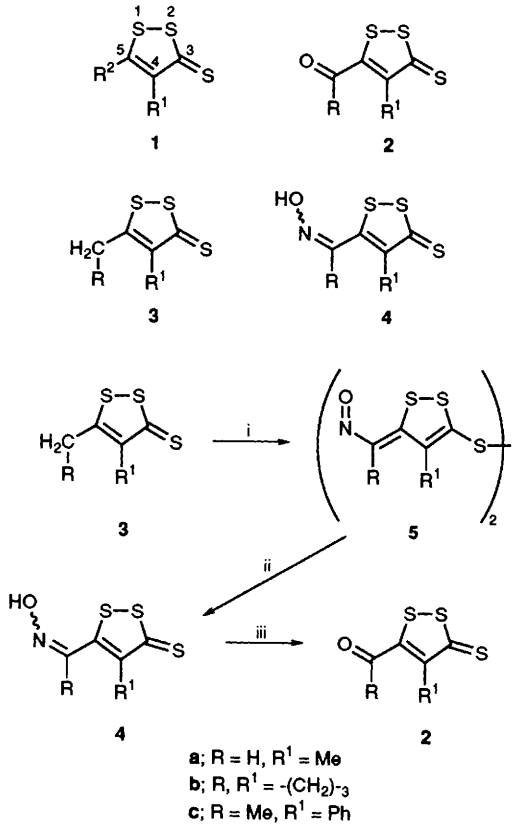
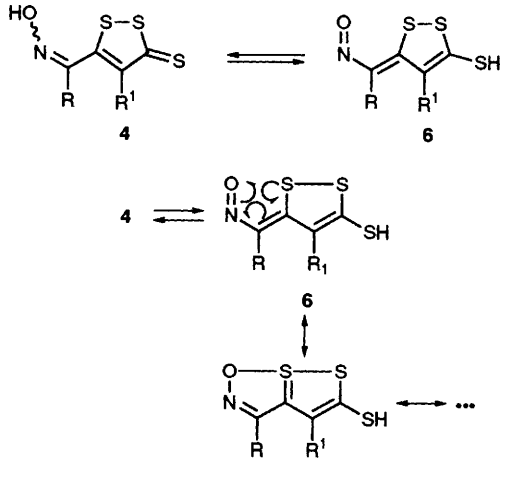
A synthetic pathway to obtain, in three steps, acceptable yields of 5-acyl-1,2-dithiole-3-thiones is described.

1,2-dithiole-3-thiones **1** are compounds of growing pharmaceutical interest.[1] As few of the numerous compounds **1** described in the literature are functionalized in position 5 (or indeed in position 4),[2a] we devoted our studies to the synthesis of 5-acyldithiolethiones **2**.



Scheme 1 *Reagents and conditions*: i, crystalline $NaNO_2$/anhydrous $MeCO_2H$, room temp., 2 h; ii, Na_2S, H_2O, Me_2SO, room temp. 2 h, finally H^+, extraction with diethyl ether and evaporation; iii, CH_2O, H_3O^+, toluene, reflux, 2 h



Only three dithiolethiones of this type have been described.[3] We report a method to synthesize dithiolethiones **2** from the 5-methyl-(or methylene-) dithiolethiones **3** *via* the corresponding 5-(1-hydroxyiminoalkyl)-1,2-dithiole-3-thiones **4** (oxime dithiolethiones).

5-Methyl-(or methylene-) dithiolethiones **3** are easily synthesised.[2b] Our method is based on the 2- and 4-methyl-(or methylene-) pyridine-like reactivity of 5-methyl-(or methylene-) dithiolethiones **3**.[2c] The reaction was performed with dithiolethiones **3a**, **3b** and **3c** (Scheme 1); (**3a** can be considered as a typical 5-methyldithiolethione; **3b** and **3c** were chosen because 5-methylenedithiolethiones do not undergo some condensations.[4])

Addition of an excess of sodium nitrite to an acetic acid solution of **3** gives highly insoluble **5a** mp 206 °C, 70%, **5b** mp 104 °C, 55% and **5c** mp 243 °C, 63%.

Disulfides **5** treated with sodium sulfide gave oxime dithiolethiones, **4a** mp 193 °C, 60%, **4b** mp 195 °C, 75% and **4c** mp 162 °C, 70%. The reaction of oximes **4a**, **4b** and **4c** with formaldehyde in acidic solvolytic conditions produces the 5-acyldithiolethiones **2a** mp 105 °C, 60%, **2b** mp 95 °C, 73% and **2c** mp 85 °C, 80%. Compounds **5** are disulfides of the corresponding 5-mercapto-1-oxa-6,6a-S^{IV}-dithia-2-azapentalenes **6** which are the tautomeric forms of the oximes **4**.

It is very likely that disulfides **5** are the result of oxidation of the oxime dithiolethiones **4** by the reagent itself as the oxime dithiolethiones **4** are easily oxidised by the reagent in the same experimental conditions. When sodium nitrite is not added in excess to the dithiolethiones to avoid the formation of disulphides, only the latter are still significantly formed.

Both isomers *E* and *Z* of **4a** have been characterized by NMR spectroscopy while for **4b** and **4c** isomers *Z* and *E* only have been respectively detected. 5-Mercaptoheteropentalenes **6a**, **6b** and **6c**, which are the tautomeric forms of oximes **4a**, **4b** and **4c**, have not been characterized. This is an interesting finding because 1-oxa-6,6a-S^{IV}-dithia-2-azapentalenes are considered as bicyclic aromatic compounds with considerable π-electron delocalisation.[5]

However, the NMR data are those obtained by recording spectra as soon as crude oximes **4** are dissolved in $(CD_3)_2SO$ at 25 °C. Crude oximes were isolated in mild conditions from their ethereal solution, by evaporation of the solvent at room temp. The ratio *E*:*Z* can vary according to different parameters.

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