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# Oxidation of Dithiocarbamates and Synthesis of a Stable Sulfine

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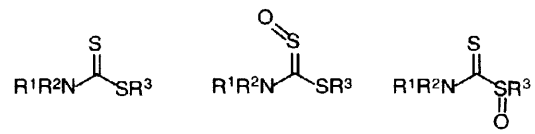
**Abstract.** Investigation of the oxidation reaction of various dithiocarbamates demonstrated that the corresponding sulfines (*S*-oxides) are formed. Though their stabilities are very moderate, a number of sulfines could be isolated and characterised. When left at ambient temperature they decomposed to thiolocarbamates and dithiocarbamates. The sulfines from secondary dithiocarbamates led to disulfides which formation was explained. With a sterically hindered aryl group present on the sulfur atom, a stable sulfine was prepared and its crystal structure was analysed. 

Dithiocarbamates are intensively used as fungicides.[1-3] The mode of action and the metabolism of thiocarbonyl compounds has been studied.[4-9] Among other possibilities it has been proposed that the biological active species would be the corresponding sulfines (thiocarbonyl *S*-oxides) arising from the cytochrome P-450 monoxygenase mediated oxidation of the C=S moiety. Moreover, a dithiocarbamate oxide has recently been evidenced[10-12] as the oxidation product of a cruciferous phytoalexin (brassinin) by *Phoma lingam* fungi strains.




1 Sulfine "Sulfoxide"

Some studies[5,8,13-16] on the chemical oxidation of dithiocarbamates are available. However the characterisation and information on the stabilities of the corresponding sulfines is scant and deserve further investigation. The first synthesis of sulfines by Walter *et al* was carried out[13,17] in a time when NMR spectroscopy was not available. Conflicting results have been reported later: whereas Watanabe described[15] the synthesis of the (*E*) and (*Z*) isomers of methyl *N,N*-diethyldithiocarbamate *S*-oxide, Faiman proposed[5] that one of the compounds had the (*E*) sulfine structure and the other one has a "sulfoxide" moiety. We wish to report our investigation of acyclic dithiocarbamates, isolation of the various products of oxidation, including sulfines and disulfides, and evaluation of the sulfine stabilities.

We first checked the preparation of sulfine **2a** ($R^1$,$R^2$,$R^3$=Me) according to Watanabe,[15] from **1a** and MCPBA, and were surprised to be unable to detect sulfine **2a** by $^1$H NMR. The crude mixture was actually

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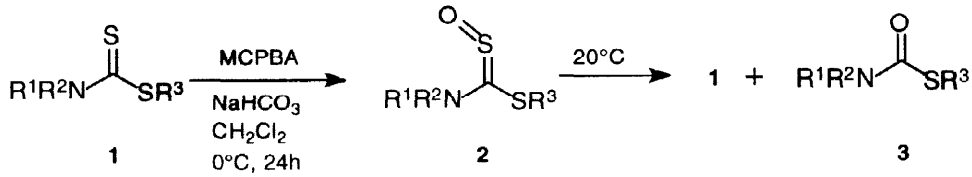
composed of dithiocarbamate **1a** and thiolocarbamate **3a**. Assuming a low stability of sulfine **2a** under the conditions which are acidic, we added a mineral base ($Na_2CO_3$) during the oxidation procedure and were rewarded to detect the formation of sulfine **2a**, mixed with **1a** and **3a**. Investigation of a variety of dithiocarbamates **1b-j** revealed a similar course for the oxidation reaction. Attempts to isolate pure sulfines from these mixtures were successful in five examples (entries 1,4,5-7) by flash chromatography and in two examples (entries 8,9) by crystallisation leading to compounds **2b**, **2e-j** in yields from 30 to 60% (Table).

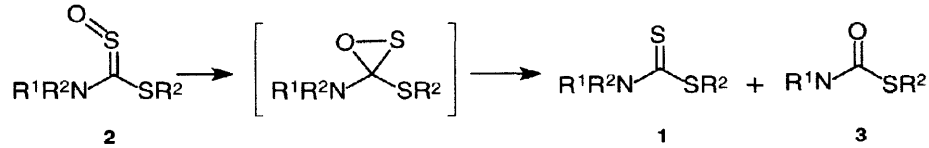



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1a | Me | Me | Me | 1f | H | 2,4,6-tri-*i*-Pr-Ph | Me |
| 1b | Et | Et | $CH_2Ph$ | 1g | Me | Ph | Me |
| 1c | H | Ph | Me | 1h | H | Me | *t*-Bu |
| 1d | H | Ph | *i*-Bu | 1i | H | Me | 2,6-di-Me-Ph |
| 1e | H | 2,6-di-Me-Ph | Me | 1j | H | Me | 2,4,6-tri-*i*-Pr-Ph |

The C=S=O group was characterised by $^{13}C$ NMR in the range of 176 to 196 ppm (upfield from the corresponding C=S group observed at 196-205 ppm). The sulfoxide structure proposed by Faiman can be ruled out as the methylthio groups of compounds **2a,c,e-g** were observed in the range of 11.8-21.4 ppm, incompatible with a methylsulfinyl group expected at lower field.

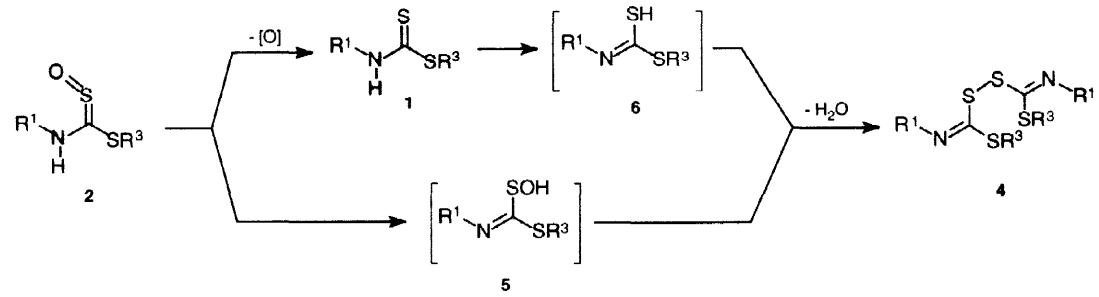
An attractive feature of the oxidation reaction is the detection of a ***single isomer*** for the sulfine. Its (*E*) stereochemistry was assigned by comparison of the $^1H$ NMR signals of the starting C=S molecules, in analogy with previous reports[18,19] for a variety of sulfines. For instance, the methylthio group of **2a** is observed at higher field (2.23 ppm) than the one of dithiocarbamate **1a** (2.63 ppm). The highly anisotropic S=O bond generates along its axis a shielding cone which includes the SMe group of the (*E*) isomer and not the one of the (*Z*) isomer. Selective formation of the (*E*) isomer may be related to a dipole alignment of the peroxycarboxylic acid O-O bond with the N-C=S moiety involving the *syn* sulfur lone pair.

Having in hands pure sulfines we were able to evaluate their stabilities and monitor their transformation. As a typical example, sulfine **2g** ($R^1$=Me, $R^2$=Ph, $R^3$=Me) in a $CDCl_3$ solution was transformed with a half reaction time of 15 days into a 1:1 mixture of thiocarbamate **3g** and dithiocarbamate **1g**. In all other cases which do not bear an aromatic substituent to nitrogen, a similar behaviour was evidenced with various **3/1** ratios and $t_{1/2}$ (Table). The formation of thiocarbonyl compounds **1** from sulfines has few precedents,[18,20] the usual pathway of decomposition being the formation of the carbonyl compound with loss of sulfur. The accompanying mechanism can be proposed, involving electrocyclisation of the sulfine to an intermediate oxathiirane and subsequent sulfur atom (or oxygen) extrusion to generate **1** or **3**. The form under which these species are eliminated is intriguing.[21]



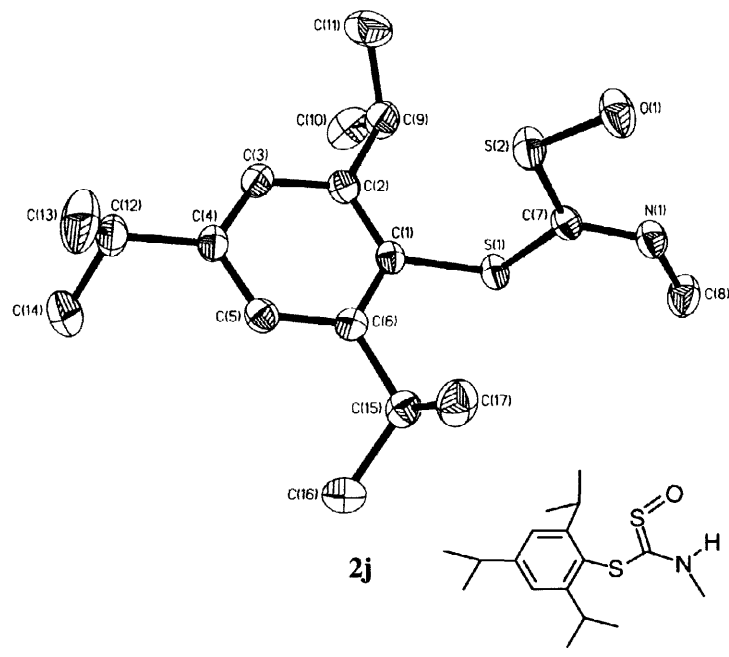

The oxidation reaction of secondary dithiocarbamates bearing an aromatic group on the nitrogen atom provided information which shed light on analogous results with thionocarbamates.[22] The initial products

were sulfines **2** which, left at ambient temperature for some days (9 days in the example of **2f**), were transformed into disulfides **4**. The detection of a transient amount of dithiocarbamate **1** during this process led us to propose a mechanism involving formation of both the sulfine **2** and the dithiocarbamate **1**, which were respectively tautomerised to an iminosulfenic acid **5** and an iminothiol **6** which combined[23] to produce disulfides with $H_2O$ elimination. Our experiments led us to rule out the direct oxidation of the iminothiol tautomer as proposed in the literature.[22]




Using a sterically hindered group to provide a kinetic protection of a very reactive functional group[24] is now a classical strategy. However we were unsuccessfull to prepare a stable sulfine when we installed a 2,6-diisopropylphenyl group on the nitrogen atom (dithiocarbamate **1f**) as a result of the thermodynamically favoured formation of disulfide **4f**. We decided to introduce a 2,4,6-triisopropylphenyl group as $R^3$ on the *sulfur* atom, instead of nitrogen. Oxidation of dithiocarbamate **1j** ($R^1$=H, $R^2$=Me) with MCPBA took place nicely in a matter of minutes at 0°C providing a 97% conversion to the (*E*) sulfine **2j**. It showed a satisfactory *stability* in $CDCl_3$ solution (only 10% transformation after 2 weeks) and a complete one in the solid state. Single crystals were obtained by crystallisation in a petroleum ether/dichloromethane mixture (mp=146°C) and submitted to X-ray diffraction analysis.

The sulfine structure is nicely confirmed[25] with a planar arrangement and the oxygen atom located *trans* to the bulky aryl group. The lengths of the C=S and S=O bonds are 1.69 and 1.53 Å respectively. The planes of the sulfinyl group and the aromatic ring are almost orthogonal (94°). The *N*-methyl group lies in the plane of the sulfine moiety, demonstrating a planar arrangement around the C(7)-N(1) bond and a nitrogen atom with an $sp^2$ character, similarly to thioamides. An intermolecular S=O····HN hydrogen bond (1.93 Å) is observed.




In conclusion our study revealed a number of surprising observations. Reaction of dithiocarbamates with a standard oxidising agent (MCPBA) provides an efficient synthesis of (*E*) sulfines, which are very

moderately stable compounds. These oxides are transformed into C=S *and* C=O compounds, or disulfides. The synthesis of a relatively stable dithiocarbamate oxide was achieved by using kinetic steric protection.

**Table. Oxidation of dithiocarbamates 1 with MCPBA**

| Entry | $R^1$(N) | $R^2$(N) | $R^3$(S) | Time | Sulfine **2** | Product composition (crude mixture)[a] % | | | | Isolated yield of **2** | NMR δ $C^{13}$ C=S=O |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **1** | **2** | **3** | **4** | | ppm |
| 1 | Et | Et | $CH_2Ph$ | 4 h | **2b** | 30 | 52 | 6 | | 45 | 176.7 |
| 2 | H | Ph | Me | 4 h | **2c** | 15 | 50 | | 18 | | 191.8 |
| 3 | H | Ph | *i*-Bu | 4 h | **2d** | 12 | 61 | | 11 | | 190.0 |
| 4 | H | 2,6-diMe-Ph | Me | 30 min | **2e** | 39 | 50 | | 10 | 60 | 195.2 |
| 5 | H | 2,4,6-tri-*i*-Pr-Ph | Me | 10 min | **2f** | 18 | 81 | | | 61 | |
| 6 | Me | Ph | Me | 15 min | **2g** | 40 | 30 | 25 | | 47 | 183.1 |
| 7 | H | Me | *t*-Bu | 30 min | **2h** | 20 | 63 | | | 30 | 184.7 |
| 8 | H | Me | 2,6-diMe-Ph | 30 min | **2i** | 10 | 79 | | | 52 | 195.4 |
| 9 | H | Me | 2,4,6-tri-*i*-Pr-Ph | 30 min | **2j** | 3 | 97 | | | 60 | 197.7 |

[a] Determined by NMR analysis approximately 1h after the end of the oxidation procedure. Some percents of thiolformates[14] were also observed.

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25. Atomic coordinates, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre under number 103111. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code +(1223) 336-033; e-mail: teched@ccdc.cam.ac.uk).