

## Thiophilic Addition of Organolithiums to Aliphatic Sulfoxines

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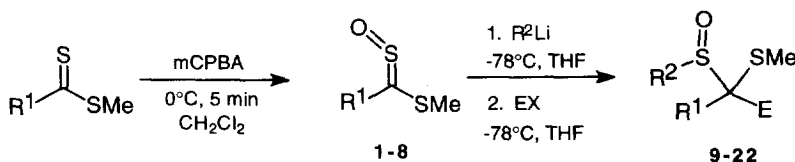
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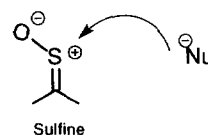
**Abstract.** Enethiolizable sulfoxines, freshly generated by oxidation of dithioesters, have been reacted with organolithiums. The reaction follows a selective thiophilic course leading to stabilised dithioacetal oxide carbanions, which have been subsequently treated with electrophiles. The resulting dithioacetal oxides are readily transformed into aldehydes or spontaneously to ketones. The specificity of this "Umpolung" related chemistry is that it involves an addition reaction and not a deprotonation. Carbophilic addition has not been evidenced and enethiolization appears very limited. Copyright © 1996 Elsevier Science Ltd

Sulfoxines<sup>1,2</sup> have attracted our attention as they may lead to addition of nucleophiles through the electron poor sulfur atom<sup>2</sup> of the heterocumulene moiety. The first evidence for this inversion of reactivity (as compared to C=O) is due to Schultz and Schlessinger.<sup>3</sup> Since, some scattered examples have been reported in the literature,<sup>4</sup> and more extensive studies are due to the group of Zwanenburg<sup>5</sup> mostly with aromatic sulfoxines derived from dithioesters.

Such a reaction has not yet been reported for aliphatic and enethiolizable sulfoxines, as these compounds were formerly considered<sup>2,6</sup> as not accessible by oxidation of the corresponding thiocarbonyl compounds. In contrast to these expectations, we have reported recently that aliphatic sulfoxines can be prepared by oxidation of dithioesters,<sup>7</sup> thionesters<sup>8</sup> and thioketones<sup>9</sup> with one equivalent of mCPBA in dichloromethane at 0°C. A study of their stabilities has taught us in which conditions these fragile molecules can be used.



There was however a major concern with a possible competition between addition and deprotonation. Thiocarbonyl compounds<sup>10</sup> bear highly acidic  $\alpha$ -protons (pKa for MeCS<sub>2</sub>Me has got a value of 12.5 - ref<sup>11</sup>)



and the analogous protons of sulfines have also been assumed to exhibit the same behaviour.<sup>12</sup> We wish to report here the successful and selective reaction of dithioester oxides with organolithiums.

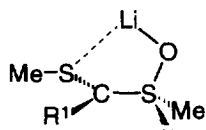
We have submitted a variety of aliphatic sulfines **1-8** (freshly prepared<sup>7</sup>) to the reaction of methyllithium at  $-78^{\circ}\text{C}$  in THF. The resulting mixture was treated with  $\text{H}_2\text{O}$ ,  $\text{D}_2\text{O}$  or  $\text{MeI}$ . The crude materials consisted of essentially pure dithioacetal oxides **9-16**, **19-22** (Table). The structures were assigned ( $E = H$ ) by the  $^1\text{H}$  NMR singlets of  $\text{MeS}$  at 2.2-2.3 ppm,  $\text{MeS}=\text{O}$  at 2.6-2.7 ppm and  $\text{CH}$  at 3.1-3.3 ppm. Two diastereoisomers are present with a ratio from 55:45 to 87:13. The compounds could be chromatographed or crystallised. However the chromatography on silica gel causes decomposition to a rather critical extent. Improved but still moderate yields (37-74 %) were attained by chromatography on alumina. For synthetic purposes this purification step may be avoided and yields of crude materials are in the range of 80-95 %, calculated from the dithioesters.

The *high electrophilic character* of these sulfines is impressive: reaction appears to be instantaneous at  $-78^{\circ}\text{C}$  and in one experiment (entry 8) we have observed that the reaction is still fast at  $-100^{\circ}\text{C}$ . *n*-Butyllithium and phenyllithium can also be employed to afford compounds **17** and **18** (entries 10 and 11).

We have not detected any product resulting of carbophilic addition. A compound arising from deprotonation was observed only in one case (entry 5) by quenching with iodomethane: we isolated (*Z*)-1-methylsulfinyl-1-methylthio-1-octene in a 10 % yield.

So thiophilic addition is a general reaction of aliphatic sulfines with organolithiums. Stabilised dithioacetal oxide carbanions are intermediately formed. Such species are known from the works of Ogura<sup>13,14</sup> and Schlessinger<sup>15</sup> in an "*Umpolung*" type chemistry.<sup>16</sup> It must be stressed here that these anions are generated by an addition reaction and not by deprotonation, thereby offering a different potential for synthesis, especially if other functional groups are present.

An intriguing question raises from the diastereoselectivity of the thiophilic addition. We were eager to evidence a possible stereospecificity of the process. We therefore conducted two experiments with sulfine **1** and methyllithium (entry 1): one with the (*E*)-isomer **1** and another with a 1 : 1 mixture of (*E*) and (*Z*) isomers. After water quench the very same diastereomeric ratio of 87 : 13 was measured. The reaction is thus non stereospecific. Two explanations may be considered: thermodynamic control or formation of a species with lithium being linked to oxygen (and coordinated to the other sulfur atom) instead of being close to carbon. The stereocontrol would then take place during electrophilic attack of a diastereotopic species. Further experiments are necessary to approach the nature of the intermediate, which is supported by structure of metalated benzyl sulfoxides:<sup>17</sup> lithium bound to oxygen and an almost planar arrangement of the  $\alpha$ -carbon.



Our interest in the use of dithioacetal oxides also stemmed from their facile conversion into aldehydes or ketones.<sup>14,15,18</sup> The conditions necessary are rather mild and do not involve hard metals ( $\text{Hg}$ ,  $\text{Ag}$ ,...): simple treatment with a mineral acid is generally efficient.

Table. Thiophilic Addition of Organolithiums to Sulfoxes 1-8

Entry	Sulfoxide	Organolithium		Electrophile	Product <sup>a)</sup>	Diastereomer ratio A/B (%)	Yield <sup>b)</sup> (%)	
	R <sup>1</sup>	R <sup>2</sup>	Temp. (°C)					
1	i-Pr	1	Me	-78	H <sub>2</sub> O	9	87 : 13	58
2	i-Pr	1	Me	-78	D <sub>2</sub> O	10	85 : 15	37
3	i-Bu	2	Me	-78	H <sub>2</sub> O	11	66 : 34	56
4	n-Oct	3	Me	-78	H <sub>2</sub> O	12	61 : 39	42
5	n-Oct	3	Me	-78	MeI	13	55 : 45	c)
6	n-Non	4	Me	-78	H <sub>2</sub> O	14	57 : 43	a)
7	Cyclohexyl	5	Me	-78	H <sub>2</sub> O	15	83 : 17	63 <sup>d)</sup>
8	Cyclohexyl	5	Me	-100	H <sub>2</sub> O	15	73 : 27	a)
9	Cyclohexyl	5	Me	-78	D <sub>2</sub> O	16	80 : 20	74
10	Cyclohexyl	5	n-Bu	-78	H <sub>2</sub> O	17	70 : 30	a)
11	Cyclohexyl	5	Ph	-78	H <sub>2</sub> O	18	67 : 33	50
12	Cyclohexyl	5	Me	-78	MeI	19	55 : 45	c)
13	Cyclopentyl	6	Me	-78	H <sub>2</sub> O	20	61 : 39	46
14	Methylallyl	7	Me	-78	H <sub>2</sub> O	21	65 : 35	58
15	2-Methyl-3-butenyl	8	Me	-78	H <sub>2</sub> O	22	11:21:31:37	55

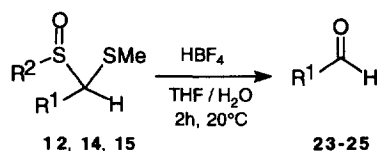
a) Crude materials were isolated with a 80-95% yield and approximately 90% purity.

b) Yields for products isolated by chromatography (entries 3,4,5,7,13,14,15) or crystallisation (entries 9,11).

c) Ketones **26** and **27** were isolated in 61 and 60% yields when products **13** and **19** were left at room temperature overnight.

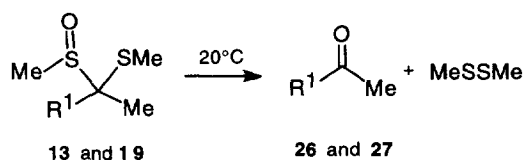
d) Isomers **15A** and **16A** are crystalline: mp 99-100°C and 100-101°C.

We have submitted dithioacetal oxides **12**, **14**, **15** in an HBF<sub>4</sub> H<sub>2</sub>O/THF solution for 2 hr. The corresponding aldehydes **23-25** were obtained with 60-70% yields.



For dithioacetal oxides **13** and **19** (arising from the reaction of the anions with MeI) we have made a remarkable observation. These compounds, when left at ambient temperature overnight, undergo a spontaneous formation of the corresponding ketones **26** and **27** accompanied with dimethyl disulfide. Addition of the mineral acid is thus not even necessary to carry out this transformation. There are some

scattered precedents for this reaction in the literature<sup>19</sup> but it was not reported in the field of *Umpolung* chemistry with these structures. This rearrangement probably involves formation (concerted or not) of an alkylthioalkanesulfonate and migration of the alkylthio group toward the electrophilic sulfur and subsequent cleavage of the S-O bond.



In conclusion we have shown that aliphatic sulfines undergo selective thiophilic addition with organolithiums, in contrast to the carbophilic addition which takes place with amines.<sup>20</sup> The resulting dithioacetal oxides are readily cleaved to aldehydes or ketones, either with a mineral acid or by a spontaneous rearrangement. We are presently attempting to exploit this reaction with sulfines bearing other functional groups.

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