# Selective Deoxygenation of Sulfoxides to Sulfides with Phosphites Catalyzed by Dichlorodioxomolybdenum(VI)

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**Abstract:** Chemoselective deoxygenation of sulfoxides to sulfides was carried out by  $P(OPh)_3$  in mild conditions catalyzed by dichlorodioxomolybdenum(VI).

Key words: sulfoxides, sulfides, molybdenum(VI), oxotransfer, catalysis

Sulfoxides are important intermediates in a variety of synthetic transformations, mainly as chiral auxiliaries in asymmetric synthesis.<sup>1</sup> In most cases, sulfoxides are removed from the target molecules and they are usually eliminated by a two-step process involving deoxygenation to sulfides,<sup>2</sup> which are then reductively cleaved by catalytic hydrogenation or other chemical methods.<sup>3</sup> On the other hand, deoxygenation of sulfoxides is important from a biological point of view and examples of relevant processes in biological systems are the deoxygenation of DMSO and that of biotin-S-oxide, catalyzed by DMSO reductase and biotin-S-oxide reductase respectively.<sup>4</sup> So, the reduction of sulfoxides to their corresponding sulfides continues to attract considerable attention and much effort has been devoted to the development of milder procedures where the presence of various sensitive and/or reducible functional groups can be tolerated.<sup>5</sup>

It has been for long assumed that the co-factors in sulfoxide reductases consist of oxomolybdenum complexes bearing S-coordinated ligands.<sup>6</sup> Also, it is known that some dioxomolybdenum(VI) complexes that mimic oxotransferases are efficient catalysts for the oxo-transfer reaction from DMSO to PPh<sub>3</sub> in mild conditions.<sup>7</sup> Furthermore, in our laboratory we have found that a number of dioxomolybdenum(VI) complexes, in particular addition compounds of dichlorodioxomolybdenum(VI), are able to catalyze a variety of oxo-transfer processes.<sup>8</sup> Based on these findings we have recently reported the facile oxidation of thiols to disulfides with DMSO, catalyzed by MoO<sub>2</sub>Cl<sub>2</sub>(dmso)<sub>2</sub>.<sup>9</sup> We now report the selective reduction of sulfoxides to sulfides with P(OPh)<sub>3</sub> catalyzed by  $Mo^{VI}O_2Cl_2$ , which is used in the form of the readily available DMF adduct,  $MoO_2Cl_2(dmf)_2$ .

In order to choose an optimal oxo-acceptor for sulfoxides under dioxomolybdenum(VI) catalysis some considerations need to be kept in mind. Based on the nature of the S=O and P=O bonds, the oxo-transfer reaction from sulfoxides to phosphines and phosphites is expected to be, in general, a thermodynamically favorable process. In this context, Smith et al. reported that tervalent phosphorus compounds functionalized either with strong electronwithdrawing or electron-donating groups were effective for the deoxygenation of sulfoxides.<sup>10</sup> Phosphites were usually preferred over phosphines due to their greater reactivity and readiness to be removed in the oxidized form.<sup>11</sup> However, in most cases the reaction requires rather high temperatures and long reaction times. To avoid these limitations, some reducing systems have been developed such as 1,3,2-benzodioxaphospholes,<sup>12</sup> PPh<sub>3</sub>/CCl<sub>4</sub>,<sup>13</sup>  $P(OEt)_3/I_2/NaI_1^{14}$   $P(NMe_2)_3/I_2/NaI_1^{15}$  or  $P(OSiMe_3)_3^{16}$ among others. However, these reagents are either expensive or they provide undesirable side products. On the other hand, compounds such as  $PCI_3$ ,<sup>17</sup>  $PI_3$ ,<sup>18</sup>  $P_2I_4$ <sup>19</sup> or  $ClP(OEt)_2^{20}$  are very effective deoxygenating agents but several functional groups are also sensitive to these reagents.

Thus,  $P(OPh)_3$  was the oxo-acceptor of choice as it is a readily available material and not very active in its reaction with sulfoxides. Also, it has a low vapor pressure at ambient temperature so that it lacks the unpleasant smell characteristic for other phosphines and phosphites. As we were unable to prepare a ready-to-use addition compound of  $MoO_2Cl_2$  with  $OP(OPh)_3$ , we used  $MoO_2Cl_2(dmf)_2$  as catalyst. The overall reaction that we propose could be written as shown in Scheme 1.

RR <sup>1</sup> SO	MoO <sub>2</sub> Cl <sub>2</sub> (dmf) <sub>2</sub> (cat.)	RR <sup>1</sup> S
+ P(OPh)₃		+ OP(OPh) <sub>3</sub>
(- /)		- (- /)

#### Scheme 1

Commercially available *p*-tolyl sulfoxide **1a** was first chosen to test the oxo-transfer process under dioxomolybdenum(VI) catalysis. A few preliminary tests were carried out to optimize the reaction conditions and the results are summarized in Table 1.

The reactions were carried out with 1.1 equivalents of  $P(OPh)_3$  and 2 mol% of catalyst. The slight excess of phosphite is used to compensate the presence of some phosphate in the commercial product. We had expected that a good solvent might be able to solubilize the products and at same the time should be insufficiently basic to avoid competition with the sulfoxide for the coordination

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**Table 1**Deoxygenation of p-Tolyl Sulfoxide 1a with P(OPh)3

<i>p</i> -Tol	0    .S	Cl <sub>2</sub> (dmf) <sub>2</sub> (2 mol%) P(OPh) <sub>3</sub> Solvent, time	p-Tol S	p-Tol
Entry	Solvent	Temp.	Time (h)	Conversion (%)
1	acetone	reflux	4	93
2	THF	reflux	2	77
3	MeCN	20°C	4	74
4 <sup>a</sup>	MeCN	reflux	1	100
5	$CH_2Cl_2$	reflux	4	95

<sup>a</sup> Under the same conditions but without catalyst, 19% conversion was observed after 26 h at reflux.

sphere of molybdenum. As shown in Table 1, we observed that solvents such as THF, acetone, MeCN or  $CH_2Cl_2$  could be used in this process but MeCN turned out to be the most suitable one. Indeed, complete conversion of sulfoxide **1a** to thioether **2a** was produced after one hour at reflux. It should be pointed out that without catalysis P(OPh)<sub>3</sub> requires 3 days at 110 °C to completely reduce methyl phenyl sulfoxide.<sup>11</sup>

Also, we have tested other possible reducing agents for this transformation. PPh<sub>3</sub> was effective to deoxygenate **1a** but two hours were needed to reach a complete conversion. Interestingly, the catalysts  $P(OEt)_3$  and  $P(OMe)_3$ were able to reduce **1a** completely within four hours. However, when these phosphites were heated with sulfoxides at 110 °C, deoxygenation of the sulfoxide moiety did not take place but rather the rearrangement of the trialkylphosphite to dialkyl alkylphosphonate was observed<sup>11</sup> (Scheme 2). On the other hand, classical inorganic reducing agents such as nitrites, hydrogensulfites, thiosulfates, dithionites or hypophosphites showed no activity under these catalytic conditions. This fact shows the high selectivity of the catalyst for P(III) compounds.

RR <sup>1</sup> SO	$\frac{\text{MoO}_2\text{Cl}_2(\text{dmf})_2}{(2 \text{ mol}\%)} \rightarrow \text{RR}^1\text{S} + \text{OP}(\text{OMe})_3$	
+ P(OMe) <sub>3</sub>	110 °C → RR <sup>1</sup> SO + MeP(O)(OMe)	2

Scheme 2 Comparative reaction of sulfoxides with trimethylphosphite with and without  $MoO_2Cl_2(dmf)_2$ .

Using our optimized conditions, i.e. 1.1 equivalents of  $P(OPh)_3$  in MeCN at reflux and with 2 mol% of  $MoO_2Cl_2(dmf)_2$ , efficient deoxygenation of several sulfoxides to the corresponding sulfides was achieved in excellent yields (Table 2).

It is worth noting that dialkyl sulfoxides were deoxygenated in a few minutes whereas the less basic diaryl sulfoxides needed between 30 minutes and 2 hours depending on the electronic and steric characteristics of the sulfoxide. In particular, the reduction of dibenzyl sulfoxide **1g**  
$$\begin{array}{c} O \\ II \\ R \\ \hline S \\ 1 \end{array} \xrightarrow{R^{1}} R^{1} & \begin{array}{c} MoO_{2}Cl_{2}(dmf)_{2} (2 \text{ mol}\%) \\ P(OPh)_{3} \\ MeCN, \text{ reflux} \end{array} \xrightarrow{R^{1}} R^{1} \end{array}$$

Product	R	<b>R</b> <sup>1</sup>	Time	Yield (%) <sup>a</sup>
2a	4-MeC <sub>6</sub> H <sub>4</sub>	$4-\text{MeC}_6\text{H}_4$	1 h	98
2b	Ph	Ph	30 min	96
2c	$4-ClC_6H_4$	$4-ClC_6H_4$	2 h	93
2d	Ph	PhCH <sub>2</sub>	2 h	90
2e	Ph	Me	20 min	92
2f	Ph	CH=CH <sub>2</sub>	45 min	52
2g	PhCH <sub>2</sub>	PhCH <sub>2</sub>	4 h	89
2h	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -		10 min	70
2i	<i>n</i> -Bu	<i>n</i> -Bu	10 min	73

<sup>a</sup> Isolated yields based on the starting sulfoxide **1**.

serves as a measure of the utility of the reaction, since many methods either fail completely with this substrate or provide only poor yields of dibenzylsulfide.<sup>21</sup> All the substrates were quantitatively reduced to the corresponding sulfides as proved by <sup>1</sup>H NMR and GC analysis. However, in some cases (**2f,h,i**) lower isolated yields were obtained due to partial decomposition in the purification process or due to the volatility of the sulfides.

Next, we decided to examine the reduction of sulfoxides with potentially reducible groups in their structures. The corresponding sulfides 2j-n could be isolated in excellent yields, thus showing the chemoselectivity of our procedure (Figure 1).



Figure 1

The sulfoxides possessing  $\beta$ -keto and  $\beta$ -ethoxycarbonyl functionalities were chemoselectively reduced to the corresponding sulfides **2j**,**k** in good yields without affecting the carbonyl functionalities. Moreover, hydroxy, allyl and propargyl functionalities also remained intact under the reduction conditions although in the case of the sulfide **2l** the solvent had to be changed to CH<sub>2</sub>Cl<sub>2</sub> in order to pre-

vent the dehydration and subsequent formation of the corresponding vinyl sulfide.

In order to further show the selectivity of this method, we have carried out the reduction of sulfoxide **1a** in the presence of *p*-toluenesulfonyl chloride, diphenyl disulfide, diphenylsulfone, iodobenzene, *o*-chloronitrobenzene and the acetone ketal of glycerine, with an excess of triphenylphosphite according to the protocol showed in Table 2. In all the cases the sulfoxide was the only compound that was reduced. These results suggest that our conditions may be generally useful for the conduction of similar chemoselective deoxygenation reactions in poly-functional molecules.

The catalytic cycle involved could be represented as shown in Scheme 3.



**Scheme 3** Representation of the catalytic cycle in the deoxygenation of sulfoxides to sulfides with P(OPh)<sub>3</sub>.

When the colorless solution of MoO<sub>2</sub>Cl<sub>2</sub>(dmf)<sub>2</sub> in CD<sub>3</sub>CN is treated with P(OPh)<sub>3</sub> (molar ratio 1:2) it turns brown, which is consistent with the formation of oxomolybdenum(IV) species.<sup>22</sup> At the same time transformation of  $P(OPh)_3$  to  $OP(OPh)_3$  takes place, as evidenced by <sup>31</sup>P NMR. Indeed, two singlets were observed at 130.0 and -15.8 ppm, corresponding to P(OPh)<sub>3</sub> and OP(OPh)<sub>3</sub>, respectively. These signals are in the same position as those observed in the absence of the catalyst, thus showing that neither P(OPh)<sub>3</sub> nor OP(OPh)<sub>3</sub> is coordinated to molybdenum. Furthermore, <sup>1</sup>H NMR spectrum of the mixture in CD<sub>3</sub>CN shows that the DMF remains coordinated. However, the position of the signals appears slightly displaced to higher field with respect to that of the parent MoO<sub>2</sub>Cl<sub>2</sub>(dmf)<sub>2</sub>, which is consistent with coordination to the less acidic Mo(IV) center.23

Upon addition of excess DMSO to the above mixture the solution becomes progressively clearer to finally colorless. The <sup>31</sup>P and <sup>1</sup>H NMR spectra are consistent with the complete oxidation of  $P(OPh)_3$  to  $OP(OPh)_3$  and the presence of free DMF. This evidences that DMSO is able to displace DMF from the coordination sphere of molybdenum(VI). So, it is probable that the more basic sulfoxides will coordinate to the oxomolybdenum(IV,VI) species facilitating the oxotransfer process. However, it should be noted that the removal of an oxygen atom from  $MoO_2Cl_2(dmf)_2$  produces a vacancy for the coordination of the less basic sulfoxides, thus enabling their deoxygenation. Finally, we think that the differences we observed in the time required for the complete deoxygenation of sulfoxides, not always easy to explain in a straightforward manner, are due to a subtle combination of electronic and steric effects.

In conclusion, we have demonstrated that dichlorodioxomolybdenum(VI) complex  $MoO_2Cl_2(dmf)_2$  is an excellent catalyst for convenient deoxygenation of various types of sulfoxides using triphenylphosphite. Moreover, the present procedure also shows very good chemoselectivity, and though involving the production of triphenylphosphate, this method is a useful addition to the existing methodologies.

Sulfoxides and phospites were obtained from Aldrich or Across Organics and used without purification. Functionalized sulfoxides were prepared according to the established procedures.<sup>24</sup> Na<sub>2</sub>MoO<sub>4</sub>·2H<sub>2</sub>O to prepare the catalyst was obtained from Acros Organics. DMF was purified by vacuum distillation. Commercial MeCN was reagent grade. Products were characterized by comparison of their spectral data with those of known samples. Melting points were determined on the Electrothermal apparatus and are uncorrected. All yields refer to isolated products. NMR spectra were recorded on a Varian VXR 200 and Varian INOVA 400 spectrometer. The reaction monitoring was accomplished by GC–MS on a HP 5890 Serie II/5971-A.

## MoO<sub>2</sub>Cl<sub>2</sub>(dmf)<sub>2</sub>; Typical Procedure

The catalyst can be prepared as previously reported<sup>25</sup> or more readily as follows. To a solution of powdered  $Na_2MoO_4{\cdot}2H_2O$  (2.42 g, 10 mmol) in H<sub>2</sub>O (5 mL), concd HCl (8.3 g, ca. 100 mmol) was added. The mixture was stirred at r.t. for 10-15 min resulting in a colorless solution along with a significant amount of precipited NaCl. Then Et<sub>2</sub>O (15 mL) was added with stirring and the mixture vigorously shaken for 1-2 min. The upper Et<sub>2</sub>O layer was collected and the extraction process repeated twice more. The combined ethereal extract was stirred for 15 min with anhyd MgSO<sub>4</sub> (2 g). The solution was collected by filtration and the  $MgSO_4$  was washed with  $Et_2O$  (3  $\times\,3$  mL). The resulting solution, containing approximately 98% of the original molybdenum, was treated with a solution of DMF (1.54 g, 21 mmol) in Et<sub>2</sub>O (10 mL). The resulting mixture was stirred for 5 min and the white microcrystalline precipitate filtered, washed with Et<sub>2</sub>O ( $3 \times 3$  mL) and dried under vacuum. Yield: 3.67 g (97.5%).

# Deoxygenation of Sulfoxides with P(OPh)<sub>3</sub> Catalyzed by MoO<sub>2</sub>Cl<sub>2</sub>(dmf)<sub>2</sub>; General Procedure

To a solution of sulfoxide (3 mmol) and P(OPh)<sub>3</sub> (1.02 g, 3.3 mmol) in reagent grade MeCN (5 mL),  $MoO_2Cl_2(dmf)_2$  (21 mg, 0.06 mmol) was added, and the resulting solution was stirred at reflux. The completion of the reduction was monitored by GC–MS. The reaction mixture was treated with 2 M NaOH (25 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvents evaporated under reduced pressure. The resulting residue was purified by column chromatography (hexane–EtOAc).

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