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# A novel method for the reduction of sulfoxides and pyridine *N*-oxides with the system silane/$MoO_2Cl_2$

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**Abstract**—A novel method for the reduction of sulfoxides and pyridine *N*-oxides using a silane and a catalytic amount of $MoO_2Cl_2$ in excellent yields and with a wide functional group tolerance is reported. A green protocol for this reaction was developed in water with the air-stable catalytic system PMHS/$MoO_2Cl_2(H_2O)_2$.

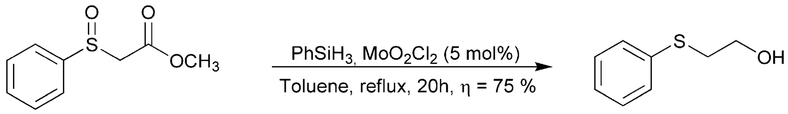
## 1. Introduction

The reduction (or deoxygenation) of sulfoxides and amine *N*-oxides to the corresponding sulfides and amines is an important organic and biological reaction. Over the years, several methods have been developed to reduce sulfoxides[1–8] and amine *N*-oxides,[9–15] however, many of these transformations are limited by side reactions, low yields, lack of chemoselectivity or harsh conditions. For example, the use of hydrogen halides is somewhat restricted with acid-sensitive substrates, the reductions with the strong hydride systems $LiAlH_4$–$TiCl_4$ and $NaBH_4$–$CoCl_2$ are incompatible with several functional groups, and the reactions with phosphorus reagents, in most cases, require elevated temperature and/or prolonged reaction times.

Among the variety of metal complexes that have been used as catalysts for the deoxygenation of sulfoxides and amine *N*-oxides, molybdenum complexes have attracted considerable interest. This metal is found in a class of enzymes that are commonly referred to as mononuclear molybdoenzymes or oxotransferases, such as dimethyl sulfoxide reductases, that catalyze oxygen atom transfer to or from a physiological donor/acceptor.[16,17] Several studies have shown that Mo(VI)$O_2$ complexes catalyze the oxygen atom transfer reaction from the sulfoxides or aromatic *N*-oxides to a phosphine, yielding the corresponding sulfides or amines and the oxidized phosphine.[5,9,18–20]

Recently, we have demonstrated that the high valent molybdenum-dioxo complex, $MoO_2Cl_2$, is an effective catalyst for organic reductions, such as hydrosilylation of aldehydes and ketones,[21] and reduction of imines[22] and esters.[23] These results confirm the new role of oxo complexes in catalytic reductions, which unexpectedly adds to their well-established abilities to catalyze oxygen-transfer reactions to olefins, phosphines, and sulfites.

During the course of our studies on the reaction of esters with the system $PhSiH_3$/$MoO_2Cl_2$, we observed the reduction of both sulfinyl and carboxyl groups of methyl(phenylsulfinyl)acetate, giving the 2-(phenylthio)ethanol in 75% yield (Scheme 1). This result suggested the extension of the system silane/$MoO_2Cl_2$ for the reduction of other sulfoxides. In this work, we investigated the deoxygenation of sulfoxides and pyridine *N*-oxides using the catalysts $MoO_2Cl_2$ and $MoO_2Cl_2(H_2O)_2$ in the presence of a silane in organic and aqueous solvents.



**Scheme 1**.

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*Keywords*: Reduction; Sulfoxides; Pyridine *N*-oxides; Dioxomolybdenum dichloride.

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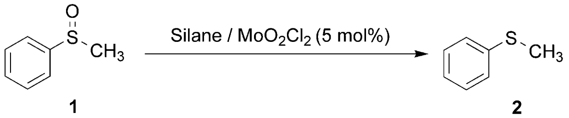
## 2. Results and discussion

To optimize the reaction conditions, we first studied the reduction of methyl phenyl sulfoxide **1** with several silanes and solvents as summarized in Table 1. This sulfoxide was completely reduced with phenylsilane ($PhSiH_3$) in the presence of 5 mol % of $MoO_2Cl_2$ in refluxing tetrahydrofuran after 2 h (entry 1). At room temperature, the reaction required significantly longer reaction times (20 h) and sulfide **2** was obtained in only 66% conversion (entry 2).

**Table 1**. Reduction of methyl phenyl sulfoxide **1** catalyzed by $MoO_2Cl_2$



| Entry | Silane[a] | Solvent | Temperature (°C) | Time (h) | Conversion[b] (%) |
|---|---|---|---|---|---|
| 1 | $PhSiH_3$ | THF | 67 | 2 | 100 |
| 2 | $PhSiH_3$ | THF | rt | 20 | 66 |
| 3 | $PhSiH_3$ | Toluene | 110 | 2 | 100 |
| 4 | $PhSiH_3$ | $CH_2Cl_2$ | 40 | 2 | 95 |
| 5 | $PhSiH_3$ | $CH_3CN$ | 80 | 2 | 21 |
| 6 | PMHS | THF | 67 | 20 | 100 |
| 7 | DMPHS | THF | 67 | 24 | 65 |
| 8 | $Et_3SiH$ | THF | 67 | 24 | 35 |
| 9 | $Ph_3SiH$ | THF | 67 | 48 | No reaction |

[a] The reactions were carried out with 100 mol % of $PhSiH_3$, DMPHS, $Et_3SiH$ or $Ph_3SiH$ and with 0.3 mol % of PMHS.

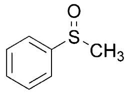
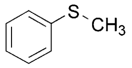
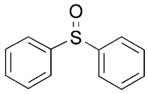
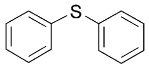
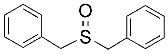
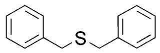
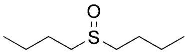
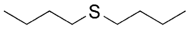
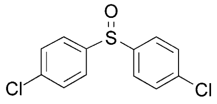
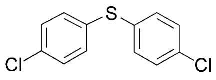
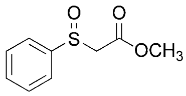
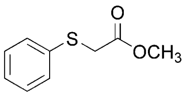
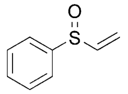
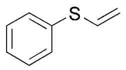
[b] Conversion was determined by $^1H$ NMR.

To evaluate the effect of solvents, the reduction of sulfoxide **1** was carried out in tetrahydrofuran, toluene, dichloromethane, and acetonitrile. Sulfide **2** was obtained in 100% conversion in THF and toluene (entries 1 and 3), in 95% conversion in dichloromethane (entry 4), but in acetonitrile it was obtained in only 21% conversion (entry 5).

This reaction was also investigated with several silanes. With the polymethylhydrosiloxane (PMHS), sulfoxide **1** was completely reduced (entry 6) and with dimethylphenylsilane (DMPHS) and triethylsilane ($Et_3SiH$), sulfide **2** was obtained in 65% and 35% conversion, respectively (entries 7 and 8). No catalysis was observed with the triphenylsilane (entry 9).

To explore the scope of this catalytic reaction, the reduction of a variety of sulfoxides with the system $PhSiH_3/MoO_2Cl_2$ (5 mol %), in refluxing tetrahydrofuran, was investigated (Table 2). As shown in Table 2, the sulfoxides were reduced in excellent yields. This catalytic reaction is suitable for the deoxygenation of aromatic and aliphatic sulfoxides, in particular, for the reduction of benzyl sulfoxide (entry 3), since several methods fail completely with this substrate or only provide poor yields of benzyl sulfide. This reaction is also compatible with other functional groups such as halo, carboxyl, and vinyl (entries 5–7). The chemoselective reduction of methyl(phenylsulfinyl)acetate, in 97% yield (Table 2, entry 6), was possible in THF, contrary to the reduction of both sulfinyl and carboxyl groups observed in refluxing toluene (Scheme 1) and reported in our previous work.[23]

**Table 2**. Reduction of sulfoxide with the system $PhSiH_3/MoO_2Cl_2$[a]

| Entry | Sulfoxide | Sulfide | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  | 2 | 97 |
| 2 |  |  | 2 | 97 |
| 3 |  |  | 20 | 96 |
| 4 |  |  | 7 | 92 |
| 5 |  |  | 2 | 96 |
| 6 |  |  | 2.5 | 96 |
| 7 |  |  | 2 | 92 |

[a] All reactions were carried out in refluxing THF with 1.0 mmol of sulfoxide, 1.0 mmol of $PhSiH_3$, using 5 mol % of $MoO_2Cl_2$.

[b] Isolated yield.

Attempted reduction of phenyl sulfone and 4-fluorophenyl methyl sulfone resulted in only the recovery of starting material.

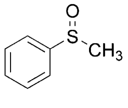
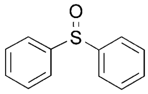
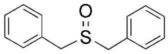
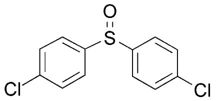
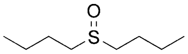
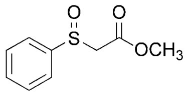
The reduction of sulfoxides was also carried out with the complex $MoO_2Cl_2(H_2O)_2$, which was easily prepared by extraction from a hydrochloric acid solution of $Na_2MoO_4$ with diethyl ether.[19]

The catalytic activity of $MoO_2Cl_2(H_2O)_2$ was studied with the silanes $PhSiH_3$ and PMHS. The reduction of the substrates, methyl phenyl sulfoxide, phenyl sulfoxide, and benzyl sulfoxide with the system $PhSiH_3/MoO_2Cl_2(H_2O)_2$ (5 mol %) in refluxing THF, afforded the corresponding sulfides in 95%, 96%, and 95%, respectively (Table 3, entries 1, 4, and 7). These yields and the reaction times are comparable to those obtained with the system $PhSiH_3/MoO_2Cl_2$ (Table 2, entries 1–3).

The reaction of sulfoxides with PMHS in the presence of 5 mol % of $MoO_2Cl_2(H_2O)_2$, in refluxing methanol, was carried out in air and produced the sulfides in excellent yields (Table 3). The chemoselective reduction of methyl(phenylsulfinyl)acetate was also possible in this reaction conditions in good yield (entry 12).

Finally, we tried the reduction of sulfoxides with the system $PMHS/MoO_2Cl_2(H_2O)_2$ in water at 80 °C (Table 3). This green system reduced the methyl phenyl sulfoxide in 52%

**Table 3**. Reduction of sulfoxides catalyzed by $MoO_2Cl_2(H_2O)_2$[a]

| Entry | Sulfoxide | Silane | Solvent[b] | Time (h) | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 |  | $PhSiH_3$ | THF | 1.5 | 95 |
| 2 | | PMHS | Methanol | 2 | 95 |
| 3 | | PMHS | $H_2O$[d] | 20 | 52 |
| 4 |  | $PhSiH_3$ | THF | 2 | 96 |
| 5 | | PMHS | Methanol | 20 | 96 |
| 6 | | PMHS | $H_2O$[d] | 20 | 92 |
| 7 |  | $PhSiH_3$ | THF | 20 | 95 |
| 8 | | PMHS | Methanol | 20 | 95 |
| 9 |  | PMHS | Methanol | 20 | 95 |
| 10 | | PMHS | $H_2O$[d] | 20 | 50 |
| 11 |  | PMHS | Methanol | 20 | 94 |
| 12 |  | PMHS | Methanol | 20 | 90 |

[a] All reactions were carried out with 1.0 mmol of sulfoxide, 100 mol % of $PhSiH_3$ or 0.3 mol % of PMHS, using 5 mol % of $MoO_2Cl_2(H_2O)_2$.

[b] Reflux temperature.

[c] Isolated yield.

[d] The reaction was carried out at 80 °C.

yield, the phenyl sulfoxide in 92% yield, and the 4-chlorophenyl sulfoxide in 50% yield (Table 3, entries 3, 6, and 10). The benzyl sulfoxide and butyl sulfoxide did not react in water.

The analysis of the $^1H$ NMR spectrum of the reaction mixture obtained in the reduction of the phenyl vinyl sulfoxide with the system $PMHS/MoO_2Cl_2(H_2O)_2$ in methanol or in water showed that the double bond was affected.

The system $PMHS/MoO_2Cl_2(H_2O)_2$ proved to be very efficient for the reduction of sulfoxides in organic solvents. The use of PMHS is more attractive than $PhSiH_3$ because it is easily handled, stable to air and water, inexpensive, and non-toxic. However, the reductions with PMHS required longer reaction times.

The easy and inexpensive preparation of ether solution of $MoO_2Cl_2(H_2O)_2$ and its air stability make this catalyst an excellent alternative to $MoO_2Cl_2$, which has a difficult preparation and a great air instability.

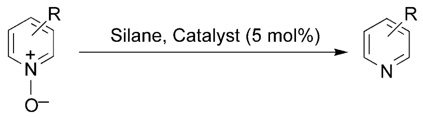
Other important advantage of the system $PMHS/MoO_2Cl_2(H_2O)_2$ is related to the environmental concerns and increased restrictions on the use of hazardous organic solvents. With this system, the reduction, in water, was possible for some sulfoxides in moderate to good yields.

In this work, we also performed a brief investigation of the deoxygenation of pyridine *N*-oxides with the silanes $PhSiH_3$ and PMHS catalyzed by $MoO_2Cl_2$ and $MoO_2Cl_2(H_2O)_2$ (Table 4). As shown in Table 4, the catalytic systems $PhSiH_3/MoO_2Cl_2$, $PhSiH_3/MoO_2Cl_2(H_2O)_2$, and $PMHS/MoO_2Cl_2(H_2O)_2$ reduced the 3- and 4-methylpyridine *N*-oxides in good yields in organic solvents. As observed in the reduction of sulfoxides, the reaction with PMHS required longer reaction times than with $PhSiH_3$. Due to the wide functional group tolerance verified in the reduction of sulfoxides, we believe that this novel method can be suitable for the deoxygenation of other pyridine *N*-oxides. Unfortunately, the pyridine *N*-oxides were not reduced in water with the system $PMHS/MoO_2Cl_2(H_2O)_2$.

In order to verify that $MoO_2Cl_2$ plays an active role in the deoxygenation process, we carried out the reaction of sulfoxide **1** with an excess of phenylsilane without catalyst and the reaction of sulfoxide **1** with 5 mol % of $MoO_2Cl_2$ without phenylsilane in refluxing THF during 2 h. In both cases, sulfoxide **1** was not reduced. These results suggest that $MoO_2Cl_2$ catalyzes the reaction by activation of the silane, producing a hydride species (Mo-H).

In the reaction of the complex $MoO_2Cl_2(Bz_2SO)_2$, prepared by the addition of benzyl sulfoxide to the ether solution of $MoO_2Cl_2(H_2O)_2$,[19] with 1 equiv of the phenylsilane in refluxing THF was observed the reduction of the sulfoxide,

**Table 4**. Deoxygenation of pyridine *N*-oxides catalyzed by $MoO_2Cl_2$ or $MoO_2Cl_2(H_2O)_2$[a]



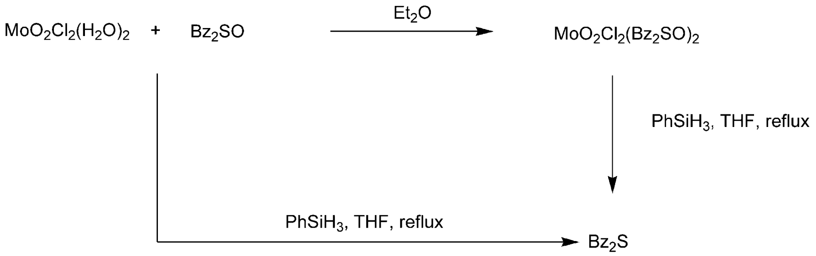
| Entry | R | Silane | Catalyst | Solvent[b] | Time (h) | Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | 4-$CH_3$ | $PhSiH_3$ | $MoO_2Cl_2$ | THF | 3 | 85 |
| 2 | | $PhSiH_3$ | $MoO_2Cl_2(H_2O)_2$ | THF | 3 | 84 |
| 3 | | PMHS | $MoO_2Cl_2(H_2O)_2$ | Methanol | 20 | 86 |
| 4 | | PMHS | $MoO_2Cl_2(H_2O)_2$ | $H_2O$[d] | 20 | No reaction |
| 5 | 3-$CH_3$ | $PhSiH_3$ | $MoO_2Cl_2$ | THF | 3 | 85 |
| 6 | | $PhSiH_3$ | $MoO_2Cl_2(H_2O)_2$ | THF | 3 | 83 |
| 7 | | PMHS | $MoO_2Cl_2(H_2O)_2$ | Methanol | 20 | 85 |
| 8 | | PMHS | $MoO_2Cl_2(H_2O)_2$ | $H_2O$[d] | 20 | No reaction |

[a] All reactions were carried out with 1.0 mmol of pyridine *N*-oxide, 100 mol % of $PhSiH_3$ or 0.3 mol % of PMHS using 5 mol % of catalyst.

[b] Reflux temperature.

[c] Isolated yield.

[d] The reaction was carried out at 80 °C.



**Scheme 2**.

giving the benzyl sulfide (Scheme 2). A similar result was obtained when the benzyl sulfoxide was reduced with the system $PhSiH_3/MoO_2Cl_2(H_2O)_2$ (Table 3, entry 7). This result suggests the initial activation of the sulfoxide by the oxygen coordination to the molybdenum, yielding the complex $MoO_2Cl_2$(sulfoxide)$_2$. This complex weakens the S–O bond and renders the sulfur atom more susceptible to the reduction. After the addition of the silane, the complex $MoO_2Cl_2$(sulfoxide)$_2$ is reduced with elimination of the sulfide and a siloxane.

## 3. Conclusion

In summary, we have developed a novel method for the reduction of sulfoxide and pyridine *N*-oxides to the corresponding sulfides and pyridines using the silane $PhSiH_3$ in the presence of a catalytic amount of $MoO_2Cl_2$ in excellent yields and with a wide functional group tolerance. This catalytic system can be a useful alternative to the traditional methods for the reduction of sulfoxides, especially, in natural products and pharmaceutical synthesis, which require mild conditions, selectivity, and functional group tolerance.

A green protocol for the reduction of sulfoxides was also developed with the system $PMHS/MoO_2Cl_2(H_2O)_2$ in water or methanol. This novel, air-stable catalyst system reduced sulfoxides in moderate to excellent yields. The simplicity and environmental-friendly conditions of this protocol make this novel method suitable for large-scale reductions.

Other organic reductions with this system are now under investigation in our group.

## 4. Experimental

### 4.1. General methods

Toluene and THF were distilled under nitrogen from sodium, and $CH_2Cl_2$ and acetonitrile from $CaH_2$ before use. Silanes were obtained from Aldrich, PMHS ($M_n$=1700–3200). Flash chromatography was performed on MN Kieselgel 60 M 230–400 mesh. All compounds were characterized by $^1H$ NMR, $^{13}C$ NMR, and IR spectroscopy. $^1H$ NMR and $^{13}C$ NMR spectra were measured on a Bruker AMX 300 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from an internal $Me_4Si$ standard. IR spectra were measured on a Unicam Mattson model 7000 FTIR spectrometer.

### 4.2. General procedures

**4.2.1. General procedure for the reduction of sulfoxides and pyridine *N*-oxides with the system $PhSiH_3/MoO_2Cl_2$.** To a solution of $MoO_2Cl_2$ (5 mol %) in dry THF (5 ml) was added the sulfoxide or the pyridine *N*-oxide (1.0 mmol) and $PhSiH_3$ (1.0 mmol) under nitrogen atmosphere. The reaction mixture was stirred at reflux temperature (the reaction times are indicated in Tables 2 and 4) and monitored periodically by TLC. Upon completion, the reaction mixture was evaporated and purified by silica gel column chromatography with the appropriate mixture of *n*-hexane and ethyl acetate to afford the sulfides and pyridines, which are all known compounds.

**4.2.2. Green protocol for the reduction of sulfoxides with the system $PMHS/MoO_2Cl_2(H_2O)_2$.** To a solution of the sulfoxide (1.0 mmol) in water (5 ml) or in methanol (3 ml) were added the ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol %) and PMHS (0.3 mol %). The reaction mixture was stirred at reflux temperature in methanol or at 80 °C in water (the reaction times are indicated in Table 3). Upon completion, the reaction mixture was extracted with diethyl ether (3×20 ml), dried over sodium sulfate, evaporated, and purified by silica gel column chromatography with the appropriate mixture of *n*-hexane and ethyl acetate.

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