Simple and Selective Oxidation of Thiols to Disulfides with Dimethylsulfoxide Catalyzed by Dichlorodioxomolybdenum(VI)

Roberto Sanz,* Rafael Aguado, María R. Pedrosa, Francisco J. Arnáiz*

Departamento de Química, Universidad de Burgos, 09001-Burgos, Spain
Fax +34(94)7258831; E-mail: farnaiz@ubu.es

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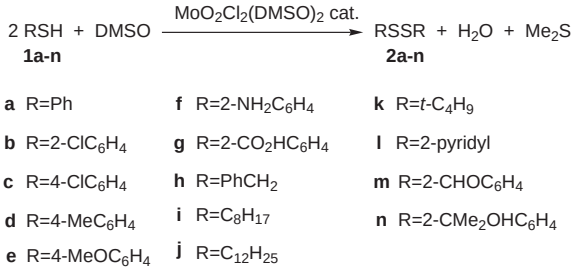
Abstract: Selective and quantitative conversion of thiols to disulfides was effected by dimethyl sulfoxide under mild conditions catalyzed by dichlorodioxomolybdenum(VI).

Key words: thiols, disulfides, molybdenum(VI) complexes, oxotransfer catalysis, sulfoxides

Selective oxidation of thiols to disulfides is of interest from both a biological and a synthetic perspective.[1] Thiols are among functional groups that can be over oxidized so that many studies have been carried out for their controlled oxidation.[2] Thus, a wide number of oxidizing agents ranging from molecular oxygen,[3] to halogens and derivatives,[4] metal oxides,[5] and oxo and peroxosalts,[6] have been used to oxidize thiols to disulfides. It is known that the oxidation of mercaptans proceeds in dimethyl sulfoxide (DMSO) solution, but the reaction requires high temperature and a prolonged reaction time.[7] Recently, a mild and efficient oxidation with hydrogen peroxide in fluoroalcohols has been reported.[8] Moreover, the air oxidative coupling of thiols has been catalyzed in different ways.[9]

However, most of the reported procedures involve the use of strong oxidants that are also capable of reacting with other oxidizable sites such as aldehyde and amino groups, or severe conditions as happens with the mild oxidant DMSO. Hence the interest in the search for new procedures to transform thiols into disulfides while preserving as much functionalities as possible.

On the other hand, it has been shown that dioxomolybdenum(VI) complexes that mimic oxotransferases are able to oxidize some thiols to disulfides[10] at room temperature. In the oxotransfer processes it is assumed that oxomolybdenum(IV) species are formed, which in turn are readily oxidized to the parent dioxomolybdenum(VI) complexes by a number of oxidants including sulfoxides. The unavailability of these complexes has precluded their use as oxotransfer catalysts in oxygenation/deoxygenation processes implying organic substrates. However, we have found that MoO_2Cl_2 and its addition compound with DMSO, $MoO_2Cl_2(DMSO)_2$, are excellent catalysts for oxotransfer reactions involving phosphines, thiols and sulfoxides.[11] $MoO_2Cl_2(DMSO)_2$ is specially useful for this purpose as it can be readily prepared in a pure form from easily available chemicals, is air stable and can be stored for months without special precautions.[12] Here we report the facile, selective and essentially quantitative conversion of a number of thiols to disulfides by DMSO catalyzed by such a dioxomolybdenum(VI) complex. The overall oxidation process we propose could be written as shown in the Scheme 1.



Scheme 1

Commercially available and functionalized aromatic thiols **1a**–**g** were first chosen to test our procedure. The reactions were carried out at room temperature, using DMSO as solvent and 1 mol % of the catalyst. Under these conditions, the mercaptans were selectively and quantitatively oxidized to the corresponding disulfides (see Table) in 5–30 minutes. It is worth noting that thiols having electron-withdrawing substituents were oxidized within 10 minutes whereas, for instance, 4-methoxybenzenethiol (**1e**) needed 30 minutes to afford the corresponding disulfide **2e**. This fact suggests that the rate of reaction is dependent on the acidity of the mercaptan.

Of these examples, the oxidation of *o*-aminothiophenol (**1f**) and thiosalicylic acid (**1g**) are remarkable due to the low yields and problems found with these thiols in their oxidation by other procedures.[8]

Next, we turned our attention to non-aromatic thiols and so, phenylmethanethiol (**1h**) could be quantitatively oxidized to dibenzyl disulfide. However, in this case we consider it more appropriate to use 5% of the catalyst and carrying out the reaction at 70 °C. Under these conditions the reaction was complete after 6 hours and the disulfide was isolated in 94% yield. In the same way, aliphatic thiols **1i**–**k** were completely oxidized in 24 hours and the corresponding disulfides were isolated in good yields (see Table).

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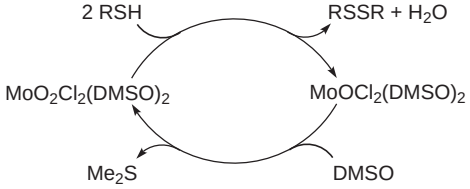
Table Catalytic Oxidation of Thiols **1** to Disulfides **2**

R[a]	Catalyst (%)	Conditions Temp/Time	Yield (%)[b]	mp(°C) or bp(°C)/Torr	
				found	reported
a	1	r.t./20 min	98	60–62	62[13]
b	1	r.t./10 min	94	80–82	84[14]
c	1	r.t./10 min	95	70–72	72–73[6a]
d	1	r.t./30 min	96	46–48	47.5[13]
e	1	r.t./30 min	95	42–43	42–44[4b]
f	1	r.t./30 min	91	88–89	91–92[7a]
g	1	r.t./30 min	90	288–290	289–290[15]
h	5	70 °C/6 h	94	70–71	71–72[9a]
i	5	70 °C/24 h	87	205/15	198–199/10[16]
j	5	70 °C/24 h	86	34–35	33–34[7b]
k	5	70 °C/24 h	85	82–84/18	83–86/18[3c]
l	1	r.t./12 h	89	55–57	56–58[6f]
m	1	r.t./30 min	91	149–150	148–149[18b]
n	1	r.t./30 min	88	139–141	141–143[19]

[a] For R, see Scheme.
[b] Isolated yield.

The utility of this catalyst in the oxidation of heteroaromatic thiols was also tested. Thus 2-pyridinethiol (**1l**) was quantitatively transformed to 2,2′-dipyridine disulfide (**2l**) with DMSO in 12 hours at 20 °C in the presence of 1% $MoO_2Cl_2(dmso)_2$. The disulfide, a very useful reagent in peptide chemistry, could be isolated in 89% yield.

Finally, due to the easy selective oxidation of aromatic thiols we decided to examine the reaction with other functionalized arylthiols not commercially available. So, on the basis of the method described for the regioselective *ortho*-lithiation of benzenethiol,[17] we synthesized thiosalicylaldehyde (**1m**) and 2-(1-hydroxy-1-methylethyl)benzenethiol (**1n**). After carrying out the reactions of these thiols under the conditions above described the corresponding disulfides **2m**[18] and **2n**[19] were isolated in 91% and 88% yield respectively. The catalytic cycle involved could be represented as shown in Scheme 2.



Scheme 2 Representation of the catalytic cycle in the oxidation of thiols to disulfides

The mercaptan undergoes an oxidative coupling to the corresponding disulfide by the dioxomolybdenum(VI) complex which in turn is reduced to an oxomolybdenum(IV) species. Then DMSO reoxidizes Mo(IV) to Mo(VI) with the release of dimethyl sulfide. The following observations are consistent with this proposal: (i) The colorless solutions of thiols in DMSO become brown or reddish upon addition of white $MoO_2Cl_2(dmso)_2$ suggesting the formation of Mo(IV) species.[11a] (ii) The foul-smelling dimethyl sulfide is always generated in the reaction as proved by GC.

The catalyst is very resistant to degradation. Addition of new batches of thiol to the resulting reaction mixture showed that no significant loss of activity was produced. This is probably due to the fact that dioxomolybdenum(VI) species are unable to oxidize chloride ions under mild conditions. Moreover, although water is generated in the coupling process the catalyst is not noticeably affected because water is miscible with DMSO and excess of this is present in the reaction mixture. Indeed, we have proved that $MoO_2Cl_2(dmso)_2$ can be efficiently isolated from aqueous solutions,[12] and that coordinated water in $MoO_2Br_2(H_2O)_2$ is immediately displaced by DMSO at room temperature to yield the closely related complex $MoO_2Br_2(dmso)_2$.[20]

The order of reactivity observed for thiols, ArSH>$ArCH_2SH$>AlkSH, roughly correlates with their acidity and is in agreement with other reports in the literature.[7b] Thus, it is probable that a crucial, rate determining step in the process is the protonation of the oxo ligands on the dioxomolybdenum(VI) center.

The method here described could be carried out on a multigram scale and thus 0.2 mol of benzenethiol was quantitatively oxidized to diphenyl disulfide with 0.22 mol of DMSO catalyzed by 0.2 mmol (0.1%) of the catalyst in 30 minutes at room temperature. Addition of aqueous NaOH to the mixture allowed the easy isolation of the disulfide by filtration, as the decomposition products of the catalyst – sodium chloride and molybdate – remain in solution.

In summary, we have presented a mild, efficient and selective oxidation of thiols to disulfides by DMSO catalyzed by a dioxomolybdenum(VI) complex. The present procedure, though involving the production of dimethyl sulfide, is attractive because of its simplicity, general applicability and excellent yields of the products, making this method a useful addition to the existing methodologies.

Thiols were obtained from Aldrich or Across Organics and used without purification. Molybdenum(VI) oxide to prepare the catalyst[12] was obtained from Fluka. Commercial DMSO was reagent grade. Products were characterized by comparison of their physical data with those of known samples. Melting points were determined on a 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.

Oxidation of Thiophenol (1a) with DMSO Catalyzed by $MoO_2Cl_2(DMSO)_2$; Diphenyl Disulfide (2a); Typical Procedure
A 50 mL Erlenmeyer flask was charged with DMSO (7.1 mL, 100 mmol) and $MoO_2Cl_2(DMSO)_2$ (35 mg, 0.1 mmol). Then thiophenol (1.1 g, 10 mmol) was added and the resulting solution was stirred for 30 min at 20 °C. The completion of the oxidation was ascertained by GC/MS. The reaction mixture was treated with 2 M NaOH (25 mL). The precipitated diphenyl disulfide was collected by filtration, washed with H_2O (3 × 20 mL), and dried under vacuum. In that way crude diphenyl disulfide (1.07 g, 98%) was obtained, that was pure by GC and NMR analysis (Table).

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