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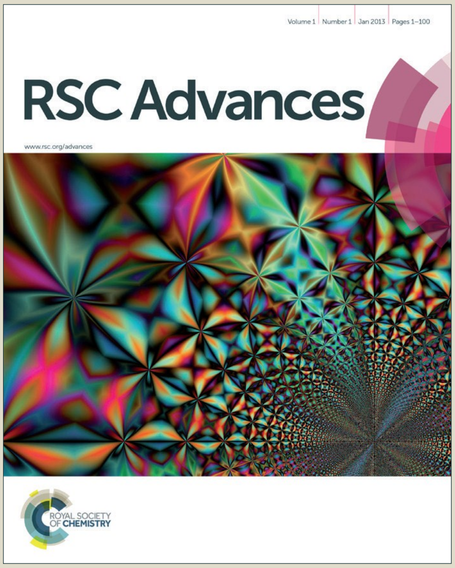

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Practical and Chemoselective Mo-Catalysed Sulfoxide Reduction Protocol using 3-Mercaptopropyl-functionalized Silica Gel (MPS)†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A convenient sulfoxide deoxygenation procedure using mercaptopropyl-functionalized silica gel as reducing agent is described. This new protocol based in a heterogeneous reagent displays broad scope and tolerance to reducible functional groups and, from an experimental point of view, enhances previous methods by simplifying the isolation of the sulfide to a simple filtration.

The development of sustainable catalytic protocols for the deoxygenation of organic compounds, frequently involved in the synthesis of bioactive targets and in the production of renewable fuels from vegetable oils, is an important goal for chemists and engineers from both academia and industry.[1] Particularly, the deoxygenation of sulfoxides is of extraordinary relevance in biological processes, to preclude the oxidative damage of cells,[2] as well as in organic synthesis as a key step in several reaction sequences. Accordingly, numerous catalytic methods have been developed in the past decades to perform this transformation.[3]

In this sense, considerable efforts have been done in the catalyst development for sulfoxide reduction and, therefore, significant achievements have been accomplished including the use of non-metal[4] or abundant, inexpensive and non toxic Mo,[5] Zn,[6] Cu[7] or Fe[8] based catalysts. These procedures encompass the use of stoichiometric or excess amounts of silanes, boranes, hydrogen or phosphorous(III)-based reagents as oxygen-acceptors. So, most of them are limited by side reactions, poor yields and/or selectivities, harsh reaction conditions and the requirement of laborious purification processes due to the generation of toxic by-products difficult to remove from the reaction mixture. Therefore, more sustainable catalytic protocols for the chemoselective reduction of sulfoxides are still highly desirable. An ideal procedure should be selective, display high functional group tolerance, circumvent the employment of catalysts derived from precious metals as well as hazardous/toxic reagents, do not generate side products and avoid arduous purification techniques.

In this context, as part of our ongoing research in the development of new redox protocols catalyzed by dioxomolybenum(VI) complexes,[5a,9] we have recently reported the use of alcohols such as pinacol (2,3-dimethyl-2,3-butanediol) and glycerol as environmentally benign reductants in the chemoselective deoxygenation of sulfoxides.[10] Notably, these reactions were typically conducted in air and under solvent free conditions and the corresponding sulfides were isolated by a liquid-liquid extraction to remove the catalyst, the remaining alcohol and the water, acetone or formic acid generated as by-products.

Continuing with our interest in the development of sustainable reductions protocols, we envisaged an expedient sulfoxide deoxygenation procedure using a solid supported[11] reducing agent that would simplify the reaction work-up to just filtration and solvent evaporation. To this aim we selected 3-mercaptopropyl-functionalized silica gel (MPS) as reducing agent. This heterogeneous reagent has been mainly used to support catalysts[12] or as heavy metal scavenger[13] and, although the ability of thiols as oxygen acceptors in sulfoxide reductions is well known,[14] as far as we are aware, the use of MPS as reductant was unexplored.

Considering our experience with other reducing agents,[10] the deoxygenation of bis(*p*-tolyl)sulfoxide in the presence of catalytic amounts of $MoO_2Cl_2(dmf)_2$ (2 mol%) under microwave irradiation was chosen as model reaction to assess the reduction ability of MPS (1.1 equiv.). Initial experiments conducted in toluene at different temperatures showed that heating at 130 °C was necessary to reach complete conversion to the corresponding sulfide in 20 min, whereas at lower temperatures or under solvent-free conditions low conversions were observed (Table 1, entries 1‑3). The reaction time could be cut by half by just increasing the temperature to

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†Electronic Supplementary Information (ESI) available: Experimental details and NMR spectra of all the experiments. See DOI: 10.1039/x0xx00000x

140 °C (entry 4). In this essay, bis(*p*-tolyl)sulfide was obtained in almost quantitative yield (97%) and in pure form after simple filtration of the reaction mixture and solvent evaporation. At this point, a parallel reaction with not linked 3-mercaptopropyl trimethoxysilane instead of MPS was performed. As a result, complete conversion to the sulfide was also detected supporting the role of the thiol entity as functional group reducing agent (entry 5). Notably, in this case column chromatography purification was required to remove the subproducts formed in stoichiometric amounts derived from the reductant. Consequently, in this homogeneous conditions, besides the need of a time and resource consuming purification step, a significant decrease in the yield compared with the reaction under heterogeneous conditions was observed (entries 4 vs 5), proving the advantageous use of the solid-supported reagent.

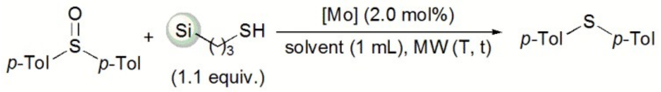
Next, the influence of the catalyst was examined. As expected, no appreciable reaction took place without catalyst (entry 6), whereas other dioxomolybdenum(VI) complexes such as $MoO_2Cl_2(dmso)_2$, $MoO_2(acac)_2$, $MoO_2(dipic)(dmso)$, $MoO_2Cl_2(OPPh_3)_2$, $MoO_2Br_2(dmso)_2$ or commercially available MoO_2Cl_2 also worked as active catalysts for this transformation (entries 7-12).[15] The cleanest reaction and the highest yield was obtained with easily prepared and highly stable $MoO_2Cl_2(dmf)_2$ complex[5a] and so, it was selected as catalyst for the following experiments.

As we are aware that numerous synthetic labs do not have access to microwave reactors, and intending to extend the applicability of the reported reduction procedure to all the research community, we have also studied the model reaction under conventional heating techniques. Thus, after screening several reaction parameters, we found that bis(*p*-tolyl)sulfoxide was completely transformed in the corresponding sulfide in the presence of 1.1 equivalents of MPS and 2 mol% of $MoO_2Cl_2(dmf)_2$ by heating them in toluene at reflux for 7 h or in mesitylene at 170 °C for 1 h (entries 13-14).

Further tests, performed under both microwave irradiation and conventional heating, increasing the amount of supported reducing agent led to no improvements in yield or reaction time, whereas incomplete conversions were observed by lowering the catalyst loading. In addition, the hydrocarbon solvents (toluene or mesitylene) could be replaced by a more sustainable solvent such as ethanol, although slightly lower yields were obtained and the use of a sealed tube under conventional heating was mandatory due to the lower boiling point of the solvent (entries 15-16).

Furthermore, it should be noted that same results were achieved with both commercial available Quadrasil® MP,[16] with a reported loading in the range of 1.0 to 1.5 mmol/g, and synthesized MPS, with an equivalent 1.2 mmol/g loading,[17] indistinctly employed as supported reagent along the study.

Table 1. Optimization of the reaction conditions for the Mo-catalysed deoxygenation of bis(*p*-tolyl)sulfoxide with mercaptopropyl-functionalized silica gel (MPS) as reducing agent.[a]

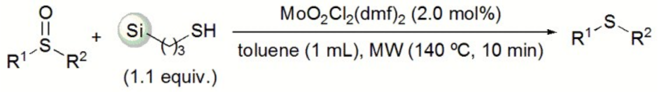


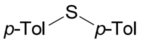
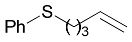
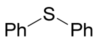
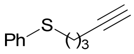
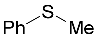
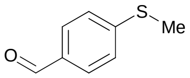
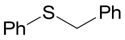
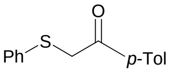
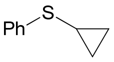
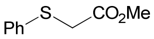
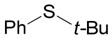
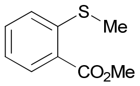
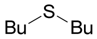
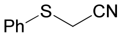
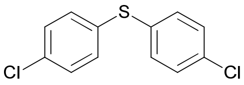
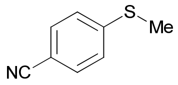
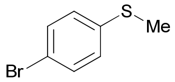
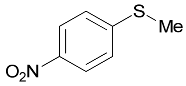
entry	[Mo]	solvent	T (°C)	t (min)	yield (%)[b]
1	$MoO_2Cl_2(dmf)_2$	Toluene	120	30	–(30)
2	$MoO_2Cl_2(dmf)_2$	Toluene	130	20	93(100)
3	$MoO_2Cl_2(dmf)_2$	–	130	20	–(40)
4	$MoO_2Cl_2(dmf)_2$	Toluene	140	10	97(100)
5[c]	$MoO_2Cl_2(dmf)_2$	Toluene	140	10	84(100)
6	–	Toluene	140	10	–(0)
7	$MoO_2Cl_2(dmso)_2$	Toluene	140	10	96(100)
8	$MoO_2(acac)_2$	Toluene	140	10	93(100)
9	$MoO_2(dipic)(dmso)$	Toluene	140	10	93(100)
10	$MoO_2Cl_2(OPPh_3)_2$	Toluene	140	10	92(100)
11	$MoO_2Br_2(dmso)_2$	Toluene	140	10	83(100)
12	MoO_2Cl_2	Toluene	140	10	89(100)
13[d]	$MoO_2Cl_2(dmf)_2$	Toluene	110	420	93(100)
14[d]	$MoO_2Cl_2(dmf)_2$	Mesitylene	170	60	94(100)
15	$MoO_2Cl_2(dmf)_2$	Ethanol	140	10	87(100)
16[d,e]	$MoO_2Cl_2(dmf)_2$	Ethanol	170	60	89(100)

[a] All reactions were performed with 0.25 mmol of sulfoxide under microwave irradiation (maximum wattage 300 W; see ESI† for details) unless otherwise stated. [b] Based on the starting bis(*p*-tolyl)sulfoxide; in brackets conversion estimated by ^1H NMR (300 MHz) from the crude reaction mixture after filtration. [c] Reaction performed under homogeneous conditions using 3-mercaptopropyl trimethoxysilane (1.1 equiv.) as reducing agent. [d] Reactions conducted under conventional heating. [e] Reaction conducted in a sealed tube.

Once we had demonstrated the viability of employing MPS as solid-supported reducing agent of sulfoxides, the scope of this Mo-catalyzed deoxygenation was explored. These reactions were conducted using the optimal conditions determined, that is, 1.1 equivalents of MPS, $MoO_2Cl_2(dmf)_2$ (2.0 mol%) as catalyst in toluene at 140 °C for 10 min under microwave irradiation. The results have been summarized in Table 2. Reactions of a variety of representative diaryl, aryl-alkyl (either linear or branched), as well as dialkyl sulfoxides efficiently occurred to give the corresponding thioethers (entries 1, 4, 6 and 8–11). Moreover, the suitability of the alternative protocol under conventional heating was demonstrated for a few examples (entries 3, 5, 7). Interestingly, although most of the reactions were conducted starting with 0.5 mmol of the sulfoxide, increasing the scale to 3 mmol with the model substrate did not affect the outcome of the process (entry 2).

Table 2. Mo-catalysed deoxygenation of sulfoxides using mercaptopropyl-functionalized silica gel (MPS) as reducing agent.[a]



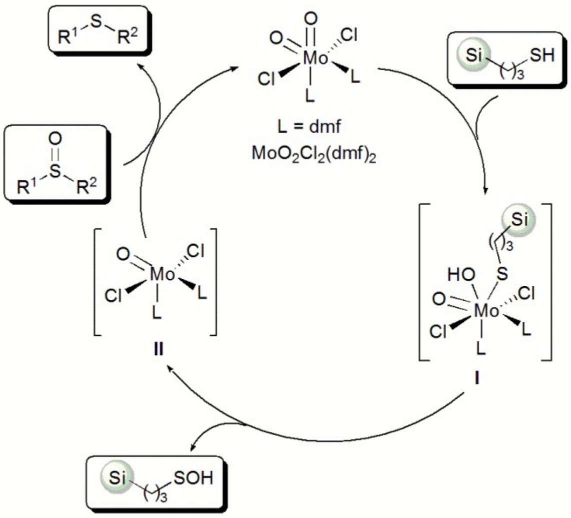
entry	product	yield (%)[b]	entry	product	yield (%)[b]
1		97	14		71
2[c]		96			
3[d]		94			
4		94	15		67
5[d]		91			
6		89	16		85
7[d]		91			
8		93	17		87
9		89	18		86
10		91	19		87
11		69	20		81
12		88	21		92
13		91	22		87

[a] All reactions were conducted with 0.5 mmol of sulfoxide under microwave irradiation (maximum wattage 300 W; see ESI† for details) unless otherwise stated. [b] Based on the starting sulfoxide. [c] Reaction conducted at 3 mmol scale. [d] Reactions conducted at 170 °C in mesitylene under conventional heating for 1 h.

Next, reductions of a wide range of sulfoxides possessing the most representative potentially reducible functionalities such as halogens, C-C multiple bonds, aldehyde, ketone, ester, cyano or nitro groups were analyzed in order to evaluate the chemoselectivity of the developed reduction procedure. Notably, the deoxygenation of all these substrates gave exclusively the corresponding sulfides with the additional functional group unaltered (entries 12–22). It should be noted that this Mo-catalyzed reduction with MPS as reducing agent displayed, in general, an excellent 90% average yield. Even the inferior yields, around 70%, observed with dibutylsulfoxide and sulfoxides bearing an olefin or an alkyne moiety are synthetically useful, considering the simplicity of the protocol.

To summarize, under the developed protocol using microwave irradiation all the sulfides were obtained in good yields from the corresponding sulfoxides in less than 30 minutes, including both reaction set-up and work-up, in pure form by a simple filtration, without the need of further purification techniques. In a representative experiment, a mixture of 458 mg of the silica gel-supported reagent (Quadrasil® MP or synthesized MPS), bis(*p*-tolyl)sulfoxide (115 mg, 1 mmol) and $MoO_2Cl_2(dmf)_2$ (3.5 mg, 2.0 mol%) in toluene (1 mL) was irradiated in a sealed tube in the microwave cavity at 140 °C for 10 min. Then, the reaction mixture was cooled to room temperature and the silica gel was removed by filtration and washed with Et_2O (2 x 5 mL). The solvents of the filtrate were removed under reduced pressure to yield bis(*p*-tolyl)sulfide in pure form (104 mg, 97% yield).

Considering our previous results in this field,[10] we postulate a mechanism that would start with reaction of the dioxomolybdenum(VI) catalyst with the thiol leading to the thiolate complex **I** (Scheme 1). At this point, reductive elimination of an heterogeneous sulfenic acid derivative would lead to the reduction of the dioxomolybenum(VI) catalyst to a formal monooxomolybdenum(IV) species **II**, which would be able to deoxygenate the sulfoxide to the corresponding sulphide regenerating the active catalyst (Scheme 1).



Scheme 1 Proposed catalytic cycle for the molybdenum-catalyzed deoxygenation of sulfoxides

Conclusions

In summary, we have developed a convenient protocol for the Mo-catalysed sulfoxide deoxygenation based on the unknown use of mercaptopropyl-functionalized silica gel (MPS) as reducing agent. The improved strategy reduces the work-up of the reaction to just a simple filtration of the solid waste without affecting the scope or tolerance to potential reducible functional groups that has been demonstrated to be extremely high. Therefore, purification protocols including chromatography and liquid-liquid extractions, which are time consuming and difficult to scale up, are not required. Moreover, the reactions are performed in air using easily available and environmentally friendly $MoO_2Cl_2(dmf)_2$ as catalyst and the products are obtained in good to excellent yields from the corresponding starting materials in a few minutes.

Acknowledgements

We are grateful to the Ministerio de Economía y Competitividad (MINECO) and FEDER (CTQ2013-48937-C2-1P) and Junta de Castilla y León (BU237U13) for financial support. P. G.-G. thanks MINECO for a “Ramón y Cajal” contract.

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16 Obtained from Sigma-Aldrich (ca. 3.2 €/mmol)

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