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Aerobic oxidation of benzyl alcohols by Mo^{VI} compounds

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Selective and controlled aerobic oxidation of activated benzyl alcohols to the corresponding aldehydes is achieved in refluxing CH_3CN using catalytic amounts of $MoO_2Cl_2(L)_2$ where L is DMSO, DMF or THF. The catalysis reactions are possible under open air in the absence of any other external co-oxidants. However, bubbling of oxygen to the reaction mixture is useful in making the catalysis reaction sustained. Both activated and deactivated varieties of α-substituted benzyl alcohols (secondary alcohols) give ketones in the same reaction conditions. The inexpensive catalyst is selective towards activated primary benzyl alcohols and also, being mild, stops the oxidation at the aldehyde stage, making it synthetically useful. **Copyright © 2006 John Wiley & Sons, Ltd.**

KEYWORDS: alcohols; oxidation; molybdenum; homogeneous catalysis

INTRODUCTION

MoO(molybdopterin) moiety is considered to be the metal-centered functional unit of the oxomolybdoenzymes.[1,2] Variations in the coordination chemistry and, therefore, the properties of the metal centre occur with the binding of various ligands. Another important property is the various redox processes necessary for the operation of the catalytic cycles. Oxotransferases and hydroxylases are the terms associated with these enzymes owing to their known reactivities. We are interested in probing oxomolybdenum compounds for their possible reactivity towards organic substrates. We explored alcohol oxidation in this perspective, keeping in mind the function of molybdoenzymes as well as developing reagents for organic syntheses.

From a synthesis point of view, oxidation of alcohols to the corresponding carbonyl compounds, although it can be performed by various methods, still remains one of the most important reactions in organic synthesis.[3–13] Chromium reagents are widely used for alcohol oxidation, however the requirement for stoichiometric amounts, safety hazards, formation of by-products and difficulty in work-up are major experimental problems.[6] Recently, catalytic oxidation of alcohols employing complexes of transition metal ions, such as Ru, Co, Cu, Pd, V and Os have been reported.[7–13] From an enzymatic perspective, aldehyde dehydrogenase from *Pseudomonas testosteroni* having the common cofactors of molybdenum hydroxylases uses a wide range of aldehydes as substrates.[14] There are only few reports available for alcohol oxidation in homogeneous condition using molybdenum compounds, along with H_2O_2 or some other compounds as additives.[15–18]

The Mo^{VI} salt MoO_2Cl_2 has been used as an efficient catalyst for some organic transformations.[19–24] We have used MoO_2Cl_2 for selective oxidation of sulfides to sulfoxides and sulfones using H_2O_2 at room temperature.[25] Synthesis of some simple and stable adducts of this salt, i.e. $MoO_2Cl_2(L)_2$ where L = DMSO, **1,** DMF, **2,** and THF **3** (Scheme 1) are reported in literature.[26–32] We have prepared compounds **1** and **2** using $H_2MoO_4 \cdot H_2O$, whereas Na_2MoO_4 or Pb_2MoO_4 is used in earlier reports. Some of these adducts are already used for catalyzed reactions like oxidation of sulfides to disulfides,[21,28] deoxygenation of sulfoxides,[22] and N-oxides[23] and oxidation of triphenylphosphine to triphenylphosphine oxide.[29] There is no report available for oxidation of alcohols using these simple adducts of MoO_2Cl_2. We have observed an interesting result using the Mo-adducts in that selective, mild and efficient oxidation of activated benzyl alcohols is possible in a controlled and quantitative manner.

RESULTS AND DISCUSSION

In our preliminary experiments, we investigated the possible oxidation of 4-methoxybenzyl alcohol (Scheme 2), and

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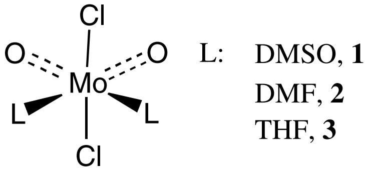
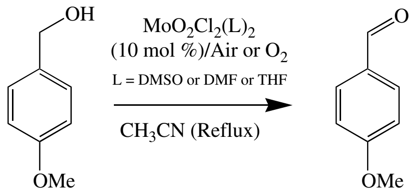


Scheme 1. Structures of the catalysts.



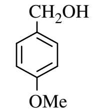
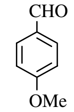
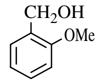
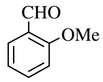
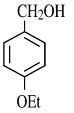
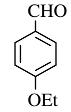
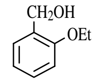
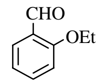
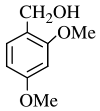
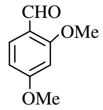
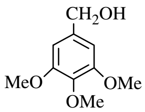
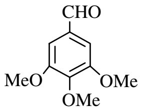
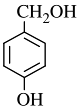
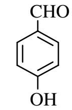
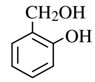
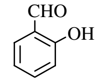
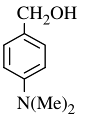
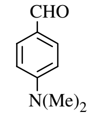
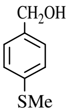
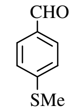
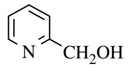
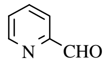
Scheme 2. Oxidation of 4-methoxybenzyl alcohol.

Table 1. Oxidation of 4-methoxybezyl alcohol in various solvents[a]

Catalyst	Amount (mol%)	Solvent	Time (h)	Yield (%)[b]
$MoO_2Cl_2(DMSO)_2$ (**1**)	10	DMSO	2	90
		CH_2Cl_2	2	53
		CH_3CN	2	93
$MoO_2Cl_2(DMF)_2$ (**2**)	10	DMF	2	65
		CH_2Cl_2	2	48
		CH_3CN	2	81
$MoO_2Cl_2(THF)_2$ (**3**)	10	THF	2	67
		CH_2Cl_2	2	50
		CH_3CN	2	80

[a] Reaction conditions: 1 mmol of substrate/10 mol% of catalyst/stirred with bubbling of oxygen under reflux condition.
[b] GC yields.

Table 2. Oxidation of various activated primary benzyllic alcohols by the catalyst $MoO_2Cl_2(DMSO)_2$, **1**[a]

Entry	Substrates	Product	Time (h)	Yield (%)[b]
1			2	91
2			2	86
3			2	89
4			2	90
5			1.5	85
6			3	71
7			3	69^{c}
8			2.5	82^{c}
9			2.5	91
10			3	93
11			4	78

[a] Reaction conditions: 1 mmol of substrate/10 mol% of catalyst/stirred with bubbling of oxygen in CH_3CN under reflux condition. [b] Isolated yields. [c] Some 5–8% of corresponding acid was isolated. Another product was also detected in TLC as a very faint spot, but the corresponding product could not be isolated.
[d] A concentration of 15 mol% catalyst was used.

benzyl alcohol by using the catalysts **1, 2** and **3** separately. The reactions are performed with continuous bubbling of oxygen in varied solvents (Table 1) under reflux. We observed quantitative conversion of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde in acetonitrile solvent using **1** as catalyst. In the same conditions there was no reaction detected when benzyl alcohol was used as a substrate. The range of primary alcohols used as substrates is shown in Table 2. In the case of secondary alcohols, initially we studied oxidation of benzoin to benzil (Scheme 3) under the same reaction condition followed by other secondary alcohols, as shown in Table 3.

It can be seen from Tables 2 and 3 that primary alcohols are oxidized faster than secondary alcohols under identical reaction conditions. Oxidation of 4-methoxybenzyl alcohol (entry 1) and 4-methoxy-α-methylbenzyl alcohol (entry 13) was performed in one pot to compare the reactivity of primary and secondary alcohols and the result is shown in Fig. 1.

The substrates noted in Table 2 show that the presence of electron-donating substituents on the aromatic ring such as OMe (entries 1, 2, 5 and 6), OEt (entries 3 and 4), OH (entries 7 and 8), $N(CH_3)_2$ (entry 9), SMe (entry 10) and heteroatom in the ring (entry 11) facilitates oxidation of the benzyllic alcohol group.

The fact that all activated primary alcohols are oxidized to form aldehyde and the reaction does not proceed further to give carboxylic acid (except entries 7 and 8) is also of

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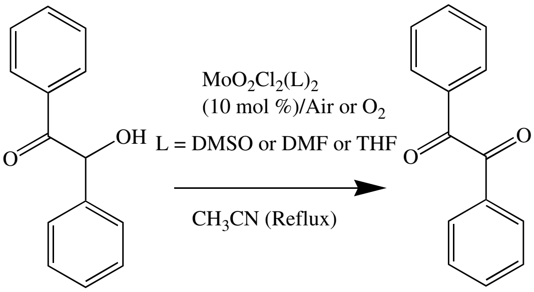
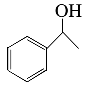
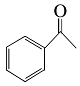
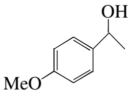
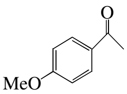
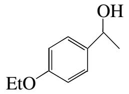
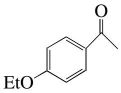
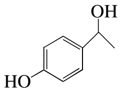
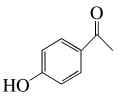
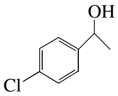
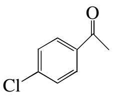
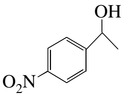
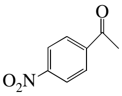
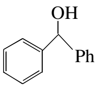
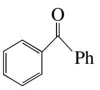
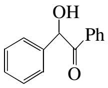
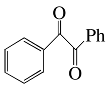
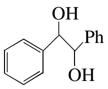
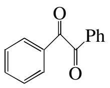
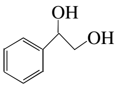
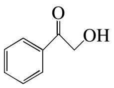


Scheme 3. Oxidation of benzoin.

Table 3. Oxidation of secondary alcohols by using $MoO_2Cl_2(DMSO)_2$, **1**[a]

Entry	Substrates	Product	Time(h)	Yield(%)[b]
12			5	83
13			3	80
14			3	78
15			4.5	65[c]
16			5	73
17			7	71
18			3	85
19			2.5	93
20			4	92[d]
21			5	91[d]

[a] Reaction condition: 1 mmol of substrate/10 mol% of catalyst/stirred with bubbling of oxygen in CH_3CN under reflux conditions. [b] Isolated yields. [c] Another product was detected in TLC as a very faint spot but the corresponding product could not be isolated. [d] A concentration of 15 mol% catalyst was used.

synthetic interest. Substrates having electron-withdrawing substituents like chloro and nitro groups are not oxidized at all, suggesting the discriminating behavior of the catalysts.

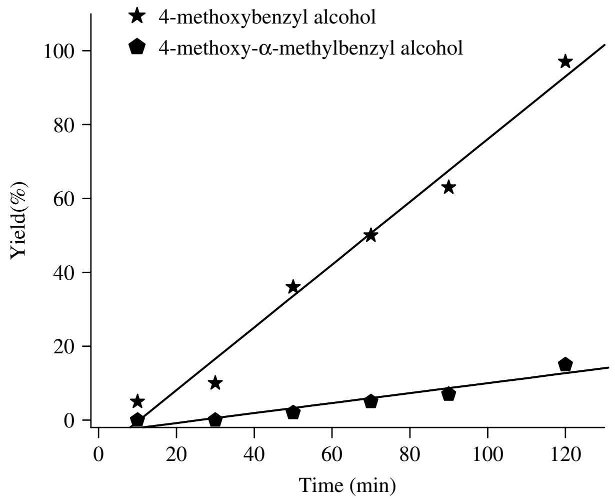


Figure 1. Competitive oxidation of 4-methoxybenzyl alcohol and 4-methoxy-α-methylbenzyl alcohol by the catalyst **1** in one pot under bubbling of oxygen.

In the case of oxidation of secondary alcohols (Table 3), a variety of α-substituted and ring-substituted benzyl alcohols are subjected to oxidation reactions. It is observed that oxidation takes place irrespective of the electron-donating or -withdrawing substituents on the ring. Interestingly, diol having both primary and secondary alcohol groups in the same substrate (entry 21) showed oxidation of only secondary alcohol part.

To throw some light on the possible mechanism for the oxidation reaction, we studied oxidation of benzoin under various conditions like open air, oxygen and inert atmosphere (Table 4). When the catalyzed reaction was performed under bubbling oxygen, the catalysts showed comparatively higher reactivity. However, under strict Ar atmosphere and degassed conditions the reactivity is much less. When the reaction was carried out under open air or Ar atmosphere the colorless catalyst gave blue coloration during/after complete reaction, indicating reduction of the Mo^{VI} center; the catalyst also became inactive. However, under deliberate bubbling of oxygen or addition of H_2O_2, the catalyst remained active. Addition of a fresh batch of substrate, under bubbling oxygen condition, to the reaction vessel showed once again rapid conversion of the alcohol to the corresponding carbonyl compound. This process could be

Table 4. Oxidation of benzoin under various conditions[a]

Condition[a]	Time (h)	Yield (%)
Open air	2.5	76
Oxygen	2.5	93
Inert atmosphere	24	28

[a] Reaction conditions: 1 mmol of benzoin/10 mol% of catalyst **1**/refluxed in 5 ml CH_3CN.

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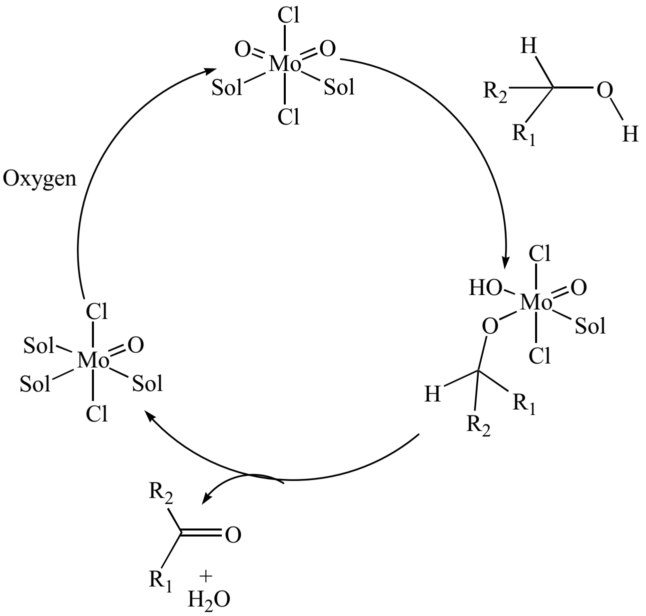

Scheme 4. Proposed mechanism for alcohol oxidation in presence of catalyst (sol = solvent).

repeated at least 10 times. Thus we propose the participation of aerobic oxygen in the oxidation process.

A proposed reaction mechanism is shown in Scheme 4. Usually addition of an OH group across the Mo–O double bond is the first step.[33] Theoretical calculation shows that such addition of MeOH to MO_2Cl_2 is facile when M is Cr and not so in Mo compounds.[33] In our work, benzyl alcohol could not be oxidized even under oxygen bubbling conditions. Thus, we suggest that the presence of an electron-releasing group in the benzyl alcohol is needed to initiate the addition and subsequently catalysis occurs. Under air where oxygen pressure is low, during the oxidation reaction a possible competitive reaction renders the reduction of catalyst to a blue mass.

EXPERIMENTAL

Molybdic acid ($H_2MoO_4 \cdot H_2O$) was purchased from Fischer Inorganics & Aromatics Ltd, India. The solvents, i.e. DMSO, DMF, THF, CH_2Cl_2 and CH_3CN, were purchased from SRL Ltd, India. We have prepared the compounds **1**[28,30] and **2**[22,30] using $H_2MoO_4 \cdot H_2O$, whereas Na_2MoO_4 or Pb_2MoO_4 is used in earlier reports; **3** was prepared following the reported method.[31,32] All the alcohols were purchased from Aldrich except entries 9, 14, 15 and 17. Entry 9 was purchased from SRL Ltd, India and entries 14, 15 and 17 were prepared by using literature procedures.[34,35] All the carbonyl compounds were characterized by recording their ^1H NMR, IR and melting points using Bruker 400 MHz, Jasco FT/IR 660 plus and Toshnival-India melting point apparatus, respectively. The analytical data obtained for the carbonyls were compared with reported data.[36–46] The mass spectral data for the reduced catalyst were obtained from a Voyager DE PRO Biospectrometry Workstation (Applied Biosystems) MALDITOF MS instrument.

Synthesis of the catalysts

$MoO_2Cl_2(DMSO)_2$,**1**

$H_2MoO_4.H_2O$ (1.80 g, 10 mmol) was dissolved in 10 mL of concentrated HCl by stirring for 10 min. To this solution 10 mL of DMSO were added drop-wise, whereupon a white solid was precipitated out within 5 min. The solid was separated by filtration under vacuum, washed with acetone and dried at room temperature to obtain the title compound (3.2 g, 90%). Identity of the catalyst **1** was established by collecting and comparing the analytical data with the literature.[28,30]

$MoO_2Cl_2(DMF)_2$, **2**

The catalyst **2** was prepared using the method described above for **1** except that 10 mL of DMF were added instead of DMSO. The compound was also isolated as a white solid (3.0 g, 86%). The identity of the catalyst **2** was established by collecting and comparing the analytical data with literature.[30]

Catalysis reaction

In a typical experiment 1 mmol of substrate was dissolved in 5 mL of acetonitrile followed by the addition of the catalyst $MoO_2Cl_2(DMSO)_2$ (33.6 mg, 0.1 mmol). The mixture was stirred under bubbling O_2 under reflux conditions and the progress of the reaction was monitored by TLC. After completion, the solvent was evaporated and the crude mixture was subjected to aqueous work-up followed by column chromatography purification to afford the carbonyl compound. All substrates were oxidized following this general method.

Analysis of the reduced catalyst

Investigation of the blue mass that is formed from the reduction of the catalyst during the oxidation of a alcohol under open air was carried out by using MALDI-TOF MS. The spectrum showed peaks at $m/z = 495$ and 551 corresponding to the proposed formula $[MoO(\mu\text{-}O)Cl]_3$ and $[MoO(\mu\text{-}OH)Cl]_3 \cdot (H_2O)_3$, respectively. Some other peaks are also shown in the spectrum, thus, the blue solid may be a mixture of compounds.

CONCLUSION

In conclusion, we have demonstrated the use of $MoO_2Cl_2(L)_2$ as a catalyst for alcohol oxidation. No additives are required and the catalyst acts mildly and selectively so that, while benzyl alcohol is untouched, 4-methoxybenzyl alcohol is quantitatively transformed to anisaldehyde. Catalytic activity of these simple adducts with variation of ligands is our next goal.

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