Chemoselective hydrogenation of nitroarenes and deoxygenation of pyridine N-oxides with H₂ catalyzed by MoO₂Cl₂

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ABSTRACT

A chemoselective and highly efficient hydrogenation of nitroarenes and deoxygenation of pyridine N-oxides using a cheap and environmentally friendly H_2/MoO_2Cl_2 system has been developed.

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Oxygen atom transfer (OAT) reactions mediated by transition metals hold great interest in biological systems, organic synthesis, and industrial processes.[1] It is known that some dioxomolybdenum(VI) complexes that mimic oxo-transferase enzymes are efficient catalysts for oxo transfer reaction from DMSO to PPh₃ in mild conditions.[2–4] In particular, MoO_2Cl_2 was shown to transfer an oxygen atom efficiently from sulfoxides and N-oxides to an appropriate oxygen acceptor such as phosphites and phosphines (Scheme 1).[5,6]

During the course of our investigations on high-valent dioxomolybdenum species as catalysts in reduction reactions,[7–9] we found that MoO_2Cl_2 catalyzes the deoxygenation of sulfoxides to sulfides with H₂ (Scheme 2).[10] This is a very exciting result since it allows us to replace phosphines or silanes[11] by a cheaper reducing agent, H₂. This method is of particular interest because water is the only waste product. This result prompted us to extend the studies on the reducing abilities of the system H_2/MoO_2Cl_2.

The deoxygenation of pyridine N-oxides to pyridines is an important step in the synthesis of heterocycles.[12] A number of methods have been developed for the reduction of pyridine N-oxides;[13–16] however, they often suffer from serious disadvantages, such as incompatibility with other functional groups, low yields, harsh reaction conditions, and difficult work-up procedures. Recently, efficient methods for deoxygenation of N-oxides to amines under mild conditions with Mo(CO)₆[17] and CuI[18] were reported, but stoichiometric amounts of catalysts relatively to the amine N-oxide were needed.

The selective hydrogenation of nitro compounds is also a difficult process, commonly used to manufacture amines, which are important intermediates for fine chemical industry.[19] Hydrogenation with heterogeneous catalysts is the method of choice for the conversion of aromatic nitro compounds to the corresponding anilines. Whereas the hydrogenation of simple nitroarenes is readily carried out with various commercial catalysts, the situation is different if other reducible functional groups are present in the molecule.[20] Corma et al. have recently developed excellent methods
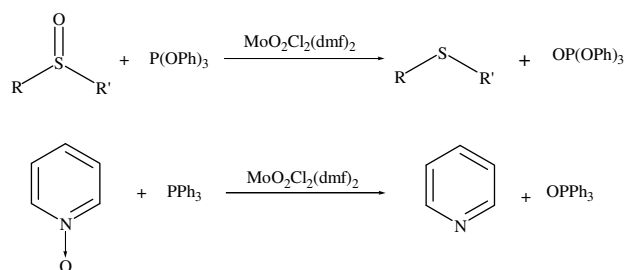
Scheme 1. Deoxygenation of sulfoxides and pyridine N-oxides with phosphines and phosphates.
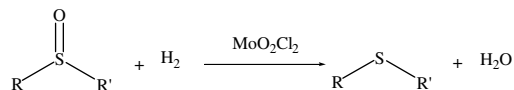

Scheme 2. Deoxygenation of sulfoxides with H₂.

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for the chemoselective hydrogenation of nitro compounds by means of supported nanosized metals.[21]

With the increasing interest in environmental protection, more attention is paid to 'green chemistry'. Thus, we decided to explore the capability of our clean and cheap system to perform these types of reduction reactions. We herein report the environmentally friendly and highly efficient and selective method for the hydrogenation of nitro compounds and deoxygenation of pyridine N-oxides with H_2 in the presence of catalytic amounts of MoO_2Cl_2.

As depicted in Scheme 3, hydrogenation of nitroarenes is simply achieved by reaction of nitro compounds with H_2 in the presence of catalytic amounts of MoO_2Cl_2 under mild reaction conditions (50 bar, 120 °C) in EtOH.[22] Other solvents such as acetonitrile and toluene were found to be suitable for the reaction. As shown in Table 1, this method is highly chemoselective, and it is successfully used to reduce aromatic nitro compounds containing olefinic bonds, carbonyl functions, and cyano and halo groups. The hydrogenation of 3-nitrostyrene gave conversion of 100% with 100%
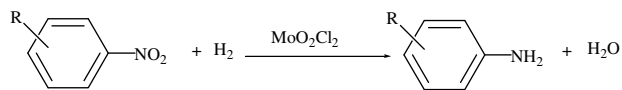
Scheme 3. Hydrogenation of nitroarenes with H_2/MoO_2Cl_2.

Table 1
Hydrogenation of nitroarenes with H_2 catalyzed by MoO_2Cl_2[a]

Entry	Substrate	Product	Yield[b] (%)
1			100
2			100
3			100
4			100
5			100
6			100[c]
7			100

[a] Reaction conditions: 1 mmol of nitroarene, 10 mol % of catalyst, 50 atm of H_2 in EtOH at 120 °C.
[b] Yield determined by GC analysis and/or ^1H NMR spectroscopy.
[c] Yield determined after 48 h of reaction. A 70% yield of the amine was observed after 20 h of reaction.

selectivity to 3-vinylaniline (Table 1, entry 6). The chemoselective reduction of the nitro group in the presence of carbonyl groups has been studied through the hydrogenation of 4-nitroacetophenone and 4-nitrobenzamide. Chemoselective reduction product of the nitro group is obtained in quantitative yields (Table 1, entries 4 and 7). No decarboxylated products were detected in the reaction. Nitro groups can also be reduced selectively in the presence of nitriles. Thus, 4-nitrobenzonitrile was reduced to the corresponding amine with 100% yield. This method also tolerates functional groups such as halogens (Table 1, entry 3). A detrimental effect in the yield of the corresponding amines has been observed by decreasing the hydrogen pressure (15% yield of aniline when 25 atm of H_2 was used).

The catalyst MoO_2Cl_2 can be reused, and three successive reactions were performed by sequential addition of fresh 4-nitrobenzonitrile. The conversion to 4-aminobenzonitrile was monitored by GC showing 100% of conversion in all three cycles. Thus, the active catalytic species is stable under the catalytic conditions used.

Using the same method, a variety of pyridine N-oxides were reduced to the corresponding pyridines (Scheme 4). The results are summarized in Table 2. The reactions yield quantitative conversions to the corresponding pyridines in all cases. For the reduction of pyridine N-oxides, better yields were obtained by using toluene as a solvent instead of ethanol. Quantitative conversions were obtained at 50 atm of H_2 pressure; when lower H_2 pressure was applied, a detrimental effect in the yield was obtained, for example, 7% yield of 4-pyridinecarbonitrile with 25 atm of H_2. To explore the scope and limitation of this method, we have tested its applicability for selective deoxygenation of pyridine oxides bearing other potentially sensitive functional groups. The functional tolerance is excellent, and chloro, cyano, carboxyl, and methoxy substituents remain unchanged under the reaction conditions.

Further investigations of our H_2/MoO_2Cl_2 system as reducing agent in organic synthesis include the deoxygenation of azoxybenzene and deoxygenation of arsenium oxide (Scheme 5).

As a control, blank experiments for the reduction of nitroarenes, pyridine N-oxides, and arsenium oxide were performed by reacting the substrates with H_2 without MoO_2Cl_2. No reaction was found under similar reaction conditions in the absence of catalyst.
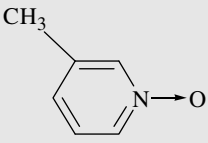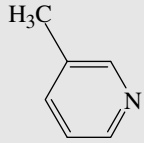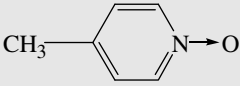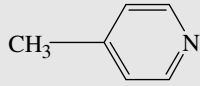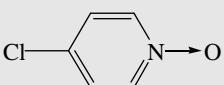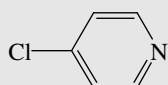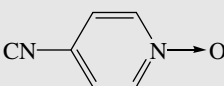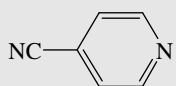
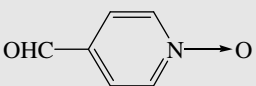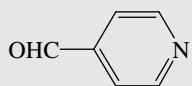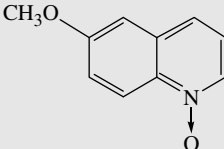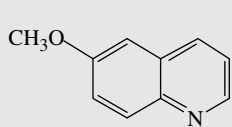According with our previous report in the activation of H_2 by MoO_2Cl_2, our catalyst does not react with H_2 in the absence of substrates.[10] DFT calculations showed that the mechanism for H_2 activation by Mo(VI) complexes starts with a [2+2] addition of the H–H bond to the Mo=O, followed by hydride migration to yield the water complex $[MoO(OH_2)Cl_2]$ (**1**) (Scheme 6).[10] It was impossible to find a pathway for water elimination from **1**, meaning that substrate-dependent reaction has to be considered. Probably, under catalytic conditions, the first step of the reaction is the coordination of the substrates to MoO_2Cl_2 forming the corresponding adducts, for example, $MoO_2Cl_2(Py-NO)_2$. These adducts may rapidly transform into the catalytically active reduced species, as has been proposed by Arnáiz et al. in the deoxygenation of azoxibenzene with $PPh_3/MoO_2Cl_2(Me_2SO)_2$.[23]
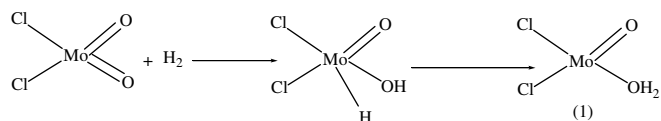
Although we could not characterize any molybdenum species from the catalytic reactions, we have isolated Mo(V) species from the reduction of MoO_2Cl_2 adducts with H_2. The reaction of $MoO_2Cl_2(^tBuBipy)$ (**2**) with H_2 in toluene affords $Mo_2O_3Cl_4(^tBuB$-
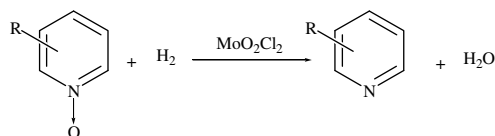
Scheme 4. Deoxygenation of pyridine N-oxides with H_2.

Table 2
Deoxygenation of pyridine N-oxides with H_2 catalyzed by MoO_2Cl_2[a]

Entry	Substrate	Product	Yield[b] (%)
1	CH₃ structure with N→O	H₃C structure with N	100
2	CH₃ structure with N→O	CH₃ structure with N	100
3	Cl structure with N→O	Cl structure with N	100
4	CN structure with N→O	NC structure with N	100
5	OHC structure with N→O	OHC structure with N	100[c]
6	CH₃O quinoline structure with N→O	CH₃O quinoline structure with N	100

[a] Reaction conditions: 1 mmol of pyridine N-oxide, 10 mol % of catalyst, 50 atm of H_2 pressure in toluene at 120 °C.
[b] Yield determined by ^1H NMR spectroscopy.
[c] Yield determined after 48 h of reaction. A 55% yield of the pyridine was observed after 20 h of reaction.
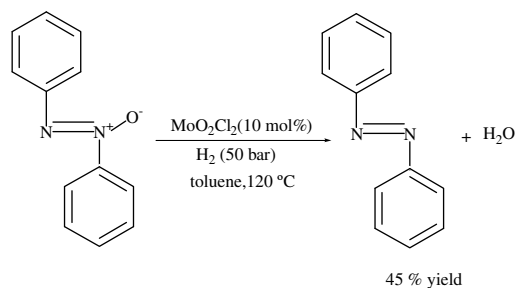
Scheme 5. Deoxygenation of azoxybenzene and triphenylarsenium oxide with H_2.

Scheme 6. [2+2] addition of H_2 to Mo=O bonds.
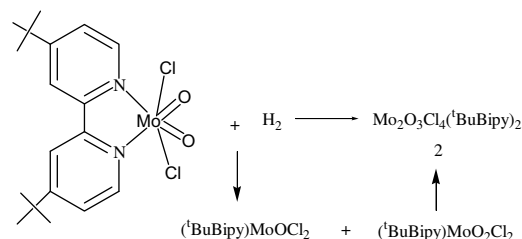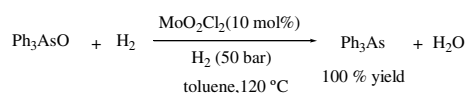
Scheme 7. Reaction of MoO_2Cl_2(ᵗBuBipy) with H_2.

ipy)₂, which is probably the result of the reduction of **2** to the oxomolybdenum(IV) MoOCl₂(ᵗBuBipy), followed by conproportionation, Scheme 7.[24] This is consistent with the well known tendency of oxomolybdenum(IV) and dioxomolybdenum(VI) to associate leading to stable conproportionation products of oxomolybdenum(V), which are more resistant to reduction.[1] Similar results have been published by Arnáiz and co-workers in their studies on the reduction of dioxomolybdenum(VI) complexes with phophines.[25]

In addition, our previous results on the hydrogenation of alkynes based on spin trap experiments[10] suggested that radical species were present in the reaction. Similar radical scavenger

experiments performed in the deoxygenation reaction of sulfoxides, pyridine N-oxide, arsenium oxide, and hydrogenation of nitroarenes indicated that no radicals are involved in these reduction reactions, since addition of radical traps does not affect the reaction.[26]

In conclusion, an efficient method for the reduction of aromatic nitro compounds and pyridine N-oxides employing H_2 as reducing agent and MoO_2Cl_2 as catalyst is reported. This catalytic system is simple, inexpensive, clean, reusable, and applicable for preparing different substituted aromatic amines and pyridines with excellent conversion and chemoselectivity. This method does not generate any harmful and/or wasteful co-products, only water is generated in the reaction.

Acknowledgments

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22. In a typical experiment, a mixture of MoO_2Cl_2 (0.1 mmol) and substrate (1.0 mmol) in ethanol (8 mL) was added to the reactor, previously degassed with nitrogen, and provided with a magnetic stirrer. The reactor was flushed with 50 atm of H_2 pressure and heated to 120 °C for 20 h. Conversion was determined by gas chromatography (GC).
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24. Characterization of $Mo_2O_3Cl_4(^tBuBipy)_2$: IR(cm^{-1}): ν(Mo=O) 965(s); ν(Mo–O–Mo) 786(m). ^{1}H NMR (CD_2Cl_2): 9.09 ppm (d, $^3J_{H–H}$ = 6.1 Hz, 2H); 8.88 ppm (d, $^3J_{H–H}$ = 5.8 Hz, 2H); 8.16 ppm (s, 2H); 8.10 ppm (s, 2H); 7.59 ppm (d, $^3J_{H–H}$ = 6.0 Hz, 2H); 7.53 ppm (d, $^3J_{H–H}$ = 5.1 Hz, 2H); 1.49 ppm (s, 18H); 1.42 ppm (s, 18H). Anal. Calcd for $C_{36}H_{48}Mo_2Cl_4N_4O_3$: C, 47.07; H, 5.26; N, 6.1. Found: C, 47.14; H, 5.08; N 6.21. MS (ES): *m/z* 884 [M]$^+$−Cl. $MoO_2Cl_2(^tBuBipy)$ catalyzes the redution of PhMeSO to PhMeS with 80% yield.
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