

Reduction of amides with silanes catalyzed by MoO_2Cl_2

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Abstract

A novel method for the reduction of amides to the corresponding amines using a silane in presence of a catalytic amount of dioxomolybdenum dichloride (10 mol%), in moderate to good yields, is reported. This method is especially suitable for the reduction of tertiary amides with bulky N-substituents.

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1. Introduction

The synthesis of amines is an important area of research and sometimes is a key step in the industrial synthesis of medicinal supplies and agricultural chemicals. One of the methods used for the synthesis of amines consists in the reduction of amides. This reduction is usually carried out with lithium aluminium hydride [1] or with borane [2–6]. Reduction of primary and secondary amides with LiAlH_4 affords the corresponding primary and secondary amines in good yields. However, the reduction of tertiary amides, generally gives secondary amines when the N-substituents are bulky. Catalytic hydrogenation of amides requires vigorous conditions (high pressure and elevated temperatures) [7].

In last years, the reduction of amides with silanes catalyzed by transition metal has received a great deal of attention. This reaction was studied with complexes containing the metals Ti, Rh, Ru, Pt, Pd, Re and Mn as catalysts [8–13].

Recently, we have developed a novel system for hydrosilylation and reduction reactions using a silane and a catalytic amount of the high valent dioxomolybdenum complex, MoO_2Cl_2 . This novel system proved to be very efficient for the hydrosilylation of aldehydes and ketones, yielding the corresponding silyl ethers [14], and for the reduction of imines [15], esters [16], sulfoxides [17] and pyridine N-oxides [17] to the corresponding amines, alcohols, sulfides and pyridines (see Scheme 1).

In this work, we investigated the reduction of amides to the corresponding amines using a silane in presence of a catalytic amount of dioxomolybdenum dichloride.

2. Results and discussion

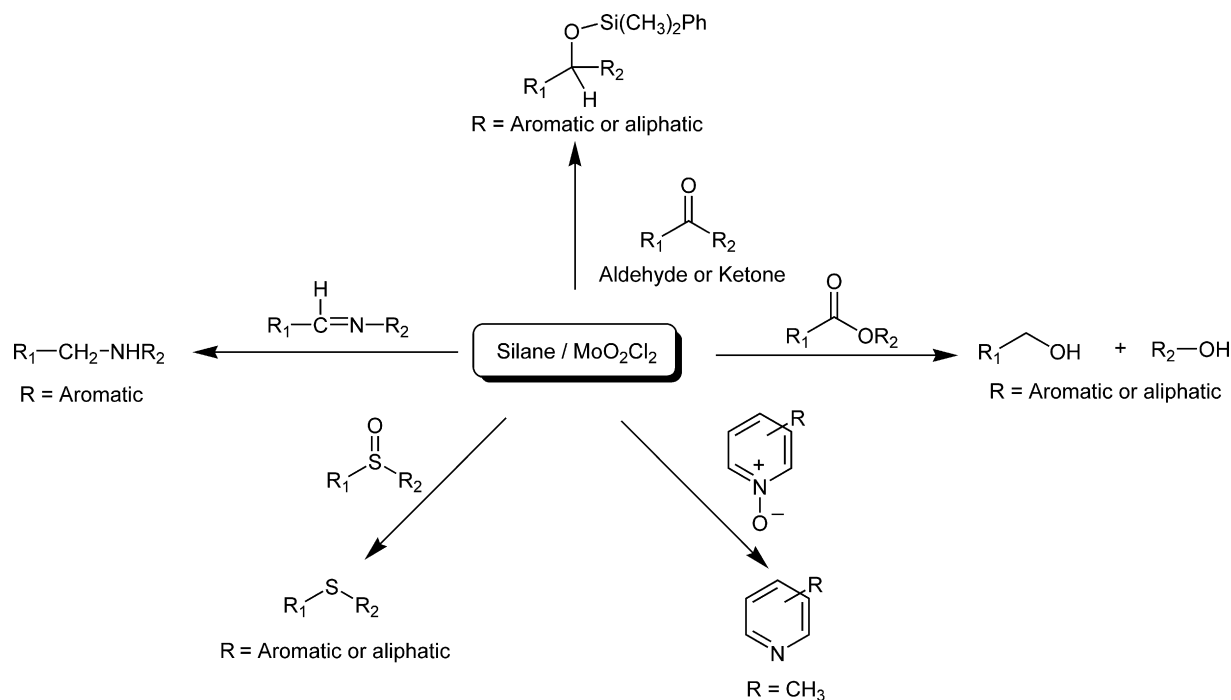
We studied the reduction of amide **1** with several solvents and silanes (Table 1). The best results were observed with phenylsilane in refluxing toluene (entry 1). In dichloromethane or THF the amine **2** was obtained in 95 and 56% conversion, respectively (entries 2 and 3) but in acetonitrile the reduction did not occur (entry 4).

The study performed with several silanes showed the reduction of amide **1** in excellent conversions with PhSiH_3 , polymethylhydrosiloxane (PMHS) and dimethylphenylsilane (DMPSH) (entries 1, 5 and 6) and in 70% conversion with triethylsilane (Et_3SiH) (entry 7). No catalysis was observed with triphenylsilane (entry 8).

The reduction of a variety of amides was investigated with the system $\text{PhSiH}_3/\text{MoO}_2\text{Cl}_2$ (10 mol%) in refluxing toluene (Table 2). As shown in Table 2, secondary and tertiary amides were reduced by this catalytic system in moderate to good yields.

The results obtained with 5-acetylindolizine and 1-acetylindoline (entries 1 and 2) showed the efficiency of this method for the reduction of tertiary amides with bulky N-substituents. The development of suitable methods for the reduction of tertiary amides is crucial, since the reaction with LiAlH_4 fails when the N-substituents are bulky. Furthermore, tertiary amines are an important class of compounds for the

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Scheme 1.

drug discovery process, due to their good intestinal absorption, CNS (central nervous system) penetration, and the potential for involvement of the tertiary nitrogen in ligand binding.

Secondary amides (entries 3–7) were also reduced with the system PhSiH₃/MoO₂Cl₂ (10 mol%) in moderate to good yields (40–78%) with tolerance of halo groups.

The reactivity of the primary amides with this catalytic system is very low. The reduction of 4-(trifluoromethyl)benzamide gave the corresponding amine in only 20% yield, and in the ¹H NMR spectrum of the reaction mixture obtained in the reduction of 4-chlorobenzamide was not detected the presence of the

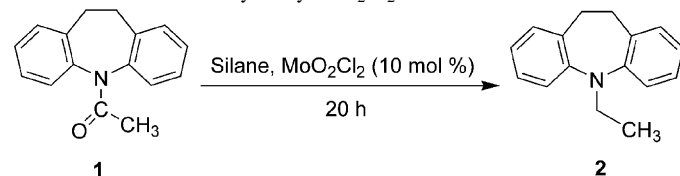
amine. Other methods using silanes also showed low reactivity or were inactive in the reduction of primary amides [9,10,12].

Comparing our results with other catalytic systems reported in literature, we concluded that our system has some advantages. For example, the dioxomolybdenum dichloride catalyzes the reduction of amides with several silanes including hydrosilanes and polysiloxanes, in contrast to platinum catalysts, such as H₂PtCl₆·6H₂O, that only catalyze the reduction of tertiary amides with siloxanes containing more than two Si–H groups, specially with PMHS. These platinum catalysts are inactive with hydrosilanes and the system PMHS/H₂PtCl₆·6H₂O did not reduce secondary and primary amides [12].

The catalytic methods using rhodium complexes have also some limitations, for example, the system Ph₂SiH₂/RhH(CO)(PPh₃)₃ reduces tertiary amides in good yields but is inactive with secondary and primary amides [10] and the systems Ph₂SiH₂/[RhCl(cod)]₂/4 PPh₃ and Ph₂SiH₂/[RhCl(PPh₃)₃] only reduce secondary amides and when the substrates have sterically bulky substituents, the yields of the amines are moderate and the corresponding imines are producing in competitive yields [9].

We observed that amide **1** was not reduced when the reaction was carried out with an excess of phenylsilane without catalyst. This result shows that MoO₂Cl₂ plays an active role in the reduction. The computational studies performed by Costa et al. [18] for the reduction of carbonyl group with silanes catalyzed by MoO₂Cl₂ suggest the activation of the Si–H bond of the silane by MoO₂Cl₂, yielding a hydride species (Mo–H). Although we have been unable to detect the Mo–H, similar Re-hydrides are formed and also found to be active in carbonyl reduction [19,20]. We believe that the mechanism of this reduction involves the reaction of amide with the hydride species,

Table 1
Reduction of amide **1** catalyzed by MoO₂Cl₂



Entry	Silane	Silane (mol%)	Solvent ^a	Conversion ^b (%)
1	PhSiH ₃	200	Toluene	100
2	PhSiH ₃	200	CH ₂ Cl ₂	95
3	PhSiH ₃	200	THF	56
4	PhSiH ₃	200	CH ₃ CN	No reaction
5	PMHS	10	Toluene	97
6	DMPHS	300	Toluene	96
7	Et ₃ SiH	300	Toluene	70
8	Ph ₃ SiH	300	Toluene	No reaction

^a Reflux temperature.

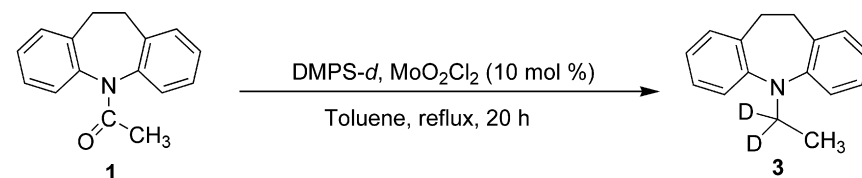
^b Conversion was determined by ¹H NMR.

Table 2
Reduction of amides with the system PhSiH₃/MoO₂Cl₂

Entry	Amide	Product	Yield ^a
1			87
2			81
3			78
4			54
5			56
6			52
7			40

All reactions were carried out in refluxing toluene with 1.0 mmol of amide, 2.0 mmol of PhSiH₃, using 10 mol% of MoO₂Cl₂.

^a Isolated yield.



Scheme 2.

giving the imine first, and then the imine is reduced to the corresponding amine by reaction with a second equivalent of hydride species (Mo–H), as we have demonstrated in our previous article [15]. This result is consistent with the incorporation of two deuterium atoms in the carbonyl carbon of amine **3**, obtained in the reaction of amide **1** with DMPS-*d* in presence of MoO₂Cl₂ (see Scheme 2).

3. Experimental

All manipulations were carried out using standard Schlenk-line techniques under a nitrogen atmosphere. Solvents were purified by conventional methods and distilled under nitrogen, prior to use. Amides and silanes were obtained from Aldrich, PMHS (Mn = 1700–3200). Dimethylphenylsilane-*d* was prepared by reduction of chlorodimethylphenylsilane with LiAlD₄. Flash chromatography was performed on MN Kieselgel 60M

230–400 mesh. All compounds were characterized by ¹H NMR, ¹³C NMR and IR spectroscopy. ¹H NMR and ¹³C NMR spectra were measured on a Bruker AMX 300 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from an internal Me₄Si standard. IR spectra were measured on a Unicam Mattson model 7000 FTIR spectrometer.

3.1. General procedure for the reduction of amides with the system PhSiH₃/MoO₂Cl₂

To a solution of MoO₂Cl₂ (10 mol%) in dry toluene (5 ml) was added the amide (1.0 mmol) and PhSiH₃ (2.0 mmol) under nitrogen atmosphere. The reaction mixture was stirred at reflux temperature during 20 h. After evaporation, the reaction mixture was purified by silica gel column chromatography with the appropriate mixture of n-hexane and ethyl acetate to afford the amines, which are all known compounds.

4. Conclusion

In summary, we have developed a novel method for the reduction of amides to the corresponding amines using a silane in presence of a catalytic amount of MoO_2Cl_2 , in moderate to good yields. These results confirm the excellent catalytic activity of this high valent oxo-complex for organic reductions and extend the scope of the system silane/ MoO_2Cl_2 .

This novel method is a good alternative to the traditional methods, especially for the reduction of tertiary amides with bulky N-substituents.

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

References

- [1] J. March, *Advanced Organic Chemistry*, fourth ed., Wiley, New York, 1992, 1212.
- [2] A.F.D. Alcantara, H. dos Santos Barroso, D. Pilo-Veloso, *Quim. Nova* 25 (2002) 300.
- [3] H.C. Brown, S. Narasimhan, Y.O.N.G.M. Choi, *Synthesis* (1981) 441.
- [4] H.C. Brown, P. Heim, *J. Org. Chem.* 38 (1973) 912.
- [5] Z.B. Papanastassiou, J.B. Robert, *J. Org. Chem.* 29 (1964) 2870.
- [6] H.C. Brown, P. Heim, *J. Am. Chem. Soc.* 86 (1964) 3566.
- [7] C. Hirosawa, N. Wakasa, T. Fuchikami, *Tetrahedron Lett.* 37 (1996) 6749.
- [8] K. Selvakumar, K. Rangareddy, J. Harrod, *Can. J. Chem.* 82 (2004) 1244.
- [9] T. Ohta, M. Kamiya, M. Nobutomo, K. Kusui, I. Furukawa, *Bull. Chem. Soc. Jpn.* 78 (2005) 1856.
- [10] R. Kuwano, M. Takahashi, Y. Ito, *Tetrahedron Lett.* 39 (1998) 1017.
- [11] Y. Motoyama, K. Mitsui, T. Ishida, H. Nagashima, *J. Am. Chem. Soc.* 127 (2005) 13150.
- [12] S. Hanada, Y. Motoyama, H. Nagashima, *Tetrahedron Lett.* 47 (35) (2006) 6173.
- [13] M. Igarashi, T. Fuchikami, *Tetrahedron Lett.* 42 (2001) 1945.
- [14] A.C. Fernandes, R. Fernandes, C.C. Romão, B. Royo, *Chem. Commun.* (2005) 213.
- [15] A.C. Fernandes, C.C. Romão, *Tetrahedron Lett.* 46 (2005) 8881.
- [16] A.C. Fernandes, C.C. Romão, *J. Mol. Catal. A: Chem.* 253 (2006) 96.
- [17] A.C. Fernandes, C.C. Romão, *Tetrahedron* 62 (2006) 9650.
- [18] P.J. Costa, C.C. Romão, A.C. Fernandes, B. Royo, P.M. Reis, M.J. Calhorda, *Chem. Eur. J.* 13 (2007) 3934.
- [19] J.J. Kennedy-Smith, K.A. Nolin, H.P. Gunterman, F.D. Toste, *J. Am. Chem. Soc.* 125 (2003) 4056.
- [20] L.W. Chung, H.G. Lee, Z. Lin, Y.-D. Wu, *J. Org. Chem.* 71 (2006) 6000.