Molybdate Sulfuric Acid/$NaNO_2$: A Novel Heterogeneous System for the *N*-Nitrosation of Secondary Amines under Mild Conditions

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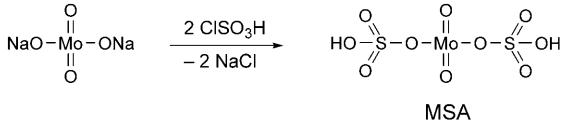
Wet molybdate sulfuric acid (=dioxo[bis(sulfato-κO)]molybdenum; MSA), a new solid acid, can be used in combination with sodium nitrite ($NaNO_2$) to transform a variety of secondary amines to the corresponding *N*-nitroso compounds under mild, heterogeneous conditions (*Table*). The process has several advantages: the reagents are inexpensive and non-hazardous, the reaction is clean, fast, and high-yielding, and MSA can be readily removed by filtration and re-used (after treatment with HCl) without loss of activity. Further, only *N*-nitrosation was observed, but no *C*- or *O*-nitrosation.

Introduction. – Currently, the search for and application of (new) heterogeneous chemical systems is an active field both in industry and academia, especially in view of simplified handling procedures, reduction of corrosion, avoidance of undesired by-products, and clean, ecologically friendly reactions and workup procedures. With regard to the wide application of acids as reagents or catalysts in organic chemistry, the introduction of an inorganic solid acid can be useful in this direction. Several solid acids such as silica sulfuric acid [1] and *Nafion-H* [2] have been used for a wide variety of chemical transformations, *e.g.*, preparation of disulfides from thiols, oxidation of 1,4-dihydropyridines [3], *N*-nitrosation of secondary amines [4], acetal deprotection [5], oxidation of alcohols [6], alkylation with olefins, alkyl halides, and alkyl esters, isomerization, transalkylation, acylation, nitration, ether and ester synthesis, acetal formation, and rearrangements [7].

In continuation of our recent studies [8] on the application of inorganic solid acids, we herein present molybdate sulfuric acid (=dioxo[bis(sulfato-κO)]molybdenum; MSA) as a new solid regent. MSA was prepared according to a previously published protocol [8c], as shown in *Scheme 1*.

Scheme 1



MSA

To evaluate the synthetic utility of MSA, we turned to nitrosation reactions, especially because of the mutagenic and carcinogenic properties of *N*-nitrosamines [9]. *N*-nitrosamines have been used as pesticides, lubricants, and antioxidants [10]. They play a

key role in the preparation of various *N,N′*-bonded functionalities, and their easy lithiation, followed by denitrosative electrophilic reaction, can be applied for electrophilic substitutions of secondary amines at the α-position [11]. Some nitrosating agents such as *Fremy*'s salt [12], *N*-halogenoamides/$NaNO_2$ under phase-transfer conditions [13], nitrogen tetroxide, [14] oxyhyponitrite [15], and oxalic acid [16] have been reported before. *In situ* generated HNO_2 from $NaNO_2$ and an inorganic acid in H_2O or H_2O/alcohol mixtures is the most general reagent for nitrosations. In this paper we report the new heterogeneous system MSA/$NaNO_2$ for the *in situ* generation of HNO_2 for *N*-nitrosation reactions.

Results and Discussion. – First, we were interested to examine MSA as a H^+ source in combination with various oxidants in organic solvents. For this reason, we chose wet 10% (*w*/*w*) MSA/$NaNO_2$ for the *N*-nitrosation of a series of secondary amines (**1a**–**14a**), which were transformed to the corresponding *N*-nitrosamines (**1b**–**14b**) in CH_2Cl_2. All reactions were run under mild, heterogeneous conditions at room temperature and gave, in good-to-excellent yields, the expected *N*-nitrosamines (*Table*).

All nitrosation reactions were complete in short time (*ca*. 15–20 min), and without formation of any by-products. The products were obtained by simple filtration and evaporation of the solvent. A further advantage of the new system is that the solid acid can be easily recovered and used again after treatment with dilute HCl. Thus, recovered MSA from the nitrosation reaction of, *e.g.*, **14a** was reused in another reaction with $NaNO_2$, which afforded **14b** in 88% yield (compared to 90% in the first run; see *Table*).

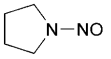
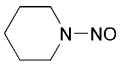
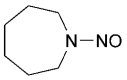
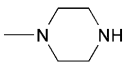
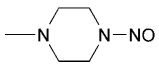
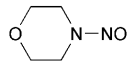
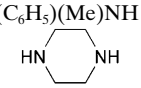
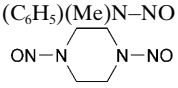
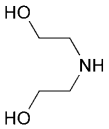
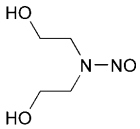
In the amines **12a**, **13a**, and **14a**, there are two or three positions susceptible to nitrosation. With two equivalent N-atoms present, as in **12a**, double nitrosation took place in good yield (85%) when using 2 equiv. of reagent. As expected, no selective mononitrosation was observed with only 1 equiv. of MSA/$NaNO_2$. In **13a**, theoretically both *O*- and *N*-nitrosation could take place, but only *N*-nitrosation to **13b** was observed under the applied reaction conditions. This result is in accord with the well-known observation that *N*-nitroso forms are thermodynamically distinctly more stable than the corresponding *O*-nitroso isomers. Finally, in the case of diphenylamine (**14a**), *N*-nitrosation took place without *C*-nitrosation at the Ph rings, further highlighting the chemoselectivity of our method.

Based on other literature reports [4][17], we propose that the reactions proceed *via* formation of NO^+ upon reaction of wet MSA with $NaNO_2$ according to *Scheme 2*.

Finally, it is noteworthy to point to the role of H_2O in the MSA/$NaNO_2$ system. We decided to run a series of parallel reactions, one under anhydrous conditions (anh. MSA), the other under hydrous conditions (wet MSA). The results clearly indicated that H_2O is essential for the generation of HNO_2 (see *Scheme 2*), since no nitrosation was observed under strictly anhydrous conditions.

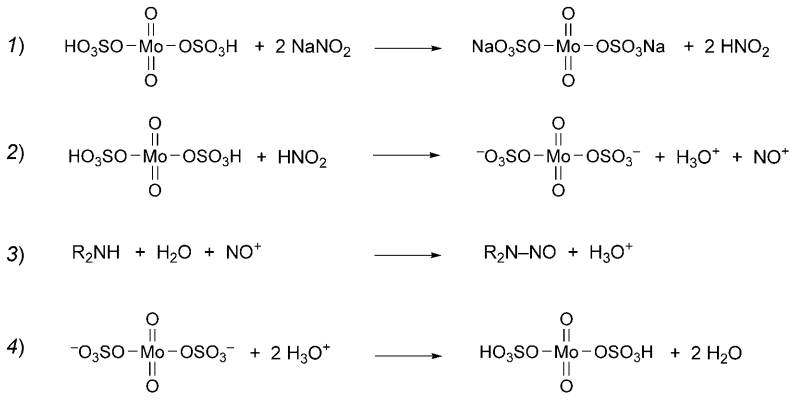
Conclusions. – Molybdate sulfuric acid (MSA) is a versatile solid acid in heterogeneous reactions in which H^+ acts as catalyst or reagent. MSA is an efficient H^+ source, can be readily prepared, is insoluble in all organic solvents, can be readily handled, poses no problem during workup (filtration), is inexpensive, and gives rise to clean, fast, high-yielding reactions, as exemplified by a novel method for the selective *N*-nitro-

Table. *Nitrosation of the Secondary Amines* **1a**–**14a** *with MSA/$NaNO_2$.* Conditions: secondary amine (2 mmol), wet MSA (1 mmol), $NaNO_2$ (2 mmol), CH_2Cl_2 (8 ml), r.t.

No.	Substrate (**a**)	Product (**b**)[a])	Time [min]	Yield [%][b])
1	Me_2NH	Me_2N–NO	15	90
2	Et_2NH	Et_2N–NO	15	90
3	$(i\text{-}Pr)_2NH$	$(i\text{-}Pr)_2N$–NO	15	95
4	$(C_6H_{11})(Me)NH$	$(C_6H_{11})(Me)N$–NO	15	90
5	$(C_6H_{11})_2NH$	$(C_6H_{11})_2N$–NO	15	90
6			15	95
7			15	95
8			15	95
9			15	90
10			16	84
11	$(C_6H_5)(Me)NH$	$(C_6H_5)(Me)N$–NO	17	90
12[c])			15	85
13			20	90
14	$(C_6H_5)_2NH$	$(C_6H_5)_2N$–NO	15	90

[a]) Identified by comparison of the physical and spectroscopic data with those given in the literature [1–7][17]. [b]) Yield of isolated compound. [c]) With 2 mmol of **12a**, 2 mmol of wet MSA, and 4 mmol of $NaNO_2$.

Scheme 2



sation of secondary amines. Structural investigations of MSA and similar solid acids, as well as other applications of these systems in various organic reactions, are currently under investigation.

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Experimental Part

General. The amines **1a**–**14a** and all other chemicals were purchased from *Merck*, *Fluka*, and *Aldrich*. All reactions were monitored by TLC. The products were identified by comparison of their physical and spectroscopic data with those of authentic samples prepared according to previous methods [1–7][17]. IR Spectra were recorded on a *Jasco 680* FT-IR spectrometer; in cm^{-1}. ^{1}H-NMR Spectra were obtained on a *Bruker DPX-300* apparatus; δ in ppm.

Preparation of Molybdate Sulfuric Acid (= *Dioxo[bis(sulfato-κO]molybdenum*; *MSA*). To chlorosulfonic acid (23.30 g, 0.2 mol) in a 250-ml round-bottom flask immersed in an ice bath, anh. sodium molybdate (20.58 g, 0.1 mol) was added gradually. After completion of the addition, the mixture was agitated for 1 h, which gave rise to crude MSA as a bluish-white solid, which was filtered off and washed with cold H_2O. Yield: 28 g (87.5%).

General Procedure for the N-*Nitrosation of Secondary Amines.* To a soln. of the amine (2 mmol) in CH_2Cl_2 (8 ml), wet MSA (1 mmol; 10% (*w*/*w*)) and $NaNO_2$ (2 mmol) were added. The heterogeneous mixture was stirred at r.t., and the reaction was monitored by TLC (SiO_2; hexane/AcOEt). After completion of the reaction (*ca.* 15–20 min), the mixture was filtered and washed with CH_2Cl_2 (4 ml). Then, anh. Na_2SO_4 was added to the filtrate, and after 10 min, the mixture was filtered and the CH_2Cl_2 was removed on a water bath at 40–50°. The products **1b**–**14b** were purified by simple distillation (*Table*) and, when necessary, further purified by flash chromatography (SiO_2; hexane/AcOEt). Some physical and spectroscopic data of selected products are given below.

N-*Methyl*-N-*nitrosomethanamine* (**1b**). B.p. 152°. IR: 2850–2950 (CH), 1450 (N=O), 1350 (C–N), 1375 (Me). ^{1}H-NMR ($CDCl_3$): 2.95 (*s*, Me); 3.69 (*s*, Me).

N-*Nitrosopyrrolidine* (**6b**). B.p. 214°. IR: 2850–2950 (CH), 1430 (N=O and CH_2), 1300 (C–N), 1050 (N–N). ^{1}H-NMR ($CDCl_3$): 4.07 (*t*, 2 H); 3.35 (*t*, 2 H); 1.85 (*q*, 2 H); 1.89 (*q*, 2 H).

N-*Methyl*-N-*nitrosoaniline* (**11b**). Solid, decomposing at 70°. IR: 3050–3100 (arom. CH); 2900–3000 (aliph. CH); 1500, 1600 (arom. C=C); 1450 (N=O and CH_2); 1320 (C–N); 1050 (N–N). ^{1}H-NMR ($CDCl_3$): 7.44–7.51 (*m*, 5 arom. H); 1.69 (*s*, Me). ^{13}C-NMR: 30.5 (Me); 141.7; 128.8; 126.6; 118.5.

1,4-Dinitrosopiperazine (**12b**). Isolated as a mixture of two isomers having either a plane of symmetry (isomer A) or a C_2-axis (isomer B). M.p. 156–160°. IR: 2850–2950 (CH), 1430 (N=O and CH_2), 1350 (C–N). ^{1}H-NMR ($CDCl_3$): 4.50 (*s*, 4 H of *B*); 4.40 (*t*, 4 H of *A*); 4.60 (*s*, 4 H of *A*); 3.83 (*s*, 4 H of *B*). ^{13}C-NMR: 37.2 (*A*); 40.5 (*B*); 46.6 (*B*); 49.2 (*A*).

2,2′-(Nitrosoimino)diethanol (**13b**). Solid, decomposing at 200°. IR: 3200–3400 (OH), 2850–2950 (CH), 1100–1350 (C–O and C–N), 1450 (N=O and CH_2), 1350 (C–N), 1050 (N–N). ^{1}H-NMR ($CDCl_3$): 7.3 (*s*, OH); 4.37 (*t*, CH_2); 4.09 (*t*, CH_2); 3.9 (*t*, CH_2); 3.8 (*t*, CH_2).

N-*Nitroso*-N-*phenylaniline* (**14b**). M.p. 64–66°. IR: 3050–3100 (arom. CH); 1500, 1600 (arom. C=C); 1450 (N=O and CH_2); 1300 (C–N); 1050 (N–N). ^{1}H-NMR ($CDCl_3$): 7.0–7.3 (*m*, arom. H).

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