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Simple, Efficient, and Selective Deprotection of Phenolic Methoxymethyl Ethers Using Silica-Supported Sodium Hydrogen Sulfate as a Heterogeneous Catalyst[1]

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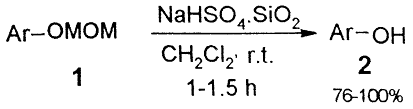
Abstract: A simple and efficient method has been developed for chemoselective deprotection of phenolic methoxymethyl (MOM) ethers using silica-supported sodium hydrogen sulfate as a heterogeneous catalyst. The conversions occur at room temperature, and the yields of the deprotected phenols are excellent. The method is suitable for deprotection of phenolic MOM ethers of multifunctional bioactive natural products.

The protection and subsequent deprotection of a hydroxyl group is the usual practice in multistep transformations and synthesis of complex organic molecules.[2] The methoxymethyl (MOM) group is widely used as a hydroxy-protecting group because it can easily be introduced and is stable under a variety of reaction conditions, including strongly basic and weakly acidic media.[2] MOM-protected phenols also undergo ortho metalation efficiently.[3] Recently, MOM-protected 2,2′-dihydroxynaphthalene has been suggested as the most effective synthone for the synthesis of enantiopure 3,3′-derivatives through directed ortho metalation.[3b] The cleavage of MOM ethers can be carried out under strongly acidic conditions using HCl,[4] BBr_3,[5] *p*-TsOH, or pyridinium *p*-toluenesulfonate.[6] However, these catalysts can also affect other acid-sensitive groups. Mild Lewis acids (e.g., $ZnBr_2$ and $TiCl_4$) cleave the MOM ethers very slowly in an aprotic environment.[7] Different derivatives of boron bromide (Me_2BBr,[8a] (i-PrS)$_2$BBr[8b]) and CBr_4[9] have also been applied for deprotection of MOM ethers. However, some of these catalysts have not been studied in detail to determine their selectivity toward the deprotection of the MOM ethers of aliphatic and aromatic hydroxyls. Some catalysts showed similar roles toward the cleavage of the MOM ethers of both the hydroxyls.[8,9] Most of the catalysts also work under homogeneous conditions, and so handling and removal from the reaction mixture is sometimes a problem. Recently, clay-catalyzed deprotection of phenolic MOM ethers has been reported.[10] The catalyst works only for ortho-substituted MOM-protected phenols containing a heteroatom in this ortho position. We have developed a simple and efficient procedure for the cleavage of phenolic MOM ethers using $NaHSO_4{\cdot}SiO_2$ as a heterogeneous catalyst. Several phenolic MOM ethers were deprotected to the corresponding phenols (Scheme 1, Table 1) by applying this catalyst.

SCHEME 1



The deprotection occurred under mild reaction conditions at room temperature. The conversion took a short reaction time, and the yields of the regenerated phenols were very high. The structures of all the products were confirmed by their spectral (^{1}H NMR and MS) data and by direct comparison with authentic samples.

The catalyst, $NaHSO_4{\cdot}SiO_2$, can easily be prepared[11] from the readily available reagents, $NaHSO_4$ and silica gel (finer than 200 mesh), but it should be properly activated. Both the ingredients are inexpensive and nonhazardous. Thus, on the basis of economic and ecological considerations, the catalyst is highly valuable. The experimental procedure is very simple, and as the reaction is heterogeneous in nature, the catalyst can easily be removed by filtration. We observed that $NaHSO_4$ or silica gel alone could not deprotect the MOM ether under similar experimental conditions.

The present deprotection method is associated with high chemoselectivity. Phenolic MOM ethers can be cleaved selectively in the presence of a wide range of functional groups present in the phenols. Alkyl and benzylic ethers were not cleaved. Acetate, ester, aldehydes, and OTs groups also remained unaffected. Thus, if the phenolic compounds contain two hydroxyl groups, one of them can be protected with a MOM and the other with an ester group and subsequently they can be deprotected in different stages of a synthetic sequence. The method has efficiently been applied for deprotection of phenolic MOM ethers of bioactive natural products (entries t and x) containing various functionalities. An interesting observation is that the catalyst showed very weak activity toward the cleavage of MOM ethers of aliphatic hydroxyl groups. The MOM-protected phenyl methanol (entry m) and phenyl ethanol (entry n) underwent ~10% deprotection with the catalyst under the present experimental conditions (1.5 h). If the time was

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(1) Part 26 in the series "Studies on Novel Synthetic Methodologies".

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TABLE 1. Deprotection of MOM Ethers Using $NaHSO_4 \cdot SiO_2$[a]

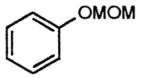
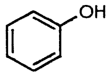
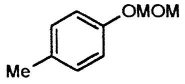
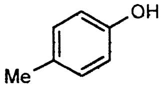
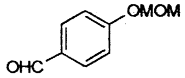
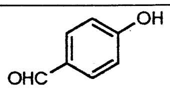
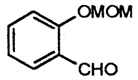
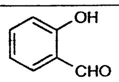
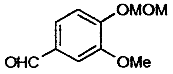
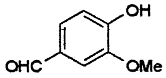
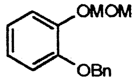
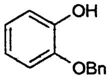
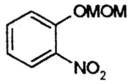
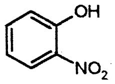
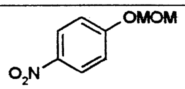
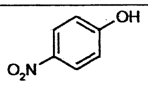
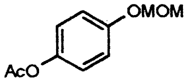
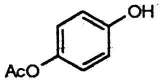
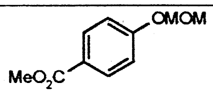
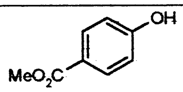
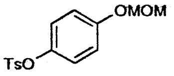
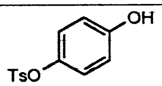
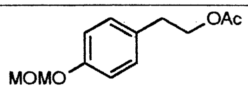
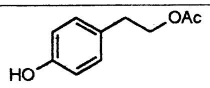
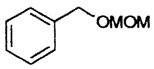
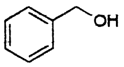
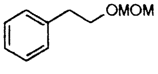
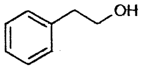
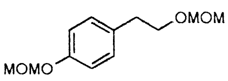
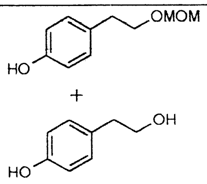
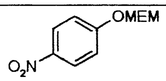
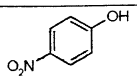
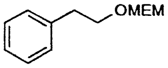
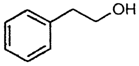
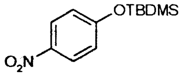
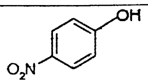
Entry	MOM ether (**1**)	Product (**2**)	Time (h)	Isolated Yield (%)
a			1.5	94
b			1.5	99
c			1.5	100
d			1.5	98
e			1	92
f			1	100
g			1	100
h			1	100
i			1.5	91
j			1	96
k			1	95
l			1.5	95
m			1.5	12
n			1.5	10
o			1.5	76 + 12
p			1.5	99
q			1.5	10
r			1.5	5

Table 1. (Continued)

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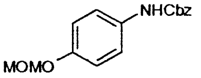
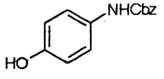
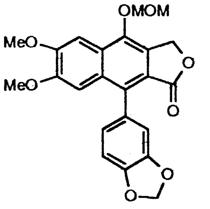
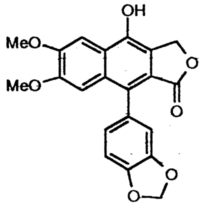
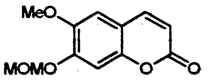
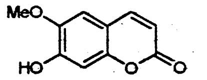
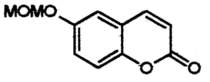
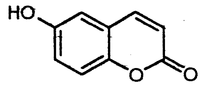
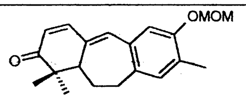
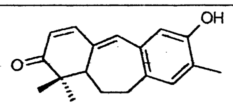
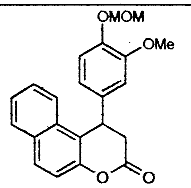
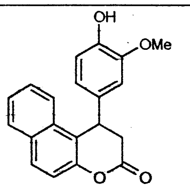
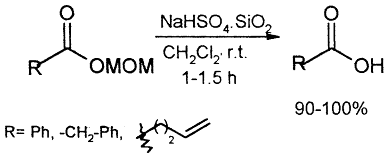
s			1.5	88
t			1.5	94
u			1.5	91
v			1.5	86
w			1.5	89
x			1.5	93

[a] All products were characterized from their spectral (^{1}H NMR and MS) data and by comparison with authentic samples.

SCHEME 2



increased, the deprotection was increased somewhat more. TBDBS ether (entry r) of *p*-nitrophenol also underwent a small degree of deprotection (5%) after treatment with the catalyst for 1.5 h. However, phenolic MEM (methoxyethoxymethyl) ethers could be deprotected with equal activity. Thus, MEM ethers (entry p) of *p*-nitrophenol afforded the corresponding phenol with a yield of 99% in the presence of $NaHSO_4{\cdot}SiO_2$ at room temperature for 1.5 h.

The method has also been extended for the cleavage of MOM esters of carboxylic acids (Scheme 2). However, in this case the MOM esters of both the aliphatic and aromatic acids were equally deprotected. As for an example, the MOM esters of benzoic and phenylacetic acids could be converted quantitatively into the corresponding acids using $NaHSO_4{\cdot}SiO_2$ at room temperature for 1.5 h.

In conclusion, we have developed an exceedingly mild, simple, and efficient methodology for the deprotection of phenolic methoxymethyl ethers using $NaHSO_4{\cdot}SiO_2$ as a heterogeneous catalyst at room temperature. The operational simplicity, shorter reaction times, application of an inexpensive and nontoxic catalyst, excellent yields, and high chemoselectivity are the great advantages of the present procedure. The method has been found to be suitable for deprotection of phenolic MOM ethers of multifunctional bioactive compounds. The procedure can also be extended for deprotection of phenolic MEM ethers and the MOM esters of both the aliphatic and aromatic acids. We feel that the present process will find important applications in synthetic organic chemistry.

Typical Experimental Procedure

To a stirred solution of the MOM ether of *p*-nitrophenol (183 mg, 1 mmol) in DCM (10 mL) was added activated (while hot) $NaHSO_4{\cdot}SiO_2$ (200 mg) (the catalyst was kept in an oven at 120 °C for 48 h before using it) at room temperature. After completion of the reaction (monitored by TLC, 1 h) the catalyst was filtered off and washed with DCM (2 × 5 mL). The filtrate and washings were combined, and the solvents were removed under vacuum to give pure *p*-nitrophenol (139 mg, 1 mmol, 100%) as a solid.

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