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Simple and Practical Protocol for the Silylation of Phenol Derivatives Using Reusable $NaHSO_4$ Dispread on Silica Gel Under Neutral Conditions

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A simple and mild procedure for the trimethylsilylation of a wide variety of phenols with hexamethyldisilazane (HMDS) on the surface of silica gel dispersed with $NaHSO_4$ *at r.t. in a few minutes with excellent yields under neutral conditions is reported. This procedure also allows an excellent selectivity for the silylation of phenols in the presence of amine and* CO_2H *groups.*

Keywords Hexamethyldisilazane (HMDS); hydroxy group; $NaHSO_4/SiO_2$; recycling; selective silylation

INTRODUCTION

The trimethylsilylation of organic compounds having mobile hydrogen atoms is an important organic transformation.[1] It is a frequently used protection method in multistep synthesis of natural products due to the enhanced stability of the silyl derivatives under a variety of conditions, the solubility in nonpolar solvents, and the thermal stability and ease of the removal of silylan groups. Desilylation is simply accomplished by acid- or base-induced hydrolysis, which gives only unreactive siloxane as a byproduct. Silylation is also extensively used for the derivatization of hydroxy compounds in order to increase their volatility for gas chromatography and mass spectrometry.[2]

A wide variety of methods using silylating agents, such as chlorotrimethylsilane and a base,[3] bis-(trimethylsilyl)trifluoro acetamide,[4] allylsilanes together with an acid,[5] and bistrimethylsilyl ether,[6] have been reported. However, these reagents require the addition of bases, and the difficulty in removing the ammonium salts is

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frequently encountered. A longer reaction time is an additional disadvantage of these reagents.

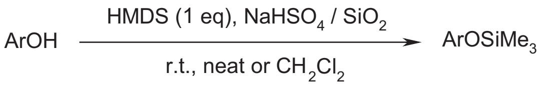
Hexamethyldisilazane (HMDS) is frequently used for the trimethylsilylation of hydroxy groups. HMDS is an inexpensive and commercially available reagent. Its handling does not require special precautions, and the workup is not time consuming because the byproduct of the reaction ammonia can be easily removed from the reaction medium. The low silylation power of HMDS is the main drawback to its application. There are a variety of catalysts for activating this reagent, such as I_2[7], $(CH_3)_3SiCl$,[8] and K-10 montmorillionite.[9] Recently, trimethylsilyl azide and $LiClO_4$ were used as an efficient reagent for the silylation of hydroxy groups in neat conditions.[10]

Organic reactions under solvent-free conditions are of great current interest, particularly in relation to green chemistry. On the other hand, organic reactions using reusable and water-tolerant catalysts also received much attention in recent years. Therefore, organic reactions using simple and efficient catalysts under solvent-free conditions would be the ideal methodology, provided that the catalysts show a high catalytic activity.[11]

RESULTS AND DISCUSSION

As part of our research on the application of solid support in organic synthesis under solvent-free conditions,[12] we describe in this article a simple method for the protection of phenol derivatives using a catalytic amount of $NaHSO_4$ dispersed on SiO_2 under solvent-free conditions and in organic solvents (Scheme 1).

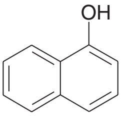
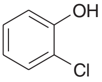
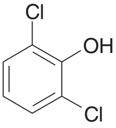
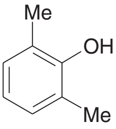
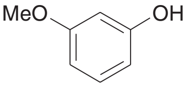
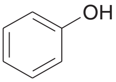
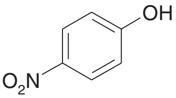
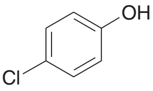
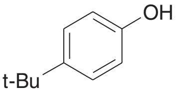
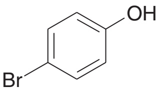
By using different reaction conditions for the silylation of phenols with HMDS, we found out that best results are obtained using $NaHSO_4$ dispersed on SiO_2 (chromatography grade, $NaHSO_4/SiO_2$ with 1:3 ratio, 0.2 g), HMDS (10 mmol) and ROH (10 mmol) at r.t. with solvent-free conditions. Interestingly, reactions catalyzed by $NaHSO_4$ or by silica alone under solvent-free conditions resulted in low yields. In the case of solid substrates, when the reaction is carried out in the presence of an organic solvent (such as CH_2Cl_2, CH_3CN, toluene, THF, or diethyl ether), it is completed after long reaction times in comparison to solvent-free conditions. $NaHSO_4$ dispersed on SiO_2 was used for the silylation of the hydroxy group for a variety of phenols applying simple and highly efficient reaction conditions. The results are summarized in Table I. All

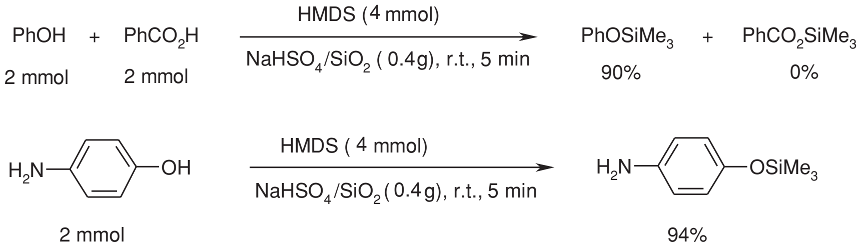


$$\mathrm{ArOH} \xrightarrow[\text{r.t., neat or } \mathrm{CH_2Cl_2}]{\text{HMDS (1 eq), } \mathrm{NaHSO_4/SiO_2}} \mathrm{ArOSiMe_3}$$

SCHEME 1

TABLE I The Silylation of Various Phenols with HMDS

ArOH	Time (min)	Yield (%)
	5	86
	5	92
	5	89
	5	90
	5	94
	5	90
	100	00
	5	94
	5	90
	5	93



SCHEME 2

phenol derivatives can be converted to corresponding trimethyl silyl ethers under these conditions. The reactions are fast and proceed with high yields at r.t. even for less reactive phenols, which usually require long reaction times (a few days) when silylated by conventional reported methods.

We also explored the chemoselectivity of the $NaHSO_4/SiO_2$ system. Scheme 2 shows that in the presence of both a COOH and a phenolic OH group, the phenolic hydroxy group is selectively silylated, and the corresponding silylated phenol is the only reaction product. Similarly, in the presence of an amino group, only the hydroxy group reacts with HMDS to give the corresponding silylated phenol. Although the mechanism of this reaction is not clear, silica gel plays an important role, and its presence was found to be essential for the high efficiency of the reaction.

In summary, $NaHSO_4/SiO_2$ is found to be an efficient and useful catalyst for the silylation of various phenols with HMDS under mild and neutral conditions. This procedure provides an efficient and general methodology for the preparation of phenol trimethylsilyl ethers in high yields. In addition, $NaHSO_4/SiO_2$ is an inexpensive, stable, easy-to-handle, and nontoxic reagent, and the workup is very simple. $NaHSO_4/SiO_2$ can be reused several times after activation. Furthermore, HMDS in combination with the $NaHSO_4/SiO_2$ system exhibits excellent selectivity for the silylation of phenols in the presence of amines and carbonic acids.

EXPERIMENTAL

The Preparation of the $NaHSO_4/SiO_2$ Catalyst

To a solution of 4.14 g (0.03 mol) of $NaHSO_4/SiO_2$ in 20-mL of water in a 100-mL beaker containing a stir bar was added 10 g of SiO_2

(column chromatographic grade, 60 Å, 200–400 mesh). The mixture was stirred for 15 min and then gently heated on a hotplate with intermittent swirling until a free-flowing white solid was obtained. The catalyst was further dried by placing the beaker in an oven maintained at 120°C for at least 48 h prior to use.

The Silylation of Phenols Under Solvent-Free Conditions: General Procedure

To a stirred solution of phenol (5 mmol) and 0.2 g of $NaHSO_4/SiO_2$ in a test tube, HMDS (5 mmol) was added and stirred at r.t. under an argon atmosphere for the specified time (Table I). When the reaction was complete (TLC or GC analysis), CH_2Cl_2 or petroleum ether (5 mL) was added, and the $NaHSO_4/SiO_2$ was removed by filtration. The solvent was evaporated, and the silylated phenol was isolated as an almost pure crude product. Further purification if necessary was carried out by short column chromatography on silica gel eluting with ethyl acetate-petroleum ether. All silylated phenols prepared are known and were identified on the basis of their spectroscopic data (IR, NMR).

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