Efficient Trimethylsilylation of Alcohols and Phenols with HMDS in the Presence of a Catalytic Amount of 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) as a Safe and Cheap Industrial Chemical

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1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) is found to be an effective catalyst for trimethylsilylation various alcohols and phenols with hexamethyldisilazane (HMDS) in dichloromethane at room temperature.

Keywords: Alcohols; Phenols; Hexamethyldisilazane; 1,3-Dibromo-5,5-dimethylhydantion; Trimethylsilyl ether.

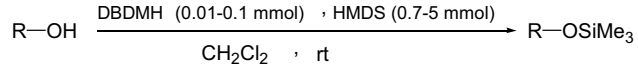
INTRODUCTION

Many chemical conversions and multiple synthesis sequences often require protection of hydroxy groups. The trimethylsilyl group is one of the most widely used protecting groups in organic synthesis and is often used to prepare silyl ethers as volatile derivatives of alcohols and phenols.[1-4] One of the reported reagents for trimethylsilylation is 1,1,1,3,3,3-hexamethyldisilazane (HMDS)[5,6] which is a cheap and commercially available reagent. Its handling does not need special precautions; trimethylsilylation using this reagent is nearly neutral and the work-up of the reaction mixture is not time consuming. However the major disadvantage and drawback of this reagent is its poor silylating power, which needs forceful conditions and long reaction times in many reactions. Hence, a variety of catalysts have been reported for the activation of HMDS.[7-18] However, in most cases drastic reaction conditions and tedious workup are needed and reactions using hindered alcohols do not occur. In addition, many of these reagents are moisture sensitive, toxic and expensive. The lack of a facile and general synthetic methodology for the trimethylsilylation of hydroxyl groups (alcohols, phenols), under neutral conditions, prompted us to develop an efficient and convenient procedure for the protection of hydroxyl groups under mild conditions.

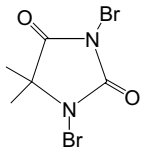
RESULTS AND DISCUSSION

In continuation of our interest in the application of N-halo compounds in organic synthesis,[19] we have found that 1,3-dibromo-5,5-dimethylhydantion (DBDMH) is an inexpensive, commercially available reagent, which can be used as an alternative to bromine or NBS. This safe industrial chemical has never had a real breakthrough in organic laboratories, and its use in organic chemistry is mostly limited to bromination and oxidation reactions.[20] In this paper we wish to report the catalytic application of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a new protocol for the mild trimetylsilylation of several alcohols and phenols using HMDS in dichloromethane at room temperature (Scheme I).

Scheme I



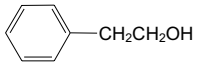
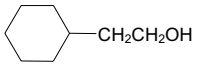
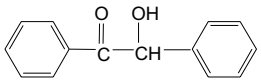
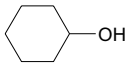
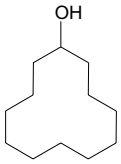
R=Alkyl, Aryl



DBDMH

We first examined the effect of different ratios of ROH/HMDS/catalyst. The 1/2/0.01 and 1/0.7/0.01 ratios for alcohols and phenols respectively gave the best results and produced trimethylsilyl ethers in quantitative yields (Tables 1, 2).

Table 1. Trimethlysilylation of alcohols using HMDS catalyzed with DBDMH in dichloromethane at room temperature

Entry	ROH	Subst/HMDS/DBDMH	Time (h:min)	Yield (%)[a,b]
1	$PhCH_2OH$	1:2:0.01	1:06	84
2	$4\text{-}CH_3\text{-}C_6H_4CH_2OH$	1:2:0.01	2	95
3	$4\text{-}Br\text{-}C_6H_4CH_2OH$	1:2:0.01	1:18	96
4	$4\text{-}F\text{-}C_6H_4CH_2OH$	1:2:0.01	2	93
5	$2,4\text{-}(Cl)_2C_6H_4CH_2OH$	1:2:0.01	1	99
6	$4\text{--}NO_2\text{-}C_6H_4CH_2OH$	1:2:0.01	1	95
7		1:2:0.01	2	92
8		1:2:0.01	2:06	95
9	$CH_3(CH_2)_6CH_2OH$	1:2:0.01	0:40	87
10	PhCH (OH) Ph	1:2:0.01	4	90
11		1:2:0.01	8:30	97
12		1:2:0.01	8:18	99
13		1:0.8:0.01	1:27	80
14	$CH_3CH_2CHOHCH_2CH_3$	1:0.8:0.01	3	85
15	1-adamantanol	1:5:0.1	12	90
16	$CH_3C(CH_3)(OH)CH_2Ph$	1:5:0.1	17	87

[a] All products were characterized by comparison of their spectral data (^{1}H-NMR; IR) with those of authentic samples.
[b] Yields of isolated products.

Table 2. Trimethylsilylation of phenols using HMDS catalyzed with DMDBH in dichloromethane at room temperature

Entry	ROH	Subst/HMDS/DBDMH	Time (min)	Yield (%)[a,b]
1	C_6H_5OH	1:0.7:0.01	25	95
2	$4\text{-}(CH_3)C_6H_4OH$	1:0.7:0.01	1	97
3	$4\text{-}(MeO)C_6H_4OH$	1:0.7:0.01	1	96
4	$4\text{-}(Cl)C_6H_4OH$	1:0.7:0.01	15	96
5	2-Naphthol	1:0.7:0.01	1	90
6	1-Naphthol	1:0.7:0.01	20	95
7	Resorcinol	1:2:0.01	67	70
8	2,6-Diisopropyl phenol	1:0.7:0.01	180	30[c]
9	$C_6H_5NH_2$	1:2:0.01	48h	0
10	C_6H_5SH	1:2:0.01	48h	0

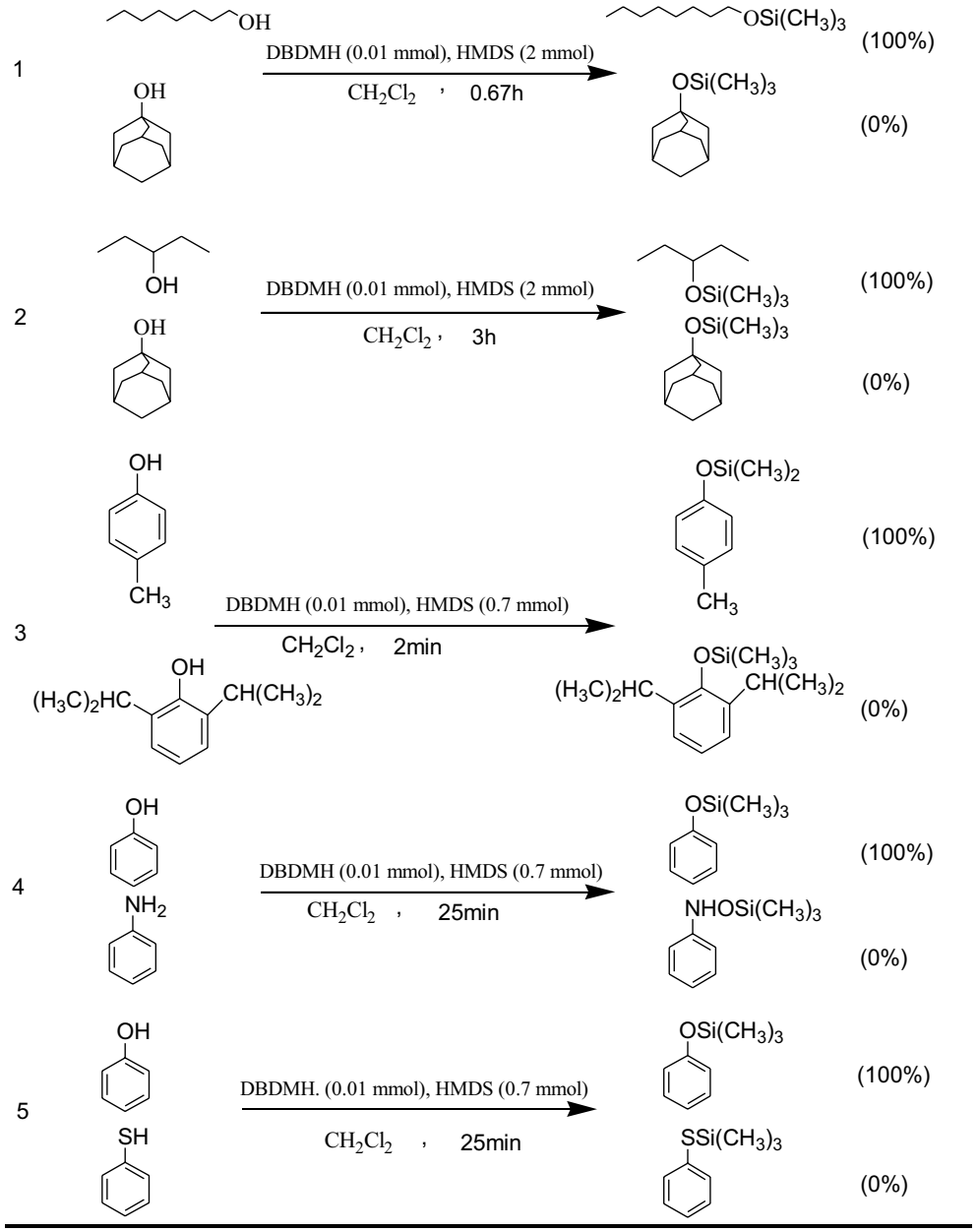
[a] All products were characterized by comparison of their spectral data (^{1}H-NMR; IR) with those of authentic samples.
[b] Yields of isolated products.
[c] Reaction did not complete.

Treatment of several alcohols with HMDS and the catalyst in dichloromethane at room temperature produced the corresponding trimethylsilyl ether in excellent yields (Table 1). Interestingly, tertiary and acid-sensitive tertiary alcohols were converted to the corresponding silyl ether at room temperature; their trimethylsilylation required longer reaction times and greater amount of HMDS and reagents at room temperature (Table 1, entries 15, 16). Due to the nearly neutral nature of the reaction medium, there were not any side products.

The data in Table 2 clearly show that different types of phenols were successfully converted to the corresponding silyl ethers in a short time and in almost quantitative yields. We observed that amines and thiols were not converted under this reaction even after prolonged reaction times. (Table 2, entries 9, 10).

In order to show selectivity of this catalytic system, we tried several competitive reactions under similar condi-

Table 3. Selective reactions of different binary mixtures with HMDS/DBDMH at room temperature



tions. In a binary mixture of n-octanol (as a model for primary alcohol) and 1-adamantanol (as a model for tertiary alcohol), the primary alcohol was completely converted to the corresponding silylether, while 0% conversion was observed for the tertiary alcohol (Table 3, entry 1). Excellent selectivity was also observed for secondary alcohols in the presence of a tertiary alcohol (Table 3, entry 2).

Similarly, we used this procedure for the selective trimethylsilylation of 4-methyl phenol in the presence of 2,6-diisopropyl phenol (as a model for hindered phenol). The only observed product was 4-methyl phenyl trimethylsilyl ether in 100% conversion (Table 3, entry 3). Also this method showed excellent selectivity for the conversion of phenol in the presence of aniline or thiophenol (Table 3, entries 4, 5).

In order to learn the catalytic activity of DBDMH, we compared our obtained results for the trimethylsilylation of 1-naphtol (as a model for phenols) with the best of the well known data from the literature (Table 4). The advantages or the characteristic aspects of the described method in this communication in comparison with other previously reported catalysts are the following: a variety of phenols[14,7] can be trimethylsilylated in good to high yield[15,18] at room temperature.[18,16] In addition, the catalyst DBDMH is inexpensive, no moisture sensitivity[15] and no large amount of catalyst required.[15]

The actual role of DBDMH is not clear. On the basis of a previously reported mechanism for applying I_2 for the trimethylsilylation of alcohols using HMDS[14] and our observation during the course of the reaction (evolution of acid), a hypothesis is that DBDMH may generate small quantities of HBr, which may be the actual catalyst for the trimethylsilylation reactions (as a protic acid). DHDMH may act as an alternative as a source for the formation of Br^+. However, at this time the precise role of DBDMH is not clear and the actual role of this reagent should be further studied in detail.

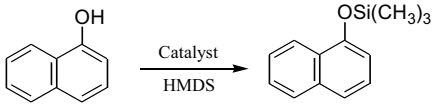
In conclusion, our methodology shows that 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) is an effective and practically neutral catalyst for trimethylsilylation of various hydroxyl groups using HMDS. The main advantages of our protocol are: fast reaction, selectivity, excellent yields, low cost reagent, and easy work-up conditions. For these reasons our protocol compares favorably to the existing methodologies in the field of protection of the hydroxyl group as TMS-ether.

EXPERIMENTAL SECTION

General Procedure

To a mixture of HMDS (0.7-2 mmol) and DBDMH (0.01-0.1 mmol) in CH_2Cl_2 (7 mL) alcohols or phenols (1 mmol) were added, and the mixture was stirred at room temperature for the specified time (Tables 1, 2). The progress was monitored by TLC. After completion of the reaction, water (10 mL) was added to destroy the extra amounts of HMDS for alcohols and NaOH %5 (10 mL) for phenols, then the organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated, and n-hexane (20 mL) was added to the residual solid. Insoluble catalyst was removed by filtration. Evaporation of the n-hexane under reduced pressure gave pure product without further purification.

Table 4. Comparison of the activity of various catalysts in the trimethylsilylation of 1-naphtol with HMDS



Entry	Catalyst	Condition	HMDS:Cat	Time	Yield (%)	Ref
1	DBDMH	CH_2Cl_2, rt	0.8:0.06	30 min	95	This work
2	$CuSO_4.5H_2O$	CH_3CN, reflux	0.7:0.1	38 h	50	18
3	$LiClO_4$	Solvent-Free, rt	0.7:0.5	20 min	80	15
5	$H_3PW_{12}O_{40}$*	Solvent-Free, 55 °C-60 °C	0.8:0.01	-	-	16
6	I_2	CH_2Cl_2, rt	0.8:0.01	-	-	14
7	$Si(CH_3)_3Cl$	Solvent-Free, 125 °C	0.8:two drops	-	-	7

* Reaction with other derivatives of phenols has been reported.

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