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CONVENIENT TREMETHYLSILYLATION OF HYDROXY GROUPS WITH HEXAMETHYLDISILAZANE UNDER SOLVENT-FREE CONDITIONS

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CONVENIENT TRIMETHYLSILYLATION OF HYDROXY GROUPS WITH HEXAMETHYLDISILAZANE UNDER SOLVENT-FREE CONDITIONS

Submitted by (07/20/07)

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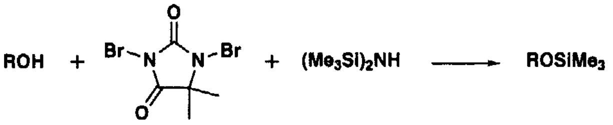
The protection of the hydroxy group is often necessary in organic synthesis, one of the popular means being conversion to the corresponding silyl ethers. Several methods are available for the silylation of the hydroxy group.[1] 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) readily silylates alcohols, acids, amines, thiols, phenols, amides, thioamides, sulfonamides and enolizable ketones; ammonia, the by-product of the reaction, is readily removed from the reaction medium. However, the low silylating power of HMDS is the main drawback to its use and thus various catalysts such as $(CH_3)_3SiCl$,[2] $ZnCl_2$,[3] zirconium sulfophenyl,[4] K-10 montmorillionite,[5] I_2,[6] $LiClO_4$,[7] $H_3PW_{12}O_{40}$,[8] $Al(OTf)_3$,[9] $CuSO_4{\bullet}5H_2O$,[10] and 1,3-dibromo-5,5-dimethylhydantoin (DBH)[11] have been used for the activation of this reagent. Solvent-free reactions have attracted considerable attention in chemical processes for different reasons.

They are valuable with respect to environmental safety and from the economic standpoint and because of facile work-ups, high yields of the products and their usually rapid reaction times.[12] The absence of a facile and general methodology for the trimethylsilylation of hydroxy groups (alcohols and phenols), under essentially neutral conditions, prompted us to develop an efficient, convenient, and practical procedure for the protection of hydroxyl groups under solvent-free conditions.

In continuation of our interest in the application of *N*-bromo compounds in organic synthesis,[13] we now report the use of readily available HMDS for trimethylsilylation of alcohols and phenols in the presence catalytic amount of safe and inexpensive 1,3-dibromo-5,5-dimethylhydantoin (DBH) under environmentally benign and natural conditions (*Scheme 1*). Various



R = benzylic, aliphatic, cyclic, aryl

Scheme 1

ratios (see *Table 1*) of phenols and alcohols, HMDS and the catalyst (DBH) generally gave excellent yields of the O-silyl ethers. Even tertiary alcohols were silylated. Amines, thiols and

Table 1. Trimethylsilylation of Alcohols and Phenols Using HMDS Catalyzed with DBH

Entry	Substrate	Subst/HMDS/ (DBH)	Time (hrs)	Yield[a] (%)	bp. (°C)	bp(lit)[b] (°C)
1	$PhCH_2OH$	1:2:0.01	0.5	91	207	216
2	$4\text{-}(CH_3)C_6H_4CH_2OH$	1:2:0.01	0.5	90	197	204
3	$4\text{-}(Br)C_6H_4CH_2OH$	1:2:0.01	1.25	95	263	274
4	$2,4\text{-}(Cl)_2C_6H_4CH_2OH$	1:2:0.01	0.33	95	242	251
5	$4\text{-}(NO_2)C_6H_4CH_2OH$	1:2:0.01	0.42	96	240	----
6	PhCH(OH)Ph	1:2:0.01	1.1	80	>300	379
7	PhCOCH(OH)Ph	1:2:0.01	3	90	>300	456
8	$PhCH_2CH_2OH$	1:2:0.01	0.55	91	230	239
9	2-Cyclohexylethanol	1:5:0.06	7	96	225	232
10	$CH_3(CH_2)_6CH_2OH$	1:2:0.01	0.67	73	215	----
11	Cyclododecanol	1:5:0.06	6	80	>300	349
12	1-Adamantanol	1:5:0.1	6	71	>300	319
13	$(CH_3)_3COH$	1:5:0.1	10	80	105	117
14	$CH_3C(CH_3)(OH)CH_2Ph$	1:5:0.2	18	87	275	281
15	C_6H_5OH	1:2:0.01	0.21	97	187	193
16	$4\text{-}(CH_3)C_6H_4OH$	1:2:0.01	0.05	90	217	221
17	$4\text{-}(MeO)C_6H_4OH$	1:2:0.01	immediate	90	265	274
18	$4\text{-}(Cl)C_6H_4OH$	1:2:0.01	0.25	98	232	243
19	2-Naphthol	1:2:0.01	immediate	96	>300	309
20	1-Naphthol	1:2:0.01	0.33	95	>300	309
21	Resorcinol	1:2:0.01	0.11	90	285	301
22	2,6-Diisopropylphenol	1: 2:0.1	1.33	0	----	----
23	$C_6H_5NH_2$	1:2:0.01	48	0	----	----
24	C_6H_5SH	1:2:0.01	48	0	----	----

a) All products were characterized by comparison of their spectral data (^{1}H-NMR, IR spectroscopy) with those of authentic samples. b) Chem. Prop (Chem Office 2005).

highly hindered 2,6-diisopropylphenol failed to react even after prolonged times. The data in *Table 1* clearly show that different types of phenols were successfully converted to the corresponding silyl ethers in very short time and in nearly quantitative yields. In order to determine the catalytic activity of DBH, our results for the trimethylsilylation of 2-naphthol were compared with data from literature (*Table 2*). The advantages of our method are the variety of phenols[6,2] silylated,[10,7] the rapid rate[10,7,8] under solvent-free conditions[10,6] at room temperature,[2,8,10] in addition to the low cost, insensitivity of DBH to moisture,[7] and its low toxicity.[6] It should be noted that, although DBH has previously been reported as a catalyst for the trimethylsilylation of alcohols *in solution*,[11] no phenol was subjected to these conditions and the reaction had failed with tertiary alcohols.

Table 2. Comparison of the Activity of Various Catalysts in the Trimethylsilylation of 2-Naphthol with HMDS

Entry	Catalyst	Conditions	HMDS:Cat	Time	Yield (%)	Ref.
1	DBH	Solvent-free	2: 0.01	immediate	96	This work
2	$CuSO_4 \cdot 5H_2O$	CH_3CN, reflux	0.7: 0.1	38 h	50	10
3	$LiClO_4$	Solvent-free, rt	0.7: 0.5	20 min	80	7
4	$H_3PW_{12}O_{40}$	Solvent-free, 55 °C-60 °C	0.8: 0.01	6 min	90	8
5	I_2*	CH_2Cl_2, rt	0.8: 0.01	----	----	6
6	$Si(CH_3)_3Cl$*	Solvent-free, 125°	0.8: two drops	----	----	2

*Silylation of phenols with these reagents has not been reported

EXPERIMENTAL SECTION

General Procedure for the Preparation of Trimethylsilyl Ethers.- The substrate (10 mmol) was added to a mixture of HMDS (20 mmol) and DBH (0.1 mmol), and the mixture was stirred at room temperature for the specified time (*Table 1*). After completion of the reaction, water (10 mL) (or 5% NaOH for remove of excess phenols) was added to destroy excess HMDS. The trimethylsilyl ether were then extracted into *n*-hexane (2 x 20 mL) and the organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the product, pure without further purification.

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