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Poly(*N*-bromobenzene-1,3-disulfonamide) and *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide as novel catalytic reagents for silylation of alcohols, phenols, and thiols using hexamethyldisilazane

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Abstract—Poly(*N*-bromobenzene-1,3-disulfonamide) [PBBS] and *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] are effective catalysts for the silylation of alcohols, phenols, and thiols in the presence of hexamethyldisilazane with, or without solvent, and also under microwave irradiation.

1. Introduction

Trimethylsilylation of organic compounds[1,2] having labile hydrogen atoms is an important organic transformation. It is a frequently used protection method in multistep synthesis due to its enhanced stability under a variety of conditions, solubility in non-polar solvents, thermal stability, and the ease of removal, which is simply accomplished by acid or base induced hydrolysis giving only siloxane as a by-product. It is also used extensively for the derivatization of hydroxyl compounds to increase their volatility for gas chromatography and mass spectrometry. Many silylating agents, such as chlorotrimethylsilane,[3,4] hexamethyldisiloxane, *N*,*O*-bis(trimethylsilyl)acetamide, and ethyl(trimethylsilyl)acetate, have been used for the introduction of a trimethylsilyl group onto a variety of alcohols.[1] Hexamethyldisilazane (HMDS) is a stable, cheap, and commercially available compound that can be used for the preparation of trimethylsilyl ethers from hydroxy or thio compounds. Its handling does not require special precautions, and the work-up is not time consuming, as the by-product of the reaction is ammonia, which is simple to remove from the reaction medium. However, the poor silylating power of HMDS is the main drawback to its application. Therefore, a variety of catalysts have been used for activating this reagent, such as sulfuric acid,[1] $ZrCl_4$,[5] nitrogen–ligand complexes of metal chlorides,[6] Montmorillonite,[7] zirconium sulfophenyl phosphonate,[8] iodine,[9] $H_3PW_{12}O_{40}$,[10] $LiClO_4$,[11] and $CuSO_4{\cdot}5H_2O$.[12] Although several of these procedures are useful, most suffer from the use of homogeneous[8,13,14] and often corrosive catalysts, which are usually non-recoverable and thus potentially polluting,[6,8,10] tedious work-ups, and/or long reaction times.[3,4,13] Consequently, new procedures that address these drawbacks are desirable.

In continuation of our interest in the application of *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] **1** and poly(*N*-bromobenzene-1,3-disulfonamide) [PBBS] **2** in organic synthesis,[15] we report a convenient method for the silylation of alcohols, phenols, and thiols in the presence of TBBDA **1** and PBBS **2** (Scheme 1) with HMDS under (i) solvent-free, (ii) microwave irradiation, and (iii) solvent conditions.

The reaction of alcohols, phenols, and thiols with HMDS in the presence of PBBS or TBBDA brought about O- or S-silylation without side-product formation (Scheme 2).

We also found that PBBS and TBBDA were reusable catalysts and after several runs, the catalytic activities of the reagents were almost the same as those of fresh catalysts.

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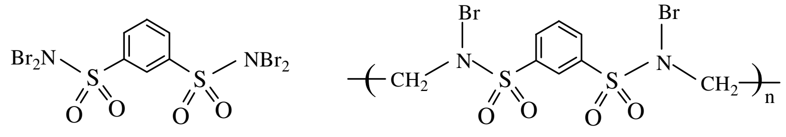
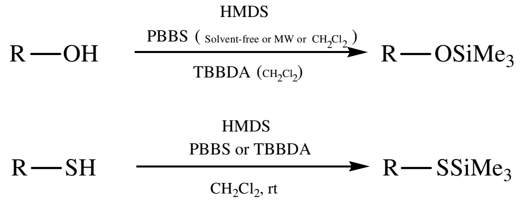
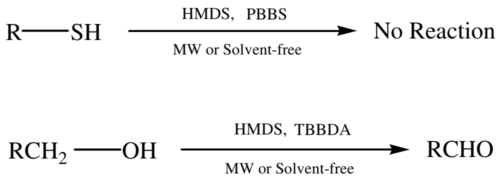


TBBDA **1** PBBS **2**

Scheme 1.



Scheme 2.



Scheme 3.

As shown in Table 1, treatment of a variety of alcohols, phenols and thiols with HMDS in the presence of solvent (CH_2Cl_2) and PBBS or TBBDA gave the corresponding trimethylsilyl ethers in good to excellent yields. Also, primary and secondary benzylic and tertiary alcohols and phenols were all protected using PBBS in excellent yields under microwave or solvent-free conditions. Several attempts to oxidize thiols and amines using PBBS or TBBDA under microwave irradiation or solvent-free conditions failed. We found that TBBDA was not suitable for the silylation of alcohols under microwave and solvent-free conditions, as this reagent converted alcohols to the corresponding aldehydes, instead of the silyl ethers (Scheme 3).

In contrast to our previous reports,[15] halogenation of aromatic rings did not occur and only hydroxyl group silylation was observed.

The method was found to be highly selective for primary alcohols. In a mixture of benzyl alcohol and phenol, the primary alcohol was completely converted to the corresponding silyl ether (Table 2, entry 1). Similarly, benzyl alcohol was silylated in the presence of cyclohexanol and adamantol, and cyclohexanol was silylated in the presence of adamantol (Table 2, entries 2–4).

It is likely that these reagents release Br^+ in situ, which can act as an electrophilic species.[15,16] Therefore, the mechanism shown in Scheme 4 can be suggested for the conversion of the alcohol to the silyl ether.[9,10]

The advantages of PBBS and TBBDA over reported reagents in the silylation of β-naphthol, *p*-nitrobenzyl alcohol, cyclohexanol, and benzyl alcohol are shown in Table 3. It is noteworthy that most of these reported reagents require long times to effect reaction.

Table 1. Trimethylsilylation of alcohols, phenols, and thiols catalyzed by TBBDA or PBBS under different conditions

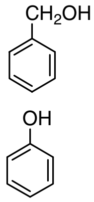
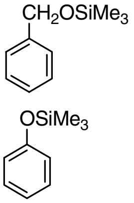
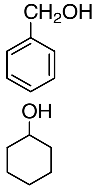
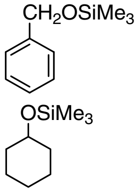
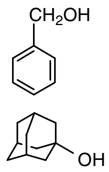
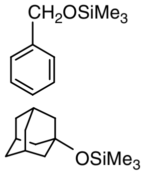
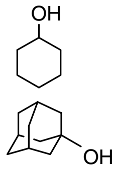
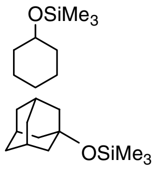
Entry	Substrate	Solvent (TBBDA, CH_2Cl_2)		Solvent (PBBS, CH_2Cl_2)		Solvent-free (PBBS)		MW (PBBS)	
		Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)
1	$PhCH_2OH$	0.5	90	1.5	90	0.08	98	0.07	100
2	$4\text{-}O_2NC_6H_4CH_2OH$	0.6	80	1	90	0.1	94	0.1	98
3	$4\text{-}HOC_6H_4CH_2OH$	0.5	83	0.4	90	0.08	85	0.07	90
4	$4\text{-}MeOC_6H_4CH_2OH$	3.5	90	3.5	89	0.1	90	0.1	92
5	$2\text{-}ClC_6H_5OH$	0.6	85	0.5	90	0.08	92	0.05	98
6	$2,4\text{-}Cl_2C_6H_3CH_2OH$	1.2	85	2	90	0.05	96	0.07	100
7	2-Naphthol	0.25	85	0.25	85	0.1	76	0.14	82
8	$2\text{-}HOC_5H_5S$	12	90[b]	15	85[b]	0.08	80	0.14	86
9	Cinnamyl alcohol	12	90	15	85	0.1	78	0.14	84
10	Adamantol	5	85	5	82	0.1	—[c]	0.1	—[c]
11	C_6H_5SH	24	85	48	80	0.1	—[c]	0.1	—[c]
12	$4\text{-}MeC_6H_4SH$	12	80	28	80	0.1	—[c]	0.1	—[c]
13	2-Naphthalenethiol	48	90	72	95	0.1	—[c]	0.1	—[c]
14	Thiosalicylic acid	48	—[c]	72	—[c]	0.1	—[c]	0.1	—[c]
15	$PhNH_2$	24	—[c]	48	—[c]	0.1	—[c]	0.1	—[c]

[a] Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

[b] The reaction was performed under reflux.

[c] No reaction.

Table 2. Competitive silylation reactions of alcohols using HMDS and PBBS or TBBDA in the presence of solvent (CH_2Cl_2)

Entry	Mixture	Product	Time (min)	Conversion (%)[a]
1			10[b] or 20[c]	100 0
2			5[b] or 15[c]	100 0
3			15[b] or 25[c]	100 0
4			15[b] or 25[c]	100 0

[a] The conversion was detected by TLC and NMR spectroscopy.
[b] The conversion was complied with TBBDA.
[c] The conversion was complied with PBBS.

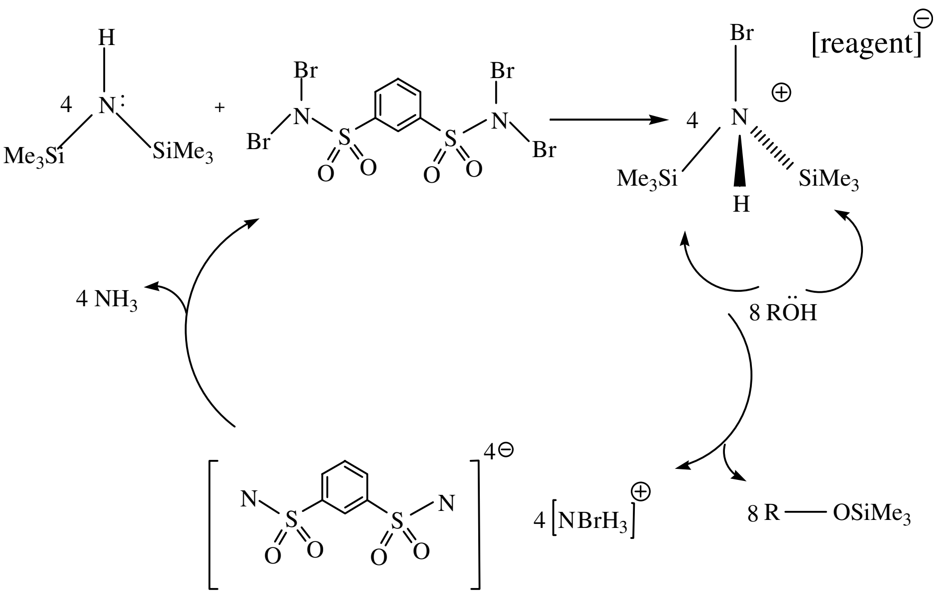
Table 3. Reaction times and yields for TMS protection with various catalysts and HMDS using published procedures

Substrate	Conditions	Reaction time (h)	Yield (%)
Cyclohexanol	$CuSO_4\cdot 5H_2O$	30	97[12]
Cyclohexanol	H-β zeolite, 80 °C	2	98[17]
Cyclohexanol	Silica chloride, reflux	0.2	89[18]
Cyclohexanol	$LiClO_4$	0.16	95[11]
β-Naphthol	H-β zeolite, 80 °C	2.5	89[17]
β-Naphthol	Silica chloride, reflux	6.25	60[18]
β-Naphthol	$LiClO_4$	0.3	84[11]
β-Naphthol	$CuSO_4\cdot 5H_2O$	38	40[12]
p-Nitrobenzyl alcohol	$CuSO_4\cdot 5H_2O$	7.5	91[12]
p-Nitrobenzyl alcohol	$H_3PW_{12}O_{40}$, 55–60 °C	120	0[10]
p-Nitrobenzyl alcohol	$LiClO_4$	0.16	95[11]
Benzyl alcohol	H-β zeolite, 80 °C	1.3	97[17]
Benzyl alcohol	Silica chloride, reflux	0.4	99[18]
Benzyl alcohol	$H_3PW_{12}O_{40}$, 55–60 °C	0.4	90[10]
Benzyl alcohol	$CuSO_4\cdot 5H_2O$	0.2	98[12]
Benzyl alcohol	$LiClO_4$	0.4	99[11]

In conclusion, we have introduced the novel catalytic reagents *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide TBBDA and poly[*N*-bromobenzene-1,3-disulfonamide] PBBS as the activators of HMDS for the efficient protection of a variety of alcohols, phenols and thiols under solvent, solvent-free or microwave irradiation conditions. The catalysts are heterogeneous, recyclable, non-corrosive and environmentally benign. Isolation of the products involved simple extraction and evaporation of the solvent.

2. General method for the silylation of alcohols, phenols, and thiols using HMDS with PBBS and TBBDA in the presence of solvent

To a stirred solution of alcohol, phenol or thiol (1 mmol) and PBBS (0.02 g) or TBBDA (0.04 mmol) in CH_2Cl_2 (10 mL) was added HMDS (1.4 mmol in



Scheme 4.

15 mL CH_2Cl_2) over 5 min at room temperature. The reaction was monitored by TLC (9:1, carbon tetrachloride/acetone). After completion of the reaction, the reagent was filtered and the organic phase was washed with Na_2CO_3 solution (10 mL, 5%), H_2O (10 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the product. Further purification was achieved by distillation or recrystallization to afford pure silyl ethers (Table 1).

$C_9H_{14}SSi$ (entry 11): IR (KBr): ν 3090, 2959, 1614, 1250 (S-TMS) cm^{-1}; ^1H NMR [$(CD_3)_2CO$, FT-90 MHz]: δ 7.30–7.50 (m, 5H, aromatic), 0.05 [s, 9H (TMS)].

$C_{10}H_{16}SSi$ (entry 12): IR (KBr): ν 3022, 2954, 1490, 1249 (S-TMS) cm^{-1}; ^1H NMR [$(CD_3)_2CO$, FT-90 MHz]: δ 7.00–7.40 (m, 4H, aromatic), 2.20 (s, 3H), 0.05 [s, 9H (TMS)].

$C_{13}H_{16}SSi$ (entry 13): IR (KBr): ν 3056, 2910, 1462, 1252 (S-TMS) cm^{-1}; ^1H NMR [$(CD_3)_2CO$, FT-90 MHz]: δ 7.20–7.80 (m, 7H, aromatic), 0.03 [s, 9H (TMS)].

3. General method for solvent-free silylation of alcohols and phenols using HMDS and PBBS

Alcohol or phenol (1 mmol), PBBS (0.2 g) and HMDS (1.5 mmol) were added to a mortar and the mixture was pulverized vigorously with a pestle. A spontaneous reaction took place [3–6 min, Table 1, monitored by TLC (9:1, carbon tetrachloride/acetone)]. After completion of the reaction, CH_2Cl_2 (15 mL) was added, and the reagent was removed by filtration. The organic phase was washed with Na_2CO_3 solution (10 mL, 5%) and H_2O (10 mL), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the product. Further purification was achieved by distillation or recrystallization to afford pure silyl ethers (Table 1).

4. General method for the silylation of alcohols and phenols using HMDS with PBBS under microwave irradiation

Alcohol or phenol (1 mmol), PBBS (0.15 g), and HMDS (1.5 mmol) were added to a round-bottomed flask (25 mL). The flask was placed in a bath containing SiO_2 to enable absorption of additional microwave irradiation. The flask was irradiated in a microwave oven at a power output of 900 W (LG Co. microwave, 230 V ~ 50 Hz, RF output 900 W). After completion of the reaction, [3–8 min, Table 1, monitored by TLC (9:1, carbon tetrachloride/acetone)], CH_2Cl_2 (15 mL) was added, and the reagent was removed by filtration. The organic phase was washed with Na_2CO_3 solution (10 mL, 5%), H_2O (10 mL), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the product. Further purification was achieved by distillation or recrystallization to afford pure silyl ethers (Table 1).

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