N-Bromosuccinimide (NBS) — Selective and effective catalyst for trimethylsilylation of alcohols and phenols using hexamethyldisilazane and their regeneration under mild and neutral reaction conditions

Ardeshir Khazaei, Amin Rostami, Ayeh Raiatzadeh, and Marjan Mahboubifar

Abstract: Structurally diverse alcohols and phenols were trimethylsilylated in a clean and efficient reaction with hexamethyldisilazane (HMDS) based on the use of a catalytic amount of *N*-bromosuccinimide under both dichloromethane and solvent-free conditions at room temperature. Deprotection of trimethylsilyl ethers was also be achieved efficiently in the presence of a catalytic amount of NBS in methanol at ambient temperature.

Key words: N-bromosuccinimide, solvent-free, alcohols, phenols, hexamethyldisilazane, trimethylsilyl ether, catalyst, detrimethylsilylation.

Résumé : Opérant à la température ambiante, on a effectué d'une façon propre et efficace la triméthylsilylation d'alcools et de phénols de structures différentes par réaction avec de l'hexaméthyldisilazane (HMDS), dans du dichlorométhane ou sans solvant, en présence d'une quantité catalytique de *N*-bromosuccinimide (NBS). La déprotection des éthers triméthylsilyles peut aussi se faire d'une façon efficace en présence d'une quantité catalytique de NBS, dans le méthanol, à la température ambiante.

Mots clés : N-bromosuccinimide, sans solvant, alcools, phénols, hexaméthyldisilazane, éther triméthylsilyle, catalyseur, détriméthylsilylation.

[Traduit par la Rédaction]

Introduction

The protection of hydroxy groups through the formation of silyl ethers has been extensively utilized in organic synthesis (1). Silyl ethers are easily prepared, show resistance to oxidation, have good thermal stability and low viscosity, and are easily recoverable from their parent compounds. Moreover, numerous silylating methods can be utilized today; among them, trimethylsilylation is one of the most often used. Generally, the formation of trimethylsilyl ethers is carried out by the treatment of alcohols with trimethylsilyl chlorides or trimethylsilyl triflates in the presence of a base (2), Li_2S (3), and sometimes a nonionic super base catalyst (4). However, some of these methods frequently suffer from drawbacks such as a lack of reactivity or a difficulty removing amine salts derived from the reaction during the silylation reaction. HMDS is a stable, cheap, and commercially available compound that can be used for the preparation of trimethylsilyl ethers from hydroxy compounds, giving ammonia as the only by-product. Even though the handling of this reagent is easy, its main drawback is its poor silylating ability; forceful conditions and long reaction times are required (5). Therefore, for the activation of HMDS a variety of catalysts have been reported such as $(CH_3)_3SiCl$ (6), $ZnCl_2$ (7), zirconium sulfophenyl phosphonate (8), montmorillonite K-10 (9), I_2 (10), $LiClO_4$ (11), $H_3PW_{12}O_{40}$ (12), $Al(OTf)_3$ (13), $CuSO_4{\cdot}5H_2O$ (14), KBr (15), and $LiClO_4$–SiO_2 (16). Although these methods produce good results in many instances, few of these catalysts can do both protection and deprotection of alcohols and phenols as trimethylsilyl ethers. Therefore, there is still a demand to develop new mild methods for the trimethylsilylation of hydroxyl compounds and their regeneration in the presence of inexpensive and benchtop catalysts.

Similar to protection, deprotection of the trimethylsilyl ethers constitutes an important process in the synthetic chemistry of polyfunctional molecules, including the total synthesis of natural products. Although several methods

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Received 1 January 2007. Accepted 21 March 2007. Published on the NRC Research Press Web site at canjchem.nrc.ca on 5 May 2007.

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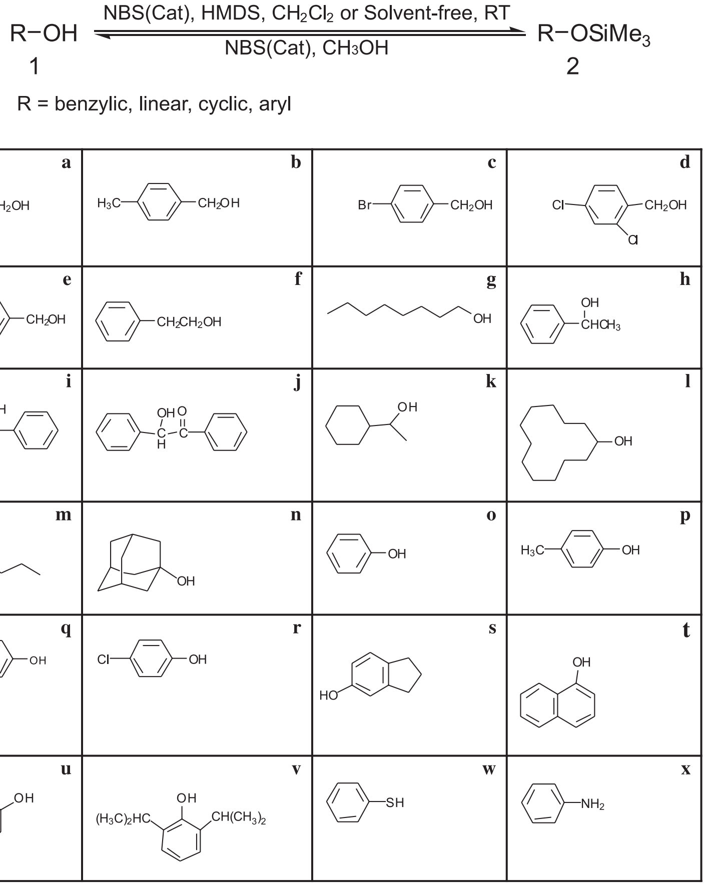
doi:10.1139/V07-029

Scheme 1.



Scheme 1

have been reported for the deprotection of trimethylsilyl ethers (17), the development of mild, efficient, ecofriendly, and selective reagents for the deprotection of trimethylsilyl ethers continues to be desirable.

Solvent-free reactions have attracted considerable attention in chemical processes for different reasons. They are valuable due to environmental safety, economic viewpoint, easy workup, high yields of the products, and (usually) fast reaction times (18). This is why we tried to develop a solvent-free version of this new reaction.

Results and discussion

In continuation of our interest in the application of *N*-halo compounds (19) in organic synthesis, we have found that NBS is an inexpensive commercially available reagent that has been used as an effective catalyst for the acetalization of carbonyl compounds (20*a*, 20*b*), the conversion of aldehydes to 1,1-diacetates (20*c*), and the acylation of alcohols (20*d*) under mild and nearly neutral reaction conditions.

In this present work, the catalytic application of NBS has been investigated as a selective reagent for the efficient trimethylsilylation of a wide range of alcohols and phenols under both solution and solvent-free conditions as well as the desilylation of the corresponding TMS ethers in methanol (Scheme 1).

We first examined the effect of different ratios of ROH–HMDS–catalyst. The 1:2:0.01 ratio for alcohols and phenols gave the best results and produced trimethylsilyl ethers in quantitative yields. As shown in Table 1, using a mixture of HMDS (2 mmol) and a catalytic amount of NBS (0.01 mmol), primary (alkyl and benzylic), secondary (hindered and unhindered), and tertiary alcohols and a variety of phenols (with electron-withdrawing and electron-releasing groups) were transformed into the corresponding trimethylsilyl ethers in good to high yield under both dichloromethane (I) and solvent-free (II) conditions at room temperature (RT). We observed that amines and thiols were not converted to the corresponding silyl ethers under these reaction conditions, even after prolonged reaction times.

Because of the nearly neutral nature of the reaction medium, no elimination by-products were observed at all. Subsequently, we discovered that the desilylation of the trimethylsilyl ethers can be carried out to obtain the corresponding alcohols and phenols in good to excellent yields by using the same catalyst in methanol at RT (Scheme 1 and Table 2).

We used this procedure for the selective trimethylsilylation of *n*-octanol (as a model for primary alcohols) or 2-pentanol (as a model for secondary alcohols) in the presence of 1-adamantanol (as a model for tertiary alcohols). The only observed products were *n*-octyl trimethylsilyl ether or 2-pentyl trimethylsilyl ether in 100% conversion (Scheme 2).

Similarly, in a binary mixture of 4-methoxyphenol and

Table 1. Trimethylsilylation of alcohols and phenols using HMDS catalyzed with NBS under both dichloromethane (I) and solvent-free (II) conditions at RT.

			Time (h)		Yield (%)[a]		Yield (%)[b]	
Entry	Substrate	Product[c]	I	II	I	II	I	II
1	**1a**	**2a**	2.10	1.10	90	100	84	95
2	**1b**	**2b**	2.35	1.00	93	100	85	95
3	**1c**	**2c**	2.35	0.84	95	100	91	96
4	**1d**	**2d**	2.30	1.00	95	100	89	93
5	**1e**	**2e**	1.46	1.50	95	95	89	90
6	**1f**	**2f**	1.00	0.50	85	100	80	96
7	**1g**	**2g**	2.10	1.50	81	100	78	94
8	**1h**	**2h**	0.75	1.50	90	80	87	77
9	**1i**	**2i**	5.11	5.00	95	90	90	86
10	**1j**	**2j**	8.00	8.00	83	80	79	74
11	**1k**	**2k**	12.00	10.00	95	80	91	76
12	**1l**	**2l**	6.00	5.00	94	100	90	95
13	**1m**	**2m**	2.50	5.00	80	100	74	93
14	**1n**	**2n**	48.00	30.00	95	100[d]	92	96[d]
15	**1o**	**2o**	0.75	0.50	96	100	91	95
16	**1p**	**2p**	2.00	0.75	90	100	85	93
17	**1q**	**2q**	0.50	0.58	90	100	83	95
18	**1r**	**2r**	2.10	0.84	99	100	95	95
19	**1s**	**2s**	2.21	1.00	97	100	91	95
20	**1t**	**2t**	3.00	1.50	99	90	93	85
21	**1u**	**2u**	2.30	1.00	85	100	80	92
22	**1v**	**2v**	5.00	5.50	30	100	23	94
23	**1w**	**2w**	15.00	15.00	0	0	0	0
24	**1x**	**2x**	15.00	15.00	0	0	0	0

[a] Conversion yields.

[b] Isolated yields.

[c] All products were characterized by comparison of their spectral data (^{1}H NMR and IR spectroscopy) with those of authentic samples.

[d] In this case the ratio of substrate–HMDS–NBS was 1:8:0.2.

2,6-diisopropylphenol (as a model for hindered phenol), 4-methoxyphenol was completely converted to the corresponding silyl ether, while 0% conversion was observed for 2,6-diisopropylphenol (Scheme 3).

To assess the catalytic activity of NBS for trimethylsilylation, we compared our results for the trimethylsilylation of 1-naphtol with the best of the well-known procedures from the literature (Table 3). The advantages and the characteristic aspects of the described method in this communication, in comparison with other previously reported catalysts, are the following: a variety of phenols (6, 10, 12) can be trimethylsilylated in good to high yields (11, 14) at RT (12, 14). In addition, the catalyst NBS is inexpensive, has no sensitivity to moisture (11), does not require a large amount of catalyst (11), and no special efforts are required for the reaction (14).

On the basis of the previously reported mechanism for the application of I_2 for the trimethylsilylation of alcohols (10) and the catalytic application of NBS for the protection of carbonyl and hydroxyl functional groups (18), one explanation for this process is that NBS may act as a source for the formation of Br^+, which polarizes the Si–N bond in HMDS to produce the reactive silylating agent (as a Lewis acid). Therefore, the mechanism shown in Scheme 4 is proposed.

Table 2. Deprotection of trimethylsilyl ethers in the presence of catalytic NBS (0.2 mmol) in methanol at RT.

Entry	Substrate	Product	Time (h)	Yield (%)[a]	Yield (%)[b]
1	**2a**	**1a**	1.17	100	94
2	**2b**	**1b**	1.00	100	95
3	**2c**	**1c**	0.84	100	95
4	**2d**	**1d**	0.84	100	96
5	**2e**	**1e**	1.33	80	76
6	**2f**	**1f**	2.50	100	94
7	**2g**	**1g**	4.00	90	83
8	**2h**	**1h**	2.00	100	96
9	**2i**	**1i**	6.00	30	23
10	**2j**	**1j**	14.00	100	95
11	**2k**	**1k**	8.00	100	93
12	**2l**	**1l**	3.50	100	95
13	**2m**	**1m**	5.00	100	94
14	**2n**	**1n**	24.00	100	96
15	**2o**	**1o**	0.42	95	89
16	**2p**	**1p**	0.75	95	89
17	**2q**	**1q**	0.42	100	94
18	**2r**	**1r**	0.84	100	95
19	**2s**	**1s**	1.00	95	90
20	**2t**	**1t**	1.00	95	91
21	**2u**	**1u**	0.84	100	95
22	**2v**	**1v**	5.00	100	95

[a] Conversion yields.

[b] Isolated yields.

Conclusion

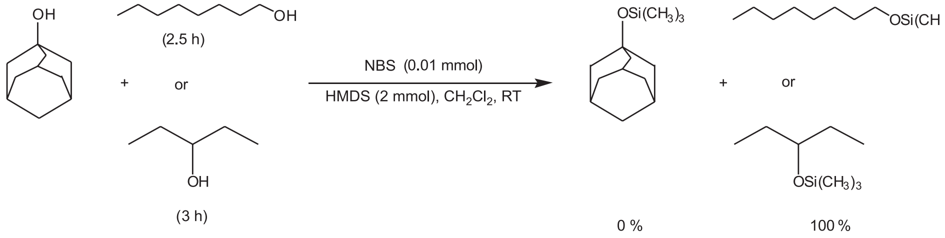
In summary, we have shown that NBS is an efficient and selective catalyst for the protection of a variety of alcohols and phenols as TMS ethers using HMDS and their deprotection under very mild conditions. The product yields are good to high and the procedure is easy and clean. Therefore, this procedure could be utilized in transformations that need mild reaction conditions.

Experimental

General procedure for the trimethyisilylation of alcohols and phenols using HMDS catalyzed with NBS in solution

Alcohols or phenols (1 mmol) were added to a mixture of HMDS (2 mmol) and NBS (0.01 mmol) in CH_2Cl_2 (7 mL), and the mixture was then stirred at RT for the specified time (Table 1). 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 5% aq. NaOH (10 mL) for phenols, then the organic layer was separated and dried over anhydr. Na_2SO_4. The solvent was evaporated, and *n*-hexane (20 mL) was added to the residual mixture. Insoluble catalyst was removed by filtration. Evaporation of the *n*-hexane under reduced pressure gave pure product without further purification.

Scheme 2.



Scheme 3.

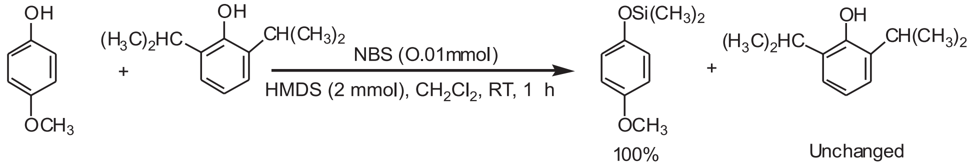
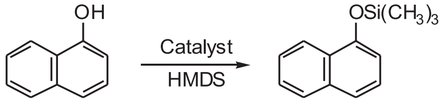
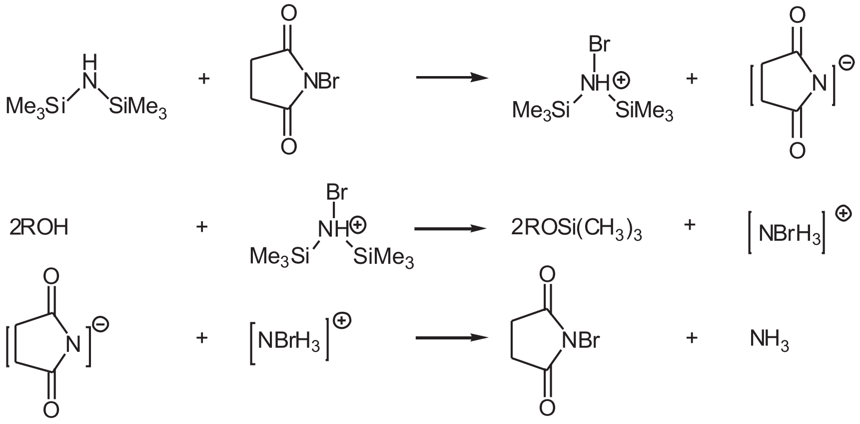


Table 3. Comparison of the activity of various catalysts in the trimethylsilylation of 1-naphtol with HMDS.



Entry	Catalyst	Conditions	HMDS–Cat	Time (h)	Yield (%)	Reference
1	NBS	Solvent-free, RT	2.0:0.01	1.50	85	This work
2	NBS	CH_2Cl_2, RT	2.0:0.01	3.00	93	This work
3	$CuSO_4$•$5H_2O$	CH_3CN, reflux	0.7:0.10	38.00	50	14
4	$LiClO_4$	Solvent-free, RT	0.7:0.50	0.33	80	11
6	$H_3PW_{12}O_{40}$	Solvent-free, 55–60 °C	0.8:0.01	—	—	12
7	I_2	CH_2Cl_2, RT	0.8:0.01	—	—	10
8	$Si(CH_3)_3Cl$	Solvent-free, 125 °C	0.8:2 drops	—	—	6
9	Montmorillonite K-10	CH_2Cl_2, RT	—	—	92	9
10	KBr	CH_3CN, RT	0.7:0.10	0.13	85	15
11	$LiClO_4$-SiO_2	CH_2Cl_2, RT	0.7:0.10 g	2.00	90	16

Scheme 4.



General procedure for the trimethyisilylation of alcohols and phenols using HMDS catalyzed with NBS under solvent-free conditions

Alcohols or phenols (1 mmol) were added to a mixture of HMDS (2 mmol) and NBS (0.01 mmol), and the mixture was then stirred at RT for the specified time (see Table 1). 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 5% aq. NaOH (10 mL) for phenols. The trimethylsilyl ethers were then extracted with *n*-hexane (20 × 2 mL), and the organic layer was dried over anhydr. Na_2SO_4. Evaporation of the *n*-hexane under reduced pressure gave pure product without further purification.

General procedure for the deprotection of trimethylsilyl ethers catalyzed with NBS

NBS (0.2 mmol) was added to a mixture of TMS ethers (1 mmol) in MeOH (3 mL), and the mixture was then stirred at RT for the specified time (Table 2). The progress of the reaction was monitored by TLC. On completion of the reaction, methanol was removed under reduced pressure and the product was purified through a short column of silica gel to obtain pure alcohol or phenol.

Acknowledgments

We are thankful to the Bu-Ali Sina University Research Councils for partial support of this work.

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