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Tetrabutylammonium Tribromide (TBATB)–MeOH: An Efficient Chemoselective Reagent for the Cleavage of *tert*-Butyldimethylsilyl (TBDMS) Ethers

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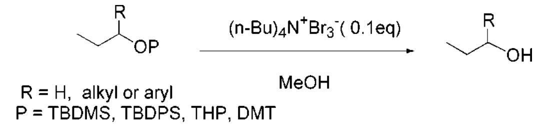
ABSTRACT



TBDMS, THP, and DMT ethers are efficiently deprotected with tetrabutylammonium tribromide in methanol. The apparent order of stability of different protecting group is phenolic TBDMS > 1° OTBDPS > 2° OTBDMS > 2° OTHP > 1° OTHP > 1° OTBDMS > 1° ODMT. TBDMS ether has been cleaved selectively in the presence of isopropylidine, Bn, Ac, Bz, THP, and TBDPS groups. This method is high yielding, fast, clean, safe, cost-effective, and therefore most suitable for practical organic synthesis.

The protection−deprotection of alcohol functionalities is important in synthetic organic chemistry, and a plethora of reagents and methods have been devised to this end. The importance of protecting the hydroxyl group frequently appears in the synthesis of biologically active molecules. Tetrahydropyranyl (THP) ethers in combination with silyl ethers have been used extensively for this purpose, and the 4,4′-dimethoxytrityl (DMT) group has been used widely for the protection of 5′-hydroxyl groups of nucleosides in oligonucleotide synthesis. Of all the hydroxyl-protecting groups,[1] *tert*-butyldimethylsilyl (TBDMS) ether still occupies a prominent position because of its easy preparation[2] and stability to a wide range of reaction conditions. A variety of reagents exist for the removal of TBDMS ethers,[1] and very recently several methods for the deprotection of silyl ethers under various reaction conditions have been reported in the literature.[3]

However, many of these procedures require long reaction times, drastic reaction conditions, a large excess of phase transfer reagents, and moisture sensitive and expensive reagents causing serious problem for large-scale reaction. Most of these reagents are strongly acidic, basic, oxidizing, or reducing in nature, a property that is not always desirable.

Tetrabutylammonium tribromide (TBATB) is known as an efficient brominating agent for a number of substrates in various solvents.[4−6] When we used this reagent in methanol

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(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. Kocieñski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, 1994.

(2) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(3) (a) Lipshutz, B. H.; Keith, J. *Tetrahedron Lett.* **1998**, *39*, 2495. (b) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209. (c) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915. (d) Oriyama, T.; Kobayashi, Y.; Noda, K. *Synlett* **1998**, 1047. (e) Grieco, P. A.; Markworth, C. J. *Tetrahedron Lett.* **1999**, *40*, 665. (f) Jarowicki, K.; Kocieñski, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, pp1590−1592 and references cited therein. (g) Kartha, K. P. R.; Field, R. A. *Synlett* **1999**, 311. (h) Ramasamy, K. S.; Averett, D. *Synlett* **1999**, 709. (i) Ranu, B. C.; Jana, U.; Majee, A. *Tetrahedron Lett.* **1999**, *40*, 1985. (j) Crouch, R. D.; Stieff, M.; Frie, J. L.; Cadwallader, A. B.; Bevis, D. C. *Tetrahedron Lett.* **1999**, *40*, 3133. (k) Hunter, R.; Hinz, W.; Richards, P. *Tetrahedron Lett.* **1999**, *40*, 3643. (l) Sabitha, G.; Syamala, M.; Yadav, J. S. *Org. Lett.* **1999**, *1*, 1701. (m) Bajwa, J. S.; Vivelo, J.; Slade, J.; Repiè, O.; Blacklock, T. *Tetrahedron Lett.* **2000**, *41*, 6021.

(4) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247.

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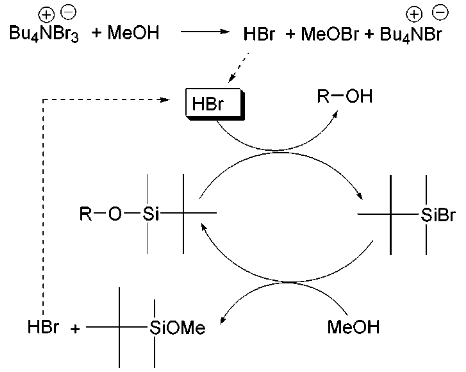
for the bromination of TBDMS-protected cinnamyl alcohol (**6**) for an ongoing project, we discovered that TBDMS ether was removed quantitatively within 10 min. This result was not surprising since the other halogen (I_2),[7] I_2/MeOH,[3a] interhalogen compounds I−Cl and I−Br,[3g] and $BiBr_3$/MeCN[3m] have been used for the deprotection of TBDMS ethers. It is believed that the haloacids generated in situ from the above reagents might be the species responsible for the hydrolysis of TBDMS ethers. It has been shown that benzyltrimethylammonium tribromide generates HBr and MeOBr in methanol.[8] In the present case the hydrolysis may be catalyzed by HBr that is generated in situ from the reaction of TBATB with MeOH as shown in Scheme 1. In a control experiment, treatment of silyl ether **(1)** with 0.01 equiv of 48% HBr in MeOH at room temperature in < 5 min leads to a deprotected alcohol in a quantitative yield. When the TBDMS ether of 2-propanol was treated with TBATB in 2-propanol, no deprotection was observed even after 48 h. This is because the deprotected 2-propanol reacts with *tert*-butyldimethylsilyl bromide to yield the starting TBDMS ether, rendering its effective concentration practically unaltered. However, addition of methanol shifted the equilibrium to the right, leading to a 90% deprotection after 5 h in support of the mechanism proposed in Scheme 1. We therefore explored the possibility of utilizing tetrabutylammonium tribromide (TBATB) as an effective reagent for the cleavage of TBDMS ethers.

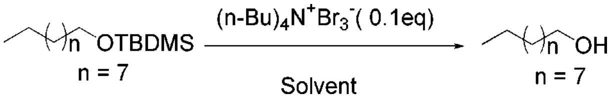
Scheme 1. Proposed Mechanism of Deprotection of TBDMS Group



The results of solvent dependent cleavage of primary TBDMS ether (**1**) with TBATB (0.1 mol %) as shown in Table 1 suggests that polar organic solvents are relatively more suitable for deprotection and methanol turns out to be the best protic medium for desilylation.

In a typical reaction, to a solution of TBDMS ether (1 mmol) in methanol (5 mL) is added TBATB (0.1 mmol). The reaction times are as shown for each substrate in Table 2. It is important to note that a lower quantity of TBATB (i.e., 0.01 mol %) also gave satisfactory results at longer reaction times. For instance, substrate **1** containing a primary TBDMS group was deprotected at room temperature in a quantitative yield within 2.5 h, but a TBDMS-protected secondary alcohol (**4**) could be deprotected in up to 93% yield in 4 days at room temperature. However, refluxing the reaction mixture can accelerate the reaction rate (90%, 6 h). For the present investigation, 0.1 mol % of the reagent has been used for each substrate.

Table 1. Solvent-Dependent Cleavage of C_{10}-TBDMS Ether



solvent(s)	time/h	yield/%[a]
MeOH	0.40	99
MeOH:H_2O (9:1)	1.80	99
EtOH	1.80	93
i-PrOH	10.0	98
CH_3CN	3.00	95
toluene	24.0	nil
CH_2Cl_2	24.0	nil

[a] GC determined.

A wide spectrum of structurally varied TBDMS ethers was subjected to deprotection by this procedure, and the result is summarized in Table 2. Aliphatic TBDMS-protected primary alcohols **1**, **2**, and **3** were deprotected quantitatively in nearly 1 h. TBDMS-protected secondary alcohols **4** and **5** produced the corresponding alcohols in excellent yields, but the reaction rates were relatively slow. The slow rate of deprotection of TBDMS-protected cholesterol (**5**) could be in part due to the different solvent (MeOH:CH_2Cl_2, 1:1) system used for this substrate.

The compatibility of the reagent is further illustrated by selective deprotection of TBDMS-protected alcohols containing ethylenic (**6**) and acetylenic (**7**) systems. Importantly, no other side product viz. bromination was observed, although this reagent is an efficient brominating agent for ethylenic and acetylenic substrates.[5]

The selectivity of this methodology is further tested with other substrates containing *tert*-butyldiphenylsilyl (TBDPS) ethers (**8**), phenolic TBDMS ethers (**9**), primary THP ether (**10**), secondary THP ether (**11**), and DMT ethers (**12** and **13**), and the results are shown in Table 2. Facile deprotection of acid-sensitive DMT ethers (**12** and **13)** further supports the formation of HBr, proposed in Scheme 1.

We also examined the intramolecular chemoselective deprotection of TBDMS ethers in the presence of isopropylidene (**14**), Bn (**15**), Ac (**16**), Bz (**17**), THP (**18**), and TBDPS (**19**), and the result is very encouraging as shown in Table 2. Intermolecular chemoselectivity[9] for aliphatic TBDMS ether (**1**) in the presence of phenolic TBDMS ether (**9**), secondary TBDMS ether (**8**), and primary DMT ether **(12)**

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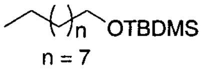
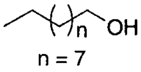
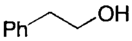
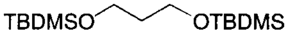
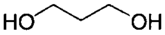
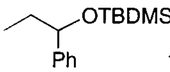
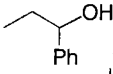
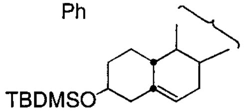
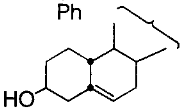
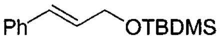
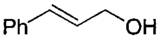
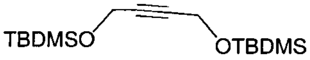
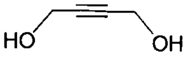
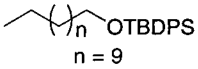
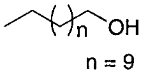
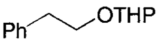
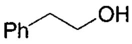
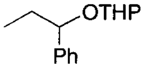
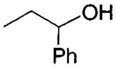
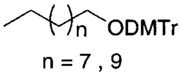
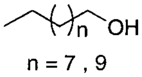
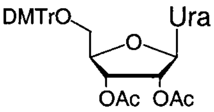
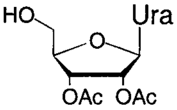
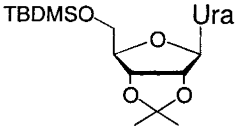
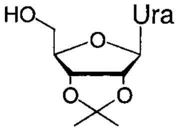
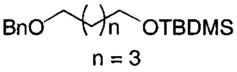
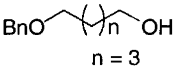
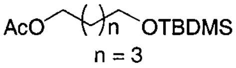
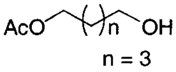
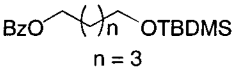
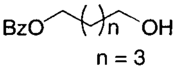
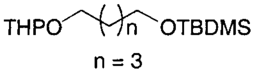
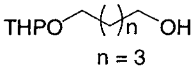
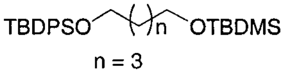
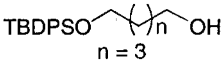
(5) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163.

(6) Paquette, L. A., Ed. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: New York: 1995; Vol. 7, pp 4738.

(7) Vaino, A. R.; Szarek, W. A. *Chem. Commun.* **1996**, 2351.

(8) Kajigaeshi, S.; Kakinami, T.; Hirakawa, T. *Chem. Lett.* **1987**, 627.

Table 2. Deprotection[a] of TBDMS, TBDPS, and THP Ethers with TBATB (0.1 equiv) in Methanol

substrate	time/h	product[b]	yield (%)[c]
 **(1)**	0.41		97
 **(2)**	0.66		97
 **(3)**	1.15		99[d]
 **(4)**	7.00		98
 **(5)**	8.00[e]		97
 **(6)**	0.08		95
 **(7)**	0.50		94
 **(8)**	6.00[f, g]		50
PhOTBDMS **(9)**	6.00[g]	PhOH	92
 **(10)**	0.83		96
 **(11)**	1.20		97
 **(12)**	0.41		98
 **(13)**	1.50		98
 **(14)**	9.50		95
 **(15)**	0.41		98
 **(16)**	0.41		96
 **(17)**	0.41		98
 **(18)**	0.30		95
 **(19)**	0.35		98

[a] Reactions were monitored by TLC, GC. [b] Confirmed by comparison with IR and ^{1}H NMR of the authentic sample. [c] Isolated yield. [d] GC yield. [e] The reaction was performed in MeOH : CH_2Cl_2 (1:1) and [f] MeOH : CH_2Cl_2 (5:2). [g] The reaction was performed at reflux temperature.

were 100% (0.5 h), 92% (0.5 h), and 95% (0.08 h), respectively, in methanol at room temperature.

The reagent *o*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluranium tetrafluoroborate (TBTU)[3h] selectively deprotected primary THP ether in the presence of TBDMS ether. The exact opposite selectivity was observed with TBATB for both, with intermolecular as well as intramolecular deprotection. In a competitive intermolecular deprotection[9] between a primary TBDMS ether (**2**) and a primary THP ether (**10**) in methanol at room temperature, it was observed that both were deprotected with nearly equal rates (only 8% selectivity, 0.5 h). Notably, a better intermolecular chemoselectivity (60%) was obtained for **2** by performing the reaction under ice-cooled conditions, although a longer reaction time (4 h) was required for the process. However, a quantitative intramolecular selectivity (100%) was observed as demonstrated for substrate **18**. In contrast to the preferential deprotection of primary TBDMS over primary THP ethers, a completely opposite selectivity was observed for the corresponding secondary ethers. Thus, in a competitive deprotection study[9] between secondary TBDMS ether (**4**) and secondary THP ether (**11**), the use of methanol at room temperature gave 78% selectivity after 2.2 h for **11**. It is interesting to note that the desilylation becomes much slower when methanol is replaced with the more sterically hindered alcohol. The use of 2-propanol as solvent, however, enhances the selectivity (88%, 5.6 h) of **11** over **4**, although longer reaction times were required. Thus, we have found a better intramolecular selectivity as compared to the intermolecular selectivity in our investigation.

These results indicate that TBATB can readily differentiate not only THP over TBDMS but also TBDMS over TBDPS ethers. The apparent order of stability as obtained from our present study is phenolic TBDMS > 1° OTBDPS > 2° OTBDMS > 2° OTHP > 1° OTHP > 1° OTBDMS > 1° ODMT. This method is high yielding, chemoselective, safe, operationally simple under mild reaction conditions, fast, cost-effective, and clean and no precaution is needed to exclude moisture or oxygen from the reaction system. Moreover, no strongly acidic or basic conditions are used; therefore it is most suitable for practical organic synthesis. Chemoselective studies of different silyl ethers and other protecting groups are now underway.

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Supporting Information Available: Detailed experimental procedures for desilylation of primary TBDMS ether (**2**) and intermolecular chemoselective deprotection of primary TBDMS ether (**2**) and primary THP ether (**10**). This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Intermolecular chemoselectivity was determined by treating an equimolar mixture of two different substrates (X) and (Y) with 0.1 mol % of the reagent in an appropriate solvent, and the reaction was monitored by GC. An internal standard was used when both deprotected products were same. Selectivity = % Y deprotected − % X deprotected at time *t*.