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A Novel and Convenient Chemoselective Deprotection Method for Both Silyl and Acetyl Groups on Acidic Hydroxyl Groups Such as Phenol and Carboxylic Acid by Using a Nitrogen Organic Base, 1,1,3,3-Tetramethylguanidine

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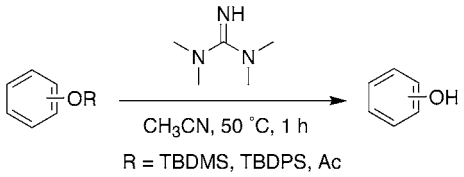
ABSTRACT



1,1,3,3-Tetramethylguanidine (TMG)[1], a nitrogen organic base, is a convenient and useful reagent for chemoselective deprotection of both silyl and acetyl groups on acidic hydroxyl groups such as phenol and carboxylic acid without affecting aliphatic silyl and acetyl groups. The chemoselectivity is dependent on the acidity of the hydroxyl group.

Silyl and acetyl groups are widely used for protection of phenolic hydroxyl groups in the synthesis of biologically significant products.[2] Phenolic compounds such as flavonoid glycosides, lignan glycosides, anthracycline glycosides, and phenolic glycopeptide antibiotics have attracted considerable attention due to their antioxidant, antitumor, and antibacterial activities.[3] For synthesis of these phenolic glycoconjugates, selective deprotection is an essential synthetic tool. TBAF is used as a typically desilylating reagent,[2] but it generally has no selectivity[4] and side-reactions may occur due to the nucleophilicity of the fluoride ion.[5] Only a few types of selective desilylation of phenolic TBDMS ether have been realized by treatment with basic reagents, often accompanied by deacylation,[6−9] though many selective desilylations of

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(1) Berning, D. E.; Noll, B. C.; DuBois, D. L. *J. Am. Chem. Soc.* **1999**, *121*, 11432.

(2) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley and Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*; George Thieme Verlag: New York, 1994.

(3) Fraser-Reid, B. O., Tatsuta, K., Thiem, J., Eds. *Glycoscience: Chemistry and Chemical Biology III*; Springer: Berlin, 2001.

(4) A method of chemoselective cleavage of the phenolic silyl ether by using TBAF has been reported, but carefully controlled conditions were required: Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681.

(5) Ranu, B. C.; Jana, U.; Majee, A. *Tetrahedron Lett.* **1999**, *40*, 1985 and references therein.

(6) For a review of selective desilylation: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.

(7) Basic reagents for selective deprotection of phenolic TBDMS ether are reported inorganic bases such as KF,[7a,b] K_2CO_3[7c,d], and NaOH[7e] and triethylamine *N*-oxide/CH_3OH:[7f] (a) Just, G.; Zamboni, R. *Can. J. Chem.* **1978**, *56*, 2725. (b) Schmittling, E. A.; Sawyer, J. S. *Tetrahedron Lett.* **1991**, *32*, 7207. (c) Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1994**, *35*, 7565. (d) Wilson, N. S.; Keay, B. A. *Tetrahedron Lett.* **1997**, *38*, 187. (e) Crouch, R. D.; Stieff, M.; Frie, J. L.; Cadwallader, A. B.; Bevis, D. C. *Tetrahedron Lett.* **1999**, *40*, 3133. (f) Zubaidha, P. K.; Bhosale, S. V.; Hashmi, A. M. *Tetrahedron Lett.* **2002**, *43*, 7277.

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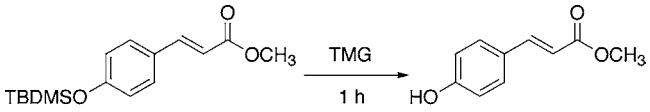
aliphatic TBDMS ether with acidic reagents have been developed.[6,10] Selective deacylation of phenolic acetates, among polyacylates, needs strictly controlled conditions or specific reagents, despite a number of reports of success.[2,11] Herein we document an efficient chemoselective deprotection method for both silyl and acetyl groups on acidic hydroxyl groups such as phenol and carboxylic acid using a nitrogen organic base, TMG.

In general, the Si−O bond is stable to nitrogen organic bases such as Et_3N, $(i\text{-}Pr)_2NEt$, pyridine, collidine, and 1,1,3,3-tetramethylurea. Surprisingly, methyl *p*-coumarate TBDMS ether (**1**) was desilylated completely by treatment with TMG in CH_3CN (Table 1, entry XIV). To study this

Table 1. Desilylating Reactions of the Phenolic Silyl Ether by Using TMG



1 **2**

entry	solvent	TMG (equiv)	temp (°C)	yield (%)[a,b]
I	CH_2Cl_2	1	rt	nr
II	toluene	1	rt	nr
III	THF	1	rt	trace
IV	CH_3OH	1	rt	44
V	DMF	1	rt	69
VI	DMSO	1	rt	67
VII	CH_3CN	0.1	rt	66 (25)[c] 66 (21)[d]
VIII	CH_3CN	0.1	50	87 (4)[e]
IX	CH_3CN	1	rt	72
X	CH_3CN	2	rt	75
XI	CH_3CN	4	rt	78
XII	CH_3CN	1	50	78
XIII	CH_3CN	2	50	83
XIV	CH_3CN	4	50	92

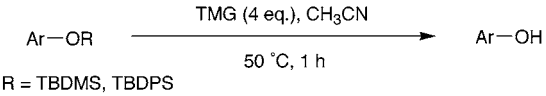
[a] Isolated yield. [b] Value in parentheses is the recovery of the starting material. [c] Reaction was performed for 13 h. [d] Reaction was performed in the presence of H_2O (2 equiv) for 13 h. [e] Reaction was performed in the presence of H_2O (2 equiv) for 8 h.

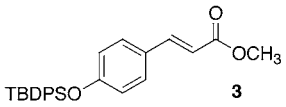
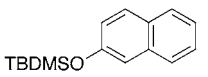
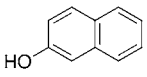
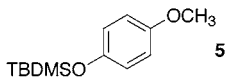
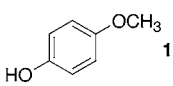
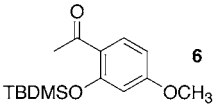
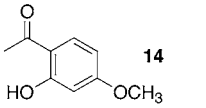
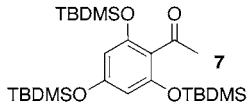
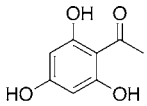
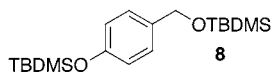
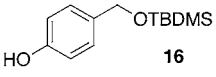
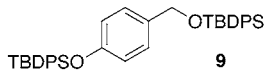
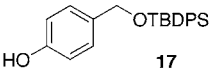
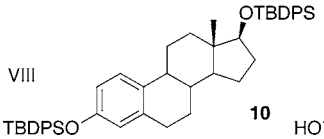
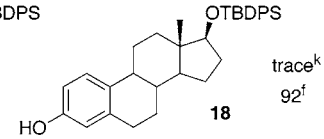
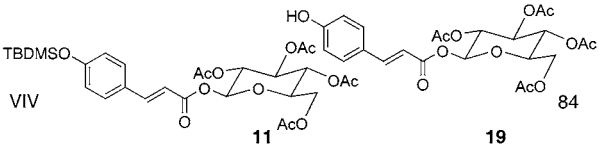
reaction in detail, the solvent effect was examined. Polar aprotic solvents such as DMF, DMSO, and CH_3CN were effective for this reaction (Table 1, entries V, VI, and IX). In contrast, nonpolar aprotic solvents such as CH_2Cl_2, toluene, and THF were ineffective (Table 1, entries I−III). The protic solvent, CH_3OH, demonstrated a moderate effect (Table 1, entry IV). Among the described solvents, CH_3CN was the most effective.

Further, the effects of temperature, H_2O as an additive, and the amount of TMG were examined (Table 1) so that optimized reaction conditions could be determined (4 equiv of TMG in CH_3CN at 50 °C for 1 h; Table 1, entry XIV).[12]

(8) A method of chemoselective cleavage of the phenolic silyl ether by using DMSO/H_2O/90 °C has been reported, but this has no chemoselectivity between benzylic and phenolic TBDMS ethers: Maiti, G.; Roy, S. C. *Tetrahedron Lett.* **1997**, *38*, 495.

Table 2. Chemoselective Desilylation of the Various Phenolic Silyl Ethers by Using TMG



entry	substrate	product	yield (%)[a,b]
I	 **3**	**2**	94
II	 **4**	 **12**	38 (53)[c] 69 (20)[d] 85 (5)[e] 93
III	 **5**	 **13**	32 (46) 51 (27)[f] 78 (3)[f,g] 81 (0)[f,h]
IV	 **6**	 **14**	52 90[i]
V	 **7**	 **15**	92[i]
VI	 **8**	 **16**	71
VII	 **9**	 **17**	84
VIII	 **10**	 **18**	trace[k] 92[f]
VIV	 **11** **19**		84

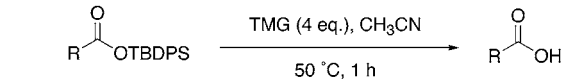
[a] Isolated yield. [b] Value in parentheses is the recovery of the starting material. [c] Reaction was performed by using TMG (0.1 equiv) for 13 h. [d] Reaction was performed by using TMG (0.1 equiv) in the presence of H_2O (2 equiv) for 13 h. [e] Reaction was performed by using TMG (0.1 equiv) in the presence of H_2O (2 equiv) for 24 h. [f] Solvent was 1/1 (v/v) TMG/CH_3CN. [g] Reaction was performed for 4 h. [h] Reaction was performed for 49 h. [i] Reaction was carried out at room temperature for 20 min. [j] TMG was used 12 equiv. [k] Solvent was 1/1 (v/v) THF/CH_3CN.

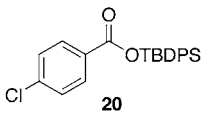
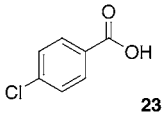
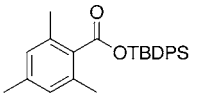
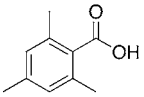
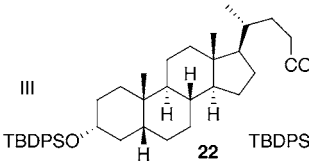
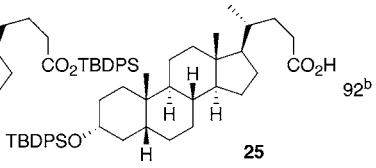
This novel method for desilylation could be applied to a variety of silylated compounds. The desilylation of silyl ethers **1**, **3**−**7**, **11** by using TMG in CH_3CN afforded the corresponding phenols in virtually quantitative isolated yields (Table 1, entry XIV; Table 2, entries I−V and VIV). Notably, the desilylation of silyl ether **11** had no influence on acetyl groups. Further, it should be noted that the desilylation of

TBDMS ether **5** bearing an electron-donating group was very slow in comparison with the desilylation of TBDMS ethers **1** and **4**. Phenolic silyl ethers bearing an electron-withdrawing group were deprotected more easily than those bearing an electron-donating group. Therefore, it was found that more acidic phenolic silyl ethers are deprotected easily.[6] The chemoselective desilylation of bis-silyl ethers **8**−**10** bearing both phenolic silyl and aliphatic silyl groups in the same moleclue was also investigated.[13] Phenolic TBDMS or TBDPS ethers were completely desilylated without affecting aliphatic TBDMS or TBDPS ethers (Table 2, entries VI−VIII).[14−16] To the best of our knowledge, this is the first successful chemoselective desilylation of phenolic TBDPS ethers in the presence of an aliphatic TBDPS ether.[17]

This desilylation reaction was applied to silyl esters. As expected, the desilylation of TBDPS esters **20** and **21** by using TMG could be performed smoothly to give high yields (Table 3, entries I and II). The desilylation of **22** bearing both carboxylic and aliphatic silyl groups gave only the corresponding carboxylic acid, without affecting the aliphatic TBDPS group, in high yield (Table 3, entry III).[13]

Table 3. Chemoselective Desilylation of Various Silyl Esters by Using TMG

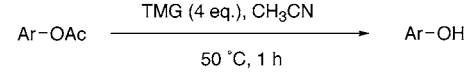


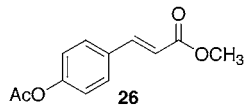
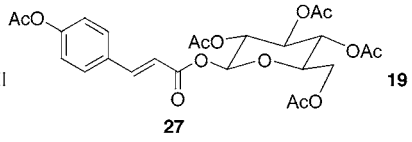
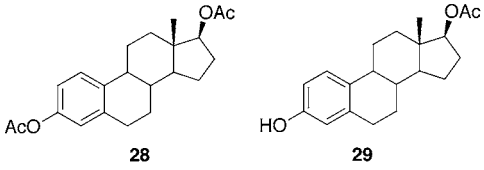
entry	substrate	product	yield (%)[a]
I	 **20**	 **23**	91
II	 **21**	 **24**	92
III	 **22**	 **25**	92[b]

[a] Isolated yield. [b] Solvent was 1/1 (v/v) THF/CH_3CN.

Furthermore, we found that this method was applicable for chemoselective deacetylation. When phenolic acetates **26**−**28** were examined, the phenolic acetyl group was selectively deprotected (Table 4, entries I−III).[16]

Table 4. Chemoselective Deacetylation of the Various Phenolic Acetates by Using TMG



entry	substrate	product	yield (%)[a]
I	 **26**	**2**	92
II	 **27**	**19**	81
III	 **28** **29**		trace 83[b]

[a] Isolated yield. [b] Solvent was 1/1 (v/v) TMG/CH_3CN.

To clarify the mechanism of the deprotection reaction,[18] it was followed by ^1H NMR. A 1:1 mixture of **1** and TMG in CD_3CN was observed at room temperature. The methyl signal of TMG was downfield-shifted by 0.07 ppm in comparison with that in CD_3CN, while the proton signals of

(9) Two examples of chemoselective cleavage of the phenolic TBDMS ether by using acidic reagents, 10% HCl (aqueous)[9a] and camphorsulfonic acid,[9b] have been reported, but these examples are special cases. Generally, it is known that basic conditions favor the chemoselective cleavage of phenolic silyl ether, while acidic conditions favor the chemoselective cleavage of aliphatic silyl ether:[6] (a) Davis, F. A.; Clark, C.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1994**, *59*, 1184. (b) Angle, S. R.; Wada, T. *Tetrahedron Lett.* **1997**, *38*, 7955.

(10) For the selective deprotection of aliphatic TBDMS by using acidic conditions: (a) Lee, A. S.-Y.; Yeh, H.-C.; Tsai M.-H. *Tetrahedron Lett.* **1995**, *36*, 6891. (b) Lee, A. S.-Y.; Shie, J.-J. *Tetrahedron Lett.* **1998**, *39*, 5249. (c) Lipshutz, B. H.; Keith, J. *Tetrahedron Lett.* **1998**, *39*, 2495. (d) Lee, A. S.-Y.; Yeh, H.-C.; Shie, J.-J. *Tetrahedron Lett.* **1998**, *39*, 5249. (e) Oriyama, T.; Kobayashi, Y.; Noda, K. *Synlett* **1998**, 1047.

(11) For the selective deprotection of phenolic acetyl esters: (a) González, A. G.; Jorge, Z. D.; Dorta, H. L.; Luis, F. R. *Tetrahedron Lett.* **1981**, *22*, 335. (b) Kunesch, N.; Miet, C.; Poisson, J. *Tetrahedron Lett.* **1987**, *28*, 3569. (c) Ono, M.; Itoh, I. *Tetrahedron Lett.* **1989**, *30*, 207. (d) Bandgar, B. P.; Uppalla, L. S.; Sagar, A. D.; Sadavarte, V. S. *Tetrahedron Lett.* **2001**, *42*, 1163.

(12) Typical procedure: to a solution of TBDMS ether **1** (58 mg, 0.2 mmol) in CH_3CN (1.0 mL) was added TMG (1,1,3,3-tetramethylguanidine) (92 mg, 0.8 mmol) at room temperature. The solution was stirred for 1 h at 50 °C. The reaction was then quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The combined extract was dried over anhydrous $MgSO_4$, and evaporation of the solvent afforded the crude product. This was purified by thin-layer chromatography (1:1 hexane−AcOEt) to afford the corresponding phenol (33 mg, 92%).

(13) Because **10** and **22** were insoluble in CH_3CN, 1:1 THF/CH_3CN was used as a solvent.

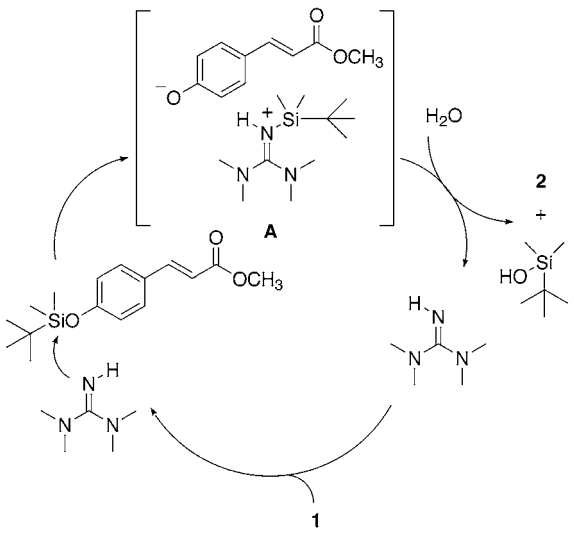
(14) The desilylation position of the TBDMS group was determined by ^1H NMR. The *tert*-butyl signals of aliphatic TBDMS ethers and phenolic TBDMS ethers were found to be 0.85 and 0.98 ppm, respectively.[7c]

(15) In the case of TBDPS ethers, there is no crucial difference in the chemical shift for the *tert*-butyl group between aliphatic TBDPS and phenolic TBDPS ethers. Therefore, the desilylation position was determined by acetylation of the desilylated compounds **17** and **18** to acetates (see Supporting Information).

(16) The position of the acetyl group was determined by acylation shift and methyl signals of acetyl esters. Hydroxyl methylene and methine signals of the compounds did not show any acylation shift. The methyl signals of aliphatic acetyl esters and phenolic acetyl esters are 2.02−2.10 and 2.25−2.36 ppm, respectively: (a) Santaniello, E.; Fiecchi, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2765. (b) Paradisi, M. P.; Zecchini, G. P.; Torrini, I. *Tetrahedron Lett.* **1986**, *27*, 5029. (c) Allevi, P.; Ciuffreda, P.; Longo, A.; Anastasia, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2915. (d) Yang, J.; Breslow, R. *Tetrahedron Lett.* **2000**, *41*, 8063.

(17) Selective deprotection of aliphatic TBDPS without affecting phenolic TBDPS ethers has been reported,[10c−e] but selective deprotection of phenolic TBDPS without affecting aliphatic TBDPS ethers has not been reported.

Scheme 1. Proposed Mechanism for Desilylation by Using TMG



the aromatic ring of the phenolate were upfield-shifted by ca. 0.18 ppm in comparison with those of **2** in CD_3CN. It was ascertained that intermediate A is formed, as shown in Scheme 1. Therefore, this desilylation might involve nucleophilic attack of TMG on the Si atom.[19] Next, the effect of H_2O was examined in the desilylation reaction with silyl ethers **1** and **4** by using 0.1 equiv of TMG in the presence of 2.0 equiv of H_2O. As shown in Tables 1 and 2, it turned out that the addition of H_2O accelerated the desilylation reaction. From these results, we assume the catalytic mechanism for our desilylation reaction in the presence of H_2O as shown in Scheme 1.

In conclusion, we have demonstrated that TMG, a nitrogen organic base, is a convenient and useful reagent for chemoselective deprotection of both silyl and acetyl groups on acidic hydroxyl groups such as phenol and carboxylic acid, without affecting aliphatic silyl and acetyl groups. We believe that this novel chemoselective deprotection method will serve as a useful tool for the synthesis of biologically significant products.

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Supporting Information Available: Spectroscopic characterization of new compounds and copies of ^1H NMR spectrum of **1**, **2**, TMG, and a 1:1 mixture of **1** and TMG in CD_3CN. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Verkade et al. have reported the desilylating reagent, $P(MeNCH_2CH_2)_3N$, as a nonionic base. Although TMG is also a nonionic base, its reactivity is different from that of $P(MeNCH_2CH_2)_3N$. In the case of $P(MeNCH_2CH_2)_3N$, chemoselectivity is not observed between phenolic and aliphatic TBDMS ethers and the desilylation of phenolic TBDPS ethers gives only a low yield: Yu, Z.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 2065.

(19) (a) Chaudhry, S. C.; Kummer, D. *J. Organomet. Chem.* **1988**, *339*, 241. (b) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 553.