The chemoselective and efficient deprotection of silyl ethers using trimethylsilyl bromide†

Syed Tasadaque A. Shah and Patrick J. Guiry*

Received 7th March 2008, Accepted 10th March 2008
First published as an Advance Article on the web 18th April 2008
DOI: 10.1039/b803949f

An efficient and chemoselective cleavage of silyl ethers (primary, secondary and aromatic) by using catalytic quantities of trimethylsilyl bromide (TMSBr) in methanol is reported. A wide range of alkyl silyl ethers such as TBS, TIPS, and TBDPS can be chemoselectively cleaved in high yield in the presence of aryl silyl ethers. The deprotection of silyl esters was also achieved employing catalytic quantities of TMSBr.

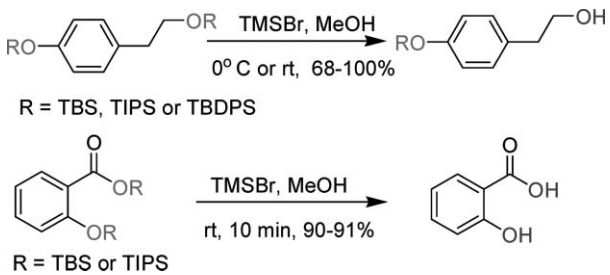
Introduction

The protection of acid and hydroxy groups and their subsequent deprotection is frequently applied in multistep transformations and in the synthesis of complex organic molecules.[1] Silyl esters and ethers are among the most frequently used protecting groups for acid and alcohol functionalities.[2,3] Cleavage of silyl ethers can be effected either using acidic conditions or a fluoride source. However, cleavage using fluoride is often associated with poor selectivity in the case of compounds having two different siloxy groups which can give rise to unwanted side reactions such as silyl migration.[4] A number of Lewis acids and other reagents have been reported to be effective in promoting cleavage of silyl-protected acids and alcohols.[1,5,6] Examples from the recent literature include: BF_3,[5] BCl_3,[6] $PdCl_2(CH_3CN)_2$,[7] $BiBr_3$,[8] $CuBr_2$,[9] $ZnBr_2$,[10] and NIS.[11] Many of these reagents provide the added advantage of promoting selective desilylation of bis-silyl ethers.[12]

Others approaches to desilylation require the use of relatively expensive reagents, longer reaction times and heating.[13] Previously, Friedrich and Delucca have reported the cleavage of ethers and esters using TMSBr catalyzed by iodine monobromide.[14] Moreover, in a very recent report Li and Peng have demonstrated the desilylation of the TBS group using TMSCl and KF dihydrate in acetonitrile.[15]

Results and discussion

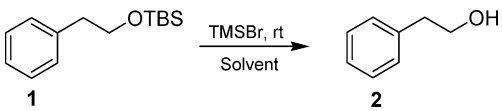
In this paper, we wish to report the desilylation of a wide range of silyl-protected primary, secondary and aromatic hydroxy and acid groups in the presence of a catalytic amount of trimethylsilyl bromide in methanol (*in situ* generated HBr) without any added reagent (Scheme 1). The *in situ* generation of HX (X = Br or Cl) from TMS halides in methanol has been exploited by Yu and Jin for the preparation of α-halo vinyl ethers from the corresponding alkynyl ethers.[16] However, to our knowledge, studies exploiting this catalyst system for deprotection transformations have not been reported previously.



Scheme 1

In order to explore the generality of this reagent system for desilylation, we examined the solvent effect by employing TBS ether **1** as substrate (Table 1). When methanol was employed, desilylation went smoothly within minutes. Other alcoholic solvents such as EtOH and isopropanol did afford high yields of desilylation product but required longer reaction times of 1 and 5 h. The use of acetonitrile or an acetonitrile–H_2O mixture gave similar yields of 73–88%, respectively. The reaction was also successful in the polar aprotic solvent DMF although the reaction was slower than in MeOH. Dichloromethane was a less effective reaction medium as a longer reaction time of 24 h was required to achieve

Table 1 Desilylation of silyl ethers by using catalytic amount of TMSBr (0.2 equiv.) in various solvents



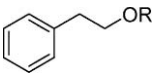
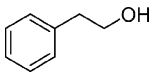
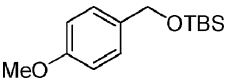
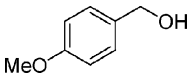
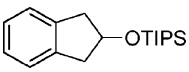
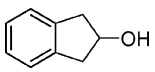
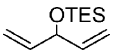
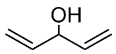
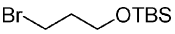
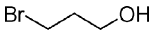
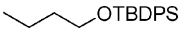
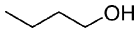
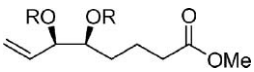
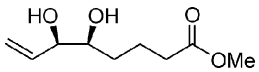
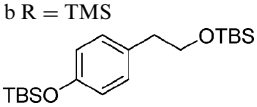
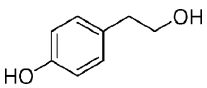
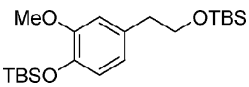
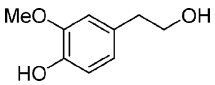
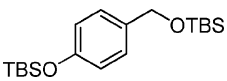
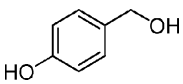
Entry	Solvent	Time	Yield (%)
1	MeOH	10 min	94
2	EtOH	1 h	82
3	Isopropanol	5 h	74
4	CH_3CN	3 h	73
5	$CH_3CN + H_2O$	1 h	88
6	DMF	2 h	91
7	CH_2Cl_2	24 h	75
8	THF	24 h	66
9	*n*-Hexane	24 h	—
10	Toluene	24 h	—

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland. E-mail: patrick.guiry@ucd.ie; Fax: +353 1 716 2501

† Electronic supplementary information (ESI) available: Spectral data. See DOI: 10.1039/b803949f

 This journal is © The Royal Society of Chemistry 2008

Table 2 Deprotection of silyl-protected hydroxy groups using catalytic amount of TMSBr (0.2 equiv.)

Entry	Substrate	Temp, time	Product	Yield (%)
1				
	a R = TES	rt, 10 min[a]		98
	b R = TIPS	rt, 5 h		90
	c R = DPMS	rt, 1 h		—
2		rt, 10 min		84
3		rt, 6 h		99
4		rt, 5 min[a]		92
5		rt, 5 min		83
6		rt, 9 h		90
7				
	a R = TBS	rt, 10 min[a]		92
	b R = TMS	rt, 5 min[b]		92
8		rt, 5 h		95
9		rt, 5 h		92
10		rt, 5 h		96

[a] 0.1 equiv. TMSBr. [b] 0.05 equiv. TMSBr. All products were characterized from spectral (^{1}H, ^{13}C NMR and MS) data and by comparison with the parent alcohols.

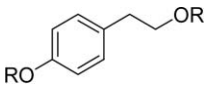
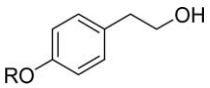
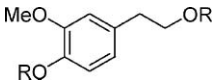
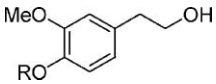
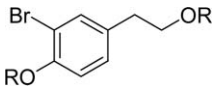
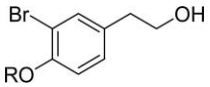
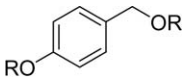
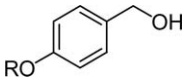
75% yield and the use of THF gave 66% yield in a similar reaction time. There was no observable reaction in hydrocarbon solvents such as *n*-hexane or toluene.

A wide range of silyl-protected hydroxy groups were cleaved in high to excellent yields under our optimized reaction conditions using catalytic quantities of TMSBr in MeOH, Table 2. The silyl-protecting group employed has a significant effect on the reaction rate, and cleavage of the diphenylmethylsilyl (DPMS) ether did not occur, entry 1. The deprotection of mono-protected silyl ethers proceeded in 83 to 99% yield, entries 2–6.

In conjunction with an ongoing total synthesis project in our laboratory, we have prepared a bis-*tert*-butyldimethylsilyl (TBS) ether as a key synthetic intermediate.[17] With this compound at hand we applied our new deprotection methodology to afford the corresponding diol in 92% yield after 20 min at room temperature, entry 7a. In addition, we observed that the corresponding bis-trimethylsilyl (TMS) ether was also effectively cleaved in 92% yield using 0.05 equiv. of TMSBr, entry 7b. Our first attempts at chemoselective deprotection of aryl alkyl silyl ethers were not successful as we obtained the corresponding bis-deprotected diols in 92–96% yield, entries 8–10.

In the literature, alcoholic and phenolic hydroxy groups are present in many complex natural products such as vancomycin and teicoplanian, and the chemoselective deprotection of alcoholic and phenolic silyl ethers is of considerable interest.[18] In this context, we were pleased to find that we could develop a mild and efficient methodology in which by controlling the reaction conditions, alkyl silyl ethers were chemoselectively deprotected in the presence of aryl silyl ethers using a catalytic amount of trimethylsilyl bromide, Table 3.[19] Surprisingly, exposure of a solution of the bis-TBS ether at 0 °C in methanol to a catalytic amount of TMSBr provided mono-deprotected ether in 91% yield with no traces of the fully deprotected material, entry 1. In contrast, in the case of bulkier silyl ethers such as TIPS and TBDPS, chemoselective deprotection occurred at room temperature. However, longer reaction times were required compared to less sterically hindered silyl groups, entries 1, 2, 4. This chemoselective silyl cleavage procedure is much faster than the previously reported method using TMSCl.[12c]

Table 3 Chemoselective deprotection of bis-silyl-protected hydroxy groups by using a catalytic amount of TMSBr (0.2 equiv.)

Entry	Substrate	Temp, time	Product	Yield (%)
1				
	a R = TBS	0° C, 20 min[a]	a R = TBS	91
	b R = TIPS	rt, 5 h	b R = TIPS	90
	c R = TBDPS	rt, 12 h	c R = TBDPS	85
	d R = DPMS	0° C, 20 min	d R = DPMS	—
2				
	a R = TBS	0° C, 20 min[a]	a R = TBS	99
	b R = TIPS	rt, 5 h	b R = TIPS	100
	c R = TBDPS	rt, 12 h	c R = TBDPS	68
3				
	R = TBS	0° C, 20 min[a]	R = TBS	77
4				
	R = TBDPS	rt, 12	R = TBDPS	85

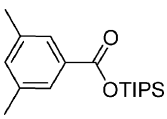
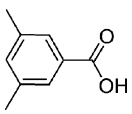
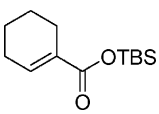
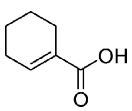
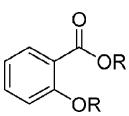
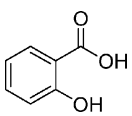
[a] 0.1 equiv. TMSBr. All products were characterized from spectral (^{1}H, ^{13}C NMR and MS) data and by comparison with the parent alcohols.

Collington and co-workers have used aqueous HF in acetonitrile for the selective deprotection of alkyl silyl ethers in the presence of aryl silyl ethers.[20] We believe that our method is superior to Collington's as they use HF which is hazardous, toxic and also requires special care for its use whereas we have introduced a simple, rapid, inexpensive and environmentally friendly method.

To further explore the utility of this novel desilylation procedure we have also investigated the cleavage of silyl-protected esters, Table 4. This proceeded in high yields (90–95%) for aromatic and α,β-unsaturated esters, entries 1–2. However, chemoselective cleavage of silyl esters in the presence of silyl ethers was not achieved, entry 3.

In conclusion, the use of trimethylsilyl bromide in alcoholic solution provides a mild, efficient and chemoselective means of removing alkyl silyl ethers such as TBS, TIPS and TBDPS in the presence of aryl silyl ethers. The advantages of this procedure over earlier reported processes include its simplicity, the non-requirement of additional reagents and the clean and rapid reactions it promotes.

Table 4 Deprotection of silyl-protected acid groups by using catalytic amount of TMSBr (0.1 equiv.)

Entry	Substrate	Temp, time	Product	Yield (%)
1		rt, 4 h		90
2		0 °C, 10 min		95
3				
	a R = TBS	0 °C, 10 min		91
	b R = TBDPS	rt, 4 h		90

All products were characterized from spectral data and by comparison with the parent alcohols.

 This journal is © The Royal Society of Chemistry 2008

By controlling the reaction conditions, selective desilylation can be accomplished in the presence of bulkier silyl groups and other acid-sensitive protecting groups. Nonetheless, the facile conditions, high yields, and demonstrated applicability to complex, highly functionalized molecules suggest that this protocol will find widespread utility in synthesis.

Experimental

General

^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) were recorded at room temperature in $CDCl_3$ with Varian-Unity spectrometers. Chemical shifts (δ) are in parts per million relative to $CHCl_3$ (7.26, ^{1}H), $CDCl_3$ (77.0, ^{13}C). Coupling constants are given as absolute values expressed in Hz. High resolution mass spectra were measured on a Waters/Micromass instrument. Thin layer chromatography was carried out using Merck Kieselgel 60 F254 silica gel plates. Column chromatography separations were performed using Merck Kieselgel 60 (Art. 7734). Dried solvents were purchased from Sigma-Aldrich.

General procedure for the preparation of silyl ethers[1]

To a magnetically stirred solution of the alcohol (1.0 mmol), in dry CH_2Cl_2 or DMF (3.0 ml), imidazole (1.5 or 3.0 mmol) and trialkylsilyl chloride (1.5 or 3.0 mmol) were added sequentially. After the starting material disappeared on TLC, brine was poured into the reaction mixture. The organic layer was washed with brine (10.0 ml) twice, separated, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography. When DMF was used, the resulting reaction mixture was directly purified by the flash chromatography elution with diethylether–pentane (1 : 20).

General procedure for the preparation of silyl esters[1]

To a magnetically stirred solution of the acids (1.0 mmol), in dry DMF (3.0 ml), imidazole (1.5 mmol) and trialkylsilyl chloride (1.5 mmol) were added sequentially. After the starting material disappeared on TLC, the resulting reaction mixture was purified by flash chromatography elution with diethylether–pentane (1 : 20).

General procedure for silyl ether and ester cleavage

To a stirred solution of bis-silyl ether, silyl ether or ester (1.0 mmol) at 0 °C or room temperature in MeOH TMSBr (0.1–0.2 mmol) was added. After stirring for the indicated time the reaction was quenched by the addition of a saturated aqueous sodium bicarbonate solution (1 ml) and diluted with water (10 ml). The product was extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were washed with brine (20 ml) and concentrated *in vacuo*. If necessary, the crude product was purified on silica gel. Elution with diethylether–pentane (1 : 4) or ethyl acetate–pentane (1 : 1) afforded the required products.

(5*S*,6*R*)-5,6-Dihydroxy-oct-7-enoic acid methyl ester. Table 2, entry 7, ref. 17.

2-[4′-(*tert*-Butyldimethylsilyloxy)phenyl]ethanol. See Table 3, entry 1a, ref. 21.

2-[4′-(Tri-isopropylsilyloxy)phenyl]ethanol. Table 3, entry 1b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (2H, d, J = 8.4 Hz), 6.83 (2H, d, J = 8.4 Hz), 3.82 (2H, t, J = 6.5 Hz), 2.80 (2H, t, J = 6.5 Hz), 1.59 (1H, brs), 1.20–1.29 (18H, m), 1.05–1.10 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 130.5, 129.8, 119.9, 63.8, 38.3, 17.9, 12.6.

2-[4′-(*tert*-Butyldiphenylsilyloxy)phenyl]ethanol. Table 3, entry 1c. Eluted with diethylether–pentane = 3 : 1, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.71 (10H, m), 6.93 (2H, d, J = 8.4 Hz), 6.70 (2H, d, J = 8.4 Hz), 3.74 (2H, t, J = 6.5 Hz), 2.71 (2H, t, J = 6.5 Hz), 1.53 (1H, brs), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 135.4, 132.9, 130.6, 129.8, 129.6, 127.7, 119.7, 63.6, 38.2, 26.5, 19.4.

2-[3′-Methoxy-4′-(*tert*-butyldimethylsilyloxy)phenyl]ethanol. Table 3, entry 2a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65–6.79 (3H, m), 3.82 (2H, t, J = 6.4 Hz), 3.79 (3H, s), 2.79 (2H, t, J = 6.4 Hz), 1.59 (1H, brs), 0.98 (9H, s), 0.14 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 143.6, 131.6, 121.0, 120.8, 112.9, 63.7, 55.4, 38.8, 25.7, 18.4, −4.6.

2-[3′-Methoxy-4′-(tri-isopropylsilyloxy)phenyl]ethanol. Table 3, entry 2b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65–6.82 (3H, m), 3.82 (2H, t, J = 6.5 Hz), 3.80 (3H, s), 2.80 (2H, t, J = 6.5 Hz), 1.42 (1H, brs), 1.21–1.30 (3H, m), 1.09–1.10 (18H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 144.4, 131.5, 121.2, 120.6, 113.3, 63.9, 55.7, 39.0, 18.1, 18.0, 17.9, 13.1.

2-[3′-Methoxy-4′-(*tert*-butyldiphenylsilyloxy)phenyl]ethanol. Table 3, entry 2c. Eluted with diethylether–pentane = 3 : 1, colorless oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.71 (10H, m), 6.47–6.65 (3H, m), 3.76 (2H, t, J = 6.4 Hz), 3.55 (3H, s), 2.72 (2H, t, J = 6.4 Hz), 1.57 (1H, brs), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 143.7, 135.3, 133.8, 131.4, 129.5, 127.4, 120.8, 120.1, 113.6, 63.6, 55.3, 38.7, 26.7, 19.7.

2-[3′-Bromo-4′-(*tert*-butyldimethylsilyloxy)phenyl]ethanol. Table 3, entry 3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79–7.39 (3H, m), 3.82 (2H, t, J = 6.4 Hz), 2.77 (2H, t, J = 6.4 Hz), 1.57 (1H, brs), 1.03 (9H, s), 0.24 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 133.6, 132.6, 128.7, 120.1, 115.2, 63.5, 37.9, 25.7, 18.3, −4.2.

4-(*tert*-Butyldipheylsilyloxy)benzyl alcohol. Table 3, entry 4. Eluted with diethylether–pentane = 3 : 1, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.71 (10H, m), 7.07 (2H, d, J = 8.4 Hz), 6.74 (2H, d, J = 8.4 Hz), 4.51 (2H, s), 1.63 (1H, brs), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 135.4, 133.3, 132.8, 129.8, 128.3, 127.7, 119.6, 65.0, 26.4, 19.4.

Acknowledgements

We express our gratitude to the Irish Research Council for Science, Engineering and Technology (IRCSET) and Higher Education Authority (HEA) for a post-doctoral fellowship, granted to Syed T. A. Shah. We also acknowledge the facilities provided by the Centre for Synthesis and Chemical Biology (CSCB), funded by the Higher Education Authority's Programme for Research in Third-Level Institutions (PRTLI). We are grateful to Dr. Jimmy

Muldoon and Dr. Dilip Rai of the CSCB for NMR and mass spectra, respectively.

References

1 (*a*) P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, 1994; (*b*) T. W. Green and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, John Wiley and Sons, New York, 3rd edn, 1999.
2 K. Jarowicki and P Kocienski, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1589.
3 T. D. Nelson and R. D. Crouch, *Synthesis*, 1996, 1031.
4 B. C. Ranu, U. Jana and A. Majee, *Tetrahedron Lett.*, 1985, **26**, 681.
5 K. Toshima, S. Takai, Y. Maeda, R. Takano and S. Matsumura, *Angew. Chem., Int. Ed.*, 2000, **39**, 3656.
6 Y.-Y. Yang, W.-B. Yang, C.-F. Teo and C.-H. Lin, *Synlett*, 2000, 1634.
7 I. Kadota, C. Kadowaki, C. Yoshida and Y. Yamamoto, *Tetrahedron Lett.*, 1998, **39**, 6369.
8 J. S. Bajwa, J. Vivelo, J. Slade, O. Repic and T. Blacklock, *Tetrahedron Lett.*, 2000, **41**, 6021.
9 S. Bhatt and S. K. Nayak, *Tetrahedron Lett.*, 2006, **48**, 8395.
10 G. J. McGarvey, Zinc Bromide in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, John Wiley, New York, 1995, vol. 8, pp. 5539.
11 B. Karimi, A. Zamani and D. Zareyee, *Tetrahedron Lett.*, 2004, **45**, 9139.
12 (*a*) C.-E. Yeom, H. W. Kim, S. Y. Lee and B. M. Kim, *Synlett*, 2007, 146; (*b*) T. D. Nelson and R. D. Crouch, *Synthesis*, 1996, 1031; (*c*) P. A. Grieco and C. J. Markworth, *Tetrahedron Lett.*, 1999, **40**, 665.
13 (*a*) T. Oriyama, Y. Kobayashi and K. Noda, *Synlett*, 1998, 1047; (*b*) G. Sabitha, R. S. Babu, M. Rajkumar, R. Srividya and J. S. Yadav, *Org. Lett.*, 2001, **3**, 1149; (*c*) G. Bartoli, G. Cupone, R. Dalpozzo, A. De Nino, L. Maiuolo, A. Procopio, L. Sambri and A. Tagarelli, *Tetrahedron Lett.*, 2002, **43**, 5945.
14 E. C. Friedrich and G. Delucca, *J. Org. Chem.*, 1983, **48**, 1678.
15 Y. Peng and W.-D. Z. Li, *Synlett*, 2006, 1165.
16 W. Yu and Z. Jin, *J. Am. Chem. Soc.*, 1972, **94**, 7210.
17 T. O'Sullivan, K. S. A. Vallin, S. T. A. Shah, J. Fakhry, P. Maderna, M. Scannell, A. L. F. Sampaio, M. Perretti, C. Godson and P. J. Guiry, *J. Med. Chem.*, 2007, **50**, 5894.
18 A. V. Ankala and G. Fenteany, *Tetrahedron Lett.*, 2002, **43**, 4729.
19 Attempts to chemoselectively cleave the bis-TBS ether with HBr (generated *in situ* from 0.1 equiv. of TMSBr and 1.0 equiv. of water) in acetonitrile gave rise after 3 h to only a 55% yield of mono-deprotected ether along with 28% of the fully deprotected material and 8% of recovered starting material.
20 E. W. Collington, H. Finch and I. J. Smith, *Tetrahedron Lett.*, 1985, **26**, 681.
21 C.-E. Yeom, Y. J. Kim, S. Y. Lee, Y. J. Shin and B. M. Kim, *Tetrahedron*, 2005, **61**, 12227.

This journal is © The Royal Society of Chemistry 2008