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Selective Deprotection Of *tert*-Butyldimethylsilyl Ether With Lithium Bromide And 18-Crown-6

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Abstract: Lithium bromide, in the presence of a crown ether, has been found to selectively remove primary *tert*-butyldimethylsilyl ethers under controlled conditions. This selectivity has been utilized to synthesize 3'-TBDMS-2'-deoxyuridine in one step from the diprotected compound.

In organic synthesis a large number of hydroxyl protecting groups have been developed.[1] Silyl ethers such as *tert*-butyldimethylsilyl ethers (TBDMS) are particularly useful due to their stability toward various reagents and conditions.[1] Deprotection of TBDMS ethers can be effected by a variety of conditions including fluoride ion[2], protic acids[3], and Lewis acids.[4,5]

It is often necessary to deprotect a primary silyl ether in the presence of a secondary silyl ether. This is sometimes achieved by first protecting the two hydroxyl groups with different silyl groups and then selectively removing one. This methodology however adds unnecessary steps in the synthesis. In other cases

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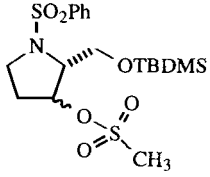
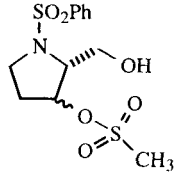
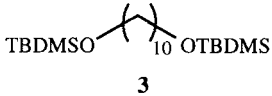
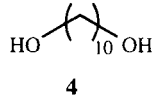
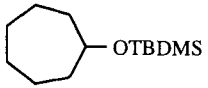
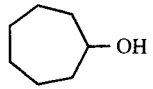
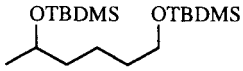
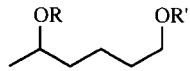
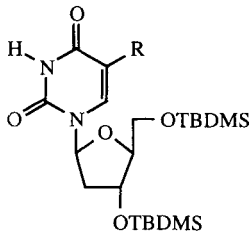
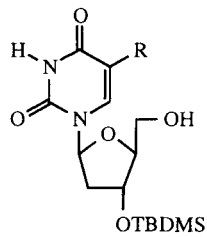
the primary TBDMS group can be selectively removed under acidic conditions if the secondary silyl group is sterically hindered.[6] This procedure generally however shows poor selectivity. Recently it has been demonstrated that neutral activated alumina[5] can preferentially remove the primary ether over the secondary in the *bis*-TBDMS ether of 1,5-hexanediol.

We now report the selective cleavage of primary TBDMS ethers using lithium bromide and 18-crown-6. During an attempted displacement of the mesylate group in **1** with LiBr in acetone under reflux we observed that the TBDMS group in the product **2** had been cleaved while the mesylate was still intact (Table).[7] This was surprising since the cleavage of silyl ethers with LiBr had not been previously reported. We then decided to test the generality of this reaction with the TBDMS ethers of 1,10-decane diol (**3**) and cycloheptanol (**5**).[1b] On heating **3** and **5** in sealed tubes with LiBr and acetone, no formation of their respective alcohols was observed. However, on the addition of 18-crown-6 to the reaction mixtures, the corresponding alcohols **4** and **6** were obtained. It was also observed that, to deprotect the silyl ether of cycloheptanol required higher temperatures and longer heating time as compared to **3**. This led us to believe that some selectivity could be achieved between a secondary and a primary TBDMS ether. To test this, the *bis*-TBDMS ether of 1,5-hexane diol (**7**) was heated in a sealed tube at 85 °C with lithium bromide and 18-crown-6. The monosilylated ethers **8** and **9** obtained were in a ratio of 92:8, respectively. Control experiments carried out using tetrabutylammonium fluoride and aqueous acetic acid[1b] in THF displayed little or no selectivity between the primary and secondary TBDMS ether in **7**.

To further demonstrate the applicability of this reaction, the *bis*-TBDMS ethers of thymidine (**10**) and 2'-deoxyuridine (**12**) were treated with LiBr and 18-crown-6

Table: Deprotection of TBDMS Ethers with LiBr and 18-Crown-6

Compound	Reaction Conditions (LiBr:18-Crown-6) (eq)	Product	Yield (%)[a]
 **1**	Reflux 80 °C, 10 h (5:0)	 **2**	81
 **3**	Sealed tube 85 °C, 36 h (10:3)	 **4**	88
 **5**	Sealed tube 110 °C, 48 h (10:6)	 **6**	60
 **7**	Sealed tube 85 °C, 48 h (3:3)[b]	 **8** R=TBDMS, R'=H **9** R=H, R'=TBDMS	**8**:**9** 92:8[d] 75[c]
 **10** R = H **12** R = CH_3	Reflux 85 °C, 36 h (5:3)	 **11** R = H **13** R = CH_3	**11** 71 **13** 71

[a] Isolated yields. [b] The reaction was first heated with 1.5 eq of LiBr and 18-crown-6 for 36 h. Then another 1.5 eq of each were added and the reaction mixture was heated for an additional 12 h. [c] The ratio was determined by ^{1}H NMR spectroscopy. [d] 1,5-Hexanediol and **7** were also obtained in a yield of 12% and 7%, respectively.

under reflux. Only the secondary silyl ethers **11** and **13** were obtained in 71% yield. The structures of these useful intermediates in oligonucleotide synthesis were confirmed by comparison with authentic compounds synthesized by known routes.[8,9]

In conclusion, a new procedure has been developed to cleave primary TBDMS ethers over secondary ones with very high selectivity under neutral conditions and in good yields. This reaction should find wide application in organic synthesis.

Experimental

All reagents and solvents were of reagent grade. All compounds were identified by comparison with authentic compounds synthesized by known routes.[10]

General procedure for deprotection: To a solution of 3',5'-*bis*-TBDMS-2'-deoxyuridine (**10**) (0.054 g, 0.12 mmol) in acetone was added LiBr (0.052 g, 0.6 mmol) and 18-crown-6 (0.095 g, 0.36 mmol). The reaction was refluxed or heated in a sealed tube for 36 h. After the reaction was complete the solvent was removed under vacuum. Water was added to the residue and the aqueous layer extracted with ethyl acetate. The organic extract was dried with sodium sulfate and concentrated. Flash column chromatography (SiO_2: 75% ethyl acetate/25% hexane) afforded **11** (0.0287) in 71% yield. The starting material **10** was also obtained in 4% yield. The products were then identified by NMR spectroscopy.[10]

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References

1. (a) Greene, T. W. and Wuts, P. G. M., "Protective groups in Organic Synthesis", John Wiley & Sons, New York 1991. (b) Corey E. J.; Venkatserwarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
2. (a) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *20*, 3981. (b) Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* **1974**, *96*, 2250. (c) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.
3. (a) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797. (b) Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19.
4. (a) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295. (b) Metcalf, B. W.; Burkhart, J. P.; Jund, K. *Tetrahedron Lett.* **1980**, *21*, 35. (c) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912. (d) Batten, R. J.; Dixon, A. J.; Taylor, R. J. K.; Newton, R. F. *Synthesis* **1980**, 234.
5. Feixas, J.; Capdevila, A.; Guerrero, A. *Tetrahedron* **1994**, *50*, 8539.
6. (a) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117. (b) Kawai, A.; Hara, O.; Hamada, Y.; Shiari, T. *Tetrahedron Lett.* **1988**, *29*, 6331.
7. The synthesis of **1** will be reported separately.
8. (a) Ogilvie, K. *Can. J. Chem.* **1973**, *51*, 3799. (b) Ogilvie, K.; Thompson, E. A.; Quilliam, M. A.; Westmore, J. B. *Tetrahedron Lett.* **1974**, 2865.
9. The compounds **11** (50%), **10** (30%) and the 2'-deoxyuridine (20%) were obtained .
10. The analytical data for the compounds **1-12** are as follows:

    TBDMS Ether 1(mixture of diastereomers). 300MHz ^{1}H NMR ($CDCl_3$) δ 7.9 (m, 2H), 7.55 (m. 3H), 5.1 (m, 1H), 4.14-3.10 (m, 5H), 3.08, 2.65 (s, 3H), 2.4-2.0 (m, 2H), 0.9 (s, 9H), 0.1 (s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 137.2, 136.3, 133.1, 132.9, 129.3, 129.0, 127.8, 127.3, 81.9, 79.6, 67.4, 64.3, 63.2, 61.5, 46.9, 46.6, 38.3, 38.1, 31.8, 31.0, 26.0, 25.8, 18.2, 18.1, -5.4, -5.5; FABMS [$(M+H)^+$]=450 *m/e*. HRMS calc. for $C_{18}H_{32}NO_6SiS_2$: 450.1440; found: 450.1440.

    Alcohol 2 (mixture of diastereomers). 400MHz ^{1}H NMR ($CDCl_3$) δ 7.9 (m, 2H), 7.6 (m. 3H), 5.1 (m, 1H), 4.15-3.20 (m, 5H), 3.1, 2.7 (s, 3H),

2.53 (m, 1H), 2.4-2.0 (m, 2H); 100 MHz ^{13}C NMR ($CDCl_3$) δ 136.3, 135.7, 133.4, 133.2, 129.5, 129.2, 127.9, 127.5, 81.8, 79.5, 67.6, 63.8, 63.6, 61.5, 47.2, 47.0, 38.4, 38.1, 31.6, 31.1; FABMS [$(M+H)^+$]=336 *m/e*. HRMS calc. for $C_{12}H_{18}NO_6S_2$: 336.0576; found: 336.0578.

1,10-bis-TBDMS-decanediol (3). 200MHz ^1H NMR ($CDCl_3$) δ 3.6 (t, J = 8 Hz, 4H), 1.65-1.15 (m, 16H), 0.9 (s, 18H), 0.05 (s, 12H).

1,10-Decanediol (4). 200MHz ^1H NMR ($CDCl_3$) δ 3.65 (t, J = 8 Hz, 4H), 1.8-1.1 (m, 18H).

Cycloheptanol-TBDMS Ether (5). 200MHz ^1H NMR ($CDCl_3$) δ 3.85 (m, 1H), 1.95-1.2 (m, 12H), 0.9 (s, 9H), 0.05 (s, 6H).

Cycloheptanol (6). 200MHz ^1H NMR ($CDCl_3$) δ 3.85 (m, 1H), 2.1-1.1 (m, 13H).

1,5-bis-TBDMS-hexanediol (7). 200MHz ^1H NMR ($CDCl_3$) δ 3.75 (m, 1H), 3.6 (t, J = 6.3 Hz, 2H), 1.6-1.2 (m, 6H), 1.06 (d, J = 6.1 Hz, 3H), 0.89, 0.88 (2xs, 18H), 0.05 (s, 12H).

5-TBDMS-hexane-1,5-diol (8). 200MHz ^1H NMR ($CDCl_3$) δ 3.79 (m, 1H), 3.65 (t, J = 6.4 Hz, 2H), 1.7-1.3 (m, 7H), 1.12 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); FABMS [$(M+H)^+$]=233 *m/e*.

1-TBDMS-hexane-1,5-diol (9). 200MHz ^1H NMR ($CDCl_3$) δ 3.83 (m, 1H), 3.6 (t, J = 6.4 Hz, 2H), 1.7-1.3 (m, 7H), 1.2 (d, J = 8.0 Hz, 3H), 0.9 (s, 9H), 0.05 (s, 6H).

3',5'-bis-TBDMS-2'-deoxyuridine (10). 200MHz ^1H NMR ($CDCl_3$) δ 8.15 (bs, 1H), 7.9 (d, J = 8.4 Hz,1H), 6.28 (t, J = 6.4 Hz, 1H), 5.67 (d, J = 8.4 Hz, 1H), 4.42 (m, 1H), 4.0-3.7 (m, 3H), 2.45-1.95 (m, 2H), 0.95, 0.90 (2xs, 18H), 0.15, 0.10 (2xs, 12H); FABMS [$(M+H)^+$]=457 *m/e*. HRMS calc. for $C_{21}H_{41}N_2O_5Si_2$: 457.2554; found: 457.2553.

3'-TBDMS-2'-deoxyuridine (11). 400MHz ^1H NMR ($CDCl_3$) δ 8.73 (bs, 1H), 7.64 (d, J = 8.24 Hz,1H), 6.17 (t, J = 6.4 Hz, 1H), 5.73 (d, J = 8.24 Hz, 1H), 4.45 (m, 1H), 4.0-3.6 (m, 3H), 2.57-2.4 (m, 1H), 2.38-2.15

(m, 2H), 0.89 (s, 9H), 0.08 (s, 6H); FABMS [(M+H)$^+$]=343 *m/e*. HRMS calc. for $C_{15}H_{27}N_2O_5Si$: 343.1689; found: 343.1695.

3',5'-bis-TBDMS-2'-deoxythymidine (11). 200MHz ^{1}H NMR ($CDCl_3$) δ 7.9 (bs, 1H), 7.45 (s, 1H), 6.32 (t, *J* = 7.0 Hz, 1H), 4.4 (m, 1H), 4.0-3.65 (m, 3H), 2.35-1.95 (m, 2H), 1.9 (s, 3H), 0.95, 0.90 (2xs, 18H), 0.13, 0.10 (2xs, 12H); FABMS [(M+H)$^+$]=471 *m/e*.

3'-TBDMS-2'-deoxythymidine (12). 400MHz ^{1}H NMR ($CDCl_3$) δ 8.95 (bs, 1H), 7.38 (s, 1H), 6.15 (t, *J* = 7.0 Hz, 1H), 4.50 (m, 1H), 4.0-3.7 (m, 3H), 2.77 (bs, 1H), 2.4-2.2 (m, 2H), 1.9 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H); FABMS [(M+H)$^+$]=357 *m/e*. HRMS calc. for $C_{16}H_{29}N_2O_5Si$: 357.1846; found: 357.1846.

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