A mild and efficient method for the deprotection of *tert*-butyldimethylsilyl ethers using iodine in methanol

Andrew R. Vaino and Walter A. Szarek*†

Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

An effective method for the cleavage of *tert*-butyldimethylsilyl ethers using a 1% solution of iodine in methanol is described.

The protection and deprotection of the hydroxy functional group remain critical challenges to organic chemists in general, and to carbohydrate chemists in particular. Indeed, an astounding array of hydroxy-protecting groups exists.[1] Since its introduction by Corey and Venkateswarlu in 1972,[2] the *tert*-butyldimethylsilyl (TBDMS) ether has become, perhaps, the most popular silicon-containing protecting group used in organic synthesis.[1] It is of particular benefit in nucleoside and carbohydrate chemistry, where the steric bulk of the TBDMS ether allows chemoselective introduction.[3]

As with most protecting groups, many methods are available for the removal of the TBDMS ether, under a wide variety of conditions. One of the most common methods for the cleavage of silyl ethers is the exploitation of the high affinity that silicon has for fluoride ions. Thus, many routes for the deprotection of the TBDMS ether involve one form of fluoride or another. Tetrabutylammonium fluoride (TBAF) has been used often,[2,4] however, this method suffers somewhat in that the use of the strongly basic fluoride anion is not compatible with substrates prone to elimination; indeed, TBAF is used often to induce elimination reactions.[5] Furthermore, in the case of polyhydroxy compounds, TBDMS ethers are known to migrate under basic conditions.[6] Additionally, the use of such basic conditions may also be problematic with polyhydroxy compounds in which other hydroxy groups are protected as esters; acetic, and to a lesser extent benzoic, esters are known to migrate under basic conditions.[7]

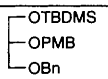
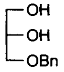
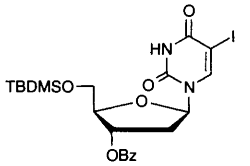
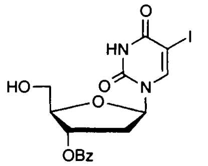
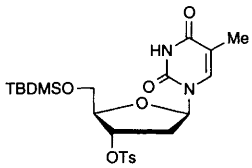
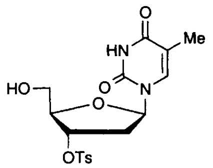
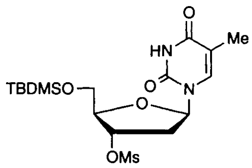
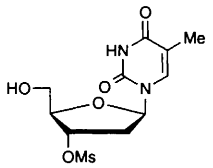
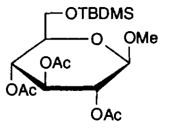
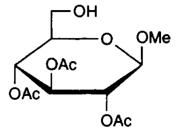
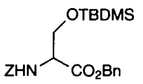
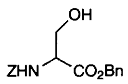
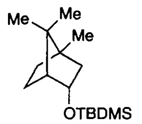
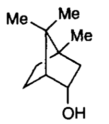
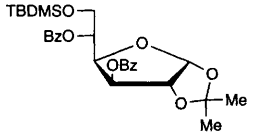
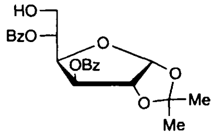
A host of other reagents and methods for the deprotection of the TBDMS ether exist. These include: acetic acid in aqueous THF,[8] HCl in EtOH,[8] tetrafluoroborate salts,[9] tetrafluorosilane,[10] fluorosilicic acid,[11] diethylboryl ethers,[12] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[13] diisobutylaluminium hydride,[14] aqueous HF in acetonitrile,[15] catalytic hydrogenation,[16] pyridinium toluene-*p*-sulfonate,[17] ceric ammonium nitrate[18] and $PdCl_2(CH_3CN)_2$.[19]

The use of iodine in methanol is a well-known method for the deprotection of cyclic acetals and thioacetals.[20] Recently, we reported that iodine in methanol selectively cleaves *p*-methoxybenzyl ethers in the presence of benzyl ethers.[21] There are many advantages to the use of iodine in methanol; no strongly basic or acidic conditions are used, nor are expensive reagents required, and no precautions need be taken to exclude moisture or oxygen from the reaction system.

The deprotection proceeds simply by the treatment of the compound with a 1% (*m*/*v*) solution of iodine in methanol at reflux temperature until TLC indicates that no starting material remains. The reaction is quenched by cooling and adding $Na_2S_2O_3$ to reduce the remaining iodine. The solvent is removed, the residue extracted into a suitable organic solvent, and the solution is washed with water and dried. Removal of the organic solvent affords the desired alcohol in high yield. Purification of the product can be achieved readily by column chromatography. The TBDMS ether is typically removed in 90–120 min. Some examples of the application of the method are given in Table 1; of note are the lack of acyl migration, particularly in entries 5 and 8, and the lack of any effect at the anomeric position in the case of entries 2–5 and 8. Entry 1 also provides another example of the selective cleavage of a *p*-methoxybenzyl (PMB) ether in the presence of a benzyl (Bn) ether, and is a reflection of the substantially longer time required for the cleavage of a PMB ether than a TBDMS ether.[21]

The mechanism for this cleavage is unclear. Many complex processes are known to occur with iodine in methanol,[22] thus, ascribing its mode of action to any one factor is difficult. A reasonable explanation may be that the combination of a Lewis

Table 1 Cleavage of TBDMS ethers by I_2 in MeOH

Entry	Starting material	Product[a]	*t*/h	Yield (%)
1			12	90
2			2	86
3			2	85
4			2	82
5			1.5	92
6			2	92
7			3	94
8			1.5	96

[a] All products were identified by ^1H and ^{13}C NMR spectroscopy.

acid-like species that polarizes the ether oxygen, and a trace amount of HI,[‡] which is known to be produced by the oxidation of methanol by iodine,[23] serves to effect easily the deprotection.

Regardless of the rationale of the iodine-in-methanol approach, it is clear that its simplicity, the low cost of reagents, and the ease of use make the method a very favourable process.

The authors thank the Natural Sciences and Engineering Research Council of Canada for financial support of this research.

Footnotes

[†] E-mail: szarekw@chem.queensu.ca

[‡] Accurate measurement of pH for solvents other than H_2O is difficult, and, thus, was not attempted; see, for example, V. Gold and S. Grist, *J. Chem. Soc., Perkin Trans. 2*, 1972, 89. The evolution of formaldehyde, under the reaction conditions has been demonstrated qualitatively.[21]

References

1 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd edn., Wiley, Toronto, 1991.
2 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.
3 K. K. Ogilvie, S. L. Beaucage, A. L. Schifman, N. Y. Theriault and K. L. Sadana, *Can. J. Chem.*, 1978, **56**, 2768; K. K. Ogilvie, A. L. Schifman and C. L. Penney, *Can. J. Chem.*, 1979, **57**, 2230.
4 E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, 1972, **94**, 2549.
5 J. H. Clark, *Chem. Rev.*, 1980, **80**, 429.
6 K. K. Ogilvie and D. W. Entwistle, *Carbohydr. Res.*, 1981, **89**, 203; S. S. Jones and C. B. Reese, *J.Chem. Soc., Perkin Trans. 1*, 1979, 2762.
7 A. H. Haines, *Adv. Carbohydr. Chem. Biochem.*, 1976, **33**, 11.
8 H. Wetter and K. Oertle, *Tetrahedron Lett.*, 1985, **26**, 5515.
9 B. W. Metcalf, J. P. Burkhart and K. Jund, *Tetrahedron Lett.*, 1980, **21**, 35.
10 E. J. Corey and K. Y. Yi, *Tetrahedron Lett.*, 1992, **33**, 2289.
11 A. S. Pilcher, D. K. Hill, S. J. Shimsock, R. E. Waltermire and P. DeShong, *J. Org. Chem.*, 1992, **57**, 2492.
12 W. V. Dahlhoff and K. M. Taba, *Synthesis*, 1986, 561.
13 K. Tanemura, T. Suzuki and T. Horaguchi, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2997.
14 E. J. Corey and G. B. Jones, *J. Org. Chem.*, 1992, **57**, 1028.
15 R. F. Newton and D. P. Reynolds, *Tetrahedron Lett.*, 1979, 3981.
16 J. F. Cormier, *Tetrahedron Lett.*, 1991, **32**, 187.
17 C. Prakash, S. Saleh and I. A. Blair, *Tetrahedron Lett.*, 1989, **30**, 19.
18 A. DattaGupta, R. Singh and V. K. Singh, *Synlett*, 1996, 69.
19 N. S. Wilson and B. A. Keay, *Tetrahedron Lett.*, 1996, **37**, 153; N. S. Wilson and B. A. Keay, *J. Org. Chem.*, 1996, **61**, 2918.
20 W. A. Szarek, A. Zamojski, K. N. Tiwari and E. R. Ison, *Tetrahedron Lett.*, 1986, **27**, 3827.
21 A. R. Vaino and W. A. Szarek, *Synlett*, 1995, 1157.
22 F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, 5th edn., Wiley, Toronto, 1988.
23 F. R. Cruickshank and S. W. Benson, *J. Phys. Chem.*, 1969, **73**, 733.

Received, 22nd July 1996; Com. 6/05107C