Letter

A mild and selective cleavage of *tert*-butyldimethylsilyl ethers by indium(III) chloride†

Jhillu S. Yadav,* Basi V. Subba Reddy and Chinnala Madan

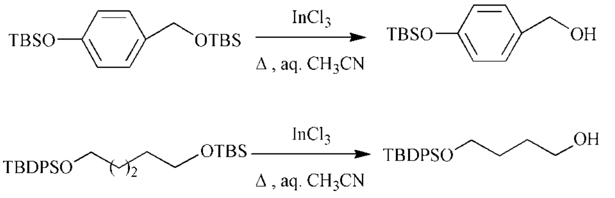
Organic Chemistry Division I, Indian Institute of Chemical Technology, Hyderabad, 500 007, India

Received (in Montpellier, France) 19th June 2000, Accepted 27th July 2000
First published as an Advance Article on the web 6th October 2000

Alkyl *tert*-butyldimethylsilyl ethers are selectively deprotected to the corresponding alcohols in high yields for the first time by indium(III) chloride in refluxing aqueous acetonitrile. Several functional groups like OBn, Boc, CBz, OBz, O-allyl, OTBDPS, OAc, OMe, ethers, esters and olefins present in the substrate are unaffected.

The strategy of protecting a hydroxy group and subsequently deprotecting it is frequently used in the multi-step synthesis of complex natural products.[1] Among various hydroxy protective groups, *tert*-butyldimethylsilyl (TBS) ethers are the most versatile[2] due to their ease of installation/removal and also to their stability under basic or mildly acidic conditions. A variety of reagents[3–10] are employed for their cleavage under various reaction conditions. Furthermore, a few methods[11] are reported for the selective cleavage of alkyl TBS ethers over aryl TBS ethers. Many of these methods involve acidic, basic, reducing or oxidizing conditions that limit their efficiency. However, in spite of their potential utility, these methods often encounter some disadvantages like unsatisfactory yields, incompatibility with other functional groups, long reaction times and the use of large quantities of polar solvents such as DMSO, DMF and HMPA, which require tedious aqueous work-up. Consequently, the development of new reagents that are more efficient and lead to convenient procedures and better yields is desirable. In recent years indium(III) chloride mediated transformations[12] have received considerable attention due to its stability and recoverability from water.

In continuation of our interest in the applications of indium for various transformations,[13] herein we report a new, efficient and practical method for the selective cleavage of TBS ethers using indium(III) chloride in aqueous acetonitrile. The cleavage was effected by a catalytic amount of $InCl_3$ in refluxing aqueous acetonitrile with high chemoselectivity. The procedure is highly selective to cleave alkyl TBS ethers over TBDPS (the diphenylsilyl) and aryl TBS ethers (Scheme 1). Such selectivity is a highly desirable feature in the cleavage of silyl ethers, offering various beneficial prospects in organic synthesis. It is of interest to note that longer reaction times (6–10 h) and the use of a large quantity of catalyst (50%) cleaves aryl TBS ethers in fairly good yields whereas TBDPS ethers are unaffected under similar conditions. It indicates the selectivity among alkyl and aryl TBS ethers. TBDPS ethers did not cleave under the present reaction conditions even by increasing reaction time or amount of catalyst. Furthermore, a catalytic amount of indium(III) chloride (10% w/w of ether) in refluxing acetonitrile–water (1 : 1) smoothly deprotected primary alkyl TBS ethers, leaving secondary alkyl TBS ethers intact (Table 1, entry i). Such selectivity can be applied in synthetic sequences in which two protected hydroxy groups must be unmasked at different stages of the synthesis. The alkyl TBS ethers are deprotected in high yields (75–93%) within 0.5–3 h reaction time. The cleavage required relatively longer reaction times with hydrated indium(III) chloride to afford yields comparable to those obtained with anhydrous indium(III) chloride. The reaction conditions are compatible with various functional groups like Boc, Cbz, O-allyl, OBz, OTBDPS, OAc, OBn, ethers and olefins present in the molecule.



Scheme 1

In conclusion, this letter describes a mild and efficient procedure using indium(III) chloride for the selective removal of alkyl TBS ethers over TBDPS and aryl TBS ethers. The method offers several advantages like mild reaction conditions, greater selectivity, compatibility with other acid-sensitive functional groups and high yields of the desilylated products, which makes it a useful addition to the existing methods.

Experimental

General procedure for the cleavage of alkyl TBS ethers

A mixture of alkyl TBS ether (10 mmol) and indium(III) chloride (1 mmol) and in acetonitrile–water (1 : 1, 20 ml) was stirred under reflux for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mass was diluted with water (10 ml) and extracted twice with ether (2 × 25 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2 : 8) to give pure alcohol.

Entry d. *Silyl ether*: liquid. ^1H NMR ($CDCl_3$): δ 0.05 (s, 6H), 0.85 (s, 9H), 1.05 (s, 9H), 1.25–1.35 (m, 2H), 1.45–1.55 (m, 4H), 3.55–3.65 (m, 4H), 7.45–7.65 (m, 10H, Ar-H). *Alcohol*: 1.05 (s, 9H), 1.25–1.35 (m, 2H), 1.45–1.55 (m, 4H), 2.5 (br s, OH), 3.55–3.65 (m, 4H), 7.45–7.65 (m, 10H, Ar-H).

Entry m. *Silyl ether*: ^1H NMR ($CDCl_3$): δ 0.05 (s, 6H), 0.15 (s, 6H), 0.85 (s, 9H), 0.95 (s, 9H), 4.55 (s, 2H), 6.7 (d, 2H, $J = 7.8$ Hz), 7.15 (d, 2H, $J = 7.8$ Hz). *Alcohol*: 0.05 (s, 6H), 0.80 (s, 9H), 1.5 (br s, OH), 4.35 (s, 2H), 6.55 (d, 2H, $J = 7.8$ Hz), 7.0 (d, 2H, $J = 7.8$ Hz).

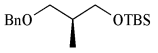
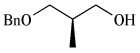
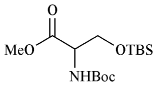
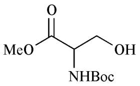
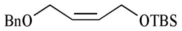
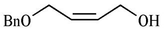
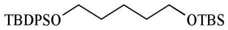
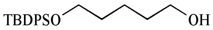
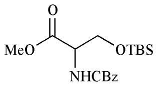
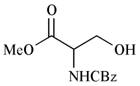
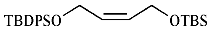
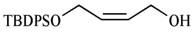
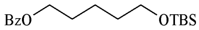
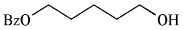
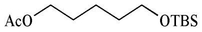
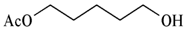
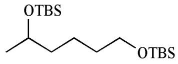
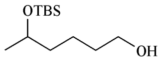
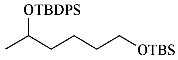
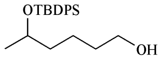
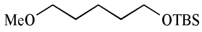
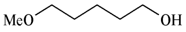
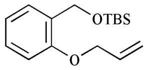
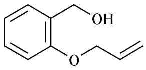
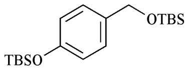
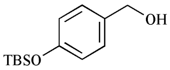
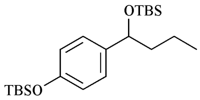
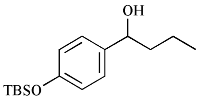
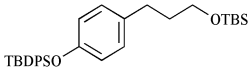
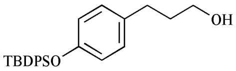
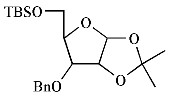
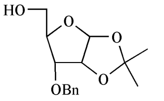
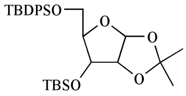
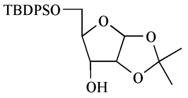
---

† IICT Communication No. 4515.

DOI: 10.1039/b004937i

This journal is © The Royal Society of Chemistry and the Centre National de la Recherche Scientifique 2000

Table 1 Indium(III) chloride catalyzed selective cleavage of TBS ethers

Entry	Silyl ether	Product[a]	Reaction time/h	Yield (%)[b]
a			2.0	90
b			3.0	87
c			0.5	91
d			0.5	89
e			3.0	93
f			1.0	88
g			1.5	84
h			0.5	81
i			0.5	75[c]
j			1.5	90
k			1.0	85
l			2.0	91
m			0.5	78
n			0.5	82
o			1.5	90
p			2.5	85
q			3.0	87

[a] All products were characterized by ^{1}H NMR and IR spectra. [b] Isolated yields after purification. [c] Secondary alkyl TBS ether was deprotected after 6 h reaction time.

Acknowledgement

B.V.S. thanks CSIR, New Delhi for the award of a fellowship.

References

1 D. Nelson and R. D. Crouch, *Synthesis*, 1996, 1031.
2 (*a*) T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, 3rd edn., Wiley, New York, 1999; (*b*) P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, 1994.
3 (*a*) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190; (*b*) E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, 1972, **94**, 2549.
4 S. Kawahara, T. Wada and M. Sekin, *Tetrahedron Lett.*, 1996, **37**, 509.
5 A. S.-Y. Lee, H.-C. Yeh and J. J. Shie, *Tetrahedron Lett.*, 1998, **39**, 5249.
6 (*a*) J. Farras, C. Serra and J. Vilarrasa, *Tetrahedron Lett.*, 1998, **39**, 327; (*b*) G. Maiti and S. C. Roy, *Tetrahedron Lett.*, 1997, **38**, 495.
7 G. Bartori, M. Bosco, E. Marcantoni, L. Sambri and E. Torregiani, *Synlett*, 1998, 209.
8 B. C. Ranu, U. Jana and A. Majee, *Tetrahedron Lett.*, 1999, **40**, 1985.
9 (*a*) E. J. Corey and G. B. Jones, *J. Org. Chem.*, 1992, **57**, 1028; (*b*) J. F. Cormier, *Tetrahedron Lett.*, 1991, **32**, 187.
10 (*a*) D. A. Gupta, R. Singh and V. K. Singh, *Synlett*, 1996, 69; (*b*) K. Tanemura, T. Suzuki and T. Horaguchi, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2997.
11 (*a*) E. W. Collington, H. Finch and I. J. Smith, *Tetrahedron Lett.*, 1985, **26**, 681; (*b*) T. Oriyama, Y. Kobayashi and K. Noda, *Synlett*, 1998, 1047; (*c*) B. H. Lipshutz and J. Keith, *Tetrahedron Lett.*, 1998, **39**, 2495; (*d*) P. A. Gricco and C. J. Markworth, *Tetrahedron Lett.*, 1999, **40**, 665.
12 G. Babu and P. T. Perurnal, *Aldrichimica Acta*, 2000, 331 and references cited therein.
13 (*a*) J. S. Yadav, B. V. Subba Reddy and M. Muralidhar Reddy, *Tetrahedron Lett.*, 2000, **41**, 2623; (*b*) J. S. Yadav, B. V. Subba Reddy and G. S. Kiran Kumar Reddy, *Tetrahedron Lett.*, 2000, **41**, 2629.