Pergamon

Tetrahedron Letters 39 (1998) 2495–2498

TETRAHEDRON LETTERS

SELECTIVE DEPROTECTION OF ALKYL *vs.* ARYL SILYL ETHERS

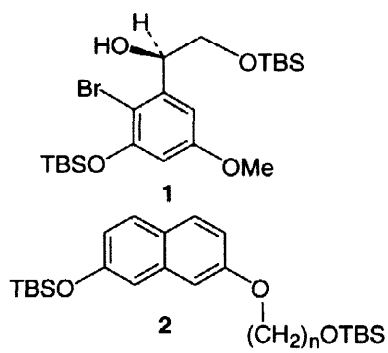
Bruce H. Lipshutz* and John Keith
Department of Chemistry
University of California
Santa Barbara, CA 93106

[Fax: 805-893-8265; E-Mail: Lipshutz@chem.ucsb.edu]

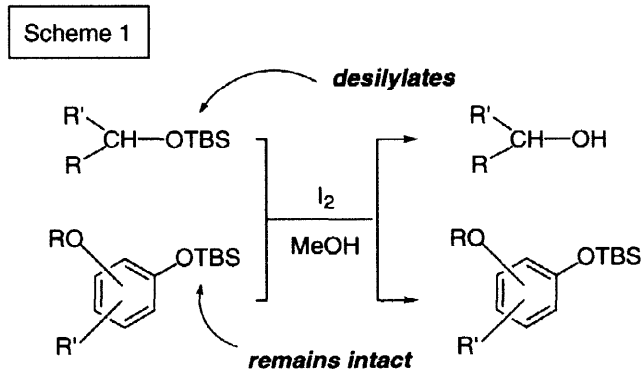
Received 12 December 1997; revised 4 February 1998; accepted 11 February 1998

Abstract. *Alkyl silyl ethers, in particular t-butyldimethylsilyl derivatives, can be selectively cleaved in high yields over aryl silyl ethers using small percentages of I_2 in MeOH at ambient temperatures.* © 1998 Elsevier Science Ltd. All rights reserved.

In the course of preparing various intermediates associated with projects involving biaryl couplings, we were faced with the prospects of removing alkyl *t*-butyldimethylsilyl (TBS) ethers in the presence of aryl TBS derivatives, such as in educts **1** (relating to vancomycin)[1] and **2** (associated with new *cyclo*-BINOLs).[2] To our knowledge, only aqueous 40% HF in CH_3CN is known to effect a selective deprotection of this type.[3] However, a highly acidic medium presents obvious limitations in terms of functional group compatibility. In searching for reagents known to cleave silyl ethers, we were drawn to a recent report describing the use of iodine in methanol, conditions which tolerate acid-labile residues.[4] We were delighted to find, as we now report, that this combination is especially effective for the *selective* unmasking of alkyl TBS ethers over even highly electron-rich TBS aryl ethers (Scheme 1).



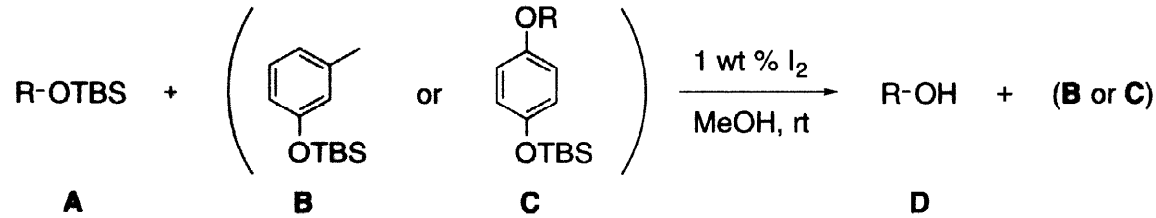
Scheme 1

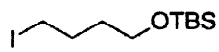
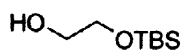
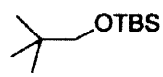
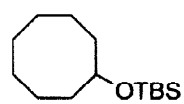
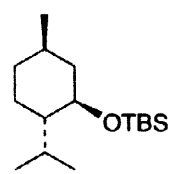


Initially, competition experiments (Table 1) were performed by mixing equal amounts of an alkyl (**A**) and aryl (**B** or **C**) TBS ether in methanol containing 1% by weight I_2. Upon consumption of the former (usually ≤ 2 h at 0.1 M) as indicated by TLC, the product alkanol (ROH, **D**) was isolated along with recovered aryl ether. In general, very high yields of **D** were realized. Only in the case of *hindered* alkyl TBS ethers **3** and **5** was recovery of the hydroquinone *bis-*

0040-4039/98/$19.00
PII: S0040-4039(98)00381-5

Table 1. Competition experiments between alkyl and aryl TBS ethers.



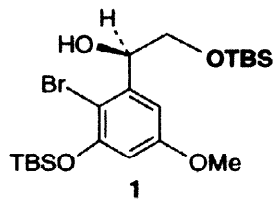
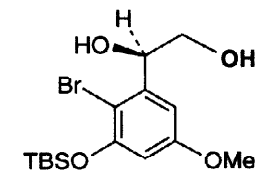
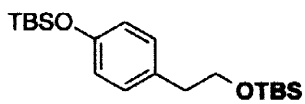
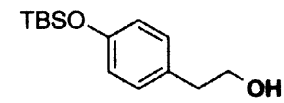
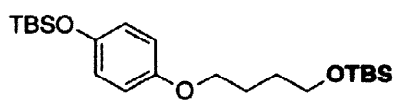
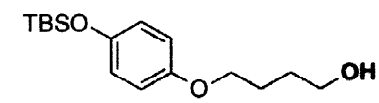
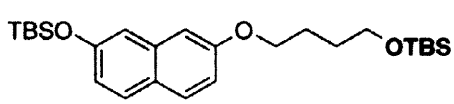
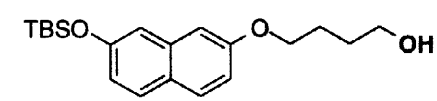
alkyl ether **A**	aryl ether **B** or **C** R = *n*-Bu	reaction time (h)	isolated yield of alcohol **D** (%)[a]	recovery of aryl ether (%)[a]
	**B**	1	b	83
	C	1	b	90
	**B**	2	b	98
	C	2	b	93
 **3**	**B**	5	b	98
	C	4.5	b	56
 **4**	**B**	1	98	quant
	C	1	91	98
 **5**	**B**	5.7	96	87
	C	4	97	56

[a]Isolated, chromatographically purified material. [b]Not attempted due to water solubility of the product alcohol.

ether **C** compromised. Hydrolysis of unhindered secondary TBS ethers (*e.g.*, **4**), as with primary alkanols, proceeded as expected without competing aryl TBS ether cleavage. Treatment of aryl TBS ether **C** (R = Me) *alone* under these conditions produced the corresponding phenol in 99% yield, although the process required over 13 h. By contrast, aryl ether **B**, which is less electron-rich than is **C**, was converted to the phenol to the extent of only 33% after 22 h. Taken together, these data support the premise that an electrophilic species (*e.g.*, H-I)[5] is responsible for these transformations.

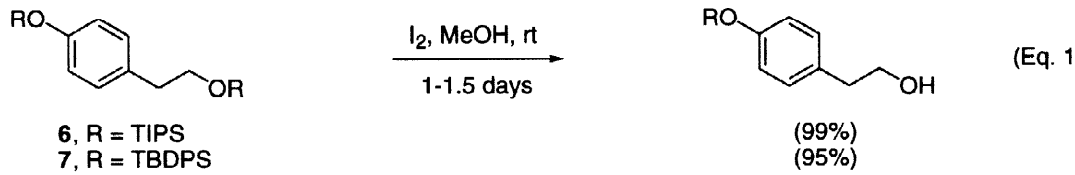
Intramolecular competition studies were particularly informative. Four examples, illustrated in Table 2, reflect varying degrees of complexity as well as electron rich character to the aromatic rings. In all cases, independent of the aryl moiety and substitution pattern, monodesilylation of the *alkyl* TBS ether ensued.

Table 2. Selective deprotections of *bis*-TBS diethers *via* I_2 in MeOH at room temperature.[a]

TBS diether	time / yield	product alkanol[b]
 **1**	5.7 h (97%)	
	2.7 h (95%)	
	45 min (quant)	
	50 min (97%)	

[a]All reactions were conducted using the typical procedure provided (*cf.* ref. 9). [b]Yield of isolated, pure material.

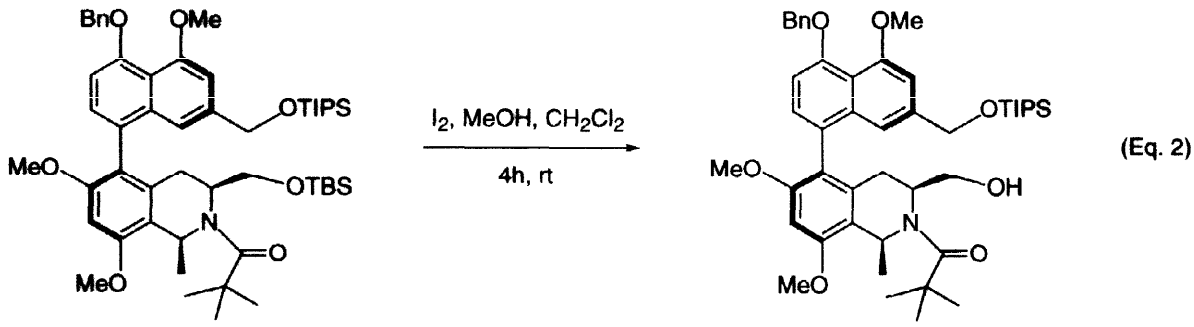
Extensions of this method to *bis*-triisopropylsilyl (TIPS) and *bis*-*t*-butyldiphenylsilyl (TBDPS) ethers were also investigated using model substrates **6** and **7**. Although complete desilylation of the alkyl TIPS and TBDPS ethers required between 1-1.5 days for completion, neither of the aryl silyl ethers was lost and close to quantitative yields of the monoprotected phenethyl alcohols were isolated (Equation 1).



6, R = TIPS (99%)
7, R = TBDPS (95%)

(Eq. 1)

Lastly, it has also been found that these deprotection conditions will discrimminate between silyl protecting groups within the alkyl ether series. For example, the TBS ether in korupensamine derivative **8** (related to the michellamines),[6] could be cleaved with 100% selectivity to give alcohol **9** in close to quantitative yield (Equation 2).[7]



(Eq. 2)

8 **9** (99%)

In summary, the use of I_2 in MeOH has been identified as an extremely effective means of selectively removing alkyl TBS ethers in the presence of aryl TBS ethers. Just what the active agent is in this chemistry is not known with certainty, given the complexity of events surrounding the dissolution of iodine in this alcoholic medium.[8] Nonetheless, the mild conditions, high yields, and demonstrated applicability to complex, highly functionalized molecules suggests that this protocol will find utility in synthesis.[9]

Acknowledgement. We warmly thank the NIH (GM 40287) for continued support of our programs.

References and Notes

1. Evans, D.A.; Dinsmore, C.J.; Ratz, A.M.; Evrard, D.A.; Barrow, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 3417; Nicolaou, K.C.; Chu, X-J.; Ramanjulu, J.M.; Natarajan, S.; Brase, S.; Rubsam, F.; Boddy, C.N.C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1539.
2. Lipshutz, B.H.; James, B.; Vance, S.; Carrico, I. *Tetrahedron Letters* **1997**, *38*, 753.
3. Collington, E.W.; Finch, H.; Smith, I.J. *Tetrahedron Letters* **1985**, *26*, 681.
4. Vaino, A.R.; Szarek, W.A. *J. Chem. Soc., Chem. Commun.*,**1996**, 2351.
5. In a control experiment, treatment of a disilyl ether (Table 2, entry 2) in MeOH at 0.1 M with 1 drop of 47% aqueous HI at rt led to complete monodeprotection in <5 min, along with some (<5%) dideprotected material. This supports the notion that I_2 in MeOH is slowly releasing HI into the medium, and hence, may well be effecting these selective deprotections. The 'pH' (water-wet indicator paper) for this HI/MeOH solution is 2-3, while that for I_2/MeOH is *ca.* 5.
6. Hallock, Y.F.; Manfredi, K.P.; Dai, J-R.; Cardellina, J.H.; Gulakowski, R.J.; McMahon, J.B.; Schaffer, M.; Stahl, M.; Gulden, K-P.; Bringmann, G.; Francois, G.; Boyd, M.R. *J. Nat. Prod.*, **1997**, *60*, 677, and references therein.
7. For this substrate, it was necessary to use CH_2Cl_2 (*ca* 20%) as a co-solvent, which seems to have no effect on the efficiency of silyl ether cleavage.
8. Cruickshank, F.R.; Benson, S.W. *J. Phys. Chem.* **1969**, *73*, 733.
9. *General procedure:* Equimolar amounts of aryl and alkyl TBS ethers were added to a round bottomed flask and diluted to 0.1 M concentration in methanol. Once the substrates dissolved, 1 wt% (10 mg/mL) of I_2 was added. Reaction progress was monitored by TLC. Upon consumption of the alcoholic silyl ether, solid $Na_2S_2O_3$ was added and the heterogeneous mixture stirred until the iodine color had dissipated. The methanolic solution was then diluted with methylene chloride and washed with saturated aqueous $NaHCO_3$ and then brine (x 2). Drying over anhydrous $MgSO_4$, filtering, and evaporation to dryness gives material that was then purified by flash column chromatography.