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On the Chemoselectivity and Mechanism of Desilylation of *tert*-Butyldimethylsilyl ethers with TMSOTf

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Abstract: A modified literature procedure is presented for desilylating primary and secondary *tert*-butyldimethylsilyl ethers involving TMSOTf followed by breakdown of the *bis*-silyloxonium ion in methanol. The chemoselectivity of the process with respect to TBDPS, TIPS, MEM, ester, ketal, acetate, benzoate and NBoc functionalities has been evaluated, and a mechanism involving intermediacy of a transient *tert*-butyldimethylsilylium ion is proposed.

Keywords: Deprotection; silyl ether; mechanism.

Chemoselective protection/deprotection reactions continue to be developed as organic synthesis strives for ever-increasing levels of efficiency. In this regard, the popular *tert*-butyldimethylsilyl ether (TBS) for hydroxyl group protection has generated a significant number of methods,[1-3] but levels of chemoselectivity, particularly towards other similar groups, *eg* TIPS, are not always satisfactory and mechanistic rationalisation is invariably absent. A few years ago we noticed[4] that the reagent combination $BH_3 \cdot SMe_2$ / TMSOTf deprotected *tert*-butyldimethylsilyl ethers in CH_2Cl_2 at -78°C and we were intrigued as to whether this was a reductive or hydrolytic (aq $NaHCO_3$ work-up) deprotection reaction. More recently, in conjunction with chemoselective deprotection of a malic acid-derived intermediate for which lactonisation following deprotection was a problem, we decided to revisit the TMSOTf-mediated reaction. Investigation of the literature revealed two papers reporting the use of TMSOTf in conjunction with TBS group deprotection. In 1986, Dahlhoff[5] reported the use of catalytic TMSOTf in conjunction with tetraethyldiboroxane as reagent, while in 1990 Bou and Vilarrasa[6] published a short communication on the use of TMSOTf as reagent in CH_2Cl_2 in which they used addition of neutral alumina followed by a filtration through alumina for isolation of the product. In this communication we report on a modified procedure of Bou and Vilarrasa's original work which we have used to develop the chemoselectivity profile of the reaction, as well as allowing us to comment on mechanistic aspects of the process. In our hands, we have found that a convenient experimental procedure for breakdown of the intermediate *bis*-silyloxonium ion is to add methanol (equal volume to solvent). Subsequent addition of triethylamine (homogeneous medium) or aqueous sodium carbonate in order to neutralise the acidic medium, followed by a work-up afforded crude material for chromatography. This procedure deprotects primary and secondary *tert*-butyldimethylsilyl ethers in a chemoselective manner at -78°C and -40°C respectively, Scheme 1.

Scheme 1

$$\text{ROTBS} \xrightarrow{\text{(i) - (iii)}} \text{ROH}$$

(i) TMSOTf (2eq) / CH_2Cl_2 / -78°C
(ii) MeOH (excess) / -78°C
(iii) NEt_3 ; aq. $NaHCO_3$

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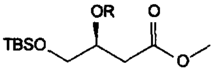
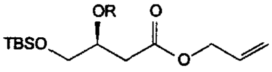
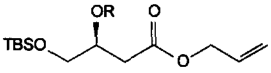
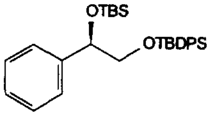
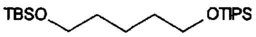
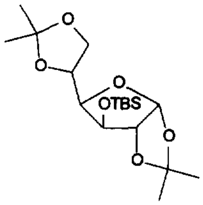
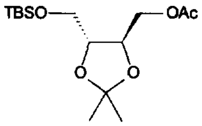
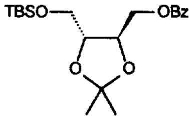
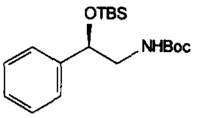
TABLE 1

Entry	Substrate	Conditions[a]	Product : St. Material[b]
1	 R = TBDPS	2 eq / -78°C	67 : 20[c]
2	 R = TBDPS	2 eq / -78°C	77 : 15[d]
3	 R = MEM	2 eq / -78°C	72 : 23
4		2 eq / -40°C	81 : 12
5		2 eq / -78°C	68 : 24[e]
6		12 eq / -40°C	46 : 47
7		2 eq / -78°C 2 eq / -40°C	65 : 28 70 : 17
8		4 eq / -78°C 4 eq / -40°C	83 : 14 91 : 9
9		2 eq / -40°C	24 : 75[f]

a: eq. refers to TMSOTf ; b: all yields were after column chromatography; c: with 12% trans-silylated product (see Scheme for Table 2); d: with 3% lactone and 5% trans-silylated product; e: < 4% with TIPS removed and TBS intact by HPLC; f: a higher temperature than -40°C resulted in NBoc deprotection.

Methanol proved to be the best protic medium for desilylation and did not result in transesterification or ketal exchange reactions at the temperatures studied (up to -40°C), an aspect of chemoselectivity not addressed in the original work.The results of applying this methodology to a number of substrates are shown in Table 1 in which both primary and secondary ethers were tested as well as the chemoselectivity with respect to TBDPS, TIPS, ester, ketal, MEM, acetate, benzoate and NBoc functionalities. Several points deserve mentioning. At a workable level for small scale work of two equivalents of Lewis acid, unreacted silyl ether was always obtained which was easily separated by chromatography from the more polar product alcohol. The primary silyl ethers could be desilylated at –78°C, while the secondary substrates required -40°C for maximum conversion. All of the aforementioned functional groups were stable under the reaction conditions except the NBoc group (entry 9) at -40°C. A notable case of chemoselectivity was that involving the TIPS ether (entry 5). Desilylation of the malic acid-derived allyl ester using our conditions was compared to three other popular methods,[7-9] all of which are known to be chemoselective for a TBS group in the presence of a TBDPS group. The results shown in Table 2 reveal that the TMSOTf method rates as the second best in terms of degree of unwanted lactonisation and trans-silylated by-products. However, it is by far the quickest of the methods.

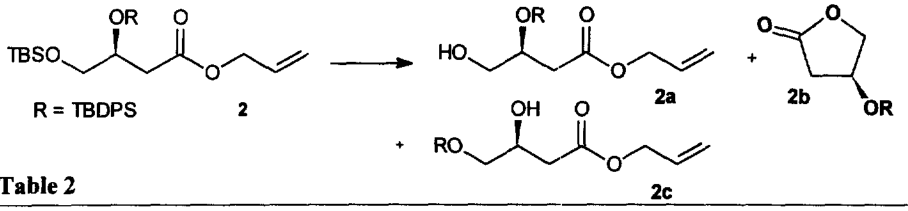


Table 2

Conditions	% Yield 2 (st mat)	2a (product)	2b (lactone)	2c
HF (trace) / CH_3CN / RT / 4 days [7]	4	88	3	0
TMSOTf ; MeOH / CH_2Cl_2 / -78°C	15	77	3	5
AcOH / THF / H_2O / 65°C / 6h[8]	15	72	11	0
PPTS / EtOH / 60°C / 6h[9]	40	39	10	5

A number of experiments involving changing the order of addition of reactants were carried out in order to gain some mechanistic insight into the reaction. As seen in Scheme 2, premixing the TMSOTf with methanol either stoichiometrically or in excess prior to addition of ROTBS resulted in no observable desilylation. We consider these results to be highly significant in that they provide strong evidence against protonated MeOTMS, protonated MeOH or triflic acid being responsible for desilylation via a reversible equilibrium involving a *bis*-silylated oxonium ion and methanol in which eventual attack would be on the TBS group, attack on the TMS group being initially preferred on steric grounds. Omission of the methanol using the desilylation conditions shown in Scheme 1 (NEt_3 quench) also resulted in only starting material being obtained indicating that methanol is crucial to to the oxonium ion breakdown and that the species in the flask after addition of TMSOTf is indeed the oxonium ion and not trans-silylated material.

$$\text{(a) or (b)} \xrightarrow[\text{(ii) NEt}_3]{\text{(i) ROTBS / CH}_2\text{Cl}_2} \textbf{NO REACTION}$$

(a): (i) TMSOTf (2 eq) / -78°C / CH_2Cl_2 ; MeOH (2.2 eq)

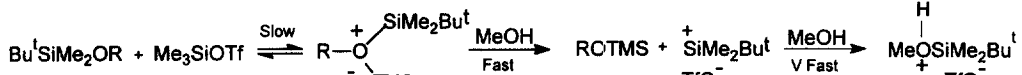
(b): (i) TMSOTf (2 eq) / -78°C / CH_2Cl_2 ; MeOH (excess)

Scheme 2

Mechanistically, we consider these results to be most conveniently explained by a reaction sequence involving silylation of the ether by TMSOTf to give a *bis*-silyloxonium ion which undergoes heterolytic fission with loss of a *tert*-butyldimethylsilylium ion ($S_N1$mechanism) on addition of the protic, poorly nucleophilic methanol.

The reduction in product yield to 20% (remainder starting material) when using 2 equivalents of methanol rather than excess (equal volume to solvent), and in which the ionicity of the medium is thus lowered supports an S_N1 mechanism. The silylium ion would be extremely transient and rapidly intercepted by methanol; however, desilylation of the oxonium ion via an S_N2 mechanism or one which involves coordination to silicon[10] prior to silicon-oxygen bond cleavage would result in preferential loss of the trimethylsilyl group back to starting material in view of steric considerations.[11] Hydrolysis of the TMS ether on work-up then produces the product alcohol. Scheme 3.

Scheme 3



Although the existence of silylium ions (R_3Si^+) in solution has been the topic of much controversial debate,[12] it is generally accepted that difficulty in observing them is due to their high kinetic reactivity rather than low thermodynamic stability; in fact they are thermodynamically more stable than their carbon counterparts, and in this case the ion would be stabilised by the t-butyl group. Complete silylation in step 1 of the mechanism requires a significant amount of Lewis acid (compare entries 7 and 8) as reported by the Spanish group, and at a two equivalent loading some starting material is inevitable. However, the high yield of desilylated product at high Lewis acid loading as reported both by us (entry 8) as well as the Spanish group indicates that exclusive loss of the TBS group in preference to the TMS group is likely to be operating, and that starting material is observed only as a result of incomplete silylation and not competitive loss of the TMS group via nucleophilic attack by methanol. Similarly, the origin of chemoselectivity in the TIPS/TBS case (entry 5) would appear to be in the silylation step. The poor conversion of the sugar derivative even with a large number of equivalents of TMSOTf can be explained by preferential silylation of the ketal oxygens, indicating that this is not the reagent of choice for polysaccharide targets. We consider this mechanistic picture to be of benefit to the design[13] of superior chemoselective desilylating reagents which avoid large quantities of activating (silylating) agent.

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