Bromine in Methanol: An Efficient Reagent for the Deprotection of the *tert*-Butyldiphenylsilyl Group

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Abstract: A selective reagent for the deprotection of a *tert*-butyldiphenylsilyl (TBDPS) ether in the presence of other protecting groups, using a solution of bromine in methanol under reflux is presented. By extension, this reagent has been introduced for the deprotection of TBDPS amines and esters and has also shown good selectivity in the removal of a TBDMS ether in the presence of a TBDPS one.

Key words: *tert*-butyldiphenylsilyl (deprotection of), TBDPS, silyl ether, silylamine, silyl ester

Since its introduction by Hanessian¹ in 1975, the *tert*-butyldiphenylsilyl (TBDPS) group has become a standard in the protection of the alcoholic hydroxyl function.²⁻⁴ Its great bulkiness induces a good selectivity in the protection of one hydroxyl group in the presence of more hindered ones, but also a good resistence to nucleophilic attack or other chemical reactions. Furthermore, the use of TBDPS has been extended^{3,5,6} to the protection of phenols, amines, carboxylic acids, amides and other functional groups. The different possibilities for the cleavage of the TBDPS group in multiply functionalized substrates are primordial in synthetic chemistry. Generally, the cleavage of TBDPS derivatives can be achieved by the same methods as for the very similar TBDMS group and TBDPS groups can be easily cleaved without affecting other nonsilvlated groups. As a general rule, most of the methods for the deprotection of silvl ethers are based on the affinity of silicon for fluorine, or of a strongly acidic or basic hydrolysis. For the first method, the most common source of fluoride ions is lipophilic tetrabutylammonium fluoride (TBAF), which cleaves silvl groups rapidly at room temperature without affecting most other protecting groups. Unfortunately, the high basicity of fluoride, particularly under anhydrous conditions, can affect base-sensitive molecules adversely and has been responsible of acyl migrations in numerous exemples. The deprotection of TB-DPS ethers by acidic hydrolysis, as opposed to acidic fluorolysis, is normally carried out with 1-5% alcoholic hydrochloric acid.^{1,7-9} Another method with trifluoroacetic acid requires higher temperatures and longer reaction times.¹⁰ In general, the methods used for the desilylation of TBDPS ethers, as described in the literature, often required long reaction times and/or forcing conditions (particularly during acidic hydrolysis), and are most of the time accompanied by acyl migration where possible.

Recently we have studied the use of selective silylation/ desilylation¹¹ and we required a selective method for the deprotection of a TBDPS group in the presence of benzoates, without benzoyl migration. As the recent method of Vaino and Szarek¹² (using iodine in methanol at reflux for the deprotection of a TBDMS group) was not applicable to the bulkier TBDPS ether, we have managed to deprotect the silyl ether by treatment with a solution of the smaller halogen, bromine in methanol.

The reaction procedure consists simply of the treatment of the silvl ether with a solution of X% bromine in methanol (see Table for the number of equivalents of bromine and the dilution m/v of the solution) under reflux. When TLC showed no more initial compound, the remaining bromine was reduced by a solution 5% of Na₂S₂O₃. The standard treatment was then to extract the product with dichloromethane, to dry the organic layers and to concentrate. A purification by silica-gel chromatography or by distillation gave the pure product. In the case of very polar products (entries 1, 3 and 9), after neutralisation the overall was concentrated and a part of the resulting crystals was redissolved in an apropriate solvent. Filtration and evaporation of the solvent furnished an oil which was purified by chromatography. By varying the reaction time, the number of equivalents of bromine and the concentration of bromine in methanol, we have managed to obtain from good to excellent yields of deprotection. As an example, only thirty minutes of reflux are necessary for the obtention of the 1,2-ethanediol (entry 1) with 3.0 equivalents of bromine (1.0% solution in methanol) in 99%-yield. Three hours were needed to obtain the same yield with only 0.5 equivalents of bromine (solution 1.0% in methanol). In the presence of other protective groups, it was advantageous to decrease the percentage of bromine in the solution (entries 2, 4). Other groups such as methyl ester (entry 3), methyl ether (entries 8, 9), benzyl (entry 4), tosylate (entry 2), benzoate (entries 5, 8) or tri-O-methyl gallate (entry 6) are stable under the conditions of deprotection. In particular, we noted the absence of migration of the benzoate (entries 5, 8) or tri-O-methyl gallate (entry 6) groups¹³ and the conservation of stereochemistry at other hydroxyl groups (entry 3). Furthermore, the short reaction times and the mild conditions allowed us to work with disaccharides such as a protected sucrose (entries 4-7) without notable degradation of the glycosidic link. Entry 9 provides another example of the selective cleavage of a

Entry ^a	Initial	Product	Time (min)	(% MeOH)	Yield ^b
I		но	180 30	0.5 (1.0%) 3.0 (1.0%)	99% 99%
2		OTs OH	45 60	1.0 (1.0%) 1.0 (0.3%)	71% 94%
3		мео он	90	1.0 (0.4%)	88% ^c
$\frac{4}{R = Bn}$	RO	RO-	25 20	1.0 (0.3%) 1.0 (0.4%)	85% 64%
5 R = Bz			360	0.4 (1.0%)	69%
6 R = Gal(OM	e) ₃ RO		360	1.0 (0.1%)	74%
7	TBDPSO BZO TBDPSO BZO BZO OTBDMS BZO	TBDPSO BZO TBDPSO BZO BZO OH BZO	180*	10.0 (4.0%) RT	84%
8	TBDPS O OBZ BZ O BZ O BZ O		60	1.0 (0.4%)	92%
9	TBDPSO PBON OMB BOMO BOMO		20	1.7 (0.4%)	99%
10	NHTBDPS	NH ₂	24 hours	1.5 (1.5%)	95%
11	M602C CO2TBDPS	MeO ₂ C ^{CO₂Me}	20	1.0 (0.5%)	84%

TableDeprotection of the silyl group

^a All reactions were carried out under reflux, except entry 7 (room temperature).

^b All the products have physical characteristics which are in accordance with the previously reported values.

^c The enantiomeric purity of the product was determined by comparison of the specific rotation of the pure product with that reported in the literature.

BOM ether in the presence of a methyl ether. We also studied the possibility of deprotection of a TBDMS ether in the presence of TBDPS ethers and benzoate esters (entry 7) without migration of these latter, by running the reaction at room temperature and using a more concentrated solution of the reagent. The scope of this reagent was extended to the deprotection of silyl amines and silyl esters, we have obtained the corresponding amine (entry 10) and the unexpected symmetric dimethyl ester (entry 11), respectively. In conclusion, we have shown the utility of the solution of bromine in methanol for the deprotection of a TBDPS group (ether, ester or amine; reaction under reflux) or a TBDMS ether (reaction at room temperature). The reagent is inexpensive, used in diluted solutions and no particular precautions have to be taken to avoid moisture from the air. Added to this, the conservation of stereochemistry and the absence of migration of acyl groups make this reagent a very useful alternative method for the removal of the silyl group from heteroatoms.

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References and Notes

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