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Deprotection of *t*-butyldimethylsilyl ethers promoted by cerium(IV) triflate

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Abstract—*t*-Butyldimetylsilyl ethers are mildly cleft by catalytic amounts of cerium(IV) triflate. Dependence from water amount was observed. © 2002 Elsevier Science Ltd. All rights reserved.

The chemical manipulation of complex polyfunctional molecules often requires the sequential protection and deprotection of the various functionalities. Silyl ethers have attained a position of prominence in the area of hydroxyl group protection due to their easy formation and removal and their stability to a wide range of reagents and reaction conditions.[1] Among silyl ethers, *t*-butyldimethylsilyl (TBS) is the most popular because it can be easily installed in high yields and is robust to a variety of reaction conditions.[1] There are several methods for the deprotection of TBS ethers, which involve basic, reducing, oxidizing, high-temperature conditions,[2] which are the limitation and the usefulness of this protecting group at the same time.

Recently, stoichiometric amounts of cerium salts, namely $CeCl_3$/NaI mixture, have been proved useful in promoting under neutral conditions deprotections which need acid catalysts,[3] among them, silyl ethers, too have been deprotected.[4]

In conjunction with another ongoing project in our laboratory, the synthesis of oligo- nucleotides and saccharides, we focused on the goal to deprotect hydroxyl functionality with cerium salt in catalytic amounts.

Commercial cerium(IV) triflate was found to be useful in this endeavor. In fact, at room temperature, in acetonitrile, a 10% molar amount of this salt is able to deprotect *t*-butyldimethylsilyloxyoctane (**1**) and *t*-butyldimethylsilyloxybenzene (**2**) in high yields in 5 and 30 min, respectively.[5] We used commercial products and solvents without purification.

Dry solvents or dry salts[6] in fact resulted in lower yields, while low temperature slowed down the reaction rate. Deprotections of many TBS ethers were performed (Table 1). Aromatic ethers are cleft more slowly than primary or secondary aliphatic and allyl ones. A strong dependence from electronic and steric factors was found in aromatic ethers. Electron withdrawing and/or *ortho* substituents slower the reaction rate.

In order to establish the chemoselectivity of the method, other octyl ethers (**3**–**6**) were allowed to cleave in acetonitrile in the presence of catalytic amounts of cerium(IV) triflate (Table 2).

Table 1. Deprotection of TBS ethers to alcohols in acetonitrile at room temperature

Entry	Ether	Time (h)]	Yield (%)
1	1-$TBSOC_8H_{17}$	0.08	95
2	3-$TBSOC_8H_{17}$	0.08	94
3	AllylOTBS	0.08	86
4	$PhCH_2OTBS$	0.62	92
5	PhOTBS	0.50	90
6	4-MeC_6H_4OTBS	0.33	87
7	2-MeC_6H_4OTBS	0.60	82
8	4-ClC_6H_4OTBS	13	75
9	2-ClC_6H_4OTBS	17	70
10	4-$NO_2C_6H_4OTBS$	52	38[a]
11	4-$CHOC_6H_4OTBS$	52	57[b]

[a] 52% of unreacted starting material was also recovered.
[b] 33% of unreacted starting material was also recovered.

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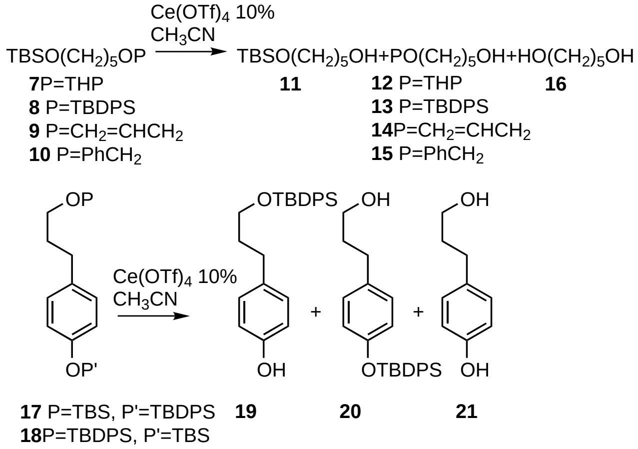
Table 2. Attempts of deprotection of protected octanol in acetonitrile at room temperature with 10% of cerium(IV) triflate

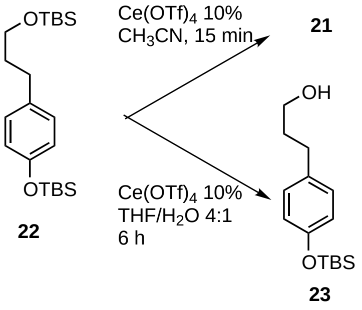
Product	Protecting group	Time [h]	Yield [%]
3	THP	48	78
4	TBDPS	27	89
5	Allyl	>96	0
6	$PhCH_2$	>96	0



Scheme 1.

Allyl and benzyl groups are unscathed under these conditions, while tetrahydropyranyl (THP) and *t*-butyldiphenylsilyl ethers are hardly removed.

Then we attempted chemoselective cleavage of 1,5-pentandiol protected as TBS ether at one terminus and as THP (**7**), TBDPS (**8**), allyl (**9**) and benzyl (**10**) at the other one (Scheme 1). Only benzyl and allyl protecting groups were not removed, the other ones being partially or completely cleaved (Table 3, entries 1–4). In the same manner, 3-(4-hydroxyphenyl)propanol protected as TBDPS or TBS at the aromatic or aliphatic terminus, respectively (**17**–**18**, Scheme 1), afforded the selective cleavage of the TBS ether both when it was bound to the aliphatic or to the aromatic moiety (Table 3, entries 5 and 6).



Scheme 2.

Recently, the selective cleavage of multisilylated nucleosides was reported to occur in THF/H_2O 4:1 mixture as solvent.[7] Therefore the cleavage of protected alcohols **1**–**6** was performed in THF alone and in the THF/H_2O 4:1 mixture. Only TBSO-octane (**1**) was cleaved in a reasonable reaction time (48 and 8 h, respectively) in almost quantitative yields.

The same reactions were then made with diprotected diols **7**–**10**, **17**–**18** and in all cases protecting groups different from TBS were unscathed, but reaction times were considerably longer.

Selective deprotection of alkyl TBS ether in the presence of aryl TBS ethers was recently attempted by several research groups.[8] Since we have in hand a potential method to perform such interesting selective deprotection, a competitive cleavage of TBSO-benzene and TBSO-octane in the presence of 10% of cerium(IV) triflate was attempted and after 2.5 h only octanol was deprotected. Therefore, bis(*t*-butyldimethylsilyl)-3-(4-hydroxyphenyl)propanol (**22**) was prepared and submitted to deprotection in THF/H_2O 4:1 at room temperature in the presence of 10% amount of cerium (IV) triflate (Scheme 2). After 6 h, the selective removal of the aliphatic protecting group was observed.[9] On the other hand, in acetonitrile, full deprotection occurs and unprotected **21** was recovered in 15 min.

In conclusion, cerium(IV) triflate was demonstrated to be a convenient deprotecting agent for TBS group. The advantages of the method are: (i) the catalytic amounts

Table 3. Chemoselective deprotections of protected diols in acetonitrile or THF/H_2O 4:1 at room temperature with 10% of cerium(IV)triflate

Entry	Starting material	Solvent	Time (h)	Composition (%)	Overall yield (%)
1	**7**	MeCN	2	**7** (21), **11** (26), **12** (53)	>98
2	**8**	MeCN	1	**11** (13), **13** (71), **16** (16)	>98
3	**9**	MeCN	0.5	**14** (100)	91
4	**10**	MeCN	2.5	**15** (100)	>98
5	**17**	MeCN	0.5	**20** (100)	85
6	**18**	MeCN	0.5	**19** (100)	75
7	**7**	THF/H_2O 4:1	2	**12** (100)	>98
8	**8**	THF/H_2O 4:1	24	**13** (100)	80
9	**9**	THF/H_2O 4:1	18	**14** (100)	90
10	**10**	THF/H_2O 4:1	2	**15** (100)	83
11	**17**	THF/H_2O 4:1	8	**20** (100)	75
12	**18**	THF/H_2O 4:1	7	**19** (100)	70

requested, (ii) co-reagents unneeded, (iii) the extremely simple experimental procedure, (purification, anhydification, inert or dry atmosphere are not requested), (iv) very high deprotection yields, (v) high selectivity towards TBS group, and (vi) selectivity towards alkyl TBS group in the presence of aromatic ones. These advantages are very useful in complex multistep syntheses, which require the sequential protection and deprotection of the various functionalities.

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9. Between the two *t*-butyl group signals, only that resonating at 0.98 ppm is retained in the final product spectrum, while the signal resonating at 0.91 ppm disappeared. It is known that aliphatic *t*-butyl signals are upfielded with respect to aromatic ones. (Prahash, C.; Saleh, B.; Blair, I. A. *Tetrahedron Lett.* **1994**, *35*, 7565–7568).