

An Efficient and Chemoselective Deprotection of *tert*-Butyldimethylsilyl Protected Alcohols Using $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ as Catalyst

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Abstract: An efficient and selective method for the deprotection of primary alcoholic *tert*-butyldimethylsilyl (TBS) ethers using $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ as catalyst is described. The reaction conditions allow primary alcoholic TBS ethers to be desilylated chemoselectively in the presence of phenolic TBS ethers, secondary and tertiary alcoholic TBS ethers, and the extensively used TBDPS-, acetyl-, benzyloxycarbonyl-, *p*-toluenesulfonyl- and benzyl protective groups.

Keywords: *tert*-Butyldimethylsilyl (TBS) ethers, deprotection, tin dichloride.

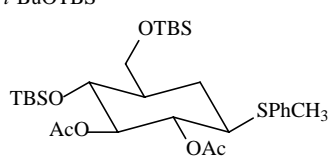
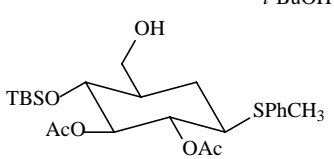
Protection/deprotection sequences continue to be crucially important in the synthesis of natural products and other complex organic molecules¹. Ever since its discovery by Corey *et al.*^{1b} in 1972, *t*-butyldimethylsilyl (TBS) group has become one of the most popular protective groups for hydroxyl groups in organic synthesis because it can be easily installed in high yields and is robust to a variety of reaction conditions. Methods generally used to cleave Si-O bond in TBS ethers for parent alcohol regeneration included acid-catalyzed Si-O cleavage with protic acids and Lewis acids such as BF_3 ², BCl_3 ³, $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ ⁴, BiBr_3 ⁵, $\text{Sc}(\text{OTf})_3$ ⁶, InCl_3 ⁷, cerium(III) chloride heptahydrate/ NaI ⁸, $\text{Zn}(\text{BF}_4)_2$ ⁹, $\text{Ce}(\text{OTf})_4$ ¹⁰ and ZnBr_2 ¹¹, and Lewis base-catalyzed Si-O cleavage employing fluoride ion. Other reagents such as $\text{P}(\text{MeNCH}_2\text{CH}_2)_3\text{N}$, salts of BF_4^- , organotin reagents, $(\text{Me}_2\text{N})_3\text{S}[\text{F}_2\text{SiMe}_3]$ have also been reported to desilylate TBS ethers of alcohols¹². Recently, we have disclosed our works on selective desilylation of TBS-protected phenols using CsCO_3/DMF or KOH/EtOH ¹³. As a part of our effort to develop highly selective methods for deprotection of TBS ethers, herein we would like to report a procedure for the selective desilylation of TBS-protected primary alcohols employing $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ as catalyst.

Initially, we used 1 equiv. of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ to selectively remove the silyl group of TBS-protected alcohols in the presence of phenolic TBS ethers in CH_3CN according to Cort's method¹⁴. However, both yields and chemoselectivities were not satisfactory. Then we investigated the effects of solvents and the amount of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ on the reaction, and found that catalytic amount of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in $\text{EtOH}-\text{H}_2\text{O}$ is the favored condition for deprotection of primary alcoholic TBS ethers.

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Investigation of reaction conditions demonstrated that the reaction could be performed smoothly using 0.5 equiv. of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in ethanol- H_2O (10:1) at room temperature. We examined a variety of substrates including primary, secondary and tertiary alcoholic TBS ethers. As shown in **Table 1**, only primary alcoholic TBS ethers could be deprotection in excellent yields (**Table 1**, entries 1-4). The cleavage of secondary and tertiary alcoholic TBS ethers was very difficult even in a prolonged reaction time (**Table 1**, entries 5 and 6). The compound with both primary and secondary hydroxyl TBS ethers gave a primary hydroxyl-deprotected product in 83% yield (**Table 1**, entry 7).

Table 1 Desilylation of alcoholic TBS ethers^a

| Entry | Silyl ethers | Products | Time (h) | Yield (%) ^b |
|-------|---|--|----------|------------------------|
| 1 | $n\text{-C}_8\text{H}_{17}\text{OTBS}$ | $n\text{-C}_8\text{H}_{17}\text{OH}$ | 2.1 | 96 |
| 2 | $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OTBS}$ | $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}$ | 1.5 | 96 |
| 3 | $\text{C}_6\text{H}_4\text{CH}_2\text{OTBS}$ | $\text{C}_6\text{H}_4\text{CH}_2\text{OH}$ | 1.9 | 87 |
| 4 | $p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{OTBS}$ | $p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{OH}$ | 3.4 | 90 |
| 5 | $\text{Cyclo-C}_6\text{H}_{11}\text{OTBS}$ | $\text{Cyclo-C}_6\text{H}_{11}\text{OH}$ | 12 | 24 |
| 6 | $t\text{-BuOTBS}$ | $t\text{-BuOH}$ | 12 | Trace |
| 7 |  |  | 4.0 | 83 |

^aAll reactions were performed on a 1 mmol scale using 0.5 equiv of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in 1 mL of EtOH- H_2O (10:1) at room temperature for the time indicated. ^bIsolated yield.

Table 2 Selective cleavage of alcoholic TBS ethers^a

| Entry | Silyl ethers | Time (h) | Products | Yields (%) ^b |
|-------|--|----------|--|-------------------------|
| 1 | $p\text{-TBSOC}_6\text{H}_4\text{CH}_2\text{OTBS}$ | 1.5 | $p\text{-TBSOC}_6\text{H}_4\text{CH}_2\text{OH}$ | 94 |
| 2 | $p\text{-TBSOC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OTBS}$ | 1.5 | $p\text{-TBSOC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OH}$ | 96 |
| 3 | $p\text{-TBSOC}_6\text{H}_4\text{CH}=\text{CHCH}_2\text{OTBS}$ | 1.8 | $p\text{-TBSOC}_6\text{H}_4\text{CH}=\text{CHCH}_2\text{OH}$ | 87 |
| 4 | TBDPSO-CH ₂ -CH ₂ -CH ₂ -OTBS | 2.8 | TBDPSO-CH ₂ -CH ₂ -CH ₂ -OH | 77 |
| 5 | AcO-CH ₂ -CH ₂ -CH ₂ -OTBS | 2.0 | AcO-CH ₂ -CH ₂ -CH ₂ -OH | 96 |
| 6 | CbzO-CH ₂ -CH ₂ -CH ₂ -OTBS | 1.5 | CbzO-CH ₂ -CH ₂ -CH ₂ -OH | 91 |
| 7 | TsO-CH ₂ -CH ₂ -CH ₂ -OTBS | 2.0 | TsO-CH ₂ -CH ₂ -CH ₂ -OH | 95 |
| 8 | BnO-CH ₂ -CH ₂ -CH ₂ -OTBS | 1.5 | BnO-CH ₂ -CH ₂ -CH ₂ -OH | 93 |
| 9 | THPO-CH ₂ -CH ₂ -CH ₂ -OTBS | 1.5 | THPO-CH ₂ -CH ₂ -CH ₂ -OH | 24 |

^aAll reactions were performed on a 1 mmol scale using 0.5 equiv of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in 1 mL of EtOH- H_2O (10:1) at room temperature for the time indicated. ^bIsolated yield.

To establish the chemoselectivity of this method, deprotection of the alcoholic TBS ethers bearing phenolic TBS silyl ethers and other sensitive protective groups were studied. The results are summarized in **Table 2**. The alcoholic TBS ethers could be deprotected completely, while TBS-protected phenols (**Table 2**, entries 1-3) as well as TBDPS (**Table 2**, entry 4), acetyl (**Table 2**, entry 5), benzyloxycarbonyl (**Table 2**, entry 6), *p*-toluenesulfonyl (**Table 2**, entry 7) and benzyl (**Table 2**, entry 8) protected alcohols were not touched under the reaction conditions. Tetrahydropyranyl (THP) ether could be partially removed (**Table 2**, entry 9).

In summary, we have developed a facile and efficient procedure for the cleavage of alcoholic TBS ethers using 0.5 equiv. SnCl₂·2H₂O in EtOH-H₂O (10:1) at room temperature. The method is specific for deprotection of primary alcoholic TBS ethers. The phenolic TBS ethers, secondary and tertiary alcoholic TBS ethers, and the extensively used TBDPS, acetyl, benzyloxycarbonyl, *p*-toluenesulfonyl and benzyl protective groups remained to be not touched.

Acknowledgment

This work was financially supported by the National Natural Science Foundation of China (NO. 20272051) as well as the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, P. R. China.

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Received 3 November, 2003