

Efficient and chemoselective cleavage of TBS ethers by a sub-stoichiometric amount of decaborane

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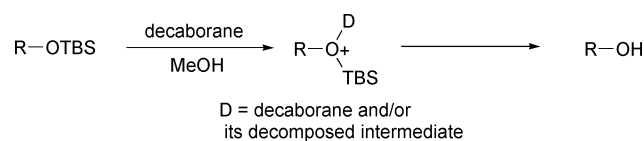
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TBS ethers of aliphatic alcohols in THF–MeOH (or methanol) were deprotected chemoselectively to the corresponding alcohols using a sub-stoichiometric amount of decaborane at rt under nitrogen in high yields.

Protection and deprotection of alcohols play a key role in the organic synthesis of polyfunctional organic molecules and a lot of protecting groups have been developed for this purpose. Among silyl ethers, *tert*-butyldimethylsilyl (TBS) ether is the most popular protecting group for alcohols because of its easy preparation^{1,2} and stability in a variety of reaction conditions. Although tetra-*n*-butylammonium fluoride³ is the most common reagent for the cleavage of TBS ethers, the strong basicity of the fluoride anion makes it inappropriate for base-sensitive substrates.⁴ In addition, the phase transfer properties of tetrabutylammonium cations often cause difficulties in the work-up and purification of products. A variety of reagents for the removal of TBS ethers have been developed to solve these problems.^{1,2,5–6} However, most of these procedures require complicated procedures, drastic reaction conditions, moisture sensitive reagents and cumbersome work-up. As synthetic targets become increasingly complex, selective methods to deprotect in the presence of another are very demanding. Here we report a mild, selective, simple and efficient deprotection of TBS ethers of alcohols using a sub-stoichiometric amount of decaborane (Scheme 1).



Scheme 1

Decaborane ($B_{10}H_{14}$)^{7,8} is a commercially available white solid that decomposes only slowly in air. Decaborane has been reported as a reducing reagent in organic synthesis, but it is inefficient from a synthetic point of view due to its low reducing power in polar solvents.⁹ By changing the solvent to protic solvents and/or adding additives, decaborane was found to be a mild reducing agent in reactions such as reductive amination,^{10a} reductive etherification,^{10b} and reduction of carbonyls.^{10c} Decaborane is also a good Lewis acid that can form adducts with Lewis bases (SH, OH, NH *etc.*).¹¹ As a continuous study on decaborane, decaborane was used for the deprotection of TBS ethers as a Lewis acid catalyst. The TBS ethers used in this experiment were prepared from the corresponding alcohols using well-known procedures³ and the TBS ethers were subjected to deprotection using a sub-stoichiometric amount of decaborane in a solution of methanol and THF (or methanol as a sole solvent) at room temperature. The deprotection results for TBS ethers of primary, secondary alcohols and phenolic TBS ethers are collected in Tables 1 and 2. Although the reaction proceeds well with 1 mol% of decaborane, 2 mol% of decaborane was used to reduce the reaction time, especially with the less reactive TBS ethers. If the amount of methanol in

the solution was increased, the reaction rate was increased. The reaction of piperonyl alcohol TBS ether was complete within 25 min in methanol, whereas the reaction took 50 min for the completion in a solution of THF and methanol (1 : 1) (entry 1). The TBS ethers of primary aliphatic alcohols under the reaction conditions were deprotected to give the corresponding alcohols in high yields in the two systems (Table 1). While deprotection of electron sufficient TBS ethers proceeded quickly, the electron deficient substrates were deprotected slowly. For example, the TBS ethers of acetyl protected glucose (entry 7) and benzyl alcohols with nitro groups (entries 5 and 6) were deprotected slowly compared to the TBS ethers of benzyl protected glucose (entry 8) and other primary alcohols (entries 1, 3 and 4) respectively. The reaction is mild enough not to affect the carbon–carbon double bond in conjugated systems (entry 2) and acetals (entries 7–8).

Under the conditions, TBS ethers of secondary alcohols were deprotected slowly and not completely even at extended reaction times (entries 1–4, Table 2). The exact reason is not clear and is under investigation. The TBS ether of phenethyl alcohol in a solution of THF and methanol (1 : 1) (or in methanol) gave deprotected alcohol and recovered starting material in 80% (89%) and 13% (8%) respectively (entry 1). The deprotection rate also depends on the electronic effect of the substituent. The TBS ether of a lactone (entry 4) was deprotected very slowly to give an alcohol in 10% (method A) and 26% yield (method B), respectively, and starting material was recovered in 85% (method A) and 72% (method B) yield, respectively. We believe that the mechanism of this selective hydrolysis involves the coordination of decaborane and/or its decomposed derivatives to the oxygen of the TBS ether to form an oxonium ion followed by nucleophilic attack of methanol (Scheme 1). The oxonium intermediate was surmised on the basis of experimental results that deprotection of electron deficient TBS ethers (with electron withdrawing substituents) and sterically more hindered TBS ethers (secondary alcohol TBS ethers) was relatively slow compared with that of electron sufficient TBS ethers and sterically less hindered THP ethers (primary alcohol TBS ethers). The phenolic TBS ethers were not deprotected at all after 25 h stirring at rt in the two solvent systems (entries 5 and 6). Therefore, our conditions could be used for the selective deprotection of alkyl TBS ethers in the presence of aryl ethers.⁶

Extension of the method was investigated using piperonyl alcohol as a model to compare the relative stability of the TBS group with other protecting groups such as TBDPS, TIPS, Tr and TPS using 2 mol% of decaborane in a solution of THF and methanol (1 : 1),¹² and the results are shown in Table 3. The TBS ether was found to be more labile than TIPS, Tr and TBDPS ethers and more stable than TPS ethers under the conditions. This trend is the same as that of silyl cleavage using $BF_3 \cdot Et_2O$ in methylene chloride at rt.¹³ The TIPS ether was deprotected to give an alcohol in only 7% yield even in the case of extended reaction time (24 h) and other bulky protecting groups such as trityl and TBDPS remained intact even after 24 h stirring at rt.

In conclusion, TBS ethers of primary aliphatic alcohols in THF–MeOH (or MeOH) were converted to the corresponding

Table 1 Deprotection of TBS ethers of primary alcohols

Entry	Substrate ^c	Product	Reaction time	Yield ^a
1			50 min ^b (25 min) ^c	97% ^b (98%) ^d
2			1 h (30 min)	98% (97%)
3			50 min (30 min)	96% (96%)
4			1.5 h (1 h)	97% (97%)
5			9 h (5 h)	90% (93%)
6			9 h (5 h)	92% (94%)
7			9 h (7 h)	97% (95%)
8			6 h (2.5 h)	90% (99%)
9			6 h (5 h)	96% (93%)

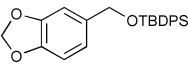
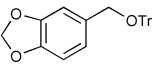
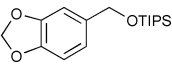
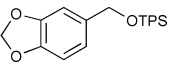
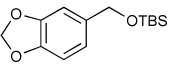
^a Isolated yields. ^b Yields obtained in THF and methanol (1 : 1). ^c Parenthesis times show reaction time in methanol. ^d Parenthesis yields were obtained in methanol. ^e TBS: *tert*-butyldimethylsilyl, Ac: acetyl, Bn: benzyl, Cbz: benzyloxycarbonyl.

Table 2 Deprotection of TBS ethers of secondary alcohols and phenols

Entry	Substrate	Product	Reaction time ^d	Yield ^a
1			12 h	A: 80% (13%) ^b B: 89% (8%)
2			9 h	A: 1: 75% 2: 19% B: 1: 36% 2: 59%
		1: X=TBS, 2:X=H		
3			12 h	A: 70% (28%) B: 92% (7%)
4			12 h	A: 10% (85%) B: 26% (72%)
5			12 h	N.R.
6			12 h	N.R.
7			1.5 h	A: 93% B: 94%

^a Isolated yields. N.R. = no reaction. ^b The yields in parentheses are those of recovered substrates. ^c A: method A, B: method B. ^d The reactions were quenched and worked up after the same reaction time in both methods.

Table 3 The relative stability of other protecting groups

Entry	Substrate	Time	Yield (%) ^a
1		24 h	N.R.
2		24 h	N.R.
3		24 h	7 % (91 %) ^b
4		6 min	97 %
5		50 min	97 %

^a Isolated yields. ^b Yield of the recovered substrate in parentheses.
^c Relative stability based on the reaction: TBDPS = Tr > TIPS ≫ TBS > TPS. **TBDPS**: *tert*-butyldiphenylsilyl, **TPS**: triphenylsilyl, **TIPS**: triisopropylsilyl, **Tr**: triphenylmethyl or trityl.

alcohols using a sub-stoichiometric amount of decaborane (2 mol%) at rt under nitrogen in excellent yields. The deprotection of TBS ethers of secondary alcohols is slow and incomplete, but gave the corresponding alcohols in high yields and recovered substrate in low yield. The reaction conditions are mild enough not to affect the double bond of allyl alcohols, acetals and TBS ethers of phenolic alcohols. In addition, TBS ether showed selectivity against TBDPS, Tr and TIPS ethers under our conditions.

Experimental

Typical experimental procedure:

Method A

To a solution of TBS ether of piperonyl alcohol (100 mg, 0.38 mmol) in 3 ml of a solution of THF and methanol (1 : 1) was added decaborane (0.9 mg, 2 mol%) and the resulting solution was stirred at rt. Reaction was monitored by TLC using a solution of ethyl acetate and hexane (1 : 4). After 50 min, the reaction was concentrated and chromatographed on silica gel using a solution of ethyl acetate and hexane (1 : 4). The concentration gave the alcohol as a light yellow solid in 97% yield (55.4 mg).

Method B

The procedure is the same as that of method A except for the solvent used. 3 ml of methanol was used instead of 3 ml of a solution of THF and methanol used in method A.

Acknowledgements

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