

SELECTIVE DE-PROTECTION OF SILYL ETHERS

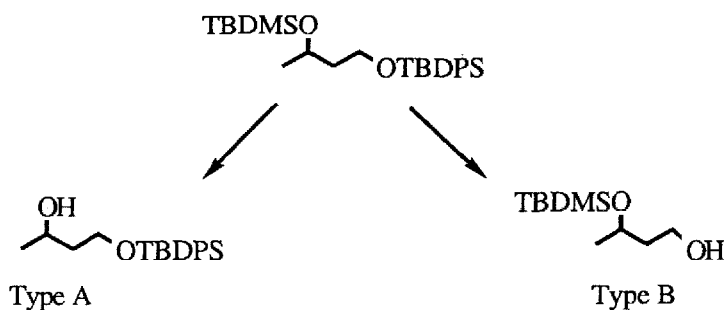
Chandra Prakash, Samir Saleh, and Ian A. Blair

Departments of Pharmacology and Chemistry, Vanderbilt University, Nashville, TN 37232

Summary: Pyridinium *p*-toluenesulfonate has been found to remove *t*-butyldimethylsilyl ethers selectively in the presence of *t*-butyldiphenylsilyl ethers. This methodology should find wide applicability in complex organic synthesis.

A large number of protecting groups are available for free hydroxyl groups¹. Silyl ethers such as *t*-butyldimethylsilyl (TBDMS) and *t*-butyldiphenylsilyl (TBDPS) are among the most widely used due to their stability towards many reagents and reaction conditions^{1c}. De-protection of silyl ethers can be accomplished using a variety of reagents such as tetrabutylammonium fluoride^{1c,2}, boron trifluoride etherate³, alkali metal tetrafluoroborate⁴, aqueous hydrofluoric acid⁵, *N*-bromosuccinimide in dimethyl sulphoxide⁶ and tetraethyldiboroxane in the presence of catalytic amounts of trimethylsilyl triflate⁷. Often, more than one protecting group has to be used during the synthesis of complex natural products⁸⁻¹⁰. Removal of a selected protection group is often necessary in order to reveal an essential hydroxyl moiety during a complex synthesis. Tetrahydropyranyl (THP) ether derivatives in combination with silyl ethers have been used extensively for this purpose. Selective removal of the silyl ether can be readily accomplished by treatment with tetrabutylammonium fluoride. However, there are some problems with the use of THP ether derivatives. For example, derivatization of optically active alcohols results in the formation of a mixture of diastereomers. This can be inconvenient both for interpretation of NMR spectra and for purification by column chromatography or HPLC. Further, the THP derivative is rather labile to acid and is often not compatible with desired reaction conditions.

Silyl ethers offer an attractive alternative because of their stability to a wide range of reaction conditions as noted above. To date there has been no way to make use of this stability because there has been no convenient way to distinguish the different silyl ethers. We envisaged that it may be possible to distinguish the TBDMS group from the TBDPS because of the potential difference in reactivity of the two groups. Thus, a substrate containing the two protecting groups could cleave preferentially at the least bulky silyl ether group (Scheme) to form the mono-TBDPS (product type A) rather than the mono-TBDMS (product type B). We report that this reaction occurs with pyridinium *p*-toluenesulfonate (PPTS) under mild conditions and so it is possible to use this methodology to selectively protect hydroxyl groups.









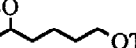

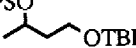
Scheme: Possible reaction products from bis-silyl ethers

The treatment of bis-silyl ethers with PPTS in ethanol either at room temperature or 55 °C for 1.2 to 2.0 h afforded mono-silyl ethers in 80-92 % isolated yield (Table). ¹H-NMR studies of the isolated product showed a signal for the *t*-butyl group (δ 1.06 ppm) from the *t*-butyldiphenyl moiety but the signals for the *t*-butyl group (δ 0.88 ppm) and the two methyl groups (δ 0.06 ppm) from the *t*-butyldimethylsilyl moiety were absent. This indicated that the TBDMS group had been removed preferentially by PPTS to give type A products. However, ¹H-NMR spectroscopy lacked sufficient sensitivity to completely characterize the product profile. Detailed studies were then carried out by capillary column GC/electron impact (EI) MS on the crude reaction products to determine the absolute selectivity of the reaction. The crude reaction products were converted¹² to their corresponding trimethylsilyl (TMS) ethers in order to improve their GC/MS characteristics. The type B (mono-TBDMS) derivatives eluted from the column¹³ with relatively short retention times (3-5 min) compared with the type A (mono-TBDPS) derivatives (9-12 min). Full scanning analysis¹⁴ was carried out and peak areas corresponding to the total ion currents of the individual products were calculated using the automated integration program of the GC/MS data system. The mass spectra of the products were confirmed by comparison with authentic standards. It was shown that in most cases the reaction proceeded to give > 99.7 % of type A products in which the TBDMS group had been removed. This selectivity was apparent even when a primary TBDPS group and a secondary TBDMS group were present in the same molecule (entries 6 and 7). The poorest selectivity was observed in the case of 1,5-pentane system (entry 1) where 3.5 % of product type B was observed. The reason for this discrepancy is not apparent at this time. With longer chain lengths selectivity was always > 99 %.

General procedure:

The bis-silyl ether (1.0 mmol) was dissolved in absolute ethanol (5 ml) and PPTS (75 mg, 0.3 mmol) was added in one portion. The reaction mixture was stirred at room temperature (or 55 °C) for 1.2-2 h (see Table). The solvent was removed in vacuo and the residue was dissolved in ethyl acetate. The organic solution was washed with saturated aqueous brine, water and then dried (MgSO₄). The solvent was evaporated in vacuo and the crude product was purified on a silica-gel column using hexane:ethyl acetate (9:1) as solvent.

Table: Reaction of bis-silyl ethers with PPTS.

Entry	Substrate ¹⁵	Reaction conditions		Product		
		Time (h)	Temperature (°C)	Type A (%)	Type B (%)	Yield ¹⁶ (%)
1	TBDPSO  OTBDMS	2.0	22	96.5	3.5	88.0
2	TBDPSO  OTBDMS	1.5	22	99.1	0.9	92.0
3	TBDPSO  OTBDMS	1.2	22	99.8	0.2	92.0
4	TBDPSO  OTBDMS	1.2	22	99.9	0.1	90.0
5	TBDPSO  OTBDMS	2.0	22	99.8	0.2	82.0
6	TBDMSO  OTBDPS	2.0	55	99.6	0.4	82.0
7	TBDMSO  OTBDPS	2.0	55	99.7	0.3	80.0
8	TBDPSO  OTBDMS	1.8	22	99.7	0.3	84.0
9	TBDPSO  OTBDMS	1.8	22	99.4	0.6	84.0

In summary, conditions have been established that allow selective removal of a TBDMS ether in the presence of a TBDPS ether. Secondary TBDMS ethers can be removed with high selectivity even if the TBDPS is in a primary position. This reaction should find wide application in organic synthesis where selective protection of hydroxyl groups is required.

ACKNOWLEDGEMENTS

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- Trimethylsilyl ethers were prepared by treatment of the crude reaction product with bis-trimethylsilyl-trifluoroacetamide at 60 °C for 1 h.
- GC/MS analysis was carried out on a 10 m SPB-1 fused silica capillary column (0.32 mm id; 0.25 μm coating thickness) using helium as carrier gas at a flow rate of 1 ml min⁻¹. Injections were made in the splitless mode. The column temperature was held at 60 °C for 2 min then programmed to 300 °C at 15 °C/min.
- Full scan EI mass spectra of the TMS derivatives were obtained from *m/z* 30 to *m/z* 600 with a scanning time of 1.5 sec. The silyl derivatives all showed characteristic M-57 ions corresponding to M-t-Bu.
- Mono-silyl ethers were prepared by treatment of the corresponding diols with 1.1 equiv. of sodium hydride followed by reaction with the appropriate silyl chloride (11). Bis-silyl ethers were prepared from the corresponding mono-silyl ethers. Satisfactory analytical data was obtained on all new compounds.
- Products were characterized by MS and ¹H-NMR. Yields refer to isolated compounds.

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