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Selective Removal of Phenolic and Alcoholic Silyl Ethers

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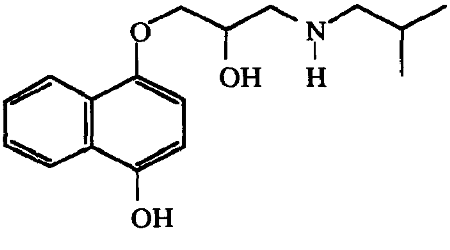
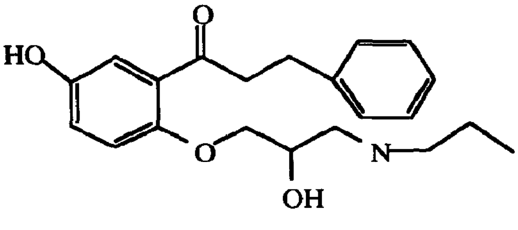
Abstract: Potassium carbonate/Kriptofix 222 and pyridinium *p*-toluenesulfonate or BF_3-etherate have been found to remove the *tert*-butyldimethylsilyl group from phenolic and alcoholic silyl ethers, respectively. This methodology should find wide applicability in complex organic synthesis.

In the course of research directed towards a synthesis of positional isomers of glucuronides of 4-hydroxypropranolol[1] 1 and 5-hydroxypropafenone[2] 2, we required a protecting group, at phenolic and alcoholic groups, that could be removed selectively in the presence of each other. A large number of groups are available for protection of free hydroxyl groups.[3] Silyl ethers such as *tert* -butyldimethylsilyl (TBDMS) provide versatile protecting groups for alcohol and phenols in organic synthesis. Owing to its stability under alkaline conditions, Grignard and alkyl lithium and to alkylating and acylating reagents, TBDMS is widely used for hydroxyl group protection.[3c] De-protection of silyl ethers can be accomplished using a variety of reagents,[3,4] among which n-tetrabutylammonium fluoride[3c,4a] is frequently used. However, use of this reagent has some limitations, due to the basicity of the "naked" fluoride ion, which may promote transacylation of O-acyl-protected sugars[5] and other undesired reactions.[3]



1



2

We have reported that pyridinium *p*-toluenesufonate (PPTS)[6] under mild conditions can be used to remove TBDMS ether in the presence of a TBDPS ether. This reagent is very selective. It removes only primary

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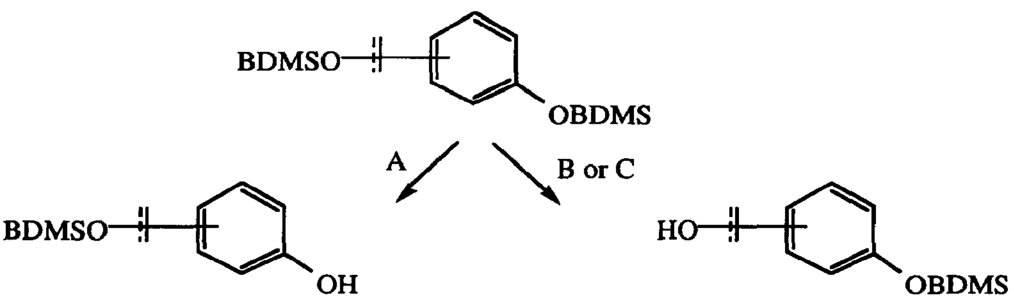
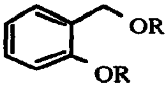
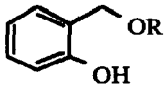
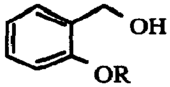
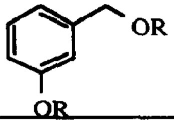
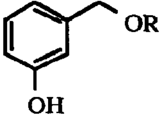
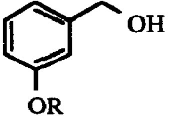
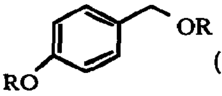
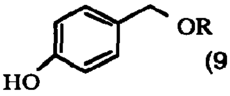
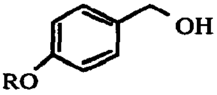
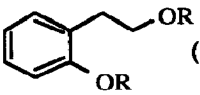
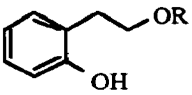
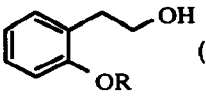
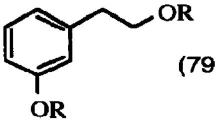
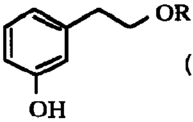
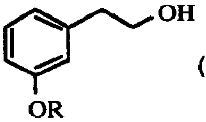
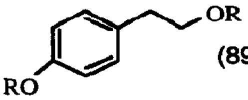
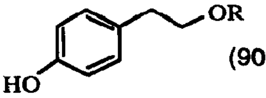
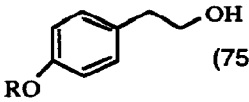
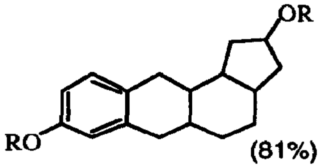
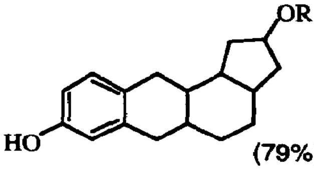
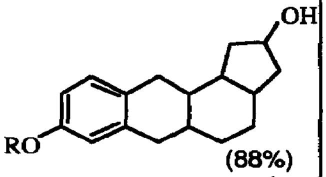
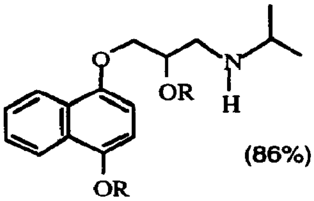
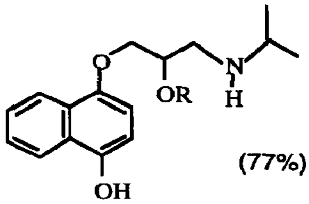
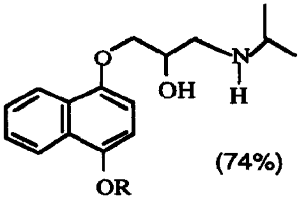
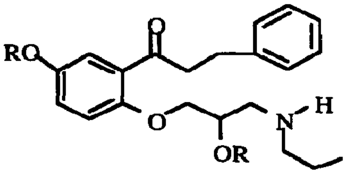
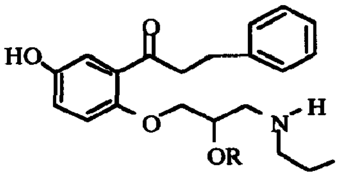
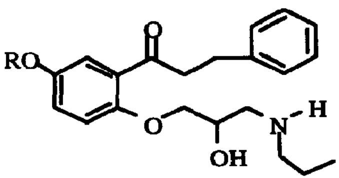
and secondary alcoholic silyl ethers without affecting aromatic silyl ethers. Selective removal of a protection group from aromatic and alcoholic silyl ethers is often necessary in order to reveal an essential hydroxyl moiety during a complex synthesis. Collington *et al.*[7] have reported that under carefully controlled conditions, aqueous hydrofluoric acid in acetonitrile selectively removes the alcoholic silyl ether whereas tetrabutylammonium fluoride in THF regenerates the phenol function[7]. The use of reagent in excess results in complete deprotection and poor yields.

We have discovered that K_2CO_3/Kriptofix 222 under mild conditions deprotects aromatic silyl ethers. Thus, treatment of TBDMS ether of 4-hydroxypropiophenone in acetonitrile with K_2CO_3 and a catalytic amount of Kriptofix 222 yields 4-hydroxypropiophenone in quantitative yield (Method A). Further, we have found that under these conditions the alcoholic silyl ethers remain unaffected. However, PPTS or BF_3-etherate[4b] removes only the alcoholic silyl ethers. Thus, the reaction of *bis* -silyl ethers **1-8**[8] in acetonitrile with K_2CO_3/Kriptofix 222 yields mono-silyl ethers in 70-95% yield (Table).



^{1}H NMR studies of the isolated product showed a signal for the *tert*-butyl group (δ 0.85 ppm) from the *tert*-butyl group of alcoholic silyl ethers but the signal for the *tert*-butyl (δ 0.98 ppm) from the *tert*-butyl group of aromatic silyl ethers was absent. On the other hand, the ^{1}H NMR of monosilyl ether obtained by treatment of *bis* -silyl ethers with PPTS showed a signal for the *tert*-butyl (δ 0.98 ppm) from phenolic TBDMS ethers. This indicated that the TBDMS from phenolic silyl ethers had been removed preferentially by K_2CO_3/Kryptofix and alcoholic silyl ethers were removed by PPTS. In separate experiments, a 1:1 mixture of 4-hydroxypropiophenone and 1-hexanol TBDMS ethers were treated with K_2CO_3/Kriptofix and PPTS. It was found that these reagents removed the silyl group preferentially from phenolic and alcoholic silyl ethers, respectively. Detailed studies were also carried out by capillary column GC/electron impact (EI) MS[9] on the crude reaction products[10] to determine the absolute selectivity of the reaction. It was shown that both the reactions proceed very cleanly and afford the mono-silyl ethers in 70-95 % isolated yield[11] (Table). Although the deprotection of silyl ethers with PPTS takes a longer time and gives reduced yield when the hydroxyl group is sterically hindered (entry 8, 9). Both primary and secondary TBDMS ethers can be removed in excellent yields by PPTS and BF_3-etherate without affecting the aromatic TBDMS ether. In summary, it is evident from the Table that the new reagent selectively removes phenolic silyl ether in the presence of alkyl silyl ethers. This reaction should find wide application in organic syntheses where selective protection of hydroxyl groups is required.[12]

Table

entry	substrate (yield)		Reaction conditions			
			Method A	(yield)	Method B or C	(yield)
1		(88%)		(94%)		(85%)
2		(93%)		(93%)		(81%)
3		(97%)		(91%)		(84%)
4		(75%)		(79%)		(71%)
5		(79%)		(85%)		(76%)
6		(89%)		(90%)		(75%)
7		(81%)		(79%)		(88%)
8		(86%)		(77%)		(74%)
9		(79%)		(72%)		(70%)

R=TBDMS

Method A: To a solution of the *bis*-silyl ether (0.13 mmol) in acetonitrile (0.5 ml) were added K_2CO_3 (0.5 mmol) and kriptofix 222 (0.065 mmol). The reaction mixture was heated at 55 ^{0}C for 2 h and allowed to cool. It was then filtered and the solvents removed in *vacuo*. Purification was carried out by flash chromatography.
Method B: PPTS (0.1 Equiv) was added to a solution of the *bis*-silyl ether in ethanol and the reaction was heated at 50 ^{0}C for 1 h. The solvents were removed and the residue purified by flash chromatography.
Method C: The *bis*-silyl ether was stirred with 2 equiv.of BF_3-etherate at room temperature[4b] and the product purified in the same way.

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8. *Bis*-silyl ethers were prepared by a standard procedure (Ref 3c) and were obtained in yields of 75-97%. Briefly, To a solution of the substrate (1 equiv) in DMF was added imidazole (3 equiv) and *tert*-butyldimethylsilyl chloride (3 equiv) at 0 ^{0}C and the reaction mixture was stirred at room temperature over night. All new compounds possessed satisfactory spectroscopic and analytical data.
9. GC/MS analysis was carried out as described in ref. 6. Full scan EI mass spectra of the TMS derivatives were obtained from the *m/z* 50 to *m/z* 500 with a scanning time of 1.5 sec. The silyl derivatives all showed characterstic M-57 ions corresponding to M-*tert*-Bu.
10. Trimethyl silyl ethers were prepared by treatment of the crude reaction product with *bis*-trimethylsilyl-trifluroacetamide at 60 ^{0}C for 1 h.
11. Products were characterized by MS and ^{1}H NMR. Yields refer to isolated compounds.

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