A Mild, Efficient and Selective Cleavage of Aryl *tert*-Butyldimethysilyl Ethers Using KOH in Ethanol

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An efficient and selective method for the deprotection of aryl *tert*-butyldimethysilyl (TBS) ethers is described. The protecting group TBS could be cleaved from aryl silyl ethers in the prensence of alkyl TBS ethers using KOH in ethanol at room temperature to give the corresponding phenols in excellent yields (87–99%).

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, *tert*-butyldimethysilyl (TBS) is the most popular because it can be easily installed in high yields and is robust to a variety of reaction conditions.[1]

It is very important to seek a mild reagent to deprotect aryl TBS ethers in the presence of alkyl TBS ethers, since the selectivity can be applied to advantage in complex synthetic sequences in which one of two protected hydroxyl groups must be unmasked at different stages of the synthesis. Although camphorsulfonic acid/methanol[2] and aqueous DMSO[3] have been used to cleave aryl TBS ethers in the presence of alkyl TBS ethers, a survey of the methods reported to effect selective desilylation of aryl silyl ethers reveals basic conditions to be the norm.[4] Davies has demonstrated that, while the desilylation of the TBS ether of *p*-cresol in 5% NaOH has a half-life of 3.5 min, the TBS ether of *n*-hexanol is stable over 24 h.[5] Among the systematically studied basic regents reported to effect selective removal of silyl groups from phenols are: TBAF/THF,[6,7] KF/18-crown-6,[7] KF/alumina/ultrasound,[8] K_2CO_3/kryptofix/CH_3CN,[9] K_2CO_3/ ethanol,[10] NaOH/*n*-Bu_4NHSO_4/dioxane,[11] KF/alumina,[12] and LiOH/DMF.[13] Other methods employing TBAF have been reported as parts of total syntheses.[14–17] Some of these methods require elevated reaction temperature,[3,9,10] lengthy reaction times.[3,7] using large amounts of base.[11,13] Herein we report a new method for the selective cleavage of phenol TBS ethers using KOH in ethanol at room temperature in relative short time, which utilizes conventional laboratory reagents and equipment, does not require an aqueous workup, and tolerate a wide variety of other functional groups.

Investigation of reaction conditions for the cleavage of aryl silyl ethers using KOH demonstrated that 1.5 equiv. of KOH in ethanol at room temperature was optimal for the desired deprotection. We examined a variety of substrates including aryl TBS ethers and alkyl desired deprotection.[18] As shown in Table 1, aryl TBS ethers could be cleaved smoothly (Table 1, Entries 1–9), while benzyl and alkyl had poor yield or no reaction in the same conditions (Table 1, Entries 10–12). We also observed that the rate of deprotection of aryl TBS ethers was accelerated if an electron-withdrawing group was present on the aromatic ring (Table 1, Entries 1–3). On the other hand, the presence of an electron-donating group on the aromatic ring decelerated the desired transformation (Table 1, Entries 8–9).

Table 1. Deprotection of aryl and alkyl TBS ethers to phenols and alcohols using 1.5 equiv. solid KOH in ethanol

Entry	Silyl ethers	Reaction time/h	Yield/%[a]
1	4-ClC_6H_4OTBS	0.3	99
2	4-CHOC_6H_4OTBS	0.3	98
3	2-CHOC_6H_4OTBS	0.5	98
4	C_6H_5OTBS	0.7	95
5	4-MeC_6H_4OTBS	1.0	92
6	4-*t*-BuC_6H_4OTBS	1.0	97
7	2-MeC_6H_4OTBS	1.6	93
8	3-$NH_2C_6H_4$OTBS	2.0	91
9	4-MeOC_6H_4OTBS	2.0	87
10	$C_6H_5CH_2$OTBS	18	23
11	*n*-C_8H_{17}OTBS	24	No reaction
12	*i*-C_8H_{17}OTBS	24	No reaction

[a] Isolated yield.

To establish the chemoselectivity of this method, the aryl silyl ethers containing alkyl silyl ethers and other sensitive groups were allowed to cleave in ethanol in the presence of 1.5 equiv. of KOH at room temperature (Scheme 1), and the results are summarized in Table 2. The aryl silyl ethers could be deprotected cleanly to give corresponding phenols in very high yields, while TBS-protected alcohols (Table 2, Entries 1–4), carboxylic esters (Table 2, Entries 5–6), and tetrahydropyranyl (THP)-protected alcohol (Table 2, Entry 7) were unscathed under these conditions.

In summary, we have developed a simple, inexpensive, selective and mild procedure for the cleavage of aryl silyl ethers in the presence of alkyl silyl ethers using 1.5 equiv. of KOH in ethanol. The reaction conditions can also allow selective deprotection of aryl TBS-protected phenols in the presence of phenyloxycarbonyl or tetrahydropyranyl-protected alcohols.

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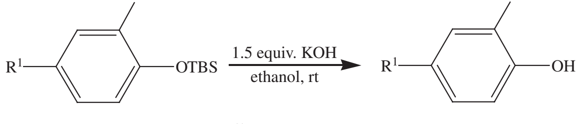

Scheme 1.

Table 2. Selective deprotection of aryl TBS ethers

Entry	R^1	R^2	Reaction time/h	Yield/ %[a]
1	CH_2OTBS	H	0.75	97
2	CH_2CH_2OTBS	H	1.0	98
3	$CH_2CH_2CH_2OTBS$	H	1.0	98
4	$CH_2CH_2CH_2OTBS$	OMe	3.0	92
5	CO_2CH_3	H	0.7	95
6	$CO_2C_2H_5$	H	1.5	97
7	CH_2OTHP	H	1.5	96

[a] Isolated yield.

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18 General procedure for the deprotection of *tert*-butyldimethylsilyl ethers: A mixture of *tert*-butyldimethylsilyl ethers (0.5 mmol), KOH (0.75 mmol) in ethanol (0.5 mL) was stirred at room temperature until the reaction was finished as indicated by thin-layer chromatography (TLC). The reaction mixture was filtered through Celite, and the ethanol removed on a rotary evaporator. The crude material was taken in a suitable organic solvent, washed with water, and brine. After drying (Na_2SO_4) and solvent removal, the crude product was purified by column chromatography. The phenol obtained was identical with an authentic sample by TLC, ^1H NMR, and IR.

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