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A mild, efficient and selective deprotection of *t*-butyldimethylsilyl-protected phenols using cesium carbonate

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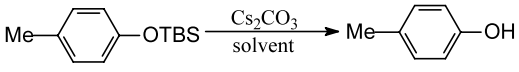
Abstract—A mild and efficient method for the deprotection of aryl *t*-butyldimethysilyl (TBS) ethers is described. The protecting group TBS could be cleaved from aryl silyl ethers using cesium carbonate in DMF–H_2O at room temperature to give the corresponding phenols in excellent yields. The reaction conditions allowed selective deprotection of aryl TBS-protected phenols in the presence of TBS, phenyloxycarbonyl or tetrahydropyranyl-protected alcohols.

As synthetic targets have become increasingly complex, protection/deprotection protocols using silyl groups have been the most popular methods due to their easy formation and removal, and their stability to a wide range of reagent and reaction conditions.[1] Among silyl ethers, those carrying the *t*-butyldimethylsilyl (TBS) groups are the most popular for the latter's easy installation and stability. The deprotection of TBS is usually carried out with tetrabutylammonium fluoride (TBAF),[1] aqueous acid[2] and aqueous HF–CH_3CN.[3] Although a large number of deprotection methods are available for discrimination between different trialkylsilyl groups,[4–12] relatively few methods have been developed for the selective removal of aryl TBS ethers in the presence of alkyl TBS ethers.[9,13] Considering that both alcoholic and phenolic hydroxyl groups are present in many complex natural products such as vancomycin and teicoplanian, the differential deprotection of alcoholic and phenolic silyl ethers is of considerable interest.[13] In this context, we have developed a mild and efficient methodology wherein aryl TBS ethers are selectively deprotected in the presence of alkyl TBS ethers by using cesium carbonate (Cs_2CO_3), which is a non-toxic and mild base.

Initially, we found that aryl trimethylsilyl (TMS) ethers and aryl TBS ethers could couple with aryl halides to give the corresponding biaryl ethers in excellent yields by using cesium carbonate in DMF.[14] This result prompted us to investigate the deprotecting effects of Cs_2CO_3 on aryl silyl ethers. We then found that *p*-methylphenylsilyl ether could be cleaved using 0.5 equiv. Cs_2CO_3 in DMF–H_2O (10:1, v/v) at room temperature to give *p*-methylphenol (Scheme 1). We also tested other solvents such as THF–H_2O, dichloromethane–H_2O, acetonitrile–H_2O, dioxane–H_2O, water, and ethanol–H_2O. As shown in Table 1, the results indicate that wet DMF is the most suitable solvent.

We examined a variety of substrates including aryl TBS ethers and alkyl TBS ethers.[15] As shown in Table 2, all aryl TBS ethers could be cleaved smoothly using 0.1–0.5 equiv. Cs_2CO_3 in wet DMF at room temperature (Table 2, entries 1–11), while alkyl (Table 2, entries 14–17), benzyl and allyl TBS ethers gave very poor deprotected products or did not react under the same conditions. However, benzyl and allyl TBS ethers could be cleaved at 100°C to afford the corresponding alcohols in high yields (Table 2, entries 12 and 13). We observed that the deprotection of aryl TBS ethers was facilitated if an electron-withdrawing group was present on the aromatic ring (Table 2, entries 1–4). On the other hand, the presence of an electron-donating group on the aromatic ring impeded the desired transformation (Table 2, entries 10–11).

In order to establish the chemoselectivity of this method, the aryl silyl ethers containing other sensitive groups were allowed to cleave in DMF–H_2O (10:1, v/v)



Scheme 1.

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Table 1. Deprotection of TBS ethers in various solvents

Entry	Equiv. of Cs_2CO_3	Solvent	T (°C)	Reaction time (h)	Yield (%)
1	0.5	DMF–H_2O (10:1, v/v)	rt	2.5	97[a]
2	1.0	THF–H_2O (50:1, v/v)	rt/reflux	24	No reaction
3	1.0	DCM–H_2O[b]	rt/reflux	24	No reaction
4	0.5	CH_3CN–H_2O (10:1, v/v)	rt/reflux	24	Trace/61[a]
5	1.0	Dioxane–H_2O (10:1, v/v)	rt/reflux	24	No reaction
6	1.0	H_2O	rt/reflux	24	No reaction
7	0.5	EtOH–H_2O (10:1, v/v)	rt/reflux	24	Trace

[a] Isolated yield (average of two runs).
[b] H_2O-saturated dichloromethane.

Table 2. Deprotection of aryl and alkyl TBS ethers to phenols and alcohols using Cs_2CO_3 in DMF–H_2O (10:1, v/v)

Entry	Silyl ethers	Equiv. of Cs_2CO_3	T (°C)	Reaction time (h)	Yield (%)[a]
1	4-$NO_2C_6H_4$OTBS	0.1	rt	0.5	99
2	4-ClC_6H_4OTBS	0.1	rt	1.0	99
3	4-$CHOC_6H_4$OTBS	0.5	rt	1.0	99
4	2-$CHOC_6H_4$OTBS	0.5	rt	2.5	95
5	C_6H_5OTBS	0.5	rt	2.5	98
6	4-MeC_6H_4OTBS	0.5	rt	2.5	97
7	4-*t*-BuC_6H_4OTBS	0.5	rt	2.5	96
8	2-MeC_6H_4OTBS	0.5	rt	3.0	95
9	3-MeC_6H_4OTBS	0.5	rt	3.0	92
10	3-$NH_2C_6H_4$OTBS	0.5	rt	3.0	88
11	4-$MeOC_6H_4$OTBS	0.5	rt	3.0	88
12	$C_6H_5CH_2$OTBS	1.0	100	1.0	95
13	$C_6H_5CH{=}CHCH_2$OTBS	1.0	100	3.0	89
14	$ClCH_2CH_2$OTBS	1.0	100	12	37
15	*n*-C_8H_{17}OTBS	1.0	100	24	23
16	*i*-C_8H_{17}OTBS	1.0	100	48	8[b]
17	Cyclo-C_6H_{11}OTBS	1.0	100	48	No reaction

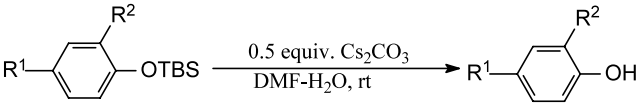
[a] Isolated yield (average of two runs).
[b] Yield based on GC analysis.

in the presence of 0.5 equiv. of cesium carbonate at room temperature.[15] Our results are summarized in Table 3. The aryl silyl ethers could be deprotected cleanly to give the corresponding phenols in very high yields, while TBS-protected alcohols (Table 3, entries 1 and 10), carboxylic esters (Table 3, entries 2–4, 7 and 9), and a representative example each of a tetrahydropyranyl (THP)-protected alcohol (Table 3, entry 5), sulfonate (Table 3, entry 6) as well as phenyloxycarbonyl-protected alcohol (Table 3, entry 8) were unscathed under these conditions.

It is important to seek a method to deprotect aryl TBS ethers in the presence of alkyl TBS ethers, since this selectivity is often required in the synthesis of complex molecules in many laboratories. Although TBAF is widely used for deprotection of silyl ethers, its use in this particular transformation requires carefully controlled reaction conditions. Recently, Ankala and coworkers[13] reported a selective deprotection of aryl TBS ethers in the presence of alkyl TBS ethers, but an excess of base (i.e. 3.0 equiv. of LiOH in DMF) must be used. In our case, the bis-TBS ethers **1** and **4** were deprotected selectively to the corresponding phenols **2** and **5** using 0.5 equiv. of cesium carbonate at room temperature. Indeed, we found that complete desilylation can be achieved with 1.0 equiv. of cesium carbonate at 100°C (Scheme 2).

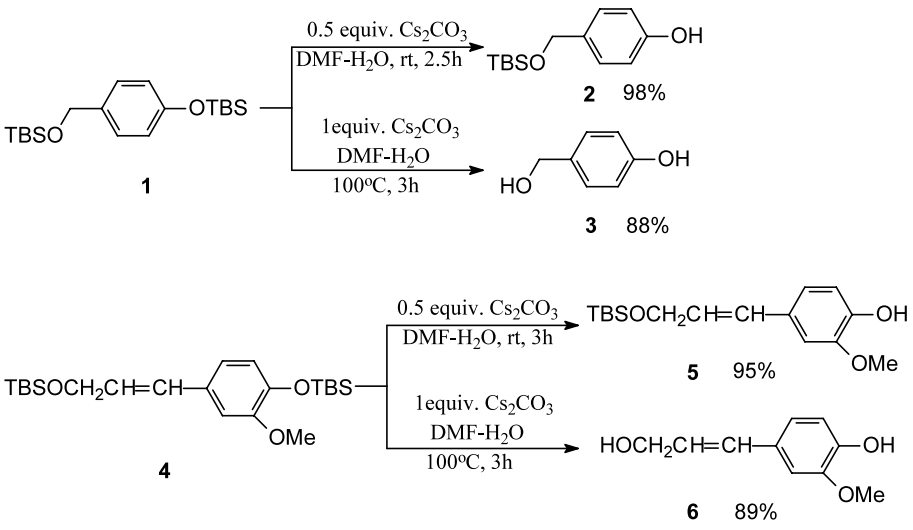
It has been reported that K_2CO_3/EtOH[7] and LiOH/DMF[13] could cleave aryl silyl ethers easily. Further-

Table 3. Selective deprotection of aryl TBS ethers



Entry	R^1	R^2	Reaction time (h)	Yield (%)[a]
1	CH_2OTBS	H	2.5	98
2	$CH_2CO_2CH_3$	H	2.5	96
3	CO_2CH_3	H	1.0	96
4	$COOC_2H_5$	H	1.0	95
5	CH_2OTHP	H	2.5	90
6	CH_2OTs	H	2.5	93
7	CH_2O_2CPh	H	2.0	91
8	$CH_2OCO_2CH_2Ph$	H	2.0	91
9	$CH{=}CHCOOCH_3$	OMe	2.0	92
10	$CH{=}CHCH_2$OTBS	OMe	3.0	95

[a] Isolated yield (average of two runs).



Scheme 2.

more, a study of the stability of alkyl and aryl silyl ethers under acidic and basic conditions by Davies et al. revealed that while acidic conditions facilitate cleavage of alkyl silyl ethers, basic conditions favor cleavage of aryl silyl ethers.[16] Our investigation has shown that Cs_2CO_3 can serve as an appropriate base to perform the required selective deprotection.

In summary, we have developed a mild and efficient method for the deprotection of aryl TBS ethers. The protecting group TBS could be cleaved from aryl TBS ethers using cesium carbonate in DMF–H_2O at room temperature to give the corresponding phenols in high yields. The reaction conditions allow selective deprotection of aryl TBS-protected phenols in the presence of TBS, phenyloxycarbonyl or tetrahydropyranyl-protected alcohols. This method can be used for a wide range of substrates.

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