Desilylation of *tert*-Butyldimethylsilyl Ethers of Phenols

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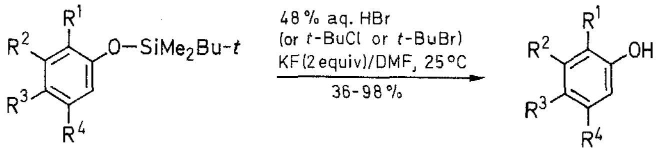
Treatment of *tert*-butyldimethylsilyl ethers of phenols and diphenols with potassium fluoride in the presence of catalytic amounts of hydrobromic acid in dimethylformamide generates the corresponding phenols or diphenols in high yields.

The *tert*-butyldimethylsilyl (TBDMS) group is widely used as a protecting group for the hydroxy functionality.[2] Although there are many reagents available for the regeneration of alcohols from their TBDMS ethers,[2,3] the choice of reagents for the regeneration of phenols from their TBDMS ethers is limited to tetrabutylammonium fluoride (TBAF)[2-4] in tetrahydrofuran or aqueous hydrofluoric acid/sodium fluoride buffer at pH 5 in tetrahydrofuran.[5] The former reagent is by far the most widely used one, whereas the latter, although useful for the regeneration of a base-sensitive phenol, has been applied to only one example. In this paper, we report on a mild method for the desilylation of TBDMS ethers of phenols and diphenols.

In initial experiments we found that the treatment of TBDMS ethers of phenols with potassium fluoride in dimethylformamide in the presence of *tert*-butyl bromide generates the corresponding phenols in high yields (Table 2, entry 1).[6] Desilylation is mostly incomplete if either *tert*-butyl bromide or potassium fluoride is omitted (entries 2 and 3). *tert*-Butyl chloride also catalyzes desilylation (entry 4), but it is less effective than *tert*-butyl bromide under comparable conditions. The mechanism by which *tert*-butyl bromide catalyzes desilylation is not clear. It is possible that *tert*-butyl bromide weakens the O–Si bond through the co-ordination of the incipient *tert*-butyl carbocation with oxygen, thereby facilitating attack by fluoride ion on silicon. However, it is also possible that the actual catalyst is the trace amounts of hydrogen bromide produced by the reaction of *tert*-butyl bromide with traces of water that may be present in the solvent. Indeed, hydrobromic acid is a more effective catalyst than *tert*-butyl bromide for the desilylation of a variety of TBDMS ethers both in terms of equivalents of catalyst and of time required for completion of the reaction (compare entries 1 and 5). Dimethylformamide is the solvent of choice for this



1 TBDMS ethers
3 bis(TBDMS) ethers

2 phenols
4 diphenols

1, 3	R^1	R^2	R^3	R^4
1a	H	CHO	F	H
1b	H	H	F	H
1c	F	CHO	H	H
1d	H	H	H	H
1e	OMe	H	H	H
1f	H	OMe	H	H
1g	H	H	OMe	H
1h	H	OCH$_2$Ph	OCH$_2$Ph	H
3a	H	H	H	OSiMe$_2$Bu-*t*
3b	F	CHO	H	OSiMe$_2$Bu-*t*
3c	H	CHO	OSiMe$_2$Bu-*t*	H

2, 4	R^1	R^2	R^3	R^4
2a	H	CHO	F	H
2b	H	H	F	H
2c	F	CHO	H	H
2d	H	H	H	H
2e	OMe	H	H	H
2f	H	OMe	H	H
2g	H	H	OMe	H
2h	H	OCH$_2$Ph	OCH$_2$Ph	H
4a	H	H	H	OH
4b	F	CHO	H	OH
4c	H	CHO	OH	H

Table 1. Properties of TBDMS Ethers

Compound	bp (°C)/Torr or mp (°C)	Molecular Formula[c]	MS[a] *m/z*	Exact Mass[a] *m/z*	IR (neat) ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ
1a	108–109/2.2	$C_{13}H_{19}FO_2Si$ (254.1)	254 (M$^+$)	calc. 254.1137 found 254.1137	1690	0.20 (s, 6H); 0.98 (s, 9H); 6.99–7.10 (m, 2H); 7.22–7.30 (m, 1H); 10.30 (s, 1H)
1b	71–72/0.4	$C_{12}H_{19}FOSi$ (226.1)	226 (M$^+$)	calc. 226.1188 found 226.1179		0.18 (s, 6H); 1.00 (s, 9H); 6.58–6.92 (m, 4H)
1c	114–115/2.4	$C_{13}H_{19}FO_2Si$ (254.1)	254 (M$^+$)	calc. 254.1137 found 254.1144	1690	0.21 (s, 6H); 1.02 (s, 9H); 7.04–7.45 (m, 3H); 10.34 (s, 1H)
1d	220–221/750	$C_{12}H_{20}OSi$ (208.1)	208 (M$^+$)	calc. 208.1282 found 208.1286		0.16 (s, 6H); 1.00 (s, 9H); 6.82–7.35 (m, 5H)
1e	120–121/15	$C_{13}H_{22}O_2Si$ (238.1)	238 (M$^+$)	calc. 238.1388 found 238.1383		0.18 (6H); 1.00 (s, 9H); 3.72 (s, 3H); 6.79 (s, 4H)
1f	134–136/15	$C_{13}H_{22}O_2Si$ (238.1)	238 (M$^+$)	calc. 238.1388 found 238.1386		0.17 (s, 6H); 0.98 (s, 9H); 3.70 (s, 3H); 6.30–6.50 (m, 3H); 6.95–7.17 (m, 1H)
1g	127–129/15	$C_{13}H_{22}O_2Si$ (238.1)	238 (M$^+$)	calc. 238.1388 found 238.1383		0.18 (s, 6H); 1.00 (s, 9H); 3.72 (s, 3H); 6.75 (s, 4H)
1h	49	$C_{26}H_{32}O_3Si$ (420.2)	420 (M$^+$)	calc. 420.2119 found 420.2118		0.20 (s, 6H); 1.00 (s, 9H); 5.06 (s, 2H); 5.15 (s, 2H); 6.23–6.87 (m, 3H); 7.25–7.46 (m, 10H)
3a	130/0.25	$C_{18}H_{34}O_2Si_2$ (338.2)	338 (M$^+$)	calc. 338.2095 found 338.2088		0.20 (s, 12H); 1.00 (s, 18H); 6.28–6.50 (m, 3H); 6.93–7.20 (m, 1H)
3c	156–158/0.5	$C_{19}H_{34}O_3Si_2$ (366.2)	367[b] (M$^+$ + 1)	calc. 367.2123[b] found 367.2119[b]	1680	0.18 (s, 6H); 0.24 (s, 6H); 0.97 (s, 9H); 1.01 (s, 9H); 6.69–6.93 (m, 2H); 7.21–7.26 (m, 1H); 10.38 (s, 1H)

[a] Unless noted otherwise, MS data refer to EIMS.

[b] Chemical Ionization.

reaction and little or no desilylation takes place in tetrahydrofuran or acetonitrile. Hydrochloric acid is less effective than hydrobromic acid as larger amounts of it and longer reaction times are needed to effect complete desilylation.

In general, when compared to the desilylation of the unsubstituted TBDMS ether **1d**, desilylation is faster and requires smaller amounts of hydrobromic acid when electron-withdrawing groups are present in the ring (entries 5–8, 17, 18), and is slower and requires larger amounts of hydrobromic acid when electron-donating groups are present in the ring (entries 11–16). The method is particularly suitable for the regeneration of a base-sensitive phenol (or diphenol). Thus, while attempted desilylation of the bis(TBDMS) ether **3b** with TBAF/THF gives mostly tar, application of the present method affords the diphenol **4b** in 91% yield (entry 17).

Table 2. Desilylation of TBDMS Ethers of Phenols[a]

Entry	TBDMS Ether	KF (equiv)[b]	Alkyl or Inorganic[c] Halide (equiv)[b]	Reaction Time (h)	Product (Yield %)[d]
1	**1a**	2	*t*-BuBr (1.2)	24	**2a** (95)
2	**1a**	2	none	24	**2a** (27) + **1a** (70)
3	**1a**	none	*t*-BuBr (1.2)	48	**2a** (20) + **1a** (72)
4	**1a**	2	*t*-BuCl (1.2)	24	**2a** (75) + **1a** (22)
5	**1a**	2	HBr (0.1)	0.5	**2a** (95)
6	**1a**	2	HBr (0.01)	2	**2a** (36) + **1a** (52)
7	**1b**	2	HBr (0.1)	0.5	**2b** (93)
8	**1c**	2	HBr (0.1)	0.5	**2c** (94)
9	**1d**	2	HBr (0.1)	22	**2d** (90)
10	**1d**	2	HBr (0.2)	2	**2d** (90)
11	**1e**	2	HBr (0.3)	2	**2e** (92)
12	**1f**	2	HBr (0.3)	2	**2f** (93)
13	**1g**	2	HBr (0.3)	2	**2g** (96)
14	**1h**	2	HBr (0.2)	6	**2h** (97)
15	**1h**	2	HBr (0.3)	4	**2h** (98)
16	**3a**	2	HBr (0.3)	2	**4a** (91)
17	**3b**	2	HBr (0.1)	1	**4b** (91)
18	**3c**	2	HBr (0.2)	2	**4c** (87)

[a] All reactions were done at 25°C in anhydrous DMF.

[b] Molecular equivalents per TBDMS ether group.

[c] In all cases the halide was 48% hydrobromic acid.

[d] Yields of isolated pure products. Purities were checked by TLC (silica gel, Analtech) and ^{1}H-NMR analyses.

Table 3. Phenols **2** or Diphenols **4** obtained by Desilylation of Their TBDMS Ethers **1** or **3**, Respectively[a]

Compound	mp (°C) or bp (°C)/Torr		IR (Nujol) ν(cm^{-1})
	found	Lit.	
2a	73–75 (Et_2O/PE[b])	74–75[8]	1680 (C=O); 3430 (OH)
2b	47–48 (PE)	48[11]	
2c	111–112 (Et_2O/PE)	112–113[8]	1660 (C=O); 3200 (OH)
2d	181–182/1 atm	181.75/1 atm[13]	
2e	204–205/1 atm]	205.5/1 atm[13]	
2f	142–144/25	144/25[13]	
2g	56–57 (Et_2O/pentane)	57[13]	
2h	111–112 (toluene/hexane)	111–112[10]	
4a	109–111 (Et_2O/pentane)	111[13]	
4b	180–182 (Et_2O/PE)	[c]	1660 (C=O); 3200, 3430 (OH)
4c	97–98 (Et_2O/PE)	99[12]	

[a] For yields, see Table 2.

[b] PE = petroleum ether.

[c] $C_7H_5FO_3$ calc. C 53.86 H 3.23
(156.1) found 53.97 3.10
MS (EI): $m/z = 156$ (M^+).
^{1}H-NMR ($CDCl_3$/DMSO-d_6): $\delta = 6.67$–6.78 (m, 2H); 8.87 (s, 1H, OH); 9.24 (s, 1H, OH); 10.20 (s, 1H, CHO).

The advantages of this method of desilylation of TBDMS ethers of phenols over the existing methods are that the reagents used are inexpensive and readily available, the procedure is simple, and the conditions are mild enough for the regeneration of a base-sensitive phenol.

Compounds **1a**,[8] **1c**,[8] and **3b**[7] were prepared following literature procedures. Compounds **1b**, **1d–h**, and **3a, c** were prepared by the method of Ref. 9 in > 90% yield, in each case, from the corresponding phenols. Phenols **2b**, **2d–g**, and **4a, c** were obtained from commercial sources and phenol **2h** was prepared from 3,4-bis(benzyloxy)benzaldehyde following the literature procedure.[10] The physical properties and analytical data for the new TBDMS ethers and for the known TBDMS ethers which have not been adequately characterized earlier, are given in Table 2.

Cleavage of *tert*-Butyldimethylsilyl (TBDMS) Ethers 1, 3 of Phenols or Diphenols; General Procedure:

A mixture of the TBDMS ether **1** or **3** (1 equiv, generally 1–10 mmol), anhydrous KF (2 equiv per TBDMS group), and the alkyl halide or 48% aqueous HBr (in the amounts indicated in Table 2) in dry DMF (3–6 mL per mmol of TBDMS group) is stirred under argon at 25°C until the reaction is complete as judged by TLC (see Table 2). The mixture is then poured, with cooling, into 2N aqueous HCl (15 mL per mmol of TBDMS group). The aqueous mixture is extracted with Et_2O (3 × 20 mL per mmol of TBDMS group). The combined extracts are washed with saturated NaCl solution (30 mL), and dried (Na_2SO_4). The solvent is evaporated under reduced pressure and the residue is chromatographed (products phenols **2a, c** and **4b, c**, on a column of 70–230 mesh silica gel with CH_2Cl_2/MeOH 10:1 as the eluent) or distilled (products **2d, f**) or recrystallized (products **2b, e, g, h** and **4a**).

The known phenols thus obtained were characterized by comparing their mp or bp with those reported (Table 3) and by obtaining satisfactory ^{1}H-NMR-spectral data (not shown).

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