Selective Cleavage of *tert*-Butyldimethylsilyl Ethers with Neutral Alumina

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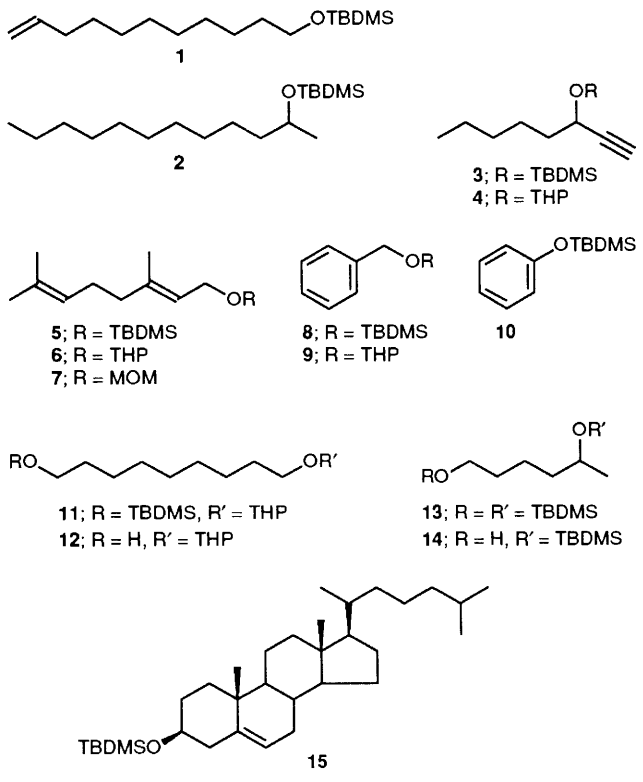
Neutral alumina, partially deactivated with 1.5–3% water, is an efficient and selective agent for cleavage of *tert*-butyldimethylsilyl ethers in the presence of other acid-sensitive protective groups for alcohols.

Conversion of alcohols into *tert*-butyldimethylsilyl ethers is a widely used method of protection in organic synthesis.[1] Selective removal of the *tert*-butyldimethylsilyl (TBDMS) group has been achieved by using among others tetrabutylammonium fluoride–tetrahydrofuran,[2] aq. HF–MeCN,[3] KF–crown ether,[4] $BF_3 \cdot Et_2O$–$CHCl_3$,[5] *N*–bromosuccinimide–aq. dimethylformamide,[6] $CF_3SO_3SiMe_3$–CH_2Cl_2,[7] NH_4F–MeOH[8] and SiF_4–MeCN.[9] However, while fluoride ions are very basic especially under anhydrous conditions and therefore cannot be used in base-sensitive molecules,[10,11] other



procedures are obviously not acceptable for acid-sensitive systems and, consequently, the development of alternative selective methods of deprotection under neutral conditions would be desirable.

In connection with our synthesis of a new difluoro analogue of the sex pheromone of the pine processionary moth,[11] we have found that cleavage of *tert*-butyldimethylsilyl ethers occurs in almost quantitative yield upon purification on neutral alumina. This reaction, which to our knowledge is surprisingly unprecedented in the literature, takes place when neutral alumina is mixed with silyl ethers in non-polar solvents, *i.e.* hexane, whereas no desilylation occurs in more polar solvents, such as diethyl ether, ethyl acetate or methanol. This observation agrees with previous reports wherein no desilylation has been detected when TBDMS ethers were treated with basic alumina in acetonitrile[12] or after purification by column chromatography eluting with CH_2Cl_2–MeOH.[7]

As shown in Table 1, when a variety of TBDMS ethers (primary, secondary, allylic, propynylic, *etc.*) were allowed to react at room temperature with activated neutral alumina containing 1.5–3% of water, cleavage of the ethers occurred and the corresponding alcohols obtained in good to excellent yields. As expected, while primary allylic TBDMS ethers (*i.e.* **5**) reacted faster than the corresponding saturated (compounds **1**, **11**, entries 1, 11) and benzylic ethers (compound **8**, entry 8), secondary compounds **2** and **15** required more active alumina than the corresponding primary ethers (*cf.* entries 1, 2, 11, 13). Therefore, selective cleavage of a primary TBDMS group in the presence of a secondary one, *i.e.* in compound **13**, could be achieved straightforwardly and in excellent yield (compound **14**,† entry 12). In addition, removal of a propynylic secondary TBDMS group, such as in compound **3**, occurs readily in only 6 h using alumina impregnated with 1.5% water (entry 3), and faster than that of the corresponding non-propynylic ether (entry 2). Moreover, different alcohols protected with other acid-sensitive groups, such as tetrahydropyranyl (THP) (compounds **4**, **6** and **9**) and methoxymethyl (MOM) (compound **7**[13]), were recovered unchanged when treated with the less activated support (entries 6, 7, 9) and only slightly deprotected (*i.e.* **4**) with the more active alumina (entry 4). This fact was exploited to remove selectively the TBDMS group in the presence of a THP function in excellent yield (compound **11**,[14] entry 11). The method cannot be applied, however, to silylated phenols (*i.e.* **10**, entry 10) since, although complete deprotection occurs under similar reaction conditions to those for alcohols, the resulting phenol remains tightly adsorbed to the support and, consequently, cannot be successfully recovered.

Table 1 Selective cleavage of *tert*-butyldimethylsilyl ethers in the presence of other acid-sensitive protective groups with neutral alumina

Entry	Substrate	Alumina[a] (% water)	Time/h	Method[b]	Alcohol[c]	Other[c]
1	**1**	3	20	A	98	
2	**2**	1.5	21	B	83	
3	**3**	1.5	6	B	85	
4	**4**	1.5	6	B	18	**4:** 57
5	**5**	3	6	A	81	
6	**6**	3	22	A	0	**6:** 98
7	**7**	3	6	A	0	**7:** 95
8	**8**	3	15	A	98	
9	**9**	3	16	B	0	**9:** 98
10	**10**	3	25	B	41	
11	**11**	3	16	B	**12:** 98	
12	**13**	3	17	B	**14:** 97	—[d]
13	**15**	1.5	24	B	86	

[a] Commercial neutral alumina was activated by heating at 85 °C at 0.1 Torr (1 Torr ≈ 133 Pa) for 16 h. After cooling, the specified amount of water was added and the mixture vigorously stirred to get the ready-to-use support. [b] See text. [c] Isolated yield. [d] Traces of diol were also detected.

The general procedure is as follows. To a solution of the TBDMS ether (*ca.* 200 mg) in hexane (20 ml) was added neutral alumina (Merck 70–230 mesh, 10 g, 50 : 1 with respect to the substrate), prepared as indicated in Table 1, and n-tridecane (2 μl) as internal standard. The mixture was stirred at room temperature and the reaction progress (disappearance of the silyl ether since the resulting alcohol remains adsorbed to the support) directly monitored by GC analysis (SPB-5 fused silica capillary column 30 m × 0.32 mm i.d.). When the reaction was complete, the mixture was filtered through a sintered-glass funnel (No. 4) and washed thoroughly with hexane to remove traces of unreacted starting material. Further washings with ethyl acetate or methanol yields the expected alcohol, in pure form as shown by TLC, GC and NMR spectroscopy (Method A). The resulting alcohol may be contaminated with *tert*-butyldimethylsilanol, which can be removed under reduced pressure. In the case of volatile alcohols, the hexane washings were omitted and, after recovery of the crude products from the alumina with ethyl acetate or methanol, conventional column chromatography on silica gel afforded the pure alcohols, free from the silanol, in good to excellent yields (Method B).

In summary, selective cleavage of TBDMS ethers in the presence of other acid-sensitive protective groups (THP, MOM, *etc.*) can be easily attained with neutral alumina under very mild conditions and in high yields. Moreover, the easy availability and low price of the support makes the process attractive in comparison with other deprotection agents.

† *Selected spectroscopic data* for **14** based on 2D HETCOR experiments: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (1H, m, CHO), 3.64 (2H, t, *J* 6.3 Hz, CH_2OH), 1.54 (2H, m, CH_2CH_2OH), 1.45 (1H, c, 4-H_A), 1.39 (1H, c, 3-H_B), 1.36 (1H, c, 4-H_B), 1.30 (1H, c, 3-H_A), 1.09 (3H, d, *J* 6.1 Hz, CH_3CH), 0.87 (9H, s, Me_3C) and 0.04 (6H, ds, Me_2Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.5 (C-5), 62.8 (C-1), 39.3 (C-4), 32.7 (C-2), 25.8 (Me_3), 23.7 (C-6), 21.8 (C-3), 18.1 (Me_3C), −4.4 and −4.7 (Me_2Si). Satisfactory C and H analyses were obtained.

We gratefully acknowledge DGICYT (PB 90-0089) for financial support and Departament d'Ensenyament (Generalitat de Catalunya) for a predoctoral fellowship to J. F. and A. C.

Received, 6th July 1992; Com. 2/03534K

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