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Silyl group deprotection by Pd/C/H_2. A facile and selective method

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Abstract—An easy, high yield, RT, short-reaction-time Pd/C hydrogenation of silyl groups is described. This includes TES, TPS, TBS, TBDMS, TIPS, and TBDPS. The relative selectivity of the process has been investigated and we can show, for example, that TES, TPS, TBS, and TBDMS removal can be performed in the presence of TIPS and TBDPS.

A variety of methods are available for the deprotection of silyl groups.[1,2] Among the most widely used are fluorides and acids. Recently, the use of catalysts, palladium hydroxide,[3] PdO,[4] and Pd/C[5,6] has been reported.

We are describing here a method, which complements the known procedures and also provides some unique advantages. This method, which is based on the use of Pd/C/H_2, deprotects silyl groups such as TES, TPS, TBS, and the more resilient, TBDMS, TIPS, and TBDPS. In addition, remarkable selectivity can be achieved by this procedure, allowing for the removal of one group in the presence of others, cleanly and in high to quantitative yield.

Perhaps the most attractive features of this procedure are its simplicity, short reaction times, ease of operation and the lack of aqueous work-up. The substrate is stirred in methanol, 5% Pd/C under H_2 at atmospheric pressure and room temperature for 1 min to a few hours, depending on the silyl group to be removed. The reaction mixture is filtered through celite and the solvent evaporated.[7] In many cases, a chromatography is not necessary. Tables 1 and 2 show examples we have selected. We were particularly interested in the removal of resistant silyl groups such as TBDMS, TIPS, and TBDPS (Table 1), and in the selectivity process (Table 2).

As can be seen, the reactivity of the groups toward the hydrogenolysis is TES > TPS > TBS ≫ TBDMS > TIPS > TBDPS. Entries 1, 10, 11, 14, 15, and 21 show that the TES group requires only 1–2 min reaction times. At the other end of the spectrum, the deprotection of TBDPS derivatives (entries 5 and 8) takes much longer. Also, the deprotection yields are not as high as the other silyl groups.

As a general rule, the time for the hydrogenolysis is determined by the amount of catalyst used. TES, TPS, and TBS are cleaved easily with small amounts of catalyst in 1 or 2 min. On the other hand, TBDMS, TIPS, and TBDPS are removed with 3–4 times the amount of catalyst. With smaller quantities of catalyst, however, TBDMS and TIPS can still be reduced cleanly and in high yields, albeit in longer reaction times, for example, entry 4, takes 20 min for complete hydrogenolysis under condition c (data not shown). The ease of hydrogenolysis also depends on the structure of the silylated molecule; for example, entries 6 and 12 are both primary TBDMS derivatives. However, it takes longer to deprotect the bicyclic prostaglandin synthon (entry 12) than the straight chain TBDMS compound (entry 6). In this case, it is likely that the β-carbon steric effect is also a factor in the binding of the TBDMS group to the catalyst.

As can be seen from the tables, in selected cases we also carried out the reaction without hydrogen (Method 2). We wanted to make sure that hydrogenolysis was really responsible for the cleavage of the silyl protecting group.

Keywords: Hydrogenolysis; TES; TPS; TBS; TBDMS; TIPS; TBDPS.
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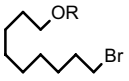
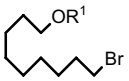
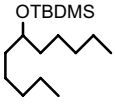
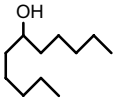
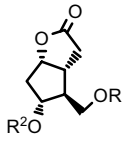
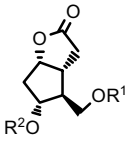
Table 1. Desilylation of primary and secondary silyl compounds

Entry	Substrate	Product	Method[a] (1) = Pd/C/ H_2 (2) = Pd/C	Reaction time	Yield (%)[b]
					
1	R = TES	R^1 = H	1[c] (2[d])	2 min (5 h)	>99 (>99)
2	R = TPS	R^1 = H	1[c] (2[d])	2 min (7 h)	99 (99)
3	R = TBS	R^1 = H	1[c]	6 min	>99
4	R = TBDMS	R^1 = H	1[d]	5 min	96
5	R = TBDPS	R^1 = H	1[e]	19 h	69
					
6	R = TBDMS	R^1 = H	1[d]	5 min	96
7	R = TIPS	R^1 = H	1[e]	7 h	94
8	R = TBDPS	R^1 = H	1[e]	15 h	74
9			1[d]	1.5 h	97
10			1[c]	1.5 min	98
					
11	R = TES, R^2 = Bz	R^1 = H, R^2 = Bz	1[d]	2 min	100
12	R = TBDMS, R^2 = Bz	R^1 = H, R^2 = Bz	1[e]	4 h	>99
13	R = TBDMS, R^2 = H	R^1 = H, R^2 = H	1[e]	50 min	>99

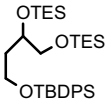
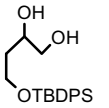
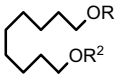
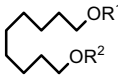
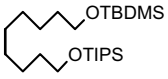
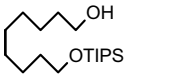
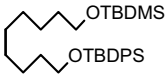
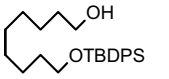
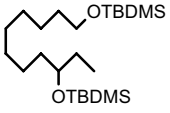
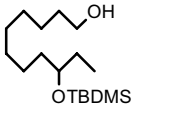
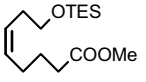
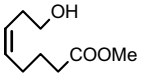
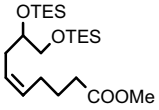
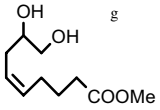
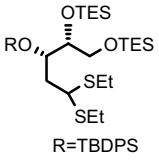
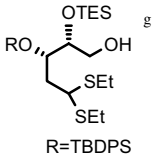
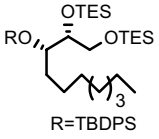
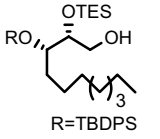
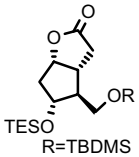
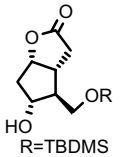
[a] In all entries, 5% Pd/C was used and reactions were carried out in MeOH.
[b] Isolated yield. Entry 7 is 86% based on recovered starting material.
[c] 0.036 mmol substrate, 2.5 mg Pd/C.
[d] 0.036 mmol substrate, 10 mg Pd/C.
[e] 0.036 mmol substrate, 30 mg Pd/C.

We were also interested to check if the more widely used TBDMS, TIPS, and TBDPS could also react under those conditions. We found out that, in contrast to TES, TPS, TBS, they cannot be removed by procedure 2.

Entries 15–17 of Table 2 show that TES, TPS, TBS can be hydrogenolyzed in the presence of TBDMS in close to quantitative yields. It is also of interest to note that TBDMS could be easily removed in the presence of TIPS (entry 18) and TBDPS (entry 19), affording further flexibility in the selection of protecting groups when multi-protection is necessary. TIPS, which is slightly more reactive toward hydrogenolysis than TBDPS, cannot be selectively removed in the presence of TBDPS (data not shown). One interesting observation, which is also worth mentioning is that in the TES hydrogenolysis (entries 21 and 22) the double bond has survived. In one instance, we attempted to hydrogenolyze a TES group in the presence of a secondary acetylene. Partial hydrogenation of the acetylene also occurred (data not shown). Entries 23 and 24 show that we can get good selectivity with the hydrogenolysis of the primary silyl group. This is of particular interest since these synthons could be used for synthesis of natural products containing vicinal diols such as lipoxins and diHETEs. We used a greater amount of catalyst in entry 23 in order to overcome the poisoning due to sulfur in the molecule.

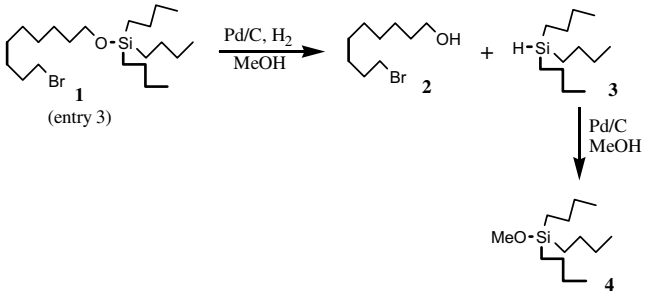
The silyl deprotection probably proceeds through the Pd-mediated hydrogenolysis of the silyl ether

Table 2. Selective desilylation

Entry	Substrate	Product	Method[a] (1) = Pd/C/ H_2 (2) = Pd/C	Reaction time	Yield (%)[b]
14			1[d]	2 min	99
					
15	R = TES, R^2 = TBDMS	R^1 = H, R^2 = TBDMS	1[c] (2[d])	1.3 min (4.5 h)	>99 (>99)
16	R = TPS, R^2 = TBDMS	R^1 = H, R^2 = TBDMS	1[c] (2[d])	1.5 min (7 h)	98 (97)
17	R = TBS, R^2 = TBDMS	R^1 = H, R^2 = TBDMS	1[c]	5 min	97
18			1[d]	10 min	97
19			1[d]	30 min	98
20			1[d]	12 min	88
21			1[d] (2[d])	1 min (4.5 h)	98 (>99)
22		 [g]	1[d] (2[d])	2 min (11 h)	>99 (94)
23	 R=TBDPS	 [g] R=TBDPS	1[e] (2)	3.5 min (73 h)	82 (71)
24	 R=TBDPS	 R=TBDPS	1[f]	3 min	83
25	 R=TBDMS	 R=TBDMS	1[d]	2 min	97

[a] In all entries, 5% Pd/C was used and reactions were carried out in MeOH.
[b] Isolated yield. Entry 7 is 86% based on recovered starting material.
[c] 0.036 mmol substrate, 2.5 mg Pd/C.
[d] 0.036 mmol substrate, 10 mg Pd/C.
[e] 0.028 mmol substrate, 10.2 mg Pd/C.
[f] 0.040 mmol substrate, 3.25 mg Pd/C.
[g] Spectroscopic data of the products of entries 22 and 23 are shown in references 9 and 10, respectively.

affording the alcohol and silane (Scheme 1). We are assuming that the silanes under these conditions are converted to methoxysilanes, which we have isolated in two instances. Tributylmethoxysilane and



Scheme 1. Pd-mediated deprotection of silyl ether.

t-butyldiphenylmethoxysilane were isolated in entries 3 and 8, respectively.

In support of this hypothesis, we have treated commercially available tributylsilane in methanol with Pd/C. Within minutes, tributylmethoxysilane was formed. It is known that silanes afford alkoxysilanes under alcoholysis with several catalysts.[8]

Acknowledgements

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References and notes

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7. The reviewer inquired about the possibility of recycling the Pd/C. We have not attempted to do that since the recovery of the Pd/C is rather tedious and we were concerned about possible contamination of our samples.
8. Sudhakar, S.; Luh, T. Y. *J. Org. Chem.* **2002**, *67*, 6860–6862, and references cited therein.
9. Spectroscopic data of the product of entry 22: ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.71 (qt, $J = 7.32$ Hz, 2H), 2.06–2.38 (m, 6H), 3.5 (dd, $J = 7.0$, 4.0 Hz, 1H), 3.64–3.80 (m, 5H), 5.50 (m, 2H); ^{13}C NMR (360 MHz, $CDCl_3$): δ 24.0, 26.0, 30.5, 31.5, 51.5, 66.0, 71.5, 126.0, 132.0. 174.1.
10. Spectroscopic data of the product of entry 23: ^{1}H NMR (360 MHz, $CDCl_3$): 0.60 (q, $J = 7.86$, 6H), 0.95 (t, $J = 7.89$, 9H), 1.00–1.10 (m, 15H), 1.85–2.02 (m, 2H), 2.05–2.20 (m, 2H), 2.28–2.40 (m, 3H), 3.50 (t, $J = 7.2$ Hz, 1H), 3.58–3.68 (m, 1H), 3.70–3.86 (m, 1H), 4.15–4.22 (m, 1H), 7.34–7.47 (m, 6H), 7.72 (dd, $J = 17.4$, 6.7 Hz, 4H); ^{13}C NMR (360 MHz, $CDCl_3$): δ 14.0, 19.5, 23.2, 23.4, 26.8, 26.9, 27.1, 27.2, 40.8, 48.4, 63.8, 74.4, 75.7, 127.7, 127.6, 129.8, 129.6, 133.0, 134.2, 136.0, 136.3.