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The undesirable lability of *tert*-butyldimethylsilyl ethers under Pd/C-catalyzed hydrogenation conditions and solution of the problem by using a Pd/C(en) catalyst

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Abstract

While the frequent and unexpected loss of the TBDMS protective group of a variety of hydroxylic functions was demonstrated under neutral and mild hydrogenation conditions using 10% Pd/C, the undesirable problem was perfectly overcome by using a 10% Pd/C-ethylenediamine complex catalyst. © 2000 Elsevier Science Ltd. All rights reserved.

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The continuing evolution of organic synthesis is dependent in many ways on complementary advances in the introduction and manipulation of protective groups. Protective groups suitable for contemporary synthesis should comprise efficiency of preparation, selective removal and stability under the intended reaction conditions. Since the introduction of a *tert*-butyldimethylsilyl (TBDMS) group to synthetic chemistry by Corey and Venkateswarlu in 1972,¹ the TBDMS ether has become among the most frequently used silyl protective groups for a hydroxylic function. It is well known that the TBDMS ether is remarkably more stable to a variety of organic reaction conditions than the trimethylsilyl (TMS) ethers, yet it undergoes selective removal under mild conditions that do not attack other functional groups.² Although it has been common knowledge that the TBDMS ether is inert towards hydrogenation conditions,¹ we have made the critical observation that the TBDMS ether can be hydrogenolyzed frequently to form the parent alcohols (e.g. using 10% Pd/C, 1 atm H₂, MeOH solvent, at 20°C).³ This is a serious problem, not only because of the fundamental importance of the TBDMS protective group, but also with regard to its role in multi-step synthesis of complex natural products. The unexpected loss of the TBDMS protective group from a hydroxylic function would cause extensive damage to a synthetic process. We describe herein the frequent loss of the TBDMS protective group when a variety of TBDMS

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ethers were subjected to 10% Pd/C-catalyzed hydrogenation at ambient pressure and temperature. Further, we now also disclose a very practical catalyst that overcomes this undesirable problem.

In our initial investigations, the stability of the *O*-TBDMS group of 3-phenyl-1-propyl TBDMS ether (**1a**),⁴ 3,7-dimethyl-1-octyl TBDMS ether (**1b**) and *O*-TBDMS-cholesterol (**1c**)⁵ under hydrogenation conditions [0.25 mmol of the substrate (**1a–c**) in MeOH (1 mL) under hydrogen atmosphere (1 atm) at room temperature for 24 h] using 10% Pd/C (10% of the weight of the substrate) purchased from Aldrich was studied. Under the reaction conditions, the TBDMS ether (**1a**) was surprisingly and completely hydrogenolyzed to give 3-phenylpropane-1-ol (**2a**) as the sole product in 97% isolated yield (100% conversion yield) and further, the TBDMS ether of **1b** or **1c** underwent slow but appreciable hydrogenolysis (41 or 44%, respectively) under these conditions to give a mixture of **1b** and **2b** or **1c** and **2c** (Fig. 1). On the other hand, the tri-substituted olefin function of **1c** was stable under the conditions. To eliminate the possibility of a contaminated acid or base in 10% Pd/C-catalyzed cleavage of the TBDMS protective group, the reaction of **1a** was performed without hydrogen. As a consequence of the reaction, no desilylation occurred, even after 24 h.

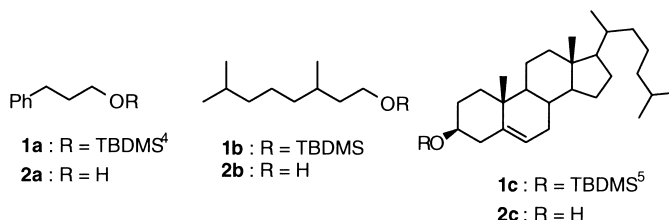


Figure 1.

Recently, we reported a couple of chemo- and regio-selective hydrogenation methods using a carbon-supported Pd-ethylenediamine complex [Pd/C(en)]⁶ which possesses less catalytic activity toward benzyl ethers,^{6a} *N*-Z protective groups,^{6a} aromatic carbonyls,^{6b} and epoxides,^{6c} compared to commercial Pd/C because the coordinated ethylenediamine acts as a gentle catalyst-poison. We expected that employment of 10% Pd/C(en)⁷ instead of 10% Pd/C for the hydrogenation of the TBDMS ethers could not be induced to deprotect the TBDMS group. In fact, the hydrogenolysis of the TBDMS ethers (**1a–c**), using 10% Pd/C(en), led to complete recovery of the starting materials.

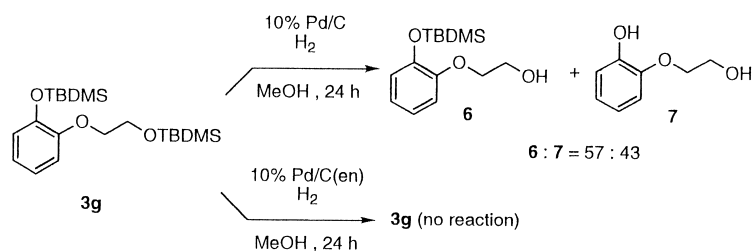
In the light of these results, we decided to explore the generality of the undesirable hydrogenolysis of the TBDMS ether with commercial 10% Pd/C and the adaptability to the chemoselective hydrogenation of 10% Pd/C(en) using various substrates possessing some other reducible functionality such as an olefin, benzyl ether or nitro group within the molecule. The results shown in Table 1 demonstrate that the hydrogenation of readily reducible (less steric hindrance) olefin (entries 1–6, 9 and 10) and nitro (entries 11 and 12) functionalities can be successfully carried out using either 10% Pd/C or 10% Pd/C(en). Although the hydrogenolytic debenzoylation of **3d**⁸ using commercial 10% Pd/C proceeded smoothly (entry 7), the hydrogenation using 10% Pd/C(en) thoroughly tolerates the benzyl ether of **3d** (entry 8) as already reported by us.^{6a} We have made the unexpected and extremely serious observation that the TBDMS protective group of alkyl alcohols (**3a–d**) can be hydrogenolyzed easily using commercial 10% Pd/C (Aldrich) as a catalyst to form the parent alcohols as the sole product,⁹ although an aryl TBDMS

Table 1
Hydrogenation in the presence of *O*-TBDMS group using 10% Pd/C or 10% Pd/C(en) as a catalyst^a

| | | $\text{R}'\text{-OTBDMS } \mathbf{3} \xrightarrow[\text{H}_2, \text{MeOH}, 24 \text{ h}]{\begin{matrix} \text{A } 10\% \text{ Pd/C}^{\text{b}} \\ \text{B } 10\% \text{ Pd/C(en)}^{\text{f}} \end{matrix}} \text{R}'\text{-OTBDMS } \mathbf{4} + \text{R}'\text{-OH } \mathbf{5} \text{ (or } \mathbf{2a})$ | | | | |
|-------|-------------------------|---|--|-------------------------|--|-----|
| Entry | Substrate | Catalyst | Ratio of <i>O</i> -TBDMS cleavage (%) ^d | Product ^e | Yield (%) ^f | |
| 1 | 3a ¹³ | A | 100 | 2a ^e | PhCH ₂ CH ₂ CH ₂ OH | 88 |
| 2 | 3a ¹³ | B | 0 | 4a | PhCH ₂ CH ₂ CH ₂ OTBDMS | 93 |
| 3 | 3b ¹⁴ | A | 100 | 5b ^e | C ₁₀ H ₂₁ OH | 80 |
| 4 | 3b ¹⁴ | B | 0 | 4b ¹³ | C ₁₀ H ₂₁ OTBDMS | 100 |
| 5 | 3c | A | 100 | 5c ^e | CyCH ₂ OH | 74 |
| 6 | 3c | B | 0 | 4c | CyCH ₂ OTBDMS | 92 |
| 7 | 3d ⁸ | A | 100 | 5d ^e | HOCH ₂ CH ₂ OH | 73 |
| 8 | 3d ⁸ | B | 0 | 3d | recovery | 100 |
| 9 | 3e ¹⁰ | A | 8 | 4i + 5i | | - |
| 10 | 3e ¹⁰ | B | 0 | 4i | | 98 |
| 11 | 3f | A | 0 | 4f | | 96 |
| 12 | 3f | B | 0 | 4f | | 99 |

^aUnless otherwise specified, the reaction was carried out using 0.25 mmol of the substrate (**3a-f** and **2a**) with catalyst (10% of the weight of the substrate) in MeOH (1 mL) under hydrogen atmosphere (1 atm) at room temperature for the given reaction time. ^b10% Pd/C was purchased from Aldrich. ^c10% Pd/C(en) was prepared from 10% Pd/C (Aldrich).³ ^dDetermined by ¹H NMR. ^eAll the products were identified by ¹H NMR, ¹³C NMR and/or HRMS. ^fIsolated yield. ^gCommercially available (Aldrich or TCI).

ether (**3e**)¹⁰ seems to be more stable than alkyl TBDMS (only 8% of the *O*-TBDMS cleaved, entry 9, see also Scheme 1).¹¹ It should be noted that the hydrogenolysis tolerates the TBDMS ethers in which an amino moiety forms to coexist (e.g. arylamine) within a molecule of the product due to the catalyst-poisonous effect (**4f**, entry 11).¹² On the other hand, when the 10% Pd/C(en) was used as a catalyst, competitive and reluctant hydrogenolysis of the TBDMS ether was perfectly suppressed without exception under the same conditions (entries 2, 4, 6, 8, 10 and 12). Furthermore, extension of these reactions to bis-TBDMS ethers was also investigated using a



Scheme 1.

model substrate (**3g**). Although complete desilylation of the alkyl TBDMS ether and partial desilylation of the aryl TBDMS ether were observed with commercial 10% Pd/C (6:7 = 57:43), no hydrogenolysis of either the alkyl or aryl TBDMS ether occurred when 10% Pd/C(en) was used as a catalyst (Scheme 1).

In summary, we have clearly demonstrated the unreliability of the TBDMS protective group for hydroxylic functions under the hydrogenation conditions using 10% Pd/C catalyst. Moreover, we have found that the use of the 10% Pd/C(en) catalyst totally suppressed the hydrogenolysis of the TBDMS ether and also applied the catalyst to develop a reliable and chemoselective hydrogenation method of olefin and nitro functionalities in the presence of the TBDMS ether. These findings further reinforce the versatile potential of TBDMS ethers as one of the most popular protective groups in organic synthesis.

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