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A New, Simple, and Selective Palladium-Catalyzed Cleavage of Triethylsilyl Ethers

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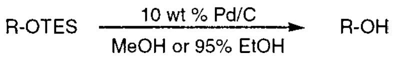
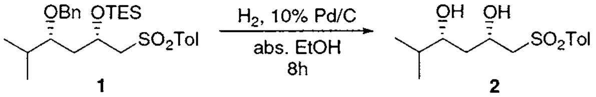
ABSTRACT



A simple procedure for the cleavage of triethylsilyl (TES) ethers in the presence of 10 wt % Pd/C in methanol or 95% ethanol is reported. This method allows selective removal of alkyl TES ethers in the presence of aromatic TES ethers or *tert*-butyldimethylsilyl (TBS) protecting groups.

As part of an ongoing project directed toward the total synthesis of Dolabelides,[1] we found that debenzylation of compound **1** by hydrogenolysis with 10 wt % Pd/C in absolute ethanol provided diol **2** and not the expected monosilylated product (Scheme 1).

Scheme 1



In fact, it has previously been reported in the literature that primary and secondary silyl-protected alcohols such as the TBS and DEIPS ethers could be cleaved using various hydrogenolysis conditions [Pd(OH)$_2$,[2] wet Pd/C,[3] catalytic transfer hydrogenation[4]]. Smith et al. had also noticed, during their synthesis of (+)-phyllanthoside, that it was necessary to carefully monitor hydrogenolysis of the benzyl ethers using 10% Pd/C in freshly distilled ethyl acetate to minimize deprotection of the silyl ethers.[5]

This prompted us to further investigate our case of TES ether deprotection using catalytic Pd/C in ethanol. We thus found that TES ethers could be cleaved in the absence of hydrogen but that a catalytic amount of Pd/C was required to complete the reaction. Herein, we report the use of catalytic Pd/C conditions to affect simple and selective removal of TES ethers from alkyl derivatives without deprotection of TBS groups. This paper encompasses the scope and limitations of this method.

Since first being reported in the early 1970s as protective hydroxyl groups,[6] silyl ethers have received a great deal of attention and a large number of such silyl protective groups are now available to the organic chemist. Among these, TES ethers are very attractive. TES ethers are 10−100 times more stable than TMS ethers and can withstand a much wider range of reaction conditions,[6b] without being as hindered as their TBS counterparts.

To date, a great number of methods have been reported for the cleavage of TES groups,[7] most of them involving acidic, basic, or oxidative conditions. Although selective

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[1] (a) Grimaud, L.; de Mesmay, R.; Prunet, J. *Org. Lett.* **2002**, *4*, 419. (b) Grimaud, L.; Rotulo, D.; Ros-Perez, R.; Guitry-Azam, L.; Prunet, J. *Tetrahedron Lett.* **2002**, *43*, 7477.

[2] Toshima, K.; Yanagawa, K.; Mukaiyama, S.; Tatsuta, K. *Tetrahedron Lett.* **1990**, *31*, 6697.

[3] Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 7808.

[4] (a) Cormier, J. F. *Tetrahedron Lett.* **1991**, *32*, 187. (b) Cormier, J. F.; Isaac, M. B.; Chen, L.-F. *Tetrahedron Lett.* **1993**, *34*, 243.

[5] Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092.

[6] For a review on silyl protective groups, see: (a) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991.

[7] For a review on selective silyl ethers deprotection, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.

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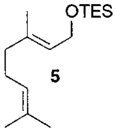
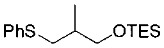
deprotection of such groups in the presence of TBS ethers has also been reported,[7] it was usually as random examples, part of a total synthesis. To our knowledge, only two groups have recently focused on the selective cleavage of TES groups in the presence of TBS. One used a mesoporous silica MCM-41/MeOH system[8] (not always accessible to the organic chemist), and the other used IBX in DMSO[9] (sometimes leading to partial oxidation of the product). Pd/C as catalyst for selective TES ether deprotection would be an interesting alternative.

First, deprotection of primary and secondary TES ethers was attempted at room temperature using 10 wt % Pd/C under different solvent conditions. In methanol, 95% ethanol, and absolute ethanol, desilylation of primary TES ethers worked well (Table 1). It seemed that 5% water in ethanol sped up the deprotection (Table 1, entry 3 vs 4) and that the reaction was faster in methanol than in 95% ethanol (Table 1, entry 1 vs 2 and entry 6 vs 7 and Table 2, entry 2 vs 3). On the other hand, in solvents such as THF, acetonitrile, and ethyl acetate, even if a catalytic amount of water was added, deprotection was sluggish, with a high recovery of starting material after 24 h (Table 1, entries 5, 9, and 10).

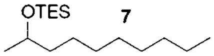
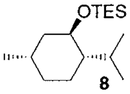
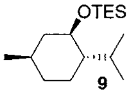
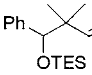
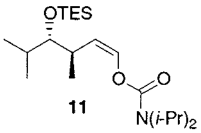
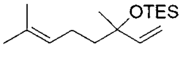
Table 1. Desilylation of Primary TES Ethers

entry	silyl ether	reaction conditions	conversion	yield
1	$CH_3(CH_2)_9OTES$ **3**	MeOH, RT, 1h	>95%[b]	
2		95% EtOH, RT, 1h	90%[b]	
3		95% EtOH, RT, 2h	>95%[b]	100%
4		EtOH, RT, 2h	82%[b]	
5		AcOEt/cat.H_2O, RT, 24h	<5%[b]	
6	 **4**	MeOH, RT, 2h	>95%[a]	93%
7		95% EtOH, RT, 5.5h	89%[a]	
8	 **5**	MeOH, RT, 2h	>95%[a]	98%
9		THF/cat.H_2O, RT, 24h	7%[a]	
10		CH_3CN/cat.H_2O, RT, 24h	32%[a]	
11	 **6**	MeOH, RT, 6h	>95%[a]	96%

[a] Determined by ^{1}H NMR. [b] Determined by ^{13}C NMR.

With these preliminary results in mind, we chose to carry out the reactions using 10% Pd/C in methanol or 95% ethanol at room temperature, to examine the scope and limitations of this mild TES deprotection reaction.

Table 2. Desilylation of Secondary and Tertiary TES Ethers

entry	silyl ether	reaction conditions	conversion	yield
1	 **7**	MeOH, RT, 3h	>95%[a]	95%
2	 **8**	MeOH, RT, 22h	>95%[c]	92%
3		95% EtOH, RT, 22h	60%[c]	
4	 **9**	MeOH, RT, 6h	>95%[a]	
5	 **10**	MeOH, RT, 3 weeks	58%[a]	
6		MeOH, reflux, 8h	96%[a]	96%
7	 **11**	MeOH, RT, 3 weeks	5%[a]	
8		MeOH, reflux, 100h	52%[a]	49%[d]
9	 **12**	MeOH, RT, 3 weeks	46%[a]	
10		MeOH, reflux, 70h		56%[e]

[a] Determined by ^{1}H NMR. [b] Determined by ^{13}C NMR. [c] Determined by GC. [d] Corrected yield: 84%. [e] Degradation of starting material and product accounts for the low yield.

Primary TES ethers were easily cleaved under these conditions, in high yields (Table 1). It is noteworthy that (i) terminal alkynes protected with a TMS group were stable (Table 1, entry 6) and (ii) the presence of a sulfur atom on the molecule only slightly slowed the reaction, even though sulfur is a well-known poison of palladium catalysts (Table 1, entry 11).

The rate of deprotection of secondary TES ethers appeared to be variable and highly dependent upon the number and size of the substituents branched α to the carbon bearing the silylated oxygen atom (Table 2). A secondary TES ether bearing no α-substituents was readily removed (Table 2, entry 1), whereas secondary TES ethers bearing one substituent required longer reaction times (Table 2, entries 2 and 4). Secondary TES ethers branched twice on the same α-position or branched on both α- and α′-positions, or tertiary TES ethers resisted the deprotection at room temperature: removal of the TES moiety of **10**−**12** was only ca. 5−58% complete after 3 weeks at room temperature (Table 2, entries 5, 7, and 9). However, these TES ethers could be desilylated upon heating the reaction mixture at reflux (Table 2, entries 6, 8, and 10) to afford the corresponding alcohols in excellent yields insofar as the compound

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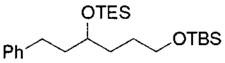
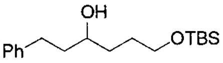
(8) Itoh, A.; Kodama, T.; Masaki, Y. *Synlett* **1999**, 357.

(9) Wu, Y.; Huang, J.-H.; Shen, X.; Hu, Q.; Tang, C.-J.; Li, L. *Org. Lett.* **2002**, *4*, 2141.

Table 3. TBS Ethers

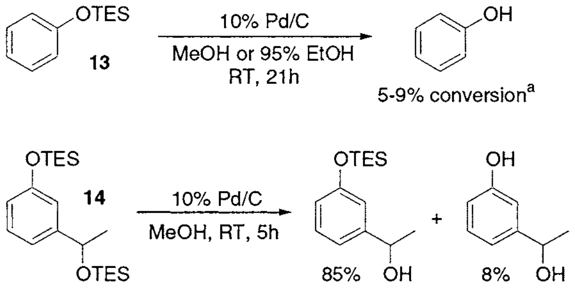
entry	silyl ether	reaction conditions	product	conversion	yield
1	$CH_3(CH_2)_9OTBS$ **15**	MeOH, RT, 15h	$CH_3(CH_2)_9OH$	<5%[b]	
2		95% EtOH, RT, 15h		<5%[b]	
3	 **16**	MeOH, RT, 5h		>95%[a]	95%

[a] Determined by ^1H NMR. [b] Determined by ^{13}C NMR

was stable upon heating and the reflux was carried out for a sufficient length of time (Table 2, entry 6).

Interestingly, aromatic TES ether **13** remained almost intact under our standard conditions for TES ether deprotection (Scheme 2). This reaction allows for selective cleavage of alkyl TES ethers in the presence of aromatic TES ethers as shown by the selective deprotection of the secondary TES ether of compound **14** (Scheme 2).

Scheme 2



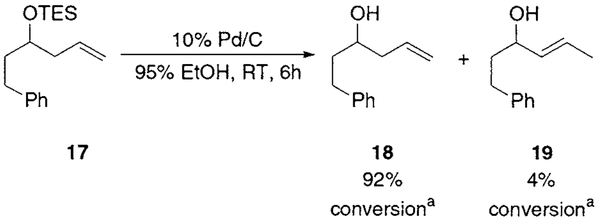
[a] Determined by GC.

Next, our attention was directed toward the potential selectivity of TES ethers cleavage in the presence of TBS ethers. Thus, we compared the cleavage of those two silyl ether groups on similar compounds and within the same molecule.

Whereas primary TES ether **3** was readily cleaved within 1−2 h (Table 1, entries 1 and 3), under identical reaction conditions, its primary TBS ether counterpart **15** remained intact, even after 15 h (Table 3, entries 1 and 2). One case of mixed silylated diol was examined to undertake intramolecular competitive cleavage of TES/TBS ethers. Considering that TES ether cleavage was faster for a primary group than for a more hindered secondary TES group, we chose compound **16**, bearing both a primary TBS group and a secondary TES group to be a suitable example. As expected, the reaction was very selective and the secondary TES ether was removed cleanly without deprotection of the primary TBS group to afford the corresponding alcohol in excellent yield (Table 3, entry 3).

In the course of our investigations, we observed that partial isomerization of the double bond of **17** occurred under our conditions for TES cleavage (Scheme 3), and it was found that with extended reaction times, further isomerization occurred.

Scheme 3



[a] Conversion determined by ^1H NMR.

We thus carried out further deprotection reactions to evaluate the importance of this double-bond isomerization process. TES ethers **20** and **21** (Figure 1) containing a double bond were treated under our standard conditions. The reactions with these two compounds resulted in approximately 10−15% yield of a mixture of byproducts that were not characterized.

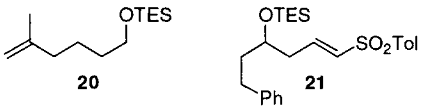


Figure 1. TES ethers containing double bonds.

Since the deprotection only occurs in MeOH or EtOH, the mechanism probably involves a transfer of the silyl group to the alcoholic solvent assisted by palladium. The reaction also takes place at the same rate under argon in carefully degassed MeOH, so the presence of hydrogen or oxygen is not necessary. Suspecting, however, that Pd(II) species were the true catalysts, we submitted silyl ether **3** (Table 1) to

10% $Pd(OAc)_2$ and 10% $PdCl_2$ in MeOH. In the first case, the reaction is much slower and conversion is complete after 24 h. With $PdCl_2$, the deprotection is complete in 2 min! Further experiments are in progress to determine the scope of this new reaction.

In conclusion, the work described here presents a mild (under neutral conditions), simple procedure (inert atmosphere not required) with an easy workup (filtration to remove Pd/C) to cleave TES ethers from alkyl derivatives. Unhindered TES ethers can be easily removed at room temperature in good yields (79−100%), whereas more hindered ones require higher temperatures. This is a selective method: neither aromatic TES nor TBS ethers are cleaved under these conditions.

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Supporting Information Available: Protection and deprotection procedures and characterization for compounds **4**, **6**, **8**, **10**−**12**, and **15**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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