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Cleavage of the THP protecting group under Pd/C-catalyzed hydrogenation conditions

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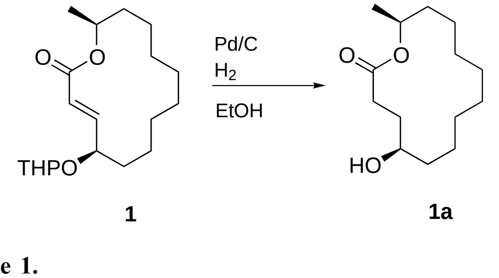
Abstract—Alcohol and phenol THP or ethoxyethyl ether protecting groups may be cleaved in high yield under Pd/C-catalyzed hydrogenation conditions in EtOH, owing to the inadvertent presence of small quantities of HCl in the reaction mixture. MOM ethers are not cleaved under these conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Prompted by recent reports by Hattori and co-workers[1] of TBDMS ether cleavages under hydrogenolytic conditions, we wish to report that analogous protecting group cleavage occurs in THP and ethoxyethyl ethers. In contrast to the Japanese workers, we do not visualise any of these reactions as truly hydrogenolytic but ascribe them *to the presence of small quantities of HCl* in the reaction mixture, generated from residual $PdCl_2$ in the commercial Pd/C catalyst. A hydroxylic solvent, normally ethanol, appears to be essential in all these cleavages.

During recent studies concerning the synthesis and reactions of certain macrolides, reduction of the THP-protected macrolide **1** under standard conditions[2] unexpectedly gave the γ-hydroxylactone **1a** as the sole product instead of the THP ether of **1a** (Scheme 1).[3] In the literature there are a few reports of complete[4] or partial[5] deprotections of THP groups under hydrogenation conditions but no comments were offered to explain such phenomena. A study of a variety of alcohol or phenol THP ethers established that this is a general deprotection method for THP ethers (Table 1).



1 **1a**

Scheme 1.

It is obvious that a prime candidate responsible for these unexpected acetal cleavages is an acidic impurity in the reaction mixture, capable of catalysing a trans-acetalization reaction between the THP ether and the ethanol solvent. However, rinsing the catalyst with aq. $NaHCO_3$ *before* hydrogenation did not prevent deprotection of **4** (entry 6), while addition of a small amount of pyridine to the reaction mixture (entry 7) did. No reaction was detected in the absence of H_2 (entry 4). Interestingly, when 2-(dec-9-en-1-yloxy)tetrahydropyran **4** was treated with Pd/C in the absence of H_2 the terminal double bond migrated to give a mixture of decenol THP ether isomers (entry 8). As expected, the Pd/C-catalyzed hydrogenation of the benzylic THP–ether **6** gave the hydrogenolysis product *p*-cymene **6a** (entry 10).

In a comparison of various commercial Pd/C catalysts (Table 2), complete cleavage of the THP group took place in 24 h[7] only when Pd/C (Aldrich) was used in an equal amount to the substrate (entry 3). Pd/C catalysts from other suppliers (entries 4–6) were less effective in promoting the THP cleavage. As expected, the THP moiety ends up as EtOTHP,[8] confirming an acid-catalyzed acetal exchange with the solvent ethanol. In keeping with this, the reaction fails completely in cyclohexane solution (entry 7).

Pd/C catalysts are usually prepared by the reduction of $PdCl_2$ in the presence of activated charcoal.[9] If some residual $PdCl_2$ remains in the catalyst it will liberate HCl first during the hydrogenation (cf. Table 1, entries 6 and 8). Electron spectroscopic analysis ESCA[10] of Pd/C (10%, Fluka) showed that the palladium on the surface layer of the catalyst was ca. 1:1 Pd(0):Pd(2^+) but

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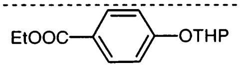
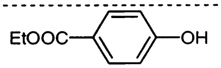
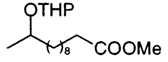
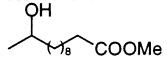
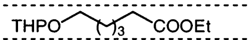
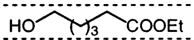
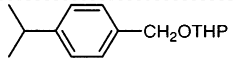
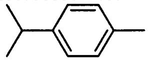
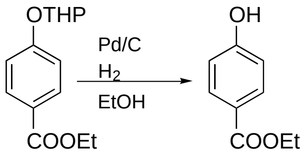
Table 1. Reactions of THP protected hydroxy compounds under Pd/C-catalyzed hydrogenation conditions[6]

Entry	Substrate		Catalyst[a]	Product		Ratio[b] OH:OTHP	Yield[c]
1	**1**		A	**1a**		OH only	76%
2	**2**		A	**2a**		OH only	81%
3	**3**		A	**3a**		OH only	95%
4	**3**		A no H_2	**3**	no reaction	OTHP only	100%
5	**4**		A	**4a**		98:2	100%
6	**4**		base washed A	**4a**		97:3	79%
7	**4**		A+pyridine[d]	**4b**		OTHP only	92%
8	**4**		A no H_2		isomers of 4	OTHP only	84%
9	**5**		A	**5a**		OH only	100%
10	**6**		A	**6a**		–	73%

a) 10% Pd/C (Aldrich) b) by GLC c) isolated yield d) 0.1 equiv. of pyridine

Table 2. Pd/C-catalyzed hydrogenation of ethyl 4-(2-tetrahydropyranyloxy)benzoate **2**

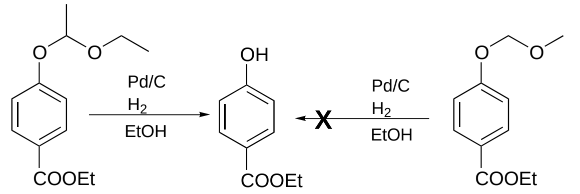


2 **2a**

Entry	Pd/C catalyst[a]	Amount of Pd/C (%)[b]	Solvent	Ratio[c] OH:OTHP
1	A	25	EtOH	14:86
2	A	50	EtOH	56:44
3	A	100	EtOH	100:0
4	J	100	EtOH	12:88
5	F	100	EtOH	0:100
6	D[d]	100	EtOH	5:95
7	A	100	Cyclohexane	0:100
8	J+0.02 equiv. $PdCl_2$	100	EtOH	100:0

[a] A = Aldrich, J = Johnson Matthey Chemicals Ltd, F = Fluka, D = Degussa.
[b] Ratio Pd/C: **2** w/w%.
[c] By GLC.
[d] 5% Pd/C.

that Pd/C (10%, Aldrich) was nearly all Pd(2^+). Chlorine values on the surface layers were 0.3 and 1.6 at%, respectively. Total chlorine in bulk Pd/C (Aldrich) was estimated as 0.65% (w/w, combustion analysis[11]) or 0.4% (at%, X-ray). It is thus likely that there are significant quantities of $PdCl_2$ particularly in the Aldrich Pd/C material, and possibly of Pd/O also. In the event, the addition of 0.02 equiv. (w/w) of $PdCl_2$ to Johnson Matthey's Pd/C, having a low THP-cleaving tendency, resulted in a complete loss of the THP protecting group (Table 2, entries 4 and 8). The presence of $PdCl_2$ in the catalyst also explains the isomerization of the terminal double bond (Table 1, entry 8).[12] However, the presence of even major quantities of $PdCl_2$ does not appear to affect the reduction of double bonds (Table 1, entries 1, 5–7). Presumably all the Pd(2^+) is reduced to Pd(0) during the course of the reaction.



7 **8**

Scheme 2.

A complete deprotection also occurred during Pd/C-catalyzed (Aldrich) hydrogenation of the EE protected phenol **7** (Scheme 2). Interestingly, the corresponding methoxymethyl (MOM) ether **8** tolerates the Pd/C–H_2 conditions (Scheme 2), undoubtedly due to the less well stabilized carbocation in the alcoholysis mechanism.

In conclusion, Pd/C catalysts may contain residual amounts of $PdCl_2$, which during hydrogenation liberate HCl and cause the cleavage of acid sensitive THP, EE or silyl groups. If deprotection is not desired, MOM ether protection should be used instead. The use of an aprotic solvent or the addition of a small amount of amine to the reaction mixture before hydrogenation effectively prevents the deprotection of acid sensitive protecting groups during Pd/C-catalyzed hydrogenation.

Acknowledgements

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6. *General procedure for hydrogenation:* 10% Pd on activated charcoal (in equal amount to the substrate) was added to a THP protected starting material (0.15–0.3 mmol) in 10 mL of EtOH. After evaporation, the mixture was hydrogenated under a H_2 balloon at rt for 3 h (**1**) or overnight. After filtration through a pad of Celite the filtrate was evaporated to give the product.[8]
7. The deprotection reaction is slow. After 1 h only 12% of product **2a** was observed, and after 7 h there was still 6% of the protected phenol left.
8. Products were identified by GC and NMR comparison with authentic material.
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