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Bis-benzyl protected 6-amino cyclitols are poisonous to Pd/C catalysed hydrogenolysis of benzyl ethers

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Abstract—Pd/C and $Pd(OH)_2/C$ catalysts are both poisoned by bis-benzyl protected 6-aminocyclitols thereby inhibiting the hydrogenolysis of benzyl ethers but removing *N*-Cbz groups chemoselectively. This outcome was unaltered by the use of different hydrogen donors. Replacement of the C-6 nitrogen atom by oxygen resulted in the starting materials being fully deprotected under similar conditions. These findings add cyclitolamines to the list of amines/bases that are poisonous to Pd/C catalysts during hydrogenolysis.
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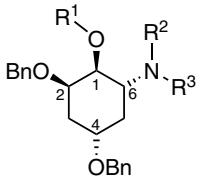
Functional group manipulation is fundamental in synthetic organic chemistry and hence the development of new chemoselective transformations continues to be of great importance. Although benzyl groups are widely used as excellent protecting groups for hydroxyl functions, the lack of chemoselectivity between benzyl groups and other functional groups sensitive to Pd-catalysed hydrogenation is a serious problem.[1] While many applications of catalyst poisons to Pd/C catalysed hydrogenation have been evaluated to obtain a chemoselective catalyst, only two, the Lindlar catalyst and the Rosenmund's reaction, have been accepted as general methodologies.[2] Recently, it has been shown that the addition of ammonia, pyridine or ammonium acetate to Pd/C catalysed reduction systems strongly inhibited the hydrogenolysis of an aliphatic benzyl ether with smooth hydrogenation of other reducible functions such as olefins, Cbz, benzyl esters and azides.[3] While addition of pyridine also allowed the selective hydrogenation of phenolic benzyl ethers in the presence of the 4-methoxybenzyl (PMB) protective group,[4] the use of ethylenediamine in hydrogenation reactions prevented removal of phenolic benzyl ethers as well as *tert*-butyldimethylsilyl (TBDMS) protecting groups.[5] Here we describe a series of Pd/C catalysed hydrogenolysis reactions performed on bis-benzyl protected 6-aminocyclitols **1**, intermediates in the synthesis of novel inhibitors of inositol monophosphatase (EC 3.1.3.25).[6,7] The Pd/C catalysed deprotection of *O*-benzyl ethers, the final step towards the synthesis of these inhibitors, was inhibited by the starting materials while replacement of the nitrogen atom at the C-6 position by an oxygen atom allowed smooth removal of the benzyl groups.



1

R^1 = H or $CH_3P(O)OH$
R^2 = H or Cbz
R^3 = *n*-butyl, *n*-hexyl, *n*-octyl, CH_2CH_2Ph or $CH_2(CH_2)_2CH_2Ph$

Removal of the benzyl groups by hydrogenolysis in methanol using either 10% palladium on activated charcoal[8–12] or the more efficient 10% palladium hydroxide on activated charcoal[8,9] as catalyst in the presence of hydrogen gas was attempted on five aminoalcohols **2a**–**e**[7] using various reaction conditions (Table 1). These amino alcohols were unreactive and only starting material was recovered with the exception of phenylethylaminoalcohol **2d**, which was slowly converted into the corresponding aminotriol **3d** in 65% yield.

The effect of 6-aminocyclitols on the Pd/C catalyst was further studied when diaminoalcohols **4a**–**c**[7] were subjected to hydrogenolysis using standard reaction

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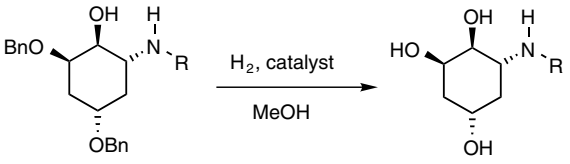
Table 1. Reagents and conditions used for the attempted hydrogenolysis of aminoalcohols **2a**–**e**[13]



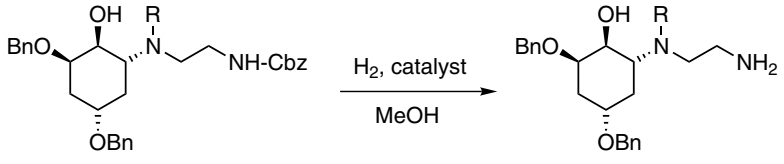
2a- e **3a-e**

a R = n-butyl; **b** R = n-hexyl; **c** R = n-octyl; **d** R = 4-phenylethyl; **e** R = 4-phenylbutyl

Substrate	Catalyst	Temperature	Time (h)	Attempt (s)	Yield (%)[a] of **3**
2a	10% Pd–C	Reflux	5	1	0
2a	10% $Pd(OH)_2$/C	RT	5	2	0
2b	10% Pd–C	Reflux	15	1	0
2c	10% Pd–C	Reflux	12	1	0
2d	10% Pd/C	RT	5	3	65
2d	10% $Pd(OH)_2$/C	RT	5	1	0
2e	10% Pd–C	RT	15	1	0
2e	10% Pd–C	Reflux	12	1	0

[a] Reactions followed by TLC and the outcome confirmed by ^{1}H NMR spectroscopy.

Table 2. Chemoselective hydrogenolysis of Cbz groups[13]



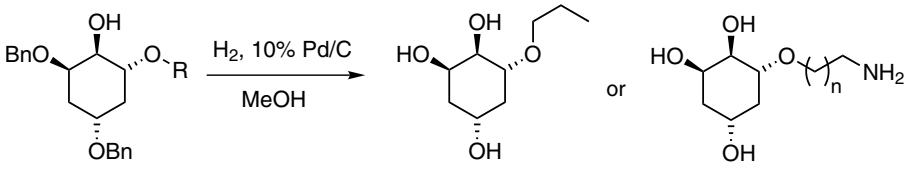
4a-c **5a-c**

a R = H; **b** R = *n*-hexyl; **c** R = 4-phenylbutyl

Substrate	Temperature	Time (h)	Yield (%)[a,b] of **5**
4a	RT	5	95
4b	RT	12	98
4c	Reflux	12	95

[a] Reactions followed by TLC and confirmed by ^{1}H and ^{13}C NMR spectroscopy.
[b] Ninhydrin positive.

Table 3. Successful removal of *O*-benzyl and Cbz protecting groups in the absence of a nitrogen atom at C-6



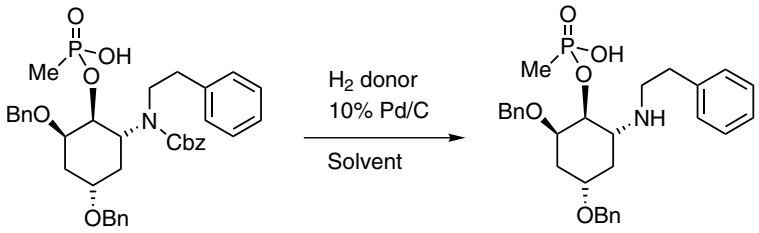
6a-c **7a** **7b-c**

6a R = *n*-propyl; **6b** R = CH_2CH_2NH-Cbz; **6c** $CH_2CH_2CH_2NH$-Cbz;
7b n = 1; **7c** n = 2

Substrate	Temperature	Time (h)	Yield (%)[a] of **7**
6a	RT	3	100
6b	RT	3	100[b]
6c	RT	3	100[b]

[a] Reactions followed by TLC and confirmed by HRMS, ^{1}H and ^{13}C NMR spectroscopy.
[b] Ninhydrin positive.

Table 4. Chemoselective deprotection of the Cbz group during the hydrogenolysis of methylphosphonate **8**[13]



8 **9**

Substrate	Reagent	Solvent	Temperature (°C)	Time (h)	Yield (%)[a] of **9**
8	Hydrogen	MeOH	25	5	98
8	1,4-Cyclohexadiene	MeOH	25	5	0
8	Formic acid	MeOH	25	3	95
8	Hydrogen	MeOH	25	24	100
8	Hydrogen	Ethyl acetate	25	3	100
8	Hydrogen	Ethanol	80	3	100

[a] Reactions followed by TLC and the outcome confirmed by ES, ^{1}H and ^{13}C NMR spectroscopy.

conditions (Table 2). The reactivity of the benzyl groups and the Cbz group towards the poisoned catalyst showed that the Cbz group was removed chemoselectively after just 2 h to afford diaminoalcohols **5a–c** in near quantitative yield, while the benzyl groups remained untouched even after 12 h. These results show that the reactivity of the Pd/C catalyst in the presence of 6-aminocyclitols is similar to the addition of ammonia, pyridine, ammonium acetate and ethylenediamine as previously reported by Sajiki and Hitaro.[3–5] It is therefore clear that the starting materials, behaving as amine bases, poison the Pd/C catalyst and alter its reactivity towards *O*-benzyl protective groups.

In order to substantiate further the poisonous nature of the 6-aminocyclitols mentioned above, alcohols **6a–c** were synthesised[7] and subjected to hydrogenation under similar conditions to those described above (Table 3). Replacement of the nitrogen atom at C-6 meant that compounds **6a–c** had no basic properties and therefore should not be potential catalyst poisons. This fact was confirmed when compounds **6a–c** were fully deprotected in 3 h to afford products **7a–c** in quantitative yield. Moreover, removal of the Cbz group first from alcohols **6b–c** to free the primary amine functionality does not seem to influence the reactivity of the catalyst towards further deprotection of the two benzyl ethers. It therefore appears that the presence of an amine group at C-6 alters the poisonous nature of the starting materials.

In our strategy to synthesise reduced charged inhibitors of inositol monophosphatase, based on the natural substrate inositol 1-phosphate, which would have the potential to cross the lipophilic blood brain barrier, the methylphosphonate **8** was synthesised.[6,7] Once again, during the last deprotection step, difficulties were encountered with the removal of benzyl groups. Hydrogenolysis of methylphosphonate **8** was attempted using 10% palladium on activated charcoal under a variety of different reaction conditions.[8–10,14,15] As shown in Table 4, despite using different hydrogen donors, reaction times and solvents, none of these methods were successful in removing the benzyl ether groups. Once again, reactivity of the catalyst towards the Cbz group was chemoselective and afforded the phosphonate **9** in quantitative yield. These results also confirm that the source of hydrogen has no effect on the reactivity of the poisoned catalyst towards benzyl ethers.

In conclusion, it has been demonstrated that bis-benzyl protected 6-aminocyclitols are poisonous to both Pd/C and $Pd(OH)_2$ catalysts thereby causing self-inhibition of hydrogenation of *O*-benzyl ethers. This effect is not observed when the C-6 nitrogen atom is replaced by oxygen. Chemoselective removal of the Cbz protecting group is achieved by the poisoned catalyst, while the source of hydrogen, choice of solvent and variation in temperature do not affect the reactivity of the poison catalyst towards the removal of *O*-benzyl protecting groups.

Acknowledgements

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References and notes

1. (a) Green, T. W.; Wuts, P. G. In *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 47–53, 156–158; (b) Rylander, P. N. In *Hydrogenation Methods*; Academic: New York, 1985; pp 157–163; (c) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic: New York, 1979; pp 271–279; (d) Freifelder, M. *Practical Catalytic Hydrogenation*

Techniques and Applications, 2nd ed. Wiley: New York, 1971; pp 398–413 and 428–440.
2. (a) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 8; p 417; (b) Hudlicky, M. In *Reductions in Organic Chemistry*; American Chemical Society: Washington, DC, 1996.
3. (a) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465–3468; (b) Sajiki, H.; Hitaro, K. *Tetrahedron* **1998**, *54*, 13981–13996; (c) Sajiki, H. *Yakugaki Zasshi* **2000**, *120*, 1091–1103; (d) Sajiki, H.; Hattori, K.; Hitaro, K. *J. Org. Chem.* **1998**, *63*, 7990–7992.
4. (a) Sajiki, H.; Hiroko, K.; Hitaro, K. *Tetrahedron Lett.* **1997**, *38*, 399–402; (b) Sajiki, H.; Hiroko, K.; Hitaro, K. *Tetrahedron Lett.* **1998**, *39*, 7127–7130.
5. Hattori, K.; Sajiki, H.; Hitaro, K. *Tetrahedron Lett.* **2000**, *41*, 5711–5714.
6. Surfraz, M. B.; Miller, D. J.; Gani, D.; Allemann, R. K. *Tetrahedron Lett.* **2003**, *44*, 7677–7679.
7. Miller, D. J.; Surfraz, M. B.; Akhtar, M.; Gani, D.; Allemann, R. K. *Org. Biomol. Chem.*, submitted for publication.
8. Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 4969–4974.
9. Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Aromoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654–8664.
10. Willson, T. W.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, R. M.; Faller, A.; Campbel, S. F. *Tetrahedron* **1990**, *46*, 1767–1782.
11. Bieg, T.; Szeja, W. *Synthesis* **1985**, 76–79.
12. Hanessian, S.; Trembley, M.; Kornienko, A.; Moitessier, N. *Tetrahedron* **2001**, *57*, 3255–3265.
13. Typically, the experimental procedure was carried out as follows: After two vacuum/H_2 cycles to remove air from the reaction flask, the stirred mixture of the bis-benzyl protected 6-aminocyclitol (0.50 mmol) and 10% Pd/C (50 mg) in MeOH (unless stated, 10 ml) was hydrogenated at atmospheric pressure with varying temperature and reaction time. The reaction mixture was filtered (Celite pad), the filtrate concentrated and then dried under high vacuum before being analysed by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy.
14. El Amin, B.; Anantharamaiah, G. *J. Org. Chem.* **1979**, *44*, 3442–3444.
15. Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194–4196.