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Facile Deprotection of *O*-Cbz-Protected Nucleosides by Hydrogenolysis: An Alternative to *O*-Benzyl Ether-Protected Nucleosides

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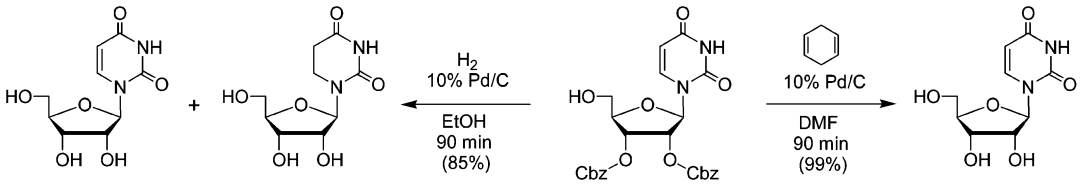
ABSTRACT



Because of side-reactions encountered during hydrogenolysis, benzyl ethers are usually not an effective protecting group for nucleosides. Benzyloxycarbamates provide an alternative to traditional benzyl ethers for protection of nucleoside hydroxyl groups, as they are much more labile to hydrogenolysis. Deprotection conditions using transfer hydrogenolysis are described that avoid the reduction of the pyrimidine nucleobase during deblocking of *O*-Cbz-protected nucleosides. Additionally, an experiment is described that suggests the nucleobase component of a nucleoside is responsible for the sluggish hydrogenolysis of nucleosides.

The benzyl moiety is widely used as a hydroxyl protecting group, in part, because its removal (via hydrogenolysis) is effected under conditions orthogonal to many other functionalities and protecting groups. Yet, in the field of nucleoside chemistry, the benzyl moiety is primarily used as a monophosphate protecting group,[1] receiving limited attention as a hydroxyl protecting group. This may be, in part, because difficulties often arise during hydrogenolysis of *O*-benzyl-protected nucleosides. An often observed side-reaction is the reduction of the nucleobase, particularly with the pyrimidines: uridine,[2] cytosine,[3] and to a lesser extent, thymidine.[4] Thus, hydrogenolysis is often eschewed in favor of other means to deblock benzyl-protected nucleosides (BCl_3,[5] BBr_3,[6] or dissolving metal reduction[7]) and/or through modification of the benzyl moiety (e.g., use of the *p*-methoxybenzyl ether, which is acid-labile[8]). However, there are situations when hydrogenolysis is a highly desirable method for deprotection of benzyl-protected nucleosides. Hydrogenolysis, which can be conducted under neutral conditions, is advantageous when working with nucleosides containing phosphoanhydride bonds. Nucleoside diphosphates, and especially nucleoside triphosphates, degrade under acidic conditions. Therefore, we explored ways to facilitate hydrogenolysis of *O*-benzyl groups from nucleosides and found that the benzyloxycarbonyl (Cbz) moiety functions as a versatile alternative to the traditional *O*-benzyl ether protecting group for use in nucleoside chemistry.

While determining optimum reaction conditions for hydrogenolysis of a benzyl-protected uridine (**1**), we observed that hydrogenolysis of the *O*-benzyl moieties did not occur

(1) Freel Meyers, C. L.; Borch, R. F. *Org. Lett.* **2001**, *3* (23), 3765−3768.
(2) Reitz, G.; Pfleiderer, W., *Chem. Ber.* **1975**, *108*, 2878−2894.
(3) Christensen, L. F.; Broom, A. D., *J. Org. Chem.* **1972**, *37* (22), 3398−3401.
(4) Pedersen, D. S.; Koch, T., *Synthesis* **2004**, *4*, 578−582.
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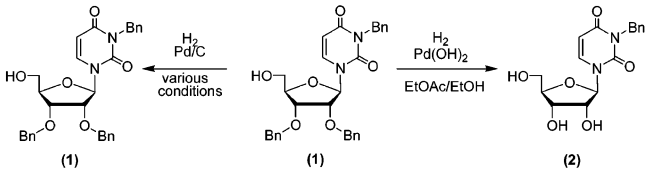
when using palladium on charcoal catalyst.[9] However, the simple expedient of Pearlman's catalyst[10] [$Pd(OH)_2$] led to facile hydrogenolysis of the *O*-benzyl moieties in excellent yield (92%), although the *N*-benzyl group of the imide moiety did not hydrogenolyze (Scheme 1). *N*-Benzyl imides are a

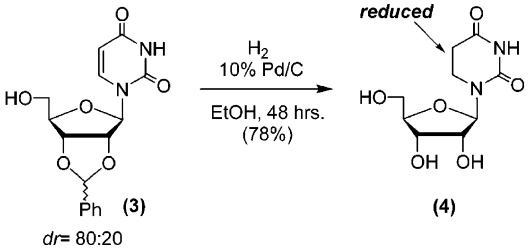
Scheme 1. Pearlman's Catalyst Is More Effective for Hydrogenolysis of Nucleoside *O*-Bn Groups than Pd/C



particularly difficult functionality to hydrogenolyze,[4,11] and previous reports[12,13] attest to the difficulty associated with the hydrogenolysis of *N*-benzyl pyrimidine nucleosides. Thus, the per-benzyl-protected nucleoside (**1**) was deemed to be incompatible with our future plans.

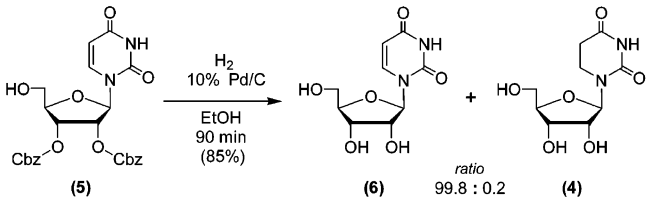
The benzylidene moiety has been used with purine nucleosides as a diol protecting group that is labile to hydrogenolysis. Therefore, we explored whether the benzylidene acetal of a pyrimidine nucleoside (i.e., uridine **3**) is also labile to hydrogenolysis. Deprotection of the benzylidene-protected pyrimidine requires 2 days to reach complete reaction. Upon isolating the product (**4**), we find that reduction of the nucleobase C_5-C_6 alkene occurs (Scheme 2).

Scheme 2. Reduction of the Nucleobase-alkene Occurs during Prolonged Hydrogenolysis



The long reaction times and concomitant reduction of the nucleobase, as well as the resistance of the *N*-benzyl imide toward hydrogenolysis, prompted us to investigate alternate means to use hydrogenolysis for deblocking pyrimidine-containing nucleosides. Although a detailed mechanism for the hydrogenolysis of benzyl-protected moieties is unknown, data in the literature supports that ester groups undergo hydrogenolysis with greater facility than ether groups.[14] Therefore, we reasoned that the hydroxyl groups of nucleosides functionalized as benzyloxycarbamates (Cbz) may be more labile toward hydrogenolysis than their benzyl ether counterparts. Indeed, hydrogenolysis of Cbz-protected uridine **5** was complete in less than 90 min using palladium on carbon catalyst in ethanol. Given that palladium on charcoal catalysts promoted the reduction of the nucleobase for the benzylidene-protected uridine, we carefully examined the products from the hydrogenolysis of Cbz-protected uridine **5** using NMR spectroscopy. We observed evidence consistent with minor reduction (0.2%) of the nucleobase (Scheme 3).

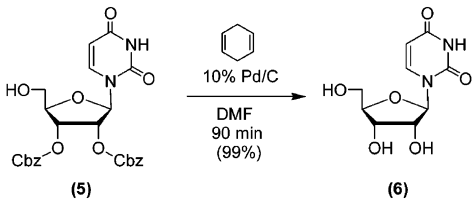
Scheme 3. Minor Reduction (0.2%) of the Nucleobase Can Occur with Pyrimidine Nucleosides



The separation of uridine **6** from its reduced side-product **4** is nontrivial. Therefore, we explored other conditions to affect hydrogenolysis of the Cbz moieties that would avoid even this small amount of reduction of the nucleobase. To that end, transfer hydrogenolysis has been reported by Rapoport et al.[15] as a method to avoid reduction of the pyrimidine C_5-C_6 alkene.

Transfer hydrogenolysis of Cbz-protected uridine **5** (Scheme 4) gives no appreciable reduction of the nucleobase in the

Scheme 4. Transfer Hydrogenolysis Avoids Minor Reduction of Pyrimidine Nucleobase



product (**6**), within the limits detectable by NMR spectroscopy (see Supporting Information for spectra).

The Cbz-protecting group is easily installed in high yield for various pyrimidines and purine nucleosides using benzylchloroformate (1.5 equiv/OH group) and DMAP (2 equiv/OH group) in dichloromethane. Under these conditions, the

(9) A variety of reaction conditions were explored using 10% Pd/C catalyst (1 mg of catalyst/5 mg of nucleoside). Solvents (EtOH, EtOAc, THF), additives (AcOH/ heat), and reaction times (up to 48 h) were also investigated but were not observed to promote hydrogenolysis.

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(13) Bar, N. C.; Patra, R.; Achari, B.; Mandal, S. B. *Tetrahedron* **1997**, *53* (13), 4727−4738.
(14) Kieboom, A. P. G.; De Kreuk, J. F.; Van Bekkum, H. *J. Catal.* **1971**, *20*, 58−66.
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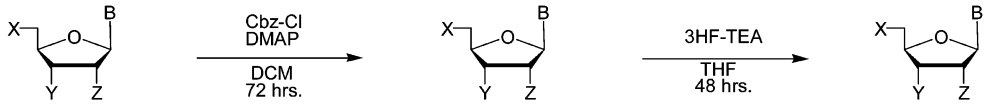
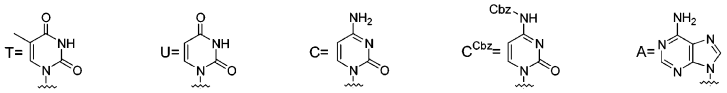
Table 1. Carbonylation/Carbamoylation of Representative Purine and Pyrimidine Nucleosides in Ribo- and Deoxyribonucleic Acid Forms



	B	X	Y	Z		B	X	Y	Z	%		B	X	Y	Z	%
7:	T	OTBS	OH	H	**8:**	T	OTBS	OCbz	H	95	**9:**	T	OH	OCbz	H	99
10:	U	OTBS	OH	OH	**11:**	U	OTBS	OCbz	OCbz	93	**5:**	U	OH	OCbz	OCbz	98
12:	C	OTBS	OH	OH	**13:**	C^{Cbz}	OTBS	OCbz	OCbz	72	**14:**	C^{Cbz}	OH	OCbz	OCbz	99
15:	A	OH	OH	OH	**16:**	A	OTBS	OCbz	OCbz	54[a]	**17:**	A	OH	OCbz	OCbz	95

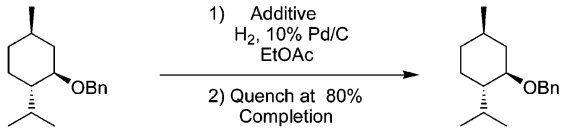


[a] Yield for the two-step procedure: 5′-silyation followed by carbonylation.

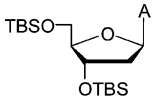
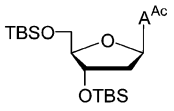
amino functionality of cytosine is carbamoylated along with carbonylation of the nucleoside hydroxyl groups. However, the aromatic amino functionality of adenosine is not carbamoylated. A particularly salient feature about the installation of the Cbz-protecting group is that the imide nitrogens of uridine and thymidine are not carbamoylated (Table 1). Silyl-ethers are easily removed in high-yield from the Cbz-protected nucleosides using a buffered fluoride source such as triethylamine trihydrofluoride (Table 1).

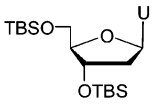
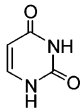
As found in other published reports, we observe that hydrogenolysis of benzyl-protected nucleosides (both purine and pyrimidine) sometimes requires long reaction times. There are a number of possible reasons for this. The amino functionalities of nucleosides may inhibit hydrogenolysis.

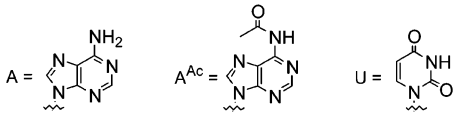
Table 2. Hydrogenolysis[a] of *O*-Benzyl Menthol Is Inhibited in the Presence of Nucleoside Additives[b]



(18) **(18)**

Additive	Equivalents of Additive	% of 18 Recovered[c]
—	—	16
 **(19)**	0.25	92
	0.50	98
	1.00	86
	2.00	84
 **(20)**	0.25	98
	0.50	98
	1.00	99
	2.00	91

Additive	Equivalents of Additive	% of 18 Recovered[c]
 **(21)**	0.25	24
	0.50	38
	1.00	66
	2.00	96
 **(22)**	0.50	33
	1.00	51
	2.00	67



[a] Hydrogenolysis reaction was performed for 22 min, as monitored by a stopwatch. The "start" of the reaction was considered to be the moment the H_2 balloon pierced the septum. At completion, the reaction was promptly filtered through Celite 545. [b] Additives were present prior to introduction of H_2. [c] Percent of **18** recovered is representative of the inhibitory influence additives have upon hydrogenolysis of *O*-benzyl menthol.

Free amines have been shown to inhibit the hydrogenolysis of *O*-benzyl ethers,[16] presumably by formation of a complex[17] between the amine and the palladium catalyst, thereby deactivating the catalyst. Another possibility is that the nucleoside adsorbs to the catalyst in some fashion, thereby hindering hydrogenolysis. To better understand the hydrogenolysis of benzyl-protected nucleosides, we examined the effect nucleosides have upon the hydrogenolysis of a model compound, *O*-benzyl menthol.

The hydrogenolysis of *O*-benzyl menthol is complete in 28 min using 10% Pd/C in ethyl acetate under an atmosphere of hydrogen. Menthol is a volatile compound, whereas *O*-benzyl menthol is not volatile. One can examine the effect nucleosides have upon the hydrogenolysis of *O*-benzyl menthol by quenching the reaction at 80% completion, separating the catalyst by filtration, and removing of all volatile components under reduced pressure. The remaining *O*-benzyl menthol is easily separated from the nucleoside additive. The isolated *O*-benzyl menthol is representative of the effect a nucleoside has upon the hydrogenolysis process.

Under these experimental conditions we find that representative purine and pyrimidine nucleosides inhibit the hydrogenolysis process (Table 2). The amino functionality of adenosine does not appear to be responsible for the inhibition, as both amino-adenosine **19** and amido-adenosine **20** show similar inhibitory effects upon the hydrogenolysis of *O*-benzyl menthol. The representative pyrimidine (uridine **21**) also inhibits hydrogenolysis, but much less effectively than the purines (adenosines **19** or **20**). To rule out the possibility that the silyl-ethers interfered with the hydrogenolysis process, we examined the effect an isolated nucleobase (i.e., uracil) had upon the hydrogenolysis process. Uracil (**22**) also inhibits the hydrogenolysis of *O*-benzyl menthol. Interestingly, uracil inhibits hydrogenolysis with the same general efficacy as uridine **21**. These data suggest that the nucleobase component of a nucleoside is responsible for the sluggish hydrogenolysis of *O*-benzyl-protected nucleosides.

In this communication we have demonstrated the problematic nature of deblocking benzyl-ether protecting groups from nucleosides. The long reaction times and accompanying reduction of pyrimidine nucleobases are easily avoided by use of carbobenzyloxy protecting groups and deprotection under transfer hydrogenolysis conditions. Further, we have shown experimental evidence that the sluggish deprotection of *O*-benzyl-protected nucleosides may be a result of inhibition due to the presence of the nucleobase.

Supporting Information Available: Experimental procedures and spectral data (^{1}H, ^{13}C, MS, IR) for all compounds synthesized in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Sajiki, H., *Tetrahedron Lett.* **1995**, *36* (20), 3465−3468.
(17) Sajiki, H.; Hattori, K.; Hirota, K., *J. Org. Chem.* **1998**, *63*, (22), 7990−7992.