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Facile oxidative cleavage of benzylidene acetals using molecular oxygen catalyzed by *N*-hydroxyphthalimide/$Co(OAc)_2$

Yongsheng Chen and Peng George Wang*

Department of Chemistry, Wayne State University, Detroit, MI 48202, USA

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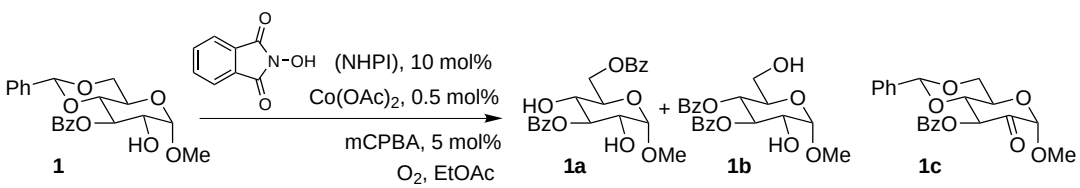
Abstract—Benzylidene acetals derived from 1,2- and 1,3-diols undergo facile oxidative cleavage to give hydroxy benzoate esters with molecular oxygen in the presence of catalytic amount of *N*-hydroxyphthalimide/$Co(OAc)_2$.

A benzylidene acetal is a widely used protective group for 1,2- and 1,3-diols in organic synthesis[1] due to its tolerance to a variety of chemical conditions. As it provides selective protection of the 4- and 6-hydroxyl moieties of the pyranoses of common monosaccharides such as glucose, galactose, and mannose, the benzylidene acetal group has found extensive applications in oligosaccharide and glycoconjugate synthesis.[2,3] Adding greatly to the utility of this group are methodologies for the selective cleavage of the benzylidene acetal, allowing formation of a benzyl ether (under reductive condition) or a benzoate ester (under oxidative condition) at either the C4 or C6 hydroxyl group.

An interesting approach for the oxidation of alcohols to carbonyl compounds using molecular oxygen (O_2) catalyzed by *N*-hydroxyphthalimide (NHPI) combined with a Co species has recently appeared in the literature.[4] In the course of our studies towards bicyclic sugars, we carried out the oxidation of glucoside **1** with the reported NHPI/$Co(OAc)_2/O_2$ system. Instead of the desired ketone **1c**, the corresponding 4-hydroxy-6-*O*-benzoate ester **1a** and 6-hydroxy-4-*O*-benzoate ester **1b** were isolated in 82% combined yield in a ratio of 2:1 (Scheme 1).

A survey of the literature revealed that oxidative cleavage of benzylidene acetals to hydroxyesters has been in place since 1973. Various reagents, such as trityl fluoroborate ($Ph_3C^+BF_4^-$),[5] ozone,[6] *t*-butyl hydroperoxide,[7] NBS/H_2O,[8] $NaBO_3$,[9] 2,2′-bipyridinium chlorochromate/*m*-CPBA,[10] and $NaBrO_3/Na_2S_2O_4$,[11] have been employed for this transformation with varying degrees of regioselectivity. However, most of these procedures suffer from the use of a toxic reagent, or rather harsh or environmentally unfriendly conditions.

To examine the generality of the current oxidative cleavage system, the benzylidene acetals of a couple of 1,2- and 1,3-diols, including several sugar substrates, were subjected to the oxidation conditions (Table 1). In each instance except for entry 5, the benzylidene acetal was smoothly cleaved to give the hydroxy benzoate ester(s) in good to excellent yields. Under the reaction conditions, compound **6** gave a complex mixture. While symmetrical substrates **2** and **4** yielded only one



Scheme 1. Oxidative cleavage of 4,6-*O*-benzylidene acetal **1**.

* Corresponding author. Tel.: 313-993-6759; fax: 313-577-2554; e-mail: pwang@chem.wayne.edu

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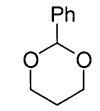
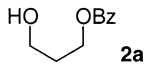
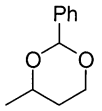
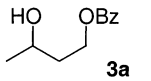
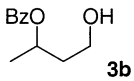
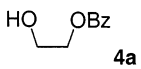
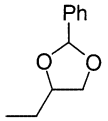
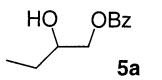
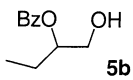
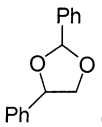
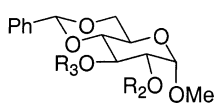
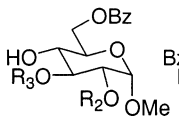
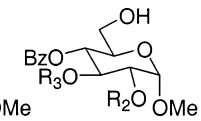
Table 1. Oxidative cleavage of benzylidene acetals

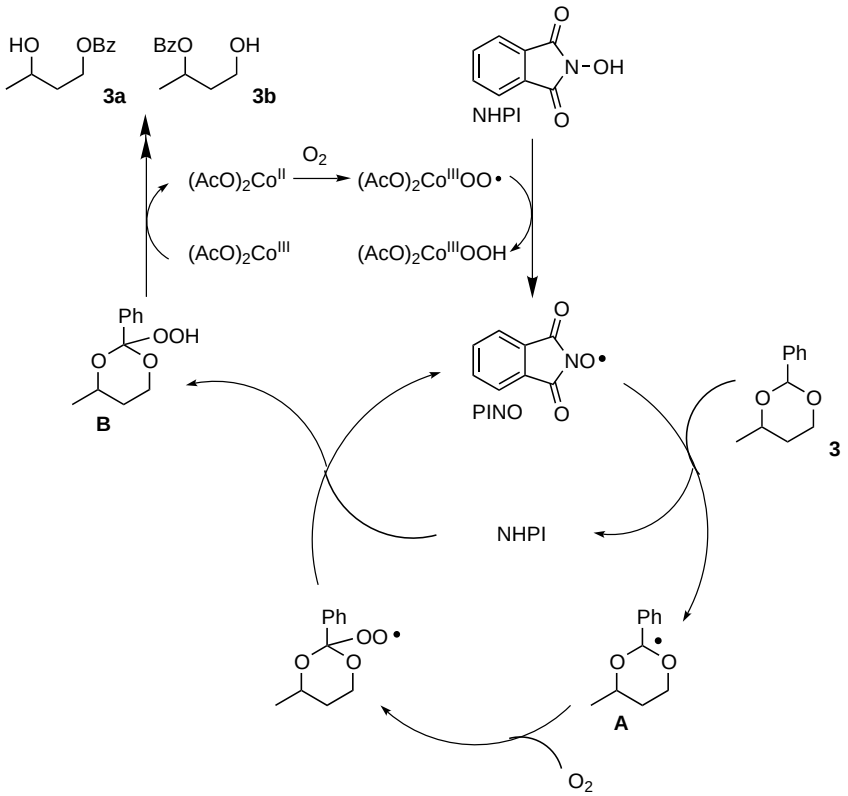
Entry	Substrate	Product(s)[a]		Yield (%)	Ratio **a:b**
1	 **2**	 **2a**		85	NA
2	 **3**	 **3a**	 **3b**	87[b]	1.2:1
3	 **4**	 **4a**		90	NA
4	 **5**	 **5a**	 **5b**	87	1:1
5	 **6**	complex mixture			
					
6	**1** R_2 = H, R_3 = Bz	**1a**	**1b**	82	2:1
7	**7** R_2 = R_3 = Bz	**7a**	**7b**	91	1.3:1
8	**8** R_2 = R_3 = Ac	**8a**	**8b**	66	1.2:1
9	**9** R_2 = R_3 = Bn	**7a**	**7b**	34[c]	1:1

[a] Satisfactory spectral data were obtained for all products. [b]Based on 78.5% conversion after 45 min.
[c] Plus two other products with a combined yield of 66%.

product, the other benzylidenes gave a roughly 1:1 mixture of regioisomers. The deprotection of sugar substrates **1**, **7**–**9** (entries 6–9) showed functional group tolerance of this NHPI/$Co(OAc)_2$/O_2 system towards esters and glycosidic methyl acetals. However, in the case of **9**, oxidation of the *O*-benzyl group to *O*-benzoyl and accompanying *O*-debenzoylation were observed,[7b] giving rise to products with a free C2 or C3 hydroxyl group in addition to the two major products shown. The reactions with simple substrates (entries 1–4) usually took place within 1–2 h. In fact, if the reaction with **3** was run for 5 h, the only product isolated was the ketone corresponding to **3a** in quantitative yield.

A plausible reaction path for the aerobic oxidative cleavage of **3** by the present catalytic system is illustrated in Scheme 2. Ishii et al. showed that the generation of a Co(III)–dioxygen complex, derived from $Co(OAc)_2$ and O_2, is important to initiate the oxidation and that the Co(III)–dioxygen complex assists the formation of a phthalimide *N*-oxyl radical (PINO) from NHPI.[4,12] The PINO radical thus generated abstracts a hydrogen atom from **3** to form α,α′-dialkoxy benzyl radical **A**, which is eventually converted into hydroxyesters **3a** and **3b** through the formation of α,α′-dialkoxy benzyl hydroperoxide **B**. This mechanism explains the complexation with substrates **6** and **9**, where the formation of an α-alkoxy benzyl radical at another carbon is highly possible and competes with the main deprotection reaction. Because the collapse of hydroperoxide **B** to form hydroxyesters has little bias toward either side of the molecule, this mechanism also accounts for the low regioselectivities observed for all the substrates.

In a typical procedure, methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside **1** (247 mg, 0.64 mmol), NHPI (10 mg, 10 mol%), $Co(OAc)_2$ (0.8 mg, 0.5 mol%), and *m*-CPBA (5 mg, 5 mol%) in EtOAc (5 mL) were



Scheme 2. A plausible reaction path for the aerobic oxidative cleavage of benzylidene acetal **3**.

placed in a flask equipped with a balloon filled with O_2. The mixture was stirred at ambient temperature for 15 h. Removal of the solvent under reduced pressure, followed by silica-gel chromatography (EtOAc:Hexanes 1:1 to 5:3) provided **1a** (140 mg, 54%) as a solid and **1b** (70 mg, 27%) as a liquid.†

In conclusion, we have reported a facile procedure for the oxidative cleavage of benzylidene acetals to the corresponding hydroxy benzoate ester(s). The methodology is environmentally benign and experimentally simple, and utilizes mild reaction conditions compatible with common carbohydrate protecting groups.

† Spectra for **1a** were compared with those from: Klausener, A.; Runsink, J.; Scharf, H.-D. *Liebigs Ann. Chem.* **1984**, *4*, 783–790. For **1b**, see: Willard et al. *Can. J. Chem.* **1963**, *41*, 1223, 1229. For **2a**, **3a**, **3b** and **4a**, see: Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996–1002. For **4a**, see also: Li, P.; Alper, H. *Can. J. Chem.* **1993**, *71*, 84–89. For **5a**, see: Sakai, T.; Wada, K.; Murakami, T.; Kohra, K.; Imajo, N. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 631–638. Compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, $J=7.8$ Hz), 1.73 (quint., 2H, $J=7.3$ Hz), 3.28 (br s, 1H), 3.74 (dd, 1H, $J=12.0$, 5.6 Hz), 3.79 (dd, 1H, $J=12.4$, 3.2 Hz), 5.06 (m, 1H), 7.39 (m, 2H), 7.52 (m, 1H), 8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.98, 23.99, 64.46, 77.67, 128.59, 129.89, 130.39, 133.29, 167.19. For **7a**, see: Hakamata, W.; Nishio, T.; Oku, T. *Carbohydr. Res.* **2000**, *324*, 107–115 and Varela, O.; Cicero, D.; de Lederkremer, R. M. *J. Org. Chem.* **1989**, *54*, 1884–1890. For **7b**, see: Verduyn, R.; Douwes, M.; van der Klein, P. A. M.; Moesinger, E. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 7301–7316. For **8a** and **8b**, see: Ref. 11.

Acknowledgements

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