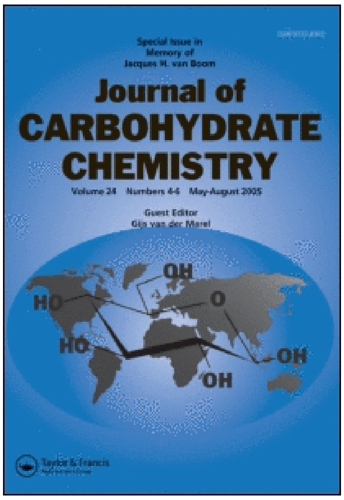

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A New Oxidative Conversion of Carbohydrate Benzyl Ethers to Benzoyl Esters with $RuCl_3$-NaIO

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COMMUNICATION

A NEW OXIDATIVE CONVERSION OF CARBOHYDRATE BENZYL ETHERS TO BENZOYL ESTERS WITH $RuCl_3$-$NaIO_4$.

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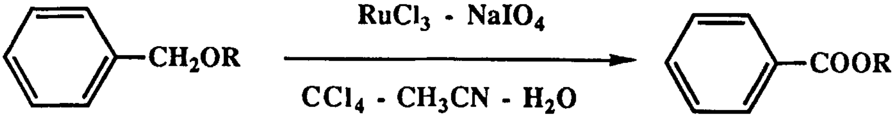
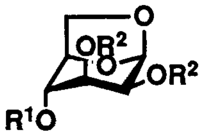
The benzyl group is often used in organic synthesis, especially in carbohydrate chemistry, as one of the most useful of the hydroxyl protecting groups. Benzyl ethers are stable to basic conditions and the benzyl group is removed easily by hydrogenolysis or under Birch reduction conditions. Alternatively, the benzyl ether group is oxidized to benzoyl ester and removed under basic conditions. A few oxidation methods have been reported using more than a stoichiometric amount of chromium reagents such as CrO_3-H_2SO_4 (Jones reagent)[1] or CrO_3-AcOH.[2] Here we report a new and mild oxidation of benzyl ether to benzoyl ester with a catalytic amount of RuO_4 derived from $RuCl_3$ and $NaIO_4$. This method has proved effective in removing benzyl ether groups chemoselectively in the presence of benzylidene acetal and benzyl glycosidic functions.

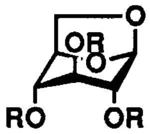
This oxidizing reagent has been used for oxidation of secondary alcohols of carbohydrates to the corresponding uloses[3] and RuO_4 has also been reported to oxidize the α-position of tetrahydrofuran effectively.[4] We have applied this oxidation to various carbohydrate benzyl ethers.



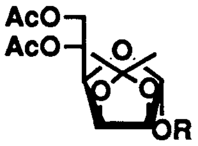
R = Carbohydrate



(1a) R^1=Bn, R^2=Isop
(1b) R^1=Bz, R^2=Isop
(3a) R^1=Bn, R^2=Ac
(3b) R^1=Bz, R^2=Ac
(4a) R^1=Bn, R^2=TMS
(4b) R^1=Bz, R^2=TMS

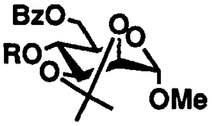


(2a) R=Bn
(2b) R=Bz

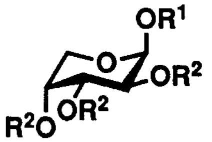


(5a) R=Bn
(5b) R=Bz

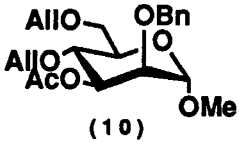
(9a) R=Bn
(9b) R=Bz



(6a) R=Bn
(6b) R=Bz



(7a) R^1=Bn, R^2=Me
(7b) R^1=Bz, R^2=Me
(8) R^1=Bn, R^2=Ac



(10)

Table 1.
Oxidation of benzyl ethers of carbohydrates

Entry	Starting Material	$RuCl_3 \cdot 3H_2O$ (equiv)	$NaIO_4$ (equiv)	Product	Yield (%)
1	1a	0.2	4.2	1b	72
2*	1a	0.2	4.1	1b	72
3**	1a	1.7	3.0	1b	65
4	2a[10]	0.3	17.9	2b[11]	32
5	3a	0.2	9.0	3b	82
6*	4a	0.4	12.5	4b	76
7	5a	0.2	8.6	5b	41
8	6a	0.2	4.2	6b	65
9	7a	0.2	4.0	7b	54
10	8[12]	0.2	4.3	no reaction	
11	9a[13]	0.2	12.4	9b[14]	37
12	10	0.2	12.9	decomposition	

* Basic condition in the presence of $NaHCO_3$
** This reaction was complete within 3 hours.

In a typical experiment,[5] $RuCl_3 \cdot 3H_2O$[6] (10 mg, 0.04 mmol) and $NaIO_4$ (activity : 0.96) (53mg, 0.25mmol) were added to a solution of the benzyl ether **1a** (62 mg, 0.21 mmol) in CCl_4 (0.8 mL), CH_3CN (0.8 mL) and H_2O (1.2 mL) with stirring at 0 °C. This solution was stirred at 16 °C and $NaIO_4$ (138mg, 0.65mmol) was added portionwise for 1 day. When **1a** disappeared on TLC, excess isopropyl alcohol was added. After addition of several mL of H_2O, this solution was extracted with $CHCl_3$, and the extract was washed with aq $NaHCO_3$ and brine, and dried with $MgSO_4$. Crude residue obtained by evaporation of solvent was purified on a silica-gel column (n-hexane-ethyl acetate) to yield **1b** (47 mg, 72%).

Various carbohydrate benzyl ethers were examined under the above oxidation conditions and the results are summarized in **Table 1**. The structures of products were confirmed by ^1H and ^{13}C NMR.[7] This method has some important features. Although the reaction mixture was slightly acidic, isopropylidene and benzylidene groups as well as 1,6-anhydropyranose structures were stable to these conditions (entries 1, 3~5, 7, 8, and 11). In the oxidation mechanism it is proved that dehydrogenation occurs at the α-position of ether in the first step.[8] Acetyl and benzoyl groups present on the carbohydrate retarded the reactivity (entries 5, 7, 8, and 10). The yield and the rate of the reaction was found to be unchanged in the presence of $NaHCO_3$ (entry 2), and trimethylsilyl ether was stable to the reaction conditions (entry 6). In the case of **9a**, non–anomeric benzyl ethers were oxidized chemoselectively in the presence of anomeric benzyl ether as well as benzylidene acetal. The allyl ether group was unstable under the reaction conditions (entry 12). The oxidation was complete within a few hours when the amount of $RuCl_3 \cdot 3H_2O$ was increased (entry 3).

Solvent also has an important role in this reaction. While **1b** was obtained in moderate yields in the standard solvent system ($CCl_4 : CH_3CN : H_2O = 2 : 2 : 3$), in other solvent systems {$CCl_4 : H_2O = 4 : 3$, $CH_3CN : H_2O = 4 : 3$, and $(CH_3)_2CO : H_2O = 3 : 2$} **1b** was obtained in 18, 31, and 37% yields, respectively, with debenzylation and further oxidation occuring to yield 1,6-anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-4-ulose.[9] These yields were improved by addition of $NaHCO_3$ to 70 and 77%, respectively, in the latter two solvent systems, but the first one was not altered.

This oxidative conversion of benzyl ether groups into benzoyl esters followed by benzoate deprotection seems to be promising for synthetic organic chemistry and especially synthetic carbohydrate chemistry.

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6. Though a large excess of $NaIO_4$ was needed, RuO_2 could be used instead of $RuCl_3 \cdot 3H_2O$. No reaction proceeded with $NaIO_4$ alone.

7. Satisfactory spectral data were obtained for the new compounds in accord with the structures. Selected spectral data are as follows. ^1H and ^{13}C NMR were measured at 100 and 22.5MHz in $CDCl_3$ respectively.

   1a : ^1H NMR; δ 1.34 and 1.54 (2 s, 6 H, 2 CCH_3), 3.64 (s, 1 H, H-4), 3.71 (dd, 1 H, $J_{5,6a}$=6.2, $J_{6a,6b}$=7.0 Hz, H-6a), 3.86 (dd, 1 H, $J_{5,6b}$=1.8 Hz, H-6b), 4.05 (dd, 1 H, $J_{1,3}$=3.0, $J_{2,3}$=6.0 Hz, H-3), 4.23 (broad d, 1 H, H-5), 4.56 (dd, 1 H, $J_{1,2}$<0.5 Hz, H-2), 4.67 (s, 2 H, CH_2Ph), 5.30 (dd, 1 H, H-1), 7.34 (s, 5 H, Ph). ^{13}C NMR; δ 25.89 and 26.04 (2 CCH_3), 99.22 (C-1), 109.80 {$C(OCH_3)_2$}.

   1b : ^1H NMR; δ 1.36 and 1.60 (2 s, 6 H, 2 CCH_3), 3.81 (dd, 1 H, $J_{5,6a}$ and $J_{6a,6b}$=6.0 and 7.6 Hz, H-6a), 4.04-4.22 (m, 2 H, H-5 and 6b), 4.30 (m, 1 H, H-3), 4.70 (m, 1 H, H-2), 5.27 (s, 1 H, H-4), 5.41 (d, 1 H, $J_{1,2}$=5.0 Hz, H-1), 7.2-7.6 (m, 3 H, Ph), 7.9-8.1 (m, 2 H, Ph). ^{13}C NMR; δ 25.84 and 25.99 (2 CCH_3), 99.32 (C-1), 110.24 {$C(OCH_3)_2$}, 165.38 (C=O).

   4a : ^1H NMR; δ 0.09 and 0.18 (2 s, 18 H, 6 $SiCH_3$), 3.38 (m, 1 H, H-4), 3.58-3.78 (m, 2 H, H-6a and 6b), 3.90 (m, 1 H, H-5), 4.22 (broad d, 1 H, $J_{2,3}$=6.0 Hz, H-3), 4.48 (broad d, 1 H, H-2), 4.66 (s, 2 H, CH_2Ph), 5.21 (m, 1 H, H-1), 7.33 (s, 5 H, Ph). ^{13}C NMR; δ 0.10 {2 $Si(CH_3)_3$}, 102.29 (C-1).

   4b : ^1H NMR; δ 0.21 (s, 18 H, 6 $SiCH_3$), 3.70-3.88 (m, 2 H, H-6a and 6b), 3.99 (m, 1 H, H-5), 4.44 (d, $J_{2,3}$=6.0 Hz, 1 H, H-3), 4.63 (broad d, 1 H, H-2), 5.03 (m, 1 H, H-1), 5.34 (m, 1 H, H-4). 7.36-7.72 (m, 3 H, Ph), 8.02-8.20 (m, 2 H, Ph). ^{13}C NMR; δ 0.20 {2 $Si(CH_3)_3$}, 102.39 (C-1), 165.43 (C=O).

   7a : ^1H NMR; δ 3.46, 3.49, and 3.52 (3 s, 9 H, 3 CH_3), 3.4-3.9 (m, 5 H, H-2, 3, 4, 5a, and 5e). 4.53 and 4.77 (ABq, 2 H, J=11.5 Hz, CH_2Ph), 5.01 (s, 1 H, H-1), 7.20-7.44 (m, 5 H, Ph). ^{13}C NMR; δ 96.83 (C-1).

   7b : ^1H NMR; δ 3.53 and 3.58 (2 s, 9 H, 3 CH_3), 3.4-4.0 (m, 5 H, H-2, 3, 4, 5a, and 5b), 6.55 (d, $J_{1,2}$=3.5 Hz, 1 H, H-1), 7.2-7.6 (m, 3 H, Ph), 7.9-8.1 (m, 2 H, Ph). ^{13}C NMR; δ 91.27 (C-1), 165.19 (C=O).

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