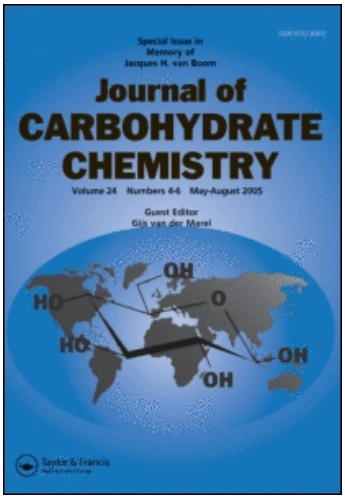

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Practical Synthesis of 1,2-*O*-Benzylidene and 1,2-*O*-*p*-Methoxybenzylidene Hexopyranoses

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ABSTRACT

An improved and practical synthesis of 1,2-*O*-benzylidene and 1,2-*O*-*p*-methoxybenzylidene hexopyranoses as useful synthons in carbohydrate chemistry is described. The reaction of 2-benzoyloxyglycosyl bromide with sodium borohydride using excess amount of potassium iodide proceeded smoothly to give the corresponding 1,2-*O*-benzylidene derivative in good yields.

Key Words: Benzylidene; Reductive acetalization; Protecting group.

INTRODUCTION

The benzylidene group has been widely used in organic synthesis to protect two hydroxyl groups selectively and provide conformational stability.[1] A number of studies involving regioselective ring-opening reactions have been performed in carbohydrate chemistry[2] using 4,6-*O*-benzylidene protected sugars. In contrast, 1,2-*O*-benzylidene sugar derivatives have not been frequently utilized.[3] The general nature of the 1,2-*O*-benzylidene group is not well known, but this group is attractive as a

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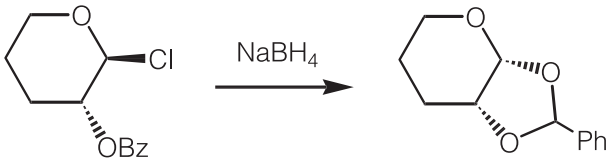

Figure 1. Reductive benzylidenation.

protecting and/or activating group for the anomeric position. The 1,2-*O*-benzylidene group has been constructed by acetal exchange reactions of corresponding acetonide[4] or orthoester[5] derivatives under acidic conditions. In addition, reduction of a 1,2-*trans*-2-benzoyloxyglycosyl chloride using sodium borohydride generated the 1,2-*O*-benzylidene group as shown in Figure 1.[6] Use of tetra-*n*-butyl ammonium iodide (TBAI) in a reductive cyclization system was effective for the synthesis of 1,2-*O*-benzylidene from 1,2-*cis*-2-benzoyloxyglycosyl chloride (A few reports using 1,2-*O*-benzylidene derivatives were published. For example; Ref. [7]). However, this reaction was not successful even if we performed it under similar conditions as previously described ($NaBH_4$ 1.5 mol, TBAI 0.5 mol in MeCN). This result prompted us to optimize the conditions of this reaction. In this communication, we would like to report a practical synthesis of 1,2-*O*-benzylidenehexopyranoses as promising useful glycosidic synthons.

RESULTS AND DISCUSSION

To compare the difference of the reactivity of 1,2-*trans* with 1,2-*cis*-2-benzoyloxyglycosyl halide, two configurationally different types of glycosyl bromide, **1**–**4**,

Table 1. Reductive 1,2-*O*-benzylidenation reaction.

Entry	Substrate	Condition*	Time	Product (yield %)
1	**1**	A	0.5 h	**5** (96%)
2	**2**	A	0.5 h	**6** (86%)
3	**3**	A	0.5 h	none
4	**4**	A	0.5 h	none
5	**3**	B	20 h	no reaction
6	**4**	B	20 h	no reaction
7	**3**	C	8 h	**7** (85%)
8	**4**	C	8 h	**8** (76%)
9	**3**	D	20 h	**7** (98%)
10	**4**	D	20 h	**8** (92%)
11	**1**	D	20 h	**5** (94%)
12	**2**	D	20 h	**6** (90%)

*A: $NaBH_4$ (5.0 eq), MeCN, reflux; B: TBAI (0.5 eq), $NaBH_4$ (1.5 $\sim$ 5.0 eq), MeCN, rt $\sim$ reflux; C: TBAI (2.5 eq), $NaBH_4$ (2.0 eq), MeCN, rt; D: KI (1.5 eq), $NaBH_4$ (1.0 eq), MeCN, rt.

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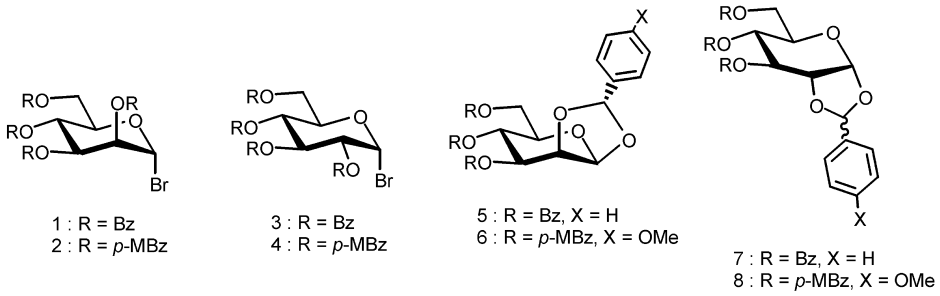

Figure 2. Substrates and products.

manno- and *gluco*-type, were prepared as substrates. The results of the reductive benzylidenation are shown in Table 1 (Figure 2).

To a solution of *manno*-type bromide **1** or **2** in acetonitrile was added 5 equiv of sodium borohydride. The mixture was stirred for 30 min at reflux temperature to afford 1,2-*O*-benzylidene derivatives **5**, **6** (entry 1, 2).[a] Under these conditions, *gluco*-type bromides **3** or **4** were not converted to the corresponding 1,2-*O*-benzylidene derivatives but gave complex mixtures.[b] Apparently, the oxocarbenium-ion intermediate, which is necessary for the reductive acetalization, did not form when starting from **3** or **4**, as it did from the 1,2-*cis* glycosyl halide (entry 3,4). Addition of TBAI, which reacts with the 1,2-*cis* glycosyl halide to give the 1,2-*trans* glycosyl halide, should be able to promote the construction of a 1,2-*O*-benzylidene derivative from a 1,2-*cis* glycosyl halide. However, using the previously reported conditions ($NaBH_4$ 1.5 mol, n-Bu_4NI 0.5 mol, acetonitrile), the 1,2-*O*-benzylidene group was not produced at all and starting materials **3** and **4** were recovered (entry 5, 6).[c] We thought that excess $NaBH_4$ trapped the iodide ion necessary for the halogen exchange of 1,2-*cis* glycosyl halide. This hypothesis was supported by results of carrying out the reaction using excess TBAI (entry 7, 8). Use of potassium iodide (KI) as an inexpensive iodide ion source was much more effective for this reaction (entry 9, 10). In the reactions using KI, *manno*-type glycosyl bromide **1** or **2** were converted at room temperature to the corresponding 1,2-*O*-benzylidene **5** and **6** in a satisfactory yield, respectively (entry 11, 12).

The structures of 1,2-*O*-benzylidene derivatives **5** and **6** were confirmed by ^1H NMR. A NOE was observed between H-2 and the methine proton of the benzylidene

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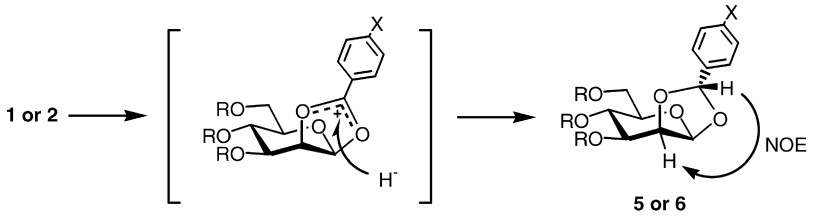
[a]Selected spectral data for 3,4,6-tri-*O*-*p*-methoxybenzoyl-1,2-*O*-*p*-methoxybenzylidene-α-D-mannopyranose **6**: ^1H NMR ($CDCl_3$) δ 6.12 (dd, $J_{3,4}$ = 10.1, $J_{4,5}$ = 9.9 Hz, H-4), 5.95 (s, benzylidene), 5.67 (dd, $J_{2,3}$ = 3.5, $J_{3,4}$ = 10.1 Hz, H-3), 5.58 (d, $J_{1,2}$ = 1.8 Hz, H-1), 4.80 (dd, H-2), 4.65 (dd, $J_{5,6a}$ = 2.2, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.36 (dd, $J_{5,6b}$ = 3.3 Hz, H-6b), 4.10 (ddd, H-5); 3,4,6-tri-*O*-*p*-methoxybenzoyl-1,2-*O*-*p*-methoxybenzylidene-α-D-glucopyranose **8**(**R**): ^1H NMR ($CDCl_3$) δ 5.92 (s, benzylidene), 5.87 (d, $J_{1,2}$ = 5.1 Hz, H-1), 5.71 (dd, $J_{2,3}$ = 2.9, $J_{3,4}$ = 1.8 Hz, H-3), 5.50 (ddd, $J_{2,4}$ = 1.1, $J_{4,5}$ = 8.8 Hz, H-4), 4.62 (dd, $J_{5,6a}$ = 2.6, $J_{6a,6b}$ = 11.7 Hz, H-6a), 4.52 (m, H-5), 4.45 (m, H-2), 4.41 (dd, $J_{5,6b}$ = 5.1 Hz, H-6b).

[b]All of glycosyl bromides underwent decomposition, and the products were not isolated.

[c]A small amount of the glycal, 2,3,4,6-tetra-*O*-benzoyl-D-glucal was obtained in the heating condition.



Scheme 1. Less hindered side attack of H^- and the NOE observation with the *manno*-type 1,2-*O*-benzylidene **5** or **6**.

group. The highly stereoselective formations of the (*R*)-benzylidene isomer may be due to attack by the borohydride ion on the sterically less hindered side of the acyloxonium ion intermediate (Scheme 1). The *gluco*-type 1,2-*O*-benzylidene product mixture **7** and **8**,[a] whose ^{1}H NMR spectrum showed a (*R*): (*S*) = 7: 3 diastereomeric mixture at the benzylidene position, was converted into the known 3,4,6-tri-*O*-acetate.[d] Interestingly, the *gluco* and *manno* types of benzylidene derivatives have different pyranose ring conformations. A large coupling of the $J_{3,4}$ indicates $^4C_1$ in *manno* type **5** and **6**, but small coupling of the $J_{2,3}$, $J_{3,4}$ and the characteristic long-range coupling $^4J_{2,4}$ in *gluco* type **7** and **8** implies a flexible (skew-boat) conformation.[8] These conformation differences may account for the different reactivity in ring-opening reactions of the 1,2-*O*-benzylidene group.

Thus, a practical synthesis of 1,2-*O*-benzylidenehexopyranoses as useful synthons in carbohydrate chemistry was accomplished.

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[d]The mixture of *gluco*-type 1,2-*O*-benzylidene products **7** or **8** was treated with a catalytic amount of sodium methoxide in methanol, then acetylated with acetic anhydride in pyridine to give 3,4,6-tri-*O*-acetyl-1,2-*O*-benzylidene derivative[5] which was separable into its diastereomeric components.

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