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Direct Glycosylation of Unprotected and Unactivated Carbohydrates under Mild Conditions

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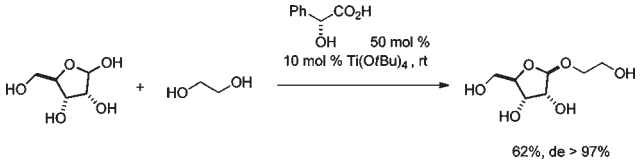
ABSTRACT



Ligand exchange acetalization of acetals in the presence of catalytic amounts of mandelic acid and titanium *tert*-butoxide is reported. This transformation is successfully extended to glycosylation of unprotected and unactivated pentoses. Even unreactive pentoses such as D-arabinose or D-lyxose can be transformed by this new methodology into corresponding isopropyl glycosides.

Glycoconjugates or glycosides are very important examples of biomolecules. Due to different arranged and configured hydroxyl groups of carbohydrates a general applicable chemical synthesis to glycosides of all carbohydrates does not exist. Therefore the syntheses of glycosides have been of great interest for a long time. In order to achieve the required stereo-, chemo-, and regioselectivity many different and complex methods of glycosidation have been developed. Frequently, these synthetic maneuvers are associated with an extensive handling of protecting groups and additional activation of the anomeric carbon atom.[1] In order to avoid these multistep approaches to defined glycosides, several attempts have been made to increase and to utilize reactivity differences between the hemiacetal function and the remaining unprotected hydroxyl groups of carbohydrates.[2] Also, methods have been developed to deploy unprotected and unactivated carbohydrates in direct glycosidation processes. These transformations are associated with high reaction

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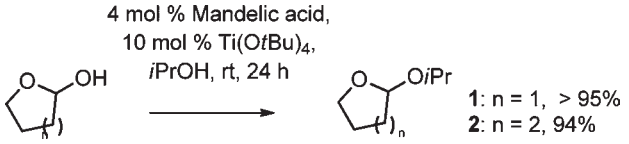
temperatures[3] and/or the deployment of strong bases,[4] strong acids,[5] or Lewis acids[6] as catalysts. During our ongoing studies on the application of ligand-exchange mediated C−C bond formation processes, we observed substantial amounts of products derived from acetalization. These reactions were performed in the presence of titanium(IV) alkoxides and α-hydroxy acids.[7] By optimizing our findings, we were able to achieve acetalization of hemiacetals in the tetrahydrofuran and tetrahydropyran series, under neutral reaction conditions (Scheme 1).

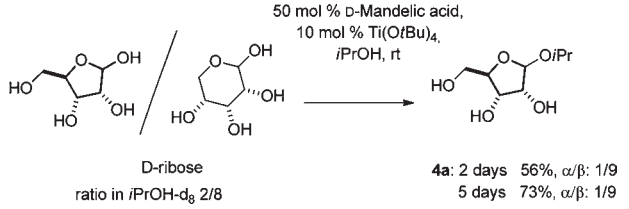
Scheme 1. Acetalization of Hemiacetals



Only by deployment of titanium(IV) alkoxides and α-hydroxy acids was acetalization of hemiacetals observed. Corresponding isopropyl acetals **1** and **2** were isolated in quantitative yields in both runs (n = 1 or 2) at room temperature within 24 h.

Encouraged by these results we tested this catalytic system in the glycosylation of unprotected carbohydrates. For this purpose, D-ribose was reacted with isopropanol under the following reaction conditions. When titanium(IV) *tert*-butoxide (10 mol %) and D-mandelic acid (50 mol %) were employed at room temperature the corresponding isopropyl-D-riboside **4a** was isolated in good yield (Scheme 2).

Scheme 2. Direct Glycosylation of D-Ribose



Investigations revealed that primary as well as secondary alcohols can be successfully applied in the reactions with D-ribose. Also *tert*-butanol reacts under these reaction conditions but in a lower yield (*cf*. Scheme 4). A ratio of 5:1 (D-mandelic acid/Ti(O*t*Bu)$_4$) and a ratio of 1:2 for 2-deoxy-D-ribose was identified as optimal for glycosylation of D-pentoses with isopropanol. Preformed titanium(IV) alkoxide/D-mandelic acid complexes did not lead to glycosylation products under these reaction conditions. Our optimized reaction conditions were applied to glycosylation reactions with isopropanol for the D-pentoses mentioned in Figure 1. The highest yields were obtained by deployment of 2-deoxy-D-ribose (**3a**: 61%) and D-ribose (**4a**: 56%). The lowest yields were detected for D-lyxose and D-arabinose (**6a**; **7a** < 10%). The yields can be increased by longer reaction times. Isopropyl glycosides of D-xylose, D-lyxose, and D-arabinose were isolated after 12 days at room temperature, in approximately 30% yield (**5a**: 28%, **6a**: 23%, **7a**: 20%) (green line, Figure 1). Under these conditions the exclusive formation of isopropyl furanosides is observed (kinetic control). Also, substantial amounts of isopropyl pyranosides could not be detected after 12 days at room temperature.

Table 1. Yields and Anomeric Ratios of Isopropyl Furanosides for D-Pentoses[a]

		yields (%)			
entry	compd	**2d**	**5d**	**12d**	α/β ratio (%)
1	**3a**	61	76	62	50/50
2	**4a**	56	78	73	7/93
3	**5a**	11	13	28	50/50
4	**6a**	5	9	23	75/25
5	**7a**	2	5	20	35/65

[a] Reaction conditions: 50 mol % D-mandelic acid, 10 mol % Ti(O*t*Bu)$_4$, *i*PrOH, rt. Deoxyribose: 4 mol % D-mandelic acid, 10 mol % Ti(O*t*Bu)$_4$, *i*PrOH, rt.

These findings contrast with results obtained by the Fischer- or other acid-mediated glycosidation methods. Different ratios of pyranoid/furanoid glycosides were detected under Fischer conditions depending on reaction times.[8] The following different anomeric ratios (α/β) were detected for the isolated isopropyl furanosides under our new conditions for D-pentoses (*cf*. Table 1).

This strong substrate selectivity is not consistent with results obtained by Fischer glycosylation with MeOH.[9] Both yield and anomeric ratios of glycosides formed by our method are dictated by the configuration of the hydroxy groups of D-pentoses deployed.

In order to demonstrate the scope of this direct glycosylation, several functionalized alcohols were reacted with unprotected D-ribose under these conditions. Again, only furanoid ribosides were observed after 2 days. A preference

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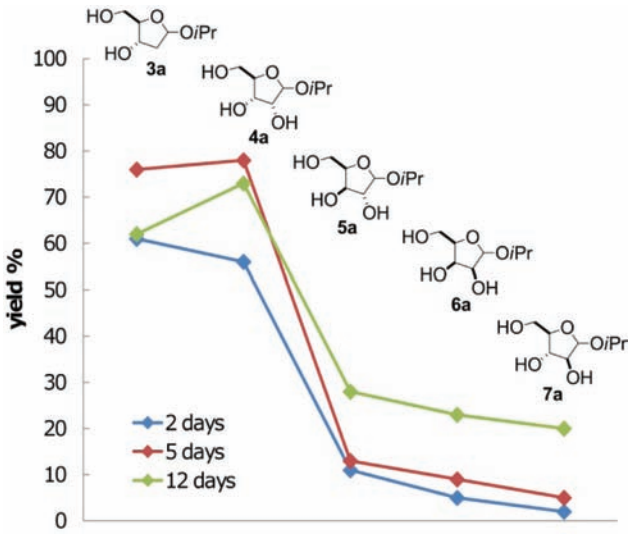


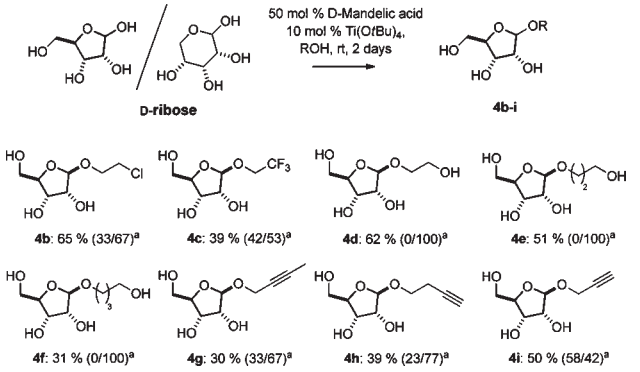
Figure 1. Yields of isopropyl glycosides for D-pentoses as a function of time. Lines are drawn to guide the eye. Reaction conditions: 50 mol % D-mandelic acid, 10 mol % Ti(O*t*Bu)$_4$, *i*PrOH, rt. Deoxyribose: 4 mol % D-mandelic acid, 10 mol % Ti(O*t*Bu)$_4$, *i*PrOH, rt.

for the formation of β-configured ribosides was observed. β-Configured anomers were solely detected in the diol series (**4d**–**4f**, *cf.* Scheme 3). The results demonstrate that under our new reaction conditions both the aglycon as well as the unprotected carbohydrate have a great influence on the anomeric ratio of glycosides formed.

Several attempts were made to decrease the long reaction times. To this end, different additives were tested. As a result of this optimization, lithium salts, especially lithium bromide, proved to be beneficial for these transformations.[10] The results are depicted in Figure 2.

A marked improvement in yield was found between Figures 1 and 2 for all D-pentoses used under the LiBr

Scheme 3. Glycosidation of D-Ribose under Mild Reaction Conditions[a]



[a] α/β ratio.

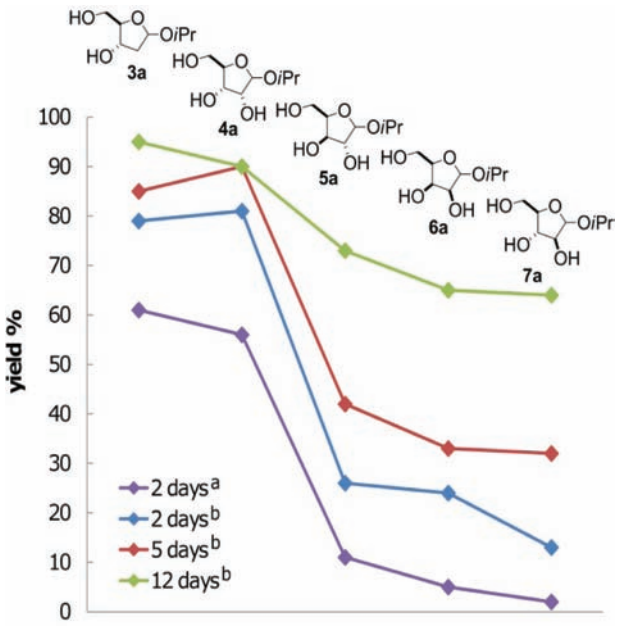
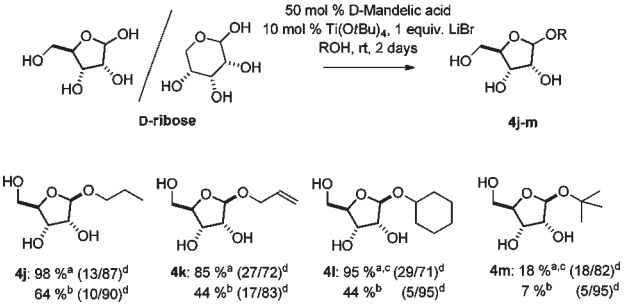


Figure 2. Yields of isopropyl glycosides for D-pentoses as a function of time in the presence of lithium bromide[b] and for comparison without lithium bromide.[a] Lines are drawn to guide the eye. [b]Reaction conditions: 50 mol % D-mandelic acid, 10 mol % Ti(O*t*Bu)$_4$, 1 equiv of LiBr, *i*PrOH, rt. Deoxyribose: 4 mol % D-mandelic acid, 10 mol % Ti(O*t*Bu)$_4$, *i*PrOH, rt.

conditions (**3a**: 95%, **4a**: 90%, **5a**: 73%, **6a**: 65%, **7a**: 64%, 12 days, rt). Furanoid glycosides were the major products after 2 days at room temperature (80–100%). Pyranoid glycosides were detected after longer reaction times (*cf.* Table 1 in the Supporting Information). To demonstrate this property of lithium bromide, several alcohols were reacted under the described reaction conditions for 2 days (*cf.* Scheme 4). These results clearly emphasize the yield-increasing feature of lithium bromide.

Scheme 4. Comparison of Glycosylation

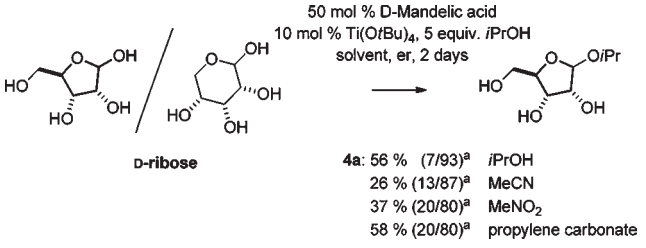


[a] In the presence of lithium bromide. [b]In the absence of lithium bromide .[c] > 85% furanoid structure. [d]α/β ratio.

We next studied the effect of different solvents on the glycosylation outcome. We were keen to reduce the amount of aglycon and thus enable the application of solid

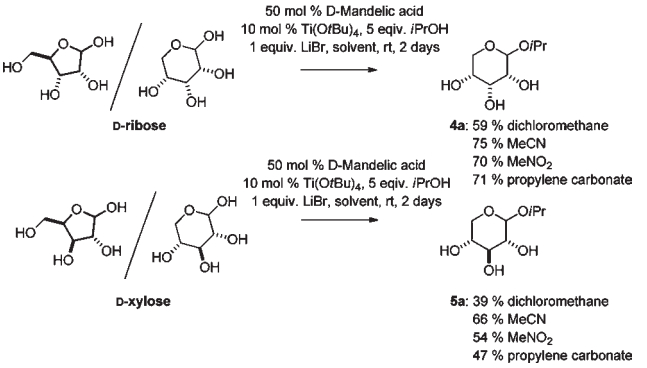
aglycons. Reactions were not observed in the presence of DMSO or DMF.[11]

Scheme 5. Direct Glycoslyation of D-Ribose in Different Solvents[a]



[a] α/β ratio.

Scheme 6. Direct Glycosydation of D-Ribose and D-Xylose in the Presence of Solvents and Lithium Bromide



The favored solvent for these reactions turned out to be propylene carbonate. Comparable yields were obtained when used with propylene carbonate and reduced amounts of isopropanol (5 equiv, Scheme 5). Furanoid glycosides were detected exclusively with similar anomeric ratios to neat isopropanol.

To study the influence of lithium bromide under these reaction conditions, the optimal solvents were used for a survey of the glycosylation reactions of D-ribose and D-xylose (cf. Scheme 6; Table 2 in the Supporting Information). The formation of thermodynamically controlled pyranoside was observed. These findings stand in contrast to results observed in the absence of solvents (see kinetic control, Scheme 4).[12]

In summary, we have developed a new method for direct glycosylation of unprotected and unactivated carbohydrates under mild reaction conditions. This new transformation utilizes titanium(IV) *tert*-butoxide and D-mandelic acid. By deployment of these reaction conditions, the exclusive formation of furanoid glycosides is observed. Also, the use of lithium bromide as an additive strongly increases the yields of products observed. When lithium bromide is employed in polar solvents, thermodynamic control of glycosidation is observed. As a result, pyranosides were almost exclusively formed with high degrees of selectivity. Thus, an optional access to furanoid or pyranoid glycosides is provided by the choice of reaction conditions (solvents and catalysts component). Further extension of these findings to hexoses is underway.

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Supporting Information Available. NMR data for all of the synthesized compounds and full characterization of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org

(11) This is possibly due to the chelating effect of these solvents.

(12) For investigations in thermodynamically and kinetically controlled glycosylation reactions, see: Bishop, C. T.; Coopper, F. P. *Can. J. Chem.* **1962**, *40*, 224.

The authors declare no competing financial interest.