A NEW METHOD FOR SELECTIVE PROTECTION OF TWO HYDROXYL GROUPS IN CARBOHYDRATES, GLYCALs IN PARTICULAR

Cedric W. Holzapfel,* Johan J. Huyser, Thilo L. van der Merwe, and Fanie R. van Heerden*

Department of Chemistry and Biochemistry, Rand Afrikaans University, P.O. Box 524, Johannesburg 2000, South Africa.

Abstract - The regioselective conversion of selected carbohydrate derivatives into their allylic cyclic acetals was achieved by successive treatment with dibutyltin oxide, acrolein diacetate and catalytic amount of tetrakis(triphenylphosphine)palladium(0). Methods for the removal of the new protecting group are discussed.

Carbohydrates are important starting materials in chiral synthesis and 4,6-0-protected glycals in particular have recently received much attention in this context. However, the selective simultaneous protection of two hydroxyl groups under neutral conditions remains a problem in carbohydrate chemistry. Protecting groups for adjacent hydroxyl functions in classical sugar chemistry, e.g. isopropylidene and benzylidene groups, are introduced by means of acid catalyzed reactions, and can therefore not be applied to acid sensitive substrates. The acid catalyzed acetalization of glycals generally results in the facile rearrangement of the 1,2-double bond to the 2,3-position, and the required protected glycal is usually obtained in an unacceptably low yield. In our hands, attempts to protect a-glucal (1) in the presence of a catalytic amount of HSO₄ resulted in rapid rearrangement of the starting material to 2-(a-glycero-1,2-dihydroxyethyl)furan. The same product was also reported to be obtained by reaction of 3,6-anhydro-a-glucal with dilute hydrochloric acid. 4,6-0-Protected glycals are, therefore, generally prepared via long, cumbersome routes. To our knowledge, the only methodology for the introduction of a 4,6-0-protecting group to methyl a-a-glucopyranoside under non-acidic conditions is by the use of the reagent 1,3-dichloro-1,1,3,3-tetraisopropaylvdisiloxane.
The use of tin reagents, e.g. dibutyltin oxide and bis(tributyltin) oxide, provides an extremely effective method for the selective activation of carbohydrate hydroxyl groups. Tin ethers are good nucleophiles in acylation, alklyation, as well as in palladium catalyzed substitution reactions. We investigated the application of the latter reaction for the selective introduction of a two hydroxyl protecting group under non-acidic conditions.

The bifunctionality of allylic diacetates and dicarbonates in Pd(0) catalyzed reactions with nucleophiles received much less attention in the literature than monoallylation of nucleophiles. There are, however, a few reports on the Pd(0) catalyzed reaction of bifunctional allylic diesters with bifunctional nucleophiles where an intramolecular reaction yielded cyclic products. We herein report the selective protection of two hydroxyl groups of a sugar under neutral conditions, by combining the selective activation of carbohydrate hydroxyls via a tin ether with the bifunctionality of allylic diacetates in Pd(0) catalyzed reactions.

In a typical reaction (Scheme 1), acrolein diacetate was used to protect e-glucal (1) selectively. The results obtained with several other carbohydrate substrates are summarized in the Table.

Scheme 1

The selectivity of the reactions is in agreement with tin-mediated acylation reactions. The position of the protecting group was determined unambiguously by esterification of the unprotected hydroxyl group(s) and subsequent evaluation of the down-field shifts of the proton and carbon signals in the $^1$H and $^{13}$C nmr spectra. Single regioisomers were obtained with glucose and mannose derivatives, whereas galactose derivatives yielded two regioisomers. In the reaction with galactal (entry 2) and methyl $\beta$-d-
Table: Selective Pd(0) catalyzed protection of carbohydrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Products$^a$</th>
<th>Time(h)</th>
<th>Total Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /> + <img src="image3" alt="Image" /></td>
<td>1</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /> + <img src="image6" alt="Image" /></td>
<td>1.5</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /> + <img src="image9" alt="Image" /></td>
<td>1.2</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /> + <img src="image12" alt="Image" /></td>
<td>1.6</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /> + <img src="image15" alt="Image" /></td>
<td>1.5</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td><img src="image16" alt="Image" /></td>
<td><img src="image17" alt="Image" /> + <img src="image18" alt="Image" /></td>
<td>1</td>
<td>80</td>
</tr>
</tbody>
</table>

$^a$All new compounds gave satisfactory spectral data.

galactopyranoside (entry 4), the 3,4-0-protected isomer was the major compound. The amount of the 4,6-0-protected product could be increased by performing the reaction at -30°C (65% in the case of entry 2 and 70% for entry 4). These conditions, however, required a considerably longer reaction time (14-16 hours).
All protected carbohydrate substrates, except for 4,6-\(\beta\)-protected \(\beta\)-galactald, where only traces of a second isomer was found, were obtained as mixtures of diastereomers. The formation of two diastereomers is not a disadvantage, since the protecting group will be removed at a later stage. The diastereomers could be separated by chromatography, except for 3,4-\(\beta\)-protected galactal and 4,6-\(\beta\)-protected methyl \(\beta\)-glucose and methyl \(\alpha\)-\(\beta\)-mannose. In these cases the diastereomeric ratios were estimated from \(\text{\textsuperscript{1}}\text{H-}
abla\text{nmr spectroscopy. With the exception of the reactions with \(\beta\)-galactal and \(\beta\)-glucal (diastereomeric ratio=8:2), the ratio of diastereomers obtained was 1:1. The stereochemistry of the acetal group in \(\beta\)-galactal and \(\beta\)-glucal was determined by NOE experiments.

The allylic acetal protecting group can be removed by treatment of the carbohydrate with 1% \(\text{H}_2\text{SO}_4\) in refluxing dioxane (3 hours, yields in excess of 80%). Both the benzoyl protecting groups and the glycal double bond remained intact under these conditions. We also investigated deprotection of the diol under conditions generally used for selective removal of the closely related allyl ethers.\(^\text{14,15}\) Treatment of the allylic cyclic acetal (2) with Wilkinson catalyst \([\text{PPh}_3\text{RhCl}]\) in refluxing ethanol did not result in any isomerization of the double bond, and even after prolonged heating, the starting material was recovered unchanged. The allylic cyclic acetals of the saturated carbohydrates were also stable under these reaction conditions. However, the addition of 1 eq. of trifluoroacetic acid\(^\text{15}\) resulted in deprotection of the acetal, but acid-labile groups present in the substrate (e.g. benzoate) were removed as well. Treatment of the benzyl ether (3) with 1 mol\% \((\text{PPh}_3)_3\text{RhCl}\) and 1 eq. TFA in refluxing ethanol, resulted in selective removal of the protecting group.

The above-mentioned methodology was successfully applied to the preparation of (5), a required intermediate in the synthesis of C-\(\text{\textsuperscript{\text{\textgreek{g}}}I\text{\textsuperscript{\text{\textgreek{g}}}coplyranosides from carbohydrate starting materials.}\(^\text{16}\)

Pseudoglycal (4) was prepared from (2) and \(N,N\)-dimethylacetamide dimethyl acetal by the Eschenmoser version of the Claisen rearrangement (Scheme 2).\(^\text{16}\) In this case, treatment of the amide (4) with \((\text{PPh}_3)_3\text{RhCl}\) in refluxing 96% ethanol (in the absence of trifluoroacetic acid) resulted in removal of the protecting group (yield 90%). The same result was obtained with amide (6).
These results illustrate that acrolein diacetate can be effectively used for the selective protection of two adjacent hydroxyl groups in carbohydrate derivatives. More specifically, the method allows the selective protection of the 4- and 6-hydroxyl groups of glycals, providing ready access to substrates for subsequent Claisen rearrangements.

ACKNOWLEDGEMENT

We gratefully acknowledge the financial support of the Foundation for Research Development.

REFERENCES AND NOTES.


17. General experimental procedure: The sugar (3.5 mmol) and Bu₂SnO (870 mg, 3.5 mmol) were suspended in toluene (30 ml). The reaction mixture was heated under reflux for 4 h with the azeotropic removal of water. The solvent was then removed under anhydrous conditions, the residue was dissolved in THF (50 ml) and Pd(PPh₃)₄ (404 mg, 0.35 mmol) and acrolein diacetate (1.107 g, 7 mmol) were added. The reaction mixture was stirred at room temperature until complete disappearance of the starting material as monitored by tlc. The reaction mixture was worked up and the products were isolated by flash column chromatography (SiO₂, hexane – ethyl acetate).

Received, 14th May, 1991