Facile Preparation of Benzyl β-Glycosides of 2-Acylamino-2-deoxy-D-glucopyranoses

WILLIAM D. RHoads1 and PAUL H. Gross

Department of Chemistry, University of the Pacific, Stockton, California (USA)

Facile Preparation of Benzyl β-Glycosides of 2-Acylamino-2-deoxy-D-glucopyranoses are usually prepared by multistep processes employing the glycosyl halides. Mixtures of benzyl glycosides which contain predominantly the α-glycoside result from acid catalyzed reactions with benzyl alcohol in one phase. In a two phase system, however, the lower solubility of the β-D-anomer becomes the determining factor in the resultant tandem equilibrium, and the β-D-glycoside predominates in the final product.

Introduction

Work in this laboratory centered on benzyl glycosides of aminosugars which are of value in synthetic work, because the benzyl group can be readily removed by hydrogenolysis under mild conditions.

Ballou, Roseman, and Link2 have already shown that the relative rates of hydrogenolysis of anomeric benzyl D-glucosides are quite different. The β-D-glycoside was cleaved in 3 min, while the α-anomer required 8 hours under comparable conditions.

In the chemistry of peptides, rates of hydrogenolytic removal for benzyl esters and benzoxycarbonyl protective groups often become very small for large molecules. In oligosaccharide chemistry, the facile hydrogenolytic removal of β-benzyl glycoside protective groups may therefore be an advantage.

The preparation of a β-glycoside from the α-halide3 is time consuming and overall yields are low. Horton, Woflrom et al.4 have investigated several routes to glycosyl halides via the thioglycosides. Inch and Fletcher5 have employed solvolysis of esters to prepare methyl β-D-glycosides.

The method of Fischer6 usually gives a mixture of anomers containing predominantly the α-anomer. Kuhn, Zilliken, and Gauche7 found, that the acidic glycosidation of 2-acetamido-2-deoxy-D-glucopyranose gave a mixture of methyl glycosides (α:β = 7:1). Fractional recrystallization of the tri-O-acetyl derivatives was employed to separate the anomeric mixture.

Discussion of Results

Gross and Zimmernann8 reported a ratio of α:β = 7:1 for the benzyl glycosides of 2-benzyloxy carbamylamino-2-deoxy-D-glucopyranose. In this method, the acid catalyst had to be neutralized by lead carbonate before the workup which involved precipitation of the product by diisopropylether.

In an attempt to simplify this procedure by elimination of the neutralization step, the concentration of HCl was decreased to 0.5%, and diethyl ether was used to precipitate the product. The anomeric mixture of benzyl glycosides that was thus obtained had a ratio α:β = 4:1.

Since it is mostly found that the β-anomer of a glucosamine derivative is less soluble than the α-anomer, the slower crystallization of the anomeric mixture from the acidic solvent might have led to a crystalline product which was enriched with the less soluble β-anomer. By systematic variation of reaction conditions, a method was developed for the preparation of an anomeric mixture of benzyl 2-benzyloxy carbamylamino-2-deoxy-α and β-D-glucopyranosides which contained up to 2/3 of β-anomer (Table I).

Conditions can also be chosen so that a 40% yield of benzyl 2-benzyloxy carbamylamino-2-deoxy-β-D-
glucopyranoside is obtained virtually pure, if stirring is omitted during the precipitation with ether and the batch is seeded with the pure \( \beta \)-anomer.

Conditions which led to mixtures enriched with \( \beta \)-anomer were also found for the glycosidation of 2-acetamido 2-deoxy-D-glucopyranose with benzyl alcohol (Table II).

**Table I. Preparation of benzyl 2-benzyloxy carbonylamido-2-deoxy-\( \alpha \) and -\( \beta \)-D-glucopyranoside.**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction temperature ([^\circ C])</th>
<th>Reaction time ([h])</th>
<th>Days for di-ethyl ether addition</th>
<th>Yield of crude anomeric mixture ([%])</th>
<th>Percentage ( \beta ) anomer in crude mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5% Hydrochloric acid</td>
<td>90-95</td>
<td>3</td>
<td>2</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>0.5% Hydrochloric acid</td>
<td>90-95</td>
<td>5</td>
<td>2</td>
<td>63</td>
<td>67</td>
</tr>
<tr>
<td>0.5% Trifluoroacetic acid</td>
<td>90-95</td>
<td>6</td>
<td>2</td>
<td>71</td>
<td>67</td>
</tr>
<tr>
<td>1.0% Trifluoroacetic acid</td>
<td>90-95</td>
<td>5</td>
<td>2</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>1.0% Trifluoroacetic acid</td>
<td>90-95</td>
<td>7</td>
<td>4</td>
<td>48</td>
<td>68</td>
</tr>
<tr>
<td>1.5% Trifluoroacetic acid</td>
<td>90-95</td>
<td>5</td>
<td>2</td>
<td>62</td>
<td>68</td>
</tr>
<tr>
<td>0.5% Paratoluene sulfonic acid</td>
<td>90-95</td>
<td>5</td>
<td>2</td>
<td>76</td>
<td>44</td>
</tr>
<tr>
<td>1.0% Boron trifluoride etherate (shelf sample)</td>
<td>90-95</td>
<td>5</td>
<td>2</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>0.5% Boron trifluoride etherate (redistilled)</td>
<td>90-95</td>
<td>5</td>
<td>2</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>1.5% Boron trifluoride etherate (redistilled)</td>
<td>90-95</td>
<td>4</td>
<td>2</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>0.5% 70% Perchloric acid</td>
<td>70-80</td>
<td>4</td>
<td>4</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>0.5% 70% Perchloric acid</td>
<td>70-80</td>
<td>4</td>
<td>4</td>
<td>46</td>
<td>10 (( \beta ) anomer seed crystal used)</td>
</tr>
<tr>
<td>1.0% 70% perchloric acid</td>
<td>90-95</td>
<td>4</td>
<td>4</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table II. Preparation of benzyl 2-acetamido-2-deoxy-\( \alpha \) and -\( \beta \)-D-glucopyranoside.**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction temperature ([^\circ C])</th>
<th>Reaction time ([h])</th>
<th>Days for di-ethyl ether addition</th>
<th>Yield of crude anomeric mixture ([%])</th>
<th>Percentage ( \beta ) anomer in crude mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0% Trifluoroacetic acid</td>
<td>90-95</td>
<td>7</td>
<td>2</td>
<td>84</td>
<td>21</td>
</tr>
<tr>
<td>1.5% Trifluoroacetic acid</td>
<td>90-95</td>
<td>9</td>
<td>4</td>
<td>80</td>
<td>29</td>
</tr>
<tr>
<td>2.0% Trifluoroacetic acid</td>
<td>90-95</td>
<td>7</td>
<td>2</td>
<td>77</td>
<td>30</td>
</tr>
<tr>
<td>1.5% Boron trifluoride etherate (redistilled)</td>
<td>90-95</td>
<td>3</td>
<td>4</td>
<td>56</td>
<td>5</td>
</tr>
</tbody>
</table>

The usual method, with benzyl alcohol and 2\% hydrochloric acid, gave only 10-12\% benzyl 2-acetamido-2-deoxy-\( \beta \)-D-glucopyranoside.

Table I lists results of studies with several acid catalysts. Conditions which favored the formation of the \( \beta \)-anomer, were met using hydrochloric acid, trifluoroacetic acid and para-toluene-sulfonic acid. Boron trifluoride and perchloric acid favored \( \alpha \)-anomer predominance. It is possible that the two latter catalysts changed the solubilities of \( \alpha \)- and \( \beta \)-glycosides or brought about degradations of the more sensitive \( \beta \)-glycoside. The total yields found in those cases are quite low. The results with trifluoroacetic acid are of special interest. It will be noted, that in every case the crude anomeric mixture contained from 67 to 68\% of the \( \beta \)-anomer of benzyl 2-benzyloxy carbonylamino-2-deoxy-D-glucopyranoside. The finding of an increased proportion of \( \beta \)-anomer can be explained by considering phase equilibria. During the process of crystallization, a mixture of a solid \( \alpha \)-benzyl and \( \beta \)-benzyl glycosides may exist together with a solution that is saturated with respect to this mixture.

$$a_{\text{solid}} = a_{\text{solution}} \Rightarrow \beta_{\text{solution}} \Rightarrow \beta_{\text{solid}}$$

The Gibbs phase rule states for the degrees of freedom of a chemical system in equilibrium:

$$F = C - P + 2.$$
Because of the equilibrium $a = \beta$, only one component is necessary to describe the system. It is therefore $C = 1$, and $P = 3$ (liquid, solid $a$, and solid $\beta$). $F = 1 - 3 - 2 = 0$, leaves no degree of freedom, i.e. this system with 3 phases can only be in equilibrium at an invariance point at a certain temperature and pressure. At all other temperatures, one solid phase has to vanish. The one solid phase left, must not necessarily be a pure anomer; it may be a solid solution of both anomers. It was indeed observed before, and in this work that the anomers co-crystallized readily if one anomer was in large excess. In the intermediate composition range gelatinous, amorphous precipitates were formed.

The process of selectively crystallizing an equilibrium mixture in favor of the least soluble compound which may be the minor component in solution, was already recognized by Dimroth18.

The findings related here also may provide an explanation for some results of Yoshimura et al., who found increased proportions of $\beta$-anomer under certain conditions, when N-acetyl-D-glucosamine was reacted with alcohols in the presence of Lewis acids.

**Experimental**

**Benzyl 2-benzoyloxyxycarbonylamino-2-deoxy-$\beta$-glucopyranosides**

A mixture of 2-benzoyloxyxycarbonylamino-2-deoxy-2-deoxy-D-glucopyranose (5 g), anhydrous distilled benzyl alcohol (60 ml), and acid catalyst (Table I), was stirred at elevated temperature 1 hour beyond the point of clear solution (“Reaction time,” Table I), in a flask equipped with condenser and calcium chloride drying tube. Diethyl ether was obtained pure by crystallization from ethanol. From the filtrate, diethyl ether was distilled, and the mixture kept 36 hours at 40 °C. The product (16 g) was filtered off. By TLC, it was found to be almost pure $\beta$-glycoside, with a trace each of starting material and $\alpha$-anomer. It could be obtained pure by crystallization from ethanol. From the residual liquid, isopropyl ether (1000 ml) precipitated at -5 °C an anomeric mixture ($a : \beta = 3 : 2$; 14 g) which could be separated after acetylation8.

1 From the dissertation of W. D. Rhoads, University of the Pacific Stockton, California. We reserve the patent rights for this method. Supported by grant GP-4587 of the National Science Foundation.

2 C. E. Ballou, S. Roseman, and K. P. Link, J. Amer. chem. Soc. 75, 1140 [1953].


7 R. Kuhn, F. Zilliken, and A. Gauhe, Chem. Ber. 86, 466 [1953].


