TMSCl as a Mild and Effective Source of Acidic Catalysis in Fischer Glycosidation and Use of Propargyl Glycoside for Anomeric Protection

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Practical Fischer glycosidation was effected at room temperature or 60°C by using 5 to 10 equiv. of TMSCl. The anomeric propargyl group formed by this method was found to be a versatile new protecting group, being stable in neat TFA but readily cleaved by treatment with Co₂(CO)₈ and TFA in CH₂Cl₂ via the formation of an alkyne–Co complex.

Key words: Fischer glycosidation; protective group; TMSCl; acid catalyst

Chlorotrimethylsilane (TMSCl) has been used as an acid catalyst for esterification and ketal formation.¹,² In these reactions, TMSCl first reacts with alcohols or carboxylic acids to form HCl which is probably the ultimate catalyst for these reaction systems. TMSCl can also trap water and thus effectively promote dehydration reactions when more than a stoichiometric amount of TMSCl is used.

Fischer glycosidation has been used for the anomeric protection of monosaccharides. Since the reaction is carried out in the presence of an acid catalyst in alcohols under reflux, certain amounts of by-products are generally formed. In the present study, we found that TMSCl effectively promoted Fischer glycosidation under milder reaction conditions.

Glycosidation proceeded at room temperature by using 10 equiv. of TMSCl and alcohols as solvents (Table 1, entries 1–8). At the early stage of the reaction, β-anomers were preferentially formed. Three days were required for sufficient anomerization from β-anomers to α-anomers, although most of the starting materials were glycosidated after 1 d. α-Glycosides were obtained with high selectivity after being converted to the 4,6-benzylidene derivative with subsequent crystallization. Since the anomerization rate of the allyl glycoside of N-acetylglucosamine was slow, a mixture of α- and β-anomers was obtained even after the reaction had proceeded for 3 d (Table 1, entry 4). The glycosidation reaction proceeded more rapidly at 60°C; in this case, 5 equiv. of TMSCl was sufficient for the reaction (Table 1, entries 9–14). With the present glycosidation reaction, a large excess of alcohols as solvents was required; the reaction didn't proceed in THF, dioxane, or toluene (TMSCl, 10 equiv.; alcohol, 3 equiv.).

We have recently reported a propargyloxycarbonyl group for protecting amino and hydroxy functions.³ This new protecting group is stable against neat TFA.

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Abbreviations: Alloc, allyloxycarbonyl; Troc, 2,2,2-trichloroethoxycarbonyl

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Note

Table 1. Fischer Glycosidation with TMSCl

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>ROH Temp.</th>
<th>Time</th>
<th>Product (%)</th>
<th>Yield (%: α:β)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>HCl</td>
<td>r.t.</td>
<td>3 d</td>
<td>2a 64 (1:0)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>HCl</td>
<td>r.t.</td>
<td>3 d</td>
<td>2b 70 (1:0)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>HCl</td>
<td>r.t.</td>
<td>3 d</td>
<td>2c 66 (1:0)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>HCl</td>
<td>r.t.</td>
<td>3 d</td>
<td>2d 66 (1:1)</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>HOAc</td>
<td>r.t.</td>
<td>3 d</td>
<td>3a 70 (0:1)</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>HOAc</td>
<td>r.t.</td>
<td>3 d</td>
<td>3b 66 (1:0)</td>
</tr>
<tr>
<td>7</td>
<td>1c</td>
<td>HOAc</td>
<td>r.t.</td>
<td>3 d</td>
<td>3c 70 (0:1)</td>
</tr>
<tr>
<td>8</td>
<td>1d</td>
<td>HOAc</td>
<td>r.t.</td>
<td>3 d</td>
<td>3d 64 (0:1)</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>MeOH</td>
<td>60°C</td>
<td>5 h</td>
<td>2b 70 (1:0)</td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>MeOH</td>
<td>60°C</td>
<td>5 h</td>
<td>2c 66 (1:0)</td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>MeOH</td>
<td>60°C</td>
<td>5 h</td>
<td>2d 66 (1:0)</td>
</tr>
<tr>
<td>12</td>
<td>1d</td>
<td>MeOH</td>
<td>60°C</td>
<td>5 h</td>
<td>2e 66 (1:0)</td>
</tr>
<tr>
<td>13</td>
<td>1a</td>
<td>MeOH</td>
<td>60°C</td>
<td>5 h</td>
<td>4a 61 (1:0)</td>
</tr>
<tr>
<td>14</td>
<td>1a</td>
<td>MeOH</td>
<td>60°C</td>
<td>5 h</td>
<td>5a 61 (1:0)</td>
</tr>
</tbody>
</table>

³ The ratio was determined by NMR.
but is readily cleaved at ambient temperature by treatment with Co$_2$(CO)$_6$ and TFA in CH$_2$Cl$_2$ via formation of the corresponding alkyne–Co complex. We, therefore, expected propargyl glycosides to similarly serve as a good protecting group for anomeric hydroxy functions. Propargyl glycosides have been prepared from glycosyl acetate with propargyl alcohol in the presence of BF$_3$·Et$_2$O, since Fischer glycosidation with propargyl alcohol under conventional conditions affords complex mixtures owing to polymerization of the propargyl group. We found that propargyl glycosides could be obtained in good yields under the present mild conditions by using 10 equiv. of TMSCl in CH$_2$Cl$_2$.5) Both the benzylidene and alkyne–Co complex, and cleaving the complex with TFA in CH$_2$Cl$_2$. Both the benzylidene and propargyl groups were cleaved by a treatment with Co$_2$(CO)$_6$ and TFA.

Propargyl glycosides are stable under various reaction conditions, e.g., treatment with neat TFA, alkaline hydrolysis, and benzylation with BnBr and NaH. However, the 1-O-propargyl group could be readily removed by treating with Co$_2$(CO)$_6$, purifying the alkyne–Co complex, and cleaving the complex with TFA and H$_2$O in CH$_2$Cl$_2$.5) Both the benzylidene and propargyl groups were cleaved by a treatment with 50% TFA in CH$_2$Cl$_2$ (Table 2).

As described, TMSCl works as both an acid catalyst and dehydrating agent in the presence of an alcohol. Although excess TMSCl was required for commercial conditions, the reaction mixture gave a solid which was successively washed with water and Et$_2$O-hexane (1:1) to give pure product 2a in a yield of 1.97 g (64%).

Experimental

NMR spectra were taken with a Jeol Lambda-600 NMR spectrometer (600 MHz for protons). Unless otherwise stated, the chemical shift in CDCl$_3$ is given in δ values from tetramethylsilane (0 ppm) as an internal standard. Elemental analyses were performed by the staff of our department. Anhydrous solvents were purchased from Kanto Chemicals Co., all other commercially obtained materials being used as received.

The typical procedure for Fischer glycosidation at room temperature used 10 equiv. of TMSCl. To a suspension of glucose 1a (1.80 g, 10 mmol) in allyl alcohol (29.1 ml, 500 mmol) was added chlorotrimethylsilane (12.6 ml, 100 mmol). The mixture was stirred at room temperature for 3 d and then concentrated under reduced pressure. Toluene was added to the residue, and the solution evaporated. To a solution of the residue in CH$_2$CN (25 ml) were added benzaldehyde dimethylacetal (2.25 ml, 15 mmol) and p-toluenesulfonic acid (0.19 g, 1 mmol). The mixture was stirred at room temperature for 5 h. The addition of a saturated aqueous NaHCO$_3$ solution (50 ml) to the reaction mixture gave a solid which was successively washed with water and Et$_2$O-hexane (1:1) to give pure product 2a in a yield of 1.97 g (64%).

### Table 2. Cleavage of the 1-O-Propargyl Group with Co$_2$(CO)$_6$ and TFA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>TFA (%)</th>
<th>H$_2$O (%)</th>
<th>Time</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
</table>
| 1     | 3a       | 50      | 5          | 1 h  | 1a      | quant.
| 2     | 3b       | 50      | 5          | 1 h  | 1b      | quant.
| 3     | 3c       | 50      | 5          | 1 h  | 1c      | quant.
| 4     | 3d       | 50      | 5          | 1 h  | 1d      | quant.

### Notes

δ wv in CDCl$_3$
5.2 Hz, H-3), 4.34 (1H, t, J = 10.1 Hz, H-6a), 4.79–4.82 (2H, m, CCl₃C=CH₂), 4.93 (1H, d, J = 3.4 Hz, H-1), 5.56 (1H, s, PhCHO₂). Anal. Found: C, 47.54; H, 4.08; N, 2.95%. Calcd. for C₁₆H₁₈O₇N: C, 47.47; H, 4.19; N, 2.91%.

3c: ²H-NMR (CDCl₃) δ: 2.42 (1H, t, J = 3.0 Hz, OCH₂–CCH), 3.52 (t, 1H, J = 10.9 Hz, H-3), 3.68–3.78 (3H, m, H-4, H-5 and H-6), 3.81–3.84 (2H, m, OCH₂–CH₂), 4.28 (1H, dd, J = 8.3 Hz, H-2), 5.06–5.25 (2H, m, OCH₂–CH₂ = CH₃), 5.55 (1H, s, PhCHO₂), 5.86–5.92 (1H, m, OCH₂–CH₂ = CH₃), 7.34–7.50 (5H, m, PhCHO₂). Anal. Found: C, 59.45; H, 5.89; N, 3.48%. Calcd. for C₂₀H₂₃O₇NCl: C, 59.84; H, 6.11; N, 3.49%.

3d: ²H-NMR (CDCl₃) δ: 2.06 (3H, s, AcNH), 2.91 (1H, t, J = 3.0 Hz, OCH₂–CCH), 3.48–3.63 (2H, m, H-4 and H-6b), 3.73–3.95 (3H, m, H-2, H-3 and H-5), 4.17–4.39 (4H, m, OCH₂–CCH, H-4 and H-6a), 4.89 (1/6H, d, J = 8.3 Hz, H-1b), 5.03 (5/6H, d, J = 4.0 Hz, H-1a), 5.56 (1H, s, PhCHO₂), 7.35–7.50 (5H, m, PhCHO₂). Anal. Found: C, 60.54; H, 6.09; N, 3.87%. Calcd. for C₁₈H₂₀O₇N·1/2H₂O: C, 60.67; H, 6.22; N, 3.93%.

4a: ²H-NMR (CDCl₃) δ: 2.66 (1H, s, 3-OH), 3.30 (3H, s, OCH₃), 3.55–3.62 (3H, m, H-2, H-4 and H-6b), 3.86–3.88 (1H, m, H-6a), 4.23 (1H, dd, J = 9.1, 5.2 Hz, H-3), 4.34 (1H, t, J = 9.1 Hz, H-5), 4.75 (1H, d, J = 3.6 Hz, H-1), 5.54 (1H, s, PhCHO₂), 7.35–7.48 (5H, m, PhCHO₂).

5a: ²H-NMR (CDCl₃) δ: 2.67 (1H, s, 3-OH), 3.59–3.60 (2H, m, H-2 and H-4), 3.62 (1H, d, J = 5.2 Hz, H-6b), 3.86–4.10 (2H, m, H-3 and H-5), 4.26 (1H, dd, J = 10.4, 5.2 Hz, H-6a), 4.46 (2H, d, J = 8.9 Hz, PhCH₂), 5.01 (1H, d, J = 4.0 Hz, H-1), 5.56 (1H, s, PhCHO₂), 7.26–7.50 (10H, m, PhCH₂ and PhCHO₂).

The typical procedure for Fischer glycosidation at 60°C used 5 equiv. of TMSCl. To a suspension of glucose 1a (1.80 g, 10 mmol) in allyl alcohol (29.1 ml, 500 mmol) was added chlorotrimethylsilane (6.3 ml, 50 mmol). The mixture was stirred at 60°C for 5 h, concentrated under reduced pressure, and the residual volatile material was coevaporated with toluene. The residue was dissolved in CH₂CN (25 ml). To the resulting mixture were added benzaldehyde dimethylacetal (2.25 ml, 15 mmol) and p-toluenesulfonylic acid (0.19 g, 1 mmol). The mixture was stirred at room temperature for 5 h. The solution was neutralized with a saturated aqueous NaHCO₃ solution (50 ml) to give a solid which was successively washed with water and Et₂O-hexane (1:1) to give pure product 2a in a yield of 2.16 g (70%).

Acknowledgments

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References & Notes

2) Chan, T. H., Brook, M. A., and Chaly, T., A simple procedure for the acetalization of carbonyl compounds. Synthesis, 203–205 (1983). Esterification was basically effected by using 2.2 equiv. of TMSCl and an alcohol as the solvent at room temperature or under reflux in THF. We found that the esterification of N-fluorenlymethoxycarbonyl (Fmoc) amino acids also proceeded smoothly in CH₂Cl₂ at room temperature by using 2 equiv. of an alcohol and 5 equiv. of TMSCl against a carboxylic acid to give the desired ester quantitatively.
5) A typical cleavage reaction of a propargyl glycoside with CO₂ and HCl involved adding to a solution of 1-propargyl glycoside 3a (30.6 mg, 0.10 mmol) in
CH₂Cl₂ (4 ml), TFA (0.5 ml), water (0.5 ml) and Co₂(CO)₈ (34.1 mg, 0.10 mmol). The mixture was stirred at r.t. for 5 h and then an aqueous saturated NaHCO₃ solution was added. The mixture was extracted with AcOEt, and the organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was washed with ether to give 1a in a yield of 18.1 mg (quant.).