TiCl₄/Et₃SiH-Mediated Regioselective Reductive Opening of Benzylidene Acetals

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ABSTRACT

The reductive ring opening of benzylidene acetals of 1,2- and 1,3-diol in the presence of titanium tetrachloride/triethyl silane has been described. All the substrates studied are unsymmetrical and found that the opening occurs from sp²-carbon side over sp³-carbon.

Keywords: Benzylidene acetal; Titanium tetrachloride; Triethylsilane.

1. INTRODUCTION

Benzylidene acetal is a commonly used protecting group for the immediate protection of 1,2 and 1,3-diol derivatives.¹ In particular, it plays a major role in carbohydrate chemistry.² The advantage of this group is either it can be deprotected to get back the diol or it can be reductively opened to get the monobenzyl ether having one free-hydroxyl group. The later approach results the selective protection of one hydroxyl group of the diol functionality, which is very significant for organic synthesis.³ Previously, various reductive ring opening reactions of 1,3-benzylidene acetal have been studied in which a secondary benzyl ether having free primary hydroxyl group, is the usually obtained product.⁴ In addition, the reductive opening of 1,2-benzylidene acetal was also explored, which may give the mixture of products.⁵ However, the opening of benzylidene acetal of unsymmetrical 1,2-diols is less explored.⁶ During one of our ongoing projects, we required to have an a method for the regioselective opening of benzylidene acetal of a unsymmetrical 1,2-diol. Towards this, we found titanium tetrachloride/triethylsilane as an efficient reagent system and the results of our study are described in this paper (Table 1).

2. RESULTS AND DISCUSSION

Firstly, benzylidene acetal of the 1,2-diol 1a, derived from cinnamyl alcohol using a literature procedure⁷ was subjected to reductive opening using TiCl₄ and Et₃SiH in dichloromethane at -78 °C for 20 min., which provided (1S,2S)-2-(benzoyloxy)-3-(tert-butyldimethylsilyloxy)-1-phenylpropan-1-ol (2a) in 92% yield without any traces of the other isomer (entry 1). This example clearly demonstrates the regioselectivity of benzylidene acetal opening is from sp2-carbon side over sp3-carbon to give the the product 2a having free benzylic hydroxy group. After this success, the reductive opening of another unsymmetrical 1,2-benzylidene acetal 1b⁸ containing one side an alkyl group and the other side α,β-unsaturated ester under TiCl₄/Et₃SiH reaction conditions. To our delight this reaction is also provided exclusively single isomer 2b in 96% yield, in which the reductive opening occurred from α,β-unsaturated ester (sp2-carbon) side (entry 2). Similarly, the 1,2-benzylidene acetal 1c⁹ having TBDPS-protecting group was also gave the reductive opening product 2c in 94% yield as a single isomer (entry 3). It is noteworthy to mention that the TBDPS protecting group is stable under the present reaction conditions. Finally, we have tested the reductive opening of a 1,3-benzylidene acetal 1d¹⁰, derived from tri-O-acetyl-D-glucal, using TiCl₄/Et₃SiH reagent system. In this case, the reductive opening was observed from primary alcohol side to give the product 2d in 95% yield (entry 4), which demonstrates that steric factor played a role over electronic factor (sp²/sp³ carbon).

The plausible mechanism of acetal opening

The reaction pathway may be explained through the mechanism shown in Figure 1. In first step, the reversible formation of a linear silane-titanium adduct A which undergoes following nucleophilic attack by the acetal of the substrate to yield an O-silylated cationic intermediate B along with a titanium hydride anion. The titanium hydride ion then transfers a hydride to the carbon center of the O-
silylated cation to yield the reduction product C and regenerated free titanium. The compound gives the required product D upon acid hydrolysis.

\[
\begin{align*}
\text{Et}_3\text{SiH} \ + \ TiCl_4 & \rightarrow [\text{Et}_3\text{SiH} \ + \ TiCl_4]_2 \\
\text{Et}_3\text{Si} & \rightarrow Et_3\text{SiH} \ + \ TiCl_4 \\
\text{Chemical Reaction Diagram}
\end{align*}
\]

**Fig. 1: Proposed Mechanism**

**Table 1: Reductive Opening of Benzylidene acetal**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (a)</th>
<th>Time (min)</th>
<th>Product (b)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(\text{O}+\text{O}^-\text{Et})TBS 1a</td>
<td>20</td>
<td>Ph(\text{O}+\text{O}^-\text{Et})TBS 1b</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Ph(\text{O}+\text{O}^-\text{Et}) labelled 2a</td>
<td>25</td>
<td>Ho(\text{O}+\text{O}^-\text{Et}) 2b</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>TBDPSO(\text{O}+\text{O}^-\text{Et}) 3a</td>
<td>15</td>
<td>TBDPSO(\text{O}+\text{O}^-\text{Et}) 3b</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>Ph(\text{O}+\text{O}^-\text{Et}) 4a</td>
<td>20</td>
<td>Ph(\text{O}+\text{O}^-\text{Et}) 4b</td>
<td>96</td>
</tr>
</tbody>
</table>

*(All the reactions were carried out using 4 equiv. of Et\(_3\)SiH and 1.5 equiv of TiCl\(_4\) in CH\(_2\)Cl\(_2\))

**3. Experimental section**

**General procedure** To a solution of acetal (Entry 3, 0.96 mmol) and Et\(_3\)SiH (0.61 ml, 3.84 mmol) in CH\(_2\)Cl\(_2\) (10 ml) was added TiCl\(_4\) (1M solution in CH\(_2\)Cl\(_2\); 1.4 ml, 1.4 mmol) at -78 °C and the resulting yellow solution was stirred at this temperature for 20 min. The mixture was diluted with 50 ml of EtOAC and added 10 ml of H\(_2\)O. The organic layer was extracted and aqous layer was washed with 10 ml of ethyl acetate. The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. The crude product was purified by silicagel column chromatography to afford the compound.

**Spectral data for the new compounds**

tert-Butyl(((4S,5S)-2,5-diphenyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (1a)

Data on diastereoisomeric mixture [α]\(_D\) = +20.2 (c 2.0, CHCl\(_3\)); IR (KBr): \(\nu_{max}\) 2929, 2858, 1459, 1405, 1360, 1254, 1217, 1140, 1092, 1025, 1001, 835, 775, 754 cm\(^{-1}\); \(^1\)H
Data on diastereoisomeric mixture [α]D = -5.0 (c 1.0, CHCl3); IR (KBr): νmax 2932, 2928, 2859, 1717, 1658, 1457, 1306, 1270, 1174, 1093, 1043, 983, 871, 983, 739, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.75-7.45 (2H, stack), 7.44-7.34 (3H, stack), 6.96, 6.93 (d, J = 5.9 Hz, 1H), 6.22-6.12 (1H, stack), 6.02, 5.94 (s, 1H), 4.39-4.30 (1H, stack), 4.27-4.17 (2H, stack), 3.93-3.84 (1H, stack), 3.82-3.71 (1H, stack), 1.82-1.21 (1H, stack), 0.96-0.84 (3H, stack); ¹³C NMR (CDCl₃, 75 MHz): δ 165.9, 165.9, 143.9, 143.2, 129.4, 129.2, 128.3, 126.6, 126.4, 122.9, 122.4, 103.7, 103.4, 82.5, 81.4, 81.0, 80.2, 60.6, 32.3, 31.9, 31.6, 25.6, 25.5, 22.4, 14.1, 13.9; HRMS (ESI): (m/z) calcd for C₁₃H₂₀O₂N₃ 341.1723 [M+H⁺]; found, 341.1723.
6.10 (dd, J = 15.4, 1.5 Hz, 1H), 4.54 (AB q, J = 11.5 Hz, 2H), 4.25-4.12 (m, 3H), 3.35 (q, J = 5.6 Hz, 1H), 2.56 (s, 1H), 0.89 (t, J = 6.9 Hz, 3H) ; 13C NMR (CDCl₃, 75 MHz): δ 165.7, 142.5, 137.9, 128.3, 127.9, 127.7, 122.4, 79.2, 72.8, 72.7, 60.5, 31.6, 30.4, 25.1, 22.4, 14.1, 13.9; HRMS (ESI): (m/z) calcd for C₁₉H₂₈O₄Na 343.1879 [M+H]+; found, 343.1876.

4. CONCLUSION
In conclusion, we have demonstrated the regioselective opening of benzylidene acetal of unsymmetrical 1,2-diol using TiCl₄/Et₃SiH reagent system to obtain the exclusively single product. This study disclosed that the reductive opening occurs from sp²-carbon side over sp³-carbon.

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REFERENCES