PREPARATION AND REACTION OF NOVEL OXYGEN ESTER ENOLATES, 2, REACTION OF GLYCOLATE WITH ALDEHYDES USING DIALKYLBORLY TRIFLATE

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The introduction of an oxygen atom substituent into the α-position of oxygen ester made it possible to generate corresponding boron enolates by the use of dialkylboryl trifluoromethanesulfonate. These novel boron enolates of oxygen ester proceeded aldol reaction with various aldehydes in high yield and with excellent syn diastereoselectivity to provide glyceric acid derivatives.

KEYWORDS aldol reaction; boron enolate; α-substituent; glycolate; oxygen ester; dialkylboryl trifluoromethanesulfonate; electron-withdrawing effect; syn diastereoselectivity; acidity

We have already reported the novel preparation of boron enolates directly from the corresponding oxygen esters of thioglycolate derivatives (1, X=S) by the use of dialkylboryl trifluoromethanesulfonate (triflate),\(^1\) The electron-withdrawing effect of the sulfur substituent made possible the boron enolate formation without the conversion to thiol esters (2).\(^2\) Extending that research, we describe here the preparation of boron enolate from the oxygen esters of glycolic acid derivatives (1, X=O) and their stereoselective aldol condensations.

\[ \begin{align*}
X &= S, O \\
\text{Figure} \\
\end{align*} \]

As a representative instance, methyl phenylxycetate (3) was expected to be readily transformed into corresponding boron enolates using dialkylboryl triflate, because the phenyloxy group increases acidity of the adjacent carbon acid about 4 to 5 pK\(_a\) units, so the effect of the phenyloxy group of 3 is comparable to the effect of the divalent sulfur substituent.\(^3\) To verify our assumption, butyraldehyde (4) was added to the pentane solution of dibutylborly triflate, diisopropylethylamine and 3 at -78°C. After the usual work up, the syn aldol product (5) was obtained in 98% yield and with more than a 95% diastereomeric excess.\(^4\) Consequently, it was confirmed that an α-oxygen substituted oxygen ester could be converted to the corresponding boron enolate by dialkylboryl triflate.

\[ \begin{align*}
\text{Chart 1} \\
\end{align*} \]

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Although the phenyloxy group of 3 was selected as a proper substituent for enolization, we examined protected hydroxyl groups for the general application of this reaction. Indeed, a similar reaction successfully proceeded in the case of alkyl benzylxoyacetate (6). According to the aforementioned procedure, 6 was treated with dibutylboryl triflate in the presence of diisopropylethylamine in pentane or ethyl ether at -78°C, and then aldehyde was added. After the usual work-up, the aldol product was obtained in good yield and without any side reaction. The yield and diastereoselectivity of the aldol reaction with several aldehydes are summarized in the table. All syn and anti authentic samples were prepared by the LDA-mediated aldol reaction and a following chromatographic separation. The relative stereochemistry was determined by the procedure previously reported.

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²CHO</th>
<th>Reagent</th>
<th>Yield</th>
<th>syn : anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>PhCHO</td>
<td>Bu₂BOTf</td>
<td>82%</td>
<td>96 : 4</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>PhCHO</td>
<td>Bu₂BOTf</td>
<td>84%</td>
<td>93 : 7</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>CH₃CHO</td>
<td>Bu₂BOTf</td>
<td>84%</td>
<td>97 : 3</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>CH₃CHO</td>
<td>Bu₂BOTf</td>
<td>86%</td>
<td>96 : 4</td>
</tr>
<tr>
<td>5</td>
<td>Buᵗ</td>
<td>PhCHO</td>
<td>Bu₂BOTf</td>
<td>76%</td>
<td>99 : (1d)</td>
</tr>
<tr>
<td>6</td>
<td>Buᵗ</td>
<td>PhCHO</td>
<td>Bu₂BOTf</td>
<td>71%</td>
<td>99 : (1d)</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>PhCHO</td>
<td>Pen₆₂BOTf</td>
<td>77%</td>
<td>99 : (1d)</td>
</tr>
<tr>
<td>8</td>
<td>Buᵗ</td>
<td>PhCHO</td>
<td>Pen₆₂BOTf</td>
<td>74%</td>
<td>99 : (1d)</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>PhCHO</td>
<td>Pen₆₂BOTf</td>
<td>73%</td>
<td>99 : (1d)</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>PhCHO</td>
<td>Bu₂BOTf</td>
<td>80%</td>
<td>86 : 14</td>
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<tr>
<td>11</td>
<td>Me</td>
<td>PhCHO</td>
<td>LDA</td>
<td>83%</td>
<td>37 : 63</td>
</tr>
<tr>
<td>12</td>
<td>Me</td>
<td>PhCHO</td>
<td>LDA</td>
<td>78%</td>
<td>34 : 66</td>
</tr>
</tbody>
</table>

a) Dialkylboryl triflate was used with diisopropylethylamine.
b) The isolated yield is described, and all products gave satisfactory NMR, IR and MS data.
c) The ratio was determined by 270MHz ¹H NMR spectra.
d) In case of entry 5-9, we could not detect the benzylic signal of anti isomer in NMR spectra of the reaction mixture.

As shown in the table, the aldol reaction of the boron enolate proceeded syn-stereoselectively in good yield. The alkyl substituents of the boron triflate and the carboxyl protective group of the substrate had a rather small effect on the yield and the stereochimistry of the product, so various carboxyl protective groups and boron triflate were usable in the present reaction. Especially when the carboxyl protective group was bulky tert-butyl ester and/or dicyclopentlylboryl triflate, there were no anti products (entries 5,6,7,8 and 9). The reaction of the boron enolate sharply contrasted with that of the corresponding lithium enolate (generated with LDA at -78°C), which reacted virtually non-stereoselectively with the aldehydes (entries 11 and 12). Although, we had investigated several bases, the present reaction was critically dependent on the choice of tertiary amine. Only when diisopropylethylamine, which is fairly basic, was used, did the reaction proceed. Other bases, 2,6-lutidine, triethylamine or 1-ethylpiperidine, failed to promote the reaction at all and almost all of the starting material was recovered.
With easy removal of the benzyl protective group, this reaction afforded glyceric acid derivatives directly. Furthermore, LAH reduction of (7) and the following catalytic hydrogenation afforded glycerol derivatives (8). It was clear that this synthetic method was useful for the synthesis of some hydroxyl groups containing glycerols, glycidyl acids, sugars and their derivatives.

In conclusion, the aldol condensations described herein have the following many definite advantages. The oxygen esters can be directly converted to the corresponding boron enolate without conversion to other carboxylic acid derivatives such as thiol esters. The reactions proceed in good yield with excellent stereoselectivity, and various carboxyl protective groups can be used. The mild reaction conditions (almost neutral and low temperature) is appropriate to apply to the condensation containing LDA-sensitive groups such as ester groups. So this aldol reaction is well suited for the synthesis complex natural products.

REFERENCES AND NOTES
2) In general, dialkyloboryl triflate cannot derive oxygen esters into corresponding boron enolates7) probably because of insufficient acidity of their α-proton.
LAH reduction of aldol product followed by treatment with 2,2-dimethoxypropane and p-toluenesulfonic acid gave the corresponding 1,3-dioxanes. The 270 MHz NMR spectra showing coupling constants between H4 and H5 of the 1,3-dioxane indicated the relative stereochemistry of the aldol products.

Several PAF analogs were reported.

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