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Dehydroxymethylation: an unusual reverse reaction of nucleophilic addition to formaldehyde

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Received 17 June 2006; revised 2 September 2006; accepted 5 September 2006
Available online 25 September 2006

Abstract—An unusual dehydroxymethylation has been observed in an acyclic primary alcoholic system. The relief of steric congestion is considered as the primary driving force in this reaction.

The nucleophilic additions of carbon nucleophiles to aldehydes or ketones are highly favourable processes. Nucleophilic addition of carbon anion to a carbonyl group is normally exothermic. This is attributed to the high reactivity of carbon anion. Moreover, thermodynamically stable products are generated in this reaction. As a result, the reverse process, b-cleavage of alkoxy anion, is rare. The b-cleavage of alkoxy anion becomes a facile process mainly in a ring-fused system, in which the hydroxyl group is positioned at a bridgehead. The driving force for this process is obviously the relief of the fused-ring strain. This type of b-cleavage has been successfully utilized in the synthesis of medium- to large-sized rings.1 In this letter, we report an unusual alkoxy anion b-cleavage in a non-cyclic system.

In connection with our study on stereoselective [2,3] α rearrangement of sulfur ylides generated from metal carbene and allyl sulfides, a series of tertiary sulfides 1a–j was prepared.2

Oxidation of the sulfides 1a with mCPBA gave sulfone 2a. When sulfone 2a was treated with sodium hydride, a new product was isolated. Inspection of the spectral data suggested that the structure of this product was 3a, in which the hydroxymethyl group was lost (Scheme 1). The structure of 3a was further confirmed by X-ray crystallography analysis, as shown in Figure 1.

This dehydroxymethylation was found to be general for sulfones 2b–j. As shown in Table 1, the oxidation of 1b–j with mCPBA gave sulfones 2b–j in high yields, subsequent treatment of 2b–j with sodium hydride in THF afforded dehydroxymethylation products in moderate to good yields. The substituent on the Ar group was found to have no influence on the reaction. As shown by entries 2 and 7, both the electron-withdrawing NO2 group and electron-donating OMe group gave dehydroxymethylation products in similar yields.

The extrusion of hydroxymethyl group from 2a is surprising.4 A mechanism is proposed for this process. Upon treatment with sodium hydride, the alkoxide anion A is first generated and then followed by the b-cleavage of C–C bond to afford 3a after protonation. The carbon

Keywords: Dehydroxymethylation; Retro-aldol reaction; Primary alcohol; Formaldehyde.

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doi:10.1016/j.tetlet.2006.09.017

Table 1

<table>
<thead>
<tr>
<th>Sulfone</th>
<th>Ar</th>
<th>Ar′</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>4-BrC6H4</td>
<td>2-ClC6H4</td>
</tr>
<tr>
<td>1b</td>
<td>3,4-Cl2C6H3</td>
<td>2-ClC6H4</td>
</tr>
<tr>
<td>1c</td>
<td>4-NO2C6H4</td>
<td>2-ClC6H4</td>
</tr>
<tr>
<td>1d</td>
<td>3-MeC6H4</td>
<td>2-ClC6H4</td>
</tr>
<tr>
<td>1e</td>
<td>C6H5</td>
<td>C6H5</td>
</tr>
<tr>
<td>1f</td>
<td>3-ClC6H4</td>
<td>C6H5</td>
</tr>
<tr>
<td>1g</td>
<td>4-ClC6H4</td>
<td>C6H5</td>
</tr>
<tr>
<td>1h</td>
<td>3-ClC6H4</td>
<td>C6H5</td>
</tr>
</tbody>
</table>
| 1i     | Ar = \[
\begin{array}{c}
\text{O} \\
\text{Ar'} \\
\text{Ar'} \\
\end{array}
\] | Ar′ = C6H5 |
| 1j     | C6H5 | C6H5 |

Scheme 1

Figure 1
anion B is stabilized by the strong electron-withdrawing sulfonyl group and the aromatic substituent, as shown by its resonance structure of C (Scheme 2).

To confirm the extrusion of formaldehyde, the reaction of 2j with NaH was carried out, and then the reaction mixture was treated with benzylamine (Scheme 3). The reaction gave 3j, together with 4, which was derived from the reaction of formaldehyde with benzylamine. The isolation of 4 is a conclusive evidence to support the extrusion of formaldehyde.

In order to gain insights into the effects of the structure on this reaction, alcohols 1a and 5–11 were subjected to identical conditions with NaH in THF (Scheme 4). First, no reaction occurred for 1a under the same conditions. Compound 5, in which the aryl group on the carbon is replaced with methyl, was found to give an aromatic substitution product 11. No dehydroxymethylation product was identified. If the chloro substituent on the sulfonyl aromatic ring is removed, no dehydroxymethylation occurred under the same conditions, as shown by 6. Interestingly, compound 7, in which the methyl group has been replaced by hydrogen, gave a diene derivative 12 in 71% yield. On the other hand, when phenylsulfonyl substrate 8 was subjected to NaH/THF, the dehydroxymethylation product 13 was isolated in 81% yield. However, when the substituent on sulfur is changed to o-chlorobenzyl group, no dehydroxylation product could be observed, as shown by the example of 10.
Finally, with alcohol 2a as the substrate we tried to trap the intermediate anion by the addition of methyl iodide or allyl bromide. However, only dehydroxymethylation product 3a could be isolated. The expected product 14 or 15 was not observed (Scheme 5).

These experiments demonstrate the remarkable influence of the structure on this unusual dehydroxymethylation reaction. The results suggest that the reaction is very sensitive to steric congestion around the reaction site, as demonstrated by the reactions of 8 and 9. The relief of steric congestion seems to be a major driving force for the dehydroxymethylation. On the other hand, electronic effect is also critical for the reaction. A strong electron withdrawing group is required to stabilize the carbon anion. The aromatic substituent is also important in stabilizing the anion, as shown by the reactions of 5 and 6.

In conclusion, we have observed an unusual dehydroxymethylation reaction. This unusual reaction suggests that the steric congestion and electronic effect may work together to reverse the equilibrium of carbon anion addition to carbonyl group, although the latter is usually a highly favourable process.

Acknowledgements

This project was generously supported by the Natural Science Foundation of China (Grant No. 20572002, 20521202, 20225205, 20390050) and the Ministry of Education of China (Cheung Kong Scholars Program).

References and notes


3. General procedure for oxidation and subsequent reaction with NaH. Sulfides 1 (0.5 mmol) and mCPBA (1.5 mmol) were mixed in CH$_2$Cl$_2$ at room temperature. After about 0.5 h, 1 disappeared as judged by TLC. Then saturated NaHSO$_3$ was added and the mixture was extracted with CH$_2$Cl$_2$, the organic layers were washed by saturated NaHCO$_3$ and dried over Na$_2$SO$_4$. Removal of the solvent in vacuo gave 2. Under a nitrogen atmosphere, 2 and NaH (0.6 mmol) were mixed in THF at room temperature. When 2 disappeared as judged by TLC, saturated NH$_4$Cl was added. After removal of THF in vacuo the mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and evaporated, and the residue was purified by silica gel column, eluted with petroleum ether/acetone (30:1) to afford 3.

4. Transition metal-catalyzed dehydroxymethylation of acyclic alcohol has been known, see: (a) Ishige, M.; Sakai, K.;