Communication to the Editor

Oxidative Rearrangement of Cyclobutanone Derived \(N,O\)-Ketals Leading to Pyrrolidone Derivatives

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A halogen-induced oxidative rearrangement of \(N,O\)-ketals prepared from cyclobutanones, leading to pyrrolidone derivatives, is developed. The reaction proceeds via an iminium ether intermediate and, depending on the reaction medium, two types of pyrrolidone derivative, containing a halogen atom or hydroxyl group, can be obtained.

Key words rearrangement; halogen; oxidation; \(N,O\)-ketal; pyrrolidone

1,2-Carbon migration reactions to a nitrogen atom are an important class of transformations in organic synthesis; for example, the Schmidt reaction, 1,2) Beckmann rearrangement 3,4) and Hofmann rearrangement 5) are traditionally used to obtain a wide range of heterocyclic compounds. In these reactions, azide, hydroxylamine derivatives and haloamides are typically used as electrophilic nitrogen sources. However, \(N\)-haloamines have rarely been used as electrophilic nitrogen sources in 1,2-carbon migration reactions, although their use in intermolecular amination reactions has been actively studied. 6–15) There are only a few reports on the rearrangement of \(N\)-chloroamines.16–19) In these transformations, the use of silver salts is generally necessary for activation of the \(N\)-X bond to promote the rearrangement, and this could be one reason for the limited use of \(N\)-haloamines. We recently reported that \(N\)-haloamines generated from \(N,N\)-ketal underwent rearrangement without the use of silver salts. As a result of the assistance of another nitrogen atom in the \(N,N\)-kets, ring expansion occurred spontaneously to give bicyclic amidines such as synthetically useful 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) type bicyclic amidines and biologically important 3,4-dihydroquinazolines, 20,21) (Chart 1(1)). Based on these results, we assumed that other haloamines with electron-donating groups at their \(\alpha\)-positions could be used for similar rearrangements. In this paper, we report the oxidative rearrangement of cyclobutanone-derived \(N,O\)-ketals, which provide pyrrolidone derivatives via iminium ether intermediates (Chart 1(2)). The reaction represents an alternative to Schmidt reaction using hydroxyalkyl azides. 22–28)

Studies of halogen-induced oxidative rearrangements of \(N,O\)-ketals were performed using 1a as a test substrate. Compound 1a was readily prepared by the condensation of cyclobutanone with a commercially available amino alcohol, 2-amino-3-phenylpropan-1-ol. When 1a was treated with \(N\)-bromosuccinimide (NBS) in \(CH_2Cl_2\), i.e., the same conditions as for the \(N,N\)-kets rearrangement, the ring-expanding rearrangement proceeded as expected, to give pyrrolidone derivative 2a, suggesting that an oxygen atom in the \(N,O\)-ketals efficiently enhances the 1,2-migration reaction with \(N\)-haloamines (Chart 2(1)). We found that bromine atoms were introduced into product 2a. The rearrangement also proceeded in MeOH, Chart 2. Reaction with 1a

![Chart 1. Oxidative Rearrangement of \(N,N\)- and \(N,O\)-Ketal](chart-1)

(1) Our previous work

(2) This work

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but it was found that different types of product were produced by the rearrangement, e.g., the pyrrolidone 3a containing a hydroxyl group was produced (Chart 2(2)). It was noted that the corresponding methyl ether 3a’ was not formed.

The plausible reaction pathways to the two types of products are shown in Chart 3. In this transformation, the common iminium ether intermediate ii is initially generated through bromination of nitrogen in the N,O-ketal with NBS, and subsequent rearrangement assisted by oxygen atom. In the case of the reaction in CH2Cl2, nucleophilic attack by the bromine, which was generated during the elimination step in the rearrangement (i to ii), at the C4 position of the oxazoline ring in intermediate ii affords the brominated product 2a.29) In contrast, in the case of the reaction in MeOH, addition of MeOH to intermediate ii occurs in preference to addition of the bromine. The iminium ether intermediate ii has ambident electrophilicity, and the C2 and C4 positions of the oxazoline ring can react with nucleophiles.22–28,30–33) Methyl ether 3a’ is not produced, and therefore nucleophilic attack by MeOH on intermediate ii selectively occurs at the C2 position rather than the C4 position of the oxazoline ring, to give a possible intermediate iii, which affords alcohol 3a on aqueous work-up.

The generality of the oxidative rearrangement of N,O-ketals was investigated (Table 1). In addition to the case of NBS (entry 1), N-chlorosuccinimide (NCS) also promoted the oxidative rearrangement to give a chloride-induced product 2b in comparable yield (70%, entry 2). The reaction with bulky amine 1b also proceeded with NBS in good yield (73%, entry 3). The substrate 1c, which has an easily oxidizable benzylic amine structure, gave pyrrolidone derivative 2d, without undesirable imine formation (entry 4). Alcohol formation was next briefly investigated. The reaction of 1a under the conditions in Chart 2 (NBS, in MeOH) gave 3a in 46% yield, but we found that addition of a small amount of H2O effectively improved the yield. The reaction performed in the presence of 2.0 eq. of H2O gave 3a in 64% yield (entry 5). Under these conditions, the tricyclic amide 3b was also produced from substrate 1d (entry 6).

The bromine-induced pyrrolidone derivatives obtained in this transformation are useful for preparing various other pyrrolidone derivatives.34–36) To demonstrate the usefulness of the reaction, several transformations of 2a were performed (Chart

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**Table 1. Generality of Rearrangement of N,O-Ketals**

<table>
<thead>
<tr>
<th>Entry</th>
<th>N,O-Acetal</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a (X=Br) 75%</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2b (X=Cl) 70%</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>2c 73%</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>2d 61%</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>3a 64%</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>3b 49%</td>
</tr>
</tbody>
</table>

*a) Conditions for 2: Unless otherwise noted, the reaction was carried out with 1 (1.0 eq.) and NBS (1.1 eq.) in CH2Cl2 (0.1 M) at 0°C–rt; conditions for 3: the reaction was carried out with 1 (1.0 eq.), NBS (1.1 eq.), and H2O (2.0 eq.) in MeOH (0.1 M) at 0°C–rt. b) NCS was used instead of NBS.*

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**Chart 3. Plausible Reaction Pathway**
29) It was suggested that in intermediate ii C4 atom has the largest coefficient at the highest reactivity LUMO based on quantum chemical calculations (details see, supplemental material).