Base Induced Chemical Conversion of 3-Carbamoyl-2-isoxazolines

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Abstract: 3-Carbamoyl-2-isoxazolines, prepared by cycloaddition of functionalized nitrile oxide, serve as masked 3-unsubstituted isoxazolines to afford 2-isoxazoline-3-carboxylic acid, β-cyanoalcohol, α,β-unsaturated nitrile, and α,β-unsaturated amide upon heating in the alkaline solution. The present reaction is also applicable to synthesis of 3,4-difunctionalized isoxazoles and β-hydroxy-γ-lactone.

Key words: ring opening reaction, isoxazoline, nitrile oxide, cyanoalcohol, hydroxylactone

1 INTRODUCTION

2-Isoxazolin-5-one derivatives 1 readily undergo the ring opening reaction synchronized with deprotonation at the 3-position leading to multiply functionalized compounds1,2). In cases of benzoisoxazoles 2, the similar reactions are often observed, which is applied to development of antibody catalyst3,4). On the other hand, the similar type ring opening reaction of monocyclic isoxazolines leading to cyanoalcohols 5-10) is not common in organic syntheses except for a few examples (Scheme 1)11-14). This different reactivity is due to the stability of the leaving group.

Meanwhile, the cycloaddition of nitrile oxide with dipolarophiles is a powerful method for construction of versatile five membered azaheterocyclic compounds35). However, 3-unsubstituted isoxazolines 3 are not generally prepared by this procedure31-14) since the corresponding unsubstituted nitrile oxide 5 (H-C≡N–O) is not easily treatable because of instability, toxicity, and forming explosive salts36). If unsubstituted isoxazolines 3 are readily available by cycloaddition of nitrile oxide, synthetic utility of the ring opening reaction of 3 will be also improved because modification of the 4- and the 5-positions of 3 are easily performed by changing dipolarophiles.

We previously demonstrated nitrile oxide having a carbamoyl group 6 is generated by only stirring nitroisoxazolone 7 in water at room temperature without any base or special reagent35). The cycloaddition of nitrile oxide 6 with versatile alkenic or alkynic dipolarophiles effectively proceeds to afford corresponding 3-carbamoyl-2-isoxazolines 8 and isoxazoles in moderate to high yields (Scheme 2). Since cycloadducts 8 are regarded as the masked 3-unsubstituted isoxazolines 3 when the carbamoyl group is hydrolyzed followed by decarboxylation. In other words, nitrile oxide 6 serves as the synthetic equivalent of the unsubstituted nitrile oxide 5. From this viewpoint, we studied hydrolysis of cycloadducts 8.

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afford unsaturated nitrile 10a (eluted with hexane/AcOEt = 90/10, 5 mg, 0.035 mmol, 7% yield), cyanoalcohol 4a (eluted with hexane/ AcOEt = 50/50, 41 mg, 0.28 mmol, 56% yield), and isoxazoline 8a (eluted with hexane/ AcOEt = 20/80, 35 mg, 0.17 mmol, 34% recovery).

3 RESULTS AND DISCUSSION

While 5-phenyl-2-isoxazoline 8a (R1 = Ph, R2 = H) was quite stable under acidic conditions even at 100°C, the carbamoyl group was hydrolyzed under basic conditions to afford isoxazoline-3-carboxylic acid 9a, β-cyanoalcohol 4a and α,β-unsaturated nitrile 10a (Table 1, run 1). When the reaction was conducted at lower temperature, the total mass balance was considerably diminished (run 2), which might be due to the hydration of 8a leading to water-soluble product such as 11a (Scheme 3). Cyanoalcohol 4a was mainly obtained in the reaction at 100°C (run 3), however prolonged reaction time or the use of larger amount of sodium hydroxide caused hydration of the nitrile function giving unsaturated amide 12a (runs 4 and 5). Potassium hydroxide was found to be suitable base for the present

### Table 1 Base induced conversion of isoxazoline 8a.

<table>
<thead>
<tr>
<th>run</th>
<th>Base (equiv.)</th>
<th>Temp. /°C</th>
<th>Time /h</th>
<th>Yield % 9a</th>
<th>Yield % 4a</th>
<th>Yield % 10a</th>
<th>Yield % 12a</th>
<th>Recovery of 8a %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH(1)</td>
<td>80</td>
<td>3</td>
<td>38</td>
<td>26</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>NaOH(1)</td>
<td>60</td>
<td>3</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>NaOH(1)</td>
<td>100</td>
<td>3</td>
<td>0</td>
<td>49</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>NaOH(1)</td>
<td>100</td>
<td>6</td>
<td>0</td>
<td>41</td>
<td>24</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>NaOH(2)</td>
<td>100</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>13</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>LiOH(1)</td>
<td>100</td>
<td>3</td>
<td>0</td>
<td>49</td>
<td>10</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>KOH(1)</td>
<td>100</td>
<td>3</td>
<td>0</td>
<td>56</td>
<td>7</td>
<td>0</td>
<td>34</td>
</tr>
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</table>
reaction with regard to both the yield of cyanoalcohol 4a and the mass balance (runs 6 and 7). The optimized conditions for 8a (Table 1, run 7) were applied to other isoxazolines 8b-e (Table 2). It was possible to modify the α-position of β-cyanoalcohols 4b-e having a propyl, an ethoxyethyl, an (acetylamino)methyl groups and an acetal function, respectively.

When isoxazoline 8f derived from dimethyl maleate was subjected to this reaction, only hydrolysis of ester functions proceeded to give dicarboxylic acid 13f in 80% yield without any detectable of cyanoalcohol 4f. The reaction of monoester 8g (R1 = COOEt, R2 = H) also resulted in the hydrolysis of only ester group. In these reactions, the ester function was hydrolyzed prior to the carbamoyl group, and the resultant carboxylate anion is the electron-donating group which prevented the further hydrolysis of the carbamoyl group.

On the other hand, different reactivity was observed in the case of 5-ethoxyisoxazoline 8i (R1 = OEt, R2 = H); aromatization together with elimination of ethanol predominantly proceeded to give 3-carbamoylisoxazole 14h in 37% yield. This experimental fact prompted us to conduct the similar reaction by using bicyclic isoxazoline 8i derived from 2,3-dihydrofuran. As a result of the similar aromatization, 3,4-difunctionalized isoxazole 14i was formed in 23% yield, in which the fused tetrahydrofuran ring of 8i remained as a β-hydroxyethyl group at the 4-position4-14 (Scheme 5).

When 5-hydroxymethyl isoxazoline 8j was employed, isolated product showed different spectral pattern from those of cyanoalcohols 4. Namely, the presence of a carbonyl group was confirmed by both IR and 13C NMR spectra. On the basis of spectral data, the product was determined as β-hydroxy-γ-lactone 15j (53% yield). A plausible mechanism for is illustrated in Scheme 6. After cyanoalcohol 4j is similarly formed as a result of the ring opening reaction of intermediate 9j, the terminal hydroxy group intramolecularly attacks the cyano group to construct a tetrahydrofu-

### Table 2: Synthesis of other β-cyanoalcohols 4.

<table>
<thead>
<tr>
<th>run</th>
<th>R1</th>
<th>Yield/%</th>
<th>Recovery of 8/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pr</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>EtOCH2</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>AcNHCH2</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Me(Oxolanyl)C</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

* Oxolanyl: 1,3-dioxolan-2-yl

4 SUMMARY

As mentioned so far, 3-carbamoyl-2-isoxazolines 8 serve as the masked 3-unsubstituted isoxazolines 3, and are converted to polyfunctionalized compounds such as β-cyanoalcohols 4 although optimization of the reaction conditions are necessary for each isoxazolines 8. Since the cycloaddition of nitrile oxide 6 with versatile dipolarophiles is performed without any special reagents under mild conditions with only simple experimental manipulations, the synthetic utility of this method is concluded to be high.
References