UNUSUAL FORMATION OF OXAZOLES BY BASE- OR ACID-CATALYZED RING OPENING OF 2-ACYL-2H-AZIRINES

Kazuaki Isomura, Youichi Hirose, Hideo Shuvama, Sumiko Abe, Gen-ichiro Ayabe, and Hiroshi Taniguchi*

Department of Applied Chemistry, Faculty of Engineering, Kyushu University, Hakozaki, Higashiku, Fukuoka 812, Japan

Formation of 2-acyl-2H-azirines was confirmed in thermolyses of β-acylvinyl azides to establish the generality of azirine formation from vinyl azides. Unusual C-C bond fission of 3-unsubstituted 2-acyl-2H-azirine to give oxazole was found to be a base catalyzed reaction. On the other hand, 3-substituted analogues were found to undergo acid-catalyzed reaction to give oxazoles.

Maiorana reported that thermolysis of β-azidomethacrylophenone 1a gave 4-methyl-5-phenylisoxazole 4a besides 2-benzoylpropionitrile 3a, whereas Nesmeyanov and his co-workers reported that 4-methyl-5-phenyloxazole 5a was the main cyclic product which was formed via 2-benzoyl-2-methyl-2H-azirine 2a. These reports brought us two interesting questions. One is whether 2H-azirine does surely intervene in this reaction, since 2H-azirines have not yet been detected in decomposition of β-acylvinyl azides, although formation of 2H-azirine can be thought as the general reaction of vinyl azides. The other is how oxazole is formed. Thermal reaction of 2-acyl-2H-azirines was reported to give isoxazoles by C-N bond fission. However, some 2-
acyl-2H-azirines were postulated as the intermediates in thermal transposition reaction of isoxazoles into oxazoles,\textsuperscript{8,9} which must be formed by C-C bond fission of 2H-azirines. Recently, Schmid et al. confirmed that an 2-acyl-2H-azirine gave an oxazole on heating.\textsuperscript{10} In this paper, we wish to make clear whether 2-acyl-2H-azirines are formed from \( \beta \)-acylvinyln azides and how oxazoles are formed from these azirines.

The azide \( \sim 1a \) (mp 69-70°C)\textsuperscript{11} was thermolyzed by heating in toluene (0.020 M) under reflux for 8 hr. Separation of the resulting yellow oil by chromatography on silica gel gave \( \sim 3a \), \( \sim 4a \), and \( \sim 5a \), which were identified by comparison with authentic compounds. Examination of the nmr spectrum of the crude product showed that \( \sim 3a \), \( \sim 4a \), and \( \sim 5a \) were formed in 37, 23, and 40\% yields, respectively. Product distributions were remarkably influenced by the concentration of \( \sim 1a \) as shown in Table 1.

Table 1. Dependence of the product distributions on the concentration in thermolyses of \( \sim 1a \) in toluene under reflux for 8 hr.

<table>
<thead>
<tr>
<th>Conc. of ( \sim 1a ) (M)</th>
<th>( \sim 3a ) (%)</th>
<th>( \sim 4a ) (%)</th>
<th>( \sim 5a ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>29</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>0.10</td>
<td>31</td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>0.020</td>
<td>37</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>0.0040</td>
<td>42</td>
<td>42</td>
<td>16</td>
</tr>
</tbody>
</table>

When thermolysis of \( \sim 1a \) in chlorobenzene (0.30 M) at 95°C was monitored at interval of time by nmr spectroscopy, formation of a labile compound which changed into both \( \sim 4a \) and \( \sim 5a \) was detected as shown in Figure. This compound was easily assigned as 2-benzyol-2-methyl-2H-azirine \( \sim 2a \) by comparing its nmr signals at \( \delta \) 1.44 (3H, d J 1.5 Hz) and 9.75 (1H, q J 1.5 Hz) with those of 2-methyl-2-phenyl-2H-azirine \textsuperscript{12} [\( \delta \) 1.50 (3H, d J 1.5 Hz), 7.2-7.4 (5H, m), and

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9.80 (1H, q J 1.5 Hz)]. This result clearly shows that the primary products in thermolysis of \( \text{la} \) are \( \text{2a} \) and \( \text{3a} \), and that \( \text{2a} \) is unstable enough to change mainly into \( \text{4a} \) and \( \text{5a} \) under the present conditions, as shown in Scheme 1.

An interesting point is that the curve for the formation of \( \text{5a} \) in Figure could not be explained by assuming a consecutive two-step reaction from \( \text{la} \) via \( \text{2a} \), since the slope of the curve for the formation of \( \text{5a} \) is not largest at the time when \( \text{2a} \) becomes maximum in concentration.\(^{13}\) This situation indicates that \( \text{5a} \) is formed by catalysis of some product in the reaction mixture.

\[
\begin{align*}
\text{Ph-C} = \text{CHN}_3 \quad & \xrightarrow{\Delta} \quad \text{Ph-C} = \text{C-H} \\
\text{Me} \quad & \quad \text{Me} \\
\text{1a} \quad & \quad \text{2a} \\
\text{Ph-C} = \text{CH-CN} \quad & \xrightarrow{\Delta \text{base}} \quad \text{Ph} \quad \text{5a} \\
\text{Me} \quad & \quad \text{Me} \\
\text{3a} \quad & \quad \text{Ph} \\
\end{align*}
\]

Scheme 1.

In an attempt to obtain detailed insight into the oxazole formation, thermolysis of \( \text{la} \) in chlorobenzene at \( 95^\circ \text{C} \) was quenched at the maximum concentration of \( \text{2a} \) (110 min after heating) by cooling the reaction mixture to room
temperature. The nmr spectrum of this reaction mixture did not changed at 35.5°C appreciably even for 6 hr, but addition of 20 mole% of pyridine caused smooth disappearance of the signals of 2a with a half life of 40 min, and appearance of transient signals at δ 1.46 (3H, d J 6 Hz) and 4.60 (1H, q J 6 Hz). Addition of diazabicyclo[2.2.2]octane, which is more stronger base than pyridine, showed the stronger effect and the signals of 2a disappeared completely in 2 min. As the transient signals decreased the signals of 5a increased. The ir spectrum also showed transient bands at 1690 and 2160 cm⁻¹, which finally disappeared and the absorption band of 5a intensified. On the basis of these spectral properties, this transient compound was assigned as the β-ketoisonitrile 6a. Facile cyclization of β-ketoisonitrile into an oxazole was reported by Hagedorn et al. Therefore, oxazole formation from 2a would be written as shown in Scheme 2, in which base-catalyzed formation of 6a from 2a is the key step. Monitoring of thermolysis of 1a in the presence of D₂O (5 mole eq.) showed no H-D exchange of C₃-H of 2a, but 5a formed had D at its 2-position. This result may be accomodated with a concerted abstraction of C₃-H synchronous with C₂-C₃ bond fission, giving an anion which is assisted by the carbonyl group to stabilize the negative charge. Large s character (58.5%) of the exocyclic orbital of C₃, which is obtained by ¹³C-H coupling constant (242.5 Hz) by proton coupled ¹³C-nmr spectrum of 3-phenyl-2H-azirine, would also be the reason for easy hydrogen abstraction. Although an 3-unsubstituted 2-acyl-2H-azirine has been recently shown to form
an oxazole thermally,\textsuperscript{14} our results clearly show that base is necessary for this transformation.

On the basis of above consideration, the results shown in Table 1 can be explained as follows. The formation of \( 5a \) is dependent on the concentration of the solution, since this transformation is catalyzed by bases such as \( 4a \) and \( 5a \). On the other hand, the rate of isoxazole formation, which is considered as an unimolecular first-order thermal reaction of \( 2a \) is independent of the concentration. At high concentration, even a small amount of basis product is enough to catalyze the transformation of \( 2a \) into \( 5a \). But formation of \( 5a \) is suppressed at lower concentration resulting in the predominant formation of \( 4a \). Increased yield of \( 3a \) at lower concentration would imply that some amounts of \( 3a \) are also formed by thermal reaction of \( 2a \).

Detection of 2H-azirine \( 2a \) in thermolysis of \( 1a \) led us to examine thermolyses of other \( \beta \)-acylvinylnitrogen. Heating the benzene solution of \( \beta \)-azidocrotonophenone \( 1b \textsuperscript{17} \) under reflux for 2 hr followed by chromatography on silica gel afforded colorless crystalline compound of mp 40-41°C in 80% yield. This compound was identified as 2-benzoyl-3-methyl-2H-azirine \( 2b \) by comparison with the authentic sample prepared by the reported photochemical ring contraction of 3-methyl-5-phenylisoxazole.\textsuperscript{18} Thermal decomposition of a mixture of \( E \)- and \( Z \)-\( \beta \)-azidocinnamaldehyde \( 1c \textsuperscript{19} \) in benzene at 50°C followed by sublimation (35°C/0.05 mmHg) also gave 2-formyl-3-phenyl-2H-azirine \( 2c \), mp 45.5-47°C,\textsuperscript{20} in 57% yield.

These two azirines \( 2b \) and \( 2c \) were stable under the conditions of thermolyses, but on heating the chlorobenzene solutions of these azirines at
higher temperatures in sealed tubes, there were obtained isoxazoles with small amount of oxazoles. Thermal reaction of 2-acyl-2H-azirines, including 2b and 2c, under various conditions were performed and the results obtained by nmr

\[
\begin{align*}
\text{R} & - \text{C} - \text{C} - R' \\
\Delta & \rightarrow \\
\text{R} & - \text{N} - \text{C} - \text{R}'
\end{align*}
\]

\[
\begin{align*}
\text{4} & + \\
\text{5}
\end{align*}
\]

Table 2. Thermal reactions of 2b-e.

<table>
<thead>
<tr>
<th>Run</th>
<th>2H-Azirine</th>
<th>Compd Added.</th>
<th>Temp. (°C)</th>
<th>Time (hr)</th>
<th>Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>none</td>
<td>170</td>
<td>17</td>
<td>91 (4) 9 (5)</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>pyridine (10)</td>
<td>170</td>
<td>17</td>
<td>96 (4) 4 (5)</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>PhCO₂H (10)</td>
<td>170</td>
<td>17</td>
<td>55 (4) 45 (5)</td>
</tr>
<tr>
<td>4</td>
<td>2c</td>
<td>none</td>
<td>180</td>
<td>18</td>
<td>96 (4) 4 (5)</td>
</tr>
<tr>
<td>5</td>
<td>2c</td>
<td>PhCO₂H (10)</td>
<td>180</td>
<td>18</td>
<td>69 (3) 31 (4)</td>
</tr>
<tr>
<td>6</td>
<td>2c</td>
<td>BF₃·OEt₂ (10)</td>
<td>150</td>
<td>5</td>
<td>0 (4) 100 (5)</td>
</tr>
<tr>
<td>7</td>
<td>2c</td>
<td>none</td>
<td>120</td>
<td>80</td>
<td>94 (6) 6 (7)</td>
</tr>
<tr>
<td>8</td>
<td>2c</td>
<td>PhCO₂H (8)</td>
<td>120</td>
<td>80</td>
<td>69 (3) 31 (4)</td>
</tr>
<tr>
<td>9</td>
<td>2c</td>
<td>none</td>
<td>120</td>
<td>270ᵃ</td>
<td>79 (21)</td>
</tr>
<tr>
<td>10</td>
<td>2c</td>
<td>PhCO₂H (8)</td>
<td>120</td>
<td>140</td>
<td>15 (8) 85 (9)</td>
</tr>
<tr>
<td>11</td>
<td>2c</td>
<td>PhCO₂H (21)</td>
<td>120</td>
<td>38</td>
<td>8 (9) 92 (10)</td>
</tr>
<tr>
<td>12</td>
<td>2c</td>
<td>BF₃·OEt₂ (10)</td>
<td>120</td>
<td>2</td>
<td>0 (4) 100 (5)</td>
</tr>
<tr>
<td>13</td>
<td>2c</td>
<td>none</td>
<td>180</td>
<td>30</td>
<td>86 (14)</td>
</tr>
</tbody>
</table>

ᵃ) 73% conversion
and glc analyses are shown in Table 2. From the Table we see that addition of pyridine to the reaction of 2b gives almost no effect on the yield of 5b. This result is in marked contrast with that in thermal reaction of 2a. However this fact is quite reasonable, because 2b has no hydrogen at 3-position. On the contrary, it was found that the yield of 5b increased in the presence of benzoic acid. Addition of benzoic acid raised the yields of oxazoles in thermal reactions of other azirines also. Control experiments under the same conditions as in Table 2 confirmed no interconversion between isoxazoles and oxazoles, showing that the products were directly formed from azirines.

Table 3. Rate constants of thermal reaction of 2e and partial rate constants for the formation of 4e and 5e at 120°C.

<table>
<thead>
<tr>
<th>Benzoic Acid Added (mole %)</th>
<th>Rate Constant for Consumption of 2e (10^{-5} sec^{-1})</th>
<th>Partial Rate Constants (10^{-5} sec^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.16</td>
<td>0.13 0.03</td>
</tr>
<tr>
<td>8</td>
<td>1.03</td>
<td>0.16 0.86</td>
</tr>
<tr>
<td>21</td>
<td>2.95</td>
<td>0.24 2.71</td>
</tr>
</tbody>
</table>

The reactions of 2e both in the absence and the presence of benzoic acid were followed by nmr spectroscopy. The rate constants for the consumption of 2e and the partial rate constants for formation of 4e and 5e are shown in Table 3. The data in Table 3 show that formation of 4e is profoundly accelerated by the benzoic acid while formation of 4e is accelerated only a little. Oxazole formation was also attained by BF_3·OEt_2 in the reactions of 2c and 2e, and in these cases reactions were selective.

On the basis of these results, thermal reaction of 3-substituted-2-acyl-2H-azirines would be depicted as Scheme 3. Isoxazoles may be formed by the
usually observed C-N bond fission producing vinyl nitrene intermediates followed by recyclization. The oxazole formation would be explained by attack of the carbonyl oxygen to the imino carbon, which has partial positive charge owing to some contribution of the canonical form B. Dependence of the product distributions on temperatures (120 and 180°C) in the thermal reaction of 2e implies that the entropy of activation for the formation of 5e is lower than that for the formation of 4e by 12.7 eu, which is also consistent with Scheme 3, because degree of freedom of the transition state for the formation of 5e is much restricted. Acceleration of oxazole formation by acids would be ascribed to the positive charge caused by addition of acid to nitrogen. A good chemical analogy is provided by the transformation of 2-vinylcyclopropylidene into 3-cyclopentenylidene, which was considered as the π\(_2\) + σ\(_2\)\(_a\) electrocyclic reaction where the attractive interaction of the vacant p-orbital with the vinylic π-bond plays the important role.
In conclusion, we could make clear that 2H-azirines were also formed from 2-acylvinyl azides, which is very important to establish the generality of azirine formation from vinyl azides. Unusual C-C bond fission of 2-unsubstituted 2-acyl-2H-azirine forming oxazole, which competes with the usually observed C-N bond fission forming isoxazole, was revealed to be catalyzed by a base. On the other hand, the thermal reactions of 3-substituted ones giving oxazoles were found to be catalyzed by an acid.

ACKNOWLEDGEMENT We are grateful to the Asahi Glass Foundation for financial support to this work.

REFERENCES AND NOTES


11. Prepared by the same method reported in ref. 1. mp 70°C.
12. Prepared by photolysis of β-azido-α-methylstyrene with a 100W high pressure mercury lamp.
17. Prepared by the reaction of β-chlorocrotonophenone with NaN₃ in H₂O-MeOH at 0°C and purified by chromatography on silica gel.
19. The reaction of β-chlorocinnamaldehyde with NaN₃ in DMF at 0°C gave a mixture of 1c (70%), 2c, and small amount of 5-phenylisoxazole.
21. Azirines 2d (mp 31-33°C) and 2e (mp 77-78°C) were prepared by irradiation of the ether solutions of 4d and 4e with a 15W low pressure mercury lamp. Oxazoles and isoxazoles were identified by comparison with the authentic samples.

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