RUTHENIUM-CATALYZED ROM-RCM OF CYCLOPENTENE-YNE.
CONCISE SYNTHESIS OF A PYRROLIZIDINE DERIVATIVE†

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Abstract – ROM-RCM (Ring-Opening Metathesis and Ring-Closing Metathesis) of cyclopentene-yne having an ester moiety was demonstrated using first- and second-generation Grubbs’ catalysts. When the reaction of cycloalkene-yne was carried out in the presence of 5 mol % of a ruthenium carbene complex under ethylene atmosphere at room temperature, ROM-RCM proceeded smoothly to give a pyrrolidine derivative in good yield, which could be converted to a pyrrolizidine derivative.

It is known that pyrrolizidine alkaloids (PAs) are found in Asteraceae, Boraginaceae, Leguminosae and other plants, and are distributed worldwide. While attention must be paid to the toxicity of these plants, some PAs are used as useful medicine.1,2 Enyne metathesis is an attractive reaction, which proceeds between the double and triple bonds to afford a diene derivative.3 We have already reported intra- and inter- molecular enyne metatheses catalyzed by first- and second-generation ruthenium carbene complexes (1a, 1b).4 During the course of our work, we have recently developed ROM-RCM5 of cycloalkene-yne under ethylene atmosphere (Eq. 1).4d-g In this reaction, the double bonds of cycloalkene and ethylene were cleaved, and each alkylidene part was recombined with the alkyne moiety to afford a

† Dedicated to Professor Barry M. Trost on the occasion of his 65th birthday.
new cyclic compound having a triene moiety.\textsuperscript{4d}

We report herein a novel concise synthesis of pyrrolizidine derivative (5) from cyclopentene derivative (3) having alkyne moiety in the side chain using ROM-RCM of cycloalkene-yne developed by our group. Our plan is shown in Scheme 1.

![Scheme 1. Plan for the Synthesis of Pyrrolizidine Derivative](image)

For the synthesis of the substrate (3a), commercially available 2 was reacted with thionyl chloride in MeOH\textsuperscript{b} followed by treatment with NsCl and Et\textsubscript{3}N in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C to afford cyclopentene derivative (6) in 98% yield (Scheme 2). Introduction of an alkyne side chain to 6 was achieved by the Mitsunobu reaction\textsuperscript{7} with propargyl alcohol to afford substrate (3a) in 68% yield.

![Scheme 2. Synthesis of Substrate. Ns=\textit{o}-Nitrobenzenesulfonyl.](image)

When a CH\textsubscript{2}Cl\textsubscript{2} solution of 3a and 10 mol % of 1a\textsuperscript{b} was stirred under ethylene atmosphere at room temperature for 40 h, pyrrolidine derivative (4a) was obtained in 17% yield and the starting material (3a) was recovered in 55% yield (Scheme 3). Although the yield of pyrrolidine derivative (4a) was low, the result indicated that the desired ROM-RCM of cycloalkene-yne occurred to give 4a.
The possible reaction course for the formation of pyrrolidine derivative (4a) from cyclopentene derivative (3) is shown in Scheme 4.

Scheme 4. Possible Reaction Course for ROM-RCM

Table 1. ROM-RCM of Cyclopentene-yne (3a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>“Ru” Cat. (mol %)</th>
<th>Temp.</th>
<th>Time (h)</th>
<th>4a (%)</th>
<th>Rec. 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>10</td>
<td>rt</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>10</td>
<td>reflux</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>10</td>
<td>rt</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>10</td>
<td>reflux</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>5</td>
<td>rt</td>
<td>6</td>
<td>76</td>
</tr>
</tbody>
</table>

To improve the yield of 4a, the reaction was carried out under the various conditions. Although the reaction temperature was raised to reflux condition in CH₂Cl₂ using 1a as a catalyst, the result was unsatisfactory (Table 1, Entry 2). On the other hand, when the second-generation ruthenium carbene complex (1b)⁹ was used for this reaction, ROM-RCM proceeded smoothly to give 4a in 75% yield (Entry 3). It is generally accepted that catalyst (1b) is used under higher reaction temperature, however poor yield and incomplete conversion were shown in this reaction (Entry 4). Even upon lowering the use of 1b to 5 mol %, 4a was obtained in high yield (Entry 5).

Subsequently, we tried to synthesize pyrrolizidine derivative (7) from triene (4a) under several reaction conditions.¹⁰ Although the nosyl group of 4a could be removed by treatment with mercaptoethanol and
DBU in DMF, cyclization did not proceed at room temperature. Thus, the reaction mixture was warmed at 40 °C to give pyrrolizidine derivative (7) in 78% yield.\textsuperscript{11}

\[\text{MeO}_2\text{C}_2\text{H}_2\text{OH, DBU, DMF} \rightarrow \text{MeO}_2\text{C}_2\text{H}_2\text{OH, DBU, DMF}\]

\[\text{NOE} \rightarrow \text{7 (78%)}\]

\textbf{Scheme 5. Synthesis of Pyrrolizidine Derivative (7)}

In conclusion, we have developed a simple construction method for a pyrrolizidine skeleton via ROM-RCM of cyclopentene-yne catalyzed by the second-generation Grubbs’ ruthenium carbene complex (1b). Further studies of ROM-RCM of enyne are in progress in our laboratory.

\textbf{REFERENCES AND NOTES}


11. The stereochemistry of 7 was determined by NOE experiment. In this reaction, the double bond of the substituent was isomerized to conjugate with the carbonyl group. Presumably this is a thermodynamic product and the isomerization would occur in the presence of DBU. It is not clear whether the isomerization of the double bond and then ring construction occur or the ring construction and then the isomerization of the double bond occur.