Cyclization of N-Allyl-5-allyl-5-hydroxylactams to 8α-Hydroxy-1,5,8α-tetrahydro-2H-indolizin-3-ones Using Grubbs’ Catalyst

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A short and highly efficient synthetic method to prepare synthetically useful tetrahydroidolizinone derivatives from the ring-closing metathesis of N-allyl-5-allyl-5-hydroxylactams is described.

Key Words : Grubbs’ catalyst, Ring-closing metathesis (RCM), Tetrahydroidolizinone, N-Acyliminium ion

Introduction

Indolizidine alkaloids which contain 1-azabicycle[4.3.0]nonane skeleton play important role in medicinal chemistry. Diabetes, anti-cancer, anti-viral and anti-AIDS activities have also been reported for polyhydroxylated indolizidine alkaloids.1 Lentiginosine,1 swainsonine2 and castanospermin3 are naturally occurring indolizidine alkaloids which are known to inhibit enzymatic glycosidase hydrolysis.

Cyclization of N-Allyl-5-allyl-5-hydroxylactams (Scheme 2) could be potentially useful for the synthesis of more complex indolizidine derivatives. Although a number of examples of metathesis have been described,3–7 only one example was reported involving the participation of hetero-substituted hydroxylactams.8 It is reported that the presence of free polar groups close to the double bonds inhibits the RCM reaction with Grubbs’ catalyst in most cases.9 We employed bis-alkenyl substituted hydroxylactams 4 and showed that RCM underwent smoothly to afford unsaturated cyclic olefins 5 in moderate to good yields (Scheme 1).

Results and Discussion

For the synthesis of fused bicyclic systems 5, N-allyl cyclic imides 8 which were readily obtained from succinimide, phthalimide, maleic anhydride, and tartaric anhydride were used as starting materials. We previously reported that the zinc mediated Barbier type allylation of cyclic imides in the presence of a catalytic amount of PhBr went very efficiently.10 The resulting hydroxylactams were transformed into the corresponding fused bicyclic systems 5 in good yields using intramolecular ring-closing olefin metathesis. The unsaturated hydroxylactams could also serve as a potentially valuable synthetic intermediate for the synthesis of certain natural products containing an azabicycle system.11

The RCM reaction was performed using 3 mol% of Grubbs’ ruthenium catalyst 6 or 7 (Fig. 1). We used Grubbs’ 1st generation catalyst 6 for the RCM of 4c, 4d and 2nd generation catalyst 7 for 4a and 4b. After stirring in dichloromethane at 35 under Ar atmosphere for 4h, the cyclized products were isolated in high yields (Scheme 2).

The results are summarized in Table 1. When RCM of hydroxylactam 4a and of 4b were carried out in dichloromethane at 35 in the presence of 3 mol% Grubbs’ 1st generation catalyst 6, almost starting material 4a and 4b were recovered. The use of Grubbs’ 2nd generation catalyst 7 gave increased isolated yields of 5a and 5b in 55% and 45%, respectively. In case of 4b, higher dosage of catalyst 6 (10 mol%) gave 5b in 85% yield. The RCM of hydroxylactam 4c and 4d were carried out in dichloromethane at 35 in the

Figure 1. Grubbs’ catalysts used for RCM reactions.
presence of 3 mol% Grubbs 1st generation catalyst 6, the cyclized products 5c and 5d were isolated in almost quantitative yield.

The stereochemical assignment of 5c was carried out using nuclear Overhauser effect, as illustrated in Figure 2. Irradiation of the angular hydroxyl hydrogen led to a 7.3% increment in the H2 signal and no increment in the H1 signal. Accordingly, irradiation of the hydrogen at C2 led to a 4.6% increment in the hydroxyl hydrogen signal, indicating that 5c possesses S-configurations at 8 position.

In order to check the versatility of our tetrahydroindolizinone derivatives, intermolecular alkylations with different carbon nucleophiles were accomplished under mild conditions using Lewis acid. The reactions first tested were with allyltrimethylsilane, trimethylsilyl cyanide as carbon nucleophiles and BF3- OEt2 to generate the N-acyliminium ion. Thus, to a solution of 5 and a carbon nucleophile in dichloromethane was added BF3- OEt2 at -78 °C, stirred for 2 h, then the reaction mixture was allowed to warm to room temperature. The yields were relatively low because of dehydration to conjugated dienes. The results are summarized in Table 2.

As described here, we have developed a simple method for the cyclization of N-allyl-5-allyl-5-hydroxylactams, using RCM to construct tetrahydroindolizinone derivatives. This synthetic approach is short and highly efficient. Substitution of hydroxyl group in compounds 5b-d by carbon-based nucleophiles via N-acyliminium ion intermediate promoted by Lewis acid were also achieved in order to prove synthetic versatility. The methodology described herein has potential applicability in the synthesis of complex natural and non-natural indolizidine compounds because of the presence of the double bond, carbonyl group and hydroxyl group available for further functionalization.

Table 2. Addition of carbon nucleophiles to 5-hydroxytetrahydroindolizinones 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>hydroxylactams</th>
<th>Nucleophiles</th>
<th>Products 9</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5b</td>
<td>allyltributyltin</td>
<td>O(N)</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>trimethylsilyl cyanide</td>
<td>O(CN)</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>trimethylsilyl cyanide</td>
<td>O(N)</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>trimethylsilyl cyanide</td>
<td>O(CN)</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>5d</td>
<td>allyltributyltin</td>
<td>O(N)</td>
<td>72</td>
</tr>
</tbody>
</table>

Reaction condition: 1 eq. BF3- OEt2 in CH2Cl2, -78 °C, then slowly warmed up to rt, 1 day

![Figure 2. Nuclear Overhauser effect of 5c.](image-url)
Cyclization of N-allyl-5-allyl-5-hydroxylactams

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References


