Efficient Synthesis of Spirolactams by Ring-Closing Olefin Metathesis

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Spirobicyclic cores play an important role in the development of new bioactive substances. This type of spiro system exists as a key framework of numerous steroids. Construction of spirocyclics can be achieved by intramolecular alkylation, cycloaddition reaction, radical cyclization and ring-closing metathesis reaction. Various approaches for the preparation of spirocyclics encountered problems related with functional group incompatibility at one or more stages, and they have been restricted to a single substitution pattern. Only in a few instances, the newly generated ring system was left with useful functional groups for further transformations. Therefore, there has been a continuous need to develop new methods for the preparation of spiro-linkage with additional functionality for further synthetic manipulation under mild conditions.

In this paper, we intend to report an efficient and versatile synthetic method for the preparation of spirolactams which involves zinc-mediated alkylation of cyclic imides followed by ring-closing metathesis using Grubbs catalyst. We previously reported that gem-diallylated precursors 3a-b can be prepared efficiently from cyclic imides 1a-b. Babier-type zinc-mediated alkylation of cyclic imides 1a-b with allyl bromide in the presence of catalytic amount of PbBr2 gave hydroxylactams 2a-b. Subsequent alkylation of 2a-b with allyltributyltin in the presence of BF3·OEt2 afforded precursors 3a-b in good overall yield (Scheme 1).

Next, we utilized this reaction to transform it into the corresponding spirolactams in an excellent yield by intramolecular ring-closing olefin metathesis. The RCM reaction was performed using 3 mol % of Grubbs ruthenium catalyst [(Cy3P)2Cl2Ru=CH-Ph]. After stirring in dichloromethane at 35 °C under Ar atmosphere for 4hr, the cyclized products were isolated in high yield (Scheme 2).

The results are summarized in Table 1. Structures of the spirolactams were assigned on the basis of 1H NMR and 13C NMR spectra.

Table 1. Allylation of cyclic imides and ring-closing metathesis of diallyl lactams

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclic Imide</th>
<th>Hydroxyl Lactam</th>
<th>Diallyl Lactam</th>
<th>Spirolactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>O=C(O)C(O)</td>
<td>O=C(O)CH2(O)</td>
<td>O=C(O)CH2(O)</td>
<td>Spirolactam</td>
</tr>
<tr>
<td>b</td>
<td>O=C(O)C(O)</td>
<td>O=C(O)CH2(O)</td>
<td>O=C(O)CH2(O)</td>
<td>Spirolactam</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

88% 23% 98%
94.5% 98% 98%
NMR spectroscopic data.

In conclusion, we have demonstrated that diallyl lactams can be utilized in conjunction with ring-closing metathesis as an efficient method for construction of spirolactams. This RCM method as developed in this study offers very mild conditions for direct formation of spirolactams in an excellent yield. The methodology described herein may lead to interesting applications in synthesis of complex natural and non-natural products due to the presence of double bond and carbonyl group for further functionalization.

**Experimental Section**

5-Allyl-1-benzyl-5-hydroxy-2-pyrolidinone (2a). To a mixture of N-benzylsuccinimide (5 mmol), zinc granule (10 mmol) and catalytic amount of PbBr₂ in THF (10 mL) was added ally bromide (10 mmol) slowly at 0-5 °C, stirred for 5 hr until it became sticky greenish gray slurry. The reaction mixture was quenched with aq. NH₄Cl solution (30 mL), extracted with methylene chloride (2 × 50 mL). The methyl chloride solution was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give almost pure 2a (88%) which was crystallized out from ether/hexane to give as a white solid: mp 88 °C; 1H NMR (400 MHz, CDCl₃) δ 7.1-7.3 (m, 5H), 5.4-5.5 (m, 2H), 4.9-5.0 (m, 2H), 4.6 (d, 1H), 4.3 (d, 1H), 2.4 (m, 2H), 1.9-2.2 (m, 4H); 13C NMR (100 MHz, CDCl₃) δ 176.2, 138.8, 129.4, 129.2, 128.7, 127.7, 127.3, 70.5, 43.9, 43.7, 35.6, 30.4.

Similarly, the reaction of the diallyl lactam 3b afforded spirolactam 4b in 98% yield: 1H NMR (400 MHz, CDCl₃) δ 7.85-7.87 (d, 1H), 7.22-7.35 (m, 8H), 5.79 (s, 2H), 4.64 (s, 2H), 2.31-2.36 (dd, 4H); 13C NMR (100 MHz, CDCl₃) δ 168.2, 155.1, 138.9, 132.4, 131.0, 129.5, 128.6, 128.35, 27.5, 123.8, 121.1, 71.3, 44.1, 43.5.

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**References**