Ring-Closing Metathesis with Vicinal Dibromoalkenes as Protected Alkynes: A Synthetic Approach to Macrocyclic Enynes

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Supporting Information

ABSTRACT: A new strategy to access macrocyclic enynes was developed. To block undesired ene–yne cyclization pathways, alkynes were protected via bromination and the resultant acyclic vic-(E)-dibromoalkenes participated in selective ene–ene ring closing metathesis reactions. Zinc-promoted deprotection of (E)-dibromoalkynes provided macrocyclic enynes in high yields.

Cyclic enynes gained importance with interest in annulene chemistry in the 1960s, and their significance increased as novel biologically active natural products were discovered. Enyne rings constitute the core of potent antitumor antibiotics and cytotoxic alkaloids. Cyclic enynes were also used in natural product syntheses and transannular rearrangements. These discoveries stimulated studies on the construction of enyne rings. Traditional syntheses encompass functionalized acyclic enynes participating in intramolecular transformations. Other methods involved introduction of alkyn or alkene units via cycloelimination reactions and intermolecular processes involving double coupling or substitution.

Ring-closing metathesis (RCM) is one of the most powerful tools in organic synthesis, so ene–ene RCM of dienynes could be an efficient alternative for the preparation of macrocyclic enynes. However, a thermodynamically favored ene–yne RCM pathway is preferred in transformations with an ene–ene vs ene–yne reactivity competition. Few exceptions are observed for this chemoselectivity. Indeed, our attempts at RCM of diyne 1 led to low yields of enyne 2 (Scheme 1).

Scheme 1. Synthesis of Cyclic Enyne 2

Attempting to circumvent this reactivity (Co2(CO)8)−alkyne complexes were employed as protected alkynes in RCM. However, this often led to side reactions, high catalyst loadings, and poor yields. Most metathesis reactions require heat, and (Co2(CO)8)−dienyne complexes readily undergo thermal Pauson–Khand reactions. More importantly, these complexes can release π-acidic CO which reacts with the catalyst leading to metathesis-inactive complexes. In fact, we tested the synthesis of dicobalt complex 4 without success (Table 1). Cyclic enyne 4 was formed in yields even lower than the yield of metal-free enyne 2 from an RCM reaction of “unprotected” diene 1 (Scheme 1). The destructive effects of CO on catalysis were clear, and development of an alternative protection method was essential.

RCM reactivity is principally determined by olefin substitution patterns. Trisubstituted alkynes have low reactivity and tetrasubstituted alkynes have almost no metathesis reactivity, especially for initiation. We utilized this low reactivity as the basis for an alkyne protection strategy. We proposed that tetrasubstituted vic-dibromoalkenes with general structure would serve as protected alkynes and be inert in metathesis reactions while being deprotected via zinc-promoted elimination (Scheme 2). Since its discovery in the late 1800s, alkyne bromination has had limited use as a protection method.

Table 1. Synthesis of Cyclic Enyne Complex 4

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RCM of 8a was tested to synthesize the 10-membered-ring product 9a (Table 2). However, mixtures of polyether oligomers were formed instead of the target molecule possibly due to its high ring strain.

**Table 2. Optimization of the RCM Reaction**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>°C</th>
<th>h</th>
<th>catalyst (equiv)</th>
<th>yield, %</th>
<th>E/Z</th>
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</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>25</td>
<td>12</td>
<td>Grubbs I (0.20)</td>
<td>30</td>
<td>8:1</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>25</td>
<td>12</td>
<td>Grubbs II (0.05)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>12</td>
<td>Grubbs I (0.05)</td>
<td>69</td>
<td>2.5:1</td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>12</td>
<td>Grubbs III (0.05)</td>
<td>10</td>
<td>100:0</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>12</td>
<td>Grubbs II (0.05)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields are of isolated products. <sup>b</sup>E/Z ratios were determined by NMR spectroscopy. <sup>c</sup>CH<sub>2</sub>Cl<sub>2</sub> = 1,2-dichloroethane. <sup>d</sup>For entries 1, 2, and 4, 90%, 78%, and 68% of 8c were recovered, respectively. [8c] = 0.002 M. [9c] = 0.004 M.

To avoid oligomerization, we considered larger rings, so triene 8b was tested in RCM reactions (Table 2). At rt with the Grubbs I catalyst, the target ring was formed in a 30% yield (Table 2, entry 1), but with a high catalyst loading of 20%. A trial with the more reactive<sup>34b</sup> Grubbs II catalyst at rt failed to form 9b and instead gave a mixture of decomposition products (entry 2).

Since the alkyne protecting group is heat-tolerant, we tested the RCM of 9a (Table 2). However, mixtures of polyether oligomers were formed instead of the target molecule possibly due to its high ring strain.

**Table 3. Synthesis of Protected Cyclic Diene 9c**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent&lt;sup&gt;6&lt;/sup&gt;</th>
<th>°C</th>
<th>h</th>
<th>catalyst (equiv)</th>
<th>yield, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>12</td>
<td>Grubbs I (0.05)</td>
<td>2</td>
<td>100:0</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>DCE</td>
<td>85</td>
<td>36</td>
<td>Grubbs I (0.05)</td>
<td>9</td>
<td>1.7:1</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>12</td>
<td>Grubbs II (0.05)</td>
<td>50</td>
<td>1:5.3</td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>36</td>
<td>Grubbs III (0.10)</td>
<td>54</td>
<td>1.7:1</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>DCE</td>
<td>85</td>
<td>36</td>
<td>Grubbs II (0.10)</td>
<td>2</td>
<td>100:0</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>12</td>
<td>Grubbs II (0.10)</td>
<td>90</td>
<td>1:5.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields are of isolated products. <sup>b</sup>E/Z ratios were determined by NMR spectroscopy. <sup>c</sup>DCE = 1,2-dichloroethane. For entries 1, 2, and 5, 90%, 78%, and 68% of 8c were recovered, respectively. [8c] = 0.002 M. [9c] = 0.004 M.

Cyclic sulfonamide (9e). Tetrasubstituted vic-dibromoalkanes were excellent protecting groups, as each reaction proceeded smoothly providing only the terminal ene—ene RCM product. The RCM was not limited to formation of medium rings, as 19- and 16-membered 9g and 16-membered 9h were synthesized successfully in 65% and 87% yields, respectively (Figure 1).

The 1H NMR spectra of 9b–f and h exhibited unexpected diastereotopicity for protons α and β to the dibromoalkene units. This was attributed to rigidity imposed by the bromine atoms restricting rotations leading to favored conformations with the geminal protons and esters located in different environments. Larger and less strained 9g did not exhibit such behavior. The Z-isomer of 9c was interesting, as the 1H NMR displayed two sets of multiplets for the vinyl protons, suggesting it exists as a mixture of two planar chiral conformers and interconversion between the enantiomeric conformers is slow on the NMR time scale. To support these proposals, quantum-chemical simulations were performed. Calculated chemical shifts and coupling constants based on populations of conformers were in good agreement with the experimental spectra.

Stereoselective synthesis of large rings via metathesis is challenging, although stereoselective RCM catalysts for macrocyclization were recently reported. Traditional metathesis catalysts lack kinetic selectivity, as E/Z ratios are determined by...
the stabilities of the macrocycles based on ring size and/or substitution patterns. RCM of dibromotrienes 8 exhibited similar behavior. While formation of symmetric 16-membered 9h showed no stereoselectivity, 13-membered 9b and 19-membered 9g formed with a modest 2.5:1 E/Z ratio. There is a pronounced allylic halogen effect in macrocyclization RCM. Under identical conditions, 12-membered rings 9d and 9f formed as single isomers, but with opposite selectivity. Substrates with allyl ether linkages (8b, 8f, 8g) gave E macrocyclic isomers as the sole or major isomer (Figure 1).

Macrocyclic dienes 9b–h were then subjected to deprotection. Zn metal effectively promoted elimination reactions and cyclic enynes were formed in high yields (Figure 2).

Isomeric distributions were not affected by deprotection, as the E/Z ratios were maintained. Rings with allyl and homoallyl moieties (10b–g) are typically inaccessible by RCM of unprotected acyclic dienynes since ene–yne RCM is preferred. This method is superior to the Co2(CO)6 deactivation. Macrocycles very low yields while our approach provided protection method which su

The isomeric ratio of 10g was preserved in cycloisomerization to 11g, and NMR spectra confirmed that the 3,4-dihydropyran ring 11g was preferred over a tetrahydrofuran ring (11g').

In conclusion, a new strategy to access macrocyclic enynes was developed. Vicinal-dibromo tetrasubstituted alkenes were excellent protected alkenes, and (E)-dibromotrienes participated in selective ene–ene RCM reactions. The RCM reactions were general, tolerated high temperatures, and used low catalyst loadings. Diverse macrocyclic enynes in various ring sizes were prepared in high yields by Zn-promoted deprotection reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02595.

Experimental details and spectral data for isolated products (PDF)
NMR spectra (PDF)
Calculations (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES
