Synthesis of Cyano Cyclic Olefins through Ring-Closing Metathesis

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Ring-closing metathesis has become a very powerful, versatile, and widely used method for the construction of cyclic ring systems in organic synthesis.1 The superior reactivity of Grubbs second generation catalyst 1, which has air-stability and thermal stability, is very important for the formation of tri- and tetra-substituted olefins having electron withdrawing groups. Recently, Weinreb,2a Salim,2b and Rutjes2c reported on the formation of carbocyclic and heterocyclic olefin by ring-closing metathesis of halogen (F, Cl, CF₃ ) substituted olefins. Literature survey reveals that most of bisterminal olefins with electron withdrawing groups such as CO₂Et, Br, and CN resulted in little to no yield of the RCM product under the condition of using the Grubbs first generation catalyst,3 but the microwave irradiation on olefin with carboxymethyl substituent (CO₂Me) provided the desired product.4

As part of synthesis of a drug against Alzheimer disease, we became interested in the introduction of a nitrile group to huperzine B analog system. Monocyclic olefins with cyano group were prepared. Alkylations with 2-(bromoethyl)-acrylonitrile⁶ were carried out to obtain several allylated substrates 3a-e from the carbon and heteroatom nucleophiles 2a-e⁷-⁹ in DMF in the presence of NaH as base. The RCM reaction of the bisterminal olefins 3a-e with a cyanide group has been explored for a variety of substrates, and some of the results are shown in Table 1. The substrates 3a-e reacted smoothly and furnished the olefinic cyanides containing six to seven membered cycles in high yields (Entry1-5). With successful outcome for the preparation of monocyclic cyanoolefins, we applied this method to the synthesis of tricyclic system of huperzine B analog (Scheme 3).10 Subjection of olefinic intermediate 6 to the standard condition (5 mol % catalyst 1 and 3×10⁻³ M substrate in CH₂Cl₂) provided a poor yield (5%) of cyclized product 6a despite the complete consumption of starting material. Thus, the reaction was performed at elevated temperature of 100 °C under microwave irradiation with 5 mol % catalytic amount using the concentration of 0.05 M of the substrate in CH₂Cl₂. After 4 min of the irradiation, the RCM reaction provided an improved yield of 6a with no sign of other undesired reactions based on the recovered starting material.

In conclusion, we have revealed an example of the ring-
1. For recent metathesis reviews, see: (a) Grubbs, R. H.; Chang, S.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Vinyl nitrile</th>
<th>Reaction conditions</th>
<th>Cyclized product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-CN</td>
<td>60 °C, 1.5 h</td>
<td>3 × 10⁻³ M CH₂Cl₂</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>Ph-CN</td>
<td>60 °C, 1 h</td>
<td>3 × 10⁻³ M CH₂Cl₂</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Eto-CN</td>
<td>60 °C, 1.5 h</td>
<td>3 × 10⁻³ M CH₂Cl₂</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>Ph-CN</td>
<td>60 °C, 2 h</td>
<td>3 × 10⁻³ M CH₂Cl₂</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Eto-CN</td>
<td>60 °C, 2 h</td>
<td>3 × 10⁻³ M CH₂Cl₂</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>NH-OMe</td>
<td>100 °C, 300 W, 20 psi, 4 min.</td>
<td>CH₂Cl₂</td>
<td>30 (82)</td>
</tr>
</tbody>
</table>

* The yield in parentheses is the yield based on the recovered starting material.

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References

1. For recent metathesis reviews, see: (a) Grubbs, R. H.; Chang, S.


5. Procedure for ring closing metathesis of 6 to give 6a. A solution of the vinyl nitrile 6 (0.012 mmol) and catalyst 1 (5 mol %) in CH₂Cl₂ (2.5 mL) was microwave irradiated in a sealed tube for 4 min at 100 °C using an Personal Chemistry Optimizer and Creator. The solvent was removed in vacuo and the residue was purified by column chromatography (35% ethyl acetate in hexane) to provide product 6a. IR (νmax, neat) 2925, 2854, 2220, 1597, 1475, 1257 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.50 (brs, 1H), 4.05, 3.99 (ABq, J = 13.8 Hz, 2H), 3.89 (s, 3H), 3.77 (brs, 1H), 3.13 (dd, J = 17.2, 4.8 Hz, 1H), 2.64 (d, J = 17.2, 4.8 Hz, 1H), 2.06 (d, J = 16.8 Hz, 1H), 2.30 (d, J = 16.8 Hz, 1H), 1.56 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 164.2, 163.7, 151.5, 136.3, 135.0, 131.1, 124.2, 115.1, 110.4, 99.3, 69.8, 55.0, 54.1, 49.0, 41.0, 34.9, 23.4; HRMS (EI) Calcd for C₁₇H₁₇N₃O (M⁺) 279.1372, found 279.1372. 6


11. Typical procedure for RCM of vinyl nitrile: To a solution of the vinyl nitrile (0.102 mmol) in dry CH₂Cl₂ (34.0 mL) was added the Grubbs second generation catalyst (10 mol %). The reaction mixture was stirred for 1-2 h at 60 °C. The solvent was removed in vacuo and the residue was purified by column chromatography (20% ethyl acetate in hexane) to yield the product.