

## Synthesis of Cyano Cyclic Olefins through Ring-Closing Metathesis

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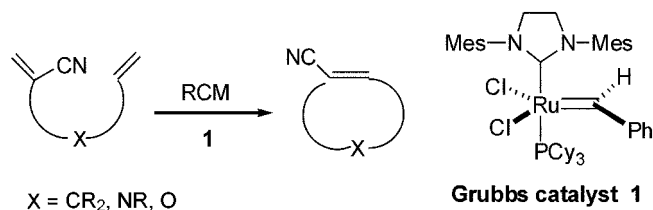
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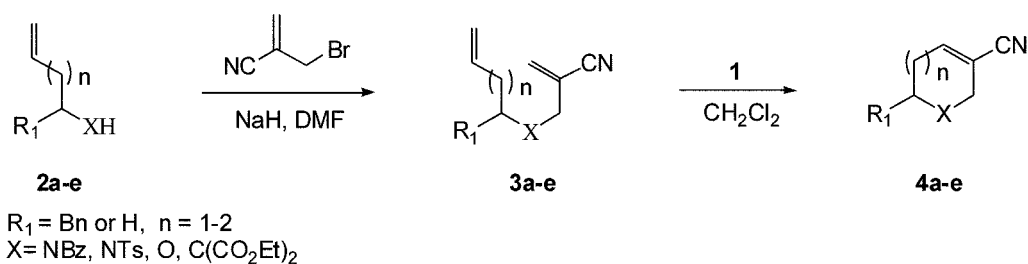
Ring-closing metathesis has become a very powerful, versatile, and widely used method for the construction of cyclic ring systems in organic synthesis.<sup>1</sup> The superior reactivity of Grubbs second generation catalyst **1**, which has air-stability and thermal stability, is very important for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



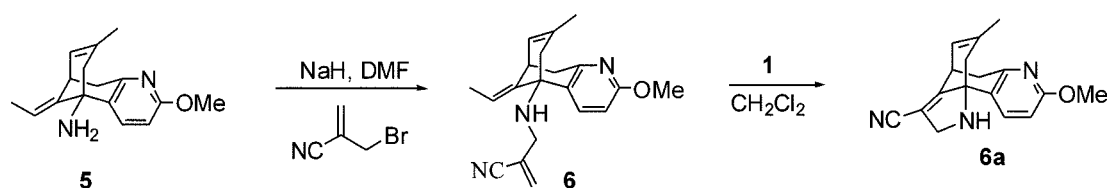
**Scheme 1.** Ring-Closing Metathesis (RCM) Reaction of Cyano Bisolefins.

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)acrylonitrile<sup>6</sup> were carried out to obtain several allylated substrates **3a-e** from the carbon and heteroatom nucleophiles **2a-e**<sup>7-9</sup> in DMF in the presence of NaH as base. The RCM reaction of the biterminal olefins **3a-e** with a cyano 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 (Entry 1-5). 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).<sup>10</sup> Subjection of olefinic intermediate **6** to the standard condition (5 mol % catalyst **1** and  $3 \times 10^{-3}$  M substrate in CH<sub>2</sub>Cl<sub>2</sub>) 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 CH<sub>2</sub>Cl<sub>2</sub>. 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-

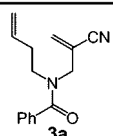
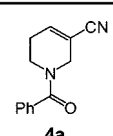
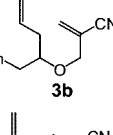
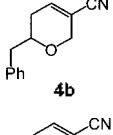
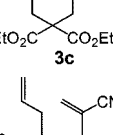
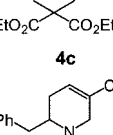
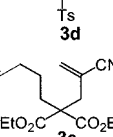
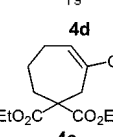
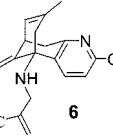
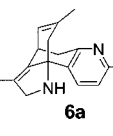
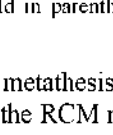
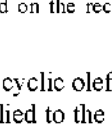


**Scheme 2.** RCM Reaction of Monocyclic Cyanoalkenes.



**Scheme 3.** RCM Reaction for A Cyano Derivative of Huperzine B.

**Table 1.** Ring-Closing Metathesis Reactions of Vinyl Nitrile<sup>1)</sup>

Entry	Vinyl nitrile	Reaction conditions	Cyclized product	Isolated yield (%)
1		60 °C, 1.5 h 3 × 10 <sup>-3</sup> M CH <sub>2</sub> Cl <sub>2</sub>		86
2		60 °C, 1 h 3 × 10 <sup>-3</sup> M CH <sub>2</sub> Cl <sub>2</sub>		81
3		60 °C, 1.5 h 3 × 10 <sup>-3</sup> M CH <sub>2</sub> Cl <sub>2</sub>		96
4		60 °C, 1.5 h 3 × 10 <sup>-3</sup> M CH <sub>2</sub> Cl <sub>2</sub>		93
5		60 °C, 2 h 3 × 10 <sup>-3</sup> M CH <sub>2</sub> Cl <sub>2</sub>		93
6		5 × 10 <sup>-2</sup> M CH <sub>2</sub> Cl <sub>2</sub> 100 °C, 300 W, 20 psi, 4 min.		30 (82) <sup>*</sup>

<sup>\*</sup>The yield in parentheses is the yield based on the recovered starting material.

closing metathesis reaction for cyano cyclic olefins. Also we proved the RCM reaction can be applied to the construction of complicated structure of tribicyclic huperzine B analog with help of the irradiation of microwave.

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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 CH<sub>2</sub>Cl<sub>2</sub> (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 **6a**: IR ( $\nu_{\max}$ , neat) 2925, 2854, 2220, 1597, 1475, 1257 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  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), 3.06 (dd, *J* = 17.2, 1.8 Hz, 1H), 2.64 (d, *J* = 16.8 Hz, 1H), 2.30 (d, *J* = 16.8 Hz, 1H), 1.56 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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 C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O (M<sup>+</sup>) 279.1372, found 279.1372.
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11. Typical procedure for RCM of vinyl nitrile: To a solution of the vinyl nitrile (0.102 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (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.