Synthesis of Heterocycles Containing an N-O Bond by Ring-Closing Metathesis of Dienes Tethered by Hydroxylamine

Young-Keun Yang, Jinsung Tae*

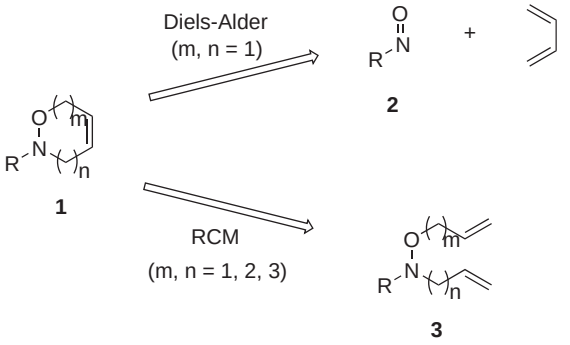
Department of Chemistry, Yonsei University, Seoul 120-749, Korea
Fax +82(2)3647050; E-mail: jstae@yonsei.ac.kr

Received 15 March 2003

Abstract: The dienes tethered by hydroxylamine were efficiently cyclized into 6- to 10-membered heterocycles containing an N-O bond by catalytic ring-closing metathesis.

Key words: cyclizations, heterocycles, metathesis, ring closure, ruthenium

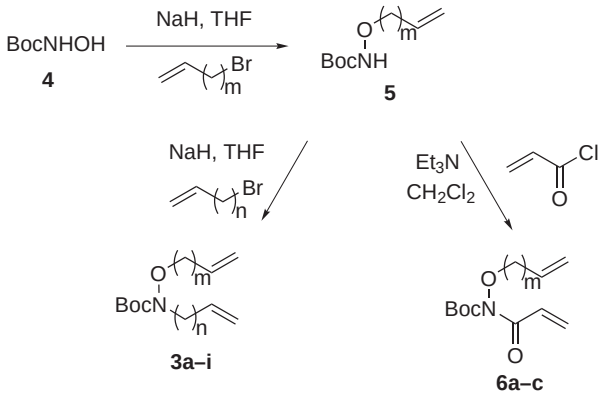
Heterocyclic compounds containing an N-O bond are valuable synthetic intermediates. The 1,2-oxazines (6-membered rings) are easily accessible by Diels–Alder reactions of nitroso compounds[1] and by many other synthetic methods.[2] But the synthesis of medium rings of this class are still difficult. Recently, ring-closing metathesis (RCM)[3] have been applied extensively in organic synthesis, but little attention has been given to the synthesis of heterocycles containing the 1,2-oxaza group. Only few references were reported in the literature concerning the synthesis of 1,2-oxazines and 1,2-oxazepines by RCM.[4] Herein, we report a general synthetic method of 6- to 10-membered heterocycles containing an N-O bond (**1**) by ring-closing metathesis of alkenes tethered by hydroxylamine (**3**) as shown in Scheme 1.



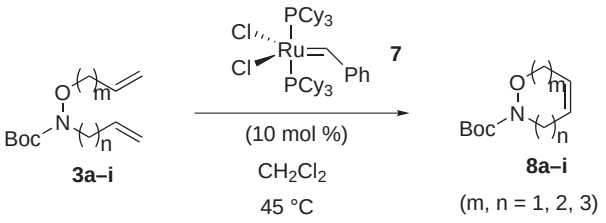
Scheme 1

The starting dienes (**3a**–**i**) were prepared by double alkylation reactions of the *N*-Boc-hydroxylamine (**4**) with suitable bromoalkenes under the standard alkylation conditions (Scheme 2). The alkylations of **4** with the first bromoalkenes afforded the *O*-alkylation products (**5**) which were further reacted with the second bromoalkenes to give **3a**–**i**. The *N*-alkenyloxyacrylamides (**6a**–**c**) were also prepared from **5** with acryloyl chloride in the presence of triethylamine.

The substrates **3a**–**i** were reacted with 10 mol% Grubbs' catalyst (**7**) under refluxing dichloromethane solution (Scheme 3). The results of the metathesis reactions were summarized in Table 1. We first tried the synthesis of 1,2-oxazine and 1,2-oxazepine. The *O*,*N*-Diallyl-hydroxylamine (**3a**) cyclized smoothly into the 1,2-oxazine (**8a**) in less than 4 hours in 93% yield (Table 1, entry 1). The next homologues (**3b**–**c**) required a little longer reaction times (24 h and 14 h respectively), however, produced the 1,2-oxazepines (**8b**–**c**) in good yields (Table 1, entries 2 and 3).



Scheme 2



Scheme 3

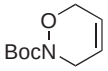
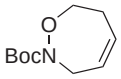
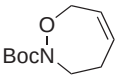
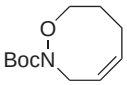
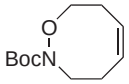
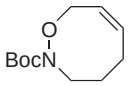
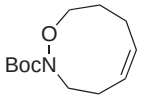
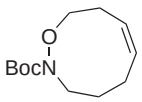
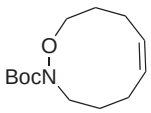
We then moved to the synthesis of medium rings. The synthesis of 1,2-oxazocines (**8d**–**f**, 8-membered rings), from the corresponding substrates **3d**–**f** required high dilution conditions (0.006 M) for the best cyclization yields (Table 1, entry 4–6). The product yields (82–90%) were good under the optimized conditions. Interestingly, the positions of the double bond in 1,2-oxazocine products affected little to the metathesis reactions. Treatments of the

Synlett 2003, No. 7, Print: 02 06 2003.
Art Id.1437-2096,E;2003,0,07,1043,1045,ftx,en;U05203ST.pdf.

next homologues **3g** and**d 3h** with Grubbs' catalyst (**7**) afforded the 1,2-oxazonines (**8g** and **8h**, 9-membered rings) in 63% and 80% yields (Table 1, entry 7 and 8). Furthermore, the metathesis approach can even be applicable for the preparation of a 1,2-oxazecine (10-membered ring) as exemplified in the synthesis of **8i** (Table 1, entry 9).

According to the literature surveys, only few examples of the preparation of 1,2-oxazocines were known,[5] however, no metathesis approaches to this class of heterocycles were reported. Surprisingly, the related 9- and 10-membered heterocycles are, to our knowledge, unprecedented structures.[6]

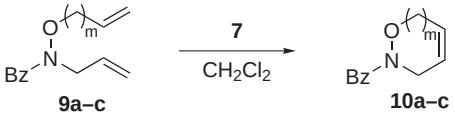
Table 1 Metathesis of *N*-Boc-protected Substrates[a]

Entry	Substrate	Conditions	Product	Yields (%)[b]
1	**3a**, m = 1 n = 1	4 h 0.02 M	 **8a**	93
2	**3b**, m = 2 n = 1	24 h 0.02 M	 **8b**	84
3	**3c**, m = 1 n = 2	14 h 0.02 M	 **8c**	90
4	**3d**, m = 3 n = 1	20 h 0.006 M	 **8d**	82
5	**3e**, m = 2 n = 2	14 h 0.006 M	 **8e**	90
6	**3f**, m = 1 n = 3	18 h 0.006 M	 **8f**	85
7	**3g**, m = 3 n = 2	26 h 0.005 M	 **8g**	63
8	**3h**, m = 2 n = 3	23 h 0.005 M	 **8h**	80
9	**3i**, m = 3 n = 3	17 h 0.005 M	 **8i**	88

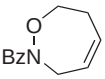
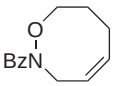
[a] Conditions: 10 mol% **7**, CH_2Cl_2, 45 °C.
[b] Isolated yields.

To see the effects of the protecting groups in the metathesis reactions, the *N*-benzoyl-protected substrates (**9a**–**c**) were examined (Table 2). In general, *N*-benzoyl-protected substrates (**9a**–**c**) cyclized faster than the corresponding *N*-Boc-protected ones (**3a**, **3b**, and **3d**) and delivered the cyclized products in higher yields.

Table 2 Metathesis of *N*-Benzoyl-protected Substrates[a]



9a–c **10a–c**

Entry	Substrate	Conditions	Product	Yields (%)[b]
1	**9a**, m = 1	3 h 0.02 M	 **10a**	98
2	**9b**, m = 2	11 h 0.02 M	 **10b**	96
3	**9c**, m = 3	13 h 0.006 M	 **10c**	90

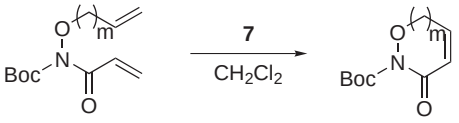
[a] Conditions: 10 mol% **7**, CH_2Cl_2, 45 °C.
[b] Isolated yields.

Next, the *N*-alkenyloxyacrylamides (**6a**–**c**) were subjected to the metathesis conditions (Table 3). Cyclizations of the substrate **6a** and **6b** produced the corresponding 3-oxo-1,2-oxazine **11a** (88%) and 3-oxo-1,2-oxazepine **11b** (84%) respectively (Table 3, entries 1 and 2). The next homologue **6c**, however, was unreactive under the reaction conditions and the starting material was recovered (Table 3, entry 3). To our surprise, only a few patents of the synthesis of 3-oxo-3,6-dihydro-[1,2]oxazine were known[7] and none of the 3-oxo-6,7-dihydro-3*H*-[1,2]oxazepine structures were reported in the literature.[6]

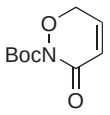
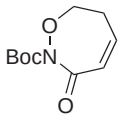
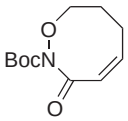
In conclusion, the ring-closing metathesis was successfully applied for the synthesis of small and medium heterocycles containing an N-O bond. We were able to synthesize several unprecedented structures, such as 1,2-oxazonine, 1,2-oxazecine, and 3-oxo-6,7-dihydro-3*H*-[1,2]oxazepine.

General procedure for the ring-closing metathesis: A solution of **3h** (60 mg, 0.24 mmol) and Grubbs' catalyst **7** (10 mg, 0.012 mmol) in CH_2Cl_2 (48 mL) was refluxed at 45 °C for 7 h under N_2 and treated with another portion of Grubbs' catalyst **7** (10 mg, 0.012 mmol). The reaction mixture was refluxed for a total of 23 h before cooled to room temperature. The solvent was removed under reduced pressure and the product mixture was column chromatographed on silica gel (elution with 5% ethyl acetate in hexanes) to give 44 mg (80%) of **8h**.[8]

Table 3 Metathesis of *N*-Alkenyloxy-acrylamides[a]



6a–c **11a–c**

Entry	Substrate	Conditions	Product	Yields (%)[b]
1	**6a**, m = 1	3 h 0.02 M	 **11a**	88
2	**6b**, m = 2	11 h 0.02 M	 **11b**	84
3	**6c**, m = 3	13 h 0.006 M	 **11c**	0[c]

[a] Conditions: 10 mol% **7**, CH_2Cl_2, 45 °C.
[b] Isolated yields.
[c] Starting material was recovered.

Acknowledgment

This work was supported by a Korea Research Foundation Grant (KRF-2002-003-C00080).

References

(1) For reviews on the synthesis of 1,2-oxazines by Diels–Alder reactions, see: (a) Streith, J.; Defoin, A. *Synlett* **1996**, 198. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (c) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317.

(2) (a) Peglow, T.; Blechert, S.; Streckhan, E. *Chem. Commun.* **1999**, 433. (b) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632. (c) Shin, I.; Lee, M.-R.; Lee, J.; Jung, M.; Lee, W.; Yoon, J. *J. Org. Chem.* **2000**, *65*, 7667. (d) Koenig, S. G.; Leonard, K. A.; Lowe, R. S.; Austin, D. J. *Tetrahedron Lett.* **2000**, *41*, 9393. (e) Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S. *J. Am. Chem. Soc.* **2001**, *123*, 4607.

(3) For reviews on metathesis, see: (a) Chang, S.; Grubbs, R. H. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012.

(4) (a) Koide, K.; Finkelstein, Z. B.; Verdine, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 398. (b) Miyabe, H.; Yoshida, K.; Matsumura, A.; Yamauchi, M.; Takemoto, Y. *Synlett* **2003**, 567.

(5) (a) Hu, J.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 6379. (b) Oyama, H.; Morita, T.; Ono, T. Jap. Pat. Appl., JP 02229175, **1990**; *Chem. Abstr*. **1991**, *114*, 81858. (c) Carruthers, W.; Johnstone, R. A. W. *J. Chem. Soc*. **1965**, 1653.

(6) The Scifinder searches for 1,2-oxazonine, 1,2-oxazecine, and 3-oxo-6,7-dihydro-3*H*-[1,2]oxazepine hit no known related compounds.

(7) (a) Wolfe, S.; Shustov, G. P. C. T. Int. Appl., WO 0311298, **2003***; Chem. Abstr*. **2003**, *138*, 153829. (b) Zong, K.; Shin, S. I.; Kim, H. K.; Kim, H. R.; Jeon, D. J.; Ryu, E. K. *Bull. Kor. Chem. Soc.* **1999**, *20*, 965.

(8) Spectral data for **8h**: colorless oil; R_f = 0.5 (hexane/EtOAc = 2:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.64–5.53 (m, 2 H), 4.10–4.02 (t, *J* = 5.6 Hz, 2 H), 3.44–3.35 (t, *J* = 6.0 Hz, 2 H), 2.48–2.32 (m, 2 H), 2.36–2.24 (m, 2 H), 1.79–1.68 (m, 2 H), 1.49 (s, 9 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 158.3, 130.8, 128.3, 81.2, 72.6, 52.7, 28.6, 26.2, 25.9, 23.0; IR (film, cm^{-1}) 2971, 2931, 1729, 1709, 1459, 1393, 1368, 1337, 1164, 1123, 1082; MS: *m/z* (rel. intensity): 18 (7), 29 (10), 41 (20), 57 (100), 69 (7), 83 (8), 96 (15), 110 (3), 127 (10), 207 (M^+, 1).