Ring-Closing Metathesis of Ene-Ynamide: Application to the Synthesis of Medium-Sized Cyclic Dienamide

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Summary: Ring-closing metathesis (RCM) of ene-ynamide, which could be applied to the synthesis of various heterocycles containing 7- and 8-membered rings, was investigated. Ene-ynamides are easily synthesized by the known method. When a toluene solution of ene-ynamide was stirred in the presence of a catalytic amount of second-generation ruthenium carbene complex **1** under an ethylene atmosphere, RCM proceeded smoothly to provide a heterocyclic compound having a diene moiety in good to high yield. A substituent of the ynamide moiety affected the yield of the cyclized product.

Keywords: metathesis; medium-sized heterocycles; ring-closing metathesis; synthesis; ynamide

Introduction

Ynamines and ynamides have been shown to be useful building blocks in organic synthesis.[1] The distinctive reactivity of ynamides, which have an electron-deficient π-orbital and stability relative to ynamines, is attractive for an organic chemist. Several kinds of transition metal-catalyzed reactions of ynamides have been reported in recent years.[2] We have studied the ring-closing metathesis of ene-ynamide, which can be applied to useful synthetic methods for a wide range of heterocycles.[3] Herein, we wish to report the synthesis of 7- and 8-membered rings using RCM of ene-ynamide.

Construction of 7-Membered Ring

At first, the construction of a benzazepine ring was examined. When a toluene solution of **2a** was stirred with 10 mol% of second-generation Grubbs catalyst **1** at 80 °C for 1.5 h under an ethylene atmosphere, cyclized product **3a** was obtained in 22% yield (Table 1, Entry 1).[4] A corresponding reaction was carried out under an argon atmosphere to provide an improved yield of **3a** to 49% (Entry 2). We then tried to perform RCM of **2b**, which was prepared by the introduction of an ethoxycarbonyl group on the alkyne. When a reaction of **2b** was carried out in a similar manner, benzazepine derivative **3b** was obtained in 69% yield (Entry 3). The yield could be enhanced to 84% by performing the reaction under an argon atmosphere (Entry 4).

Next, RCM of linear α,ω-ene-ynamides was examined. When a reaction of **4a** was carried out in toluene at 80 °C for 1 h, starting material **4a** was recovered in 53% yield (Table 2, Entry 1). Replacement of the solvent from toluene to CH_2Cl_2 lead to a progressive result, and **5a** was provided in 36% yield upon heating for 15 h, together with 38% of **4a** (Entry 2).[5] A similar result was obtained, when the reaction was conducted under an argon atmosphere or prolonged reaction time (Entry 3,4). In the case of **4b**, as a substrate having an

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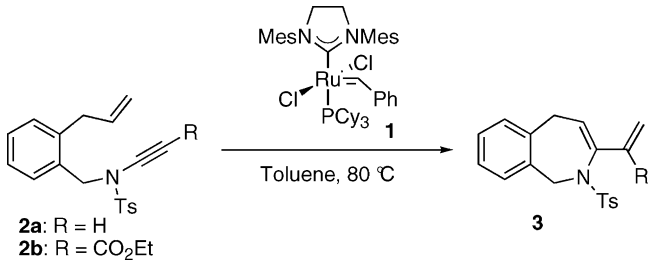
Table 1.
Synthesis of benzazepine derivatives.



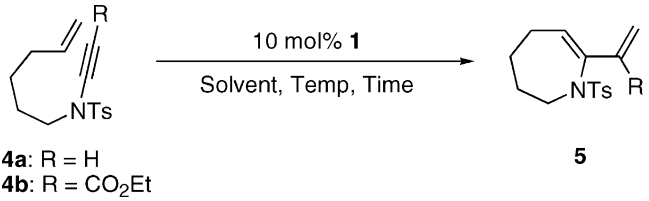
Entry	Substrate	Atmosphere	**1** (mol%)	Time (h)	**3** (%)[a]
1	**2a**	$CH_2=CH_2$	10	1.5	22
2	**2a**	Ar	5	0.5	49
3	**2b**	$CH_2=CH_2$	10	3.5	69
4	**2b**	Ar	5	0.5	84

[a] Isolated yield.

ethoxycarbonyl group on the alkyne, the yield of cyclized product **5b** was only 5% when the reaction was carried out in toluene upon heating (Entry 5). However, a higher yield of **5b** was obtained when the reaction was carried out in CH_2Cl_2 (entry 6).

Subsequently, the synthesis of benzodiazepine derivatives was examined. When a toluene solution of **6a** was exposed to a catalytic amount of **1** at 80 °C for 1 h, starting material **6a** was not consumed and an inseparable complex mixture, which was composed of **6a**, cyclized product **7a**, an intermolecular metathesis product with ethylene, and undefined products, was obtained (Table 3, Entry 1). Replacement of the solvent and a longer reaction time lead to a similar result (Entry 2). However, we were very surprised to find that when **6b** was used as the substrate instead of **6a**, benzodiazepine **7b** was obtained in quantitative yield (Entry 3).[6] A reduction of the catalyst amount did not affect the yield of **7b** (Entry 4). RCM proceeded smoothly in CH_2Cl_2 as the solvent, although a longer

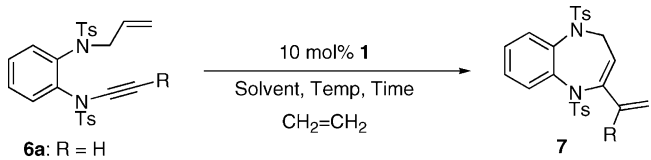
Table 2.
Synthesis of azepine derivatives.



Entry	Substrate	Atmosphere	Solvent	Temp (°C)	Time (h)	**5** (%)[a]	Recovery of **4** (%)[a]
1[b]	**4a**	$CH_2=CH_2$	Toluene	80	1	–	53[c]
2	**4a**	$CH_2=CH_2$	CH_2Cl_2	reflux	15	36	38
3	**4a**	Ar	CH_2Cl_2	reflux	26	37	33
4	**4a**	Ar	CH_2Cl_2	reflux	48	33	31
5[b]	**4b**	$CH_2=CH_2$	Toluene	80	3	5	74
6	**4b**	$CH_2=CH_2$	CH_2Cl_2	reflux	1.5	74[c]	–

[a] Yields were determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as the internal standard.
[b] 5 mol% of **1** was used.
[c] Isolated yield.

Table 3.
Synthesis of benzodiazepine derivatives.



6a: R = H
6b: R = CO_2Et

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Entry	Substrate	Solvent	Temp (°C)	Time (h)	**7** (%)[a]
1	**6a**	Toluene	80	1	–
2	**6a**	CH_2Cl_2	reflux	28	–
3	**6b**	Toluene	80	0.5	99
4[b]	**6b**	Toluene	80	0.5	99
5	**6b**	CH_2Cl_2	reflux	15	97
6[c]	**6b**	CH_2Cl_2	reflux	20	95

[a] Isolated yield.
[b] 5 mol% of **1** was used.
[c] Reaction was carried out under argon atmosphere.

reaction time was required (Entry 5). Excellent yield of **7b** was also accomplished when the reaction was carried out under an argon atmosphere (Entry 6).

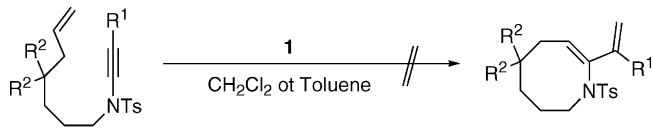
Construction of 8-Membered Ring

Encouraged by the success of the construction of a 7-membered ring, we were also interested in the synthesis of 8-membered heterocycles.

At first, to synthesize azocine derivative **9**, various linear enynes were examined. However, cyclized product **9** was not obtained in any case (Scheme 1).

Thus, RCM of linear ene-ynamide **10**, which contained two tosylamide groups in a chain, was examined. When a CH_2Cl_2 solution of **10a** was carried out in the presence of 10 mol% of **1** upon heating for 21 h, starting material **10a** was recovered in 33% yield (Table 4, Entry 1). The introduction of an ethoxycarbonyl group on the alkyne affected the formation of an 8-membered ring, and **11b** could be obtained in 15% yield (Entry 2).[7] Improved yield was accomplished when the reaction was performed under an argon atmosphere (Entry 3). Higher recovery of starting material **10b** was observed by using toluene as the solvent (Entry 4). Successful result for the construction of an 8-membered ring could be achieved and **11b** was obtained in 78% yield when the reaction was conducted under a high-dilution condition (Entry 5).

The synthesis of benzodiazocine was examined. The reaction of **12a** with second-generation Grubbs catalyst **1** provided only recovered **12a** (Table 5, Entry 1), and the shorter reaction time did not affect the



R^1 = H or CO_2Et
8a: R^2 = H
8b: R^2 = CH_2OBn
8c: R^2 = -$CH_2OCMe_2OCH_2$-

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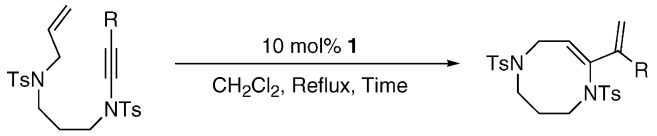
Scheme 1.
Synthesis of azocine derivatives.

Table 4.
Synthesis of diazocine derivatives.



10a: R = H
10b: R = CO_2Et

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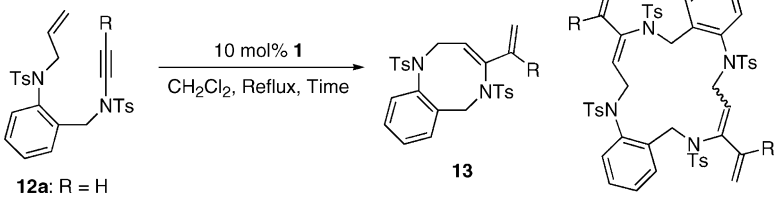
Entry	Substrate	Atmosphere	Time (h)	**11** (%)[a]	Recovery of **10** (%)[a]
1	**10a**	$CH_2=CH_2$	21	–	33
2	**10b**	$CH_2=CH_2$	21	15	49
3	**10b**	Ar	21	33	25
4[b]	**10b**	$CH_2=CH_2$	6	–	68
5[c]	**10b**	Ar	24	78[d]	–

a) Yields were determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as the internal standard.
b) Reaction was carried out in the presence of 5 mol% of **1** in toluene at 80 °C.
c) Reaction was carried out under low concentration condition (0.002 M).
d) Isolated yield.

result (Entry 2). However, when a reaction of **12b** was carried out using **1** upon heating in CH_2Cl_2 for 21 h, a new spot appeared on TLC (Entry 3). It seemed likely that ^{1}H NMR indicated that compound **13** had been obtained. However, the peaks were separated clearly when ^{1}H NMR was measured at a low temperature (−50 °C). Furthermore, the largest *m/z* value of FAB-MS spectra was at 1133 ($M^+ + H$). These results indicated that the metathesis product is dimeric compound **14**, not **13**. An argon atmosphere was effective for the dimerized cyclization of **12b**, and the yield of **14b** was increased to 52% (entry 4). Replacing the solvent to toluene from CH_2Cl_2, a high recovery of **12b** was observed under an ethylene atmosphere (Entry 5), and a high yield of **14b** was provided under an argon atmosphere (Entry 6).

When metathesis product **14b** was treated with $NaBH_4$ in the presence of

Table 5.
Synthesis of benzodiazocine derivatives.



12a: R = H
12b: R = CO_2Et

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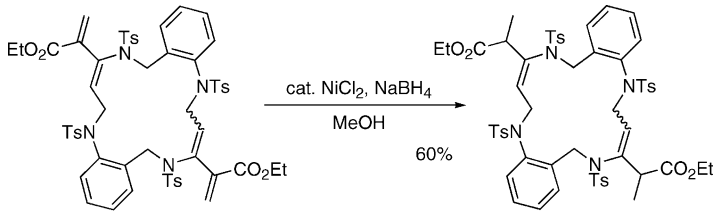
Entry	Substrate	Atmosphere	Time (h)	**13** (%)	**14** (%)[a]	Recovery of **12** (%)[a]
1	**12a**	$CH_2=CH_2$	21	–	–	58
2[b]	**12a**	$CH_2=CH_2$	0.5	–	–	53
3	**12b**	$CH_2=CH_2$	21	–	14	63
4	**12b**	Ar	21	–	52	44
5[b]	**12b**	$CH_2=CH_2$	6	–	–	86
6[b]	**12b**	Ar	2	–	77	–

a) Isolated yield.
b) Reactions were carried out in the presence of 5 mol% **1b** in Toluene at 80 °C.



14b **15b**

Scheme 2.
1,4-Reduction of **14b**.

$NiCl_2$, an exo olefin moiety of the metathesis product was reduced to provide **15b** (Scheme 2).

Conclusion

In summary, the synthesis of 7- and 8-membered heterocycles catalyzed by ruthenium carbene complex **1** was investigated. Various medium-sized heterocyclic compounds could be synthesized by RCM of ene-ynamides in high yields. In the case of RCM of **12b**, 16-membered macrocycle **14b** was produced.

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[3] (a) M. Mori, H. Wakamatsu, N. Saito, Y. Sato, R. Narita, Y. Sato, R. Fujita, *Tetrahedron* **2006**, *62*, 3881. (b) N. Saito, Y. Sato, M. Mori, *Org. Lett.* **2002**, *4*, 803.

[4] The spectrum data of 2-(*p*-Toluenesulfonyl)-3-vinyl-2,5-dihydro-1*H*-benzo[*c*]azepine (**3a**): IR (neat) ν 1597 (w), 1338 (s), 1159 (s) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.30 (d, J=5.8Hz, 2H), 4.81 (s, 2H), 5.13 (d, J=10.6Hz, 1H), 5.43 (d, J=16.9Hz, 1H), 5.77 (t, J=5.8Hz, 1H), 6.38 (dd, J=10.6, 16.9Hz, 1H), 6.73 (d, J=7.7Hz, 1H), 6.97 (d, J=8.2Hz, 2H), 7.06 (ddd, J=1.9, 7.3, 7.3Hz, 1H), 7.11-7.19 (m, 2H), 7.27 (d, J=8.2Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.4, 33.9, 53.5, 115.1, 125.0, 126.3, 127.3, 127.4, 128.8, 129.0, 129.6, 129.8, 135.2, 135.3, 137.0, 141.1, 142.6; EI-LRMS *m/z* 325 (M^+), 260, 170, 117, 91; EI-HRMS *m/z* calcd for $C_{19}H_{19}O_2NS$ (M^+) 325.1136, found 325.1121.

[5] The spectrum data of 1-(*p*-Toluenesulfonyl)-7-vinyl-2,3,4,5-tetrahydro-1*H*-azepine (**5a**): IR (neat) ν 1599 (w), 1343 (s), 1158 (s) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 1.29-1.36 (m, 2H), 1.66-1.73 (m, 2H), 1.84-1.90 (m, 2H), 2.42 (s, 3H), 3.49 (br, 2H), 5.05 (d, J=10.6Hz, 1H), 5.29 (d, J=17.2Hz, 1H), 5.94 (dd, J=6.8, 7.3Hz, 1H), 6.25 (dd, J=10.6, 17.2Hz, 1H), 7.27 (d, J=8.2Hz, 2H), 7.76 (d, J=8.2Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 21.5, 23.6, 26.0, 29.2, 49.1, 114.6, 127.5, 129.4, 131.9, 134.6, 139.1, 142.4, 143.1; EI-LRMS *m/z* 277 (M^+), 212, 155, 122, 91; EI-HRMS *m/z* calcd for $C_{15}H_{19}O_2NS$ (M^+) 277.1136, found 277.1134.

[6] The spectrum data of Ethyl 2-[1,5-Bis-(*p*-toluenesulfonyl)-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-yl]-acrylate (**7b**): IR (KBr) ν 1720 (m), 1598 (w), 1355 (s), 1164 (s) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 1.24 (t, J=7.2Hz, 3H), 2.42 (s, 3H), 2.44 (s, 3H), 3.73 (dd, J=2.9, 18.4Hz, 1H), 4.06-4.15 (m, 2H), 4.57 (dd, J=3.9, 18.4Hz, 1H), 5.30 (dd, J=2.9, 3.9Hz, 1H), 5.88 (s, 1H), 6.25 (s, 1H), 7.26-7.36 (m, 7H), 7.46 (m, 1H), 7.72 (d, J=8.2Hz, 2H), 7.87 (d, J=8.2Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.1, 21.6, 21.6, 49.1, 61.0, 121.4, 125.7, 127.5, 128.1, 128.3, 128.4, 129.1, 129.5, 129.9, 130.4, 136.3, 136.9, 137.0, 137.8, 139.4, 140.3, 143.7, 144.0, 165.1; EI-LRMS *m/z* 552 (M^+), 507, 397, 242, 169, 139, 91; EI-HRMS *m/z* calcd for $C_{28}H_{28}O_6N_2S_2$ (M^+) 552.1389, found 552.1399.

[7] The spectrum data of Ethyl 2-[1,5-Bis-(toluene-4-sulfonyl)-1,4,5,6,7,8-hexahydro-[1,5]diazocin-2-yl]-acrylate (**11b**): IR (neat) ν 1717 (s), 1598 (w), 1343 (s), 1161 (s) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 1.15 (t, J=7.3Hz, 3H), 1.86-1.93 (m, 2H), 2.40 (s, 3H), 2.44 (s, 3H), 3.41-3.47 (m, 2H), 3.63 (t, J=5.3Hz, 2H), 3.85 (d, J=8.2Hz, 2H), 3.90 (q, J=7.3Hz, 2H), 5.81 (s, 1H), 6.16 (s, 1H), 6.18 (t, J=8.2Hz, 1H), 7.23 (d, J=7.7Hz, 2H), 7.31 (d, J=7.7Hz, 2H), 7.58 (d, J=8.2Hz, 2H), 7.65 (d, J=8.2Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 13.9, 21.5, 21.5, 27.9, 44.1, 48.5, 51.8, 60.9, 127.0, 127.4, 129.4, 129.8, 130.5, 131.0, 136.2, 136.7, 137.8, 139.3, 143.4, 143.4, 165.0; EI-LRMS *m/z* 518 (M^+), 473, 397, 363, 335, 317, 267, 238, 207, 180, 155, 134, 91; EI-HRMS *m/z* calcd for $C_{25}H_{30}O_6N_2S_2$ (M^+) 518.1545, found 518.1538.

