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Tetrahedron Letters 45 (2004) 3757–3760
Tetrahedron Letters

Synthesis of cyclic hydrazines by ring-closing metathesis of dienes and enynes tethered by an N–N bond

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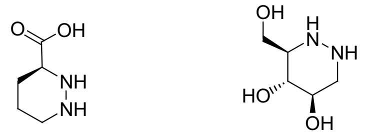
Received 16 February 2004; revised 11 March 2004; accepted 15 March 2004

Abstract—Ring-closing metathesis of dienes and enynes tethered by an N–N bond produced 6- to 10-membered cyclic 1,2-diaza compounds. The enyne RCM adducts were further transformed by Diels–Alder reaction into aromatic compounds.

Several biologically active natural and unnatural compounds consist of heterocycles containing an N–N bond. Piperazic acid (**1**) and 1-azafagomine (**2**) are well-known six-membered compounds with cyclic hydrazine skeleton (Fig. 1). Piperazic acid[1] and substituted piperazic acids are key amino acid components of several biologically active natural peptides including novel cyclophilin-binding sanglifehrins.[2] 1-Azafagomine (**2**) and related aza-sugar derivatives are known as potent glycosidase inhibitors.[3] A number of methods have been reported to synthesize the six-membered cyclic hydrazine structures.[4] In general, the hetero Diels–Alder approach between dienes and azodicarboxylate esters constitutes one of the earliest synthetic methods.[5] More recently, the electrophilic hydrazination of enolates represent the most practical method to this class of compounds, especially when asymmetric synthesis concern.[6] Unlike the six-membered cyclic hydrazines, only limited synthetic methods are available to medium-size (7- to 10-membered) congeners.[7] Most of them utilize alkylation method and therefore limited to simple substrates. Developments of general synthetic methods for the medium-size rings of this class of compounds are in great demand.



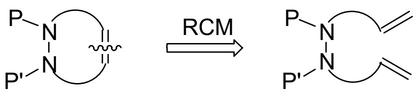
piperazic acid (**1**)   1-azafagomine (**2**)

Figure 1.

Although the ring-closing metathesis (RCM)[8,9] have been extensively utilized in the synthesis of various organic frameworks, to the best of our knowledge, however, there is no literature precedent of the synthesis of cyclic 1,2-diaza skeletons by RCM. As a part of our research program directed toward the synthesis of heterocyclic compounds, we have recently reported the synthesis of heterocycles by ring-closing metathesis.[10] Herein, we report the synthesis of 6- to 10-membered cyclic hydrazines by the RCM reaction (Scheme 1).

The starting dienes (**5a–e**) were prepared by double alkylation reactions of the 1-*tert*-butoxycarbonyl-2-carbobenzyloxyhydrazine (**3**) with bromoalkenes under the standard alkylation conditions (Scheme 2). Alkylation of **4** with propargyl bromide afforded the enynes (**6a–c**).[11]

The ring-closing metathesis reactions of dienes were first examined. The diene substrates (**5a–e**) were treated with



Scheme 1.

Keywords: Cyclizations; Cyclic hydrazines; Diels–Alder reaction; Ring-closing metathesis; Ruthenium.

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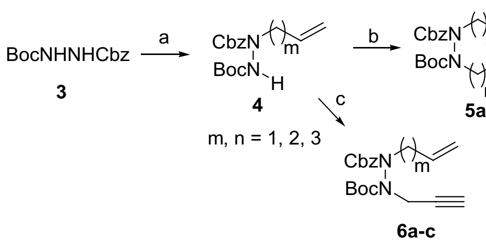
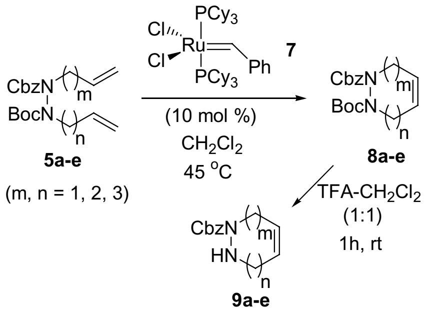
doi:10.1016/j.tetlet.2004.03.075

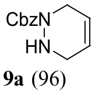
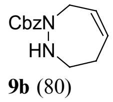
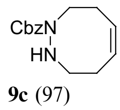
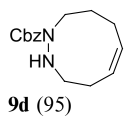
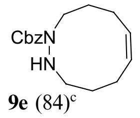


Scheme 2. Reagents and conditions: (a) NaH (1.2 equiv), *n*-Bu_4NI (cat.), DMF, $Br(CH_2)_mCH{=}CH_2$ (1.1 equiv), 25 °C, 33–67% (12–45% of dialkylation products); (b) NaH (1.2 equiv), *n*-Bu_4NI (cat.), DMF, $Br(CH_2)_nCH{=}CH_2$ (1.1 equiv), 25 °C, 87–89%; (c) NaH (1.2 equiv), *n*-Bu_4NI (cat.), DMF, $BrCH_2CCH$ (1.1 equiv), 25 °C, 94–99%. Cbz = carbobenzyloxy, Boc = *tert*-butoxycarbonyl.

10 mol% Grubbs' catalyst (**7**)[12] under refluxing dichloromethane solution (Table 1). The protected *N*,*N′*-diallylhydrazine (**5a**) produced the 3,6-dihydropyridazine (**8a**) in good yield (93%) under the conditions (Table 1, entry 1). The next homologue **5b** yielded the seven-membered cyclic hydrazine **8b** in 98% (Table 1, entry 2). Lower substrate concentrations (0.008–0.005 M) were required for the efficient cyclizations of the 8- to 10-membered rings. The yields for the synthesis of medium-size rings were 74–70% (Table 1, entries 3–5). Because the ^1H and ^{13}C NMR spectra of cyclic hydrazine compounds (**8a–e**) were broad and complicate, the Boc groups in **8a–e** were deprotected with 50% TFA in CH_2Cl_2 to give **9a–e** where ^1H and ^{13}C NMR spectra were clean. In the case of 10-membered ring (**8e**), unlike the smaller rings (**8a–d**), only 40% of the desired product (**9e**) was obtained under the same TFA conditions. Thus, the Boc group in **8e** was removed with $BF_3{\cdot}OEt_2$ to yield **9e** in 84% (Table 1, entry 5).

Table 1. Ring-closing metathesis of **5** and deprotection of the Boc in **8**



Entry	5	Conditions[a]	Yields (%)[b]	
			8	9
1	**5a** *m* = 1 *n* = 1	8 h 0.02 M	**8a** (93)	 **9a** (96)
2	**5b** *m* = 1 *n* = 2	8 h 0.02 M	**8b** (98)	 **9b** (80)
3	**5c** *m* = 2 *n* = 2	16 h 0.008 M	**8c** (74)	 **9c** (97)
4	**5d** *m* = 3 *n* = 2	16 h 0.006 M	**8d** (72)	 **9d** (95)
5	**5e** *m* = 3 *n* = 3	16 h 0.005 M	**8e** (70)	 **9e** (84)[c]

[a] Reaction time and concentration for the RCM.

[b] Isolated yields.

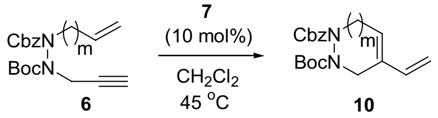
[c] Conditions for the deprotection of the Boc in **8e**: $BF_3{\cdot}OEt_2$, 4 Å molecular sieves, CH_2Cl_2.

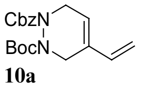
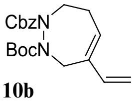
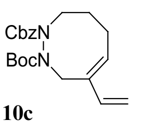
We then moved to the ring-closing enyne metathesis of **6a–c** (Table 2). Yields for the synthesis of 6- to 8-membered cyclic dienes were moderate to good (70–99%). The Diels–Alder reactions between the enyne metathesis adducts and dimethyl acetylenedicarboxylate (DMAD) were studied as shown in Scheme 3.

Conjugated dienes (**10a–c**) were reacted with DMAD at 110 °C for 6 h to give the cycloaddition adducts (**11a–c**), which were oxidized with DDQ to the bicyclic aromatic compounds (**12a–c**). The two step overall yields were uniformly good (Table 3). Again due to the broadenings of the NMR spectra of **12a–c**, the Boc groups in **12a–c** were removed to obtain **13a–c** for the full characterizations.

In conclusion, we have shown that small and medium-size cyclic hydrazines can be synthesized by ring-closing metathesis of dienes and enynes tethered by an N–N

Table 2. Ring-closing enyne metathesis of **6**



Entry	Substrate	Conditions[a]	Product	Yield (%)[b]
1	**6a** *m* = 1	4 h 0.02 M	 **10a**	99
2	**6b** *m* = 2	8 h 0.02 M	 **10b**	70
3	**6c** *m* = 3	10 h 0.02 M	 **10c**	70

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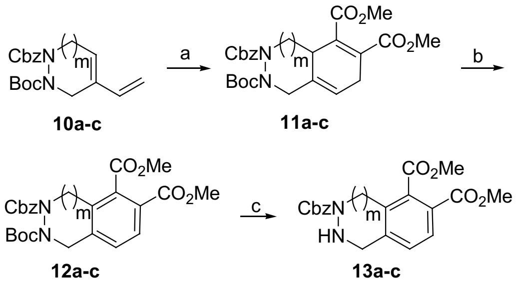
[a] Reaction time and concentration.

[b] Isolated yields.



Scheme 3. Reagents and conditions: (a) DMAD (1.2 equiv), toluene, 110 °C, 6 h; (b) DDQ (2.0 equiv), toluene, 110 °C; (c) 50% TFA–CH_2Cl_2, rt, 1 h. DMAD = dimethyl acetylenedicarboxylate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TFA = trifluoroacetic acid.

Table 3. Conversion of **10** to **13**

Entry	**10**	Yield (%)[a]		
		11	**12**	**13**
1	**10a** *m* = 1	**11a** (88)	**12a** (82)	**13a** (75)
2	**10b** *m* = 2	**11a** (97)	**12b** (87)	**13b** (75)
3	**10c** *m* = 3	**11a** (92)	**12c** (92)	**13c** (50)

[a] Isolated yields.

bond. The enyne RCM adducts were converted to bicyclic aromatic heterocycles by the Diels–Alder reaction/oxidation sequence.

General procedures for RCM/deprotection of Boc group: A solution of **5a** (88 mg, 0.25 mmol) and Grubbs' catalyst **7** (22 mg, 0.025 mmol) in CH_2Cl_2 (13 mL) was refluxed at 45 °C for 8 h under N_2. The solvent was removed under reduced pressure and the residue mixture was column chromatographed on silica gel (hexane/EtOAc = 20:1) to give 75 mg (93%) of **8a**. A solution of **8a** in 50% TFA–CH_2Cl_2 (4 mL) was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the residue mixture was column chromatographed on silica gel (hexane/EtOAc = 5:1) to give 49 mg (96%) of **9a**.[13]

Acknowledgements

This work was supported by a grant from the Korea Research Foundation (KRF-2003-015-C00360).

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11. The first alkylation sites were the nitrogens protected by Cbz, which was confirmed by comparisons of the ^1H

NMR chemical shifts of the propargylic and allylic methylene protons of **6** and those of their derivatives where the Boc groups were deprotected.

12. The use of the second generation Grubbs' catalyst did not improve the yields.
13. Spectral data, for **9a**: colorless oil; $R_f = 0.2$ (silica gel, hexane/EtOAc = 2:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50–7.20 (m, 5H), 6.00–5.85 (m, 1H), 5.85–5.70 (m, 1H), 5.20 (s, 2H), 4.07 (s, 2H), 3.48 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 156.0, 136.6, 128.6, 128.3, 125.8, 123.6, 67.6, 46.3, 44.1; IR (film, cm^{-1}); 3273, 2939, 2848, 1701, 1409, 1347, 1224, 1117; HRMS: m/z calcd for $C_{12}H_{14}N_2O_2$ (M^+): 218.1055; found: 218.1057.
For **13c**: colorless solids; $R_f = 0.1$ (silica gel, hexane/EtOAc 1:1); mp = 116–118 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.88 (d, $J = 7.7$ Hz, 1H), 7.34 (s, 6H), 5.16 (s, 2H), 4.06 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.33 (br s, 2H), 2.85–2.65 (m, 2H), 1.99 (br s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 170.0, 166.0, 156.1, 143.8, 137.5, 136.4, 131.9, 128.7, 128.6, 128.3, 127.9, 127.5, 67.8, 54.3, 52.7, 52.6, 49.2, 29.0, 26.4; IR (film, cm^{-1}) 3298, 2950, 1726, 1696, 1445, 1399, 1276, 1199, 1117; HRMS: m/z calcd for $C_{22}H_{24}N_2O_6$ (M^+): 412.1634; found: 412.1634.