Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 47 (2006) 3893–3896

Tetrahedron Letters

Microwave-assisted ring-closing metathesis of diallylamines: a rapid synthesis of pyrrole and pyrroline derivatives

Qian Yang, Xin-Yong Li, Hong Wu and Wen-Jing Xiao*

The Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China

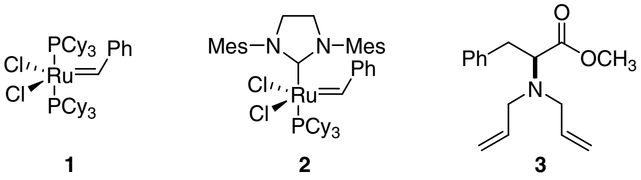
Received 30 December 2005; revised 27 March 2006; accepted 28 March 2006
Available online 27 April 2006

Abstract—The ring-closing metathesis (RCM) reactions of diallylamines occurred under controlled microwave irradiation. In addition to the high reaction rate, the key features of the reaction are that it can be carried out without deactivation of the substrates and without the use of Lewis acids.

Ring-closing metathesis (RCM) has been established as a powerful and effective method for the construction of many functionalized carbocycles and heterocycles from acyclic diene precursors.[1] Many useful transformations have been reported for industrial applications as well as for the synthesis of complex molecules because of major advances in catalyst design.[2] However, RCM reaction of free amines is rather difficult. They have to be deactivated by conversion to amides, carbamates, or sulfonamides or by protonation to perform the RCM reactions, in order to get reasonable yields.[3] Recently, we have reported that such substrates, without deactivation, can participate in RCM reactions with the use of the second generation Grubbs ruthenium catalyst in the presence of catalytic amount of $Ti(O^iPr)_4$.[4]

Microwave (MW) irradiation as a nonconventional energy source has emerged as a very useful technique to promote various reactions and has become increasingly popular within the pharmaceutical and academic arenas.[5] By taking advantage of this efficient source of energy, a few studies on microwave-assisted metathesis have been reported,[6] but few involve RCM reactions of diallylamines possessing basic or nucleophilic nitrogen atoms. Recently, Wilson and co-workers reported an example of MW-accelerated RCM of diolefin substrates containing an external carboxymethyl substituent, which, in certain cases, resulted in the formation of carboxymethyl substituted dihydropyrroles or pyrroles.[5c] As part of our ongoing project aimed at investigating the MW effects in organic synthesis under green chemistry conditions[5a] and based on the pioneering work of Wilson and co-workers,[5c] we report herein our study on microwave-assisted ruthenium-catalyzed RCM of diallylamines. This process leads to a straightforward procedure for the preparation of pyrrole and/or pyrroline derivatives.

Initial optimization reactions of microwave-assisted RCM reactions with catalyst **1** or **2** were conducted with methyl 2-(diallylamino)-3-phenylpropanoate **3** as the model substrate (Scheme 1). A variety of microwave irradiation conditions including time, temperature, and solvents were investigated. All reactions were performed in a Smith synthesizer producing controlled irradiation at 2450 MHz with a power of 0–300 W in closed vessels. It was found that the highest conversion was obtained by exposing substrate **3** (0.1 M) in CH_2Cl_2 to sealed-vessel under microwave irradiation at 150 °C for 10 min with 5 mol % catalyst **2**. With optimal conditions,



Scheme 1.

Keywords: Microwave; Ring-closing metathesis; Pyrrole; Pyrroline.

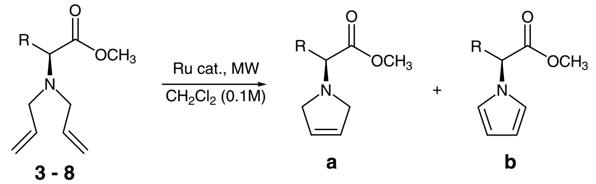
* Corresponding author. Tel./fax: +86 27 67862041; e-mail: wxiao@mail.ccnu.edu.cn

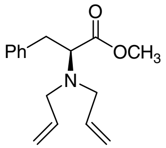
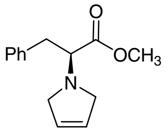
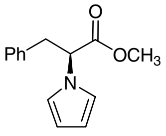
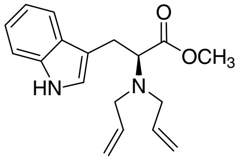
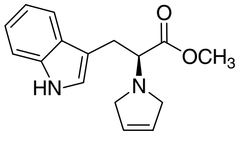
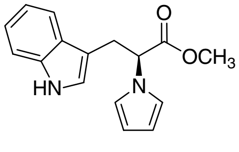
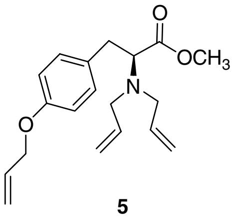
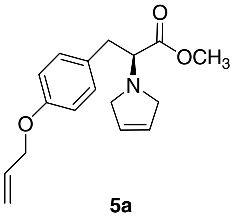
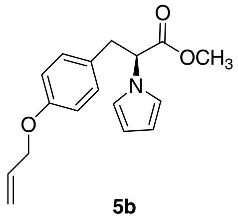
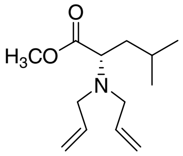
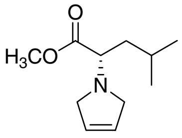
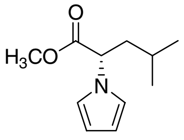
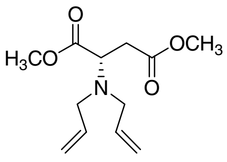
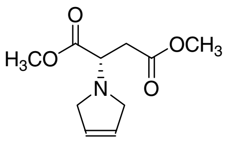
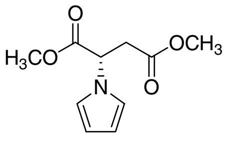
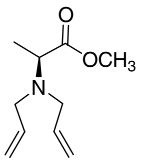
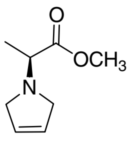
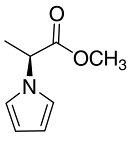
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.164

several chiral diallylamine substrates, which were generated from L-amino acids, were subjected to RCM reactions and the results are summarized in Table 1.

The data in Table 1 indicate that under microwave irradiation, all substrates cyclized smoothly in substantially less time than using conventional conditions.[4]

Table 1. Microwave-assisted RCM reactions of diallylamines[7]

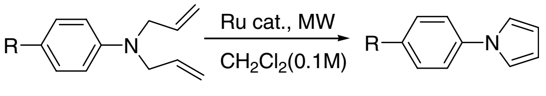


Entry	Substrate	Product[a]		Conditions	Yield[b]	
					a (%)	**b** (%)
1	 **3**	 **3a**	 **3b**	0.1 M in **3** 5 mol % of **2** 150 °C, 10 min	40	57
2	 **4**	 **4a**	 **4b**	0.1 M in **4** 5 mol % of **2** 150 °C, 10 min	39	54
3	 **5**	 **5a**	 **5b**	0.1 M in **5** 5 mol % of **2** 150 °C, 10 min	28	61
4	 **6**	 **6a**	 **6b**	0.1 M in **6** 5 mol % of **2** 150 °C, 10 min	35	53
5	 **7**	 **7a**	 **7b**	0.1 M in **7** 5 mol % of **2** 100 °C, 10 min	75	16
6	 **8**	 **8a**	 **8b**	0.1 M in **8** 5 mol % of **2** 150 °C, 10 min	10	75

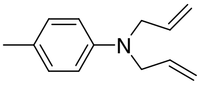
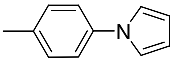
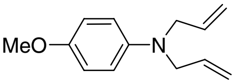
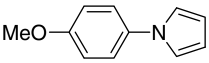
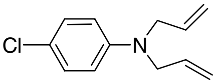
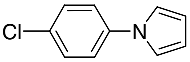
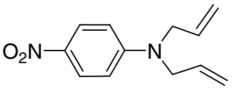
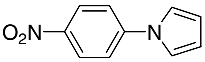
[a] All compounds were characterized by ^{1}H NMR and ^{13}C NMR data.

[b] Isolated yields.

Table 2. Microwave-assisted RCM reactions of less basic diallylamines



9 - 12 **13 - 14**

Entry	Substrate	Product[a]	Conditions	Yield[b] (%)
7	 **9**	 **13**	0.1 M in **9** 5 mol % of **1** 100 °C, 10 min	94
8	 **10**	 **14**	0.1 M in **10** 5 mol % of **1** 100 °C, 10 min	89
9	 **11**	 **15**	0.1 M in **11** 2 mol % of **1** 100 °C, 10 min	98
10	 **12**	 **16**	0.1 M in **12** 2 mol % of **1** 100 °C, 10 min	98

[a] Compounds were characterized by ^{1}H NMR and ^{13}C NMR.
[b] Isolated yields.

The reactions gave pyrrole derivatives as the main products,[8] except in the case of **7** (entry 5).

We then examined how the basicity of the nitrogen atom affected the RCM reactions under microwave irradiation. Some substituted aromatic amines **9**–**11** were synthesized and subjected to the optimal microwave irradiation conditions. The reactions gave pyrrole derivatives in excellent yields. Among these substrates, Evans et al. have used compound **10** in the RCM reaction with CH_2Cl_2 as the solvent in the presence of catalyst **1**.[9] Thus, we chose **1** as the catalyst and reduced catalyst loadings from 5 to 2 mol %. The excellent yields were obtained under these conditions (Table 2).

As illustrated in Tables 1 and 2, the basicity of diallylamines had obvious effect on the microwave-accelerated RCM reactions. When the substrate was more basic, the more active catalyst **2** had to be used to make the reaction complete (Table 1). In the case of less basic substrates, for example, *N*,*N*-diallylaniline, comparable results could be obtained in the presence of less active catalyst **1** and with catalyst loadings reduced to 2 mol % (Table 2). Pyrroles were isolated as the sole products instead of the expected corresponding 3-pyrrolines (Table 2, entries 7–10), which suggested that not only RCM took place but also isomerization and dehydrogenation occurred under microwave irradiation.

In conclusion, we have established an efficient method for the RCM of diallylamines using microwave activation. The RCM reaction gives the pyrrole as a major product in most cases. The key features of this process are that it can be carried out without deactivation of the substrates and without the use of Lewis acids.

Acknowledgements

We are grateful to the Natural Science Foundation of China (20472021), the National Key Project for Basic Research of China (2004CCA00100), and the Hubei Province Science Fund for Distinguished Young Scholar (2004ABB011), for funding. We thank Materia, Inc., Pasadena, CA, for the generous gift of catalysts.

References and notes

1. For recent reviews, see: (a) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239; (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592; (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900; (d) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
2. For recent examples, see: (a) Langenhan, J. M.; Griffith, B. R.; Thorson, J. S. *J. Nat. Prod.* **2005**, *68*, 1696; (b) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200; (c) Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513; (d) Takahashi, S.; Hishinuma, N.; Koshino, H.; Nakata, T. *J. Org. Chem.* **2005**, *70*, 10162; (e) Briggs, T. F.; Dudley, G. B.

Tetrahedron Lett. **2005**, *46*, 7793; (f) Cumpstey, I. *Tetrahedron Lett.* **2005**, *46*, 6257; (g) Chang, M.-Y.; Pai, C.-L.; Chen, H.-P. *Tetrahedron Lett.* **2005**, *46*, 7705.

3. (a) Evans, P.; Grigg, R.; Ramzan, M. I.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1999**, *40*, 3021; (b) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082; (c) Williams, R. M.; Liu, J. *J. Org. Chem.* **1998**, *63*, 2130; (d) Furstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2466; (e) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855; (f) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.
4. (a) Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871; (b) Taber, D. Organic Chemistry Highlights, October 17, 2005. Please see: http://www.organic-chemistry.org/Highlights/2005/170october.shtm.
5. Representative examples include (a) Cao, H.; Xiao, W.-J. *Can. J. Chem.* **2005**, *83*, 826; (b) Efskind, J.; Undheim, K. *Tetrahedron Lett.* **2003**, *44*, 2837; (c) Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783; (d) Declerck, V.; Ribière, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372; (e) Mayo, K. G.; Nearhoof, E. H.; James, J.; Kiddle, J. *J. Org. Lett.* **2002**, *4*, 1567; (f) Thanh, G. V.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091; (g) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136; (h) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653.
6. Representative examples include (a) Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 8160; (b) Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. . *Org. Lett.* **2005**, *7*, 2723; (c) Bargiggia, F.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 9636; (d) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2004**, *45*, 3089; (e) Grigg, R.; Martin, W.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, *44*, 4899; (f) Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 1869.
7. Typical procedure: In a microwave vial with a stir-bar, the catalyst **2** (5 mol %) was dissolved in 0.2 mL CH_2Cl_2, and substrates **3**–**10** (0.1 mmol), dissolved in 0.8 mL CH_2Cl_2, were added to the vial and heated at 150 °C for 10 min. After cooling, the reaction mixture was evaporated under reduced pressure. The crude product was analyzed by GC and purified by flash chromatography (silica gel 200–300 mesh) to afford the corresponding product.
8. For reports on pyrroles' formation using RCM reactions, see: (a) Bujard, M.; Briot, A.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 8785; (b) Dieltiens, N.; Stevens, C. V.; Vos, D. D.; Allaert, B.; Drozdzak, R.; Verpoort, F. *Tetrahedron Lett.* **2004**, *45*, 8995.
9. Evans, P.; Grigg, R.; Monteith, M. *Tetrahedron Lett.* **1999**, *40*, 5247.