Report

Construction of a 3-Amino-2-pyridone Library by Ring-Closing Metathesis of □-Amino Acrylamide

Yihua Chen, Huajie Zhang, and Fajun Nan

J. Comb. Chem., **2004**, 6 (5), 684-687• DOI: 10.1021/cc049939x • Publication Date (Web): 26 June 2004

Construction of a 3-Amino-2-pyridone Library by Ring-Closing Metathesis of α-Amino Acrylamide

Yihua Chen, Huajie Zhang, and Fajun Nan*

Chinese National Center for Drug Screening, Shanghai Institute of Materia Medica, Shanghai Institutes of Biological Sciences, Graduate School of the Chinese Academy of Sciences, 189 Guo Shou Jing Road, Shanghai 201203, China

Received March 10, 2004

Over the past decade, the olefin metathesis reaction has become one of the most important methods for carbon−carbon double-bond formation in organic synthesis.[1] In particular, ring-closing olefin metathesis (RCM) has been widely applied as a key step in constructing cyclic olefins of many sizes containing ether, ester, amide, or amino groups in several total syntheses of complex natural products.[2]

Recently, a few RCM reactions of olefins connected directly to a heteroatom have been reported, such as enol ethers, enamides, vinyl chlorides, and fluorides.[3] Although the preparation of conjugated amides has been well-investigated,[3f] and the ring-closing metathesis of enamines has also been described,[3g] the utilization of these methods has been limited as a result of the low reactivity and the special functional groups required for these olefin substrates.

In this paper, en route to α-amino acrylamides via RCM to afford the corresponding α-amino α,*β*-unsaturated lactams. When compared to the reported RCM of nitrogen-substituted olefins,[3g] the present method provides for more versatile lactam moieties, which can be further converted into structural units that exist in many bioactive molecules. A 3-amino-2-pyridone library was constructed in good yield using this strategy (Figure 1).

The RCM precursors were synthesized in 60−78% yield, as shown in Scheme 1, by coupling an α-aminoacrylic acid **6** with the corresponding free amine **5** or *N*-dimethoxybenzyl (DMB)-protected amine **7,** employing ethylene 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC)/HOBt. The acrylic acids **6** were obtained using two different reported methods.[4] The DMB-protected amines **7** were synthesized from various amines **5** ($n = 0-3$) according to the conventional reductive amination using 2,4-dimethoxybenzaldehyde in the presence of $NaBH_4$ in EtOH.[5]

We initially attempted to use nonprotected acrylic amides as substrates to perform the RCM reaction. Unfortunately, the RCM of **8** was found to be unsuccessful, as shown in Scheme 2. Using a Grubbs catalyst (either **1** or **2**) at room temperature or by refluxing in different solvents, the cyclization did not proceed, and only the starting material was recovered. When *N*-DMB-protected precursors **3** were used,

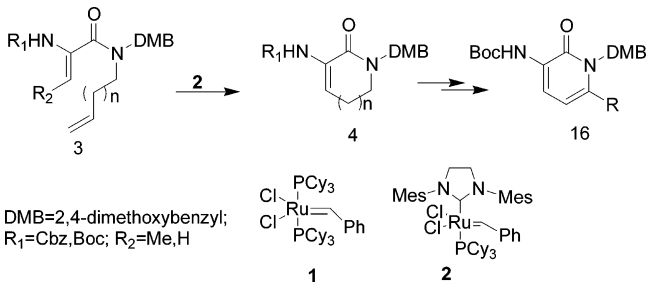
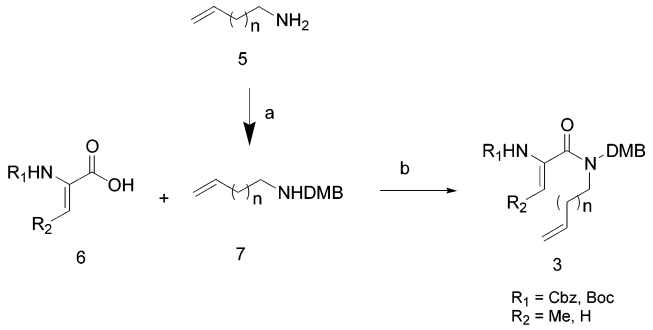


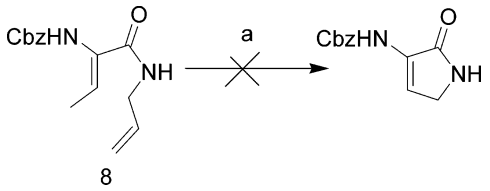
Figure 1. The RCM of α-amino-acrylamide.

Scheme 1. Synthesis of RCM Precursors[a]



[a] Reagents and conditions: (a) 2,4-dimethoxybenzaldehyde/Et_3N then $NaBH_4$; (b) EDC, HOBt, dry DMF,4 Å molecular sieves.

Scheme 2. RCM Reaction of Nonprotected Acrylic Amides[a]



[a] Reagents and conditions: (a) 10 mol % catalyst **1**, DCM, rt 20 h and then reflux 5 h; or 10 mol % catalyst **2**, DCM, r.t. 20 h and then reflux 5 h; or 10 mol % catalyst **2**, DCE, r.t. 20 h and then reflux 5 h, or 10 mol% catalyst **2**, DCE, r.t. 20 h and then reflux 5 h.

the cyclization proceeded in the presence of 10 mol % catalyst **2** at room temperature in dichloromethane (DCM) to yield a series of lactams. The results are listed in Table 1.

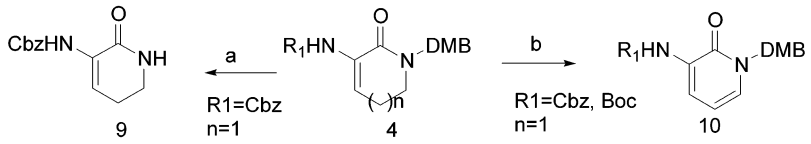
As can be seen from the data in Table 1, it was realized that the presence of the *N*-DMB group is necessary to ensure the success of this type of RCM reaction and that the size of the ring plays an important role in the success of the reaction. Five-, six-, and seven-membered-ring substrates afforded cyclic products in good yields. Cyclization did not proceed for the eight-membered-ring substrate, even when using Grubbs catalyst (either **1** or **2**) at room temperature or under reflux in different solvents.

The influence of the R group was also investigated. Both six-membered-ring substrates reacted smoothly in DCM with 10 mol % Grubbs catalyst **2**, but for R = H, substrate **3f** afforded cyclic products in a low yield, even with long reaction times and high temperatures. This may be due to the precursor **3f** of the seven-membered ring's experiencing decomposition before cyclization. Interestingly, substrate **3h**, an acetoxy derivative of **3c**, afforded a very good yield,

* To whom correspondence should be addressed. Phone: +86-21-50801313, ext 231. Fax: +86-21-50800721. E-mail: fjnan@mail.shcnc.ac.cn.

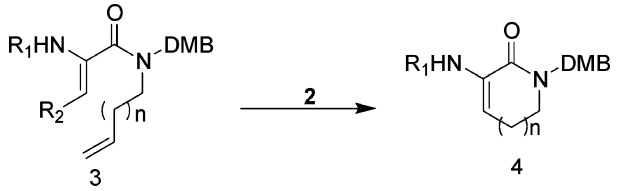
10.1021/cc049939x CCC: $27.50
Published on Web 06/26/2004

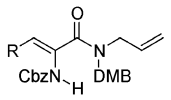
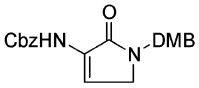
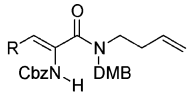
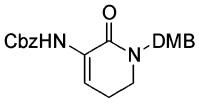
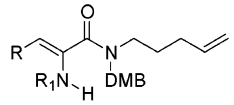
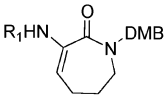
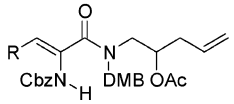
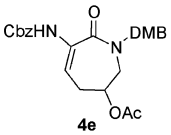
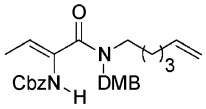
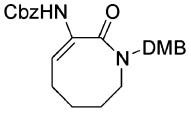
Scheme 3. Some Applications of the Present RCM-Type Reaction[a]



[a] Reagents and conditions: (a) TFA/DCM r.t. 62%; (b) DDQ/DCM r.t. 84%.

Table 1. RCM Reactions of Different Substrates



Diene, reaction time	Lactams, yield
 **3a** R=Me, 24h **3d** R=H, 2h	 **4a** 69% 76%
 **3b** R=Me, 2h **3e** R=H, 2h	 **4b** 85% 81%
 **3c** R=Me, R1=Cbz, 20h **3f** R=H, R1=Cbz, 36h **3i** R=Me, R1=Boc, 24h	 **4c** R1=Cbz, 81% 35% **4f** R1=Boc, 85%
 **3h** 2h	 **4e** 95%
 **3g** 36h	 **4d** 0%

which indicates that the present RCM reaction can tolerate substitution on the substrate.

The metathesis products synthesized using this method have considerable potential for a wide range of further transformations. First, the DMB group can be easily removed in the presence of trifluoroacetic acid (TFA) or cerium (IV) ammonium nitrate acetate nitrate (CAN) in good yield[6] to afford the further modifiable deprotected products **9**. Second, modification of the six-membered-ring lactam will result in functionalized 3-amino lactams **12**, which are considered to be constrained surrogates of dipeptides.[7] Another potential successful transformation is the dehydrogenation of the six-membered-ring products by treatment with DDQ[8] (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (Scheme 3). The resulting 2-pyridone structural unit has been found in several bioactive compounds, such as amrinone **11**,[9] an inhibitor of cyclic guanosine monophosphate (cGMP)-inhibited cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE), and the recently discovered 2-pyridone tissue factor VIIa inhibitor **13**[10] (Figure 2). Using this method, we have synthesized a sublibrary of 2-pyridone, which can be converted further to form tissue factor VIIa inhibitors (Scheme 4). Therefore, the present method provides a new potential synthesis route and approach to further derivatives, as well as a small molecule library of 3-amino lactams.

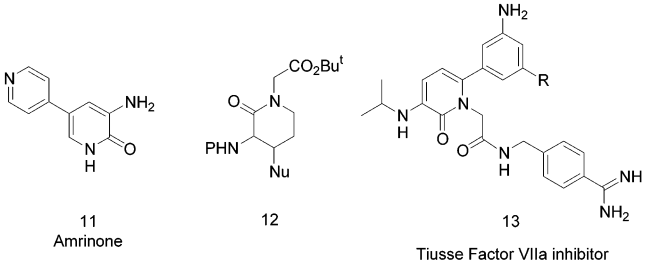
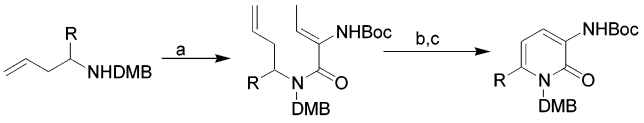


Figure 2. Some bioactive compounds including 2-pyridone structural unit.

Scheme 4. Preparation of the 2-Pyridone Sublibrary[a]



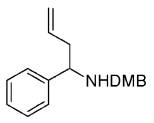
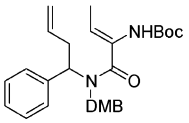
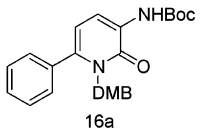
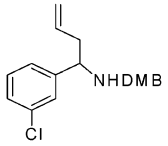
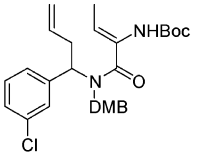
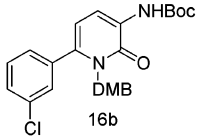
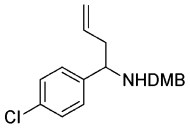
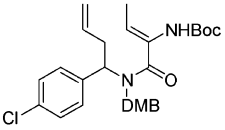
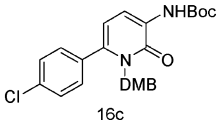
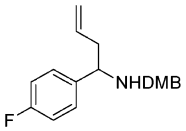
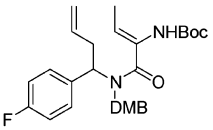
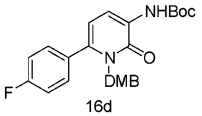
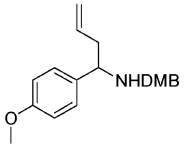
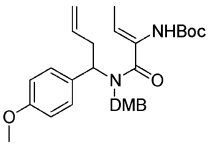
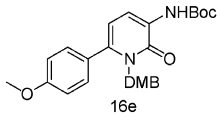
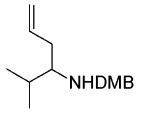
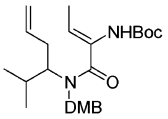
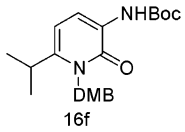
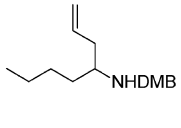
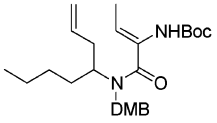
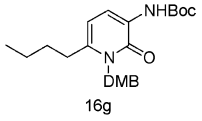
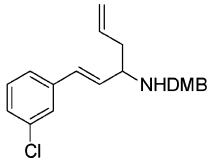
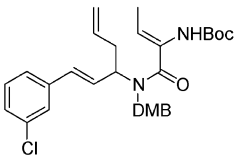
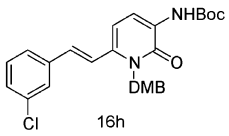
[a] Reagents and conditions: (a) 2-*tert*-butoxycarbonylamino-butyl-2-enoic acid, EDC, HOBt, dry DCM, 4-Å molecular sieves, 60−73%; (b) **2**, DCM; (c) DDQ, overall yield 51-84% from 15.

The construction of 3-amino-2-pyridone was investigated to further demonstrate the utility of the present method. Employing the strategy used for compound **10**, the substituted *N*-DMB amide **14** was subjected to the ring-closing metathesis (RCM) reaction, followed by a treatment using the same reaction system with DDQ. The 3-amino-2-pyridone product was obtained in a high yield, as shown in Scheme 4.

The detailed reaction procedure is listed in Scheme 4. The substituted DMB-protected amine **14**, which was obtained by treatment of the corresponding imine with allyl bromide and Zn powder in the presence of a catalytic amount of titanium (IV) chloride,[11] was converted to the RCM precursor **15** by coupling with 2-*tert*-butoxycarbonylaminobutyl-2-enoic acid employing the usual method. The derivatives of 2-pyridone **16** can be synthesized via the RCM reaction of **15** followed oxidation by DDQ. The product **16** and its precursor **15** are listed in Table 2.[12]

As shown by the data in Table 2, the RCM/DDQ oxidation proceeded smoothly to afford good-to-excellent yields in a "one-pot" reaction. The 6-position-substituted

Table 2. Preparation of the Derivatives of 2-Pyridone via the RCM Reaction

Entry	DMB-amine	RCM precursor	2-pyridone	Yield (%)[a]
1			 16a	51
2			 16b	52
3			 16c	84
4			 16d	70
5			 16e	71
6			 16f	77
7			 16g	65
8			 16h	75

[a] Isolated yield for the preparation of 16 from 15.

groups varied from electron-rich to electron-deficient aromatic rings and also from long-chain alkyl groups to hindered alkyl groups. The most interesting entry is entry 8: the RCM reaction proceeded in a very high regioselectivity, as the terminal double bond showed a higher reactivity than the aromatic vinyl group. This provided one more double bond for further modifications.

In this work, a solution-phase synthesis is described for the construction of a 2-pyridone library. The *N*-dimethoxybenzyl (DMB) protection of the parent pyridone is easily removed and facilitates further N-modification. In addition, it may also facilitate solid-phase syntheses, making it amenable for general use in the synthesis of medicinal chemistry libraries in an automated platform.

In conclusion, we have reported the first RCM reactions of α-amino acrylamide to generate α-amino α,*β*-unsaturated lactams. We have developed a new and simple procedure to construct an exploratory sublibrary of pyridone in anticipation of its bioactivity. We are now investigating variations on this methodology as well as its application to the total synthesis of natural products.

Acknowledgment. The Major State Hi-tech Research and Development Program (Grant 2001AA234011), the Chinese

Academy of Sciences, and the Shanghai Commission of Science and technology are appreciated for their financial support.

Supporting Information Available. ^{1}H NMR spectra of compounds **3(a−i)**, ^{1}H, ^{13}C NMR spectra of compounds **4(a−c)**, **4e**, **4f**, **9**, **10**, and **16(a−h)** and mass spectral data and HPLC data of the compounds above. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) For recent reviews of olefin metathesis, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Furstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3012. (d) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2037. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed*. **2003**, *42*, 1900.

(2) (a) Crimmins, M. T.; Tabet, E. A. *J. Org. Chem*. **2001**, *66*, 4012. (b) Furstner, A.; Rumbo, A. *J. Org. Chem*. **2000**, *65*, 2608. (c) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc*. **2003**, *125*, 13618. (d) Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2003**, *125*, 6042. (e) Biswas, K.; Lin, H.; Njardarson, J. .; Chappell, M. D.; Chou, T.-C.; Guan, Y.; Tong, W. P.; He, L.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2002**, *124*, 9825. (f) Deiters, A.; Martin, S. F.; *Chem. Rev*. **2004**, *104*, 2199. (g) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* (h) Walters, M. A. *Progress in Heterocyclic Chemistry*; Gribble, G., Joule, J., Eds.; Pergamon: New York, 2003; p 1−36.

(3) (a) Rainier, J. D.; Allwein, S. P. *J. Org. Chem*. **1998**, *63*, 5310. (b) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623. (c) Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett*. **2001**, *42*, 179. (d) Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett*. **2001**, *42*, 8029. (e) Whitehead, A.; Moore, J. D.; Hanson, P. R. *Tetrahedron Lett.* **2003**, *44*, 4275. (f) Rodríguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185. (g) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett*. **2001**, *3*, 2045. (h) Salim, S. S.; Bellingham, R. K.; Satcharoen, V.; Brown, R. C. D. *Org. Lett.* **2003**, *5*, 3403. (i) Chao, W.; Weinre, S. M. *Org. Lett*. **2003**, *5*, 2505.

(4) (a) Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem*. **1980**, 45, 4817. (b) Kolar, A. J.; Olsen, R. K. *Synthesis*. **1977**, 457.

(5) Tamaki, K.; Huntsman, E. W. D.; Petsch, D. T.; Wood, J. L. *Tetrahedron Lett.* **2002**, *43*, 379.

(6) Creighton, C. J.; Reitz, A. B. *Org. Lett.* **2001**, *3*, 893.

(7) (a) Fernandez, M. M.; Diez, A.; Rubiralta, M.; Montenegro, E.; Casamitjana, N.; Kogan, M. J.; Giralt, E. *J. Org. Chem.* **2002**, *67*, 7587. (b) Estiarte, M. A.; Rubiralta, M.; Thormann, M.; Giralt, E. *J. Org. Chem*. **2000**, *65*, 6992. (c) Ecija, M.; Diez, A.; Rubiralta, M.; Casamitjana, N. *J. Org. Chem*. **2003**, *68*, 9541.

(8) Ahluwalia, V. K.; Arora, K. K. *Tetrahedron* **1981**, *37*, 1437.

(9) Fossa, P.; Menozzi, G.; Dorigo, P.; Floreani, M. Mosti, L. *Bioorg. Med. Chem*. **2003**, *11*, 4749.

(10) Parlow, J. J.; Kurumbail, R. G.; Stegeman, R. A.; Stevens, A. M.; Stallings, W. C.; South, M. S. *J. Med. Chem*. **2003**, *46*, 4696.

(11) (a) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *69*, 7766. (b) Tanake, H.; Inoue, K.; Pokarski, U.; Taniguchi, M.; Torii, S. *Tetrahedron. Lett*. **1990**, *31*, 3023.

(12) A general experimental procedure for the RCM and oxidation of DDQ to **16** is as follows: To a stirred solution of 0.05 mM α-amino-acrylic amide **15** in 20 mL of dry, degassed DCM, a second-generation Grubbs catalyst **2** (10 mol %) in 20 mL of dry, degassed DCM was added drop-wise to the mixture under and argon atmosphere at room temperature for ∼12 to 36 h. After removal of most of the solvent in vacuo, 23 mg of DDQ was added to the residue (in ∼5 mL DCM). The mixture was stirred for 2 h at room temperature, and the residue was purified using silica gel chromatography to afford the desired product **16**.

CC049939X