Organic LETTERS

Letter

pubs.acs.org/OrgLett

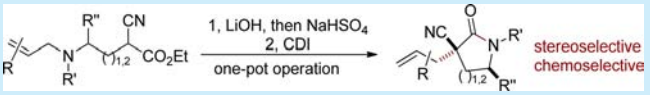
One-Pot Conversion of *N*-Allyl-α-cyano Esters to α-Allyl-α-cyano Lactams through a Hydrolysis/Ketene Formation/Cyclization/Claisen Rearrangement Sequence

Mei-Hua Shen,* Mei Han, and Hua-Dong Xu*

School of Pharmaceutical Engineering and Life Science, Changzhou University, 1 Middle Gehu Road, Changzhou, Jiangsu Province 213164, China

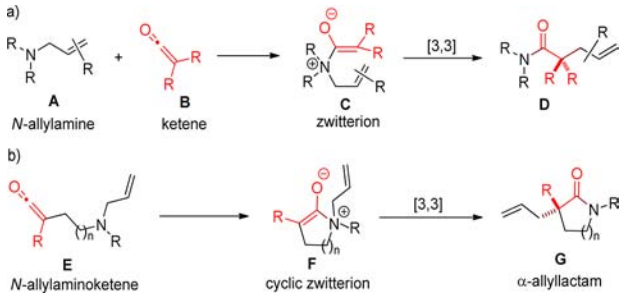
Supporting Information

ABSTRACT: An intramolecular ketene aza-Claisen rearrangement is developed for the first time to enable the stereoselective synthesis of α-ally-α-cyano-lactams from *N*-allyl amino esters. This reaction also exhibits outstanding chemoselectivity when an unsymmetrical bis-*N*-allyl group is present in the starting molecule. The usefulness of this method is demonstrated by a short synthesis of optically active bicyclolactam from L-proline.



Proceeding via a highly ordered transition state, aza-Claisen rearrangement, as a typical 3,3-sigmatropic reaction, recomposes molecular structure in a predictable fashion; in particular, this transformation converts a relatively easier C−N bond to a normally more challenging C−C bond in a controllable manner.[1] Ketene aza-Claisen rearrangement characterizes a zwitterionic intermediate C generated via the combination of *N*-allyl tertiary amine **A** with reactive ketene **B** (Scheme 1a) and

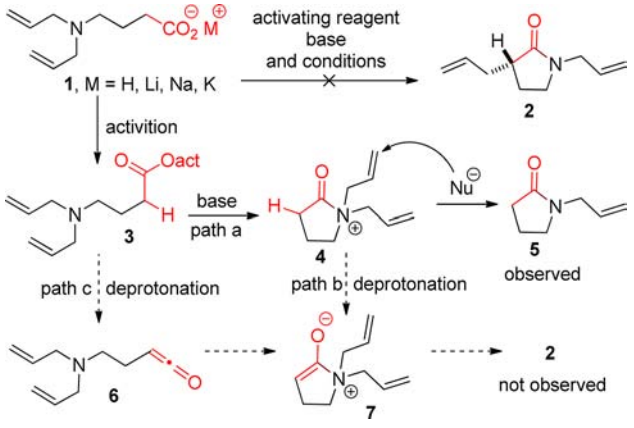
Scheme 1. (a) Intermolecular and (b) Intramolecular Zwitterionic Aza-Claisen Reaction



therefore avoids harsh reaction conditions normally required for other types of aza-Claisen reactions (Scheme 1a).[2] Recently, the ketene aza-Claisen reaction has attracted much interest and has been advanced to an asymmetric version in addition to its numerous applications in organic synthesis.[3] We envisaged that an imaginary ketene **E** with a pendent tertiary amine would cyclize readily to cyclic zwitterion **F** and then would transform to highly valuable α-allyl lactam **G** (Scheme 1b). An intensive literature search found no precedent example; therefore, we launched a program aiming to realize this useful transformation.

Initially, *N*-allyl amino acid **1** (M = H) and its metal salts **1** (M = Li, Na, K) were chosen as the ketene precursor. Various activator/base/solvent combinations have been tested,[4] and the desired lactam **2** could not be obtained in all cases. Instead, either recovery of the starting amino acid or isolation of lactam **5** was observed. It was reasoned that the activated intermediate **3** was directly attacked by the pendent tertiary amine to form cyclic amide cation **4** which eliminates one allyl group to give rise to a von Braun-type product **5** (Scheme 2, path a) before β-proton

Scheme 2. Interpretation of the Formation of *N*-Allyl Butyrolactam from the Reaction of Amino Acid/Carboxylates 1



elimination to zwitterion **7** (path b).[5] However, the favored intramolecular nucleophilic attack of the amino group on **3** (path a) precluded the β-proton elimination to ketene **6** (path c).

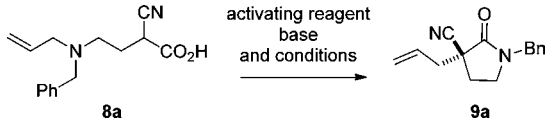
On the basis of the above analysis, it was further proposed that enhancement of the acidity of the α-proton in **3** and **4** would facilitate the deprotonating event and favor the formation of ketene and zwitterion (Scheme 2, path b and c). An electron withdrawing cyano group at the α-position would meet this purpose. Therefore, α-cyano *N*-allyl amino acid **8a** was taken as a

Received: October 1, 2015
Published: February 12, 2016

DOI: 10.1021/acs.orglett.5b02843
Org. Lett. 2016, 18, 889−891

substrate to test this idea. When a solution of acid **8a** in THF was treated with NaH (2.0 equiv) for 10 min and then mesyl chloride at rt for 8 h, the desired lactam **9a** was isolated in 36% yield (Table 1, entry 1). After approving the hypothesized working

Table 1. Condition Optimization for the Intramolecular Ketene Aza-Rearrangement[a]



8a **9a**

entry	base	solvent	activating agent	yield (%)[b]
1	NaH	THF	MsCl	36
2	DIEPA	DCM	MsCl	54
3	DABCO	DCM	MsCl	66
4		DCM	DCC	32
5		DCM	CDI	81

[a]Reaction conditions: **8a** (0.3 mmol), base (0.45 mmol), solvent (3 mL), activating agent (0.45 mmol), rt, 8 h. [b]Isolated yield. CDI: carbonyl diimidazole.

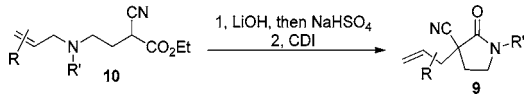
mechanism, condition optimization was carried out (entries 2–5). Organic bases such as DIPEA and DABCO are more effective to give increased yields in DCM. It was further found that dehydrating agent DCC can also promote this reaction delivering **9a** in 32% yield. Research along this direction finally led to great enhancement of yield to 81% when carbonyl diimidazole (CDI) was applied as a dehydration agent.

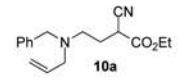
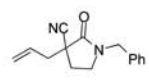
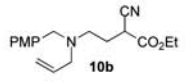
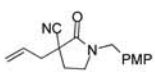
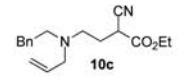
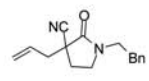
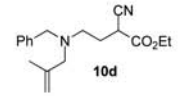
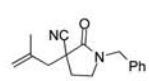
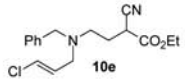
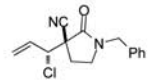
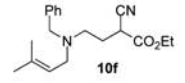
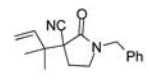
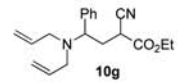
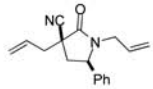
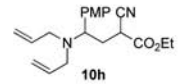
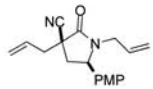
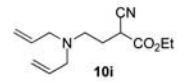
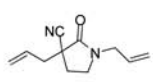
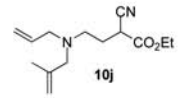
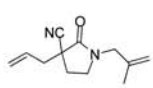
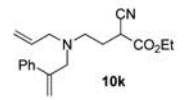
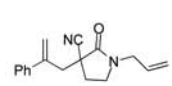
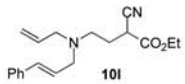
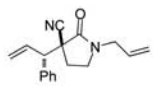
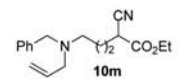
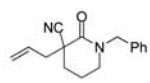
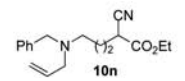
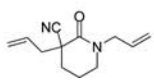
To overcome the difficulties associated with handling substrate **8**, which is essentially an amino acid, a two-step protocol using amino ester **10a** as starting material was established. Hydrolysis of **10a** with LiOH/$NaHSO_4$ afforded a residue of crude amino acid after exhaust removal of volatiles. Without further purification, this residue was then submitted to the optimized ketene aza-Claisen reaction conditions to smoothly furnish lactam **9a** in 81% yield (Table 2, entry 1). With this improved procedure, more α-cyano *N*-allyl amino esters **10** were made to explore the substrate scope.

By changing the *N*-benzyl substituent to *p*-methoxylbenzyl or phenylethyl group, the yields were improved to 85% and 88%, respectively (entries 2 and 3). Variations on the allyl segment were also checked briefly. **10d** and **10k** with 2-methyl allyl and 2-phenyl allyl on the nitrogen atom were converted to **9d** and **9k** with high yields. **9e** and **9l** were obtained both with high yields and stereoselectivity from **10e** and **10l** indicating that these reactions proceeded through highly organized transition states. Allyl lactam **9f** with two adjacent quaternary carbon centers was also obtained smoothly and highlighted the usefulness of this methodology. The isolation of sole diastereomers **9g** and **9h** from the reactions of **10g** and **10h** further approved the organized transition states of these reactions. A chemoselective issue arises when the substrates bear two different *N*-allyl moieties (entries 10–12).

It was surprising that in the reaction of **10j** only **9j** was detected (80%), whereas the simple allyl group outcompetes the 2-methylallyl group in the [3,3] sigmatropic process. Interestingly, the chemoselectivity inverted for **10k** as the 2-phenylallyl group outcompeted the parent allyl group to give **9k** in 86% yield. The conversion of **10l** to **9l** in both regio- and diatereoselectivities led to a conclusion that 3-phenylallyl is also favorable over the substituted allyl group. Though the exact reason for this intriguing chemoselectivity is elusive at this stage, we argue

Table 2. Substrate Scope for the Ketene Aza-Rearrangement[a]



entry	substrate	product	yield (%)[b]
1	 **10a**	 **9a**	81
2	 **10b**	 **9b**	85
3	 **10c**	 **9c**	88
4	 **10d**	 **9d**	83
5	 **10e**	 **9e**	82
6	 **10f**	 **9f**	88
7	 **10g**	 **9g**	75
8	 **10h**	 **9h**	70
9	 **10i**	 **9i**	78
10	 **10j**	 **9j**	80
11	 **10k**	 **9k**	86
12	 **10l**	 **9l**	82
13	 **10m**	 **9m**	40
14	 **10n**	 **9n**	30

[a]Conditions: step 1, **10** (0.5 mmol), LiOH·H_2O (0.6 mmol), MeOH/THF (3/3 mL), overnight, rt, $NaHSO_4$ (0.6 mmol); step 2, CDI (0.75 mmol), DCM (5 mL), rt, 8 h.

that in the proposed transition state **TS-I** for this reaction (Figure 1) a methyl group at C2 would give a 2-fold 1,3-diaxial repulsion. However, this transition state might be stabilized by an extended conjugation system acquired by an aromatic substitution on the allylic double bond as in **10k** and **10l**. Substrates with one-carbon-elongation of the tether between the allyl amine and ester group were also viable for this reaction giving six-membered lactam in modest yields (entries 13 and 14). The relative

DOI: 10.1021/acs.orglett.5b02843
Org. Lett. 2016, 18, 889–891

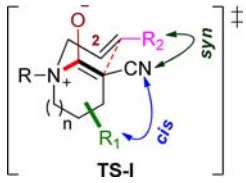
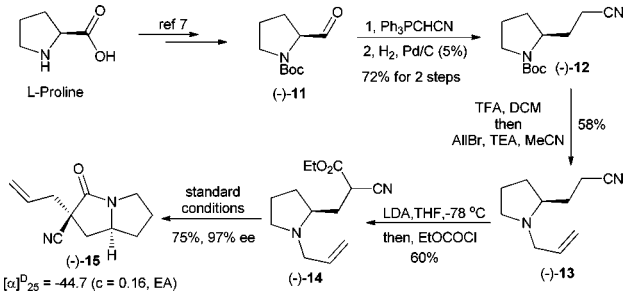


Figure 1. Proposed chair transition state for the aza-Claisen rearrangement.

stereochemistry of **9g** was established by ^{1}H−^{1}H Cosy and ^{1}H−^{1}H NOESY NMR experiments; and the same stereochemistry was applied to **9h** by analogy. Attempts to determine the relative stereochemistry of **9e** and **9l** through chemical manipulations were not fruitful to date; alternatively, their structures were assigned tentatively as shown according to the transition state **TS-I**, which was an analogue of ketene−imine aza-Claisen rearrangement.[6] In **TS-I**, the CN group resides *cis* to the R_1 group on the newly formed lactam ring, and the R_2 is *syn* to the CN group.

To demonstrate the usefulness of this method, optically pure L-prolidinyl aldehyde (−)-**11** was made readily from L-proline[7] and was converted to nitrile (−)-**12** by a Wittig olefination[8]/hydrogenation reaction sequence. Removal of the Boc group with TFA followed by N-allylation afforded amino nitrile (−)-**13**. Installation of the ethoxycarbonyl on the carbon α to the cyanide group was achieved by C-acylation with EtO_2CCl after LDA deprotonation.[9] The standard protocol was applied to (−)-**14** to furnish optical active bicyclic lactam (−)-**15** in 75% yield. To acquire an authentic sample of rac-**15** for comparison, the same synthetic steps shown in Scheme 3 were followed using D/L-

Scheme 3. Synthesis of Highly Functionalized Bicyclic Amide



proline as the starting point. HPLC analysis using a chiral IC-H column demonstrated that (−)-**15** from L-proline was virtually in its optically pure form (97% ee value).

In summary, the first intramolecular ketene aza-Claisen rearrangement reaction has been developed to enable the stereoselective synthesis of α-ally-α-cyano-lactams from *N*-allyl amino esters. This reaction also exhibited outstanding chemoselectivity when an unsymmetrical bis-*N*-allyl group was present in the starting molecule. The highly functionalized lactam products could be further elaborated to numerous new alkaloids. By application of this protocol, a short synthesis of optically pure bicyclolactam from L-proline has been efficiently achieved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02843.

Experimental procedures, characterization of new compounds and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*(M.-H.S.) E-mail: shenmh@cczu.edu.cn.
*(H.-D.X.) E-mail: huadongxu@gmail.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Natural Science Foundation of China (21402014 and 21272077), the Natural Science Foundation of Jiangsu Province (BK20131143), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PADA), and Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110).

■ REFERENCES

(1) (a) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, *2009*, 2117. (c) Nubbemeyer, U. In *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M. N., Nubbemeyer, U., Eds.; Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007. (d) Nubbemeyer, U. *Top. Curr. Chem.* **2005**, *244*, 149.

(2) (a) Ishida, M.; Muramaru, H.; Kato, S. *Synthesis* **1989**, *1989*, 562. (b) Roberts, S. M.; Smith, C.; Thomas, R. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1493. (c) Cid, M. M.; Eggnauer, U.; Weber, H. P.; Pombo-Villar, E. *Tetrahedron Lett.* **1991**, *32*, 7233. (d) Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6690. (e) Diederich, M.; Nubbemeyer, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1026. (f) Sudau, A.; Nubbemeyer, U. *Angew. Chem., Int. Ed.* **1998**, *37*, 1140. (g) Yu, C.-M.; Choi, H.-S.; Lee, J.; Jung, W.-H.; Kim, H.-J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 115.

(3) (a) Sudau, A.; Münch, W.; Nubbemeyer, U.; Bats, J. W. *J. Org. Chem.* **2000**, *65*, 1710. (b) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726. (c) Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2448. (d) Nubbemeyer, U. *J. Org. Chem.* **1995**, *60*, 3773. (e) Nubbemeyer, U. *J. Org. Chem.* **1996**, *61*, 3677. (f) Laabs, S.; Münch, W.; Bats, J. W.; Nubbemeyer, U. *Tetrahedron* **2002**, *58*, 1317. (g) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911.

(4) (a) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363. (b) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764. (c) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835.

(5) (a) Braun, J. V. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 3914. (b) Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, *1989*, 1.

(6) Xu, H.-D.; Jia, Z.-H.; Xu, K.; Han, M.; Jiang, S.-N.; Cao, J.; Wang, J.-C.; Shen, M.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9284.

(7) Bhat, C.; Tilve, S. G. *Tetrahedron Lett.* **2011**, *52*, 6566.

(8) Jagadeesh, Y.; Reddy, K. K. S.; Rao, B. V. *Tetrahedron: Asymmetry* **2011**, *22*, 1485.

(9) Trost, B. M.; Miller, J. R.; Hoffman, C. M. *J. Am. Chem. Soc.* **2011**, *133*, 8165.

DOI: 10.1021/acs.orglett.5b02843
Org. Lett. 2016, 18, 889−891