Stereospecific Preparation of γ-Lactam Derivatives via Ring Expansion of *cis* and *trans* β-Lactam Derivatives: α-Substituent Effect of β-Lactam Derivatives

Mi-Ji Lee and Chuljin Ahn*

Department of Chemistry, Changwon National University, Changwon 641-773, Korea.
**E-mail: cjahn@cwnu.ac.kr*
Received March 26, 2015, Accepted December 3, 2015, Published online March 18, 2016

Keywords: β-Lactam derivatives, Ring expansion, γ-Lactam derivatives

The stereochemistry in γ-lactam has been a great importance in medicinal and synthetic chemistry due to a wide variety of biological activities.[1–4] The various substituted γ-lactam derivatives have been prepared stereospecifically via ring expansion from their corresponding β-lactam derivatives.[5–13] However, few examples have been reported about the effects of substituents on the α-position in β-lactam derivatives via ring expansion to lead γ-lactam derivatives stereospecifically. We herein have shown the effects of substituents on the α-position and stereochemistry in β-lactam derivatives **1a**, **1b**, **3a**, and **3b** via ring expansion to lead γ-lactam derivatives **2**, **4a**, **and 4b** (Schemes 1 and 2). In the case of aryl substituents such as phenyl and thiophenyl in β-lactam derivatives **1a**, **1b**, only one γ-lactam derivative **2** was obtained (Scheme 1).

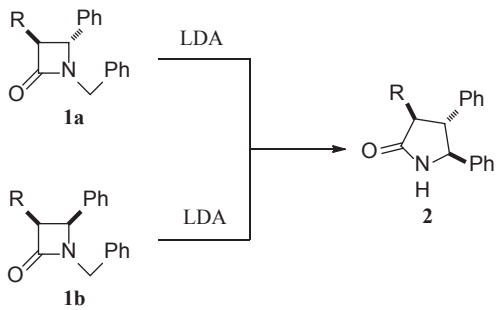
On the other hand, the γ-lactam derivatives **4a**, **4b** were obtained stereospecifically from the alkyl substituents such as methyl, and ethyl in β-lactam derivatives **3a**, **3b** (Scheme 2).

Two isomers of (3*S*,4*R*)-1-benzyl-3,4-diphenylazetidin-2-one (**7a**) in 57% yield and the (3*S*,4*S*)-1-benzyl-3,4-diphenylazetidin-2-one (**7b**) in 21% yield were prepared by treatment of *S*-pyridin-2-yl 2-phenylethanethioate (**5**) and (*E*)-*N*-benzylidene-1-phenylmethanamine (**6**) with $TiCl_4$ in triethyl amine at room temperature.

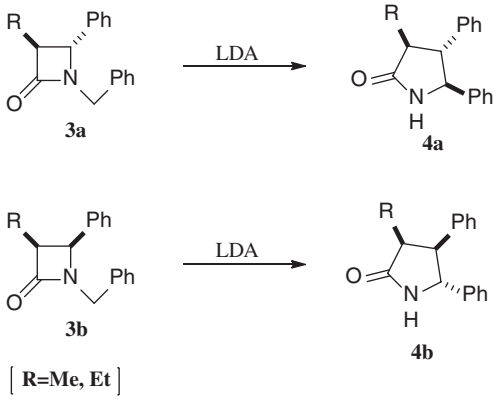
Each isomer of *trans* β-lactam **7a** and *cis* β-lactam **7b** was separated by column chromatography, respectively. The configurations of *trans* β-lactam **7a** and *cis* β-lactam **7b** were determined by ^{1}H NMR coupling constant, where the coupling constant of *cis* β-lactam is larger than that of *trans* β-lactam.[14] The coupling constant of *trans* β-lactam **7a** was 2.6 and the coupling constant of *cis* β-lactam **7b** was 5.4.

Furthermore, the *trans* isomer **7a** reacted with LDA in THF to obtain (3*R*,4*R*,5*S*)-3,4,5-triphenylpyrrolidin-2-one, (**8**) in 50% yield. In the same manner, the *cis* isomer (**7b**) provided the compound **8** in 35% yield. In the case of the Ph substituent on α-carbon of β-lactam derivatives, a single diastereomer **8** was obtained from *trans* β-lactam **7a** and *cis* β-lactam **7b** (Scheme 3). The stereochemistry of *anti*, *anti*-3,4,5-triphenyl-2-pyrolidine(**8**) was established by NMR techniques, particularly by vicinal proton coupling constant and NOE difference spectra.[12a]

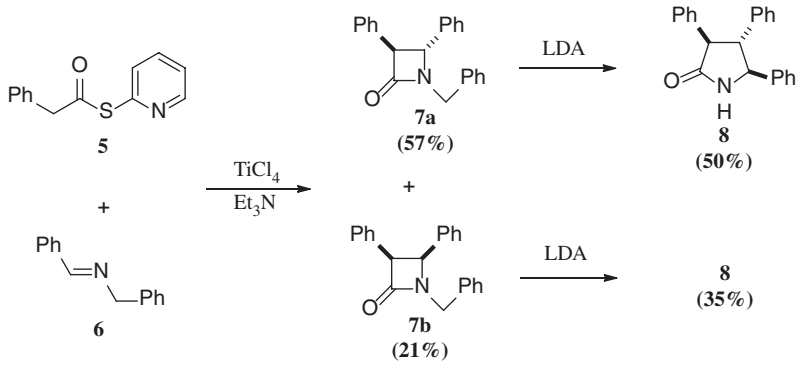
Scheme 4 illustrates *S*-pyridin-2-yl 2-(thiophen-2-yl)ethanethioate (**9**) reacted with imine **6** by treatment with $TiCl_4$ and triethyl amine to provide the mixtures of *trans* β-lactam **10a** in 20% and *cis* β-lactam **10b** in 17% yields.[14] Isolated (3*S*,4*R*)-1-benzyl-4-phenyl-3-(thiophen-2-yl)azetidin-2-one (**10a**) was treated under basic condition, LDA in THF to give (3*S*,4*R*,5*S*)-4,5-diphenyl-3-(thiophen-2-yl)pyrrolidin-2-one (**11**) in 53% yield. In the same manner, (3*S*,4*S*)-1-benzyl-4-phenyl-3-(thiophen-2-yl)azetidin-2-one (**10b**) yielded



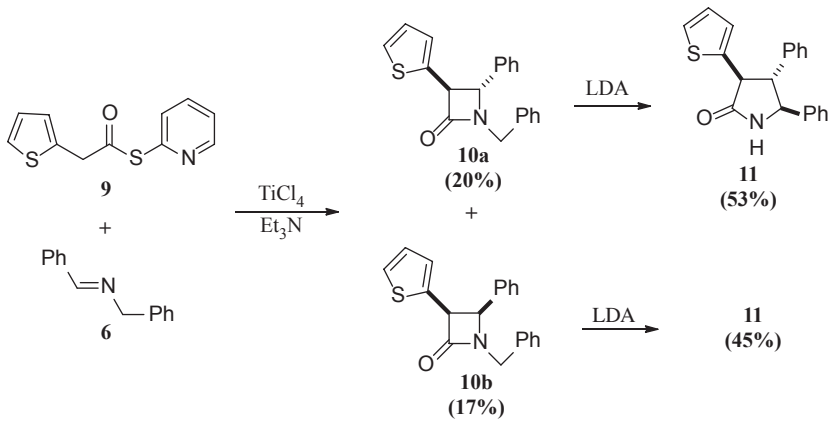
Scheme 1. The formation of γ-lactam derivatives **2**



Scheme 2. The formation of γ-lactam derivatives **4a, 4b**



Scheme 3. The formation of γ-lactam **8**



Scheme 4. The formation of γ-lactam **11**

45% of the *anti*, *anti* γ-lactam **11**. Surprisingly, in the case of thiophenyl substituent, only a single stereoisomer, *anti*, *anti* γ-lactam diastereomer **11** was observed. The structure of *anti*, *anti*-4,5-diphenyl-3-(thiophen-2-yl)pyrrolidin-2-one (**11**) was expected by vicinal proton coupling which was compared with compound **8**. In compound **8**, the coupling constant (*J*) of *anti*, *anti* vicinal protons (C2─C3, C3─C4) has large values, which are 8.4 and 11.6 Hz. The vicinal proton coupling constants of C2─C3 and C3─C4 in (3*S*,4*R*,5*S*)-4,5-diphenyl-3-(thiophen-2-yl)pyrrolidin-2-one (**11**) are 12.8 and 14.8 Hz which are large values. From these results, we expected the structure of γ-lactam **11** should have *anti*, *anti* relationship with one another.[12a]

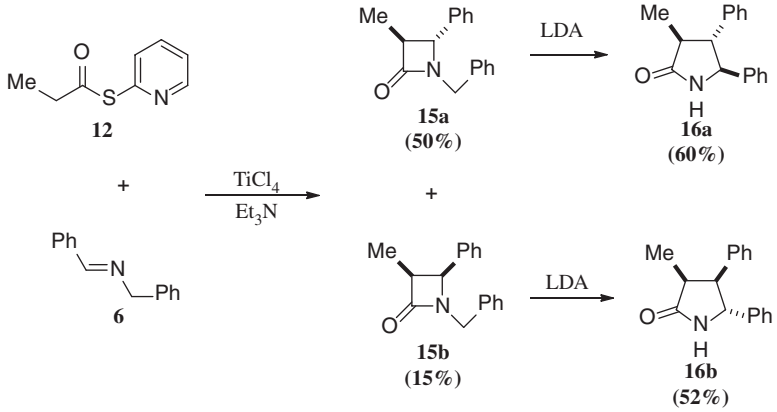
Scheme 5 illustrates *S*-pyridin-2-yl propanethioate (**12**) reacted with (*E*)-*N*-benzylidene-1-phenylmethanamine (**6**) by treatment with $TiCl_4$ in triethyl amine to provide the mixtures of *trans* β-lactam **15a** in 50% and *cis* β-lactam **15b** in 15% yield.[14] Under the LDA in THF condition, *trans* β-lactam **15a** leads to *anti*, *anti* γ-lactam **16a** in 60% yield, and *cis* β-lactam **15b** leads to *syn*, *anti* γ-lactam **16b** in 52% yield. Unlike phenyl or thiophenyl substituents, methyl substituent on the α-carbon in the *trans* β-lactam **15a** generated the *anti*, *anti* γ-lactam **16a**, and *cis* β-lactam **15b**, which gave the *syn*, *anti* γ-lactam **16b**. The structure of *anti*, *anti* and *syn*, *anti* relationships in γ-lactams (**16a**, J = 10.5, 8.4 Hz and **16b**, J = 9.0, 6.0 Hz) was established based on a relative vicinal coupling constant determining stereochemistry of γ-lactam **8**.[12a]

Scheme 6 illustrates *S*-pyridin-2-yl propanethioate (**17**) reacted with (*E*)-N-benzylidene-1-phenylmethanamine (**6**) by treatment with $TiCl_4$ in triethyl amine to provide the mixtures of *trans* β-lactam **18a** in 52% and *cis* β-lactam **18b** in 21% yield.[14] Under the LDA in THF condition, *trans* β-lactam **18a** leads to *anti*, *anti* γ-lactam **19a** in 74% yield, and *cis* β-lactam **18b** leads to *syn*, *anti* γ-lactam **19b** in 42% yield. Unlike phenyl or thiophenyl substituent, the ethyl substituent on the α-carbon in *trans* β-lactam **18a** generated the *anti*, *anti* γ-lactam **19a**, and *cis* β-lactam **18b** gave the *syn*, *anti* γ-lactam **19b**. The structures of *anti*, *anti* and *syn*, *anti* relationships in γ-lactams (**19a**, J = 9.0, 4.2 Hz and **19b**, J = 3.0, 3.0 Hz) were established based on a relative vicinal coupling constant determining stereochemistry of γ-lactam **8**.[12a]

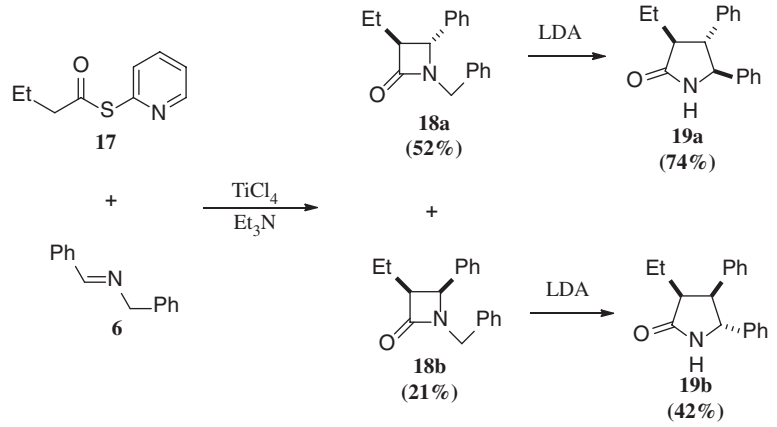
Further studies are underway to prove the mechanism in forming the γ-lactam derivatives stereospecifically from *cis* and *trans* β-lactam derivatives via ring expansion.

Experimental

General. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Brucker Avance 400 spectrometer. Chemical shifts are reported in parts per million (δ)



Scheme 5. The formation of γ-lactam **16a, 16b**



Scheme 6. The formation of γ-lactam **19a, 19b**

downfield from tetramethylsilane. Coupling constant (*J* values) are given in hertz (Hz).

Infrared spectra were recorded on a Jasco FT/IR-6300 spectrometer. Band positions are given in reciprocal centimeters (cm^{-1}) and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak).

General Procedure for Preparation of γ-Lactam Derivatives. LDA (1.5 M in cyclohexane, 1.5 equiv) was added at room temperature to a solution containing β-lactam derivatives **7a**, **7b**, **10a**, **10b**, **15a**, **15b**, **18a**, **18b** (1 equiv) in THF. The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aq. NH_4Cl. The reaction mixture was extracted with EtOAc after evaporating THF in the rotavapor. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo* to give crude solid. Purification by flash chromatography (80% EtOAc/hexane) for γ-lactam derivatives **8**, **11**, **16a**, **16b**, **19a**, **19b**.

(3*R*,4*R*,5*S*)-3,4,5-Triphenyl-2-pyrrolidinone (8): IR (KBr): 3170 (m), 3080 (m), 3027 (w), 2915 (m), 2380 (m), 1702 (s), 1432 (w); ^{1}H NMR ($CDCl_3$): δ 3.37 (dd, *J* = 8.5 Hz, 14.6, 1H), 4.04 (d, *J* = 14.6 Hz, 1H), 4.75 (d, *J* = 8.5 Hz, 1H), 6.16–7.38 (m, 15H); ^{13}C NMR ($CDCl_3$): 56.0, 61.4, 63.6, 111.7, 129.1, 127.3, 127.5, 128.0, 128.3, 128.5, 128.7, 128.8, 137.0, 137.6, 139.6, 176.1.

(3*S*,4*R*,5*S*)-4,5-Diphenyl-3-(thiophen-2-yl)pyrrolidin-2-one (11): IR (ATR) : 3235 (w), 2900 (w), 1662 (s); ^{1}H NMR ($CDCl_3$) : 1.25 (bs,1H), 3.35 (d, *J* = 14.8 Hz, 1H), 3.69 (dd, *J* = 12.8, 14.8 Hz, 1H), 4.45 (d, *J* = 12.8 Hz, 1H), 5.94–6.92 (m, 3H), 7.26–7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) : 32.26, 47.45, 57.15, 121.16, 127.44, 128.12, 128.43, 128.57, 128.69, 128.90, 129.35, 137.18, 137.44, 138.64, 140.62, 175.01.

(3*S*,4*R*,5*S*)-3-Methyl-4,5-diphenyl-2-pyrrolidinone (16a): IR (KBr): 3045 (w), 2915 (w), 2800 (m), 1702 (s), 1586 (w), 1486 (w), 1430 (m); ^{1}H NMR ($CDCl_3$): δ 1.20 (d, *J* = 5.1 Hz, 3H), 2.81 (m, 1H), 2.8 (dd, 1H, *J* = 8.4, 10.5 Hz), 4.6 (d, 1H, *J* = 8.4 Hz), 5.9 (s, 1H), 7.08–7.33 (m, 10H); ^{13}C NMR: 13.9, 44.4, 60.8, 63.8, 126.1, 127.4, 128.0, 128.1, 128.7, 128.8, 138.3, 140.0, 178.4.

(3*R*,4*R*,5*S*)-3-Methyl-4,5-diphenyl-2-pyrrolidinone (16b): IR (KBr): 3055 (w), 2915 (w), 2800 (m), 1702 (s), 1586 (w), 1486 (w), 1430 (m); ^{1}H NMR ($CDCl_3$): δ 0.86 (d, *J* = 7.5 Hz, 3H), 2.88 (m, 1H), 3.51 (dd, *J* = 4.2, 9.0 Hz, 1H), 4.95 (d, *J* = 4.2 Hz, 1H), 6.26 (s, 1H), 7.12–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$): 11.7, 39.7, 54.7, 61.7, 125.6, 127.2, 127.9, 128.2, 128.6, 128.8, 139.0, 141.4, 180.1.

(3*S*,4*R*,5*S*)-3-Ethyl-4,5-diphenyl-2-pyrrolidinone (19a): IR (KBr): 3177 (w), 3091 (w), 2913 (w), 2864 (w), 1713 (s),

1594 (m); ^{1}H NMR ($CDCl_3$): δ 0.86 (t, J = 9.0 Hz, 3H), 1.63–1.77 (m, 2H), 2.75 (m, 1H), 3.0 (dd, J = 6.0, 9.0 Hz, 1H), 4.59 (d, J = 6.0 Hz, 1H), 6.01 (s, 1H), 7.08–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$): 10.9, 22.3, 50.1, 57.5, 64.2, 125.5, 126.0, 127.3, 128.0, 128.1, 128.7, 139.5, 140.4, 178.0.

(3*R*,4*R*,5*S*)-3-Ethyl-4,5-diphenyl-2-pyrrolidinone (19b): IR (KBr): 3192 (w), 3085 (w), 2961 (w), 2870 (w), 1707 (s), 1600 (m); ^{1}H NMR ($CDCl_3$): δ 0.76 (t, J = 9.0 Hz, 3H), 1.07–1.62 (m, 2H), 2.67 (m, 1H), 3.52 (dd, J = 3.0, 3.0 Hz, 1H), 4.85 (d, J = 3.0 Hz, 1H), 6.17 (s, 1H), 7.10–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$): 12.1, 19.4, 45.8, 54.1, 62.3, 125.5, 127.3, 127.9, 128.1, 128.6, 128.9, 139.5, 141.5, 179.2.

Acknowledgments. This work is financially supported by Changwon National University in 2015–2017.

References

1. P. A. Wright, R. C. Wilmouth, I. J. Clifton, C. J. Schofield, *Biochem. J.* **2000**, *351*, 335.
2. R. Yao, H. Osada, *Exp. Cell Res.* **1997**, *234*, 233.
3. G. K. Kar, B. C. Roy, S. D. Adhikari, J. K. Ray, N. K. Brahma, *Bioorg. Med. Chem. Lett.* **1998**, *6*, 2397.
4. J. J.-W. Duran, Z. Lu, C.-B. Xue, X. He, J. L. Seng, J. J. Roderick, Z. R. Wasserman, R.-Q. Liu, M. B. Covington, R. L. Magolda, R. C. Newton, J. M. Trzaskos, C. P. Decicco, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2035.
5. M. Jayaraman, V. G. Puranik, B. M. Bhawal, *Tetrahedron* **1996**, *52*, 9005.
6. D.-C. Ha, S. Kang, C.-M. Chung, H.-K. Lim, *Tetrahedron Lett.* **1998**, *39*, 7541.
7. J. Escalante, M. A. Gonzalez-Tototzin, *Tetrahedron: Asymmetry* **2003**, *14*, 981.
8. J. Anaya, A. Fernandez-Mateos, M. Grande, J. Martianez, G. Ruano, R. Rubio-Gonzalez, *Tetrahedron* **2003**, *59*, 241.
9. B. Alcaide, P. Almendros, J. M. Alonso, *J. Org. Chem.* **2004**, *69*, 993.
10. W. Van Brabandt, N. De Kimpe, *J. Org. Chem.* **2005**, *70*, 8717.
11. W. Van Brabandt, N. De Kimpe, *J. Org. Chem.* **2005**, *70*, 3369.
12. (a) C. Ahn, J.-H. Park, S.-J. Oh, J.-A. Kim, D.-S. Shin, T.-J. Won, Y.-F. Lam, *Tetrahedron Lett.* **2005**, *46*, 1755; (b) C. Ahn, D.-S. Shin, J.-H. Park, *J. Korean Chem. Soc.* **1999**, *43*(4), 489.
13. S. Dekeukeleire, M. D'hooghe, N. De Kimpe, *J. Org. Chem.* **2009**, *74*, 1644.
14. B. Alcaide, P. Almendros, N. R. Salgado, A. Rodrı'guez-Vicente, *J. Org. Chem.* **2005**, *65*, 4453.

