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Tetrahedron Letters 46 (2005) 1755–1757
Tetrahedron Letters

The stereoselective synthesis of γ-lactam derivatives through N(1)–C(4) one carbon ring expansion of β-lactam derivatives

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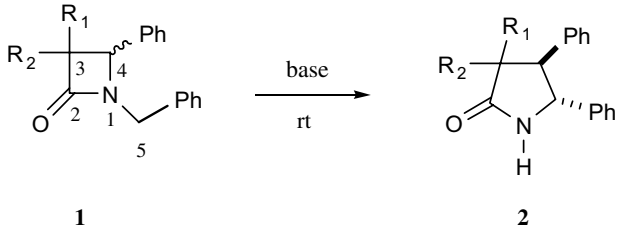
Received 27 July 2004; revised 4 October 2004; accepted 20 December 2004

This paper is dedicated to the memory of Professor Suk-Ku Kong

Abstract—The base induced ring opening of β-lactam derivatives, **3**, **5**, **7**, **9**, **11** with LDA gave γ-lactam derivatives, **4**, **6**, **8**, **10**, **12** stereoselectively. The γ-lactam derivatives were formed stereoselectively depending on C-3 substituent of β-lactam derivatives.

The general methods to prepare monocyclic γ-lactams through one-carbon ring expansion of β-lactams have been shown[1] powerful synthetic tools. These reactions frequently involve strained nitrogen rings in which the strain release acts as a driving force for the enlargement. The general methods of ring expansion in β-lactam derivatives have been known as the cleavage of the C(2)–C(3) bond,[1a] N(1)–C(4) bond[1b] or N(1)–C(2)[1c] in β-lactam derivatives. Recently, we have found that γ-lactam derivatives **2** were prepared from β-lactam derivatives **1** through the N(1)–C(4) cleavage and C(5) carbon insertion with lithium diisopropylamide (LDA), and the stereochemistry on C-4 and C-5 in γ-lactam derivatives **2** was controlled by the substituents on C-3 in β-lactam derivatives **1**. NOE experiments indicated the relative stereochemistry of C-3, C-4, and C-5 in the γ-lactam derivatives **2** (Scheme 1).



1 **2**

Scheme 1.

2-Azetidinones, **3**, **5** as starting substrates, were prepared from imines and ketene derived from acid chloride.[3] Treatment of 1-benzyl-3,3,4-triphenyl-2-azetidinone (**3**) and 1-benzyl-3,3-methyl-4-phenyl-2-azetidinone (**5**), which has no stereogenic center at C(3) with lithium diisopropylamide (LDA) gives the corresponding 3,3,4,5-tertraphenyl-2-pyrrolidinone (**4**)[7a] and 3,3-dimethyl-4,5-diphenyl-2-pyrrolidinone (**6**)[7b] in good yield. From our proposed mechanism,[2a] our results could be explained the ring expansion through N(1)–C(4) bond cleavage process on the four-membered lactam ring and then recyclization. The stereochemistry of the ring expansion reaction is depend on the substituents at C(3) of the starting β-lactam derivatives, **3**, **5**. In the case of the two phenyl or two methyl substituents, the *anti* relationship stereochemistry at C(4) and C(5) in γ-lactam derivatives, **4**, **6**, were obtained as a single diastereomer. *syn* Relationship stereochemistry at C(4) and C(5) in γ-lactam derivatives does not observed. The bulkyness of two phenyl or two methyl substituents at C3 on β-lactam ring may control the stereochemistry to get γ-lactam with high diastereoselectivity. The structure of stereochemistry was tentatively assigned by relative stability of each compounds (Scheme 2).

Starting substrate, spiro β-lactam **7** was prepared from imines and acid chloride in the presence of Et_3N.[4]

Keyword: Ring expansion.
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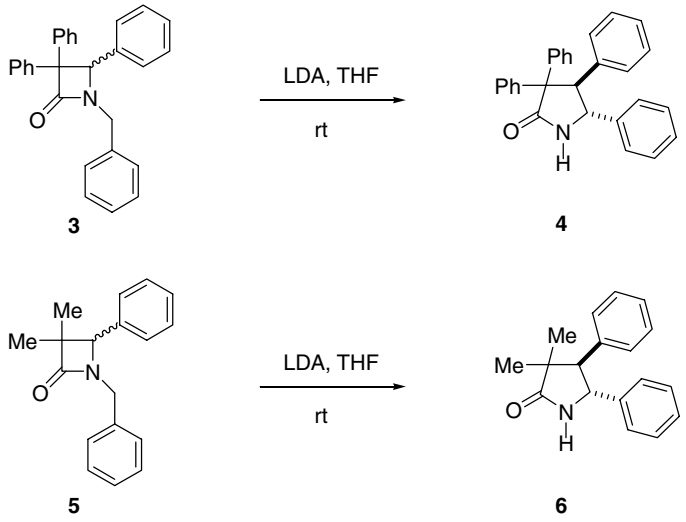
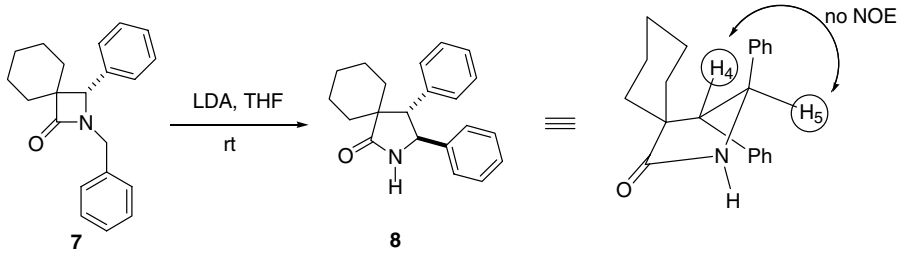
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.12.086



Scheme 2. Product **4** (65%), product **6** (67%).



Scheme 3. Product **8** (63%).

2-Benzyl-3-phenyl-2-aza-spiro[3,5]nonan-1-one (**7**), which has cyclohexyl group substituent at C(3), was treated with LDA at room temperature to get the *trans*-3,4-diphenyl-2-aza-spiro[4,5]decan-1-one (**8**)[7c] as a single diastereomer (Scheme 3).

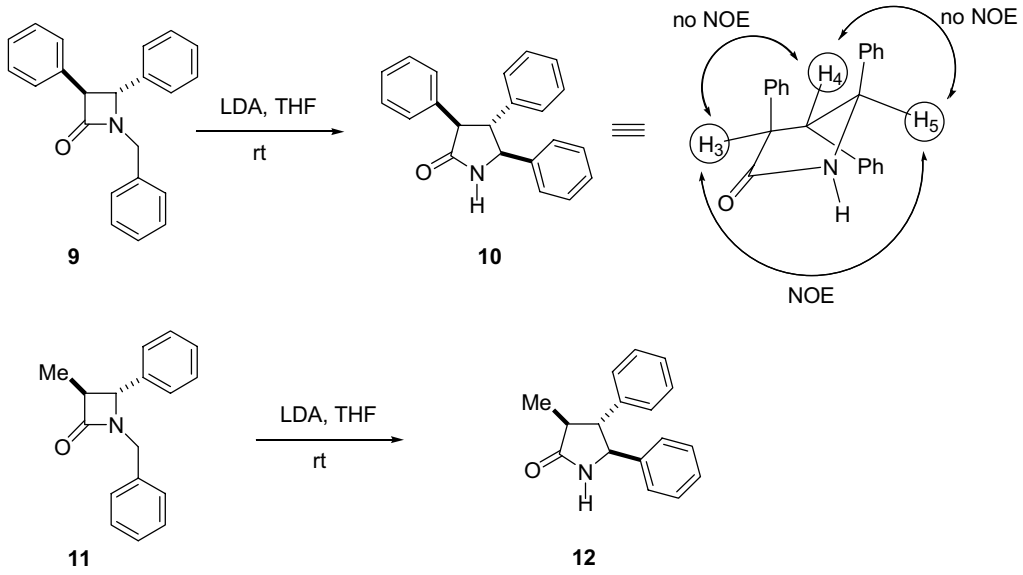
The stereochemistry of the *trans*-3,4-diphenyl-2-aza-spiro[4,5]decan-1-one (**8**) was determined by NOE difference spectra.[6] The coupling constant of H_4 and H_5 in γ-lactam derivative **8** is 12 Hz, which has relatively large value which two protons have close to 0° or 180° by Karplus equation. If two protons have close to 0°, the NOE between two protons have effect, but two protons have close to 180°, the NOE between two protons have no effect. No NOE effect was observed between H_4 and H_5 by our NOE experiment. Thus, an *anti* relative stereochemistry of these two protons was assigned for compound **8**.

In the case of two stereogenic center in β-lactam derivatives, **9**, **11**, the bulky group on the α-position in β-lactam would control the β-, γ-stereogenic center in the recyclization step to forming the γ-lactam derivatives.

trans-1-Benzyl-3,4-diphenyl-2-azetidinone (**9**) and *trans*-1-benzyl-3-methyl-4-phenyl-2-azetidinone (**11**), which have two stereogenic center (C-3 and C-4) were prepared.[3] The assignment of the *trans*-stereochemistry of β-lactam derivatives **9**, **11** was based on the observed coupling constants between H_3 and H_4, which has 2.6 Hz in *trans*-β-lactam and 5.6 Hz in *cis*-β-lactam, comparing with the literature values revealed.[5] Formation of *anti*,*anti*-3,4,5-triphenyl-2-pyrrolidione (**10**)[7d] and *anti*,*anti*-3-methyl-4,5-diphenyl-2-pyrrolidione (**12**),[7e] which have three stereogenic centers, is accomplished by treatment of *trans*-β-lactam derivatives **9**, **11** with LDA in THF at rt (Scheme 4).

β-Lactam derivatives **9**, **11** underwent ring expansion to provide one diastereomer **10**, **12** with high diastereoselectivity. The formation of one diastereomer was anticipated that bulky phenyl or methyl group on C-3 in β-lactam derivatives would control the stereogenic center at C-4 and C-5 in γ-lactam derivatives, **10**, **12** during the recyclization.

The stereochemistry of the *anti*,*anti*-3,4,5-triphenyl-2-pyrrolidione (**10**) was established by NMR techniques, particularly by vicinal proton coupling and NOE difference spectra. The coupling constant of H_3 and H_4 in γ-lactam derivative **10** is 9 Hz, which has relatively large value. By our NOE experiment results, the significant NOE effect on H_3 and no NOE effect on H_4 were observed upon irradiation on H_5. NOE irradiation of H_3 resulted in significant NOE effect on H_5 and no NOE effect on H_4. No NOE effect was observed on H_3 and H_5 upon irradiation on H_4. Thus, an *anti*,*anti* relative stereochemistry was assigned for 3,4,5-triphenyl-2-pyrrolidione (**10**).



Scheme 4. Product **10** (72%), product **12** (71%).

Further studies were underway to prove the mechanism of the formation of γ-lactam derivatives from β-lactam derivatives and the electronic or steric effect of C(5) substituents in β-lactam derivatives.

Acknowledgements

This Research is financially supported by Kyung Sang Nam Do in 2003 and Changwon National University in 2002. The author thanks Professor Philip DeShong for his stimulating discussion.

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7. *General experimental*: The solution of β-lactam (1.0 equiv) in THF was treated with LDA (1.2 equiv) at rt. After 5 h, the reaction mixture was added water and extracted with EtOAc. (a) *γ-Lactam* **4**: IR (KBr, cm^{-1}): 3242(m), 3066(w), 1930(w), 1890(w), 1691(s), 1442(m), 639(s). ^1H NMR (200 MHz, $CDCl_3$): 7.48 (br s, 1H), 6.69–7.15 (m, 20H), 5.62 (d, $J = 8.5$, 1H), 4.85 (d, $J = 8.5$, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 177.8, 142.5, 142.4, 138.1, 134.7, 130.3, 129.9, 129.4, 127.8, 127.6, 127.4, 127.3, 127.2, 126.8, 126.6, 126.5, 77.2, 64.6, 63.5, 55.7;
(b) *γ-Lactam* **6**: IR (KBr, cm^{-1}): 3198(m), 3096(m), 2965(w), 2900(w), 2380(w), 1707(s), 1600(w), 1500(m), 1460(m). ^1H NMR (300 MHz, $CDCl_3$): 7.29 (m, 10H), 6.36 (br s, 1H), 5.02 (d, $J = 9.9$, 1H), 3.15 (d, $J = 9.9$, 1H), 1.2 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 181.3, 140.3, 135.3, 129.2, 128.6, 128.2, 127.9, 127.3, 126.1, 63.2, 58.8, 45.3, 23.5, 20.6;
(c) *γ-Lactam* **8**: IR (KBr, cm^{-1}): 3433(m), 3029(w), 2929(m), 2857(m), 1707(s), 1550(s), 1459(m). ^1H NMR (400 MHz, $CDCl_3$): 7.18–7.30 (m, 10H), 6.01 (s, 1H), 4.97 (d, $J = 12.0$, 1H), 3.11 (d, $J = 12.0$, 1H), 1.04–2.15 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): 181.1, 141.2, 136.7, 129.7, 128.7, 128.2, 127.8, 127.3, 125.8, 63.6, 59.7, 47.0, 34.0, 29.8, 25.3, 21.8, 21.3;
(d) *γ-Lactam* **10**: IR (KBr, cm^{-1}): 3170(m), 3080(m), 3027(w), 2915(m), 2380(m), 1702(s), 1432(w). ^1H NMR (400 MHz, $CDCl_3$): 6.16–7.38 (m, 15H), 4.75 (d, $J = 8.8$, 1H), 4.04 (d, $J = 11.6$, 1H), 3.37 (dd, $J = 8.8, 11.6$, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.6, 140.1, 138.1, 137.7, 129.2, 129.1, 129.1, 128.9, 128.7, 128.4, 127.9, 127.7, 126.5, 64.0, 61.8, 56.5;
(e) *γ-Lactam* **12**: IR (KBr, cm^{-1}): 3045(w), 2915(w), 2800(m), 1702(s), 1586(w), 1486(w), 1430(m). ^1H NMR (300 MHz, $CDCl_3$): 7.08–7.33 (m, 10H), 5.9 (s, 1H), 4.6 (d, $J = 8.4$, 1H), 2.88 (dd, $J = 8.4, 5.1$, 1H), 2.81 (m, 1H), 1.20 (d, $J = 5.1$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 178.4, 140.0, 138.3, 128.8, 128.7, 128.1, 128.0, 127.4, 126.1, 63.8, 60.8, 44.4, 13.9.