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단 신

β-락탐으로부터 γ-락탐의 합성: 고리확장에 대한 연구

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One Carbon Ring Expansion in γ-Lactam from β-Lactam

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The lactam ring expansion reactions are important for the preparation of functionalized five- and six-membered N-heterocyclic compounds.[1] For the specific case, the 1-benzyl-4-phenyl-2-azetidinone transformed to the *trans*- and *cis*-4,5-diphenylpyrrolidine-2-ones stereoselectively through the 5-endo electrophilic cyclization.

As a part of study of the hydroxylation of the 1-benzyl-4-phenyl-2-azetidinone (**1**)[2] in α-position, we attempted the preparation of 1-benzyl-3-hydroxy-4-phenyl-2-azetidinone (**4**) by reaction of 1-benzyl-4-phenyl-2-azetidinone (**1**) with LDA in THF solution at 0 °C and addition of (+)-(2S, 8aR)-(camphoryl sufonyl) oxaziridine (**3**) in THF.[3] Instead of the desired product, we obtained 4,5-diphenylpyrrolidin-2-ones (**5a**) and (**5b**) in virtually quantitative yield. Suspecting that oxidation does not effect this reaction, we carried out this reaction without oxaziridine **3** at room temperature. Rearrangement of 1-benzyl-4-phenyl-2-azetidinone (**1**) at room temperature yielded the 4,5-diphenylpyrrolidin-2-ones (**5a**) and (**5b**) in a 4:1 ratio (*Scheme* 1).

The cleavage and recombination process yielded different ratios of *trans* and *cis* 4,5-diphenylpyrrolidin-2-ones (**5a** and **5b**) depending on reaction temperature. As for the mechanism, we propose that the the β-lactam anion **6** should be generated from 1-benzyl-4-phenyl-2-azetidinone (**1**) with LDA at room temperature and the anion **6** rearrange to give imine anion **7** to release the ring strain of 4-membered ring in equilibrium. A Michael type reaction for the ring closure of imine anion **7** would give the more stable *trans* 4,5-diphenylpyrrolidin-2-one (**5a**) as a major product, of which structure was tentatively assigned by relative stability of each compounds (*Scheme* 2).

Further studies are underway to probe the mechanism of the formation of γ-lactam **5** from β-lactam **1** and to exploit the reaction to prepare δ-lactam derivatives of chemotherapeutic value.

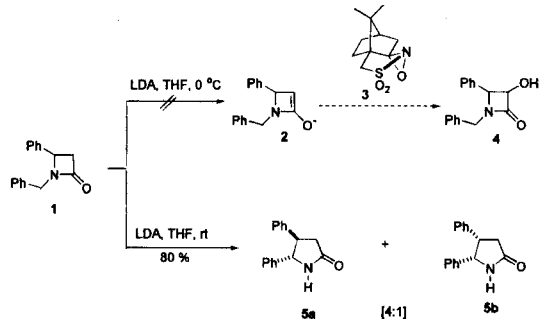
EXPERIMENTAL

General. Melting points were taken in Kimex soft-glass capillary tubes using a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406 K) and are corrected.

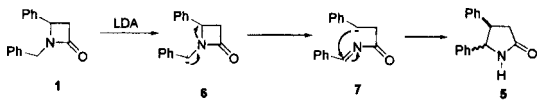
Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on either Brüer AF-200 or AM-400 spectrometers.Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Coupling constants (J values) are given in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Deuterated NMR solvents contained 99.0-99.8% deuterium in the indicated position.

Infrared spectra were recorded on a Nicolet 5DXC FT-IR spectrophotometer. Band positions are given in reciprocal centimeters (cm^{-1}) and relative intensities are listed as: br (broad), s (strong), m (medium), or w (weak).

Thin layer chromatography (tlc) was performed on 0.25 mm Merck silica-coated glass plates, with the compounds being identified in one or more of the



Scheme 1.



Scheme 2.

following manners: UV (254 nm, unless otherwise specified), iodine, sulfuric acid, or vanillin/sulfuric acid charring. Flash chromatography was performed according to the procedure of Still[6] using thick-walled glass columns and Merck Silica Gel 60 (230-400 Mesh). All solvents were distilled from calcium chloride before use unless noted otherwise. Tetrahydrofuran (THF), diethyl ether (Et_2O), and hexanes were distilled from sodium/benzophenone ketyl. All reagents were distilled, recrystallized, or chromatographed prior to use unless otherwise noted.

Glassware used in the reactions described below was dried in an oven at 120 °C overnight (12 hours) and assembled under an inert atmosphere of nitrogen, or flame-dried under vacuum and then cooled under nitrogen.

4,5-Diphenylpyrrolidin-2-one (5). LDA (1.5 M in cyclohexane, 0.05 mL, 0.076 mmol) was added at room temperature to a solution containing 1-benzyl-4-phenyl-2-azetidinone (**1**) (12 mg, 0.05 mmol) in THF (3 mL). The reaction mixture was stirred at room temperature for 1 h and quenched with saturated aq. NH_4Cl (3 mL). The reaction mixture was extracted with EtOAc (3×10 mL) after evaporation of THF in the rotavapor. The organic layer was dried (Na_2SO_4), and concentrated in vacuo to give a crude solid. Purification by flash chromatography (80% EtOAc/hexane) afforded 10 mg (83%) of a diastereomeric mixture of major *trans* 4,5-diphenylpyrrolidin-2-one (**5a**) and minor cis 4,5-diphenylpyrrolidin-2-one (**5b**) as a white solid of 4:1 ratio. A 4:1 ratio of these was determined by ^1H NMR: major *trans* 4,5-diphenylpyrrolidin-2-one (**5a**): Rf 0.36, 80% EtOAc/hexane; mp 198-200 °C; IR (CCl_4): 3431 (m), 1703 (vs), 1443 (m), 1398 (m), 1353 (m), 905 (s); ^1H NMR ($CDCl_3$): 2.69 (dd, A of ABX, 1 H, J=17.1, 9.7 Hz), 2.87 (dd, B of ABX, 1 H, J=17.1, 8.8 Hz), 3.37 (ddd, 1 H, J =9.7, 8.8, 7.4 Hz), 4.67 (d, 1 H, J=7.4 Hz), 6.03 (br s, 1 H), 7.03-7.34 (m, 10 H); ^{13}C NMR ($CDCl_3$): 14.2, 38.4, 51.3, 125.9, 127.4, 128.2, 128.2, 128.9, 176.5; mass spectrum, m/z (relative intensity, %): 237 (M^+, 62), 209 (2), 194 (1), 178 (2), 165 (2), 152 (1), 130 (2), 104 (100), 91 (3), 77 (13). Minor *cis* 4,5-diphenylpyrrolidin-2-one (**5b**): Rf 0.35 80% EtOAC/hexane; IR (CCl_4): 3431 (m), 1703 (vs), 1443 (m), 1398 (m), 1353 (m), 905 (s); ^1H NMR ($CDCl_3$): 2.68 (dd, A of ABX, 1 H, J=17.1, 9.7 Hz), 2.86 (dd, B of ABX 1 H, J=17.1, 8.8 Hz), 4.03 (ddd, 1 H, J =9.7, 8.8, 7.5 Hz), 5.01 (d, 1 H, J=7.5 Hz), 5.96 (br s, 1 H), 7.03-7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$): 21.0, 60.4, 66.0, 125.9, 127.4, 128.3, 128.9, 166.3.

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