4-SUBSTITUTED AZETIDINONES AS INTERMEDIATES FOR CARBAPENEM SYNTHESIS

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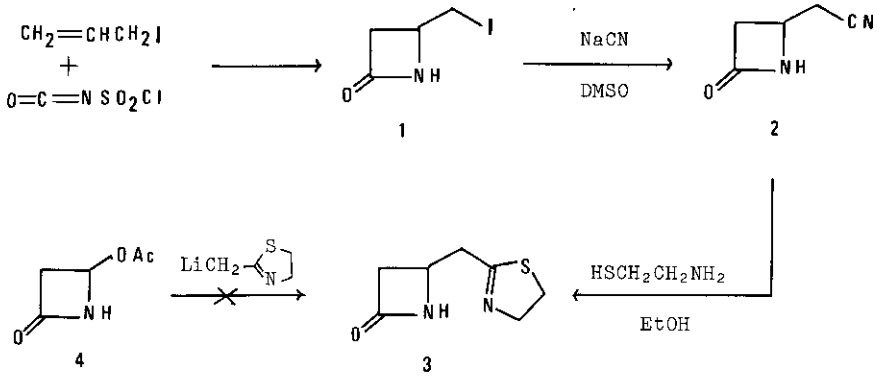
Abstract —— 4-Iodomethylazetidin-2-one(1) was prepared by [2+2]cycloaddition reaction of allyl iodide with chlorosulfonyl isocyanate and utilized for the synthesis of 4-(thiazolin-2-yl)methylazetidin-2-one(3).

The unique structure and wide antibacterial spectrum of thienamycin has aroused a great deal of interest in carbapenem and penem derivatives leading to the establishment of various methods for constructing the skeletons. Our initial interest was directed toward the finding of novel synthetic methods for preparing a wide variety of penem compounds.[1] The present work is concerned with 4-substituted azetidin-2-one derivatives, 4-iodomethyl- and 4-(thiazolin-2-yl)-methylazetidin-2-one(1 and 3), useful for the synthesis of carbapenem or related compounds. A thiazoline-substituted azetidinone has already been described by Kametani and coworkers[2] as a possible intermediate for the preparation of the thienamycin derivatives. In spite of its potential usefulness, there is no literature on the synthesis of such azetidinone derivatives. We report herein the synthesis of 3, along with a convenient one-step synthesis of 4-iodomethyl-azetidin-2-one(1).

The desired compound 3 seemed to be obtainable from 4-acetoxyazetidin-2-one(4) and lithiated 2-methylthiazoline,[3] but our attempt to do so was unsuccessful as previously described.[2] The azetidinone derivative(3) was eventually produced in two steps starting from the iodomethylazetidinone(1). The starting material 1 has been prepared by two different methods involving multi-step reactions starting from L-aspartic acid[4] and butadiene,[5] respectively. We have found that the iodomethyl compound(1) could be conveniently prepared in a one-pot reaction from allyl iodide and chlorosulfonyl isocyanate. The cycloaddition reaction proceeded on standing chlorosulfonyl isocyanate in excess allyl iodide at room temperature over a long period of time. The yield

based on chlorosulfonyl isocyanate was 37.5%, when the mixture was allowed to react for one week. It is noteworthy that 4-bromomethyl-, 4-chloromethyl-, and 4-cyanomethylazetidin-2-one could not be obtained by the reactions of allyl bromide, allyl chloride and allyl cyanide with chlorosulfonyl isocyanate under the same conditions. This type of cycloaddition reaction is likely significantly retarded by the electron-withdrawing property of the substituent at the allylic position. The iodine atom of 1 was displaced by the cyano group on warming a



mixture of 1 and sodium cyanide in dimethyl sulfoxide at 50°C. The cyano compound(2) was converted into the thiazoline derivative 2 in low yield by treating with cysteamine in ethanol at 85°C. The thiazoline structure was assigned by the analytical and spectral data described in the Experimental.

The synthetic utility of 1 has already been demonstrated in the synthesis of thienamycin.[4] We will utilize the potentially important compound 3 for carbapenem synthesis.

EXPERIMENTAL

Melting points are uncorrected. Solutions were concentrated below 30° with rotary evaporators under reduced pressure. The silica gel plates used for preparative thick layer chromatography were obtained from E. Merck, Darmstadt, West Germany. NMR spectra were recorded on a Varian A-60, a Hitachi R-24 or a Varian HA-100 spectrometer and signals are given in δ units downfield from

tetramethylsilane as an internal standard. IR spectra were measured on a Nihon-Bunko Jasco IR-A. A Nihon-Denshi JMS-01-SG spectrometer was used to obtain mass spectra.

4-Iodomethylazetidin-2-one(1)----- Allyl iodide(71 g, 423 mmol) was added to chlorosulfonyl isocyanate(40.6 g, 287 mmol) with stirring at -40° and the mixture was allowed to stand in darkness for a week. The reaction mixture was poured into a vigorously stirred mixture of Na_2SO_3(52.9 g) and $NaHCO_3$ (67.9 g) in ice-water(200 ml). AcOEt was added and the mixture was stirred for 30 min with ice-cooling. The organic layer was separated and the aq. layer was extracted with AcOEt four times. The AcOEt extracts were combined, dried over Na_2SO_4, and the solvent was evaporated. Chromatography of the residue on Merck silica gel with $CHCl_3$-MeOH= 9:1 afforded 1(22.7 g, 37.5%). A sample was recrystallized from AcOEt. mp 106-106.5°. Anal. Calcd for C_4H_6NOI: C, 22.76; H, 2.86; N, 6.63, I, 60.14. Found: C, 22.77; H, 2.89; N, 6.50; I, 59.89. MS m/e: 211(M^+), 168(base peak), 142, 141, 127, 85, 70. IR(Nujol): 3300, 1763, 1720 cm^{-1}. NMR($CDCl_3$)δ: 2.72 (1H, ddd, J=15.0, 2.5, 1.5 Hz, 3-H), 3.14(1H, ddd, J=15.0, 5.0, 2.0 Hz, 3-H), 3.38(2H, d, J=6.5 Hz, CH_2I), 3.70-4.10(1H, m, 4-H), 6.90(1H, b, NH).

4-Cyanomethylazetidin-2-one(2)----- Powdered NaCN(171 mg) was added to a solution of 1(670 mg) in DMSO(6 ml) and the mixture was stirred for 2 hr at 50°. The reaction mixture was diluted with AcOEt, the precipitate was removed by filtration, and the filtrate was concentrated. The residue was chromatographed on a column of silica gel eluting with AcOEt to give 2(169 mg, 48.4%) as an oil, which was crystallized as colorless needles, mp 51.0-51.5°, from AcOEt-hexane. Anal. Calcd for $C_5H_6N_2O$: C, 54.53; H, 5.49; N, 25.44. Found: C, 54.72; H, 5.58; N, 25.60. MS m/e. 111(M^+), 84, 67, 52, 42. IR($CHCl_3$): 3410(NH), 2240(CN), 1770 cm^{-1}(β-lactam). NMR($CDCl_3$)δ: 2.78(2H, d, J=5.5 Hz, CH_2CN), 3.24(1H, ddd, J=15.0, 5.0, 2.0 Hz, 3-H), 2.86(1H, ddd-like, J=15.0 Hz, 3-H), 4.03(1H, m, 4-H), 6.92(1H, m, NH).

4-(Thiazolin-2-yl)methylazetidin-2-one(3)----- A solution of 2(3.34 g) and cysteamine(4.68 g) in EtOH(50 ml) was heated at 85° for 2 hr under nitrogen. The reaction mixture was concentrated and the residue was chromatographed on a column of silica gel eluting with $CHCl_3$-MeOH(9:1) to give 3(676 mg, 13.1%) as a colorless oil, which was further purified by preparative TLC(AcOEt) and crystallized from AcOEt-hexane to give colorless needles, mp 70-71°. Anal. Calcd for $C_7H_{10}N_2OS$: C, 49.38; H, 5.92; N, 16.45; S, 18.83. Found: C, 49.18; H, 5.76; N, 16.07; S, 18.79. MS m/e: 170(M^+), 153, 142, 128, 101, 93, 84, 70, 60(base peak).

IR($CDCl_3$): 3420(NH), 1765(β-lactam), 1625cm^{-1}(C=N). NMR($CDCl_3$)δ: 2.61(1H, ddd-like, J=14.5 Hz, 3-H), 3.05(1H, ddd, J=14.5, 5.0, 2.0 Hz, 3-H), 2.73(2H, d, J=5.0 Hz, CH_2-thiazoline), 3.25(2H, t, J=8.0 Hz, 2xthiazolynyl H), 4.18(2H, t, J=8.0 Hz, 2xthiazolynyl H), 3.90(1H, m, 4-H), 6.72(1H, b, NH).

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