Arch. Pharm. Res. 11(2), 163-165(1988)

Synthetic Studies on Carbapenem and Penem Antibiotics(VI) Improved synthesis of (3S,4S)-4-acetoxy-3-phenylacetamido-azetidin-2-one

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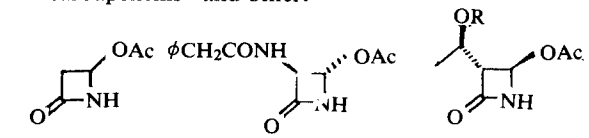
(Received May 25, 1988)

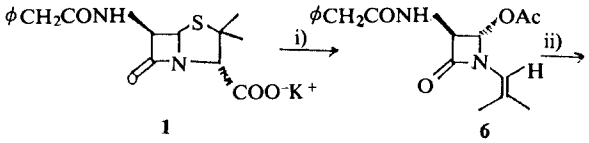
Abstract □ Penicillin G potassium salt was transformed in high yield to 4-acetoxy-3-phenylacetaminoazetidinone by treatment of mercury acetate, ozonolysis and methanol in sequence.

Keywords □ penicillin G, derivatives of 4-acetoxyazetidinone

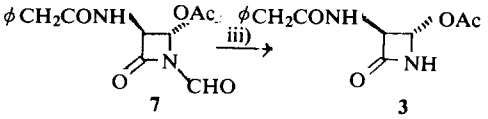
Penicillin G(**1**) is regarded as one of the best starting materials because it is currently available from fermentation at low cost and can be transformed to specific goal compounds stereo-specifically[1]. For synthetic study of thienamycin[2] and its analogs[3], we have examined the transformation of penicillin G to the 4-acetoxyazetidin-2-one derivatives[4-6] (**2, 3, 4** and **5**). These compounds are very attractive starting material for construction of biologically interesting bicyclic systems like penems[7], carbapenems[8] and other.[9]



2 **3** **4** R = TCE, **5** R = $Me_2{}^tBu$



1 **6**



7 **3**

i) $Hg(OAc)_2$, AcOH, ii) O_3, CH_2Cl_2, -78 °C, iii) MeOH

The transformation of methyl or benzyl penicillanate to (3S, 2S)-4-acetoxy-3-phenylacetamido-azetidine-2-one (**3**) was reexamined to improve its efficiency[4,10]. Further examination of this transformation, we have found a better and simple, but highly effective method, which we wish to report in this note.

When mercurry (II) acetate was heated with acetic acid at 80 °C for 10 min, followed by addition of penicillin G-potassium salt, the oxidatively decarboxylated product, (3S, 4S)-4-acetoxy-1-(2-methyl-1-propenyl)-3-phenylacetamidoazetidine-2-one(**6**) could be obtained in 61% yield.

The most effective procedure for oxidation of the side chain attached at the nitrogen atom of the β-lactam ring was found to be ozonolysis. Ozonolysis of the double bond of compound(**6**) in methylene chloride at −78 °C gave the product (**7**) in 88.6% yield. The compound (**7**) is methanolyzed to give the desired product (**3**) in 60% yield. The assignment of peaks in the ^1H NMR spectrum was achieved by examination of the effect of D_2O on the ^1H NMR peaks as a function of time.

EXPERIMENTAL

General

IR spectra were recorded by using Perkin-Elmer 710B, Beckman IR 20-A or Perkin-Elmer 1710 FT-

IR spectrophotometer. ^{1}H NMR spectra were obtained from Varian EM-360A (60 MHz) or Brucker WP-SY (80 MHz) spectrophotometer. Melting points were measured with Fisher-Johns melting measuring apparatus without correction. Commercial gracial acetic acid was used after distillation over P_2O_5 and methylene chloride was distilled over calcium hydride before use.

(3S, 4S)-4-Acetoxy-1-(2-methyl-1-propenyl)-3-phenylacetamidoazetidin-2-one(6)

The compound was prepared from penicillin G potassium salt employing a modified procedure of the Stoodley's method[10]. In a round bottomed flask (100m*l*) with a magenetic stirring bar, gracial acetic acid (30m*l*) and mercury(II) acetate (3.2g, 10mmol) were added and heated in an oil bath to 85 °C. After mercury acetate was dissolved completely, penicillin G potassium salt (1.87g, 5mmol) was added slowly.

The mixture was further stirred at 85 °C in an oil bath for 2 hrs. Then, it was cooled in room temperature and in an ice bath, the cold reaction mixture was filtered through celite to remove the mercury salt. The filtrate was concentrated by evaporating with rotary evaporator under reduced pressure. The residure was dissolved with methylene chloride (50m*l*), washed with sodium bicarbonate solution (5%) for three times and with sodium chloride solution (5%) for two times. The methylene chloride solution was dried over sodium sulfate and evaporated to give an oily residue, which was further purified by chromatography on a colum packed with silica gel by eluting with ethyl acetate-hexane (11 : 1). ^{1}H NMR ($CDCl_3$, δ ppm): 1.72 (s, 6H, gem 2 CH_3), 2.08 (s, 3H, OAc), 3.56 (s, 2H, CH_2CO), 4.64 (dd, 1H, J = 8 and 1.5 Hz,3-H), 5.60 (s, 1H vinyl H), 6.05 (d, 1H, J = 1.5 Hz, 4H), 6.82 (d, 1H, J = 8 Hz, NH), 7.27 (s, 5H, Ar); IR(neat, cm^{-1}): 3310 (NH), 1780 (β-lactam C = 0), 1660 (amide C = 0).

(3S,4S)-4-Acetoxy-1-formyl-3- phenylacetamidoazetidin-2-one(7)

A two necked round bottomed flask equipped with a calcium chloride tube and a gas inlet containing compound **6** (316 mg, 1 mmol) dissolved in methylene chloride (40 m*l*) was cooled to -78 °C in a dry ice-acetone bath. Ozone was passed through the methylene chloride solution for 5 hrs. Then, the flask was warmed to room temperature and was added with dimethylsulfide (3 m*l*). After the solution was stirred for 24 hrs, it was rotary evaperated, to give an oily residue which was purified by thin layer chromatography (ethyl acetate-hexane = 1 : 1). Yield 257 mg (88.6%); ^{1}H NMR ($CDCl_3$, δ ppm): 2.11(s, 2H, OAc), 3.63(s, 2H, CH_2CO), 4.40 (dd, 1H, J = 8 and 2.4 Hz, 3-H), 6.25 (d, 1H J = 8 Hz), 6.47 (d, 1H, J = 2.4 Hz, 4-H), 7.30 (s, 5H, Ar), 8.77 (s, 1H, CHO); IR (neat, cm^{-1}): 3260 (NH), 1760 (β-lactam C = O), 1720 (aldehyde CO), 1680 (amide CO).

(3S,4S)-4-Acetoxy-3-phenylacetamidoazetidin-2-one(3)

Compound **7** (127 mg, 0.4 mmol) was stirred in methanol (20 m*l*) at room temperature for 25 hrs. Evaporation of the solvent gave a residue which was crystallized in chloroform-petroleum ether. Crystallized product yield, 78 mg (68%); m.p. 146-148 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 2.15 (s, 3H, OAc), 3.61 (s, 2H, CH_2CO), 4.64 (dd, 1H, J = 7.2 and 1.3 Hz, 3-H), 6.00 (d, 1H, J = 1.3 Hz, 4-H), 6.04(d, 1H, J = 7.2 Hz, NH), 6.02(s, 1H NH), 7.30 (s, 5H, Ar); IR(neat, cm^{-1}): 3350, 3280, 1775 (β-lactam C = O), 1725, 1685 (amide C = O).

ACKNOWLEDGEMENT

This paper was supported by non-directed fund.

LITERATURE CITED

1. Goo, Y.M.: Antibiotics, research and development of penicillins and cephalosporins, Seoul National University Press, Seoul, Korea, pp. 234-364 (1983).
2. Albers-Schongerg, G., Arison, K., Kaczka, E.A., Rhodes, R.E., Kahn, J.S., Kahan, F.M., Ratcliffe, R.W., Walton, E., Ruswinkel, L.J. Morin, R.B., and Christensen, B.G.: Structure and absolute configuration of thienamycin. *J. Am. Chem. Soc.* **100**, 6491 (1978).
3. Lee, Y.Y., Wang, H.C., and Goo, Y.M.: Synthetic studies on penems and carbapenems(I). Improved synthesis of 4(*S*)-acetoxy-3-(*S*)-phenylacetamidoazetidine-2-one. *J. Kor. Chem. Soc.* **30**, 138 (1986).
4. Lee, Y.Y., Kim, K.-T., Kim, H.H., Goo, Y.M., Lee, Y.B., and Joe, Y.A.: Synthetic studies on penems and carbapenems(V). Preparation of 6-acetylpenicillanate derivatives. *Bull. Kor. Chem. Soc.* **8**, 130 (1987).
5. Goo, Y.M., Lee, Y.B., Kim, H.H., Lee, Y.Y., and Lee, W.Y.: Synthetic studies on penems and carbapenems(IV). Practical Preparation of (3R,4R)-4-acetoxy-3-[(1R)-1-hydroxyethyl]-azetidin-2-one derivatives from 6-aminopeni-

cillanic acid. *Bull. Korean Chem. Soc.* **8,** 15 (1987).
6. Chung, J.-K., Goo, Y.M., and Lee, Y.Y.: Synthetic studies on penems and carbapenems (II). Transformation of penicillin G to derivatives of 6-bromo-6-phenylacetoxypenicillanic acid. *Bull. Korean Chem. Soc.* **7,** 405 (1986).
7. Lang, M., Prasad, K., Gosteli, J., and Woodward, R.B.: The penems, a new class of β-lactam antibiotics. Synthesis of 2-alkylthiopenem carboxylic acid. *Helv. Chem. Acta.* **63,** 1093 (1980).
8. Kametani, T., Huang, S.-P., Yokohama, S., Suzuki, Y., Masataka Ihara, M.: Studies on the syntheses of heterocyclic componuds. A formal total syntheses of (±)-thienamycin and a (±)-decysteaminylthienamycin derivative. *Heterocycle* **14,** 1305 (1980).
9. Goo, Y.M.: Antibiotics, research and development of penicillins and cephalosporins, Seoul National University Press, Seoul, Korea, p. 463-592 and p. 593-694 (1983).
10. Stoodley, R.J., and Whitehouse, N.R.: Studies related to penicillins. Part IX. Degradation of penicillanic acid derivatives by mercury(II) acetate. *J. Chem. Soc., Perkin Trans.* I, 32 (1973).