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(*Journal of the Korean Chemical Society*)
Vol. 30, No. 1, 1986
Printed in the Republic of Korea

단 신

펜엠과 카르바펜엠의 합성에 관한 연구(I). 4(*S*)-아세톡시-3(*S*)-페닐아세트아미도아제티딘-2-온의 개선된 합성법

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(1985. 8. 20 접수)

Synthetic Studies on Penems and Carbapenems (I). Improved Synthesis of 4(*S*)-Acetoxy-3(*S*)-phenylacetamidoazetidin-2-one

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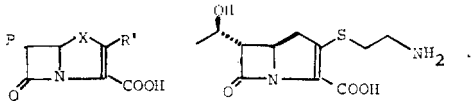
(Received August 20, 1985)

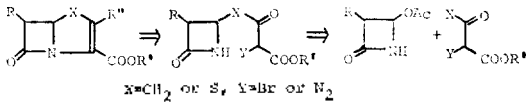
Penicillin and cephalosporin antibiotics were recognized as most useful antimicrobial agents for human pathogenic microbial control and many structural modifications were done to develop new more effective ones.[1] In 1976 Woodward suggested that the antimicrobial activity of penicillin is partly due to the chemical reactivity of the ß-lactam carbonyl group and increase in the strain of the ß-lactam ring would increase the antimicrobial activity. On the basis of this assumption a penem (**1a**) was suggested as a new kind of ß-lactam antibiotics having better antimicrobial activity.[2] Thienamycin (**2**), a carbapenem (**1b**) analog, was found in 1976 from a *Streptomyces* sp. and was reported as the most active antibiotic ever found in nature.[3] It was reported to kill almost all living microbials in the world. Following these suggestions and findings, many synthetic methods for penems and carbapenems have been reported.[4]

For the preparation of new penems and carbapenems, penicillin G 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 stereospecifically.[5] During synthetic studies of



1a X=S
1b X=CH_2

2



X=CH_2 or S, Y=Br or N_3

Scheme 1.

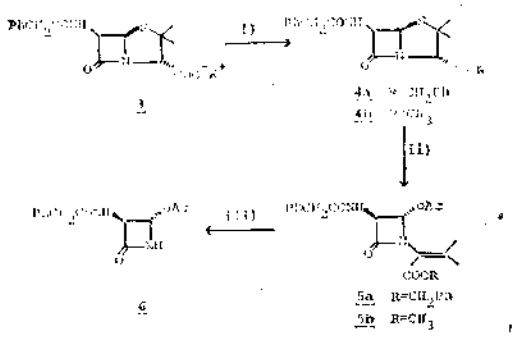
penems and carbapenems by the retro-synthetic analysis as shown in *Scheme* 1, we improved the transformation procedure of penicillin G to the 4-acetoxyazetidin-2-one derivative, which can be employed for the synthesis of penems,

carbapenems, penicillins and other cephalosporins in many ways.[6]

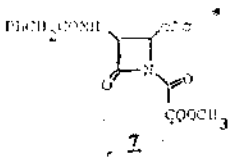
It was reported[7] that benzyl or methyl ester of penicillin G (**4a** or **4b**) was transformed to 1-(1-benzyloxycarbonyl- or 1-(1-methoxycarbonyl-2-methylpropenyl)-4(*S*)-acetoxy-3(*S*)-phenylacetamidoazetidin-2-one (**5a** or **5b**) in 30 ~40% yield by heating with mercury acetate in acetic acid at 90~100°C for 2 hr. However, when the mercury acetate was heated with acetic anhydride in acetic acid at 80~90°C for 30 min followed by addition of **4a** or **4b**, the 4-acetoxyazetidin-2-one derivatives (**5a** or **5b**) could be obtained in 60~90% yield.

The oxidation procedures which were employed for other *N*-alkylidene derivatives of azetidin-2-one were used to achieve the transformation of **5a** or **5b** to 4(*S*)-acetoxy-3(*S*)-phenylacetamidoazetidin-2-one (**6**). Their oxidation with permanganate in acetone gave very poor yield of **6**.

This poor yield seemed partly due to oxidation of the NH of the amido group. Many other conditions were attempted to improve the yield without success. When the oxidation was carried out in acetone with 1 equivalent of permanganate and 3 equivalents of ammonium chloride, 4-acetoxy-1-methoxalyl-3-phenylacetamidoazetidinone (**7**) was produced as a major product in



Scheme 2.



about 50% yield. The methoxalyl group was easily hydrolyzed to compound **6** during column chromatography. 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 **5b** in methylene chloride-methanol at −78°C gave the desired product in 81% yield. The compound **7** is presumed to be produced during ozonolysis and is methanolyzed to give the desired product, **6**.

Our synthetic goal was coupling of the 4-acetoxyazetidin-2-one derivative with various other carbon chains with proper functional groups for the construction of penem or carbapenem rings by displacing the acetoxy group with various nucleophiles. Actually the acetoxy group is a good functional group for the formation of new carbon-sulfur or carbon-carbon bonds. However, still more research is necessary for the development of nucleophilic substitution reactions with the acetoxy group as the leaving group. The intermediates obtained in this process can be utilized for the synthesis of carbapenems or penems. Their reaction with acetoacetates and malonates are under examination and will be reported in a separate paper.

EXPERIMENTAL

Infrared spectra were recorded with Perkin Elmer 710 Spectrophotometer. ^{1}H NMR spectra were taken on a 60 MHz Varian EM-360A Spectrometer using tetramethylsilane as an internal reference. Ozonolysis was carried out on Welsbach T-408 Ozonator. Melting point was

obtained with Fisher-Johns Melting Point Apparatus without correction. Anhydrous acetic acid was obtained by distillation of prerefluxed glacial acetic acid with P_2O_5 or distillation of acetic acid with benzene azeotropically. Acetone was purified by distillation after stirring with $KMnO_4$ at room temperature. Benzyl or methyl ester of penicillin G (**4a** or **4b**) was obtained by stirring the potassium salt of penicillin G with benzyl chloride or methyl iodide in DMF for 3 days at room temperature. All other chemicals used were reagent grade.

4(*S*)-Acetoxy-1-(1-benzyloxycarbonyl-2-methylpropenyl)-3(*S*)-phenylacetamidoazetidin-2-one (5a): Mercury acetate (9.0 g, 28 m mol) was dissolved in 40 m*l* of acetic acid with 4 m*l* of acetic anhydride, heated to 80°C in an oil bath, and stirred for 30 min. As the temperature of the oil bath was maintained on 85~90°C, **4a** (8.0 g, 19 mmol) was added in small portions and stirred at the same temperature range for 2 hr. The reaction mixture was cooled, filtered through Celite, and evaporated to give an oily residue. It was dissolved in methylene chloride, washed with 5% sodium bicarbonate and 5% sodium chloride, dried over sodium sulfate, filtered, and evaporated. Column chromatography of the residue on a silica gel column by elution with hexane-ethyl acetate (2 : 1) gave an amorphous solid; yield: 4.1 g (60%); IR($CHCl_3$): 3325, 1780, 1720 and 1695 cm^{-1}; ^1H NMR($CDCl_3$): δ(ppm) 7.45(s, 5H), 7.10(s, 5H), 6.12~6.20(d, 1H, J=8 Hz), 6.05(d, 1H, J=1.5 Hz), 5.15(s, 2H), 4.85~4.97(q, 1H, J=8 and 1.5 Hz), 3.57(s, 2H), 2.23(s, 2H) and 2.02(6H).

4(*S*)-Acetoxy-1-(1-methoxycarbonyl-2-methylpropenyl)-3(*S*)-phenylacetamidoazetidin-2-one (5b): After 100 m*l* of acetic acid with 10 m*l* of acetic anhydride was heated to 80°C for 20 min, mercury acetate (14.4 g, 45 mmol) was added and stirred for 20 min at 85°C. Then **4b** (11.0 g, 32 mmol) was added in small portions and stirred for 2 hr at the same range of temperature. The reaction mixture was filtered through Celite and evaporated to give an oily residue. It was dissolved in methylene chloride, washed with 5% sodium bicarbonate and 5% sodium chloride, dried over sodium sulfate, evaporated, and chromatographed on a silica gel column by elution with methylene chloride-ethyl acetate (2 : 1) to give an amorphous solid; yield: 9.8 g (87.5%); IR($CHCl_3$): 3325, 1795, 1730 and 1698 cm^{-1}; ^1H NMR($CDCl_3$): δ(ppm) 7.3(s, 5H), 6.65~6.75(d, 1H, J=7 Hz), 6.15 (d, 1H, J=1.5 Hz), 4.93~5.15(q, 1H, J=7 and 1.5 Hz), 3.75(s, 3H), 3.43(s, 2H), 2.25 (s, 3H), 2.05(s, 3H) and 1.90(s, 3H).

Oxidation of 5a and 5b to obtain 4(*S*)-acetoxy-3(*S*)-phenylacetamidoazetidin-2-one (6): Method 1; The compound **5a** (1.5 g, 4.1 m mol) was dissolved in 50 m*l* of acetone with 5 m*l* of diluted water and 20 drops of potassium phosphate buffer (1N, pH=7.0) and was added 0.65 g (4.1 mmol) of $KMnO_4$. After stirring at room temperature for 1 hr, additional $KMnO_4$ was added in several portions until the $KMnO_4$ color was sustained. The reaction mixture was diluted with 100 m*l* of ethyl acetate, stirred for 5 min, filtered through Celite, washed with 5% NaCl, dried over sodium sulfate, and evaporated to give 0.4 g of an oily residue. Chromatography on a silica gel column gave the product, **6**; yield: 0.21 g (20.7%); mp: 146~148°C, IR(KBr): 3330, 1795, 1725 and 1690 cm^{-1}; ^1H NMR($CDCl_3$): δ(ppm) 7.82(broad, 1H, J=2 Hz), 7.25~7.45(5H), 5.85(q, 1H, J=2 and 2 Hz), 4.05(q, 1H, J=8 and 2 Hz), 3.55(s, 2H), 2.15(s, 3H).

Method 2: The compound **5b** (10.0 g, 30 m mol) was dissolved in 200 m*l* of methanol-methylene chloride, cooled to −78°C in dry

ice-acetone bath, and ozone was passed for 150 min with stirring. After degasification of the solution, 20 m*l* of dimethyl sulfide was added and stirred overnight at room temperature. Rotary evaporation of the solvent and column chromatography of the residue gave 4.8 g of **6**; yield: 81%.

Method 3: The compound **5b** (10.0 g, 30 m mol) was dissolved in 270 m*l* of acetone with 20 m*l* of distilled water and added 10 m*l* of phosphate buffer(1N, pH=7.0). Then 4.5 g (30 mmol) of $KMnO_4$ was added in small portions with stirring. After 30 min additional 4.5 g (30 mmol) of $KMnO_4$ was added until the color of $KMnO_4$ sustained. After 1 hr stirring, the reaction mixture was diluted with ethyl acetate, filtered through Celite, and treated with solid $Na_2S_2O_3$ to destroy the excess $KMnO_4$. The organic phase was separated and evaporated. The residue was dissolved in ethyl acetate, washed with 5% NaCl three times, dried over sodium sulfate, and chromatographed on a silica gel column with methylene chloride-ethyl acetate(2 : 1) to give the crystalline residue. Recrystallization was performed in light petroleum ether; yield: 1.5 g (19%).

4(*S*)-Acetoxy-1-methoxalyl-3(*S*)-phenylacetamidoazetidin-2-one(7): The compound **5b** (9.0 g, 24 mmol) was dissolved in 150 m*l* of acetone with 15 g of NH_4Cl and 20 m*l* of water. Then 3.2 g(24 mmol) of $KMnO_4$ was added slowly with cooling to maintain the temperature around 29°C. After stirring the reaction mixture for 45 min at room temperature, additional 0.45 g of $KMnO_4$ was added with stirring. After stirring 15 min more, the reaction mixture was diluted with ethyl acetate, stirred for 10 min, and filtered through Celite. The organic layer was separated, washed with 5% sodium chloride three times, dried over sodium sulfate, and evaporated to give an amorphous solid residue. Column chromatography of the residue gave **7**; yield: 4.0 g (50%); IR($CHCl_3$): 3330, 1780, 1710 and 1680 cm^{-1}; ^1H NMR($CDCl_3$): δ(ppm) 7.25(s, 5H), 7.05~6.95(d, 1H, J=8 Hz), 5.75(d, 1H, J=2 Hz), 4.75~4.60(q, 1H, J=8 and 2 Hz), 3.55(s, 3H), 3.0(s, 2H) and 2.05 (s, 3H).

ACKNOWLEDGEMENT

This work was supported by the Korea Research Foundation Grant for 1984.

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