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RING EXPANSION REACTIONS OF PENICILLIN DERIVATIVES BY RHODIUM-CATALYZED DECOMPOSITION OF DIAZOKETONES ——— STEREOSELECTIVE SYNTHESES OF EIGHT-MEMBERED OXA-β-LACTAMS

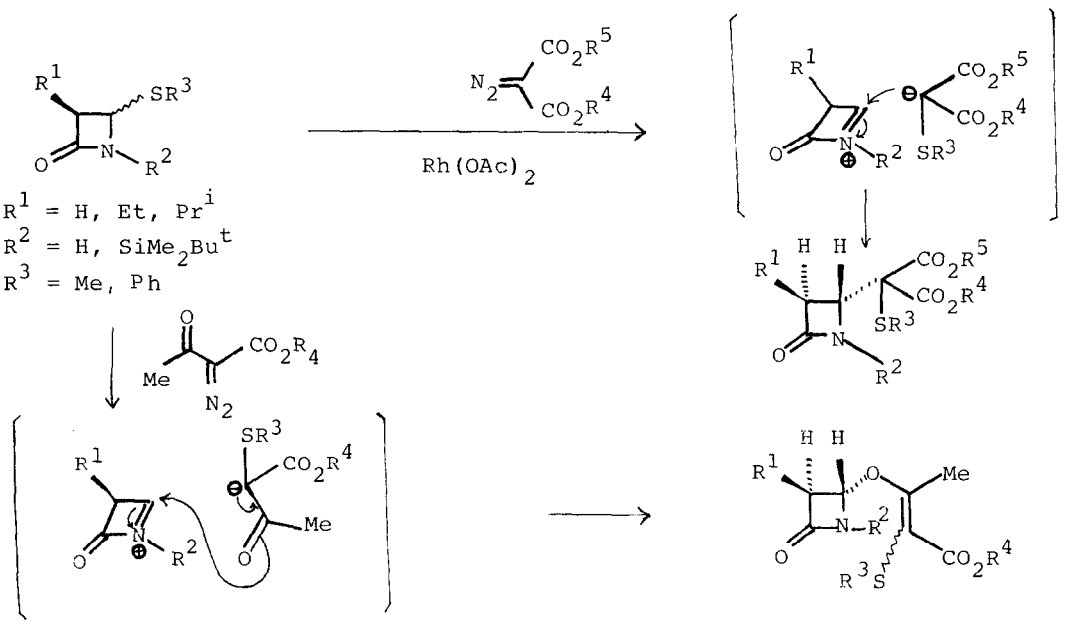
Tetsuji Kametani*, Naoaki Kanaya, Tomoko Mochizuki, and Toshio Honda
Institute of Medicinal Chemistry, Hoshi University
Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Summary The reaction of penicillin derivatives (1 - 3) with p-nitrobenzyl α-diazoacetoacetate (8) in the presence of a catalytic amount of rhodium acetate afforded the corresponding ring-expanded oxa-derivatives (5 - 7) stereoselectively, in moderate yields.

Recently we have demonstrated[1] the carbon introducing reactions at the C_4 position of the azetidinones employing rhodium-catalyzed decomposition reactions of α-diazomalonates with 4-phenylthioazetidinones. When α-diazoacetoacetate was used as a carbene precursor in the above reaction, the oxygen function was introduced at the C_4 position of the azetidinone with the stereochemistry of trans-relationship between the C_3 and C_4 positions, as shown in Scheme 1.

As an extension of this work, we have investigated the reactivity of the carbene derived from the p-nitrobenzyl α-diazoacetoacetate (8) by rhodium-catalyzed decomposition in case of penicillins to give the eight-membered oxa-derivatives.

In the amino-substituted β-lactams, such as penicillins and cephalosporins, the relative stereochemistry at the C_3 and the C_4 positions of the azetidinone ring would be desirable to be cis to display biological activities[2]. We considered that the stereochemical controll at the C_3 and C_4 positions of an azetidinone would be possible by the application of a carbene insertion reaction to penicillin derivatives, since the β-face, which is opposite to the C_3-ester, is assumed to be less hindered side and the addition of a carbene to sulfur atom followed by a rearrangement would occur at the β-face preferentially, as shown in Scheme 2.



Scheme 1

Thus, the reaction of penicillin G methyl ester (1) with p-nitrobenzyl α-diazoacetoacetate in methylene chloride-benzene (1 : 1 v/v) in the presence of rhodium acetate at 70 - 80°C was carried out to afford the oxa-derivative (5) with the desired stereochemistry in 27 % yield. Since the spectral data (Table 2) are consisted with structure 5 and the stereochemical assignment at the C_3 and C_4 positions of azetidinone ring was made on the basis of the n.m.r. spectrum, the above assumption is presumed to be correct. In order to confirm the above observation, benzyl 3,4-trans-6-phthalimidylpenicillanate (3), prepared by treatment of the corresponding cis-isomer (4) with sodium hydride in DMF, was treated with 8 as described above to yield the trans oxa-derivative (7) together with the bond cleaved compounds (9), which was characterized by its convertion into 10, in 22 % and 55 % yield respectively. The spectroscopic data and the yields for the products obtained are summarized in Table 1 and 2.

Treatment of penicillin V benzyl ester (2) with 8 in the presence of rhodium acetate again yielded the oxa-derivative (6) in 26 % yield. Though the reaction of 4 with 8 afforded none of the desired product but the bond-cleaved compound (11) in 81 % yield, this method would provide the useful route for the synthesis of oxa-β-lactam derivatives, and the biological activities of the oxa-derivatives prepared are under investigation.

Scheme 2

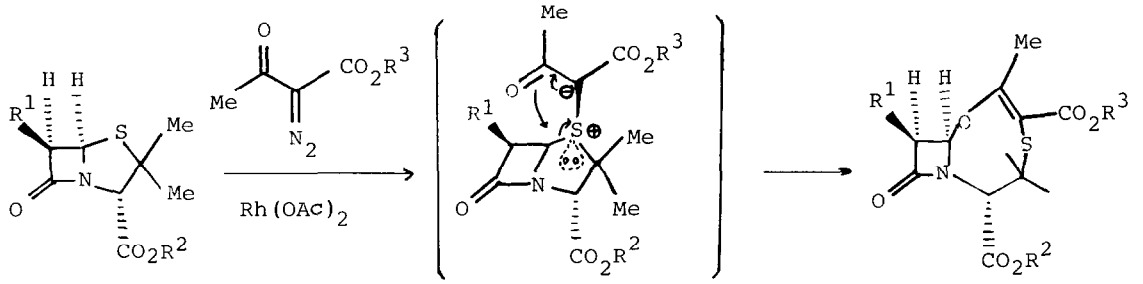


Table 1

The reactions of penicillins with p-nitrobenzyl α-diazoacetoacetate (8) $CH_3COC(N_2)CO_2PNB$ in the presence of $Rh(OAc)_2$

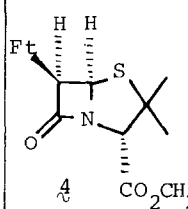
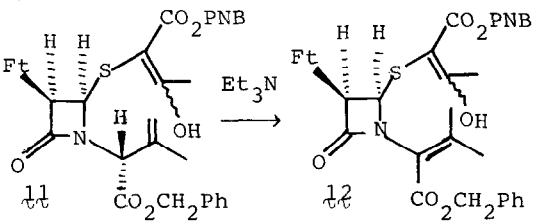
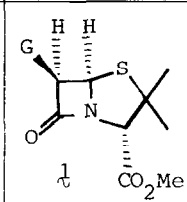
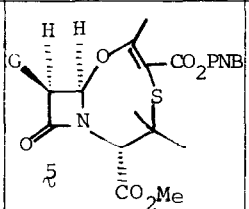
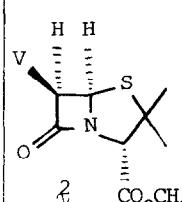
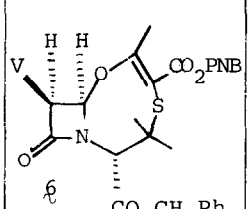
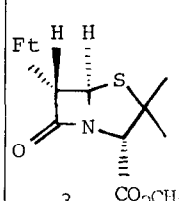
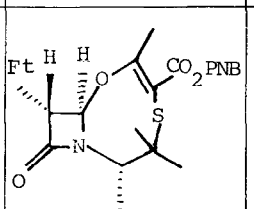
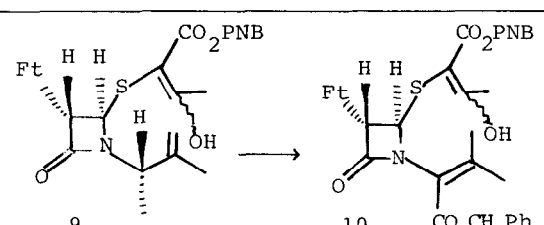
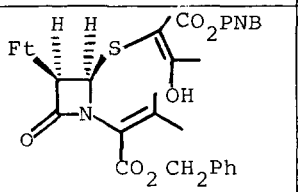
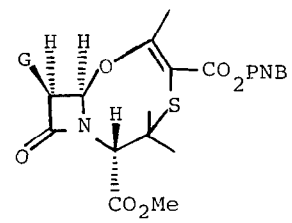
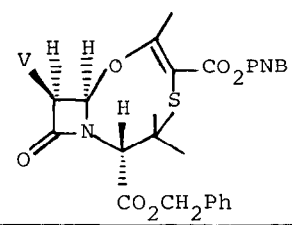
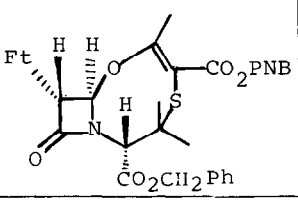
	Starting material	Products		Yield
		Oxa-derivative	Bond-cleaved compound	
1)	 4		 11 → 12	81 %
2)	 1	 5		27 %
3)	 2	 6		26 %
4)	 3	 7	 9 → 10	77 % (7 : 10 = 1 : 2.5)

Table 2

The spectral data for the reaction products of carbene insertion reaction

Compound	NMR $\delta(CDCl_3)$ ppm	IR $\nu_{max.}^{CHCl_3}$ cm^{-1}
	2.05 (3H, s, $-CH_3$), 2.22 (3H, s, $-CH_3$), 2.33 (3H, s, $-CH_3$), 4.94 (1H, d, J = 5.4 Hz, C_3-H or C_4-H), 5.53 (1H, d, J = 5.4 Hz, C_3-H or C_4-H), 7.67 (4H, broad s, 4 x ArH), 13.20 (1H, s, -OH)	1780, 1765 and 1720 (C=O) 1345 (NO_2)
	1.26 (3H, s, $-CH_3$), 1.48 (3H, s, $-CH_3$), 1.91 (3H, s, $-CH_3$), 3.65 (2H, s, $-CH_2-$), 3.76 (3H, s, $-OCH_3$), 4.25 (1H, s, $>N-CH-$) 5.26 (2H, s, $-CH_2-Ar$), 5.56 (1H, dd, J = 4.6, 9.1 Hz, C_9-H), 7.50 (1H, s, ArH), 7.59 (1H, s, ArH), 8.18 (1H, s, ArH), 8.27 (1H, s, ArH), 6.24 (1H, d, J = 9.1 Hz, NH), 7.00 (1H, d, J = 4.6 Hz, C_8-H)	3420 (NH), 1780, 1735, 1700 and 1680 (C=O), 1350 (NO_2)
	1.31 (3H, s, CH_3), 1.47 (3H, s, CH_3), 2.00 (3H, s, CH_3), 4.35 (1H, s, $>N-CH-$), 4.56 (1H, s, $-O-CH-$), 4.57 (1H, s, $-O-CH-$), 5.56 (1H, dd, J = 4.5, 9.1 Hz), 7.49 (1H, s, ArH), 7.58 (1H, s, ArH), 8.18 (1H, s, ArH), 8.27 (1H, s, ArH)	3425 (NH), 1780, 1740, 1700 and 1965 (C=O), 1350 (NO_2)
	1.35 (3H, s, $-CH_3$), 1.41 (3H, s, $-CH_3$), 2.42 (3H, s, $-CH_3$), 4.56 (1H, $>N-CH-$), 5.37 (1H, d, J = 1.7 Hz, C_9-H), 6.79 (1H, d, J = 1.7 Hz, C_8-H)	1790, 1780, 1740 and 1730 (C=O), 1350 (NO_2)

References

(1) T. Kametani, N. Kanaya, T. Mochizuki, and T. Honda, Heterocycles, 1982, 19, 1023, and the similar reactions were also reported by Sandoz grous; see K. Prasad, P. Knuessel, G. Schulz, and P. Stütz, Tetrahedron Letters, 1982, 23, 1247; C.-P. Mak, K. Baumann, F. Mayerl, C. Mayerl, and H. Fliri, Heterocycles, 1982, 19, 1647; K. Prasad and P. Stütz, ibid., 1982, 19, 1597.

(2) "Cephalosporins and penicillins", ed. by E. H. Flynn, Academic Press, New York, 1972.

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