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단 신

카르베노이드에 의한 페니실란산 에스테르의 티아졸리딘고리 절단반응에 대한 재검토

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Reexamination for the Fission of the Thiazolidine Ring of Penicillanates by Carbenoids

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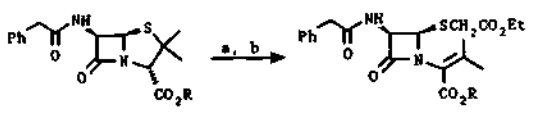
Several reports have been published concerning the fission of the thiazolidine ring of penicillins. Nayler *et al.* obtained a 1,2-secopenicillin by the reaction with methyl iodide in the presence of a strong base[1], and recently Shoji *et al*[2]. reported the reaction of a penicillin with carbene, which resulted in the cleavage of the 1,2-bond of the penicillin ring also. They have used copper powder or copper(II) acetoacetate as catalyst and obtained the 1,2-secopenicillin derivatives in moderate yields (*Scheme* 1).

Also, Kametani *et al*[3]. investigated the reactivity of the carbene derived from the p-nitrobenzyl α-diazoacetoacetate by rhodium-catalyzed decomposition with penicillins and found formation of 1,6, 3-oxathiazolidine derivatives (**6**).

We have been interested in the efficient conversion of penicillins into penem or cephem derivatives. It has been suggested that carbene would provide one of the most promising pathways to synthesize functionalized 1,2-secopenicillins from penicillins[4]. Thus, we have examined the fission of the thiazolidine ring of penicillins to see whether we can obtain some products which we can empoly for the synthesis of carbapenem skeletons. When we treated various penicillanates (**1**) with diazoacetate compounds (**2**) in the presence of rhodium acetate, various 1,2-secopenicillin derivatives (**4**) were obtained in high yields (*Scheme* 2). The reaction of penicillins with the carbene derived from the decomposition of diazo compounds by rhodium acetate was interesting mechanistically and synthetically due to the possible utilization of the products for the synthesis of other β-lactam compounds. And we reexamined the fission of the thiazolidine ring by carbenoids and wish to report our results in this note.

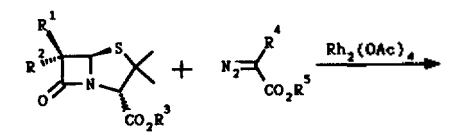


a) N_2=$CHCO_2Et$, $Cu(acac)_2$ b) Et_3N

Scheme 1

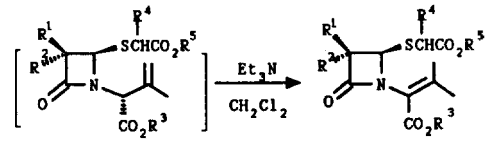
The reaction of electrophilic carbenes and carbenoids with divalent sulfur compounds to give sulfonium ylides is well described[5]. The formation of the intermediate **3** evidently proceeds through the sulfonium ylide **8** (*Fig.* 1).

It is notable that sulfonium ylide **8** is isoelectronic with penicillin sulfoxide **9**, which, upon the thermal sigmatropic rearrangement, suffers the fission of the 1,2-bond to afford sulfenic acid[8] **10**.



1a R^1=NHCOCH$_2$Ph R^2=H, R^3=Me
1b R^1=NHCOCH$_2$Ph R^2=H, R^3=CH$_2$Ph
1c R^1=R^2=Br, R^3=Me

2a R^4=H, R^5=Et
2b R^4=CH$_2$Ph, R^5=Me



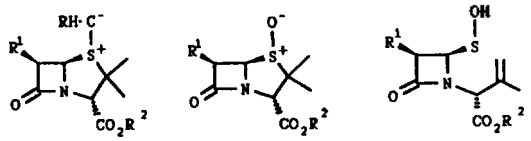
3

4a R^1=NHCOCH$_2$Ph, R^3=Me R^2=R^4=H, R^5=Et
4b R^1=NHCOCH$_2$Ph, R^2=H R^3=R^5=Me, R^4=CH$_2$Ph
4c R^1=NHCOCH$_2$Ph, R^2=R^4=H R^3=CH$_2$Ph, R^5=Et
4d R^1=NHCOCH$_2$Ph, R^2=H R^3=R^4=CH$_2$Ph, R^5=Me
4e R^1=R^2=Br, R^3=Me R^4=H, R^5=Et
4f R^1=R^2=Br, R^3=R^5=Me R^4=CH$_2$Ph

Scheme 2

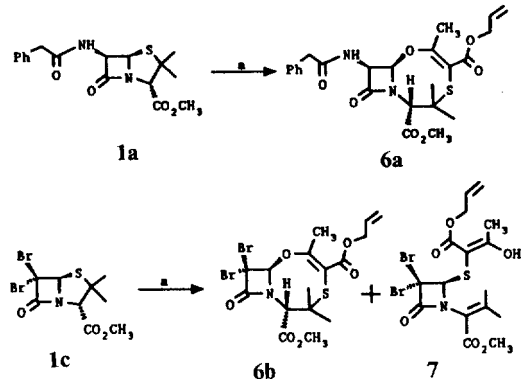
The 1,2-bond cleavage of **8**, affords 4-alkylthioazetidin-2-one derivatives **3**, which structurally correspond to sulfenic acid **10**, but unlike sulfenic acid **10**, 4-alkylthioazetidin-2-one derivatives (**3**) did not undergo further reaction and were isolated as reaction products. In the amino substituted β-lactams, such as penicillins and cephalosporins, the relative stereochemistry at the C_3 and C_4 position of the azetidinone ring would be desirable to be *cis* to display biological activities[6]. In the case of 1,2-secopenicillins (**4a-4d**), the coupling constant, 4.6 Hz, between C_3-H and C_4-H of azetidinone ring established the *cis*-configuration. We obtained 1,6,3-oxathiazocine derivative (**6a**) from the reaction of **1a** with allyl α-diazoacetoacetate in same condition in 20% yield. But the reaction of dibromopenicillanate (**1c**) and allyl α-diazoacetoacetate gave 1,6,3-oxathiazocine derivative (**6b**) and 1,2-secopenicillin **7** in 15% and 45% yield, respectively (*Scheme* 3).

The fission of the thiazolidine ring of pencillins by carbenoids was found to be one of the best methods obtaining 1,2-secopenicillin dervatives.



8 9 10

Fig. 1.



a) 1. $CH_3COC(N_2)CO_2CH_2CH=CH_2$, $Rh_2(OAc)_4$, 2. Et_3N

Scheme 3

The 1,2-secopenicillins obtained in this reaction should be utilizable for the synthesis of penem skeletons.

EXPERIMENTAL

The ^{1}H NMR spectra were measured with Bruker WP-80-SY (80 MHz) spectrometer. Chemical shifts are given in δ units (ppm) relative to tetramethylsilane as an internal standard. Infrared spectra were obtained on Perkin-Elmer 782 spectrometer. Analytical thin layer chromatography was performed on precoated silica gel plate (0.2 mm thickness, 60 F_{254}, E. Merck) and silica gel (Kieselgel 60, 70~230 mesh, E. Merck) was used for the column chromatography. Ethyl diazoacetate was prepared by the reported method[7] in the yield of 92%. Methyl 2-diazo-3-phenylpropanoate[8] and allyl α-diazoacetoacetate[9] were prepared by adapting the reported method in the yields of 74% and 77%, respectively. Methyl 2-diazo-3-phenylpropanoate: ^{1}H NMR ($CDCl_3$), δ, 3.68(s, 2H), 3.84(s, 3H), 7.40(s, 5H); IR (neat), 2090 (N_2), 1700 cm^{-1}. Allyl α-diazoacetoacetate: ^{1}H NMR ($CDCl_3$), δ, 2.48 (s, 3H), 4.65(d, 2H, J=4.6 Hz), 5.21~5.20(m, 3H):

Table 1. Spetral data and yield of compound 4, 6 and 7

Comp.	^{1}H NMR ($CDCl_3$), ppm	IR ($CHCl_3$)	Yield
4a	1.24(t, 3H, J=7.0 Hz), 1.96(s, 3H), 2.16(s, 3H), 3.11(s, 2H), 3.58(s, 2H), 3.83 (s, 3H), 4.12(q, 2H, J=7.0 Hz), 5.10(d, 1H, J=4.6 Hz), 5.26(dd, 1H, J=6.5 & 4.6 Hz), 7.20(d, 1H, J=6.5 Hz), 7.26(s, 5H).	3300, 1730, 1675, 1640.	82%
4b	1.87(s, 3H), 2.15(s, 3H), 3.40(t, 1H, J=4.5 Hz), 3.57(d, 2H, J=4.5 Hz), 3.62(s, 2H), 3.75(s, 3H), 3.82(s, 3H), 5.02(d, 1H, J=4.3 Hz), 5.20(dd, 1H, J=6.6 & 4.3 Hz), 7.15(d, 1H, J=6.6 Hz), 7.30(s, 10H).	3320, 1765, 1730, 1645.	79%
4c	1.25(t, 3H, J=7.0 Hz), 1.92(s, 3H), 2.18(s, 3H), 3.10(s, 2H), 3.62(s, 2H), 4.12 (q, 2H, J=7.0 Hz), 4.95(s, 2H), 5.12(d, 1H, J=4.6 Hz), 5.24(dd, 1H, J=6.5 & 4.6 Hz), 7.15(d, 1H, J=6.5 Hz), 7.20(s, 5H), 7.40(s, 5H).	3330, 1775, 1730, 1670, 1645.	80%
4d	1.93(s, 3H), 2.20(s, 3H), 3.45(t, 1H, J=4.5 Hz), 3.55(d, 2H, J=4.5 Hz), 3.70(s, 2H), 3.76(s, 3H), 4.95(s, 2H), 5.12(d, 1H, J=4.5 Hz), 5.24(dd, 1H, J=6.5 & 4.5 Hz), 7.15(d, 1H, J=6.5 Hz), 7.25(s, 5H), 7.42(s, 5H).	3300, 1770, 1740, 1640.	75%
4e	1.32(t, 3H, J=7.1 Hz), 1.87(s, 3H), 2.14(s, 3H), 3.08(s, 2H), 3.87(s, 3H), 4.26(t, 2H, J=7.1 Hz), 5.32(s, 1H).	1775, 1740, 1660, 1640.	75%
4f	1.97(s, 3H), 2.11(s, 3H), 3.36(t, 1H, J=4.5 Hz), 3.57(d, 2H, J=4.5 Hz), 3.87(s, 3H), 3.92(s, 3H), 5.36(s, 1H), 7.02(s, 5H).	1770, 1730, 1670, 1640	70%
6a	1.26(s, 3H), 1.48(s, 3H), 1.91(s, 3H), 3.65(s, 2H), 3.76(s, 3H), 4.70(d, 2H, J=7.4 Hz), 4.96(m, 2H), 5.20(m, 1H,), 5.56(dd, 1H, J=9.1 & 4.6 Hz), 6.24(d, 1H, J=9.1 Hz), 6.82(s, 1H), 7.00(d, 1H, J=4.6 Hz), 7..15(s, 5H).	3420, 1780, 1740, 1700, 1690.	20%
6b	1.26(s, 3H), 1.48(s, 3H), 1.91(s, 3H), 4.56(s, 3H), 4.87(d, 2H, J=7.5 Hz), 5.02 (m, 2H), 5.23(m, 1H), 6.93(s, 1H), 7.12(s, 1H).	1780, 1730, 1700.	45%
7	2.05(s, 3H), 2.21(s, 3H), 2.32(s, 3H), 4.82(d, 2H, J=7.6 Hz), 5.01(m, 2H), 5.20(m, 1H), 5.36(s, 1H), 13.21(s, 1H).	3510, 1770, 1680.	45%

IR (neat), 2150 (N_2), 1720, 1660 cm^{-1}.

General procedure for the preparation of 1,2-secopenicillins. The following procedure for the synthesis of (3*S*, 4*R*)-4-ethoxycarbonylmethylthio-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-3-phenylacetamidoazetidin-2-one (**4a**) is representative. To a solution of methyl 6-phenylacetamidopenicillanate (**1a**, 400 mg, 1.15 mmol) and rhodium acetate (5% mol) in benzene (10 m*l*) and methylene chloride (10 m*l*) was added dropwise ethyl diazoacetate (**2a**, 40 mg 3.45 mmol) at 80℃ under nitrogen atmosphere. The resulting mixture was refluxed for 20 hr. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride (20 m*l*). To this solution was added trimethylamine (0.5 m*l*) and stirred for 24 hr at the room temperature. After removal of the solvent, the crude product was purified by silica gel column chromatography with *n*-hexane-ethyl acetate (3 : 2, v/v) to give pure product (**4a**). Yields and spectral data of all 1,2-secopenicillins are given in *Table* 1.

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