SYNTHETIC STUDIES ON CARBAPENEM ANTIBIOTICS: A CARBON-INTRODUCED REACTION AT THE C-4 POSITION OF A β-LACTAM BY CARBENE INSERTION REACTION

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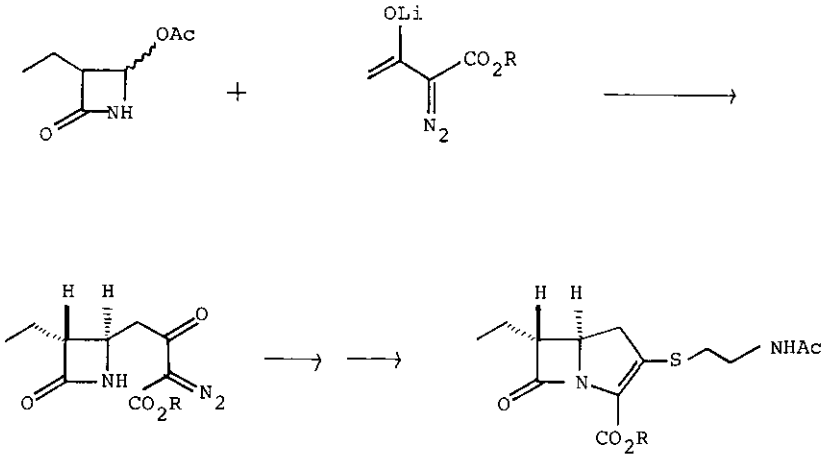
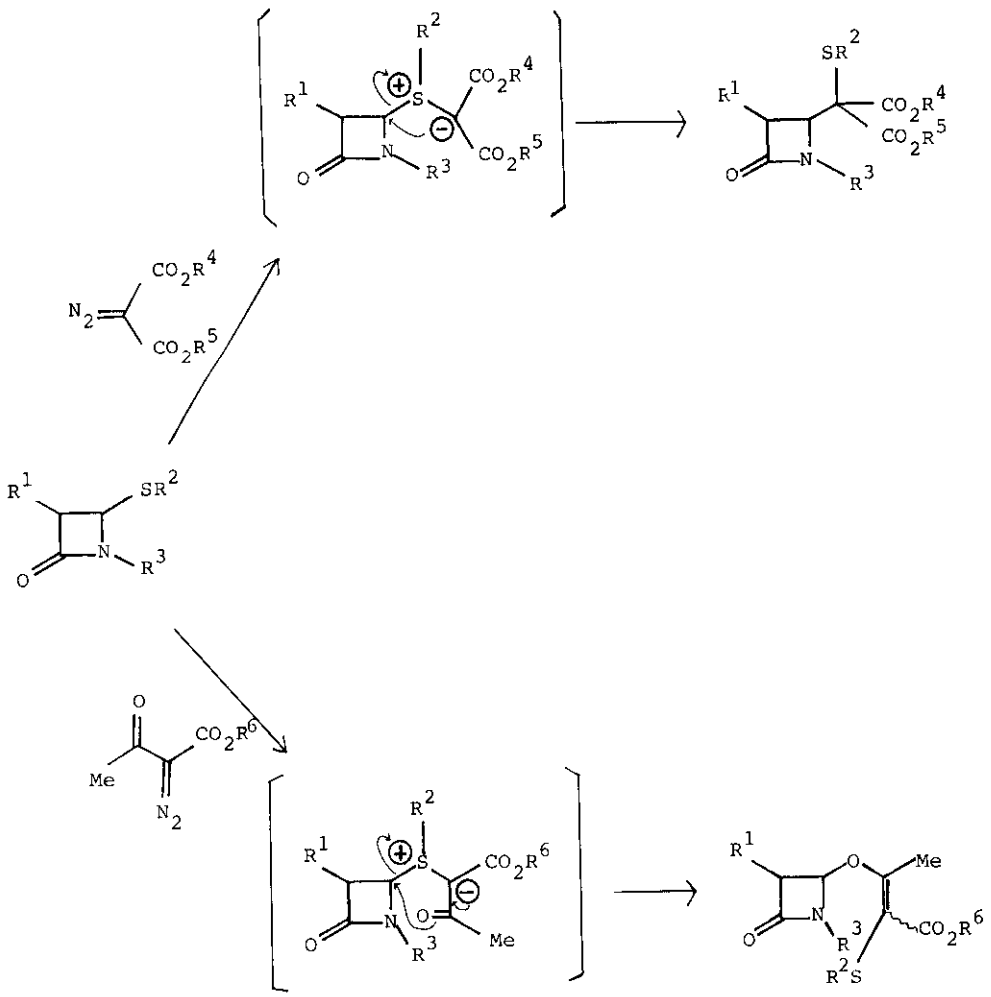
Abstract —— The reaction of 4-thia-azetidinones with diazomalonates in the presence of a catalytic amount of rhodium (II) acetate afforded the carbon-introduced products at the C_4-position of β-lactams.

Recently, much attention[1-11] has been focused on the introduction of functionalized carbon units at the C_4-position of β-lactams directed for synthesizing carbapenem antibiotics, such as thienamycin, PS-5, and olivanic acid, since these antibiotics are currently very important compounds from the biological point of view. We have already published[12] the synthesis of antibiotic PS-5 related compounds by the application of the above methodology, as shown in scheme 1.



Scheme 1



Scheme 2

We report here an alternative carbon-introduced reaction using carbene insertion reaction to sulfur as a key step.

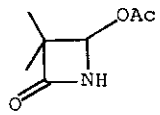
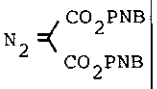
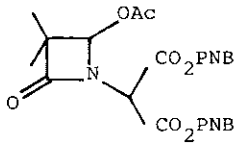
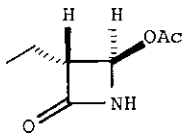
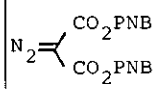
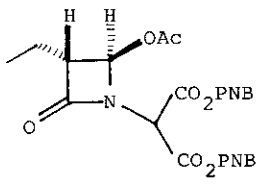
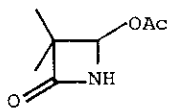
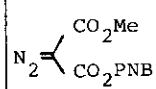
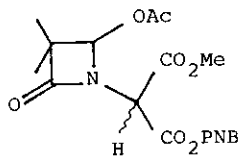
3-Ethyl-4-methylthio-2-azetidinone was treated with 1 eqiv. of di-p-nitrobenzyl α-diazomalonate in refluxing benzene-methylene chloride (1 : 1 v/v) in the presence of a catalytic amount of rhodium (II) acetate to afford the 4-substituted product (Entry No. 5). The stereochemistry at the C_3- and C_4-positions was deduced to be trans based on its nmr data. Similarly, 3-ethyl-4-phenylthio-2-azetidinone with α-diazomalonate, under the same reaction conditions, gave the desired product in moderate yield (Entry No. 6). Though both groups are effective to this carbene insertion reaction, thiophenyl group is superior to thiomethyl group in terms of reaction time and yield. 3-Isopropyl-4-phenylthio-2-azitidinone (Entry No. 12) and 3-phthalimido-4-phenylthio-2-azetidinone (Entry No. 16) with α-diazomalonate also afforded the C_4-displaced products, respectively. The spectroscopic data for all the substituted β-lactams prepared are summarized in Table.

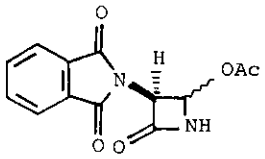
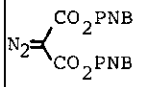
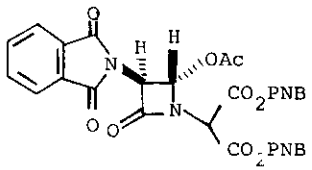
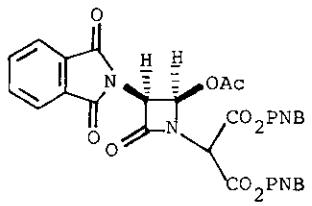
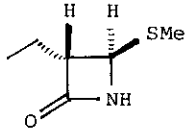
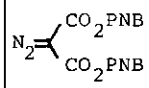
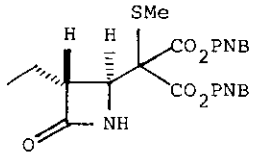
Interestingly, treatment of 3-substituted 4-phenylthio-2-azitidinone with α-diazoacetoacetate in refluxing benzene-methylene chloride (1 : 1 v/v) in the presence of a catalytic amount of rhodium (II) acetate afforded the 4-oxa-2-azetidinones (Entry No. 14 and 15) as an inseparable mixture of E/Z isomers, as shown in Table, which may be the potential compounds for the synthesis of 1-oxapenems.

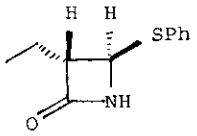
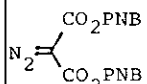
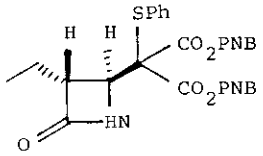
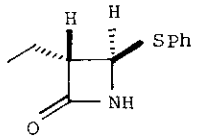
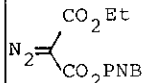
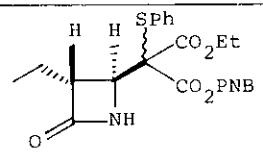
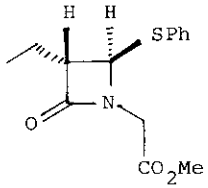
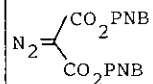
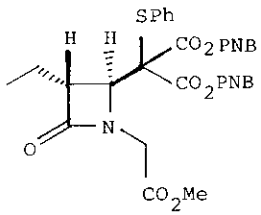
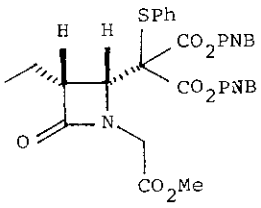
When 4-acetoxy-2-azetidinones were treated with α-diazomalonate, N-substituted β-lactams were produced in moderate yield (Entry No. 1 ∿ 4).

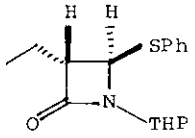
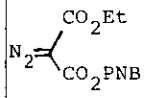
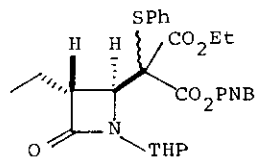
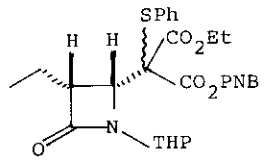
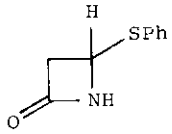
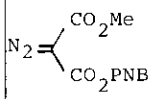
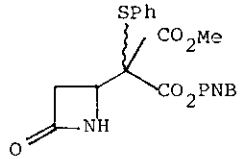
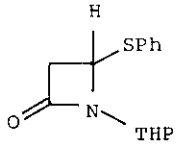
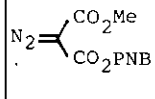
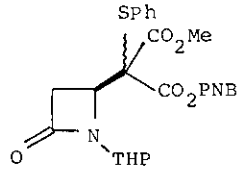
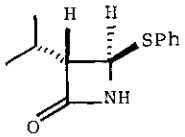
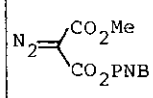
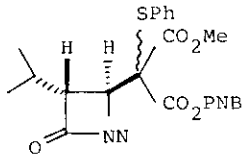
Thus, a facile carbon-introduced reaction at the C_4-position of β-lactams has been achieved by using carbene insertion reaction to sulfur, and the synthesis of carbapenem antibiotic by the adoption of this method is under investigation in this laboratory.

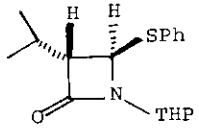
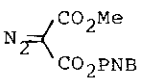
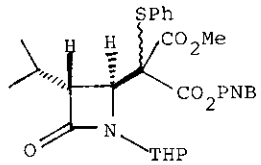
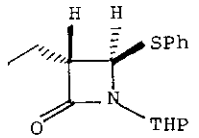
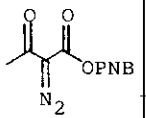
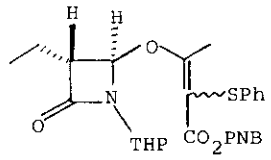
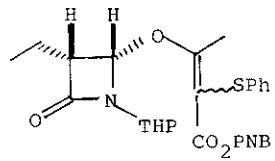
Table

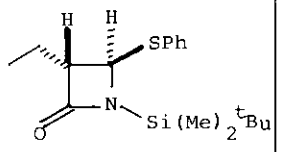
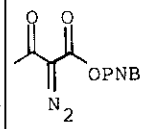
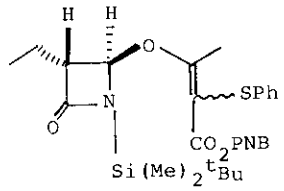
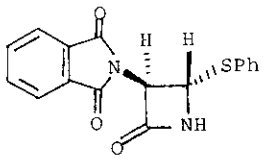
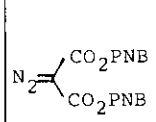
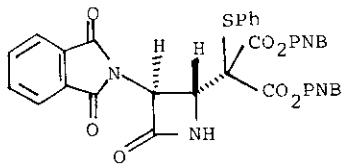
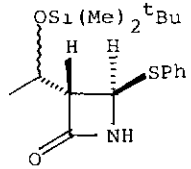
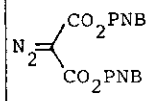
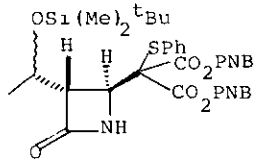
No.	starting material	diazo compound	product	yield	I.R. $\nu_{max}^{CHCl_2}$	N.M.R. δ ($CDCl_3$)
1		 PNB = p-nitrobenzyl		23.7 %	1345 (NO_2) 1750 (C=O) 1765 (C=O)	1.2 (3H, s, Me), 1.33 (3H, s, Me), 5.08 (1H, s, N–  –H), 5.33 (4H, s, 2 x $C\underline{H}_2Ar$), 5.83 (1H, s, C_4-H), 6.3 (3H, s, OAc), 7.5 (4H, d, J = 8 Hz, ArH), 8.16 (4H, d, J = 8 Hz, ArH)
2				22.3 %	1350 (NO_2) 1750 (C=O) 1770 (C=O)	1.0 (3H, t, J = 6.8 Hz, $CH_2C\underline{H}_3$), 1.67 (2H, q, J = 6.8 Hz, $C\underline{H}_2CH_3$), 2.1 (3H, s, -OAc), 3.17 (1H, dt, J = 1 Hz and 6 Hz, C_3H), 5.27 (4H, s, 2 x $C\underline{H}_2Ar$), 5.4 (1H, s, N––H), 5.8 (1H, d, J = 1 Hz, C_4H), 7.37 (2H, d, J = 8 Hz, ArH), 8.07 (2H, d, J = 8 Hz, ArH)
3				21.5 %	1340 (NO_2) 1735 1740 (C=O) 1750 1785	1.17 (1.5H, s, CH_3), 1.2 (1.5H, s, CH_3), 1.33 (1.5H, s, CH_3), 2.1 (3H, s, OAc), 2.37 (1.5H, s, CH_3), 3.8 (3H, s, CO_2Me), 5.27 (2H, s, $C\underline{H}_2Ar$), 5.33

						(0.5H, s, -N⟨H), 5.37 (0.5H, s, -N⟨H), 7.4 (2H, d, J = 13.3Hz, ArH), 8.3 (2H, d, J = 13.3 Hz, ArH)
4				22.4 %	1340 (NO_2) 1720 (C=O)	2.07 (3H, s, OAc), 6.07 (1H, d, J = 1.4 Hz, C_4-H)
				5.6 %	1750 (C=O) 1760 (C=O)	2.1 (3H, s, OAc), 5.93 (1H, d, J = 6 Hz, C_4-H)
5				30 %	1350 (NO_2) 1740, 1770 (C=O) 3420 (NH)	1.0 (3H, t, J = 7.1 Hz, $CH_2\underline{CH}_3$), 2.69 (2H, m, $C\underline{H}_2CH_3$), 2.14 (3H, s, SMe), 3.57 (1H, dt, J = 2.8 and 7.1 Hz, C_3-H), 3.94 (1H, d, J = 2.8 Hz, C_4-H), 5.31 (4H, s, 2 x $C\underline{H}_2$Ar), 6.0 (1H, br s, NH), 7.49 (4H, d, J = 8.6, ArH), 8.2 (4H, d, J = 8.6, ArH)

6				50.8 %	1350 (NO_2) 1740 (C=O) 1770 (C=O) 3420 (NH)	1.0 (3H, t, J = 6 Hz, $CH_2\underline{CH}_3$), 1.67 (2H, q, J = 6 Hz, $\underline{CH}_2CH_3$), 3.27 (1H, dt, J = 2 and 6 Hz, C_3-H), 3.87 (1H, d, J = 2 Hz, C_4-H), 6.27 (1H, br s, NH)
7				46.6 %	1350 (NO_2) 1730, 1760 (C=O) 3400 (NH)	3.34 (1H, dt, J = 2 and 7.1 Hz, C_3-H), 3.94 (1H, d, J = 2 Hz, C_4-H), 5.88 (1H, br s, NH)
8				77.2 %	1350 (NO_2) 1745, 1765 (C=O)	1.05 (3H, t, J = 5.7 Hz, $CH_2\underline{CH}_3$), 1.77 (2H, q, J = 5.7, $\underline{CH}_2CH_3$), 3.37 (1H, dt, J = 2 and 7.1 Hz, C_3-H), 3.5 (1H, d, J = 18.6 Hz, $\underline{CH}$-CO_2Me), 3.7 (3H, s, CO_2Me), 4.2 (1H, d, J = 18.6 Hz, $\underline{CH}$-CO_2Me), 4.41 (1H, d, J = 2 Hz, C_4-H), 5.77 (4H, s, 2 x $\underline{CH}_2$Ar)
				14 %	1360 (NO_2) 1750, 1775 (C=O)	1.06 (3H, t, J = 5.7 Hz, $CH_2\underline{CH}_3$), 3.63 (1H, d, J = 18.6 Hz, $\underline{CH}$-CO_2Me), 3.69 (3H, s, CO_2Me), 4.34 (1H, d, J = 18.6 Hz, $\underline{CH}$-CO_2Me), 4.71 (1H, d, J = 5.7 Hz, C_4-H)

9	 THP = tetrahydropyranyl			70 %	1350 (NO_2) 1740, 1760 (C=O)	4.17 (1H, d, J = 2.8 Hz, C_4-H)
				11.4 %	1350 (NO_2) 1750 (broad, C=O)	4.54 (1H, d, J = 5.7 Hz, C_3-H)
10				59 %	1355 (NO_2) 1740, 1750 (C=O) 3420 (NH)	3.13 (2H, m, C_3-H), 3.6 (1.64H, s, CO_2Me), 3.77 (1.36H, s, CO_2Me), 4.16 (0.6H, d, J = 3.1 Hz, C_4-H), 4.21 (0.4H, d, J = 3.1 Hz, C_4-H), 5.26 (0.9H, s, CH_2Ar), 5.3 (1.1H, s, CH_2Ar), 5.97 (1H, br s, NH)
11				81.6 %	1340 (NO_2) 1730, 1760 (C=O)	3.69 (1.38H, s, CO_2Me), 3.71 (1.62H, s, CO_2Me)
12				45.3 %	1350 (NO_2) 1730, 1765 (C=O) 3420 (NH)	1.03 (6H, d, J = 6.3 Hz, 2 x Me), 3.14 ∿ 3.32 (1H, m, C_3-H), 3.66 (1.5H, s, CO_2Me), 3.71 (1.5H, s, CO_2Me), 4.02 (1H, d,

12						2.2 Hz, C_3-H), 5.87 (1H, br s, NH)
13				80.2 %	1345 (NO_2) 1735, 1750 (C=O)	4.26 (1H, d, J = 2.6 Hz, C_4-H)
14				79.2 %	1345 (NO_2) 1700 (C=O) 1760 (C=O)	1.01 (1.8H, t, J = 6.28 Hz, CH_2-$C\underline{H}_3$), 1.04 (1.2H, t, J = 6.28 Hz, CH_2-$C\underline{H}_3$), 2.57 (1.8H, s, Me), 2.63 (1.2H, s, Me), 3.06 (1H, dt, J = 1.43 Hz, C_3-H), 5.17 (2H, s, $C\underline{H}_2Ar$), 5.44 (0.6H, d, J = 1.4 Hz, C_4-H), 5.63 (0.4H, d, J = 1.4 Hz, C_4-H)
				2.2 %	1350 (NO_2) 1695 (C=O) 1765 (C=O)	1.00 (3H, t, J = 7.14 Hz, CH_2-$C\underline{H}_3$), 3.22 (1H, dt, J = 4.85 and 8 Hz, C_3-H), 5.16 (2H, s, $C\underline{H}_2Ar$), 5.99 (H, d, J = 4.85 Hz, C_4-H)

15				80 %	1350 (NO_2) 1700 (C=O) 1760 (C=O)	0.2 (6H, s, $Si(Me)_2$), 0.9 (9H, s, $SiC(Me)_3$), 2.5 (3H, s, Me), 3.0 (1H, dt, J = 1.4 and 8.3 Hz, C_3-H), 5.07 (2H, s, $C\underline{H}_2Ar$), 5.2 (0.6H, d, J = 1.4 Hz, C_4-H), 5.37 (0.4H, d, J = 1.4 Hz, C_4-H)
16				50 %	1345 (NO_2) 1730 (C=O) 1790 (C=O) 3425 (NH)	4.68 (1H, d, J = 2.4 Hz, C_4-H), 5.02 (2H, s, $C\underline{H}_2Ar$), 5.32 (2H, s, $C\underline{H}_2Ar$), 5.67 (1H, d, J = 2.4 Hz, C_3-H)
17	 (8R*/8S*= 4/3 or 3/4)			48.4 %	1355 (NO_2) 1730 (C=O) 1770 (C=O) 3410 (NH)	4.22 (0.57H, d, J = 2 Hz, C_4-H), 4.56 (0.43H, d, J = 2 Hz, C_4-H), 5.24 (4H, s, 2 x $C\underline{H}_2Ar$), 6.10 (0.57H, s, NH), 6.17 (0.43H, s, NH)

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