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Synthetic Studies on Penems and Carbapenems (II)[1]. Substitution of the Acetoxy Group in 4-Acetoxyazetidin-2-one with Various Nucleophiles

Eugene Oh, Youn Young Lee, and Yang Mo Goo*

*Department of Chemistry and *Department of Pharmacy, Seoul National University, Seoul 151*

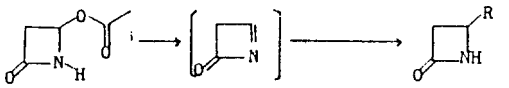
Seung-Un Park

Department of Cheistry, Konkuk University, Seoul 133. *Received April 29, 1986*

The availability and ease with which the acetoxy group could be exchanged with other groups has made 4-acetoxyazetidin-2-one derivatives[1-3] as attractive starting materials for construction of biologically interesting bicyclic systems like penems[4], carbapenems[5] and others[6]. Much attention has been focused on carbon-carbon bond formation at the 4-position of β-lactam compounds and many reports[5,7] have dealt with this carbon-extension reaction; however, there are limitations on the functionalities the extending units may contain. For example, the replacement of the acetoxy group in 4-acetoxyazetidin-2-one analogs by an enolizable carbon atom is fraught with difficulty; generally, the yields of β-lactam compounds having a 2-oxoalkyl group at C-4 position, which are obtained from 4-acetoxyazetidin-2-one by reaction with enolate anions, are poor[5,8,9] presumably due to the ring fragmentation[7]. The stability of a 4-substituted β-lactam compound seems to be very much depend on the availability of the non-bonding electron pair existing at the α-position of the substituent group; the non-bonding electron pair should induce decomposition of the β-lactam ring by breakage of the bond between C-4 and N-1. In this paper, we report new methods for formation of carbon-carbon, carbon-phosphorus, carbon-sulfur, carbon-oxygen, and carbon-nitrogen bonds at the C-4 position of 4-acetoxyazetidin-2-one by nucleophilic substitution of the 4-acetoxy group with various nucleophiles.

4-Acetoxyazetidin-2-one (**1**) was obtained by reaction of chlorosulfonylisocyanate (CSI) with vinyl acetate. Generally, CSI has been shown to react with a variety of olefinic substances through $[_2\pi_s + _2\pi_s]$ cycloaddition reactions to give N-chlorosulfonyl-β-lactams[10,11]. The N-chlorosulfonyl group of the addition product can be reduced to N-H by (a) benzene-2-mercaptopyridine in acetone at −30°C[12,13], (b) potassium iodide in aqueous sodium hydroxide[12,13], and (c) Raney nickel in ethanol[12,13] followed by aqueous hydrolysis[12] with 4N KOH in acetone[13] or saturated methanolic KOH[15]. We modified the Durst and O'Sullivans' method[16] to obtain 4-acetoxyazetidin-2-one in 39% yield, in which CSI was stirred with vinyl acetate at 10°C for 30 min to give the desired CSI addition product, and the N-chlorosulfonyl group was reduced by pouring the reaction mixture into a cold aqueous solution (0-5°C), with crushed ice, of sodium sulfite, sodium bicarbonate and potassium iodide with vigorous stirring.

Recent development of new carbapenem antibiotics, including thienamycin, demand new methods for formation of a new carbon-carbon bond by substitution of the acetoxy group of 4-acetoxyazetidin-2-one derivatives with carbanions. Treatment of 4-acetoxyazetidin-2-one(**1**) with various carbanion nucleophiles did not give good yields of substituted azetidinone products, especially with those of enolizable ones. Several special methods were developed for formation of new carbon-carbon bonds by substitution of the acetoxy group or the phenylsulfonyl group of 4-acetoxy- or 4-phenylsulfonylazetidin-2-one by reaction with silyl enol ether in the presence of Lewis acid catalyst[17,18] or by reaction with monoorganocuprate[19]. For substitution of the acetoxy group in 4-acetoxyazetidin-2-one with alkyl carbanions (Scheme 1), we examined several lithium organocuprates obtained by mixing copper iodide in various ratios to the alkyllithium (CuI-



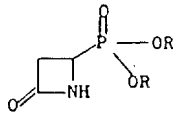
1 2a - 2c

a: R = $-CH_2COO$-t-But, b: R = n-But
c: R = 2-oxocyclohexyl

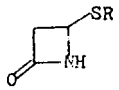
Scheme 1

RLi=1:3, 1:2 and 1:1) for nucleophilic substitution of the acetoxy group in **1** and found that the alkyllithium cuprate, $LiCuR_2$ or Li_2CuR_3 gave good yields of 4-alkylazetidin-2-ones **2a-2c** [$Li_2Cu(CH_2COO$-*t*-$Bu)_3$: 85% and $LiCu(CH_2COO$-*t*-$Bu)_2$: 51%; $LiCu(n$-$Bu)_2$: 86%; LiCu(2-oxocyclohexyl)$_2$: 87%]. The carbon bond formation reaction was carried out by addition of the THF solution of 4-acetoxyazetidin-2-one to the alkyllithium cuprate solution which was made under nitrogen gas in THF by gradually increasing the temperature of the mixture of CuI and lithium organo-carbanion from −78°C (or −40°C for *n*-BuLi) to 0°C. The mixture was stirred at 0°C for 0.5-1.5 hr and finally at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with saturated ammonium chloride solution until no blue color was noticed in the aqueous layer. Evaporation of the ethyl acetate layer gave crude products. The crude products were further purified by chromatography on silica gel columns.

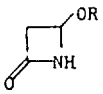
Also, we are interested to examine the scope of nucleophilic substitution reactions on the 4-acetoxy group of the 4-



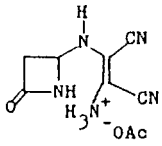
3a: R = Me
3b: R = Et
3c: R = Ph



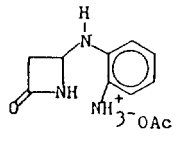
4a: R = n-Pro
4b: R = n-But
4c: R = Ph



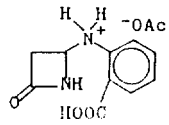
5a: R = 3-methylphenyl
5b: R = 3-formylphenyl
5c: R = 4-formylphenyl



7a



7b



7c

Table 1. Spectroscopic (IR and ^{1}H NMR) Data of Synthesized Compounds

	β-lactam C=O	N-H	solvent	1-NH	3-CH_2	4-CH	R
2a	1755	3320	DMSO-d_6	6.75(s)	2.6-3.3(m)	3.75(dd)	1.35(s, 9H, CH_3) 2.5(d, 2H, CH_2)
2b	1750	3350	$CDCl_3$	-**	2.3-3.4(m)	3.65(dd)	0.95(t, 3H, CH_3) 1.4(bm, 6H, CH_2)
2c	1790	3400	$CDCl_3$	-***	-***	3.25(m)	0.6-2.7(m, cyclohexanone)
3a$^+$	1760	3200	$CDCl_3$	7.4(s)	3.3(m)	-**	3.83(6H, d, J_{HP}=13Hz)
3b$^+$	1780	3200	$CDCl_3$	7.36(s)	3.16(m)	-***	1.36(6H, t, J=6Hz) 3.76(4H, m)
3c$^+$	1760	3200	$CDCl_3$	5.9(s)	3.75(m)	2.2(m)	7.0(aromatic)
4a	1770	3250	$CDCl_3$	6.9(s)	3-3.75(m)	4.85(dd)	1.1(t), 1.7(m), 2.7(t)
4b	1780	3300	$CDCl_3$	6.90(s)	3-3.65(m)	4.75(dd)	1.0(t), 1.5(m), 2.65(t)
4c	1750	3200	$CDCl_3$	6.65(s)	2.7-3.7(m)	5.0(dd)	7.4(aromatic)
5a	1785	3350	$CDCl_3$	-****	2.8-3.4(m)	5.5(dd)	2.25(3H, s), 6.9(m, Ph)
5b	1760	3450	DMSO-d_6	7.8(s)	2.7-3.6(m)	5.65(dd)	7.4(m, Ph), 9.95(s, CHO)
5c	1775	3450	DMSO-d_6	5.4(bs)	2.6-3.6(m)	5.8(dd)	7.4(m, Ph), 9.7, 9.95 (s, CHO)
7a	1750	3240-3380 $^+NH_3$;3150	DMSO-d_6	8.7(s)	2.5-3.5(m)	5.85(dd)	2.1(3H, s, CH_3) 5.0(3H, s, NH_3^+)
7b	1790	3350 NH_3^+;3100	DMSO-d_6	7.9(s)	2.74-3.5(m)	5.8(dd)	2.1(3H, s, CH_3) 4.0(3H, s, NH_3^+) 6.7(s, Ph), 6.75(s, NH)
7c	1755	3450 NH_3^+;3250	DMSO-d_6	6.8(s)	2.75-3.5(m)	5.8(dd)	6.7(Ph), 4.0(2H, s, NH_3^+) 8.7(1H, s, COOH)

*: NMR data were obtained with TMS as the internal standard with Varian EM-360 NMR spectrometer and IR data were obtained with Perkin-Elmer 710B spectrophotometer with samples as KBr pellets of thin films, **: not obvious in the spectrum, ***: observed in the cyclohexanone region, +: IR data for P=O **3a**: 1240; **3b**: 1230; and **3c**: 1220 cm^{-1} and for P-O-C, **3a**: 1030; **3b**: 1020; and **3c**: 1020 cm^{-1}, ++: covered by the doublets at 3.83 ppm, +++: covered by the multiplets at 3.76 ppm, ++++: covered by aromatic peaks.

acetoxyazetidin-2-one with various heteroatom-nucleophiles, since the new heteroatom substituted azetidin-2-ones would be very much useful as new starting materials for synthesis of heteroatom-substituted thienamycin analogs. The acetoxy group in 4-acetoxyazetidin-2-one(**1**) were found to be readily displaceable by heteroatom-nucleophiles. For the displacement of the acetoxy group in 4-acetoxyazetidin-2-one with trivalent phosphorus nucleophiles[20], 4-acetoxyazetidin-2-one(**1**) was refluxed with methyl, ethyl, or phenylphosophite in toluene for 2-5 hr. The reaction residues, obtained after evaporation of the solvent, were chromatographed on silica gel columns to give 4-dimethoxy-, 4-diethoxy- and 4-diphenoxyoxophosphinylazetidin-2-one (**3a, 3b** and **3c,** respectively) in 70-80% yields. Similarly, treatment of 4-acetoxyazetidin-2-one(**1**) with sulfur nucleophiles, such as *n*-propylmercaptan, *n*-butylmercaptan, and phenylmercaptan or oxygen nucleophiles, such as 3-methylphenol, 3-formylphenol, and 4-formylphenol gave the corresponding 4-alkylthio-(**4a** and **4b**) or 4-phenylthio-(**4c**) azetidin-2-ones and 4-(3′-methylphenoxy)-(**5a**), 4-(3′-formylphenoxy)-(**5b**), and 4-(4′-formylphenoxy)-(**5c**) azetidin-2-ones in 70-95% yields. However, the products obtained by nucleophilic substitution of the acetoxy group of 4-acetoxyazetidin-2-one with *n*-butylamine was unstable and decomposed[23]. On the other hand the acetoxy group of 4-acetoxyazetidin-2-one was successfully substituted by nitrogen nucleophiles such as diaminomaleonitrile (DAMN), *o*-phenylenediamine and anthranilic acid by stirring in acetic acid to give 4-nitrogen-substituted azetidin-2-one products **7a, 7b,** and **7c,** respectively in very good yields. The diaminomaleonitrile substituted azetidinone, **7a** is interesting since ring closure of its side chain with deamination will give azapenem analogs of thienamycin. Results of all spectroscopic data for the compounds obtained in this study are given in Table 1.

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