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TOTAL SYNTHESIS OF THIENAMYCIN ANALOGS. II

SYNTHESIS OF 2-ALKYL AND 2-ARYL THIENAMYCIN NUCLEI

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A new general synthesis leading to 2-alkyl and 2-aryl-1-carba-2-penem-3-carboxylic acids involves the preparation of a key thiolester intermediate **3**. This is reacted with Me_2CuLi or $(C_6H_5)_2MgCuX$ to give the corresponding methyl or phenyl ketone which undergoes a Wittig reaction to give the desired penems, which can be deblocked photolytically or by hydrogenolysis to give acids with good antibacterial activity.

Recently we reported[1] the total synthesis of the thienamycin nucleus **6** (R=H), involving a Wittig reaction for ring closure. We now wish to report an extension of this synthesis, which provides a general method for synthesizing 2-substituted 1-carba-2-penems. The synthesis involves the preparation of ketone intermediate **4** via the reaction of easily available lithium or magnesium aryl or alkyl cuprate on a thioester. These ketones (**4**) undergo a Wittig cyclization to give 2-alkyl and 2-aryl substituted analogs of thienamycin (**1**),[2] making available a large number of such analogs. The aryl analog **6b** shows activity superior to that of the nucleus **6** (R = H).

Oxidation of 1-(o-nitrobenzyloxycarbonylmethyltriphenylphosphoranyl)-4-(2-hydroxy-ethyl)-2-azetidinone (**2**)[1] using a small excess of Jones reagent in acetone at 0°, provided the corresponding acid which without purification was converted to the acid chloride (excess oxalyl chloride, CH_2Cl_2). Treatment of the crude acid chloride with 1.5 eq C_6H_5SH and pyridine in CH_2Cl_2, 0°, 1/2 h gave the thiolester **3** (66% from **2**) after chromatography on silica gel, 50% EtOAc/C_6H_6. IR 1740 (β-lactam), 1700 (thiolester), 1625 (ester).

Thiolester **3** is a key intermediate which on reaction with a lithium alkyl or aryl cuprate or a magnesium alkyl or aryl cuprate in ether/THF,[3] provides the corresponding alkyl or aryl ketones **4**, which can be cyclized by heating in xylene to the corresponding 2-alkyl- or 2-aryl-1-carba-2-penems **5**. This general sequence is exemplified by the preparation of sodium 1-carba-2-methyl-2-penem-3-carboxylate **6a** and sodium 1-carba-2-phenyl-2-penem-3-carboxylate **6b**.

Treatment of thiolester **3** with 2 eq of Me_2CuLi in 1:1 THF/Et_2O at -50° to -20° for 20 min and a further 5 min at -20° followed by NH_4Cl quench gave 28% of the methyl ketone **4a**. IR[4] 1740 (β-lactam), 1710 (ketone), 1620 (ester). NMR 2.16 s (CH_3C); after chromatography on silica gel (EtOAc elution), and 17% of recovered starting material.

Heating **4a** in xylene in the presence of a trace of pyridine, 45 min, gave the carbapenem **5a** in 25% yield. IR 1775 (β-lactam), 1720 (ester), 1630 (C=C). NMR (100 MHz) 7.3-8.2 (m, ArH), 5.72 (ABq, $C\underline{H}_2$-Ar), 4.2 (m, C-5 H), 3.5 (dd, αC-6 H, J_{5-6} = 5, J_{gem} = 16), 2.92 (dd, βC-6 H, J_{5-6} = 2.8, J_{gem} = 16), 2.86 (C-1 H, d, J = 10), 2.18 (s, $C\underline{H}_3$-). The p-nitrobenzyl ester of **4a** has been prepared by an entirely different route which does not comprise a general route to these ketones. Moreover, no attempts to deblock the p-nitrobenzyl-2-methyl-1-carba-2-penem-3-carboxylate obtained by cyclization of that ketone, are reported.[5] Photolysis of **5a** (degassed dioxane/water 50%, pH 7 phosphate buffer 0.5M, 5%, 1 hr) gave the desired **6a**, 15%.[6] UV $\lambda_{max}^{H_2O}$ 262 (NH_2OH extinguishable).

Treatment of **3** with 2 eq of $(C_6H_5)_2MgCuX$ (prepared from 4 eq C_6H_5MgBr and 2 eq CuI in Et_2O/THF 1:1, -15°, 20 min) at -15° to 0° for 45 min gave the ketone **4b** in 66% yield after chromatography on silica gel (50% EtOAc/C_6H_6). IR 1740 (β-lactam), 1680 (ketone), 1620 (ester).

Cyclization of **4b** was achieved by heating in refluxing xylene for 40 min (23% yield after recycling recovered **4b** once). IR 1780 (β-lactam), 1725 (ester), 1610 (C=C), 1525 (NO_2). NMR (300 MHz) 7.2-8.2 m (ArH), 5.68 (ABq, $C\underline{H}_2$-Ar), 4.4 (m, C-5 H), 3.59 (dd, J = 15, J = 5, αC-6 H), 3.3 (octet C-1 H), 3.1 (dd, J = 15, J = 3, βC-6 H). UV $\lambda_{max}^{CH_2Cl_2}$ 268, 300 (ε = 5000, NH_2OH extinguishable).

Hydrogenolysis of **5b** (10% Pd/C, equal wt, dioxane-water 1:1, $NaHCO_3$, 1 eq, 40 lbs H_2 pressure, 20 min) gave **6b**. UV $\lambda_{max}^{H_2O}$ 297 (NH_2OH extinguishable), NMR (300 MHz, D_2O) 7.39 (ArH), 4.37 (m, C-5 H) 3.5 (dd, J_{gem} = 18, $J_{5,6}$ = 5, C-6 αH), 3.23 (dd, J = 16, J = 9, C-1 α or βH), 3.16 (dd, J_{gem} = 18, $J_{5,6}$ = 3, C-6 βH), 3.07 (dd, J = 16, J = 7, C-1 α or βH).

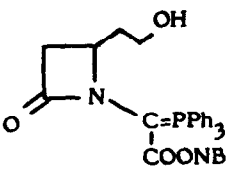
The antibacterial activity of **6a** could not be meaningfully determined because of its instability at the incubation temperature of 37°; however, as shown in Table I, **6b** has activity superior to the thienamycin nucleus (**6**, R = H). Like the thienamycin nucleus, **6b** is susceptible to β-lactamases as shown by its lower activity against penicillinase producing strains.

TABLE I

Inhibitory Zone Diameters (Millimeters)

vs. Penicillin-Sensitive and Resistant Bacterial Strains

Compound	Disc Content μg (nmol)	S. aureus		E. coli		Enterobacter Clocae	
		MB2985	MB2314	MB2482	MB2964	MB2647	MB2646
Ampicillin	10 (28)	33.5	13	20.3	0	18	0
6 (R = H)	8.2 (54)	20.5	0	20	0	21	16.5
6b	12.3 (49)	36	24	28.7	0	25.5	9.5

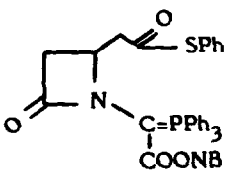


2

1) Jones Reagent

2) $(C\text{-}Cl)_2$, CH_2Cl_2

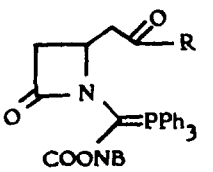
3) PhSH, pyridine



3

R_2CuLi

or R_2CuMgX



4

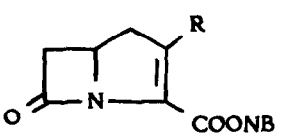
Δ

xylene

4a,5a,6a; R = CH_3

4b,5b,6b; R = Ph

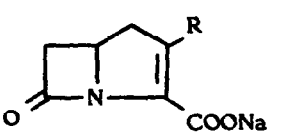
NB = o-nitrobenzyl



5

hν

or H_2, 10% Pd/C



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References and Notes

1) L. D. Cama and B. G. Christensen, "Total Synthesis of Thienamycin Analogs I," J. Am. Chem. Soc., 100, 8006 (1978).

2) See references 1 and 2 in "Total Synthesis of Thienamycin Analogs I" for isolation, bioactivity and structure of thienamycin.

3) R. J. Anderson, C. A. Henrich and L. D. Rosenblum, J. Am. Chem. Soc., 96, 3654 (1974).

4) IR spectra were run as thin film and are reported in cm^{-1}; NMR spectra were run in $CDCl_3$ on a Varian T-60 instrument unless otherwise specified, and are reported in δ units.

5) A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, J. C. S. Chem. Commun., 236 (1979).

6) Compound **6a** could not be lyophilized without considerable decomposition. IR and NMR spectra of **6a** are therefore not available; its presence in aqueous solution is inferred from its UV maximum at 262 nm (NH_2OH extinguishable). Its yield is calculated using an assumed ε = 7800 similar to descysteaminyl-thienamycin, D. H. Shih, J. Hannah and B. G. Christensen, J. Am. Chem. Soc. 100, 8004 (1978).

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