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FROM PENICILLIN TO PENEM AND CARBAPENEM. III[1)]
C_1-UNIT INTRODUCTION AT C-4 POSITION OF AZETIDINONE

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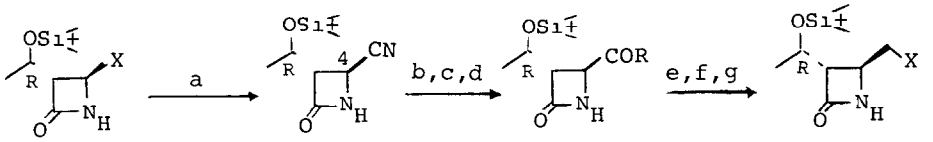
Summary Monocyclic β-lactams (1) were converted into 4-cyano derivative 2 (C_1-unit introduction) under two phase reaction conditions. The cyano group in 2 was successively transformed into 3 and 4, which are thought to be important precursors for the carbapenem synthesis.

In the previous communications we reported the efficient syntheses of the monocyclic β-lactams 1 from penicillin[1),2)]. Here we want to describe a new method for C_1-unit introduction at C_4-position of these β-lactams. To our best krowledge no method was reported for the cyano group substitution at C_4 position of 4-acetoxyazetidinone[3)], but in the case of our β-lactams 1 which have substituent at C_3-position we found that the cyano group was introduced in high yield.

Azetidinone 1a or 1b was treated with excess KCN in THF in the presence of 18-crown-6 (0.1 eq.), or more conveniently with KCN in a two phase reaction conditions (C_6H_6-H_2O, cat. $Bu_4\overset{+}{N}\overset{-}{B}r$) for 18 hr to give the crystalline cyano derivative 2, mp 138°C in 68 % isolated yield. NMR ($CDCl_3$) δ 0.08 (6H,s), 0.88 (9H,s), 1.25 (3H,d, J=6 Hz), 3.65 (1H,t, J=2.5 Hz), 4.35 (1H,d, J=2.5 Hz), 4.30 (1H, dq, J=6 and 2.5 Hz), 6.65 (1H, br.s). IR (Nujol) ν cm^{-1} : 3220, 2240, 1780, 1755. The dimeric product 5, mp 158°C was obtained in 10 % yield as a by-product, but when the methylsulfonyl derivative 1c was used



1 a : X = OAc
b : X = $SO_2C_6H_5$
c : X = SO_2Me

2

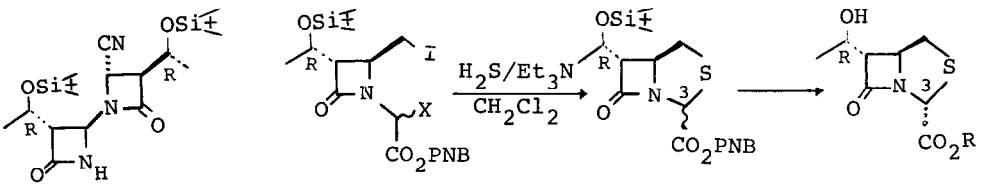
3 a . R = NH_2
b : R = OH
c : R = OMe

4 a : X = OH
b : X = OTs
c : X = I

a, ex. KCN /C_6H_6-H_2O, cat. $Bu_4\overset{+}{N}\overset{-}{B}r$, b, 2 eq.$Na_2CO_3$-$H_2O_2$/ Acetone-$H_2O$, 1 hr c, 3 eq. KOH / H_2O-EtOH, 20 hr, r.t. ; d, CH_2N_2 ; e, 10 eq. $NaBH_4$ / THF:H_2O (4:1), 1 hr, 10°C; f, 2 eq. TsCl,Et_3N:DMAP/ THF:CH_2Cl_2(1:4) ; g, 3 eq. NaI/ Acetone, reflux, 6 hr.

instead of 1a or 1b the formation of the dimeric product 5 was suppressed to less than 10 % of the monomer 2. Manipulation of the cyano group in 2 was carried out as follows. Alkali hydrolysis of 2 in the presence of H_2O_2 gave the amide derivative 3a, mp 87°C in 85 % isolated yield, which was further hydrolyzed to the acid 3b, mp 134°C (80%). After esterification with diazomethane the ester derivative 3c, mp 78°C, $[\alpha]_D^{25}$-12.8 (c=1.01, $CHCl_3$) was converted into the alcholic derivative 4a, mp 90°C which was tosylated to the tosyl derivative 4b, mp 89°C. The Finkelstein substitution reaction to 4b was successfully performed to afford the 4-iodomethyl azetidinone derivative 4c, mp 129°C in 95 % yield.

Compound 4c could be converted to thienamycin[4], and was a useful precursor for the synthesis of iso-penam derivative 8[5]. The aminal 6a prepared from 4c and p-nitrobenzyl glyoxylate in refluxing benzene was chlorinated ($SOCl_2$, 2,6-lutidine/THF) to 6b, which was transformed into iso-penam derivative 7a, mp 95°C and 7b (2:1) with H_2S-Et_3N in CH_2Cl_2. Under the deprotection conditions ($Bu_4\overset{+}{N}F^-$/AcOH/THF) both 7a and 7b gave the same alcholic derivative 8a. In the presence of one equivalent of aq. $NaHCO_3$ 8a was hydrogenolysed to give the Na salt 8b, which has no remarkable antibacterial activity.



5

6a : X=OH
b : X=Cl

7a : 3α isomer
b : 3β isomer

8a : R = PNB
b : R = Na

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