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ONE STEP SYNTHESIS OF α-AMIDO-β-LACTAMS[1]

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All clinically useful penicillin and cephalosporin antibiotics are characterized by the presence of an α-amido side chain on a cis-β-lactam. α-Azido-β-lactams have been synthesized in this laboratory as progenitors of α-amino and α-amido-β-lactams[2] and utilized for the synthesis of trans-penicillin V methyl ester[3] It seemed desirable, however, to seek a more direct access to α-amido-β-lactams — preferably with the cis configuration

Attempts to prepare the acid chloride from α-acylamino acids usually lead to azlactones which combine with imines to produce imidazolidones[4] The use of acid chlorides from N-alkyloxy carbonylglycines which do not form azlactones was, therefore, of interest. From a scrutiny of the literature it was apparent that only limited and unsuccessful attempts have been made in the past to prepare a β-lactam from N-benzyloxycarbonylglycyl chloride and an imine.[5] Our efforts in this direction have been more successful.

Reaction of benzyloxycarbonylglycyl chloride (1a) (prepared separately or in situ) or p-nitrobenzyloxycarbonylglycyl chloride (1b) with p-anisylidene-p-toluidine (2a) in the presence of triethylamine gave the corresponding β-lactams (3a, 3b) The stereochemistry of the β-lactams formed was difficult to assign because the relevant protons in both cases were grouped together in a multiplet centered in the region τ 4 80-5.00 The cis stereochemistry of H-3 and H-4, however, became apparent from the following sequence of reactions

The benzyloxycarbonyl or p-nitrobenzyloxycarbonyl group in (3a) and (3b) was easily cleaved by treatment with hydrobromic acid in acetic acid solution The α-amino-β-lactam (3c) formed in this reaction was acylated with phenoxyacetyl chloride to give phenoxyacetamido-β-lactam (3d) In the PMR spectrum of (3d) H-3 appeared at τ 4 23 as a doublet of doublets It was reduced to a doublet (J = 5 5 Hz) at τ 4 66 on the addition of D_2O This value of the coupling constant between the C-3 and C-4 protons[6] establishes the cis stereochemistry of the β-lactam (3d). Furthermore, since no epimerization is involved in the conversion of (3a) and (3b) to (3c), cis stereochemistry can be assigned to these β-lactams as well

The stereochemistry of 1-(p-anisyl)-3-(benzyloxycarbonylamino)-4-(2-furyl)-azetidine-2-one (3e) prepared by the reaction of (1a) with (2b) was determined using $Eu(Fod)_3$ shift reagent Addition of the shift reagent resolved the multiplet at τ 4 45-4 67 in the nmr spectrum of (3e) such that H-4 appeared as a distinct doublet (J = 5 Hz) indicating its cis geometry

This method for preparing α-substituted β-lactams was next extended to the synthesis of bicyclic systems. The penam (6a) was obtained in a poor yield from (1a) and the thiazoline (4a) Better yields (50-70%) of the cephams (6b) and (6c) were obtained from the corresponding dihydrothiazines (5a) and (5b). Cleavage of the benzyloxycarbonyl group followed by acylation with phenoxyacetyl chloride gave cepham (6d) and (6e) with penicillin V side chain in satisfactory yields. The cepham (6d) obtained by this method was identical in all respects with the compound synthesized earlier in this laboratory through the use of azidoacetyl chloride.[6] The cepham (6e) was catalytically reduced to the corresponding aminocepham (6f). The cepham analog (7a) was obtained by the condensation of (1a) with 2,2-dimethyl-3-phenyl-5,6-dihydro-1,4-thiazine.[7] Conversion of (7a) to (7b) was carried out essentially by the same method as described above.

The reaction of (1b) with the thiazoline (4b) gave a product which lacked the β-lactam carbonyl absorption (1770-1780 cm^{-1}) in its ir spectrum. The carbamate NH absorption (3250-3300 cm^{-1}) was also absent. There was however, a peak at 1745 cm^{-1}, which could be assigned to a fused imidazolidinone carbonyl function. The nmr spectrum of this product was significant. Besides the expected signals for the various protons in the molecule there appeared a downfield resonance at τ 2.96 corresponding to one proton (C_5-H) . On the basis of these data coupled with the fact that it was isomeric with the expected β-lactam as revealed by its mass spectral analysis (M^+ at m/e 409), we have assigned structure (8) to this product Mechanistically the formation of (8) could be formulated as arising via the acylinium intermediate as shown in Fig 1. At this stage we are unable to account for the difference between thiazoline (4b) and the thiazoline (4a) or the dihydrothiazines (5a) and (5b) in their reaction with acid chlorides.

By analogy with some of our previously reported work on desulfurization of penam and cepham derivatives,[8] the E-configuration can be assigned to the bicyclic β-lactams (6a-6f) The exclusive formation of cis-β-lactams from Schiff bases (2a and 2b) would indicate that the reaction mechanism does not involve a ketene as an intermediate.[9] The cis stereochemistry of 3a-3d is of potential synthetic interest since appropriately substituted monocyclic

β-lactams have been used as intermediates for the synthesis of penicillins, cephalosporins and analogs.

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$ROCONHCH_2COX$

1

(a) $R = C_6H_5CH_2$, $X = Cl$

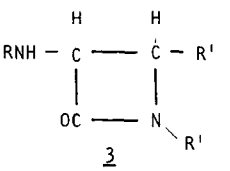
(b) $R = p\text{-}NO_2C_6H_4CH_2$, $X = Cl$

$R'' - CH{=}N - R'$

2

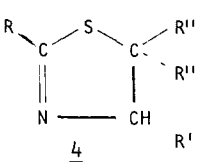
(a) $R' = p\text{-}CH_3C_6H_4$, $R'' = p\text{-}CH_3OC_6H_4$

(b) $R' = p\text{-}CH_3OC_6H_4$, $R'' =$ 



3

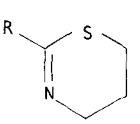
	R	R'	R''
(a)	$PhCH_2OCO$	$p\text{-}CH_3C_6H_4$	$p\text{-}CH_3OC_6H_4$
(b)	$p\text{-}NO_2C_6H_4CH_2OCO$	$p\text{-}CH_3C_6H_4$	$p\text{-}CH_3OC_6H_4$
(c)	H	$p\text{-}CH_3C_6H_4$	$p\text{-}CH_3OC_6H_4$
(d)	$C_6H_5OCH_2CONH$	$p\text{-}CH_3C_6H_4$	$p\text{-}CH_3OC_6H_4$
(e)	$PhCH_2OCO$	$p\text{-}CH_3OC_6H_4$	



4

(a) $R = p\text{-}NO_2C_6H_4$, $R' = R'' = H$

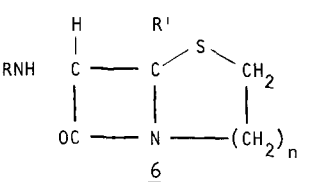
(b) $R = H$, $R' = CO_2Me$, $R'' = CH_3$



5

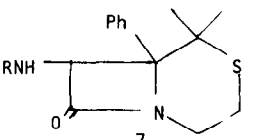
(a) $R = C_6H_5$

(b) $R = p\text{-}NO_2C_6H_4$



6

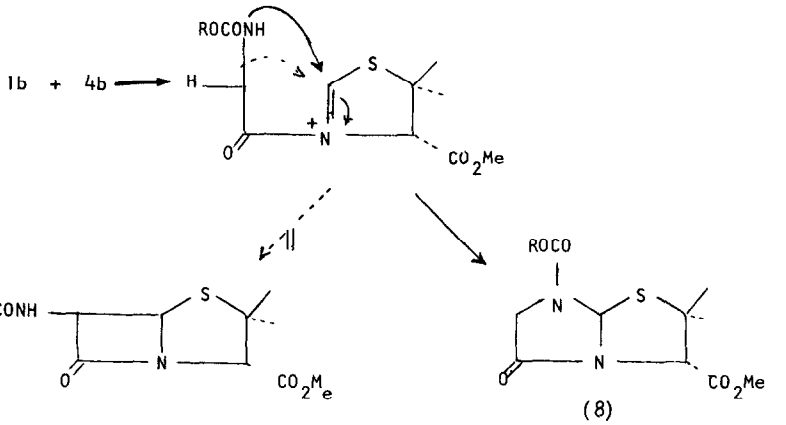
	R	R'	n
(a)	$PhCH_2OCO$	$p\text{-}NO_2C_6H_4$	1
(b)	$PhCH_2OCO$	C_6H_5	2
(c)	$PhCH_2OCO$	$p\text{-}NO_2C_6H_4$	2
(d)	$PhOCH_2CO$	C_6H_5	2
(e)	$PhOCH_2CO$	$p\text{-}NO_2C_6H_4$	2
(f)	$PhOCH_2CO$	$p\text{-}NH_2C_6H_4$	2



7

(a) R= $PhCH_2OCO$

(b) R= $PhOCH_2CO$



(8)

R = $p\text{-}NO_2C_6H_4CH_2$

Fig 1

1 Part XXVI of Studies on Lactams For part XXV see A.K. Bose, J C Kapur, S.D. Sharma, and M S Manhas, Tetrahedron Lett , 000(1973)

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