STEREOSELECTIVE PREPARATION OF 6-β–BROMOPENICILLANIC ACID DERIVATIVES

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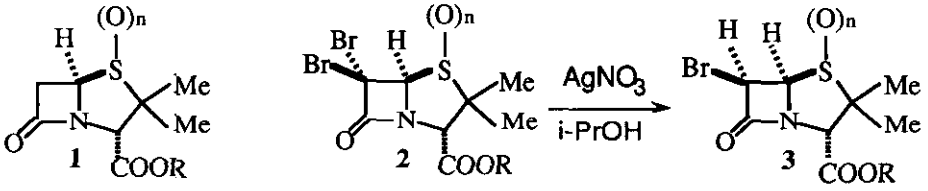
Abstract - A new stereoselective method for the preparation of 6-β-bromopenicillanates is described. It comprises the reaction of 6,6-dibromopenicillanates with silver nitrate in 2-propanol.

Previously we have reported the electrochemical dehalogenation of 6-halopenicillanic acids,[1] an useful method for the preparation of penicillanic acid and its 1,1-dioxide (**1**),which was one of the semisynthetic β–lactamase inhibitors.[2] In the present paper we wish to report a stereoselective hydrogenolysis of 6,6-dibromopenicillanic acid derivatives (**2**), what may be used as one of suitable methods for the preparation of 6-β-bromopenicillanic acid derivatives (**3**). 6-β-Bromopenicillanic acid (**3**) (R=H, n=0) is another specific, powerful and irreversible inhibitor of β-lactamases.[3-6]



R= -H, -Me, -CH_2Ph, -$CH(Ph)_2$, -$CH_2OCOCMe_3$

n = 0, 2

There are three principal routes for the preparation of 6-β–bromopenicillanates reported in the literature: (a) an epimerisation of 6–α-bromopenicillanates,[7-9] (b) hydrogenolysis of 6,6-dibromopenicillanates, [8,10-13] and (c)nucleophilic S_N2 displacement on penicillin 6-triflates or nonaflates with soft nucleophils.[14-16]

During the course of our work on reductive dehalogenation of 6-halopenicillanates into penicillanates it was found that the reaction of 6,6-dibromopenicillanic acid derivatives (**2**) with silver nitrate in 2-propanol gave 6-β-bromopenicillanic acid derivatives (**3**) in high yield (Table 1).

To the obtained compounds (**3**) were assigned beta configurations at C-6 on the basis of H(5)-H(6) coupling constants, which in all cases were predominantly in the region of 4.4 Hz.[17] It should be noted that the reaction at C-6 of various derivatives of penicillanic acid are known to result in 6-α substitution.[18] In relation to other procedures[8,11] in which the products were the mixtures containing unchanged 6,6-dibromo-, 6–α-bromo, desired 6-β-bromopenicillanates and over-reduced 6,6-dihydropenicillanates, by this method only derivative of 6-β–bromopenicillanic acid was obtained. It should be noted that only 6-β-bromo-derivatives are active. When benzyl

Table 1

Yields and some Physicochemical Data of 6-β-Bromopenicillantes (3)							
			^{1}H Nmr $CDCl_3$ (δppm)#				
Entry	n	R	5-H	6-H	J (Hz)	Rf	Yield %
1*	0	CH_2Ph	5.57	5.30	3.8	0.48 a	89
2**	0	$CH_2OCOC(Me)_3$	5.59	5.34	4.0	0.41 a	74
3	2	Me	4.80	5.37	4.5	0.30 b	83
4*	2	CH_2Ph	4.76	5.34	4.4	0.44 b	83
5***	2	$CH(Ph)_2$	5.27	5.87	4.5	0.31 a	73
6	2	$CH_2OCOC(Me)_3$	4.81	5.44	4.0	0.27 a	76

#Internal reference: TMS; JEOL Fx 90 Spectrometer

a) cyclohexane-ethyl acetate (8:2); b) benzene-acetone (95:5)

* see also Ref. 11, ** see also Ref. 16, ***see also Ref. 27.

ester of 6,6-dibromopenicillanic acid (**2**) (R=-CH_2Ph, n=0) was treated with silver nitrate in 2-propanol benzyl ester of 6-β–bromopenicillanic acid (**3**) (R=-CH_2Ph, n=0) was obtained, which upon oxidation with potassium permanganate gave benzyl ester 6-β-bromopenicillanic acid 1,1-dioxide (**3**) (R=-CH_2Ph, n=2). The identical product (**3**) was obtained, when first oxidation was performed and then the reaction with silver nitrate in 2-propanol.

Since l,l-dioxides (**3**) are more stable, all experiments were done on corresponding 1,1-dioxides of protected 6,6-dibromopenicillanic acid. The obtained product could not be purified by column chromatography on silica gel, because during the chromatography 6-β- derivative was completely transformed into 6-α-derivative.

To gain further information about the course of the reduction process, benzyl ester of 6,6-dibromopenicillanic acid 1,1-dioxide was treated with silver nitrate in completely deuteriated 2-propanol /$(CD_3)_2CDOD$/ instead of 2-propanol. The ^{1}H nmr spectrum (taken in $CDCl_3$, 90 MHz) has shown that H-(6) doublet at 5.34 ppm has disappeared, while the H-(5) doublet at 4.76 ppm has sharpened to singlet at 4.74 ppm. The same reaction was performed with methyl ester of 6,6-dibromopenicillanic acid 1,1-dioxide as substrate.. The ^{1}H nmr spectrum (taken in $CDCl_3$, 90 MHz) has shown that H-(6) doublet at 5.37 ppm has disappeared, while H-(5) doublet at 4.80 ppm has sharpened to singlet at 4.78 ppm. On the contrary, the identical reaction in Me_2CHOD has shown no evidence of deuterium incorporation. These results indicate that hydrogen is selectively transfered from the methine group of 2-propanol.[19]

The significance of the present findings is not only the preparation of 6-β-bromopenicillanates, but also the application of this reaction to the synthesis of deuterium labelled penam derivatives, since regiospecific and streoselective labelling of C-6-α- is possible, what is complementary to labelling C-6-β-penam. Labelling the carbon-6 of penam derivatives [20-22] is very useful in mechanistic studies of β-lactamase inactivators such as 6-β–

bromo- and 6-β-iodopenicillanic acid, [23] 6-α-chloro- [24] and penicillanic acid 1,1-dioxide[25] for various β-lactamases.[26]

However, hydrogenolysis depends not only on different salts but also on the solvent used. The effect of solvents and salts on product formation was examined on benzyl ester of 6,6-dibromopenicillanic acid 1,1-dioxide as substrate according to the general procedure.While no reaction in benzene, methylene chloride and acetonitrile was observed, in dioxane and methanol degradation occurred, in secondary alcohols the reaction proceeded well, particularly in 2- propanol. Different salts in 2-propanol were also investigated. Nitrates (sodium, mercury or cobalt) gave 6-β-bromo isomer, but with the starting substance and degradation products (^{1}H nmr and tlc) in law yield. Among silver salts good results were obtained with silver trifluoroacetate when 6-β–bromo isomer was obtained as solvate with 2-propanol (^{1}H nmr).The best results were obtained with silver nitrate and 2-propanol. On the contrary, silver tetraflouroborate gave 6-α-bromo derivative, silver acetate gave the mixture of 6-α-bromo- and 6,6-dihydropenicillanate, while silver chromate was unreactive under the same reaction conditions. Reaction with other salts which were no silver salts nor nitrates were slower and the mixtures of products were obtained. In addition, reaction with zinc chloride was also slow and 6-β-bromo isomer was obtained.

It should be noted that there was no reaction when thus obtained 6-β-bromopenicillanic acid derivative itself was treated with silver nitrate in 2-propanol, what confirmed the stereoselectivity of this reaction. Contrary to that, no rules existed in the same reaction with 6-α–bromopenicillanates; some of them were unreactive like benzyl 6-α-bromopenicillanate and methyl 6-α-bromopenicillanate 1,1-dioxide, but benzyl 6-α-bromopenicillanate 1,1-dioxide gave the mixture of 6,6-dihydropenicillanate 1,1-dioxide and the starting material. Molar ratio of 6,6-dibromo derivative of penicillanic acid and silver nitrate was 1:4. Higher molar ratio (1:8) did not lead to dihydro-penicillanates. Catalytic quantities of silver nitrate were inefficient and the reaction was slow.

According to this method several derivatives of 6-β-bromopenicillanate and their 1,1-dioxides were prepared, indicating that the new procedure could be used as a general method for the preparation of 6-β-bromopenicillanic acid derivatives.

The typical experimental procedure is illustrated as follows:

The mixture of 6,6-dibromopenicillanic acid derivative (1 mmol), silver nitrate (4 mmol) and 2-propanol (20 ml) was stirred under reflux (1 to 10 h) till the starting substance disappeared (tlc). The reaction mixture was filtered off and the filtrate was evaporated. Methylene chloride (5 ml) was added and precipitate was filtered again. Filtrate was washed with water and after evaporation of dried ($MgSO_4$) organic layer the derivative of 6-β-bromopenicillanic acid was obtained.

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