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THE SYNTHESIS OF β-LACTAMS BY THE CYCLIZATION OF β-HALOPROPIONAMIDES

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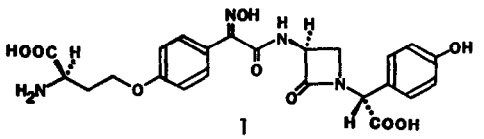
There has been considerable recent interest in the synthesis of monocyclic β-lactams as a result of the isolation, from fermentation cultures, of antibiotics such as nocardicin A (1)[1,2,3] and the observation of the remarkably high antimicrobial activity associated with these products.[1]



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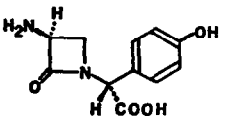

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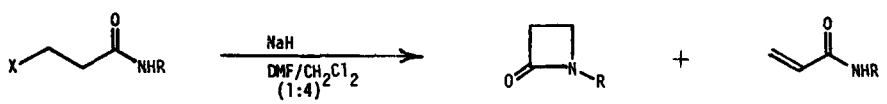
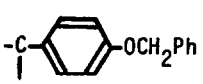
In connection with our work on the synthesis of naturally-occurring β-lactams, we have recently explored new methods for the formation of the azetidinone ring, including cyclopropanone ring expansion[4,5,6] and oxidative decarboxylation of azetidine carboxylates[7,8,9]. We now describe studies on the cyclization of β-halopropionamides, a procedure which provides another useful general route to 4-unsubstituted monocyclic β-lactams[10].

Table I



3 4 5

R	X	0.1M[a]	0.05M[b]	0.1M	0.05M
$-CH_2CH_2Ph$	Br	0	50	70	0
$-C(CH_3)_2-COOEt$	Cl	0	86	74	0
	Cl	32	76	20	0

a, 30 min. addition; b, 2-5 hr. addition.

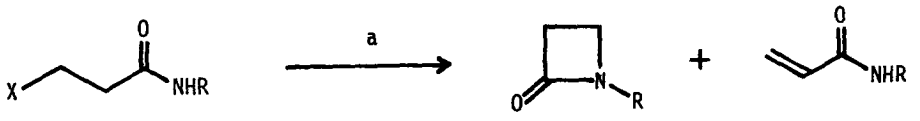
The cyclization of β-halopropionamides to azetidinones has been investigated by earlier workers[11,12,13], principally, Knunyants[11], and has been effective in recent syntheses of fused β-lactam systems[14,15,16] where geometrical factors are unfavorable for the competing elimination reaction. However, because of the readiness with which such β-halo amides are converted to acrylamides this method of ring-closure has not been previously regarded as an attractive route to unsubstituted azetidinones.

Our initial attempts to apply this cyclization to the preparation of N-alkyl unsubstituted β-lactams were only partially successful. Under the usual conditions employed for the ring closure[14] (NaH, DMF/CH_2Cl_2, 0.1M, 25°, 1 hr), β-elimination predominated, providing azetidinone only as a minor side-product (Table I). Accordingly we sought to develop reliable experimental conditions which might favor the desired cyclization over the competing elimination. This report describes our findings on the role of dilution, rate of addition and choice of halide in favoring ring-formation. As is shown in the following discussion, conditions can be found for developing this reaction into an efficient general method for the preparation of monocyclic β-lactams related to the nocardicins.

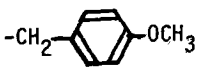
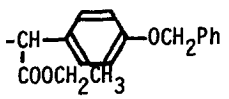
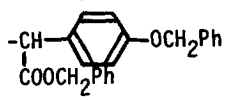
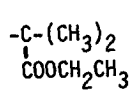
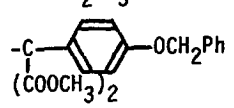
We have outlined, below, a typical procedure for the formation of an intermediate β-bromo amide (3) followed by conversion to the corresponding β-lactam (4). The β-chloro and β-bromo amides[17] were prepared by reaction of β-chloropropionyl chloride or β-bromopropionyl chloride with the corresponding primary amines in methylene chloride in the presence of N,N-dimethylaniline[19]. The cyclization of the amide to the β-lactam was markedly dependent on the concentration of the solution and the rate of addition of amide to base. As shown in Table I dilution clearly favors the intramolecular displacement over the competing elimination reaction. (In practice, it was found most advantageous to add a solution of the β-halo amide in DMF/CH_2Cl_2 (1:4) (0.1M) to a suspension (0.1M) in NaH in DMF/CH_2Cl_2 (1:4) to avoid formation of acrylamide side-products.)

Table II summarizes the results obtained when the halide is varied. The β-bromo amides gave more favorable ratios of lactam to acrylamide in cases where mixtures of 4 and 5 are obtained. For example, even in dilute solution, 3-chloro-N-phenethylpropionamide yielded little β-lactam compared to the corresponding 3-bromo derivative.

Table II[17]



3 4 5

R	X	yield (%)	
	Br	41	32
	I[18]	56	13
$-CH_2CH_2Ph$	Cl	22	61
	Br	50	0
	Cl	26	50
	Br	60	6
	Br	80	0
	Cl	14	20
	Br	46	0
	Cl	86	0
	Br	66	0
	Cl	76	0
	Br	64	0

a, NaH (0.05M) in DMF/CH_2Cl_2 (1:4), 2-5 hr. addition.

N-(3-Bromopropionyl)-2-[p-(benzyloxy)phenyl]glycine ethyl ester.

To a stirred solution of 2.5g (5.5mmol) of 2-[p-(benzyloxy)phenyl]glycine ethyl ester hydrotosylate and 2.3ml of N,N-dimethylaniline in 65ml of dry methylene chloride at -20°C (ice-methanol bath) was added over 20 min 1.15ml (11mmol) of 3-bromopropionyl chloride in 5ml dry methylene chloride. After completion of addition, the reaction was allowed to come to room temperature and stirred for 1.5 hr. The clear solution was diluted with methylene chloride and washed successively with 10% HCl, H_2O, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give 2.5g of a white solid. Recrystallization from aqueous EtOH gave white crystals, 2.0g (87%); mp 98-99°C.[17]

Ethyl α-[p-(benzyloxy)phenyl]-2-oxo-1-azetidineacetate.

To a suspension of 0.375g(7.8mmol)of a 50% mineral oil dispersion of NaH (pre-washed

with pentane) and 15ml of dry N,N-dimethylformamide in 55ml of CH_2Cl_2 was added over 3.5 hr, a solution containing 2.98g (7.1mmol) of N-(3-bromopropionyl)-2-[p-(benzyloxy)phenyl]glycine ethyl ester and 15ml of dry N,N-dimethylformamide in 55ml of CH_2Cl_2. After completion of the addition the reaction was stirred for 3 hr at room temperature, treated with 10ml of a saturated NH_4Cl solution, and the resulting mixture diluted with ether and CH_2Cl_2. The organic phase was separated, washed with H_2O, then with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave an orange oil which was crystallized from ether-hexane to give 1.9g (80%) of white solid, mp 52-54°C.[17]

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References and Notes

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17. All new compounds had satisfactory spectroscopic properties and elemental analysis.

18. Prepared by reaction of 3-chloro-N-cyclohexylpropionamide with NaI in dry methyl ethyl ketone (reflux, 4 hr) (90%).

19. Use of pyridine or triethylamine resulted in low yields of lactam, along with substantial amounts of acrylamide, 5.

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