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A Convenient Synthesis of *cis*-3-Aryl-2-Azetidinones[1]

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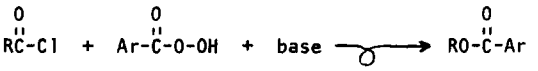
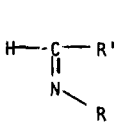
Denney and Sherman[2] have described a molecular rearrangement mediated by m-chloroperoxybenzoic acid for the efficient conversion of the acid chloride 1 to the ester 2. In the course of our studies on the synthesis of substituted β-lactams we became interested in the application of this method to a β-lactam acid chloride to obtain a 3-hydroxy-2-azetidinone derivative.



1 2

Acid chloride-β-lactams 4 (a-d) were prepared in good yield by refluxing phenylmalonyl chloride with the appropriate imine 3 in benzene according to the method of Ziegler et al.[3] m-Chloroperoxybenzoic acid was added to the β-lactam 4 in dichloromethane at 0° followed by dropwise addition of triethylamine. The reaction mixture was stirred overnight and then washed with 5% sodium bicarbonate, water and dried over $MgSO_4$ and stripped of solvent. The material so obtained was purified by column chromatography and crystallization. To our surprise, the products proved to be the β-lactams 5 (a-d). PMR spectroscopy showed that in each case the *cis* isomer was produced exclusively.



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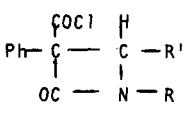

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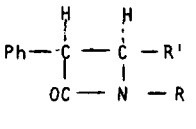
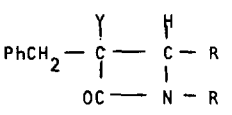


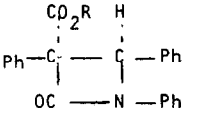
5

	R	R'	m.p.
a.	C_6H_5	C_6H_5	183-184°[6]
b.	p-C_6H_4-CH_3	p-$C_6H_4OCH_3$	165°
c.	β-naphthyl	p-$C_6H_4OCH_3$	175-175.5°
d.	α-naphthyl	C_6H_5	153°

Ziegler et al[3] have hydrolyzed the β-lactam acid chloride 6 with dilute acetic acid to the acid 7 and decarboxylated 7 to 8 by fusion. Repetition of this work and PMR examination of the product revealed that a *cis*-β-lactam had been formed. But the acid chloride β-lactam 6 did not react with m-chloroperoxybenzoic acid.



6, Y=COCl
7, Y=CO_2H
8, Y=H



9, R=CH_3
10, R=CH_2Ph
11, R=H

To obtain information about reaction mechanism, it was decided to study the stereochemistry of decarboxylation of the free acid corresponding to 4a. Attempts to hydrolyze 4a by the method successfully used by Ziegler and coworkers for 6 led, however, to the scission of the β-lactam ring. On the other hand, reaction with methanol gave the β-lactam methyl ester 9 readily. Saponification of 9 without cleavage of the β-lactam ring was not possible. Treatment of 4a with benzyl alcohol gave the benzyl ester 10 which could be hydrogenated over Pd/C to the free acid 11. Since the thermolysis of 11 gave the *cis* β-lactam 5a, it is possible that this acid 11 is an intermediate in the transformation of 4 to 5. On the basis of data at hand, however, it is difficult to account satisfactorily for the divergence between 4 and 6 in this reaction with m-chloroperoxybenzoic acid or dilute acetic acid. Further studies on

the mechanism of the conversion of 4 to 5 under the influence of m-chloroperoxybenzoic acid are necessary.

Since decarboxylation usually takes place with retention of configuration, it would appear that the β-lactam formation from the substituted malonyl chloride proceeds stereospecifically to the E form of 4. Furthermore, in the conversion of 4 to 5, an explicit anion at C-3 is unlikely to be involved since such an anion has been shown to rearrange a *cis* β-lactam to its more stable *trans* form.[4]

It is interesting to note that a previous synthesis[5] by a direct method, namely the reaction of phenylacetyl chloride with N-benzylideneaniline in presence of triethylamine, produced the *trans* isomer of 5a exclusively.

Notwithstanding the lack of mechanistic details, m-chloroperoxybenzoic acid mediated facile dechlorocarbonylation of readily available β-lactams of type 4 constitutes a short, stereospecific synthesis[6] of *cis*-3-aryl-2-azetidinones. In recent years *cis*-β-lactams have assumed importance because some appropriately substituted members of this family have been used as key intermediates in the synthesis of penicillins, cephalosporins, and analogs.[7]

All the new compounds reported in this communication have been characterized by satisfactory elemental and spectral analyses.

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