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SYNTHESIS OF β-LACTAMS THROUGH THE REACTION OF MIXED ANHYDRIDES AND IMINES[1]

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Among the various methods for the preparation of β-lactams, the "acid chloride-imine[2]" reaction is very widely in use. The α-azido-β-lactams which serve as progenitors of α-amino-β-lactams are obtained from azidoacetyl chloride and imines. *trans*-Penicillin V methyl ester has been synthesised through this approach[3]. The preparation of azidoacetyl chloride, however, is not without the danger of explosive decomposition.

The stereochemistry of the β-lactams formed in the "acid chloride-imine" reaction is unpredicable[4] and no single mechanism explains satisfactorily the course of this reaction. Since steric control over the β-lactam formation is highly desirable, we examined the possibility of modifying the stereochemistry of β-lactam formation by changing from acid chloride to other acid derivatives capable of forming a peptide bond.

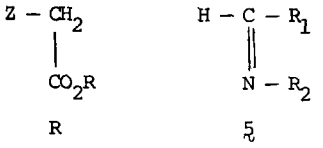
A modified method that we have developed for the synthesis of α-azido-β-lactams and analogs involves the use of mixed anhydrides in place of acid chlorides. The anhydride 2 can be prepared *in situ* by stirring the carboxylic acid 1 with trifluoroacetic anhydride in dichloromethane at room temperature for 10 min. followed by dropwise addition of triethylamine. After stirring another 20 min., the Schiff base 5 and triethylamine in dichloromethane are added dropwise, refluxed for 1 hr. and stirred overnight. Thereafter the reaction mixture is washed with water, dried over $MgSO_4$ and stripped of solvent to give the crude β-lactams (7a-d). The yields of β-lactams obtained by this method (30-70%) were comparable to those formed through the "acid chloride-imine" reaction.

In a previous publication[5], we have described the use of silylated carboxy substituted imines for the preparation of β-lactams with free carboxy groups. We have found that the mixed anhydride method can also be used with the Schiff base 6 to give the free acid β-lactam 7b.

During the course of this work it was found that the mixed anhydrides (3 and 4) obtained from carboxylic acids and ethyl chloroformate or isobutyl chloroformate can also be used for

β-lactam synthesis. The yields of the 2-azetidinones using these mixed anhydrides were nearly comparable with those obtained through the intermediacy of a mixed anhydride of trifluoroacetic acid.

A study of the nmr spectra of β-lactams 7a-d prepared using this method and those formed by the "acid chloride-imine" procedure showed that similar *cis/trans* ratios were obtained in both cases. Probably the same mechanism is operative in these reactions.



1. H
2. $COCF_3$
3. $CO_2C_2H_5$
4. CO_2iBu

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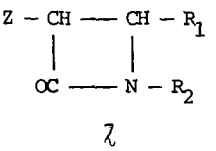

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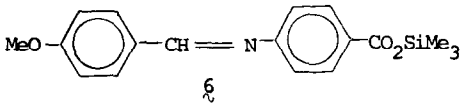
	Z	R_1	R_2	Config.
a.	PhO	C_6H_4OMe-p	$CHPh_2$	*cis*
b.	N_3	C_6H_4OMe-p	$C_6H_4CO_2H$-p	*trans*
c.	N_3	Ph	Ph	*cis/trans*
d.	PhO	Ph	Ph	*cis/trans*



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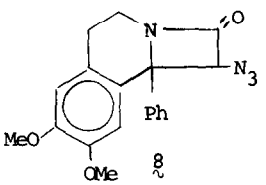

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Although the mixed anhydride procedure does not substantially modify the steric course of β-lactam formation, it does provide a short and safe alternative to the azidoacetyl chloride-imine reaction. Formation of the azido polycyclic β-lactam 8 in good yield through a mixed anhydride further demonstrates the scope of this method.

References

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