Asymmetric Synthesis of β-Lactams

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Summary Cycloaddition of chiral carbodi-imides to prochiral ketens yields diastereoisomeric, non-racemic mixtures of 2-iminoazetidin-4-ones, the formation of one of the diastereoisomers being preferred; the composition of these mixtures was determined.

ONE possible route to β-lactam systems is the cycloaddition of carbodi-imides to ketens, and this reaction has been investigated using achiral substrates.[1] We now report the use of optically active carbodi-imides and prochiral ketens in this synthesis.

R^1–N=C=N=R^2

(I) $R^1 = R^2$ = (−)-menthyl
(II) R^1 = (*S*)-MeCH(Ph), R^2 = Bu^t
(III) $R^1 = R^2$ = (*R*)-pinacolyl

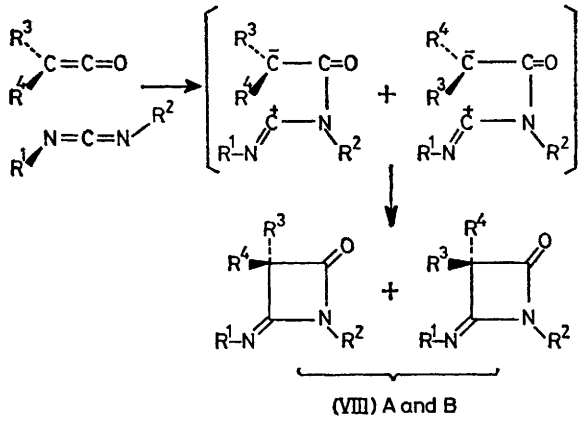
R^3R^4C=C=O

(IV) R^3 = Me, R^4 = Ph
(V) R^3 = EtO_2C, R^4 = Bu^t
(VI) R^3 = EtO_2C, R^4 = Me_2C(Ph)
(VII) R^3 = CF_3, R^4 = Ph

Pinacolyl = Bu^tCH(Me)–

$[\alpha]_{365}^{20}$ values: (I) −374·8° (*c* 1·52 in $CHCl_3$); (II), −390·8° (*c* 0·076 in CCl_4); (III) (derived from the amine in *ca.* 60% optical purity), −278·5° (*c* 4·22 in hexane).

The cycloaddition of carbodi-imides to ketens takes place by an ionic mechanism,[2] in which β-lactam ring closure, in this case leading to the formation of a new chiral centre, is the slowest stage (Scheme).



SCHEME

Regioselectivity in this cycloaddition was observed earlier with achiral carbodi-imides having two different substituents at the nitrogen atoms.[3] In this reaction the geometry of the diastereoisomeric transition states is similar to that of the products, indicating that non-bonding interactions between the chiral substituent R^1 and the prochiral ionic centre should cause diastereoselectivity of the cycloaddition.

In the Scheme the diastereoisomeric β-lactams are shown in only one of the two possible configurations with respect to the imine double bond, in this case as the (*E*)-diastereoisomers.

In the cycloaddition of the carbodi-imides (I) or (II) with the ketens (IV), (V), or (VI), β-lactam formation is highly stereoselective and, using (II), regiospecific.

Further we have proved that the adducts obtained do not undergo thermal interconversion (xylene; 150 °C), which shows that they are epimeric at C-3 rather than invertomers at the imine nitrogen atom.

A detailed study of Dreiding models led us to conclude that the *E*-configuration of the imine double bond is clearly preferred to the (*Z*)-configuration; in the latter case a large chiral substituent on nitrogen, *e.g.* a menthyl group, would cause strong steric hindrance.

The cycloadditions were carried out under dry argon using ketens prepared in solution *in situ* or isolated by distillation. The method and the order of introduction of the reagents had no effect on the result of the synthesis. The qualitative and quantitative compositions of the mixtures of products were determined by column chromatography or by high pressure liquid chromatography (h.p.l.c.) with u.v. detection. The fractions were identified by their i.r. spectra (for azetidinones: lactam C=O ν 1800—1825 m, C=N 1600—1700 s, and ester C=O 1705—1740 s cm^{-1}). The homogeneity of the fractions was determined by dividing them into several portions and determining the rotation of each sample at five wavelengths. In addition mass spectra were obtained for each fraction and the principal fragments were identified (keten, carbodi-imide, isocyanate, and ketenimine). Some of the products were unstable when chromatographed on SiO_2 and as a result complex mixtures were obtained which did not contain azetidiones.

The experimental results are shown in the Table.

TABLE

Starting compounds	% yield of (VIII) (A)	(B)	M.p./°C	$[\alpha]_{365}^{25}$
(I)+(IV)	36·6	3·3	130	−439° (*c* 0·07, CCl_4)
			114	−555° (*c* 0·06, CCl_4)
(I)+(V)	63·6	—	90	−249° (*c* 0·18, $CHCl_3$)
(I)+(VI)	75·0	—	oil	−116° (*c* 0·4, CCl_4)
(II)+(V)	28·5	—	oil	−18·8° (*c* 0·45, CCl_4)
(III)+(VII)	53·0	31·0	oil[a]	

[a] Proportions of (A); and (B) based on integration of CF_3 signals in the ^{19}F n.m.r. spectra.

The experiment with (III) and (VII) (Table) gave different results from the others. In this case the carbodi-imide was synthesized from (*R*)-pinacolylamine (*ca.* 60% optical purity) so it consisted of *ca.* 80% of the (*RR*)-isomer and *ca.* 20% of the (*SS*)- and (*SR*)-isomers. Consequently, we would expect the formation of four diastereoisomers and their enantiomers in the cycloaddition. Possible *Z*–*E* isomerism would double the number of products.

Our attempts to isolate the individual products by t.l.c. and h.p.l.c. (SiO_2) showed the existence of five or six labile products. All were β-lactams (i.r.) and they differed only in their specific rotations. Their lability was demonstrated by their interconversion in pairs during chromatography on SiO_2 or on heating. The ratio of isomers given in the Table is approximate, because it is a function of temperature or time of contact with SiO_2.

This behaviour can be explained by inversion at the imine nitrogen. Dreiding models show clearly that, in contrast to menthyl derived β-lactams, the pinacolyl-substituted β-lactams show no preference for either the (*Z*)- or the (*E*)-configuration.

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[1] W. T. Brady, E. D. Dorsey, and F. H. Parry, *J. Org. Chem.*, 1969, **34**, 2846.
[2] W. T. Brady and E. D. Dorsey, *J. Org. Chem.*, 1970, **35**, 2732.
[3] C. Metzger and J. Kurz, *Chem. Ber.*, 1971, **104**, 50.