Tetrahedron Letters, Vol.31, No.17, pp 2483-2486, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

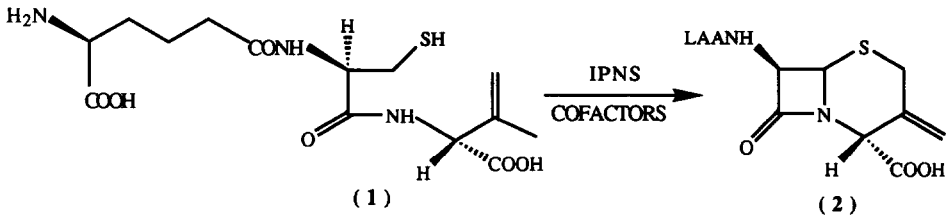
1,3-DIPOLAR CYCLOADDITIONS OF 3-METHYLENECEPHAMS WITH DIAZOALKANES

Jack E. Baldwin* and Janos Pitlik

The Dyson Perrins Laboratory and Oxford Centre for Molecular Sciences,
South Parks Road, Oxford OX1 3QY

Summary: The 3-methylenecephams underwent 1,3-dipolar cycloaddition reactions with diazomethane to give spiropyrazolinocephams in a completely stereo- and regioselective manner. Thermal breakdown of these 1-pyrazolines led to spirocyclopropane and vinyl derivatives.

3-Methylenecephams are well known and very useful members of the large family of cephalosporin antibiotics. In the chemical literature one can find several, mostly reductive pathways for their preparation[1]. More recently a new, enzymatic method also was developed in our laboratory[2]. In this procedure the unsaturated tripeptide, L-α-aminoadipoyl-L-cysteinyl-D-β,γ-didehydrovaline (1) was transformed to the corresponding 3-methylenecepham (2) by means of isopenicillin N synthase (IPNS) (SCHEME 1).



(1) (2)

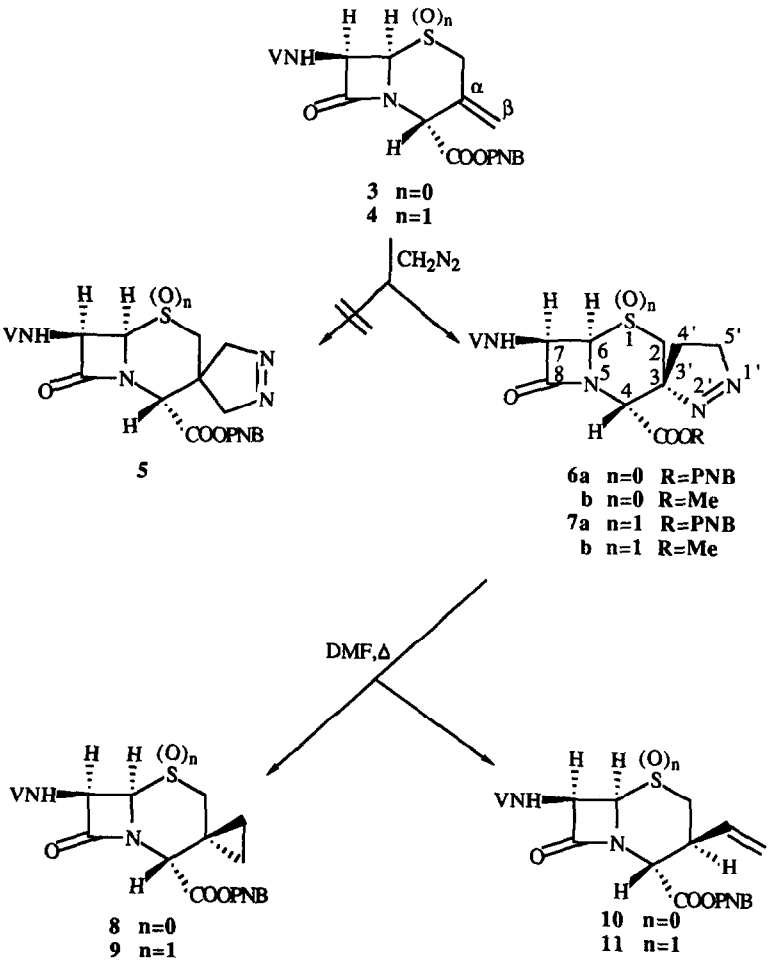
SCHEME 1

Despite the several synthetic routes towards these compounds, their chemistry is not well developed. Only their transformation into deacetoxy-[3a], O-alkyl-[3b] and halocephems[3c] is described. However, the preparation of novel cephams *via* cycloaddition reactions of the exocyclic double bond have not been examined.

In this paper we describe the 1,3-dipolar cycloaddition reactions of the 3-methylenecephams with diazomethane to give 3-spiropyrazolines and their subsequent transformation into 3-spirocyclopropylcephams as well as 3- vinylcephams.

When the 3-methylenecepham **3** (SCHEME 2) was allowed to stand with a large excess of diazomethane in dichloromethane at 5 °C we found that the reaction proceeded to completion only after one week. Based on this finding one can state that the reactivity of the exo double bond in 3-methylenecephams towards diazomethane is very similar to that of the endo Δ^3 double bond of 3-cephems[4] and is in contrast to the highly reactive double bonds of 2-methylenecephems[5] and 3-vinylcephems[6]. This was not surprising in the light of the fact that the methyl ester of 3-methylenecephalosporins could be prepared, without destruction of the double bond[7] during the transformation. The 200 MHz ^{1}H nmr spectrum of the reaction mixture revealed that two β-lactams were formed in a ratio of approximately 10:1. These two products were purified by flash column chromatography. Surprisingly, all of the physical data showed that they differ only in the nature of the ester functionality (**6a** and **b**). The minor product was a methyl ester

indicating that an unexpected transesterification had taken place along with the cycloaddition. To the best of our knowledge no similar reaction has been reported to date.



PNB= p-nitrobenzyl-
V = phenoxyacetyl-

SCHEME 2

In the 500 MHz ^1H nmr spectra of the cycloadducts **6a** and **b** the two singlets characteristic of the methylene hydrogens were absent and two new multiplet systems were seen. In the COSY spectra couplings were observed between the new hydrogens(5' and 4') indicating that the

products cannot be "α-adducts"(**5**) but are "β-adducts"(**6**)(i.e. the new carbon-carbon bond is formed in the β-position to C-3, at the methylene carbon), the 1-pyrazolines being formed in a completely ***regioselective*** manner. The 500 MHz ^{13}C nmr data corroborated this fact.

In order to determine the C-3 configurations of the molecules **6a** and **b** n.O.e. experiments were also carried out. Enhancement was observed at H-4 when the pyrazolino-4'-CH_2 was irradiated indicating the 3S configuration of the molcules. Hence compounds **6a** and **b** are formed by attack of diazomethane on the the less hindered α-face of the methylene group in a completely ***stereoselective*** reaction.

In the cycloaddition reaction of 3-methylenecephalosporin sulphoxide **4** and diazomethane (5 °C, dichloromethane, one week) the pyrazolines **7a** and **b** were formed in a ratio of 20:1 virtually quantitatively. The sulphoxide was stable in solution, no spontaneous decomposition taking place, unlike the case of the sulphide **3** where a large amount of decomposition occured. The rate of transesterification was also slower, and hence less methyl ester was formed. However, there was no significant difference between the reactivities of **3** and **4** towards diazomethane unlike the case of different oxidation states of vinylcephems[6]. The PBr_3 reduction products of **7a** and **b** were identical to **6a** and **b** (500 MHz ^1H nmr) indicating that they have the same 3S configuration.

The pyrazolines had considerable thermal stability. They did not decompose to cyclopropanes even after refluxing for 8 days in toluene[8]. However, they underwent thermal breakdown after 8 hours reflux in DMF (150 °C). Unfortunately, the thermolysis of **6a** gave only non β-lactam decomposition products. In contrast, the reaction of **7a** gave two new β-lactams. One of them was the expected cyclopropane (**9**). The other product has an unusual structure, which based on 500 MHz ^1H and ^{13}C nmr data is that of the open chain vinyl-cepham (**11**). The assignment of the signals were supported by COSY, DEPT and 2D ^1H - ^{13}C heterocorrelated experiments. The n.O.e. data revealed that the molecule has 3S configuration. A possible mechanism to account for this is a 1,2-hydrogen shift along with nitrogen elimination from the pyrazolino derivative **7a**. A similar transformation of pyrazolines was reported earlier in the case of the cycloadducts of vinylphosphonates and ethyl diazoacetate[9]. Compounds **8** and **10** were prepared by AcCl-KI reduction of molecules **9** and **11**.

Attempts to gain cyclopropane derivatives directly form the 3-methylenecephams ($CH_2N_2/Pd(OAc)_2$; CH_2N_2/UV light; $CHBr_3$/t-BuOK; CH_2Ph_2/Δ) were not successful.

The biological evaluation of the free carboxylic acid derivatives of **6**, **8** and **10** are in progress. Details of the chemistry, structural elucidation and biological properties of these novel cephalosporins will be published elsewhere.

Acknowledgements: The authors wish to thank Shaun D. Abbott and Andy Russell for reviewing the manuscript and Robert M. Adlington for advice and encouragement.

References:

1. See for example: M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki and Y. Asahi, *J.Chem.Soc., Perkin Trans. I.* **1974,** 258.;
R. R. Chauvette and P. A. Pennington, *J. Org. Chem.*, **38,** 2994 (1973);
M. Ochiai, O.Aki, A. Morimoto, T. Okada and H. Shimadzu, *J. Chem. Soc., Chem. Commun.*, **1972,** 800;
M. Kobayashi, M. Kato and I. Ueda, *Chem. Pharm. Bull.*, **36,** 582 (1988).

2. a)J. E. Baldwin, R. M. Adlington, S. L. Flitsch, H.-H. Ting and N. J. Turner, *J. Chem. Soc., Chem. Commun.* **1986,** 1305.;
b) J. E. Baldwin, R. M. Adlington, L. G. King, M. F. Parisi, W. J. Sobey, J. D. Sutherland and H.-H. Ting, *J. Chem. Soc., Chem. Commun.*, **1988,** 1635.

3. a) R. R. Chauvette, P.A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen and G. W. Huffman, *J. Org. Chem.*, **36**, 1259 (1971);
b) R. Scartazzini and H. Bickell, *Helv. Chim. Acta*, **57**, 1919 (1974);
c) R. R. Chauvette and P. A. Pennington, *J. Org. Chem.*, **38**, 2994 (1973).

4. E. R. Farkas, E. T. Gunda and J. Cs. Jaszberenyi, *Tetrahedron Lett.*, **1973**, 5127.

5. a) J. Cs. Jaszberenyi, J. Pitlik, K. E. Kover, Gy. Batta and K. Kollar, *Magn. Reson. Chem.*, **26**, 658 (1988)
b) J. Pitlik and J. Cs. Jaszberenyi, *J. Heterocyclic Chem.*, **26**, 461 (1989).

6. a) J. Pitlik, I. Miskolczi, K. E. Kover, J. Cs. Jaszberenyi and F. Sztaricskai, *Tetrahedron Lett.*,**30**, 2005 (1989);
b) J. Pitlik, T. E. Gunda and I. Miskolczi, *J. Heterocyclic Chem.*, in press.

7. D. O. Spry, *Tetrahedron Lett.*, **1973**, 165

8. J. H. Bateson, D. F. Corbett and R. Southgate, in "Recent Advances in the Chemistry of β-Lactam Antibiotics",(A. G. Brown and S. M. Roberts, eds.), The Royal Society of Chemistry, Spec. Publ. No. 152, London, 1985, pp 116-130.

9. A. N. Pudovik, R. D. Gareev, L. A. Stabrovskaya, A. V. Aganov, O. E. Raevskaya, *Zh. Obschc. Khim.*, **40**, 2181 (1970).

(Received in UK 7 February 1990)