Tetrahedron Letters,Vol.26,No.26,pp 3167-3170,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

REGIOSELECTIVITY IN THE PHOTOCHEMICAL RING CONTRACTION OF 4-DIAZOPYRAZOLIDINE-3,5-DIONES TO GIVE AZA-β-LACTAMS

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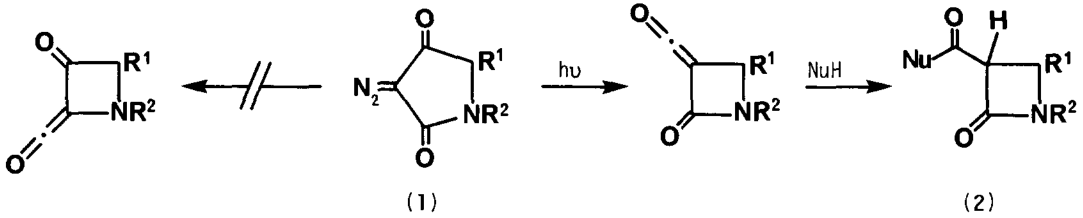
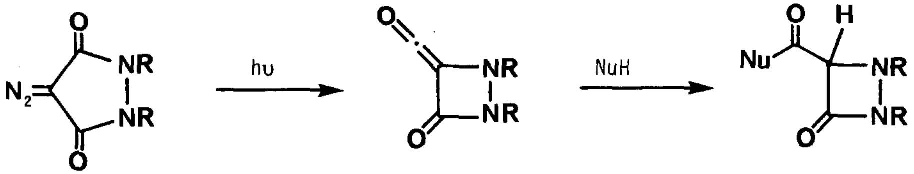
Summary: The photochemical decomposition of unsymmetrically substituted 4-diazopyrazolidine-3,5-diones leads to aza-β-lactams, and provides some indication of the relative migratory aptitude of nitrogen groups in the Wolff rearrangement.

The photochemical Wolff rearrangement is a useful method of effecting the ring contraction of alicyclic and heterocyclic systems. One particularly elegant example of this reaction is the β-lactam synthesis developed independently by Lowe[1] and by Stork.[2] In this, irradiation of 3-diazopyrrolidine-2,4-diones (**1**) results in exclusive migration of C-5, rather than N-1, to the electron deficient centre, and formation of β-lactams (**2**) *via* nucleophilic addition to the intermediate ketenes (Scheme 1).



Scheme 1.

The marked reluctance[1,2,3] of N-C bonds to migrate in the photochemical Wolff rearrangement is generally explained by participation of the nitrogen lone pair in amide resonance, especially in photo-excited states, and indeed the migration of nitrogen in the Wolff rearrangement is rare with only a few examples reported.[4] We have recently described more examples of nitrogen migration in the Wolff rearrangement in the photochemical ring contraction of symmetrically substituted 4-diazopyrazolidine-3,5-diones (**3**) which gives, after nucleophilic trapping of the ketene intermediate, aza-β-lactams (**4**) (Scheme 2),[5] interesting nuclear analogues of β-lactam antibiotics.[6]

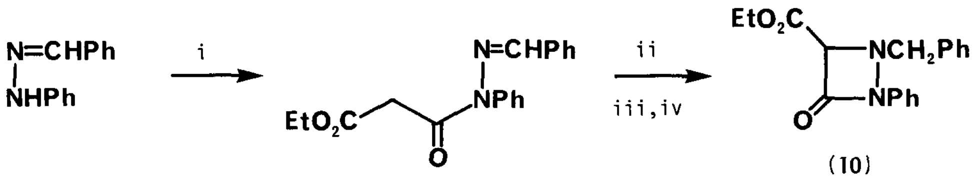


(3) (4)

Scheme 2. R = CH_2Ph, ^nPr, or RR = $(CH_2)_4$; Nu = EtO, ^tBuO, HO, or Et_2N

We have now investigated this reaction in more detail and studied the electronic and steric requirements for nitrogen atoms to migrate in the Wolff rearrangement. The results on the photochemical ring contraction of unsymmetrically substituted 4-diazopyrazolidine-3,4-diones reported herein provide the first indication of the relative migratory aptitudes of differently substituted nitrogen atoms in the Wolff rearrangement.

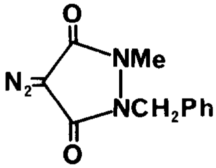
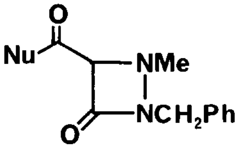
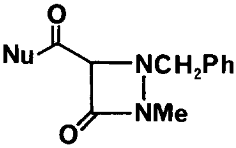
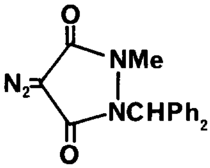
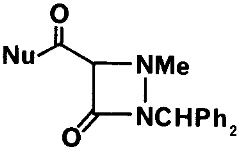
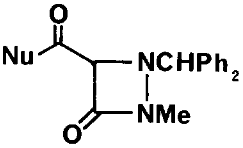
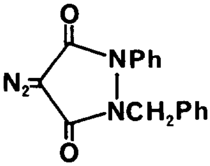
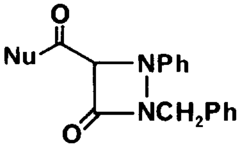
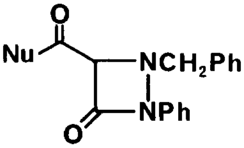
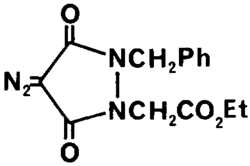
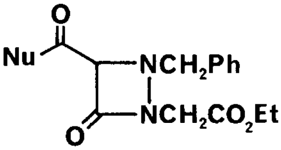
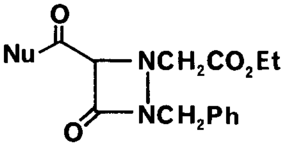
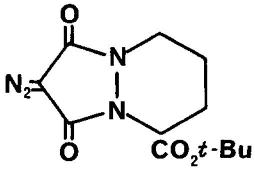
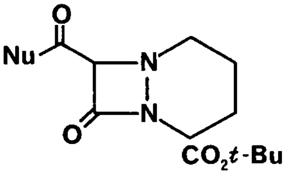
The required diazo compounds (**5**-**9**) were obtained by diazo-transfer[7] to the corresponding pyrazolidinediones using tosyl azide in dichloromethane in the presence of triethylamine. Irradiation of the 4-diazopyrazolidine-3,5-diones (**5**-**8**) in diethyl ether containing 5-10% v/v ethanol or water as the ketene trapping agent, gave mixtures of both possible regioisomeric aza-β-lactams (**A**) and (**B**) (Table). The ratio of the four-membered ring products was determined by integration of appropriate signals in the ^1H n.m.r. spectra of the mixtures. The assignment of signals corresponding to the regioisomers (**A**) and (**B**) was confirmed by chromatographic separation of the aza-β-lactams either as the ethyl esters (Nu = OEt), obtained directly from photolysis in the presence of ethanol, or as the 4-unsubstituted compounds obtained by decarboxylation[5] of the corresponding carboxylic acids (Nu = OH). In the case of ethyl 1-benzyl-2-phenyl-3-oxodiazetidine-4-carboxylate (**10**), m.p. 71.5°C, regioisomer (**B**) from photolysis of diazo compound (**7**) in ethanol, the structure was further confirmed by its independent synthesis[8] from the phenylhydrazone of benzaldehyde (Scheme 3).



(10)

Scheme 3. Reagents: i, NaH, THF, EtO_2CCH_2COCl; ii, H_2, Pd/C; iii, TsN_3, Et_3N, CH_2Cl_2; iv, $Rh_2(OAc)_4$, C_6H_6

Table. Photochemical Ring Contraction of 4-Diazopyrazolidine-3,5-diones to Aza-β-lactams.

Diazo Compound	NuH	Aza-β-lactam (A)	Product(s) (B)	Ratio (A):(B)	Yield (%)
 (5)	EtOH			1:1	30
	HOH			1:1	33
 (6)	EtOH			1:1	36
	HOH			1:1	33
 (7)	EtOH			1.7:1	72
	HOH			1.6:1	55
 (8)	HOH			2.8:1	47
 (9)	EtOH	 (11)	—	>10:1	12
	HOH			>10:1	14

The results suggest that although N-methyl, N-benzyl, and N-benzhydryl groups have similar migratory aptitudes leading to 1:1 mixtures of both possible aza-β-lactams from diazo compounds (**5**) and (**6**), an N-phenyl group shows a slight preference to migrate over N-benzyl in the photolysis of (**7**). Greater regioselectivity was observed in the photolysis of the diazopyrazolidinedione (**8**), the N-benzyl group migrating more readily than the N-alkyl group bearing the electron withdrawing ester substituent. This reluctance of an N-alkyl group bearing an ester to migrate is more marked in the ring contraction of the bicyclic diazo compound (**9**), where the Wolff rearrangement was highly regio- and stereo-selective, and only one of the possible regioisomeric aza-β-lactams was isolated, the cis-stereochemistry being assigned on the basis of nuclear Overhauser effect difference experiments. However, the yield was low since fragmentation of the carbene intermediate competes with rearrangement. This fragmentation, which was noted previously,[5] results in extrusion of carbon suboxide, isolated as diethyl malonate (46%), and formation of t-butyl 1,4,5,6-tetrahydropyridazine-3-carboxylate (47%).

Thus the photochemical ring contraction of unsymmetrical 4-diazopyrazolidine-3,5-diones exhibits some degree of regioselectivity, the relative migratory aptitudes of the nitrogen groups following the order: $NPh > NCHPh_2 \sim NCH_2Ph \sim NMe > NCH_2CO_2R$. The high degree of selectivity in the bicyclic case is difficult to rationalise on electronic grounds, and is probably related to the conformation of the precursor in that the C1-N9 bond is better aligned for overlap with the vacant p-orbital of the intermediate carbene in the transition state. Although the bicyclic aza-β-lactams (**11**) are only formed in low yield by the present route, the work does demonstrate that these interesting strained bicyclic nuclear analogues of β-lactam antibiotics are isolable compounds.

We thank the S.E.R.C. and Roche Products Ltd. for a CASE award to C.J.P.

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6. For other examples of aza analogues of β-lactams, see M.J. Pearson, J. Chem. Soc., Perkin Trans. 1, 1981, 2544, and references therein.
7. M. Regitz, Synthesis, 1972, 351.
8. This new route to aza-β-lactams is described in the following Letter.

(Received in UK 19 April 1985)