Synthesis of Aza-β-lactams by Photochemical Ring Contraction

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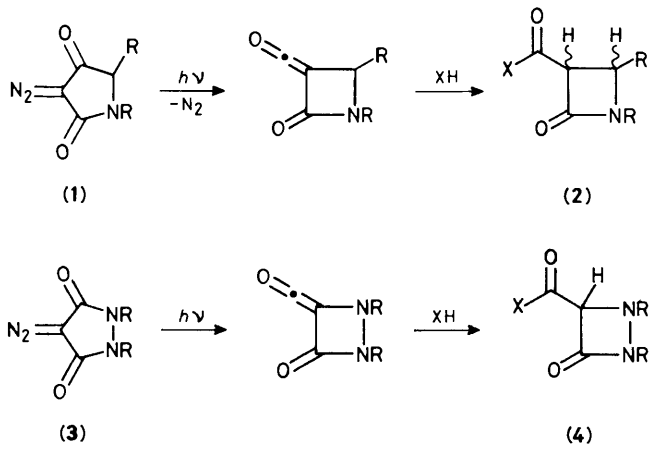
Photochemical decomposition of 4-diazopyrazolidine-3,5-diones (**3**) in the presence of nucleophiles, XH, leads to the aza-β-lactams (**4**); decarboxylation of (**4e**) gives the aza-β-lactam (**7**), which undergoes reductive ring cleavage to (**8**), and ring expansion to (**9**) on treatment with base.

In the search for modified and improved antibacterial agents, the β-lactams continue to play a key role, and in recent years there has been considerable interest in the modification of the ring system of naturally occurring β-lactams. This has led to the synthesis of a range of nuclear analogues, particularly aza-analogues which incorporate one or more nitrogen atoms into the ring fused to the β-lactam.[1] However, with the exception of some recent work from Taylor and co-workers,[2] aza-β-lactams based on 1,2-diazetidinones have not been extensively investigated. We now report a concise route to these structurally simple, but relatively rare aza-β-lactams.

The route is based on the photochemical ring contraction of 4-diazopyrazolidine-3,5-diones (**3**), and subsequent trapping of the intermediate ketenes with nucleophiles (Scheme 1).



(1) (2)

(3) (4)

a; R = Ph

b; R = CH_2Ph

c; R = Pr^n

d; RR = $-[CH_2]_4-$

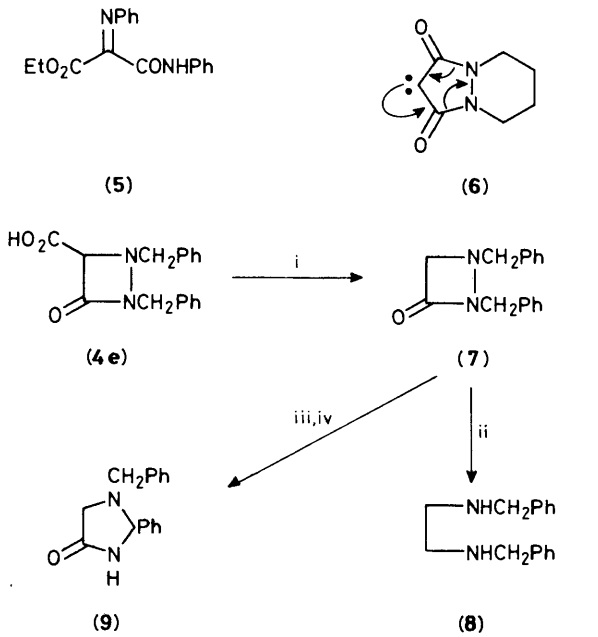
Scheme 1

Table 1. Aza-β-lactams, (**4**), from 4-diazopyrazolidine-3,5-diones, (**3**).

	Compound (**4**)				
(**3**)		R	X	% Yield	$\nu_{max.}$/cm^{-1}
a	**a**;	Ph	EtO	0	—
b	**b**;	$PhCH_2$	EtO	45	1785
b	**c**;	$PhCH_2$	Bu^tO	30	1785
b	**d**;	$PhCH_2$	Et_2N	17	1785
b	**e**;	$PhCH_2$	HO	50	1785
c	**f**;	Pr^n	EtO	48	1785
c	**g**;	Pr^n	HO	56	1780
d	**h**;	$-[CH_2]_4-$	EtO	4	1770

Although β-lactams (**2**) have been prepared analogously from 3-diazopyrrolidine-2,4-diones (**1**),[3] it was by no means certain that in the photolysis of (**3**) the nitrogen would migrate to the electron deficient carbene centre, since in the photolysis of (**1**) exclusive migration of carbon rather than nitrogen was observed.[3] However, there are a few examples of nitrogen substituents migrating in the photochemical Wolff rearrangement[4] despite the participation of the nitrogen lone pair in amide resonance, and therefore the preparation and decomposition of a series of symmetrical diazopyrazolidinediones (**3**) was investigated.

The diazo compounds (**3**) were simply prepared (39—78%) by diazo-transfer[5] to the corresponding readily available[6,7] pyrazolidine-3,5-diones using tosyl azide in acetonitrile in the presence of triethylamine, and are isolable pale yellow solids or oils exhibiting the characteristic absorption at *ca.* 2140 cm^{-1} in their i.r. spectra. Irradiation of (**3a**) in diethyl ether containing ethanol gave one major product (39%) together with a trace of azobenzene (2%). That the product was not the required aza-β-lactam (**4a**) was immediately apparent from the absence of a high frequency carbonyl absorption in its i.r. spectrum, and on the basis of its spectral properties it was assigned the structure (**5**). This structure was confirmed by an independent synthesis from ethylmalonyl chloride by reaction with aniline, followed by condensation with nitrosobenzene. It is likely that (**5**) arises by photochemical homolytic cleavage of the N–N bond in (**4a**), and since aryl



(5) (6)

(4e) (7)

(9) (8)

Scheme 2. *Reagents*: i, C_6H_6, reflux; ii, diborane–THF; iii, LDA, THF, −78 °C; iv, MeI, −78 °C to room temp., then aqueous work-up.

substituents would facilitate such a process by stabilising the resulting diradical, attention was turned to 1,2-dialkyl substituted pyrazolidinediones.

The dibenzyl compound (**3b**) was irradiated in diethyl ether containing ethanol to give the required aza-β-lactam (**4b**) (45%) as a colourless oil. The four-membered ring structure was supported by a high frequency carbonyl stretch at 1785 cm^{-1} in the i.r. spectrum, and by the n.m.r. spectra which showed *inter alia* a singlet for H-4 at δ 4.47, AB quartets for the N-1 and N-2 benzylic protons at δ 3.85 (*J* 13 Hz) and 4.45 (*J* 15 Hz) respectively in the proton spectrum, and singlets for the ester and lactam carbonyls at δ 162.3 and 164.3 and a doublet for C-4 at δ 78.1 in the off-resonance ^{13}C spectrum. Similarly photolysis of (**3b**) in diethyl ether in the presence of t-butyl alcohol, diethylamine, or water gave the corresponding aza-β-lactams (**4c**), (**4d**), and (**4e**) in moderate yields (Table 1).

The 1,2-dipropyl compounds (**3c**) and the bicyclic diazo compound (**3d**) also underwent ring-contraction to 1,2-diazetidinones on irradiation in the presence of a nucleophile (Table 1), although the yield of the bicyclic aza-β-lactam (**4h**) was disappointingly low. The major product in the photolysis of (**3d**) in the presence of ethanol was diethyl malonate. Whereas Wolff rearrangement of the intermediate carbene (**6**) gives the four-membered ring, a competing fragmentation [arrows in (**6**), although not necessarily concerted] would lead to the formation of carbon suboxide (rapidly quenched with ethanol to give diethyl malonate), and the azo compound, 3,4,5,6-tetrahydropyridazine, although no products resulting from this fragment were isolated. Presumably a similar fragmentation accounts for the formation of small amounts of azobenzene in the photolysis of (**3a**).

The chemistry of these aza-β-lactams has been briefly investigated in the dibenzyl series (Scheme 2). Thus the carboxylic acid (**4e**) is decarboxylated in quantitative yield by heating in benzene to give the aza-β-lactam (**7**), m.p. 38 °C, $\nu_{max.}$ 1765 cm^{-1}. The n.m.r. spectrum of (**7**) contains an AB quartet for the hydrogens on C-4 at δ 4.38; on warming, this coalesces to a singlet at 390 K giving a value for the inversion barrier at N-1 of 19 kcal mol^{-1} [2c,8] (1 kcal = 4.18 kJ). The

aza-β-lactam ring in (**7**) is moderately stable to hydrolysis, requiring prolonged (>4 h) refluxing in aqueous tetrahydrofuran (THF) containing hydrochloric acid to effect complete destruction of the ring, as monitored by the disappearance of the high frequency carbonyl in the i.r. spectrum. The ring is also cleaved under reducing conditions. Thus, treatment of (**7**) with diborane in THF gave 1,2-dibenzylaminoethane (**8**) by reduction of the carbonyl and reductive cleavage of the N–N bond. Attempted formation and alkylation of the anion at C-4 using lithium di-isopropylamide (LDA), followed by iodomethane, led to the unmethylated ring expanded imidazolin-4-one (**9**) (68%), presumably by rearrangement of the dipole stabilised anion formed by deprotonation of the N-2 benzyl group.[2a,9]

In summary, the photochemical ring contraction of 4-diazopyrazolidine-3,5-diones provides a short route to aza-β-lactams.

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