Novel Hydrolytic Cleavage of 4-(Pyrrol-2-yl)azetidin-2-ones

Anil K. Upadhyaya and Kailash N. Mehrotra *
Department of Chemistry, Banaras Hindu University, Varanasi 221 005, India

Alkaline hydrolysis of 1-aryl-3,3-diphenyl-4-(pyrrol-2-yl)azetidin-2-ones results in an unusual dual-path fragmentation of the β-lactam ring to give diphenylacetic acid, 2-iminomethylpyrroles, arylamines, and 1,1-diphenyl-2-(pyrrol-2-yl)ethylene. The product distribution is shown to be dependent on temperature.

It has been observed that 1-diphenylmethyl- or 1-benzyl-4-phenylazetidin-2-ones readily undergo ring opening on treatment with ethanolic potassium hydroxide to give β-amino acid derivatives.[1] Similar results have been reported with 3-phenyl- or 3,4-diphenyl-*N*-aryl or -alkylarylazetidin-2-ones.[2] However, 3,3,4-triarylazetidin-2-ones have been found to be stable to hydrolysis.[3] Steric factors have been invoked to explain this: the presence of two bulky aryl groups at position 3 in the ring may hinder the attack of base on the carbonyl carbon.[4] We now report a unique ring-opening reaction of 1-aryl-3,3-diphenyl-4-(pyrrol-2-yl)azetidin-2-ones on treatment with alcoholic potassium hydroxide. Initial abstraction of a proton from the nitrogen of the highly reactive pyrrole ring in these 3,3-diphenylazetidinones leads to an anion, which initiates a dual-path fragmentation. The choice of route is temperature-dependent.

The azetidinones (**1a–c**) and (**1c′**) were prepared by the reaction of benzoyl(phenyl)diazomethane with 2-iminomethylpyrroles or *N*-methylpyrroles following a reported method,[3] and were characterised by analysis and spectroscopic data.

The reaction of 1,3,3-triphenyl-4-(pyrrol-2-yl)azetidin-2-one (**1a**) with saturated ethanolic potassium hydroxide for 4 h at reflux temperature and subsequent acidification gave four products, of which three have been identified as diphenylacetic acid (**2**), the 2-iminomethylpyrrole (**3a**), and aniline (**4a**) (as hydrochloride) by comparison (mixed m.p., i.r. spectra, and t.l.c.) with authentic samples. The fourth product was characterised as 1,1-diphenyl-2-(pyrrol-2-yl)ethylene (**5**) on the basis of elemental analyses and spectroscopic data. Similar results were obtained on hydrolysis of compounds (**1b** and **c**). In one run, alkaline hydrolysis of the azetidinone (**1c**) for a shorter time (1.5 h) gave a similar product distribution (Table).

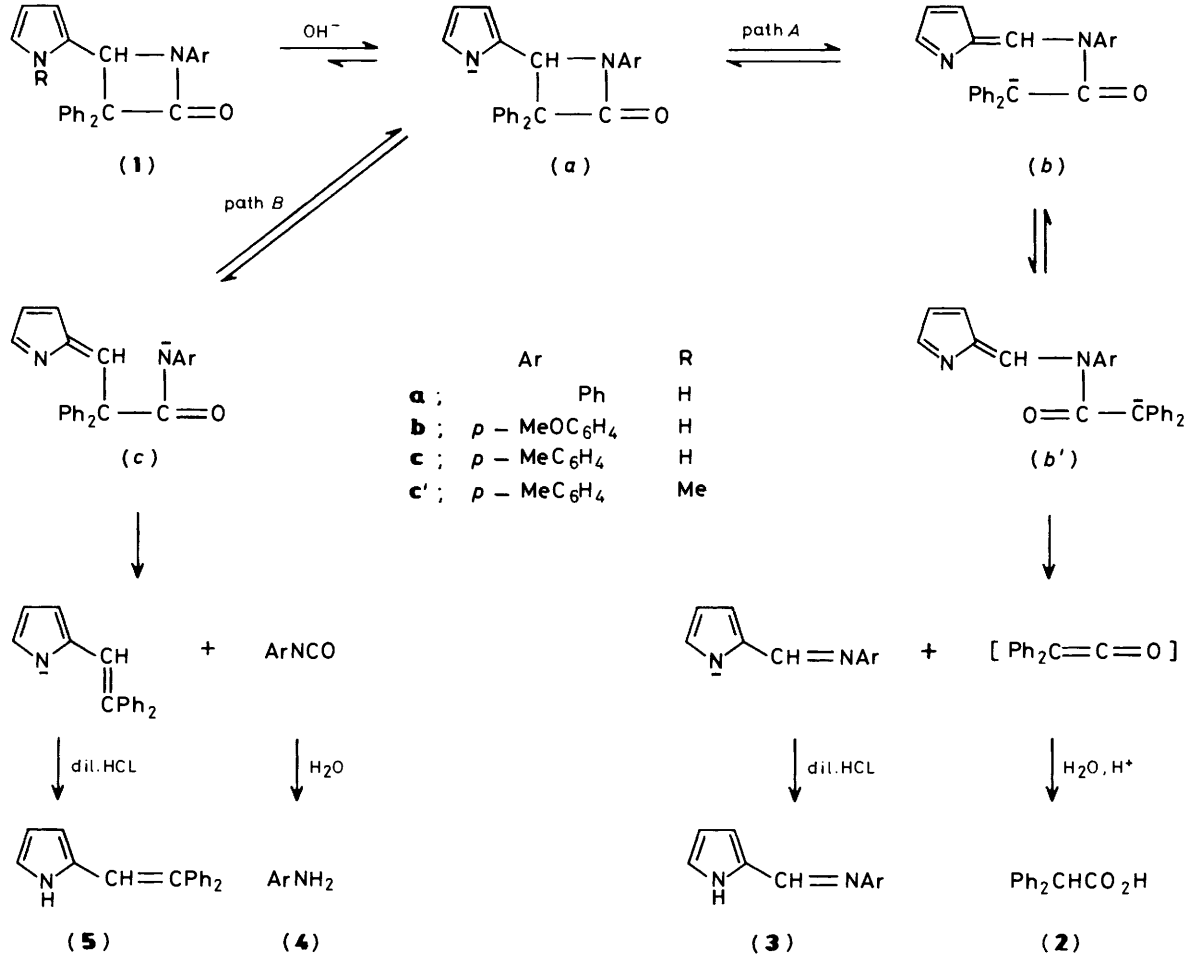

Table. Hydrolysis of 4-pyrrolylazetidin-2-ones (**1a—c**) and attempted hydrolysis of the 4-(1-methylpyrrol-2-yl)azetidin-2-one (**1c'**)

	Temp.	Time (h)	Yields of products (%) (2)	(3)	(4)	(5)
(**1a**)	Reflux	4	47	32	7	6
(**1b**)	Reflux	4	53	21	3	3
(**1c**)[a]	Reflux	4	40	34	5	9
(**1c**)	Reflux	1.5	36	33	4	8
(**1c**)	50 °C	4	10	12	20	46
(**1c'**)	Reflux	24		no reaction		

[a] Reaction of the azetidinone (**1c**) with phenylmagnesium bromide and the usual work-up gave the products (**2**)—(**5**) (t.l.c.).

When the azetidinone (**1c**) was hydrolysed for 4 h at lower temperature (50 °C), the products were the same [(**2**)—(**5**)] but the distribution was different (Table). At reflux temperature products (**2**) and (**3c**) were formed predominantly, but at 50 °C the major products were (**4c**) and (**5**). It seems that two different modes of ring opening of the anion (*a*), formed by proton abstraction from the pyrrole ring, are operating; path *A* gives products (**2**) and (**3**), the major ones at high temperature, and path *B* leads to products (**4**) and (**5**), formed predominantly at lower temperature. If we compare the anions (*b*) and (*c*) which apparently give rise to two different modes of cleavage, on the basis of the pK_a values of amides[5] and diarylmethanes[6] (17.31 and 33.50, respectively), we would expect the anion (*c*) to be more stable. Higher temperature would permit bond rotation in (*b*) and its rotamer (*b'*), in which the negatively charged carbon is distant from the pyrrole ring, and this would lead to the fragmentation products (**2**) and (**3**). Furthermore, the stereoelectronic repulsion between the lone pair on nitrogen of the pyrrole ring and the negatively charged carbon would destabilise the anion (*b*); such repulsion is absent in the rotamer (*b'*). This accounts for the change in product distribution with change in temperature. The intervention of several anions [(*a*), (*b*), (*c*), and others] finds support in the observed methyl signals at δ 1.3, 2.2, 2.3, 2.6, 2.7, and 3.6 in the n.m.r. spectrum of the crude reaction mixture obtained after 30 min and treated with an excess of methyl iodide.

The validity of the proposed mechanism is supported by the Grignard reagent-mediated fragmentation of the azetidinone (**1c**) into the products (**2**)—(**5**), and further confirmed by the remarkable stability of 1-*p*-tolyl-3,3-diphenyl-4-(1-methylpyrrol-2-yl)azetidin-2-one (**1c'**) towards hydrolysis. This compound remains unchanged even on heating for 24 h in saturated ethanolic potassium hydroxide.

Experimental

M.p.s were taken with a Büchi apparatus (capillary method). ^{1}H N.m.r. spectra were recorded with a JEOL JNM-FX-90Q spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. The i.r. spectra were obtained with a Perkin-Elmer 720 spectrophotometer for Nujol mulls. The u.v. spectra were recorded with a Cary-14 spectrophotometer. The mass spectrum was taken with a Hitachi–Perkin-Elmer RMU-6E spectrometer.

General Method for the Preparation of Azetidin-2-ones.—The Schiff's bases were obtained by heating to reflux equimolar amounts of appropriate aldehydes and amines in benzene for 2 h. The water formed was collected by using a Dean-Stark separator. Benzene was removed at reduced pressure and the residual matter was crystallised from ethanol to give the products, which afforded satisfactory analytical and spectral (i.r., u.v., and n.m.r.) data. 1-Methylpyrrole-2-carbaldehyde was obtained by methylation (MeI) of pyrrole-2-carbaldehyde in the presence of aqueous NaOH.

A mixture of α-diazo-α-phenylacetophenone (10 mmol) and the appropriate Schiff's base (10 mmol) was heated to reflux in thiophene-free dry benzene (80 ml) for 6–8 h under nitrogen. The mixture was kept overnight. Benzene was removed by evaporation and the residue was crystallised from ethanol to give the azetidinones (**1a—c**) and (**1c'**). From the mother liquor 1,1',4,4'-tetraphenyl-2,2'-azinodiethanone[3] was recovered by evaporation and recrystallisation of the residue matter from hexane–ethanol (1:1).

1,3,3-*Triphenyl*-4-(*pyrrol*-2-*yl*)*azetidin*-2-*one* (**1a**) (2.61 g, 72%) had m.p. 157 °C; $\nu_{max.}$(Nujol) 3 410 (NH) and 1 745 cm^{-1} (C=O); $\lambda_{max.}$(EtOH) 244 (ε 27 000) and 290 nm (6 000); δ($CDCl_3$) 7.63 (2 H, m, ArH), 7.06 (13 H, m, ArH), 6.31 (3 H, m, pyrrolyl H), 5.86 (1 H, br s, exch., NH), and 5.73 (1 H, s, 4-H) (Found: C, 82.6; H, 5.8; N, 7.5. $C_{25}H_{20}N_2O$ requires C, 82.4; H, 5.5; N, 7.7%).

1-p-*Methoxybenzyl*-3,3-*diphenyl*-4-(*pyrrol*-2-*yl*)*azetidin*-2-*one* (**1b**) (2.76 g, 70%) had m.p. 163 °C; $\nu_{max.}$(Nujol) 3 410 (NH) and 1 745 cm^{-1} (C=O); $\lambda_{max.}$(EtOH) 256 (ε 26 000) and 300 nm (5 000); δ($CDCl_3$) 7.69 (2 H, m, ArH), 7.15 (12 H, m, ArH), 6.35 (3 H, m, pyrrolyl H), 5.90 (1 H, s, 4-H), 5.83 (1 H, br s, exch., NH), and 3.75 (3 H, s, OMe) (Found: C, 79.2; H, 5.2; N, 7.0. $C_{26}H_{22}N_2O_2$ requires C, 79.4; H, 5.3; N, 7.1%).

3,3-*Diphenyl*-1-p-*tolyl*-4-(*pyrrol*-2-*yl*)*azetidin*-2-*one* (**1c**) (2.02 g, 54%) had m.p. 152 °C; $\nu_{max.}$(Nujol) 3 410 (NH) and 1 740 cm^{-1} (C=O); $\lambda_{max.}$(EtOH) 244 (ε 22 000) and 295 nm (3 000); δ($CDCl_3$) 7.65 (2 H, m, ArH), 7.10 (12 H, m, ArH), 6.25 (3 H, m, pyrrolyl H), 5.78 (1 H, br s, exch., NH), 5.60 (1 H, s, 4-H), and 2.25 (3 H, s, Me) (Found: C, 82.25; H, 6.2; N, 7.3. $C_{26}H_{22}N_2O$ requires C, 82.7; H, 5.8; N, 7.4%).

3,3-*Diphenyl*-1-p-*tolyl*-4-(1-*methylpyrrol*-2-*yl*)*azetidin*-2-*one* (**1c'**) (2.80 g, 73%) had m.p. 118 °C; $\nu_{max.}$(Nujol) 1 755 cm^{-1} (C=O); $\lambda_{max.}$(EtOH) 285 nm (ε 9 000); δ($CDCl_3$) 7.16 (14 H, m, ArH), 6.06 (3 H, m, pyrrolyl H), 5.42 (1 H, s, 4-H), 3.00 (3 H, s, NMe), and 2.13 (3 H, s, CMe) (Found: C, 82.4; H, 6.1; N, 7.2. $C_{27}H_{24}N_2O$ requires C, 82.5; H, 6.0; N, 7.1%); *m/z* 392 (M^+).

General Procedure for Hydrolysis of 4-*Pyrrolylazetidin*-2-*ones.*—To the 1-aryl-3,3-diphenyl-4-(pyrrol-2-yl)azetidin-2-one (**1**) (1 g) was added saturated ethanolic potassium hydroxide (50 ml), and the mixture was heated to reflux (or kept at 50 °C) for 4 (or 1.5) h, they were allowed to cool to room temperature. The solvents were removed under reduced pressure at a bath temperature of 80 °C. The residue was treated with 2N-HCl (100 ml) and extracted with ether (2 × 50 ml). Evaporation of water from the aqueous layer gave the hydrochloride of the amines (**4**). The ethereal layer was dried (Na_2SO_4). Ether was removed under reduced pressure. Repeated fractional crystallisation of the residue from ethanol gave three products, identified as diphenylacetic acid (**2**), 2-iminomethylpyrrole (**3**), and 1,1-diphenyl-2-(pyrrol-2-yl)ethylene (**5**), m.p. 98 °C (from EtOH); $\nu_{max.}$(Nujol) 3 470 (NH) and 1 600 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 255 and 332 nm; δ($CDCl_3$) 7.30 (10 H, m, ArH), 6.84 (1 H, s, HC=C), 6.40 (1 H, m, pyrrolyl α-H), 6.00 (2 H, m, pyrrolyl β-H), and 4.93 (1 H, br s, exch., NH) (Found: C, 87.9; H, 6.2; N, 5.6. $C_{18}H_{15}N$ requires C, 88.2; H, 6.1; N, 5.7%) (yields in Table).

Acknowledgements

We thank Professors S. M. Verma and I. S. Ahuja for facilities and Dr. K. P. Madhusudnan, CDRI, Lucknow, for the mass spectrum.

References

1 R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, 1949, **71**, 2124.
2 F. F. Blick and W. A. Gould, *J. Org. Chem.*, 1958, **23**, 1102.
3 K. N. Mehrotra and S. B. Singh, *Ind. J. Chem., Sect. B*, 1980, **19**, 702; *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1838.
4 J. A. Moore in 'Heterocyclic Compounds with Three and Four Membered Rings,' Part II, ed. A. Weissberger, Interscience, New York, 1964, p. 944.
5 R. B. Homer and C. D. Johnson in 'Chemistry of Amides,' ed. J. Zabicky, Interscience, New York, 1970, p. 238.
6 A. Streitweiser, Jr., W. B. Hollyhead, G. Sonnichsen, A. H. Pudjaatmaka, C. J. Chang, and T. L. Kruger, *J. Am. Chem. Soc.*, 1971, **93**, 5096.

Received 14*th April* 1987; *Paper* 7/676