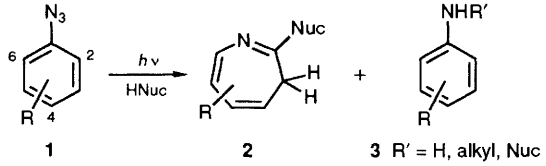
Photolysis of 3,4-Diamidophenyl Azides: Evidence for Azirine Intermediates

Charles G. Younger and Russell A. Bell

Department of Chemistry, McMaster University, Hamilton, Ontario L8S 4M1, Canada

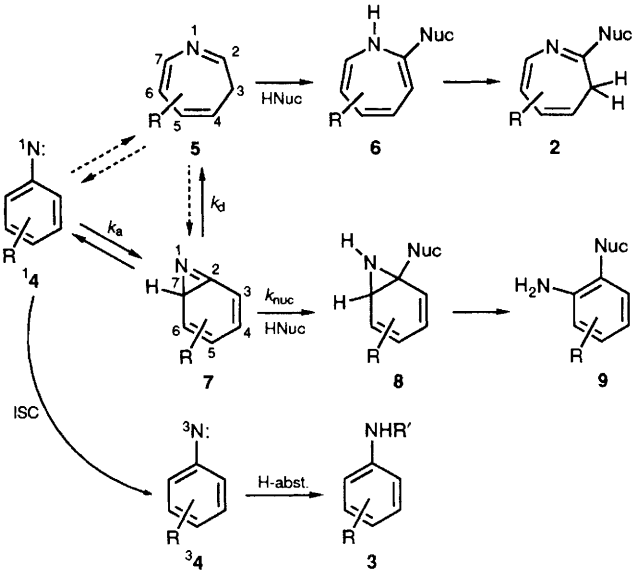
Photolysis of the monocyclic aryl azide 3-acetamido-4-trifluoroacetamidophenyl azide, **1a**, furnished a long-lived, trapable azirine intermediate, **7**, which was in equilibrium with the initially formed nitrene and subsequently rearranged to the didehydroazepine intermediate **5**; the data presented demonstrate that mono- and bi-cyclic aryl azides follow the same chemistry, with the substituents controlling the observed product distributions.

The photolysis of aryl azides to yield a variety of products, among them ring expanded azepines, **2** (Scheme 1), has been studied[1] for more than 60 years and a diversity of credible reaction pathways have been proposed. Improved spectroscopic techniques[1a–c] have enabled methods to define the problem and to explore intermediates with lifetimes ranging from nanoseconds upwards. The singlet state nitrene, ^{1}**4** (Scheme 2), is considered[1b] to be on the pathway from the decomposing excited state aryl azide to the first observed intermediate (time scale 40 ns to 10 μs) and it is the singlet state manifold which leads ultimately to the ring expanded azepine products, **2**, or to the rearranged aromatic products, **9**, that are of concern in this communication. Trapping of the first formed intermediate with nucleophiles[1d–g] leads to synthetically useful yields of azepines but the nature of the intermediate has remained under debate for some time. Early studies of the photolysis of phenyl azide by Huisgen[1h] suggested the first intermediate formed from ^{1}**4** was the bicyclic azirine, **7** (see Scheme 2), a view which was consistent with later work on the photolysis of vinyl azides.[1i] Later photochemical investigations on matrix isolated phenyl azide by Chapman and Le Roux[1j] and by solution laser flash photolysis of *para*-substituted phenyl azides by Schuster[1a] produced compelling IR spectroscopic evidence for the direct formation of the didehydroazepine, **5**. Currently, the general consensus is that in the photolysis of monocyclic aryl azides the didehydroazepine intermediate, **5**, is formed directly from singlet nitrene, ^{1}**4** and the originally proposed azirine, **7**, is not considered an active participant in monocyclic aryl azide photolyses.

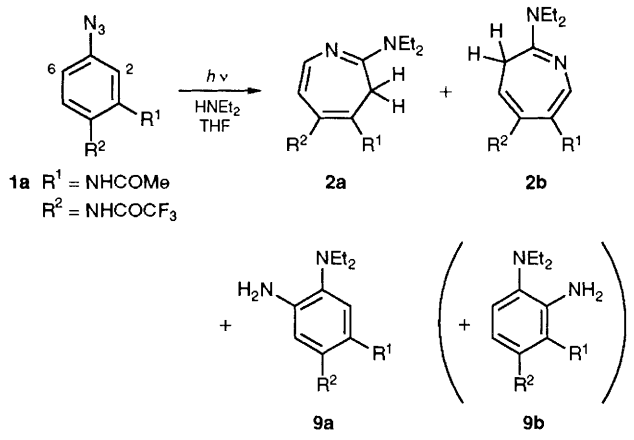


Scheme 1

In contrast to the monocyclic azides, the photolysis of bicyclic aryl azides[2] appears to involve both **5** and **7** as intermediates. Dunkin and Thomson[2a] reported IR evidence from the continuous photolysis of either 1- or 2-azidonaphthalene at 12 K that two species were formed sequentially in both systems, **7** (1708–1736 cm^{-1}) and then **5** (1911–1923 cm^{-1}). In the solution phase however, 1-azidonaphthalene gives rise to only triplet derived azo products or the reduction product 1-naphthylamine when in the presence of amine nucleophiles.[2d] 2-Azidonaphthalene in the presence of amine nucleophiles gave rearranged 1-naphthylamine derivatives that contained the nucleophile as a substituent and that are derived from the azirine intermediate[2d] (Scheme 2). On the other hand, the azido-quinolines[2b,e] give good yields of



Scheme 2



Scheme 3

Table 1 Product distributions from the photolysis of **1a** in THF at 300 nm

Entry	[**1a**] /mmol dm^{-3}	[Nucleophile] /mmol dm^{-3}	T/°C	Relative product yield[c] (%)			
				2a	**2b**	**9a**	**9b**
1	5.0	2000[a]	30	0	0	100	0
2		2000[a]	−70	0	0	100	0
3	4.5	4.5[a]	−70	0	0	100	0
4		5.0[a]	−30	0	46	54	0
5		5.0[a]	0	8	67	26	0
6		5.0[a]	35	16	43	41	0
7		5.0[a]	60	37	47	15	0
8	3.5	3.5[b]	30	31	69	0	0

[a] Nucleophile = $HNEt_2$. [b] Nucleophile = $HNPr^i_2$. [c] From 500 MHz ^1H NMR spectroscopy at 10% conversion of **1a**.

singlet nitrene products and can be induced to furnish preferentially either *o*-diamine products, **9**, or azepines, **2**, depending on the nature of the trapping amine. For the bicyclic azides, substituents appear to be crucial in influencing the fate of the singlet nitrene and in the lifetimes of the subsequent intermediates.

It is our view that mono- and bi-cyclic azides should be consistent in their photochemical behaviour and in this communication we present evidence that an appropriately substituted monocyclic azide, 3-acetamido-4-trifluoroacetamido-phenyl azide, **1a** (see Scheme 3 and Table 1), can form an azirine intermediate and/or a didehydroazepine intermediate and that these intermediates can be trapped in an entirely controllable manner. Only one previous report by Nielson and Buchardt[3] notes the formation of products analogous to **9** from the photolysis of 4-azido-2-nitro-*N*-methylaniline in methanol–diethylamine.

Photolysis of 3-acetamido-4-trifluoroacetamido-phenyl azide, **1a** (see Table 1), in tetrahydrofuran (THF) at 30 °C in the presence of high concentrations of diethylamine (DEA, 2.0 mol dm^{-3}), yielded one product, 3-acetamido-2-diethylamino-4-trifluoroacetamido-aniline, **9a**, as evidenced by its spectroscopic properties.† Photolyses at low temperatures (−70 °C) in the presence of DEA at 5.0 mol dm^{-3}*or* 2 × 10^{-3} mol dm^{-3} in THF led again to the diamine **9a** as the sole product. However, at 30 °C, with DEA at 2 × 10^{-3} mol dm^{-3} the azepines **2a**‡ and **2b**‡ appeared as competing products (see Table 1, entries 4, 5, 6 and 7) and increasing the temperature showed decreasing formation of the diamine **9a** and corresponding increases in azepines **2a** and **2b**. The use of the more hindered amine diisopropylamine, a slower trapping agent than DEA,[1k] at 30 °C likewise increased azepine formation (entry 8) to the complete exclusion of the diamine. A particular point of interest in all these experiments was the absence of the diamine from ring closure to the 2-position, **9b**. Similar azirine derived products were obtained during the photolysis of 3,4-di(trifluoroacetamido)phenyl azide in THF and DEA (2 × 10^{-3} to 2.0 mol dm^{-3}, −70 to 30 °C) with the exclusion of any azepine products.

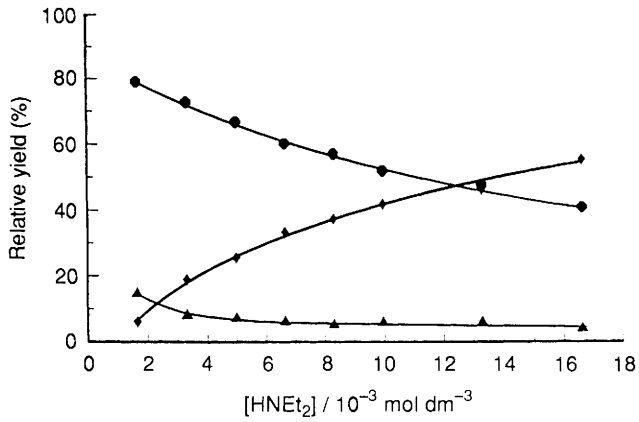


Fig. 1 Relative yields of **2a**, **2b** and **9a** from the photolysis of **1a** (300 nm, 10% conversion) in THF at 0 °C *vs.* [$HNEt_2$]; ◆ **9a**, ▲ **2a**, ● **2b**

A series of photolyses with constant azide concentration and variable DEA concentration at 0 °C led to the plot shown in Fig. 1. The product ratio of [**9a**]:[**2a**] *vs.* [DEA] was linear over the 2–16 mmol dm^{-3} range with a slope of 721 dm^3 mol^{-1} (SE = 77, R = 0.967) indicating the azirine, **7a**, was trapped by DEA at a relative rate (k_{nuc}[HNuc]) of 721 × [$HNEt_2$] dm^3 mol^{-1} relative to its rearrangement (k_d) to the didehydroazepine, **5**. The zero intercept (−0.29, SE = 1.03) implied that the didehydroazepine intermediate was formed irreversibly from the azirine and that the didehydroazepine was trapped efficiently by the diethylamine and did not rearrange further to triplet nitrene[1b] or polymerize.[1l] The ratio of products derived from closure in the 6 position, **2a** and **9a**, over those from 2-position closure, **2b**, *vs.* [DEA] was also linear with a slightly positive slope: that is, as the [DEA] increased, the formation of **9a** *increased* but the production of

† *Spectroscopic data* for **9a**: ^1H NMR: (500 MHz, $CDCl_3$, J in Hz) δ 0.96 (H-2″, 6H, t, J 7.1), 2.10 (H-4‴, 3H, s), 2.87 (H-2′, 4H, q, J 7.1), 4.23 (H-1′, 2H, br), 6.35 (H-3, 1H, s), 7.20 (H-6, 1H, s), 8.06 (H-4′, 1H, br), 9.57 (H-5′, 1H, br); ^{13}C NMR (125 MHz, $CDCl_3$, J in Hz) δ 12.4 (C-2″, *Me*), 23.3 (C-4‴, *Me*), 47.3 (C-2′, CH_2), 109.7 (C-3, *CH*), 116.2 (C-4‴, CF_3, q, J_{CF} 286), 118.8 (C-5, *C*), 120.6 (C-6, *CH*), 127.0 (C-4, *C*), 135.8 (C-1. *C*), 143.4 (C-2, *C*), 155.7 (C-5″, *C*=O, q, J_{CF} 37), 170.3 (C-4″, *C*=O); HRMS (high resolution mass spectrometry) mass found 332.1470 calc. ($C_{14}H_{19}F_3N_4O_2$) 332.1460 (−1.0 MMU).

‡ *Spectroscopic data* for **2a**: ^1H NMR: (200 MHz, $CDCl_3$, J in Hz) δ 1.10 (H-2‴, 6H, br), 1.73 (H-4‴, 3H, s), 3.09 (H-2″, 4H, br), 5.80 (H-6, 1H, d, J 8.5), 6.93 (H-7, 1H, d, J 8.5), 8.65 (br, 1H), 10.4 (br, 1H; owing to conformational exchange, the proton resonances for the CH_2 in the ring, H-3, were too weak to be reliably distinguished from noise; ^{13}C NMR: (50 MHz, $CDCl_3$, J in Hz) δ 14.0 (C-2‴, *Me*), 23.1 (C-4‴, *Me*), 32.7 (C-3, CH_2), 43.7 (C-2″, CH_2), 106.5 (C-6, *CH*), 111.0 (C-4, *C*), 115.8 (C-5‴, CF_3, q, J 286), 121.6 (C-5, *C*), 137.5 (C-7, *CH*), 146.6 (C-2, *C*), 155.0 (C-5″, $COCF_3$, J 37), 169.5 (C-4″, *CO*); HRMS mass found 332.1468 calc. ($C_{14}H_{19}F_3N_4O_2$) 332.1460 (−0.8 MMU).

2b: ^1H NMR: (200 MHz, $CDCl_3$) δ 1.10 (H-2‴, 6H, br), 2.03 (H-6‴, 3H, s), 3.41 (H-2″, 4H, br), 5.47 (H-4, 1H, t, J 7.9), 7.11 (H-7, 1H, s), 9.2 (H-6′, 1H, br), 10.5 (H-5′, 1H, br), owing to conformational exchange, the proton resonances for the CH_2 in the ring, H-3, were too weak to be reliably distinguished from noise; ^{13}C NMR: (50 MHz, $CDCl_3$, J in Hz) δ 12.4 (C-2‴, *Me*), 22.3 (C-6‴, *Me*), 29.4 (C-3, *Me*), 43.4 (C-2″, CH_2), 105.9 (C-4, *CH*), 114.4 (C-5, *C*), 115.8 (C-5‴, CF_3, q, J 287), 132.4 (C-6, *C*), 141.0 (C-7, *CH*), 147.8 (C-2, *C*), 155.7 (C-5″, $COCF_3$, q, J 37), 172.1; (C-6″, *CO*); HRMS mass found 332.1468 calc. ($C_{14}H_{19}F_3N_4O_2$) 332.1460 (−0.8 MMU).

2b decreased indicating the regiochemical nitrene closure pathways are in equilibrium with each other.

These data together with the compelling literature evidence for didehydroazepine formation, suggest that the photochemical decomposition of aryl azides through the singlet manifold may be viewed as proceeding *via* the azirine and didehydroazepine intermediates with differences in the activation energies between the various species and their trapping coming into play as the temperature and nature of the nucelophile is changed. The initial ring closure of the singlet nitrene to the azirine is *reversible* while the rearrangement of the azirine to the didehydroazepine is *irreversible*. The azirine from 6-closure, **7a** (R = 5-NHCOCF$_3$-6-NHCOMe), which has an unusually long lifetime, may be trapped by DEA in a bimolecular process to give **8**, or may undergo a unimolecular conversion to the didehydroazepine **5**. Below −30 °C the rate for this latter process approaches zero. The trapping of the azirine or didehydroazepine intermediates is irreversible with each trapped species proceeding to its final product without any interconversions. The decreasing yield of **2b** as the [DEA] is increased indicates that there is an equilibrium between the nitrene, ^{1}**4**, and the azirines, **7**, at least at 0 °C and above, with the bimolecular trapping of **7a** driving the equilibrium towards the formation of **9** as the [DEA] increases. The activation barrier for formation of the didehydroazepine from 2-closure, **5b** (R = 5-NHCOCF$_3$-6-NHCOMe) is lower than that for formation of **5a** (R = 4-NHCOMe-5-NHCOCF$_3$) as observed by the initial formation of **2b** as the temperature was increased. The azirine from 2-closure, **7b** (R = 4-NHCOMe-5-NHCOCF$_3$) must have an exceedingly short lifetime since it was never trapped even at −30 °C when the formation of **2b** became significant. In this respect it is behaving as a normal monocyclic azide where, if such intermediates exist, they are formed with lifetimes which must be in the nanosecond or less range.

The rationale for the differing lifetimes of the azirines is dependent on the interplay between very subtle structural factors and is the subject of continuing investigation. One factor which may have some importance is a simple steric one. The 6-closure azirine has the two amido groups separated by a single bond (C_4–C_5) and has the two groups moved slightly away from each other because of the twisted nature of the diene unit. In the didehydroazepine derived from 6-closure, the two amido groups are separated by a double bond (C_4=C_5) and are in the same plane; that is the steric congestion has *increased*. The didehydroazepine from 2-closure in contrast is in the exact reverse situation; opening of the azirine ring results in the *removal* of steric strain and the process should therefore possess a lower activation barrier than that for the latter azirine, as is observed. The previously recorded example of azirine trapping by Nielsen and Burchardt[3] contains a similar 3,4-substitution pattern.

We thank the NSERC of Canada for an operating Grant and a Postgraduate NSERC Scholarship (C. G. Y.).

Received, 29th May 1992; Com. 2/02826C

References

1 (*a*) C. J. Shields, D. R. Chrisope, G. B. Schuster, A. J. Dixon, M. Poliakoff and J. J. Turner, *J. Am. Chem. Soc.*, 1987, **109**, 4723; (*b*) Y.-Z. Li, J. P. Kirby, M. W. George, M. Poliakoff and G. B. Schuster, *J. Am. Chem. Soc.*, 1988, **110**, 8092; (*c*) C. J. Shields, D. E. Falvey, G. B. Shuster, O. Buchardt and P. E. Nielson, *J. Org. Chem.*, 1988, **53**, 3501; (*d*) B. A. DeGraff, D. W. Gillespie and R. J. Sundberg, *J. Am. Chem. Soc.*, 1974, **96**, 7491; (*e*) W. von E. Doering and R. A. Odum, *Tetrahedron*, 1966, **22**, 81; (*f*) S. E. Carroll, B. Nay, E. F. V. Scriven, H. Suschitzky and D. R. Thomas, *Tetrahedron Lett.*, 1977, **36**, 3175; (*g*) K. Lamara and R. K. Smalley, *Tetrahedron*, 1991, **47**, 2277; (*h*) R. Huisgen, D. Vossius and M. Appl, *Chem. Ber.*, 1958, **91**, 1; (*i*) R. A. Abramovitch and B. A. Davies, *Chem. Rev.*, 1964, **64**, 149; (*j*) O. L. Chapman and J.-P. Le Roux, *J. Am. Chem. Soc.*, 1978, **100**, 282; (*k*) N. Soundararajan and M. S. Platz, *J. Org. Chem.*, 1989, **55**, 2034; (*l*) E. W. Meijer, S. Nijuis and F. C. B. M. van Vroonhoven, *J. Am. Chem. Soc.*, 1988, **110**, 7209.

2 (*a*) I. R. Dunkin and P. C. P. Thomson, *J. Chem. Soc., Chem. Commun.*, 1980, 499; (*b*) D. I. Patel, E. F. V. Scriven, R. K. Smalley and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1911; (*c*) R. Hayes, J. M. Schofield, R. K. Smalley and D. I. C. Scopes, *Tetrahedron*, 1990, **46**, 2089; (*d*) A. K. Schrock and G. B. Schuster, *J. Am. Chem. Soc.*, 1984, **106**, 5228; (*e*) Z. U. Khan, D. I. Patel, R. K. Smalley, E. F. V. Scriven and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2495.

3 P. E. Nielson and O. Buchardt, *Photochem. and Photobiol.*, 1982, **35**, 317.