Formation of Bicyclic Azepines by Intramolecular Trapping of Didehydroazepines

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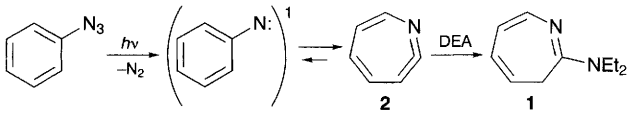
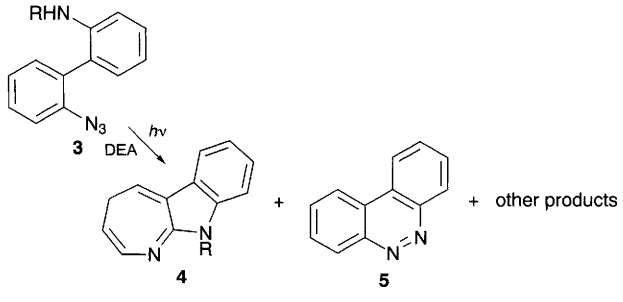
Photolysis of 2-(3-aminopropyl)phenyl azides **6** gives 2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-*b*]azepines **7** in good yields, which are formed by intramolecular trapping of the ring-expanded didehydroazepine intermediate with an amino group.

It has been established that the photolysis of phenyl azide in diethylamine (DEA) affords 2-(diethylamino)-3*H*-azepine **1**,[1,2] and that this reaction proceeds through the ring-expanded isomer of singlet phenylnitrene, didehydroazepine **2** (Scheme 1) which has been directly observed by means of IR spectroscopy in Ar matrices[3] and in fluid solutions.[4] Despite the possibilities of this reaction leading to a useful synthetic route to polycyclic azepines, no attempt to trap didehydroazepines with an intramolecular nucleophilic substituent has been reported. Recently, in the photolysis of 2-amino-2′-azidobiphenyls **3** in DEA we obtained the azepine **4** formed by intramolecular trapping of the didehydroazepine intermediate. However, the yield of **4** was very low (5–7%), owing to the preferential formation of benzo[*c*]cinnoline **5** through the interaction of the singlet nitrene with an amino group (Scheme 2).[5] Here, we report the first practical success in capturing didehydroazepines intramolecularly with an amino group in the photolysis of 2-(ω-aminoalkyl)phenyl azides, which gives new heterocyclic ring-annulated azepines.

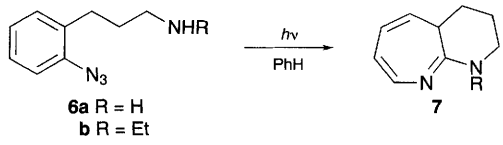
Irradiation (λ > 300 nm, 2 h) of a degassed solution of 2-(3-aminopropyl)phenyl azide **6a**[6] (30 mg, 0.17 mmol) in benzene (30 ml) with a high-pressure mercury lamp at room temperature exclusively gave 2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-*b*]azepine **7a** (56%; Scheme 3),† which could be isolated after chromatographic separation as the sole photoproduct. The 3*H*-azepine structure of **7a** was characterized by comparison of ^{1}H and ^{13}C NMR spectra with those of analogous azepines.[1] The methine proton of the 4a-position of **7a** appeared at δ 2.00 in the ^{1}H NMR spectrum. This observation indicated that this proton was located in the shielding zone of the C_7=C_8 double bond owing to the restriction of the azepine ring inversion. The bicyclic azepine **7a** was obtained in other organic solvents, such as cyclohexane, methanol and acetonitrile in analogous yields. The use of longer wavelengths (Corning glass filter #CS-052, λ > 350 nm) for the photolysis of **6a** resulted in a slight increase in the yield of **7a**, probably owing to the suppression of photodecomposition of the product. Furthermore, it was found that an *N*-ethyl derivative **6b** also gave the corresponding pyrido[2,3-*b*]azepine derivative **7b** in a comparable yield to the photolysis of **6a**. The results are summarized in Table 1.



Scheme 1



Scheme 2



Scheme 3

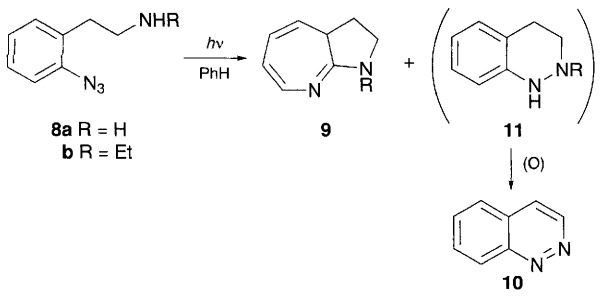
Thus, in contrast to the photochemical reactivities of 2-amino-2′-azidobiphenyls **3**, where **4** was obtained only in the presence of a nucleophile which could trap didehydroazepines effectively,[5] the bicyclic azepines **7** were readily obtained in the photolysis of **6**. To our knowledge, this is the first example of practical intramolecular trapping of didehydroazepines with a nucleophilic substituent. It would be interesting to determine how effectively an internal amino group can capture the ring-expanded intermediate compared with an external nucleophile. However, irradiation (λ > 350 nm) of **6a** in DEA yielded **7a** in 47% yield, where no azepines derived from external trapping of didehydroazepine with DEA were detected. This observation implies that, in spite of the lower nucleophilicity of the primary amino group in **6a** compared with DEA, the rate of nucleophilic attack of the internal amino group is much faster than that of the external nucleophile.‡

To test the usefulness of this method in the synthesis of pyrrolo[2,3-*b*]azepine derivatives, the photochemistry of 2-(2-aminoethyl)phenyl azide **8a**[6] was examined. Irradiation (λ > 350 nm) of **8a** in benzene yielded a complex mixture, the ^{1}H NMR spectrum of which showed a set of signals characteristic of an azepine skeleton (δ 5.17, 5.79, 6.19 and 6.94). Unfortunately, attempts to isolate this azepine from the mixture were unsuccessful because of its instability. In the case of an *N*-ethyl derivative **8b**, however, the corresponding bicyclic azepine, 1-ethyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]azepine **9b**, was obtained in 27% yield, which could be isolated after separation by chromatography (Scheme 4). In this reaction, cinnoline **10** was also isolated in 9% yield. The formation of **10** was rationalized in terms of dehydrogenation of the tetrahydrocinnoline derivative **11b** by air in the course of the separation, since **11b** instead of **10** was detected in the ^{1}H NMR spectrum of the reaction mixture recorded immediately after the photolysis.§ These results indicate that the singlet nitrene generated from **8** reacted directly with the internal amino group in competition with the ring-enlargement process.

Table 1 Yields of **7** in the photolysis (λ > 300 nm) of **6** in various solvents

Solvent	Yield (%)[a] 7a	7b
Benzene	56	64
Benzene[b]	69	73
Cyclohexane	53	40
Methanol	42	37
Acetonitrile	55	64

[a] Determined by the integration of the ^{1}H NMR spectrum. [b] Irradiation with longer wavelength light (λ > 350 nm).



Scheme 4

Thus, it was found that the yield of internally trapped didehydroazepines was greatly dependent on the structure of the starting azides. The high yield of the bicyclic azepine **7** in the photolysis of **6** seems to be attributable to an unfavourable direct interaction of the generated singlet nitrene with an amino group. In the case of the nitrenes generated from **8**, as well as **3**, the interaction of the nitrene with an amino group resulted in the generation of the relatively stable ylide with a six-membered ring, which led to the formation of **11** through proton migration. The photoreaction described in this paper provides a new strategy for the synthesis of heterocyclic ring-annulated azepines, which are of pharmacological interest.[7] Further work to apply this method to the preparation of other polycyclic azepines is ongoing in our laboratory.

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Footnotes

† *Spectroscopic data* for **7a**: colourless granules; mp 101–102 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.7–1.9 (2H, m), 2.00 (1H, m), 2.1–2.3 (2H, m), 3.2–3.3 (1H, m), 3.38 (1H, td, *J* 11.2, 4.4 Hz), 4.66 (1H, brs), 4.95 (1H, dd, *J* 8.6, 5.4 Hz), 5.75 (1H, dd, *J* 7.9, 5.6 Hz), 6.21 (1H, dd, *J* 8.6, 5.6 Hz), 6.90 (1H, d, *J* 7.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 20.1, 25.8, 38.5, 42.6, 111.2, 121.6, 127.0, 139.4, 146.7. For **7b**: oil; ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, t, *J* 7.1 Hz), 1.8–2.0 (3H, m), 2.0–2.2 (1H, m), 2.2–2.3 (1H, m), 3.0–3.1 (1H, m), 3.3–3.5 (3H, m), 4.92 (1H, dd, *J* 8.6, 5.7 Hz), 5.69 (1H, dd, *J* 7.9, 5.8 Hz), 6.22 (1H, dd, *J* 8.6, 5.8 Hz), 7.07 (1H, d, *J* 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 11.4, 20.6, 26.2, 39.5, 44.8, 47.7, 109.5, 121.1, 126.7, 140.3, 145.0. For **9b**: oil; ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, t, *J* 7.3 Hz), 2.1–2.2 (1H, m), 2.3–2.5 (2H, m), 3.0–3.1 (1H, m), 3.2–3.3 (1H, m), 3.3–3.5 (2H, m), 5.08 (1H, dd, *J* 8.9, 3.6 Hz), 5.71 (1H, dd, *J* 8.2, 5.6 Hz), 6.1–6.2 (1H, m), 7.11 (1H, d, *J* 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 11.9, 26.1, 39.9, 43.1, 48.0, 110.5, 118.1, 127.7, 141.7, 151.5.

‡ The possibility cannot be ruled out that the azepine formed by external trapping of the didehydroazepine with DEA is converted to **7a** by the substitution of the diethylamino group with the internal amino group. This mechanism has been proposed in the formation of **4** in the photolysis of **3** in DEA.[5]

§ A set of signals assigned to the ethyl group at around δ 1.1 and 2.7, and peaks at δ 5.28 (brs), 6.63 (d, *J* 7.6 Hz) and 6.76 (t, *J* 7.3 Hz) were assigned to **11b**. The ratio of **11b** to **9b** was estimated to be 0.94 by the integration of ^{1}H NMR spectrum. After aeration of the sample solution, the peaks owing to **11b** disappeared totally and the new peaks assigned to **10** appeared.

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