Gas-phase pyrolysis of 1-(2-azidophenyl)imidazole

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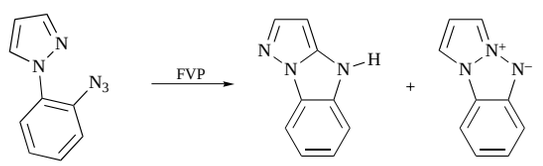
Flash vacuum pyrolysis (FVP) of the azide 4 leads to imidazo[1,2-*a*]benzimidazole 8 exclusively, *via* highly regioselective insertion of the triplet nitrene intermediate 5 into the 2-CH bond of the imidazole ring. The X-ray crystal structure and NMR spectroscopic properties of 8 are discussed in detail.

In a recent communication,[1] we have shown that pyrolysis of 1-(2-azidophenyl)pyrazole **1** in the gas-phase under flash vacuum pyrolysis (FVP) conditions leads to much more efficient cyclisation processes *via* the corresponding nitrene than take place when the reactions are conducted in solution.[2] In particular, the triplet component of the nitrene pathway undergoes C–H insertion to give pyrazolobenzimidazole **2** whereas only hydrogen abstraction and dimerisation products were found under solution conditions. The singlet component of the nitrene pathway is trapped by the lone pair on the pyrazole 2-nitrogen atom to give the pyrazolobenzotriazole **3** (Scheme 1).



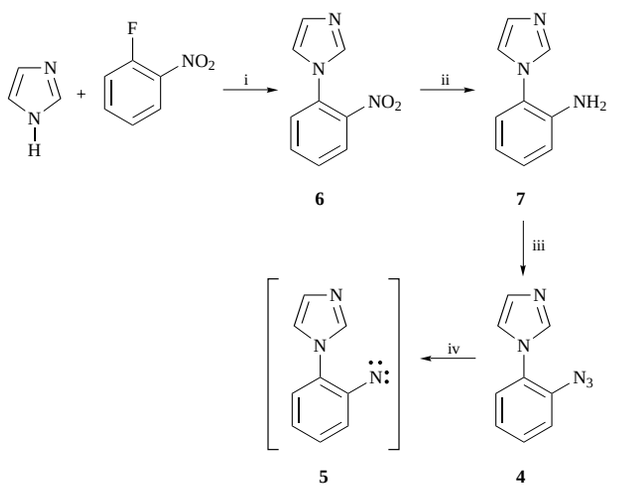
1 **2** **3**

Scheme 1

In view of these results, we have extended our studies to the parent 1-(2-azidophenyl)imidazole **4** case. Although there is no corresponding trapping mechanism for the singlet nitrene, we anticipated that two possible products might be formed by triplet insertion into the 2- or 5-CH bonds of the imidazole. When the nitrene **5** was generated in solution by phosphite-mediated deoxygenation of the nitro compound **6**, the only reported product was 2-nitroaniline (29%).[2] Other reactions of imidazoles with electron-deficient intermediates are surprisingly scarce.[3] Busby *et al.* have studied the gas-phase intermolecular reaction of a number of imidazoles with dichlorocarbene and obtained ring expansion products which were rationalised by insertion mechanisms into C–C or C–N bonds.[4]

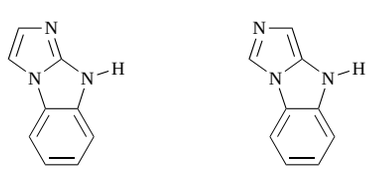
For the gas-phase generation of the nitrene, we employed the azide precursor **4** which was efficiently prepared by the method shown in Scheme 2. The nitro compound **6** was made in 92% yield by reaction of imidazole with 2-fluoronitrobenzene using a minor modification of the literature method,[2] and reduction to the amine **7** was achieved by catalytic hydrogenation in 99% yield. Diazotisation and reaction with sodium azide gave the azide **4** (98%).

Upon attempted FVP at 500 °C under our standard vacuum conditions (10^{-2}–10^{-3} Torr), the azide **4** proved to be exceedingly involatile and showed evidence of extensive decomposition at temperatures at or below its sublimation point. (**CAUTION:** azides are potentially explosive. Although we had no problems with this pyrolysis, all precautions were taken and particularly a metal inlet heater was used to contain any explosion which might take place.) The situation was improved somewhat by the use of a diffusion pump (10^{-4} Torr), but even then only small quantities of the azide could be pyrolysed in a single run, and the yield of recovered products was poor (*ca.* 12%). The pyrolysate was obtained as white crystals whose mass spectrum showed a molecular ion at *m/z* 157, as expected following loss of dinitrogen from the azide **4**. However it was clear from the ^{13}C NMR spectrum of the crude pyrolysate that just one heterocyclic product was formed, even though two insertion products, imidazo[1,2-*a*]benzimidazole **8** and imidazo[1,5-*a*]benzimidazole **9**, could in principle be obtained.



6 **7** **5** **4**

Scheme 2 *Reagents and conditions*: i, K_2CO_3–pyridine, 16 h; ii, H_2–Pd/C, 3 atm, 4 h; iii, HNO_2, NaN_3, 30 min; iv, FVP



8 **9**

Only the imidazo[1,2-*a*]benzimidazole **8** is a known compound,[5] but its spectra were not reported in sufficient detail to allow unambiguous identification in this case.

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Table 1 Selected bond lengths (Å) and angles (°) for **8**

N(1)–C(1a)	1.319(2)
N(1)–C(2)	1.401(2)
C(2)–C(3)	1.350(2)
C(3)–N(4)	1.395(2)
N(4)–C(1a)	1.364(2)
N(4)–C(4a)	1.399(2)
C(4a)–C(5)	1.376(2)
C(4a)–C(8a)	1.407(2)
C(5)–C(6)	1.386(2)
C(6)–C(7)	1.392(2)
C(7)–C(8)	1.390(2)
C(8)–C(8a)	1.389(2)
C(8a)–N(9)	1.398(2)
N(9)–C(1a)	1.372(2)
C(1a)–N(1)–C(2)	102.22(13)
C(3)–C(2)–N(1)	113.17(14)
C(2)–C(3)–N(4)	104.34(15)
C(1a)–N(4)–C(3)	106.54(12)
C(1a)–N(4)–C(4a)	109.38(12)
C(3)–N(4)–C(4a)	143.99(14)
C(5)–C(4a)–N(4)	132.10(15)
C(5)–C(4a)–C(8a)	122.54(15)
N(4)–C(4a)–C(8a)	105.36(13)
C(4a)–C(5)–C(6)	117.1(2)
C(5)–C(6)–C(7)	121.2(2)
C(8)–C(7)–C(6)	121.7(2)
C(7)–C(8)–C(8a)	117.6(2)
C(8)–C(8a)–N(9)	131.22(15)
C(8)–C(8a)–C(4a)	119.84(14)
N(9)–C(8a)–C(4a)	108.94(13)
C(1a)–N(9)–C(8a)	106.90(13)
N(1)–C(1a)–N(4)	113.73(14)
N(1)–C(1a)–N(9)	136.96(15)
N(4)–C(1a)–N(9)	109.31(13)

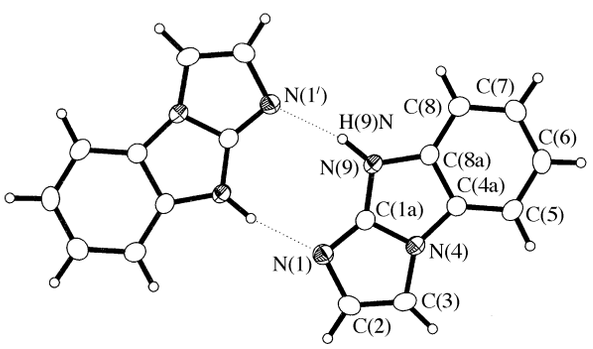


Fig. 1 A view of a dimer of molecule **8** showing crystallographic numbering scheme

It proved surprisingly difficult to distinguish the two systems unambiguously by ^{1}H NMR spectroscopy, in particular because 3- and 4-bond proton coupling constants in imidazole-like systems are of comparable magnitude,[6] and because NOE experiments involving the two imidazole-derived protons at δ_H 7.58 and 7.10 (J 1.8 Hz) were inconclusive (see below). The problem was finally solved unambiguously by single crystal X-ray analysis which confirmed that the unknown compound was imidazo[1,2-*a*]benzimidazole **8**. Structural parameters are given in Table 1 and a view of the molecule with the crystallographic numbering system is shown in Fig. 1. The bond lengths N(1)–C(1a) [1.319(2) Å] and C(2)–C(3) [1.350(2) Å] in particular serve to exclude the alternative structure **9**, as well as the location of each hydrogen atom as a difference electron density feature in the range 0.64–0.78 electrons Å^{-3} with the remaining features less than 0.20 electrons Å^{-3}.

Bond lengths in the imidazole-derived ring show some evidence of increased localisation with respect to imidazole itself;[7] in particular, all the formal single bonds are much longer than in the parent molecule. In the central ring of **8**, the length of the N(9)–C(1a) bond [1.372(2) Å] is significantly shorter than that

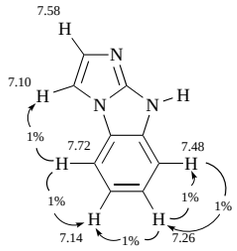


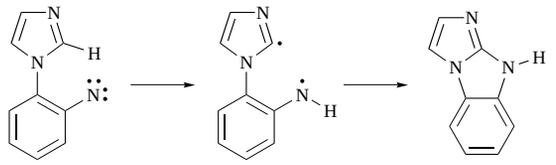
Fig. 2 Proton chemical shift ([^{2}H$_6$]acetone) and NOE data for **8**

of N(9)–C(8a) [1.398(2) Å], indicating that electron delocalisation for the N(9) lone pair takes place predominantly into the imidazole ring rather than the benzenoid ring. The expected angular distortion at each of the ring junction positions is present, with all the exocyclic angles being >130° and that at N(4) [C(3)–N(4)–C(4a)] being >140°. In addition, the ring fusion leads to some distortion of both the bond lengths and angles in the benzenoid ring.

Each individual ring of **8** is almost planar [RMS deviation of the imidazole-derived ring N(1)–C(2)–C(3)–N(4)–C(1a) is 0.0011 Å, that of the central ring C(1a)–N(4)–C(4a)–C(8a)–N(9) is 0.012 Å and that of the benzenoid ring is 0.005 Å], but the molecule as a whole is very slightly bowl-shaped (angle between normals to the two 5-membered rings is 2.4° and between the central ring and the benzenoid ring is 1.6°). As shown in Fig. 1, the molecules are linked into dimeric pairs by hydrogen bonding between H(9)N and N(1′), where N(1′) is in a molecule related by inversion. The H · · · N′ distance is 1.98 Å, and the N–H · · · N′ angle is 166°. The two molecules in the dimeric unit are parallel but not coplanar, the centres of the best planes being offset by 0.466 Å. The dimers pack in parallel stacks related by inversion ($1 - x$, $1 - y$, $1 - z$); the closest approach of molecules within individual stacks is 3.23 Å.

In view of the paucity of literature data on the imidazo[1,5-*a*]-benzimidazole system, the NMR spectroscopic properties of **8** were investigated in some detail. The ^{1}H NMR spectrum was highly solvent dependent, but solutions in [^{2}H$_6$]acetone were fully resolved at 360 MHz and could be fully assigned on the basis of NOE studies (Fig. 2), which showed the order of increasing chemical shift in the benzenoid portion of the molecule to be H(6) < H(7) < H(8) < H(5). In the fully coupled ^{13}C NMR spectrum, all the methine signals appeared as doublets of doublets. The signals at δ_C 126.68 and 105.74, which had large values of $^1J_{CH}$ (189–196 Hz), were assigned as the C(2) and C(3) resonances, respectively, with the signal of lower chemical shift corresponding to the more electron-rich position. The absence of a $^1J_{CH}$ value >200 Hz provides good supporting evidence for the imidazo[1,2-*a*]benzimidazole rather than the isomeric imidazo[1,5-*a*]benzimidazole structure, since it is known that the $^1J_{CH}$ values of C(2) in imidazole systems are especially large in magnitude.[8] No attempt was made to correlate the benzenoid carbon signals of **8**, which occurred in the range δ_C 123.36–110.89. One-bond and long-range coupling constants $^nJ_{CH}$ are quoted in the Experimental section. The fine couplings were due to 2-bond interactions in the case of the imidazole-derived ring, and to 3-bond interactions in the case of the benzenoid ring.

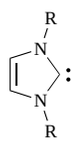
In conclusion, these results show that thermolysis of the azide **4** leads to a nitrene intermediate which inserts *exclusively* into the 2-CH bond of the imidazole ring with no corresponding reaction at the 5-CH bond. We believe that this reaction is the first example of such high regioselectivity in the imidazole system and an unusual example of selectivity in reactive intermediate chemistry. It seems unlikely that a concerted insertion reaction of a singlet nitrene would be able to distinguish H(2) and H(5) in this way. However, hydrogen abstraction by a triplet nitrene would generate an intermediate diradical **10** in which one electron is located in an imidazole σ-orbital (Scheme 3), a



10

Scheme 3

conclusion supported by independent evidence on the multiplicity of the nitrene responsible for insertion reactions in the analogous pyrazolyl case.[1] It is well known that the imidazole 2-position conveys special stability to reactive intermediates located at that site. Examples include the remarkable isolable imidazol-2-ylidenes[9] **11** and the well known reactivity of imid-



11

azole 2-hydrogen atoms towards strong bases which generate an imidazolyl 2-carbanion. In the present case, stabilisation may be conferred by lateral overlap of the orbital containing the single electron with the lone pair orbital on C(3). Finally, our results reinforce our previous comments[1] on the utility of gas-phase FVP methods in such fundamental studies of nitrene reactions.

Experimental

^{1}H and ^{13}C NMR Spectra were recorded at 200 and 50 MHz respectively for solutions in [^{2}H]chloroform unless otherwise stated. Coupling constants (*J*) are quoted in Hz.

1-(2-Nitrophenyl)imidazole 6

A stirred mixture of imidazole (1.09 g, 16 mmol), 2-fluoronitrobenzene (2.26 g, 16 mmol), anhydrous potassium carbonate (2.24 g, 16 mmol) and copper(II) oxide (0.08 g) in pyridine (4.0 cm^3) was heated under reflux for 16 h under nitrogen. Dichloromethane (100 cm^3) and activated charcoal (2.0 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a Celite pad then washed thoroughly with dichloromethane. The solvents were removed under reduced pressure to give the title compound **6** as orange crystals (2.80 g, 92%), mp 96–98 °C (from cyclohexane–chloroform) (lit.,[2] mp 96–98 °C); δ_H 7.92 (1 H, dd, ^3J 8.0, ^4J 1.6), 7.67 (1 H, td, ^3J 7.7, ^4J 1.6), 7.58–7.52 (2 H, m), 7.40 (1 H, dd, ^3J 7.8, ^4J 1.5), 7.11 (1 H, br s) and 7.00 (1 H, t, ^3J 1.2).

1-(2-Aminophenyl)imidazole 7

Palladium-on-charcoal (10%, 0.27 g) was carefully added to a solution of 1-(2-nitrophenyl)imidazole **6** (2.00 g, 10.6 mmol) in ethanol (150 cm^3) and the mixture was hydrogenated at medium pressure (3 atm) and ambient temperature for 4 h. The mixture was filtered through a Celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give the *amine* **7** as a brown solid (1.67 g, 99%) which did not require further purification; mp 103–106 °C (from cyclohexane–toluene) (Found: C, 67.9; H, 5.85; N, 26.2. $C_9H_9N_3$ requires C, 67.9; H, 5.65; N, 26.4%); δ_H 7.59 (1 H, s), 7.25–7.16 (2 H, m), 7.09–7.05 (2 H, m), 6.82–6.73 (2 H, m) and 4.24 (2 H, br s); δ_C 141.81 (q), 137.44, 129.68, 129.59, 126.91, 123.01 (q), 119.92, 118.25 and 116.17; *m/z* 159 (M^+, 51%), 132 (100), 131 (98), 119 (34), 104 (21), 77 (15), 65 (28), 52 (19) and 39 (16).

1-(2-Azidophenyl)imidazole 4

To stirred solution of 1-(2-aminophenyl)imidazole **7** (1.03 g, 6.5 mmol) in concentrated hydrochloric acid solution (35%, 3 cm^3) and water (10 cm^3) at 0 °C was added a solution of sodium nitrite (0.50 g, 7.2 mmol) in water (3 cm^3). The resulting solution was added carefully, with stirring, to a solution of sodium azide (0.47 g, 7.2 mmol) and sodium acetate (2.5 g) in water (15 cm^3) at 0 °C. On addition a light brown precipitate appeared, however the mixture was stirred at room temperature for a further 30 min. The mixture was extracted with diethyl ether (3 × 50 cm^3), the organic extracts were washed with dilute aqueous sodium hydroxide (2 M, 10 cm^3) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40 °C to yield the *title compound* **4** as a brown oil (1.17 g, 98%) (HRMS: found, 185.0704. $C_9H_7N_5$ requires *M*, 185.0701); ν_{max}/cm^{-1} 2130 and 2097; δ_H 7.64 (1 H, t, ^4J 1.1), 7.38 (1 H, ddd, ^3J 8.1, 7.0, ^4J 1.9), 7.25–7.13 (3 H, m) and 7.11–7.09 (2 H, m); δ_C 137.25, 134.05 (q), 129.02, 128.11 (q), 126.34, 125.18, 120.02 and 119.27 (one quaternary overlaps with another signal); *m/z* 185 (M^+, 74%), 157 (100), 130 (65), 104 (26), 103 (94), 90 (33), 77 (35) and 76 (45).

Flash vacuum pyrolysis of 1-(2-azidophenyl)imidazole 4

1-(2-Azidophenyl)imidazole **4** (0.09 g, 0.4 mmol) was allowed to sublime at room temperature and 10^{-4} Torr (mercury diffusion pump) over a period of 7 h through the silica furnace tube (35 × 2.5 cm) which was maintained at 500 °C by an electrical heater. The inlet tube was covered with a metal cylinder to aid volatilisation and act as a safety screen in the event of an azide explosion. Substantial decomposition of the substrate in the inlet was observed. The pyrolysis was repeated three times in order to obtain enough material for NMR analysis. Upon completion of each pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. Acetone was then distilled into the trap, the resulting solution was removed and the combined products purified by dry-flash chromatography eluting with a 1:20 mixture of methanol and ethyl acetate. The pyrolyses afforded only 9*H*-imidazo[1,2-*a*]benzimidazole **8** (24 mg, total from 3 runs, 12%), mp 188 °C (decomp.) [lit.,[5] 190 °C (decomp.)]; δ_H([$^2H_6$]acetone) 7.72 (1 H, d, ^3J 6.7), 7.58 (1 H, d, ^3J 1.8), 7.48 (1 H, d, ^3J 6.0), 7.26 (1 H, td, ^3J 7.7, ^4J 1.4), 7.14 (1 H, td, ^3J 7.7, ^4J 1.3) and 7.10 (1 H, d, ^3J 1.8); δ_C 149.56 (q), 137.89 (q), 126.88 (^1J 189.7, ^2J 10.3), 124.73 (q), 123.36 (^1J 157.3, ^3J 5.7), 119.56 (^1J 161.1, ^3J 7.7), 113.55 (^1J 163.9, ^3J 8.8), 110.89 (^1J 161.4, ^3J 8.8) and 105.74 (^1J 196.1, ^2J 14.8); *m/z* 157 (M^+, 33%), 88 (12), 86 (62), 84 (100), 49 (13), 47 (20), 40 (12) and 32 (100).

X-Ray crystallography

A red–brown crystal of dimensions 0.50 × 0.35 × 0.25 mm was mounted on a glass fibre and transferred to a Stoe Stadi-4 four-circle diffractometer equipped with an Oxford Cryosystems low-temperature device.[10]

Crystal data. $C_9H_7N_3$, *M* = 157.18, monoclinic, space group $P2_1/n$ with *a* = 9.6989(11), *b* = 5.4692(7), *c* = 13.863(2) Å, β = 100.315(14)°, *U* = 723.5 Å^3 {from 2θ values of 31 reflections measured at ±ω [30 ⩽ 2θ ⩽ 33°, λ(Mo-Kα) = 0.71 073 Å, *T* = 150.0(2) K]}, D_c = 1.443 g cm^{-3}, *Z* = 4, μ = 0.092 mm^{-1}.

Data collection and processing. Diffraction data were acquired to $2\theta_{max}$ = 50° using ω–2θ scans. Of 1287 unique reflections collected, 1000 had $F \geqslant 4\sigma(F)$ and 1282 were retained in all calculations. No crystal decay was observed and no corrections were applied for absorption.

Structure solution and refinement. Automatic direct methods[11] identified the positions of all non-H atoms, which were then refined anisotropically. Hydrogen atoms were located from a ΔF synthesis and freely refined[12] with individual isotropic thermal parameters. The weighting scheme $w^{-1} = [\sigma^2(F_o^2) + (0.035P)^2 + 0.23P]$, $P = \frac{1}{3}[\mathrm{MAX}(F_o^2, 0) + 2F_c^2]$ led to

final convergence with R_1 [$F \geqslant 4\sigma(F)$] = 0.0337, wR_2 (all data) = 0.0846‡, $S(F^2)$ = 1.062 for 138 refined parameters. An extinction correction[12] refined to 0.011(2) and the final ΔF synthesis showed no peaks above ±0.18 e Å^{-3}. Fig. 1 was produced using SHELXTL/PC.[13]

Acknowledgements

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‡ $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{\frac{1}{2}}$.

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