Medium-dependent Trapping of Diazoalkane Intermediates During Photolysis of Diazirines

Peter Bennett,[a] Laurence M. Harwood,*[b] Jason Macro[b] and Andrew McGregor[b]

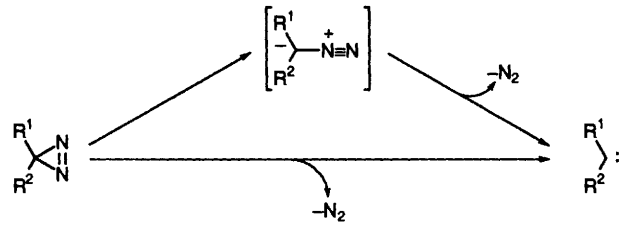
[a] *Horsell Graphic Industries, Howley Park Estate, Morley, Leeds, UK LS27 0QT*
[b] *Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY*

Photolysis of an intimate mixture of methyl(phenyl)diazirine and *N*-methylmaleimide in the absence of solvent permits the diazoalkane intermediate to be trapped, whereas the equivalent reaction in solution gives only cyclopropanated adducts.

Diazirines are widely used as photoaffinity reagents for labelling biological receptor sites,[1] as they demonstrate the advantages of useful thermal stability coupled with efficient photolysis by light with a wavelength around 362 nm (the λ_{max} of the diazirine chromophore), a region in which most biological molecules are transparent. On photolysis, diazirines ultimately furnish carbenes which may be trapped or undergo further rearrangement.[2] However, there has been some debate as to the actual pathway by which the carbenes are formed, as photolytic decomposition might proceed either by a concerted loss of nitrogen to furnish singlet carbene directly, or *via* ring opening to the isomeric diazoalkane with subsequent loss of nitrogen (Scheme 1).[3]

Photolysis of diazirine produces singlet carbene,[4] although it has been proposed that there is a substantial degree of photoisomerisation to diazomethane initially.[5] Photolysis of 3-phenyl-3*H*-diazirine has been observed to give rise to an intermediate species in low concentration which, although photolabile, was less so than the starting diazirine.[6] On the basis of the changes in UV absorption spectrum during reaction it was suggested that this species was the linear aryl diazo compound. IR studies of solution phase photolyses of cycloalkane spirodiazirines indicated the intermediacy of diazoalkanes,[7] and other workers subsequently succeeded in trapping the diazoalkane intermediate generated by photolysis of cyclohexanespirodiazirine in toluene.[8] Diphenyldiazirine is known to be thermally unstable with regard to the corresponding diphenyldiazomethane[9] and the photointerconversion of diazoamides and diazirine carboxamides has been demonstrated.[10]

No intermolecular trapping experiments which indisputedly indicate the intermediacy of diazo species on photolysis of simple aryl diazirines have been reported. Herein we report the effect of the photolysis medium upon the product mixture composition when 3-phenyl-3-methyldiazirine **1** is irradiated in the presence of *N*-methylmaleimide.



Scheme 1

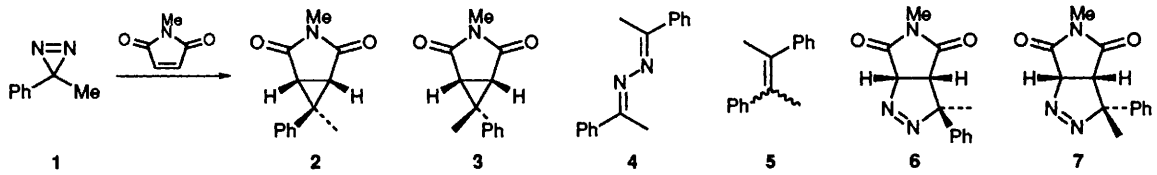
Substrate **1** was prepared by an adaptation of a procedure of Schmitz and Ohme[11] from *N*-benzylmethyl(phenyl)ketimine, prepared following the method of Reddelein.[12] A solution of **1** in diethyl ether containing an equimolar quantity of *N*-methylmaleimide was irradiated through Pyrex using a 450 W medium pressure lamp until **1** was completely consumed (4 h). The resultant mixture furnished cyclopropane adducts **2** and **3** in 23% and 20% isolated yields respectively, together with lesser quantities of acetophenone azine (**4**, 8%) and a mixture of (*E*)- and (*Z*)-2,3-diphenylbut-2-enes [(*E*)- and (*Z*)-**5**)] (1%). No other materials could be identified in the crude reaction mixture (Scheme 2).

However, irradiation of the same starting mixture in the form of a gum obtained by removal of the solvent, until disappearance of starting diazirine (8 h), furnished pyrazolines (**6**, 12%) and (**7**, 11%) in addition to the previously observed materials (**2** 27%, **3** 14%, **4** 4% and **5** 2%), providing incontrovertible evidence for the operation of a decomposition pathway involving the intermediacy of the diazoalkane. The relative stereochemistries of **2**, **3**, **6** and **7** were demonstrated by NOE difference experiments.†

Irradiation of each of the purified adducts **6** and **7** in the absence of solvent led stereoselectively to **2** and **3** respectively; whereas solution-phase photolysis of **6** gave **2** and **3** in a ratio of 34 : 1 and solution-phase photolysis of **7** gave **2** and **3** in a ratio of 1 : 15, indicating slight loss of stereocontrol under these conditions.

Carrying out photolysis of **1** in either methanol or acetic acid gave the corresponding insertion products (1-methoxyethyl)benzene and α-methylbenzyl acetate respectively in quantitative yields. However, during these solution photolyses a transient red colour developed which disappeared on consumption of starting material. The observation of such colouration has been previously associated with the presence of diazo species.[7,9]

Following the evolution of photolysis in the absence of solvent by NMR analysis of aliquots removed from the reaction showed that the rates of formation of the cyclopropanated materials **2** and **3** and pyrazolines **6** and **7** were appreciably the same in the initial stages of photolysis. As the pure pyrazolines decompose more slowly than the rate of appearance of **2** and **3** during photolysis of **1** under these



1 2 3 4 5 6 7

Conditions	Isolated yield (%)					
hν, Et_2O	23	20	8	1	–	–
hν, no solvent	27	14	4	2	12	11

Scheme 2

conditions, it is possible to conclude that both carbene and diazoalkane decomposition pathways are operating.[5–8] The different chemical outcomes of the photolyses in the presence or absence of solvent presumably reflect the relative rates of intermolecular trapping of the initially formed diazoalkane in competition with nitrogen extrusion and, as previously noted,[1] this differential reactivity may have implications for biological photoaffinity labelling studies of proteins. The quantitative yields of insertion products when the photolyses were carried out in methanol or acetic acid, despite the fact that two parallel pathways for decomposition are operating, indicates the need for caution when asserting that such products result solely from the diazoalkane pathway.

In conclusion, we have been able to demonstrate that photolytic decomposition of 1-methyl-1-phenyldiazirine *via* a diazomethane intermediate occurs in parallel with the pathway involving direct extrusion of nitrogen to form a carbene and the outcome of trapping the intermediates is dependent upon the nature of the reaction medium.

We thank the SERC for a studentship (to J. M.) and Horsell Graphic Industries for financial support (to A. M.).

Received, 6th January 1994; Com. 4/00084F

Footnote

† *Spectroscopic data*: **2** mp 165–167 °C; ν_{max}/cm^{-1} (KBr) 1698, 1765; δ (500 MHz, $CDCl_3$) 1.47 (3H, s), 2.81 (2H, s), 2.97 (3H, s), 7.34 (5H, m); *m/z* (CI) 216 (MH^+), 187, 158, 130.

3 mp 176–178 °C, ν_{max}/cm^{-1} (KBr) 1698, 1776; δ (500 MHz, $CDCl_3$) 1.50 (3H, s), 2.29 (3H, s), 2.71 (2H, s), 7.27 (5 H, m); *m/z* (CI) 216 (MH^+), 187, 158, 130.

6 mp 118 °C (decomp.), ν_{max}/cm^{-1} (KBr) 1707, 1774 cm^{-1}; δ (200 MHz, $CDCl_3$) 1.78 (3H, s), 3.02 (3H, s), 3.30 (1H, d, *J* 8.5 Hz), 5.90 (1H, d, *J* 8.5 Hz), 7.30 (5H, m); *m/z* (CI) 261 (MNH_4^+), 244 (MH^+), 233, 216.

7 mp 150 °C (decomp.), ν_{max}/cm^{-1} (KBr) 1707, 1774; δ (200 MHz, $CDCl_3$) 1.94 (3H, s), 2.68 (3H, s), 3.07 (1H, d, *J* 8.5 Hz), 6.00 (1H, d, *J* 8.5 Hz), 7.37 (5H, m); *m/z* (CI) 261 (MNH_4^+), 244 (MH^+), 233, 216.

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