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Polyfluorinated Aryl Azides as Photoaffinity Labelling Reagents; The Room Temperature CH Insertion Reactions of Singlet Pentafluorophenyl Nitrene with Alkanes

by

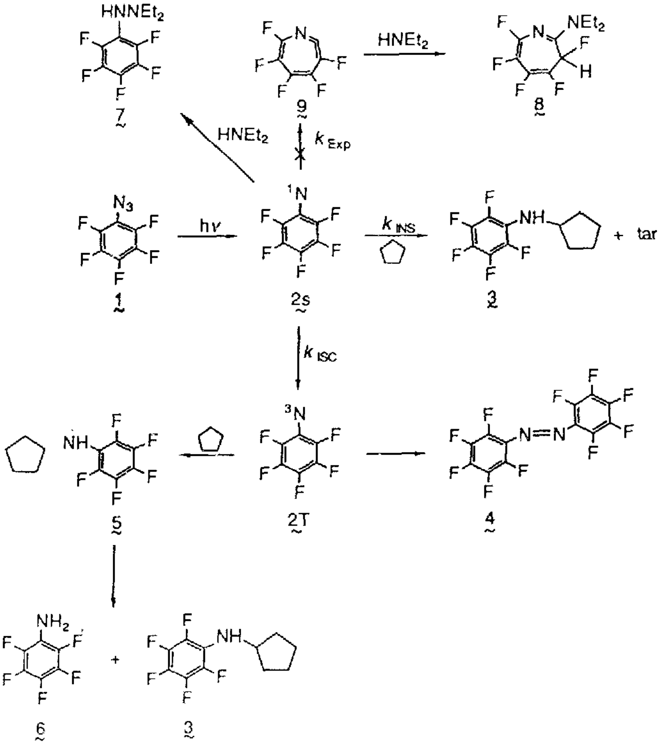
Mary Jennifer T. Young and Matthew S. Platz*
Department of Chemistry
The Ohio State University
Columbus, Ohio 43210

Abstract. Photolysis of pentafluorophenyl azide in alkanes releases singlet pentafluorophenylnitrene which inserts into the CH bond of cyclopentane to produce an adduct in 28% yield.

In a photoaffinity labelling[1] experiment one appends a light sensitive moiety to a natural ligand of a biomolecule. Upon photolysis of the bound substrate the appendage is transformed into a reactive intermediate which it is hoped will react rapidly and indiscriminately with neighboring bonds to ultimately form a permanent covalent linkage between ligand and biomolecule. Photolysis of phenyl azide produces molecular nitrogen and singlet phenyl nitrene which rapidly ring expands to form dehydroazepine.[2] To our knowledge singlet phenyl nitrene has never been chemically intercepted at temperatures suitable for a PAL experiment. The dehydroazepine can be intercepted with amines[3] but polymerizes in the absence of a potent nucleophile. Thus phenyl azide is expected to be an effective PAL reagent only when there is a nucleophile present in the binding pocket of the biomolecule. In this communication fluorinated aryl azides are proposed as PAL reagents because in addition to their desirable reactivity patterns,[4] fluorine is a small substituent[5] and it enables an additional analytical probe of the reaction products, ^{19}F NMR, which is well suited for biomolecules.[6] We have previously reported that photolysis of polyfluorinated aryl azides in toluene at -196° is an effective strategy for photoaffinity labelling.[7] In this communication we are pleased to report that these reagents also show promise in alkane solvents at ambient temperature as well.

Photolysis of pentafluorophenyl azide **1** in cyclopentane at 25° produces adduct **3** in 28% yield in addition to tar.[8] Although the yield of 3 is admittedly low, by contrast no trace of the corresponding product is observed upon photolysis of phenyl azide under the same conditions.[2] Insertion product 3 is likely derived from **2S** because the characteristic triplet nitrene (**2T**) derived products pentafluoroaniline **6** and decafluoroazobenzene **4** are not formed at this temperature. Compounds **4** and **6** are the major products formed upon 4-benzoylbiphenyl sensitization at 25° or upon direct photolysis in cyclopentane at -50° (Table 1), thus triplet nitrene chemistry predominates upon cooling the sample below ambient temperature or upon triplet photosensitization.

Upon photolysis of 1 in diethylamine (DEA) a 46% yield of hydrazine 7 is realized presumably by nucleophilic capture of singlet nitrene **2S**. There is no evidence for the formation of 8 produced by capture of putative dehydroazepine 9[9]. By contrast upon photolysis of phenyl azide in DEA the non fluorinated counterpart of 8 is produced and no trace of a hydrazine is observed.[3]



Photolysis of 1 in polycrystalline alkanes at -196° gives low yields of adducts presumably because the matrix is opaque. However, photolysis of **1** in glassy 3-methylpentane gives a 58% combined yield of the 4 possible formal CH insertion adducts. At this temperature the triplet nitrene **2T** is formed as a long lived species and undergoes secondary photolysis.[7] Photolysis of the nitrene leads to a radical pair by H atom abstraction from the matrix. Collapse of the radical pair leads to the products of formal insertion.

$$C_6F_5N_3 \xrightarrow[-196^\circ C]{h\nu} {}^3C_6F_5N \xrightarrow[C_5H_{12}]{h\nu} C_6F_5\dot{N}H \quad \dot{C}_5H_{11} \longrightarrow C_6F_5NHC_5H_{11}$$

Photolysis of **1** in n-butane or 2,3-dimethylbutane at 25° gave regiochemically pure secondary and tertiary CH insertion adducts in 7.3% and 16% yield respectively. With these alkanes the 2°/1° and 3°/1° selectivities are ∞ as compared with singlet phenyl carbene[10] for which 2°/1° = 9.6 and 3°/1° = 69 with the same two alkanes, but at 0°. The 3°/2° selectivity of singlet nitrene **2S** was obtained by photolysis of **1** in a mixture of cyclopentane and 2,3-dimethylbutane and is equal to 9.8 at 25°. A kinetic isotope effect to insertion into cyclohexane versus cyclohexane-d_{12} was found equal to 3.15 at 25°; the corresponding KIE for singlet phenyl carbene is only 2.1.[11]

Photolysis of **1** in toluene at 25° gave a mixture of aromatic and benzylic substitution products similar to that obtained by deoxygenation of pentafluoronitrosobenzene.[4,12,13] At 25° naphthalene is 16 times more effective at trapping **2S** than toluene.[14] This selectivity increases to a factor of 128 at -78°[15] corresponding to a $\Delta\Delta H^{\ddagger} = 2.0$ kcal/mol. This is quite distinct from singlet carbene chemistry where $\Delta H^{\ddagger}$'s and consequently $\Delta\Delta H^{\ddagger}$'s are essentially equal to zero resulting in little change in product mixtures[16] with varying temperature. The chemical trapping data indicates that **2S** is much more selective and presumably less reactive towards alkanes and aromatics than simple singlet aryl carbenes.

In summary polyfluorinated aryl azides are proposed as PAL reagents because in contrast to phenyl azide, photolysis produces a singlet nitrene which is captured by alkanes, aromatics and amines to give stable covalent adducts.

Acknowledgement

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Table 1. The absolute yields of products formed on photolysis of 1 in cyclopentane.

Temp (°C)	**3**	**4**	**6**
25	28	0	0
25[a]	4.4	5.1	12
0	30	0	4.8
-25	18	9.8	5.2
-50	12	17	4.6
-78	4.1	36	2.6
-196[b]	0.6	16	0

(a) 4-benzoylbiphenyl triplet sensitization

(b) polycrystalline solid

References

1. For a review of photoaffinity labelling see Bayley, H.; "Photogenerated Reagents in Biochemistry and Molecular Biology," Elsevier, New York (1983) and references therein.
2. For reviews of the photochemistry of phenyl azide see Smith, P.A.S.; "Azides and Nitrenes," Scriven, E.F.V., Ed.; Academic Press, San Diego, CA (1984) p.95. For recent laser flash photolysis studies of phenyl azide see Shrock, A. K.; Schuster, G. B.; J. Am. Chem. Soc. (1984) **106**, 5228 and Leyva, E.; Platz, M. S.; Persy, G.; Wirz, J.; J. Am. Chem. Soc. (1986) **108**, 3783. Li, Y.-Z.; Kirby, J. P.; George, M. W.; Poliakoff, M.; Schuster, G. B.; J. Am. Chem. Soc. (1988) **110**, 8092.
3. Doering, W. von E.; Odum, R. A.; Tetrahedron (1966) **22**, 81.
4. Motivation to study the photochemistry of **1** derived from 3 observations: (1) that electron withdrawing groups increase the reactivity of triplet phenyl nitrenes (Reiser, A.; Leyshon, L. J.; J. Am. Chem. Soc. (1971) **93**, 4051), (2) that deoxygenation of pentafluoronitrosobenzene in aromatic solvents yields formal nitrene CH insertion adducts (Abramovitch, R. A.; Challand, S. R.; Scriven, E. F. V.; J. Am. Chem. Soc. (1972) **94**, 1374.) and (3) that pyrolysis of 4-azido-2,3,5,6 tetrafluoropyridine in cycloalkanes yields CH insertion adducts (Banks, R. E.; Sparkes, G. R.; JCS Perkin I (1972) 2964).
5. The atomic radii in covalent bonds for H and F are 0.37 and 0.72Å respectively; Gordon, A. J.; Ford, R. A.; "Chemists Companion"; Wiley, New York, N.Y. (1972) pp. 82-85.
6. (a) Berliner, L. J.; Landis, B. H.; "Nuclear Magnetic Resonance Spectroscopy in Molecular Biology," Pullman, B. (ed) (1978), D. Reidel Publishing, Dordrecht, Holland P.311.
   (b) Landis, B. H.; Berliner, L. J.; J. Am. Chem. Soc. (1980) **102**, 5350; 5354.
7. Leyva, E.; Young, M.J.T.; Platz, M. S.; J. Am. Chem. Soc. (1986) **108**, 8307.
8. Pentafluorophenylazide absorbs strongly ($\varepsilon > 10,000$) in the deep UV region and modestly at the following mercury lines 313 nm ($\varepsilon = 71\ M^{-1}cm^{-1}$), 365 nm ($\varepsilon = 7\ M^{-1}cm^{-1}$), 405 nm ($\varepsilon = 2.6\ M^{-1}cm^{-1}$) and 430 nm ($\varepsilon = 1.8\ M^{-1}cm^{-1}$). It is rapidly consumed upon exposure to 365 nm radiation. Gas chromatography analyses were performed on a Perkin Elmer 8500 gas chromatograph equipped with a split/splitless injector, a flame ionization detector and a 30 m x 0.254 mm J & W Scientific Fused Silica capillary column (5% DB-1701, 0.25 μm). GC/MS spectra were obtained on a Finnegan 4021 gas chromatograph/mass spectrometer by Mr. David Chang and Ms. Kathy Ault of the OSU Campus Chemical Instrumentation Center.
9. Upon flash photolysis of phenyl azide in solution the nonfluorinated analogue of **9** is easily detected by transient IR spectroscopy. Under the same conditions dehydroazepine **9** can not be detected, thus there is no chemical trapping or spectroscopic evidence for its intermediacy (Personal communication from Professor G. B. Schuster). Upon photolysis of **1** in diethylamine two minor products were also formed $C_6F_5N{=}CH{-}N(C_2H_5)_2$ and $C_6F_5N{=}C(CH_3){-}N(C_2H_5)_2$ and will be discussed elsewhere. Thus tar formation from **1** does not originate from a dehydroazepine as seems to be the case with phenyl azide.[2]. Tar formation clearly is limiting the yields of adducts but the mechanism of polymerization, or the identity of the chain propagating species is not presently known.
10. Tomioka, H.; J. Am. Chem. Soc. (1979) **101**, 256.
11. (a) Baer, T. A.; Gutsche, C. D.; J. Am. Chem. Soc. (1971) **93**, 5180.
    (b) Savino, T. A.; Kanakarajan, K.; Platz, M. S.; J. Org. Chem. (1986) **51**, 1305.
12. The adducts of pentafluorophenylnitrene 2S with aromatics are known to be singlet (**2S**) derived because they are not formed on triplet photosensitized photolysis of **1**, and their yields do not increase on dilution of aromatic with an inert diluent (CH_2Cl_2).
13. The aromatic insertion adducts are most likely formed via prior formation of a bicyclic aziridine, see reference 4.
14. The yield of substitution in the 1-position of naphthalene far exceeds 2-substituted product formation.
15. The photochemistry of 1 in toluene at -78°C is dominated by singlet **2S** chemistry, unlike the photochemistry in cyclopentane at this temperature. **2S** is far more reactive towards aryls than cyclopentanes, hence, the lower isokinetic temperature in these systems.
16. (a) Gould, I. R.; Turro, N. J.; Butcher, J., Jr.; Doubleday, C, Jr.; Hacker, N. P.; Lehr, G. F.; Moss, R. A.; Cox, D. P.; Guo, W.; Munjal, R. C.; Perez, L. A.; Fedorynski, M.; Tetrahedron (1985) **41**, 1587, see also reference 11b.

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