

High Yields of Nitrene Insertion into Unactivated C–H Bonds. First Example of X-Ray Crystallographic and ^{19}F NMR Analysis of the Photochemically Produced C–H Inserted Adduct

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Photolysis of 4-azido-tetrafluorobenzonitrile results in the highest yield reported to date, (75–80% as estimated from ^{19}F NMR spectroscopy) for nitrene insertion into the unactivated C–H bond of cyclohexane; the photochemical adduct is characterized by ^1H and ^{13}C NMR spectroscopy and the structure is confirmed by X-ray crystallography for the first time.

Increments in the photochemical yields of C–H insertion processes may bring about significant advances in the utility of photochemically induced reactions.^{1–4} In fact, the covalent attachment of molecular probes by photochemically induced bond insertion reactions has numerous applications in the labelling of macromolecules,⁵ bifunctional cross-linking agents,⁶ electron microscopy,⁷ modification of surfaces⁸ and photolithography.⁹ Therefore, singlet nitrene production by the photolysis of perfluoroarylazides has been the subject of extensive research since its discovery by Dunkin *et al.*,¹⁰ and pioneering studies by Platz *et al.*¹¹ and Keena *et al.*^{12,13} These studies have shown that the fluorine substitution on the aromatic ring hinders the competing ring-expansion reactions, thus increasing the efficiency of the trapped singlet nitrene.¹⁴ Numerous studies have been reported on the search for derivatives of perfluoroaryl azides which give high yields for singlet nitrene insertion into unactivated C–H bonds, because there is a growing consensus that one of the key applications of the photochemically induced C–H insertion reactions is in the attachment of photoprobes across the C–H bonds of the biologically useful molecules (*e.g.* receptors, peptides and proteins). Therefore, the critical assessment of the utility of photogenerated reagents in the topological mapping of proteins and receptors requires evaluation of the C–H insertion ability and the efficiency of the photoprobes.¹⁵ In fact, the preferred mode is the formation of a stable covalent C–H insertion linkage into macromolecules of interest, as opposed to the abstraction of hydrogens leading to polar anilino-type products. In general, the insertion of singlet nitrenes, produced by the photolysis of *p*-substituted perfluoroarylazides, into unactivated C–H bonds has an efficiency in the range 30–60%.^{1,12a,16,17} Herein, we report that 75–80% of the nitrene derived from the photolysis of 4-azido-tetrafluorobenzonitrile *p,p*- $\text{C}_6\text{F}_4(\text{CN})(\text{N}_3)$, **1**, is trapped by insertion into the unactivated C–H bonds of cyclohexane. We believe that this is the highest yield yet reported.^{12a} The structure of the photochemically induced C–H inserted adduct has been confirmed, for the first time, by single crystal X-ray diffraction analysis. We also demonstrate the application and utility of ^{19}F NMR spectroscopy for the direct determination of

insertion and quantum efficiency for the photochemical insertion reactions.

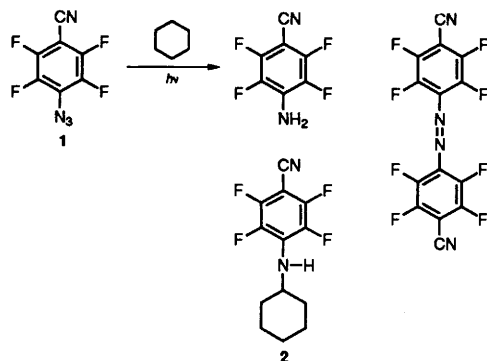
The decomposition of **1** irradiated in cyclohexane with a 200 W super pressure Hg lamp filtered below 320 nm was monitored by HPLC.[†] The orange-red product mixture was evaporated and fractionated by flash chromatography[‡] to obtain a white, flaky solid, $\text{C}_6\text{F}_4(\text{CN})\text{N}(\text{H})\text{C}_6\text{H}_{11}$, **2** which was characterized by single crystal X-ray crystallography and multiprobe NMR,[§] and was subsequently used as an HPLC standard for independent determination of insertion efficiency.

The general photochemical behaviour of **1** (Scheme 1) can occur in two possible ways: (i) the photoproducted singlet nitrene may insert into C–H bonds of cyclohexane to form **2**, or (ii) undergo intersystem crossing (ISC) to triplet nitrene.¹² The triplet nitrene forms an anilino-type product through the successive abstraction of hydrogens and an azo compound, possibly by dimerization of the triplet.¹² The chemical constitution of adduct **2** has been confirmed by X-ray crystallographic analysis.[¶]

Single crystals of **2** were obtained upon cooling the methanolic solutions of the photolysed samples at 0 °C. The ORTEP plot and the salient features of bond parameters are summarized in Fig. 1.

Additional proof for the C–H insertion is provided by ^{13}C NMR spectroscopy. The carbon at which insertion occurs undergoes a characteristic ^{13}C NMR shift from δ 27 for cyclohexane to δ 53.7 for **2**. This resonance also remained positive upon application of the DEPT sequence, while the remaining CH_2 carbon signals became negative.

A significant feature of this investigation is the demonstration that ^{19}F NMR spectroscopy can be used as a diagnostic tool to (i) follow the course of the photochemical reaction (Scheme 1), (ii) estimate quantitatively the formation of **2**, and (iii) calculate the quantum yield for the conversion of **1** to **2**. This is possible because the signals due to the anilino product (multiplets centred at δ 72.3 and 97.6), diazo



Scheme 1

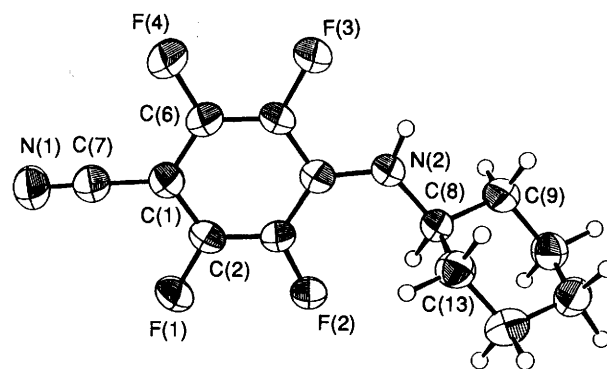


Fig. 1 ORTEP diagram of **2** showing 50% probability ellipsoids. Salient bond lengths (Å) and bond angles (°): N(2)–C(4) 1.356(25), N(2)–C(8) 1.465(24), C(8)–C(9) 1.521(3), C(8)–C(13) 1.519(3); C(4)–N(2)–C(8) 127.14.

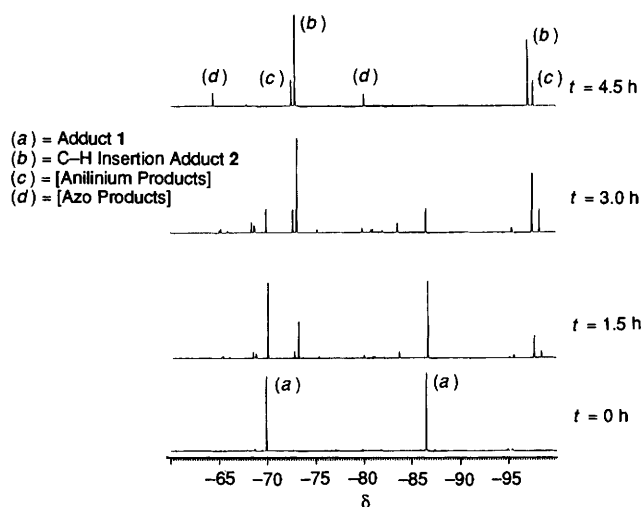


Fig. 2 ^{19}F NMR spectra of the photolysis of **1** showing the C–H insertion into cyclohexane at various time intervals

compound (multiplets centred at δ 64.3 and 80.0) and the adduct **2** (multiplets centred at δ 72.8 and 80.0) resonate at different frequencies in the ^{19}F NMR spectra (Fig. 2). The signals centred at δ 72.8 and 80.0 were also seen in the ^{19}F NMR spectrum of an authentic sample of **2** and thus confirm the assignment made above for **2**. The relative yields of **2** vs. the anilino- and diazo-based photochemical byproducts were calculated by estimation of the relative integrals of the signals of the individual components. This technique indicated yields of 75–80% from the photochemical C–H insertion of **1** into cyclohexane. These yields are comparable to the yield (72–75%) as shown by the HPLC analysis of the photochemical products in which crystallized adduct is used as a standard for peak height measurement. These values exceed the 57% yield reported for nitrene insertion from photolysis of 4-azido-tetrafluoromethylbenzoate,^{12a} and suggest that the CN functionality may have stabilized the singlet nitrene or increased its reactivity relative to the ISC process. Similarly, quantum yields at 20 and 50% decomposition of **1** were calculated and found to be 0.35 and 0.42, respectively. || These values correspond to a quantum yield of ca. 0.5 for the parent azide destruction.

This work was supported by funds provided by DOE Grant DEFG0289E R60875 and by the Departments of Chemistry and Radiology and Research Reactor, University of Missouri, Partial funding of the X-ray diffractometer by the National Science Foundation, Grant No. CHE[90-11804], is gratefully acknowledged. R. S. P. acknowledges useful discussions with Dr P. Lusiak.

Received, 11th February 1994; Com. 4/00850B

Footnotes

† C18 reverse-phase column eluted with $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ mixture in the ratio 2:1—parent azide $t_{\text{R}} = 1.8$ min azide adduct $t_{\text{R}} = 2.5$ min.

‡ Using a mixture of hexane, ethyl acetate and methanol in the ratio 10:1:1.

§ ^{19}F NMR (CDCl_3) referenced to trifluorotoluene. δ/ppm before photolysis -70.4 (m, 2F), -86.6 (m, 2F); after photolysis adduct: -72.8 (m, 2F), -97.1 (m, 2F); anilinium product: -72.4 (m, 2F), -97.6 (m, 2F); azo compound: -64.3 (m, 2F), -80.0 (m, 2F). ^1H NMR (CDCl_3), ref. to SiMe_4 δ/ppm : 4.24 (s, N–H), 3.64 (m, C–H), 1.96–0.8 cyclohexane peaks. ^{13}C NMR (CDCl_3), ref. CD_3CN , δ/ppm

adduct: aromatic region: 149(m), 147(m), 136(m), 134(m), 132(s); aliphatic region: 53.7(t), $^4J(^{13}\text{C}-^{19}\text{F})$ 4.8 Hz, 34.4, 25.2 and 24.6. After DEPT sequence, 53.7 negative. All others positive.

¶ Crystal data for **2**: $\text{C}_{13}\text{H}_{12}\text{N}_2\text{F}_4$, M 271.24, monoclinic, $a = 6.1894(8)$, $b = 20.8863(6)$, $c = 9.6015(1)$ Å, $\beta = 94.626(7)^\circ$, $V = 1237.2$ Å³, $Z = 4$, $D_c = 1.46$ g cm⁻³, space group $P2_1/c$, $\mu = 1.11$ mm⁻¹, $F(000)$ 562.22, 1824 unique reflections, $R = 0.045$, $R_w = 0.070$, GOF = 2.69. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

|| Quantum yields for cyclohexane adduct formation were determined at 313 nm using 10 nm bandwidth monochromator in conjunction with a 1000 W Xe(Hg) lamp and a calibrated radiometer. Analysis was done by integrated ^{19}F method.

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