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The Preparation and Photochemistry of 6-Azido-4,5,7-Trifluoroindole in Toluene. Evaluation of a New Reagent for Photoaffinity Labelling

by

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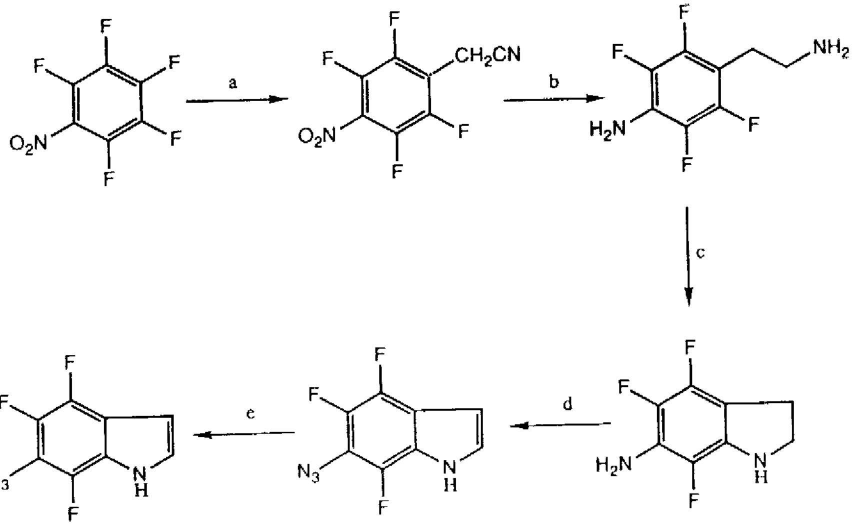
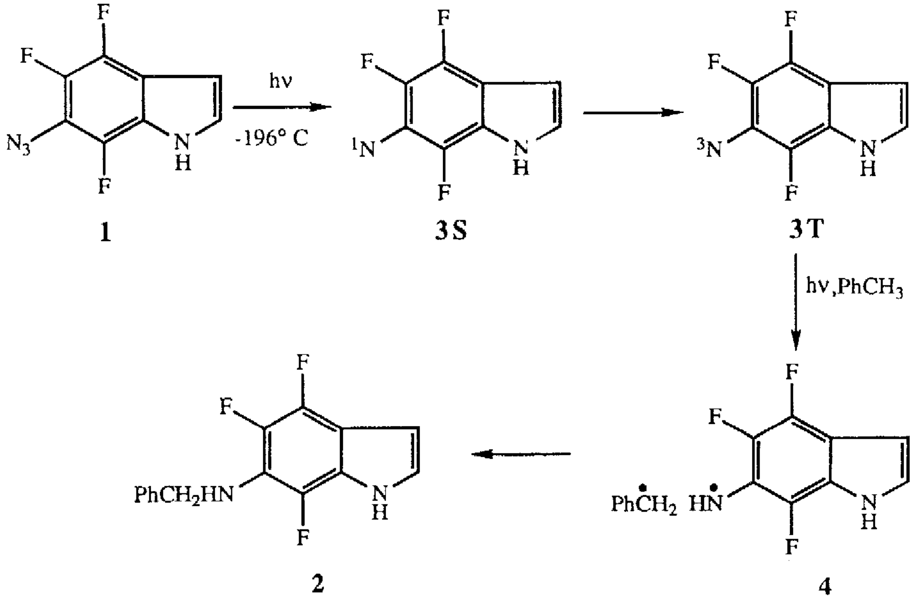
Abstract. 6-Azido-4,5,7 trifluoroindole **1** was synthesized and its photochemistry examined. Although photolysis of **1** at 25° invariably leads to tars, photolysis at -196° in frozen toluene produced a benzylic CH insertion adduct in 70-80% isolated yield. The data suggests that **1** and its derivatives may be useful in photoaffinity labelling at low temperature.

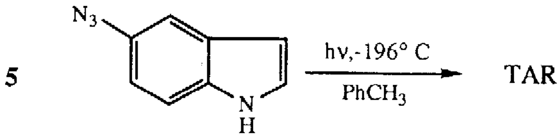
We have recently reported that the yield of nitrene derived adducts produced upon photolysis of an aryl azide in toluene can be dramatically enhanced by fluorine substitution on the aromatic ring and/or by performing the photolysis at -196°.[1] It was noted that this might have practical benefits in photoaffinity labelling (PAL) experiments. This prompted a synthesis[2] of 6-azido-4,5,7-trifluoroindole (**1**) since indoles bind to many enzymes (e.g. α-chymotrypsin),[3] as well as an evaluation of its potential as a reagent for PAL experiments.



Photolysis of **1** in toluene, methanol, or diethylamine at 25° led only to a dark tarry material. However, upon photolysis of **1** in frozen toluene at -196° a 70-80% isolated yield of benzylic insertion adduct 2 was obtained. By analogy to other systems[4] it seemed likely that photolysis of **1** at -196° produced singlet nitrene **3S** which rapidly underwent intersystem crossing to the triplet nitrene (**3T**). The nitrene was subsequently characterized by EPR, absorption and emission spectroscopy (**vide infra**). At -196° nitrene **3T** was long lived, however it can undergo secondary photolysis to form a radical pair **4**, which collapsed to form coupling product **2**.



By comparison, photolysis of a nonfluorinated analog, 5-azidoindole (**5**),[5] in toluene produced only tars at both 25° and -196°.



Photolysis of **1** in toluene at -196° in the cavity of an EPR spectrometer ($\lambda > 350$ nm)[6] produced an EPR spectrum characteristic of a triplet nitrene which was attributed to **3T**. ($|D/hc| = 0.9538$ cm^{-1}, $|E/hc| \sim 0$ cm^{-1}).[7] The triplet nitrene spectrum was rapidly destroyed (Figure 1) by exposure of the sample to short wavelength light ($\lambda > 290$ nm). The disappearance of the EPR spectrum of **3T** was accompanied by the appearance of the EPR spectrum of radical pair **4** ($|D/hc| = 0.011$ cm^{-1}).

Cooling a solution of **1** in EPA to -196° (5:5:2 ether: isopentane: alcohol) produces an optically clear glass. Brief photolysis of the glass (λ=366 nm) led to the disappearance of azide **1** (λ_{max} = 275 nm, Figure 2) and the formation of 3 new bands (Figure 3, 305 nm, strong; 365 nm, moderate; 440 nm, weak). The new bands are similar to those of triplet phenyl nitrene[4] (λ_{max}, 305, 381 tailing to 500 nm) and were attributed to **3T**. The absorption spectrum of **3T** easily explains why short wavelength light is so much more effective at destroying **3T** than light of 366 nm.

Two fluorescence bands at 510 and 550 nm were detected upon excitation (465 nm) of a glass containing azide **1**, previously exposed to long wavelength (λ > 350 nm) light. The emission bands are in good agreement with those of triplet phenyl nitrene[4] and were attributed to **3T**. The maximum of the fluorescence excitation spectrum was at 465 nm which is in reasonable agreement with the weak long wavelength absorbtion band of the nitrene.

In conclusion we have found that matrix photolysis of 6-azido-4,5,7 trifluoroindole **1** leads to good yields of CH benzylic insertion into toluene. The product was formed via secondary photolysis of the corresponding triplet nitrene. This suggests that **1** or its tryptophan derivatives may be useful labelling reagents at -196°. Photolysis of non-fluorinated azide **5** in toluene at 25° or -196° failed to produce an adduct.

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References

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2. All compounds were characterized by ^{1}H, ^{13}C, and ^{19}F-NMR spectroscopy and high resolution mass spectroscopy. A satisfactory C,H,N analysis of **1** was obtained. a: (1) $NCCH_2COOEt$, NaOEt, (2) 50% aq. HOAc, H_2SO_4, Δ (Yield: 72%), b: (H_2, Pd/C, HCl, CH_3OH, (Yield: 100%), c: (DMF, K_2CO_3, Δ, (Yield: 88%), d: (1) CF_3COOH, $NaNO_2$, (2) NaN_3, c: DDQ, Benzene, (Yield: d+c = 88%).
3. (a) Blow, D. M.; Accts. Chem. Res. (1976) **9**, 145.
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6. Product Studies: Azido indole (0.01M) solutions were placed in 5 mm pyrex tubes and sealed after 3 freeze-pump-thaw cycles. Photolysis was performed using 2 350 nm Rayonet Reactor bulbs. After photolysis, tar was removed by passing the reaction mixture through celite.
   Spectroscopic Studies. Compound **1** in the appropriate solvent was placed in either a cylindrical 4 mm cell (EPR) or a rectangular (1 cm^2) cell made of syprasil quartz. The EPR sample tube was placed in a Wilmad EPR dewar and immersed in liquid nitrogen. The

UV sample cell was placed in an Oxford UV-VIS cryostat and cooled to 77K. Samples were irradiated with a Hg-Xe arc lamp (1000 watt-EPR; 200 watt-UV-VIS) whose beam could be filtered through a glass 350 nm long pass filter.

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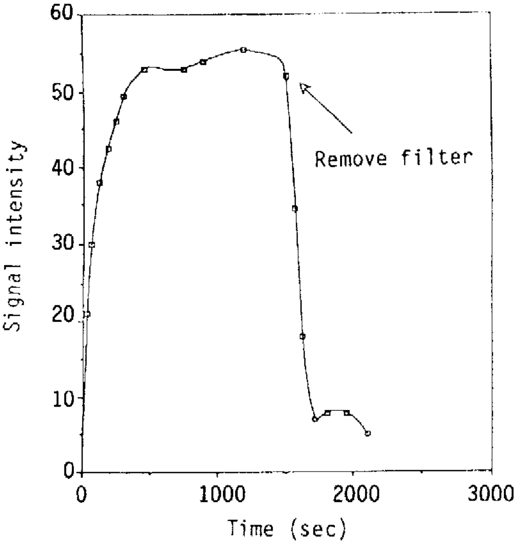

Figure 1. The build up of the EPR signal of 3T produced by long wavelength photolysis (λ > 350 nm) and its destruction caused by short wavelength (λ > 290 nm, removal of a filter) photolysis at 77K.

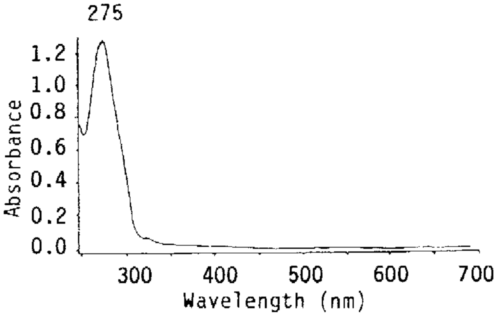

Figure 2. The UV spectrum of **1** in EPA glass at 77K.

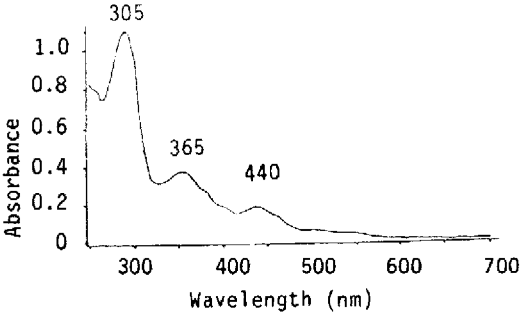

Figure 3. The UV spectrum of **3T** in EPA glass at 77K produced by long wavelength (λ > 350 nm) photolysis of **1**.

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