Tetrahedron Letters, Vol.31, No.17, pp 2443-2444, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ARYL AZIDES AS PHOTOLABELS. RETENTION OF IODINE DURING PHOTOCHEMICAL RING EXPANSION OF AN IODINATED TYROSINE DERIVATIVE

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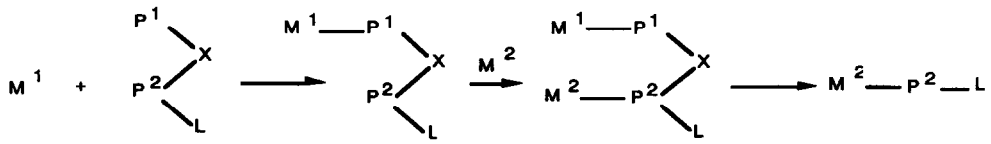
Abstract : In contrast to the photochemical behaviour of iodinated aromatic azides with iodine and azide in the same ring, iodinated N-(4-azidobenzoyl)tyrosine readily undergoes singlet photochemistry with ring expansion and trapping of nucleophiles while retaining iodine substituents in the phenol nucleus.

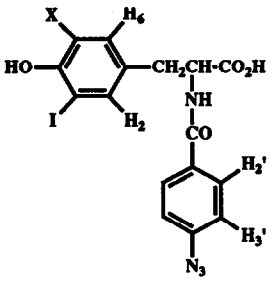
One the most useful applications of the important biochemical technique, photoaffinity labelling, requires label (L) transfer from one macromolecule (M^1) to a target molecule (M^2) followed by cleavage (at X).[1,2]



Three factors are crucial for the use of ^{125}I labelled aromatic azides as photo labelling reagents in biochemistry, i: the photoreaction must proceed from a singlet state *via* a dehydrazepine and/or an azirine[3] with subsequent trapping of a nucleophilic group in the target molecule; ii: iodine substituents must be retained during the reaction, and iii: the reagent must be suited for ^{125}I labelling in the last step prior to use.

In a recent paper Watt et al.[4] reported that the ostensibly very useful type of photoaffinity reagents with ^{125}I as label in an azidophenyl ring, upon photolysis were reduced to anilines (probably *via* a triplet state), or they initially dissociated, thereby losing iodine and their ability as label transfer agents. Instead, they might lead to non-specific labeling.[5]

We have now solved this problem by placing the iodine in one phenyl ring and the azido group in another. We prepared N-(4-azidobenzoyl)tyrosine[6] and found that this compound was easily iodinated exclusively in the hydroxyphenyl ring, and that the products undergo singlet photochemistry with ring expansion and trapping of nucleophiles while retaining iodine. N-(4-azidobenzoyl)tyrosine was iodinated[7] to various mixtures of mono- and diiodo compounds (**1a,b**) and irradiated[8] in methanol and methanol containing 10% diethylamine. In all cases we detected the unreacted iodinated phenol ligand connected with the azepines (**2a,b**), in >50% yield.[9] The NMR data for one example are given in Table 1, and we conclude that derivatives of N-(4-azidobenzoyl)tyrosine may be useful as ^{125}I transfer photoaffinity labelling reagents.[10]



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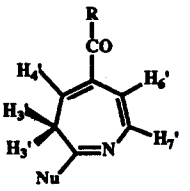

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a: X=H
b: X=I

R= Tyrosine
Nu= -NEt_2 or -OCH_3

References and Notes

1. O. Buchardt, U. Henriksen, T. Koch, P. E. Nielsen, in *Photochemical Probes in Biochemistry*, NATO ASI Series, Vol. C272, edited by P. E. Nielsen, Kluwer Academic Publishers, p. 1 (1989).
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4. D. S. Watt, K. Kawada, E. Leyra, M. S. Platz, *Tetrahedron Lett.* 30, 899 (1989).
5. E. Suenson, T. Koch, O. Buchardt. Unpublished results.
6. *N-(4-Azidobenzoyl)tyrosine* was prepared from tyrosine and the N-hydroxysuccinimide ester of 4-azidobenzoic acid (1:1) in dioxane-water (1:1) containing the calculated amount of Et_3N. After 24 h at ambient temperature, the reaction mixture was filtered and evaporated to dryness, dissolved in water, whereupon addition of conc. HCl caused precipitation of the title compound (70%).
7. *Mono- and diiodo N-(4-azidobenzoyl)tyrosine* (**1a,b**). N-(4-azidobenzoyl)tyrosine, excess of NaI and NaOH were dissolved in MeOH, and chloramine-T in MeOH was slowly added at ambient temperature until the yellow color was preserved for ca. 20 min, yielding mixtures of **1a** and **b** depending on the amount of chloramine-T added. Isolation as above,[6] followed by several recrystallizations from ethyl acetate/petrol ether gave mixtures consisting of pure **1a** and **b**.
8. Samples of ca. 10 mg **1a** and **b** in 10 ml MeOH or 10 ml MeOH containing 10% Et_2NH were irradiated through a pyrex filter for 45 min at ambient temperature using an SP200 mercury lamp. The reaction mixtures containing **2a,b** were evaporated, washed with chloroform and analyzed by TLC, NMR (cf. Table 1), HPLC and MS. All analytical results supported the assigned structures.
9. No absolute yields were determined. Some starting materials were recovered (ca. 30%) and other products than **2a,b** were formed in small amounts but were not identified.
10. This is corroborated in a model study with heterobifunctional photoaffinity labels containing such photoprobes; N. Imai, T. Kometani, P. J. Crocker, J. B. Bowdan, A. Demir, L. D. Dwyer, D. M. Mann, T. C Vanaman, D. S. Watt, *Bioconjugate Chem.*, in press.

Table 1. ^1H NMR Data[a] of Starting Materials and Products (**2a,b**) Formed on Photolysis of **1a,b**.[b]

Compound	4-Hydroxyphenyl-			4-Azidobenzoyl-		Azepine		
	H_2	H_5	H_6	H_2'	H_3'	H_4'	H_6'	H_7'
1a	7.62d[c]	6.76d	7.1dd[c]	7.86d	7.19d			
1b	7.68s		7.68s	7.86d	7.19d			
2a } Nu=Et_2N	7.65d[c]	6.84d	7.1dd[c]			6.23t	6.47d	7.2d
2b }	7.68s		7.68s			6.23t	6.47d	7.2d

(a) Chemical shifts are given as δ-values in DMSO-d_6. (b) A mixture of **1a** and **b** (ca. 1:1) was irradiated in MeOH containing 10% Et_2NH. (c) J = 2 Hz; all other coupling constants are ca. 8 Hz.

(Received in UK 6 March 1990)