Tetrahedron Letters,Vol.30,No.40,pp 5409-5412,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

4-AZIDO-2-IODO-3,5,6-TRIFLUOROPHENYLCARBONYL DERIVATIVES. A NEW CLASS OF FUNCTIONALIZED AND IODINATED PERFLUOROPHENYL AZIDE PHOTOLABELS

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Summary: Iodinated perfluorophenyl azide **4** and NHS ester **7** were synthesized. Photolysis of azide **4** in DEA/cyclohexane gave N-H insertion product **9** (24%). For photolabeling purposes, this constitutes a significant improvement over the behavior of non-fluorinated analogues.

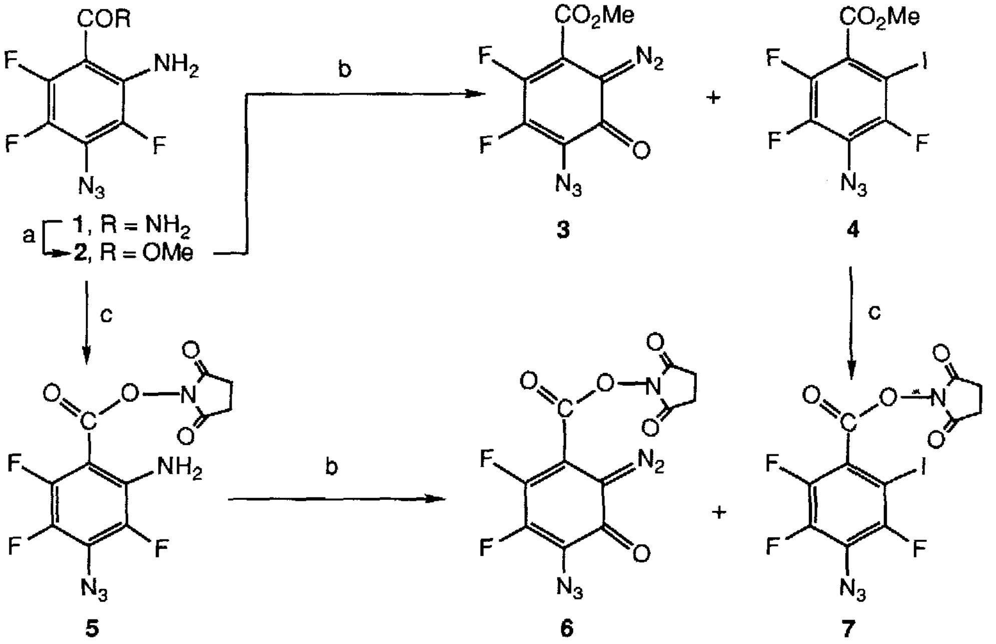
Photoaffinity labeling[1] is a widely applied technique for establishing a covalent bond between a photoreactive ligand and nearby molecules. Aryl azides constitute an important class of photolabels. The main disadvantage of the aryl azides is the tendency of the nitrene intermediate to undergo processes other than the desired C-H or N-H insertion reaction.[2,3] The observation that perfluorophenyl nitrene readily undergoes C-H insertion[4] served as the basis for our development of a series of functionalized perfluorophenyl azides as photoaffinity labels showing enhanced C-H insertion capabilities.[5]

The presence of a radiolabel such as a radioactive iodine atom in the aryl azides has been often used to monitor the incorporation of the photolabel into other molecules.[6] In a study of the effect of the iodine atom on the properties of the nitrene intermediate, Watt *et al.*[7] photolyzed 4-azido-3-iodotoluene in the presence of diethylamine. No product of C-H or N-H insertion was isolated. Instead, the corresponding aniline was formed which likely came from H-atom abstraction by the triplet nitrene intermediate. Photolysis of 4-azido-2-iodotoluene under the same conditions gave mainly the corresponding aniline, and the *deiodinated* ring expansion product 3H-azepine. These limitations of iodinated aryl azides as photolabels prompted us to incorporate an iodine atom into a representative member of our perfluorophenyl azide series of photolabels[5] and to investigate the photochemical properties of this new iodinated photoactive reagent.

Ester **2**[8], mp 82 - 83°C, was prepared by refluxing 2-amino-4-azido-3,5,6-trifluorobenzamide (**1**)[5] in methanol for 70 h in the presence of amberlyst 15 resin.[9] Since diazotization of several perfluoronitroanilines under aqueous acidic conditions was known to produce the corresponding nitro diazo-oxide,[10] diazotization of ester **2** was carried out under non-aqueous acidic conditions.[11] To a stirred solution of 0.1 mL of concentrated H_2SO_4 and 26.0 mg (0.377 mM) of $NaNO_2$ at 0°C was added a solution of 32.0 mg (0.130 mM) of **2** in 0.5 mL of CH_3CO_2H. The solution was stirred at 15°C for 1 h, then 60.0 mg (0.400 mM) of solid NaI was added, followed by

0.5 mL of CH_3CO_2H. The mixture was stirred for 0.5 h, then it was diluted by 2 mL of water and the precipitate was filtered, washed with water and dried to leave a solid. Preparative TLC (silica gel, 1 : 1 CH_2Cl_2 - hexane) gave 10.8 mg (32%) of diazo-oxide **3**[8,12] as a yellow crystalline solid, mp 127 - 128°C, and 14.1 mg (30%) of iodide **4**[8,13] as a colorless solid, mp 73 - 74°C. When aqueous NaI was used the yield of **3** increased to 48% whereas the yield of **4** decreased to 5%. Apparently nucleophilic substitution of the ortho fluorine atom by water is faster than the substitution of the diazonium group by iodide ion.

Scheme 1



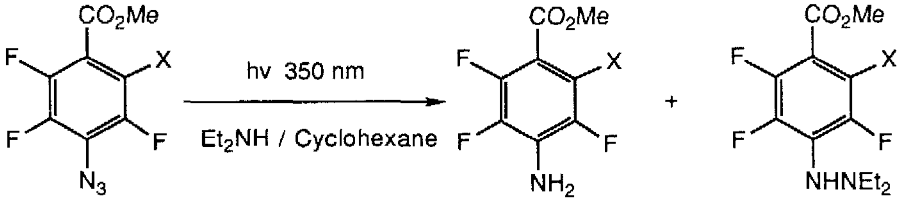
a. MeOH, Amberlyst 15 resin, reflux 70 h.

b. 1) $NaNO_2$, H_2SO_4, CH_3CO_2H; 2) solid NaI.

c. 1) NaOH, H_2O, MeOH, 25°C, 2 h; then HCl; 2) DCC, N-hydroxysuccinimide, THF, 25°C.

In order to enable the attachment of this new iodinated and photoactive reagent to other molecules, the N-hydroxysuccinimidyl (NHS) ester **7**[8], mp 136 - 137°C, was synthesized from ester **4** in 80% yield (scheme 1). Alternatively, the NHS ester **5**[8], mp 184 - 185°C, was synthesized from ester **2** (82%). Diazotization of active ester **5** followed by treatment with NaI gave a mixture of **6** and **7**. Compound **6**[8,14] (56%) was obtained as a yellow crystalline solid, mp 125 - 126°C, via fractional crystallization ($CHCl_3$ - petroleum ether) of the mixture. Compound **7** (20%) was separated from the mixture by preparative TLC (silica gel, 5 : 5 : 2 hexane - $CHCl_3$ - acetone, **6**: R_f = 0.0 - 0.3, **7**: R_f = 0.5), or simply by filtration through silica gel (Aldich, 200 - 425 mesh) with the same solvents.

Photolysis[15] of **4** (3.0×10^{-3} M) in a 0.05 M diethylamine/cyclohexane solution produced the aniline **8**[8,16] (57%) and substituted hydrazine **9**[8,17] (24%) as the only isolated products.[18] Photolysis of the non-iodinated perfluorinated compound **10**[5] under identical conditions produced aniline **11** (24%) and substituted hydrazine **12**[8, 19] (65%). The diminished yield of N-H insertion product from **4** compared to **10** was likely due to the heavy atom effect.[7,20] The fact that azide **4** gave a moderate yield of N-H insertion product without losing the iodine upon photolysis suggests that, as photolabels, iodinated perfluorophenyl azides may be superior to their non-fluorinated counterparts.



4, X = I
10, X = F

8, X = I
11, X = F

9, X = I
12, X = F

ACKNOWLEDGMENT. This work was supported by NIH Grants GM-34916 and GM-27137.

References and Notes

1. Bayley, H. *Photogenerated Reagents in Biochemistry and Molecular Biology*, Elsevier, New York, 1983.
2. Photolysis of phenyl azide gives almost no C-H insertion products in hydrocarbon solvents (Torres, M. J.; Zayas, J.; Platz, M. S. *Tetrahedron Lett.* **1986**, *27*, 791).
3. The nitrene produced from phenyl azide undergoes ring expansion to dehydroazepine which could be trapped by diethylamine (Shields, C. J.; Chrisope, D. R.; Schuster, G. B.; Dixon, A. J.; Poliakoff, M.; Turner, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 4723; Li, Y.-Z.; Kirby, J. P.; George, M. W.; Poliakoff, M.; Schuster, G. B. *J. Am. Chem. Soc.* **1988**, *110*, 8092).
4. It has been reported a) that pyrolysis of 4-azido-tetrafluoropyridine in cyclohexane gave C-H insertion product in 45% yield (Banks, R. E.; Sparkes, G. R. *J. Chem. Soc. Perkin I*, **1972**, 2964); b) that pentafluorophenyl nitrene did not undergo ring expansion photochemically in N_2 or

Ar matrices at 12K (Dunkin, I. R.; Thomson, P. C. P. *J. Chem. Soc. Chem. Commun.* **1982,** 1192); c) that photolysis of pentafluorophenyl azide at 25°C gave C-H insertion product in 52% yield in toluene (Leyva, E.; Young, M. J. T.; Platz, M. S. *J. Am. Chem. Soc.* **1986,** *108,* 8307) and 28% yield in cyclopentane (Young, M. J. T.; Platz, M. S. *Tetrahedron Lett.* **1989,** *30,* 2199).

5. Keana, J. F. W.; Cai, S. X. *J. Fluorine Chem.* **1989,** *43,* 151.
6. For examples, see a) Bercovici, T.; Gitler, C. *Biochemistry,* **1978,** *17,* 1484; b) Ji, J. H.; Ji, I. *Anal. Biochem.* **1982,** *121,* 286.
7. Watt, D. S.; Kawada, K.; Leyva, E.; Platz, M. S. *Tetrahedron Lett.* **1989,** *30,* 899.
8. For new compounds **2 - 9** and **12**, either a satisfactory elemental (C, H, N) analysis or else a high resolution mass spectrum was obtained.
9. Greenlee, W. J.; Thorsett, E. D. *J. Org. Chem.* **1981,** *46,* 5351.
10. The strongly electron withdrawing diazonium group activated the ring toward nucleophilic displacement of the ortho fluorine atom by water. See Hudlicky, M.; Bell, H. M. *J. Fluorine Chem.* **1974,** *4,* 149.
11. Hodgson, H. H.; Walker, J. *J. Chem. Soc.* **1934,** 1620.
12. Compound **3:** ^{19}F NMR (C_6F_6, -162.9 ppm as internal standard), -131.820, -134.314, J = 19.20 Hz; IR, 2150, 2121, 1717, 1591, 1470, 1333, 1287 cm^{-1}; MS, 255 (M^+), 227 (M^+- N_2), 199 (M^+- $2N_2$), 140 (M^+- $2N_2$ - CO_2Me), 59 (base peak, CO_2Me).
13. ^{19}F NMR of methyl 4-azido-2-iodo-3,5,6-trifluorobenzoate (**4**): -103.459 (F_3), -139.156 (F_6), -143.896 (F_5), $J_{3,5}$ = 5.75, $J_{3,6}$ = 11.32, $J_{5,6}$ = 20.03 Hz. Note that F_3 is deshielded by the ortho iodine. See Gunther, H. *NMR Spectroscopy,* Chichester, New York, 1980, p. 347.
14. Compound **6**: MS, 338 (M^+), 310 (M^+- N_2), 282 (M^+- $2N_2$), 140 (base peak, M^+- $2N_2$ - CONHS).
15. Photolysis was carried out in a Rayonet photochemical reactor with 350 nm lamps. The solution was purged with Ar for 1 min then photolysed for 1 h at ambient temperature.
16. Compound **8** : ^{19}F NMR, -113.653 (F_3), -140.703 (F_6), -155.733 (F_5), $J_{3,5}$ = 12.67, $J_{3,6}$ = 9.99, $J_{5,6}$ = 20.55 Hz; MS, 331 (M^+, base peak), 300 (M^+- OMe), 272 (M^+- CO_2Me), 145 (M^+- CO_2Me - I).
17. Compound **9:** ^{19}F NMR, -108.863 (F_3), -140.006 (F_6), -149.149 (F_5), $J_{3,5}$ = 10.26, $J_{3,6}$ = 9.37, $J_{5,6}$ = 19.88 Hz; MS, 402 (M^+, base peak), 387 (M^+- Me), 371 (M^+- OMe), 330 (M^+- NEt_2), 260(M^+- I - Me).
18. The products were separated by preparative TLC (silica gel, 5 : 5 : 1 hexane - $CHCl_3$ - acetone).
19. ^{19}F NMR of **12** shows the characteristic AA'XX' pattern for 1,4-disubstituted-tetrafluorobenzene: -141.655 (AA'), -159.900 (XX'), $J_{A,X}$ = 21.01, $J_{A,A'}$ = 3.26, $J_{A,X'}$ = 8.19, $J_{X,X'}$ = 0 Hz. No ring expansion product was observed.
20. Turro, N. J. *Modern Molecular Photochemistry,* Benjamin/Cummings, Menlopark, CA, **1978,** p. 125.

(Received in USA 7 July 1989)