Tetrahedron Letters,Vol.30,No.18,pp 2427-2428,1989   0040-4039/89 $3.00 + .00
Printed in Great Britain   Pergamon Press plc

THE PHOTOREACTIONS OF 2-FLUORO-4-NITROANISOLE WITH AMINES. THE SEARCH FOR NEW BIOCHEMICAL PHOTOPROBES

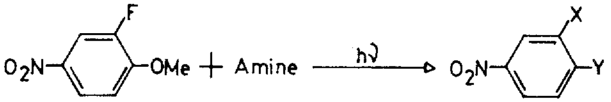
M.Figueredo, J.Marquet,* M.Moreno-Mañas* and R.Pleixats
Department of Chemistry. Universitat Autònoma of Barcelona.
08193 Bellaterra. Barcelona. Spain.

Summary: The photosubstitutions of 2-fluoro-4-nitroanisole with several amines are studied from the preparative and the preliminary mechanistic points of view. The possible usefulness of this structure as biochemical photoprobe is discussed.

The Nucleophilic Aromatic Photosubstitution has been the object of intense research for more than twenty years[1]. Cantor et al.[2] suggested the use of nitrophenyl ethers as *photoprobes in photoaffinity* labelling[3] studies of biological receptor sites[4]. The introduction of fluorine in a molecule normally alters its chemical and biological properties without dramatically altering its steric bulk[5]. These features make fluoro analogues of natural substrates interesting study subjects from the chemical and pharmacological point of view. Moreover the introduction of fluorine in the proper position of a molecule can produce a photoactivatable new molecule. Nevertheless and as far as we know, very little is known about the photochemistry of polysubstituted fluoroaromatic compounds[6], the efficiencies and preparative yields being in general very low for non specially activated compounds. Following our research on new biochemical photoprobes[7] we have considered the possibilities of the fluorine substituent as leaving group. An efficient photohydrolysis has been described[8] for 2-fluoro-4-nitroanisole but no reports exist about photoreactions with amines, nucleophiles of particular relevance in biological chemistry.

The photoreactions of 2-fluoro-4-nitroanisole with several amines are described in the Table. The high preparative photosubstitution yields and the low selectivity versus the nucleophiles present in the solution, are remarkable. Thus, photohydrolysis is always present and when the amine becomes less reactive even methoxide or methanol can act as nucleophiles (exp. 5 and 6). Amines with high ionization potential are better nucleophiles (exp. 1 and 2) than amines with lower ionization potential (exp. 6). Dimethylamine produces appreciable photosubstitution of the methoxy group in para position with respect to the nitro group. Preliminary mechanistic studies indicate that this methoxy substitution is produced from a radical ion pair via electron transfer from the amine to a triplet excited state. In exp. 6 the para-photosubstitution product results from the cleavage of one N-Me bond in the primary photosubstitution product. Similar cases were reported[9]. This general behaviour makes the 2-fluoro-4-nitrophenyl ethers possible better choices as photoprobes for photoaffinity labelling studies than other previously studied nitrophenyl ethers.

Table.- Photoreactions of 2-fluoro-4-nitroanisole with amines.



Exp.	Amine	Reaction Conditions[a]	Reaction Products[b] X	Y	Yield(%)[c]	Total Yield(%)[c]
1	$H_2NCH_2CO_2Et$	H_2O/CH_3CN(80:20) pH 10, 7h	$HNCH_2CO_2Et$ OH	OMe OMe	43 23	66
2	$MeNH_2$	H_2O/MeOH(80:20) 1h	HNMe F OH	OMe HNMe OMe	40 15 13	68
3	$\underline{n}-C_4H_9NH_2$	H_2O/CH_3CN(80:20) pH 10, 4h	$HNC_4H_9-\underline{n}$ F OH	OMe $HNC_4H_9-\underline{n}$ OMe	26 19 29	74
4	$H_2N(CH_2)_4\underset{NH_2}{CH}CO_2Et$	H_2O/CH_3CN(80:20) pH 10, 4h	$\underset{\llcorner(CH_2)_3\lrcorner}{HNCHCONHCH_2}$ OH	OMe OMe	6 22	28
5	$\underline{n}-C_6H_{13}NH_2$	H_2O/MeOH(80:20) 1h	$HNC_6H_{13}-\underline{n}$ F OMe OH	OMe $HNC_6H_{13}-\underline{n}$ OMe OMe	23 5 9 17	54
6	Me_2NH	H_2O/MeOH(80:20) 4h	NMe_2 F OMe OH	OMe HNMe OMe OMe	6 15 12 36	69

a) 400 W Medium pressure Hg lamp with pyrex filter. Room temperature. Excess of amine. b) The new products gave correct elemental analyses. Their full characterization will be reported elsewhere c) Isolated yields with respect to non recovered starting material.

Acknowledgements.- Financial support from CAICYT (project 0343/84) and DGICYT (project PB87-0032) is gratefully acknowledged

References.-

1.- See preceding letter in this Journal and references cited therein.
2.- P.C.Jelenc, C.R.Cantor, S.R.Simon, Proc. Natl. Acad. Sci. USA, 1978, 75, 3564.
3.- "Photoaffinity Labelling", by H.Bailey and J.R.Knowles, in Methods in Enzymology, 1977, 46, 69,. W.B.Jakoby and M.Wilchek, Eds. Academic Press. New York.
4.- H.Gozlan, V.Homburger, M.Lucas, J.Bockaert, Biochem. Pharmacol., 1982, 31, 2879.
5.- J.Mann, Chem. Soc. Rev., 1987, 16, 381.
6.- a) J.A.Barltrop, N.J.Bunce, A. Thompson, J. Chem. Soc. (C), 1967, 1142. b) J.G.Lammers, J.Lugtenburg, Tetrahedron Lett., 1973, 1777. c) D.Brice-Smith, A.Gilbert, S.Krestonosich, J.C.S. Chem. Commun., 1976, 405. d) M.Zupan, B.Sket, B.Pahor, Tetrahedron Lett., 1977, 4541. e) A.Gilbert, S.Krestonosich, J.C.S. Perkin I. 1980, 1393. f) J.R.Siegman, J.J.Houser, J. Org. Chem. 1982, 47, 2773. g) J.H.Liu, R.G.Weiss, J. Org. Chem., 1985, 50, 3657. h) N.J.Bunce, S.R.Cater, J.C.S. Perkin II, 1986, 169.
7.- a) A.Castelló, J.Cevelló, J.Marquet, M.Moreno-Mañas, X.Sirera, Tetrahedron, 1986, 42, 4073. b) "Nucleophilic Aromatic Photosubstitutions on Nitrophenyl Ethers" by J.Marquet and M.Moreno-Mañas, in "Photochemical Probes in Biochemistry"; NATO ASI Series, ed. by P.E.Nielsen, Kluver Academic Publishers. In press.
8.- P.Brasen, J.G.Lammers, J.Cornelisse, J.Lugtenburg, E.Havinga, Tetrahedron Lett., 1972, 685.
9.- K.Mutai, K.Yokoyama, S.Kanno, K.Kobayashi, Bull. Chem. Soc. Jpn. 1982, 55, 1112.

(Received in UK 14 February 1989)