A NEW GENERAL METHOD OF HOMOLYTIC ALKYLATION OF PROTONATED HETEROAROMATIC BASES

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Abstract-Alkyl iodides and benzoyl peroxides provide a new general method of homolytic alkylation of protonated heteroaromatic bases.Yields are good and the substitution is selective in the positions ortho and para to the heteroatom.

-The homolytic substitution of protonated heteroaromatic bases by nucleophilic carbon-centered free radicals has gained increasing synthetic and theoretical interest becoming one of the most important methods of aromatic substitution.<sup>1</sup> Now we describe a new general method of homolytic alkylation of protonated heteroaromatic compounds, based on the reaction of an alkyl iodide, benzoyl peroxide (or in general aroyl peroxide) and protonated heteroaromatic bases.

The reaction conditions are very simple: the solution of the reagents in solvents such as acetonitrile, acetic acid, benzene are heated at 60-80 °C till the complete decomposition of the benzoil peroxide. The reaction is faster in the presence of small amounts of Fe(III) salt, but it occurs also in the absence of Fe(III) salt. The stoichiometry of the reaction is shown by eq.1:

(1)  $\operatorname{ArH}_{2}^{+}$  + R-I + (PhCOO)<sub>2</sub>  $\longrightarrow$   $\operatorname{Arc}_{R}^{+}^{H^{+}}$  + PhI + PhCOOH + CO<sub>2</sub> Some results are reported in Table 1. The mechanism of the reaction is described by the Scheme 1:



## Scheme 1

A key step,which makes selective the overall process, is the Iodine abstraction (eq.2), a very fast reaction close to the diffusion controlled limit(1.2 x  $10^9$   $M^{-1}$  s<sup>-1</sup>)<sup>2</sup>, three-four order of magnitude higher than those of hydrogen abstraction of the phenyl radical.<sup>2,3</sup>

Thus reaction(2) by far prevails over other possible competitive reactions of the phenyl radical. The second important step is the induced decomposition of the benzoyl peroxide (eq.3) by the strongly nucleophilic pyridinil<sup>4</sup> radical  $\frac{1}{\sim}$  which determines the chain character of the reaction. The decomposition rate of the benzoyl peroxide is in fact four-five times higher in the presence of the protonated base, stoichiometric amounts of benzoic acid are formed and the reaction is inhibited by the presence of oxigen.

TABLE 1-Alkylation of heteroaromatic base trifluoroacetates by alkyl iodides and benzoyl peroxide in acetonitrile at 80 C.

Heteroaromatic base	Alkyl iodide	Position of C substitution	a onversion	Yie	ld <sup>b</sup>
Acridine	Cyclohexyl iodide	e 9	82%	94	(f)
Isoquinoline <sup>C</sup>	Cyclohexyl iodide	e 1	93	85	(£)
2-Methylquinoline <sup>C</sup>	Cyclohexyl iodide	e 4	92	88	(f)
4-Methylquinoline <sup>C</sup>	Cyclohexyl iodide	2	86	86	(£)
4-Methylquinoline <sup>e</sup>	Cyclohexyl iodide	2	76	95	(f)
4-Methylquinoline <sup>e</sup>	n-Butyl iodide	2	76	88	(g)
4-Methylquinoline <sup>e,d</sup>	n-Butyl iodide	2	60	78	(f)
4-Methylquinoline <sup>e</sup>	Isopropyl iodide	2	75	98	(f)
4-Methylquinoline <sup>e</sup>	Isopropyl iodide	2	100	77	(g)
Benzothiazole	Isopropyl iodide	2	66	90	(g)
4-Cyanopyridine <sup>e</sup>	Isopropyl iodide	2(66);2,6(34	1) 72	100	(g)
4-Methylquinoline <sup>e</sup> d.e	2-Hydroxycyclohex	yl 2	92	85	(g)
4-Methylquinoline	3-Iodo-Ethyl prop	pionate 2	43	100	(g)
4-Methylquinoline <sup>e</sup>	3-Iodo-Ethyl prop	ionate 2	60	93	(g)
4-Methylquinoline <sup>e</sup>	2-Iodo-pentane	2	68	97	(g)
4-Methylquinoline <sup>e</sup>	2-Iodo-pentane	2	98	85	(g)
4-Methylquinoline <sup>e</sup>	Methyl iodide	2	34	56	(g)

a)Amount of starting heterocycle consumed,determined by g.l.c.with the method of internal standard.

b)Percentage yield of isolated product with reference to amount of starting material consumed.

c) in the absence of Fe(III) salt.

d)Benzene was used as solvent instead of acetonitrile.

e)In the presence of Fe(III) salt,3%.

f)Molar ratios alkyl iodide:benzoyl peroxide:base,5:1:1.

g)Molar ratios alkyl iodide:benzoyl peroxide:base,5:2:1.

Primary and secondary alkyl iodides give good yields and high selectivity; with methyl iodide the reaction takes place more slowly due to its low boiling point,whereas with t-alkyl iodide the yields are till now rather low,due to the competitive reactions between the peroxide and the t-alkyl iodides,which do not involve phenyl radicals.

The availability of a very large variety of primary and secondary alkyl iodides and the general character of the reaction with the heteroaromatic bases makes the process of undoubted synthetic interest.

Acknoledgement-This work was supported by "Progetto Finalizzato Chimica Fine e Secondaria" C.N.R., Roma.

## REFERENCES

1-F.Minisci, Top. Curr. Chem. (1976), 62, 1.

E.Vismara, Chim.Ind. (Milan), (1983), 65, 34.

2-G.Kriger, J.P.Lorand, N.R.Stevens and N.R.Herron J.Am.Chem.Soc. (1977), <u>99</u>, 7589.

3-J.C.Scaiano and L.C.Stewart

J.Am.Chem.Soc. (1983), 105, 3609.

4-C.Giordano, F.Minisci, V.Tortelli and E.Vismara J.Chem.Soc. Perkin II (1984), 293.

(Received in UK 18 June 1984)