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A NEW GENERAL METHOD OF HOMOLYTIC ALKYLATION OF PROTONATED HETEROAROMATIC BASES BY CARBOXYLIC ACIDS AND IODOSOBENZENE DIACETATE .

by Francesco Minisci*, Elena Vismara*, Francesca Fontana and
Maria Claudia Nogueira Barbosa .
Dipartimento di Chimica , Politecnico
piazza Leonardo da Vinci , 32 - 20133 Milano - Italy

A new general , simple and mild procedure is reported in this communication , based on the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate to obtain the substitution of bases by nucleophilic alkyl radicals .

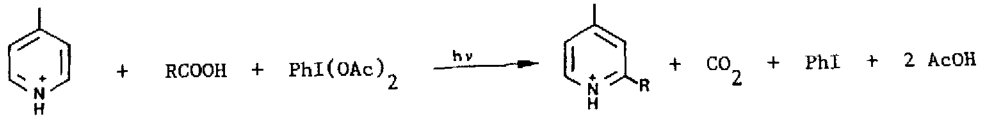
The oxidative decarboxylation of carboxylic acids is a quite general route to alkyl radicals , useful for the heteroaromatic substitution [1] (eq.1)

$$\mathrm{RCOOH} \longrightarrow \mathrm{R^{\bullet}} + \mathrm{CO_2} + \mathrm{H^+} \qquad (1)$$

A large variety of chemical or electrochemical oxidations have been utilized [1]. Generally, the method of choice is the silver-catalyzed decarboxylation by persulfate , because of the simplicity , the low price of the oxidant and the high yields and selectivity [1,2] . A slight solubility of the carboxylic acid in water or in mixtures of water and organic solvents (the protonated base is always soluble in water), is sufficient for the reaction to proceed effectively by persulfate . On the other hand , the substitution of protonated heteroaromatic bases by nucleophilic alkyl and carbonyl radicals has been developed as one of the most important general reactions of this class of aromatic compounds[1]. Thus , the availability of general and simple sources of nucleophilic radicals , useful for the heteroaromatic substitution , is of undoubted synthetic interest.

Now we report a new simple and general procedure , based on the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate ; the method can be useful in those cases in which the reagents have particular problems of solubility or a particular sensitivity to other oxidants .

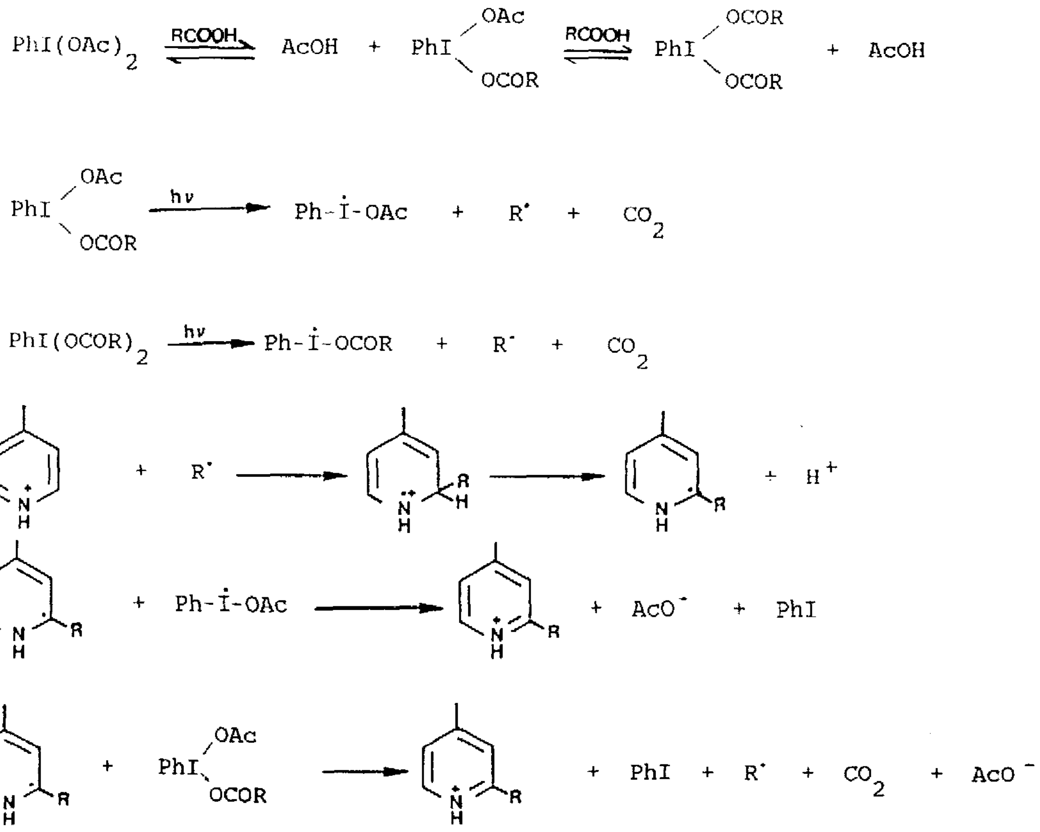
The stoichiometry of the reaction is shown by eq.2


(2)

$$\mathrm{PhI} + \mathrm{H_2O_2} + 2\ \mathrm{Ac_2O} \longrightarrow \mathrm{PhI(OAc)_2} + 2\ \mathrm{AcOH} \qquad (3)$$

Since the iodosobenzene diacetate is easily prepared from iodobenzene , Ac_2O and hydrogen peroxide (eq.3) , the iodobenzene , generated in the reaction , can be recovered and recycled for synthesis on a large scale .

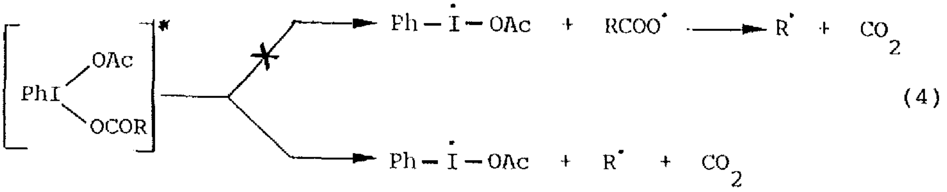
Scheme 1 illustrates the mechanism of the reaction :



SCHEME I

The *high reducing character of the pyridinyl radical* [3] *accounts for the induced decomposition* of the iodosocarboxylate in a chain process.

The fact that only traces of methylation of the heteroaromatic base were obtained would suggest that the excited iodosocarboxylate could undergo homolysis giving directly the alkyl radical , without intermediate formation of an acyloxy radical (eq.4)



The stability of the alkyl radical would , therefore , govern the selectivity of the homolysis . Similarly , the decarboxylation would occur simultaneously to the electron-transfer process in the chain reaction of scheme I . The relative rates reported in Table 1 among AcOH , primary , secondary and tertiary carboxylic acids , obtained in competitive experiments , indicate that the selectivity is high between the methyl and the other alkyl radicals , whereas it is lower among primary , secondary and tertiary alkyl radicals . These relative rates well explain the selective use of the iodosobenzene diacetate for the selective alkylation of heteroaromatic bases by carboxylic acids , even if the meaning of these data is affected by the fact that we do not know the equilibria between iodosobenzene diacetate and the carboxylic acids (scheme I) .

Table 1 - Competitive experiments in the Alkylation of Lepidine.

Ratios of alkylation		Relative rates	
n-Pr/Me	$>$ 20	AcOH	$<$ 0.05
i-Pr/n-Pr	3.3	n-PrCOOH	1
t-Bu/i-Pr	1.6	i-PrCOOH	3.3
		t-BuCOOH	5.3

Table 2 - Alkylation of heteroaromatic bases by carboxylic acids and iodosobenzene diacetate .

Heteroaromatic Base	Carboxylic Acid	Substitution (%)	Conversion (%)	Yields (%)
Lepidine	valerianic	2	45	86
Lepidine	i-butyric	2	58	92
Lepidine	cyclohexane carboxylic	2	61	94
Lepidine	pivalic	2	70	91
Quinaldine	valerianic	4	38	82
Quinaldine	i-butyric	4	65	93
Quinaldine	cyclohexane carboxylic	4	66	94
Quinoline	i-butyric	2 (37) 4 (49) 2,4 (13)	65	98
Quinoline	cyclohexane carboxylic	2 (35) 4 (48) 2,4 (17)	62	96
4-Acetyl-pyridine	cyclohexane carboxylic	2	49	78
Quinoxaline	cyclohexane carboxylic	2	53	76

(a) Conversion of the starting base ; (b) Yields based on the converted base .The reactions were carried out in a Rayonet RPR-100 photochemical reactor , equipped with low pressure mercury lamp , using quartz vessels . A solution of 2 mmoles of the base, 2 mmoles of CF_3 COOH , 4 mmoles of iodosobenzene diacetate and 8 mmoles of carboxylic acid in 40 ml of solvent (acetonitrile or benzene) were irradiated for 2 hours at 254 nm .

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