Tetrahedron Letters,Vol.27,No.27,pp 3187-3190,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

POLAR EFFECTS IN FREE-RADICAL REACTIONS. NEW SELECTIVE ALKYLATIONS OF HETEROAROMATIC BASES BY BENZOYLPEROXIDE AND OLEFINS.

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Abstract- The decomposition of benzoylperoxide in the presence of cyclohexene and 1-methylcyclohexene and protonated lepidine provides a new type of selective homolytic aromatic substitution.

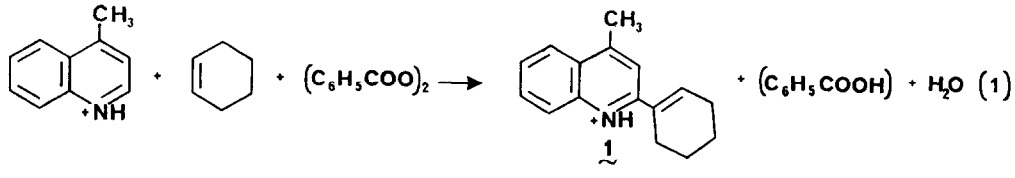
The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals is a general reaction of great synthetic interest in that it reproduces most of the numerous aspects of the Friedel-Crafts aromatic alkylation and acylation, but with opposite reactivity and selectivity.[1] The high rates of addition (10^5-10^8 $M^{-1}s^{-1}$)[2] of the nuclephilic radicals to the protonated heterocyclic rings, mainly due to the polar effects, determine a very high regio- and chemoselectivity and at the same time the efficient trapping of the intermediate radicals heps to elucidate the mechanism of free radicals reactions.

A general source of nucleophilic carbon-centered radicals involves the initial generation of an electrophilic radical ($E^{\cdot}$), which does not react with the heterocyclic ring (Het), but, reacting with a different substrate (S), selectively gives a nucleophilic radical ($N^{\cdot}$) (Scheme 1), suitable for the heteroaromatic substitution.

$$\text{Source} \longrightarrow E^{\cdot}$$
$$E^{\cdot} + S \longrightarrow N^{\cdot}$$
$$N^{\cdot} + \text{Het} \longrightarrow \text{N-Het}$$

Scheme 1

We report a new example of selective heteroaromatic substitution, which falls in this general Scheme. When benzoylperoxide is decomposed in the presence of cyclohexene and a protonated heteroaromatic base ,the selective cyclohexenylation of the heterocyclic ring occurs (eq.1)



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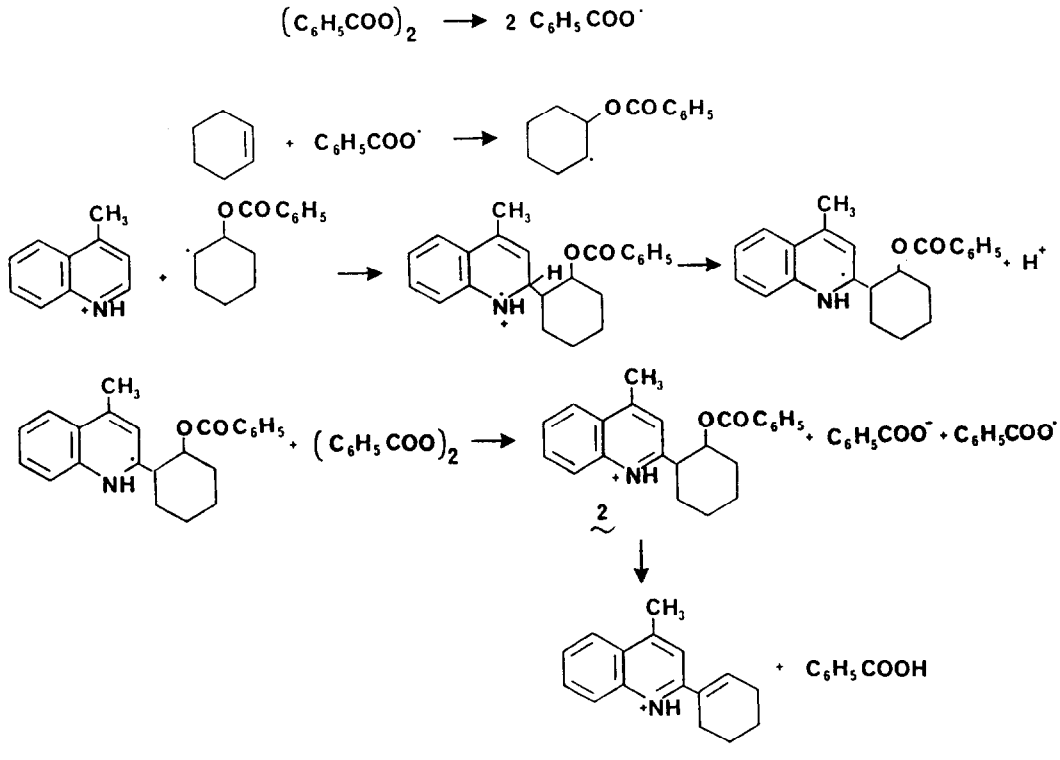
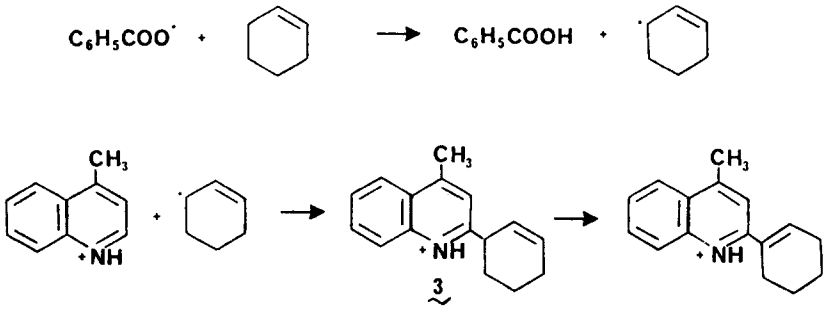
A typical experiment was as follows: a solution of 2.1 mmol of lepidine, 2.1 mmol of CF_3COOH, 6 mmol of benzoylperoxide in 20 ml of cyclohexene was refluxed for 40 hrs. 50 ml of 5% aqueous H_2SO_4 was added and the mixture extracted with EtOAc. The aqueous solution was made basic by 10% NaOH, extracted with EtOAc and the residue of the extraction chromatographed on SiO_2 (hexane : EtOAc 8:2) to give only two products: lepidine (0.93 mmol) and 2-cyclohexenyl-4-methylquinoline 1 (0.87 mmol), ($NMR_{(CCl_4)}$ δ: 1.3-2 (m,4H,$-CH_2-CH_2$), 2-2.5 (m,2H, $>C=CH-\underline{CH_2}$), 2.5-2.9 (m,2H,$-CH=C-\underline{CH_2}$), 2.63 (s,3H,CH_3), 6.65 (t,1H,$-\underline{CH}=C<$), 7.26 (s,1H,aromatic H_3), 7.35-8.1 (m,4H,aromatic); MS m/e : 223 ($M^{\cdot+}$), 222, 208, 197, 181, 157, 77, 51.

A possible mechanism is shown by Scheme 2



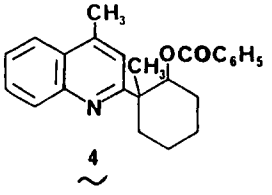
Scheme 2

An alternative mechanism could involve the allylic hydrogen abstraction by the peroxy radical, the substitution of the heterocyclic ring by the allyl radical and the final isomerization of the double bond (Scheme 3).



Scheme 3

However the allylderivative 3, synthesized by an independent procedure[3], does not undergo isomerization under the reaction conditions. Thus the mechanism of Scheme 2 appeared to be the most probable. This mechanism has been supported by utilizing 1-methyl-cyclohexene under the same conditions utilized with cyclohexene: the only reaction product obtained from lepidine is 4, (IR, $\nu_{max.}$ 1715 cm^{-1}; NMR$_{(CDCl_3)}$ δ : 1-2.3 (m,8H), 1.45 (s,3H,CH_3) 2.55 (s,3H,CH_3), 6.0 (dd,1H,CHOCOPh), 7.2-8.1 (m,10H,aromatic); MS m/e: 359 ($M^{\cdot+}$), 254, 237, 157, 105, 77), corresponding to the intermediate 2, not isolated with cyclohexene.



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In this case the absence of the hydrogen atom in the position α to the heterocyclic ring makes stable the substitution product.

Several values of rate constants have been reported for the decarboxylation of benzoyloxy radical (eq.2); the most recent estimation[4] is $\leqslant 1 \times 10^5\ s^{-1}$ for the radical at 55°.

Thus, the addition of the benzoyloxy radital to the double bond must be very fast.

$$PhCOO^{\cdot} \xrightarrow{k} Ph^{\cdot} + CO_2 \qquad k \leqslant 10^5\ s^{-1} \text{ at } 80°C \qquad (2)$$

Alyphatic acyl peroxides are not suitable for a similar reaction because the rate of decarboxylation of the corresponding acyloxy radicals are too high ($1.6 \times 10^9\ s^{-1}$ at 60°C for acetyloxy radical)[5].

Similar results were obtained using a different source of aroyloxy radicals: the silver-catalyzed oxidation of benzoic acid by peroxydisulphate (eq.3 and 4)

$$S_2O_8^{--} + Ag^{+} \longrightarrow Ag^{2+} + SO_4^{--} + SO_4^{\cdot -} \qquad (3)$$

$$C_6H_5COOH + Ag^{2+} \longrightarrow C_6H_5COO^{\cdot} + Ag^{+} + H^{+} \qquad (4)$$

The reaction has been carried out in water-acetonitrile solution (1:3) with lepidine and cyclohexene and the cyclohexenyl derivative 1 has been the only reaction product of lepidine. The conversion,however, were low (~12%), due to the difficulty to keep in solution all the sorgents (a heterogeneous mixture was utilized).

Acknowledgement- This work was supported by Progetto Finalizzato "Chimica Fine e Secondaria" CNR.

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(Received in UK 8 May 1986)